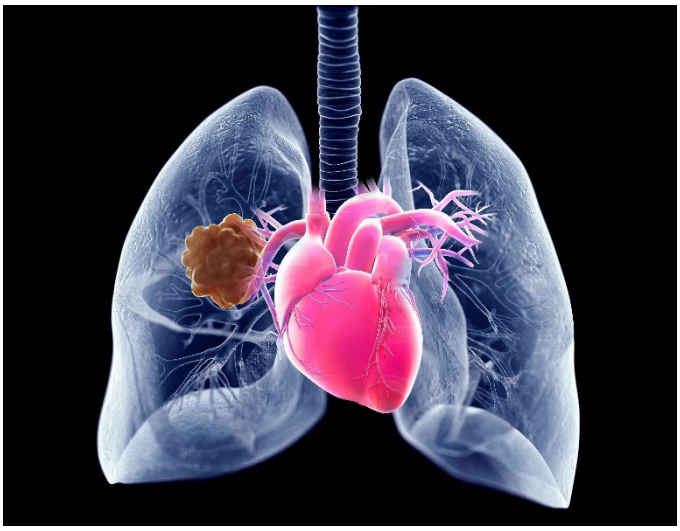
EVALUATION OF CARDIOTOXIC EFFECTS OF NON-SMALL CELL LUNG CANCER (NSCLC) TREATMENTS: INSIGHTS FROM MULTIPLE DATABASES IN THE UNITED KINGDOM



A thesis submitted to the University of Hertfordshire in partial fulfilment of the requirement of the degree of

Doctor of Philosophy (PhD)

by

Ho Yi Stefanie Chan

School of Life and Medical Sciences

University of Hertfordshire, Hatfield, United Kingdom

May 2024

Acknowledgement

I would like to express my deepest gratitude to my principal supervisor, Professor Sam Salek, for giving me his dedicated support and guidance throughout the research. I would also like to extend my appreciation to my second supervisors, Professor Deborah Layton and Dr Sherael Webley, for their insightful contributions and continuous support during my PhD study at University of Hertfordshire.

I would like to acknowledge the Jenny Greenhorn Memorial Scholarship Fund for funding my academic endeavours.

I am grateful to Dr Yasmin Khatib for her contribution as the second reviewer in the systematic review. I am also extremely thankful to Professor Ray W Fitzpatrick for sharing his expertise in the DEFINE database. I would like to extend my gratitude to the entire team at IQVIA for their invaluable assistance with the protocols' development and access to the databases. Additionally, I would like to acknowledge the university statistical team for their statistical support throughout this research.

Lastly, I would like to thank my parents, Ms Irene Cheng and Mr Patrick Chan, for their endless love and support which means the absolute world to me.

Abstract

Cancer and heart diseases are two of the major causes of death in the world. In the last few decades, there is a rapid development in cancer therapies and early detection strategies, hence the death rates caused by cancer have decreased. Although survival rates have improved, it is observed that cardiovascular disease has become the second leading cause of long-term morbidity and fatality among cancer survivors. Thus, the risk of cardiotoxicity is one of the major limitations of oncology drug development. Cardiotoxicity can occur during any stage of the cancer, and it includes, but is not limited to, subclinical myocardial toxicity, ischemia, hypertension, supraventricular and ventricular arrhythmias, systolic and diastolic cardiac dysfunction, coronary artery disease and heart failure. Therefore, the aim of this study was to investigate the association between non-small cell lung cancer (NSCLC) drugs and cardiotoxicity by using real-world data and clinical trials data available from public domains, reports and published literatures.

A systematic review using several electronic databases was completed to evaluate randomised controlled trials data, in which cardiotoxicity was developed in non-small cell lung cancer patients after the administration of anticancer drugs. A full version protocol of this systematic review (CRD42020191760) is published on PROSPERO. A total of 1785 records were identified using specific search terms through the databases and registers; 74 eligible studies were included for data extraction. Based on data extracted from the included studies, anticancer drugs for NSCLC that reported to be associated with cardiovascular events included bevacizumab, carboplatin, cisplatin, crizotinib, docetaxel, erlotinib, gemcitabine and paclitaxel. Hypertension was the most reported cardiotoxicity as 30 studies documented this cardiovascular adverse event. Other reported treatment-related cardiotoxicities included arrhythmias, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, coronary artery disease, heart failure, ischemia, left ventricular dysfunction, myocardial infarction, palpitations, and tachycardia.

A feasibility assessment was conducted to identify the most suitable database for investigating the association between non-small cell lung cancer and cardiotoxicity. A total of 103 data sources were identified from the Health Data Research Innovation Gateway and public domain using the search term ‘cancer’. Data sources which healthcare settings are primary care only were not suitable for this research question. Primary care only data is a major limitation for

oncology studies as oncology treatment and follow-ups are mostly followed in secondary care settings. Consequently, only 2 eligible data sources (#34 and #54) were included for data extraction.

An observational study based on a retrospective design using real-world data from the DEFINE database in England was performed. Monthly secondary data of 40 shortlisted drugs (20 anticancer drugs and 20 cardiology drugs) from April 2017 to July 2022 were extracted. From the correlation matrix, it can be concluded that hypertension was the most associated cardiovascular disease with the 20 shortlisted oncology drugs.

A pharmacovigilance study was conducted utilising the UK Yellow Card System. All NSCLC drugs available within the UK Yellow Card System were shortlisted. Proportional reporting ratio (PRR) and reporting odds ratio (ROR) were calculated to detect signals. The total number of adverse events reported was 128,214 with 6133 reports being cardiovascular adverse reactions. Alectinib had the highest signal for potential cardiovascular adverse events among the drugs analysed, as indicated by both the highest ROR and PRR values.

Due to drug-induced cardiotoxic complications, it is important to understand the suspected associations in order to maintain a benefit-risk balance between therapeutic gain and risk of cardiotoxicity. The combined findings of the systematic review, the pharmacoepidemiology study and the pharmacovigilance report have elucidated the types of cardiotoxicities associated with certain NSCLC therapeutics. To enhance the therapeutic management of NSCLC, continued research on identifying patients at elevated risk of cardiovascular adverse events as well as implementation of early detection and screening strategies are imperative.

List of Abbreviations

5-FU	5-Fluorouracil
ACE	Angiotensin-Converting Enzyme
ADRs	Adverse Drug Reactions
AJCC	American Joint Committee On Cancer
ALK	Anaplastic Lymphoma Kinase
ATC	Anatomical Therapeutic Chemical
ATC/DDD	Anatomical Therapeutic Chemical/Defined Daily Dose
ATS	American Thoracic Society
BCPNN	Bayesian Confidence Propagation Neural Network
BCR-ABL	Breakpoint Cluster Region Gene-Abelson Murine Leukaemia Viral Oncogene Homolog 1
BNF	British National Formulary,
BNP	Brain Natriuretic Peptide
BRAF	B-Raf proto-oncogene, serine/threonine kinase
bsAbs	Bispecific Antibodies
CAR	Chimeric Antigen Receptor
CAS	Cancer Analysis System
CDK	Cyclin-Dependent Kinase
COSD	Cancer Outcomes And Services Dataset
CPMP	Committee On Proprietary Medicinal Products

CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen 4
CV	Cardiovascular
DAPs	Drug Analysis Profiles
DDD	Defined Daily Dose
DOACs	Direct Oral Anticoagulants
DURG	Drug Utilisation Research Group
EGFR	Epidermal Growth Factor Receptor
EHRs	Electronic Health Records
EMA	European Medicines Agency
EPhMRA	European Pharmaceutical Market Research Association
ERS	European Respiratory Society
ESMO	European Society For Medical Oncology
EU	European Union
FDA	Food And Drug Administration
GDPR	General Data Protection Regulation
H&E	Haematoxylin And Eosin
HES	Hospital Episode Statistics
HIPAA	Health Insurance Portability And Accountability Act
HLGTs	High-Level Group Terms
HLTs	High-Level Terms
HPA	Hospital Pharmacy Audit

HTI	Hospital Treatment Insight
IARC	International Agency For Research On Cancer
IASLC	International Association For The Study Of Lung Cancer
ICD	International Classification Of Diseases
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL-6	Interleukin-6
ILCD	International List Of Causes Of Death
INR	International Normalised Ratio
ISEAC	Independent Scientific and Ethical Advisory Committee
KCMO	Keele University Centre For Medicines Optimisation
KRAS	Kirsten Rat Sarcoma 2 Viral Oncogene Homolog
LLT	Lowest Level Terms
LoT	Line Of Therapy
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
mAbs	Monoclonal Antibodies
MedDRA	Medical Dictionary For Regulatory Activities
MEK	Mitogen-activated Protein Kinase
MET	Mesenchymal Epithelial Transition
MGPS	Multi-Item Gamma Poisson Shrinker

MHRA	Medicines And Healthcare Products Regulatory Agency
mTOR	Mechanistic Target Of Rapamycin
MTX	Methotrexate
NCI	National Cancer Institute
NCRAS	National Cancer Registration And Analysis Service
NICE	National Institute For Health And Care Excellence
NTRK	Neurotrophic Tyrosine Receptor Kinase
NSCLC	Non-Small Cell Lung Carcinoma
PARP	Poly (ADP-ribose) Polymerase
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Ligand 1
PHE	Public Health England
PRADA	Prevention Of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy
PRR	Proportional Reporting Ratio
PT	Preferred Terms
RCTs	Randomised Controlled Trials
RET	Rearranged During Transfection
ROR	Reporting Odds Ratio
ROS	Reactive Oxygen Species
ROS1	Proto-Oncogene1, Receptor Tyrosine Kinase

RWD	Real-World Data
RWE	Real-World Evidence
SACT	Systemic Anti-Cancer Therapy
SCLC	Small Cell Lung Carcinoma
SD	Standard Deviation
SIGN	Scottish Intercollegiate Guidelines Network
SOC	System Organ Class
SPACE	Structured Pre- And Post-Approval Comparative Study Design Framework To Generate Valid And Transparent Real-World Evidence
SPCs	Summaries Of Product Characteristics
SPIFD	Structured Process To Identify Fit-For-Purpose Data
TCA	Tricarboxylic Acid
TKIs	Tyrosine Kinase Inhibitors
TNM	Tumour, Node, Metastasis
TRK	Tropomyosin Receptor Kinase
UICC	Union For International Cancer Control
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
VKAs	Vitamin K Antagonists
WHO	World Health Organization

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Chapter 1

General Introduction

1.1 Background

According to the GLOBOCAN 2022 database released by the International Agency for Research on Cancer (IARC), it was estimated that there were 20 million new cancer cases and 9.7 million cancer deaths worldwide in 2022 (Ferlay et al., 2024). And in the GLOBOCAN 2020 database, it was estimated that there were 19.3 million new cancer cases and 10 million cancer deaths worldwide in 2020 alone (Ferlay et al., 2020). Figure 1.1 shows the worldwide age-standardised incidence and mortality rate per 100,000 for both sexes in all types of cancer in 2022 (Ferlay et al., 2024).

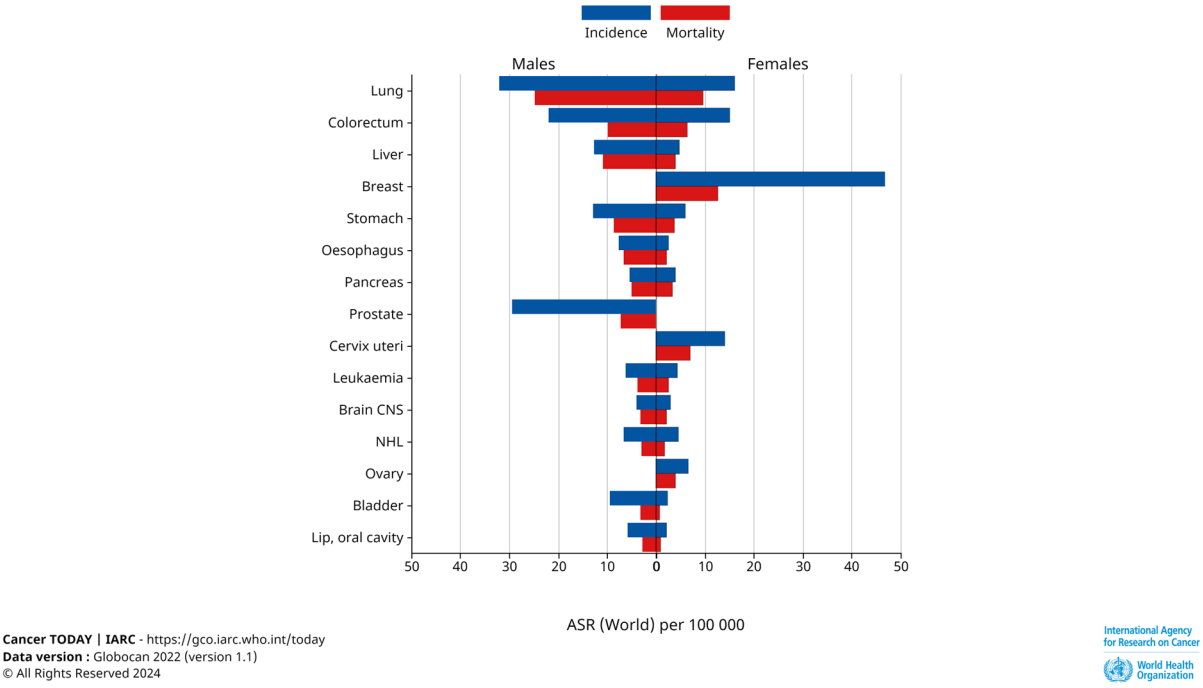

Figure 1.1: Worldwide age-standardised incidence and mortality rate per 100,000 for both sexes in all types of cancer in 2022 (Ferlay et al., 2024).

In recent years, there has been a breakthrough in the development of novel targeted oncology drugs. There was an increase of 22% oncology trials starting in 2022, compared to that of 2018. According to the Global Oncology Trends 2023, there was an average of 23 novel oncology therapeutic drugs launched annually from 2018-2022 and a total of 237 since 2003 (IQVIA, 2023). Due to this continuous innovation and balanced by the rising adoption of biosimilars in major markets, the global spending on cancer medications increased to USD $196 billion in 2022 and is projected to reach USD $375 billion by 2027 (IQVIA, 2023).

In 2020, female breast cancer was the most commonly diagnosed cancer with an estimated 2.26 million new cases (11.7%), followed by lung cancer with an estimated 2.21 million new cases (11.4%). However, lung cancer remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%) (Ferlay et al., 2020). Furthermore, in the newest released GLOBOCAN 2022, lung cancer once again was the most commonly diagnosed cancer worldwide with an estimated 2.48 million new cases, and also the most common cause of cancer death with an estimated 1.82 million deaths (Ferlay et al., 2024). Figure 1.2 shows the world map of age-standardised incidence rate of lung cancer per 100,000 in 2022 (Ferlay et al., 2024).

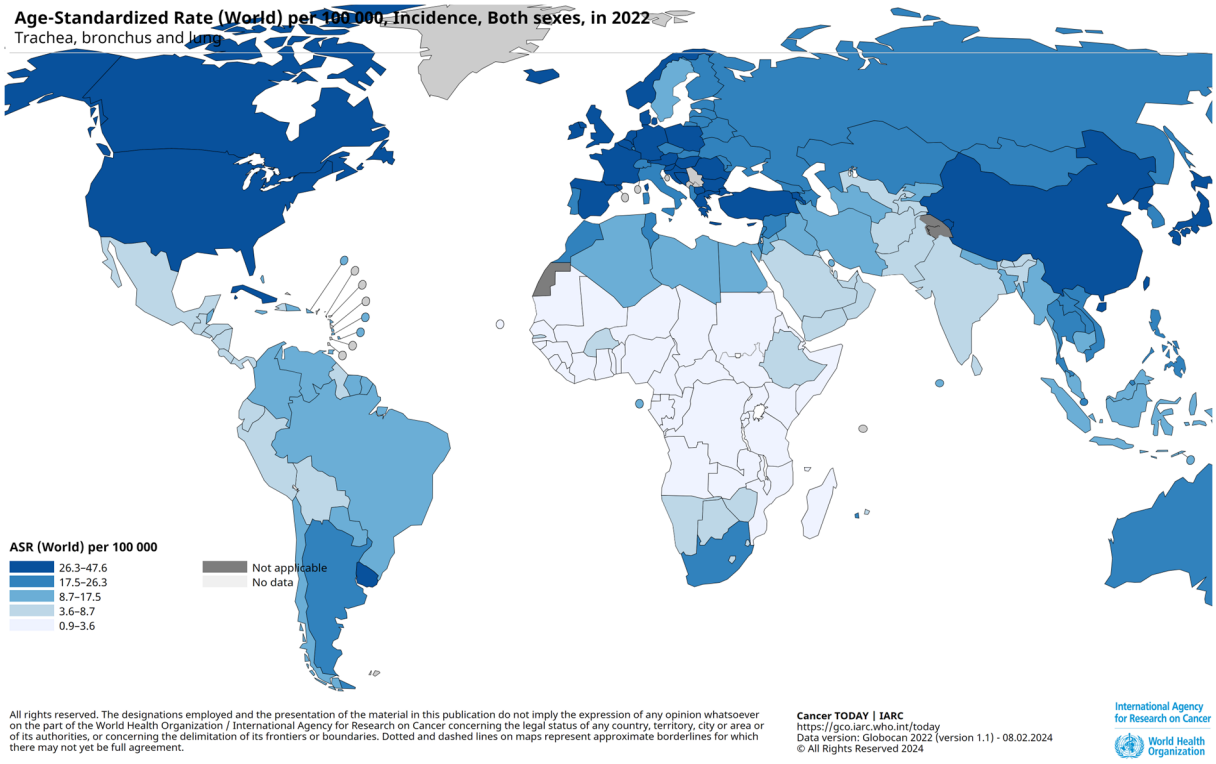

Figure 1.2: A world map of age-standardised incidence rate per 100,000 for both sexes in trachea, bronchus and lung cancer in 2022 (Ferlay et al., 2024).

In 2020, there was a notable 12% decline in the number of all cancer diagnoses in England, decreasing from 327,174 new cases in 2019 to 288,753. This marked a deviation from the typical small annual increases observed until 2019. In 2021, the total number of cancers diagnosed in England was back to 329,665. This represented a return to the gradual upward trend in annual cancer diagnoses that was interrupted by the pandemic in 2020 (NHS England Digital, 2023). According to the GLOBOCAN 2022 database, there was 454,954 new cancer cases with 181,807 cancer deaths in the United Kingdom in 2022. The age-standardised

incidence and mortality rate were 307.8 and 98.3, respectively. The 5-year prevalent cases were 1,435,322 (Ferlay et al., 2024). In 2022 alone, the UK recorded 50,700 new cases of lung cancer, accounting for 11.1% of all cancer diagnoses. Thus, making it the third most common type of cancer in the country, following breast and prostate cancer. The leading cause of cancer mortality was lung cancer with 35,394 deaths (19.5%). The cumulative risk for an individual to be diagnosed with lung cancer and dying from lung cancer in the UK were 3.7% and 2.3%, respectively. The five-year prevalence of lung cancer was 60,603 cases, with a proportion of 4.2 cases per 100,000 individuals (Ferlay et al., 2024). Figure 1.3 shows the age-standardised incidence rate of the top 15 cancer sites by males and females in the United Kingdom in 2022.

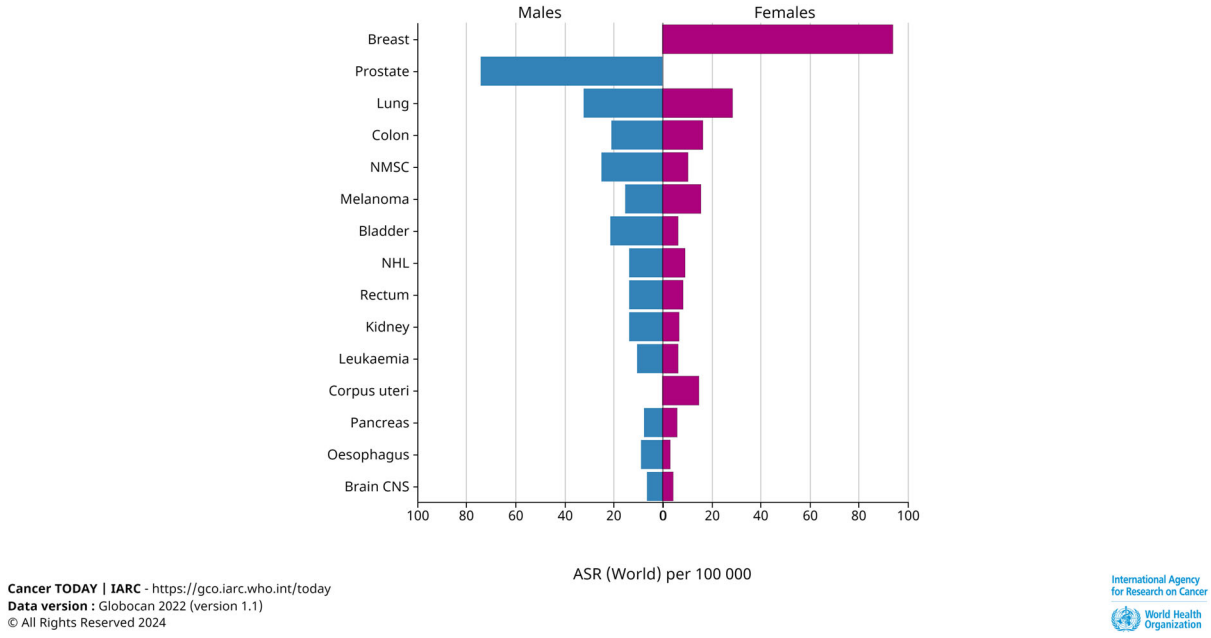

Figure 1.3: The age-standardised incidence rate of the top 15 cancer sites by males and females in the United Kingdom in 2022 (Ferlay et al., 2024).

1.2 History of Lung Cancer

Lung cancer was once a reportable medical condition more than 100 years ago, and now it is one of the leading causes of death globally (Spiro and Silvestri, 2005). Early mentions of lung cancer can be dated back to 1520s (Brewer, 1982). In the 'Dictionnaire des Sciences Medicales' (1815) and 'De L'Auscultation Mediate' (1819), Dr René Théophile Hyacinthe Laënnec referred lung cancer to 'encephaloid', thus distinguishing it from tuberculosis (Laënnec, 1819, 1815). By 1839, the term encephaloides was replaced with "cancer du poumon" for the pathological diagnosis of lung cancer (Brewer, 1982). Dr Issac Adler first

published a literature review about lung cancer, reporting all cases of lung cancer – he only managed to verify 374 cases using several European registries – in his book 'Primary Malignant Growths of the Lungs and Bronchi' in 1912 (Adler, 1912).

The first successful pneumonectomy for lung cancer was in 1933 by Dr Evarts A. Graham (Graham and Singer, 1933). Not only was it a breakthrough for one-stage total pulmonary excision, it also notably showed the world that this was a curable disease with adequate pulmonary resection as the patient who was a 48-year-old physician continued practicing medicine (Brewer, 1982; Graham and Singer, 1933).

As a medical student, Dr Alton Ochsner was asked to observe an autopsy of a lung cancer patient in 1910s and was told at the time that lung cancer was so rare that he might never see it again. It was not until 17 years later, he came across another case of lung cancer. Thereafter, he observed eight more cases within six months, all male smokers who picked up the habit in World War I, which led him to suspect cigarette smoking might be the cause (Ochsner, 1973).

One of the major milestones for lung cancer was the landmark article published in the British Medical Journal in 1950 by Sir Richard Doll and Austin Hill, which confirmed suspicions that lung cancer was associated with cigarette smoking (Doll and Hill, 1950). The Royal College of Physicians of London then published a report addressing the link between smoking and health, including lung cancer, in 1962 (The Royal College of Physicians of London, 1962). Another significant publication was a report by the US Surgeon General's Advisory Committee in 1964, which declared that smoking poses health risks, and it advised individuals should either avoid starting the habit or make efforts to quit (U.S. Public Health Service, 1964).

1.3 Classification and Pathophysiology of Lung Cancer

The 2015 World Health Organization (WHO) Classification of Tumours of the Lung, Pleura, Thymus, and Heart has recently been released, following prior WHO Classifications in 1967, 1981, 1999, and 2004. This latest edition reflects substantial advancements in the understanding of lung cancer genetics and therapy over the past decade. Significant updates have been made since the 2004 WHO classification. These updates largely incorporated the 2011 lung adenocarcinoma classification endorsed by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), with only minor modifications (Travis et al., 2015b). The most

significant updates in lung cancer in this classification encompass a reorganisation of the adenocarcinoma group, a narrowing of the criteria that define lesions as large cell carcinoma, a revision in the nomenclature for variants of squamous cell carcinoma, and the inclusion of small cell lung carcinoma (SCLC) to the newly established neuroendocrine tumours group (Travis et al., 2015b).

Despite the existence of numerous subtypes of lung cancer, the most crucial classification has been the distinction between non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma (SCLC). Figure 1.4 shows the haematoxylin and eosin (H&E)-stained image demonstrating the histological profile of the three main types of NSCLC (adenocarcinoma, squamous cell carcinoma and large cell carcinoma) and SCLC.

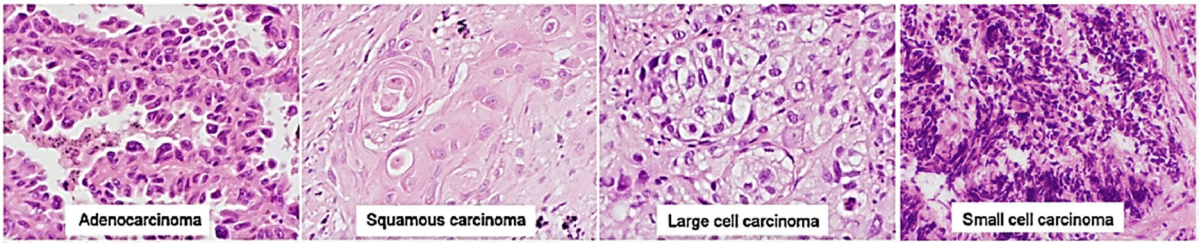

Figure 1.4: H&E-stained image showing the histological profile of three main types of NSCLC (adenocarcinoma, squamous cell carcinoma and large cell carcinoma) and SCLC, from left to right, 20x magnification (Motadi et al., 2007).

The NSCLC accounts for approximately 85% of all lung cancer cases and is further divided into three main subtypes – adenocarcinoma (40%), squamous cell carcinoma (25-30%) and large cell carcinoma (5-10%) (Alduais et al., 2023; Travis et al., 2015a). Adenocarcinoma is the most prevalent type of lung cancer among non-smokers, but also occurs in smokers. It typically originates in the outer regions of the lungs and grows more slowly compared to other forms of lung cancer. Squamous cell carcinoma is often associated with a smoking history, and generally develops in the central parts of the lungs near a bronchus. Large cell carcinoma, which can develop in any part of the lung, grows and spreads quickly (Alduais et al., 2023).

The SCLC accounts for about 15% of lung cancers and is strongly associated with cigarette smoking (Yuan et al., 2022). It is characterised by its rapid growth and early metastasis to distant parts of the body. SCLC is predominantly treated with chemotherapy and radiation since surgery is rarely effective by the time of diagnosis (Raso et al., 2021). Traditionally, SCLC has been staged using the two-stage system – limited stage and extensive stage. Limited

stage SCLC is confined to one side of the chest, affecting a part of the lung and potentially adjacent lymph nodes. This stage is often targeted with local therapies, such as radiation. In contrast, extensive stage SCLC has spread beyond the initial region to other areas of the chest or to distant parts of the body, including lymph nodes and other organs. The treatment for extensive stage typically focuses on systemic therapies, such as chemotherapy (Jackman and Johnson, 2005; Rudin et al., 2021).

Histologically, adenocarcinoma is characterised by the presence of a round to oval nuclei with conspicuous nucleoli and a copious. Glandular or acinar structures or mucin production by the tumour cells are also commonly observed. These structures are encased in a dense, fibrous stroma, a result of a desmoplastic reaction (Borczuk, 2022). Squamous cell carcinoma is characterised by the presence of squamous cells, which are flat cells that line the airways. These are malignant epithelial tumours that are generally well differentiated. Individual tumour cells exhibit features such as epithelial pearl formation, keratinisation, and the presence of intercellular bridges (Franklin, 2000). Large cell carcinoma is characterised by large cells with prominent nuclei and abundant cytoplasm but lacks the distinct cellular features that characterise adenocarcinomas and squamous cell carcinomas (Yoshimura et al., 2021). SCLC is distinguished by its histological presentation of diminutive, densely aggregated cells with limited cytoplasm, which results in the nuclei appearing congested. These nuclei are hyperchromatic and exhibit a ‘salt and pepper’ chromatin distribution, with poorly defined nucleoli. This type often grows in tight clusters and demonstrates extensive necrosis as well as a high nucleus-to-cytoplasm ratio (Raso et al., 2021).

1.4 Non-Small Cell Lung Cancer (NSCLC)

Non-small cell lung cancer (NSCLC) consists of several subtypes, each with unique characteristics, etiologies, and treatment responses. As mentioned previously, adenocarcinoma, squamous cell carcinoma, and large cell carcinoma are the most prevalent among all the subtypes. Understanding these subtypes is crucial for improving diagnostic accuracy, treatment strategies, and ultimately patient outcomes. In general, NSCLC prognosis depends on the stage at diagnosis, with earlier detection leading to better outcomes.

Adenocarcinoma is the most common subtype of NSCLC. It typically originates in the outer, peripheral areas of the lungs and tends to develop in smaller airways, e.g. bronchioles and alveoli, which are responsible for gas exchange. The pathogenesis of adenocarcinoma involves

various genetic and environmental factors. Mutations in genes like KRAS, EGFR, and ALK are particularly common in this subtype. These mutations lead to uncontrolled cell growth and tumour formation. Besides smoking, environmental risk factors, e.g. exposure to radon, asbestos and other air pollutants can also cause adenocarcinoma. Moreover, adenocarcinoma has been associated with interstitial pulmonary fibrosis as scarring can cause malignant transformation of hyperplastic epithelial cells (Motadi et al., 2007). The incidence of adenocarcinoma is higher in women and younger patients compared to other types of lung cancer. Patients with adenocarcinoma might not experience symptoms in the early stages. However, symptoms include coughing, chest pain, wheezing, and shortness of breath. As the tumour grows, it can cause complications such as pleural effusion (fluid around the lungs), which exacerbates respiratory symptoms. Treatment options typically involves a combination of surgery, radiation, and chemotherapy, especially when detected early. Targeted therapies are particularly effective in adenocarcinoma with specific genetic alterations, such as those affecting the EGFR gene or ALK rearrangements. Immunotherapy has also emerged as a beneficial treatment in advanced stages (Saito et al., 2018).

Squamous cell carcinoma arises from the epithelial surface of a segmental bronchus and spread in a stratified or ductal pattern to affect the lobar bronchi. This subtype is strongly associated with smoking (Franklin, 2000). The carcinogenesis in squamous cell carcinoma is closely linked to the inhalation of carcinogenic compounds found in tobacco smoke. These compounds cause mutations that disrupt the normal cell cycle, thus leading to cancer. Symptoms typically include a persistent cough, coughing up blood, and breathing difficulties. Because of its central location, this subtype may also lead to obstructions in the airway, which presents as wheezing or recurrent pneumonia. Treatments usually involves surgery for early-stage disease, combined with chemotherapy and radiation. For advanced stages, more advanced treatments such as targeted therapies and immunotherapy are being explored (Socinski et al., 2016).

Large cell carcinoma is a less common subtype. However, its prognosis is generally poorer than other subtypes due to its aggressive nature and tendency to be diagnosed at a later stage. It can occur in any part of the lung and is characterised by large, abnormal cells. This subtype is particularly aggressive and tends to grow and spread rapidly, making it a challenging subtype to treat. The specific genetic changes in large cell carcinoma are less well understood compared to other NSCLC subtypes. But similar to other subtypes, it is influenced by smoking and environmental factors. The large cells lack the squamous or glandular differentiation observed in the other types, which categorises them as ‘undifferentiated’ (Rossi et al., 2014). Due to its

rapid growth rate, symptoms can progress quickly and include severe respiratory issues, chest pain, and weight loss. The aggressive nature of this cancer often leads to early metastasis before a diagnosis is made. The treatment strategy for large cell carcinoma typically involves a combination of chemotherapy and radiation, as these tumours are often too advanced for surgery at diagnosis. Targeted therapies are less effective due to the lack of specific molecular targets.

Developed and published by the Union for International Cancer Control (UICC), the American Joint Committee on Cancer (AJCC) and the International Association for the Study of Lung Cancer (IASLC), the 8th edition of the Tumour, Node, Metastasis (TNM) classification of lung cancers is in effect since 2017 (Amin et al., 2017; IASLC, 2017; UICC, 2017). This system classifies the tumour size and extent (T), the spread to regional lymph nodes (N), and the presence of distant metastases (M) individually (Table 1.1). These classification are then aggregated to determine the overall stage group, as shown in Table 1.2 (Goldstraw et al., 2016; Lim et al., 2018).

Table 1.1: Tumour, Node, Metastasis (TNM) Classification of lung cancer.

T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤ 3 cm across, surrounded by lung or visceral pleura
T1mi	Minimally invasive adenocarcinoma
T1a	Tumour ≤ 1 cm across
T1b	Tumour > 1 cm but ≤ 2 cm across
T1c	Tumour > 2 cm but ≤ 3 cm across
T2	(i) Tumour size > 3 cm but ≤ 5 cm across; OR (ii) Involvement of the main bronchus but not the carina; OR (iii) Invasion of visceral pleura; OR (iv) Atelectasis/obstructive pneumonitis extending to the hilum
T2a	Tumour > 3 cm but ≤ 4 cm across
T2b	Tumour > 4 cm but ≤ 5 cm across
T3	(i) Tumour size > 5 cm but ≤ 7 cm across; OR (ii) Invasion into the chest wall, phrenic nerve, or parietal pericardium; OR (iii) Separate tumour nodule in the same lobe
T4	(i) Tumour size > 7 cm; OR (ii) Invasion of the diaphragm, mediastinum, heart, great vessels, trachea, carina, recurrent laryngeal nerve, oesophagus, or vertebral body; OR

	(iii) Separate tumour nodule in a different lobe of the same lung

N – Regional Lymph Nodes			**M – Distant Metastasis**	
NX	Regional lymph nodes cannot be assessed		M0	No distant metastasis
N0	No lymph node metastasis		M1	Distant metastasis
N1	Metastasis to ipsilateral peribronchial or hilar lymph nodes		M1a	Separate tumour nodule in the other lung; Tumour with pleural or pericardial nodules; Malignant pleural or pericardial effusion
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes		M1b	A single metastasis outside the chest
N3	Metastasis to scalene or supraclavicular lymph nodes; Metastasis to contralateral hilar or mediastinal lymph nodes		M1c	Two or more metastases outside the chest

The NSCLC staging describes the extent of the disease and is crucial to help determine the most effective treatment strategies and provide insight into prognosis. NSCLC stages range from Stage 0 (indicates a very localised cancer) to Stage IV (represents advanced disease with distant metastasis). Figure 1.5 illustrated NSCLC Stage I – Stage IV.

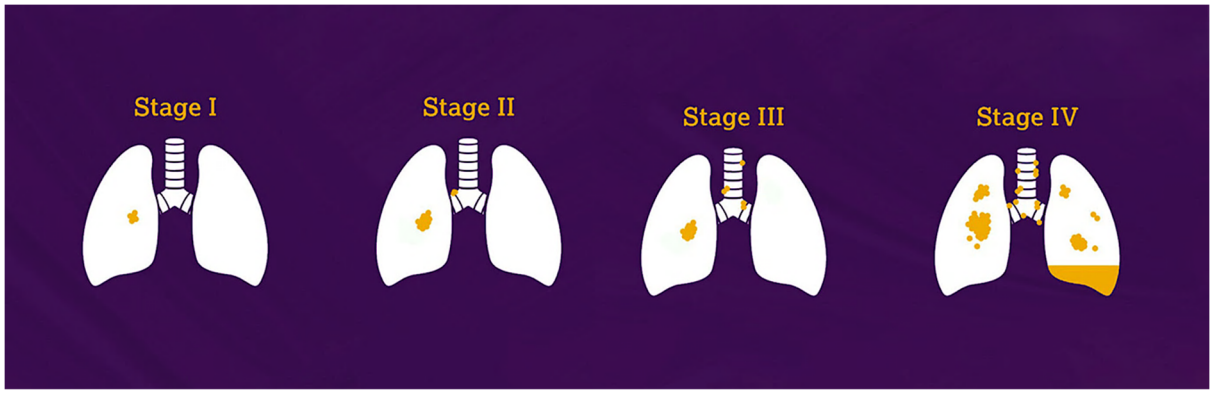

Figure 1.5: NSCLC Stage I – Stage IV (AstraZeneca, 2021)

Stage 0 means 'carcinoma in situ' that is NSCLC has not spread beyond the inner lining of the lungs at Stage 0. It is often detected accidentally through imaging tests done for other reasons, as there are typically no symptoms. Treatments usually involve surgery to remove the affected

area of the lung. Stage I represents localised NSCLC, meaning cancer is only confined to the lungs and has not spread to any lymph nodes, and is subdivided into Stage IA and Stage IB based on tumour size. Treatment options include (1) surgical removal of the tumour, possibly followed by chemotherapy if there is a high risk of recurrence, and (2) radiotherapy for patients who cannot undergo surgery (AstraZeneca, 2021a; K. Zarogoulidis et al., 2013). Stage II indicates local spread to nearby lymph nodes or into structures near the lungs and is further subdivided into Stage IIA and Stage IIB. At this stage, surgery is typically recommended, often followed by chemotherapy or radiotherapy (AstraZeneca, 2021a). Stage III NSCLC is more advanced and reflects regional spread, with significant involvement of local lymph nodes or surrounding tissues. Stage IIIA indicates that tumour has spread into lymph nodes on the same side of the chest as the primary tumour and may involve nearby structures, while Stage IIIB means tumour may have spread into lymph nodes near the collarbone or opposite side of the chest, indicating more extensive lymph node involvement. Stage IIIC represents even more extensive involvement, potentially impacting heart, trachea, and other central chest structures. Treatments at this stage usually include a combination of chemotherapy, radiation therapy and possibly surgery, depending on the extent and specific location of the cancer (Hoffman et al., 2000; K. Zarogoulidis et al., 2013). Stage IV denotes distant metastasis, which marks the spread of lung cancer to distant organs. Stage IVA means that the tumour has spread within the chest or to one distant site, whereas Stage IVB represents widespread (two or more metastases outside the chest). The prognosis for this stage of NSCLC is generally poor, with treatment focusing on palliation rather than cure (K. Zarogoulidis et al., 2013).

Table 1.2: Stage group of lung cancer according to TNM classification.

Stage Group	**TNM Classification**		
	Tumour (T)	**Node (N)**	**Metastasis (M)**
IA1	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1 – T2	N1	M0
IIB	T3	N0	M0
IIIA	T1 – T2	N2	M0
IIIA	T3	N1	M0
IIIA	T4	N0 – N1	M0
IIIB	T1 – T2	N3	M0

IIIB	T3 – T4	N2	M0
IIIC	T3 – T4	N3	M0
IVA	Any T	Any N	M1a – M1b
IVB	Any T	Any N	M1c

Over the past two decades, the IASLC has been working on a global initiative to update the TNM classification of lung cancer. The first two phases of this staging project resulted in recommended changes that were incorporated into the seventh and eighth editions of the TNM classification by the UICC and the AJCC. Currently, in its third phase, the IASLC Staging Project has compiled a new database comprising lung cancer cases diagnosed from January 2011 to December 2019. Analysis of this database is expected to provide recommendations for adjustments to the 9th edition of TNM classification, which is originally anticipated to be adopted in January 2024 (Asamura et al., 2023; Ruffini et al., 2023).

The upcoming 9th edition of the TNM classification for lung cancer will maintain the existing T descriptors without any changes. However, modifications have been made within the N and M categories (Asamura et al., 2023; Huang et al., 2023). Specifically, the N2 stage will be subdivided into N2a and N2b. N2a indicates involvement of a single N2 lymph node station, while N2b refers to involvement of multiple N2 stations (Huang et al., 2023). Additionally, the M1c stage will be subdivided into M1c1 and M1c2. M1c1 represents multiple extra-thoracic metastases located within a single organ system, whereas M1c2 denotes these metastases are present in multiple organ systems (Fong et al., 2024). Consequently, these alterations in the N and M descriptors necessitate a revised TNM stage grouping (Huang et al., 2023; Rami-Porta et al., 2024), as shown in Table 1.3.

Table 1.3: Stage group of lung cancer based on the proposed 9th edition of the TNM classification.

T Classification	**M Classification**	**N Classification**				
		N0	N1	N2a	N2b	N3
T1a	M0	IA1	IIA	IIB	IIIA	IIIB
T1b	M0	IA2	IIA	IIB	IIIA	IIIB
T1c	M0	IA3	IIA	IIB	IIIA	IIIB
T2a	M0	IB	IIB	IIIA	IIIB	IIIB
T2b	M0	IIA	IIB	IIIA	IIIB	IIIB
T3	M0	IIB	IIIA	IIIA	IIIB	IIIC
T4	M0	IIIA	IIIA	IIIB	IIIB	IIIC

Any T	M1a	IVA	IVA	IVA	IVA	IVA
Any T	M1b	IVA	IVA	IVA	IVA	IVA
Any T	M1c1	IVB	IVB	IVB	IVB	IVB
Any T	M1c2	IVB	IVB	IVB	IVB	IVB

1.4.1 NSCLC Treatments and Mechanisms

The UK National Institute for Health and Care Excellence (NICE) guideline (NG122) on 'Lung cancer: diagnosis and management' provides treatment pathways for advanced non-small-cell lung cancer that integrated NICE-recommended treatment options along with relevant technology appraisal guidance (NICE, 2024). These pathways outline the recommended treatment options at each decision point (Appendix I). It was first published in March 2019, with the latest updates published in March 2024.

The cell cycle consists of a sequence of structured phases that a cell progresses through during division and proliferation. Abnormalities in cell cycle control are a hallmark of cancer cells, which typically display unregulated division and growth. By understanding the cell cycle mechanisms, oncological therapies can be designed to interrupt this process at various stages, thereby reducing tumour growth and improving patient outcomes.

The cell cycle comprises four distinct phases: G1, S, G2, and M, as illustrated in Figure 1.6. The S phase and the M phase are particularly critical; they are separated by two gap phases, G1 and G2. Cell grows and prepares to synthesise DNA in G1 phase (Gap 1). The G1 phase follows mitosis and is a period during which the cell is particularly responsive to external growth signals, both stimulatory and inhibitory (Payne and Miles, 2018). DNA replication occurs in S phase (Synthesis), and the cell then continues to grow and prepares for mitosis in G2 phase (Gap 2). Finally, the division of the nucleus into two daughter cells happens in M phase (Mitosis) (Murray and Hunt, 1993). Another phase, known as G0, occurs when cells temporarily or permanently exit the cell cycle in response to factors like high cell density or lack of growth factors. This exit can be reversible, leading to a quiescent state, or irreversible, leading to cell differentiation or senescence (Zetterberg and Larsson, 1985). Progression through these phases is primarily regulated by the cyclin-dependent kinase (CDK) family of serine/threonine kinases as well as their regulatory partners, the cyclins. The combinations of Cyclin D-CDK4 and Cyclin D-CDK6 are pivotal for the progression through G1 up to the restriction point, which commits the cell to complete the cycle. Cyclin A-CDK2 is essential

for initiating S phase, while Cyclin B-CDK1 is crucial for the progression through G2 and the entry into mitosis (Nigg, 2001; Planas-Silva and Weinberg, 1997).

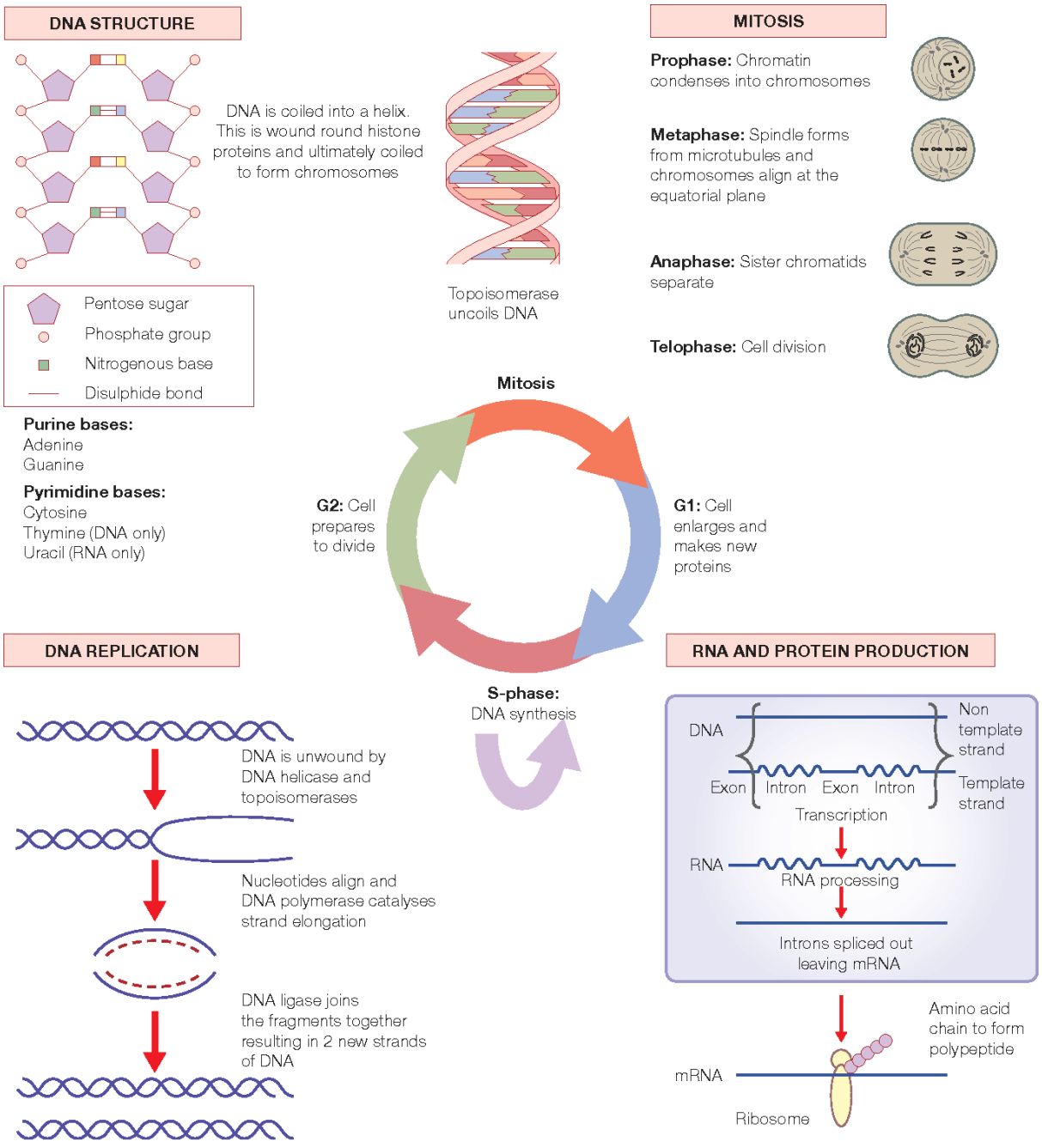

Figure 1.6: Cell cycle (Payne and Miles, 2018).

Chemotherapy drugs are among the most common cancer treatments that exploit the cell cycle. They are cytotoxic drugs that interfere with cell division and DNA replication, targeting cells

at various phases of the cell cycle. The aim is to kill rapidly dividing cells, which is a common characteristic of cancer cells. Tyrosine kinase inhibitors (TKIs) are a class of targeted therapies that inhibit the action of enzymes called tyrosine kinases, which are crucial in the signalling pathways that regulate the cell cycle, i.e. growth and division. By blocking these enzymes, TKIs stop cancer cells from proliferating and can induce programmed cell death (Lenihan and Kowey, 2013). Immunotherapy leverages the body's immune system to fight cancer by influencing the cell cycle indirectly, i.e. destruction of cancer cells in various cell cycle stages. For example, checkpoint inhibitors can block proteins that cancer cells use for protection from immune system attacks. These proteins regulate the cell cycle, and by inhibiting them can result in enhanced apoptosis and reduced cellular proliferation. This dual action not only disrupts the cancer cells' defence mechanisms but also impedes their ability to proliferate, thus contributing to tumour suppression.

1.4.1.1 Chemotherapy Drugs

Chemotherapy aims to destroy the maximum number of tumour cells with minimal damage to other healthy tissues. However, this can be difficult to achieve due to the non-selectivity of chemotherapeutics (Bursác, 2018).

Chemotherapies can be divided into cell cycle-specific drugs and cell cycle-nonspecific drugs. Cell cycle-specific drugs target specific phases of the cell cycle while cell cycle-nonspecific drugs can affect cells at any stage of the cycle (Figure 1.7). For example, alkylating agents, anthracyclines, platinum compounds and transcription inhibitors are cell cycle-nonspecific drugs, so they can act at various stages of the cell cycle. Anti-metabolite agents act primarily during S phase, while anti-microtubule agents and anti-mitotic agents both act in M phase. Topoisomerase inhibitors act in both S and G2 phases.

Alkylating agents, such as cyclophosphamide and ifosfamide, act by adding alkyl groups to the DNA of cells, which leads to cross-linking and breaks in DNA strands, and consequently causing cell death. By altering the DNA structure, these agents prevent cancer cells from replicating and dividing, thus halting their proliferation. This is particularly damaging to the rapidly dividing cells of cancer (Fu et al., 2012).

Anthracyclines, such as doxorubicin and daunorubicin, act primarily by causing DNA damage, both directly and indirectly. They target proliferating cells during the S and G2 phases of cell growth. The mechanism involves the anthracene nucleus of anthracyclines inserting non-

specifically into DNA, forming a stable complex due to its positive charge and high affinity for the negatively charged DNA. This interaction blocks enzymes, which leads to the disruption of DNA replication and transcription (Davies and Doroshow, 1986; Nishi et al., 2021). Moreover, anthracyclines promote oxidative damage and DNA double-strand breaks by enhancing the production of reactive oxygen species. They also inhibit the activities of DNA helicase and topoisomerase type 2, which are crucial for DNA strand separation and unwinding (Sala et al., 2020).

Anti-metabolites drugs, such as methotrexate and 5-fluorracil, mimic the building blocks of DNA and RNA, and thus interrupt the synthesis and function of DNA. They are incorporated into DNA during the S phase of the cell cycle, which lead to interruption in DNA replication, hence causing cell death (Tiwari, 2012).

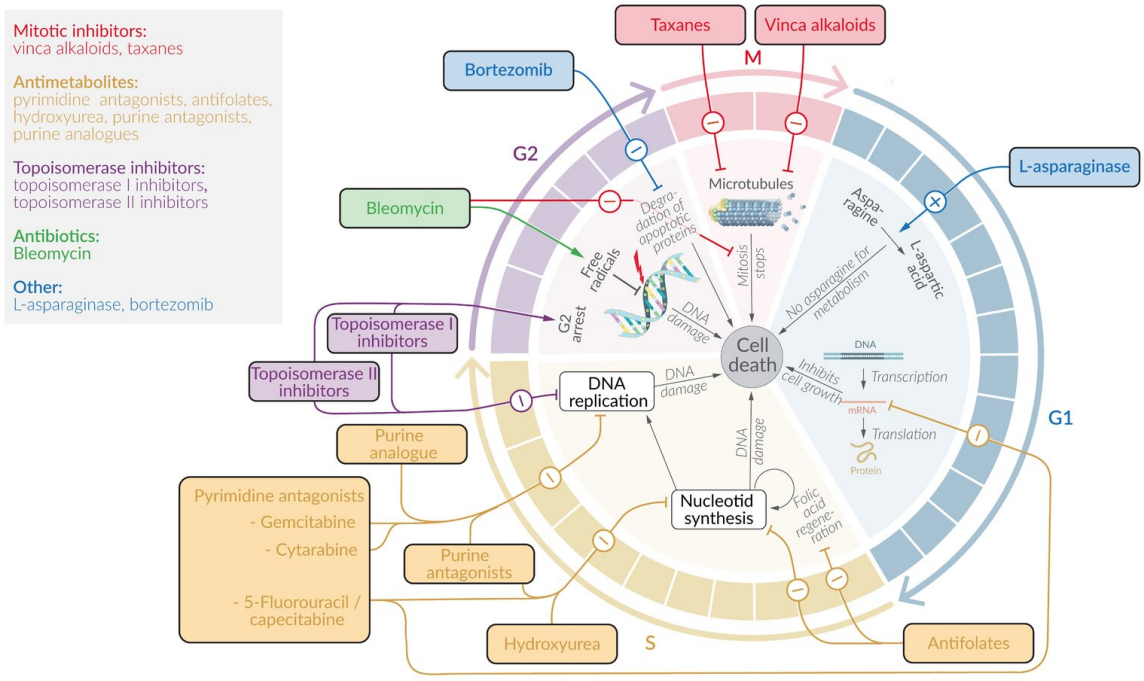

Figure 1.7: Mechanisms of action of some of the common chemotherapies in NSCLC (AMBOSS, 2023).

Anti-microtubule agents (Taxanes), such as paclitaxel and docetaxel, stabilise microtubules, which are essential for cell division. These agents disrupt the mitotic spindle by preventing the disassembly of microtubules, which then block the progression of mitosis and lead to cell death (Jordan and Wilson, 2004).

Anti-mitotic agents, such as vincristine, also target the mitotic spindles. However, they inhibit the function of proteins which are essential for pulling apart the sister chromatids during mitosis, thus effectively disrupt cell division and lead to apoptosis (van Vuuren et al., 2015).

Platinum compounds, such as cisplatin and carboplatin, act by forming platinum-DNA adducts, which lead to DNA cross-linking and cause significant distortions in the DNA helix. Thus, inhibit DNA synthesis and transcription, and consequently causing cell death (Johnstone et al., 2014; Zhang et al., 2022).

Topoisomerase inhibitors, such as topotecan and irinotecan, block the action of topoisomerases, which are enzymes that uncoil DNA strands during replication, and ultimately cause a double-stranded break in the DNA (Liang et al., 2019).

Transcription inhibitors interrupts RNA synthesis by blocking the transcription of RNA, thus halting protein production which are essential for cell survival and proliferation (Laham-Karam et al., 2020).

1.4.1.2 Tyrosine kinase inhibitors (TKIs)

Tyrosine kinase inhibitors (TKIs) act by competing with ATP for binding sites on tyrosine kinases, and thus reducing phosphorylation of tyrosine residues and inhibiting cancer cell proliferation. These agents are characterised by their high selectivity, minimal adverse reactions, and the convenience of oral administration. The antitumour mechanisms of TKIs include inhibiting tumour cell repair, blocking cell division at the G1 phase, as well as inducing and sustaining apoptosis (Lenihan and Kowey, 2013). Figure 1.8 demonstrates the mechanisms of action of some of the common targeted kinase therapies in NSCLC.

Anaplastic Lymphoma Kinase (ALK) inhibitors block the kinase activity of ALK, thus preventing it from signalling the cancer cells to grow and divide (Kohno et al., 2015). The ALK gene, which encodes a tyrosine kinase receptor, is situated on the short arm of chromosome 2 (2p23). It is part of the insulin receptor superfamily and is responsible for producing the ALK protein (Duyster et al., 2001). This gene contributes to cancer development by activating pathways that promote cell growth and division. Crizotinib is the first generation of ALK. Second generation ALKs include alectinib, brigatinib and ceritinib, while third generation include ensartinib and lorlatinib (Wu et al., 2016).

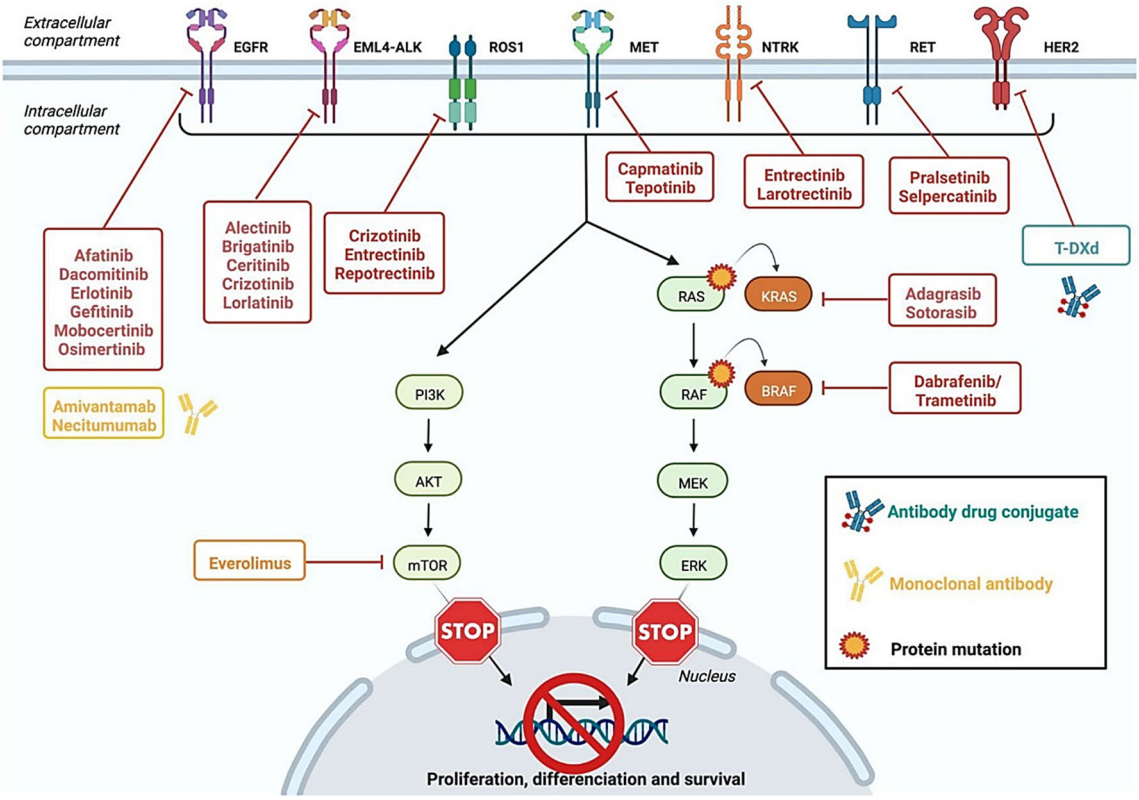

Figure 1.8: An illustration demonstrating the mechanisms of action of some of the common targeted kinase therapies in NSCLC (Bourreau et al., 2023).

Angiogenesis inhibitors block the growth of new blood vessels that tumours need to grow and metastasise. By blocking the action of angiogenic signals, these inhibitors starve the tumour of the necessary oxygen and nutrients (El-Kenawi and El-Remessy, 2013).

B-Raf proto-oncogene, serine/threonine kinase (BRAF) inhibitors target mutations in the BRAF gene, which can lead to uncontrolled cell growth. By inhibiting the activity of the BRAF protein, these drugs help stop or slow the growth of cancer (Proietti et al., 2020).

Breakpoint cluster region gene-Abelson murine leukaemia viral oncogene homolog 1 (BCR-ABL) inhibitors act by blocking the BCR-ABL kinase and related kinases, thereby preventing the phosphorylation of proteins that are crucial in the signalling pathways of cancer cells. Imatinib is the first generation BCR-ABL inhibitor, whereas bosutinib, dasatinib and nilotinib are second generation BCR-ABL inhibitors. Ponatinib is the third generation BCR-ABL inhibitor (Rossari et al., 2018).

Epidermal Growth Factor Receptor (EGFR) inhibitors target the epidermal growth factor receptor, which is frequently overexpressed or mutated in NSCLC cells. By blocking EGFR,

these inhibitors prevent the receptor from activating downstream signalling pathways that are critical for cell division and survival, and therefore inhibit the growth and proliferation of cancer cells (Liu et al., 2018). Erlotinib and gefitinib are first-generation EGFR inhibitors, which act as reversible antagonists to the receptor. Afatinib and dacomitinib represent the second generation EGFR inhibitors, which bind covalently to EGFR, thus establishing an irreversible link (Westover et al., 2018). Osimertinib is notable as the first third-generation EGFR tyrosine kinase inhibitor (TKI), designed to overcome resistance seen with earlier generations of these drugs (Remon et al., 2018; Soria et al., 2018).

The proto-oncogene Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) encodes the small GTPase transductor protein, KRAS (Wright, 2020). Mutations in KRAS activate the RAF-MEK-ERK signalling pathway, which promotes cell growth and division (Canon et al., 2019). Sotorasib is a small molecule KRAS inhibitor, which targets the RAS GTPase family and irreversibly binds to the P2 pocket of the inactive GDP-bound form of KRAS. This binding involves a covalent bond formation with the cysteine residue at position G12C (a glycine to cysteine substitution at codon 12) in KRAS, hence effectively locking the protein in an inactive state and inhibiting its function (Canon et al., 2019; Nakajima et al., 2022).

Mitogen-activated protein kinase (MEK) inhibitors, such as trametinib, block the MEK enzyme. It is part of the MAPK/ERK pathway, which is involved in cell growth and survival. Inhibition of this pathway can lead to reduced tumour growth (Hatzivassiliou et al., 2013).

Mesenchymal Epithelial Transition (MET) inhibitors target the MET proto-oncogene, which encodes the hepatocyte growth factor (HGF) receptor. The MET receptor, encoded by the MET oncogene, is located on the long arm of human chromosome 7 (7q31). Binding of the hepatocyte growth factor to the MET receptor leads to receptor homodimerisation and phosphorylation of tyrosine residues within the intracellular domain, and hence activating MET (Park et al., 1986; Santarpia et al., 2021). Activation of MET initiates several key downstream signalling pathways, including RAS/ERK/MAPK, PI3K-AKT, Wnt/catenin, and STAT, which are crucial for various cancer cell processes such as proliferation, survival, and migration (Drilon et al., 2017).

Mechanistic target of rapamycin (mTOR) inhibitors target the mammalian target of rapamycin, a key protein in a cell-signalling pathway that promotes cell growth and survival. Inhibiting mTOR can block cancer cell metabolism and growth (Zou et al., 2020).

Neurotrophic tyrosine receptor kinase (NTRK) inhibitors bind to the ATP-binding site of TRK kinases, and thus prevent ATP from binding and being used as an energy source for the kinase activity of TRK. Without this activity, the TRK fusion proteins cannot phosphorylate downstream signalling proteins. The primary signalling pathways activated by TRK fusion proteins include the PI3K/AKT/mTOR pathway, the MAPK/ERK pathway, and the PLC-gamma pathway. These pathways are crucial for transmitting signals that lead to cell growth, survival, differentiation, and migration. NTRK inhibitors disrupt these pathways, effectively blocking the signals that lead to tumorigenic behaviours (Cocco et al., 2018).

Poly (ADP-ribose) polymerase (PARP) inhibitors block PARP enzymes, and thus preventing them from repairing single-strand DNA breaks. This action leads to the accumulation of DNA damage, causing double-strand breaks and cell death in cancer cells, particularly those deficient in the homologous recombination repair (HRR) pathway due to BRCA mutations (Chen, 2011).

Rearranged during transfection (RET) inhibitors, such as pralsetinib, block the RET kinase that can exhibit abnormal activity in cancers due to genetic mutations or rearrangements. The transmembrane glycoprotein receptor-tyrosine kinase is synthesised because of the expression of the RET proto-oncogene, which is situated on chromosome 10 (Drilon et al., 2018). Inhibiting RET kinase activity can stop or slow cancer progression.

Proto-oncogene1, receptor tyrosine kinase (ROS1) inhibitors, such as ceritinib, crizotinib, entrectinib and lorlatinib, act by selectively binding to the ATP-binding site of the ROS1 tyrosine kinase domain. The ROS1 gene is located on chromosome 6 at position 6q22.1. This binding prevents ROS1 from phosphorylating itself and other downstream signalling molecules, and therefore halting the transmission of cancer growth and survival signals (Acquaviva et al., 2009; D'Angelo et al., 2020).

Tropomyosin receptor kinase (TRK) inhibitors selectively block the ATP-binding sites of TRK proteins, inhibiting kinase activity and downstream signalling pathways such as PI3K/AKT/mTOR and MAPK/ERK. This disruption halts cancer cell growth and induces apoptosis, primarily in cells with constitutively active TRK fusion proteins (Imaoka et al., 2021).

Vascular Endothelial Growth Factor (VEGF) inhibitors block the activity of the VEGF receptors. These inhibitors can either be small molecule tyrosine kinase inhibitors that prevent ATP binding and kinase activity or monoclonal antibodies that block the receptor's ability to bind VEGF (Melincovici et al., 2018). VEGF is a potent pro-angiogenic growth factor that

exerts significant effects on endothelial cells, which promotes mitogenesis and inhibiting apoptosis. Additionally, VEGF increases vascular permeability and stimulates cell migration (Escalante and Zalpour, 2011). The first VEGF inhibitor to be authorised for cancer treatment is bevacizumab (Garcia et al., 2020).

1.4.1.3 Immunotherapy

Immunotherapy aims to boost the body's natural defences to destroy cancer cells. Several innovative approaches are being employed in the immunotherapy of lung cancer (Figure 1.9). Firstly, monoclonal antibodies (mAbs) are being applied to target specific parts of cancer cells, offering a focused approach to interfere with cancer cell functions and inhibit their growth. Another strategy is the use of Chimeric Antigen Receptor (CAR) T-cell therapy, where either donor or patient T-cells are collected and modified in vitro to express CAR receptors. These cells are then mass-produced in the laboratory and reintroduced into the patient, where they target and destroy the tumour cells. Additionally, oncolytic viruses are utilised to specifically infect and lyse lung cancer cells, disrupting the cancer through viral oncolysis. Lastly, the use of a tumour-specific vaccine designed to trigger the immune system to combat the cancer. These diverse techniques highlight the advancements in targeted therapies aiming to improve outcomes in lung cancer treatment (Lahiri et al., 2023).

Programmed Cell Death Protein 1 (PD-1), a co-inhibitory molecule, is expressed on T cells, B cells, monocytes, and activated natural killer cells. Binding of PD-1 to its ligand, Programmed Cell Death Ligand 1 (PD-L1), results in the suppression of T cell proliferation and migration. PD-L1 is frequently found on tumours or within the tumour microenvironment. Interaction between PD-L1 and PD-1 molecules on T lymphocytes infiltrating tumour sites leads to the inhibition of T-cell activity, hence facilitating immune evasion by tumour cells. Therefore, PD-1 or PD-L1 inhibitors can reactivate immune responses at the tumour site, thus causing the death of tumour cells (Han et al., 2020).

Cytotoxic T-Lymphocyte-Associated Antigen 4 (CTLA-4) inhibitors enhance anti-tumour immunity by blocking CTLA-4's interaction with B7 molecules on antigen-presenting cells, thereby outcompeting the co-stimulatory receptor CD28 and promoting T cell activation. This blockade mitigates the immune dampening effects of CTLA-4, leading to increased T cell proliferation and reduced regulatory T cell suppression within the tumour microenvironment. Consequently, these actions not only amplify the immediate immune response against cancer

cells but also support the development of memory T cells for sustained immunological vigilance (Rudd et al., 2009; Seidel et al., 2018).

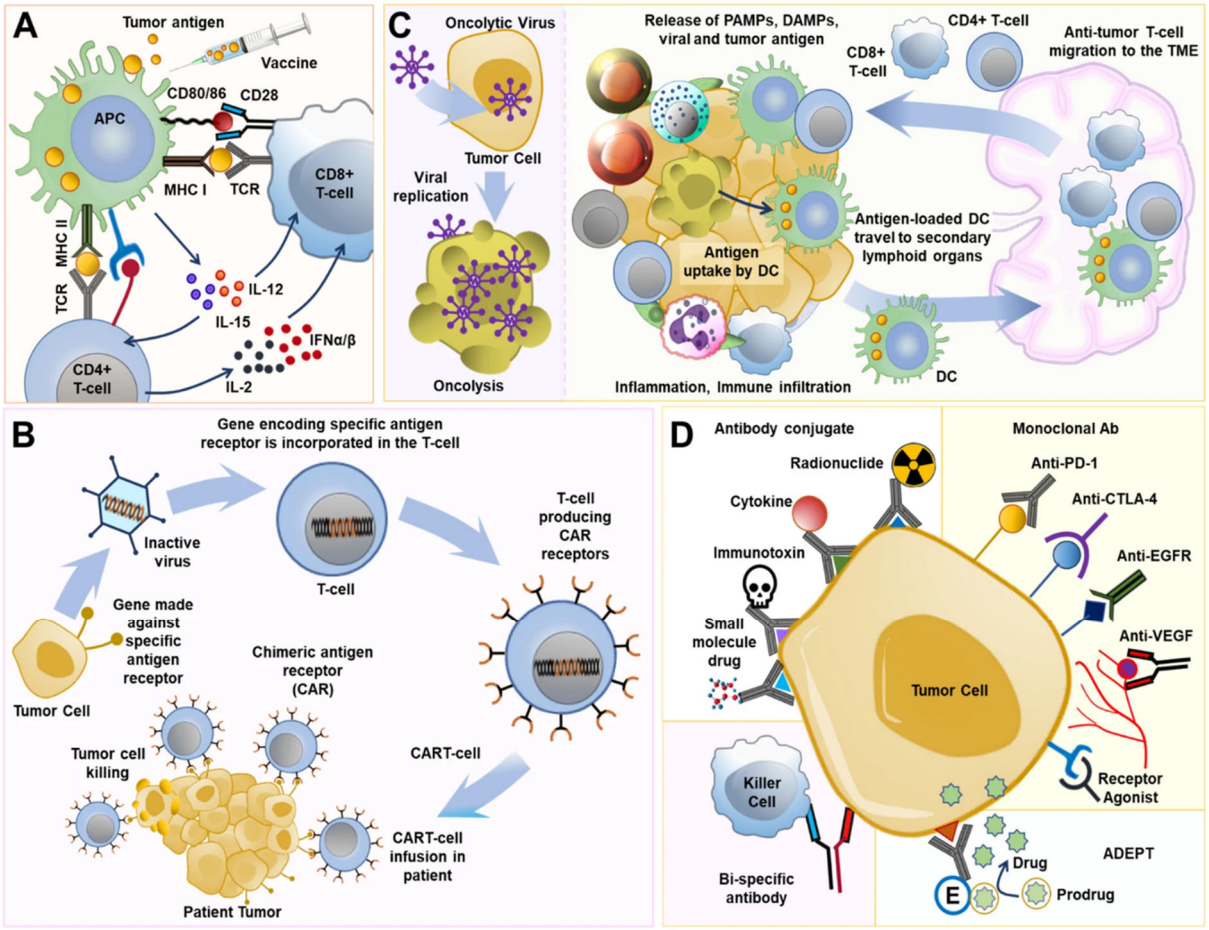

Figure 1.9: Different aspects of lung cancer immunotherapy (Lahiri et al., 2023).

1.4.2 Recent Development in NSCLC Treatments

During the past three years, PD-1/PD-L1 inhibitors and kinase inhibitors have been included as the standard care for non-small cell lung cancer treatments (IQVIA, 2023). Between 2017 and 2020, spending on NSCLC treatments had increased by 50% to USD $16.6 billion, with three-quarters of this growth attributed to PD-1 inhibitors (IQVIA, 2021). On the other hand, there are notable advancements of NSCLC targeted therapies in the development and utilisation of EGFR and ALK inhibitors, which are majorly 2nd and 3rd generation small molecules therapeutics, aimed at enhancing clinical outcomes through improved safety profiles and increased effectiveness against common resistance mutations (IQVIA, 2021).

Recently, there is an increasing number of small molecules TKIs available for NSCLC patients. In 2020, capmatinib was granted accelerated approval by the Food and Drug Administration

(FDA) as the first therapy for targeting metastatic non-small cell lung cancer (NSCLC) with mesenchymal-epithelial transition (MET) exon 14 skipping while both pralsetinib and selpercatinib were approved for rearranged during transfection (RET)-altered NSCLC (Center for Drug Evaluation and Research, 2021; IQVIA, 2021; Wolf et al., 2020). Capmatinib was then granted regular approval by the FDA and European Medicines Agency (EMA) in 2022 (IQVIA, 2023). Capmatinib along with sotorasib and tepotinib were approved by the EMA based on results of Phase I or Phase II clinical trials. However, sotorasib is approved on conditional marketing authorisation, meaning additional data is needed post-approval to show the drug's benefit-risk balance (IQVIA, 2023).

As of April 2023, there are six bispecific antibodies in cancer treatments available in the market globally – three for haematological cancers, one for cervical cancer, one for NSCLC and one marketed for all solid tumours (IQVIA, 2023). Bispecific antibodies (bsAbs) were first developed in 1960s, and have since been extensively investigated in clinical and translational studies (Brinkmann and Kontermann, 2017; Nisonoff and Rivers, 1961). These antibodies bind with multiple targets simultaneously – either by bringing immune cells to cancer cells or by simultaneously inhibiting or activating two distinct epitopes or antigens (Wang et al., 2021). Amivantamab was first marketed in 2021 for the treatment of NSCLC with EGFR exon 20 insertion mutations, which acts by binding and blocking EGFR and MET receptors on tumour cells (IQVIA, 2021).

Moreover, the COVID-19 pandemic heightened interest in mRNA vaccines. Decades of prior research in mRNA vaccines in oncology contributed to the rapid development of COVID-19 vaccines. In 2022, there were 21 oncology mRNA vaccines in development with 4.8% intended for NSCLC (IQVIA, 2023). mRNA vaccines are not only being explored as standalone treatments for cancer but are also being tested in combination with immuno-oncologics, such as PD-1 checkpoint inhibitors. This approach aims to boost the body's immune response against tumours (IQVIA, 2023).

1.5 Cardio-oncology

Cardio-oncology is a field that focuses on the cardiovascular (CV) diseases in cancer patients and addresses the prevention, diagnosis and treatment of cardiotoxicity brought about by oncology drugs or radiotherapy. The World Health Organization (WHO)'s Global Health Estimates reported that lung cancer and heart diseases are two of the major causes of death in

the world (World Health Organization (WHO), 2020). Due to drug development in cancer therapies and early detection strategies, death rates from cancer have decreased over the last 30 years (Howlader et al., 2010; Jemal et al., 2010, 2005). However, even though survival rates have improved, cardiovascular (CV) disease has become the second leading cause of long-term morbidity and fatality among cancer survivors (Bodai, 2019; DeSantis et al., 2014). Therefore, the risk of cardiotoxicity is one of the major limitations of oncology drug development, due to drug-induced cardiotoxic complications (Csapo and Lazar, 2014).

Cardiotoxicity refers to the detrimental effects of cancer treatments on the heart and blood vessels, which can lead to various cardiovascular complications. While the primary goal of cancer treatment is to eliminate or control the malignant cells, the unintended consequence of some therapies is damage to the heart, compromising its ability to function optimally. The incidence of cardiotoxicity varies across different treatment modalities, and its impact can range from mild, reversible effects to severe and irreversible damage (Kerkelä et al., 2006; Santoni et al., 2017). Cardiotoxicity can occur during any stage of the cancer treatments and it includes, but is not limited to, subclinical myocardial toxicity, ischemia, hypertension, supraventricular and ventricular arrhythmias, systolic and diastolic cardiac dysfunction, coronary artery disease and heart failure (Curigliano et al., 2016; Ewer and Ewer, 2015; Hahn et al., 2014).

Cardiotoxicity was first observed in 1967 in treating leukaemia patients with daunomycin (a type of anthracycline) (Tan et al., 1967). More reports on cardiotoxicity induced by anthracycline emerged in the early 1970s. Thereafter, there has been an increasing number of reports of cardiotoxicity induced by different oncology drugs, e.g. trastuzumab, cyclophosphamide and ifosfamide (Gollerkeri et al., 2001; Moslehi, 2016).

Cardiotoxicity can be generally defined in two ways, according to time of onset or mechanisms. Based on the time cardiotoxicity occurs after receiving chemotherapy, it can be divided into acute (during and up to 2 weeks after chemotherapy), subacute (2-4 weeks after chemotherapy) and chronic (more than 4 weeks after the completion of course) (Bursác, 2018). Chronic cardiotoxicity can be further divided into two types: early onset (cardiotoxicity developing within the first year after chemotherapy); and late onset (cardiotoxicity developing years after the completion of chemotherapy). Initially, there are two types of cardiotoxicity when categorised by mechanisms – Type I is often caused by anthracyclines and chemotherapeutics, of irreversible cardiac cells death and is related to cumulative dosage; while Type II is usually

caused by biological or target therapy, of reversible cells dysfunction and is not dose related (Bursác, 2018). However, with the surge in number of new promising anticancer drugs, increasingly more mechanisms of cardiotoxicity have been identified, thus this cardiotoxicity classification is likely to change accordingly (Tocchetti et al., 2019).

1.6 Cardiotoxicity of NSCLC Therapies

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer, and its treatment involves various approaches including chemotherapies, targeted therapies, and immunotherapies. Each of these treatments can potentially lead to cardiotoxicity, impacting the heart via different mechanisms (Figure 1.10).

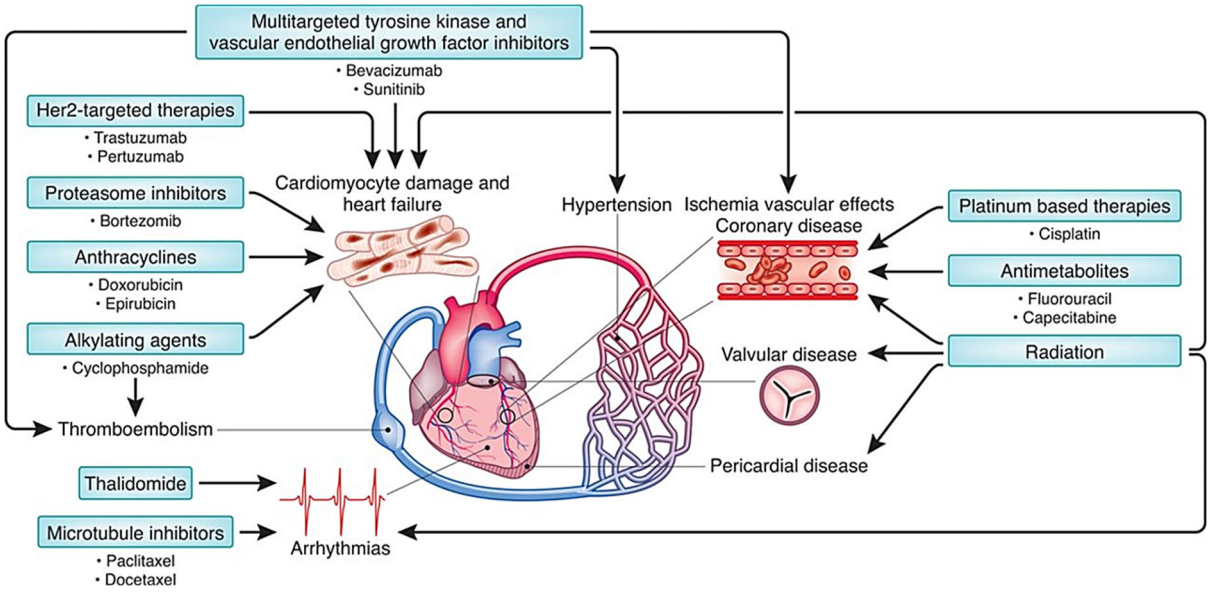

Figure 1.10: Different mechanisms of actions of NSCLC treatments associated with cardiotoxicity (Lenneman and Sawyer, 2016).

For example, platinum-based treatments can cause oxidative stress and inflammation in cardiac cells, which lead to ischemic complications, arrhythmias, and hypertension. The vascular toxicity of these drugs can further contribute to thromboembolic events (Mudd et al., 2021). Studies suggested that angiogenesis inhibitors, i.e. bevacizumab, primarily increase the risk of cardiac ischemia, hypertension and thromboembolic events, which then cause other cardiovascular adverse events such as myocardial infarction and heart failure (Economopoulou et al., 2015).

1.6.1 Anthracycline-induced cardiotoxicity

Cardiotoxicity is a dose-limiting side effect of anthracyclines, and the magnitude of toxicity increases with cumulative doses. Anthracyclines induced cardiotoxicity through multiple mechanisms, including abnormal autophagy, dysregulated homeostasis of calcium ions, mitochondrial dysfunction and oxidative stress, as illustrated in Figure 1.11.

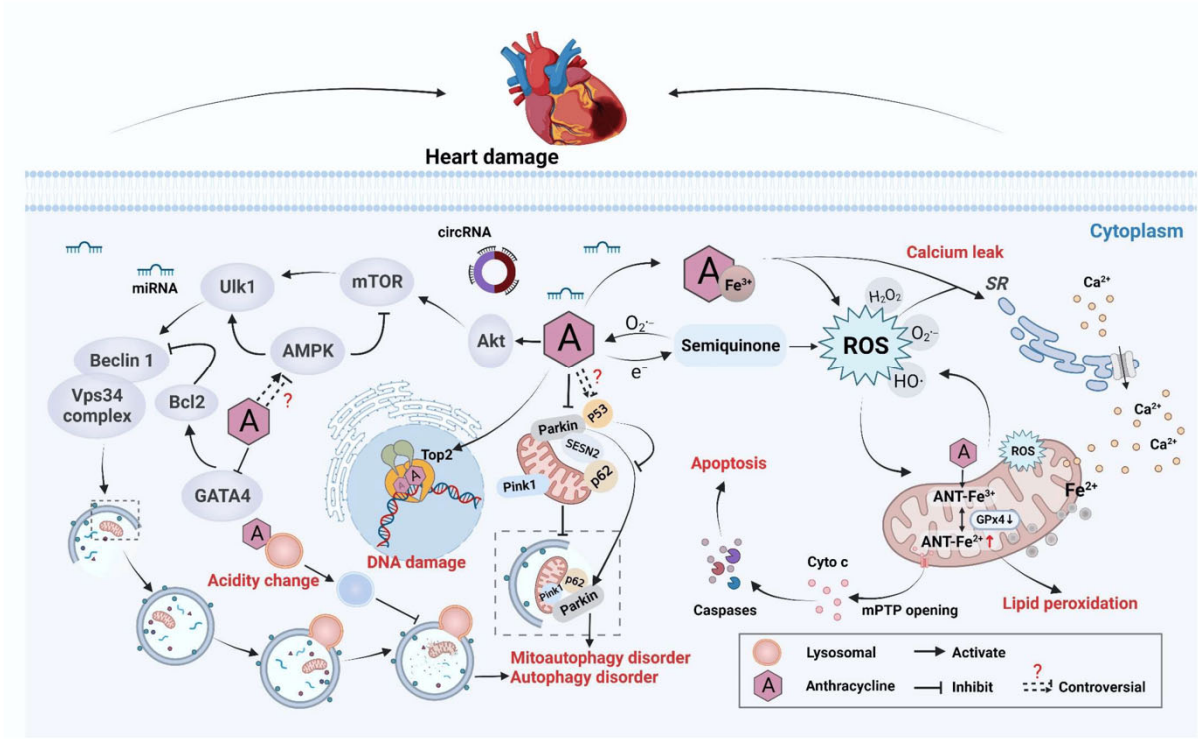

Figure 1.11: Anthracycline-induced cardiotoxicity (Liang et al., 2022).

A primary mechanism of anthracycline-induced cardiotoxicity is the generation of reactive oxygen species (ROS). ROS are critical in anthracyclines-induced cardiotoxicity. Anthracyclines are converted into semiquinones by mitochondrial enzymes, producing superoxide anions that contribute to oxidative stress (Kong et al., 2022). Cardiomyocytes, which lack sufficient oxygen-radical-scavenging enzymes like superoxide dismutase, catalase, and glutathione peroxidase, are particularly vulnerable to this stress. This imbalance in the redox reaction leads to the degradation of heart heme, release of free iron, and lipid peroxidation in mitochondria. Furthermore, anthracyclines interact with iron to catalyse the Fenton reaction, producing hydrogen peroxide and other ROS-related substances that trigger a DNA damage response and result in the death of cardiomyocytes (Menna and Salvatorelli, 2017).

1.6.2 Non-anthracycline induced cardiotoxicity

Non-anthracycline-based chemotherapeutic agents can cause cardiotoxicity through various mechanisms (Figure 1.12). Cisplatin-induced cardiac damage involves oxidative stress, inflammation, endoplasmic reticulum stress, and the activation of the ERK1/2 and p38 MAPK signalling pathways. Cyclophosphamide leads to myocardial injury primarily through the induction of oxidative and nitrative stress, as well as by inhibiting the PI3K/AKT/mTOR pathway. Methotrexate (MTX) contributes to cardiac harm by activating proinflammatory pathways, suppressing Bcl2 expression, and promoting apoptosis in cardiomyocytes. Additionally, 5-Fluorouracil (5-FU) triggers mitochondrial dysfunction by activating mitophagy and obstructing the tricarboxylic acid (TCA) cycle (Csapo and Lazar, 2014; FLORESCU et al., 2013; Mudd et al., 2021).

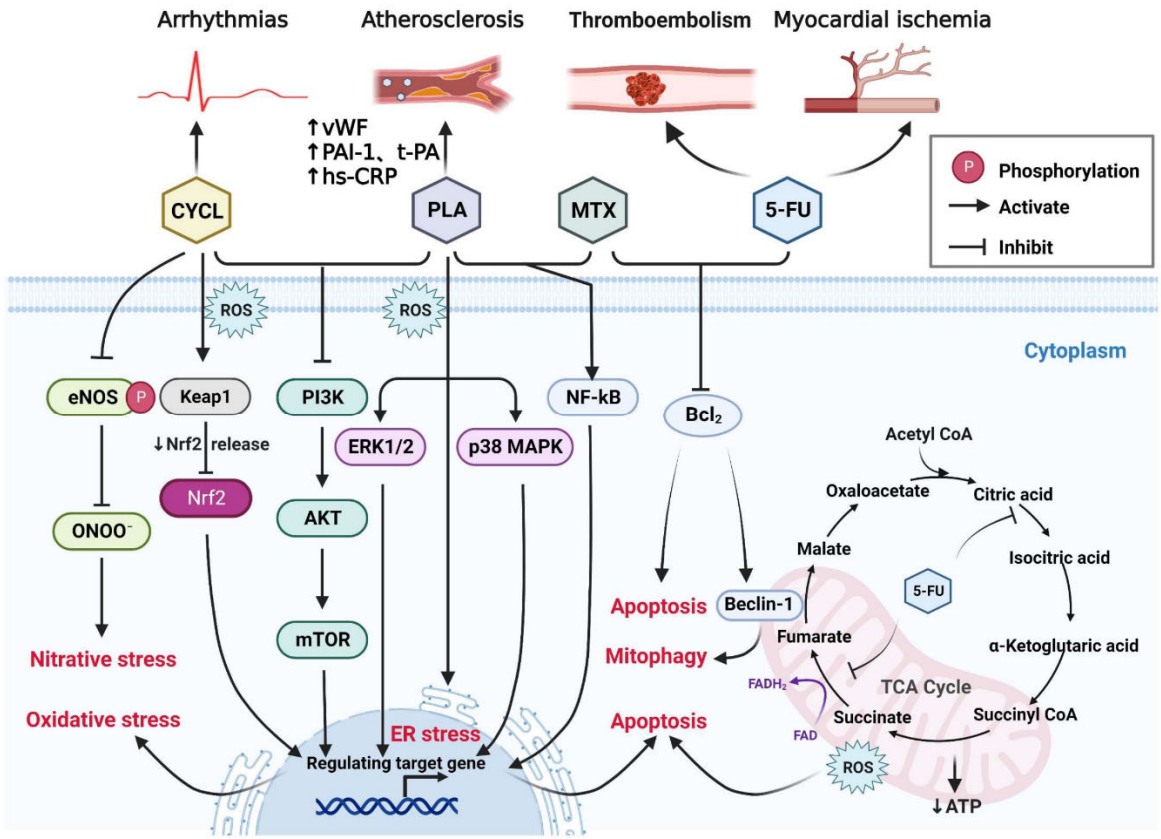

Figure 1.12: Other chemotherapies induced cardiotoxicity (Liang et al., 2022).

1.6.3 Tyrosine kinase inhibitors induced cardiotoxicity

Tyrosine kinase inhibitors (TKIs) specifically block tyrosine kinases, which are enzymes involved in the signalling pathways that regulate cell growth and survival. Despite their

therapeutic benefits, TKIs can induce cardiotoxic effects that potentially limit their use. Different TKIs might have different mechanism of action that induce cardiotoxicity (Figure 1.13).

Tyrosine kinase inhibitors (TKIs) can interfere with mitochondrial function in cardiomyocytes, which lead to decreased ATP production and increased oxidative stress. Mitochondria are crucial for energy production in heart cells, and their impairment can lead to energy deficits in the heart, and consequently contributing to reduced myocardial contractility and heart failure. In addition, TKIs can trigger apoptosis in cardiac cells directly by activating pro-apoptotic pathways or indirectly through increased oxidative stress and mitochondrial dysfunction. This loss of cardiomyocytes diminishes the heart's ability to function efficiently and maintain its structural integrity (Cheng and Force, 2010; Force et al., 2007)

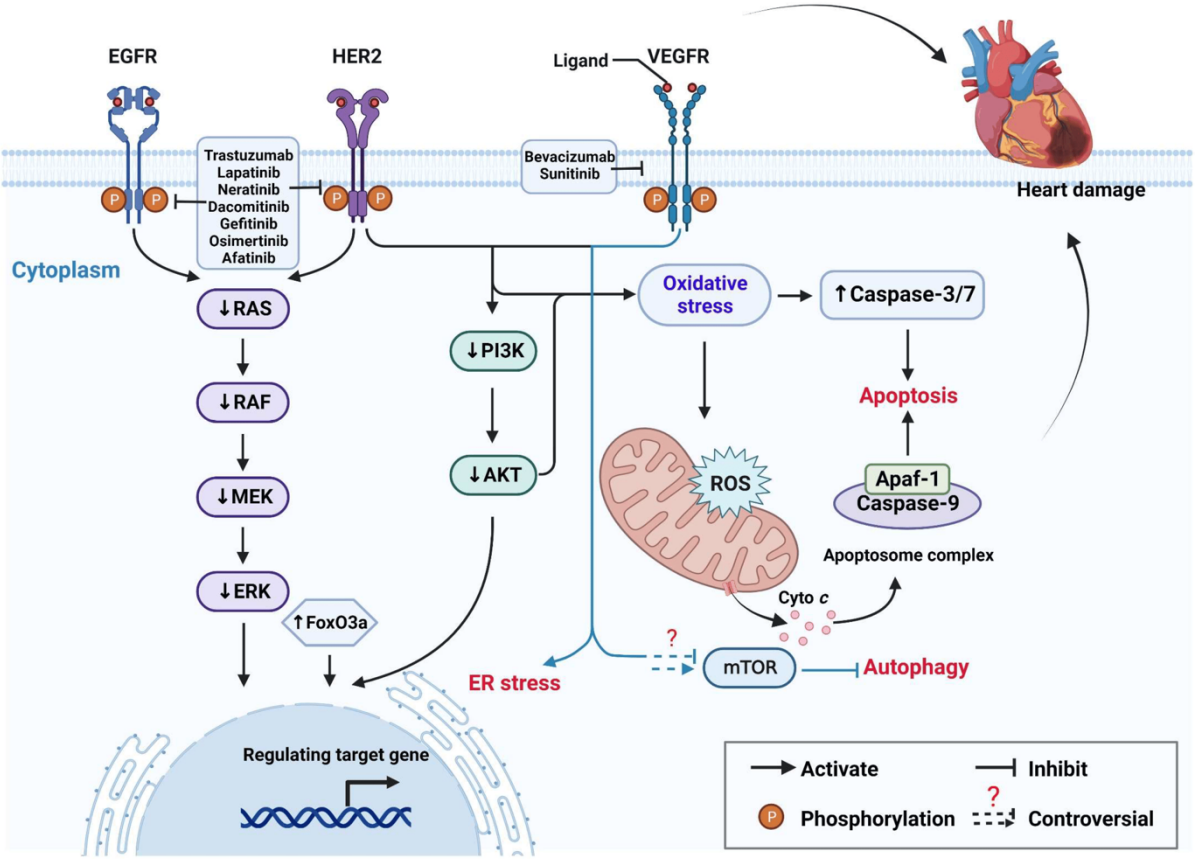

Figure 1.13: Tyrosine Kinase inhibitors (TKIs)-induced cardiotoxicity (Liang et al., 2022).

Existing studies suggested that different oncology drugs, even within the same class of drugs, demonstrate different cardiotoxicity potential (Kerkelä et al., 2006; Santoni et al., 2017; Shah et al., 2018). Imatinib, dassatinib, and ponatinib are all TKIs, but they are associated with

different drug-induced cardiotoxicities. According to several different clinical trials' results, severe left ventricular dysfunction and heart failure were observed for imatinib (Kerkelä et al., 2006), while pulmonary arterial hypertension and thrombocytopenia were observed for dassatinib and ponatinib, respectively (Cortes et al., 2013; Özgür Yurttaş and Eşkazan, 2018).

By blocking the activity of tyrosine kinase, nintedanib prevents the formation of collagen and other extracellular matrix components in the heart, which can lead to cardiotoxicity. In addition, nintedanib may also act directly on the heart, leading to cardiotoxicity. It is believed that the drug can increase the activity of the Na^+/K^+-ATPase enzyme, which can lead to a decrease in cardiac output. This decrease in cardiac output can lead to arrhythmias, myocardial infarction, decreased contractility, and even heart failure (Ameri et al., 2021). Both sunitinib and sorafenib are in the same class as nintedanib, but they are believed to induce vascular endothelial growth factor receptor (VEGFR) inhibition, which lead to a decreased production of the vasorelaxant nitric oxide by endothelial cells, thus resulting in hypertension (León-Mateos et al., 2015; Wu et al., 2008).

1.6.4 Immunotherapy-induced cardiotoxicity

Patients treated with anti-PD-1 therapies developed myocarditis and rhabdomyolysis; analysis revealed that T cells infiltrating the myocardium were clonally identical to those in the tumour, indicating that myocarditis was mediated by non-specific T-cell autoimmunity (Delgobo and Frantz, 2018). Inhibition of CTLA-4 has been associated with the proliferation and accumulation of CD8+ T cells in cardiac tissue, leading to severe myocarditis (Sun et al., 2021).

Other immunotherapeutic strategies, such as chimeric antigen receptor (CAR) T-cell therapy, have been associated to cardiovascular complications including sinus tachycardia, newly emerging arrhythmias, and decompensated heart failure. The exact causative relationship between CAR T cells and these cardiac events remains uncertain but can possibly be due to the complex immune and inflammatory pathways activated by the therapies (Ghosh et al., 2020; Patel et al., 2021).

Possible mechanisms of immunotherapy-induced cardiotoxicity are illustrated in Figure 1.14.

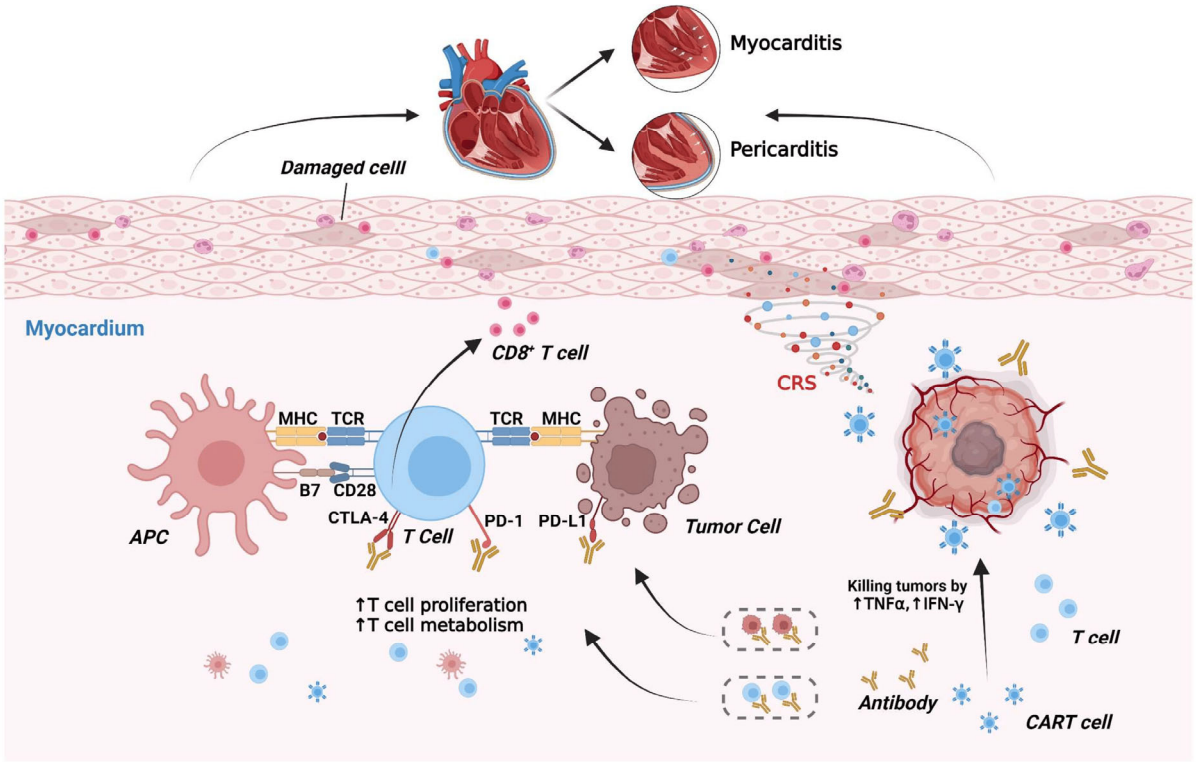

Figure 1.14: Immunotherapy-induced cardiotoxicity (Liang et al., 2022).

1.7 Monitoring, Screening, and Management of Cardiotoxicity

1.7.1 Biomarkers

The role of biomarkers is important in detecting early stage of cardiotoxicity, so to prevent damages caused by anticancer drugs. Abnormal expression or change in levels of biomarkers are indicators for screening and assessing the risk factors for cardiotoxicity complications. Current biomarkers include left ventricular ejection fraction (LVEF), troponin, brain natriuretic peptide (BNP), interleukin-6 (IL-6) and plasma myeloperoxidase (Guo et al., 2012; Tromp et al., 2017).

Left ventricular ejection fraction (LVEF)

Assessment of left ventricular ejection fraction (LVEF) is the most common method used to diagnose both early and late cardiomyopathy and heart failure. According to the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines 2012, patients are considered to have cardiotoxicity if (1) there is ≥15% reduction of LVEF from baseline despite normal function, or (2) an LVEF decline to below 50%, or (3) a decline in LVEF which is regarded as clinically significant by cardiologists (Bosch et al., 2013).

Troponin

Troponin is a biomarker of myocardial injury and is routinely measured in acute myocardial infarction. Previous clinical trials showed that there is a positive correlation between troponin levels and anthracyclines agents (Simões et al., 2018). Another clinical trial also suggested a correlation between increasing troponin levels and reduced left ventricular contractility (Šimůnek et al., 2003). An existing study demonstrated that troponin can be used to identify high-risk cancer patients and help tailor patient-specific treatments (Cardinale et al., 2006). However, one of the limitations of troponin is that if troponin elevation is observed, that indicates myocardial cell death has already occurred, thus hindering the use of troponin as an effective early biomarker of cardiotoxicity.

Brain natriuretic peptide (BNP)

Brain natriuretic peptide (BNP) with its inactive N-terminal amino acid fragment NT-proBNP, is released by the ventricles due to volume overload and/or wall stress (Weber and Hamm, 2006). Several studies showed that significantly elevated BNP levels were associated with cardiotoxicity and/or cardiac events (De Iuliis et al., 2016; Lenihan et al., 2016). Another study observed that elevation of NT-proBNP taken early after high-dose chemotherapy was associated with the development of left systolic and diastolic dysfunction at 1-year follow up (Sandri et al., 2005).

1.7.2 Potential Prevention Treatments

Dexrazoxane is a cardioprotective agent being used to reduce both acute and chronic cardiotoxicity induced by anthracyclines (Minotti et al., 2004). However, its use has been limited due to its adverse side effects, including increased rates of bone marrow suppression and more febrile neutropenia events (Jain et al., 2017; Tahover et al., 2017). Beta-blockers, angiotensin-converting enzyme (ACE) inhibitor, angiotensin inhibitors and mineralocorticoid receptor antagonists are all potential treatment in preventing cardiac damage, but more evidence are needed to prove their effectiveness (Tromp et al., 2017).

Present studies suggested several potential preventive measures – MANTICORE was a randomised, placebo-controlled trial for the prevention of trastuzumab-mediated cardiotoxicity, it was proved that perindopril and bisoprolol protected HER2-postivie early breast cancer patients against cancer therapy-related declines in left ventricular ejection fraction (LVEF) (Pituskin et al., 2017). Another study by Cardinale *et al.* (2006) showed that

early treatment with enalapril can potentially prevent the development of late cardiotoxicity in high risk, high-dose chemotherapy treated patients (Cardinale et al., 2006). The OVERCOME trial suggested that combined treatment with enalapril and carvedilol may prevent left ventricular systolic dysfunction (LVSD) in malignant hemopathies' patients, but clinical relevance of this outcome needs to be confirmed with larger studies (Bosch et al., 2013). In addition, more real-world data are needed to further support these findings as some of them showed contradictive results. It was suggested in the 'Prevention of cardiac dysfunction during adjuvant breast cancer therapy' (PRADA) study – a randomised, placebo-controlled, double-blind clinical trial of candesartan and metoprolol – that candesartan can prevent the development of systolic dysfunction in breast cancer patients who were treated with anthracyclines (Gulati et al., 2016). In contrast, another randomised clinical trial argued that candesartan (compared to placebo) did not show promising results in preventing cardiotoxicity in breast cancer patients who were treated with anthracyclines. This might be caused by the timing of angiotensin II-receptor blocker administration as the effect of this treatment might have a better result if candesartan treatment had started simultaneously with administration of anthracyclines and before trastuzumab (Boekhout et al., 2016).

1.8 Real-world Data

Real-world data (RWD) is increasingly recognised as a crucial asset in regulatory science, hence transforming the landscape of healthcare regulation. This refers to the data collected outside the confines of conventional randomised controlled trials (RCTs) and offers insights into patient outcomes, medication adherence, and treatment variability in real-world settings, hence providing a more comprehensive understanding of a drug's effectiveness and safety. It can support healthcare treatment decisions and has increasingly been used to complement clinical trial data.

The RWD is derived from a variety of sources that document health status and the delivery of healthcare in routine settings, such as electronic health records (EHRs), patient registries, insurance claims and billing systems, patient-reported outcomes as well as patient-generated data from mobile devices or wearable devices. For instance, EHRs provide comprehensive data on patient demographics, medical history, diagnostics, treatments, and outcomes. Therefore, EHRs are useful in observing clinical practices and patient outcomes over time. Data from patient registries collect detailed information about patients' sociodemographic and

medical history, thus beneficial in research in disease trajectories and long-term outcomes; while data from insurance claims and billing systems offer insights into healthcare utilisation and pharmacoeconomics. Patient-reported outcomes are often collected via surveys or mobile apps, these outcomes provide data on patient health status, treatment adherence, as well as quality of life from the patient's perspective. Patient-generated data from mobile devices or wearable devices capture continuous health data in real-time, hence offering insights into patient mobility, vital signs, physical and psychosocial activity levels.

However, RWD is often collected from diverse sources that may not follow standardised data collection protocols, which leads to variability in data quality, hence posing significant challenges in data integration and interpretation. It is also important to note that the use of RWD must comply with stringent data protection laws, such as the General Data Protection Regulation (GDPR) in Europe and the Health Insurance Portability and Accountability Act (HIPAA) in the U.S.

1.9 Pharmacoepidemiology and Pharmacovigilance

Pharmacoepidemiology and pharmacovigilance are critical disciplines in the field of healthcare and regulatory science which focus on the effects of drugs and their safety profiles within the population (Delcher et al., 2021). The introduction of RWD has significantly transformed these fields, providing new insights and methodologies for understanding drug efficacy and monitoring adverse drug reactions across diverse patient populations. And therefore, help individuals make informed choices about their treatments.

Pharmacoepidemiology is the study of the utilisation, efficacy and harm of drugs in a large population. It aims to maintain the balance of the benefits and risks of drug exposures by identifying and characterising their effects in real-world settings. This utilises pharmacoepidemiological methods to provide evidence for medication practices and policy-making that optimise drug use (Montastruc et al., 2019). Regulatory bodies, such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA), are leveraging RWD to complement and sometimes augment data from RCTs. This is caused by the need to accelerate drug approval process and to understand how medical products perform in more diverse populations and healthcare settings, especially when conducting traditional RCTs is not feasible due to ethical concerns and rare diseases. Furthermore, pharmacoepidemiology

supports the ongoing monitoring of drug safety, which deliver insights into long-term risks and benefits that are essential for the continuous assessment of therapeutic strategies. Although there are many advantages of pharmacoepidemiology, there are also some challenges. For example, the accuracy of conclusions drawn from pharmacoepidemiological research heavily depends on the quality of the data used, hence incomplete data, coding errors, and missing data can all skew results. In addition, unlike RCTs, pharmacoepidemiological studies are observational and can suffer from confounding, which makes it difficult to establish causality from associations observed in the data. Selection bias can also limit the generalisability of the findings (Moore et al., 2019).

In pharmacovigilance, RWD is crucial for post-marketing surveillance as it continues to monitor a pharmaceutical's safety and efficacy after it is launched in the market. Pharmacovigilance involves activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related issues. It aims to improve patient care and safety in relation to the use of medicines. It helps identify adverse events that may not have been detected during pre-marketing studies due to the limited duration and scope of most clinical trials (Härmark and van Grootheest, 2008). Regulatory agencies use RWD to quickly identify potential safety issues, which can significantly reduce the health risks associated with new drugs and devices. For instance, the WHO's *Vigibase* system, the FDA's *Adverse Event Reporting* System (FAERS), the EMA's *EudraVigilance* system and the MHRA's *Yellow Card* system, are platforms that utilise RWD to monitor the safety of marketed drugs and biologics in real-time. It provides evidence needed for modifying drug labels, updating safety guidelines, and informing public health policies. For example, during the COVID-19 pandemic, regulatory agencies relied on RWD to quickly assess the usage trends and side effects of repurposed medicines as well as new vaccines, thus enabling rapid decision-making in response to the pandemic. Additionally, pharmaceutical companies use similar systems to fulfil their legal obligations to benefit-risk management of their products in the marketplace by applying pharmacovigilance techniques. Information from pharmacovigilance activities could lead to further clinical trials, especially if new safety concerns arise or additional data are needed on specific populations or dosing strategies. However, one of the major limitations in pharmacovigilance is the underreporting of adverse drug reactions (ADRs) by healthcare providers and patients, resulting in data gaps that can distort the perceived safety profile of a drug. Factors contributing to underreporting include a lack of awareness about the importance of reporting, reluctance to report due to perceived intricacies of the reporting mechanism, and

the presumption that established ADRs do not require further documentation. Secondly, considering the vast amount of data generated in the pharmacovigilance database, there is a high chance of the existence of 'noise', which is regarded as irrelevant or misleading information that can obscure actual safety signals and hence causality (Beninger, 2018; Nour and Plourde, 2019; Waller and Harrison-Woolrych, 2017).

1.10 Relevant Guidelines

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) has provided a comprehensive set of safety guidelines, in which ICH S7A, S7B and S9 are the most relevant. ICH S7A and S7B outline the 'safety pharmacology studies for human pharmaceuticals' and 'the non-clinical evaluation of the potential for delayed ventricular repolarisation (QT interval prolongation) by human pharmaceuticals' respectively, while ICH S9 focuses on the nonclinical evaluation for anticancer pharmaceuticals. Additionally, ICH S9 states that if there are concerns of the cardiotoxicity of a certain drug, the safety pharmacology studies stated in ICH S7A and S7B should then be carried out (Abraham, 2010). Practically, optimisation process should be carried out individually for each oncology drug by treating a potentially lethal cancer effectively while preventing the occurrence of acute and/or chronic cardiotoxicity. Generally, pre-clinical findings can be used as a guide for cardiac monitoring during subsequent human studies, but due to the difficulty of using non-clinical models to detect cardiotoxicity, the early prediction of clinical behaviours of drugs (i.e. early detection of cardiotoxicity) remains a challenge (Robert, 2007). For example, the results of *in-vitro* / *in-vivo* tests in pre-clinical / clinical stage are considered as good but proved otherwise in real-world data (Raschi et al., 2008).

1.11 Classification

1.11.1 International Classification of Diseases, 10th Revision (ICD-10)

The history of International Classification of Diseases (ICD) can be trace back to 1763, when French physician Dr Francois Bossier de Lacroix published a system to help doctors with diagnoses, outlining 10 major disease categories and 2,400 individual diseases (Jetté et al., 2010). During the first International Statistical Congress in 1853, William Farr and Jacob Marc d'Espine were appointed to develop an internationally accepted mortality classification. This formed the foundation for the International List of Causes of Death (ILCD), first formulated

by a committee led by Jacques Bertillon in 1893 and presented in Chicago at the International Statistical Institute in 1898 (Hirsch et al., 2016). The WHO took over the ICD in 1948, and adopted it in 1949 to also include morbidity coding. Revisions were then continued on an approximately decade-by-decade basis, with the seventh and eight revisions published in 1957 and 1968 respectively (Manchikanti et al., 2011). The ninth revision, ICD-9, was introduced in 1977 with a significant increase in granularity, which expanded the system with detailed four-digit categories and a range of optional five-digit subdivisions (Hirsch et al., 2016).

The development of ICD-10 began in 1983 and concluded in 1992. The ICD-10 was first made compulsory for use in the UK in 1995. NHS Digital currently oversees the publication and upkeep of the NHS Information Standards, i.e. ICD and OPCS-4, for the UK. The UK is now using ICD-10 (5th Edition), which was implemented on 1 April 2016. ICD-10 further increased the granularity from ICD-9. It significantly expanded the coding system to over 155,000 different codes, hugely surpassing the 17,000 codes of ICD-9, which enables the tracking of numerous new diagnoses and procedures (Hirsch et al., 2016; Manchikanti et al., 2011; Meyer, 2011). There are a total of 22 chapters in ICD-10 (Chapter I to Chapter XXII). Neoplasms are under Chapter II with code range C00-D48.

1.11.2 Medical Dictionary for Regulatory Activities (MedDRA)

The Medical Dictionary for Regulatory Activities (MedDRA) is a multi-axial, five-level hierarchical terminology system used for classifying clinical information in adverse events reports (Wood, 1994). At the meeting of the Committee on Proprietary Medicinal Products (CPMP) in December 1993, all member states of the European Union endorsed MedDRA (Wood, 1994). It was developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and is now maintained by a separate entity and available through subscription. The MedDRA terminology is maintained under an ISO 9001:2015 registered quality management system (ISO, 2015).

System Organ Class (SOC) is the highest level of the hierarchy and represents a grouping of terms based on aetiology or body site (e.g., Gastrointestinal Disorders, Cardiac Disorders). High-Level Group Terms (HLGTs) are aggregate terms that share a condition or are part of a defined area of interest within a SOC. High-Level Terms (HLTs) further refine the categorisation within High-Level Group Terms (HLGTs), typically denoting a more specific aspect of a system or condition. Preferred Terms (PT) are unique terms for a symptom, sign,

disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic. Lowest Level Terms (LLT) represent the most detailed level of terminology, often including synonyms or lexical variants of the PTs. LLTs map upwards to a single PT (Mozzicato, 2009). The latest version (MedDRA 27.0) was released in March 2024.

1.11.3 Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) System

The Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) system is a global system monitored by WHO. It is designed to enhance the quality of drug use by monitoring and researching drug utilisation. The WHO Regional Office for Europe formally recognised the ATC/DDD system for drug utilisation studies in 1981, and subsequently formed the WHO Collaborating Centre for Drug Statistics Methodology in 1982. In 1996, the WHO officially endorsed the ATC/DDD system for global use and took over its management (WHO International Working Group for Drug Statistics Methodology et al., 2003).

A groundbreaking study conducted between 1966 and 1967 by the WHO Regional Office for Europe highlighted variations in drug utilisation among different population groups across six European countries (Engel and Siderius, 1967). In response to these findings, a WHO symposium in 1969 emphasised the necessity for a globally recognised classification system. Subsequently, the Drug Utilisation Research Group (DURG) was formed to advance methods for drug utilisation research. Due to this, the Anatomical Therapeutic Chemical (ATC) classification system was created, it refined and expanded the existing European Pharmaceutical Market Research Association (EPhMRA) classification system (Ronning, 2002).

The ATC classification uses both alphabetical and numerical codes to describe the properties of an active ingredient. The ATC classification system consists of a hierarchical format with five levels, each providing more specific information about the drug. First level is the anatomical group – the drugs are first divided into groups based on the organ or system on which they act. This level is denoted by one letter (e.g., "A" for Alimentary tract and metabolism). Second level is the therapeutic subgroup, which uses two digits, and provides a broader categorisation of the therapeutic use (e.g., A10 for drugs used in diabetes). Third level represents the pharmacological subgroup; it is denoted by one letter and narrows down the drugs based on their pharmacological properties (e.g., A10B for blood glucose lowering drugs).

Fourth level is the chemical subgroup, this level further classifies the drugs based on their chemical structure and denoted by one letter (e.g., A10BA – Biguanides). The 5th level is the most specific level, which represents the chemical substance. It is denoted by two digits (e.g., A10BA02 – Metformin) (WHO Collaborating Centre for Drug Statistics Methodology, 2024).

To effectively measure drug use, it is critical to utilise both classification system and measurement unit. To overcome the limitations of conventional measurement units, a specialised unit known as the Defined Daily Dose (DDD) was introduced for drug utilisation studies (Hollingworth and Kairuz, 2021). The DDD represents the average daily maintenance dose for the primary indication of the drug in adults. It is expressed in different units, such as milligrams or grams, and these units can vary depending on the route of administration (WHO Collaborating Centre for Drug Statistics Methodology, 2024).

Coding plays a crucial role in pharmacoepidemiologic studies because it enhances accuracy by precisely identifying the medicine. However, the ATC/DDD system is linked to the dosage form of a drug, which means a single drug can have multiple ATC codes and possibly different DDDs. For instance, a medication available in both tablet and injection forms would have distinct ATC codes and potentially two DDDs for each form (Hollingworth and Kairuz, 2021).

Chapter 2

Study Rationale and Methodological Framework

2.1 Study Rationale

Despite the rapid development of oncology drugs, drug-induced cardiotoxicity has become an alarming issue, hence it is important to maintain a balance between therapeutic gain and risk of cardiotoxicity. Through analysing real-world data, this study aims to explore if a certain therapeutic class of drugs (e.g. anthracyclines, alkylating agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies) have a higher frequency of occurrence of certain cardiotoxicities, such as arrhythmias, atrial fibrillation, bradycardia, congestive heart failure, coronary vasospasm, left ventricular (systolic and diastolic) dysfunction, myocardial ischemia, myopericarditis, thromboembolism and QT prolongation; and to potentially identify which sub-group of NSCLC patients have a greater risk in developing cardiovascular (CV) diseases, so suitable preventive measurements can be implemented accordingly. By combining results from clinical data, real-world data, including pharmacoepidemiology and pharmacovigilance studies, it may provide a better understanding and more thorough basis to implement suitable guidelines and preventive measures accordingly.

2.1.1 Aim

The aim of this study is to investigate the association between anticancer drugs and cardiotoxicity by using real-world data and clinical trials data available from public domains, reports and published literatures; and thus develop potential mitigation related to cardiotoxicity in cancer patients.

2.1.2 Primary Objective

To determine the association between anticancer drugs and cardiotoxicity by describing the clinical features of incident reports of cardiotoxicity in cancer patients following NSCLC treatments.

2.1.3 Secondary Objectives

1. To describe the utilisation of different studies to achieve the aim and objectives of this research.

2. To understand the use of electronic medical data and different data sources, and assessing the feasibility of using these databases for the research question.
3. To observe whether different dosage of the same treatment affect the degree of cardiotoxicities.
4. To investigate how different classes of drugs, e.g. anthracyclines, alkylating agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies, demonstrate different cardiotoxicity potentials in NSCLC treatments.
5. To compare the real-world data obtained from this study with existing literature and/or clinical trials data.

2.2 Methodological Framework

2.2.1 Evidence Synthesis

According to the Royal Society and the Academy of Medical Sciences, evidence synthesis is a 'process of bringing together information and knowledge from a range of sources and disciplines to inform debates and decisions on specific issues' (The Royal Society, 2018). Evidence synthesis plays an essential role in the conceptualisation of health evidence as it acts as a tool to aid the decision-making processes, e.g. development of relevant guidelines (Cartabellotta and Tilson, 2019). Methods of evidence synthesis includes systematic reviews, scoping reviews, rapid reviews, living reviews, overviews of reviews, evidence mapping and concept analysis. Each has its own purpose and aims, so a suitable approach should be used based on the research objectives.

A scoping review is a relatively new approach to evidence synthesis (Munn et al., 2018). A scoping review is often used as an overview of existing literature or evidence and to identify research gaps without producing a summary answer to a specific research question (Arksey and O'Malley, 2005). Thus, risk of bias and limitations of the review are usually not required. A scoping review is especially useful when a topic has not been fully explored and/or is complex and diverse (Peters et al., 2015). But because a detailed quality assessment of included studies is not required, this may affect the overall reliability of the conclusions draw from the review.

A systematic review is currently the most comprehensive way to gather all relevant information of a certain topic and use them as a high-quality synthesised evidence base (The Royal Society,

2018). In contrast to a scoping review, a systematic review often has a focused research question and a set of defined inclusion and exclusion criteria. It also systematically assesses the quality of studies and extracts relevant data to draw a conclusion to a specific research question (Brien et al., 2010).

A rapid review was first mentioned in 1997 by Best et al., in describing the rapid health technology programme in the south and west regions of England (Best et al., 1997). Although there is no formal consensus in the definition of rapid reviews, it is suggested that rapid reviews are a streamlined form of systematic reviews by simplifying or omitting steps such as comprehensive literature searches, extensive data extraction and detailed quality assessment (Khangura et al., 2012). A rapid review is designed to produce evidence which quickly informs decision-making, particularly when time is restricted. However, due to the compromise in the methodology compared to a systematic review, it may potentially affect the reliability and completeness of the evidence synthesised. It may also increase the risk of bias by conducting more limited literature searches (Hamel et al., 2021; Harker and Kleijnen, 2012).

This study aims to identify gaps in existing research knowledge by comprehensively summarising existing research using a rigorous and structured approach to investigate if there is an association between anticancer drugs and cardiotoxicity. Therefore, systematic review, which is a high-quality evidence synthesis method, is a more appropriate approach.

2.2.2 Healthcare Data

Healthcare data consists of a wide range of information related to patients, populations as well as healthcare systems. It is crucial in improving patients' outcomes, optimising healthcare delivery, guiding policy decisions as well as enhancing medical research (Olaronke and Oluwaseun, 2016). Clinical trials data and real-world evidence (RWE) are two of the essential elements in medical research and healthcare decision-making. They both play a crucial role in understanding the utilisation, efficacy and safety of medical interventions, and yet they are distinctly different in terms of contexts and methodologies (Hannan, 2008).

Randomised controlled trials (RCTs) are regarded as the gold standard in evaluating the efficacy and safety of medical interventions (Silverman, 2009). They are normally conducted in phases, each with its specific objectives and methodologies, including safety assessment, dosage optimisation and comparison of its efficacy against the standard of care / existing

medication (Kendall, 2003). RCTs aim to minimise bias by random allocation, thus ensuring that the outcomes observed are purely due to the intervention(s) being investigated and not external factors. In addition, most RCTs use blinding and sometimes double-blinding, which further reduces bias and ensures the objectivity of results obtained. Also, RCTs are designed to directly assess causations. Because participants are randomly allocated, these trials can more confidently attribute changes in outcomes to the intervention (Hariton and Locascio, 2018). However, RCTs are expensive and time-consuming to design, conduct, and analyse, hence the high costs associated with these trials can limit the availability of funding and prolong the time it takes for interventions to become available to the public (Sibbald and Roland, 1998). Besides, the inclusion and exclusion criteria of RCTs, which are necessary for controlling variables, can result in study populations that do not fully represent the broader patient population, thus limiting the applicability of RCT results to real-world settings (Kostis et al., 2019).

Real-world evidence (RWE) is increasingly important in healthcare decision-making, as it supplements traditional evidence methods, such as RCTs. RWE refers to clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (RWD) (Sherman et al., 2016). RWD reflects a more diverse patient population, including various ages, races, genetic backgrounds and comorbidities. This diversity is crucial for understanding the cardiotoxic effects of cancer treatments across different subgroups, which might not be adequately represented in clinical trials (Dreyer, 2018). Patients with pre-existing cardiovascular conditions are often excluded from clinical trials, whereas RWD allows for the inclusion of these patients, hence providing insights into how cancer treatments affect individuals with various cardiovascular risk factors or pre-existing heart conditions (Bonsu et al., 2019; Moslehi, 2016). Moreover, patients often receive combination therapies, sequential treatments and different dosages of treatments in real-world settings, which may not be explored in clinical trials, and thus RWD captures these complex treatment patterns, offering a more accurate assessment of associated cardiotoxic risks (Di Maio et al., 2020). Due to its nature, RWD enables the analysis of long-term health outcomes, which is essential for detecting late-onset cardiotoxicity including after the completion of cancer treatment, that may not become apparent within the typical duration of RCTs.

Therefore RWE, which offers a comprehensive and nuanced view of how cancer treatments might impact cardiovascular health outside the controlled environment of clinical trials, will be used to investigate the research question in this study.

2.2.3 Pharmacoepidemiology Study

Pharmacoepidemiology is a scientific discipline that combine principles of pharmacology and epidemiology to study the use and effects of drugs in large, diverse populations. This provides essential insights into how medications affect people in real-world settings, rather than under controlled clinical trial conditions. The findings from these studies help improve medication guidelines, influence policy-making, and ensure drug safety, enhancing public health outcomes (Moore et al., 2019).

Observational studies are critical in pharmacoepidemiology as they are designed to observe outcomes without any intervention from researchers. These studies are essential in identifying and understanding trends, adverse effects, as well as the effectiveness of treatments across different populations and settings (Hannan, 2008; Ligthelm et al., 2007). Observational studies include cohort studies, case-control studies, nested case-control studies, cross sectional studies, and ecological studies.

Cohort studies follow patients who have been exposed to a particular drug or treatment over time and compare their outcomes with a control group that has not been exposed. This longitudinal study can be prospective or retrospective. This is crucial in understanding causation. However, it is relatively time-consuming and expensive due to long follow-up periods, and may also introduce bias due to risk of loss to follow-up (Peipert and Phipps, 1998; Song and Chung, 2010). Case-control studies identify patients with a specific outcome (cases) and compare their exposure to a drug or treatment with that of patients without the outcome (controls). This method requires a smaller sample size, and is more efficient and cost-effective (Song and Chung, 2010). Nested case-control studies are a type of case-control study conducted within a cohort study. At the onset of the cohort study, outcomes of interest remain unknown, hence allows the comparison between cases (those who develop the outcome) and controls (those who do not) within the same cohort. This is more efficient than a full cohort study in terms of time and cost. It also reduces selection bias and ensures that cases and controls are drawn from the same population (Essebag et al., 2003). Cross-sectional studies assess both exposure and outcome at a single point in time. These studies are often used to estimate the prevalence of health outcomes or diseases in a population. Cross-sectional studies are usually relatively inexpensive and easy to conduct compared to case-control or cohort studies. However, it cannot determine causality or the direction of associations; and is also vulnerable to confounding variables which will affect the outcome (Kesmodel, 2018; Pandis,

2014). Ecological studies examine the association between exposure and outcome at aggregated level instead of at individual level. These studies often utilise existing data sources, thus making them useful for exploratory research. However, ecological studies lack the detailed data needed to adjust for potential confounding factors at individual level, hence the observed associations may not accurately reflect a causal relationship (Morgenstern, 1995).

2.2.4 Pharmacovigilance Study

Pharmacovigilance plays a critical role in public health by ensuring that the benefits of medications outweigh their risks. Through continuous monitoring and evaluation, it provides essential insights that help in making informed decisions about medication use, policy formulation and patient safety. It employs a variety of methods to monitor and evaluate the safety of medicine, such as spontaneous monitoring and prescription event monitoring (Beninger, 2018).

Spontaneous monitoring is a passive surveillance system that relies on healthcare professionals, patients and others to report any suspected adverse drug reactions (ADRs) to a national or international drug safety authority or organisation (van Grootheest et al., 2004; van Grootheest and de Jong-van den Berg, 2004). Reports are submitted on a voluntary basis. It is also cost-effective as it is relatively inexpensive to maintain the system. Moreover, it is highly effective in early signal detection, especially the identification of rare, serious, and unexpected adverse reactions that may not have been detected during pre-marketing clinical trials (Edwards, 1999).

Prescription event monitoring is a post-marketing surveillance system specifically designed to monitor the safety of newly licensed drugs in a real-world setting. Upon the launch of a new medication, patients who are prescribed with the drug are identified through prescription databases and followed for a defined period. Reports on adverse events are collected proactively through questionnaires sent to the prescribing physicians after a certain time has elapsed, instead of voluntary reports (Layton and Shakir, 2012).

Although prescription event monitoring reduces the selection bias in spontaneous monitoring by systematically monitoring all patients prescribed the medication, its effectiveness is influenced by the prescribing habits of doctors, which may not always reflect the broader population (Heeley et al., 2001). Therefore, due to the broader scope, diversity and availability of data in spontaneous monitoring, as well as the inclusion of NSCLC treatments that exist

before the introduction of prescription event monitoring in the 1980s, spontaneous monitoring will be used in this study.

Disproportionality analysis in spontaneous monitoring is used to detect signals of adverse drug reactions (ADRs) from databases of reported incidents. It involves statistical methods that compare the observed frequency of reports of a specific drug-event pair to the frequency expected if there were no association between drug-event pair (Härmark and van Grootheest, 2008; Nour and Plourde, 2019). Statistical methods include proportional reporting ratio (PRR), reporting odds ratio (ROR), Bayesian Confidence Propagation Neural Network (BCPNN) and Multi-item Gamma Poisson Shrinker (MGPS) (Härmark and van Grootheest, 2008; Montastruc et al., 2011). PRR and ROR are more straightforward and widely used for spontaneous reporting data, whereas methods such as BCPNN and MGPS require more complex data and computational resources. Thus, PRR and ROR will be used in this study.

The Proportional Reporting Ratio (PRR) measures the proportion of all adverse event reports for a given drug that are for a specific adverse event and compares this to the proportion for all other drugs. The PRR gives an indication of whether the observed proportion is significantly higher than expected. A PRR value ≥ 2, a chi-squared (x^2) value ≥ 4, and at least 3 cases are reported, suggests a positive signal (Evans et al., 2001).

The PRR will be calculated as:

$$PRR=(a/(a+b))/(c/(c+d)) \quad \text{[Eq. 1]}$$

where

a is the number of reports of a specific adverse event for the drug of interest,

b is the number of reports of all other adverse events for the drug of interest,

c is the number of reports of the specific adverse event for all other drugs,

d is the number of reports of all other adverse events for all other drugs.

The Reporting Odds Ratio (ROR) compares the odds (not the proportion) of reporting a specific adverse event for the drug of interest to the odds of reporting that event for all other drugs. ROR can provide an estimate of the relative risk and it can be accompanied by a confidence interval to assess the precision of the estimate. When the lower limit of the 95% confidence interval (CI) is larger than 1, then ROR is considered significant (Anand et al., 2019).

The ROR will be calculated as:

$$ROR = (a/b)/(c/d) \quad [Eq. 2]$$

where a, b, c and d are the same as for the PRR.

2.2.5 Data Processing and Analysis

Descriptive statistics will be used to describe and summarise data. Descriptive statistics include measures of central tendency and measures of variability or spread (Kaur et al., 2018). Measure of central tendency include the mean, median, and mode. These measures will give a central point around which the data is distributed. Measures of variability include range (difference between the highest and lowest values), variance (average of the squared differences from the mean), standard deviation (a measure of the amount of variation or dispersion of a set of values), and interquartile range. These measures will provide insights into the spread and dispersion of the data (Fisher and Marshall, 2009; Kaur et al., 2018).

When considering which inferential statistical test will be conducted, the flowchart below (Figure 2.1) will be used as a guide to make an appropriate decision (Nam and Chung, 2012).

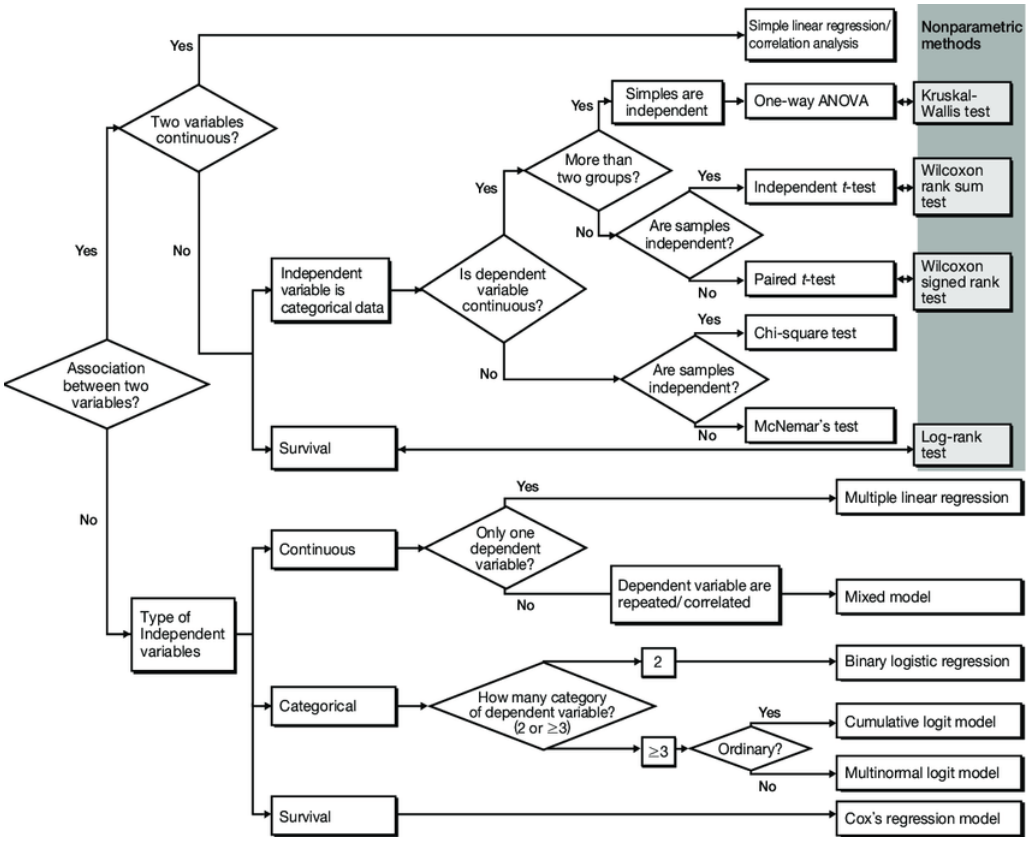

Figure 2.1: A flow chart of inferential statistical test (Nam and Chung, 2012)

Inferential statistics will be used to describe and make inferences about a random sample of data taken from a population. These statistics use the laws of probability to make predictions or inferences about population parameters based on sample data (Marshall and Jonker, 2011).

The following inferential statistical tests will be used in this study.

2.2.5.1 Pearson Correlation Test

The association between the usage of the cancer drugs and cardiology drugs will be explored by the Pearson's correlation test (Equation 3).

$$x = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum(x_i - \bar{x})^2 (y_i - \bar{y})^2}} \quad \text{[Eq. 3]}$$

If there is strong correlation (values close to ± 1) between anticancer drugs and cardiology drugs, then linear regression calculation will be carried out. This process will provide a comprehensive statistical summary of the linear relationship between the independent and dependent variables, including the direction, strength, and fit of the relationship.

2.2.5.2 Linear Regression Model

Linear regression analysis is used to predict the value of a variable based on the value of another variable. The variable to be predicted is the dependent variable (y), while the variable that is being used to predict the other variable's value is the independent variable (x). The aim of linear regression is to find the best-fitting straight line through the points of data.

The equation for a simple linear regression model, which predicts a dependent variable y based on a single independent variable x, is given by

$$y = \beta_0 + \beta_{1x} + \varepsilon \quad \text{[Eq. 4]}$$

where y is the dependent variable to be predicted,

x is the independent variable used to make predictions,

β_0 is the y-intercept of the regression line (representing the predicted value of y when x is 0),

β_{1x} is the slope of the regression line (representing the change in y for a one-unit change in x),

ε is the error term (representing the difference between the observed values and the values predicted by the model).

The following formulas will be used to calculate β_0 and β_{1x}

$$\beta_1 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sum_{i=1}^{n}(x_i - \bar{x})^2} \quad \text{[Eq. 5]}$$

$$\beta_0 = \bar{y} - \beta_1 \bar{x} \quad \text{[Eq. 6]}$$

where x_i and y_i are individual sample points,

$\bar{x}$ and $\bar{y}$ are the means of the independent and dependent variables respectively,

n is the number of observations

The R^2 value measures how well the regression predictions approximate the real data points. An R^2 of 1 indicates that the regression predictions perfectly fit the data.

$$R^2 = 1 - \frac{SS_{res}}{SS_{tot}} \quad \text{[Eq. 7]}$$

where SS_{res} is the sum of squares of residuals, i.e. $\sum_{i=1}^{n}(y_i - \hat{y}_i)^2$,

SS_{tot} is the total sum of squares, i.e. $\sum_{i=1}^{n}(y_i - \bar{y})^2$,

$\hat{y}_i$ is the predicted value of y for x_i based on the regression line

2.2.5.3 t-test

The t-test will be used to compare the means of two groups or to compare the mean of a group to a specific value. It is applicable when the data follows a normal distribution, and the sample size is small. There are different types of t-tests, including the independent samples t-test and the paired sample t-test.

2.2.5.4 Mann-Whitney U Test

The Mann-Whitney U test, also known as the Wilcoxon rank-sum test, is a nonparametric test that compares two independent groups. It will be used when the assumptions of the t-test are

not met (e.g., non-normal distribution). It will assess whether the distributions of two groups are different without the assumption that it follows the normal distribution.

The test will rank all the values from both groups, then calculate the sum of ranks for each group. The test statistic U will be derived from these ranks.

2.2.5.5 Chi-square Test

The Chi-square test is widely used in research for hypothesis testing related to categorical data, such as assessing the effectiveness of a treatment across different groups or understanding the relationship between two categorical variables.

The Chi-square (x^2) test will be used to determine whether there is a significant association between two categorical variables. It compares the observed frequencies in each category of a contingency table with the expected frequencies, which are calculated under the assumption of independence.

2.2.5.6 p-value

The p-value is the probability of obtaining test results at least as extreme as the ones observed during the test, assuming that the null hypothesis is correct. It quantifies the strength of the evidence against the null hypothesis provided by the data. The threshold of $p \leq 0.05$ has been widely used as a criterion for statistical significance in many scientific disciplines. A small p-value (typically ≤ 0.05) indicates strong evidence against the null hypothesis, so it is rejected, thus suggesting a significant difference between the groups.

2.2.5.7 Confidence Intervals

Confidence intervals will provide a range estimated to contain the population parameter with a certain level of confidence. This will be based on the sample data and the variability observed within that sample. The width of the confidence interval provides an idea about the margin of error and the precision of the estimate. The narrower the intervals, the more precise it is; whereas the wider the intervals, the less certainty the estimate is.

2.2.6 Sample Size

All the following studies will be exploratory study and descriptive in nature. The study population will be derived from all patients within databases to which the inclusion criteria apply and thus will be a convenience sample.

2.2.7 Ethics Approval

Ethics application forms EC1A (main application form), EC3 (consent form), EC5 (risk assessment) and EC6 (participant information sheet) were submitted to the Ethics Committee of University of Hertfordshire. It had been confirmed by the UH Ethics Committee that ethics approval is not required for this study as there is no direct involvement of human participants.

2.2.8 Research Plan

The research plan of this study is illustrated below (Figure 2.2).

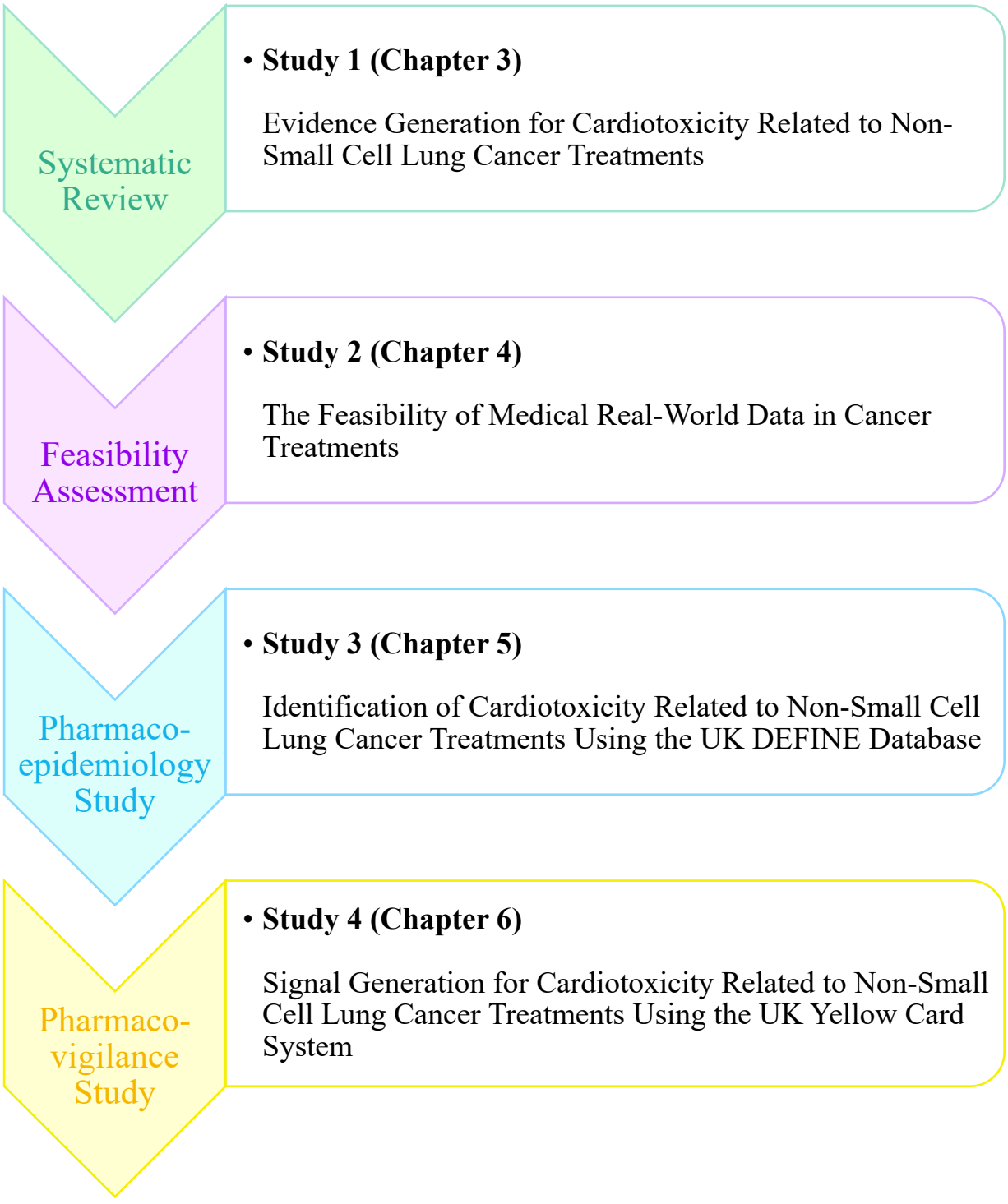

Figure 2.2: A flow chart demonstrating the research plan of this study.

Chapter 3

Evidence Generation for Cardiotoxicity Related to Non-Small Cell Lung Cancer Treatments

3.1 Introduction

Systematic reviews can be broadly defined as a type of research synthesis that are conducted by review groups with specialised skills, who set out to identify and retrieve international evidence that is relevant to a particular question or questions and to appraise and synthesise the results of this search to inform practice, policy and in some cases, further research. According to the Cochrane handbook, a systematic review 'uses explicit, systematic methods that are selected with a view to minimising bias, thus providing more reliable findings from which conclusions can be drawn and decisions made' (Higgins et al., 2022).

As mentioned in previous chapters, systematic review may be undertaken to confirm or refute whether or not current practice is based on relevant evidence, to establish the quality of that evidence, and to address any uncertainty or variation in practice that may be occurring. Such variations in practice may be due to conflicting evidence and undertaking a systematic review should resolve such conflicts. Conducting a systematic review is particularly useful to identify gaps, deficiencies, and trends in the current evidence and can help underpin and inform future research in the area (Uman, 2011). Systematic reviews can be used to produce statements to guide clinical decision-making, the delivery of care, as well as policy development.

There are many studies on complications, including cardiotoxicity, relating to thoracic surgery and radiotherapy complications, however there is much less research on the clinical and prognostic impact of toxicity of systemic therapy in non-small cell lung cancer (Zaborowska-Szmit et al., 2020). Therefore, this systematic review aims to investigate associations between oncology drugs used in the treatment of NSCLC and cardiotoxicity.

3.2 Objectives

The objectives of this study were to:

(1) investigate if there is an association between NSCLC drugs and cardiotoxicity,

(2) explore whether different classes of drugs, e.g. anthracyclines, alkylating agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies, demonstrate different cardiotoxicity potentials,

(3) examine whether different dosages of the same drug in initial treatment affect the degree of cardiotoxicities, and

(4) whether accumulated dosage and/or duration of treatments affect the degree of cardiotoxicities.

3.3 Methods

This systematic review followed the guideline recommended in the 'Preferred Reporting Items for Systematic Review and Meta-Analysis' 2020 statement (Page et al., 2021a, 2021b). A full version protocol of this systematic review has been published on PROSPERO (CRD42020191760) (Chan et al., 2020).

3.3.1 Search Strategy

Electronic databases including Cochrane Library, National Cancer Institute (NCI) Database, PubMed, Scopus and Web of Science were searched for articles reporting clinical trials of cytotoxic drugs where cardiotoxicity was being observed in NSCLC patients. ClinicalTrials.gov and the European Union (EU) Clinical Trials Register were also used to search for recently completed trials. The reference lists of retrieved papers were also hand-searched. All databases and registers were searched from the earliest available date up until November 2020. This time frame was chosen given cardiotoxicity was first observed in 1967 with the use of daunomycin in leukaemia patients (Tan et al., 1967) and more reports on cardiotoxicity induced by anthracyclines emerged in the early 1970s. In addition, from 1997 onwards, there has been a rapid development in targeted treatments and immunotherapies.

Two reviewers (SHYC and Dr Yasmin Khatib) independently screened all the articles according to the eligibility criteria until the final list of articles to be reviewed was identified. SHYC and YK independently reviewed all final set of identified articles meeting the eligibility criteria. SHYC extracted all data using the agreed template. Professor Sam Salek (SS) acted as an adjudicator when there was discrepancy between the two independent reviewers.

3.3.2 Eligibility Criteria

This review included studies of patients of ≥18 years old with NSCLC and excluded studies of participants whose treatments involved multiple cancers or radiotherapy only. Only completed clinical trials including at least two arms were included. Other types of studies and reports, e.g. observational studies and conference abstracts were excluded. Observational studies were

excluded as they are more prone to bias and confounding associated with their study design than that of RCTs. Participants and/or studies without dosage details and duration of treatments were also excluded. Only records reported in English were included.

3.3.3 Search Term

('non small cell lung cancer') AND ('chemotherapy' OR 'targeted therapy' OR 'immunotherapy' OR 'cancer treatment' OR 'systemic anticancer therapy' OR 'anticancer') AND ('cardiac adverse events' OR 'cardiovascular events'' OR 'cardiotoxicity' OR 'drug-related side effects and adverse reactions')

3.3.4 Data Extraction

The standardised data extraction tool from Cochrane Collaboration's Tool was adopted for data extraction. Data items were collected under three main areas – setting, participants and outcome.

Setting – 'Title of Paper', 'Name of Authors', 'Publication Year', 'Reporting Country', 'Aim of Study', 'Primary Objective', 'Secondary Objectives', 'Study Design', 'Unit of Allocation', 'Enrolment Start Date', 'Enrolment End Date', 'Follow-Up End Date', 'Ethics Approval', 'Clinical Trial Identifier / Registration Number'.

Participants – 'Population Description', 'Inclusion Criteria', 'Exclusion Criteria', 'Informed Consent', 'Method of Recruitment', 'Total Number of Cluster Groups, 'Total Number of Participants', 'Age', 'Sex', 'Severity of Illness', 'Co-Morbidities', 'Subgroups Measured', 'Name of NSCLC Drug', 'Mode of Administration', 'Dosage Details', 'Duration of Treatment', 'Frequency of Treatment' and 'Delivery of Treatment'.

Outcome – 'Overall Incidence of Cardiotoxicity', 'Type of Cardiotoxicity', 'Incidence of Each Type of Cardiotoxicity' and 'Key Conclusion from Authors'.

Data items were repeatedly collected for each individual placebo or treatment arm where relevant. All data items were input into Microsoft Excel®, where each row represented one publication. If certain data items were not available within the publication, then the data and results listed under their corresponding clinical trial identifier were cross-checked to complete the data extraction.

3.3.5 Risk of Bias in Individual Studies

The risk of bias assessment in individual studies was carried out according to the guideline listed in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2022).

The following criteria were assessed –

– Attrition bias: Incomplete outcome data

– Performance & detection bias: Blinding of participants, Blinding of outcome assessors

– Reporting bias: Selective reporting

– Selection bias: Random sequence generation

– Allocation bias: Allocation concealment

3.4 Results

3.4.1 Results of literature search

A total of 1785 records were identified from the seven databases and registers using the search term listed in 'Methodology'. This search time frame (earliest available date up until November 2020) was used in order to maximise the records identified as cardiotoxicity was first observed in 1967 in treating leukaemia patients with daunomycin and more reports on cardiotoxicity induced by anthracycline emerged in the early 1970s. A PRISMA 2020 flow diagram explaining the selection process for this systematic review is presented in Figure 3.1. A total number of 74 eligible studies were included for data extraction. A summary of the study design, patient population and NSCLC drugs used for all publication is listed in Table 3.1.

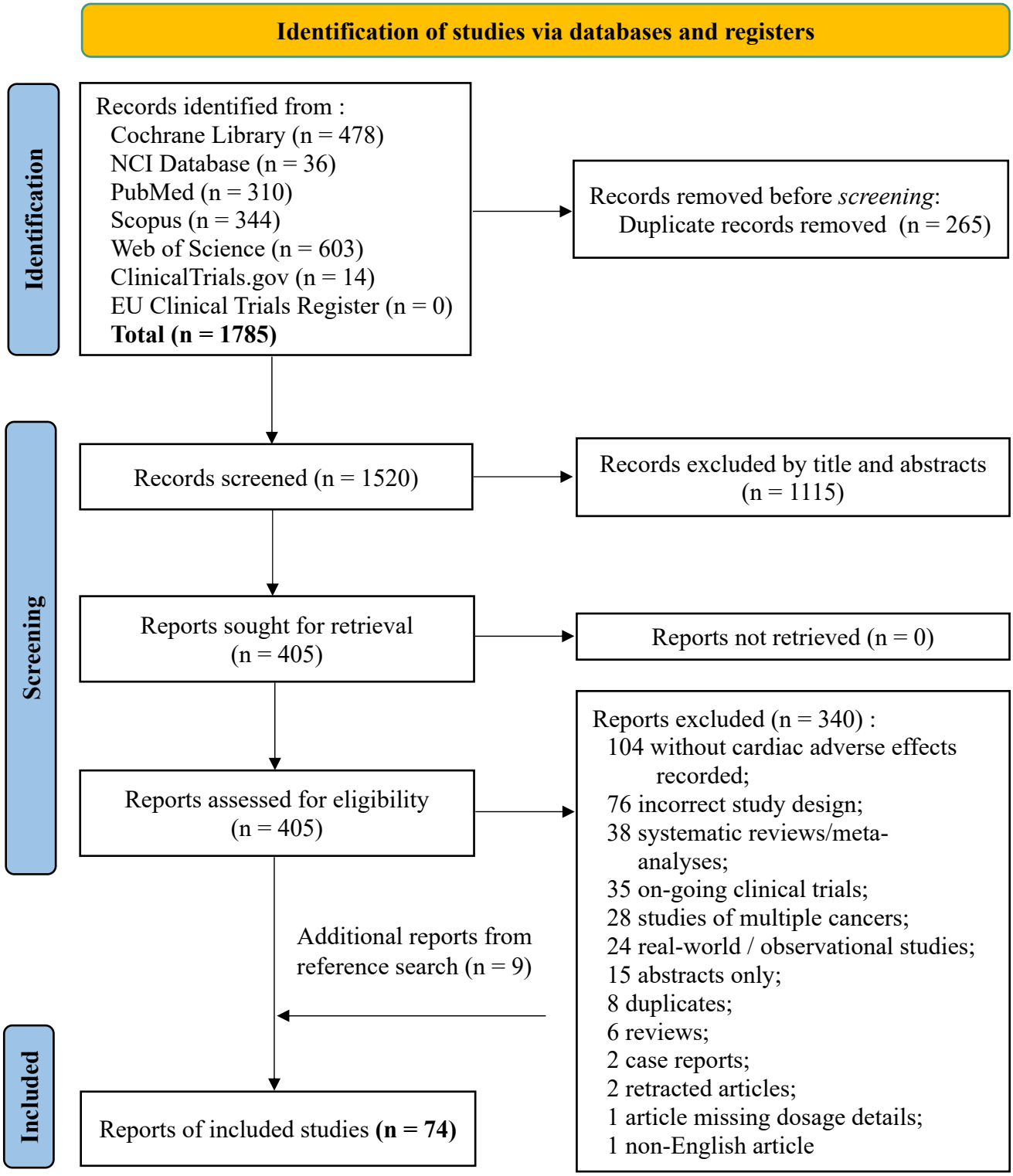

Figure 3.1: PRISMA 2020 flow diagram for this new systematic review which included searches of databases and registers only.

Table 3.1: Summary of the study design, patient population and non-small cell lung cancer (NSCLC) drug used for each publication.

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Mizugaki H, 2015 (Mizugaki et al., 2015)	NCT01617928	Japan	Open-label, Phase I Study	3	12	67 (44 – 73 years old)	10M 2F	Stage IIIIB, Stage IV, Postoperative recurrence	Smoker status	Dose	Carboplatin, Paclitaxel, Veliparib
Huang M, 2020 (Huang et al., 2020)	NCT03201146	China	Phase I Study	3	12	53.4 (42.2 – 63.4 years old)	7M 5F	Stage IVA, Stage IVB	Smoker status	Dose	Apatinib, Carboplatin, Pemetrexed
Sebastian M, 2019 (Sebastian et al., 2019)	N/A	Germany & Switzerland	Prospective, multicenter, open-label, uncontrolled phase I/IIa trial	4	46	64.7 (SD: 10.2)	29M 17F	Stage IIIB, Stage IV	N/A	Dose	CV9201 (generated using proprietary RNActive® Technology)
Novello S, 2014 (S. Novello et al., 2014)	NCT01086254	Italy, France, Germany, Spain, United Kingdom	Phase II, randomised, open-label, non-comparative study	2	119	58.7 (29 – 73 years old)	90M 29F	Stage I, Stage III, Stage IV	Smoker status	N/A	Cisplatin, Iniparib, Gemcitabine
Cappuzzo F, 2006 (Cappuzzo et al., 2006)	N/A	Italy	Phase II, randomised Study	2	117	72.5 (54 – 81 years old)	98M 19F	Stage IIIB, Stage IV	N/A	Infusion Duration	Chemotherapy, Gemcitabine
Srinivasa GY, 2020 (Srinivasa et al., 2020)	N/A	India	Randomised prospective study	2	36	57 (45 – 65 years old)	33M 3F	Stage IIIA, Stage IIIB	N/A	N/A	Carboplatin, Cisplatin, Etoposide, Paclitaxel
Yoshioka H, 2017 (Yoshioka et al., 2017)	NCT01207011	Japan	Randomised, open-label, phase III trial	2	197	20-75 years old	135M 62F	Stage IIIIB, Stage IV, Postoperative recurrence	Smoker status	N/A	Amrubicin, Docetaxel

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Johnson BE, 2013 (Johnson et al., 2013)	NCT00257608	USA	Randomised, Double-Blind, Placebo-Controlled, Phase IIIB Trial	2	743	64 (23 – 88 years old)	389M, 354F	Stage IIIB, Stage IV, Recurrent	Smoker Status	N/A	Bevacizumab, Erlotinib (Chemotherapy prior to trial)
Yang JJ, 2014 ("EudraCT Number 2011-000634-11 - Clinical trial results - EU Clinical Trials Register," n.d.)	MEK114653 (EU Clinicals Register)	France, Greece, Hungary, Italy, Netherlands, South Korea, Spain, USA	Phase II, Open-label, Multicenter, Randomised Study	2	134 (4 drop out)	61.2 (18 – 64 years old)	69M, 65F	Stage IIIB, Stage IV	N/A	Crossover Phase	Docetaxel, GSK1120212
Gridelli C, 2001 (Gridelli et al., 2001)	N/A	Italy	Pilot Single-Stage Phase II Study	2	98	74 (70 – 82 years old)	83M, 15F	Stage IIIB, Stage IV	N/A	N/A	Gemcitabine, Vinorelbine
Martoni A, 1991 (Martoni et al., 1991)	N/A	Italy	Phase I Trial	4	24	60 (36 – 68 years old)	24M, 0F	Stage IIIB, Stage IV	N/A	Dose, LVEF values	Epirubicin
Wu Y, 2018 (Boehringer Ingelheim, 2018a; Sequist et al., 2013; Wu et al., 2018)	NCT00949650 (LL3)	Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, France, Germany, Hong Kong,	Global, randomised, open-label phase III study	2	345	60.3 (S.D. 10.1 years old)	121M, 224F	Stage IIIB, Stage IV	Smoker Status	N/A	Afatinib, Cisplatin, Pemetrexed

		Hungary, Ireland, Italy, Japan, Malaysia, Peru, Philippines, Romania, Russia, South Korea, Taiwan, Thailand, Ukraine, United Kingdom, USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Boehringer Ingelheim, 2018 (Boehringer Ingelheim, 2018b)	NCT01121393	China, South Korea, Thailand	Randomised, Open-label, Phase III Study	2	364	56.4 (SD: 10.9)	126M, 238F	Stage IIIB, Stage IV	Smoker Status	N/A	Afatinib (BIBW2992), Cisplatin, Gemcitabine
Boehringer Ingelheim, 2020 (Boehringer Ingelheim, 2020)	NCT01466660	Australia, Canada, China, France, Germany, Hong Kong, Ireland, Norway, Singapore, South Korea, Spain, Sweden, Taiwan,	Randomised, Open-label Phase IIB Trial	2	319	62.4 (SD: 11.0)	122M, 197F	Stage IIIB, Stage IV	Smoker Status	N/A	Afatinib, Gefitinib

		United Kingdom									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Hida T, 2017 (Hida et al., 2017)	JapicCTI-132316 (Japan Pharmaceutical Information Centre)	Japan	Phase III, Open-label, Multicenter, Randomised Trial	2	207	60.2 (25 – 85 years old)	82M, 125F	Stage IIIIB, Stage IV, Postoperative recurrence	Smoker Status	N/A	Alectinib, Crizotinib
Berghmans T, 2013 (Berghmans et al., 2013)	NCT00622349	Belgium, France, Greece, Spain	Phase III Trial	3	693	58 (28 – 84 years old)	523M, 170F	Stage IIB, Stage IIIA, Stage IIIB, Stage IV	N/A	N/A	Cisplatin, Docetaxel, Gemcitabine, Ifosfamide
GSK, 2014 (GlaxoSmith Kline, 2014)	NCT01362296	France, Greece, Hungary, Italy, Netherlands, South Korea, Spain, USA	Phase II, Open-label, Multicenter, Randomised Trial	2	134	61.2 (SD: 9.32)	69M, 65F	Stage IV	Smoker Status	N/A	Docetaxel, GSK1120212 (Trametinib)
Martoni A, 1999 (Martoni et al., 1999)	N/A	Italy	Pilot Study	2	212	61 (42 – 72 years old)	179M, 33F	Stage IIIA, Stage IIIB, Stage IV, Recurrence	N/A	N/A	Epirubicin, cisplatinum, vinorelbine
Reck M, 2015 (Reck et al., 2015)	NCT00805194	Austria, Belarus, Belgium, Bulgaria, China, Croatia, Czech Republic, Denmark, France, Georgia, Germany, Greece,	Randomised, Placebo-Controlled, Phase III trial	2	1314	59.8	955M, 359F	<Stage IIIB, Stage IIIB, Stage IV	Smoker Status	N/A	Docetaxel, Nintedanib

		India, Israel, Italy, Lithuania, Poland, Portugal, Romania, Russia, Slovakia, South Africa, South Korea, Spain, Switzerland, Ukraine, UK									
Saito K, 2003 (Saito et al., 2003)	N/A	Japan	Parallel	2	25	61.8 (40 – 79 years old)	16M, 9F	Stage III, Stage IV	N/A	LVEF	Carboplatin, Docetaxel, Paclitaxel
Barlesi F, 2018 (Barlesi et al., 2018)	NCT02395172	Argentina, Australia, Belgium, Brazil, Bulgaria, Chile, Colombia, Croatia, Czech Republic, Denmark, Estonia, France, Hungary, Israel, Italy, Japan, Latvia, Mexico, Peru, Poland, Romania, Russia, Slovakia, South	Open-label, multicentre, randomised Phase III trial	2	792	63.5 (57 – 69 years old)	542M 250F	Stage IIIB, Stage IV, Recurrent NSCLC with disease progression after previous platinum doublet treatment	Smoker Status	N/A	Avelumab, Docetaxel

		Africa, South Korea, Spain, Switzerland, Taiwan, Turkey, UK, and USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Camidge DR, 2018 (Camidge et al., 2018)	NCT02737501	Australia, Austria, Canada, Denmark, France, Germany, Hong Kong, Italy, South Korea, Luxembourg, Netherlands, Norway, Singapore, Spain, Sweden, Switzerland, Taiwan, UK, USA	Open-label, multicenter, randomised, international, Phase III trial	2	275	59 (27 – 89 years old)	125M 150F	Stage IIIB, Stage IV	Smoker Status	N/A	Brigatinib, Crizotinib
Wachters FM, 2004 (Wachters et al., 2004)	N/A	Netherlands	Randomised phase III trial	2	69	61 (43 – 76 years old)	49M 20F	Stage IIIA, Stage IIIB Stage IV	N/A	LVEF	Cisplatin, Epirubicin, Gemcitabine
Shaw AT, 2013 (Shaw et al., 2013)	NCT00932893	Australia, Brazil, Bulgaria, Canada, China, France,	Phase 3, Randomised, Open-label Study	2	347	50 (22 – 85 years old)	154M 193F	Advanced	Smoker Status	N/A	Crizotinib (PF-02341066), Docetaxel, Pemetrexed

		Germany, Greece, Hong Kong, Hungary, Ireland, Italy, Japan, Netherlands, Poland, Russian Federation, South Korea, Spain, Sweden, Taiwan, United Kingdom, USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Solomon BJ, 2014 (Solomon et al., 2014)	NCT01154140	Australia, Austria, Belgium, Brazil, Canada, Chile, China, Finland, France, Germany, Hong Kong, India, Ireland, Italy, Japan, Luxembourg, Mexico, Netherlands, Norway,	Phase 3, Randomised, Open-label Study	2	343	53 (19 – 78 years old)	131M 212F	Advanced	Smoker Status	N/A	Crizotinib, Carboplatin, Cisplatin, Pemetrexed

		Peru, Portugal, Russian Federation, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Bonomi P, 2000 (Bonomi et al., 2000)	N/A	USA	A Phase III Study	3	574	61.8	365M 209F	Stage IIIB, Stage IV	N/A	Dose	Cisplain, Etoposide, Paclitaxel
Zatloukal P, 2004 (Zatloukal et al., 2004)	N/A	Czech Republic	Prospective, randomised open, parallel group study	2	102	61.5 (42 – 75 years old)	69M 33F	Stage IIIA, Stage IIIB	N/A	N/A	Cisplatin, Vinorelbine
Zarogoulidis P, 2013 (P. Zarogoulidis et al., 2013)	N/A	Greece	Four-arm Phase III Trial	4	229	62.5	187M 37F	Stage IIIB, Stage IV	Smoker Status	N/A	Bevacizumab, Carboplatin, Docetaxel, Erlotinib
Koch A, 2011 (Koch et al., 2011)	NCT00300729	Sweden	Double-blind, placebo-controlled multicentre Phase III Trial	2	316	65.5 (37 – 85 years old)	160M 156F	Stage IIIB, Stage IV	Smoker Status	N/A	Celecoxib, Chemotherapy (carboplatin/cisplatin / gemcitabine / vinorelbine)

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Bi N, 2019 (Bi et al., 2019)	NCT01503385	China	A Phase II Randomised Clinical Trial	2	96	60	73M 23F	Stage IIIA, Stage IIIB	Smoker Status	N/A	Celecoxib, Cisplatin, Etoposide
Herbst RS, 2011 (Herbst et al., 2011)	NCT00130728	12 countries including USA	Double-blind, Placebo-Controlled, Randomised Phase 3 trial	2	636	64.9	341M 295F	N/A	Smoker Status	N/A	Bevacizumab, Erlotinib
Seto T, 2014 & Kato T, 2018 (Kato et al., 2018; Seto et al., 2014)	JapicCTI-111390 (Japan Pharmaceutical Information Centre)	Japan	Open-label, randomised, multicentre, Phase II Study	2	152	67 (59 – 73 years old)	56M 96F	Stage IIIB, Stage IV, Postoperative recurrence	Smoker Status	N/A	Bevacizumab, Erlotinib
National Cancer Institute, 2019 (National Cancer Institute (NCI), 2019)	NCT00126581	USA	A Phase II Randomised, Open label Study	2	181	59 (32 – 81 years old)	74M 107F	Stage III, Stage IV	Smoker Status	N/A	Carboplatin, Erlotinib, Paclitaxel
Stathopoulos GP, 2004 (Stathopoulos et al., 2004)	N/A	Greece	Multicenter, randomised, phase III trial	2	360	65 (30 – 84 years old)	312M 48F	Stage IIIA, Stage IIIB, Stage IV	N/A	N/A	Carboplatin, Paclitaxel, Vinorelbine
Valdivieso M, 1984 (Valdivieso et al., 1984)	N/A	USA	Prospective, randomised study	2	100	56.5 (33 – 78 years old)	79M 21F	N/A	Biopsy	Weekly VS once every 3 weeks doxorubicin	Cisplatin, Cyclo-phosphamide, Doxorubicin, Ftorafur

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Baggstrom MQ, 2017 (Baggstrom et al., 2017)	NCT00693992	USA	Randomised, double-blind, placebo-controlled phase III trial	2	210	64.9 (25 – 89 years old)	117M 93F	Stage IIIB, Stage IV	Smoker Status	N/A	Chemotherapy, Sunitinib
Paz-Ares L, 2015 (Paz-Ares et al., 2015)	NCT00863746	Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Israel, Italy, Japan, South Korea, Netherlands, Pakistan, Peru, Phillippines, Poland, Russia, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand,	Phase III, randomised, double-blind, placebo-controlled trial	2	703	≥ 18 years old	395M 308F	N/A	Smoker Status	N/A	Best supportive care, Sorafenib

		Turkey, UK, USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Novello S, 2014 (S Novello et al., 2014)	NCT00460317	32 countries including Italy, Germany, Romania, Ukraine, UK, USA	Phase 3, randomised, placebo-controlled, doubleblind study	2	360	60.8 (31 – 81 years old)	295M 65F	Stage IIIB, Stage IV	Smoker Status	N/A	Carboplatin, Paclitaxel, Motesanib
Akamatsu H, 2018 (Akamatsu et al., 2018)	NCT02151981	Australia, Canada, China, France, Germany, Hong Kong, Hungary Italy, Japan, Mexico, Netherlands, Russia, South Korea, Spain, Sweden, Taiwan, UK, USA	Randomised, open-label, phase III clinical trial	2	419	62.5 (20 – 90 years old)	150M 269F	N/A	Smoker Status	N/A	Carboplatin, Cisplatin, Pemetrexed, Osimertinib
Kosmidis PA, 2008 (Kosmidis et al., 2008)	N/A	Greece	Phase III Study	2	452	63 (36 – 83 years old)	378M 74F	Stage IIIB, Stage IV	N/A	N/A	Carboplatin, Paclitaxel, Gemcitabine
Reinmuth N, 2019 (Reinmuth et al., 2019)	NCT02364999	Australia, Brazil, Bulgaria, Chile, Croatia, Czech Republic,	Multinational, double-blind, randomised, parallel-group study	2	719	61.5 (25 – 87 years old)	467M 252F	Stage IIIB, Stage IV, Recurrent	Smoker Status	N/A	Bevacizumab, Carboplatin, Paclitaxel, PF-06439535

		France, Germany, Greece, Hungary, India, Italy, Japan, South Korea, Malaysia, Netherlands, Philippines, Poland, Romania, Russia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, USA									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Blumenschein GR, 2010 (Blumenschein et al., 2010)	NCT00094835	USA	Multicenter, Open-label, Dose-finding, Phase IB study of motesanib	3	45	61.3 (32 – 79 years old)	29M 16F	Stage IIIB, Stage IV	Smoker Status	N/A	Carboplatin, Paclitaxel, Panitumumab, Motesanib
Choy H, 2013 (Choy et al., 2013)	NCT00482014	India, USA	Open-label, Randomised Trial	2	98	63.6 (43.7 – 85.2 years old)	61M 37F	Stage IIIA, Stage IIIB	N/A	N/A	Carboplatin, Cisplatin Pemetrexed
William WN, 2007 (William et al., 2007)	N/A	USA	Open-label, Phase I, Dose-escalation Study	4	21	52 (38 – 71 years old)	13M 8F	Stage IV	N/A	Dose	Cisplatin, Docetaxel, Motexafin gadolinium

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Chang AY, 1993 (Chang et al., 1993)	N/A	USA	Phase II Study	3	103	61.3 (31 – 85 years old)	70M 33F	Stage IV	N/A	N/A	Merbarone, Piroxantrone, Taxol
Kubota K, 2017 (Kubota et al., 2017)	JapicCTI-121887 (Japan Primary Registries Network)	Japan, South Korea, Hong Kong, Taiwan	Phase III, Randomised, Placebo-Controlled, Double-blind Study	2	401	65 (Upper Quartile: 58; Lower Quartile: 70)	288M 113F	Stage IV, Recurrent	Smoker Status	N/A	Carboplatin, Motesanib, Paclitaxel
Zinner RG, 2015 (Zinner et al., 2015)	NCT00948675	USA	Multicenter, Randomised, Open-label, US-only Phase III Trial	2	361	65.6 (38.4 – 86.2 years old)	209M 152F	Stage IV	Smoker Status	N/A	Bevacizumab, Carboplatin, Paclitaxel Pemetrexed
Heigener DF, 2013 (Heigener et al., 2013)	NCT00160069	Germany	Prospective, Multicenter, Phase II study	3	128	63	83M 45F	Stage IIIB, Stage IV	N/A	Dose, Duration of Infusion	Sagopilone
Wang XJ, 2018 (Jie Wang et al., 2018)	N/A	China	Randomised Controlled Trial	2	128	No mean/median (36 – 76 years old)	96M 32F	N/A	N/A	N/A	Cisplatin, Endostar, Pemetrexed
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019a)	NCT01469000	China, Japan, South Korea, Taiwan	Multicenter, Randomised, open-label, parallel-arm, phase II study	2	191	61.71 (S.D.: 9.38)	68M 123F	Stage IV	N/A	N/A	Gefitinib, Pemetrexed
Douillard JY, 2004	N/A	Belgium, Canada, France,	Randomised, Double-blind, Placebo-	2	75	61.4	56M 19F	Stage IIIB, Stage IV	N/A	N/A	BMS-275291, Carboplatin, Paclitaxel

(Douillard, 2004)		Germany, Italy, Spain, USA	controlled, Phase II Feasibility Study								
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Butts CA, 2007 (Butts et al., 2007)	N/A	Canada, USA	Multicenter, Open-label, Randomised Phase II study	2	131	66 (35 – 84 years old)	58M 73F	Stage IIIB Stage IV, Recurrent	N/A	N/A	Carboplatin, Cisplatin, Cetuximab, Gemcitabine
Fukuda M, 2019 (Fukuda et al., 2019)	UMIN000008771 (University Hospital Medical Information Network)	Japan	Randomised Phase II Study	2	40	78 (75 – 83 years old)	23M 17F	Stage IIIB, Stage IV, Postoperative recurrence	Smoker Status	N/A	Bevacizumab, Pemetrexed
Passardi A, 2008 (Passardi et al., 2008)	N/A	Italy	Randomised Phase II Trial	2	81	63 (35 – 77 years old)	65M 16F	Stage IV	N/A	N/A	Docetaxel, Gemcitabine
Gatzemeier U, 2004 (Gatzemeier et al., 2004)	N/A	Canada, Italy, Germany, Netherlands, UK	Randomised, Open-label, Phase II study	2	101	58.5 (35 – 76 years old)	63M 38F	Stage IB, Stage IIIB, Stage IV	N/A	N/A	Cisplatin, Gemcitabine, Trastuzumab
Park C, 2017 (Park et al., 2017)	NCT01282151	South Korea	Open-label, Multicenter Prospective Phase III Study	2	148	63.3	103M 45F	Stage IIIB, Stage IV	Smoker Status	N/A	Cisplatin, Docetaxel, Pemetrexed
Movsas B, 2005 (Movsas et al., 2005)	N/A	Canada, USA	Randomised Trial	2	242	≥ 18 years old	150M 92F	Stage IIA, Stage IIB, Stage IIIA, Stage IIIB	N/A	N/A	Amifostine, Carboplatin, Paclitaxel
Jänne P, 2014	N/A	Canada, Germany, Spain, USA	Randomised, Double-Blind, Phase II Trial	3	200	61.4	127M 68F	Stage IIIB, Stage IV	Smoker Status	Dose	Cisplatin, Gemcitabine, LY293111

(Jänne et al., 2014)						(27.8 – 87.8 years old)					
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Groen HJ, 2011 (Groen et al., 2011)	N/A	Netherlands	Randomised, Placebo-Controlled Phase III Study	2	561	61 (33 – 84 years old)	355M 206F	Stage IIIB, Stage IV	N/A	N/A	Carboplatin, Celecoxib, Docetaxel
Currow D, 2017 (Currow et al., 2017)	NCT01395914	Australia, Belarus, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Poland, Russia, Serbia, Slovenia, Spain, Ukraine	Double-blind, safety extension Phase III Study	2	513	62.0	387M 126F	Stage IIIA, Stage IIIB, Stage IV	N/A	N/A	Anamorelin, Placebo
Langer CJ, 2017 (Langer et al., 2017)	NCT00789373	Australia, Belgium, Canada, Finland, France, Germany, Greece, India, Italy, Netherlands, Poland, Portugal, Romania,	Phase 3, Double-Blind, Placebo-Controlled Study	2	939	61.3 (24.4 – 83.0 years old)	577M 362F	Stage IIIB, Stage IV	Smoker Status	N/A	Cisplatin, Pemetrexed, Placebo

		Spain, Turkey, United Kingdom									
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Kotsakis A, 2015 (Kotsakis et al., 2015)	NCT00620971	Greece	A Multicenter, Randomised, Phase II study.	2	77	59 (36 – 77 years old)	57M 20F	Stage IIIB, Stage IV	Smoker Status	N/A	Bevacizumab, Cisplatin, Docetaxel, Gemcitabine, Vinorelbine
Eli Lilly and Company, 2015 (Eli Lilly and Company, 2015)	NCT00112294	USA	A Phase III, Randomised, Open Label Study	2	676	64 (S.D.: 10.2)	396M 280F	N/A	N/A	N/A	Carboplatin, Cetuximab, Taxane (Paclitaxel/Docetaxel)
GSK, 2019 (GlaxoSmith Kline, 2019)	NCT01868022	Belgium, Denmark, Netherlands, Russia, Spain, UK, USA	Multi-arm, Non-randomised, Open-Label Phase IB Study	9	65	66.52 (S.D.: 3.08)	52M 13F	Stage IIIB, Stage IV	N/A	Dose	Carboplatin, Cisplatin, Docetaxel, GSK3052230, Paclitaxel, Pemetrexed
Lara PN, 2016 (Lara et al., 2016)	N/A	USA	Randomised, Phase II Selection Design Trial	2	59	73.1 (40.9 – 85.9 years old)	24M 35F	Stage IIIB, Stage IV	Smoker Status	N/A	Carboplatin, Erlotinib, Paclitaxel
Wu YL, 2020 (Wu et al., 2020)	NCT01982955	China, Italy, Malaysia, Singapore, South Korea Spain, Taiwan	Open-label, randomised, Phase 1b/2 study	5	88	N/A	36M 52F	Advanced	N/A	N/A	Carboplatin, Cisplatin, Gefitinib, Pemetrexed, Tepotinib,
Umsawasdi T, 1989)	N/A	N/A	Randomised Study	2	102	56.5 (33 – 78 years old)	71M 31F	Stage III	N/A	N/A	Cisplatin, Cyclophospha

(Umsawasdi et al., 1989)											mide, Doxorubicin
Reference (Publication Year)	**Clinical Trial Identifier**	**Reporting Country**	**Study Design**	**Total number of cluster groups**	**Total number of patients**	**Age, Median (Range)**	**Sex (M/F)**	**Severity of Illness / NSCLC Stage**	**Co-morbidities**	**Subgroups Measured**	**Drugs involved**
Cortot AB, 2020 (Cortot et al., 2020)	NCT01763671	France	Double-arm, Randomised, Open-label, Multicentre, Phase III Clinical Trial	2	166	59.7 (18.6 – 81.8 years old)	120M 46F	Stage III, Stage IV	Smoker Status	N/A	Bevacizumab, Docetaxel, Paclitaxel
AstraZeneca, 2021 (AstraZeneca, 2021b)	NCT01933932	Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, France, Germany, Hungary, Israel, Italy, Mexico, Netherlands, Peru, Poland, Portugal, Romania, Russian Federation, Spain, Sweden, Turkey, Ukraine, UK, USA	A Phase III, Double-Blind, Randomised, Placebo-Controlled Study	2	510	61.4 (S.D.: 8.3)	303M 207F	Stage IIIB, Stage IV	N/A	N/A	Docetaxel, Selumetinib

Reference (Publication Year)	Clinical Trial Identifier	Reporting Country	Study Design	Total number of cluster groups	Total number of patients	Age, Median (Range)	Sex (M/F)	Severity of Illness / NSCLC Stage	Co-morbidities	Subgroups Measured	Drugs involved
Johnson DH, 2004 (Johnson et al., 2004)	N/A	USA	Randomised Phase II Study	3	99	≥ 18 years old	60M 39F	Stage IIIB, Stage IV	N/A	Dose	Bevacizumab, Carboplatin, Paclitaxel
Eli Lilly and Company, 2022 (Eli Lilly and Company, 2022)	NCT00981058	Australia, Austria, Belgium, Brazil, Canada, Croatia, France, Germany, Greece, Hungary, Italy, South Korea, Philippines, Poland, Portugal, Romania, Russia, Serbia, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, UK, USA	Multinational, Randomised, Multicenter, Open-label, Phase III Study	2	1093	62 (32 – 86 years old)	908M 185F	Stage IIIB, Stage IV	Smoker Status	N/A	Cisplatin, Gemcitabine, Necitumumab
Eli Lilly and Company, 2021 (Eli Lilly and	NCT00982111	Australia, Austria, Belgium, Brazil, Canada, Croatia,	Multinational, Randomised, Multicenter, Open-label Phase III Study	2	633	61 (26 – 88 years old)	424M 209F	Stage IIIB, Stage IV	Smoker Status	N/A	Cisplatin, Pemetrexed, Necitumumab

Company, 2021)		France, Germany, Greece, Hungary, Italy, Poland, Portugal, Romania, Russia, Slovakia, South Africa, Spain, UK, USA									
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019b)	NCT01769391	Germany, South Korea, Mexico, Poland, Russia, USA	Randomised, Multicenter, Open-Label, Phase II Study	2	167	65.3	131M 36F	Stage IV	N/A	N/A	Carboplatin, Paclitaxel, Necitumumab

Of the 74 eligible studies, 67 reported treatment emergent cardiovascular events, i.e. arrhythmias, atrial fibrillation, bradycardia, cardiac arrest, cardiac failure, coronary artery disease, heart failure, hypertension, ischemia, left ventricular dysfunction, myocardial infarction, palpitations, and tachycardia.

Based on data extracted from the included studies, anticancer drugs for NSCLC that are associated with cardiovascular events include bevacizumab, carboplatin, cisplatin, crizotinib, docetaxel, erlotinib, gemcitabine and paclitaxel.

Treatment details and patients' characteristics of each eligible study are available in Table 3.2, whereas Table 3.3 demonstrated the types of cardiotoxicities and their corresponding number of occurrences reported per publication.

Table 3.2: Summary of treatment details and patients' characteristics of each publication.

Reference (Publication Year)	Drug Combination	Delivery / Schedule	Treatment Period	Dose	Number Randomised to Group (M/F)	Age, Median (Range)	NSCLC Stage	Smoker Status (Former/Current/Never)
Mizugaki H, 2015 (Mizugaki et al., 2015)	Carboplatin, Paclitaxel, Veliparib	All patients received veliparib (40, 80, or 120 mg) BID orally at intervals of approximately 12 h on days 1–7 of each 21-day cycle. Carboplatin (AUC 6 mg/mL min) and paclitaxel (200 mg/m^2) were given via intravenous (IV) administration on day 3.	21-day cycle for ≤6 cycles	V-40 mg	3 (3M)	71 (67 – 72)	Stage IIIB: 0 Stage IV: 2	Former: 3 Current: 0 Never used: 0
				V-80mg	3 (3M)	56 (44 – 60)	Stage IIIB: 0 Stage IV: 3	Former: 3 Current: 0 Never used: 0
				V-120mg	6 (4M, 2F)	67 (47 – 73)	Stage IIIB:1; Stage IV: 4; Postoperative recurrence: 1	Former: 2 Current: 2 Never used: 2
Huang M, 2020 (Huang et al., 2020)	Apatinib, Carboplatin, Pemetrexed	During each cycle, pemetrexed (500 mg/m2) and carboplatin (AUC = 5) were given intravenously on days 1. The initial dose, 750 mg qd of apatinib was based on the maximum administered dose as monotherapy and the dosage reduced from 750 mg qd, 500 mg qd, 500 mg schedule 2/1, to 250 mg qd in sequence.	21-day cycle for 4 cycles Therapeutic evaluation was assessed every six weeks.	A-750mg	3 (1M, 2F)	53.9 (52.4 – 64.8)	Stage IVA: 3 Stage IVB: 0	Former: 0 Current: 1 Never used: 2
				A-500mg	3 (2M, 1F)	63.6 (52.9 – 66.6)	Stage IVA: 2 Stage IVB: 1	Former: 2 Current: 0 Never used: 1
				A-500mg 2/1 (500 mg/day 2 weeks on 1 week off)	6 (4M, 2F)	49.8 (42.2 – 63.4)	Stage IVA: 3 Stage IVB: 3	Former: 1 Current: 2 Never used: 3
Sebastian M, 2019 (Sebastian et al., 2019)	CV9201 - generated using proprietary RNActive® Technology	The mRNAs encoding the five antigens of CV9201 were formulated separately and administered at doses of 80, 160, or 320 µg mRNA (total dose 400, 800 or 1600µg mRNA respectively). Each CV9201 component was administered individually at up to 160 µg per injection to the thighs and upper arms. The 320 µg dose was split into two injections resulting in up to 10	During Phase I, CV9201 was administered at weeks 1, 3, 7, 11, and 15 and at weeks 1, 2, 3, 5, and 7 during Phase IIA since early tumour progressions were observed during phase I preventing	Cohort I - 400µg	3 (3M)	75.0 (SD: 12.2)	Stage IIIB: 1 Stage IV: 2	N/A
				Cohort II - 800µg	3 (3M)	62.7 (SD: 8.3)	Stage IIIB: 1 Stage IV: 2	N/A
				Cohort III - 1600 µg	3 (1M, 2F)	62.3 (SD: 9.1)	Stage IIIB: 0 Stage IV: 3	N/A
				Phase IIA (1600µg)	37 (22M, 15F)	64.2 (SD: 10.1)	Stage IIIB: 5 Stage IV: 32	N/A

		injections per administration visit due to technical restrictions to 200 µL per injection with a maximal concentration of 0.8 µg/µL mRNA. Individual components were administered to the same body sides at each visit during phase I and to the opposite body side at different visits in phase IIA.	the administration of all five scheduled injections.					
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Novello S, 2014 (S. Novello et al., 2014)	Cisplatin, Iniparib, Gemcitabine	Patients were randomised to gemcitabine 1250 mg/m^2 (days 1 and 8) plus cisplatin 75 mg/m^2 (day 1), with or without iniparib 5.6 mg/kg (1-h intravenous infusion, days 1, 4, 8, and 11) every 3 weeks for six cycles.	21-day cycle for 6 cycles	GC	39 (26M, 13F)	58 (29 – 73)	Stage I: 1 Stage III: 3 Stage IV: 35	Former/Current: 35 Never used: 4
				GCI	80 (64M, 16F)	59 (37 – 73)	Stage I: 1 Stage III: 2 Stage IV: 77	Former/Current: 71 Never used: 9
Cappuzzo F, 2006 (Cappuzzo et al., 2006)	Chemotherapy, Gemcitabine	At study entry, all eligible patients were randomly assigned to chemotherapy with gemcitabine 1500mg/m^2 on days 1 and 8 every 3 weeks by standard 30 min intravenous infusion (arm A), or gemcitabine 10mg/m^2/min for 150 min on days 1 and 8 every 3 weeks by intravenous infusion at fixed dose rate (arm B).	21-day cycle Following completion of therapy, patients were followed every 3 months.	Standard (50mg/min)	56 (46M, 10F)	72 (55 – 81)	Stage IIIB: 19 Stage IV: 38	N/A
				Low (10mg/min)	61 (52M, 9F)	73 (54 – 81)	Stage IIIB: 20 Stage IV: 41	N/A
Srinivasa GY, 2020 (Srinivasa et al., 2020)	Carboplatin, Cisplatin, Etoposide, Paclitaxel	Patients were given external beam radiotherapy (EBRT) to a total dose of 60 Gy in 30 fractions at 2 Gy/fraction along with concurrent chemotherapy of the following:	First follow-up was done at 6 weeks. Subsequent follow-up was twice a month for the first year,	Cis-Etop	18 (16M, 2F)	57 (45 – 65)	Stage IIIA: 10 Stage IIIB: 8	Smokers: 18 Never: 0
				Car-Pac	18 (17M, 1F)	59 (45 – 65)	Stage IIIA: 9 Stage IIIB: 9	Smokers: 18 Never: 0

		Control arm: injection cisplatin 20 mg/m^2/day intravenous (iv) and injection etoposide 50 mg/m^2/day iv days 1–5 and days 29–33 of starting radiation. Study arm: injection paclitaxel 50 mg/m^2 IV and injection carboplatin AUC every Monday concomitant with radiation.	followed by once in 4 months for 2 years and once in 6 months after that.					
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Yoshioka H, 2017 (Yoshioka et al., 2017)	Amrubicin, Docetaxel	Amrubicin hydrochloride was intravenously administered at a dose of 35 mg/m^2/day in ~20 ml of saline or 5% glucose over ~5 min. Amrubicin was administered on days 1, 2, and 3 of each 21-day cycle. Docetaxel was intravenously administered at a dose of 60 mg/m^2/day (the approved dose in Japan), in physiological saline or 5% glucose over at least 1 h on day 1 of each course.	21-day cycle	Amrubicin	98 (66M. 32F)	N/A	Stage IIIB: 5 Stage IV: 81 Postoperative recurrence: 12	Former/Current: 72 Never: 26
				Docetaxel	99 (69M, 30F)	N/A	Stage IIIB: 10 Stage IV: 74 Postoperative recurrence: 15	Former/Current: 73 Never: 26
Johnson BE, 2013 (Johnson et al., 2013)	Bevacizumab, Erlotinib (Chemotherapy prior to trial)	Bevacizumab (15 mg/kg) with or without erlotinib (150 mg/day) to progressive disease	21-day cycle (B) / Progressive disease (E)	Bev-Plac	373 (196M, 177F)	64 (23 – 83)	Stage IIIB: 37 Stage IV: 310 Recurrent: 25 Missing: 1	Former: 178 Current: 129 Never used: 66
				Bev-Erlo	370 (193M, 177F)	64 (31 – 88)	Stage IIIB: 32 Stage IV: 317 Recurrent: 21	Former: 180 Current: 129 Never used: 61
Gridelli C, 2001	Gemcitabine, Vinorelbine	Single-agent gemcitabine is given intravenously at the dose of 1200 mg/m^2; gemcitabine and vinorelbine	21-day cycle for ≤6 cycles	Gem	49 (42M, 7F)	74 (70 – 82)	Stage IIIB: 17 Stage IV: 32	N/A

(Gridelli et al., 2001)		are given at the doses of 1000 and 25 mg/m^2; both schedules are administered on days 1 and 8 of a 21-day cycle.		Gem-Vin	49 (41M, 8F)	74 (70 – 82)	Stage IIIB: 18 Stage IV: 31	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Martoni A, 1991 (Martoni et al., 1991)	Epirubicin	Epirubicin (120 mg/m^2, 135 mg/m^2, 150 mg/m^2 and 165 mg/m^2 was administered by intravenous bolus (5-10 min) and repeated every 3 weeks if there was recovery from myelotoxicity(WBC ≥ 4000/µ, platelets ≥ 100,000/µl). Treatment was interrupted when a cumulative dose of about 900 mg/m^2 was reached.	21-day cycle	120Epi	10	N/A	N/A	N/A
				135Epi	4	N/A	N/A	N/A
				150Epi	7	N/A	N/A	N/A
				165Epi	3	N/A	N/A	N/A
Wu Y, 2018 (Boehringer Ingelheim, 2018a; Sequist et al., 2013; Wu et al., 2018)	Afatinib, Cisplatin, Pemetrexed	Patients received afatinib monotherapy 40 mg film-coated tablets orally once daily. Patients received Pemetrexed 500 mg/m^2 lyophilised powder as intravenous infusion after Cisplatin 75 mg/m^2 solution for infusion as intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles.	21-day cycle for ≤6 cycles	Afatinib	230 (83M, 147F)	60.5 (SD: 10.1)	Stage IIIB: 20 Stage IV: 210	Former: 70 Current: 5 Never used: 155
				Pemetrexed/ Cisplatin Chemotherapy	115 (38M, 77F)	59.9 (SD: 10.0)	Stage IIIB: 17 Stage IV: 98	Former: 32 Current: 2 Never used: 81
Boehringer Ingelheim, 2018 (Boehringer Ingelheim, 2018b)	Afatinib, Cisplatin, Gemcitabine	Patients received afatinib film-coated tablets 40 mg once daily (q.d.) orally with possible dose escalation to 50 mg q.d. and dose reduction to 40 mg q.d. (if applicable), 30 mg q.d., or 20 mg q.d. (according to the protocol-defined	21-day cycle for ≤6 cycles	Afatinib	242 (87M, 155F)	56.7 (SD: 11.2)	Stage IIIB: 16 Stage IV: 226	Former: 44 Current: 17 Never used: 181
				Cisplatin,	122 (39M, 83F)	55.6 (SD: 10.1)	Stage IIIB: 6 Stage IV: 116	Former: 13 Current: 10

		dose-escalation and dose-reduction scheme), if required. Patients received Gemcitabine (lyophilised powder) 1000 mg/m² as an intravenous infusion over 30 minutes on day 1 and day 8, cisplatin (solution for infusion) 75 mg/m² as an intravenous infusion on Day 1 of each 21-day treatment course up to 6 cycles		Gemcitabine Chemotherapy				Never used: 99
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Boehringer Ingelheim, 2020 (Boehringer Ingelheim, 2020)	Afatinib, Gefitinib	Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Afatinib	160 (69M, 91F)	61.7 (SD: 11.5)	Stage IIIB: 8 Stage IV: 152	Former: 106 Current: 6 Never used: 181
				Gefitinib	159 (53M, 106F)	63.0 (SD: 10.4)	Stage IIIB: 3 Stage IV: 156	Former: 50 Current: 3 Never used: 106
Hida T, 2017 (Hida et al., 2017)	Alectinib, Crizotinib	Patients received oral alectinib (eight capsules totalling 300 mg; or crizotinib (one capsule totalling 250 mg; twice daily until progressive disease (unless continuation of treatment was considered clinically meaningful by a physician), unacceptable toxicity, death, or a desire to withdraw.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Alectinib	103 (41M, 62F)	61 (27 – 85)	Stage IIIB: 3 Stage IV: 76 Postoperative recurrence: 24	Former: 45 Current: 2 Never used: 56
				Crizotinib	104 (41M, 63F)	59.5 (25 – 84)	Stage IIIB: 3 Stage IV: 75 Postoperative recurrence: 26	Former: 40 Current: 3 Never used: 61

Reference (Publication Year)	Drug Combination	Delivery / Schedule	Treatment Period	Dose	Number Randomised to Group (M/F)	Age, Median (Range)	NSCLC Stage	Smoker Status (Former/Current/Never)
Berghmans T, 2013 (Berghmans et al., 2013)	Cisplatin, Docetaxel, Gemcitabine, Ifosfamide	Patients were randomised on a 1:1:1 ratio between IG (ifosfamide 3 g/m^2 day 1; gemcitabine 1g/m^2 days 1+8), GIP (gemcitabine 1 g/m^2 days 1+8; ifosfamide 3 g/m^2 day 1; cisplatin 50 mg/m^2 day 1), and DP (docetaxel 75 mg/m^2 plus cisplatin 50 mg/m^2, both on day 1)	21-day cycle	IG	229 (172M, 57F)	59 (30 – 84)	Stage IIB: 3 Stage IIIA: 12 Stage IIIB: 27 Stage IV: 186 Missing: 1	N/A
				GIP	231 (174M, 57F)	58 (29 – 78)	Stage IIB: 2 Stage IIIA: 7 Stage IIIB: 30 Stage IV: 191 Missing: 1	N/A
				DP	233 (177M, 56F)	58 (28 – 81)	Stage IIB: 1 Stage IIIA: 14 Stage IIIB: 31 Stage IV: 187 Missing: 0	N/A
Yang JJ, 2014 & GSK, 2014 ("EudraCT Number 2011-000634-11 - Clinical trial results - EU Clinical Trials Register," n.d.; GlaxoSmith Kline, 2014)	Docetaxel, GSK1120212 (Trametinib)	Patients were randomly assigned in a 2 : 1 ratio to trametinib 2 mg orally once daily or docetaxel 75 mg/m^2 IV every 3 weeks.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Doc	43 (23M, 20F)	63 (34 – 79)	Stage IV: 43	Former: 23 Current: 13 Never used: 7
				Tra	86 (46M, 40F)	63 (40 – 79)	Stage IV: 86	Former: 67 Current: 13 Never used: 6
Martoni A, 1999 (Martoni et al., 1999)	Epirubicin, Cisplatin, Vinorelbine	Epirubicin was administered at the dose of 120 mg/m^2 by i.v. bolus and cisplatin at the dose of 60 mg/m^2 in one hour by i.v. on day 1.	21-day cycle for ≤12 cycles	HDEpi-Cis	112	Only summarised as overall	Only summarised as overall	N/A
				Vin-Cis	116			N/A

		VNR was administered at the dose of 25 mg/m^2 by i.v. bolus on day 1 and 8 and cisplatin as above on day 1.				61 (42 – 72)	Stage IIIA: 25 Stage IIIB: 85 Stage IV: 88 Recurrence: 14 Missing: 16	
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Reck M, 2015 (Reck et al., 2015)	Docetaxel, Nintedanib	Standard intravenous docetaxel (75 mg/m^2) on day 1 and nintedanib (200 mg bid) or matching placebo on days 2–21	N/A	Doc-Nin	655 (476M, 179F)	59.7 (S.D. = 9.7)	Stage <IIIB: 105 Stage IIIB: 148 Stage IV: 399 Missing: 3	Former/Current: 490 Never: 165
				Doc-Plac	659 (479M, 180F)	59.8 (S.D. = 9.0)	Stage <IIIB: 105 Stage IIIB: 146 Stage IV: 408 Missing: 0	Former/Current: 498 Never: 161
Saito K, 2003 (Saito et al., 2003)	Carboplatin, Docetaxel, Paclitaxel	In the docetaxel group, 16 patients were treated with 60 mg/m^2 of docetaxel combined with 300 mg/m^2 of carboplatin intravenously every 3 weeks for three cycles. In the paclitaxel group, 9 patients were treated with 180 mg/m^2 of paclitaxel combined with 300 mg/m^2 of carboplatin intravenously every 3 weeks for three cycles.	21-day cycle for 3 cycles	Car-Doc	16 (10M, 6F)	60.75	N/A	N/A
				Car-Pac	9 (6M, 3F)	63.6	N/A	N/A
Barlesi F, 2018 (Barlesi et al., 2018)	Avelumab, Docetaxel	Participants in the avelumab group received 10 mg/kg avelumab intravenously over 1h once every 2 weeks.	Until progressive disease, unacceptable	Ave	396 (269M, 127F)	64 (58 – 69)	N/A	Former/Current: 324 Never: 70 Missing: 2

		An antihistamine and paracetamol (eg, oral diphenhydramine 25–50 mg and oral or intravenous paracetamol 500–600 mg, or equivalent) were given 30–60 min before each infusion of avelumab. Participants in the docetaxel group received 75 mg/m² docetaxel intravenously over 1h every 3 weeks according to label instructions and local guidelines. Dexamethasone was given before each infusion of docetaxel according to local standard of care.	toxicity, death, or a desire to withdraw.	Doc	396 (273M, 123F)	63 (57 – 69)	N/A	Former/Current: 333 Never: 63
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Camidge DR, 2018 (Camidge et al., 2018)	Brigatinib, Crizotinib	They were randomly assigned (in a 1:1 ratio) to receive oral brigatinib at a dose of 180 mg once daily after a 7-day lead-in period of 90 mg once daily or oral crizotinib at a dose of 250 mg twice daily.	N/A	Brig	137 (68M, 69F)	58 (27 – 86)	Stage IIIB: 8 Stage IV: 129	Former: 49 Current: 4 Never used: 84
			N/A	Crizo	138 (57M, 81F)	60 (29 – 89)	Stage IIIB: 12 Stage IV: 126	Former: 56 Current: 7 Never used: 75
Wachters FM, 2004 (Wachters et al., 2003)	Cisplatin, Epirubicin, Gemcitabine	Eligible patients were randomised to receive either cisplatin or epirubicin both with gemcitabine (1125 mg/m^2) administered during a 30-minute infusion on days 1 (before cisplatin or epirubicin) and 8. Cisplatin 80 mg/m^2 was administered intravenously over 3 hours after prehydration with 0.9% NaCl on day 2 of each 21-day treatment cycle. Epirubicin 100 mg/m^2 was	21-day cycle for ≤5 cycles or until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Gem-Cis	31 (25M, 6F)	61 (45 – 76)	Stage IIIA: 2 Stage IIIB: 7 Stage IV: 22	N/A
				Gem-Epi	38 (24M, 14F)	61 (43 – 76)	Stage IIIA: 5 Stage IIIB: 14 Stage IV: 19	N/A

		administered as an intravenous bolus injection within 5 minutes on day 1 of each 21-day cycle.						
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Shaw AT, 2013 (Shaw et al., 2013)	Crizotinib, Docetaxel, Pemetrexed	Crizotinib (PF-02341066) 250 mg (administered as two 100-mg tablets and one 50-mg tablet) orally twice daily continuously in 21-day cycles. Pemetrexed 500 mg/m^2 intravenous infusion over 10 minutes or docetaxel 75 mg/m^2 intravenous infusion over 1 hour on Day 1 of 21-day cycle.	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Criz	173 (75M, 98F)	50.3 (SD: 13.1)	N/A	Former: 59 Current: 5 Never used: 108
				Doc-Pem	174 (79M, 95F)	49.8 (SD: 13.0)	N/A	Former: 354 Current: 9 Never used: 111
Solomon BJ, 2014 (Solomon et al., 2014)	Crizotinib, Carboplatin, Cisplatin, Pemetrexed	Crizotinib 250 mg capsule, orally twice daily was administered in treatment cycle of 21 days. Chemotherapy were administered intravenously on Day 1 of each cycle. Pemetrexed 500 mg/m^2 IV infusion according to standard of care was administered over 10 min; either cisplatin 75 mg/m^2 IV infusion was administered approximately 30 min after the end of the pemetrexed infusion or carboplatin was administered at a dose calculated to produce an AUC of 5 or 6 mg*min/mL, approximately 30 min after end of pemetrexed infusion.	21-day cycle for ≤6 cycles	Criz	172 (68M, 104F)	50.94 (SD: 11.9)	N/A	Former: 56 Current: 10 Never used: 106
				Pem-Car/Cis	171 (63M, 108F)	52.89 (SD: 13.1)	N/A	Former: 54 Current: 5 Never used: 112
Bonomi P, 2000 (Bonomi et al., 2000)	Cisplain, Etoposide, Paclitaxel	Patients were randomised to one of three chemotherapy regiments: (1) etoposide/cisplatin (EC) regimen: cisplatin 75mg/m^2 intravenously (IV) over 1 hour on day 1 plus etopside	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Cis-Etop	193 (127M, 66F)	61.7	Stage IIIB: 29 Stage IV: 164	N/A
				Cis-250Pac	191 (120M, 71F)	60.8	Stage IIIB: 38 Stage IV: 153	N/A

		100mg/m^2 IV over 45 minutes on days 1, 2 and 3; (2) high dose paclitaxel (PCG) regimen: cisplatin 75 mg/m^2 IV over 1 hour on day 2 preceded by paclitaxel 250 mg/m^2 IV as a 24-hour infusion on day 1, plus filgrastim 5 mcg/kg subcutaneously beginning on day 3 and continuing until the granulocyte count was ≥ 10,000/μL; (3) low dose paclitaxel (PC) regimen: cisplatin 75 mg/m^2 IV over 1 hour on day 2 preceded by paclitaxel 135 mg/m^2 IV as a 24-hour infusion starting on day 1.		Cis-135Pac	190 (118M, 72F)	62.7	Stage IIIB: 44 Stage IV: 146	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Zatloukal P, 2004 (Zatloukal et al., 2004)	Cisplatin, Vinorelbine	Both arms received the same chemotherapy (CT) and radiotherapy (RT) treatment dosage, but received either concurrent treatment or sequential treatment. The chemotherapy regimen consisted of a combination of cisplatin 80mg/m^2 on day 1, and vinorelbine 25mg/m^2 on day 1, 8, and 15. The dose of vinorelbine was reduced to 12.5mg/m^2 during cycles 2 and 3.	28-day cycle for ≤4 cycles	Con	52 (33M, 19F)*	62 (42 – 75)	Stage IIIA: 8 Stage IIIB: 44	N/A
				Seq	50 (36M, 14F)*	61 (49 – 75)	Stage IIIA: 7 Stage IIIB: 43	N/A
					* Three patients were not evaluated for response because of consent withdrawal in one patient before treatment start and early death during first cycle due to pulmonary embolism in two patients.			
Zarogoulidis P, 2013 (P. Zarogoulidis et al., 2013)	Bevacizumab, Carboplatin, Docetaxel, Erlotinib	All patients initially received two cycles of chemotherapy with docetaxel 100 mg/m^2 and carboplatin at a dose of area under the concentration-time curve of 5.5 every 28 days.	Each group is slightly different	Car-Doc	61 (52M, 4F, Missing: 5)	65	Stage IIIB: 10 Stage IV: 51	Former: 39 Current: 14 Never used: 8
				CDE	52 (40M, 12F)	62.5	Stage IIIB: 13 Stage IV: 39	Former: 39 Current: 5 Never used: 8
				BCD	56 (45M, 11F)	62.5	Stage IIIB: 15 Stage IV: 41	Former: 45 Current: 2

		The first group (controls) received a further four cycles of docetaxel-carboplatin and continued with observation until disease progression. The second group (erlotinib) received four cycles of docetaxel-carboplatin plus erlotinib administered orally at 150 mg/dL per day beginning on the first day of the third cycle and continued with erlotinib monotherapy thereafter until progression. The third group (bevacizumab) received four cycles of docetaxel-carboplatin plus bevacizumab 7.5 mg/kg by intravenous infusion every 28 days and continued with bevacizumab every 21 days until disease progression. The fourth group (combination therapy) received four cycles of chemotherapy plus bevacizumab 7.5 mg/kg every 28 days and erlotinib 150 mg/dL, and continued with bevacizumab every 21 days and erlotinib until disease progression.						Never used: 9
				BCDE	60 (50M, 10F)	60	Stage IIIB: 10 Stage IV: 50	Former: 53 Current: 5 Never used: 2
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Koch A, 2011 (Koch et al., 2011)	Celecoxib, Chemotherapy (carboplatin/cisplatin / gemcitabine / vinorelbine)	Patients were randomised to celecoxib 400 mg b.i.d. or placebo. Celecoxib or matching placebo capsules were taken from the first day of chemotherapy for a maximum of 1 year.	Chemotherapy for 4 cycles, Celecoxib maximum 1 year	Celeco	158 (73M, 85F)	66 (38 – 85)	Stage IIIB: 37 Stage IV: 121	Former: 77 Current: 65 Never used: 16
				Placebo	158 (87M, 71F)	65 (37 – 85)	Stage IIIB: 38 Stage IV: 120	Former: 84 Current: 58

		Chemotherapy with four cycles of a combination of a platinum compound (carboplatin or cisplatin) and a third generation drug (primarily gemcitabine or vinorelbine) was recommended.						Never used: 16
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Bi N, 2019 (Bi et al., 2019)	Celecoxib, Cisplatin, Etoposide	The CCRT regimen was identical in both arms. Patients were randomly assigned to CCRT alone or CCRT with celecoxib. In the concurrent schedule, chemotherapy consisted of 50mg/m^2 of etoposide on days 1 to 5 and 50mg/m^2 of cisplatin on days 1 and 8, every 4 weeks (EP regimen) for 2 cycles. Celecoxib, at 200mg twice daily, was started 1 week before the initiation of radiotherapy and was continued without interruption until the end of radiotherapy.	28-day cycle for 2 cycles	CE	51 (39M, 12F)		Stage IIIA: 20 Stage IIIB: 31	Former/Current: 39 Never: 12
				CE-Cele	45 (36M, 9F)		Stage IIIA: 15 Stage IIIB: 30	Former/Current: 34 Never: 11
Herbst RS, 2011 (Herbst et al., 2011)	Bevacizumab, Erlotinib	Patients received placebo or bevacizumab administered at 15 mg/kg by intravenous infusion on the first day of 3-week cycles (±4 days). Erlotinib was taken orally at 150 mg per day, beginning on the first day of the first cycle.	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Erlo	317 (170M, 147F)	65 (S.D. = 10.3)	N/A	Former: 212 Current: 72 Never used: 33
				Erlo-Bev	319 (171M, 148F)	64.8 (S.D. = 10.4)	N/A	Former: 237 Current: 48 Never used: 34
Seto T, 2014 & Kato T, 2018 (Kato et al., 2018;	Bevacizumab, Erlotinib	Patients assigned to the erlotinib plus bevacizumab group received bevacizumab 15 mg/kg by intravenous infusion on day 1 of a 21-day cycle and erlotinib orally once	21-day cycle, until progressive disease, unacceptable	Erlo	77 (26M, 51F)	67.0 (60 – 73)	Stage IIIB: 0 Stage IV: 62 Postoperative recurrence: 15	Former: 6 Current: 26 Never used: 45
				Erlo-Bev	75 (30M, 45F)	67.0	Stage IIIB: 1	Former: 9

Seto et al., 2014)		daily at 150 mg/day, starting from day 1 of cycle 1. Patients in the erlotinib alone group received erlotinib orally once a day at 150 mg/day.	toxicity, death, or a desire to withdraw.			(59 – 73)	Stage IV: 60 Postoperative recurrence: 14	Current: 24 Never used: 42
				#Study 171 & 174 are duplicates, patients' characteristics from 171 and cardiotoxicity data from 174				
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
National Cancer Institute, 2019 (National Cancer Institute (NCI), 2019)	Carboplatin, Erlotinib, Paclitaxel	Arm A: Patients receive oral erlotinib once daily on days 1-21. Arm B: Apart from receiving erlotinib, patients also receive paclitaxel IV over 1-3 hours and carboplatin IV over 15-30 minutes on day 1.	21-day cycle for ≤6 cycles or until progressive disease, unacceptable toxicity, death, or a desire to withdraw. After completion of 6 courses of treatment, patients may continue to receive erlotinib alone as above.	Erlo	81 (32M, 49F)	58 (32 – 78)	N/A	Former/Current: 17 Never: 64
				Erlo-Car-Pac	100 (42M, 58F)	60 (34 – 81)	N/A	Former/Current: 21 Never: 79
Stathopoulos GP, 2004 (Stathopoulos et al., 2004)	Carboplatin, Paclitaxel, Vinorelbine	Arm A patients received carboplatin and paclitaxel. The doses were standard for carboplatin, 6 AUC (area under the curve), and for paclitaxel, 175 mg/m^2, repeated every 21 days. Paclitaxel was initially infused for 3 h followed by carboplatin at the 1-day outpatient clinic. Premedication included ondasentron 8mg IV, dexamethasone 8mg IV and diphenhydramine 50mg IV with modified timing 1 h before the beginning of treatment and repeated 4 and 8 h thereafter.	21-day cycle Pac-Car: for 6 cycles Pac-Vin: for 9 cycles	Pac-Car	185 (160M, 25F)	65 (30 – 83)	Stage IIIA: 15 Stage IIIB: 79 Stage IV: 91	N/A
				Pac-Vin	175 (152M, 23F)	65 (36 – 84)	Stage IIIA: 11 Stage IIIB: 81 Stage IV: 83	N/A

		Arm B patients received paclitaxel and vinorelbine at the following doses: paclitaxel 135 mg/m^2 and vinorelbine 25 mg/m^2 repeated every 2 weeks. The dose reduction of paclitaxel was counterbalanced by the earlier (once every 2 weeks instead of every 3 weeks) administration.						
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Valdivieso M, 1984 (Valdivieso et al., 1984)	Cisplatin, Cyclo-phosphamide, Doxorubicin, Ftorafur	All patients received 3 g/m^2 ftorafur on days 1 and 4, 500 mg/m^2 cyclophosphamide on day 1, and 15 mg/m^2 cisplatin IV on days 1 through 4. Patients receiving standard doxorubicin, received 60 mg/m^2 IV on day 1 every 3 weeks. Patients receiving weekly doxorubicin received 20 mg/m^2 IV weekly.	21-day cycle	Weekly Dox	52 (38M, 14F)	54 (36 – 78)	N/A	N/A
				Standard Dox	48 (41M, 7F)	59 (33 – 76)	N/A	N/A
Baggstrom MQ, 2017 (Baggstrom et al., 2017)	Chemotherapy, Sunitinib	Patients were registered 3 to 5 weeks after day 1 of cycle 4 of prior chemotherapy and then randomly assigned 1:1 in a double-blind fashion to receive maintenance sunitinib, 37.5 mg/d continuously, or placebo until disease progression or intolerable toxicity.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	CT-Placebo (prior use of bev – Y: 24; N: 80)	104 (60M, 44F)	67.0 (44.0 – 89.0) [Mean, S.D. = 66.3 ± 9.3]	Stage IIIB: 12 Stage IV: 92	Former: 67 Current: 27 Never used: 10
				CT-Sunitinib (prior use of bev – Y: 23; N: 83)	106 (57M, 49F)	65.0 (25.0 – 84.0) [Mean, S.D. = 63.6±10.0]	Stage IIIB: 14 Stage IV: 92	Former: 76 Current: 25 Never used: 5
Paz-Ares L, 2015 (Paz-Ares et al., 2015)	Best supportive care, Sorafenib	Patients were randomised 1:1 in a double-blind fashion to receive oral sorafenib (two tablets of 200 mg) plus BSC or matching placebo twice	Until progressive disease, unacceptable	BSC-Placebo	353 (209M, 144F)	62.0	N/A	Former/Current: 216 Never: 134 Missing: 3

		daily (morning and evening) plus BSC on a continuous basis.	toxicity, death, or a desire to withdraw.	BSC-Sorafenib	350 (186M, 164F)	59.0	N/A	Former/Current: 181 Never: 161 Missing: 8
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Novello S, 2014 (S Novello et al., 2014)	Carboplatin, Paclitaxel, Motesanib	Patients in Arm A received a median of four cycles of carboplatin and paclitaxel; Patients in Arm B received a median of six cycles of carboplatin and paclitaxel. The median daily doses of motesanib or placebo administered were 125 mg in both treatment arms.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Car-Pac-Placebo	178 (150M, 28F)	59.5 (32 – 81)	Stage IIIB: 25 Stage IV / recurrent: 153	Former/Current: 159 Never: 19
				Car-Pac-Mote	182 (145M, 37F)	62.0 (31 – 79)	Stage IIIB: 28 Stage IV / recurrent: 154	Former/Current: 153 Never: 29
Akamatsu H, 2018 (Akamatsu et al., 2018)	Carboplatin, Cisplatin, Pemetrexed, Osimertinib	In the osimertinib group, patients received oral osimertinib at a dose of 80 mg once daily. In the platinum-pemetrexed group, patients received pemetrexed (IV) 500 mg/m^2 plus either carboplatin at an area under the plasma concentration-time curve of 5, or cisplatin 75 mg/every 3 weeks for up to 6 cycles.	Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Osim	279 (107M, 172F)	62 (25 – 85)	N/A	Former: 76 Current: 14 Never used: 189
				Plat (car/cis)-Pem	140 (43M, 97F)	63 (20 – 90)	N/A	Former: 38 Current: 8 Never used: 94
Kosmidis PA, 2008 (Kosmidis et al., 2008)	Carboplatin, Paclitaxel, Gemcitabine	Eligible patients received either paclitaxel 200 mg/m^2 as a 3-h infusion on day 1 in combination with a 30-min infusion of gemcitabine 1 g/m^2 on days 1 and 8 (group A) or carboplatin at an AUC of 6 mg according to the Calvert formula, as a 1-h IV infusion, in combination with a 30-min infusion of gemcitabine 1 g/m^2 on days 1 and 8 (group B).	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Gem-Pac	225 (194M, 31F)	63 (42 – 82)	Stage IIIB: 30 Stage IV: 195	N/A
				Gem-Car	227 (184M, 43F)	63 (36 – 83)	Stage IIIB: 31 Stage IV: 196	N/A
					* Only 219 patients from each group were analysed, but cardiotoxicity data of 7 patients from Group A (Gem-Pac), and 9 patients from Group B (Gem-Car) were missing.			

Reference (Publication Year)	Drug Combination	Delivery / Schedule	Treatment Period	Dose	Number Randomised to Group (M/F)	Age, Median (Range)	NSCLC Stage	Smoker Status (Former/Current/Never)
Reinmuth N, 2019 (Reinmuth et al., 2019)	Bevacizumab, Carboplatin, Paclitaxel, PF-06439535	On treatment days when PF-06439535 or bevacizumab- was administered in combination with CT, the order of administration was paclitaxel, carboplatin, and PF-06439535 or bevacizumab. Paclitaxel was administered at an initial dose of 200 mg/m^2, carboplatin at an initial dose targeting an area under the concentration versus time curve of 6.0 mg/mL·min, and PF-06439535 or bevacizumab at an initial dose of 15 mg/kg.	21-day cycle, After CT was dis-continued, PF-06439535 or bev monotherapy could be administered until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Car-Pac-Bev	361 (230M, 131F)	61.0 (31 – 83)	Stage IIIB: 29 Stage IV: 282 Recurrent: 50	Former: 135 Current: 117 Never used: 109
				Car-Pac-PF06439535	358 (237M, 121F)	62.0 (25 – 87)	Stage IIIB: 48 Stage IV: 265 Recurrent: 45	Former: 135 Current: 117 Never used: 109
Blumenschein GR, 2010 (Blumenschein et al., 2010)	Carboplatin, Paclitaxel, Panitumumab, Motesanib	In arm A, patients received motesanib orally at escalating doses of 50 mg once daily, 125 mg once daily, or 75 mg twice daily starting on day 3 of cycle 1, and then from day 1 of each subsequent cycle. Paclitaxel was given concomitantly through a 3-h IV infusion at 200 mg/m^2 and carboplatin was given through a 30-min IV infusion at an area under the AUC of 6 mg/mL·min. Carboplatin/paclitaxel was administered once on day 1 of each 21-d cycle for up to six cycles. In arm B, patients received motesanib orally beginning on day 3 at escalating doses at 50 mg once daily, 125 mg once daily, or 75 mg twice daily plus panitumumab 9 mg/kg through IV infusion on day 1 of each 21-d cycle.	21-day cycle, for ≤6 cycles Patients received motesanib alone until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Mote(E)-CP	23 (16M, 7F)	64 (39 – 79)	Stage IIIB: 4 Stage IV: 19	Former: 16 Current: 3 Never used: 4
				Mote(E)-Pani	16 (10M, 6F)	58 (32 – 76)	Stage IIIB: 3 Stage IV: 13	Former: 9 Current: 3 Never used: 4
				Mote(125)-CP-Pani	6 (3M, 3F)	60 (56 – 64)	Stage IIIB: 1 Stage IV: 5	Former: 6 Current: 0 Never used: 0

		In arm C, patients received 125 mg once daily motesanib plus carboplatin/paclitaxel beginning on day 3 (dose and schedule as described in arm A) and panitumumab (9 mg/kg through IV infusion on day 1 of each 21-d cycle). Enrollment in arm C started after the 125 mg once daily dose had been established as safe and tolerable in treatment arms A and B. There was no dose escalation in arm C. Car/Pac treatment and panitumumab dosing followed the same rules as outlined for arms A and B, respectively.						
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Choy H, 2013 (Choy et al., 2013)	Carboplatin, Cisplatin, Pemetrexed	Arm A: pemetrexed 500 mg/m^2 (IV) administered on day 1 followed by carboplatin area under the curve five intravenously on day 1. Arm B: pemetrexed 500 mg/m^2 (IV) administered on day 1 followed by cisplatin 75 mg/m2 on day 1.	21-day cycle, for 3 cycles	Pem-Car	46 (30M, 16F)	62.8 (43.7 – 82.4)	Stage IIIA: 20 Stage IIIB: 26	N/A
				Pem-Cis	52 (31M, 21F)	64.3 (45.8 – 85.2)	Stage IIIA: 27 Stage IIIB: 25	N/A
William WN, 2007 (William et al., 2007)	Cisplatin, Docetaxel, Motexafin gadolinium	For all cohorts, docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were given on day 1 plus different doses of MGd for each cohort. Cohort 1, MGd 2.5 mg/kg on day 1 Cohort 2, MGd 5 mg/kg on day 1 Cohort 3, MGd 10 mg/kg on day 1 Cohort 4, MGd 7.5 mg/kg on days 1 and 2		2.5MGd	3	Only have overall data	Only have overall data	Only have overall data
				5MGd	6			
				10MGd	7			
				15MGd	5			

Reference (Publication Year)	Drug Combination	Delivery / Schedule	Treatment Period	Dose	Number Randomised to Group (M/F)	Age, Median (Range)	NSCLC Stage	Smoker Status (Former/Current/Never)
Chang AY, 1993 (Chang et al., 1993)	Merbarone, Piroxantrone, Taxol	Merbarone – 1000 mg/m^2 merbarone by continuous intravenous infusion through a central catheter daily for 5 days. Piroxantrone – 150 mg/m^2 piroxantrone by intravenous infusion over 1 hour. Taxol – 250 mg/m^2 taxol by a 24-hour intravenous infusion.	21-day cycle	Merba	35 (26M, 9F)	62 (42 – 80)	N/A	N/A
				Piro	44 (27M, 17F)	61 (31 – 85)	N/A	N/A
				Taxol	24 (17M, 7F)	61 (38 – 82)	N/A	N/A
Kubota K, 2017 (Kubota et al., 2017)	Carboplatin, Motesanib, Paclitaxel	Once-daily oral motesanib 125 mg or matching placebo; all patients also received paclitaxel 200 mg/m^2 IV and carboplatin area under the concentration-time curve 6 mg/mL·min IV on day 1 of each cycle.	21-day cycle, for ≤6 cycles	Car-Pac-Placebo	204 (147M, 57F)	64 (upper quartile: 58; lower quartile: 69)	Stage IV: 194 Recurrent: 10	Former: 108 Current: 32 Never used: 64
				Car-Pac-Mote	197 (141M, 56F)	65 (upper quartile: 59; lower quartile: 70)	Stage IV: 171 Recurrent: 26	Former: 131 Current: 17 Never used: 49
Zinner RG, 2015 (Zinner et al., 2015)	Bevacizumab, Carboplatin, Paclitaxel Pemetrexed	Planned chemotherapy doses were pemetrexed 500 mg/m^2; carboplatin, area under the curve = 6, (as of December 31, 2010, maximum possible dose of 900 mg), paclitaxel 200 mg/m^2; bevacizumab 15 mg/kg.	21-day cycle, after 4 cycles of induction therapy, maintenance continued until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Car-Pem	182 (105M, 77F)	65.8 (38.4 – 84.1)	Stage IV: 181 Missing: 1	Former/Current: 164 Never: 18
				Car-Bev-Pac	179 (104M, 75F)	65.4 (41.2 – 86.2)	Stage IV: 179	Former/Current: 172 Never: 7
Heigener DF, 2013	Chemotherapy, Sagopilone	Arm A: 3h infusion of 16 mg/m^2 sagopilone	21-day cycle, for 2 – 6 cycles	S-16,3h	44 (27M, 17F)	63	TNM Stage I: 2 Stage II: 0	N/A

(Heigener et al., 2013)		Arm B: 0.5h infusion of 22 mg/m^2 sagopilone Arm C: 3 h infusion of 22 mg/m^2 sagopilone					Stage III: 19 Stage IV: 23	
				S-22, 0.5h	41 (27M, 14F)	62	TNM Stage I: 1 Stage II: 3 Stage III: 13 Stage IV: 24	N/A
				S-22,3h	43 (29M, 14F)	62	TNM Stage I: 0 Stage II: 4 Stage III: 15 Stage IV: 24	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Wang XJ, 2018 (Jie Wang et al., 2018)	Cisplatin, Endostar, Pemetrexed	Patients in the control group were treated with pemetrexed 500 mg/m^2 IV day 1 and intracavitary cisplatin with a total dose of 75 mg/m^2, days 2, 5 and 8. Patients in the treatment group were treated with pemetrexed 500 mg/m^2 IV day 1, intracavitary cisplatin with a total dose of 75 mg/m^2, days 2, 5 and 8, and intracavitary endostar 45mg, days 1, 4 and 7.	21-day cycle, for 3 cycles	Cis-Pem	62 (47M, 15F)	No mean / median (38 – 76)	N/A	N/A
				Cis-Pem-Endostar	66 (49M, 17F)	No mean / median (36 – 75)	N/A	N/A
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019a)	Gefitinib, Pemetrexed	Gef: 250 mg gefitinib taken orally once daily (QD) Gef-Pem: 250 mg gefitinib taken orally once daily (QD) and 500 milligrams per square meter (mg/m²) pemetrexed taken intravenously (IV) once every 3 weeks concurrently with Gefitinib QD.	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Gef	65 (24M, 41F)	60.94 (S.D.: 9.45)	N/A	N/A
				Gef-Pem	126 (44M, 82F)	62.11 (S.D.: 9.36)		

Reference (Publication Year)	Drug Combination	Delivery / Schedule	Treatment Period	Dose	Number Randomised to Group (M/F)	Age, Median (Range)	NSCLC Stage	Smoker Status (Former/Current/Never)
Douillard JY, 2004 (Douillard, 2004)	BMS-275291, Carboplatin, Paclitaxel	BMS-275291 or placebo was initiated on the same day as paclitaxel/carboplatin and administered on an outpatient basis at a daily oral dosage of 1200 mg (two 600 mg tablets). Paclitaxel 200mg/m^2 was administered as a continuous in fusion over 3 h followed by carboplatin calculated using the Calvert formula for a target AUC of 6 mg/(ml min) and given intravenously as a 30 min infusion.	21-day cycle, for ≤8 cycles, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Car-Pac-Placebo	37 (26M, 11F)	59.5	Stage IIIB: 3 Stage IV: 34	N/A
				Car-Pac-BMS275291	38 (30M, 8F)	63.2	Stage IIIB: 4 Stage IV: 34	N/A
Butts CA, 2007 (Butts et al., 2007)	Carboplatin, Cisplatin, Cetuximab, Gemcitabine	Arm A: cetuximab 400mg/m^2 IV over 2 hours at week 1 followed by 250 mg/m^2 weekly (IV over 60 minutes), plus either gemcitabine 1,250 mg/m^2 days 1 and 8 and cisplatin 75 mg/m^2 day 1 every 3 weeks, or gemcitabine 1,000 mg/m^2 (days 1 and 8) and carboplatin area under the concentration-versus-time curve (AUC) of 5 on day 1 of each cycle. Arm B: platinum plus gemcitabine identical to arm A, but without cetuximab.	21-day cycle, for ≤6 cycles, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Car-Cis-Gem	66 (33M, 33F)	64 (35 – 84)	Stage IIIB: 8 Stage IV: 55 Recurrent: 3	Former/Current: 57 Never: 9
				Car-Cis-Gem-Cet	65 (25M, 40F)	66 (36 – 84)	Stage IIIB: 5 Stage IV: 55 Recurrent: 5	Former/Current: 55 Never: 10
Fukuda M, 2019 (Fukuda et al., 2019)	Bevacizumab, Chemotherapy, Pemetrexed	All patients received chemotherapy and with either (1) pemetrexed (500 mg/m^2; a 10-min intravenous infusion; every 21 days) or (2) pemetrexed plus bevacizumab (15 mg/kg; an intravenous infusion; every 21 days)	21-day cycle, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	CT-Pem	20 (12M, 8F)	77.5 (75 – 82)	Stage IIIB: 0 Stage IV: 15 Postoperative recurrence: 5	Former/Current: 12 Never: 8
				CT-Pem-Bev	20 (11M, 9F)	78.5 (75 – 83)	Stage IIIB: 1 Stage IV: 15	Former/Current: 10

							Postoperative recurrence: 4	Never: 10
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Passardi A, 2008 (Passardi et al., 2008)	Docetaxel, Gemcitabine	The experimental regimen (arm A), defined in the phase I trial as docetaxel 70 mg/m^2 on day 1 and gemcitabine 900 mg/m^2 on days 3–8, or the empirical regimen (arm B), consisting of gemcitabine 900 mg/m^2 on days 1 and 8, and docetaxel 70 mg/m^2 on day 8.	21-day cycle, for ≤8 cycles, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Gem3,8-Doc1	40 (33M, 7F)	63 (35 – 77)	N/A	N/A
				Gem1,8-Doc8	41 (32M, 9F)	63 (48 – 74)	N/A	N/A
Gatzemeier U, 2004 (Gatzemeier et al., 2004)	Cisplatin, Gemcitabine, Trastuzumab	All patients received gemcitabine 1250 mg/m^2 IV over 30 min on days 1 and 8 of a 21-day cycle in combination with cisplatin 75 mg/m^2 IV over 1 h on day 1 with mannitol diuresis. In the experimental arm, trastuzumab was administered before CT as a 4 mg/kg initial dose IV over 90 min on day 1, followed by 2 mg/kg IV over 30 min weekly. After completion of CT, Trastuzumab was administered alone.	21-day cycle, CT for ≤6 cycles, Trastuzumab until disease progression	Cis-Gem	50 (30M, 20F)	60 (35 – 76)	Stage IB: 0 Stage IIIB: 6 With effusion: 5 Stage IV: 39	N/A
				Cis-Gem-Tras	51 (33M, 18F)	57 (35 – 76)	Stage IB: 1 Stage IIIB: 9 With effusion: 3 Stage IV: 38	N/A
Park C, 2017 (Park et al., 2017)	Cisplatin, Docetaxel, Pemetrexed	Patients with chemotherapy-naive NSq-NSCLC were randomised into 2 groups: cisplatin 70 mg/m^2 combined with either docetaxel 60 mg/m^2 (Doc-Cis group) or pemetrexed 500 mg/m^2 (Pem-Cis group).	21-day cycle, for ≤4 cycles, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Cis-Doc	71 (50M, 21F)	63.6 (S.D. = 9.7)	Stage IIIB: 3 Stage IV: 68	Former/Current: 35 Never: 14 Missing: 22
				Cis-Pem	77 (53M, 24F)	63.0 (S.D. = 8.9)	Stage IIIB: 5 Stage IV: 72	Former/Current: Never: 37 Missing: 26
Movsas B, 2005		Paclitaxel 225 mg/m^2 was administered intravenously (IV; 3-	21-day cycle, for 2 cycles (CT)	Car-Pac	122 (79M, 43F)	<60: 51 60-64: 24	Stage IIA: 1 Stage IIB: 1	N/A

(Movsas et al., 2005)	Amifostine, Carboplatin, Paclitaxel	hour infusion) followed by carboplatin (AUC 6) on days 1 and 22. This was followed by concurrent weekly paclitaxel (50 mg/m^2 IV during 1 hour) and carboplatin (AUC 2) with hyperfractionated RT starting on day 43. In the AM arm, AM 500 mg IV during 5 minutes was administered before the afternoon treatment 4 days per week (Monday to Thursday).				64-69: 25 ≥70: 22	Stage IIIA: 59 Stage IIIB: 61	
				Car-Pac-Ami	120 (71M, 49F)	<60: 45 60 – 64: 32 64 – 69: 15 ≥70: 28	Stage IIA: 1 Stage IIB: 1 Stage IIIA: 61 Stage IIIB: 57	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Jänne P, 2014 (Jänne et al., 2014)	Cisplatin, Gemcitabine, LY293111	Patients were randomly assigned to receive (1) LY293111 200 mg twice daily, (2) LY293111 600 mg twice daily or (3) placebo, followed by gemcitabine (1250 mg/m^2; days 1 and 8), and cisplatin (75 mg/m^2, day 1), every 21 days.	21-day cycle, for ≤6 cycles, until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Cis-Gem-Placebo	61 (37M, 24F)	60.9 (27.8 – 76.6)	Stage IIIB: 7 Stage IV: 54	N/A
				Cis-Gem-200LY	70 (42M, 28F)	62.4 (36.7 – 81.2)	Stage IIIB: 14 Stage IV: 56	N/A
				Cis-Gem-600LY	64 (48M, 16F)	60.7 (28.5 – 87.8)	Stage IIIB: 9 Stage IV: 55	N/A
Groen HJ, 2011 (Groen et al., 2011)	Carboplatin, Celecoxib, Docetaxel	All patients received carboplatin area under the curve (AUC) of 6mg/mL/min intravenously and docetaxel 75 mg//m^2 both on day 1 of each 21-day cycle, repeated for five cycles. Patients were randomly assigned by telephone to receive celecoxib 400 mg orally twice per day or placebo. Celecoxib started on day 1 of the first chemotherapy cycle.	21-day cycle, for 5 cycles, celecoxib continued until progression of disease or a maximum of 3 years.	Car-Doc	280 (171M, 109F)	61 (33 – 84)	Stage IIIB: 44 Stage IV: 236	N/A
				Car-Doc-Celeco	281 (184M, 97F)	62 (40 – 84)	Stage IIIB: 49 Stage IV: 232	N/A
Currow D, 2017	Anamorelin, Placebo	Patients enrolled in ROMANA 1 or ROMANA 2 were randomised (2 : 1)	Until progressive disease,	Anamorelin	345 (262M, 83F)	62.0 (S.D. = 8.5)	Stage IIIA: 34 Stage IIIB: 66	N/A

(Currow et al., 2017)		to 12 weeks of daily oral anamorelin 100 mg or placebo. Patients enrolled in ROMANA 3 continued to receive treatment once daily for an additional 12 weeks.	unacceptable toxicity, death, or a desire to withdraw.				Stage IV: 244 Missing: 1	
			Until progressive disease, unacceptable toxicity, death, or a desire to withdraw.	Placebo	168 (125M, 43F)	62.2 (S.D. = 8.4)	Stage IIIA: 18 Stage IIIB: 35 Stage IV: 115 Missing: 0	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Langer CJ, 2017 (Langer et al., 2017)	Cisplatin, Pemetrexed, Placebo	All patients first entered the induction stage which they received 500 mg/m^2 pemetrexed IV and 75 mg/m^2 cisplatin IV, on Day 1 of each 21-day cycle for 4 cycles. Then they either received 500 mg/m^2 pemetrexed IV or placebo (normal saline) IV, plus best supportive care, as maintenance.	21-day cycle, for ≤ 4 cycles until progression of disease unacceptable toxicity, death, or a desire to withdraw.	Cis-Pem-Pem	Only summarised as overall 939 (577M, 363F)	Only summarised as overall 61.3 (24.4 – 83.0)	N/A	Only summarised as overall Former: 757 Never used: 175 Unknown: 7
				Cis-Pem-Pla			N/A	
Kotsakis A, 2015 (Kotsakis et al., 2015)	Bevacizumab, Cisplatin, Docetaxel, Gemcitabine, Vinorelbine	Arm A: 3 cycles of VCB (vinorelbine 60 mg/m^2 day 1 and 8, cisplatin 80 mg/m^2 on day 1 and bevacizumab 15 mg/kg on day 1), followed by 3 cycles of DGB (docetaxel 75 mg/m^2 on day 1, gemcitabine 1100 mg/m^2 on day 1 and 8 and bevacizumab 15 mg/kg on day 1) Arm B: 6 cycles of DCB (docetaxel 75 mg/m^2, cisplatin 80 mg/m^2 and bevacizumab 15 mg/kg all on day 1).	21-day cycle, for 6 cycles	VCB -> DGB	38 (29M, 9F)	60.0 (36 – 77)	Stage IIIB (with pleural effusion): 9 Stage IV: 29	Former: 12 Current: 18 Never used: 8
				DCB	39 (28M, 11F)	58.0 (39 – 75)	Stage IIIB (with pleural effusion): 6 Stage IV: 33	Former: 11 Current: 21 Never used: 7
Eli Lilly and Company, 2015 (Eli Lilly and	Carboplatin, Cetuximab, Taxane	TC Arm: Taxane was paclitaxel 225 mg/m^2 infused over 180 minutes on Day 1 and subsequently every 3 weeks or docetaxel 75 mg/m^2 infused over 60	21-day cycle, for ≤ 6 cycles until progression of disease	Tax-Car	338 (204M, 134F)	63.9 (S.D.: 10.3)	N/A	N/A
				Tax-Car-Cel	338 (192M, 146F)	64.0 (S.D.: 10.0)	N/A	N/A

Company, 2015)	(Paclitaxel/Docetaxel)	minutes on Day 1 and subsequently every 3 weeks. Carboplatin was infused over 30 minutes on Day 1 and subsequently every 3 weeks. TC-Cel Arm: Cetuximab was administered at an initial dose (Week 1) of 400 mg/m^2 IV infusion (infused over 120 minutes) and a weekly maintenance dose of 250 mg/m^2 IV infusion (infused over 60 minutes). Taxane and carboplatin were given as described above.	unacceptable toxicity, death, or a desire to withdraw.					
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
GSK, 2019 (GlaxoSmith Kline, 2019)	Carboplatin, Cisplatin, Docetaxel, GSK3052230, Paclitaxel, Pemetrexed	**Arm A: GSK3052230, paclitaxel/carboplatin** Subject received 5/10/20 mg/kg GSK3052230 as 30-minute intravenous (IV) infusion once a week (Day 1, Day 8, Day 15) of each 21-day cycle and 200 mg/m^2 paclitaxel (constant infusion for 3 hrs) and 900 mg carboplatin (constant infusion for 30 to 60 minutes) IV on Day 1 of each 21-day cycle. **Arm B: GSK3052230, docetaxel** Subject received 5/10/20 mg/kg GSK3052230 as 30-minute intravenous (IV) infusion once a week (Day 1, Day 8, Day 15) of each 21-day cycle and 75 mg/m^2 docetaxel as 1 hour IV infusion on Day 1 of each 21-day cycle.	21-day cycle, For Arm A, paclitaxel/carboplatin it was limited to 4 to 6 cycles, others until progression of disease unacceptable toxicity, death, or a desire to withdraw.	5GSK-Car-Pac	3 (3M)	71.0 (S.D.: 5.29)	N/A	N/A
				10GSK-Car-Pac	3 (3M)	71.7 (S.D.: 5.03)	N/A	N/A
				20GSK-Car-Pac	14 (13M, 1F)	65.0 (S.D.: 7.55)	N/A	N/A
				5GSK-Doc	3 (3M)	58.0 (S.D.: 8.19)	N/A	N/A
				10GSK-Doc	3 (3M)	67.0 (S.D.: 12.00)	N/A	N/A

		Arm C: GSK3052230, pemetrexed and cisplatin Subject received 10/15/20 mg/kg GSK3052230 as 30 minute IV infusion once a week (Day 1, Day 8, Day 15) of each 21 day cycle, 500 mg/m^2 pemetrexed IV infusion over 10 minutes on Day 1 of each 21 day cycle followed 30 minutes later by 75 mg/m^2 cisplatin infused over 2 hours. *GSK3052230 A clear to opalescent, colorless to pale yellow solution for IV infusion once weekly (Day 1, Day 8, Day 15) in each 21-day cycle with unit dose strengths/dose level of 5, 10, 15, and 20 mg/kg supplied in a sterile 25 mL glass vial.						
				20GSK-Doc	3 (2M, 1F)	65.7 (S.D.: 5.77)	N/A	N/A
				10GSK-Cis-Pem	3 (2M, 1F)	72.3 (S.D.: 7.51)	N/A	N/A
				15GSK-Cis-Pem	25 (17M, 8F)	57.1 (S.D.: 13.9)	N/A	N/A
				20GSK-Cis-Pem	8 (6M, 2F)	70.9 (S.D.: 6.06)	N/A	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Lara PN, 2016 (Lara et al., 2016)	Carboplatin, Erlotinib, Paclitaxel	Arm 1: 150 mg of erlotinib orally daily Arm 2: 150 mg of erlotinib orally daily on days 2 – 16 plus four cycles of carboplatin (area under the curve = 5 on day 1) and paclitaxel (200 mg/m^2 IV on day 1) followed by 150 mg of erlotinib orally.	21-day cycle, for 4 cycles, erlotinib continued until progression of disease unacceptable toxicity, death, or a desire to withdraw.	Erlo	33 (14M, 19F)	74.9 (45.2 – 84.9)	Stage IIIB: 1 Stage IV: 32	Former: 17 Current: 10 Never used: 6
				Erlo-Car-Pac	26 (10M, 16F)	70.8 (40.9 – 85.9)	Stage IIIB: 1 Stage IV: 25	Former: 11 Current: 9 Never used: 6
Wu YL, 2020 (Wu et al., 2020)	Carboplatin, Cisplatin, Gefitinib, Pemetrexed, Tepotinib,	Phase 1b: Tepotinib 300 or 500 mg and Gefitinib 250 mg tablets orally once daily over a 21-day cycle Phase 2 with MET + T790 Negative: (i) Tepotinib 500 mg and Gefitinib	21-day cycle, for 6 cycles (4 cycles if followed by pemetrexed as maintenance), erlotinib continued	1b-300Tep-Gef	6 (3M, 3F)	N/A	N/A	N/A
				1b-500Tep-Gef	12 (5M, 7F)	N/A	N/A	N/A
				2Neg-Tep-Gef	31 (11M, 20F)	N/A	N/A	N/A

		250 mg orally once daily over a 21-day cycle or (ii) 500 mg/m^2 pemetrexed IV over 10 minutes in combination with cisplatin (75 mg/m^2 as an intravenous infusion over 2 hours) or carboplatin IV at a dose of AUC 5 or AUC 6 on Day 1 Phase 2 with MET + T790 Positive: Tepotinib 500 mg and Gefitinib 250 mg tablets orally once daily over a 21-day cycle	until progression of disease unacceptable toxicity, death, or a desire to withdraw.	2Neg-Pem-Car/Cis	24 (12M, 12F)	N/A	N/A	N/A
				2Pos-Tep-Gef	15 (5M, 10F)	N/A	N/A	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Umsawasdi T, 1989) (Umsawasdi et al., 1989)	Cisplatin, Cyclophosphamide, Doxorubicin	Pateints were randomised to receive doxorubicin either as a 6-hour continuous infusion every 3 weeks or as a 30-minute infusion every week. All patients received doxorubicin on day 1 followed by cyclophosphamide and cisplatin on day 2.	21-day cycle	Weekly-Dox	51 (34M, 17F)	59 (41 – 77)	N/A	N/A
				Triweekly-Dox	51 (37M, 14F)	54 (33 – 78)	N/A	N/A
Cortot AB, 2020 (Cortot et al., 2020)	Bevacizumab, Docetaxel, Paclitaxel	Within 28 days after selection, patients were randomised to receive either 90 mg/m^2 of paclitaxel (D1, D8, D15) and 10 mg/kg of bevacizumab (D1, D15) every four weeks or 75 mg/m^2 of docetaxel every three weeks.	Until progression of disease unacceptable toxicity, death, or a desire to withdraw.	Bev-Pac	111 (78M, 33F) Prior exposure to Bev: 34	59.6 (18.6 – 81.8)	N/A	Former/Current: 102 Never: 9
				Doc	55 (42M, 13F) Prior exposure to Bev: 17	59.7 (35.8 – 78.9)	N/A	Former/Current: 46 Never: 9
AstraZeneca , 2021	Docetaxel, Selumetinib	Three placebo / 25mg selumetinib capsules were administered orally	21-day cycle, until progression of	Doc-Plac	256 (145M, 111F)	60.9 (S.D.: 8.08)	N/A	N/A

(AstraZeneca, 2021b)		uninterrupted twice daily in combination with docetaxel 75 mg/m^2 intravenously administered on day 1 of each 21-day cycle.	disease unacceptable toxicity, death, or a desire to withdraw.	Doc-Selu	254 (158M, 96F)	61.9 (S.D.: 8.48)	N/A	N/A
Reference (Publication Year)	**Drug Combination**	**Delivery / Schedule**	**Treatment Period**	**Dose**	**Number Randomised to Group (M/F)**	**Age, Median (Range)**	**NSCLC Stage**	**Smoker Status (Former/Current/Never)**
Johnson DH, 2004 (Johnson et al., 2004)	Bevacizumab, Carboplatin, Paclitaxel	Control: carboplatin ad paclitaxel alone. Paclitaxel (200mg/m^2 was administered over 3 hours every 3 weeks. Carboplatin dosing was based on the Calvert formula with a target area under the curve of 6 mg/mL X min. Low Dose: Carboplatin and paclitaxel plus low-dose (7.5 mg/kg) bevacizumab. High Dose: Carboplatin and paclitaxel plus high-dose (15 mg/kg) bevacizumab.	≤ six cycles of carboplatin and paclitaxel. Patients were followed for survival information every 2 months until death or loss to follow-up.	Car-Pac	32 (24M, 8F)	N/A	Stage IIIB: 6 Stage IV: 26	N/A
				Car-Pac-7.5Bev	32 (20M, 12F)	N/A	Stage IIIB: 2 Stage IV: 30	N/A
				Car-Pac-15Bev	35 (16M, 19F)	N/A	Stage IIIB: 7 Stage IV: 28	N/A
Eli Lilly and Company, 2022 (Eli Lilly and Company, 2022)	Cisplatin, Gemcitabine, Necitumumab	Cisplatin: 75 mg/m^2 IV on Day 1 of every 3-week cycle. Gemcitabine: 1250 mg/m^2 on Days 1 and 8 of every 3-week cycle. Necitumumab: 800 mg I.V. infusion on Days 1 and 8 of every 3-week cycle.	21-day cycle, cis/gem for ≤6 cycles, necitumumab until progression of disease unacceptable toxicity, death, or a desire to withdraw.	Cis-Gem	548 (458M, 90F)	62.0 (32 – 86)	Stage IIIB: 1 Stage IV: 546 Missing: 1	Former: 26 Current: 495 Never used: 27 Missing: 0
				Cis-Gem-Nec	545 (450M, 95F)	62.0 (32 – 84)	Stage IIIB: 1 Stage IV: 543 Missing: 1	Former: 18 Current: 500 Never used: 26 Missing: 1
Eli Lilly and Company, 2021 (Eli Lilly and	Cisplatin, Pemetrexed, Necitumumab	Cisplatin: 75 mg/m2 I.V. on Day 1 of every 3-week cycle.	21-day cycle, cis/pem for ≤6 cycles, necitumumab suntil	Cis-Pem	318 (210M, 108F)	60.0 (34 – 88)	Stage IIIB: 1 1 Stage IV: 307 Missing: 0	Former: 27 Current: 238 Never used: 53

Company, 2021)		Pemetrexed: 500 mg/m2 I.V. on Day 1 of every 3-week cycle. Necitumumab: 800 mg (absolute dose) on Days 1 and 8 of every 3-week cycle, administered as an I.V. infusion	progression of disease unacceptable toxicity, death, or a desire to withdraw.	Cis-Pem-Nec	315 (214M, 101F)	61.0 (26 – 84)	Stage IIIB: 9 Stage IV: 305 Missing: 1	Former: 26 Current: 238 Never used: 51
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019b)	Carboplatin, Paclitaxel, Necitumumab	Carboplatin AUC6 administered IV on Day 1 of every 3-week cycle. Paclitaxel 200 mg/m² administered IV on Day 1 of every 3-week cycle. Necitumumab 800 mg administered intravenously (IV) on Days 1 and 8 of every 3-week cycle.	21-day cycle, car/pac for ≤6 cycles, necitumumab until progression of disease unacceptable toxicity, death, or a desire to withdraw.	Car-Pac	57 (44M, 13F)	64.7 (S.D.: 8.27)	N/A	N/A
				Car-Pac-Nec	110 (87M, 23F)	65.5 (S.D.: 9.36)	N/A	N/A

3.4.2 Dose-related Cardiotoxicity

As shown in Table 3.3, twelve studies reported the use of different or escalating dosage of anticancer drugs.

According to the study by Mizugaki et al., cardiotoxicity, i.e. hypertension, was observed only in the 80 mg veliparib cohort, but neither in the 40 mg nor the 120 mg cohort, so it cannot be concluded that veliparib is associated with dose-related cardiotoxicity (Mizugaki et al., 2015).

In the study by Huang M, 2020, patients received oral apatinib combined with intravenous pemetrexed and intravenous carboplatin for 4 cycles. Pemetrexed (500 mg/m^2) and carboplatin (AUC=5) were given on day 1 of 21-day cycle. The incidence of hypertension of the cohort which received 500 mg of apatinib per day for 2 weeks and then 1 week off (16.7%) was lower than the other two cohorts which received 500 mg (66.7%) and 700 mg (66.7%) of apatinib per day for 3 weeks respectively (Huang et al., 2020). In the study by Huang M, 2020, patients received oral apatinib combined with intravenous pemetrexed and intravenous carboplatin for 4 cycles. Pemetrexed (500 mg/m^2) and carboplatin (AUC=5) were given on day 1 of 21-day cycle. The incidence of hypertension of the cohort which received 500 mg of apatinib per day for 2 weeks and then 1 week off (16.7%) was significantly lower than the other two cohorts which received 500 mg (66.7%) and 700 mg (66.7%) of apatinib per day for 3 weeks respectively.

For CV9201, no dose-limiting toxicity was found across the three cohorts (400 µg, 800 µg, 1600 µg) during the Phase I trial, so 1600 µg was chosen to be used for the Phase II trial. With a larger sample size (n=37), it was reported that one patient suffered from atrial tachycardia, however this adverse event was considered unrelated to the treatment by the clinicians of this trial (Sebastian et al., 2019).

Although reported incidence of cardiotoxicity in Arm A (standard infusion duration 50 mg/min) and Arm B (low infusion duration 10 mg/min) were 28.5% and 18.1% respectively in the study by Cappuzzo et al., it was believed that only one event of cardiac stroke in Arm B was associated with gemcitabine (Cappuzzo et al., 2006).

It was reported in Martoni et al., that 1 of the 3 patients in the cohort who initially received 165 mg/m^2 dose and later continued the treatment at the reduced dose of 150 mg/m^2, suffered from severe leukopenia, hypotension and fever after the third course. The patient later died 8 days after the epirubicin dose, which was believed to be caused by septic shock (Martoni et al., 1991). Besides, treatments were discontinued for 4 patients out of the total 24 patients as their

LVEF values dropped by 14%, 20%, 25% and 31% at the cumulative doses of 240 mg/m^2 (120Epi), 560 mg/m^2 (120Epi), 300 mg/m^2 (150Epi) and 516 mg/m^2 (150Epi) respectively. Despite the drop of LVEF values, no patients experienced any clinical signs of cardiotoxicity either at that time or subsequently. Also, no systematic pattern was observed in decrease of LVEF values across cohorts of different dosage and accumulated dosage, so it cannot be concluded that whether certain single and/or accumulated dosage of epirubicin will possibly cause a decrease in LVEF values (Martoni et al., 1991).

In Bonomi P, et al, fatal cardiac events were observed in 0.5% (Cis-Etop), 0.5% (Cis-Pac-250) and 2% (Cis-Pac-135) patients respectively. The frequency of cardiotoxicity was significantly higher when using higher dose (250 mg/m^2) of paclitaxel (P = 0.026) whereas that of lower dose (135 mg/m^2) of paclitaxel was insignificant (P = 0.143). Grade 5 cardiac events were also observed in 6 patients, including 3 sudden deaths, 2 myocardial infarction and 1 hypotension with acute pericarditis. However, this data needs to be considered carefully as four of the above-mentioned patients had a history of cardiovascular disease – two patients suffered from coronary artery disease, one patient had hypertension and the remaining was previously treated for cardiac arrhythmia (Bonomi et al., 2000).

A study published by Valdivieso et al. in 1984 demonstrated that the administration of weekly 20 mg/m^2 of doxorubicin was associated with a lower incidence of cardiotoxicity than that of the standard regimen (every three weeks at 60 mg/m^2 of doxorubicin) (Valdivieso et al., 1984). Cardiotoxicity were determined by an objective grading system of myocardial damage by endomyocardial biopsy. This study's results aligned with previous studies which also suggested that the weekly treatment schedule was less cardiotoxic (Weiss et al., 1976; Weiss and Manthel, 1977). Due to the reduced risk of cardiotoxicity in weekly schedule of doxorubicin, it was suggested that the cardiotoxicity of doxorubicin is associated with its peak plasma levels (Valdivieso et al., 1984).

Dose-limiting cardiotoxicities were observed in the 10 mg/kg (day 1 only) and 7.5 mg/kg (day 1 and/or day 2) motexafin gadolinium cohorts in William Jr. et al. Four patients suffered from hypertension and two patients suffered from myocardial ischemia within the first 24 hours administration of motexafin gadolinium (William et al., 2007). For the two patients who suffered from myocardial ischaemia – one experienced chest pain during the infusion of cycle 2 docetaxel, while the other patient experienced dyspnea 5 hours after completion of chemotherapy. Cardiac enzyme elevations were observed in both patients; T-wave inversion

on the electrocardiogram and non-specific ST segment alterations in the electrocardiogram was observed in respective patient (William et al., 2007).

In Heigener DF et al, one patient, who was treated with 22 mg/m^2 sagopilone at 0.5-hour infusion every 3 weeks, suffered from cardiac failure. However, it is considered that this was not a dose-limiting factor and also non-related to the drug as this is a single case and the cause of death for other cases were also miscellaneous events (Heigener et al., 2013).

In Jänne. et al, it was reported that there was a treatment-related death caused by cardiorespiratory arrest, which was treated with 200 mg LY293111 with gemcitabine and cisplatin. However, no treatment-related cardiotoxicity was reported in the 600 mg LY293111 cohort (Jänne et al., 2014).

In a non-randomised, 9-arm, open label Phase IB clinical trial which evaluated anticancer activity of GSK3052230, three different combinations of drugs were used – (i) GSK3052230 with carboplatin and paclitaxel, (ii) GSK3052230 with docetaxel and (iii) GSK3052230 with cisplatin and pemetrexed. For each combination, there were three arms which consists of different dosage of GSK3052230, i.e. 5mg/kg, 10 mg/kg and 20 mg/kg of GSK3052230 (GlaxoSmithKline, 2019). Counts of cardiotoxicity reported for each individual arm are shown in table 2. As there was no systematic pattern of cardiotoxicity across arms, so it cannot be concluded that if there was dose-related cardiotoxicity associated with GSK3052230 (GlaxoSmithKline, 2019).

In a clinical trial conducted by Johnson. et al, carboplatin and paclitaxel were used as a control arm, and 2 arms consists of different dosages of bevacizumab with carboplatin and paclitaxel were investigated. It was reported that higher dosage (15mg/kg) of bevacizumab experienced a higher incidences of cardiotoxicity than that of 7.5 mg/kg of bevacizumab (Johnson et al., 2004).

Table 3.3: Types of cardiotoxicities and their corresponding number of frequencies reported per publication.

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia						Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
			Arrhythmia (general)	Atrial/Supra-ventricular Arrhythmia		Ventricular Arrhythmia													
				Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation											
Mizugaki H, 2015 (Mizugaki et al., 2015)	Carboplatin, Paclitaxel, Veliparib	V-40mg										0							
		V-80mg										2							
		V-120mg										0							
Huang M, 2020 (Huang et al., 2020)	Apatinib, Carboplatin, Pemetrexed	A-750mg										2							
		A-500mg										2							
		A-500mg 2/1 (500 mg/day 2 weeks on 1 week off)										1							
Sebastian M, 2019 (Sebastian et al., 2019)	CV9201	CI - 400µg					0												
		CII - 800µg					0												
		CIII - 1600µg					0												
		Phase IIA - 1600µg					1												
Novello S, 2014 (S. Novello et al., 2014)	Cisplatin, Iniparib, Gemcitabine	GC										9							
		GCI										12							
Cappuzzo F, 2006 (Cappuzzo et al., 2006)	Chemotherapy Gemcitabine	Standard 50mg/min									16								
		Low 10mg/min									11								
Srinivasa GY, 2020 (Srinivasa et al., 2020)	Carboplatin, Cisplatin, Etoposide, Paclitaxel	Cis-Etop									0								
		Car-Pac									0								

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Yoshioka H, 2017 (Yoshioka et al., 2017)	Amrubicin, Docetaxel	Amrubicin		1	1											2	1		Ventricular extrasystole: 2 Cardiac tamponade: 1
		Docetaxel		0	0											0	0		
Johnson BE, 2013 (Johnson et al., 2013)	Bevacizumab, Erlotinib (CT prior to trial)	Bev-Plac									31	85							
		Bev-Erlo									29	88							
Gridelli C, 2001 (Gridelli et al., 2001)	Gemcitabine, Vinorelbine	Gem									0								
		Gem-Vin									6								
Martoni A, 1991 (Martoni et al., 1991)	Epirubicin	120Epi																	LVEF value decrease
		135Epi																	
		150Epi																	
		165Epi											1						
Wu Y, 2018 (Boehringer Ingelheim, 2018a; Sequist et al., 2013; Wu et al., 2018)	Afatinib, Cisplatin, Pemetrexed	Afatinib			0							14	1		0		1	1	Mitral valve incompetence: 1
		Pemetrexed/Cisplatin Chemotherapy			1							14	0		1		0	2	
Boehringer Ingelheim, 2018 (Boehringer Ingelheim, 2018b)	Afatinib, Cisplatin, Gemcitabine	Afatinib								0								0	
		Cisplatin, Gemcitabine Chemotherapy								1								1	

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Boehringer Ingelheim, 2020 (Boehringer Ingelheim, 2020)	Afatinib, Gefitinib	Afatinib		0								0			2		1		Acute coronary syndrome: 1 Angina pectoris: 1 Coronary heart disease: 1
		Gefitinib		1								1			0		3		Coronary heart disease: 1 Coronary artery occlusion: 1
Hida T, 2017 (Hida et al., 2017)	Alectinib, Crizotinib	Alectinib				1													
		Crizotinib				6													
Berghmans T, 2013 (Berghmans et al., 2013)	Cisplatin, Docetaxel, Gemcitabine, Ifosfamide	IG									10								
		GIP									8								
		DP									20								
Yang JJ, 2014 & GSK, 2014 ("EudraCT Number 2011-000634-11 - Clinical trial results - EU Clinical Trials Register," n.d.; GlaxoSmithKline, 2014)	Docetaxel, GSK1120212 (Trametinib)	Doc										1							
		Tra										13							
		HDEpi-Cis					3												>15% LVEF decrease: 9

Martoni A, 1999 (Martoni et al., 1999)	Epirubicin, Cisplatinum, Vinorelbine	Vin-Cis					0												>15% LVEF decrease: 3
Reference (Publication Year)	**Drug Combination**	**Dose Escalation Study**	**Arrhythmia**	**Atrial Fibrillation**	**Atrial Flutter**	**Bradycardia**	**Tachycardia**	**QT Prolongation**	**Cardiac Arrest**	**Cardiac Failure**	**Cardiotoxicity (Grade 1 – 4)**	**Hypertension**	**Hypotension**	**Ischaemia**	**Myocardial Infarction**	**Palpitations**	**Pericardial Effusion**	**Thromboembolic Event (both arterial / venous)**	**Other cardiovascular event**
Reck M, 2015 (Reck et al., 2015)	Docetaxel, Nintedanib	Doc-Nin										23						22	
		Doc-Plac										6						19	
Saito K, 2003 (Saito et al., 2003)	Carboplatin, Docetaxel, Paclitaxel	Car-Doc									4								
		Car-Pac									2								
Barlesi F, 2018 (Barlesi et al., 2018)	Avelumab, Docetaxel	Avelumab								1									Person with acute cardiac failure also suffered from autoimmune myocarditis
		Docetaxel								0									Cardiovascular insufficiency: 1
Camidge DR, 2018 (Camidge et al., 2018)	Brigatinib, Crizotinib	Brigatinib,				7						31						0	
		Crizotinib				17						10						8	
Wachters FM, 2004 (Wachters et al., 2004)	Cisplatin, Epirubicin, Gemcitabine	Gem-Cis									7				0				
		Gem-Epi									21				1				
Shaw AT, 2013 (Shaw et al., 2013)	Crizotinib, Docetaxel, Pemetrexed	Criz	1			9	0		1					1			1		Cardiac tamponade: 1 Coronary artery disease: 1 Syncope: 1
		Doc-Pem	0			0	1		0					0			2		Cardiac tamponade: 1

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Solomon BJ, 2014 (Solomon et al., 2014)	Crizotinib, Carboplatin, Cisplatin, Pemetrexed	Criz		1		33			0					0			0		Atrioventricular block: 1 Cardiac tamponade: 2
		Pem-Car/Cis		1		1			1					1			1		Pericarditis: 1 Syncope: 2
Bonomi P, 2000 (Bonomi et al., 2000)	Cisplain, Etoposide, Paclitaxel	Cis-Etop																	Fatal cardiac events: 1
		Cis-250Pac																	Fatal cardiac events: 1
		Cis-135Pac																	Fatal cardiac events: 4
		*The six fatal Grade 5 cardiac events listed above were summarised overall instead of by treatment group - sudden death in 3 patients, myocardial infarction in 2 patients, and hypotension with acute pericarditis in 1 patient.																	
Zatloukal P, 2004 (Zatloukal et al., 2004)	Cisplatin, Vinorelbine	Con									1								
		Seq									0								
Zarogoulidis P, 2013 (P. Zarogoulidis et al., 2013)	Bevacizumab, Carboplatin, Docetaxel, Erlotinib	Car-Doc									2								
		Car-Doc-Erlo																	
		Bev-Car-Doc										3							
		Bev-Car-Doc-Erlo										2							
Koch A, 2011 (Koch et al., 2011)	Celecoxib, Chemotherapy (carboplatin/cisplatin/gemcitabine/vinorelbine)	Celecoxib												2				17	Cerebrovascular ischaemia: 4
		Placebo							;					1				12	Cerebrovascular ischaemia: 1
Bi N, 2019 (Bi et al., 2019)	Celecoxib, Cisplatin, Etoposide	CE									5								
		CE-Cele									0								

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Herbst RS, 2011 (Herbst et al., 2011)	Bevacizumab, Erlotinib	Erlo										4						1	
		Erlo-Bev										15						12	
Seto T, 2014 & Kato T, 2018 (Kato et al., 2018; Seto et al., 2014)	Bevacizumab, Erlotinib	Erlo									2	11						3	
		Erlo-Bev								1		58						3	
National Cancer Institute, 2019 (National Cancer Institute (NCI), 2019)	Carboplatin, Erlotinib Paclitaxel	Erlo	1	1		0	1				1	8	0	0		3	0	3	
		Erlo-Car-Pac	1	0		1	4				0	9	6	1		2	1	12	
Stathopoulos GP, 2004 (Stathopoulos et al., 2004)	Carboplatin, Paclitaxel, Vinorelbine	Pac-Car									3								
		Pac-Vin									6								
Valdivieso M, 1984 (Valdivieso et al., 1984)	Cisplatin, Cyclo-phosphamide, Doxorubicin, Ftorafur	Weekly-Dox																	
		Standard-Dox																	
		* By an objective grading system of myocardial damage by endomyocardial biopsy, it was suggested that the weekly administration of doxorubicin was associated with lower cardiac toxicity than that of the standard/tri-weekly administration of doxorubicin.																	
Baggstrom MQ, 2017 (Baggstrom et al., 2017)	Chemotherapy Sunitinib	CT-Placebo										9						1	
		CT- Sunitinib										27						0	
Paz-Ares L, 2015 (Paz-Ares et al., 2015)	Best supportive care, Sorafenib	BSC-Placebo										16							
		BSC-Sorafenib										68							

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Novello S, 2014 (S Novello et al., 2014)	Carboplatin, Paclitaxel, Motesanib	Car-Pac-Placebo										15	2						
		Car-Pac-Mote										47	3						
Akamatsu H, 2018 (Akamatsu et al., 2018)	Carboplatin, Cisplatin, Pemetrexed, Osimertinib	Osim						7		9									
		Plat (car/cis)-Pem						1		0									
Kosmidis PA, 2008 (Kosmidis et al., 2008)	Carboplatin, Paclitaxel, Gemcitabine	Gem-Pac									2								
		Gem-Car									1								
Reinmuth N, 2019 (Reinmuth et al., 2019)	Bevacizumab, Carboplatin, Paclitaxel, PF-06439535	Car-Pac-Bev								3		32						10	Cardiac disorders: 12
		Car-Pac-PF06439535								1		34						14	Cardiac disorders: 10
Blumenschein GR, 2010 (Blumenschein et al., 2010)	Carboplatin, Paclitaxel, Panitumumab, Motesanib	Mote(E)-CP		1			0					10							Conduction disorder: 1
		Mote(E)-Pani		1			1					6							
		Mote(125)-CP-Pani		0			0					1							
Choy H, 2013 (Choy et al., 2013)	Carboplatin, Cisplatin, Pemetrexed	Pem-Car											2						
		Pem-Cis											4						
William WN, 2007 (William et al., 2007)	Cisplatin, Docetaxel, Motexafin gadolinium	MGd-2.5										0			0				
		MGd-5										1			1				
		MGd-10										1			1				
		MGd-15										2			0				
Chang AY, 1993 (Chang et al., 1993)	Merbarone, Piroxantrone, Taxol	Merba									3								
		Piro									1								
		Taxol									4								

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Kubota K, 2017 (Kubota et al., 2017)	Carboplatin, Motesanib, Paclitaxel	Car-Pac-Placebo										29							
		Car-Pac-Mote										86							
Zinner RG, 2015 (Zinner et al., 2015)	Bevacizumab, Carboplatin, Paclitaxel Pemetrexed	Car-Pem										0						0	
		Car-Bev-Pac										4			1			4	
Heigener DF, 2013 (Heigener et al., 2013)	Chemotherapy Sagopilone	S-16,3h								0									
		S-22, 0.5h								1									
		S-22,3h								0									
Wang XJ, 2018 (Jie Wang et al., 2018)	Cisplatin, Endostar, Pemetrexed	Cis-Pem															40		
		Cis-Pem-Endostar															54		
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019a)	Gefitinib, Pemetrexed	Gef		0						1		4	0			1		0	Angine pectoris: 0
		Gef-Pem		1						0		8	1			1		1	Angina pectoris: 1
Douillard JY, 2004 (Douillard, 2004)	BMS-275291, Carboplatin, Paclitaxel	Car-Pac-Placebo	0			0	1							2					
		Car-Pac-BMS275291	1			1	0							1					
Butts CA, 2007 (Butts et al., 2007)	Carboplatin, Cisplatin, Cetuximab, Gemcitabine	Car-Cis-Gem											2						
		Car-Cis-Gem-Cet											2						
Fukuda M, 2019 (Fukuda et al., 2019)	Bevacizumab, Pemetrexed	CT-Pem										0						0	
		CT-Pem-Bev										0						0	

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Passardi A, 2008 (Passardi et al., 2008)	Docetaxel, Gemcitabine	Gem3,8-Doc1									0								
		Gem1,8-Doc8									1								
Gatzemeier U, 2004 (Gatzemeier et al., 2004)	Cisplatin, Gemcitabine, Trastuzumab	Cis-Gem																	LVEF decrease >15%: 0 LVEF <30%: 0
		Cis-Gem-Tras																	LVEF decrease >15%: 8 LVEF <30%: 0
Park C, 2017 (Park et al., 2017)	Cisplatin, Docetaxel, Pemetrexed	Cis-Doc																1	
		Cis-Pem																2	
Movsas B, 2005 (Movsas et al., 2005)	Amifostine, Carboplatin, Paclitaxel	Car-Pac									11								
		Car-Pac-Ami									30								
Jänne P, 2014 (Jänne et al., 2014)	Cisplatin, Gemcitabine, LY293111	Cis-Gem-Placebo																	
		Cis-Gem-200LY																	Cardiorespiratory arrest: 1
		Cis-Gem-600LY																	
Groen HJ, 2011 (Groen et al., 2011)	Carboplatin, Celecoxib, Docetaxel	Car-Doc		0								0					1	0	Pulmonary embolism: 2
		Car-Doc-Celeco		1								1					0	1	Pulmonary embolism: 3
Currow D, 2017 (Currow et al., 2017)	Anamorelin, Placebo	Anamorelin									13								Electrocardiogram:4 Ischemic Heart Disease: 4
		Placebo									4								Electrocardiogram:7 Ischemic Heart Disease: 0

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
Langer CJ, 2017 (Langer et al., 2017)	Cisplatin, Pemetrexed, Placebo	Induction: Cis-Pem	1	1			3		3	1		2		3	3	1	2	2	Acute coronary syndrome: 1 Cardiac tamponade: 1 Cardio-respiratory arrest: 3 Diastolic dysfunction: 1 Pericarditis: 1
		Maintenance: Pem	1	0			0		0	0		0		0	1	0	0	0	Pericarditis: 2 Ventricular fibrillation: 1
		Maintenance: Place	0	0			0		1	0		0		0	0	0	1	0	
Kotsakis A, 2015 (Kotsakis et al., 2015)	Bevacizumab, Cisplatin, Docetaxel, Gemcitabine, Vinorelbine	VCB -> DGB										0							
		DCB										1							
Eli Lilly and Company, 2015 (Eli Lilly and Company, 2015)	Carboplatin, Cetuximab, Taxane (Paclitaxel/Docetaxel)	Tax-Car	1	1	1		7		3				20	0	2		1	5	
		Tax-Car-Cel	1	6	0		27		3				39	1	5		4	3	Cardio-respiratory arrest: 2
GSK, 2019 (GlaxoSmithKline, 2019)	Carboplatin, Cisplatin, Docetaxel, GSK3052230, Paclitaxel, Pemetrexed	5GSK-Car-Pac	0	0			0					0	0		0	0	0	0	
		10GSK-Car-Pac	0	0			0					0	0		0	0	0	0	
		20GSK-Car-Pac	0	0			1					2	0		0	0	0	1	Cardiomegaly: 1
		5GSK-Doc	0	0			1					0	0		1	0	1	0	Acute Coronary Syndrome: 1 Angina Pectoris: 1

		10GSK-Doc	0	0			0					0	1		0	0	0	0	
		20GSK-Doc	1	0			0					0	0		0	0	0	0	
		10GSK-Cis-Pem	0	1			0					0	0		0	1	0	0	
		15GSK-Cis-Pem	0	0			0					5	1		0	1	0	0	Conduction disorder: 1
		20GSK-Cis-Pem	0	0			1					2	1		0	0	0	0	Conduction disorder: 1 Left ventricular hypertrophy: 1 Ventricular extrasystoles: 1
Reference (Publication Year)	**Drug Combination**	**Dose Escalation Study**	**Arrhythmia**	**Atrial Fibrillation**	**Atrial Flutter**	**Bradycardia**	**Tachycardia**	**QT Prolongation**	**Cardiac Arrest**	**Cardiac Failure**	**Cardiotoxicity (Grade 1 – 4)**	**Hypertension**	**Hypotension**	**Ischaemia**	**Myocardial Infarction**	**Palpitations**	**Pericardial Effusion**	**Thromboembolic Event (both arterial / venous)**	**Other cardiovascular event**
Lara PN, 2016 (Lara et al., 2016)	Carboplatin, Erlotinib, Paclitaxel	Erlo									3								
		Erlo-Car-Pac									3								
Wu YL, 2020 (Wu et al., 2020)	Carboplatin, Cisplatin, Gefitinib, Pemetrexed, Tepotinib,	1b-300Tep-Gef	0	0													0		
		1b-500Tep-Gef	1	1													1		Cardiac discomfort: 1
		2Neg-Tep-Gef	0	0													0		
		2Neg-Pem-Car/Cis	0	0													0		
		2Pos-Tep-Gef	0	0													0		Supraventricular extrasystoles: 1
Umsawasdi T, 1989) (Umsawasdi et al., 1989)	Cisplatin, Cyclophosphamide, Doxorubicin	Weekly-Dox																	
		Triweekly-Dox																	
		* Endomyocardial biopsies were done when a total cumulative doxorubicin dose of 300 or 480 mg/m^2 was reached. Results showed an increase in cardiotoxicity with an increase dosage of doxorubicin, and that the weekly administration of doxorubicin was less toxic than that of the standard/tri-weekly administration of doxorubicin.																	
Cortot AB, 2020 (Cortot et al., 2020)	Bevacizumab, Docetaxel, Paclitaxel	Bev-Pac										22							Ischaemic stroke leading to death: 1
		Doc										0							

Reference (Publication Year)	Drug Combination	Dose Escalation Study	Arrhythmia	Atrial Fibrillation	Atrial Flutter	Bradycardia	Tachycardia	QT Prolongation	Cardiac Arrest	Cardiac Failure	Cardiotoxicity (Grade 1 – 4)	Hypertension	Hypotension	Ischaemia	Myocardial Infarction	Palpitations	Pericardial Effusion	Thromboembolic Event (both arterial / venous)	Other cardiovascular event
AstraZeneca, 2021 (AstraZeneca, 2021b)	Docetaxel, Selumetinib	Doc-Plac		4		0	10			2		3	8			0	5	4	Cardiovascular insufficiency: 1 Cardiomegaly: 1
		Doc-Selu		5		2	6			8 (1 is congestive)		4	15			1	0	7	Bundle branch block left: 1 Coronary artery dissection: 1 Diastolic dysfunction: 1 Left Ventricular Dysfunction:1 Mitral valve imcopetence: 1 Pericarditis constrictive: 1
Johnson DH, 2004 (Johnson et al., 2004)	Bevacizumab, Carboplatin, Paclitaxel	Car-Pac										1						3	
		Car-Pac-7.5Bev										5						4	
		Car-Pac-15Bev										6						6	
Eli Lilly and Company, 2022 (Eli Lilly and Company, 2022)	Cisplatin, Gemcitabine, Necitumumab	Cis-Gem		4	1		0		0	4*			0	1	3		1	4	Acute Coronary Syndrome: 1 Cardio-respiratory arrest: 1 Pericarditis: 1 * including 1 acute, 1 congestive
		Cis-Gem-Nec		3	0		2		2	1*			2	0	4		0	9	Cardiac Tamponade: 1

																			Cardio-respiratory arrest: 3 Coronary artery disease: 1 * including 1 congestive
Reference (Publication Year)	**Drug Combination**	**Dose Escalation Study**	**Arrhythmia**	**Atrial Fibrillation**	**Atrial Flutter**	**Bradycardia**	**Tachycardia**	**QT Prolongation**	**Cardiac Arrest**	**Cardiac Failure**	**Cardiotoxicity (Grade 1 – 4)**	**Hypertension**	**Hypotension**	**Ischaemia**	**Myocardial Infarction**	**Palpitations**	**Pericardial Effusion**	**Thromboembolic Event (both arterial / venous)**	**Other cardiovascular event**
Eli Lilly and Company, 2021 (Eli Lilly and Company, 2021)	Cisplatin, Pemetrexed, Necitumumab	Cis-Pem	0	2	0		1			0		30			1		2	2	Angina pectoris: 1 Cardiomyopathy: 1
		Cis-Pem-Nec	1	2	2		1			2		17			2		3	6	Cardiac tamponade: 2 Cardio-respiratory arrest: 1 Cardiopulmonary failure: 1
Eli Lilly and Company, 2019 (Eli Lilly and Company, 2019b)	Carboplatin, Paclitaxel, Necitumumab	Car-Pac		4					0	0			7		0			1	
		Car-Pac-Nec		4					1	1*			13		2			1	* including 1 congestive

3.4.3 Risk of Bias Assessment

Risk of bias assessment is important as it can provide insight of possible bias for each study, thus aiding the transparency of results and findings in this systematic review. Table 3.4 includes a summary of the risk of bias assessment of each individual study. Green (+) indicates low risk; red (–) indicates high risk and yellow (?) means unclear as there is not enough information to make a clear judgement.

Table 3.4: A summary of the risk of bias assessment of all eligible studies.

Reference (Publication Year)	Random sequence generation (Selection Bias)	Allocation concealment (Selection Bias)	Blinding of participants and personnel (Performance Bias)	Blinding of outcome assessment (Detection Bias)	Incomplete outcome data (Attrition Bias)	Selective reporting (Reporting Bias)	Other bias
9 (Mizugaki H, 2015) (Mizugaki et al., 2015)	?	–	–	–	+	+	?
20 (Huang M, 2020) (Huang et al., 2020)	?	?	?	?	+	+	?
30 (Sebastian M, 2019) (Sebastian et al., 2019)	?	?	?	?	+	+	?
34 (Novello S, 2014) (S. Novello et al., 2014)	?	+	?	?	+	+	?
47 (Cappuzzo F, 2006) (Cappuzzo et al., 2006)	?	?	?	?	+	?	–
49 (Srinivasa GY, 2020) (Srinivasa et al., 2020)	?	?	?	?	+	+	?
50 (Yoshioka H, 2017) (Yoshioka et al., 2017)	+	–	–	–	+	+	?
53 (Johnson BE, 2013) (Johnson et al., 2013)	+	+	+	+	+	+	+
58 (Yang JJ, 2014) ("EudraCT Number 2011-000634-11 - Clinical trial results - EU Clinical Trials Register," n.d.)	?	+	?	?	+	+	?
62 (Gridelli C, 2001) (Gridelli et al., 2001)	+	+	?	?	+	+	?
63 (Martoni A, 1991) (Martoni et al., 1991)	?	?	–	–	+	+	?
72.3 (Wu Y, 2018) (Boehringer Ingelheim, 2018a; Sequist et al., 2013; Wu et al., 2018)	+	+	–	–	+	+	?
72.6 (Boehringer Ingelheim, 2018) (Boehringer Ingelheim, 2018b)	+	+	–	–	+	+	?
72.7 (Boehringer Ingelheim, 2020) (Boehringer Ingelheim, 2020)	+	+	–	–	+	+	?
77 (Hida T, 2017) (Hida et al., 2017)	+	–	–	–	+	+	?
80 (Berghmans T, 2013) (Berghmans et al., 2013)	+	+	?	?	+	+	?
83 (GSK, 2014) (GlaxoSmithKline, 2014)	+	+	+	+	+	+	+

85 (Martoni A, 1999) (Martoni et al., 1999)	+	+	–	–	+	+	?
87 (Reck M, 2015) (Reck et al., 2015)	?	?	+	?	+	+	?
95 (Saito K, 2003) (Saito et al., 2003)	?	?	?	?	+	+	?
98 (Barlesi F, 2018) (Barlesi et al., 2018)	+	+	–	?	+	+	?
102 (Camidge DR, 2018) (Camidge et al., 2018)	+	?	?	?	+	+	?
108 (Wachters FM, 2004) (Wachters et al., 2004)	+	?	?	?	+	+	?
131.1 (Shaw AT, 2014) (Shaw et al., 2013)	–	–	–	–	+	+	?
131.2 (Solomon BJ, 2014) (Solomon et al., 2014)	–	–	–	–	+	+	?
132 (Bonomi P, 2000) (Bonomi et al., 2000)	+	?	?	?	+	+	?
137 (Zatloukal P, 2004) (Zatloukal et al., 2004)	+	?	–	–	+	+	?
139 (Zarogoulidis P, 2013) (P. Zarogoulidis et al., 2013)	+	?	?	?	+	+	?
143 (Koch A, 2011) (Koch et al., 2011)	+	+	+	+	+	+	+
145 (Bi N, 2019) (Bi et al., 2019)	+	+	–	–	+	+	?
163 (Herbst RS, 2011) (Herbst et al., 2011)	+	+	+	+	+	+	+
171 (Seto T, 2014) (Seto et al., 2014)	+	+	–	+	+	+	?
173 (National Cancer Institute, 2019) (National Cancer Institute (NCI), 2019)	+	+	+	+	+	+	+
174 (Kato T, 2018) (Kato et al., 2018)	+	+	–	+	+	+	?
185 (Stathopoulos GP, 2004) (Stathopoulos et al., 2004)	+	–	?	?	+	+	?
198 (Valdivieso M, 1984) (Valdivieso et al., 1984)	+	?	?	?	+	+	?
209 (Baggstrom MQ, 2017) (Baggstrom et al., 2017)	+	–	?	?	+	+	?
213 (Paz-Ares L, 2015) (Paz-Ares et al., 2015)	+	–	+	?	+	+	?
214 (Novello S, 2014) (S Novello et al., 2014)	+	+	+	?	+	+	?
222 (Akamatsu H, 2018) (Akamatsu et al., 2018)	+	+	–	–	+	+	?
225 (Kosmidis PA, 2008) (Kosmidis et al., 2008)	+	+	–	?	+	+	?
231 (Reinmuth N, 2019) (Reinmuth et al., 2019)	+	+	+	?	+	+	?
235 (Blumenschein GR, 2010) (Blumenschein et al., 2010)	?	?	–	–	+	+	?
237 (Choy H, 2013) (Choy et al., 2013)	+	?	–	–	+	+	?
257 (William WN, 2007) (William et al., 2007)	?	?	–	–	+	+	?
276 (Chang AY, 1993) (Chang et al., 1993)	+	?	?	?	+	+	?
281 (Kubota K, 2017) (Kubota et al., 2017)	+	–	+	+	+	+	?
292 (Zinner RG, 2015) (Zinner et al., 2015)	+	–	?	?	+	+	?
295 (Heigener DF, 2013) (Heigener et al., 2013)	+	?	–	–	+	+	?
299 (Wang XJ, 2018) (Jie Wang et al., 2018)	+	?	?	?	+	+	?

300 (Eli Lilly and Company, 2019) (Eli Lilly and Company, 2019a)	+	+	+	+	+	+	+
302 (Douillard JY, 2004) (Douillard, 2004)	+	?	+	?	+	+	?
304 (Butts CA, 2007) (Butts et al., 2007)	+	–	–	+	+	+	?
306 (Fukuda M, 2019) (Fukuda et al., 2019)	+	–	?	?	+	?	?
307 (Passardi A, 2008) (Passardi et al., 2008)	+	?	?	?	+	?	?
308 (Gatzemeier U, 2004) (Gatzemeier et al., 2004)	+	?	–	?	+	?	?
309 (Park C, 2017) (Park et al., 2017)	+	?	?	?	+	?	?
311 (Movsas B, 2005) (Movsas et al., 2005)	+	+	+	+	+	+	+
313 (Jänne P, 2014) (Jänne et al., 2014)	+	?	?	?	+	+	?
315 (Groen HJ, 2011) (Groen et al., 2011)	+	?	?	?	+	?	?
322 (Currow D, 2017) (Currow et al., 2017)	+	?	+	+	+	?	?
324 (Langer CJ, 2017) (Langer et al., 2017)	+	?	?	?	+	?	?
340 (Kotsakis A, 2015) (Kotsakis et al., 2015)	+	?	–	–	+	?	?
345 (Eli Lilly and Company, 2015) (Eli Lilly and Company, 2015)	+	+	+	+	+	+	+
346 (GSK, 2019) (GlaxoSmithKline, 2019)	+	+	–	+	+	+	+
348 (Lara PN, 2016) (Lara et al., 2016)	+	?	–	?	+	?	?
353 (Wu YL, 2020) (Wu et al., 2020)	+	+	+	+	+	?	?
373 (Umsawasdi T, 1989) (Umsawasdi et al., 1989)	+	?	–	?	+	?	?
374 (Cortot AB, 2020) (Cortot et al., 2020)	+	+	–	?	+	+	?
375 (AstraZeneca, 2021) (AstraZeneca, 2021b)	+	+	+	+	+	+	+
377 (Johnson DH, 2004) (Johnson et al., 2004)	+	+	–	+	+	+	?
378 (Eli Lilly and Company, 2022) (Eli Lilly and Company, 2022)	+	+	+	+	+	+	+
379 (Eli Lilly and Company, 2021) (Eli Lilly and Company, 2021)	+	+	+	+	+	+	+
380 (Eli Lilly and Company, 2019) (Eli Lilly and Company, 2019b)	+	+	+	+	+	+	+

It was observed that for most publications, the risk of blinding of outcome assessment were unclear. Hence, there should be a more comprehend guideline for developing and reporting clinical trials, so to ensure clinical trials are conducted in a manner with as little bias as possible.

3.5 Discussion

Cardiotoxicity is a type of cardiovascular side effect caused by chemotherapy drugs used to treat NSCLC. This type of toxicity occurs when the chemotherapy drugs damage the heart or its surrounding structures, leading to a range of symptoms including arrhythmias, congestive heart failure, and high blood pressure. While the risk of cardiotoxicity is low in patients with early-stage NSCLC, it is higher in those with advanced or metastatic cancer. There are several factors that can increase the risk of cardiotoxicity in those receiving NSCLC treatments, such as age, pre-existing heart conditions, and the specific drugs used. Certain NSCLC drugs are more likely to cause cardiotoxicity than others, and certain combinations of drugs may also increase the risk. For example, traditional chemotherapy agents including gemcitabine, cisplatin, and carboplatin are all known to cause cardiotoxicity in some patients. With the rapid development of targeted therapies and immunotherapies, it is observed among the included eligible studies that a lot of treatments were still used in combination with conventional treatments, such as cisplatin, carboplatin, docetaxel and paclitaxel. Similar findings were reported by other literature, in which cytotoxic chemotherapies are still being used in ~30% of cancer regiments (McGowan et al., 2017).

Hypertension was observed in over 30 studies, making it the most reported cardiotoxicity. Hypertension is mostly acute and self-limited and is known to be one of the common non-hematologic adverse events of antiangiogenic agents (Li et al., 2013). This systematic review also found that other drug classes such as anti-microtubule agents, alkylating agents were associated with treatment-induced hypertension which aligns with findings by Chung et al (Chung et al., 2020). Hypertension was also observed with the combination use of cisplatin, docetaxel and motexafin gadolinium; they were normally observed within the first 24 hours administration of motexafin gadolinium, and subsided after receiving oral clonidine (William et al., 2007).

As most studies reported cardiotoxicity at aggregate level, it is unclear whether certain patient experienced more than one type of cardiotoxicity, therefore it cannot be determined to what extent hypertension could have potentially contributed to other cardiovascular diseases, such as ischaemia in individual patients. Hence, the lack of information available may result in overestimation of the association between NSCLC drugs and cardiotoxicity.

Anthracyclines are effective anticancer treatments, however, their benefits are often limited by possible fatal dose-dependent cardiotoxicity (Smith et al., 2010). Anthracyclines, such as doxorubicin, are believed to cause direct damage to the heart by inducing oxidative stress and direct damage to the cardiomyocytes (Zhang et al., 2012). According to an included study by Valdivieso et al, higher dose of doxorubicin leads to a higher incidence of cardiotoxicity (Valdivieso et al., 1984). This finding is supported by Swain et al., which suggested the incidence of heart failure after doxorubicin treatment increases with cumulative dose (Swain et al., 2003). An included study by Wachters et al., suggested that epirubicin caused a much higher incidence of cardiotoxicity than that of cisplatin (Wachters et al., 2004). In a study by Martoni et al., it was discovered that a higher dose of epirubicin was linked to a higher decrease in LVEF values, but no systematic pattern was observed in decrease of LVEF values across cohorts of different dosage and accumulated dosage, so it cannot be concluded that whether certain single and/or accumulated dosage of epirubicin will possibly cause a decrease in LVEF values (Martoni et al., 1991). But this assumption can be supported by other studies, which concluded that epirubicin is associated with cumulative-dose cardiotoxicity (Feld et al., 1992; Smit et al., 1992; Wils et al., 1990). Others such as daunorubicin are believed to cause indirect damage to the heart by interfering with calcium homeostasis. One of the potential mechanisms of anthracycline cardiotoxicity is the inhibition of topoisomerase, which causes mitochondrial dysfunction, leading to the activation of cell death pathways and generation of reactive oxygen species (Carrasco et al., 2021). Additionally, different anthracyclines may have different levels of cardiotoxicity due to the presence of different metabolites or active forms of the drug, which could also contribute to the different onset of cardiotoxicity. For anti-microtubule agents, mechanisms of onset of cardiotoxicity include interfering with the normal function of the heart's cells, such as the contractility of the cells and the electrical conduction pathways, blocking the formation of new microtubules, which is necessary for the heart's cells to divide and multiply and direct damage to the heart tissue, leading to arrhythmias, heart failure, and other cardiotoxic effects (Zhang et al., 2019).

Cisplatin is a type of alkylating agents and is also a commonly used drug to treat NSCLC. As listed in Table 3.3, several studies demonstrated that cisplatin can cause cardiotoxicity, which ranges from arrhythmias, hypertension, myocardial infarction to chronic heart failure (Berghmans et al., 2013; Butts et al., 2007; Choy et al., 2013; Eli Lilly and Company, 2022, 2021; Gatzemeier et al., 2004; Jänne et al., 2014, p. 4; Jie Wang et al., 2018; S. Novello et al., 2014; Park et al., 2017; Srinivasa et al., 2020; Wachters et al., 2004). The cisplatin-induced

cardiotoxicities are possibly related to the imbalance of electrolytes (Miller et al., 2010; Oun and Rowan, 2017). Increased platelet reactivity by activation of arachidonic pathway is believed to be one of the mechanisms of cardiotoxicity caused by alkylating drugs. Oxidative stress and direct endothelial capillary damage with resultant extravasation of proteins, erythrocytes, and toxic metabolites, can then damage the myocardium, leading to cardiomyocyte degeneration and necrosis (Mudd et al., 2021).

For angiogenesis inhibitors that interfere with the vascular endothelial growth factor (VEGF) pathway, such as bevacizumab, can lead to hypertension, cardiac arrhythmias, and congestive heart failure due to decreased oxygenation. Bevacizumab is a targeted therapy that starves tumours by preventing new blood vessels from growing. It was observed among a number of eligible studies that there were higher incidence rates of hypertension with the addition of bevacizumab in anticancer treatments than those without. Several studies showed that with the addition of bevacizumab, there was an increased incidence of arterial thromboembolic events. This result is expected as arterial thromboembolism is a known adverse reaction to bevacizumab (Herbst et al., 2011; Johnson et al., 2013; Kato et al., 2018; Reinmuth et al., 2019). These adverse events were potentially caused by the VEGFR inhibition effects of bevacizumab, which negatively affected the coagulation system (Reck et al., 2015). Same as bevacizumab, sorafenib and sunitinib are also angiogenesis inhibitors, and more specifically VEGF receptor kinase inhibitor and multitargeted RTK inhibitors respectively. The mechanism of this class of drug is to inhibit neovascularisation which will then inhibit the growth of tumour as new blood vessels are needed for tumours to grow. Sorafenib and sunitinib demonstrated similar cardiotoxicity potentials as only hypertension was observed in both of them (Baggstrom et al., 2017; Paz-Ares et al., 2015). In contrast, inhibitors of the fibroblast growth factor (FGF) pathway can lead to cardiomyopathy and increased risk of ischemic events due to increased myocardial oxygen consumption. Other angiogenesis inhibitors can cause cardiomyopathy due to their direct effect on the myocardium, leading to decreased contractility (Maurea et al., 2016; Dobbin et al., 2021).

In Gatzemeier et. al, it was reported that cardiotoxicity is associated with the use of trastuzumab (Gatzemeier et al., 2004). This clinical finding differed from the safety profile of preclinical studies as there was no evidence of neither acute nor dose-related cardiotoxicity (Mellor et al., 2011). Inhibition of the NRG-1/ErbB2 signalling – a protective intracellular signalling pathway – is one of the proposed mechanisms that causes trastuzumab-induced cardiotoxicity (Perez and Rodeheffer, 2004). It was reported in Barlesi et al. that the patient in the avelumab

group with acute cardiac failure also suffered from autoimmune myocarditis (Barlesi et al., 2018). One of the possible mechanisms that avelumab might cause myocarditis was that coronary spasm causing ST elevation secondary to PD-1 inhibitor treatment (Nykl et al., 2017). In Butts et al., it was demonstrated that the addition of cetuximab to platinum/gemcitabine treatment did not increase cardiotoxicity as both groups report the same percentage of cardiovascular events (Butts et al., 2007).

Through this systematic review, it is suggested that several NSCLC treatments are associated with cardiotoxicity, but the actual incidence of cardiotoxicity induced by NSCLC treatments is still undefined. This is because systematic cardiac monitoring was not carried out in most of the clinical trials, thus compromising the ability to detect cardiotoxicity during clinical trials. Moreover, all included clinical trials had different eligibility criteria, treatment regimens and reporting styles, therefore the lack of standardisation makes it difficult to compare the safety data among different clinical trials.

In addition, most treatments reported were a combination of several anticancer drugs, hence it is difficult to identify exactly which drug contributes to cardiotoxicity or if a single drug has higher cardiotoxic potential.

This systematic review analysed data collected from clinical trials (i.e. aggregate data instead of individual patients' data), hence it is difficult to tell whether one person suffers from more than one type of cardiotoxicities. Also, based on the eligibility criteria, some of the studies which did not match the required study design (i.e. single arm study) were excluded even though counts of cardiotoxicity were recorded, so this might have caused selection bias of studies. In addition, the authors of some included publications mentioned that the incidences of cardiotoxicity were believed to be unrelated to the anticancer treatments. Therefore, for this systematic review, we adopted their opinions and did not include those cardiotoxicities thought not to be associated with NSCLC treatments. Moreover, due to the limitations of the eligibility criteria, the drugs included in the eligible studies might not necessarily be the most commonly used first/second-line treatments of NSCLC. Another limitation is that differences in duration of follow-up period among studies may potentially result in inaccurate representation of the frequency of cardiotoxicity associated with corresponding anticancer drug. In some studies, only adverse events with an overall incidence of ≥10% were reported, thus might cause reporting bias. One of the limitations observed is that most cardiotoxicities reported are symptomatic cardiotoxicities, whereas some expected asymptomatic cardiotoxicities such as

QT prolongation are not commonly reported, thus it is suggested that systematic cardiac monitoring should be carried out and corresponding data should be reported. Lastly, by restricting our literature search only to studies reported in English, other relevant studies might have been missed.

3.6 Summary

- The findings of this systematic review have provided a better understanding of the types of cardiotoxicities each anticancer drug is associated with.
- NSCLC treatments across different classes are associated with cardiotoxicity, however as systematic cardiac monitoring was not carried out in most of the clinical trials, the actual incidence of cardiotoxicity induced by NSCLC treatments remains undefined.
- Cardiotoxicity reported ranges from hypertension to heart failure with hypertension being the most common contributor.
- Although some cardiac adverse events are reversible, further research on identifying patients at risk for potentially serious cardiovascular events as well as implementation of early detection and screening strategies are needed to improve benefit-risk balance of treatments in cancer patients.

Chapter 4

The Feasibility of Medical Real-World Data in Cancer Treatments

4.1 Introduction

Pharmacoepidemiology is a multidisciplinary field that examines the use of medications in real-world populations to assess their benefits and risks (Hennessy, 2006). Historically, pharmacoepidemiology studies have relied on data from only a few data sources, which may not be fully representative of the source population and sample size may not be sufficient for very rare outcomes, thus hindering the generalisability of findings. However, the emergence of medical big data, which encompasses vast quantities of healthcare information from various sources, has opened new avenues for research in pharmacoepidemiology (Hall et al., 2012).

Information derived from individual datasets or records might not be satisfactory for certain research questions as it also depends on what information is available within that certain data source, but big data can potentially solve this issue by linking multiple databases together (Sinha et al., 2009). By analysing large-scale data, such as healthcare databases, claims databases and disease registries, one can identify signals of potential adverse drug reactions more efficiently than traditional methods such as individual case reports and smaller, less comprehensive studies (Takahashi et al., 2012). For example, electronic health records can provide longitudinal record on patient demographics, diagnoses, medications, and laboratory results, facilitating the timely identification and assessment of adverse events. In addition, medical big data enhances post-marketing surveillance by evaluating potential safety signals in large, diverse populations, providing insights into the long-term safety profile of medications. Moreover, medical big data enables the generation of evidence for personalised medicine, as it allows for the analysis of treatment responses and outcomes in subgroups of patients (Roski et al., 2014). Medical big data also helps the identification of unmet healthcare needs and knowledge gaps, and thus enabling policymakers to allocate resources efficiently. Therefore, medical big data has the potential to significantly impact healthcare decision-making by informing treatment guidelines and policy decisions.

Although medical big data can provide insights of certain issues efficiently, it is also important to note that as the size of data increases, qualitative issue also increases, such as processing, storage, analysis, interpretation and visualisation of data (Bellazzi, 2014).

4.2 Objective

To identify the most suitable database for investigating the research question and other study objectives, listed in Section 4.3, Methods.

4.3 Methods

Health Data Research Innovation Gateway and public domain were searched for databases reporting cancer. The Health Data Research Innovation Gateway is managed by Health Data Research UK and in collaboration with the UK Health Data Research Alliance. The feasibility assessment in this chapter followed the guideline recommended in the '2019 Structured Pre- and Post-approval Comparative study design framework to generate valid and transparent real-world evidence (SPACE) framework as well as the 'Structured Process to Identify Fit-For-Purpose Data (SPIFD) (Gatto et al., 2019, 2022).

The keyword 'cancer' was used in the search. This feasibility assessment included data sources of patients of ≥18 years old with lung cancer (C34) or NSCLC and excluded data sources of participants whose treatments involved radiotherapy only.

The objectives of the study are as follows:

Primary Objective

To describe the frequencies of cardiotoxicity-related outcomes of interest (all and by sub-type) within first 6 months following diagnosis index date in patients diagnosed with NSCLC, overall and following start of anticancer treatments according to first therapy received.

Secondary Objectives

1. To define NSCLC patients and their corresponding first treatment recorded.
2. To describe the clinical characteristics of the overall cohort of patients with NSCLC at diagnosis date.
3. To describe different drugs' combinations within first treatment of the overall cohort of patients with NSCLC at treatment date.
4. To describe the association between first treatment patterns (e.g. dose and duration) and cardiotoxicity-related outcome of interest, following initial NSCLC diagnosis.
5. To describe and compare the characteristics of sub-groups receiving first treatment recorded, according to start of treatment date.
6. To describe and compare progression-free survival of sub-groups following first treatment.

7. To describe the clinical features of incident reports of cardiotoxicity in patients following first treatment.
8. To describe and compare the characteristics of cancer patients with cardiotoxicity and without cardiotoxicity at the end of the follow-up period.

Exploratory Objectives

1. To identify important risk factors for cardiotoxicity by comparing characteristics of cardiotoxicity cases to non-cases at start of first treatment recorded.
2. To determine the associated healthcare cost (including hospital utilisation and drug prescription costs) from diagnosis date through till the end of follow-up period
3. To determine the cost-effectiveness of different treatments included in this study if the data are available.

4.3.1 SPIFD Step 1 (extension to SPACE step 3): Operationalise and rank minimal criteria required to answer the research question.

The minimal criteria were identified as per SPACE step 3, and during this step, those criteria were ranked by importance and/or how difficult the criterion is to achieve. Table 4.1 is a template of this step suggested by Gatto et al. (Gatto et al., 2022).

Table 4.1: SPIFD Step 1 (extension to SPACE step 3): Further operationalise and rank minimal criteria for valid capture.

Row	Design element	Operationalised definition*	Minimal criteria for valid capture*	Rank for uniqueness (and importance)†
1	Study population (inclusion and exclusion criteria)	Inclusion criteria • Criterion 1 • … • Criterion n Exclusion criteria • Criterion 1 • … • Criterion n	Minimum cohort size Data elements needed for: Inclusion criteria • Criterion 1 • … • Criterion n Exclusion criteria • Criterion 1 • … • Criterion n	
2	Treatment/Exposure group		Data elements needed Minimum number	
3	Comparator group(s)		Data elements needed Minimum number	
4	Primary outcome (definition & ascertainment)		Data elements needed Minimum baseline risk	
5	Key secondary outcome(s) (definition & ascertainment)		Data elements needed	
6	Length of follow-up and data recency		Minimum follow-up Maximum lag	
7	Confounding variable 1		Data elements needed	
. . . N	. . . Confounding variable N			

Derived from SPACE Step 1c-1d

Derived from SPACE Step 3

Derived from SPACE Step

SPIFD Step 1

* Refine and/or add detail as needed to fully operationalise definitions

† Where relevant and known to the researchers

4.3.2 SPIFD Step 2 Identify and narrow down data source options

SPIFD step 2 was conducted in a systematic approach as shown in Figure 4.1, and eventually excluded all ineligible data sources. Eligible data sources were then included for a detailed feasibility assessment (SPIFD step 3).

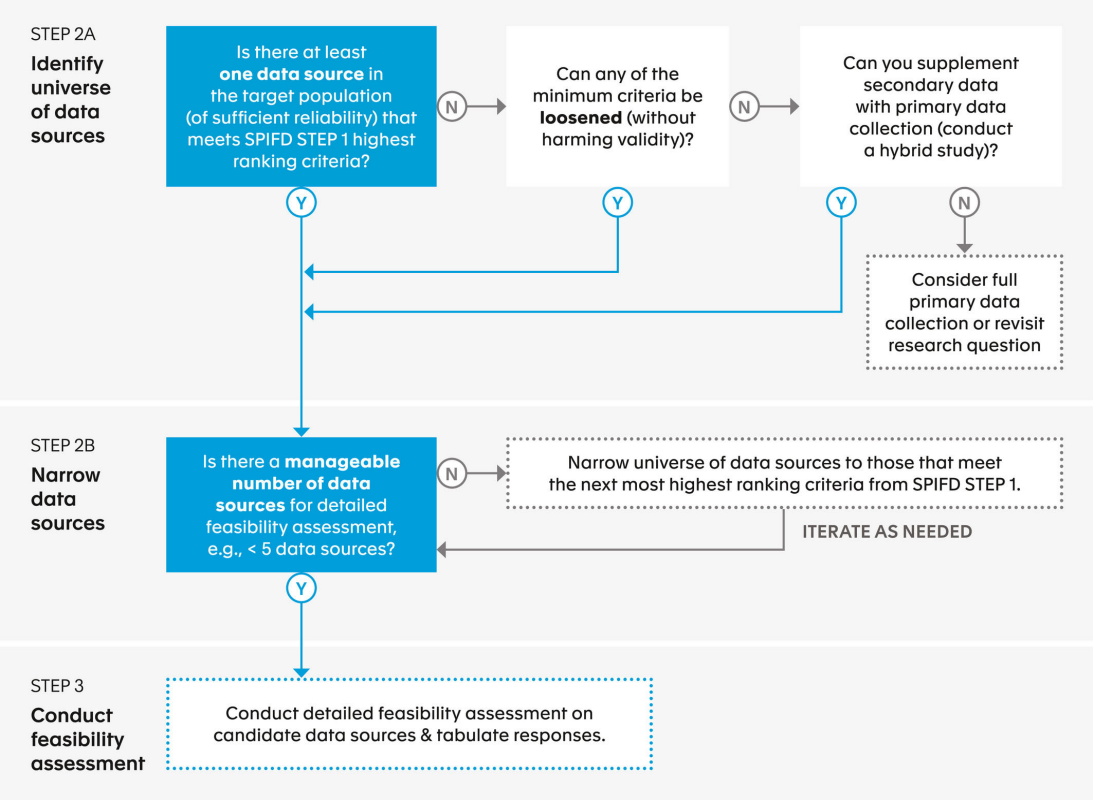

Figure 4.1: SPIFD Step 2: Identify and narrow data source options. SPIFD, Structured Process to Identify Fit-For-Purpose Data (Gatto et al., 2022).

4.3.3 SPIFD Step 3 Conduct detailed data feasibility assessment

Necessary details of each data source were gathered to justify whether a certain data source was suitable for the aforementioned research objectives. Besides the information listed in SPIFD Step 1, other important logistical information, such as data accessibility, time to data availability, time to execution, frequency of data updates and cost were also considered.

4.4 Results

4.4.1 Feasibility Assessment

Table 4.2 shows the information required for this study and their respective minimum criteria. Each information was ranked according to their importance, with 1 being most important and 18 being least important. The inclusion and exclusion criteria were ranked the two most

important factors, so to make sure the correct study population were identified. Cohort size was listed as least important as this study is an exploratory study, thus did not require a certain number of sample size.

Table 4.2: SPIFD Step 1 (extension to SPACE Step 3) applied to this study.

Row	Design element	Requested information	Minimal criteria for valid capture	Rank for Importance
1	Study population (inclusion and exclusion criteria)	• Inclusion Criteria: Patients (aged ≥ 18 years old at diagnosis index date) diagnosed with lung cancer (C34) / Non-Small Cell Lung Cancer (NSCLC)	Patients Diagnostic Data	1
		• Exclusion Criteria: Participants whose treatments involved radiotherapy only.		2
		• Cohort size	Not applicable (exploratory)	18
		• Population / Region	England	11
2	Treatment/exposure group	• Availability of drug used and drug dosage	Prescription Data	5
3	Comparator group(s)	• Availability of drug used and drug dosage	Prescription Data	6
4	Primary outcome (definition and ascertainment)	• Association of NSCLC treatments and cardiotoxicity		3
5	Key secondary outcome(s)	• Drug utilisation pattern		7
		• Patients' sociodemographic data		4
6	Exploratory outcome(s)	• Risk Factors		15
		• Cost-Effectiveness		16
7	Length of follow-up and data recency	• 28 days (for acute) • Ideally 6 month (for chronic)	28 days minimum	10
		• Most recent update of data	At least till end of 2021	12
		• Data lag time	Not applicable	14
		• Frequency of data refreshes	Not applicable	17

8	Confounding variable 1	• Baseline comorbidities		9
	Confounding variable 2	• Cardiovascular disease history		8
9	Access to Data			13

A total of 103 data sources were identified from the Health Data Research Innovation Gateway and public domain using the search term ‘cancer’, as listed in ‘Methodology’. A flow diagram explaining the selection process for this feasibility assessment is presented in Figure 4.2. A total number of 2 eligible data sources (#34 and #54) were included for data extraction. A summary of the required information, including design elements and data access considerations, of each data source is listed in Table 4.3.

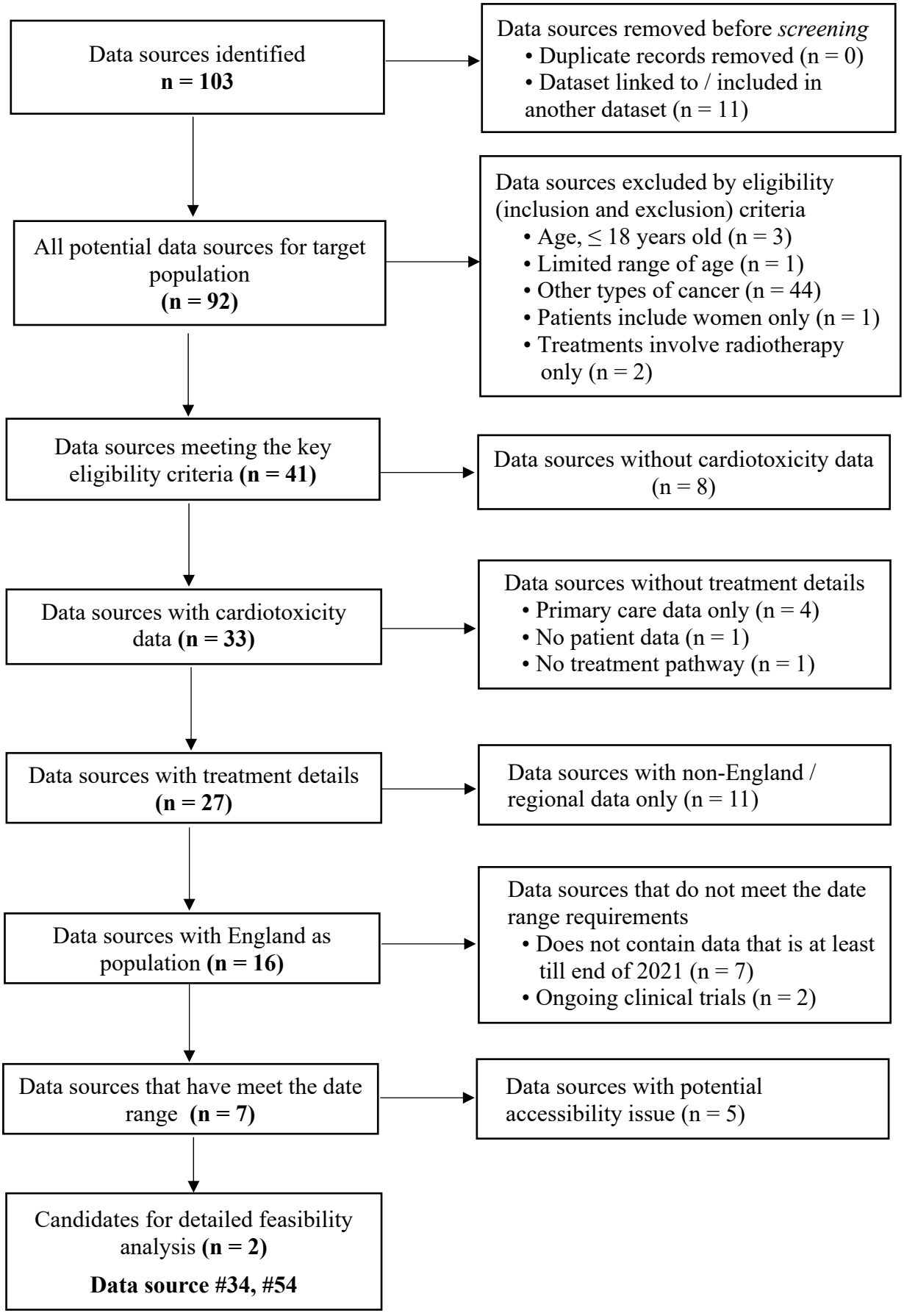

Figure 4.2: SPIFD Step 2 applied to this study.

Table 4.3: Required information (design and data access).

	Name of Database	Provider / Owner	Include	Exclude	Reason 1	Reason 2	Remarks
1	A dataset of hospitalised patients with Sarcoma	PIONEER		1	Other types of cancer		Sarcoma
2	ARIA Medonc	OXFORD UNIVERSITY HOSPITALS		1	No cardiotoxicity		Prescribing pathway only
3	Barts CTU	TISSUE DIRECTORY		1	Other types of cancer		Benign neoplasm of prostate, Carcinoma in situ of breast
4	Bowel Screening Wales (SBSW)	SAIL		1	Other types of cancer		Bowel cancer
5	Breast Test Wales (SBTW)	SAIL		1	Other types of cancer		Breast cancer
6	Cam-UroOnc Biorepository	TISSUE DIRECTORY		1	Other types of cancer		Carcinoma in situ of prostate
7	Cancer and cerebrovascular events: frequency, cancer types and outcomes	PIONEER		1	No cardiotoxicity		Only cerebrovascular/stroke
8	Cancer Group CTR Cardiff trials	TISSUE DIRECTORY		1	Region		Cardiff
9	Cancer Network Information System (CNIS / CANISC)	SAIL		1	No cardiotoxicity	Region	Wales
10	Cancer Patient Experience Survey (CPES) for CPRD Aurum	CPRD		1	Date	Data no longer routinely available	01012010 - 31122018

11	Cancer Patient Experience Survey (CPES) for CPRD GOLD	CPRD		1	Date	Data no longer routinely available	01012010 - 31122018
12	Cancer Registration Data	NHS Digital		1	Used to link other data by NCRAS		
13	Cancer Registration Data	NHS England		1	Used to link other data by NCRAS		
14	Cancer registration data for CPRD Aurum	CPRD		1	Used to link other data by NCRAS		
15	Cancer registration data for CPRD GOLD	CPRD		1	Used to link other data by NCRAS		
16	Cancer registry data for QResearch	QRESEARCH		1	Linked NCRAS data		Qresearch linked National Cancer Registration and Analysis Service (NCRAS) cancer registration data contain a record for each notified, registrable tumour, diagnosed or treated in England.
17	Cervical Screening Wales (SCSW)	SAIL		1	Other types of cancer		Cervical cancer
18	Children's Kidney Cancers - Great Ormond Street Hospital	DATA-CAN		1	Age		
19	Children's Cancer and Leukaemia Group (CCLG) Tissue Bank	TISSUE DIRECTORY		1	Age		

20	Comprehensive Patient Records for Cancer Outcomes	DATA-CAN		1	Date		01012008-01122018
21	CPRD GOLD	CPRD		1	Primary care only		
22	Daisy Tumour Bank	TISSUE DIRECTORY		1	Other types of cancer		Leukaemia, disease, Malignant tumour of rectum (disorder),Malignant tumour of colon, Malignant tumour of oesophagus, Mesothelioma (malignant, clinical disorder)
23	DARWIN1 Trial	TISSUE DIRECTORY		1	Ongoing clinical trial, in follow up stage		
24	DEFINE Database			1	No patient data and treatment pathway		
25	Demography	HEALTH INFORMATICS CENTRE - UNIVERSITY OF DUNDEE		1	Demographic data only		
26	DiscoverNow			1	Region		Northwest London only
27	Edinburgh Ovarian Cancer Database	DATALOCH		1	Other types of cancer		Ovarian cancer
28	GENOMICS ENGLAND 100K BIOINFORMATICS DATA	GENOMICS ENGLAND		1	No cardiotoxicity		

29	GENOMICS ENGLAND 100K CANCER & COMMON	GENOMICS ENGLAND		1	No cardiotoxicity		
30	GENOMICS ENGLAND 100K NHSD LINKED DATA	GENOMICS ENGLAND		1	Date		2014-01-01 - 2019-01-01
31	GENOMICS ENGLAND 100K PHE LINKED DATA	GENOMICS ENGLAND		1	Date		1 january 1995 -31 december 2017
32	GENOMICS ENGLAND 100K QUICK VIEW	GENOMICS ENGLAND		1	No cardiotoxicity		
33	HPB Biobank	TISSUE DIRECTORY		1	Other types of cancer		Malignant neoplasm of liver, Malignant tumour of colon, Malignant tumour of pancreas
34	HTI Database		1				
35	ICON9 Trial	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of ovary
36	IMPORT HIGH trial blood samples	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of breast
37	IMRD Database			1	Primary care only		
38	INCA Trial	TISSUE DIRECTORY		1	Other types of cancer		Malignant lymphoma (disorder)
39	Infoflex Cancer Registry	OXFORD UNIVERSITY HOSPITALS		1	Access issue		Available locally within Trust Clinical Data Warehouse System and authorised

							access by Trust staff only.
40	interNational Anaplastic Thyroid Cancer Tissue Bank (iNATT)	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of thyroid gland
41	IoN Trial	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of thyroid gland (disorder).
42	JANUS	OXFORD UNIVERSITY HOSPITALS		1	Other types of cancer		Colorectal cancer
43	King's Health Partners Cancer Biobank	TISSUE DIRECTORY		1	Other types of cancer	Guy's & st thomas' nhs trust	Malignant tumour of breast.
44	LBIH Biobank	TISSUE DIRECTORY		1	Other types of cancer		
45	Leeds Breast Research Tissue Bank	TISSUE DIRECTORY		1	Other types of cancer		Breast cancer
46	Leeds Multidisciplinary Research Tissue Bank	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of kidney
47	Leeds NIHR Biomarker Research Tissue Bank	TISSUE DIRECTORY		1	Other types of cancer		Related to liver disease
48	Leeds-IQVIA Collaboration	DATA-CAN		1	Region		Leeds
49	Manchester Cancer Research Centre (MCRC) Biobank	TISSUE DIRECTORY		1	Region		
50	MesobanK	TISSUE DIRECTORY		1	Other types of cancer		Mesothelioma (malignant, clinical disorder).
51	Myeloma XII clinical trial samples	TISSUE DIRECTORY		1	Other types of cancer		Multiple myeloma (disorder).

52	National Bowel Cancer Audit - clinical dataset	HQIP		1	Other types of cancer		Bowel cancer
53	National Bowel Cancer Audit - Organisational Survey dataset	HQIP		1	Other types of cancer		Bowel cancer
54	National Cancer Registration and Analysis Service	UK HEALTH SECURITY AGENCY	1				
55	National Cancer TRE	DATA-CAN		1	Access issue		Approved research projects will help to guide national decision making and recommend potential interventions to reduce the severity of COVID-19 outcomes.
56	National Oesophago-Gastric Cancer Audit - clinical dataset	HQIP		1	Other cancer		Invasive, epithelial cancer of the oesophagus, gastro-oesophageal junction
57	NHS Grampian Biorepository	TISSUE DIRECTORY		1	Region	Date	Scotland
58	NHS Lothian Secondary Care - Lothian extract from Scottish Morbidity Records	DATALOCH		1	Region		Scotland
59	Northern Ireland Biobank (NIB)	TISSUE DIRECTORY		1	Other types of cancer	Region	Carcinoma in situ of prostate, Fit and well, Malignant

							neoplasm of endometrium of corpus uteri (disorder), Malignant tumour of breast, Malignant tumour of colon, Malignant tumour of ovary.
60	Oncology Clinical Trials Office, University of Oxford	TISSUE DIRECTORY		1	Other types of cancer		Barrett's oesophagus (disorder), Malignant tumour of oesophagus, Malignant tumour of ovary, Malignant tumour of pancreas.
61	OpenSafely			1	Access issue		
62	Pancreatic Cancer - Early Detection Prediction	MANCHESTER UNIVERSITY HOSPITALS NHS FOUNDATION TRUST		1	Other types of cancer		Pancreatic cancer
63	PHM and Cancer Outcomes in the WYH Cancer Alliance	DATA-CAN		1	Part of COSD	Region	West Yorkshire and Harrogate
64	PHOENIX DDR-Anti-PD-L1 Trial	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of breast
65	PHOTO Translational bladder cancer biorepository	TISSUE DIRECTORY		1	Other types of cancer		Carcinoma in situ of bladder

66	plasmaMATCH	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of breast.
67	POUT-T	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of urinary bladder (disorder), Transitional cell carcinoma.
68	Prevention, detection, treatment: adult lung disease/cancer in rural Tamil Nadu	BREATHE		1	Other country		Tamil nadu
69	Quality of Life of Cancer Survivors: Pilot Patient Reported Outcomes (GOLD)	CPRD		1	Other types of cancer	Date	Breast, colorectal, prostate cancer or non-Hodgkin's lymphoma, diagnosed 2006-2010
70	Quality of Life of Cancer Survivors: Pilot Patient Reported Outcomes(Aurum)	CPRD		1	Other types of cancer	Date	Breast, colorectal, prostate cancer or non-Hodgkin's lymphoma, diagnosed 2006-2010
71	Quality of Life of Colorectal Cancer Survivors: Patient Reported Outcomes (GOLD)	CPRD		1	Other types of cancer		Colorectal cancer
72	Quality of Life of Colorectal Cancer Survivors:Patient	CPRD		1	Other types of cancer		Colorectal cancer

	Reported Outcomes (Aurum)						
73	Real Time Data Network (RTDN)	DATA-CAN		1	Access issue	Region	For the purpose of testing the effect of the COVID-19 pandemic on cancer diagnostic and cancer treatment pathways.
74	REQUITE	TISSUE DIRECTORY		1	Radiotherapy only		
75	RIO	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of breast
76	RTDS - Radiotherapy treatment data set for QResearch	QRESEARCH		1	Radiotherapy only		
77	SACT - systemic anticancer treatment for QResearch	QRESEARCH		1	Linked NCRAS data		
78	SCOT translational sample collection	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of colon
79	Scottish Cancer Registry (SMR06)	PUBLIC HEALTH SCOTLAND		1	Region		Scotland
80	Scottish Human Papillomavirus Archive	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of cervix
81	Somerset Cancer Registry	BARTS HEALTH		1	Access issue		Authorised access by Trust staff only.
82	South East Scotland Cancer Database - Core Oncology Dataset	DATALOCH		1	Region		South East Scotland only
83	South West Primary Care Dataset	DATA-CAN		1	Primary care only		

84	Suspected Cancer Pathway Monthly (SCPM)	SAIL		1	No cardiotoxicity	Region	Wales
85	Systemic Anti-Cancer Therapy Dataset (SACT)	SAIL		1	Part of NCRAS	Region	Wales
86	Systemic Anti-Cancer Treatment (SACT) data for CPRD Aurum	CPRD		1	Part of CPRD Aurum		
87	Systemic Anti-Cancer Treatment (SACT) data for CPRD GOLD	CPRD		1	Part of CPRD GOLD		
88	The EPIC-Norfolk Study	MRC EPIDEMIOLOGY UNIT - UNIVERSITY OF CAMBRIDGE		1	Date		Baseline recruited between 1993 and 1998, and followed for over 25 years
89	The EPIC-Oxford Study	THE EPIC-OXFORD STUDY, CANCER EPIDEMIOLOGY UNIT, NUFFIELD DEPARTMENT OF POPULATION HEALTH, UNIVERSITY OF OXFORD		1	No treatment pathway		
90	The PEACE Study	TISSUE DIRECTORY		1	Clinical trial		Ongoing recruitment till October 2023
91	Theory of Planned Behaviour Intervention: respiratory disease in South India	BREATHE		1	Region		South india
92	TNT: Triple Negative breast cancer Trial	TISSUE DIRECTORY		1	Other types of cancer		Breast cancer

93	TRICON8	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of ovary
94	TRICON8B	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of ovary
95	UHB 100K Genomics patient clinical data including their acute care contacts	PIONEER		1	Date		01012000 - 05052020
96	UK Biobank	UK BIOBANK		1	Age		40 and 69 years old and living in the UK
97	UKCTOCS Longitudinal Women's Cohort (UKLWC)	TISSUE DIRECTORY		1	Women only		
98	UNIRAD UK Sample collection	TISSUE DIRECTORY		1	Other types of cancer		Malignant tumour of breast
99	University of Liverpool - GCP Laboratory Facility	TISSUE DIRECTORY		1	Other types of cancer		
100	University of Southampton Faculty of Medicine Tissue Bank	TISSUE DIRECTORY		1	Tissue bank		
101	Wales Cancer Bank	TISSUE DIRECTORY		1	Region		Wales
102	Welsh Cancer Intelligence and Surveillance Unit (WCSU)	SAIL		1	No cardiotoxicity	Region	
103	Yorkshire Specialist Register of Cancer in Children and Young People	DATA-CAN		1	Age	Region	

After conducting SPIFD Step 3, it was concluded that between the two shortlisted data sources, NCRAS (#54) was the most suitable data source, as it not only provides the ICD-10 code, but also provides clinical details, such as the morphology and histology of the cancer. This can help distinguish NSCLC from the ICD-10 code of all lung cancer (C34) (Table 4.4).

Based on the feasibility assessment, HTI database was not the most suitable database for this research question as the diagnosis was only based on the ICD-10 codes, which cannot distinguish NSCLC specifically from all lung cancer (C34) as cancer patients tracked in the HTI dataset cannot be stratified by stage, morphology or other necessary clinical details. However, after substantial consideration, it was also considered to be an eligible data source, as a backup. With the above-mentioned issue, therefore if this database is to be used, an algorithm will be needed in order to define NSCLC by broad case and narrow case definition (more in discussion – Section 4.5.2).

Table 4.4: SPIFD Step 3 applied to this study.

Design element	Requested information	Data source #34	Data source #54
Design elements			
Study population (inclusion and exclusion criteria)	Inclusion Criteria: Patients (aged ≥ 18 years old at diagnosis index date) diagnosed with lung cancer (C34) / Non-Small Cell Lung Cancer (NSCLC)	Yes	Yes
	Exclusion Criteria: Participants whose treatments involved radiotherapy only.	Yes	Yes
	Population / Region	~25% of hospital trusts in England will be included	Nearly all England population within NHS
Treatment/exposure group and comparator group(s)	Availability of drug used and drug dosage	Yes, from HPA	Yes
Primary outcome	Association of NSCLC treatments and cardiotoxicity	ICD-10, OPCS Codes	ICD-10, morphology, histology
Key secondary outcome(s)	Drug utilisation pattern	Yes	Yes
	Patients' sociodemographic data	Yes	Yes
Exploratory outcomes(s)	Risk factors	Partial	Partial
	Cost-effectiveness	Partial	Partial
Length of follow-up and data recency	28 days minimum (for acute) 6-month minimum (for chronic)	Yes	Yes
	Most recent update of data	Feb 2021	August 2021
	Data lag time	~ 6 months	Varies

	Frequency of data refresh	Updated quarterly	Irregular / at least annually
Confounding variables	Baseline comorbidities	Yes	Yes
	Cardiovascular disease history	Yes	Yes
Data access considerations			
Timeline	Time to data access	3 – 12 months	3 – 6 months
	Time to analyse	2 months	2 months
Contracting logistics	Cost	£££	£££
	Time to fully executed contract (from the date of receiving data)	3 months	3 months
Final data source selection		✓	✓

4.4.2 HTI Database (Data source #34)

Hospital Treatment Insight (HTI) is a database of electronic health records in England. HTI is linked to the hospital patient records in the Hospital Episode Statistics (HES) database with dispensing information stored within hospital pharmacy systems. HTI contains data from ~25% hospital trusts in England. In these participating trusts, HES routinely captures hospital activity information, e.g. sociodemographic, admission details and diagnoses information. From 2010 onwards, patient-level data on brand, type, data and quantity of dispensed drugs obtained from Hospital Pharmacy Audit (HPA) are made available by linking dispensing data to HES. HTI is maintained by IQVIA. IQVIA has obtained Section 251 support for NHS Digital to receive and link identifiable pharmacy data to patient level HES data on its behalf. IQVIA then receives non-identified data from NHS Digital on a regular basis. The database is updated quarterly with a current lag of ~6 months.

Although HTI database had been selected as a potential candidate for the research question, there were a few limitations of this database, apart from inability to directly identify NSCLC patients. Another limitation of the data source was that only drug information dispensed from the pharmacy to an individual patient will be captured, which means medicines administered from ward stocks would not be captured, so this might affect the completeness of data we received. Also, the vital status (death) and death cause of a patient would only be known if they pass away in any HES hospitals. It was also possible that the recordkeeping of how many times a certain service was used by each patient might be inaccurate due to reimbursement issues. This could affect the accuracy of the direct medical cost calculated.

4.4.3 NCRAS Database (Data source #54)

The National Cancer Registration and Analysis Service (NCRAS) in Public Health England (PHE) collects data on all patients diagnosed with cancer from across the population of England and has permission to do so without specific patient consent under Section 251 of the NHS Act 2006. The data collected by PHE is then linked with other data to create the Cancer Analysis System (CAS). It provides timely data, with detailed clinical information, on all 350,000 cancers diagnosed annually in England, in addition to having more than 141 million historical cancer records extending back over 30 years. The data is sensitive and confidential, and PHE has an absolute responsibility to protect patient privacy and to ensure that the duty of confidence is maintained by any users of the data. The CAS is an important and valuable data source used

to understand patient care, outcomes, and support research. CAS data are captured in a range of formats from multiple healthcare sources, including hospitals and histopathology laboratories. The number of data records processed each year has grown from 500,000 in 2011 to 32 million in 2016. The responsibility of management of NCRAS has transferred from PHE to NHS Digital as of 1 October 2021; and on 1 February 2023, the responsibility is transferred from NHS Digital to NHS England. NHS England is now the new controller of this data.

PHE collects data on nearly all cancer patients in England. These data are maintained in the CAS database. The CAS comprises the well-known Systemic Anti-Cancer Therapy (SACT) dataset, the Cancer Outcomes and Services Dataset (COSD), which contains detailed information about tumours and mortality, and other linked datasets. IQVIA is currently working to increase the accessibility of these data to facilitate research that will ultimately benefit patients. COSD has been the national standard for reporting cancer in the NHS in England since January 2013, providing unparalleled clinical detail on patients diagnosed with cancer, including morphology, histology, staging, grade, TNM, surgery and patient date of death. The SACT dataset captures nearly all treatments for cancer patients in the hospital inpatient, outpatient and community settings. This includes traditional chemotherapy drugs (infusion/injection/orals), biologics, immunotherapy, hormones and includes drugs for patients treated in clinical trials.

4.5 Discussion

In the UK, a multitude of organisations hold health datasets, which poses a challenge for researchers, innovators, as well as members of the public and patients who want to explore the available datasets. To address this issue, the Health Data Research Innovation Gateway was established in 2020 as a centralised platform for researchers and innovators to conveniently discover and request access to various health-related datasets in the UK. The Health Data Research Innovation Gateway provides comprehensive information about each dataset, including descriptions, population size encompassed by the dataset, and the legal framework governing access. This information aids the process in determining the relevance of a dataset to specific research question.

Data sources which health care settings are primary care only, such as the IMRD database, were not suitable for this research question. Primary care only data is a major limitation for oncology studies as oncology treatment and follow-ups are mostly followed in secondary care settings. Primary care data typically focuses on general health conditions and may lack detailed information specific to oncology, such as cancer staging, tumour characteristics, and treatment regimens. This can restrict the depth of analysis and the ability to draw precise conclusions regarding cancer-specific outcomes and interventions. Also, primary care data may not capture all cases of cancer, especially if patients receive their oncology care primarily from specialists or oncology centres. This can lead to underrepresentation of certain cancer types or stages, potentially skewing the findings and limiting the generalisability of the results.

Some other data sources were also suitable for the research objectives, in terms of the information/data required. But after considering the availability or accessibility of the data sources, they had been excluded. For example, Infoflex Cancer Registry is used for the management of cancer patients within the trust. Although this data source might be suitable for this study, it is currently only available locally within Trust Clinical Data Warehouse System and authorised access by Trust staff only. Similarly for Somerset Cancer Registry, it is only available locally within Trust Corporate Data Warehouse System and authorised access by Trust staff only and may also be available directly from the OpenExeter team as the system is centrally hosted. Organisations and individuals who want to use certain kinds of data within National Cancer TRE need to show they meet strict data governance standards by completing the NHS Digital DARS application process. OpenSAFELY, is also a suitable data source for our research question, in terms of the information/data required. It is a secure analytics platform developed for the National Health Service (NHS) to provide timely results during the global COVID-19 pandemic. However, currently, OpenSAFELY is only available to defined team members and the first wave of external pilot users.

Therefore, NCRAS was decided to be the most suitable data source in this feasibility assessment, while HTI database had been selected as a potential (second to NCRAS) candidate. Detailed proposed protocols for the NCRAS database (data source #54) and the HTI database (data source #34) are included in Section 4.5.1 and Section 4.5.2 respectively.

4.5.1 Proposed protocol for NCRAS Database (Data source #54)

Aim

To investigate how different classes of drugs, e.g. anthracyclines, alkylating agents, angiogenesis inhibitors, tyrosine kinase inhibitors (TKIs), and monoclonal antibodies, demonstrate different cardiotoxicity potentials in the selected type of cancer, i.e. non-small cell lung cancer (NSCLC).

Primary objective

To describe the association between cardiotoxicity-related outcomes of interest (all and by sub-type) within first 3 months following diagnosis index date in patients diagnosed with NSCLC, overall and following treatment index date according to first Line of Therapy (LoT) Systemic Anti-Cancer Therapies (SACT) Regimens received.

Secondary objectives

1. To describe the clinical characteristics of the overall cohort of patients with cancer at diagnosis date, by cancer type (i.e. NSCLC).
2. To describe first LoT SACT regimen patterns (including dose and duration) following initial cancer diagnosis, by cancer type (i.e. NSCLC).
3. To describe and compare the characteristics of sub-groups receiving first LoT SACT regimens, according to start of treatment date.
4. To describe the clinical features of incident reports of cardiotoxicity in patients following first LoT SACT regimens.
5. To identify important risk factors for cardiotoxicity by comparing characteristics of cardiotoxicity cases to non-cases at start of first LoT SACT treatment.

Research methods

Types of studies

This is a secondary database study based on a retrospective, longitudinal cohort design using the Cancer Analysis System (CAS) in England (see section 3.4). CAS is a data source containing specific cancer registry information for England in several datasets under control of the UK National Cancer Registration and Analysis Service (NCRAS). The study population

will be comprised of a cohort of adult patients diagnosed with NSCLC (all stages) in the database within the study time period and treated with at least 1 SACT regimen during follow-up. Demographic and clinical characteristics will be described at diagnosis and at start of treatment. Treatment patterns will also be described during follow-up.

Setting

England is the proposed setting for this study.

Study time period

The study time period for the data source will be as follows:

01 January 2012 to 30 June 2019 (or until most recent available diagnostic data available) to identify incident cases of NSCLC*

The treatment pathway time period and recording of SACT follow-up time is extended past the diagnosis index date identification window to include the full study period:

01 January 2012 to 31 December 2019 (or most recent data available) to profile treatment pathways

These dates coincide with the current availability of information in COSD and SACT, respectively.

* We ensure incident cases excluding likely prevalent cases of malignancy, as set out in the exclusion criteria (section 3.3.2).

Index dates

Depending on study objectives, different index dates will be defined as follows:

The ***study diagnosis index date*** will be defined as 'the date of first diagnosis of NSCLC within the study time period'.

The ***study treatment index date*** will be defined as 'the date of first prescription of SACT following diagnosis of NSCLC within the study time period'.

Follow-up and censoring

All patients will be followed from index date (diagnosis/treatment) until they experience an outcome of interest (endpoint) or until cohort exit (date of censoring) as relevant to the study objectives.

Exit from follow-up will occur at the earliest of the following dates:

- Vital status date (date of death, or last date patient is confirmed alive in COSD)
- End of the study period (31st December 2019)
- End of 6-month observation window → 6-month window is to ensure 3 months of follow-up time from start of treatment

The distribution of follow up time (from diagnosis and from treatment) will be summarised overall, and by sub-cohorts of interest as appropriate. The frequency of cardiotoxicity and adverse events will be analysed per month (28-day period), from both diagnosis dates and treatment start date.

Look back period

All information relevant to defining study variables at diagnosis date and any inclusion or exclusion criteria will be assessed from available records from start of CAS. All patients will share the same duration of look-back period to avoid bias.

Study Population

Inclusion criteria

CAS patients who fit ***all of the following criteria*** will be included in the study:

- A diagnosis of NSCLC within COSD within the study period
- Aged ≥ 18 years old at diagnosis index date of NSCLC
- A record of a systemic anti-cancer treatment in the SACT dataset
- An initial treatment index date of the drug regimen before 30th April 2018

The inclusion diagnoses International Classification of Diseases (ICD)-10 codes are defined in Table 4.5 below.

Table 4.5: ICD-10 codes used to identify NSCLC (NCRAS Database).

	Cancer	**Morphology**	**Histology/Behaviour**
NSCLC	Lung Cancer	Non-small Cell Carcinoma	
Code	C34	8046	3

Exclusion criteria

Patients will be excluded from the study if they satisfy ***any of the criteria*** below at the diagnosis index date:

- Record of SACT more than 30 days prior to diagnosis index date
- Combined diagnoses of NSCLC
- Diagnosed with one or more other primary malignancies before diagnosis index date, apart from non-melanoma skin cancer

Sub-populations

Additional criteria may be applied to create sub-groups of interest for specific study objectives as appropriate.

These sub-groups may include:

- Age categories: 18-64, 65-74, >75 years
- Gender: male, female
- Prior medical history of cardiovascular outcomes
- Initial SACT regimens sub-group

Data management

Data source

The data source will be the Cancer Analysis System (CAS), derived from a national cancer registry dataset in England.

The National Cancer Registration and Analysis Service (NCRAS) in Public Health England (PHE) collects data on all patients diagnosed with cancer from across the population of England and has permission to do so without specific patient consent under Section 251 of the NHS Act 2006. The data collected by PHE is then linked with other data to create the Cancer Analysis System (CAS). The data is sensitive and confidential and PHE has an absolute responsibility to protect patient privacy and to ensure that the duty of confidence is maintained by any users of the data. The CAS is an important and valuable data source used to understand patient care, outcomes, and support research. IQVIA proposes that Simulacrum and CAS be used to conduct the study, with anonymous, aggregated CAS data ultimately released to AbbVie.

PHE collects data on nearly all cancer patients in England. These data are maintained in the CAS database. The CAS comprises the well-known Systemic Anti-Cancer Therapy (SACT) dataset, the Cancer Outcomes and Services Dataset (COSD), which contains detailed information about tumours and mortality, and other linked datasets. IQVIA is currently working to increase the accessibility of these data to facilitate research that will ultimately benefit patients.

COSD has been the national standard for reporting cancer in the NHS in England since January 2013, providing unparalleled clinical detail on patients diagnosed with cancer, including morphology, histology, staging, grade, TNM, surgery and patient date of death. The SACT dataset captures nearly all treatments for cancer patients in the hospital inpatient, outpatient and community settings. This includes traditional chemotherapy drugs (infusion/injection/orals), biologics, immunotherapy, hormones and includes drugs for patients treated in clinical trials.

The National Cancer Registration and Analysis Service (which collects the data that feeds into CAS) is one of the most granular cancer registries in the world. It provides timely data, with detailed clinical information, on all 350,000 cancers diagnosed annually in England, in addition to having more than 141 million historical cancer records extending back over 30 years. CAS data are captured in a range of formats from multiple healthcare sources, including hospitals and histopathology laboratories. The number of data records processed each year has grown from 500,000 in 2011 to 32 million in 2016.

The following data within CAS database are the most relevant to this study:

- Patient demographic characteristics (e.g. age, sex, ethnicity, region)

- Tumour characteristics (e.g. site, tumour-node-metastasis [TNM] classification and histology)
- Mortality (e.g. date of death)
- SACT treatments (e.g. regimen, number of cycles)
- Performance status at diagnosis (indication of general wellbeing and activities of daily living, as specified in CAS)

Access to data using the Simulacrum

The Simulacrum has been developed to increase the accessibility of the CAS, given the legal constraints regarding access to confidential patient records. It contains only artificial data that models many of the properties of CAS but contains no real patient data. It can, therefore, be used by IQVIA to perform exploratory analyses, feasibility work and test coding of data records without compromising patient confidentiality. Completing these tasks and refining our proposed approach on the Simulacrum allows for more in-depth review and discussion up front and saves considerable time in later stages of the project (see table 4.6). Final analyses are run on the most current CAS data controlled and maintained by PHE.

Table 4.6: Simulacrum and CAS Data (NCRAS Database).

Dataset	Simulacrum Data	CAS Data
Purpose	To allow structuring, refining and quality assurance of study queries	To provide real-world data to run the Simulacrum-validated queries on
Data contained	Synthetic data which models CAS properties	Patient-level data from NCRAS
Develop programming code in	Yes (primary function)	May refine Simulacrum code to reflect CAS data
Provide analysis outputs	No	Yes
Derive insights on cancer populations	No	Yes

Data source considerations

Data content

In general, whilst data quality in CAS (i.e. in the underlying datasets including COSD and SACT) has been steadily improving, not all cancer patients tracked in the COSD dataset may be stratified by stage, morphology, biomarker status or other necessary clinical details. Similarly, whilst SACT data quality has improved since its inception, it may still manifest the typical imperfections of large-scale real-world data in terms of inconsistent data quality by time-period and/ or geography and incompleteness of certain non-mandatory elements. These challenges around data quality and completeness may impact upon the success of any analysis hence a feasibility stage should be included.

In addition, to gain diagnostic data for prevalent comorbidity, records linked to the Hospital Episode Statistics (HES) dataset can be derived to match the cancer registration records at a patient level. The time window of look back period between 27 months to 3 months before diagnosis will be used in this study.

Access to data

For NCRAS to fully register a cancer patient, all diagnosis information, pathology reports and details must be ascertained, translated, and reviewed by clinicians. This process results in a lag of approximately 12 months in the COSD dataset. SACT captured in CAS maintain a lag of approximately 9-12 months but may be longer at certain sites of care. This does not preclude IQVIA from running code on Simulacrum and testing approaches but may translate to an elongated feasibility phase that requires more data testing when CAS results are returned. Final analyses run on CAS will always use the most up-to-date data available.

PHE is currently working in partnership with NHS England (NHSE) on the use of cancer data. This work includes an evaluation of drugs that have entered the new Cancer Drugs Fund (CDF) programme to support NICE decision making. PHE have agreed with NHSE to temporarily restrict the release of outcomes data relating to CDF evaluations that we have been commissioned to provide. These analyses typically include calculating treatment duration and survival. Broadly speaking, these are drug outcomes. These restrictions apply until when NICE make their decision public as to whether the drug will go into routine commissioning or be de-

commissioned; PHE does release information on these patients regarding number of patients and cohort-based characteristics.

The need for personalised or de-personalised data as part of this study is not within scope and would require an application to be submitted to PHE's Office of Data Release (ODR). For this reason, only anonymised CAS data are permitted.

Variables

Exposure definitions

The main exposure of interest is SACT treatment; defined as any chemotherapy, immunotherapy or targeted biological therapy.

Within the cohort of NSCLC, patients will be classified into sub-cohorts based on the first LoT SACT treatments they received at treatment index date. Index date will be used to determine the start of the first LoT; the number of days used to determine the regimen for the first LoT normally ranges from 3 – 30 days. First LoT can mean a single medication or a combination of drugs. The earliest occurrence of either one of the following items will be used to determine the end of first LoT – (1) usage of drug(s) that are not listed within the regimen of the first LoT, in this case the day before starting a new regimen will be considered the end of the first LoT; (2) discontinuation of ALL agents listed in the first LoT; (3) end of study period; (4) death.

Non-small cell lung cancer (NSCLC)

- ***Chemotherapy:*** Cisplatin, Carboplatin, Docetaxel, Paclitaxel, Gemcitabine, Vinorelbine
- ***Targeted therapy:*** Afatinib, Bevacizumab, Certinib, Crizotinib, Erlotinib, Gefitinib
- ***Immunotherapy:*** Nivolumab, Pembrolizumab

Table 4.7: Anticancer drugs for NSCLC categorised by therapeutic class (NCRAS Database).

Alkylating Agent	Anti-microtubule Agent	Anti-metabolite Agent	Anti-mitotic Agent	Tyrosine Kinase Inhibitors	Angiogenesis Inhibitor	Monoclonal antibody
Cisplatin	Docetaxel	Gemcitabine	Vinorelbine	Afatinib	Bevacizumab	Nivolumab

Carboplatin	Paclitaxel	Pemetrexed		Ceritinib		Pembrolizumab
				Crizotinib		
				Erlotinib		
				Gefitinib		

First line of treatment of non-small cell lung cancer (NSCLC)

1. Advanced NSCLC –cetuximab, cisplatin & vinorelbine
2. Advanced or metastatic NSCLC – carboplatin & paclitaxel
3. Anaplastic lymphoma kinase (ALK)-positive metastatic NSCLC – ceritinib
4. EGFR-positive metastatic NSCLC with exon 19 deletions or exon 21 (L858R) substitution mutation – erlotinib & ramucirumab
5. EGFR-positive metastatic NSCLC with exon 19 deletions or exon 21 (L858R) substitution mutation – gefitinib
6. Inoperable, locally advanced or metastatic NSCLC – carboplatin & gemcitabine
7. Late stage NSCLC – cisplatin
8. Locally advanced or metastatic NSCLC - Vinorelbine & every-4-week cisplatin
9. Locally advanced or metastatic NSCLC - Vinorelbine every-6-week cisplatin.
10. Metastatic non-squamous NSCLC without EGFR or ALK mutations - atezolizumab, bevacizumab, carboplatin & paclitaxel
11. Metastatic NSCLC with non-resistant EGFR mutations – afatinib
12. Metastatic squamous NSCLC – carboplatin, pembrolizumab & paclitaxel/nab-paclitaxel
13. Metastatic, EGFR- and ALK-negative, nonsquamous NSCLC - pembrolizumab pemetrexed & platinum chemotherapy
14. Metastatic, non-squamous, NSCLC – carboplatin, pemetrexed & pembrolizumab
15. NSCLC patients who are not candidates for potentially curative surgery and/or radiation therapy - cisplatin & paclitaxel
16. Stage III NSCLC who (1) does not have surgical resection or definitive chemoradiation, or metastatic NSCLC, and (2) express PD-L1 (Tumour Proportion Score (TPS) 1% or higher) and (3) are EGFR- and ALK-negative - pembrolizumab
17. Stage IIIB or IV NSCLC – carboplatin & pemetrexed
18. Unresectable, locally advanced or metastatic NSCLC – carboplatin & docetaxel

19. Unresectable, locally advanced or metastatic NSCLC – cisplatin & docetaxel
20. Unresectable, locally advanced or metastatic NSCLC – docetaxel & gemcitabine
21. Unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC - bevacizumab, carboplatin & paclitaxel

* Nivolumab is not being used as a first line of treatment in NSCLC

SACT regimens as recorded in the source SACT data will be reported without any modifications to naming or groups. SACT received will be determined through extracting the data of 'Regimen grouping – benchmark reports (Code: Benchmark_Group)'. In addition, adjuvant and curative treatments will be determined through extracting the data of 'Drug treatment intent (Code: Intent_Of_Treatment)'.

For the primary objective analysis, all agents within each of the SACT treatment groups of interest will be considered interchangeable in terms of exposure. Exposure is considered continuous between treatment index date and end of exposure.

Switching will be defined as the interruption of a SACT treatment within the first LoT SACT regimen and initiation of a second SACT from a different class within the same LoT, following suspension of the first SACT.

For patients switching agents, the following rules will be applied:

- Switching within groups – patients will remain classified as being exposed to that group.
- Switching between alternative groups – patient exposure time will be censored at the point of switching.

Dose

Information on dose will be identified using the SACT data variable: 'Actual dose (Code: Actual_Dose_Per_Administration)'.

An additional variable reporting dose reduction during treatment 'Regimen modification indicator – dose reduction (Code: Regimen_Mod_Dose_Reduction)', will be considered for analysis as a proxy binary indicator for accumulated dosage requiring medical intervention.

Duration

Treatment duration in days will be derived from information in the SACT dataset and defined according to time from first LoT SACT regimen initiation to the start date of the second SACT regimen. These data will be categorised into 30-day intervals.

An additional variable reporting days reduced during treatment 'Regimen modification indicator – days reduced (Code: Regimen_Mod_Stopped_Early)' will be considered for analysis as a proxy binary indicator for accumulated exposure requiring treatment cessation.

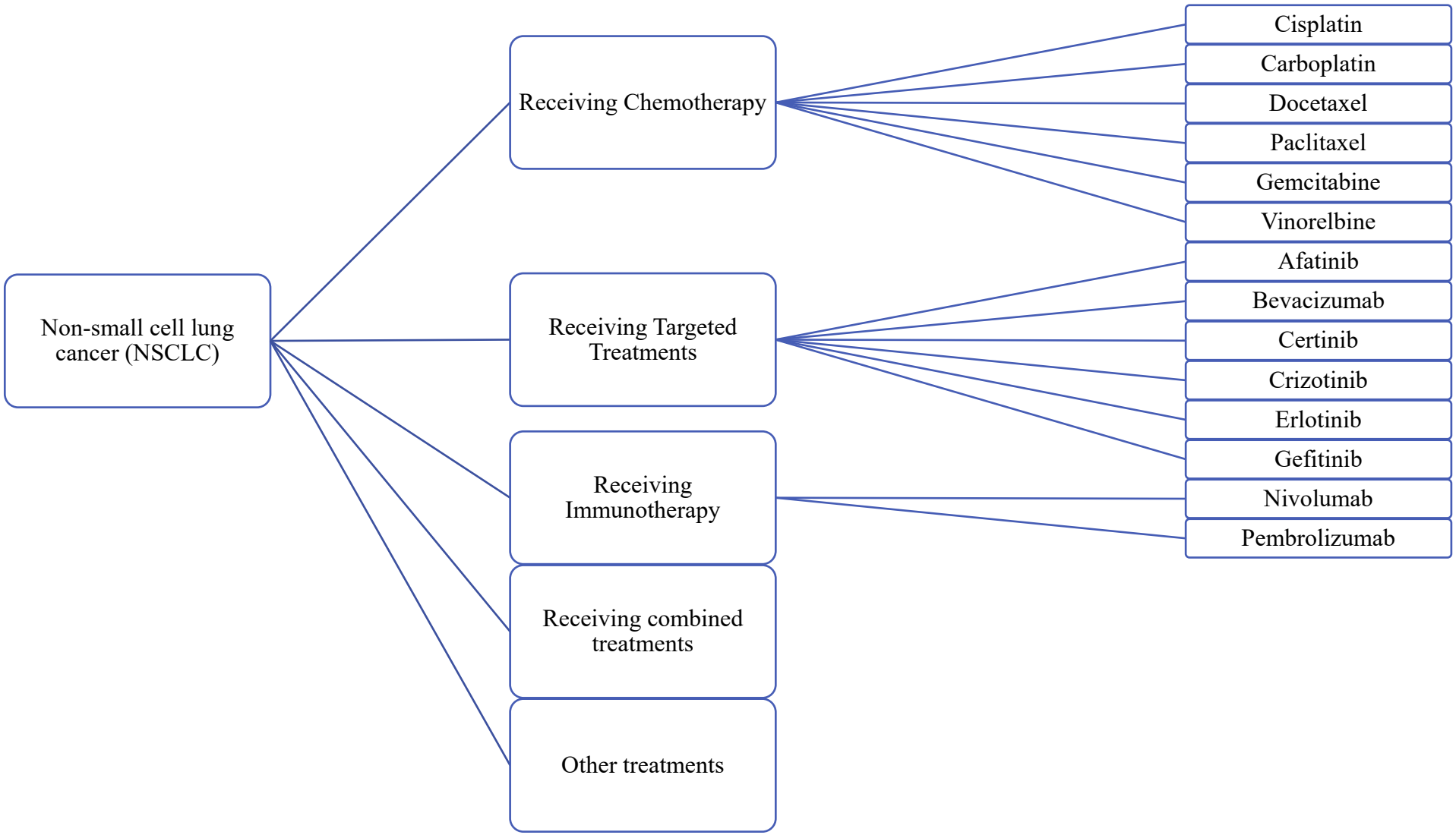

Figure 4.3: A diagram showing expected treatments of non-small cell lung cancer (NSCLC).

Endpoint definitions

Two case definitions of cardiotoxicity will be used. These definitions will be based on an algorithm that will be fully developed in a statistical analysis plan.

Primary endpoint – narrow case definition

For the narrow case definition for the variable, 'Planned treatment change reason (Code: Regimen_Outcome_Summary)' will be used as reported in the SACT dataset as the proxy indicator to identify eligible cases of cardiotoxicity. Patients with NSCLC will be identified in Stage 1 and then will be grouped according to the treatment they received (Stage 2) as shown in Figure 4.4.

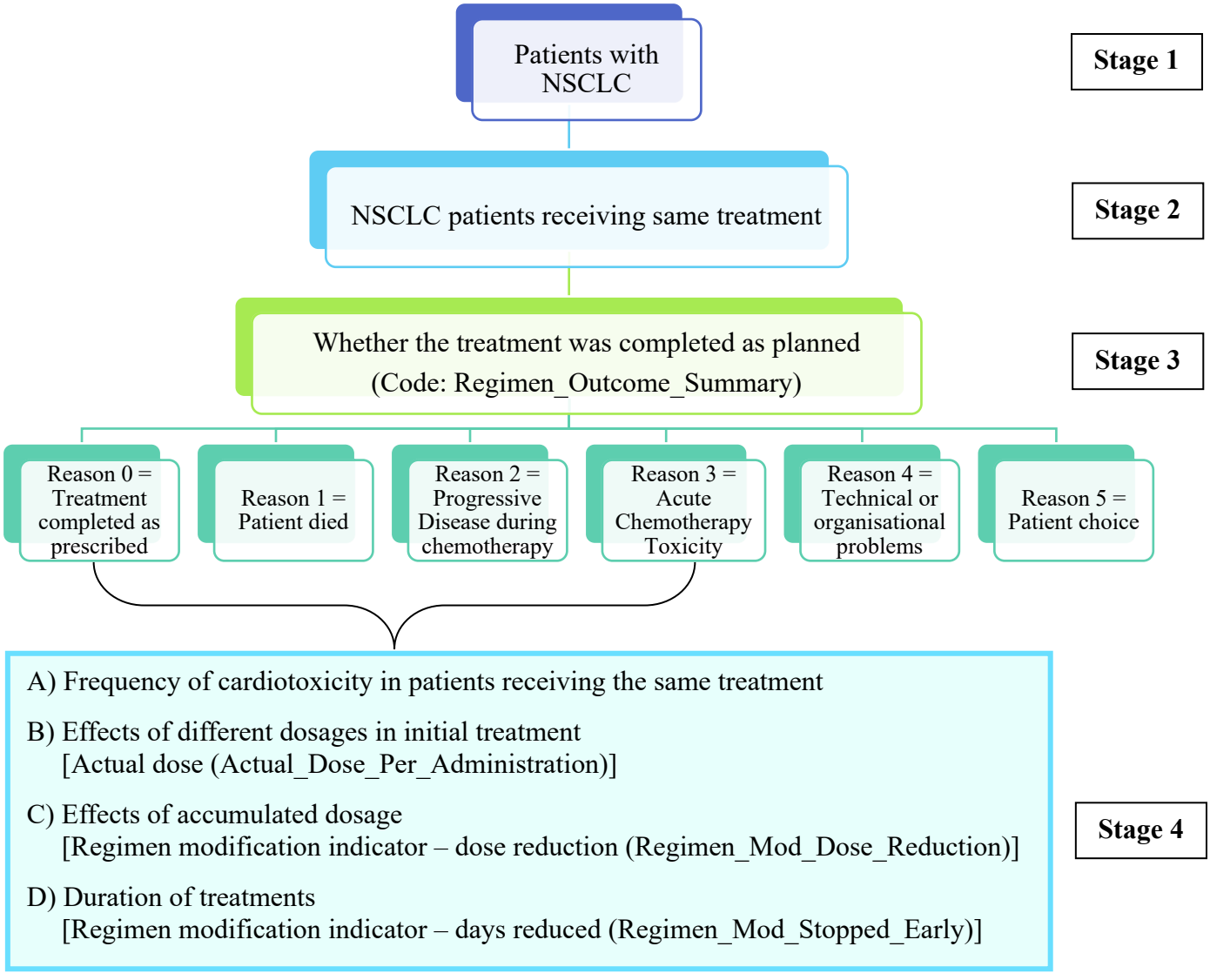

Figure 4.4: A flow chart of the study design within the same cohort (NCRAS Database).

After grouping patients who received the same treatments together, data of whether the treatment was completed as planned will then be evaluated (Stage 3). This can be done through analysing the data extracted under 'Planned treatment change reason (Code: (Regimen_Outcome_Summary)'. The reason will be numbered as 0 – 5 in the data table. Eligible cases of cardiotoxicity may be identified under reasons 1 – 3, where cardiotoxicity-related death cause, cardiotoxicity-related progressive disease or acute chemotherapy toxicity will be considered as a possible development of cardiotoxicity respectively. In addition to the categorical number 1-5 shown under the 'Planned treatment change reason', the nature of the reason will also be listed out as text in the database to aid identification of diseases / adverse events. After identification, item A – D in the flow chart (Figure 4.4) will then be evaluated.

Primary endpoint – broad case definition

For the broad case definition, additional eligible cases will be considered where at least one of the following biomarkers: assessment of left ventricular ejection fraction (LVEF), troponins and brain natriuretic peptide (BNP) are suggestive of cardiotoxicity. Because it was observed in a previous study that elevation of NT-proBNP taken early after high-dose chemotherapy was associated with the development of left systolic and diastolic dysfunction at 1-year follow up (Sandri et al., 2005). Therefore, in this study, at least one-year of follow-up period is required in the inclusion criteria.

Data elements to be obtained

An indicative list of study parameters for the analysis of patient demographics, clinical characteristics and treatment patterns is shown below. Code lists that will inform on the definition of these variables will be developed in the statistical analysis plan.

Table 4.8: List of variables for the analysis of patients' demographics, clinical characteristics and treatment patterns (NCRAS Database).

Outcome/ Endpoint	Variables	Reason to include this variable	How the data will be presented
	Age	Make sure the patient is ≥18 years old (one of the inclusion criteria)	Numerical – continuous
	Sex		Categorical (0,1,2,9)

Patients' Demographics	Ethnicity	In case want to do analysis on whether sex and ethnicity has an impact of risk of cardiotoxicity	Categorical with alphabets
	Region	Maybe useful in analysing which region has most missing data, etc	Categorical
	Height	To calculate body mass index	Numerical – continuous
	Weight		Numerical – continuous
	Whether the patient has a HES Record	Need to be linked to HES record to derive data for comorbidity	Text (Yes/No)
Clinical Characteristics	Site of neoplasm	Describes site of origin of the neoplasm	Text
	Morphology code (Available in COSD and SACT)	Data needed to identify NSCLC	Categorical / Text
	Behaviour of the cancer, in the ICD-10-O2 system	Describe whether the cancer is malignant, benign, primary or secondary, etc	Categorical / Text
	Charlson Comorbidity Index (CCI) / Adult Comorbidity Evaluation 27	To understand if there is another disease other than cancer and whether the said disease affect treatment decision	Numerical – discrete
	Vital Status (death)	To understand if the patients are still alive	Categorical (A,D,X)
	Date of vital status	Back up as an exit date if the actual date is not recorded	Date
	Death cause	To understand if any cause of death is related to heart / cardiotoxicity	Text
	LVEF values	Biomarker for cardiotoxicity	Numerical
	Troponin levels		Numerical
	Brain natriuretic peptide (BNP) levels		Numerical
	Prescribed dose	For dosage analysis to determine if the dose is an impact of risk of cardiotoxicity	Numerical
	SACT drug route of administration	In case want to do analysis on whether	Categorical

		route of administration has an impact of risk of cardiotoxicity	
Treatment Patterns (Patient-level)	SACT administration date	Need the date to determine the date a drug was administered to the patients	Date
	Regimen modification indicator – dose reduction	To help determine if dosage has an impact to risk of / associated with cardiotoxicity	Text (Yes/No)
	Regimen modification indicator – days reduced	To help determine if accumulated dosage has an impact to risk of / associated with cardiotoxicity	Text (Yes/No)
	Planned treatment change reason	To understand if any reason is related to heart / cardiotoxicity	Text
	Regimen grouping (benchmark reports)	To know which drug(s) have been used for first line of treatment	Text
	Drug treatment intent	To distinguish adjuvant and curative treatment	Categorical
	Start Date (Drug Regimen)	To keep track of the duration of treatment	Date
	Cycle identifier	To know which cycle it is on	Numerical
	Start date (Cycle)	To keep track of the duration of certain cycle of treatment	Date
	Treatment duration first LoT	To keep track of the duration of treatment	Numerical

The following listed cardiotoxicities will be of particular interest under ‘planned treatment change reason’ and ‘death cause’:

- Coronary artery disease
- Heart failure
- Hypertension
- Ischemia
- Subclinical myocardial toxicity
- Supraventricular and ventricular arrhythmias
- Systolic and diastolic cardiac dysfunction

Sample size

This is an exploratory study and descriptive in nature. The study population will be derived from all patients within the database to which the inclusion criteria apply and thus is a convenience sample. An initial feasibility count indicated the possibility of carrying out the project considering the size of the population, i.e. number of relevant records.

Table 4.9 and 4.10 show preliminary search of the number of records listed in Simulacrum and CAS dataset respectively.

Table 4.9: Preliminary search of the number of records listed in Simulacrum dataset (NCRAS Database).

	Cancer	**Morphology**	**Behaviour**	**All 3 Criteria**	**Cancer & Behaviour only**
NSCLC	Lung Cancer	Non-small Cell Carcinoma			
Code	C34	8046	3		
Counts	100,556			7750	100,380

Table 4.10: Preliminary search of the number of records listed in CAS dataset (NCRAS Database).

Year	**Gender**	**Age Group**	**Tumour Site**	**ICD10**	**Health Geography**	**Total Number of Tumours**
2001 - 2017	Persons	All	Malignant Neoplasm of Lung and Bronchus	C34	England	587,696

Statistical analysis

General approach

A detailed statistical analysis plan will be prepared for this study and will include a full description of the CAS data source. An overview of the general statistical methods and planned approach for analyses related to primary and secondary objectives are provided in this section.

Descriptive analyses will be conducted using number and percent within each category with 95% confidence intervals for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

Only available data will be summarised; no imputation methods will be used to handle missing data. The number and percentage of missing values will also be reported as appropriate.

Primary objective – ***To describe the association between cardiotoxicity-related outcomes of interest (all and by sub-type) within first 3 months following diagnosis index date in patients diagnosed with NSCLC, overall and following treatment index date according to first Line of Therapy (LoT) Systemic Anti-Cancer Therapies (SACT) Regimens received***

The counts and proportions of incident reports of cardiotoxic events in all patients within each cancer group will be summarised for the total three-month period following diagnosis. The association between cardiotoxic events LoT SACT regimen will be explored by the chi-squared hypothesis test (χ^2). It will be used to test if an observed distribution of frequencies happened purely by chance or is there an underlying factor that caused it (Bosch et al., 2013; Currell and Dowman, 2009). In this study, the most common form of χ^2 test – contingency test / table – will be used to investigate if there is an association between the observed distribution (i.e. frequency of cardiotoxicity) and the given factor (i.e. anticancer drugs).

The counts and proportions of incident reports of cardiotoxic events in all patients within each cancer group will be summarised for the total three-month period following start of treatment.

Secondary objective 1 – ***To describe the clinical characteristics of the overall cohort of patients with cancer at diagnosis date, by cancer type (i.e. NSCLC)***

Descriptive analyses will be conducted using number and percent within each category with 95% confidence intervals for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

Secondary objective 2 – ***To describe first LoT SACT regimen patterns (including dose and duration) following initial cancer diagnosis, by cancer type (i.e. NSCLC)***

Pearson's correlation coefficient (r) will be calculated to determine if there is association between anticancer drugs and cardiotoxicity, including different dosages and duration. The

square of Pearson's correlation coefficient (r^2), i.e. coefficient of determination, will be used as a measure of correlation. If it has been proved that there is correlation between anticancer drugs and cardiotoxicity, then regression calculation will be carried out to calculate the actual values of the best-fit slope and intercept.

Secondary objective 3 – ***To describe and compare the characteristics of sub-groups receiving first LoT SACT regimens, according to start of treatment date***

One-way ANOVA will be used to compare the characteristics within and between sub-groups. A boxplot will also be presented to provide a graphical summary of distribution.

Secondary objective 4 – ***To describe the clinical features of incident reports of cardiotoxicity in patients following first LoT SACT regimens***

Descriptive analyses will be conducted using number and percent within each category with 95% confidence intervals for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

Secondary objective 5 – ***To identify important risk factors for cardiotoxicity by comparing characteristics of cardiotoxicity cases to non-cases at start of first LoT SACT treatment***

A univariate analysis will be performed for all variables to assess the relationship between potential risk factors and cardiotoxicity. Relative risk (RR) will be calculated to determine the risk associated with an exposure; the risk/incidence of those exposed will be compared against those non-exposed. The relative risk will be reported alongside a p-value and/or 95% confidence interval. Potential risk factors with P values < 0.05 may then be included in a multivariable analysis.

4.5.2 Proposed protocol for HTI Database (Data source #34)

Aim

To determine if it is feasible to use the HTI database to identify any suspected association between cardiotoxicity and anticancer treatments. The study will investigate how different classes of drugs, e.g. anthracyclines, alkylating agents, angiogenesis inhibitors, tyrosine kinase

inhibitors (TKIs), and monoclonal antibodies, differ in their cardiotoxicity potentials in a selected type of cancer, i.e. NSCLC. The potential impact of any suspected associations will be explored in order to contribute to a benefit-risk balance between therapeutic gain and risk of cardiotoxicity, which can benefit cancer patients.

Primary objective

Within the HTI database, we will explore the feasibility to describe the frequencies of cardiotoxicity-related outcomes of interest (all and by sub-type) within first 6 months following diagnosis index date in patients diagnosed with NSCLC, overall and following start of anticancer treatments according to first therapy received.

Secondary objectives

1. To explore the completeness of data elements/variables within the HTI database.
2. To define NSCLC patients and their corresponding first treatment recorded in HTI.
3. To describe the clinical characteristics of the overall cohort of patients with NSCLC at diagnosis date.
4. To describe different drugs' combinations within first treatment of the overall cohort of patients with NSCLC at treatment date.
5. To describe the association between first treatment patterns (e.g. dose and duration) and cardiotoxicity-related outcome of interest, following initial NSCLC diagnosis.
6. To describe and compare the characteristics of sub-groups receiving first treatment recorded, according to start of treatment date.
7. To describe and compare progression-free survival of sub-groups following first treatment.
8. To describe the clinical features of incident reports of cardiotoxicity in patients following first treatment.
9. To describe and compare the characteristics of cancer patients with cardiotoxicity and without cardiotoxicity at the end of the follow-up period.
10. To identify important risk factors for cardiotoxicity by comparing characteristics of cardiotoxicity cases to non-cases at start of first treatment recorded.

Outcome measures

Primary end point

The feasibility of using HTI to determine the association between cardiotoxicity and anticancer drugs will be observed using the following data variables – drug code, drug quantity and patients' diagnosis with additional information obtained from basic or advanced cardiovascular (CV) support, emergency visits, intensive care stays and additional operating procedures. Patients with NSCLC will first be divided into two cohorts namely: (1) patients who do not have cardiovascular diseases and (2) patients who have pre-existing cardiovascular diseases. This will be achieved by identifying multiple ICD-10 codes from patients' diagnosis. Diagnosis / documented dates of CV diseases that exist before diagnosis date of NSCLC are defined as pre-existing CV disease and will be put into Cohort 2. NSCLC patients without any pre-existing CV diseases will be put into Cohort 1. After defining the proportion of patients that have pre-existing CV diseases and those without, patients who received the same treatment will be allocated to the same sub-cohort. Cardiotoxicity will be identified using multiple ICD-10 codes from patients' diagnosis in the 'Outcomes' stage. Diagnosis / documented dates of CV diseases that exist after diagnosis date of NSCLC are defined as cardiotoxicity associated with anticancer drugs.

Secondary end points

These include: (1) Clinical characteristics of the overall cohort, (2) different treatment combinations for NSCLC patients within the HTI dataset, (3) drug utilisation pattern of first treatment of NSCLC regimen, (4) characteristics and progression-free survival between sub-groups, (5) incidence/frequency and risk factors of cardiotoxicity, (6) associated healthcare costs (prescriptions and hospital visits), which can be determined using Hospital Pharmacy Audit (HPA) data and (7) feasibility of conducting cost-effective analysis of different treatments included in this study.

Research methods

Study type

Longitudinal, Retrospective Cohort

Numbers needed

This is an exploratory study and descriptive in nature. The study population will be derived from all patients within HTI to which the inclusion criteria apply and thus is a convenience sample.

Setting

England is the proposed setting for this study, but due to limitation of the database, only data of ~25% of hospital trusts in England will be included. This study will include three cohorts of different corresponding study time periods. One-year survival rate of NSCLC is ~40%, so a primary analysis of 6-month follow-up and an extended analysis of 12-month follow-up period will be used for this study. Also, an extended analysis of 6-month follow-up during the COVID-19 pandemic will be observed.

(1) Primary Analysis – Cases with diagnosis date between 01 January 2010 to 31 May 2019 will be included and will be followed-up for a 7-month period with 31 December 2019 being the last follow-up date.

(2) Extended Analysis 1 (COVID-19) – Cases with diagnosis date between 01 January 2020 to 31 January 2020 will be included and will be followed-up for a 7-month period with 31 August 2020 being the last follow-up date. If there are more recent data available, i.e. those after 31 August 2020, then the cut-off diagnosis date will be postponed accordingly. For example, the most recent data available in the HTI database is now 31 October 2020, then the cut-off diagnosis date will be extended from 31 January 2020 to 31 March 2020.

(3) Extended Analysis 2 (12-month) – Cases with diagnosis date between 01 January 2010 to 30 November 2019 will be included and will be followed-up for a 13-month period with 31 December 2019 being the last follow-up date.

Sensitivity analysis will be carried out to determine how these three different study periods impact the outcomes of interest, e.g. drug utilisation pattern, association between anticancer treatments and CV events of interest. A tornado diagram will also be presented if necessary.

Index dates definition

HTI does not directly report either date of diagnosis or date of NSCLC recurrence, so proxy time points are defined below for relevant events.

The '***primary lung cancer diagnosis index date***' is the date of the first recorded International Classification of Diseases (ICD)-10 code in HTI that corresponds to NSCLC, in this case it will be C34 (lung cancer).

The '***NSCLC treatment index date***' is the date of the first treatment related to NSCLC recorded, following diagnosis of NSCLC within the study time period.

The '***recurrence index date***' is the start date of the second treatment related to NSCLC recorded.

'***Progression-free survival***' is the time between diagnosis index date and recurrence index date.

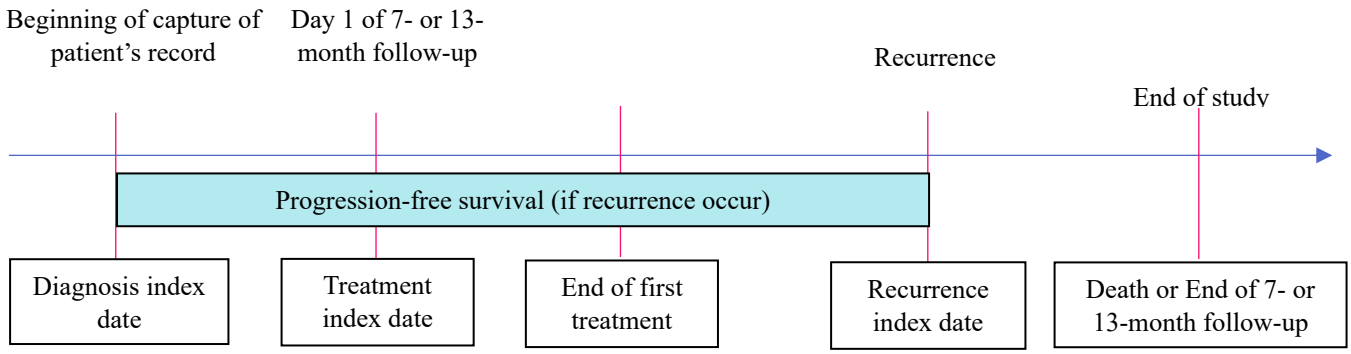

Figure 4.5: A figure showing how a patient will be observed from the start till the end of the study.

Eligibility

Inclusion criteria:

Patients who fit ***all of the following criteria*** will be included in the study:

- A diagnosis of NSCLC within the study period
- Aged ≥ 18 years old at diagnosis index date of NSCLC
- A record of a systemic anti-cancer treatment in the dataset
- An initial treatment index date of the drug before 31 January 2020

Exclusion criteria

Patients will be excluded from the study if they satisfy ***any of the criteria*** below at the diagnosis index date:

- Record of diagnosis more than 30 days prior to diagnosis index date
- Diagnosed with one or more other primary malignancies before diagnosis index date, apart from non-melanoma skin cancer

Datasource limitations

In general, whilst data quality in HTI (i.e. in the underlying datasets including HES and HPA) has been steadily improving, cancer patients tracked in the HTI dataset may not be stratified by stage, morphology or other necessary clinical details. Another limitation of the data source is that only drug information dispensed from the pharmacy to an individual patient will be captured, which means medicines administered from ward stocks will not be captured, so this might affect the completeness of data we received. Also, the vital status (death) and death cause of a patient will only be known if they pass away in any HES hospitals. It is also possible that the recordkeeping of how many times a certain service was used by each patient might be inaccurate due to reimbursement issues. This could affect the accuracy of the direct medical cost calculated.

NSCLC case-finding algorithm

NSCLC case-finding algorithm – narrow case definition

Inclusion criteria for the proposed algorithm are based on the drugs approved for non-small cell lung cancer (NSCLC) in the UK and available through NHS, and exclusion criteria includes drugs approved for small cell lung cancer (SCLC) in the UK and available through NHS, as shown in Table 4.11. Drugs highlighted in yellow are available in both types of cancer (i.e. crossover drugs). If a single drug is used, that drug alone will be used to determine whether that patient will be included for the narrow case or broad case definition; patients whose treatments involving only one drug and is a crossover drug will be included in the broad case definition. In cases of a combination of drugs, non-crossover drugs will first be used to distinguish the type of cancer. If all the drugs in that combination are crossover drugs, then these cases will be excluded in the narrow case definition but included in the broad case definition.

Table 4.11: A list of approved drugs to treat SCLC and NSCLC and available through NHS (HTI Database).

Drugs Approved for Small Cell Lung Cancer (SCLC)	Drugs Approved for Non-Small Cell Lung Cancer (NSCLC)
Doxorubicin	Afatinib
Durvalumab	Bevacizumab
Etoposide	Carboplatin
Everolimus	Ceritinib
Ifosfamide	Crizotinib
Methotrexate	Dabrafenib
Nivolumab	Docetaxel
Pembrolizumab	Doxorubicin
Temozolomide	Erlotinib
Topotecan	Everolimus
	Gefitinib
	Gemcitabine
	Ipilimumab
	Methotrexate
	Nivolumab
	Osimertinib
	Paclitaxel
	Pembrolizumab
	Pemetrexed
	Ramucirumab
	Selpercatinib
	Trametinib
	Vinorelbine

NSCLC case-finding algorithm – broad case definition

Under broad case definition, cases of crossover drugs (i.e. drugs approved for use in both NSCLC and SCLC) will be included. Moreover, additional eligible cases will be

considered/included if patients are treated with one of the following drugs, which are unclear whether are available through NHS at this stage.

Small Cell Lung Cancer (SCLC) – Atezolizumab, Lurbinectedin

Non-small Cell Lung Cancer (NSCLC) – Alectinib, Atezolizumab, Brigatinib, Capmatinib, Dacomitinib, Durvalumab, Entrectinib, Lorlatinib, Necitumumab, Pralsetinib

Sensitivity analysis for NSCLC case-finding algorithm

Sensitivity analysis determines how different underlying elements impact an outcome under a given test of assumption, here the two different definitions of NSCLC case-finding algorithm will be used as independent variables to explore how they might affect the number of eligible cases recorded.

Exposure definition

The main exposure of interest is the first treatment of NSCLC recorded across all the tables within the HTI database and will be further defined by therapeutic class and as any chemotherapy, immunotherapy or targeted biological therapy listed below.

Within the cohort of NSCLC, patients will be classified into sub-cohorts based on the first anticancer treatment they received at treatment index date. Index date will be used to determine the start of the first treatment; the number of days used to determine the regimen for the first treatment normally ranges from 3 – 30 days. First treatment can mean a single medication or a combination of drugs. The earliest occurrence of either one of the following items will be used to determine the end of first treatment: (1) usage of drug(s) that are not listed within the regimen of the first treatment, in this case the day before starting a new regimen will be considered the end of the first treatment; (2) discontinuation of ALL agents listed in the first treatment; (3) end of study period; (4) death.

Non-small cell lung cancer (NSCLC)

- ***Chemotherapy:*** Cisplatin, Carboplatin, Docetaxel, Paclitaxel, Gemcitabine, Vinorelbine
- ***Targeted therapy:*** Afatinib, Bevacizumab, Certinib, Crizotinib, Erlotinib, Gefitinib
- ***Immunotherapy:*** Nivolumab, Pembrolizumab

Table 4.12: Anticancer drugs for NSCLC categorised by therapeutic class.

Alkylating Agent	**Anti-microtubule Agent**	**Anti-metabolite Agent**	**Anti-mitotic Agent**	**Tyrosine Kinase Inhibitors**	**Angiogenesis Inhibitor**	**Monoclonal antibody**
Cisplatin	Docetaxel	Gemcitabine	Vinorelbine	Afatinib	Bevacizumab	Nivolumab
Carboplatin	Paclitaxel	Pemetrexed		Ceritinib		Pem-brolizumab
				Crizotinib		
				Erlotinib		
				Gefitinib		

Treatments recorded in the HTI dataset will be reported without any modifications to naming or groups. The first treatment received will be determined through extracting the data of 'Drug code (Code: IMS_Drug_Code_FCC)' and 'Product name (Code: IMS_PROD_SHRT_NM).

For the primary objective analysis, all agents within each of the treatment groups of interest will be considered interchangeable in terms of exposure. Exposure is considered continuous between treatment index date and end of exposure. Switching will be defined as the interruption of a treatment within the first treatment and initiation of a second anticancer drug from a different class, following suspension of the first treatment.

For patients switching agents, the following rules will be applied:

- Switching within groups – patients will remain classified as being exposed to that group
- Switching between alternative groups – patient exposure time will be censored at the point of switching

The following rules will be used to define patients whose treatments involved change of dosage:

- Follow-up dispensing dosage is greater than the initial maintenance dosage
- Increased frequency of the same maintenance dosage (e.g. from fortnightly to weekly)

Data items to be collected

An indicative list of study parameters for the analysis of patient demographics, clinical characteristics and treatment patterns is shown below. A list of proposed data variables to be extracted from HTI is included in Table 4.13. Code lists that will inform on the definition of these variables will be developed in the statistical analysis plan.

Table 4.13: Proposed data variables to be extracted

Column Name	Column Description	To be extracted from the following table
ENCRYPTED_HESID	Patient ID	ALL_AE_DIAG
ARRIVALDATE	Arrival date Year-Month-Day	ALL_AE_DIAG
SEX	Gender of patient	ALL_AE_DIAG
AGE	Age in years (integer)	ALL_AE_DIAG
DIAG	ICD10 codes for diagnoses	ALL_AE_DIAG
ENCRYPTED_HESID	Patient ID	ALL_APC_DIAG
EPISTART	Episode start date (Year-Month-Day)	ALL_APC_DIAG
SEX	Gender of patient	ALL_APC_DIAG
AGE	Age in years (integer)	ALL_APC_DIAG
DIAG	ICD10 codes for diagnoses	ALL_APC_DIAG
ENCRYPTED_HESID	Patient ID	ALL_APC_OPER
EPISTART	Episode start date	ALL_APC_OPER
SEX	Gender of patient	ALL_APC_OPER
AGE	Age in years (integer)	ALL_APC_OPER
OPER	Operation codes (OPCS codes)	ALL_APC_OPER
AEATTENDCAT	Categorical variable for A&E attendance (whether initial or follow-up attendnace within a particular A&E department).	ALL_HES_AE
AEATTENDDISP	Attendance disposal. The way in which an A&E attendnace might end.	ALL_HES_AE
ARRIVALDATE	Arrival date (Year-Month-Day)	ALL_HES_AE
DIAG_01 to DIAG_12	A&E diagnosis	ALL_HES_AE
ENCRYPTED_HESID	Patient ID	ALL_HES_AE
ETHNOS	The ethnicity of the patient, as specified by the patient. This field uses the ethnic data categories as defined in the 2001 census. Note that ETHNOS is very poorly populated on activity prior to the 2011-12 data year.	ALL_HES_AE
HRGNHS	The Trust generated HRG code	ALL_HES_AE

HRGNHSVN	The version number for Trust generated HRG code	ALL_HES_AE
PEREND	Reporting period end date	ALL_HES_AE
RTTPEREND	RTT period end date. The end date of a referral to treatment period.	ALL_HES_AE
RTTPERSTART	RTT period start	ALL_HES_AE
SEX	Gender of patient	ALL_HES_AE
SUSHRG	Healthcare resource groups (HRG) data	ALL_HES_AE
SUSHRGVERS	SUS generated HRG version number	ALL_HES_AE
TREAT_01 to TREAT_12	A&E treatment	ALL_HES_AE
EXTRACT_SITECODE	Trust code	ALL_HES_AE
DIAG_01 TO DIAG_20	Diagnosis codes. The field diag_01 contains the primary diagnosis. The other fields contain secondary/subsidiary diagnoses.	ALL_HES_APC
DISDATE	Date of discharge. This field contains the date on which the patient was discharged from hospital. ; It is only present in the record for the last episode of a spell.	ALL_HES_APC
DISMETH	Method of discharge	ALL_HES_APC
DISREADYDATE	Discharge ready date. The date that a patient was medically ready for discharge from a hospital bed, but couldn't be discharged, therefore qualifying for delayed discharge payments.	ALL_HES_APC
DOMPROC	Trust derived dominant procedure. Contains the dominant procedure (operation) code assigned as part of the (NHS) HRG derivation process and submitted to SUS.	ALL_HES_APC
ELECDATE	Date of decision to admit. The patient may or may not be admitted immediately. The time between elecdate and admidate (admission date) is known as the waiting time.	ALL_HES_APC
ENCRYPTED_HESID	Patient ID	ALL_HES_APC
EPIDUR	Episode duration. This field contains the difference in days between the episode start date (epistart) and the episode end date (epiend). This is the full duration	ALL_HES_APC

	of a finished episode only. Episode duration is not applicable for 'other maternity events' and shall therefore remain null	
EPIEND	Episode end date	ALL_HES_APC
EPIORDER	Episode order. This field contains the number of the episode within the current spell. All spells start with an episode where epiorder is 01. Many spells finish with this episode, but if the patient moves to the care of another consultant, a new episode begins.	ALL_HES_APC
EPISTART	Episode start date. This field contains the date on which a patient was under the care of a particular consultant. If a patient has more than one episode in a spell, for each new episode there is a new value of epistart. However, the admission date which is copied to each new episode in a spell will remain unchanged and will be equal to the episode start date of the first episode in hospital.	ALL_HES_APC
EPISTAT	Episode status. This field tells you whether the episode had finished before the end of the HES data-year	ALL_HES_APC
ETHNOS	The ethnicity of the patient, as specified by the patient	ALL_HES_APC
FIRSTREG	First regular day or night admission. This field indicates whether the episode falls within a sequence of regular day and night admissions and, if so, whether it is the first or subsequent episode within the sequence	ALL_HES_APC
HRGNHS	The Trust generated HRG code	ALL_HES_APC
HRGNHSVN	The version number for Trust generated HRG code	ALL_HES_APC
OPCS43	OPCS codes 4.3	ALL_HES_APC

OPDATE_01 to OPDATE_24	Date of first operation, if had one, to 24th op. This field contains the date of the procedure recorded in the respectively numbered procedure code (opertn_nn) field. There is room for twenty four dates (twelve prior to April 2007 and four before April 2002).	ALL_HES_APC
OPERSTAT	Operation status code	ALL_HES_APC
OPERTN_01 TO OPERTN_24	Operation code for 1st to 24th op if had ops. There are twenty-four fields (twelve before April 2007), oper_01 to oper_24, which contain information about a patient's operations.	ALL_HES_APC
SEX	Gender of patient	ALL_HES_APC
SUSCOREHRG	SUS generated Core Spell HRG	ALL_HES_APC
SUSHRG	SUS generated HRG	ALL_HES_APC
SUSHRGVERS	SUS generated HRG version number	ALL_HES_APC
SUSRECID	SUS record ID	ALL_HES_APC
SUSSPELLID	SUS generated spell identifier	ALL_HES_APC
EXTRACT_SITECODE	Trust code	ALL_HES_APC
APPTDATE	Appointment date	ALL_HES_OP
DIAG_01 to DIAG_12	The field diag_01 contains the primary diagnosis. The other fields contain secondary/subsidiary diagnoses.	ALL_HES_OP
ENCRYPTED_HESID	Patient ID	ALL_HES_OP
ETHNOS	The ethnicity of the patient, as specified by the patient	ALL_HES_OP
EXTRACT_SITECODE	Trust code	ALL_HES_OP
HRGNHS	The Trust generated HRG code	ALL_HES_OP
HRGNHSVN	The version number for Trust generated HRG code	ALL_HES_OP
OPERSTAT	Operation status code	ALL_HES_OP
OPERTN_01 TO OPERTN_24	Operation code for 1st to 24th op if had ops	ALL_HES_OP
Outcome	Outcome of attendance	ALL_HES_OP
ENCRYPTED_HESID	Patient ID	ALL_OP_DIAG
APPTDATE	Appointment date	ALL_OP_DIAG
SEX	Gender of patient	ALL_OP_DIAG
AGE	Age in years (integer)	ALL_OP_DIAG
DIAG	ICD10 codes for diagnoses	ALL_OP_DIAG
ENCRYPTED_HESID	Patient ID	ALL_OP_OPER
APPTDATE	Appointment date	ALL_OP_OPER
SEX	Gender of patient	ALL_OP_OPER

AGE	Age in years (integer)	ALL_OP_OPER
OPER	Operations	ALL_OP_OPER
SEX	Gender of patient	ALL_HES_OP
SUSHRG	SUS generated HRG	ALL_HES_OP
SUSHRGVERS	SUS generated HRG version number	ALL_HES_OP
FCC	Drug code (FCC)	FCC_Lookup
IMS_PROD_SHRT_NM	Product Name	FCC_Lookup
CTRY_SPEC_PACK_CU_QTY		FCC_Lookup
FORM_DESC	The form the drug is in such as caps (capsules), vial, pellet etc.	FCC_Lookup
ABS_STRNT_QTY		FCC_Lookup
VOL_QTY	Volume quantity	FCC_Lookup
PACK_VOL_TXT	Pack volume text	FCC_Lookup
PACK_VOL_OR_WGT_TXT		FCC_Lookup
ATC_1_CD	ATC code level 1, should be Ephmra codes	FCC_Lookup
ATC_2_CD	ATC code level 2, should be Ephmra codes	FCC_Lookup
ATC_3_DESC	ATC code description	FCC_Lookup
ATC_4_CD	ATC code level 4, should be Ephmra codes	FCC_Lookup
NFC_123_CD_AND_SHRT_DESC_TXT	Description if drug forms with 3 letter code at the start	FCC_Lookup
CUR_REC_IND		FCC_Lookup
PACK_DESC	Description of packs	FCC_Lookup
FCC	Drug Code (FCC)	FCC_to_Molecule
COMBINATION_MOLECULE	Name of molecule	FCC_to_Molecule
ENCRYPTED_HESID	Patient ID	IMSDrugFile
IMS_Drug_Code_FCC	Drug code (FCC)	IMSDrugFile
DateTime_of_Issue	Issue date and time Year-Month-Day, time 24 hours	IMSDrugFile
IMS_Speciality_Code	Speciality code for ward. Such as whether in rheumatology or demeratology etc.	IMSDrugFile
Drug_Quantity	Quantity of drug given	IMSDrugFile
EXTRACT_SITECODE	Site code that drug was dispensed at	IMSDrugFile
MATCH_RANK	Goodness of rank	IMSDrugFile
acardsupdays	Advanced cardiovascular support days	ALL_HES_CC
bcardsupdays	Basic cardiovascular support days	ALL_HES_CC
ccapcrel	Critical care APC relationship ID. A comparison of the dates of the	ALL_HES_CC

	critical care period and those of the associated admitted patient care episode. This is used in the derivation of the best match flag by producing a hierarchy of relationships.	
ccdisdate	Critical care discharge date. Discharge date from unit if alive, date of death or date of declaration of brain stem death.	ALL_HES_CC
ccstartdate	Critical care start date	ALL_HES_CC
ccunitfun	Critical care unit function	ALL_HES_CC
susrecid	SUS record ID	ALL_HES_CC
CHANNEL	Whether in, out or homecare patient	UK_HPA_Ward_Department_Speciality
WARD	Ward code, matches to specialty code in IMSDrugFile	UK_HPA_Ward_Department_Speciality
DEPARTMENT	Department type	UK_HPA_Ward_Department_Speciality
SPECIALITY	Speciality of ward/department	UK_HPA_Ward_Department_Speciality
WardCode	Ward code, matches to specialty code in IMSDrugFile	WardCode_Lookup
Ward_Name	Ward name	WardCode_Lookup
Ward_In_Out	Whether in, out or homecare patient	WardCode_Lookup

Listed below are the ideal variables to be extracted for the analysis of patients' demographics, clinical characteristics and treatment patterns.

(1) Patients' Demographics – age, sex, ethnicity;

(2) Clinical Characteristics – site of neoplasm, vital status (death), date of vital status, death cause;

(3) Treatment Patterns (Patient-level) – administration date, drug code, drug quantity, basic cardiovascular support days, advanced cardiovascular support days, operating procedures and intensive care days.

All ICD-10 codes as listed below will be noted but the following listed cardiotoxicities (Table 4.14) will be of particular interest under patients' diagnosis information, including 'ALL_AE_DIAG', 'ALL_APC_DIAG', 'ALL_HES_APC', 'ALL_HES_OP', 'ALL_OP_DIAG'.

Abnormalities of Heart Rhythm

R00.1 - Bradycardia, unspecified

R00.8 - Other abnormalities of heart beat

R00.2 - Palpitations

R00.0 - Tachycardia, unspecified

R00.9 - Unspecified abnormalities of heart beat

Acute Myocarditis

I40.0 - Infective myocarditis

I40.1 - Isolated myocarditis

I40.8 - Other acute myocarditis

I40.9 - Acute myocarditis, unspecified

Atrial Fibrillation and Flutter

I48.4 - Atypical atrial flutter

I48.2 - Chronic atrial fibrillation

I48.0 - Paroxysmal atrial fibrillation

I48.1 - Persistent atrial fibrillation

I48.3 - Typical atrial flutter

I48.91 - Unspecified atrial fibrillation

I48.92 - Unspecified atrial flutter

Cardiac Arrest

I46.0 - Cardiac arrest with successful resuscitation

I46.1 - Sudden cardiac death, so described

I46.9 - Cardiac arrest, unspecified

Cardiac Arrhythmias

I49.1 - Atrial premature depolarisation

I49.9 - Cardiac arrhythmia, unspecified

I49.2 - Junctional premature depolarisation

I49.49 - Other premature depolarisation

I49.8 - Other specified cardiac arrhythmias

I49.5 - Sick sinus syndrome

I49.40 - Unspecified premature depolarisation

I49.01 - Ventricular fibrillation

I49.02 - Ventricular flutter

I49.3 - Ventricular premature depolarisation

Cardiomyopathy

I42.0 - Dilated cardiomyopathy

I42.1 - Obstructive hypertrophic cardiomyopathy

I42.2 - Other hypertrophic cardiomyopathy

I42.3 - Endomyocardial (eosinophilic) disease

I42.4 - Endocardial fibroelastosis

I42.5 - Other restrictive cardiomyopathy

I42.6 - Alcoholic cardiomyopathy

I42.7 - Cardiomyopathy due to drugs and other external agents

I42.8 - Other cardiomyopathies

I42.9 - Cardiomyopathy, unspecified

Chest Pain

I20.1 - Angina pectoris with documented spasm

I20.9 - Angina pectoris, unspecified

R07.1 - Chest pain on breathing

R07.9 - Chest pain, unspecified

R07.82 - Intercostal pain

R07.89 - Other chest pain

I20.8 - Other forms of angina pectoris

R07.81 - Pleurodynia

R07.2 - Precordial pain

I20.0 - Unstable angina

Heart Failure

I50.41 - Acute combined systolic (congestive) and diastolic (congestive) heart failure

I50.31 - Acute diastolic (congestive) heart failure

I50.43 - Acute on chronic combined systolic (congestive) and diastolic (congestive) heart failure

I50.33 - Acute on chronic diastolic (congestive) heart failure
I50.23 - Acute on chronic systolic (congestive) heart failure
I50.21 - Acute systolic (congestive) heart failure
I50.42 - Chronic combined systolic (congestive) and diastolic (congestive) heart failure
I50.32 - Chronic diastolic (congestive) heart failure
I50.22 - Chronic systolic (congestive) heart failure
I50.9 - Heart failure, unspecified
I50.1 - Left ventricular failure, unspecified
I50.40 - Unspecified combined systolic (congestive) and diastolic (congestive) heart failure
I50.30 - Unspecified diastolic (congestive) heart failure
I50.20 - Unspecified systolic (congestive) heart failure

Hypertension
I10 - Essential (primary) hypertension
I11.0 - Hypertensive heart disease with (congestive) heart failure
I11.9 - Hypertensive heart disease without (congestive) heart failure

Ischaemic Heart Diseases
I21.0 - Acute transmural myocardial infarction of anterior wall
I21.1 - Acute transmural myocardial infarction of inferior wall
I21.2 - Acute transmural myocardial infarction of other sites
I21.3 - Acute transmural myocardial infarction of unspecified site
I21.4 - Acute subendocardial myocardial infarction
I21.9 - Acute myocardial infarction, unspecified
I22.0 - Subsequent myocardial infarction of anterior wall
I22.1 - Subsequent myocardial infarction of inferior wall
I22.8 - Subsequent myocardial infarction of other sites
I22.9 - Subsequent myocardial infarction of unspecified site
I23.0 - Haemopericardium as current complication following acute myocardial infarction
I23.1 - Atrial septal defect as current complication following acute myocardial infarction
I23.2 - Ventricular septal defect as current complication following acute myocardial infarction
I23.3 - Rupture of cardiac wall without haemopericardium as current complication following acute myocardial infarction

I23.4 - Rupture of chordae tendineae as current complication following acute myocardial infarction
I23.5 - Rupture of papillary muscle as current complication following acute myocardial infarction
I23.6 - Thrombosis of atrium, auricular appendage, and ventricle as current complications following acute myocardial infarction
I23.8 - Other current complications following acute myocardial infarction
I24.0 - Coronary thrombosis not resulting in myocardial infarction
I24.1 - Dressler syndrome
I24.8 - Other forms of acute ischaemic heart disease
I24.9 - Acute ischaemic heart disease, unspecified
I25.0 - Atherosclerotic cardiovascular disease
I25.1 - Atherosclerotic heart disease
I25.2 - Old myocardial infarction
I25.3 - Aneurysm of heart
I25.4 - Coronary artery aneurysm
I25.5 - Ischaemic cardiomyopathy
I25.6 - Silent myocardial ischaemia
I25.8 - Other forms of chronic ischaemic heart disease
I25.9 - Chronic ischaemic heart disease, unspecified

Nonrheumatic Valve Disorders (Aortic Valve Disorders)
I35.1 - Nonrheumatic aortic (valve) insufficiency
I35.0 - Nonrheumatic aortic (valve) stenosis
I35.2 - Nonrheumatic aortic (valve) stenosis with insufficiency
I35.9 - Nonrheumatic aortic valve disorder, unspecified
I35.8 - Other nonrheumatic aortic valve disorders

Nonrheumatic Valve Disorders (Mitral Valve Disorders)
I34.0 - Nonrheumatic mitral (valve) insufficiency
I34.1 - Nonrheumatic mitral (valve) prolapse
I34.2 - Nonrheumatic mitral (valve) stenosis
I34.9 - Nonrheumatic mitral valve disorder, unspecified
I34.8 - Other nonrheumatic mitral valve disorders

Paroxysmal Tachycardia

I47.0 - Re-entry ventricular arrhythmia

I47.1 - Supraventricular tachycardia

I47.2 - Ventricular tachycardia

I47.9 - Paroxysmal tachycardia, unspecified

Others

I51.0 - Cardiac septal defect, acquired

I51.1 - Rupture of chordae tendineae, not elsewhere classified

I51.2 - Rupture of papillary muscle, not elsewhere classified

I51.3 - Intracardiac thrombosis, not elsewhere classified

I51.4 - Myocarditis, unspecified

I51.5 - Myocardial degeneration

I51.6 - Cardiovascular disease, unspecified

I51.7 - Cardiomegaly

I51.8 - Other ill-defined heart diseases

I51.9 - Heart disease, unspecified

Table 4.14: A list of cardiotoxicities of particular interest.

Name of Disease	**ICD-10 Code**
Abnormalities of heart beat	R00
Acute myocardial infarction	I21
Acute myocarditis	I40
Atrial fibrillation & flutter	I48
Cardiac arrest	I46
Cardiac arrhythmias	I49
Cardiomegaly	I51.7
Cardiomyopathy	I42
Coronary artery disease	I25.1, including I25.10 – I25.119
Essential primary hypertension	I10
Heart disease, unspecified (including systolic and diastolic cardiac dysfunction)	I51.9
Heart failure	I50
Hypertensive heart disease	I11
Ischemia	I20 – I25
Paroxysmal tachycardia	I47

OPCS codes of particular interest are listed below.

Cardiac Surgery

Open chest procedures on the valves or septum of heart; does not include coronary artery bypass graft, surgery on vessels, heart transplantation, or pacemaker implantation.

K04 Repair of tetralogy of Fallot

Includes: Fallot-type pulmonary atresia with ventricular septal defect

K04.1 Repair of tetralogy of Fallot using valved right ventricular outflow conduit

K04.2 Repair of tetralogy of Fallot using right ventricular outflow conduit NEC

K04.3 Repair of tetralogy of Fallot using transannular patch

Includes: Repair of tetralogy of Fallot using right ventricular outflow patch

K04.4 Revision of repair of tetralogy of Fallot

K04.5 Repair of tetralogy of Fallot with absent pulmonary valve

K04.6 Repair of Fallot-type pulmonary atresia with aortopulmonary collaterals

K04.8 Other specified

K04.9 Unspecified

K05 Atrial inversion operations for transposition of great arteries

K05.1 Reconstruction of atrium using atrial patch for transposition of great arteries

K05.2 Reconstruction of atrium using atrial wall for transposition of great arteries

K05.8 Other specified

K05.9 Unspecified

K06 Other repair of transposition of great arteries

Includes: Repair of transposition of great arteries with ventricular septal defect

Repair of transposition of great arteries with left ventricular outflow tract obstruction

Repair of congenitally corrected transposition of great arteries

K06.1 Repositioning of transposed great arteries

Includes: Arterial switch procedure

K06.2 Left ventricle to aorta tunnel with right ventricle to pulmonary trunk direct anastomosis

K06.3 Left ventricle to aorta tunnel with right ventricle to pulmonary artery valved conduit

K06.4 Atrial inversion and repositioning of transposed great artery

Includes: Double switch procedure

K06.8 Other specified

K06.9 Unspecified

K07 Correction of total anomalous pulmonary venous connection

K07.1 Correction of total anomalous pulmonary venous connection to supracardiac vessel

K07.2 Correction of total anomalous pulmonary venous connection to coronary sinus

K07.3 Correction of total anomalous pulmonary venous connection to infradiaphragmatic vessel

K07.8 Other specified

K07.9 Unspecified

K08 Repair of double outlet ventricle

K08.1 Repair of double outlet right ventricle with intraventricular tunnel

K08.2 Repair of Fallot-type double outlet right ventricle

K08.3 Repair of double outlet right ventricle

K08.4 Repair of double outlet left ventricle

K08.8 Other specified

K08.9 Unspecified

K09 Repair of defect of atrioventricular septum

K09.1 Repair of defect of atrioventricular septum using dual prosthetic patches

K09.2 Repair of defect of atrioventricular septum using prosthetic patch NEC

K09.3 Repair of defect of atrioventricular septum using tissue graft

K09.4 Repair of persistent ostium primum

K09.5 Primary repair of defect of atrioventricular septum NEC

K09.6 Revision of repair of defect of atrioventricular septum

K09.8 Other specified

K09.9 Unspecified

K10 Repair of defect of interatrial septum

Excludes: When associated with repair of tetralogy of Fallot (K04)

Percutaneous transluminal repair of defect of interatrial septum (K13.3, K13.4)

K10.1 Repair of defect of interatrial septum using prosthetic patch

K10.2 Repair of defect of interatrial septum using pericardial patch

K10.3 Repair of defect of interatrial septum using tissue graft NEC

K10.4 Primary repair of defect of interatrial septum NEC

K10.5 Revision of repair of defect of interatrial septum

K10.8 Other specified

K10.9 Unspecified

K11 Repair of defect of interventricular septum

Excludes: When associated with repair of tetralogy of Fallot (K04)

Percutaneous transluminal repair of defect of interventricular septum (K13.1, K13.2)

K11.1 Repair of defect of interventricular septum using prosthetic patch

K11.2 Repair of defect of interventricular septum using pericardial patch

K11.3 Repair of defect of interventricular septum using tissue graft NEC

K11.4 Primary repair of defect of interventricular septum NEC

K11.5 Revision of repair of defect of interventricular septum

K11.6 Repair of multiple interventricular septal defects

K11.7 Repair of interventricular septal defect using intraoperative transluminal prosthesis

K11.8 Other specified

K11.9 Unspecified

K12 Repair of defect of unspecified septum of heart

Excludes: When associated with repair of tetralogy of Fallot (K04)

Percutaneous transluminal repair of defect of unspecified septum (K13.5–K13.9)

K12.1 Repair of defect of septum of heart using prosthetic patch NEC

K12.2 Repair of defect of septum of heart using pericardial patch NEC

K12.3 Repair of defect of septum of heart using tissue graft NEC

K12.4 Primary repair of defect of septum of heart NEC

K12.5 Revision of repair of septum of heart NEC

K12.8 Other specified

K12.9 Unspecified

K14 Other open operations on septum of heart

K14.1 Open enlargement of defect of atrial septum

K14.2 Open atrial septostomy

Includes: Open atrial septal fenestration

Atrial septostomy NEC

K14.3 Atrial septectomy

K14.4 Surgical atrial septation

K14.5 Open enlargement of defect of interventricular septum

K14.8 Other specified

K14.9 Unspecified

K17 Repair of univentricular heart

K17.1 Total cavopulmonary connection with extracardiac inferior caval vein to pulmonary artery conduit

K17.2 Total cavopulmonary connection with lateral atrial tunnel

K17.3 Aortopulmonary reconstruction with systemic to pulmonary arterial shunt

Includes: Primary palliation of hypoplastic left heart syndrome

K17.4 Aortopulmonary reconstruction with right ventricle to pulmonary arterial valveless conduit

Includes: Primary palliation of hypoplastic left heart

K17.5 Biventricular repair of hypoplastic left heart syndrome

K17.6 Takedown of total cavopulmonary connection

K17.7 Conversion of atrial pulmonary anastomosis to total pulmonary connection

K17.8 Other specified

K17.9 Unspecified

K18 Creation of valved cardiac conduit

Excludes: When associated with repair of tetralogy of Fallot (K04)

K18.1 Creation of valved conduit between atrium and ventricle of heart

K18.2 Creation of valved conduit between right atrium and pulmonary artery

K18.3 Creation of valved conduit between right ventricle of heart and pulmonary artery

K18.4 Creation of valved conduit between left ventricle of heart and aorta

K18.5 Revision of valved cardiac conduit

K18.6 Creation of valved conduit between left ventricle of heart and pulmonary artery

K18.7 Replacement of valved cardiac conduit

K18.8 Other specified

K18.9 Unspecified

K19 Creation of other cardiac conduit

Excludes: When associated with repair of tetralogy of Fallot (K04)

K19.1 Creation of conduit between atrium and ventricle of heart NEC

K19.2 Creation of conduit between right atrium and pulmonary artery NEC

K19.3 Creation of conduit between right ventricle of heart and pulmonary artery NEC

K19.4 Creation of conduit between right ventricle of heart and vena cava

K19.5 Creation of conduit between left ventricle of heart and aorta NEC

K19.6 Revision of cardiac conduit NEC

K19.8 Other specified

K19.9 Unspecified

K20 Refashioning of atrium

K20.1 Correction of persistent sinus venosus

K20.2 Correction of partial anomalous pulmonary venous drainage

K20.3 Repair of cor triatriatum

K20.4 Repair of coronary sinus abnormality

K20.8 Other specified

K20.9 Unspecified

K22 Other operations on wall of atrium

Excludes: Operations on coronary artery (K40-K51) or conducting system of heart (K52, K57, K58)

K22.1 Excision of lesion of atrium

K22.2 Repair of atrium NEC

K22.8 Other specified

K22.9 Unspecified

K23 Other operations of wall of heart

Excludes: Operations on coronary artery (K40–K51) or conducting system of heart (K52, K57–K58)

K23.1 Excision of lesion of wall of heart NEC

Includes: Excision of lesion of ventricle of heart

K23.2 Biopsy of lesion of wall of heart

Includes: Biopsy of wall of heart

Biopsy of lesion of heart NEC

Biopsy of heart NEC

K23.3 Repair of wall of heart NEC

K23.5 Partial left ventriculectomy

K23.6 Cardiomyoplasty

K23.8 Other specified

K23.9 Unspecified

K24 Other operations on ventricles of heart

K24.1 Relief of right ventricular outflow tract obstruction

K24.2 Repair of double chambered right ventricle

K24.3 Repair of right ventricular aneurysm

K24.4 Repair of left ventricular aneurysm

K24.5 Relief of left ventricular outflow tract obstruction

K24.6 Myectomy of left ventricular outflow tract

K24.7 Myotomy of left ventricular outflow tract

K24.8 Other specified

K24.9 Unspecified

K25 Plastic repair of mitral valve

Excludes: Annuloplasty of mitral valve (K34.1)

K25.1 Allograft replacement of mitral valve

K25.2 Xenograft replacement of mitral valve

K25.3 Prosthetic replacement of mitral valve

K25.4 Replacement of mitral valve NEC

K25.5 Mitral valve repair NEC

Includes: Mitral valvuloplasty NEC

K25.8 Other specified

K25.9 Unspecified

K26 Plastic repair of aortic valve – use as a supplementary code for concurrent multiple replacement of valves of heart (e.g. K25)

K26.1 Allograft replacement of aortic valve

K26.2 Xenograft replacement of aortic valve

K26.3 Prosthetic replacement of aortic valve

K26.4 Replacement of aortic valve NEC

K26.5 Aortic valve repair NEC

Includes: Aortic valvuloplasty NEC

K26.8 Other specified

K26.9 Unspecified

K27 Plastic repair of tricuspid valve

K27.1 Allograft replacement of tricuspid valve

K27.2 Xenograft replacement of tricuspid valve

K27.3 Prosthetic replacement of tricuspid valve

K27.4 Replacement of tricuspid valve NEC

K27.5 Repositioning of tricuspid valve

K27.6 Tricuspid valve repair NEC

Includes: Tricuspid valvuloplasty NEC

K27.8 Other specified

K27.9 Unspecified

K28 Plastic repair of pulmonary valve

K28.1 Allograft replacement of pulmonary valve

K28.2 Xenograft replacement of pulmonary valve

K28.3 Prosthetic replacement of pulmonary valve

K28.4 Replacement of pulmonary valve NEC

K28.5 Pulmonary valve repair NEC

Includes: Pulmonary valvuloplasty NEC

K28.8 Other specified

K28.9 Unspecified

K29 Plastic repair of unspecified valve of heart

Includes: Plastic repair of other specified valve of heart

K29.1 Allograft replacement of valve of heart NEC

K29.2 Xenograft replacement of valve of heart NEC

K29.3 Prosthetic replacement of valve of heart NEC

K29.4 Replacement of valve of heart NEC

K29.5 Repair of valve of heart NEC

Includes: Valvuloplasty of heart NEC

K29.6 Truncal valve repair

Includes: Truncal valvuloplasty

K29.7 Replacement of truncal valve

K29.8 Other specified

K29.9 Unspecified

K30 Revision of plastic repair of valve of heart

Includes: Revision of replacement of valve of heart

K30.1 Revision of plastic repair of mitral valve

K30.2 Revision of plastic repair of aortic valve

K30.3 Revision of plastic repair of tricuspid valve

K30.4 Revision of plastic repair of pulmonary valve

K30.5 Revision of plastic repair of truncal valve

K30.8 Other specified

K30.9 Unspecified

K31 Open incision of valve of heart

Includes: Incision of valve of heart NEC

K31.1 Open mitral valvotomy

K31.2 Open aortic valvotomy

K31.3 Open tricuspid valvotomy

K31.4 Open pulmonary valvotomy

K31.5 Open truncal valvotomy

K31.8 Other specified

K31.9 Unspecified

Includes: Valvotomy NEC

K32 Closed incision of valve of heart

K32.1 Closed mitral valvotomy

K32.2 Closed aortic valvotomy

K32.3 Closed tricuspid valvotomy

K32.4 Closed pulmonary valvotomy

K32.8 Other specified

K32.9 Unspecified

K34 Other open operations on valve of heart

K34.1 Annuloplasty of mitral valve

K34.2 Annuloplasty of tricuspid valve

K34.3 Annuloplasty of valve of heart NEC

K34.4 Excision of vegetations of valve of heart

Excludes: Open excision of vegetations of heart NEC (K55.4)

K34.5 Closure of tricuspid valve

K34.6 Closure of pulmonary valve

K34.8 Other specified

K34.9 Unspecified

K36 Excision of valve of heart

K36.1 Tricuspid valvectomy

K36.2 Pulmonary valvectomy

K36.8 Other specified

K36.9 Unspecified

K67 Excision of pericardium

K67.1 Excision of lesion of pericardium

K67.8 Other specified

K67.9 Unspecified

K69 Incision of pericardium

K69.1 Freeing of adhesions of pericardium

K69.2 Fenestration of pericardium

K69.8 Other specified

K69.9 Unspecified

Coronary artery bypass graft

Open chest procedure to perform direct revascularisation of heart, for example, using suitable vein from leg for grafting, internal mammary artery, etc.

K40 Saphenous vein graft replacement of coronary artery

K40.1 Saphenous vein graft replacement of one coronary artery

K40.2 Saphenous vein graft replacement of two coronary arteries

K40.3 Saphenous vein graft replacement of three coronary arteries

K40.4 Saphenous vein graft replacement of four or more coronary arteries

K40.8 Other specified saphenous vein graft replacement of coronary artery

K40.9 Unspecified saphenous vein graft replacement of coronary artery

K41 Other autograft replacement of coronary artery

K41.1 Autograft replacement of one coronary artery not elsewhere classified

K41.2 Autograft replacement of two coronary arteries not elsewhere classified

K41.3 Autograft replacement of three coronary arteries not elsewhere classified

K41.4 Autograft replacement of four or more coronary arteries not elsewhere classified

K41.8 Other specified autograft replacement of coronary artery

K41.9 Unspecified other autograft replacement of coronary artery

K43 Prosthetic replacement of coronary artery

K43.1 Prosthetic replacement of one coronary artery

K43.2 Prosthetic replacement of two coronary arteries

K43.3 Prosthetic replacement of three coronary arteries

K43.4 Prosthetic replacement of four or more coronary arteries

K43.8 Other specified prosthetic replacement of coronary artery

K43.9 Unspecified prosthetic replacement of coronary artery

K44 Other replacement of coronary artery

Includes: Coronary artery bypass graft not elsewhere classified

K44.1 Replacement of coronary arteries using multiple methods

K44.2 Revision of replacement of coronary artery

K44.8 Other specified other replacement of coronary artery

K44.9 Unspecified other replacement of coronary artery

K45 Connection of thoracic artery to coronary artery

K45.1 Double anastomosis of mammary arteries to coronary arteries

K45.2 Double anastomosis of thoracic arteries to coronary arteries not elsewhere classified

K45.3 Anastomosis of mammary artery to left anterior descending coronary artery
K45.4 Anastomosis of mammary artery to coronary artery not elsewhere classified
K45.5 Anastomosis of thoracic artery to coronary artery not elsewhere classified
K45.6 Revision of connection of thoracic artery to coronary artery
K45.8 Other specified connection of thoracic artery to coronary artery
K45.9 Unspecified connection of thoracic artery to coronary artery

K46 Other bypass of coronary artery
Excludes: Coronary artery bypass graft (K40-K44)
K46.1 Double implantation of mammary arteries into heart
K46.2 Double implantation of thoracic arteries into heart not elsewhere classified
K46.3 Implantation of mammary artery into heart not elsewhere classified
K46.4 Implantation of thoracic artery into heart not elsewhere classified
K46.5 Revision of implantation of thoracic artery into heart
K46.8 Other specified other bypass of coronary artery
K46.9 Unspecified other bypass of coronary artery

Statistical Analysis

General approach

A detailed statistical analysis plan will be prepared for this study and will include a full description of the HTI database. An overview of the general statistical methods and planned approach for analyses related to primary and secondary objectives are provided in this section.

Descriptive analyses will be conducted using number and percent within each category with 95% confidence intervals (whenever appropriate) for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables. Only available data will be summarised; no imputation methods will be used to handle missing data. The number and percentage of missing values will also be reported as appropriate.

Primary objective – ***To describe the association between cardiotoxicity-related outcomes of interest (all and by sub-type) within first 6 months following diagnosis index date in patients diagnosed with NSCLC, overall and following treatment index date according to first therapy received***

The counts and proportions of incident reports of cardiotoxic events in all patients within each cancer group will be summarised for the total six-month period following diagnosis. The association between cardiotoxic events and first therapy will be explored by the chi-squared hypothesis test (χ^2). It will be used to test if an observed distribution of frequencies happened purely by chance or is there an underlying factor that caused it.[35] In this study, the most common form of χ^2 test – contingency test / table – will be used to investigate if there is an association between the observed distribution (i.e. frequency of cardiotoxicity) and the given factor (i.e. anticancer drugs). The counts and proportions of incident reports of cardiotoxic events in all patients within each cancer group will be summarised for the total six-month period following start of treatment. A time-to-event analysis by Kaplan-Meier method will also be used. The event here is defined as the capture of cardiotoxicity-related outcome of interest.

Secondary objective 1 – ***To explore the completeness of data elements/variables within the HTI database***

A list of ideal variables to be extracted from the database is listed out in Table 4.13. After gaining access to the database, data extraction process will be carried out using SQL to explore how many ideal variables are collected to support this kind of study. The level of missingness of variables will also be reported.

Secondary objective 2 – ***To define NSCLC patients and their corresponding first treatment recorded in HTI***

Details of NSCLC case-finding algorithm by narrow and broad case definition is explained previously. Sensitivity analysis will be conducted to determine the capability of the data source to define NSCLC patients. A tornado diagram will also be presented if necessary.

Secondary objective 3 – ***To describe the clinical characteristics of the overall cohort of patients with NSCLC at diagnosis date***

Descriptive analyses will be conducted using number and percent within each category with 95% confidence intervals (whenever appropriate) for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

Secondary objective 4 – ***To describe different drugs' combinations within first treatment of the overall cohort of patients with NSCLC at treatment date***

Statistical analysis same as that of Secondary Objective 3. Drug utilisation pattern (e.g. proportion of first line of therapy (LoT) used as first treatment) will also be described if possible. A suggestive list of first LoT (provided in the full protocol and statistical analysis plan) will be used for identification purposes. Any drug that is recorded in the first 30 days will be considered as part of the same regimen.

Secondary objective 5 – ***To describe the association between first treatment patterns (e.g. dose and duration) and cardiotoxicity-related outcome of interest, following initial NSCLC diagnosis***

First treatment patterns will be described using descriptive analyses same as that of Secondary Objective 3. Duration of treatment will be followed from start of first treatment to end of first treatment. Kaplan-Meier analysis will be used, and the event here will be the end of first treatment. Pearson's correlation coefficient (r) will then be calculated to determine if different dosages and duration of the same anticancer drug affect its association with cardiotoxicity. The square of Pearson's correlation coefficient (r^2), i.e. coefficient of determination, will be used as a measure of correlation. If it has been proved that there is significant correlation between anticancer drugs and cardiotoxicity, then logistic regression calculation will be carried out. However, if there is a lot of missing data, then Cox regression with be used instead.

Secondary objective 6 – ***To describe and compare the characteristics of sub-groups receiving first treatment, according to start of treatment date***

Categorical data/characteristics will be summarised in a table. For continuous data, one-way ANOVA will be used to compare other characteristics within and between sub-groups whereas for non-parametric data, Mann-Whitney test will be used. A boxplot will also be presented to provide a graphical summary of distribution.

Secondary objective 7 – ***To describe and compare progression-free survival of sub-groups following first treatment***

Categorical data/characteristics will be summarised in a table. A boxplot will also be presented to provide a graphical summary of distribution. Kaplan-Meier analysis will also be used; patients will be followed up from diagnosis date to progression date and the event here will be progression. Progression is defined as a proxy using the start date of the second treatment related to NSCLC recorded or death. The median duration of progression-free survival will then be compared among various sub-groups. For continuous data, one-way ANOVA will be used to compare other characteristics within and between sub-groups whereas for non-parametric data, Mann-Whitney test will be used.

Secondary objective 8 – ***To describe the clinical features of incident reports of cardiotoxicity in patients following first treatment***

Statistical analysis same as that of Secondary Objective 3.

Secondary objective 9 – ***To describe and compare the characteristics of cancer patients with cardiotoxicity and without cardiotoxicity at the end of the follow-up period***

Categorical data/characteristics will be summarised in a table. For continuous data, one-way ANOVA will be used to compare other characteristics between patients with or without CV events of interest at the end of the follow-up period whereas for non-parametric data, Mann-Whitney test will be used. A boxplot will also be presented to provide a graphical summary of distribution.

Secondary objective 10 – ***To identify important risk factors for cardiotoxicity by comparing characteristics of cardiotoxicity cases to non-cases at start of first treatment***

A multiple logistic regression analysis will be performed for all variables to assess the relationship between potential risk factors and cardiotoxicity. Odds ratio will be calculated to determine the association between the exposure and an outcome, i.e. CV events of interest. The odds ratio compares the odds of cardiotoxicity happening with certain exposure to that of without the same exposure. However, if there is a considerable amount of missing data, Cox regression will be used instead. Hazard ratio will be calculated to determine the association between the exposure and an outcome, i.e. CV events of interest. The odds ratio / hazard ratio will be reported alongside a p-value and/or 95% confidence interval.

4.6 Concluding Remarks

Based on results from the feasibility assessment, NCRAS database was first used. As mentioned in Section 4.5.1, Simulacrum, which contains artificial patient data, mimics the structure and types of CAS data. Therefore, it was used for feasibility work as well as the development of debugging and validation of programming code. Initial agreement with IQVIA was that a team member would then run the analyses on the CAS database. However, owing to factors beyond our control, that was no longer possible. And thus, necessitated a pivot from the initially selected NCRAS database to the next most suitable database – HTI database. This shift was driven not by a change in research focus but by external factors that were unavoidable.

Application for investigation involving the UK HTI Database was submitted to the Independent Scientific and Ethical Advisory Committee (ISEAC) and had been approved on 8 September 2021. A copy of the approval letter is available in Appendix III. While preparations for utilising the HTI database were in progress, an unexpected audit on HTI's data handling and storage practices was initiated. This audit led to a temporary suspension of data access, halting all data retrieval activities. This pause was crucial to ensure compliance with the latest data governance and privacy standards, but it inevitably delayed the research timeline significantly. During this interim, further complications arose as the National Health Service (NHS) underwent a structural reorganisation. This reorganisation affected various aspects of data accessibility and integration, leading to additional delays.

Given these compounded delays and the escalating costs associated with accessing alternative databases that could meet the same criteria as NCRAS or HTI, the decision was made to utilise the DEFINE database. The DEFINE database, while not initially considered, offered a feasible compromise between data comprehensiveness and accessibility. The use of DEFINE database involves adapting the study's objectives and methods to fit the specific data structures and available variables. Further details regarding this database are elaborated in Chapter 5.

In conclusion, while the transition from NCRAS to HTI, and ultimately to the DEFINE database, was not without challenges, it emphasises the importance of flexibility and adaptability in research. Each database shift brought its own set of requirements and limitations, which were meticulously addressed to maintain the integrity and scientific rigor of the study. The final selection of the DEFINE database, driven by a combination of inevitable constraints, highlights the dynamic nature of conducting large-scale pharmacoepidemiological research in an ever-evolving healthcare sector.

Chapter 5

Identification of Cardiotoxicity Related to Non-Small Cell Lung Cancer Treatments Using the UK DEFINE Database

5.1 Introduction

Understanding cardiotoxicity is of paramount importance due to its potential impact on cancer survivors' long-term health and quality of life. As the number of cancer survivors continues to rise, it becomes crucial to identify and manage cardiotoxicity early on, allowing for timely intervention and minimising long-term cardiac complications. Moreover, with the rapid development of novel cancer treatments, including targeted therapies, immunotherapies, and emerging modalities, an in-depth understanding of the associated cardiotoxicity profiles is crucial for both oncologists and cardiologists.

A U.K. Hospital Medicines Usage Database (DEFINE), which is an NHS prescribing database of hospital medicines usage, was used in this study. The DEFINE software package provides intelligence in medicines usage in secondary care in a similar way to the ePACT system used in primary care. The DEFINE database runs within the NHS's secure N3 network. The essence and transformative capability of this system lies in its ability to track the use of medicines across various facilities. This is achieved by integrating the data into a comprehensive cross-hospital data repository that adheres to standardised pharmaceutical coding systems, such as the World Health Organization (WHO)'s Anatomical Therapeutic Chemical (ATC) classification, the NHS dictionary of medicines' and devices (dm+d), the structures of the British National Formulary (BNF), and NHS clinical specialty codes. The organised data, augmented by an extensive collection of reports, enables unprecedented levels of exploration, analysis, and comparison of medications and clinical specialties (Hey, 2022).

The Defined Daily Dose (DDD) system is part of the Anatomical Therapeutic Chemical (ATC) classification system, which classifies drugs into different groups according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. The use of DDD helps monitor and compare drug consumption patterns, evaluate adherence to clinical guidelines, plan and manage healthcare resources, as well as conduct pharmacoepidemiological research. Although the DDD system is a valuable tool for drug utilisation research, it has limitations as the standard DDD values may not reflect the actual prescribed doses, which can vary based on individual patient needs, comorbidities, and local clinical practices. Therefore, while DDD is useful for population-level analyses, DDD should not be used for determining the appropriate dose for individual patients (Hollingworth and Kairuz, 2021).

As the DEFINE database is the only hospital medicines usage database which is easily accessible and covers over 90% of NHS hospitals, it provides a large sample size, thus providing a more representative view of certain trends. Whilst the database potentially allows access to individual hospitals medicines use, this requires permissions from each hospital. As there are over 200 NHS Trusts in England this was not possible, so the data available for this research was aggregated data. Since the DEFINE database allows hospitals to monitor and analyse drug usage, it can help researchers and healthcare professionals to understand drug treatment patterns, identify variances in prescribing practices, as well as optimise drug stock levels. Moreover, by providing detailed information on medication expenditures, the database helps healthcare providers manage budgets more effectively, and identify areas where cost savings can be made without compromising patient care. Hospitals can also use the DEFINE database to benchmark their performance against other NHS trusts, thus enabling them to identify best practices and areas for improvement in drug management. The DEFINE database also supports clinical research by providing data on the real-world use of medications, which are invaluable for observational studies and post-marketing surveillance, hence contributing to improved patient safety and quality of care.

For this research, 40 drugs were shortlisted—20 cardiology and 20 oncology drugs. 20 cardiology drugs were shortlisted based on the results analysed from systematic review (Chapter 3), which were identified to treat the top eight most common cardiotoxicities. Top 20 most commonly used non-small cell lung cancer (NSCLC) treatments, based on the count of NSCLC drugs by Hospital Treatment Insight (HTI) database, were also shortlisted.

5.2 Aim and Objectives

5.2.1 Aim

The aim of this study was to determine the association between cardiotoxicity and cancer treatments, using the DEFINE database.

5.2.2 Primary Objective

To explore the feasibility of using the DEFINE database to investigate if there is an association between 20 shortlisted cardiology drugs that are identified to treat the top eight most common cardiotoxicities with top 20 most commonly used NSCLC treatments.

5.2.3 Secondary Objectives

1. To describe the overall utilisation of the 40 shortlisted drugs, by regional and national level.
2. To describe the general trend of utilisation of the 40 shortlisted drugs.

5.3 Methods

5.3.1 Types of Studies

The study was a retrospective analysis of UK secondary care utilisation of shortlisted drugs in oncology and cardiology specialities using the DEFINE database in England (see section 5.3.3).

5.3.2 Setting

England was the setting for this study, with over 90% of acute NHS hospitals as well as specialist centres and mental health trusts throughout the UK. The DEFINE software is an NHS prescribing database of medicines usage covering over 90% of acute NHS hospitals as well as specialist centres and mental health trusts throughout the UK. It was developed by a software company (Rx-Info) in conjunction with the West Midlands Regional Pharmaceutical Officer and the Chief Pharmacist of Royal Wolverhampton NHS Trust.

5.3.2.1 Study time period

The study time period for the data source was as follows:

01 April 2017 to 31 July 2022

These dates coincide with the availability at the time of data extraction (August 2022) of information in the DEFINE database.

5.3.3 Data Source

The data source was the DEFINE database. Hospital Treatment Insight (HTI) was only used here as a reference/rationale for the 20 shortlisted NSCLC drugs, as listed in Table 5.1.

The DEFINE software/database is a comprehensive and up-to-date database developed by Rx-Info for pharmacovigilance and drug safety surveillance. Data were at gross national level or

regional level, not at institutional or patient level. The volume comparator was the defined daily dose (DDD), which is defined by the World Health Organization (WHO) as the mean maintenance daily dose of a medicine for its principal indication in adults.

Hospital Treatment Insight (HTI) is a database of electronic health records in England. HTI is linked to the hospital patient records in the Hospital Episode Statistics (HES) database with dispensing information stored within hospital pharmacy systems. HTI contains data from ~25% hospital trusts in England. In these participating trusts, HES routinely captures hospital activity information, e.g. sociodemographic, admission details and diagnoses information. From 2010 onwards, patient-level data on brand, type, data and quantity of dispensed drugs obtained from Hospital Pharmacy Audit (HPA) are made available by linking dispensing data to HES. HTI is maintained by IQVIA. IQVIA has obtained Section 251 support for NHS Digital to receive and link identifiable pharmacy data to patient level HES data on its behalf. IQVIA then receives non-identified data from NHS Digital on a regular basis. The database is updated quarterly with a current lag of ~6 months.

5.3.3.1 Data source considerations

A limitation of the data source is that it only captures the different drugs usage, so any suspected correlation can happen purely by random as cardiology drugs can be used for all sorts of reasons and are not limited just to the use for non-small lung cancer patients. Another limitation is that some of the traditional chemotherapy drugs are used for multiple cancers, and in this database, it is not possible just to capture the usage of that drug by NSCLC patients only, so it might not be accurate to describe the correlation as NSCLC-related. Furthermore, it is not possible to divide NSCLC drugs by DDD to get actual patient numbers as each patient has varying treatment dosage and duration.

5.3.4 Data Extraction

Although the software was developed by a commercial company in conjunction with the NHS, the actual medicines use data is held on a server in an NHS hospital. All NHS hospitals contributing to this database upload data via the software to the database on a monthly basis. Therefore, the data is protected by NHS security systems and firewalls. Only Rx-Info and hospitals with a DEFINE software licence can access the data. Keele University Centre for Medicines Optimisation (KCMO) holds a licence to access the DEFINE data. Access to the

database from outside the NHS (i.e. Keele University) requires a secure VPN installed on computers accessing the database in order to pass through the NHS computer firewalls. In addition, only registered users may access the data using their own user specific passwords. In this way Rx-Info can monitor what data is being accessed by specific users. For this study, a specific individual within KCMO accessed the data. This was undertaken in two stages, firstly by opening up the secure VPN, and secondly by logging on to the DEFINE database using the individual's username and password. For the purposes of this study, national aggregated data was accessed and not individual hospitals, as the latter would require the permission of each individual hospital which was not practical within the time constraints of the study. However, the database does allow analysis down to NHS regions. The data collected as described in section 5.3.7 was downloaded from DEFINE into an Excel spreadsheet by the registered user within KCMO. These spreadsheets were emailed to the researcher. As these were aggregated data, it contained no information about specific hospitals or patients. Monthly secondary care data were taken from the DEFINE software from April 2017 to July 2022.

5.3.5 Data Management

5.3.5.1 Source Document

As described in section 5.3.4, the raw data was held on an NHS hospital server. Source documents were filed in an encrypted drive. Data entered in other electronic files that were transcribed from source documents were consistent with the source documents or the discrepancies were explained.

5.3.5.2 Storage of Records

The study site retained the source documents and essential documents until the end of study.

5.3.6 Sample Size

This was an exploratory study and descriptive in nature. The study population was derived from all patients within the database to which the inclusion criteria apply and thus was a convenience sample.

5.3.7 Variables

The variables extracted for the analysis were as follows:

- Month (April 2017 – July 2022)
- Region (East of England, East Midlands, London, North East, North West, South Central, South East Coast, South West, West Midlands, Yorkshire and the Humber)
- 40 shortlisted drugs (please see below for the detailed list of drugs)

5.3.7.1 Shortlisted NSCLC drugs

Table 5.1 showed the top 24 most commonly used lung cancer (ICD-10 code: C34) treatments, based on the count of C34 drugs by HTI database from 1 January 2010 to 31 January 2020. Etoposide and topotecan were used only to treat small cell lung cancer (SCLC), hence were excluded from the shortlisted list.

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used to treat various forms of pain and inflammation, such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis and dysmenorrhea. Its specific mechanism of action involves selectively inhibiting the enzyme cyclooxygenase-2 (COX-2), which plays a key role in the inflammation process. Unlike other NSAIDs, celecoxib is designed to reduce gastrointestinal toxicity due to its selective inhibition of COX-2, as COX-1 inhibition (which is more common in non-selective NSAIDs) is associated with a higher risk of gastrointestinal issues (Gong et al., 2012). Celecoxib has been studied as an adjuvant therapy, to be used alongside chemotherapy and radiation therapy. It is thought to potentially enhance the effectiveness of these treatments by making cancer cells more susceptible to them (Liu et al., 2017). Since the DEFINE database cannot first identify C34 patients and then extract their corresponding drug usage, celecoxib was also excluded from the shortlisted list due to its nature of treating several non-cancer conditions.

Irinotecan is a chemotherapy medication used primarily to treat cancers of the colon and rectum (Fujita et al., 2015). However, it has also been studied and used in various combinations for the treatment of other types of cancer, including SCLC and NSCLC, often in clinical trials or as part of off-label use when other treatments have not been successful or are not suitable (Chen et al., 2017; Nogami et al., 2012; Socinski, 2002; Takiguchi et al., 2007; Xu et al., 2018). As irinotecan is used majorly to treat colorectal cancer, it was excluded from the shortlisted list.

Table 5.1: Top 24 most commonly used lung cancer treatments (based on the count of C34 drugs by HTI database from 1 January 2010 to 31 January 2020).

NSCLC Drugs	Number Of Patients with C34 Diagnosis and Drug at Any Time
Carboplatin	20991
Cisplatin	8308
Pemetrexed	7839
Etoposide	7199
Gemcitabine	7015
Vinorelbine	6336
Pembrolizumab	3332
Docetaxel	2403
Erlotinib	2271
Cyclophosphamide	1657
Methotrexate	1359
Doxorubicin	1212
Vincristine	1120
Paclitaxel	1110
Atezolizumab	995
Gefitinib	752
Nintedanib	574
Afatinib	570
Celecoxib	488
Epirubicin	401
Topotecan	367
Osimertinib	345
Irinotecan	329
Bevacizumab	310

Non-small cell lung cancer (NSCLC) treatments

- ***Chemotherapy:*** Carboplatin, Cisplatin, Cyclophosphamide, Docetaxel, Doxorubicin, Epirubicin, Gemcitabine, Methotrexate, Paclitaxel, Pemetrexed, Vincristine, Vinorelbine
- ***Targeted therapy:*** Afatinib, Bevacizumab, Erlotinib, Gefitinib, Nintedanib, Osimertinib
- ***Immunotherapy:*** Atezolizumab, Pembrolizumab

5.3.7.2 Shortlisted cardiology drugs

Table 5.2 listed the 20 shortlisted cardiology drugs that were identified to treat the top eight most common cardiotoxicities (i.e. arrythmia, arterial/venous thromboembolic event, atrial filbrillation, cardiac failure/arrest, hypertension, ischemia, myocardial infarction and tachycardia) based on results analysed from systematic review (Chapter 3). Drugs in red represent that drug is used to treat more than one CV event.

Table 5.2: 20 shortlisted cardiology drugs that were identified to treat the top 8 most common cardiotoxicities.

Arrhythmia	Arterial / Venous Thromboembolic Event	Atrial Fibrillation	Cardiac Failure / Arrest
• Amiodarone • Verapamil	• Rivaroxaban • Streptokinase	• Apixaban	• Adrenaline / Epinephrine • Lisinopril • Losartan • Ramipril

Hypertension	Ischamia	Myocardial Infarction	Tachycardia
• Amlodipine • Atenolol • Bisoprolol • Candesartan • Diltiazem • Doxazosin • Lisinopril • Losartan • Ramipril • Verapamil	• Atenolol • Bisoprolol	• Alteplase • Anistreplase • Reteplase • Streptokinase • Tenecteplase	• Lidocaine

5.3.8 Statistical Analysis

5.3.8.1 General approach

Descriptive analyses were conducted using number and percent within each category with 95% confidence intervals (whenever appropriate) for categorical variables, and mean (standard

deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables. All data were summarised to 2 decimal places. All statistical analyses were done through Microsoft Excel and/or R.

5.3.8.2 Primary objective – To describe the association between 20 shortlisted cardiology drugs that are identified to treat the top 8 most common cardiotoxicities (based on results analysed from systematic review) with top 20 most commonly used NSCLC treatments (based on the count of NSCLC drugs by HTI database)

The counts and proportions of usage of cancer drugs and cardiology drugs was summarised by region and by national level.

The association between the usage of the cancer drugs and cardiology drugs was explored by the Pearson's correlation test.

If there was strong correlation (values close to ± 1) between anticancer drugs and cardiology drugs, then linear regression calculation was carried out. This process provided a comprehensive statistical summary of the linear relationship between the independent and dependent variables, including the direction, strength, and fit of the relationship.

5.3.8.3 Secondary objective 1 – To describe the overall utilisation of the 40 shortlisted drugs, by regional and national level

Table shells were used for the descriptive analyses. Graphs (e.g. doughnut charts) were also used for illustration purposes.

5.3.8.4 Secondary objective 2 – To describe the general trend of utilisation of the 40 shortlisted drugs

Drug utilisation was examined over the period of April 2017 and July 2022. Linear regression analyses were used with time (monthly) as the independent variable and utilisation in DDD as the dependent variable. The regression coefficient values were divided by the baseline utilisation DDD (in April 2017) to calculate the average monthly percentage increase or decrease in drug utilisation. Due to the nature of oncology treatments, it might not be possible to define every cancer drug by DDD. In the case where this was not feasible, then linear regression analyses for this objective was not carried out.

5.3.8.5 Handling of Missing and Incomplete Data

Only available data were summarised; no imputation methods were used to handle missing data. The number and percentage of missing values were also reported as appropriate. For categorical variables, the percentages were calculated based on all available data (missing and non-missing). The subjects with missing information were included in the calculations.

5.4 Results

The following data were collected from the database and recorded electronically by investigators (or designees) during the study period – the quantity of the 40 shortlisted drugs used at regional level, per month from April 2017 to July 2022.

Figure 5.1 showed the overview of monthly utilisation of selected cancer drugs between April 2017 and July 2022 at national level, while Table 5.3 showed the total amount of dispensed dosage of each selected cancer drug at national level between April 2017 and July 2022. Due to the nature of oncology treatments, i.e. the dosage of treatment for each patient can be different, therefore DDD is not available for oncology drugs. In addition, the unit of each drug is also different, hence the usage among each drug can only be compared by trends instead of quantity.

The usage of atezolizumab increased from only 8.40 grams in total at national level in April 2017 to 2832.00 grams in total at national level in July 2022, with March 2022 recorded the highest usage of atezolizumab (3024.11 grams) (Table 5.3). The usage of osimertinib increased from 205.52 grams in total at national level in April 2017 to 3320.48 grams in total at national level in July 2022, with May 2022 recorded the highest usage of osimertinib (3439.40 grams) (Table 5.3).

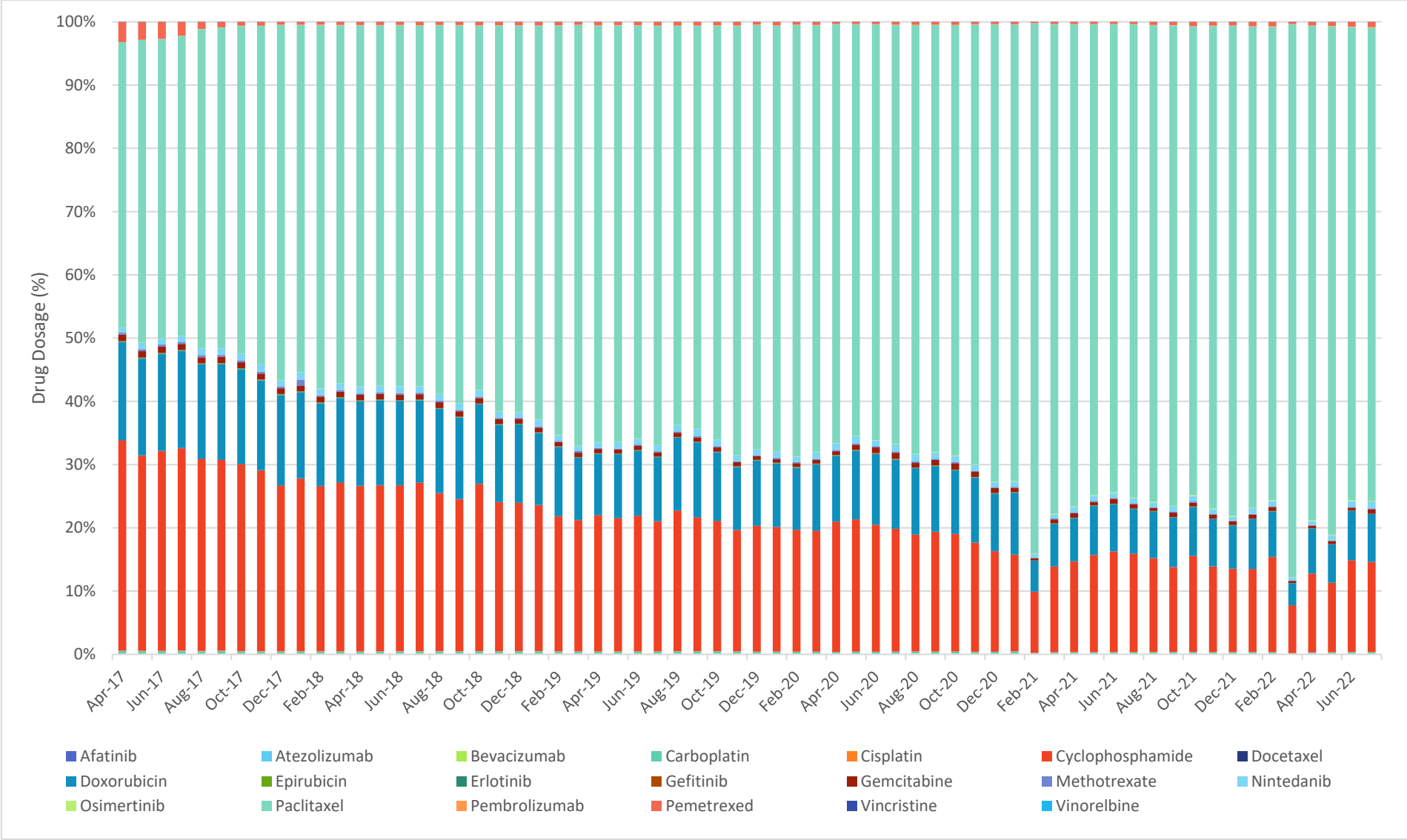

Figure 5.1: Monthly utilisation of selected cancer drugs between April 2017 and July 2022 (at national level).

Table 5.3: Total amount (grams unless marked with *, then it is incomparable units) of dispensed dosage of each selected cancer drug at national level between April 2017 and July 2022.

	Afatinib	Atezolizumab	Bevacizumab	Carboplatin	Cisplatin	Cyclophosphamide*	Docetaxel	Doxorubicin*	Epirubicin	Erlotinib	Gefitinib	Gemcitabine	Methotrexate	Nintedanib	Osimertinib	Paclitaxel*	Pembrolizumab	Pemetrexed*	Vincristine	Vinorelbine
Apr-17	336.89	8.40	756.59	4482.13	598.30	352290.57	842.54	163769.14	666.77	1041.53	292.50	10974.42	3148.84	8800.60	205.52	477674.17	247.38	33956.26	9.07	171.53
May-17	409.67	13.20	846.54	5317.18	669.77	382652.47	923.32	189642.57	733.90	1117.88	322.50	12622.29	3839.43	12743.10	242.40	594084.89	288.14	35155.02	10.93	189.07
Jun-17	387.31	10.80	858.52	5100.13	658.53	391712.86	915.18	189761.23	715.97	1091.40	366.25	12620.31	3998.35	12142.60	256.96	587340.73	335.12	33220.62	11.38	196.83
Jul-17	374.59	4.80	767.80	5438.09	633.37	381742.99	829.28	182892.12	680.39	1102.03	326.00	11351.79	4159.44	11461.70	239.20	566001.87	350.35	26061.55	9.98	190.96
Aug-17	409.25	7.20	795.11	5013.34	687.41	392507.89	924.16	192976.99	731.95	1144.90	270.00	12429.97	4497.24	13192.55	263.84	653697.00	462.28	14327.90	11.49	210.35
Sep-17	398.60	2.40	695.75	5219.54	635.61	367516.09	876.98	183684.28	675.78	1046.88	322.50	11823.55	3786.56	12762.90	285.40	617570.71	446.91	10374.62	10.04	189.39
Oct-17	381.82	4.80	727.50	5040.60	668.13	388052.50	858.91	196608.77	693.18	1117.83	344.50	12147.08	4165.13	13588.10	331.60	680276.17	554.42	7938.70	10.63	212.24
Nov-17	448.83	10.80	734.45	5078.93	681.72	393138.14	895.57	195349.14	694.26	1042.73	532.50	12622.54	4007.44	15846.90	347.28	736648.31	575.66	8153.90	10.42	201.13
Dec-17	417.58	18.00	660.71	4580.23	641.19	339590.18	861.08	184797.77	608.14	951.58	885.00	11621.58	3804.45	11837.70	323.44	728927.77	549.46	5859.56	9.75	182.06
Jan-18	459.94	38.40	734.49	5045.49	683.39	390287.05	975.05	194098.62	661.50	1042.10	787.50	12275.73	14305.33	17077.70	351.44	784370.97	636.03	6457.53	11.47	192.94
Feb-18	399.74	48.00	641.12	4470.43	599.97	336230.81	821.94	168299.17	560.56	838.60	270.00	11668.83	2765.80	13553.00	347.52	740295.49	583.04	5605.56	9.14	172.89
Mar-18	455.92	75.60	688.19	4883.08	642.69	377790.57	920.01	188439.02	658.18	978.98	326.25	12362.10	3227.33	14845.80	402.40	801821.57	681.09	6937.90	10.29	211.73
Apr-18	474.25	122.40	696.25	4505.44	608.70	355610.83	909.69	181604.70	591.50	890.18	267.50	12093.44	2797.15	13490.95	406.52	777727.14	694.27	6953.90	9.70	189.00
May-18	484.25	340.80	738.94	4941.89	673.56	391263.44	934.33	199855.32	646.86	1033.28	232.50	13056.86	3096.98	16228.30	455.56	849384.23	721.77	7429.10	11.03	220.46
Jun-18	459.52	483.60	688.39	4618.43	640.61	364357.23	852.25	185256.60	595.52	989.50	228.75	12134.71	3001.50	14814.10	468.24	793722.28	698.80	6704.40	9.88	199.81
Jul-18	500.42	626.40	737.28	4692.19	626.74	384791.70	898.72	187678.04	609.29	919.93	270.00	12563.28	3252.23	15038.30	473.60	824362.62	711.39	7581.80	10.53	211.47
Aug-18	549.78	727.20	753.90	4894.54	656.94	366287.97	934.64	195553.52	636.91	922.40	202.50	13482.52	3147.21	15950.65	500.48	856108.72	746.66	7080.20	11.01	222.40
Sep-18	460.70	742.80	675.86	4447.32	577.32	335686.41	844.22	179812.90	589.10	906.05	232.50	12263.70	2786.59	14340.90	436.80	835036.38	680.98	7152.10	9.94	196.37
Oct-18	560.20	878.40	797.79	5104.75	667.51	412292.20	949.34	195285.94	648.87	1008.08	292.50	13455.32	3330.76	16345.65	557.60	898989.41	779.88	8107.85	10.71	230.13
Nov-18	532.49	946.50	793.92	5034.30	657.70	382009.48	953.01	197071.62	630.80	894.90	232.50	12910.78	3236.81	16908.85	579.52	988380.82	790.03	8582.50	10.27	205.39

Dec-18	511.86	875.64	722.19	5083.74	630.55	353533.52	887.03	186729.16	562.63	778.23	292.50	11597.14	3146.18	12175.90	507.60	923104.07	727.42	8126.10	9.69	193.59
	Afatinib	Atezolizumab	Bevacizumab	Carboplatin	Cisplatin	Cyclophosphamide*	Docetaxel	Doxorubicin*	Epirubicin	Erlotinib	Gefitinib	Gemcitabine	Methotrexate	Ninetedanib	Osimertinib	Paclitaxel*	Pembrolizumab	Pemetrexed*	Vincristine	Vinorelbine
Jan-19	542.12	1019.76	806.71	5743.71	652.91	390714.91	988.62	192521.48	634.66	969.85	375.00	12654.06	3166.04	18083.90	539.68	1055820.41	866.56	9432.19	10.34	218.45
Feb-19	504.44	896.40	666.68	4825.71	551.67	342728.52	845.49	175745.40	555.98	872.05	143.50	11094.20	2882.82	14415.35	517.80	1040414.71	753.83	8314.40	8.86	201.88
Mar-19	552.25	993.48	736.94	5344.26	609.70	371175.71	920.21	176076.30	632.70	945.83	210.00	12413.40	4318.31	14579.85	563.64	1190482.58	1003.31	8056.20	10.19	220.33
Apr-19	571.79	1031.28	724.31	5019.83	528.95	384010.15	914.42	173112.42	596.92	959.20	187.50	11965.20	2787.01	14830.10	518.96	1177065.95	877.06	9608.94	9.58	204.88
May-19	594.51	1121.70	839.09	5360.44	570.30	389413.34	949.84	186897.01	637.07	908.55	231.50	12283.74	2580.76	18516.90	633.60	1218811.37	953.95	9337.44	9.79	204.01
Jun-19	505.25	1052.40	734.90	4577.96	507.74	342333.05	819.02	163989.17	540.31	763.55	134.00	10395.50	3150.27	15234.00	521.20	1042519.52	889.23	8436.49	9.25	168.00
Jul-19	672.48	1156.08	812.47	5316.88	605.88	383905.66	932.55	189331.73	631.02	876.10	246.50	12355.84	3337.35	17684.80	683.88	1238176.68	1077.64	10849.84	10.05	196.67
Aug-19	598.57	1150.56	778.51	5115.50	567.92	365342.76	900.21	188623.20	594.65	828.80	275.00	11291.45	3230.57	16063.50	588.52	1037517.41	1074.15	9396.29	10.15	195.20
Sep-19	509.81	1103.28	744.06	4975.80	537.61	332361.86	837.12	186119.50	578.28	786.88	269.00	10718.01	2892.99	18122.00	638.80	1002173.67	1031.15	8561.04	9.86	189.85
Oct-19	619.01	1291.26	817.92	5659.57	583.05	375410.65	957.30	197314.37	613.30	837.74	344.83	12444.59	3478.28	19185.85	620.16	1193235.15	1171.23	9631.00	10.97	199.83
Nov-19	562.52	1202.94	754.20	5141.38	544.43	339750.78	898.50	176218.50	606.07	774.43	537.25	11784.31	2744.84	16907.00	638.44	1203685.09	1068.57	9784.26	10.67	179.40
Dec-19	587.86	1135.38	779.35	5203.53	543.31	390074.14	881.09	201202.56	622.77	765.08	722.00	11326.31	3483.31	17433.30	595.08	1314876.80	1100.72	8358.13	21.52	166.70
Jan-20	617.63	1282.74	897.08	5701.36	586.05	399223.55	981.79	203648.43	646.92	767.30	737.75	11997.39	3754.13	21148.30	608.64	1365947.43	1233.52	10900.38	25.78	188.63
Feb-20	532.91	1069.92	772.12	5318.77	584.94	370493.36	814.59	188246.17	555.70	776.75	915.75	11346.74	3589.27	16365.10	576.88	1312711.11	1033.55	8512.90	26.81	152.53
Mar-20	714.45	1116.36	868.28	5185.29	516.22	371296.65	844.39	202780.42	609.94	982.48	1126.75	11177.88	3650.17	19617.80	719.28	1311393.26	1218.42	9474.55	19.68	161.42
Apr-20	600.61	875.88	649.91	3873.00	358.04	337264.66	596.61	170038.26	429.88	697.55	1110.00	9374.92	3086.50	17279.90	602.64	1084764.78	1016.80	5189.38	17.96	114.23
May-20	495.67	938.53	603.23	3934.34	316.97	308302.67	543.20	160088.14	376.60	658.58	937.50	12106.34	2941.33	16813.50	605.96	960309.64	1085.83	4872.90	18.25	115.21
Jun-20	535.61	1283.41	682.25	4143.44	371.28	346576.31	568.25	192809.38	490.41	757.03	1031.25	15812.77	3331.84	15928.70	978.84	1134465.38	1182.96	6066.50	20.82	144.73
Jul-20	552.91	1558.69	683.22	4699.09	388.59	355453.52	572.29	200022.96	499.85	643.18	1001.25	17829.52	3889.27	20795.30	1127.68	1214172.64	1260.24	7484.26	19.21	159.46
Aug-20	409.71	1485.91	653.04	4235.93	375.95	292935.51	540.26	166858.78	399.56	558.73	859.75	11179.03	3651.09	18110.25	1065.08	1076637.32	1175.12	7194.45	20.34	111.51
Sep-20	463.12	1663.87	712.05	4907.84	420.35	350164.29	617.84	191853.26	451.84	518.85	926.25	16119.74	3363.95	18672.10	1415.12	1248241.22	1236.89	7987.55	22.14	152.74

Oct-20	407.73	1805.83	701.44	4945.89	461.63	350779.18	601.86	190192.08	458.81	481.13	756.75	19197.95	3353.90	18103.50	1402.96	1284669.54	1244.52	8743.92	20.56	158.36
	Afatinib	Atezolizumab	Bevacizumab	Carboplatin	Cisplatin	Cyclophosphamide*	Docetaxel	Doxorubicin*	Epirubicin	Erlotinib	Gefitinib	Gemcitabine	Methotrexate	Nintedanib	Osimertinib	Paclitaxel*	Pembrolizumab	Pemetrexed*	Vincristine	Vinorelbine
Nov-20	392.91	1849.21	714.71	5149.57	513.82	367784.32	590.83	219240.53	498.16	561.73	732.25	17533.92	3464.40	20481.45	1589.44	1482710.17	1269.16	8024.50	18.94	158.43
Dec-20	396.38	2164.03	861.19	5748.03	564.87	379168.65	671.98	216887.24	554.92	501.63	680.75	19593.88	3655.24	18587.85	1884.88	1724776.66	1418.53	8107.21	19.91	182.37
Jan-21	331.84	2185.21	905.62	6087.37	536.37	325262.54	647.41	208985.20	521.21	457.75	608.00	14958.25	3375.88	17478.35	1772.72	1538584.63	1306.73	8139.65	17.80	158.66
Feb-21	305.73	2045.11	858.63	4956.67	671.58	346981.00	594.82	175766.78	500.98	396.65	567.00	13117.31	3272.41	19259.00	1732.36	3013794.36	2188.34	7352.90	23.76	153.64
Mar-21	324.80	2481.36	913.69	5657.04	577.64	413141.25	721.79	206047.03	605.51	435.20	700.75	19456.38	4100.97	19798.50	2152.52	2362801.92	1972.36	9112.35	22.29	172.63
Apr-21	309.68	2268.61	917.18	4985.31	453.42	370131.99	656.72	176135.06	547.58	395.88	518.50	18925.77	3728.78	21744.30	2100.76	1967351.23	1952.32	8236.53	20.46	168.11
May-21	271.60	2261.17	865.47	4852.25	460.39	370279.92	636.97	188241.73	486.20	374.38	576.25	12929.87	3544.92	19140.00	2132.44	1799122.43	1315.62	7837.95	21.72	156.64
Jun-21	271.88	2465.71	911.68	5110.23	470.78	403673.05	707.41	189799.42	538.29	351.98	484.50	20097.90	3394.29	19895.55	2340.40	1880843.73	1393.58	8117.15	18.76	182.29
Jul-21	244.58	2607.01	957.27	5280.61	474.95	400881.49	706.45	182734.38	558.21	342.30	581.25	18513.79	3564.71	20017.55	2588.04	1933140.27	1448.34	9098.85	20.81	163.21
Aug-21	248.36	2516.71	997.84	5287.50	430.66	365783.99	687.65	182184.52	550.53	275.18	540.00	12250.56	3460.11	17870.10	2402.72	1860443.90	1396.74	12243.35	16.68	161.67
Sep-21	250.46	2535.67	982.80	5598.76	464.14	343387.89	740.55	200260.58	575.20	366.60	561.50	17855.13	3606.04	20961.50	2669.40	1946172.04	1510.78	13076.35	24.09	160.71
Oct-21	212.16	2480.17	977.51	4810.81	423.85	359513.81	707.58	183230.80	556.33	288.83	595.75	14503.50	4160.57	21116.30	2638.44	1756325.87	1411.31	15951.55	23.60	152.62
Nov-21	206.02	2600.35	1009.56	5572.92	463.76	351874.73	742.93	194317.36	601.66	331.70	417.25	17174.16	3620.45	19183.20	2816.32	1987102.82	1473.28	15775.15	23.97	165.94
Dec-21	197.54	2727.73	1127.87	5434.60	471.01	349878.56	765.99	181941.06	585.36	266.45	454.75	16125.59	3425.48	16098.45	2912.60	2063428.07	1471.45	15080.35	23.38	157.64
Jan-22	191.52	2645.71	1094.46	5399.44	453.98	320256.95	720.54	193157.88	533.44	266.05	426.50	15775.05	3123.70	21627.90	2864.20	1861023.09	1437.35	17285.30	22.70	151.78
Feb-22	169.88	2490.24	1024.23	4848.70	420.22	357493.17	688.45	171543.84	531.75	221.45	428.50	15358.72	2835.44	19197.20	2658.80	1783373.40	1381.20	17303.90	25.67	146.19
Mar-22	182.84	3024.11	1581.93	6347.79	845.30	427838.49	800.11	198608.92	590.34	265.30	514.25	18408.76	2874.79	25118.70	3266.84	4962127.86	1799.15	19749.00	23.44	167.21
Apr-22	169.75	2711.51	1073.58	5356.71	245.22	368395.40	712.21	210978.13	517.12	288.90	409.25	12109.13	2757.10	18858.65	3122.28	2315433.04	1415.43	17269.25	17.72	160.30
May-22	176.68	2903.12	1336.30	5613.68	591.95	352586.89	759.37	195220.48	537.24	284.95	434.25	15701.20	3132.65	25250.10	3439.40	2584906.02	1842.12	20756.85	17.07	172.75
Jun-22	153.36	2938.64	1189.03	5483.83	469.32	372074.39	742.02	200311.74	586.39	224.40	396.25	11677.34	3013.27	22998.35	3038.72	1924880.29	1537.91	19097.10	18.59	156.75
Jul-22	145.32	2832.00	1140.32	5410.70	434.24	355363.18	689.34	188682.09	507.25	225.80	351.25	18430.94	2940.34	27044.50	3320.48	1869791.68	2248.60	20833.50	23.92	162.16

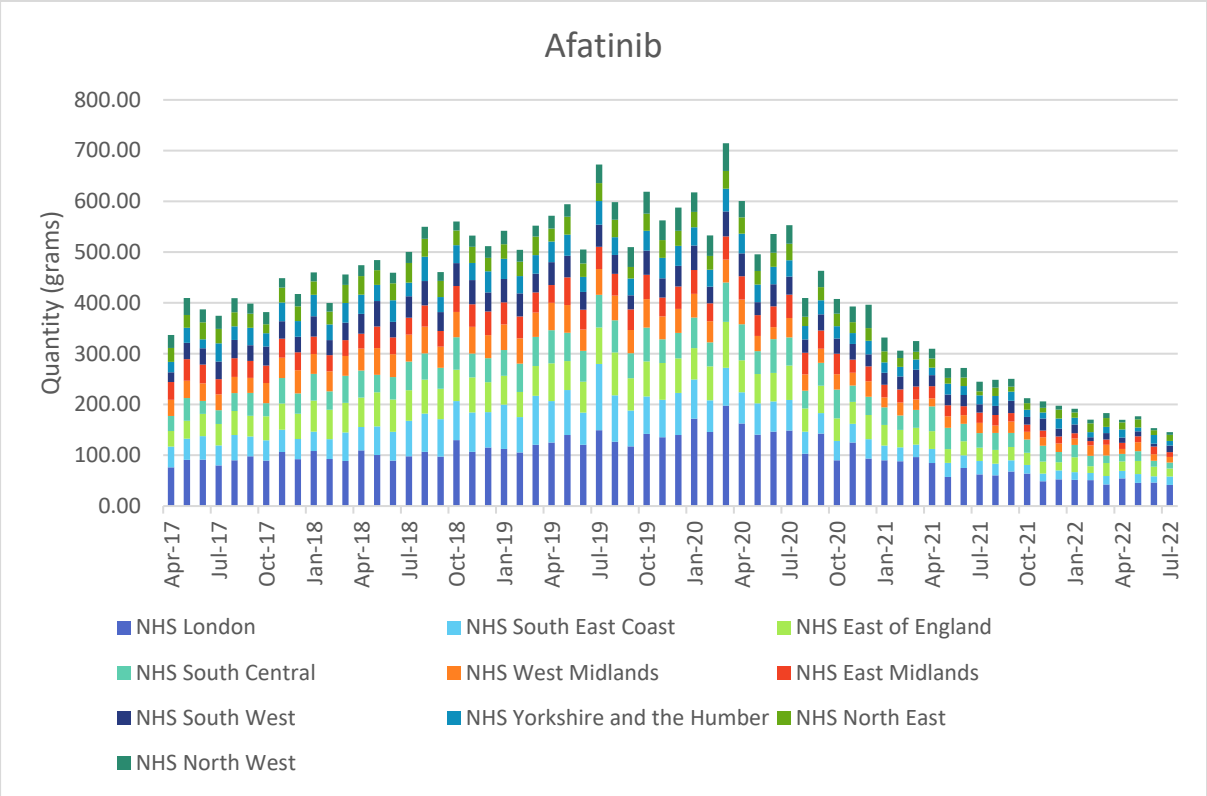

Figure 5.2: Monthly utilisation of afatinib between April 2017 and July 2022 (at regional level).

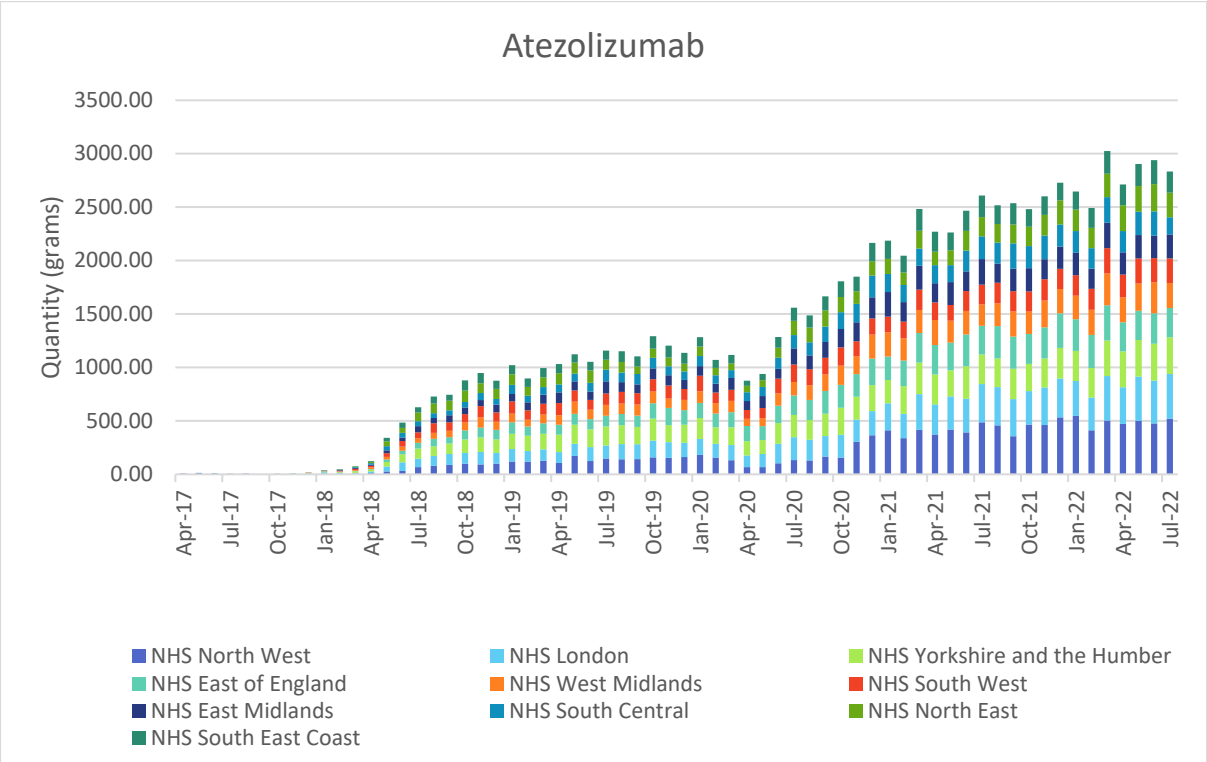

Figure 5.3: Monthly utilisation of atezolizumab between April 2017 and July 2022 (at regional level).

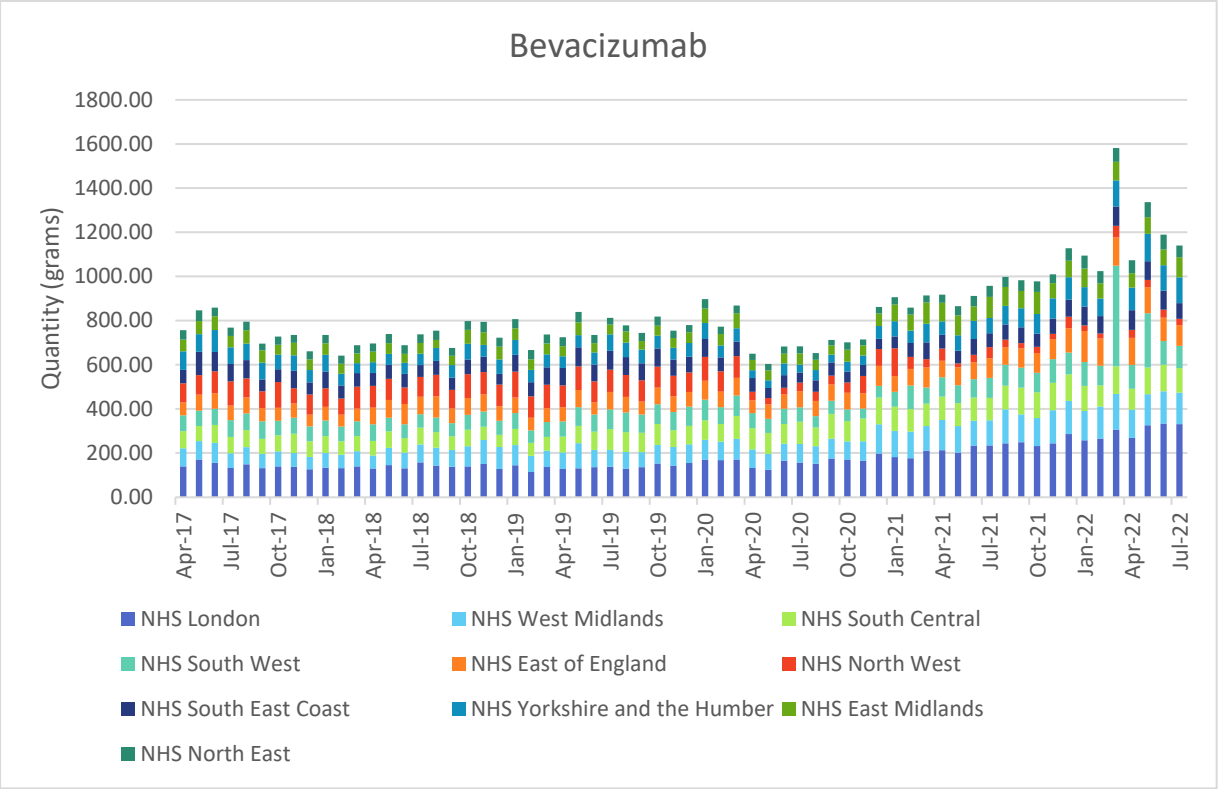

Figure 5.4: Monthly utilisation of bevacizumab between April 2017 and July 2022 (at regional level).

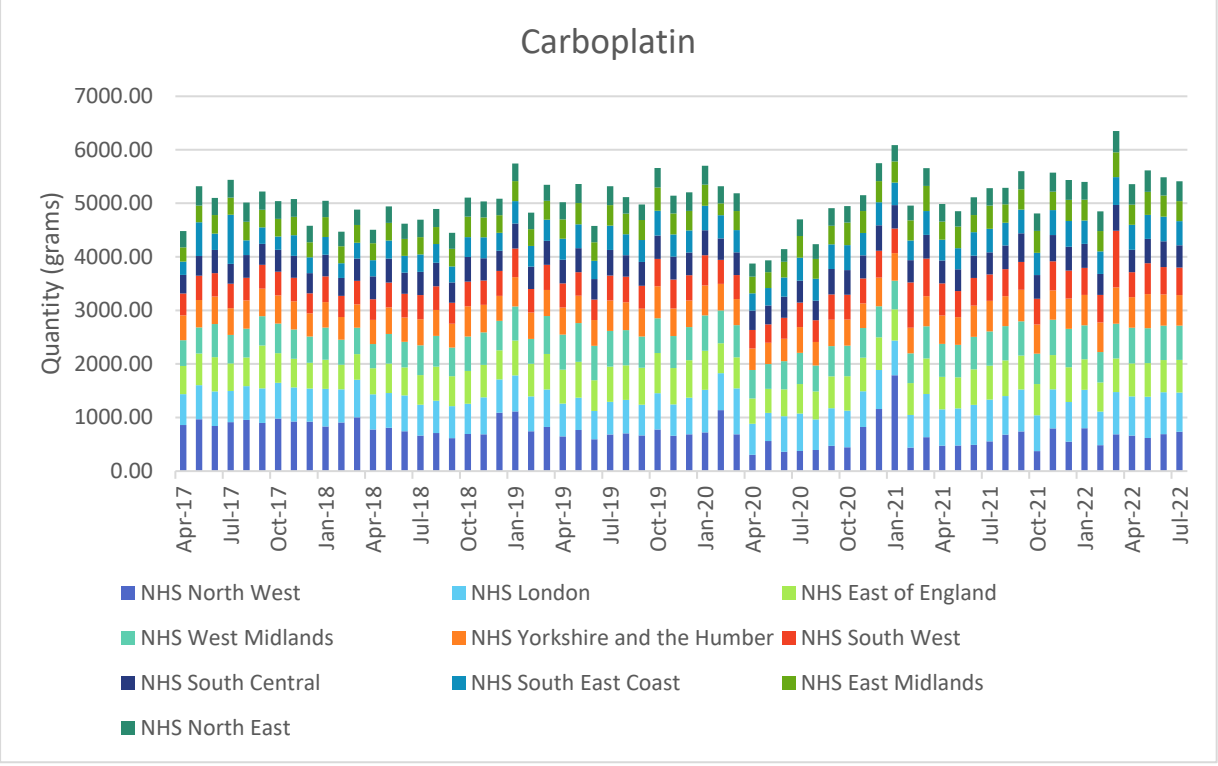

Figure 5.5: Monthly utilisation of carboplatin between April 2017 and July 2022 (at regional level).

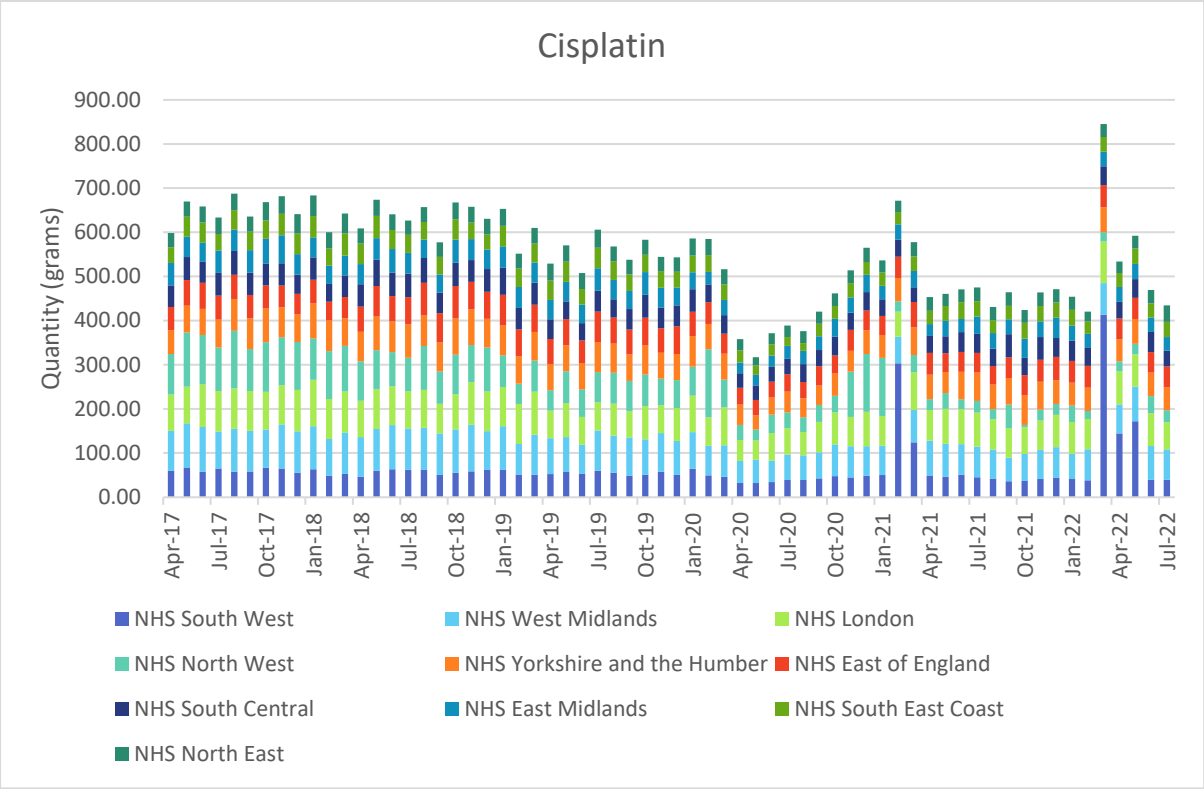

Figure 5.6: Monthly utilisation of cisplatin between April 2017 and July 2022 (at regional level).

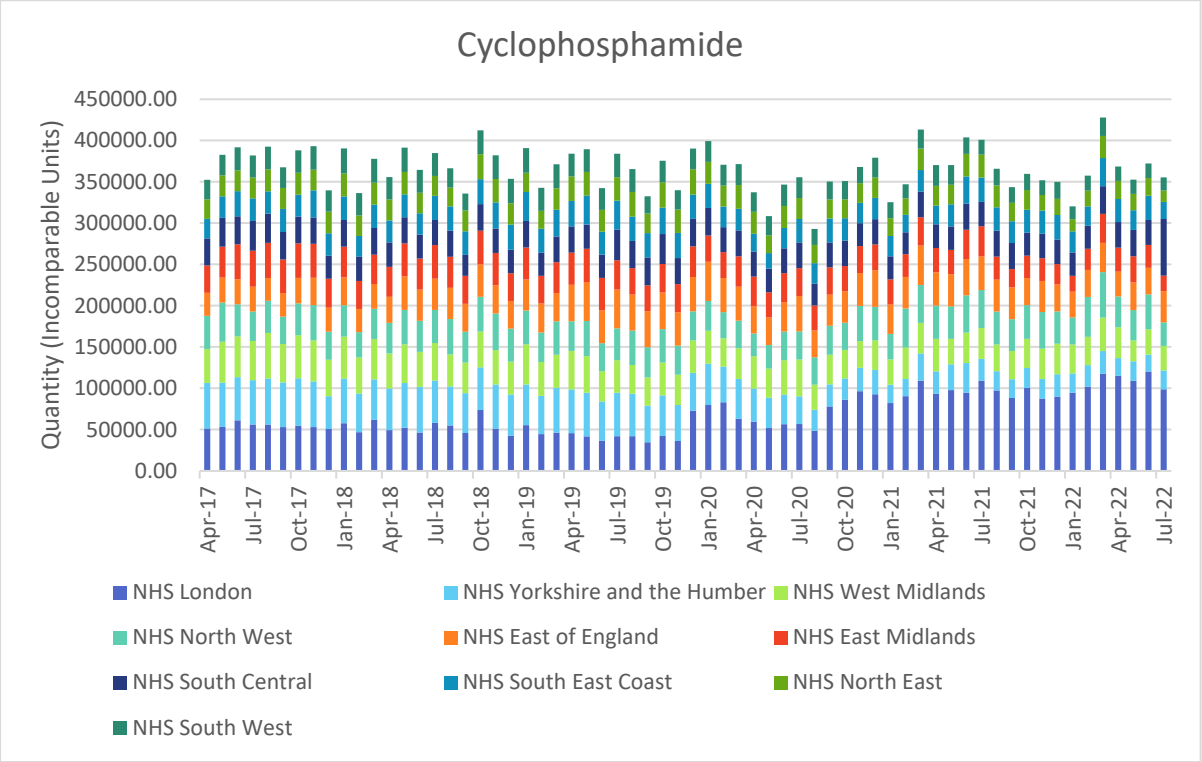

Figure 5.7: Monthly utilisation of cyclophosphamide between April 2017 and July 2022 (at regional level).

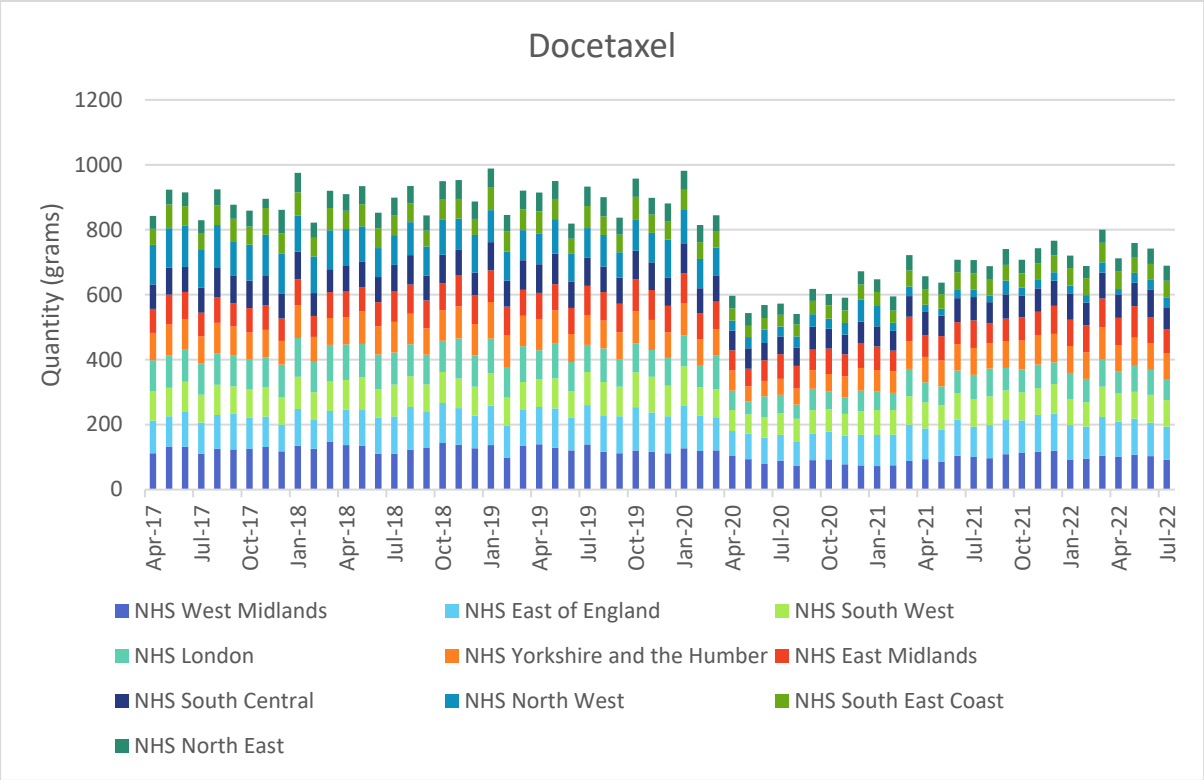

Figure 5.8: Monthly utilisation of docetaxel between April 2017 and July 2022. (at regional level).

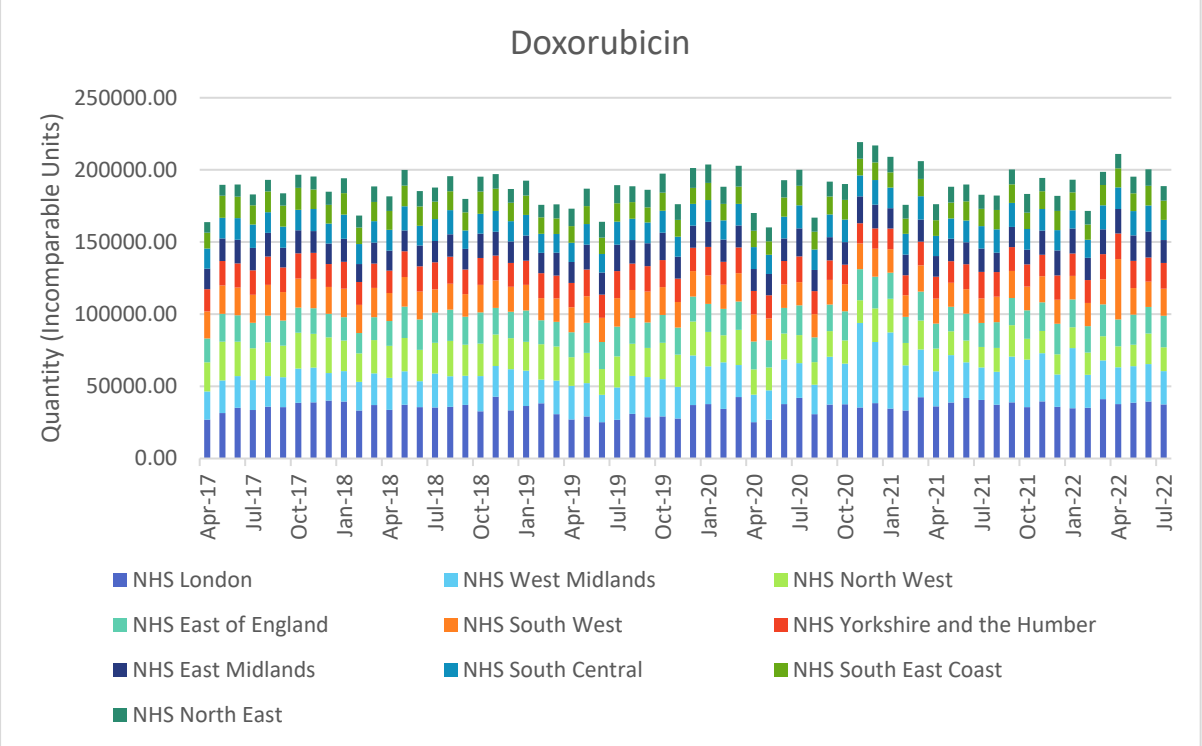

Figure 5.9: Monthly utilisation of doxorubicin between April 2017 and July 2022 (at regional level).

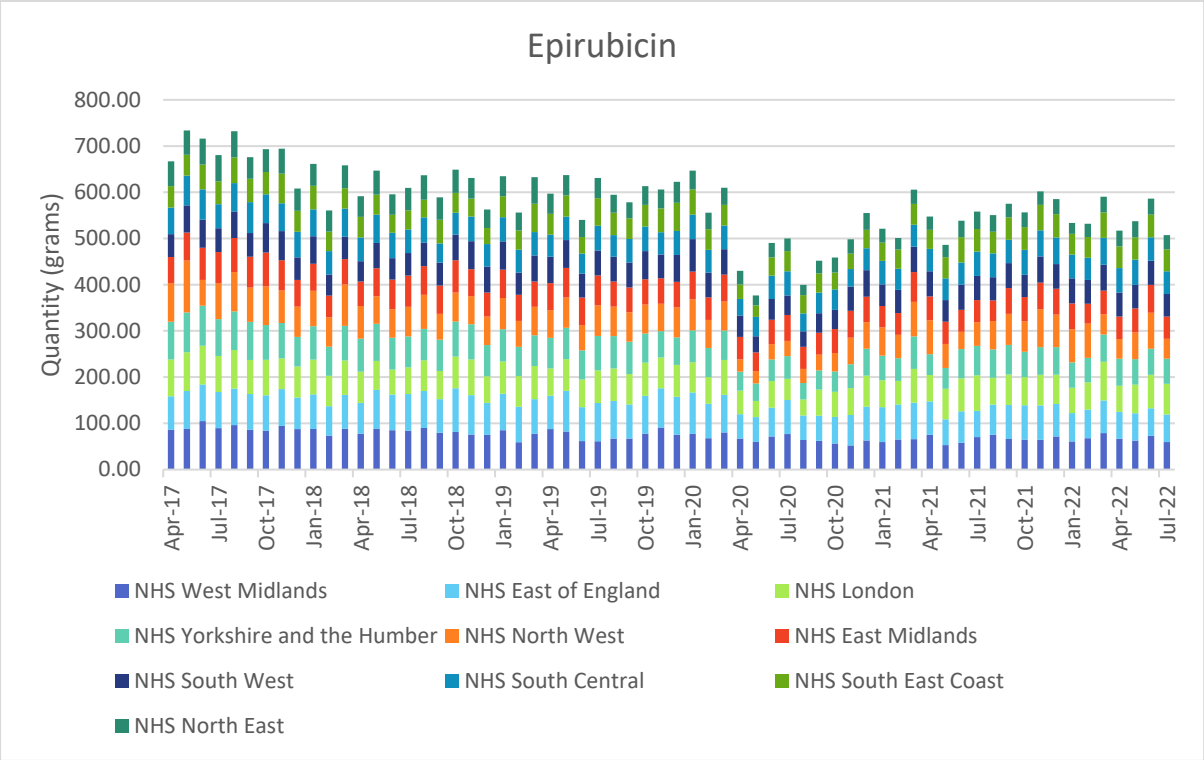

Figure 5.10: Monthly utilisation of epirubicin between April 2017 and July 2022 (at regional level).

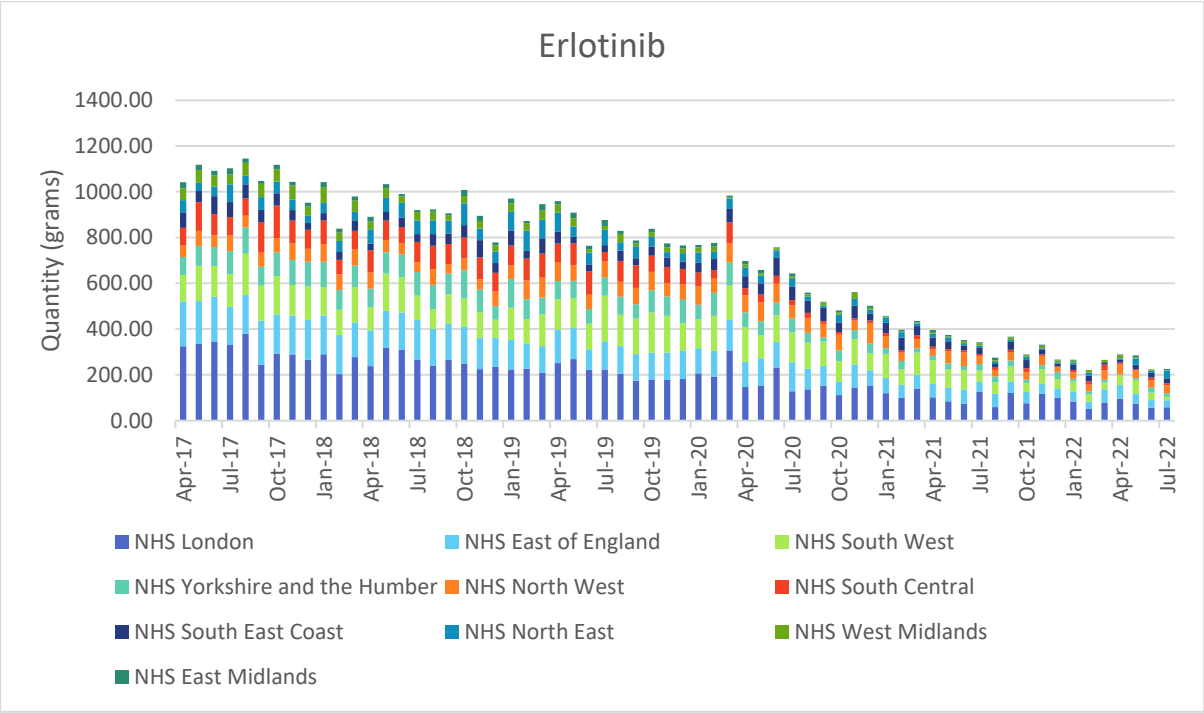

Figure 5.11: Monthly utilisation of erlotinib between April 2017 and July 2022 (at regional level).

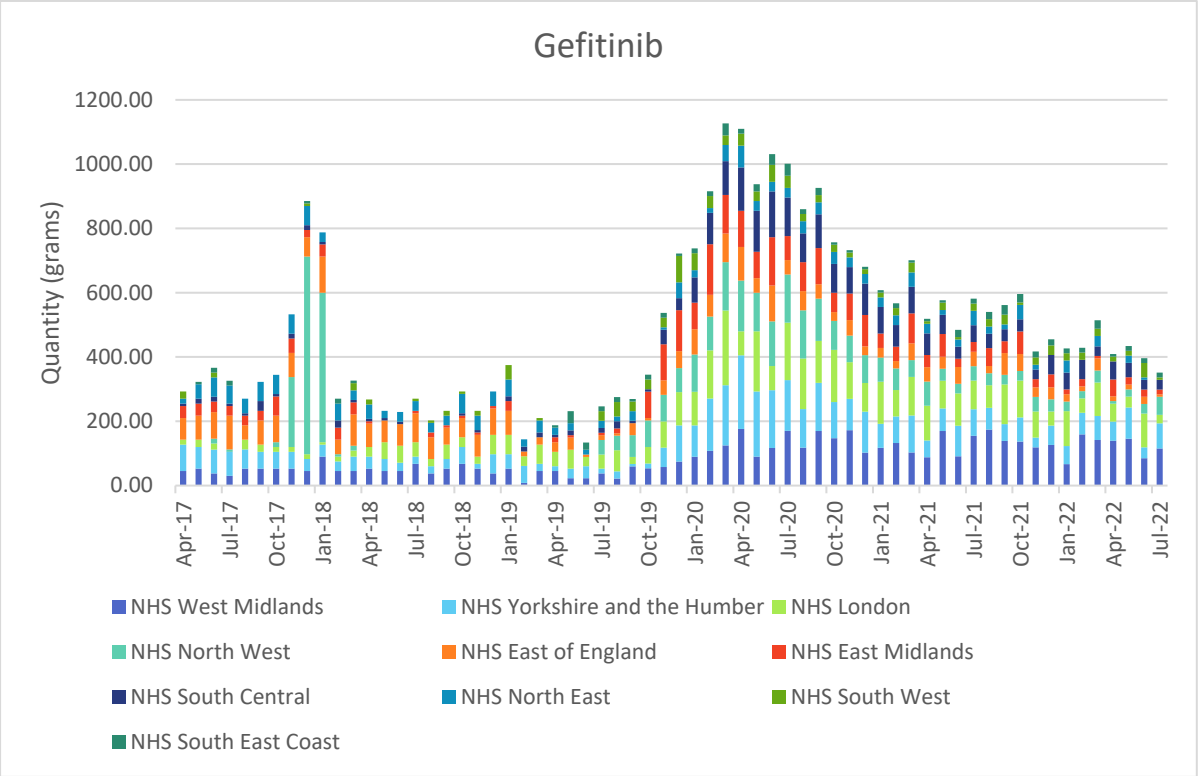

Figure 5.12: Monthly utilisation of gefitinib between April 2017 and July 2022 (at regional level).

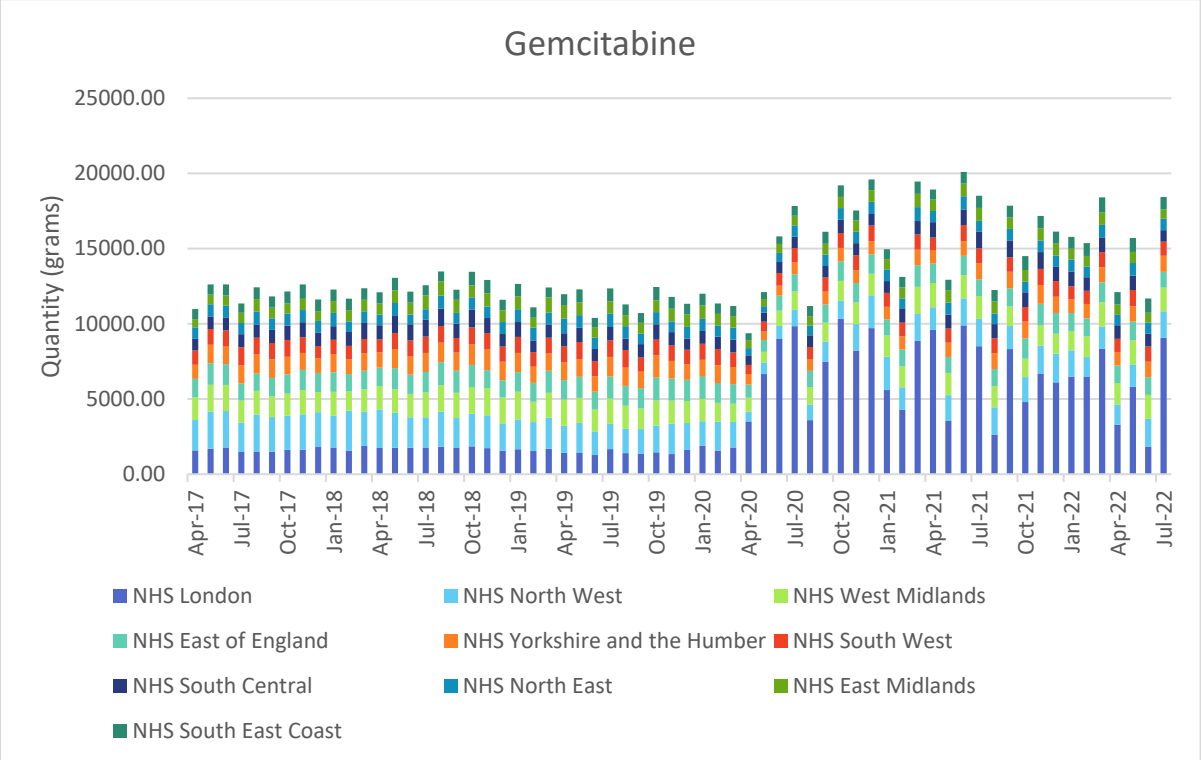

Figure 5.13: Monthly utilisation of gemcitabine between April 2017 and July 2022 (at regional level).

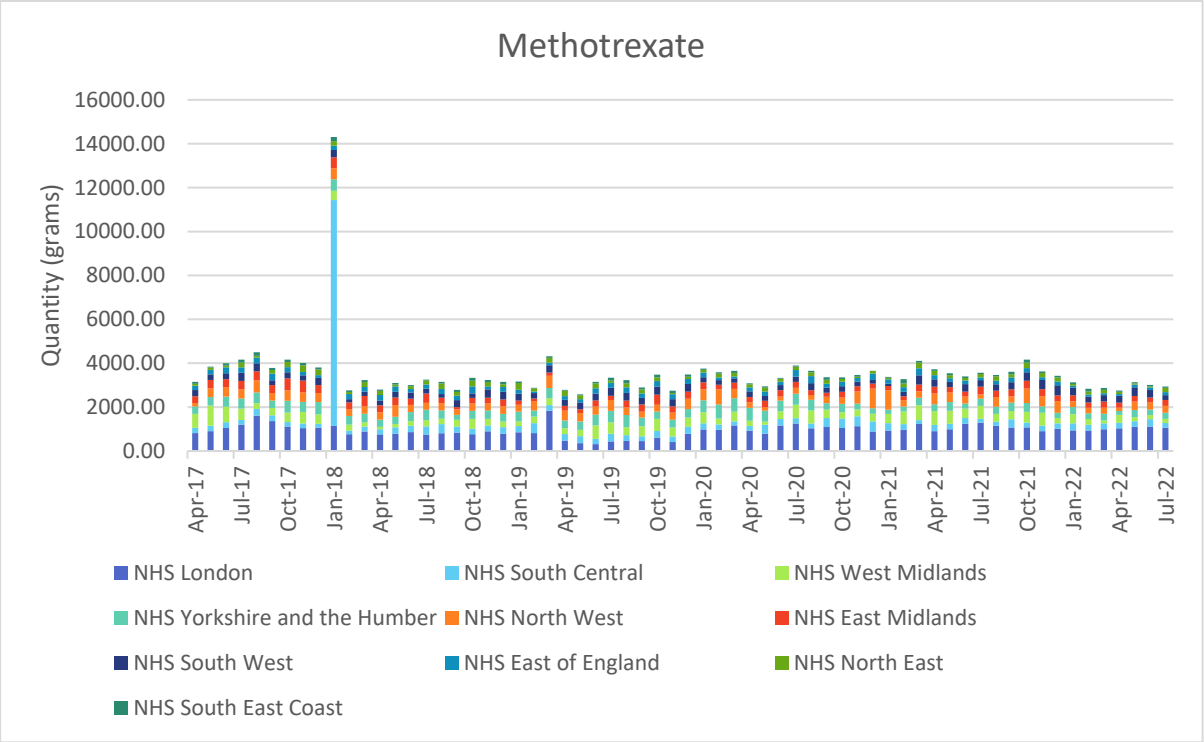

Figure 5.14: Monthly utilisation of methotrexate between April 2017 and July 2022 (at regional level).

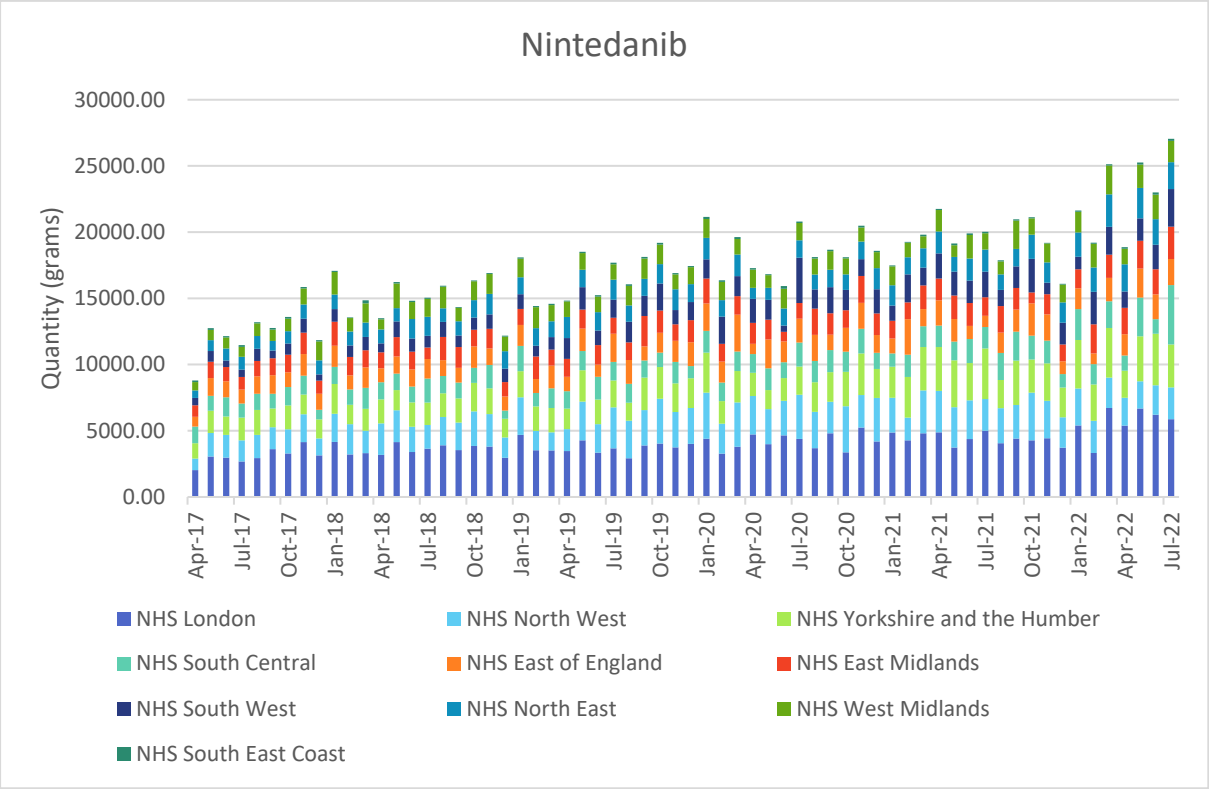

Figure 5.15: Monthly utilisation of nintedanib between April 2017 and July 2022 (at regional level).

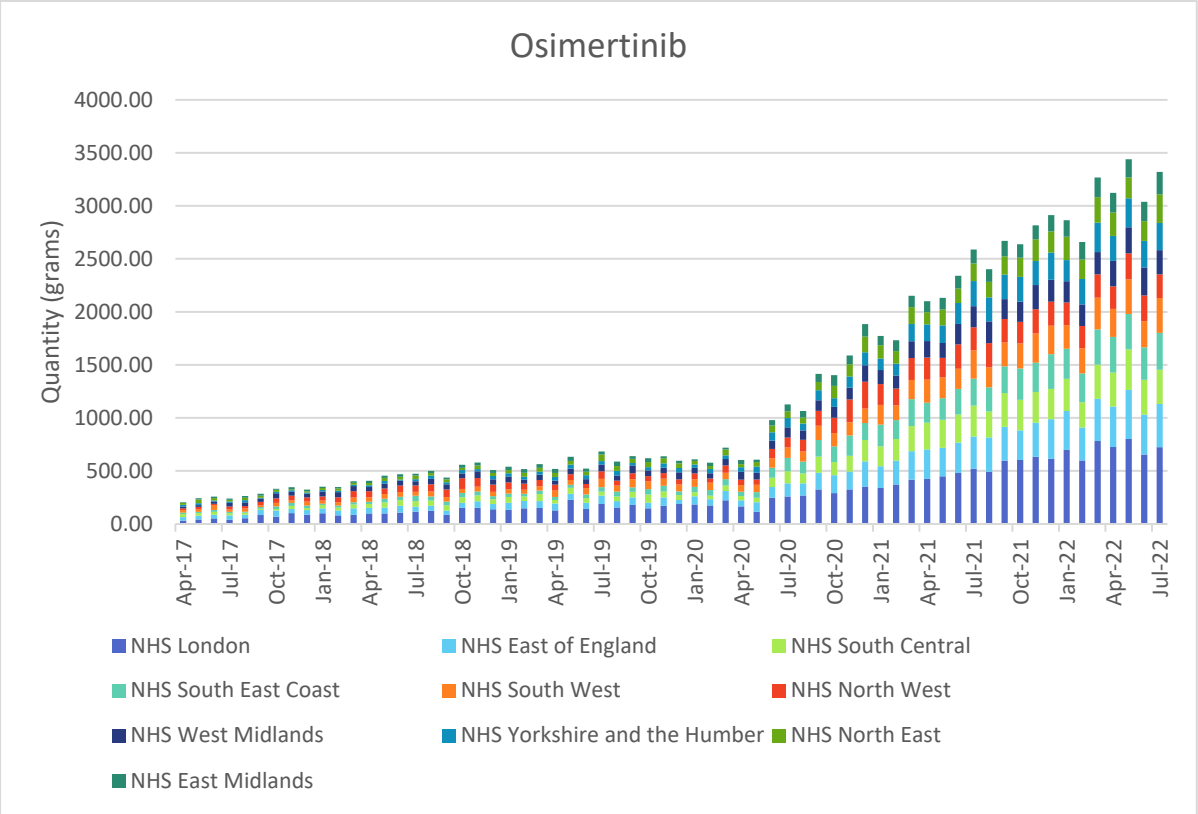

Figure 5.16: Monthly utilisation of osimertinib between April 2017 and July 2022 (at regional level).

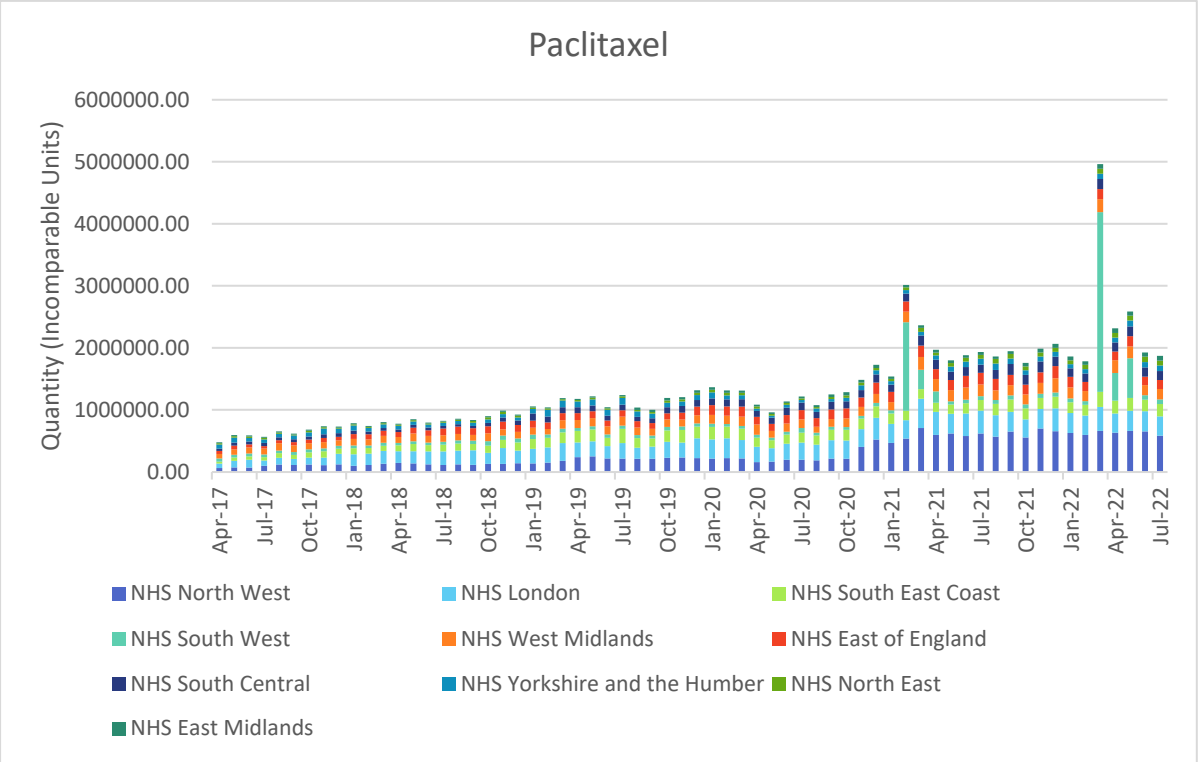

Figure 5.17: Monthly utilisation of paclitaxel between April 2017 and July 2022 (at regional level).

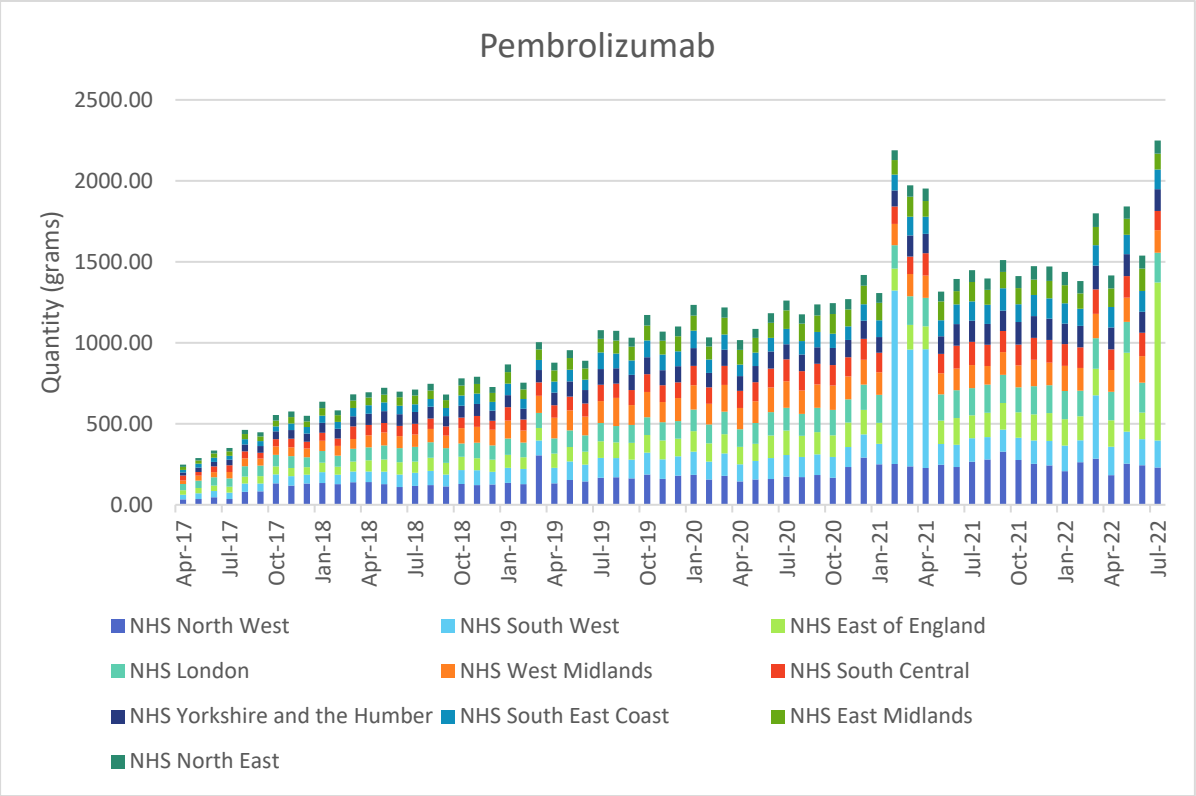

Figure 5.18: Monthly utilisation of pembrolizumab between April 2017 and July 2022 (at regional level).

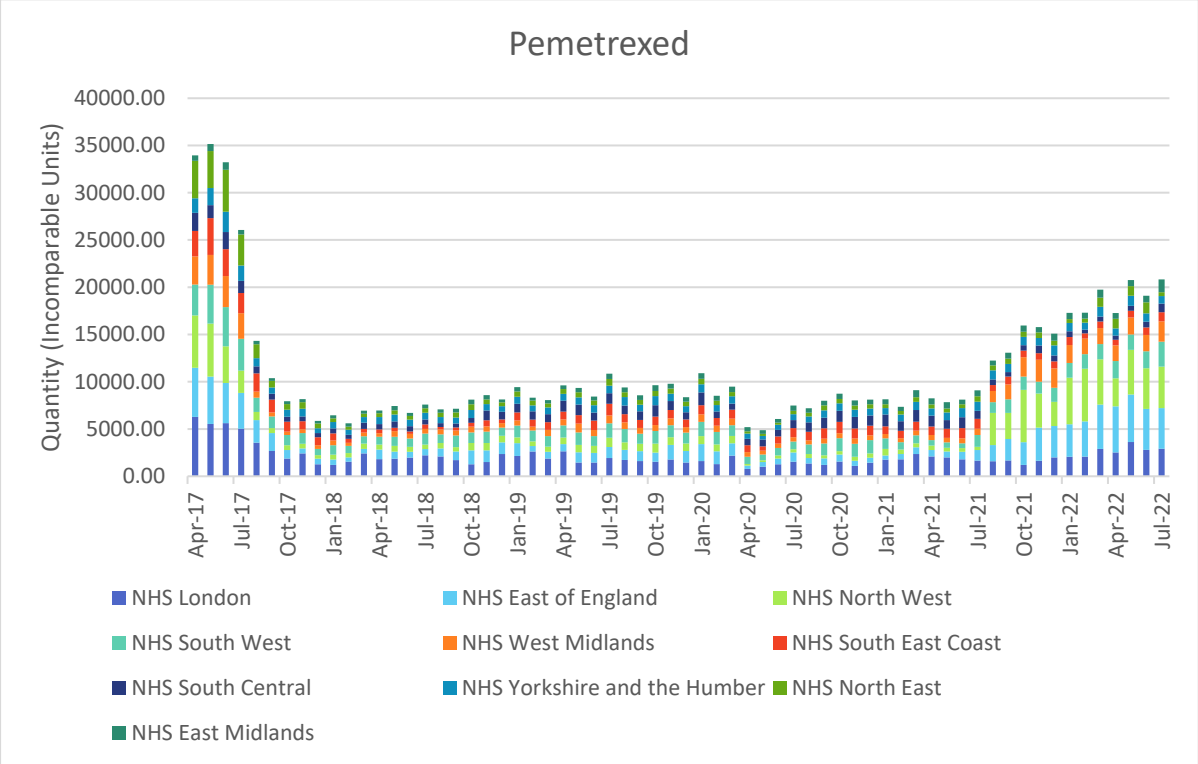

Figure 5.19: Monthly utilisation of pemetrexed between April 2017 and July 2022 (at regional level).

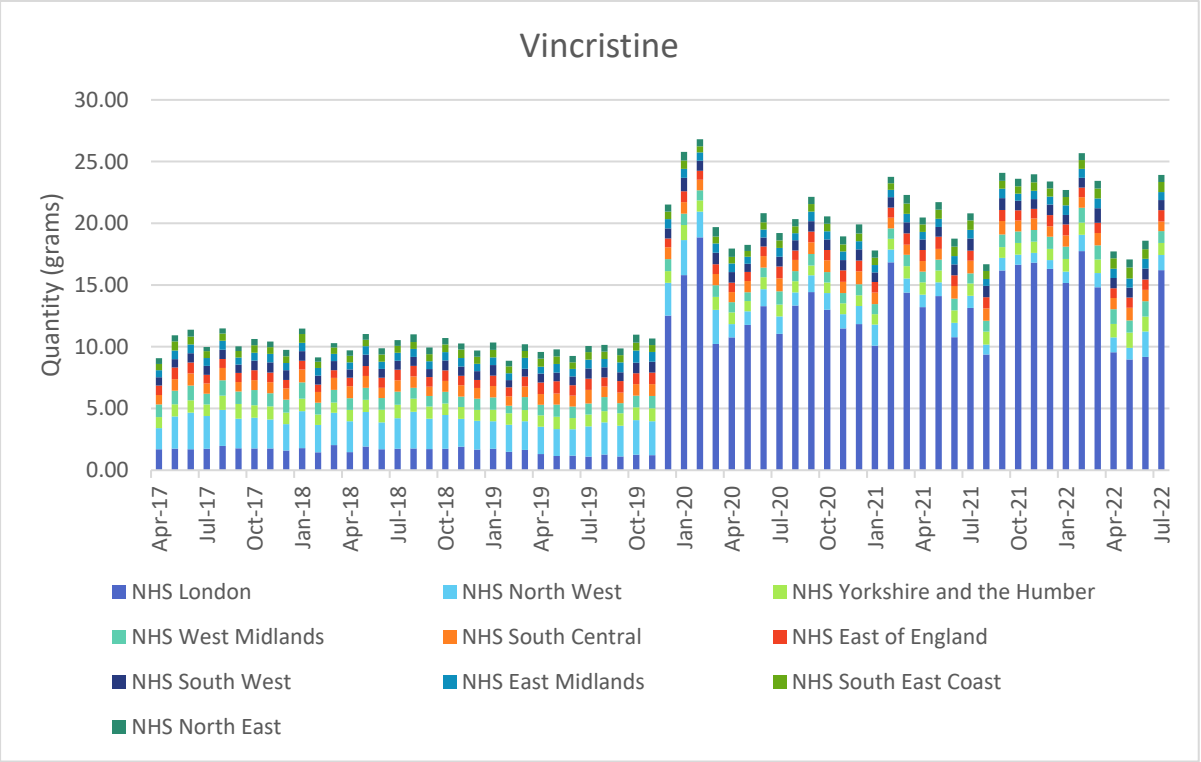

Figure 5.20: Monthly utilisation of vincristine between April 2017 and July 2022 (at regional level).

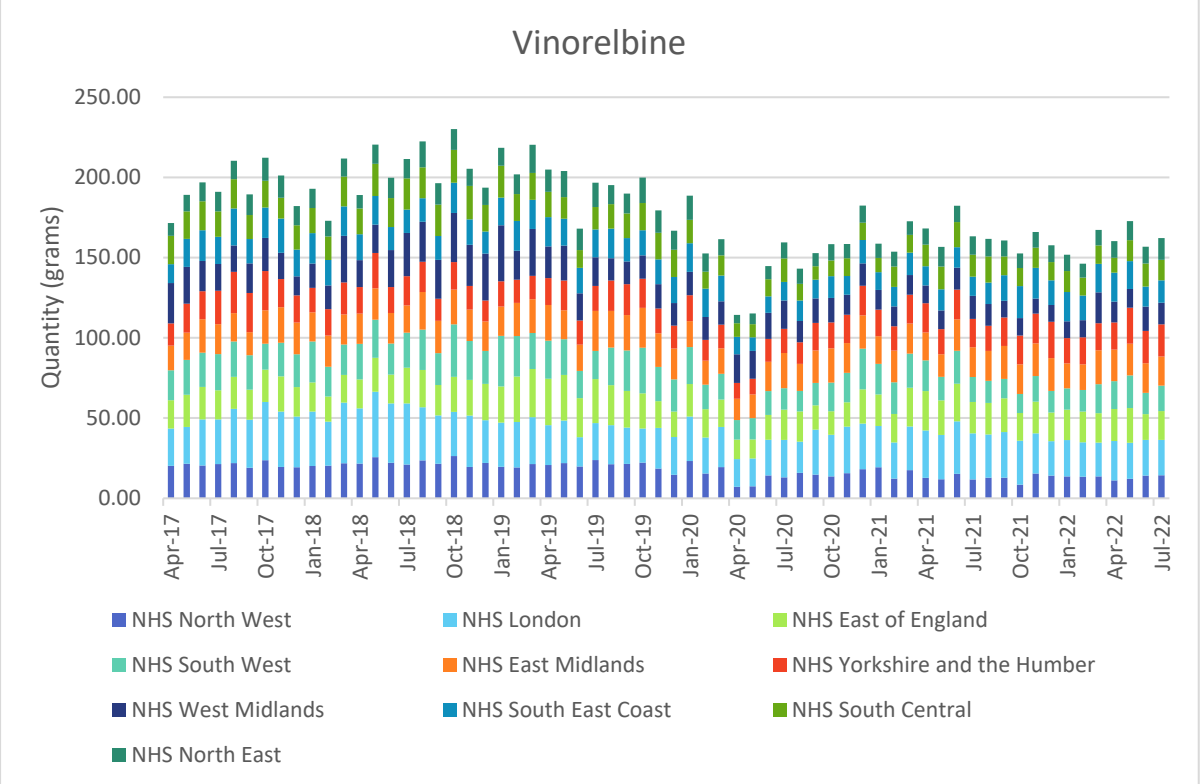

Figure 5.21: Monthly utilisation of vinorelbine between April 2017 and July 2022 (at regional level).

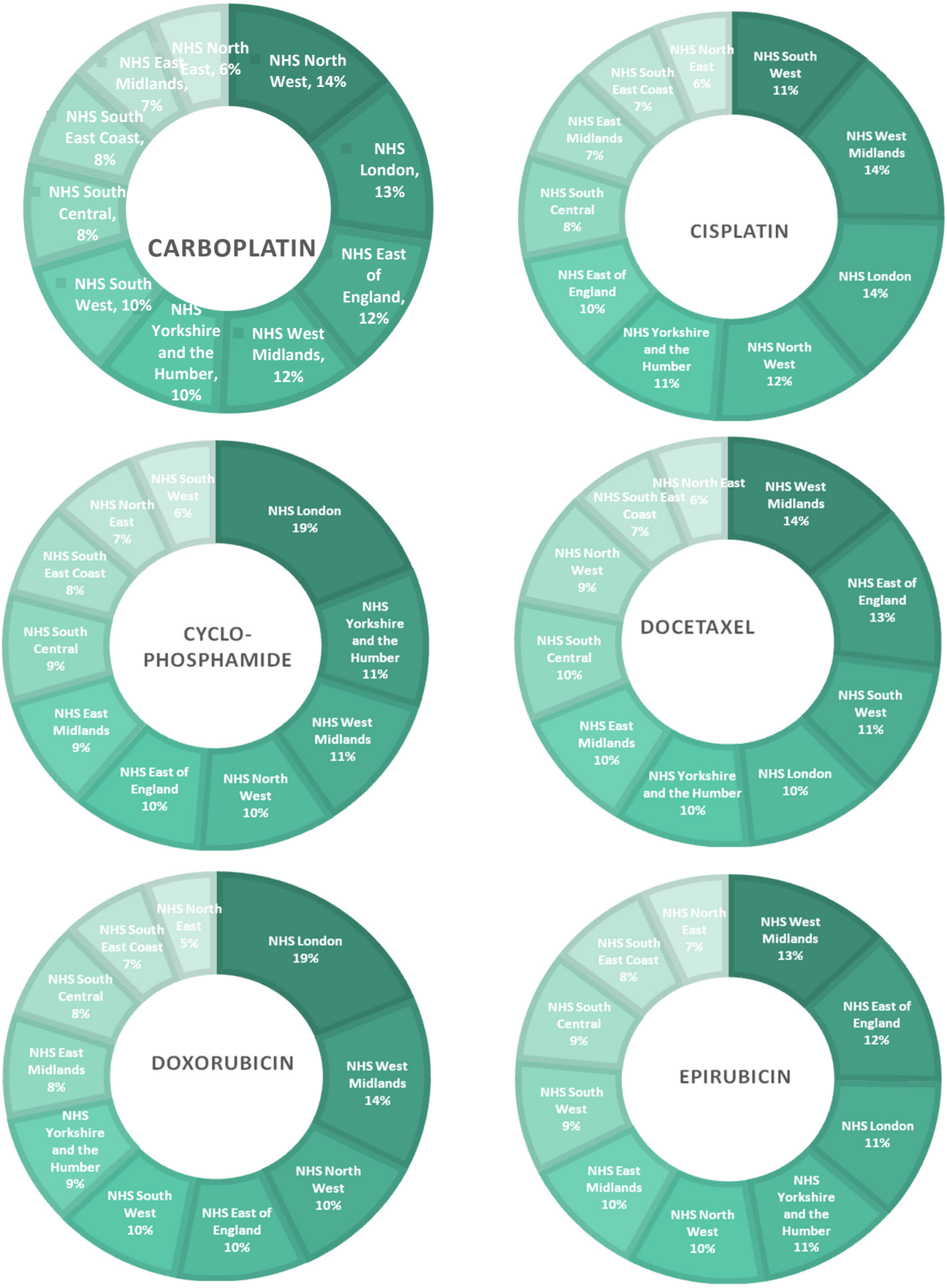

Figure 5.22: Distribution of total use by region of carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin and epirubicin at regional level between April 2017 and July 2022.

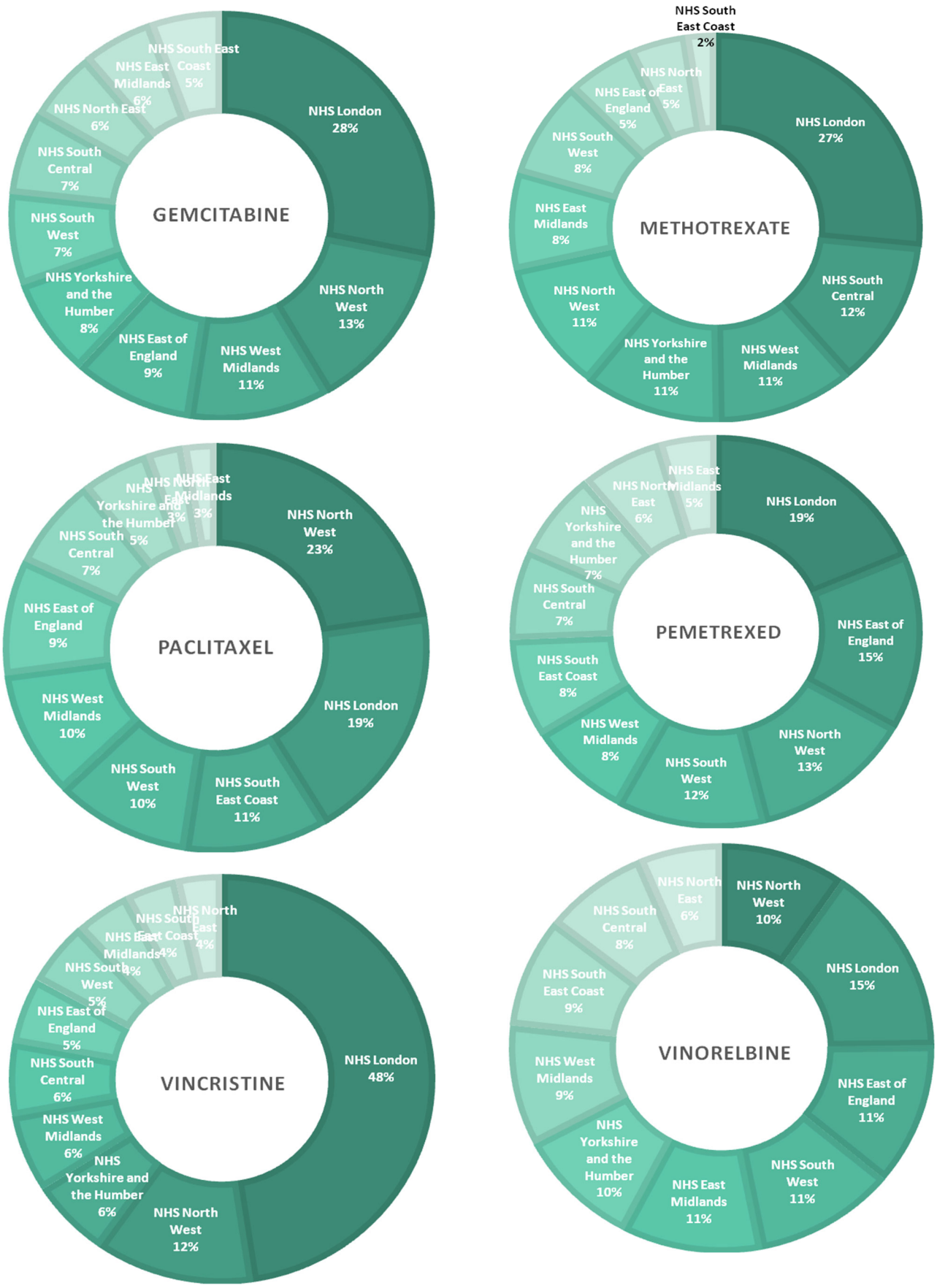

Figure 5.23: Distribution of total use by region of gemcitabine, methotrexate paclitaxel, pemetrexed, vincristine and vinorelbine at regional level between April 2017 and July 2022.

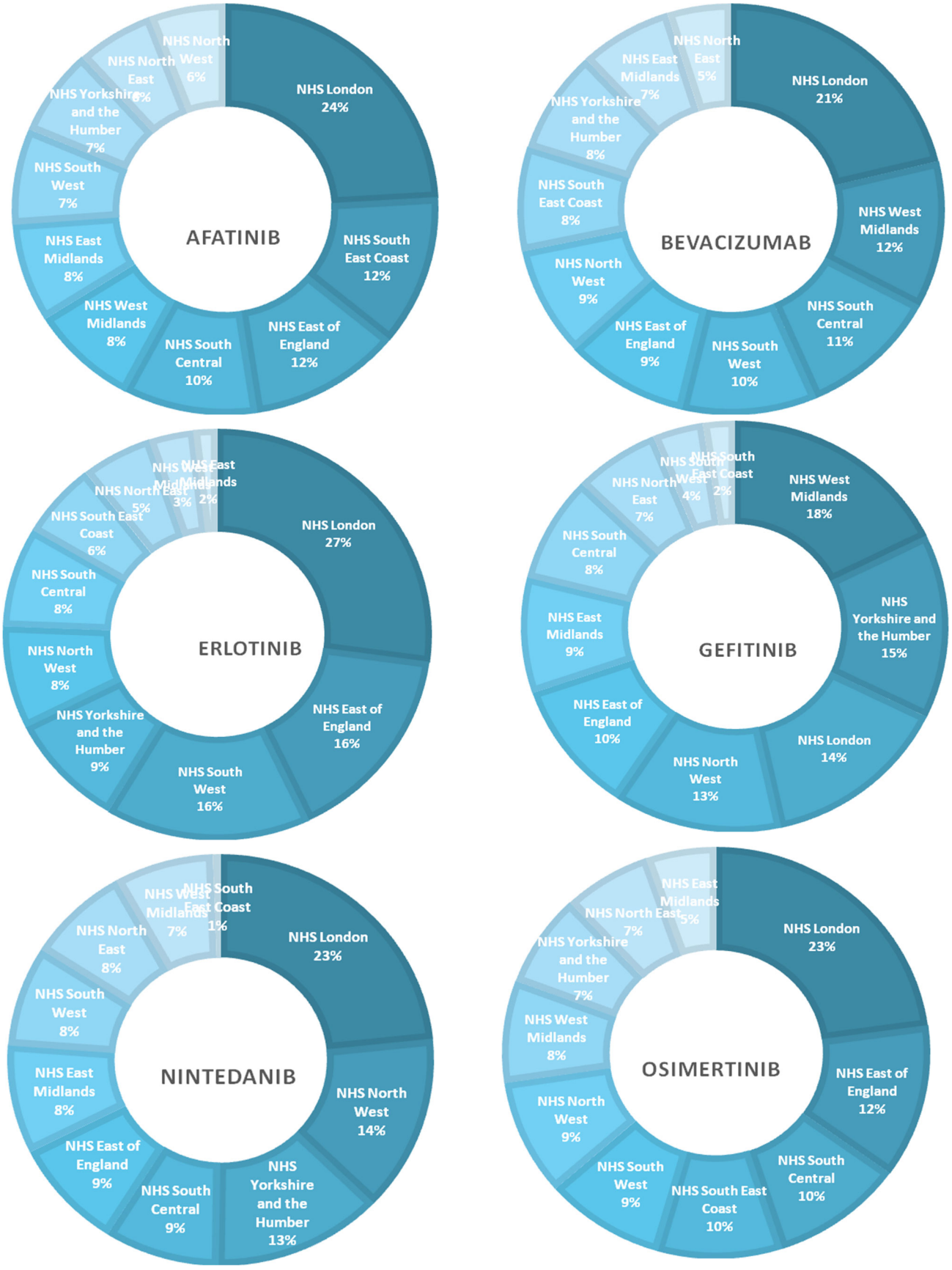

Figure 5.24: Distribution of total use by region of afatinib, bevacizumab, erlotinib, gefitinib, nintedanib and osimertinib at regional level between April 2017 and July 2022.

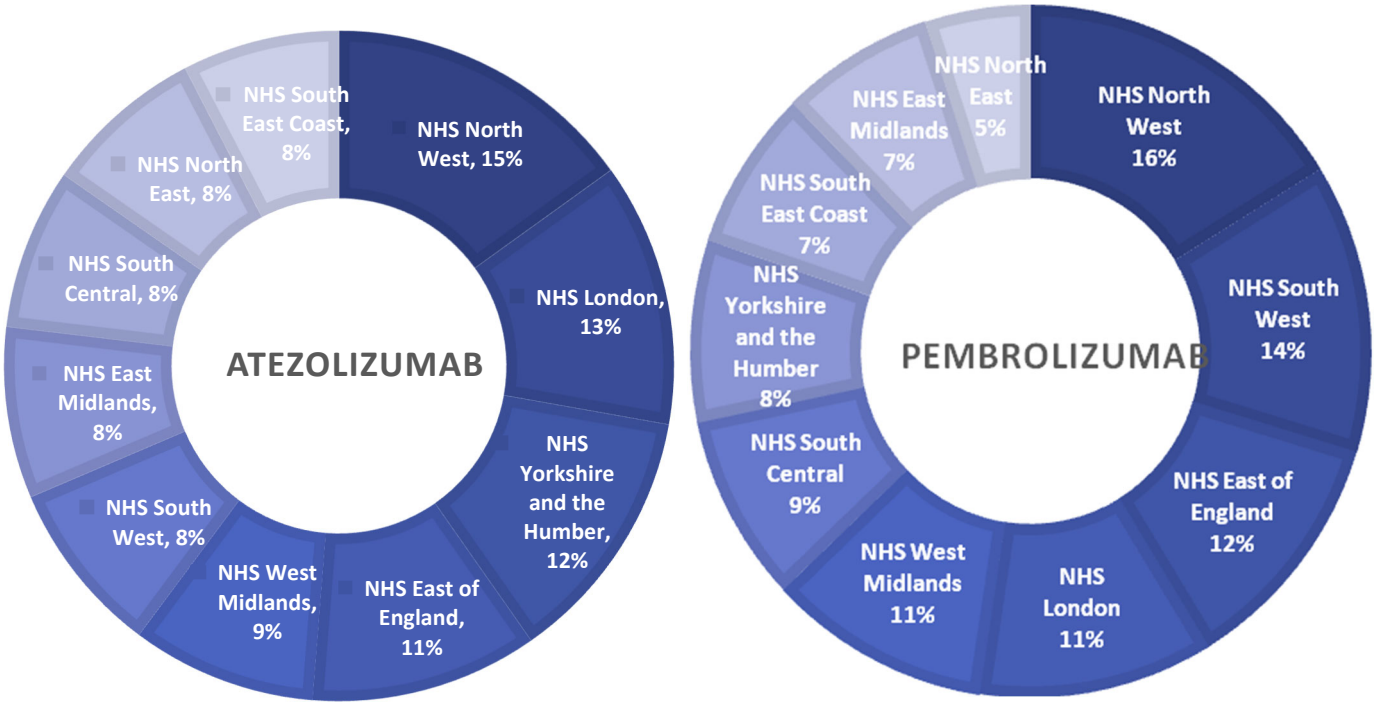

Figure 5.25: Distribution of total use by region of atezolizumab and pembrolizumab at regional level between April 2017 and July 2022.

It was discovered that for all shortlisted oncology drugs, London was among the Top 4 regions reported the highest among usage of the drug in between April 2017 and July 2022. This was possibly due to there are several cancer centres and hospitals in London, such as The Royal Marsden Hospital, University College Hospital Macmillan Cancer Centre, and Nuffield Health Cancer Centre London (CCL).

Among the 20 shortlisted cardiology drugs, it was discovered during the data extraction phase that there are no available data for anistreplase or reteplase. Figure 5.26 shows the overview of monthly utilisation of selected cardiology drugs between April 2017 and July 2022 at national level, while Table 5.4 shows the total amount of dispensed dosage of each selected cardiology drug at national level between April 2017 and July 2022.

A heat map showing the correlation between 20 shortlisted cardiology drugs and 20 shortlisted cancer treatments is presented in Table 5.5.

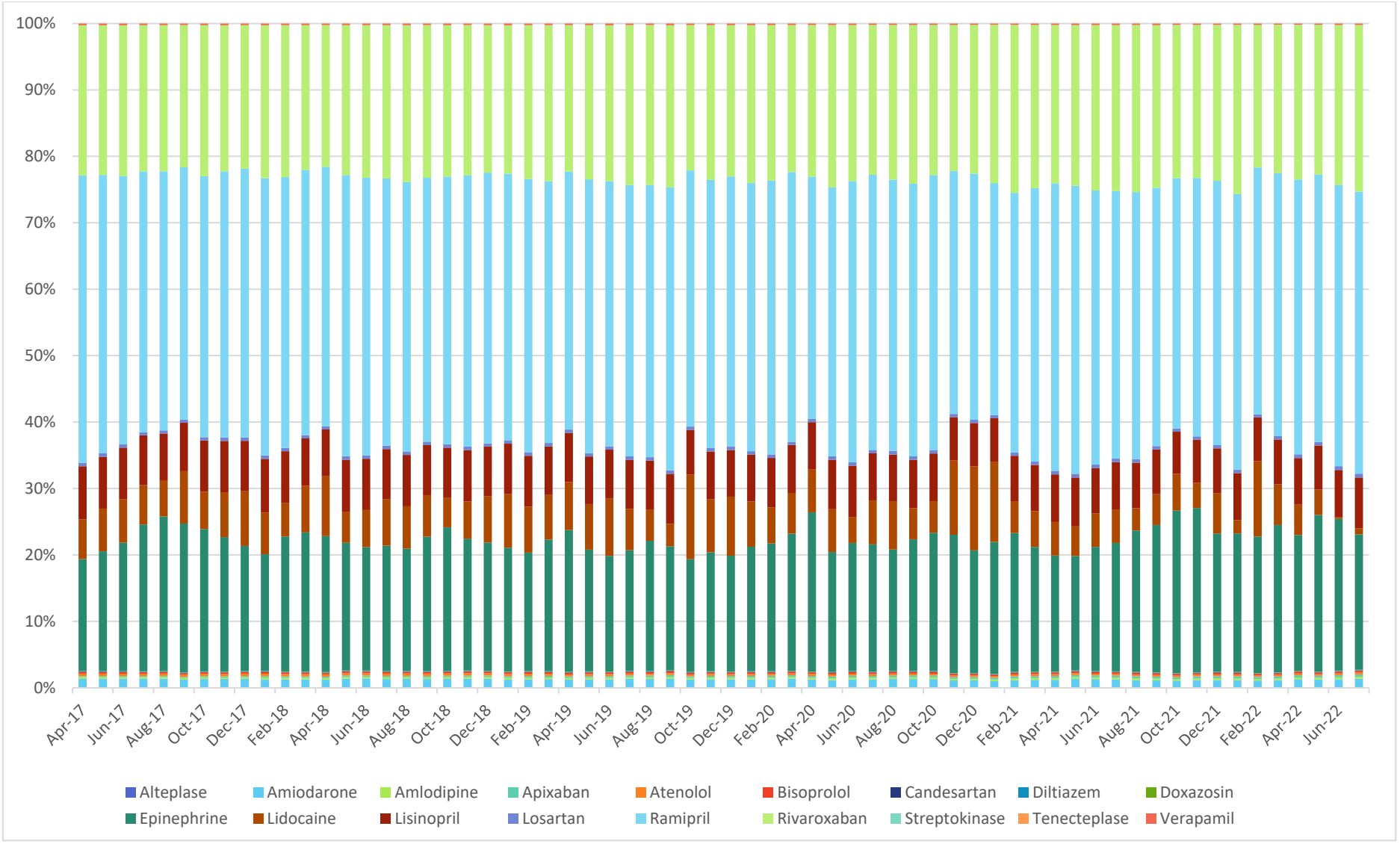

Figure 5.26: Monthly utilisation of selected cardiology drugs between April 2017 and July 2022 (at national level).

Table 5.4: Total amount of dispensed dosage of each selected cardiology drug at national level between April 2017 and July 2022.

	Alteplase	Amiodarone	Amlodipine	Apixaban	Atenolol	Bisoprolol	Candesartan	Diltiazem	Doxazosin	Epinephrine	Lidocaine	Lisinopril	Losartan	Ramipril	Rivaroxaban	Streptokinase	Tenecteplase	Verapamil
Apr-17	100.97	34369.01	6604.31	4100.99	9459.30	6132.46	1673.71	1141.00	1187.45	433516.50	153325.00	206124.00	13179.78	1113405.00	581336.00	66.50	1.59	6823.24
May-17	115.03	38165.60	7059.85	4622.31	10267.03	6691.32	1759.09	1354.04	1284.41	508977.90	181150.00	220949.50	13971.02	1184088.00	636484.00	46.75	1.05	7266.65
Jun-17	122.94	37669.35	6643.45	4645.03	9811.28	6472.22	1664.50	1197.22	1248.29	538652.50	183005.00	215632.00	13949.24	1124992.00	632098.00	95.25	0.81	7231.35
Jul-17	119.36	38110.15	6408.99	4500.95	9276.87	6209.86	1658.98	1164.01	1196.29	613890.15	165500.00	207578.00	12865.86	1090391.00	611823.00	68.50	0.43	6799.83
Aug-17	115.30	39247.15	6873.93	4777.10	9859.76	6535.69	1717.22	1144.86	1210.59	666718.40	153050.00	204136.00	13618.23	1116482.00	630048.00	70.25	0.49	7099.63
Sep-17	109.39	34835.83	6603.33	4652.43	9412.52	6320.61	1686.12	1155.66	1182.11	634583.30	223950.00	206539.00	13916.03	1076717.00	606800.60	185.75	1.12	6664.31
Oct-17	111.99	37952.05	6884.42	5098.90	10042.29	6614.62	1699.48	1337.54	1275.00	615080.90	161500.00	221407.00	13965.56	1128431.00	653084.00	87.50	1.02	6980.66
Nov-17	116.99	37815.10	7114.03	5200.86	9367.11	6824.08	1813.26	1403.40	1297.99	586704.85	195500.00	224108.00	14462.53	1162136.00	637985.00	136.50	1.34	7420.89
Dec-17	120.23	39169.50	7168.88	5264.35	10069.92	6902.96	1834.70	1161.18	1309.74	550181.65	240000.00	221334.00	14460.40	1180793.00	631009.00	122.75	1.20	7009.54
Jan-18	127.50	37813.75	7541.26	5827.47	11028.41	7284.10	1903.52	1343.87	1373.09	518459.35	184550.00	238179.50	15205.91	1230439.50	678195.00	71.00	1.00	7752.61
Feb-18	111.15	33631.55	6679.85	5198.98	9166.57	6437.11	1717.52	1236.16	1276.20	543574.85	135500.00	207578.50	13715.66	1089971.50	611803.00	69.50	0.72	6557.89
Mar-18	117.65	38253.25	7605.43	5879.96	9825.51	7148.08	1866.22	1363.14	1337.41	635846.10	213050.00	216292.00	14743.03	1211094.50	661310.00	56.50	1.45	7409.63
Apr-18	112.66	34944.05	6883.21	5614.70	9121.67	6620.68	1764.32	1220.66	1288.36	587976.30	258500.00	202588.00	13935.31	1121996.00	613196.00	40.00	1.19	6577.28
May-18	119.17	38218.00	7363.30	5866.22	9691.21	6964.78	1840.19	1418.60	1364.09	539361.85	129000.00	221526.00	14909.56	1187615.00	633100.50	119.25	0.49	6843.26
Jun-18	117.09	36522.80	6675.38	5531.00	8825.21	6420.12	1727.63	1330.82	1273.20	493413.40	148250.00	205219.00	13664.65	1109649.00	610001.00	42.50	0.52	6351.23
Jul-18	114.08	36114.47	6906.25	5670.96	9483.30	6498.27	1776.21	1307.60	1257.51	517775.00	190800.00	207782.92	14119.11	1103674.46	633171.00	93.50	0.44	6857.80
Aug-18	126.08	36440.13	7084.94	5697.67	9464.91	6570.93	1796.21	1163.78	1272.83	506635.20	175550.00	213060.00	14209.03	1117065.00	649985.00	88.25	0.86	6545.16
Sep-18	110.22	33972.85	6514.79	5280.41	8814.81	6133.34	1705.99	1113.64	1208.00	522141.05	161000.00	194762.00	13233.65	1025133.80	593662.00	45.75	1.18	6077.42
Oct-18	117.06	38617.90	7399.15	6100.72	10039.02	7023.27	1808.42	1373.04	1455.00	627599.15	131000.00	218384.50	15245.69	1170944.00	662879.00	58.00	1.15	6951.46
Nov-18	122.18	38668.50	7403.61	6007.53	9699.08	6952.96	1842.56	1385.08	1364.16	562543.65	158000.00	219868.00	14727.28	1157130.00	641108.00	76.00	1.29	6692.18
Dec-18	124.82	38682.20	7278.61	6113.57	9311.82	6982.79	1796.35	1206.34	1357.99	550033.70	198000.00	213965.00	14320.88	1161753.00	632927.00	79.25	1.10	7057.68

	Alteplase	Amiodarone	Amlodipine	Apixaban	Atenolol	Bisoprolol	Candesartan	Diltiazem	Doxazosin	Epinephrine	Lidocaine	Lisinopril	Losartan	Ramipril	Rivaroxaban	Streptokinase	Tenecteplase	Verapamil
Jan-19	119.73	37390.95	7683.31	6637.18	9988.33	7387.07	1941.86	1419.03	1480.95	557608.25	241850.00	227481.00	15688.98	1202643.00	669092.00	24.50	1.11	7946.60
Feb-19	109.06	33312.30	6957.38	6150.71	8663.72	6561.23	1662.78	1320.00	1297.73	467727.35	181000.00	201417.00	14025.95	1078837.04	607363.00	46.00	1.10	6458.54
Mar-19	120.69	35566.40	7204.15	6309.31	8255.48	6862.19	1829.16	1456.60	1329.23	544864.30	185000.00	201250.00	13800.93	1084681.76	646397.00	130.75	1.47	6952.70
Apr-19	115.33	35156.80	7205.34	6492.77	8251.41	6941.64	1854.98	1222.82	1326.59	609418.85	206000.00	212171.00	13813.50	1109732.00	629665.00	162.75	1.06	6432.77
May-19	125.04	35110.15	7305.46	6625.47	8461.76	7106.85	1878.41	1324.16	1370.75	516390.95	193600.00	201377.00	14128.96	1161937.00	653778.00	136.25	1.27	6991.00
Jun-19	115.93	32984.70	6488.20	6200.51	7565.68	6385.37	1776.55	1299.62	1220.36	455290.20	224755.00	192871.00	13420.38	1043736.00	613576.00	99.75	0.64	6772.13
Jul-19	131.31	37859.77	7208.84	6674.97	7958.12	7022.03	1888.82	1269.04	1390.39	510007.05	174936.00	208033.00	13908.13	1148227.00	675628.00	282.50	0.66	6525.55
Aug-19	118.52	34375.35	6668.06	6343.91	7288.57	6561.62	1749.77	1153.86	1330.90	513291.50	123500.00	192818.00	13291.13	1071790.00	630715.00	157.50	0.45	6099.06
Sep-19	121.03	34540.87	6704.22	6179.73	7592.18	6502.85	1789.57	1147.02	1286.07	466228.30	84500.00	188383.00	13079.45	1064823.00	609946.00	58.75	0.73	6500.37
Oct-19	132.92	38283.95	7515.09	6967.09	7937.43	7207.25	1895.74	1376.80	1412.05	520389.90	391000.00	205537.00	14886.34	1182267.00	670673.00	62.50	1.11	7117.19
Nov-19	125.63	35841.89	7125.51	6781.20	7840.00	6950.10	1903.42	1354.58	1363.63	500934.00	222503.00	201674.00	14108.96	1128668.00	652004.00	57.50	0.77	6441.06
Dec-19	135.43	37122.77	7744.04	7229.20	8395.07	7389.16	1932.12	1201.42	1471.71	516240.70	264007.00	207807.00	15126.88	1205583.00	675527.00	64.25	0.66	7278.99
Jan-20	128.87	37064.00	7733.39	7544.60	8729.12	7482.64	1924.86	1420.82	1434.87	553744.05	201504.00	208475.20	14956.14	1193350.00	701912.00	57.50	0.62	7203.44
Feb-20	119.08	33683.50	6976.17	6773.57	7342.00	6764.38	1751.99	1299.50	1345.13	508854.45	144000.00	196289.20	13948.48	1091110.00	619508.00	41.50	0.31	5969.88
Mar-20	155.64	37865.25	7498.28	6893.58	7944.15	6832.98	1705.58	982.14	1363.26	576671.10	171006.00	201228.00	13749.06	1133464.00	618300.00	78.50	2.96	6256.46
Apr-20	169.31	26730.61	5742.42	5382.84	6802.42	4742.38	1307.75	339.22	1045.35	515001.75	139500.00	152005.00	10448.96	783077.00	491233.00	60.50	1.97	4332.04
May-20	127.13	24431.45	5833.05	5839.27	6292.31	5264.33	1473.13	459.52	1121.62	384319.50	137515.00	158109.50	11682.31	861890.00	521250.00	42.50	0.59	4579.03
Jun-20	130.45	29181.85	6211.14	6302.73	6788.14	5850.79	1536.84	544.64	1139.03	445212.45	90016.00	178382.00	12097.93	976591.00	542179.00	13.50	0.82	5141.85
Jul-20	127.95	31752.55	6731.50	6617.97	7122.91	6294.14	1692.22	723.38	1250.86	489263.70	168520.00	181453.00	13421.69	1058206.00	576675.00	20.50	0.46	5156.27
Aug-20	122.05	29831.10	6108.60	6141.47	6442.13	5791.90	1690.86	638.48	1176.01	418530.15	166509.00	160917.00	12615.89	934947.00	533572.00	24.75	0.70	5001.19
Sep-20	122.92	33488.85	7054.01	6824.61	7262.07	6512.69	1796.56	847.74	1288.31	508838.40	120500.00	187132.50	13644.76	1054789.00	614616.00	20.00	0.51	5172.09
Oct-20	125.53	34444.85	7217.10	7109.27	7301.82	6639.89	1818.67	940.26	1342.28	552610.75	126011.00	190791.00	13949.94	1099066.00	600780.90	20.75	0.79	5251.75

	Alteplase	Amiodarone	Amlodipine	Apixaban	Atenolol	Bisoprolol	Candesartan	Diltiazem	Doxazosin	Epinephrine	Lidocaine	Lisinopril	Losartan	Ramipril	Rivaroxaban	Streptokinase	Tenecteplase	Verapamil
Nov-20	138.63	31429.05	7219.38	7134.89	7048.53	6315.02	1763.54	966.48	1322.38	594861.70	319504.00	186772.00	13793.30	1045657.00	628737.57	23.50	1.58	5580.86
Dec-20	141.16	34185.30	8088.42	7803.33	7821.90	7054.40	1936.35	920.02	1448.61	577538.80	396001.00	203600.00	15134.60	1159491.00	700708.00	14.00	1.19	5999.66
Jan-21	157.86	30255.76	7392.81	8107.08	7673.67	6279.04	1841.62	741.80	1354.30	605205.35	367555.00	198772.00	14465.91	1063706.00	726632.00	47.25	0.59	5166.67
Feb-21	134.80	28208.30	6774.04	7609.45	7126.41	5937.21	1661.98	824.12	1258.75	523078.30	119500.00	170994.00	12411.03	977399.00	632842.90	30.75	0.78	4994.95
Mar-21	140.78	34024.10	7884.00	8310.35	8039.68	7150.64	1902.52	1043.14	1483.34	539018.25	155000.00	199517.00	14823.26	1183300.00	706434.00	49.25	1.06	5541.52
Apr-21	121.51	31301.00	7478.46	7815.02	6987.50	6906.37	1903.20	975.06	1378.63	462518.95	133000.00	189793.00	14294.98	1146380.00	631294.10	23.50	0.65	5520.56
May-21	122.79	34875.40	7422.46	7762.09	6887.67	6835.75	1913.68	1071.52	1407.91	452272.65	116500.00	193180.00	14653.98	1137090.00	635144.00	53.75	1.09	5903.54
Jun-21	134.08	36698.45	7722.68	8070.29	7304.47	7136.05	1999.94	1144.32	1503.36	530142.20	143500.00	192442.00	15481.20	1171384.00	707100.40	144.50	0.80	6256.29
Jul-21	133.12	35495.60	7440.42	8165.81	7261.79	7035.90	1951.25	1058.94	1472.26	546140.40	143000.00	201045.00	15222.14	1138961.00	706892.90	57.50	1.23	6259.35
Aug-21	134.65	30790.70	7120.14	7986.08	6735.93	6624.67	1845.81	901.22	1377.34	568055.60	89500.00	182532.51	14273.64	1073092.12	671380.06	47.75	1.12	5599.69
Sep-21	127.56	32061.40	7504.67	8386.80	6785.00	6923.32	1847.21	1020.46	1414.93	634393.15	133000.00	192446.01	14362.18	1111582.07	700750.05	73.75	1.15	6862.46
Oct-21	127.97	31156.35	7354.07	8232.60	6755.58	6773.88	1885.07	983.26	1393.57	719428.85	162000.00	186852.01	14262.25	1108119.06	678299.03	57.75	0.98	5901.84
Nov-21	140.52	34831.00	7845.16	8890.85	7283.99	7153.73	1933.29	1108.76	1424.82	748452.65	114500.00	197303.01	14654.82	1177677.12	698755.05	48.50	0.75	5976.74
Dec-21	150.70	35877.75	8243.53	9333.50	7673.75	7554.90	1961.30	1009.20	1518.53	635331.15	184000.00	206657.01	15206.70	1213855.07	716356.93	63.75	0.97	6130.39
Jan-22	128.95	30084.40	7585.18	8928.35	6867.07	6893.17	1828.46	1007.98	1415.45	567088.90	54500.00	192865.80	14160.02	1129774.56	692876.12	130.25	0.28	5444.65
Feb-22	119.64	32044.26	7345.23	8336.43	6326.86	6898.26	1812.00	1059.48	1374.44	606103.55	335000.00	194526.02	13534.32	1096601.17	634089.17	124.00	0.30	5696.60
Mar-22	137.76	35876.77	8430.19	9518.73	7313.77	7901.92	2092.25	1155.34	1566.30	705973.45	194500.00	214902.00	16301.50	1260372.00	711833.00	65.00	0.28	5511.60
Apr-22	130.86	35403.75	7767.18	8731.16	7621.55	7219.19	2017.74	907.52	1403.76	567374.35	127050.00	195181.00	15253.15	1149859.00	646701.00	49.75	0.37	5537.83
May-22	139.09	37594.05	8252.27	9036.21	7357.28	7491.41	2001.19	1083.70	1519.83	719356.05	116500.00	202788.00	15856.45	1228720.00	688226.00	23.00	0.34	5844.45
Jun-22	122.20	33765.75	7698.54	8424.82	6634.46	6995.65	1913.12	911.24	1418.24	603983.55	7500.00	186668.00	15203.71	1119846.00	635762.00	44.75	1.01	5553.39
Jul-22	111.70	33947.25	7255.80	8103.85	7073.14	6673.71	1808.97	787.18	1338.57	506213.45	23000.00	189053.00	14545.85	1053945.00	623403.20	31.00	0.53	5155.32

Figure 5.27: Distribution of total use by region of alteplase, amiodarone, amlodipine and apixaban, atenolol and bisoprolol at regional level between April 2017 and July 2022.

Figure 5.28: Distribution of total use by region of candesartan, diltiazem, doxazosin, epinephrine, lidocaine and lisinopril at regional level between April 2017 and July 2022.

Figure 5.29: Distribution of total use by region of losartan, ramipril, rivaroxaban, streptokinase, tenecteplase and verapamil at regional level between April 2017 and July 2022.

Table 5.5: A heat map showing the correlation coefficient between 20 shortlisted cardiology drugs and 20 shortlisted cancer treatments.

	Alteplase	Amiodarone	Amlodipine	Apixaban	Atenolol	Bisoprolol	Candesartan	Diltiazem	Doxazosin	Epinephrine	Lidocaine	Lisinopril	Losartan	Ramipril	Rivaroxaban	Streptokinase	Tenecteplase	Verapamil
Afatinib	-0.06135	0.206145	-0.37158	-0.56501	0.354052	-0.19462	-0.35749	0.279264	-0.33093	-0.40718	0.271228	0.146734	-0.32167	-0.1464	-0.34068	0.232831	0.308385	0.344619
Atezolizumab	0.495496	-0.38023	0.54461	0.954542	-0.78128	0.31217	0.500109	-0.43484	0.593654	0.241511	-0.18527	-0.42996	0.338623	0.062153	0.424547	-0.24713	-0.22225	-0.59637
Bevacizumab	0.328753	0.038889	0.691602	0.772559	-0.36195	0.561412	0.611169	-0.08247	0.673685	0.523788	-0.19154	0.027309	0.572055	0.422707	0.587501	-0.07558	-0.25345	-0.21725
Carboplatin	0.274763	0.36625	0.774676	0.548643	0.004415	0.724741	0.713078	0.311425	0.752802	0.529985	0.196258	0.400432	0.7207	0.645374	0.819735	0.05578	-0.13619	0.199887
Cisplatin	-0.29461	0.648027	0.174524	-0.39411	0.741277	0.326301	0.155623	0.712809	0.129319	0.255619	0.237176	0.747161	0.321013	0.508912	0.298796	0.248417	0.049984	0.656568
Cyclophosphamide	-0.0345	0.623037	0.48332	0.026321	0.416454	0.579778	0.45019	0.532687	0.480774	0.319881	0.106957	0.599582	0.571057	0.631275	0.487575	0.224312	0.071439	0.482865
Docetaxel	-0.39343	0.783306	0.172338	-0.42469	0.785836	0.449747	0.226257	0.875638	0.157676	0.158826	0.196184	0.805704	0.350863	0.569216	0.281693	0.450601	0.129766	0.882861
Doxorubicin	0.358968	0.330335	0.582664	0.334496	0.09147	0.460399	0.436083	0.084269	0.490392	0.380003	0.189103	0.304572	0.54136	0.465504	0.517117	-0.13332	0.022788	0.093304
Epirubicin	-0.34572	0.768751	0.210833	-0.41105	0.784958	0.417927	0.208526	0.767209	0.136403	0.326955	0.152893	0.80949	0.354395	0.615797	0.369055	0.383121	0.1516	0.835846
Erlotinib	-0.44916	0.497193	-0.42452	-0.89582	0.807909	-0.17923	-0.39408	0.53728	-0.46574	-0.19461	0.209446	0.521034	-0.22838	0.050376	-0.30958	0.297103	0.272722	0.674199
Gefitinib	0.551349	-0.42345	-0.09062	0.192627	-0.40902	-0.257	-0.23294	-0.62748	-0.09757	-0.16197	0.003281	-0.44744	-0.24936	-0.32878	-0.23955	-0.37652	0.179017	-0.49096
Gemcitabine	0.288157	-0.14853	0.493277	0.608913	-0.38731	0.29624	0.410133	-0.27334	0.477271	0.247168	-0.01082	-0.11111	0.37083	0.21943	0.423866	-0.24558	-0.18908	-0.36645
Methotrexate	0.039161	0.175359	0.085224	-0.12308	0.331842	0.132387	0.077101	0.131837	0.031356	0.012923	0.040824	0.320748	0.1376	0.205468	0.145493	0.003166	0.06139	0.280836
Nintedanib	0.434215	-0.26838	0.512114	0.817751	-0.64115	0.330428	0.451472	-0.32738	0.547872	0.198484	-0.21029	-0.3323	0.35525	0.093911	0.338114	-0.2452	-0.19058	-0.47776
Osimertinib	0.407069	-0.2978	0.57249	0.905696	-0.66615	0.33996	0.509853	-0.40839	0.574847	0.385713	-0.25577	-0.32088	0.398023	0.145074	0.447211	-0.23477	-0.24805	-0.53649
Paclitaxel	0.466014	-0.24183	0.584037	0.842932	-0.56956	0.396633	0.514062	-0.27034	0.596357	0.345718	-0.12457	-0.23262	0.389735	0.195113	0.454656	-0.18742	-0.2291	-0.47145
Pembrolizumab	0.49991	-0.43294	0.453939	0.879364	-0.7585	0.223677	0.380149	-0.47089	0.493641	0.123	-0.20559	-0.48533	0.216924	-0.02601	0.319748	-0.28974	-0.19402	-0.63548
Pemetrexed	-0.14116	0.180849	0.128006	0.010528	0.082122	0.13313	0.09135	0.060507	0.068652	0.224393	-0.15309	0.16301	0.12727	0.23277	0.130862	-0.00679	-0.12897	0.106055
Vincristine	0.498881	-0.46819	0.332226	0.743786	-0.70803	0.106005	0.193364	-0.54135	0.341909	0.150973	-0.15869	-0.48758	0.089847	-0.09144	0.204703	-0.37224	-0.19542	-0.60654
Vinorelbine	-0.45246	0.759846	0.188914	-0.40851	0.779185	0.400644	0.241201	0.825375	0.155983	0.176663	0.175299	0.780339	0.382713	0.544751	0.30994	0.357742	0.075251	0.786221

From the correlation analysis (Table 5.5), it was demonstrated that the two drugs that were of the highest positive correlation were atezolizumab and apixaban (0.954542) whereas erlotinib and apixaban showed the lowest negative correlation (-0.89582) (Figure 5.30 and Figure 5.33).

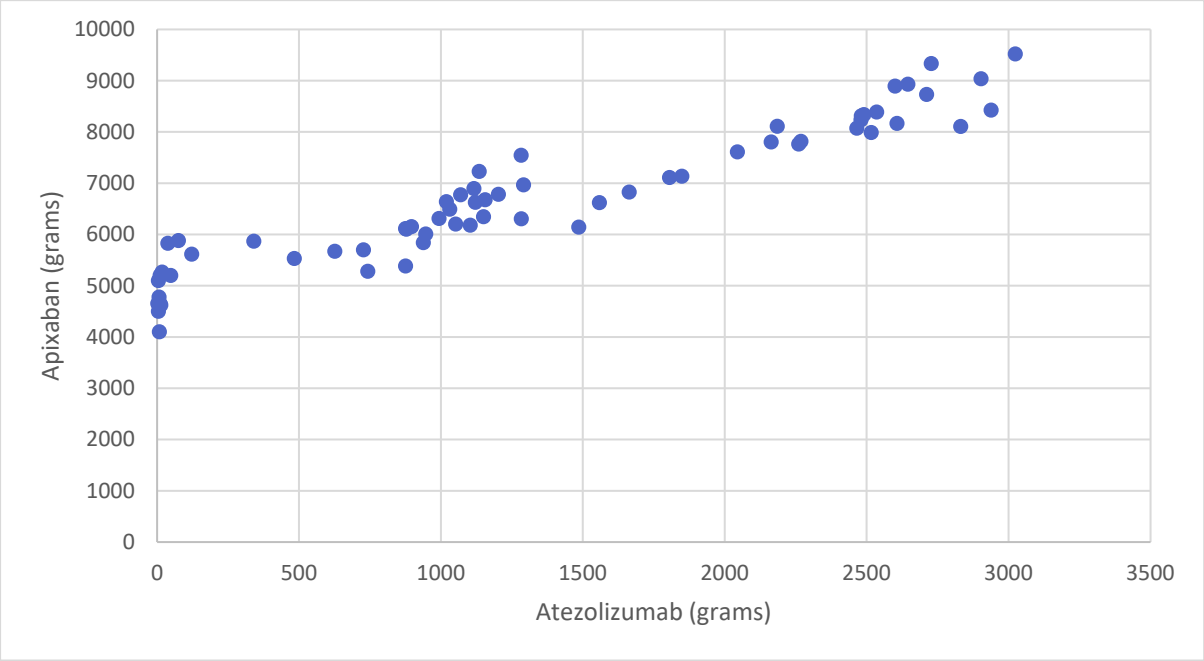

Figure 5.30: A scatter plot showing the positive correlation between atezolizumab and apixaban (0.955, cor. to 3 significant figures).

Although there was a positive correlation between atezolizumab and apixaban, it was also observed that there was a continuous increase of drug usage in both atezolizumab and apixaban (Figure 5.31). Therefore, to ensure the correlation obtained previously was not caused by this phenomenon, another scatter plot was plotted against the difference of drug usage between two consecutive months, i.e. the drug usage of April 2017 was used as standard, and then difference in drug usage between April and May 2017, followed by difference in drug usage between May and June 2017 (Figure 5.32). In this case, the correlation obtained was 0.75075, so it still showed a positive correlation, but was not as strong as previously demonstrated.

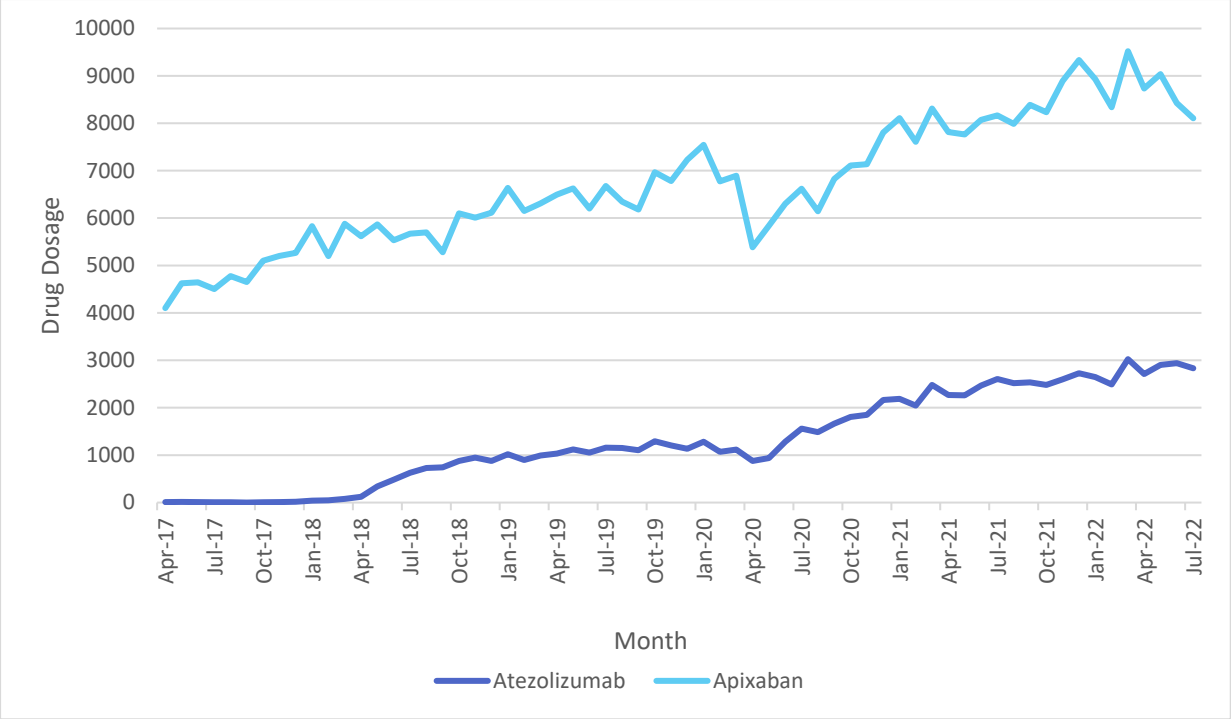

Figure 5.31: A line graph showing the continuous increasing dosage of both drugs (atezolizumab and apixaban) from April 2018.

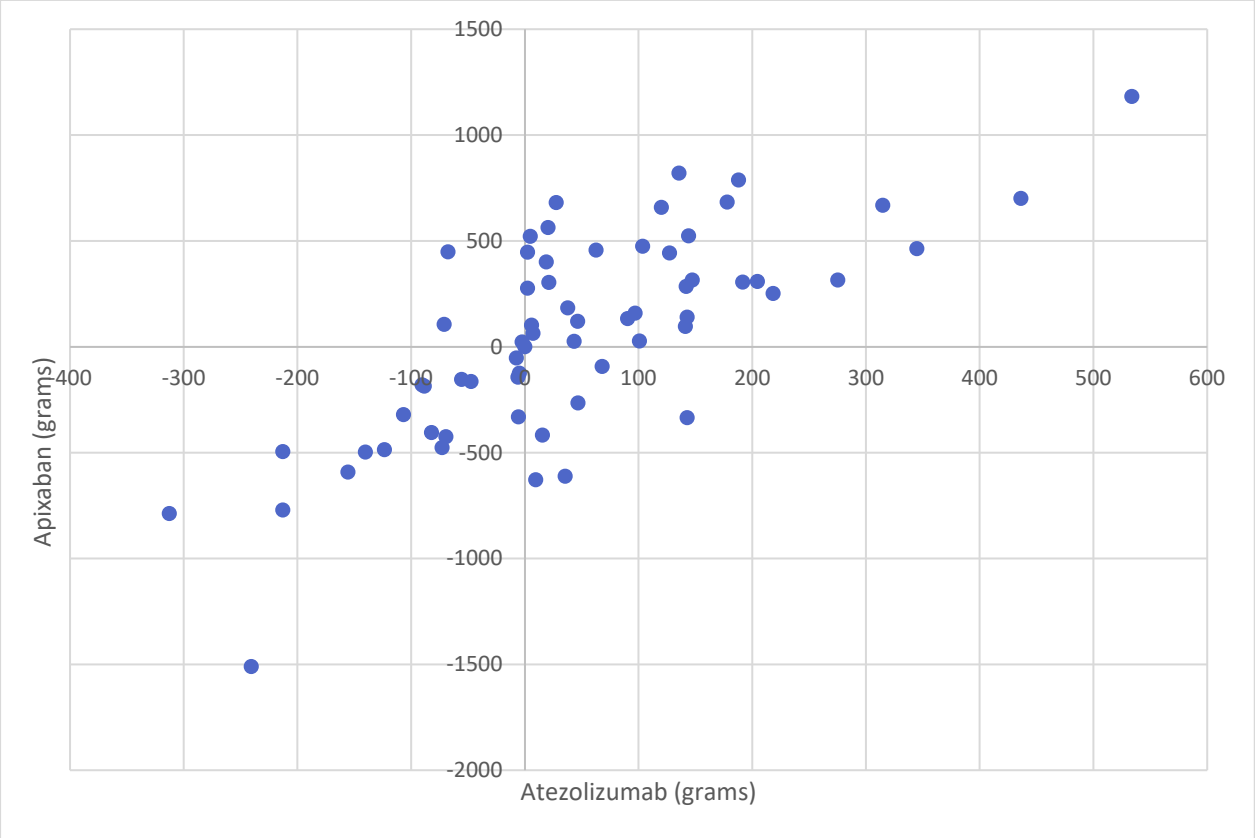

Figure 5.32: A scatter plot showing the positive correlation between atezolizumab and apixaban (0.751, cor. to 3 significant figures).

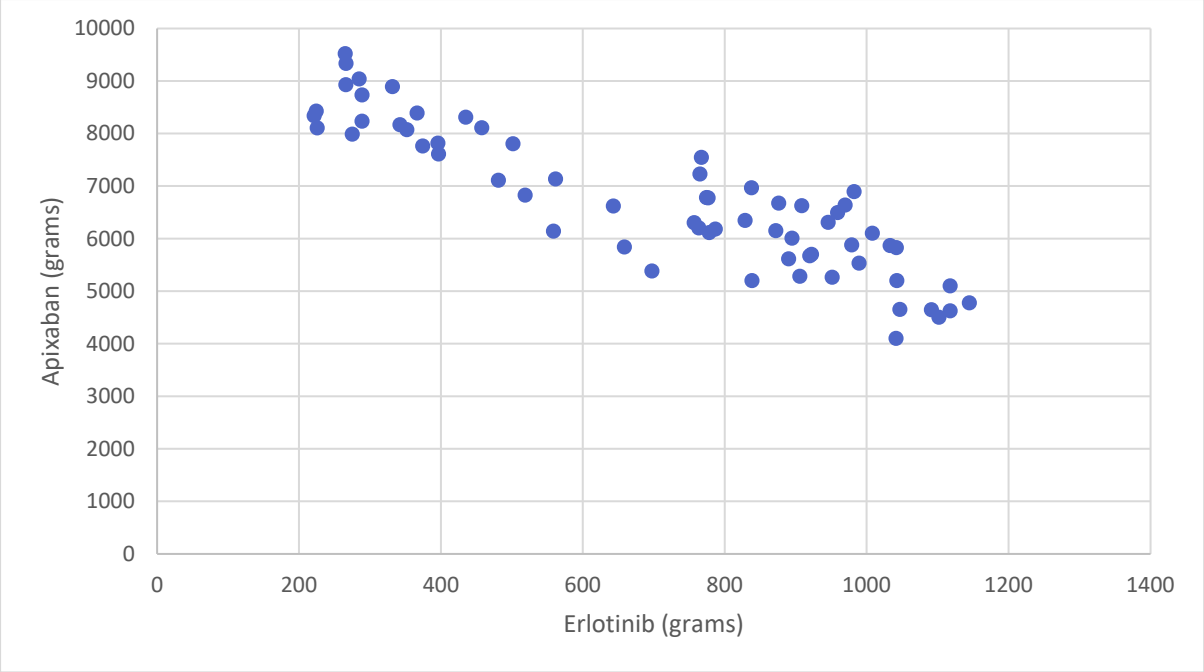

Figure 5.33: A scatter plot showing the negative correlation between erlotinib and apixaban (-0.89582).

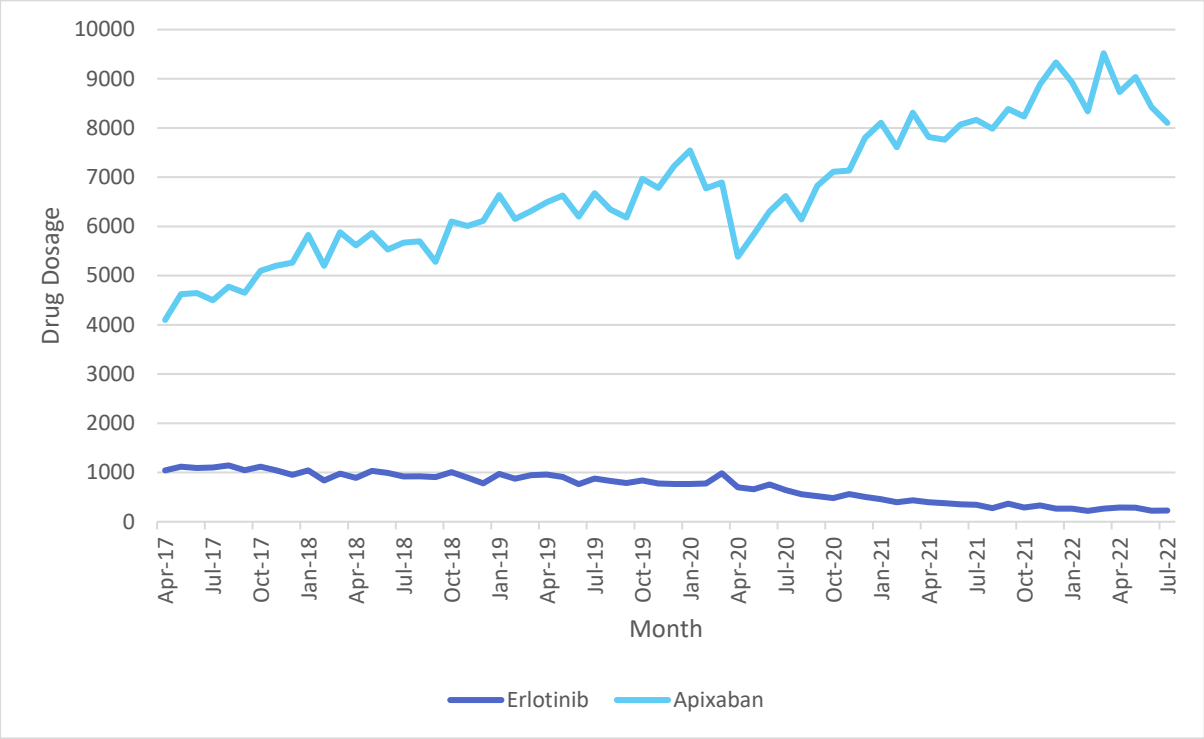

Figure 5.34: A line graph showing the continuous increase of apixaban while the use of erlotinib was continuously decreasing.

Although there was a negative correlation between erlotinib and apixaban, it was also observed that the use of apixaban was increasing continuously, while the use of erlotinib was continuously decreasing (Figure 5.34). Therefore, to ensure the correlation obtained previously was not caused by this phenomenon, another scatter plot was plotted against the difference of drug usage between two consecutive months, i.e. the drug usage of April 2017 was used as standard, and then difference in drug usage between April and May 2017, followed by difference in drug usage between May and June 2017 (Figure 5.35). In this case, the correlation obtained was 0.575654, so it actually showed a positive correlation instead of negative correlation.

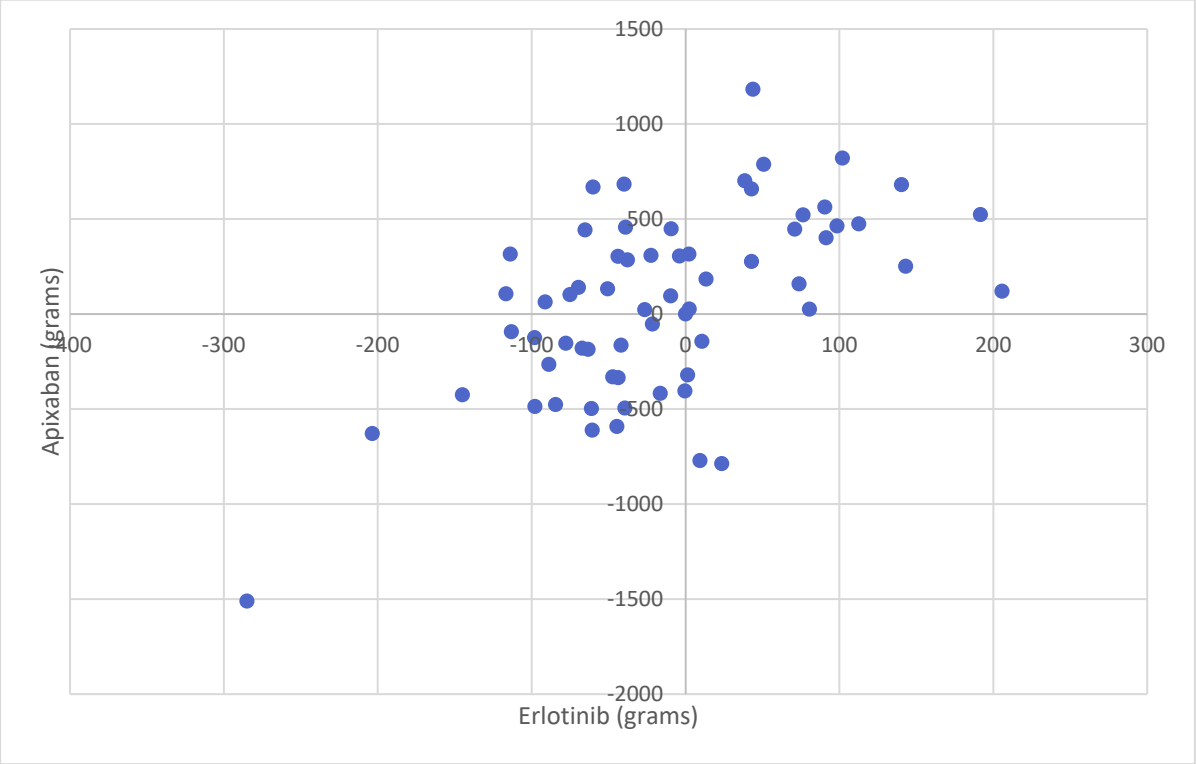

Figure 5.35: A scatter plot showing the positive correlation between erlotinib and apixaban (0.576, cor. to 3 significant figures).

Table 5.6 presents a summary linking each oncology drug with the cardiology drugs most associated with it. From the cardiology drugs listed, the cardiovascular disease(s) associated with each oncology drug was deduced.

Table 5.6: Cardiology drugs most associated with each oncology drug.

Oncology Drug	Cardiology drug that is most associated with each oncology drug	Cardiovascular disease that the corresponding cardiology drug were used to treat
Afatinib	Atenolol	Ischaemia / Hypertension
Atezolizumab	Apixaban	Atrial Fibrillation
Bevacizumab	Apixaban	Atrial Fibrillation
Carboplatin	Rivaroxaban	Arterial / Venous Thromboembolic Event
Cisplatin	Lisinopril	Hypertension / Cardiac Failure / Arrest
Cyclophosphamide	Ramipril	Hypertension / Cardiac Failure / Arrest
Docetaxel	Verapamil	Arrhythmia / Hypertension
Doxorubicin	Amlodipine	Hypertension
Epirubicin	Verapamil	Arrhythmia / Hypertension
Erlotinib	Atenolol	Ischaemia / Hypertension
Gefitinib	Alteplase	Myocardial Infarction
Gemcitabine	Apixaban	Atrial Fibrillation
Methotrexate	Atenolol	Ischaemia / Hypertension
Nintedanib	Apixaban	Atrial Fibrillation
Osimertinib	Apixaban	Atrial Fibrillation
Paclitaxel	Apixaban	Atrial Fibrillation
Pembrolizumab	Apixaban	Atrial Fibrillation
Pemetrexed	Ramipril	Hypertension / Cardiac Failure / Arrest
Vincristine	Apixaban	Atrial Fibrillation
Vinorelbine	Diltiazem	Hypertension

The cardiology drug that was associated with the greatest number of oncology drugs was apixaban. Atezolizumab, bevacizumab, nintedanib, osimertinib, paclitaxel, pembrolizumab, gemcitabine and vincristine were all mostly associated with apixaban, which indicated association with atrial fibrillation.

Afatinib, erlotinib and methotrexate were mostly associated with atenolol, hence suggested the association with ischaemia or hypertension. Docetaxel and epirubicin were associated with verapamil, which indicated association with arrhythmia or hypertension.

These drugs – amlodipine, atenolol, bisoprolol, candesartan, diltiazem, doxazosin, lisinopril, losartan, ramipril, and verapamil – are used to treat hypertension. Out of 20 shortlisted oncology drugs, 10 of them were most associated with either one of the above-mentioned

drugs, hence suggesting hypertension was the most common cardiovascular disease to be associated with oncology drugs.

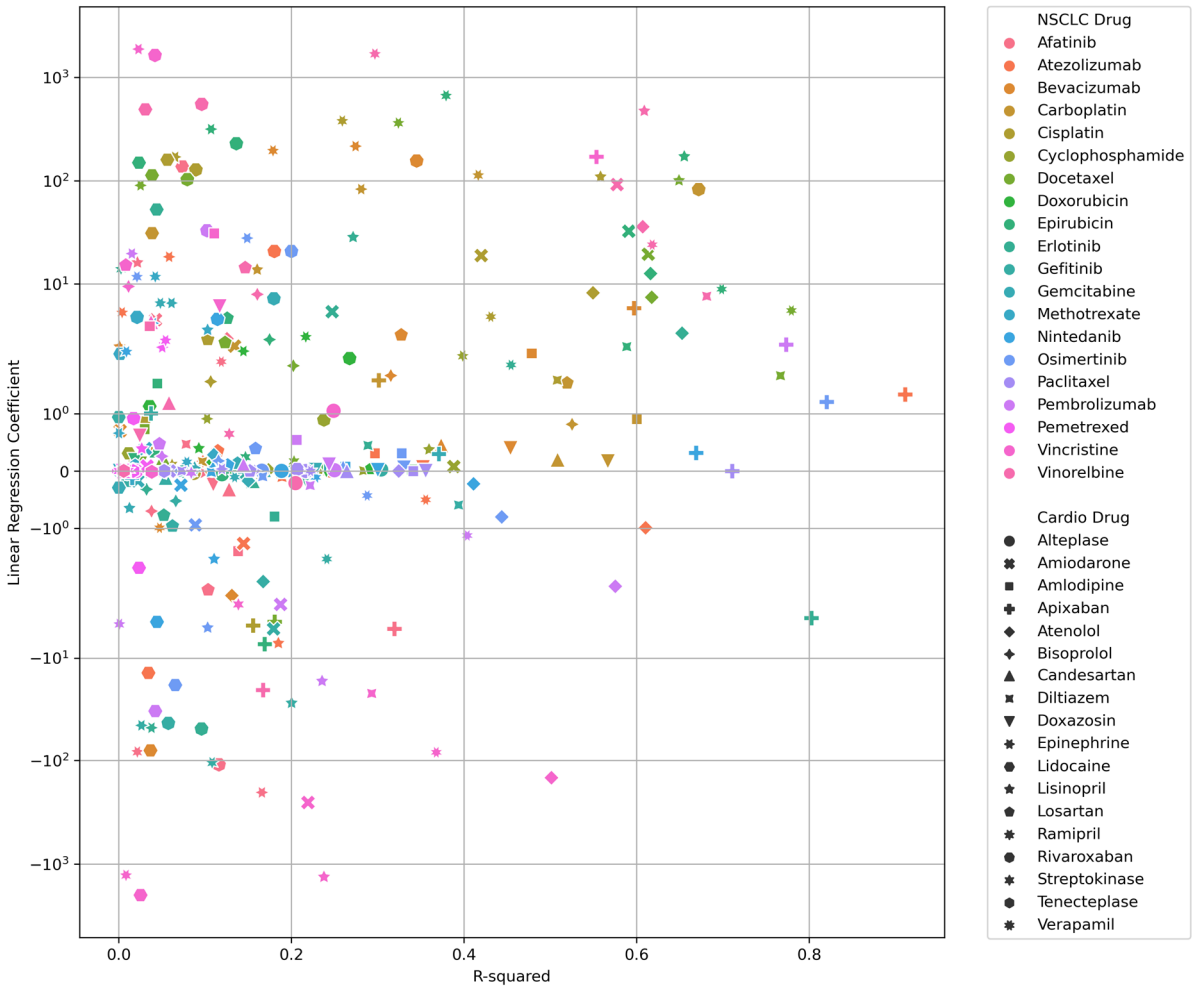

Figure 5.36: An overview of the predictive power of the regression models and the magnitude of the effect for each NSCLC-Cardio drug pair.

This plot (Figure 5.36) provides insights into the relationship between the predictive power of the regression models (as indicated by the R^2 value) and the magnitude of the effect (as indicated by the regression coefficient) for each NSCLC-Cardio drug pair. The colour of the points represents the NSCLC drugs while the shape of the points represents the cardiology drugs, and thus each point represents one NSCLC-Cardio drug pair. R^2 values close to 1 indicate that the regression predictions perfectly fit the data, while R^2 values of 0.7 or higher are often considered strong, indicating that the model explains a substantial portion of the variance in the dependent variable. R^2 values between 0.5 and 0.7 may suggest a moderate relationship, whereas R^2 values below 0.5 might indicate a weak relationship, where the model

does not explain much of the variance. Here, there were 12 drug-drug pairs with a value of above 0.7 (correct to 1 decimal place), including (from highest) Atezolizumab-Apixaban, Osimertinib-Apixaban, Docetaxel-Verapamil, Pembrolizumab-Apixaban, Docetaxel-Diltiazem, Paclitaxel-Apixaban, Epirubicin-Verapamil, Vinorelbine-Diltiazem, Carboplatin-Rivaroxaban, Nintedanib-Apixaban, Epirubicin-Lisinopril and Erlotinib-Atenolol.

Table 5.7 shows the values of correlation and regression analysis for each drug-drug pair. The sign of the correlation coefficient (positive or negative) indicates the direction of the relationship between the independent and dependent variables. A positive coefficient means that as the independent variable increases, the dependent variable also increases, and vice versa for a negative coefficient.

For linear regression analysis, the following equation are applicable for all drug-drug pairs –

Cardiology Drug Usage = NSCLC Drug Usage x Coefficient + Intercept

A high regression coefficient indicates a strong effect of the independent variable on the dependent variable. For each unit increase in the independent variable, the dependent variable increases (or decreases, if the coefficient is negative) by a large amount. This suggests a strong relationship between the two variables. A low regression coefficient suggests a weaker effect of the independent variable on the dependent variable. For each unit increase in the independent variable, the dependent variable changes by a small amount. This indicates a weaker relationship between the two variables (Table 5.7).

Table 5.7: Results from correlation and linear regression analysis.

Drug-Drug Pair			Correlation Analysis		Linear Regression Analysis		
NSCLC Drug	**Cardiotoxicity Drug**		**Correlation Coefficient**		**Coefficient**	**Intercept**	**R^2 Value**
Afatinib	Alteplase		-0.061		-0.005	127.909	0.004
Afatinib	Amiodarone		0.206		4.509	32885.611	0.042
Afatinib	Amlodipine		-0.372		-1.394	7760.697	0.138
Afatinib	Apixaban		-0.565		-5.207	8898.077	0.319
Afatinib	Atenolol		0.354		2.951	6937.508	0.125
Afatinib	Bisoprolol		-0.195		-0.699	7019.137	0.038
Afatinib	Candesartan		-0.357		-0.319	1940.548	0.128
Afatinib	Diltiazem		0.279		0.467	913.687	0.078
Afatinib	Doxazosin		-0.331		-0.236	1436.178	0.110
Afatinib	Epinephrine		-0.407		-203.709	636567.097	0.166
Afatinib	Lidocaine		0.271		137.364	116600.751	0.074
Afatinib	Lisinopril		0.147		16.139	193583.066	0.022
Afatinib	Losartan		-0.322		-2.191	15041.260	0.103
Afatinib	Ramipril		-0.146		-82.381	1148143.404	0.021
Afatinib	Rivaroxaban		-0.341		-109.673	685950.785	0.116
Afatinib	Streptokinase		0.233		0.076	39.833	0.054
Afatinib	Tenecteplase		0.308		0.001	0.513	0.095
Afatinib	Verapamil		0.345		1.905	5470.231	0.119
Atezolizumab	Alteplase		0.496		0.006	117.302	0.246
Atezolizumab	Amiodarone		-0.380		-1.264	36445.436	0.145
Atezolizumab	Amlodipine		0.545		0.311	6766.515	0.297
Atezolizumab	Apixaban		0.955		1.337	4949.882	0.911
Atezolizumab	Atenolol		-0.781		-0.990	9483.021	0.610
Atezolizumab	Bisoprolol		0.312		0.170	6501.127	0.097

Atezolizumab	Candesartan		0.500		0.068	1717.411	0.250
Atezolizumab	Diltiazem		-0.435		-0.110	1255.057	0.189
Atezolizumab	Doxazosin		0.594		0.064	1252.024	0.352
Atezolizumab	Epinephrine		0.241		18.360	527154.162	0.058
Atezolizumab	Lidocaine		-0.185		-14.259	192873.323	0.034
Atezolizumab	Lisinopril		-0.430		-7.187	209860.248	0.185
Atezolizumab	Losartan		0.339		0.350	13661.473	0.115
Atezolizumab	Ramipril		0.062		5.315	1106697.260	0.004
Atezolizumab	Rivaroxaban		0.425		20.769	612596.211	0.180
Atezolizumab	Streptokinase		-0.247		-0.012	87.966	0.061
Atezolizumab	Tenecteplase		-0.222		0.000	1.048	0.049
Atezolizumab	Verapamil		-0.596		-0.501	6930.406	0.356
Bevacizumab	Alteplase		0.329		0.023	106.654	0.108
Bevacizumab	Amiodarone		0.039		0.701	34183.070	0.002
Bevacizumab	Amlodipine		0.692		2.139	5394.848	0.478
Bevacizumab	Apixaban		0.773		5.869	1829.886	0.597
Bevacizumab	Atenolol		-0.362		-2.487	10243.329	0.131
Bevacizumab	Bisoprolol		0.561		1.662	5341.031	0.315
Bevacizumab	Candesartan		0.611		0.449	1432.584	0.374
Bevacizumab	Diltiazem		-0.082		-0.114	1203.215	0.007
Bevacizumab	Doxazosin		0.674		0.397	1006.835	0.454
Bevacizumab	Epinephrine		0.524		216.031	371376.042	0.274
Bevacizumab	Lidocaine		-0.192		-79.973	240635.495	0.037
Bevacizumab	Lisinopril		0.027		2.476	198255.471	0.001
Bevacizumab	Losartan		0.572		3.212	11448.295	0.327
Bevacizumab	Ramipril		0.423		196.095	950227.176	0.179
Bevacizumab	Rivaroxaban		0.588		155.922	510142.212	0.345
Bevacizumab	Streptokinase		-0.076		-0.020	88.655	0.006
Bevacizumab	Tenecteplase		-0.253		-0.001	1.448	0.064
Bevacizumab	Verapamil		-0.217		-0.990	7090.987	0.047

Carboplatin	Alteplase		0.275		0.007	88.884	0.075
Carboplatin	Amiodarone		0.366		2.504	22045.721	0.134
Carboplatin	Amlodipine		0.775		0.908	2562.594	0.600
Carboplatin	Apixaban		0.549		1.580	-1305.691	0.301
Carboplatin	Atenolol		0.004		0.012	8110.968	0.000
Carboplatin	Bisoprolol		0.725		0.814	2592.982	0.525
Carboplatin	Candesartan		0.713		0.199	797.088	0.508
Carboplatin	Diltiazem		0.311		0.163	282.041	0.097
Carboplatin	Doxazosin		0.753		0.168	483.829	0.567
Carboplatin	Epinephrine		0.530		82.871	130417.521	0.281
Carboplatin	Lidocaine		0.196		31.066	16083.750	0.039
Carboplatin	Lisinopril		0.400		13.765	130372.664	0.160
Carboplatin	Losartan		0.721		1.534	6331.187	0.519
Carboplatin	Ramipril		0.645		113.506	536974.758	0.417
Carboplatin	Rivaroxaban		0.820		82.480	221044.146	0.672
Carboplatin	Streptokinase		0.056		0.006	42.650	0.003
Carboplatin	Tenecteplase		-0.136		0.000	1.577	0.019
Carboplatin	Verapamil		0.200		0.345	4510.693	0.040
Cisplatin	Alteplase		-0.295		-0.033	143.922	0.087
Cisplatin	Amiodarone		0.648		18.842	24416.060	0.420
Cisplatin	Amlodipine		0.175		0.871	6700.457	0.030
Cisplatin	Apixaban		-0.394		-4.828	9377.088	0.155
Cisplatin	Atenolol		0.741		8.214	3656.904	0.549
Cisplatin	Bisoprolol		0.326		1.558	5871.298	0.106
Cisplatin	Candesartan		0.156		0.185	1706.012	0.024
Cisplatin	Diltiazem		0.713		1.583	238.578	0.508
Cisplatin	Doxazosin		0.129		0.123	1270.091	0.017
Cisplatin	Epinephrine		0.256		170.015	458122.058	0.065
Cisplatin	Lidocaine		0.237		159.692	86213.257	0.056
Cisplatin	Lisinopril		0.747		109.250	140300.077	0.558

Cisplatin	Losartan		0.321		2.907	12529.884	0.103
Cisplatin	Ramipril		0.509		380.717	904591.714	0.259
Cisplatin	Rivaroxaban		0.299		127.881	569910.219	0.089
Cisplatin	Streptokinase		0.248		0.108	12.259	0.062
Cisplatin	Tenecteplase		0.050		0.000	0.797	0.002
Cisplatin	Verapamil		0.657		4.825	3614.816	0.431
Cyclophosphamide	Alteplase		-0.034		0.000	131.811	0.001
Cyclophosphamide	Amiodarone		0.623		0.077	6404.785	0.388
Cyclophosphamide	Amlodipine		0.483		0.010	3404.292	0.234
Cyclophosphamide	Apixaban		0.026		0.001	6219.508	0.001
Cyclophosphamide	Atenolol		0.416		0.020	944.657	0.173
Cyclophosphamide	Bisoprolol		0.580		0.012	2392.781	0.336
Cyclophosphamide	Candesartan		0.450		0.002	971.466	0.203
Cyclophosphamide	Diltiazem		0.533		0.005	-744.152	0.284
Cyclophosphamide	Doxazosin		0.481		0.002	622.994	0.231
Cyclophosphamide	Epinephrine		0.320		0.910	218424.211	0.102
Cyclophosphamide	Lidocaine		0.107		0.308	61195.880	0.011
Cyclophosphamide	Lisinopril		0.600		0.375	63058.222	0.359
Cyclophosphamide	Losartan		0.571		0.022	6031.492	0.326
Cyclophosphamide	Ramipril		0.631		2.020	374362.504	0.399
Cyclophosphamide	Rivaroxaban		0.488		0.892	313452.556	0.238
Cyclophosphamide	Streptokinase		0.224		0.000	-81.177	0.050
Cyclophosphamide	Tenecteplase		0.071		0.000	0.451	0.005
Cyclophosphamide	Verapamil		0.483		0.015	710.080	0.233
Docetaxel	Alteplase		-0.393		-0.038	155.825	0.155
Docetaxel	Amiodarone		0.783		19.449	19261.962	0.614
Docetaxel	Amlodipine		0.172		0.734	6593.479	0.030
Docetaxel	Apixaban		-0.425		-4.443	10266.729	0.180
Docetaxel	Atenolol		0.786		7.436	2241.347	0.618
Docetaxel	Bisoprolol		0.450		1.834	5265.220	0.202

Docetaxel	Candesartan		0.226		0.229	1624.724	0.051
Docetaxel	Diltiazem		0.876		1.661	-215.759	0.767
Docetaxel	Doxazosin		0.158		0.128	1235.632	0.025
Docetaxel	Epinephrine		0.159		90.207	479607.955	0.025
Docetaxel	Lidocaine		0.196		112.798	84017.550	0.038
Docetaxel	Lisinopril		0.806		100.603	120115.002	0.649
Docetaxel	Losartan		0.351		2.713	11963.915	0.123
Docetaxel	Ramipril		0.569		363.634	823845.909	0.324
Docetaxel	Rivaroxaban		0.282		102.952	558087.972	0.079
Docetaxel	Streptokinase		0.451		0.167	-61.846	0.203
Docetaxel	Tenecteplase		0.130		0.000	0.548	0.017
Docetaxel	Verapamil		0.883		5.540	1848.673	0.779
Doxorubicin	Alteplase		0.359		0.000	58.278	0.129
Doxorubicin	Amiodarone		0.330		0.085	18692.798	0.109
Doxorubicin	Amlodipine		0.583		0.026	2314.742	0.339
Doxorubicin	Apixaban		0.334		0.036	-134.238	0.112
Doxorubicin	Atenolol		0.091		0.009	6473.159	0.008
Doxorubicin	Bisoprolol		0.460		0.019	3047.948	0.212
Doxorubicin	Candesartan		0.436		0.005	941.827	0.190
Doxorubicin	Diltiazem		0.084		0.002	795.197	0.007
Doxorubicin	Doxazosin		0.490		0.004	558.446	0.240
Doxorubicin	Epinephrine		0.380		2.242	128532.578	0.144
Doxorubicin	Lidocaine		0.189		1.129	-39144.420	0.036
Doxorubicin	Lisinopril		0.305		0.395	125787.164	0.093
Doxorubicin	Losartan		0.541		0.043	5923.322	0.293
Doxorubicin	Ramipril		0.466		3.089	530929.574	0.217
Doxorubicin	Rivaroxaban		0.517		1.963	269765.151	0.267
Doxorubicin	Streptokinase		-0.133		-0.001	168.745	0.018
Doxorubicin	Tenecteplase		0.023		0.000	0.753	0.001
Doxorubicin	Verapamil		0.093		0.006	5117.963	0.009

Epirubicin	Alteplase		-0.346		-0.056	158.537	0.120
Epirubicin	Amiodarone		0.769		32.446	15888.632	0.591
Epirubicin	Amlodipine		0.211		1.526	6290.501	0.044
Epirubicin	Apixaban		-0.411		-7.310	10977.842	0.169
Epirubicin	Atenolol		0.785		12.625	823.243	0.616
Epirubicin	Bisoprolol		0.418		2.897	5041.768	0.175
Epirubicin	Candesartan		0.209		0.359	1598.530	0.043
Epirubicin	Diltiazem		0.767		2.474	-330.944	0.589
Epirubicin	Doxazosin		0.136		0.188	1228.170	0.019
Epirubicin	Epinephrine		0.327		315.659	367856.830	0.107
Epirubicin	Lidocaine		0.153		149.430	86998.708	0.023
Epirubicin	Lisinopril		0.809		171.813	100349.747	0.655
Epirubicin	Losartan		0.354		4.658	11416.537	0.126
Epirubicin	Ramipril		0.616		668.703	724661.366	0.379
Epirubicin	Rivaroxaban		0.369		229.276	506759.969	0.136
Epirubicin	Streptokinase		0.383		0.242	-69.163	0.147
Epirubicin	Tenecteplase		0.152		0.001	0.385	0.023
Epirubicin	Verapamil		0.836		8.916	1077.783	0.699
Erlotinib	Alteplase		-0.449		-0.019	139.010	0.202
Erlotinib	Amiodarone		0.497		5.394	30965.968	0.247
Erlotinib	Amlodipine		-0.425		-0.790	7735.553	0.180
Erlotinib	Apixaban		-0.896		-4.095	9610.698	0.802
Erlotinib	Atenolol		0.808		3.340	5815.185	0.653
Erlotinib	Bisoprolol		-0.179		-0.319	6952.379	0.032
Erlotinib	Candesartan		-0.394		-0.174	1930.323	0.155
Erlotinib	Diltiazem		0.537		0.445	794.616	0.289
Erlotinib	Doxazosin		-0.466		-0.165	1453.801	0.217
Erlotinib	Epinephrine		-0.195		-48.291	585564.359	0.038
Erlotinib	Lidocaine		0.209		52.614	136859.715	0.044
Erlotinib	Lisinopril		0.521		28.424	180284.948	0.271

Erlotinib	Losartan		-0.228		-0.771	14670.491	0.052
Erlotinib	Ramipril		0.050		14.060	1103841.196	0.003
Erlotinib	Rivaroxaban		-0.310		-49.433	675009.721	0.096
Erlotinib	Streptokinase		0.297		0.048	37.648	0.088
Erlotinib	Tenecteplase		0.273		0.000	0.616	0.074
Erlotinib	Verapamil		0.674		1.848	4962.557	0.455
Gefitinib	Alteplase		0.551		0.026	112.849	0.304
Gefitinib	Amiodarone		-0.423		-5.234	37332.216	0.179
Gefitinib	Amlodipine		-0.091		-0.192	7272.843	0.008
Gefitinib	Apixaban		0.193		1.003	6232.862	0.037
Gefitinib	Atenolol		-0.409		-1.927	9113.371	0.167
Gefitinib	Bisoprolol		-0.257		-0.522	6982.911	0.066
Gefitinib	Candesartan		-0.233		-0.117	1864.952	0.054
Gefitinib	Diltiazem		-0.627		-0.593	1398.801	0.394
Gefitinib	Doxazosin		-0.098		-0.039	1356.824	0.010
Gefitinib	Epinephrine		-0.162		-45.799	573963.101	0.026
Gefitinib	Lidocaine		0.003		0.939	173485.554	0.000
Gefitinib	Lisinopril		-0.447		-27.814	213946.894	0.200
Gefitinib	Losartan		-0.249		-0.960	14596.935	0.062
Gefitinib	Ramipril		-0.329		-104.565	1164979.860	0.108
Gefitinib	Rivaroxaban		-0.240		-43.587	661519.750	0.057
Gefitinib	Streptokinase		-0.377		-0.070	105.774	0.142
Gefitinib	Tenecteplase		0.179		0.000	0.757	0.032
Gefitinib	Verapamil		-0.491		-1.534	7016.854	0.241
Gemcitabine	Alteplase		0.288		0.001	108.106	0.083
Gemcitabine	Amiodarone		-0.149		-0.172	37121.994	0.022
Gemcitabine	Amlodipine		0.493		0.098	5837.513	0.243
Gemcitabine	Apixaban		0.609		0.297	2657.820	0.371
Gemcitabine	Atenolol		-0.387		-0.171	10508.755	0.150
Gemcitabine	Bisoprolol		0.296		0.056	5956.214	0.088

Gemcitabine	Candesartan		0.410		0.019	1542.261	0.168
Gemcitabine	Diltiazem		-0.273		-0.024	1439.468	0.075
Gemcitabine	Doxazosin		0.477		0.018	1090.568	0.228
Gemcitabine	Epinephrine		0.247		6.551	461913.555	0.061
Gemcitabine	Lidocaine		-0.011		-0.290	177915.923	0.000
Gemcitabine	Lisinopril		-0.111		-0.647	209176.059	0.012
Gemcitabine	Losartan		0.371		0.134	12296.448	0.138
Gemcitabine	Ramipril		0.219		6.542	1024269.936	0.048
Gemcitabine	Rivaroxaban		0.424		7.229	541279.006	0.180
Gemcitabine	Streptokinase		-0.246		-0.004	129.901	0.060
Gemcitabine	Tenecteplase		-0.189		0.000	1.333	0.036
Gemcitabine	Verapamil		-0.366		-0.107	7733.284	0.134
Methotrexate	Alteplase		0.039		0.000	124.548	0.002
Methotrexate	Amiodarone		0.175		0.391	33379.495	0.031
Methotrexate	Amlodipine		0.085		0.033	7062.958	0.007
Methotrexate	Apixaban		-0.123		-0.116	7134.968	0.015
Methotrexate	Atenolol		0.332		0.282	7168.241	0.110
Methotrexate	Bisoprolol		0.132		0.048	6555.186	0.018
Methotrexate	Candesartan		0.077		0.007	1782.514	0.006
Methotrexate	Diltiazem		0.132		0.022	1028.745	0.017
Methotrexate	Doxazosin		0.031		0.002	1329.428	0.001
Methotrexate	Epinephrine		0.013		0.659	549185.177	0.000
Methotrexate	Lidocaine		0.041		2.108	166461.463	0.002
Methotrexate	Lisinopril		0.321		3.597	187550.479	0.103
Methotrexate	Losartan		0.138		0.096	13787.464	0.019
Methotrexate	Ramipril		0.205		11.789	1071899.640	0.042
Methotrexate	Rivaroxaban		0.145		4.776	623211.195	0.021
Methotrexate	Streptokinase		0.003		0.000	71.273	0.000
Methotrexate	Tenecteplase		0.061		0.000	0.841	0.004
Methotrexate	Verapamil		0.281		0.158	5703.535	0.079

Nintedanib	Alteplase		0.434		0.002	99.062	0.189
Nintedanib	Amiodarone		-0.268		-0.246	39038.015	0.072
Nintedanib	Amlodipine		0.512		0.081	5780.918	0.262
Nintedanib	Apixaban		0.818		0.316	1242.011	0.669
Nintedanib	Atenolol		-0.641		-0.224	12056.939	0.411
Nintedanib	Bisoprolol		0.330		0.050	5863.902	0.109
Nintedanib	Candesartan		0.451		0.017	1514.408	0.204
Nintedanib	Diltiazem		-0.327		-0.023	1506.433	0.107
Nintedanib	Doxazosin		0.548		0.016	1052.941	0.300
Nintedanib	Epinephrine		0.198		4.170	479286.480	0.039
Nintedanib	Lidocaine		-0.210		-4.472	251425.183	0.044
Nintedanib	Lisinopril		-0.332		-1.535	226908.566	0.110
Nintedanib	Losartan		0.355		0.102	12366.572	0.126
Nintedanib	Ramipril		0.094		2.219	1075307.868	0.009
Nintedanib	Rivaroxaban		0.338		4.571	560980.071	0.114
Nintedanib	Streptokinase		-0.245		-0.003	130.036	0.060
Nintedanib	Tenecteplase		-0.191		0.000	1.338	0.036
Nintedanib	Verapamil		-0.478		-0.111	8186.558	0.228
Osimertinib	Alteplase		0.407		0.005	119.733	0.166
Osimertinib	Amiodarone		-0.298		-0.939	35906.596	0.089
Osimertinib	Amlodipine		0.572		0.310	6803.159	0.328
Osimertinib	Apixaban		0.906		1.204	5265.088	0.820
Osimertinib	Atenolol		-0.666		-0.801	9140.157	0.444
Osimertinib	Bisoprolol		0.340		0.176	6513.818	0.116
Osimertinib	Candesartan		0.510		0.066	1727.887	0.260
Osimertinib	Diltiazem		-0.408		-0.098	1227.791	0.167
Osimertinib	Doxazosin		0.575		0.059	1265.768	0.330
Osimertinib	Epinephrine		0.386		27.830	517786.778	0.149
Osimertinib	Lidocaine		-0.256		-18.682	196593.926	0.065
Osimertinib	Lisinopril		-0.321		-5.090	206490.814	0.103

Osimertinib	Losartan		0.398		0.391	13652.739	0.158
Osimertinib	Ramipril		0.145		11.773	1099478.799	0.021
Osimertinib	Rivaroxaban		0.447		20.763	614994.053	0.200
Osimertinib	Streptokinase		-0.235		-0.011	85.084	0.055
Osimertinib	Tenecteplase		-0.248		0.000	1.044	0.062
Osimertinib	Verapamil		-0.536		-0.428	6783.911	0.288
Paclitaxel	Alteplase		0.466		0.000	114.955	0.217
Paclitaxel	Amiodarone		-0.242		-0.001	36217.595	0.058
Paclitaxel	Amlodipine		0.584		0.000	6578.065	0.341
Paclitaxel	Apixaban		0.843		0.002	4595.091	0.711
Paclitaxel	Atenolol		-0.570		-0.001	9470.626	0.324
Paclitaxel	Bisoprolol		0.397		0.000	6336.806	0.157
Paclitaxel	Candesartan		0.514		0.000	1681.706	0.264
Paclitaxel	Diltiazem		-0.270		0.000	1232.303	0.073
Paclitaxel	Doxazosin		0.596		0.000	1220.812	0.356
Paclitaxel	Epinephrine		0.346		0.035	504115.765	0.120
Paclitaxel	Lidocaine		-0.125		-0.013	191239.153	0.016
Paclitaxel	Lisinopril		-0.233		-0.005	207333.382	0.054
Paclitaxel	Losartan		0.390		0.001	13399.120	0.152
Paclitaxel	Ramipril		0.195		0.022	1083656.670	0.038
Paclitaxel	Rivaroxaban		0.455		0.030	600045.479	0.207
Paclitaxel	Streptokinase		-0.187		0.000	88.464	0.035
Paclitaxel	Tenecteplase		-0.229		0.000	1.104	0.052
Paclitaxel	Verapamil		-0.471		-0.001	6979.729	0.222
Pembrolizumab	Alteplase		0.500		0.014	111.166	0.250
Pembrolizumab	Amiodarone		-0.433		-3.032	38036.986	0.187
Pembrolizumab	Amlodipine		0.454		0.545	6590.689	0.206
Pembrolizumab	Apixaban		0.879		2.595	3926.500	0.773
Pembrolizumab	Atenolol		-0.759		-2.024	10352.082	0.575
Pembrolizumab	Bisoprolol		0.224		0.257	6449.931	0.050

Pembrolizumab	Candesartan		0.380		0.109	1690.324	0.145
Pembrolizumab	Diltiazem		-0.471		-0.252	1380.137	0.222
Pembrolizumab	Doxazosin		0.494		0.113	1215.838	0.244
Pembrolizumab	Epinephrine		0.123		19.704	530279.922	0.015
Pembrolizumab	Lidocaine		-0.206		-33.340	209893.523	0.042
Pembrolizumab	Lisinopril		-0.485		-17.092	218749.710	0.236
Pembrolizumab	Losartan		0.217		0.473	13616.620	0.047
Pembrolizumab	Ramipril		-0.026		-4.687	1118805.961	0.001
Pembrolizumab	Rivaroxaban		0.320		32.961	604626.617	0.102
Pembrolizumab	Streptokinase		-0.290		-0.030	104.392	0.084
Pembrolizumab	Tenecteplase		-0.194		0.000	1.117	0.038
Pembrolizumab	Verapamil		-0.635		-1.125	7478.153	0.404
Pemetrexed	Alteplase		-0.141		0.000	128.690	0.020
Pemetrexed	Amiodarone		0.181		0.086	33791.064	0.033
Pemetrexed	Amlodipine		0.128		0.010	7060.105	0.016
Pemetrexed	Apixaban		0.011		0.002	6700.442	0.000
Pemetrexed	Atenolol		0.082		0.015	8000.389	0.007
Pemetrexed	Bisoprolol		0.133		0.010	6609.230	0.018
Pemetrexed	Candesartan		0.091		0.002	1787.288	0.008
Pemetrexed	Diltiazem		0.061		0.002	1083.519	0.004
Pemetrexed	Doxazosin		0.069		0.001	1325.428	0.005
Pemetrexed	Epinephrine		0.224		2.442	523803.705	0.050
Pemetrexed	Lidocaine		-0.153		-1.687	193091.785	0.023
Pemetrexed	Lisinopril		0.163		0.390	195893.033	0.027
Pemetrexed	Losartan		0.127		0.019	13912.647	0.016
Pemetrexed	Ramipril		0.233		2.850	1081407.005	0.054
Pemetrexed	Rivaroxaban		0.131		0.917	629762.721	0.017
Pemetrexed	Streptokinase		-0.007		0.000	72.197	0.000
Pemetrexed	Tenecteplase		-0.129		0.000	1.008	0.017
Pemetrexed	Verapamil		0.106		0.013	6120.678	0.011

Vincristine	Alteplase		0.499		1.049	109.268	0.249
Vincristine	Amiodarone		-0.468		-254.861	38771.558	0.219
Vincristine	Amlodipine		0.332		31.023	6691.340	0.110
Vincristine	Apixaban		0.744		170.599	4044.368	0.553
Vincristine	Atenolol		-0.708		-146.874	10476.737	0.501
Vincristine	Bisoprolol		0.106		9.476	6578.441	0.011
Vincristine	Candesartan		0.193		4.293	1739.965	0.037
Vincristine	Diltiazem		-0.541		-22.513	1462.158	0.293
Vincristine	Doxazosin		0.342		6.076	1242.078	0.117
Vincristine	Epinephrine		0.151		1879.862	521993.721	0.023
Vincristine	Lidocaine		-0.159		-2000.345	205370.210	0.025
Vincristine	Lisinopril		-0.488		-1334.711	221288.100	0.238
Vincristine	Losartan		0.090		15.230	13887.438	0.008
Vincristine	Ramipril		-0.091		-1280.622	1133870.000	0.008
Vincristine	Rivaroxaban		0.205		1640.164	614399.546	0.042
Vincristine	Streptokinase		-0.372		-3.033	119.289	0.139
Vincristine	Tenecteplase		-0.195		-0.015	1.146	0.038
Vincristine	Verapamil		-0.607		-83.443	7576.282	0.368
Vinorelbine	Alteplase		-0.452		-0.211	163.356	0.205
Vinorelbine	Amiodarone		0.760		91.768	18413.891	0.577
Vinorelbine	Amlodipine		0.189		3.914	6481.215	0.036
Vinorelbine	Apixaban		-0.409		-20.789	10429.113	0.167
Vinorelbine	Atenolol		0.779		35.861	1778.631	0.607
Vinorelbine	Bisoprolol		0.401		7.946	5311.204	0.161
Vinorelbine	Candesartan		0.241		1.188	1595.664	0.058
Vinorelbine	Diltiazem		0.825		7.615	-248.661	0.681
Vinorelbine	Doxazosin		0.156		0.615	1227.931	0.024
Vinorelbine	Epinephrine		0.177		488.046	464551.269	0.031
Vinorelbine	Lidocaine		0.175		490.246	86579.351	0.031
Vinorelbine	Lisinopril		0.780		473.929	115861.880	0.609

Vinorelbine	Losartan		0.383		14.393	11561.743	0.146
Vinorelbine	Ramipril		0.545		1692.701	812096.914	0.297
Vinorelbine	Rivaroxaban		0.310		550.973	541977.373	0.096
Vinorelbine	Streptokinase		0.358		0.647	-43.583	0.128
Vinorelbine	Tenecteplase		0.075		0.001	0.681	0.006
Vinorelbine	Verapamil		0.786		23.997	1988.937	0.618

5.5 Discussion

In general, there was a dip across all NSCLC treatments in April 2020. This can be possibly related to the lockdown during the COVID-19 pandemic, as all but the most urgent of non-COVID care had to be cancelled, including many cancer treatments due to a lack of system capacity (BMA, 2022).

Atezolizumab works by binding to PD-L1, a protein found on the surface of cancer cells and certain immune cells. PD-L1 binds to programmed death-1 (PD-1) receptors on immune cells, which inhibits their ability to attack cancer cells. By blocking the PD-L1/PD-1 interaction, atezolizumab helps to unleash the immune system, allowing it to mount a more effective anti-cancer response (Socinski et al., 2018).

Atezolizumab received its first United States Food and Drug Administration (FDA) approval in May 2016. The initial approval was for the treatment of locally advanced or metastatic urothelial carcinoma, a type of bladder cancer, in patients who experienced disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. In October 2016, FDA approved atezolizumab for the treatment of metastatic NSCLC that progresses despite platinum chemotherapy. Atezolizumab has now received additional FDA approvals for various indications, including small cell lung cancer (SCLC), triple-negative breast cancer (TNBC), and hepatocellular carcinoma (HCC).

The National Institute for Health and Care Excellence (NICE), which provides guidance on healthcare interventions in England, issued its positive recommendation for atezolizumab in August 2017. This recommendation made atezolizumab available through the NHS for the treatment of advanced urothelial carcinoma in patients who were not eligible for cisplatin-containing chemotherapy or had experienced disease progression within a year of receiving platinum-based chemotherapy. This explained why only since March 2018, atezolizumab was made available across the whole nation. Prior to that, only the North West region recorded usage of atezolizumab from April 2017. South Central region recorded usage of atezolizumab from April 2017 – July 2017, and then again from January 2018. London and Yorkshire and the Humber, started recording usage of this drug from November 2017. Since then, additional approvals and recommendations for atezolizumab have been granted by NICE for other cancer types, including NSCLC and TNBC. As of January 2022, atezolizumab was the first immunotherapy approved by NHS for patients with early-stage NSCLC whose tumours

express the PD-L1 mutation, and who have undergone surgery and chemotherapy. These patients are at risk of recurring cancer. England is currently the second country in Europe to make this cutting-edge treatment available. This explained the increasing usage atezolizumab from only 8.40 grams in total at national level in April 2017 to 2832.00 grams in total at national level in July 2022.

Osimertinib is a third-generation EGFR tyrosine kinase inhibitor (TKI). It selectively targets and irreversibly binds to mutated forms of the EGFR protein, including the most common EGFR mutation (EGFR exon 19 deletions or L858R substitution). By inhibiting the activity of mutated EGFR, osimertinib blocks the signalling pathways that promote cancer cell growth, division, and survival (Khozin et al., 2017). Osimertinib received its first FDA approval in November 2015. The initial approval was for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours have specific EGFR mutations, specifically T790M mutations, and whose disease has progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy. Since its initial approval, osimertinib has received additional FDA approvals for expanded indications, including first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R mutations. NICE issued its positive recommendation for osimertinib in April 2018. This recommendation made osimertinib available through the NHS as a treatment option for advanced NSCLC with specific EGFR mutations in patients who have acquired resistance to previous EGFR TKI therapy. As of May 2021, osimertinib which is believed to half the risk of lung cancer patients suffering a return of the disease after undergoing treatment, was rolled out by NHS England.

Although osimertinib was already available across the nation in April 2017, the positive recommendation by NICE in 2018 and official rolled out by NHS in 2021 had contributed to an increase in the use of osimertinib from 205.52 grams in total at national level in April 2017 to 3320.48 grams in total at national level in July 2022, with May 2022 recorded the highest usage of osimertinib (3439.40 grams).

Atezolizumab, bevacizumab, nintedanib, osimertinib, paclitaxel, pembrolizumab and vincristine were all mostly associated with apixaban. Apixaban is an anticoagulant used for blood clots, e.g. in deep vein thrombosis and atrial fibrillation. Apixaban offers a favourable safety profile compared to warfarin, with lower rates of major bleeding and intracranial haemorrhage (Fu et al., 2021). It also avoids the need for regular international normalised ratio (INR) monitoring, reducing the inconvenience and associated costs for patients. However, it

was also important to note that the continuous increase in drug dosage of apixaban could be due to the shift from the use of vitamin K antagonists (VKAs) to direct oral anticoagulants (DOACs), according to the current NICE guideline, supported by evidence from the 2018 European Heart Rhythm Association Practical Guide on 'The use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation' (Steffel et al., 2018), the British Committee for Standards in Haematology (BCSH) Guidelines on 'Oral anticoagulation with warfarin - fourth edition' (Keeling et al., 2011), the Scottish Intercollegiate Guidelines Network (SIGN) guideline 'Antithrombotics: indications and management' (SIGN, 2013), and on information in manufacturers' Summaries of Product Characteristics (SPCs) and the British National Formulary (BNF).

For atrial fibrillation, treatments focus on rate control, rhythm control, and stroke prevention. Rate control drugs include beta-blockers and calcium channel blockers (Prystowsky et al., 2015). Rhythm control may involve antiarrhythmic drugs, e.g. amiodarone, sotalol, flecainide and verapamil. Stroke prevention is critical, with anticoagulants such as warfarin or direct oral anticoagulants (DOACs) like apixaban, dabigatran, edoxaban, and rivaroxaban being common choices. The specific drugs and treatment approach depend on individual patient factors, including symptoms, underlying heart condition, and risk for stroke (Gutierrez and Blanchard, 2016). Antihypertensives such as amlodipine, atenolol, bisoprolol, candesartan, diltiazem, lisinopril, losartan, and ramipril manage blood pressure and reduce atrial fibrillation complications. These drugs target different aspects of atrial fibrillation management, from preventing stroke to controlling heart rate and rhythm.

As mentioned previously, afatinib, erlotinib and methotrexate were mostly associated with atenolol. Atenolol is a medication belonging to the class of drugs known as beta-blockers. It is primarily used to treat various cardiovascular conditions by blocking the effects of adrenaline on the beta receptors in the heart and blood vessels. Atenolol selectively blocks beta-1 adrenergic receptors in the heart, hence reducing the effects of adrenaline and other stress hormones, leading to a decrease in heart rate and cardiac contractility. This action helps lower blood pressure and reduce the workload on the heart, making it beneficial for managing certain cardiovascular conditions, such as angina, arrhythmias, hypertension and myocardial infarction. Atenolol is commonly prescribed to manage high blood pressure. By lowering heart rate and reducing the force of contraction, it helps to relax blood vessels and improve blood flow, thereby reducing blood pressure. It is also used in the treatment of stable angina by decreasing the heart's oxygen demand and thus relieve symptoms and prevent angina

attacks. Atenolol may also be prescribed to manage certain cardiac arrhythmias, such as supraventricular tachycardia and atrial fibrillation. It helps to stabilise heart rhythm by slowing the electrical impulses in the heart. It is sometimes used in the early phase of myocardial infarction (heart attack) as well to reduce the risk of recurrent events and improve survival (Rehman et al., 2023)..

The correlation matrix and regression analysis demonstrated the relationship between each NSCLC-Cardio drug pair. Based on guidelines of cardiovascular drugs used to treat cardiovascular diseases, it suggested that hypertension was the most associated cardiovascular disease with the 20 shortlisted oncology drugs. Certain oncology drugs, including targeted therapies and immunotherapies, can directly cause or contribute to hypertension as a side effect. These drugs may interfere with signalling pathways involved in blood vessel regulation, leading to increased blood pressure. Hypertension in cancer patients can have significant implications for cardiovascular health. Uncontrolled high blood pressure can increase the risk of cardiovascular events, such as heart attack, stroke, or heart failure. Therefore, it is important to manage hypertension effectively to minimise these risks and ensure optimal cardiovascular health during cancer treatment.

Results obtained from the correlation matrix and regression analysis can be used to indicate which drug-drug pair has the strongest association, however it is important to remember that the results only showed correlation and did not imply causation. This does not necessarily mean that one drug is used to treat a condition caused by the other or that the diseases treated by these drugs are directly related. Other factors may influence these correlations, and further investigation would be necessary to determine any causal relationships.

5.6 Summary

- The cardiology drug that was associated with the greatest number of oncology drugs was apixaban.
- Atezolizumab, bevacizumab, nintedanib, osimertinib, paclitaxel, pembrolizumab, gemcitabine and vincristine were all mostly associated with apixaban, which indicated association with atrial fibrillation.
- Afatinib, erlotinib and methotrexate were mostly associated with atenolol, hence suggested the association with ischaemia or hypertension.

- Docetaxel and epirubicin were associated with verapamil, which indicated association with arrhythmia or hypertension.
- From the correlation matrix, it can be concluded that hypertension was the most associated cardiovascular disease with the 20 shortlisted oncology drugs.

Chapter 6

Signal Generation for Cardiotoxicity Related to Non-Small Cell Lung Cancer Treatments Using the UK Yellow Card System

6.1 Introduction

Non-small cell lung cancer (NSCLC) is one of the leading causes of cancer-related deaths worldwide with various treatment available, including surgery, radiation therapy, chemotherapy, targeted therapies, and immunotherapies. While these treatments have significantly improved outcomes for NSCLC patients, there is growing concern regarding their potential impact on cardiovascular events. This chapter examines the possible association between NSCLC treatments and cardiovascular events using the UK Yellow Card System.

By contributing to the monitoring and evaluation of the safety profiles of medicines and vaccines, the UK Yellow Card System is an integral part of the country's pharmacovigilance framework. Its establishment was initiated by the thalidomide tragedy of the 1960s, which underscored the need for robust systems to detect and mitigate adverse drug reactions. Thalidomide was prescribed to pregnant women which led to thousands of babies born with limb deformities, hence prompting many countries, including the UK, to re-evaluate and strengthen their drug safety monitoring processes (Botting, 2002; McBride, 1961). It was first developed by Bill Inman in 1964, which was originally designed for doctors only; and had then extended the use for pharmacists in late 1990s (Goddard, 2013). From 2005, patients and their caregivers are also allowed to report undesirable side effects or complication directly (McLernon et al., 2011). This inclusivity ensures a broader collection of data and helps in capturing real-world experiences of drug usage.

The UK Yellow Card scheme operates on a voluntary reporting basis. Apart from prescription medicines, the Yellow Card System also includes over-the-counter medicines, vaccines, herbal products as well as medical devices (Shuttleworth et al., 2023). Once a suspected adverse drug reaction (ADR) – coded as MedDRA terms – is reported, the MHRA assesses the information, collates it with other reports, and determines if the medicine or product has a potential safety issue.

The UK Yellow Card System acts as a post-marketing surveillance tool, which complements pre-market clinical trials by capturing real-world experiences and long-term effects of drugs. The system plays a crucial role in identifying previously unknown or rare side effects, monitoring the benefit-risk profiles of medicines, and facilitating regulatory decision-making. The strength of the Yellow Card System lies in its cumulative data. A single report may not lead to action, but when combined with other reports, patterns and trends emerge (Evans et al., 2001; Wilson et al.,

2004). This comprehensive approach ensures that any potential safety concern related to healthcare products can be identified, evaluated, and acted upon.

6.2 Aim and Objectives

6.2.1 Aim

Through analysing the Yellow Card System – a spontaneous reporting system, this study explored the association between non-small cell lung cancer treatments and cardiotoxicity by conducting disproportionality analyses which are used to detect safety signals according to proportional reporting ratio (PRR) and reporting odds ratio (ROR).

6.2.2 Primary objective

Within the Yellow Card database, this study described the differences of cardiotoxicity-related outcomes of interest (all and by sub-type) in patients receiving different NSCLC treatments.

6.2.3 Secondary objectives

1. To define NSCLC patients according to the treatment recorded in the dataset.
2. To describe the characteristics of patients with each NSCLC drug at recorded date.
3. To describe and compare the characteristics of sub-groups receiving NSCLC treatment.

6.3 Methods

6.3.1 Types of studies

This was a secondary database study based on a retrospective design using the Yellow Card database in the United Kingdom (see section 3.4.1). Demographic and clinical characteristics were described at the recorded date.

6.3.2 Setting

UK was the proposed setting for this study.

6.3.2.1 Study time period

From the earliest date of each corresponding drug of interest (Table 1) till August 2023.

6.3.3 Datasource

The UK's Yellow Card System is an integral part of the nation's pharmacovigilance mechanism, managed by MHRA. The scheme operates on a voluntary reporting basis. The Yellow Card scheme allows healthcare professionals, patients, and caregivers to report suspected adverse reactions voluntarily. Reports can be submitted online, via a paper form, or through a dedicated mobile application. The system collects information on the suspected drug, the reaction, patient demographics, and other relevant details. Reports can be submitted anonymously, ensuring confidentiality and encouraging reporting without fear of reprisal. The ease of reporting empowers healthcare professionals and patients to actively participate in drug safety monitoring, contributing to a more comprehensive understanding of medication risks.

6.3.3.1 Datasource considerations

One of the limitations is the under-reporting of ADRs. Many factors can contribute to this, including lack of awareness about the system, uncertainty about whether the drug caused the reaction, or perceived time constraints. In addition, being a spontaneous reporting system, it is susceptible to various biases. For instance, newer drugs might be over-reported due to increased attention whereas well-established drugs might be under-reported as their side effects are deemed "known". There is also a potential for incomplete or inaccurate data since the reporting does not undergo stringent validation.

6.3.4 Data Extraction

The data downloaded were individual drug analysis profiles (DAPs). The medicines were listed by the name of the active ingredient, and not by brand name. Each DAP consisted of a list of all suspected ADRs that had been reported by healthcare professionals, patients and pharmaceutical companies to the MHRA via the Yellow Card scheme. There was currently a time lag ~ 1 month from receipt of a report to it being included in the DAP. The most recent available data at the time of data extraction (October 2023) was up until August 2023. MedDRA version 26.0 was used.

After data extraction, data was mapped using Microsoft SQL Server / Microsoft Access. Data analyses were then carried out using R.

6.3.5 Data Management

6.3.5.1 Source Documents

Source documents were filed in an encrypted drive. Data entered in other electronic files that were transcribed from source documents were consistent with the source documents or the discrepancies were explained.

6.3.5.2 Storage of records

The study site retained the source documents and essential documents until the end of study.

6.3.6 Sample size

This was an exploratory study and descriptive in nature. The study population was derived from all patients within the Yellow Card database to which the inclusion criteria apply and thus was a convenience sample.

6.3.7 Variables

The following drugs of interest, which are lung cancer drugs (C34) available within the Yellow Card database, were extracted (Table 6.1).

Table 6.1: A list of lung cancer drugs (ICD-10: C34) available within the Yellow Card database.

Lung Cancer (ICD-10: C34) Drugs	**ATC/DDD**
Afatinib	L01EB03
Alectinib	L01ED03
Amifostine	V03AF05
Atezolizumab	L01FF05
Avelumab	L01FF04
Bevacizumab	L01FG01
Brigatinib	L01ED04
Carboplatin	L01XA02
Cabozantinib	L01EX07

Celecoxib	L01XX33
Ceritinib	L01ED02
Cetuximab	L01FE01
Cisplatin	L01XA01
Crizotinib	L01ED01
Cyclophosphamide	L01AA01
Dabrafenib	L01EC02
Dacomitinib	L01EB07
Dasatinib	L01EA02
Docetaxel	L01CD02
Doxorubicin	L01DB01
Durvalumab	L01FF03
Entrectinib	L01EX14
Erlotinib	L01EB02
Epirubicin	L01DB03
Etoposide	L01CB01
Everolimus	L01EG02 / L04AA18
Gefitinib	L01EB01
Gemcitabine	L01BC05
Ifosfamide	L01AA06
Ipilimumab	L01FX04
Irinotecan	L01CE02
Larotrectinib	L01EX12
Lorlatinib	L01ED05
Lurbinectedin	L01XX69
Methotrexate	L01BA01 / L04AX03
Nintedanib	L01EX09
Nivolumab	L01FF01
Osimertinib	L01EB04
Paclitaxel	L01CD01
Panitumumab	L01FE02
Pembrolizumab	L01FF02
Pemetrexed	L01BA04
Pralsetinib	L01EX23
Ramucirumab	L01FG02
Selpercatinib	L01EX22
Sorafenib	L01EX02
Sotorasib	L01XX73
Sunitinib	L01EX01
Tepotinib	L01EX21
Topotecan	L01CE01
Trametinib	L01EE01

Trastuzumab	L01FD01
Veliparib	L01XK05
Vemurafenib	L01EC01
Vincristine	L01CA02
Vinorelbine	L01CA04

6.3.7.1 NSCLC drug-outcome pair-finding algorithm

NSCLC drug-outcome pair-finding algorithm – narrow case definition

Inclusion criteria for the proposed algorithm were based on the drugs approved for non-small cell lung cancer (NSCLC) in the UK and available through NHS, and exclusion criteria included drugs approved for small cell lung cancer (SCLC) in the UK and available through NHS. SCLC drugs excluded were etoposide, ifosfamide, lurbinectedin and topotecan.

NSCLC drug-outcome pair-finding algorithm – broad case definition

Under broad case definition, cases of all drugs listed in Table 6.1 were included. Although etoposide, ifosfamide, lurbinectedin and topotecan were approved for treating SCLC, they were sometimes used to treat NSCLC off-label, hence they were included in the broad case definition.

Sensitivity analysis for NSCLC drug-outcome pair-finding algorithm

Sensitivity analysis determine how different underlying elements impact an outcome under a given test of assumption. Therefore, two different definitions of NSCLC drug-outcome pair-finding algorithm was used as independent variables to explore how they might affect the number of eligible cases recorded.

6.3.7.2 Data items collected

A list of data variables extracted from Yellow Card database is included in Table 6.2.

Table 6.2: List of variables extracted from the Yellow Card database.

Column Name	Column Description	Extracted from the following source table
ADR	Sequential number identifying a single ADR report	CASE
SEX	Patient sex: "Male", "Female", "Unknown"	CASE
AGE_10	Patient age at the time of the ADR. This is expressed in 10-year bands with the lowest level of the band displayed in the file e.g., 0 represents ages less than 10 years (0-9 years) 10 represents ages of 10 years or higher, but less than 20 years (10-19 years) 20 represents ages of 20 years or higher, but less than 30 years (20-29 years)	CASE
RECVD_YEAR	Year in which the ADR was first received by the MHRA	CASE
SENDER_TYPE	Describes the source of the ADR reports submitted to the MHRA: "Indirect" if the ADR was reported to the MHRA by a pharmaceutical company "Direct" if the ADR was reported to the MHRA by a healthcare professional or member of the public	CASE
CONSUMER_YN	Indicates if the ADR was reported by the consumer (the patient, their parent or a carer) of the product "Y" if the ADR was reported by a consumer or a lawyer. "N" if the ADR was not reported by a consumer or a lawyer	CASE
HCP_YN	Indicates if the ADR was reported by a healthcare professional. (examples of healthcare professionals include: Hospital Doctor, GP, pharmacist, nurse, etc) "Y" if the ADR was reported by a health professional "N" if the ADR was reported by a non-health professional Please note HCP_YN and Consumer_YN are not exclusive categories; an ADR report can be sent to the MHRA with details of both a consumer and healthcare professional reporter	CASE
NONSERIOUS_SERIOUS_FATAL_NSF	Indicates the seriousness of the ADR report "F" if the ADR was fatal "S" if the ADR was serious but not fatal. "N" if the ADR was non-serious.	CASE
ADR	Sequential number identifying a single ADR report	DRUG

SEQ	Sequential number identifying each reported administration of the suspect drug in question	DRUG
ROUTE	The route of administration for the drug (e.g. oral, intravenous, etc). Drug routes that appear in fewer than 5 ADR reports (or 1% of ADR reports for drugs with more than 500 ADRs) are displayed as "Routes with few reports"	DRUG
MULTICONST	Describes whether the drug in each ADR report contains more than one active ingredient "Y" if the drug substance of interest in the IDAP is one active ingredient in a multi- constituent product. "N" if the drug substance of interest in the IDAP is the only active ingredient in the product.	DRUG
NONSERIOUS_SERIOUS_FATALNSF	Indicates the seriousness of the ADR report. This field is also in CASE.csv "F" if the ADR was fatal "S" if the ADR was serious but not fatal. "N" if the ADR was non-serious.	DRUG
ADR	Sequential number identifying a single ADR report	EVENT
SEQ	Sequential number identifying each adverse reaction within the ADR report	EVENT
PT	MedDRA Preferred Term, describing the adverse reaction	EVENT
HLT	MedDRA High Level Term which contains the corresponding Preferred Term	EVENT
HLGT	MedDRA High Level Group Term which contains the corresponding High Level Term	EVENT
SOC_ABBREV	MedDRA System Organ Class which contains the corresponding High Level Group Term	EVENT
FATAL_YN	Describes whether the adverse reaction had a fatal outcome "Y" if the reaction was fatal "N" if the reaction was not fatal	EVENT
DRUG_NAME	The name of the drug substance of interest in this IDAP report	INFO
DATA_EXTRACT_VERSION	The software version used to generate the data in the report	INFO
DATA_EXTRACTION_DATE	The date when the data for this report were produced. Please note that a drug with less frequent ADRs reported may have an older date because new IDAP datasets are only created after new ADR reports for the drug have been received.	INFO
MEDDRA_VERSION	The version of the MedDRA dictionary that was active on the data extraction date. Values are 2-3 digit numeric strings e.g. "19" (for MedDRA version 19.0), "181" (for MedDRA version 18.1) etc.	INFO
REPORT_TYPE	The level within the dictionary hierarchy of the information included on the IDAP. Not all levels are currently routinely published online. If you	INFO

	require further information, please contact the MHRA. Levels include: "Combined substance" - A drug that contains one or more active ingredients "Substance" - An active ingredient, regardless of whether it is administered by itself or in combination with other ingredients, "Substance Variant" - A drug chemical variant of a substance "PBG" - Product Brand Generic, a family name for a group of related products	
COUNTRY	The country where the ADRs in the IDAP were reported.	INFO
MULTI_CONSTITUENT_YN	"N" indicates that the row is summarising single-constituent products "Y" indicates that the row is summarising multi-constituent products	SUMMARY
PBG	A list of the single-constituent or multi-constituent products that are summarised in the report. The products are identified by their "Product Brand Generic" (PBG) names.	SUMMARY

6.3.8 Statistical analysis

6.3.8.1 General approach

Descriptive analyses were conducted using number and percent within each category with 95% confidence intervals (whenever appropriate) for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

Only available data were summarised; no imputation methods was used to handle missing data. The number and percentage of missing values were also be reported as appropriate.

6.3.8.2 Primary objective – Within the Yellow Card database, this study described the differences of cardiotoxicity-related outcomes of interest (all and by sub-type) in patients receiving different NSCLC treatments.

The counts and types of cardiotoxic events in all patients within each cancer drug were summarised. Disproportionality analyses were used to detect signals of the ADRs for the drugs of interest. Disproportionality analyses were conducted using R (version 4.3.3). Proportional reporting ratio (PRR) and reporting odds ratio (ROR) were calculated to assess the

cardiovascular adverse effects of the 56 shortlisted lung cancer drugs. Cardiovascular events of interest were defined as 'card' or 'vasc' under SOC_ABBREV.

The ROR is a measure of the odds that an adverse event will be reported for a specific drug compared to the odds of the event being reported for all other drugs. When the lower limit of the 95% confidence interval (CI) is larger than 1, then ROR is considered significant (Anand et al., 2019). PRR compares the proportion of reports with a specific adverse event for a drug with the proportion of all other adverse event reports. A PRR value ≥ 2, a chi-squared (x^2) value ≥4, and at least 3 cases are reported suggests a positive signal (Evans et al., 2001). The data was segmented based on age cohorts and gender.

6.3.8.3 Secondary objective 1 – To define NSCLC patients and their corresponding first treatment recorded in the dataset

Details of NSCLC drug-outcome pair finding algorithm by narrow and broad case definition was explained in Section 6.3.7.1. Sensitivity analysis was conducted to determine the capability of the data source to define NSCLC patients. A tornado diagram was presented where necessary.

6.3.8.4 Secondary objective 2 – To describe the characteristics of patients with NSCLC at recorded date

Descriptive analyses were conducted using number and percent within each category with 95% confidence intervals (whenever appropriate) for categorical variables, and mean (standard deviation [SD]), median (Q1, Q3), and minimum and maximum for continuous variables.

6.3.8.4 Secondary objective 3 – To describe and compare the characteristics of sub-groups receiving NSCLC treatment, according to record date

Categorical data/characteristics was summarised in a table. For continuous data, one-way ANOVA was used to compare other characteristics within and between sub-groups whereas for non-parametric data, Mann-Whitney test was used. A boxplot was presented to provide a graphical summary of distribution.

6.4 Results

The total number of adverse events reported for the shortlisted 56 drugs was 128,214. Among those, 6133 reports were cardiovascular adverse reactions. Table 6.3 shows an overview of the total number of adverse events reports received for each drug, and the number of cardiovascular events reported for each corresponding drug. Six drugs (amifostine, lurbinectedin, pralsetinib, ramucirumab, sotorasib and veliparib) out of the 56 shortlisted drugs received no cardiovascular adverse events report. Also, only 2 drugs, alectinib and epirubicin, received over 10% of cardiovascular adverse events reports.

Table 6.3: Overview of the total number of adverse events reported for each drug and their corresponding number of cardiovascular events.

Drug	Total number of adverse events reports	Total number of cardiovascular (CV) adverse events reports	
Alectinib	160	23	14.38%
Epirubicin	1652	173	10.47%
Doxorubicin	4408	376	8.53%
Avelumab	843	69	8.19%
Selpercatinib	172	14	8.14%
Dasatinib	1289	95	7.37%
Celecoxib	5039	335	6.65%
Pemetrexed	1359	90	6.62%
Gemcitabine	2430	160	6.58%
Nintedanib	995	65	6.53%
Paclitaxel	5211	336	6.45%
Cisplatin	3611	225	6.23%
Docetaxel	7692	475	6.18%
Carboplatin	5235	318	6.07%
Vinorelbine	1920	114	5.94%
Sunitinib	2555	147	5.75%
Bevacizumab	3945	210	5.32%
Trastuzumab	13863	718	5.18%
Crizotinib	851	43	5.05%
Cyclophosphamide	8394	408	4.86%
Osimertinib	437	21	4.81%
Gefitinib	439	21	4.78%
Vincristine	3835	181	4.72%
Cetuximab	1061	50	4.71%
Etoposide	3603	165	4.58%
Sorafenib	820	37	4.51%
Ceritinib	180	8	4.44%
Irinotecan	1729	76	4.40%

Vemurafenib	569	25	4.39%
Pembrolizumab	3292	143	4.34%
Dacomitinib	48	2	4.17%
Nivolumab	3199	132	4.13%
Brigatinib	130	5	3.85%
Ipilimumab	2305	86	3.73%
Erlotinib	1155	43	3.72%
Ifosfamide	1491	54	3.62%
Entrectinib	56	2	3.57%
Durvalumab	286	10	3.50%
Lorlatinib	183	5	2.73%
Dabrafenib	1767	48	2.72%
Cabozantinib	1560	41	2.63%
Tepotinib	77	2	2.60%
Topotecan	670	17	2.54%
Trametinib	1581	37	2.34%
Methotrexate	18709	418	2.23%
Larotrectinib	46	1	2.17%
Afatinib	434	9	2.07%
Everolimus	3949	67	1.70%
Panitumumab	617	9	1.46%
Atezolizumab	2133	24	1.13%
Amifostine	3	0	0.00%
Lurbinectedin	2	0	0.00%
Pralsetinib	33	0	0.00%
Ramucirumab	40	0	0.00%
Sotorasib	130	0	0.00%
Veliparib	21	0	0.00%

Table 6.4 shows the patients' demographics, including age and gender, and seriousness of each cardiovascular adverse event reported by drug. Seriousness was divided into non-serious, serious and fatal where fatal was a subset of serious.

Table 6.4: Patients' demographics and seriousness of each cardiovascular adverse event reported by drug.

Drug	Total no. of CV reports	Gender						Age																		Seriousness					
		Female		Male		Unknown		0		10		20		30		40		50		60		70		80		90		Fatal		Non-Serious		Serious	
Afatinib	9	3	33.33%	6	66.67%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	11.11%	2	22.22%	1	11.11%	0	0.00%	4	44.44%	1	11.11%	0	0.00%	0	0.00%	9	100.00%
Alectinib	23	7	30.43%	14	60.87%	2	8.70%	0	0.00%	0	0.00%	0	0.00%	1	4.35%	2	8.70%	10	43.48%	3	13.04%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	23	100.00%
Amifostine	0																														
Atezolizumab	24	9	37.50%	14	58.33%	1	4.17%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	4.17%	7	29.17%	3	12.50%	10	41.67%	0	0.00%	0	0.00%	3	12.50%	1	4.17%	20	83.33%
Avelumab	69	13	18.84%	55	79.71%	1	1.45%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	3	4.35%	21	30.43%	24	34.78%	8	11.59%	10	14.49%	0	0.00%	3	4.35%	1	1.45%	65	94.20%
Bevacizumab	210	108	51.43%	91	43.33%	11	5.24%	2	0.95%	3	1.43%	0	0.00%	5	2.38%	15	7.14%	35	16.67%	63	30.00%	21	10.00%	8	3.81%	0	0.00%	25	11.90%	1	0.48%	184	87.62%
Brigatinib	5	2	40.00%	1	20.00%	2	40.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	20.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	5	100.00%
Cabozantinib	41	15	36.59%	21	51.22%	5	12.20%	0	0.00%	0	0.00%	0	0.00%	1	2.44%	6	14.63%	9	21.95%	19	46.34%	4	9.76%	1	2.44%	0	0.00%	6	14.63%	1	2.44%	34	82.93%
Carboplatin	318	242	76.10%	59	18.55%	17	5.35%	7	2.20%	0	0.00%	5	1.57%	12	3.77%	35	11.01%	60	18.87%	81	25.47%	52	16.35%	10	3.14%	0	0.00%	38	11.95%	34	10.69%	246	77.36%
Celecoxib	335	193	57.61%	131	39.10%	11	3.28%	0	0.00%	0	0.00%	1	0.30%	12	3.58%	28	8.36%	65	19.40%	85	25.37%	60	17.91%	36	10.75%	9	2.69%	32	9.55%	52	15.52%	251	74.93%
Ceritinib	8	8	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	12.50%	0	0.00%	5	62.50%	1	12.50%	0	0.00%	0	0.00%	0	0.00%	1	12.50%	0	0.00%	7	87.50%
Cetuximab	50	14	28.00%	35	70.00%	1	2.00%	0	0.00%	0	0.00%	0	0.00%	4	8.00%	1	2.00%	10	20.00%	13	26.00%	7	14.00%	0	0.00%	0	0.00%	10	20.00%	5	10.00%	35	70.00%
Cisplatin	225	83	36.89%	134	59.56%	8	3.56%	7	3.11%	0	0.00%	7	3.11%	23	10.22%	35	15.56%	48	21.33%	63	28.00%	12	5.33%	0	0.00%	0	0.00%	33	14.67%	4	1.78%	188	83.56%
Crizotinib	43	28	65.12%	15	34.88%	0	0.00%	0	0.00%	0	0.00%	4	9.30%	2	4.65%	11	25.58%	3	6.98%	5	11.63%	10	23.26%	1	2.33%	0	0.00%	8	18.60%	1	2.33%	34	79.07%
Cyclophosphamide	408	208	50.98%	148	36.27%	52	12.75%	34	8.33%	15	3.68%	9	2.21%	31	7.60%	72	17.65%	69	16.91%	39	9.56%	37	9.07%	9	2.21%	0	0.00%	71	17.40%	4	0.98%	333	81.62%
Dabrafenib	48	9	18.75%	34	70.83%	5	10.42%	0	0.00%	0	0.00%	2	4.17%	2	4.17%	0	0.00%	2	4.17%	14	29.17%	9	18.75%	1	2.08%	0	0.00%	11	22.92%	0	0.00%	37	77.08%
Dacomitinib	2	2	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	50.00%	0	0.00%	0	0.00%	0	0.00%	1	50.00%	0	0.00%	0	0.00%	1	50.00%	0	0.00%	1	50.00%
Dasatinib	95	40	42.11%	50	52.63%	5	5.26%	0	0.00%	0	0.00%	1	1.05%	6	6.32%	9	9.47%	11	11.58%	28	29.47%	14	14.74%	2	2.11%	0	0.00%	7	7.37%	1	1.05%	87	91.58%
Docetaxel	475	346	72.84%	109	22.95%	20	4.21%	0	0.00%	0	0.00%	1	0.21%	38	8.00%	68	14.32%	118	24.84%	85	17.89%	51	10.74%	7	1.47%	0	0.00%	87	18.32%	40	8.42%	348	73.26%
Doxorubicin	376	191	50.80%	140	37.23%	45	11.97%	23	6.12%	28	7.45%	11	2.93%	14	3.72%	47	12.50%	72	19.15%	42	11.17%	44	11.70%	9	2.39%	0	0.00%	82	21.81%	10	2.66%	284	75.53%
Durvalumab	10	4	40.00%	4	40.00%	2	20.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	10.00%	2	20.00%	2	20.00%	0	0.00%	0	0.00%	4	40.00%	0	0.00%	6	60.00%
Entrectinib	2	2	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	2	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	2	100.00%
Epirubicin	173	137	79.19%	30	17.34%	6	3.47%	2	1.16%	7	4.05%	6	3.47%	11	6.36%	29	16.76%	43	24.86%	14	8.09%	11	6.36%	0	0.00%	0	0.00%	18	10.40%	7	4.05%	148	85.55%
Erlotinib	43	22	51.16%	19	44.19%	2	4.65%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	2	4.65%	8	18.60%	13	30.23%	10	23.26%	1	2.33%	0	0.00%	14	32.56%	0	0.00%	29	67.44%
Etoposide	165	81	49.09%	76	46.06%	8	4.85%	29	17.58%	5	3.03%	8	4.85%	20	12.12%	14	8.48%	15	9.09%	23	13.94%	23	13.94%	0	0.00%	0	0.00%	20	12.12%	6	3.64%	139	84.24%
Everolimus	67	55	82.09%	7	10.45%	5	7.46%	17	25.37%	0	0.00%	0	0.00%	2	2.99%	3	4.48%	15	22.39%	10	14.93%	5	7.46%	1	1.49%	0	0.00%	13	19.40%	0	0.00%	54	80.60%

Gefitinib	21	13	61.90%	8	38.10%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	2	9.52%	5	23.81%	7	33.33%	5	23.81%	0	0.00%	3	14.29%	0	0.00%	18	85.71%
Gemcitabine	160	73	45.63%	67	41.88%	20	12.50%	0	0.00%	2	1.25%	1	0.63%	1	0.63%	9	5.63%	25	15.63%	60	37.50%	26	16.25%	5	3.13%	0	0.00%	30	18.75%	11	6.88%	119	74.38%
Ifosfamide	54	31	57.41%	21	38.89%	2	3.70%	3	5.56%	13	24.07%	1	1.85%	6	11.11%	4	7.41%	8	14.81%	7	12.96%	0	0.00%	0	0.00%	0	0.00%	6	11.11%	2	3.70%	46	85.19%
Ipilimumab	86	30	34.88%	51	59.30%	5	5.81%	0	0.00%	0	0.00%	0	0.00%	4	4.65%	0	0.00%	8	9.30%	39	45.35%	19	22.09%	2	2.33%	0	0.00%	29	33.72%	0	0.00%	57	66.28%
Irinotecan	76	31	40.79%	44	57.89%	1	1.32%	0	0.00%	0	0.00%	0	0.00%	3	3.95%	5	6.58%	27	35.53%	18	23.68%	8	10.53%	0	0.00%	0	0.00%	14	18.42%	5	6.58%	57	75.00%
Larotrectinib	1	1	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	100.00%
Lorlatinib	5	0	0.00%	5	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	20.00%	2	40.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	5	100.00%
Lurbinectedin	0																															
Methotrexate	418	229	54.78%	169	40.43%	20	4.78%	24	5.74%	40	9.57%	19	4.55%	21	5.02%	39	9.33%	58	13.88%	82	19.62%	59	14.11%	14	3.35%	1	0.24%	96	22.97%	11	2.63%	311	74.40%
Nintedanib	65	8	12.31%	52	80.00%	5	7.69%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	4	6.15%	17	26.15%	27	41.54%	9	13.85%	0	0.00%	7	10.77%	1	1.54%	57	87.69%
Nivolumab	132	45	34.09%	83	62.88%	4	3.03%	0	0.00%	0	0.00%	4	3.03%	1	0.76%	7	5.30%	9	6.82%	50	37.88%	25	18.94%	5	3.79%	0	0.00%	29	21.97%	5	3.79%	98	74.24%
Osimertinib	21	14	66.67%	7	33.33%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	4.76%	10	47.62%	6	28.57%	2	9.52%	0	0.00%	10	47.62%	0	0.00%	11	52.38%
Paclitaxel	336	283	84.23%	33	9.82%	20	5.95%	0	0.00%	1	0.30%	0	0.00%	23	6.85%	44	13.10%	65	19.35%	92	27.38%	51	15.18%	5	1.49%	0	0.00%	39	11.61%	53	15.77%	244	72.62%
Panitumumab	9	6	66.67%	3	33.33%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	11.11%	5	55.56%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	11.11%	0	0.00%	8	88.89%
Pembrolizumab	143	62	43.36%	79	55.24%	2	1.40%	0	0.00%	0	0.00%	0	0.00%	2	1.40%	4	2.80%	21	14.69%	21	14.69%	60	41.96%	15	10.49%	2	1.40%	42	29.37%	2	1.40%	99	69.23%
Pemetrexed	90	41	45.56%	48	53.33%	1	1.11%	0	0.00%	0	0.00%	0	0.00%	2	2.22%	7	7.78%	15	16.67%	42	46.67%	16	17.78%	0	0.00%	0	0.00%	21	23.33%	0	0.00%	69	76.67%
Pralsetinib	0																															
Ramucirumab	0																															
Selpercatinib	14	7	50.00%	7	50.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	4	28.57%	4	28.57%	2	14.29%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	14	100.00%
Sorafenib	37	13	35.14%	21	56.76%	3	8.11%	6	16.22%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	2.70%	6	16.22%	8	21.62%	0	0.00%	0	0.00%	4	10.81%	0	0.00%	33	89.19%
Sotorasib	0																															
Sunitinib	147	50	34.01%	95	64.63%	2	1.36%	0	0.00%	0	0.00%	0	0.00%	4	2.72%	12	8.16%	24	16.33%	42	28.57%	36	24.49%	14	9.52%	1	0.68%	26	17.69%	1	0.68%	120	81.63%
Tepotinib	2	2	100.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	1	50.00%	0	0.00%	0	0.00%	0	0.00%	1	50.00%	1	50.00%
Topotecan	17	15	88.24%	2	11.76%	0	0.00%	6	35.29%	0	0.00%	0	0.00%	0	0.00%	0	0.00%	3	17.65%	4	23.53%	0	0.00%	0	0.00%	0	0.00%	2	11.76%	0	0.00%	15	88.24%
Trametinib	37	8	21.62%	25	67.57%	4	10.81%	2	5.41%	0	0.00%	2	5.41%	2	5.41%	0	0.00%	2	5.41%	10	27.03%	5	13.51%	1	2.70%	0	0.00%	7	18.92%	0	0.00%	30	81.08%
Trastuzumab	718	692	96.38%	4	0.56%	22	3.06%	0	0.00%	0	0.00%	2	0.28%	76	10.58%	127	17.69%	140	19.50%	99	13.79%	51	7.10%	8	1.11%	0	0.00%	120	16.71%	11	1.53%	587	81.75%
Veliparib	0																															
Vemurafenib	25	12	48.00%	4	16.00%	9	36.00%	0	0.00%	0	0.00%	1	4.00%	0	0.00%	1	4.00%	0	0.00%	12	48.00%	8	32.00%	2	8.00%	0	0.00%	5	20.00%	0	0.00%	20	80.00%
Vincristine	181	51	28.18%	107	59.12%	23	12.71%	10	5.52%	18	9.94%	3	1.66%	9	4.97%	20	11.05%	32	17.68%	17	9.39%	22	12.15%	8	4.42%	0	0.00%	35	19.34%	1	0.55%	145	80.11%
Vinorelbine	114	72	63.16%	42	36.84%	0	0.00%	0	0.00%	1	0.88%	0	0.00%	2	1.75%	11	9.65%	41	35.96%	16	14.04%	17	14.91%	3	2.63%	0	0.00%	26	22.81%	1	0.88%	87	76.32%

This circular barplot presents an overview of MedDRA Preferred Term (PT) reported under cardiology or vascular class (Figure 6.1). This only included reactions with a minimum of 5 cases across the 56 shortlisted drugs.

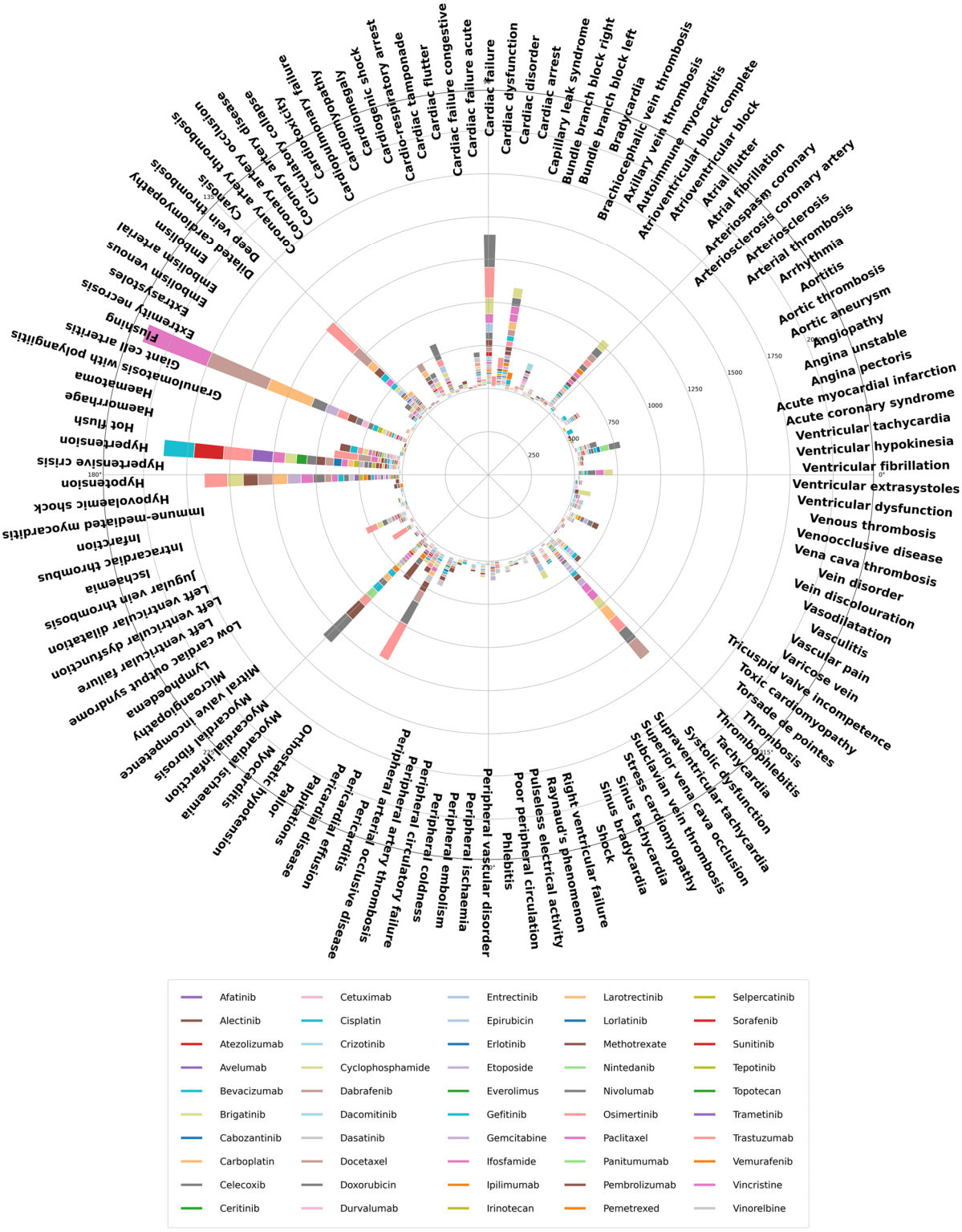

Figure 6.1: An overview of MedDRA Preferred Term (PT) reported under cardiology or vascular class across the 56 shortlisted drugs.

Flushing was the highest reported cardiovascular reactions, followed by hypertension and myocardial infarction.

The Reporting Odds Ratio (ROR) provides insights into the odds of cardiovascular adverse events for each drug. The ROR is a measure of the odds that an adverse event will be reported for a specific drug compared to the odds of the event being reported for all other drugs.

The forest plot (Figure 6.2) shows the ROR values of each drug and its corresponding 95% CI. 17 drugs (i.e. alectinib, avelumab, carboplatin, celecoxib, cisplatin, dasatinib, docetaxel, doxorubicin, epirubicin, gemcitabine, nintedanib, paclitaxel, pemetrexed, selpercatinib, sunitinib, trastuzumab and vinorelbine) had a ROR value (lower limit of the 95% CI) of ≥1, which indicated a positive signal. Alectinib had the highest ROR value of 3.35, indicating a higher odds of cardiovascular adverse event reports compared to other drugs. The confidence interval ranged from about 2.15 to 5.21, suggesting a significant association, although there was some variability in the estimate. Atezolizumab had the lowest ROR value of 0.22, suggesting fewer cardiovascular adverse event reports than expected.

Among the 17 drugs which detected a positive signal with cardiovascular adverse events – traditional chemotherapies included carboplatin, cisplatin, docetaxel, doxorubicin, epirubicin, gemcitabine, paclitaxel, pemetrexed, vinorelbine; targeted therapies included alectinib, dasatinib, nintedanib, selpercatinib, sunitinib; and immunotherapies included avelumab and trastuzumab. Celecoxib also detected a positive signal; it is often used in combination with chemotherapies.

Detailed results of each drug's ROR and PRR values, and their corresponding 95% CI and chi-squared values were listed in Appendix V.

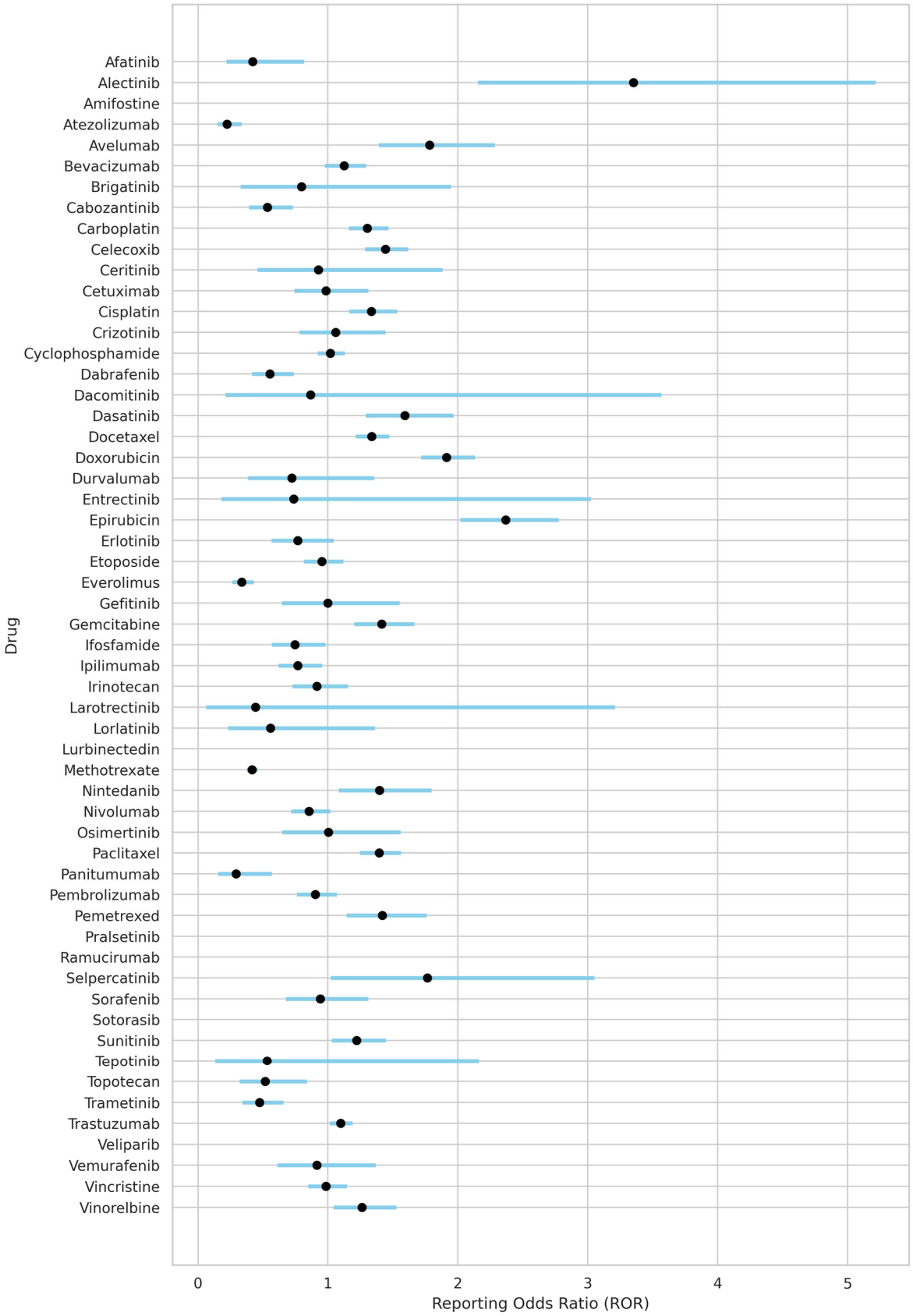

Figure 6.2: A forest plot showing the ROR values and corresponding 95% CI of each drug.

The Proportional Reporting Ratio (PRR) provides a different perspective on the same issue, focusing on the proportion of adverse event reports for each drug. The forest plot (Figure 6.3) shows the PRR values and corresponding 95% CI of each drug. Alectinib also had the highest PRR value, reinforcing the signal detected by the ROR analysis. The 95% confidence interval ranged from 2.06 to 4.40, which supported the presence of a strong signal for cardiovascular adverse events. However, according to the criteria of positive signal detected by PRR, cardiovascular adverse events signals were detected in alectinib (PRR = 3.01, x^2 = 32.36, no. of cases = 23) and epirubicin (PRR = 2.22, x^2 = 118.91, no. of cases = 173) only, as opposed to the 17 drugs detected by ROR analysis. Atezolizumab again showed the lowest PRR value of 0.23, consistent with the ROR findings.

Alectinib had the highest signal for potential cardiovascular adverse events among the drugs analysed, as indicated by both the highest ROR and PRR values. This suggested that reports of cardiovascular events associated with alectinib were more frequent than expected when compared to other drugs.

It is important to note that while these metrics can signal potential safety issues, they do not establish causality. Further investigation would be required to determine whether the associations are due to the drugs themselves, other confounding factors, or a combination of both.

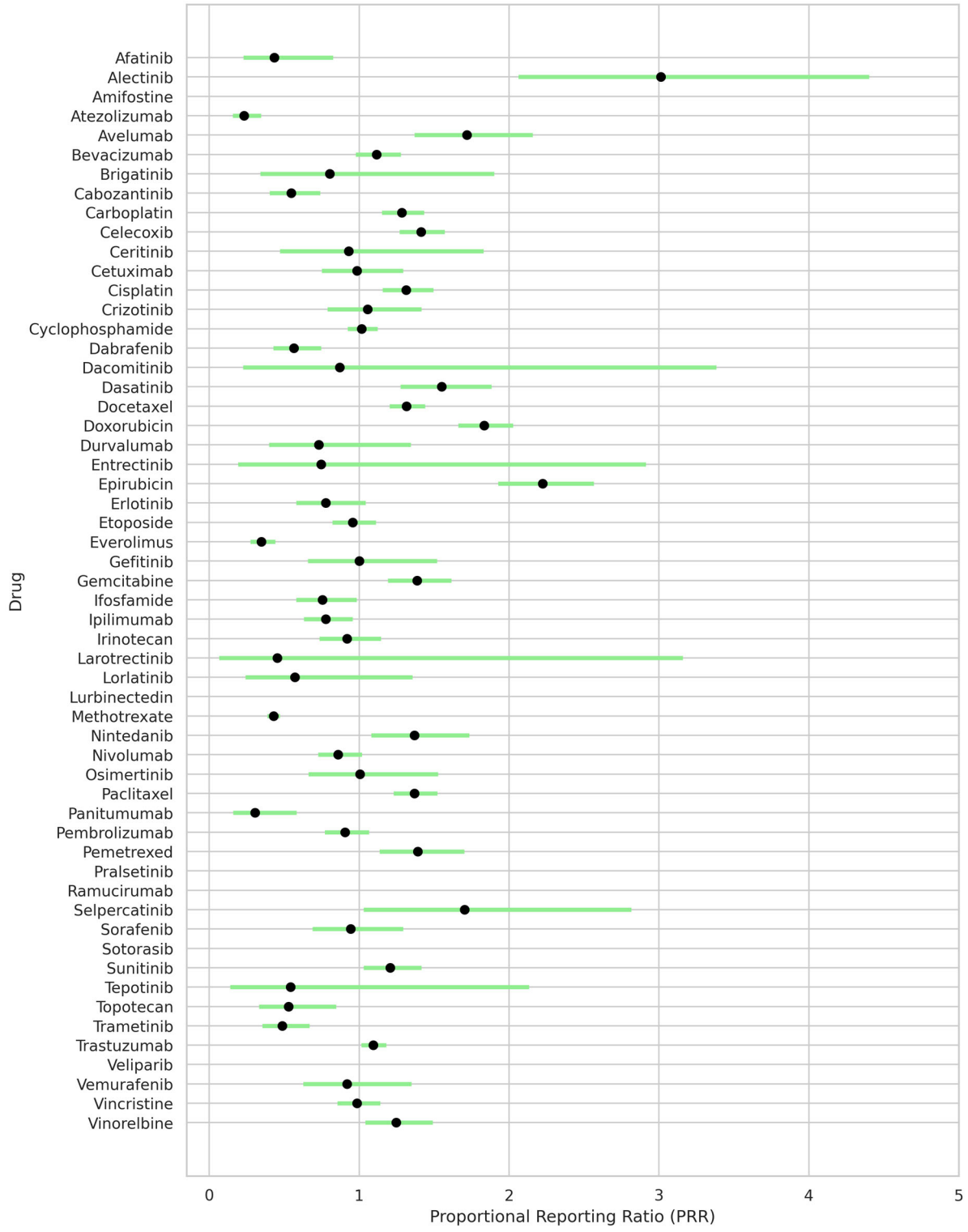

Figure 6.3: A forest plot showing the PRR values and corresponding 95% CI of each drug.

Etoposide, ifosfamide, lurbinectedin and topotecan are approved for treating SCLC, however they are also used to treat NSCLC off-label, hence they were included in the broad case definition. Table 6.5 shows the ROR and PRR values (cor. to 5 decimal places) of each drug, by narrow case and broad case definition.

Table 6.5: ROR and PRR values of each drug, by narrow case and broad case definition.

	ROR		PRR	
Drug Name	**Narrow Case (minus SCLC)**	**Broad Case**	**Narrow Case (minus SCLC)**	**Broad Case**
Afatinib	0.41765	0.42068	0.42973	0.43269
Alectinib	3.32720	3.35063	2.99266	3.01273
Amifostine	0.00000	0.00000	0.00000	0.00000
Atezolizumab	0.22175	0.22348	0.23050	0.23222
Avelumab	1.77097	1.78334	1.70786	1.71923
Bevacizumab	1.11536	1.12342	1.10922	1.11685
Brigatinib	0.79040	0.79606	0.79846	0.80390
Cabozantinib	0.53020	0.53417	0.54255	0.54641
Carboplatin	1.29410	1.30308	1.27623	1.28467
Celecoxib	1.43209	1.44172	1.40337	1.41236
Ceritinib	0.91917	0.92574	0.92276	0.92904
Cetuximab	0.97728	0.98432	0.97835	0.98506
Cisplatin	1.32578	1.33502	1.30548	1.31414
Crizotinib	1.05220	1.05975	1.04956	1.05673
Cyclophosphamide	1.01048	1.01817	1.00997	1.01729
Dabrafenib	0.54821	0.55232	0.56048	0.56449
Dacomitinib	0.85928	0.86542	0.86514	0.87102
Dasatinib	1.58192	1.59296	1.53904	1.54926
Docetaxel	1.32719	1.33616	1.30698	1.31540
Doxorubicin	1.90053	1.91220	1.82372	1.83439
Durvalumab	0.71562	0.72076	0.72556	0.73053
Entrectinib	0.73193	0.73716	0.74150	0.74655
Epirubicin	2.35152	2.36693	2.20998	2.22379
Erlotinib	0.76254	0.76810	0.77138	0.77674
Etoposide		0.95409		0.95620
Everolimus	0.33355	0.33630	0.34485	0.34756
Gefitinib	0.99293	1.00004	0.99326	1.00004
Gemcitabine	1.40405	1.41383	1.37745	1.38659
Ifosfamide		0.74578		0.75499
Ipilimumab	0.76253	0.76821	0.77139	0.77686
Irinotecan	0.90752	0.91414	0.91158	0.91791
Larotrectinib	0.43912	0.44226	0.45131	0.45438
Lorlatinib	0.55480	0.55879	0.56697	0.57084
Lurbinectedin	0.00000	0.00000	0.00000	0.00000

Methotrexate	0.40984	0.41503	0.42303	0.42810
Nintedanib	1.38564	1.39544	1.36045	1.36961
Nivolumab	0.84722	0.85356	0.85352	0.85960
Osimertinib	0.99772	1.00487	0.99783	1.00463
Paclitaxel	1.38411	1.39351	1.35935	1.36814
Panitumumab	0.29148	0.29362	0.30182	0.30392
Pembrolizumab	0.89498	0.90164	0.89954	0.90592
Pemetrexed	1.40796	1.41788	1.38094	1.39020
Pralsetinib	0.00000	0.00000	0.00000	0.00000
Ramucirumab	0.00000	0.00000	0.00000	0.00000
Selpercatinib	1.75307	1.76553	1.69177	1.70322
Sorafenib	0.93354	0.94026	0.93653	0.94296
Sotorasib	0.00000	0.00000	0.00000	0.00000
Sunitinib	1.21183	1.22045	1.19964	1.20777
Tepotinib	0.52689	0.53066	0.53918	0.54285
Topotecan		0.51688		0.52914
Trametinib	0.47031	0.47384	0.48270	0.48615
Trastuzumab	1.09060	1.09885	1.08590	1.09373
Veliparib	0.00000	0.00000	0.00000	0.00000
Vemurafenib	0.90790	0.91443	0.91195	0.91819
Vincristine	0.97836	0.98559	0.97938	0.98627
Vinorelbine	1.25247	1.26136	1.23748	1.24584

Table 6.6 demonstrates the t-test and Mann-Whitney U result of the ROR and PRR values, by narrow and broad case definition. t-test assumes that the data are normally distributed and that the variances of the two groups are equal, hence it is best suited for parametric data (i.e., data that fit a normal distribution), whereas Mann-Whitney U test does not assume a normal distribution and is a non-parametric test. It is particularly useful when the data do not meet the assumptions necessary for a t-test, such as when the data are not normally distributed or when the sample sizes are small.

With the two different set of values for ROR and PRR, t-test which assumed normal distribution showed a slight difference in t-statistic and corresponding p-value, whereas for Mann-Whitney U test, the U-statistic and p-value from the two different set of values of ROR and PRR were the same. This was because t-test compared the means of two groups and was sensitive to the actual values in the dataset as it calculated the difference between the sample means relative to the variability in the data, while Mann-Whitney U test compared the distributions of two groups as it ranked all the values from both groups together and then calculated the U statistic based on the ranks.

Table 6.6: The t-test and Mann-Whitney U result of the ROR and PRR values, by narrow and broad case definition (cor. to 5 significant figures)

	t-test		Mann-Whitney U test	
	t-statistic	**p-value**	**U-statistic**	**p-value**
ROR	-0.055008	0.95624	1320.5	0.84021
PRR	-0.055404	0.95592	1320.5	0.84021

The p-value of t-test was 0.95624 ($p \geq 0.05$) for ROR and 0.95592 ($p \geq 0.05$) for PRR, which indicated no significant difference between the narrow and broad case definitions. Similarly, the p-value of Mann-Whitney U test was 0.840, further supporting the lack of significant difference between the two case definitions.

Therefore, the slight difference in t-test results for ROR and PRR reflected minor differences in their means, while the identical Mann-Whitney U test results suggested that their overall distributions were similar. The high p-values in both tests indicated that there was no significant difference in both ROR and PRR values in both case (narrow and broad) definitions.

This sub-group analysis examined the effects of each treatment on specific sub-groups within a larger study population. It was useful in identifying whether the signals detected of an intervention varies among different groups based on age and gender. The detailed results of those detected positive signals from the sub-group analysis, stratified by age and gender were listed in Appendix VI.

Sixteen (carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, etoposide, gemcitabine, ifosfamide, irinotecan, methotrexate, paclitaxel, pemetrexed, topotecan, vincristine, vinorelbine) of the 56 drugs were chemotherapy drugs. It was observed that there was no particular trends and patterns in terms of signal detection related to age and gender. Strong positive signals detected include males of age 30-39 in docetaxel (ROR = 9.96, 95% CI = 1.82-54.37; PRR = 6.97, x^2 = 10.74), males of age 80-89 in doxorubicin (ROR = 13.28, 95% CI = 4.73-37.33; PRR = 8.37, x^2 = 40.85), males of age 80-89 vincristine (ROR = 6.64, 95% CI = 2.64-16.74; PRR = 5.23, x^2 = 21.54) and males of age 80-89 in vinorelbine (ROR = 5.97, 95% CI = 1.64-21.71; PRR = 4.83, x^2 = 9.55). Moreover, signals were only detected in females (with the exception of males aged 0-9) for topoecan.

27 (afatinib, alectinib, bevacizumab, brigatinib, cabozantinib, ceritinib, cetuximab, crizotinib, dabrafenib, dacomitinib, dasatinib, entrectinib, erlotinib, everolimus, gefitinib, larotrectinib, lorlatinib, nintedanib, osimertinib, panitumumab, selpercatinib, sorafenib, sunitinib, tepotinib, trametinib, trastuzumab, vemurafenib) of the shortlisted drugs which were targeted therapies, reported cardiovascular adverse events. Strong signals were detected in males aged 50-59 in alectinib (ROR = 13.95, 95% CI = 5.31-36.66; PRR = 8.62, x^2 = 49.44), males aged 70-79 in gefitinib (ROR = 5.24, 95% CI = 1.96-14.04; PRR = 4.36, x^2 = 13.58), females aged 60-69 (ROR = 4.10, 95% CI = 1.82-9.26; PRR = 3.57, x^2 = 13.60) as well as males aged 70-79 in osimertinib (ROR = 3.62, 95% CI = 1.25-10.51; PRR = 3.22, x^2 = 6.42), males aged 60-69 in selperacatinib (ROR = 8.53, 95% CI = 2.21-33.01; PRR = 6.27, x^2 = 13.96), females aged 80-89 in sunitinib (ROR = 3.46, 95% CI = 1.20-10.02; PRR = 3.10, x^2 = 5.97) and females aged 20-29 in vemurafenib (PRR = 20.91, x^2 = 19.91). It was also detected that certinib, dacomitinib, entrecitinib, larotrectinib, tepotinib might be gender related to females only while lorlatinib might only be related to males.

Six (atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab and pembrolizumab) of the shortlisted treatments were immunotherapies. There were no particular trends or patterns observed as a therapeutic class overall. However, strong signal was detected in females aged 90-99 in pembrolizumab (ROR = 19.91, 95% CI = 2.80-141.38; PRR = 10.46, x^2 = 17.96).

It was demonstrated in this sub-group analysis that no particular trends or patterns were observed across therapeutic class. This could be possibly due to treatments have different mechanism of actions, even within the same therapeutic class.

6.5 Discussion

Among the 56 shortlisted drugs within the UK Yellow Card system, there were 6133 cardiovascular adverse events (4.78%) reported over a total of 128,214 adverse events reports. According to the criteria of signal detection by ROR and PRR, 17 drugs and 2 drugs were positively detected respectively. There were no observations of particular higher odds or ratio of cardiovascular disease associated with certain therapeutic class.

It was also noted from the sub-group analysis that if both total adverse event and adverse event of interest were 1, then the ROR value cannot be calculated, as that was undefined. This was because with only one adverse event reported in total, there was insufficient data to compare

the occurrence of the adverse event between the drug of interest and other drugs, which is what ROR aims to quantify. However, PRR can still be calculated in this scenario as the signal detection focuses on proportions rather than odds. An example of this was positive signal detected in females aged 20-29 in vemurafenib (PRR = 20.91, x^2 = 19.91).

Cardiovascular adverse events among chemotherapy drugs used in NSCLC treatment, such as anthracyclines and platinum-based agents were reported in the UK Yellow Card System. Anthracyclines, e.g. doxorubicin and epirubicin, have been associated with dose-dependent cardiotoxicity, leading to an increased risk of heart failure, myocardial infarction, and arrhythmias (Cardinale et al., 2020). Platinum-based agents, e.g. cisplatin and carboplatin, can cause endothelial dysfunction and electrolyte imbalances, contributing to the development of cardiovascular events (Ferroni et al., 2011).

Epirubicin was one of the two drugs that detected a positive signal for cardiovascular adverse events using both methods (ROR and PRR). Epirubicin is a chemotherapy drug belonging to the anthracycline class. Previous studies had suggested that late development of chronic cardiac failure was related to epirubicin dose. Therefore, maximum cumulated doses of epirubicin (900 mg/m^2) are recommended for use (Appel et al., 2007; Ryberg et al., 1998). The mechanism of action of epirubicin involves the generation of free radicals, leading to oxidative stress and damage to cardiac cells. This damage thus results in changes to the heart muscle, which impair its function over time. Moreover, epirubicin interferes with mitochondrial function in cardiac cells, hence contributing to its cardiotoxic effects (Cersosimo and Hong, 1986; Plosker and Faulds, 1993).

Tyrosine Kinase Inhibitors (TKIs), such as EGFR inhibitors (e.g., erlotinib and gefitinib) and ALK inhibitors (e.g., crizotinib and alectinib), have significantly improved outcomes for NSCLC patients (Chang et al., 2023). But EGFR inhibitors had been reported to be associated with an increased risk of hypertension and QT interval prolongation, while ALK inhibitors were linked to bradycardia and QT prolongation. Vascular endothelial growth factor (VEGF) inhibitors, such as bevacizumab, were reported to be associated with hypertension and arterial thromboembolic events in the UK Yellow Card system.

Alectinib was one of the two drugs that detected a positive signal for cardiovascular adverse events using both methods (ROR and PRR). Alectinib is a targeted therapy drug used majorly to treat NSCLC patients whose tumours are anaplastic lymphoma kinase (ALK)-positive. It is believed that alectinib works by blocking the activity of the ALK protein, thus inhibiting the

proliferation of cancer cells and promoting their death (Paik and Dhillon, 2018). The ROR value of alectinib in this study was 3.35, which was comparable to the study by Waliany et al., in which also detected a positive signal of alectinib related to cardiovascular events using the WHO pharmacovigilance database VigiBase (Waliany et al., 2021). Another study done by Niimura et al. using VigiBase also suggested that the risk of cardiovascular disease, specifically cardiac conductive disorders, pericarditis and heart failure, may be increased in alectinib (Niimura et al., 2023). However, previous clinical studies demonstrated that alectinib largely improved progression-free survival (PFS) and overall survival in patients (Hida et al., 2017; Zhou et al., 2019). Therefore, it is important to continue monitoring the real-world use of alectinib, so that a benefit-risk balance can be maintained.

It was suggested in existing literature that there was an increased risk of cardiovascular events associated with anthracyclines in adult males' cancer population. However, despite being caused by anthracyclines, this can be due to the presence of pre-existing cardiovascular disease. It was also noted that postmenopausal females seem to be as susceptible to cardiotoxicity as males (Myrehaug et al., 2010). In another large cohort study, cancer patients who experienced cardiac events, such as heart failure and cardiac death, were significantly older, predominantly males with pre-existing cardiac risk factors and medical histories (Wang et al., 2015). This aligned with findings from this study. Positive signal was detected in males aged 80-89 in doxorubicin (ROR = 13.28, 95% CI = 4.73-37.33; PRR = 8.37, x^2 = 40.85). To date, there is no clear explanation of the sex differences in cardiac toxicity associated with anthracyclines. Several hypotheses suggested the involvement of female hormones, such as oestrogen, might reduce the risk of cardiotoxicity in females due to their cardioprotective effects. Oestrogen has been suggested to improve endothelial function and increase the expression of antioxidant enzymes, which can mitigate oxidative stress, a key mechanism by which anthracyclines cause cardiac damage (Cannatà et al., 2020; Kararigas et al., 2012). Additionally, males and females differ in body composition, e.g. fat and muscle distribution, which can affect drug distribution and metabolism. For instance, variations in body fat percentage may affect how lipophilic drugs, such as anthracyclines, are distributed in the body, which potentially lead to higher levels of the drug in plasma and tissues of males than females (Lagranha et al., 2010).

Research using a pharmacovigilance database indicated that older females could be risk factors for immunotherapy-associated myocarditis. However, these results might be skewed by several confounding factors, such as bias towards reporting only unusual or severe adverse events and the lower number of women treated for non-small cell lung cancer (Zamami et al.,

2019). Other studies suggested that female patients had a higher risk of immunotherapy-related myocarditis, but these findings lacked consistent confirmation (Wilcox et al., 2022). In this study, there were no particular trends or patterns observed in sex or age difference across different immunotherapies.

6.6 Summary

- Seventeen drugs (namely alectinib, avelumab, carboplatin, celecoxib, cisplatin, dasatinib, docetaxel, doxorubicin, epirubicin, gemcitabine, nintedanib, paclitaxel, pemetrexed, selpercatinib, sunitinib, trastuzumab, and vinorelbine) exhibited a ROR value (lower limit of the 95% CI) of ≥1, thus indicating a positive signal.
- However, based on the criteria for positive signal detection by PRR, only alectinib (PRR = 3.01, x^2 = 32.36, number of cases = 23) and epirubicin (PRR = 2.22, x^2 = 118.91, number of cases = 173) showed cardiovascular adverse events signals, in contrast to the 17 drugs identified by ROR analysis.
- Alectinib demonstrated the highest signal for potential cardiovascular adverse events among the analysed drugs, evidenced by both the highest ROR and PRR values.

Chapter 7

General Discussion and Conclusion

The field of oncology has witnessed remarkable advancements in the treatment of cancer over the past few decades. Improved diagnostic techniques, targeted therapies, immunotherapies, and precision medicine approaches have revolutionised cancer management, leading to increased survival rates and improved quality of life for patients. However, as cancer treatments become more effective, a growing concern has emerged regarding their potential cardiovascular adverse effects (Albini et al., 2010; Koutsoukis et al., 2018).

The trio of clinical trials, pharmacoepidemiology and pharmacovigilance play a pivotal role in the lifecycle management of pharmaceutical products – from pre-approval research to post-marketing surveillance. Each domain contributes uniquely to understanding and assessing the efficacy, benefits and risks associated with pharmaceuticals. Clinical trials are the gold standard in determining whether a new treatment is safe and effective in humans before it is made available to the public. It is usually conducted in a controlled and regulated environment (Umscheid et al., 2011). Pharmacoepidemiology provides real-world evidence and helps to identify long-term effects, benefits and risks of drugs, including rare side effects and interactions with other drugs or diseases that may not be evident in clinical trials (Montastruc et al., 2019). Pharmacovigilance enables detection of previously unrecognised adverse reactions or changes in the patterns of adverse events, which may influence the understanding of a drug's benefit-risk balance (Härmark and van Grootheest, 2008).

By summarising evidence in the clinical trial included in the systematic review (Study 1, Chapter 3), it consolidated the findings of different clinical trials, thus giving an overview which helps understanding the overall trends and findings. Feasibility assessment (Study 2, Chapter 4) was used to shortlist suitable databases to use for real-world studies. By comparing data from clinical trials (from systematic review), pharmacoepidemiology studies (Study 3, Chapter 5) and pharmacovigilance reports (Study 4, Chapter 6), this chapter aims to develop a more comprehensive understanding of the association between NSCLC treatments and cardiotoxicities.

Table 7.1 shows all the chemotherapy drugs, by therapeutic class, included in each of the studies. The abbreviations RCT (SR), PE and PV refer to drugs included in the systematic review, the UK DEFINE database (a pharmacoepidemiology study) and the UK Yellow Card System (a pharmacovigilance study), respectively.

Table 7.1: Chemotherapy drugs included in the studies.

Therapeutic Class	Drug	ATC/DDD	RCT (SR)	PE	PV
Alkylating Agents	Cyclophosphamide	L01AA01	✓	✓	✓
	Ifosfamide	L01AA06	✓		✓
Anthracycline	Amrubicin	L01DB10	✓		
	Doxorubicin	L01DB01		✓	✓
	Epirubicin	L01DB03	✓	✓	✓
Anti-metabolite Agents	Gemcitabine	L01BC05 – Pyrimidine analogues	✓	✓	✓
	Methotrexate	L01BA01 / L04AX03		✓	✓
	Pemetrexed	L01BA04 – folic acid analogues	✓	✓	✓
Anti-microtubule Agents (Taxanes)	Docetaxel	L01CD02	✓	✓	✓
	Paclitaxel	L01CD01	✓	✓	✓
Anti-mitotic Agents	Vincristine	L01CA02		✓	✓
	Vinorelbine	L01CA04	✓	✓	✓
Platinum Compounds	Carboplatin	L01XA02	✓	✓	✓
	Cisplatin	L01XA01	✓	✓	✓
Topoisomerase Inhibitors	Etoposide	L01CB01			✓
	Irinotecan	L01CE02			✓
	Topotecan	L01CE01			✓
Transcription Inhibitor	Lurbinectedin	L01XX69			✓

Previous research suggested that cyclophosphamide was associated with arrhythmias, cardiac tamponade and cardiac failure (Madeddu et al., 2016; Martin et al., 2017). Although cyclophosphamide was included in Chapter 3, cyclophosphamide was used alongside doxorubicin and the main aim was to assess whether doxorubicin might cause cardiotoxicity in both eligible studies of the systematic review. According to the results from the DEFINE database (Chapter 5), cyclophosphamide was suspected to be associated with hypertension, cardiac arrest and cardiac failure, while the UK Yellow Card system (Chapter 6) reported 4.86% cardiovascular events. Common CV adverse events included hypotension (7.35%), cardiac failure (7.35%), venoocclusive disease (5.64%), tachycardia (5.39%), hypertension (5.39%), cardiac arrest (4.65%) and atrial fibrillation (4.65%). However, positive signals were not detected by both reporting odds ratio (ROR) (1.02, 95% CI = 0.92 – 1.13) and proportional reporting ratio (PRR) (1.02, x^2 = 0.12) according to their thresholds. Therefore, only to a certain degree, results from this study supported previous clinical findings in cyclophosphamide-related cardiotoxicity.

As mentioned in General Introduction (Chapter 1), anthracyclines are well known to be associated with cardiotoxicity. This aligned with the findings in this research, in both clinical trials (Chapter 3) and real-world studies (Chapter 5 and Chapter 6). According to findings in the systematic review (Chapter 3), there was a three-fold increase in the cardiotoxicity frequency in the combination of gemcitabine and epirubicin, compared to the combination of gemcitabine and cisplatin (Wachters et al., 2003). It was also demonstrated using the DEFINE database (Chapter 5) that epirubicin was associated with verapamil, which are used to treat arrhythmia and hypertension. Positive signals were detected by both ROR (2.37, 95% CI = 2.02 – 2.78) and PRR (2.22, x^2 = 118.91) using the UK Yellow Card system (Chapter 6). Additionally, existing clinical studies suggested that epirubicin-associated cardiotoxicity only occurred when high doses of doxorubicin were given. However, in order to achieve the expected clinical response, such high doses of doxorubicin were needed (Zamorano et al., 2017). Therefore, the benefit-risk balance of using epirubicin needs to be carefully considered.

Anti-metabolite agents, i.e. gemcitabine and pemetrexed, were both included in all three studies (Chapter 3, 5 and 6). Gemcitabine was a widely used drug in combination of other anticancer treatments; cardiotoxicity of selected combination of treatments included in the systematic review is presented in Table 7.2. In contrast, the frequency of pemetrexed-related cardiotoxicity was relatively low when compared against other arms / treatments such as crizotinib, in clinical trials included in the systematic review (Chapter 3).

Table 7.2: Types of cardiotoxicities that are associated with gemcitabine and selected combination of treatments involving gemcitabine.

	Gemcitabine	**Gem & Carboplatin**	**Gem & Cisplatin**	**Gem & Docetaxel**	**Gem & Epirubicin**	**Gem & Paclitaxel**	**Gem & Vinorelbine**
Arrhythmia		✓	✓				
Atrial Fibrillation			✓				
Cardiotoxicity (Grade 1–4)	✓			✓		✓	✓
Hypertension			✓				
Ischaemia		✓					
Myocardial Infarction					✓		
Sinus Tachycardia			✓				

Based on the results from the DEFINE database (Chapter 5), gemcitabine was most associated with apixaban (r = 0.61) which is used to treat atrial fibrillation. In addition, a positive signal was detected in the analysis of gemcitabine using ROR (1.41, 95% CI = 1.20 – 1.66) within the UK Yellow Card System (Chapter 6). A positive signal was also detected in pemetrexed using ROR (1.42, 95% CI = 1.14 – 1.76). In chapter 5, it was demonstrated that ramipril (which is used to treat hypertension, cardiac arrest and failure) was the most associated shortlisted cardiology drug with pemetrexed, however the correlation between the two was weak (r = 0.23). Although there was a similar strength of signal of CV events detected in gemcitabine and pemetrexed using the pharmacovigilance study (Chapter 6), the types of cardiotoxicities associated with the two drugs were different as suggested by the systematic review (Chapter 3) and pharmacoepidemiology study (Chapter 5). This demonstrated that even within the same therapeutic class, the degree / type of cardiotoxicity could be different.

Anti-microtubule agents, such as docetaxel and paclitaxel, are widely used to treat various cancers. Existing studies suggested that in combination with anthracyclines, docetaxel had a relatively lower risk of cardiotoxicity than that of paclitaxel (Cardinale et al., 2020; Salvatorelli et al., 2006). This was supported by signals detected using the UK Yellow Card System (Chapter 6) as the ROR for docetaxel and paclitaxel were 1.34 (95% CI = 1.21 – 1.47) and 1.39 (95% CI = 1.24 – 1.56) respectively. Findings from the DEFINE database (Chapter 5) further suggested that paclitaxel could be associated with atrial fibrillation (Paclitaxel-Apixaban, r = 0.84), while docetaxel could be associated with arrhythmia and hypertension (Docetaxel-Verapamil, r = 0.88). However, a clinical trial result included in the systematic review (Chapter 3) suggested otherwise, as the frequency of cardiotoxicity of docetaxel with the use of carboplatin was higher than that of paclitaxel-carboplatin (Saito et al., 2003). This could be potentially due to the influence of carboplatin, which is a platinum compound, instead of anthracyclines.

According to results obtained from the systematic review (Chapter 3), with the combined use of pemetrexed, hypotension was the only type of cardiotoxicity reported in both cisplatin and carboplatin. In addition, cisplatin doubled the frequency of hypotension compared to that of carboplatin (Choy et al., 2013). However, results from the DEFINE database (Chapter 5) suggested that carboplatin and cisplatin could be associated with more types of cardiovascular events, including arrhythmia, cardiac arrest, cardiac failure, hypertension and thromboembolic events. The highest correlated drug-drug pair for carboplatin and cisplatin were rivaroxaban and lisinopril, respectively. Carboplatin was strongly associated with arterial/venous

thromboembolic events (Carboplatin-Rivaroxaban, r = 0.82), while cisplatin was highly associated with hypertension, cardiac arrest and failure (Cisplatin-Lisinopril, r = 0.75). The ROR values obtained from the UK Yellow Card System (Chapter 6) supported the possible association of these two drugs with cardiotoxicity, with positive signals detected in both – cisplatin (1.34, 95% CI = 1.16 – 1.53) and carboplatin (1.30, 95% CI = 1.16 – 1.46).

Table 7.3 shows all the TKIs, by therapeutic class, included in each of the study.

Table 7.3: Tyrosine kinase inhibitors (TKIs) included in the studies.

Therapeutic Class	Drug	ATC/DDD	RCT (SR)	PE	PV
Anaplastic Lymphoma Kinase (ALK) Inhibitor	Alectinib	L01ED03	✓		✓
	Brigatinib	L01ED04	✓		✓
	Certinib	L01ED02			✓
	Crizotinib	L01ED01	✓		✓
	Lorlatinib	L01ED05			✓
Angiogenesis Inhibitor	Cabozantinib	L01EX07			✓
	Nintedanib	L01EX09	✓	✓	✓
	Sorafenib	L01EX02	✓		✓
	Sunitinib	L01EX01	✓		✓
BCR-ABL Inhibitors	Dasatinib	L01EA02			✓
BRAF Inhibitors	Dabrafenib	L01EC02			✓
	Vemurafenib	L01EC01			✓
Epidermal Growth Factor Receptor (EGFR) Inhibitor	Afatinib	L01EB03		✓	✓
	Dacomitinib	L01EB07			✓
	Erlotinib	L01EB02	✓	✓	✓
	Gefitinib	L01EB01	✓	✓	✓
	Osimertinib	L01EB04	✓	✓	✓
KRAS G12C Inhibitor	Sotorasib	L01XX73			✓
Mitogen-activated protein kinase (MEK) inhibitors	Selumetinib	L01EE04	✓		
	Trametinib (GSK1120212)	L01EE01	✓		✓
MET inhibitor	Tepotinib	L01EX21			✓
mTOR Inhibitor	Everolimus	L01EG02 / L04AA18			✓
NTRK and ROS1 Inhibitor	Entrectinib	L01EX14			✓
Poly (ADP-ribose) polymerase (PARP) inhibitors	Veliparib	L01XK05	✓		✓
RET Inhibitor	Pralsetinib	L01EX23			✓
	Selpercatinib	L01EX22			✓
TRK inhibitor	Larotrectinib	L01EX12			✓
VEGFR (Vascular Endothelial Growth Factor) inhibitors	Bevacizumab	L01FG01	✓	✓	✓
	Ramucirumab	L01FG02			✓

Erlotinib, gefitinib and osimertinib are all epidermal growth factor receptor (EGFR) inhibitors. Although erlotinib, gefitinib and osimertinib were all included in the systematic review (Chapter 3), there were no direct comparison among the three drugs as meta-analysis was not conducted. Some common cardiovascular events associated with the three drugs included, but not limited to, hypertension, myocardial infarction, QT prolongation and cardiac failure. Results from the DEFINE Database (Chapter 5) suggested that erlotinib was positively correlated with arrhythmia, cardiac arrest, cardiac failure, ischaemia, and hypertension with the strongest correlation in ischaemia and hypertension (Erlotinib-Atenolol, r = 0.81). It was found that gefitinib was only positively correlated with one drug, i.e. alteplase (r = 0.55), which indicated potential association with myocardial infarction. Osimertinib was associated with arterial/venous thromboembolic event, atrial fibrillation, cardiac arrest, cardiac failure, hypertension and myocardial infarction. The strongest correlation of osimertinib was with atrial fibrillation (Osimertinib-Apixaban, r = 0.91). However, signals were not detected for all three drugs using the UK Yellow Card System (Chapter 6) as all their lower limits of the 95% CI were below 1. This contradicted with results of another pharmacovigilance study by Anand et al. using the U.S. Food and Drug Administration Adverse Events Reporting System (FAERS) database. Positive signals were detected in osimertinib, with association to increased atrial fibrillation, cardiac failure and QT prolongation, when compared to other EGFR-TKIs (including erlotinib and gefitinib) and all other drugs in FAERS (Anand et al., 2019).

Table 7.4 shows all the immunotherapies, by therapeutic class, included in each of the study. Different from chemotherapies and TKIs, no immunotherapies were included across all three studies.

Table 7.4: Immunotherapies included in the studies.

Therapeutic Class	Drug	ATC/DDD	RCT (SR)	PE	PV
Programmed cell death protein 1/death ligand 1 (PD-1/PDL-1) Inhibitors	Atezolizumab	L01FF05		✓	✓
	Avelumab	L01FF04	✓		✓
	Durvalumab	L01FF03			✓
	Nivolumab	L01FF01			✓
	Pembrolizumab	L01FF02		✓	✓
CTLA-4 Inhibitor	Ipilimumab	L01FX04			✓
Epidermal Growth Factor Receptor (EGFR) Inhibitor	Cetuximab	L01FE01	✓		✓
	Necitumumab	L01FE03	✓		
	Panitumumab	L01FE02	✓		✓
Human Epidermal Growth Factor Receptor 2 (HER2) Inhibitors	Trastuzumab	L01FD01	✓		✓
mRNA-based	CV9201	N/A	✓		

Among all immunotherapies, only the analyses for avelumab and trastuzumab detected a positive signal using the UK Yellow Card System (Chapter 6), with a ROR value of 1.78 (95% CI = 1.39 – 2.28) and 1.10 (95% CI = 1.01 – 1.19), respectively. This aligned with the results of a phase 1b trial by Choueiri et al., which suggested that avelumab was associated with autoimmune myocarditis (Choueiri et al., 2018). Another phase III clinical trial by Keefe suggested cardiotoxicity as an adverse event of trastuzumab (Keefe, 2002). Other existing studies also suggested that there was a higher risk of cardiotoxicity of trastuzumab when used in combination with anthracyclines (Mohan et al., 2018; Nemeth et al., 2017). Trastuzumab-associated cardiotoxicity is believed to result from its effect on HER2/neu receptors, as described in General Introduction (Chapter 1). However, unlike cardiotoxicity associated with anthracyclines, trastuzumab-related cardiotoxicities are generally regarded to be reversible, especially if detected early and managed appropriately.

Other pharmacovigilance studies using VigiBase suggested that myocarditis related to immunotherapies exhibited a mortality rate up to 50%. Furthermore, the incidence of myocarditis in patients undergoing immunotherapy treatment was elevenfold higher compared to non-immunotherapy-treated patients (Hu et al., 2019; Salem et al., 2018).

7.1 Strengths of the Study

By including a wide range of clinical studies and employing rigorous methodologies for selection and appraisal, the systematic review (Chapter 3) minimised bias and ensured a high degree of reliability and validity in the findings.

By following a structured framework when conducting the feasibility assessment (Chapter 4), various aspects of potential databases were systematically evaluated, including the scope, data quality, accessibility, and relevance to the research question. This structured approach reduced the risk of overlooking critical factors, such as completeness of data, the presence of longitudinal information, and the availability of variables of interest. Therefore, this ensured a thorough assessment, which led to a more informed decision-making process on which database was the most suitable for the specific research question.

The UK DEFINE database (Chapter 5) was tailored specifically for analysing secondary care medication data. Its specialisation enabled the in-depth insights into medication usage patterns

and trends at regional and national level and also evaluated the impact of certain interventions (Hey, 2022).

The UK Yellow Card System (Chapter 6) allowed healthcare professionals, patients, and caregivers to report ADRs directly. This enriched the data pool with more observations and reported adverse events, thus increasing the volume and diversity of data available for analysis. This early warning system can also lead to rapid interventions, such as updating safety information and even withdrawing drugs from the market to protect public's health. Reports were collected from a range of demographic, including different ages, genders, ethnicities, and patients with multiple comorbidities. This helped understands how different groups react to drugs, which is often a limitation in clinical trials. It also helped inform NICE guidelines as it can identify potential safety issues that might not have been evident during clinical trials. Information from pharmacovigilance activities can lead to further clinical trials, especially if new safety concerns arise or additional data are needed on specific populations or dosing strategies.

7.2 Limitations of the Study

The systematic review (Chapter 3) analysed data collected from clinical trials (i.e. aggregate data instead of individual patients' data), hence it was difficult to tell whether one person suffered from more than one type of cardiotoxicities. Also, based on the eligibility criteria, some of the studies which did not match the required study design (i.e. single arm study) were excluded even though counts of cardiotoxicity were recorded, so this might have caused selection bias of studies. In addition, the authors of some included publications mentioned that the incidences of cardiotoxicity were believed to be unrelated to the anticancer treatments. Therefore, their opinions were adopted, and those cardiotoxicities thought not to be associated with NSCLC treatments were not included in this systematic review, which might cause reporting bias. Moreover, due to the limitations of the eligibility criteria, the drugs included in the eligible studies might not necessarily be the most commonly used first/second-line treatments of NSCLC. Another limitation was that differences in the duration of follow-up period among studies may potentially result in inaccurate representation of the frequency of cardiotoxicity associated with corresponding anticancer drug. In some studies, only adverse events with an overall incidence of ≥10% were reported, thus might cause reporting bias. One of the limitations observed was that most cardiotoxicities reported were symptomatic cardiotoxicities, whereas some expected asymptomatic cardiotoxicities such as QT

prolongation were not commonly reported, thus it was suggested that systematic cardiac monitoring should be carried out and corresponding data should be reported. Lastly, by restricting our literature search only to studies reported in English, other relevant studies might have been missed.

A possible limitation of the feasibility assessment (Chapter 4) was that despite the systematic nature of the SPIFD framework, the assessment process can still be subject to personal biases and interpretations as the weighting and importance assigned to different criteria may vary among researchers, thus influencing the outcome of the database selection process.

One of the limitations of the DEFINE database (Chapter 5) was that it only captured the usage of drugs, so any suspected correlation can happen purely by random as cardiology drugs can be used for other reasons and were not limited just to the use of non-small lung cancer patients. Another limitation was that some of the therapies were used to treat multiple cancers, and as it was not possible to capture the usage of that drug by NSCLC patients only, so it might not be accurate to describe the correlation as NSCLC-associated. Moreover, NSCLC treatment decisions for each patient is normally tailored to one's specific needs. Factors, e.g. the type and stage of cancer, and the presence of pre-existing cardiovascular comorbidities are all considered when developing a treatment plan (Peppercorn et al., 2011). Therefore, DDD was not available for all oncology drugs, hence causing a limitation to this study as it was not possible to divide NSCLC drugs by defined daily dose (DDD) to calculate the total number of patients who used that specific drug.

As with other pharmacovigilance databases, a significant limitation of the UK Yellow Card System (Chapter 6) was the underreporting of ADRs. Factors such as lack of awareness, perceived inconvenience, or uncertainty about what constituted of an ADR can lead to fewer reports than the actual occurrence of adverse effects; hence delaying the identification of potential drug safety issues (García-Abeijon et al., 2023). If adverse effects are underreported, the drug might appear safer than it actually is, as signals are not detected, and thus skewing the perceived benefit-risk ratio. This can mislead healthcare providers and patients, which can affect treatment decisions. In addition, being a spontaneous reporting system, it was susceptible to various biases. For instance, newer drugs might be over-reported due to increased attention whereas well-established drugs might be under-reported as their side effects were more well-known. There was also a potential for incomplete or inaccurate data since the reporting did not undergo stringent validation (Kasliwal, 2012). Moreover, establishing a

suspected causality between a drug and an adverse reaction based on the UK Yellow Card System can be complex because other factors, e.g. underlying diseases, concomitant medications, or lifestyle habits, may also contribute to an observed ADR. It was also not possible to calculate incidence and prevalence rates as it provided limited information about the number of patients who consumed the drug but did not experience an ADR. Furthermore, it was noted that the public were encouraged to submit a Yellow Card report even if it was just a suspicion that the drug might have caused the ADR, hence the ADRs included in the report might not necessarily be caused by the said drug (Alomar et al., 2020).

7.3 Future Work

With the rapid development of big data, it will be useful to utilise network database for real-world evidence. By using a common data model, network databases facilitate interoperability among different data sources. This standardisation simplifies the analysis process across multiple databases, thus enhancing the efficiency and comparability of research findings (Observational Health Data Sciences and Informatics, 2021). Network databases also aggregate large amount of data from various sources, hence increasing the generalisability and applicability of real-world evidence. Future work could include using The Observational Health Data Sciences and Informatics (OHDSI) network. It is a collaborative, multi-stakeholder, interdisciplinary initiative that aims to enhance the value of health data through large-scale analytics (Hripcsak et al., 2015). The OHDSI is currently the world's largest distributed data network with more than 331 data sources consisting of over 2.1 million patients records among 34 countries (Reich et al., 2024). OHDSI network operates a distributed framework, where each participating data partner maintains complete control over their own patient-level data, while adhering to their specific institutional data governance policies. Developers within the OHDSI community have established an extensive suite of open-source analytics tools based on the OMOP Common Data Model (CDM). These tools are designed to address three main areas: 1) Clinical characterisation, which involves analysing disease progression, treatment patterns, and quality improvement measures; 2) Population-level effect estimation, which utilises causal inference techniques for monitoring the safety of medical products and assessing comparative effectiveness; and 3) Patient-level prediction, which leverages machine learning algorithms to advance precision medicine and intercept diseases at early stages (Observational Health Data Sciences and Informatics, 2021). In addition, the OHDSI team has developed various applications, such as statistical tools programmed in R and

Python, that promote the use of the OMOP CDM, enhance data quality, and support collaborative research across the OHDSI network. All these resources are open source and freely accessible on GitHub. OHDSI's dedication to open science and the provision of open-source tools have greatly accelerated progress in observational research across its network (Observational Health Data Sciences and Informatics, 2021).

Moreover, other future work could include the use of ICD-11. The ICD-10 was used in this study because at the time of data extraction, ICD-10 is still the ICD version used by NHS and thus relevant databases. However, the latest version of the ICD, i.e. ICD-11, was adopted by the 72nd World Health Assembly in May 2019 and came into effect on 1st January 2022 with transitional arrangements for WHO Member States for at least five years (Harrison et al., 2021). According to the newest update by NHS, it is expected that ICD-11 will not be made compulsory for use across the NHS in England before April 2026.

The transition from ICD-10 to ICD-11 is a significant update, which reflects advances in health science, emerging health trends, and the need for greater specificity in health data analytics. In ICD-10, a diagnosis is usually represented by a single code while ICD-11 enables the combination of codes to create clusters, hence offering enhanced expressive capability beyond what is possible with a single category alone (Harrison et al., 2021). In terms of oncology, ICD-O is used to supplement ICD-10. A full ICD-O code consists of 10 digits or characters, which are used to identify the topographic site (4 characters), histological type (4 digits), behaviour (1 digit), and grade or differentiation (1 digit). The topography code is based on the malignant neoplasm section of the ICD-10, ranging from C00 to C80 (World Health Organization, 2013). However, ICD-O is not always available within databases, hence making it difficult to differentiate NSCLC cases from all lung cancer cases (ICD-10: C34) without the histological and behaviour codes. The introduction of stem codes, extension codes, pre-coordination, post-coordination and cluster codes in ICD-11 can potentially solve this problem. The histopathology and behaviour of neoplasm can be identified using stem codes while extension code provide further specific information (World Health Organization, 2023). For example, in ICD-11, SCLC can be identified using the stem code 2C25.1 while the main types of NSCLC – adenocarcinoma, squamous cell carcinoma, large cell carcinoma – can be identified using the stem codes 2C25.0, 2C25.2 and 2C25.3, respectively. Therefore, this

change can help greatly in future work that aims to identify NSCLC cases using real-world data.

7.4 Conclusions

To conclude, the systematic approach of the feasibility assessment identified an appropriate database that aligns with the specific research questions and objectives. The combined findings of the systematic review, the pharmacoepidemiology study and the pharmacovigilance report have provided a better understanding of the types and degree of cardiotoxicity associated with some NSCLC drugs. Although some cardiac adverse events are reversible, further research on identifying patients at risk for potentially serious cardiovascular events as well as implementation of early detection and screening strategies are needed to improve the management of NSCLC treatment, taking into account the benefits and risks.

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Publications and Presentations

Publications

2023	Chan SHY, Khatib Y, Webley S, Layton D, Salek S. Identification of cardiotoxicity related to non-small cell lung cancer (NSCLC) treatments: A systematic review. Frontiers in Pharmacology. 2023;14. Available from: https://doi.org/10.3389/fphar.2023.1137983
2020	Chan SHY, Khatib Y, Webley S, Layton D, Salek S. Identification of cardiotoxicity related to cancer treatments: A systematic review. PROSPERO 2020 CRD42020191760. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020191760

Abstract Publication

2021	Chan SHY, Khatib Y, Webley S, Layton D, Salek S. ISPE Annual Meeting Abstracts. Pharmacoepidemiology and Drug Safety. 2021;30(S1):129.

Oral Presentations

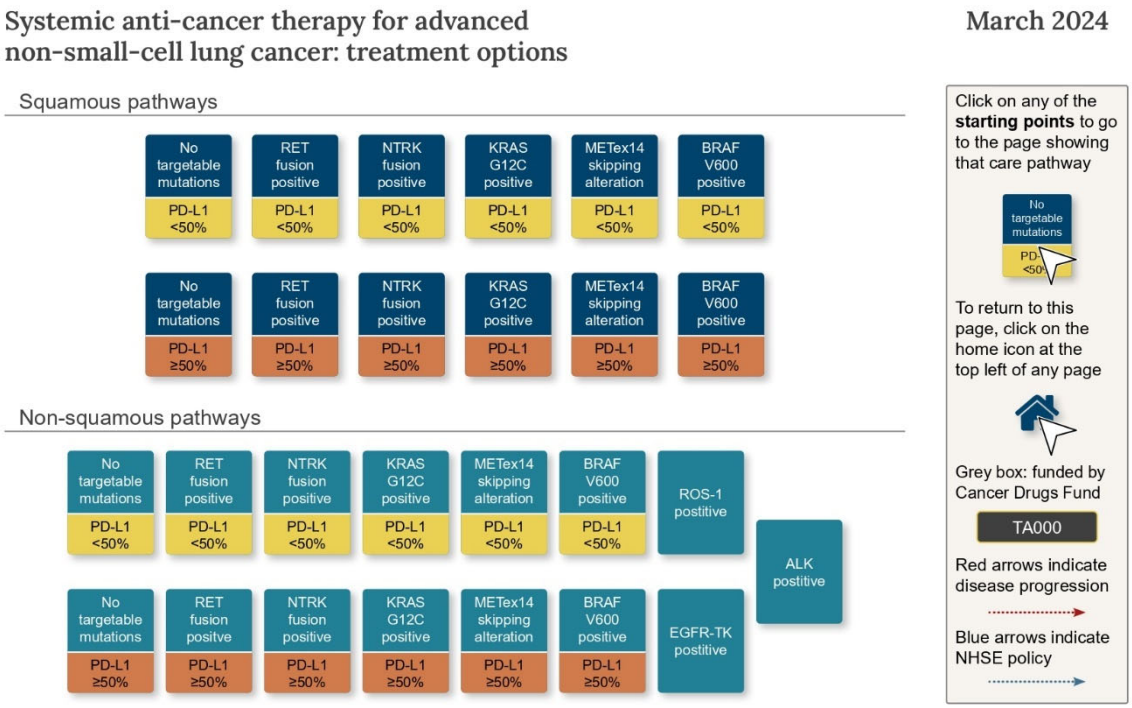
9 February 2023	**University of Hertfordshire (UH) Pharmacy Practice Research Group Meeting 2023.** Virtual.	Assessing the association between cardiotoxicity and non-small cell lung cancer (NSCLC) treatments in the United Kingdom.
5 June 2022	**University of Hertfordshire (UH) Postgraduate Pharmacy Practice Audit and Research Showcase 2022.** Hatfield, UK.	Identification of Cardiotoxicity related to Non-Small Cell Lung Cancer (NSCLC) Treatments: A Systematic Review.
10 January 2022	**University of Hertfordshire (UH) Postgraduate Seminar 2022.** Virtual.	Development of algorithms for identification and mitigation of cardiotoxicity related to cancer treatments.

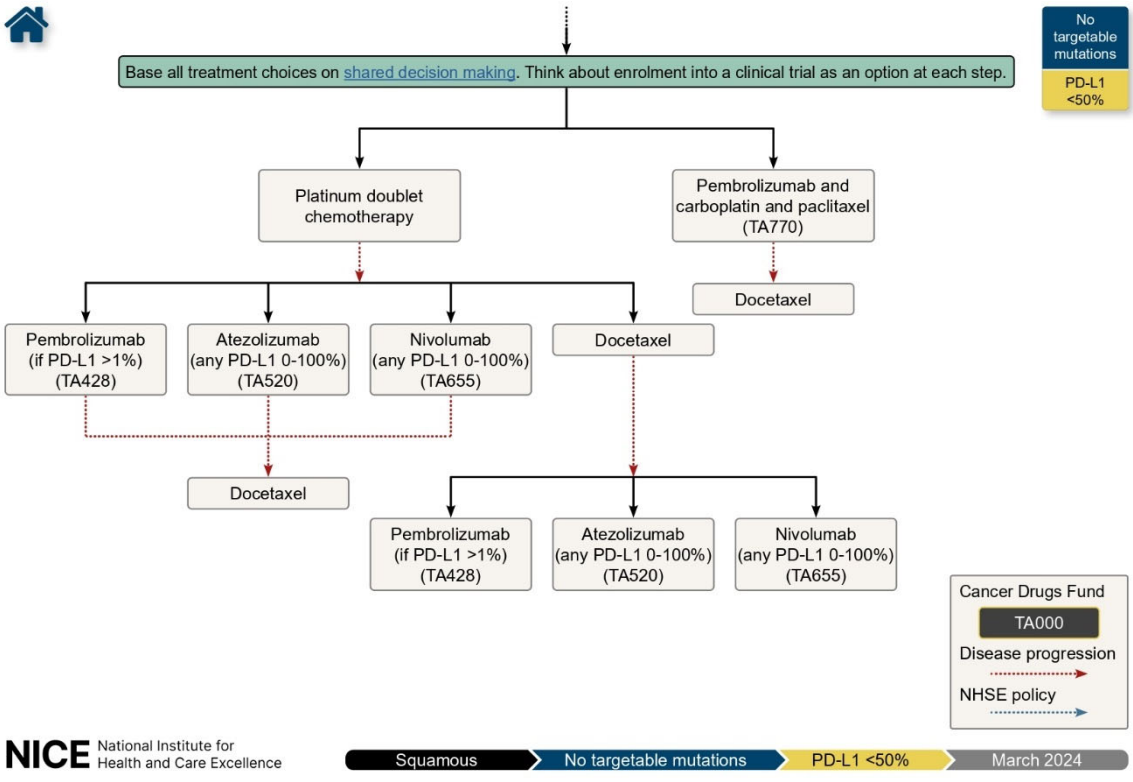
Poster Presentations

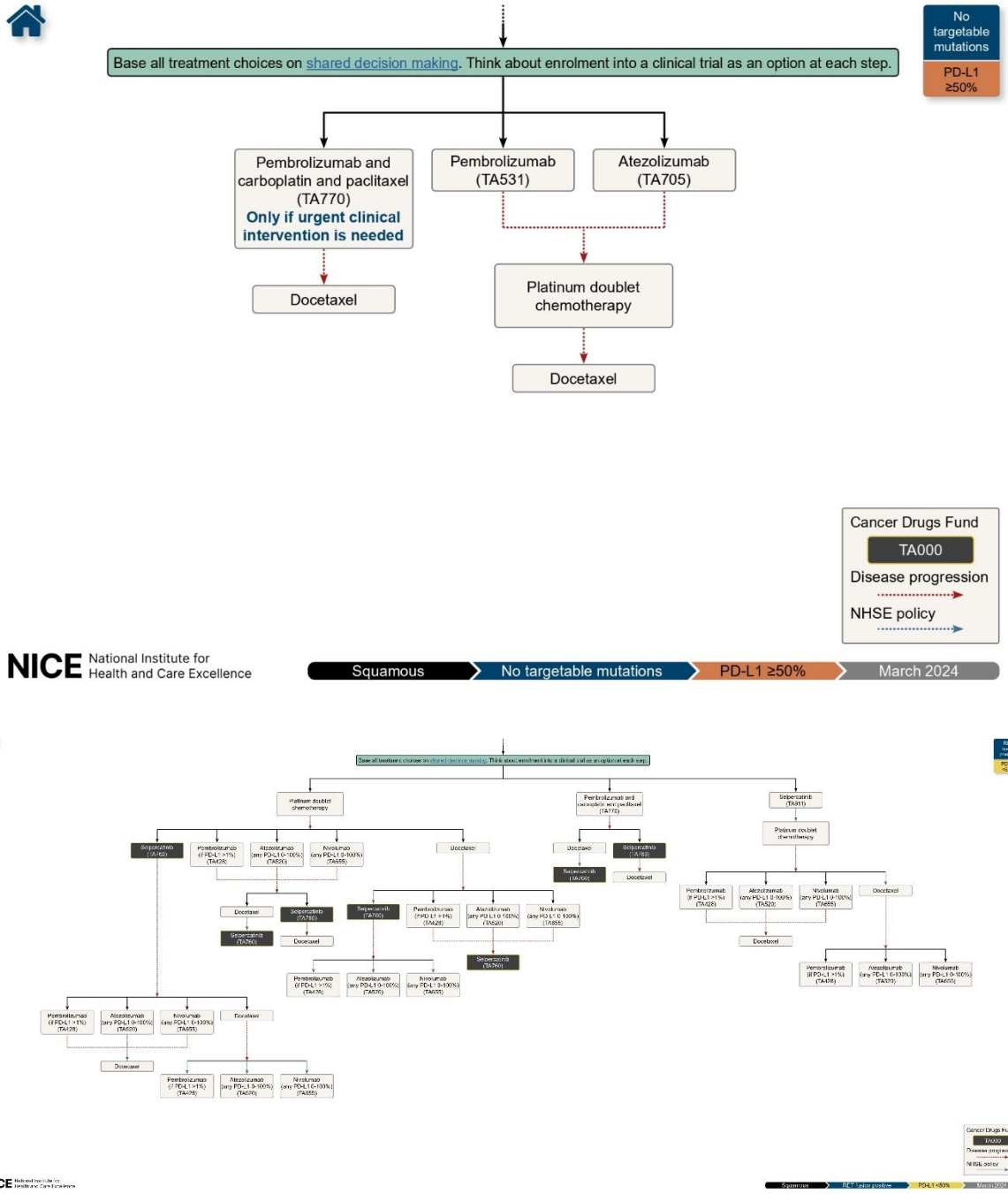
21 June 2022	**University of Hertfordshire (UH) Faculty of Life and Medical Sciences Annual Research Conference 2022.** Hatfield, UK.	Identification of Cardiotoxicity related to Non-Small Cell Lung Cancer (NSCLC) Treatments: A Systematic Review.
23-25 August 2021	**37th International Conference on Pharmacoepidemiology & Therapeutic Risk Management.** Virtual.	A Systematic Review of Non-Small Cell Lung Cancer Treatment-Related Cardiotoxicity.

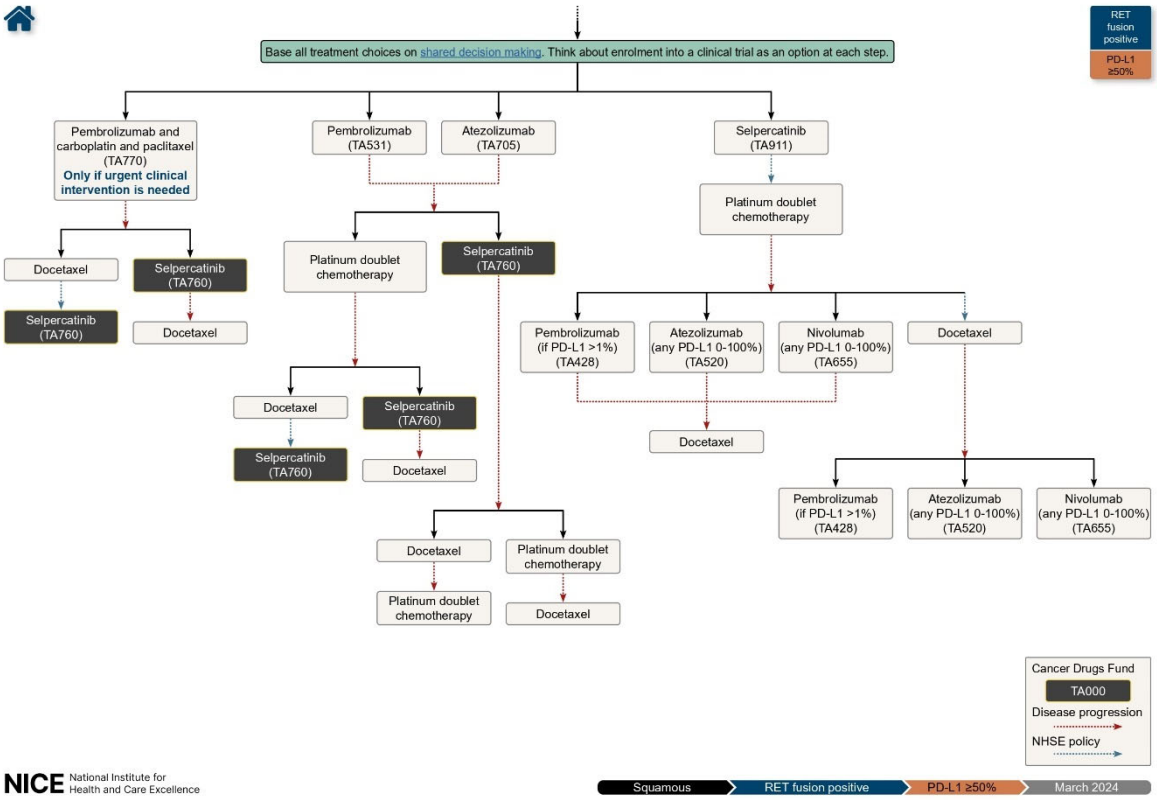
Appendices

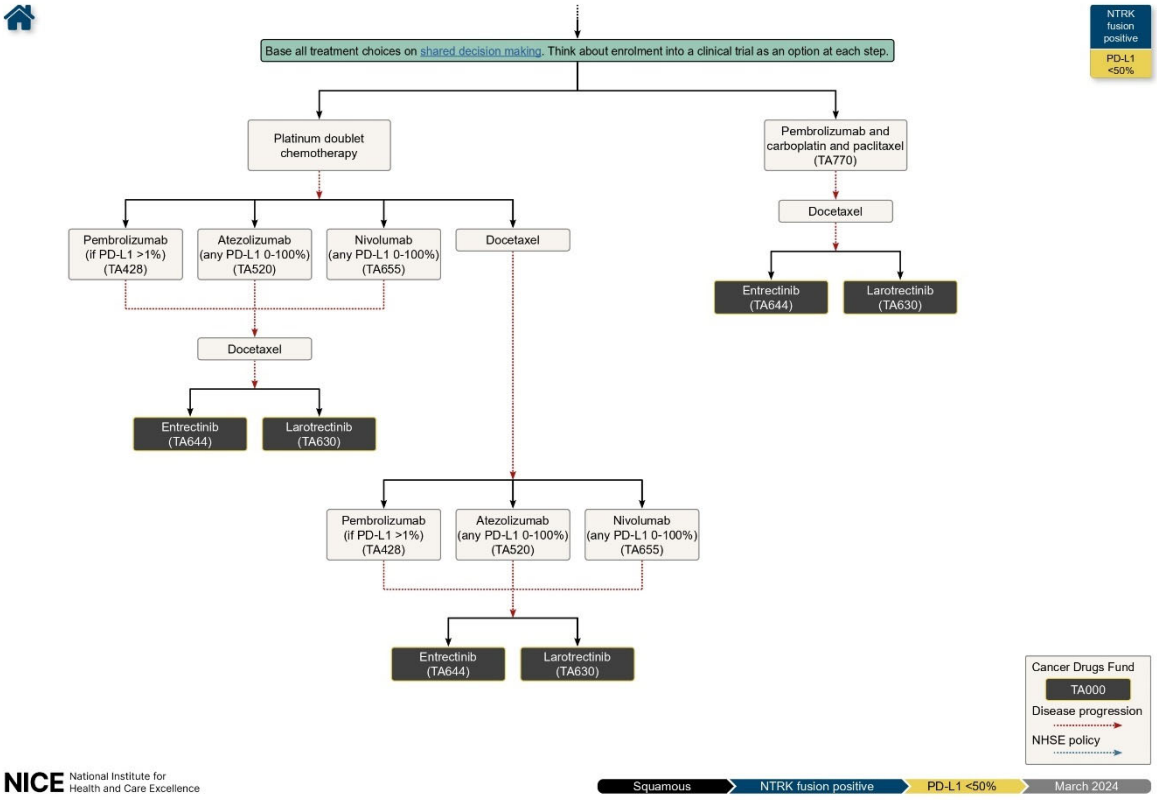
Appendix I: NSCLC Treatment Pathway

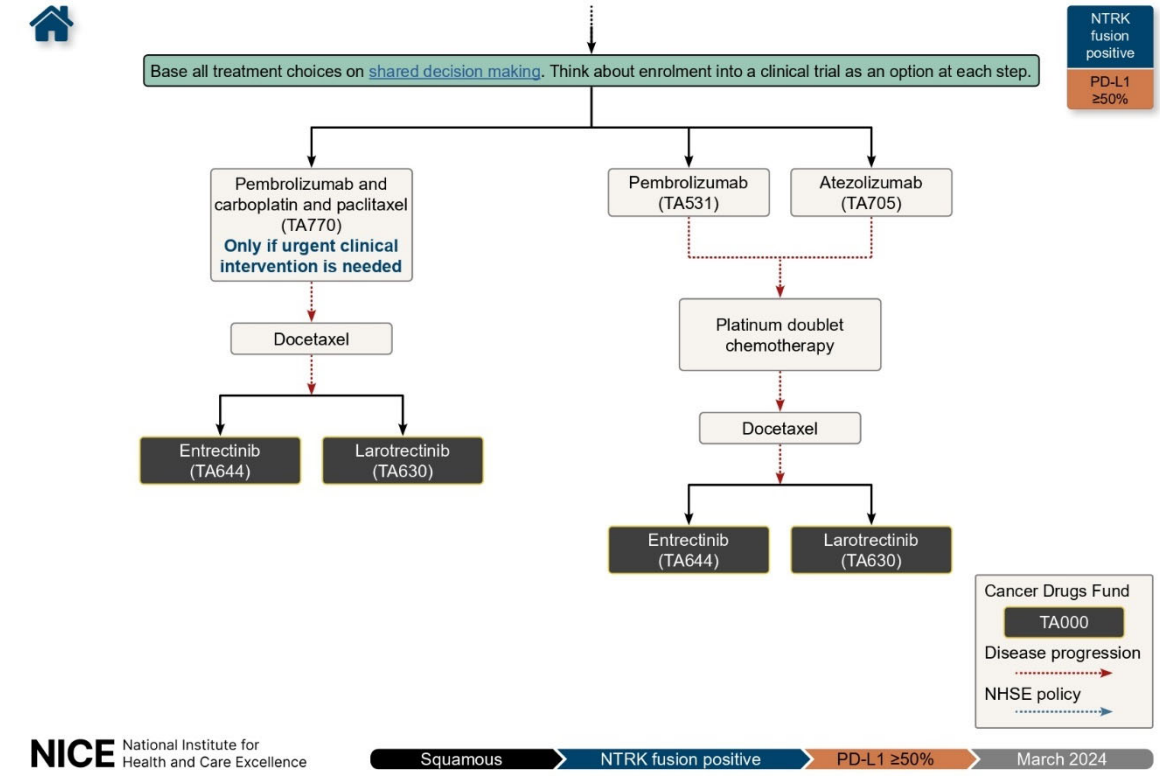


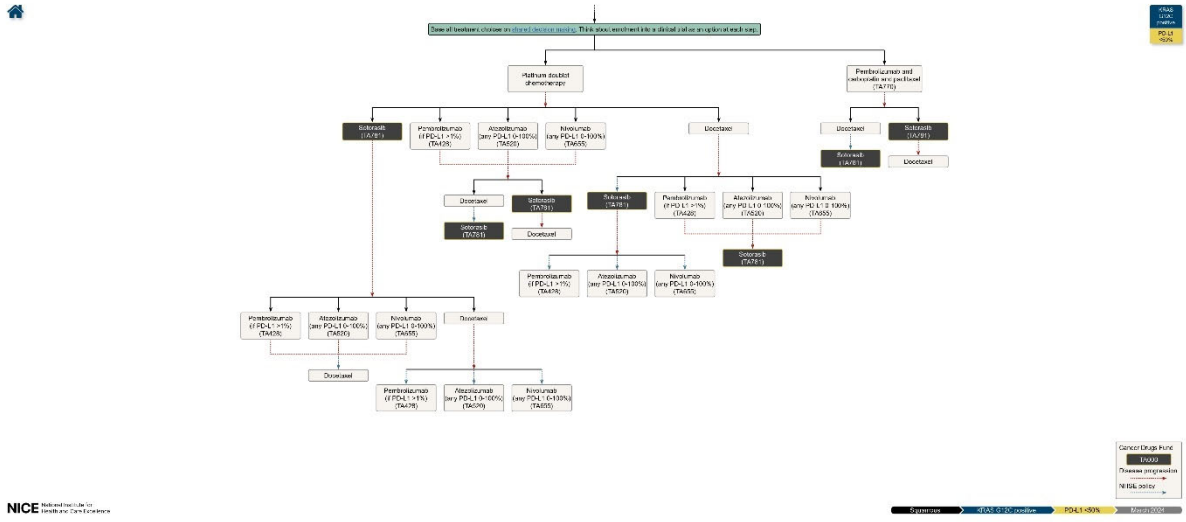


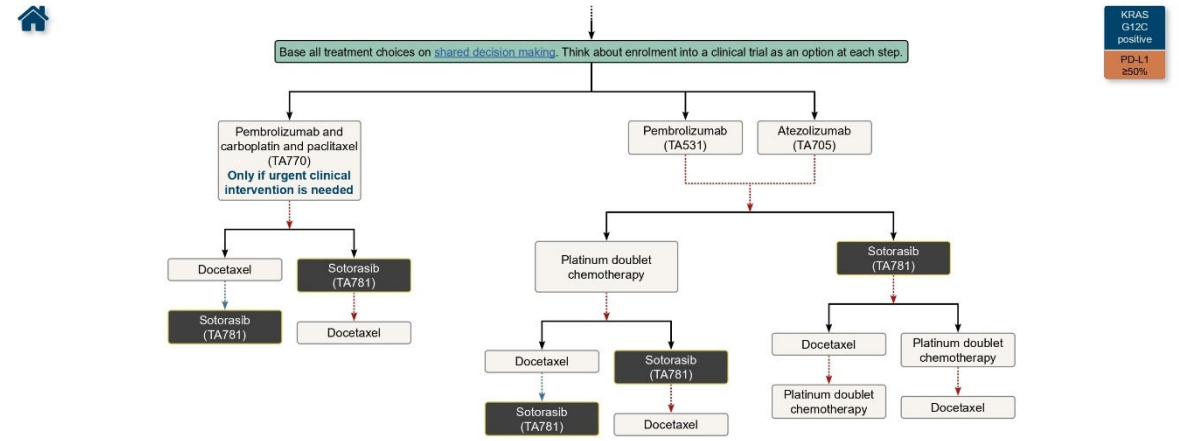

Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
No targetable mutations
PD-L1 ≥50%
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Pembrolizumab (TA531)
Atezolizumab (TA705)
Docetaxel
Platinum doublet chemotherapy
Docetaxel
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
No targetable mutations
PD-L1 ≥50%
March 2024

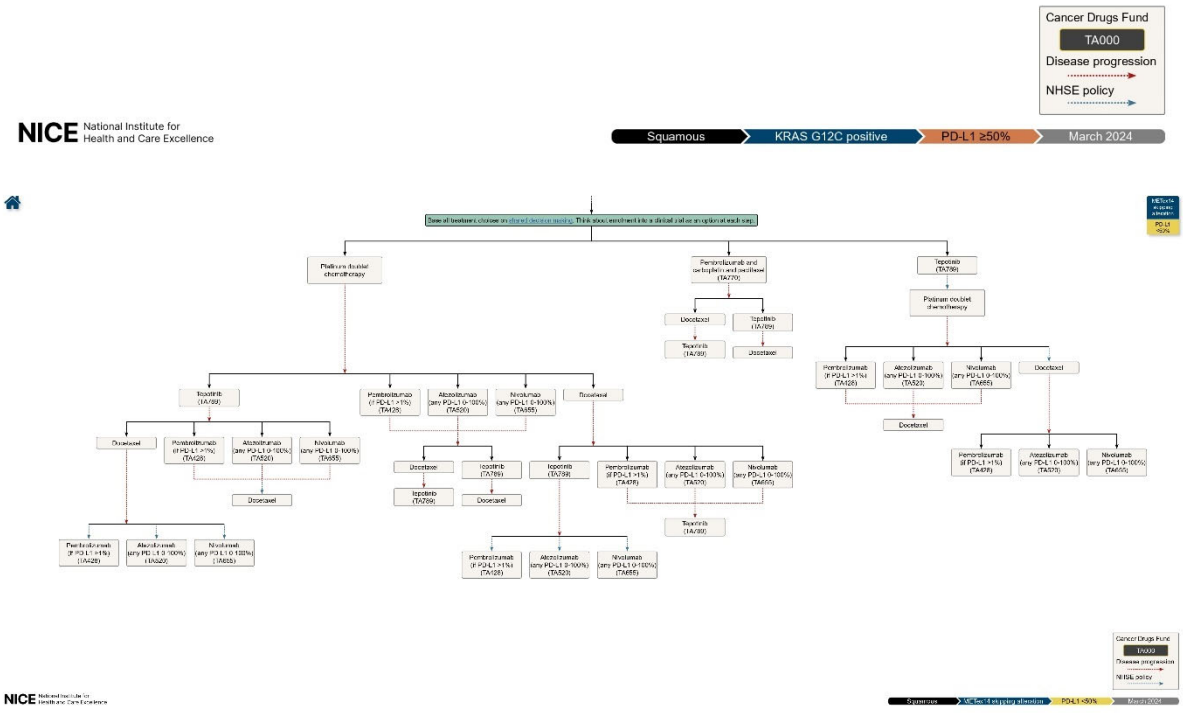

RET fusion positive
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Pembrolizumab (TA531)
Atezolizumab (TA705)
Selpercatinib (TA911)
Platinum doublet chemotherapy
Docetaxel
Selpercatinib (TA760)
Selpercatinib (TA760)
Docetaxel
Platinum doublet chemotherapy
Selpercatinib (TA760)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Docetaxel
Docetaxel
Selpercatinib (TA760)
Selpercatinib (TA760)
Docetaxel
Docetaxel
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Docetaxel
Platinum doublet chemotherapy
Platinum doublet chemotherapy
Docetaxel
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
RET fusion positive
PD-L1 ≥50%
March 2024

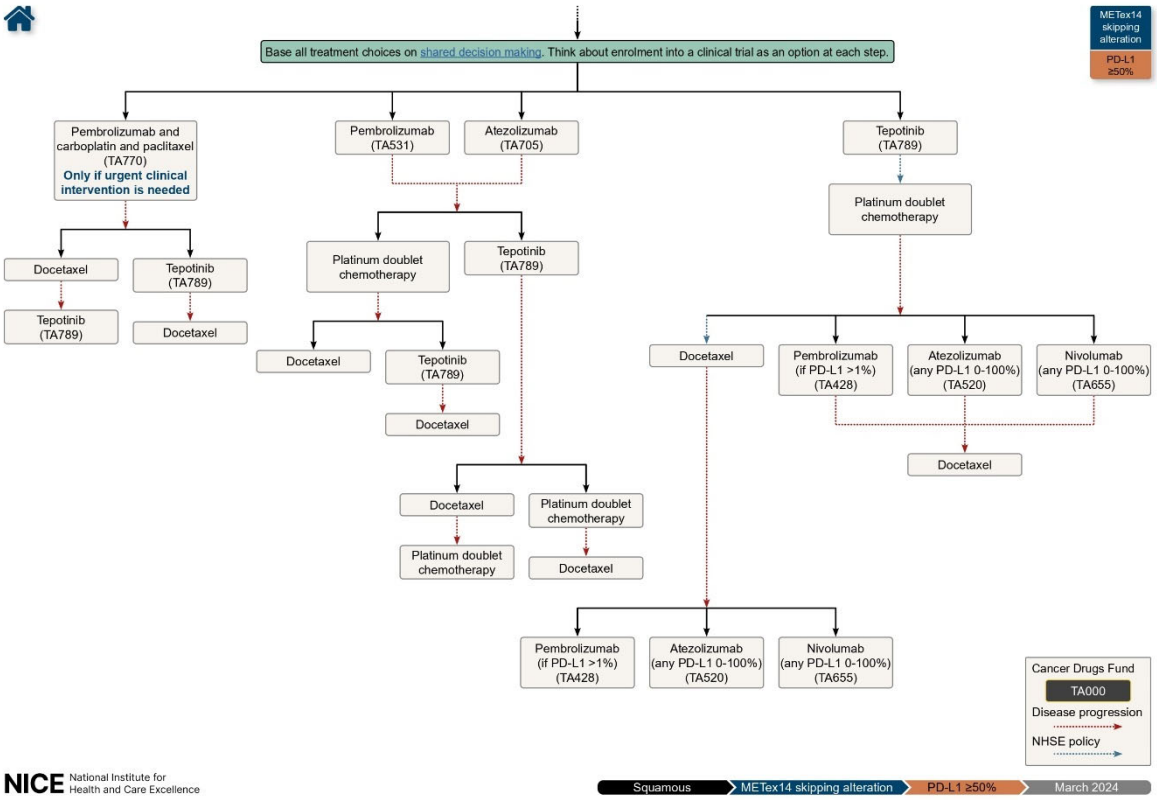

NTRK fusion positive
PD-L1 <50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Platinum doublet chemotherapy
Pembrolizumab and carboplatin and paclitaxel (TA770)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Docetaxel
Docetaxel
Entrectinib (TA644)
Larotrectinib (TA630)
Entrectinib (TA644)
Larotrectinib (TA630)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Entrectinib (TA644)
Larotrectinib (TA630)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
NTRK fusion positive
PD-L1 <50%
March 2024

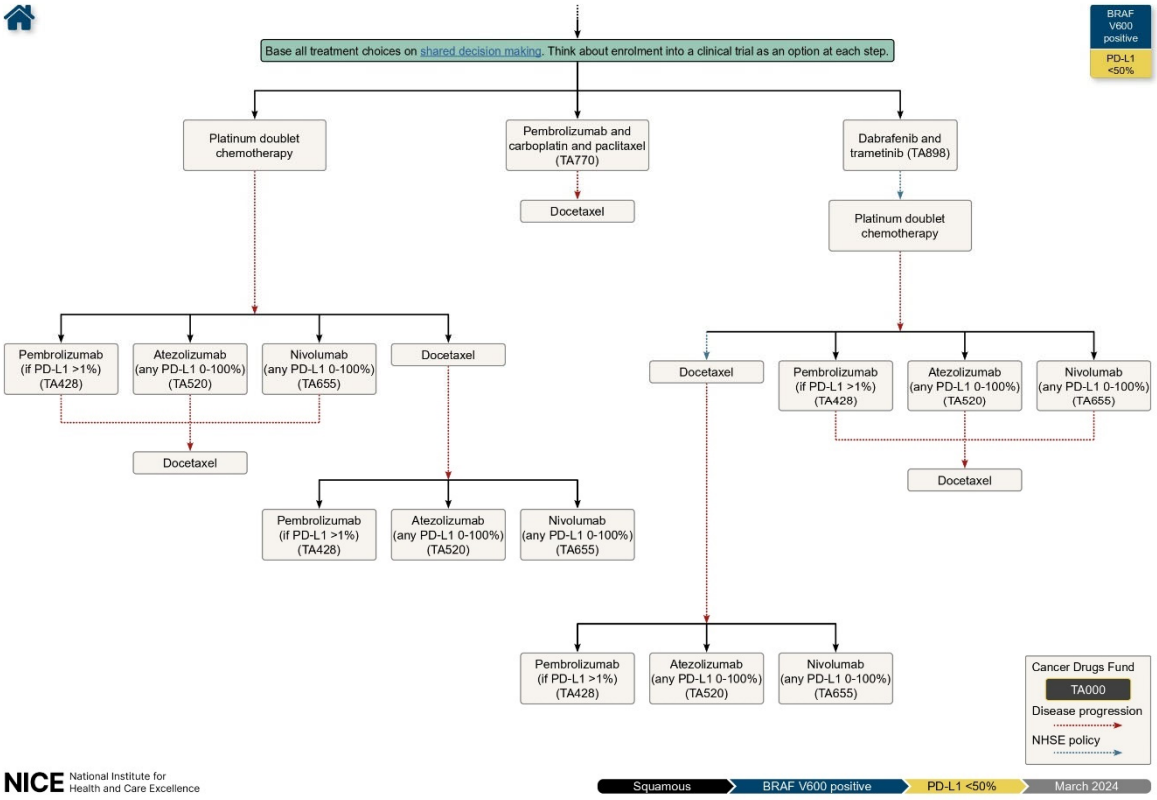

Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
NTRK fusion positive
PD-L1 ≥50%
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Docetaxel
Entrectinib (TA644)
Larotrectinib (TA630)
Pembrolizumab (TA531)
Atezolizumab (TA705)
Platinum doublet chemotherapy
Docetaxel
Entrectinib (TA644)
Larotrectinib (TA630)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
NTRK fusion positive
PD-L1 ≥50%
March 2024

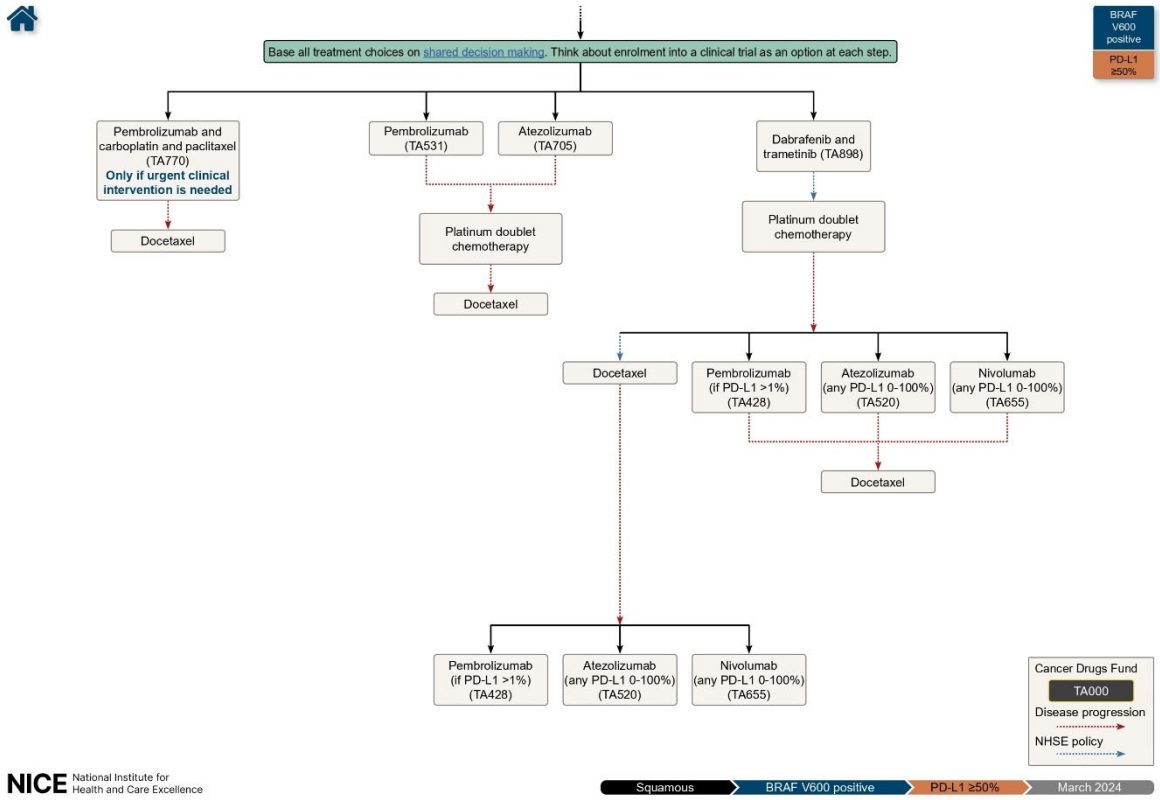


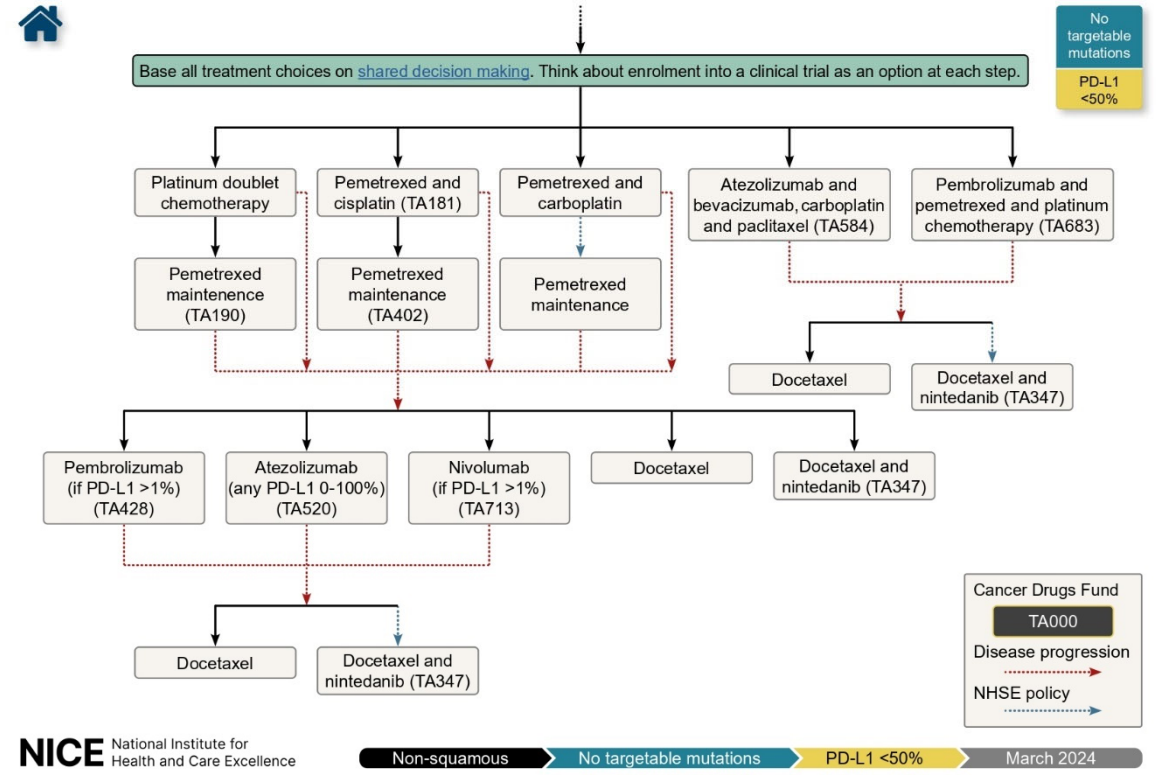

KRAS G12C positive
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Pembrolizumab (TA531)
Atezolizumab (TA705)
Docetaxel
Sotorasib (TA781)
Sotorasib (TA781)
Docetaxel
Platinum doublet chemotherapy
Sotorasib (TA781)
Docetaxel
Sotorasib (TA781)
Docetaxel
Docetaxel
Platinum doublet chemotherapy
Platinum doublet chemotherapy
Docetaxel

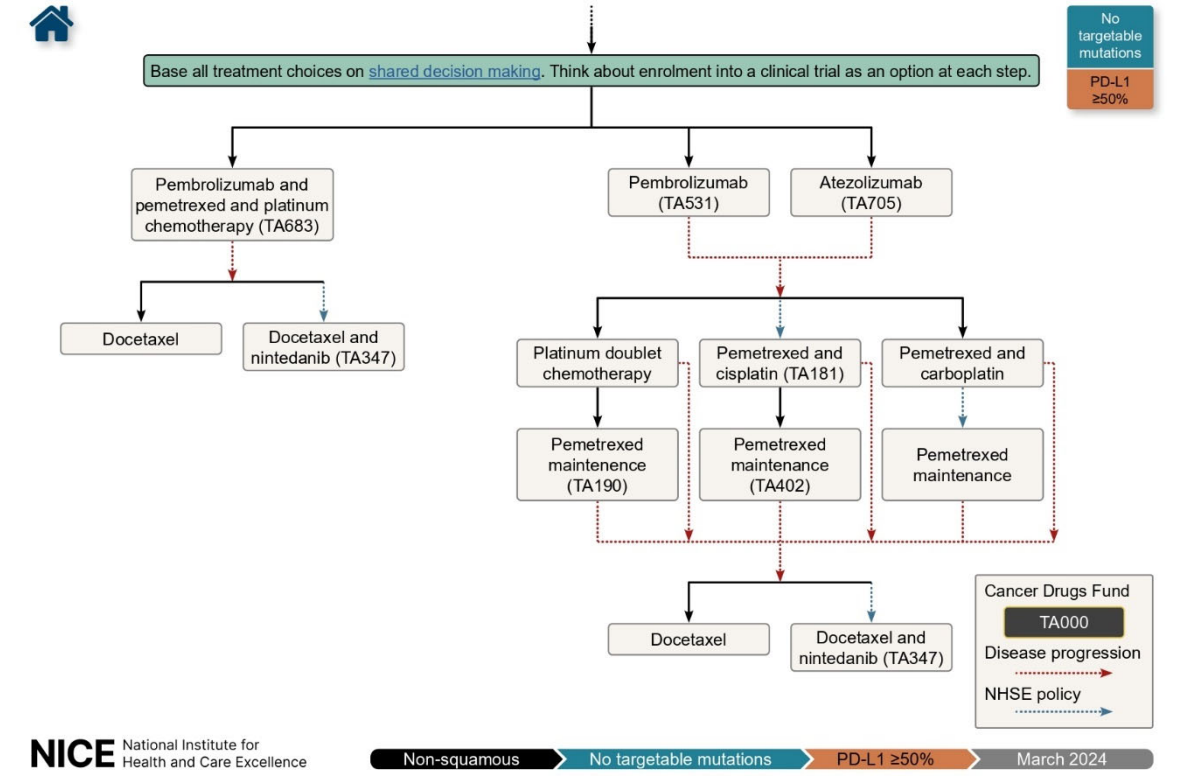

Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
KRAS G12C positive
PD-L1 ≥50%
March 2024

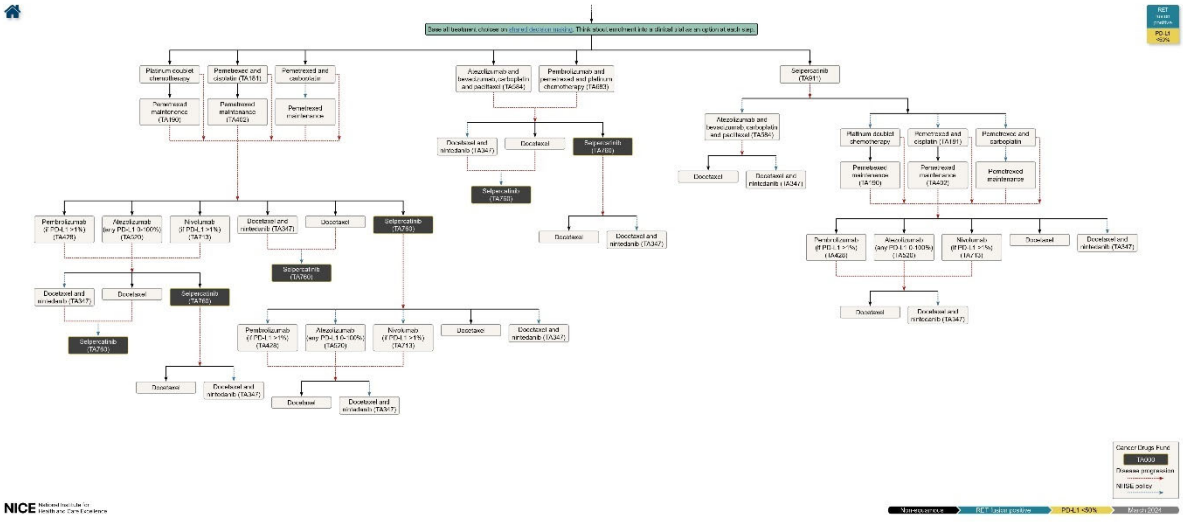

METex14 skipping alteration
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Pembrolizumab (TA531)
Atezolizumab (TA705)
Tepotinib (TA789)
Platinum doublet chemotherapy
Docetaxel
Tepotinib (TA789)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
METex14 skipping alteration
PD-L1 ≥50%
March 2024

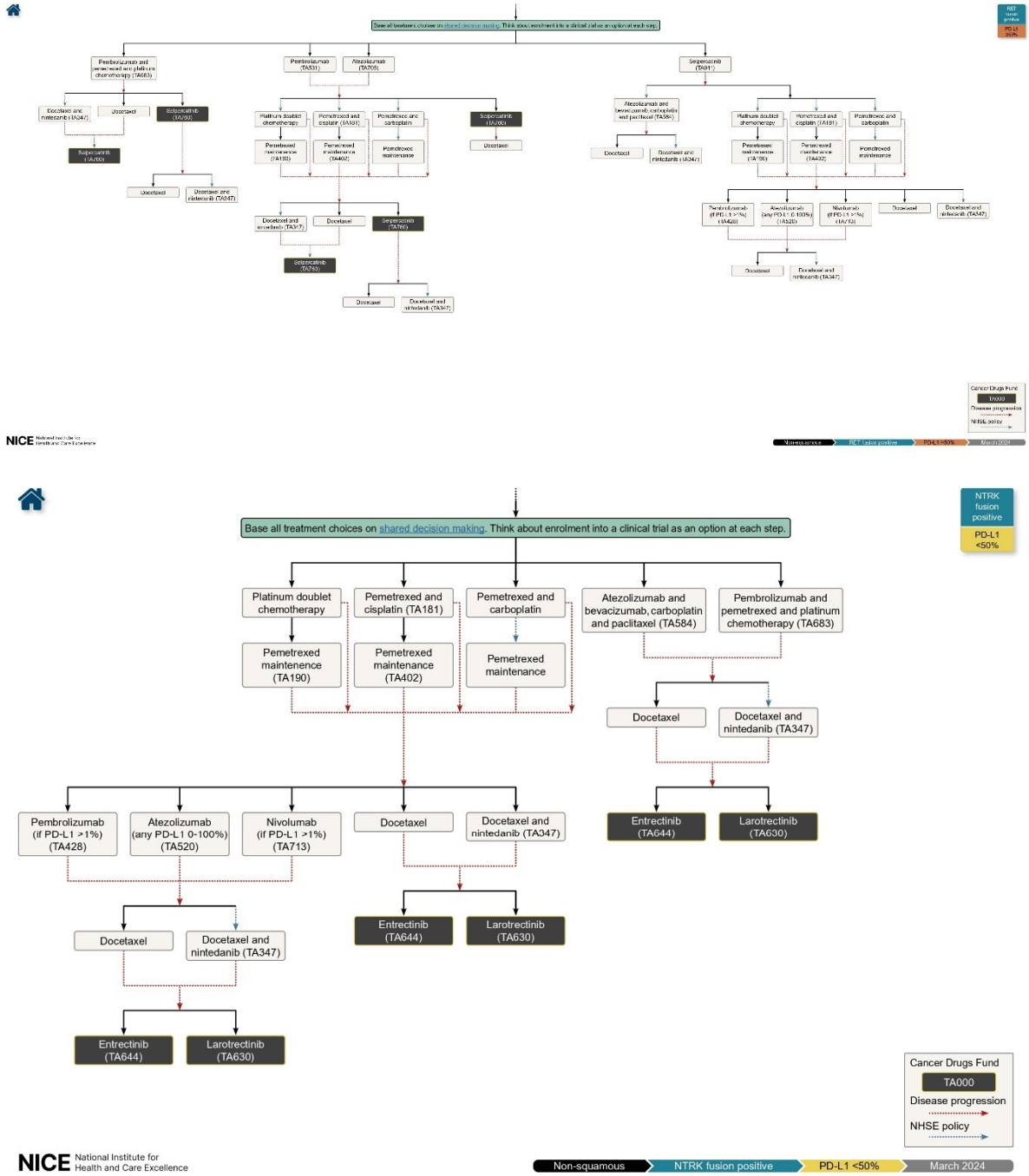

BRAF V600 positive
PD-L1 <50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Platinum doublet chemotherapy
Pembrolizumab and carboplatin and paclitaxel (TA770)
Dabrafenib and trametinib (TA898)
Docetaxel
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
BRAF V600 positive
PD-L1 <50%
March 2024

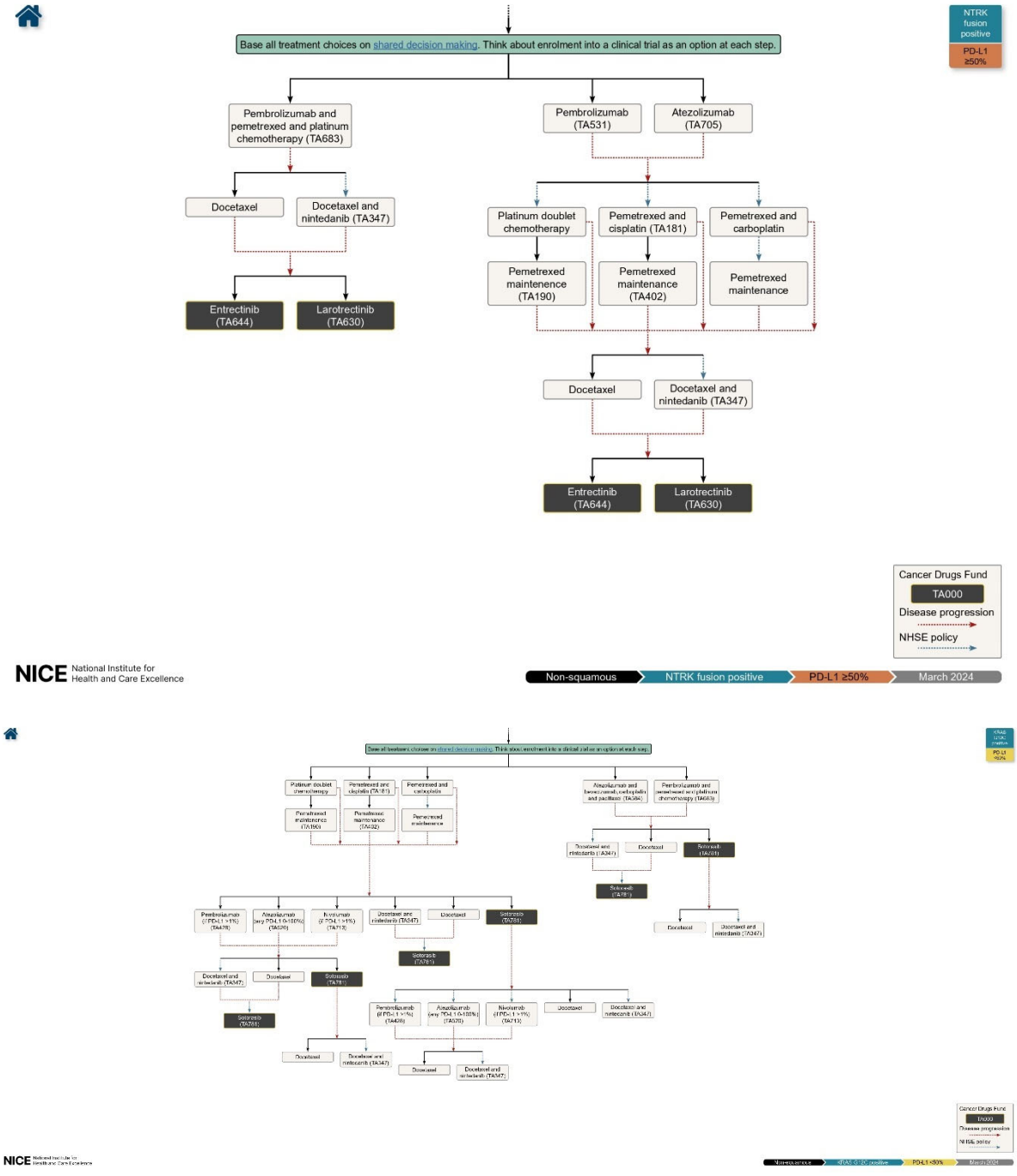

BRAF V600 positive
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and carboplatin and paclitaxel (TA770)
Only if urgent clinical intervention is needed
Docetaxel
Pembrolizumab (TA531)
Atezolizumab (TA705)
Platinum doublet chemotherapy
Docetaxel
Dabrafenib and trametinib (TA898)
Platinum doublet chemotherapy
Docetaxel
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Docetaxel
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (any PD-L1 0-100%) (TA655)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Squamous
BRAF V600 positive
PD-L1 ≥50%
March 2024

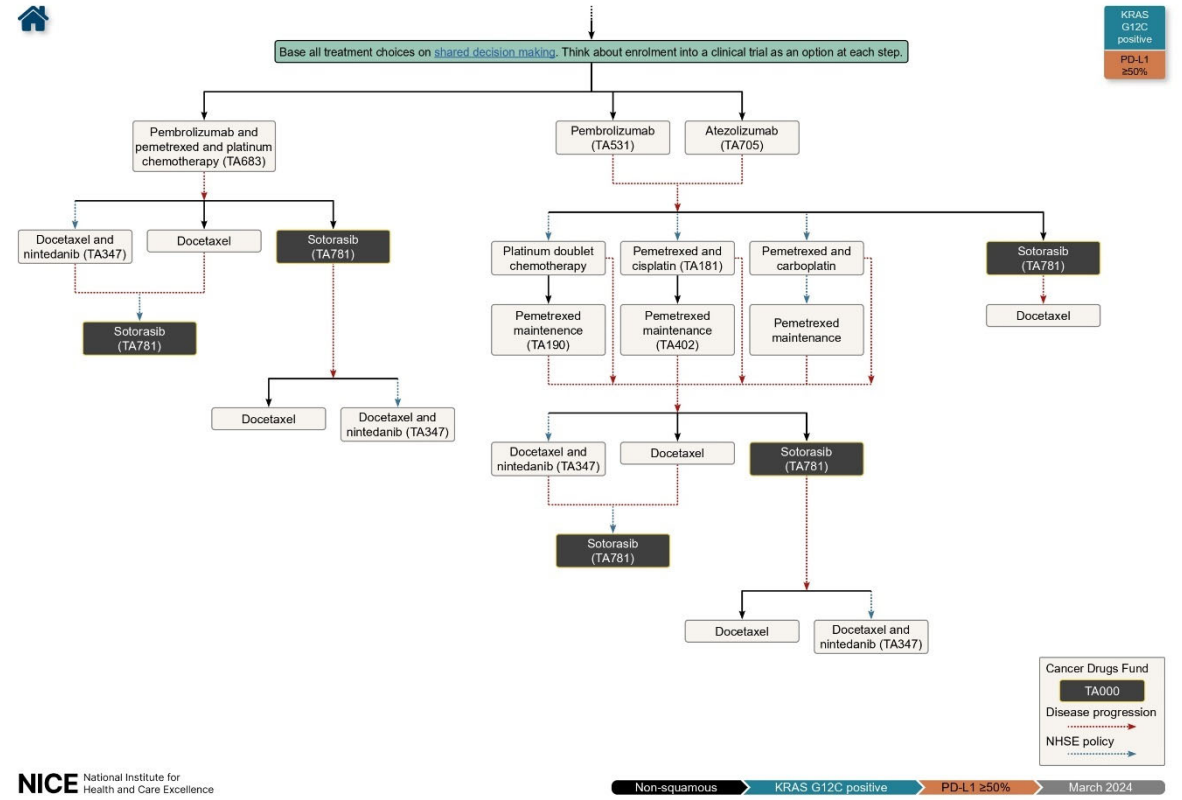

No targetable mutations
PD-L1 <50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Platinum doublet chemotherapy
Pemetrexed maintenence (TA190)
Pemetrexed and cisplatin (TA181)
Pemetrexed maintenance (TA402)
Pemetrexed and carboplatin
Pemetrexed maintenance
Atezolizumab and bevacizumab, carboplatin and paclitaxel (TA584)
Docetaxel
Pembrolizumab and pemetrexed and platinum chemotherapy (TA683)
Docetaxel and nintedanib (TA347)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (if PD-L1 >1%) (TA713)
Docetaxel
Docetaxel and nintedanib (TA347)
Docetaxel
Docetaxel and nintedanib (TA347)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Non-squamous
No targetable mutations
PD-L1 <50%
March 2024

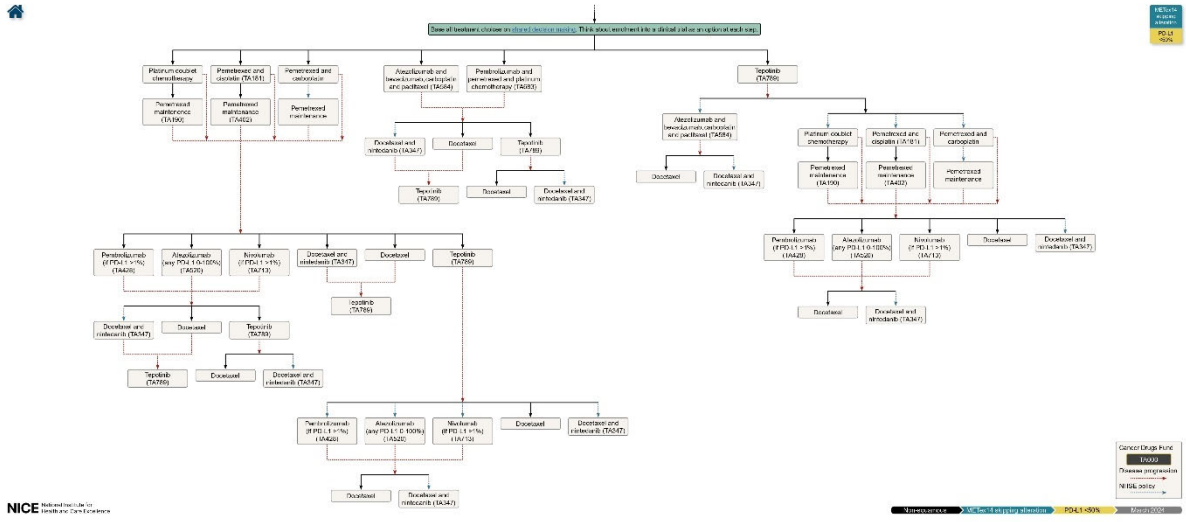

Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
No targetable mutations
PD-L1 ≥50%
Pembrolizumab and pemetrexed and platinum chemotherapy (TA683)
Pembrolizumab (TA531)
Atezolizumab (TA705)
Docetaxel
Docetaxel and nintedanib (TA347)
Platinum doublet chemotherapy
Pemetrexed and cisplatin (TA181)
Pemetrexed and carboplatin
Pemetrexed maintenence (TA190)
Pemetrexed maintenance (TA402)
Pemetrexed maintenance
Docetaxel
Docetaxel and nintedanib (TA347)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Non-squamous
No targetable mutations
PD-L1 ≥50%
March 2024

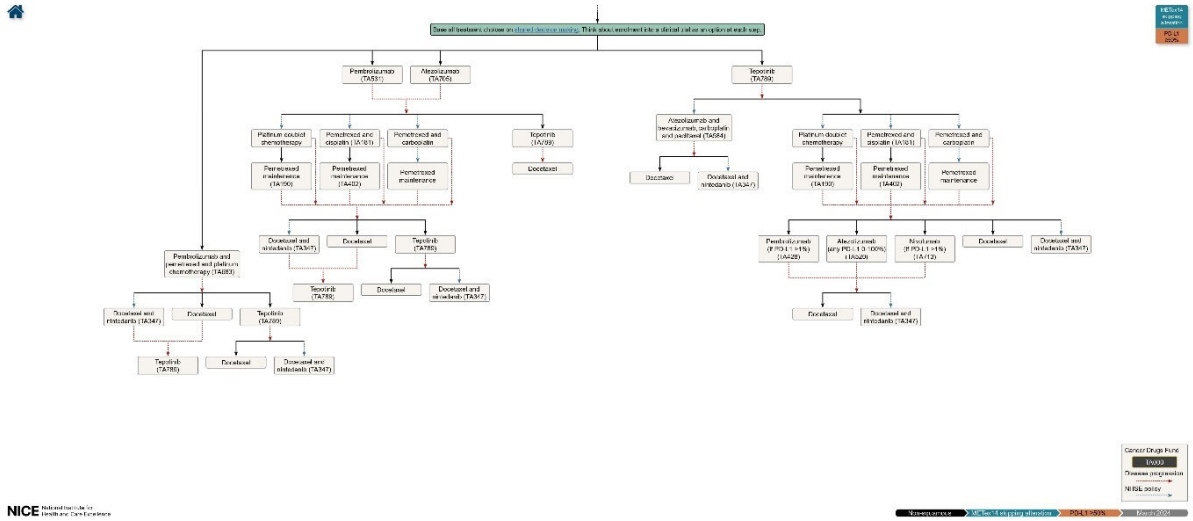


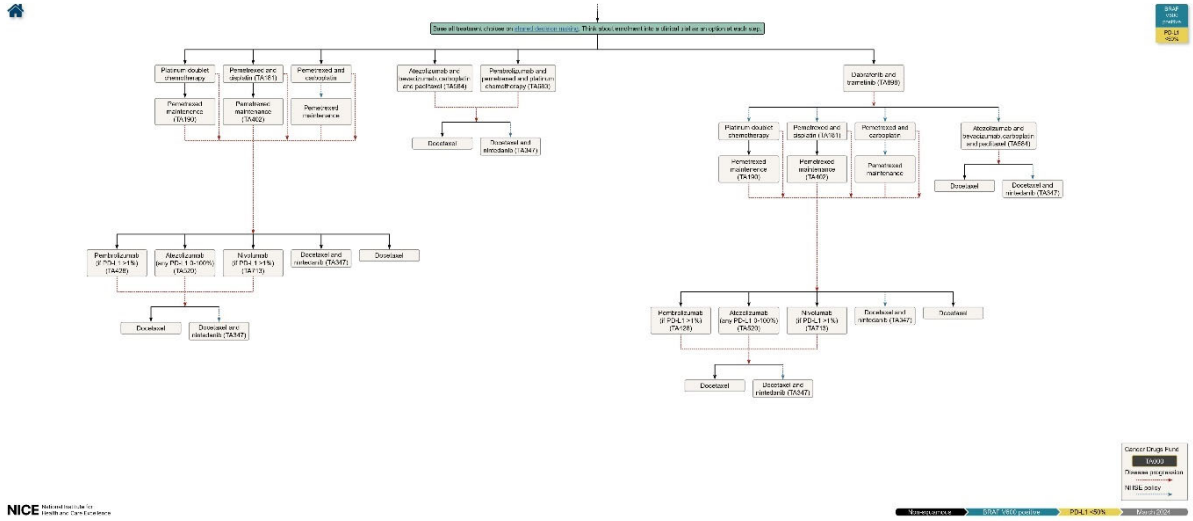

Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
NTRK fusion positive
PD-L1 <50%
Platinum doublet chemotherapy
Pemetrexed and cisplatin (TA181)
Pemetrexed and carboplatin
Atezolizumab and bevacizumab, carboplatin and paclitaxel (TA584)
Pembrolizumab and pemetrexed and platinum chemotherapy (TA683)
Pemetrexed maintenence (TA190)
Pemetrexed maintenance (TA402)
Pemetrexed maintenance
Docetaxel
Docetaxel and nintedanib (TA347)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (if PD-L1 >1%) (TA713)
Docetaxel
Docetaxel and nintedanib (TA347)
Entrectinib (TA644)
Larotrectinib (TA630)
Docetaxel
Docetaxel and nintedanib (TA347)
Entrectinib (TA644)
Larotrectinib (TA630)
Entrectinib (TA644)
Larotrectinib (TA630)
NICE National Institute for Health and Care Excellence
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
Non-squamous
NTRK fusion positive
PD-L1 <50%
March 2024

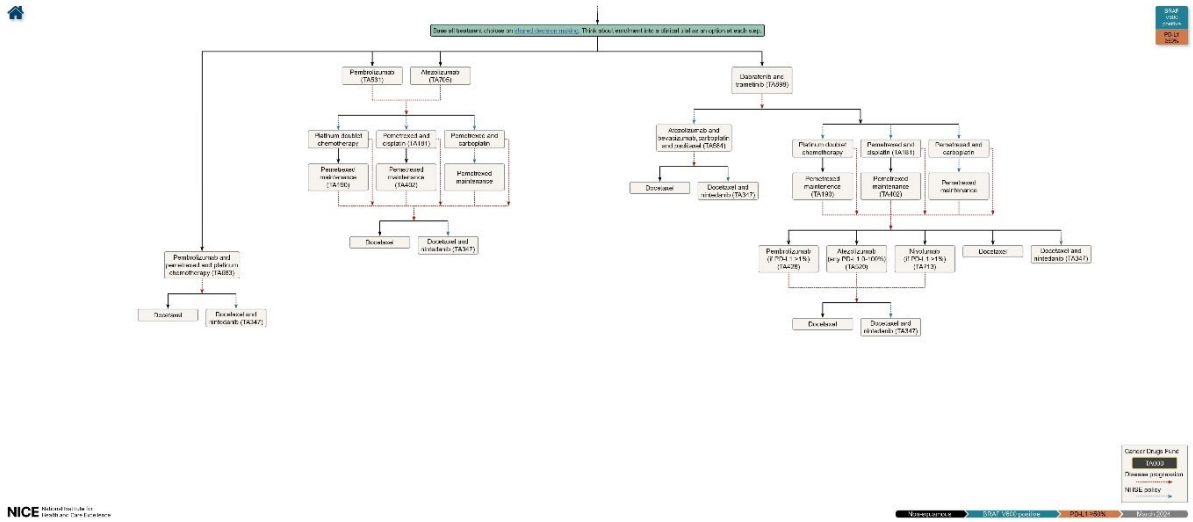

NTRK fusion positive
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and pemetrexed and platinum chemotherapy (TA683)
Docetaxel
Docetaxel and nintedanib (TA347)
Entrectinib (TA644)
Larotrectinib (TA630)
Pembrolizumab (TA531)
Atezolizumab (TA705)
Platinum doublet chemotherapy
Pemetrexed and cisplatin (TA181)
Pemetrexed and carboplatin
Pemetrexed maintenence (TA190)
Pemetrexed maintenance (TA402)
Pemetrexed maintenance
Docetaxel
Docetaxel and nintedanib (TA347)
Entrectinib (TA644)
Larotrectinib (TA630)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Non-squamous
NTRK fusion positive
PD-L1 ≥50%
March 2024

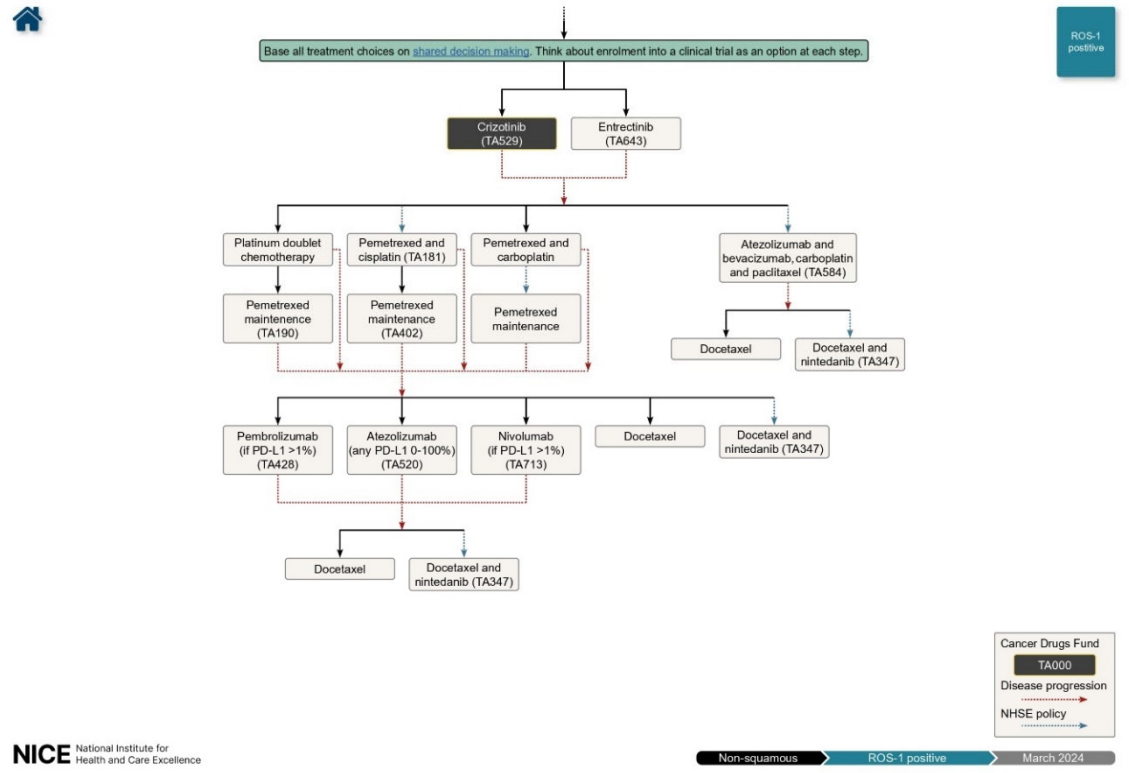

KRAS G12C positive
PD-L1 ≥50%
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Pembrolizumab and pemetrexed and platinum chemotherapy (TA683)
Pembrolizumab (TA531)
Atezolizumab (TA705)
Docetaxel and nintedanib (TA347)
Docetaxel
Sotorasib (TA781)
Sotorasib (TA781)
Docetaxel
Docetaxel and nintedanib (TA347)
Platinum doublet chemotherapy
Pemetrexed and cisplatin (TA181)
Pemetrexed and carboplatin
Sotorasib (TA781)
Pemetrexed maintenence (TA190)
Pemetrexed maintenance (TA402)
Pemetrexed maintenance
Docetaxel
Docetaxel and nintedanib (TA347)
Docetaxel
Sotorasib (TA781)
Sotorasib (TA781)
Docetaxel
Docetaxel and nintedanib (TA347)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Non-squamous
KRAS G12C positive
PD-L1 ≥50%
March 2024

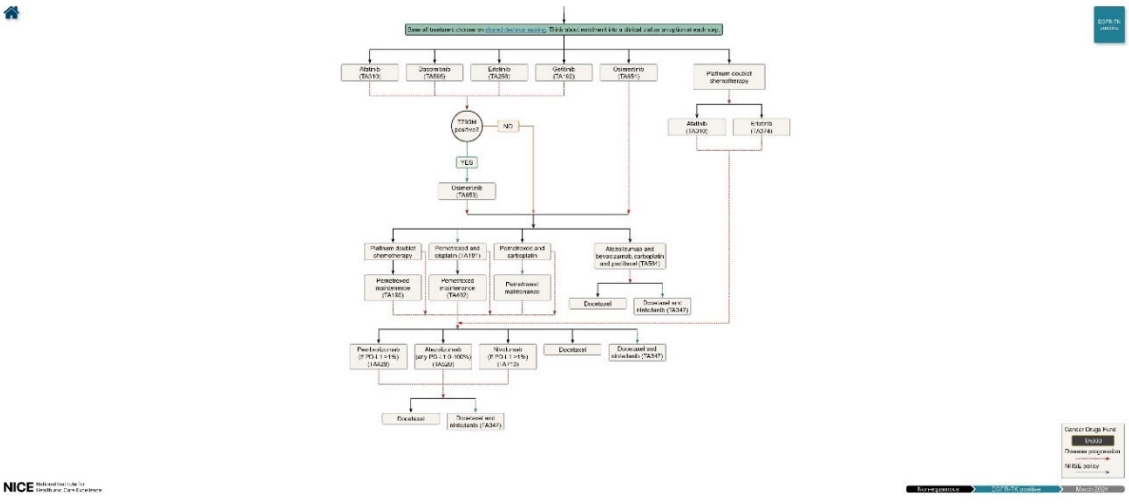


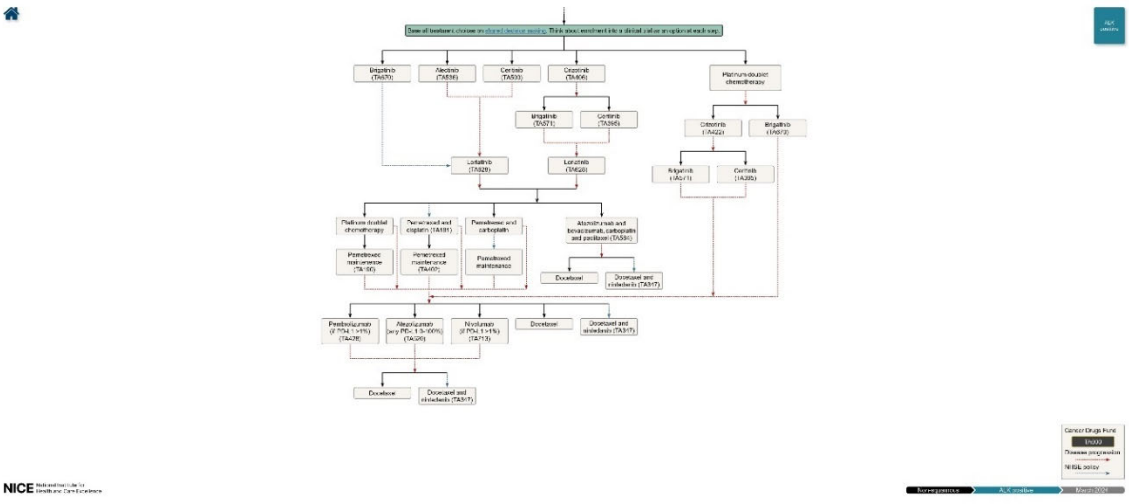







ROS-1 positive
Base all treatment choices on shared decision making. Think about enrolment into a clinical trial as an option at each step.
Crizotinib (TA529)
Entrectinib (TA643)
Platinum doublet chemotherapy
Pemetrexed and cisplatin (TA181)
Pemetrexed and carboplatin
Atezolizumab and bevacizumab, carboplatin and paclitaxel (TA584)
Pemetrexed maintenence (TA190)
Pemetrexed maintenance (TA402)
Pemetrexed maintenance
Docetaxel
Docetaxel and nintedanib (TA347)
Pembrolizumab (if PD-L1 >1%) (TA428)
Atezolizumab (any PD-L1 0-100%) (TA520)
Nivolumab (if PD-L1 >1%) (TA713)
Docetaxel
Docetaxel and nintedanib (TA347)
Docetaxel
Docetaxel and nintedanib (TA347)
Cancer Drugs Fund
TA000
Disease progression
NHSE policy
NICE National Institute for Health and Care Excellence
Non-squamous
ROS-1 positive
March 2024





Appendix II: PRISMA 2020 Checklist

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	
Study characteristics	17	Cite each included study and present its characteristics.	
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	
	23b	Discuss any limitations of the evidence included in the review.	
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Appendix III: Approval Letter by the ISEAC

ISEAC Feedback

Researcher Name: Stefanie Ho Yi Chan
Organisation: University of Hertfordshire
ISEAC Reference Number: 21SEAC001
Date: 8th September 2021
Study title: Assessing the utility of the Hospital Treatment Insights (HTI) database for the development of algorithm for identification and mitigation of cardiotoxicity related to cancer treatments.

Committee opinion: Approved

The following feedback has been supplied by ISEAC.

Notes from the Chair:

The synopsis, one minor point, section 5, the same sentence is repeated about 6 times at the beginning. I'm sure the research team will rectify that with their final version.

Approved documents:

Approved document	Version	Date
21ISEAC001 - HTI - V2 - 31082021	2	31/08/2021
21ISEAC001_Researcher response		

We are pleased to inform you of this approval allows you to proceed with the study.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to report back to NHS Digital.

Please remember to use the following statement in your published work:

"Copyright © 2021, re-used with the permission of The Health & Social Care Information Centre. All rights reserved"

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the relevant database, we recommend that you include the name of the database within your study title.

Copies of your full publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

pp. Mustafa Dungarwalla, IQVIA
(on behalf of, **ISEAC Chair**)

Appendix IV: Data by Drug (DEFINE Database)

Afatinib

	NHS London	NHS South East Coast	NHS East of England	NHS South Central	NHS West Midlands	NHS East Midlands	NHS South West	NHS Yorkshire and the Humber	NHS North East	NHS North West	Total (dosage)
Apr-17	75.88	41.26	30.52	29.48	32.06	34.86	19.32	20.38	27.44	25.69	336.89
May-17	90.86	41.72	35.28	44.80	33.94	42.72	32.06	29.70	25.20	33.39	409.67
Jun-17	91.07	46.48	43.68	25.76	34.44	37.10	31.98	17.72	33.60	25.48	387.31
Jul-17	79.66	39.56	42.28	27.24	31.15	29.96	34.52	35.97	28.35	25.90	374.59
Aug-17	90.02	49.84	47.18	35.24	31.85	36.89	36.12	26.81	27.44	27.86	409.25
Sep-17	97.72	39.04	40.88	45.12	29.40	33.60	30.94	34.16	28.00	19.74	398.60
Oct-17	89.18	40.05	47.32	25.88	39.62	34.44	37.66	26.16	17.57	23.94	381.82
Nov-17	106.19	43.93	51.74	50.10	40.11	37.45	34.44	36.71	29.40	18.76	448.83
Dec-17	92.12	39.72	49.84	39.90	45.92	35.28	30.38	31.08	29.12	24.22	417.58
Jan-18	108.08	38.36	61.11	52.64	38.92	34.44	40.18	42.25	26.32	17.64	459.94
Feb-18	92.47	38.96	58.24	36.26	39.34	31.71	29.68	30.80	25.48	16.80	399.74
Mar-18	88.76	56.00	58.24	53.42	38.92	31.22	34.44	38.92	35.56	20.44	455.92
Apr-18	109.48	45.92	57.96	53.34	43.40	29.12	39.06	38.08	36.40	21.49	474.25
May-18	100.31	56.48	67.20	34.16	52.64	42.84	49.84	32.06	28.84	19.88	484.25
Jun-18	89.18	56.90	63.56	44.08	45.15	33.04	30.66	42.56	33.39	21.00	459.52
Jul-18	97.79	69.92	60.20	56.42	52.92	33.53	42.42	26.81	38.57	21.84	500.42
Aug-18	106.75	75.25	66.85	51.52	52.78	41.86	47.88	48.09	35.28	23.52	549.78
Sep-18	97.19	73.85	59.78	41.44	41.44	31.08	37.17	29.47	31.92	17.36	460.70
Oct-18	129.72	76.72	62.02	63.98	49.84	50.82	45.22	35.28	28.96	17.64	560.20
Nov-18	106.54	77.70	69.02	46.97	52.50	44.52	47.60	33.88	31.64	22.12	532.49

Dec-18	115.03	69.65	59.22	47.04	45.50	46.69	37.66	41.51	26.32	23.24	511.86
Jan-19	112.22	87.36	56.70	50.82	50.40	43.68	46.06	39.62	28.66	26.60	542.12
Feb-19	105.42	69.65	49.56	55.58	49.84	43.40	45.15	34.16	28.44	23.24	504.44
Mar-19	120.62	96.46	58.52	57.54	47.74	39.63	36.96	36.54	36.68	21.56	552.25
Apr-19	124.88	81.80	74.20	65.38	53.90	34.86	45.22	40.66	25.48	25.41	571.79
May-19	139.73	88.48	57.12	55.86	54.39	54.67	42.56	41.50	35.56	24.64	594.51
Jun-19	120.49	63.28	60.97	60.69	42.00	39.06	35.04	29.75	26.32	27.65	505.25
Jul-19	149.03	130.61	71.96	64.19	50.82	43.75	43.75	46.55	35.28	36.54	672.48
Aug-19	126.35	91.56	84.56	63.42	48.30	43.12	36.96	35.14	34.44	34.72	598.57
Sep-19	117.25	70.56	63.70	49.28	45.64	40.74	27.86	33.18	22.68	38.92	509.81
Oct-19	141.82	73.92	69.02	66.50	56.21	47.88	47.53	39.13	33.88	43.12	619.01
Nov-19	135.24	73.78	72.73	46.48	45.15	37.17	37.73	40.60	35.00	38.64	562.52
Dec-19	139.58	83.02	68.25	49.98	47.32	44.10	40.60	39.69	29.54	45.78	587.86
Jan-20	171.85	77.28	61.88	60.20	46.48	47.04	48.30	36.05	30.19	38.36	617.63
Feb-20	145.81	62.44	66.64	47.32	41.58	35.42	32.69	33.53	27.16	40.32	532.91
Mar-20	197.50	74.76	90.37	77.70	44.94	45.85	49.14	44.66	35.00	54.53	714.45
Apr-20	162.52	61.32	63.14	70.80	48.58	46.06	45.01	39.06	31.92	32.20	600.61
May-20	140.42	61.60	57.96	44.98	29.96	40.81	25.72	34.58	26.88	32.76	495.67
Jun-20	146.30	59.78	56.00	66.64	23.52	41.09	43.30	34.58	27.72	36.68	535.61
Jul-20	148.68	60.20	67.62	55.44	38.36	45.85	35.68	32.20	32.48	36.40	552.91
Aug-20	102.97	43.40	45.78	35.00	32.20	42.56	26.18	26.46	18.20	36.96	409.71
Sep-20	142.52	40.32	53.90	45.08	27.86	35.98	31.78	27.72	25.76	32.20	463.12
Oct-20	89.88	38.08	44.52	56.63	30.52	40.32	29.82	24.20	24.64	29.12	407.73
Nov-20	124.88	36.96	43.26	31.92	25.41	25.76	30.80	21.56	21.56	30.80	392.91
Dec-20	93.24	38.36	47.50	36.12	30.45	29.26	23.80	26.81	24.92	45.92	396.38
Jan-21	89.88	29.12	40.64	34.72	19.60	24.64	23.80	20.44	21.84	27.16	331.84
Feb-21	87.92	27.51	34.48	28.28	25.48	25.76	25.76	18.90	17.36	14.28	305.73
Mar-21	96.18	24.50	33.32	35.28	20.58	25.48	32.90	20.16	15.40	21.00	324.80
Apr-21	84.42	28.00	35.00	48.72	15.68	24.08	21.84	14.84	17.92	19.18	309.68
May-21	56.98	28.00	26.88	42.00	22.82	21.56	21.14	21.56	11.48	19.18	271.60

Jun-21	74.62	24.92	28.00	34.16	17.08	17.64	22.12	17.64	16.80	18.90	271.88
Jul-21	62.30	26.32	26.32	28.56	20.16	20.30	16.38	17.50	7.84	18.90	244.58
Aug-21	60.20	22.96	27.16	33.60	14.28	20.86	18.20	19.32	16.52	15.26	248.36
Sep-21	67.90	21.98	26.12	27.72	22.40	16.80	24.28	17.92	9.80	15.54	250.46
Oct-21	63.70	16.94	24.08	26.04	15.40	14.06	15.12	14.28	12.88	9.66	212.16
Nov-21	48.50	15.12	23.80	31.08	16.66	13.52	23.60	12.04	8.96	12.74	206.02
Dec-21	52.36	17.64	16.24	20.16	16.52	13.86	15.40	20.16	17.36	7.84	197.54
Jan-22	51.52	15.12	29.40	24.08	12.60	10.36	17.36	13.44	10.36	7.28	191.52
Feb-22	50.68	14.28	13.16	20.72	20.30	8.46	7.56	10.36	17.36	7.00	169.88
Mar-22	42.14	16.80	25.76	14.70	21.14	10.50	12.60	12.04	17.36	9.80	182.84
Apr-22	54.25	14.84	18.48	14.84	9.80	12.18	10.36	15.96	14.00	5.04	169.75
May-22	45.36	17.36	26.04	19.04	17.78	11.62	9.80	7.56	15.96	6.16	176.68
Jun-22	45.99	12.32	19.04	11.76	12.88	14.98	5.80	16.87	9.52	4.20	153.36
Jul-22	41.44	16.52	15.96	11.48	11.20	9.24	13.16	8.96	12.04	5.32	145.32
Total	6429.54	3172.54	3107.86	2725.28	2215.77	2077.13	2014.05	1836.28	1593.95	1545.46	

Atezolizumab

	NHS North West	NHS London	NHS Yorkshire and the Humber	NHS East of England	NHS West Midlands	NHS South West	NHS East Midlands	NHS South Central	NHS North East	NHS South East Coast	Total (dosage)
Apr-17	6.00							2.40			8.40
May-17	10.80							2.40			13.20
Jun-17	7.20							3.60			10.80
Jul-17	3.60							1.20			4.80
Aug-17	7.20										7.20
Sep-17	2.40										2.40
Oct-17	4.80										4.80
Nov-17	6.00	3.60	1.20								10.80
Dec-17	3.60	8.40	3.60			2.40					18.00
Jan-18	7.20	12.00	4.80	3.60		3.60	2.40	2.40	2.40		38.40
Feb-18	7.20	4.80	8.40	3.60	2.40	7.20	8.40	3.60	2.40		48.00
Mar-18	7.20	6.00	14.40	2.40	8.40	12.00	8.40	8.40	3.60	4.80	75.60
Apr-18	10.80	15.60	15.60	7.20	14.40	15.60	12.00	13.20	10.80	7.20	122.40
May-18	26.40	46.80	40.80	25.20	24.00	33.60	27.60	38.40	44.40	33.60	340.80
Jun-18	31.20	80.40	74.40	33.60	38.40	52.80	32.40	43.20	46.80	50.40	483.60
Jul-18	67.20	79.20	93.60	54.00	43.20	54.00	58.80	46.80	80.40	49.20	626.40
Aug-18	78.00	93.60	90.00	70.80	55.20	88.80	49.20	45.60	90.00	66.00	727.20
Sep-18	87.60	102.00	98.40	58.80	60.00	79.20	66.00	46.80	88.80	55.20	742.80
Oct-18	99.60	100.80	124.80	86.40	73.20	78.00	62.40	51.60	105.60	96.00	878.40
Nov-18	92.04	116.40	136.80	91.20	97.20	103.26	57.60	66.00	91.20	94.80	946.50
Dec-18	99.24	100.80	126.00	88.80	76.80	87.60	70.80	55.20	93.60	76.80	875.64
Jan-19	119.76	116.40	141.60	108.00	80.40	114.00	70.80	85.20	98.40	85.20	1019.76
Feb-19	117.60	99.60	142.80	87.60	62.40	88.80	74.40	61.20	82.80	79.20	896.40
Mar-19	127.08	105.60	145.20	99.60	80.40	102.00	85.20	69.60	92.40	86.40	993.48

Apr-19	106.08	102.00	162.00	93.60	87.60	114.00	100.80	74.40	104.40	86.40	1031.28
May-19	171.30	114.00	178.80	100.80	114.00	104.40	85.20	73.20	102.00	78.00	1121.70
Jun-19	123.60	130.80	165.60	96.00	88.80	90.00	79.20	81.60	115.20	81.60	1052.40
Jul-19	146.88	122.40	177.60	100.80	102.00	105.60	114.00	109.20	93.60	84.00	1156.08
Aug-19	139.68	142.80	176.40	104.40	98.40	108.48	91.20	90.00	98.40	100.80	1150.56
Sep-19	142.08	139.20	160.80	106.80	103.20	106.80	81.60	97.20	69.60	96.00	1103.28
Oct-19	157.26	157.20	205.20	144.00	109.20	115.20	102.00	99.60	85.20	116.40	1291.26
Nov-19	153.72	146.40	158.40	162.00	87.60	121.44	96.00	84.18	82.80	110.40	1202.94
Dec-19	160.44	134.40	169.20	135.60	96.00	101.16	86.40	79.38	70.80	102.00	1135.38
Jan-20	180.84	148.80	196.80	140.40	109.20	145.32	90.00	94.98	87.60	88.80	1282.74
Feb-20	157.20	128.40	153.60	129.60	97.20	98.64	84.00	77.28	68.40	75.60	1069.92
Mar-20	130.44	142.80	166.80	140.40	105.60	103.80	110.40	74.52	61.20	80.40	1116.36
Apr-20	66.00	109.44	133.92	141.60	67.20	83.52	84.00	82.44	59.76	48.00	875.88
May-20	67.08	121.68	131.52	129.36	75.60	93.96	112.80	85.21	63.12	58.20	938.53
Jun-20	102.12	182.52	193.68	163.20	116.04	136.80	92.04	104.41	93.12	99.48	1283.41
Jul-20	132.72	213.60	207.84	183.72	126.00	163.32	150.24	125.05	132.96	123.24	1558.69
Aug-20	129.24	193.56	184.32	188.52	138.24	149.16	128.40	123.55	137.28	113.64	1485.91
Sep-20	165.12	192.36	208.92	212.28	154.92	156.24	147.96	143.71	150.72	131.64	1663.87
Oct-20	156.84	212.76	252.84	213.60	179.88	171.36	171.96	156.31	143.16	147.12	1805.83
Nov-20	302.88	208.20	215.04	210.72	167.52	139.56	178.56	171.97	118.56	136.20	1849.21
Dec-20	364.08	227.28	241.92	248.88	223.80	151.80	197.40	204.43	132.24	172.20	2164.03
Jan-21	411.60	252.12	217.56	219.84	228.12	145.32	230.16	168.97	140.88	170.64	2185.21
Feb-21	338.28	227.40	258.84	239.76	208.20	154.80	183.84	160.03	115.68	158.28	2045.11
Mar-21	415.80	333.96	294.84	276.96	215.28	189.72	223.92	161.40	165.84	203.64	2481.36
Apr-21	372.72	281.52	279.00	276.60	232.44	165.30	179.64	169.39	125.76	186.24	2268.61
May-21	418.08	310.20	244.44	258.36	206.04	145.68	215.28	158.41	139.44	165.24	2261.17
Jun-21	390.84	315.36	303.12	298.08	219.96	186.36	183.60	195.67	183.36	189.36	2465.71
Jul-21	486.48	356.88	277.92	267.24	200.64	184.80	239.88	211.45	179.76	201.96	2607.01
Aug-21	458.04	357.48	268.08	301.92	213.96	191.76	180.60	196.15	173.40	175.32	2516.71
Sep-21	355.92	346.68	285.48	300.24	235.92	188.64	211.20	235.87	176.04	199.68	2535.67

Oct-21	465.48	313.08	254.40	279.00	209.88	189.12	216.84	207.13	180.96	164.28	2480.17
Nov-21	460.80	352.20	271.08	289.92	252.00	199.08	186.24	222.19	193.44	173.40	2600.35
Dec-21	532.08	364.44	285.72	322.80	228.24	188.04	209.40	205.45	226.20	165.36	2727.73
Jan-22	546.36	325.20	282.36	296.52	220.56	190.44	210.72	203.23	200.88	169.44	2645.71
Feb-22	410.76	307.56	275.40	309.72	234.60	196.56	189.12	190.68	191.52	184.32	2490.24
Mar-22	501.84	416.52	333.00	328.92	298.92	236.04	237.84	240.23	217.68	213.12	3024.11
Apr-22	471.36	342.12	335.64	272.28	233.40	213.72	207.00	200.27	241.32	194.40	2711.51
May-22	499.44	414.24	342.36	273.24	254.16	236.52	217.44	218.72	240.24	206.76	2903.12
Jun-22	475.80	400.32	345.72	284.16	290.28	225.36	212.04	225.20	255.12	224.64	2938.64
Jul-22	520.20	417.96	343.32	273.12	233.52	231.00	224.16	161.16	229.68	197.88	2832.00
Total	12817.20	10797.84	10601.88	9335.76	7580.52	7141.68	7029.48	6610.99	6580.92	6458.88	

Bevacizumab

	NHS London	NHS West Midlands	NHS South Central	NHS South West	NHS East of England	NHS North West	NHS South East Coast	NHS Yorkshire and the Humber	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	139.10	82.20	77.69	71.50	58.28	87.01	61.10	83.65	52.80	43.26	756.59
May-17	170.43	83.60	67.86	69.83	72.70	88.07	106.30	79.70	59.30	48.75	846.54
Jun-17	155.10	90.60	81.71	72.83	70.75	99.39	87.60	99.50	62.00	39.05	858.52
Jul-17	132.40	66.10	74.24	76.20	66.30	109.23	79.10	75.15	51.90	37.19	767.80
Aug-17	149.00	77.60	77.69	75.23	72.00	86.43	82.55	75.30	60.70	38.63	795.11
Sep-17	131.70	64.90	67.70	79.61	59.20	76.66	53.35	76.40	55.50	30.73	695.75
Oct-17	139.10	68.53	72.34	66.20	58.75	116.37	58.15	66.00	44.90	37.16	727.50
Nov-17	137.50	62.91	86.58	72.93	64.20	69.05	78.95	70.25	56.60	35.49	734.45
Dec-17	126.60	55.58	70.99	67.75	52.40	91.86	55.10	55.70	48.10	36.64	660.71
Jan-18	133.80	66.10	76.55	71.17	61.70	83.79	76.55	74.85	52.30	37.69	734.49
Feb-18	131.10	61.13	60.98	66.62	53.70	72.98	59.55	53.20	44.70	37.18	641.12
Mar-18	139.53	68.39	68.36	67.88	56.80	99.59	61.85	44.45	44.20	37.15	688.19
Apr-18	129.70	58.70	66.56	74.75	75.57	98.54	59.10	48.30	48.20	36.83	696.25
May-18	145.20	78.19	74.45	61.58	80.87	95.84	63.30	49.65	48.50	41.38	738.94
Jun-18	130.90	70.77	66.10	62.48	91.94	74.70	61.60	49.90	40.80	39.20	688.39
Jul-18	157.80	80.63	76.12	61.33	78.96	90.14	53.65	50.90	48.70	39.05	737.28
Aug-18	142.80	81.44	70.40	65.70	96.82	96.63	63.15	58.75	36.60	41.61	753.90
Sep-18	137.80	76.14	61.65	59.53	66.78	83.94	56.25	56.50	41.80	35.48	675.86
Oct-18	139.50	91.31	74.50	67.88	75.47	108.39	66.70	71.25	62.70	40.10	797.79
Nov-18	150.10	108.86	60.30	68.68	78.04	100.74	69.30	53.95	56.70	47.25	793.92
Dec-18	128.05	98.90	55.13	63.97	65.79	97.99	48.60	65.65	57.70	40.42	722.19
Jan-19	144.45	91.58	72.76	71.92	70.56	117.29	76.15	67.15	53.00	41.85	806.71
Feb-19	114.05	73.37	58.46	56.93	57.29	97.19	63.40	56.25	47.70	42.05	666.68
Mar-19	136.35	73.74	62.68	67.23	63.03	106.38	78.65	58.85	49.50	40.55	736.94

Apr-19	127.90	74.83	71.13	69.05	63.95	99.51	79.10	52.55	46.20	40.10	724.31
May-19	130.45	113.94	78.18	84.83	77.87	107.28	86.20	54.85	58.50	47.00	839.09
Jun-19	135.47	78.70	82.78	77.05	56.03	94.03	76.15	55.50	42.00	37.20	734.90
Jul-19	137.64	76.55	94.40	89.03	78.56	101.15	85.85	74.20	44.50	30.60	812.47
Aug-19	129.45	75.05	90.03	89.38	70.48	99.28	81.10	65.30	50.60	27.85	778.51
Sep-19	135.60	68.50	87.70	82.11	58.82	96.63	77.30	62.00	38.70	36.70	744.06
Oct-19	152.45	84.35	94.90	89.05	75.15	95.33	82.20	58.05	45.00	41.45	817.92
Nov-19	141.70	85.65	76.13	82.17	71.45	92.40	74.20	52.70	44.70	33.10	754.20
Dec-19	154.20	85.08	83.80	86.92	66.85	88.00	71.90	61.40	48.80	32.40	779.35
Jan-20	169.50	90.50	88.28	93.38	85.40	108.23	81.05	72.95	65.00	42.80	897.08
Feb-20	167.70	83.90	79.90	76.37	69.95	92.40	62.80	54.20	51.80	33.10	772.12
Mar-20	170.15	93.95	103.95	92.23	79.95	98.95	65.50	60.60	67.80	35.20	868.28
Apr-20	131.95	84.55	96.40	67.93	58.20	38.28	62.50	35.00	46.80	28.30	649.91
May-20	124.00	72.05	94.55	64.10	65.65	28.58	45.95	34.25	44.70	29.40	603.23
Jun-20	165.10	76.90	89.25	69.30	64.65	30.50	57.20	52.65	44.20	32.50	682.25
Jul-20	156.61	84.00	101.25	64.85	73.76	37.80	46.45	36.00	50.50	32.00	683.22
Aug-20	151.10	79.25	85.23	51.50	68.96	40.90	52.70	46.20	46.50	30.70	653.04
Sep-20	174.65	90.23	112.25	59.30	74.42	39.75	59.85	34.90	42.20	24.50	712.05
Oct-20	170.83	81.45	92.60	52.40	75.56	46.30	49.90	44.20	54.90	33.30	701.44
Nov-20	165.09	88.40	102.48	45.15	69.45	78.70	49.75	43.10	45.50	27.10	714.71
Dec-20	197.05	132.80	121.31	53.25	89.95	76.18	46.90	58.10	56.25	29.40	861.19
Jan-21	181.25	119.10	109.53	67.53	70.60	126.18	53.60	69.10	75.25	33.50	905.62
Feb-21	176.59	119.85	102.69	106.38	75.48	54.10	63.25	56.20	72.10	32.00	858.63
Mar-21	210.25	112.10	101.20	73.22	90.93	37.65	75.70	84.05	96.70	31.90	913.69
Apr-21	212.35	137.40	105.94	87.79	74.75	54.65	62.40	61.30	83.60	37.00	917.18
May-21	201.85	119.90	103.80	81.33	81.10	17.80	58.05	69.05	90.60	42.00	865.47
Jun-21	233.55	112.50	105.38	83.08	76.68	33.45	72.25	81.50	66.00	47.30	911.68
Jul-21	234.30	114.05	101.13	90.89	89.10	49.75	63.20	69.45	95.10	50.30	957.27
Aug-21	243.75	153.65	107.70	94.40	80.15	34.15	68.70	84.15	85.30	45.90	997.84
Sep-21	249.05	125.75	120.99	91.06	86.91	24.20	71.50	86.65	78.15	48.55	982.80

Oct-21	231.65	126.60	117.16	88.25	89.01	28.50	59.65	88.70	100.20	47.80	977.51
Nov-21	244.10	149.60	123.92	107.30	90.85	23.90	69.55	91.30	68.85	40.20	1009.56
Dec-21	285.60	150.65	120.31	98.45	109.81	52.50	77.50	101.30	75.35	56.40	1127.87
Jan-22	257.35	132.60	114.34	107.47	140.96	25.30	85.90	87.40	84.25	58.90	1094.46
Feb-22	265.80	144.55	95.71	89.47	123.16	22.50	79.05	80.00	68.70	55.30	1024.23
Mar-22	306.05	161.85	124.50	455.87	128.91	51.65	88.25	118.10	83.95	62.80	1581.93
Apr-22	268.70	127.73	94.84	108.15	121.97	36.45	89.30	101.85	65.80	58.80	1073.58
May-22	325.50	141.05	120.70	246.27	117.78	32.65	85.10	123.55	76.00	67.70	1336.30
Jun-22	333.90	145.85	120.13	107.35	106.10	35.60	86.30	115.50	71.50	66.80	1189.03
Jul-22	330.90	142.79	110.72	100.80	93.52	28.85	71.50	116.95	91.40	52.90	1140.32
Total	11323.12	6169.42	5708.92	5464.00	4990.68	4608.11	4395.30	4336.05	3788.85	2585.41	

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	NHS North West	NHS London	NHS East of England	NHS West Midlands	NHS Yorkshire and the Humber	NHS South West	NHS South Central	NHS South East Coast	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	858.07	578.93	524.38	482.75	462.57	407.59	349.52	246.19	266.81	305.33	4482.13
May-17	965.81	637.18	592.52	486.95	511.95	452.87	368.67	629.71	310.66	360.86	5317.18
Jun-17	839.75	645.79	641.03	617.96	513.31	438.34	432.36	303.74	347.80	320.06	5100.13
Jul-17	911.92	584.00	512.37	533.94	498.90	457.13	370.57	917.23	320.55	331.49	5438.09
Aug-17	956.09	630.57	533.78	538.50	528.79	420.26	424.58	276.73	346.01	358.03	5013.34
Sep-17	898.33	644.79	802.18	546.90	512.62	445.04	390.73	309.72	329.00	340.23	5219.54
Oct-17	978.43	668.31	553.05	555.51	523.05	445.05	409.32	247.80	327.35	332.73	5040.60
Nov-17	925.02	635.97	534.29	548.50	525.66	439.20	409.63	385.38	343.15	332.13	5078.93
Dec-17	921.25	620.53	481.31	488.36	432.30	375.54	375.74	295.70	281.47	308.03	4580.23
Jan-18	832.96	701.65	542.53	601.00	476.03	480.97	402.89	332.21	371.61	303.66	5045.49
Feb-18	906.34	617.92	462.35	465.08	423.44	396.39	335.33	273.06	318.68	271.82	4470.43
Mar-18	1003.65	700.39	480.10	491.36	437.47	439.50	415.48	293.81	332.56	288.76	4883.08
Apr-18	775.45	657.61	488.44	448.94	451.65	385.59	426.53	304.26	315.70	251.28	4505.44
May-18	809.00	647.86	548.97	553.77	496.16	462.65	448.92	336.63	329.26	308.66	4941.89
Jun-18	743.84	668.81	522.21	479.32	454.25	439.83	394.95	315.11	315.91	284.21	4618.43
Jul-18	662.48	574.80	553.48	556.34	487.62	449.94	434.18	325.37	324.17	323.82	4692.19
Aug-18	709.47	604.86	636.39	573.67	484.85	441.57	438.57	348.87	318.85	337.46	4894.54
Sep-18	614.02	596.68	559.29	534.33	445.34	392.24	379.58	299.96	326.86	299.02	4447.32
Oct-18	690.54	566.27	613.14	642.93	563.81	460.48	459.17	372.25	380.42	355.74	5104.75
Nov-18	687.21	688.51	608.22	605.56	514.01	453.70	416.26	391.23	370.20	299.42	5034.30
Dec-18	1087.93	623.14	542.44	551.27	465.07	465.99	377.77	335.74	327.56	306.83	5083.74
Jan-19	1112.54	673.46	651.50	635.97	546.01	535.12	465.97	420.36	371.95	330.82	5743.71
Feb-19	743.43	650.53	609.97	462.68	494.30	438.77	417.93	386.69	312.00	309.40	4825.71
Mar-19	822.91	698.85	663.13	710.06	487.05	469.23	446.76	395.40	351.53	299.33	5344.26

Apr-19	646.78	612.64	633.25	655.52	505.58	451.65	440.12	390.98	362.40	320.93	5019.83
May-19	766.04	603.66	668.79	723.53	512.90	437.52	448.19	447.15	397.31	355.36	5360.44
Jun-19	594.21	528.18	572.20	643.84	481.07	382.32	382.53	340.68	347.64	305.30	4577.96
Jul-19	681.61	609.60	657.66	667.64	567.89	465.18	477.48	454.56	384.21	351.05	5316.88
Aug-19	702.70	624.41	645.95	659.54	519.59	477.71	398.50	393.35	384.75	309.00	5115.50
Sep-19	664.87	572.87	690.61	583.85	519.54	426.80	445.32	409.47	375.04	287.43	4975.80
Oct-19	776.23	676.41	750.55	648.65	598.02	510.74	435.74	465.82	432.20	365.21	5659.57
Nov-19	659.89	585.60	677.78	597.13	513.14	542.38	426.35	415.79	392.12	331.21	5141.38
Dec-19	687.14	682.94	700.24	617.08	495.68	474.59	422.75	414.12	362.90	346.11	5203.53
Jan-20	720.73	794.72	729.11	662.99	556.50	567.25	464.94	456.85	393.75	354.52	5701.36
Feb-20	1137.18	688.89	561.43	609.89	497.73	448.39	401.33	432.24	220.83	320.86	5318.77
Mar-20	685.55	857.90	579.13	599.89	488.67	446.75	425.02	415.84	356.67	329.87	5185.29
Apr-20	303.45	579.55	470.79	533.16	399.29	346.80	363.22	323.19	310.23	243.32	3873.00
May-20	559.34	527.52	448.65	461.22	399.14	341.90	354.51	324.51	295.97	221.58	3934.34
Jun-20	361.18	663.06	502.83	523.27	418.22	392.14	396.62	356.93	292.45	236.75	4143.44
Jul-20	375.24	697.74	551.08	582.13	480.53	459.01	409.70	428.59	404.67	310.41	4699.09
Aug-20	391.52	572.19	523.31	483.66	440.19	404.78	366.28	409.55	368.53	275.92	4235.93
Sep-20	469.31	702.74	594.76	566.56	492.29	472.94	473.14	462.32	345.23	328.57	4907.84
Oct-20	443.83	684.07	641.39	570.91	488.68	462.65	459.99	468.07	420.79	305.51	4945.89
Nov-20	822.88	668.27	626.78	552.45	460.99	465.68	430.79	416.64	411.13	293.97	5149.57
Dec-20	1157.83	729.15	608.95	579.80	536.55	502.48	473.14	429.84	396.21	334.08	5748.03
Jan-21	1789.92	647.71	583.09	533.98	514.01	460.59	436.27	421.93	394.51	305.36	6087.37
Feb-21	436.41	610.78	596.24	554.91	476.77	847.84	414.34	367.74	374.98	276.66	4956.67
Mar-21	632.76	806.67	663.47	599.01	563.02	701.32	444.01	444.95	470.02	331.81	5657.04
Apr-21	474.73	676.74	606.52	617.21	528.19	599.87	427.47	389.33	338.80	326.45	4985.31
May-21	475.63	693.45	579.55	608.49	516.57	486.94	405.81	394.96	402.32	288.52	4852.25
Jun-21	488.80	747.78	663.92	606.30	582.19	516.61	414.96	440.11	319.51	330.06	5110.23
Jul-21	553.51	781.07	634.56	636.91	571.86	493.68	413.14	437.47	434.90	323.52	5280.61
Aug-21	678.69	720.25	667.64	640.83	557.98	504.70	441.13	425.42	342.21	308.65	5287.50
Sep-21	740.77	781.32	632.66	639.64	589.74	520.35	533.35	444.17	379.42	337.33	5598.76

Oct-21	371.95	668.59	582.93	567.90	544.33	482.00	442.31	415.50	409.70	325.60	4810.81
Nov-21	795.37	731.29	637.28	661.25	546.19	546.34	487.82	467.56	342.97	356.84	5572.92
Dec-21	548.08	742.84	646.62	719.11	564.57	520.35	446.61	480.41	394.46	371.54	5434.60
Jan-22	799.62	716.76	569.67	636.20	567.26	503.76	449.88	435.77	386.90	333.63	5399.44
Feb-22	481.59	629.45	543.19	568.55	551.35	514.30	390.95	422.83	378.49	368.01	4848.70
Mar-22	685.92	789.79	626.50	649.10	677.94	1058.92	479.85	520.80	463.96	395.02	6347.79
Apr-22	660.56	733.25	616.17	667.51	570.91	464.52	418.50	467.36	374.64	383.30	5356.71
May-22	617.42	770.42	628.21	651.15	636.74	576.69	453.90	448.75	429.58	400.82	5613.68
Jun-22	688.59	784.45	598.55	642.88	582.86	510.90	482.08	460.99	393.60	338.93	5483.83
Jul-22	733.19	733.23	609.55	638.35	572.74	511.69	416.12	450.12	373.62	372.09	5410.70
Total	46717.43	42745.34	38178.60	37473.64	32823.61	30893.98	27085.53	25735.78	22999.68	20560.19	

Cisplatin

	NHS South West	NHS West Midlands	NHS London	NHS North West	NHS Yorkshire and the Humber	NHS East of England	NHS South Central	NHS East Midlands	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	59.62	90.59	82.19	91.77	53.85	52.72	48.85	51.07	35.34	32.31	598.30
May-17	67.19	99.84	83.19	123.02	60.43	58.15	51.98	46.27	45.21	34.49	669.77
Jun-17	57.84	101.16	96.74	111.65	59.10	59.04	47.63	43.16	45.73	36.49	658.53
Jul-17	64.85	83.75	91.68	98.70	63.14	54.51	51.34	50.62	37.43	37.36	633.37
Aug-17	57.63	97.25	91.43	130.42	72.04	54.97	53.88	48.45	44.09	37.26	687.41
Sep-17	58.03	92.14	90.36	94.91	69.60	53.07	50.15	51.31	41.90	34.14	635.61
Oct-17	66.23	86.82	85.64	112.25	77.23	51.64	49.44	56.13	41.56	41.19	668.13
Nov-17	64.81	99.98	88.56	108.89	67.85	49.11	50.62	63.54	48.53	39.83	681.72
Dec-17	55.56	93.52	93.87	108.35	62.47	46.75	43.46	46.49	46.70	44.03	641.19
Jan-18	63.04	97.63	105.09	94.12	79.72	52.91	50.54	45.44	48.08	46.81	683.39
Feb-18	48.19	83.61	90.45	108.49	69.63	42.27	40.47	41.23	38.92	36.72	599.97
Mar-18	52.57	94.01	92.76	103.17	62.78	47.99	49.05	44.94	50.24	45.19	642.69
Apr-18	46.51	89.57	82.09	89.46	66.82	57.08	50.62	45.63	46.52	34.39	608.70
May-18	60.01	94.36	90.07	88.39	76.26	69.16	59.55	48.89	50.24	36.62	673.56
Jun-18	63.05	100.30	87.70	77.46	69.72	57.35	53.04	53.25	43.13	35.61	640.61
Jul-18	61.97	93.50	84.53	75.83	75.35	61.65	53.66	46.79	40.93	32.52	626.74
Aug-18	62.32	94.73	85.98	99.29	69.19	73.99	56.21	41.57	40.15	33.51	656.94
Sep-18	50.11	94.20	67.17	73.30	65.48	66.28	46.57	41.17	40.14	32.90	577.32
Oct-18	55.64	97.69	79.33	90.16	81.74	73.73	53.02	52.18	46.07	37.94	667.51
Nov-18	58.42	105.45	96.44	84.06	80.90	62.27	49.63	47.33	37.48	35.72	657.70
Dec-18	61.64	87.91	89.79	99.55	65.13	61.21	51.47	44.20	34.14	35.52	630.55
Jan-19	62.46	98.35	88.61	71.95	67.36	69.47	61.45	48.60	46.36	38.30	652.91
Feb-19	51.32	69.15	90.65	46.15	61.65	61.27	48.25	47.65	41.82	33.77	551.67
Mar-19	50.85	90.78	97.47	70.36	64.84	61.49	50.01	45.93	42.57	35.42	609.70

Apr-19	52.18	81.38	62.36	46.39	59.03	56.85	44.53	43.86	43.90	38.47	528.95
May-19	57.09	78.87	76.97	72.07	58.65	59.44	40.41	44.10	45.84	36.85	570.30
Jun-19	53.44	65.25	63.14	61.92	59.95	51.46	39.09	41.85	35.44	36.20	507.74
Jul-19	59.84	91.07	64.16	68.06	68.28	68.93	47.79	50.28	46.60	40.87	605.88
Aug-19	55.62	83.69	72.32	70.23	65.90	59.15	41.16	44.04	42.22	33.58	567.92
Sep-19	48.25	87.19	59.37	68.61	59.82	56.29	46.63	40.88	37.57	32.99	537.61
Oct-19	50.86	80.08	74.89	71.88	65.67	63.28	51.57	51.57	39.06	34.18	583.05
Nov-19	57.76	87.44	62.79	60.53	58.46	55.64	46.99	44.81	37.66	32.35	544.43
Dec-19	50.42	76.83	74.47	63.49	59.05	62.64	47.47	40.46	35.73	32.75	543.31
Jan-20	64.05	83.33	82.48	65.86	69.06	55.27	50.99	38.43	37.87	38.72	586.05
Feb-20	49.51	66.96	64.21	154.34	57.35	49.36	40.12	28.49	37.86	36.75	584.94
Mar-20	46.10	71.29	85.89	62.82	58.69	45.62	41.75	34.61	35.22	34.24	516.22
Apr-20	32.08	49.84	47.43	34.23	46.12	37.91	32.98	24.52	27.46	25.49	358.04
May-20	31.87	53.02	43.48	24.71	32.51	34.45	33.19	23.85	21.50	18.40	316.97
Jun-20	34.03	48.82	62.35	41.55	38.86	35.95	33.52	26.01	25.30	24.90	371.28
Jul-20	38.91	57.61	59.80	35.53	47.21	39.40	34.85	29.26	20.06	25.95	388.59
Aug-20	38.96	55.73	53.02	33.28	42.68	36.99	40.70	30.00	17.63	26.95	375.95
Sep-20	42.41	59.25	68.97	38.20	44.09	43.65	36.83	31.19	28.15	27.60	420.35
Oct-20	47.45	71.73	72.52	37.96	50.37	40.95	42.35	40.57	28.95	28.77	461.63
Nov-20	44.52	70.66	66.68	102.26	47.39	47.29	38.94	34.89	32.03	29.15	513.82
Dec-20	48.63	66.61	78.14	130.88	53.81	44.80	41.74	39.17	28.87	32.20	564.87
Jan-21	50.00	66.83	66.92	131.75	51.84	43.04	37.77	30.52	30.20	27.50	536.37
Feb-21	303.01	60.16	57.14	23.18	53.02	48.21	38.70	34.27	27.92	25.97	671.58
Mar-21	124.03	73.80	85.04	39.03	62.49	57.79	33.33	36.88	33.08	32.18	577.64
Apr-21	49.05	79.12	69.21	24.56	55.61	49.17	38.53	26.57	30.35	31.25	453.42
May-21	46.58	74.18	79.36	35.58	47.72	42.73	38.20	34.75	33.88	27.40	460.39
Jun-21	50.88	69.15	79.44	22.06	62.32	45.17	44.69	30.02	38.07	28.99	470.78
Jul-21	44.92	69.81	76.63	26.66	64.26	44.48	43.04	39.18	34.79	31.18	474.95
Aug-21	41.96	65.64	68.55	23.49	55.33	42.13	39.01	35.56	29.18	29.80	430.66
Sep-21	35.84	53.91	66.50	53.34	60.26	46.80	52.47	33.67	30.60	30.75	464.14

Oct-21	36.68	61.36	60.55	4.84	66.67	46.10	39.42	43.24	36.08	28.91	423.85
Nov-21	41.05	66.12	66.03	25.26	62.93	49.89	51.27	35.52	34.86	30.81	463.76
Dec-21	43.57	69.57	73.33	24.57	53.84	52.64	43.01	46.00	34.28	30.20	471.01
Jan-22	41.03	57.40	71.57	37.44	52.02	49.28	45.46	34.56	35.46	29.77	453.98
Feb-22	38.04	70.26	68.67	18.18	52.76	49.47	40.72	31.80	28.37	21.95	420.22
Mar-22	413.22	71.66	94.23	21.03	56.36	50.15	42.81	33.01	33.40	29.43	845.30
Apr-22	-144.21	65.94	74.78	22.46	50.68	46.78	37.47	33.87	31.30	26.15	245.22
May-22	171.92	78.29	73.25	24.02	55.93	48.07	42.50	34.41	34.71	28.85	591.95
Jun-22	39.22	76.35	74.41	38.79	53.18	46.75	45.66	32.46	31.96	30.54	469.32
Jul-22	39.72	68.47	61.52	27.20	52.27	46.82	35.82	30.76	34.63	37.04	434.24
Total	3870.32	5020.97	4894.35	4219.96	3854.68	3348.86	2884.35	2591.72	2361.31	2114.10	

Cyclophosphamide

	NHS London	NHS Yorkshire and the Humber	NHS West Midlands	NHS North West	NHS East of England	NHS East Midlands	NHS South Central	NHS South East Coast	NHS North East	NHS South West	Total (dosage)
Apr-17	51226.79	55268.65	41108.16	40075.48	27926.29	33100.80	32778.32	23656.30	23605.06	23544.72	352290.57
May-17	53155.00	53652.90	49558.20	47312.47	30311.95	37470.30	34725.35	26301.72	25302.45	24862.14	382652.47
Jun-17	61064.89	52344.10	49392.01	38888.33	30416.69	42214.65	33850.50	30493.42	25101.40	27946.87	391712.86
Jul-17	56124.62	53710.40	47415.92	35683.59	29952.06	43621.00	36051.26	27293.94	25289.01	26601.20	381742.99
Aug-17	56067.17	55850.00	54983.61	38938.28	27531.04	42610.40	35517.14	26954.53	26553.70	27502.03	392507.89
Sep-17	52980.54	54073.15	46466.23	33139.36	28472.17	40723.65	33305.95	27892.92	25383.20	25078.91	367516.09
Oct-17	54690.96	57331.35	52282.58	38395.19	30923.63	41779.60	32318.04	26655.34	26521.15	27154.67	388052.50
Nov-17	52928.93	55294.20	49741.61	42610.09	33141.20	41064.35	31999.71	32749.17	25058.10	28550.80	393138.14
Dec-17	50605.01	39720.25	44224.17	33979.38	29112.90	35071.30	27763.24	27076.20	26271.60	25766.13	339590.18
Jan-18	57587.25	54047.09	50750.38	38163.26	33550.68	37310.50	32231.93	28489.56	27776.85	30379.55	390287.05
Feb-18	46730.90	46928.51	43676.36	30640.72	28025.23	33993.30	29593.70	24678.88	24792.85	27170.36	336230.81
Mar-18	62003.17	48783.10	48731.82	36575.28	30054.22	35471.40	32492.85	28303.64	26375.80	28999.30	377790.57

Apr-18	49285.74	50422.61	42395.35	37098.28	31438.81	36380.05	29549.67	26629.41	25252.80	27158.12	355610.83
May-18	52125.44	54113.15	47028.51	41475.30	40822.32	39964.70	31532.20	27723.73	27138.85	29339.25	391263.44
Jun-18	46385.41	55150.18	42535.77	37527.71	37929.55	37415.95	29225.55	25706.65	24814.10	27666.36	364357.23
Jul-18	58065.23	51381.63	45186.95	40118.02	37892.21	40735.25	30324.39	29340.76	24030.80	27716.47	384791.70
Aug-18	54883.67	47368.20	38771.32	42793.94	37718.15	37533.15	31967.65	29259.20	22622.90	23369.79	366287.97
Sep-18	45894.14	48100.40	37074.39	37430.08	33744.04	33820.55	25510.67	28407.52	25141.35	20563.28	335686.41
Oct-18	73737.25	51464.31	43554.81	41882.11	39407.29	40688.70	32155.27	30164.40	30349.32	28888.74	412292.20
Nov-18	50992.65	53597.74	41679.38	44366.33	34005.53	39132.10	29764.00	31461.67	28341.13	28668.96	382009.48
Dec-18	42519.41	49991.76	39760.37	39891.39	33581.04	33373.80	28638.05	30444.16	25611.43	29722.12	353533.52
Jan-19	55331.12	49137.71	48694.58	40900.88	37526.34	38827.65	32108.08	35182.47	23227.75	29778.34	390714.91
Feb-19	44487.80	46341.95	40793.67	35910.97	35017.14	33458.70	27933.81	29076.10	21686.80	28021.60	342728.52
Mar-19	46191.29	54498.13	39811.65	40572.77	34230.32	37261.20	31159.43	32405.96	25872.20	29172.76	371175.71
Apr-19	45611.52	52941.74	46759.91	35789.59	44065.59	38993.90	31853.70	30701.32	29629.95	27662.94	384010.15
May-19	41831.79	52908.67	44108.97	42628.33	47096.35	40278.35	29327.61	35115.86	28503.60	27613.81	389413.34
Jun-19	36282.37	47626.34	36679.76	34007.74	39653.18	39303.75	28185.09	27874.71	26318.16	26401.95	342333.05

Jul-19	41999.24	52643.81	39420.99	38569.09	46900.13	35443.20	37145.86	35079.70	28290.95	28412.69	383905.66
Aug-19	41982.27	51492.15	34706.89	41579.42	43756.14	31799.70	33046.72	29448.66	29874.45	27656.36	365342.76
Sep-19	34677.70	44319.71	34060.94	36704.71	43546.77	31189.75	33869.51	29513.70	23638.20	20840.88	332361.86
Oct-19	42164.73	49147.48	39848.14	40357.64	44470.39	34433.90	36214.02	32072.34	30511.10	26190.92	375410.65
Nov-19	36142.61	43568.86	36725.11	35115.69	40278.85	34248.00	31513.93	30434.05	28307.60	23416.09	339750.78
Dec-19	72666.57	46074.04	39014.96	35398.79	41443.60	37067.78	33325.31	29535.60	30544.80	25002.69	390074.14
Jan-20	79702.26	49988.85	39868.63	36097.26	47440.56	31750.38	33384.28	29241.30	26626.05	25123.98	399223.55
Feb-20	82965.18	43326.25	34148.61	31644.67	41398.31	31329.80	30251.33	25030.25	25367.15	25031.82	370493.36
Mar-20	62995.44	48271.00	36973.75	33702.53	40897.25	36837.50	31507.61	26182.90	28521.64	25407.03	371296.65
Apr-20	59589.56	40147.47	39039.72	27549.20	32931.70	35956.60	30287.03	21493.45	26690.55	23579.38	337264.66
May-20	51882.80	36508.10	35372.28	28667.54	33198.35	30550.85	28668.35	18734.55	21404.60	23315.26	308302.67
Jun-20	56542.55	35825.08	41649.14	34715.12	35357.02	35297.90	30006.53	24699.36	26479.65	26003.96	346576.31
Jul-20	56740.77	33508.40	44429.48	34251.39	42736.50	33660.60	31277.42	28256.92	25373.75	25218.30	355453.52
Aug-20	48477.65	25362.35	30487.87	33214.93	32570.90	30100.55	26647.75	24639.90	21971.25	19462.36	292935.51
Sep-20	77968.63	26792.10	35797.26	35148.16	37502.35	33071.20	30231.01	29029.40	22990.15	21634.03	350164.29

Oct-20	86161.79	25790.20	34373.51	32968.22	38100.52	30437.90	30884.73	27207.30	22765.75	22089.25	350779.18
Nov-20	96383.58	28229.35	32418.51	42619.50	39789.10	32662.15	27818.38	24553.05	23789.60	19521.10	367784.32
Dec-20	92798.17	29293.00	35994.17	40336.37	44500.20	31080.40	30601.05	25935.20	24545.10	24085.00	379168.65
Jan-21	82066.07	22360.10	30514.64	30866.29	35548.14	30502.25	27906.35	24620.10	21392.58	19486.01	325262.54
Feb-21	90441.83	20872.15	37902.51	47268.42	38242.80	27585.45	26540.68	20995.09	20041.80	17090.28	346981.00
Mar-21	109273.32	32950.44	36900.84	45874.79	47776.40	34173.35	31042.14	26198.58	26019.55	22931.85	413141.25
Apr-21	93214.71	27191.13	39275.42	40326.88	40432.18	29371.05	28647.94	22794.16	23782.00	25096.52	370131.99
May-21	97682.09	31234.41	30809.85	39272.97	39139.21	29412.20	28442.25	26819.80	23575.26	23891.89	370279.92
Jun-21	94663.00	35890.85	36679.78	45144.34	44068.35	35461.05	31547.36	33010.45	27347.90	19859.98	403673.05
Jul-21	109064.10	26526.56	37401.46	45914.40	40580.43	36619.30	29460.44	29478.68	27772.77	18063.36	400881.49
Aug-21	97354.66	23186.55	32406.54	39915.07	38597.13	27897.05	31376.73	28279.93	26543.50	20226.84	365783.99
Sep-21	88268.37	22622.58	34094.92	38652.07	38487.43	22051.50	31617.69	26394.16	22331.70	18867.48	343387.89
Oct-21	100549.02	23862.60	35392.53	40771.39	32876.12	27099.25	27906.88	27686.18	23787.20	19582.64	359513.81
Nov-21	87455.31	23798.25	36659.33	44400.24	37678.15	27467.95	29651.33	28063.04	18703.70	17997.44	351874.73
Dec-21	89851.12	27110.80	37030.20	39065.98	32690.75	24595.40	29776.47	29685.38	19470.50	20601.96	349878.56

Jan-22	94710.58	23281.85	34942.86	32837.05	31084.66	19229.50	28288.61	25516.14	14884.60	15481.09	320256.95
Feb-22	102045.62	25993.25	34206.05	48246.92	32799.20	25482.45	28014.63	23366.67	18995.60	18342.78	357493.17
Mar-22	117504.14	27542.50	40542.91	54929.14	35440.40	35107.55	33490.05	34194.47	26777.10	22310.24	427838.49
Apr-22	115026.33	21464.25	37351.81	37210.67	30049.85	29024.45	31165.38	27863.29	21929.30	17310.07	368395.40
May-22	108989.63	23635.11	25196.64	36749.51	33569.73	31531.80	32056.29	23727.57	19799.49	17331.12	352586.89
Jun-22	120160.35	20659.38	30583.20	42233.61	32192.33	27755.20	30200.14	29446.13	21330.10	17513.96	372074.39
Jul-22	98722.92	22897.11	29604.43	28495.14	37745.45	18770.15	68650.61	20716.70	13877.35	15883.31	355363.18
Total	4417674.73	2585416.29	2534992.22	2463609.93	2349363.27	2167654.12	2014325.86	1779983.66	1582626.64	1535161.08	

Docetaxel

	NHS West Midlands	NHS East of England	NHS South West	NHS London	NHS Yorkshire and the Humber	NHS East Midlands	NHS South Central	NHS North West	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	111.711	100.756	89.389	96.129	84.4936	73.832	75.242	121.631	49.242	40.117	842.5426
May-17	132.166	93.16	87.8945	99.064	95.6774	91.95	83.113	121.538	73.0214	45.733	923.3173
Jun-17	131.7362	109.232	91.068	100.679	92.6736	83.326	76.822	126.562	60.6092	42.472	915.18
Jul-17	110.36	96.065	85.8205	96.933	82.955	72.346	77.801	115.546	52.1442	39.31	829.2807
Aug-17	125.342	104.2298	93.206	96.201	94.294	77.756	93.4897	130.03	61.2144	48.3982	924.1611
Sep-17	123.521	110.7286	83.5344	96.196	87.9	72.012	83.816	107.198	68.9484	43.13	876.9844
Oct-17	126.0884	95.892	85.9294	92.134	83.474	75.264	84.809	110.187	55.7028	49.432	858.9126
Nov-17	130.742	94.04	89.8294	92.526	84.523	75.458	92.6282	124.796	82.286	28.738	895.5666
Dec-17	117.5542	82.494	83.5748	101.053	73.219	68.684	77.346	123.408	61.33	72.414	861.077
Jan-18	134.977	113.268	98.9116	119.458	100.694	80.218	85.1059	110.377	71.908	60.134	975.0515
Feb-18	125.739	88.438	85.504	93.473	76.712	64.632	70.3278	113.096	57.238	46.78	821.9398
Mar-18	146.733	94.988	90.7591	112.945	82.8218	79.598	70.85	119.514	68.704	53.0957	920.0086
Apr-18	137.076	108.74	91.8334	109.058	84.436	78.414	78.7502	113.818	56.452	51.108	909.6856
May-18	135.516	109.09	100.7876	102.908	99.9736	73.916	80.385	108.092	68.112	55.55	934.3302
Jun-18	110.728	110.222	87.5274	107.356	86.649	74.246	77.541	89.058	61.202	47.72	852.2494
Jul-18	110.444	114.4915	98.2427	99.246	94.1058	93.094	81.947	91.806	61.817	53.528	898.722
Aug-18	123.164	130.875	94.932	98.112	94.364	89.61	91.023	101.524	56.784	54.252	934.64
Sep-18	127.95	112.9735	82.698	91.597	81.364	85.76	76.038	90.002	49.081	46.752	844.2155
Oct-18	143.232	123.1755	95.458	96.502	93.96	83.08	87.436	109.196	60.328	56.968	949.3355
Nov-18	137.636	112.8225	91.254	123.44	99.184	94.614	80.587	94.78	60.462	58.2289	953.0084
Dec-18	127.004	100.553	89.32	96.114	96.599	88.11	70.552	115.544	49.48	53.752	887.028
Jan-19	136.752	121.814	99.498	106.568	112.986	97.48	86.667	98.64	68.754	59.456	988.615
Feb-19	98.4694	98.685	86.01	94.258	98.57	86.98	80.575	88.91	61.992	51.04	845.4894
Mar-19	134.202	111.07	85.992	110.354	93.6	79.908	90.906	92.528	63.918	57.7346	920.2126

Apr-19	139.2572	114.829	84.9271	90.26	96.1298	80.296	87.812	94.104	68.824	57.984	914.4231
May-19	128.976	120.882	92.5601	108.479	100.676	80.448	94.404	106.464	61.838	55.112	949.8391
Jun-19	120.34	101.928	80.6362	89.526	86.6464	80.044	80.276	86.262	46.236	47.128	819.0226
Jul-19	138.976	121.104	101.8024	83.387	92.2148	89.948	85.859	91.67	68.164	59.424	932.5492
Aug-19	116.493	112.066	102.6891	103.231	85.855	87.544	79.004	96.84	57.148	59.34	900.2101
Sep-19	111.812	113.655	91.4976	83.628	83.5648	87.64	81.22	77.544	54.204	52.356	837.1214
Oct-19	120.176	133.62	107.4609	89.077	98.1848	98.544	87.967	97.092	68.966	56.212	957.2997
Nov-19	115.99	121.413	109.6526	82.373	92.608	92.128	85.666	90.67	56.239	51.76	898.4996
Dec-19	111.651	113.679	94.2414	85.643	78.8098	81.468	86.18	117.828	55.272	56.32	881.0922
Jan-20	126.773	130.932	121.5044	95.595	99.5	90.816	92.966	102.766	62.236	58.704	981.7924
Feb-20	118.3592	109.8948	86.4724	68.491	80.44	78.372	77.894	90.33	51.31	53.024	814.5874
Mar-20	120.529	102.13	85.922	105.165	79.776	84.864	79.462	87.05	48.832	50.664	844.394
Apr-20	103.4676	76.928	64.56	59.308	62.212	62.272	60.73	30.662	37.75	38.716	596.6056
May-20	93.2318	79.254	58.895	40.093	46.1	54.596	62.948	34.296	34.347	39.436	543.1968
Jun-20	78.7654	80.876	63.576	63.79	47.582	63.46	53.44	41.124	35.707	39.928	568.2484
Jul-20	89.106	79.144	67.044	56.406	49.136	76.16	54.553	30.372	35.946	34.424	572.291
Aug-20	72.932	75.746	69.384	43.423	49.378	69.876	56.656	33.996	36.618	32.252	540.261
Sep-20	90.272	82.482	71.63	65.964	57.0418	62.968	70.796	39.042	40.46	37.184	617.8398
Oct-20	92.92	85.198	69.172	54.091	54.36	78.324	61.027	31.31	40.844	34.616	601.862
Nov-20	77.922	87.566	67.546	51.37	64.39	67.276	60.649	36.39	38.564	39.156	590.829
Dec-20	74.442	93.826	72.492	63.504	69.942	77.196	65.184	68.518	46.048	40.832	671.984
Jan-21	72.07	95.708	77.11	56.672	66.65	72.272	62.001	62.548	43.646	38.736	647.413
Feb-21	74.824	93.882	76.274	52.725	66.092	63.716	61.398	24.624	37.336	43.944	594.815
Mar-21	87.82	111.95	87.246	84.178	84.812	75.888	63.98	29.592	48.93	47.392	721.788
Apr-21	93.462	94.616	80.432	61.753	77.988	67.156	71.287	22.384	46.125	41.512	656.715
May-21	85.887	99.118	75.018	57.67	80.076	74.7	63.218	20.848	45.29	35.14	636.965
Jun-21	104.062	111.308	80.528	70.374	81.56	67.28	74.332	27.228	52.296	38.444	707.412
Jul-21	100.2806	93.016	83.78	76.014	82.912	84.988	71.68	23.704	48.852	41.224	706.4506
Aug-21	96.6368	101.78	88.2934	85.911	78.09	60.568	65.613	20.606	48.332	41.82	687.6502
Sep-21	108.7786	105.478	91.002	69.175	82.752	68.964	75.032	42.474	48.363	48.536	740.5546

Oct-21	112.8006	99.902	86.942	69.798	89.312	71.148	67.618	25.01	43.154	41.892	707.5766
Nov-21	116.5672	113.254	81.962	72.872	91.4276	71.424	72.006	25.754	50.472	47.188	742.9268
Dec-21	118.9832	115.054	90.427	67.252	87.55	86.404	77.5	25.9	52.448	44.476	765.9942
Jan-22	92.3672	106.12	80.346	80.166	82.732	81.168	81.164	24	53.844	38.632	720.5392
Feb-22	94.7012	99.368	75.03	71.688	81.724	82.932	70.476	22.934	51.7933	37.808	688.4545
Mar-22	103.8822	119.4518	93.5268	84.88	97.183	89.206	79.96	31.412	60.342	40.264	800.1078
Apr-22	100.5646	108.13	88.1067	67.853	80.4224	83.44	72.342	16.572	55.36	39.424	712.2147
May-22	107.4744	110.512	83.082	79.932	86.6654	96.984	71.877	30.556	48.642	43.648	759.3728
Jun-22	102.7948	103.036	85.986	76.662	82.9836	79.79	85.0218	31.008	47.44	47.296	742.0182
Jul-22	91.6698	101.876	81.766	62.771	82.0874	72.442	68.456	29.252	52.826	46.192	689.3382
Total	7146.861	6658.516	5519.497	5363.454	5312.795	5034.998	4873.413	4638.517	3461.775	3013.983	

Doxorubicin

	NHS London	NHS West Midlands	NHS North West	NHS East of England	NHS South West	NHS Yorkshire and the Humber	NHS East Midlands	NHS South Central	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	26909.50	19476.00	20152.50	16545.00	18726.80	15418.00	14295.00	13976.34	10880.00	7390.00	163769.14
May-17	31436.50	22637.17	26852.00	19300.50	19629.50	16948.00	15613.00	14277.20	15374.70	7574.00	189642.57
Jun-17	35064.78	21939.80	23925.35	18321.94	19107.50	16788.50	16364.00	14954.86	14905.50	8389.00	189761.23
Jul-17	33573.02	20711.00	22102.80	17566.48	19492.20	16925.50	15474.00	16204.30	13296.82	7546.00	182892.12
Aug-17	35815.31	21200.50	23389.10	18519.48	21308.90	19634.50	16500.00	14231.30	14431.90	7946.00	192976.99
Sep-17	35584.50	20704.00	21795.60	17465.06	19784.40	17066.50	13589.50	14707.22	14469.50	8518.00	183684.28
Oct-17	38521.22	23691.00	24914.00	17444.48	20044.10	17489.50	15990.50	14219.06	15157.70	9137.21	196608.77
Nov-17	38885.42	24074.40	23351.50	17807.84	20255.00	18120.00	15036.50	15348.78	13477.50	8992.20	195349.14
Dec-17	40059.02	19047.00	24836.25	16211.50	18696.34	15797.00	14213.00	13853.66	13024.50	9059.50	184797.77
Jan-18	39370.08	21129.00	21164.90	16230.34	19746.84	18589.00	15940.50	16742.36	14883.80	10301.80	194098.62
Feb-18	33207.70	19813.00	19768.60	14126.92	19488.18	15818.00	12490.00	13829.27	11448.50	8309.00	168299.17
Mar-18	37022.28	21872.00	23083.90	15920.00	20228.34	16928.00	14530.50	14847.98	13309.52	10696.50	188439.02

Apr-18	33678.50	22149.00	22189.80	17184.50	19405.88	15519.00	13836.00	14473.52	13066.00	10102.50	181604.70
May-18	37196.00	23157.70	23139.90	21691.92	20498.18	17910.00	14379.00	16744.62	14358.50	10779.50	199855.32
Jun-18	35479.60	18024.00	21681.90	21115.04	19347.18	17461.50	14476.00	13596.38	13431.50	10643.50	185256.60
Jul-18	35279.50	23564.50	21258.50	21022.00	16028.50	18806.00	14717.00	15141.54	12174.00	9686.50	187678.04
Aug-18	35769.50	21155.50	24529.00	21676.00	17888.00	18751.00	15589.50	16657.02	13093.00	10445.00	195553.52
Sep-18	37063.00	20233.00	21532.00	19426.50	15578.50	17045.00	14348.50	12750.40	12564.00	9272.00	179812.90
Oct-18	32644.00	24461.00	22482.50	21651.66	19036.00	18584.00	16921.00	13739.78	15416.50	10349.50	195285.94
Nov-18	42779.50	21280.00	21790.30	18467.32	19061.50	17167.50	16547.00	14426.62	15361.38	10190.50	197071.62
Dec-18	33352.00	28471.74	21477.90	18324.90	17276.50	16531.50	14881.00	14091.62	12735.00	9587.00	186729.16
Jan-19	36364.50	24473.42	19969.50	21754.14	17699.82	16743.50	17380.50	14343.10	13482.50	10310.50	192521.48
Feb-19	38214.00	16383.66	24511.20	16647.64	15287.32	17356.50	14088.50	13218.48	11383.60	8654.50	175745.40
Mar-19	30702.00	23252.60	23664.00	16983.54	16295.88	15761.50	15878.50	13046.88	10666.90	9824.50	176076.30
Apr-19	27033.50	23203.60	19858.00	17389.48	17254.30	16822.10	14612.50	13278.94	11555.50	12104.50	173112.42
May-19	29050.00	23138.91	20956.72	20798.70	18467.40	18500.00	17207.00	14324.28	12405.00	12049.00	186897.01
Jun-19	25080.50	18999.60	17898.94	18661.66	16804.35	16047.00	15301.00	12852.28	11309.20	11034.64	163989.17

Jul-19	26805.00	22344.60	21536.90	20598.20	19765.59	18802.00	18216.50	16052.74	12711.70	12498.50	189331.73
Aug-19	30880.50	26233.40	22361.00	17822.22	19456.62	18293.00	16235.00	14782.86	11516.10	11042.50	188623.20
Sep-19	28492.50	27937.00	20092.44	17686.66	21367.40	17641.50	15845.00	14501.50	10368.00	12187.50	186119.50
Oct-19	29053.00	25912.50	25147.70	19272.46	19377.51	18707.50	18976.00	15143.92	12529.70	13194.08	197314.37
Nov-19	27639.00	21984.50	22249.50	18779.04	17712.74	16278.50	15145.00	13876.12	11641.60	10912.50	176218.50
Dec-19	36965.50	34412.84	23540.70	17261.26	17603.84	16169.00	15398.00	15004.62	11131.80	13715.00	201202.56
Jan-20	37653.00	26170.02	23893.10	19303.96	19840.89	19730.50	17329.00	15137.26	11885.00	12705.70	203648.43
Feb-20	34347.50	32269.34	18707.70	18356.66	16755.81	15827.60	15382.50	13348.36	11445.70	11805.00	188246.17
Mar-20	42576.70	22114.64	24412.00	19624.74	19598.80	17907.00	15133.00	15063.34	11929.20	14421.00	202780.42
Apr-20	25072.90	19109.00	17546.50	19230.92	18944.58	16167.00	15232.00	15179.06	11308.80	12247.50	170038.26
May-20	26742.80	20401.00	15906.80	18866.42	15052.50	16053.50	14768.00	13386.12	9311.00	9600.00	160088.14
Jun-20	37623.00	30983.00	17918.50	17778.20	16295.00	16150.00	15711.00	15101.18	13302.00	11947.50	192809.38
Jul-20	41931.50	24108.10	19434.90	20563.50	16163.18	17813.50	19374.50	16034.48	13464.30	11135.00	200022.96
Aug-20	30667.00	20439.54	15570.00	17236.00	16026.18	15967.50	14643.50	14196.16	12335.40	9777.50	166858.78
Sep-20	37297.50	33155.04	17718.90	18472.00	17068.68	13547.20	16116.50	15653.84	12431.10	10392.50	191853.26

Oct-20	37566.40	28147.50	16051.00	20219.74	18766.18	13514.50	15628.00	15619.26	13697.00	10982.50	190192.08
Nov-20	35260.97	58621.54	15766.00	21512.84	17806.86	13992.50	18623.00	14536.22	11598.10	11522.50	219240.53
Dec-20	38318.50	42316.00	23326.50	22015.84	19318.68	14131.50	16359.50	17085.72	12287.50	11727.50	216887.24
Jan-21	34572.50	52705.00	23315.50	18128.34	16325.64	14310.00	14032.00	14307.42	10578.80	10710.00	208985.20
Feb-21	33202.80	31254.56	15540.00	18092.42	15022.68	13837.50	14229.50	14526.38	10468.70	9592.24	175766.78
Mar-21	42367.25	33072.06	20074.00	20060.62	18201.00	16419.00	15330.50	16161.52	12028.00	12333.08	206047.03
Apr-21	36054.90	24356.90	15691.00	17380.00	17202.00	15199.50	14377.50	13969.78	10877.90	11025.58	176135.06
May-21	38748.50	32827.80	16499.00	16954.33	16660.50	15027.50	15512.00	14035.06	10991.80	10985.24	188241.73
Jun-21	41847.50	24690.00	15112.50	18610.00	17013.50	17344.50	15193.50	15057.52	13282.90	11647.50	189799.42
Jul-21	40528.50	22483.90	14213.50	16674.50	16926.00	18384.50	16209.00	15569.20	11984.20	9761.08	182734.38
Aug-21	37180.50	22833.30	16587.50	17868.50	17610.46	17010.50	13444.00	16262.06	13390.20	9997.50	182184.52
Sep-21	38867.50	31721.80	21734.00	18892.00	18733.00	16532.00	13976.00	16555.68	12866.60	10382.00	200260.58
Oct-21	35496.00	32925.00	14515.00	19654.00	16503.00	15354.50	10209.00	14343.00	11246.30	12985.00	183230.80
Nov-21	39528.00	33381.00	15463.50	19847.00	18008.68	14860.50	16818.00	14954.68	12298.50	9157.50	194317.36
Dec-21	35707.00	22505.50	13898.00	21257.50	16631.84	16775.50	17314.50	14107.22	13301.50	10442.50	181941.06

Jan-22	34800.50	41612.00	14421.50	19361.00	16238.68	15569.50	17352.00	12621.80	12388.40	8792.50	193157.88
Feb-22	35124.50	22867.50	15402.50	18225.50	16063.34	15969.90	15399.00	12468.30	10578.30	9445.00	171543.84
Mar-22	41026.50	26893.00	16749.00	22048.50	17441.84	17365.50	17235.50	16664.78	14018.80	9165.50	198608.92
Apr-22	37664.75	25503.50	14468.50	18655.50	41822.84	17721.00	17023.00	14972.84	13201.20	9945.00	210978.13
May-22	38600.42	25306.00	14843.00	20917.00	18397.70	18880.50	17565.50	16881.86	12283.50	11545.00	195220.48
Jun-22	39401.50	25954.50	21181.50	18427.50	17533.90	16769.00	17888.00	18155.64	13664.20	11336.00	200311.74
Jul-22	37385.01	23059.00	16586.00	21844.74	18756.20	17830.50	15830.50	14001.24	13281.40	10107.50	188682.09
Total	2258132.82	1660854.98	1279752.30	1205754.15	1180451.25	1072383.80	999254.50	945196.53	805287.72	670062.84	

Epirubicin

	NHS West Midlands	NHS East of England	NHS London	NHS Yorkshire and the Humber	NHS North West	NHS East Midlands	NHS South West	NHS South Central	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	86.15	72.50	79.49	81.69	83.67	56.21	49.70	57.48	46.25	53.65	666.77
May-17	87.88	82.06	83.82	86.21	112.36	60.56	58.89	64.20	45.16	52.77	733.90
Jun-17	104.72	79.57	83.56	86.76	55.75	69.46	61.16	65.41	53.78	55.81	715.97
Jul-17	89.61	78.11	78.16	79.55	77.97	67.00	51.65	52.25	49.52	56.59	680.39
Aug-17	96.17	78.85	83.75	83.24	85.26	73.79	57.30	61.60	55.14	56.85	731.95
Sep-17	86.22	77.07	73.68	82.46	74.23	66.72	51.44	66.70	50.72	46.54	675.78
Oct-17	83.61	77.11	76.69	75.17	83.65	73.36	63.57	62.31	48.39	49.34	693.18
Nov-17	94.57	79.59	66.60	76.47	70.24	65.50	62.87	60.43	64.06	53.96	694.26
Dec-17	87.41	68.50	67.13	63.90	65.42	58.03	48.80	55.34	45.54	48.09	608.14
Jan-18	87.68	74.84	75.21	72.39	76.69	58.36	59.70	58.23	50.82	47.59	661.50
Feb-18	73.39	63.71	65.71	62.93	63.53	47.23	45.58	50.68	42.09	45.74	560.56
Mar-18	88.10	73.48	74.52	74.84	89.81	54.48	48.52	61.00	44.05	49.40	658.18
Apr-18	77.45	66.93	67.55	71.16	70.71	52.97	44.06	51.24	44.61	44.84	591.50
May-18	87.94	84.54	62.42	80.40	59.53	60.65	54.75	61.30	43.30	52.05	646.86
Jun-18	84.96	77.46	53.87	68.89	61.75	64.04	46.27	55.31	38.65	44.34	595.52
Jul-18	84.14	79.08	57.98	66.85	64.22	67.36	48.92	50.81	41.64	48.31	609.29
Aug-18	90.00	80.01	66.39	68.06	73.61	61.99	51.44	54.29	38.11	53.03	636.91
Sep-18	79.66	72.61	61.01	67.70	55.89	61.34	49.51	41.66	51.26	48.48	589.10
Oct-18	81.24	94.41	68.61	75.97	62.84	69.84	55.42	47.37	42.85	50.33	648.87
Nov-18	75.79	85.15	77.29	76.21	60.93	58.29	60.38	53.53	38.70	44.54	630.80
Dec-18	75.09	69.13	57.51	67.77	61.31	52.08	56.47	48.35	34.88	40.05	562.63
Jan-19	85.11	78.84	69.67	69.95	67.53	61.29	61.54	52.13	45.43	43.20	634.66
Feb-19	59.13	76.92	66.15	63.42	56.05	56.35	48.27	49.64	41.50	38.57	555.98
Mar-19	77.57	74.76	71.57	66.56	61.70	54.84	56.25	50.57	61.48	57.42	632.70

Apr-19	87.37	72.67	58.59	66.35	59.72	58.72	56.99	47.92	45.06	43.55	596.92
May-19	82.28	87.95	68.62	68.02	65.38	64.14	60.23	50.70	45.93	43.84	637.07
Jun-19	61.40	73.56	59.93	63.02	54.88	59.47	51.90	43.46	35.65	37.06	540.31
Jul-19	61.35	82.66	70.61	74.42	66.10	64.83	54.11	53.59	59.58	43.78	631.02
Aug-19	66.99	81.46	70.19	70.22	63.66	54.29	53.82	46.74	48.43	38.87	594.65
Sep-19	67.16	73.72	65.63	70.11	63.66	53.64	54.07	50.87	44.96	34.50	578.28
Oct-19	77.95	81.70	71.65	63.13	62.66	54.46	61.25	53.35	46.73	40.44	613.30
Nov-19	90.84	85.03	66.40	57.31	59.00	55.26	51.51	48.10	51.70	40.95	606.07
Dec-19	75.35	81.98	68.90	59.69	64.94	55.24	58.14	52.15	60.87	45.54	622.77
Jan-20	77.11	89.54	65.72	68.72	67.23	59.83	70.64	52.85	54.24	41.06	646.92
Feb-20	67.61	75.12	57.46	63.04	60.37	48.97	53.57	49.19	44.93	35.46	555.70
Mar-20	80.34	81.33	75.47	63.84	62.48	58.15	55.24	51.38	44.58	37.15	609.94
Apr-20	66.98	52.82	50.95	40.96	26.59	48.61	46.40	35.85	31.38	29.37	429.88
May-20	59.71	53.92	34.76	37.75	26.68	40.52	35.03	41.76	24.99	21.50	376.60
Jun-20	71.44	62.51	57.47	46.85	33.28	52.44	45.14	50.62	39.32	31.35	490.41
Jul-20	76.80	73.62	45.72	49.21	32.94	56.03	42.51	52.15	43.77	27.11	499.85
Aug-20	64.11	52.67	34.92	35.63	30.40	47.80	33.75	38.69	39.29	22.32	399.56
Sep-20	62.37	54.24	56.42	41.71	33.89	47.42	42.33	44.47	41.62	27.39	451.84
Oct-20	56.18	57.69	54.22	44.08	39.85	52.02	41.36	44.54	36.45	32.43	458.81
Nov-20	52.28	65.64	58.37	51.58	57.45	58.20	52.58	37.81	33.13	31.13	498.16
Dec-20	62.87	73.19	67.02	58.20	57.56	55.08	57.68	47.28	39.77	36.28	554.92
Jan-21	59.53	75.37	58.17	53.26	61.16	46.37	46.78	50.80	39.50	30.29	521.21
Feb-21	64.87	75.84	51.03	49.06	50.68	47.08	50.40	45.54	41.55	24.95	500.98
Mar-21	65.69	79.07	72.91	70.45	74.88	64.30	55.09	47.47	44.96	30.69	605.51
Apr-21	75.19	72.09	57.43	44.80	73.36	51.62	54.49	48.38	41.39	28.85	547.58
May-21	52.85	55.95	65.88	44.98	52.04	48.28	46.71	46.93	45.75	26.86	486.20
Jun-21	57.73	68.40	71.20	63.20	37.43	47.69	54.38	48.11	54.72	35.45	538.29
Jul-21	70.15	56.90	76.75	63.97	51.04	47.96	52.05	52.88	48.84	37.68	558.21
Aug-21	75.46	65.11	58.00	61.37	61.36	44.62	50.38	51.58	46.54	36.12	550.53
Sep-21	66.00	73.95	65.80	64.07	67.04	55.90	54.01	50.55	48.56	29.34	575.20

Oct-21	64.57	74.63	60.89	54.77	65.96	52.50	47.90	54.36	49.01	31.76	556.33
Nov-21	64.27	74.40	66.28	59.90	81.96	57.65	56.84	56.26	55.29	28.83	601.66
Dec-21	71.68	70.23	63.48	59.44	70.35	56.06	53.48	57.40	50.49	32.75	585.36
Jan-22	60.87	61.15	54.79	55.21	71.63	55.65	54.36	51.46	45.01	23.33	533.44
Feb-22	67.71	62.03	59.03	52.99	74.15	42.79	51.56	48.31	44.70	28.50	531.75
Mar-22	79.02	70.34	84.06	58.63	44.17	51.03	55.81	58.38	55.08	33.83	590.34
Apr-22	66.65	58.25	56.46	58.46	42.83	48.48	51.69	53.06	46.95	34.31	517.12
May-22	62.70	59.20	62.05	55.00	57.80	51.94	50.84	54.72	48.24	34.77	537.24
Jun-22	72.95	59.61	72.22	56.61	77.88	60.16	52.32	50.60	49.09	34.96	586.39
Jul-22	59.49	59.45	66.72	54.39	42.63	48.24	49.00	49.25	47.20	30.88	507.25
Total	4749.32	4630.15	4170.48	4042.80	3941.69	3595.01	3358.68	3301.19	2933.08	2516.54	

Erlotinib

	NHS London	NHS East of England	NHS South West	NHS Yorkshire and the Humber	NHS North West	NHS South Central	NHS South East Coast	NHS North East	NHS West Midlands	NHS East Midlands	Total (dosage)
Apr-17	325.03	195.45	115.70	78.70	49.70	77.30	68.25	53.30	51.10	27.00	1041.53
May-17	335.50	186.15	155.03	86.80	65.10	125.45	48.75	35.50	56.50	23.10	1117.88
Jun-17	345.70	195.15	134.40	83.35	51.00	92.90	77.85	42.40	48.60	20.05	1091.40
Jul-17	330.40	165.90	143.28	100.95	68.25	80.50	65.55	77.20	43.75	26.25	1102.03
Aug-17	380.05	168.60	180.30	114.35	52.20	74.90	62.25	36.60	57.05	18.60	1144.90
Sep-17	244.20	192.50	152.70	82.98	61.20	131.75	55.00	55.90	57.90	12.75	1046.88
Oct-17	293.35	170.55	167.18	103.15	63.00	142.25	53.45	50.25	54.85	19.80	1117.83
Nov-17	289.35	169.70	133.35	109.38	72.70	99.35	45.75	45.70	61.25	16.20	1042.73
Dec-17	266.20	174.20	145.85	107.48	56.55	83.75	28.80	33.70	39.30	15.75	951.58
Jan-18	289.55	169.60	124.50	110.50	76.80	103.05	32.45	45.00	68.45	22.20	1042.10
Feb-18	203.40	170.10	110.95	86.55	67.75	63.30	34.35	48.75	36.00	17.45	838.60
Mar-18	277.30	151.45	155.35	93.28	70.25	81.00	46.50	36.75	49.10	18.00	978.98
Apr-18	238.40	156.20	101.45	80.58	69.75	98.20	28.50	63.00	33.40	20.70	890.18
May-18	316.85	163.20	161.85	93.03	53.75	85.25	37.50	61.20	42.70	17.95	1033.28
Jun-18	309.10	163.40	154.60	99.65	47.00	71.85	42.00	63.55	28.60	9.75	989.50
Jul-18	266.10	174.05	106.50	102.68	42.50	88.90	34.35	59.45	36.50	8.90	919.93
Aug-18	240.20	160.95	85.20	107.18	67.95	102.55	51.00	60.10	37.53	9.75	922.40
Sep-18	264.95	157.13	130.25	89.78	42.00	87.40	46.20	55.65	22.20	10.50	906.05
Oct-18	249.75	160.20	123.08	124.05	51.75	90.55	54.75	95.10	32.35	26.50	1008.08
Nov-18	224.53	137.10	113.60	96.98	45.00	96.00	75.45	50.05	33.70	22.50	894.90
Dec-18	234.90	127.05	78.55	59.68	63.75	81.65	42.75	50.30	27.60	12.00	778.23
Jan-19	223.55	128.65	141.15	125.05	59.25	86.90	66.75	80.85	36.10	21.60	969.85
Feb-19	227.03	110.20	105.30	86.88	82.50	96.30	33.00	88.10	33.00	9.75	872.05
Mar-19	208.90	116.80	137.85	74.48	87.00	104.60	67.05	80.20	40.75	28.20	945.83

Apr-19	251.25	146.55	132.45	79.90	80.00	83.40	51.00	83.70	37.00	13.95	959.20
May-19	268.88	135.75	129.75	76.13	68.15	95.40	29.25	44.70	35.80	24.75	908.55
Jun-19	221.70	89.85	111.45	64.45	62.25	101.75	31.50	51.70	14.85	14.05	763.55
Jul-19	223.70	122.55	199.60	80.20	70.50	39.90	30.00	67.50	15.90	26.25	876.10
Aug-19	204.45	121.05	136.80	78.95	65.25	90.00	45.75	36.75	36.30	13.50	828.80
Sep-19	174.60	116.00	154.80	63.03	71.25	98.75	30.75	52.65	12.30	12.75	786.88
Oct-19	179.40	117.21	176.48	95.65	81.00	70.95	40.50	41.90	20.40	14.25	837.74
Nov-19	177.60	120.15	159.65	84.58	58.50	70.50	40.90	23.70	21.60	17.25	774.43
Dec-19	182.10	122.65	120.60	101.95	69.00	66.10	31.50	37.45	21.08	12.65	765.08
Jan-20	206.55	109.85	126.10	64.00	78.75	62.15	43.50	43.55	21.60	11.25	767.30
Feb-20	191.20	113.55	152.95	100.30	61.50	38.15	48.45	31.50	21.90	17.25	776.75
Mar-20	306.90	132.50	150.75	101.08	84.00	90.75	58.40	45.65	4.20	8.25	982.48
Apr-20	147.05	110.10	152.05	63.85	74.25	31.30	52.50	38.10	12.60	15.75	697.55
May-20	153.25	118.90	100.05	62.13	81.75	34.80	48.75	34.50	8.70	15.75	658.58
Jun-20	232.75	109.85	118.05	54.98	82.55	34.00	78.85	32.80	8.70	4.50	757.03
Jul-20	128.10	126.05	130.65	61.58	57.00	23.65	59.25	35.30	8.40	13.20	643.18
Aug-20	136.75	89.85	114.30	42.53	63.00	24.75	53.55	17.50	9.30	7.20	558.73
Sep-20	152.45	85.85	106.85	18.75	58.70	11.80	58.50	10.50	12.45	3.00	518.85
Oct-20	111.60	57.65	90.80	46.28	69.00	11.80	42.00	34.30	8.70	9.00	481.13
Nov-20	145.10	100.00	110.35	39.83	42.00	9.05	55.20	30.20	27.00	3.00	561.73
Dec-20	153.60	66.40	73.35	43.28	90.00	10.75	29.25	17.60	8.40	9.00	501.63
Jan-21	120.15	66.00	105.75	24.45	53.05	12.50	45.90	22.75	4.20	3.00	457.75
Feb-21	99.60	56.55	68.00	36.45	36.00	9.00	56.80	24.05	4.20	6.00	396.65
Mar-21	140.30	58.98	97.35	18.83	39.25	17.80	40.50	12.00	4.20	6.00	435.20
Apr-21	101.40	58.90	103.35	18.83	28.50	12.00	39.75	18.00	6.15	9.00	395.88
May-21	84.00	59.25	81.10	25.58	54.00	8.50	33.75	18.00	4.20	6.00	374.38
Jun-21	74.00	62.05	84.60	17.88	60.00	7.75	21.00	7.50	11.20	6.00	351.98
Jul-21	125.55	44.05	49.50	27.90	36.00	8.00	26.40	10.50	8.40	6.00	342.30
Aug-21	59.10	58.30	49.75	25.58	28.50	10.75	15.20	9.00	7.00	12.00	275.18
Sep-21	120.35	50.25	65.80	25.95	37.50	9.25	34.30	9.00	11.20	3.00	366.60

Oct-21	76.20	48.60	39.80	13.95	33.00	17.38	35.80	14.10	7.00	3.00	288.83
Nov-21	118.05	42.00	64.55	17.40	40.50	6.75	22.05	4.50	11.40	4.50	331.70
Dec-21	100.25	40.75	40.50	31.20	21.00	3.00	13.50	4.50	8.75	3.00	266.45
Jan-22	83.75	43.00	43.50	12.60	28.00	10.50	22.50	10.50	7.20	4.50	266.05
Feb-22	50.85	31.75	31.50	13.50	29.25	13.75	26.25	13.50	10.20	0.90	221.45
Mar-22	79.40	57.60	28.95	12.60	41.50	25.00	9.75	0.00	10.50		265.30
Apr-22	95.15	60.05	42.00	4.50	44.25	7.50	14.25	4.50	12.20	4.50	288.90
May-22	73.90	44.10	58.90	9.00	32.80	6.25	19.50	27.00	4.50	9.00	284.95
Jun-22	56.10	33.90	32.20	22.50	32.80	10.50	21.00	9.40	6.00		224.40
Jul-22	58.20	30.90	14.65	16.20	34.50	8.00	22.50	32.70	1.40	6.75	225.80
Total	12249.55	7123.56	7007.53	4095.68	3645.50	3549.53	2678.30	2431.65	1535.35	794.95	

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	NHS West Midlands	NHS Yorkshire and the Humber	NHS London	NHS North West	NHS East of England	NHS East Midlands	NHS South Central	NHS North East	NHS South West	NHS South East Coast	Total (dosage)
Apr-17	45.00	82.50	15.00		67.50	37.50	7.50	15.00	22.50		292.50
May-17	52.50	67.50	22.50		75.00	37.50	15.00	45.00		7.50	322.50
Jun-17	37.50	74.50	18.75	15.00	82.50	33.00	15.00	60.00	15.00	15.00	366.25
Jul-17	30.00	75.00		7.50	105.00	30.00	7.50	56.00		15.00	326.00
Aug-17	52.50	60.00	30.00		45.00	30.00	7.50	45.00			270.00
Sep-17	52.50	52.50	22.50		75.00	30.00	30.00	60.00			322.50
Oct-17	52.50	52.50	15.00	15.00	82.50	59.50	7.50	60.00			344.50
Nov-17	52.50	52.50	15.00	217.50	75.00	45.00	15.00	60.00		0.00	532.50
Dec-17	45.00	37.50	15.00	615.00	60.00	22.50	15.00	60.00	7.50	7.50	885.00
Jan-18	90.00	37.50	7.50	465.00	112.50	37.50	7.50	30.00			787.50
Feb-18	45.00	30.00	15.00	7.50	45.00	37.50	22.50	52.50		15.00	270.00
Mar-18	45.00	45.00	18.75	15.00	97.50	37.50	7.50	30.00	22.50	7.50	326.25
Apr-18	52.50	37.50	30.00		72.50	7.50	7.50	45.00	15.00		267.50
May-18	45.00	37.50	52.50		67.50	0.00	7.50	22.50			232.50
Jun-18	45.00	26.25	52.50		67.50		7.50	30.00			228.75
Jul-18	67.50	22.50	45.00		90.00	7.50	0.00	30.00	7.50		270.00
Aug-18	37.50	22.50	22.50		67.50	15.00	0.00	30.00	7.50		202.50
Sep-18	52.50	30.00	45.00		52.50	7.50	0.00	30.00	15.00		232.50
Oct-18	67.50	52.50	30.00		60.00	7.50	7.50	60.00	7.50		292.50
Nov-18	52.50	15.00	22.50		67.50	7.50	7.50	45.00	15.00		232.50
Dec-18	37.50	60.00	60.00		82.50	7.50		45.00			292.50
Jan-19	52.50	45.00	60.00		75.00	30.00	15.00	52.50	45.00		375.00
Feb-19	8.50	52.50	30.00		15.00		15.00	22.50			143.50
Mar-19	45.00	22.50	60.00		22.50		15.00	37.50	7.50		210.00

Apr-19	45.00	15.00	45.00		30.00	15.00	7.50	22.50		7.50	187.50
May-19	22.50	30.00	59.00		37.50	7.50	15.00	22.50		37.50	231.50
Jun-19	22.50	37.50	29.00		7.50			15.00		22.50	134.00
Jul-19	37.50	15.00	44.00	45.00	15.00	7.50	15.00	22.50	30.00	15.00	246.50
Aug-19	21.50	22.50	66.00	45.00	7.50	15.00	22.50	15.00	45.00	15.00	275.00
Sep-19	59.50	7.50	22.00	67.50	37.50		7.50	30.00	30.00	7.50	269.00
Oct-19	53.75	15.00	51.00	82.50	7.58	82.50	7.50		30.00	15.00	344.83
Nov-19	57.75	60.00	82.00	82.50	45.00	112.50	45.00	7.50	30.00	15.00	537.25
Dec-19	74.50	112.50	103.50	75.00	52.50	127.50	37.50	49.00	82.50	7.50	722.00
Jan-20	89.50	97.50	104.50	116.25	78.75	82.50	78.75	22.50	52.50	15.00	737.75
Feb-20	108.00	162.75	150.00	105.00	67.50	157.50	97.50	15.00	37.50	15.00	915.75
Mar-20	124.75	187.50	232.50	150.00	89.50	120.00	105.00	50.00	30.00	37.50	1126.75
Apr-20	176.25	228.75	75.00	157.50	105.00	112.50	135.00	67.50	37.50	15.00	1110.00
May-20	90.00	202.50	187.50	120.00	45.00	82.50	127.50	30.00	30.00	22.50	937.50
Jun-20	116.75	180.00	75.00	138.75	112.00	150.00	142.50	30.00	52.50	33.75	1031.25
Jul-20	170.25	157.50	179.00	150.00	44.50	75.00	120.00	30.00	37.50	37.50	1001.25
Aug-20	117.75	120.00	157.50	150.00	59.50	90.00	90.00	37.50	22.50	15.00	859.75
Sep-20	169.75	150.00	130.25	131.25	45.00	112.50	105.00	37.50	22.50	22.50	926.25
Oct-20	147.25	112.50	162.25	90.00	27.75	60.00	89.50	37.50	22.50	7.50	756.75
Nov-20	172.00	97.50	114.25	82.50	48.50	82.50	82.50	30.00	15.00	7.50	732.25
Dec-20	102.25	127.50	89.50	86.25	27.75	97.50	97.50	30.00	15.00	7.50	680.75
Jan-21	117.25	75.00	130.75	75.00	30.00	45.00	82.50	30.00	15.00	7.50	608.00
Feb-21	132.25	82.75	82.00	67.50	22.50	45.00	67.50	30.00	22.50	15.00	567.00
Mar-21	102.75	115.00	120.00	52.50	52.50	93.00	82.50	45.00	30.00	7.50	700.75
Apr-21	87.75	52.50	108.25	75.00	45.00	37.50	67.50	30.00	7.50	7.50	518.50
May-21	169.75	70.25	85.75	37.50	37.50	70.50	60.00	15.00	22.50	7.50	576.25
Jun-21	90.75	95.50	100.25	30.00	52.50	25.50	37.50	22.50	7.50	22.50	484.50
Jul-21	154.75	82.50	89.00	45.00	45.00	30.00	52.50	45.00	22.50	15.00	581.25
Aug-21	174.25	67.50	70.25	37.50	22.50	55.50	45.00	22.50	22.50	22.50	540.00
Sep-21	138.75	52.50	123.25	30.00	67.50	37.00	37.50	15.00	30.00	30.00	561.50

Oct-21	136.75	75.00	114.75	30.00	52.50	70.50	37.50	45.00	7.50	26.25	595.75
Nov-21	119.00	30.00	81.50	45.00	30.00	25.50	30.00	15.00	22.50	18.75	417.25
Dec-21	126.50	60.00	44.00	37.50	37.50	40.50	60.00		30.00	18.75	454.75
Jan-22	66.50	56.25	108.75	30.00	22.50	15.00	52.50	37.50	22.50	15.00	426.50
Feb-22	159.00	67.50	44.50	22.50	15.00	22.50	60.00		22.50	15.00	428.50
Mar-22	141.50	75.00	104.00	37.50	37.50	7.50	30.00	32.50	22.50	26.25	514.25
Apr-22	139.25	60.00	55.75	7.50	15.00	52.50	56.25		15.00	8.00	409.25
May-22	145.50	97.50	33.75	22.50	15.00	22.50	45.00	22.50	15.00	15.00	434.25
Jun-22	85.00	33.75	105.00	30.00	22.50	22.50	30.00	7.50	45.00	15.00	396.25
Jul-22	115.25	78.50	26.25	56.25	7.50	15.00	30.00		7.50	15.00	351.25
Total	5545.00	4556.75	4491.50	4001.25	3283.33	2850.50	2632.00	2040.00	1200.00	754.25	

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	NHS London	NHS North West	NHS West Midlands	NHS East of England	NHS Yorkshire and the Humber	NHS South West	NHS South Central	NHS North East	NHS East Midlands	NHS South East Coast	Total (dosage)
Apr-17	1588.92	2016.00	1508.29	1229.29	937.90	941.02	783.98	762.13	538.24	668.66	10974.42
May-17	1691.09	2478.56	1780.12	1427.45	1226.12	1049.72	839.80	806.44	641.30	681.69	12622.29
Jun-17	1778.93	2419.60	1738.20	1380.09	1163.54	1089.19	860.97	769.07	686.48	734.24	12620.31
Jul-17	1480.39	1957.98	1455.89	1151.25	1202.09	1194.17	863.41	748.43	679.44	618.74	11351.79
Aug-17	1515.75	2449.85	1578.61	1149.62	1263.81	1120.46	878.18	868.15	816.60	788.94	12429.97
Sep-17	1487.22	2309.09	1388.23	1222.38	1229.72	1089.97	868.00	770.43	706.58	751.93	11823.55
Oct-17	1618.73	2274.57	1463.50	1280.19	1172.94	1120.74	952.12	795.76	669.98	798.54	12147.08
Nov-17	1622.77	2352.04	1616.95	1345.14	1124.64	1042.11	1006.81	807.46	738.40	966.21	12622.54
Dec-17	1808.04	2319.21	1342.25	1265.84	967.75	822.70	882.73	779.35	648.82	784.90	11621.58
Jan-18	1771.78	2131.28	1577.99	1297.48	1212.34	946.00	901.73	887.10	788.92	761.12	12275.73
Feb-18	1575.75	2648.73	1277.70	1154.76	975.83	894.90	934.83	695.10	742.98	768.26	11668.83
Mar-18	1886.83	2285.74	1466.03	1241.50	1158.74	956.02	1061.01	772.91	767.94	765.37	12362.10
Apr-18	1747.72	2558.46	1541.55	1238.03	1008.80	868.02	941.13	714.95	734.46	740.32	12093.44
May-18	1753.70	2330.06	1554.39	1412.89	1267.58	1066.85	1173.99	819.47	841.33	836.60	13056.86
Jun-18	1762.31	2022.73	1554.76	1292.00	1191.85	1067.67	1077.67	640.96	790.07	734.67	12134.71
Jul-18	1776.99	2010.45	1652.44	1354.44	1266.16	1088.35	1112.51	710.37	913.37	678.20	12563.28
Aug-18	1834.68	2327.07	1751.07	1534.39	1302.77	1104.74	1160.32	861.83	930.90	674.75	13482.52
Sep-18	1746.12	1993.27	1671.67	1476.63	1194.16	967.68	965.99	711.36	873.74	663.07	12263.70
Oct-18	1850.83	2185.58	1753.21	1478.76	1363.16	1133.12	1172.87	813.59	800.10	904.10	13455.32
Nov-18	1730.27	2185.52	1807.31	1193.03	1375.35	1093.14	994.09	773.31	872.77	885.99	12910.78
Dec-18	1561.39	1821.74	1718.75	1140.77	1239.74	1009.80	825.07	798.76	774.17	706.95	11597.14
Jan-19	1664.35	1972.40	1849.49	1297.69	1277.58	1062.62	993.16	853.70	852.30	830.78	12654.06
Feb-19	1547.07	1923.08	1346.06	1253.63	1074.33	969.45	782.97	846.93	659.11	691.58	11094.20
Mar-19	1695.10	2067.90	1656.15	1463.75	1173.54	1016.91	882.99	794.04	1007.39	655.63	12413.40

Apr-19	1436.09	1788.67	1746.10	1286.64	1163.46	1082.35	868.48	970.24	898.55	724.61	11965.20
May-19	1443.38	1971.90	1654.87	1408.48	1167.31	1143.21	940.95	846.00	850.64	856.99	12283.74
Jun-19	1279.63	1566.57	1446.83	1194.77	1010.57	1025.41	804.19	748.70	700.55	618.27	10395.50
Jul-19	1668.27	1680.64	1685.30	1460.79	1303.03	1098.76	893.08	893.56	810.75	861.66	12355.84
Aug-19	1403.94	1616.98	1531.07	1325.39	1203.46	1173.86	758.88	823.77	733.14	720.96	11291.45
Sep-19	1377.63	1627.62	1364.20	1349.80	1099.97	940.93	887.18	697.04	723.67	649.97	10718.01
Oct-19	1456.73	1776.51	1683.80	1509.74	1462.73	1062.64	1013.73	808.47	791.38	878.86	12444.59
Nov-19	1337.58	2024.60	1532.19	1470.44	1164.79	1022.49	890.29	713.41	843.46	785.06	11784.31
Dec-19	1615.18	1788.16	1461.30	1413.01	1029.72	972.68	729.20	787.20	823.16	706.71	11326.31
Jan-20	1904.19	1612.12	1498.10	1521.40	1072.62	1059.58	853.92	810.63	880.39	784.44	11997.39
Feb-20	1573.48	1919.93	1251.13	1324.06	1177.69	1070.18	834.83	732.10	774.38	688.97	11346.74
Mar-20	1774.20	1706.44	1211.21	1299.89	1141.34	958.39	855.03	795.83	764.18	671.37	11177.88
Apr-20	3511.92	648.48	928.54	873.74	692.47	614.99	632.33	481.99	529.20	461.26	9374.92
May-20	6656.75	775.11	710.36	781.15	555.45	664.19	589.01	435.74	484.57	454.02	12106.34
Jun-20	8994.88	866.17	1009.17	998.13	659.59	846.30	737.99	597.40	604.61	498.53	15812.77
Jul-20	9837.20	1086.10	1221.27	1147.56	785.69	959.82	753.94	747.77	640.78	649.38	17829.52
Aug-20	3598.84	1041.14	1151.11	1084.96	738.20	839.57	779.31	636.40	608.98	700.52	11179.03
Sep-20	7481.18	1338.70	1253.46	1215.64	844.95	941.13	769.53	755.06	717.78	802.31	16119.74
Oct-20	10344.59	1185.12	1317.87	1288.33	903.12	990.38	888.73	777.72	737.18	764.91	19197.95
Nov-20	8226.93	1752.90	1440.51	1290.92	834.50	1018.46	801.66	747.57	750.19	670.29	17533.92
Dec-20	9715.65	2176.96	1434.42	1292.73	862.57	1054.11	759.48	808.46	784.19	705.30	19593.88
Jan-21	5593.61	2220.01	1407.74	1079.37	829.75	925.63	788.04	771.99	687.59	654.51	14958.25
Feb-21	4294.49	1487.07	1382.49	1124.64	871.00	911.13	959.25	661.44	732.19	693.62	13117.31
Mar-21	8859.68	1793.55	1804.40	1439.75	1033.27	1011.25	890.19	919.99	887.48	816.83	19456.38
Apr-21	9614.78	1480.61	1619.99	1289.04	853.51	881.92	1014.38	741.73	758.09	671.73	18925.77
May-21	3537.67	1720.07	1474.41	1068.65	947.31	931.20	937.60	799.16	822.33	691.48	12929.87
Jun-21	9889.23	1805.82	1541.85	1282.49	972.90	1074.86	1034.80	876.03	844.49	775.42	20097.90
Jul-21	8513.84	1817.25	1511.43	1113.54	1060.06	1003.22	1122.14	705.14	860.79	806.39	18513.79
Aug-21	2641.05	1809.51	1404.17	1134.42	1052.03	1004.46	930.38	705.53	800.12	768.90	12250.56
Sep-21	8322.62	1526.14	1312.34	1196.92	1098.68	974.92	1114.95	759.88	755.65	793.02	17855.13

Oct-21	4794.85	1661.70	1226.97	1349.67	1116.62	972.54	970.76	702.55	777.72	930.10	14503.50
Nov-21	6690.34	1865.17	1356.97	1420.61	1244.80	1073.18	1119.84	775.25	810.12	817.89	17174.16
Dec-21	6106.33	1912.30	1318.92	1387.73	1071.54	1042.62	943.71	761.26	781.69	799.49	16125.59
Jan-22	6486.77	1743.35	1277.21	1203.10	906.51	869.04	993.33	783.20	723.09	789.44	15775.05
Feb-22	6463.17	1324.79	1380.73	1192.01	958.27	869.67	911.63	703.93	709.59	844.94	15358.72
Mar-22	8347.46	1472.23	1611.89	1328.62	987.58	1022.24	977.13	832.63	835.43	993.55	18408.76
Apr-22	3301.12	1339.85	1418.62	1167.12	901.25	871.42	905.89	687.56	685.84	830.47	12109.13
May-22	5805.38	1492.19	1595.53	1255.62	1012.03	1082.87	963.57	834.62	735.92	923.46	15701.20
Jun-22	1820.35	1876.16	1575.91	1178.29	1026.23	1013.07	864.07	719.59	664.47	939.19	11677.34
Jul-22	9075.97	1755.48	1578.23	1050.13	1060.30	937.92	763.94	764.19	618.15	826.63	18430.94
Total	247293.67	117094.99	94383.22	81080.30	68247.30	63727.94	58163.69	48922.31	48417.91	48112.64	

Methotrexate

	NHS London	NHS South Central	NHS West Midlands	NHS Yorkshire and the Humber	NHS North West	NHS East Midlands	NHS South West	NHS East of England	NHS North East	NHS South East Coast	Total (dosage)
Apr-17	818.31	238.17	633.64	343.32	156.02	306.59	280.01	198.54	88.35	85.91	3148.84
May-17	902.44	249.35	917.54	384.48	401.65	381.33	252.08	207.84	108.02	34.72	3839.43
Jun-17	1051.12	263.22	705.85	455.07	435.11	359.45	270.63	273.82	81.36	102.71	3998.35
Jul-17	1196.68	219.79	514.88	461.78	414.34	383.28	370.43	251.76	211.54	134.97	4159.44
Aug-17	1609.26	304.03	262.38	492.99	549.93	408.76	366.08	265.40	80.93	157.47	4497.24
Sep-17	1359.68	264.59	333.62	336.79	346.11	362.36	222.31	302.38	164.02	94.72	3786.56
Oct-17	1116.25	200.48	434.56	535.96	476.45	547.75	275.38	235.63	233.61	109.08	4165.13
Nov-17	1040.56	209.22	526.64	459.09	434.27	537.84	241.41	152.27	309.68	96.47	4007.44
Dec-17	1061.04	176.83	431.78	562.00	404.13	365.99	328.97	125.84	264.50	83.37	3804.45
Jan-18	1146.93	10284.02	427.17	523.16	505.54	492.62	335.49	195.61	209.40	185.40	14305.33
Feb-18	765.23	163.49	272.25	394.29	312.91	309.18	145.31	235.18	89.21	78.76	2765.80
Mar-18	885.65	227.32	187.62	398.23	338.60	473.04	190.99	213.45	223.40	89.03	3227.33
Apr-18	758.97	234.56	109.72	322.94	333.82	315.02	226.82	252.50	185.09	57.74	2797.15
May-18	787.02	292.89	152.13	324.49	536.21	343.00	261.93	248.55	79.09	71.69	3096.98
Jun-18	855.85	292.17	215.99	409.13	328.48	283.79	278.91	166.65	119.50	51.02	3001.50
Jul-18	752.59	366.00	289.24	474.69	309.77	422.16	229.08	186.24	174.69	47.79	3252.23
Aug-18	811.15	410.19	249.02	380.93	326.26	247.76	173.11	226.48	249.28	73.05	3147.21
Sep-18	840.89	270.34	312.47	226.00	243.18	104.69	321.81	203.49	168.08	95.65	2786.59
Oct-18	767.51	246.08	454.44	359.94	338.48	250.31	209.40	319.47	257.96	127.18	3330.76
Nov-18	892.87	274.97	297.48	382.93	319.28	257.54	380.76	141.75	190.73	98.52	3236.81
Dec-18	787.53	295.38	260.39	349.99	346.84	306.93	347.75	222.43	123.42	105.54	3146.18
Jan-19	854.56	281.47	211.87	447.18	312.99	190.79	313.16	182.95	300.39	70.70	3166.04
Feb-19	812.12	455.33	300.93	272.77	435.16	112.13	253.71	66.90	146.16	27.62	2882.82
Mar-19	1834.09	260.24	303.38	472.74	556.63	143.26	336.43	120.85	217.96	72.74	4318.31

Apr-19	473.56	296.87	263.47	359.72	440.92	220.90	273.39	170.93	250.79	36.48	2787.01
May-19	359.60	315.46	287.51	381.69	384.23	176.63	309.48	148.78	171.49	45.91	2580.76
Jun-19	309.29	247.01	605.96	491.75	374.46	276.80	308.62	241.78	227.99	66.63	3150.27
Jul-19	433.44	355.25	518.48	521.55	496.47	190.67	361.28	231.03	101.78	127.42	3337.35
Aug-19	458.20	266.03	359.43	554.48	353.41	302.29	351.44	257.05	183.58	144.67	3230.57
Sep-19	452.97	217.35	460.28	389.84	269.27	334.02	297.82	204.99	178.73	87.73	2892.99
Oct-19	613.82	293.70	554.38	337.46	308.64	454.12	375.37	250.73	167.91	122.15	3478.28
Nov-19	410.20	254.39	404.96	359.49	320.92	280.82	331.69	225.71	50.49	106.19	2744.84
Dec-19	784.28	321.00	421.09	386.02	469.44	321.24	353.53	226.96	101.46	98.31	3483.31
Jan-20	980.75	281.57	502.68	542.56	505.38	311.82	236.54	220.02	112.74	60.08	3754.13
Feb-20	966.35	243.06	269.87	641.77	690.18	208.29	207.51	127.25	163.60	71.41	3589.27
Mar-20	1165.57	185.13	445.49	611.71	423.90	278.68	200.02	90.00	157.00	92.69	3650.17
Apr-20	927.17	212.29	235.94	588.79	252.15	237.64	262.28	184.16	142.39	43.71	3086.50
May-20	784.16	418.72	136.27	499.11	155.01	294.95	221.52	201.05	173.88	56.67	2941.33
Jun-20	1161.82	297.84	346.80	490.89	181.10	288.41	237.68	152.89	138.14	36.26	3331.84
Jul-20	1252.04	240.47	612.68	506.25	266.02	272.38	237.02	300.99	153.10	48.35	3889.27
Aug-20	1033.20	220.45	589.94	487.29	216.93	224.18	316.39	325.47	176.26	60.98	3651.09
Sep-20	1093.27	405.72	387.65	291.57	290.99	187.31	231.33	177.09	175.36	123.67	3363.95
Oct-20	1049.29	427.18	290.32	385.96	285.18	259.18	251.41	207.23	124.02	74.14	3353.90
Nov-20	1129.98	454.10	307.91	263.39	556.96	241.61	207.83	163.39	58.19	81.05	3464.40
Dec-20	888.11	459.52	351.02	249.69	893.18	224.54	169.23	294.75	112.16	13.06	3655.24
Jan-21	935.59	333.59	421.74	195.14	881.58	189.26	110.05	198.22	72.32	38.41	3375.88
Feb-21	974.25	246.70	581.81	222.85	289.70	173.76	208.89	207.94	169.49	197.02	3272.41
Mar-21	1232.19	174.97	673.93	344.02	293.14	303.41	422.88	324.76	255.18	76.50	4100.97
Apr-21	901.20	285.69	629.94	310.17	493.74	311.79	333.72	192.69	190.73	79.14	3728.78
May-21	991.49	244.78	589.51	404.82	427.43	250.07	237.69	169.54	136.60	93.00	3544.92
Jun-21	1238.57	265.78	428.59	229.42	317.19	224.77	346.21	167.11	104.98	71.69	3394.29
Jul-21	1291.20	170.65	590.62	327.78	198.87	350.74	297.02	126.93	155.79	55.13	3564.71
Aug-21	1152.52	180.99	354.88	329.97	435.26	294.87	291.05	161.57	206.17	52.85	3460.11
Sep-21	1070.20	368.76	380.40	381.77	285.95	317.72	330.35	219.46	146.39	105.05	3606.04

Oct-21	1078.34	216.55	488.70	406.24	655.85	353.86	389.90	187.05	250.32	133.79	4160.57
Nov-21	900.33	259.67	581.95	294.64	465.03	313.30	425.21	117.93	193.88	68.52	3620.45
Dec-21	1015.49	243.68	239.61	244.14	530.84	257.10	464.05	166.15	189.27	75.17	3425.48
Jan-22	936.61	321.17	419.50	326.11	252.44	282.50	346.08	86.38	81.36	71.58	3123.70
Feb-22	933.20	263.28	261.59	261.27	251.07	235.05	274.05	93.99	141.46	120.49	2835.44
Mar-22	993.32	265.55	131.36	309.30	274.50	274.97	297.25	85.49	151.56	91.49	2874.79
Apr-22	1036.78	253.13	354.41	179.72	154.37	220.08	315.47	80.73	103.52	58.90	2757.10
May-22	1097.45	259.12	191.68	316.67	383.58	259.36	396.87	123.75	53.58	50.60	3132.65
Jun-22	1112.74	338.52	180.09	259.24	320.37	224.58	343.84	113.41	50.66	69.84	3013.27
Jul-22	1066.68	207.26	189.34	279.45	312.63	270.10	218.32	136.50	197.63	62.44	2940.34
Total	60393.50	27793.06	24846.72	24734.45	24520.35	18599.21	18402.20	12357.76	10248.16	5320.90	

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	NHS London	NHS North West	NHS Yorkshire and the Humber	NHS South Central	NHS East of England	NHS East Midlands	NHS South West	NHS North East	NHS West Midlands	NHS South East Coast	Total (dosage)
Apr-17	2025.60	870.00	1161.70	1259.60	731.70	873.70	549.50	570.50	636.40	121.90	8800.60
May-17	3057.00	1768.70	1679.40	1124.90	1342.80	1230.40	811.40	826.00	777.40	125.10	12743.10
Jun-17	2964.00	1719.40	1392.90	1448.10	1211.50	1071.80	493.80	907.50	832.60	101.00	12142.60
Jul-17	2673.50	1606.20	1710.30	1065.90	1049.80	959.10	546.00	967.70	754.20	129.00	11461.70
Aug-17	2933.90	1749.40	1892.95	1215.20	1320.00	1160.80	913.20	974.40	951.70	81.00	13192.55
Sep-17	3604.60	1662.70	1415.90	1113.80	1391.40	1284.20	578.10	730.00	860.20	122.00	12762.90
Oct-17	3279.10	1831.30	1797.00	1393.60	1111.20	1330.00	839.20	936.80	935.90	134.00	13588.10
Nov-17	4137.60	2104.40	1490.30	1421.40	1635.60	1624.60	1047.20	1072.40	1210.40	103.00	15846.90
Dec-17	3144.70	1270.50	1441.50	728.40	1204.60	996.70	469.00	1063.40	1427.70	91.20	11837.70
Jan-18	4149.00	2133.70	2241.70	1302.40	1593.80	1811.80	947.00	1101.20	1702.20	94.90	17077.70
Feb-18	3209.80	2281.40	1462.10	1162.00	1060.40	1397.80	873.40	1047.00	1013.50	45.60	13553.00
Mar-18	3302.20	1701.95	1655.20	1579.20	1550.75	1290.80	1005.00	1083.40	1453.90	223.40	14845.80
Apr-18	3176.35	2383.20	1807.70	1295.60	1051.20	1209.40	675.60	1055.20	758.10	78.60	13490.95
May-18	4140.05	2404.20	1526.00	1240.40	1299.80	1463.00	1186.40	1002.00	1855.20	111.25	16228.30
Jun-18	3394.20	1906.60	1841.70	1192.40	1288.60	1346.80	996.00	1474.20	1269.90	103.70	14814.10
Jul-18	3649.30	1790.80	1690.90	1804.80	1483.00	860.40	885.20	1445.60	1352.70	75.60	15038.30
Aug-18	3896.00	2142.20	1790.15	1303.80	1202.30	1747.40	1141.00	1022.00	1627.00	78.80	15950.65
Sep-18	3540.90	2077.00	1825.00	1195.00	1115.90	1561.60	875.40	1080.20	1013.70	56.20	14340.90
Oct-18	3849.50	2615.20	2146.70	1141.60	1612.20	1265.00	917.00	1315.95	1428.10	54.40	16345.65
Nov-18	3799.60	2461.70	1941.40	1767.80	1241.00	1482.20	1098.00	1543.20	1502.15	71.80	16908.85
Dec-18	2956.50	1534.80	1410.10	621.80	1064.00	1081.00	1020.00	1323.80	1097.50	66.40	12175.90
Jan-19	4680.70	2850.40	1969.30	1904.80	1587.90	1201.00	1109.00	1285.00	1405.40	90.40	18083.90
Feb-19	3522.90	1465.40	1852.60	1013.40	1046.05	1709.20	807.00	1331.60	1580.20	87.00	14415.35
Mar-19	3512.80	1368.20	1837.20	1480.60	1723.10	1207.80	939.00	1192.45	1222.70	96.00	14579.85

Apr-19	3465.20	1652.80	1548.90	1322.80	1087.30	1343.30	1577.40	1597.80	1172.40	62.20	14830.10
May-19	4280.50	2916.80	2370.10	1445.60	1694.20	1441.90	1693.50	1311.00	1266.10	97.20	18516.90
Jun-19	3342.40	2152.60	1863.90	1709.60	924.00	1469.60	1104.00	1392.20	1168.90	106.80	15234.00
Jul-19	3673.40	3088.80	2035.20	1405.00	2122.50	1202.40	1368.00	1509.10	1158.40	122.00	17684.80
Aug-19	2921.40	2835.50	1362.70	1420.80	1801.30	1330.80	1551.40	1239.80	1469.40	130.40	16063.50
Sep-19	3888.20	2667.20	2459.20	1296.00	1054.90	2301.70	1524.40	1280.60	1533.20	116.60	18122.00
Oct-19	4035.80	3379.70	2393.25	1085.20	1497.50	1685.00	2035.80	1472.80	1467.40	133.40	19185.85
Nov-19	3737.20	2681.90	2163.00	1620.20	1591.90	1241.50	1072.00	1570.10	1124.60	104.60	16907.00
Dec-19	4013.70	2699.10	2246.80	918.20	1799.40	1668.50	1372.20	1347.80	1285.20	82.40	17433.30
Jan-20	4399.80	3479.60	3017.60	1649.40	2058.00	1888.20	1447.10	1618.00	1433.00	157.60	21148.30
Feb-20	3267.00	2265.50	1703.00	1406.80	1576.40	1348.10	2052.60	1243.00	1377.10	125.60	16365.10
Mar-20	3786.90	3350.00	2374.10	1468.20	2784.10	1397.80	1511.80	1632.60	1177.00	135.30	19617.80
Apr-20	4724.00	2898.95	1746.50	1421.40	772.60	1578.40	1819.50	830.40	1377.75	110.40	17279.90
May-20	3983.20	2642.40	1442.30	1647.40	2173.40	1497.00	1496.60	905.00	959.20	67.00	16813.50
Jun-20	4652.80	2604.00	1723.20	1196.60	1567.60	720.60	470.40	1302.60	1476.10	214.80	15928.70
Jul-20	4381.90	3338.70	2127.50	1807.40	1798.50	1195.80	3409.80	1323.20	1302.90	109.60	20795.30
Aug-20	3684.15	2739.00	2239.00	1605.40	1965.60	1989.10	1443.80	1127.60	1204.60	112.00	18110.25
Sep-20	4803.55	2384.95	2239.50	1657.20	1165.60	1621.70	1973.60	1309.60	1402.40	114.00	18672.10
Oct-20	3367.00	3476.50	2600.00	1521.80	1805.00	1330.60	1530.40	1175.60	1210.20	86.40	18103.50
Nov-20	5245.40	2445.00	3145.85	1857.00	1966.60	2030.40	1265.00	1324.20	1072.40	129.60	20481.45
Dec-20	4191.80	3280.20	2189.60	1228.00	1343.20	1620.30	1826.40	1601.40	1201.30	105.65	18587.85
Jan-21	4866.05	2625.60	2337.20	1007.00	1120.80	1350.20	1141.60	1535.70	1421.40	72.80	17478.35
Feb-21	4276.80	1709.80	3073.20	1682.80	2684.80	1262.60	2111.40	1300.80	1095.40	61.40	19259.00
Mar-21	4809.40	3234.20	3282.60	1562.90	1300.20	1781.80	1343.00	1463.20	901.60	119.60	19798.50
Apr-21	4879.20	3125.00	3314.00	1623.40	1911.80	1639.40	1893.80	1655.60	1628.10	74.00	21744.30
May-21	3730.60	3047.60	3539.50	1412.60	1709.30	1777.40	1793.20	1118.60	879.20	132.00	19140.00
Jun-21	4371.25	2921.80	2822.40	1814.80	983.90	1728.80	1691.00	1671.80	1775.60	114.20	19895.55
Jul-21	4997.85	2396.90	3812.60	1626.10	841.80	1403.30	1936.60	1670.20	1222.20	110.00	20017.55
Aug-21	4051.50	2656.30	2124.00	2043.40	1537.40	2005.90	1210.40	1173.40	986.80	81.00	17870.10
Sep-21	4412.10	2534.00	3348.40	2185.40	1673.70	1625.50	1637.40	1317.00	2135.20	92.80	20961.50

Oct-21	4277.30	3595.00	2502.30	1803.70	2438.20	831.00	2536.60	1822.60	1226.40	83.20	21116.30
Nov-21	4431.80	2826.70	2827.70	1713.10	1986.80	1516.60	875.00	1534.00	1426.30	45.20	19183.20
Dec-21	3718.95	2294.00	2252.90	1006.30	978.10	1268.40	1640.00	1529.20	1341.60	69.00	16098.45
Jan-22	5395.50	2790.90	3662.10	2334.80	1572.80	1437.40	943.00	1831.80	1569.60	90.00	21627.90
Feb-22	3321.70	2432.15	2739.85	1534.80	814.30	2198.90	2446.20	1840.00	1787.30	82.00	19197.20
Mar-22	6719.10	2293.40	3741.20	2021.10	1768.10	1750.10	2097.70	2459.80	2171.80	96.40	25118.70
Apr-22	5381.00	2111.10	2039.25	1154.30	1601.30	1995.70	1234.00	2048.00	1174.80	119.20	18858.65
May-22	6681.50	2056.60	3397.90	2924.40	2183.70	2098.70	1697.60	2292.30	1765.00	152.40	25250.10
Jun-22	6206.40	2229.80	3888.70	1103.10	1868.80	1892.85	1847.40	1938.30	1844.60	178.40	22998.35
Jul-22	5871.50	2402.25	3237.60	4490.00	1967.60	2444.35	2830.00	2038.70	1602.60	159.90	27044.50
Total	258844.60	153961.65	143914.30	96510.50	96411.60	95078.10	87174.00	86706.90	83463.80	6699.30	

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	NHS London	NHS East of England	NHS South Central	NHS South East Coast	NHS South West	NHS North West	NHS West Midlands	NHS Yorkshire and the Humber	NHS North East	NHS East Midlands	Total (dosage)
Apr-17	30.64	33.60	28.80	13.20	24.32	16.64	16.32	16.80	18.00	7.20	205.52
May-17	42.40	36.00	24.00	12.00	25.60	21.44	16.48	18.00	34.80	11.68	242.40
Jun-17	51.60	36.00	26.40	18.80	44.24	12.00	23.68	8.40	22.80	13.04	256.96
Jul-17	38.24	42.00	21.60	12.00	23.68	26.40	34.64	13.12	15.60	11.92	239.20
Aug-17	53.52	34.08	19.20	9.60	30.24	21.60	34.32	22.56	22.24	16.48	263.84
Sep-17	84.00	48.84	9.60	16.80	17.52	31.20	32.08	7.20	19.20	18.96	285.40
Oct-17	68.16	59.84	13.20	24.00	32.80	43.04	47.52	14.40	19.20	9.44	331.60
Nov-17	102.00	40.08	27.60	28.80	24.40	43.20	36.96	14.40	9.60	20.24	347.28
Dec-17	87.20	43.20	18.56	24.56	37.76	38.24	36.88	9.60	12.00	15.44	323.44
Jan-18	100.64	46.48	32.16	12.00	29.20	39.20	46.48	14.40	18.00	12.88	351.44
Feb-18	81.44	46.56	27.60	16.80	32.32	46.56	48.40	14.40	20.40	13.04	347.52
Mar-18	85.52	62.24	36.00	21.60	42.88	60.00	48.72	12.00	18.00	15.44	402.40
Apr-18	99.32	52.64	36.00	21.60	42.40	57.12	38.96	16.80	20.40	21.28	406.52
May-18	98.36	57.04	48.00	34.40	44.48	52.80	45.84	24.00	29.36	21.28	455.56
Jun-18	106.16	65.28	52.80	32.40	43.36	62.40	46.72	10.72	24.56	23.84	468.24
Jul-18	115.28	47.12	52.80	51.60	36.48	59.84	39.12	20.40	34.16	16.80	473.60
Aug-18	124.80	47.28	48.40	38.40	47.20	67.20	51.36	31.04	24.56	20.24	500.48
Sep-18	85.52	40.08	50.80	34.80	42.24	71.84	48.72	19.20	28.16	15.44	436.80
Oct-18	151.68	47.28	52.64	40.80	37.60	100.64	46.00	31.20	22.16	27.60	557.60
Nov-18	152.24	61.68	56.00	35.68	45.92	81.60	63.04	21.60	32.96	28.80	579.52
Dec-18	137.76	49.68	45.60	28.80	41.04	68.48	49.28	32.40	28.16	26.40	507.60
Jan-19	133.68	66.32	54.72	31.20	41.68	64.80	54.72	31.12	29.36	32.08	539.68
Feb-19	147.36	69.04	43.20	25.20	37.76	57.52	36.92	27.60	38.40	34.80	517.80
Mar-19	150.80	63.92	67.20	32.32	41.52	58.80	50.28	28.80	35.36	34.64	563.64

Apr-19	127.12	65.12	33.60	28.80	60.24	56.40	37.92	33.60	38.96	37.20	518.96
May-19	227.12	57.60	55.20	30.00	45.28	54.00	52.32	38.40	34.16	39.52	633.60
Jun-19	141.28	58.80	43.20	36.00	58.00	39.60	45.12	37.60	34.16	27.44	521.20
Jul-19	188.16	80.48	36.00	42.00	78.32	70.64	65.36	31.12	61.80	30.00	683.88
Aug-19	155.36	60.40	43.20	46.80	55.76	46.80	47.84	44.40	45.56	42.40	588.52
Sep-19	178.48	71.12	52.80	43.20	75.92	56.40	74.08	22.80	38.40	25.60	638.80
Oct-19	147.52	52.32	76.80	51.60	72.24	50.40	53.68	31.20	48.00	36.40	620.16
Nov-19	172.28	78.16	55.20	54.24	67.28	52.80	51.28	40.80	48.00	18.40	638.44
Dec-19	188.88	37.56	46.56	34.80	64.96	48.00	66.32	40.80	43.20	24.00	595.08
Jan-20	182.88	78.40	38.40	50.40	71.60	55.20	52.48	31.20	33.76	14.32	608.64
Feb-20	175.20	57.60	33.60	52.80	69.76	39.60	50.08	40.80	26.40	31.04	576.88
Mar-20	222.64	88.40	50.40	61.20	60.00	69.60	60.72	34.72	55.04	16.56	719.28
Apr-20	165.84	56.80	40.80	40.80	61.68	51.60	73.36	44.40	29.36	38.00	602.64
May-20	115.36	88.84	43.20	52.80	69.52	48.88	63.52	58.80	42.00	23.04	605.96
Jun-20	249.28	98.92	87.60	94.80	87.60	89.84	77.84	77.84	64.72	50.40	978.84
Jul-20	259.44	123.64	114.88	124.64	98.60	93.76	96.72	87.52	62.96	65.52	1127.68
Aug-20	267.84	115.64	93.60	111.60	94.80	110.24	88.56	64.56	56.40	61.84	1065.08
Sep-20	326.16	156.72	152.08	157.20	134.24	140.40	99.44	94.56	78.00	76.32	1415.12
Oct-20	290.72	168.80	123.52	148.56	125.28	145.20	102.80	81.60	115.76	100.72	1402.96
Nov-20	325.60	169.68	147.12	191.60	125.60	213.60	112.56	105.20	115.76	82.72	1589.44
Dec-20	352.72	236.88	202.48	159.52	136.32	254.24	155.20	121.76	148.16	117.60	1884.88
Jan-21	339.76	204.80	187.04	205.12	185.60	196.32	133.36	107.60	125.36	87.76	1772.72
Feb-21	372.72	224.08	203.76	178.32	139.52	158.40	123.60	111.60	117.00	103.36	1732.36
Mar-21	418.00	268.08	236.96	254.00	181.52	206.40	158.24	162.72	159.00	107.60	2152.52
Apr-21	424.48	278.40	252.80	188.32	217.00	208.64	154.96	156.76	115.80	103.60	2100.76
May-21	449.52	268.00	264.88	203.28	196.08	184.88	140.08	166.72	149.40	109.60	2132.44
Jun-21	481.68	286.60	264.24	241.36	189.84	228.96	193.20	197.84	136.20	120.48	2340.40
Jul-21	520.16	305.36	290.24	255.04	266.64	217.12	199.36	236.40	167.40	130.32	2588.04
Aug-21	491.12	324.52	244.64	228.88	186.72	229.52	205.68	225.12	147.00	119.52	2402.72
Sep-21	597.52	318.00	319.20	251.84	224.72	221.84	187.60	229.92	172.20	146.56	2669.40

Oct-21	603.92	278.80	287.84	295.64	235.36	204.00	190.08	234.28	181.80	126.72	2638.44
Nov-21	632.84	322.76	288.72	276.72	275.56	228.00	228.08	227.36	204.12	132.16	2816.32
Dec-21	613.44	374.68	284.80	328.88	268.12	226.16	206.96	256.24	199.64	153.68	2912.60
Jan-22	697.68	368.20	302.16	284.72	221.32	214.64	201.36	199.12	220.20	154.80	2864.20
Feb-22	598.88	310.48	239.52	270.80	236.52	211.20	202.40	240.12	184.80	164.08	2658.80
Mar-22	782.56	398.00	322.32	331.84	298.96	220.56	209.44	277.92	240.60	184.64	3266.84
Apr-22	726.16	380.88	320.88	336.40	264.52	212.24	239.44	236.52	220.04	185.20	3122.28
May-22	801.68	463.28	381.80	333.12	326.92	245.28	246.16	273.56	195.60	172.00	3439.40
Jun-22	654.56	375.48	329.84	306.12	246.24	242.40	265.28	250.64	185.20	182.96	3038.72
Jul-22	724.00	407.48	323.44	347.16	329.04	222.96	227.44	257.12	271.04	210.80	3320.48
Total	17718.88	9356.04	7808.20	7348.28	7069.84	7069.28	6233.36	5671.40	5190.40	4123.84	

Paclitaxel

	NHS North West	NHS London	NHS South East Coast	NHS South West	NHS West Midlands	NHS East of England	NHS South Central	NHS Yorkshire and the Humber	NHS North East	NHS East Midlands	Total (dosage)
Apr-17	63020.80	72410.48	30018.33	50204.84	73721.90	49717.89	34741.13	66531.06	21723.83	15583.90	477674.17
May-17	71625.73	106939.10	52597.90	45452.53	87684.82	59055.40	49337.48	78321.75	24475.89	18594.30	594084.89
Jun-17	70313.25	126777.99	52839.55	46288.19	98116.19	49111.01	47907.59	54763.54	23812.61	17410.80	587340.73
Jul-17	97448.98	86185.81	53049.20	44413.70	95625.88	38778.00	52722.20	56692.39	24588.22	16497.50	566001.87
Aug-17	118640.32	108788.26	74675.63	41166.98	118404.99	48750.40	47479.23	56051.50	21033.90	18705.80	653697.00
Sep-17	111723.69	96090.00	65138.76	47542.63	108699.20	51305.64	45032.78	61570.40	13945.60	16522.00	617570.71
Oct-17	119900.34	110443.08	85660.80	47978.17	98611.71	59047.32	48406.37	67711.40	26145.78	16371.20	680276.17
Nov-17	108937.62	120488.61	103360.35	45287.48	100993.83	68873.94	59578.28	92656.40	19401.90	17069.90	736648.31
Dec-17	121110.87	169452.82	84852.96	43946.70	88550.90	57298.01	59682.11	71622.00	16694.60	15716.80	728927.77
Jan-18	98530.35	185092.88	98551.21	43920.37	104623.93	77439.43	57595.57	82158.02	18297.10	18162.10	784370.97
Feb-18	111448.46	183225.60	90623.94	40336.33	97574.43	81946.80	45306.32	58145.10	16297.11	15391.40	740295.49
Mar-18	131472.69	207868.47	82082.80	48521.10	110387.78	81984.49	44783.93	58661.20	17873.50	18185.60	801821.57

Apr-18	143380.91	189285.17	96136.33	38541.95	94708.70	80629.04	39883.84	59346.90	19763.40	16050.90	777727.14
May-18	136400.56	196451.32	117080.20	41803.18	128799.02	90824.31	47846.23	54491.30	18746.90	16941.20	849384.23
Jun-18	120117.57	209493.88	100806.62	41517.24	107867.30	90941.80	44057.88	48098.70	15751.30	15070.00	793722.28
Jul-18	110610.52	218840.60	110458.77	44991.04	106063.80	107549.31	43098.96	50872.90	17332.03	14544.70	824362.62
Aug-18	120505.58	223078.56	114017.80	51499.11	102734.50	119488.25	38744.67	51635.30	18492.35	15912.60	856108.72
Sep-18	114295.34	234030.22	101942.33	51861.45	95181.30	106530.02	35530.38	51559.04	28386.11	15720.20	835036.38
Oct-18	128140.35	179829.45	114602.51	71865.74	126534.10	114320.27	54977.81	56448.09	32913.20	19357.90	898989.41
Nov-18	129535.03	255107.01	130974.68	70162.75	100741.90	122872.08	67217.41	53612.70	36998.65	21158.60	988380.82
Dec-18	138614.44	203378.00	132279.42	66035.98	104367.50	111146.01	73072.43	49512.70	26891.20	17806.40	923104.07
Jan-19	136448.19	235585.70	155831.64	73249.01	110444.00	114282.06	116032.60	71199.60	22904.90	19842.70	1055820.41
Feb-19	149407.50	245573.08	154713.11	53414.24	88002.90	104936.73	97919.35	106029.30	23394.30	17024.20	1040414.71
Mar-19	177056.44	287412.27	173203.99	60167.68	135066.30	114404.84	95955.03	107142.93	21121.51	18951.60	1190482.58
Apr-19	236994.53	238626.70	185521.00	46884.20	127326.82	110399.07	97114.74	92985.89	21703.40	19509.60	1177065.95
May-19	250181.23	243094.87	190528.13	50808.28	131607.60	110783.19	92473.22	100204.65	26598.80	22531.40	1218811.37
Jun-19	215950.92	200355.70	134426.95	53025.28	130566.70	93233.10	77535.53	95444.63	24447.30	17533.40	1042519.52

Jul-19	214267.03	250968.03	229178.51	51475.75	144259.19	102535.52	91146.86	109213.20	25144.20	19988.40	1238176.68
Aug-19	211297.46	178785.30	155392.33	49113.61	120805.16	103255.09	69402.55	86878.60	24877.40	37709.90	1037517.41
Sep-19	212584.20	195014.46	132317.33	45883.21	109315.53	92756.16	77344.09	74902.60	25886.19	36169.90	1002173.67
Oct-19	227419.35	257408.83	183974.19	56853.30	120244.30	99720.04	97154.46	71674.08	36325.20	42461.40	1193235.15
Nov-19	232654.38	238308.20	205398.17	56688.09	111198.90	110176.17	109723.24	71428.74	32567.70	35541.50	1203685.09
Dec-19	222988.35	319967.83	187649.28	51919.45	131322.85	138058.32	105291.44	82003.87	34891.90	40783.50	1314876.80
Jan-20	213114.78	309862.25	202676.24	49975.66	143664.42	156665.88	109462.49	97170.79	41977.90	41377.00	1365947.43
Feb-20	221368.40	319693.80	188648.12	42439.46	134709.25	147776.52	113316.10	65501.57	41660.70	37597.20	1312711.11
Mar-20	216693.08	296504.11	183324.87	45274.83	148156.83	163025.85	119655.77	62311.61	40780.90	35665.40	1311393.26
Apr-20	157501.30	246911.00	148440.91	45907.06	165451.30	124392.95	95272.37	36061.39	34399.60	30426.90	1084764.78
May-20	164963.05	217142.53	128920.28	39950.86	110593.70	113418.86	98725.06	32817.00	27109.30	26669.00	960309.64
Jun-20	196381.90	258909.03	144972.60	46331.88	132632.60	137593.31	118526.37	46571.00	29801.80	22744.90	1134465.38
Jul-20	196327.15	277050.73	159766.80	73450.21	138455.73	150031.48	122348.29	41329.85	26134.89	29277.50	1214172.64
Aug-20	185946.80	251914.33	149272.95	44328.90	97011.47	137741.61	101016.11	54093.85	23669.80	31641.50	1076637.32
Sep-20	213776.25	295921.60	170187.35	47432.17	124101.96	155776.24	122365.62	45620.82	32005.40	41053.80	1248241.22

Oct-20	211086.55	293771.53	173382.58	43944.15	139634.60	163436.43	111480.72	57673.37	39117.41	51142.20	1284669.54
Nov-20	403211.00	284906.57	170773.82	43976.60	145564.15	151309.73	119337.43	75580.74	45463.20	42586.93	1482710.17
Dec-20	521547.25	351275.53	183917.44	55251.61	144212.70	182934.38	130903.65	67665.90	37408.60	49659.60	1724776.66
Jan-21	467825.43	306169.23	167526.66	50670.95	132207.55	165184.89	117592.69	55355.37	35469.65	40582.20	1538584.63
Feb-21	537346.65	297137.35	151778.75	1426441.49	170019.90	165814.87	124389.99	57544.70	45127.46	38193.20	3013794.36
Mar-21	707283.00	472184.99	153566.36	312397.31	206463.43	182741.35	162405.90	61164.53	62885.85	41709.20	2362801.92
Apr-21	595106.05	373254.37	147165.44	183514.10	197098.53	159114.01	152094.33	70916.38	44143.80	44944.23	1967351.23
May-21	619378.90	318028.35	149701.05	50873.52	179996.12	163677.06	133625.66	82511.27	56794.50	44535.98	1799122.43
Jun-21	578819.05	362461.20	164432.14	56844.29	197786.83	186647.26	142142.60	89159.60	62077.10	40473.66	1880843.73
Jul-21	619644.70	369390.12	170458.65	60560.89	188357.65	188054.32	131112.44	95737.69	63874.50	45949.30	1933140.27
Aug-21	566513.35	345815.38	185445.11	60171.44	156821.07	184301.63	144807.19	103037.53	75455.00	38076.20	1860443.90
Sep-21	649475.10	318043.94	197616.26	67601.34	164981.00	164890.72	175186.95	87689.37	74795.71	45891.66	1946172.04
Oct-21	554169.30	291456.22	177421.61	66323.69	158264.50	158269.01	158139.78	73299.03	64029.90	54952.83	1756325.87
Nov-21	699069.66	313693.23	180058.68	65403.97	176491.78	170159.15	175437.19	81013.49	64644.40	61131.26	1987102.82
Dec-21	656431.30	367172.38	189159.71	65988.14	230975.36	195728.90	151167.98	78969.07	63023.61	64811.62	2063428.07

Jan-22	627137.32	322666.11	172993.51	61495.59	179122.38	169525.96	135470.48	69009.34	59708.41	63893.99	1861023.09
Feb-22	596417.57	312883.62	172829.32	58555.52	162691.40	147432.71	134711.21	72063.80	69541.21	56247.03	1783373.40
Mar-22	659483.30	387841.83	243248.96	2897291.23	208888.78	162151.55	161944.42	85303.30	79783.00	76191.50	4962127.86
Apr-22	633397.75	308648.71	206586.36	446841.36	206545.75	139181.10	145761.21	78860.50	73584.50	76025.80	2315433.04
May-22	659292.85	326424.21	205839.63	641224.46	189667.00	164695.55	158906.27	94257.68	77149.20	67449.16	2584906.02
Jun-22	653985.10	323020.85	185423.18	73716.87	161762.07	138188.85	148126.94	86934.12	86673.73	67048.56	1924880.29
Jul-22	582435.50	313882.68	196757.01	75579.02	168589.10	143280.98	144103.52	90634.65	76754.41	77774.82	1869791.68
Total	1941815 2.38	1620839 6.06	9402177. 06	8972578. 12	8671072. 88	7895292. 83	6323632. 43	4545429. 79	2434473. 42	2170545. 44	

Pembrolizumab

	NHS North West	NHS South West	NHS East of England	NHS London	NHS West Midlands	NHS South Central	NHS Yorkshire and the Humber	NHS South East Coast	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	32.89	28.88	28.05	38.30	21.95	30.24	19.40	15.05	19.05	13.58	247.38
May-17	35.72	34.82	33.22	45.30	30.67	22.13	27.25	24.50	19.95	14.59	288.14
Jun-17	45.94	38.73	33.40	51.40	31.45	35.91	27.65	25.40	27.25	18.00	335.12
Jul-17	35.50	39.73	36.58	50.75	40.10	41.49	33.73	24.59	27.30	20.60	350.35
Aug-17	80.18	50.68	42.48	64.73	48.25	43.48	42.90	32.60	31.15	25.85	462.28
Sep-17	83.03	48.45	44.63	65.20	43.99	35.06	41.68	31.11	28.25	25.53	446.91
Oct-17	132.46	54.61	50.00	70.80	52.90	44.24	48.60	30.23	35.15	35.45	554.42
Nov-17	118.63	57.99	50.63	72.43	55.10	53.02	52.93	40.58	39.65	34.73	575.66
Dec-17	131.14	54.40	46.28	61.43	54.55	40.78	50.85	40.64	34.90	34.51	549.46
Jan-18	134.30	67.28	57.50	72.65	62.92	49.48	61.30	44.80	46.15	39.68	636.03
Feb-18	127.49	57.90	49.95	67.85	60.33	45.32	60.00	42.96	40.85	30.40	583.04
Mar-18	138.96	66.63	60.78	79.39	60.11	78.45	61.45	51.90	45.65	37.80	681.09
Apr-18	139.59	65.68	68.69	80.33	73.98	64.17	69.40	52.25	47.80	32.40	694.27
May-18	127.58	76.15	75.89	86.65	80.05	58.78	72.90	53.98	47.95	41.85	721.77
Jun-18	108.91	77.33	76.41	87.23	73.70	62.97	72.18	52.85	51.95	35.30	698.80
Jul-18	116.39	81.27	68.94	91.28	75.35	66.34	72.93	47.28	55.30	36.33	711.39
Aug-18	121.06	87.92	80.98	95.63	82.60	63.70	73.85	47.18	52.05	41.70	746.66
Sep-18	113.19	73.69	71.48	91.60	76.25	57.71	62.80	50.48	49.15	34.65	680.98
Oct-18	128.53	85.68	82.37	81.95	94.55	65.57	72.53	63.50	61.20	44.03	779.88
Nov-18	121.56	91.15	74.79	95.85	97.33	67.12	74.33	64.43	59.15	44.33	790.03
Dec-18	125.38	78.23	74.85	87.43	97.15	55.72	61.60	55.15	54.45	37.48	727.42
Jan-19	134.55	93.00	80.40	101.25	110.05	83.21	73.90	71.50	71.05	47.65	866.56
Feb-19	127.03	93.78	72.25	90.58	74.65	67.82	66.48	60.36	59.65	41.25	753.83
Mar-19	304.55	92.83	76.88	93.05	104.85	83.16	76.60	61.73	65.65	44.03	1003.31

Apr-19	132.30	95.70	87.45	94.03	127.40	77.93	77.50	68.11	69.35	47.30	877.06
May-19	152.45	114.73	89.68	102.08	123.35	85.53	93.43	72.65	72.33	47.75	953.95
Jun-19	143.53	104.30	79.93	100.78	115.85	80.45	83.35	64.65	68.78	47.63	889.23
Jul-19	167.11	121.93	103.30	112.38	135.40	100.71	97.28	102.60	83.95	53.00	1077.64
Aug-19	169.66	118.18	96.83	100.80	174.55	87.89	94.60	90.55	80.10	61.00	1074.15
Sep-19	162.41	115.75	103.65	110.83	122.25	93.57	93.60	89.40	84.40	55.30	1031.15
Oct-19	186.46	135.25	109.10	109.73	155.35	110.02	105.13	103.70	92.10	64.40	1171.23
Nov-19	159.35	121.12	115.98	112.63	125.40	103.80	92.60	96.80	85.30	55.60	1068.57
Dec-19	179.95	119.40	108.78	108.65	141.75	96.77	99.73	92.00	92.80	60.90	1100.72
Jan-20	184.88	143.35	126.10	132.90	150.60	119.74	109.85	107.80	92.80	65.50	1233.52
Feb-20	156.20	110.63	112.73	116.20	127.20	102.20	89.20	82.90	79.50	56.80	1033.55
Mar-20	178.48	137.90	119.53	138.55	165.40	117.72	99.40	93.85	104.40	63.20	1218.42
Apr-20	144.13	105.28	107.70	109.40	131.05	105.40	91.70	71.00	90.80	60.35	1016.80
May-20	155.40	114.78	106.10	128.05	135.00	117.40	100.00	82.40	91.00	55.70	1085.83
Jun-20	158.80	129.60	139.20	144.00	152.10	116.96	105.50	83.80	93.70	59.30	1182.96
Jul-20	173.80	133.10	151.50	140.33	163.55	135.56	93.20	94.30	114.50	60.40	1260.24
Aug-20	171.00	124.60	129.60	135.80	144.20	119.32	103.00	82.90	107.90	56.80	1175.12
Sep-20	183.60	127.53	137.30	149.80	144.80	127.06	102.10	94.30	101.90	68.50	1236.89
Oct-20	166.80	127.95	133.90	157.20	149.55	126.52	106.00	87.80	122.10	66.70	1244.52
Nov-20	232.80	123.98	151.30	142.40	141.45	118.61	106.63	84.20	105.30	62.50	1269.16
Dec-20	290.80	143.92	151.20	155.60	153.15	129.61	111.65	102.30	114.10	66.20	1418.53
Jan-21	249.60	126.33	129.35	173.00	139.15	121.05	96.75	103.80	108.10	59.60	1306.73
Feb-21	251.40	1071.45	135.40	143.80	131.60	107.86	98.73	98.20	90.10	59.80	2188.34
Mar-21	236.70	721.60	152.40	176.70	136.90	107.86	130.30	115.60	124.00	70.30	1972.36
Apr-21	227.10	733.50	140.50	176.50	137.35	138.32	119.60	105.55	97.00	76.90	1952.32
May-21	246.65	128.98	144.20	162.10	130.40	118.75	109.50	98.20	116.45	60.40	1315.62
Jun-21	233.00	137.23	165.35	171.50	133.40	141.90	132.60	122.00	82.40	74.20	1393.58
Jul-21	265.90	144.38	142.20	167.30	142.20	143.76	130.70	119.30	119.80	72.80	1448.34
Aug-21	279.40	137.93	151.00	173.70	114.60	131.56	128.30	118.55	91.30	70.40	1396.74
Sep-21	327.40	136.38	164.00	174.70	139.80	130.40	125.90	137.80	101.60	72.80	1510.78

Oct-21	276.80	137.35	156.90	153.60	135.40	128.56	139.20	109.90	100.40	73.20	1411.31
Nov-21	252.30	144.13	161.60	174.10	163.00	135.00	134.45	131.00	94.20	83.50	1473.28
Dec-21	243.10	150.85	172.10	171.60	139.40	140.00	131.40	126.10	107.30	89.60	1471.45
Jan-22	207.40	158.25	162.90	174.00	154.60	134.60	126.90	125.30	111.60	81.80	1437.35
Feb-22	262.20	135.60	148.20	158.20	140.60	127.00	132.80	105.50	95.10	76.00	1381.20
Mar-22	284.40	391.25	164.40	188.10	150.70	151.00	146.60	125.80	112.90	84.00	1799.15
Apr-22	182.90	175.73	163.20	175.60	134.30	127.90	135.40	126.40	114.20	79.80	1415.43
May-22	253.90	197.40	487.20	191.00	148.70	133.72	135.40	119.50	98.70	76.60	1842.12
Jun-22	244.10	160.85	164.40	184.10	164.20	143.96	130.20	128.10	138.40	79.60	1537.91
Jul-22	229.60	167.70	974.60	184.10	139.80	118.10	134.60	121.80	97.30	81.00	2248.60
Total	11168.22	9322.54	7978.11	7698.81	7258.26	6069.89	5851.95	5171.42	5018.60	3468.80	

Pemetrexed

	NHS London	NHS East of England	NHS North West	NHS South West	NHS West Midlands	NHS South East Coast	NHS South Central	NHS Yorkshire and the Humber	NHS North East	NHS East Midlands	Total (dosage)
Apr-17	6279.07	5193.90	5539.00	3263.45	2982.00	2694.00	1911.30	1541.30	3961.24	591.00	33956.26
May-17	5540.00	5000.80	5616.40	4103.50	3150.80	3902.60	1365.10	1818.10	3914.72	743.00	35155.02
Jun-17	5620.00	4253.60	3878.40	4143.90	3292.00	2836.60	1805.20	2165.40	4424.52	801.00	33220.62
Jul-17	5020.00	3803.20	2348.40	3369.70	2707.00	2143.45	1280.80	1633.80	3271.20	484.00	26061.55
Aug-17	3555.95	2393.90	861.80	1492.60	656.60	1928.35	740.60	864.90	1466.20	367.00	14327.90
Sep-17	2676.00	1898.90	520.90	1235.80	418.40	1364.20	624.20	661.00	697.22	278.00	10374.62
Oct-17	1873.00	895.70	517.00	1076.90	355.80	1055.10	528.90	734.10	601.20	301.00	7938.70
Nov-17	2425.00	515.80	492.30	1136.50	409.40	841.01	515.09	807.50	688.30	323.00	8153.90
Dec-17	1271.01	591.60	372.20	653.30	387.20	858.85	430.60	512.10	515.70	267.00	5859.56
Jan-18	1207.00	575.70	500.10	1008.40	501.00	744.83	522.50	682.60	383.40	332.00	6457.53
Feb-18	1535.00	456.90	466.00	759.10	317.80	424.50	428.56	538.70	325.00	354.00	5605.56
Mar-18	2414.00	484.50	549.80	780.80	394.40	389.03	665.80	588.40	360.18	311.00	6937.90
Apr-18	1811.00	1007.70	527.40	827.50	377.60	413.60	551.00	745.60	406.50	286.00	6953.90
May-18	1860.00	740.50	608.20	975.20	585.60	367.70	671.60	725.30	444.00	451.00	7429.10
Jun-18	1986.00	603.00	518.80	885.20	494.80	247.30	564.50	686.60	400.20	318.00	6704.40
Jul-18	2220.00	648.80	488.00	1155.30	498.60	473.60	524.20	711.30	479.00	383.00	7581.80
Aug-18	2095.00	854.80	565.50	914.20	523.00	262.20	413.10	643.40	444.00	365.00	7080.20
Sep-18	1709.00	918.00	456.60	1231.80	531.00	319.70	424.90	617.10	543.00	401.00	7152.10
Oct-18	1277.00	1457.70	790.20	1112.55	614.80	393.80	519.10	851.20	600.50	491.00	8107.85
Nov-18	1503.00	1243.60	769.20	1210.20	557.20	644.90	1031.20	669.80	505.40	448.00	8582.50
Dec-18	2360.80	1224.00	692.60	864.30	483.40	380.20	816.50	600.80	401.50	302.00	8126.10
Jan-19	2157.00	1354.80	604.99	1250.60	537.60	849.20	916.70	736.10	565.20	460.00	9432.19
Feb-19	2626.20	573.90	489.10	1151.80	409.20	750.10	868.50	624.70	520.90	300.00	8314.40
Mar-19	1879.20	710.00	542.90	1109.80	664.00	818.80	837.00	713.50	428.00	353.00	8056.20

Apr-19	2642.80	752.25	699.35	1289.44	629.30	819.70	1154.90	737.20	506.00	378.00	9608.94
May-19	1461.20	1080.55	777.80	1314.09	934.60	896.30	1122.50	752.40	553.00	445.00	9337.44
Jun-19	1450.80	1023.70	735.80	1041.29	640.20	1001.40	841.10	774.70	509.50	418.00	8436.49
Jul-19	1927.80	1175.90	969.15	1534.49	822.40	1233.60	1118.20	800.80	704.50	563.00	10849.84
Aug-19	1731.00	1067.60	790.70	1408.79	711.80	855.60	917.60	901.00	498.90	513.30	9396.29
Sep-19	1606.80	1052.60	771.65	1074.22	605.60	844.78	922.40	691.40	501.00	490.60	8561.04
Oct-19	1532.00	978.40	950.65	1325.88	623.40	904.68	1202.90	972.20	526.80	614.10	9631.00
Nov-19	1769.20	1545.90	815.65	1261.29	730.80	878.53	956.20	777.60	536.40	512.70	9784.26
Dec-19	1462.40	1211.90	788.55	1158.28	576.00	811.40	770.70	634.90	477.40	466.60	8358.13
Jan-20	1611.60	1796.60	841.05	1514.25	786.00	973.98	1345.30	871.00	566.40	594.20	10900.38
Feb-20	1283.40	1357.50	722.10	1319.60	672.20	803.50	690.20	689.10	457.60	517.70	8512.90
Mar-20	2175.40	1304.40	787.50	1131.15	702.80	933.20	659.90	763.00	455.00	562.20	9474.55
Apr-20	780.00	350.00	174.70	763.50	489.78	723.50	684.80	556.80	229.70	436.60	5189.38
May-20	1018.80	493.90	183.80	600.50	404.40	455.70	744.30	359.70	218.20	393.60	4872.90
Jun-20	1262.00	623.80	306.40	801.60	455.00	771.60	687.70	543.40	224.00	391.00	6066.50
Jul-20	1546.00	971.45	346.40	802.80	463.81	971.10	846.70	621.40	351.60	563.00	7484.26
Aug-20	1361.00	573.80	422.25	1007.30	422.20	917.60	999.80	634.90	385.00	470.60	7194.45
Sep-20	1201.40	689.45	322.30	1261.80	508.00	1091.90	1127.40	769.40	528.00	487.90	7987.55
Oct-20	1555.40	754.30	355.50	1366.40	522.40	1194.66	1168.96	810.20	443.00	573.10	8743.92
Nov-20	1103.60	538.60	424.30	1368.00	562.00	1060.20	1229.90	757.80	443.00	537.10	8024.50
Dec-20	1442.00	522.30	450.15	1413.80	501.40	1016.26	1085.80	721.10	459.70	494.70	8107.21
Jan-21	1758.00	445.00	690.85	1124.20	453.80	810.50	1249.50	687.10	395.00	525.70	8139.65
Feb-21	1785.20	570.00	464.80	791.00	426.00	772.30	1015.70	709.20	373.60	445.10	7352.90
Mar-21	2347.00	717.50	416.90	846.50	489.00	950.20	1247.65	860.00	483.40	754.20	9112.35
Apr-21	2092.20	686.10	465.20	589.60	529.33	900.00	1148.20	774.30	419.00	632.60	8236.53
May-21	1999.20	620.90	392.20	576.20	481.20	953.00	922.55	807.10	413.00	672.60	7837.95
Jun-21	1790.00	799.70	385.20	519.20	515.75	1090.20	1149.60	954.80	418.00	494.70	8117.15
Jul-21	1657.75	1112.40	345.20	1259.50	657.60	1046.20	850.30	953.20	581.00	635.70	9098.85
Aug-21	1584.20	1720.80	3399.60	1140.90	1185.15	621.30	593.80	955.90	524.00	517.70	12243.35
Sep-21	1677.60	2271.20	2760.20	1435.20	1572.35	836.10	476.90	864.00	557.00	625.80	13076.35

Oct-21	1205.80	2397.60	5534.10	1418.10	2041.25	691.00	574.80	889.70	541.50	657.70	15951.55
Nov-21	1636.00	3508.50	3609.80	1248.90	2319.55	689.00	826.10	792.40	591.30	553.60	15775.15
Dec-21	1988.60	3328.20	2556.10	1497.70	2041.65	751.50	612.20	1076.00	482.50	745.90	15080.35
Jan-22	2064.80	3433.50	4939.00	1545.40	1899.30	851.10	599.20	893.60	392.10	667.30	17285.30
Feb-22	2079.20	3735.30	5555.00	1548.90	1637.10	566.90	389.80	748.40	424.80	618.50	17303.90
Mar-22	2894.60	4695.90	4788.35	1609.00	1697.40	688.30	520.80	1028.00	971.65	855.00	19749.00
Apr-22	2528.80	4864.80	2962.10	1835.40	1665.80	590.90	442.55	758.20	1019.10	601.60	17269.25
May-22	3630.20	5017.20	4727.25	1631.40	1792.80	711.00	517.90	1073.90	1010.00	645.20	20756.85
Jun-22	2792.80	4342.80	4296.10	1798.10	1721.30	799.00	597.50	893.80	1166.60	689.10	19097.10
Jul-22	2911.80	4306.40	4372.75	2647.10	2153.05	956.00	920.80	799.20	408.30	1358.10	20833.50
Total	135248.58	105840.00	94012.24	85533.16	59892.67	59537.28	53890.06	52532.10	47093.62	32829.10	

Vincristine

	NHS London	NHS North West	NHS Yorkshire and the Humber	NHS West Midlands	NHS South Central	NHS East of England	NHS South West	NHS East Midlands	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	1.70	1.71	0.89	1.02	0.77	0.76	0.68	0.57	0.51	0.47	9.07
May-17	1.75	2.61	0.98	1.10	0.94	0.95	0.67	0.70	0.74	0.49	10.93
Jun-17	1.70	2.97	0.99	1.20	0.98	0.87	0.75	0.71	0.65	0.56	11.38
Jul-17	1.74	2.66	0.94	0.87	0.83	0.70	0.72	0.63	0.57	0.34	9.98
Aug-17	1.97	2.91	1.15	1.25	1.00	0.72	0.76	0.71	0.59	0.42	11.49
Sep-17	1.77	2.40	1.19	1.01	0.77	0.74	0.68	0.56	0.54	0.37	10.04
Oct-17	1.76	2.49	1.01	1.24	0.80	0.80	0.79	0.62	0.61	0.52	10.63
Nov-17	1.76	2.35	1.05	1.06	0.89	0.78	0.83	0.70	0.54	0.45	10.42
Dec-17	1.59	2.13	0.94	1.05	0.91	0.69	0.79	0.58	0.55	0.52	9.75
Jan-18	1.79	2.99	1.02	1.32	1.03	0.72	0.77	0.67	0.72	0.44	11.47
Feb-18	1.45	2.22	0.84	0.96	0.87	0.59	0.73	0.62	0.50	0.35	9.14
Mar-18	2.03	2.62	0.83	1.02	0.97	0.63	0.74	0.58	0.52	0.34	10.29
Apr-18	1.47	2.49	0.93	0.94	0.98	0.70	0.67	0.57	0.52	0.44	9.70
May-18	1.92	2.79	0.99	0.98	0.96	0.80	0.92	0.69	0.51	0.47	11.03
Jun-18	1.70	2.18	1.02	0.94	0.83	0.82	0.71	0.58	0.59	0.51	9.88
Jul-18	1.73	2.48	1.08	1.07	0.91	0.86	0.73	0.64	0.56	0.46	10.53
Aug-18	1.76	2.97	1.06	0.89	0.92	0.85	0.73	0.64	0.56	0.63	11.01
Sep-18	1.71	2.45	1.00	0.85	0.75	0.78	0.65	0.64	0.56	0.55	9.94
Oct-18	1.74	2.74	0.93	0.95	0.89	0.85	0.80	0.68	0.62	0.52	10.71
Nov-18	1.90	2.25	0.96	0.84	0.92	0.77	0.75	0.69	0.68	0.50	10.27
Dec-18	1.67	2.33	0.88	0.91	0.87	0.65	0.72	0.59	0.57	0.50	9.69
Jan-19	1.73	2.24	0.92	1.01	0.92	0.84	0.86	0.62	0.61	0.60	10.34
Feb-19	1.49	2.19	0.94	0.62	0.76	0.73	0.58	0.57	0.56	0.45	8.86
Mar-19	1.65	2.32	0.90	1.05	0.87	0.79	0.64	0.88	0.55	0.54	10.19

Apr-19	1.31	2.21	0.93	0.85	0.87	0.94	0.72	0.56	0.65	0.55	9.58
May-19	1.15	2.17	1.01	0.99	0.89	0.99	0.70	0.70	0.61	0.57	9.79
Jun-19	1.17	2.14	0.91	0.94	0.89	0.84	0.71	0.61	0.54	0.51	9.25
Jul-19	1.10	2.45	0.97	0.89	1.10	0.90	0.84	0.71	0.60	0.49	10.05
Aug-19	1.27	2.60	0.91	1.14	0.86	0.74	0.82	0.68	0.59	0.54	10.15
Sep-19	1.11	2.49	1.02	0.81	0.86	0.93	0.71	0.81	0.59	0.54	9.86
Oct-19	1.26	2.80	1.04	0.94	0.94	0.89	0.86	0.98	0.64	0.64	10.97
Nov-19	1.21	2.75	1.05	1.01	0.95	0.93	0.88	0.79	0.56	0.53	10.67
Dec-19	12.51	2.66	0.95	0.97	0.96	0.71	0.81	0.75	0.62	0.56	21.52
Jan-20	15.80	2.84	1.21	0.93	0.93	0.88	1.09	0.73	0.67	0.70	25.78
Feb-20	18.86	2.09	0.91	0.81	0.86	0.72	0.82	0.67	0.50	0.57	26.81
Mar-20	10.23	2.75	1.06	0.94	0.91	0.79	0.94	0.75	0.56	0.75	19.68
Apr-20	10.76	1.07	0.94	0.84	0.82	0.76	0.86	0.69	0.54	0.67	17.96
May-20	11.77	1.10	0.82	0.72	0.91	0.74	0.65	0.57	0.47	0.49	18.25
Jun-20	13.28	1.38	0.96	0.78	0.94	0.77	0.74	0.65	0.57	0.75	20.82
Jul-20	11.04	1.42	0.96	1.07	1.05	0.97	0.78	0.71	0.62	0.59	19.21
Aug-20	13.33	1.07	0.91	0.81	0.91	0.76	0.83	0.57	0.56	0.58	20.34
Sep-20	14.43	1.36	0.78	0.94	0.94	0.87	0.83	0.78	0.61	0.59	22.14
Oct-20	13.01	1.35	0.86	0.85	0.95	0.83	0.85	0.66	0.60	0.60	20.56
Nov-20	11.49	1.16	0.87	0.83	0.91	0.94	0.82	0.71	0.56	0.65	18.94
Dec-20	11.84	1.46	0.87	0.89	1.04	0.87	0.91	0.66	0.62	0.73	19.91
Jan-21	10.08	1.71	0.84	0.82	0.94	0.85	0.78	0.59	0.60	0.58	17.80
Feb-21	16.84	1.04	0.87	0.83	0.88	0.81	0.84	0.60	0.53	0.52	23.76
Mar-21	14.38	1.15	1.00	0.92	0.82	0.92	0.89	0.69	0.83	0.69	22.29
Apr-21	13.20	1.01	1.00	0.87	0.86	0.90	0.86	0.60	0.62	0.55	20.46
May-21	14.10	1.12	0.95	0.89	0.87	0.98	0.79	0.66	0.74	0.62	21.72
Jun-21	10.78	1.16	1.00	0.95	1.03	0.86	0.88	0.67	0.76	0.65	18.76
Jul-21	13.14	0.99	1.00	0.81	1.02	0.81	0.99	0.71	0.75	0.58	20.81
Aug-21	9.38	0.80	1.05	0.89	1.00	0.91	0.92	0.56	0.65	0.54	16.68
Sep-21	16.18	1.03	0.86	1.03	1.09	0.89	0.96	0.76	0.63	0.66	24.09

Oct-21	16.65	0.81	0.95	0.93	0.89	0.83	0.78	0.57	0.60	0.61	23.60
Nov-21	16.82	0.78	0.91	0.95	0.93	0.77	0.80	0.67	0.69	0.65	23.97
Dec-21	16.31	0.71	0.91	0.99	0.84	0.92	0.85	0.65	0.67	0.55	23.38
Jan-22	15.17	0.92	1.01	1.01	0.90	0.90	0.76	0.77	0.68	0.57	22.70
Feb-22	17.75	1.33	0.98	1.20	0.85	0.79	0.78	0.74	0.71	0.55	25.67
Mar-22	14.82	1.14	1.11	1.14	0.99	0.82	1.19	0.78	0.81	0.62	23.44
Apr-22	9.55	1.21	1.09	1.19	0.91	0.78	0.84	0.74	0.85	0.56	17.72
May-22	8.97	0.94	1.24	0.99	1.02	0.83	0.81	0.74	0.89	0.65	17.07
Jun-22	9.18	2.06	1.22	1.24	0.92	0.84	0.88	0.79	0.77	0.69	18.59
Jul-22	16.20	1.23	0.98	0.96	0.78	0.91	0.82	0.65	0.82	0.57	23.92
Total	478.92	121.96	62.34	61.71	58.32	52.50	51.27	43.11	39.83	35.46	

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	NHS North West	NHS London	NHS East of England	NHS South West	NHS East Midlands	NHS Yorkshire and the Humber	NHS West Midlands	NHS South East Coast	NHS South Central	NHS North East	Total (dosage)
Apr-17	20.23	23.20	17.67	18.66	15.33	13.88	25.17	11.76	17.68	7.94	171.53
May-17	21.52	22.87	20.14	21.75	16.88	18.07	23.00	17.38	17.21	10.25	189.07
Jun-17	20.33	28.76	20.29	21.37	20.78	17.47	18.86	19.15	18.14	11.68	196.83
Jul-17	21.30	27.84	18.15	22.51	18.72	20.79	16.73	16.91	15.93	12.09	190.96
Aug-17	21.89	33.77	20.04	22.03	17.66	25.73	16.45	23.06	18.30	11.44	210.35
Sep-17	18.99	29.91	18.81	21.42	14.31	24.49	18.41	15.18	15.05	12.82	189.39
Oct-17	23.66	36.30	20.18	16.17	20.85	24.45	20.69	18.90	16.72	14.33	212.24
Nov-17	19.52	34.48	21.98	20.92	22.20	17.50	16.36	21.39	12.91	13.86	201.13
Dec-17	19.31	31.64	18.30	20.44	19.80	16.99	11.81	16.71	15.11	11.96	182.06
Jan-18	20.09	33.94	18.11	25.56	18.19	15.19	15.18	18.94	15.68	12.06	192.94
Feb-18	20.30	27.46	15.61	18.56	19.49	16.42	14.82	15.85	14.67	9.70	172.89
Mar-18	21.79	37.85	17.25	18.91	18.75	19.96	29.05	18.34	18.60	11.23	211.73
Apr-18	21.60	34.43	18.01	22.12	18.89	16.62	16.67	16.23	16.00	8.42	189.00
May-18	25.61	40.73	21.14	23.81	19.53	22.05	17.67	17.86	20.01	12.04	220.46
Jun-18	22.06	37.04	18.00	19.36	19.06	16.09	23.07	14.36	18.03	12.75	199.81
Jul-18	20.96	38.09	22.28	21.85	16.99	18.29	26.90	14.56	19.43	12.12	211.47
Aug-18	23.56	33.12	23.27	25.15	23.39	18.94	24.88	14.68	19.23	16.17	222.40
Sep-18	21.45	30.14	18.94	19.85	20.19	13.75	24.26	14.87	19.56	13.34	196.37
Oct-18	26.29	27.51	21.83	32.74	21.63	17.15	30.66	18.86	20.44	13.02	230.13
Nov-18	19.48	32.02	22.27	24.23	19.56	14.77	25.68	15.79	20.93	10.67	205.39
Dec-18	22.01	26.64	22.56	20.59	18.38	13.09	29.22	13.74	16.62	10.74	193.59
Jan-19	19.58	27.57	22.50	31.52	18.27	15.76	34.95	17.30	19.85	11.15	218.45
Feb-19	19.14	28.41	28.29	25.28	20.60	14.45	18.07	18.61	16.77	12.25	201.88
Mar-19	21.27	29.25	30.01	22.45	21.06	14.59	29.25	18.10	16.83	17.52	220.33

Apr-19	20.66	24.89	28.89	23.79	22.25	16.78	19.70	18.27	15.79	13.86	204.88
May-19	21.84	26.56	28.43	22.25	18.09	18.59	21.67	16.83	13.46	16.30	204.01
Jun-19	19.77	18.28	24.31	16.94	16.45	15.03	16.96	15.88	11.05	13.33	168.00
Jul-19	23.79	23.07	27.43	17.49	24.94	15.65	17.80	17.42	13.91	15.16	196.67
Aug-19	21.21	24.31	24.94	23.44	22.81	19.00	13.92	18.44	15.20	11.93	195.20
Sep-19	21.42	22.62	22.81	25.30	21.99	19.31	14.13	14.59	15.33	12.34	189.85
Oct-19	22.21	21.21	21.94	28.49	24.80	18.18	14.52	15.74	16.95	15.79	199.83
Nov-19	18.46	25.37	16.66	21.31	20.99	15.44	15.19	15.42	16.60	13.95	179.40
Dec-19	14.64	23.50	15.87	20.08	19.21	14.27	14.08	16.28	16.95	11.83	166.70
Jan-20	23.18	27.74	20.23	23.06	16.12	16.18	14.57	17.88	14.52	15.14	188.63
Feb-20	15.42	22.41	17.63	15.25	14.97	13.04	14.29	17.63	10.55	11.34	152.53
Mar-20	19.37	25.01	17.11	16.10	15.86	14.71	14.55	16.13	12.59	9.99	161.42
Apr-20	7.14	17.28	12.17	12.10	13.32	9.88	17.86	10.84	8.48	5.17	114.23
May-20	7.40	17.42	11.85	13.22	14.78	9.80	17.39	8.40	8.26	6.70	115.21
Jun-20	14.18	22.22	15.50	14.85	18.24	14.35	16.22	10.24	10.70	8.23	144.73
Jul-20	13.00	23.36	18.88	13.33	21.98	15.04	17.63	11.59	14.73	9.93	159.46
Aug-20	-15.80	19.47	18.85	12.76	16.83	13.53	13.27	12.70	10.44	9.47	111.51
Sep-20	14.71	28.07	15.13	13.93	20.32	17.17	15.25	11.67	8.34	8.17	152.74
Oct-20	13.55	25.99	14.66	17.85	21.35	16.17	15.25	13.60	9.79	10.15	158.36
Nov-20	15.55	29.11	15.16	18.29	18.61	17.68	12.43	11.64	11.07	8.89	158.43
Dec-20	18.09	28.40	21.41	25.28	20.79	18.46	13.98	14.53	10.76	10.67	182.37
Jan-21	19.23	25.83	19.56	19.14	17.25	16.56	12.29	11.08	8.85	8.86	158.66
Feb-21	12.16	22.56	17.79	19.71	19.79	15.13	12.39	12.17	12.73	9.21	153.64
Mar-21	17.48	27.29	24.14	21.23	18.75	17.94	12.33	13.92	11.11	8.44	172.63
Apr-21	12.65	29.59	24.52	19.16	17.37	18.21	11.16	11.89	13.50	10.05	168.11
May-21	11.83	27.60	21.55	14.65	14.14	15.63	11.61	13.21	14.21	12.21	156.64
Jun-21	15.21	32.74	23.47	20.54	19.51	18.54	13.71	12.81	15.60	10.17	182.29
Jul-21	11.71	28.72	19.54	15.61	18.53	17.67	14.38	11.94	13.68	11.41	163.21
Aug-21	12.75	27.02	19.64	13.70	18.70	15.63	13.60	13.39	16.23	11.00	161.67
Sep-21	12.81	28.45	21.04	12.10	20.55	17.71	10.41	15.91	11.74	9.99	160.71

Oct-21	8.38	27.47	17.30	11.81	18.44	18.01	10.81	19.97	11.26	9.16	152.62
Nov-21	15.39	25.06	19.77	15.96	20.31	18.58	9.39	19.12	12.57	9.79	165.94
Dec-21	14.09	21.41	17.87	13.47	20.51	22.62	10.52	15.29	11.42	10.44	157.64
Jan-22	13.59	22.68	18.98	13.18	15.59	15.74	10.57	18.18	13.15	10.13	151.78
Feb-22	13.41	21.39	19.22	13.47	15.98	16.78	10.77	15.31	11.14	8.72	146.19
Mar-22	13.57	21.09	18.30	18.14	21.08	16.92	19.24	17.74	11.51	9.63	167.21
Apr-22	11.07	24.55	20.02	17.35	19.59	17.03	12.98	18.01	9.29	10.42	160.30
May-22	12.11	22.49	21.64	20.28	19.83	22.39	11.72	17.31	13.09	11.89	172.75
Jun-22	14.08	22.30	16.03	13.32	18.39	20.20	15.17	12.47	14.30	10.49	156.75
Jul-22	14.28	22.11	17.88	15.92	18.10	20.12	13.42	13.96	12.81	13.57	162.16
Total	1097.51	1729.54	1283.77	1241.11	1217.61	1096.16	1094.95	997.91	923.36	723.47	

Alteplase

	NHS London	NHS North West	NHS East of England	NHS South Central	NHS West Midlands	NHS Yorkshire and the Humber	NHS South West	NHS North East	NHS East Midlands	NHS South East Coast	Total (dosage)
Apr-17	17.32	13.79	13.96	9.12	10.29	6.42	8.72	6.59	8.24	6.50	100.97
May-17	21.04	15.92	14.71	11.93	11.13	9.08	8.66	7.31	7.14	8.11	115.03
Jun-17	20.26	17.09	14.75	11.11	13.71	10.84	10.96	8.08	7.99	8.14	122.94
Jul-17	19.96	16.61	16.97	10.60	10.99	9.31	9.26	9.20	9.03	7.43	119.36
Aug-17	19.57	14.87	14.29	11.50	14.20	7.63	10.09	9.06	6.64	7.45	115.30
Sep-17	20.18	11.78	15.08	10.23	8.59	10.56	9.33	7.36	7.70	8.59	109.39
Oct-17	18.87	13.45	14.41	13.09	10.42	9.18	8.88	9.12	7.09	7.47	111.99
Nov-17	20.72	14.96	15.57	11.72	12.15	7.74	10.90	7.73	9.71	5.77	116.99
Dec-17	21.08	15.54	14.81	9.64	13.55	8.36	10.59	10.17	9.23	7.26	120.23
Jan-18	23.58	17.72	13.62	11.69	9.44	11.50	10.45	9.54	10.16	9.80	127.50
Feb-18	16.62	13.41	14.90	10.66	13.14	9.43	9.83	9.33	7.67	6.16	111.15
Mar-18	19.49	15.86	13.99	12.89	10.48	8.37	9.56	9.01	9.52	8.48	117.65
Apr-18	19.36	13.74	15.19	10.76	11.75	8.42	7.26	9.25	8.17	8.75	112.66
May-18	19.52	13.98	14.92	13.25	10.99	9.36	11.46	9.60	9.17	6.91	119.17
Jun-18	20.58	16.10	13.89	10.94	10.95	10.19	10.49	7.99	7.77	8.19	117.09
Jul-18	20.86	13.79	15.55	10.40	9.47	9.24	9.07	8.65	9.09	7.95	114.08
Aug-18	23.74	12.73	16.65	13.02	12.31	10.77	10.80	9.48	7.93	8.64	126.08
Sep-18	19.95	13.77	14.17	9.64	12.88	6.65	9.37	8.67	6.01	9.10	110.22
Oct-18	21.05	13.48	15.03	10.63	12.78	9.03	10.90	8.70	9.14	6.33	117.06
Nov-18	24.10	14.17	12.85	12.65	12.43	11.25	10.09	8.35	8.14	8.16	122.18
Dec-18	23.15	16.22	13.72	12.62	14.43	11.06	8.33	8.60	8.41	8.29	124.82
Jan-19	21.59	13.15	14.70	8.64	13.49	9.72	9.47	10.91	10.21	7.85	119.73
Feb-19	16.82	11.69	14.91	11.76	11.24	7.82	9.66	9.41	7.31	8.44	109.06
Mar-19	18.89	14.11	16.40	11.60	12.92	9.70	8.54	10.57	10.08	7.89	120.69

Apr-19	21.65	14.07	13.28	11.50	9.93	9.89	9.42	8.00	8.19	9.41	115.33
May-19	21.46	17.99	14.39	12.82	12.99	9.51	8.88	10.48	8.89	7.64	125.04
Jun-19	21.06	15.56	13.92	10.15	12.60	10.25	9.66	6.99	6.97	8.77	115.93
Jul-19	25.54	15.80	15.77	12.38	11.34	11.56	10.39	9.50	10.69	8.34	131.31
Aug-19	18.11	13.52	14.56	11.37	14.52	9.92	10.28	8.90	9.28	8.06	118.52
Sep-19	18.64	14.93	13.52	12.28	11.34	10.17	11.25	10.98	9.87	8.06	121.03
Oct-19	23.22	15.03	18.60	12.59	13.51	11.63	9.75	9.15	10.95	8.49	132.92
Nov-19	22.28	17.27	17.09	11.34	10.89	11.39	10.88	7.07	9.12	8.30	125.63
Dec-19	22.82	14.36	17.59	13.09	15.01	11.97	12.27	9.26	9.35	9.73	135.43
Jan-20	20.71	14.83	14.87	14.76	14.82	11.43	12.43	8.00	8.75	8.27	128.87
Feb-20	24.19	12.32	14.05	10.11	12.10	9.34	9.08	9.67	9.71	8.48	119.08
Mar-20	29.61	16.27	20.62	17.43	16.14	12.39	13.10	10.34	8.15	11.60	155.64
Apr-20	33.50	22.31	18.60	17.03	16.82	14.14	12.65	10.46	11.65	12.16	169.31
May-20	21.84	15.42	16.23	12.52	13.36	10.01	11.88	8.92	8.54	8.39	127.13
Jun-20	23.10	16.92	18.22	14.63	11.93	11.28	8.32	8.09	7.84	10.13	130.45
Jul-20	24.20	13.77	17.89	12.46	11.98	10.72	9.91	8.52	8.95	9.57	127.95
Aug-20	18.85	16.21	16.71	10.59	12.11	10.86	9.03	9.24	8.30	10.14	122.05
Sep-20	24.15	12.33	14.94	11.84	13.97	9.53	10.92	9.75	8.56	6.95	122.92
Oct-20	21.36	16.39	15.35	13.71	13.43	11.29	9.85	7.46	8.91	7.78	125.53
Nov-20	22.26	17.31	19.45	14.69	10.52	12.84	11.63	9.79	8.20	11.95	138.63
Dec-20	27.47	17.75	15.02	15.51	12.60	11.46	11.31	9.56	11.43	9.07	141.16
Jan-21	38.70	18.25	17.21	14.48	18.76	9.55	12.79	9.07	11.31	7.74	157.86
Feb-21	24.39	16.57	15.32	15.07	16.81	10.01	11.19	9.21	8.37	7.86	134.80
Mar-21	28.90	19.17	16.47	17.09	11.94	11.09	8.70	9.36	10.03	8.03	140.78
Apr-21	20.44	15.18	13.78	12.95	11.27	11.09	10.84	9.02	8.79	8.15	121.51
May-21	21.08	17.36	15.00	13.49	13.36	9.42	8.24	9.12	9.05	6.66	122.79
Jun-21	21.84	18.20	15.00	13.51	13.37	11.88	11.19	9.73	10.08	9.28	134.08
Jul-21	24.16	16.21	13.49	13.97	12.72	10.91	11.35	9.98	9.37	10.97	133.12
Aug-21	20.93	18.64	15.11	16.45	14.57	13.42	9.81	8.45	8.26	9.02	134.65
Sep-21	19.95	17.51	17.08	13.02	14.68	11.02	9.22	8.65	9.88	6.55	127.56

Oct-21	24.09	15.23	15.00	15.15	10.55	12.81	9.05	8.84	8.33	8.90	127.97
Nov-21	22.53	19.75	19.15	15.95	11.52	12.98	10.60	10.07	8.08	9.89	140.52
Dec-21	23.59	18.88	15.70	16.26	16.47	10.74	12.49	13.77	10.17	12.63	150.70
Jan-22	21.40	15.99	16.79	13.43	11.53	11.14	13.20	9.32	9.51	6.64	128.95
Feb-22	22.31	15.22	15.75	10.45	10.32	10.12	10.74	8.26	9.59	6.87	119.64
Mar-22	22.79	17.05	16.00	15.21	12.67	11.77	12.94	10.59	10.11	8.63	137.76
Apr-22	25.48	16.30	13.93	14.79	11.20	11.80	7.75	10.19	9.52	9.90	130.86
May-22	23.10	17.83	16.15	15.53	14.53	14.45	9.99	11.13	7.85	8.53	139.09
Jun-22	17.69	17.04	16.16	13.04	12.30	14.02	9.14	7.57	8.27	6.97	122.20
Jul-22	19.76	15.29	14.69	9.96	10.81	13.00	7.88	8.60	5.15	6.56	111.70
Total	1417.43	1003.96	993.45	812.73	805.00	674.44	652.65	583.75	565.58	538.72	

Amiodarone

	NHS London	NHS North West	NHS East of England	NHS West Midlands	NHS South Central	NHS South West	NHS Yorkshire and the Humber	NHS South East Coast	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	6747.80	5649.90	3913.90	3465.01	3076.50	2555.45	2468.35	2522.40	2565.50	1404.20	34369.01
May-17	7114.45	6132.05	4483.60	3917.50	3218.45	2840.20	2939.10	2904.15	2926.40	1689.70	38165.60
Jun-17	6842.50	5641.90	4135.00	3689.75	3547.90	2942.30	3116.15	2883.20	3133.60	1737.05	37669.35
Jul-17	7037.45	7773.30	4026.10	3368.45	3139.25	2585.80	2613.65	2964.10	2776.80	1825.25	38110.15
Aug-17	6848.30	8143.60	4243.20	3652.95	3225.90	3186.50	2786.50	2715.90	2714.05	1730.25	39247.15
Sep-17	6635.49	5151.39	4065.10	3711.30	2935.50	3186.10	2563.60	2515.35	2649.05	1422.95	34835.83
Oct-17	7155.85	5532.65	4102.80	3850.70	3706.80	3024.70	3136.95	2959.90	2895.75	1585.95	37952.05
Nov-17	7333.35	5263.45	4005.65	4088.20	3671.45	3109.80	2960.40	3031.10	2661.30	1690.40	37815.10
Dec-17	7804.70	5022.45	4216.45	4375.45	3419.15	3165.60	3329.05	3009.20	3064.35	1763.10	39169.50
Jan-18	6992.40	5884.45	4130.50	3915.40	3214.05	3379.85	2939.85	2912.60	2717.60	1727.05	37813.75
Feb-18	6619.95	4718.30	3818.60	3803.35	2719.55	2760.10	2819.90	2538.20	2340.75	1492.85	33631.55
Mar-18	7419.45	5376.10	4198.30	4290.45	3240.50	3045.70	3274.90	3065.80	2782.95	1559.10	38253.25
Apr-18	6991.70	5012.25	4302.50	3449.00	3474.95	2476.10	2639.55	2591.25	2398.30	1608.45	34944.05
May-18	7131.20	5402.80	4368.65	4190.25	3395.55	3073.25	3191.25	2741.55	2993.55	1729.95	38218.00
Jun-18	7718.25	4915.95	3952.90	3704.65	3123.65	2883.00	2904.75	2934.30	2822.45	1562.90	36522.80
Jul-18	6652.15	5276.87	4281.60	4002.25	3357.30	3010.75	2919.25	2529.60	2593.50	1491.20	36114.47
Aug-18	6620.35	4754.28	4014.05	4131.80	2894.05	3050.75	3012.00	3045.30	3096.15	1821.40	36440.13
Sep-18	6347.15	5103.40	4251.10	3351.80	2817.50	2945.95	2709.95	2702.50	2396.70	1346.80	33972.85
Oct-18	6933.55	5665.85	4198.20	4195.40	3951.00	3116.30	3293.85	2815.10	2860.75	1587.90	38617.90
Nov-18	7536.15	6095.70	4459.45	3870.95	3565.20	3172.00	3275.05	2545.40	2616.20	1532.40	38668.50
Dec-18	7512.35	6034.90	4106.20	4115.05	3599.20	3021.35	3142.80	2976.00	2602.15	1572.20	38682.20
Jan-19	6805.25	5764.15	4509.80	3998.35	3283.15	3078.30	2918.20	2833.10	2887.75	1312.90	37390.95
Feb-19	6130.60	5053.10	3587.85	3832.00	2854.85	2814.20	2668.15	2536.40	2505.05	1330.10	33312.30
Mar-19	6504.80	5650.70	4087.10	3857.35	2931.80	2740.95	2878.80	2914.50	2815.60	1184.80	35566.40

Apr-19	5798.40	5334.80	4095.95	3931.45	3046.40	3179.00	2927.20	2877.90	2433.80	1531.90	35156.80
May-19	6201.60	5335.10	3486.50	4106.05	2882.55	3250.85	2993.30	2732.10	2625.00	1497.10	35110.15
Jun-19	6005.50	4701.15	3517.25	3749.50	2831.10	2769.90	2815.50	2862.10	2554.80	1177.90	32984.70
Jul-19	6998.77	5630.35	4296.10	4199.50	3101.85	3193.20	2956.65	3274.75	2862.30	1346.30	37859.77
Aug-19	6459.90	4983.15	3701.55	4219.10	2737.60	2754.20	2431.05	2862.45	2733.60	1492.75	34375.35
Sep-19	6641.52	4758.10	3736.75	3963.45	2899.40	2875.55	2892.55	2626.50	2690.30	1456.75	34540.87
Oct-19	6786.80	5540.35	4222.20	4567.20	3392.60	3366.75	2879.70	2804.20	3040.30	1683.85	38283.95
Nov-19	6182.64	4540.50	4432.45	3918.30	3357.45	3212.90	3138.05	2697.00	2752.30	1610.30	35841.89
Dec-19	6165.77	5428.55	4140.30	4515.60	3188.45	2687.05	3185.05	2841.20	3327.40	1643.40	37122.77
Jan-20	6767.65	5470.40	4257.65	4045.00	3121.30	3004.55	3403.15	2840.25	2937.45	1216.60	37064.00
Feb-20	6107.89	4865.16	4010.85	3732.40	2959.40	2473.80	3103.10	2485.40	2801.15	1144.35	33683.50
Mar-20	7191.60	5071.85	4554.95	4193.60	3225.40	2712.95	3534.30	2988.60	3203.40	1188.60	37865.25
Apr-20	4870.00	3888.80	2916.10	3103.36	2696.10	1831.15	2284.10	2309.20	1885.40	946.40	26730.61
May-20	3699.75	3779.15	2780.25	2832.90	2241.50	2101.75	1919.40	2202.00	1806.00	1068.75	24431.45
Jun-20	4408.50	4503.55	3370.65	2976.45	2696.55	2493.60	2338.75	2515.65	2522.40	1355.75	29181.85
Jul-20	5157.75	5170.05	3635.40	3604.30	2802.75	2708.90	2340.10	2570.05	2567.85	1195.40	31752.55
Aug-20	5237.10	3807.75	3775.70	3442.95	2993.90	2325.50	2391.35	2413.60	2193.35	1249.90	29831.10
Sep-20	5906.80	4897.20	4298.50	3962.80	3061.75	2725.75	2562.05	2468.45	2439.65	1165.90	33488.85
Oct-20	6156.90	4556.15	4366.75	3791.95	3125.70	3293.00	2695.00	2568.80	2481.60	1409.00	34444.85
Nov-20	5857.60	4187.55	3615.10	3747.20	3010.65	2527.80	2417.90	2281.35	2497.70	1286.20	31429.05
Dec-20	6514.35	4641.05	4008.95	3236.80	3638.30	2894.70	2609.95	2822.40	2436.65	1382.15	34185.30
Jan-21	5719.76	4537.15	2955.80	3196.30	2946.45	2519.90	2396.80	2583.50	2015.70	1384.40	30255.76
Feb-21	5066.45	4653.20	2933.30	2571.40	2708.75	2440.80	2355.50	2145.10	2123.20	1210.60	28208.30
Mar-21	6205.00	5439.20	3864.55	3605.95	2809.95	3033.45	2607.95	2769.60	2359.60	1328.85	34024.10
Apr-21	6021.60	5181.60	3438.15	3288.00	2618.15	2758.20	2614.45	2074.80	2149.45	1156.60	31301.00
May-21	6394.00	5505.65	3563.60	3715.15	2947.60	3472.30	2778.85	2630.95	2301.85	1565.45	34875.40
Jun-21	7135.75	5403.50	3662.60	4318.15	3170.10	3300.35	2973.75	2616.05	2516.10	1602.10	36698.45
Jul-21	6659.40	5053.25	3866.35	3812.20	3212.60	2901.70	3060.80	2628.95	2707.70	1592.65	35495.60
Aug-21	5632.95	4399.20	3627.50	3500.70	2743.65	2421.75	2518.15	2550.20	2033.50	1363.10	30790.70
Sep-21	6070.00	4728.15	3734.90	3381.45	2547.15	2734.10	2359.95	2570.30	2487.70	1447.70	32061.40

Oct-21	5663.60	5045.60	3235.90	3506.40	2731.60	2766.90	2576.95	2512.50	2026.55	1090.35	31156.35
Nov-21	6782.70	5163.45	3772.65	3682.30	2936.95	2774.45	2971.95	2763.50	2550.00	1433.05	34831.00
Dec-21	6568.80	5570.75	3919.60	3760.80	3345.05	3098.75	2932.80	2602.95	2587.95	1490.30	35877.75
Jan-22	4986.60	4638.10	3168.60	3464.10	2580.20	2517.45	2359.15	2407.65	2365.85	1596.70	30084.40
Feb-22	5940.35	4632.51	3716.10	3376.75	2785.90	2988.60	2170.25	2365.40	2505.30	1563.10	32044.26
Mar-22	6075.50	5578.05	4008.55	4067.37	3177.20	3409.70	2727.90	2755.90	2464.45	1612.15	35876.77
Apr-22	6340.15	5515.50	3926.00	4379.25	2980.60	2739.10	2902.10	2799.65	2366.70	1454.70	35403.75
May-22	6644.70	5349.85	4259.15	4312.35	3428.00	3154.85	3061.45	2716.95	2938.70	1728.05	37594.05
Jun-22	6545.20	4781.85	3523.70	3606.95	2810.70	2839.75	3128.70	2416.90	2646.65	1465.35	33765.75
Jul-22	6554.45	4765.00	3536.20	3610.25	3167.55	3176.20	2706.50	2319.60	2589.05	1522.45	33947.25
Total	409558.94	332051.76	249391.70	241823.04	197022.05	184596.15	179524.15	171461.30	166344.65	93365.75	

Amlodipine

	NHS London	NHS North West	NHS West Midlands	NHS East of England	NHS Yorkshire and the Humber	NHS South Central	NHS East Midlands	NHS South West	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	1488.22	867.69	651.71	679.14	771.30	516.62	487.97	417.39	383.46	340.83	6604.31
May-17	1557.67	953.37	684.38	690.10	846.41	567.61	510.84	481.64	408.91	358.94	7059.85
Jun-17	1480.53	864.19	653.04	617.57	802.43	522.47	487.58	475.61	383.96	356.09	6643.45
Jul-17	1445.54	817.83	634.36	602.34	788.27	511.66	460.98	447.26	379.95	320.83	6408.99
Aug-17	1550.86	890.45	675.12	651.87	816.31	523.35	572.43	455.62	401.41	336.54	6873.93
Sep-17	1473.62	850.42	627.55	620.94	802.63	512.69	500.21	465.42	393.56	356.32	6603.33
Oct-17	1544.57	877.33	679.21	669.77	815.43	554.73	528.98	429.04	420.99	364.39	6884.42
Nov-17	1592.28	914.78	702.73	654.48	855.36	566.00	543.02	497.07	432.71	355.62	7114.03
Dec-17	1591.17	937.91	698.84	664.44	872.49	554.27	528.88	476.80	456.61	387.48	7168.88
Jan-18	1620.53	996.23	727.91	693.30	907.54	609.66	623.21	495.35	487.38	380.16	7541.26
Feb-18	1462.29	858.38	672.50	619.58	829.28	542.23	515.57	409.65	417.72	352.67	6679.85
Mar-18	1706.50	967.00	757.83	721.09	904.01	524.39	563.34	585.11	492.24	383.93	7605.43
Apr-18	1510.78	879.06	687.41	677.46	798.48	563.70	524.17	460.37	430.65	351.15	6883.21
May-18	1640.02	978.43	718.44	713.28	847.84	576.95	549.06	501.65	435.52	402.14	7363.30
Jun-18	1445.67	852.45	670.58	674.09	827.55	523.35	507.84	422.44	401.15	350.28	6675.38
Jul-18	1566.17	883.62	708.50	651.25	876.16	520.93	495.30	442.89	394.36	367.10	6906.25
Aug-18	1592.18	916.04	746.42	655.46	858.63	543.15	513.00	474.80	416.33	368.94	7084.94
Sep-18	1450.12	860.23	662.67	618.67	780.33	510.86	476.06	436.04	379.24	340.60	6514.79
Oct-18	1594.52	956.59	740.77	692.66	916.65	636.93	581.89	455.13	430.55	393.48	7399.15
Nov-18	1616.19	940.86	750.16	713.34	921.81	575.34	564.96	507.71	460.37	352.88	7403.61
Dec-18	1564.77	943.05	755.01	689.52	906.93	527.84	565.69	504.09	448.98	372.76	7278.61
Jan-19	1618.99	979.92	799.80	724.69	914.83	655.94	587.41	528.34	449.64	423.78	7683.31
Feb-19	1494.35	869.93	713.64	678.58	839.14	528.10	524.38	519.61	425.46	364.20	6957.38
Mar-19	1597.85	923.86	775.09	709.05	626.62	587.65	582.56	568.22	453.72	379.54	7204.15

Apr-19	1558.43	967.91	801.20	712.24	608.83	557.53	586.51	549.35	449.00	414.36	7205.34
May-19	1613.19	945.81	764.62	732.37	617.19	585.18	598.85	581.91	464.12	402.23	7305.46
Jun-19	1409.72	887.49	683.51	649.10	558.30	531.57	513.98	489.34	403.32	361.89	6488.20
Jul-19	1615.27	961.21	738.24	684.19	607.78	600.10	579.42	581.54	450.97	390.13	7208.84
Aug-19	1438.97	889.52	696.04	631.95	557.47	551.61	560.83	554.42	433.29	353.97	6668.06
Sep-19	1469.39	901.53	705.27	685.60	550.50	543.60	552.06	491.36	406.61	398.32	6704.22
Oct-19	1644.21	1007.96	782.92	721.65	638.13	624.90	603.38	617.41	444.72	429.83	7515.09
Nov-19	1559.33	919.81	746.76	706.35	600.20	578.51	571.26	571.26	450.74	421.31	7125.51
Dec-19	1727.31	1000.66	803.00	746.14	672.98	670.67	608.32	604.00	471.63	439.34	7744.04
Jan-20	1713.05	1017.71	792.37	778.11	642.92	630.90	634.12	622.97	492.79	408.47	7733.39
Feb-20	1546.73	923.30	736.87	683.16	562.83	562.68	580.06	555.98	440.03	384.56	6976.17
Mar-20	1699.28	994.89	759.05	732.91	601.71	615.37	632.91	594.49	452.92	414.78	7498.28
Apr-20	1302.26	802.34	580.85	527.93	456.91	488.06	477.80	427.43	373.13	305.73	5742.42
May-20	1204.09	838.09	585.09	589.71	466.88	561.32	443.93	462.89	391.28	289.79	5833.05
Jun-20	1305.73	858.01	629.09	631.85	498.94	539.30	505.74	474.06	418.33	350.12	6211.14
Jul-20	1451.17	904.36	667.16	697.98	567.17	574.86	553.77	520.64	421.57	372.84	6731.50
Aug-20	1270.16	843.98	621.75	624.48	507.39	533.75	470.39	485.02	396.90	354.79	6108.60
Sep-20	1510.56	939.00	728.04	711.28	578.55	584.36	560.93	559.39	454.81	427.12	7054.01
Oct-20	1549.49	974.58	723.64	757.96	610.70	578.56	578.31	562.20	477.29	404.39	7217.10
Nov-20	1520.30	982.19	734.92	726.15	598.61	611.72	578.18	587.26	455.93	424.15	7219.38
Dec-20	1826.83	1096.22	792.48	833.43	626.14	691.39	617.68	630.59	528.18	445.49	8088.42
Jan-21	1627.62	994.67	742.92	741.03	583.06	662.73	577.92	559.52	476.49	426.88	7392.81
Feb-21	1424.61	942.67	676.87	701.70	544.59	568.73	554.22	529.23	439.05	392.41	6774.04
Mar-21	1683.56	1063.75	809.07	808.92	686.75	660.46	625.29	622.91	498.17	425.14	7884.00
Apr-21	1643.15	983.19	772.32	776.72	600.09	637.49	594.23	579.66	470.41	421.23	7478.46
May-21	1637.55	1004.82	757.57	785.68	592.72	598.90	586.84	552.43	483.46	422.50	7422.46
Jun-21	1620.25	1028.47	766.12	808.77	622.34	634.22	645.58	605.37	533.24	458.34	7722.68
Jul-21	1611.47	989.00	707.59	781.74	603.98	629.33	621.71	563.14	497.46	435.00	7440.42
Aug-21	1560.39	970.00	698.21	726.25	578.59	601.91	580.97	516.98	484.19	402.67	7120.14
Sep-21	1693.12	1029.31	750.52	762.43	618.05	563.78	627.57	512.91	510.02	437.00	7504.67

Oct-21	1630.87	1003.47	718.88	734.41	618.93	576.39	608.94	498.59	505.76	457.83	7354.07
Nov-21	1757.78	1099.96	794.59	782.90	655.18	595.39	610.46	522.48	538.96	487.47	7845.16
Dec-21	1793.87	1141.04	840.55	837.43	698.19	674.36	660.58	567.12	551.83	478.58	8243.53
Jan-22	1660.46	1028.73	760.92	786.05	629.94	602.69	619.35	522.23	515.03	459.80	7585.18
Feb-22	1623.06	1021.72	732.19	745.86	618.51	593.52	594.96	477.27	505.62	432.55	7345.23
Mar-22	1865.93	1147.09	836.38	869.65	711.70	667.20	670.84	570.17	582.39	508.87	8430.19
Apr-22	1749.92	1012.93	755.25	778.29	656.71	622.89	654.46	536.65	537.35	462.74	7767.18
May-22	1820.18	1116.88	824.86	839.12	700.50	663.46	687.17	552.90	550.86	496.35	8252.27
Jun-22	1694.51	1117.74	789.47	789.27	652.51	532.34	634.89	531.92	499.46	456.46	7698.54
Jul-22	1633.93	1036.66	687.92	753.41	619.79	509.46	597.34	509.02	470.52	437.77	7255.80
Total	100872.96	61168.21	46388.63	45456.69	44248.57	37067.47	36356.94	33311.12	29112.53	25453.74	

Apixaban

	NHS London	NHS North West	NHS West Midlands	NHS South Central	NHS Yorkshire and the Humber	NHS South West	NHS East of England	NHS East Midlands	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	754.76	602.77	424.48	413.75	487.74	306.28	391.21	285.13	233.19	201.70	4100.99
May-17	855.20	677.92	473.36	494.38	533.42	352.67	442.11	306.66	260.40	226.21	4622.31
Jun-17	831.98	694.83	491.83	462.19	549.93	363.60	452.89	326.11	245.36	226.34	4645.03
Jul-17	786.06	639.50	472.29	482.92	555.05	365.54	410.98	325.75	235.38	227.49	4500.95
Aug-17	842.92	739.01	508.68	484.39	558.83	369.25	431.88	322.78	278.60	240.77	4777.10
Sep-17	815.23	703.25	495.72	459.97	554.63	346.30	432.61	344.03	255.30	245.39	4652.43
Oct-17	939.63	755.88	550.57	523.83	596.64	363.30	471.74	363.94	280.50	252.87	5098.90
Nov-17	947.24	770.52	560.48	518.32	607.80	365.19	478.93	403.02	270.90	278.47	5200.86
Dec-17	923.40	751.04	581.62	527.95	598.64	414.13	519.64	387.85	291.41	268.69	5264.35
Jan-18	998.18	848.23	704.37	603.21	651.67	436.19	557.10	409.55	316.83	302.16	5827.47
Feb-18	895.92	758.44	646.32	527.08	596.83	383.23	475.18	379.57	262.11	274.30	5198.98
Mar-18	1051.21	859.16	704.32	582.69	671.84	432.37	521.91	415.71	328.91	311.86	5879.96
Apr-18	969.24	826.46	687.09	596.83	639.84	387.04	497.04	406.77	318.77	285.63	5614.70
May-18	989.22	822.47	671.64	630.76	667.89	433.40	495.73	469.96	367.79	317.38	5866.22
Jun-18	979.79	770.23	638.44	544.00	660.73	443.09	485.44	399.99	322.21	287.09	5531.00
Jul-18	942.34	798.16	658.53	601.39	660.96	436.58	509.45	433.99	327.46	302.12	5670.96
Aug-18	919.36	817.56	651.65	605.86	665.19	439.64	482.99	462.71	340.54	312.17	5697.67
Sep-18	876.87	736.56	625.48	546.17	644.58	430.13	420.50	438.64	305.81	255.68	5280.41
Oct-18	997.68	852.63	756.08	654.47	723.16	468.07	488.43	470.11	360.48	329.62	6100.72
Nov-18	993.83	820.80	704.65	634.99	714.06	445.84	503.52	498.94	371.92	319.00	6007.53
Dec-18	998.53	846.57	726.02	631.62	737.64	500.17	495.49	476.36	368.68	332.50	6113.57
Jan-19	1049.08	926.78	762.99	685.00	777.22	538.50	568.17	537.27	420.54	371.64	6637.18
Feb-19	978.88	828.31	686.78	673.59	727.00	538.78	515.11	485.57	382.21	334.47	6150.71
Mar-19	1037.70	872.06	744.20	667.87	658.61	511.66	528.00	521.22	394.10	373.91	6309.31

Apr-19	1059.22	903.61	773.12	673.91	685.82	548.79	548.71	533.89	395.54	370.17	6492.77
May-19	1037.47	924.67	782.18	719.54	728.93	561.45	552.88	510.85	417.51	390.02	6625.47
Jun-19	1012.35	838.96	774.34	607.43	608.99	517.92	516.19	502.01	409.92	412.40	6200.51
Jul-19	1091.00	913.50	803.43	687.79	685.68	568.21	558.69	562.04	411.60	393.04	6674.97
Aug-19	1033.46	862.13	784.80	638.41	634.39	567.84	510.92	532.25	405.16	374.57	6343.91
Sep-19	1002.23	846.84	758.37	619.76	625.66	577.40	480.80	518.83	388.39	361.46	6179.73
Oct-19	1100.90	906.15	876.80	739.51	708.46	653.97	576.38	557.70	445.60	401.63	6967.09
Nov-19	1052.67	913.49	874.68	706.74	687.85	598.27	533.36	553.83	444.59	415.72	6781.20
Dec-19	1127.87	969.67	912.13	758.53	756.81	682.75	564.67	566.79	476.39	413.61	7229.20
Jan-20	1156.38	1002.73	994.96	815.61	778.85	649.50	604.21	618.10	502.49	421.79	7544.60
Feb-20	1090.49	910.96	862.85	680.87	661.69	661.13	526.17	537.41	444.15	397.87	6773.57
Mar-20	1107.54	908.24	882.27	719.19	704.96	649.72	517.65	539.66	441.48	422.88	6893.58
Apr-20	947.02	744.57	707.80	572.68	508.28	442.24	404.68	387.63	351.00	316.97	5382.84
May-20	947.92	810.47	803.14	642.09	546.82	491.87	469.84	423.83	367.97	335.33	5839.27
Jun-20	1031.87	871.49	851.21	657.85	604.97	549.13	506.57	444.17	410.56	374.92	6302.73
Jul-20	1098.86	906.05	850.67	661.61	652.62	589.67	541.79	477.92	437.76	401.04	6617.97
Aug-20	970.51	833.63	798.74	654.32	632.16	527.49	501.36	431.64	420.24	371.39	6141.47
Sep-20	1097.30	931.61	885.58	712.66	663.06	648.20	516.95	484.20	456.49	428.57	6824.61
Oct-20	1097.62	991.25	926.43	716.17	711.93	660.77	588.67	514.86	477.66	423.91	7109.27
Nov-20	1099.93	1047.43	978.44	707.93	711.39	614.58	555.14	501.87	469.37	448.83	7134.89
Dec-20	1210.73	1087.66	1042.95	835.39	731.46	712.46	624.89	536.44	522.76	498.61	7803.33
Jan-21	1468.08	1061.90	1066.11	834.43	736.72	687.81	719.56	547.78	503.31	481.39	8107.08
Feb-21	1264.89	1047.70	1094.73	799.04	666.94	619.04	623.29	538.54	498.86	456.42	7609.45
Mar-21	1267.17	1105.63	1114.59	897.85	773.21	754.71	665.32	630.63	556.01	545.24	8310.35
Apr-21	1172.97	1043.29	1087.90	832.81	735.27	707.18	653.83	564.48	507.80	509.50	7815.02
May-21	1148.51	1069.61	990.45	862.52	747.30	763.89	620.58	531.67	536.48	491.10	7762.09
Jun-21	1249.97	1122.78	1045.57	863.20	752.93	732.06	646.93	564.71	559.91	532.24	8070.29
Jul-21	1241.91	1099.30	1056.95	889.18	794.82	700.72	696.55	574.36	584.21	527.81	8165.81
Aug-21	1214.37	1074.30	1005.21	866.93	771.73	745.09	653.66	580.46	566.14	508.20	7986.08
Sep-21	1327.87	1135.58	1072.58	901.37	829.65	749.73	666.22	586.31	575.94	541.56	8386.80

Oct-21	1231.23	1092.21	1073.73	897.93	786.81	735.78	677.80	624.37	555.01	557.74	8232.60
Nov-21	1332.68	1244.54	1195.78	919.37	834.59	845.04	695.30	626.55	613.26	583.75	8890.85
Dec-21	1420.68	1293.47	1155.14	1016.36	872.01	833.13	762.87	681.89	690.81	607.16	9333.50
Jan-22	1348.87	1205.62	1167.30	950.28	852.22	786.81	755.36	660.06	624.42	577.42	8928.35
Feb-22	1271.51	1143.75	1057.12	919.44	756.26	792.28	669.91	623.78	553.55	548.84	8336.43
Mar-22	1489.69	1278.20	1219.66	1039.24	868.59	893.40	759.47	697.11	672.24	601.14	9518.73
Apr-22	1281.74	1121.16	1158.15	913.80	833.69	838.99	718.49	633.91	653.38	577.86	8731.16
May-22	1323.60	1180.51	1131.89	1082.44	862.07	761.49	752.59	685.35	672.25	584.05	9036.21
Jun-22	1323.84	1183.47	1047.88	800.55	827.64	763.71	661.21	633.70	612.15	570.67	8424.82
Jul-22	1286.24	1077.55	1024.89	826.25	792.78	725.41	625.98	603.15	553.96	587.64	8103.85
Total	69413.33	59424.72	53618.04	45194.11	44365.83	36980.46	35801.44	32196.26	27725.66	25641.84	

Atenolol

	NHS North West	NHS London	NHS Yorkshire and the Humber	NHS West Midlands	NHS East Midlands	NHS South Central	NHS East of England	NHS North East	NHS South West	NHS South East Coast	Total (dosage)
Apr-17	1308.62	1272.35	1580.00	943.05	790.63	808.23	845.20	734.26	683.28	493.70	9459.30
May-17	1369.92	1338.73	1711.10	1095.33	936.95	936.75	837.98	732.55	752.78	554.95	10267.03
Jun-17	1346.43	1390.46	1636.71	877.82	912.93	852.66	743.20	714.03	815.33	521.73	9811.28
Jul-17	1239.58	1161.88	1586.05	962.68	808.35	849.15	756.25	675.38	743.15	494.43	9276.87
Aug-17	1383.43	1307.46	1604.38	932.53	933.78	799.60	847.30	766.35	780.49	504.48	9859.76
Sep-17	1244.45	1311.66	1616.08	870.18	759.00	851.10	781.35	785.10	708.88	484.73	9412.52
Oct-17	1200.51	1508.37	1541.08	981.70	879.55	916.75	843.80	877.60	762.18	530.78	10042.29
Nov-17	1182.31	1336.33	1534.68	891.15	802.69	895.60	766.40	794.38	671.38	492.20	9367.11
Dec-17	1394.81	1399.53	1514.40	963.08	934.72	757.05	799.90	924.83	761.88	619.75	10069.92
Jan-18	1360.76	1337.71	1700.48	1083.46	1415.06	916.95	929.43	853.70	777.43	653.45	11028.41
Feb-18	1191.39	1178.58	1472.78	936.23	853.41	800.72	792.21	710.03	691.53	539.72	9166.57
Mar-18	1266.70	1298.60	1591.33	1050.28	949.68	653.20	846.38	826.95	761.20	581.20	9825.51
Apr-18	1164.66	1272.73	1455.40	925.33	843.56	855.18	739.25	712.23	664.05	489.30	9121.67
May-18	1233.16	1247.13	1450.41	986.60	891.76	848.28	831.65	869.00	791.20	542.03	9691.21
Jun-18	1117.96	1185.60	1456.59	902.96	822.73	702.83	774.30	765.44	597.55	499.28	8825.21
Jul-18	1233.58	1168.56	1552.85	953.36	1063.67	769.00	732.80	788.69	705.83	514.98	9483.30
Aug-18	1270.57	1259.81	1547.90	980.02	968.60	840.43	715.00	670.85	670.48	541.26	9464.91
Sep-18	1235.12	1180.83	1390.30	856.83	854.28	798.78	764.90	635.78	641.65	456.36	8814.81
Oct-18	1340.30	1294.18	1638.96	1006.91	902.75	1081.95	785.80	746.58	722.38	519.23	10039.02
Nov-18	1292.22	1338.49	1481.93	1056.23	828.81	920.82	840.58	736.65	674.58	528.80	9699.08
Dec-18	1356.69	1197.75	1543.06	991.47	845.48	716.69	796.55	713.38	656.53	494.25	9311.82
Jan-19	1324.38	1381.06	1722.98	975.53	862.67	1032.48	718.33	729.57	719.30	522.05	9988.33
Feb-19	1170.14	1124.42	1442.20	862.90	761.25	816.85	710.52	737.73	603.80	433.93	8663.72
Mar-19	1212.23	1072.88	949.86	914.58	742.23	737.10	814.32	648.62	661.25	502.43	8255.48

Apr-19	1081.57	1136.38	918.92	857.09	794.44	795.69	797.65	725.15	715.53	429.00	8251.41
May-19	1139.03	1169.18	973.52	853.33	731.23	878.68	746.98	775.31	686.13	508.40	8461.76
Jun-19	1057.33	1036.28	931.60	835.32	741.40	663.70	668.82	628.98	572.23	430.05	7565.68
Jul-19	1144.42	992.23	993.28	802.48	726.20	806.23	711.53	662.50	614.68	504.60	7958.12
Aug-19	1010.49	1006.58	898.64	766.15	668.55	636.43	679.99	595.40	585.73	440.62	7288.57
Sep-19	1073.69	1100.68	821.93	891.47	633.65	767.95	626.11	671.93	576.60	428.19	7592.18
Oct-19	1068.43	1118.08	906.12	877.48	733.05	735.65	684.23	658.94	681.30	474.18	7937.43
Nov-19	1089.20	1123.75	917.51	890.92	729.98	779.00	683.35	565.43	646.40	414.48	7840.00
Dec-19	1123.82	1179.63	979.53	1013.70	768.79	726.33	750.20	761.00	641.66	450.43	8395.07
Jan-20	1139.06	1307.35	977.77	914.43	813.36	823.88	764.23	766.68	698.41	523.98	8729.12
Feb-20	1025.11	1117.98	807.18	826.54	730.90	675.05	623.53	617.18	535.05	383.50	7342.00
Mar-20	1056.51	1136.73	982.75	934.53	776.52	707.25	659.70	621.82	625.57	442.78	7944.15
Apr-20	1010.97	1096.93	781.38	689.80	584.00	639.29	566.58	544.06	505.43	384.00	6802.42
May-20	909.48	803.13	745.14	684.16	548.52	726.13	571.83	523.85	444.00	336.09	6292.31
Jun-20	959.65	917.10	792.44	724.38	666.43	635.06	661.25	514.33	525.60	391.92	6788.14
Jul-20	976.95	908.45	845.15	731.55	695.66	756.90	713.73	543.18	591.85	359.51	7122.91
Aug-20	876.37	853.07	683.20	740.62	540.11	657.98	684.80	516.65	502.68	386.68	6442.13
Sep-20	1025.36	990.20	857.05	728.58	722.49	754.88	630.75	525.53	610.40	416.85	7262.07
Oct-20	1117.22	1024.80	836.83	744.69	721.08	637.78	658.33	570.93	567.05	423.13	7301.82
Nov-20	1009.50	927.96	849.61	756.63	637.90	642.88	555.80	683.98	560.74	423.55	7048.53
Dec-20	1158.93	1059.77	862.00	774.13	709.10	749.68	768.05	680.55	588.93	470.78	7821.90
Jan-21	1147.72	1152.88	914.32	755.48	681.88	754.18	649.28	620.28	492.78	504.90	7673.67
Feb-21	1122.85	1008.15	865.83	712.84	659.47	588.98	696.68	598.25	471.48	401.90	7126.41
Mar-21	1133.85	1116.83	1012.10	804.29	729.87	785.77	669.27	681.90	593.11	512.70	8039.68
Apr-21	1005.66	1011.50	762.68	678.32	630.53	697.14	623.80	582.30	574.73	420.86	6987.50
May-21	938.78	831.48	720.10	767.86	616.75	713.95	701.11	616.55	575.00	406.10	6887.67
Jun-21	1039.28	1022.11	807.02	628.63	748.19	747.40	670.88	607.40	581.35	452.23	7304.47
Jul-21	1000.42	973.16	882.55	743.23	657.33	696.58	680.30	594.80	559.93	473.50	7261.79
Aug-21	1029.21	841.60	801.66	731.28	624.47	594.65	629.20	521.58	532.88	429.43	6735.93
Sep-21	1029.21	955.80	743.68	748.39	632.30	527.66	601.83	560.38	557.48	428.30	6785.00

Oct-21	959.43	941.36	777.89	773.03	677.38	542.11	615.73	520.90	524.03	423.75	6755.58
Nov-21	1079.33	1039.20	813.23	861.59	669.38	581.06	619.33	603.18	569.10	448.63	7283.99
Dec-21	1095.63	1047.50	918.31	902.70	722.78	590.99	646.23	664.72	612.29	472.62	7673.75
Jan-22	899.97	996.70	830.03	746.79	614.99	569.90	611.43	623.93	527.25	446.10	6867.07
Feb-22	1003.77	828.48	772.41	626.28	568.48	486.94	576.20	593.68	474.57	396.08	6326.86
Mar-22	1085.89	989.78	879.41	807.50	735.38	531.63	695.23	613.25	529.98	445.75	7313.77
Apr-22	1040.48	1153.85	799.42	824.90	766.81	650.00	662.85	684.05	593.83	445.38	7621.55
May-22	989.30	1146.70	817.98	715.58	701.44	651.40	664.58	623.18	589.90	457.24	7357.28
Jun-22	1003.30	912.40	798.83	738.80	614.33	495.83	593.42	538.03	549.74	389.80	6634.46
Jul-22	1106.82	1029.89	784.46	752.13	636.45	527.80	742.55	573.83	536.58	382.65	7073.14
Total	72203.73	71570.61	70784.81	54357.62	48725.95	47088.39	45570.60	42725.10	39939.93	29875.54	

Bisoprolol

	NHS North West	NHS London	NHS Yorkshire and the Humber	NHS East of England	NHS West Midlands	NHS South Central	NHS South West	NHS East Midlands	NHS North East	NHS South East Coast	Total (dosage)
Apr-17	934.56	921.74	774.06	603.26	569.01	520.88	486.78	483.19	441.38	397.61	6132.46
May-17	1026.58	986.50	830.86	657.04	637.91	567.13	534.24	546.96	464.78	439.32	6691.32
Jun-17	985.92	987.90	790.15	631.97	615.87	539.94	527.27	539.26	453.28	400.67	6472.22
Jul-17	928.83	918.06	792.61	610.23	583.79	521.52	505.40	487.52	451.62	410.30	6209.86
Aug-17	1006.75	959.95	815.29	620.91	651.26	543.89	529.82	511.97	466.09	429.75	6535.69
Sep-17	958.56	939.21	817.07	604.47	607.76	518.75	510.99	501.81	454.63	407.36	6320.61
Oct-17	982.26	1009.71	852.57	656.46	630.66	552.89	512.95	526.26	457.36	433.50	6614.62
Nov-17	1027.97	1016.54	875.29	682.21	647.81	565.58	531.98	553.84	485.85	437.02	6824.08
Dec-17	1037.36	1007.97	840.80	672.48	677.12	579.71	558.34	537.93	521.82	469.43	6902.96
Jan-18	1104.61	1058.57	914.43	720.60	707.60	592.27	583.55	574.58	547.88	480.02	7284.10
Feb-18	960.83	954.12	816.62	621.43	657.83	531.37	503.13	516.56	450.71	424.51	6437.11
Mar-18	1084.38	1080.19	875.14	708.44	721.51	560.39	572.33	552.99	512.52	480.20	7148.08
Apr-18	1005.51	968.61	816.24	655.76	664.42	560.65	512.09	534.56	483.93	418.93	6620.68
May-18	1039.83	1019.69	846.82	694.04	673.41	586.32	567.26	563.30	510.31	463.81	6964.78
Jun-18	962.48	957.93	785.14	648.55	629.49	530.16	512.45	511.40	468.83	413.70	6420.12
Jul-18	980.66	967.49	814.38	651.61	639.15	531.91	515.39	511.08	460.46	426.12	6498.27
Aug-18	994.10	957.80	809.42	651.48	665.15	552.39	522.49	510.42	488.93	418.76	6570.93
Sep-18	944.65	917.73	755.84	609.70	614.62	503.45	493.42	499.49	405.15	389.30	6133.34
Oct-18	1052.41	1028.86	858.46	690.75	729.91	585.63	561.79	554.09	496.53	464.84	7023.27
Nov-18	1045.10	1032.82	875.61	677.09	697.99	581.89	549.91	585.75	460.97	445.82	6952.96
Dec-18	1038.23	1003.55	863.93	680.67	730.13	564.07	593.34	554.42	501.14	453.33	6982.79
Jan-19	1111.49	1081.93	908.96	732.42	741.59	623.49	595.06	595.80	512.37	483.96	7387.07
Feb-19	996.17	968.51	822.91	638.53	653.93	540.62	538.62	519.11	464.30	418.53	6561.23
Mar-19	1027.28	1041.43	727.04	693.88	715.23	585.01	560.35	559.63	502.36	449.97	6862.19

Apr-19	1058.20	1020.94	731.45	716.31	705.86	578.70	579.74	581.18	499.36	469.92	6941.64
May-19	1083.43	1041.24	756.11	728.20	717.33	594.09	598.80	593.39	519.34	474.93	7106.85
Jun-19	966.27	890.48	687.69	674.95	668.52	532.01	534.11	536.41	466.84	428.10	6385.37
Jul-19	1068.67	1004.99	731.62	739.91	740.84	595.11	558.68	578.95	531.19	472.07	7022.03
Aug-19	983.10	931.96	698.65	660.46	698.71	571.64	568.29	554.05	451.52	443.25	6561.62
Sep-19	994.57	929.84	701.23	645.41	697.95	565.10	545.98	530.89	463.39	428.50	6502.85
Oct-19	1088.78	1023.91	756.56	745.38	760.75	618.36	630.40	601.83	507.02	474.27	7207.25
Nov-19	1034.14	998.27	750.26	710.15	721.50	597.35	598.90	575.88	497.38	466.28	6950.10
Dec-19	1131.83	1075.95	786.98	741.34	778.48	647.75	617.69	595.73	538.29	475.10	7389.16
Jan-20	1139.65	1097.90	796.82	795.74	784.02	649.52	605.28	606.75	505.15	501.83	7482.64
Feb-20	1022.16	993.90	720.79	700.74	703.02	585.16	550.29	569.52	476.18	442.63	6764.38
Mar-20	1029.52	985.74	727.80	704.57	708.83	597.50	568.72	578.17	491.84	440.28	6832.98
Apr-20	755.76	690.58	496.99	465.67	467.79	423.46	388.43	379.35	351.04	323.32	4742.38
May-20	837.89	689.74	523.10	551.60	532.95	490.01	461.80	434.54	376.36	366.34	5264.33
Jun-20	925.74	788.38	594.52	600.01	594.66	529.82	514.79	476.34	426.05	400.49	5850.79
Jul-20	942.67	865.84	647.95	667.59	644.15	550.77	558.47	533.51	460.58	422.62	6294.14
Aug-20	883.72	778.05	620.78	610.61	585.42	532.05	502.01	454.62	427.14	397.51	5791.90
Sep-20	981.30	913.46	686.16	699.42	670.15	578.47	552.49	532.02	459.11	440.10	6512.69
Oct-20	1011.73	933.08	692.88	693.08	681.34	574.67	582.87	535.32	480.94	453.98	6639.89
Nov-20	950.98	903.66	646.91	651.24	655.32	551.36	556.37	509.64	452.67	436.88	6315.02
Dec-20	1091.92	1012.62	709.42	739.02	717.64	634.46	582.79	563.89	524.01	478.64	7054.40
Jan-21	999.12	878.04	643.51	626.70	633.25	573.11	535.14	513.08	458.75	418.34	6279.04
Feb-21	897.84	808.43	598.36	612.14	611.56	553.85	508.14	492.53	446.92	407.46	5937.21
Mar-21	1062.66	993.68	742.49	750.56	746.92	646.06	617.94	585.86	525.59	478.89	7150.64
Apr-21	1039.24	988.71	682.50	730.33	713.65	630.57	604.47	553.00	504.80	459.12	6906.37
May-21	1045.49	998.89	704.41	705.62	689.32	607.96	584.13	534.11	521.99	443.84	6835.75
Jun-21	1063.18	1034.93	736.13	755.21	716.21	624.38	607.03	594.42	550.46	454.09	7136.05
Jul-21	1020.97	1017.14	706.12	774.90	678.92	624.52	593.93	590.23	549.54	479.63	7035.90
Aug-21	988.82	932.01	690.61	716.94	648.71	609.48	561.55	535.02	484.55	456.98	6624.67
Sep-21	1041.25	990.21	716.90	727.45	675.59	611.66	577.28	583.42	530.40	469.17	6923.32

Oct-21	1037.33	977.27	688.53	691.94	651.84	600.34	569.46	556.67	532.91	467.59	6773.88
Nov-21	1105.39	1044.02	731.73	727.68	709.08	619.09	596.66	601.77	550.10	468.22	7153.73
Dec-21	1143.54	1051.75	783.48	784.95	738.24	689.86	664.56	631.48	566.37	500.68	7554.90
Jan-22	1026.10	978.14	720.39	722.46	696.75	605.97	590.75	587.80	510.01	454.80	6893.17
Feb-22	1064.88	992.84	683.99	721.05	701.75	597.13	586.47	569.85	529.78	450.53	6898.26
Mar-22	1207.57	1145.26	815.84	843.48	810.37	674.47	673.77	652.91	563.48	514.78	7901.92
Apr-22	1038.78	1055.65	744.71	752.62	719.62	683.36	611.29	588.80	535.29	489.07	7219.19
May-22	1146.29	1058.89	780.03	809.71	746.30	625.03	641.87	613.95	561.38	507.97	7491.41
Jun-22	1098.87	985.15	724.04	733.05	702.34	631.81	567.36	576.80	533.58	442.66	6995.65
Jul-22	1023.75	963.42	709.19	748.36	626.67	489.92	608.07	551.99	519.23	433.12	6673.71
Total	65269.56	62251.73	47947.23	43990.51	43315.43	37035.81	35835.68	35067.54	31343.70	28490.73	

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	NHS London	NHS South Central	NHS North West	NHS South West	NHS Yorkshire and the Humber	NHS East of England	NHS West Midlands	NHS East Midlands	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	227.21	204.28	208.67	178.16	189.56	171.15	162.75	122.91	102.05	106.97	1673.71
May-17	276.00	229.01	199.88	189.24	195.58	163.97	168.87	124.98	107.74	103.82	1759.09
Jun-17	237.39	209.46	213.04	176.44	191.58	159.12	169.85	119.84	94.82	92.97	1664.50
Jul-17	237.79	192.47	212.18	198.99	182.96	159.68	148.82	122.49	107.28	96.32	1658.98
Aug-17	243.77	187.54	235.11	205.83	199.65	150.74	155.66	136.39	100.96	101.59	1717.22
Sep-17	232.18	210.91	205.46	188.35	204.60	151.80	160.83	127.00	108.01	96.99	1686.12
Oct-17	239.08	192.27	212.27	185.10	214.79	159.92	148.31	136.93	110.67	100.13	1699.48
Nov-17	261.41	220.90	225.45	221.92	226.10	150.33	156.17	140.88	110.86	99.24	1813.26
Dec-17	241.86	244.08	244.71	204.66	224.17	162.05	165.02	141.50	122.80	83.85	1834.70
Jan-18	262.23	242.23	237.86	202.25	205.88	176.11	192.11	136.51	134.84	113.50	1903.52
Feb-18	232.26	230.48	204.83	174.40	205.20	167.46	164.61	120.01	111.98	106.30	1717.52
Mar-18	270.74	239.86	236.44	209.68	224.68	162.82	176.38	134.01	111.30	100.31	1866.22
Apr-18	242.83	247.67	216.13	215.78	201.48	155.20	154.54	117.25	113.29	100.17	1764.32
May-18	239.70	242.43	241.56	212.64	192.95	163.07	190.11	135.32	119.88	102.53	1840.19
Jun-18	214.58	216.03	234.61	173.83	198.72	167.34	174.90	148.21	110.90	88.51	1727.63
Jul-18	240.82	232.08	246.18	176.33	203.46	161.82	175.41	140.92	106.93	92.27	1776.21
Aug-18	240.64	251.05	219.81	198.80	214.67	163.93	164.79	133.48	111.51	97.54	1796.21
Sep-18	244.12	218.88	223.35	181.62	207.11	158.56	167.07	123.85	98.86	82.56	1705.99
Oct-18	229.31	221.69	220.05	203.40	207.94	181.15	188.53	132.23	120.38	103.75	1808.42
Nov-18	258.15	244.18	226.21	195.81	208.77	190.56	180.43	129.86	111.42	97.17	1842.56
Dec-18	261.62	218.92	238.77	201.71	204.14	161.85	177.71	134.85	117.03	79.75	1796.35
Jan-19	266.43	287.19	247.19	204.87	216.60	174.03	177.18	157.12	118.50	92.76	1941.86
Feb-19	221.20	201.61	210.98	195.04	183.73	158.39	145.59	137.97	119.85	88.42	1662.78
Mar-19	245.12	244.32	248.89	206.59	162.15	174.23	172.40	156.44	129.41	89.61	1829.16

Apr-19	241.43	255.81	244.30	199.35	184.01	172.71	181.36	153.27	112.54	110.20	1854.98
May-19	260.85	227.10	236.09	215.70	188.19	173.43	193.04	164.62	113.20	106.18	1878.41
Jun-19	235.89	233.35	235.67	208.59	185.92	163.69	156.74	146.75	102.00	107.94	1776.55
Jul-19	260.09	258.35	247.56	215.10	183.30	166.26	172.25	161.18	118.69	106.05	1888.82
Aug-19	216.55	230.48	216.71	207.17	168.85	161.41	175.74	139.73	119.07	114.06	1749.77
Sep-19	241.58	240.26	254.22	213.72	168.09	155.85	178.81	133.43	115.01	88.61	1789.57
Oct-19	269.03	248.38	265.62	220.29	171.04	160.69	171.22	138.86	133.50	117.11	1895.74
Nov-19	257.46	280.51	244.24	208.19	173.77	174.66	181.07	148.02	131.59	103.92	1903.42
Dec-19	270.27	247.82	247.70	216.13	181.94	195.68	181.68	148.10	132.01	110.79	1932.12
Jan-20	268.04	249.75	258.00	226.58	187.75	171.68	167.17	160.64	135.57	99.69	1924.86
Feb-20	245.49	231.92	222.92	201.87	182.83	150.61	163.07	143.50	114.07	95.71	1751.99
Mar-20	219.22	246.70	232.52	182.92	173.80	158.80	161.53	135.25	107.25	87.59	1705.58
Apr-20	165.44	207.35	189.99	135.39	117.76	120.56	126.72	97.18	69.68	77.69	1307.75
May-20	171.61	234.68	196.39	152.88	140.82	156.15	133.98	110.62	88.73	87.26	1473.13
Jun-20	213.85	209.77	225.96	165.98	155.30	130.93	138.97	106.69	95.48	93.91	1536.84
Jul-20	208.47	278.10	238.68	181.69	141.07	156.03	148.95	124.01	109.79	105.43	1692.22
Aug-20	227.72	236.66	240.15	192.25	173.96	163.50	138.74	125.72	102.39	89.76	1690.86
Sep-20	224.42	255.91	231.83	211.67	160.47	181.42	160.17	136.07	132.98	101.61	1796.56
Oct-20	227.58	261.44	249.82	210.63	178.61	186.27	165.92	129.57	112.97	95.87	1818.67
Nov-20	240.14	256.97	211.97	216.08	171.60	160.18	157.79	133.94	90.69	124.18	1763.54
Dec-20	287.66	291.38	233.73	183.80	193.41	169.85	163.01	158.56	133.88	121.06	1936.35
Jan-21	263.80	269.01	226.53	190.21	186.16	182.18	160.86	137.39	111.95	113.54	1841.62
Feb-21	201.81	266.41	232.60	173.35	137.26	164.59	144.35	115.86	110.79	114.97	1661.98
Mar-21	241.91	275.16	255.53	208.72	169.79	193.77	159.02	142.62	120.73	135.27	1902.52
Apr-21	240.01	293.65	244.73	207.74	185.26	192.43	167.63	139.17	120.98	111.60	1903.20
May-21	237.11	291.98	238.29	204.66	187.84	193.77	178.39	143.27	129.37	108.99	1913.68
Jun-21	267.08	284.14	264.36	209.78	184.39	191.46	202.84	138.52	131.47	125.90	1999.94
Jul-21	252.38	288.52	240.60	215.56	187.30	196.12	174.03	155.52	126.71	114.52	1951.25
Aug-21	251.13	276.97	242.45	201.02	175.80	172.65	160.12	127.56	125.88	112.23	1845.81
Sep-21	236.79	265.40	248.63	190.35	175.59	191.52	159.22	144.30	126.86	108.54	1847.21

Oct-21	252.32	255.56	256.42	206.10	180.97	188.59	167.41	121.89	124.19	131.61	1885.07
Nov-21	280.30	246.41	266.91	194.00	190.31	190.46	180.15	140.05	119.67	125.02	1933.29
Dec-21	268.65	252.56	264.71	222.33	187.11	194.90	172.26	133.54	141.12	124.12	1961.30
Jan-22	253.83	244.41	243.61	196.12	160.55	186.19	152.75	151.22	128.26	111.52	1828.46
Feb-22	236.39	242.27	263.99	207.56	170.73	182.95	156.97	139.47	108.07	103.61	1812.00
Mar-22	271.73	268.03	286.76	234.39	192.16	210.20	188.60	160.13	128.08	152.18	2092.25
Apr-22	281.63	278.47	249.50	228.30	196.78	179.70	180.42	145.98	128.96	147.99	2017.74
May-22	293.26	261.75	271.43	226.78	178.48	200.53	188.02	127.77	129.19	123.98	2001.19
Jun-22	267.32	248.10	258.09	208.45	183.87	183.62	167.00	141.74	134.44	120.49	1913.12
Jul-22	263.86	226.74	237.65	199.22	184.13	180.07	142.47	123.33	111.15	140.36	1808.97
Total	15680.54	15647.78	15126.53	12792.05	11863.45	10951.30	10658.44	8736.01	7430.22	6788.01	

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	NHS London	NHS North West	NHS Yorkshire and the Humber	NHS West Midlands	NHS East of England	NHS South East Coast	NHS South Central	NHS South West	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	273.60	178.88	164.20	106.80	108.68	84.60	69.52	61.20	52.12	41.40	1141.00
May-17	385.18	145.86	160.80	132.00	114.80	137.60	62.40	92.20	61.00	62.20	1354.04
Jun-17	322.86	150.60	169.40	122.30	99.00	81.60	57.86	81.00	63.80	48.80	1197.22
Jul-17	292.88	153.00	159.40	118.20	114.48	101.40	67.40	76.95	50.30	30.00	1164.01
Aug-17	346.48	149.40	126.80	93.60	109.40	97.18	51.00	91.40	38.60	41.00	1144.86
Sep-17	280.52	172.80	154.20	147.00	99.82	85.92	57.60	66.60	69.00	22.20	1155.66
Oct-17	376.20	195.62	197.00	108.00	95.40	105.80	74.12	84.00	62.40	39.00	1337.54
Nov-17	328.88	186.80	171.60	147.04	141.60	131.02	94.00	85.86	70.20	46.40	1403.40
Dec-17	280.18	138.00	171.20	126.60	130.40	93.00	60.60	65.80	51.00	44.40	1161.18
Jan-18	371.52	176.60	178.80	146.80	128.40	100.20	51.35	67.80	68.40	54.00	1343.87
Feb-18	339.62	166.80	156.26	128.40	109.20	119.60	51.00	69.00	52.48	43.80	1236.16
Mar-18	390.92	181.20	182.20	144.00	130.20	88.22	69.40	71.00	58.20	47.80	1363.14
Apr-18	310.20	165.60	153.00	133.80	125.40	67.80	68.00	83.46	69.60	43.80	1220.66
May-18	394.20	191.40	171.20	138.60	117.60	119.40	81.40	68.40	84.00	52.40	1418.60
Jun-18	343.82	175.20	169.80	123.60	117.00	102.60	78.00	82.40	78.00	60.40	1330.82
Jul-18	366.60	177.00	155.46	120.62	117.00	92.60	64.80	80.80	79.92	52.80	1307.60
Aug-18	318.32	167.00	127.80	115.20	114.26	61.20	86.60	77.40	59.00	37.00	1163.78
Sep-18	320.40	143.40	140.60	117.60	95.06	87.06	58.80	56.52	61.80	32.40	1113.64
Oct-18	394.24	198.00	159.00	122.40	118.20	87.00	82.00	78.40	83.40	50.40	1373.04
Nov-18	407.40	190.40	172.80	111.60	124.46	104.40	74.60	91.82	65.60	42.00	1385.08
Dec-18	349.80	154.20	129.60	115.20	104.40	88.34	81.20	82.20	58.80	42.60	1206.34
Jan-19	427.20	190.40	182.43	108.60	115.20	113.40	87.40	70.20	76.20	48.00	1419.03
Feb-19	396.00	174.00	172.00	116.40	112.20	76.80	75.80	67.40	72.60	56.80	1320.00
Mar-19	379.20	204.20	175.00	161.40	122.80	107.60	80.00	83.00	85.80	57.60	1456.60

Apr-19	316.82	169.20	178.00	109.20	108.60	76.80	77.20	84.80	65.60	36.60	1222.82
May-19	341.44	194.80	145.20	126.00	109.80	108.60	78.12	106.20	66.00	48.00	1324.16
Jun-19	336.20	218.20	169.22	121.20	111.60	82.20	79.40	82.80	57.60	41.20	1299.62
Jul-19	370.80	183.60	169.80	119.60	100.40	77.00	63.60	80.84	57.40	46.00	1269.04
Aug-19	307.80	170.80	142.20	127.20	99.80	72.60	78.46	71.40	47.40	36.20	1153.86
Sep-19	297.60	185.40	178.20	87.22	95.40	76.20	61.80	77.60	52.20	35.40	1147.02
Oct-19	351.00	184.20	189.60	119.94	183.60	82.20	63.60	71.20	76.20	55.26	1376.80
Nov-19	401.40	199.80	157.80	118.72	106.26	94.80	70.60	93.00	71.40	40.80	1354.58
Dec-19	334.60	172.82	148.20	103.60	116.40	86.60	70.60	63.60	66.60	38.40	1201.42
Jan-20	378.00	181.80	210.60	138.54	134.66	94.80	88.20	79.40	77.60	37.22	1420.82
Feb-20	375.00	195.00	161.40	105.70	92.40	94.20	88.00	82.80	70.20	34.80	1299.50
Mar-20	220.80	157.80	136.20	94.54	78.80	68.40	72.20	68.00	54.60	30.80	982.14
Apr-20	75.60	37.80	50.40	23.62	33.60	40.80	22.80	21.60	16.20	16.80	339.22
May-20	90.00	72.00	56.00	40.32	45.20	33.00	43.20	34.20	19.80	25.80	459.52
Jun-20	125.40	69.00	60.60	52.58	54.60	38.26	39.20	47.40	33.00	24.60	544.64
Jul-20	172.80	96.00	82.80	83.18	62.40	49.20	73.80	51.00	34.20	18.00	723.38
Aug-20	132.00	85.80	93.00	62.56	58.32	50.00	47.40	47.60	39.60	22.20	638.48
Sep-20	196.80	97.16	103.80	85.48	73.80	62.40	65.70	67.80	56.40	38.40	847.74
Oct-20	232.20	129.60	99.60	96.66	90.00	62.60	73.40	66.20	46.80	43.20	940.26
Nov-20	247.00	115.20	90.40	70.08	98.60	75.60	88.80	83.60	69.60	27.60	966.48
Dec-20	191.40	138.40	108.60	103.32	110.40	60.20	70.90	55.80	50.40	30.60	920.02
Jan-21	154.20	112.40	108.00	65.60	69.60	39.80	64.80	70.40	18.00	39.00	741.80
Feb-21	159.60	133.40	103.20	81.72	74.20	55.80	66.30	64.50	42.20	43.20	824.12
Mar-21	240.60	148.40	121.86	125.96	85.80	55.32	73.80	98.40	55.80	37.20	1043.14
Apr-21	218.40	139.20	120.80	92.18	98.40	56.42	74.46	76.20	54.60	44.40	975.06
May-21	270.00	130.40	134.80	104.24	97.80	62.86	78.80	75.60	77.40	39.62	1071.52
Jun-21	295.80	162.12	118.60	116.76	114.00	87.14	91.80	66.30	60.00	31.80	1144.32
Jul-21	250.26	123.00	138.00	106.56	113.40	87.20	91.92	67.60	47.40	33.60	1058.94
Aug-21	213.02	122.40	123.60	89.80	88.40	65.40	61.20	53.40	49.80	34.20	901.22
Sep-21	234.60	150.00	122.40	102.26	97.80	73.80	79.40	64.20	58.20	37.80	1020.46

Oct-21	230.60	157.80	136.20	87.24	86.40	75.42	65.00	65.40	43.80	35.40	983.26
Nov-21	258.62	134.40	141.66	102.20	114.60	96.20	93.08	71.40	56.40	40.20	1108.76
Dec-21	235.80	145.20	117.60	98.68	109.80	81.86	75.20	57.60	51.00	36.46	1009.20
Jan-22	215.40	164.40	124.20	104.18	90.00	64.80	73.80	60.80	60.00	50.40	1007.98
Feb-22	236.40	171.40	134.80	107.86	114.02	63.00	90.60	53.40	52.80	35.20	1059.48
Mar-22	312.00	142.20	126.06	99.94	136.26	71.22	90.60	84.06	56.40	36.60	1155.34
Apr-22	229.80	133.24	93.60	75.36	94.20	89.72	69.60	57.80	35.40	28.80	907.52
May-22	264.66	176.40	134.92	103.66	103.20	78.00	73.86	59.20	48.60	41.20	1083.70
Jun-22	269.40	148.20	100.20	71.84	80.40	54.00	60.60	51.00	45.60	30.00	911.24
Jul-22	249.02	131.04	109.20	57.32	64.20	39.00	45.00	36.60	40.20	15.60	787.18
Total	18429.06	9906.34	8941.87	6788.38	6562.08	5117.76	4521.65	4505.51	3654.62	2515.76	

Doxazosin

	NHS London	NHS North West	NHS West Midlands	NHS South Central	NHS Yorkshire and the Humber	NHS East of England	NHS East Midlands	NHS South West	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	274.93	181.21	129.59	101.89	142.75	99.80	85.19	58.75	61.40	51.96	1187.45
May-17	290.23	180.02	149.58	131.19	152.12	107.67	93.83	68.75	59.52	51.50	1284.41
Jun-17	286.53	165.64	152.32	121.05	141.97	104.79	92.51	74.42	63.09	45.99	1248.29
Jul-17	263.57	171.67	138.21	118.84	141.96	95.82	85.65	68.44	62.32	49.83	1196.29
Aug-17	273.91	175.58	139.35	99.47	135.91	99.95	106.41	66.69	62.04	51.28	1210.59
Sep-17	271.11	163.88	140.90	131.67	127.62	88.20	89.49	56.38	65.07	47.79	1182.11
Oct-17	287.94	180.80	143.75	118.79	140.52	109.08	102.10	66.78	72.02	53.22	1275.00
Nov-17	279.83	176.90	155.87	121.58	152.91	110.90	110.43	67.11	71.82	50.64	1297.99
Dec-17	285.71	193.59	153.59	112.97	144.80	114.16	101.37	69.66	79.71	54.19	1309.74
Jan-18	297.01	197.56	169.20	118.92	156.92	113.96	113.98	77.08	70.28	58.19	1373.09
Feb-18	267.53	174.04	146.33	132.68	158.00	105.48	97.06	76.28	73.37	45.44	1276.20
Mar-18	305.17	203.85	154.25	89.99	153.72	106.52	106.71	80.99	79.53	56.68	1337.41
Apr-18	280.00	182.46	148.69	126.65	134.57	118.40	99.16	69.98	72.34	56.14	1288.36
May-18	300.14	197.28	155.14	148.38	134.37	114.78	112.64	69.85	72.47	59.05	1364.09
Jun-18	285.78	179.59	150.78	112.58	141.25	118.02	98.78	66.90	70.97	48.56	1273.20
Jul-18	300.37	168.54	142.35	115.63	140.14	106.61	95.43	67.38	68.42	52.64	1257.51
Aug-18	293.95	177.66	144.71	122.91	144.67	103.31	93.49	72.83	73.33	46.00	1272.83
Sep-18	265.61	172.03	144.03	115.24	140.12	104.34	91.06	61.99	66.72	46.87	1208.00
Oct-18	332.84	193.00	169.27	161.13	149.93	120.33	120.42	75.91	77.11	55.07	1455.00
Nov-18	303.12	188.51	160.94	139.60	145.74	123.77	119.80	64.02	74.25	44.42	1364.16
Dec-18	296.19	192.36	171.32	124.36	154.76	117.66	109.71	75.41	70.01	46.21	1357.99
Jan-19	308.28	205.60	166.22	194.68	160.10	117.70	110.19	85.45	78.93	53.81	1480.95
Feb-19	282.11	183.37	143.27	134.21	137.12	114.13	103.11	74.91	72.47	53.05	1297.73
Mar-19	299.29	198.01	158.01	124.82	105.01	123.01	111.20	82.93	70.09	56.86	1329.23

Apr-19	282.34	195.49	158.77	130.18	120.57	113.37	121.77	77.13	72.25	54.73	1326.59
May-19	289.97	189.12	175.29	140.17	120.84	125.81	114.29	78.20	78.77	58.30	1370.75
Jun-19	258.60	169.36	171.26	121.23	107.73	103.19	106.02	64.16	67.49	51.32	1220.36
Jul-19	295.39	195.59	220.28	137.17	119.02	115.71	104.63	77.70	73.93	50.95	1390.39
Aug-19	281.42	174.38	213.34	138.87	116.29	105.88	108.81	73.27	69.55	49.12	1330.90
Sep-19	271.44	179.61	180.74	131.04	105.70	109.18	113.30	71.49	71.43	52.14	1286.07
Oct-19	307.55	202.71	187.77	132.67	120.13	124.35	116.78	80.17	81.11	58.81	1412.05
Nov-19	293.24	192.68	157.99	143.78	119.47	112.71	123.42	76.63	85.36	58.35	1363.63
Dec-19	335.19	202.63	181.06	147.11	128.01	125.90	114.58	92.16	83.33	61.74	1471.71
Jan-20	315.48	209.46	177.72	134.02	119.81	124.83	125.98	88.17	79.41	60.00	1434.87
Feb-20	291.53	193.29	156.56	140.95	117.77	128.66	108.45	77.08	79.18	51.66	1345.13
Mar-20	316.24	196.11	163.63	125.67	122.42	114.84	111.08	81.71	73.60	57.97	1363.26
Apr-20	225.26	163.36	118.79	109.65	87.56	93.78	83.35	55.93	64.32	43.35	1045.35
May-20	219.44	166.84	126.43	155.59	83.47	103.10	92.06	62.45	66.98	45.27	1121.62
Jun-20	227.94	165.30	128.65	124.27	91.91	113.12	96.43	66.51	73.79	51.12	1139.03
Jul-20	240.43	181.17	146.91	144.97	96.09	126.30	102.67	70.79	79.75	61.78	1250.86
Aug-20	231.85	161.41	133.81	116.87	104.56	120.18	104.18	70.71	77.13	55.31	1176.01
Sep-20	254.34	167.24	154.18	137.84	115.84	127.45	112.72	78.10	79.26	61.34	1288.31
Oct-20	279.00	194.83	162.87	131.59	116.40	123.83	109.67	80.07	77.81	66.23	1342.28
Nov-20	277.78	188.42	146.42	148.85	109.58	116.96	112.62	86.63	74.03	61.10	1322.38
Dec-20	323.06	197.22	159.52	158.21	123.44	134.30	114.64	84.27	87.11	66.86	1448.61
Jan-21	294.84	185.62	160.91	137.94	116.56	124.73	116.76	75.08	79.91	61.96	1354.30
Feb-21	265.10	176.26	143.40	138.78	119.67	116.90	103.81	72.65	70.96	51.21	1258.75
Mar-21	303.51	207.62	173.14	162.48	130.47	140.85	116.11	89.90	86.47	72.78	1483.34
Apr-21	282.75	192.71	154.01	142.90	115.93	138.13	113.30	86.47	87.63	64.80	1378.63
May-21	306.80	178.84	165.23	141.67	129.97	144.92	102.91	88.14	83.57	65.85	1407.91
Jun-21	331.99	201.46	163.33	157.23	121.58	153.13	126.02	88.71	92.65	67.27	1503.36
Jul-21	307.55	200.86	157.03	151.43	122.30	160.59	120.33	94.77	89.53	67.89	1472.26
Aug-21	286.24	190.80	162.46	139.58	126.30	131.17	110.64	84.78	85.02	60.35	1377.34
Sep-21	305.40	203.81	174.20	101.78	127.37	131.84	121.73	94.02	87.22	67.58	1414.93

Oct-21	300.84	200.53	173.34	104.34	128.79	132.58	114.50	91.72	84.08	62.85	1393.57
Nov-21	309.92	206.52	185.81	109.01	131.94	135.58	114.76	90.69	80.59	60.00	1424.82
Dec-21	318.33	224.25	182.81	123.33	138.61	141.85	134.15	92.99	91.32	70.89	1518.53
Jan-22	309.32	193.80	165.40	120.92	123.55	140.80	131.38	89.89	76.60	63.78	1415.45
Feb-22	285.34	193.90	164.28	109.45	125.53	137.67	119.63	89.88	86.98	61.78	1374.44
Mar-22	332.07	216.99	189.67	129.01	142.24	154.40	134.32	99.00	96.25	72.35	1566.30
Apr-22	310.83	198.25	155.23	114.77	128.41	126.63	118.52	88.62	94.02	68.49	1403.76
May-22	325.61	223.78	173.47	128.74	136.74	150.09	118.32	96.74	97.99	68.34	1519.83
Jun-22	316.58	202.22	154.32	110.32	127.54	145.16	123.94	94.48	85.69	57.99	1418.24
Jul-22	274.38	203.03	140.83	96.11	130.78	142.77	123.41	84.79	78.04	64.44	1338.57
Total	18516.03	12090.62	10188.54	8289.64	8207.84	7751.59	7011.64	4985.50	4917.35	3643.36	

Epinephrine

	NHS London	NHS North West	NHS West Midlands	NHS South Central	NHS East of England	NHS Yorkshire and the Humber	NHS South West	NHS North East	NHS East Midlands	NHS South East Coast	Total (dosage)
Apr-17	89603.45	83239.80	37687.30	36016.80	44726.25	40656.30	33443.10	27295.50	23489.65	17358.35	433516.50
May-17	84951.45	102927.85	49102.80	43745.90	47863.35	43157.40	40538.40	31968.60	46324.75	18397.40	508977.90
Jun-17	106168.55	85955.70	48598.30	48388.00	50451.45	56805.75	50685.80	38329.70	27642.95	25626.30	538652.50
Jul-17	118510.40	100004.55	52962.45	56915.80	56554.20	58742.35	47024.35	41871.25	51034.95	30269.85	613890.15
Aug-17	133985.15	129711.10	53911.90	58922.45	57241.55	51082.90	49992.65	48216.30	53312.80	30341.60	666718.40
Sep-17	117100.70	114592.35	55370.30	53966.00	70470.40	52057.20	54830.95	45354.00	36666.15	34175.25	634583.30
Oct-17	138713.75	100872.10	51599.20	55799.10	60801.00	48254.15	54363.55	34863.25	39563.95	30250.85	615080.90
Nov-17	131388.55	90293.80	48664.85	57308.85	57956.75	52339.20	50115.20	38757.65	33537.15	26342.85	586704.85
Dec-17	122712.75	82221.60	50452.10	46864.30	58515.00	45667.65	46002.55	32738.10	38848.50	26159.10	550181.65
Jan-18	103076.80	114896.45	34076.30	44029.65	47658.40	49482.40	40203.80	31128.85	32176.35	21730.35	518459.35
Feb-18	123385.85	85947.50	45377.95	48808.45	61818.95	50113.60	40784.05	31246.10	34980.35	21112.05	543574.85
Mar-18	147806.80	100639.55	54468.40	51426.15	53119.25	46925.50	55633.15	52282.60	41783.35	31761.35	635846.10

Apr-18	138565.55	102543.50	51634.45	42429.85	68414.65	46566.15	44886.80	34118.40	34863.35	23953.60	587976.30
May-18	102060.05	96338.70	39311.20	50018.60	51881.85	55029.55	42364.30	31903.85	40634.85	29818.90	539361.85
Jun-18	110039.85	59348.80	40480.20	46109.60	55941.05	45620.80	43476.95	30122.50	39859.50	22414.15	493413.40
Jul-18	113076.65	72491.40	43182.35	52967.35	57338.45	42822.80	44599.65	32534.20	31446.00	27316.15	517775.00
Aug-18	115278.30	78292.45	39043.30	42440.80	50572.50	43091.70	47617.60	35958.30	30481.00	23859.25	506635.20
Sep-18	103495.70	84664.10	44139.55	44927.95	46665.85	47465.10	47742.85	47265.30	29820.50	25954.15	522141.05
Oct-18	128006.20	89033.05	50378.80	67275.40	70189.20	37987.00	54139.50	54830.45	48501.20	27258.35	627599.15
Nov-18	134590.95	102034.80	47414.45	49813.75	53635.45	34576.20	46962.80	24311.80	44307.20	24896.25	562543.65
Dec-18	127388.80	88587.15	37248.15	55347.50	59602.75	55056.75	39374.05	31376.70	34159.55	21892.30	550033.70
Jan-19	125499.65	99189.90	42209.55	40779.25	59816.50	50105.80	39048.55	35261.75	41163.80	24533.50	557608.25
Feb-19	89442.30	77563.50	38862.20	41151.45	51015.05	51193.40	37671.95	27927.55	34500.00	18399.95	467727.35
Mar-19	122853.60	77089.75	37540.80	37072.60	57996.65	69953.60	38320.40	30349.15	52966.45	20721.30	544864.30
Apr-19	115507.85	95070.10	63834.45	50499.35	67502.35	49919.10	57074.15	36319.65	39678.35	34013.50	609418.85
May-19	120935.10	76766.55	50513.65	46656.45	54621.10	45604.20	42513.25	27331.85	25193.60	26255.20	516390.95
Jun-19	81497.15	78888.20	48890.25	37408.10	45466.35	40157.15	44135.70	26647.60	33411.15	18788.55	455290.20

Jul-19	110743.15	79171.60	64694.80	48347.40	38392.60	45114.60	39693.75	33236.45	25463.00	25149.70	510007.05
Aug-19	116233.45	81471.25	49826.30	48900.75	36702.50	40850.50	47042.40	31037.75	38369.95	22856.65	513291.50
Sep-19	100724.15	82661.85	48013.50	40366.35	34285.90	42120.60	34944.45	32167.75	27058.45	23885.30	466228.30
Oct-19	95041.05	91720.70	55885.35	46173.35	45461.30	50640.35	47488.45	34275.10	29611.95	24092.30	520389.90
Nov-19	115247.30	80636.15	56891.45	46137.95	37807.65	42142.95	42060.10	30680.70	27709.30	21620.45	500934.00
Dec-19	113295.55	74373.25	49941.10	50021.40	55727.95	37409.65	45010.15	32117.70	32662.00	25681.95	516240.70
Jan-20	119768.20	95981.70	60427.55	44961.35	51690.65	47445.70	44973.30	32031.40	32710.10	23754.10	553744.05
Feb-20	100328.10	74611.35	58740.20	38789.95	39145.50	39422.15	43482.00	41808.75	46499.30	26027.15	508854.45
Mar-20	134172.25	91141.70	61360.65	53066.20	43480.75	49586.20	44052.25	30909.30	40573.40	28328.40	576671.10
Apr-20	167554.25	84863.75	38758.20	45226.10	33231.45	46324.60	33966.65	22996.95	23805.00	18274.80	515001.75
May-20	90414.75	56395.60	33113.65	37370.05	24503.55	29918.80	32731.60	28785.75	35944.10	15141.65	384319.50
Jun-20	97066.60	82998.90	36708.10	37644.20	29930.05	38994.05	41415.60	27511.65	34026.35	18916.95	445212.45
Jul-20	112199.15	76458.55	41276.80	50124.85	35076.65	37829.95	41633.10	37084.50	33767.05	23813.10	489263.70
Aug-20	95861.55	67867.80	42022.55	39382.15	31820.05	33712.70	25813.10	31562.65	30292.50	20195.10	418530.15
Sep-20	126607.85	76574.35	48999.55	47883.85	39590.45	42191.20	41713.65	38456.50	19771.25	27049.75	508838.40

Oct-20	105593.05	91977.90	63917.70	48364.90	44130.15	47232.55	44907.65	31175.95	47311.40	27999.50	552610.75
Nov-20	147229.25	90323.75	52365.90	58116.05	46082.30	58085.30	51809.75	30773.95	29908.90	30166.55	594861.70
Dec-20	131058.55	93489.20	47373.95	63620.70	54807.00	45505.10	48617.65	33201.70	27167.25	32697.70	577538.80
Jan-21	169894.00	96506.20	52562.50	59488.15	43595.95	38681.30	48042.90	42807.75	26307.40	27319.20	605205.35
Feb-21	129344.05	89491.30	52092.15	46625.50	32864.95	35582.95	39301.50	47205.15	28985.85	21584.90	523078.30
Mar-21	110043.15	84659.10	44877.70	42015.10	36648.70	78418.55	37946.35	34416.05	45992.60	24000.95	539018.25
Apr-21	108084.15	74387.00	36458.95	39120.95	36523.85	45426.15	40572.40	29256.85	31782.10	20906.55	462518.95
May-21	100694.85	69296.70	47436.70	40116.80	35441.45	40809.55	35692.30	31543.70	32085.05	19155.55	452272.65
Jun-21	133645.30	76634.30	49930.60	52109.50	40341.55	40702.40	40055.85	49916.15	25063.10	21743.45	530142.20
Jul-21	114713.65	81425.95	53192.70	47347.65	46360.30	57873.05	37219.30	33320.35	49298.50	25388.95	546140.40
Aug-21	132434.00	70394.15	49650.00	52423.70	42993.15	54854.25	50971.35	57425.50	32136.80	24772.70	568055.60
Sep-21	160273.40	91187.05	60205.90	61625.45	50829.50	46429.60	55458.20	55017.40	26572.65	26794.00	634393.15
Oct-21	163593.50	116880.80	79795.00	66937.90	52314.75	55494.60	67278.50	55526.50	28937.20	32670.10	719428.85
Nov-21	154636.10	116221.70	52818.05	70596.85	63143.30	57592.75	64163.05	50472.20	79201.20	39607.45	748452.65
Dec-21	157299.65	96122.00	73022.55	53964.10	51765.60	39167.05	48369.85	50965.55	31224.15	33430.65	635331.15

Jan-22	144790.45	92256.80	50268.35	41135.10	34232.00	57544.05	43134.70	49652.05	32364.90	21710.50	567088.90
Feb-22	120278.55	98302.20	53997.50	55444.50	44017.40	45505.35	46799.35	70024.50	42022.45	29711.75	606103.55
Mar-22	165631.95	104662.75	55824.25	61174.15	53925.50	68106.70	60147.15	50341.60	57026.95	29132.45	705973.45
Apr-22	120648.40	83790.85	69093.55	49952.10	53123.55	40417.10	42370.85	46594.75	30779.85	30603.35	567374.35
May-22	152298.05	89668.50	93265.05	63004.80	49891.25	56802.20	57898.75	53109.40	66749.30	36668.75	719356.05
Jun-22	140772.40	80920.15	66497.75	54024.35	45553.65	46521.60	47547.50	48674.05	44506.70	28965.40	603983.55
Jul-22	119725.05	59525.15	45600.70	43278.40	43181.45	44530.85	45761.30	45249.10	36870.40	22491.05	506213.45
Total	7823580.75	5614256.30	3253862.45	3151972.05	3096450.60	3035420.70	2893632.79	2441644.05	2350905.80	1635909.20	

Lidocaine

	NHS London	NHS South East Coast	NHS East Midlands	NHS East of England	NHS North West	NHS West Midlands	NHS Yorkshire and the Humber	NHS South West	NHS South Central	NHS North East	Total (dosage)
Apr-17	43000.00	39500.00	10500.00	18500.00	11795.00		2500.00	14500.00	8030.00	5000.00	153325.00
May-17	53000.00	37500.00	2500.00	32000.00	22650.00	1000.00	12500.00	4000.00	1000.00	15000.00	181150.00
Jun-17	60000.00	42000.00	17500.00	11000.00	7505.00	21000.00	6500.00	12500.00	3500.00	1500.00	183005.00
Jul-17	73500.00	25500.00	5500.00	16500.00	14000.00	12000.00	9000.00	0.00	5000.00	4500.00	165500.00
Aug-17	80000.00	36000.00	4500.00	500.00	3550.00	8000.00	6500.00	500.00	5000.00	8500.00	153050.00
Sep-17	111500.00	35000.00	32500.00	5000.00	17950.00	10500.00	6500.00	1500.00	1500.00	2000.00	223950.00
Oct-17	43000.00	20500.00	27500.00	19500.00	9500.00	7500.00	15500.00	1000.00	3500.00	14000.00	161500.00
Nov-17	56000.00	16000.00	35500.00	42495.00	9505.00	11000.00	14500.00	1000.00	500.00	9000.00	195500.00
Dec-17	112000.00	24000.00	12000.00	13000.00	12500.00	16000.00	38000.00	2000.00	1500.00	9000.00	240000.00
Jan-18	74000.00	13000.00	15500.00	10000.00	9050.00	11500.00	26500.00	8500.00	8500.00	8000.00	184550.00
Feb-18	48500.00	26000.00	8500.00	2500.00	9000.00	9500.00	14500.00	8000.00	7500.00	1500.00	135500.00
Mar-18	66500.00	30000.00	25000.00	3000.00	16550.00	7500.00	9000.00	44500.00	5000.00	6000.00	213050.00

Apr-18	79500.00	33000.00	34500.00	41500.00	10000.00	7500.00	16500.00	22000.00	10000.00	4000.00	258500.00
May-18	42000.00	34000.00	4500.00	8000.00	2000.00	4500.00	7000.00	8500.00	9500.00	9000.00	129000.00
Jun-18	39500.00	30500.00	17500.00	12500.00	7750.00	8000.00	10000.00	5500.00	7000.00	10000.00	148250.00
Jul-18	45000.00	31500.00	21500.00	6000.00	32300.00	9000.00	5500.00	17500.00	14500.00	8000.00	190800.00
Aug-18	40000.00	40500.00	14500.00	21000.00	14550.00	18500.00	6500.00	12000.00	4000.00	4000.00	175550.00
Sep-18	69000.00	14000.00	28000.00	5500.00	13000.00	2500.00	6500.00		14000.00	8500.00	161000.00
Oct-18	32500.00	38500.00	16000.00	4000.00	13500.00	8500.00	3500.00	8000.00	3500.00	3000.00	131000.00
Nov-18	67000.00	21000.00	3000.00	10500.00	16000.00	6500.00	8500.00	11000.00	7500.00	7000.00	158000.00
Dec-18	73000.00	34000.00	11000.00	21500.00	9500.00	2500.00	30500.00		4500.00	11500.00	198000.00
Jan-19	82500.00	34500.00	40000.00	27500.00	19350.00	3500.00	19500.00	8000.00	2500.00	4500.00	241850.00
Feb-19	44500.00	42500.00	21500.00	5500.00	15000.00	29000.00	6000.00	2000.00	10000.00	5000.00	181000.00
Mar-19	71000.00	12500.00	32500.00	19500.00	15000.00	4500.00	16000.00	1500.00	1000.00	11500.00	185000.00
Apr-19	50000.00	26500.00	10500.00	22000.00	21500.00	23500.00	25000.00	1500.00	8000.00	17500.00	206000.00
May-19	62000.00	22500.00	21500.00	27500.00	13600.00	19000.00	16000.00	1000.00	0.00	10500.00	193600.00
Jun-19	67000.00	40500.00	25000.00	3000.00	6255.00	25500.00	23000.00	29500.00	4000.00	1000.00	224755.00

Jul-19	49506.00	33500.00	17500.00	12500.00	10430.00	22000.00	20000.00	4000.00	3000.00	2500.00	174936.00
Aug-19	41000.00	26000.00	14000.00	2000.00	17500.00	5000.00	2500.00	4500.00	6000.00	5000.00	123500.00
Sep-19	36000.00	16500.00	8000.00	1000.00	2000.00	2500.00	6500.00	1000.00	5500.00	5500.00	84500.00
Oct-19	220500.00	40500.00	18500.00	26500.00	27500.00	12000.00	20500.00	6500.00	12000.00	6500.00	391000.00
Nov-19	68003.00	38000.00	22500.00	6500.00	18000.00	14000.00	26500.00	11000.00	6000.00	12000.00	222503.00
Dec-19	81007.00	34500.00	24000.00	25500.00	18500.00	20500.00	14500.00	21000.00	7500.00	17000.00	264007.00
Jan-20	70504.00	17500.00	25500.00	9500.00	23500.00	4500.00	10000.00	1500.00	24500.00	14500.00	201504.00
Feb-20	79500.00	29500.00	2500.00	11500.00	5500.00	500.00	6000.00	2000.00	4500.00	2500.00	144000.00
Mar-20	118006.00	10500.00	8000.00	1000.00	16500.00	2000.00	7500.00	500.00	2000.00	5000.00	171006.00
Apr-20	42500.00	23000.00	5000.00	15000.00	5000.00	18500.00	6500.00	15500.00	8000.00	500.00	139500.00
May-20	23015.00	23500.00	7500.00	6000.00	9000.00	16500.00	6500.00	8500.00	25500.00	11500.00	137515.00
Jun-20	19516.00	14500.00	8500.00	14500.00	21000.00	5000.00	1000.00		4500.00	1500.00	90016.00
Jul-20	39005.00	32500.00	28500.00	7000.00	13015.00	18500.00	15000.00	4000.00	7000.00	4000.00	168520.00
Aug-20	40509.00	6500.00	29000.00	26500.00	20000.00	13500.00	8500.00	9000.00	9000.00	4000.00	166509.00
Sep-20	50000.00	25000.00	7500.00	2000.00	8500.00	1000.00	11500.00	1000.00	10000.00	4000.00	120500.00
Oct-20	37511.00	23000.00	17500.00	6500.00	4000.00	9000.00	16000.00	2000.00	6500.00	4000.00	126011.00

Nov-20	77004.00	21500.00	39000.00	14500.00	24000.00	39000.00	27500.00	7000.00	14500.00	55500.00	319504.00
Dec-20	81501.00	29500.00	48500.00	55500.00	44500.00	25500.00	22000.00	37000.00	22000.00	30000.00	396001.00
Jan-21	110505.00	18500.00	19000.00	49000.00	20050.00	114000.00	6500.00	14000.00	5000.00	11000.00	367555.00
Feb-21	27500.00	36000.00	1000.00	12500.00	25000.00	7500.00	4500.00	500.00	5000.00		119500.00
Mar-21	71500.00	39500.00	9500.00	6500.00	3500.00	9500.00	4000.00	1000.00	7500.00	2500.00	155000.00
Apr-21	47000.00	11000.00	7500.00	11500.00	5500.00	4500.00	11500.00	17000.00	11500.00	6000.00	133000.00
May-21	34000.00	14000.00	16000.00	7500.00	16000.00	8500.00	1500.00	4000.00	11500.00	3500.00	116500.00
Jun-21	38000.00	17000.00	21000.00	2500.00	0.00	12500.00	9000.00	32500.00	10000.00	1000.00	143500.00
Jul-21	56000.00	8500.00	10000.00	0.00	16500.00	14500.00	12500.00		24500.00	500.00	143000.00
Aug-21	39500.00	3000.00	8500.00	9000.00	8000.00	2500.00	10500.00	4500.00	3000.00	1000.00	89500.00
Sep-21	12500.00	8500.00	25000.00	11500.00	16000.00	1500.00	15000.00	1000.00	41000.00	1000.00	133000.00
Oct-21	49500.00	27500.00	17500.00	3500.00	12000.00	18500.00	9500.00	11000.00	8500.00	4500.00	162000.00
Nov-21	32000.00	11000.00	16000.00		2000.00	31000.00	13500.00	1000.00	6500.00	1500.00	114500.00
Dec-21	85000.00	11000.00	21000.00	7000.00	19000.00	14000.00	16000.00		3500.00	7500.00	184000.00
Jan-22	4500.00	5500.00	12000.00	3000.00	11500.00	0.00	3500.00		14000.00	500.00	54500.00
Feb-22	196000.00	18000.00	14000.00	19500.00	11500.00	1000.00	16000.00	42000.00	11000.00	6000.00	335000.00

Mar-22	47000.00	18000.00	29000.00	10500.00	6500.00	28000.00	32000.00	3000.00	13500.00	7000.00	194500.00
Apr-22	4000.00	29500.00	8000.00	24000.00	23050.00	6500.00	500.00	11500.00	11500.00	8500.00	127050.00
May-22	6000.00	22000.00	7500.00	32000.00	5000.00	2500.00	11500.00	8500.00		21500.00	116500.00
Jun-22		2000.00	1000.00	1500.00		3000.00		0.00			7500.00
Jul-22		1000.00		1500.00		2000.00		15000.00	3500.00		23000.00
Total	3720592.00	1548000.00	1073500.00	865495.00	842405.00	799000.00	767500.00	528500.00	519530.00	468000.00	

Lisinopril

	NHS London	NHS North West	NHS North East	NHS East of England	NHS South West	NHS Yorkshire and the Humber	NHS South Central	NHS West Midlands	NHS East Midlands	NHS South East Coast	Total (dosage)
Apr-17	32296.00	30663.00	24282.00	20045.00	19028.00	24112.00	16539.00	15211.00	13145.00	10803.00	206124.00
May-17	36149.00	29041.00	27824.00	21386.00	19992.00	24197.50	18409.00	18094.00	13261.00	12596.00	220949.50
Jun-17	33637.00	30826.00	27105.00	19736.00	19332.00	24046.00	19902.00	16600.00	13218.00	11230.00	215632.00
Jul-17	30869.00	29178.00	25395.00	18859.00	20119.00	21883.00	21300.00	15687.00	13946.00	10342.00	207578.00
Aug-17	35481.00	28664.00	22577.00	18692.00	19287.00	22124.00	17078.00	15539.00	15061.00	9633.00	204136.00
Sep-17	34972.00	30153.00	24110.00	17368.00	18680.00	25016.00	16914.00	15398.00	13546.00	10382.00	206539.00
Oct-17	35474.00	31954.00	27458.00	21755.00	18862.00	23547.00	19268.00	17436.00	13862.00	11791.00	221407.00
Nov-17	37131.00	32206.00	26561.00	20353.00	20605.00	23635.00	19245.00	17431.00	14877.00	12064.00	224108.00
Dec-17	35310.00	33118.00	28066.00	21447.00	19289.00	22517.00	19145.00	17154.00	14228.00	11060.00	221334.00
Jan-18	38081.00	32751.00	29401.00	21696.00	22924.00	25025.00	21209.00	19716.50	16793.00	10583.00	238179.50
Feb-18	34378.00	27306.00	25589.00	20156.00	19190.00	23140.00	17398.00	17573.00	12451.00	10397.50	207578.50
Mar-18	36088.00	29770.00	26378.00	20742.00	20780.00	24936.00	13098.00	20335.00	12559.00	11606.00	216292.00

Apr-18	33027.00	28950.00	23300.00	20365.00	18556.00	22335.00	16762.00	16824.00	11805.00	10664.00	202588.00
May-18	34625.00	31166.00	27608.00	22487.00	16932.00	23566.00	19891.00	18721.00	14896.00	11634.00	221526.00
Jun-18	31241.00	29477.00	25872.00	19852.00	18292.00	21773.00	17917.00	18516.00	12097.00	10182.00	205219.00
Jul-18	32211.92	29094.00	27893.00	18704.00	18062.00	22205.00	20107.00	16660.00	12700.00	10146.00	207782.92
Aug-18	33243.00	31572.00	26819.00	19184.00	18823.00	24338.00	17939.00	16993.00	13689.00	10460.00	213060.00
Sep-18	33669.00	28282.00	23144.00	16085.00	18339.00	21030.00	14655.00	17354.00	13076.00	9128.00	194762.00
Oct-18	34616.00	31341.00	26114.00	19913.00	18225.00	25596.50	23027.00	15916.00	13328.00	10308.00	218384.50
Nov-18	38060.00	30462.00	26342.00	21472.00	18789.00	23992.00	18424.00	17893.00	13667.00	10767.00	219868.00
Dec-18	35570.00	32489.00	24258.00	20183.00	18409.00	23278.00	16335.00	18876.00	12982.00	11585.00	213965.00
Jan-19	36594.00	32344.00	27007.00	21914.00	19871.00	24089.00	21606.00	18342.00	14322.00	11392.00	227481.00
Feb-19	34581.00	28153.00	24725.00	18595.00	17454.00	23591.00	16297.00	15853.00	11991.00	10177.00	201417.00
Mar-19	34898.00	28622.00	25898.00	18798.00	17402.00	16216.00	17874.00	17666.00	14064.00	9812.00	201250.00
Apr-19	35385.00	31448.00	27198.00	20200.00	20167.00	16460.00	17394.00	18795.00	14210.00	10914.00	212171.00
May-19	31671.00	31014.00	24622.00	20553.00	20257.00	16763.00	15246.00	17792.00	12671.00	10788.00	201377.00
Jun-19	32239.00	27370.00	24648.00	20007.00	17562.00	14333.00	16475.00	16747.00	12757.00	10733.00	192871.00

Jul-19	33666.00	32665.00	25192.00	19894.00	18081.00	15694.00	19662.00	16846.00	13894.00	12439.00	208033.00
Aug-19	32576.00	28685.00	25084.00	17697.00	17464.00	15593.00	16261.00	15598.00	12891.00	10969.00	192818.00
Sep-19	32971.00	28060.00	24244.00	18341.00	17850.00	15395.00	15392.00	14347.00	11088.00	10695.00	188383.00
Oct-19	36575.00	30027.00	25720.00	20065.00	17848.00	16126.00	18223.00	17932.00	11677.00	11344.00	205537.00
Nov-19	36070.00	30131.00	25054.00	19960.00	17895.00	14912.00	16600.00	16486.00	12890.00	11676.00	201674.00
Dec-19	35395.00	31608.00	25121.00	20367.00	17941.00	16029.00	17678.00	18479.00	13018.00	12171.00	207807.00
Jan-20	33621.20	30173.00	26329.00	24481.00	16841.00	15882.00	16472.00	18265.00	13639.00	12772.00	208475.20
Feb-20	37099.20	28341.00	24383.00	19802.00	15647.00	14508.00	16980.00	16301.00	13007.00	10221.00	196289.20
Mar-20	34603.00	28021.00	25176.00	20061.00	17981.00	16944.00	17784.00	16496.00	13528.00	10634.00	201228.00
Apr-20	25048.00	26703.00	19910.00	14638.00	12524.00	11234.00	12287.00	12636.00	8642.00	8383.00	152005.00
May-20	23368.00	25426.00	19794.00	15548.50	15635.00	10920.00	17323.00	12859.00	8918.00	8318.00	158109.50
Jun-20	26343.00	26408.00	23693.00	18915.00	16221.00	14231.00	16745.00	15347.00	9595.00	10884.00	178382.00
Jul-20	26512.00	27650.00	23572.00	19519.00	15906.00	13942.00	15870.00	15913.00	11716.00	10853.00	181453.00
Aug-20	23926.00	21620.00	20128.00	17204.00	16031.00	12788.00	14163.00	13740.00	10955.00	10362.00	160917.00
Sep-20	29940.00	27611.00	24945.00	18152.00	17224.00	13316.00	16923.00	16457.50	12763.00	9801.00	187132.50

Oct-20	31296.00	29609.00	23328.00	18778.00	17711.00	14674.00	16810.00	15606.00	12121.00	10858.00	190791.00
Nov-20	29511.00	26994.00	26081.00	19650.00	17227.00	14459.00	14562.00	15010.00	13681.00	9597.00	186772.00
Dec-20	34425.00	31966.00	27538.00	21314.00	17349.00	14501.00	19566.00	14938.00	11715.00	10288.00	203600.00
Jan-21	34390.00	30056.00	27830.00	21728.00	17243.00	15686.00	16808.00	14232.00	10998.00	9801.00	198772.00
Feb-21	28231.00	25192.00	24237.00	17298.00	14591.00	12533.00	16006.00	13322.00	10550.00	9034.00	170994.00
Mar-21	28914.00	31020.00	27612.00	21673.00	17399.00	15494.00	18122.00	15436.00	13034.00	10813.00	199517.00
Apr-21	26988.00	30912.00	25926.00	21444.00	18315.00	14349.00	15803.00	14171.00	11756.00	10129.00	189793.00
May-21	28051.00	29050.00	27612.00	20131.00	18331.00	14651.00	18130.00	14293.00	11335.00	11596.00	193180.00
Jun-21	26124.00	29972.00	27715.00	19464.00	18129.00	14434.00	18905.00	14020.00	12219.00	11460.00	192442.00
Jul-21	32619.00	29313.00	27310.00	21375.00	18626.00	14155.00	17939.00	15792.00	13460.00	10456.00	201045.00
Aug-21	25651.01	28136.50	24870.00	20998.00	17041.00	12826.00	15232.00	13737.00	11857.00	12184.00	182532.51
Sep-21	31723.01	30899.00	26350.00	19883.00	17319.00	14056.00	11876.00	17288.00	11443.00	11609.00	192446.01
Oct-21	29860.01	27749.00	23819.00	18387.00	18305.00	14285.00	12829.00	18084.00	11656.00	11878.00	186852.01
Nov-21	32612.01	30823.00	25171.00	19501.00	19741.00	15420.00	13210.00	16585.00	11308.00	12932.00	197303.01
Dec-21	29916.01	32516.00	28140.00	23157.00	20576.00	15771.00	13552.00	18160.00	13379.00	11490.00	206657.01

Jan-22	30079.80	34574.00	23411.00	19475.00	18379.00	14745.00	13556.00	15959.00	11083.00	11604.00	192865.80
Feb-22	29788.02	33312.00	26139.00	19095.00	17062.00	15473.00	13252.00	15944.00	12721.00	11740.00	194526.02
Mar-22	31606.00	36185.00	29958.00	24212.00	19670.00	15742.00	14501.00	18925.00	12364.00	11739.00	214902.00
Apr-22	30082.00	31250.00	27254.00	20540.00	19478.00	14239.00	12877.00	17990.00	10947.00	10524.00	195181.00
May-22	32930.00	33490.00	26283.00	21535.00	19558.00	15650.00	15320.00	14795.00	12373.00	10854.00	202788.00
Jun-22	28758.00	32645.00	24602.00	19807.00	17595.00	15160.00	11108.00	14743.00	12340.00	9910.00	186668.00
Jul-22	31305.00	30378.00	25674.00	20266.00	18921.00	15969.00	10264.00	13882.00	11728.00	10666.00	189053.00
Total	2064070.19	1916584.50	1635399.00	1274902.50	1164883.00	1145530.00	1068045.00	1049737.00	807491.00	693861.50	

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	NHS London	NHS West Midlands	NHS Yorkshire and the Humber	NHS North West	NHS East of England	NHS East Midlands	NHS South Central	NHS South West	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	2275.95	1444.98	2176.25	1462.24	1271.94	1051.78	1138.88	990.60	790.50	576.68	13179.78
May-17	2509.22	1656.89	2321.20	1471.29	1174.09	1181.48	1146.51	987.03	926.98	596.35	13971.02
Jun-17	2478.24	1580.99	2324.38	1506.14	1247.34	1125.06	1217.50	992.35	905.05	572.20	13949.24
Jul-17	2196.83	1453.20	2256.98	1385.35	1104.56	1051.14	1072.25	841.93	905.33	598.31	12865.86
Aug-17	2373.55	1560.36	2199.17	1450.18	1283.34	1213.48	1097.86	1013.80	753.88	672.63	13618.23
Sep-17	2284.06	1708.18	2313.83	1470.49	1210.20	1213.75	1135.95	957.66	955.40	666.51	13916.03
Oct-17	2462.74	1666.41	2229.63	1368.55	1282.45	1240.45	1127.25	942.21	993.53	652.35	13965.56
Nov-17	2573.23	1660.06	2473.28	1570.64	1217.10	1207.10	1103.65	1037.25	980.15	640.08	14462.53
Dec-17	2570.98	1668.36	2291.98	1602.21	1294.40	1260.93	1100.40	1087.95	901.53	681.68	14460.40
Jan-18	2588.29	1795.89	2663.48	1601.95	1202.81	1271.94	1271.23	1014.90	1068.51	726.93	15205.91
Feb-18	2281.19	1598.99	2428.88	1417.69	1240.94	1204.60	1038.98	1003.61	906.10	594.70	13715.66
Mar-18	2505.10	1818.99	2212.60	1624.48	1297.53	1244.85	1051.40	1207.59	1145.58	634.93	14743.03
Apr-18	2355.33	1752.96	2293.15	1362.23	1277.26	1178.58	1126.34	968.84	939.68	680.96	13935.31
May-18	2383.15	1847.75	2389.28	1684.79	1448.03	1225.88	1254.15	1051.93	900.13	724.50	14909.56
Jun-18	2307.05	1661.33	2218.05	1386.05	1318.04	1122.45	1081.38	961.84	947.88	660.60	13664.65
Jul-18	2249.95	1686.90	2489.04	1489.54	1380.30	1085.95	1217.29	1006.86	900.54	612.75	14119.11
Aug-18	2284.04	1804.36	2481.58	1322.40	1215.39	1296.33	1141.40	1079.24	930.73	653.58	14209.03
Sep-18	2211.78	1592.55	2286.78	1391.93	1224.70	1074.54	1075.24	903.03	909.25	563.88	13233.65
Oct-18	2437.20	1831.08	2666.44	1472.75	1504.13	1295.85	1420.50	1007.70	1007.35	602.70	15245.69
Nov-18	2322.05	1775.50	2614.13	1500.65	1263.04	1336.93	1224.39	1016.50	1086.29	587.81	14727.28
Dec-18	2362.91	1797.11	2522.03	1563.73	1174.70	1186.78	1196.25	951.40	934.13	631.85	14320.88
Jan-19	2545.05	1804.28	2569.63	1686.19	1338.94	1472.35	1593.73	1052.55	980.54	645.74	15688.98
Feb-19	2281.03	1862.66	2249.75	1403.70	1282.95	1275.88	1149.08	1042.24	845.58	633.10	14025.95
Mar-19	2636.68	1868.60	1291.43	1439.84	1378.30	1229.39	1203.30	1006.86	1050.19	696.35	13800.93

Apr-19	2360.68	1827.05	1332.33	1462.46	1404.28	1360.73	1266.90	1110.68	1023.78	664.64	13813.50
May-19	2367.08	1924.66	1352.13	1629.90	1348.18	1369.25	1313.33	1172.65	975.55	676.25	14128.96
Jun-19	2295.93	1817.70	1391.18	1570.48	1258.03	1302.68	1198.85	975.41	952.23	657.91	13420.38
Jul-19	2269.59	1840.08	1421.35	1601.36	1344.34	1354.84	1415.85	1090.30	950.83	619.60	13908.13
Aug-19	2375.28	1701.75	1301.73	1484.70	1303.54	1314.70	1278.33	1156.94	852.90	521.28	13291.13
Sep-19	2132.90	1681.04	1394.43	1508.61	1257.19	1153.06	1323.81	1110.84	895.73	621.85	13079.45
Oct-19	2393.45	2026.94	1446.64	1663.61	1549.53	1387.88	1493.83	1291.69	1018.43	614.36	14886.34
Nov-19	2391.65	1887.59	1367.93	1496.83	1509.23	1282.13	1384.18	1032.70	1127.88	628.88	14108.96
Dec-19	2520.80	2052.35	1519.25	1828.78	1600.04	1291.99	1366.70	1170.96	1097.40	678.61	15126.88
Jan-20	2474.80	1878.91	1424.38	1829.01	1627.20	1544.70	1234.13	1107.53	1080.03	755.46	14956.14
Feb-20	2432.75	1765.70	1302.40	1569.94	1454.78	1296.50	1448.16	995.96	990.70	691.59	13948.48
Mar-20	2344.00	1805.54	1300.10	1711.45	1435.18	1345.08	1341.66	980.40	848.93	636.74	13749.06
Apr-20	1845.75	1285.84	1015.30	1365.26	1074.19	1009.30	987.31	702.81	740.90	422.30	10448.96
May-20	1731.43	1515.29	1188.60	1480.91	1119.05	1018.21	1437.49	857.66	873.20	460.48	11682.31
Jun-20	1907.61	1681.73	1186.68	1536.93	1210.38	1162.66	1158.19	880.15	869.65	503.96	12097.93
Jul-20	1973.18	1807.03	1297.78	1667.54	1370.96	1318.79	1305.06	1033.88	987.23	660.26	13421.69
Aug-20	1803.05	1760.63	1347.66	1608.50	1325.53	1118.01	1193.18	921.95	933.73	603.66	12615.89
Sep-20	2061.64	1822.98	1401.03	1690.38	1422.88	1206.43	1275.83	1065.64	978.70	719.29	13644.76
Oct-20	2298.75	1823.94	1492.08	1712.39	1368.70	1358.84	1252.10	1037.90	993.88	611.38	13949.94
Nov-20	2302.30	1891.04	1454.65	1613.60	1377.40	1192.54	1326.39	1061.10	888.88	685.41	13793.30
Dec-20	2558.60	1952.84	1423.20	1786.40	1568.74	1429.36	1458.10	1055.20	1119.03	783.14	15134.60
Jan-21	2512.73	1836.84	1419.85	1766.30	1450.08	1262.05	1490.24	1044.04	1019.80	664.00	14465.91
Feb-21	1895.18	1695.86	1340.70	1457.75	1250.00	1250.00	1223.29	813.36	864.08	620.81	12411.03
Mar-21	2361.80	1846.61	1495.90	1840.40	1568.25	1421.83	1516.15	1095.01	1027.13	650.19	14823.26
Apr-21	2353.49	1851.98	1439.50	1765.70	1393.50	1395.23	1261.38	1086.20	1049.35	698.66	14294.98
May-21	2290.79	1822.95	1474.98	1704.16	1588.85	1342.18	1505.79	1118.05	1120.35	685.89	14653.98
Jun-21	2340.58	2140.20	1557.93	1832.60	1580.41	1462.13	1577.81	1048.78	1171.50	769.28	15481.20
Jul-21	2462.98	1906.60	1511.53	1905.99	1616.60	1476.54	1471.16	1048.90	1115.45	706.40	15222.14
Aug-21	2319.15	1604.60	1423.23	1847.76	1597.28	1418.06	1327.80	1024.80	1079.20	631.76	14273.64
Sep-21	2363.18	1856.80	1446.13	1892.19	1495.99	1406.80	1088.11	1053.71	1133.63	625.65	14362.18

Oct-21	2346.52	1969.98	1417.88	1867.31	1461.16	1282.91	1055.15	1154.15	1074.33	632.88	14262.25
Nov-21	2330.73	1891.89	1401.53	1866.38	1549.46	1355.95	1220.31	1050.56	1142.15	845.86	14654.82
Dec-21	2401.25	2064.48	1450.85	1867.19	1668.38	1398.73	1245.93	1161.11	1179.15	769.65	15206.70
Jan-22	2259.21	1943.34	1336.03	1779.18	1505.43	1376.63	1119.49	1127.86	1019.00	693.88	14160.02
Feb-22	2249.20	1786.51	1157.53	1724.69	1386.79	1366.04	1137.43	1011.68	987.60	726.86	13534.32
Mar-22	2615.05	2074.70	1605.40	2006.88	1750.80	1427.39	1556.86	1253.76	1155.85	854.81	16301.50
Apr-22	2601.38	1992.69	1457.33	1889.81	1509.14	1523.56	1390.55	1099.45	1016.68	772.58	15253.15
May-22	2567.51	2054.18	1505.75	2077.30	1713.50	1553.19	1424.31	1132.21	1134.63	693.88	15856.45
Jun-22	2399.96	1961.89	1525.15	2026.18	1512.36	1356.63	1227.26	1424.99	1071.75	697.55	15203.71
Jul-22	2575.20	1817.68	1398.00	1900.78	1544.28	1418.03	1105.19	1061.78	992.40	732.54	14545.85
Total	149562.61	114768.70	111688.80	104472.51	88703.98	82358.91	80588.43	66748.59	63218.29	41997.29	

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	NHS London	NHS North West	NHS Yorkshire and the Humber	NHS West Midlands	NHS East of England	NHS South Central	NHS East Midlands	NHS South West	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	181834.00	158770.00	168066.00	108755.00	104050.00	91874.00	98149.00	83827.00	65193.00	52887.00	1113405.00
May-17	190994.00	174647.00	175232.00	117172.00	104706.00	100964.00	102098.00	94865.00	67081.00	56329.00	1184088.00
Jun-17	180031.00	157936.00	164336.00	113772.00	99606.00	95476.00	100482.00	95166.00	64275.00	53912.00	1124992.00
Jul-17	171357.00	151441.00	170555.00	109752.00	94972.00	95747.00	94894.00	84096.00	63114.00	54463.00	1090391.00
Aug-17	174634.00	156292.00	167178.00	111227.00	100208.00	90958.00	103801.00	91263.00	66689.00	54232.00	1116482.00
Sep-17	171269.00	156139.00	162724.00	108357.00	93002.00	89573.00	98742.00	83072.00	63509.00	50330.00	1076717.00
Oct-17	181330.00	159737.00	167251.00	113230.00	101340.00	96570.00	102657.00	88693.00	66223.00	51400.00	1128431.00
Nov-17	182291.00	160256.00	181558.00	117500.00	104562.00	100362.00	101387.00	93274.00	69413.00	51533.00	1162136.00
Dec-17	188413.00	165315.00	171349.00	122491.00	101795.00	101080.00	101423.00	94726.00	75819.00	58382.00	1180793.00
Jan-18	190181.00	173068.00	189675.00	122132.00	113630.00	103113.00	107371.50	97426.00	73198.00	60645.00	1230439.50
Feb-18	171799.00	151636.00	166192.00	111589.00	95678.00	92318.00	95043.50	87325.00	66003.00	52388.00	1089971.50
Mar-18	201153.50	175143.00	174808.00	123826.00	113897.00	98143.00	98372.00	96417.00	71758.00	57577.00	1211094.50

Apr-18	178917.00	160598.00	161070.00	119231.00	101410.00	96165.00	96751.00	91888.00	63892.00	52074.00	1121996.00
May-18	191343.00	171480.00	166156.00	121735.00	107072.00	102590.00	103486.00	99571.00	67785.00	56397.00	1187615.00
Jun-18	179108.00	159317.00	159471.00	114837.00	104373.00	98968.00	94426.00	87981.00	60492.00	50676.00	1109649.00
Jul-18	179700.46	158760.00	175963.00	111296.00	102477.00	92855.00	78737.00	90620.00	59813.00	53453.00	1103674.46
Aug-18	172648.00	154895.00	165458.00	114685.00	98741.00	91909.00	93428.00	101559.00	69293.00	54449.00	1117065.00
Sep-18	160424.00	145632.00	160771.80	103703.00	91489.00	85603.00	85125.00	81527.00	64220.00	46639.00	1025133.80
Oct-18	185562.00	163553.00	177580.00	124773.00	103534.00	106521.00	88452.00	99985.00	69807.00	51177.00	1170944.00
Nov-18	186939.00	161155.00	176703.00	120800.00	110164.00	96473.00	98143.00	86841.00	68320.00	51592.00	1157130.00
Dec-18	181846.00	165580.00	171385.00	124975.00	103504.00	99159.00	98686.00	97837.00	65643.00	53138.00	1161753.00
Jan-19	185400.00	169373.00	176741.00	132280.00	104476.00	103443.00	108835.00	95454.00	73634.00	53007.00	1202643.00
Feb-19	166248.04	150422.00	160651.00	114676.00	92479.00	95242.00	90671.00	89528.00	66332.00	52588.00	1078837.04
Mar-19	180080.76	153413.00	130813.00	118275.00	93499.00	94820.00	93590.00	98524.00	65923.00	55744.00	1084681.76
Apr-19	182966.00	160636.00	124297.00	117386.00	108163.00	101109.00	88465.00	99959.00	70136.00	56615.00	1109732.00
May-19	190197.00	161844.00	135633.00	122766.00	108423.00	105291.00	109482.00	95839.00	72251.00	60211.00	1161937.00
Jun-19	168363.00	147163.00	120790.00	115546.00	99205.00	91936.00	94666.00	87907.00	65046.00	53114.00	1043736.00

Jul-19	184986.00	169343.00	126059.00	128198.00	107745.00	104440.00	107348.00	91745.00	70707.00	57656.00	1148227.00
Aug-19	167603.00	154911.00	113576.00	119518.00	99276.00	96570.00	100236.00	94454.00	68996.00	56650.00	1071790.00
Sep-19	171149.00	155333.00	116229.00	112213.00	100350.00	98229.00	100744.00	90987.00	66639.00	52950.00	1064823.00
Oct-19	190484.00	166955.00	126855.00	133125.00	114253.00	111362.00	111047.00	98951.00	71871.00	57364.00	1182267.00
Nov-19	179488.00	161564.00	125447.00	122661.00	108002.00	103268.00	96870.00	104387.00	71673.00	55308.00	1128668.00
Dec-19	197151.00	170946.00	141281.00	127763.00	111382.00	113284.00	106747.00	101646.00	76184.00	59199.00	1205583.00
Jan-20	192145.00	168124.00	131056.00	132226.00	114840.00	107268.00	112605.00	104688.00	72144.00	58254.00	1193350.00
Feb-20	174268.00	158942.00	119934.00	120323.00	102837.00	102198.00	98542.00	95754.00	62960.00	55352.00	1091110.00
Mar-20	183558.00	161619.00	122928.00	124944.00	107961.00	104170.00	105137.00	99864.00	66287.00	56996.00	1133464.00
Apr-20	125059.00	119635.00	85850.00	78491.00	69804.00	78583.00	70245.00	64022.00	52152.00	39236.00	783077.00
May-20	124259.00	128804.00	93622.00	90001.00	82313.00	91464.00	75840.00	73276.00	57468.00	44843.00	861890.00
Jun-20	144757.00	150311.00	107036.00	104587.00	95252.00	91426.00	87984.00	86035.00	60932.00	48271.00	976591.00
Jul-20	170408.00	160216.00	114509.00	106159.00	103919.00	98665.00	92376.00	94815.00	65058.00	52081.00	1058206.00
Aug-20	147875.00	141681.00	103813.00	98170.00	90030.00	86504.00	82210.00	81561.00	56826.00	46277.00	934947.00
Sep-20	161539.00	159180.00	113309.00	111405.00	103593.00	99035.00	95531.00	91686.00	66871.00	52640.00	1054789.00

Oct-20	170776.00	168046.00	119797.00	114826.00	111558.00	101210.00	96182.00	91266.00	68645.00	56760.00	1099066.00
Nov-20	166652.00	156761.00	111176.00	109660.00	102105.00	99126.00	91131.00	89159.00	61538.00	58349.00	1045657.00
Dec-20	195596.00	174927.00	118541.00	116952.00	110517.00	113450.00	102162.00	96603.00	73319.00	57424.00	1159491.00
Jan-21	173622.00	162709.00	113017.00	106582.00	98646.00	107758.00	95661.00	93195.00	59459.00	53057.00	1063706.00
Feb-21	150389.00	147426.00	105658.00	102396.00	95486.00	89626.00	88684.00	86660.00	59881.00	51193.00	977399.00
Mar-21	176005.00	174226.00	128989.00	123236.00	120415.00	111122.00	103135.00	114115.00	70206.00	61851.00	1183300.00
Apr-21	183475.00	167833.00	118198.00	119009.00	115090.00	111594.00	98422.00	102678.00	68699.00	61382.00	1146380.00
May-21	181199.00	169805.00	122970.00	114591.00	106054.00	112365.00	98341.00	99245.00	68980.00	63540.00	1137090.00
Jun-21	185116.00	176983.00	123930.00	115467.00	114895.00	110627.00	106000.00	108753.00	71337.00	58276.00	1171384.00
Jul-21	189454.00	165007.00	121099.00	110009.00	113166.00	110473.00	102743.00	100578.00	68037.00	58395.00	1138961.00
Aug-21	168175.12	158694.00	117190.00	106947.00	104504.00	101509.00	95790.00	94699.00	69787.00	55797.00	1073092.12
Sep-21	179657.07	165296.00	119198.00	114974.00	108982.00	103511.00	96144.00	97810.00	70783.00	55227.00	1111582.07
Oct-21	175729.06	168502.00	120500.00	114370.00	105829.00	98000.00	100311.00	96617.00	71953.00	56308.00	1108119.06
Nov-21	192737.12	175605.00	125562.00	118078.00	108077.00	110258.00	105419.00	105402.00	73448.00	63091.00	1177677.12
Dec-21	184978.07	184838.00	130113.00	124859.00	116250.00	114740.00	109563.00	105302.00	81551.00	61661.00	1213855.07

Jan-22	177341.06	170475.00	122800.00	113721.50	107974.00	107157.00	102779.00	98254.00	70379.00	58894.00	1129774.56
Feb-22	178439.17	167366.00	116696.00	111036.00	103311.00	100572.00	94607.00	94848.00	67367.00	62359.00	1096601.17
Mar-22	195669.00	190077.00	133049.00	129631.00	124951.00	122078.00	108677.00	112569.00	78194.00	65477.00	1260372.00
Apr-22	186691.00	161836.00	122955.00	115726.00	113721.00	104278.00	103722.00	105784.00	74802.00	60344.00	1149859.00
May-22	196457.00	187498.00	126931.00	124670.00	119557.00	111979.00	110468.00	110231.00	79081.00	61848.00	1228720.00
Jun-22	180582.00	170713.00	125078.00	108359.00	106949.00	95796.00	103472.00	100474.00	71679.00	56744.00	1119846.00
Jul-22	163498.00	170046.00	114801.00	102477.00	103667.00	86537.00	95456.00	97727.00	64313.00	55423.00	1053945.00
Total	11341995.43	10386434.00	8822158.80	7384127.50	6679716.00	6428494.00	6279694.00	6071010.00	4345068.00	3541429.00	

Rivaroxaban

	NHS London	NHS East of England	NHS Yorkshire and the Humber	NHS South West	NHS South East Coast	NHS West Midlands	NHS South Central	NHS North West	NHS East Midlands	NHS North East	Total (dosage)
Apr-17	113383.00	64402.00	63982.00	60958.00	53123.00	50148.00	48886.00	50330.00	50087.00	26037.00	581336.00
May-17	121544.00	73648.00	68624.00	64453.00	57741.00	58571.00	51120.00	55888.00	58543.00	26352.00	636484.00
Jun-17	124896.00	72665.00	65560.00	62596.00	54129.00	56849.00	55711.00	53755.00	59026.00	26911.00	632098.00
Jul-17	120373.00	73324.00	65243.00	61553.00	55162.00	53918.00	47946.00	54683.00	57150.00	22471.00	611823.00
Aug-17	118602.00	75814.00	61176.00	61363.00	54407.00	62363.00	56389.00	53418.00	59801.00	26715.00	630048.00
Sep-17	116396.00	75464.00	61941.00	66903.00	56253.60	49988.00	41526.00	52620.00	61268.00	24441.00	606800.60
Oct-17	120409.00	79880.00	66461.00	67535.00	60736.00	62840.00	50925.00	55797.00	61363.00	27138.00	653084.00
Nov-17	121992.00	76982.00	64551.00	64940.00	57500.00	58941.00	49996.00	56951.00	59417.00	26715.00	637985.00
Dec-17	119348.00	73651.00	68191.00	67570.00	59969.00	56614.00	47292.00	52365.00	58629.00	27380.00	631009.00
Jan-18	126816.00	84529.00	69236.00	69240.00	64369.00	62046.00	53616.00	58255.00	61813.00	28275.00	678195.00
Feb-18	108468.00	74086.00	65925.00	65000.00	57540.00	55327.00	49751.00	49889.00	60031.00	25786.00	611803.00
Mar-18	120744.00	84448.00	69194.00	67307.00	60084.00	61327.00	48269.00	54883.00	67014.00	28040.00	661310.00

Apr-18	110895.00	79668.00	67433.00	59705.00	54641.00	55276.00	43362.00	54473.00	60677.00	27066.00	613196.00
May-18	118971.00	81572.00	63810.00	64577.00	59260.50	56081.00	47741.00	57111.00	58613.00	25364.00	633100.50
Jun-18	115943.00	78089.00	65003.00	57450.00	56062.00	54200.00	48478.00	51608.00	58050.00	25118.00	610001.00
Jul-18	116374.00	82534.00	67543.00	65880.00	55780.00	54909.00	53150.00	55355.00	54322.00	27324.00	633171.00
Aug-18	122461.00	82695.00	69681.00	66425.00	55893.00	58306.00	47081.00	58531.00	60771.00	28141.00	649985.00
Sep-18	111102.00	75439.00	68204.00	61785.00	51144.00	53902.00	43249.00	54452.00	50275.00	24110.00	593662.00
Oct-18	129100.00	83301.00	73227.00	66495.00	57561.00	59647.00	49447.00	57536.00	60676.00	25889.00	662879.00
Nov-18	122534.00	82727.00	68525.00	61376.00	54022.00	59984.00	51589.00	55649.00	60492.00	24210.00	641108.00
Dec-18	112365.00	87522.00	71061.00	62981.00	55433.00	57661.00	47592.00	54373.00	58025.00	25914.00	632927.00
Jan-19	121383.00	85164.00	68954.00	64380.00	54457.00	65419.00	56883.00	58082.00	65849.00	28521.00	669092.00
Feb-19	119218.00	76983.00	66442.00	56504.00	55841.00	56451.00	46518.00	50346.00	55320.00	23740.00	607363.00
Mar-19	122544.00	85374.00	64103.00	62253.00	59129.00	62408.00	47579.00	52332.00	62553.00	28122.00	646397.00
Apr-19	110638.00	83635.00	65761.00	60370.00	53669.00	61070.00	52729.00	53820.00	58960.00	29013.00	629665.00
May-19	115151.00	90039.00	70110.00	64647.00	55384.00	64136.00	51197.00	56443.00	59802.00	26869.00	653778.00
Jun-19	108272.00	83758.00	65767.00	58148.00	51731.00	55084.00	57003.00	52599.00	53653.00	27561.00	613576.00

Jul-19	122802.00	89604.00	67739.00	67219.00	56097.00	64798.00	55751.00	55380.00	56045.00	40193.00	675628.00
Aug-19	114357.00	84469.00	62041.00	68466.00	53906.00	57533.00	52170.00	53544.00	55397.00	28832.00	630715.00
Sep-19	112326.00	83336.00	63721.00	57988.00	53004.00	56766.00	50437.00	51638.00	52449.00	28281.00	609946.00
Oct-19	127622.00	90404.00	65940.00	63537.00	59238.00	63541.00	57473.00	59174.00	55752.00	27992.00	670673.00
Nov-19	121746.00	83659.00	64658.00	69650.00	55042.00	64345.00	61354.00	52056.00	50806.00	28688.00	652004.00
Dec-19	125937.00	88175.00	65255.00	66518.00	59623.00	66440.00	60410.00	59129.00	54202.00	29838.00	675527.00
Jan-20	146658.00	91511.00	67642.00	66923.00	59171.00	71126.00	56686.00	59699.00	52569.00	29927.00	701912.00
Feb-20	123270.00	80725.00	62814.00	56214.00	53963.00	62403.00	53697.00	52892.00	45823.00	27707.00	619508.00
Mar-20	121088.00	77253.00	63153.00	57508.00	55609.00	61001.00	55207.00	52611.00	45631.00	29239.00	618300.00
Apr-20	97243.00	61304.00	48918.00	44005.00	44176.00	47182.00	41976.00	44664.00	35946.00	25819.00	491233.00
May-20	98389.00	67739.00	50107.00	47937.00	45911.00	47372.00	53100.00	44181.00	38820.00	27694.00	521250.00
Jun-20	103027.00	75258.00	52935.00	54306.00	48506.00	48387.00	46096.00	45731.00	41674.00	26259.00	542179.00
Jul-20	117991.00	79377.00	58183.00	56565.00	52993.00	51807.00	46875.00	49171.00	38159.00	25554.00	576675.00
Aug-20	106997.00	72013.00	51018.00	52121.00	52564.00	45914.00	44966.00	45417.00	40044.00	22518.00	533572.00
Sep-20	124333.00	81568.00	53818.00	63594.00	57649.00	51743.00	55736.00	51365.00	46999.00	27811.00	614616.00

Oct-20	116889.90	85802.00	59161.00	59924.00	60606.00	54872.00	62063.00	54174.00	12731.00	34558.00	600780.90
Nov-20	122481.90	82921.67	67961.00	56519.00	57390.00	52938.00	57788.00	50909.00	41841.00	37988.00	628737.57
Dec-20	141078.00	88312.00	61521.00	63166.00	67145.00	60623.00	72775.00	59351.00	49370.00	37367.00	700708.00
Jan-21	179999.00	86874.00	66120.00	65336.00	71433.00	54327.00	55003.00	55174.00	47833.00	44533.00	726632.00
Feb-21	139382.90	84380.00	60082.00	60152.00	59680.00	50937.00	49062.00	49739.00	43719.00	35709.00	632842.90
Mar-21	167414.00	86465.00	61901.00	68340.00	61922.00	55011.00	62100.00	64432.00	46513.00	32336.00	706434.00
Apr-21	124160.10	87717.00	66029.00	55785.00	53536.00	56420.00	54416.00	55514.00	43960.00	33757.00	631294.10
May-21	122241.00	88498.00	64202.00	61791.00	57657.00	53520.00	60239.00	55893.00	43879.00	27224.00	635144.00
Jun-21	154185.40	96073.00	66240.00	67941.00	56264.00	58770.00	68151.00	60562.00	47026.00	31888.00	707100.40
Jul-21	134767.90	97763.00	69541.00	69043.00	60836.00	59180.00	72237.00	61687.00	44166.00	37672.00	706892.90
Aug-21	133453.06	93421.00	65044.00	58530.00	59799.00	58590.00	65305.00	59594.00	43161.00	34483.00	671380.06
Sep-21	147445.05	95068.00	66751.00	61010.00	59362.00	58294.00	73236.00	61509.00	41819.00	36256.00	700750.05
Oct-21	131401.03	89927.00	66775.00	62426.00	59755.00	56106.00	74888.00	58909.00	42730.00	35382.00	678299.03
Nov-21	139183.05	91066.00	71405.00	66550.00	60374.00	58088.00	67891.00	63321.00	45746.00	35131.00	698755.05
Dec-21	134493.93	99277.00	75225.00	67350.00	65595.00	59725.00	69116.00	63750.00	45714.00	36111.00	716356.93

Jan-22	134939.12	83170.00	79101.00	67787.00	59300.00	58802.00	70085.00	59300.00	46230.00	34162.00	692876.12
Feb-22	125229.17	81771.00	69927.00	61164.00	56711.00	51087.00	59086.00	56966.00	39117.00	33031.00	634089.17
Mar-22	138172.00	94218.00	77423.00	65068.00	65132.00	57527.00	71678.00	61658.00	42743.00	38214.00	711833.00
Apr-22	127563.00	89509.00	67559.00	63125.00	61298.00	47818.00	62902.00	53480.00	41448.00	31999.00	646701.00
May-22	140902.00	96159.00	69969.00	61359.00	63290.00	53034.00	73507.00	56618.00	42564.00	30824.00	688226.00
Jun-22	124712.00	93562.00	65202.00	53492.00	52688.00	50732.00	64723.00	58184.00	38435.00	34032.00	635762.00
Jul-22	133823.20	86683.00	68007.00	56395.00	51057.00	47351.00	50999.00	60589.00	37603.00	30896.00	623403.20
Total	7967624.71	5332424.67	4188796.00	3977198.00	3649303.10	3637576.00	3554209.00	3529509.00	3230844.00	1903128.00	

Streptokinase

	NHS London	NHS North West	NHS South East Coast	NHS Yorkshire and the Humber	NHS North East	NHS East of England	NHS West Midlands	NHS East Midlands	NHS South Central	NHS South West	Total (dosage)
Apr-17	12.75	3.00	1.50	1.00	10.25	10.50	6.50		10.25	10.75	66.50
May-17	14.00	6.25	-1.00	2.25	-3.50	0.75	7.25	1.50	13.25	6.00	46.75
Jun-17	6.75	20.00	6.75	6.50	7.00	4.50	7.25	4.50	13.25	18.75	95.25
Jul-17	21.75	23.75	9.25	5.50	1.75	1.50	-13.50		8.50	10.00	68.50
Aug-17	14.00	6.00	20.25	1.00	12.25	4.25	1.50		8.75	2.25	70.25
Sep-17	21.00	20.00	16.50	17.00	23.00	12.00	26.75	18.25	15.75	15.50	185.75
Oct-17	14.75	2.25	16.50	12.00	5.25	7.75	-0.50	3.25	6.50	19.75	87.50
Nov-17	23.75	20.25	12.25	3.50	27.50	13.50	7.50	8.00	7.75	12.50	136.50
Dec-17	10.50	14.75	14.00	13.50	32.00	3.00	4.50	15.00	7.00	8.50	122.75
Jan-18	29.50	5.25	16.00	-2.75	1.00	-3.50	1.00	0.25	18.75	5.50	71.00
Feb-18	19.25	1.75	16.50	1.50	1.50	-0.25	5.00	12.00	8.25	4.00	69.50
Mar-18	7.25	15.25	9.75	-1.25	0.75	2.50	6.00	1.50	10.75	4.00	56.50
Apr-18	-3.25	5.25	2.25	9.75	0.25	5.25	1.00	5.50	4.25	9.75	40.00
May-18	26.00	17.25	12.00	10.50	12.75	7.00	4.00	1.75	20.75	7.25	119.25
Jun-18	11.25	0.25	4.75	10.25	1.75		2.50	2.50	7.50	1.75	42.50
Jul-18	20.50	16.25	15.25	11.25	6.50	2.25	4.75	0.00	7.75	9.00	93.50
Aug-18	15.25	8.75	14.50	6.00	11.00	8.00	1.50	3.00	12.25	8.00	88.25
Sep-18	14.50	6.00	7.25	9.25	2.50	3.25	2.25	0.00	0.25	0.50	45.75
Oct-18	12.25	8.25	6.75	4.50	6.50	7.50	0.50		9.00	2.75	58.00
Nov-18	34.25	9.25	14.00	4.00	0.25	3.25	0.50		9.25	1.25	76.00
Dec-18	39.25	11.50	11.00	0.50	4.00		1.50	0.25	6.50	4.75	79.25
Jan-19	-18.50	5.25	12.00	1.50	1.75	6.00	3.50		7.75	5.25	24.50
Feb-19	5.00	2.25	1.25	1.25	1.00	5.75	1.50		11.75	16.25	46.00
Mar-19	31.75	8.25	7.75	13.00	12.50	19.50	5.50	2.25	13.50	16.75	130.75

Apr-19	25.00	27.50	20.75	14.25	6.75	20.00	2.75	5.25	24.25	16.25	162.75
May-19	25.00	19.75	14.00	11.75	11.00	12.50	8.00	4.75	18.75	10.75	136.25
Jun-19	8.75	20.00	14.75	12.75		6.00	7.75	10.50	16.00	3.25	99.75
Jul-19	40.50	35.25	22.75	30.00	50.75	12.00	33.50	31.75	19.75	6.25	282.50
Aug-19	10.00	32.00	9.25	30.75	19.75	9.00	0.00	4.50	7.00	35.25	157.50
Sep-19	22.75	6.00	7.50	3.75	2.75	7.50	0.50	-6.00	8.00	6.00	58.75
Oct-19	3.50	2.75	15.25	3.25	4.50	1.50	2.25	3.00	10.00	16.50	62.50
Nov-19	21.00	3.25	4.25	2.75	2.25	5.50	1.50		11.50	5.50	57.50
Dec-19	20.75		0.25	4.00	0.25	0.50		1.50	16.00	21.00	64.25
Jan-20	7.75	2.00	8.75	2.50	-1.50	6.00	2.25	4.50	23.50	1.75	57.50
Feb-20	5.75	7.25	9.25	6.75	1.50	1.50	0.75	1.50	3.25	4.00	41.50
Mar-20	16.00	12.75	11.25	9.75	3.25	2.75	3.00	0.00	3.00	16.75	78.50
Apr-20	9.25	4.75	11.75	11.00	2.00	1.50	2.00	10.50	7.50	0.25	60.50
May-20	11.25	11.75	9.00	1.75	0.50	1.75	0.00		2.00	4.50	42.50
Jun-20	-4.50	3.00	3.25	3.00	1.75	4.75	-8.75		11.00	0.00	13.50
Jul-20	3.00	2.75	1.50	-2.25	4.25	1.75		1.50	6.25	1.75	20.50
Aug-20	10.25	-4.50	3.25	0.25	3.25	1.75	10.00		0.50		24.75
Sep-20	4.75		0.50	6.75	1.50		-0.50	1.50	5.50		20.00
Oct-20	7.00	4.00	0.25	2.25	-1.50		1.75	6.00	0.50	0.50	20.75
Nov-20	7.25	1.50	7.00	0.50	1.00	0.00			0.75	5.50	23.50
Dec-20	1.50		4.75	2.00	1.50	1.50	-0.25		2.25	0.75	14.00
Jan-21	5.00	3.25	5.75	11.25	8.75	0.75	1.25	3.00	3.25	5.00	47.25
Feb-21	3.25	5.50	3.00	0.25	1.50	7.00	-1.25	0.50	4.00	7.00	30.75
Mar-21	22.00	7.75	3.75	7.00	1.25	2.25	-3.00	1.50	3.25	3.50	49.25
Apr-21	10.00	2.25	0.50	0.25	3.50	3.00	2.00		2.00		23.50
May-21	5.00	23.50	9.50	1.75		3.00	3.50		0.00	7.50	53.75
Jun-21	21.25	20.75	29.50	7.50	15.50	9.00	9.25	-3.00	12.25	22.50	144.50
Jul-21	7.75	15.75	0.25	9.00	3.00	3.25	7.50	0.00	5.00	6.00	57.50
Aug-21	10.00	10.25	3.00	4.50	3.00	7.50	3.00	1.50	1.25	3.75	47.75
Sep-21	16.00	12.50	4.25	6.50	4.50	8.50	0.75	3.50	12.25	5.00	73.75

Oct-21	14.75	1.50	6.75	5.50	1.25	3.25	1.50	0.25	19.25	3.75	57.75
Nov-21	3.25	4.75	6.25		6.25	10.25	1.75		15.25	0.75	48.50
Dec-21	7.50	14.50	12.25	5.25	0.75	1.50	8.50	1.50	10.00	2.00	63.75
Jan-22	9.75	20.25	13.50	15.75	24.25	5.25	9.00	18.00	3.50	11.00	130.25
Feb-22	10.50	34.25	14.00	15.50	6.00	3.00	1.50	12.00	1.75	25.50	124.00
Mar-22	8.25	12.00	12.75	7.00	3.00	3.75	6.00	3.00	3.50	5.75	65.00
Apr-22	19.75	13.75	4.00	-1.50	3.00	1.50		1.50	3.00	4.75	49.75
May-22	2.00	3.00	0.75	7.75	1.50	3.00	2.00		3.00		23.00
Jun-22	10.25	7.75	7.75	3.00	2.00	1.50	3.00	6.00	2.00	1.50	44.75
Jul-22	13.75	9.00	1.75	1.75	1.50	0.25	0.00	0.00	1.00	2.00	31.00
Total	840.00	651.00	565.50	407.00	385.50	299.50	211.00	209.50	542.00	474.50	

Tenecteplase

	NHS Yorkshire and the Humber	NHS East of England	NHS South East Coast	NHS West Midlands	NHS South West	NHS East Midlands	NHS North East	NHS North West	NHS London	NHS South Central	Total (dosage)
Apr-17	0.16	0.11	0.19	0.22	0.14	0.01	0.05	0.44	0.10	0.16	1.59
May-17	0.08	0.16	0.23	0.09	0.09	0.00	0.04	0.15	0.15	0.08	1.05
Jun-17	0.07	0.05	0.10	0.09	0.06	0.03	0.00	0.17	0.10	0.15	0.81
Jul-17	0.10	0.10	0.04	0.05	0.05	-0.03	0.02	0.03	0.06	0.02	0.43
Aug-17	0.11	0.05	0.01	0.08		0.04	0.02	0.07	0.07	0.03	0.49
Sep-17	0.16	0.21	0.18	-0.01	0.04	0.11	0.05	0.27	0.04	0.07	1.12
Oct-17	0.11	0.10	0.07	0.01	0.04	0.02	0.05	0.21	0.27	0.15	1.02
Nov-17	0.17	0.13	0.09	0.09	0.07	0.09	0.07	0.35	0.16	0.13	1.34
Dec-17	0.12	0.16	0.10	0.14	0.15	0.03	0.06	0.20	0.12	0.13	1.20
Jan-18	0.10	0.16	0.10	0.09	0.04	0.07	0.01	0.20	0.14	0.09	1.00
Feb-18	0.03	0.11	0.12	0.04	0.08		0.02	0.21	0.08	0.04	0.72
Mar-18	0.12	0.10	0.17	0.04	0.12	0.10	0.08	0.37	0.17	0.16	1.45
Apr-18	0.05	0.27	0.10	0.09	0.12	0.02	0.10	0.21	0.10	0.13	1.19
May-18	0.03	0.03	0.08	0.01	0.05	0.02	-0.01	0.15	0.09	0.04	0.49
Jun-18	0.01	0.09	0.12		0.05		0.03	0.03	0.16	0.04	0.52
Jul-18	0.04	0.10	0.05		0.06	0.03	0.01	0.09	0.02	0.04	0.44
Aug-18	0.07	0.16	0.07	0.01	0.05	0.08		0.19	0.16	0.07	0.86
Sep-18	0.14	0.09	0.11	0.13	0.08	0.02	0.06	0.30	0.16	0.08	1.18
Oct-18	0.04	0.06	0.17	0.08	0.10	0.06	0.03	0.30	0.22	0.08	1.15
Nov-18	0.16	0.09	0.13	0.13	0.10	0.04	0.04	0.34	0.09	0.17	1.29
Dec-18	0.08	0.05	0.15	0.04	0.03	0.13	0.08	0.21	0.28	0.07	1.10
Jan-19	0.11	0.16	0.10	0.06	0.14	0.04	0.03	0.18	0.23	0.07	1.11
Feb-19	0.17	0.17	0.00	0.16	0.06	0.03	0.07	0.31	0.07	0.06	1.10
Mar-19	0.08	0.10	0.15	0.25	0.19	0.13	0.10	0.24	0.11	0.13	1.47

Apr-19	0.12	0.09	0.13		0.11	0.06	0.05	0.25	0.17	0.09	1.06
May-19	0.13	0.16	0.14	0.02	0.12	0.04	0.12	0.36	0.13	0.06	1.27
Jun-19	0.12	0.08	0.07	0.01	0.01	0.01	0.03	0.13	0.13	0.05	0.64
Jul-19	0.02	0.02	0.10	0.12	0.08	0.03	-0.02	0.11	0.13	0.07	0.66
Aug-19	0.07	0.07	0.12	0.04	0.03			0.06	0.05	0.01	0.45
Sep-19	0.06	0.09	0.02	0.03	0.06	0.03	0.01	0.23	0.17	0.03	0.73
Oct-19	0.04	0.11	0.14	0.08	0.06	0.06	0.02	0.28	0.11	0.21	1.11
Nov-19	0.03	0.10	0.12	0.05	0.09	0.02	0.06	0.10	0.09	0.11	0.77
Dec-19	0.10	0.05	0.09	0.02	0.03		0.06	0.17	0.09	0.05	0.66
Jan-20	0.03	0.04	0.08	0.03	0.07	0.08	0.01	0.05	0.15	0.08	0.62
Feb-20	0.04	0.09	0.02	0.00	0.01	-0.01	0.02	0.07	0.05	0.02	0.31
Mar-20	0.29	0.24	0.20	0.40	0.22	0.32	0.08	0.54	0.38	0.29	2.96
Apr-20	0.37	0.16	0.13	0.16	0.10	0.01	0.07	0.51	0.13	0.33	1.97
May-20	0.07	0.02	0.02	0.01	0.01	0.03	0.06	0.21	0.03	0.13	0.59
Jun-20	0.13	0.00	-0.01	-0.03	0.02	0.05	0.00	0.24	0.33	0.09	0.82
Jul-20	0.05	0.04	-0.03	0.04	0.03	0.02	0.04	0.02	0.23	0.02	0.46
Aug-20	0.01	0.08	0.17	0.02	0.09	0.07	0.02	0.13	0.03	0.08	0.70
Sep-20	0.00	0.05	0.01	0.16	0.09	0.00		0.06	0.09	0.05	0.51
Oct-20	0.11	0.05	0.04	0.24	0.04	0.04	0.01	0.10	0.09	0.07	0.79
Nov-20	0.07	0.14	0.11	0.06	0.23	0.02	0.05	0.37	0.34	0.19	1.58
Dec-20	0.10	0.08	0.04	0.20	0.08	0.10	0.01	0.24	0.19	0.15	1.19
Jan-21	-0.03	0.07	-0.02	0.05	0.03	0.01		0.16	0.22	0.10	0.59
Feb-21	0.05	0.07	0.08	0.12	0.07	0.06		0.12	0.13	0.08	0.78
Mar-21	0.13	0.02	0.07	0.08	0.03	0.03	0.05	0.22	0.16	0.27	1.06
Apr-21	0.02	0.08	0.11	0.00	0.08	0.02	-0.01	0.08	0.10	0.17	0.65
May-21	0.10	0.12	0.09	0.01	0.09	0.02	0.02	0.25	0.30	0.09	1.09
Jun-21	0.05	0.05	0.03	0.02	0.06	0.03	0.01	0.21	0.11	0.23	0.80
Jul-21	0.13	0.12	0.07	0.15	0.03	0.03	0.03	0.29	0.12	0.26	1.23
Aug-21	0.11	0.02	0.10	0.40	0.07	0.08	0.02	0.03	0.08	0.21	1.12
Sep-21	0.16	0.02	0.09	0.16	0.07	0.13	0.01	0.22	0.15	0.14	1.15

Oct-21	0.22	0.13	0.08	0.16	0.04		0.02	0.13	0.16	0.04	0.98
Nov-21	0.09	-0.04	0.03	0.12	0.06	0.01		0.25	0.13	0.10	0.75
Dec-21	0.05	0.07	0.06	0.10	0.05	0.10		0.33	0.15	0.06	0.97
Jan-22	0.03	0.02	0.02	0.07	-0.03	0.02	0.01	0.02	0.05	0.07	0.28
Feb-22	0.01	0.04	0.03	-0.01	0.01			0.12	0.04	0.06	0.30
Mar-22	0.03	0.03	0.03	0.02		0.01		0.07	0.00	0.09	0.28
Apr-22	0.01	0.02	0.02	0.01	0.05			0.03	0.13	0.10	0.37
May-22	0.07	0.05	0.01	0.01	0.05	0.00	0.00	0.08	0.06	0.01	0.34
Jun-22	0.07	0.12	0.04	0.15	0.11	0.09	0.04	0.20	0.10	0.09	1.01
Jul-22	0.09	0.02	0.03	-0.06	0.03	0.04	0.01	0.20	0.12	0.05	0.53
Total	5.63	5.59	5.28	5.10	4.37	2.72	1.91	12.45	8.58	6.59	

Verapamil

	NHS North West	NHS London	NHS West Midlands	NHS Yorkshire and the Humber	NHS East of England	NHS South West	NHS East Midlands	NHS South Central	NHS South East Coast	NHS North East	Total (dosage)
Apr-17	1235.34	935.91	708.49	925.02	670.09	495.15	552.24	337.77	436.52	526.73	6823.24
May-17	1261.67	1087.18	706.09	1002.84	724.05	522.40	612.20	500.82	468.03	381.40	7266.65
Jun-17	1188.13	1093.27	1043.70	902.32	640.93	569.72	677.17	346.20	441.67	328.24	7231.35
Jul-17	1050.96	1094.60	869.69	930.99	628.35	477.22	599.18	404.71	437.89	306.26	6799.83
Aug-17	1246.70	1086.62	866.20	897.21	631.29	508.42	554.55	534.80	427.93	345.93	7099.63
Sep-17	1019.86	920.39	966.60	917.51	648.10	484.38	554.48	431.11	342.67	379.25	6664.31
Oct-17	1027.17	1105.15	806.44	955.79	699.13	433.73	558.90	521.38	466.02	406.97	6980.66
Nov-17	1223.89	1051.31	820.50	1091.09	659.24	522.92	760.77	482.96	461.90	346.32	7420.89
Dec-17	1039.49	997.06	863.61	1102.15	745.17	646.87	513.60	392.92	346.38	362.32	7009.54
Jan-18	1307.74	991.33	751.56	1205.28	811.24	645.69	676.81	471.04	477.38	414.56	7752.61
Feb-18	1002.89	931.34	820.91	980.88	729.54	441.77	489.90	439.00	387.64	334.05	6557.89
Mar-18	1160.02	1144.74	912.67	1016.16	651.18	564.49	592.05	485.13	468.96	414.25	7409.63
Apr-18	1001.21	1163.05	701.17	871.21	634.35	513.11	527.28	446.42	344.42	375.08	6577.28
May-18	1006.69	1006.73	741.49	761.81	822.94	662.77	507.02	486.72	448.93	398.17	6843.26
Jun-18	1078.96	905.88	697.66	960.15	628.51	467.10	382.12	443.18	462.21	325.49	6351.23
Jul-18	1170.49	962.31	824.45	977.69	657.84	564.55	430.24	400.97	468.61	400.67	6857.80
Aug-18	1038.36	977.18	738.55	941.89	588.36	550.79	530.51	406.58	392.63	380.33	6545.16
Sep-18	905.33	929.96	724.26	879.91	582.60	622.29	414.38	381.82	385.66	251.23	6077.42
Oct-18	982.04	1223.68	776.43	940.64	638.75	567.77	546.14	486.19	446.09	343.76	6951.46
Nov-18	1121.72	1059.43	755.12	1005.91	531.39	492.75	498.71	468.99	441.23	316.97	6692.18
Dec-18	1162.76	1047.57	793.26	970.13	597.54	495.41	597.19	518.31	506.56	368.97	7057.68
Jan-19	1218.47	1528.70	798.73	1049.53	699.53	649.85	620.75	458.63	564.99	357.44	7946.60
Feb-19	1019.66	986.85	786.14	827.05	711.22	532.81	516.27	448.35	289.01	341.20	6458.54
Mar-19	1055.59	1059.60	951.17	837.42	688.13	550.68	579.71	452.59	386.36	391.48	6952.70

Apr-19	1006.60	915.96	811.23	773.04	717.46	630.22	435.14	447.37	380.78	314.98	6432.77
May-19	1032.34	959.20	906.16	653.27	662.26	671.55	630.01	571.68	307.44	597.11	6991.00
Jun-19	1189.31	901.97	836.31	860.59	490.35	534.44	653.36	490.26	371.23	444.34	6772.13
Jul-19	949.58	984.26	887.39	902.15	663.94	452.32	474.75	440.23	309.90	461.05	6525.55
Aug-19	1058.55	913.57	788.11	682.11	589.12	453.28	436.31	457.41	369.29	351.33	6099.06
Sep-19	1018.05	922.40	805.59	680.56	790.80	513.47	407.03	459.06	415.36	488.07	6500.37
Oct-19	1027.46	1081.30	1079.95	656.93	712.79	634.06	596.14	469.06	452.91	406.62	7117.19
Nov-19	940.32	793.02	770.85	864.91	701.91	534.49	581.97	437.07	484.39	332.16	6441.06
Dec-19	1098.73	1223.70	993.09	828.51	741.94	521.66	500.06	548.55	431.44	391.34	7278.99
Jan-20	922.96	1089.38	991.45	794.60	720.39	550.00	600.63	503.49	563.69	466.88	7203.44
Feb-20	804.44	925.36	887.50	672.53	619.08	474.30	449.20	450.27	336.64	350.57	5969.88
Mar-20	902.96	886.36	676.65	743.18	658.59	494.05	569.46	433.33	411.77	480.13	6256.46
Apr-20	697.84	474.82	628.91	494.58	485.72	388.46	345.54	281.74	289.66	244.80	4332.04
May-20	687.47	597.40	599.38	472.66	508.90	417.65	311.31	376.03	385.21	223.03	4579.03
Jun-20	742.24	783.79	760.19	506.83	685.00	348.97	393.90	368.73	274.84	277.38	5141.85
Jul-20	698.97	707.62	924.01	499.38	498.55	466.41	488.08	315.64	323.56	234.08	5156.27
Aug-20	716.03	663.09	745.29	564.52	666.58	407.87	328.18	273.86	374.64	261.15	5001.19
Sep-20	656.41	603.74	709.47	685.19	560.77	497.12	364.16	329.34	414.10	351.80	5172.09
Oct-20	721.35	647.12	796.94	545.10	534.63	492.76	418.06	378.03	384.29	333.49	5251.75
Nov-20	860.62	747.99	872.57	688.10	600.02	397.53	345.80	443.16	373.58	251.51	5580.86
Dec-20	799.75	708.04	899.25	718.02	609.66	524.20	416.13	433.17	437.32	454.15	5999.66
Jan-21	794.91	635.86	760.13	588.93	506.35	383.58	329.69	358.93	479.07	329.24	5166.67
Feb-21	815.92	567.85	788.70	519.73	495.11	407.05	371.48	400.27	314.37	314.50	4994.95
Mar-21	879.25	820.85	780.13	524.40	633.12	385.31	467.93	357.13	333.02	360.40	5541.52
Apr-21	818.83	820.76	863.99	563.42	553.77	407.78	407.69	376.62	366.82	340.90	5520.56
May-21	1084.90	659.89	791.00	601.32	759.36	498.78	372.58	394.48	426.49	314.76	5903.54
Jun-21	1077.59	765.28	1050.72	707.71	749.82	463.80	436.09	375.84	369.86	259.60	6256.29
Jul-21	916.40	899.60	831.94	636.20	673.42	567.85	475.84	486.51	447.57	324.05	6259.35
Aug-21	995.88	752.47	1021.06	393.34	551.91	466.08	365.47	384.49	296.58	372.44	5599.69
Sep-21	1079.77	951.70	1478.21	685.27	604.94	486.55	336.68	478.03	327.07	434.27	6862.46

Oct-21	980.80	721.99	769.11	520.22	613.31	560.30	426.18	446.57	478.66	384.73	5901.84
Nov-21	1010.61	788.34	794.09	646.05	621.48	489.94	446.19	443.48	366.45	370.13	5976.74
Dec-21	782.73	743.74	782.33	750.18	686.42	429.39	408.14	450.65	496.19	600.64	6130.39
Jan-22	984.71	671.65	699.69	492.95	567.38	404.88	384.67	395.68	383.33	459.72	5444.65
Feb-22	965.21	811.48	935.65	554.46	588.47	395.31	387.81	375.36	382.84	300.03	5696.60
Mar-22	850.69	805.42	757.91	614.85	537.12	341.45	411.30	275.57	494.66	422.66	5511.60
Apr-22	835.70	629.57	842.60	551.33	622.80	506.70	400.87	325.11	365.23	457.94	5537.83
May-22	978.39	772.18	865.44	477.69	684.79	509.65	436.53	399.85	307.16	412.79	5844.45
Jun-22	1003.38	801.48	655.54	612.36	556.93	382.49	447.83	287.59	397.78	408.04	5553.39
Jul-22	867.89	814.57	649.23	527.63	574.25	495.95	399.56	206.66	406.91	212.69	5155.32
Total	62780.51	57254.44	52912.51	48205.23	40818.53	31970.13	30749.79	26872.72	25831.62	23592.40	

Appendix V: UK Yellow Card System. Detailed results of each drug's ROR and PRR values, and their corresponding 95% CI and chi-squared values.

Drug	Total Reports	CV Adverse Events	Non-Adverse Events	ROR	95% CI Lower	95% CI Upper	Chi-square	PRR	95% CI Lower	95% CI Upper	Chi-square
Afatinib	434	9	425	0.42	0.22	0.81	6.44	0.43	0.23	0.83	7.02
Alectinib	160	23	137	3.35	2.15	5.22	30.28	3.01	2.06	4.40	32.36
Amifostine	3	0	3								
Atezolizumab	2133	24	2109	0.22	0.15	0.33	62.92	0.23	0.16	0.35	63.73
Avelumab	843	69	774	1.78	1.39	2.28	20.81	1.72	1.37	2.16	21.56
Bevacizumab	3945	210	3735	1.12	0.98	1.29	2.48	1.12	0.98	1.28	2.60
Brigatinib	130	5	125	0.80	0.33	1.95	0.09	0.80	0.34	1.90	0.25
Cabozantinib	1560	41	1519	0.53	0.39	0.73	15.63	0.55	0.40	0.74	16.11
Carboplatin	5235	318	4917	1.30	1.16	1.46	19.68	1.28	1.15	1.43	19.97
Celecoxib	5039	335	4704	1.44	1.29	1.62	39.62	1.41	1.27	1.57	40.04
Ceritinib	180	8	172	0.93	0.46	1.88	0.00	0.93	0.47	1.83	0.05
Cetuximab	1061	50	1011	0.98	0.74	1.31	0.00	0.99	0.75	1.29	0.01
Cisplatin	3611	225	3386	1.34	1.16	1.53	16.77	1.31	1.16	1.50	17.09
Crizotinib	851	43	808	1.06	0.78	1.44	0.08	1.06	0.79	1.42	0.14
Cyclophosphamide	8394	408	7986	1.02	0.92	1.13	0.10	1.02	0.92	1.12	0.12
Dabrafenib	1767	48	1719	0.55	0.41	0.74	16.35	0.56	0.43	0.75	16.81
Dacomitinib	48	2	46	0.87	0.21	3.57	0.00	0.87	0.22	3.38	0.04
Dasatinib	1289	95	1194	1.59	1.29	1.97	18.56	1.55	1.27	1.88	19.13
Docetaxel	7692	475	7217	1.34	1.21	1.47	34.48	1.32	1.20	1.44	34.80
Doxorubicin	4408	376	4032	1.91	1.71	2.13	139.83	1.83	1.66	2.03	140.68
Durvalumab	286	10	276	0.72	0.38	1.36	0.78	0.73	0.40	1.34	1.04
Entrectinib	56	2	54	0.74	0.18	3.02	0.01	0.75	0.19	2.91	0.18
Epirubicin	1652	173	1479	2.37	2.02	2.78	117.65	2.22	1.93	2.57	118.91
Erlotinib	1155	43	1112	0.77	0.57	1.04	2.65	0.78	0.58	1.04	2.88

Etoposide	3603	165	3438	0.95	0.81	1.12	0.29	0.96	0.82	1.11	0.34
Everolimus	3949	67	3882	0.34	0.26	0.43	84.54	0.35	0.27	0.44	85.24
Gefitinib	439	21	418	1.00	0.64	1.55	0.00	1.00	0.66	1.52	0.00
Gemcitabine	2430	160	2270	1.41	1.20	1.66	17.24	1.39	1.19	1.61	17.64
Ifosfamide	1491	54	1437	0.75	0.57	0.98	4.22	0.75	0.58	0.98	4.47
Ipilimumab	2305	86	2219	0.77	0.62	0.95	5.47	0.78	0.63	0.96	5.71
Irinotecan	1729	76	1653	0.91	0.73	1.15	0.50	0.92	0.74	1.15	0.58
Larotrectinib	46	1	45	0.44	0.06	3.21	0.23	0.45	0.07	3.16	0.69
Lorlatinib	183	5	178	0.56	0.23	1.36	1.27	0.57	0.24	1.36	1.69
Lurbinectedin	2	0	2								
Methotrexate	18709	418	18291	0.42	0.38	0.46	311.89	0.43	0.39	0.47	312.54
Nintedanib	995	65	930	1.40	1.08	1.80	6.36	1.37	1.08	1.73	6.74
Nivolumab	3199	132	3067	0.85	0.72	1.02	2.96	0.86	0.73	1.02	3.11
Osimertinib	437	21	416	1.00	0.65	1.56	0.00	1.00	0.66	1.53	0.00
Paclitaxel	5211	336	4875	1.39	1.24	1.56	32.66	1.37	1.23	1.52	33.04
Panitumumab	617	9	608	0.29	0.15	0.57	14.32	0.30	0.16	0.58	15.05
Pembrolizumab	3292	143	3149	0.90	0.76	1.07	1.34	0.91	0.77	1.07	1.43
Pemetrexed	1359	90	1269	1.42	1.14	1.76	9.80	1.39	1.14	1.70	10.20
Pralsetinib	33	0	33								
Ramucirumab	40	0	40								
Selpercatinib	172	14	158	1.77	1.02	3.05	3.55	1.70	1.03	2.82	4.26
Sorafenib	820	37	783	0.94	0.68	1.31	0.08	0.94	0.69	1.29	0.13
Sotorasib	130	0	130								
Sunitinib	2555	147	2408	1.22	1.03	1.44	5.17	1.21	1.03	1.42	5.39
Tepotinib	77	2	75	0.53	0.13	2.16	0.40	0.54	0.14	2.13	0.81
Topotecan	670	17	653	0.52	0.32	0.84	6.97	0.53	0.33	0.85	7.46
Trametinib	1581	37	1544	0.47	0.34	0.66	20.44	0.49	0.35	0.67	20.98
Trastuzumab	13863	718	13145	1.10	1.01	1.19	5.25	1.09	1.01	1.18	5.35
Veliparib	21	0	21								
Vemurafenib	569	25	544	0.91	0.61	1.37	0.11	0.92	0.63	1.35	0.19

Vincristine	3835	181	3654	0.99	0.85	1.15	0.02	0.99	0.85	1.14	0.04
Vinorelbine	1920	114	1806	1.26	1.04	1.53	5.45	1.25	1.04	1.49	5.70

Appendix VI: Sub-group analysis of the UK Yellow Card System

Drug	Age	Sex	ROR	ROR 95% CI Lower	ROR 95% CI Upper	PRR	PRR 95% CI Lower	PRR 95% CI Upper	Chi-squared
Afatinib	40.00s	Male	1.81	0.23	14.02	1.74	0.27	11.38	0.33
Afatinib	50.00s	Female	2.34	0.54	10.14	2.20	0.59	8.17	1.38
Afatinib	60.00s	Male	1.81	0.23	14.02	1.74	0.27	11.38	0.33
Afatinib	80.00s	Female	2.21	0.28	17.46	2.09	0.33	13.42	0.60
Afatinib	80.00s	Male	1.22	0.38	3.91	1.21	0.40	3.62	0.11
Afatinib	90.00s	Male				20.91	20.40	21.43	19.91
Alectinib	30.00s	Female	3.98	0.47	34.09	3.48	0.58	20.86	1.86
Alectinib	40.00s	Female	2.21	0.51	9.54	2.09	0.56	7.79	1.20
Alectinib	50.00s	Female	6.64	1.80	24.53	5.23	1.96	13.94	10.77
Alectinib	50.00s	Male	13.95	5.31	36.66	8.62	4.88	15.22	49.44
Alectinib	60.00s	Female	2.49	0.31	19.90	2.32	0.37	14.75	0.79
Alectinib	60.00s	Male	1.73	0.41	7.34	1.67	0.44	6.32	0.57
Alectinib	Unknown	Male	4.53	1.71	11.96	3.87	1.76	8.55	11.19
Alectinib	Unknown	Unknown	5.69	1.18	27.39	4.65	1.37	15.78	6.01
Atezolizumab	40.00s	Male	0.35	0.05	2.52	0.36	0.05	2.52	1.19
Atezolizumab	50.00s	Female	0.08	0.03	0.21	0.08	0.03	0.22	43.28
Atezolizumab	50.00s	Male	1.57	0.49	5.09	1.53	0.51	4.55	0.58
Atezolizumab	60.00s	Female	0.16	0.04	0.65	0.17	0.04	0.67	8.58
Atezolizumab	60.00s	Male	0.42	0.06	3.07	0.44	0.06	3.03	0.77
Atezolizumab	70.00s	Female	0.19	0.05	0.75	0.19	0.05	0.77	7.07
Atezolizumab	70.00s	Male	0.54	0.27	1.09	0.55	0.28	1.09	3.10
Atezolizumab	Unknown	Female	0.27	0.04	1.93	0.28	0.04	1.95	1.96
Atezolizumab	Unknown	Male	0.66	0.09	4.87	0.67	0.10	4.64	0.17
Atezolizumab	Unknown	Unknown	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Avelumab	40.00s	Male	1.61	0.50	5.24	1.57	0.53	4.66	0.65

Avelumab	50.00s	Female	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Avelumab	50.00s	Male	3.16	1.95	5.13	2.86	1.88	4.35	24.12
Avelumab	50.00s	Unknown	0.90	0.12	6.71	0.91	0.13	6.18	0.01
Avelumab	60.00s	Female	2.99	1.48	6.03	2.73	1.48	5.02	10.34
Avelumab	60.00s	Male	1.99	1.17	3.39	1.90	1.17	3.08	6.73
Avelumab	70.00s	Female	0.77	0.19	3.14	0.77	0.20	3.02	0.14
Avelumab	70.00s	Male	0.99	0.43	2.24	0.99	0.45	2.16	0.00
Avelumab	80.00s	Male	4.33	2.19	8.59	3.74	2.13	6.56	21.02
Avelumab	Unknown	Female	0.44	0.06	3.21	0.45	0.07	3.16	0.69
Avelumab	Unknown	Male	0.52	0.13	2.13	0.54	0.14	2.11	0.84
Bevacizumab	0.00s	Male	4.98	1.06	23.45	4.18	1.21	14.45	5.08
Bevacizumab	10.00s	Male	2.84	0.85	9.54	2.61	0.91	7.54	3.14
Bevacizumab	30.00s	Female	0.41	0.10	1.66	0.42	0.11	1.66	1.66
Bevacizumab	30.00s	Male	1.49	0.46	4.83	1.46	0.49	4.35	0.45
Bevacizumab	40.00s	Female	0.88	0.43	1.79	0.88	0.45	1.74	0.13
Bevacizumab	40.00s	Male	0.84	0.40	1.80	0.85	0.41	1.76	0.19
Bevacizumab	50.00s	Female	0.74	0.50	1.09	0.75	0.51	1.09	2.36
Bevacizumab	50.00s	Male	0.83	0.42	1.61	0.83	0.44	1.58	0.32
Bevacizumab	60.00s	Female	0.84	0.57	1.24	0.85	0.58	1.23	0.76
Bevacizumab	60.00s	Male	1.45	1.04	2.02	1.42	1.04	1.94	4.73
Bevacizumab	70.00s	Female	1.66	0.92	2.99	1.61	0.93	2.77	2.90
Bevacizumab	70.00s	Male	0.65	0.33	1.27	0.66	0.35	1.26	1.63
Bevacizumab	80.00s	Female	0.94	0.34	2.55	0.94	0.36	2.45	0.02
Bevacizumab	80.00s	Male	1.05	0.25	4.34	1.05	0.27	4.04	0.00
Bevacizumab	80.00s	Unknown	2.34	0.54	10.14	2.20	0.59	8.17	1.38
Bevacizumab	Unknown	Female	1.99	1.37	2.90	1.90	1.35	2.67	13.35
Bevacizumab	Unknown	Male	2.41	1.50	3.89	2.26	1.48	3.46	13.99
Bevacizumab	Unknown	Unknown	2.76	1.37	5.54	2.54	1.38	4.70	8.85
Brigatinib	50.00s	Male	4.98	0.56	44.54	4.18	0.72	24.14	2.54
Brigatinib	Unknown	Female	1.28	0.31	5.37	1.27	0.33	4.86	0.12

Brigatinib	Unknown	Unknown				20.91	20.41	21.43	39.81
Cabozantinib	30.00s	Female	1.42	0.19	10.82	1.39	0.21	9.26	0.12
Cabozantinib	40.00s	Female	1.06	0.46	2.40	1.05	0.48	2.30	0.02
Cabozantinib	50.00s	Female	0.41	0.10	1.68	0.43	0.11	1.68	1.62
Cabozantinib	50.00s	Male	0.28	0.12	0.67	0.29	0.12	0.69	9.18
Cabozantinib	50.00s	Unknown	3.98	0.87	18.18	3.49	0.98	12.35	3.72
Cabozantinib	60.00s	Female	0.97	0.39	2.37	0.97	0.41	2.28	0.01
Cabozantinib	60.00s	Male	1.40	0.78	2.51	1.37	0.79	2.37	1.27
Cabozantinib	60.00s	Unknown	7.96	1.54	41.06	5.97	1.85	19.28	8.70
Cabozantinib	70.00s	Male	0.36	0.14	0.98	0.37	0.14	0.99	4.38
Cabozantinib	80.00s	Female	0.83	0.11	6.13	0.84	0.12	5.71	0.03
Cabozantinib	Unknown	Unknown	1.05	0.14	7.83	1.05	0.15	7.06	0.00
Carboplatin	0.00s	Female	0.76	0.28	2.06	0.77	0.29	2.01	0.30
Carboplatin	0.00s	Male	0.71	0.22	2.25	0.72	0.24	2.19	0.34
Carboplatin	20.00s	Female	1.59	0.58	4.41	1.55	0.60	3.98	0.82
Carboplatin	20.00s	Male	0.62	0.08	4.55	0.63	0.09	4.37	0.22
Carboplatin	30.00s	Female	1.53	0.78	3.02	1.49	0.80	2.81	1.54
Carboplatin	30.00s	Male	0.44	0.06	3.21	0.45	0.07	3.16	0.69
Carboplatin	30.00s	Unknown	3.62	0.80	16.34	3.22	0.90	11.51	3.21
Carboplatin	40.00s	Female	1.03	0.70	1.51	1.03	0.71	1.48	0.02
Carboplatin	40.00s	Male	0.85	0.31	2.30	0.85	0.33	2.23	0.11
Carboplatin	40.00s	Unknown	5.31	1.76	16.01	4.40	1.84	10.52	11.04
Carboplatin	50.00s	Female	1.39	1.05	1.83	1.36	1.05	1.76	5.40
Carboplatin	50.00s	Male	0.56	0.25	1.26	0.57	0.26	1.26	2.01
Carboplatin	60.00s	Female	1.52	1.17	1.98	1.49	1.16	1.90	9.91
Carboplatin	60.00s	Male	1.56	0.96	2.52	1.52	0.97	2.37	3.34
Carboplatin	60.00s	Unknown	1.99	0.61	6.53	1.90	0.65	5.59	1.34
Carboplatin	70.00s	Female	1.22	0.84	1.78	1.21	0.85	1.73	1.12
Carboplatin	70.00s	Male	1.04	0.66	1.64	1.04	0.68	1.60	0.03
Carboplatin	70.00s	Unknown	1.61	0.50	5.24	1.57	0.53	4.66	0.65

Carboplatin	80.00s	Female	2.49	1.19	5.20	2.32	1.21	4.47	6.33
Carboplatin	80.00s	Male	2.34	0.54	10.14	2.20	0.59	8.17	1.38
Carboplatin	Unknown	Female	1.67	1.24	2.26	1.62	1.23	2.14	11.65
Carboplatin	Unknown	Male	0.94	0.34	2.55	0.94	0.36	2.45	0.02
Carboplatin	Unknown	Unknown	0.91	0.37	2.24	0.92	0.39	2.16	0.04
Celecoxib	20.00s	Male	0.52	0.07	3.82	0.54	0.08	3.71	0.42
Celecoxib	30.00s	Female	1.03	0.50	2.09	1.03	0.52	2.02	0.01
Celecoxib	30.00s	Male	1.40	0.51	3.85	1.37	0.53	3.54	0.42
Celecoxib	40.00s	Female	1.06	0.62	1.81	1.05	0.63	1.76	0.04
Celecoxib	40.00s	Male	2.13	1.23	3.70	2.02	1.23	3.33	7.56
Celecoxib	50.00s	Female	1.24	0.89	1.73	1.23	0.90	1.68	1.62
Celecoxib	50.00s	Male	2.16	1.45	3.22	2.05	1.43	2.94	15.18
Celecoxib	50.00s	Unknown	0.62	0.08	4.55	0.63	0.09	4.37	0.22
Celecoxib	60.00s	Female	1.16	0.86	1.56	1.15	0.87	1.52	0.91
Celecoxib	60.00s	Male	2.22	1.57	3.13	2.10	1.54	2.86	21.57
Celecoxib	60.00s	Unknown	2.13	0.65	7.02	2.02	0.69	5.93	1.63
Celecoxib	70.00s	Female	1.10	0.79	1.54	1.10	0.80	1.50	0.34
Celecoxib	70.00s	Male	1.51	0.99	2.31	1.47	0.99	2.18	3.64
Celecoxib	80.00s	Female	1.20	0.79	1.83	1.19	0.80	1.77	0.74
Celecoxib	80.00s	Male	1.82	1.03	3.22	1.75	1.04	2.95	4.42
Celecoxib	90.00s	Female	1.69	0.82	3.49	1.64	0.84	3.19	2.10
Celecoxib	90.00s	Male	1.53	0.20	11.71	1.49	0.23	9.87	0.17
Celecoxib	Unknown	Female	2.42	1.52	3.85	2.26	1.50	3.43	14.78
Celecoxib	Unknown	Male	2.42	1.33	4.40	2.26	1.33	3.86	8.86
Celecoxib	Unknown	Unknown	5.58	2.41	12.90	4.58	2.38	8.81	20.53
Ceritinib	30.00s	Female	3.98	0.47	34.09	3.48	0.58	20.86	1.86
Ceritinib	50.00s	Female	3.21	1.25	8.26	2.91	1.29	6.56	6.56
Ceritinib	60.00s	Female	4.98	0.56	44.54	4.18	0.72	24.14	2.54
Ceritinib	Unknown	Female	1.42	0.19	10.82	1.39	0.21	9.26	0.12
Cetuximab	30.00s	Female	1.33	0.18	10.05	1.31	0.20	8.72	0.08

Cetuximab	30.00s	Male	1.30	0.40	4.18	1.28	0.43	3.83	0.19
Cetuximab	40.00s	Male	1.17	0.16	8.80	1.16	0.17	7.80	0.02
Cetuximab	50.00s	Female	0.30	0.04	2.17	0.31	0.04	2.18	1.59
Cetuximab	50.00s	Male	1.08	0.53	2.19	1.07	0.55	2.11	0.04
Cetuximab	50.00s	Unknown	3.98	0.47	34.09	3.48	0.58	20.86	1.86
Cetuximab	60.00s	Female	0.75	0.24	2.36	0.76	0.25	2.30	0.25
Cetuximab	60.00s	Male	1.03	0.55	1.95	1.03	0.56	1.89	0.01
Cetuximab	70.00s	Female	1.81	0.72	4.52	1.74	0.75	4.04	1.66
Cetuximab	70.00s	Male	0.42	0.10	1.70	0.43	0.11	1.70	1.58
Cetuximab	Unknown	Female	1.81	0.65	5.04	1.74	0.68	4.45	1.33
Cetuximab	Unknown	Male	1.39	0.75	2.56	1.36	0.77	2.41	1.11
Cisplatin	0.00s	Female	0.89	0.33	2.44	0.90	0.34	2.35	0.05
Cisplatin	0.00s	Male	0.96	0.30	3.07	0.96	0.32	2.91	0.00
Cisplatin	20.00s	Female	0.31	0.04	2.24	0.32	0.05	2.25	1.50
Cisplatin	20.00s	Male	1.07	0.47	2.43	1.06	0.49	2.32	0.02
Cisplatin	30.00s	Female	0.17	0.05	0.52	0.17	0.06	0.54	12.42
Cisplatin	30.00s	Male	2.70	1.69	4.30	2.49	1.65	3.77	18.73
Cisplatin	40.00s	Female	1.79	1.03	3.09	1.72	1.04	2.85	4.45
Cisplatin	40.00s	Male	2.02	1.29	3.17	1.93	1.28	2.90	9.83
Cisplatin	50.00s	Female	1.48	0.95	2.31	1.45	0.96	2.19	3.07
Cisplatin	50.00s	Male	1.30	0.88	1.91	1.28	0.89	1.84	1.71
Cisplatin	60.00s	Female	1.88	1.29	2.74	1.81	1.28	2.55	11.28
Cisplatin	60.00s	Male	1.70	1.19	2.44	1.65	1.18	2.30	8.50
Cisplatin	60.00s	Unknown	0.51	0.07	3.72	0.52	0.08	3.62	0.46
Cisplatin	70.00s	Female	0.88	0.32	2.41	0.89	0.34	2.32	0.06
Cisplatin	70.00s	Male	0.86	0.42	1.74	0.86	0.44	1.70	0.19
Cisplatin	Unknown	Female	0.85	0.38	1.93	0.86	0.39	1.88	0.15
Cisplatin	Unknown	Male	1.88	1.14	3.10	1.81	1.15	2.85	6.41
Cisplatin	Unknown	Unknown	2.45	1.12	5.37	2.29	1.14	4.61	5.32
Crizotinib	20.00s	Female	3.98	0.87	18.18	3.49	0.98	12.35	3.72

Crizotinib	20.00s	Male	3.62	0.80	16.34	3.22	0.90	11.51	3.21
Crizotinib	30.00s	Female	2.10	0.49	9.00	1.99	0.53	7.44	1.04
Crizotinib	40.00s	Female	2.06	1.04	4.10	1.96	1.05	3.65	4.45
Crizotinib	40.00s	Male	3.98	0.87	18.18	3.49	0.98	12.35	3.72
Crizotinib	50.00s	Female	0.51	0.07	3.72	0.52	0.08	3.62	0.46
Crizotinib	50.00s	Male	0.49	0.12	2.00	0.50	0.13	1.98	1.03
Crizotinib	60.00s	Female	0.62	0.20	1.94	0.63	0.21	1.91	0.70
Crizotinib	60.00s	Male	0.46	0.11	1.86	0.47	0.12	1.85	1.26
Crizotinib	70.00s	Female	1.10	0.48	2.49	1.09	0.50	2.38	0.05
Crizotinib	70.00s	Male	1.81	0.65	5.04	1.74	0.68	4.45	1.33
Crizotinib	80.00s	Female	1.17	0.16	8.80	1.16	0.17	7.80	0.02
Crizotinib	Unknown	Female	1.08	0.39	2.94	1.07	0.41	2.79	0.02
Crizotinib	Unknown	Male	1.01	0.32	3.23	1.01	0.34	3.05	0.00
Cyclophosphamide	0.00s	Female	1.01	0.58	1.77	1.01	0.59	1.72	0.00
Cyclophosphamide	0.00s	Male	0.78	0.43	1.43	0.79	0.44	1.42	0.63
Cyclophosphamide	0.00s	Unknown	1.99	1.04	3.82	1.90	1.05	3.44	4.49
Cyclophosphamide	10.00s	Female	0.41	0.20	0.83	0.42	0.21	0.84	6.66
Cyclophosphamide	10.00s	Male	0.41	0.18	0.92	0.42	0.19	0.93	4.95
Cyclophosphamide	10.00s	Unknown	0.59	0.08	4.28	0.60	0.09	4.12	0.29
Cyclophosphamide	20.00s	Female	0.99	0.40	2.42	0.99	0.42	2.32	0.00
Cyclophosphamide	20.00s	Male	0.17	0.06	0.46	0.18	0.07	0.47	15.82
Cyclophosphamide	30.00s	Female	0.90	0.55	1.47	0.91	0.57	1.44	0.17
Cyclophosphamide	30.00s	Male	1.01	0.45	2.30	1.01	0.46	2.21	0.00
Cyclophosphamide	30.00s	Unknown	3.71	1.74	7.89	3.28	1.74	6.20	13.32
Cyclophosphamide	40.00s	Female	1.63	1.18	2.26	1.58	1.17	2.14	8.76
Cyclophosphamide	40.00s	Male	1.52	1.06	2.18	1.49	1.06	2.08	5.31
Cyclophosphamide	40.00s	Unknown	0.87	0.12	6.41	0.87	0.13	5.93	0.02
Cyclophosphamide	50.00s	Female	1.32	0.95	1.83	1.30	0.95	1.77	2.71
Cyclophosphamide	50.00s	Male	1.28	0.89	1.84	1.26	0.89	1.77	1.73
Cyclophosphamide	60.00s	Female	0.65	0.41	1.03	0.66	0.42	1.03	3.49

Cyclophosphamide	60.00s	Male	0.74	0.48	1.16	0.75	0.49	1.16	1.68
Cyclophosphamide	70.00s	Female	1.23	0.84	1.79	1.21	0.85	1.73	1.14
Cyclophosphamide	70.00s	Male	0.35	0.18	0.71	0.37	0.18	0.73	9.26
Cyclophosphamide	80.00s	Female	1.13	0.35	3.61	1.12	0.37	3.37	0.04
Cyclophosphamide	80.00s	Male	1.27	0.56	2.90	1.25	0.58	2.73	0.33
Cyclophosphamide	Unknown	Female	1.95	1.39	2.73	1.86	1.37	2.54	15.49
Cyclophosphamide	Unknown	Male	1.21	0.80	1.82	1.20	0.81	1.76	0.80
Cyclophosphamide	Unknown	Unknown	1.21	0.84	1.72	1.19	0.85	1.67	1.05
Dabrafenib	20.00s	Male	1.42	0.34	5.97	1.39	0.37	5.32	0.23
Dabrafenib	30.00s	Female	0.66	0.16	2.71	0.67	0.17	2.64	0.33
Dabrafenib	50.00s	Female	0.47	0.12	1.93	0.49	0.12	1.91	1.14
Dabrafenib	60.00s	Female	0.35	0.09	1.41	0.36	0.09	1.42	2.39
Dabrafenib	60.00s	Male	1.13	0.63	2.03	1.13	0.65	1.95	0.18
Dabrafenib	70.00s	Female	0.41	0.06	2.94	0.42	0.06	2.91	0.85
Dabrafenib	70.00s	Male	1.58	0.77	3.24	1.54	0.79	2.99	1.56
Dabrafenib	80.00s	Male	3.32	0.40	27.57	2.99	0.49	18.34	1.39
Dabrafenib	Unknown	Female	0.13	0.03	0.51	0.13	0.03	0.53	11.83
Dabrafenib	Unknown	Male	1.27	0.69	2.33	1.25	0.70	2.22	0.58
Dabrafenib	Unknown	Unknown	1.19	0.48	2.92	1.17	0.50	2.75	0.14
Dacomitinib	30.00s	Female	9.95	0.90	109.80	6.97	1.41	34.54	5.37
Dacomitinib	70.00s	Female	3.98	0.47	34.09	3.48	0.58	20.86	1.86
Dasatinib	20.00s	Female	2.49	0.31	19.90	2.32	0.37	14.75	0.79
Dasatinib	30.00s	Female	1.59	0.58	4.41	1.55	0.60	3.98	0.82
Dasatinib	30.00s	Unknown	1.21	0.29	5.03	1.19	0.31	4.59	0.07
Dasatinib	40.00s	Female	2.10	0.90	4.86	1.99	0.93	4.27	3.11
Dasatinib	40.00s	Male	1.99	0.61	6.53	1.90	0.65	5.59	1.34
Dasatinib	50.00s	Female	2.49	0.98	6.31	2.32	1.02	5.31	3.96
Dasatinib	50.00s	Male	0.94	0.34	2.55	0.94	0.36	2.45	0.02
Dasatinib	50.00s	Unknown	6.64	1.34	32.89	5.23	1.57	17.37	7.18
Dasatinib	60.00s	Female	0.96	0.35	2.62	0.96	0.37	2.50	0.01

Dasatinib	60.00s	Male	3.33	2.16	5.13	2.99	2.07	4.34	33.35
Dasatinib	70.00s	Female	0.69	0.17	2.81	0.70	0.18	2.72	0.28
Dasatinib	70.00s	Male	2.72	1.49	4.97	2.51	1.48	4.27	11.44
Dasatinib	80.00s	Female	1.73	0.41	7.34	1.67	0.44	6.32	0.57
Dasatinib	Unknown	Female	1.69	1.01	2.81	1.63	1.02	2.62	4.12
Dasatinib	Unknown	Male	1.04	0.49	2.22	1.04	0.50	2.14	0.01
Dasatinib	Unknown	Unknown	0.60	0.08	4.41	0.61	0.09	4.24	0.25
Docetaxel	20.00s	Female	0.41	0.06	3.00	0.43	0.06	2.97	0.81
Docetaxel	30.00s	Female	1.08	0.77	1.51	1.07	0.78	1.48	0.19
Docetaxel	30.00s	Male	9.96	1.82	54.37	6.97	2.25	21.62	10.74
Docetaxel	40.00s	Female	0.81	0.62	1.04	0.82	0.64	1.04	2.66
Docetaxel	40.00s	Male	3.19	1.11	9.16	2.88	1.16	7.17	5.17
Docetaxel	40.00s	Unknown	3.73	1.09	12.82	3.30	1.17	9.33	5.05
Docetaxel	50.00s	Female	1.67	1.37	2.05	1.62	1.34	1.95	25.30
Docetaxel	50.00s	Male	0.40	0.23	0.69	0.41	0.24	0.70	11.74
Docetaxel	50.00s	Unknown	1.42	0.34	5.97	1.39	0.37	5.32	0.23
Docetaxel	60.00s	Female	1.58	1.19	2.10	1.54	1.18	2.00	10.12
Docetaxel	60.00s	Male	1.17	0.79	1.72	1.16	0.80	1.67	0.62
Docetaxel	60.00s	Unknown	3.62	1.52	8.65	3.22	1.54	6.72	9.63
Docetaxel	70.00s	Female	2.25	1.32	3.84	2.12	1.31	3.43	9.32
Docetaxel	70.00s	Male	1.10	0.79	1.54	1.10	0.80	1.51	0.33
Docetaxel	80.00s	Male	0.77	0.36	1.63	0.77	0.37	1.60	0.48
Docetaxel	Unknown	Female	3.70	2.90	4.71	3.28	2.67	4.02	127.98
Docetaxel	Unknown	Male	1.21	0.77	1.91	1.20	0.78	1.84	0.71
Docetaxel	Unknown	Unknown	3.52	1.73	7.15	3.14	1.72	5.74	13.76
Doxorubicin	0.00s	Female	3.59	2.10	6.11	3.19	2.03	5.01	25.22
Doxorubicin	0.00s	Male	1.76	0.81	3.82	1.70	0.84	3.46	2.13
Doxorubicin	10.00s	Female	1.98	1.16	3.37	1.89	1.17	3.07	6.60
Doxorubicin	10.00s	Male	2.64	1.48	4.72	2.45	1.47	4.09	11.71
Doxorubicin	20.00s	Female	1.69	0.68	4.21	1.63	0.70	3.79	1.29

Doxorubicin	20.00s	Male	0.53	0.23	1.19	0.54	0.25	1.19	2.46
Doxorubicin	30.00s	Female	1.05	0.46	2.38	1.05	0.48	2.28	0.01
Doxorubicin	30.00s	Male	1.40	0.51	3.85	1.37	0.53	3.54	0.42
Doxorubicin	30.00s	Unknown	3.79	1.30	11.05	3.35	1.36	8.22	6.91
Doxorubicin	40.00s	Female	2.32	1.54	3.48	2.18	1.51	3.14	17.35
Doxorubicin	40.00s	Male	1.36	0.86	2.14	1.34	0.87	2.04	1.78
Doxorubicin	40.00s	Unknown	1.33	0.18	10.05	1.31	0.20	8.72	0.08
Doxorubicin	50.00s	Female	2.68	1.94	3.71	2.48	1.87	3.30	38.82
Doxorubicin	50.00s	Male	2.05	1.41	2.99	1.95	1.39	2.75	14.57
Doxorubicin	60.00s	Female	1.19	0.81	1.74	1.18	0.82	1.69	0.77
Doxorubicin	60.00s	Male	1.45	0.84	2.50	1.42	0.86	2.36	1.84
Doxorubicin	70.00s	Female	3.31	2.26	4.85	2.98	2.15	4.14	42.70
Doxorubicin	70.00s	Male	1.21	0.69	2.12	1.20	0.71	2.03	0.44
Doxorubicin	80.00s	Female	2.30	0.70	7.59	2.16	0.74	6.32	1.97
Doxorubicin	80.00s	Male	13.28	4.73	37.33	8.37	4.50	15.56	40.85
Doxorubicin	Unknown	Female	1.38	0.87	2.20	1.36	0.88	2.10	1.87
Doxorubicin	Unknown	Male	2.91	1.94	4.37	2.67	1.88	3.80	29.49
Doxorubicin	Unknown	Unknown	1.91	1.38	2.65	1.83	1.36	2.46	15.75
Durvalumab	50.00s	Male	0.71	0.10	5.23	0.72	0.11	4.95	0.11
Durvalumab	60.00s	Female	1.59	0.38	6.73	1.55	0.41	5.88	0.41
Durvalumab	70.00s	Female	0.60	0.08	4.41	0.61	0.09	4.24	0.25
Durvalumab	70.00s	Male	0.43	0.06	3.14	0.44	0.06	3.09	0.73
Durvalumab	Unknown	Female	0.71	0.10	5.23	0.72	0.11	4.95	0.11
Durvalumab	Unknown	Male	1.99	0.47	8.52	1.90	0.51	7.13	0.90
Durvalumab	Unknown	Unknown	2.34	0.54	10.14	2.20	0.59	8.17	1.38
Entrectinib	50.00s	Female	19.91	2.80	141.38	10.46	3.92	27.87	17.96
Epirubicin	0.00s	Female	1.66	0.22	12.76	1.61	0.24	10.57	0.24
Epirubicin	0.00s	Male	1.81	0.23	14.02	1.74	0.27	11.38	0.33
Epirubicin	10.00s	Male				20.93	20.42	21.45	139.35
Epirubicin	20.00s	Female	4.43	1.83	10.73	3.80	1.84	7.85	13.01

Epirubicin	30.00s	Female	2.03	1.09	3.78	1.93	1.10	3.40	5.20
Epirubicin	40.00s	Female	1.87	1.27	2.76	1.80	1.26	2.57	10.39
Epirubicin	40.00s	Male	1.00	0.13	7.42	1.00	0.15	6.74	0.00
Epirubicin	50.00s	Female	2.90	2.09	4.01	2.66	2.00	3.53	45.23
Epirubicin	50.00s	Male	0.40	0.05	2.88	0.41	0.06	2.85	0.89
Epirubicin	60.00s	Female	0.31	0.10	0.96	0.32	0.10	0.98	4.61
Epirubicin	60.00s	Male	2.01	1.08	3.74	1.92	1.09	3.37	5.07
Epirubicin	70.00s	Female	0.89	0.33	2.44	0.90	0.34	2.35	0.05
Epirubicin	70.00s	Male	1.78	0.71	4.44	1.71	0.74	3.97	1.56
Epirubicin	70.00s	Unknown	9.96	1.82	54.37	6.97	2.25	21.62	10.74
Epirubicin	Unknown	Female	6.47	4.56	9.17	5.13	3.94	6.68	145.79
Epirubicin	Unknown	Male	2.84	1.00	8.11	2.61	1.04	6.54	4.18
Epirubicin	Unknown	Unknown	2.84	1.00	8.11	2.61	1.04	6.54	4.18
Erlotinib	40.00s	Female	0.66	0.16	2.71	0.67	0.17	2.64	0.33
Erlotinib	50.00s	Female	0.75	0.24	2.36	0.76	0.25	2.30	0.25
Erlotinib	50.00s	Male	0.87	0.36	2.14	0.88	0.37	2.07	0.09
Erlotinib	60.00s	Female	0.38	0.12	1.18	0.39	0.13	1.19	3.06
Erlotinib	60.00s	Male	1.04	0.51	2.12	1.04	0.53	2.04	0.01
Erlotinib	60.00s	Unknown	9.96	1.82	54.37	6.97	2.25	21.62	10.74
Erlotinib	70.00s	Female	0.99	0.46	2.11	0.99	0.48	2.04	0.00
Erlotinib	70.00s	Male	0.69	0.22	2.20	0.70	0.23	2.14	0.39
Erlotinib	80.00s	Female	1.42	0.19	10.82	1.39	0.21	9.26	0.12
Erlotinib	Unknown	Female	1.28	0.56	2.93	1.27	0.58	2.75	0.35
Erlotinib	Unknown	Male	0.78	0.24	2.46	0.78	0.26	2.38	0.19
Etoposide	0.00s	Female	4.99	3.09	8.06	4.19	2.86	6.15	53.42
Etoposide	0.00s	Male	0.85	0.37	1.92	0.85	0.39	1.87	0.16
Etoposide	0.00s	Unknown	3.98	0.87	18.18	3.49	0.98	12.35	3.72
Etoposide	10.00s	Female	0.64	0.24	1.72	0.65	0.25	1.70	0.80
Etoposide	10.00s	Male	0.16	0.02	1.18	0.17	0.02	1.21	4.21
Etoposide	20.00s	Female	0.28	0.04	2.05	0.29	0.04	2.06	1.78

Etoposide	20.00s	Male	0.92	0.43	1.96	0.92	0.45	1.90	0.05
Etoposide	30.00s	Female	0.33	0.12	0.89	0.34	0.13	0.91	5.26
Etoposide	30.00s	Male	2.20	1.26	3.82	2.08	1.26	3.42	8.21
Etoposide	30.00s	Unknown	3.06	0.69	13.58	2.79	0.77	10.13	2.41
Etoposide	40.00s	Female	0.89	0.36	2.18	0.89	0.38	2.11	0.07
Etoposide	40.00s	Male	0.82	0.40	1.66	0.82	0.42	1.63	0.32
Etoposide	40.00s	Unknown	4.98	0.56	44.54	4.18	0.72	24.14	2.54
Etoposide	50.00s	Female	0.47	0.25	0.88	0.48	0.26	0.89	5.84
Etoposide	50.00s	Male	0.38	0.16	0.92	0.39	0.16	0.93	4.98
Etoposide	60.00s	Female	0.70	0.36	1.37	0.71	0.37	1.35	1.10
Etoposide	60.00s	Male	1.42	0.81	2.50	1.39	0.82	2.36	1.52
Etoposide	60.00s	Unknown	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Etoposide	70.00s	Female	1.05	0.63	1.77	1.05	0.64	1.72	0.04
Etoposide	70.00s	Male	1.03	0.51	2.11	1.03	0.53	2.03	0.01
Etoposide	Unknown	Female	1.53	0.85	2.76	1.49	0.87	2.58	2.06
Etoposide	Unknown	Male	1.73	1.00	2.99	1.67	1.01	2.77	3.98
Etoposide	Unknown	Unknown	0.35	0.09	1.41	0.36	0.09	1.42	2.39
Everolimus	0.00s	Female	0.48	0.29	0.77	0.49	0.30	0.78	9.56
Everolimus	30.00s	Female	0.66	0.16	2.71	0.67	0.17	2.64	0.33
Everolimus	40.00s	Female	0.36	0.11	1.13	0.37	0.12	1.14	3.36
Everolimus	50.00s	Female	1.37	0.78	2.40	1.35	0.80	2.28	1.21
Everolimus	50.00s	Male	0.29	0.07	1.16	0.30	0.08	1.18	3.46
Everolimus	60.00s	Female	0.40	0.18	0.90	0.41	0.19	0.91	5.24
Everolimus	60.00s	Male	0.24	0.09	0.65	0.25	0.09	0.66	9.45
Everolimus	70.00s	Female	0.65	0.27	1.60	0.67	0.28	1.58	0.88
Everolimus	80.00s	Female	0.80	0.11	5.88	0.80	0.12	5.50	0.05
Everolimus	Unknown	Female	0.32	0.16	0.63	0.33	0.16	0.65	11.71
Everolimus	Unknown	Male	0.09	0.01	0.63	0.09	0.01	0.65	9.37
Everolimus	Unknown	Unknown	0.23	0.09	0.55	0.24	0.10	0.57	12.89
Gefitinib	50.00s	Male	2.21	0.51	9.54	2.09	0.56	7.79	1.20

Gefitinib	60.00s	Female	0.72	0.29	1.75	0.73	0.31	1.72	0.54
Gefitinib	70.00s	Female	0.81	0.20	3.34	0.82	0.21	3.19	0.08
Gefitinib	70.00s	Male	5.24	1.96	14.04	4.36	2.00	9.51	13.58
Gefitinib	80.00s	Female	3.11	1.21	7.99	2.83	1.25	6.39	6.19
Gefitinib	Unknown	Female	0.52	0.07	3.82	0.54	0.08	3.71	0.42
Gefitinib	Unknown	Male	0.77	0.10	5.64	0.77	0.11	5.30	0.07
Gemcitabine	10.00s	Male	2.49	0.57	10.83	2.32	0.63	8.58	1.58
Gemcitabine	20.00s	Female	0.80	0.11	5.88	0.80	0.12	5.50	0.05
Gemcitabine	30.00s	Female	0.52	0.07	3.82	0.54	0.08	3.71	0.42
Gemcitabine	40.00s	Female	1.44	0.67	3.10	1.41	0.69	2.88	0.87
Gemcitabine	40.00s	Male	1.05	0.25	4.34	1.05	0.27	4.04	0.00
Gemcitabine	50.00s	Female	1.47	0.87	2.49	1.44	0.88	2.35	2.11
Gemcitabine	50.00s	Male	0.88	0.45	1.71	0.88	0.47	1.67	0.15
Gemcitabine	50.00s	Unknown	1.99	0.25	15.55	1.90	0.29	12.32	0.45
Gemcitabine	60.00s	Female	2.35	1.54	3.59	2.21	1.51	3.22	16.54
Gemcitabine	60.00s	Male	1.83	1.29	2.61	1.76	1.28	2.44	11.74
Gemcitabine	60.00s	Unknown	39.82	3.61	439.27	13.94	6.26	31.04	25.22
Gemcitabine	70.00s	Female	1.86	0.97	3.56	1.79	0.99	3.24	3.64
Gemcitabine	70.00s	Male	0.94	0.57	1.55	0.94	0.58	1.52	0.06
Gemcitabine	80.00s	Female	3.83	1.47	9.98	3.37	1.51	7.53	8.76
Gemcitabine	Unknown	Female	0.87	0.46	1.65	0.88	0.48	1.61	0.18
Gemcitabine	Unknown	Male	0.98	0.36	2.68	0.98	0.38	2.56	0.00
Gemcitabine	Unknown	Unknown	2.71	1.63	4.50	2.51	1.60	3.92	16.13
Ifosfamide	0.00s	Female	1.01	0.32	3.23	1.01	0.34	3.05	0.00
Ifosfamide	10.00s	Female	0.78	0.37	1.67	0.79	0.38	1.64	0.41
Ifosfamide	10.00s	Male	1.53	0.67	3.52	1.49	0.69	3.23	1.03
Ifosfamide	20.00s	Male	0.08	0.01	0.57	0.08	0.01	0.60	10.47
Ifosfamide	30.00s	Female	0.49	0.12	2.00	0.50	0.13	1.98	1.03
Ifosfamide	30.00s	Male	1.17	0.28	4.88	1.16	0.30	4.47	0.05
Ifosfamide	30.00s	Unknown	3.98	0.87	18.18	3.49	0.98	12.35	3.72

Ifosfamide	40.00s	Female	2.10	0.75	5.87	1.99	0.78	5.06	2.07
Ifosfamide	50.00s	Female	1.14	0.42	3.12	1.13	0.44	2.93	0.06
Ifosfamide	50.00s	Male	0.90	0.33	2.47	0.91	0.35	2.37	0.04
Ifosfamide	60.00s	Female	0.60	0.15	2.46	0.61	0.16	2.41	0.51
Ifosfamide	60.00s	Male	1.84	0.74	4.61	1.77	0.77	4.10	1.77
Ifosfamide	Unknown	Female	1.34	0.68	2.63	1.32	0.70	2.48	0.72
Ifosfamide	Unknown	Male	0.50	0.16	1.56	0.51	0.17	1.56	1.49
Ipilimumab	30.00s	Female	0.55	0.08	4.03	0.56	0.08	3.91	0.35
Ipilimumab	30.00s	Male	1.61	0.50	5.24	1.57	0.53	4.66	0.65
Ipilimumab	50.00s	Female	0.24	0.06	0.97	0.25	0.06	0.99	4.72
Ipilimumab	50.00s	Male	0.67	0.30	1.52	0.69	0.31	1.51	0.91
Ipilimumab	60.00s	Female	1.66	1.01	2.73	1.61	1.02	2.54	4.11
Ipilimumab	60.00s	Male	1.53	0.99	2.37	1.50	1.00	2.24	3.77
Ipilimumab	70.00s	Female	0.53	0.22	1.29	0.54	0.23	1.29	2.00
Ipilimumab	70.00s	Male	1.32	0.77	2.27	1.30	0.78	2.16	1.02
Ipilimumab	80.00s	Female	0.95	0.13	7.05	0.95	0.14	6.45	0.00
Ipilimumab	80.00s	Male	0.52	0.07	3.82	0.54	0.08	3.71	0.42
Ipilimumab	Unknown	Female	0.34	0.12	0.90	0.35	0.13	0.92	5.17
Ipilimumab	Unknown	Male	0.31	0.13	0.75	0.32	0.13	0.76	7.62
Ipilimumab	Unknown	Unknown	2.03	0.81	5.10	1.94	0.84	4.46	2.38
Irinotecan	30.00s	Female	0.51	0.07	3.72	0.52	0.08	3.62	0.46
Irinotecan	30.00s	Male	1.17	0.28	4.88	1.16	0.30	4.47	0.05
Irinotecan	40.00s	Female	0.33	0.05	2.39	0.34	0.05	2.39	1.32
Irinotecan	40.00s	Male	0.86	0.31	2.33	0.86	0.33	2.25	0.09
Irinotecan	50.00s	Female	2.16	1.35	3.48	2.05	1.34	3.15	10.71
Irinotecan	50.00s	Male	0.94	0.46	1.92	0.94	0.48	1.86	0.03
Irinotecan	60.00s	Female	0.47	0.15	1.47	0.48	0.16	1.46	1.79
Irinotecan	60.00s	Male	1.07	0.64	1.80	1.07	0.65	1.75	0.07
Irinotecan	70.00s	Female	1.35	0.54	3.33	1.32	0.57	3.09	0.41
Irinotecan	70.00s	Male	0.55	0.18	1.74	0.56	0.18	1.72	1.06

Irinotecan	Unknown	Female	0.18	0.04	0.73	0.19	0.05	0.75	7.36
Irinotecan	Unknown	Male	3.62	1.96	6.71	3.22	1.91	5.42	19.26
Irinotecan	Unknown	Unknown	0.42	0.06	3.07	0.44	0.06	3.03	0.77
Larotrectinib	50.00s	Female	1.24	0.16	9.38	1.23	0.18	8.24	0.05
Lorlatinib	50.00s	Male	0.57	0.08	4.15	0.58	0.08	4.01	0.32
Lorlatinib	60.00s	Male	3.06	0.69	13.58	2.79	0.77	10.13	2.41
Lorlatinib	Unknown	Male	2.65	0.61	11.61	2.46	0.67	9.05	1.82
Methotrexate	0.00s	Female	0.66	0.36	1.21	0.68	0.38	1.21	1.79
Methotrexate	0.00s	Male	0.75	0.40	1.42	0.76	0.41	1.40	0.77
Methotrexate	0.00s	Unknown	1.61	0.50	5.24	1.57	0.53	4.66	0.65
Methotrexate	10.00s	Female	0.31	0.17	0.56	0.32	0.18	0.58	16.58
Methotrexate	10.00s	Male	1.06	0.73	1.55	1.06	0.74	1.51	0.10
Methotrexate	20.00s	Female	0.52	0.29	0.92	0.53	0.30	0.93	5.26
Methotrexate	20.00s	Male	0.41	0.20	0.88	0.43	0.20	0.89	5.68
Methotrexate	30.00s	Female	0.14	0.07	0.27	0.14	0.07	0.28	48.11
Methotrexate	30.00s	Male	0.69	0.39	1.23	0.70	0.40	1.22	1.62
Methotrexate	40.00s	Female	0.29	0.18	0.46	0.30	0.19	0.47	31.07
Methotrexate	40.00s	Male	0.72	0.46	1.12	0.72	0.47	1.12	2.18
Methotrexate	40.00s	Unknown	1.00	0.13	7.42	1.00	0.15	6.74	0.00
Methotrexate	50.00s	Female	0.42	0.30	0.58	0.43	0.32	0.59	30.57
Methotrexate	50.00s	Male	0.35	0.21	0.56	0.36	0.22	0.57	20.68
Methotrexate	50.00s	Unknown	0.72	0.18	2.97	0.73	0.19	2.86	0.20
Methotrexate	60.00s	Female	0.42	0.32	0.56	0.44	0.33	0.57	38.15
Methotrexate	60.00s	Male	0.66	0.46	0.94	0.67	0.48	0.95	5.33
Methotrexate	70.00s	Female	0.61	0.45	0.82	0.62	0.46	0.83	10.94
Methotrexate	70.00s	Male	0.42	0.24	0.71	0.43	0.25	0.72	11.22
Methotrexate	80.00s	Female	0.23	0.10	0.52	0.24	0.11	0.53	15.20
Methotrexate	80.00s	Male	0.65	0.32	1.31	0.66	0.33	1.31	1.46
Methotrexate	90.00s	Male	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Methotrexate	Unknown	Female	0.41	0.28	0.59	0.42	0.29	0.60	23.70

Methotrexate	Unknown	Male	0.53	0.34	0.84	0.54	0.35	0.85	7.59
Methotrexate	Unknown	Unknown	0.34	0.20	0.57	0.35	0.21	0.58	17.99
Nintedanib	50.00s	Male	2.10	0.75	5.87	1.99	0.78	5.06	2.07
Nintedanib	60.00s	Female	1.40	0.57	3.47	1.38	0.59	3.21	0.54
Nintedanib	60.00s	Male	2.19	1.18	4.09	2.07	1.18	3.64	6.41
Nintedanib	60.00s	Unknown	1.42	0.19	10.82	1.39	0.21	9.26	0.12
Nintedanib	70.00s	Female	0.48	0.12	1.95	0.49	0.12	1.93	1.10
Nintedanib	70.00s	Male	2.36	1.54	3.60	2.22	1.52	3.24	16.73
Nintedanib	70.00s	Unknown	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Nintedanib	80.00s	Male	2.10	1.01	4.35	1.99	1.03	3.85	4.15
Nintedanib	80.00s	Unknown	2.84	0.35	23.12	2.61	0.42	16.35	1.05
Nintedanib	Unknown	Female	0.38	0.05	2.77	0.39	0.06	2.75	0.98
Nintedanib	Unknown	Male	1.08	0.44	2.66	1.08	0.46	2.53	0.03
Nintedanib	Unknown	Unknown	0.55	0.14	2.25	0.56	0.14	2.22	0.70
Nivolumab	20.00s	Female	2.06	0.63	6.76	1.96	0.67	5.76	1.48
Nivolumab	20.00s	Male	1.05	0.14	7.83	1.05	0.15	7.06	0.00
Nivolumab	30.00s	Male	0.74	0.10	5.43	0.75	0.11	5.12	0.09
Nivolumab	40.00s	Female	0.61	0.23	1.66	0.62	0.24	1.64	0.95
Nivolumab	40.00s	Male	0.38	0.12	1.18	0.39	0.13	1.19	3.02
Nivolumab	50.00s	Female	0.33	0.12	0.88	0.34	0.13	0.89	5.48
Nivolumab	50.00s	Male	0.36	0.15	0.87	0.37	0.16	0.89	5.58
Nivolumab	60.00s	Female	0.98	0.57	1.68	0.98	0.59	1.64	0.00
Nivolumab	60.00s	Male	1.73	1.23	2.44	1.67	1.22	2.29	10.17
Nivolumab	70.00s	Female	0.31	0.10	0.96	0.32	0.10	0.97	4.65
Nivolumab	70.00s	Male	1.77	1.14	2.74	1.71	1.14	2.55	6.73
Nivolumab	80.00s	Female	0.74	0.10	5.43	0.75	0.11	5.12	0.09
Nivolumab	80.00s	Male	1.85	0.66	5.16	1.78	0.70	4.55	1.43
Nivolumab	Unknown	Female	0.98	0.59	1.62	0.98	0.61	1.59	0.00
Nivolumab	Unknown	Male	0.45	0.25	0.82	0.47	0.26	0.84	7.08
Nivolumab	Unknown	Unknown	1.53	0.55	4.24	1.49	0.58	3.84	0.68

Osimertinib	50.00s	Female	0.64	0.09	4.70	0.65	0.09	4.50	0.19
Osimertinib	60.00s	Female	4.10	1.82	9.26	3.57	1.82	7.02	13.60
Osimertinib	60.00s	Male	2.39	0.72	7.92	2.24	0.77	6.53	2.16
Osimertinib	70.00s	Female	0.61	0.15	2.50	0.62	0.16	2.44	0.48
Osimertinib	70.00s	Male	3.62	1.25	10.51	3.22	1.31	7.93	6.42
Osimertinib	80.00s	Female	1.24	0.30	5.19	1.23	0.32	4.72	0.09
Osimertinib	Unknown	Female	0.38	0.09	1.54	0.39	0.10	1.54	2.00
Paclitaxel	10.00s	Male	2.21	0.28	17.46	2.09	0.33	13.42	0.60
Paclitaxel	30.00s	Female	1.81	1.15	2.87	1.74	1.15	2.66	6.65
Paclitaxel	30.00s	Male	2.21	0.51	9.54	2.09	0.56	7.79	1.20
Paclitaxel	30.00s	Unknown	3.98	0.47	34.09	3.48	0.58	20.86	1.86
Paclitaxel	40.00s	Female	1.16	0.83	1.62	1.15	0.84	1.58	0.77
Paclitaxel	40.00s	Male	3.79	1.30	11.05	3.35	1.36	8.22	6.91
Paclitaxel	40.00s	Unknown	3.14	0.93	10.63	2.85	1.00	8.16	3.79
Paclitaxel	50.00s	Female	1.44	1.11	1.87	1.41	1.11	1.80	7.56
Paclitaxel	50.00s	Male	0.14	0.05	0.39	0.15	0.06	0.40	20.10
Paclitaxel	60.00s	Female	1.56	1.25	1.94	1.52	1.23	1.86	15.62
Paclitaxel	60.00s	Male	0.72	0.23	2.28	0.73	0.24	2.22	0.32
Paclitaxel	60.00s	Unknown	3.73	1.09	12.82	3.30	1.17	9.33	5.05
Paclitaxel	70.00s	Female	1.45	1.05	2.01	1.42	1.05	1.93	5.12
Paclitaxel	70.00s	Male	1.45	0.81	2.60	1.42	0.82	2.45	1.55
Paclitaxel	80.00s	Female	1.69	0.68	4.21	1.63	0.70	3.79	1.29
Paclitaxel	Unknown	Female	1.84	1.30	2.60	1.77	1.29	2.43	12.18
Paclitaxel	Unknown	Male	2.73	1.24	6.03	2.52	1.26	5.06	6.76
Paclitaxel	Unknown	Unknown	2.31	1.30	4.11	2.18	1.30	3.64	8.67
Panitumumab	40.00s	Male	0.90	0.12	6.71	0.91	0.13	6.18	0.01
Panitumumab	50.00s	Female	1.03	0.38	2.83	1.03	0.40	2.69	0.00
Panitumumab	50.00s	Male	0.54	0.07	3.92	0.55	0.08	3.81	0.39
Panitumumab	Unknown	Female	0.25	0.06	1.00	0.26	0.06	1.02	4.53
Panitumumab	Unknown	Male	0.41	0.06	2.94	0.42	0.06	2.91	0.85

Pembrolizumab	30.00s	Male	1.14	0.27	4.73	1.13	0.29	4.35	0.03
Pembrolizumab	40.00s	Female	0.15	0.02	1.05	0.15	0.02	1.07	4.95
Pembrolizumab	40.00s	Male	1.39	0.43	4.48	1.36	0.46	4.07	0.31
Pembrolizumab	50.00s	Female	0.98	0.56	1.71	0.98	0.58	1.67	0.00
Pembrolizumab	50.00s	Male	0.58	0.29	1.16	0.59	0.30	1.17	2.42
Pembrolizumab	60.00s	Female	0.48	0.22	1.09	0.50	0.23	1.10	3.20
Pembrolizumab	60.00s	Male	0.95	0.55	1.62	0.95	0.57	1.59	0.04
Pembrolizumab	60.00s	Unknown	1.66	0.22	12.76	1.61	0.24	10.57	0.24
Pembrolizumab	70.00s	Female	1.19	0.76	1.87	1.18	0.77	1.81	0.57
Pembrolizumab	70.00s	Male	1.77	1.28	2.45	1.71	1.27	2.30	12.24
Pembrolizumab	80.00s	Female	1.21	0.64	2.29	1.19	0.65	2.18	0.33
Pembrolizumab	80.00s	Male	0.88	0.36	2.16	0.89	0.38	2.09	0.08
Pembrolizumab	90.00s	Female	19.91	2.80	141.38	10.46	3.92	27.87	17.96
Pembrolizumab	Unknown	Female	0.99	0.52	1.87	0.99	0.54	1.82	0.00
Pembrolizumab	Unknown	Male	0.32	0.15	0.68	0.33	0.16	0.70	9.79
Pembrolizumab	Unknown	Unknown	0.29	0.04	2.11	0.30	0.04	2.12	1.68
Pemetrexed	30.00s	Female	2.10	0.49	9.00	1.99	0.53	7.44	1.04
Pemetrexed	40.00s	Female	1.26	0.51	3.11	1.24	0.53	2.91	0.25
Pemetrexed	40.00s	Male	0.87	0.21	3.57	0.87	0.22	3.38	0.04
Pemetrexed	50.00s	Female	1.01	0.55	1.86	1.01	0.57	1.80	0.00
Pemetrexed	50.00s	Male	0.70	0.26	1.89	0.71	0.27	1.86	0.50
Pemetrexed	60.00s	Female	2.03	1.26	3.25	1.93	1.26	2.97	8.93
Pemetrexed	60.00s	Male	1.80	1.17	2.76	1.73	1.17	2.56	7.45
Pemetrexed	70.00s	Female	1.94	0.70	5.43	1.86	0.73	4.74	1.67
Pemetrexed	70.00s	Male	1.86	1.00	3.45	1.78	1.01	3.14	3.97
Pemetrexed	70.00s	Unknown	9.95	0.90	109.80	6.97	1.41	34.54	5.37
Pemetrexed	Unknown	Male	2.61	1.25	5.46	2.43	1.26	4.66	7.03
Selpercatinib	50.00s	Female	4.27	1.23	14.85	3.69	1.32	10.31	6.18
Selpercatinib	50.00s	Male	1.05	0.14	7.83	1.05	0.15	7.06	0.00
Selpercatinib	60.00s	Female	0.46	0.06	3.36	0.48	0.07	3.30	0.61

Selpercatinib	60.00s	Male	8.53	2.21	33.01	6.27	2.43	16.18	13.96
Selpercatinib	70.00s	Male	1.81	0.43	7.70	1.74	0.46	6.57	0.66
Selpercatinib	Unknown	Female	4.27	1.23	14.85	3.69	1.32	10.31	6.18
Selpercatinib	Unknown	Male	1.66	0.22	12.76	1.61	0.24	10.57	0.24
Sorafenib	0.00s	Female	5.43	2.20	13.40	4.48	2.20	9.12	17.04
Sorafenib	50.00s	Female	0.66	0.09	4.87	0.67	0.10	4.64	0.17
Sorafenib	60.00s	Female	0.60	0.15	2.46	0.61	0.16	2.41	0.51
Sorafenib	60.00s	Male	0.48	0.15	1.51	0.49	0.16	1.51	1.64
Sorafenib	60.00s	Unknown	9.95	0.90	109.80	6.97	1.41	34.54	5.37
Sorafenib	70.00s	Female	0.59	0.08	4.28	0.60	0.09	4.12	0.29
Sorafenib	70.00s	Male	1.10	0.51	2.35	1.09	0.53	2.25	0.06
Sorafenib	Unknown	Female	1.99	0.61	6.53	1.90	0.65	5.59	1.34
Sorafenib	Unknown	Male	2.52	1.34	4.72	2.35	1.35	4.10	8.93
Sorafenib	Unknown	Unknown	0.71	0.17	2.91	0.72	0.18	2.81	0.23
Sunitinib	30.00s	Male	1.50	0.54	4.15	1.47	0.57	3.78	0.62
Sunitinib	40.00s	Female	0.60	0.08	4.41	0.61	0.09	4.24	0.25
Sunitinib	40.00s	Male	1.96	1.05	3.64	1.87	1.06	3.29	4.68
Sunitinib	50.00s	Female	1.57	0.93	2.66	1.53	0.94	2.49	2.89
Sunitinib	50.00s	Male	0.41	0.21	0.80	0.43	0.22	0.82	7.27
Sunitinib	60.00s	Female	1.89	1.15	3.12	1.82	1.15	2.86	6.52
Sunitinib	60.00s	Male	1.22	0.81	1.83	1.21	0.82	1.77	0.94
Sunitinib	70.00s	Female	1.34	0.70	2.54	1.32	0.72	2.40	0.79
Sunitinib	70.00s	Male	1.48	0.99	2.21	1.45	1.00	2.10	3.76
Sunitinib	80.00s	Female	3.46	1.20	10.02	3.10	1.25	7.66	5.97
Sunitinib	80.00s	Male	1.03	0.55	1.95	1.03	0.56	1.89	0.01
Sunitinib	90.00s	Female				20.91	20.40	21.43	19.91
Sunitinib	Unknown	Female	0.51	0.13	2.08	0.52	0.13	2.05	0.92
Sunitinib	Unknown	Male	1.61	0.84	3.06	1.56	0.86	2.84	2.11
Sunitinib	Unknown	Unknown	0.87	0.21	3.57	0.87	0.22	3.38	0.04
Tepotinib	70.00s	Female	0.95	0.13	7.05	0.95	0.14	6.45	0.00

Tepotinib	Unknown	Female	1.66	0.22	12.76	1.61	0.24	10.57	0.24
Topotecan	0.00s	Female	3.98	1.36	11.66	3.49	1.42	8.53	7.44
Topotecan	0.00s	Male	3.06	0.69	13.58	2.79	0.77	10.13	2.41
Topotecan	50.00s	Female	1.99	0.61	6.53	1.90	0.65	5.59	1.34
Topotecan	60.00s	Female	3.79	1.30	11.05	3.35	1.36	8.22	6.91
Topotecan	Unknown	Female	1.15	0.42	3.16	1.15	0.44	2.97	0.08
Trametinib	0.00s	Female	3.62	0.80	16.34	3.22	0.90	11.51	3.21
Trametinib	20.00s	Male	0.83	0.20	3.41	0.84	0.22	3.25	0.07
Trametinib	30.00s	Female	0.62	0.15	2.54	0.63	0.16	2.48	0.45
Trametinib	50.00s	Female	0.53	0.13	2.16	0.54	0.14	2.13	0.81
Trametinib	60.00s	Female	0.22	0.03	1.60	0.23	0.03	1.63	2.67
Trametinib	60.00s	Male	0.92	0.47	1.79	0.92	0.49	1.75	0.06
Trametinib	70.00s	Male	1.13	0.46	2.79	1.12	0.48	2.64	0.07
Trametinib	80.00s	Male	6.64	0.69	63.81	5.23	0.96	28.54	3.59
Trametinib	Unknown	Female	0.08	0.01	0.54	0.08	0.01	0.56	11.27
Trametinib	Unknown	Male	1.00	0.49	2.04	1.00	0.51	1.97	0.00
Trametinib	Unknown	Unknown	0.98	0.36	2.68	0.98	0.38	2.56	0.00
Trastuzumab	20.00s	Female	0.27	0.07	1.08	0.28	0.07	1.10	3.97
Trastuzumab	30.00s	Female	0.78	0.62	0.98	0.78	0.63	0.98	4.68
Trastuzumab	40.00s	Female	0.99	0.83	1.19	0.99	0.83	1.18	0.01
Trastuzumab	40.00s	Male	0.83	0.11	6.13	0.84	0.12	5.71	0.03
Trastuzumab	40.00s	Unknown	4.15	1.58	10.88	3.61	1.62	8.01	9.88
Trastuzumab	50.00s	Female	1.13	0.95	1.34	1.12	0.95	1.32	1.80
Trastuzumab	50.00s	Unknown	1.23	0.45	3.36	1.21	0.47	3.14	0.16
Trastuzumab	60.00s	Female	1.15	0.94	1.42	1.15	0.94	1.39	1.89
Trastuzumab	60.00s	Male	1.81	0.23	14.02	1.74	0.27	11.38	0.33
Trastuzumab	70.00s	Female	1.34	1.00	1.79	1.32	1.00	1.73	3.91
Trastuzumab	70.00s	Male	1.81	0.43	7.70	1.74	0.46	6.57	0.66
Trastuzumab	80.00s	Female	1.08	0.53	2.19	1.07	0.55	2.11	0.04
Trastuzumab	Unknown	Female	1.62	1.40	1.88	1.58	1.38	1.80	43.13

Trastuzumab	Unknown	Unknown	1.93	1.09	3.42	1.85	1.10	3.11	5.33
Vemurafenib	20.00s	Female				20.91	20.40	21.43	19.91
Vemurafenib	40.00s	Male	0.69	0.09	5.04	0.70	0.10	4.79	0.14
Vemurafenib	60.00s	Female	0.43	0.06	3.14	0.44	0.06	3.09	0.73
Vemurafenib	60.00s	Male	0.95	0.23	3.92	0.95	0.25	3.68	0.01
Vemurafenib	60.00s	Unknown	5.12	2.46	10.67	4.28	2.39	7.67	23.73
Vemurafenib	70.00s	Female	2.41	1.16	5.03	2.26	1.17	4.35	5.91
Vemurafenib	80.00s	Female	1.33	0.32	5.55	1.31	0.34	5.00	0.15
Vemurafenib	Unknown	Male	0.54	0.07	3.92	0.55	0.08	3.81	0.39
Vincristine	0.00s	Female	0.56	0.25	1.26	0.57	0.26	1.25	2.05
Vincristine	0.00s	Male	0.18	0.06	0.55	0.18	0.06	0.57	11.39
Vincristine	0.00s	Unknown	1.11	0.15	8.29	1.10	0.16	7.41	0.01
Vincristine	10.00s	Female	0.89	0.44	1.82	0.90	0.46	1.77	0.10
Vincristine	10.00s	Male	1.20	0.63	2.27	1.19	0.65	2.17	0.31
Vincristine	20.00s	Female	0.38	0.05	2.72	0.39	0.06	2.70	1.02
Vincristine	20.00s	Male	0.56	0.14	2.29	0.57	0.15	2.25	0.67
Vincristine	30.00s	Male	2.25	1.03	4.92	2.12	1.05	4.28	4.36
Vincristine	30.00s	Unknown	3.98	0.87	18.18	3.49	0.98	12.35	3.72
Vincristine	40.00s	Female	0.45	0.11	1.82	0.46	0.12	1.81	1.34
Vincristine	40.00s	Male	1.38	0.85	2.23	1.35	0.87	2.12	1.75
Vincristine	50.00s	Female	1.19	0.52	2.72	1.18	0.54	2.58	0.18
Vincristine	50.00s	Male	1.95	1.30	2.92	1.87	1.29	2.69	10.91
Vincristine	60.00s	Female	0.43	0.19	0.96	0.44	0.20	0.97	4.54
Vincristine	60.00s	Male	1.09	0.60	2.01	1.09	0.61	1.94	0.09
Vincristine	70.00s	Female	2.02	1.21	3.38	1.92	1.21	3.07	7.45
Vincristine	70.00s	Male	0.52	0.23	1.17	0.53	0.24	1.17	2.61
Vincristine	80.00s	Female	2.21	0.51	9.54	2.09	0.56	7.79	1.20
Vincristine	80.00s	Male	6.64	2.64	16.74	5.23	2.61	10.46	21.54
Vincristine	Unknown	Female	0.53	0.20	1.43	0.54	0.21	1.43	1.62
Vincristine	Unknown	Male	1.70	1.05	2.75	1.65	1.06	2.56	4.77

Vincristine	Unknown	Unknown	0.89	0.57	1.40	0.90	0.58	1.38	0.25
Vinorelbine	10.00s	Male	0.95	0.13	7.05	0.95	0.14	6.45	0.00
Vinorelbine	30.00s	Female	0.61	0.15	2.50	0.62	0.16	2.44	0.48
Vinorelbine	40.00s	Female	1.50	0.79	2.85	1.46	0.80	2.66	1.53
Vinorelbine	40.00s	Male	1.33	0.18	10.05	1.31	0.20	8.72	0.08
Vinorelbine	50.00s	Female	1.72	1.23	2.39	1.66	1.22	2.25	10.39
Vinorelbine	50.00s	Male	0.69	0.22	2.17	0.70	0.23	2.12	0.42
Vinorelbine	60.00s	Female	0.72	0.37	1.40	0.73	0.38	1.39	0.93
Vinorelbine	60.00s	Male	2.11	0.97	4.61	2.01	0.99	4.06	3.70
Vinorelbine	70.00s	Female	1.47	0.68	3.16	1.44	0.70	2.93	0.97
Vinorelbine	70.00s	Male	1.70	0.89	3.25	1.65	0.91	2.99	2.67
Vinorelbine	80.00s	Male	5.97	1.64	21.71	4.83	1.79	13.02	9.55
Vinorelbine	Unknown	Female	0.61	0.27	1.37	0.62	0.28	1.37	1.46
Vinorelbine	Unknown	Male	4.04	2.40	6.80	3.53	2.28	5.44	32.22