Faculty of science and technology

A Meta Analysis of Various Targeted Therapies in the Treatment of Non-Small Cell Lung Cancer

A dissertation submitted as part of the requirement for the BSc (Biomedical Science)

Aaron Mulrooney

S5411158

25/04/2024

Abstract

Cancer is now the leading cause of death in the UK according to Imperial College London and continues to grow as a serious threat to the entire population. A quote by Siddhartha Mukherjee encapsulates the formidable nature of cancer while also implying the necessity of meeting the challenge head-on; ‘To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are’. In recent times, with the emergence of targeted therapy, our ability to adapt has come leaps and bounds. This study aims to investigate the efficacy of targeted therapies in the treatment of non-small cell lung cancer (NSCLC) by using a meta-analysis of clinical trials. PubMed and Clinicaltrials.gov were searched by using keywords related to the topic on 21 December 2023. Overall response rate (ORR) and progression-free survival (PFS) were analysed as performance indicators. A total of 44 clinical trials were included in the final analysis of 11 treatment options. Compared with chemotherapy, both ORR and PFS were significantly improved for afatinib, alectinib, and crizotinib, cabozantinib, ceritinib, gefitinib, bevacuzimab, cetuximab, vandetanib, erlotinib and osimertinib. Crizotinib and alectinib showed the highest probability for the first-line treatment ranking in ORR and PFS, respectively. This meta-analysis shows a comprehensive comparison of different types of targeted therapies, which can help clinicians devise treatment plans tailored to patients

Acknowledgements

I would like to thank my personal tutor, Hannah Rickman for helping with this project. Hannah provided invaluable guidance throughout this dissertation, without this, this project would not have been possible.

Contents

Introduction

Non-Small Cell Lung Cancer (NSCLC) is any type of epithelial lung cancer apart from Small Cell Lung Cancer. Worldwide, lung cancer is the second most commonly diagnosed form of cancer and NSCLC makes up 81% of these diagnoses (National Cancer Institute). NSCLC can be divided into 3 subtypes; Adenocarcinomas, Squamous cell carcinomas, and large cell carcinomas. These types of cancer are becoming increasingly more prevalent and, in the USA alone, expected to affect 234,580 new cases of NSCLC while 125,070 die from the same diagnosis (American Cancer Society).

The unsanctioned and uncontrolled growth of tumours in the lung can affect patients severely in their day-to-day functioning and has a prolificity for death. The most common cause of mortality in NSCLC is the burden of the tumour on peripheral organs; restricting the patients' ability to breathe swallow or clear debris from the lung, causing approximately one third of NSCLC patient mortality (Nichols et al.). Infections and pulmonary malfunctions are also common in these patients, Infections such as pneumonia and sepsis killing around 20% of NSCLC patients, pulmonary haemorrhage and embolisms accounting for 22% of these deaths. Figure 1 is a CT scan of an NSCLC patients lungs as it progresses in stages, we can see images of stages 2, 3 and 4 of lung cancer. From CT scan images, doctors can diagnose the stage by using the size of the tumour (and in some cases the position of the tumour). This image highlights the importance of early cancer detection, with the stage 2 tumour causing little damage in comparison to a stage 4 tumour.

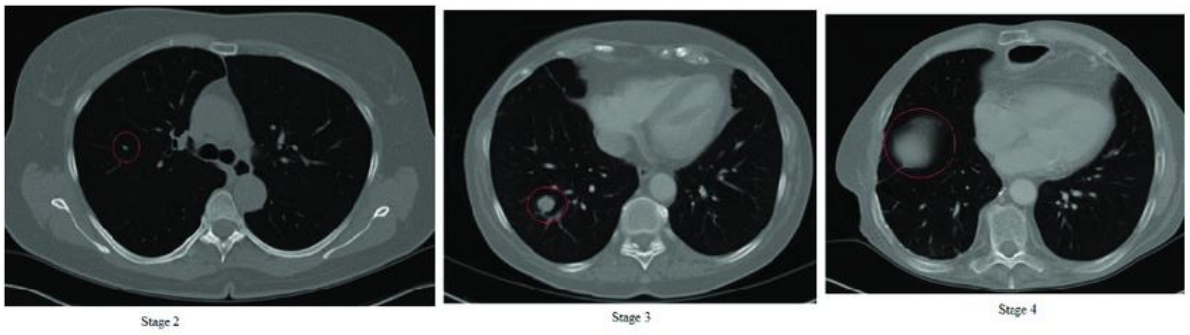

Figure 1. CT scan images of an NSCLC patient through stages 2, 3, and 4 (Jakimovski and Davcev).

Treatment regime innovation has made untellable improvement for patients with NSCLC. Progressing from the introduction of chemotherapy in 1943, NSCLC patients could only expect a 2 – 4-month lifespan expectancy and even shorter odds for remission (Jaklitsch et al.). With the introduction of more fine-tuned treatment regimens; such as Targeted Therapy, the average 5-year relative survival rate for (localized) NSCLC patient is 65%. Targeted therapies aim to produce similar clinical outcomes as chemotherapy by removing cancerous cells by interfering with genes and proteins and interacting with periphery to truncate the growth of a tumour.

Signalling pathways are the key target for these treatments and each treatment will have a specific pathway that it intends to affect. Signalling pathways are a series of chemical reactions in which a group of molecules in a cell work together to control a cell function, such as cell division or cell death. Cancer hijacks these pathways and repurposes them to kill immune cells and reproduce cancerous cells. Figure 2 displays the mechanism of action for an EGFR inhibitor.

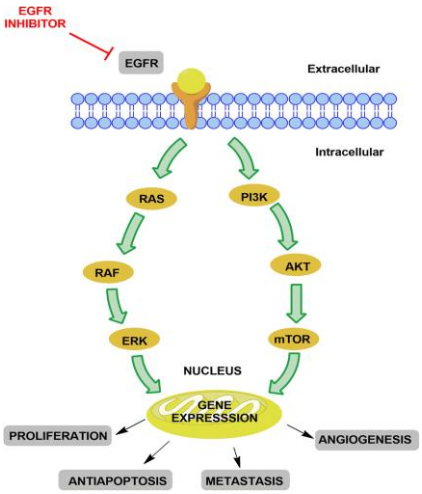

Figure 2. EGFR Signalling pathway (Srivastava et al.)

The Epidermal Growth Factor Receptor (EGFR) signalling pathway is targeted by many therapies, as it is one of the most important genes in cell division, proliferation and survival. The EGFR is susceptible to mutation and changes in this gene can cause EGFR proteins to be produced at a faster rate than normal, which in turn, can accelerate the growth of cancer also. Very similar to this, is the Vascular Epidermal Growth Factor (VEGF), which controls proliferation, promotes endothelial cell growth, migration, and survival from peripheral blood vessels. Changes to VEGF can ultimately cause angiogenesis; the formation of new blood vessels which cancer can use to enhance the availability of nutrients from the bloodstream to tumours (Adair and Montani). This can also unlock the potential for cancers to metastasize and spread around the body.

The Rearranged During Transfusion (RET) signalling pathways are similar in function to the EGFR as it also controls growth, proliferation and cell division, yet this gene affects renal organs; developing spermatogonial stem cells, urinary tract, and kidneys (TAKAHASHI).However when this gene mutates, it is linked to cases of NSCLC and Thyroid cancer. The MET signalling pathway resides within the cell, and is the communicator for internals and externals. When mutated and functioning in a tumour, MET's will promote cell mitosis and survival, whilst also increasing motility and promoting metastasis. The final signalling pathway mentioned in this paper is the Anaplastic Lymphoma Kinase (ALK) signalling pathway, ALK's are present in the body from an embryo and controls the growth and development of the nervous system and gastrointestinal system. ALK produces proteins that promote cell division, and therefore are maladministrated by cancer cells, producing more cancerous cells.

The drug weight of each of these treatments is also monitored as this can affect the bioavailability of the drug. There is a problem, in that, smaller molecules can penetrate cell membranes easily whereas larger molecules cannot penetrate all membranes, and often must donate energy to cross membranes into cells. This is largely down to the solubility of a drug and as smaller particle drugs have higher solubility, simple diffusion can occur. Large particle drugs require carrier proteins or energy to initiate active transport of these particles, delaying the delivery of drug and increasing the resources needed to absorb the drug (Ascendia Pharma). Thus smaller drug weight, in theory, is more efficient in terms of absorbing drugs.

Targeted Therapy has lots of conflicting studies on its efficacy, tolerability, and eligibility. Efficacy is typically judged by monitoring progression free survival (PFS) and overall response rate (ORR). PFS is defined as the time from random assignment in a clinical trial to disease progression or death from any cause (Gutman et al.). PFS is a useful outcome to measure as it shows the length the patient can live with this treatment before the disease progresses further or the patient dies. PFS eludes to the idea of how long the patient will live comfortably after undertaking this course of treatment. ORR is the proportion of patients in a trial that responds to treatment as is designed, this is different from study to study as the objective changes. The ORR is incredibly helpful at assessing functionality without the influence of other variables. ORR values can allow for direct comparison of functionality, highlighting trials where drugs are underperforming, which can then be looked at again with more evidence to find what is affecting this.

Response rates for targeted therapy in general sits at 25% - 75% however this treatment is hard to access and requires vigorous genetic and morphologic screenings, ultimately only 20% of patients are able to receive this (Gal Dinstag et al.). These statistics only consider diagnosed patients, patients with cancer in developing and low-income countries have limited access to targeted cancer therapies. The transitional nature of these economies has influenced health care funding, which has resulted in the unavailability of targeted cancer treatments (Kurtovic-Kozaric et al.).These conflicting studies create a bubble of confusion, where drugs become misunderstood and treatment options are used inefficably.

The forms of targeted therapy analysed and evaluated in this paper all target one of five different signalling pathways. Erlotinib, Cetuximab, Gefitinib and Afatanib target the aforementioned EGFR pathway, Bevacuzimab and Osimertinib target the VEGF pathway, Crizotinib, Ceritinib, and Alectinib target the ALK pathway whilst Vandetanib and Cabozantinib target the RET and MET signalling pathways respectively. The number of treatments assigned to each pathway also shows how prevalent they are clinically; EGFR being the most common target in existing and new therapies, ALK, VEGF, RET, and, MET are less commonly targeted and are represented accordingly.

Target	Pharmaceutical name
EGFR – Epidermal Growth Factor Receptor	Erlotinib (Tarceva) Cetuximab (Erbitux) Gefitinib (Iressa)

	Afatanib (Giotrif)
VEGF- Vascular Epidermal Growth Factor	Bevacuzimab (Avastin) Osimertinib (Tagrisso)
ALK – Anaplastic Lymphoma Kinase	Crizotinib (Xalkori) Ceritinib (Zykadia) Alectinib (Alecense)
RET – Rearranged During Transfusion	Vandetanib (Caprelsa)
MET – Mesenchymal; Epithelial Transition	Cabozantinib (Cabometyx)

Figure 3. Table displaying drugs analysed in this paper and their respective signalling pathway target.

1. Aims and Objectives

The overarching aim of this investigation is to evaluate targeted therapy in the treatment of non-small cell lung cancer. A secondary aim, if possible, is to crown one of these therapies as the 'best' using predetermined variables (PFS, ORR, QOL, Adverse Events) pertaining to functionality and effect on patients.

To achieve this, particular objectives must be completed as follows;

1. Which treatment extends life the longest without disease progression.

2. Which treatment has the greatest responsivity in the most patients.

3. Which treatment incurs the least Adverse Effects / the least detrimental Adverse Effects.

4. Which treatment has the greatest improvement on Quality of Life.

All these criteria carry the same weighting, thus positive improvements in life extension with a worsening in quality of life would nullify each other. The 'best' treatment will be determined by a combination of the aforementioned criteria. Collecting data on these parameters will create a summarised report on the efficacy of each treatment; Weaknesses and strengths of each can be identified and treatment regimens can be constructed to fit NSCLC patients for improved clinical outcomes.

2. Methods

To conduct this investigation, particular procedures must be undertaken, and various processes must follow a strict criterion to ensure the data is easily understood and any inferences drawn are accurate and reproducible. The first method put in place is the purposive sampling used when collating papers for analysis. Purposive sampling is a type of sampling technique where candidates are chosen based on favourable characteristics (Palinkas et al.). In this case, eligible studies were drawn from two databases: Pubmed and ClinicalTrials.gov from 2004 to 2024. The keywords required must include 'NSCLC' or 'non – small cell lung cancer' and one or more, 'Bevacuzimab', 'Alectinib', 'Afatanib', 'Gefitinib', 'Vandetanib','Ceritinib', 'Osimertinib', 'Crizotinib', 'Erlotinib','Cabozantinib', 'Cetuximab'. Duplicate papers and papers

waiting on result submission were removed accordingly. Figure 4 shows the process followed during data acquisition.

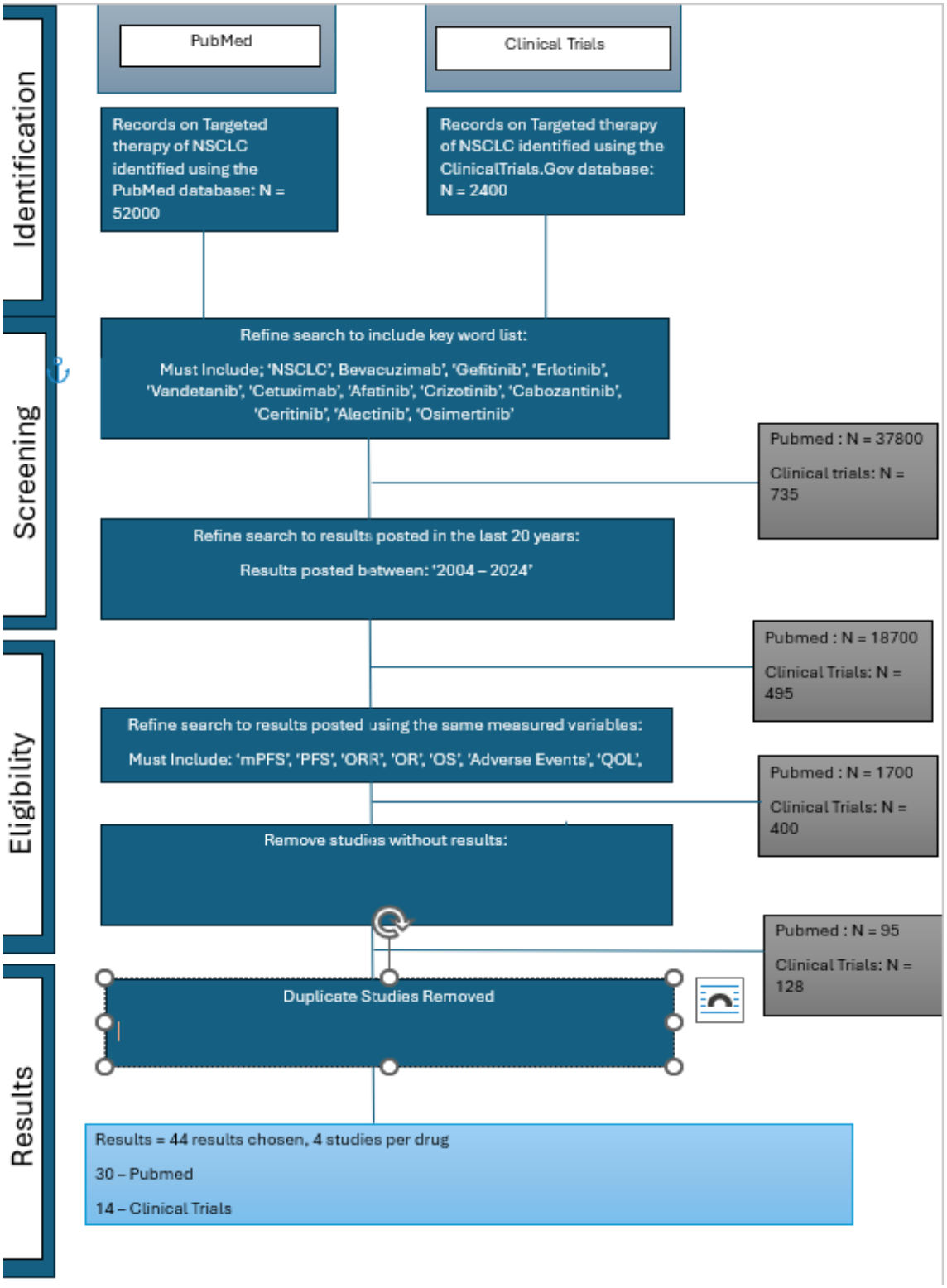

Figure 4. Flowchart depicting the exclusion process during data acquisition.

Results

All selected targeted therapies were first compared based on the average progression-free survival (PFS) experienced by patients (Figure 1). The targeted therapies that resulted in the greatest PFS were Alectinib (14.95 months) and Afatanib (14.87 months), shortly followed by Gefitinib at 13.33 months. Vandetanib. Certinib, Bevacuzimab, Osimertinib, Crizotinib and Erlotinib all performed similarly, with average PFS ranging from 8.82 to 11.1 months. The therapies that offered the shortest PFS were Cabozantinib (4.3 months) and Cetuximab (4.225 months). The mean average across all the targeted therapies was 10.293 months.

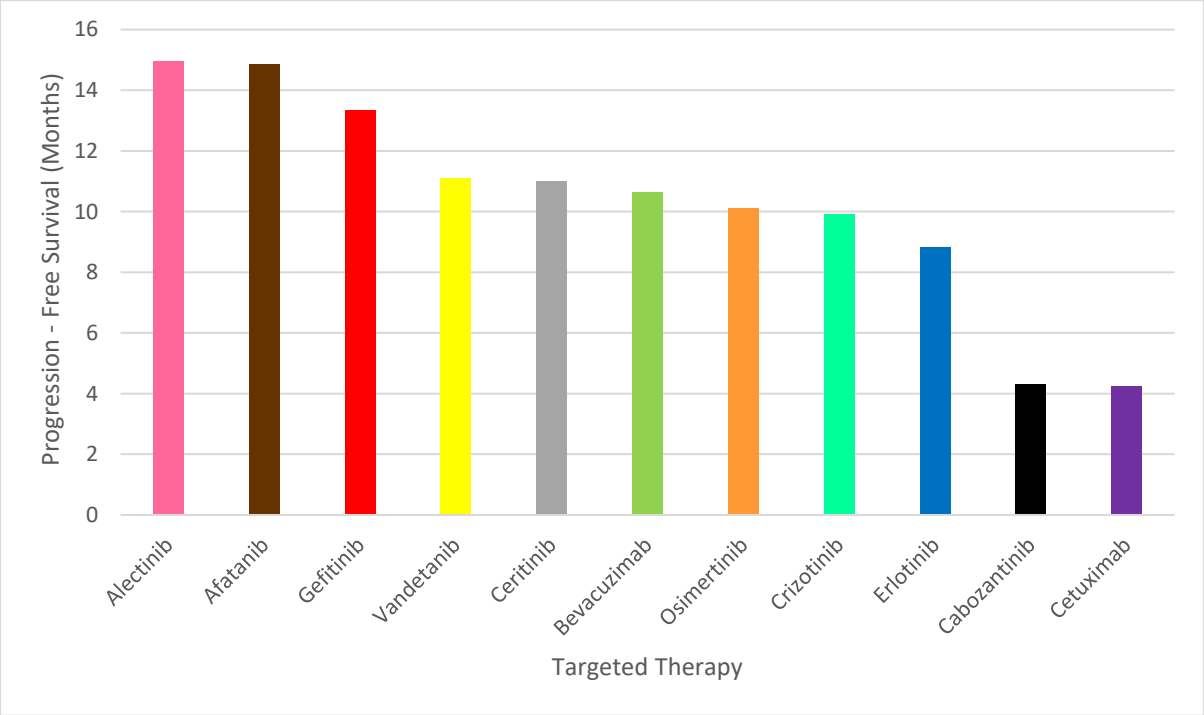

Figure 5. Average progression-free survival (PFS) of patients treated with a targeted therapy. Therapies are displayed in order of average PFS, from left to right.

The selected targeted therapies were next compared based on the average overall response rate (Figure 2). The targeted therapies showing the highest ORR were Crizotinib (76%) and Osimertinib (65%) (Shaw et al.). ORR lulls to an average between 25% and 40% for Alectinib, Bevacuzimab, Erlotinib, Gefitinib, and Cetuximab. The lowest performing therapies were Afatanib and Cabozantinib, recording 20% and 8.2% objective response rate(Miller et al.). Vandetanib and

Ceritinib have been excluded from this figure and ORR data for these therapies was not available.

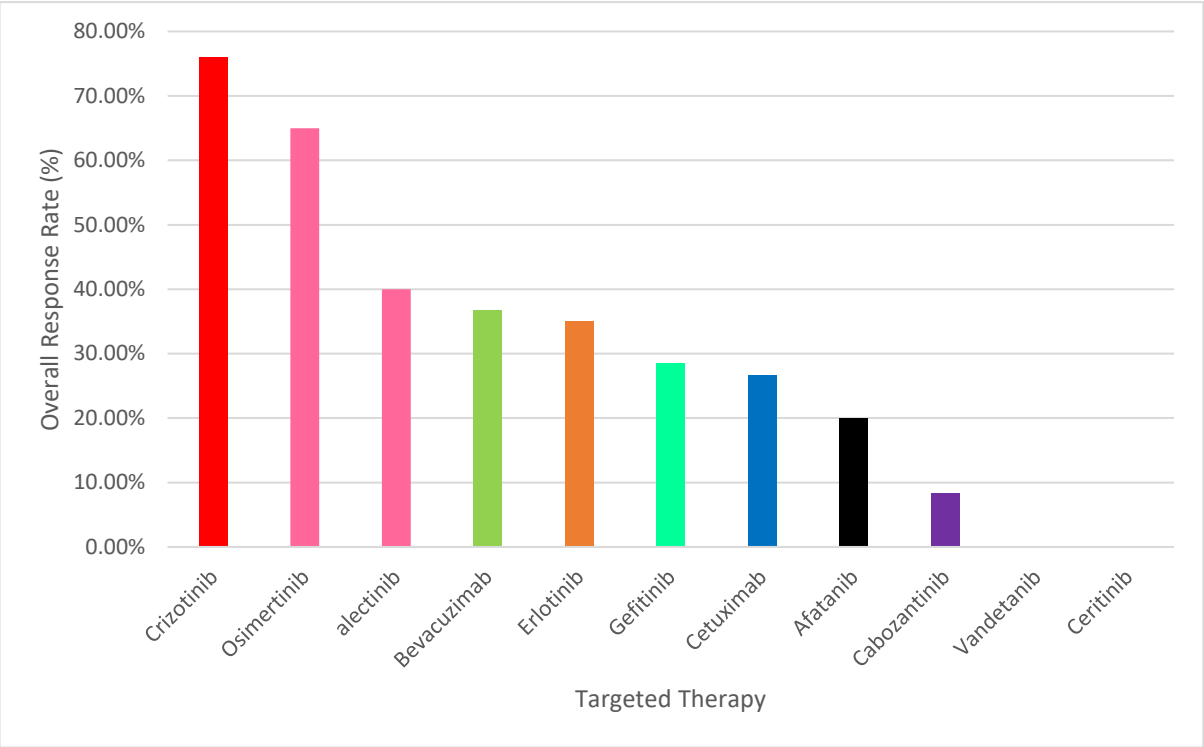

Figure 6. Average overall response rate (ORR) displayed from greatest ORR to lowest ORR, from left to right.

The PFS was next assessed in relation to the targeting approach of the therapy (Figure 3). All targeted therapies were sorted into the signalling pathways that they are designed to affect, EGFR, VEGF, ALK, MET, and RET. EGFR had the greatest range of datapoints, from 2.9 to 25 months, followed closely by the MET pathway ranging from 4 to 18.7 months. VEGF and ALK pathways had similar sized ranges; VEGF displaying 4.8 to 17.7 months and ALK slightly higher from 5.4 to 20.3 months. RET had only one datapoint for PFS (Cabozantinib) which was an average of 4.3 months.

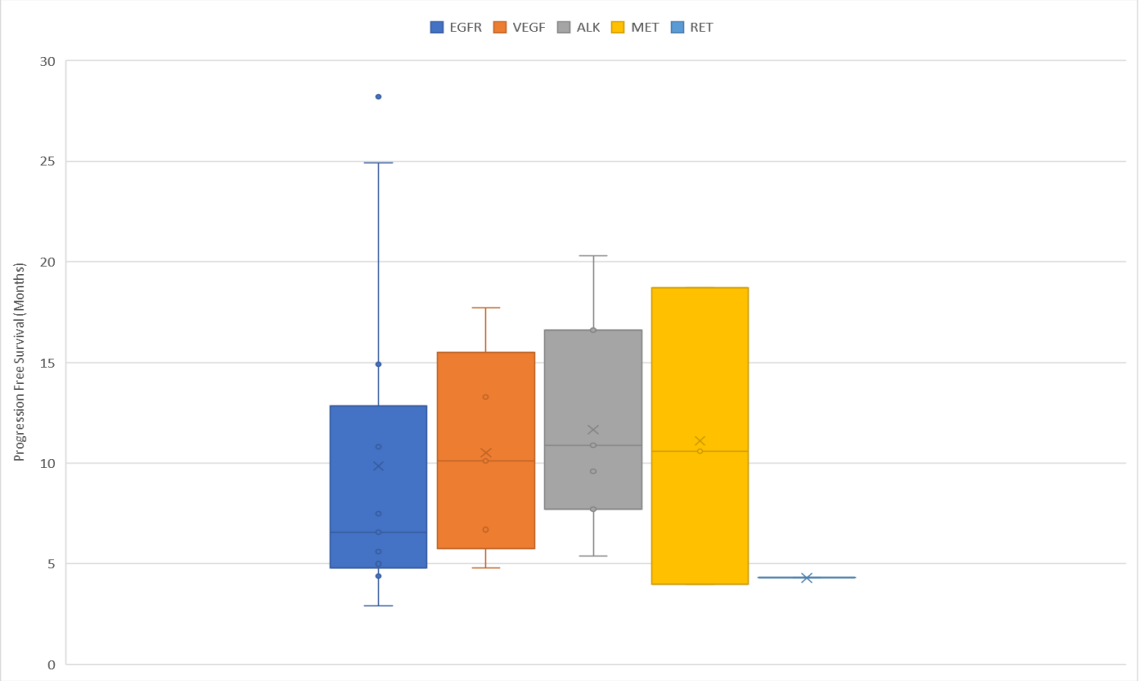

Figure 7. Box and Whisker Plot for the PFS of each targeted therapy option.

The ORR was next evaluated in relation to the signaling pathway targeted (Figure 4). The targeted therapies were again sorted into their respective targets to display any relationships between the pathway targeted and responsivity by the patient. The greatest range of ORR is the ALK signalling pathway with response rates from 26% to 87.5%. EGFR and VEGF are the next two greatest ranges, with VEGF starting higher with 31.5% to 65%, and EGFR with a lower range of 7% to 43.3%. The MET pathway had only one datapoint with 0% responsivity and RET had only one 8.2% response rate datapoint.

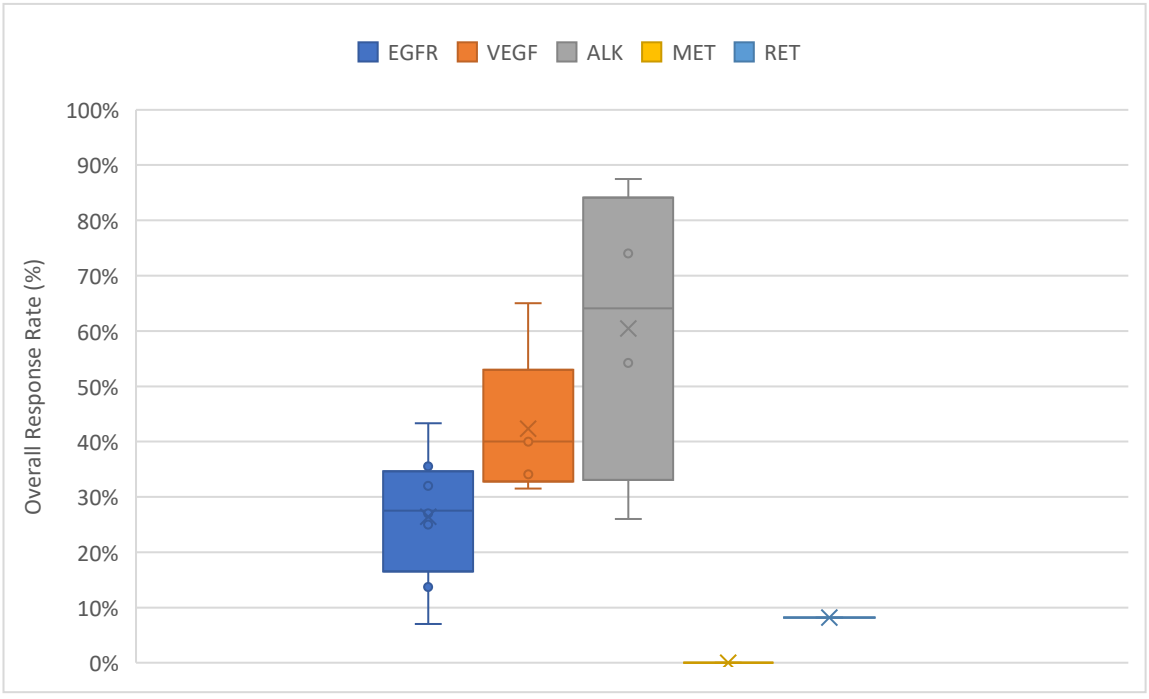

Figure 8. Box and Whisker Plot for the ORR of each targeted therapy option

The next variable assessed was drug weight to assess the relationship between PFS and the size of the drug. There is a positive trend of higher drug weights, providing higher lengths of PFS. The heaviest drug (Afatanib) had the second highest PFS length of 14.86 months, closely beaten by Alectinib with 14.95 month PFS (Hida et al.). The lightest drug (Cetuximab) had the lowest PFS of 4.225 months (Kim et al.). Two treatments fail to follow the trendline, Bevacuzimab and Cabozantinib, as Bevacuzimab is the second lightest treatment options but boasts a 10 month PFS length. Cabozantinib is the second largest treatment option yet only provides 4.3 months of PFS, only 0.05 more months than the lightest treatment(Neal et al.). All other treatments continue to increase PFS as weight increases.

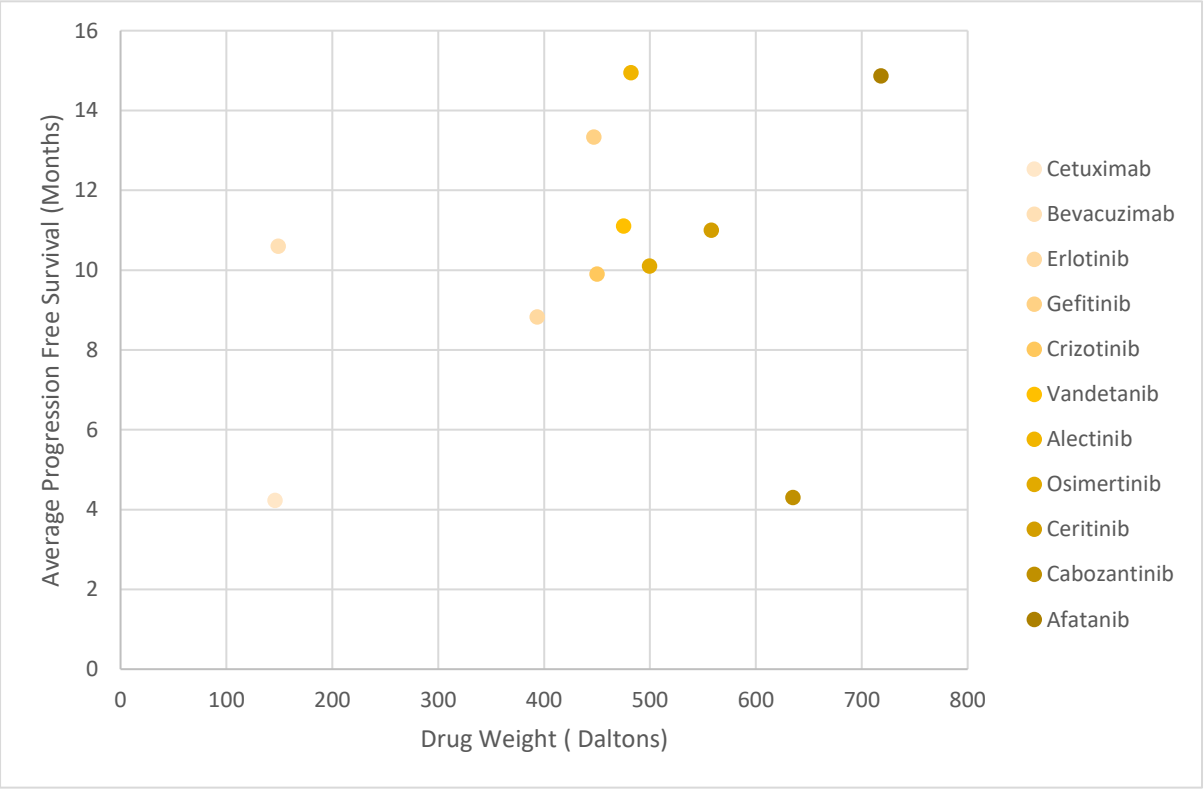

Figure 9. Scatter Plot for Drug weight and PFS of each Treatment Option

PFS was then swapped for ORR in the next figure, displaying the relationship between the size of the drug and the response rates of each treatment. Again, Vandetanib and Ceritinib have been excluded from this figure as ORR data for these therapies was not available. There is not as definitive of a trend as figure 5 yet the greatest ORR values stem from drugs that weigh between 300 and 500 Daltons. Cabozantinib and Afatanib, were the heaviest drugs with ORR's of 8.2% and 20% respectively, whilst Cetuximab and Bevacuzimab had ORR's of 26% and 36.65% despite being the two lightest drugs.

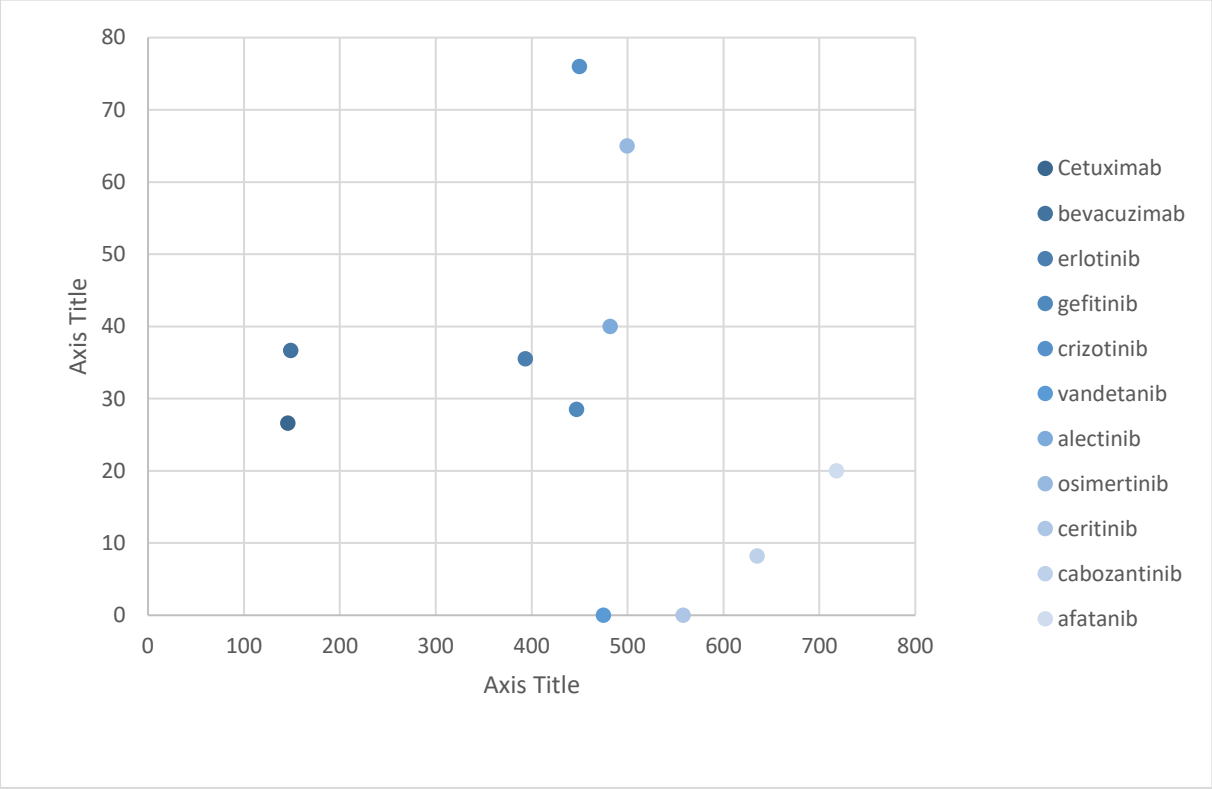

Figure 10. Scatter Plot for Drug weight and PFS for each Targeted Therapy.

To assess the overall performance of each targeted therapy in both PFS and ORR simultaneously, a hierarchy was made for the treatment options based on performance. A combined score of both PFS and ORR would not provide a reliable ranking for the treatment options, as ORR had a higher range of values. To avoid this problem, both treatments were given a rank for PFS and ORR, and the combined ranking provided an overall ranking determined by performance in both PFS and ORR. The formula used to determine ranking was as follows:

For each treatment option :RankPFS = $\left(\frac{MinimumPFS - PFS\ score}{MaximumPFS - MinimumPFS}\right)$

For each treatment option: RankORR =$\left(\frac{MinimumORR - ORR\ score}{MaximumORR - MinimumORR}\right)$

Overall Rank = RankPFS + RankORR

This gave each treatment a number from 0 to 1 depending on their performance in that variable. A rank value of 0 would mean that is the worst performing drug, and

vice versa, a rank of 1 means that it is the best performing drug. These scores are then combined to find the best performer over both measurements.

The worst performing drugs were Cabozantinib, and Cetuximab with 0.115 and 0.35 composite scores, respectively. This is starkly contrasted by the two highest performing drugs: Alectinib and Crizotinib. Alectinib with a composite score of 1.526, just behind Crizotinib with a 1.529 composite score. Treatment options in the mid-range from 0.632 to 1.4 included: Ceritinib, Vandetanib, Gefitinib, Erlotinib, Bevacuzimab, and Afatanib. Unsurprisingly, the two top performers for PFS and ORR were the two top performers overall also, however an interesting statistic presents itself. Crizotinib trumps Alectinib by a mere 0.003 in terms of overall rank however has almost double the ORR score of Alectinib. This is a 90% percentage increase in ORR compared to a 50% decrease in PFS (Peters et al.). suggesting that PFS is a better indicator of performance than ORR, as it holds more weight in terms of performance rank. Furthermore, Ceritinib and Vandetanib, which had no ORR data, ranked higher than Cabozantinib and Cetuximab, again implying that PFS is a more valuable indicator of performance.

DRUG	PFS	ORR	MIN-PFS	PFSRANK	MIN-ORR	OR-RANK	RANK
cabozantin	4.3	8.2	0.075	0.00699301	8.2	0.107895	0.114888
Cetuximab	4.225	26.6	0	0	26.6	0.35	0.35
ceritinib	11	0	6.775	0.63170163	0	0	0.631702
vandetanib	11.1	0	6.875	0.64102564	0	0	0.641026
erlotinib	8.82333	35.5	4.5983	0.42874592	35.5	0.467105	0.895851
bevacuzim	10.6	36.65	6.375	0.59440559	36.65	0.482237	1.076643
gefitinib	13.3333	28.5	9.083	0.84689977	28.5	0.375	1.2219
afatanib	14.8667	20	10.642	0.99226107	20	0.263158	1.255419
osimertinib	10.1	65	5.875	0.54778555	65	0.855263	1.403049
alectinib	14.95	40	10.725	1	40	0.526316	1.526316
crizotinib	9.9	76	5.675	0.52913753	76	1	1.529138

Figure 11. Table Displaying Targeted Therapies in Order of Performance

Treatments that had the greatest increase in both PFS and ORR are further dissected here by displaying the prevalence of adverse effects during treatment. The treatment options displayed in this figure are as follows: Alectinib, Afatanib, Gefitinib, Bevacuzimab, Osimertinib, and Crizotinib. The Adverse effects are limited to symptoms of: Diarrhoea, Rash, Hypertension, Infection, and Neuropathy. Rash and Diarrhoea were the most prevalent adverse events with symptoms existing in at least one patient for every treatment option and the highest percentage of any adverse events; over 60% of patients using Crizotinib experienced diarrhoea and over 60% of Afatanib users experienced a rash. Hypertension had the lowest prevalence with Afatanib and Gefitinib showing low percentage of this event whilst Bevacuzimab registered 15.6% of patients exhibiting new symptoms of hypertension (Johnson et

al.). Afatanib had the smallest number of any adverse event, with no reports of neuropathy and less than 10% prevalence for Diarrhoea, Hypertension, and Infection.

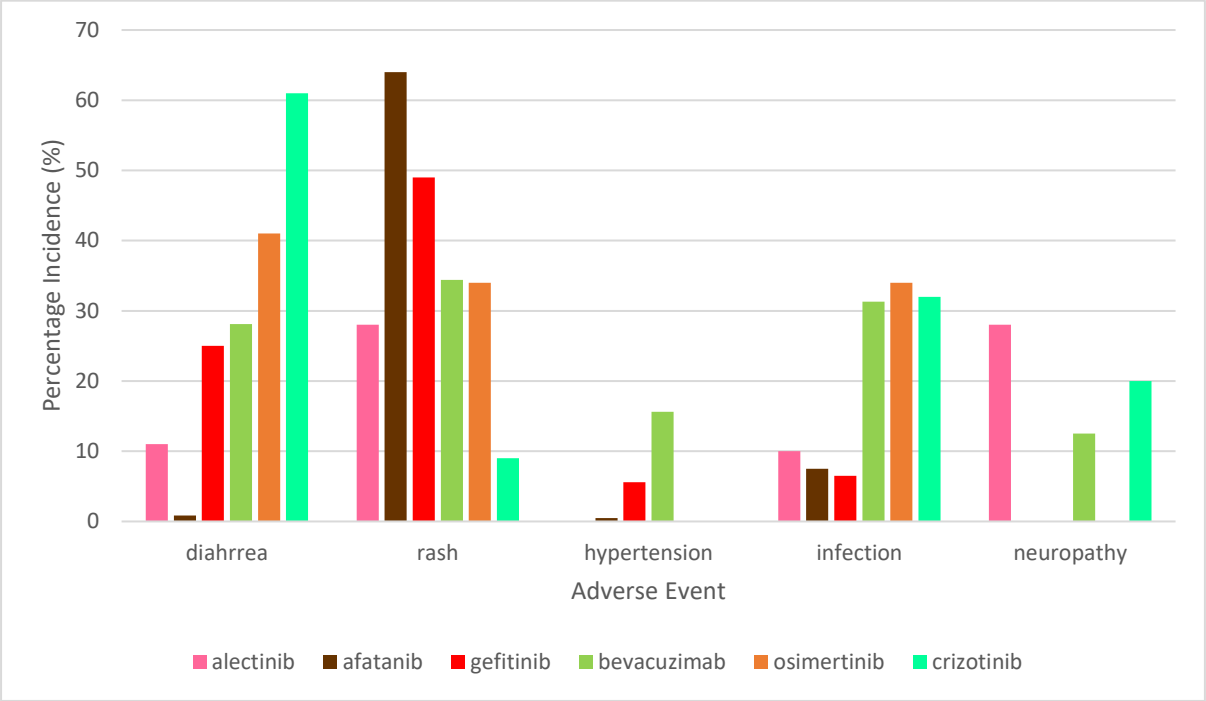

Figure 12. Clustered Bar Chart displaying the prevalence of Adverse events in the highest performing targeted therapies.

Discussion

PFS

The majority of treatments assessed proved to be valid treatment options for NSCLC patients by improving PFS, ORR and exhibiting minimal adverse events. Figure 1 displays the average PFS of each targeted therapy from highest to lowest. The scores showed a steady decrease in PFS for each therapy yet the highest and lowest PFS were disparate in length. Alectinib, Afatanib and Gefitinib were the highest scores of 14.95, 14.87 and 13.333 months respectively. Treatment options decrease steadily and the next six treatments; Vandetanib, Ceritinib, Bevacuzimab, Osimertinib, Crizotinib, and Erlotinib scored PFS' of 11.1 to 8.8 months. These are then followed by a sudden drop to the two worst performing drugs in terms of PFS: Cabozantinib and Cetuximab,over 3 times shorter PFS than the highest treatments with 4.3 and 4.225 month PFS scores. Despite Cabozantinib and Cetuximab performing considerably worse than all the other treatment options in this figure, it should be noted that the average PFS for chemotherapy, is 4.2 to 5.2 months (Miyazaki et al.), Therein, even the worst targeted therapy treatment matches the ability of chemotherapy and the best treatments are significantly better at improving PFS.

Expanding on this, PFS is a good indicator of improvement in disease progression as it eludes how much time can be given back to the patient post diagnosis. Yet PFS is limited for a number of reasons, one being that it is a hard variable to measure. The time for the patient to begin its 'PFS' is subject to discussion as this could be before, after or during treatment, and even when the disease does progress, this is hard to measure efficiently as asymptomatic disease progression is also common. The clinical benefit of PFS is hard to measure also as it is subjective to the patients point of view, data on this is hard to come by and the value placed on PFS by patients is incredibly misunderstood (Fallowfield and Fleissig). Undeniably, a high PFS is a good marker for a drug and should be seen as a positive attribute, however the goal should be to be rid of the disease and so more variables must be assessed to determine which treatment can provide the greatest clinical outcome.

PFS by signalling pathway

To better understand the relation between these treatment options and PFS, the treatment options are organised into the signalling pathways they are designed to target. Figure 3 displays the PFS scores of multiple studies for each drug in boxplots categorised by EGFR, VEGF, ALK, MET, and RET as a measure of dispersion. EGFR had the greatest range of PFS scores, from 2.9 to 25 months, EGFR being targeted by Erlotinib, Cetuximab, Gefitinib, and Afatanib. This was closely followed closely by the MET pathway ranging from 4 to 18.7 months. VEGF and ALK pathways had similar sized ranges; VEGF displaying 4.8 to 17.7 months and ALK slightly higher from 5.4 to 20.3 months.

Figure 3 displays stark differences in PFS among different pathways and eludes that EGFR targeted drugs have the potential to extend life by two years disease free. However, it should be noted that EGFR targeted drugs simultaneously starts its rage considerably lower than the other signalling pathways, the lowest datapoint being 2.9 months. This would insinuate that EGFR has the greatest potential for treatment success, however there is lots of evidence of these drugs not reaching this potential and even having the lowest PFS of all signalling pathways. The reason for EGFR being such a popular target and providing high PFS scores is that it is one of the most important pathways in mammalian cells. EGFR mutations, and in particular exon 20 mutations on the EGFR gene are a major cause for cancer, occurring in 1 in every 30 cases of lung cancer (Wang et al.). Thus, a treatment that focuses on one of the largest causes of cancer would be incredibly effective against the majority, yet EGFR will struggle with more specialised cancer with different mutations as the targeting mechanisms are no longer effective.

It could be argued that VEGF and ALK are more suitable targets for treatment for the average NSCLC patient as there is less variability in data. PFS with VEGF or ALK as targets would not reach as high as 25 months like EGFR, yet the minimum score would be double that of EGFR, and thus an average PFS is more likely. Targeting these signalling pathways could be of more use to patients who have tried EGFR targeted therapies in the past. This also highlights the need for genetic screening when diagnosing and treating patients with targeted therapies as the targeting mechanisms clearly play a major factor in its effectiveness.

PFS by drug weight

Continuing the introspection into the PFS of these treatments, drug weight was the next variable to be analysed in comparison. Figure 5 depicts a scatter plot for drug weight and PFS of each treatment option with treatments plotted in order of lowest to highest drug weight. There is a clear correlation between drug weight and PFS as PFS increases as drug weight increases, the heaviest drug; Afatanib had the second highest PFS (14.87 months), closely beaten by Alectinib (14.9 months). The lightest drug was Cetuximab with 4.225 months of PFS (Lynch et al.). Two treatments buck the trend, Bevacuzimab has the second lowest drug weight yet has a 10.6 month PFS and the second heaviest drug, Cabozantinib has a PFS of 4.3 months. The 'goldilocks region' of drug weights for PFS efficacy is between 300 and 600 Daltons as all treatment options within this range has a PFS between 8.8 months and 14.95 months.

Drug weight is already a massive limiting factor in the uptake of drugs due to membrane permeability. Small molecule drugs pass through membranes much easier as they can use simple diffusion. Larger molecules must use a carrier protein or donate energy in active transport instead. The blood brain barrier (BBB) is a key membrane filtering substances form the bloodstream to the brain and molecules up to 450 Daltons are able to diffuse across it (Melanie et al.). This means that Cetuximab, Bevacuzimab, Crizotinib, Erlotinib, and Gefitinib are eligible for BBB diffusion, yet are lower in PFS in comparison to the heavier drugs. This would elude to the idea that drugs capable of crossing this barrier are less effective and perhaps are expelled when attempting this. There is also always the possibility of one of these drugs entering the brain and causing neural damage by interfering with the signalling pathway genes that are also present in the brain (Dotiwala et al.).

ORR

Moving onto another performance indicator of these drugs, the average objective response rate (ORR) was recorded for each of these treatment options. ORR is a great indicator of the efficacy of the drug and is defined as the proportion of patients who have a partial or complete response to therapy; it does not include stable disease and is a direct measure of drug tumoricidal activity (Villaruz and Socinski). ORR in clinical trials is usually graded, for example, an ORR > 60% is rated as Grade 3, while an ORR of 40–60% is considered as Grade 2. Thus, a high ORR is highly valued (Oda and Narukawa). ORR is a good clinical endpoint as it shows the likelihood of a partial or complete response, yet ORR does not show the breakdown of how well a patient responds, for example: an ORR of 99% could be 99 patients having a partial response, and an ORR of 50% could be 50 patients exhibiting a complete response. This can cause discrepancies and make a high ORR deceivingly desirable.

In this study, the ORRs of the 11 investigated treatments ranged from 8.2% to 76%. Figure 2 displays the average ORR of each treatment in a bar graph, Vandetanib and Ceritinib have been excluded from this figure and ORR data for these therapies was not available. The targeted therapies showing the highest ORR were Crizotinib (76%) and Osimertinib (65%). Alectinib, Bevacuzimab, Erlotinib, Gefitinib, and

Cetuximab have the next highest ORR with an average between 25% and 40%. The lowest performing therapies were Afatanib and Cabozantinib, recording 20% and 8.2% objective response rate. Only Crizotinib and Osimertinib reached a grade 3 ORR, Alectinib, a grade 2 and the remaining treatment options receiving a grade 1 / no grade. Therefore, Crizotinib and Osimertinib are the most favourable as they provide the highest chance of a partial or complete response.

ORR by signalling pathway

To better understand the involvement of signalling pathways and its effect on ORR, the treatment options are divided into the signalling pathways they target; EGFR, VEGF, ALK, MET, and RET. Each signalling pathway performed very differently in terms of ORR compared to PFS, the greatest range of values coming from therapies targeting the ALK pathway (26% to 74%). The next greatest range is close between EGFR and VEGF. EGFR has a range between 7% and 43.3% whilst VEGF has a range between 31% and 65%, although similar in size, VEGF's range begins much higher than EGFR and which would suggest that it is more prevalent in providing responses. The RET pathway had no available ORR data and the MET pathway had only one datapoint of 8.2%, consolidating the idea that ALK, VEGF and EGFR are more plausible options and have higher rates of responsivity.

Box and whisker plots are helpful in identifying the variance of data and allow for a large scale of datapoints to be visualised. However, these charts are generally used to identify outliers, especially when there is an uneven distribution of data. This relies upon using quartiles as the measure of skewness, representing a loss in data and lack of detail behind the distribution of data (Meloun and Militký).

ORR by drug weight

To explain the relationship between these drugs and ORR, the drugs have been weighed, placed in a scatter plot in order of size against their respective ORR scores. Scatter plots are incredibly useful to display data in a manner easier to identify trends and correlations. There are, however, drawbacks with scatter plots predominantly; issues with drawing conclusions from the data. A clear representation of the data in a 'readable' figure allows for a relationship to be deduced, however the scatter plot cannot provide the precise extent of association and cannot indicate a quantitative measure of this correlation. As such any relationships identified need to be statistically tested as they are merely a visualisation of datapoints, and the correlation does not hold any scientific merit.

Figure 6 plots the weight of each drug against their respective ORR scores. Again, Vandetanib and Ceritinib have been excluded from this figure as ORR data for these therapies was not available. The heaviest drug in this figure is Afatanib with a relatively low ORR of 20%, this is similar to the lightest drug, Cetuximab, which has an ORR of 25%. Already the relationship seen in Figure 5 cannot be the case for ORR, as there is a decrease in ORR between the lightest and heaviest drug. On the

other hand, the drugs within 300 and 500 Daltons, like Figure 5, performed the best in terms of ORR with a range of 35% to 76%.

Treatments weighing in the range of 300 to 500 Daltons had the highest ORR scores and 2 out of 3 of the highest PFS scores. Therein, drugs weighing in this range are the most likely to produce a positive impact to treatment. This is most likely a consequence of smaller drugs being more motile in the body. Lighter drugs don't require energy when diffusing across cell membranes and can infiltrate large areas of the body quickly and efficiently. This does not mean that large particle drugs are futile, the strengths of large particle lie in its function rather than motility. As they are more specific in function, less unregulated damage occurs and due to its size, less cells are affected (Ngo and Garneau-Tsodikova).

Performance Assessment

The rank scores for both PFS and ORR for each drug were combined to create a comparison of the drugs combined scores. First the data was normalised, assigning each PFS/ORR score a rank from zero to one , zero the worst, one the best. These rank numbers where then combined to create a composite score, indicatory of the drugs performance in both PFS and ORR. Figure 11 displays this table with the treatments in order of their overall rank. The highest performing treatments were Crizotinib and Alectinib with ranks of 1.529 and 1.526 respectively. Crizotinib has a substantially higher ORR score than Alectinib (90% increase), yet has only a 50% decrease when it comes to PFS. This would suggest that PFS is a better indicator of performance than ORR, as it holds more weight in terms of performance rank. Furthermore, Ceritinib and Vandetanib, which had no ORR data, ranked higher than Cabozantinib and Cetuximab, the two lowest performing drugs, again implying that PFS is a more valuable indicator of performance. Ceritinib, Vandetanib, Erlotinib, Bevacuzimab, Gefitinib, Afatanib, and Osimertinib are in the mid-range, from 0.631 to 1.403.

Erlotinib had the most even distribution of performance over both PFS and ORR with 0.428 and 0.467, suggesting that it has similar capacity for extending life and responsivity. Although excelling in both PFS and ORR would be ideal for the 'greatest performer' in curing NSCLC, it is more realistic that high PFS scores incur low ORR and vice versa. A high PFS is less likely to occur for all patients, reducing the overall response rate, simultaneously it is more likely for all patients to have a shorter extension of life and thus the parameters for these statistics need to be well thought out.

Adverse events

The top performing drugs were then further analysed for the occurrence of adverse events during treatment. The 5 adverse events focused on were Diarrhoea, Rash,

Hypertrophy, Infection, and Neuropathy, these were chosen so as to show the proportion of mild, considerate, and severely adverse events. Figure 8 is a clustered bar chart to show the prevalence of these adverse events for each of the highest performing treatment options. Unsurprisingly, Diarrhoea and Rash were the most commonly occurring adverse events amongst these treatments and are common amongst all targeted therapies. This is caused by a number of reasons, signal pathway inhibitors / agonists can have multiple effects on cells and cause unwanted side effects. Targeted therapies often come in the form of biological agents such as monoclonal antibodies like Bevacuzimab, this can cause irritation in the bowels and elicit symptoms such as Diarrhoea. Monoclonal antibodies are also commonly associated with bowel perforations, whereas EGFR inhibitors are frequently associated with Diarrhoea (Dahiya et al.). Hypertension was the least prevalent in all studies, only experienced by patients taking Afatanib, Gefitinib, and Bevacuzimab. 0.5% of Afatanib and Gefitinib patients experienced hypertension whilst 15% of Bevacuzimab patients experienced this symptom.

There are some flaws with the information provided here however, as the data is not reproducible as a sample for the wider population. There are many more adverse events occurring in these treatment trials, some much more severe and impactful on the patient. The figure above does not display the severity of the symptoms experienced by the patient. For example, a large portion of patients may incur symptoms of Diarrhoea, yet it doesn't state the grade of adverse event. Many of the patients experiencing hypertension could have a slight raise in blood pressure, whereas there may be cases of hypertension severely affecting the patients ability to function. It is also impossible to know if the patients experiencing adverse events during trials are experiencing this as a cause of the treatments themselves, or from something else unrelated. Diarrhoea is a common symptom in clinical trials as it is also common in life, occurring commonly from poor food hygiene or poor dieting. This can cause uneven statistics around the prevalence of adverse events occurring and can misplace stress induced hypertension with a possible treatment induced side effect.

3. Conclusion

In conclusion, the assessment of targeted therapy in the management of Non-Small Cell Lung Cancer (NSCLC) reveals both promising advancements and critical considerations. All aspects of this study have been critically evaluated to ensure the conclusions drawn are valid and reproducible. PFS and ORR proved to be reliable indicators of efficacy and the relationship between them has consolidated targeted therapy as a promising treatment option and highlights the need for innovation. As seen in Figure 11, the greatest performer in terms of PFS and ORR, was Crizotinib. Crizotinib had the highest ORR of 76%, a considerable PFS of 9.9, and a moderate prevalence of adverse events. Alectinib was the next closest in rank with a PFS of 14.95, ORR of 40% and a similar prevalence of adverse events. Both these treatments target the ALK signalling pathway, suggesting that ALK targeting treatments are the most effective.

Based purely upon efficacy, Crizotinib and Alectinib are the ‘best’ treatment options for NSCLC, yet some patients will place more importance on toxicity, favouring a drug with less adverse events occurring. The best performing treatment with the least adverse events was Osimertinib. Osimertinib patients only experienced small symptoms of Diarrhoea, rash and infection, suggesting that vulnerable patients such as immunosuppressed or elderly patients would benefit the most from this treatment option. Osimertinib was still the third highest performing drug and as such is a valid treatment option.

However, challenges persist, and the future of targeted therapy is still in question. Further innovation and funding must be placed in targeted therapy to reduce its cost and increase its availability. Addressing these challenges necessitates ongoing research efforts to overcome problems with selectiveness, and enhance access to these life-saving treatments for all NSCLC patients.

Reference list

1. Adair, T. H. and Montani, J.-P., 2010. *Overview of Angiogenesis* [online]. Nih.gov. Available from: https://www.ncbi.nlm.nih.gov/books/NBK53238/.
2. American Cancer Society, 2023. *What Is Lung Cancer? | Types of Lung Cancer* [online]. www.cancer.org. Available from: https://www.cancer.org/cancer/types/lung-cancer/about/what-is.html.
3. Ascendia Pharma, 2021. *4 Factors Affecting Solubility of Drugs | Ascendia Pharmaceuticals* [online]. ascendiapharma.com. Available from: https://ascendiapharma.com/newsroom/2021/07/05/factors-affecting-drug-solubility.
4. Dahiya, D. S., Wani, F., Guidi, J. C. and Kichloo, A., 2020. Gastrointestinal Adverse Effects of Immunotherapeutic Agents: A Systematic Review. *Gastroenterology Research*, 13 (6), 227–232.
5. Dotiwala, A. K., McCausland, C. and Samra, N. S., 2023. *Anatomy, Head and Neck: Blood Brain Barrier* [online]. PubMed. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519556/#:~:text=%5B1%5D%20The%20BBB%20is%20composed.
6. Fallowfield, L. J. and Fleissig, A., 2011. The value of progression-free survival to patients with advanced-stage cancer. *Nature Reviews Clinical Oncology*, 9 (1), 41–47.
7. Gal Dinstag, Shulman, E. D., Elis, E., Ben-Zvi, D. S., Tirosh, O., Maimon, E., Meilijson, I., Elalouf, E., Temkin, B., Philipp Vitkovsky, Schiff, E., Hoang, D.-T., Sinha, S., Nishanth Ulhas Nair, Joo Sang Lee, Schäffer, A. A., Ze’ev Ronai, Juric, D., Apolo, A. B.

and Dahut, W. L., 2023. Clinically oriented prediction of patient response to targeted and immunotherapies from the tumor transcriptome. *Med (New York. Online)* [online], 4 (1), 15-30.e8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10029756/#:~:text=Response%20rates%20in%20the%20setting.

8. Gutman, S. I., Piper, M., Grant, M. D., Basch, E., Oliansky, D. M. and Aronson, N., 2013. *Background* [online]. www.ncbi.nlm.nih.gov. Agency for Healthcare Research and Quality (US). Available from: https://www.ncbi.nlm.nih.gov/books/NBK137763/.
9. Hida, T., Nokihara, H., Kondo, M., Kim, Y. H., Azuma, K., Seto, T., Takiguchi, Y., Nishio, M., Yoshioka, H., Imamura, F., Hotta, K., Watanabe, S., Goto, K., Satouchi, M., Kozuki, T., Shukuya, T., Nakagawa, K., Mitsudomi, T., Yamamoto, N. and Asakawa, T., 2017. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *The Lancet* [online], 390 (10089), 29–39. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30565-2/fulltext.
10. Jakimovski, G. and Davcev, D., 2019. Using Double Convolution Neural Network for Lung Cancer Stage Detection. *Applied Sciences* [online], 9 (3), 427. Available from: https://www.mdpi.com/2076-3417/9/3/427.
11. Jaklitsch, M. T., Strauss, G. M., Healey, E. A., DeCamp, M. M., Liptay, M. J. and Sugarbaker, D. J., 1995. An historical perspective of multi-modality treatment for resectable non-small cell lung cancer. *Lung Cancer (Amsterdam, Netherlands)* [online], 12 Suppl 2, S17-32. Available from: https://pubmed.ncbi.nlm.nih.gov/7551946/.
12. Johnson, D. H., Fehrenbacher, L., Novotny, W. F., Herbst, R. S., Nemunaitis, J. J., Jablons, D. M., Langer, C. J., DeVore, R. F., Gaudreault, J., Damico, L. A., Holmgren, E. and Kabbinavar, F., 2004. Randomized Phase II Trial Comparing Bevacizumab Plus Carboplatin and Paclitaxel With Carboplatin and Paclitaxel Alone in Previously Untreated Locally Advanced or Metastatic Non-Small-Cell Lung Cancer. *Journal of Clinical Oncology*, 22 (11), 2184–2191.
13. Kim, E. S., Neubauer, M. A., Allen Lee Cohn, Schwartzberg, L. S., Garbo, L., Caton, J. E., Robert, F., Reynolds, C. W., Katz, T., Sreeni Chittoor, Simms, L. and Saxman, S., 2013. Docetaxel or pemetrexed with or without cetuximab in recurrent or progressive non-small-cell lung cancer after platinum-based therapy: a phase 3, open-label, randomised trial. *Lancet Oncology*, 14 (13), 1326–1336.

14. Kurtovic-Kozaric, A., Vranic, S., Kurtovic, S., Hasic, A., Kozaric, M., Granov, N. and Ceric, T., 2018. Lack of Access to Targeted Cancer Treatment Modalities in the Developing World in the Era of Precision Medicine: Real-Life Lessons From Bosnia. *Journal of Global Oncology*, (4), 1–5.
15. Lynch, T. J., Patel, T., Dreisbach, L., McCleod, M., Heim, W. J., Hermann, R. E., Paschold, E. H., Iannotti, N., Dakhil, S. R., Gorton, S., Virginie Pautret, Weber, M. and Woytowitz, D., 2010. Cetuximab and First-Line Taxane/Carboplatin Chemotherapy in Advanced Non–Small-Cell Lung Cancer: Results of the Randomized Multicenter Phase III Trial BMS099. *Journal of Clinical Oncology*, 28 (6), 911–917.
16. Melanie, Halwes, M., Nisbet, D. and Collins, D. J., 2023. Breaking barriers: exploring mechanisms behind opening the blood–brain barrier. *Fluids and Barriers of the CNS*, 20 (1).
17. Meloun, M. and Militký, J., 2011. *2 - The exploratory and confirmatory analysis of univariate data* [online]. ScienceDirect. Available from: https://www.sciencedirect.com/science/article/abs/pii/B9780857091093500029.
18. Miller, V. A., Hirsh, V., Cadranel, J., Chen, Y.-M., Park, K., Kim, S.-W., Zhou, C., Su, W.-C., Wang, M., Sun, Y., Heo, D. S., Crino, L., Tan, E.-H., Chao, T.-Y., Shahidi, M., Cong, X. J., Lorence, R. M. and Yang, J. C.-H., 2012. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *The Lancet Oncology* [online], 13 (5), 528–538. Available from: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(12)70087-6/fulltext [Accessed 12 Dec 2019].
19. Miyazaki, K., Toshihiro Shiozawa, Shinichiro Okauchi, Sakurai, H., Hiroaki Satoh and Nobuyuki Hizawa, 2023. NSCLC Patients Achieving Long-term Progression-free Survival With Docetaxel Plus Ramucirumab: A Retrospective Study. *Cancer Diagnosis & Prognosis* [online], 3 (2), 215–220. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9949548/#:~:text=Despite%20these%20evaluations%2C%20the%20median [Accessed 20 Apr 2024].
20. National Cancer Institute, 2021. *Non-Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version - National Cancer Institute* [online]. www.cancer.gov. Available from: https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#:~:text=NSCLC%20is%20any%20type%20of.

21. Neal, J. W., Dahlberg, S. E., Wakelee, H. A., Aisner, S. C., Bowden, M., Huang, Y., Carbone, D. P., Gerstner, G. J., Lerner, R. E., Rubin, J. L., Owonikoko, T. K., Stella, P. J., Steen, P. D., Khalid, A. A. and Ramalingam, S. S., 2016. Erlotinib, cabozantinib, or erlotinib plus cabozantinib as second-line or third-line treatment of patients with EGFR wild-type advanced non-small-cell lung cancer (ECOG-ACRIN 1512): a randomised, controlled, open-label, multicentre, phase 2 trial. *The Lancet Oncology*, 17 (12), 1661–1671.
22. Ngo, H. X. and Garneau-Tsodikova, S., 2018. What are the drugs of the future? *MedChemComm*, 9 (5), 757–758.
23. Nichols, L., Saunders, R. and Knollmann, F. D., 2012. Causes of Death of Patients With Lung Cancer. *Archives of Pathology & Laboratory Medicine*, 136 (12), 1552–1557.
24. Oda, Y. and Narukawa, M., 2022. Response rate of anticancer drugs approved by the Food and Drug Administration based on a single-arm trial. *BMC Cancer*, 22 (1).
25. Palinkas, L., Horwitz, S., Green, C., Wisdom, J., Duan, N. and Hoagwood, K., 2015. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. *Administration and Policy in Mental Health and Mental Health Services Research* [online], 42 (5), 533–544. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4012002/.
26. Peters, S., Camidge, D. R., Shaw, A. T., Gadgeel, S., Ahn, J. S., Kim, D.-W., Ou, S.-H. I., Pérol, M., Dziadziuszko, R., Rosell, R., Zeaiter, A., Mitry, E., Golding, S., Balas, B., Noe, J., Morcos, P. N. and Mok, T., 2017. Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. *New England Journal of Medicine*, 377 (9), 829–838.
27. Shaw, A. T., Kim, D.-W., Nakagawa, K., Seto, T., Crinó, L., Ahn, M.-J., De Pas, T., Besse, B., Solomon, B. J., Blackhall, F., Wu, Y.-L., Thomas, M., O'Byrne, K. J., Moro-Sibilot, D., Camidge, D. R., Mok, T., Hirsh, V., Riely, G. J., Iyer, S. and Tassell, V., 2013. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *The New England journal of medicine* [online], 368 (25), 2385–94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/23724913.
28. Srivastava, J. K., Pillai, G. G., Bhat, H. R., Verma, A. and Singh, U. P., 2017. Design and discovery of novel monastrol-1,3,5-triazines as potent anti-breast cancer agent via attenuating Epidermal Growth Factor Receptor tyrosine kinase. *Scientific Reports*, 7 (1).

29. TAKAHASHI, M., 2022. RET receptor signaling: Function in development, metabolic disease, and cancer. *Proceedings of the Japan Academy, Series B*, 98 (3), 112–125.
30. Villaruz, L. C. and Socinski, M. A., 2013. The Clinical Viewpoint: Definitions, Limitations of RECIST, Practical Considerations of Measurement. *Clinical Cancer Research* [online], 19 (10), 2629–2636. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4844002/.
31. Wang, F., Li, C., Wu, Q. and Lu, H., 2020. EGFR exon 20 insertion mutations in non-small cell lung cancer. *Translational Cancer Research*, 9 (4), 2982–2991.