Efficacy Analysis of Tyrosine Kinase Inhibitor Combinations in Phase II Clinical Trials of Non-Small Cell Lung Cancer

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

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Declaration

Hereby it is proclaimed that

1. The project provided is my own genuine work completed while pursuing a degree at BRAC University.

2. No formerly published or written by a third-party content is present in the thesis., with the exception of where this is properly cited with complete and precise referencing

3. The thesis contains no material that has been approved or submitted for any other degree or certificate at a university or other institution.

4. All significant sources of support have been acknowledged.

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Approval

The thesis titled "Efficacy Analysis of Tyrosine Kinase Inhibitor Combinations in Phase II Clinical Trials of Non-Small Cell Lung Cancer" submitted by Sanzida Alam Flora (19146078), of Summer, 2023 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trials.

Abstract

Research is required in the area of non-small cell lung cancer, due to its widespread prevalence. Efforts to enhance the accessibility, evaluative simplicity, and prediction accuracy of endpoints in clinical trials are continuously being pursued. In this study, with particular emphasis on sub-groups, we examine the efficacy and impact of tyrosine kinase inhibitor (TKI) by analyzing endpoints from Phase II clinical trials. We estimated the relative treatment effects for overall survival and progression-free survival using quantitative analysis and appropriate statistical methods. We observed a highly strong and significant positive correlation between OS and PFS ($r = 0.79$, 95% CI = 0.75–0.83, $P < 0.001$), while no statistically significant difference was seen across the OS of any treatment size. Additionally, a negative correlation (very weak or no correlation, although statistically significant) between median age and overall survival ($r = -0.15$, 95% CI = -0.25– -0.04, $P = 0.002$). However, further investigation in this area of study is required.

Keywords: Phase II, NSCLC, TKI, Efficacy endpoints, Progression-free survival, Targeted therapy.

Dedication

dedicated to my parents

Acknowledgment

First and foremost, I want to thank God Almighty for all of the blessings I have received, which have given me the willpower and fortitude to finish this endeavor. Secondly, I am grateful to my parents for their encouragement and support, which motivated me to work harder to overcome the obstacles.

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List of Acronyms:

TKI	Tyrosine Kinase Inhibitor
SCLC	Small cell lung cancer
NSCLC	Non-small cell lung cancer
ADC	Adenocarcinoma
BAC	Bronchioloalveolar carcinomas
PFS	Progression-free Survival
OS	Overall Survival
ORR	Overall Response Rate
PR	Partial response
CR	Complete response
QoL	Quality of Life

Chapter 1

Introduction:

1.1 Introduction

Cancer poses an enormous and widespread public health concern (Zugazagoitia et al., 2016), causing 8.8 million deaths each year, which exceeds that of HIV/AIDS, malaria, and TB altogether. This accounts for one in six deaths worldwide. Instead of being one single disease, cancer is comprised of several different disorders exhibiting a variety of subtypes, that requires specialized diagnostic and treatment methods. For such complexity to be dealt with, coordinated multidisciplinary treatment is essential (Torre et al., 2016). It is expected that, in 2023, around 609,820 individuals residing in the US will lose their lives due to cancer, resulting in an average of 1670 deaths daily (Siegel et al., 2023).

Lung cancer is widely considered the second leading cause of cancer-related mortality, among the numerous types of cancer, including esophageal, colorectal, stomach, liver, pancreatic, and breast cancers. Lung Cancer kills around 350 people per day, nearly 2.5 times as many as colorectal cancer. About 103,000 of the 127,070 lung cancer deaths expected in 2023 (or 81%) are anticipated to be connected to smoking, while an additional 3,560 deaths are expected to be linked to indirect smoke exposure (Siegel et al., 2023). Due to important clinical distinctions, two primary categories for lung cancer formerly were non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is accountable for the vast majority (ranging from 80% to 85%) of lung cancer cases (Schabath & Cote, 2019).

According to statistics reported at the American Society of Clinical Oncology (ASCO), the relative 5-year survival rate for NSCLC is 28%. In the US, for women 33% and for men 23% respectively. For patients with locally advanced non-small cell lung cancer, the overall 5-year relative survival rate is 65%. On the other hand, for regional NSCLC (the disease has progressed to surrounding lymph nodes from the lung), the relative survival rate of 5 years, is around 37%. In contrast, for metastatic lung cancer, the rate accounts for 9% (Lung Cancer - Non-Small Cell: Statistics, 2023).

Additionally, the four primary histologic subtypes of lung cancer are as follows: adenocarcinoma (ADC), small-cell and large-cell carcinoma, and squamous cell carcinoma. Among these, roughly

40% are classified as adenocarcinoma, squamous cell carcinoma accounts for 25% to 30%, and large cell is for 10% to 15%. Since the 1970s, in women, the most often identified histologic subtype was adenocarcinoma, and in 1994, lung adenocarcinoma's incidence rate exceeded squamous cell carcinoma's (Schabath & Cote, 2019).

For the selection of therapy, precise diagnosis is an essential element that highly depends on small biopsies and cytology procedures. The present study has addressed the concept regarding the diagnosis of lung cancer through small biopsies as well as cytology with an officially new standard classification (Travis, 2011). According to the new classification, bronchioloalveolar carcinomas (BAC) is no longer used. Non-mucinous BAC is presently referred to as lepidic-predominant ADC, while invasive mucinous BAC is now termed invasive mucinous ADC. Additionally, the revised ADC classifications introduce some new terminology such as micropapillary ADC, adenocarcinoma in-situ (AIS) as well as minimally invasive adenocarcinoma (MIA). However, Invasive lung adenocarcinoma should be classified histologically based on the dominant subtype, not the "mixed subtype" (Chalela et al., 2017).

NSCLC therapies highly depend on stage, histology, mutation in genes, and patient health conditions. Based on this, treatment strategies may include surgery, chemotherapy, radiation, and molecularly targeted therapy such as immunotherapy provided individually or in combination (Alexander et al., 2020). For instance, adenocarcinoma patients and NSCLC not otherwise specified (NSCLC-NOS) patients may be suitable for EGFR TKIs when any mutation in EGFR is present; however in this case patients may be allowed to receive other targeted therapies such as bevacizumab (Travis, 2011). Medically fit individuals having Stage I, II, and IIIA early stages of NSCLC should have undergone curative surgical resection. On the other hand, platinum-based chemotherapy as an adjuvant treatment, is suggested for stages II-IIIA illness, even though increased rates of relapse and toxicity.

The FDA approved the first genome-targeted therapy in November 2004, for the treatment of EGFR mutations in NSCLC patients. Since that time, their influence on a variety of outcomes has been proven, in fact, molecular testing is frequently conducted in people who have locally advanced as well as metastatic adenocarcinoma (Chalela et al., 2017). As targeted treatment has resulted in better clinical outcomes for many advanced NSCLC patients, therefore, a wide panel-based strategy is advised for molecular testing to find actionable genetic changes. Tyrosine kinase

inhibitors (TKI) targeting genetic mutations such as EGFR, ALK, ROS1, RET, BRAF V600E, MET Exon 14, and NTRK are licensed for treating a variety of NSCLC subtypes. If no targetable mutations are found, PD-L1 expression could help select a treatment concerning both squamous as well as non-squamous NSCLC (Alexander et al., 2020).

Clinical trials are crucial in determining the effectiveness of novel therapeutic modalities and the development of drugs to incorporate as a new therapy into cancer treatment (Unger et al., n.d.). Primary end-point selection for clinical trial effectiveness assessment is the most important choice that must be made to ensure proper assessment and approval. Endpoints for cancer clinical trials are an ongoing effort to be more quickly accessible, simpler to evaluate, and highly predictive of a final endpoint (Driscoll & Rixe, 2009). In clinical trials involving oncology, overall survival (OS) is the primary endpoint that is considered the "gold standard" for evaluating the efficacy of any drug, biologic, treatment, or intervention. (Fiteni et al., 2014). OS is the time frame that runs from randomization or treatments starting till the point the patient is still alive. It is a patient-centered outcome that is simple to quantify, accurate, clinically significant endpoint that is unaffected by the time of evaluation (Cheema & Burkes, 2013). In contrast, progression-free survival (PFS) provides a direct assessment of the impact of treatment on tumors. In cases where PFS is employed, the result is dependent on the frequency at which patients are checked for disease symptoms. Many tumors have five-year survival rates since patients who are able to survive 5 years have a higher chance of being cured of the illness. However, PFS's efficiency as a metric is well accepted, and accessible sooner than OS, it may speed up medication development (Driscoll & Rixe, 2009). The combined evaluation of target, nontarget as well as newly developed lesions yields an overall response. The overall response rate (ORR) is an important endpoint for evaluating the outcomes of trials and is useful for therapeutic choices of treatment regimens for routine practice (Aykan & Özatlı, 2020). A patient who has a history of solid tumors might use the objective response rate (ORR) to determine how a particular therapy is affecting their tumor burden (Delgado & Guddati, n.d.).

As mentioned earlier, OS is the gold standard. However, it could be a lengthy process for the regulatory approval of new drugs, as the authority waits to compare the OS differences across therapeutic arms. It is possible to substitute OS endpoints using data that encompass ORR along with PFS. Additionally, in the age of significant advancement in genomics, generating clinical

studies for an endpoint of OS might become less suitable because of fewer homogenous populations; as a result, the (ORR) response rate and length of the response in a single-arm trial may expedite the process of approval of novel medications (Aykan & Özatlı, 2020).

In one study, the reviewer summarized the scientific literature and evidence of EGFR TKIs to propose the use of targeted therapy as monotherapy and in combination treatments with other medications. According to the findings of the study, based on EGFR TKI, the use of combined therapy might be considered a beneficial treatment regimen, since it provides improved effectiveness along with manageable adverse effects (Nan et al., 2017).

It is important to note that, the majority of lung cancer patients get their diagnosis at the most advanced stage of the illness, when there are few possibilities for recovery. Local treatment for early-stage illness may improve the overall survival rate. Additional studies must be conducted to identify possible medications that might lower the incidence of lung cancer, particularly among ex-smokers. The medical management of nodules may be improved by improvements in screening technologies and biomarkers, which might minimize false positives and overdiagnosis. The possibilities and efficacy of counseling regarding quitting smoking in the context of lung cancer screening still require further study (Schabath & Cote, 2019).

1.2 Aims and objectives

- To investigate the connection between different treatment strategies, (notably using TKI alongside other medications like chemotherapy and immunological therapy).
- To provide medical practitioners insight for appropriately selecting medications and avoiding misconceptions in treatment choices.

Chapter 2

Methodology

2.1 Efficacy Endpoint and Predictor Variable

The efficacy endpoint is the clinical or biological outcome that is measured in clinical trials to determine how effective the intervention is and to evaluate treatment alternatives (Fiteni et al., 2014). The PFS of a clinical study reflects the period from the treatment initiation till the onset of the progression of the disease. Data having PFS and OS expressed in the month, were taken into account. In contrast, if OS and PFS were expressed in weeks and days, those were converted to months. Additionally, median age was also taken into consideration.

2.2 Data Source

We decided to concentrate our search employing one primary database, PubMed as a resource to facilitate accessing Phase II NSCLC clinical trial articles. We searched PubMed using particular terms such as 'phase II clinical trial lung cancer' to narrow down the selection of articles that were directly relevant to our area of interest. This project aims to systematically collect and extract key efficacy endpoints from the initial 500 Phase II NSCLC clinical trial articles. In addition, using a single database reduces the complexity, and provides better management of data within the limited time.

2.3 Inclusion and Exclusion Criteria

Precise parameters have been implemented to efficiently conduct the inclusion or exclusion criteria of searched articles. Although our primary concern for the inclusion and exclusion criteria was phase II NSCLC clinical trial publications including, TKI but those clinical trials were also accepted that comprised TKI along with other treatment strategies such as radiation, immune therapy, and chemotherapy. Articles that did not have cancer drugs, had been excluded. On the other hand, we included articles comprising two or more endpoints. Similarly, OS and PFS in

percentages have been removed from this count since those data are not relevant. If PFS was absent, TTP was collected.

2.4 Study Plan

The endpoints include PFS, ORR, and OS. According to our data, among the 364 articles, we found 428 ORR, 470 PFS, and 374 OS respectively. Based on these efficacy endpoints, we should highlight two essential characteristics. In the first place, one of our primary objectives was to investigate whether or not the use of certain medications as part of the treatment plan has an impact on the overall probability of the patient overcoming the ailment. Second, we investigated whether there is a connection between the different types of treatment strategies more specifically TKI in combination with other drugs, such as chemotherapy and immune therapy, and the effect that these treatments have on the efficacy endpoint.

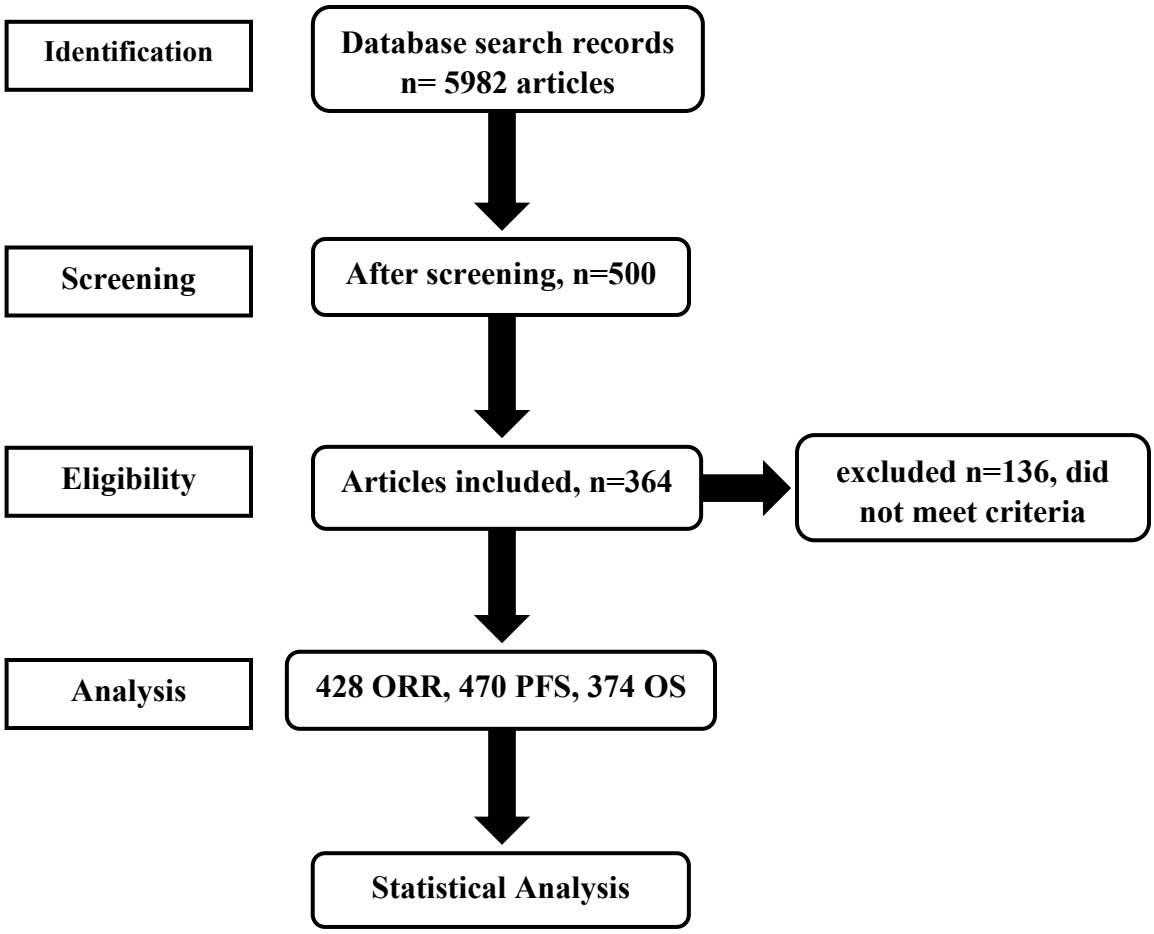

Figure 1: Study plan

2.5 Statistical Analysis

A two-tailed welch t-test with a significance level of 5% was conducted to compare the OS between treatment sizes. Similarly, a two-tailed welch t-test with a significance level of 5% was done to compare the progression-free survival (PFS) among the same treatment sizes. Pearson correlation was used to identify a correlation between OS, PFS, and age. To predict variables and determine additional parameters, a linear regression analysis was carried out. All the tests were performed by Microsoft Excel 2019.

Chapter 3

Result:

3.1 Dataset Overview

The collected data contains 218 1-agent trials, in contrast to 106 2-agent and 32 3-agent trials. Among the 364 articles, we found 428 ORR, 470 PFS, and 374 OS. To be more precise, the PFS counts were 284, 137, and 38 for agents 1, 2, and 3. Regarding OS, the counts were 205, 121, and 37 respectively. In the case of the ORR counts were 267, 115, and 38 respectively.

Table 1: Summary of the collected dataset

Treatment Agent	1-Agent	2-Agent	3-Agent
Mean PFS (month)	7.6 (6.9–8.2) [1]	6.6 (5.7–7.4)	9 (7–10.9)
Mean OS (month)	15.2 (13.8–16.6)[2]	14.5 (12.7–16.4)	17.7 (13.9–21.6)
Observations	218	106	32

[1, 2] 95% confidence interval (CI)

3.2 Relationship Between OS and PFS

According to our analysis, the scatterplot line indicates a strong, positive significant correlation (r = 0.79, 95% CI = 0.75–0.83, p < 0.001) between OS and PFS in non-small cell lung cancer. The scatterplot in Figure 2 shows a distinct increasing trend extending from left to right, indicating that the relationship between the two variables is linear. In particular, the plot suggests that a rise in PFS is related to a rise in OS whereas a drop in PFS is related to the reduction in OS.

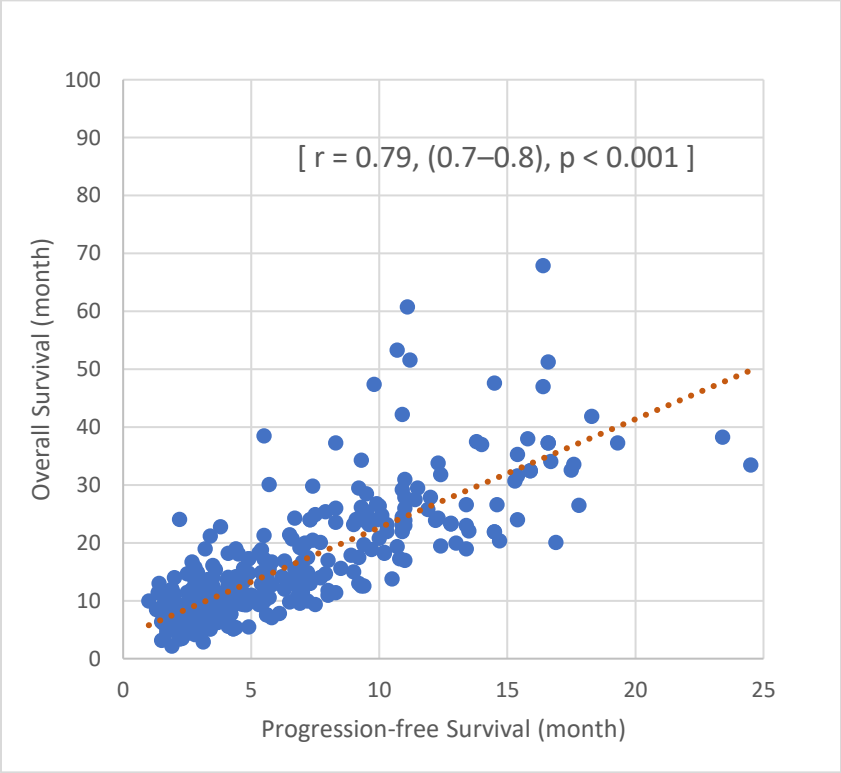

Figure 2: Scatterplot of overall survival and progression-free survival of phase II clinical trials of non-small cell lung cancer containing tyrosine kinase inhibitor combinations. Progression-free survival (month) is shown on the x-axis, while overall survival (month) is plotted on the y-axis. The dotted diagonal line indicates linear regression.

Conversely, there was a very weak negative correlation between OS and age in patients with NSCLC, that points in the opposite direction as illustrated by the scatterplot line in Figure 3 (r = -0.15, 95% CI = -0.25– -0.04, p = 0.002), signifying that the connection between those two variables

does not follow a linear pattern. For instance, the graph implies a negative relationship between OS and age.

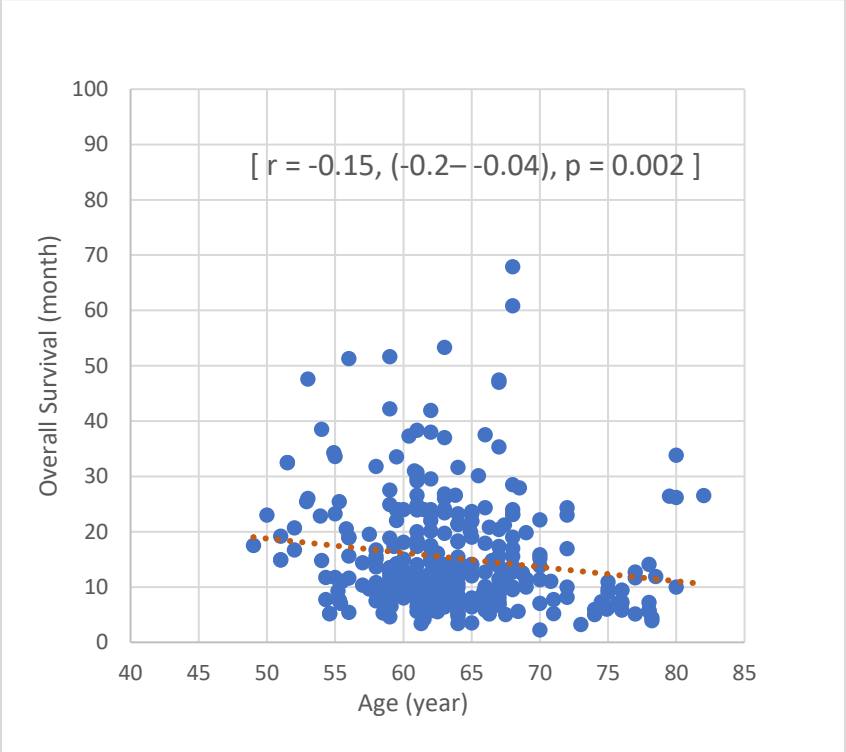

Figure 3: Scatterplot of overall survival and age of phase II clinical trials of non-small cell lung cancer containing tyrosine kinase inhibitor combinations. Age (year) is shown on the x-axis, while overall survival (month) is plotted on the y-axis. The dotted diagonal line indicates linear regression.

Table 2: Linear relationship between overall survival, progression-free survival, and age.

	Coefficients	*Standard Error*	*P-value*	*Lower 95% CI*	*Upper 95% CI*
Intercept	10.583	3.711	0.004	3.281	17.884
Median age	-0.105	0.056	0.063	-0.216	0.006
Median PFS	1.875	0.080	1.32991E-71	1.716	2.033

The predicted equation was derived using linear regression:

OS = 10.583 + 1.875 (PFS) - 0.105 (Age)

The obtained adjusted R square value was 0.62, indicating that the independent variables (PFS, age) could account for 62% of the variability in the dependent variable (OS), considering the variable number. According to this value, the selected variables provide a significant contribution to the model, while avoiding the addition of irrelevant variables. There was a marginal increase in the R square value compared to the adjusted R square value (R^2 = 0.63). The intercept of the regression model is 10.583, indicating that the dependent variable (OS) will have a value of 10.58 when the independent variables (PFS and age) are equal to 0. Additionally, 95% CI demonstrates, that the likelihood that the actual value will not fall within the error bar's range is only 5%. This method is for representing the degree of uncertainty in a graph by the size of the error bar.

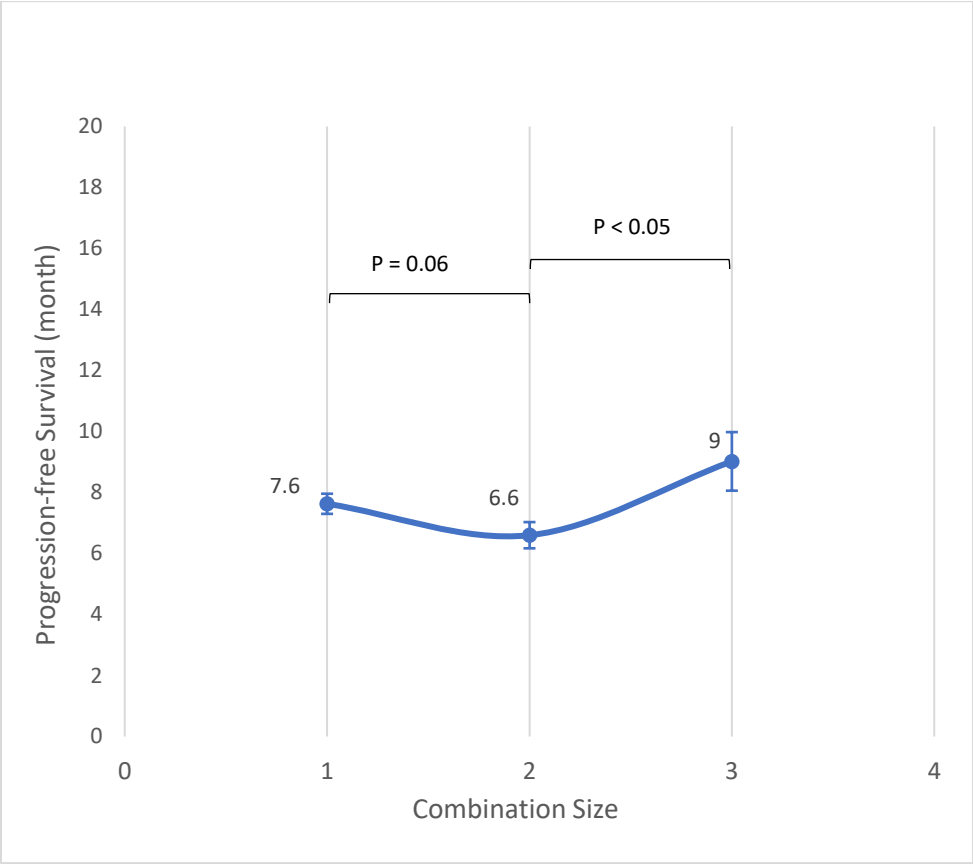

Figure 4: Impact of combination size on progression-free survival. The X-axis reflects the treatment size and the Y-axis reflects the mean value of progression-free survival, measured in months. Error bars indicate standard error.

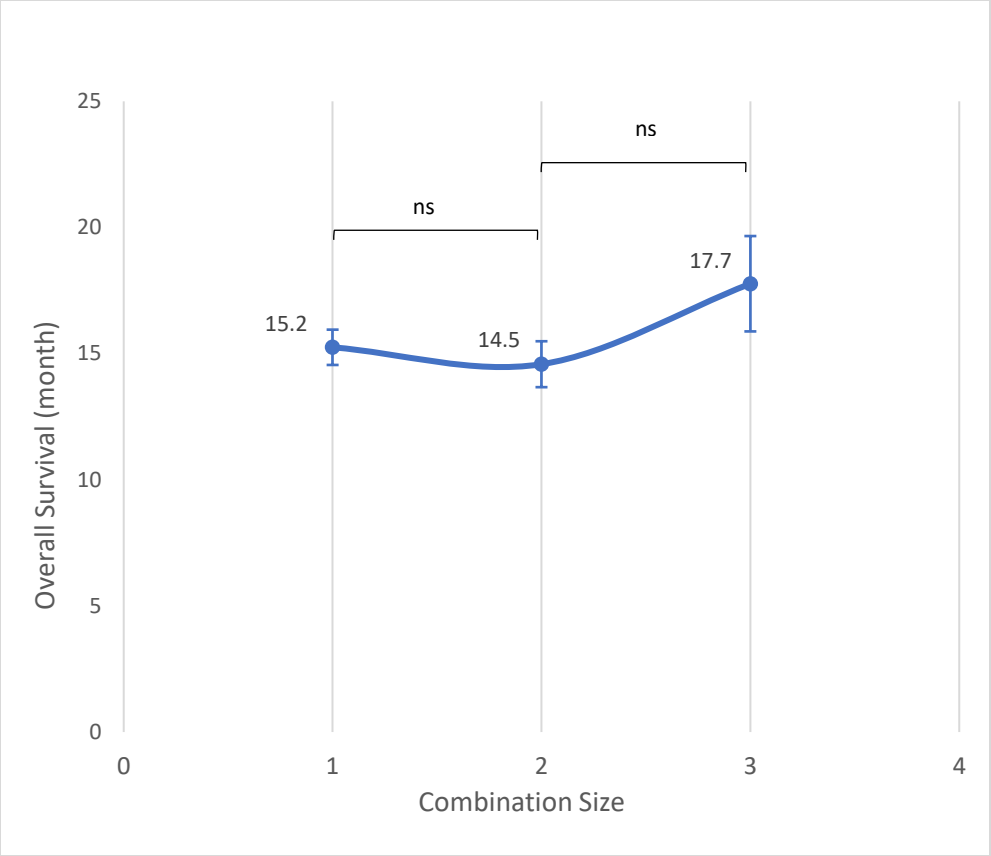

Figure 4: Impact of combination size on overall survival. In the graph, the X-axis reflects the treatment size, on the other side the Y-axis reflects the mean value of overall survival, measured in months, indicating no significant relation. Error bars indicate standard error.

In Figures 3 and 4, the line plot presented in the graph points out the relationship between the treatment size and the PFS as well as the OS. In the case of PFS, there is a statistically significant difference ($p = 0.02$) between treatment sizes 2 and 3. On the other hand, since the p-value of 0.06 was obtained from this comparison, as per the normal significance levels, there is no statistically significant difference between treatment sizes 1 and 2. In contrast, for OS the p-values of 0.56 and 0.13 indicate no significant difference as well.

Chapter 4

Discussion

TKIs are being considered as the first-line therapy for advanced NSCLC with gene (EGFR) mutations. These targeted therapies are a new class of anticancer agents with fewer side effects established for the treatment of lung cancer. In EGFR mutation-positive patients TKIs targeting lung cancer cells, had a two-fold higher response rate than platinum chemotherapy. The use of two tyrosine kinase inhibitors (TKIs) that target distinct signaling pathways has been shown to induce a transition of cells from drug-resistant to increased sensitivity to the drugs. Several studies have shown evidence that combination treatment may effectively maximize the benefits of individual medications. Additionally, the co-administration of drugs has been shown to potentially influence the regulation of specific cell effects. In recent decades, there has been a significant focus on the extensive investigation of combination treatment in the area of cancer. Because, utilization of combination treatment holds the possibility for enhancing treatment effectiveness, minimizing the possibility of drug resistance, and limiting the occurrence of adverse effects that are often linked to mono-chemotherapy (Wu et al., 2017). As stated previously, the main objective of this study was to examine the relationship between TKI with combination therapy and several measures of this treatment effectiveness to investigate the impact of medicine on the overall probability of survival.

In this study, Pearson correlation was implemented to assess the correlation between PFS and OS, then OS and age, and also to determine the degree to which the relation falls from -1 to +1. The correlation test ($r = 0.79$, 95% CI = 0.75–0.83, $p < 0.001$,) suggests a strong positive, highly significant relationship between PFS and OS. Conversely, the observed negative, statistically significant correlation ($r = -0.15$, 95% CI = -0.25– -0.04, $P = 0.0026$) between OS and age.

One study utilizing 15 clinical trials, suggested no statistically significant correlation despite an anticipated trend between the PFS hazard ratio and the OS hazard ratio, with the calculated weighted Pearson correlation of 0.48 and the weighted linear regression p-value of 0.095 (Solomon et al., 2022). On the other hand, in our analysis, we found a statistically significant and positive correlation between PFS and OS. Another study examined 15 clinical trials of solid tumors, using Kendall's Tau, affirmed a robust positive correlation between PFS2 and OS, registering a correlation of 0.70 equates to a Pearson's correlation of 0.86. It is indicating a significant

correlation (>0.7) between OS and PFS2. In this context, a value of 0 denotes no relationship. This particular study suggested, that when OS data is unavailable, using PFS2 can assure an experimental agent as a starting treatment before a second therapy is more effective than starting with standard therapy followed by second therapy. Moreover, this particular study found consistently strong correlations in specific tumor types and when analyzing combined data from various indications (Chowdhury et al., 2020).

According to our analysis, the efficacy of a single targeted drug (TKI such as erlotinib, or gefitinib) on cancer patients demonstrated more effective outcomes in terms of OS (mean 15.25) and PFS (mean 7.63). Surprisingly we found that there was a drop with a narrow difference in the mean value of both OS (mean 14.58) and PFS (mean 6.60), while a combination of two drugs had been used as treatments. This implies that it is more beneficial for patients to treat with a single tyrosine kinase inhibitor (TKI) and has a greater influence by reducing tumor progression and enhancing survival compared to TKIs used in combination with another drug as treatment size 2. However, no significant difference was detected in the case of OS among different treatment groups. Similarly, in the case of groups who were treated with treatment sizes one and two, there was an insignificant difference in PFS. The results of one randomized study showed that combining two drugs such as cetuximab to afatinib did not enhance clinical outcomes in comparison to using afatinib alone. Unexpectedly, the combination led to higher toxicity, which in turn led to a greater number of dosage reductions and treatments being stopped altogether (Goldberg et al., 2020). This may be why dual-drug treatment with TKI was found to be less successful than monotherapy.

Despite this, we observed the difference was statistically significant between the PFS of treatment sizes two and three, with the obtained p-value of 0.026. In contrast, the analysis reveals an even more substantial increase in the OS and PFS mean values with 17.77 and 9.02 respectively, when employing three drugs in combination for example: TKI with two other drugs compared to treatment strategies involving monotherapy or even dual drug treatment. Typically, it means the use of combination treatment, such as the concurrent administration of tyrosine kinase inhibitors (TKIs) like erlotinib or gefitinib, with additional agents like immune therapy (e.g., bevacizumab) and chemotherapy (e.g., docetaxel or paclitaxel), has shown enhanced efficacy compared to monotherapy, as it decreasing the tumor progression and increasing the survival of lung patients.

Moreover, combining three medications might potentially provide a synergistic impact. Most of the time cytotoxic drugs (such as pemetrexed and docetaxel) are used in combination with TKI. It is believed that the increased effectiveness of combining these medications is mediated by a variety of different mechanisms, not all of which are directly connected to the tumor cell's genetic characteristics. Pemetrexed was shown to enhance EGFR phosphorylation and lower Akt phosphorylation in cell line tests, as a result making tumor cells sensitive to erlotinib. On the other hand, erlotinib was found to inhibit thymidylate synthase expression and activity, similarly which in turn could make tumor cells susceptible to pemetrexed. Combinations of docetaxel and EGFR inhibitors were tested in cancer cell lines and tumor models, and it was shown that they increased the antiproliferative and cytotoxic efficacy of the separate medicines (Aerts et al., 2013).

Hence, our finding suggests that the utilization of multiple drug combinations with TKI exhibits greater efficacy endpoints and has the potential to improve long-term patient survival. The absence of a sufficient number of reported clinical trials resulted in the non-performance of a T-test when dealing with combinations of more than three drugs. However, to reach more definitive conclusions, additional research may be required.

Chapter 5

Conclusion:

We carried out this research with the aim that it would be advantageous for healthcare professionals in terms of the correct selection of drugs and avoiding instances of misinterpretation. Our study has shown that the number of medications used in treatment has a direct correlation with the efficacy endpoints (PFS, OS, and ORR). The findings of our study indicate that the greatest improvement in survival can be achieved by using three drugs in combination, one of which is a TKI. The PFS for treatment sizes 1 and 2 showed a p-value of 0.06, whereas for treatment sizes 2 and 3 yielded a p-value indicating statistical significance at 0.026. Turning to OS, the p-value of treatment sizes 2 and 3 was 0.13, whereas the p-value of treatment sizes 1 and 2 was 0.56. Remarkably, the expected statistical significance between all the treatment sizes was not achieved in the case of OS. Despite this, it was clear that for the combination of 3 drugs there was prolongation in both OS and PFS. To be more specific, it implies that TKI is more effective in reducing the progression of tumors and enhances patient survival when used in combination with other 2 more treatments. Conversely, using it as a dual treatment strategy is unexpectedly less effective than even using a single TKI therapy to enhance the survival rate of lung cancer patients. This was found by comparing the effectiveness of using TKI alone to that of using with another drug (such as TKI, immunotherapy, cytotoxic drug) as a treatment size 2. In the next stages of our research, one of our primary goals is to improve the precision of our prediction models by using more extensive datasets. More research has to be done to figure out why dual therapy strategies are not more effective. Besides that, additional clinical tests are necessary to be carried out in order to identify the TKI combinations that work the best.

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