Pooled Analysis of Response Rate and Overall Survival of Tyrosine Kinase Inhibitor Combinations in Phase II Clinical Trials of Non-Small Cell Lung Cancer

By

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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

The thesis titled "Pooled analysis of response rate and overall survival of tyrosine kinase inhibitor combinations in phase II clinical trials of non-small cell lung cancer" submitted by Samia Binte Karim (19146084) of Spring'2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

The study does not involve any human or animal trial.

Abstract

Lung cancer is a prominent cause of death annually. It is the most common cancer worldwide and the leading cause of cancer deaths in men and women. In this research, we focused mostly on non-small cell lung cancer (NSCLC) which is the most prevalent subtype. The primary objective of treatment strategies and patient care is to improve quality of life (QoL) and extend survival. Thus, various medications and therapies are being tested in clinical trials. Our evaluation included phase II clinical trial data because it provides a comprehensive and reliable review of safety and effectiveness. A total of 487 data were collected from a sample of 364 papers, comprising 428 overall response rate (ORR) and 374 overall survival (OS) data. To understand patients' survival and response to different treatment sizes, efficacy endpoints were evaluated and differentiated. The relationship between median age, ORR, and OS was examined using correlation analysis. Median age had a weak negative relation with OS, but ORR had a strong positive correlation. Moreover, we found that a combination of three drugs yielded the most beneficial outcome compared to therapy with one or two agents.

Keywords: NSCLC; ORR; OS; Median age; Clinical Trial; Combination size.

Dedication

Dedicated to my parents

Acknowledgement

First and foremost, I would like to express my gratitude to the Almighty for providing me with the strength and determination to complete this project.

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List of Acronyms

NSCLC	Non-Small Cell Lung Cancer
SCLC	Small Cell Lung Cancer
LCNEC	Large Cell Neuroendocrine Carcinoma
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-free Survival
TKI	Tyrosine Kinase Inhibitor
CR	Complete Response
PR	Partial Response

Chapter 1

Introduction

1.1 Background of Non-Small Cell Lung Cancer (NSCLC)

Cancer refers to uncontrollable cell growth that can remain benign or spread through metastasis. Cancer cells exhibit growth even without growth-inducing signals, disregarding apoptosis or programmed cell death. The immune system typically eradicates damaged cells, but cancer cells can manipulate immune cells to prioritize tumor defense. Some cancer cells have double-normal chromosomal counts, making them perilous to the human body's overall well-being. These unique characteristics make cancer cells perilous to the immune system (*What Is Cancer? - NCI*, n.d.). Throughout the world, cancer is a significant public health issue. The projected rise in cancer incidence over the coming decades is anticipated to be influenced by global demographic factors, leading to an estimated yearly increase of 420 million new cancer cases by the year 2025 (Zugazagoitia et al., 2016). Among males, lung cancer is the most prevalent, with around 1.37 million reported cases. When it comes to malignancies that affect women, breast cancer is by far the most common with 2.09 million cases, followed by cancers that affect the lung with nearly 0.72 million cases (Mattiuzzi & Lippi, 2019).

Lung cancer, a prevalent disease characterized by abnormal cell proliferation in pulmonary tissues, is the most prevalent cancer worldwide, contributing to high mortality rates among men and ranking second among women. It accounted for one-fifth of all cancer-related mortality in 2018, accounting for 1.8 million deaths (Schabath & Cote, 2019). Lung cancer can be classified into two distinct subtypes-small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Small cell lung cancer (SCLC) is a highly aggressive form of neuroendocrine carcinoma that predominantly occurs in smokers and characterized by its high-grade nature.

Approximately 15% of all cases of lung cancer can be attributed to this particular type, with a majority of patients being diagnosed at an advanced stage of the disease, defined by the presence of metastasis. One-third of individuals present with the disease in its earliest stages, which can be managed through the utilization of a variety of therapeutic approaches, hence offering the possibility of achieving a cure (Rudin et al., 2018). Non-small cell lung cancer (NSCLC) exhibits a comparatively less aggressive nature and a higher prevalence, accounting for approximately 80% to 85% of all lung cancer cases, in contrast to small cell lung cancer (SCLC). Adenocarcinoma accounts for 40% of NSCLC cases, while squamous cell carcinoma makes up 25%-30% , and large cell carcinoma accounts for 10%-15% (Schabath & Cote, 2019).

Adenocarcinoma represents the predominant histological subtype of lung cancer, accounting for approximately 40% of the total incidence. Adenocarcinoma is commonly observed in the mucus-producing or glandular cell lining located in the peripheral parts of the lungs. It affects both smokers and nonsmokers of all ages and genders. Adenocarcinoma exhibits a relatively slower growth rate and possesses a higher degree of detectability before metastasis (Zappa & Mousa, 2016). Squamous cell cancer, linked to tobacco use, targets squamous cells in the airway epithelial tissue of the bronchial tube and is the second most common form of lung cancer. Large cell carcinoma, a variant of large cell carcinoma, can manifest in any lung region and is characterized by rapid proliferation and dissemination, making it challenging to treat. Large-cell neuroendocrine carcinoma (LCNEC) is similar to small-cell lung cancer (Araujo et al., 2020).

Following the identification of the specific form of lung cancer, the subsequent stage of the diagnostic procedure involves the process of staging; determining the localization of cancerous cells, tumor dimensions, and the presence of metastasis. Non-small cell lung cancer can be categorized into five distinct stages. Stage 0 is an early stage, affecting the upper lining of the

lung or bronchus. Stage I is divided into two sub-stages, 1A and 1B, based on tumor dimensions. Stage II is divided into two sub-stages, IIA and IIB, based on tumor size, location, and lymph node metastasis. Stage III is divided into three sub-stages, IIIA, IIIB, and IIIC, based on tumor dimensions, position, and metastasis extent. Stage IV is the most advanced stage, characterized by metastasis of cancer cells to the lung lining or distant organs. The staging process offers insights into available therapeutic modalities and helps in identifying the most effective treatment for lung cancer (Rami-Porta et al., 2018).

The advancement of non-small cell lung cancer (NSCLC) plays a crucial role in determining the appropriate therapeutic interventions. Patients in stages I, II, and IIIA commonly receive surgical intervention to remove the tumor, with operability being assessed through the use of biopsies and imaging studies (Zappa & Mousa, 2016). The implementation of adjuvant therapy, which comprises radiation, chemotherapy, and targeted therapy, has been shown to effectively mitigate the risk of relapse in patients with lung cancer. Chemotherapy is frequently employed as an adjunctive treatment following surgical intervention in order to enhance overall survival rates (Chaft et al., 2021). The current standard treatment for patients diagnosed with inoperable, locally progressed, node-positive non-small cell lung cancer (NSCLC) in stages IIB to IIIC involves the administration of concomitant chemotherapy and radiation therapy, followed by a one-year course of durvalumab (Cho et al., 2017). Cytotoxic combination chemotherapy is the first-line treatment for stage IV NSCLC. According to the American Society of Clinical Oncology, the recommended treatment for stage 4 patients are the combination of platinum agents (cisplatin or carboplatin) along with pemetrexed, docetaxel, paclitaxel, irinotecan, vinorelbine, or gemcitabine (Hanna et al., 2017). Cytotoxic chemotherapy treatments typically have minimal survival duration (typically lasting between 6 and 18 months), however, epidermal growth factor receptor mutations led to the development of selective tyrosine kinase inhibitors (TKI) for NSCLC patients. These therapies showed better overall response rates and

progression-free survival (PFS) compared to traditional chemotherapy. PFS was increased from six months to twelve months in these patients (Kumar & Sarkar, 2022).

The percentage of patients who are still alive 5 years following their diagnosis is known as the 5-year survival rate. Five-year relative survival rates evaluate how many patients with lung cancer are still alive after five years in comparison to the whole population. The combined 5-year relative survival rate for both non-small cell lung cancer and small cell lung cancer is reported to be 19%. Furthermore, the 5-year survival rate for NSCLC is higher at 23% compared to SCLC, which stands at 6%. Despite significant advancements in survival rates for several cancer types in the United States, the progress in 5-year survival rates for patients diagnosed with lung cancer has been rather modest. The primary reason for the lack of improvement can be attributed to the fact that a significant proportion of patients receive a diagnosis at an advanced stage of the disease, resulting in discouraging survival statistics (Schabath & Cote, 2019).

Clinical trials are research studies that evaluate the efficacy and safety of new medications or treatments, particularly in cancer management. They typically involve four phases: Phase I, where a small group of volunteers tests the drug, Phase II, where a large cohort is tested, Phase III, where the treatment is administered to larger populations, and Phase IV, where post-market monitoring is conducted. Researchers focus on specific outcomes, known as "end points," to assess the drug's effectiveness and safety. These endpoints, such as disease-free survival, progression-free survival (PFS), overall response rate (ORR), quality of life (QoL), and overall survival (OS) are crucial in both standard and accelerated approval processes (Administration, 2018).

1.2 Aims and Objectives of the Study

- Determine whether or not there is a correlation between the endpoints (OS, ORR and patients' median age) seen in phase II clinical trials and the administration of targeted therapies, primarily tyrosine kinase inhibitors with combinations as treatment.
- Analyze the efficacy of various treatment sizes and develop a model that could predict the link between the variables.
- Make an assessment and gain a deeper comprehension of the endpoints though this evaluation.

Chapter 2

Methodology

2.1 Efficacy Endpoint

The predetermined goal or outcome of a clinical trial that is assessed statistically in order to establish the efficacy and safety of the treatment being researched is called an end point. The end points we are using in our study are overall response rate (ORR) and overall survival (OS). The overall response rate (ORR) is referred to as the ratio of patients who experience a reduction in tumor size by a predetermined magnitude and for a specified duration. RECIST method has established a definition for objective response rate (ORR) as the total number of partial responses and complete responses (CR). Complete response (CR) is characterized by the absence of any apparent signs of tumor. This definition of ORR makes it possible to assess a drug's anticancer activity directly in single-arm research. A rise in the overall response rate (ORR) indicates the efficacy of the treatment. Overall survival (OS) is measured in the population that was intended to be treated and is defined as the amount of time that has passed from randomization without a participant passing away from any cause of death. Survival is widely regarded as the most dependable measure of cancer outcomes, and it is typically the preferred endpoint for conducting studies to evaluate survival appropriately. Since the date of death is recorded, this conclusion can be measured precisely and without any issues. To evaluate clinical benefit, survival improvement should be examined through a risk-benefit analysis (Administration, 2018).

2.2 Data Source

The phase II clinical trial of NSCLC was the primary focus of our study. To make an accurate estimation, we needed to collect a minimum of 400 efficacy endpoint data. For the optimum duration of data collection and feasibility, we extracted relevant clinical trial data from the latest database “PubMed”. We narrowed our search for suitable data by using particular phrases, such as "Phase II Clinical Trials of Lung Cancer," to search the relevant literature. As a result, we gathered 487 data from 364 articles, which was greater than the minimal we anticipated.

2.3 Study Inclusion and Exclusion Criteria

We used a systematic search to identify phase II trials’ articles so, our inclusion and exclusion criteria for the data were straightforward. The main focus was placed on the articles about TKI targeted therapy. In addition, the articles that were included in the analysis contained two effectiveness outcomes, namely ORR, and OS. The measurement for OS was recorded in units of time, specifically months. On the other hand, the measurement of ORR was expressed as a percentage (%). In certain cases where the ORR was not directly provided, the partial response (PR) was utilized as a substitute. Moreover, the publications also incorporated data on the median age of the patients, as well as the utilization of additional therapeutic approaches such as targeted therapies (mab), chemotherapy, radiation, and surgery. Additionally, information regarding treatment size was also included. In contrast, articles with only a single effectiveness endpoint, not containing TKI in trials, phase I or phase III clinical trials, and so on were not included in the search.

2.4 Study Plan

Following the process of data extraction, a total of 487 efficacy endpoints were identified from a total of 364 articles. Within this set of endpoints, the observed overall response rate (ORR) amounted to 428, and overall survival (OS) was recorded as 374. The median age of the patients was observed in 447 cases.

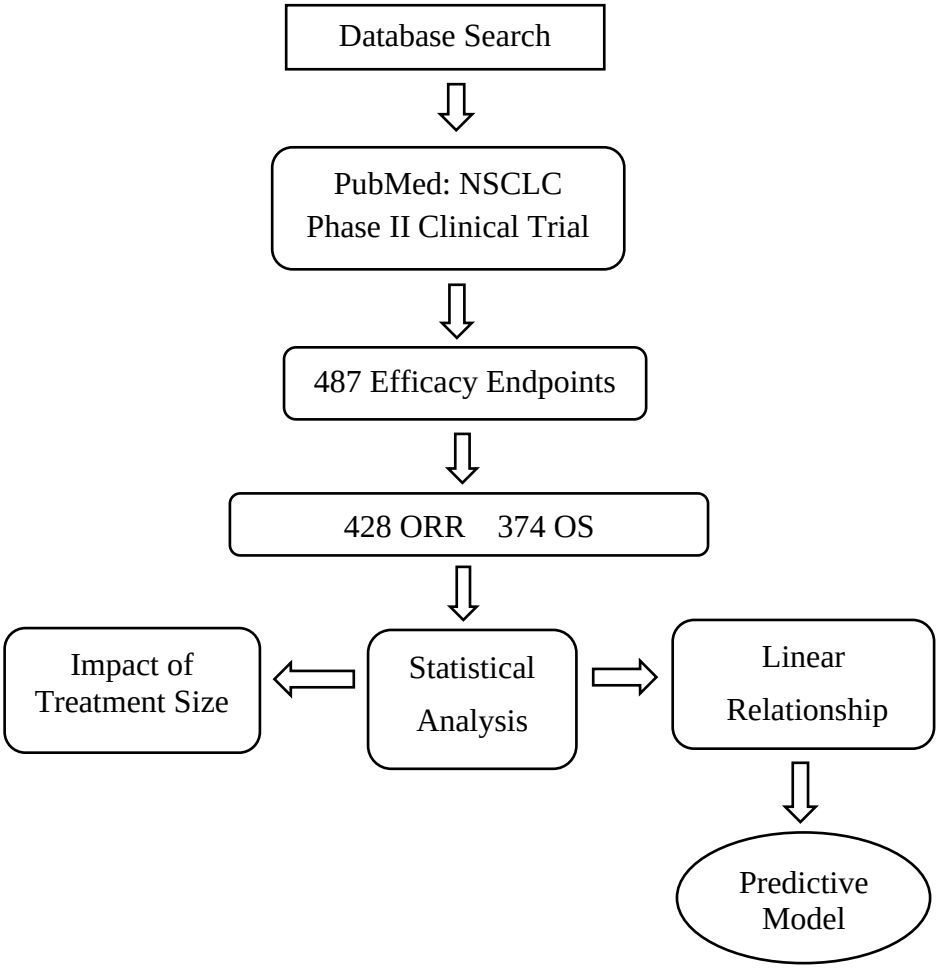

Figure 1: Study Plan

Following the procedure for data extraction described above, we constructed a linear relationship between the variables, and as a result, we established a prediction model for a better understanding of the outcome.

2.5 Statistical Analysis

At the very beginning, we looked into the correlation between the median age of the patients and overall survival, as well as the correlation between ORR and overall survival. To ascertain the linear relationship between the median age-OS and ORR-OS, the Pearson correlation coefficient, r, was calculated. A multiple regression analysis was conducted onward to ascertain the relationship between the variables-OS, ORR and median age. Finally, two-tailed Welch t-tests were run with a 5% significance level to compare the variance in the mean value of overall survival and overall response rate across the various treatment sizes. Microsoft excel was used for all of the of the statistical analysis.

Chapter 3

Results

Table 1: Summary of the dataset

Treatment Size	1-agent	2-agent	3-agent
Observations	293	140	42
Mean ORR	39.9% (36.9 - 42.9)[1]	36.5% (31.7 - 42.3)	46.2% (37.4 - 54.9)
Mean OS	15.3 months (13.9 - 16.6)[2]	14.6 months (12.8 - 16.4)	17.8 months (13.9 - 21.6)

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

After conducting a comprehensive search and analysis of 364 articles, we obtained a total of 487 data points. One agent therapy has been used in 293 of these trial cases, two agent therapy being applied in 140 of these cases, and three agent therapy was administered in 42 of these cases. To be more precise the ORR count was 267, 115, and 38 for treatment sizes 1,2 and 3 respectively. Similarly, the OS count was 205, 121, and 37 for 1, 2, and 3 agent trials respectively. We also collected 428 ORR, 374 OS, and 447 median age data for our statistical analysis.

3.1 Relationship between ORR & OS

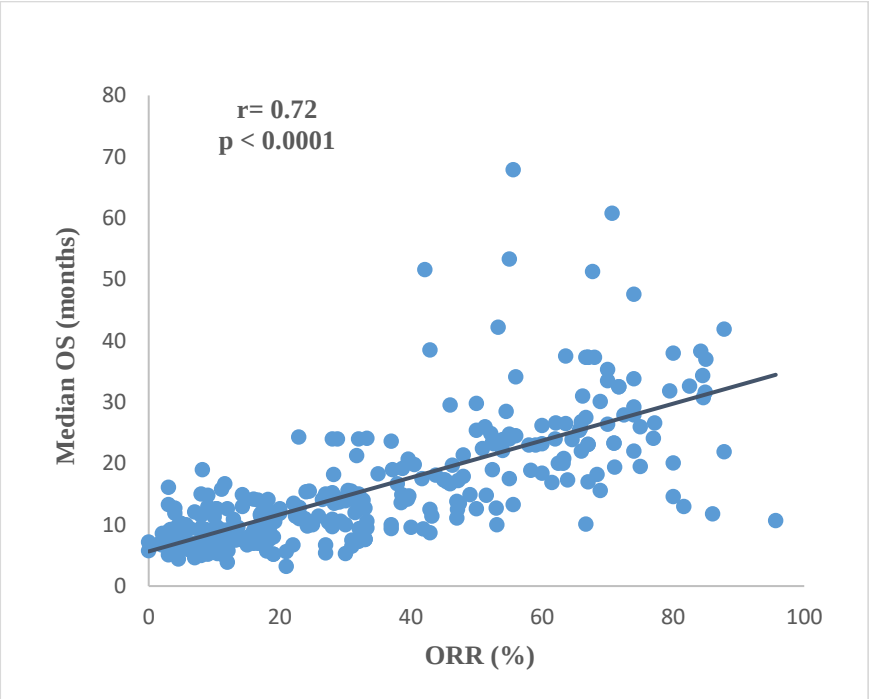

Figure 2: Scatterplot of response rate and overall survival in phase II trials of non-small cell lung cancer. The X axis represents overall response rate (%) and the y axis represents overall survival (months) and the scatterplot line shows a positive correlation between ORR and OS.

In this study, the correlation coefficient r = 0.72 ($p < 0.0001$) was found, indicating that there is a strong positive connection between overall survival (OS) and overall response rate (ORR) in patients with non-small cell lung cancer (NSCLC) having TKI combinations.

The scatterplot graph presented above has a noticeable upward trend in the data pattern as one moves from the left to the right, indicating a positive association. Hence, the observed linear pattern signifies a positive correlation between the variables. Therefore, a rise in one variable will increase the other variable. Based on the graphical representation, it is evident that the dependent variable OS will increase if there is an increase in the independent variable, ORR. In contrast, the OS exhibits a drop in response to a reduction in the ORR. The following predictive equation was generated from the model that was presented earlier in the graph:

OS (month) = 0.3011 (ORR%) + 5.6449

The model's R-squared value is 53%, which indicates that the ORR regression line explains 53% of the observed OS variability.

3.2 Relationship between Median Age & OS

While determining the Pearson correlation coefficient in this case, we included these median age data that reported ORR and OS both to achieve a precise model.

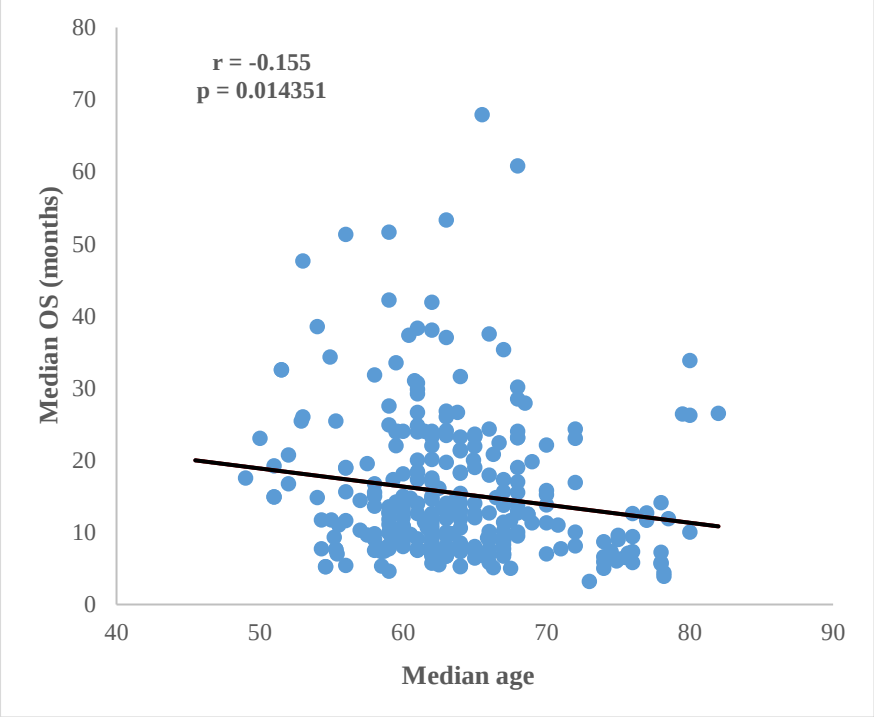

Figure 3: Scatterplot of median age and overall survival in phase II trials of non-small cell lung cancer. The X axis represents median age (years) and the y axis represents overall survival(months) and the scatterplot line shows a negative correlation between median age and OS.

In this study, the Pearson correlation coefficient r = -0.155 (p = 0.014351) was found, indicating that there is a weak negative correlation between overall survival (OS) and median age of the patients with non-small cell lung cancer (NSCLC) treated with TKI combinations.

The scatterplot graph presented above has a noticeable downward trend in the data pattern as one moves from the left to the right, indicating a negative association. Hence, the observed

linear pattern signifies a negative correlation between the variables. Therefore, a rise in one variable will cause a decrease in the other variable. Based on the graphical representation, it is evident that the dependent variable OS will decrease if there is an increase in the independent variable, median age. In contrast, the OS will increase in response to a reduction in the median age. The following predictive equation was generated from the model that was presented earlier in the graph: OS (months) = (-0.251) median age + 31.408

The model's R-squared value is 2%, which indicates that the regression line of median age explains 2% of the observed OS variability.

3.3 Impact of Combination Size on Overall Response Rate (ORR)

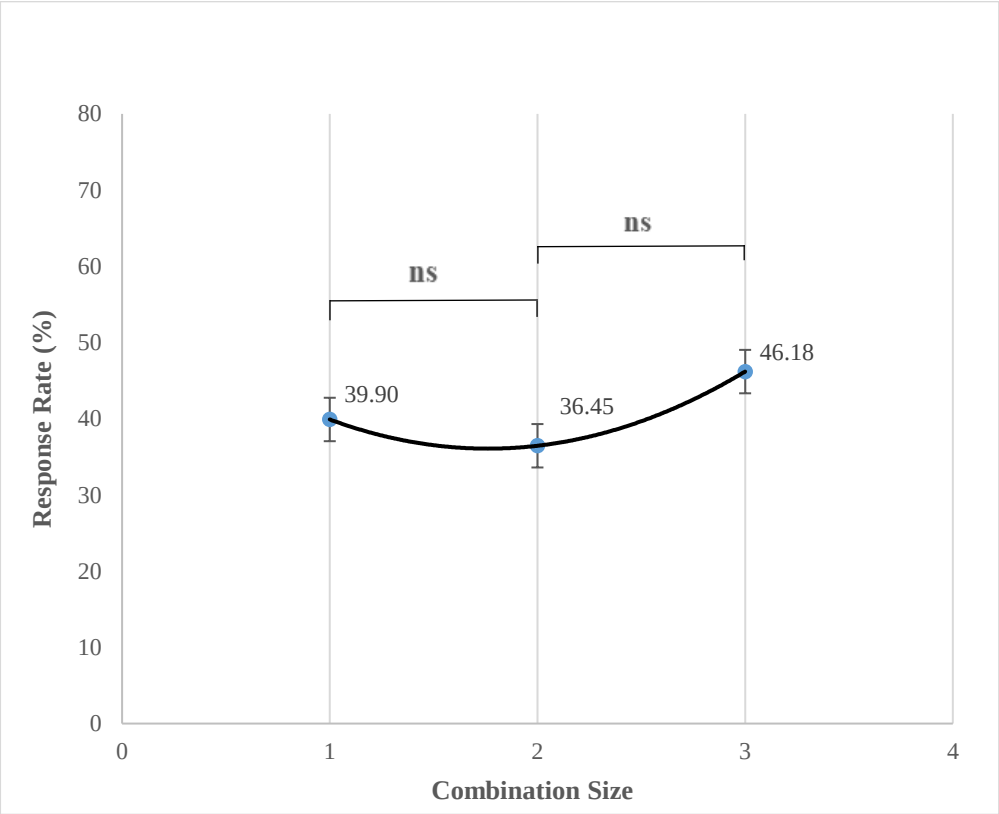

Figure 4: Impact of combination size on response rate. The X axis represents the number of drugs used in the combination and the Y axis represents response rate in percentage (%). The error bars represents standard error and the level of significance is 5%.

Here, the overall response rate (ORR) was compared according to the treatment size which is measured in terms of the number of medications utilized in the treatment, as seen in the graph above. The ORR was 39.90% when only one TKI was used which dropped to 36.45% when one other drug was given with TKI at the same time. On the other hand, there was a noticeable increase in this incidence when two drugs were administered with TKI in combination. The overall response rate increased to 46.18%, which demonstrates the significant influence treatment sizes have on ORR.

3.4 Impact of Combination Size on Overall Survival (OS)

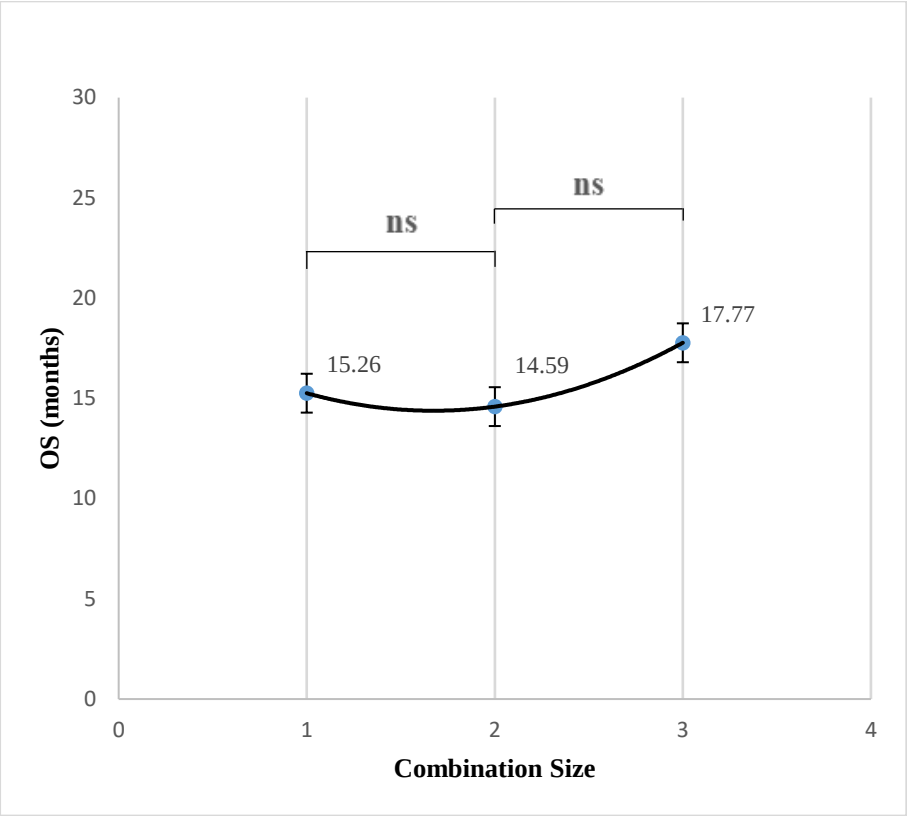

Figure 5: Impact of combination size on overall survival. The X axis represents the number of drugs used in the combination and the Y axis represents overall survival (OS) in months. The error bars represents standard error and the level of significance is 5%.

According to the graph above, the overall survival (OS) was compared according to the combination size, which is the number of medications that were employed in the treatment. However, utilizing a single TKI drug in the trial, the OS rate was 15.26 months which did not demonstrate any improvement in patients overall survival. When a different drug was administered with TKI at the same time, there is a distinct decrease in OS. Thus, for treatment size 2, the duration was 14.59 months. In contrast, there was an apparent improvement in OS when three medicines were given together (containing one TKI atleast) as seen by the fact that it climbed to 17.77 months in this case.

Chapter 4

Discussion

As it was noted previously, the purpose of this study was to analyze the relationship between the efficacy end-points, OS and ORR, along with constructing a model to compare the impact of the treatment size on the end-points.

In order to analyze the association, we determined Pearson's correlation coefficient, denoted as the r-value, for two specific instances. To begin with, it is worth noting that Figure 2 demonstrates a correlation coefficient (r) of 0.72, demonstrating a strong positive association between the median OS and ORR. This outcome aligns with the anticipated expectations. Hence, the p-value demonstrated statistical significance as it was found to be less than 0.0001. This indicates that an increase in the ORR will ultimately lead to an increase in OS. An increase in ORR is indicative of a corresponding rise in the number of patients exhibiting positive responses to treatment. This phenomenon is observed exclusively when there is a reduction in tumor size. The mentioned factor positively influences the patient's likelihood of survival post-treatment. The observed reduction in tumor size indicates that the administered medicine is exhibiting efficacy in the treatment. Moreover, an R^2 value of 0.53 is obtained, indicating that 53% of the variability in the dependent variable can be explained by a variation in the independent variable being investigated. The regression line of ORR can explain 53% of the variability observed in OS. Based on this study, it is expected that there will be a positive connection between the OS and the ORR. Moreover, an equation was developed from Figure 2, indicating that an increase in the ORR to the drug/drugs utilized in the treatment is associated with an improvement in the patient's OS.

In Figure 3, a negative correlation was observed between the median age of the patients and their OS. With a r value of -0.155, the correlation between these two variables is weakly

negative. The data suggests that there is an inverse relationship between a patient's median age and their overall survival or likelihood of surviving lung cancer following therapy. In addition, the R^2 value was 0.02, which means that 2% of the variation in the dependent variable can be accounted for by a change in the independent variable. The regression line corresponding to the median age exhibits the ability to account for 2% of the observed variability in OS, hence indicating a modest negative association. We could also predict an equation from the graph supporting this negative correlation fact.

In the statistical analysis utilizing the t-test, we examined the comparative effectiveness of ORR and OS as outcomes across various treatment groups. The Figure 4 illustrates the influence of combination size on the overall response rate of patients undergoing therapy. When comparing the efficacy of a single-agent study with a dual-agent trial, it is observed that the ORR is lower in the latter. This indicates that patients who received the combination of two agents had a reduced response compared to those who received only one agent. This phenomenon exhibits distinct characteristics compared to the three agent experiments. The administration of a combination of three drugs has been observed to cause a more favorable response to therapy in patients. The three-agent combination patients exhibit a better rate of tumor size reduction. This observation is applicable in the context of total survival. Based on the data presented in Figure 5, it can be observed that patients who received a combination of two medications had a lower survival rate compared to those who were treated with a single agent during the clinical study. Nevertheless, if three medications are delivered concurrently, there exists a significant probability that patients will experience an extended period of survival following the treatment. Both t-tests were conducted with standard error data, and the plots included error bars to indicate a 5% level of significance for the study. It should be noted that the p-value of the two-tailed t-test in both cases did not meet the criterion of being less than 0.05. This suggests that the study lacks significance.

The trial-level and patient-level studies conducted by the US Food and Drug Administration could not find any correlation between the treatment's effects on OS and ORR, with an R^2 value of 0.09. Upon excluding the three targeted therapy trials that had sample sizes below 500 from the linear model analysis, the association between OS and ORR ($R^2 < 0.44$) improved but remained modest. The reasons for this weak correlation are uncertain, although it could be due to the absence of any actual relationship or the influence of other variables that may obscure the analysis of OS, such as cross-over or subsequent therapy (Blumenthal et al., 2015). According to the findings of another study, there is a moderately negative correlation between ORR and OS with a Pearson coefficient, r value of -0.58 ($p = 0.036$). Based on this finding, it appears that an increase in ORR would lead to a reduction in OS, and vice versa (Solomon et al., 2022). On the other hand, the results of our research showed that there is a significant positive correlation between OS and ORR with Pearson coefficient, r value of 0.72 ($p < 0.0001$) and the value of R^2 for this association is 0.53. Thus, the outcomes of our investigation were completely different in comparison to the other two studies.

Based on the results of our t-test analysis, it was observed that the combination of two drugs did not significantly improve the overall survival or response rate of the patients. However, it is worth exploring the potential of combining multiple molecularly targeted agents in carefully designed clinical studies for patients with non-small cell lung cancer (NSCLC) who have tumor cells with the EGFR TK mutation (Cohen et al., 2012).

Chapter 5

Conclusion

To sum up, it can be stated that the primary objective of any cancer therapy remains the enhancement of patients' post-treatment survival rates. Considering its high global mortality rate, NSCLC requires the development of more effective treatment and disease management strategies. Therefore, the primary emphasis of our study was on targeted therapy, specifically tyrosine kinase inhibitors (TKIs). We observed that ORR is an appropriate surrogate endpoint for OS due to the moderate correlation between the two, although age is not a reliable predictor of OS. Following the completion of our research, it became abundantly evident that expanding the treatment combination to include other targeted and non-targeted medicines would almost certainly improve patients' reactions to the therapy while also raising the patient's chances of surviving it. The optimal combination size is three since this yields the best results by enhancing patients' survival and response to the treatment. However, if we could add more data, it would be much simpler for us to gain a deeper comprehension of these efficacy endpoints.

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