Effect of Performance Status on Efficacy Endpoints in Phase II Trials of Non-Small Cell Lung Cancer

By

Pulock Paul

19346040

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a 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.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Pulock Paul

19346040

Approval

The project titled “Effect of performance status on efficacy endpoints in phase II trials of non-small cell lung cancer” submitted by Pulock Paul (19346040) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of pharmacy on December, 2023.

Supervised By:

_____

Faruque Azam

Lecturer

School of Pharmacy

Approved By:

Program Director:

_____

Professor Dr. Hasina Yasmin

Program Director and Assistant Dean

School of Pharmacy

Brac University

Dean:

_____

Professor Dr. Eva Rahman Kabir

Dean

School of Pharmacy

Brac University

Ethics Statement

This study does not involve any human or animal trials.

Abstract

Researchers must prioritize non-small cell lung cancer clinical research due of its high mortality. Ongoing endeavors are being made to improve the accessibility, evaluation simplicity, and prediction accuracy of endpoints in clinical studies. In this study, we investigated the correlation of the primary endpoint overall survivals (OS) with overall response rate (ORR) and progression free survival (PFS). Also, the impact of performance status (PS) was examined through spearman rank correlation. The ORR, PFS, and OS all have a strong and significant positive relationship. Spearman correlation coefficient between OS and ORR, $r_s = 0.697$ ($p < 0.0001$), OS and PFS, $r_s = 0.765$ ($p < 0.0001$). Any change in ORR or PFS notably affects the OS. The PS did not correlate with the endpoints, indicating poor correlation. Therefore, a larger collection of clinical trials' endpoints is needed to better understand the relationship between endpoints.

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

Dedication

“Dedicated to my beloved Parents”

Acknowledgment

I would want to express my utmost gratitude to the divine entity for the numerous benefits bestowed upon me, which have served as a source of motivation and resilience in successfully completing this undertaking. Additionally, I express my gratitude towards my parents for their unwavering encouragement and support, as it served as a catalyst for my increased efforts in surmounting the challenges I encountered.

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List of Acronyms:

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

Chapter 1

Introduction

Cancer is a complex and widespread collection of diseases that is distinguished by the unregulated growth and division of cells, which disrupts the normal regulatory processes of the cell cycle. The process of initiation frequently entails the occurrence of genetic mutations that gradually accumulate, so impacting crucial genes involved in cellular development, division, and processes for repair. The occurrence of these mutations can be initiated by a wide range of circumstances, encompassing genetic predisposition, exposure to carcinogens, and environmental impacts. The defining characteristic of cancer is the formation of neoplastic growths, known as tumors, which can exhibit either benign or malignant properties. Malignant neoplasms, specifically, exhibit the ability to infiltrate neighboring tissues and disseminate to remote locations via metastasis, a mechanism that substantially contributes to the morbidity and mortality rates associated with this pathology. Cancer is a significant and pervasive public health issue, resulting in an annual mortality rate of 8.8 million individuals (Zugazagoitia et al., 2016). This figure surpasses the combined death toll of HIV/AIDS, malaria, and tuberculosis. This statistic represents around 16.7% of global mortality. Cancer, as a complex ailment, encompasses multiple distinct illnesses characterized by diverse subtypes, necessitating the utilization of specialized diagnostic and therapeutic approaches. In order to address such intricacy, it is imperative to implement a comprehensive and coordinated approach including multiple disciplines (Torre et al., 2016). It is projected that in the year 2023, an estimated 609,820 individuals residing inside the United States will experience mortality as a consequence of cancer, leading to an average of approximately 1670 deaths occurring on a daily basis (Siegel et al., 2023).

The global burden of morbidity and mortality caused by lung cancer is substantial, making it one of the most challenging and common malignancies. Among the various kinds of cancer, lung cancer is commonly regarded as the second greatest cause of cancer-related mortality. Smoking tobacco cigarettes is largely considered the main cause of lung cancer. Lung cancer may arise from the utilization of various forms of tobacco, such as pipes or cigars, which include around 7000 detrimental chemicals present in tobacco smoke. Additionally, the inhalation of secondhand smoke, exposure to asbestos or radon within residential or occupational settings, or inheriting a familial predisposition to lung cancer can also contribute to its development. Given that 76% of individuals diagnosed with lung cancer engage in smoking, it is reasonable to infer that tobacco-related malignancies contribute to around 27.1% of the total cancer cases (Marolia et al., 2022). Both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) are the two main categories under which it falls. In Western countries, more than 85 percent of lung cancer diagnoses are NSCLC. Notably, a significant proportion, ranging from 20% to 30%, of NSCLC cases are observed in individuals with no history of smoking (Forde & Ettinger, 2013). Lung cancer is responsible for the mortality of approximately 350 individuals on a daily basis, which is nearly 2.5 times more than the corresponding figure for colorectal cancer. Approximately 81% of the projected 127,070 lung cancer fatalities in 2023, amounting to almost 103,000 deaths, are anticipated to be attributed to smoking. Furthermore, an estimated 3,560 deaths are likely to be associated with indirect exposure to smoke (Siegel et al., 2023). The illness is notorious for its slow start, often leading to late-stage diagnosis and limited treatment choices.

Based on statistical data presented by the American Society of Clinical Oncology (ASCO), an estimated 28% of patients with NSCLC will survive to the fifth year after diagnosis. In the United States, the prevalence of the aforementioned statistic is 33% for women and

23% for males. Those who have non-small cell lung cancer that has spread locally have a relative survival rate of 65% at 5 years. On the other hand, over 37% of patients with localized NSCLC will still be alive five years after treatment ends, even when the disease has spread to nearby lymph nodes. Alternatively, metastatic lung cancer has a 9% incidence rate. (Lung Cancer - Non-Small Cell: Statistics, 2023).

Furthermore, it is important to note that there exist four main histologic subtypes of lung cancer, namely adenocarcinoma (ADC), small-cell carcinoma, large-cell carcinoma, and squamous cell carcinoma. About 40% of these cases are adenocarcinoma, 25% to 30% are squamous cell carcinoma, and 10% to 15% are large cell carcinoma. Since the 1970s, adenocarcinoma has been consistently identified as the most often observed histologic subtype in women. Notably, the rate of lung adenocarcinoma was higher than the rate of squamous cell cancer in 1994 (Schabath & Cote, 2019).

The cardinal manifestations commonly associated with lung cancer are diminished appetite, inexplicable weight reduction, dyspnea, and sensations of fatigue or debility. People who have NSCLC can get the following treatments: surgical intervention, chemotherapy, targeted therapy, radiation therapy, or a combination of these therapeutic approaches. Yet, chemotherapy and radiation therapy are the most common ways to treat people with SCLC.

Alternative treatment options, such as photo dynamic therapy, internal radiation, or laser therapy, may serve as viable alternatives to surgical intervention for certain forms of cancer that have not yet advanced beyond stage 0. If the cancer is indeed in stage 0, it is expected that these therapies will effectively treat the patient. There is a lack of necessity for the administration of chemotherapy or radiation therapy. If the individual who has received a diagnosis is deemed to be in a sufficiently stable state to undergo surgical

intervention, it is probable that they would be considered eligible for treatment by either segmentectomy or wedge resection, both of which involve the removal of a portion of the lung lobe. Patients who have been diagnosed with stage I non-small cell lung cancer (NSCLC) have access to a range of treatment options, including surgical interventions like wedge resection or segmentectomy. By administering adjuvant chemotherapy subsequent to surgical intervention, individuals diagnosed with stage I NSCLC who demonstrate an increased risk of relapse as a result of tumor size, location, or other relevant factors may experience a reduced likelihood of cancer recurrence. Patients who have received a stage II NSCLC diagnosis and are in good physical condition to undertake surgical intervention. The rationale for this practice lies in the common surgical procedures employed, namely lobectomy or sleeve resection, which are typically utilized for the removal of cancerous growths. Non-small cell lung cancer in stage IIIA is predominantly treated with radiation therapy, chemotherapy, surgical intervention, or a combination of these modalities. As a result, the involvement of a thoracic surgeon, a medical oncologist, and a radiation oncologist is often required in the therapeutic planning for stage IIIA NSCLC. The available therapeutic interventions are dependent upon several factors, including the dimensions of the tumor, its specific anatomical placement within the lung, the extent of lymph node involvement, the overall health status of the patients, and their capacity to endure the prescribed treatment regimen. Radiation therapy, often combined with chemotherapy in certain instances, is commonly prescribed for individuals whose medical condition precludes them from undergoing surgical intervention.

The term "chemotherapeutics" describes a group of chemical substances that have shown effectiveness in the fight against cancer. These pharmaceutical compounds disrupt essential cellular reproduction mechanisms in highly proliferating cancerous cells. In conjunction with hormone therapy and cytotoxic chemotherapy, targeted therapy,

alternatively referred to as molecularly targeted therapy, is a key method employed in the medical management of cancer. Targeted therapy is a treatment approach that aims to administer drugs specifically to genes or proteins that are exclusive to cancer cells or the microenvironment that facilitates cancer progression. The success of therapy relies on the ability to provide targeted therapeutic release at the site of disease, while minimizing off-target negative effects on healthy tissues. It is frequently employed in conjunction with other therapeutic interventions for the treatment of cancer. Orally given monoclonal antibodies are utilized in targeted therapy.

The surgical procedure lacks the capacity to completely excise these tumors. The provision of medical intervention for lung cancer at this particular stage, as well as at earlier stages, is dependent upon the overall health condition of the individual. If a patient is diagnosed with NSCLC in stages IVA or IVB, it means the cancer has spread to other parts of the body. Treating these tumors poses significant challenges. Several factors contribute to the determination of treatment options for individuals, including their overall health status, the geographical distribution and magnitude of the disease, together with the existence or lack of certain protein or genetic anomalies in cancer cells.

Clinical trials are research studies that are done to find out how well and safely new drugs, drugs that have already been approved, medical technologies, or different treatment methods work. These trials provide valuable insights into the effectiveness and ineffectiveness of various medical and healthcare approaches. They provide the most efficacious approach to determining the efficacy of therapy for cancer and other severe illnesses. Clinical investigations are typically conducted in sequential phases that progressively advance the research process. Various phases exist in research, such as Phase I, Phase II, and Phase III. Following the successful conclusion of phase I clinical studies, the newly discovered drug will move on to phase II clinical trials. This

transformation is essential for determining the medicine's effectiveness in treating particular cancers. The physicians' pursuit of an advantage in therapy is contingent upon the specific objective of the treatment. There is a potential interpretation that suggests an improvement or even remission of the cancer. Additionally, it is plausible that this indicates a period of significant stasis in cancer growth, or a substantial delay before its recurrence. Based on the results of specific research, it is suggested that the advantage could potentially lead to an enhancement in the overall quality of life. Due to the larger patient population involved in phase II research, it is plausible that a reduced incidence of side effects may be detected. Phase III clinical trials will be initiated if there is a significant proportion of patients who experience a favorable outcome from the treatment and if the bad effects can be effectively managed.

To guarantee proper evaluation and approval, it is crucial to pick the key endpoint for a clinical trial's effectiveness evaluation with care. The accessibility, evaluative simplicity, and prediction accuracy of endpoints in cancer clinical trials are continuously being pursued (Driscoll & Rixe, 2009). In the context of clinical trials pertaining to oncology, the key outcome measure that is widely regarded as the benchmark for assessing the effectiveness of any pharmaceutical agent, biologic substance, therapeutic modality, or intervention is known as overall survival (OS) (Fiteni et al., 2014). The overall survival (OS) period encompasses the duration from the initiation of randomization or treatment until the patient's ongoing survival. According to Cheema and Burkes (2013), the patient-centered outcome in question is a quantifiable, accurate, and clinically meaningful endpoint that remains consistent regardless of the timing of evaluation. Conversely, progression-free survival (PFS) provides a simple way to measure the treatment's impact on tumors. The outcome of utilizing PFS is contingent upon the frequency at which patients are monitored for illness signs. The five-year survival rates of several tumors are

indicative of the likelihood of patients achieving a cure for their condition, as those who live for a period of five years exhibit a higher probability of successful treatment. Nevertheless, the efficiency of PFS as a metric is widely acknowledged and its accessibility is greater than that of OS. Consequently, it has the potential to expedite the process of medicine development (Driscoll & Rixe, 2009). The comprehensive assessment of both target and nontarget lesions, along with newly formed lesions, results in an overall response. The evaluation of trial outcomes and the selection of treatment regimens for routine practice are facilitated by the consideration of the overall response rate (ORR), as highlighted by Aykan and Özatlı (2020). Individuals who have a documented medical history of solid tumors may utilize the overall response rate (ORR) as a quantitative measure to evaluate the effect of a specific therapeutic intervention on the tumor mass's size (Delgado & Guddati, 2021).

1.2 Aims & objectives of the study

- To find out the correlation between performance status (PS) and other clinical endpoints of phase II non-small cell lung cancer clinical trials.
- To investigate the relation of median overall survival (OS) with overall response rate (ORR) and progression free survival (PFS).

Chapter 2

Methodology

2.1 Efficacy Endpoints

In clinical trials, the efficacy endpoint is the clinical or biological result that is assessed in order to determine the intervention's effectiveness and to compare alternative treatments. The progression-free survival (PFS) of a clinical trial is the amount of time that has passed since therapy began until the disease starts to advance (I. Gutman et al., 2013). A patient's "overall survival" (OS) is defined as the duration of time they remain alive following the start of treatment (Hess et al., 2019). Information containing PFS and OS expressed per month was considered. In addition, a quantifiable metric known as the overall response rate (ORR) is employed to evaluate the impact of a specific treatment on the tumor burden of patients with a history of solid tumors (Aykan & Özatlı, 2020). "Response rate" denotes the percentage of patients who demonstrate either a full or partial improvement in response to a specific therapeutic intervention (Villaruz & Socinski, 2013). The ORR is expressed as a percentage (%). When OS and PFS were indicated in days and weeks, respectively, they were converted to months.

2.2 Predictor Variables

This study considers three parameters as predictors. The aforementioned factors encompass the performance status of patients with NSCLC, the overall response rate (ORR), and the progression free survival (PFS). In the majority of investigations, the Eastern Cooperative Oncology Group (ECOG) performance status is frequently employed to evaluate performance status. The ECOG performance status is subsequently transformed into the karnofsky performance status (KPS). Healthcare practitioners utilize the karnofsky performance status (KPS) scale to assess an individual's readiness to

perform daily activities and their general functional state (Crooks et al., 1991). The scale exhibits a range spanning from 0 to 100, where a score of 100 signifies typical functioning, while lower scores correspond to escalating levels of disability.

2.3 Data Source

The principal aim of this endeavor is to utilize PubMed, a unified database, to optimize the retrieval process of publications pertaining to clinical trials in Phase II NSCLC. A systematic search was conducted on the PubMed database using specific keywords, such as 'phase II clinical trial lung cancer', in order to refine the pool of publications and identify those that were directly pertinent to the research focus. The objective of this research is to methodically gather and extract essential effectiveness outcomes from a set of 400 Phase II clinical trial publications focused on NSCLC. Moreover, the implementation of a unified database reduces complexity and enables more streamlined data management under time constraints.

2.3 Inclusion and Exclusion Criteria

The implementation of precise parameters has been undertaken to effectively carry out the process of applying inclusion or exclusion criteria to the articles that were searched. The primary objective of this research was to examine publications from phase II clinical trials that utilized tyrosine kinase inhibitors (TKIs) in the treatment of NSCLC. Nevertheless, the data set also encompassed clinical trials that combined TKIs with additional therapeutic approaches, including chemotherapy, radiation therapy, and immunological therapy. The articles lacking cancer medicines were removed from the analysis. Conversely, this study incorporated papers that encompassed two or more endpoints. In a similar vein, the inclusion of OS and PFS provided in percentages has been omitted from this calculation as these statistics are deemed irrelevant. In the event of the absence of

PFS, time to progression (TTP) was taken. Furthermore, the ECOG performance status was assessed and subsequently transformed into the Karnofsky performance status (KPS).

2.4 Study Plan

The goals encompass progression-free survival (PFS), overall response rate (ORR), and overall survival (OS). 183 overall response rates (ORR), 178 progression-free survival (PFS), and 178 overall survival (OS) were identified commensurately through the examination of the 158-publication dataset. Based on the aforementioned efficacy endpoints, it is imperative to underscore two fundamental attributes. Initially, one of the main aims was to examine the potential influence of specific medications within the therapy regimen on the overall likelihood of patients recovering from the condition. Furthermore, the primary aim of this research endeavor was to examine the potential correlation that might exist among various therapeutic methodologies, specifically the association between overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) with performance status (PS), as well as the association between ORR, PFS, and OS.

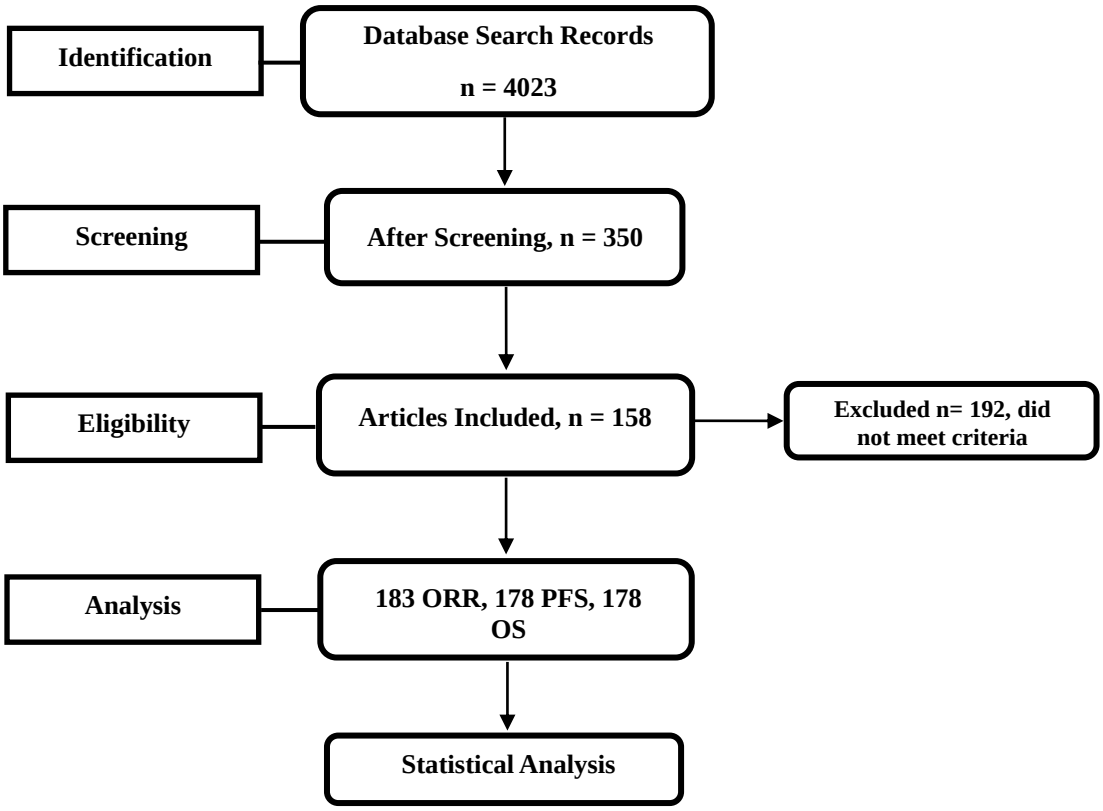

Figure 1: Study Plan

2.5 Statistical Analysis

The correlation between overall survival (OS), progression-free survival (PFS), overall response rate (ORR), and performance status (PS) was determined using the Spearman correlation coefficient. Furthermore, an analysis of the correlation between overall response rate (ORR), progression-free survival (PFS), overall survival (OS), and performance status (PS) was conducted using scatterplots. A scatterplot was generated to display the relationship between overall survival (OS) and progression-free survival (PFS), as well as overall response rate (ORR). To determine additional parameters and prognostic factors, a linear regression analysis was performed to investigate the correlation between OS, ORR, and PFS. The interpretation of the Spearman correlation coefficient 'r_s' is

conducted according to the rules proposed by Cohen (1988) for interpreting the strength of a correlation. All tests were conducted using Microsoft Excel 2019.

Chapter 3

Results

3.1 Dataset Overview

progression-free survival, overall response rate, and overall survival rate were a few of the efficacy outcomes that were primarily calculated for this study. Following an exhaustive search, 157 papers were ultimately chosen for inclusion in the study. The analysis encompassed 182 ORR (mean = 40.97, 95% CI, 37.3 to 44.6), 177 PFS (mean = 7.54, 95% CI, 6.7 to 8.4), 177 OS (mean= 15.58, 95% CI, 14.2 to 16.9), and 195 Karnofsky performance status (mean= 84.79, 95% CI, 83.85 to 85.74) outcomes.

Table 1: Summary of the collected dataset

Data type	Total Observation	Mean	95% Confidence Interval
Overall Response Rate (ORR)	182	40.97	37.3 – 44.6
Progression Free Survival (PFS)	177	7.54	6.7 – 8.4
Overall Survival (OS)	177	15.58	14.2 – 16.9
Performance Status (KPS)	195	84.79	85.74 – 83.85

3.2 Relationship of ORR, PFS, and OS with PS

Utilizing the Spearman correlation coefficient, the prospective relationship between the provided data and performance status (PS) was determined. The correlation coefficients (r_s-value) for overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) with performance status (PS) are 0.154, 0.208, and 0.256, respectively. The correlation coefficient between the ORR and PS is determined to be $r_s = 0.154$, suggesting a poor relationship among these two variables. Furthermore, the correlation coefficient (r_s

= 0.208) between PFS and PS indicates a weak relationship between these variables. Likewise, the correlation coefficient of r_s = 0.256 similarly suggests a poor correlation between the observed variable OS and the predictor variable PS. The scatterplot of these criteria also indicates a weak linear relationship between them. This implies that alterations in one variable do not exhibit a consistent linear relationship with changes in the other variable.

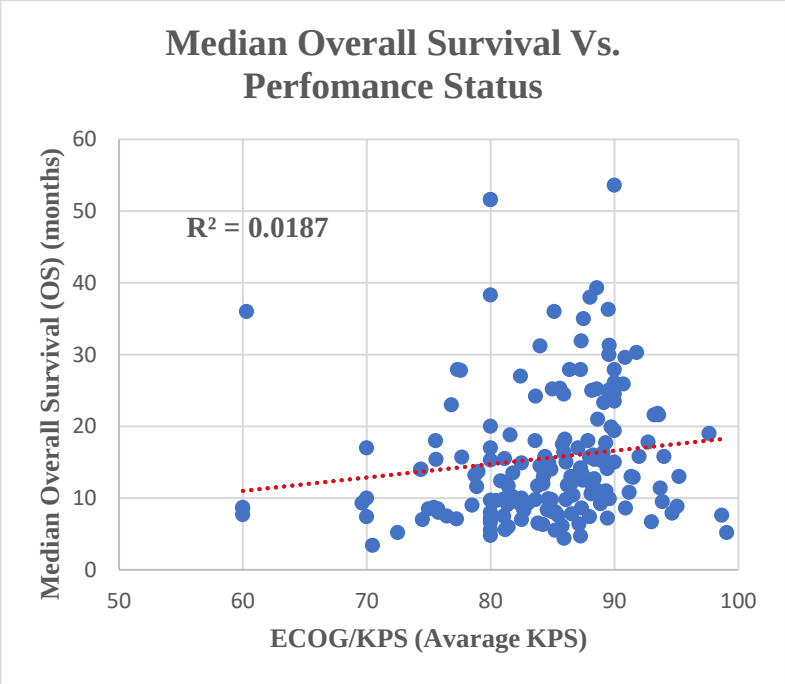

Figure 2: Scatterplot of median overall survival and performance status of phase II clinical trials of non-small cell lung cancer. Median overall survival is shown on the x-axis, while performance status is plotted on the y-axis. The dotted line shows the trendline.

3.3 Relationship of ORR and PFS with PS

On the contrary, a Spearman correlation analysis was conducted to examine the relationship between overall survival (OS) and overall response rate (ORR), as well as between OS and progression-free survival (PFS) in patients diagnosed with non-small cell

lung cancer (NSCLC). The findings of this analysis yielded intriguing outcomes. The correlation coefficient between OS and ORR is denoted as r_s = 0.697. This finding suggests a significant positive relationship between OS and ORR. Likewise, the correlation coefficient 'r' between OS and PFS is determined to be 0.765, indicating a robust positive relation between these two variables.

Moreover, suggesting a positive linear relationship between these two variables, the scatterplot showing the link between overall survival (OS) and overall response rate (ORR) displays an increasing trendline. The scatterplot depicted in Figure 3 (r = 0.3725) exhibits a clear and discernible upward trend that extends horizontally from the left to the right. This indicates that the two variables are related in a linear fashion. Specifically, the narrative suggests that an increase in ORR is positively correlated OS, whereas a reduction in ORR is linked to a decline in OS.

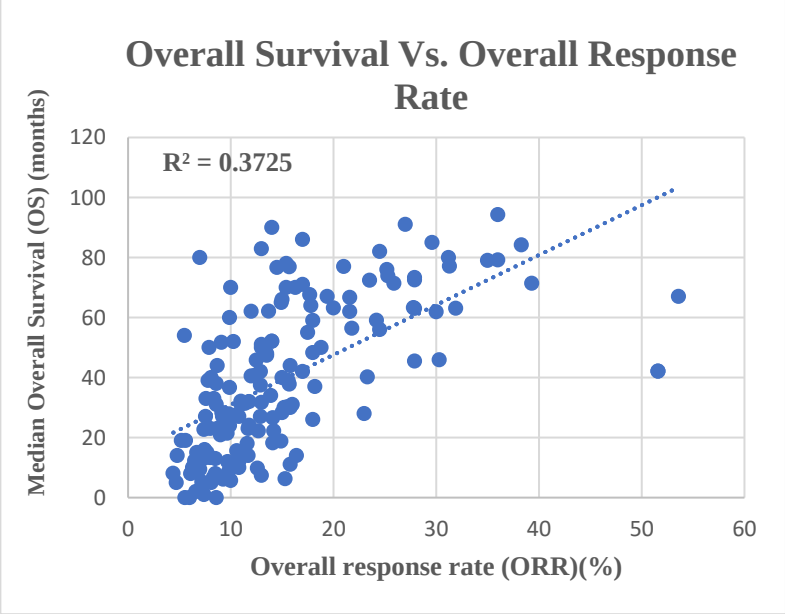

Figure 3: Scatterplot of median overall survival and overall response rate of phase II clinical trials of non-small cell lung cancer patients. Overall response rate is shown on the x-axis, while median overall survival (month) is plotted on the y-axis. The dotted line shows upward trendline.

Likewise, upon analysis of the scatterplot illustrated in Figure 4, which represents OS and PFS, one can discern a consistent upward trendline. A positive linear correlation between OS and PFS is also suggested by this. This indicates that an improvement in progression-free survival (PFS) correlates with a higher rate of overall survival (OS), whereas a reduction in PFS correlates with a lower rate of OS.

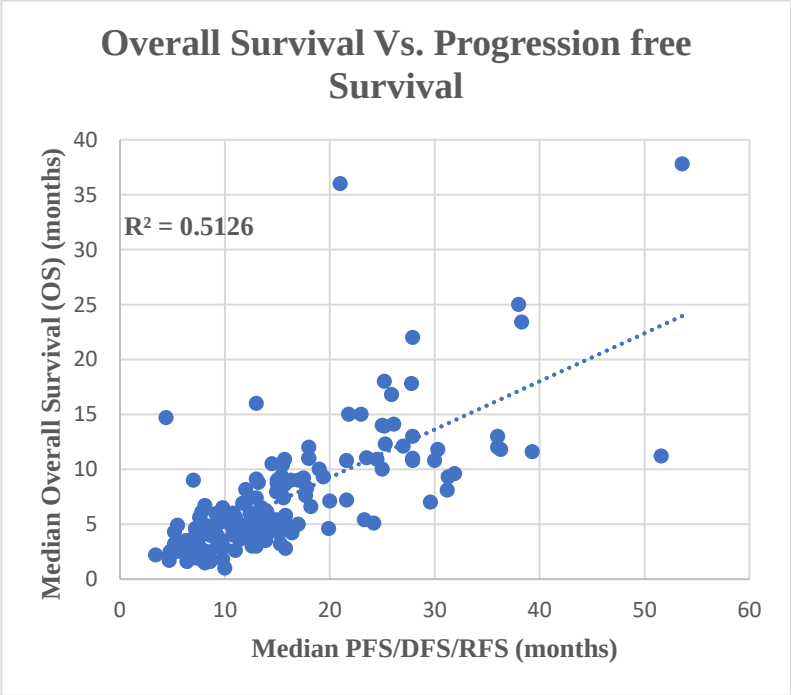

Figure 4: Scatterplot of median overall survival and median progression-free survival of phase II clinical trials of non-small cell sell lung cancer. Median progression-free survival is shown on the x-axis, while median overall survival (month) is plotted on the y-axis. The dotted line shows upward trendline.

Table 2: Linear regression between median overall survival, overall response rate, and median progression-free survival.

	Coefficients	Standard Error	P-value	Lower 95% CI	Upper 95% CI
Intercept	5.03	0.93	2.82575E-07	3.19	6.88
ORR (%)	0.12	0.03	5.22161E-06	0.07	0.17
Median PFS/TTP (months)	0.76	0.12	1.40607E-09	0.53	0.99

The predicted equation was derived using linear regression:

$OS = 5.033 + 0.764 \times (PFS) + 0.121 \times (ORR)$

The adjusted R square value of 0.54 indicates that, taking into consideration the number of variables, the independent variables (PFS, ORR) could explain 54% of the variance in the dependent variable (OS). 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 ($R^2 = 0.55$). The regression model's intercept is estimated to be 5.03, suggesting that the dependent variable (OS) is expected to have a value of 5.03 when the independent variables (PFS and ORR) are both set to zero.

Chapter 4

Discussion

The assessment of the efficacy of innovative treatments in cancer drug clinical trials heavily relies on the link between overall survival (OS), progression free survival (PFS), and overall response rate (ORR). OS represents the duration between the initiation of treatment and the patient's demise, irrespective of the cause. It offers a comprehensive perspective on the treatment's influence on overall mortality. On the contrary, progression-free survival (PFS) measures the time elapsed between the initiation of treatment and the occurrence of disease progression or mortality, excluding extraneous events that are not associated with cancer. The acronym ORR denotes the proportion of patients who undergo a predetermined tumor response. Although overall survival (OS) is often regarded as the primary measure for assessing the long-term effectiveness of a treatment, PFS and ORR provide significant insights into disease management and the immediate therapeutic effects. For a comprehensive evaluation of the therapeutic benefits of cancer treatments, research articles, including those published in reputable journals like the New England Journal of Medicine, often emphasize the importance of holistically assessing multiple endpoints (Seymour et al., 2017). The assessment of therapy efficacy and patient outcomes in cancer drug clinical trials heavily relies on the link between OS, PFS, ORR, and PS. The assessment of performance status, commonly evaluated by instruments such as ECOG scale, serves as an indicator of a patient's general state of health and capacity to engage in routine tasks. According to a study, there is evidence to suggest that performance status, as measured by the Karnofsky performance status (KPS), possesses predictive capabilities in relation to OS, cancer-specific survival (CSS), and PFS (Evers et al., 2014). There is often a notable association between a positive performance status and enhanced OS, extended

PFS, and heightened ORR. This underscores the importance of considering the functional state of patients when forecasting treatment response and the overall advantages in terms of survival.

This study tried to find out the relation of ORR, PFS and OS with PS. Subsequently, the Relation of OS with PFS and ORR has also been tried to determine. For this Spearman correlation technique has been applied. The correlation coefficients (r-values) between ORR, PFS, and OS and predictor, which is performance status (PS) are 0.154, 0.208, and 0.256, correspondingly. All of the three correlation coefficients suggest all three variables have weak correlation with performance status (KPS) according to the rules proposed by Cohen (1988) for interpreting the strength of a correlation. Additionally, the scatterplot of these three variables, ORR, PFS, and OS against Ps shows statistically insignificant positive weak linear relationship. This suggests that modifications in one variable do not demonstrate a uniform linear correlation with fluctuations in the other variable.

On the other hand, The Spearman correlation value r= 0.697 between OS and ORR suggests a statistically significant and fairly strong positive link. Based on Cohen's (1988) criteria for evaluating correlation, it can be inferred that a correlation coefficient of 0.697 lies within the range of 0.50 to 0.69, indicating a modest effect size. From a practical standpoint, it can be observed that there exists a significant and identifiable correlation between OS and ORR. A positive correlation between these two variables implies that an increase in the overall response rate is associated with a corresponding increase in overall survival. This observation suggests a potential correlation between treatments that result in a greater overall response rate and enhanced overall survival outcomes. Similarly, the correlation coefficient value of OS and PFS is r_s= 0.765, indicates a strong positive relationship. In accordance with Cohen's (1988) recommendations, a correlation coefficient of 0.765 is classified as having a significant effect size, as it falls within the

range of 0.70 to 0.89. From a practical standpoint, this suggests that there is a strong and significant connection between OS and PFS.

Figures 3 and 4 depict the scatterplot illustrating the relationship between OS and ORR, as well as OS and PFS. The scatterplots exhibit a statistically significant positive linear relationship in both criteria. This suggests that an upward trend in PFS or ORR will have a positive impact on OS; conversely, a downward trend in ORR or PFS will have a detrimental effect on OS.

However, it is crucial to remember that the existence of correlation does not automatically imply causation, as there may be additional variables that play a role in the observed association. In addition to evaluating other variables and considering potential confounding factors, a more comprehensive analysis is necessary to fully comprehend and interpret the observed correlation of OS with ORR and PFS.

Chapter 5

Conclusion

This study aims to find out the correlation of overall survival with overall response rate (ORR), and progression free survival as well as ORR, PFS, and OS with performance status (PS). The application of correlation analysis can offer researchers valuable insights in the identification of appropriate endpoints for clinical investigations. If progression-free survival (PFS) and overall survival (OS) exhibit a strong and reliable correlation, then it is possible that PFS could function as a dependable surrogate endpoint, facilitating the accelerated assessment of therapeutic efficacy in clinical trials. Subsequently, healthcare providers can employ these connections to augment their clinical judgement in the process of determining treatment decisions for specific patients. An example of this is when considering progression-free survival and overall survival; it is predictable that a patient who demonstrates a high overall response rate will be granted a more favorable prognosis. Furthermore, these correlations can be utilized by pharmaceutical companies and researchers to prioritize patients according to their need. Gaining an understanding of the relationship between treatment response and survival outcomes can yield significant knowledge for the development of innovative therapeutic strategies that are more likely to demonstrate clinical effectiveness. Further investigation is needed to employ a larger dataset of cancer therapy clinical trials in order to gain deeper insights and enhance our understanding of the precise relationships between various endpoints.

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