Efficacy Analysis and Prediction 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 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.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “Efficacy Analysis and Prediction in Phase II Clinical Trials of Non-Small Cell Lung Cancer” submitted by Ismoth Ara Hoque (18346044) of Spring, 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 trial.

Abstract

The American Cancer Society estimates that lung cancer is the most common type of cancer and nearly 25% cancer deaths result from lung cancer, of which three subtypes account for 80% of cases. This is the rationale behind our study's selection of NSCLC subtypes. Moreover, drugs approved after passing clinical trials. Phase II clinical studies rely on "interim" data about safety and efficacy, enabling quicker drug approval. However, patient's diversity is a cause of treatment failure, as the risk of adverse events or treatment failure can be influenced by individual genetic variation. To solve this, finding an efficacy endpoint (PFS, ORR, OS) type from clinical studies allow the effectiveness of treatment to be quantified. In our study, we gathered effective endpoints and analysed to determine whether any relationships existed and if so, constructed a predictive model with the best predictor endpoint.

Keyword: Lung cancer, PFS; ORR; OS; NSCLC subtypes.

Dedication

dedicated to my parents

Acknowledgment

First and foremost, I would want to express my gratitude to Almighty Allah, who is the source of our perseverance, power, wisdom and who has made it possible for me to complete this project work diligently and in good physical health.

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List of Acronyms

PFS	Progression Free Survival
ORR	Overall Response Rate
OS	Overall Survival
PR	Partial Response
CR	Complete Response
NSCLC	Non-Small Cell Lung Cancer
SCLC	Small Cell Lung Cancer
QoL	Quality of Life
HRQoL	Health-Related Quality of Life

Chapter1

Introduction

1.1 Background

One of the most dreaded diseases of the 20th century is cancer that has become more prevalent in the 21st century and is expanding farther (Roy & Saikia, 2016). Every fourth person has a lifetime risk of developing cancer which is a highly serious situation. It is the outcome of uncontrolled cell division that has the ability to expand or infiltrate the entire body. Normal human cell division primarily aids in cell growth and multiplication as well as the formation of new cells as needed by the body. Apoptosis and necrosis, the two ways that cells naturally die when they get old or injured respectively, new cells will take their place. This systematic mechanism is destroyed in cancer; abnormal or damaged cells proliferate and expand when they should not. Unlike healthy cells, cancer cells disobey signals to cease reproducing or to pass away and be shed. Unable to discern its own natural boundaries and growing uncontrollably. According to the WHO, cancer will account for over 10 million deaths worldwide in 2020, with cervical cancer accounting for the majority of cases in 23 countries. The National Cancer Institute estimates that roughly 39.5 percent of men and women in the United States receive cancer diagnosis at some point in their life (What Is Cancer?, n.d.). There are some malignancies that are more prevalent than others; the current most prevalent in the country are listed as follows: breast, stomach, cervical, thyroid, lung and prostate cancer.

While the prevalence of most cancers is declining but some like- melanoma, have actually increased in the previous few decades. Cancer can develop anywhere in the body. One of the most prevalent cancers in women is breast cancer whereas prostate cancer affects men. Both men and women are at greater risk for colorectal and lung cancer.

The most significant form of cancer is lung cancer as it is the leading one in terms of death. A type of cancer that develops in the lung's tissues, typically in the cells lining airways called lung cancer. Compared to colon, breast and prostate cancers combined, lung cancer claims more lives every year. This type of cancer was the reason of death for nearly 1.8 million individuals worldwide in 2020, making it the most common cancer.

Two forms of lung cancer exist. Firstly, small cell lung cancer (SCLC) and secondly, non-small cell lung cancer (NSCLC). Small cell carcinoma (oat cell cancer) and combine cell carcinoma are the two subtypes of SCLC. Adenocarcinoma is one of the three kinds of NSCLC. Squamous cell, large cell are two other types. In 80% of patients across all categories, NSCLC and its 3 subtypes appear the most (Gadgeel et al., 2012).

Adenocarcinomas are peripheral tumors that are histologically diverse, rapidly spread and frequently develop in people who already have a lung condition. According to American cancer society, among young people it is the more prevalent form and women are more likely to develop this malignancy than men (Cancer Facts & Figures 2022| American Cancer Society, n.d.). Often, adenocarcinoma is found before spreading to another organ. Unlike certain other forms of lung cancer, the prognosis for adenocarcinoma in situ is frequently very favorable (when doctors discover abnormal cells in glandular tissue that lines the lungs). Squamous cell carcinomas often manifest as centrally placed endobronchial masses and may hemoptyse, have post-obstructive pneumonia or have lobar collapse. Squamous cell carcinomas typically develop metastases later than adenocarcinomas. Small cell carcinomas have an aggressive clinical behavior which centrally situated with significant mediastinal involvement, and are linked to early extra-thoracic metastases, such as paraneoplastic syndrome.

The prognosis for individuals with small cell carcinoma is often poor since they are frequently advanced at the time of diagnosis, despite the fact that they respond well to chemotherapy. There is little differentiation in large cell carcinoma like- large peripheral masses (tumours) are linked to early metastasis. Additionally, almost 20% of lung cancers are neuroendocrine tumors; the majorities (around 14%) of them are small cell lung cancers (SCLC). In the United States, 33,000 additional cases of SCLC are anticipated in 2021. The male to female incidence ratio is now 1:1, despite the fact that the incidence of SCLC has been declining and the rate is growing in women (Ganti et al., 2021).

The early stages of lung cancer sometimes show no signs or symptoms. Lung cancer symptoms and signs usually appear when the condition has progressed. A new persistent cough is an indications and symptoms of lung cancer. Even little bit of blood being coughed up, breathlessness, hoarseness, weight loss without attempting bone discomfort, headache etc are some symptoms.

There are two types of potential risk factors: direct and indirect. Smoking is the main cause of lung cancer, with a relative risk (RR) of 10 to 30compared to non-smokers (Bade, 2020). Moreover,79%of men and 90% of women who smoke develop lung cancer as a direct result of doing so. The relative risk for smokers is 22.4; for strong smokers (more than 25 packets per day), it can go as high as 50. Another danger factor is being among people who doesn't smoke (There is a dose-response association between the length and intensity of secondhand smoke exposure and the annual death toll of about 3,000 persons). Evidence also indicates that long-term smoking affects and delay how to seek medical attention. This may be partly a result of people blaming themselves, associating their symptoms with smoking, or fearing the stigma associated with smoking (Crane et al., 2016).

Lung cancers risk factors include particle and exposure to particular dangerous substances. Working with substances like- asbestos, uranium, arsenic, cadmium, chromium, nickel and some petroleum products are particularly risky. Both radiation therapy and other lung conditions like pulmonary fibrosis and COPD are at risk. Additionally, linked to higher lung cancer rates are pulmonary illness, idiopathic pulmonary fibrosis and tuberculosis. In specific circumstances, patients are at a significant risk of their cancer spreading to other organs. According to forecasts based on present trends, 10 million people would die from tobacco use yearly by 2030, with 70 percent of those fatalities occurring in developing countries (JHA, 2006).

The National Cancer Institute finds prognosis (probable outcome) and available treatments are influenced by a number of variables. There are other factors to consider, including the tumor's size, whether it has migrated outside of the lung or to other parts of the body, how it is categorized, and whether it has metastasized, whether the EGFR gene or the anaplastic lymphoma kinase gene- two examples of genes that can be altered and show mutations in the malignancy, whether there are any symptoms, including coughing or breathing difficulties and general health of the patient.

Lung cancer can be described by referencing its stage. Cancer stage can reveal a lot about the condition, such as the severity of the disease, the best course of treatment, including any available clinical trial alternatives, healing potential following treatment, chances of the cancer coming back (recurrence). For assessing the stage of cancer, specific tests like- a computed tomography (CT) scan or a biopsy needed. Not every cancer is staged using the same methodology. However, the method that is most frequently employed consists of these stages: In Stage 0, cancer cells stay in the same location they first appeared (in the top lining of bronchus). Cancer that has not developed or spread is referred to as cancer in situ. In Stage 1, no lymph nodes or adjacent tissues have been affected by the cancer that means cancer will not spread beyond lung. Stage 2: The cancer has spread to adjacent tissues and perhaps lymph nodes. Stage 3, cancer has spread to adjacent lymph nodes and has gotten deeper into local tissues, but it has not reached other sections of the body that are far away. Lastly Stage 4, cancer has spread to additional body organs or tissues. Another name for this is metastatic or advanced cancer. Depending on the cancer's histology, stage when it is first diagnosed and functional assessment of the patient, the course of treatment varies. In case of Stage 0, in patients the cancer is not progressive, photo dynamic therapy (PDT), laser therapy or brachy therapy (internal radiation) is used as an alternate of surgery. Patients with stage I through stage IIIA non-small cell carcinoma (NSCLC) should consider surgery as the preferred

course of therapy. Symptoms of cough have been reported more frequently in the earlier stages of lung cancer (stage I-III). Segmentectomy or wedge resection is also used in this stage. In individuals with non-small cell carcinoma (NSCLC) recent results indicate that preoperative chemotherapy increases survival. Individuals who are having complete resection before operative care typically received adjuvant chemotherapy. In patients with stage I non-small cell lung cancer (NSCLC) who are more likely to experience a recurrence due to the size, location, or other characteristics of the tumor, this procedure given after surgery lowers the likelihood of the cancer returning. lobectomy or sleeve resection is frequently used to remove tumors in stage II NSCLC patients who are healthy enough to undergo surgery.

Chemotherapy and radiotherapy may be used as a kind of treatment for stage III and non-resectable small cell carcinoma (Molina et al., 2008). For resectable carcinoma surgery, chemotherapy and radiotherapy is given as combination therapy. Target specific treatment particularly the antivascular endothelial growth factor drug bevacizumab (Avastin) and chemotherapy increased survival along with drugs like– osimertinib, crizotinib. Surgically unfit patients, frequently advised additional chemotherapy with radiation therapy. As stage IIIB non-small cell lung cancer are advanced into vital chest structures and has metastasised to lymph nodes in the neck or close to the other lung so it is quite complicated to eliminate tumours completely with surgery. The patient's overall health will determine how they respond to treatment for lung cancer at this stage as well as earlier stages. When NSCLC in stages IV is found, cancer has grown far. Treatment for tumors is challenging. Individuals treatment options are influenced by their general health, the location and extent of the disease's dissemination and whether or not the cancer cells have specific gene or protein abnormalities.

The five-year relative survival rate for lung cancer is 22.9% when lung cancer is discovered at any stage. According to the cancer progress in the body, here are the relative survival rates

during a five-year period: When it comes to cancer that only affects one lung which is called localized, 64% of cases were non-small cell lung cancer and 29% were small cell lung cancer (localized). For regional the survival rate is 33.5% when cancer has spread to the lymph nodes (NSCLC: 37%; SCLC: 18%). The percentage of tumors that have spread to other organs is 7% and in distant 26% for non-small cell lung cancer and 3% for small cell lung cancer (Yetman, 2022). However, in USA rates for localized-stage lung cancer climbed abruptly by 4.5% annually, helping to boost both the proportion of localized-stage diagnoses (from 17% in 2004 to 28% in 2018) and 3-year relative survival from 21% to 31% (Siegel et al., 2022).

Palliative care and hospice care are significant end-of-life treatment modalities. Patients may receive guidance in selecting the appropriate course of action from their primary care provider. It is extremely important where a high proportion of cancer patients are at an progressive stage with little chance of recovery(Collins et al., 2007).

Following their successful completion of clinical studies, these medications are introduced to the market with the assurance that they will help patients. Even though novel cancer treatments often perform well in clinical studies, patient variability makes them less effective in the real world. The requirement for validation of clinical trial efficacy endpoint methodologies, which are used to assess the efficacy of cancer medications, may be one cause of the aforementioned issue.

The field of clinical trial optimization and endpoint selection is a developing one. There are still significant problems with overall survival despite recent advances in diagnosis, categorization and therapy. Therefore, it is critical to determine the appropriate efficacy endpoint. The criteria used to assess whether a treatment is effective in a clinical study are called endpoints. As a result, it is essential to the study's overall design and must be precisely

defined to guarantee that the clinical trials findings are reliable and widely acknowledged by the medical field. Before the clinical trial begins, a primary efficacy endpoint must be chosen because it provides information on the most crucial issues (percentage of success, time to failure, OS, PFS, ORR etc).

Overall Response Rate (ORR)- ORR in a trial is the total percentage of patients that had responded to therapy. It is based on a decrease size of tumor. Response Evaluation Criteria in Solid Tumors (RECIST) is a tool used to measure objective response which considers both the full and partial effectiveness of treatment. The ability to quantify efficacy in single-arm studies and the capacity for researchers to ascribe the effect to the treatment and not to the patient's natural history are two benefits connected with employing objective response in clinical trials.

The idea has also been put forth that objective response, as opposed to OS, is a more fruitful goal for identifying predictive biomarkers. On the other hand, additional endpoints might be

required to confirm the clinical effect as objective response might not be able to capture the complete long-term advantages of treatment. An increase in ORR means the treatment is effective. Unlike PFS, ORR does not evaluate response time (Hashim, 2018).

Progression-free Survival (PFS)- In a trial, PFS is the time duration that has passed since receiving therapy before a patient's disease progressed or remained stable. It is indicated in month. Cancer clinical trials for individuals with solid tumors are increasingly using progression-free survival (PFS) as a significant and even a primary objective. Moreover, between 2009 and 2013, more than one-third of trials that get FDA marketing approval employed PFS as a primary endpoint, which is only theoretically viable if PFS approved as an OS substitute endpoint (Belin et al., 2020).

Practically this endpoint need shorter time to a given number of events compared to other endpoints and clinical factors, as well as PFS's growing popularity, are only a few of the many causes for this growth (PFS influence is less in subsequent therapy than OS and more relevant with targeted agents than response).Despite having many similarities, PFS and time to progression (TTP) are distinct goals in some ways. Death is not taken into account while evaluating TTP, despite PFS showing the period of time from randomization to the onset of disease or death. The FDA recommends PFS over TTP because it can more accurately represent OS. In situations of advanced-stage colorectal cancer, PFS has been proposed as an alternative metric rather than OS.

In a trial, overall survival or OS measures how long patients have lived after receiving the medication. It is a direct indicator of the clinical benefit received by a patient and is calculated as the interval between randomization and death from any cause. Patients who are alive or

unreachable are censored. With no compromise to quality of life (QoL), overall survival delivers the highest clinical benefit. OS is a simple endpoint to measure, one that is clear, objective and is thought to have clinical significance. It is also unaffected by the timing of assessment. The approval of new medications could be delayed because evaluating OS as an endpoint in clinical trials need a large patient population and prolonged follow-up.

Clinical trial sare research initiatives carried out to test human with the motive of evaluating medicinal, surgical, or behavioral intervention .They are the primary technique employed by researchers to ascertain the safety and effectiveness in humans of novel treatments such as new medications, diets, or medical devices (such as pacemakers).To determine whether a novel treatment is more effective and has less unfavorable side effects than the traditional treatment, clinical trials are regularly conducted.

In other studies, methods for early illness detection sometimes even without symptoms are being explored. Still some people experiment with methods of illness prevention. In some clinical trials, the goal is improving standards of patients life with chronic illnesses or life-threatening diseases. Clinical investigations are typically conducted over the course of 4 phases, each of which builds upon the previous one. Phases I, II and III are just a few examples of the various types. Phase II clinical trials conduct on a new medication if phase I clinical studies show it to be risk-free and to see whether it is efficient in treating particular types of cancer.

1.2 Aim:

The aims of the study is to find out the better efficacy endpoint in phase II trial while giving treatment (chemotherapy, targeted therapy, surgery etc) and predict which one is more effective. There are various justifications for selecting the phase II clinical study. As our ultimate focus is extending lifespan or quality of life in terms of cancer patients so the new drug approval process need to be faster. For choosing the right combination of drug relying on this phase is better. Phase II clinical studies frequently use as an alternative clinical or biochemical marker to give "interim" data concerning safety and efficacy, allowing for quicker drug approval subject to continued post-marketing safety and efficacy studies with the potential to benefit patients. Using a more effective surrogate endpoint will speed up the approval process, allowing us to achieve our core goal, which is to improve patient survival rates. In order to predictive variables (efficacy endpoint) from lung cancer clinical trial design and to construct predictive models of progression free survival and overall response rate for various lung cancer subtypes, it is necessary to develop models of overall survival. So, our goal is to find a relationship (correlation, linear relation etc) between the variables. If a relationship of any type exists, the model's prediction will be simple.

1.3 Objectives:

Our primary objectives are –

1. To find out linear relationship between efficacy endpoints in NSCLC.

2. To construct a simple predictive model based on the relationship.

3. To identify better surrogate efficacy endpoint (PFS or ORR) for survival in NSCLC.

Chapter 2

Methodology

2.1 Efficacy Endpoint

The total of the percentages of patients who had either a partial or complete response to the treatment is summed together under the term "overall response rate" (ORR). Typically, a partial response (PR) is defined as a predetermined reduction (usually less than 30%) in the targeted lesion, tumor volume or cancer cell number (PR). On the contrary, complete response means successful treatment in which patients tumor disappeared. Overall survival or OS is a measurement used to describe how long a patient survives after receiving treatment for their ailment. The progression-free survival (PFS) is the amount of time since starting treatment that has elapsed without the patient's disease advancing or remaining stable.

2.2 Data Source:

As it is a systematic search review, so the plan is to screen articles of Phase II NSCLC clinical trials and extract efficacy data. One of the most known free search engines PubMed was used which support information retrieval as well as search biomedical and biological science related publications with a view to enhancing both individual and global health. Here, from the first 200 articles, we found efficacy endpoint present in 124 articles.

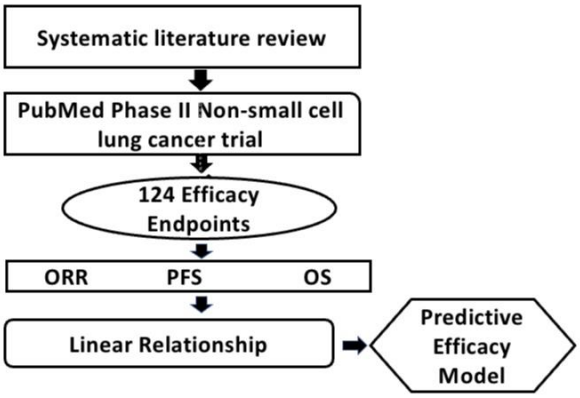

Figure 1: Study Plan

2.3 Inclusion and Exclusion Criteria:

The inclusion and exclusion criteria were being developed for simple extraction. If the efficacy objective was absent, the treatment size (number of drugs) was absent or it was a trial protocol, other than a Phase II trial (phase I / phase III) those articles were excluded. In phase II clinical trials of lung cancer or metastatic lung cancer testing cancer therapies with ORR or PFS efficacy endpoints, single-arm phase II clinical trials of lung cancer testing cancer therapies with ORR or PFS efficacy endpoints, randomised controlled (two-arm) phase II clinical trials of lung cancer trials combining phase I trial testing were eligible for inclusion. Therefore, the size of the treatment, efficacy endpoint (PFS, OS, ORR) subtypes, patient numbers, and lung

cancer trials combining phase I trial testing were eligible for inclusion. Therefore, the size of the treatment, efficacy endpoint (PFS, OS, ORR) subtypes, patient numbers, and lung cancer subtypes were the key areas of focus. Targeted therapy was included with chemotherapy, surgery, radiotherapy as treatment option. Moreover, PFS and OS unit was used in month. If it was given in days in the article we need to turn it into month. So, our main focus is to find out a relation (correlation, linear relation etc) between the variables and predict a model. Data extraction was followed by statistical analysis.

2.4 Statistical Analysis

A test of correlation between clinical endpoint variables such as ORR, PFS & OS was Spearman Rank-Correlation was used. To predict variables, simple linear regression was used with R least square method. Moreover, simple linear model was used to predict the endpoint variables to keep the predictive equation linear and simplistic and easy to interpret.

Chapter 3

Results

Our main focus is to compile efficacy results like progression-free survival, overall response rate and overall survival rate. We analyze124 indicated efficacy outcomes after extracting the information from 200 articles. Based on the data our main aim is reducing the number of deaths from non-small cell lung cancer while determining relationship between key objectives and the optimum efficacy endpoint in NSCLC. Overall survival will therefore be the primary outcome. The appendix contains data in detail.

Table no 1: Number of data collected

SL NO	Efficacy Endpoint	Number
1	ORR	94
2	PFS	97
3	OS	105

3.1 Relationship Between OS& ORR

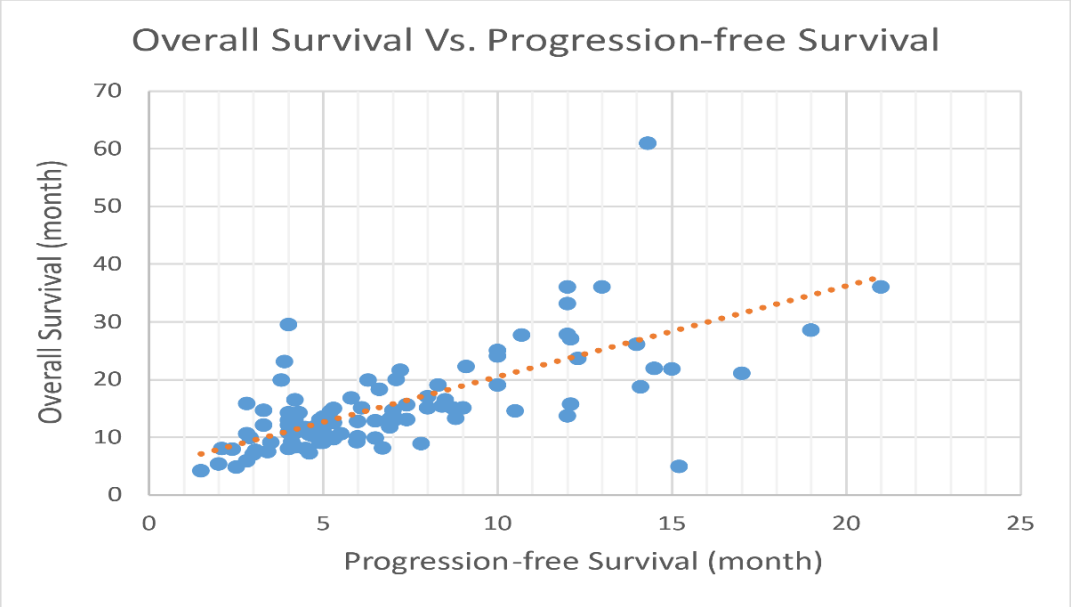

Figure 2a*: Scatterplot of OS and ORR of NSCLC. The x axis indicates response rate ((%) and y axis indicates overall survival (month). The dotted line represents regression line of OS when predicted by ORR.*

Here, we found moderate positive correlation coefficient between OS & ORR of lung cancer (NSCLC) where rs = 0.59 ($p < 0.0001$).

The above scatterplot graph demonstrates that all of the data points are in a pattern that is going higher from left to right with a positive correlation. It also means as one variable increases, so does the other variable.

According to the graph, it means OS increases when there is an increase in ORR. On the other hand, OS decreases whenever ORR decreases.

Then, we observe the predictive model and derived the predictive equation:

OS month = 0.24 (ORR) + 4.47

R- sq of the model is 38%. It indicates 38% of the variability in the OS can be explained by the regression line of ORR.

3.2 Relationship Between OS & PFS

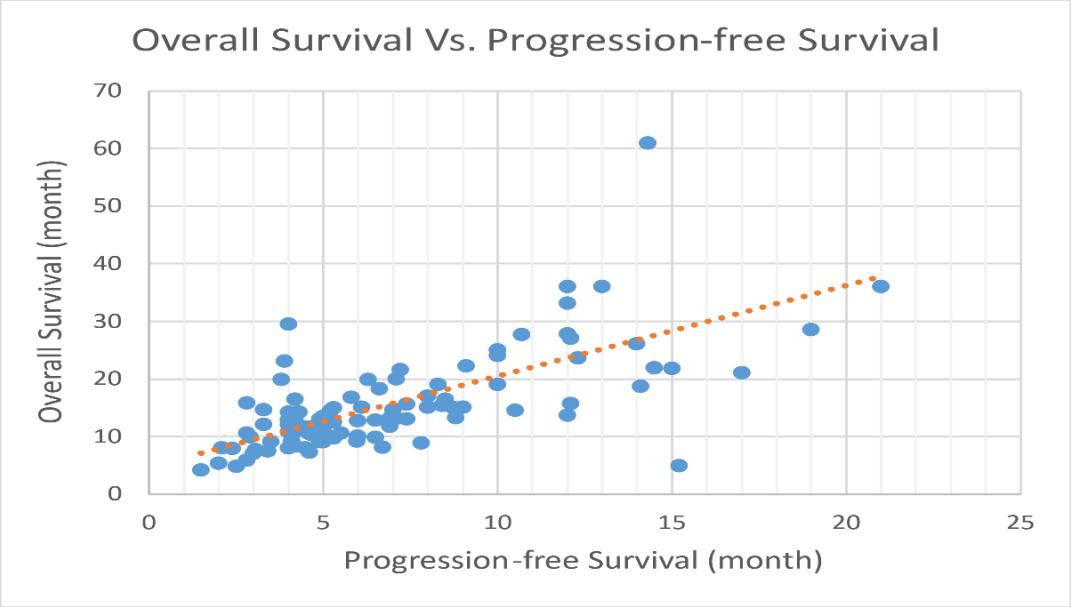

***Figure 2b**: Scatterplot of OS and PFS of NSCLC. The x axis indicates progression free survival (month) and y axis indicates overall survival (month). The dotted line represents regression line of OS when predicted by PFS.*

Here, we identified a moderately positive correlation coefficient between OS & PFS of lung cancer (NSCLC) where rs= 0.59 ($p < 0.0001$).

The above scatterplot graph demonstrates that all of the data points are in a pattern that is going higher from left to right with a positive correlation. It also means as one variable increases, so does the other variable. According to the graph, it means OS increases when there is an increase in PFS. On the other hand, OS decreases whenever PFS decreases.

Then, we observe the predictive model and derived the predictive equation:

OS month = 1.57 (PFS) + 4.72

R- squared of the model is 44%. It shows that the regression line of PFS can account for 44% of the variability in OS.

Chapter 4

Discussion

The expectation, as previously stated, is to observe the relationship between the effectiveness endpoints of overall response rate and progression-free survival with overall survival and to identify the model. The primary outcome in this case is overall survival.

The r value for figure 2a is 0.59, which is moderately positive. When the overall response rate rises and the p value is highly significant, it is expected that the overall survival rate would rise. The rise of overall response rate means total number of patients respond to the treatment increased and it happen when the tumour size reduced. There will undoubtedly be a positive impact on overall survival if the tumor size is lowered. Moreover, the tumour lesion means the drug which are used is effective. The linear model ($R^2 = 0.38$) showed 38% for ORR. According to the R-Squared value of 0.38, the independent variable's variation accounts for 38% of the variance in the dependent variable under study which means the regression line of ORR is able to account for 38% of the OS variability. We may anticipate that OS and ORR will have a positive linear connection based on the results. Predicting the strength of a positive relationship in our setting is challenging as it need more data and study to validate further results. The graph 3a shows that there is a somewhat positive correlation between OS and ORR, showing that the OS value rises as the ORR value rises, which is roughly in line with our expectation. According to an investigation, high ORR (such as statistically greater than ORR of 30%) is a suitable end point for single-arm trials intended to show the advance efficacy of a single-agent anticancer therapy but this relation is less pronounced for combination regimens (Oxnard et al., 2016).

Figure 2b to the right has a r value of 0.67, which is similarly moderately positive. It is believed that an increase will occur in progression-free survival, which indicates that the tumor size did not grow in that particular period of time and that the patient's health is stable and the p value is very significant, will lead to an increase in overall survival. 44% is what the linear model for PFS (R^2= 0.44) shows. According to the R-Squared value of 0.44, the independent variable's variation accounts for 44% of the variance in the dependent variable under study which means PFS regression line may account for 44% of the OS variability. We can anticipate a positive linear association between OS and PFS according to our findings. Predicting the strength of a positive relationship in our setting is challenging as it need more data and study to validate further results. As seen in graph 3b, there is a moderately positive correlation between OS and PFS, showing that the OS value rises as the PFS value rises, which is roughly in line with our expectation.

In support of our discussion patients with solid tumors may benefit from using the tumour response rate (RR) after immune checkpoint inhibitor-based therapy as a substitute for the progression-free survival (PFS) and overall survival (OS) endpoints where 24 trials were involved led to results that are fairly similar to ours where RR demonstrates weak associations R- squared value 32% and strong associations R-squared value 44% (Roviello et al., 2017). Additionally, in a different experiment PFS demonstrated the highest level of OS surrogacy in extensive stage small cell lung cancer (least squares R2= 0.79), accounting for 79% of the variation in OS while the RR rate is modest, tumor response endpoints exhibited lower level of surrogacy (least squares R2= 0.48) (Foster et al., 2011). Thus, it can be said the PFS has strong association than ORR.

According to several anatomic imaging modalities, ORR was largely evaluated by tumor size and total tumor load. Despite being widely accepted for almost 20 years, the WHO criteria lost favor due to variability between observers in the selection of quantitative endpoints and the number of lesions. Moreover, ORR overlooks patients with a stable condition and fails to distinguish between patients with a full response and those who have a limited response. To overcome these problems WHO replaced it with RECIST (Response Evaluation Criteria in Solid Tumors) which are anatomic response criteria created primarily for cytotoxic chemotherapy. The RECIST version 1.0 was offered as a new guideline to assess the response in 2000, and it was based on the emergence of new technologies including computed tomography (CT) and MRI, which resulted to some updated definitions for quantifiable lesions (Aykan & Ozatli, 2020).This was done to make the methodology standardized and simpler.

In addition, PFS is a desirable clinical endpoint due to its direct information on drug action and its quicker turnaround of data than OS. PFS has also drawn more interest as a clinical endpoint due to the capacity of evaluating treatment regimens which incorporate multi-stage therapy. The final findings indicate that between ORR and PFS, PFS has a stronger correlation with overall survival than response rate (correlation coefficient 0.67 vs 0.59). Therefore, PFS is the most accurate endpoint for predicting overall survival (R^2= 0.44 vs 0.39).

Chapter5Conclusion

In summary, the focus of patient-centered cancer care is extending lifetime or quality of life in terms of health (HRQoL). Our analysis has evaluated the observation that PFS is better efficacy endpoint than ORR. Moreover, PFS is also the most widely used outcome for evaluating novel cancer treatments and continuous quality improvement. Though it is not entirely apparent whether a delay in the advancement of the disease improves life quality with or without a benefit to overall survival. It is because PFS among patients are different globally, physically and emotionally. The ultimate PFS results come in less time than ORR and PFS is also cost effective. So the assessment of new drugs overall survival come rapid and the lifesaving drug can launch faster in the market after clinical trial. Contrarily, patient ORR were determined by tumor size and total tumor load but this method has some drawbacks, including the inability to measure benefits directly and the requirement for detailed drug activity analysis. However, it also fails to differentiate between patients with a complete response and those with a partial response. As PFS shows high positive correlation so it can be considered a modest surrogacy for OS, with better performance in first-line therapy trial along with different trial settings (for example- line of therapy, phase of trial, masking and therapy type). Additionally, patient-level analyses are desperately needed to offer more convincing proof of the surrogate endpoints. Therefore, in terms of predicting true OS, PFS is the better efficacy endpoint than ORR.

Limitations:

A satisfactory outcome is possible, if we can gather in a larger data set and used different search engines. There are many recognized search engines are available like- scopus, embase, clinical net etc. Due to the small amount of data (100 included) and the difficulty and effort involved in finding the same article using different search engines, only one search engine is used which is our limitation. Extraction of 100 included efficacy endpoints is the final target. Another one is with NSCLC subtypes. NSCLC subtypes were initially added to make the study more correct and appropriate but later discontinued and excluded them. This is because there was a lot of variation in the ratio of the different subtypes. As an illustration, 124 included articles yield 90 adenocarcinomas, 25 squamous cells, and 9 large cells. So the fluctuation of NSCLC subtypes along with small amounts of data will not give a significant result and make it more complex. For these reasons NSCLC subtypes were excluded.

Future recommendation:

We intend to continue this investigation using a larger data set, around 1,000 papers, because NSCLC cancer types are the most common and the death rate is quite high so the outcome can make an impact on medical and pharmaceutical sectors and the larger data set will definitely give more accurate and reliable results.

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Appendix

PMID	Stage	Subtype	Previously treated?	ORR	PFS	Overall Survival	Treatment Size	Targeted Therapy	T1	T2	T3	T4
31182249	advanced	Adenocarcinoma	0	39	7.4	15.6	1	1	Nivoluma b			
33221195	excluded	no endpoint	abstract									
34161146	excluded	HERBAL	full text									
34247580	excluded		full text									
34423518	advanced	Adenocarcinoma	0	30	5.8	16.7	1	1	anlotinib			
32564128	excluded		full text									
31990759	excluded	Adenocarcinoma	full text									
33023530	excluded	no endpoint	trial on process									
34016488												
30026059	advanced	Squamous cell	1	13.2	3.06	7.69	1	1	Apatinib			
31870132	advanced	non small	1	9.2		3	1	1	Anlotinib			
30789	exclud	no	full text									

648	ed	endpoint										
17311690	advanced	adenocarcinoma	0	77	21	36	4	0	cisplatin	gemcitabine	vinorelbine	surgery
30121602	excluded	no endpoint	full text									
8007470	excluded		no result									
25986641	excluded	abstract										
33278671	excluded	no endpoint	full text									
31445956	excluded	no endpoint	full text									
29097074	excluded	no endpoint	result									
31804689	advanced	Adenocarcinoma	0	70%	8.4	15.4	2	0	vinorelbine	Carboplatin		
32340810	advanced		0	54.5	33.5		2	1	Gefitinib	surgery		
PMID	Stage	Subtype	Previously treated?	ORR	PFS	Overall Survival	Treatment Size	Targeted Therapy	T1	T2	T3	T4
31182249	advanced	Adenocarcinoma	0	39	7.4	15.6	1	1	Nivoluma b			
33221195	excluded	no endpoint	abstract									
34161146	excluded	HERBAL	full text									
34247	exclud		full text									

580	ed											
34423518	advanced	Adenocarcinoma	0	30	5.8	16.7	1	1	anlotinib			
32564128	excluded		full text									
31990759	excluded	Adenocarcinoma	full text									
33023530	excluded	no endpoint	trial on process									
34016488												
30026059	advanced	Squamous cell	1	13.2	3.06	7.69	1	1	Apatinib			
31870132	advanced	non small	1	9.2		3	1	1	Anlotinib			
30789648	excluded	no endpoint	full text									
17311690	advanced	adenocarcinoma	0	77	21	36	4	0	cisplatin	gemcitabine	vinorelbine	surgery
30121602	excluded	no endpoint	full text									
8007470	excluded		no result									
25986641	excluded	abstract										
33278671	excluded	no endpoint	full text									
31445	exclud	no	full text									

956	ed	endpoint										
29097074	excluded	no endpoint	result									
31804689	advanced	Adenocarcinoma	0	70%	8.4	15.4	2	0	vinorelbine	Carboplatin		
32340810	advanced		0	54.5	33.5		2	1	Gefitinib	surgery		
30327236	excluded	no endpoint	abstract									
24125485	excluded	no endpoint	full text									
31894704	excluded	no result										
30143031	excluded	no endpoint	full text									
19501491	Excluded	no endpoint	Full text									
23599349	advanced	Adenocarcinoma	1	53.8	9.3		1	1	erlotinib			
27803005	advanced		1	18	4.5	11.6	1	1	Vandetanib			
35972704	excluded			52	5	17.1						
21252718	excluded	no endpoint	full text									
30826861	excluded	no endpo	full text									

		int										
31706099	excluded	no result			8.3	26						
28936567	advanced	Adenocarcinoma	0	11.7	3.9	23	1	0	Metformin			
19297279	multiple endpoint											
30611673	excluded	no endpoint	no result									
19443338	excluded	no endpoint	full text									
30993397	advanced	Adenocarcinoma	1	22.7	3.4	7.4	1	0	nab-ptx			
28427456	excluded	no endpoint	no result									
19884551	excluded	no endpoint	full text									
28625642	excluded	no endpoint	full text									
17548127	advanced	Adenocarcinoma	1	36.7	5.3	9.9	2	0	carboplatin	paclitaxel		
36076179	excluded	no endpoint	no result									
15726523	excluded	no endpo	no result									

		int										
20153912	advanced	Adenocarcinoma	0	27	4.2	12.9	1	0	gemcitabine plus			
10362328	excluded	no endpoint	no result									
22085375	excluded	no endpoint	full text									
34607698	excluded	no endpoint	no abstract									
9231930	excluded	no result										
11325486	excluded	no endpoint	no result									
10362328	excluded	no endpoint	no result									
32111801	limited		0	86	14.3	60.9	3	1	cisplatin	Etoposide	Amrubicin	
18978563	advanced	Adenocarcinoma	0		10	25	2	0	carboplatin	paclitaxel		
21353720	excluded	no endpoint	no result									
22492982	excluded	no endpoint	abstract									
7551936	advanced	Squamous cell	0	82		24.5	2	0	surgery	chemothera		

										py		
18342982	advanced	Adenocarcinoma	0		2.8	10.6	2	0	docetaxel	gemcitabine		
16902837	advanced	Adenocarcinoma	0	37.5	4	12.9	2	0	docetaxel	Carboplatin		
29191594				30.3								
20708849	excluded	no endpoint	abstract									
19622464	advanced	Adenocarcinoma	0	50	2.4	7.9	2	0	docetaxel	Oxaliplatin		
16434259	excluded	no endpoint	full text									
25130084	advanced	Squamous cell	0		3.8	19.8	2	0	HLA-A2(+)	hTERT cryptic peptide		
19832041	advanced	Adenocarcinoma	0		4	10.8	3	2	Thalidomide	Irinotecan	Gemcitabine	
12399132	advanced	Adenocarcinoma	0			11	2	0	surgery	chemotherapy		
17532073	excluded	no endpoint	no result									
25201721	excluded	no endpoint	abstract									

9683302	no article											
17909356	early		1		2.1	8	2	1	Docetaxel	Exisulind		
21277039		small cell	1	36	3	7	2	1	amrubicin	carboplatin		
25456362	advanced	small cell	0		4	29·5	1	1	Dacomitinib			
28065465	excluded	no endpoint	full text									
22306126	advanced	Adenocarcinoma	1	22.2	4.3	14.2	2	0	carboplatin	gemcitabine		
17409983	excluded	no endpoint	abstract									
15726523	excluded	no endpoint	full text									
23891283	advanced	Adenocarcinoma	0		7	13.8	2	0	pemetrexed	Tumor Treating Fields		
17328989	excluded	no endpoint	full text									
21334093			0	74	5.3	14.9	2	2	amrubicin	topotecan		
21334093				43	4.7	10.2			relapsed			

19910140	excluded	no endpoint	full text									
11165405	advanced	Adenocarcinoma	0	76.7	10.5	14.5	3	0	paclitaxel	carboplatin	radiation therapy	
25110336	excluded	no endpoint	full text									
31532584	excluded	no endpoint	no result									
22283472	advanced	Adenocarcinoma	0	29	4	14.2	2	2	irinotecan	amrubicin		
23643176									up arm	np arm		
22795583	excluded	no endpoint	result									
19603031	advanced	Adenocarcinoma	0		12	33.1	3	0	cisplatin	S-1	concurrent radiotherapy	
19287371	excluded	no endpoint	abstract									
27565912	advanced	Adenocarcinoma	1	31.7	4.9	13	1	0	nab-paclitaxel			
15310415	excluded	no endpoint	abstract									
23857398	excluded	no endpo	result									

		int										
18235125	excluded	no endpoint	full text									
18023915	advanced	Adenocarcinoma	1	39.3	5.5	10.5	2	0	gemcitabine	cisplatin		
9054882	excluded	no endpoint	result									
15694017	advanced	Adenocarcinoma	0		2.5	4.8	1	0	gemcitabine			
32548619	excluded	no endpoint	abstract									
22237116	advanced	chinese	0		6.1	15	1	0	gemcitabine			
17363535	excluded	no endpoint	result									
17488518	excluded	no endpoint	result									
16909132	excluded	no endpoint	abstract									
36064386	advanced	Adenocarcinoma	0	36.7	5	13.4	2	0	Sintilimab	docetaxel		
17658655	advanced	Squamous cell	0	76	8	15	2	0	paclitaxel	carboplatin		
31116855	excluded	no endpoint	full text									

31706099	excluded	no endpoint	full text									
17173694	advanced	Adenocarcinoma	1	24.2	6.5	9.8	1	0	gefitinib			
17379439	excluded	no endpoint	result									
17409982	advanced	no full text		30	4.8	11.8						
19179899	excluded	no endpoint	result									
25951232	excluded	no endpoint	abstract									
16670714	advanced	Adenocarcinoma	1	26.5		26.5	1	0	gefitinib			
18798231	excluded	no endpoint	result									
17869017	excluded	no endpoint	full text									
27387964	excluded	no endpoint	no abstract									
23647738	excluded	no endpoint	abstract									
20728237	excluded	no endpoint	result									
25043642	advanced	Adenocarcin	1		8.5	16.4	3	0	Docetax	cisplatin	surgery	

		oma							el			
9007124	excluded	no endpoint	abstract									
7860394	excluded	no endpoint	abstract									
25202107	advanced	Adenocarcinoma	1		7.2	21.6	2	1	Docetaxel	Bevacizumab		
27764781	advanced	Adenocarcinoma	0		5	11	1	0	gefitinib			
12871785	excluded	no endpoint	result									
17409981	advanced	Adenocarcinoma	0		6.9	11.7	2	1	irinotecan	carboplatin		
28103970	excluded	no endpoint	result									
11181999	excluded	no endpoint	abstract									
8198982	excluded	no endpoint	full text									
18160123	advanced	Adenocarcinoma	0		6	10	2	0	vinorelbine	cisplatin		
28668866	advanced	Adenocarcinoma		46		12.6						
24692732	advanced	Squamous	0	77.3	12	27.8	2	0	cisplatin	vinorelbi		

		cell								ne		
17762435	advanced	Adenocarcinoma	0	45.6		12	2	1	paclitaxel	irinotecan		
24141372	advanced	non-squamous	1	8.7	5.2	14.4	1	0	pemetrexed			
19692142	excluded	no endpoint	full text									
9331137	excluded	no endpoint	abstract									
10638975	advanced	Squamous cell	0		14.1	18.7	2	0	cisplatin	5-fluorouracil		
16549997	advanced		1	13.2		7.5	1	0	gefitinib			
16549997	advanced		1	13.7		7.1	1	0	Docetaxel			
22333554	excluded	no endpoint	full text									
27162148	excluded	no result										
9488124												
10761761	excluded	no endpoint	no full text									
16622435	excluded	no endpoint	full text									
14690568	excluded	no endpo	no full text									

		int										
21613934	excluded	no endpoint	full text									
21680048	advanced	Adenocarcinoma	0	27.4		10.4	1	1	sunitinib			
14739040	advanced	Squamous cell	0	91	12.1	27	2	0	Docetaxel	carboplatin		
8385565												
26946985	excluded	not phase 2 trial										
19556022	excluded	no endpoint	full text									
26148750		Adenocarcinoma		80	7	14.6	1	1	icotinib			
10697041	advanced	no full text			14	26	3	0	vinorelbine	ifosfamide	cisplatin	
9781595	excluded	no endpoint	no full text									
24888230	excluded	no endpoint	full text									
31917421	excluded	no endpoint	abstract									
7704495	excluded	no endpoint	abstract									
12928	advan	non-s	1	64	12.3	23.6	2	0	pacli	cispl		

126	ced	quamous							taxel	atin		
17599645	excluded	no endpoint	abstract									
18505060	excluded	no endpoint	result									
19683359	advanced		0		4.6	10.4	1	1	belotecan			
10894864	excluded	no endpoint	result									
26044164	excluded	no endpoint	result									
1327019	excluded	no endpoint	abstract									
19647333	advanced	Squamous cell	0	46.5	6.9	13.1	2	0	Docetaxel	carboplatin		
21744082	excluded	no endpoint	result									
19117690	excluded	no endpoint	result									
12057870	excluded	no endpoint	result									
16483687	advanced		0	45		14	2	0	paclitaxel	carboplatin		
17311688	excluded	no endpoint	result									

10761756	excluded	no endpoint	result									
13325 78	excluded	no endpoint	result									
29858022	advanced				15	21.8	2	0	cisplatin	vinorelbine		
24852396	no article	no author										
12644982	excluded	no author	abstract									
80700 14	excluded	no endpoint	abstract									
29258674	excluded	no endpoint	result									
16334161				43	9.25	13.75	2	0	cisplatin	paclitaxel		
16785471	advanced	Adenocarcinoma	0	75	9.7		1	0	gefitinib			
23992877	advanced	Adenocarcinoma	0		4.6		2	2	erlotinib	bevacizumab		
20940720	advanced	Adenocarcinoma	0	94.3	13	36	2	1	nedaplatin	irinotecan		
16039010	excluded	no endpoint	result									
19796840	excluded	no endpoint	result									

11390009	advanced	Squamous cell	1		8	12	2	0	Docetaxel	carboplatin		
17695466	excluded	no endpoint	result									
7763025	excluded	no endpoint	abstract									
17409913	excluded	no endpoint	result									
17767977	advanced		0	74.3	7.7	12.2	2	1	irinotecan	carboplatin		
10687149	excluded	no endpoint	abstract									
10512130	advanced	Squamous cell	1	84			1	0	paclitaxel			
34378299	advanced	Adenocarcinoma	1	63.6	17.8	27.8	1	1	erlotinib			
22843939	advanced	Adenocarcinoma	0	45			2	1	cisplatin	irinotecan		
19631403	advanced	Adenocarcinoma	1	31	4.5	16	1	0	carboplatin			
29755102	excluded	no endpoint	abstract									
16736888	excluded	no endpoint	abstract									
	advan	Adeno	0		7.9	16.5	3	1	carb	Doc		

20225327	ced	carcinoma							oplatin	etaxel		
11282433	advanced	Adenocarcinoma	1	23		8.7	1	0	paclitaxel			
7551939	excluded	no endpoint	abstract									
19628292	excluded	no endpoint	result									
15588877	advanced	Squamous cell	0	65		16	2	0	cisplatinum	Vinorelbine		
24679653	advanced		1	78			1	1	Cefepime			
20589760	excluded	no endpoint	phase 1									
16170175	excluded	no endpoint	result									
10760429	advanced		0	65		10	2	0	carboplatin	radiotherapy		