Impact of Treatment Size and Therapy Type in Phase II Clinical Trials of Non-Small Cell Lung Cancer

By

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Bachelor of Pharmacy (Hons.)

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Declaration

Hereby it is proclaimed that

1. The project provided is my own genuine work completed while pursuing a degree at Brac University.
2. No formerly published or written by a third party content is present in the thesis., with the exception of where this is properly cited with complete and precise referencing
3. The thesis contains no material that has been approved or submitted for any other degree or certificate at a university or other institution.
4. All significant sources of support have been acknowledged.

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Approval

The thesis titled "Impact of Treatment Size and Therapy Type in Phase II Clinical Trials of Non-Small Cell Lung Cancer" submitted by Tasnim Rahman (18346019), 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

There are no human or animal trials included in this project.

Abstract

In spite of recent developments in cancer therapy that are specifically targeted, a frightening number of individuals still pass away every year from lung cancer around the world. Because of this, we decided to focus our research on non-small cell lung cancer. As a consequence of the high degree of heterogeneity that characterizes lung carcinoma, the unsatisfied clinical need is the determination of a suitable combination of medications. The requirement for the validation of efficacy endpoint methods in clinical trials, which are methods by which the effectiveness of cancer medicines is determined, is one possible cause of the problem that was described above. We intend to help investigators design clinical trials by establishing two predictive efficacy models, and we plan to optimize the combination treatment for certain lung malignancies by examining a substantial amount of clinical trial efficacy data. This will allow us to do both.

Keywords: Efficacy endpoint, Clinical trial, Treatment size.

Dedication

Dedicated to my parents

Acknowledgement

I would like to start by giving thanks to the Almighty, who is our inventor and the origin of all life, power, insight, grace, and kindness. All glory to the Almighty who has given me the endurance as well as courage to complete this project. This project would not have been accomplished without the assistance of the individuals who are acknowledged here.

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List of Acronyms:

1. PFS - Progression Free Survival

2. OS- Overall Survival

3. ORR- Overall Response Rate

4. SCLC- Small cell lung cancer

5.NSCLC- Non-small cell lung cancer

6.PR- Partial response

Chapter 1

Introduction

Cancer which is a morbidity where some of the body's cells grow uncontrollably and go beyond the usual boundaries to invade adjoining parts of the body and or spread to other organs. It can start in almost any organ or tissue of the body as it is a extensive group of diseases. Generally, in cell division human cells grow and redouble and form new cells as the body needs them. Cells die when they grow old or become damaged then new cells replace them. In cancer, this methodical process is disrupted, and unusual or damaged cells grow and redouble when they should not. Unlike normal cells, cancer cells ignore signals to stop dividing, or to die and be shed. Unable to discern its own natural border as it grows uncontrollably. Globally cancer is the second leading cause of death. About 9.6 million deaths or one in six deaths recorded four years back. Less than 7% of people with lung cancer in all stages survive 10 years after diagnosis, making it the most prevalent cause of cancer-related death globally.

There are multiple types of cancer lung, stomach, prostate, breast, cervical, colorectal, thyroid, and liver cancer. Among them lung, prostate, colorectal, stomach, and liver cancer are the most common types of cancer in men, and breast, colorectal, lung, cervical, and thyroid cancer are the most common in women. Above all cancers, lung cancer is the leading cause of death. .Lung cancer is a type of cancer that evidence in the lungs cell lining. The lung cancer also spread in the bronchi and parts of the lung such as the bronchioles or alveoli. Lung cancer has been divided in two main forms. The first one is non-small cell lung cancer (NSCLC) and the second one is small cell lung cancer (SCLC). The three main subtypes of NSCLC are: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. About 80% to 85% of cases of lung cancers are NSCLC. The main focus in 1983 was small-cell lung cancer (SCLC), with expectations that it would develop into a condition that was largely treatable. In the first year, there were eight publications on lung cancer published, five of which dealt with SCLC and three with NSCLC. In 2011, 40 original articles and editorials were published, but only seven of them discussed SCLC (Schiller et al., 2013).

Lung cancer is most often caused by smoking cigarettes. Lung cancer can also be caused by using other kinds of tobacco, like pipes or cigars which more than 7000 harmful chemicals in tobacco smoke and also breathing in secondhand smoke, being exposed to asbestos or radon at home or at work, or inheriting a family history of lung cancer. Since 76% of people who develop lung cancer smoke, it seems sense that tobacco-related malignancies account for 27.1% of all cancer case (Marolia et al., 2022). In western countries, non-small-cell lung cancer (NSCLC) currently accounts for more than 85% of lung cancer cases, with 20–30% of these cases occurring in people who have never smoked (Forde & Ettinger, 2013).

The most typical signs of lung cancer are loss of appetite, unexplained weight loss, shortness of breath and feeling tired or weak. Surgery, chemotherapy, targeted therapy, radiation therapy, or a combination of these therapies may be used to treat NSCLC patients. But for SCLC patients the most used therapy is Chemotherapy and radiation therapy.

Approximately 1 in 10 persons with the disorder live at least 10 years following their diagnosis, while roughly 2 out of 5 people with the syndrome survive at least a year. Men have an 18% 5-year survival rate. Women have a 25% 5-year survival rate. NSCLC has a 26% 5-year survival rate compared to a 7% 5-year survival rate for small cell lung cancer. At each step, there are several size and spread configurations that can be classified as falling to that subcategory. For instance, the primary tumor in a cancer that is in stage III may be smaller than the original tumor in a cancer that is in stage II yet, due to other causes, the disease is at a more advanced stage. The following is a standard staging system for lung cancer. Stage 0 (in-situ) Cancer is found in the top lining of the bronchus or the lungs at this stage, which is referred to as stage 0 (in-situ). There has been no evidence that it has spread to other areas of the lung or anywhere else outside of the lung. Despite resection, more than 50% of patients with so-called early stage or surgical disease non small-cell lung cancer will pass away from their condition (Vallières, 2003).

Stage I is the first stage, cancer has not gone beyond the lung. Stage II cancer has progressed to stage II if it has grown significantly since stage I, if it has spread to lymph nodes inside the lung, or if there are numerous tumors in the same lobe of the lung. Stage III cancer has progressed to stage III when it has reached an advanced stage since stage II, it has spread to lymph nodes or structures in the area, or there are many tumors in separate lobes of the same lung. Stage IV

cancer has traveled to distant organs or the other lung, the fluid that surrounds the lung, or both. Stage IV cancer has also spread to the fluid that surrounds the heart. NSCLC treatment choices are determined primarily by the stage of the disease. There are also other aspects like person's general health and how lung is functioning. If a smoker undergoes for treatment, first requirement is to quit smoking. Smoking cigarettes is by far the biggest risk factor for lung cancer; in the US, smoking causes 82% of lung cancer fatalities. In accordance with a number of studies, those who give up smoking after being diagnosed they have lung cancer have a significantly improved survival compared to those who do not. Small cell lung cancer (SCLC) spreads more aggressively and is more difficult to cure than non-small cell lung cancer (NSCLC). Specific kinds of SCLC include small cell carcinoma which sometimes termed as cell carcinoma and combination small cell carcinoma.

Treatments such as photo dynamic therapy, internal radiation or laser therapy may be substitute to surgery for some types of cancer that have not yet progressed to stage 0. These therapies ought to cure the patient if cancer is actually at stage 0 at this point. There is no requirement for chemotherapy or radiation therapy. If the diagnosed person is in good enough condition to undergo surgical intervention, they will most likely be a candidate for treatment by segmentectomy or wedge resection which is removal of part of the lobe of the lung. The stage I NSCLC patient’s treatment option are surgery and segmentectomy or wedge resection. Adjuvant chemotherapy administered after surgery may reduce the likelihood of the cancer coming back in patients who have stage I NSCLC with a greater risk of recurrence due to the tumour’s size, location, or other variables. People who have stage II NSCLC and are healthy enough for surgery. The reason behind it is they usually have the cancer removed by lobectomy or sleeve resection. The initial treatment for stage IIIA non-small cell lung cancer may consist of radiation therapy, chemotherapy (chemo), or surgery, or a combination of these three. Because of this, the process of planning therapy for stage IIIA NSCLC typically needs the participation of a thoracic surgeon, a medical oncologist, and a radiation oncologist. The options for therapy are contingent on the size of the tumor, its location inside the lung, the lymph nodes to which it has progressed, the general state of health, and how well patients are able to tolerate treatment. Radiation treatment, which may be paired with chemotherapy in some cases, is frequently recommended for patients whose health does not permit them to undergo surgery.

Chemotherapy are chemical drugs that have been shown to be effective in treating or curing cancer. These drugs interfere with fundamental cellular replication processes in rapidly dividing cancer cells. In addition to hormone therapy and cytotoxic chemotherapy, targeted therapy, also known as molecularly targeted therapy, is a prominent modality in the medical treatment of cancer. Targeted therapy focuses at delivering medications to particular genes or proteins that are specific to cancer cells or the tissue milieu that promotes cancer growth. Targeted therapeutic release at the location of disease while limiting off-target side effects caused to normal tissues is key to the therapy's efficacy. It is commonly used with other anti-cancer therapies. Monoclonal antibodies, orally administered medicines are used in targeted therapy. Surgery does not have the capability of removing these tumors in their entirety. Treatment for this stage of lung cancer, including treatment for earlier stages, is contingent on the general health of the patient. When diagnosed, NSCLC in stages IVA or IVB has already spread. These tumors are notoriously difficult to treat. The general health, the location and extent of the disease's spread, and whether or not the cancer cells have particular gene or protein alterations all play a role in determining the treatment options available to individuals. Clinical trials are studies that are conducted to evaluate new medications, medications that have previously been licensed, medical technologies, or other types of treatment which show us what techniques to medicine and health care are successful, as well as those that are not. They offer the most effective method for discovering whether treatments are useful for cancer and other serious diseases. The majority of the time, clinical studies are carried out in phases that build upon one another. There are different type of phases like phase I, phase II, phase III. If phase I clinical trials passes the newly discovered drug, then a phase II clinical trial will be carried out. This conversion is needed to know if the drug is effective treating certain forms of cancer. The advantage that the physicians seek for in a therapy is dependant upon the treatment's intended purpose. It is possible that it means the cancer is getting better or perhaps going away. It is also possible that it means the cancer will not grow any larger for a considerable amount of time, or that it will be a while before it reappears. According to the findings of certain research, the advantage may be an improvement for overall quality of life. Because a greater number of patients participate in phase II studies, it is possible that fewer frequent adverse effects may be observed. If a sufficient number of patients experience a beneficial outcome from the medication and the adverse effects are manageable, phase III clinical trials will be initiated.

The International Agency for Research on Cancer's publication GLOBOCAN 2012 provided the incidence and death rates for 2012. Using a variety of techniques depending on the precision and availability of data, GLOBOCAN calculates the incidence and mortality rates of cancer in every nation on earth. From 1% in Africa, 6% in Asia, and 8% in Latin America to 42% in Europe, 78% in Oceania, and 95% in North America, population-based cancer registries are covered. About one-third of the world's population has access to mortality data, which are often of higher quality in high-income nations.

Overall survival (OS) also termed survival rate is the proportion of participants in a research who are still living after a specified period of time following the point at which they received a diagnosis of a disease or began treatment for it, such as cancer. It is common practice to express the overall survival rate in terms of a five year survival rate. Survival rates overall provide the greatest potential for clinical benefit, presuming that quality of life is not adversely affected. To increase the survival rate there are some points we need to detect, for an example efficacy endpoint. A endpoint in a clinical trial is an outcome that may be monitored objectively in clinical trials to establish whether or not the intervention being examined is useful. In clinical trials, the endpoints are almost often included into the overall research objectives. Efficacy endpoint is a clinical trial outcome that serves as the basis for determining whether or not the medicines being tested are successful. A correctly chosen endpoint can assure no bias. Prior to the beginning of the clinical study, a primary efficacy endpoint needs to be determined by clinical trials. The term "progression-free survival," or PFS, refers to the amount of time that a patient lives with an illness, such as cancer, but the condition does not become worse while they are being treated for it or after therapy has ended. PFS, or progression-free survival, is a term that is commonly used in oncology to refer to scenarios in which a tumor is present. This can be confirmed by laboratory testing, radio logic testing, or clinically. In a similar manner, the term "disease-free survival" refers to the amount of time that has passed after patients have been treated and there is no sign of disease. It is preferable to have a proportion of 90% rather than 30%. It is indicative of a prolonged period of stability when the progression-free survival duration is greater. Even if there is no evidence of further disease development, this does not indicate that the cancer has been cured or that it is no longer causing symptoms. It signifies that it is not moving farther. As the result will be a statistical it does not in any way guarantee anything about what will occur in the future because survival statistics are only able to indicate

whether a therapy is more or less successful than other therapies on average. They cannot be used to anticipate whether or not an individual patient will survive. Overall response rate is often known as ORR which refers to the percentage of patients who participated in a study and had their tumors eliminated or considerably lessened as a result of treatment. ORR is generally defined as the addition of complete responses which are patients with no noticeable evidence of a tumor over a specific time period. Patients with a complete response still had no distinguishable evidence of a tumor. Patients with a partial response have a drop-off in tumor size over a nominative time period. An increase in ORR provides objective evidence that the medication is effective.

Objective of the Study

One potential root cause of the issue mentioned above is the demand for the validation of efficacy endpoint methods in clinical trials, which are methods by which the efficacy of cancer therapies is established. By developing two predictive efficacy models and a thorough analysis of the efficacy data from clinical trials, we want to assist researchers in the design of clinical trials and improve the combination therapy for some lung cancers. Our objective is to determine the type and dosage of non-small cell lung cancer treatment that has the highest probability of curing the disease with the fewest side effects possible.

Chapter 2

Methodology

2.1 Efficacy Endpoint

The endpoints are the findings that were measured either throughout the duration of the research or at the ending of the study in order to determine whether or not the given drug was successful and whether or not it was effective. The term "overall response rate" is for the sum of the percentages of tolerant who experienced either a partial or complete response as a result of the treatment. A specified decrease (generally less than 30 percent) in the targeted lesion, tumor volume or cancer cell number is typically considered to be a partial response (PR). Overall survival, or OS, measures how long a patient continues to live after receiving therapy for their condition. The progression-free survival (PFS) rate measures how long a patient is able to remain disease-free after receiving treatment, this indicates that the patient is maintaining a stable condition and that their condition is not deteriorating. Nevertheless, the PFS and OS are indices of effectiveness that stand in for the OS.

2.2 Data Source

The aim of this project to collect, systematically screen, and then extract efficacy endpoint which are PFS, ORR and OS from the first 200 Phase II NSCLC clinical trial articles. Since the amount of data that we are extracting is such a relatively minimal quantity, we searched one database along with some keyword like lung cancer phase II clinical trial along with efficacy endpoint, which is PubMed using corresponding PMID within the subset of data. Using numerous sites would be complicated and time-consuming due to the minimal quantity of data that we are working with.

2.3 Inclusion and Exclusion Criteria

As this is a systematic review of the published papers, there appears to be criteria for both the inclusion and exclusion of certain articles. The criteria for inclusion include clinical trials of phase II with efficacy endpoints (PFS, ORR, and OS). If the two endpoint which is PFS and ORR are found then article is considered as inclusion. When the PFS values were found to be in days or weeks in the articles, they were converted to months so that they could be used. In

addition, the treatment size and total number of drugs were compiled from the articles that were considered as included.

Whereas the criteria for exclusion include clinical trials of phase I and phase III and also did not have efficacy objectives.

2.4 Study Plan

Following the extraction, we are left with 124 data that meet the inclusion requirements within the first 200.

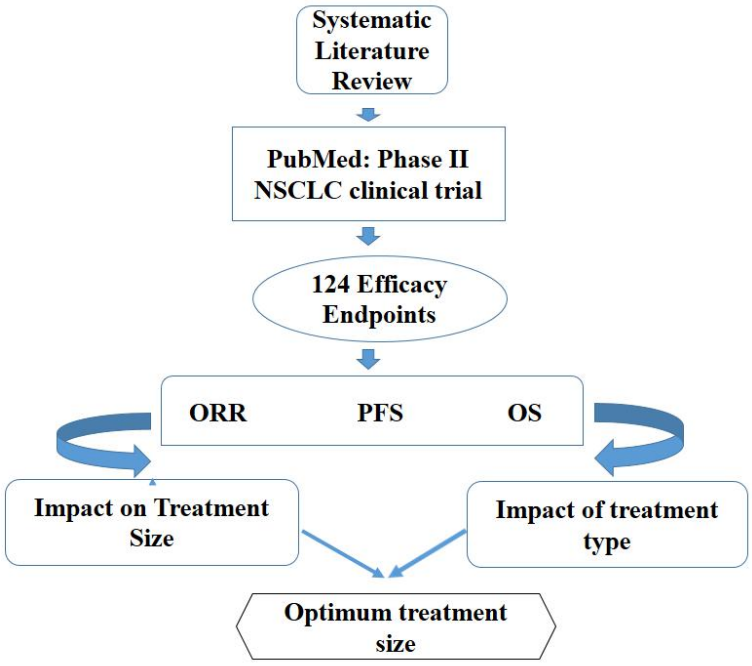

Figure 1 - Study Plan

There are two key factors that should be emphasized based on these efficacy endpoints. Firstly, we plan to observe the impact of drugs incorporated in the treatment can have on the patient's overall chance of surviving the disease. Secondly, the relationship between different forms of therapy, such as chemotherapy and targeted therapy, and the efficacy endpoint.

2.5 Statistical Analysis

T-test were performed when two ORR groups or two PFS groups' means were compared for a difference at a 5% significance level, Student's t-test with unequal variances was run. The Pearson product-moment correlation was used to assess the relationship between PFS and ORR.

Chapter 3

Results

The collection of efficacy outcomes, such as progression-free survival, overall response rate, and overall survival rate, is our primary objective. Following the extraction of 200 articles, we use the data from the 124 identified efficacy endpoints in our analysis. This data pertains to the impact that the treatment size has on overall survival. The primary efficacy endpoint of this study is overall survival since the primary objective is to reduce the number of people who perish due to non-small cell lung cancer. Details of the collected data has been provided in the appendix.

Table 1: Number of Collected Efficacy Data

SL.	Efficacy Endpoint	Number
1	ORR	94
2	PFS	97
3	OS	105

3.1 Impact of Treatment Size on Overall Survival

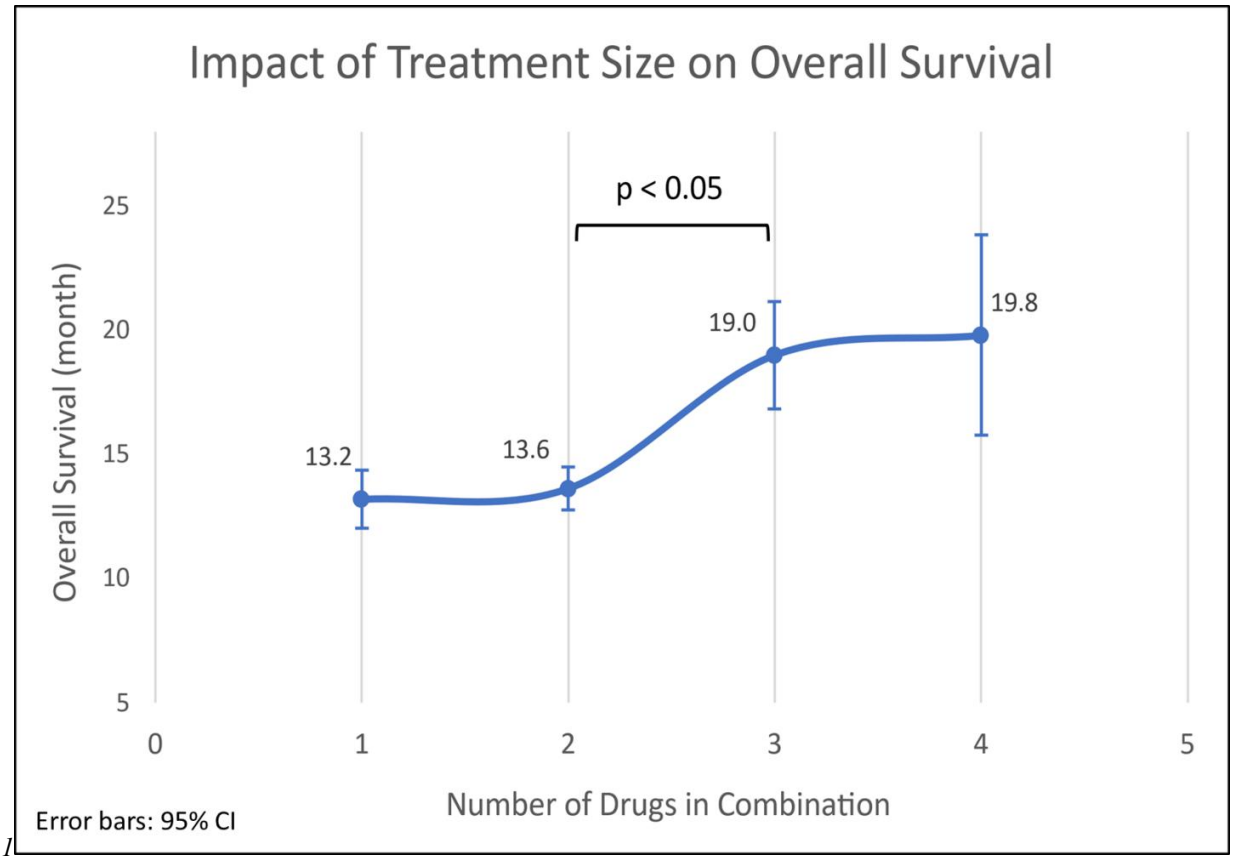

Figure 2.a - Overall survival values according to the combination size. The X axis represents number of drugs in combination and the Y axis represents overall survival. The error bars represent 95% confidence interval and level of significance was 5%.

The line plot in the figure illustrates the correlation between the treatment size, measured in terms of the number of medications, and overall survival. There seems to be no significant increase in the number of months of survival when only one drug is given. The typical amount is 13.2 months of time one can expect to live. Then, when two drugs are administered together, the survival time is 13.6 months, which is quite close to the single drug outcome. When the number of possible combination sizes is extended from two to three, the survival time increases by up to 19 months compared to what it was previously. The survival time is significantly influenced by the three different combination sizes that are available for increase the survival.

Last but not least, there is no significant difference between the three combination sizes and the four treatment sizes, despite the fact that the four treatment sizes had an slight increase survival rate of 19.8 months.

3.2 Chemotherapy vs. Targeted Therapy in Monotherapy Trials

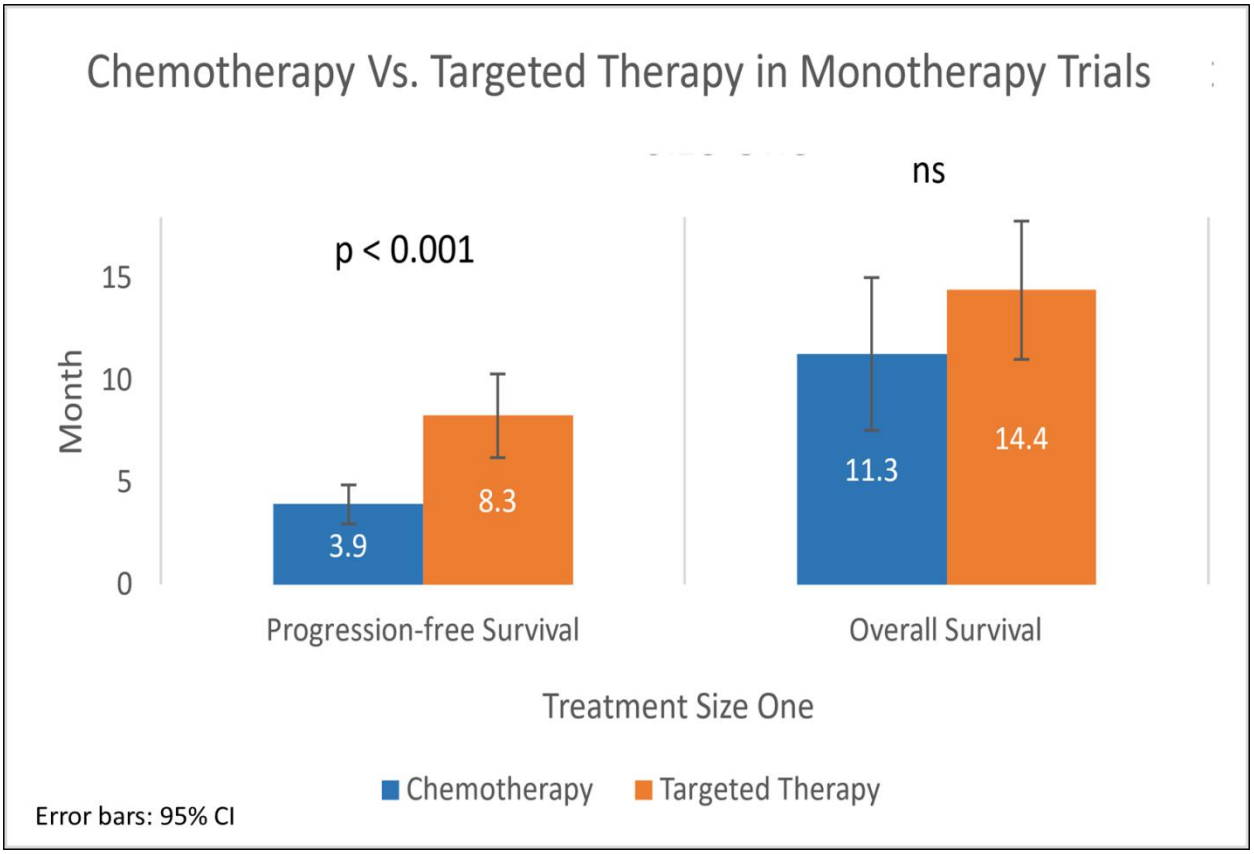

Figure 2.b - Chemotherapy and Targeted therapy in monotherapy trials. The blue bar represents chemotherapy treatment and orange bar represents Targeted Therapy. The error bars represent 95% confidence interval and level of significance was 5%

The purpose of these statistics is to determine the most effective method of treatment for non-small cell lung cancer in terms of progression-free survival and overall survival rate.

The duration of chemotherapy for PFS is 3.9 months, while the duration of targeted treatment is 8.3 months. There has been a significant alteration that can be categorized as major or tremendous. Both the targeted treatment, which lasts around 11.3 months, and chemotherapy, which lasts approximately 14.4 months, contribute to overall survival; however, none of these treatments demonstrated a significantly greater improvement than PFS, which was not anticipated.

Chapter 4

Discussion

Since overall survival is the most important measure of efficacy, it is assigned the drug number that corresponds to figure 2.a. In contrast, when only one medication is used, there is only a marginal improvement in the patient's chances of survival. The better efficacy that is achieved when two drugs are taken together leads to an increase in the mean overall survival value for combination sizes of two. This can be seen in the fact that the mean overall survival value improves. It has been determined that there is a statistically significant difference between the total survival value of combination size one and combination size two, which indicates that this difference is capable of being assessed statistically. The overall survival rate has once again increased for drug combinations involving three medications, demonstrating that combinations involving three medications perform significantly more adequately when taken together than combinations involving two medications. It is clear that a better overall survival rate has been reached with a larger number of combination points being used. The mean overall survival values of combination sizes four, five, or more could not be calculated due to a low number of reported clinical trials available under these combination sizes. Nevertheless, it is unknown for how much longer the value will continue to rise. This is due to the very small number of clinical trials that have been conducted using combination sizes of this kind. One may use statistics to determine how much of a difference there is between the mean overall survival value of combo sizes one and three. However, due to the limited quantity of data sets that were available for analysis under combination size three, it was not possible to statistically determine the difference in the mean overall survival between combination sizes two and three. A review result from 11,107 patients in 47 trial comparisons show that adjuvant chemotherapy is clearly beneficial for these patients, regardless of whether chemotherapy was administered in addition to surgery or surgery with radiation (Burdett et al., 2015). 2019 had seen the publication in ASCO of a phase II research combining docetaxel and trametinib to treat NSCLC patients with KRAS mutations which is one of the RAS protein family. After undergoing first-line or second-line therapy, the overall ORR and PFS of 54 patients were 33% and 4.1 months, respectively (Ye et al., 2021). If two to three cycles of chemotherapy were administered before to surgery, two randomized studies found that stage IIIA NSCLC patients had an enhanced chance of survival (Yang et al.,

1121). Induction chemotherapy with gemcitabine and vinorelbine followed by 42 patients were enrolled between April 2002 and November 2003, and 40 of them were used to assess toxicity and response. The median survival duration and progression-free survival were 23.2 months and 10.9 months, respectively, after a median follow-up of 23.8 months, with a 2-year survival rate of 43.9% (Dae et al., 2005).

In conclusion, we can infer that a combination of three medications is the preferable choice for a patient who has NSCLC based on the data presented in figure 2.a. The results of the one, two, and four combinations are not clearly distinguishable from one another and do not demonstrate an enhanced survival rate compared to those of the combined size three drugs.

Figure 2.b demonstrates that when it comes to PFS, targeted therapy produces significantly better results than chemotherapy. Therefore, if the chemotherapy is switched out for the targeted therapy, it will demonstrate a superior result and have a significant effect on the patient's chance of survival. Epidermal growth factor receptor tyrosine kinase inhibitors were the most frequently examined class of targeted agents, and they were assessed in 70.6% of phase I/II and II trials (Subramanian et al., 2013).

On the other hand, the results for overall survival, which we anticipate will indeed be good and significant, do not achieve the expectation. The results for overall survival for chemotherapy and targeted therapy are relatively comparable, despite the fact that targeted therapy is demonstrating a marginally better significant outcome than chemotherapy.

If we want to see an increase in the percentage of patients who are able to make it through treatment, we might come to the conclusion that targeted therapy is a preferable alternative to chemotherapy due to the fact that it demonstrates better results for both progression-free survival and overall survival.

In addition to this, one more objective has been achieved, which was to demonstrate that progression-free survival yields superior results to overall survival. It was expected to show a significant result because overall survival is the main outcome that we are focusing on, but an interesting thing happened here, which is that progression-free survival ended up giving a very much more prominent result than the primary endpoint that we are focusing on, which is overall

survival. In the last 10 years, the death rate from lung cancer has gone down. This is partly because targeted therapy has gotten better. Targeted therapy has become the first-choice treatment for people with advanced NSCLC that has a mutation gene. This has the effect of making people live longer overall (Zou et al., 2023).

Our objective is to determine the type and dosage of non-small cell lung cancer treatment that has the highest probability of curing the disease with the fewest side effects possible. We also get the result that if we use three different treatment sizes, it will indicate clinical significance. In addition, if the cancer patient is not responding to the chemotherapy, then, according to our findings, we are able to substitute the chemotherapy medicine with the medicine for the targeted therapy. The patient who is afflicted with cancer may gain an incredible amount of benefit from targeted therapy. The fact that progression-free survival displays better results for the graphs representing chemotherapy and targeted therapy came as a surprise to us. Patients with advanced non-small cell lung cancer who had received prior treatment and were chemotherapy-refractory showed a 10 to 20% response rate and a 30 to 50% symptom improvement with single-agent gefitinib treatment (Ciardiello et al., 2004).

We had anticipated that overall survival would be our primary measure of efficacy, but this was not the case. We require further efficacy data in order to arrive at a more accurate result for the efficacy endpoint. The reason why we require additional data is that the more data we have, the greater the likelihood that the results will be accurate, making it much simpler for us to draw the appropriate conclusions and reduce the number of cancer deaths.

Since NSCLC and other forms of cancer are such major killers, we hope to continue this study in the future using a larger data set, say 1,000 articles. All being well, we should have a satisfactory outcome if we manage to gather 1,000 articles meeting the specified efficiency requirement.

Chapter 5

Conclusion

In conclusion, the findings of our small scale study showed that the survival rate of NSCLC patients might be improved by using three different drug combinations rather than other different combination numbers. However, since we are not doing our study very vastly, the other combination size may be successful to increase the survival rate of the NSCLC patients. This was the primary objective of our research. When three medications are taken together, the number of months of survival is significantly increased than the other combination size. In addition, targeted therapy has demonstrated greater efficacy results than chemotherapy in terms of both progression-free survival and overall survival; this indicates that targeted therapy will be a more effective treatment option for NSCLC patients than chemotherapy.

Limitation

In contrast to what we had anticipated, overall survival was not our main indicator of achievement. To arrive at a more precise conclusion for the efficacy endpoint, we need more efficacy data. We need more data because having more data increases the likelihood that the results will be correct, which makes it much easier for us to make the right decisions and lower the rate of cancer mortality.

Future Recommendation

We intend to continue this investigation in the future using a larger data set, say 1,000 papers, because NSCLC and other cancer types are such significant deaths. If all goes according to plan, we should be able to acquire 1,000 articles that fulfill the required level of efficiency.

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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	Nivolumab			

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			
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	exclud	abstract										

	ed											
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		
31182249	advanced	Adenocarcinoma	0	39	7.4	15.6	1	1	Nivolumab			
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	advanc	non small	1	9.2		3	1	1		Anlotinib		

	ed												
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										
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			
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 endpoint	full text									
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 endpoint	no result									
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	chemotherapy		
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		

										r a p y		
17532073	excluded	no endpoint	no result									
25201721	excluded	no endpoint	abstract									
9683302	no article											
17909356	early		1		2.1	8	2	1	Docetaxel	E x i s u l i n d		
21277039		small cell	1	36	3	7	2	1	amrubicin	c a r b o p l a t i n		
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	g e m c i t a b i n e		

17409983	excluded	no endpoint	abstract									
15726523	excluded	no endpoint	full text									
23891283	advanced	Adenocarcinoma	0		7	13.8	2	0	pemetrexed	TumorTreating 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	carboplati	radiation therapy	

										n		
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 endpoint	result									
18235125	excluded	no endpoint	full text									
18023915	advanced	Adenocarcinoma	1	39.3	5.5	10.5	2	0	gemcitabine	cispl		

										a t i n		
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	Adenocarcinoma	1		8.5	16.4	3	0	Docetaxel	cisplatin	surgery	
9007124	excluded	no endpo	abstract									

	ed	int										
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 cell	0	77.3	12	27.8	2	0	cisplatin	vinorelbine		
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	exclud	no endpoint	full text									
14690568	excluded	no endpoint	no full text									
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		Adenocarci		80	7	14.6	1	1	icotinib			

		noma										
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									
12928126	advanced	non-squamous	1	64	12.3	23.6	2	0	paclitaxel	cisplatin		
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									
1332578	excluded	no endpoint	result									
29858022	advanced				15	21.8	2	0	cisplatin	vinorelb		

										ine		
24852396	no article	no author										
12644982	excluded	no author	abstract									
8070014	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	irino		

										tecan		
19631403	advanced	Adenocarcinoma	1	31	4.5	16	1	0	carboplatin			
29755102	excluded	no endpoint	abstract									
16736888	excluded	no endpoint	abstract									
20225327	advanced	Adenocarcinoma	0		7.9	16.5	3	1	carboplatin	Docetaxel		
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		