Pooled Analysis of Progression-free Survival and Overall Survival in Phase II Clinical Trials of Breast Cancer

By

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

School of Pharmacy

BRAC University

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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.

Student's Full Name & Signature:

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Approval

The thesis titled “Pooled Analysis of Progression-free Survival and Overall Survival in Phase II Clinical Trials of Breast Cancer” submitted by Sohana Shobnam (20146042), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

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Ethics Statement

This study does not involve any human or animal trials.

Abstract

Metastatic breast cancer requires more investigation because of its high incidence. Efforts to improve the accessibility, evaluative simplicity, and predictive accuracy of clinical trial endpoints are ongoing. In this paper, we analyzed 410 Phase II clinical trials' endpoints to assess the efficacy and impact of anticancer agents. We estimated the treatment effects for overall survival and progression-free survival using appropriate statistical methodologies. We found a significant moderate positive correlation between OS and PFS ($r = 0.63$, 95% CI 0.55–0.71, $P < 0.001$). Moreover, PFS predicted the OS with a 40% accuracy (R-sq= 0.40). Interestingly, PFS showed significant differences in 1-2-and-3-agent trials, however, this was not reflected in the OS for 2-and-3-agent trials, indicating the need for further validation of the surrogacy of PFS. Nonetheless, PFS is somewhat reliable surrogate of OS in phase II trials of breast cancer and we recommend finding a better surrogate than PFS.

Keywords: Phase II trials, breast cancer, efficacy endpoints, progression-free survival, overall survival, linear modeling.

Dedication

Dedicated to my parents

Acknowledgment

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

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List of Acronyms:

ADC	Adenocarcinoma
PFS	Progression-free Survival
OS	Overall Survival
ORR	Overall Response Rate
PR	Partial response
CR	Complete response
QoL	Quality of Life

Chapter 1

Introduction:

1.1 Introduction

Cancer accounts for 8.8 million deaths annually, more than HIV/AIDS, malaria, and tuberculosis combined, making it a serious public health concern (Zugazagoitia et al., 2016). This accounts for one out of every six deaths in the world. Cancer is not a single disease, but rather a collection of problems with various subtypes that necessitate specialist diagnosis and therapeutic procedures. To address such complexity, coordinated multidisciplinary treatment is required (Torre et al., 2016). Cancer is estimated to kill approximately 609,820 people in the United States by 2023, resulting in an average of 1670 fatalities per day (Siegel et al., 2023).

According to one of the most thorough assessments conducted in 2004, breast cancer is the most frequent malignancy among women worldwide. It ranked second in Southeast Asia and Africa behind cervical cancer and sixth in the Western Pacific, making it the leading cause of death for women globally, according to the World Health Organization (2008). More recent study indicates that these numbers remain accurate. Breast cancer accounted for 13.8% of all cancer cases in 2012. It was the most common type of disease (Ferlay et al., 2013). According to a 2014 study conducted in China, India, and Russia, breast cancer was the second leading cause of death for women, behind lung cancer (Goss et al., 2014).

The number of circumstances of breast cancer has gradually increased in past few years due to various contributing aspects. A 2017 study found that between 2005 and 2015, the number of cases increased by 33%. Population growth accounted for 12.6% of the rise, aging populations for 16.4%, and age-specific cases for 4.1% of the cases (Global Burden of Disease Cancer Collaboration 2017). Although there was a 91,000 decrease in death cases in the European Union in 2012 (Ferlay et al., 2013), there was a 21.3% increase in breast cancer mortality from 439,800 to 533,600 between 2005 and 2015 (Wang et al., 2016).

Breast cancer is classified into three main subtypes based on the presence or absence of molecular markers for progesterone, estrogen, or human epidermal growth factor 2 (ERBB2; formerly HER2), and hormone receptor positive/ERBB2 negative (70% of patients), ERBB2 positive (15–20%), and triple-negative (tumors lacking all three standard molecular markers; 15%). Nearly 90%

of breast tumors do not develop metastases at the time of diagnosis. The treatment objectives for patients without metastases include tumor eradication and prevention of recurrence. Triple-negative breast cancer is more likely to recur than the other 2 subtypes, with a 5-year breast cancer-specific survival rate of 85% for stage I tumors and 94% to 99% for hormone receptor positive and ERBB2 positive tumors (Adrienne et al., 2019).

Patients with hormone receptor-positive tumors receive endocrine therapy, with a small percentage also receiving chemotherapy; those with ERBB2-positive tumors receive chemotherapy in addition to small-molecule inhibitor or ERBB2-targeted antibody therapy; and those with triple-negative tumors only receive chemotherapy. These patient subtypes determine the course of systemic therapy for nonmetastatic breast cancer. Surgical resection is the only form of local therapy available to individuals with nonmetastatic breast cancer; if a lumpectomy is performed, postoperative radiation therapy may be considered. Systemic therapy is increasingly being administered in advance of surgery. One area of research is customizing postoperative care according to preoperative response to treatment. Symptom relief and life extension are the main objectives of treating metastatic breast cancer, based on the subtype (Adrienne et al., 2019).

When developing new medications to add to the treatment of cancer, clinical trials play a critical role in evaluating the efficacy of innovative therapeutic methods (Unger et al., 2016). The most crucial decision that has to be taken to guarantee accurate assessment and approval is primary end-point selection for clinical trial efficacy assessment. The goal of endpoints for cancer clinical trials is to be highly predictive of a final endpoint, easier to assess, and more readily available throughout time (Driscoll & Rixe, 2009). Overall survival (OS) is the main outcome and the "gold standard" for assessing the effectiveness of any medication, biologic, therapy, or intervention in cancer clinical trials (Fiteni et al., 2014). The length of time from therapy initiation or randomization to the patient's continued survival is known as the OS. According to Cheema and Burkes (2013), the endpoint is patient-centered, accurate, and easily quantifiable. It is also clinically significant and is not impacted by the evaluation period.

On the other hand, progression-free survival (PFS) offers a clear evaluation of how a treatment affects a tumor. The results of using PFS are influenced by how often patients are checked for illness symptoms. Many cancers have five-year survival rates because patients who live for five years have a better chance of recovering from their illness.

However, because PFS is a well-recognized parameter and is available earlier than OS, drug research may proceed more quickly (Driscoll & Rixe, 2009). An overall response is produced by evaluating newly formed lesions in addition to nontarget lesions. In ordinary practice, the overall response rate (ORR) is a valuable tool for therapeutic treatment regimen selection and evaluation of trial outcomes (Aykan & Özatlı, 2020). When determining how a medication is changing their tumor burden, a patient with a history of solid tumors may use the objective response rate (ORR) (Delgado & Guddati, 2021).

As previously stated, OS is considered the gold standard. However, the regulatory clearance of novel medications may be a lengthy procedure as the authority compares the OS differences among therapy arms. It is possible to replace OS endpoints with data that includes ORR and PFS. In the age of genomics, clinical studies for OS endpoints may become less suitable due to fewer homogeneous populations. As a result, the response rate and length of the response in a single-arm trial may expedite the process of approval of novel medications (Aykan & Özatlı 2020).

1.2 Aim of the Study

The aim of the study is to help design clinical trial investigators and cancer drug researchers to choose appropriate endpoints and effective cancer drug combinations in phase II trials of breast cancer.

1.3 Objectives of the Study

- To determine the relationship between progression-free survival and overall survival in phase II trials of breast cancer
- To model the relationship between progression-free survival and overall survival through linear regression in phase II trials of breast cancer
- To study the impact of various treatment options on progression-free survival and overall survival, including the use of anticancer drugs in combination with chemotherapy and targeted therapy.

Chapter 2

Methodology

2.1 Efficacy Endpoint and Predictor Variable

The efficacy endpoint is a clinical or biological outcome used in clinical trials to assess the effectiveness of an intervention and compare treatment options (Fiteni et al., 2014). A clinical study's PFS reflects the time between the start of treatment and the onset of disease progression. Data with PFS and OS expressed within the month were considered. In contrast, if OS and PFS were expressed in weeks or days, they were converted to months. Additionally, median age and cancer subtype, trial sample size, treatment size were collected into account as predictor variables.

2.2 Data Source

Our research strategy was centered on a primary database, PubMed, chosen to streamline access to the most relevant Phase II clinical trials' articles of breast cancer. On February 25, 2023, we conducted a comprehensive search on PubMed employing the following keywords "Phase II Clinical Trials of Breast Cancer" to narrow down the papers directly relevant to our area of investigation. This systematic approach yielded 3,000 articles on Phase II clinical trials related to breast cancer. Subsequently, we meticulously screened the initial subset of 600 articles. By confining our search to a single database, we aimed to mitigate complexities inherent in data retrieval, compilation, and curation thereby optimizing efficiency within the constraints of time.

2.3 Inclusion and Exclusion Criteria

Precise parameters have been implemented to efficiently conduct the inclusion or exclusion criteria of searched articles. Although our primary concern for the inclusion criteria was only phase II breast cancer clinical trial publications, articles with Phase I and III were excluded. Articles that did not have anti-cancer drugs, had been excluded. Additionally, articles with phase II breast cancer trials that did not have median PFS as primary, or secondary endpoint had also been excluded. Similarly, the OS and PFS rates as endpoints had been removed from this count since those data were not reported in median. Median time-to-progression (TTP) was collected in place of median PFS when the median PFS was absent.

2.4 Study Plan

The outcomes include PFS and OS. We focused on only two critical characteristics: PFS and OS. There was a total of 327 PFS and 254 OS among the 410 included articles. First and foremost, one of our key goals was to determine whether the PFS has a good linear relationship with OS and to model the relationship. Second, we looked into the impact of different treatment combinations and the influence they have on efficacy endpoints.

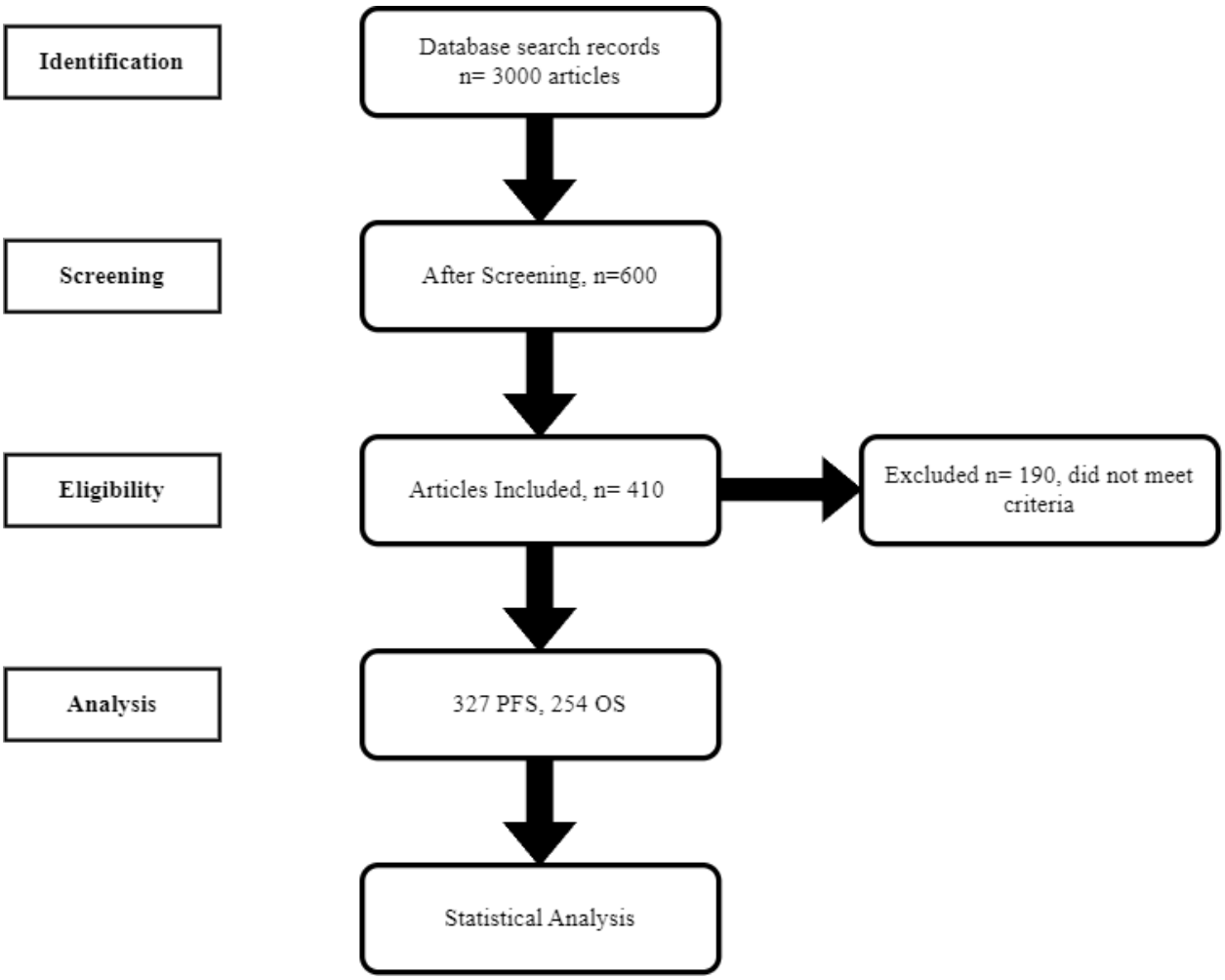

Figure 1: Study plan

2.5 Statistical Analysis

Endpoint correlation between OS and PFS was estimated by Pearson correlation coefficient assuming normal distribution. To model the relationship between PFS and OS, an ordinary linear regression analysis with the least squared method was carried out. The 95% confidence interval (95% CI) were estimated. The mean between treatment size groups were compared by two-tailed

Student's t-test assuming unequal variances at 5% significance. All the data was collected and compiled in an MS Excel 365 spreadsheet. All the tests and data analysis were performed by Microsoft 365 Excel add-in called 'Analysis ToolPAK'.

Chapter 3

Result:

3.1 Dataset Overview

Of the first 600 studies, 410 met the inclusion criteria and thus collected. The collected data contains 1-agent (n = 156), 2-agent (n = 198), and 3-agent (n = 67) trials. Among the 410 studies, the number of PFS and OS were 327 and 254, respectively. To be more precise, the PFS counts were 284, 137, and 38 for 1-agent, 2-agent, and 3-agent, respectively. Regarding OS, the counts were 205, 121, and 37 respectively. In the case of the ORR counts were 267, 115 and 38 respectively.

The mean, standard deviation, median, and interquartile range (IQR) were of PFS and OS were reported in Table 1.

Table 1: Summary of the collected dataset of phase II trials of breast cancer

	Mean	Standard Deviation (±)	Median	IQR
PFS (month)	7.03	4.00	6.50	4.86
OS (month)	18.79	8.31	17.80	11.15

3.2 Relationship Between OS and PFS

We found the Pearson correlation coefficient of $r = 0.63$ ($p < 0.0001$, 95% CI 0.55–0.71) between OS and PFS, which indicates a moderate positive correlation, and the correlation is statistically significant. The scatterplot in Figure 2 displays a clear increasing trend from left to right, demonstrating a positive linear relationship between the two variables. The plot, in particular, indicates that an increase in PFS is associated with an increase in OS, whereas a decrease in PFS

is associated with a decrease in OS. As the PFS and OS are moderate positively correlated, so the PFS can be used to predict OS.

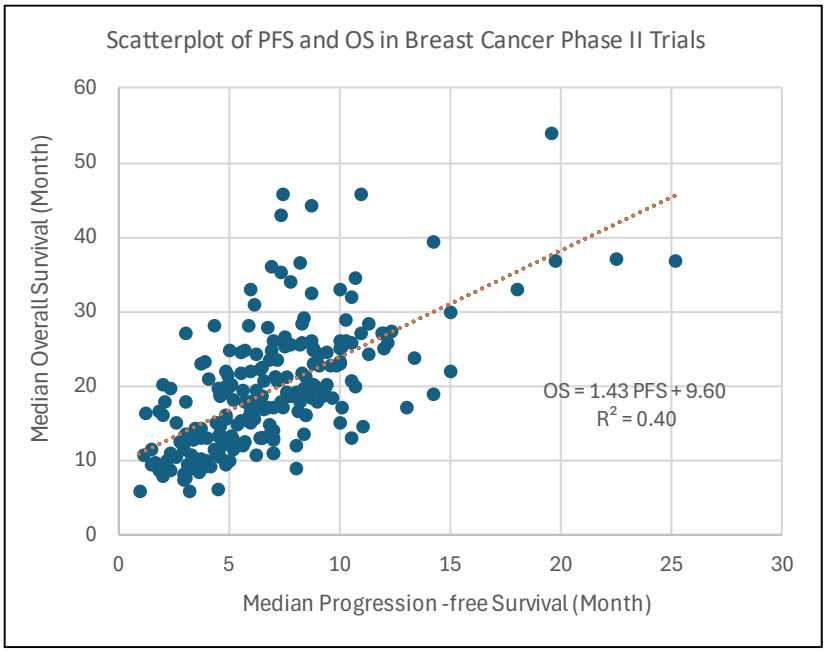

Figure 2: Scatterplot of overall survival and progression-free survival of phase II clinical trials of breast cancer. Progression-free survival (month) is shown on the x-axis, while overall survival (month) is plotted on the y-axis. The dotted diagonal line indicates linear regression.

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

	Coefficients	*Standard Error*	*P-value*	*Lower 95% CI*	*Upper 95% CI*
Intercept	9.60	0.92	1.29E-20	7.77	11.43
Median PFS	1.43	0.12	5.70E-26	1.20	1.67

The predicted linear regression equation is as follows: Median OS = 1.43 × median PFS + 9.60. The obtained R square value is 0.40, indicates that the model accuracy is 40%. That means PFS can explain 40% of the variability in the dependent variable or OS data. According to this value, the selected variable provides a significant contribution to the model, while avoiding the addition of noise. The intercept of the regression model is 9.60, indicating that the dependent variable (OS) will have a value of 9.60 month when the independent variable (PFS) is set to 0 month. Lastly, the

95% CI shows that there is only a 5% chance that the true value will not fall within the range. Thus, a narrow 95% CI indicates a lower degree of uncertainty.

3.3 Impact of Treatment Size on PFS

Next, we investigated the impact of treatment size on the PFS. The line plot in Figure 3 represents the relationship between the treatment size and the PFS. As the p-value is less than 0.05, so it indicates there is a significant difference between treatment size 1 and 2 and treatment size 2 and 3.

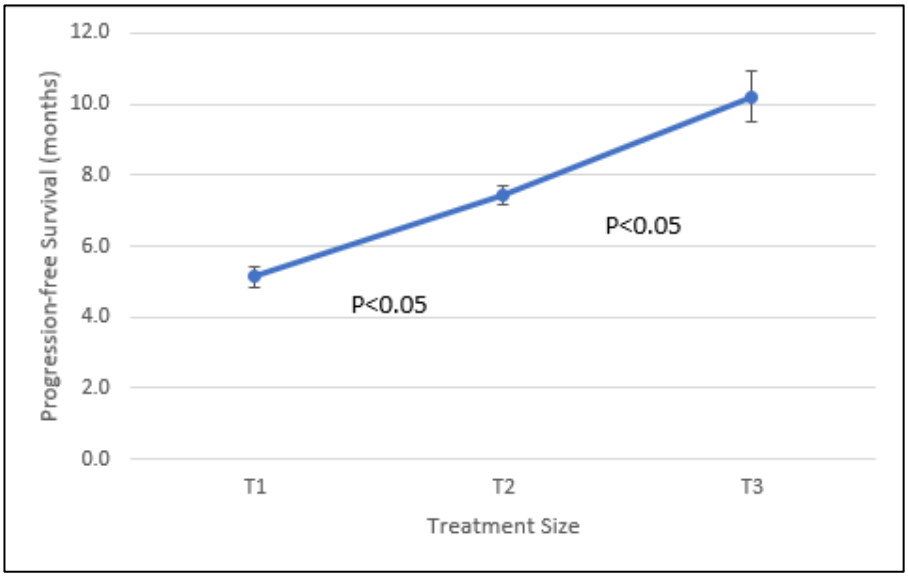

Figure 3: Impact of treatment size on progression-free survival (PFS). The X-axis reflects the treatment size, and the Y-axis reflects the mean value of median PFS, measured in months. Error bars indicate standard error.

3.4 Impact of Treatment Size on Overall Survival (OS) in Breast Cancer Phase II Trials

We then explore the impact of treatment size on the PFS. The line plot in Figure 4 represents the relationship between the treatment size and the OS. As the p-value is less than 0.05, so it indicates there is a significant difference between treatment size 1 and 2. On the other hand, there is no significant difference between treatment size 2 and 3 as the p-value is greater than 0.05.

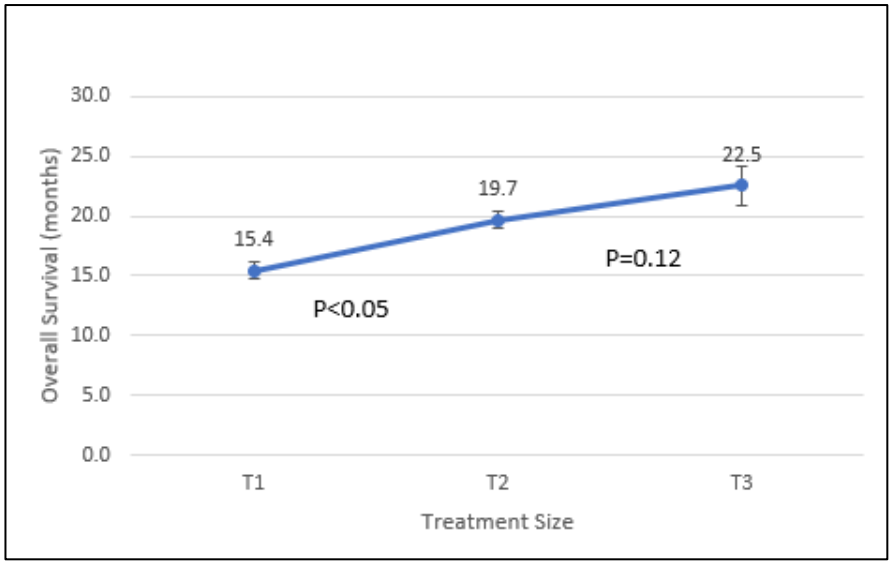

Figure 4: Impact of combination size on overall survival (OS). In the graph, the X-axis reflects the treatment size, on the other side the Y-axis reflects the mean value of OS, measured in months. Error bars indicate standard error.

Chapter 4
Discussion

Chemotherapy agents play a crucial role in the treatment of breast cancer by inhibiting tumor growth and spread. Some works by targeting and killing rapidly divided cells and some of them are targeted therapy. These targeted therapies are a novel class of anticancer drugs with fewer side effects that have been approved for the treatment of breast cancer. In many circumstances, targeted medicines are paired with non-targeted therapies to increase therapeutic efficacy, which may improve patients' conditions. Several studies have demonstrated that combination therapy can successfully maximize the benefits of individual drugs. Furthermore, drug co-administration has been found to have an impact on the control of certain cellular functions. In recent decades, there has been a substantial focus on intensive research into combination cancer treatments. The use of combination treatment has the potential to improve treatment effectiveness, reduce the probability of drug resistance, and prevent the development of undesirable effects commonly associated with mono-chemotherapy (Wu et al., 2017). As previously stated, the primary goal of this study was to assess the effectiveness of combination therapy and to investigate the impact of medication on the overall survival.

In this study, Pearson correlation was carried out to assess the correlation between PFS and OS. It also demonstrated the degree to which the relation falls from -1 to +1. The correlation test ($r = 0.63$, 95% CI = 0.55–0.71, $p < 0.001$) indicates a moderately positive and highly significant relationship between PFS and OS.

According to Solomon et. al., a study that included 15 clinical trials found no statistically significant correlation despite an expected trend between the PFS hazard ratio and the OS hazard ratio, with a calculated weighted Pearson correlation of 0.48 and a weighted linear regression p-value of 0.095. In contrast, our study revealed a statistically significant and moderately positive correlation between PFS and OS. Another study investigated 15 clinical trials of solid tumors using Kendall's Tau and found a strong positive association between PFS2 and OS, with a correlation of 0.70, equivalent to a Pearson's correlation of 0.86. It shows a strong (>0.7) correlation between OS and PFS2 where a value of 0 indicates no relationship. This study concluded that when OS data is unavailable, utilizing PFS2 to ensure an experimental agent as a starting treatment before a second therapy is more successful than starting with conventional therapy followed by second therapy.

Furthermore, Chowdhury et al. (2020) discovered strong relationships in specific tumor types and when examining data from many indications.

According to our analysis, the effect of monotherapy on breast cancer patients was less in terms of mean OS (15.4 month) and mean PFS (5.14 month). Conversely, we found that there was a rise with a significant difference in the mean value of both OS (19.65 month) and PFS (7.42 month) when a combination of two drugs had been used as treatments. This implies that it is more beneficial for breast cancer patients to treat with combination that effectively reduce tumor progression and enhance overall survival. The results of one randomized study showed that combining two drugs such as Trastuzumab and taxane enhanced clinical outcomes and therapeutic efficacy in comparison to using trastuzumab alone. Surprisingly, the combination led to synergistic interaction at molecular level, which enhanced the inhibition of cell proliferation and induction of apoptosis (Pegram et al., 2001).

Despite this, no significant difference was detected in the case of OS among treatment size 2 and 3 groups, with the obtained p-value of 0.12. One randomized study indicated that combining cetuximab with afatinib did not improve clinical outcomes when compared to using afatinib alone. Unexpectedly, the combination resulted in higher toxicity, which led to a greater number of dose reductions and treatments being terminated completely (Goldberg et al., 2020). In contrast, the research showed an even greater increase in the OS and PFS mean values of 22.52 and 10.21 month, respectively, when three medications are used in combination, such as in treatment methods comprising monotherapy vs dual or triple drug treatment. Typically, it refers to the use of combination treatment, such as the concurrent administration of doxorubicin, with additional agents such as immune therapy (e.g., durvalumab) and chemotherapy (e.g., cyclophosphamide), which has shown superior efficacy compared to monotherapy in terms of tumor progression and survival of breast cancer patients.

Furthermore, cytotoxic medicines (such as pemetrexed and docetaxel) are used in combination. It is thought that the increased efficiency of combining these drugs is caused by a range of mechanisms, not all of which are directly related to the genetic properties of the tumor cell. In cell line experiments, pemetrexed was demonstrated to increase EGFR phosphorylation while decreasing Akt phosphorylation, making tumor cells responsive to erlotinib. Erlotinib, on the other hand, has been shown to suppress thymidylate synthase expression and activity, making tumor

cells more vulnerable to pemetrexed. Combinations of docetaxel and EGFR inhibitors were investigated in cancer cell lines and tumor models, and they were found to improve the antiproliferative and cytotoxic efficacy of the individual drugs (Aerts et al., 2013).

As a result, our findings imply that using various anti-cancer drug combinations yields higher efficacy endpoints and has the potential to increase long-term patient survival. When dealing with combinations of more than three medications, a t-test could not be performed because there were insufficiently reported clinical studies in our dataset. Nonetheless, more research incorporating larger dataset of phase II trials of breast cancer is required to further investigate to obtain definitive results.

Chapter 5

Conclusion:

We conducted this study with the intention of assisting healthcare practitioners in the accurate selection of medications and avoiding instances of misinterpretation. Our study found a direct association between the number of drugs used in treatment and the efficacy endpoints (PFS and OS). Our study's findings show that utilizing two or three medications in combination results in the largest improvement in survival. The PFS for treatment sizes 1 and 2 was less than 0.05, as were the p-values for treatment sizes 2 and 3, showing a significant difference between these groups. In terms of OS, treatment sizes 2 and 3 had p-values of 0.12, but treatment sizes 1 and 2 had p-values significantly lower than 0.05. Surprisingly, the expected statistical significance between all treatment sizes did not occur in the case of OS. Despite this, it was obvious that the combination of three anticancer drugs resulted in a prolonged OS and PFS. To be more specific, anticancer medications taken in combination in breast cancer patients are more successful than monotherapy. This was discovered by comparing the efficacy of utilizing a single chemotherapy agent alone versus using it in combination with another drug (such as immunotherapy or cytotoxic drug) as a treatment size 2 or 3. One of our key aims for the next stages of our study is to increase the precision of our prediction models by utilizing larger datasets. More research is needed to determine why monotherapies aren't more effective. Aside from that, other clinical studies must be performed to determine the combinations that work best in breast cancer patients.

Reference:

Adrienne, G., Waks, M, D., Winer, P. E. (2019). Breast Cancer Treatment: A Review. *Journal of American Medical Association.* 321*(3).* 288-300. doi:10.1001/jama.2018.19323

Aerts, J. G., Codrington, H., Lankheet, N. A. G., Burgers, S., Biesma, B., Dingemans, A.-M. C., Vincent, A. D., Dalesio, O., Groen, H. J. M., & Smit, E. F. (2013). A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: The NVALT-10 study. *Annals of Oncology*, *24*(11), 2860–2865. https://doi.org/10.1093/annonc/mdt341

Aykan, N. F., & Özatlı, T. (2020). Objective response rate assessment in oncology: Current situation and future expectations. *World Journal of Clinical Oncology*, *11*(2), 53–73. https://doi.org/10.5306/wjco.v11.i2.53

Azamjah, N., Zadeh, Y., Zayeri, F. (2015). Global Trend of Breast Cancer Mortality Rate: A 25-Year Study. *Asian Pacific Journal of Cancer Prevention,* 20. DOI:10.31557/APJCP.2019.20.7.2015

Chowdhury, S., Mainwaring, P., Zhang, L., Mundle, S., Pollozi, E., Gray, A., & Wildgust, M. (2020). Systematic Review and Meta-Analysis of Correlation of Progression-Free Survival-2 and Overall Survival in Solid Tumors. *Frontiers in Oncology*, *10,* 1349. https://doi.org/10.3389/fonc.2020.01349

Delgado, A., & Guddati, A. K. (2021). *Clinical endpoints in oncology—A primer*.

Driscoll, J. J., & Rixe, O. (2009). Overall Survival: Still the Gold Standard: Why Overall Survival Remains the Definitive End Point in Cancer Clinical Trials. *The Cancer Journal*, *15*(5), 401–405. https://doi.org/10.1097/PPO.0b013e3181bdc2e0

Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al (2013), Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer, 49, 1374–1403

Goss PE, Strasser-Weippl K, Lee-Bychkovsky BL, et al (2014). Challenges to effective cancer control in China, India, and Russia. Lancet Oncol, 15, 489–538

Goldberg, S. B., Redman, M. W., Lilenbaum, R., Politi, K., Stinchcombe, T. E., Horn, L., Chen, E. H., Mashru, S. H., Gettinger, S. N., Melnick, M. A., Herbst, R. S., Baumgart, M. A., Miao, J., Moon, J., Kelly, K., & Gandara, D. R. (2020). Randomized Trial of Afatinib Plus Cetuximab Versus Afatinib Alone for First-Line Treatment of *EGFR* -Mutant Non–Small-Cell Lung Cancer: Final Results From SWOG S1403. *Journal of Clinical Oncology*, *38*(34), 4076–4085. https://doi.org/10.1200/JCO.20.01149

Pegram, M., Callaghan, C. (2001). Combining the Anti-HER2 Antibody Trastuzumab with Taxanes in Breast Cancer: Results and Trial Considerations. *Clinical Breast Cancer Supplement.* S15-S19. DOI: 10.3816/cbc.2001.s.003

Schabath, M. B., & Cote, M. L. (2019). Cancer Progress and Priorities: Lung Cancer. *Cancer Epidemiology, Biomarkers & Prevention*, *28*(10), 1563–1579. https://doi.org/10.1158/1055-9965.EPI-19-0221

Siegel, R. L., Miller, K. D., Wagle, N. S., & Jemal, A. (2023). Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*, *73*(1), 17–48. https://doi.org/10.3322/caac.21763

Solomon, B. J., Loong, H. H., Summers, Y., Thomas, Z. M., French, P., Lin, B. K., Sashegyi, A., Wolf, J., Yang, J. C.-H., & Drilon, A. (2022). Correlation between treatment effects on response rate and progression-free survival and overall survival in trials of targeted therapies in molecularly enriched populations. *ESMO Open*, *7*(2), 100398. https://doi.org/10.1016/j.esmoop.2022.100398

Torre, L. A., Siegel, R. L., Ward, E. M., & Jemal, A. (2016). Global Cancer Incidence and Mortality Rates and Trends—An Update. *Cancer Epidemiology, Biomarkers & Prevention*, *25*(1), 16–27. https://doi.org/10.1158/1055-9965.EPI-15-0578

Unger, J. M., Cook, E., Tai, E., & Bleyer, A. (2016). *The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies*.

Wang H, Naghavi M, Allen C, et al (2016). Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the global burden of disease study 2015. Lancet, 388, 1459–1544

Zugazagoitia, J., Guedes, C., Ponce, S., Ferrer, I., Molina-Pinelo, S., & Paz-Ares, L. (2016). Current Challenges in Cancer Treatment. *Clinical Therapeutics*, *38*(7), 1551–1566. https://doi.org/10.1016/j.clinthera.2016.03.026