Pooled Analysis of Overall Response Rate and Overall Survival in Phase II Clinical Trials of Breast Cancer

By

Md. Jawat Alam
20146072

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

School of Pharmacy
BRAC University
October 2024

Declaration

It is hereby declared that

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

Student's Full Name & Signature:

_____

Md. Jawat Alam

20146072

Approval

The thesis titled "Pooled Analysis of Overall Response Rate and Overall Survival in Phase II Clinical Trials of Breast cancer" submitted by Md. Jawat Alam (20146072), of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervised By:

_____

Faruque Azam
Lecturer
School of Pharmacy
BRAC University

Approved By:

Dean:

_____

A.F.M. Yusuf Haider, PhD
Acting Dean, School of Pharmacy
Professor, Department of Mathematics and Natural Sciences
BRAC University

Ethics Statement

If review or non-human or animal studies: This project does not involve any kind of animal and human trial.

Abstract

Metastatic breast cancer requires more investigation because of its high incidence. Efforts to improve clinical trials, simplification of assessments rather than complex evaluation, and validation of clinical trial endpoints are ongoing. In this paper, we analyzed 410 Phase II clinical trials' endpoints [418 Overall Response Rate (ORR) and 254 Overall Survival (OS)] to assess the efficacy and impact of anticancer agents in advanced/metastatic breast cancer. We estimated the treatment effects for OS and ORR using appropriate statistical tests. We determined that there is a moderate positive correlation between ORR and OS ($R = 0.36$, $p < 0.0001$, 95% CI 0.25-0.46). Moreover, ORR predicted the OS with a 12% accuracy (R-sq= 0.12). Interestingly, there was statistically significant difference found in the mean ORR between 1- ,2- and 3-agent trials. Furthermore, no significant difference was reflected in the OS for 2-and-3-agent trials, indicating the need for further validation of the surrogacy of ORR. Nonetheless, ORR is somewhat reliable surrogate of OS in phase II trials of breast cancer and we recommend finding a better surrogate than ORR.

Keywords: Phase II trials, breast cancer, efficacy endpoints, overall response rate, overall survival, linear modeling.

Dedication

Dedicated to my parents

Acknowledgment

I want to start by expressing my gratitude to God Almighty for all of his blessings, which have given me the strength and determination to see this project through to the end. Second, I want to thank my parents for their support and encouragement, which inspired me to put in more effort to go past the challenges.

I would especially want to thank my supervisor, Faruque Azam, lecturer of the School of Pharmacy, BRAC University, for his insightful criticism and recommendations. Without his wise counsel in the face of adversity, this project could not have been completed.

Additionally, I want to express my profound gratitude and sincere regards to A.F.M. Yusuf Haider, PhD (Acting Dean, School of Pharmacy, Professor, Department of Mathematics and Natural Science, BRAC University) and heartfelt thanks for his devotion, contribution, and leadership towards the students as well as to the department.

I also want to express gratitude to all School of Pharmacy faculties for their support and advice.

Finally, I want to express my sincere gratitude to my family, the most deserving and unquestionable aspect of my life, for their unwavering love and support, which inspired me the most during my research.

Table of contents

List of Tables

List of Figures

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 is the disease that represents 8.8 million deaths yearly, more than HIV/AIDS, malaria and tuberculosis combined, making it a serious general wellbeing concern (Zugazagoitia et al., 2016). This records for one out of each and every six deaths in the world. Cancer is certainly not a solitary disease, yet rather an assortment of problems with different subtypes that require expert diagnosis and therapeutic methodology. To address such complexity, harmonized multidisciplinary treatment is required (Torre et al., 2016). Cancer has caused around 609,820 fatalities in the US by 2023, bringing about an average of 1,670 fatalities each day (Siegel et al., 2023).

As per one of the most thorough evaluations led in 2024 by American Cancer Society (ACS), breast cancer is the most prominent malignancy among women globally with approximately 310,720 new cases of breast cancer will be diagnosed in the United States alone, making it the most frequently diagnosed malignancy. It also remains the leading cause of cancer-related deaths among Hispanic women, with around 42,250 expected breast cancer deaths in the U.S. this year. It positioned second in Southeast Asia and Africa behind cervical cancer and sixth in the Western Pacific, which makes it the most predominant cause of death for women worldwide, as per the World Health Organization (2008). The history of breast cancer dates back to ancient times. The earliest recorded cases can be found in ancient Egyptian medical texts, such as the Edwin Smith Papyrus, which described cases of tumors or ulcers of the breast that were untreatable. Hippocrates, the father of Western medicine, recognized breast cancer and documented its symptoms and progression.

Studies demonstrates the exact number of casualties. Breast cancer represented 13.8% of all cancer cases in 2012. It was the most common type of disease (Ferlay et al., 2013). Breast cancer is the most commonly diagnosed cancer among women globally. An estimated 2.3 million new cases of breast cancer were reported in 2020, accounting for 11.7% of all cancer cases (GLOBOCAN, 2020). As per a study led in China, India, and Russia, breast cancer was

the subsequent driving reason for death for women, behind lung cancer (Goss et al., 2014). In 2020, approximately 685,000 women died from breast cancer globally (GLOBOCAN, 2020).

Breast cancer is classified into three main subtypes, depending on the presence or absence of biomarkers for progesterone, estrogen, or human epidermal growth factor 2 (ERBB2; formerly HER2), and hormone receptor positive/ERBB2 negative (nearly 70% of patients), ERBB2 positive (accountable in15–20% patients), and triple-negative (tumors lacking all three standard biomarkers; 15%). Nearly 90% of breast tumors do not develop metastases at the time of diagnosis (BMC Cancer et al., 2023). The treatment objectives for patients without metastases include removal of tumors and avoidance of recurrence. Compared to the other two subtypes, triple-negative breast cancer has a higher chance of recurring, with a 5-year survival rate of 85% for stage I tumors and 94% to 99% for ERBB2 negative and ERBB2 positive tumors (Adrienne et al., 2019).

Patients with hormone receptor-positive cancers receive endocrine therapy, with a small percentage also getting chemotherapy; those with ERBB2-positive growths get chemotherapy in addition to small-molecule inhibitor or ERBB2-targeted antibody therapy; and those with triple-negative tumors just get chemotherapy. These patient subtypes decide the course of systemic therapy for nonmetastatic breast cancer. Surgical resection is the main type of nearby therapy accessible to people with nonmetastatic breast cancer; in the event that a lumpectomy is performed, postoperative radiation therapy might be thought of. Systemic therapy is progressively being managed ahead of surgery. One area of research is designing postoperative consideration according to preoperative reaction to treatment. Symptom relief and life extension are the principal goals of treating metastatic breast cancer, depending on the subtype (Adrienne et al., 2019).

While developing new medications to add to the treatment of cancer, clinical trials assume a crucial part in assessing the viability of creative therapeutic techniques (Unger et al., 2016). Primary end-point determination for clinical trial efficacy assessment is the most crucial decision that needs to be made to guarantee precise assessment and approval. The objective of endpoints for cancer clinical trials is to be profoundly prescient of an ultimate endpoint, simpler to assess, and all the more promptly accessible over the course of time (Driscoll and Rixe, 2009). Overall survival (OS) is the principal clinical endpoint and the "gold standard" for

assessing the adequacy of medicine, biologic, therapy, mediation in cancer clinical trials (Fiteni et al., 2014). OS refers to the length of time from the start of treatment for a disease, such as cancer, that patients diagnosed with the disease are still alive. As indicated by Cheema and Burkes (2013), the endpoint shows patient centered, precise, and effectively quantifiable. It is likewise clinically huge and is not influenced by the evaluation period. 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 examined for signs of illness. Many cancers have five-year survival rates due to the fact that five-year survivors have a better chance of recovering from their illness.

Overall Response Rate (ORR) is the percentage of clinical trial participants who experience a predefined amount of tumor shrinkage (partial or complete response) due to the treatment. It is a key metric used to evaluate the effectiveness of cancer therapies. However, because PFS is a well-recognized parameter and is available earlier than OS, drug research may proceed more quickly (Driscoll & Rixe, 2009). ORR is mainly influenced by patient population, tumor characteristics and the specific drug or the combination of drugs. It basically shows how good response the patients are showing towards a specific treatment or combination of treatments.

However, the race among ORR and OS for a superior parameter of cancer treatment relies upon the unique situation and explicit goals of the study or treatment evaluation. ORR can give early signs of a treatment's effectiveness, frequently inside the space of weeks or months, contrasted with OS which might require years (Blumenthal, G. M., et al. 2015). Yet, ORR does not gauge how long patients live or their personal satisfaction, which are basic endpoints in cancer treatment. Then again, OS is viewed as the gold standard endpoint in cancer preliminaries since it directly gauges the length of the time patients survive after treatment (Fiteni et al., 2014). In common practice, the ORR is an important endpoint for helpful treatment routine determination and evaluation of trial results (Aykan and Özatlı, 2020). While deciding how a medication is changing their tumor trouble, a patient with a background marked by solid tumors might utilize the ORR (Delgado and Guddati, 2021).

Previously mentioned, OS is viewed as the gold standard. Nonetheless, the regulatory clearance of novel medications might be an extensive methodology as the authority looks at the OS distinctions among therapy arms. It is feasible to switch OS endpoints with data which

incorporates ORR and PFS. At the time of genomics, clinical research for OS endpoints can sometimes turn out to be less reasonable because of less homogeneous populations. Thus, the response rate of a single-arm trials and length of response may hasten the approval process for novel medications (Aykan and Özatlı 2020).

1.2 Aim of the Study

The aim of the study is to assist in designing clinical trial examiners and cancer drug researchers to choose suitable endpoints and optimum cancer drug combinations in phase II trials of breast cancer.

1.3 Objectives of the Study

- To explore the relationship between overall response rate and overall survival in phase II trials of breast cancer.
- To model the relationship between overall response rate and overall survival through linear regression in phase II trials of breast cancer.
- To study the impact of various treatment options on overall response rate 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 result utilized in clinical trials to survey the effectiveness of an intervention and compare treatment options (Fiteni et al., 2014). A clinical study's ORR mirrors the extent of patients who have a partial or complete response to treatment. Median value of OS in months were taken. Yet, OS was converted to months if it was specified in weeks or days. Additionally, median age and cancer subtype, trial sample size, treatment size were collected into account as predictor variables.

2.2 Data Source

Our exploration procedure was focused on an essential data set, PubMed, chosen to streamline access to the most relevant Phase II clinical trials' articles of breast cancer. We conducted a comprehensive search on PubMed utilizing the accompanying keywords "Phase II Clinical Trials of Breast Cancer" to limit the papers straightforwardly pertinent to our area of examination. This orderly methodology yielded 3,000 articles on Phase II clinical trials connected with breast cancer. Consequently, we carefully screened the first 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 put in place to effectively carry out the inclusion or exclusion criteria of searched articles. As our main focus for the inclusion criteria was phase II breast cancer clinical trial publications, articles with Phase I and III were excluded. Also, articles which did not have anti-cancer medications were excluded. Partial responses were collected as ORR if there was no patient with complete response. Similarly, The OS data were excluded because they were not reported in terms of a median value.

2.4 Study Plan

The outcomes include ORR and OS. We focused on only two critical characteristics: ORR and OS. There was a total of 418 ORR and 254 OS among the 410 included articles. First and foremost, one of our key goals was to determine whether the ORR 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.

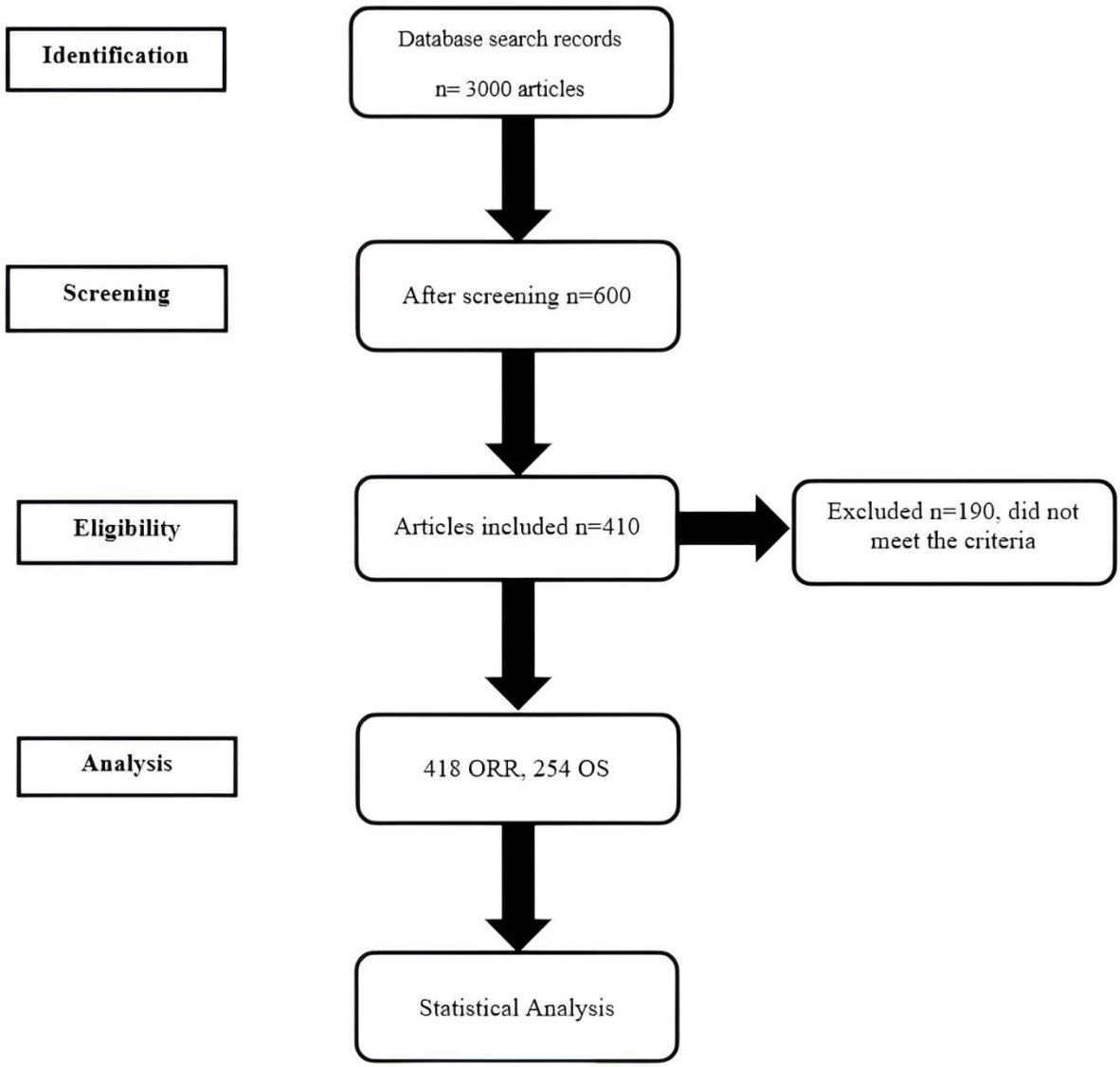

Figure 1: Study plan

2.5 Statistical Analysis

Endpoint correlation between ORR and OS was estimated by Pearson correlation coefficient assuming normal distribution. To model the relationship between ORR 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 initial 600 studies, 410 met the inclusion criteria and consequently gathered. The gathered information contains 1-agent (n = 156), 2-agent (n = 198), and 3-agent (n = 67) trials. Among the 410 studies, the number of ORR and OS were 418 and 254, respectively. To be more exact, the ORR counts were 267, 115 and 38 for 1-agent, 2-agent, and 3-agent, individually. Regarding OS, the corresponding counts were 205, 121, and 37.

The mean, standard deviation, median, and interquartile range (IQR) of ORR 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
ORR (%)	35.6	20.53	34.8	31.23
OS (month)	18.79	8.31	17.80	11.15

*ORR, Overall Response Rate; OS, Overall Survival; IQR, Interquartile range.

3.2 Relationship Between OS and ORR

We found the Pearson correlation coefficient of R = 0.36 (P < 0.0001, 95% CI 0.25-0.46) between ORR and OS, which indicates a moderate positive correlation, and the correlation is statistically significant. A positive linear relationship between the two variables is evident in the scatterplot in Figure 2, which has an increasing trend from left to right. The plot, specifically, indicates that an increase in ORR is associated with an increase in OS, while a

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

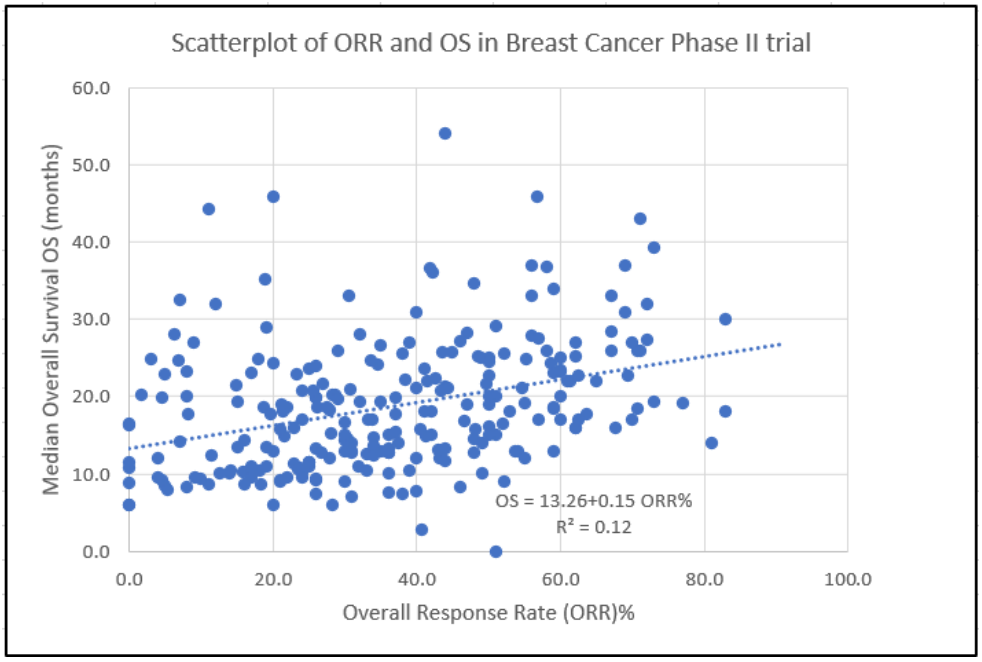

Figure 2: Scatterplot of overall survival and overall response rate of phase II clinical trials of breast cancer. The X-axis displays the overall response rate (ORR) and the Y-axis plots the overall survival (month). The dotted diagonal line indicates linear regression by the Least Squared Method (LSM).

Table 2: Linear relationship between overall survival and overall response rate

	Coefficients	*Standard Error*	*P-value*	*Lower 95% CI*	*Upper 95% CI*
Intercept	13.26	1.04	9.42E-29	11.17	15.28
ORR	0.15	0.02	5.34E-09	0.10	0.20

The predicted linear regression equation is as follows: Median OS = 13.26 + 0.15 × ORR%. The obtained R square value is 0.12, indicates the model accuracy which is 12%. That means ORR can explain 12% of the variability in the dependent variable of OS data. This value indicates that the chosen variable avoids addition of noise while making a significant contribution to the model. The regression model's intercept is 13.26, meaning that the dependent variable (OS) will be 13.26 months when the independent variable (ORR) is set to 0. 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 ORR in Breast Cancer Phase II Trials

Next, we investigated the impact of treatment size on the Overall Response Rate (ORR). The line plot in Figure 3 represents the relationship between the treatment size and the ORR. Here we can see that the p-value is less than 0.05, which indicates that there is significant difference between treatment size 1 and treatment size 2. Furthermore, there is also significant difference in mean between treatment size 2 and treatment size 3 as the p-value here is less than 0.05 also.

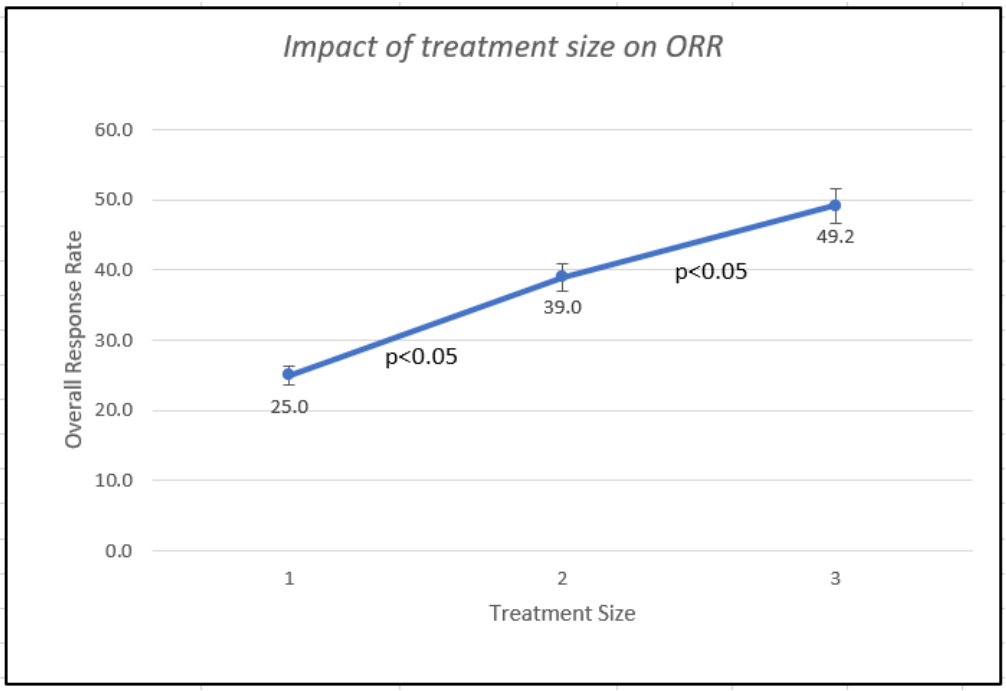

Figure 3: Impact of treatment size on overall response rate (ORR). The treatment size is shown on the X-axis, while the mean ORR value is shown on the Y-axis. Error bars indicate standard error.

.

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

We then investigated the effect of treatment size on the OS. The line plot in Figure 4 addresses the connection between the treatment size and the OS. As the p-value is less than 0.05, so it shows there is a significant difference between treatment size 1 and 2. Then again, there is no significant difference between treatment size 2 and 3 as the p-value is more than 0.05.

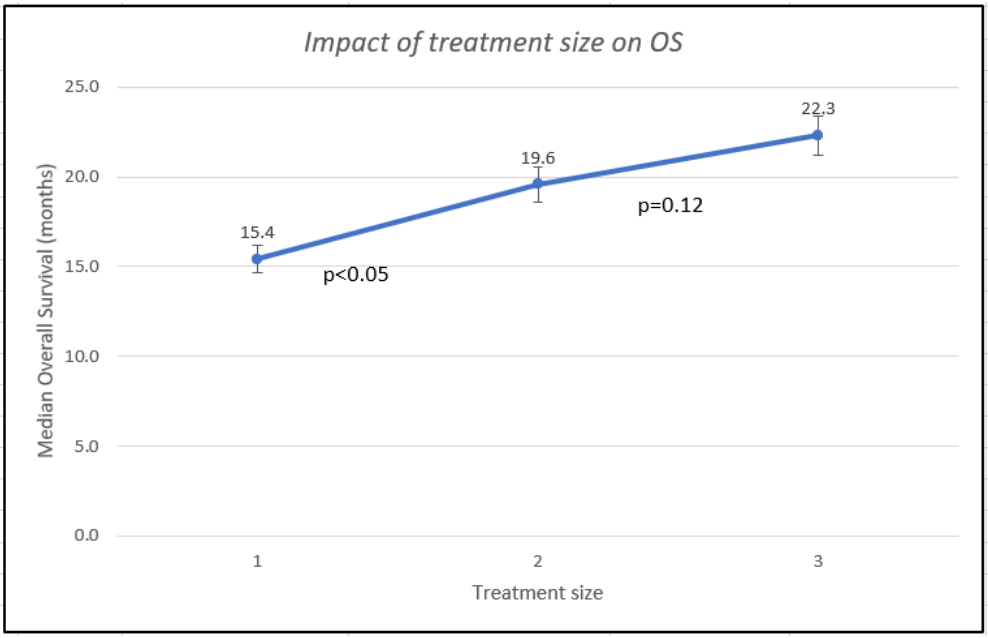

Figure 4: Impact of combination size on overall survival (OS). The X-axis reflects the treatment size, on the other side the Y-axis reflects the mean value of median OS according to treatment size, measured in months. Error bars indicate standard error.

Chapter 4
Discussion

Chemotherapy agents assume a pivotal part in the therapy of breast cancer by repressing tumor development and spread. A few works by focusing on and killing quickly separated cells and some of them are targeted therapy. These targeted therapies are a novel class of anticancer medications with less adverse effects that have been endorsed for the therapy of breast cancer. By and large, targeted drugs are matched with non-targeted treatments to increment remedial viability, which might work on patients' circumstances. Numerous studies have demonstrated how combination therapy can successfully increase the benefits of individual medications. Besides, drug co-administration affects the control of specific cell capabilities. In recent years, there has been a significant spotlight on serious examination into combination cancer treatments. Combination therapy for anticancer therapy offers critical advantages. It enhances efficacy through synergistic impacts and focuses on multiple pathways, further increasing cancer cell kill rates and defeating drug resistance of the cancer cell (Al-Lazikani et al., 2012). This approach considers lower individual medication dosages, lessening toxicity and systemic side effects (Chabner and Roberts, 2005). The primary objective of this study was to evaluate the effectiveness of combination therapy and to analyze the effect of medicine on the overall survival.

In this study, we carried out Pearson correlation to survey the correlation among ORR and OS. It also exhibited how much the connection falls from -1 to +1. The correlation test ($r = 0.36$, $p < 0.0001$, 95% CI 0.25-0.46) shows a modestly positive and highly significant relationship among ORR and OS.

As per Solomon et. al., a study that included 15 clinical trials, log OS hazard ratio correlated with the ORR odds ratio. ORR effect size was positively correlated with the log OS hazard ratio. The weighted Pearson correlation was 0.58, and the weighted linear regression P value was 0.036. Our study revealed that there is decently positive and significant relationship among ORR and OS. More from K Shitara et aI., examined 64 trials, including 10 randomized trials, showed moderately weak correlation of ORR with OS (rank correlation $p = 0.38$ for ORR), which further supports our finding.

As per our analysis, the effect of monotherapy on breast cancer patients was less with regards to mean OS (15.4 month) and mean ORR (25.0%). On the other hand, we observed that there was an ascent with a significant difference in the mean value of both OS (19.6 month) and ORR (39.0%) when a combination of two drugs had been utilized as medicines. Things get better when combination of three drugs are utilized. The mean OS was 22.3 months and mean ORR was 49.2%. This infers that it is more helpful for breast cancer patients to treat with combination that effectively diminish tumor growth and improve overall survival. The result of one randomized study showed that combination of two drugs like Trastuzumab and taxane upgraded clinical results and therapeutic efficacy in contrast with utilizing trastuzumab alone. Surprisingly, the combination prompted synergistic effect at molecular level, which upgraded the hindrance of cell proliferation and induction of apoptosis (Pegram et al., 2001).

Regardless of this, no tremendous difference was distinguished on account of OS among treatment size 2 and 3 groups, with the obtained p-value of 0.12. It is not always the case that combination therapy will be useful in all angle. Although the fact that combination therapy can yield a higher response rate and survival, it can likewise bring upon a few side effects. As per Martin et, aI., the combination of docetaxel, doxorubicin, and cyclophosphamide has shown superior survival rates in early-stage breast cancer patients. Be that as it may, it likewise brought about higher rates of neutropenia and febrile neutropenia contrasted with single-agent therapy (Martin et al., 2005). Another study revealed that the combination of trastuzumab and lapatinib for HER2-positive breast cancer patients demonstrated superior ORR and OS, yet with expanded rate of looseness of the bowels and rash contrasted with monotherapy (Baselga et al., 2012). One randomized study showed that joining cetuximab with afatinib didn't further develop clinical results when contrasted with utilizing afatinib only. Surprisingly, the combination brought about higher toxicity, which prompted a more prominent number of doses decreases and medicines being terminated totally (Goldberg et al., 2020). Conversely, the research showed a significantly more noteworthy increase in the OS and ORR mean values, when three medications are utilized in combination, for example, in treatment strategies containing monotherapy versus dual or triple drug treatment. Basically, it indicates the use of combination therapy, like the simultaneous administration of doxorubicin, with additional agents like immune therapy (e.g., durvalumab, pembrolizumab) and chemotherapy (e.g.,

cyclophosphamide, paclitaxel), which has shown better efficacy compared to monotherapy regarding tumor progression and survival of breast cancer patients.

Moreover, cytotoxic medicines for example, pemetrexed and docetaxel, are utilized in combination. It is thought that the expanded productivity of joining these medications is brought about by a range of mechanism, not which are all straightforwardly connected with the hereditary properties of the tumor cell. In cell line experiments, pemetrexed was demonstrated to expand EGFR phosphorylation while diminishing Akt phosphorylation, making cancer cells receptive to erlotinib. Erlotinib, then again, has been displayed to suppress thymidylate synthase expression and action, making growth cells more defenseless against pemetrexed. Mixes of docetaxel and EGFR inhibitors (neratinib, lapatinib etc.) were researched in cancer cell lines and growth models, and they were found to work on the antiproliferative and cytotoxic efficacy of the singular medications (Aerts et al., 2013). A study by Nabholtz et al. (2003) demonstrated that the mix of docetaxel and doxorubicin brought about a higher overall response rate and longer progression-free survival contrasted with doxorubicin alone in patients with metastatic bosom cancer. Moreover, Gradishar et al. (2004) explored the blend of gemcitabine and paclitaxel, revealing positive response rates and reasonable side effects, demonstrating this regimen as a successful treatment choice.

Lastly our findings infer that utilizing different anti-cancer drug combinations yields higher efficacy endpoints and can possibly increment long-term patient survival. While managing combinations of multiple medications, a t-test could not be performed in light of the fact that there were insufficiently reported clinical studies in our dataset. Nonetheless, more examination incorporating bigger dataset of phase II trials of breast cancer is expected to further investigate to obtain definitive results.

Chapter 5

Conclusion:

We directed this study with the intention on helping medical services experts in the accurate choice of drugs and keeping away from occurrences of error. Our study found direct relationship between the quantity of drugs utilized in treatment and the viability endpoints (ORR and OS). The outcomes were fairly intriguing. The ORR for treatment size 1 and 2 had a p-value of less than 0.05, and that implies there is significant difference in between them. Also, in the event of treatment size 2 and 3, the p-value was less than 0.05, showing a significant difference in these groups. Likewise in the event of overall survival data, the outcomes were to some degree comparable. The OS for treatment size 1 and 2 showed a significant difference between them as the p-value was less than 0.05. Although, in the event of treatment size 2 and 3, as the p-value was more than 0.05, there was no tremendous difference between them. In spite of this, clearly the combination of three anticancer drugs brought about a delayed OS and furthermore improved response rate. More specifically, anticancer medications taken in combination in breast cancer patients are more fruitful than monotherapy. This was found by looking at the efficacy of using a solitary chemotherapy agent alone as opposed to involving it in combination with another medication, for example, immunotherapy or cytotoxic medication as a treatment size 2 or 3.

Future work:

More conclusions and proof regarding patients' response and overall survival in phase II clinical trial of breast cancer will come from more research using a larger set of data. 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 are not more effective. First and foremost, accurate diagnostic and follow-up reports must be kept track of in order to elucidate the effects of drug interactions in patients to get more accurate observation. Aside from that, other clinical studies must be performed to determine the combinations that work best in breast cancer patients.

Reference:

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

Blumenthal, G. M., et al. (2015). Overall response rate (ORR) as a surrogate endpoint in metastatic cancer: FDA analysis of pooled database of prospectively planned studies. *Journal of Clinical Oncology, https://doi.org/10.1200/jco.2015.33.15

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

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

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

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

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

Pazdur, R. (2008). Endpoints for assessing drug activity in clinical trials. *The Oncologist*, *13*(S2), 19–21. https://doi.org/10.1634/theoncologist.13-s2-19

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

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

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

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

Al-Lazikani, B., Banerji, U., & Workman, P. (2012). Combinatorial drug therapy for cancer in the post-genomic era. *Nature Biotechnology*, *30*(7), 679–692. https://doi.org/10.1038/nbt.2284

Chabner, B. A., & Roberts, T. G. (2005). Chemotherapy and the war on cancer. *Nature Reviews Cancer*, *5*(1), 65–72. https://doi.org/10.1038/nrc1529

Pegram, M. D., & O'Callaghan, C. (2001). Combining the anti-HER2 antibody trastuzumab with taxanes in breast cancer: Results and trial considerations. *Clinical Breast Cancer, 2*. https://doi.org/10.3816/cbc.2001.s.003

Baselga, J., Cortés, J., Kim, S.-B., Im, S.-A., Hegg, R., Im, Y.-H., Roman, L., Pedrini, J. L., Pienkowski, T., Knott, A., Clark, E., Benyunes, M. C., Ross, G., & Swain, S. M. (2012). Pertuzumab plus trastuzumab plus docetaxel for Metastatic Breast Cancer. *New England Journal of Medicine, 366*(2), 109–119. https://doi.org/10.1056/nejmoa1113216

Martin, M., Pienkowski, T., Mackey, J., Pawlicki, M., Guastalla, J.-P., Weaver, C., Tomiak, E., Al-Tweigeri, T., Chap, L., Juhos, E., Guevin, R., Howell, A., Fornander, T., Hainsworth, J., Coleman, R., Vinholes, J., Modiano, M., Pinter, T., Tang, S. C., … Vogel, C. (2005). Adjuvant docetaxel for node-positive breast cancer. *New England Journal of Medicine, 352*(22), 2302–2313. https://doi.org/10.1056/nejmoa043681

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

Jean-marc A. Nabholtz, M. R. M. (n.d.). *Docetaxel/doxorubicin/cyclophosphamide in the treatment of metastic breast cancer*. Cancer Network. https://www.cancernetwork.com/view/docetaxeldoxorubicincyclophosphamide-treatment-metastic-breast-cancer

New ACS report: Breast cancer mortality continues three decade decline overall, but steeper increases in incidence for women <50 & asian american, Pacific Islanders of all ages. American Cancer Society MediaRoom. (n.d.). https://pressroom.cancer.org/breastcancerfactsandfigures2024

Faruque Azam

Jawat 2nd Draft

Project: Jawat 2nd Draft

Project: Jawat

PHAR

Document Details

Submission ID

trn:oid:::1:3050748996

Submission Date

Oct 22, 2024, 3:03 PM GMT+5:30

Download Date

Oct 22, 2024, 3:13 PM GMT+5:30

File Name

Project_Jawat_Alam_Edited_fourth_draft.pdf

File Size

393.8 KB

29 Pages

5,775 Words

34,807 Characters

0% detected as AI

The percentage indicates the combined amount of likely AI-generated text as well as likely AI-generated text that was also likely AI-paraphrased.

Caution: Review required.

It is essential to understand the limitations of AI detection before making decisions about a student's work. We encourage you to learn more about Turnitin's AI detection capabilities before using the tool.

Detection Groups

1 AI-generated only 0%
Likely AI-generated text from a large-language model.

2 AI-generated text that was AI-paraphrased 0%
Likely AI-generated text that was likely revised using an AI-paraphrase tool or word spinner.

Frequently Asked Questions

How should I interpret Turnitin's AI writing percentage and false positives?
The percentage shown in the AI writing report is the amount of qualifying text within the submission that Turnitin's AI writing detection model determines was either likely AI-generated text from a large-language model or likely AI-generated text that was likely revised using an AI-paraphrase tool or word spinner.

False positives (incorrectly flagging human-written text as AI-generated) are a possibility in AI models.

AI detection scores under 20%, which we do not surface in new reports, have a higher likelihood of false positives. To reduce the likelihood of misinterpretation, no score or highlights are attributed and are indicated with an asterisk in the report (*%).

The AI writing percentage should not be the sole basis to determine whether misconduct has occurred. The reviewer/instructor should use the percentage as a means to start a formative conversation with their student and/or use it to examine the submitted assignment in accordance with their school's policies.

What does 'qualifying text' mean?
Our model only processes qualifying text in the form of long-form writing. Long-form writing means individual sentences contained in paragraphs that make up a longer piece of written work, such as an essay, a dissertation, or an article, etc. Qualifying text that has been determined to be likely AI-generated will be highlighted in cyan in the submission, and likely AI-generated and then likely AI-paraphrased will be highlighted purple.

Non-qualifying text, such as bullet points, annotated bibliographies, etc., will not be processed and can create disparity between the submission highlights and the percentage shown.

Jawat 2nd Draft

ORIGINALITY REPORT

17%	17%	2%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	dspace.bracu.ac.bd:8080 Internet Source	13%
2	dspace.bracu.ac.bd Internet Source	3%
3	jamanetwork.com Internet Source	2%

Exclude quotes	Off	Exclude matches	< 2%
Exclude bibliography	On		