# Impact of Treatment Size and Molecular Types of Breast Cancer on Response Rate and Progression-free Survival

By

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

School of Pharmacy
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## Declaration

It is hereby declared that

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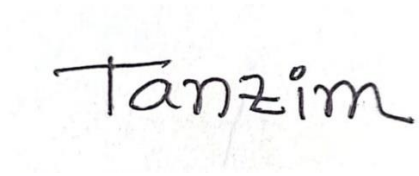

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# Approval

The project titled "Impact of Treatment Size and Molecular Types of Breast Cancer on Response Rate and Progression-free Survival" submitted by Tanzim Mahmud (18146005) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 13th September 2022.

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## Ethics Statement

This study does not involve any human or animal trial.

## Abstract

According to the American Cancer Society's projections, there will be 339,250 cases of breast cancer and 43,250 women will pass away due to this cancer in the year 2022. Moreover, breast cancer is responsible for 15% of all cancer deaths. Cancer treatments are approved in the market after successfully passing through Phase III clinical trials. However, most of the cancer drugs fail in the real world despite showing promising efficacy in the clinical trials. We have collected 95 PFS (progression free survival) and ORR (overall response rate) data of different breast cancer molecular subtypes from 140 extracted articles reporting Phase II clinical trials. We have observed how the PFS and ORR values change in response to the combination size and different breast cancer subtypes as well. We have found a moderate positive correlation (r = 0.57) between PFS and ORR. Also, the PFS and ORR increase when treatment number in combination is increased. The highest ORR and PFS values are observed under HER2+ (Human epidermal growth factor receptor 2- positive) subtype in our research. On the contrary, these values were significantly lower for HR+ (Hormone receptor-positive) and TNBC (Triple negative breast cancer). Our study will certainly help clinical trial researchers to better understand how PFS and ORR vary in response to tumor subtypes and combination size.



**Keywords:** Breast cancer; PFS; ORR; HR+ subtype; HER2+ subtype; TNBC subtype; Combination size

# Dedication

*Dedicated to my beloved parents and wife*

## Acknowledgement

I am grateful to the Almighty Allah for all the blessing and allowing me to successfully complete my undergraduate thesis.

My sincere appreciation goes to my respected supervisor, Faruque Azam, Lecturer, School of Pharmacy, Brac University for encouraging, guiding me during the duration of my thesis. It would have been really impossible for me to complete the thesis without his valuable guidelines.

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## List of Acronyms

| | |
|---|---|
| PFS | Progression Free Survival |
| ORR | Overall Response Rate |
| HER2+ | Human Epidermal Growth Factor Receptor 2-positive |
| HR+ | Hormone Receptor-positive |
| TNBC | Triple Negative Breast Cancer |
| ER | Estrogen Receptor |
| BRCA 1 | Breast Cancer Gene 1 |
| BRCA 2 | Breast Cancer Gene 2 |
| OS | Overall Survival |
| CR | Complete Response |
| PR | Partial Response |

# Chapter 1

## Introduction

Breast cancer is the most commonly diagnosed cancer in women and it has been ranked as the second leading cause of death in women from cancer (Fahad Ullah, 2019). It occurs when the cells present in the breast start growing uncontrollably. It has been diagnosed all over the world but it is more dangerous in the developing countries. It is responsible for 15% of all cancer deaths (Saud Hussein et al., 2021). According to the American Cancer Society's projections, there will be there will be 339250 cases of breast cancer and 43,250 women will pass away due to this cancer in this year 2022 (Siegel et al., 2022). After lung cancer, it is responsible for causing more deaths in women in the United States (Coughlin, 2019). The number of breast cancer patients are progressing at an alarming rate in most of the countries while the breast cancer mortality rate has been gradually decreased in highly developed countries due to diagnosing the disease early as well as excellently developed treatment. Epidemiological studies have established multiple risk factors for breast cancer including family background of cancer, ethnicity, race, different genetic traits along with modifiable exposure, for instance, high amount of alcohol consumption, inactivity, female reproductive factors and different exogenous hormones. The risk of breast cancer is influenced by different factors including menarche at a younger age, parity and first full-term pregnancy at an older age through effects on sex hormone levels for a longer period of time or by different biological mechanisms. It has been suggested by study that the triple negative breast cancer (TNBC) can have a unique etiology. Some occurrences of breast cancer have been linked to genetic variations and mutations in genes that code for proteins involved in DNA repair pathways and the homologous recombination of DNA double strand breaks (APEX1, BRCA1, BRCA2, XRCC2, XRCC3, ATM, CHEK2, PALB2, RAD51) (Coughlin, 2019).

In order to reduce the chances of producing breast cancer in the body, it is necessary to maintain the following recommendations : for the women themselves: taking a child before the age of thirty, continuing the breastfeed for plenty of months, avoid gaining or decrease excess weight after turning thirty, quit or ignore smoking, participating in physical activities, avoid alcohol consumption, for their physicians: avoid prescribing pointless thoracic irradiations or unjustified hormonal treatments (Sancho-Garnier & Colonna, 2019).

There are various types of breast cancers. The type depends on which cell of the breast is turning out into cancer. A breast is composed of three main parts including lobules, ducts, and connective tissue. Majority of the breast cancers originate in the ducts or lobules. With the help of blood vessel and lymph vessel breast cancer can spread outside the breast in the other parts of the body. When the cancer acts in this way, it is regarded to have metastasized. Invasive ductal carcinoma and invasive lobular carcinoma are the two most common types breast cancers. In the invasive ductal carcinoma, the cancer originates in the duct and then spreads into the other tissues while the cancer begins in the lobule in the invasive lobular carcinoma and then spreads out to the nearby breast tissue. The invasive lobular carcinoma results for about 5 to 15% of the total invasive breast cancer (Limaiem et al., 2022).

There are mainly five molecular subtypes of breast cancer including Luminal A, Luminal B, Triple - negative or basal like, HER2 enriched (HER2+) and normal like. Luminal A is a molecular subtype of breast cancer which is hormone-receptor positive (estrogen-receptor and/or progesterone-receptor positive) while it is HER2 negative, and has small amount of protein Ki-67. This subtype of cancer is low-grade, grow slowly and shows the best prognosis. Luminal B is also hormone receptor-positive (estrogen-receptor and/or progesterone-receptor positive) but it can be either HER2 positive or HER2 negative along with a higher amount of ki-67 level. They comparatively grow faster than the Luminal A subtype. However, their prognosis is less good as the Luminal A. The clinical characteristics of triple-negative breast

cancer (TNBC), a particular subtype of breast cancer, that lacks the expression of the ER (estrogen receptor), PR (progesterone receptor) or HER-2 receptors, include high invasiveness, high potential for metastasis, high invasiveness, poor prognosis and proneness to relapse (Yin et al., 2020).

On the other hand, the HER2 enriched breast cancer is hormone receptor negative but HER2 positive. These types of cancers can grow faster in comparison with the luminal types of cancers while having a very poor prognosis. If targeted therapies are given at the HER2 protein, this type of cancers can be treated with success. Again, the normal - like breast cancer has similarities with the luminal A type since it is also hormone receptor-positive, HER2 negative and has short amount of protein Ki - 67. However, it does have a fine prognosis but still its prognosis is not as good as the Luminal A types. The finest survival pattern was found among women with HR+/HER2- subtype (survival rate of 92.5% at 4 years) and then it was HR+/HER2+ (90.3%), HR-/HER2+ (82.7%), and lastly worst survival for triple-negative subtype (77.0%) (Howlader et al., 2018).

5 to 10% of the breast cancer incidents are regarded to be hereditary (J. Casaubon et al., 2022). It means that the cancer has been originated directly from the gene mutation transferred from the parents. The most common is the inherited gene mutation in the BRCA1 (Breast cancer gene one) and BRCA2 gene (Breast cancer gene two). The faulty BRCA1 and BRCA2 genes results in 10% of all the breast cancers. The BRCA mutation can also be responsible for the ovarian cancer. About 35% of hereditary breast cancer is due to the BRCA1 gene mutation (J. T. Casaubon et al., 2021). The chances of establishing breast cancers by the age of 70 is from 44% to 78% due to BRCA1 mutation. Possibilities of male breast cancer by age 70 is from 0.22 to 2.8%. About 25% of hereditary breast cancer is due to the BRCA2 gene mutation. The chances of establishing breast cancers with the BRCA2 gene mutation by the age of 70 is from 31% to 56%. Possibilities of male breast cancer by age 70 is from 3.2 to 12% (J. T. Casaubon

et al., 2021). Other gene mutation like PALB2 can also lead to breast cancer. This gene works together with the BRCA2 gene in repairing the damaged DNA and thus the tumor growth is stopped. When this gene is faulty the possibility of breast cancer increases up to 14% by age 50 and 35% chance by age 70 (Antoniou et al., 2014). The HER2 gene produces a protein called HER2 (human epidermal growth factor receptor 2). This protein is available on the surface of the breast cells and it helps them grow. When the HER2 gene cannot function properly, it produces too many copies of itself and insists the cells to produce excess HER2 protein production leading to uncontrollable cell growth. Majority of the breast cancers are HER2 negative. Besides, another disease named Cowden syndrome throws women at a risk of cancerous and noncancerous breast tumors growths. An inherited mutation of PTEN gene can result in Cowden syndrome. During initial screenings, PTEN mutations were found in 6% of the breast cancer cell lines. Women with a PTEN gene mutation have a 25 to 50% chance of developing breast cancer (Li et al., 1997). Another possible reasons of producing breast cancer is due to an inherited mutation in the TP53 gene that results in Li-Fraumeni syndrome (Aedma & Kasi, 2022). It is a disorder that increases the chance of breast cancer, leukemia, brain tumor etc. Furthermore, the inherited mutation of the ATM gene also increases the risk of breast and pancreatic cancers. Mutation in the other genes like BARD1, CHEK2, NBN, NF1, STK11 can also lead to the development of breast cancer.

The clinical trial is a method by which efficacy and safety of cancer treatments are assessed. The endpoints are the results measured during the study or at the completion of the study in order to determine the success of the given medication and its efficacy. Research studies involving humans are called clinical trials. Clinical trials are a way for doctors to discover novel ways to treat patients and enhance their quality of life. The clinical trials are designed by the researchers in order to cure cancer, determine cancer, control symptoms of cancer as well as adverse effects and side effects from its treatment. Clinical trials are the last stage in a

prolonged process that starts with laboratory research. Researchers spend years analyzing the impact of novel treatments on cancer cells in the lab and on animals before they are tested on humans in clinical trials. Additionally, they research any potential negative consequences. Overall survival (OS), Progression free survival (PFS) and Overall response rate (ORR) are these endpoints for clinical trials testing cancer therapies. The overall survival is the indication of how long a patient live with the given medication in comparison with the patient of the control group. This group refers to the patients either taking different medicine or inactive treatment; also known as placebo. The OS is a strong endpoint in a clinical trial since it requires comparatively a greater number of patients and longer follow ups. It is regarded as a 'gold standard' since it determines the clinical benefits of a cancer drug. On the other hand, the PFS is the determination of the effectivity of the cancer drug. In other word, it shows how long a person can survive without the disease getting worse. The PFS results are found earlier than the OS values in the clinical trial. PFS values also show a sign of diseases control and stabilization. Again, when a drug destroys the tumor of a patients or greatly reduces the size of it; the proportion of these patients in a trial are regarded as ORR. It is the sum of both the complete response (no tumor is observed in patients over a specific period of time) and partial response (the patients with a reduced tumor size over a specific period of time). Developed ORR value refers to the evidence that the drug is working.

In our research, we worked with PFS and ORR of breast cancer and observed how their values change in response to the combination size and different breast cancer subtypes. Besides, we examined the correlation between breast cancer PFS and ORR.

# Chapter 2

# Methods

## 2.1 Efficacy Endpoint

The endpoints are the results measured during the study or at the completion of the study in order to find out the success of the given medication and its efficacy. The overall response rate (ORR) refers to the sum of the percentage of the patients getting partial or complete response after the treatment. The partial response (PR) is usually a predetermined decrease (usually ≥30%) in the targeted lesion, tumor volume or cancer cell number. On the contrary, the complete response (CR) indicates to the successful patients. CR refers that the patients' tumors have been disappeared after treatment. Overall survival (OS) represents how long a patient survives after receiving the treatment. The progression free survival (PFS) refers to the disease-free time length from receiving the treatment; that a patient is still with the stable disease, without the disease getting worse. However, the PFS and OS are surrogate efficacy measures for the OS.

## 2.2 Data Source and Selection Criteria

The PFS and OS values were collected from the subset of data reported by Azam and Vazquez (Azam & Vazquez, 2021). On February 16, 2022; breast cancer's PFS and OS data were extracted from the PUBMED using corresponding PMID within the subset of data (Azam & Vazquez, 2021) . There were 140 articles. All the articles already had ORR value in the dataset, however, only 95 article's PFS and OS values were obtained. The extracted PFS values were converted to months if they were found in days in the articles. The articles which did not contain the PFS or OS as primary or secondary endpoints were disregarded. Moreover, those articles

were rejected in which the PFS values were not found. Finally, on March 22, 95 different articles provided 95 different values of PFS and only 55 articles could provide us with the OS values. Therefore, the collected OS were excluded from the analysis later and all other relevant data were compiled in a spreadsheet for subsequent analysis.

## 2.3 Statistical Analysis

Two-tailed Student's t-test assuming unequal variances was performed when two ORR groups' or PFS groups' mean were compared for a difference at 5% significance level.

The correlation between PFS and ORR was evaluated by Pearson's product-moment correlation.

# Chapter 3

# Results

## 3.1 Relationship between PFS and ORR

Pearson correlation coefficient between PFS and ORR of breast cancer was r = 0.57, indicating a moderate positive correlation exists between PFS and ORR.

The relationship between PFS or ORR is shown below in the figure 3a.

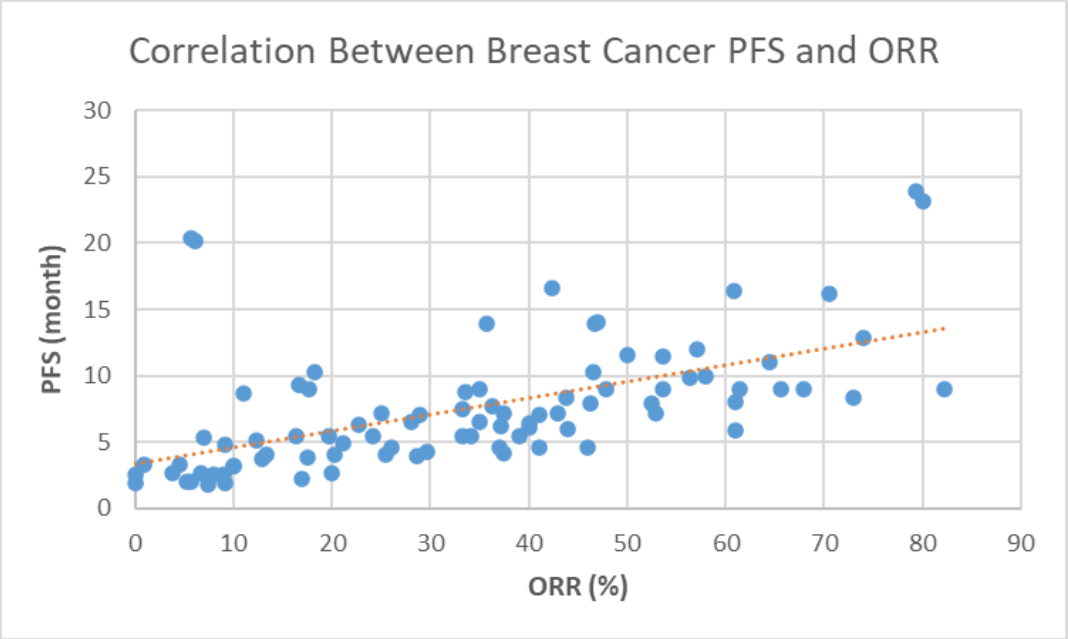


*Figure 3a: Scatterplot of PFS and ORR of Breast Cancers*

Positive correlation means PFS increases when there is an increase in the ORR. On the contrary, PFS decreases if there is a decrease in the ORR.

## 3.2 Impact of Combination Size on PFS and ORR

The ORR and PFS values reported in Figure 3b and 3c, respectively, binned according to combination size. In Figure 3b, the mean ORR value starts from 24.0% for combination size one. The value has been significantly increased by almost 14% for combination size two and

the mean ORR value of this combination size is 40.7%. The difference between mean ORR values for combination size one and two is statistically significant (p = 0.0001). Likewise, the mean ORR value has been increased for combination size three where the value is 46.2%. However, the difference between the mean ORR of combination size one and three is not statistically significant (p = 0.06). Similarly, the difference between the mean ORR of combination size two and three is not statistically significant as well (P = 0.6).

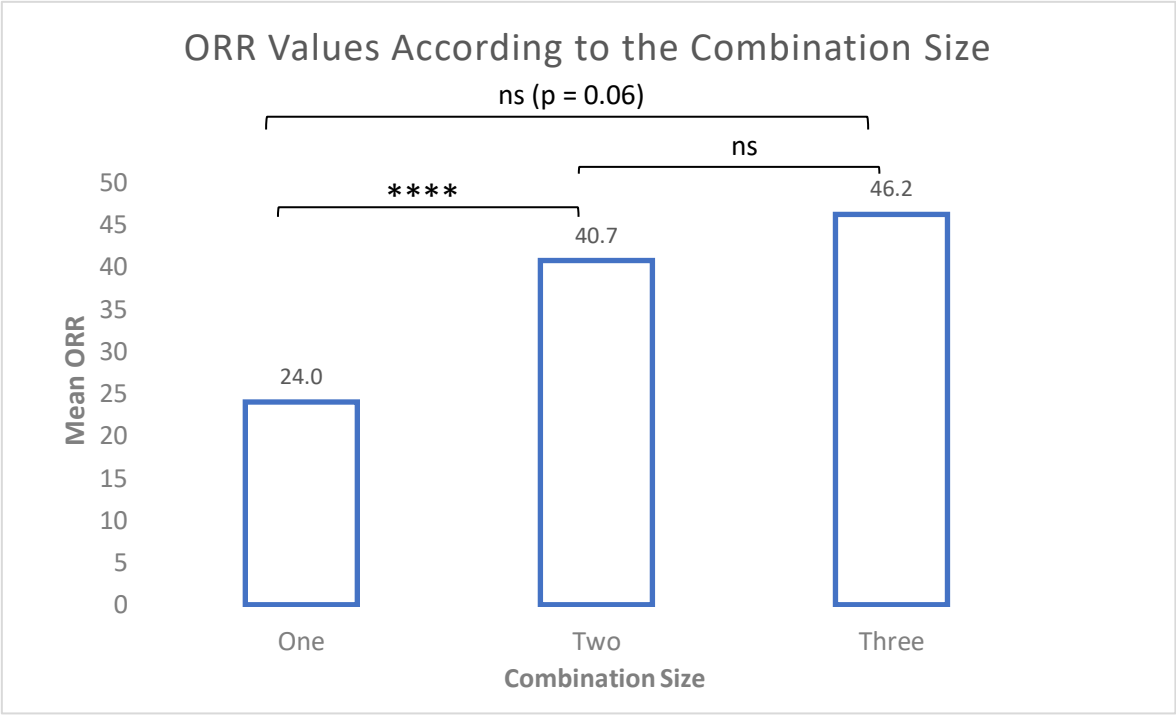


*Figure 3b: Mean ORR Values According to Combination Size*

The star in the graph refers to the statistical significance. The **** in the graph refers to a p value (P ≤ 0.0001) and ns means not significant.

The figure 3c below represents the mean PFS values according to combination size. The mean PFS value starts from 5.6 months for combination size one. However, the mean PFS value has increased in case of combination size two by 2.2 months where the value is 7.8 months, which is statistically significant (p = 0.003). The mean PFS value of combination size three is 13.7 months. However, the difference between the mean PFS of combination size one and three is

statistically significant (p = 0.02). On the contrary, the difference between the mean PFS of combination size two and three is not statistically significant (p = 0.08).

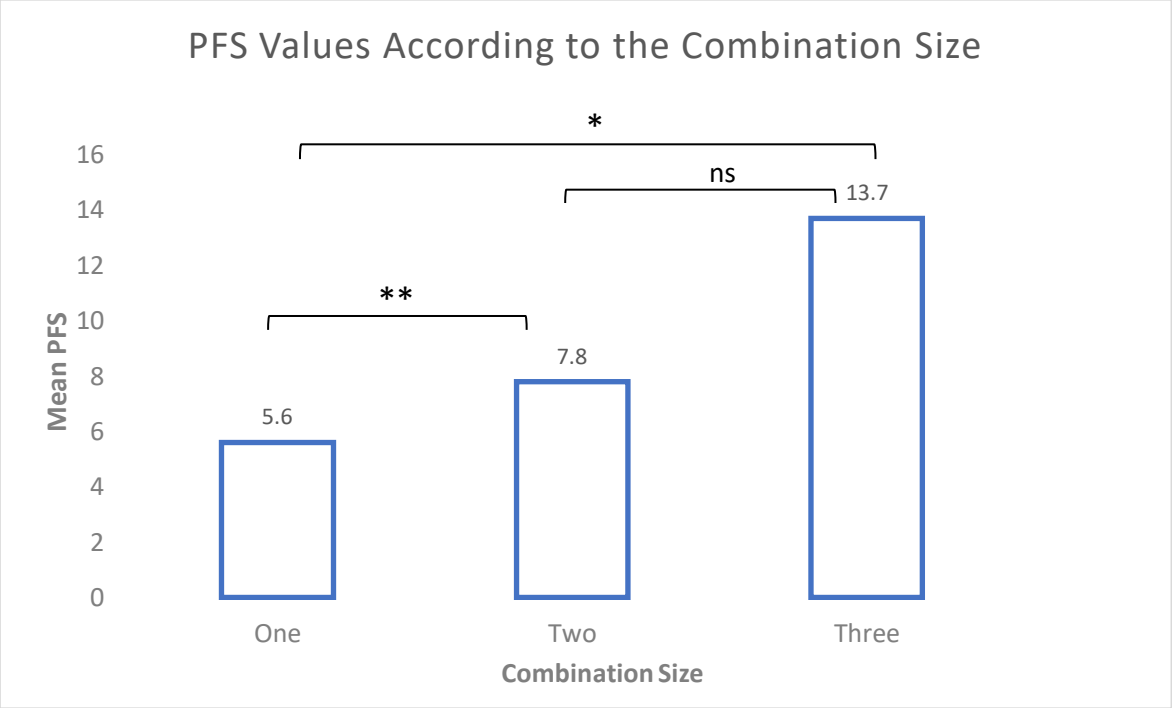


*Figure 3c: Mean PFS Values According to Combination Size*

The star in the graph refers to the statistical significance. The * in the graph means a p value ($P \leq 0.05$). The ** in the graph refers to a p value ($P \leq 0.01$) and ns means not significant.

In both cases, (Figure 3b and 3c), the better ORR and PFS values are observed with an increase in combination size. However, the number of reported clinical trials were decreased with an increase in combination size. The mean PFS and ORR values for combination size four and five could not be determined due to low number of reported clinical trials in the dataset.

## 3.3 Impact of Tumor Subtype on PFS and ORR

The mean ORR and PFS values are presented according to breast cancer subtypes in the figure 3d and 3e, respectively.

In figure 3d, the mean ORR value is 48.0% for HER2+ subtype. The mean ORR value of HR+ subtype is 28.0%. The difference between the mean ORR of HR+ subtype and HER2+ subtype is statistically significant (p = 0.03). Furthermore, the mean ORR value of TNBC subtype is 35.2%. The difference between the mean ORR of HR+ subtype and TNBC subtype is not statistically significant (p = 0.4). In addition to this, the difference between the mean ORR of HER2+ subtype and TNBC subtype is not statistically significant as well (p = 0.07).

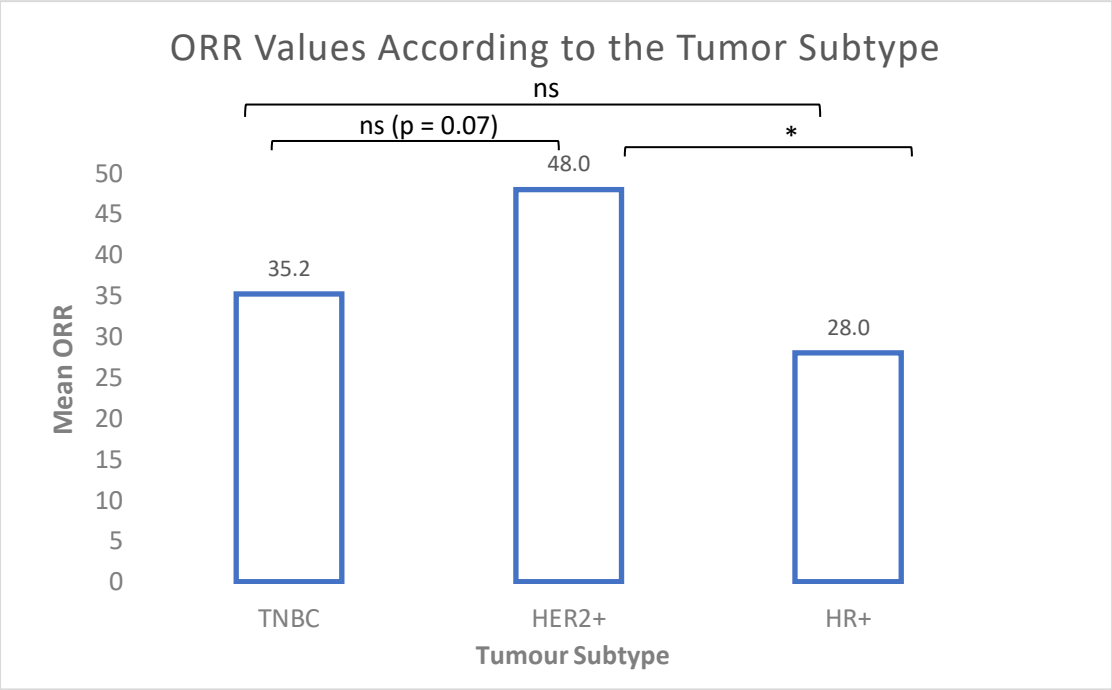


*Figure 3d: Mean ORR Values According to Tumor Subtypes*

The star in the graph refers to the statistical significance. The * in the graph means a p value ($P \leq 0.05$) and ns means not significant.

In figure 3e, the mean PFS value starts from 10.0 months for HER2+ subtypes. The mean PFS value of TNBC subtypes is 5.0 months. Their difference is statistically significant (p = 0.0004). The mean PFS value of HR+ subtype is 7.6 months that is almost 2.6 months greater than that of TNBC. However, their difference is not statistically significant (p = 0.08). In addition, the

mean PFS of HR+ is almost 2.4 months shorter than that of HER2+ subtypes. Their difference is not statistically significant as well (p = 0.18).

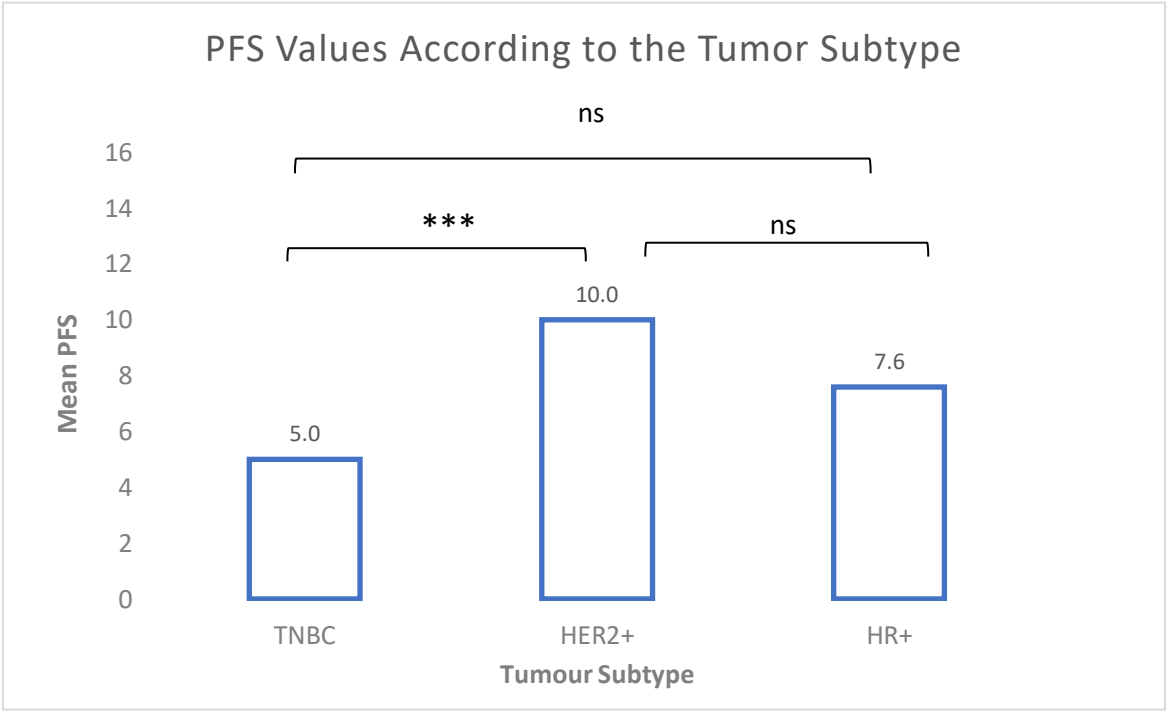


*Figure 3e: Mean PFS Values According to Tumor Subtypes*

The star in the graph refers to the statistical significance. The *** in the graph means a p value ($P \leq 0.001$) and ns means not significant.

In both the two Figures (3d and 3e), we can observe that the mean ORR and PFS values of HER2+ subtypes are higher than that of TNBC and HR+ subtypes. Surprisingly, the mean PFS value of TNBC is less than that of HR+ subtypes, while the mean ORR value of TNBC is greater than that of HR+. Moreover, the number of reported clinical trials is reduced while moving from HER2+ subtypes to TNBC and HR+ subtypes respectively.

# Chapter 4

# Discussion

It is expected that an increase in the ORR value indicates a decrease in the tumor size and ultimately the PFS value will also be increased. So, we can expect a positive linear relationship between PFS and ORR. However, predicting the strength of positive relationship on our context is difficult. From the graph 3a, we can observe the existence of a moderate positive correlation between PFS and ORR indicating that the PFS value is increased with an increase in the ORR value which has pretty much reflected our expectation.

In figure 3b representing the mean ORR values according to the combination size, the mean ORR of combination size one is lesser than that of combination size two and three. It is expected that the ORR will increase when two or three drugs are given in combination. In this figure 3b we can observe the similar picture. The ORR of combination size one is certainly lesser than that of combination size two and three respectively. The ORR is increased while two drugs are given in combination and ultimately better efficacy is achieved for combination size two. The difference between the mean ORR value of combination size one and two is statistically significant indicating that their difference could be determined statistically. The mean ORR has again seen an increase for combination size three. It portrays that ORR is increased while three drugs were given in combination and thus a much better efficacy is achieved under this combination size. From the graph, we have found that an increase in the combination size leads to a better efficacy.

However, it is undetermined how long the value will keep increasing since the mean ORR value could not be obtained for combination size four, five or more due to lower number of reported clinical trials under these combination sizes. Moreover, the difference between the

mean ORR value of combination size two and three could not be determined statistically due to small quantity of dataset present for combination size three. The difference between the mean ORR value of combination size one and three is also not statistically significant due to small quantity of dataset.

In figure 3c representing the PFS values according to the combination size, the PFS achieved for combination size one is certainly lesser than that of combination size two and three. The better efficacy is achieved while two drugs were given in combination and so the mean PFS value becomes higher for combination size two. The difference between the PFS value of combination size one and two is statistically significant indicating that their difference could be measured statistically. The PFS has been increased again for combination size three indicating that a much better efficacy is obtained while three drugs are given in combination. From the figure 3c, it is visible that a better PFS has been achieved with an increase in combination size. However, it is undetermined how long the value will keep increasing since the mean PFS values of combination size four, five or more could not be calculated due to low number of reported clinical trials available under these combination sizes. The difference between mean PFS value of combination size one and three could be measured statistically. However, the difference between the mean PFS of combination size two and three could not be determined statistically due to small quantity of dataset present under combination size three.

In figure 3d portraying the mean ORR values according to breast cancer sub-types, the greatest ORR is obtained for HER2+ subtypes. It indicates that the best efficacy is achieved for HER2+ subtypes and its corresponding survival rate is the highest. The second better efficacy is obtained under TNBC subtypes. The mean ORR value of TNBC is even found better than that of HR+ subtypes. However, it was not expected that the ORR of TNBC would be higher than

that of HR+ subtype since the death rate is actually more frequent for TNBC subtype. But we can see from the figure 3d that the TNBC sub-type carry a higher ORR value than that of HR+ subtype. It has occurred because the graph might not have accurately portrayed the ORR value for TNBC subtypes. The difference between the mean ORR values of HR+ and HER+ subtype could be measured statistically. However, the difference between the mean ORR of HER2+ and TNBC subtype and the difference between the mean ORR value of HR+ and TNBC subtype is statistically not significant due to small quantity of dataset present under HR+ and TNBC subtype.

The figure 3e portraying the mean PFS values according to breast cancer sub-types is showing that the HER2+ subtype is carrying the largest PFS value among the three subtypes. The second better efficacy is obtained for HR+ subtypes. The graph portrays the worst PFS value for TNBC subtypes. In a research, the finest survival pattern was found among women with HR+/HER2- subtype (survival rate of 92.5% at 4 years) and then it was HR+/HER2+ (90.3%), HR-/HER2+ (82.7%), and lastly worst survival for triple-negative subtype (77.0%) (Howlader et al., 2018). Here, the HER2+ subtypes and HR+ subtype has shown excellent survival rate. We can relate our findings to this research since we have also observed the highest progression free survival rate for HER2+ subtype. Furthermore, the TNBC subtype has shown the worst survival rate in our findings as well. The difference between the mean PFS values under TNBC and HER2+ subtypes could be measured statistically. However, the difference between the mean PFS of HER2+ and HR+ subtypes and the difference between HR+ and TNBC subtypes could not be measured statistically due to small quantity of dataset present under HR+ and TNBC subtypes. If more amount of dataset could be extracted, the difference could be found statistically significant.

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