A comparative meta-analysis between Trastuzumab-Deruxtecan (T-DXd) and Pertuzumab, trastuzumab, and docetaxel (PTD) in metastatic HER2-positive breast cancer

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1. Abstract

This meta-analysis investigates and compares the efficiency and safety profiles of Trastuzumab Deruxtecan (T-DXd) and the triplet regimen of Pertuzumab, Trastuzumab, and Docetaxel (PTD) in HER2-positive breast cancer. HER2-positive breast cancer is a subtype of breast cancer characterized by the overexpression of the HER2 protein. It is considered a significant subtype of breast cancer.
data from randomized controlled trials (RCTs), retrospective cohort studies, and real-world observational studies published between 2013 and 2023. Primary evaluating points included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events; moreover, the statistical heterogeneity was evaluated using the I^2 statistic.
The analysis demonstrated that the PTD has superior ORR with an average of 83% across the selected studies, compared to 59.4% for T-DXd. PTD is used as the first-line treatment, while T-DXd is used as a second-line or later-line treatment. The OS showed longer outcomes in the PTD group (median OS up to 57.1 months in CLEOPATRA trial data), while T-DXd exhibited extensive PFS outcomes in the pretreated patients, ranging from 9.3 to 17.8 months. A chi-square statistical analysis showed a significant difference in treatment efficacy favoring PTD ($p < 0.05$), particularly in first-line studies. In terms of safety, PTD was associated with a higher incidence of neutropenia, alopecia, and diarrhea, while interstitial lung disease (ILD) was associated with T-DXd.
This meta-analysis demonstrates the superior efficiency of PTD in the first-line treatment of HER2-positive breast cancer and highlights the significant role of T-DXd in later lines of treatment.

Keywords: HER2-positive breast cancer; Trastuzumab Deruxtecan (T-DXd); Pertuzumab-Trastuzumab-Docetaxel (PTD); metastatic breast cancer; targeted therapy; meta-analysis; progression-free survival (PFS); overall survival (OS); objective response rate (ORR); adverse events; interstitial lung disease (ILD); first-line therapy; second-line treatment; clinical outcomes; drug safety.

2. Introduction

Breast cancer is the most common cancer in the world. In 2020, it is estimated that there were 2.3 million new cases of breast cancer, and 685,000 died (Arnold et al., 2022)1. Based on histological grade, which is a tumor's description based on the abnormality of the tissue and cancer cells under a microscope and the likelihood of the cancer cells growing and spreading, breast cancers can be categorized into biologically and clinically meaningful subgroups (Weigelt et al., 2010)2. The median age of diagnosis for female breast cancer is 62 years old overall, but significantly younger for Black (60 years), Hispanic (57 years), Asian/Pacific Islander API (58 years), and American Indian/Alaska Native AIAN (61 years) women than for White women (64 years), in part due to differences in the age distribution of the population (Giaquinto et al., 2022)3. Breast cancer treatment expenses often increase as the disease stage upon diagnosis advances (Sun et al., 2018)4. Despite the treatment advancements in breast cancer, only 80-90% of women survive for 5 years or more after their primary diagnosis (Cao & Lu, 2016)5. There are 3 most common biomarkers for targeted therapy: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (Walter et al., 2020)6. HER2-positive breast cancer tends to be one of the most aggressive types of cancer because it grows and spreads so fast in the body (Asif et al., 2016)7. About 14% of female breast cancer patients are considered to have HER2-positive breast cancer (Tommasi et al., 2024)8. The survival rate with metastatic HER2-positive breast cancer is almost 5 years, which is considered a low prognosis in HER2 (Loibl & Gianni, 2016)9.

The HER2 gene is responsible for the synthesis of HER2 proteins (DePolo, 2025)10. HER2 proteins are receptors found in breast cells, where their main function is controlling division, growth, and repair (DePolo, 2025)10. However, in HER2-positive breast cancer, the HER2 gene is amplified, leading to uncontrolled division of HER2 proteins (Gutierrez & Schiff, 2011)11. HER2-positive tumors grow faster and spread more easily than HER2-negative ones, making HER2-positive ones of the most aggressive subtypes (Orrantia-Borunda et al., 2022)12. After introducing targeted therapies for HER2-positive, low prognosis has improved (Mercogliano et al., 2023)13. Many different medicines target HER2 receptors in breast cells. Some of them are combined with other medicines to give a higher reaction, and it is a type of targeted therapy (Nichols, 2025)14. There are three main types of targeted therapies for HER2-positive breast cancer: monoclonal antibodies, Tyrosine kinase inhibitors (TKIs), and Anti-body drug conjugates (ADC) (Conte et al., 2024)15.

as the natural antibodies in our bodies (Nichols, 2025)14. Besides targeting the HER2 receptors, they also help fight breast cancer by altering the immune system to attack the cancer cells, so they are also called immune-targeted therapies, where HER2-targeted therapies enhance immune attack on cancer cells through Antibody-Dependent Cellular Cytotoxicity (ADCC), Complement-Dependent Cytotoxicity (CDC), macrophage phagocytosis, and T cell activation. (Nichols, 2025)14. Monoclonal antibodies can be used in different combinations to form a new type of targeted therapy if there is a chemical linkage between them. Trastuzumab, Pertuzumab, and Margetuximab are examples of monoclonal antibodies (Jørgensen, 2024)16.

Pertuzumab can be effective if combined with Trastuzumab and Docetaxel, a chemotherapy drug that inhibits microtubule depolymerization, disrupting cell division and inducing cancer cell death, as a treatment for patients with metastatic HER2-positive breast cancer who have not received any prior treatments or chemotherapy (Jørgensen, 2024)16. Pertuzumab can also be used in different combinations, where it can be used with a chemotherapy medicine alone, but it will be as a complementary treatment for patients with prior treatments (Jørgensen, 2024)16.
Antibody–Drug Conjugates (ADCs) are a type of targeted therapy that is made up of monoclonal antibodies attached to a chemotherapy drug (cytotoxic), so they can work only on cancer cells and reduce damage to healthy cells (Fu et al., 2022)17. After binding the ADC to the cancer cell, the linker is cleaved, specifically in lysosomes to release the cytotoxic drug, which damages the DNA, leading to cell death (Sun, 2024)18.
T-DXd is an ADC medicine. It was approved by the FDA (Narayan et al., 2021)19. T-DXd is a promised targeted therapy for patients with HER2-positive breast cancer who received prior treatment of Trastuzumab and other medicines (Vosoughi et al., 2023)20.
PTD combination is a combined targeted therapy, where Pertuzumab and Trastuzumab are monoclonal antibodies, but Docetaxel is cytotoxic. Although this combination consists of monoclonal antibodies and cytotoxic, it is not an ADC because there is no chemical linker between the antibodies and the cytotoxic (Najjar et al., 2022)21. The FDA approved Pertuzumab for use in combination with Trastuzumab and Docetaxel for patients with metastatic HER2-positive breast cancer who have not received any prior chemotherapy or anti-HER2 therapy for metastatic disease (Blumenthal et al., 2013)22.
This study aligns with the ongoing studies about PTD combination and T-DXd and clarifies all the effects and survival on metastatic HER2-positive breast cancer patients. By reviewing the clinical trials of each medicine, the paper will discuss which medicine has a higher efficiency and which one has fewer adverse effects. In addition, there are not many studies on this specification, suggesting that there is a gap. This paper will be accessible by providing a comprehensive comparison between two efficient medicines for oncologists, pharmaceutical researchers, and policymakers in order to illustrate the guidelines of both medicines.
This research will also align with the Sustainable Development Goal (SDG): Good Health and Well-being, suggesting minimizing the danger and mortality of HER2-positive breast cancer patients.

3. Methodology

I. Definition of HER2 targeted therapy

The potential of HER2-targeted therapy was identified through Randomized Controlled Trials (RCTs), Retrospective Studies, and Real-World Evidence. HER2-targeted therapy is a treatment that targets the HER2 receptor exclusively (e.g., Trastuzumab, Pertuzumab, Lapatinib, etc.) or

as a combination of multitherapy, involving more than one treatment, to enhance the effectiveness of the medicine.

II. Selection Criteria

The studies included in this meta-analysis were selected based on the following criteria:

• Database
A comprehensive search was conducted primarily using Science Direct, PubMed, The Lancet Oncology, and The New England Journal of Medicine for studies published from 2012 onwards.

• Study Design
Eligible studies included randomized controlled trials (RCTs), cohort studies, and retrospective studies that affect the efficiency and safety profile of HER2-targeted therapies in patients with metastatic HER2-positive breast cancer. Each type of study has its purpose: RCTs assign people randomly in groups to see the actual effects, while retrospective studies look back at past data to find patterns and connections.

• Population and Intervention
Only studies involved adult patients diagnosed with metastatic HER2-positive breast cancer. Patients treated with HER2-targeted therapies, including the PTD group and T-DXd only, were included.

• Outcomes
Studies were eligible if they reported at least two of the primary and secondary outcomes: OS, PFS, ORR, or adverse events. However, some studies do not consider the primary outcomes (ORR, PFS, adverse effects). In this case, OS should be considered an alternative measure of treatment efficiency.

• Exclusion Criteria

- ❖ Studies not involving HER2-targeted therapies or focusing on cancers other than breast cancer were excluded.
- ❖ Case reports, conference abstracts, and studies with incomplete or missing data on key outcomes (e.g., ORR or PFS) were excluded unless other relevant data (e.g., OS) were provided.

sizes tend to limit the reliability of conclusions.

III. Statistical analysis

A chi-square test was performed to evaluate whether there was a significant difference in the outcomes of the patients treated with T-DXd and PTD. The null hypothesis states that there is no significant difference in patient outcomes between the two treatments, while alternative hypothesis states that a significant difference exists.

The chi-square statistics were calculated using the formula: $X = \frac{\sum(O-E)^2}{E}$

Where O represents the combination of PTD treatment, while E represents the combination of T-DXd treatment.

Table 1. Overview of Five Key Studies Assessing T-DXd Outcomes

Study	Study Type	N (Total)	Treatment Arms	Median OS (months)	Median PFS (months)	ORR (%)	Key Adverse Events	No. of Patients with ORR	No. of Patients without ORR
(Saura et al., 2023)[23]	Phase II clinical trial	184	trastuzumab deruxtecan (T-DXd) at a dose of 5.4 mg/kg	29.1	19.4	62.00%	neutropenia (27.6%), interstitial lung disease/pneumonitis (15.8%), nausea (19.7%), vomiting (13.5%), and mucositis (15.3%), with 53.8% of patients experiencing grade ≥3 treatment-emergent adverse events (TEAEs) and 17.9% discontinuing treatment due to adverse effects	114.08	69.92
(Meric-Bernstam et al., 2023)[24]	phase II clinical trial	267	T-DXd in HER2+, Low, and 0	21.1	6.9	37.10%	Nausea (55.1%), Anemia (27.7%), Diarrhea (25.8%), Vomiting (24.7%), Fatigue (24.7%), Neutropenia (10.9%), and Interstitial lung disease/pneumonitis (10.5%, with three fatal cases).	99.057	167.943
(Cortés et al., 2024)[25]	Phase III RCT	261	T-DXd vs. T-DM1	52.6	29	78.90%	Interstitial lung disease (16.7%), Pneumonitis (6.6%), Nausea (73%), Fatigue (43%), Neutropenia (33%), Thrombocytopenia (24%), and Alopecia (46%).	205.929	55.071
(Hurvitz et al., 2024)[26]	phase III clinical trial	261	(T-DXd) vs (T-DM1)	NR	15	67.40%	Nausea (72.5%), Anemia (37.5%), Diarrhea (40.0%), Fatigue (27.5%), Vomiting (40.0%), Neutropenia (10.0%), Decreased appetite (20.0%), and Interstitial lung disease/pneumonitis (10.5%)	175.914	85.086
(Harbeck et al., 2024)[27]	Phase 3b/4	263	T-DXd at a dose 5.4 mg/kg	12	17.3	51.70%	Nausea (65.4%), Fatigue (62.4%), Constipation (39.9%), Neutropenia (30.4%), Alopecia (28.5%), Diarrhea (28.1%), Musculoskeletal pain (27.8%), Vomiting (27.8%), Anemia (26.6%), and Upper respiratory tract infection (25.5%).	135.971	127.029

Table 2. Overview of Five Key Studies Assessing PTD Outcome

Study	Study Type	N (Total)	Treatment Arms	Median OS (months)	Median PFS (months)	ORR (%)	Key Adverse Events	No. of Patients with ORR	No. of Patients without ORR
(Blumenthal et al., 2013)[22]	drug approval summary	808	PTD (Pertuzumab + Trastuzumab + Docetaxel) vs. TD (with placebo replacing pertuzumab in the control arm)	NR	12.4	80%	Edema peripheral (23.1), Mucosal inflammation (27.8), Rash (33.7), Dry skin (10.6), Diarrhea (66.8), Constipation (15.0), and Febrile neutropenia (13.8).	646.4	161.6
(Martínez-Sáez & Prat, 2021)[28]	RCT	402	PTD vs. TD (Trastuzumab + Docetaxel + Placebo)	57.1	18.7	80.20%	Edema peripheral (23.1), Mucosal inflammation (27.8), Rash (33.7), Dry skin (10.6), Diarrhea (66.8), Constipation (15.0), Febrile neutropenia (13.8).	322.4	79.596
(Gogia et al., 2024)[29]	retrospective	87	PTD	42	15	85.30%	Diarrhea (9.1%), Cutaneous rash (2.2%), Thrombocytopenia (2.2%), Febrile neutropenia (2.3%), and Reversible left ventricular systolic dysfunction (2.3%).	74.211	12.789
(Miles et al., 2013)[30]	RCT	127	PTD vs. Placebo + TD in Elderly Patients	NR	18.5	80.20%	Diarrhea (66.8%), Rash (33.7%), Mucosal inflammation (27.8%), Neutropenia (48.9%), Febrile neutropenia (13.8%), Fatigue (24.9%), and Left ventricular systolic dysfunction (1.2%).	101.854	25.146
(Lee et al., 2022)[31]	Real World	228	PTD	30.3	9.9	86.80%	Neutropenia (27.6%), Febrile neutropenia (9.2%), Diarrhea (3.5%), Nausea (19.7%), Vomiting (13.5%), Mucositis (15.3%), Peripheral neuropathy (8.7%), and Bacteremia (4.8%)	197.904	30.096

4. Results

I. Overall Response Rate (ORR)

The ORR is different in the selected studies evaluating the two treatments. For T-DXd, as shown in Figure 1, the ORR ranges from 37.1% to 78.9%, with an average of 59.42%. On the other hand, as shown in Figure 2, PTD demonstrated ORR ranged from 80% to 86.8%, with an average of 83%. These results suggest a higher rate for the PTD compared to the T-DXd according to the ORR.

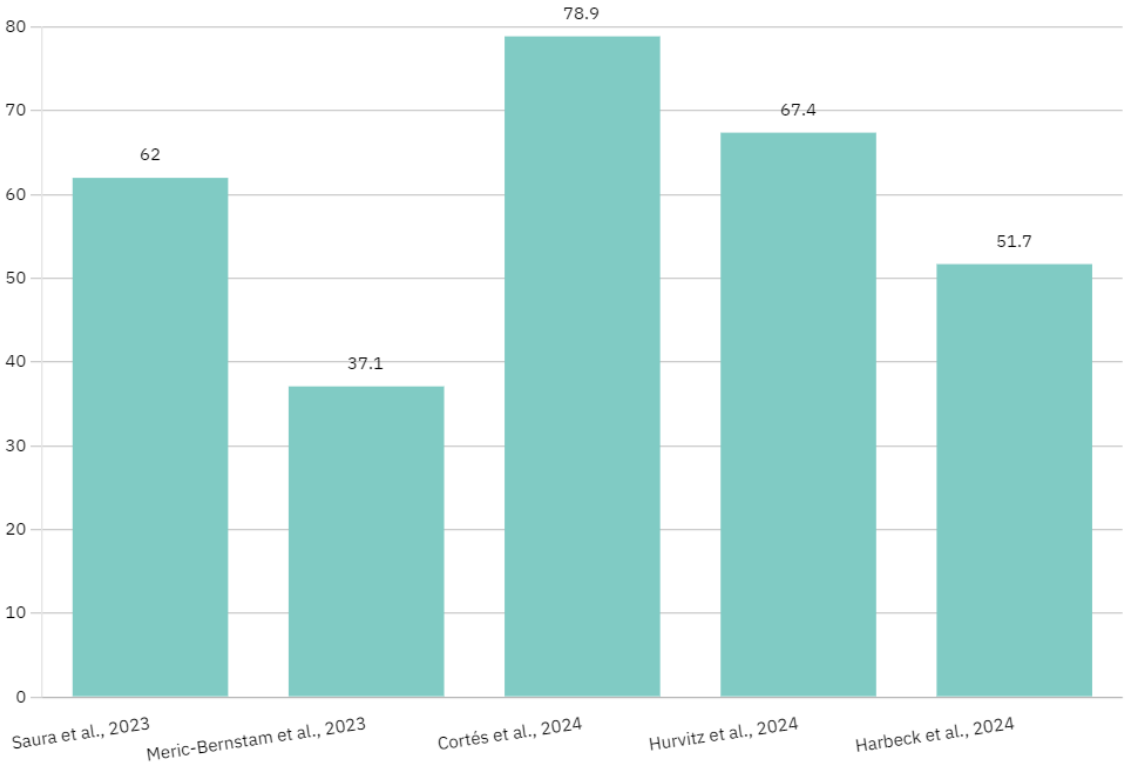

Figure 1: This bar graph demonstrates the ORR outcomes for T-DXd in the studies used in this paper.

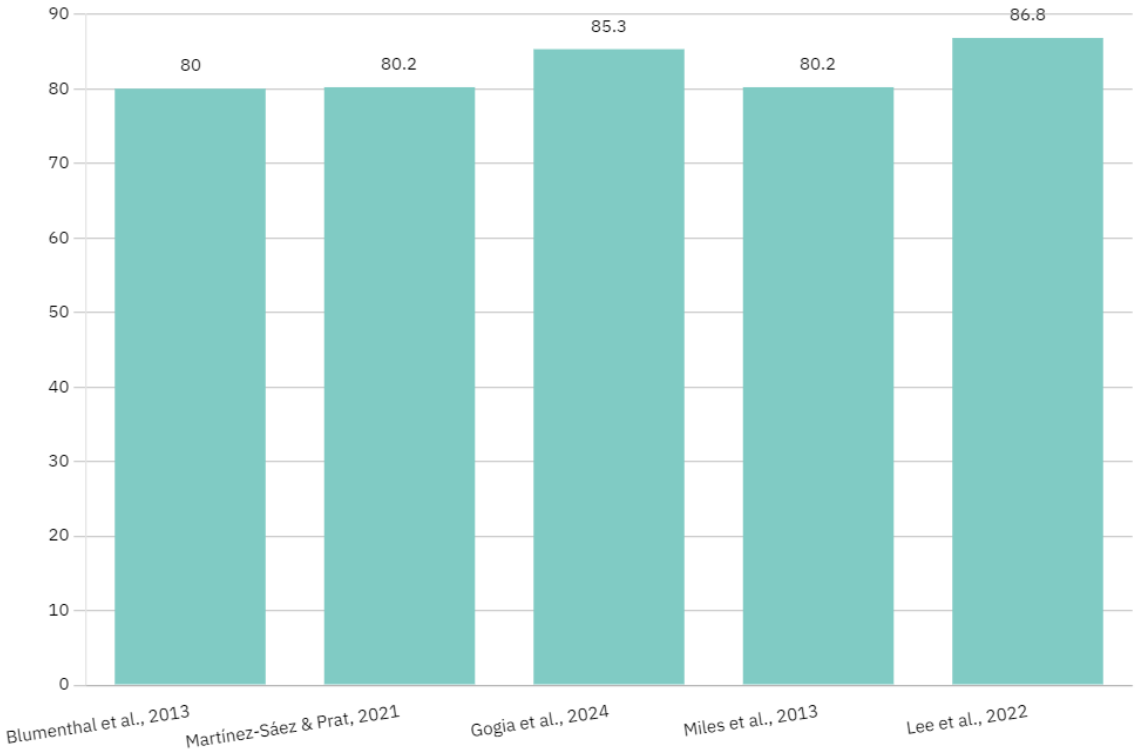

Figure 2: This bar graph demonstrates the ORR outcomes for PTD in the studies used in this paper.

II. Overall Survival (OS) and Progression-Free Survival (PFS)

For the T-DXd, the OS represents a range from 12 months to 52.6 months, while the PFS ranges between 6.9 months to 29 months.

For the PTD, the OS ranges between 30.3 months to 57.1 months and the PFS demonstrates a range between 9.9 months to 18.7 months. These findings ensure that the PTD offers a longer OS, while T-DXd offers a wider range of PFS outcomes.

III. Adverse Effects

Both treatments demonstrated different adverse effects. T-DXd was often associated with nausea, fatigue, anemia, and neutropenia, with ILD (interstitial lung disease). The most common ILD cases were reported in many studies, where 16.7% of patients experienced ILD-related complications. Other adverse events included alopecia, vomiting, diarrhea, and thrombocytopenia.

patients), neutropenia (ranging from 8% to 48.9%), and febrile neutropenia. Additionally, left ventricular systolic dysfunction was observed in some studies but remained below 2.5%.

IV. Statistical Analysis

A chi-square test was performed using Excel and by hand to compare the effects of two treatment outcomes. The analysis yields a Chi-square of 588.0275 with a degree of freedom of 1, which has a p-value less than 0.05. This indicates a statistically significant difference in the two treatment event profiles, so we reject the null hypothesis and support the alternative hypothesis that the efficacy of PTD over T-DXd in terms of response rates.

5. Discussion

The findings clarify the essential differences between the two such efficient medicines. This study fills a gap in the research, where there is no prior study published comparing these two medicines specifically; therefore, it reviews the two medicines according to clinical outcomes (ORR, OS, PFS, and adverse effects).

The findings show the clinical implications of each medicine, where, according to the findings of the ORR, PTD has a higher and more consistent response rate compared to T-DXd. This suggests that more patients experience tumor shrinkage with PTD. The Clinical consequence of this finding represents that PTD is preferable for more tumor reduction, especially in patients with aggressive disease. However, T-DXd may still be beneficial for some patients, especially those who have received prior treatments, where PTD is used as first-line therapy for HER2-positive breast cancer, while T-DXd is usually given after prior treatment therapies.

PTD offers a longer OS in most cases, suggesting patients live longer when treated with PTD. On the other hand, the range of months for T-DXd is shorter than that of PTD. For the PFS, T-DXd has a broader range of outcomes, suggesting that some patients may have prolonged disease control.

life; conversely, severe diarrhea and neutropenia are the most concerning side effects. T-DXd should be avoided in patients with pre-existing lung conditions.

The data strongly supports that PTD has higher efficiency in terms of response rates. However, treatment choice is not just dependent on statistics; but toxicity, patient condition, etc., must be considered.

The cost of the treatments for the patients is another vital factor, where PTD can offer more cost- cost-effectiveness than T-DXd. $1,266,945 is the total cost over the entire course of treatment of T-DXd (Mudumba et al., 2023)32. However, the total cost of PTD treatment in the USA over the entire course is $327,072 (Durkee et al., 2015)33. PTD offers more cost-effectiveness than T-DXd. Looking forward, HER2-positive breast cancer is ready for new advancements. New therapies can be developed with lower costs and fewer side effects by considering the genetic and molecular makeup of each patient. The main target of the treatments is not only about receiving better outcomes but also about improving the quality of life of the patients. However, with the high costs of the available therapies, it is necessary to find a balance between the advanced

progresses, we are not just looking forward to reaching the more developed therapies but also the most affordable ones to facilitate the patients' lives while beating the disease.

6. Conclusion

The treatments for HER2-positive breast cancer continue to evolve. Since there is a wide variety of existing treatments, it is necessary to review these medicines in terms of clinical implications, outcomes, safety profile, etc., in order to select the suitable treatment path for the individual's cancer; furthermore, reviewing the treatments and knowing their limitations is essential to look forward to creating new ones that have fewer limitations and adverse effects. This study aims to solve a limitation in the research by comparing two of the most effective medicines for HER2-positive breast cancer, where there is no primary study has been made to fill the gap.
The findings show that PTD has higher efficiency in terms of ORR and OS, while conversely to T-DXd, which has better outcomes in PFS. A chi-square test is used to evaluate whether there is a significant association between the two medicines and also to ensure the study's conclusion is based on data-driven or random variation. However, the results show that there is a significant difference between the two medicines, which ensures that there is a strong relationship between the variables, not just an occurrence; therefore, it supports the hypothesis of the research and certifies the results.
which medicine has higher outcomes. However, it is considered the first step to see their actual effect on the patients. The study includes their strengths, outcomes, and also their weaknesses to evaluate their limitations and start to work on them. In addition, finding that there is a medicine that has better outcomes than another does not mean that this medicine is better, as there are a lot of other considerations that

should be taken before selecting the better treatment path for the patient, including their genetic makeup and health condition, because of the adverse effects of the treatments; therefore, this low-outcomes medicine may be better for some populations. Moreover, the condition of the medicine has arrangements, as there are medicines that should be taken before others. As the research improves, our chance to reduce the existing limitations increases, and the first step is to proofread the existing data.

7. Acknowledgement

Thanks to Lumiere Education for their help in conducting this paper, especially my mentor, Anne Wei from Wellesley University, and also my writing coach, Gabriel Ortiz.

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