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Cost Effectiveness Analysis Trastuzumab Deruxtecan Versus Trastuzumab Emtansine Pada Pasien Kanker Payudara Metastatik Her2-Positif: *Systematic Review*

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Abstract

HER2-positive breast cancer is one of the subtypes of breast cancer with a poor prognosis and a strong need for effective targeted therapies. Trastuzumab deruxtecan (T-DXd) and trastuzumab emtansine (T-DM1) are two antibody-drug conjugates (ADCs) used as second-line treatments for patients with this condition. To evaluate the cost-effectiveness between T-DXd and T- DM1 through a systematic review of relevant literature. Literature search was conducted using Scopus, PubMed, Science Direct, and Google Scholar databases with the keywords "cost effectiveness analysis" AND "metastatic breast cancer" OR "HER2-positive breast cancer" AND "trastuzumab deruxtecan" AND "trastuzumab emtansine". A total of 521 articles were identified, but only 4 met the inclusion criteria. T-DXd was considered more cost-effective in high- income countries such as the United States (ICER as low as $13,342/QALY) and Finland (ICER approximately €55,360/QALY), but not in China, where the ICER reached $186,017/QALY,

Keywords**: **Cost Effectiveness Analysis, Metastatic Breast Cancer, Her2-Positive Breast Cancer, Trastuzumab Deruxtecan, Trastuzumab Emtansine

INTRODUCTION

Breast cancer is the most common malignant disease in women. With approximately 2.26 million new cases and 684,996 deaths in 2020 (Sung et al., 2021), breast cancer is the fifth largest cause of death in the world. According to the Global Cancer Observatory, there are estimated to be around 2.3 million new cases and more than 666 thousand deaths due to this disease in the world in 2022. About 15-20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2), causing faster cancer growth and worsening the prognosis (Waks and Winer, 2019). Therefore, therapies that lead to anti-HER2 are recommended as part of the treatment of patients with metastatic breast cancer (MBC) with HER2-positive status.

Trastuzumab is a monoclonal antibody that is a combination of antibodies and chemotherapy drugs designed to deliver the drug directly into cells that overexpress HER2 where the antibodies attach. Trastuzumab emtansine (T-DM1), the first ADC approved for the treatment of HER2 breast cancer was designated as a second-line standard therapy according to the results of the EMILIA and TH3RESA trials (Verma et al., 2012). However, most HER2 breast cancer patients continue to develop the disease despite treatment. Therefore, in 2022 the National Comprehensive Cancer Network (NCCN) recommended Trastuzumab Deruxtecan as a line treatment optionsecond preferred for HER2-positive breast cancer.

Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate (ADC) composed of anti-HER2 antibodies, a cleavage tetrapeptide binder and a novel cytotoxic topoisomerase I inhibitory charge (Ogitani et al., 2016). T-DXd has a very high drug-to-antibody ratio of almost 8, suggesting hope for a more effective therapy. However, the high cost of T-DXd coupled with a large number of patients poses a significant economic burden, making T-DXd unaffordable for the healthcare system. Therefore, researchers are interested in understanding the cost-effectiveness of T-DM1 and T-DXd as second-line therapies in HER2-positive breast cancer patients to determine which treatments can provide clinical benefits at an affordable cost.

RESEARCH METHODS

The method used in this article is a systematic review consisting of search strategies, inclusion and exclusion criteria, data extraction, and study quality assessment.

Search Strategy

The literature search in this systematic review uses databases with high and medium quality criteria, namely Scopus journals, Science Direct, PubMed, and Google Scholar. The keyword used in the literature search using English is "cost effectiveness analysis" AND "metastatic breast cancer" OR "HER2- positive breast cancer" AND "trastuzumab deruxtecan" AND "trastuzumab emtansine". Article selection is also reported in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow. The search strategy identified 521 literature. Title screening and duplicate removal resulted in 32 literature. Abstract filtering yielded 9 literature. Then from the 9 literature values, their feasibility is assessed according to the inclusion criteria. The search was carried out in May-June 2025, where the literature search was limited to the last five years, namely 2020-2025.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria are applied in economic evaluation to obtain relevant literature for systematic review. The search focus uses the PICO (Population, Intervention, Comparison, Outcome) framework which can assist researchers in searching databases and minimize selection bias. Here is the PICO framework for the study.

Aspect	Inclusion Criteria	Exclusion Criteria
Population	Adult female patients diagnosed with HER2-positive metastatic breast cancer who have previously received anti-HER2 therapy and taxane-based chemotherapy.	Patients with HER2-negative breast cancer, non-metastatic breast cancer, or male breast cancer patients.
Intervention	Administration of Trastuzumab Deruxtecan (T-DXd) as second-line therapy following prior anti-HER2 treatment.	Use of T-DXd as first-line therapy or its use in other breast cancer subtypes.
Comparison	Trastuzumab Emtansine (T-DM1) used as a direct comparator in the analysis.	Studies that do not provide a direct comparison between T-DXd and T-DM1.
Outcome	Economic evaluation outcomes including effectiveness and cost parameters such as Quality-Adjusted Life Years (QALYs), Incremental Cost-Effectiveness Ratio (ICER), total costs, and probability of cost-effectiveness.	Studies that do not report economic evaluation data or do not include cost-effectiveness parameters as primary outcomes.

Data Extraction and Data Analysis

Data extraction is used to sort out the data involved in the study, which includes a literature review using several indicators. These indicators include the year of publication (2020-2025). The diseases studied were HER2-positive metastatic breast cancer as well as T-DXd and T-DM1 therapy. The research setting is grouped according to the country's economic status category, namely high-income countries and middle-income countries. The research design included is a modeling-based economic model (*partitioned survival model* or Markov *model*) with a long-term time horizon (*lifetime horizon*). The calculation method used is cost effectiveness analysis with a utility-based approach (QALY) and ICER parameters. Data analysis was conducted by collecting and synthesizing information on the general characteristics of the literature (country of origin, economic status, and target population), methodological characteristics (study design, clinical data sources from the DESTINY-Breast03 trial, econometric approaches, and model assumptions), and estimated economic

burden (ICER value, QALY, total cost of therapy, and willingness-to-pay thresholdused). The analysis focused descriptively on the cost-effectiveness of T-DXd compared to T-DM1 in HER2-positive metastatic breast cancer therapy.

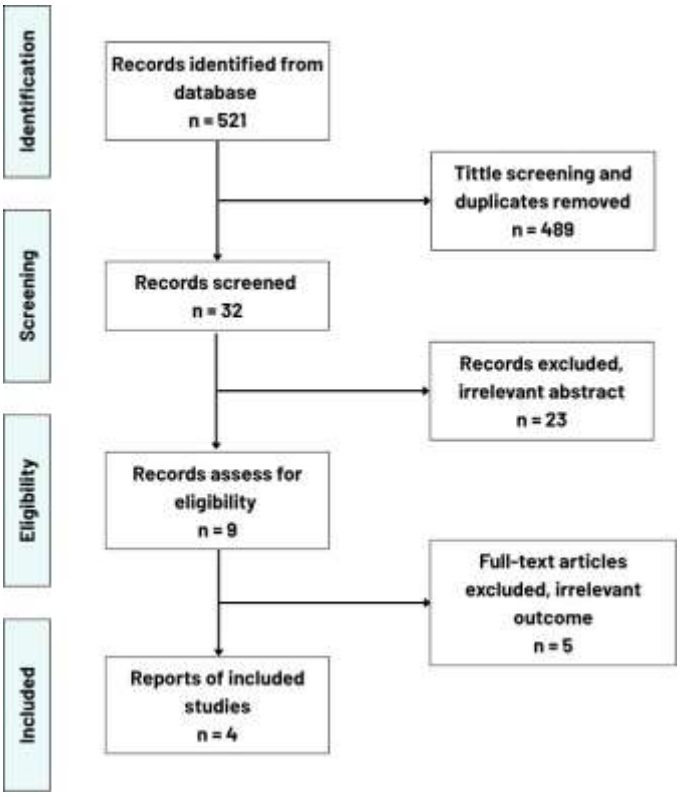
Quality Assessment

The quality assessment has several eligibility criteria based on methodological suitability, reporting transparency, and completeness of data according to the guidelines of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS). The literature is a model-based economic evaluation using data from the DESTINY-Breast03 clinical trial with a Markov model design or partitioned survival model. Each literature reports key parameters such as ICER, QALY, an annual discount method of 3%, as well as one-way sensitivity and probability analysis. The use of standard software such as TreeAge Pro, Microsoft Excel, R, as well as internal validation of models that strengthen the quality of the methodology.

RESULTS AND DISCUSSION

Based on the results of exploration from a number of databases, 521 literature was found that matched the specified keywords. Of these, a gradual selection process is carried out to filter the most relevant literature and meet the inclusion criteria. A total of 4 articles were selected for further analysis in this *systematic review*. The literature selection procedure is systematically depicted in the PRISMA chart in Figure 1.

Figure1. PRISMA chart



Researcher and Year	Title	Research Setting	Research Design	Calculation Method	Cost Perspective	Source of Data	Results
Youwen Zhu et al. (2022)	Trastuzumab deruxtecan versus trastuzumab emtansine for patients with HER2-positive metastatic breast cancer: A cost-effectiveness analysis	United States and China (high-income countries)	Markov model with a 20-year time horizon	Progression-Free Survival (PFS), Progressive Disease (PD), and death states with 6-week cycles over 20 years; estimation of total costs, Life Years (LYs), Quality-Adjusted Life Years (QALYs), and Incremental Cost-Effectiveness Ratio (ICER)	Public payer perspective in each country, including direct medical costs such as drugs, administration, monitoring, supportive care, end-of-life care, and management of adverse events	DESTINY-Breast03 clinical trial and related literature, including clinical guidelines and health technology assessment reports	T-DXd was considered cost-effective in the United States with an ICER of $13,342 per QALY, below the willingness-to-pay (WTP) threshold. In contrast, in China, T-DXd was not considered cost-effective due to higher costs relative to the national WTP threshold, with an ICER of $186,017 per QALY.

Jeroen H.J. Pauliss en et al. (2024)	*Cost-effectiveness model of trastuzumab deruxtecan as second-line treatment in HER2-positive unresectable and/or metastatic breast cancer in Finland*	*Finland (high-income country)*	*Health economic cost-effectiveness model*	*Long-term survival modeling using parametric distributions (e.g., gamma distribution) selected based on statistical goodness-of-fit tests and clinical plausibility*	*Healthcare system perspective, including direct medical costs such as drug acquisition, administration, monitoring, and related healthcare services*	*Survival data from DB-03 and EMILIA clinical trials, drug price databases, and hospital service tariffs in Helsinki*	*T-DXd demonstrated clinical benefits in terms of improved quality of life and increased QALYs compared with ado-trastuzumab emtansine (T-DM1). The analysis showed an incremental cost of €106,800 per patient with an additional 1.9 QALYs gained, resulting in an ICER of approximately €55,360 per QALY.*
Neda Yaghoubi et al. (2025)	*Trastuzumab deruxtecan versus trastuzumab emtansine for HER2-positive metastatic breast cancer: A cost-effectiveness analysis from the Iranian experience*	Iran (upper-middle-income country)	Health economic model based on survival analysis and cost-utility framework	Partitioned Survival Analysis (PartSA) conducted over a lifetime horizon with a 5.8% discount rate	Societal perspective, including direct medical costs (drug acquisition, treatment, and care), non-medical costs (transportation), and indirect costs related to productivity loss	Clinical data from the DESTINY-Breast03 trial, official Iranian cost data sources, utility values, and international literature	T-DXd was considered a cost-effective alternative compared with T-DM1. T-DXd generated 3.59 QALYs with total costs of $261,315, whereas T-DM1 generated 1.89 QALYs with total costs of $258,039. The ICER for T-DXd was

							$1,927 per QALY, below the Iranian willingness-to-pay (WTP) threshold of $2,413 per QALY.
Rahul Mudumba et al. (2024)	*Cost-Effectiveness Analysis of Trastuzumab Deruxtecan Versus Trastuzumab Emtansine for Patients With HER2-Positive Metastatic Breast Cancer in the United States*	United States (high-income country)	Health economic model using partitioned survival simulation	Clinical data from DESTINY-Breast03 including digitized Kaplan–Meier curves fitted with parametric models; hazard ratios (HRs) were applied to estimate comparative treatment effectiveness	U.S. payer perspective	DESTINY-Breast03 clinical trial data, published literature, CMS cost databases, and utility estimates from previous studies	T-DXd provided higher QALYs (approximately 5.09 QALYs) compared with T-DM1 (approximately 3.15 QALYs). However, total treatment costs for T-DXd were substantially higher (approximately $1,266,945) compared with T-DM1 (approximately $820,082). The resulting ICER for T-DXd was approximately $230,285 per QALY, exceeding the commonly accepted WTP threshold of $100,000 per QALY, indicating that T-DXd

							was not cost-effective at this threshold.

Discusion

The results of a systematic review of cost-effectiveness analysis comparing T-DXd with T-DM1 in patients with HER2-positive metastatic breast cancer. The literature analyzed showed variability in outcomes based on geography and economic level of the country. This shows that health technology adoption decisions cannot be universal and must take into account the local context of each country.

From the analyzed literature, it is shown that T-DXd provides higher clinical benefits than T-DM1 based on the results of the DESTINY-Breast03 clinical trial which is the main data source in the four literatures. Research by Zhu et al. (2022) showed a significant increase in QALYs in the United States, while the research of Paulissen et al. (2024) in Finland reported an increase of 1.93 QALYs with T-DXd compared to T-DM1. In line with the research of Yaghoubi et al. (2025) in Iran, where the T-DXd yielded 3.59 QALYs compared to 1.89 QALYs in the T-DM1, reflecting an increase of 1.70 QALYs. The results of the research of Mudumba et al. (2024) also states the highest QALYs for T-DXd (about 5.09 QALYs) compared to T-DM1 (about 3.15 QALYs), showing an increase of almost 1.94 QALYs.

Although T-DXd is considered more cost-effective based on the four literatures, there are differences based on the country's economic level. In high-income countries like America. Together, three of the four studies showed the same results. The results of the study by Zhu et al. (2022) shows T-DXd as cost-effective with an ICER of $13,342 per QALY, well below the WTP threshold. However, research by Yang et al. (2022) and Mudumba et al. (2024) shows higher ICER ($82,112 and $230,285 per QALY). These differences can be caused by variations in model assumptions, cost resources, and calculation methods. In Finland, research by Paulissen et al. (2024) shows an ICER of €55,360 per QALY, this figure is still within the acceptable range for high-income countries, although close to the upper limit of the WTP threshold. Meanwhile, in middle-income countries, the results show different patterns. A study in Iran by Yaghoubi et al. (2025) reported favorable results with an ICER of $1,927 per QALY, well below the national threshold of $2,413 per QALY. This suggests that T-DXd can be cost-effective in middle-income countries, although it needs to adapt prices to suit local purchasing power.

The results of the cost-effectiveness analysis that have been identified are influenced by several factors. First, the difference in T-DXd prices between countries where countries with strong price negotiation systems shows that ICER is more favorable. Second, variations in the WTP threshold between countries (from

$2,413 in Iran to $150,000 in the United States) indicates differences in economic capacity and priority allocation of health resources. And the last is differences in methodology such as time horizons (20 year vs lifetime), discount rates (3& vs 5.8%), and selection of parametric distributions.

CONCLUSION

Based on the results of a systematic review of five literatures, T-DXd is considered more cost-effective than T-DM1 with an increase in QALYs ranging from 1.70 to 1.94 in patients with HER2-positive metastatic breast cancer. However, the cost-effectiveness of T-DXd varies significantly by country's economic setting, with ICERs ranging from $1,927 per QALY in Iran to $305,041 per

QALY in China, reflecting differences in drug prices, WTP thresholds, and evaluation methodologies. Although T-DXd demonstrates high clinical benefit as a second-line therapy, its adoption decision requires contextual considerations that include the economic capacity of the health system, price negotiation strategies, and sustainable access mechanisms. Therefore, an approach tailored to the local conditions of each country is needed, accompanied by the development of real-world evidence to support optimal decision-making in the implementation of this health technology.

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