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Trastuzumab deruxtecan versus trastuzumab emtansine for human epidermal growth factor receptor 2 positive metastatic breast cancer: cost-effectiveness analysis from Iranian experience

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Abstract

Background This study aims to evaluate the cost-effectiveness of Trastuzumab deruxtecan (T-DXd), compared to trastuzumab emtansine (T-DM1) as second-line treatments for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer (MBC) patients in Iran.

Methods A partitioned survival model was developed based on time-to-event data from the DESTINY-Breast 03 trial to evaluate the cost-effectiveness of T-DXd versus T-DM1 from a societal perspective and over a lifetime horizon. Costs and utility inputs were derived from published literature and official Iranian sources. Key outcomes included total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICER). The willingness-to-pay (WTP) threshold of $2413/QALY was applied. One-way sensitivity analyses and probabilistic sensitivity analyses (PSA) were conducted to assess uncertainty.

Results In the base-case analysis, T-DXd yielded 3.59 QALYs for $261,315, while T-DM1 yielded 1.89 QALYs at $258,039, resulting in an ICER of $1,927 per QALY. This value is below Iran's WTP threshold of $2413/QALY. One-way sensitivity analysis identified the unit price of T-DXd as the most influential parameter. PSA results indicated that T-DXd has a 52% probability of being cost-effective.

Conclusion T-DXd represents a cost-effective alternative to T-DM1 as a second-line treatment for HER2-positive MBC in Iran. Its clinical advantages, combined with an ICER below the local WTP threshold, support its adoption in this patient population.

Keywords Breast cancer, Cost-effectiveness, HER2-positive metastatic breast cancer, Price exploration, Targeted therapy

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Background

Breast cancer (BC) is a prevalent and potentially fatal disease, predominantly affecting women worldwide. According to the Global Cancer Observatory, in 2022, an estimated 2,296,840 new cases and 666,103 deaths were attributed to BC globally. In Iran, BC is the second most common cancer and the seventh leading cause of cancer-related mortality. The age-standardized incidence rate of BC in Iranian women was estimated at 30.5 per 100,000 people, leading to 15,492 new cases in 2022, with an age-standardized mortality rate of 11 per 100,000 [1]. The incidence and mortality rates of BC are still increasing and has led to a meaningful increase in healthcare costs, despite recent advances in BC treatments. The annual cost of each BC patient in Iran was estimated at 10,000 USD. Direct medical costs (hospitalization, chemotherapy, radiotherapy) accounted for more than 70% of total costs [2, 3].

Approximately 20% of BC cases overexpress the human epidermal growth factor receptor 2 (HER2), associated with a worse prognosis and poorer overall survival outcomes [4, 5]. As a result, anti-HER-2-directed therapy is recommended as part of the treatment regimens for patients with HER2-positive metastatic breast cancer (MBC). Trastuzumab, a key medication in this approach, is commonly used with other agents [6]. The DESTINY-Breast 03 (DB-03) trial demonstrated that trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC) targeting HER2 [7–9], was superior to Trastuzumab emtansine (T-DM1) in the treatment of HER2-positive MBC [10, 11]. Consequently, the 2022 National Comprehensive Cancer Network guidelines (NCCN) guidelines now recommend T-DXd as a preferred second-line treatment option for HER2-positive MBC [12, 13].

Given the promising efficacy of T-DXd as a novel therapeutic option for MBC, its high cost imposes a significant economic burden, making it challenging for healthcare systems to afford. This study aims to evaluate the cost-effectiveness of T-DXd compared to T-DM1 as second-line treatments for HER2-positive MBC patients in Iran. The economic evaluation of new medicines is imperative for companies seeking to introduce their products into the Iranian market. These studies are crucial for providing patients access to new treatments, particularly for life-threatening conditions such as cancer. By accounting for the unique characteristics of Iran's healthcare system and economic conditions, this research seeks to provide valuable evidence to inform treatment decisions and guide healthcare policy in the region.

Material and methods

This study was conducted in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Additional file 1).

Population and interventions

The only clinical trial directly comparing T-DXd and T-DM1 is the DESTINY-Breast03 (DB03) trial. In DB03, patients with HER2-positive MBC were randomly assigned to receive either T-DXd or T-DM1 intravenously every three weeks at doses of 5.4 mg/kg and 3.6 mg/kg of body weight, respectively. Tumor measurements were taken every six weeks until disease progression or the occurrence of unacceptable adverse events (AEs), at which point treatment was discontinued.

The updated results from the DB03 trial indicated a median follow-up of 28.4 months for T-DXd and 26.5 months for T-DM1. The median progression-free survival (PFS) was 28.8 months for T-DXd compared to 6.8 months for T-DM1, with a hazard ratio (HR) of 0.33 [14].

Due to variations in third-line treatment strategies across countries, patients may receive multiple treatments after disease progression. Third-line treatment was determined based on local oncology expert opinions and guidelines. Additionally, terminal care costs were considered for deceased patients.

In this analysis, the target population consisted of patients with HER2-positive MBC. Patient characteristics were derived from the epidemiological studies on the MBC population in Iran, as shown in Table 1 [15]. These characteristics were used to calculate the model's natural mortality rate and required drug dosage.

Model structure and transition probabilities

We used TreeAge Software (TreeAge Pro 2020®) to develop a partitioned survival analysis (PartSA) model to assess the cost-effectiveness of T-DXd versus T-DM1 as second-line treatments for patients with HER2-positive MBC in Iran.

The model structure and input data were based on the clinical results from the DB03 trial for both interventions. The model includes three health states: progression-free survival (PFS), progressive disease (PD), and death (Additional file 2). This framework illustrates the typical clinical pathway in metastatic cancer and corresponds with the segmented survival models applied in oncology economic analyses. Similar modelling strategies have been employed in other cost-effectiveness studies of metastatic breast cancer [16–19].

A three-week cycle length was used to capture both clinical outcomes and treatment-related costs, which is consistent with the 21-day cycle used in the DB03 trial. The model adopted a lifetime horizon to account for the long-term effects of the treatments and the disease. Based on the model's projections, over a 20-year period, more than 99% of patients are expected to die.

The distribution of patients across the health states in each cycle was determined using time-to-event

Table 1 Summary of model inputs

Model Parameter	Value	Ref	Dist
Clinical data (Survival curves distribution)			
Weibull parameters for OS of T-DXd	Shape = 0.0031, Scale = 1.3497	[14]	Weibull
Weibull parameters for OS of T-DM1	Shape = 0.0048, Scale = 1.35	[14]	Weibull
Weibull parameters for PFS of T-DXd	Shape = 0.014, Scale = 1.1570	[14]	Weibull
Weibull parameters for PFS of T-DM1	Shape = 0.1076, Scale = 0.8481	[14]	Weibull
Weibull parameters for TTD of T-DXd	Shape = 0.0144, Scale = 1.2965	[14]	Weibull
Weibull parameters for TTD of T-DM1	Shape = 0.0821, Scale = 1.0563	[14]	Weibull
Health state utilities			
PFS (SD)	0.7 (0.56–0.84)	[21, 22]	Beta
PD (SD)	0.5 (0.4–0.6)	[21, 22]	Beta
Disutility due to AEs			
Surgery (SD)	-0.23 (0.179–0.26)	[23]	Beta
Radiotherapy (SD)	-0.163 (0.134–0.18)	[24]	Beta
Thrombocytopenia: 42.2 daya (SD)	-0.122 (0.098–0.146)	[18]	Beta
Anemia: 42.9 days (SD)	-0.12 (0.096–0.144)	[18]	Beta
Nausea: 36.2 days (SD)	-0.103 (0.082–0.124)	[18]	Beta
Leukopenia: 42.2 days (SD)	-0.09 (0.072–0.1028)	[18]	Beta
Neutropenia: 40.1 days (SD)	-0.09 (0.072–0.1028)	[18]	Beta
Fatigue: 58.3 days (SD)	-0.29 (0.223–0.348)	[18]	Beta
Aspartate aminotransferase increased 21 days (SD)	-0.157 (0.126–0.188)	[18]	Beta
Interstitial lung disease (ILD): 51.1 days (SD)	-0.13 (0.099–0.15)	[18]	Beta
Grades 3–4 AEs incidence			
Grades 3–4 AEs incidence T-DM1 (%)			
Neutrophil count decreased	3.10%	[14, 25]	-
Anemia	6.50%	[14, 25]	-
White blood cell decreased	0.8%	[14, 25]	-
Nausea	0.40%	[14, 25]	-
Fatigue	0.80%	[14, 25]	-
Increased AST	5.40%	[14, 25]	-
Interstitial lung disease (ILD)	2.70%	[14, 25]	-
Left ventricular ejection fraction (LVEF) decrease	0.40%	[14, 25]	-
Thrombocytopenia	6.10%	[14, 25]	-
Grades 3–4 AEs incidence T-DXd (%)			
Neutrophil count decreased	16%	[14, 25]	-
Anemia	9.3%	[14, 25]	-
White blood cell decreased	6.2%	[14, 25]	-
Nausea	7%	[14, 25]	-
Fatigue	5.8%	[14, 25]	-
Increased AST	0.8%	[14, 25]	-
Interstitial lung disease (ILD)	13.2%	[14, 25]	-
Left ventricular ejection fraction (LVEF) decrease	0.4%	[14, 25]	-
Thrombocytopenia	0.8%	[14, 25]	-
Patient characteristics			
Mean age	49.84 years	[15]	Normal
Average weight (SD)	65 kg (12)	[15]	Normal
Average body surface area (SD)	1.78 m^2 (0.3)	[15]	Normal
Costs ($)			
Unit price of T-DM1 (100 mg)	409 $	Local charge	-
Unit price of T-DM1 (160 mg)	671 $	Local charge	-
Unit price of T-DXd (100 mg)	1982 $	Local charge	-
Unit price of Trastuzumab (150 mg)	88 $	Local charge	-
Unit price of Trastuzumab (440 mg)	216 $	Local charge	-
T-DM1 cost/cycle (21 days)	1152 $	-	-

Table 1 (continued)

Model Parameter	Value	Ref	Dist
T-DXd cost/cycle (21 days)	6019 $	-	-
Cost of PET scan (SD)	345 $ (35)	Local charge	Gamma
Terminal care cost (SD)	3158 $ (345)	Estimated based on local data and expert opinion	Gamma
Model Structure			
Time Horizon	Lifetime	-	-
Discount rate for cost and utility	5.8%	[26]	-

T-DM1 Trastuzumab emtansine, *T-DXd* Trastuzumab deruxtecan, *AEs Adverse Events*, *PFS* Progression-free survival, *PD* Progressive disease

functions derived from the Kaplan-Meier (KM) curves for PFS and OS presented in the DB03 trial. Given the limited follow-up duration in the trial, we extrapolated the KM data for long-term predictions. For this purpose, data points from the KM curves were extracted using Get Data Graph Digitizer software [20] (available at. https://getdata-graph-digitizer.com/). Then, the extracted data were applied to fit five standard parametric survival functions. Five different distributions (Weibull, Exponential, Log-logistic, Lognormal, Gompertz) were used to test Kaplan-Meier fitness. Distribution fitness details are presented in the Additional file 3. The Weibull distributions demonstrated the best fit based on the lowest AIC and BIC values across OS and PFS data, as well as visual fitting for extrapolating the survival curves. RStudio software and the Flexsurv package were used to fit parametric survival models (Table 1).

The model accounts for time on and off treatment in addition to PFS and OS curves. Some patients continue treatment until disease progression, while others discontinue treatment before progression. To accurately capture treatment-related costs, a time-to-treatment discontinuation (TTD) curve derived from the DB03 trial was incorporated into the model.

Health state utilities and costs

The key performance indicators for the model were total costs, QALYs, and incremental cost-effectiveness ratio (ICER).

Utility values were derived from the published literature. For this analysis, we assumed an average health utility of 0.70 for patients with PFS and 0.50 for those with PD [21, 22]. The model also accounted for the utility reduction associated with grade 3/4 AEs. To do this, we calculated the weighted sum of the relevant AEs and their associated disutilities. The QALY loss due to AEs was modelled using the duration of each adverse event (Table 1).

Our analysis, conducted from a societal perspective, considered both direct and indirect costs. Direct medical costs encompassed drug acquisition costs, administration, management of serious AEs -specifically grade 3/4 AEs with an incidence rate of ≥5%-, follow-up, subsequent treatments, and terminal care. Drug acquisition costs were obtained from the official Iranian drug price website (https://irc.fda.gov.ir/nfi), while other costs were based on the Iranian government's official health tariffs. Direct non-medical costs (e.g., transportation) and indirect costs (productivity loss) were included based on national data, ensuring alignment with the societal perspective. Productivity loss is estimated considering the days off work due to different reasons related to disease, such as chemotherapy or hospitalization. The productivity loss for every day is calculated based on the minimum daily wage of an employee in Iran.

The exchange rate used was $1 = 290,000 Iranian Rials. A discount rate of 5.8% per year was applied to both costs and utilities [26]. Additionally, the willingness-to-pay (WTP) threshold, based on Iran's GDP (gross domestic product) per capita in 2022, was set at $2413/QALY [27].

Sensitivity analysis

To assess the robustness of the model and evaluate the uncertainty of variables that may impact the results, we performed both deterministic and probabilistic sensitivity analyses.

A Tornado sensitivity analysis was conducted to explore how changes in the most critical model parameters affect the results. For this analysis, we varied the values of key input parameters within a range of ± 20%.

Additionally, probabilistic sensitivity analysis (PSA) was conducted using Monte Carlo simulations to assess the variation in key model parameters. This allowed us to generate scatter plots and determine the acceptance probability of an optimal strategy. For the PSA, we assigned appropriate probability distributions based on the parameter types, the Gamma distribution was used for costs, and the Beta distribution was applied to probabilities and utility values.

Results

Base-case results

The base-case analysis showed that, over a lifetime horizon, T-DXd provided an additional 1.7 QALYs at an incremental cost of $3,276 compared to T-DM1. This resulted in an ICER of $1,927 per QALY, which is below the WTP threshold of $2413/QALY in Iran. These results

Table 2 Base-case cost-effectiveness analysis of T-DM1 and T-DXd for second-line HER2-positive MBC treatment

Strategy	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER	NMB
T-DM1	258,039	3,276	1.890	1.700	1,927	-253,476
T-DXd	261,315		3.591			-252,648

T-DM1 Trastuzumab emtansine, *T-DXd* Trastuzumab deruxtecan, *ICER* Incremental Cost Effectiveness Ratio, *NMB* Net Monetary Benefit

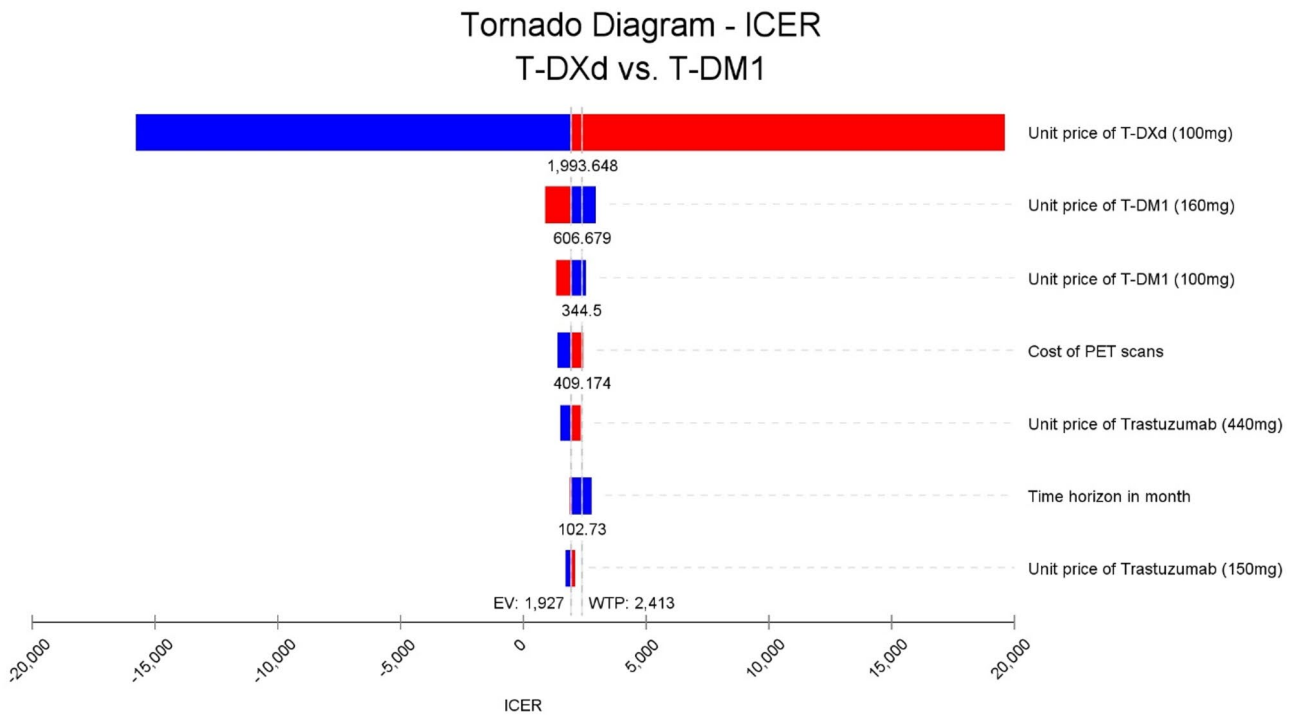

Fig. 1 Tornado diagram showing one-way sensitivity analyses of trastuzumab deruxtecan (T-DXd) strategy compared to trastuzumab emtansine (T-DM1) strategy

suggest that T-DXd may be considered a cost-effective second-line treatment for HER2-positive MBC in Iran (Table 2).

Sensitivity analyses

The results of deterministic sensitivity analysis were presented using a tornado diagram. The analysis revealed that the unit price of T-DXd was the most influential factor on the ICER, with a substantial impact on the results. Other key factors included the unit price of T-DM1, the cost of PET scans, the unit price of Trastuzumab vials, and the study's time horizon, which could cause slight increases in the ICER beyond the WTP threshold (Fig. 1).

When the lower boundary (-20%) was applied to the price of T-DXd, it resulted in more health benefits at a lower cost, making it the dominant strategy over T-DM1. However, when the upper boundary (+20%) was applied, the ICER increased to $24,053/QALY, exceeding the willingness-to-pay threshold of $2413/QALY.

PSA, which involved 1,000 random samples of input variables with associated uncertainty, assessed the robustness of the results. Using the cost-effectiveness acceptability curve and scatter plot, the PSA indicated that, at a willingness-to-pay threshold of $2413/QALY, T-DXd is likely to be cost-effective 52% of the time (Figs. 2 and 3).

Discussion

This study assessed the cost-effectiveness of T-DXd versus T-DM1 for HER2-positive MBC in Iran, providing new insights into the economic viability of T-DXd as a second- or later-line therapy. The results indicate that T-DXd offers an additional 1.7 QALYs at an incremental cost of $3,276 compared to T-DM1, resulting in an ICER of $1,927 per QALY. This ICER is well below the WTP threshold in Iran ($2,413/QALY), suggesting that T-DXd is a cost-effective second-line therapy for HER2-positive MBC in this setting. The study utilized a comprehensive modeling approach that accounted for time on and off treatment, reflecting real-world scenarios where some patients may discontinue treatment before disease progression. This model accurately captured treatment-related costs and outcomes, enhancing the reliability of the findings.

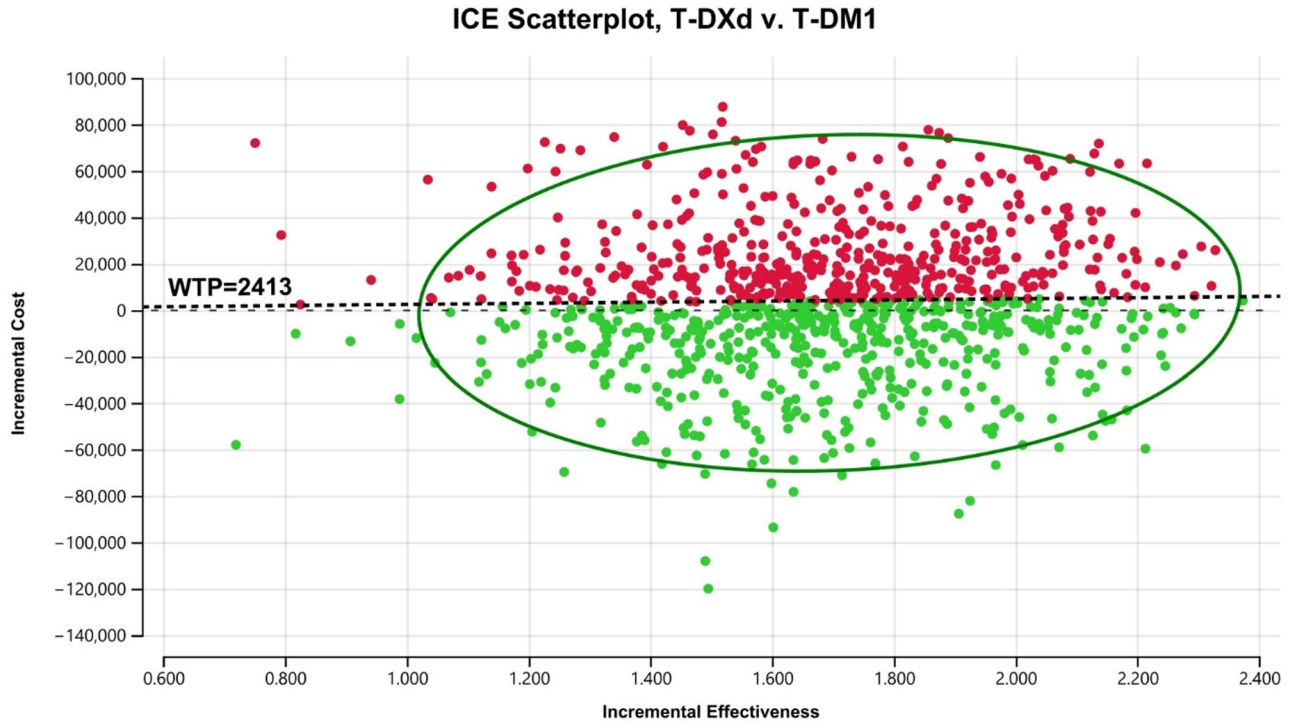

Fig. 2 PSA - scatterplot of cost-effectiveness analysis

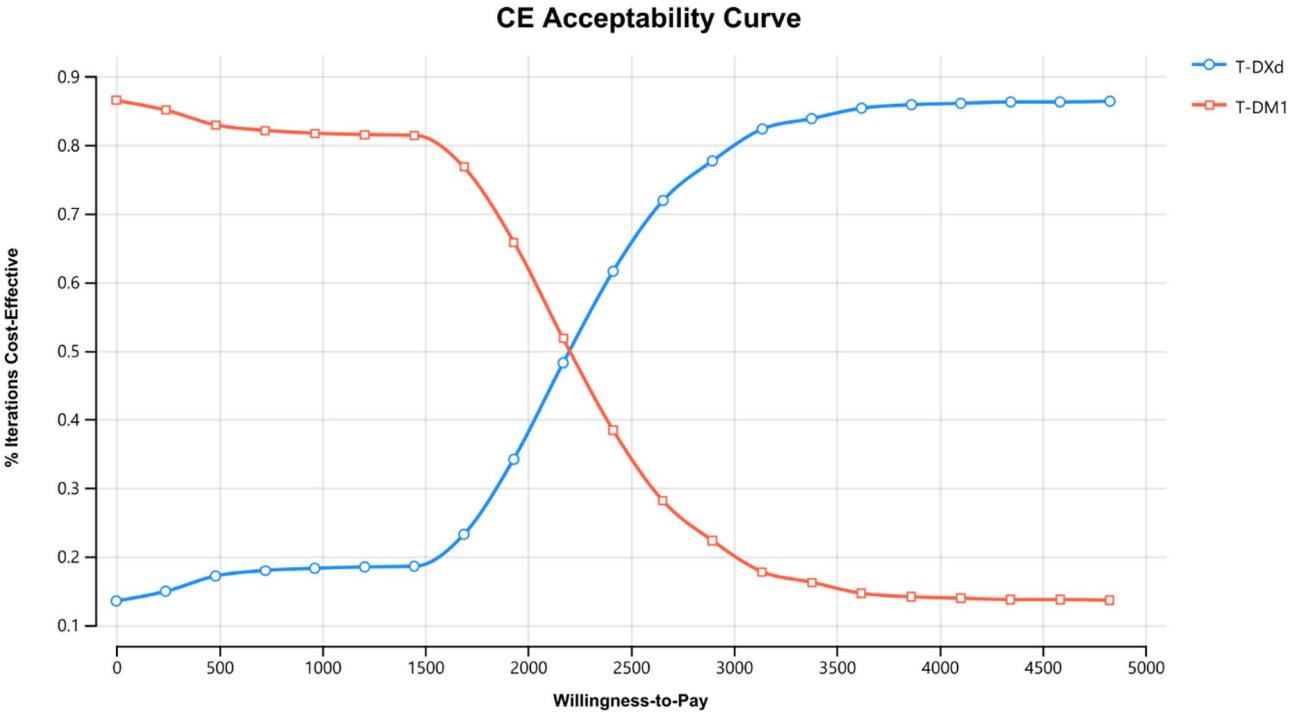

Fig. 3 The cost-effectiveness acceptability curves for T-DXd strategy compared to T-DM1 strategy

When comparing our findings to existing studies, we observe significant variations due to regional economic factors and pricing structures. For instance, the U.S.-based analysis of T-DXd versus T-DM1 utilizing a Markov model and data from the DB03 trial found an ICER of $220,533 per QALY, which far exceeded the U.S. WTP threshold of $150,000 per QALY. This suggests that T-DXd may not be cost-effective in the U.S. under

current pricing structures [19]. This divergence highlights the significant impact of drug pricing on cost-effectiveness outcomes. While acquisition costs for T-DXd substantially influence ICERs in high-income countries, other regions with different healthcare expenditures may achieve more favorable ICERs.

A Chinese study compared the cost-effectiveness of T-DXd and T-DM1 from both U.S. and Chinese perspectives in HER2-positive MBC patients. In China, T-DXd was found to have an ICER of $305,041 per QALY— far exceeding the local WTP threshold, thus deemed not cost-effective under current drug pricing. While in the U.S. T-DXd was a more cost-effective option, providing the ICER of $82,112/QALY [18]. Of interest, the results of a similar publication from a Chinese setting showed that T-DXd was not a cost-effective therapy compared with T-DM1 [28]. These results underscore the importance of considering local economic contexts in cost-effectiveness evaluations, as the affordability of T-DXd remains a challenge despite its clinical benefits.

Supporting our findings, a Finnish study conducted a partitioned survival analysis of T-DXd, yielding an ICER of €55,360 per QALY gained, which falls within the local WTP thresholds of €72,000 and €139,000 [18]. This alignment with European standards strengthens the generalizability of our results, suggesting that T-DXd offers a viable balance between clinical efficacy and economic feasibility across multiple regions. However, it is essential to account for the varying healthcare systems and drug pricing mechanisms in different countries, as these factors can significantly affect cost-effectiveness outcomes. Differences in insurance coverage, reimbursement policies, and healthcare spending priorities can also influence the affordability and accessibility of T-DXd.

Our study further stands out by performing comprehensive sensitivity analyses to examine the robustness of our results across a range of variable inputs. The deterministic sensitivity analysis showed that the unit price of T-DXd significantly affects the ICER, with even small price increases potentially pushing the ICER above acceptable WTP thresholds. This finding is consistent with other studies that have identified pricing as a key determinant of T-DXd's cost-effectiveness. In the probabilistic sensitivity analysis, T-DXd demonstrates a favorable probability of being cost-effective at a typical WTP threshold, reinforcing its potential as a viable second-line therapy option [14]. The implications for healthcare policy in Iran are significant, as adopting T-DXd could influence treatment guidelines and improve patient outcomes. This highlights the need for policies that support cost-effective treatments within the healthcare system.

Clinically, T-DXd's substantial advantage in PFS (28.8 months compared to 6.8 months for T-DM1 in the DB03 trial) suggests notable improvements in quality of life for patients receiving this therapy [14]. This survival benefit aligns with global treatment goals for HER2-positive MBC, prioritizing both life extension and quality enhancement in advanced care stages. Our findings support the inclusion of T-DXd as a preferred therapy option, especially in settings where its cost-effectiveness aligns with healthcare budget constraints.

The broader implications of this study contribute to global cost-effectiveness research on T-DXd and similar high-cost oncology therapies. However, our study has limitations, including the assumptions made in the modelling approach and the use of specific data sources. Utility values were sourced from international studies due to the lack of local data. Therefore, we strongly recommend utilizing nationally specific adjusted utility values for further analysis." Additionally, future research could address these limitations by incorporating real-world evidence and exploring long-term clinical outcomes.

Conclusion

In conclusion, this analysis demonstrates that T-DXd is a cost-effective alternative to T-DM1 for HER2-positive MBC in Iran, from a societal perspective. Its clinical benefits and favorable ICER ($1,927 per QALY) below the local WTP threshold of $2,413/QALY support its cost-effectiveness. The adoption of T-DXd could have important policy implications, highlighting the need for drug price negotiations or subsidies to improve access and affordability.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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Not applicable.

Code availability
Not applicable.

Authors' contributions
All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by SR, BF, and NY. The first draft of the manuscript was written by NY, RA, and YM and subsequently edited by BS and MV. All authors read and approved the final manuscript.

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Data availability
Data is provided within the manuscript and supplementary files.

Declarations

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Consent for publication
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Competing interests
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