Adv Ther (2025) 42:322–333
https://doi.org/10.1007/s12325-024-03033-2

ORIGINAL RESEARCH

Cost-Effectiveness of Trastuzumab Deruxtecan in Patients with Unresectable or Metastatic HER2-Low Breast Cancer Who Have Received Prior Chemotherapy

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Received: August 14, 2024 / Accepted: October 11, 2024 / Published online: November 12, 2024

ABSTRACT

Introduction: In 2021, breast cancer affected 75,619 women in Denmark. Approximately 50% of breast cancers are considered human epidermal growth factor receptor 2 (HER2)-low. The DESTINY-Breast04 (DB-04) trial led to European Medicines Agency (EMA) approval of trastuzumab deruxtecan (T-DXd) as a treatment for patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. Moreover, the Danish Breast Cancer Group guidelines recently included T-DXd as a treatment for HER2-low metastatic breast cancer. This economic evaluation aims to estimate the cost-effectiveness of T-DXd for the approved EMA indication in Denmark.

Methods: A three-state—progression-free, post-progression, and death—partitioned survival model was developed to estimate the cost-effectiveness of T-DXd versus treatment of physician's choice over a lifetime horizon following the Danish Medicines Council guidelines. Clinical data were gathered from the DB-04 trial, and cost and resource use data were sourced from the

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-024-03033-2.

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literature. Sensitivity and scenario analysis were conducted to explore uncertainty.

Results: T-DXd led to 0.78 incremental quality-adjusted life years (QALYs) gained and incurred DKK 621,325 in incremental costs compared to the treatment of physician's choice. This resulted in an incremental cost-effectiveness ratio of DKK 795,181 per QALY gained, which falls below the willingness-to-pay threshold. Sensitivity and scenario analyses showed the robustness of the deterministic result, with T-DXd remaining cost-effective.

Conclusion: Our study demonstrates that T-DXd is a cost-effective treatment for patients with HER2-low unresectable or metastatic breast cancer who have received prior chemotherapy in Denmark.

Keywords: Cost-effectiveness; HER2-low; Metastatic breast cancer; Trastuzumab deruxtecan

Key Summary Points

The results of the DESTINY-Breast04 (DB-04) trial led to a shift towards treating patients with breast cancer with a low level of human epidermal growth factor receptor 2 (HER2) expression (HER2-low).

We used an economic model with DB-04 survival using individual patient data to assess the cost-effectiveness of T-DXd in patients with unresectable or metastatic HER2-low breast cancer.

T-DXd led to 0.78 incremental quality-adjusted life years (QALYs) gained and incurred DKK 621,325 in incremental costs compared to the treatment of physician's choice.

T-DXd is a cost-effective treatment for patients with unresectable or metastatic HER2-low breast cancer in Denmark.

INTRODUCTION

Breast cancer is the second most common cancer globally and is ranked as the fourth leading cause of cancer-related deaths [1]. In 2020, Denmark had the highest cancer rate in the world for men and women combined and was amongst the 10 countries with the highest breast cancer incidence in the world [2]. Between 2017 and 2021, there were 4922 new breast cancer cases per year in the country, leading to 14.3% of all cancer-related deaths in women. At the end of 2021, breast cancer affected 75,619 people in Denmark [3].

Traditionally, breast cancers have been classified as human epidermal growth factor receptor 2 (HER2)-negative—immunohistochemical (IHC) score of 0, 1+, or 2+ with negative results on in situ hybridization (ISH)—or HER2-positive [4]. Patients with HER2-negative breast cancer were treated on the basis of their hormone receptor (HR) status. For patients with HR+/HER2– metastatic breast cancer, standard-of-care (SoC) second-line therapy consisted of either endocrine-based therapy or single-agent chemotherapy. For patients with triple-negative breast cancer, chemotherapy was SoC [5]. The DESTINY-Breast04 (DB-04) trial studied patients with HER2-low advanced breast cancer. HER2-low was defined as an IHC score of 1+ or an IHC score of 2+ with negative ISH results [6]. The results of the DB-04 trial led to a shift towards HER2-low as a treatable tumour subtype and a reclassification of HER2-negative cancers into HER2 IHC0 and HER2-low cancers [4].

DB-04 was a phase III trial investigating trastuzumab deruxtecan (T-DXd) in previously treated patients with HER2-low metastatic breast cancer who had received one or two prior lines of chemotherapy. The DB-04 trial showed that T-DXd improved median progression-free survival (PFS) compared to chemotherapy of physician's choice by 4.8 months (hazard ratio 0.50; 95% confidence interval [CI] 0.40–0.63; $p < 0.001$) and that T-DXd improved median overall survival (OS) by 6.6 months compared to the chemotherapy of physician's choice (hazard ratio 0.64; 95% CI 0.49–0.84, $p = 0.001$) [6].

The HER2-low classification accounts for 45–55% of all breast cancers, and a registry study using data from the Danish Breast Cancer Group (DBCG) showed that 59.2% of breast cancer in Denmark between 2007 and 2019 could be considered HER2-low [7, 8]. Another study, in which patients had mostly metastatic disease, showed that approximately 60% of HER2-negative tumours are HER2-low [9]. The results of the DB-04 trial and the large patient population that could benefit from T-DXd have led to approval from the US Food and Drug Administration and the European Medicines Agency (EMA) for T-DXd as a treatment for adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [10, 11]. The European Society for Medical Oncology (ESMO) guidelines state that T-DXd should be considered as second-line treatment post-chemotherapy for patients with HER2-low metastatic breast cancer [12]. Furthermore, the DBCG guidelines were recently updated to include treatment guidelines for oestrogen receptor (ER)-positive/HER2-low and ER-negative/HER2-low metastatic breast cancer for which the DBCG guidelines recommend T-DXd as second-line treatment post-chemotherapy [13].

This economic evaluation aims to estimate the cost-effectiveness of T-DXd compared to the treatment of physician's choice in Denmark for adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

METHODS

Intervention and Comparators

The model compares T-DXd to the treatment of the physician's choice. In the DBCG guidelines there is no preferred first-line or higher-line chemotherapy, and therefore the treatment of physician's choice was aligned with DB-04. Patients in the treatment of physician's choice group received eribulin (51.1%), capecitabine (20.1%), nab-paclitaxel (10.3%), gemcitabine (10.3%), or paclitaxel (8.2%) [6]. Treatment regimens for T-DXd and each chemotherapy in the treatment of physician's choice are shown in the Online Resource 1.

Model Structure

A three-state partitioned survival model was developed in Microsoft Excel 2016. The three health states were progression-free survival, post-progression, and death (Fig. 1). Health states were mutually exclusive. The proportion of patients in each health state over time was determined using the area under the curve approach utilizing clinical data from the DB-04 trial (data cutoff date Jan 2022). PFS informed the proportion of patients in the progression-free health state, OS informed the proportion of patients in the death state, and the difference between PFS and OS determined the proportion of patients in the post-progression health state.

In Fig. 1, the patients in the progression-free health state at time *t* are represented by the area under the PFS curve, the patients that are alive are represented by the area under the OS curve, and patients that are in the post-progression health state are represented by the

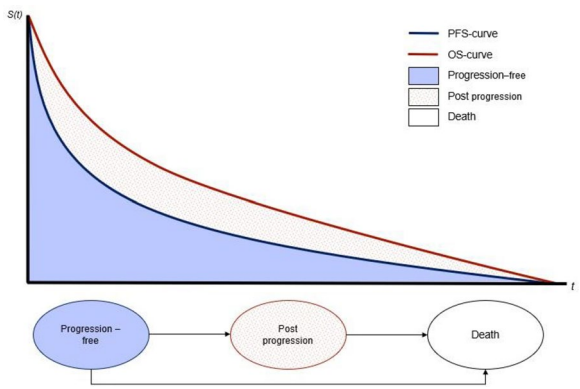

Fig. 1 Partitioned survival model structure showing area under the curve approach for state membership in progression-free, post-progression, and death health states. *PFS* progression-free survival, *OS* overall survival [14]

difference between the area under the OS curve and the area under the PFS curve—i.e. patients alive but not progression-free.

Model Settings

This economic evaluation was aligned with the Danish Medicines Council (DMC) guidelines. Following DMC guidelines, it applied yearly discount rates of 3.5% for both effects and costs and a limited societal perspective that included transport and indirect costs—based on working hours lost—as societal costs [15]. A 3-week cycle length was utilised in line with the treatment regimens for T-DXd and each chemotherapy in the treatment of physician's choice. A willingness-to-pay (WTP) threshold of DKK 969,518 suggested by Svensson et al. 2023 was used [16]. The model used a lifetime horizon—i.e. until < 1% of the patients in the T-DXd arm are alive—of 25 years, applied Danish general population mortality as background mortality, and used half-cycle correction. This study followed the Consolidated Heath Economic Evaluations Reporting Standards 2022 checklist (Online Resource 1) [17].

Clinical Data

The analysis relied on clinical data from the DB-04 trial [6]. Patient characteristics are shown in Table 1. Patients enter the model at a mean age of 56.5 years. The model included adverse events (AEs) with severity of grade 3 or higher that were experienced by 2% or more of patients treated with T-DXd or treatment of physician's choice (Online Resource 1). Interstitial lung disease and left ventricular dysfunction were included in the model regardless of incidence or severity, as they are AEs of special interest [18]. A Danish value set was used to generate treatment-specific health state utility values based on the EQ-5D-5L questionnaire data captured in the DB-04 trial. Patient-reported outcomes (PROs) were assessed at prespecified timepoints per DB-04 protocol [19, 20]. These health state utility values (Table 1) were assumed to include disutilities due to AEs.

We extrapolated the PFS and OS curves by fitting standard parametric models to the clinical data. The best-fitting curves for PFS and OS were selected on the basis of the statistical fit, the median time-to-event compared to that observed in the DB-04 trial, and the visual fit (Online Resource 2) [21]. The resulting PFS and OS curves for T-DXd and treatment of

Table 1 Patient characteristics and health state utility values used in the model

	Model input
Patient characteristic	
Mean age	56.5 years
Proportion female	99.6%
Health state utility values: LSM (95% CI); SE	
Progression-free; T-DXd	0.854 (0.843–0.865); 0.0054
Progression-free; treatment of physician's choice	0.848 (0.831–0.864); 0.0085
Post-progression; T-DXd	0.838 (0.822–0.854); 0.0082
Post-progression; treatment of physician's choice	0.793 (0.765–0.822); 0.0144

CI confidence interval, *LSM* least-square means, *SE* standard error, *T-DXd* trastuzumab deruxtecan

physician's choice are shown in Fig. 2. Time to treatment discontinuation was used to calculate the proportion of patients receiving treatment in the progression-free health state.

Cost and Resource Use Data

All cost inputs are shown in Online Resource 1. The costs of treatment and subsequent treatments were sourced from the Danish Medicines Agency [22]. Cost and resource use for disease monitoring and management were assumed equal for the progression-free and post-progression health states [23]. Vial sharing was assumed to occur 50% of the time and a relative dose intensity was applied. Administration costs, AE-related costs, and cost of resource use were taken from the diagnostic-related grouping tariffs, 2023 [24]. The cost of treating AEs was implemented as a one-off cost in the first cycle of the model. Transport costs and indirect costs were sourced from the DMC catalogue of costs [25]. All costs are reported as 2023 costs (1 DKK = EUR 0.134) [26, 27].

Sensitivity Analyses and Scenario Analyses

In addition to the base case, modelled with the parameters and assumption mentioned above,

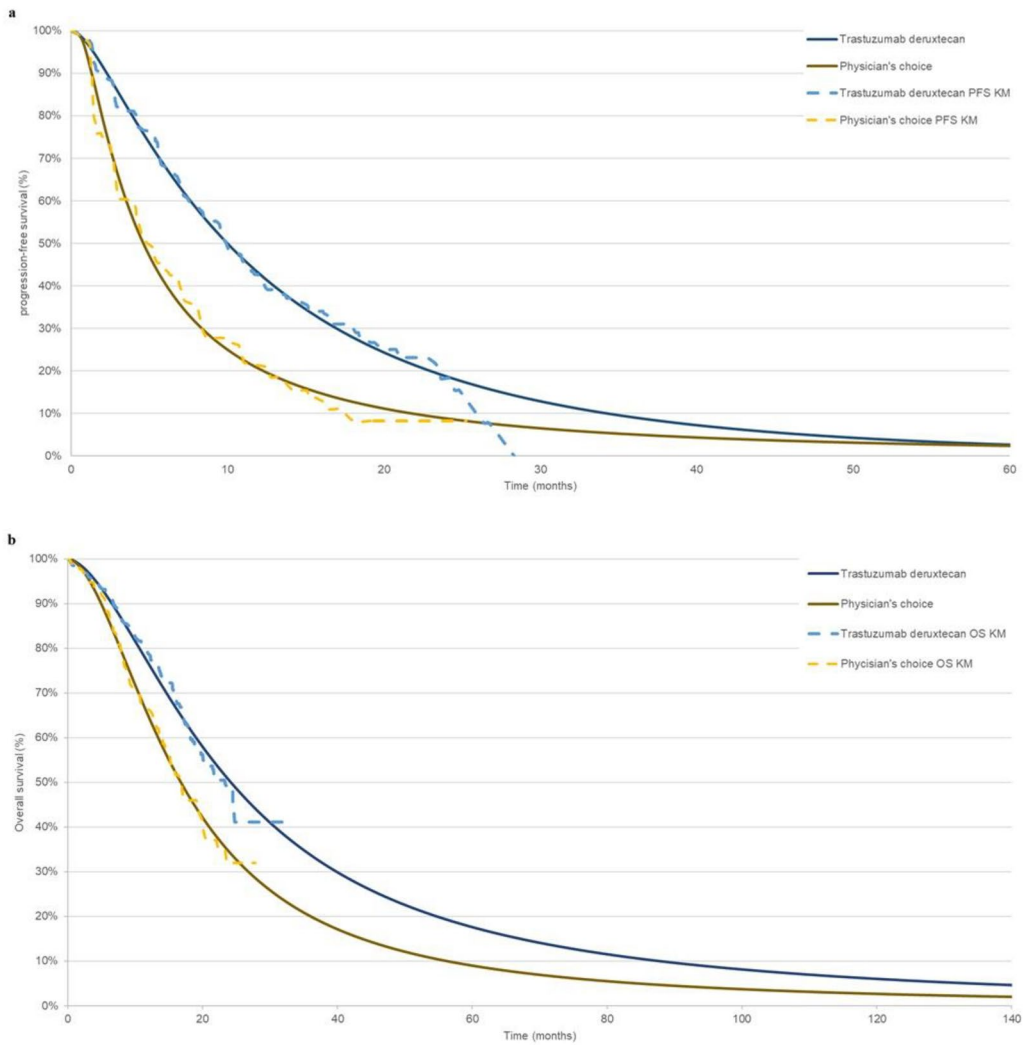

Fig. 2 Long-term predicted survival curves and their respective Kaplan–Meier curves based on the DB-04 trial for PFS (**a**) and OS (**b**). *KM* Kaplan–Meier, *PFS* progression-free survival, *OS* overall survival

a one-way sensitivity analysis (OSA) was performed to assess the sensitivity of the model to individual parameter uncertainty. Parameters included in the OSA were varied using their standard error from the respective data source or by a deviation of plus or minus 20%. A probabilistic sensitivity analysis (PSA) was conducted to estimate the overall parameter and decision uncertainty of the model. The PSA was conducted by running a Monte Carlo simulation with 1000 iterations varying all parameters. A gamma distribution was used to retrieve samples for the cost and resource use parameters and the relative dose intensity. A beta distribution was used for utility values, the incidence of AEs and AE-related hospitalization, the vial-sharing assumption, and the proportion of patients receiving subsequent treatment. Survival distribution parameters for T-DXd and treatment of physician's choice were sampled from a normal distribution using a Cholesky decomposition to account for the correlation between the parameters. Scenario analyses were performed to explore the impact of several model inputs and assumptions of the model. The scenarios explored different choices around discount rates, the time horizon, background mortality, and half-cycle correction. Moreover, they explored the impact of equal proportions of chemotherapy in the treatment of physician's choice, equal subsequent treatment use, disease-specific health state utility values in the post-progression health state, and different vial-sharing assumptions.

Ethical Statement

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Deterministic Results

Patients treated with T-DXd gained a total of 2.46 quality-adjusted life years (QALYs) over a lifetime horizon. Compared to the treatment of physician's choice, this reflects a 0.78 increase in incremental QALYs. Moreover, they gained 0.86 incremental life years (LYs) compared to the treatment of physician's choice. Treatment with T-DXd incurred incremental costs of DKK 621,325 compared to the treatment of physician's choice. The deterministic incremental cost-effectiveness ratio (ICER) was DKK 795,181 per QALY gained and DKK 719,344 per LY gained. These ICERs fall below the WTP threshold of DKK 969,518 per QALY.

One-Way Sensitivity Analysis and Scenario Analysis

The OSA showed that the model is most sensitive to parameter uncertainty in the relative dose intensity applied to T-DXd. Other influential parameters are the health state utility values, the proportion of the subsequent treatments, the assumption around vial sharing, the number of specialist physician visits per cycle, and the incidence of interstitial lung disease (Fig. 3).

Results of the scenario analyses are presented in Online Resource 1. All scenarios resulted in a cost-effective ICER. Applying disease-specific health state utility values in the post-progression health state resulted in an ICER of DKK 908,959 per QALY. Scenarios with 75% and 25% vial sharing resulted in ICERs of DKK 772,387 and DKK 817,975 per QALY, respectively. The scenario that assumed all subsequent treatments are used equally resulted in an ICER of DKK 786,611 per QALY. Other scenarios explored different model settings: using alternative discount rates of 0% and 6% for costs and health gains (DKK 695,448–867,155 per QALY), disregarding background mortality (DKK 763,741 per QALY), and using different time horizons of 10 or 30 years (DKK 790,557–890,296 per QALY). Finally, scenarios comparing T-DXd to one chemotherapy in the treatment of physician's choice (DKK 743,056–877,792 per QALY) and the scenario in which the proportion of each chemotherapy in the treatment of physician's choice was equally distributed, resulting in an ICER of DKK 823,671 per QALY, were explored.

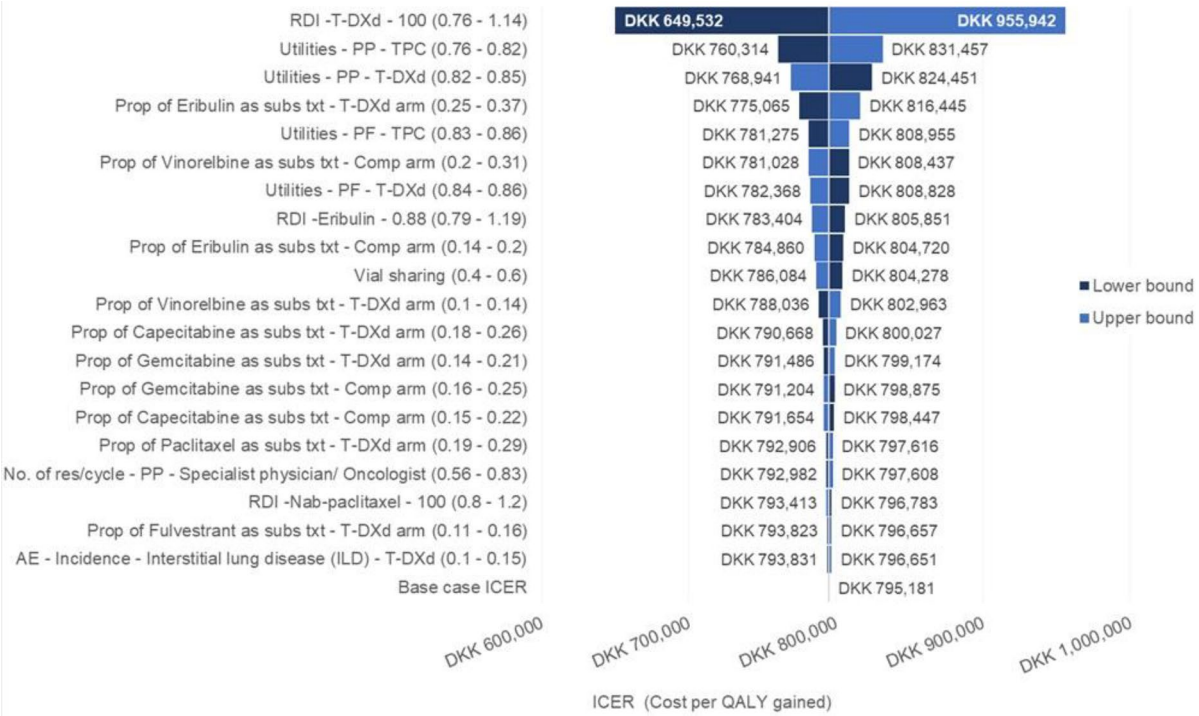

Fig. 3 Tornado diagram showing the impact of parameters on the ICER of T-DXd versus treatment of physician's choice as cost per QALY gained. *AE* adverse event, *Comp* comparator, *ICER* incremental cost-effectiveness ratio, *ILD* interstitial lung disease, *No. of res/cycle* number of resources used per cycle, *PF* progression-free, *PP* post progression, *prop* proportion, *RDI* relative dose intensity, *subs txt* subsequent treatment, *T-DXd* trastuzumab deruxtecan, *TPC* treatment of physician's choice, *QALY* quality-adjusted life years

Probabilistic Sensitivity Analysis

The PSA resulted in a mean ICER—after 1000 iterations—for T-DXd of DKK 776,801 per QALY gained with T-DXd incurring 0.79 incremental QALYs and DKK 611,980 incremental costs compared to treatment of physician's choice (Online Resource 1). Figure 4 shows the cost-effectiveness plane which portrays the incremental costs and QALYs of each iteration in the PSA for T-DXd versus treatment of physician's choice. It shows that T-DXd results in more QALYs gained while incurring more costs compared to the treatment of physician's choice for all iterations. The cost-effectiveness acceptability curve (Fig. 5) shows that T-DXd had a 72.5% probability of being cost-effective compared to the treatment of physician's choice at the WTP threshold of DKK 969,518 per QALY.

DISCUSSION

Recently, HER2-negative breast cancer has been reclassified into HER2-low and HER2 IHC0 cancers [4]. T-DXd is approved by EMA as a treatment for adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy [10]. Moreover, T-DXd is included in the ESMO and DBCG guidelines as recommended second-line treatment for patients with HER2-low metastatic breast cancer. This study evaluated whether T-DXd is a cost-effective treatment for the EMA indication using the Danish perspective. The base case results show that patients on T-DXd can gain 0.78 QALYs over a lifetime horizon, while increasing cost by DKK 621,325 compared to the current treatment

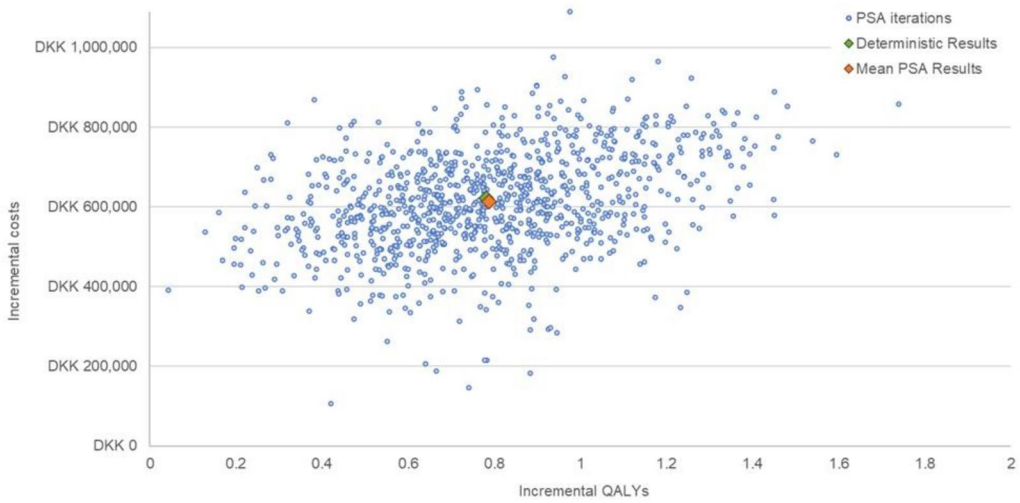

Fig. 4 Cost-effectiveness plane of T-DXd versus treatment of physician's choice. *PSA* probabilistic sensitivity analysis, *QALY* quality-adjusted life year

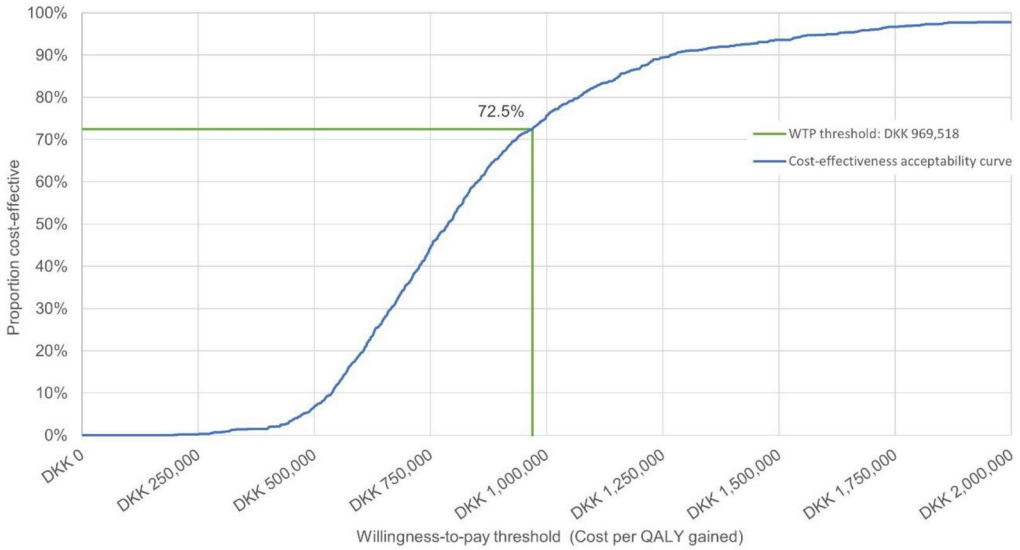

Fig. 5 Cost-effectiveness acceptability curve of T-DXd versus treatment of physician's choice. *QALY* quality-adjusted life year, *WTP* willingness-to-pay

of physician's choice, making it a cost-effective treatment with an ICER of DKK 795,181 per QALY gained.

Our model provides robust estimates of the cost-effectiveness of T-DXd versus the treatment of physician's choice for the approved EMA indication. Most importantly, it relies on clinical evidence collected from a large randomised controlled clinical trial, which provided statistically significant and mature improvement of PFS and OS, as well as data supporting the understanding of the impact on health-related quality of life in the patient population of the EMA indication [6, 20]. The results of the PSA showed that T-DXd is expected to incur more costs and increase total QALYs for patients in all

iterations and that T-DXd has a 72.5% chance of being cost-effective at a WTP threshold of DKK 969,518. These consistent results of the PSA confirm the robustness of the model and support the base case result of T-DXd being a cost-effective treatment compared to the treatment of physician's choice.

The DMC guidelines do not mention a clear WTP threshold [15]. Therefore, this study uses a WTP threshold that was suggested by Svensson et al., which utilised an average discount rate determined by Amgros to calculate a range in which the final estimated threshold falls. The exact calculation was not provided, and could therefore not be checked. However, the provided WTP threshold of DKK 969,518 aligns with a range of ICERs reported in previous DMC assessments in metastatic breast cancer, and was therefore considered the most plausible published WTP threshold [16, 23, 28].

The model was mainly constructed using data from the DB-04 trial and recent literature for its inputs. Nevertheless, the model does have limitations, introduced by several assumptions and decisions that were made for pragmatic reasons:

- To reduce the complexity of the model, subsequent treatment was modelled as one line of therapy, included only one dosing option for each subsequent treatment, and assumed patients to undergo subsequent treatments until death. These simplifications could have resulted in an overestimation of the subsequent treatment costs. In the model, these costs are higher for the T-DXd arm than for the treatment of the physician's choice arm as a result of a higher number of patients in the post-progression health state, as depicted by the differences in area under the OS and PFS curves (Fig. 2). Reducing the duration of subsequent treatments would lower their costs, resulting in less incremental costs for T-DXd, thus rendering it more cost-effective.
- The inclusion of AEs was limited to grade 3 or higher and an incidence of 2% or higher—except for interstitial lung disease and left ventricular dysfunction—possibly underestimating the costs of treating AEs, as less frequent and severe AEs were excluded. In addition, the costs of treating AEs were only applied in the first cycle of the model. This assumption can under- or overestimate these costs by lowering the duration of treatment or overestimating the patients having AEs, respectively. Overall, these limitations are expected to have little influence on the base case results.

The OSA identified influential parameters, and relevant scenarios were explored to estimate the impact of these parameters on the main model outcome. Firstly, since the base case used treatment-specific health state utility values, a scenario with disease-specific health state utility values for the post-progression health state was explored. The result of this scenario analysis showed that T-DXd remained cost-effective with an ICER of DKK 908,959 per QALY gained. Secondly, the proportions of subsequent treatments were shown to be influential parameters. To estimate the impact of these proportions a scenario was performed in which the subsequent treatments were equally distributed, with T-DXd observed to remain cost-effective. Other scenarios in which either of the treatments in the treatment of physician's choice was set to 100%—comparing T-DXd to one chemotherapy—were explored. These scenarios come with the limitation that they assume equal efficacy among all chemotherapies in the treatment of physician's choice, since the efficacy seen in the DB-04 trial was from the treatment mix. Nevertheless, they showed that T-DXd remained cost-effective throughout. Since list and reference prices were used, scenarios that varied cost inputs were deemed unnecessary. Moreover, no scenarios with the relative dose intensity were performed since the OSA showed consistent cost-effectiveness of T-DXd. Lastly, scenarios were run to explore the impact of the proportion of vial sharing. The assumption of 50% vial sharing was used in the base case analysis, as it is known to occur, although its exact extent remains uncertain. Scenarios with 25% and 75% vial sharing showed that an increase in vial sharing decreases the ICER. As more patients will gain access to T-DXd more vial sharing is expected, and with it, T-DXd is expected to become more cost-effective. Previous studies on T-DXd in HER2-low metastatic breast cancer have used PFS and OS

data from the DB-04 trial, but all of them have used pseudo-individual patient data (IPD) generated from published KM curves [29–33]. Using IPD allows for more precise modelling of the survival curves. Additionally, none of the previously published models have used health state utility values based on EQ-5D-5L data captured in the DB-04 trial. This is the first study to incorporate both IPD from the DB-04 trial and health states utility values based on the DB-04 trial.

CONCLUSION

Approximately 60% of HER2-negative metastatic breast cancers are HER2-low, creating the need for a cost-effective treatment for patients. Our study demonstrates that T-DXd is a cost-effective treatment for patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy in Denmark.

ACKNOWLEDGEMENTS

Medical Writing, Editorial, and Other Assistance. Editorial assistance in the preparation of this article was provided by Roma Kwiatkiewicz of Asc Academics and funded by Daiichi Sankyo International and AstraZeneca.

Author Contribution. Jeroen Hendrikus Jacobus Paulissen, Alexander Victor van Schoonhoven, Emma Olin, Arjan Jacobus Postma, Zacharie Mbanya, Kyle John Dunton, Maarten Jacobus Postma, Marinus van Hulst, and Roel Donald Freriks contributed to the study's conception and design. Material preparation, data collection and analysis were performed by Jeroen Hendrikus Jacobus Paulissen, Alexander Victor van Schoonhoven, and Emma Olin. The first draft of the manuscript was written by Jeroen Hendrikus Jacobus Paulissen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding. This study was funded by Daiichi Sankyo International and AstraZeneca. The journal's publication fees were funded by the University Medical Center Groningen.

Data Availability. All data are included in the manuscript and its supplementary files. The analyses were conducted based on publicly available information which is presented and referenced in the article and supplementary files. Some of the data generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on request. Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy, described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Declarations

Conflict of Interest. Jeroen Hendrikus Jacobus Paulissen, Alexander Victor van Schoonhoven, and Arjan Jacobus Postma are paid employees of Asc Academics; Emma Olin and Zacharie Mbanya are paid employees of AstraZeneca; Kyle John Dunton is a paid employee of Daiichi Sankyo International; Marinus van Hulst reports no financial interests; Maarten Jacobus Postma is advisor to Asc Academics. Roel Donald Freriks was an employee of Asc Academics at the time the research was conducted. He is currently employed by IQVIA. Asc Academics received consulting fees paid from Daiichi Sankyo International and AstraZeneca. Maarten Jacobus Postma is a non-remunerated member of the UK's Joint Committee of Vaccination and Immunization, other authors report no non-financial interests.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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