Cost-Effectiveness Analysis of Trastuzumab Deruxtecan for Patients with HER2+ Metastatic Breast Cancer

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OBJECTIVE

To assess the cost-effectiveness of trastuzumab deruxtecan compared to trastuzumab emtansine as second-line therapy for patients with human epidermal growth factor receptor 2 positive (HER2+) metastatic breast cancer.

METHODS

Model Type: Three-state partitioned survival model

Intervention: Trastuzumab deruxtecan (T-DXd) administered every 3 weeks

Comparator: Trastuzumab emtansine (T-DM1) administered every 3 weeks

Target population: Female HER2+ metastatic breast cancer patients previously treated with first-line therapy

Payers Perspective: US Healthcare Sector

Model Structure: 3 mutually exclusive health states: progression-free (stable), post-progression, death

Time Horizon: 5 years

Cycle Length: 3 weeks

Perspective: Health system payers' perspective

Clinical Efficacy & Modeling: The model transition parameters were populated with clinical efficacy data from the DESTINY-Breast03 phase III randomized clinical trial [1]. To extrapolate progression and survival beyond the time horizon of the clinical trial, we digitized the published Kaplan-Meier (KM) curves to obtain estimates of individual patient data (IPD) using the WebPlotDigitizer [2].

We then reconstructed the KM curves with the IPD estimates of the T-DM1 control arm in R 4.1.3 based on the algorithm provided by Guyot et al. and fitted them to separate parametric models for PFS and OS using various parametric distributions to determine which was the best fit based on Akaike information criterion (AIC) [3]. We performed comparisons with Surveillance, Epidemiology, and End Results Program (SEER) survival curves to assess robustness of estimates [4].

Upon using a parametric model to extrapolate PFS and OS for patients receiving T-DM1 in the control arm, we applied the hazard ratios (HRs) observed in the DESTINY-Breast03 trial to the PFS and OS curves in this arm to derive the KM curves for the intervention arm receiving T-DXd.

Key Base Case Model Assumptions:

1. Patients are treated with either T-DXd or T-DM1 as a second-line treatment in the PF state indefinitely or until disease progresses.

2. Applied hazard ratios (HRs) between T-DXd and T-DM1 from the DESTINY-Breast03 trial (0.28 and 0.55 for PFS and OS respectively) until 33 months, the length of trial follow-up [1].

3. We assume HRs regress to the midpoint of the trial HRs and 1 (0.64 and 0.775 for PFS and OS respectively) after 33 months until the model ends.

4. Assumes that the leftover contents in single-dose drug vials are discarded after opening, leading to wastage that is paid for, based on drug label recommendations [5,6].

Costs: Costs include drug costs extracted from CMS Average Sales Price and administrative, adverse event, and third-line therapy costs derived from published literature, measured in 2022 US Dollars and discounted at 3% annually.

Outcomes: Quality-adjusted life years (QALYs), including from treatment, remissions and adverse events, were sourced from published literature and discounted at 3% annually.

Sensitivity Analysis: We conducted both probabilistic and deterministic sensitivity analysis to test model assumptions and robustness.

Scenario Analysis: We also performed 3 separate scenario analyses where we assumed a constant hazard ratio between T-DXd and T-DM1 throughout the model, ignored drug wastage, and employed a 10-year time horizon, respectively.

MODEL INPUTS

Variables	Base-Case	Lower Value	Upper Value	Distribution	Reference
Clinical endpoints					
Hazard ratio for OS	0.55	0.36	0.86	Lognormal	J. Cortés 2021
Hazard ratio for PFS	0.28	0.22	0.37	Lognormal	J. Cortés 2021
Post-33-month HR for OS	0.775	0.68	0.93	Lognormal	Calculation
Post-33-month HR for PFS	0.64	0.61	0.685	Lognormal	Calculation
T-DM1 overall response rate (%)	34.2	28.5	40.3	N/A	J. Cortés 2021
T-DXd overall response rate (%)	79.7	74.3	84.4	N/A	J. Cortés 2021
Average patient bodyweight	70	56	84	Normal	Oh et al. 2017
Cost					
Dose schedule per cycle					
Trastuzumab emtansine (T-DM1)	3.6 mg/kg	N/A	N/A	Lognormal	Label
Trastuzumab deruxtecan (T-DXd)	5.4mg/kg	N/A	N/A	Lognormal	Label
Drug costs					
Trastuzumab emtansine (per 100-mg vial)	$3,618.73	$2,407.58	$4,829.89	Gamma	base case: Medicare/ASP+6%, lower: VA big4 price
Trastuzumab deruxtecan (per 100-mg vial)	$2,609.40	$1,740.27	$3,478.53	Gamma	base case: Medicare/ASP+6%, lower: VA big4 price
Intravenous (IV) administration cost	$284.58	N/A	N/A	No change	Kruse et al. 2008
Cost after disease progression(monthly)	$9,161.54	$7,365.88	$10,957.20	Gamma	Sorensen et al. 2012
LVEF exam cost (per visit)	$235.00	N/A	N/A	No change	CMS Addendum B 2022
Adverse event costs (Grades 3 & 4)					
Nausea/Vomiting	$11,319.63	N/A	N/A	Gamma	Burke et al. 2011
Decreased neutrophil count (neutropenia)	$14,679.81	N/A	N/A	Gamma	Benett et al. 2007
Anemia	$13,220.78	N/A	N/A	Gamma	Elting et al. 2004
Diarrhea	$9,085.70	N/A	N/A	Gamma	Dranitsaris et al. 2005
Decreased white-cell count (leukopenia)	$14,679.81	N/A	N/A	Gamma	Benett et al. 2007
Decreased platelet count (Thrombocytopenia)	$27,305.55	N/A	N/A	Gamma	Wong et al. 2018
Interstitial lung disease	$23,769.58	N/A	N/A	Gamma	Olson et al. 2020
Treatment Effects					
Health state utilities (QALYs)					
Stable/ PF state	0.72	0.57	0.86	Beta	Lloyd et al. 2006
Post-progression state	0.44	0.36	0.53	Beta	Lloyd et al. 2006
Treatment response	0.08	0.60	0.09	Beta	Lloyd et al. 2006

Table 1. Model parameters: base case values, lower bound values, upper bound values, and distributions for probabilistic sensitivity analysis

RESULTS

Strategy	Total Costs	Total QALYs	Δ Costs	Δ QALYs	ICER	Cost-effectiveness probability at $150,000 WTP
Base case: Time-dependent HR + 5-year Time Horizon + Drug Wastage						
T-DM1	$479,055	1.84				
T-DXd	$668,204	2.71	$189,148	0.87	$217, 397 / QALY	25.2%
Scenario 2: Constant HR + 5-year Time Horizon + Drug Wastage						
T-DM1	$479,055	1.83				
T-DXd	$679,877	2.75	$200,821	0.91	$220,075 / QALY	24.3%
Scenario 3: Time-dependent HR + 5-year Time Horizon without Drug Wastage						
T-DM1	$435,275	1.84				
T-DXd	$635,934	2.71	$200,659	0.87	$230,626 / QALY	29.0%
Scenario 4: Time-dependent HR + 10-year Time Horizon + Drug Wastage						
T-DM1	$671,701	2.57				
T-DXd	$1,008,431	4.09	$336,730	1.51	$222,373 / QALY	22.0%

Table 2. Abbreviation: *T-DM1* trastuzumab emtansine, *T-DXd* trastuzumab deruxtecan, *ICER* incremental cost-effectiveness ratio, *QALY* quality-adjusted life year, *WTP* willingness to pay

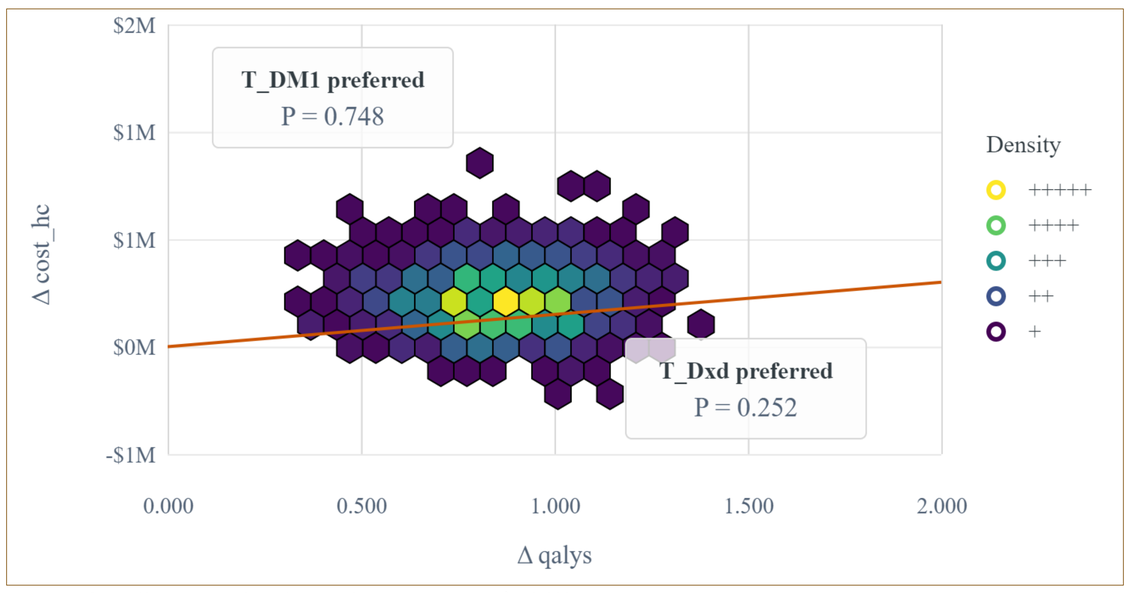

Figure 4. Cost-Effectiveness Plane for T-DXd vs. T-DM1 (WTP = $150,000)

MODEL OVERVIEW

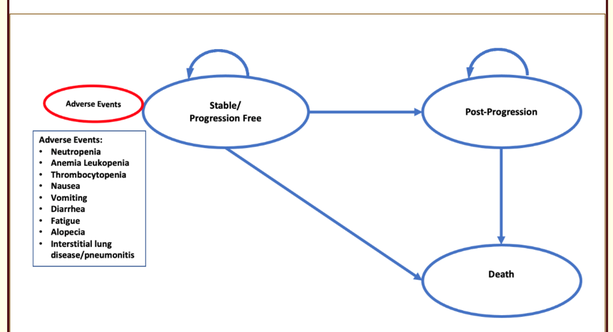

Figure 1. Partitioned survival model health states

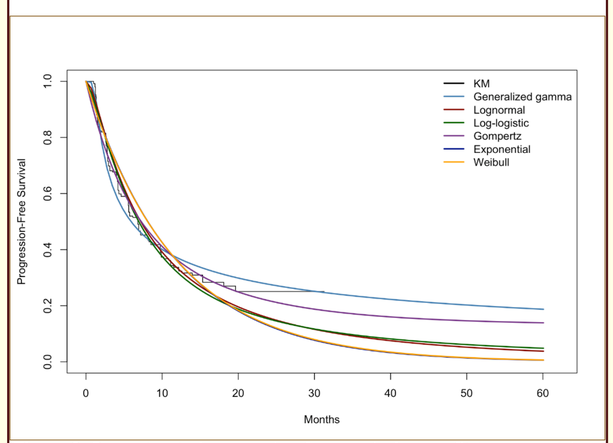

Figure 2. Reconstructed progression-free survival curve fit to parametric distributions in the T-DM1 arm; generalized gamma distribution selected

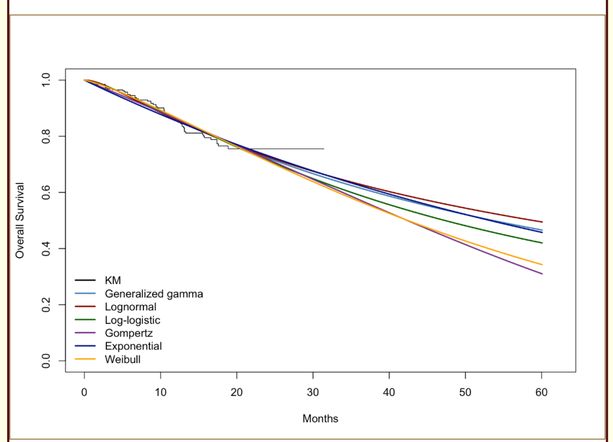

Figure 3. Reconstructed overall survival curve fit to parametric distributions in the T-DM1 arm; log-logistic distribution selected

RESULTS

Base Case results: In our base case analysis, total costs for trastuzumab deruxtecan were $668,204, compared to $479,055 for trastuzumab emtansine. Total QALYs for trastuzumab deruxtecan were 2.71, compared to 1.84 for trastuzumab emtansine. The base-case ICER was $217,397/QALY.

Sensitivity Analysis: Probabilistic sensitivity analysis indicated that trastuzumab deruxtecan had a 25.2% probability of being cost-effective at a $150,000 per QALY willingness-to-pay (WTP) threshold.

Using this WTP threshold, the value-based price of trastuzumab deruxtecan per 100-mg vial to be cost-effective was $2,349, compared to the current drug cost (ASP + 6%) of $2,609.

Scenario Analysis: Our scenario analyses incorporating a constant hazard ratio, no drug wastage, and a 10-year time horizon yielded ICERs of $218,898, $230,626 and $222,373 per QALY respectively, showing relative robustness to a variety of assumptions.

CONCLUSION

Despite the higher efficacy of trastuzumab deruxtecan in patients with HER2+ metastatic breast cancer, our findings raise concern regarding its cost-effectiveness.

REFERENCES

[1] Cortés J, Kim SB, Chung WP, et al. Trastuzumab Deruxtecan versus Trastuzumab Emtansine for Breast Cancer. N Engl J Med. 2022;386(12):1143-1154. doi:10.1056/NEJMoa2115022 https://doi.org/10.1056/NEJMoa2115022

[2] Automeris.io. 2022. WebPlotDigitizer - Extract data from plots, images, and maps. [online] https://automeris.io/WebPlotDigitizer/ Accessed Apr 29, 2022.

[3] Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9. Published 2012 Feb 1. doi:10.1186/1471-2288-12-9

[4] Cancer of the breast (female) - cancer stat facts. SEER Website. https://seer.cancer.gov/statfacts/html/breast.html. Accessed May 19, 2022.

[5] Gene.com. 2022. [online] https://www.gene.com/download/pdf/kadcyla_prescribing.pdf Accessed Apr 29, 2022.

[6] Accessdata.fda.gov. 2022. [online] https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761139s011lbl.pdf Accessed Apr 29, 2022.

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