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Economic evaluation of adjuvant trastuzumab emtansine in patients with HER2-positive early breast cancer and residual invasive disease after neoadjuvant taxane and trastuzumab–based treatment in Canada

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ABSTRACT

Background In the KATHERINE trial, adjuvant trastuzumab emtansine [T-DM1, Kadcyla (Genentech, South San Francisco, CA, U.S.A.)], compared with trastuzumab, significantly reduced the risk of recurrence or death by 50% (unstratified hazard ratio: 0.50; 95% confidence interval: 0.39 to 0.64; $p < 0.0001$) in patients with HER2-positive early breast cancer (EBC) and residual invasive disease after neoadjuvant systemic treatment. A cost–utility evaluation, with probabilistic analyses, was conducted to examine the incremental cost per quality-adjusted life–year (QALY) gained associated with T-DM1 relative to trastuzumab, given the higher per-cycle cost of T-DM1.

Methods A Markov model comprising a number of health states was used to examine clinical and economic outcomes over a lifetime horizon from the Canadian public payer perspective. Patients entered the model in the invasive disease-free survival (iDFS) state, where they received either T-DM1 or trastuzumab. Transition probabilities between the health states were derived from the KATHERINE trial, Canadian life tables, and published literature from other relevant clinical trials (EMILIA, CLEOPATRA, and M77001). Resource use, costs, and utilities were derived from KATHERINE, other clinical trials, published literature, provincial fee schedules, and clinical expert opinion. Sensitivity analyses were conducted for key assumptions and model parameters.

Results Compared with trastuzumab, adjuvant T-DM1 was associated with a cost savings of $8,300 per patient and a 2.16 incremental QALY gain; thus T-DM1 dominated trastuzumab. Scenario analyses yielded similar results, with T-DM1 dominating trastuzumab or producing highly favourable incremental cost–utility ratios of less than $10,000 per QALY.

Conclusions Adjuvant T-DM1 monotherapy is a cost-effective strategy compared with trastuzumab alone in the treatment of patients with HER2-positive EBC and residual invasive disease after neoadjuvant systemic treatment.

Key Words Early breast cancer, trastuzumab emtansine, cost–utility analyses, economic evaluations, adjuvant HER2-positive therapy

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BACKGROUND

Breast cancer (BCa) is the most commonly diagnosed malignancy affecting Canadian women (25%). Fortunately, with early detection, most cases (94%) are diagnosed in the early stages before metastatic recurrence, when cure is still possible[1].

Metastatic BCa (mBCa) is associated with significant health care and economic burdens[2]. Compared with women not having BCa, women with BCa are more likely to experience fatigue, sexual dysfunction, infertility, stress, and mental disorders[3–6]. Health-related quality of life (HRQOL) declines after metastatic recurrence given that disease recurrence and progression are associated with fear of death, inability to care for one's family, disruption in earnings[7] and the routines of young families[8,9], and loneliness[10].

Approximately 15%–20% of BCa subtypes are HER2-positive[11–14]. Since the introduction of trastuzumab for HER2-positive metastatic BCa (mBCa) more than 20 years ago, HER2-targeted therapies in the mBCa setting have been associated with significant improvements in length and quality of life. However, HER2-positive mBCa remains incurable, and despite novel HER2-targeted therapies, patients with HER2-positive mBCa experience poor prognosis and short survival[15]. For patients with HER2-positive early BCa (EBC), HER2-targeted therapies provide a unique opportunity to prevent disease recurrence and its associated morbidity, mortality, and HRQOL burden. Indeed, curative-intent HER2 therapy, delivered in the adjuvant or neoadjuvant setting, has been associated with significant improvements in the risk of local and systemic disease recurrence, and overall survival[16]. Unsurprisingly, neoadjuvant HER2-targeted therapy has become a standard therapeutic approach for high-risk HER2-positive EBC[16–24].

Patients starting neoadjuvant HER2-targeted therapy continue with adjuvant HER2 systemic treatment after surgery to complete the currently-recommended 1-year standard HER2 blockade treatment[20,23,25]. Despite the use of HER2-based therapy for the neoadjuvant treatment of EBC (for example, trastuzumab ± pertuzumab + chemotherapy), approximately 40%–80% of patients with HER2-positive EBC have residual invasive disease after neoadjuvant treatment[26–29].

Although adjuvant trastuzumab combined with chemotherapy in EBC is associated with significant improvements in both disease-free and overall survival, approximately 25% of patients will experience disease recurrence or death within 10 years of diagnosis[28,30–33]. Given the incurable nature of mBCa, all patients with HER2-positive disease in the early setting should receive optimal HER2 therapy to reduce the risk of recurrence and maximize the chance of cure[34]. The phase III KATHERINE trial is the first to demonstrate significant benefits of therapy optimization in patients with HER2-positive BCa who have residual invasive disease after neoadjuvant HER2-targeted therapy[35,a].

Compared with trastuzumab, trastuzumab emtansine [T-DM1, Kadcyla (Genentech, South San Francisco, CA, U.S.A.)] significantly reduced the risk of recurrence or death by 50% [unstratified hazard ratio (HR): 0.50; 95% CI: 0.39 to 0.64; $p < 0.0001$] and was associated with an improvement in the 3-year rate of invasive disease-free survival (iDFS) to 88.3% from 77.0%[35]. Additionally, a 40% reduction in the risk of distant recurrence was observed with T-DM1 compared with trastuzumab (HR: 0.60; 95% CI: 0.45 to 0.79).

In Canada, intravenous cancer treatment is administered in hospital and is publicly funded. Given the higher per-cycle cost of T-DM1, an economic evaluation was conducted to evaluate the cost–utility of adjuvant T-DM1 compared with trastuzumab from the publicly-funded health care perspective.

METHODS

An Excel-based (Microsoft Corporation, Redmond, WA, U.S.A.) probabilistic Markov model was developed to assess the cost–utility of adjuvant T-DM1 compared with trastuzumab in patients with HER2-positive EBC and residual invasive disease after neoadjuvant systemic chemotherapy (including taxanes and trastuzumab-based treatment). The perspective of the Canadian health care payer was adopted, which included direct medical costs to the publicly-funded health care system [medications, outpatient physician assessments, diagnostic tests and procedures, emergency department visits, and hospitalizations (including overhead costs)] that were expected to differ depending on BCa treatment.

The model is an updated version of the structure that was accepted by health technology assessment (HTA) agencies for assessment of the treatment of HER2-positive EBC with pertuzumab–trastuzumab in the neoadjuvant[36,37] and adjuvant settings[38]. The model also closely resembles the structures published by Ward *et al.*[39] and Attard *et al.*[40].

The model consisted of 6 health states: iDFS, nonmetastatic recurrence (defined as locoregional recurrence and contralateral BCa), remission from a nonmetastatic recurrence or no evidence of disease (NED), first-line mBCa, subsequent lines of treatment in mBCa, and death (Figure 1). The model cycle length was 1 month, with half-cycle correction applied to account for mid-cycle transitions. The model incorporated health state transition probabilities, together with costs and utilities in each health state (discussed in the next subsection), to examine the cumulative costs and quality-adjusted life–years (QALYs) associated with each adjuvant strategy [that is, intravenous (IV) T-DM1 3.6 mg/kg every 3 weeks compared with IV trastuzumab 6 mg/kg every 3 weeks or subcutaneous (SC) trastuzumab 600 mg every 3 weeks).

Patients entered the model with baseline demographics from the KATHERINE trial: average age 49 years, body surface area 1.77 m^2, body weight 71 kg[35]. Transition probabilities between health states were derived from the KATHERINE trial, Canadian life tables, and published literature, including other relevant clinical trials (discussed later).

Consistent with Canadian guidelines[41], a lifetime horizon was used to capture downstream costs and the effect of patients who progress to the metastatic setting.

[a] Hoffmann–La Roche. Primary CSR Study BO27938 (KATHERINE). A randomized, multicenter, open-label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy. Unpublished report.

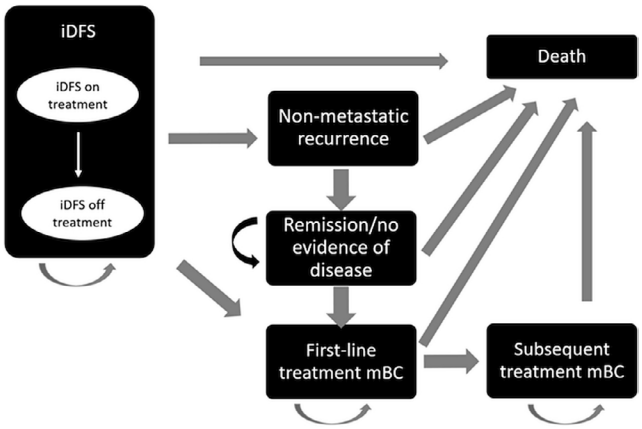

FIGURE 1 Health states included in the cost–utility model comparing adjuvant T-DM1 (trastuzumab emtansine) with trastuzumab for patients with HER2-positive early breast cancer and residual invasive disease after neoadjuvant systemic chemotherapy. iDFS = invasive disease-free survival; mBC = metastatic breast cancer.

Using a model entry age of 49 years[35], a 51-year time horizon represents a maximum lifetime of 100 years. A 1.5% discount rate was applied to both costs and outcomes after the first year[41].

Health State Transition Probabilities

The model's health state transition probabilities are detailed in Table I and in the subsections that follow.

iDFS

Patients entered the model in the iDFS health state on treatment and then discontinued (off treatment) because of completion of adjuvant therapy, intolerability, or other reasons. That distinction was made because patients on and off treatment have a different quality of life. In each model cycle, patients remained in the iDFS health state or experienced an event [nonmetastatic recurrence, metastatic recurrence, or death (consistent with the iDFS definition—primary endpoint of the KATHERINE trial)]. Transitions out of iDFS were informed by background mortality data from Canadian life tables[43] and the KATHERINE trial[35,a], with iDFS extrapolations adjusted by recurrence rates observed in the long-term follow-up of the HERA and BCIRG 006 trials[32,48].

Maximum follow-up in the KATHERINE study at the time of the clinical cut-off was 62 months[a]. The iDFS data were extrapolated beyond the trial follow-up based on the best-fit Akaike information criterion and Bayesian information criterion statistics (exponential for T-DM1; log-normal for trastuzumab)[a]. The iDFS curves were further adjusted by assuming that the proportion of patients being cured (no longer eligible to transition out of iDFS to nonmetastatic or first-line recurrence) was linearly increasing with time from 0% at 36 months to 95% at 120 months, based on observation of long-term follow-up of HERA and BCIRG 006[32,48].

The duration of treatment effect for T-DM1 relative to trastuzumab was assumed for 7 years and was then linearly decreased to null (that is, survival equal to trastuzumab) at 10 years, after which time only background mortality was applied. That duration of treatment effect is supported by the recent second interim analysis of APHINITY, which was conducted at a median follow-up of 74.1 months, at which point iDFS was significantly improved with pertuzumab–trastuzumab[49]. Additionally, Chumsri *et al.*[50] analyzed data from the NCCTG N9831 and NSABP B-31 trials. Separation between the Kaplan–Meier curves of relapse-free survival for adjuvant trastuzumab plus chemotherapy and for chemotherapy alone was maintained for 10 years (years 0–5 HR: 0.42; 95% CI: 0.35 to 0.49; years 5–10 HR: 0.69; 95% CI: 0.49 to 0.97). Those studies support the assumption that the treatment effect is sustained over time. Still, scenario analyses were conducted with a shortened duration of treatment effect.

Supplemental Figure 1 shows a summary of the effects on iDFS. Figure 2 presents the resulting iDFS curves.

Nonmetastatic Recurrence and Remission/NED Health States

The nonmetastatic recurrence state is a tunnel state in which patients reside for 12 months unless death occurs. The 12-month duration was chosen because patients were assumed to undergo another course of adjuvant therapy. After 12 months, patients who did not transition to death because of background mortality transitioned to remission/NED.

In remission/NED, patients were off treatment and assumed to have NED. Patients were at risk of death and metastatic recurrence, but not of contralateral or locoregional recurrence. If a patient developed a second nonmetastatic recurrence, the treatment pattern would be similar to that for a metastatic recurrence.

The risk of transitioning from remission/NED to first-line metastatic recurrence was based on Hamilton *et al.*[42]. That study included a cohort of 12,836 patients with EBC and estimated the risk of a second malignancy after adjuvant therapy; the mean time to recurrence was 7.6 years (monthly transition probability of 0.76%).

No transition between nonmetastatic recurrence and first-line mBCa was assumed. In the KATHERINE study, patients were assumed to experience a metastatic recurrence as first disease recurrence if the metastatic recurrence occurred less than 2 months after development of a nonmetastatic recurrence.

Metastatic Recurrence

Every disease recurrence observed during adjuvant therapy or within 6 months of its completion was assumed to be metastatic, because those patients have a worse prognosis. Survival estimates derived from the fast-progressing population of the EMILIA study were used to model the risk of progression and of death post-progression[44]. The pooled survival data from both treatment arms (T-DM1 and lapatinib–capecitabine) were used to estimate the model transition probabilities.

For patients in the first-line mBCa health state with early-recurring disease, the risk of further disease progression and death depended on the treatment that patients were likely to receive (categorized as pertuzumab–trastuzumab–chemotherapy, trastuzumab–chemotherapy, or chemotherapy alone). Because the current post-progression survival of patients who experience a metastatic recurrence

is expected to differ from that of patients in the KATHERINE trial (for example, patients might not have received the therapies considered the current standard of care for mBCa in Canada because of geographic variation in the reimbursement status of new treatments), treatment regimens and frequency of use were obtained from four Canadian

TABLE I Key model inputs

Parameter	Input	Source
iDFS recurrences that were metastatic (%)		
T-DM1 (<18 months)	85.71	von Minckwitz *et al.*, 2019[35] Hoffmann–La Roche, data on file[a]
Trastuzumab (<18 months)	72.29	
T-DM1 (>18 months)	89.36	
Trastuzumab (>18 months)	73.42	
Monthly transition probabilities		
Nonmetastatic to remission	Automatic after 12 months if alive	
Remission/NED to first-line mBCa	0.0076	Hamilton *et al.*, 2015[42]
Nonmetastatic or remission/NED to death	Background mortality	Statistics Canada, 2020 (Canadian life tables)[43]
Metastatic recurrence (<18 months)		
First-line to subsequent-line mBCa	0.0721	Dieras *et al.*, 2017 (EMILIA)[44]
First-line to death	Maximum of background mortality and death in progression-free survival from EMILIA	Dieras *et al.*, 2017 (EMILIA)[44] Statistics Canada, 2017 (Canadian life tables)[43]
Subsequent-line mBCa to death	0.0540	Dieras *et al.*, 2017 (EMILIA)[44]
Metastatic recurrence (>18 months)		
First-line to subsequent-line mBCa	PHT: 0.0317	Swain *et al.*, 2015 (CLEOPATRA)[15]
	HT: 0.0470	Swain *et al.*, 2015 (CLEOPATRA)[15]
	CTx: 0.0694	Marty *et al.*, 2005 (M77001)[45]
First-line mBCa to death	Maximum of background mortality and deaths from relevant trials. For most ages, background mortality is higher than trial data.	Swain *et al.*, 2015 (CLEOPATRA)[15] Marty *et al.*, 2005 (M77001)[45] Statistics Canada, 2020 (Canadian life tables)[43]
Subsequent-line mBCa to death	PHT: 0.0273	Swain *et al.*, 2015 (CLEOPATRA)[15]
	HT: 0.0315	Swain *et al.*, 2015 (CLEOPATRA)[15]
	CTx: 0.0598	Marty *et al.*, 2005 (M77001)[45]
	T-DM1: 0.0540	Dieras *et al.*, 2017 (EMILIA)[44]
Utility values		
iDFS on treatment	0.814	KATHERINE EQ-5D[b] with Canadian tariffs
iDFS off treatment	0.826	KATHERINE EQ-5D[b] with Canadian tariffs
Nonmetastatic recurrence	0.814	Assume equal to iDFS on treatment
Remission	0.826	Assume equal to iDFS off treatment
First-line mBCa	0.765	Lloyd *et al.*, 2006[46]
Subsequent-line mBCa	0.508	Lloyd *et al.*, 2006[46]
Age adjustment based on Canadian data	Included	Guertin *et al.*, 2018[47]
Efficacy treatment mixes (%)		
First- and subsequent-line treatment mix	PHT: 87.5 HT: 8.1 CTx: 4.4	Expert opinion
Subsequent-line treatment mix (scenario analysis)	T-DM1: 95 HT: 3.75 CTx: 1.25	Expert opinion

[a] Hoffmann–La Roche. Primary CSR Study BO27938 (KATHERINE). A randomized, multicenter, open-label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy. Unpublished report.

[b] EuroQol Research Foundation, Rotterdam, Netherlands.

iDFS = invasive disease-free survival; T-DM1 = trastuzumab emtansine; NED = no evidence of disease; mBCa = metastatic breast cancer; PHT = pertuzumab–trastuzumab–chemotherapy; HT = trastuzumab–chemotherapy; CTx = chemotherapy.

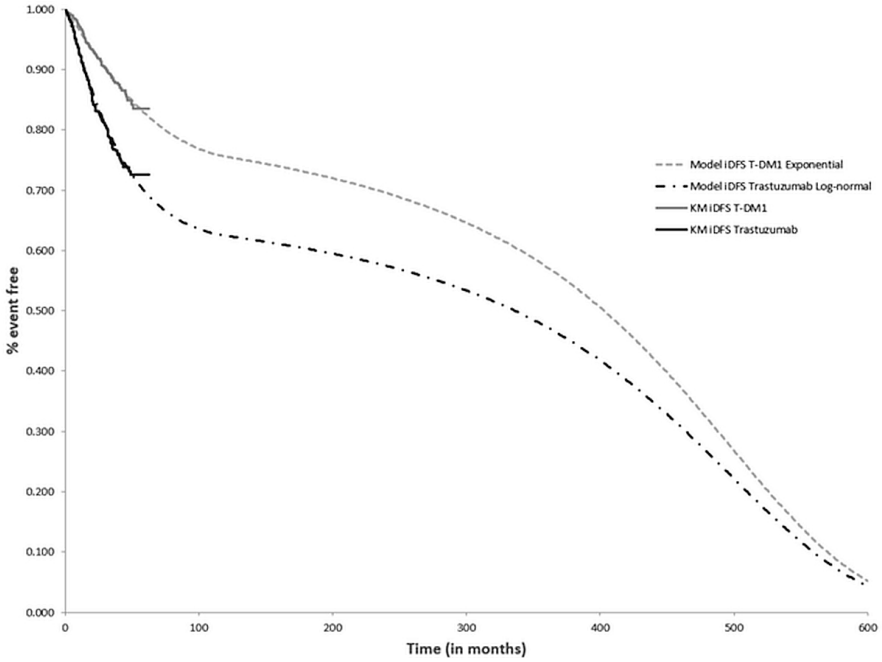

FIGURE 2 Curves illustrating the probability of remaining invasive disease–free over time for patients treated with T-DM1 (trastuzumab emtansine) and trastuzumab. iDFS = invasive disease-free survival; KM = Kaplan–Meier.

medical oncologists who served as clinical advisors (Table I). The same treatment mix used in first-line mBCa was applied to determine survival in the subsequent-line mBCa setting. Although treatment options in subsequent-line mBCa could affect the survival of affected patients, no data about the sequential use of pertuzumab–trastuzumab–chemotherapy and T-DM1 in mBCa are available. Additionally, the effect of therapies on overall survival is greater in first-line than in subsequent-line mBCa[15]. Still, a scenario analysis was conducted to explore specific subsequent-line treatment mixes.

The risk of progression and death were extrapolated using the available evidence about such treatment regimens in the metastatic setting. For pertuzumab–trastuzumab–chemotherapy and trastuzumab–chemotherapy, CLEOPATRA trial data were used, where pertuzumab–trastuzumab–taxane was compared with trastuzumab–taxane[15]. For chemotherapy, M77001 trial data were used, where trastuzumab–taxane was compared with taxane alone[45]. To avoid the use of time-dependent transition probabilities and to keep the model complexity at a reasonable level, Kaplan–Meier data from those trials were extrapolated using an exponential distribution. Although not the best parametric fit, the average survival predicted by the exponential extrapolation is similar to the truncated survival predicted with Kaplan–Meier estimates alone.

Death

Once transitioned, patients remained in the death health state for the remainder of the time horizon. Transitions to death from iDFS, nonmetastatic, and remission/NED health states were based on background mortality rates, given an assumption that a patient would first move to a metastatic health state before dying from their disease. To ensure that the risk of death was at least equal to that observed in the general population, the death rate was estimated as the maximum of the risk of dying without recurrences (as observed in KATHERINE) or of the age- and sex-adjusted background mortality rate.

Utilities

Effectiveness was measured in terms of QALYs by applying utility values to the various health states. In the iDFS health state, utilities were derived using EQ-5D-3L (EuroQol Research Foundation, Rotterdam, Netherlands) data from the KATHERINE trial, which were collected at screening, during treatment, and every 6 months for 1 year after the study completion visit[a]. Canadian tariffs were assigned to the EQ-5D-3L scores to derive iDFS utilities for the on- and off-treatment statuses[51]. Data from both trial treatment arms were pooled, because the data were similar and had a minimal effect on results. Those values were also assumed for the nonmetastatic recurrence and remission/NED health states.

Utilities for the metastatic health states were derived from a study by Lloyd *et al.*[46], which distinguished between patients with mBCa who did and did not progress. Those values have been extensively used in cost–utility models and are accepted by HTA bodies[46].

Finally, health state utilities were adjusted to the modelled patient's average age to ensure that the patient's HRQOL was, at most, equal to the HRQOL in the general population. The adjustment was performed using Canadian age-specific utility data from Guertin *et al.*[47] by choosing, at each model cycle, the minimum of the health state utility value and the general population utility value (Table I).

Costs and Resource Use

Table II details key resource use and cost inputs.

Regimen Use and Doses

Treatment use in the iDFS health state reflects the KATHERINE trial patients: average body surface area, 1.77 m^2; weight, 71 kg[35]; and observed treatment duration, 12.64 (T-DM1) and 12.70 (trastuzumab) cycles.

Post-iDFS treatment regimen dosing calculations were based on Ontario Health (Cancer Care Ontario) protocols[59]. The proportion of patients receiving each regimen for each post-iDFS health state was estimated by the clinical advisors.

TABLE II Resource use and cost inputs

Parameter	Input		Source
	Pre-metastatic setting	**Metastatic setting**	
Trastuzumab mix			
Branded IV	14.0%	27.4%	
Biosimilar IV	48.0%	38.2%	Assumption
SC	38.0%	34.4%	
iDFS on treatment costs per cycle			
T-DM1 per cycle	$5,474		
Trastuzumab, branded, IV	$2,799		Hoffmann–La Roche, data on file, 2019
Trastuzumab, biosimilar, IV	$2,099		
Trastuzumab SC	$2,625		
	Treatment regimen–related	**Treatment independent**	
Monthly health state cost			
iDFS			
Years 1–2	See above, year 1 only	$23.50	Ontario MOH, 2020[52] Ontario MOH, 2019[53] CADTH, 2019[54] Hoffmann–La Roche, data on file, 2019
Years 3–5	$0	$41.26	Ontario MOH, 2020[52] Ontario MOH, 2019[53]
Subsequent years	$0	$18.80	Ontario MOH, 2020[52] Ontario MOH, 2019[53]
Nonmetastatic recurrence	$4,382.22	$62.46	Ontario MOH, 2020[52]
Remission/NED	$0	$46.37	Ontario MOH, 2019[53] CADTH, 2019[54] Ontario MOH, 2019[55] IQVIA[a] pCODR, 2018[56] Hoffmann–La Roche, data on file, 2019
Metastatic 1st line, <18 months			Ontario MOH, 2020[52]
T-DM1	$10,013.70	$65.88	Ontario MOH, 2019[53]
Trastuzumab	$8,617.76	$65.88	CADTH, 2019[54]
Metastatic 2nd line+, <18 months	$6,101.05	$65.88	Ontario MOH, 2019[55]
Metastatic 1st line, >18 months	$9,681.35	$65.88	IQVIA[a]
Metastatic 2nd line, >18 months	$8,070.12	$65.88	pCODR, 2018[56] Hoffmann–La Roche, data on file, 2019
End-of-life [mean (95% CI)]	$30,865.34 ($23,149.13 to $38,581.89)		Walker *et al.*, 2011[57]
Grade 3 or greater AEs			
Peripheral sensory neuropathy	$18.96		Goeree *et al.*, 2016[58]
Thrombocytopenia	$84.06		Clinical advisors Ontario MOH, 2020[52] Ontario MOH, 2019[53]
Neutrophil count decrease	$0		Clinical advisors

[a] IQVIA, Durham, NC, U.S.A. (https://www.iqvia.com/).

IV = intravenous; SC = subcutaneous; iDFS = invasive disease-free survival; T-DM1 = trastuzumab emtansine; MOH = Ministry of Health; CADTH = Canadian Agency for Drugs and Technologies in Health; NED = no evidence of disease; pCODR = pan-Canadian Oncology Drug Review; CI = confidence interval; AEs = adverse events.

In all treatment health states, a mix of branded, SC, and biosimilar trastuzumab was included. Because of uncertainty in public funding at the time of the analysis, the proportions in the nonmetastatic and metastatic health states were based on estimated market uptake in a funded environment.

Cost Inputs

Drug costs and costs obtained from fee schedules are reported in 2019 Canadian dollars. Where inflating a published cost was required, prices were inflated to 2018 Canadian dollars using the most recent Consumer Price Index[60]. Unless otherwise stated, costs were obtained from standard fee schedules[52,53,55,61].

Unit costs for T-DM1, branded IV trastuzumab, and SC trastuzumab were obtained from the manufacturer (Hoffmann–La Roche. Data on file, 2019). Given the lack of a list price at the time of analysis, the IV trastuzumab biosimilar cost was assumed to be 75% of the branded cost[54]. Post-iDFS regimen costs were obtained from the Ontario Drug Formulary for oral medications[55], IQVIA Delta PA [IQVIA, Durham, NC, U.S.A. (https://www.iqvia.com/)], or prior HTA submissions[56] (paclitaxel and docetaxel). Vial sharing for IV treatments, with no wastage, was assumed. The regimens used in all post-iDFS health states, and the proportion of patients receiving each regimen was estimated by the clinical advisors.

Administration costs included laboratory tests, pretreatment medications, and IV administration for each treatment (regimen preparation, chair time, pharmacist and chemotherapy nurse time, and cancer centre overhead). Treatment-specific resource use, including for routine laboratory tests, was obtained from the manufacturer, BC Cancer, and Ontario Health (Cancer Care Ontario) BCa chemotherapy protocols[59,62] and validated by the clinical advisors. The cost of IV administration was estimated using the hourly rate estimated by Tam *et al.*[63] ($203.79/h). Time for administration of each regimen was assumed by summing administration times for each treatment in the regimen.

In each pre-death health state, patients incurred specific direct medical costs independent of treatment regimen (oncologist and general practitioner assessments, mammograms, bone mineral density scans, and computed tomography). Frequency of use was estimated by the clinical advisors and averaged to obtain a single input for each resource. In the iDFS health state, costs were differentiated by year in the health state, given that different resources were assumed on and off treatment and over time.

End-of-life costs were obtained from Walker *et al.*[57] and included direct medical costs for palliative and end-of-life care in the last 6 months of life.

Patients experiencing treatment-related adverse events in the iDFS health state incurred a one-time cost for the adverse events at the start of the simulation. Only grade 3 and greater adverse events that were experienced by 1% or more of the patients in either arm in the KATHERINE trial were included.

Analysis

The base case was performed using a Monte Carlo analysis of 1000 simulations. Parameters were varied probabilistically with the following distributions: utility values, beta; parameter estimates for the parametric iDFS and post-iDFS functions, multivariate normal; number and costs of adverse events, log-normal; monthly supportive care costs for the iDFS and post-iDFS health states, log-normal; and administration costs, log-normal. Distributions were chosen so as to follow the recommendations of Briggs *et al.*[64]. To test the effect of key assumptions on the model's robustness, probabilistic scenario analyses were performed (Table III).

RESULTS

Compared with trastuzumab, adjuvant T-DM1 was associated with incremental life–years gained, longer time spent in iDFS, and less time spent in the nonmetastatic and metastatic recurrence health states (Table IV), translating to an estimated gain of 2.16 QALYs (95% CI: 1.52 QALYs to 4.02 QALYs). Upfront treatment costs were higher for T-DM1 than for trastuzumab ($77,400 vs. $37,300), resulting in an incremental cost of $40,200 in the iDFS state. That cost was offset primarily by savings in the metastatic setting (first-line: $48,300 vs. $69,600; subsequent line: $44,700 vs. $65,800), because fewer patients progressed to those more costly health states. The total incremental cost for T-DM1 compared with trastuzumab was –$8,300 (95% CI: –$46,200 to $23,600). From a cost–utility standpoint, T-DM1 therefore dominated trastuzumab (T-DM1 dominated trastuzumab in 66.2% of the simulations).

At all willingness-to-pay thresholds, T-DM1 was the most cost-effective treatment. At a very conservative willingness-to-pay threshold of $20,000 per QALY, T-DM1 had a 97.5% likelihood of being the most cost-effective treatment. The likelihood increased to 100% by $40,000 per QALY (see the supplemental material for the cost–utility acceptability curve).

Scenario analyses consistently yielded similar results, with T-DM1 dominating trastuzumab or resulting in highly-favourable incremental cost–utility ratios (ICURs, Table III). A highly pessimistic and unlikely scenario in which all incremental treatment benefits of T-DM1 terminated at 41 months (the median follow-up period in KATHERINE) was still associated with a highly-favourable ICUR of $7,100 per QALY gained. Because SC trastuzumab and IV trastuzumab biosimilar were not reimbursed by any provincial public drug plan at the time of analysis, the potential uptake by cancer agencies and the list prices of the biosimilar products were unknown. However, even with a 25% discount in biosimilar list price relative to the innovator list price, and assuming that 100% of trastuzumab used the biosimilar product, T-DM1 continued to dominate trastuzumab. All other scenario analyses yielded similar results, with T-DM1 continuing to dominate trastuzumab or to result in ICURs less than $10,000 per QALY.

DISCUSSION

In the present study, we examined the cost–utility of adjuvant T-DM1 compared with trastuzumab in patients with HER2-positive EBC who have residual invasive disease after neoadjuvant taxane and trastuzumab–based systemic treatment. The first trial to provide clinical evidence for

TABLE III Probabilistic scenario analyses

Scenario	Cost		QALYs		Difference		ICUR ($/QALY)
	T-DM1	Trastuzumab	T-DM1	Trastuzumab	Cost	QALYs	
Base case	$177,826	$186,131	18.32	16.16	–$8,305	2.16	Dominant
Time horizon: 28 years	$175,683	$182,529	15.08	13.47	–$6,846	1.61	Dominant
Comparator							
Only trastuzumab IV branded included	$180,511	$195,464	18.26	16.12	–$14,953	2.14	Dominant
Only trastuzumab IV biosimilar included	$175,475	$180,249	18.27	16.12	–$4,774	2.16	Dominant
Duration of incremental T-DM1 treatment effect relative to trastuzumab							
Maintained for 4 years then decreases linearly to null at 7 years	$184,253	$186,588	18.17	1.97	–$2,335	1.97	Dominant
Null at 41 months (median trial follow-up duration)	$197,769	$186,885	17.69	16.15	$10,883	1.54	$7,062
Cure proportion: 0% cure rate	$291,575	$282,109	15.48	13.88	$9,466	1.60	$5,927
Treatment mix							
Regimens included in each health state used in equal proportion (effect on cost)	$140,562	$135,098	18.31	16.13	$5,464	2.19	$2,501
Metastatic health state efficacy based on HT only	$165,264	$169,621	18.23	16.05	–$4,357	2.18	Dominant
Metastatic health state efficacy based on equal proportion of patients in each of PHT, HT, and CTx categories	$151,053	$150,795	18.24	16.03	$258	2.21	$117
Efficacy for subsequent-line metastatic health states based on clinical advisor input (95% T-DM1, 3.75% HT, 1.25% CTx)	$161,351	$164,342	18.16	16.00	–$2,991	2.16	Dominant
Efficacy for subsequent line based on T-DM1 only	$161,537	$165,461	18.28	16.09	–$3,925	2.19	Dominant
Utilities: first-line metastatic = 0.81 subsequent-line metastatic = 0.58	$178,046	$187,112	18.38	16.26	–$9,066	2.12	Dominant
iDFS parametric extrapolations							
Exponential for both arms	$195,568	$219,934	17.91	15.37	–$24,366	2.55	Dominant
Log–normal for both arms	$166,035	$186,003	18.53	16.06	–$19,967	2.47	Dominant
No vial sharing, wastage allowed	$179,617	$188,532	18.30	16.14	–$8,915	2.16	Dominant

T-DM1 = trastuzumab emtansine; QALYs = quality-adjusted life–years; ICUR = incremental cost–utility ratio; IV = intravenous; HT = trastuzumab–taxane; PHT = pertuzumab–trastuzumab–taxane; CTx = chemotherapy; iDFS = invasive disease-free survival.

using residual invasive disease to guide adjuvant therapy in this patient population was KATHERINE.

The results of the base-case analysis in patients with HER2-positive EBC estimated adjuvant T-DM1 to dominate the current standard of care, trastuzumab. Extensive scenario analyses were performed, and results remained highly favourable for T-DM1, indicating the robustness of the model results.

The cost savings predicted in the model are driven by the lower treatment regimen costs in metastatic health states incurred with the adjuvant T-DM1 strategy relative to the trastuzumab strategy. Treatment regimens at recurrence often involve multiple or costly agents (or both), thereby driving up the cost per cycle. For example, the standard first-line systemic therapy in the metastatic setting currently uses pertuzumab–trastuzumab–chemotherapy, at a cost of approximately $9,000 per cycle. Patients receiving T-DM1 were predicted to spend more time in iDFS off treatment, and they therefore did not incur additional metastatic regimen costs to the same extent that patients treated with trastuzumab did. However, even by lowering the average monthly metastatic regimen cost in a scenario analysis by assuming that more patients were receiving less-costly alternatives, T-DM1 remained highly cost-effective compared with trastuzumab, with an ICUR of $2,500 per QALY.

Treatment with T-DM1 in the EBC setting is likely to significantly lower the number of patients with residual invasive disease progressing to mBCa, which requires costly care. A recent epidemiologic model for relapsed mBCa cases predicted a 27% reduction in mBCa incident cases over 10 years after the launch of T-DM1 in the European Union Five (France, Germany, Italy, Spain, United Kingdom), above the current reduction as a result of treating with trastuzumab[65]. That reduction can translate into substantial savings for the health care system and have a significant impact on HRQOL for patients.

Most of the QALY benefits were incurred in the iDFS health state and beyond the trial period, and were subject to uncertainties related to extrapolations. Scenario analyses

TABLE IV Discounted clinical and economic probabilistic base-case results

Parameter	T-DM1	Trastuzumab	Incremental
Effectiveness			
Life–years	23.00	20.41	2.59
iDFS	21.94	18.50	3.44
Nonmetastatic	0.02	0.06	–0.04
Remission/NED	0.15	0.53	–0.38
First-line metastatic	0.41	0.61	–0.20
Subsequent-line metastatic	0.48	0.71	–0.24
QALYs	18.32	16.16	2.16
iDFS	17.66	14.89	2.76
Nonmetastatic	0.01	0.05	–0.04
Remission/NED	0.12	0.44	–0.31
First-line metastatic	0.29	0.43	–0.14
Subsequent-line metastatic	0.23	0.35	–0.12
Costs	$177,826	$186,131	–$8,305
iDFS	$77,421	$37,252	$40,168
Nonmetastatic	$938	$3,286	–$2,349
Remission/NED	$85	$298	–$214
First-line metastatic	$48,293	$69,570	–$21,277
Subsequent-line metastatic	$44,685	$65,760	–$21,075
End of life	$6,405	$9,964	–$3,559
ICUR (incremental cost per QALY)			T-DM1 dominated trastuzumab

T-DM1 = trastuzumab emtansine; iDFS = invasive disease-free survival; NED = no evidence of disease; QALY = quality-adjusted life–year; ICUR = incremental cost–utility ratio.

were conducted in which iDFS curves were varied by T-DM1 treatment duration effect, cure proportion, and use of different parametric distributions; T-DM1 continued to dominate trastuzumab or produced ICURs less than $10,000 per QALY, confirming the robustness of the model.

The favourable cost–utility associated with adjuvant T-DM1 in the present study should be examined within the context of cost–utility analyses of other neoadjuvant and adjuvant HER2-targeted therapies in Canada, including trastuzumab and pertuzumab. Examples include the association of adjuvant trastuzumab with ICURs of $13,100–$127,900 per QALY gained when compared with placebo[66,67]. As well, adjuvant pertuzumab–trastuzumab, compared with trastuzumab alone, has been associated with ICURs of $32,200–$75,900 per QALY gained[38]. To the best of our knowledge, adjuvant T-DM1 for women with residual invasive disease after neoadjuvant systemic therapy is the first HER2-targeted therapy that is associated with both QALY gains and cost savings (that is, dominant strategy).

A major strength of the present study is that the model structure has been validated and accepted in HTA submissions in both neoadjuvant and adjuvant treatment for BCa[36–38,68]. The structure is considered clinically plausible and accurately reflects the disease progression process. Where possible, conservative assumptions were used, and key assumptions were tested in scenario analyses. Additionally, 4 medical oncologists from various provinces served as clinical advisors, capturing a more complete estimate of practices in Canada.

The model is not without limitations. To capture all relevant benefits over a lifetime horizon, all economic models conducted in the adjuvant setting involve survival extrapolation beyond the relatively short follow-up period in clinical trials. In our analysis, as in other adjuvant cost-effectiveness or utility analyses, most of the incremental life–year gains accumulated beyond the trial follow-up period and in the absence of the yet-to-be observed survival benefit in the KATHERINE trial. We have also assumed a 7-year treatment effect, with tapering until 10 years, as supported by updated analyses from the APHINITY trial[49] and Chumsri *et al.*[50]. Nonetheless, further follow-up in the KATHERINE trial is required to confirm those plausible and yet less-certain assumptions. As well, all models involve a number of assumptions or input parameters that cannot be directly derived from the relevant clinical trial and are often validated by clinical expert opinion or sensitivity analyses, or both. For example, the average age at model entry was slightly younger than that observed in Canada. However, the clinicians felt that it would have little, if any, impact on efficacy. Additionally, at the time of analysis, SC trastuzumab and a biosimilar were not reimbursed by any public drug plans, and therefore future uptake by provincial cancer agencies and the list price of the biosimilar were unknown. Still, under the extreme scenario in which the trastuzumab treatment price was reduced by assuming that all use would result from a trastuzumab biosimilar, T-DM1 remained dominant.

The model did not include a trastuzumab loading dose (8 mg/kg); the maintenance dose (6 mg/kg) was assumed throughout, because the proportion of patients who would have discontinued trastuzumab long enough to require reintroduction of a loading dose was not known. That assumption is conservative, and therefore the treatment costs in the trastuzumab arm were likely underestimated.

Finally, key inputs were obtained from trial data, given that real-world outcomes were not available. Future research using real-world data, when available, can strengthen the study findings.

CONCLUSIONS

Adjuvant T-DM1 in patients with HER2-positive EBC who have residual invasive disease after neoadjuvant systemic treatment, is associated, compared with trastuzumab, with a 50% reduction in the risk of recurrence or death[35]. In the present economic analysis, the observed clinical outcomes in the KATHERINE trial translated to incremental QALY gains and cost savings associated with T-DM1 relative to trastuzumab. Adjuvant treatment with T-DM1 is cost-effective, and T-DM1 is the first HER2-targeted therapy that is economically dominant compared with the standard of care. The economic analysis suggests that investing in adjuvant T-DM1 in this well-defined patient population offers

an opportunity to reduce health care costs by preventing patients from progressing to mBCa. As acknowledged by the Canadian Agency for Drugs and Technologies in Health, the national health technology assessment agency[69], investment in treating HER2-positive EBC is likely to have substantial long-term benefits for Canadian patients, caregivers, the health care system, and society.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TY and NB have received fees as advisory board members for Hoffmann–La Roche Limited. DB and AL have received fees to adapt the model to the Canadian setting and conduct the analysis, as well as to develop and finalize the manuscript after extensive input and review by all co-authors. MEC, CR, and GSJ are employees of Hoffmann–La Roche Ltd. TY previously served as a member of the pCODR Expert Review Committee at the pan-Canadian Oncology Drug Review (pCODR), but the views presented here are those of the authors and not of pCODR or the Canadian Agency for Drugs and Technologies in Health.

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