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ORIGINAL ARTICLE



Cost-effectiveness of lapatinib plus letrozole in HER2-positive, hormone receptor–positive metastatic breast cancer in Canada

T.E. Delea MSIA, J. Amdahl BS,* A. Chit MBiotech,†‡ and M.M. Amonkar PhD§*

ABSTRACT

Background

The cost-effectiveness of first-line treatment with lapatinib plus letrozole for postmenopausal women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–positive (HER2+) metastatic breast cancer (MBC) has not been assessed from the Canadian health care system and societal perspectives.

Methods

A partitioned survival analysis model with 3 health states (alive, pre-progression; alive, post-progression; dead) was developed to estimate direct and indirect costs and quality-adjusted life years (QALYS) with lapatinib–letrozole, letrozole, anastrozole, or trastuzumab–anastrozole as first-line treatment. Clinical inputs for lapatinib–letrozole and letrozole were taken from the EGF30008 trial (NCT00073528). Clinical inputs for anastrozole and trastuzumab–anastrozole were taken from a network meta-analysis of published studies. Drug costs were obtained from the manufacturer's price list, the Quebec list of medications, and IMSBrogan. Other costs were taken from the Ontario Health Insurance Plan's Schedule of Benefits and Fees and published studies. A 10-year time horizon was used. Costs and QALYS were discounted at 5% annually. Deterministic and probabilistic sensitivity analyses were performed to assess the effects of changes in model parameters.

Results

Quality-adjusted life years gained with lapatinib–letrozole were 0.236 compared with trastuzumab–anastrozole, 0.440 compared with letrozole, and 0.568 compared with anastrozole. Assuming a health care system perspective, incremental costs were $5,805, $67,029, and $67,472 respectively. Given a cost per QALY threshold of $100,000, the probability that lapatinib–letrozole is preferred was 21% compared with letrozole, 36% compared with anastrozole, and 68% compared with trastuzumab–anastrozole. Results from the societal perspective were similar.

Conclusions

In postmenopausal women with HR+/HER2+ MBC receiving first-line treatment, lapatinib–letrozole may not be cost-effective compared with letrozole or anastrozole, but may be cost-effective compared with trastuzumab–anastrozole.

KEY WORDS

Metastatic breast cancer, lapatinib, letrozole, trastuzumab, anastrozole, cost-effectiveness, cost–utility

1. INTRODUCTION

Trastuzumab is a humanized monoclonal antibody directed against the human epidermal growth factor receptor 2 (HER2, encoded by the *ERBB2* gene), which used in the treatment of metastatic breast cancer (MBC) that overexpresses HER2. Lapatinib is an orally administered dual inhibitor of HER1 (encoded by the *ERBB1* gene) and HER2. Clinical trials of lapatinib and trastuzumab used in combination with aromatase inhibitors in patients with HER2-positive (HER2+) and hormone receptor–positive (HR+) MBC have shown favourable efficacy results[1,2]. The EGF30008 trial (NCT00073528) was a phase III, randomized, double-blind, placebo-controlled study in which 1286 postmenopausal women with HR+ MBC were randomized to first-line therapy with lapatinib–letrozole or letrozole–placebo[1]. Compared with HER2+ MBC patients receiving letrozole–placebo, those receiving lapatinib–letrozole experienced a significant increase in median progression-free

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survival (PFS: 8.2 months vs. 3.0 months, $p = 0.019$)[1]. The TANDEM trial was a phase III open-label multicenter study of 208 postmenopausal patients with HR+ and HER2+ MBC randomized to receive first-line treatment with trastuzumab–anastrozole or anastrozole alone[2]. Median PFS (4.8 months vs. 2.4 months respectively, $p = 0.0016$) and median time to progression (4.8 months vs. 2.4 months respectively, $p = 0.0007$) were significantly greater in the combination arm than in the monotherapy arm[2].

The baseline characteristics of patients in both trials were similar, although the median age in the EGF30008 trial was slightly greater at 59–60 years compared with 54–56 years in the TANDEM trial[1,2]. Although the EGF30008 trial was open to stage IIIB and IIIC patients, most entrants (≥94% in each arm) had MBC[1]. The median number of metastatic sites in both trials was 2, and similar numbers of patients had received prior chemotherapy or anti-estrogen therapy, or both[1,2].

The adverse event (AE) profiles of lapatinib and trastuzumab differ. Common AEs seen with lapatinib include grade 1 or 2 diarrhea, rash, and fatigue. Grade 4 AEs and cardiac toxicity are rarely seen with lapatinib. Cardiotoxicity is observed with trastuzumab. The rate of trastuzumab treatment discontinuation because of cardiotoxicity is very low, but higher than that in patients not receiving trastuzumab. In the TANDEM and EGF30008 trials, rates of diarrhea and nausea were higher in the experimental arms than in the control arms. In the EGF30008 trial, the incidence of rash was higher with lapatinib–letrozole than with letrozole[1]. In the TANDEM trial, rates of dyspnea and cardiac events were higher with trastuzumab–anastrozole than with anastrozole, but no differences were observed in the rates of grade 3 and 4 cardiotoxicities between the treatment arms[2]. The overall incidence of grade 3 or 4 AEs was low in both trials[1,2].

The TANDEM and EGF30008 trials provided evidence for clinical benefit as described, but they did not assess the cost-effectiveness of the therapies. Cost-effectiveness information is required by decision-making authorities in Canada, the United States, the United Kingdom, and other countries in their deliberations about pricing, reimbursement, and access to novel therapies. The objective of the present study was to assess, from the Canadian health care system and societal perspectives, the cost-effectiveness of first-line treatment with lapatinib–letrozole compared with other widely used therapies for postmenopausal women with HR+ HER2+ MBC. The analyses reported here were the basis of an economic evaluation included in the manufacturer's submission to the Institut national d'excellence en santé et en services sociaux, which makes recommendations for drug funding to the public drug plan of Quebec administered by the Régie de l'assurance maladie du Québec.

2. METHODS

2.1 Approach

A partitioned survival analysis was used to evaluate the cost-effectiveness of lapatinib–letrozole in postmenopausal women receiving first-line treatment for HR+ HER2+ MBC. With this modelling approach, patients were assumed to be

- alive with no progression (PFS),
- alive with progression [post-progression survival (PPS)], or
- dead.

Patients were assumed to be progression-free at model entry and receiving treatment until detection of progression. The proportion of patients in each health state over time was estimated based on empirical or fitted survival functions for PFS and overall survival (OS). Expected PFS and expected OS were then calculated as the area under the PFS and the OS curve respectively. Expected PPS was calculated as the difference between expected OS and expected PFS. Costs and quality of life were assumed to be conditioned on treatment and disease state, and were calculated by multiplying expected PFS and expected PPS by corresponding cost and utility estimates. All cost estimates are in Canadian dollars. A daily cycle length was used so that no half-cycle correction was required.

The primary analysis of cost-effectiveness focused on comparisons of lapatinib–letrozole with letrozole alone, with trastuzumab–anastrozole, and with anastrozole alone. The comparisons were based on effectiveness information from a published systematic review and network meta-analysis[3] and were therefore considered to represent the strongest comparisons in terms of level of evidence.

In a secondary analysis, we compared lapatinib–letrozole with trastuzumab–docetaxel and with trastuzumab–paclitaxel (Appendix A). Effectiveness information for those analyses were based on an adjusted indirect treatment comparison (conducted for the present study) that was constrained by the availability of controlled trials with which to construct a connected evidence network; hence, the strength of evidence for those comparisons is considerably less.

In a tertiary analysis, we compared lapatinib–letrozole with trastuzumab–exemestane and with trastuzumab–fulvestrant (Appendix A). For those comparators, it was infeasible to construct a linked evidence network and make an indirect treatment comparison. The relative effectiveness of the comparators is therefore based on assumption, and the level of evidence for the comparison is low.

Pairwise comparisons of the cost-effectiveness of lapatinib–letrozole and each of the other comparators were made. The incremental cost-effectiveness ratio

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(ICER) for each comparison was calculated as the ratio of the difference in expected total lifetime breast cancer costs to the difference in QALYS. Incremental cost-effectiveness analyses, comparing all treatments simultaneously, were also conducted for the primary, secondary, and tertiary analyses (secondary and tertiary analyses are shown in Appendix A). In conducting the incremental cost-effectiveness analyses, comparators that were more costly and no more effective than one or more other comparators were excluded by the principle of "pure" or "strong" dominance. The remaining comparators were then ordered by effectiveness, and ICERS were calculated for each comparator and for the next most effective alternative. Comparators with an ICER greater than that of a more effective comparator were excluded by the principle of "extended" or "weak" dominance. The remaining therapies were assumed to constitute the efficiency frontier.

The primary analyses were conducted from the Canadian health care system and societal perspectives. The former analysis considers only direct medical care costs. The latter analysis includes direct nonmedical costs and indirect costs and benefits. Secondary and tertiary analyses focused on the societal perspective only. The model estimated the expected lifetime costs of breast cancer care, life expectancy or life-years (LYS), progression-free LYS (PFLYS), post-progression LYS (PPLYS), and QALYS for each treatment strategy considered. Costs and outcomes were evaluated over a 10-year time horizon and were discounted at 5% annually. The model was developed in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, U.S.A.). Funding for this research was provided to PAI (Policy Analysis Inc.) by GlaxoSmithKline. Authors at GlaxoSmithKline had a role in the conception and design of the study and in the collection, analysis, and interpretation of data; they also had final manuscript approval.

2.2 Model Estimation

Table I presents parameter estimates. For letrozole, the PFS and OS were estimated by using accelerated failure time regression to fit Weibull survival functions to the observed failure time data from the EGF30008 trial[11]. The Weibull is a flexible survival function that allows for increasing or decreasing risk of events over time[12] and takes the general form $S[t] = \exp(-\lambda t^{\gamma})$ where t is days since treatment initiation. Figure 1 shows the empirical and fitted Weibull distributions. Although the Weibull curves diverged from the empirical survival distributions in some segments, the restricted means at the end of follow-up (that is, the areas under the curve) for the Weibull distributions were similar to those for the empirical distributions.

The hazard ratios for PFS and OS for lapatinib–letrozole compared with letrozole alone were obtained from the EGF30008 trial[1]; those for trastuzumab–anastrozole compared with anastrozole alone were obtained from a published network meta-analysis based on a systematic review of the literature by Riemsma *et al.*[3]. Figure 2 presents the evidence network used in the present analysis.

2.3 Utilities and Costs

Utility values were assumed to depend on progression and AES, but to be otherwise independent of treatment. Health-related quality of life was assessed in the EGF30008 trial using the Functional Assessment of Cancer Therapy–General (FACT-G: FACIT, Elmhurst, IL, U.S.A.) plus the breast cancer subscale (FACT-B), which were administered every 12 weeks until withdrawal of the study medications[4]. A generic preference-based instrument—for example, the EQ-5D (EuroQol Group, Rotterdam, Netherlands)—was not administered. Utility scores for patients in EGF30008 were therefore derived from the FACT-G using a published algorithm mapping from the FACT-G to time trade-off utilities[8]. The utility value for patients in the PFS state without AES was based on the mean utility value among all HER2+ patients in EGF30008 considering all follow-up assessments before progression and without grade 3 or greater AES[9]. Because FACT-B assessments were not routinely completed after disease progression, post-progression utility values were not generalizable to the entire post-progression period. The mean decrement in utility associated with progression was therefore estimated using results from a vignettes-based study of predictors of utilities for various stages of MBC in a community sample of 100 people in the United Kingdom[10]. Decrements in utilities associated with alopecia, diarrhea, fatigue, and vomiting also were obtained from that study[10]. Utility values for other AES were obtained from a vignettes-based study of utilities for MBC health states in a sample of 100 people from each of the Netherlands and Sweden[18], supplemented with estimates from a similar study for advanced metastatic non-small cell lung cancer[19], and assumptions. The QALYS lost with each AE were calculated by multiplying the decrement in utility with each AE by the estimated mean duration of the AE. The mean durations of the AES were estimated using data from EGF30008.

Unit costs of medications were based on manufacturer price lists, Quebec formulary prices (July 6, 2011), and IMSBrogan (http://www.imshealth.com/portal/site/ims/) wholesale acquisition costs[20]. For oral regimens, the drug acquisition costs were based on a mean cost per tablet; for trastuzumab, acquisition costs were estimated according to the mean cost per vial. Dosages were assumed to be the same as in EGF30008 and TANDEM, except for trastuzumab, which was assumed to be administered every 3 weeks, consistent with clinical practice in Canada.

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TABLE I Model inputs

Parameter	*Estimate*	*SE*	*Source*
Weibull survival function parameters			
Progression-free survival [PFS (months)]			
Letrozole			
λ	0.15258	0.01756	Johnston *et al.,* 2009[1]
γ	0.87727	0.07003	Johnston *et al.,* 2009[1]
Hazard ratio (HR) vs. letrozole			
Lapatinib–letrozole	0.65	0.17	Johnston *et al.,* 2009[1]
Trastuzumab–anastrozole	0.73	0.19	Riemsma *et al.,* 2012[3]
Anastrozole	1.22	0.12	Riemsma *et al.,* 2012[3]
Overall survival [OS (months)]			
Letrozole			
λ	0.01732	0.01062	Johnston *et al.,* 2009[1]
γ	1.10926	0.13154	Johnston *et al.,* 2009[1]
HR vs. letrozole			
Lapatinib–letrozole	0.77	0.2	Johnston *et al.,* 2009[1]
Trastuzumab–anastrozole	0.90	0.19	Riemsma *et al.,* 2012[3]
Anastrozole	1.08	0.12	Riemsma *et al.,* 2012[3]
Fisher transformation of correlation between log HR for PFS and log HR for OS	0.46	0.13	Sherrill *et al.,* 2008[4]
Costs ($)			
Medications			
Lapatinib (250 mg tablet)	23.50	NA	Manufacturer price list
Letrozole (2.5 mg tablet)	1.58	NA	Quebec List of Medications, July 6, 2011
Trastuzumab (440 mg vial)	2,913.00	NA	Manufacturer price list
Anastrozole (1 mg tablet)	4.95	NA	Quebec List of Medications, July 6, 2011
Pharmacy, per dispensing			
Lapatinib, letrozole, anastrozole	8.44	2.11	Régie de l'assurance maladie du Québec
Facility, per day of use (trastuzumab)			
Trastuzumab	76.42	19.11	Leung *et al.,* 1999[5]
Monitoring, per month (lapatinib–trastuzumab)	78.78	19.69	OHIP Schedule of Services and Fees, 2008[6]
Other per month			
Pre-progression	652.89	139.35	Will *et al.,* 2000[7]
Post-progression	652.89	139.35	Will *et al.,* 2000[7]
Relative dose intensity (actual vs. planned daily dose)			
Lapatinib–trastuzumab	0.95	0.0053	Johnston *et al.,* 2009[1]
Letrozole–anastrozole	1.04	0.0144	Johnston *et al.,* 2009[1]
Utilities			
Pre-progression	0.86	0.01	Dobrez *et al.,* 2007[8], Delea *et al.,* 2010[9]
Post-progression, reduction	0.24	0.06	Lloyd *et al.,* 2006[10]

SE = standard error; OHIP = Ontario Health Insurance Plan.

Trastuzumab administered every 3 weeks was assumed to have the same effectiveness as once-weekly trastuzumab[20–22]. Planned dosages for lapatinib–letrozole and letrozole were adjusted using relative dose intensity estimates from EGF30008. The relative dose intensity for trastuzumab was assumed to be the same as that for lapatinib. The relative dose intensities for other hormonal therapies were assumed to be the same as that for letrozole.

Administration costs for trastuzumab were based on estimates reported in a cost–utility analysis by Leung and colleagues[5]. Cardiac monitoring via

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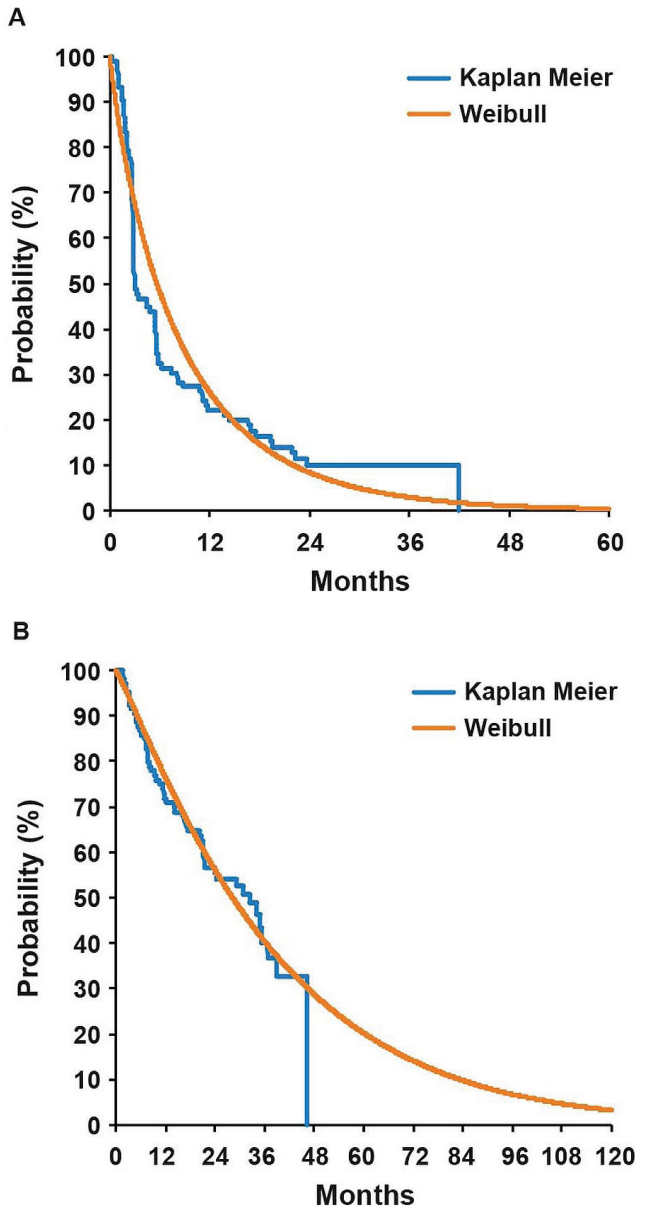


FIGURE 1 Weibull and Kaplan–Meier estimated (A) progression-free survival and (B) overall survival with letrozole.

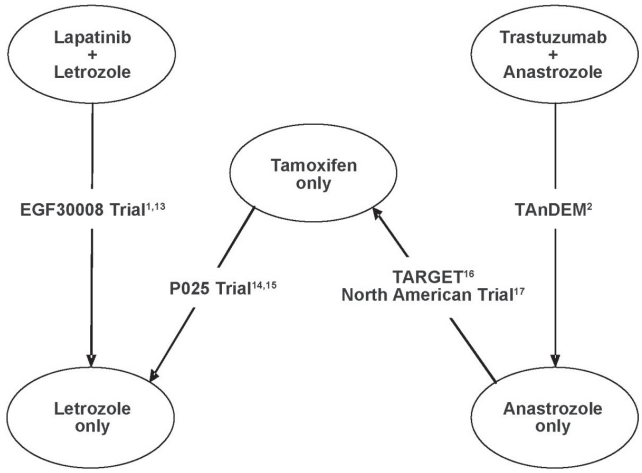


FIGURE 2 Evidence network for comparators in the primary analysis[1,2,13–17].

echocardiogram (50%) or multiple-gated acquisition imaging (50%) once every 3 months was assumed for all patients receiving lapatinib or trastuzumab. Costs of those services were based on the 2008 OHIP (Ontario Health Insurance Plan) Schedule of Benefits and Fees[6].

The costs of grades 3 and 4 diarrhea were based on a published estimate of the cost of severe chemotherapy-induced diarrhea in patients with colorectal cancer[23]. Costs of other AEs were based on treatment algorithms and published estimated unit costs of medications and medical services. Treatment algorithms were estimated based on the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 3.0[24]; on other published sources[26,27]; and on discussions with a practicing oncologist. For simplicity, we assumed that all AEs would require 1 additional visit.

Patients with non-pruritic papular eruption rash were assumed also to require prescriptions for betamethasone 0.1% cream (60 g tube), chlorpheniramine maleate 4 mg every 4–6 hours for 30 days, and doxycycline 100 mg daily for 30 days. Patients with nausea and vomiting were assumed to receive prescriptions for oral dexamethasone 12 mg daily for 30 days and ondansetron 8 mg twice daily for 5 days, and to be hospitalized. Unit costs of drugs used in the treatment of AEs were obtained from the Ontario Drug Benefit Formulary[27] or the IMSBrogan database. Unit costs of visits were based on the OHIP Schedule of Benefits and Fees[6]. The costs of hospitalization for nausea and vomiting were based on the average cost of hospitalization for poisoning by drugs, medicaments, and biologic substances as reported by the Canadian Institute for Health Information[28].

Other breast cancer treatment costs (per month) and terminal care costs were obtained from a study of the lifetime costs of breast cancer in Canada[7]. Estimated probabilities, disutilities, mean durations, and costs of grade 3 or greater AEs are included in Appendix A.

Travel costs per visit were estimated by multiplying the estimated average travel distance per visit by the Canadian Revenue Agency's travel reimbursement rate[29]. The average travel distance was assumed to be 26 miles roundtrip, based on the reported median distance from home to hospital where first treatment was received in the study by Lauzier *et al.*[30]. Information about per-trip parking costs being lacking, those costs were not included. Other nonmedical direct costs were approximated in the current study based on the 30-day out-of-pocket costs reported for all cancer patients in the study by Longo *et al.* ($297 excluding

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drugs, family care, travel costs, and parking or transit fares in the current study)[31].

Patient work loss was assumed to include loss because of major absences and because of treatment and cardiac monitoring. Expected monthly losses because of major absences were estimated to total $84.81 based on data from a study of major absences in 646 women with newly diagnosed breast cancer in Quebec[32] combined with estimates of the proportion of Canadian breast cancer patients who are employed[30] and with the mean hourly wage in Quebec[33]. Data being lacking, the monthly cost of work loss was assumed to be the same during PFS and PPS. To calculate the cost of work loss because of treatment and monitoring, it was assumed that visits for trastuzumab treatment and cardiac monitoring would require a half-day off work. We assumed that the costs of work loss to obtain prescriptions for oral medications would be similar across all treatments, and they therefore were not considered.

Expected total monthly costs of caregiver work loss were estimated to be $80.63 during PFS and $301.36 during PPS. Caregiver work loss per month was obtained from a study of caregiver burden in 89 caregivers of women with advanced breast cancer in Ontario[34]. For employed caregivers, work loss during the patient's PFS was estimated based on reported mean caregiver work loss during palliative care, and work loss during the patient's PPS was estimated based on reported mean work loss during the terminal stage. The proportion of employed caregivers was estimated to be 56%, and 55% of caregivers were assumed to be male[34].

For each treatment, indirect benefits were calculated by multiplying the expected LYS gained in a comparison with anastrozole (the treatment with the lowest expected survival in the base case) by the estimated employment rate from Lauzier *et al.*[30], the estimated number of work hours in a year, and the mean hourly wage of women in Quebec[33].

2.4 Sensitivity Analyses

Probabilistic sensitivity analyses were conducted by simultaneously sampling from estimated probability distributions of model parameters to obtain 1000 sets of model input estimates. For each simulation, we calculated incremental costs and QALYS for each comparison. Confidence intervals for incremental costs and QALYS were approximated based on percentiles of the simulations, and cost-effectiveness acceptability curves were calculated for lapatinib–letrozole contrasted with each comparator. Acceptability curves were also calculated for the incremental cost-effectiveness analysis to identify the preferred comparator among all comparators, given each threshold value of cost-effectiveness. Deterministic sensitivity analyses were also conducted to assess the effects of changes in key model parameters on the resulting cost-effectiveness estimates.

3. RESULTS

3.1 Comparisons with Letrozole, Trastuzumab–Anastrozole, and Anastrozole

Lapatinib–letrozole was projected to increase all measures of effectiveness when contrasted with each of the comparators (Table II). The cost of medications was higher with lapatinib–letrozole than with any comparator, which is in part attributable to the longer PFS afforded by lapatinib–letrozole. Expected total costs were greater for lapatinib–letrozole than for the other comparators regardless of whether nonmedical direct and indirect costs were considered. From the health care system perspective, the costs per QALY gained with lapatinib–letrozole was $140,679 compared with letrozole, $10,266 compared with trastuzumab–anastrozole, and $107,207 compared with anastrozole. Results were similar when a societal perspective was taken.

From the health care perspective, incremental cost-effectiveness analyses showed that anastrozole was the least costly option, followed by letrozole, trastuzumab–anastrozole, and lapatinib–letrozole. Trastuzumab–anastrozole is dominated by lapatinib–letrozole by extended dominance. Anastrozole, letrozole, and lapatinib–letrozole thus constitute the efficiency frontier from the health care perspective. The cost per QALY gained with anastrozole compared with letrozole was $3,471 [Figure 3(A)].

Given a cost-per-QALY threshold of $100,000, acceptability curves for pairwise comparisons showed an estimated 18% probability that lapatinib–letrozole is preferred over letrozole, a 29% probability that lapatinib–letrozole is preferred over anastrozole, and a 66% probability that lapatinib–letrozole is preferred over trastuzumab–anastrozole [Figure 3(B)]. Acceptability curves for the incremental analysis showed an estimated 68% probability that letrozole is preferred, a 15% probability that anastrozole is preferred, a 14% probability that lapatinib–letrozole is preferred, and a 4% probability that trastuzumab–anastrozole is preferred [Figure 3(C)]. Results were similar when a societal perspective was taken [Figure 3(D–F)].

For the deterministic sensitivity analyses, the cost-effectiveness of lapatinib–letrozole compared with letrozole and lapatinib–letrozole compared with anastrozole was not below $50,000 per QALY in any scenario. However, the cost-effectiveness of lapatinib–letrozole compared with trastuzumab–anastrozole was more sensitive to model parameters and assumptions. The cost per QALY gained with lapatinib–letrozole compared with trastuzumab–anastrozole was not greater than $100,000 in any scenario examined.

When PFS and OS for trastuzumab–anastrozole were assumed to be the same as for lapatinib–letrozole, total costs were estimated to be $3,209 greater for trastuzumab–anastrozole. The QALYS were estimated to be 0.001 greater for trastuzumab–anastrozole,

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TABLE II Base case results[a]

Parameter		*LAP–LET compared with*		
	LAP–LET	*LET*	*TRZ–ANA*	*ANA*
Effectiveness, not discounted				
Progression-free life years (PFLYS)	1.238	0.479	0.152	0.632
Post-progression life years (PPLYS)	2.521	0.208	0.266	0.242
Life-years (LYS)	3.759	0.687	0.419	0.874
Quality-adjusted life years (QALYS)	2.627	0.54	0.295	0.693
Effectiveness, discounted				
PFLYS	1.159	0.43	0.135	0.573
PPLYS	2.106	0.114	0.196	0.122
LYS	3.265	0.544	0.33	0.695
QALYS	2.302	0.44	0.236	0.568
Costs ($)				
Direct medical costs				
Study medications				
Anti-HER2 therapy	61,988	61,988	5,755	61,988
Hormonal therapy	764	268	(1,381)	($532)
Chemotherapy	—	—	—	—
Total study drugs	62,752	62,256	4,373	61,457
Administration	393	313	(1,237)	327
Monitoring	1,181	405	127	539
Treatment of adverse events	391	252	258	256
Other pre-progression	9,791	3,353	1,050	4,465
Post-progression	34,434	450	1,233	428
TOTAL	108,942	67,029	5,805	67,472
Direct nonmedical costs, indirect costs, and indirect benefits				
Direct nonmedical costs and indirect costs	27,242	3,973	2,147	5,010
Indirect benefits	(11,629)	(9,106)	(5,525)	(11,629)
TOTAL	15,613	(5,133)	(3,378)	(6,619)
TOTAL	124,555	61,896	2,426	60,853
Cost-effectiveness ($)				
Health care system perspective				
ΔCost/ΔLY		123,165	17,579	97,083
ΔCost/ΔPFLY		155,850	43,118	117,797
ΔCost/ΔQALY		152,344	24,561	118,868
Societal perspective				
ΔCost/ΔLY		113,734	7,348	87,559
ΔCost/ΔPFLY		143,916	18,023	106,242
ΔCost/ΔQALY		140,679	10,266	107,207

[a] Outcomes of the primary analysis with pairwise comparisons based on societal and health care perspectives; outcomes of the secondary analysis are also included. Negative values are shown in parentheses. All costs are shown in Canadian dollars.

LAP = lapatinib; LET = letrozole; TRZ = trastuzumab; ANA = anastrozole; HER2 = human epidermal growth factor receptor 2.

reflecting differences between lapatinib–letrozole and trastuzumab–anastrozole in the effects of AEs on utilities. The cost-effectiveness of trastuzumab–anastrozole compared with lapatinib–letrozole was therefore estimated to be $4,585,468 per QALY gained.

4. DISCUSSION

The Canadian health authorities at the federal and provincial levels have no explicit guidelines specifying a threshold value for cost per QALY gained to

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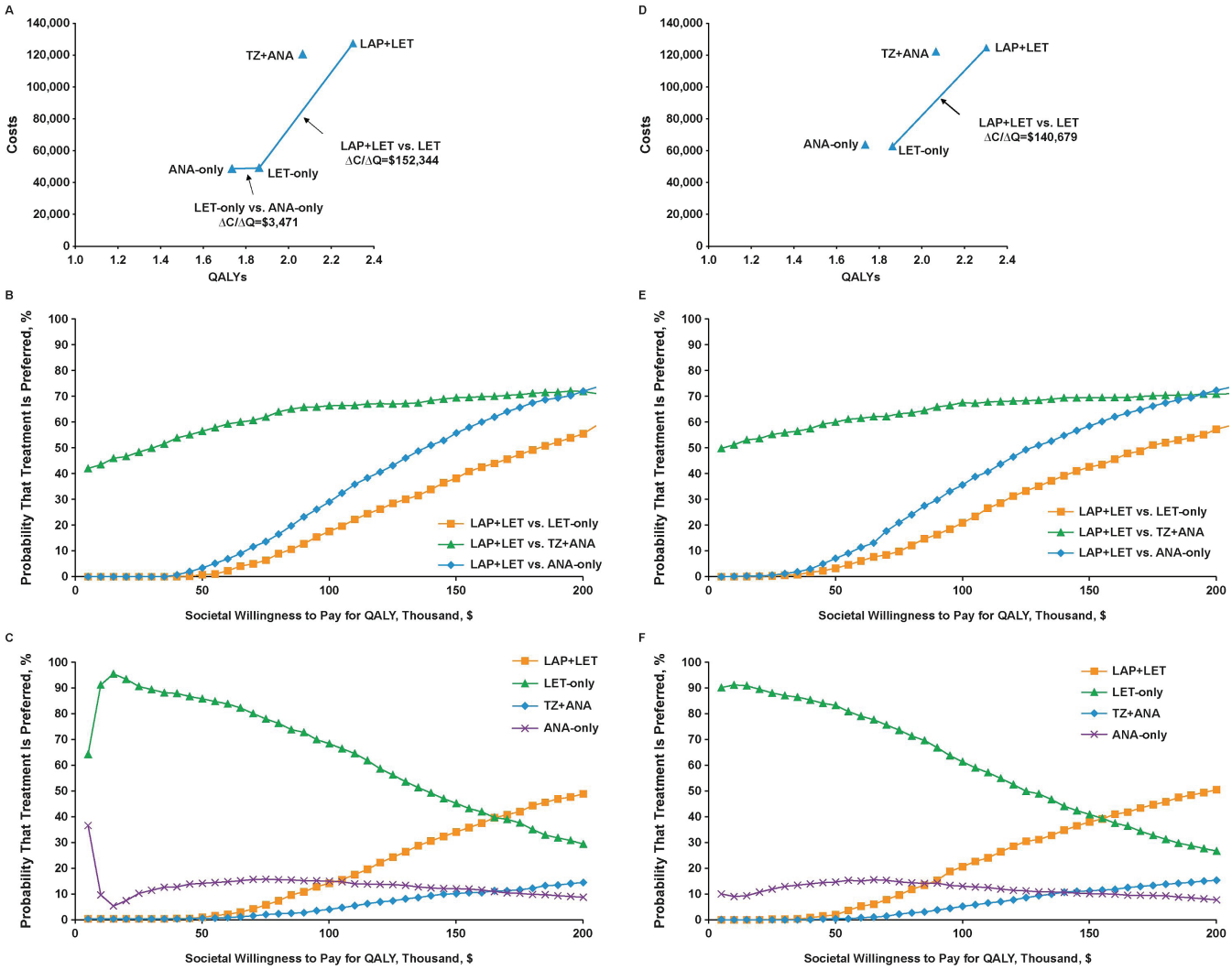


FIGURE 3 (A–C) Cost-effectiveness analyses based on a health care perspective. (A) Incremental analysis of costs and quality-adjusted life years (QALYS) for each comparator, with the efficiency frontier. (B) Percentage of simulations in which lapatinib–letrozole is preferred over the comparator, given the cost-per-QALY threshold. (C) Incremental analysis results showing the percentage of simulations in which a therapy is preferred among all comparators, given the cost-per-QALY threshold. (D–F) Cost-effectiveness analyses based on a societal perspective. (D) Incremental analysis of costs and QALYS for each comparator, with the efficiency frontier. (E) Percentage of simulations in which lapatinib–letrozole is preferred over the comparator, given the cost-per-QALY threshold. (F) Incremental analysis results showing the percentage of simulations in which a therapy is preferred among all comparators, given the cost-per-QALY threshold. All costs shown in Canadian dollars. TZ = trastuzumab; ANA = anastrozole; LAP = lapatinib; LET = letrozole.

determine whether a therapy provides good value. Studies have been conducted to identify implicit thresholds for reimbursement in Australia and the United Kingdom[35], but no such analysis has been conducted for Canada. Laupacis *et al.*[36,37] suggested that therapies with a cost less than $20,000 per QALY gained in 1990 Canadian dollars should be considered cost-effective. In the United States, US$50,000 per QALY is frequently quoted as a defining threshold for determining whether a drug is cost-effective[38]. In the United Kingdom, the National Institute for Health and Clinical Excellence uses a threshold of £30,000 per QALY[39]. Estimates of the cost-effectiveness of lapatinib–letrozole compared with the aromatase inhibitor monotherapies reported in the present study are above those thresholds, but estimates of the cost per QALY gained with lapatinib–letrozole compared with trastuzumab–anastrozole are below them. Results of probabilistic sensitivity analysis indicate an estimated 68% probability that lapatinib–letrozole is preferred over trastuzumab–anastrozole given a cost-effectiveness threshold of $100,000 per QALY gained. However, because of structural uncertainty with many parameter estimates not reflected in the probabilistic sensitivity analysis, it is difficult to draw any firm conclusions concerning the relative

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cost-effectiveness of lapatinib–letrozole compared with trastuzumab–anastrozole.

Like most cost-effectiveness evaluations, our analyses are based on a number of necessary simplifying assumptions, and they use data from a variety of primary and secondary data sources. As a result, certain limitations must therefore be recognized. Most importantly, studies directly comparing lapatinib–letrozole with anastrozole and with trastuzumab–anastrozole are unavailable, and estimates of the relative efficacy and safety of those regimens were based on an adjusted indirect comparison. Although this approach is preferred in instances in which direct evidence is unavailable, such indirect comparisons are associated with uncertainty, given the potential differences in patients and methods in the various studies, and our findings with respect to relative cost-effectiveness must be interpreted with caution. In particular, the beneficial effect of trastuzumab on OS observed in the TANDEM trial was likely confounded by the post-progression cross-over of approximately 70% of patients from anastrozole to trastuzumab[41]. Published estimates of OS hazard ratios for trastuzumab–anastrozole compared with anastrozole that use methods to control for cross-over were not publicly available at the time our study was conducted, and so it was not possible to adjust for the related confounding. There was almost universal post-progression cross-over from tamoxifen to letrozole in the P025 trial[14,15], and cross-over in that trial, which was part of the evidence network, may have biased the comparison of trastuzumab–anastrozole with letrozole in favour of trastuzumab–anastrozole.

Patients with extensive symptomatic visceral, rapidly progressing, or life-threatening disease were excluded from the EGF30008 trial, but no such exclusion occurred in TANDEM. To the extent that treatment effects, measured as hazard ratios, are modified by such factors, the indirect comparisons may be biased. Although no available published data document such an interaction, the possibility of confounding must be recognized. Also, in the P025 trial of letrozole compared with tamoxifen, 33% of patients had an unknown hormone status[14]. In contrast, in the TARGET and North American trials of anastrozole compared with tamoxifen, 55% of patients had an unknown hormone status[17]. Many of the participants with unknown hormone status were likely HR-negative (patients for whom no benefit would accrue to aromatase inhibitors compared with tamoxifen). However, because the percentage of patients with an unknown hormone status was similar in each trial, that factor probably did not materially bias the comparison. Finally, the P025 trial and the trials of anastrozole compared with tamoxifen included both HER2+ and HER2-negative patients[15]. However, there are no data suggesting that the treatment effects of aromatase inhibitors compared with tamoxifen are modified by HER2 status.

Data on the costs of breast cancer–related health care services, direct nonmedical costs, indirect costs, and utility values were not collected in the EGF30008 trial, and those data were obtained from a variety of secondary sources. Model results were generally insensitive to those estimates.

5. CONCLUSIONS

Results of the present analysis suggest that lapatinib–letrozole is not likely to be cost-effective compared with letrozole or anastrozole. However, lapatinib–letrozole may be cost-effective compared with trastuzumab–anastrozole.

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Results of a similar analysis of the cost-effectiveness of lapatinib–letrozole from a U.K. National Health Service perspective were presented at the American Society of Clinical Oncology 2010 Annual Meeting; June 7, 2010; Chicago, IL, U.S.A.

7. CONFLICT OF INTEREST DISCLOSURES

TED and JA are employees of PAI, which has received research funding and consulting fees from GSK for activities related to the present study and has also received support for travel to meetings to present the study results. TED's institution also received consulting fees and research funding from GSK for activities unrelated to this study. MMA is an employee of, and holds stock in, GSK. AC was an employee of GSK while this study was being prepared.

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Correspondence to: Thomas E. Delea, Policy Analysis Inc., Four Davis Court, Brookline, Massachusetts 02445 U.S.A.
E-mail: tdelea@pai2.com

* PAI (Policy Analysis Inc.), Brookline, MA, U.S.A.
† GlaxoSmithKline, Mississauga, ON.
‡ University of Toronto, Toronto, ON.
§ GlaxoSmithKline, Collegeville, PA, U.S.A.

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APPENDIX A: INDIRECT TREATMENT COMPARISONS

Comparing Trastuzumab–Paclitaxel and Trastuzumab–Docetaxel with Letrozole

To calculate hazard ratios (HRS) for trastuzumab–paclitaxel and trastuzumab–docetaxel compared with letrozole, it was necessary to construct a linked-evidence network based on studies that compared one or more of the therapies examined in the primary analyses with trastuzumab–paclitaxel and trastuzumab–docetaxel (Figure A.1). The necessary studies were identified from the Riemsma *et al.*[10] systematic review and were supplemented with online and hand searches.

The indirect comparison was conducted using the method of Bucher *et al.*[11]. Using their method, an unbiased comparison of two treatments can be obtained by combining direct comparisons of each treatment with respect to a common control group. The direct comparisons can be based on the results of a single controlled clinical trial contrasted with a common comparator or with a pooled estimate based on multiple trials of the treatment contrasted with the common comparator. If $\log HR_{AvB}$ (from the estimate of the HR of treatment A compared with treatment B from one or more controlled trials) and $\log HR_{BvC}$ (from the estimate of the HR of treatment B compared with treatment C from one or more controlled trials) are known, then an estimate of the HR of treatment A compared with treatment C can be determined using the calculation

$$\log HR_{AvB} + \log HR_{BvC} = \log HR_{AvC}.$$

Because $\log HR_{AvB}$ and $\log HR_{BvC}$ are statistically independent, the variance of $\log HR_{AvC}$ equals the sum of the variances of $\log HR_{AvB}$ and $\log HR_{BvC}$. If not reported, the variances of the log HRS can be calculated from confidence intervals on the HRS.

Estimates of the relative effectiveness of tamoxifen and letrozole were taken from the P025 trial[1,2]. It should be noted that because approximately 100% of patients in the tamoxifen arm crossed over to letrozole after tamoxifen, the results may be biased against letrozole. That potential bias may in turn introduce a bias against letrozole (and consequently, against lapatinib–letrozole) into the comparisons of trastuzumab–paclitaxel with letrozole and trastuzumab–docetaxel with letrozole.

Estimates of the relative effectiveness of tamoxifen compared with anthracycline-based chemotherapy are taken from the Forbes and Australian and New Zealand Breast Cancer Trials Group COSA trial[3]. That trial is the only one identified by Riemsma *et al.*[10] that compared hormonal therapy with chemotherapy.

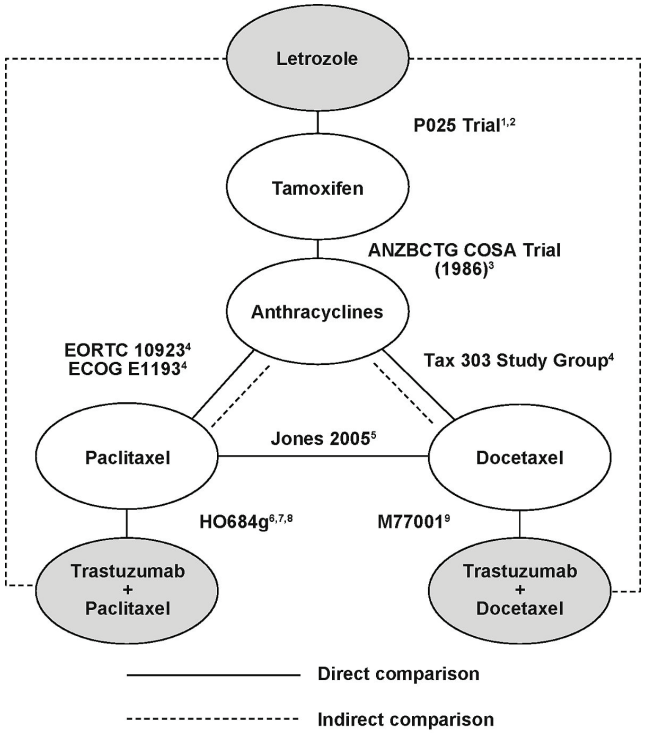


FIGURE A.1 Evidence network for comparators in the supplementary analyses[1–9].

It concluded that, overall, efficacy was similar for hormonal and anthracycline-based chemotherapy. However, only 25% of patients were estrogen receptor–positive. For that subgroup, median overall survival (OS) was 23 months for tamoxifen patients and 27 months for chemotherapy patients. Based on those data, it was assumed that tamoxifen and anthracycline-based chemotherapy are equally effective in HER2+ HR+ patients (HR for both PFS and OS: 1.0). Because of that assumption, the resulting estimates are associated with a very high degree of uncertainty. Also, information on the variance of the log HRS for PFS and OS for tamoxifen compared with anthracycline-based chemotherapy (required to calculate the variances of the log HRS for those treatments compared with letrozole) being lacking, they were approximated by arbitrarily assuming that the standard errors for the log HRS for PFS and OS for tamoxifen compared with chemotherapy would be 0.25 [approximate 95% confidence interval (CI): 0.6 to 1.65].

Estimates of the relative effectiveness of paclitaxel compared with anthracycline-based chemotherapy were based on a mixed-treatment comparison (MTC) of trials comparing paclitaxel with anthracycline-based chemotherapy[12,13], paclitaxel with docetaxel[14], and docetaxel with anthracycline-based chemotherapy[15]. An MTC provides an estimate of relative treatment effect using information from both direct and indirect comparisons. The MTC of direct and indirect evidence was conducted by random effects meta-analysis.

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Trials comparing paclitaxel and docetaxel with anthracycline-based chemotherapy were identified from a meta-analysis of taxanes compared with anthracyclines as first-line therapy for metastatic breast cancer (MBC) reported by Piccart–Gebhart *et al.*[4]. Estimates of the relative effectiveness of docetaxel and anthracycline-based chemotherapy were calculated similarly, based on an MTC of a trial comparing docetaxel with anthracycline-based chemotherapy[15], a trial comparing paclitaxel with docetaxel[14], and trials comparing paclitaxel with anthracycline-based chemotherapy[12,13].

Estimates of the relative effectiveness of trastuzumab–paclitaxel compared with paclitaxel were based on results of the pivotal trial (H0648g)[7] of trastuzumab in MBC positive for the human epidermal growth factor receptor 2 (HER2+). This multicentre randomized controlled clinical trial compared trastuzumab [loading dose of 4 mg/kg intravenously (IV), followed by 2 mg/kg IV once weekly] plus anthracycline or paclitaxel (175 mg/m^2 IV once every 3 weeks) with anthracycline or paclitaxel alone (175 mg/m^2 IV once every 3 weeks) in 469 patients with HER2+ MBC who had not been previously treated with chemotherapy for metastatic disease. The expression levels of HER2 were determined by immunohistochemical analysis (IHC), with patients having an IHC score of 2 or more (IHC 2+) being eligible for study enrolment. Compared with patients randomized to paclitaxel alone, the patients randomized to trastuzumab and paclitaxel experienced a significantly longer median time to disease progression (TTP: 6.9 months vs. 3.0 months for paclitaxel alone), longer median OS (22.1 months vs. 18.4 months for paclitaxel alone). The relative risk for TTP was 0.38 (95% CI: 0.27 to 0.53), and the relative risk for OS was 0.80 (95% CI: 0.56 to 1.11). Upon disease progression, 75% of patients in the paclitaxel arm and 47% of patients in the trastuzumab arm entered a nonrandomized open-label study in which trastuzumab was administered alone or in combination with other therapies.

A subgroup analysis of the H0648g trial reported by Baselga[15] showed that, compared with the combined IHC 2+ and 3+ HER2 patient population, the IHC 3+ HER2 patients derived a greater clinical benefit from trastuzumab plus paclitaxel (median TTP: 7.1 months vs. 3.0 months for paclitaxel alone; median OS: 25 months vs. 18 months for paclitaxel alone). The study did not report the HRs for TTP and OS.

Because of concerns about the reliability of IHC assays to accurately assess tumour HER2 status, with the possibility of false-positive and false-negative outcomes[17–19], a study by Mass *et al.*[8] used patient data from the H0648g study to analyze the influence of HER2 gene amplification as determined by fluorescence *in situ* hybridization (FISH) on TTP and OS for trastuzumab plus chemotherapy compared with chemotherapy alone. The study examined the combined anthracycline and paclitaxel patient populations of H0648g and did not evaluate the clinical benefits of trastuzumab plus paclitaxel compared with paclitaxel alone[7]. Of the 469 patients in the H0648g study population, 344 were identified as FISH-positive (FISH+). Of those 344, 176 were enrolled in the trastuzumab plus chemotherapy arm, and 50, in the chemotherapy-alone arm. Patients with FISH+ tumours experienced a significant improvement in TTP and OS when receiving trastuzumab plus chemotherapy (median TTP: 7.3 months vs. 4.6 months for chemotherapy alone; TTP risk ratio: 0.45; 95% CI: 0.35 to 0.57; $p < 0.0001$; median OS: 26.2 months vs. 20.3 months for chemotherapy alone; OS risk ratio: 0.71; 95% CI: 0.55 to 0.92; $p = 0.009$).

Estimated HRs for TTP and OS for trastuzumab–paclitaxel compared with paclitaxel in IHC 3+ or FISH+ HER2+ patients in the H0648g trial have not been reported. The HRs for TTP and OS for trastuzumab–paclitaxel compared with paclitaxel were therefore calculated using the reported median TTP and OS reported by Baselga[16] for IHC 3+ patients receiving trastuzumab–paclitaxel and paclitaxel, assuming that TTP and OS follow Weibull distributions. Based on that assumption, the HRs can be calculated as the ratio of the median survival times, taken to the power of the γ parameters of the corresponding Weibull distributions. The γ parameters for TTP and OS (1.22 and 1.17 respectively) were estimated by fitting Weibull models to the reported TTP and OS curve for FISH+ patients receiving chemotherapy as reported by Mass *et al.*[8] (similar curves for IHC 3+ or FISH+ patients receiving trastuzumab–paclitaxel or paclitaxel weren't available). The estimated HR for TTP was used as a proxy for the HR for PFS.

Lacking estimates of the variance of the log HRs for TTP and OS for trastuzumab–paclitaxel compared with paclitaxel in IHC 3+ patients, we estimated them based on the log HRs for TTP and OS for trastuzumab–chemotherapy compared with chemotherapy in the FISH+ patients in the H0648g trial as reported by Mass *et al.*[8]. The resulting values were adjusted for differences in the sample sizes between the two populations, assuming that the variances of the log HRs are approximately proportionate to the ratio of the sample sizes. It should be noted that the estimate of the HR for OS for trastuzumab–paclitaxel compared with paclitaxel from the H0648g trial may be biased against trastuzumab; approximately 75% of patients in paclitaxel arm and 47% of patients in the trastuzumab–paclitaxel arm were enrolled in a study of trastuzumab given after disease progression[20].

Estimates of the relative effectiveness of trastuzumab–docetaxel compared with docetaxel were based on a phase II randomized controlled trial reported by Marty *et al.* that examined the efficacy of a combination therapy with trastuzumab (loading dose of 4 mg/kg IV, followed by 2 mg/kg IV once weekly) plus docetaxel (100 mg/m^2 IV once every 3 weeks) compared with docetaxel monotherapy in

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186 patients with HER2+ MBC who had not previously been treated with chemotherapy for metastatic disease and who had not received prior taxanes or anti-HER therapy[9]. Overall, 95% of patients had IHC 3+ or FISH+ disease (or both). Median TTP was 11.7 months for trastuzumab plus docetaxel compared with 6.1 months for docetaxel alone (log-rank $p = 0.0001$). Median OS was 31.2 months for trastuzumab plus docetaxel compared with 22.7 months for docetaxel alone (log-rank $p = 0.0325$). Of 94 patients enrolled in the docetaxel-alone treatment arm, 53 patients (57%) crossed over to receive trastuzumab at disease progression (30 patients), after discontinuation of docetaxel (10 patients), or for other reasons (13 patients). Among patients who were randomized to docetaxel and who crossed over to trastuzumab, median OS was 16.6 months. Because the HRS for TTP and OS for trastuzumab–docetaxel compared with docetaxel were not reported, we used the methods of Tierney *et al.*[20] to estimate them based on *p* values.

Estimated Probabilities, Disutilities, Mean Durations, and Costs of Grade 3 or Greater Adverse Events

Data on the incidence of adverse events reported in the randomized controlled trials used in the adjusted indirect comparison are reported in Table A.I. Estimates of the probabilities, disutilities, mean durations, and costs of grade 3 or greater adverse events included in the model are reported in Table A.II.

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TABLE A.I Incidence of adverse events reported in randomized controlled trials used in adjusted indirect comparison

Adverse event	*Reference (trial name)*																			
	Johnston et al., *2009*[22,a] *(EGF30008)*				*Mouridsen* et al., *2003*[2,b] *(P025)*				*Nabholtz* et al., *2003*[23,b] *(North American trial)*				*Kaufman* et al., *2009*[24,a] (TANDEM)				*Paridaens* et al., *2003*[25,a]			
	LAP–LET *(n=654)*		LET *(n=624)*		LET *(n=455)*		TAM *(n=455)*		ANA *(n=506)*		TAM *(n=511)*		ANA *(n=103)*		TAM *(n=104)*		ANA *(n=182)*		TAM *(n=189)*	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Alopecia	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Anorexia	5	(0.8)	2	(0.3)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	1	(0.5)	2	(1.1)
Arthralgia	7	(1.1)	8	(1.3)	71	(15.6)	67	(14.7)	—	0.0	—	0.0	1	(1.0)	1	(1.0)	—	0.0	—	0.0
Asthenia	5	(0.8)	5	(0.8)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Back pain	12	(1.8)	14	(2.2)	82	(18.0)	86	(18.9)	—	0.0	—	0.0	1	(1.0)	—	0.0	—	0.0	—	0.0
Bone pain	4	(0.6)	10	(1.6)	99	(21.8)	95	(20.9)	—	0.0	—	0.0	3	(2.9)	1	(1.0)	—	0.0	—	0.0
Chills	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	1	(1.0)	—	0.0	—	0.0	—	0.0
Constipation	—	0.0	2	(0.3)	45	(9.9)	48	(10.5)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Cough	2	(0.3)	2	(0.3)	61	(13.4)	59	(13.0)	—	0.0	—	0.0	2	(1.9)	2	(1.9)	—	0.0	—	0.0
Diarrhea[c]	60	(9.2)	6	(1.0)	—	0.0	—	0.0	184	(36.4)	207	(40.5)	1	(1.0)	—	0.0	—	0.0	—	0.0
Dry skin	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Dyspnea	6	(0.9)	9	(1.4)	81	(17.8)	79	(17.4)	—	0.0	—	0.0	2	(1.9)	—	0.0	3	(1.6)	5	(2.6)
Epistaxis	1	(0.2)	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Fatigue[d]	10	(1.5)	3	(0.5)	58	(12.7)	59	(13.0)	6	(1.2)	17	(3.3)	—	0.0	—	0.0	2	(1.1)	2	(1.1)
Headache	2	(0.3)	3	(0.5)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Hot flush	3	(0.5)	—	0.0	84	(18.5)	74	(16.3)	139	(27.5)	123	(24.1)	—	0.0	—	0.0	1	(0.5)	—	0.0
Hypertension	4	(0.6)	3	(0.5)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Nail disorder	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Nasopharyngitis	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	2	(1.9)	—	0.0	—	0.0	—	0.0
Nausea	6	(0.9)	4	(0.6)	78	(17.1)	77	(16.9)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	1	(0.5)
Pain in extremity	2	(0.3)	5	(0.8)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Pruritus	2	(0.3)	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Pyrexia	5	(0.8)	3	(0.5)	—	0.0	—	0.0	—	0.0	—	0.0	1	(1.0)	—	0.0	—	0.0	—	0.0
Rash	7	(1.1)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0
Vomiting	8	(1.2)	5	(0.8)	—	0.0	—	0.0	—	0.0	—	0.0	2	(1.9)	4	(3.8)	—	0.0	—	0.0
Musculoskeletal pain[e]	25	(3.8)	37	(5.9)	252	(55.4)	248	(54.5)	—	0.0	—	0.0	5	(4.9)	2	(1.9)	—	0.0	—	0.0
Fatigue, asthenia, lethargy[f]	15	(2.3)	8	(1.3)	58	(12.7)	59	(13.0)	6	(1.2)	17	(3.3)	—	0.0	—	0.0	2	(1.1)	2	(1.1)
Skin and nail disorders[g]	11	(1.7)	1	(0.2)	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0	—	0.0

[a] Reported grade 3 or greater adverse events.
[b] Reported all grades of adverse events.
[c] For Mouridsen study, includes gastrointestinal disturbance.
[d] For Nabholtz study, includes lethargy.
[e] Includes arthralgia, back pain, bone pain, pain in extremities.
[f] Includes fatigue, asthenia, lethargy.
[g] Includes dry skin, nail disorders, pruritus, and rash.

TABLE A.II Estimated probabilities, disutilities, mean durations, and costs of grade 3 or greater adverse events

Adverse event	*Probabilities*								*Disutility*		*Duration*		*Cost (£)*	
	LAP–LET[a]		*LET*[a]		*TRZ–ANA*		*ANA*							
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Alopecia	0.0030	0.0022	0.0016	0.0016	0.0016	0.0046	0.0016	0.0048	0.11	0.03	27.2	4.9	158	20
Anorexia	0.0091	0.0038	0.0048	0.0028	0.0049	0.0125	0.0048	0.0115	0.03	0.01	160.0	144.0	362	122
Chills	0.0015	0.0015	0.0016	0.0016	0.0032	0.0066	0.0016	0.0048	0.03	0.01	27.2	4.9	99	5
Constipation	0.0015	0.0015	0.0048	0.0028	0.0052	0.0109	0.0052	0.0088	0.03	0.01	5.0	0.0	99	5
Cough	0.0046	0.0026	0.0048	0.0028	0.0047	0.0087	0.0047	0.0083	0.05	0.01	12.0	8.6	99	5
Diarrhea	0.0930	0.0125	0.0112	0.0043	0.0186	0.0282	0.0094	0.0160	0.10	0.03	23.1	10.5	454	69
Dyspnea	0.0107	0.0041	0.0160	0.0051	0.0436	0.0507	0.0157	0.0242	0.05	0.01	33.5	13.5	722	284
Epistaxis	0.0030	0.0022	0.0032	0.0023	0.0033	0.0086	0.0032	0.0082	0.03	0.01	78.5	69.5	99	5
Headache	0.0046	0.0026	0.0064	0.0032	0.0065	0.0165	0.0065	0.0147	0.03	0.01	55.8	53.1	255	92
Hot flush	0.0061	0.0031	0.0016	0.0016	0.0017	0.0033	0.0016	0.0017	0.03	0.01	14.7	7.7	99	5
Hypertension	0.0076	0.0034	0.0064	0.0032	0.0065	0.0165	0.0065	0.0147	0.03	0.01	74.5	46.5	247	70
Nasopharyngitis	0.0015	0.0015	0.0016	0.0016	0.0045	0.0082	0.0016	0.0048	0.03	0.01	27.2	4.9	99	5
Nausea	0.0107	0.0041	0.0080	0.0036	0.0080	0.0169	0.0079	0.0129	0.10	0.03	9.3	2.2	420	132
Pyrexia	0.0091	0.0038	0.0064	0.0032	0.0128	0.0227	0.0065	0.0147	0.03	0.01	9.4	3.1	947	1205
Vomiting	0.0137	0.0046	0.0096	0.0039	0.0058	0.0165	0.0097	0.0212	0.10	0.03	5.9	2.0	1398	1843
Musculoskeletal pain	0.0396	0.0079	0.0607	0.0102	0.1195	0.1389	0.0592	0.0869	0.07	0.02	33.8	9.5	326	44
Fatigue, asthenia, lethargy	0.0244	0.0062	0.0144	0.0048	0.0061	0.0148	0.0060	0.0050	0.12	0.03	38.1	14.7	446	86
Skin and nail disorders	0.0183	0.0053	0.0032	0.0023	0.0033	0.0086	0.0032	0.0082	0.15	0.04	21.2	5.0	203	35

[a] To ensure valid indirect estimates, one event was added to each cell of 2×2 table.
LAP = lapatinib; LET = letrozole; TRZ = trastuzumab; ANA = anastrozole; SE = standard error.

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