VALUE IN HEALTH 22 (2019) 408–415

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Effectiveness Analysis of Pertuzumab With Trastuzumab and Chemotherapy Compared to Trastuzumab and Chemotherapy in the Adjuvant Treatment of HER2-Positive Breast Cancer in the United States

Louis P. Garrison, Jr, PhD[1,2,*], *Joseph Babigumira, MBChB, MS, PhD* [1], *Clément Tournier, MSc* [3], *Hans-Peter Goertz, MPH* [4], *Solomon J. Lubinga, BPharm, MSc, PhD* [1], *Edith A. Perez, MD* [4]

[1]*The Comparative Health Outcomes, Policy & Economics (CHOICE) Institute, Department of Pharmacy, University of Washington, Seattle, WA, USA;* [2]*VeriTech Corporation, Mercer Island, WA, USA;* [3]*F. Hoffmann-La Roche Ltd, Basel, Switzerland;* [4]*Genentech, Inc., South San Francisco, USA*

ABSTRACT

Objective: The APHINITY trial assessed the effectiveness and the safety of adding pertuzumab to trastuzumab and chemotherapy (THP) compared to trastuzumab and chemotherapy (TH) in the adjuvant management of human epidermal growth factor 2-positive (HER2+) breast cancer. We performed a study to project the potential cost-effectiveness of THP vs. TH. **Study Design:** Trial-based cost-utility modeling analysis. **Methods:** We performed an economic evaluation from a payer perspective using a Markov model with six health states: invasive disease-free survival, non-metastatic recurrence, remission, first-line metastatic, subsequent line metastatic, and death. We parameterized the model using data from both arms in APHINITY extrapolated to a patient's lifetime horizon. Estimates of health state utilities were based on EQ-5D trial data and the literature, and costs were estimated from government sources and the published literature. The primary outcomes of the model were life-years (LYs), quality-adjusted LYs (QALYs), costs, and incremental cost-effectiveness ratios (ICERs). Uncertainty was addressed via univariate and probabilistic sensitivity analyses. **Results:** For the intention-to-treat population, the model projected improved outcomes (by 0.50 LYs and 0.45 QALYs) and increased costs (by $74 420) for ICERs of $147 774/LY gained and $167 185/QALY gained for PHT vs. HT patients. In the node-positive patient population, the model projected improved outcomes (by 0.86 LYs and 0.76 QALYs) and increased costs (by $66 647) for ICERs of $77 684/LY gained and $87 929/QALY gained. For the hormone-receptor-negative patient population, the model projected health gains, increased costs, and ICERs of $147 022/LY gained and $166 518/QALY gained. The results were sensitive to changes in the model time horizon. **Conclusion:** The addition of pertuzumab to the available regimens for HER2+ early breast cancer is likely to be cost-effective for patients in the U.S. at high risk of recurrence.

Keywords: adjuvant treatment, cost-effectiveness analysis, HER2-positive early breast cancer, pertuzumab, trastuzumab

Introduction

An estimated 253 000 women in the United States were found to have breast cancer in 2017, and nearly 41 000 women died from the disease.[1] Fifteen to 20% of women with new diagnoses of breast cancer—an estimated 38 000 to 50 000 women—had tumors that overexpressed human epidermal growth factor 2 (HER2-positive breast cancer). HER2-positive (HER2+) breast cancer tumors are more aggressive, more likely to invade lymph nodes, more likely to recur and metastasize, and are associated with shorter patient survival.[2,3] Nevertheless, patients with HER2-positive breast cancer respond to HER2-targeted therapy with significant clinical benefit.[4,5]

Pertuzumab (Perjeta; Genentech, Inc.) is one of four HER2-targeting therapies approved for patients with HER2--positive breast cancer. Pertuzumab is a recombinant humanized monoclonal antibody, the first in a class of agents known as HER2 dimerization inhibitors.[6,7] Pertuzumab demonstrates

* *Address correspondence to*: Louis P. Garrison, Jr, PhD, Department of Pharmacy, University of Washington, Box 357630, Seattle, WA 98195, USA.

E-mail: lgarrisn@uw.edu

1098-3015/$36.00 - see front matter

https://doi.org/10.1016/j.jval.2018.11.014

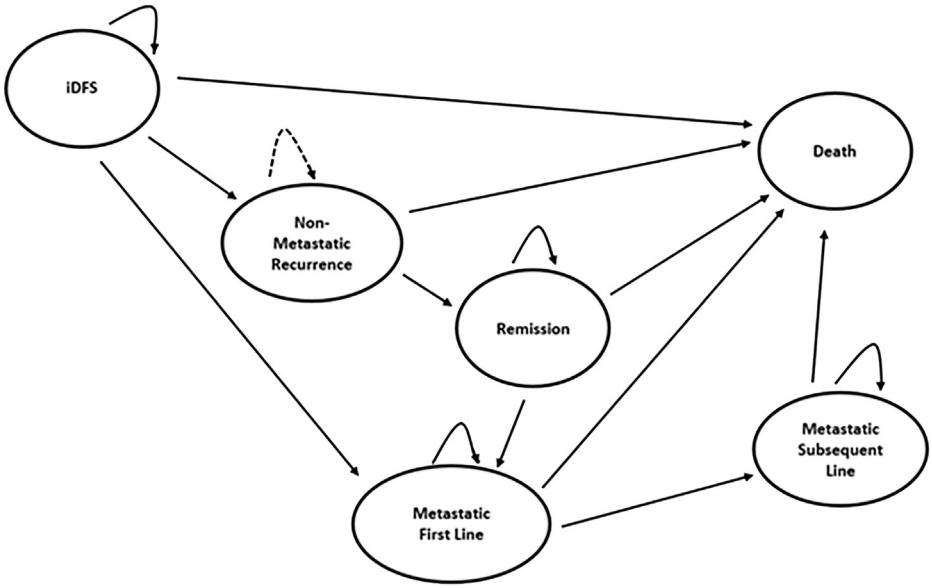

Fig. 1 – Markov model. The model illustrates the different health states through which patients with primary breast cancer transition. The curved, "hashed" arrow represents a limit on the number of cycles—12—that patients can remain in the nonmetastatic recurrence state. iDFS, invasive disease-free survival.

complementary action when used in combination with trastuzumab and chemotherapy.[8,9]

Dual HER2-targeted therapy with pertuzumab and trastuzumab in the adjuvant setting is currently recommended as an option for some patients as part of the National Comprehensive Cancer Network (NCCN) guidelines.[10,11] Data on the efficacy and safety of duo HER2-targeted therapy in the adjuvant setting have recently been published (APHINITY trial).[12] The APHINITY trial compared pertuzumab in combination with trastuzumab and chemotherapy (PHT) to placebo with trastuzumab and chemotherapy (HT) in the treatment of HER2-positive early breast cancer.[12] In the primary analysis, the hazard ratio (HR) comparing the pertuzumab group to the control group was 0.81 (95% confidence interval [CI], 0.66-1.00). The 4-year invasive disease-free survival (iDFS) was 90.6% in the pertuzumab arm and 92.3% in the control arm. In the preplanned subgroup analyses among high-risk subgroups, comparing the pertuzumab group to the control group, there was a risk reduction of recurrence or death of 23% (HR 0.77, 95% CI 0.62-0.96) among patients with node-positive tumors and a risk reduction of 24% (HR 0.76, 95% CI, 0.56-1.04) among patients with hormone receptor−negative tumors with pertuzumab over placebo. Consistent with standard methodology, safety analysis was performed in all treated patients according to the therapy received (pertuzumab vs placebo). Results were in keeping with previous trials and the known safety profile of pertuzumab. Of those patients who experienced primary cardiac events, only 1 patient in the placebo safety population was initially randomized to pertuzumab.

In December 2017, pertuzumab was approved for adjuvant treatment in combination with trastuzumab and chemotherapy of patients with HER2-positive early breast cancer at high risk of recurrence. Before this, pertuzumab was approved in the United States for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early breast cancer (either greater than 2 cm in diameter or node-positive) as part of the complete treatment regimen for early breast cancer. Pertuzumab is also approved for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior HER2-targetted therapy or chemotherapy for metastatic disease.

The objective of this model-based analysis was to estimate the potential cost-effectiveness of duo HER2-targeted therapy. Using the results of the APHINITY trial, we modeled the lifetime effectiveness and costs of pertuzumab-trastuzumab HER2-targeted therapy. The results of this study are of interest to US payers and other stakeholders because they make coverage and reimbursement decisions that can greatly affect patient access to this new treatment.

Methods

Analytic Overview

The base-case intention-to-treat (ITT) population modeled in the study was women with HER2-positive breast cancer in the United States with a starting age of 51 years, the median patient age at treatment initiation in the APHINITY trial.[12] We also assessed the cost-effectiveness of pertuzumab separately in both the node-positive and hormone-receptor-negative populations, which are populations that include patients with tumors that are at higher risk of recurrence. The perspective of the analysis was that of the third-party payer. The treatments compared in the analysis were pertuzumab, trastuzumab, and chemotherapy (PHT) versus trastuzumab and chemotherapy (HT). The model is based on a typical patient of age 51 years, and the projected impact is over a time horizon of the rest of a patient's life. Costs and outcomes were discounted at 3% per annum.[8] Effectiveness—the health outcomes—was assessed in the analysis in terms of life-years (LYs) and quality-adjusted life-years (QALYs). The primary economic endpoint is the projected incremental cost-effectiveness ratio (ICER).

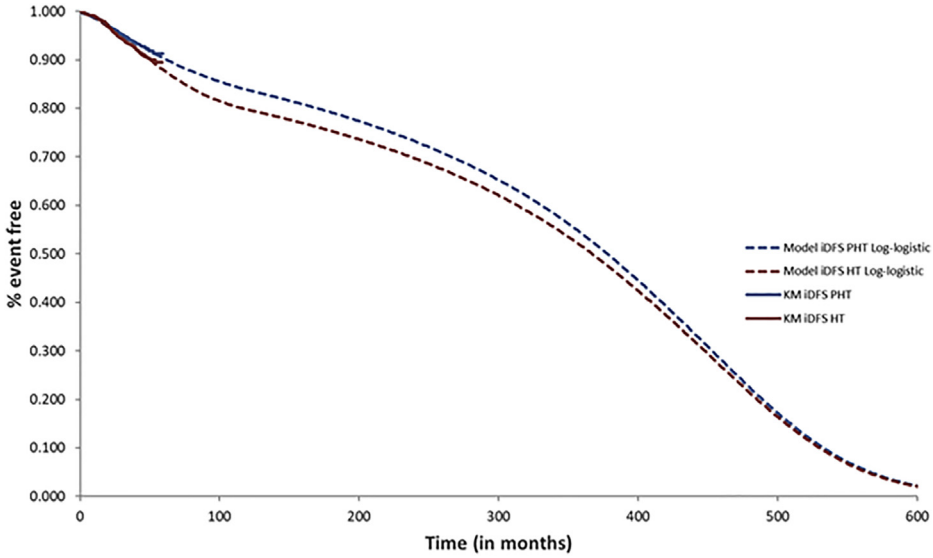

Fig. 2 – Extrapolation of invasive disease-free survival curves used in the base-case analysis.

Decision-Analytic Model

We used a Markov-based decision-analytic (state transition) model (Fig. 1) with the following 6 health states: (1) invasive disease-free survival (iDFS); (2) nonmetastatic recurrence; (3) remission; (4) first-line metastatic breast cancer (mBC); (5) subsequent lines in mBC; and (6) death. All patients began in the iDFS state after surgery. The nonmetastatic recurrence state included both locoregional recurrence and contralateral breast cancer. The Markov cycle time of analysis in the model was 1 month. The half-cycle correction was applied to all estimates except treatment costs for the iDFS state to avoid reducing the actual cost of the loading doses of trastuzumab and pertuzumab.

During each monthly cycle, patient transitions from state to state were modeled as follows:

1. In the iDFS state, patients remained in the state, transitioned to nonmetastatic recurrence, transitioned to first-line mBC, or died from nonbreast cancer causes (ie, background mortality).
2. In the nonmetastatic recurrence state, patients stayed in that state for a fixed 1-year period (12 monthly cycles) and then transitioned to remission or died from nonbreast cancer causes.
3. In the remission state, patients stayed in that state, transitioned to the first-line mBC state, or died from nonbreast cancer causes.
4. In the first-line metastatic state, patients stayed in that state, transitioned to the subsequent lines in mBC state, or died from breast or nonbreast cancer causes (patients are expected to progress before dying from the disease).
5. In the subsequent lines in mBC state, patients stayed in that state or died from breast cancer or nonbreast cancer causes.

Model Inputs

Rates of progression

The APHINITY trial was used to model the probability of remaining in the iDFS state. To extrapolate beyond the observation period, multiple parametric distributions—exponential, Weibull, lognormal, gamma, log-logistic, Gompertz—were fit to the survival curves of the PHT and HT arms in the APHINITY trial. After assessing goodness-of-fit using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC), in addition to conformity to the original Kaplan-Meier survival curves, the log-logistic distribution was chosen for the base-case analysis. The survival curves for both arms were fit separately to relax the proportional hazards assumption, which was not supported by the primary trial data. The extrapolated recurrence rate beyond the observation period was adjusted considering the available evidence (HERA and BCIRG-006 studies) to reflect the decrease in the risk of recurrence that is expected over time. For both treatment arms, the fraction of the population no longer at risk of disease recurrence linearly increases from 0% at 48 months to 90% at 120 months. This means that after 120 months, if a patient were still disease-free, their risk of disease recurrence would be 10% of the extrapolated recurrence rate observed in the trial. US life tables were used to ensure that the modeled death rate was at least equal to the general population mortality at every cycle of the model. The treatment effect of pertuzumab was assumed to remain for 7 years and fade to be null at 10 years. This assumption was considered conservative considering the observed efficacy profile of trastuzumab in the adjuvant setting and pertuzumab in the metastatic setting. Figure 2 shows the curves resulting from the adjusted log-logistic extrapolations.

Data from the APHINITY trial were used to parameterize the split in transitions from the iDFS state between the nonmetastatic recurrence and the first-line mBC states: 76.8% of all recurrences in the APHINITY trial were distant recurrences. This estimate is consistent with the HERA trial.[13] This split was modeled consistently across the timeframe of possible recurrences. Patients who entered the nonmetastatic recurrence state were modeled to remain in that state for a maximum of 12 cycles (1 year) and thereafter transition to the remission state. Further disease recurrences from the nonmetastatic recurrence state were assumed to be metastatic.

The transition between the remission state and the first-line mBC state was modeled based on the study by Hamilton et al.[14] that estimated 7.6 years to second malignancy after adjuvant therapy. This is converted to a monthly probability (of transition between the remission and metastatic nonprogressed state) of 0.0076.

The rate of progression from the first-line mBC to the subsequent lines in mBC state was modeled to depend on regimens received for metastatic treatment:

1. Patients who received pertuzumab, trastuzumab, and chemotherapy in mBC had a monthly probability of progression as observed in the CLEOPATRA trial of 0.0317.[15]
2. Patients who received trastuzumab and chemotherapy in mBC had a monthly probability of progression as observed in the CLEOPATRA trial of 0.047.[15]

This means that—in the base-case analysis—the projected relative distribution of patients in the metastatic nonprogressed state receiving PHT and HT would be 44% and 56%, respectively.

Mortality

The rate of progression from the subsequent lines in mBC state to death was modeled to depend on the regimen received for metastatic treatment as follows:

1. Patients who received pertuzumab, trastuzumab, and chemotherapy in mBC have a monthly probability of death as observed in the CLEOPATRA trial of 0.0273.[15]
2. Patients who received trastuzumab and chemotherapy in mBC have a monthly probability of death as observed in the CLEOPATRA trial of 0.0315.[15]

We modeled a different prognosis for patients with a progression event on or shortly after adjuvant therapy (within 18 months of adjuvant treatment initiation): a shorter postprogression survival was observed in the HERA[13] and BCIRG-006,[16] both trastuzumab trials for patients with early recurrence. These patients may also have different treatment options postprogression: trastuzumab-emtansine is approved by the FDA for patients with a recurrence within 6 months of completion of adjuvant therapy.

The background (non–breast-cancer) mortality, which allowed for the transition from the iDFS, nonmetastatic recurrence, remission, and first-line mBC states, was modeled based on actuarial estimates of mortality among women in the United States, obtained from the US Social Security Administration.[17] The model was parameterized to mirror age- and sex-adjusted mortality in the US general population.

Health state utilities

Health-related quality of life was incorporated into the analysis using estimated utility values from the APHINITY trial, which gathered patient-reported outcomes using the EuroQoL Group's five-dimensional (EQ-5D) generic health-related quality-of-life instrument. These EQ-5D estimates were used to compute utility values for participants and health states based on a scoring algorithm and tariffs obtained from a survey of the noninstitutionalized general population in the United States.[18] Utilities were estimated separately for patients on and off treatment, on and off chemotherapy, and for different disease states. The model also adjusted utilities of patients in the general population (iDFS and remission states) over the long-term to account for increasing comorbidity with age.[19] Utilities for metastatic states were obtained from the published literature.[20] Table 1 includes a summary of the utility estimates used in the model.

Table 1 – Utility and cost parameters used in the model

Parameter	Value	Reference
Health state utilities		
General population utilities		
50-54 years	0.87	Fryback et al.[34]
55-64 years	0.84	Fryback et al.[34]
65-74 years	0.84	Fryback et al.[34]
75-84 years	0.82	Fryback et al.[34]
85 years and above	0.67	Fryback et al.[34]
Health state utilities		
iDFS on chemotherapy	0.830	Primary analysis of APHINITY data
iDFS on treatment (off chemotherapy)	0.834	Primary analysis of APHINITY data
iDFS off treatment	0.867	Primary analysis of APHINITY data
Nonmetastatic recurrence	0.830	Primary analysis of APHINITY data
Remission	0.867	Primary analysis of APHINITY data
First-line mBC	0.716	Lloyd et al.[20] Adjusted by US/UK ratio
Subsequent lines in mBC	0.472	Lloyd et al.[20] Adjusted by US/UK ratio
Costs		
Drug costs (per mg)		
Pertuzumab	$10.79	Genentech data
Trastuzumab	$9.50	Genentech data
Docetaxel	$2.72	ASP (April 2014)
Paclitaxel	$0.15	ASP (April 2014)
Doxorubicin	$0.49	ASP (April 2014)
Epirubicin	$0.69	ASP (April 2014)
Cyclophosphamide	$0.42	ASP (April 2014)
5-Fluorouracil	$0.004	ASP (April 2014)
Carboplatin	$0.007	ASP (April 2014)
Drug administration		
First hour of infusion	$136.61	von Minckwitz et al.[12]
Additional hour of infusion	$28.71	von Minckwitz et al.[12]
Additional drug to infuse	$63.04	von Minckwitz et al.[12]
Management of adverse events		
Pertuzumab + trastuzumab arm	$292.86	Gianni et al.[26] Primary analysis of APHINITY data
Trastuzumab arm	$184.90	Gianni et al.[26] Primary analysis of APHINITY data
Supportive care (per month)		
iDFS (years 1 and 2)	$6 201	Blumen et al.[22]
iDFS (years 3-5)	$20.92	von Minckwitz et al.[12]
iDFS (subsequent years)	$19.88	von Minckwitz et al.[12]
Nonmetastatic recurrence	$12 236	Blumen et al.[22]
Remission	$29.21	von Minckwitz et al.[12]
Metastatic first-line	$9 976	Blumen et al.[22]
Metastatic subsequent line	$5 145	Blumen et al.[22]
End-of-life care	$72 585	Chastek et al.[23]
Discount rate	3%	Cortes et al.[8]

ASP indicates average sale price; iDFS, invasive disease-free survival; mBC; metastatic breast cancer

Treatment patterns

Patients in the APHINITY trial received sequential chemotherapy (4 cycles of anthracycline chemotherapy followed by a taxane in combination with targeted therapy) or concurrent chemotherapy (docetaxel plus carboplatin in combination with targeted therapy). In the base-case analysis, we modeled patients to remain on treatment as long as they were disease-free and did not

have a major toxicity event. This implied 18 cycles for pertuzumab and trastuzumab including one loading dose and chemotherapy for a maximum of 6 cycles. The dose of each drug was based on the label recommendation.

Costs

The analysis included the costs of drugs, drug administration, management of adverse events, state-specific supportive care, and end-of-life care, estimated in 2017 US dollars.

Data on drug costs for pertuzumab and trastuzumab targeted therapies were based on projected January 2018 Average Sale Price (ASP) (Genentech data). Data on the costs of other chemotherapy drugs were obtained from the Centers for Medicare and Medicaid (CMS) Average Sales Price (ASP) list for 2017.[11] Drug dosages for pertuzumab, trastuzumab, and chemotherapy were based on the APHINITY protocol. We used the costs of trastuzumab-emtansine (TDM-1), lapatinib, and capecitabine to estimate treatment costs of patients who progressed to metastatic states. For purposes of cost estimation, we assumed that patients who advanced to local recurrence would receive another round of adjuvant treatment.

The costs of drug administration were estimated based on reimbursement rates by CMS for services related to chemotherapy infusions: these infusion costs depend on the number of drugs infused in all chemotherapy cycles and the infusion times required for each drug.[12]

The mean cost of adverse events for the PHT and HT arms was estimated by multiplying the probability of occurrence of individual adverse events by the cost of managing each adverse event. The costs of managing adverse events from CMS data were estimated based on the mean expected treatment pattern and unit costs from the physician fee schedule[12] and Medicare diagnosis-related groups.[21]

To estimate the costs of supportive care, we used estimates from the published literature for costs of Markov-state-specific supportive care, excluding the already-included costs of drugs and drug administration.[22] For the iDFS state, we excluded surgery costs because the patients in the APHINITY trial were randomized after surgery. End-of-life health care costs were estimated based on the published literature.[23]

Table 1 includes a summary of cost parameters used in the model.

Sensitivity analysis

Sensitivity analyses were performed to determine which variables, when varied, would have a substantial impact on projected costs and outcomes. We present one-way sensitivity analyses as tornado diagrams. We also performed a probabilistic sensitivity analysis using Monte Carlo simulation to further test the robustness of the results.

Results

Base-Case Analysis

Table 2 shows the detailed results of the base-case analyses.

ITT population

In the analysis based on the ITT population, the projected mean outcomes were better for the PHT arm (18.63 LYs and 15.57 QALYs) compared with the HT are (18.13 LYs and 15.12 QALYs). The projected mean costs were also higher for the PHT arm ($350 305) compared with the HT arm ($275 885). Thus, the ICERs comparing the PHT arm to the HT arm were $147 774 per LY gained and $167 185 per QALY gained.

Table 2 – Base-case results of the mean effectiveness, costs, and cost-effectiveness of THP vs TH (intention-to-treat population)

	PHT	HT	Difference
Intention-to-treat population			
LYs	18.63	18.13	0.50
QALYs	15.57	15.12	0.45
Costs			
Cost of pertuzumab	$84 778	$0	$84 778
Cost of trastuzumab	$69 309	$69 363	−$53
Other costs in iDFS	$159 897	$157 985	$1912
Cost in nonmetastatic recurrence	$3920	$5145	−$1224
Cost in remission	$69	$90	−$22
Cost in first-line mBC	$15 838	$21 345	−$5507
Cost in subsequent lines in mBC	$9348	$12 583	−$3235
Cost of end-of-life care	$7144	$9374	−$2230
Total payer costs	$350 305	$275 885	$74 420
ICER ($/LY)			$147 774
ICER ($/QALY)			$167 185
Node-positive population			
LYs	17.97	17.11	0.86
QALYs	14.98	14.22	0.76
Costs			
Cost of pertuzumab	$84 420	$0	$84 420
Cost of trastuzumab	$69 008	$69 056	−$48
Other costs in iDFS	$158 706	$156 533	$2173
Cost in nonmetastatic recurrence	$4373	$6019	−$1646
Cost in remission	$77	$106	−$29
Cost in first-line mBC	$21 822	$30 944	−$9122
Cost in subsequent lines in mBC	$12 886	$18 248	−$5362
Cost of end-of-life care	$9942	$13 681	−$3739
Total payer costs	$361 234	$294 588	$66 647
ICER ($/LY)			$77 684
ICER ($/QALY)			$87 929
Hormone receptor-negative population			
LYs	18.46	17.94	0.52
QALYs	15.42	14.95	0.46
Costs			
Cost of pertuzumab	$84 609	$0	$84 609
Cost of trastuzumab	$69 167	$68 852	$315
Other costs in iDFS	$159 382	$156 459	$2923
Cost in nonmetastatic recurrence	$4252	$5472	−$1219
Cost in remission	$75	$97	−$22
Cost in first-line mBC	$17 040	$21 662	−$4623
Cost in subsequent lines in mBC	$10 065	$12 803	−$2738
Cost of end-of-life care	$7796	$10 034	−$2238
Total payer costs	$352 385	$275 379	$77 006
ICER ($/LY)			$147 022
ICER ($/QALY)			$166 518

ICER indicates incremental cost-effectiveness ratio; iDFS, invasive disease-free survival; LY, life-year; mBC; metastatic breast cancer; QALY, quality-adjusted life-year.

Node-positive population

In the analysis based on the node-positive population, the projected mean outcomes were better for the PHT arm (17.97 LYs and 14.98 QALYs) compared with the HT arm (17.11 LYs and 14.22

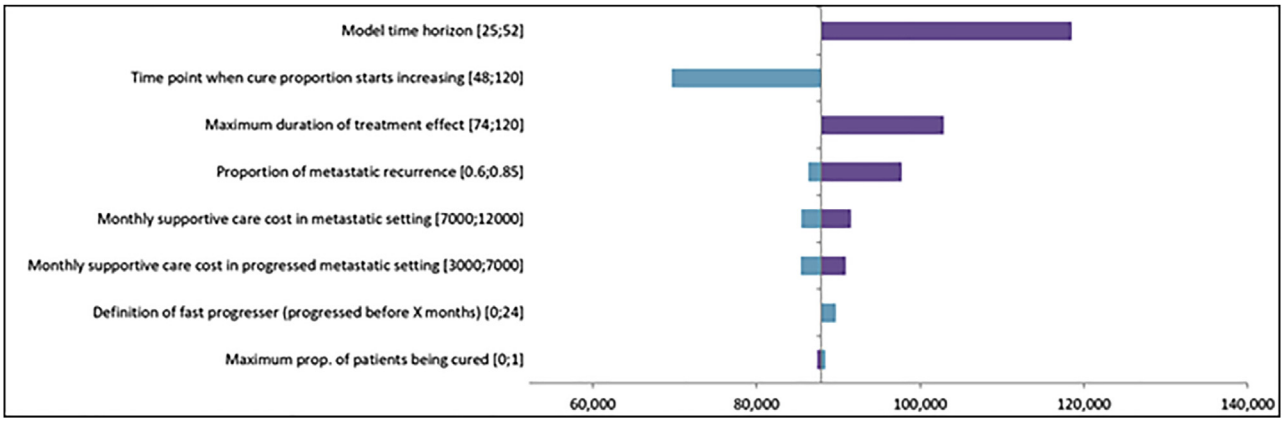

Fig. 3 – Tornado diagram of univariate sensitivity analysis for node-positive population.

QALYs). The projected mean costs were also higher for the PHT arm ($361 234) compared with the HT arm ($294 588). Thus, the ICERs comparing the PHT arm to the HT arm were $77 684 per LY gained and $87 929 per QALY gained.

Hormone-receptor-negative population

In the analysis based on the hormone receptor–negative population, the projected mean outcomes were better for the PHT arm (18.46 LYs and 15.42 QALYs) compared with the HT arm (17.94 LYs and 14.95 QALYs). The projected mean costs were also higher for the PHT arm ($352 385) compared with the HT arm ($275 379). Thus, the ICERs comparing the PHT arm to the HT arm were $147 022 per LY gained and $166 518 per QALY gained.

Sensitivity Analysis

On performing univariate sensitivity analysis, shown in Figure 3 as a tornado diagram for the node-positive population, the ICERs for the ITT population, the node-positive population, or the hormone receptor–negative population were most sensitive to the model time horizon (varied from 25-52 years) and the timing of onset of increasing cure proportion (varied from 48-120 months). At its most extreme, the ICER for the node-positive population increased by approximately 35% (to approximately $120 000 per QALY saved) at a time horizon of 25 years.

Based on the probabilistic sensitivity analysis, a cost-effectiveness acceptability curve (CEAC) for the ITT population (Fig. 4) showed that the proportion of simulations that were cost-effective (one regimen relative to the other) were equivalent in the PHT and HT arms at a willingness to pay of $162 500. At a threshold of $150 000 per QALY, 45% of simulations generated a result in which the PHT was more cost-effective than HT. At this same threshold, the CEAC analysis for the node-positive population found that 77% of the simulations were cost-effective, and for the hormone-receptor negative population, 45% were cost-effective.

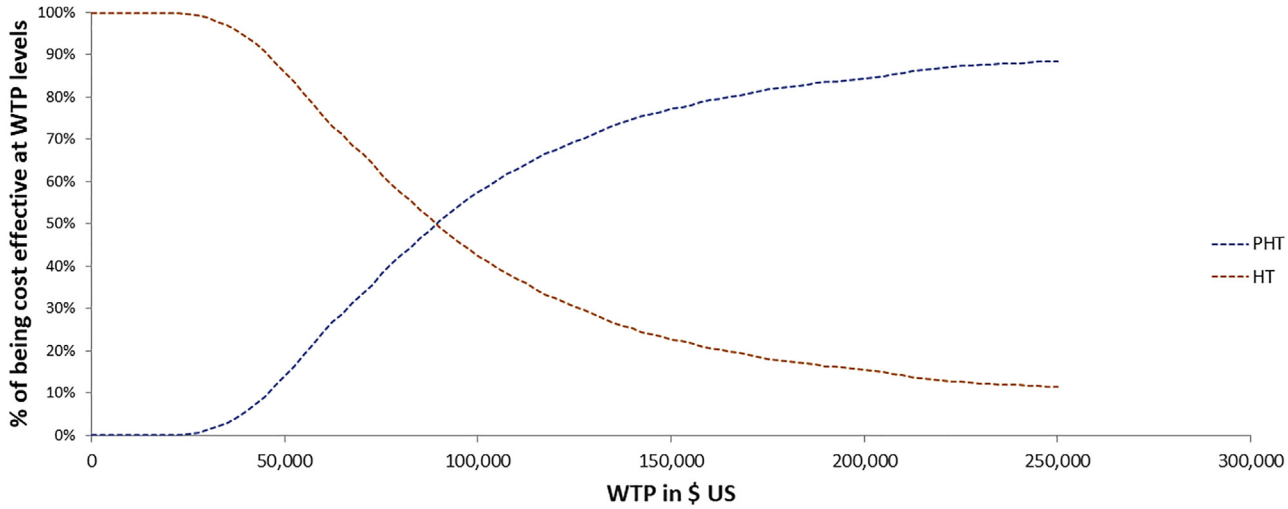

Fig. 4 – Cost-effectiveness acceptability curve obtained from probabilistic sensitivity analysis in the node-positive population. The curve shows for PHT and HT, the proportion of 1000 simulated samples for which the strategy was cost-effective at varying levels of WTP per additional QALY. HT indicates trastuzumab and chemotherapy; PHT, pertuzumab, trastuzumab, and chemotherapy; QALY, quality-adjusted life-years; WTP, willingness to pay.

Discussion

In this model-based cost-effectiveness analysis of adjuvant treatment for HER2+ breast cancer, leveraging clinical and outcomes data for all patients in the APHINITY trial, we projected an ICER of $87 929 per QALY gained for patients with node-positive disease with the addition of pertuzumab to trastuzumab and chemotherapy, compared with trastuzumab and chemotherapy. For all trial patients and those with hormone receptor–negative disease, the ICERs were $ $167 185 per QALY gained for and $166 518 per QALY gained, respectively. It has been recommended that $50 000 per QALY gained and $200 000 per QALY gained be considered as the lower and upper thresholds for cost-effectiveness.[24] The increasingly influential Institute for Clinical and Economic Review uses a threshold of $50 000 to $150 000 per QALY gained, with possible extension up to $175 000 per QALY to deal with uncertainty.[25] Therefore, the use of pertuzumab is projected to be cost-effective in patients with early HER2+ breast cancer with a high risk of recurrence.

In the United States, the average life expectancy of women aged 51 is 31 years. In contrast, the life expectancy of women who developed a metastatic recurrence is slightly over 5 years. The cost-effectiveness of pertuzumab is driven by the additional life years gained for these patients who avoid distant disease recurrence. This also provides a cost-offset that accrues from preventing advanced disease, for an average per patient of $21 000 in the node-positive population, $12 000 in the hormone-receptor-negative population, and $13 000 in all early breast cancer patients. This cost-offset is a result of reductions in the percentage of patients transitioning to the nonmetastatic and metastatic states in addition to the costs of end-of-life care.

The US Food and Drug Administration (FDA) first granted pertuzumab approval in the metastatic setting because of the demonstration of efficacy in the CLEOPATRA study.[15] The FDA also granted accelerated approval for pertuzumab in the neoadjuvant setting owing to biological synergy in its complementarity with trastuzumab, efficacy in the metastatic setting, relative safety when used in a large number of patients, and demonstrated efficacy (by the surrogate endpoint pathologic complete response [pCR]) in the NeoSphere trial.[26] Published estimates based on list prices suggest that this pertuzumab regimen is unlikely to be cost-effective on average in metastatic HER2+ breast cancer at $500 000 per QALY gained[27,28]; however, pertuzumab is likely to be cost-effective in the neoadjuvant setting.[29,30] The recent FDA approval of pertuzumab for use in HER2-positive early breast cancer patients at high risk of recurrence expands the population for clinical benefit. Although the favorable cost-effectiveness result is strongest for the node-positive subgroup, it is also likely to hold for other patients at high risk of recurrence.

Since the publication of the results of the APHINITY trial, there have been reports alluding to the modest clinical benefits as compared with the high number needed to treat (NNT) to prevent recurrences as well as possible toxicity associated with the addition of pertuzumab to trastuzumab and chemotherapy.[31,32] Although the number needed to treat can be useful as a metric for population effect for some diseases by focusing on a single point in time, in some instances, it does not adequately characterize the benefit-risk balance because it does not reflect the degree of benefit accruing to a given individual over time. In this instance, preventing a single recurrence implies a gain of multiple LYs and QALYs, each addition of which matters to individuals and a population of at-risk individuals. In addition, the high proportion of HER2+ patients who are cured after adjuvant breast cancer treatment implies substantial medical cost savings as well as gains in productivity. The latter—often considered from a "societal" perspective—has not been considered in this analysis.

A limitation inherent in the use of clinical trial data extrapolated to a lifetime horizon for economic evaluations is the uncertainty about the additional benefit of the intervention after the follow-up period. Although the median follow-up period in the APHINITY trial was 45.4 months,[12] we modeled a sustained treatment effect up to 84 months with attenuation toward null at 120 months. This is consistent with data from the long-term follow-up of patients receiving trastuzumab regimens in the HERA and BCIRG-006 trials.[13,16] Estimates of the likely cost-effectiveness of pertuzumab will need to be updated as new data on long-term efficacy emerge from ongoing follow-up (up to 2023) of patients enrolled in APHINITY.[33] In addition, although previous cost-effectiveness analyses extrapolate to the lifetime time horizon based on disease-free survival (DFS), the use of iDFS here is not expected to affect the model results.

Ultimately, oncologists and other clinicians must advise individual patients on treatment options given considerations of recurrence risk (eg, varying by nodal and hormone-receptor status), tolerability, adverse events, previous regimens received, financial burden or cost, and importantly patients' preferences for health states and risk tolerance. Pertuzumab in combination with trastuzumab has better efficacy than trastuzumab alone and can be a cost-effective addition to the therapeutic choices available to clinicians as they provide treatment advice to patients with HER2-positive breast cancer in the adjuvant setting in the United States.

Acknowledgment

This research was supported in part by Genentech, Inc., via an unrestricted contract with VeriTech Corporation.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017;67:7–30.
2. Dai X, Li T, Bai Z, et al. Breast cancer intrinsic subtype classification, clinical use and future trends. *Am J Cancer Res*. 2015;5:2929–2943.
3. Makki J. Diversity of breast carcinoma: histological subtypes and clinical relevance. *Clin Med Insights Pathol*. 2015;8:23–31.
4. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med*. 2005;353:1673–1684.
5. Eiermann W. Trastuzumab combined with chemotherapy for the treatment of HER2-positive metastatic breast cancer: pivotal trial data. *Ann Oncol*. 2001;12(Suppl 1):S57–S62.
6. Cho HS, Mason K, Ramyar KX, et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature*. 2003;421:756–760.
7. Fendly BM, Winget M, Hudziak RM, et al. Characterization of murine monoclonal antibodies reactive to either the human epidermal growth factor receptor or HER2/neu gene product. *Cancer Res*. 1990;50:1550–1558.
8. Cortes J, Fumoleau P, Bianchi GV, et al. Pertuzumab monotherapy after trastuzumab-based treatment and subsequent reintroduction of trastuzumab: activity and tolerability in patients with advanced human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol*. 2012;30:1594–1600.
9. Zhang X, Zhang XJ, Zhang TY, et al. Effect and safety of dual anti-human epidermal growth factor receptor 2 therapy compared to monotherapy in patients with human epidermal growth factor receptor 2-positive breast cancer: a systematic review. *BMC Cancer*. 2014;14:625.
10. Gradishar W, Salerno KE. NCCN Guidelines Update: Breast Cancer. *J Natl Compr Canc Netw*. 2016;14:641–644.
11. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN Guidelines Insights: Breast Cancer, Version 1.2017. *J Natl Compr Canc Netw*. 2017;15:433–451.
12. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med*. 2017;377:122–131.
13. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast

cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet*. 2017;389:1195–1205.
14. Hamilton SN, Tyldesley S, Li D, et al. Second malignancies after adjuvant radiation therapy for early stage breast cancer: is there increased risk with addition of regional radiation to local radiation? *Int J Radiat Oncol Biol Phys*. 2015;91:977–985.
15. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med*. 2015;372:724–734.
16. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med*. 2011;365:1273–1283.
17. Social Security Administration. Actuarial Life Table 2013. https://www.ssa.gov/oact/STATS/table4c6.html. Accessed September 10, 2017.
18. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care*. 2005;43:203–220.
19. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010;13:509–518.
20. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. *Br J Cancer*. 2006;95:683–690.
21. Centers for Medicare and Medicaid Services. Acute Inpatients Prospective Payment System 2017. https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/AcuteInpatientPPS/FY2016-IPPS-Final-Rule-Home-Page-Items/FY2016-IPPS-Final-Rule-Tables.html. Accessed September 10, 2017.
22. Blumen H, Fitch K, Polkus V. Comparison of treatment costs for breast cancer, by tumor stage and type of service. *Am Health Drug Benefits*. 2016;9:23–32.
23. Chastek B, Harley C, Kallich J, et al. Health care costs for patients with cancer at the end of life. *J Oncol Pract*. 2012;8:75s–80s.
24. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50 000-per-QALY threshold. *N Engl J Med*. 2014;371:796–797.
25. Institute for Clinical and Economic Review. Overview of the ICER value assessement framework and update for 2017-2019. 2017. https://icer-review.org/wp-content/uploads/2018/03/ICER-value-assessment-framework-update-FINAL-062217.pdf. Accessed June 22, 2017.
26. Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2012;13:25–32.
27. Durkee BY, Qian Y, Pollom EL, et al. Cost-effectiveness of pertuzumab in human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2016;34:902–909.
28. Leung HWC, Chan ALF, Muo CH, et al. Cost-effectiveness of pertuzumab combined with trastuzumab and docetaxel as a first-line treatment for HER-2 positive metastatic breast cancer. *Expert Rev Pharmacoecon Outcomes Res*. 2018;18:207–213.
29. Attard CL, Pepper AN, Brown ST, et al. Cost-effectiveness analysis of neoadjuvant pertuzumab and trastuzumab therapy for locally advanced, inflammatory, or early HER2-positive breast cancer in Canada. *J Med Econ*. 2015;18:173–188.
30. Squires H, Pandor A, Thokala P, et al. Pertuzumab for the neoadjuvant treatment of early-stage HER2-positive breast cancer: an evidence review group perspective of a NICE single technology appraisal. *Pharmacoeconomics*. 2018;36:29–38.
31. Miller KD. Questioning our APHINITY for more. *N Engl J Med*. 2017;377:186–187.
32. Stanton SE, Davidson NE. Breast cancer: what lies beyond APHINITY for HER2-positive breast cancer? *Nat Rev Clin Oncol*. 2017;14:715–716.
33. ClinicalTrials.gov. A study of pertuzumab in addition to chemotherapy and trastuzumab as adjuvant therapy in participants with human epidermal growth receptor 2 (HER2)-positive primary breast cancer (APHINITY). https://clinicaltrials.gov/ct2/show/study/NCT01358877. Accessed September 10, 2017.
34. Fryback DG, Dunham NC, Palta M, et al. US norms for six generic health-related quality-of-life indexes from the National Health Measurement study. *Med Care*. 2007;45:1162–1170.