Cost-Effectiveness Analysis of Adjuvant Neratinib Following Trastuzumab in Early-Stage HER2-Positive Breast Cancer

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ABSTRACT

BACKGROUND: Disease-free survival (DFS) in early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer is significantly greater with the addition of neratinib after adjuvant trastuzumab versus no additional therapy. However, it remains uncertain whether these survival gains represent good value for the money, given the substantial cost of neratinib.

OBJECTIVE: To evaluate clinical and economic implications of adding neratinib after adjuvant trastuzumab based on results from the phase III ExteNET trial.

METHODS: A 3-state Markov model was developed to estimate the cost-effectiveness of neratinib for women with early-stage (I-III) HER2-positive breast cancer. Five-year recurrence rates were derived from the ExteNET trial. Mortality and recurrence rates after 5 years were derived from the HERceptin Adjuvant (HERA) trial. Outcomes included life-years, quality-adjusted life-years (QALYs), and direct medical expenditures. The analysis was performed from a payer perspective over a lifetime horizon. One-way sensitivity and probabilistic analyses were conducted to evaluate uncertainty.

RESULTS: Total cost of neratinib following adjuvant trastuzumab was \$317,619 versus \$152,812 for adjuvant trastuzumab alone. A gain of 0.4 QALYs (15.7 vs. 15.3) and 0.1 years of projected life expectancy (18.3 vs. 18.2) favored neratinib after trastuzumab versus trastuzumab alone. The neratinib cost per QALY gained was \$416,106. At standard willingness-to-pay thresholds of \$50,000, \$100,000, and \$200,000 per QALY gained, neratinib has a probability of 2.8%, 16.7%, and 33.9% of cost-effectiveness, respectively. The cost per QALY gained in a scenario analysis only including patients with hormone-receptor positive disease was \$275,311.

CONCLUSIONS: Based on 5-year data from ExteNET, neratinib following adjuvant trastuzumab is not projected to be cost-effective, even among those patients shown to derive the greatest clinical benefit. Future analyses should reassess the cost-effectiveness associated with neratinib treatment as trial data mature.

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What this study adds

- This is the first independent assessment of the value of neratinib after adjuvant trastuzumab.
- This study found that neratinib is not projected to be cost-effective, even among patients who derived the most clinical benefit.
- Study findings are important because they can help guide policy decisions and clinical guidelines.

Approximately 15%-25% of breast cancers in the United States overexpress or have amplification of human epidermal growth factor receptor 2 (HER2),¹⁻³ an adverse prognostic factor associated with increased rate of recurrence and significantly worse 5-year breast cancer-specific survival compared with HER2-negative disease (68% vs. 96%).⁴ Targeted therapy, such as trastuzumab in combination with chemotherapy, has altered the natural history of the disease, decreasing the rate of disease progression by approximately 25%-40%.⁵⁻⁷ However, despite targeted therapy, approximately 20%-30% of early-stage patients will experience a recurrence within 10 years after diagnosis, two thirds of which is distant disease.^{5,7} Ten-year disease-free survival (DFS) after trastuzumab, while significantly better than observation alone, remains at only 69%-74%.^{5,7} This finding illustrates the potential role for additional therapies following adjuvant trastuzumab.

Ongoing efforts to further improve DFS in early-stage HER2-positive disease have led to several phase III clinical trials evaluating additional targeted therapies after or in conjunction with adjuvant trastuzumab.⁸⁻¹⁰ The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial did not find any additional benefit associated with adding lapatinib,⁸ whereas the APHINITY and ExteNET trials demonstrated modest benefits in DFS with the addition of pertuzumab or neratinib, respectively.⁹ Subsequently, pertuzumab and neratinib were approved by the U.S. Food and Drug Administration.^{11,12}

The approval of neratinib was controversial due to concerns about efficacy and drug safety. Critics highlighted the relatively small absolute margin of improvement in DFS (5-year DFS 90% vs. 88%) and the severity of the side effects, with 40% of women experiencing grade 3 diarrhea.¹⁰ Compounding these issues, neratinib was projected to cost \$10,500 a month (\$126,000 per year),¹³ far exceeding the mean treatment cost

What is already known about this subject

- Neratinib after adjuvant trastuzumab significantly improves disease-free survival (DFS) in women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, but the median absolute DFS gain is only 1.3 months.
- There has been much controversy in the clinical and lay media as to whether minimal gains in DFS are outweighed by the substantial cost and significant side effect profile.

FIGURE 1 Markov Model with 3 Health States and Transitions Between States

for stage I/II breast cancer in the first year after diagnosis (\$82,121).¹⁴

As such, there is a need to understand whether therapies producing marginal gains in DFS, which have not been shown to be reliable predictors of overall survival (OS),¹⁵ can continue to be supported in an era of burgeoning health care expenditures. The objective of this analysis was to evaluate the cost per quality-adjusted life-year (QALY) gained of neratinib for early-stage HER2-positive breast cancer after adjuvant trastuzumab based on the ExteNET trial. Findings will aid in policy development and clinical decision making in the treatment of patients with HER2-positive breast cancer.

Methods

Model Overview

To conduct this cost-effectiveness analysis, we developed a Markov state-transition model composed of 3 health states: (1) remission/no evidence of disease, (2) recurrence, and (3) death (Figure 1). We estimated survival, QALYs, and direct medical expenditure in women with stage I-III HER2-positive breast cancer after 1-2 years of adjuvant trastuzumab followed by either observation or 1 year of neratinib. The model tracked cohorts in 1-month cycles over a lifetime horizon of up to 50 years of follow-up. Costs and outcomes were discounted at 3%, following the recommendation of the Panel on Cost-Effectiveness in Health and Medicine.¹⁶ The analysis was performed from a health care payer perspective.

Patient Population

The base case analysis evaluated a cohort of women with a mean starting age of 50 years, reflecting the ExteNET patient population.¹⁰ Eligible women were aged ≥ 18 years with no evidence of recurrent disease. Patients were required to have completed trastuzumab therapy less than 2 years before randomization and to have an Eastern Cooperative Oncology Group performance status of 0 or 1, normal organ function, and normal left ventricular ejection fraction. Patients with clinically significant cardiac, gastrointestinal, or psychiatric

comorbidities were excluded, as were patients unable to swallow oral medications. Estimates of disease recurrence were based on 5-year follow-up data.¹⁷

Direct Medical Expenditure

Estimated costs of breast cancer recurrence and remission were based on peer-reviewed literature,^{18,19} as presented in a cost-effectiveness analysis comparing adjuvant trastuzumab regimens (Table 1).²⁰ The cost of breast cancer recurrence included chemotherapy, supportive and end-of-life care, and up to 9 months of trastuzumab therapy. The monthly cost of neratinib was based on the wholesale acquisition cost. Costs of grade 3 and grade 4 adverse events (AEs) were derived from discharge data from the Nationwide Inpatient Sample and the Healthcare Cost and Utilization Project.²¹ All costs were inflation-adjusted to 2018 U.S. dollars using the medical care component of the Consumer Price Index.²²

Disease-Free and Overall Survival

Survival outcomes for the 5 years following initiation of treatment with neratinib were based on follow-up data from ExteNET, the only phase III clinical trial studying outcomes associated with neratinib treatment (Table 1).¹⁷ To model a conservative effect of neratinib, it was assumed that the relative effect of neratinib (modeled as the DFS hazard ratio [HR]) was limited to the 5 years of follow-up. DFS after 60 months was based on annualized HRs from long-term follow-up of the HERceptin Adjuvant (HERA) trial⁵—a study that included early stage HER2-positive patients randomized to receive observation or adjuvant trastuzumab for 1 year or 2 years following completion of locoregional therapy and neo- or adjuvant chemotherapy. Because long-term follow-up data suggest that the risk of relapse in treated HER2-positive breast cancer is minimal beyond 10 years,²³ we assumed that no recurrences occurred among women who were disease-free after 120 months.

In women without recurrence, the probability of death was derived from the most recent (2014) age-specific mortality estimates from the Social Security Administration.²⁴ After

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TABLE 1 Model Inputs

Input Parameters	Point Estimate	Low Value	High Value	Distribution	Reference
Costs (undiscounted), \$					
Well state, monthly					
50-54 years	258.69	238.28	291.23	Normal	20
55-64 years	303.96	314.50	342.19	Normal	20
65-74 years	386.74	357.26	435.38	Normal	20
≥ 75 years	381.57	344.90	429.56	Normal	20
Breast cancer recurrence, monthly	4,835.85	4,546.29	5,556.57	Normal	20
Breast cancer end of life care, monthly					
< 65 years	109,840.27	108,392.13	120,824.30	Normal	46
≥ 65 years	73,226.85	75,000.96	80,549.54	Normal	46
Neratinib, monthly	11,445.00	10,300.50	12,589.50	Normal	47
Diarrhea, one-time cost	7,927.53	7,134.78	8,720.28	Normal	21
Abdominal pain, one-time cost	6,471.30	5,824.17	7,118.43	Normal	21
Nausea, one-time cost	5,185.89	4,666.40	5,703.38	Normal	21
Vomiting, one-time cost	6,471.30	5,824.17	7,118.43	Normal	21
Fatigue, one-time cost	7,782.12	7,003.91	8,560.33	Normal	21
Two outpatient clinic visits, one-time cost	203.91	183.52	224.30	Normal	48
Recurrence, first 5 years (hazard ratio)	0.73	0.46	0.84	Beta	17
Recurrence after 5 years (yearly hazard rates)					
Years 5-6	0.019	0.013	0.029	Beta	5
Years 6-7	0.027	0.019	0.038	Beta	5
Years 7-8	0.015	0.010	0.025	Beta	5
Years 8-9	0.011	0.006	0.020	Beta	5
Years 9-10	0.014	0.010	0.025	Beta	5
Years 10+	0.000	0.000	0.000	Beta	Assumed
Death due to breast cancer recurrence	0.0272	0.022	0.033	Beta	49
Noncancer-related death	Age dependent	+20%	-20%		24
Grade 3/4 adverse events, neratinib (one-time probability)					
Diarrhea	0.40	0.320	0.480	Beta	10
Abdominal pain	0.02	0.016	0.024	Beta	10
Nausea	0.02	0.016	0.025	Beta	10
Vomiting	0.03	0.024	0.036	Beta	10
Fatigue	0.02	0.016	0.024	Beta	10
Grade 3/4 adverse events, standard care (one-time probability)					
Diarrhea	0.02	0.016	0.024	Beta	10
Abdominal pain	0.00	0.000	0.000	Beta	10
Nausea	0.01	0.008	0.012	Beta	10
Vomiting	0.00	0.000	0.000	Beta	10
Fatigue	0.00	0.000	0.000	Beta	10
Health state utilities					
Remission, neratinib					
Baseline	0.863	0.858	0.868	Beta	25
Month 1-2	0.841	0.836	0.846	Beta	25
Month 3-5	0.841	0.836	0.847	Beta	25
Month 6-8	0.841	0.835	0.848	Beta	25
Month 9-11	0.849	0.843	0.856	Beta	25
Month 12	0.857	0.851	0.865	Beta	25
Remission, placebo					
Baseline	0.861	0.856	0.866	Beta	25
Month 1-2	0.863	0.858	0.869	Beta	25
Month 3-5	0.841	0.841	0.851	Beta	25
Month 6-8	0.846	0.835	0.847	Beta	25
Month 9-11	0.841	0.840	0.851	Beta	25
Month 12	0.849	0.853	0.857	Beta	25
Remission, no drug (after 12 months)	0.850	0.680	1.000	Beta	25
Disease progression	0.600	0.400	0.700	Beta	28

FIGURE 2 Cost per QALY Gained: Tornado Diagram of the 10 Most Influential Model Inputs

recurrence, the mortality rate was derived from follow-up observations in the HERA trial.⁵

Health-Related Quality of Life

We incorporated estimates of health state utility for neratinib treatment, remission, and disease progression. Utilities were derived from health-related quality of life questionnaires from the ExteNET trial.²⁵ Patients completed EuroQol-5D questionnaires at baseline and months 1, 3, 6, 9, and 12. Of the 2,840 patients randomized to study treatment, 2,427 (85.5%) completed questionnaires at baseline and at least 1 post-baseline time point (1,186 in the neratinib arm, 1,241 in the placebo arm).²⁵ Remission after 12 months was assigned a utility of 0.85,²⁶ and disease recurrence was assigned a utility of 0.6 based on previous publications.^{27,28}

Adverse Events

We modeled the probability of grade 3 and grade 4 AEs that occurred in at least 2% of the ExteNET trial population, including diarrhea, abdominal pain, nausea, vomiting, and fatigue.¹⁰ The model included one-time probabilities of AEs for each treatment arm, based on reported occurrences in ExteNET (Table 1). Any effect of AEs on quality of life was assumed to be captured by the health state utilities derived from the ExteNET trial. Thus, no utility decrements were assigned to individual AEs.

Analyses

We conducted a probabilistic analysis with 5,000 simulations to evaluate the cost per QALY gained and the range of incremental outcomes given uncertainty in all parameters. The base

case HR for recurrence was varied within the 95% confidence intervals [CIs] reported in the ExteNET trial,¹⁷ using a log-normal distribution. Costs were varied $\pm 10\%$ using normal distributions. Ranges for health state utilities and transition probabilities were varied within 20% using a beta distribution or based on published values when available.

We also conducted a one-way sensitivity analysis to evaluate the most influential model inputs. The ranges of costs per QALY gained associated with uncertainty in each input are presented in the form of a tornado diagram (Figure 2).

Scenario and Threshold Analyses

Because prophylactic treatment with loperamide has been shown to diminish the duration and severity of neratinib-associated diarrhea,²⁹ we considered an alternative scenario in which diarrhea was treated during 2 outpatient clinic visits rather than during inpatient visits. We also did this for nausea, vomiting, fatigue, and abdominal pain. Additionally, neratinib conferred more clinical benefit to individuals with hormone receptor-positive disease (hormone receptor-positive invasive DFS HR=0.60, 95% CI=0.43-0.83 vs. hormone receptor-negative HR=0.95, 95% CI=0.66-1.35), so we constructed an alternative scenario in which the treatment population consisted only of hormone receptor positive patients.

To account for limited follow-up from the ExteNET trial, we explored a scenario in which the effect of neratinib persisted through 120 months, after which no recurrences were modeled. We also performed a threshold analysis to assess the price at which neratinib would be cost-effective.

TABLE 2 Base Case Cost-Effectiveness Results

Results	Neratinib	Observation After Trastuzumab	Difference
Cost, \$	317,619	152,812	164,806
Life-years	18.31	18.17	0.14
Quality-adjusted life-years	15.67	15.28	0.40
Cost per life-year, \$	—	—	1,183,223
Cost per quality-adjusted life-year, \$	—	—	416,106

Results

Base Case

In the base case, neratinib treatment after trastuzumab yielded 15.67 QALYs at a cost of \$317,619 compared with 15.28 QALYs at a cost of \$152,812 with trastuzumab alone (Table 2). The addition of neratinib after trastuzumab produced an estimated life expectancy of 18.31 years compared with 18.17 years for trastuzumab alone, resulting in a difference of 0.14 life-years (LY). The difference in cost was \$164,806. The cost per QALY gained was \$416,106, and the cost per LY gained was \$1,183,223. At typical willingness-to-pay thresholds of \$50,000 per QALY, \$100,000 per QALY, and \$200,000 per QALY,³⁰ the probability for neratinib to be considered cost-effective is limited to 2.8%, 16.7%, and 33.9%, respectively (Figure 3).

Sensitivity Analyses

A one-way sensitivity analysis demonstrated that the results were most sensitive to variations in the DFS HR, the annual discount rate, and the probability of recurrence between 9 and 10 years (Figure 2).

Substituting the cost of 2 outpatient visits with inpatient care for treatment of AEs decreased costs to \$313,965 for neratinib therapy and \$152,608 for observation after trastuzumab. The resulting cost per QALY gained was \$407,396.

When the patient population was limited to only include patients with hormone-receptor positive disease, treatment with neratinib cost \$317,369 and produced 15.77 QALYs and 18.42 LYs. Observation after trastuzumab cost \$154,530 and produced 15.18 QALYs and 18.07 LYs. The resulting cost per QALY gained was \$275,311.

Extending the effect of neratinib to 120 months produced 15.91 QALYs and 18.57 LYs in the neratinib arm. The total cost of neratinib therapy decreased to \$315,462 with a cost per QALY gained of \$255,438.

To be cost-effective at a willingness-to-pay threshold of \$150,000 per QALY gained in the base case analysis, neratinib would need to cost \$1,700 per month. There was no price at which neratinib was cost-effective at a willingness-to-pay threshold of \$100,000 per QALY gained.

Discussion

Our analysis shows that adding neratinib after 1-2 years of adjuvant trastuzumab compared with trastuzumab alone in women with stage I-III HER2-positive breast cancer marginally improved life expectancy (18.31 years vs. 18.17 years) but did so at substantial additional cost (\$317,619 vs. \$152,812). At a base case cost of \$416,106 per QALY gained, neratinib is not cost-effective at implied willingness-to-pay thresholds for cancer treatment in the United States.^{31,32} To be considered a cost-effective use of scarce resources at a willingness-to-pay threshold of \$150,000 per QALY gained, the price of neratinib would need to be reduced by 85% (\$9,745). Patients with hormone-receptor positive breast cancer derived more clinical benefit from neratinib than those with hormone-receptor negative disease through 5 years of follow-up,¹⁷ but even among these patients, the clinical benefit achieved does not justify the high cost of neratinib, since the resulting cost per QALY gained of \$275,311 still exceeds willingness-to-pay thresholds. Even with additional sensitivity analyses that accounted for improved management of AEs (e.g., loperamide to decrease diarrhea) and limited the population to patients who received the greatest clinical benefit, we were unable to identify a scenario in which neratinib would be cost-effective.

Since the introduction of trastuzumab for HER-2 positive breast cancer, survival has improved significantly.^{5,7,33,34} Results from several cost-effectiveness analyses indicate that trastuzumab is cost-effective,^{20,27,35,36} with costs per QALY gained ranging from \$18,970 per QALY³⁵ to \$39,982 per QALY.²⁰ Trastuzumab is a high-value cancer treatment that substantially improves clinical outcomes at an acceptable price. New additive adjuvant therapies must demonstrate similar cost-effectiveness to add value to current HER2-targeted breast cancer treatment. In this context, neratinib appears to be low value.

Interestingly, the results of our study are comparable to findings from cost-effectiveness analyses of pertuzumab, a frequently used HER2-targeted adjuvant therapy. Although there are no U.S.-based cost-effectiveness studies for the addition of pertuzumab to trastuzumab in early-stage breast cancer, in a cost-effectiveness analysis of dual-blockade pertuzumab and trastuzumab versus trastuzumab alone among metastatic breast cancer patients enrolled in CLEOPATRA, pertuzumab had a cost per QALY gained of \$472,668.³⁷ This highlights the need for higher value drugs to be developed in this disease area.

Limitations

There are several limitations to this study. For the base case analysis, we assumed the disease control effect of neratinib was limited to the 5 years of follow-up data available from the ExteNET trial. To address this limitation, we performed an analysis extending the effect of neratinib to 120 months and found that even with extended therapeutic benefit, the cost per QALY gained was higher than standard willingness-to-pay

FIGURE 3 Cost-Effectiveness Acceptability Curve for Treatment with Neratinib in the Base Case

QALY = quality-adjusted life-year.

thresholds. Additionally, because OS data were not available from the ExteNET trial, we used OS data from the HERA trial. This was based on the assumption that, while neratinib reduces the risk of recurrence, it is unlikely to reduce the risk of death once recurrence occurs. Finally, because there is no long-term clinical data for neratinib use, our model only includes AEs that occurred during treatment. If neratinib increases the risk of future negative outcomes such as cardiac events, then that would result in an increased cost per QALY gained.

Conclusions

Over the past 2 decades, the price of cancer drugs has spiraled upward.^{38,39} This increase in treatment cost presents a considerable financial burden to patients, creating barriers to access and negatively affecting patient outcomes.⁴⁰ This disproportionately affects patients of lower socioeconomic status, furthering health disparities.⁴⁰ To combat skyrocketing prices, emphasis has been placed on “value-based” pricing,⁴¹ a method for pricing drugs based on how much the drug improves outcomes. However, defining the “value” of a drug is a complex task, since it requires assigning limits to the price of life. To assist with this, the American Society of Clinical Oncology and the European Society for Medical Oncology have developed frameworks to evaluate the clinical benefit of oncology drugs.^{42,43} Studies using these tools have revealed that a substantial proportion of recent therapies fail to meet thresholds

for meaningful clinical benefit,^{44,45} underscoring the need to develop drugs that provide substantial clinical benefit over and above the standard of care.

Although treatment with neratinib significantly, though marginally, improves DFS, there is still no data available on the long-term clinical benefit or OS. Until further evidence is available, neratinib should be reserved for high-risk patients with hormone-receptor positive disease. The high cost of neratinib coupled with the clinical benefit it currently confers prevents it from being recommended for use in all HER2-positive patients.

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