original reports abstract

Cost Effectiveness of Trastuzumab for Management of Breast Cancer in India

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PURPOSE We undertook this study to evaluate the incremental cost per quality-adjusted life-year (QALY) gained with use of adjuvant trastuzumab as compared with chemotherapy alone among patients with nonmetastatic breast cancer in India.

METHODS We used a Markov model to estimate the incremental cost of using trastuzumab (for 1 year, 6 months, or 9 weeks) as compared with chemotherapy alone using a societal perspective, excluding indirect productivity losses. Although the outcomes (QALYs) in the standard chemotherapy arm were estimated after calibrating the model as per survival data from 2 Indian cancer registries, effectiveness estimates from the HERA trial and a joint analysis of the NSABP B-31 and NCCTG N9831 trials were used to estimate the consequences of 1-year trastuzumab use. The cost of treatment was estimated using national standard treatment guidelines and real-world use estimates for different treatment modalities as per data from Indian cancer registries. Probabilistic sensitivity analysis was undertaken to evaluate parameter uncertainty.

RESULTS For 1 year of trastuzumab use, the incremental benefit per patient, incremental cost per QALY gained, and probability of being cost effective using HERA trial estimates were 1.29 QALYs, 178,877 Indian national rupees (INRs; US$2,558), and 4%, respectively, whereas the corresponding figures using joint analysis estimates were 1.69 QALYs, INR 134,413 (US$1,922), and 57.3%, respectively.

CONCLUSION Use of trastuzumab for 1 year is not cost effective in India at the current price. However, trastuzumab use for 9 weeks is cost effective and should be included in clinical guidelines and reimbursement policies. A price reduction of 15% to 35% increases the probability of 1-year trastuzumab use being cost effective, to 90%.

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INTRODUCTION

Breast cancer is the most common cancer among women in India and accounts for 27% of all cancers in that country.[1] Overexpression of the oncogene human epidermal growth factor receptor 2 (*HER2/neu*) is associated with poor prognosis and high risk of recurrence.[2-4] Addition of the HER2-targeted monoclonal antibody trastuzumab to chemotherapy in adjuvant treatment has been shown to improve disease-free survival (DFS) by 50% and overall survival (OS) by 30%.[5-7] However, trastuzumab is an expensive drug. It was reported to have been used in only 8.6% of eligible patients, half of whom were enrolled in a clinical trial.[8]

The low rate of trastuzumab use raises the important question of whether public resources should be used to make this treatment routinely accessible in India. This question is highly relevant because of the recently announced ambitious Indian health insurance program, Ayushman Bharat, which includes coverage of chemotherapy for cancer treatment under the Prime Minister's Jan Aarogya Yojana (PMJAY) component.[9,10]

Many cost-effectiveness analyses of trastuzumab have been reported, with variable results.[11-19] The variability in findings can be attributed to differences in perspective, modeling method, context, health care delivery structure, price, and other input parameters.

A major limitation of the existing literature is that a majority of these model-based cost-effectiveness analyses have based their outcome valuation on the interim results of clinical trials with relatively short follow-up. No cost-effectiveness analysis has yet been published taking into account the long-term clinical benefits based on the Herceptin Adjuvant (HERA) trial (ClinicalTrials.gov identifier: NCT00045032).[7] Moreover, although a majority of previous economic evaluations have used effectiveness estimates from the

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CONTEXT

Key Objective

Is the use of Trastuzumab cost effective for patients with nonmetastatic breast cancer in low-income countries like India?

Knowledge Generated

Addition of trastuzumab to chemotherapy in the adjuvant setting for 1 year was not cost effective at the current price, but addition of trastuzumab for 9 weeks was cost effective. At the current price, 1-year trastuzumab use has just a 4% to 57% probability of being cost effective. In contrast, 9-week adjuvant trastuzumab therapy incurs an incremental cost per quality-adjusted life-year gained, ranging from 34,268 Indian national rupees (INRs; US$490) to INR 43,264 (US$619).

Relevance

Nine weeks of adjuvant trastuzumab is an efficient option for use in India and other low-income countries where a large majority of patients do not experience the benefits of trastuzumab because of its cost.

HERA trial, the HERA trial protocol is not commonly followed in routine clinical practice by oncologists in India.[20]

We undertook this cost-effectiveness analysis of adjuvant trastuzumab in combination with standard chemotherapy compared with chemotherapy alone in the Indian context. The base case presents the analysis for 1-year use of trastuzumab, which is standard practice. Detailed subgroup analyses were also undertaken, and we present cost-effectiveness findings for 6-month and 9-week trastuzumab use.

METHODS

Model Overview

A Markov model was developed for HER2-positive breast cancer in Indian women (Fig 1). The 5 health states were as follows: disease-free state, locoregional recurrence (LR), metastasis, death resulting from breast cancer, and all-cause mortality. Ten percent of those who developed LR were assumed to revert back to a disease-free state in the subsequent year.[21] Thereafter, no remission from LR to back to a disease-free state was possible. Transition probability from LR to metastasis was 3 times that of disease-free state to metastasis.

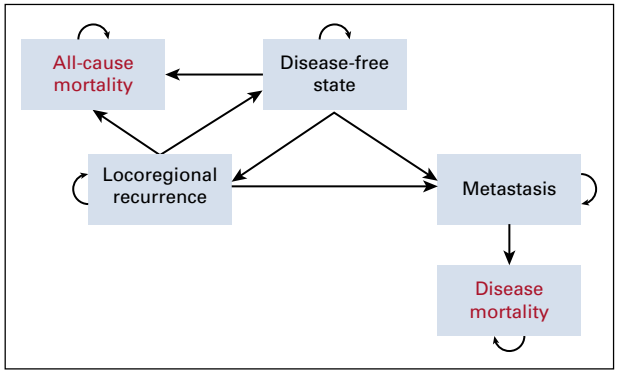

FIG 1. Model schematic.

We modeled the lifetime costs and consequences of treating a cohort of patients with surgically resected HER2-positive breast cancer at age ≥ 50 years with adjuvant chemotherapy or adjuvant chemotherapy plus trastuzumab from a societal perspective. Both health system costs and out-of-pocket expenditures were estimated. Indirect costs resulting from productivity losses were not included. Outcomes were calculated on the basis of life-years (LYs) and quality-adjusted LYs (QALYs) gained. All future costs and consequences were discounted at 3% considering international best practices, as well as recently published Indian guidelines for economic evaluation.[22-24] A cycle length of 1 year was considered appropriate based on available literature.[16,18,19,25,26] Results are reported as incremental cost (Indian national rupee [INR]) per LY and QALY gained with use of trastuzumab. As per guidelines for health technology assessment in India, we used a threshold of per-capita gross domestic product (GDP) in 2019 to evaluate cost effectiveness.[23]

Intervention and Control

We considered 1 year of trastuzumab along with adjuvant chemotherapy as an intervention and adjuvant chemotherapy (comprising anthracycline and taxane-based drugs) as a counterfactual group in the base case analysis. The base case analysis is presented in 2 scenarios. In base case 1, we used the effectiveness evidence from the HERA trial, whereas in base case 2, the effect size of the joint analysis was used; everything else remained constant. Three alternative intervention scenarios were considered based on the duration of trastuzumab use: 1 year, 6 months, and 9 weeks, respectively. Patients in a disease-free, LR, or metastatic state were assumed to be managed as per standard international (National Comprehensive Cancer Network) and national (Indian Council of Medical Research) guidelines[27,28] (Table 1).

Cost

Trastuzumab infusion at 8 mg/kg for the first cycle and 6 mg/kg for the remaining 16 cycles was considered for all

TABLE 1. Clinical Parameters for Assessing Cost Effectiveness of Adjuvant Trastuzumab Versus Chemotherapy

Parameter	Base Value	95% CI	Source
Utility			
Disease free in first year	0.749	0.579 to 0.919	16
Disease free after first year	0.847	0.703 to 0.991	16
LR	0.81	0.673 to 0.947	16
Metastatic	0.484	0.402 to 0.566	16
Transition probability			
Standard chemotherapy			
Disease free to LR	0.049	0.043 to 0.055	42,44
Disease free to metastatic	0.084	0.074 to 0.094	42,44
LR to metastatic	0.231	0.205 to 0.258	42,44
Metastatic to DC	0.73	0.647 to 0.813	42,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to disease free (second year only)	0.1	0.089 to 0.111	21
1-year trastuzumab			
Year 1			
Disease free to LR	0.021	0.018 to 0.023	47
Disease free to metastatic	0.035	0.031 to 0.039	47
Metastatic to DC	0.73	0.647 to 0.813	43,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.097	0.086 to 0.108	47
Year 2			
Disease free to LR	0.026	0.023 to 0.029	48
Disease free to metastatic	0.045	0.039 to 0.05	48
Metastatic to DC	0.73	0.647 to 0.813	43,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.123	0.109 to 0.137	48
LR to DFS	0.053	0.047 to 0.059	48
Years 3-15			
Disease free to LR	0.037	0.033 to 0.041	7,45,46
Disease free to metastatic	0.064	0.057 to 0.071	7,45,46
Metastatic to DC	0.73	0.647 to 0.813	43,44
Disease free to ACM	0.009	0.008 to 0.01	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.176	0.156 to 0.196	7,45,46
Years 16-20			
Disease free to LR	0.049	0.043 to 0.055	43,44
Disease free to metastatic	0.084	0.074 to 0.094	43,44
Metastatic to DC	0.231	0.205 to 0.258	43,44
Disease free to ACM	0.73	0.647 to 0.813	49
LR to ACM	0.009	0.008 to 0.01	49
LR to metastatic	0.009	0.008 to 0.01	43,44

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TABLE 1. Clinical Parameters for Assessing Cost Effectiveness of Adjuvant Trastuzumab Versus Chemotherapy (Continued)

Parameter	Base Value	95% CI	Source
HR for DFS from HERA trial, year			
1	0.42		47
2	0.53		48
3-4	0.76		45
5-8	0.76		46
9-15	0.76		7
HR for DFS from joint analysis of NSABP B-31 and NCCTG N9831 trials			
Year 1-15	0.6		6
Discount rate, %	3		22-24
Proportion of patients requiring management in trastuzumab and SC arms, %			
LR			
Surgery	88.1		31
Radiotherapy	57.6		31
Chemotherapy	85		31
Hormone therapy	38.4		31
Tamoxifen	50		Expert opinion
Aromatase inhibitor	50		Expert opinion
Metastasis			
Surgery	18.8		31
Radiotherapy	36.1		31
Chemotherapy	85.7		31
Hormone therapy	42.6		31
Line of therapy			
Hormone therapy	42.6		31
First	95		Expert opinion
First and second	5		Expert opinion
Chemotherapy	85.7		31
First	75		Expert opinion
First and second	20		Expert opinion
First, second, and third	5		Expert opinion
Disease free			
Hormone therapy	50		Expert opinion
Tamoxifen	50		Expert opinion
Aromatase inhibitor	50		Expert opinion
Average trastuzumab daily dose in first year, mg/kg	8 for first cycle and 6 for next 16 cycles		47
Survival rate in SC arm, %			
At 5 years	66.1		43
At 10 years	35		44

Abbreviations: ACM, all-cause mortality; DC, death resulting from breast cancer; DFS, disease-free survival; LR, locoregional recurrence; SC, standard chemotherapy.

patients in the first year in the intervention arm, assuming an average weight of 60 kg. The average weight of women with breast cancer in India was assumed as per findings of previous studies.[29,30] The cost for those with a disease-free health state in the intervention arm accounted for outpatient (OPD) oncology and cardiac consultation, electrocardiogram, echocardiography, mammography, and hormone therapy. For those with LR, the cost accounted for

clinical examination (OPD consultation), routine diagnostic tests, and radiologic tests. Additionally, the costs of performing various procedures for patient management, such as local mastectomy, radiotherapy, chemotherapy, and hormone therapy, were included. Similarly, various diagnostic tests and management protocols (chemotherapy, radiotherapy, hormone therapy, and surgery) as per the Indian Council of Medical Research cancer registry were taken into account (Tables 1 and 2). In addition, the cost of management of cardiac complications was included in intervention arm.

The cost for patients with a disease-free health state in the control arm included oncology OPD consultation, mammography, and hormone therapy. Similarly, for those in an LR or metastatic health state, an identical set of hematologic, diagnostic, and radiologic tests and recurrent breast cancer management guidelines were followed as for the intervention arm.

The treatment regimens and their use in the intervention and control arms (applicable to new or all health patients in respective health states) were followed as per standard treatment guidelines.[27,28] To make the cost of treatment more in keeping with real data, we used the rates of use of various treatment options among patients in different health states, as reported in the pooled data from Indian cancer registries[31] (Table 1).

Locally published studies were used to elicit the unit costs of various diagnostic and therapeutic services provided to these patients.[32,33] For those services, where published cost studies were not available, we relied on provider payment rates under the national social insurance scheme for central government employees.[34] Data on prices of medicine were obtained from procurement rates of the medical service corporation in Tamil Nadu state.[35]

Valuation of Consequences

Nearly 18 cost-effectiveness studies have been undertaken to evaluate trastuzumab.[11-14,16-19,21,25,26,36-42] Eight studies modeled consequences using effectiveness estimates reported in the HERA trial, whereas 6 used the joint analysis of NSABP B-31 (ClinicalTrials.gov identifier: NCT00004067) and NCCTG N9831 (ClinicalTrials.gov identifier: NCT00898898) trials. The HERA trial reported OS and DFS over a longer follow-up period and reported hazard ratios (HRs) at multiple time points, but this protocol is not commonly practiced in India or elsewhere. Moreover, crossover of patients between study arms was likely to have led to an underestimation of the benefits of adjuvant trastuzumab. The joint analysis reported a greater benefit, with an HR of 0.60, and its protocol is commonly followed in routine practice. Therefore, we used the efficacy data from both analyses to separately report the outcomes and cost effectiveness of 1 year of trastuzumab in 2 separate base case analyses.[6]

The CONCORD study, which used data on survival outcomes from 2 Indian cancer registries, reported 5-year survival of 66.1%.[43] Similarly, another Indian study that reported long-term outcomes found a 35% survival rate at 10 years.[44] We calibrated the model in the control arm (because use of trastuzumab has been reported in India among only 8.6% of eligible patients) so that the survival rates were as reported for the Indian patient population. Furthermore, using the DFS HRs from the HERA trial at each of the 5 different time points, from the first to 11th year, we applied the year-wise HRs to the control arm transition probabilities to arrive at the intervention arm transition probabilities.[7,45-48] For the 12th to 15th years, we assumed the same HR reported in the HERA trial for 11th year; beyond year 15, we did not assume any further trastuzumab effectiveness. For computing the transition probability in the intervention arm using the effectiveness estimate of the joint analysis, we used an HR of 0.60 for each year up to 15 years.

The risk of mortality resulting from metastatic breast cancer reported in published evidence from India[44] was further calibrated to match the overall breast cancer survival trends reported in the CONCORD and long-term survival analysis studies. The same risk of mortality resulting from metastasis was applied to patients in both the intervention and control arms. Age-wise risk of mortality as per Indian sample registration survey life tables was applied to women in both the intervention and control groups.[49] Utility values for the disease-free state in first and subsequent years, respectively, were 0.749 and 0.847, whereas for LR and metastatic health states, utility values were 0.484 and 0.810, respectively (Table 2).[18]

Sensitivity Analysis

A probabilistic sensitivity analysis using second-order Monte Carlo simulation was undertaken. The values for transition probability varied by 10%, whereas values for both utility and cost varied by 20% each around the base value. Beta distribution was used to parameterize transition probability and health state utility values. Similarly, gamma distribution was used for cost parameters. The number of iterations was restricted to 1,000.

We undertook a subgroup analysis to assess the cost effectiveness of 6-month and 9-week trastuzumab use compared with standard chemotherapy. The HRs for DFS and cardiac events with 6 versus 12 months of trastuzumab use were derived from estimates reported in 2 trials, PERSEPHONE and PHARE, respectively.[50,51] Because the estimates of each of the 2 trials were slightly different, the incremental cost-effectiveness ratios (ICERs) were computed separately using the HR for DFS reported in each trial. The HRs for DFS of 1.07 and 1.08 as reported in the PERSEPHONE and PHARE trials, respectively, were applied to the transition probabilities of 1-year trastuzumab use as computed earlier in the base model to derive transition probabilities for 6-month trastuzumab use. The probability of dying with metastasis was similar to that of the base case. Similarly, transition probabilities for 9-week

TABLE 2. Cost Parameters for Assessing Cost Effectiveness of 1-Year Adjuvant Trastuzumab SC

Parameter	Unit Cost		95% CI		Source
	INR	US$	INR	US$	
Drug					
Annual (lifetime) trastuzumab cost	241,963	3,447	173,825 to 275,523	2,486 to 3,940	35
Daily hormone therapy (tamoxifen)	0.86	0.01	0.66 to 1.06	0.01 to 0.02	35
Daily hormone therapy (letrozole)	0.58	0.01	0.41 to 0.72	0.01 to 0.01	35
Chemotherapy (paclitaxel + docetaxel)	544	8	436 to 653	6 to 9	35
Chemotherapy (zoledronic, 1 vial)	70	1	54 to 86	0.8 to 1.2	35
Line therapy, chemotherapy (capecitabine, 1 500-mg tablet)	15	0.2	11 to 18	0.2 to 0.3	35
Line therapy, chemotherapy (carboplatin + gemcitabine + vinorelbine)	2,696	39	2,086 to 3,306	30 to 47	35
Line therapy, hormone therapy (fulvestrant)	67,920	971	52,548 to 83,292	752 to 1,191	Review of market prices
Clinical and radiologistic tests					
ECG	18	0.3	14 to 22	0.2 to 0.3	33
Echocardiography	358	5	277 to 439	4 to 6	33
OPD cardiac consultation	259	4	109 to 408	2 to 6	33
OPD consultation	150	2	116 to 184	2 to 3	34
Mammography	370	5	286 to 454	4 to 6	34
Bone scan	3,934	56	3,044 to 4,824	44 to 69	34
CBC, BCT, and LFT	187	3	84 to 289	1 to 4	Review of market prices
CECT chest	4,500	64	3,482 to 5,518	50 to 79	34
CECT abdomen	4,500	64	3,482 to 5,518	50 to 79	34
Biopsy of recurrence	1,257	18	973 to 1,541	14 to 22	32
ER, PR, and HER2/neu	2,750	39	2,128 to 3,372	30 to 48	Review of market prices
PET scan	14,663	210	11,344 to 17,982	162 to 257	34
Local mastectomy, simple	12,650	181	9,787 to 15,513	140 to 222	34
3D CRT	75,000	1,073	58,026 to 91,974	830 to 1,315	58
Day care	958	14	741 to 1,175	11 to 17	32
Chest x-ray	60	1	46 to 74	1 to 1	34
USG abdomen	323	5	250 to 396	4 to 6	34

NOTE. 1 US$ = INR 69.92.

Abbreviations: BCT, breast-conserving therapy; CBC, complete blood count; CECT, contrast-enhanced computed tomography; CRT, conformal radiation therapy; ER, estrogen receptor; INR, Indian national rupee; LFT, liver function test; OPD, outpatient department; PET, positron emission tomography; PR, progesterone receptor; SC, standard chemotherapy; USG, ultrasound sonography.

trastuzumab use were computed using hazard rates and cardiac events from 9 weeks versus 12 months of trastuzumab separately as reported in the Short HER (HR, 1.13) and FinHER trials.[51-53]

A threshold analysis was undertaken to ascertain the price at which the ICER value was below the per capita GDP. The threshold was justified based on economic evaluations conducted in India,[22] Indian health technology assessment guidelines,[23] and a recent oncologic cost-effectiveness analysis conducted in India.[54-56]

RESULTS

One-Year Trastuzumab: Base Case 1 (HERA trial effectiveness)

The lifetime discounted cost per patient for those receiving 1 year of adjuvant trastuzumab with chemotherapy was found to be INR 341,046 (US$4,878; Table 3). Similarly, patients receiving adjuvant chemotherapy alone incurred a lifetime cost of INR 110,151 (US$1,575). The incremental cost per patient of trastuzumab use was INR 230,895 (US$3,302; Table 3).

The number of QALYs lived per patient among those receiving trastuzumab and chemotherapy alone were 6.6 and 5.3 years, respectively. The incremental health benefits gained per patient after treatment with trastuzumab were 1.48 LYs and 1.29 QALYs.

Overall, our findings show that use of trastuzumab for 1 year would incur an incremental cost of INR 156,291 (US$2,235) per LY gained and INR 178,877 (US$2,558) per QALY gained (Table 3). The value of incremental cost per QALY gained would be more than the per capita GDP of India; therefore, use of trastuzumab for 1 year would not be considered cost effective in the Indian setting.

One-Year Trastuzumab: Base Case 2 (joint analysis effectiveness)

The lifetime and incremental costs per patient with trastuzumab were INR 3,37,935 (US$4,833) and INR 2,27,784 (US$3,258), respectively. The LYs and QALYs lived per patient using trastuzumab were 8.7 and 7.0, respectively. The incremental health benefits per patient were found to be 1.93 life-years and 1.69 QALYs gained. As a result, 1-year trastuzumab use would incur an additional cost of INR 1,18,096 (US$1,689) per LY and INR 1,34,413 (US$1,922) per QALY gained (Table 3).

Subgroup and Sensitivity Analyses

The incremental cost per QALY gained with 6-month trastuzumab use was found to be INR 110,455 (US$1,580) and INR 114,060 (US$1,631) when effectiveness estimates from the PERSEPHONE and PHARE trials, respectively, were used. The incremental cost of 9-week trastuzumab use per QALY gained was found to be INR 43,264 (US$619) and INR 34,268 (US$490) considering the effectiveness reported in the Short HER and FinHER trials, respectively. Each of these ICER estimates falls within the cost-effectiveness threshold of per capita GDP (Table 4).

The findings of cost effectiveness are highly sensitive to the price of trastuzumab, DFS utility after 1 year, and transition probability from a disease-free to metastatic state in the chemotherapy arm. The findings of the probabilistic sensitivity analysis suggest that there is a 4% probability for 1-year trastuzumab use to be cost effective at a willingness-to-pay threshold equal to the per capita GDP (Figs 2 and 3). However, reducing the price by 15% to 35% increases the probability of 1-year trastuzumab use being cost effective to 90% (Fig 3).

TABLE 3. Deterministic Costs, Effects, and Cost Effectiveness of 1-Year Trastuzumab Use As Compared With SC

	1-Year Trastuzumab Use		
Finding (discounted)	HERA Trial	Joint Analysis of NSABP B-31 and NCCTG N9831 Trials	SC
Lifetime cost per patient, INR	341,046	337,935	110,151
Health consequences per patient			
LYs	8.3	8.7	6.8
QALYs	6.6	7.0	5.3
Incremental cost, INR	230,895	227,784	
Incremental benefit			
LYs	1.48	1.93	
QALYs	1.29	1.69	
ICER			
INRs per person LY gained	156,291	118,096	
INRs per person QALY gained	178,877	134,413	

Abbreviations: ICER, incremental cost-effectiveness ratio; INR, Indian national rupee; LY, life-year; QALY, quality-adjusted life-year; SC, standard chemotherapy.

TABLE 4. Probabilistic Costs, Consequences, and Probability of Being Cost Effective for 1-Year, 6-Month, and 9-Weeks Adjuvant Trastuzumab Use

	Incremental per Person							
	Cost			Cost per QALY Gained				Probability of Cost Effectiveness at per Capita GDP (%)
				Mean		95% CI		
Source of Effectiveness Data	INR	US$	QALYs (95% CI)	INR	US$	INR	US$	
1-year adjuvant trastuzumab use								
HERA trial	133,163	1,905	1.29 (1.04 to 1.54)	104,503	1,495	104,470 to 104,537	1,494 to 1,495	4.0
Joint analysis of NSABP B-31 and NCCTG N9831 trials	227,915	3,260	1.69 (1.39 to 1.99)	135,713	1,941	135,672 to 135,754	1,940 to 1,942	57.3
6-month adjuvant trastuzumab use								
PERSEPHONE trial	121,331	1,735	1.09 (0.86 to 1.31)	112,957	1,616	112,920 to 112,994	1,615 to 1,616	88.6
PHARE trial	120,954	1,730	1.06 (0.85 to 1.28)	115,282	1,649	115,243 to 115,320	1,648 to 1,649	88.2
9-week adjuvant trastuzumab use								
Short HER trial	39,309	562	0.91 (0.71 to 1.11)	43,702	625	43,684 to 43,719	625 to 625	100.0
FinHER trial	64,369	921	1.88 (1.54 to 2.22)	34,600	495	34,588 to 34,612	495 to 495	100.0

Abbreviations: GDP, gross domestic product; INR, Indian national rupee; QALY, quality-adjusted life-year.

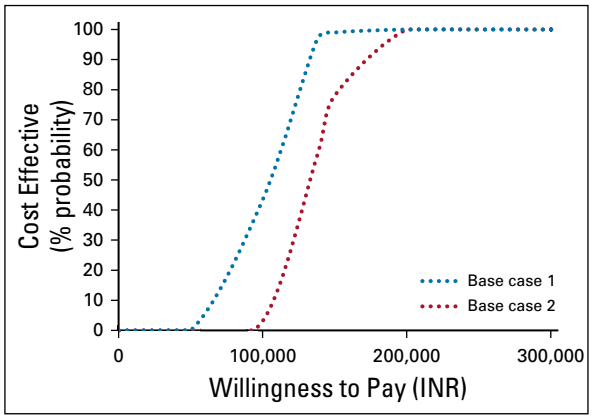

FIG 2. Probability of 1-year trastuzumab use being cost effective at varying willingness-to-pay thresholds. INR, Indian national rupee.

DISCUSSION

Overall, our findings indicate that trastuzumab use for 1 year is not cost effective at its current price. However, with a 15% to 35% reduction of price, 1-year trastuzumab use would be cost effective. Use of trastuzumab for both 6 months and 9 weeks is cost effective. However, with a statistically similar number of QALYs gained, 9 weeks of trastuzumab use has a lower incremental cost and hence is the most efficient option.

We have presented our results using effectiveness data from a variety of different trials. Second, we used estimates of HRs as reported at different time points (as in the HERA trial) rather than a constant HR, which has been assumed in most of the previous economic evaluations. Third, we calibrated our model for the counterfactual scenario to predict survival based on breast cancer survival from 2 Indian cancer registries. Therefore, our findings are much more pragmatic and representative of the Indian population.

With regard to cost, our parameter values for the cost of management of breast cancer and its complications were obtained from locally published cost studies[32,33] or reimbursement rates under 1 of India's largest social insurance programs for provider payments.[34,58] Similarly, the patterns of treatment use specific to each stage of disease were based on analysis of hospital-based cancer registries.[31] Hence, our cost analysis seems realistic from the national viewpoint.

The incremental gain in LYs has ranged from 0.6 to 2.87 in various studies, whereas QALYs gained have varied from 0.49 to 2.83.[11-14,16-19,21,25,26,36-42,59] We found the incremental health benefit after treatment with trastuzumab to be 1.48 LYs and 1.29 QALYs, both of which are well within the range of values in published evidence.

The incremental cost per QALY gained in terms of purchasing power parity ranges from 4,819 international dollars (Int$) to Int$110,283, with a median value of Int$40,998. Our study finding for an ICER (Int$8,954) fell within this range. The relatively lower ICER for trastuzumab use found in India could be attributable to India's relatively lower drug prices and differences in health care delivery structure.

Considering the huge disease and economic burden that cancer imposes, several publicly financed health insurance schemes have been implemented in India.[60] The PMJAY, which is the largest tax-funded health insurance scheme for the poor in India, also includes cancer treatment in its benefit package.[9,10] Given the evidence from our study, it is recommended that insurance schemes provide for 9-week trastuzumab treatment for patients with HER2/neu-positive

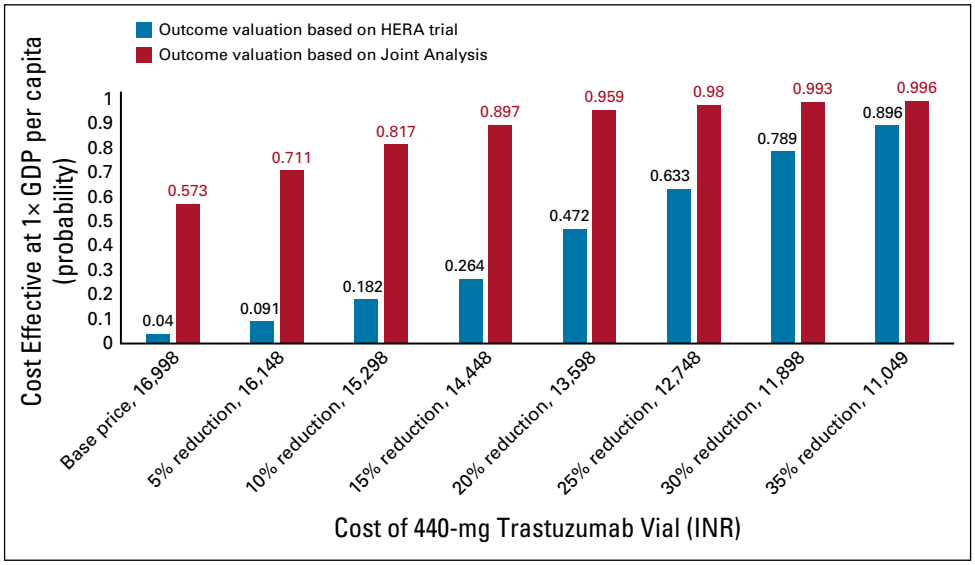

FIG 3. Price sensitivity analysis for cost effectiveness of 1-year trastuzumab use. GDP, gross domestic product; INR, Indian national rupee.

breast cancer. Furthermore, the National Pharmaceutical Pricing Authority should consider reducing the price of trastuzumab by at least 35%, such that 1-year trastuzumab use would also become cost effective. The network of cancer hospitals as part of the National Cancer Grid could develop a mechanism for common procurement of chemotherapy drugs, which would likely bring down prices.[20]

There has been significant emphasis on the development of standard treatment guidelines based on evidence from health technology assessments.[23,61] It is recommended that in addition to clinical evidence on effectiveness, evidence on cost effectiveness be considered while framing clinical guidelines.

Empirically derived evidence on transition probabilities and long-term survival to parameterize such cost-effectiveness models is currently lacking. More research is needed using longitudinal studies. Second, there is a lack of clinical data on quality of life at different stages of cancer survival. In the absence of such a study from India, we had to use a valuation study conducted elsewhere. Finally, we recommend generation of a cost database or reference cost menu that could be used by researchers to populate such economic models. This would help reduce the uncertainty.

In conclusion, our study findings show that 1-year use of trastuzumab is not cost effective, or there is significant uncertainty around its cost effectiveness. Reducing the price of the drug by 35% would make 1-year trastuzumab use cost effective. In the current scenario, use of trastuzumab for 9 weeks is the most efficient option. The clinical guidelines and provider payments for cancer treatment under health insurance schemes should be accordingly revised.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

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