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Economic Evaluation

Cost-Effectiveness Analysis of Pertuzumab Plus Trastuzumab and Docetaxel Compared With Trastuzumab and Docetaxel in the Adjuvant Treatment of Human Epidermal Growth Factor Receptor 2–Positive Metastatic Breast Cancer in Colombia

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ABSTRACT

Objectives: The addition of pertuzumab to the scheme of docetaxel plus trastuzumab (TH) in patients with metastatic breast cancer with overexpression of human epidermal growth factor receptor 2 increases survival. Nevertheless, this addition could represent a high cost for the health system of a middle-income country such as Colombia. Therefore, it is necessary to evaluate the efficiency of the pertuzumab plus TH (PTH) scheme in comparison with TH.

Methods: A partitioned survival model-based cost-utility analysis was performed. Progression-free survival and overall survival curves for each scheme were obtained from the CLEOPATRA study. The time horizon was 30 years with a discount rate of 5% for costs and quality-adjusted life-years. Total direct costs were calculated using national tariffs. Utilities were obtained from external sources. Model uncertainty was evaluated by deterministic and probabilistic sensitivity analysis. A willingness to pay value of 5180 US dollars was used.

Results: The discounted total average costs of TH and PTH were $24 109 and $60 846, respectively. These regimens' average life-years were 5.78 and 8.38, and their quality-adjusted life-years were 3.28 and 4.51, respectively. The incremental cost-effectiveness ratio was $29 867. One-way sensitivity analysis showed that the cost of pertuzumab was the variable that explained the uncertainty in the model. The probability that PTH is cost-effective in the probabilistic sensitivity analysis is 0.0724.

Conclusions: The addition of pertuzumab to the TH regimen in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer has a low probability of being cost-effective from the payer's perspective in the Colombian health system.

Keywords: breast cancer, Colombia, cost-effectiveness, human epidermal growth factor receptor 2 protein, pertuzumab, trastuzumab.

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Introduction

Breast cancer is the first cause of cancer-related mortality in Colombia, and it represents a significant burden on the health system. This condition accounted for 17.2 deaths per 100 000 inhabitants by 2018, according to the National Institutes of Health.[1] Moreover, the incidence was 63.9 cases per 100 000 women older than 15 years, with 13 376 new cases that year. According to the stage, the costs can vary from 8 996 987 to 144 400 865 Colombian pesos.[2]

Although breast cancer confines a single organ, it is not a unique type of disease.[3] With overexpression of human epidermal growth factor receptor 2 (HER2 positive), breast cancer has been associated with significant clinical and histological aggressiveness, an increased risk of lymphatic and hematogenous spread, less hormone dependence, and an increased risk of recurrence and death.[4] It is estimated that 1 in every 5 women affected with breast cancer is HER2 positive.[5] This receptor has become one of the most important therapeutic targets.[4] Targeted biological therapies such as trastuzumab, pertuzumab, and lapatinib are commonly used to treat HER2-positive cancers.[6]

These anti-HER2 targeted antibodies have improved the prognosis of patients with HER2-positive metastatic breast cancer (MBC). These agents demonstrated mortality and progression reduction.[4,7,8] These benefits have led to the proposal of combined therapeutic regimens (ie, using 2 different antibodies) to enhance efficacy in this subgroup of patients. For this reason, the clinical practice guidelines of the National Comprehensive Cancer

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Network recommend a combined scheme with 2 immunotherapy agents for the management of these patients.[6]

Nevertheless, they have significantly increased costs for health systems.[4] Studies in high-income countries have shown that the addition of pertuzumab can be prohibitively expensive, even for them. For this reason, regulatory agencies such as the National Institute of Clinical Excellence in the United Kingdom or Ontario's Committee to Evaluate Drugs recommend against funding with health system resources.[9,10] In Colombia, a model-based economic evaluation by Saenz[11] in 2014 showed that the addition of pertuzumab to the trastuzumab and docetaxel scheme was not cost-effective. Nevertheless, the effectiveness data were drawn from the 2014 CLEOPATRA study with a shorter follow-up. In addition, the cost data for that drug were provided by the manufacturer and were not subject to regulation. Currently, the 4 drugs recommended as the first line in managing the different stages of this condition (ie, trastuzumab, pertuzumab, docetaxel, and trastuzumab emtansine) are regulated by the Colombian Ministry of Health. An economic evaluation with more extended follow-up data and regulated drug costs could provide technical elements for decision makers in the Colombian context.

The objective of this study is to estimate the cost-effectiveness of pertuzumab plus trastuzumab and docetaxel (PTH) versus trastuzumab plus docetaxel (TH) in patients with MBC from the payer's perspective in Colombia under the context of regulated prices.

Methods

Setting and Location

A model-based cost-effectiveness analysis was conducted to estimate the efficiency of PTH versus TH schemes from the public payer's perspective in the Colombian health system.

The Colombian health system is based on a market mechanism. The Ministry of Health is the regulator, the health-promoting entities (Entidad Promotora de Salud) are the insurers/payers, and the health institutions (Institución Prestadora de Salud [IPS]) are the service providers. Entidad Promotora de Salud and IPS may be public or private. In addition, the IPS can be of the primary, secondary, or tertiary level of complexity. The context of this economic evaluation is for tertiary-level health institutions.

Patients

The population of this evaluation corresponds to the inclusion criteria used in the CLEOPATRA study: women aged 18 years or older diagnosed of MBC, HER2 positive with Eastern Cooperative Oncology Group 0 to 1. Patients should not have been treated with biologics in the previous 12 months. Patients may have positive or negative receptors for estrogen and progesterone.[8] Analysis by patient subgroup was not performed.

Alternatives

The alternatives evaluated were TH versus PTH. The dose of docetaxel was 75 milligrams per square meter of body surface (mg/m^2). Trastuzumab was administered at a loading dose of 8 mg per kilogram (mg/kg), followed by a 6 mg/kg maintenance dose. The loading dose of pertuzumab was 840 mg and then 420 mg. All drugs were administered intravenously in cycles once every 3 weeks. Patients received endocrine therapy if they were estrogen or progesterone receptor positive. These alternatives were chosen because they are recommended by the National Comprehensive Cancer Network guidelines and the breast cancer Colombian clinical guidelines.[6,12]

The time horizon was 30 years. This time horizon is based on the recommendation of the Colombian economic evaluation guideline, which establishes that it should be modeled over the entire life expectancy.[13] According to the CLEOPATRA study, the mean age of the patients was 54 years.[8] In Colombia, life expectancy for women is 80 years.[14] Thus, this time horizon covers the life expectancy of women in our country. According to the same methodological guideline, a discount rate for costs and health outcomes of 5% was used.

This economic evaluation was based on a clinical trial (CLEOPATRA) that lasted approximately 10 years, so additional analysis with this temporal horizon was performed.

Effectiveness, Health Outcomes, and Preferences

To identify systematic reviews or clinical trials that evaluated the effectiveness, a literature review was performed in PubMed, EBSCO, and Science Direct between August 1 and October 13, 2021. The search terms used were as follows: ("pertuzumab"[Supplementary Concept] OR "pertuzumab"[All Fields]) AND ("breast neoplasms"[MeSH Terms] OR ("breast"[All Fields] AND "neoplasms"[All Fields]) OR "breast neoplasms"[All Fields] OR ("breast"[All Fields] AND "cancer"[All Fields]) OR "breast cancer"[All Fields]) AND (clinical trial[Filter] OR meta-analysis[Filter] OR randomized controlled trial[Filter] OR systematic review[Filter]). Only phase 3 or 4 studies were considered. Studies must be published in English or Spanish.

Although no systematic review was found, 5 potential pivotal studies were evaluated for the model. The CLEOPATRA study was chosen for modeling progression-free survival (PFS) and overall survival (OS) because it has the most prolonged follow-up period.

The CLEOPATRA study was a phase III, randomized, double-blind, placebo-controlled, multicenter international clinical trial conducted to investigate the use of PTH as a first-line treatment for participants with HER2-positive MBC. Median OS was 37.6 months (95% confidence interval [CI] 34.3-not estimable) in the placebo group but was not reached (95% CI 42.4-not estimable) in the pertuzumab group. The hazard ratio was 0.66, and 95% CI was 0.52-0.84. Median PFS was 12.4 months (95% CI 10.4-13.5) in the placebo group and 18.7 months (16.6-21.6) in the pertuzumab group (hazard ratio 0.69; 95% CI 0.58-0.81).[8]

The measure of effectiveness calculated was life-years gained. Each alternative's total life-years are years in the progression-free period (PFP) and postprogression period (PPP). The years in PFP are estimated by calculating the area under the curve (AUC) of the PFS curve. The years in PPP are estimated by calculating the AUC between the PFS and OS curves.

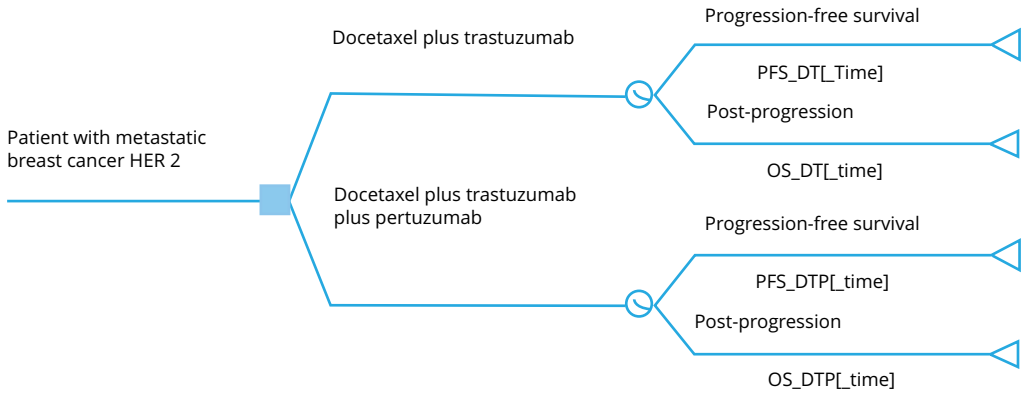
According to the methodological economic guideline for economic evaluation in Colombia, health outcomes were measured in quality-adjusted life-years (QALYs).[13] This outcome is appropriate for this type of pathology where the quality of life is a significant aspect of patient care. Unfortunately, in our country, we do not have reliable data on the utilities of the different health states in this condition. For this reason, utility weights were extracted from the Cost-Effectiveness Registry of the Center for the Evaluation of Value and Risk at Tufts Medical Center.[15] Two clinical trials evaluated the utilities of these patients for PFP and PPP.[16,17]

Choice of Model and Assumptions

A partitioned survival model (PSM) was used. This model is widely accepted and validated for economic evaluations in oncology.[18,19]

This model uses Kaplan-Meier (KM) curves for OS and PFS. The AUC under the PFS curve indicates the average time in PFP. In contrast, the AUC between the OS and PFS curves indicates the average time in the PPP.

Figure 1. Model structure.



HER2 indicates human epidermal growth factor receptor 2.

The KM curves from the CLEOPATRA study were used in our evaluation.[8] These curves were selected because they provide long-term information (ie, approximately 10 years). This duration decreases the risk derived from the extrapolation of these curves in this type of model.

The proportion of patients without progression or alive during the follow-up period was obtained from the PFS and OS curves. These values were obtained using the free-to-use WebPlotDigitizer website (web based tool developed by Ankit Rohatgi version 4.5).[20] The values in the OS curves for the TH and PTH were 250 and 222, respectively. The PFS curves for TH and PTH yielded 194 and 208 values, respectively.

The values were entered into TreeAge Pro 2021 software (TreeAge Software, LLC, Williamstown, Massachusetts). The curves were then reproduced in the software for validation.

The visual validation was performed by comparing the fitness between the curves generated by the software and the original ones, furthermore verifying that the medians of the study curves were the same as the original curves. The curves are presented in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002.

The model structure is presented in Figure 1.

Resources and Costs

According to the perspective used, only direct health costs were considered. The health resources were identified for PFP and PPP. The health resources included the acquisition and administration of drugs, severe adverse events, analytical tests, chest x-ray before chemotherapy, mammography, thoracoabdominal computerized tomography, and magnetic resonance.

The reference case was assumed to calculate medication dosage with a body surface area of 1.6 m^2 and bodyweight of 59 kg (50.6 and 62.5 kg). The quantities of health resources and their costs are presented in Table 1[8,15-18,21-29].

All patients entered the model in a PFP. On admission, all underwent extended mastectomy with nodal resection.

Mastectomy costs included surgeon, anesthesiologist, operating room fees, surgical supplies, and postsurgical hospitalization. The cost of breast reconstruction was not included, given the perspective used in this evaluation. According to the health benefit plan at this evaluation, this is a cosmetic procedure.

The patients underwent 25 sessions of intensity-modulated or 3D conformal external beam radiation therapy 1 month later. They received the chemotherapy schedules described previously. For each chemotherapy cycle, laboratory costs were calculated (ie, cell blood count, creatinine, blood urea nitrogen, alkaline phosphatase, alanine aminotransaminase, and aspartate aminotransaminase). The costs of chemotherapy administration and supervision by clinical oncology were also included.

After completing the chemotherapy sessions, the patients continued being followed up with clinical oncology. Follow-up included annual mammography and tamoxifen for 5 years if the patient has positive estrogen receptors. Visits were made twice a year for the first 5 years. After that, they have performed annually for the entire time horizon.

Patients entered the PPP if they presented the first radiological evidence of progression according to the Response Evaluation Criteria in Solid Tumors. In this case, patients received chemotherapy with trastuzumab emtansine at a 3.6 mg/kg dose with an average of 4.5 cycles per patient according to the TH3RESA and EMILIA trials.[30,31] Furthermore, this scheme is recommended by the national guidelines for breast cancer management.[12]

In this state, chemotherapy and palliative care costs were included. Palliative care costs included monthly consultations for oncology psychologists, palliative physicians, and clinical oncologists. Costs for analgesics (ie, morphine, tramadol, and acetaminophen) and home oxygen were also included. A group of palliative physicians was consulted to quantify the resources in the PPP.

The resources included in the model were valued using the national tariffs and circulars. Procedures (eg, mastectomy and chemotherapy administration) and diagnostic aids were valued using the Social Security Tariff Manual (Manual Tarifario del Seguro Social).[21] Docetaxel, trastuzumab, pertuzumab, and trastuzumab emtansine were valued according to circular 12 of 2021.[22] This circular is the official document issued by the Colombian Ministry of Health where the value per milligram for these drugs is established. The drugs other than chemotherapy were obtained from the Drug Price Information System (Sistema de Información de Precios del Medicamento).[23] In this platform, the Ministry of Health shows the value of nonregulated drugs.

The following assumptions were made: (1) All patients received the complete chemotherapy regimen in both states. (2) All patients without progression received clinical follow-up by oncology in the PFP period. (3) Febrile neutropenia was the only adverse effect incorporated into the model because of its impact on cost. Although other adverse effects were more frequent than febrile neutropenia (eg, diarrhea), they do not significantly affect the costs. (4) Febrile neutropenia was only considered after cycles 1 and 2. The chances of having febrile neutropenia after cycle 3 are less than 1%.[8] (5) Costs of treating febrile neutropenia are the same for the 2 alternatives assessed.

The PSM was evaluated with TreeAge Health Pro® 2021 software (TreeAge Software, LLC, Williamstown, Massachusetts).

Extrapolation of the Curves

The CLEOPATRA study obtained data up to 10 years of follow-up. To assess the probability of remaining in each state in the long-term (ie, 30 years), the survival function that best fitted the KM curves of that study was calculated. The parametric survival models evaluated were exponential, Weibull, Gompertz, log-normal, log-logistic, and gamma.

For this purpose, the ordered pairs were entered into the SurvHE package in R studio (package developed by Gianluca Baio).[32] This package estimated the individual data at the patient level. From these data, the goodness of fit of the models mentioned earlier was evaluated using the Akaike information criteria. The model with the lowest Akaike information criteria was selected. Visual validation was performed by contrasting the survival values obtained from the curve and those calculated with the model (Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002).

The following equations represent the survival functions used in the model:

$$OS\ TH = 1 - \frac{t^{1.64}}{3.51741^{1.64} + t^{1.64}}$$

$$PFS\ TH = 1 - \frac{t^{1.49}}{1.144^{1.49} + t^{1.49}}$$

$$OS\ PTH = 1 - \Phi\left(\frac{Ln(t) - 1.656}{1.1263}\right)$$

$$PFS\ PTH = 1 - \Phi\left(\frac{Ln(t) - 0.617}{0.192}\right)$$

where ϕ represents the cumulative standard normal distribution

Currency, Price Date, and Conversion

The costs were expressed in US dollars at the current exchange rate ($1 US dollar = 3844 Colombian pesos). The exchange rate date was October 2021, according to Banco de la República.[33]

Incremental Analysis

The incremental cost-effectiveness ratio (ICER) was calculated as represented in the following equation:

$$ICER = \frac{Cost_{PTH} - Cost_{TH}}{QALY_{PTH} - QALY_{TH}}$$

The comparator was considered cost-effective if ICER $<$ $5180. According to a recent study, this value was proposed as the willingness-to-pay (WTP) threshold in Colombia.[34]

In addition, a net monetary benefit (NMB) for each alternative was calculated. This metric is represented in the following equation:

$$NMB = (QALY \times \lambda) - Cost$$

where λ represents the WTP in our country.

Under this framework, an alternative is considered cost-effective if NMB $\geq$ 0.

Uncertainty

This type of model cannot evaluate patient heterogeneity and structural uncertainty.

Parameter uncertainty was evaluated with univariate and stochastic analysis. In the univariate analysis, the ICER was calculated for the different values of the variables presented in Table 1[8,15-18,21-29] A sensitivity analysis was performed for the cost of pertuzumab, trastuzumab, and trastuzumab emtansine equal to 0; this means that the health system payer would not absorb the costs of these drugs. Tornado diagrams were plotted for the variables that most modified the ICER.

A second-order Monte Carlo simulation with 10 000 iterations was performed for the stochastic analysis. Different probability distributions were used for the simulation according to the variable to be modeled. The probabilities of clinical events other than progression or death (eg, probability of febrile neutropenia) and the utilities of each health state and events were modeled with beta distribution, the resource quantities were modeled with Poisson distribution, and the physiological variables (eg, body surface area) were modeled with normal distribution. Costs were modeled with uniform distribution. Although this last type of distribution is not recommended, it was used because the costs are obtained from a tariff that does not show dispersion values. The distributions and their parameters used in the simulation are presented in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002.

Results

Base Case Analysis 10 Years

The expected life-years gained, costs, and QALY for each alternative are presented in Table 2. According to the model, the addition of pertuzumab to the TH scheme adds 1.17 life-years and 0.75 QALYs. The expected discounted incremental cost would be $31 894. Thus, the ICER would be $42 525 per additional QALY.

With a WTP of $5180, the NMB for TH and PTH was −$7000 and −$35 009, respectively. Thus, none of the alternatives generate benefit for the country-defined WTP in monetary terms.

Base Case Analysis 30 Years

The incremental analysis with a temporal horizon of 30 years also is presented in Table 2. PTH provides 8.38 years and 4.51 QALY. In contrast, TH provides 5.78 years and 3.28 QALY. Nevertheless, the cost of PTH was significantly greater in comparison with TH ($60 846 vs $24 109), with an incremental cost of $36 737.

Using a WTP of $5180, the NMB provided by TH and PTH is −$7118 and −$37 484, respectively.

Deterministic Sensitivity Analysis

The ICER of the model was mainly sensitive to the cost of pertuzumab. If the cost per milligram of pertuzumab ranges from $0 to $6, the ICER ranges from $857 to $50 266/QALY. The threshold analysis reveals that PTH becomes a cost-effective alternative (ICER $<$ $5180/QALY) if the milligram of pertuzumab costs $0.12.

Similar behavior was presented with the 30-year time horizon. If the cost of pertuzumab fluctuates from $0 to $6, the ICER ranges from $4202 to $35 144. Tornado diagrams are presented in the

Table 1. Parameter of model.

Parameter*	Value	Lower value	Upper value	Reference
Clinical parameters				
Body surface area (m^2)	1.6			24
Body weight (kg)	59	50.6	62.5	25,26
Probability of febrile neutropenia in trastuzumab	0.05			8
Probability of febrile neutropenia with pertuzumab	0.11			
Proportion of patients with positive estrogen receptor	0.38		0.60	27,28
Costs ($)*				
Cost of diagnostics tests				
Cell blood count	3.47	2.89	4.16	21
Total bilirubin	1.69	1.41	2.0	
Aspartate aminotransferase level	1.18	1	1.42	
Alanine aminotransferase level	1.53	1.28	1.84	
Alkaline phosphatase	1.29	1.08	1.55	
Serum creatinine	1.05	0.88	1.26	
International normalized ratio and activated partial thromboplastin time	3.17	2.64	3.8	
Chest x-ray	6.99	5.83	8.39	
Mammography	24.7	20.6	29.6	
Thoracoabdominal Computerized tomography	44.59	37.15	53.5	
Magnetic resonance imaging thoracoabdominal	124	103.3	149	
Cost of medications and procedures				
Docetaxel (cost per mg)	1.9	1.58	2.28	22
Trastuzumab (cost per mg)	2.1	0	2.5	
Pertuzumab (cost per mg)	4.98	0	6	
Trastuzumab emtansine (cost per mg)	14.4	0	17.3	17,18
Administration of a cycle of chemotherapy	83.8	70	101	21
Tamoxifen (cost per tablet)	0.19	0.09	0.64	23
Oxygen (cost per one month)	18.21	15.17	21.85	
Acetaminophen (cost per tablet)	0.0036	0.0030	0.017	23
Morphine (cost per vial)	0.076	0.06	0.09	
Acetaminophen/codeine (cost per tablet)	0.085	0.050	0.42	
Tramadol (cost per tablet)	0.40	0.39	0.47	
Bisacodyl (cost per tablet)	0.022	0.011	0.056	
Metoclopramide (cost per tablet)	0.02	0.01	0.02	
Oncologist (cost per visit)	4.5	3.75	5.4	21
Psycho-oncology (cost per visit)	2.18	1.81	2.61	
Palliativist (cost per visit)	4.23	3.53	5.08	
Social work (cost per visit)	1.89	1.58	2.27	
Radical mastectomy (cost per package)	755	629	906	
Febrile neutropenia (cost per event)	925	142	1.708	29
Quantities (through the entire time horizon)				
Cell blood count	8	1	41	15
Total bilirubin	8	1	41	

continued on next page

Table 1. Continued

Parameter*	Value	Lower value	Upper value	Reference
Aspartate aminotransferase level	8	1	41	
Alanine aminotransferase level	8	1	41	
Alkaline phosphatase	8	1	41	
Serum creatinine	8	1	41	
International normalized ratio and activated partial thromboplastin time	8	1	41	
Dose of docetaxel	75 mg/m^2	50 mg/m^2	100 mg/m^2	8,16
Dose of trastuzumab (load)	8 mg/kg	-	-	
Dose of trastuzumab (maintenance)	6 mg/kg	-	-	
Dose of pertuzumab (load)	840 mg	-	-	
Dose of pertuzumab (maintenance)	420 mg	-	-	
Dose of trastuzumab emtansine (mg/kg)	3.6	-	-	
Cycles docetaxel	8	1	41	15
Cycles trastuzumab	15	1	50	16
Cycles trastuzumab emtansine	4.5	1	16	17
Cycles pertuzumab	18	1	56	16
Mammography	10	1	120	17,18
Utilities				
Postmastectomy	0.87	-	-	
PFS under treatment with docetaxel plus trastuzumab	0.938	-	–	15
PFS under treatment with docetaxel plus trastuzumab plus pertuzumab	0.875	-	-	
PFS without treatment	0.99	-	-	
Postprogression under treatment with trastuzumab emtansine	0.603	-	-	

PFS indicates progression-free survival.
*Costs are expressed as US dollars.

Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002.

Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis results for both temporal horizons are presented in Table 3. When a 10-year temporal horizon was used, the mean total cost and standard deviation of TH and PTH were \$16 404 ± 3651 and \$37 273 ± 11 681, respectively. The mean and standard deviation of the QALY for these alternatives were 2.92 ± 0.68 and 3.68 ± 0.76, respectively.

For the 30-year case, the mean and standard deviation of the cost of TH and PTH are 17 591 ± 3976 and 40 151 ± 12 034, respectively. QALYs are 3.27 ± 0.88 and 4.5 ± 1.089 for these alternatives.

The incremental cost-effectiveness plane for 30 years is presented in Figure 2. The highest proportion of iterations is above the WTP line in quadrant I (92.74%). The probability that the addition of pertuzumab is cost-effective (ie, the number of iterations below the WTP line in quadrant I) was 0.0724.

Most iterations (94.94%) overpassed the WTP line for the 10-year case, whereas only 5.06% were cost-effective. The Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002 can find the incremental cost-effectiveness scatterplot for 10 years.

The acceptability curve for 30 years (Fig. 3) shows how the TH scheme is more likely to be cost-effective than PTH up to a WTP of \$18 500 per QALY.

The probability of NMB being equal or greater to 0 is different for the schemes using a WTP of \$5180. The TH scheme has a probability of a positive NMB of 0.4791. In contrast, the addition of pertuzumab to this scheme decreases that probability to 0.1117.

The relationship between NMB and WTP (Appendix in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2022.08.002) shows that if WTP is \$5180, none of the alternatives provides NMB greater than 0. If the WTP is \$5460, the NMB is positive for TH but not for the addition of pertuzumab. The latter scheme only provides positive NMB from a WTP of \$8920. If the WTP reaches \$18 400, the PTH scheme provides more significant benefits than its counterpart.

Discussion

Historically, the treatment of MBC has represented high costs for health systems in general and the Colombian one in particular. The advent of monoclonal antibodies represented a change in the treatment paradigm of this condition and improved survival for these patients. Nevertheless, there is concern that the increasing use of chemotherapy schemes that combine several antibodies

Table 2. Incremental analysis.

Variable	Clinical trial (10 years)		Extrapolated (30 years)	
	TH	PTH	TH	PTH
Mean years per state				
PFS life-years	2.21	3.09	2.34	3.59
Postprogression life-years	2.27	2.56	3.44	4.79
Total	4.48	5.65	5.78	8.38
Life-years gained	1.17		2.6	
Discounted cost				
Progression-free survival	14 865	48 597	14 597	49 042
Postprogression	7313	5475	9512	11 804
Total	22 178	54 072	24 109	60 846
Discounted incremental cost	31 894		36 737	
Discounted QALY				
PFS	1.79	2.44	1.80	2.67
Postprogression	1.14	1.24	1.48	1.84
Total	2.93	3.68	3.28	4.51
Discounted incremental QALY	0.75		1.23	
NMB (WTP: $5180)	−7000	−35 009	−7118	−37 484
Discounted ICER	42 525		29 867	

ICER indicates incremental cost-effectiveness ratio; NMB, net monetary benefit; PFS, progression-free survival; PTH, docetaxel plus trastuzumab plus pertuzumab; TH, docetaxel plus trastuzumab; QALY, quality-adjusted life-year; WTP, willingness to pay.

could represent a drastic increase in costs. Accordingly, our model shows that a dual immunotherapy scheme provides more gained life-years and QALY but dramatically increases healthcare costs.

Our results are similar to other studies conducted in other countries and model types. Two PSM-based analyses evaluated the same alternatives in Singapore and Japan. They concluded that adding pertuzumab to TH is not cost-effective using their corresponding WTP.[35,36] Durkee et al[37] evaluated the same schemes through a Markov model in the United States. Their model predicted a 0% chance of cost-effectiveness at a WTP $100 000 per QALY gained. Finally, a recent study in Canada using real-world data comparing the addition of pertuzumab plus trastuzumab with chemotherapy schedules in this population revealed that the probability of being cost-effective is less than 1%.[38] These results are in line with our study.

Different strategies can remedy the apparent low efficiency of pertuzumab addition. Ventola[39] proposes that this coordination and cooperation between pharmaceutical corporations, economists, and the medical community should include the use of biomarkers with improved precision to select patients with a higher probability of response and the design and implementation of value-based reimbursement mechanisms for these drugs and the incorporation of immunoprevention strategies. Our model shows that reducing the cost per milligram of pertuzumab could become cost-effective. Univariate sensitivity analysis showed that a 98% discount in the cost per milligram of pertuzumab (ie, reducing its cost from $6 to $0.12) could reduce the ICER to less than $5180 per additional QALY. An alternative in our country is to evaluate the added value provided by these schemes using methodologies that include criteria (eg, access and equity, impact on caregivers, cultural acceptability, and technical and training requirements) beyond efficiency.

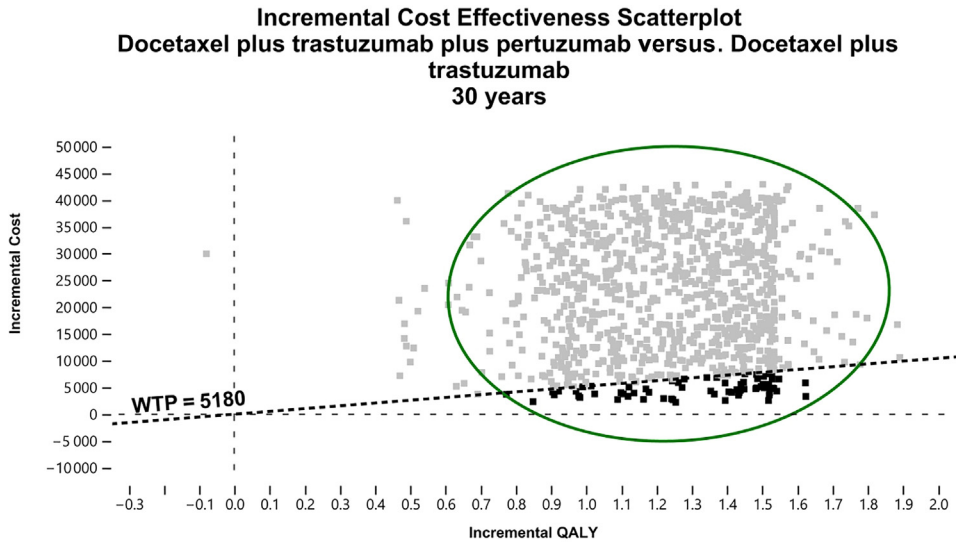
The need to use higher or differential WTP for these patients has also been proposed. Among the reasons put forward are as follows: These treatments are indicated in a small population with a short life expectancy (24 months or less)

Table 3. Probabilistic sensitivity analysis.

Parameter	Docetaxel plus trastuzumab			Docetaxel plus trastuzumab plus pertuzumab		
10 years						
	Mean	95% lower bound	95% upper bound	Mean	95% lower bound	95% upper bound
Costs ($)	16 404	16 332	16 475	37 273	37 044	3702
QALY	2.92	2.91	2.94	3.68	3.67	3.70
NMB ($)	−1251	−1351	−1151	−18 184	−18 425	−17 942
30 years						
	Mean	95% lower bound	95% upper bound	Mean	95% lower bound	95% upper bound
Costs ($)	17 591	17 513	1769	40 151	39 954	40 426
QALY	3.27	3.26	3.30	4.5	4.48	4.52
NMB ($)	−608	−727	−488	−16 836	−17 098	−16 574

Note. Costs and NMB are expressed as US dollars.
NMB indicates net monetary benefit; QALY, quality-adjusted life-year.

Figure 2. Incremental cost-effectiveness scatterplot.

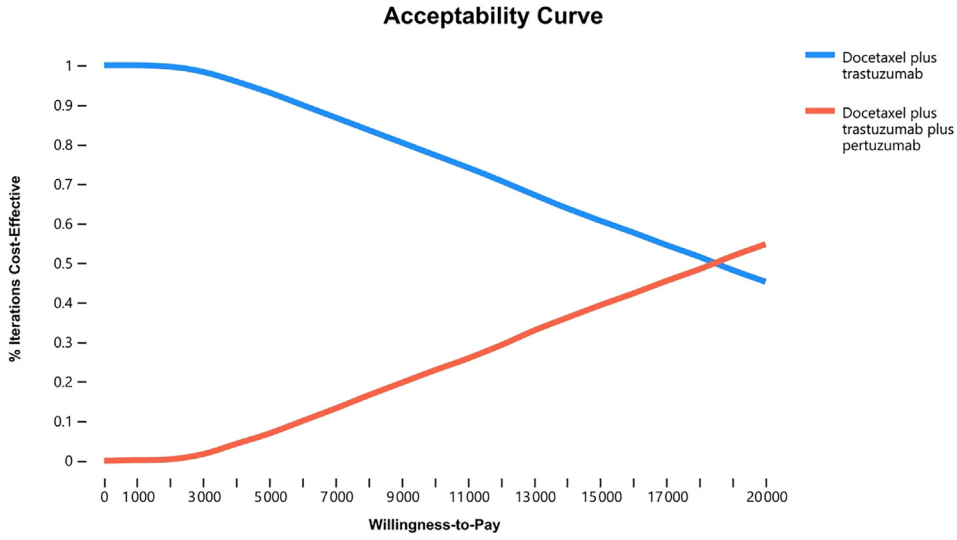


where QALY in this population might be considered more valuable than other diseases. Society might consider paying more for end-of-life treatments, especially for reducing the suffering and physical and psychological pain.[40-42] Other studies have shown that cancer stage, type of cancer, time since diagnosis, educational level, individual or national income, functional status, even political system, and cancer mortality rate might influence individuals to adopt different WTP.[43-45] In this regard, our model showed that increasing the WTP to $8920 could produce positive NMB. Nevertheless, it is crucial to evaluate other clinical and nonclinical variables' effects on efficacy and costs. This effect and benefit of these factors could be evaluated in a study with real-world data or multicriteria decision analysis.[46-48]

Our study has several limitations. First, the PSMs did not consider patient heterogeneity. Several studies have established that multiple factors influence progression and survival in these patients.[49-51] Second, the model assumes that there is full access to immunotherapy. Although there are no data on access to these drugs in our setting, some studies have reported access difficulties even in high-income countries.[52,53] Third, the model was populated with data from a controlled clinical trial. Although the CLEOPATRA study is a well-designed, long-term study, it has the inherent limitations of external validity, especially in our country.

Similarly, the utilities were obtained from a repository that could not represent our country's actual valuation of health states. Another limitation is the absence of data about the uncertainty in the OS and PFS curves used in the model. Last but not least, the

Figure 3. Acceptability curve.



behavior of progression and survival based on extrapolated curves represents an often unrealistic assumption.[54,55]

Conclusion

The addition of pertuzumab to the TH regimen in patients with HER2-positive MBC has a low probability of being cost-effective from the payer's perspective in the Colombian health system.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2022.08.002.

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