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Cost-effectiveness Analysis of Pertuzumab With Trastuzumab in Patients With Metastatic Breast Cancer

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IMPORTANCE The initial assessment of pertuzumab use for treatment of metastatic breast cancer by health technology assessment agencies suggested that pertuzumab was not cost-effective. In Ontario, Canada, pertuzumab became funded in November 2013 based on the substantial clinical benefit. To date, there is a paucity of analysis of pertuzumab using real-world data for cost-effectiveness.

OBJECTIVE To assess the cost-effectiveness of pertuzumab, trastuzumab, and chemotherapy vs trastuzumab and chemotherapy for patients with metastatic breast cancer.

DESIGN, SETTING, AND PARTICIPANTS A population-based retrospective economic evaluation was conducted in Ontario, Canada. Patients who received first-line treatments for metastatic breast cancer from January 1, 2008, to March 31, 2018, were identified. Patients were followed up from the start of treatment up to 5 years, with maximum follow-up to March 31, 2019. Patients were identified from the Ontario Cancer Registry and linked to the New Drug Funding Program database to identify receipt of first-line treatment (N = 1158).

INTERVENTIONS Treatment with pertuzumab, trastuzumab, and chemotherapy after public funding (November 25, 2013) compared with treatment with trastuzumab and chemotherapy before funding.

MAIN OUTCOMES AND MEASURES Cost-effectiveness, from a public payer perspective, was estimated from administrative data with a 5-year time horizon, adjusted for censoring, and discounted (1.5%). Incremental cost-effectiveness ratios for life-years gained and quality-adjusted life year (QALY) with bootstrapped 95% CIs were calculated. Sensitivity analysis with price reduction of pertuzumab alone or in combination with trastuzumab was conducted.

RESULTS A total of 579 pairs of matched patients receiving pertuzumab and controls were included. The mean (SD) age of the matched study cohort was 58 (12.97) years; 1151 were women (99.4%). Pertuzumab resulted in 0.61 life-years gained and 0.44 QALYs gained at an incremental cost of $192 139 (all costs measured in Canadian dollar values, CAD) with an incremental cost-effectiveness ratio of $316 203 per life-year gained and $436 679 per QALY. The main factors associated with cost included the cost of pertuzumab (60%), outpatient cancer treatment delivery (24%), and trastuzumab (15%). With 100% price reduction of pertuzumab, the incremental cost-effectiveness ratio was $174 027 per QALY. When the price of pertuzumab and trastuzumab were both reduced by more than 71%, the incremental cost-effectiveness ratio decreased below $100 000 per QALY.

CONCLUSIONS AND RELEVANCE The findings of this population-based study suggest that pertuzumab may increase survival for patients with metastatic breast cancer but would not be considered cost-effective, even after 100% price reduction, under conventional thresholds.

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Supplemental content

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The economic burden of cancer care is increasing around the world.[1,2] In Canada, the national net expenditure in Canadian dollars (CAD) for cancer care more than doubled from $2.9 billion in 2005 to $7.5 billion in 2012.[3] The estimated lifetime total cost for patients with breast cancer, which accounts for 25% of new cancer diagnoses in women in Canada,[4] is one of the highest among different tumor types.[5] One study reported that, during a period of 10 years, the 1-year treatment cost incurred after breast cancer diagnosis increased by 2-fold.[6] One factor in this increasing cancer care cost is use of chemotherapy, which has grown more than 3-fold from 2005 to 2012.[3]

With the changing treatment landscape in breast cancer, patients diagnosed with late-stage cancer often incur higher cancer-related drug costs.[7] For *ERBB2* (formerly *HER2*)-positive breast cancer, the cancer-related drug costs for *ERBB2*-positive cancer can be 6- to 10-fold higher than those for *ERBB2*-negative breast cancers.[7,8] For patients with metastatic breast cancer that is *ERBB2*-positive, the standard first-line treatment in Canada was trastuzumab, an *ERBB2*-targeted therapy, plus taxane in the earlier years, and since 2013, the addition of pertuzumab to trastuzumab with taxane became routinely available.[9]

In 2013, the Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a health technology assessment on pertuzumab.[9] At the initial health technology assessment review, the CADTH indicated the landmark CLEOPATRA trial demonstrated that the addition of pertuzumab to trastuzumab and docetaxel in patients with *ERBB2*-positive metastatic breast cancer substantially improved progression-free survival (hazard ratio [HR], 0.62; $P < .001$) and overall survival (HR, 0.66; $P < .001$).[9,10] According to the manufacturer's economic model, pertuzumab was projected to provide an incremental clinical benefit of 0.64 life-years (LY) gained (LYG) or 0.51 quality-adjusted life-years (QALY) gained, along with an incremental cost of $120 287 (dollar amounts presented herein as CAD unless otherwise indicated).[9,11] Based on these estimates, the submitted incremental cost-effectiveness ratio (ICER) was $187 376/LYG and $238 014/QALY.[9] The economic guidance panel at CADTH conducted a reanalysis and estimated the ICER was between $262 263/QALY and $303 726/QALY, which was not considered cost-effective.[9]

Similar to the CADTH evaluation, the UK National Institute for Health and Care Excellence (NICE) also suggested that the base-case ICERs generated by the manufacturer's model had a 0% probability of being cost-effective at a willingness-to-pay threshold of £30 000 per QALY (with 1 British sterling pound equal to approximately USD $1.36).[12,13] The NICE Decision Support Unit examined pertuzumab and found that the factor associated with this relatively high ICER appeared to be use of pertuzumab in combination with trastuzumab and any additional progression-free survival was accompanied by the costs of both pertuzumab and trastuzumab; thus, pertuzumab would not be considered cost-effective even at a price of $0.[12-14] After the initial NICE review in 2013, pertuzumab became available through the Cancer Drug Fund and, following a subsequent review in 2018, pertuzumab was approved for routine use.[15] Despite deeming pertuzumab as not cost-effective, the CADTH issued a conditional recommendation for the funding of pertuzumab based on the improved clinical benefit in 2013, conditional on pricing arrangements to improve the cost-effectiveness.[9] Within the same year, pertuzumab became publicly funded in Ontario for patients with *ERBB2*-positive metastatic breast cancer.[9]

Economic models developed by researchers across the globe have ranged between USD $183 901/QALY to $593 741/QALY.[16-20] Along with the wide range of variations, the estimated ICERs were all above conventional willingness-to-pay thresholds, suggesting potentially inefficient investment in pertuzumab. Moreover, the model-based cost-effectiveness studies derived the estimate of clinical benefit of pertuzumab from the CLEOPATRA trial. Similar to other literature that demonstrated the gap between the efficacy in the clinical trial and the outcomes in the real-world setting,[21-23] pertuzumab has also been reported to have lower benefit in the real world compared with the efficacy observed in the trial.[24-26]

Given these uncertainties regarding the clinical benefit and the wide variation in the economic estimates, there is an impetus for evaluating the cost-effectiveness of pertuzumab using real-world population-based data. Moreover, with the growing interest toward life-cycle health technology assessment by health technology agencies, such as CADTH and NICE, cost-effectiveness studies can also inform the reassessment of funded drugs.[27] To address these gaps, we conducted a population-based study to evaluate the cost-effectiveness of pertuzumab, trastuzumab, and chemotherapy, compared with trastuzumab plus chemotherapy in patients with metastatic breast cancer from the public payer perspective. Using population-based administrative data sets, we estimated the incremental cost per LYG and per QALY.

Key Points

Question What is the cost-effectiveness of pertuzumab, trastuzumab, and chemotherapy for patients with metastatic breast cancer?

Findings In this economic evaluation, pertuzumab treatment was associated with survival benefit but was not cost-effective based on conventional willingness-to-pay threshold ($100 000/quality-adjusted life-year), even after reducing the price of pertuzumab to $0. This finding supports previous model-based results from the UK National Institute for Health and Care Excellence that suggested pertuzumab would not be cost-effective even at a price of $0, using the conventional threshold.

Meaning Results of this study suggest that, based on the conventional willingness-to-pay threshold, pertuzumab, trastuzumab, and chemotherapy would not be considered cost-effective, even if pertuzumab was free.

Methods

Study Design and Setting

A population-based retrospective economic evaluation was conducted using data from Ontario, Canada, which has a popu-

lation of approximately 14 million people.[28] Treatments for breast cancer are administered in cancer clinics and are reimbursed by the provincial government. We identified adults diagnosed with incident breast cancer from the Ontario Cancer Registry using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* site codes C50.0 to C50.9. The cohort was linked to the New Drug Funding Program database to ascertain treatment records for patients with metastatic breast cancer between January 1, 2008, and March 31, 2018 (N = 1158). The treatments of interest included first-line use of trastuzumab and chemotherapy with or without pertuzumab administered under the respective palliative-intent funding policies.

Pertuzumab became publicly funded in Ontario on November 25, 2013. The pertuzumab group consisted of patients who received first-line treatment for metastasis comprising pertuzumab, trastuzumab, and chemotherapy after pertuzumab funding, and the control group included patients who received treatment for metastasis with trastuzumab and chemotherapy before the funding was available. We excluded patients who had a date of first dose of pertuzumab before the funding date, received treatment before the cancer diagnosis in the cancer registry, or were not an Ontario resident at the time of diagnosis. The index date of treatment was the first record of pertuzumab administration for metastatic intent for the pertuzumab case group, and the first record of trastuzumab administration for metastatic intent for the control group. The study cohort was followed up until March 31, 2019. The cohort creation process and study design are shown in eFigure 1 in the Supplement.

Data Sources and Reporting

Data were retrieved from administrative databases and were linked using unique encoded identifiers and analyzed at ICES, an independent, nonprofit research institute funded by an annual grant from the Ontario Ministry of Health and the Ministry of Long-Term Care. The databases used to create the study cohort include Registered Persons Database, Ontario Cancer Registry, Ontario Health Insurance Plan database, Canadian Institute of Health Information Discharge Abstract Database, Canadian Institute of Health Information National Ambulatory Care Reporting System, and Activity Level Reporting Systems. Baseline demographic and clinical characteristics were ascertained from linked administrative data sets (eMethods in the Supplement). As a prescribed entity under Ontario's privacy legislation, ICES is authorized to collect and use health care data for the purposes of health system analysis, evaluation, and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. This study was designed, analyzed, and reported in accordance with the RECORD-PE and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guidelines.[29,30] In accordance with the policies of ICES, small cell counts were suppressed and are reported as less than 6 to limit the risk of patient reidentification. This study was approved by the Sunnybrook Research Ethics Board, which waived informed consent for deidentified data.

Treatment Effectiveness

Treatment effectiveness was measured as life-years (LY) and QALY. Life-years were defined as 5-year survival calculated from the index date until death date or the end of the 5-year follow up. Patients who were alive at the end of the study period on March 31, 2019, or who had lost their Ontario Health Insurance Plan eligibility were censored. Quality-adjusted life-years were obtained by adjusting 5-year survival with different utilities for patients who were receiving *ERBB2*-directed treatment vs those who discontinued treatment. Utility weights were obtained from existing literature and were also used by the initial CADTH drug review.[31] The time that patients were receiving initial *ERBB2*-directed treatment was weighted with the utility value of 0.79, and the time that patients had discontinued treatment was weighted with the utility value of 0.5.[31,32]

Cost Analysis

We adopted the public payer perspective when estimating the 5-year total costs for each patient. The total cost from the index date to death or the end of the 5-year follow-up period was estimated using a validated costing algorithm available at ICES.[33] Costs were censored for patients who were alive at the maximum follow-up or had lost their Ontario Health Insurance Plan eligibility. The total costs for each patient were the sum of health care services from the following categories: outpatient visits, ambulatory hospital care visits, acute inpatient hospitalizations, chronic and rehabilitation care, and drug costs (eMethods in the Supplement). All costs were adjusted to the 2018 CAD amount using the Statistics Canada Consumer Price Index.[34]

Statistical Analysis

The study cohort was characterized using descriptive statistics. The pertuzumab case and control groups were matched using propensity score methods including variables listed in the eMethods in the Supplement. The pertuzumab and control groups were matched 1:1, with a caliper width equal to 0.2.[35] Standardized differences between the adjusted covariates were calculated, and differences less than or equal to 0.1 are generally considered to represent acceptable balance.[36] Findings were considered statistically significant with a 2-sided test at $P < .05$. Statistical analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Cost-effectiveness Analysis

Inverse probability censoring weighting was applied to the costs and effectiveness (LY or QALY), partitioned into 30-day intervals to adjust for administrative censoring.[37] All costs and effectiveness (LY and QALY) were discounted using a rate of 1.5% annually as a base case as per the CADTH guidelines.[38]

Cost-effectiveness was estimated by computing the ICER and net monetary benefit methods.[39-41] The ICER was determined by the difference in mean total costs between the pertuzumab case and control group and divided by the difference in mean total effectiveness (LYG or QALY gained) between the pertuzumab case and control groups. The 95% CIs for the ICERs were calculated by generating 1000 bootstrap resamples. Cost-effectiveness acceptability curves were plotted for

the distribution of bootstrapped ICERS that are below each willingness-to-pay threshold. The net benefit (NB), for each person (i) was calculated for the willingness-to-pay threshold (λ) between $100 000 and $700 000 as NB = (effect$_i$ × λ) − cost$_i$.[39,42] Two scenarios were conducted as part of the sensitivity analysis. The first scenario varied the base discount rate (1.5%) to no discounting (0%). The second scenario examined the outcome of reducing the price of pertuzumab (from 0% to 100%) alone and in combination with trastuzumab on the ICER.

Results

Study Population and Baseline Characteristics

A total of 1823 patients with incident breast cancer diagnosis received trastuzumab and chemotherapy with or without pertuzumab for treatment of metastasis between January 1, 2008, and March 31, 2018 (eFigure 1 in the Supplement); of these, 912 were in the pertuzumab case group and 911 were in the control group. Propensity score matching identified 579 pairs of the pertuzumab and control groups. Overall, the mean (SD) age of the matched study cohort was 58 (12.97) years, 1151 were women (99.4%), 7 were men (0.6%), and 1012 (87.4%) lived in urban regions (**Table 1**). All variables were balanced between the propensity score-matched pertuzumab case and control groups.

Cost Distribution

Figure 1 presents the breakdown of the 5-year total costs by the major resource categories. The main categories included pertuzumab drug cost (pertuzumab: 28% of total costs), outpatient cancer treatment delivery (pertuzumab: 27%; control: 29%), trastuzumab drug costs (pertuzumab: 23%; control: 30%), physician claims (pertuzumab: 6%; control 10%), other drugs (pertuzumab: 6%; control: 9%), acute inpatient hospital care (pertuzumab: 4%; control: 10%), chronic rehabilitation care costs (pertuzumab: 3%; control: 7%), and ambulatory hospital care (pertuzumab: 2%; control: 5%). The main factors associated with cost for both groups included trastuzumab cost, pertuzumab costs, and outpatient cancer delivery cost. For the pertuzumab group, the cost of pertuzumab was the main factor. The incremental cost difference between the 2 groups was $192 139. The main contributors of the incremental cost differences included the costs of pertuzumab (60%), outpatient cancer treatment delivery (24%), and trastuzumab (15%).

Incremental Cost-effectiveness

Table 2 summarizes the mean inverse probability censoring weighting-adjusted 5-year LY, QALY, total costs, and ICERs. Mean total health care cost was higher for the pertuzumab group compared with the control group. Mean LY was estimated as 3.08 for the pertuzumab group and 2.48 for the control group, with an incremental LY gained of 0.61. Mean QALYs were 2.11 for the pertuzumab group and 1.67 for the control group, with an incremental QALY gained of 0.44. The ICER for the pertuzumab group vs the control group was $316 203 per LYG and $436 679 per QALY. The scenario for no discounting was similar to the 1.5% discounting case with slightly lower ICERs. All bootstrapped samples comparing the pertuzumab case and control groups were in the northeast quadrant of the cost-effectiveness plane (**Figure 2**A). The cost-effectiveness acceptability curve noted that the probability of pertuzumab being cost-effective at a willingness-to-pay threshold of $50 000 or $100 000 was 0 (Figure 2B). eFigure 2 in the Supplement presents the incremental net benefit. At a willingness-to-pay threshold of $50 000 and $100 000, the incremental net benefit for both LYG and QALY gained were negative (ie, pertuzumab was not cost-effective at these thresholds).

Price Reduction

At 100% price reduction of pertuzumab, that is, when the price of pertuzumab is $0, the ICER was calculated to be $174 027/QALY. **Figure 3** illustrates the outcome of reducing the price of pertuzumab alone or in combination with trastuzumab associated with the calculated ICER. The ICER was reduced to less than $100 000/QALY when the combination of pertuzumab and trastuzumab was reduced by 71% and to less than $50 000/QALY when the combination was reduced by 81%.

Discussion

In this population-based, propensity score-matched economic evaluation, we examined the cost-effectiveness of pertuzumab for treatment of patients with metastatic breast cancer. The results largely support that pertuzumab was associated with improved clinical benefit but was not cost-effective at the common willingness-to-pay thresholds from a public payer's perspective. We found that the average 5-year total cost incurred by the pertuzumab group was 89% higher than that of the control group. The main cost contributors in both groups were the costs associated with outpatient cancer treatment delivery (eg, cancer clinics) and *ERBB2*-directed therapy (pertuzumab and trastuzumab). The ICERs ($316 203/LYG and $436 679/QALY) were higher than the initial economic model ($187 376/LYG and $238 014/QALY). This difference may be due to higher incremental drug cost ($192 139) compared with the initial model ($117 932). Moreover, although we limited the time horizon in our study to 5 years, the initial economic review projected the ICERs over 10 years.[11] It is expected that the ICERs might commonly decrease over a longer time horizon as the costs for the drugs may be larger during the earlier years while the survival benefit may continue to accrue.

The ICERs from this study lie within the range calculated from model-based models (USD $183 901/QALY to USD $593 741/QALY).[16-20] Our finding also largely supports the evaluation by the NICE Decision Support Unit during the initial appraisal of pertuzumab that there is 0% probability of pertuzumab being cost-effective at £30 000 and that it would not be cost-effective at any price.[12,13,43] In the real world, even at the price of $0, the ICER of pertuzumab is greater than the conventional willingness-to-pay threshold of $100 000/QALY. NICE suggested that, because pertuzumab was given in combination with trastuzumab and chemotherapy, any additional

Table 1. Baseline Characteristics of Study Population

Variable[a]	Crude cohort			Propensity score-matched cohort		
	Pertuzumab (n = 912)	Control (n = 911)	*P* value	Pertuzumab (n = 579)	Control (n = 579)	SDif
Age at index date, mean (SD), y	57.7 (12.7)	58.1 (12.8)	.50	58.3 (12.5)	58.2 (13.0)	0.01
LHIN, No. (%)						
Region 1	38 (4.2)	52 (5.7)	.08	30 (5.2)	28 (4.8)	0.02
Region 2	92 (10.1)	83 (9.1)		56 (9.7)	54 (9.3)	0.01
Region 3	41 (4.5)	41 (4.5)		27 (4.7)	29 (5.0)	0.02
Region 4	81 (8.9)	73 (8.0)		52 (9.0)	56 (9.7)	0.02
Region 5	56 (6.1)	45 (4.9)		28 (4.8)	27 (4.7)	0.01
Region 6	93 (10.2)	95 (10.4)		58 (10.0)	58 (10.0)	0
Region 7	76 (8.3)	90 (9.9)		53 (9.2)	48 (8.3)	0.03
Region 8	95 (10.4)	121 (13.3)		73 (12.6)	77 (13.3)	0.02
Region 9	88 (9.6)	92 (10.1)		56 (9.7)	53 (9.2)	0.02
Region 10	42 (4.6)	42 (4.6)		29 (5.0)	29 (5.0)	0
Region 11	136 (14.9)	103 (11.3)		70 (12.1)	75 (13.0)	0.03
Region 12	35 (3.8)	20 (2.2)		<20[b]	16 (2.8)	0.01
Region 13	33 (3.6)	41 (4.5)		25 (4.3)	22 (3.8)	0.03
Region 14	6 (0.7)	13 (1.4)		<5[b]	7 (1.2)	0.03
Neighborhood income quintile, No. (%)						
1 (lowest)	155 (17.0)	154 (16.9)	.64	99 (17.1)	99 (17.1)	0
2	202 (22.1)	191 (21.0)		135 (23.3)	133 (23.0)	0.01
3	189 (20.7)	195 (21.4)		122 (21.1)	124 (21.4)	0.01
4	174 (19.1)	195 (21.4)		113 (19.5)	114 (19.7)	0
5 (highest)	192 (21.1)	175 (19.2)		110 (19.0)	109 (18.8)	0
Urban residence, No. (%)	801 (87.8)	797 (87.5)	.82	505 (87.2)	507 (87.6)	0.01
Charlson comorbidity index score						
0	505 (55.4)	522 (57.3)	.07	333 (57.5)	327 (56.5)	0.02
1	61 (6.7)	72 (7.9)		41 (7.1)	45 (7.8)	0.03
≥2	16 (1.8)	28 (3.1)		13 (2.2)	17 (2.9)	0.04
No hospitalization	330 (36.2)	289 (31.7)		192 (33.2)	190 (32.8)	0.01
Time between diagnosis to index date, mean (SD), y	2.75 (4.1)	3.10 (3.6)	.06	2.71 (4.14)	2.72 (3.75)	0
Cancer stage at diagnosis, No. (%)						
I	50 (5.5)	36 (4.0)	<.001	30 (5.2)	33 (5.7)	0.02
II	177 (19.4)	99 (10.9)		85 (14.7)	84 (14.5)	0
III	222 (24.3)	156 (17.1)		127 (21.9)	120 (20.7)	0.03
IV	325 (35.6)	284 (31.2)		224 (38.7)	222 (38.3)	0.01
Missing/unknown	138 (15.1)	336 (36.9)		113 (19.5)	120 (20.7)	0.03
Prior therapy, No. (%)						
Hormonal	136 (14.9)	166 (18.2)	.06	85 (14.7)	93 (16.1)	0.04
Bisphosphonate	88 (9.6)	155 (17.0)	<.001	69 (11.9)	67 (11.6)	0.01
Adjuvant trastuzumab	313 (34.3)	236 (25.9)	<.001	160 (27.6)	160 (27.6)	0
Any adjuvant	209 (22.9)	238 (26.1)	.11	128 (22.1)	118 (20.4)	0.04
Neoadjuvant	122 (13.4)	82 (9.0)	.003	53 (9.2)	60 (10.4)	0.04
Adjuvant radiotherapy	326 (35.7)	326 (35.8)	.99	187 (32.3)	185 (32.0)	0.01
Prior cancer						
Breast	66 (7.2)	17 (1.9)	<.001	16 (2.8)	17 (2.9)	0.01
Other	43 (4.7)	31 (3.4)	.16	23 (4.0)	25 (4.3)	0.02
Estrogen receptor, No. (%)[c]						
Negative (20)	189 (39.0)	116 (48.9)	<.001	117 (50.6)	111 (48.3)	0.03
Positive (10)	295 (61.0)	121 (51.1)		114 (49.4)	119 (51.7)	0.02
Progesterone receptor, No. (%)[c]						
Negative (20)	252 (52.3)	152 (64.4)	<.001	149 (64.5)	146 (63.7)	0.01
Positive (10)	230 (47.7)	84 (35.6)		82 (35.5)	83 (36.3)	0

Abbreviations: LHIN, Local Health Integration Network; SDif, standardized difference.

[a] In accordance with the patient privacy policies of ICES, the numbers and percentage values for male and female populations in the data are not reported to avoid the possibility of back calculation of populations less than 5.

[b] Small cells are suppressed in compliance with ICES policy to limit the risk of patient identification.

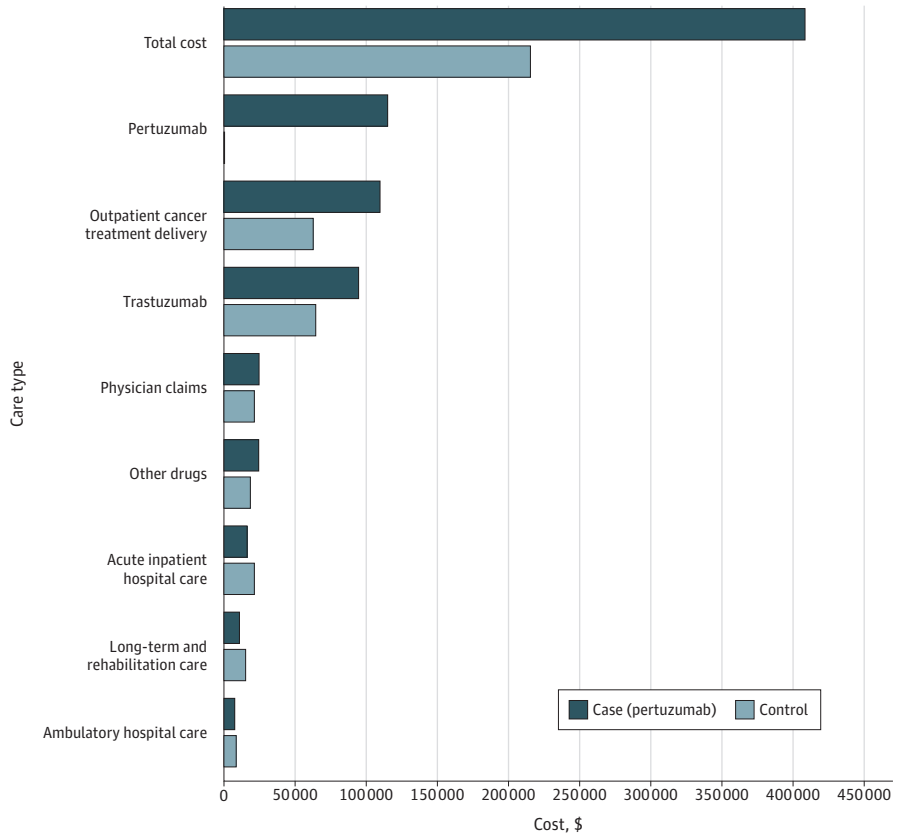
[c] Percentages are based on known cases.

survival benefit would be accompanied by cost of both pertuzumab and companion drugs.[13] We observed that the cost of trastuzumab was 44% higher in the pertuzumab group compared with the control group, thus supporting previous projections that the longer survival in the pertuzumab group led to a substantial increase in treatment and management costs in addition to the cost of pertuzumab.[13,17]

Strengths and Limitations

This study has limitations. First, inherent to the nature of observational studies are possible selection biases due to nonrandom treatment assignment. Although we used propensity score methods to minimize potential biases between groups, given that we used historical controls, there may be treatment and/or practice pattern changes over time resulting in potential bias. Second, we were only able to capture 5-year total costs in both groups owing to the public funding date. This short period limits the ability to compare with model-based estimates that estimate these outcomes based on a lifetime horizon. For example, the initial CADTH model was projected using a 10-year time horizon and the NICE model was projected using a 25-year time horizon.[11,12] Third, the approval of a novel subcutaneous formulation of pertuzumab and trastuzumab by the US Food and Drug Administration in

Figure 1. Disaggregated Cost by Cases and Controls After Accounting for Censoring



All costs reported in Canadian dollars and adjusted for censoring and 1.5% discounted.

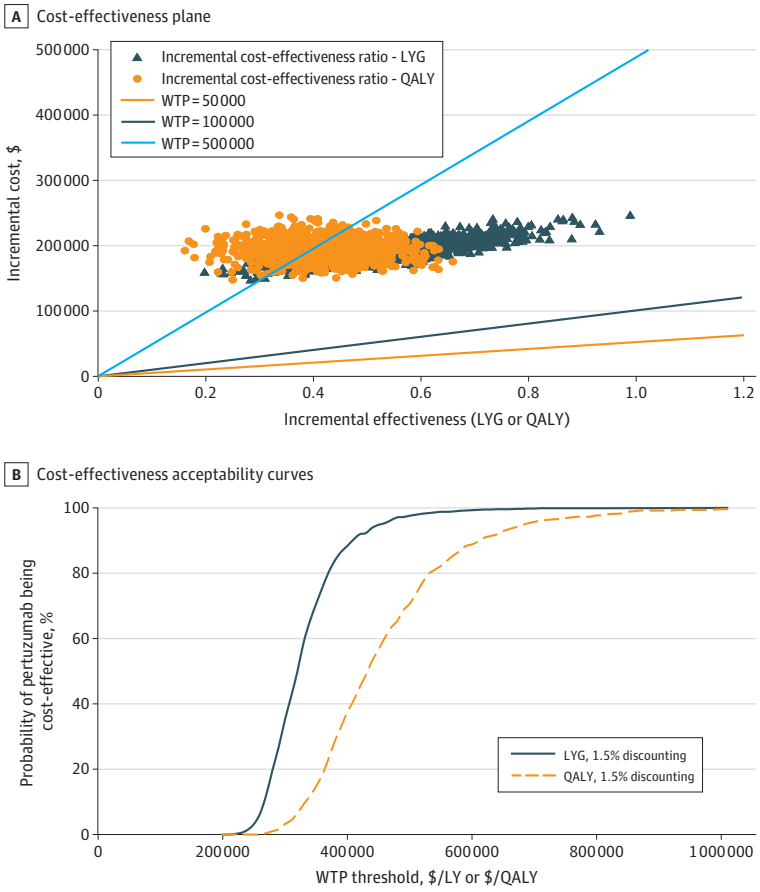
Table 2. Cost, Cost-effectiveness, and ICER[a]

Variable	Cost, mean 5-y total, $	Mean LY	Mean QALY	Incremental difference (95% CI)			ICER, $ (95% CI)	
				Cost, $	LYG	QALY	Per mean LYG	Per mean QALY gained
1.5% Discounting								
Controls	215 648	2.48	1.67	192 139 (160 715-224 736)	0.61 (0.33-0.87)	0.44 (0.23-0.63)	316 203 (247 725-498 153)	436 679 (288 990-833 190)
Pertuzumab	407 787	3.08	2.11					
Scenario: no discounting								
Controls	219 417	2.53	2.00	196 622 (180 774-219 172)	0.63 (0.48-0.84)	0.50 (0.26-0.71)	312 147 (260 753-375 492)	393 244 (273 866-759 238)
Pertuzumab	416 039	3.16	2.50					

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; LYG, LY gained; QALY, quality-adjusted life-year.

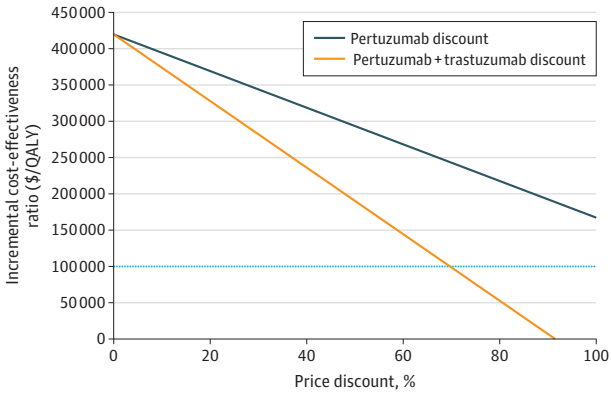
[a] All costs reported in Canadian dollars.

Figure 2. Incremental Cost-effectiveness Ratios (ICERs) for Life-years Gained (LYG) and Quality-Adjusted Life-years (QALY)



Cost-effectiveness plane (A) and acceptability curve (B) for LYG and QALY. WTP indicates willingness to pay. All costs reported in Canadian dollars.

Figure 3. Price Reduction of Pertuzumab Alone and in Combination With Trastuzumab



QALY indicates quality-adjusted life-years. All costs reported in Canadian dollars.

2020 may potentially affect the cost-effectiveness of the combination drug.[44] Although the drug acquisition cost may be higher, the reduction of nondrug costs, such as chair time, may partly offset the higher drug acquisition cost.[45] Future cost-effectiveness analysis could explore this further after approval of the subcutaneous formulation in Canada. Despite these limitations, using real-world data allowed us to avoid some of the assumptions around the parameters required for the model, such as estimating both the effectiveness from clinical trials using parametric methods or estimating costs using published data.

To our knowledge, this was the first economic evaluation of pertuzumab use for patients with metastatic breast cancer using population-based patient-level data. Although other economic studies have explored the cost-effectiveness of pertuzumab, the strength of our study was that we used data on

survival and cost accrued by the same patients who received public funding under examination. By evaluating the cost-effectiveness, we noted the initial estimation that pertuzumab would not be cost-effective at any price. Our study also suggests the feasibility of conducting economic evaluations using patient-level data that are routinely collected in Ontario. The lessons learned from this study will be important for the larger work of the CanREValue Collaboration or other initiatives that aim to develop frameworks for the reassessment of publicly funded drugs as part of life-cycle health technology management.[46-48] With the increasing costs of new drugs, life-cycle health technology management with reassessment allows decision-makers to consider alternative funding approaches, such as conditional approval contingent on collection of data or performance-based agreement.[49,50] Our study suggests the feasibility of conducting population-based economic evaluation that can support these alternative funding approaches to allow decision-makers to renegotiate drug prices that can achieve lower drug costs and improve the long-term sustainability of health care systems.

Conclusions

We conducted a population-based economic evaluation to examine the cost-effectiveness of adding pertuzumab to the treatment regimen for patients with metastatic breast cancer. Although pertuzumab is associated with clinical benefit, it comes with substantial increases in cost. The main factors associated with cost are targeted therapies and outpatient oncologic treatment delivery. Our findings largely support the results from the initial health technology assessments that the ICERs for pertuzumab would not be considered cost-effective, at any price, using commonly accepted willingness-to-pay thresholds. This finding is mostly owing to the added cost of pertuzumab in the case group, as well as longer duration of trastuzumab incurred because of longer survival after adding pertuzumab to the combination. In addition, we noted the feasibility of deriving ICERs using population-based patient-level data, which may be used to inform life cycle health technology assessment.

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