CURRENT ONCOLOGY
A Canadian Cancer Research Journal

Value assessment in oncology drugs: funding of drugs for metastatic breast cancer in Canada

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ABSTRACT

Background Life expectancy for women with metastatic breast cancer has improved since the early 2000s, in part because of the introduction of novel therapies, including chemotherapy, hormonal therapy, and targeted agents. However, those treatments can come at a cost for the patient (short- and long-term toxicities from treatment) and at a financial cost for the health care system. Given the increase in the number of costly anticancer agents being introduced into the clinical setting, the American Society of Clinical Oncology (asco) and the European Society for Medical Oncology (esmo) have developed a system to quantify the value of new cancer treatments in terms of benefit, toxicities, and costs.

Methods In our value-assessment analysis, we included drugs that were funded in Canada between 2012 and 2017 for metastatic breast cancer. We reviewed the clinical benefit of those agents (survival, progression, quality of life), their costs, their value according to the asco and esmo value frameworks, and their assessments from the pan-Canadian Oncology Drug Review [pcodr (in Canada, except Quebec)] and the Institut national d'excellence en santé et en services sociaux [iness (in Quebec)].

Results Drugs funded in Canada showed variation in their asco net health benefit scores and esmo magnitude of clinical benefit scores, but all had a cost-effectiveness ratio greater than $100,000 per quality-adjusted life–year. The strength and magnitude of the clinical benefit (for example, overall survival benefit vs. progression-free survival benefit) was not necessarily associated with a higher value score.

Conclusions Although great progress has been made in developing value frameworks, use of those frameworks has to be refined to help patients and health care providers make informed decisions about the benefit of novel cancer therapies and to help policymakers make decisions about the societal benefit of funding those therapies.

Key Words Chemotherapy, toxicities, breast cancer, targeted therapy, value

BACKGROUND

Survival for patients with metastatic breast cancer (mbca) has improved over the years, at least in part because of the introduction of new cancer therapies[1]. In a recent cohort study of patients starting therapy for metastatic disease between 2000 and 2008, median overall survival (os) was 55.5 months overall, but varied according to tumour biology[2]: median survival was not reached for the luminal–her2 subtypes (estrogen or progesterone receptor–positive, or both, and human epidermal growth factor receptor 2–positive); it was 59.9 months for luminal tumours (estrogen or progesterone receptor–positive, or both, and her2-negative),

49.9 months for the her2-enriched subtypes (estrogen and progesterone receptor–negative, her2-positive), and 18.6 months for triple-negative cancers[2]. In her2-positive mbca, os has been extended by about 4.5 years because of the introduction of her2-targeted therapies[3].

Nevertheless, improved cancer therapies for individuals with mbca come with a cost. From the patient's perspective, the toxicities associated with cancer treatment, both short-term (diarrhea and fatigue, among others) and long-term (heart failure, for instance), can negatively affect quality of life (qol). In addition, the cost of the drug itself is borne by the health care system and the patient (if not funded or if a co-pay is required), and

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patients incur out-of-pocket expenses to receive their treatment (for example, parking). Costs are also incurred if patients or their caregivers have to stop working or to take days off work. A survey of the needs of 1577 women with mBCA found that more than half the women had to change employment and that the change was associated with a decline in their income[4]. For caregivers, there is a cost for accompanying patients to their appointments. For society at large, there are costs associated with treatments and their complications and with loss of productivity by patients or their caregivers. All of those costs have to be weighed against the benefit that can be derived from treatments so that the value of each treatment option can be estimated and compared. "Value" is defined as a measure of outcomes achieved per level of monetary expenditure[5]. Outcomes can be measured in terms of os, progression-free survival (PFS), treatment toxicities, QOL, and capacity to work.

To address the effect of cancer treatments on patients, traditional endpoints such as PFS or os and adverse events are systematically collected in clinical trials; in contrast, patient-reported outcomes and QOL might not be collected. Research has demonstrated that QOL data supplement systematically collected serious adverse events[6]. For example, a cooperative group found that, in lung cancer clinical trials, toxicities were detected earlier when patient-reported outcomes were collected than when the *Common Terminology Criteria for Adverse Events* was applied, and that the two methods showed a moderate correlation[6].

For each new cancer drug, several factors have to be considered before treatment is offered to patients. From a medical point of view, a determination of whether the clinical benefit of the drug outweighs the potential toxicities associated with treatment has to be made. From the patient's point of view, an evaluation of whether treatment-associated toxicity significantly affects QOL or duration of life is important. From the societal perspective, a definition of whether the drug is cost-effective is required. In Canada [except in the province of Quebec, where the evaluation role is taken by the Institut national d'excellence en santé et en services sociaux (INESS)], the pan-Canadian Oncology Drug Review (PCODR) evaluates new drugs to guide cancer-drug funding decisions. The PCODR framework is based on overall clinical benefit, patient values, cost-effectiveness, and feasibility of adoption into health systems[7]. The American Society of Clinical Oncology (ASCO) Value in Cancer Care Task Force developed a framework for comparing relative clinical benefit, toxicity, and cost of treatment in oncology[8,9]. This ASCO initiative is based, at the clinical level, on a standardized approach to help "physicians and patients [assess] the value of a new drug treatment for cancer as compared with one or several prevailing standards of care" and, at the societal level, to assess the proposition that "the cost of a given intervention should bear a relationship to the beneficial impact it has on the patient who receive that treatment"[8]. The European Society for Medical Oncology (ESMO) has undertaken a similar process called the Magnitude of Clinical Benefit Scale (MCBS)[10]. Their rationale was that no standard tool was available to grade the benefit of an oncology drug, and so the true benefit might be overestimated. Their intention

is to apply the MCBS to all new drugs approved by the European Medicines Agency in the hope that drugs with the highest benefit score could be implemented more rapidly[10].

In the present study, we selected drugs that were funded in Canada during 2012–2017 for the treatment of mBCA, and we used the ASCO and MCBS frameworks to look at their value and the PCODR and INESS evaluations to consider their cost-effectiveness.

METHODS

Drugs Approved and Funded in Canada for mBCa

In Canada, during the period of interest, these drugs were approved and funded for mBCA: lapatinib, pertuzumab, and trastuzumab emtansine for HER2 (human epidermal growth factor receptor 2)–positive mBCA; eribulin; and everolimus for hormone receptor–positive breast cancer. Palbociclib, which had received a conditional approval by PCODR (if the cost-effectiveness were to be improved to an acceptable level), but which had not yet been funded was also included in the analysis.

Data for the Assessments of Value and Cost

We used the pivotal trial on which each drug approval was based to determine the clinical benefit (PFS and os, when available) and effect on QOL. If QOL was not included in the pivotal trial or was not reported, we obtained data about QOL from another trial using the same drug so as to have a sense of the effect on QOL. We also obtained cost-effectiveness results for each drug from PCODR and INESS. We then calculated the ASCO net health benefit score[8,9] and the ESMO MCBS[10] for each cancer drug.

Obtaining the ASCO net health benefit score is a 6-step process (Table I). The first two steps determine a regimen's clinical benefit and toxicity, and bonus points are awarded in the third step if the regimen shows either or both of improvement in the palliation of symptoms or in the treatment-free interval compared with control subjects. The clinical benefit, toxicity, and bonus points are then combined to generate a net health benefit score (step 4), which can then be weighed against the direct cost of the treatment (step 5) and integrated into an overall summary assessment of the treatment's value (step 6). We used data from the pivotal trial only (no indirect comparisons were made—for example, for QOL—if relevant data were not obtained in the pivotal trial).

The scoring grid for the ESMO MCBS (Table II) varies according to the primary endpoint (os vs. PFS) and the median os (more or less than 1 year) or PFS (more or less than 6 months) in the standard-treatment arm. Points are added or subtracted depending on QOL and toxicity. In the noncurative setting, the score varies from 1 to 5 (when os is the primary endpoint), with scores of 4 and 5 being considered substantial improvements[10].

To estimate the costs of the drugs, we used an average body surface area of 1.73 m^2 and a weight of 70 kg[7]. For oral drugs, we used the costs from the *Liste des médicaments* published by the Régie de l'assurance maladie du Québec as of April 2017 and from a drug wholesale company in the province of Quebec.

All data are presented descriptively.

TABLE I   American Society for Clinical Oncology Value Framework components for advanced disease[9]

Step	Score
1 Clinical benefit score	
(A) Is the hazard ratio (HR) for death reported?	HR score (death): _____
YES Report, and proceed to 1(F).	
Assign HR score for death by subtracting the HR from 1 and then multiplying the results by 100.	
NO Proceed to 1(B)	
(B) Is the median overall survival (OS) reported?	OS score: _____
YES Report, and proceed to 1(F).	
Assign OS score by calculating the percentage (that is, fractional) difference in median OS between the two regimens and then multiplying the result by 100.	
NO Proceed to 1(C).	
(C) Is the HR for disease progression reported?	HR score (progression): _____
YES Report, and proceed to 1(F).	
Assign HR score for disease progression by subtracting the HR from 1, multiplying the result by 100, and then multiplying that number by 0.8.	
NO Proceed to 1(D).	
(D) Is the median progression-free survival (PFS) reported?	PFS score: _____
YES Report, and proceed to 1(F).	
Assign PFS score by calculating the percentage (that is, fractional) difference in median PFS between the two regimens, multiplying the results by 100, and then multiplying that number by 0.8.	
NO Proceed to 1(E).	
(E) Is the response rate (RR) reported?	RR score: _____
YES Report, and proceed to 1(F).	
Assign RR score by adding the complete response (CR) and partial response (PR) rates, multiplying by 100, and then multiplying that number by 0.7.	
NO Proceed to 1(F).	
(F) Insert the HR score (death), OS score, HR score (progression), PFS score, or RR score as already determined.	Clinical benefit score: _____
Proceed to 2.	
2 Toxicity score	
For each regimen being assessed, compare the number and frequency of clinically relevant toxicities, and assign a toxicity score (details in Schnipper *et al.,* 2016[9])	Toxicity score: _____
3 Determine bonus points (details in Schnipper *et al.,* 2016[9]).	
(A) Tail of the curve: Is there a 50% or greater improvement in the proportion of patients alive in the test regimen at the tail of the curve?	Tail of the curve bonus: _____
YES Enter "tail of the curve" bonus points and proceed to 3(B).	
NO Proceed to 3(B).	
(B) Palliation bonus: Is there an improvement in cancer-related symptoms reported?	Palliation bonus: _____
YES Enter palliation bonus points and proceed to 3(C).	
NO Proceed to 3(C).	
(C) Quality of life (QOL) bonus: Is there an improvement in QOL reported?	QOL bonus: _____
YES Enter QOL bonus points and proceed to 3(D).	
NO Proceed to 3(D)	
(D) Treatment-free interval bonus: Are data related to treatment-free interval reported?	Treatment-free interval bonus: _____
YES Enter treatment-free interval bonus points.	
NO Proceed to 3(E).	
(E) Calculate total bonus points	Total bonus points: _____

TABLE I Continued

	Step	Score
4	Determine the regimen's net health benefit.	
	Calculate the sum of the clinical benefit score (step 1), the toxicity score (step 2), and the bonus points (step 3). Proceed to step 5.	Net health benefit: _____
5	Determine the regimen cost	
	Report the drug acquisition cost (DAC) and the patient co-pay based on how much the treatment regimen costs per month.	DAC (per month): _____
		Patient payment (per month): _____
6	Summary assessment.	Clinical benefit: _____
		Toxicity: _____
		Bonus points: _____
		Net health benefit: _____
		Cost (per month) DAC: _____
		Patient payment: _____

TABLE II European Society for Medical Oncology magnitude of clinical benefit scale, noncurative setting[10]

Item	Score
If survival is the primary endpoint ...	
Grade 1–4 according to the hazard ratio (HR) for survival and survival gain	Preliminary magnitude of clinical benefit (grade 1–4)
Upgrade by 1 level if improved quality of life (QOL), or fewer grade 3–4 toxicities affecting daily well-being, or both, are shown	Final adjusted magnitude of clinical benefit (grade 1–5)
If progression-free survival (PFS) is the primary endpoint ...	
Grade 1–3 according to the HR for PFS and PFS gain	Preliminary magnitude of clinical benefit (grade 1–3)
Adjust for toxicity and QOL (downgrade or upgrade)	Final toxicity- and QOL-adjusted magnitude of clinical benefit (grade 1–4)

RESULTS

Table III presents the trials and clinical benefits for the various drugs. Table IV presents data and calculated values relating to the ASCO and ESMO frameworks and the pCODR and INESS evaluations.

Anti-HER2 Therapies

Lapatinib, an oral tyrosine kinase inhibitor, was studied in HER2-positive mBCA patients who progressed after a taxane, an anthracycline, and trastuzumab. The EGF100151 trial randomized such patients to either capecitabine alone or capecitabine–lapatinib[11–14]. The primary outcome was achieved, with an improvement in time to progression (4.4 months vs. 8.4 months). Of the patients participating in that trial, 60% in the combination arm compared with 39% in the monotherapy arm experienced any-grade diarrhea; the percentages for rash were 27% and 15% respectively. No difference in QOL was observed. According to the ASCO value framework, the net benefit was 50.4, with a monthly cost of $4,367 for the combination of lapatinib with the original form of capecitabine

and $842 for (original) capecitabine alone. The ESMO MCBS was 3—less than the score of 4 that is considered a substantial improvement.

Pertuzumab in combination with trastuzumab was approved based on the results of the CLEOPATRA trial[15,16]. That randomized trial of trastuzumab–docetaxel plus either placebo or pertuzumab in the first line in mBCA found PFS and OS benefits, with the median survival improving to 56.6 months from 40.8 months. Even though toxicities such as diarrhea, headache, and fatigue were more common with the addition of pertuzumab, the QOL analysis found no significant difference between the treatment arms[17]. In a *post hoc* analysis, the median time to deterioration in breast symptoms was 26.7 weeks in the pertuzumab arm and 18.3 weeks in the placebo arm [hazard ratio (HR): 0.77; $p = 0.0061$]. The ASCO net health benefit score was 48.4, and the monthly cost was $10,932 for the combination of pertuzumab with trastuzumab when given with docetaxel. The ESMO MCBS score was 4.

The latest anti-HER2 therapy to be approved was trastuzumab emtansine, which was found in the EMILIA trial[18] to be superior to capecitabine–lapatinib in terms

TABLE III   Benefits of drugs funded in Canada for metastatic breast cancer, 2012–2017

Trial	Study arms	Questionnaires	Main QOL findings	Trial primary endpoint and overall survival
HER2-positive disease				
EGF100151[11–14]	Capecitabine (control arm) vs. lapatinib–capecitabine (experimental arm)	FACT-B, EuroQol (EQ-5D)	No difference in QOL as measured by the FACT-B total, FACT-G, or TOI score, or by the EQ-5D utility or EQ-5D VAS score	■ Time to progression improved with experimental combination (HR: 0.49; $p<0.001$) ■ Median time to progression: 8.4 months for the experimental arm vs. 4.4 months for the control arm ■ Overall survival: 75 weeks vs. 64.7 weeks; $p=0.21$
CLEOPATRA[15–17]	Docetaxel–trastuzumab–placebo (control arm) vs. docetaxel–trastuzumab–pertuzumab (experimental arm)	FACT-B at baseline	No difference in time to decline in the TOI–PFB (HR: 0.97; $p=0.71$)	■ Progression-free survival: 12.4 months in control arm vs. 18.5 months in experimental arm (HR: 0.62; $p<0.001$) ■ Overall survival: 56.5 months in experimental arm vs. 40.8 months in control arm (HR: 0.68; $p<0.001$)
EMILIA[18,19]	Lapatinib–capecitabine (control arm) vs. T-DM1 (experimental arm)	FACT-B	Time to symptom worsening FACT-B TOI–PFB was longer in the experimental arm (7.1 months vs. 4.6 months, $p=0.01$)	■ Time to progression and overall survival (co-primary endpoints) ■ Progression-free survival: 9.6 months in experimental arm vs. 6.4 months in control arm (HR: 0.65; $p<0.001$) ■ Overall survival: 30.9 months in experimental arm vs. 25.1 months in control arm (HR: 0.68; $p<0.001$)
Hormone receptor-positive, HER2-negative disease				
BOLERO 2[20–22]	Exemestane–placebo (control arm) vs. exemestane–everolimus (experimental arm)	EORTC QLC-C30	Time to deterioration in HRQOL (global health status) longer in the experimental arm than in the control arm (8.3 months vs. 5.8 months; HR: 0.74; $p=0.0084$)	■ Progression-free survival: 2.8 months in control arm vs. 6.9 months in experimental arm (HR: 0.43; $p<0.001$) ■ No difference in median overall survival: 31.0 months in experimental arm vs. 26.6 months in control arm (HR: 0.89; $p=0.14$)
PALOMA 2[23] (QOL data from PALOMA 3[24,25])	Letrozole–placebo (control arm) vs. letrozole–palbociclib (experimental arm)	EORTC QLQ-C30 EORTC QLQ-BR23 EQ-5D	Stable global QOL in palbociclib–fulvestrant arm but deteriorated in placebo–fulvestrant arm (–0.9 points vs. –4.0 points; $p=0.03$)	■ Progression-free survival: 24.8 months in experimental arm vs. 14.5 months in control arm (HR: 0.58; $p<0.001$)
Chemotherapy				
EMBRACE[26] (QOL data[27,28])	Treatment of physicians' choice (control arm) vs. eribulin (experimental arm)	No QOL evaluation in EMBRACE, but in another trial[27,28] EORTC QLQ-C30 EORTC QLQ-BR23	Based on another trial: No difference in global health QOL over time between the eribulin and capecitabine arms	■ Median overall survival improved: 13.1 months in experimental arm vs. 10.6 months in control arm (HR: 0.81; $p=0.041$)

QOL = quality of life; FACT-B = Functional Assessment of Cancer Therapy–Breast (FACIT.org, Elmhurst, IL, U.S.A.); FACT-G = Functional Assessment of Cancer Therapy–General (FACIT.org); TOI = Trial Outcome Index; VAS = visual analog scale; HR = hazard ratio; PFB = physical/functional/breast; EORTC = European Organisation for Research and Treatment of Cancer; QLC-C30 = 30-question core Quality of Life Questionnaire; HRQOL = health-related quality of life.

TABLE IV Values for drugs funded in Canada for metastatic breast cancer, 2012–2017

Trial name	Study arms	Cost-effectiveness ($/QALY)		ASCO value framework NHB score	Monthly cost ($)	ESMO MCBS grade
		pCODR	INESS			
EGF100151[11,12,13]	Capecitabine vs. lapatinib–capecitabine	Not available	>150,000	50.4	147 (capecitabine generic), 842 (capecitabine original) 3,672 (lapatinib with capecitabine generic) 4,367 (lapatinib with capecitabine original)	3
CLEOPATRA[15,16,17]	Docetaxel–trastuzumab–placebo vs. docetaxel–trastuzumab–pertuzumab	262,263–303,726	164,021	48.4	6,058 (trastuzumab with docetaxel generic) 6,030 (trastuzumab with docetaxel original) 10,960 (pertuzumab, trastuzumab, and docetaxel generic) 10,932 (pertuzumab, trastuzumab, and docetaxel original)	4
EMILIA[18,19]	Lapatinib–capecitabine vs. T-DM1	Not available	169,099	63.6	3,672 (lapatinib with capecitabine generic) 4,367 (lapatinib with capecitabine original) 7,488 (T-DM1)	5
BOLERO 2[20,21,22]	Exemestane–placebo vs. exemestane–everolimus	162,049	158,644	46.8	39 (exemestane generic) 155 (exemestane original) 5,619 (exemestane with everolimus generic) 5,735 (exemestane with everolimus original)	3
PALOMA 2[23] (QOL data from PALOMA 3[24,25])	letrozole–placebo vs. letrozole–palbociclib	Not cost effective	390,200–501,799	44.8	41 (letrozole generic), 164 (letrozole original) 7,005 (palbociclib with letrozole generic) 7,128 (palbociclib with letrozole original)	3
EMBRACE[26] (QOL[27,28])	Treatment of physicians' choice vs. eribulin	223,840–272,275	100,107–142,522	18.3	3,038 (varies with the particular drug)	2

QALY = quality-adjusted life year; pCODR = pan-Canadian Oncology Drug Review; INESS = Institut national d'excellence en santé et en services sociaux; ASCO = American Society of Clinical Oncology; NHB = net health benefit; ESMO = European Society for Medical Oncology; MCBS = Magnitude of Clinical Benefit Scale.

of PFS and OS, and to be associated with an improvement in median survival to 30.9 months from 25.1 months. In addition, less toxicity (mainly diarrhea and palmar–plantar erythrodysesthesia) was observed with trastuzumab emtansine than with capecitabine–lapatinib. Those differences were associated with a longer time to worsening of symptoms as measured by the Functional Assessment of Cancer Therapy–Breast (FACIT.org, Elmhurst, IL, U.S.A.) and the Trial Outcome Index (physical/functional/breast)[19]. The ASCO net health benefit score was 63.6 for an average monthly cost of $7,488, and the ESMO MCBS score was 5, which is the highest possible score, given the improved OS and better QOL. Cross-trial comparisons are difficult, given that these drugs were not administered in the same population of patients with mBCA (for example, first-line vs. second-line therapy) and had different comparators. In the second line, trastuzumab emtansine and lapatinib have similar cost-effectiveness ratios, although trastuzumab emtansine had the highest ASCO net health benefit score and the highest ESMO MCBS.

Hormone Receptor–Positive, HER2-Negative mBCa

Everolimus was approved in combination with exemestane for hormone receptor–positive, HER2-negative mBCA, based on improved PFS in the BOLERO-2 trial[20]. The median OS was numerically longer in the combination arm (31.0 months vs. 26.6 months), but the difference was not statistically significant (HR: 0.89; $p = 0.14$)[21]. Although a numerically higher proportion of patients experienced a deterioration of more than 5% from baseline in the combination arm (52% vs. 47% in the placebo arm), the median time to deterioration in health-related QOL (global health status) was 8.3 months in the exemestane–everolimus arm and 5.8 months in the exemestane–placebo arm (HR: 0.74; $p = 0.0084$)[22]. For everolimus, the ASCO net health benefit score was 46.8, with a monthly cost of $5,735 when everolimus was combined with the original form of exemestane and $155 when exemestane was given alone. The ESMO MCBS was 3.

Palbociclib is a member of the cyclin-dependent kinase 4/6 inhibitor family and, at the time of writing, was the only drug in this class to have received Health Canada approval (no funding decision has yet been made, however). The PALOMA-2 randomized trial in the first-line metastatic setting compared letrozole–placebo with letrozole–palbociclib. The OS data are not yet mature, but PFS, the primary study endpoint, was positive, with a median PFS of 24.8 months in the letrozole–palbociclib arm compared with 14.5 months in the letrozole–placebo arm (HR: 0.58; $p<0.001$)[23]. Patient-reported outcomes for PALOMA-2 have not yet been published, but outcomes in PALOMA-3, a trial of fulvestrant plus placebo or palbociclib, have been[24,25]. The ASCO net health benefit score was 44.8, with a monthly cost of $7,128 for the combination with the original form of letrozole and $164 for letrozole alone. The ESMO MCBS was 3.

Palbociclib and everolimus have similar values when either the ASCO net health benefit score or the ESMO MCBS is used. However, the absolute difference in PFS shows large variation, although the HR is similar. The fact that the data come from different settings (first-line palbociclib vs. second-line everolimus) is not taken into account.

Despite a large absolute benefit in PFS for palbociclib and endocrine therapy, the cost-effectiveness ratio falls into the range $390,200–$501,799 per quality-adjusted life-year (QALY)[29].

Chemotherapy

The only chemotherapy drug that was approved during the period of interest is eribulin. When compared with a treatment of the physician's choice, eribulin was shown to improve OS in the phase III randomized EMBRACE trial[26]. The trial had no QOL endpoint, but another phase III trial comparing eribulin with capecitabine found no difference in global QOL over time[27,28]. Eribulin was associated with an ASCO net health benefit score of 18.3 and a monthly cost of $3,038. The ESMO MCBS was 2. Although this drug was associated with a survival benefit in heavily pretreated patients with mBCA, it had the lowest value framework scores.

DISCUSSION

Two major oncology associations, ASCO and ESMO, have each worked on a value framework scoring system that takes into consideration clinical benefit, toxicities, and the QOL associated with new cancer therapies. Furthermore, the ASCO framework adds the notion of cost. A study comparing the ASCO net health benefit score with the ESMO MCBS found only weak-to-moderate correlation[30]. Another study observed a negative correlation between the ASCO net health benefit score and incremental cost[31].

Although cost-effectiveness is important for the health care system, it is a vague term for patients, and the cost of drug, and therefore its impact, can vary according to the patient's insurance coverage and income. From the patient's perspective, a cost per month, as presented by ASCO, is easier to understand than a cost-effectiveness ratio. The drug evaluation mechanism in Canada also considers all those elements and decides in the end to recommend funding (or not) based on the cost-effectiveness ratio, provided that the drug has clinical benefit. Given the limited financial resources of the health care system, a report of clinical benefit is not enough to recommend funding a drug. In the province of Quebec, the INESS report of a drug evaluation also considers the "significance" of the budget impact if the new drug is approved. For example, the additional cost of providing palbociclib for patients with estrogen receptor–positive mBCA in Quebec for 1 year was estimated to be $21,235,059[29], which corresponds to 307,755 hours of home-care nursing, or 345 long-term beds, or 312 palliative care beds, or 91,530 days of emergency care for 1 year.

At the societal level, all drugs for the treatment of patients with mBCA reviewed in the present analysis were shown to have a clinical benefit for women with mBCA, but with a cost-effectiveness ratio exceeding $100,000 per QALY. At the patient level, the clinical benefit varied: some drugs were associated with a survival benefit (for example, pertuzumab, trastuzumab emtansine, and eribulin), and others were not (lapatinib, everolimus). Value is also patient-dependent: for some, duration of survival is most important; for others, QOL is the primary objective. Patient goals and expectations must be taken into account. Fortunately, most trials report PFS, response rates, OS, and toxicities.

Quality of life is a secondary endpoint in many trials, but not all. The most recent guidelines from ASCO concerning endocrine therapy for hormone receptor–positive MBCA found only four trials in which QOL was measured[32]. That observation emphasizes the need for evaluation and reporting about the effects of new treatments for a patient's QOL. Studies have shown that, compared with no progression, disease progression is associated with a worsening of QOL[33,34]. For example, in a prospective Canadian study of QOL and utility in 202 patients with hormone receptor–positive, HER2-negative MBCA, QOL was found to be better for patients in a progression-free state than for patients with progressive disease[34].

Value frameworks have also been developed for other disease areas such as cardiology[35], and in oncology, the ASCO and ESMO frameworks are just two of the available possibilities. Others include the U.S. National Comprehensive Cancer Network's evidence blocks[36], the Institute for Clinical and Economic Review's evidence rating matrix[37], and DrugAbacus[38]. Comparison of those five tools found differences in target stakeholders and outcomes presentations, among other aspects[39]. In an era of "personalized" medicine, we ideally need a "personalized" value-assessment tool, because the benefits and toxicities of treatment can vary greatly between individuals. As suggested by Wong *et al.*[40], assessment of the patient's priorities is essential to personalize the value of a treatment that can differ from one patient to another[41]. Also, the evidence used for value inputs should ideally reflect, from either randomized trials or real-world evidence[39], the heterogeneity of the patient population and the heterogeneity of responses. For example, immunotherapy might produce "long term" survivors in diseases for which such longer survival has not been observed in the past[42]. Clinicians will have to become familiar with the value tool before presenting it to patients. Currently, the most commonly used "value" assessment for cross-discipline comparisons is the incremental cost-effectiveness ratio. For example, in prevention, vaccination against the human papillomavirus in Grade 8 girls is associated with an incremental cost-effectiveness ratio of less than $10,000 per QALY[43]. By contrast, in cardiology, left ventricular assist devices for patients with end-stage heart failure not eligible for transplantation is associated with an incremental cost of $230,692 per QALY[44].

Our study has limitations. We did not conduct a systematic review, and our analysis was restricted to pivotal trials only. Since the publication of those trials, other trial results have been made available, and they do not always show the same magnitude of benefit found in the original trial[27,45]. In addition, the trials were comparing a new drug with the previous standard. For a patient who wants to know about the benefit between "active treatment" and "palliative care only," no information about the absolute benefit is available, except through the use of cross-trial comparisons[3].

Second, we used publicly available price lists; we did not have access to the prices that are negotiated between industry and the provincial ministries of health or hospitals.

Third, we encountered some difficulties with the calculation of the toxicity score within the ASCO value framework. The first problem concerned the categorization of adverse events according to their grades and frequencies, which might not adequately reflect the entire toxicity of a treatment because the calculation does not take into account the actual percentage in each arm. The second problem is that the toxicity score excludes laboratory results, and some abnormal laboratory results (such as hemoglobin) could possibly be associated with symptoms. The third problem was that, as with any trial, calculations are based on results from a selected patient population. When those results are applied in an unselected population, external validity in terms of the clinical benefits and toxicities of the new therapies is not known. The final problem was that, in routine clinical practice, the score cannot be calculated. To help with score calculation, ASCO is planning for a Web-based application. Some difficulties with the ESMO MCBS also arose in categorizing toxicities for patients. Those difficulties are reflected in small differences between our scores and other scores published for the same drugs[31,46].

Finally, we must acknowledge that other value frameworks exist[39]; however, we elected to use two from large oncology associations, together with two from the Canadian health care system (PCODR and INESS).

In an era of novel cancer therapies, particularly targeted therapies with dual inhibition, formal assessment of the value of those drugs from a patient and a societal perspective will become even more important for provider–patient shared decision-making and for governmental decisions about drug funding. More importantly, a way has to be found to communicate with patients about treatment options (for example, with decision aids[47]) and to align those options with their values.

CONCLUSIONS

Although great progress has been made in developing value frameworks, the use of those frameworks has to be refined so that patients and health care providers can make informed decisions about the benefit of novel cancer therapies and so that policymakers can decide on the societal benefit of funding those therapies.

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