The Oncologist®

Economics of Oncology Practice

A Time-Trend Economic Analysis of Cancer Drug Trials

Sonya Cressman,[a] George P. Browman,[a,b,c] Jeffrey S. Hoch,[a,d,e,f] Laurel Kovacic,[g] Stuart J. Peacock[a,c]

[a]Canadian Centre for Applied Research in Cancer Control, British Columbia Cancer Research Centre, Vancouver, British Columbia, Canada; [b]Vancouver Island Cancer Centre, Victoria, British Columbia, Canada; [c]School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada; [d]Pharmacoeconomics Research Unit, Cancer Care Ontario, Toronto, Ontario, Canada; [e]Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada; [f]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada; [g]Sindi Ahluwalia Hawkins Centre for the Southern Interior, Kelowna, British Columbia, Canada

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Economics • Pharmaceutical • Cost-benefit analysis • Technology assessment • Biomedical • Medical oncology • Drug costs

Abstract

Background. Scientific advances have led to the discovery of novel treatments with high prices. The cost to publicly fund high-cost drugs may threaten the sustainability of drug budgets in different health care systems. In oncology, there are concerns that health-benefit gains are diminishing over time and that the economic evidence to support funding decisions is too limited.

Methods. To assess the additional costs and benefits gained from oncology drugs over time, we used treatment protocols and efficacy results from U.S. Food and Drug Administration records to calculate cost-effectiveness ratios for drugs approved to treat first- and second-line metastatic or advanced breast, colorectal, and non-small cell lung cancer during the years 1994–2013. We assessed reimbursement recommendations reached by health technology assessment agencies in the U.K., Australia, and Canada.

Results. Cost-effectiveness ratios were calculated for 50 drugs approved by the U.S. regulator. The more recent approvals were often based on surrogate efficacy outcomes and had extremely high costs, often triple the costs of drugs approved in previous years. Over time, the effectiveness gains have increased for some cancer indications; however, for other indications (non-small cell lung and second-line colorectal cancer), the magnitude of gains in effectiveness decreased. Reimbursement recommendations for drugs with the highest cost-effectiveness ratios were the most inconsistent.

Conclusion. Evaluation of the clinical benefits that oncology drugs offer as a function of their cost has become highly complex, and for some clinical indications, health benefits are diminishing over time. There is an urgent need for better economic evidence from oncology drug trials and systematic processes to inform funding decisions. ***The Oncologist*** 2015;20:1–8

Implications for Practice: High-cost oncology drugs may threaten the ability of health care systems to provide access to promising new drugs for patients. In order to make better drug-funding decisions and enable equitable access to breakthrough treatments, discussions in the oncology community should include economic evidence. This study summarizes the extra benefits and costs of newly approved drugs from pivotal trials during the postgenomic era of drug discovery. The reader will gain an appreciation of the need for economic evidence to make better drug-reimbursement decisions and the dynamics at play in today's oncology drug market.

Introduction

Drug expenditures in oncology have risen more dramatically than in any other area of health care [1]. Publically funded health care systems now face unprecedented challenges in their mission to maximize population health with limited health care funds [2–4]. There is concern among policy makers and health care providers that the health benefits gained from new oncology drugs are diminishing and that cost trends may not be sustainable for drug budgets [5]. To protect drug budgets, most health care systems now apply some form of health technology assessment (HTA) to inform decisions about which new drugs to fund with limited public resources [6].

Cost-effectiveness analysis (CEA) is a standard methodology from the field of health economics that expresses the potential value of new drugs in terms of units of currency (e.g., dollars) per health benefits gained [7]. Resource-allocation decisions are usually based on CEA or some other form of economic analysis, along with medical, social, and ethical considerations [8]. The economic evidence used in drug-funding decisions can vary

Correspondence: Sonya Cressman, Ph.D., 675 West 10th Avenue, Vancouver, British Columbia, V5Z 1L3, Canada. Telephone: 604-675-8000 ext.7063; E-Mail: scressman@bccrc.ca Received November 5, 2014; accepted for publication March 20, 2015. ©AlphaMed Press 1083-7159/2015/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2014-0437

 ©AlphaMed Press 2015

among different jurisdictions. The National Institute for Health and Clinical Excellence (NICE) in the U.K., for example, places a heavy emphasis on health gain and trial-based evidence of cost-effectiveness in its HTA process [9]. In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) relies on evidence of cost-effectiveness and national budget impact as part of its process to inform decisions about the funding of new drugs [10]. The pan-Canadian Oncology Drug Review (pCODR) is an oncology-specific agency that offers recommendations to the majority of Canada's health care jurisdictions that are responsible for funding decisions. pCODR makes recommendations to the individual provincial health care systems in Canada about reimbursement of oncology drugs. pCODR specifically considers clinical efficacy, cost-effectiveness, patient perspectives, and system feasibility in its HTA review process [11].

Much of the data required for cost-effectiveness modeling is not readily available from clinical trials, and economic models must be informed by assumptions about clinical efficacy, quality of life, and costs for new drugs relative to comparative treatments. Consequently, the economic evidence that manufacturers submit to HTA agencies at the time of assessment has a high degree of statistical uncertainty and is subject to bias toward manufacturers' interests [12]. The matter is further complicated by the need for specialized understanding in the fields of both oncology and health economics to interpret the evidence presented to HTA review committees. An unfortunate potential consequence of having evidence that is too limited to inform HTA processes is inefficient resource-allocation decisions, which displaces investment in resources that are more likely to improve population health [9]. The problem will be exacerbated by new regulatory policies that enable drugs to be approved more rapidly with limited clinical trial data [13]. Clinical development times have decreased dramatically over the past two decades and are now less than 2 years in duration before approval by the U.S. Food and Drug Administration (FDA) [14]. HTA decisions must now be made in a relatively short amount of time; however, the expertise to inform these decisions requires a specialized understanding of cancer health economics and modern issues pertaining to reimbursement of high-cost drugs, such as willingness to pay and how to manage assumptions based on limited quality-of-life data.

As a solution to the problems associated with limited economic evidence and the complexity of HTA review, it has been suggested that HTA evaluations should be better aligned with regulatory processes [15, 16]. Because some form of HTA is now necessary, whether it be at the level of a national governing body or a private health care insurer, the process has become synonymous with market access, and it is likely that early stage HTA evaluations will be more closely integrated with regulatory processes in the future [17].

In this paper, we have applied cost-effectiveness analysis to oncology drugs at the point that they were authorized for market sale by the FDA, a key regulator in the global oncology drug market. We used data from FDA approval records for cancer drugs for three major oncology indications over the past 20 years. Our results suggest that the move toward early stage HTA engagement is now critically important because post-genomic drugs reach the market with less evidence and more complexity than ever before.

Methods

Efficacy Gains From Pivotal Clinical Trials

Evidence of effectiveness that informed approval decisions of first- and second-line drugs for advanced or metastatic breast cancer, colorectal cancer, or non-small cell lung cancer (NSCLC) were obtained from the FDA review records of new drug applications or biological licensing applications. These records were obtained from publically available summaries on the FDA's website; if the required information was not available, it was specifically requested from the FDA under terms of the Freedom of Information Act (http://www.accessdata.fda.gov/scripts/foi/FOIRequest/index.cfm). Specific clinical trials that are selected by the FDA as the basis of decisions for approval or nonapproval (pivotal trials) are subjected to strict quality control and statistical review and can be considered robust sources of evidence to inform this analysis. Efficacy data from clinical trials that were identified as pivotal (i.e., the basis for establishing efficacy) were found in the FDA's medical or statistical review or on the FDA-approved product label. Overall survival (OS) was used when available at the time of approval; otherwise, surrogate progression-based outcomes were assessed. Some approvals were based on the same outcome measure but different results from more than one pivotal trial; in such cases, the trial demonstrating the outcome with the greatest magnitude of benefit was used for this analysis. This criterion reflects our purpose of comparing costs for the best possible outcomes demonstrated by trials for drug approvals over time. We compared efficacy gains (ΔE) for new drugs relative to their trial-specific comparator within the same indication by first identifying the most common and patient-relevant efficacy outcome from the FDA review for each treatment line (i.e., first or second line) and indication (i.e., metastatic or advanced breast, colorectal, and non-small cell lung cancer) at the time of approval.

Metastatic colorectal cancer and advanced NSCLC diagnoses are associated with relatively short survival, an outcome that occurs early enough in the evaluation of a trial to be measured and used in drug-approval applications. For these two cancer indications, effectiveness outcomes were usually reported as OS. Newer second-line colorectal cancer drug approvals (i.e., oxaliplatin and panitumumab) hinged on statistics for time to progression (TTP). Consequently, we calculated ΔE for the second-line colorectal cancer treatments using both OS and time-to-progression benefits. Most approvals for drugs against metastatic breast cancer were based on TTP; therefore, we used TTP differences between the new drug and the trial-specific comparator to assess the relative gain in benefits among the metastatic breast cancer drugs. It was necessary to assume that TTP is approximately equal to progression-free survival (PFS) for one approval studied in this analysis (bevacizumab for metastatic breast cancer, approved in 2008). We were unable to adjust survival and progression times with utility scores because insufficient quality-of-life data were available from clinical trials.

Measuring Differences in Cost

Per-person drug and administration costs for treatment (C_t) and comparator (C_c) were determined from the FDA-recommended dosage for each of the drugs comprising the approved regimen on the product label. A regimen is defined in this study as an

©AlphaMed Press 2015

approved combination of chemotherapy drugs for a specific indication. *P* is the price of the drug, which is a product of the dosage *(DOSE)* and the per-milligram wholesale unit cost of the drug *(UNIT COST)* obtained from pCODR reviews or at the fiscal quarter that the drug price information first became available at the British Columbia Cancer Agency (BCCA) following FDA approval:

$$P = DOSE \times UNIT\ COST$$

The total per-person drug cost (R) was calculated as a sum of *P* times the expected duration of treatment of each drug *(D)* plus *A,* the cost of administering each drug in the approved and comparative regimens, as in the following equation, in which *n* is the number of chemotherapy drugs in the approved or comparative regimen in the pivotal trial. The parameters for calculating R*, D*, and *A* are described in more detail in the supplemental online Appendix:

$$\mathrm{R} = \sum_{i=1}^{n} (P_i D_i + A_i)$$

R was converted to *C*, the total per-person cost, and converted to 2013 Canadian dollars for the purpose of comparison, using the following equation and the average change in the Consumer Price Index for Health Goods in Canada between the years 2003 and 2008 (0.74%) with exponential power to *y*, the difference between the number of years from 2013 and the year at which the drug was approved, rounded to the nearest dollar. Costs and benefits were not discounted because calculation of cost-effectiveness ratios (CERs) occurred at a stationary point in time:

$$\mathrm{C} = \mathrm{R}(1.0074)^{y}$$

Drug price information was obtained from the BCCA, one of several different Canadian cancer agencies, because of the accessibility of the information. Drug prices may vary to a small extent across different health care jurisdictions within Canada. If drug price information was not available in the BCCA pharmacy database at the time of writing, then the drug was excluded from our cost analysis. This applied to the following metastatic breast cancer drugs: toremifene, ixabepilone, and fulvestrant.

Cost-Effectiveness Ratios

Cost differences were calculated as the difference between the cost of the treatment (ΔC) and the pivotal trial comparator (i.e., $\Delta C = C_t - C_c$). The CER was calculated by dividing ΔC by the difference in effectiveness (ΔE) between treatment and comparator. CERs are expressed in terms of U.S. dollars per life-years gained (LYG) or years of TTP or PFS gained (PFLYG). A time trend was plotted for ΔC and ΔE over time, according to the date of FDA approval (Fig. 1). The results from linear regression (ordinary least squares) were assessed for increasing (positive slope) or decreasing (negative slope) trend over time with Microsoft Excel for Mac version 14.4.2 (Microsoft, Redmond, WA, https://www.microsoft.com).

HTA Recommendations

Each drug approval that was analyzed was also assessed for its HTA review results in Australia, Canada, and the U.K. The recommendations from the respective HTA review agencies were determined from publically available records. We used guidance issued from NICE in the U.K. [18], public summary documents from PBAC submissions in Australia [19], and public review summaries from pCODR (or publically available records from the Common Drug Review prior to 2010) in Canada [20, 21].

If HTA recommendations were available, a "recommendation" status was assigned. If HTA review was not available online or if a drug was reimbursed under special circumstances, despite a negative recommendation, a "reimbursement" status was assigned based on the current list of drugs paid for by the National Health Service, Pharmaceutical Benefits Scheme, or BCCA. The recommendation status (or reimbursement status if no recommendation status was available) was positive, negative, or indeterminate according to the conclusions of review records of the three HTA agencies under study. Positive recommendations included HTA reviews that recommended the drug for funding outright. Also included were recommendations for funding that were conditional on risk sharing or subsequent drug price reductions. An indeterminate recommendation status was assigned for drug reviews that were suspended (due to lack of pursuit for further review by either the manufacturer or the HTA agency), in progress, inconclusive, or deferred until a future date. An indeterminate status was assigned to drugs reimbursed under special funding provisions, such as the Herceptin Program in Australia, or the BCCA's Compassionate Access Program, which provides conditional reimbursement for drugs that apply to fewer than five individuals per calendar year.

Results

During the time of analysis, 50 pivotal trials led to FDA approvals for drugs within the indications and treatment lines under study. Seven regimens were approved based on evidence from single-arm pivotal trials and thus were incompatible with CEA. We were able to calculate CERs for 43 unique regimens with direct trial comparators according to our methods. Only 17 drug approvals were issued with evidence of significantly superior OS gains over the pivotal trial comparator. Seven regimens were approved based on noninferiority analysis of outcomes, which caused high cost-effectiveness ratios; five of these noninferiority analyses were based on an analysis of surrogate outcomes (TTP or objective response rates).

Over the years of study, 19 new drugs for metastatic breast cancer were approved. In 1998, trastuzumab-containing regimens defined a biomarker-specific market by demonstrating that patients with breast tumors that overexpress the human epidermal growth receptor type 2 (HER2/neu) receptor gained an additional 0.35 year of TTP when trastuzumab was added to paclitaxel-containing first-line regimens. The CER for trastuzumab at the time was $104,582/PFLYG. The tyrosine kinase inhibitor lapatinib was later added to the list of agents specific for patients with the HER2/neu-positive metastatic breast cancer, at a cost of $87,604/PFLYG relative to the comparator, capecitabine. The aromatase inhibitors anastrozole, first-line letrozole, and exemestane each had lower CERs calculated from their first- and second-line pivotal trials; each of these drugs cost less than $10,000/year of PFS gained over the standard tamoxifen or megestrol acetate control regimens. The newest approval for use of pertuzumab, in HER2-positive breast cancer, had a CER of $267,561/PFLYG.

For the metastatic colorectal cancer indication, CERs for the monoclonal antibody-based therapies surpassed the threshold

©AlphaMed Press 2015

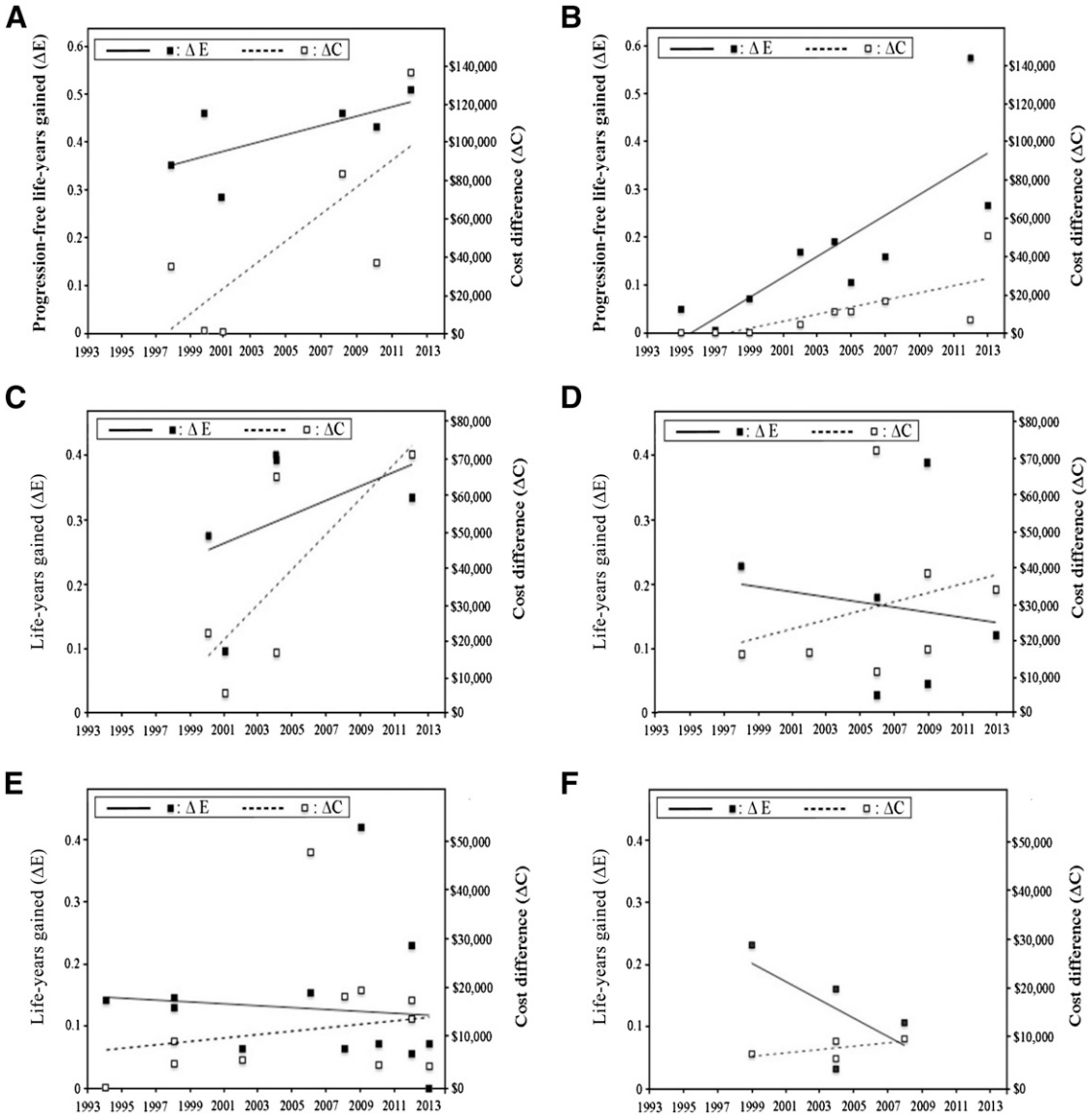

Figure 1. Time-trend for increased efficacy (solid points, solid curve) and increased cost (white points, dashed curve) of U.S. Food and Drug Administration-approved oncology drug regimens relative to pivotal trial-specific comparators. Indications: first-line metastatic breast cancer **(A)**, second-line metastatic breast cancer **(B)**, first-line metastatic colorectal cancer **(C)**, second-line metastatic colorectal cancer **(D)**, first-line advanced non-small cell lung cancer **(E)**, second-line advanced non-small cell lung cancer **(F)**.

that is considered acceptable in most HTA jurisdictions (typically HTA agencies consider CERs >$100,000/LYG to be unacceptable [22]). Very little is known about societal value for progression-free life-years in the economics literature, and it is difficult to speculate what magnitude of PFLY gains might be considered acceptable for the cost. CERs as high as $402,304/LYG for second-line bevacizumab and $423,606/LYG for panitumumab were calculated. All second-line metastatic colorectal cancer drugs had CERs greater than $70,000/LYG, and each new regimen had higher costs than the last, although additional benefits in second-line colorectal cancer decreased over time. Administration costs accounted for less than 5% of total costs, with the one exception for the 1995 approval of paclitaxel for NSCLC; the product label specifies that the drug was to be administered intravenously over 24 hours, and administrative costs in this case were 50% of the total cost.

CERs for drugs approved in first-line treatment of advanced NSCLC rose steadily over time. The 2006 approval of second-line bevacizumab for advanced NSCLC resulted in a CER that was triple the CERs calculated in previous years. Second-line advanced NSCLC treatments also had unacceptable CERs according to conventional standards. A ratio of $299,122/LYG was calculated for pemetrexed's 2004 approval. When the approval for pemetrexed was restricted to the nonsquamous subclass of NSCLC in 2008, a lower CER resulted ($55,638/LYG) and subclassification to the narrower indication improved cost-effectiveness.

When compared over time, the effectiveness gains (ΔE) increased for new drugs against metastatic breast and first-line metastatic colorectal cancers but decreased for drugs against NSCLC and second-line colorectal cancer (Fig. 1). Drugs approved for first-line metastatic breast and colorectal cancer had the most positively sloped regression curves for gains in ΔE over time, and steep, positively sloped regression curves for ΔC were seen for all indications and treatment lines over time.

The proportion of positive public funding decisions (recommended or reimbursed) versus negative decisions

©AlphaMed Press 2015

(not recommended/not reimbursed or indeterminately recommended/reimbursed) was similar among the three jurisdictions under study ($p > .1$) (Table 1). Of the 50 drug approvals assessed, the three reimbursement outcomes were in agreement for all three agencies for 32 drugs (64% of the time); 9 of 50 decisions (18%) were unanimously rejected in all three jurisdictions, and 28 of the 50 drugs assessed had high CERs (i.e., greater than $100,000 per PFLYG or LYG or were approved from a single-arm trial). For these high-cost drugs, the three jurisdictions agreed on reimbursement recommendations only 50% of the time. A total of 7 of 28 (25%) of the high-cost drugs were unanimously rejected by all three agencies. Half of the high-cost cancer drugs were approved uniquely in one jurisdiction but not in the others. The reasons for differences between reimbursement decisions include the termination, deferral, or suspension of an HTA review process in any jurisdiction; the use of different comparators according to regional practice; the use of cost-minimization analysis methods for replacement of a less expensive drug on an existing formulary; the expansion or reduction of the drug's indication for use within a jurisdiction or the desire for a reduction in drug prices following HTA review; and political considerations beyond the scope of CEA.

Discussion

Our results show that drugs approved most recently had higher and sometimes even triple the magnitude of incremental costs for drugs approved for the same indication in earlier years, underscoring concerns about rising oncology drug price trends. Sharp, positively-sloped, ΔC linear regression curves were consistent across all indications, and some indications had decreasing ΔE curves over time. The upward trend for increasing ΔC over time suggests that drug costs are likely to continue to rise in the future. Publicly funded health care systems will have to apply economic methods to consider the budget impact and the list of indications for which new cancer drugs are being considered in balance with the additional benefits and costs that could be expected from the expansion of indications over time (e.g., from the metastatic setting to earlier adjuvant treatment indications).

On occasion, cost-effectiveness ratios for the same indications were lower for newer drugs. This may be explained, in part, by price parity among existing drugs within an approved indication. Generally, competition is limited among approved indications because patented drugs tend to dominate a particular market for a decade after the product has been initially approved [23]. If an incumbent drug with a lower price is already serving the targeted market, then reimbursement may depend on displacing the incumbent. The second-line approvals for tyrosine kinase inhibitors erlotinib and afatinib in EGFR-positive NSCLC and first-line approvals for aromatase inhibitors in hormone receptor-positive metastatic breast cancer are examples of competitors with lower cost-effectiveness ratios than drugs approved in earlier years. Both approvals for second-line metastatic colorectal cancer competitors panitumumab and cetuximab, however, had high-cost effectiveness ratios and poor reimbursement results across the HTA agencies under study, indicating that reimbursement is atypical for high-cost drugs.

Lower cost-effectiveness ratios over time may also come about as a result of a drug showing better efficacy in certain groups of patients with a specific biomarker. There was an increasing trend over time for subclassification within indications, and some drugs were relabeled for a narrower indication following an initial approval. The relabeling resulted in reductions in cost-effectiveness ratios for pemetrexed for second-line use against NSCLC and panitumumab in second-line metastatic colorectal cancer.

For the period analyzed, there was an increasing trend in the use of surrogate trial endpoints to inform approval decisions. Most drugs for metastatic breast cancer were approved based on response rates or time to progression. Surrogate outcomes were also the primary endpoints for the most recent drug approvals in colorectal and non-small cell lung cancer. When trials are evaluated for PFS outcomes, cost-effectiveness models make assumptions to estimate probabilities for transition from disease progression to death. Because regulatory approval times have dramatically decreased over the past decade, it is likely that surrogacy will be a major part of future drug approvals, and economic models will need to account for the uncertainty associated with using a surrogate to predict OS [24]. More patient-relevant outcomes such as quality-of-life data are necessary from clinical trials, and if economic evaluations consider surrogate outcomes, then the outcome should be used consistently across other cancer indications to inform drug-funding priorities [25].

Key regulators, such as the FDA, already have the infrastructure to oversee the collection of economic data such as health utility data in premarket clinical trials. Regulating the availability of economic data for catastrophically priced drugs may be considered complementary to the FDA's mandate to protect public health if better funding decisions may be reached with more robust economic evidence. Our results and those in the literature suggest that inconsistency in HTA review results occurs most often for drugs with high cost-effectiveness ratios, indicating that resource-allocation decisions are likely to be based on opinion or practical considerations [26, 27]. Such decisions are at high risk for inefficiency because limited health care resources are directed away from more cost-effective alternatives. Generalizing HTA evaluations through regulatory review of economic evidence could lead to more informative economic models, minimize reliance on opinion, and improve public health by more efficient use of shared resources.

Our analysis was limited to the FDA-recommended regimen, using dosage and administration profiles that appear on the product label of the approved drugs. The findings of decreasing incremental benefits over time and break-point magnitude (>$100,000/PFLYG or LYG) CERs are of concern because the clinical trial environment is the most ideal situation in which to obtain promising efficacy results [28]. In our analysis, cost estimates did not reflect nondrug and administration costs that may be incurred during diagnosis or costs from adverse events and toxicities, supportive care, treatment, or variation in institutional practice guidelines and/or patient-level treatment decisions. The actual price that provincial pharmacies pay may deviate positively (from tariffs and administration fees) or negatively (discounts from negotiations with the manufacturer) from the Canadian distributor's price that was used in this analysis. The analysis is also limited by the absence of economic evidence about public and patient preferences for cancer outcomes and the availability of robust quality-of-life data in clinical trials.

©AlphaMed Press 2015

Table 1. Cost per efficacy benefit in clinical trial for new drug approvals and their corresponding reimbursement recommendations

Targeted subgroup	FDA approval date	Approved regimens	Cost per efficacy benefit gained, $[a]	Public funding decision[b]		
				NICE	PBAC	PCODR
First-line metastatic breast cancer						
HER2+	Sept. 25, 1998	Trastuzumab + paclitaxel	104,582/PFLYG	+	+[c]	+
PM+, HR+/?	Sept. 1, 2000	Anastrozole	3,846/PFLYG	+	+[d]	+
PM+, HR+/?	Jan. 10, 2001	Letrozole	5,124/PFLYG	+	+	+
HER2−	Feb. 22, 2008	Bevacizumab + paclitaxel	178,249/PFLYG	−	−	−
HER2+, HR+, PM+	Jan. 29, 2010	Lapatinib + letrozole	87,605/PFLYG	−	−	−
HER2+	Jun. 8, 2012	Pertuzumab + trastuzumab + docetaxel	267,561/PFLYG	/	/	+[c]
Second-line metastatic breast cancer						
	Apr. 13, 1994	Paclitaxel	n/a	+	+	+
HR+, PM+	Dec. 27, 1995	Anastrozole	1,521/PFLYG	+	+	+
	May. 14, 1996	Docetaxel	n/a	+	+	+[e]
PM+	Jul. 25, 1997	Letrozole	47,639/PFLYG	+	+[d]	+
	Apr. 30, 1998	Capecitabine	n/a	+	+	+
HER2+	Sept. 25, 1998	Trastuzumab	n/a	−	−	+
PM+	Oct. 21, 1999	Exemestane	7,035/PFLYG	+	+	+
PM+, HR+	Apr. 25, 2002	Fulvestrant	158,266/PFLYG	−	−	+
	May. 19, 2004	Gemcitabine + paclitaxel	62,396/PFLYG	+[e]	+	−
	Jan. 7, 2005	Nanoparticle-bound paclitaxel	110,046/PFLYG	−	+[c]	+[e]
HER2+	Mar. 13, 2007	Lapatinib + capecitabine	134,609/PFLYG	−[d]	+[c]	+
	Jul. 20, 2012	Evorolimus + exemestane	12,079/PFLYG	−	+[c]	+[c]
	Feb. 22, 2013	Trastuzumab emtansine	190,269/PFLYG	/	/	+
First-line metastatic colorectal cancer						
	Apr. 20, 2000	Irinotecan + fluorouracil + leucovorin	72,519/LYG	+	+	+
	Apr. 30, 2001	Capecitabine	49,703/LYG	+	+	+
	Jan. 9, 2004	Oxaliplatin + fluorouracil + leucovorin	37,425/LYG	+	+	+
	Feb. 26, 2004	Bevacizumab + fluorouracil + leucovorin + irinotecan	149,691/LYG	−	+	−
EGFR+, KRAS−	Jul. 6, 2012	Cetuximab + fluorouracil + leucovorin + irinotecan	192,075/LYG	+[c,e]	−	−
Second-line metastatic colorectal cancer						
	Oct. 22, 1998	Irinotecan + best supportive care	74,537/LYG	+	+	+
	Aug. 9, 2002	Oxaliplatin + fluorouracil + leucovorin	110,038/PFLYG	+	+	+
EGFR+	Feb. 12, 2004	Cetuximab + irinotecan	n/a	−	−	−
	Jun. 20, 2006	Bevacizumab + leucovorin + fluorouracil + oxaliplatin	402,304/LYG, (297,000/PFLYG)	−	−	−
EGFR+	Sept. 27, 2006	Panitumumab + best supportive care	199,530/PFLYG	−	+[c,e]	−
EGFR+, KRAS−	Jul. 17, 2009	Cetuximab + irinotecan	99,511/LYG (263,443/PFLYG)	−	+[c,e]	−
EGFR+, KRAS−	Jul. 17, 2009	Panitumumab + best supportive care	423,606/LYG (184,067/PFLYG)	−	+[c,e]	+[c,e]
	Aug. 3, 2012	Ziv-aflibercept	287,140/LYG (185,417/PFLYG)	−	−	−
First-line advanced NSCLC						
	Dec. 23, 1994	Vinorelbine + cisplatin	446/LYG	+	+	+
	Jun. 30, 1998	Paclitaxel + cisplatin	77,491/LYG	+	+	+

(continued)

©AlphaMed Press 2015

Table 1. (continued)

Targeted subgroup	FDA approval date	Approved regimens	Cost per efficacy benefit gained, $[a]	Public funding decision[b]		
				NICE	PBAC	PCODR
	Aug. 25, 1998	Gemcitabine + cisplatin	51,517/LYG	+	+	+
	Nov. 27, 2002	Docetaxel + cisplatin	106,597/LYG	+	+	+
	Oct. 11, 2006	Bevacizumab + paclitaxel + carboplatin	329,569/LYG	−	−	−
NS-NSCLC	Sept. 26, 2008	Pemetrexed + cisplatin	299,122/LYG	−	+[d,e]	−
NS-NSCLC	Jul. 2, 2009	Cisplatin→ pemetrexed	55,638/LYG	+	−	+[c]
	Apr. 16, 2010	Cisplatin→ erlotinib	82,201/LYG	−	−	/
ALK+	Aug. 24, 2011	Crizotinib	n/a	−	−	−
	Oct. 11, 2012	Nanoparticle-bound paclitaxel + carboplatin	257,776/LYG	−	−	−
NS-NSCLC	Oct. 17, 2012	Pemetrexed + cisplatin → pemetrexed	152,088/LYG	−	−	+
EGFR19/20	May. 14, 2013	Erlotinib	86,466/LYG	+	+[d,e]	+[d]
EGFR19/20	Jul. 12, 2013	Afatinib	Dominates	+[c,e]	+	+[d]
Second-line advanced NSCLC						
	Dec. 23, 1999	Docetaxel	27,200/LYG	+	+	+
	Aug. 19, 2004	Pemetrexed	273,489/LYG	−	+	−
	Nov. 18, 2004	Erlotinib	34,314/LYG	+[e]	+[e]	+
NS-NSCLC	Sept. 26, 2008	Pemetrexed	90,090/LYG	−	−	+
ALK+	Aug. 24, 2011	Crizotinib	n/a	−	/	+[d]

[a] $\left(\frac{\Delta C}{\Delta E}\right)$

[b] +, Recommended/reimbursed independent of review. /, Under review, deferred, or reimbursed only under special conditions. −, Not recommended, reviewed, or reimbursed.

[c] Recommendation is conditional on price reduction.

[d] Cost-effectiveness conditional on existing regional formulary.

[e] Restricted or expanded to other subgroups beyond the authorized indication.

Abbreviations: +/?, positive or unknown; ALK+, anaplastic lymphocytic kinase positive mutation; EGFR+, epidermal growth factor receptor overexpressed; EGFR19/20, activating mutations present in exon 19 and/or exon 20; FDA, U.S. Food and Drug Administration; HER2+, positive for overexpression of human epidermal growth factor 2 receptor; HR+, estrogen and/or progestrogen receptor positive; KRAS−, Kirsten rat sarcoma virus oncogene wild type; LYG, life-years gained; n/a, cost-effectiveness cannot be calculated from a single-arm trial; NICE, National Institute for Health and Clinical Excellence; NS, nonsquamous; NSCLC, non-small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; PCODR, pan-Canadian Oncology Drug Review, PFLYG, progression-free life-years gained; PM+, postmenopausal.

Conclusion

As drug prices continue to rise and affect the sustainability of oncology drug budgets, economic evaluation will become increasingly important for managing constrained oncology drug budgets. Surrogate endpoints will become more common, and subclassification within cancer indications is expected to diversify further in the postgenomic era. Early engagement of HTA agencies and health care insurers with manufacturers is an essential step toward maximizing public health. An improved evidence basis for use in HTA is necessary to more accurately assess the value of new cancer drugs while enabling public access to promising new drugs.

Author Contributions

Conception/Design: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Provision of study material or patients: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Collection and/or assembly of data: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Data analysis and interpretation: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Manuscript writing: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Final approval of manuscript: Sonya Cressman, George Browman, Jeffrey S. Hoch, Laurel Kovacic, Stuart J. Peacock

Disclosures

The authors indicated no financial relationships.

References

1. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. N Engl J Med 2009; 360:626–633.

2. Rawlins M. Paying for modern cancer care—a global perspective. Lancet Oncol 2007;8:749–751.

3. Kelly CJ, Mir FA. Economics of biological therapies. BMJ 2009;339:b3276.

4. The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: From the perspective of a large group of CML experts. Blood 2013;121:4439–4442.

5. Schrag D. The price tag on progress—chemotherapy for colorectal cancer. N Engl J Med 2004;351: 317–319.

6. Jönsson B. Technology assessment for new oncology drugs. Clin Cancer Res 2013;19:6–11.

7. Drummond M, Schulpher M, Torrance G et al. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford University Press, 2005.

©AlphaMed Press 2015

8. Drummond MF, Schwartz JS, Jönsson B et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care 2008; 24:244–258; discussion 362–368.

9. Sculpher MJ, Drummond MF. Analysis sans frontières: Can we ever make economic evaluations generalisable across jurisdictions? Pharmacoeconomics 2006;24:1087–1099.

10. Harris AH, Hill SR, Chin G et al. The role of value for money in public insurance coverage decisions for drugs in Australia: A retrospective analysis 1994-2004. Med Decis Making 2008;28:713–722.

11. Hoch JS, Sabharwal M. Informing Canada's cancer drug funding decisions with scientific evidence and patient perspectives: The Pan-Canadian Oncology Drug Review. Curr Oncol 2013;20:121–124.

12. Yong JH, Beca J, Hoch JS. The evaluation and use of economic evidence to inform cancer drug reimbursement decisions in Canada. Pharmacoeconomics 2013;31:229–236.

13. Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category–implications for patients. N Engl J Med 2014;370:1252–1258.

14. DiMasi JA, Grabowski HG. Economics of new oncology drug development. J Clin Oncol 2007;25: 209–216.

15. Frønsdal K, Pichler F, Mardhani-Bayne L et al. Interaction initiatives between regulatory, health technology assessment and coverage bodies, and industry. Int J Technol Assess Health Care 2012;28: 374–381.

16. Wonder M, Backhouse ME, Hornby E. Early scientific advice obtained simultaneously from regulators and payers: Findings from a pilot study in Australia. Value Health 2013;16:1067–1073.

17. Eichler H-G, Bloechl-Daum B, Abadie E et al. Relative efficacy of drugs: An emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010;9:277–291.

18. National Institute for Health and Care Excellence: Find guidance. Available at http://www.nice.org.uk/guidance?ACTION=FIND. Accessed March 2014.

19. The Pharmaceutical Benefits Scheme: Public summary documents by product. Available at http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product. Accessed May 2014.

20. CADTH Common Drug Review. Available at https://www.cadth.ca/cdr. Accessed June 2014.

21. CADTH pan-Canadian Oncology Drug Review. Available at https://www.cadth.ca/pcodr. Accessed May 2014.

22. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: What it is and what that means. Pharmacoeconomics 2008;26:733–744.

23. Grabowski H, Kyle M.. Generic competition and market exclusivity periods in pharmaceutical markets. Managerial Decis Econ 2007;28:491–502.

24. Gutierrez ME, Kummar S, Giaccone G. Next generation oncology drug development: Opportunities and challenges. Nat Rev Clin Oncol 2009;6: 259–265.

25. Elston J, Taylor RS. Use of surrogate outcomes in cost-effectiveness models: A review of United Kingdom health technology assessment reports. Int J Technol Assess Health Care 2009;25:6–13.

26. Spinner DS, Birt J, Walter JW et al. Do different clinical evidence bases lead to discordant health-technology assessment decisions? An in-depth case series across three jurisdictions. Clinicoecon Outcomes Res 2013;5:69–85.

27. Chabot I, Rocchi A. Oncology drug health technology assessment recommendations: Canadian versus UK experiences. Clinicoecon Outcomes Res 2014;6:357–367.

28. Seruga B, Hertz PC, Wang L et al. Absolute benefits of medical therapies in phase III clinical trials for breast and colorectal cancer. Ann Oncol 2010;21:1411–1418.

See http://www.TheOncologist.com for supplemental material available online.

©AlphaMed Press 2015