Guideposts on the journey to value

New drugs for treating cancer continue to be introduced into clinical practice at a rapid pace and at a remarkably high price, typically exceeding $10,000 US per month. While some drugs have transformed the treatment of some cancers, most recently introduced drugs continue to produce small incremental improvements in patient outcomes and there is little relationship between the magnitude of clinical benefit and the launch price of the drug. Indeed, of the 53 cancer drugs that were approved during the period 2003–2013 by the US Food and Drug Administration and the European Medicines Agency, only 43% improved mean overall survival (OS) by three or more months, 43% were associated with improved quality of life (QoL) but 45% were associated with reduced safety [1]. Sixteen (30%) of the approved drugs failed to demonstrate any improvement in OS. Indeed, many recently introduced drugs fail to meet the benchmark of producing clinically meaningful outcomes promoted by Ellis et al. [2] or by Sobrero et al. [3]. Kumar et al. found that only 25 of the 47 recently approved cancer drugs met the modest standards set by Ellis et al. [2] for producing clinically meaningful improvements in progression-free survival and only 9 of the 47 met the clinically meaningful outcome benchmark for OS [4]. In Sobrero’s analysis of 43 phase III clinical trials of drugs recently approved by the Food and Drug Administration only two studies met their criteria for demonstrating high benefit using the metrics of hazard ratio (0.6–0.7) for OS and improvement in median OS (3–6 months) and none of the studies satisfied their criteria for demonstrating a long-term benefit [3]. Nevertheless, all of the drugs studied met regulatory approval standards for marketing in the United States, and all are now used in clinical practice. Other recent analyses have failed to reveal any relationship between the cost of a drug and the benefit it delivers to patients with respect to traditional end points of PFS and OS [5]. Yet, over a recent 15 year span the price of new cancer therapies has increased ~300% [6]. These disturbing trends have spurred the development of value frameworks as tools to help guide the difficult decisions that must be made by patients, clinicians, payers and purchasers of healthcare about how to deliver better patient outcomes at acceptable cost, that is, how to assess and optimize the value of new cancer treatments.

In this issue of *Annals of Oncology*, Cherny et al. [7] present a revised version of the Magnitude of Clinical Benefit Scale (MCBS) developed by the European Society of Medical Oncology (ESMO). Like the initial version, the revised MCBS has been thoughtfully developed, thoroughly tested and carefully vetted to address some of the shortcomings of the initial version identified by users since its initial publication. Eight of 12 issues are addressed in version 1.1, primarily structural and technical issues or those stemming from the recent introduction of immune therapies for cancer. Substantive changes are few as evidenced by the fact that scores changed in only 12 of the 118 comparative studies assessed. Important modifications include revisions to allow scoring of non-comparative trials, use of novel end points for scoring such as pathologic complete response, and allowing adjustments for a long plateau on the progression-free or OS curves. Some issues were deferred pending further discussion with patient organizations including modifications to toxicity scoring, and scoring for improvement in symptoms and improved or delayed deterioration in QoL. An important limitation of the MCBS is its application only to comparative studies that make claims of proven-benefit, that is positive studies. This approach limits the utility of the MCBS to assess studies designed to show non-inferiority, something that might severely limit its applicability to the assessment of biosimilar drugs now entering the clinic. Overall, the revisions made in version 1.1 are clarifying, pragmatic and reflect advancing science and clinical experience. That said the true impact of the ESMO MCBS is still difficult to assess. The authors claim that it has been widely cited, incorporated into ESMO guidelines and served as a basis for benchmarking studies, at least one of which reveals that few recently published studies meet the ESMO standard for meaningful clinical benefit [8]. Yet, it is not clear that this or any of the recently introduced value frameworks have thus far led to significant improvements in the value of cancer care. Comparisons of the ESMO framework with that published by the American Society of Clinical Oncology (ASCO) [9] have recently been published and generally show a poor correlation in scores when studies are evaluated by both frameworks [10, 11]. Perhaps this is not surprising given that these frameworks were independently developed and intended for different purposes. Yet, the poor correlation in scores between them illustrates the complexity in assessing value and reminds us that value is, to a great extent, in the eye of the beholder.

For patients, value is defined primarily by health outcomes, e.g. cure of disease, longevity, relief of symptoms, resumption of usual daily activities, improvement in QoL and achievement of personal goals. Value is often defined in very personal ways depending on individual preferences, work requirements, comorbidities, family circumstances and financial realities.

For providers, value can be created through a shared decision-making process that lays out prognosis, goals of treatment, treatment options, and expected benefits and risks in the context of the patient’s preferences, values and personal goals. To make informed choices, patients also need information about the costs of their medical care and the relationship between the costs they will incur and the benefits they will receive for different treatment options. The ASCO value framework was developed to help guide these decisions.
Payers focus largely on the distribution of illness and wellness in the covered population, reduction in use of expensive treatments and procedures not supported by medical evidence, elimination of inefficiencies in healthcare delivery systems that lead to duplication of services and enhanced communication among providers and between providers and patients to reduce unnecessary emergency room visits or hospitalizations. For payers, achieving high value care depends not only on improving health outcomes but also on reducing waste, improving efficiency and increasing access to the primary healthcare team, all of which tend to drive down costs.

Purchasers of healthcare, whether governments or private companies, often consider multiple factors when deciding whether or not to introduce a new product or service as an option for their population. Purchasers typically have a fixed and limited budget and considerations often include the competing healthcare needs of the population, the extent of unmet medical need for a condition, available alternatives and overall affordability of a new treatment as well as its incremental benefit and toxicity. The ESMO MCBS was developed with the aim of assisting low resource European countries to make these difficult decisions.

For product innovators, value is determined in the context of research and development investment and shareholder expectations and is often assessed over the life cycle of the product as product performance can vary across patient populations, by line of therapy, and based on whether a biomarker selection strategy is employed or not.

Regardless of one’s point of view, all stakeholders can contribute to improving the value of cancer treatment. Providers need to practice evidence-based medicine focused on quality rather than quantity of care and engage in shared decision-making with their patients. Patients need a better understanding of treatment options, potential outcomes and costs to help establish realistic goals. Industry needs to responsibly price products in a way that supports true innovation but insures access by all patients who might benefit from the product. Payers need to make well-informed, fair and transparent coverage decisions. Purchasers of healthcare need to demand that the cost of a given intervention bears a relationship to the beneficial impact it has on the individuals who receive it. Together we can and we must ensure that all patients have the opportunity to achieve optimal outcomes at affordable costs, i.e. that patients receive high value, not just high cost, cancer care. The ESMO MCBS, like the ASCO value framework and other similar tools is a guidepost on the journey to value but not the destination. Nevertheless, the new and improved version 1.1 will continue to help point us in the right direction.

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