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ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options

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INTRODUCTION

Health care costs in the United States present a major challenge to the national economic well being. The Centers for Medicare and Medicaid Services (CMS) has projected that US health care spending will reach $4.3 trillion and account for 19.3% of the national gross domestic product by 2019.[1] This growth in spending—both in absolute terms and as a proportion of our gross domestic product—has not been accompanied by commensurate improvements in health outcomes, despite expenditures far exceeding those of other countries.[2-4] One of the fastest growing components of US health care costs is cancer care, the cost of which is now estimated to increase from $125 billion in 2010 to $158 billion in 2020.[1] Although cancer care represents a small fraction of overall health care costs, its contribution to health care cost escalation is increasing faster than those of most other areas because of several factors: the increasing prevalence of cancer due to the overall aging of the population and better control of some causes of competing mortality; the introduction of costly new drugs and techniques in radiation therapy and surgery; and the adoption of more expensive diagnostic tests. In some cases, the adoption of newer, more expensive diagnostic and therapeutic interventions may not be well supported by medical evidence, thereby raising costs without improving outcomes.[5] Coupled with, or even driving, some of these rising costs are sometimes unrealistic patient and family expectations that lead clinicians to offer or recommend some of these services, despite the lack of supporting evidence of utility or benefit.[6]

Historically, most individuals in the United States were shielded from the acute economic impact of expensive care because they had health insurance. However, current trends suggest that patients will find themselves increasingly responsible for a greater proportion of the cost of their health care. Cost shifting or sharing can occur through the increased use of high-deductible policies and larger copayments. These increased costs are already commonplace and may not be affordable for many families. Indeed, health care expenditures are cited as a major cause of personal bankruptcy,[7] and the term financial toxicity has entered the vernacular as a means of describing the financial distress that now often accompanies cancer treatment.[8] Like other toxicities of cancer treatment, financial toxicity resulting from out-of-pocket treatment expenses can reduce quality of life and impede delivery of high-quality care.[9,10] Patients experiencing high out-of-pocket costs have reported reducing their spending on food and clothing, reducing the frequency with which they take prescribed medications, avoiding recommended procedures, and skipping physician appointments to save money.[10,11] These unintended consequences risk an increase in health disparities, which runs counter to some of the key goals of health care reform.

In many communities, the high costs associated with cancer care have created a difficult situation for patients and the oncologists who care for them. Addressing this situation will require greater understanding of all the risks and benefits of various treatment options as well as the consequences of specific choices. In this regard, studies have shown that patients specifically want financial information about treatment alternatives along with information about medical effectiveness and treatment toxicity. However, they often do not receive it. Closing this knowledge gap will require educated providers who are able to sensitively initiate a dialogue about the cost of care with their patients when appropriate.[12,13] Patients with cancer are often surprised by and unprepared for the high out-of-pocket costs of treatments. They also overestimate the benefits of treatments that sometimes extend life by only weeks or months or not at all. Oncologists are generally aware of this conundrum but uncertain about whether and how the cost of care should affect their recommendations.[14] Although raising awareness of costs and providing tools to assess value may help to

manage costs while maintaining high-quality care, some oncologists see this as being in conflict with their duty to individual patients.[15]

Recent American Society of Clinical Oncology Efforts

Motivated by our responsibility to help oncologists deliver the highest-quality care to patients everywhere, the American Society of Clinical Oncology (ASCO) formed the Task Force on the Cost of Cancer Care in 2007. Its mission includes educating oncologists about the importance of discussing costs associated with recommended treatments, empowering patients to ask questions pertaining to the anticipated costs of their treatment options, identifying the drivers of the rising costs of cancer care, and ultimately developing policy positions that will help Americans move toward more equal access to the highest-quality care at the lowest cost.[16]

In 2012, through the work of the Task Force, ASCO responded to the Choosing Wisely Campaign of the American Board of Internal Medicine Foundation and identified specific instances of overuse in the delivery of cancer care. ASCO used a deliberative consensus process to identify five common clinical practices that are not supported by high-level evidence. A second list of five was developed using the same process and submitted to the Choosing Wisely Campaign in 2013. ASCO amplified the evidence basis for both top-five lists in two publications[17,18] and is now developing measures to evaluate the use of these practices as part of its Quality Oncology Practice Initiative. These exercises have provided opportunities to develop a rigorous but flexible approach to assessing efficacy across diagnostic and treatment domains.

Focus on Value

The high costs of cancer care affect everyone in society, but there are many stakeholders in our complex health care system with specific responsibilities and influence. These include patients, manufacturers, providers, and payers. Rising costs are distributed throughout the broader economy by causing higher insurance premiums, increased taxpayer burden, stagnant wages, and more extensive cost sharing with patients. The net effect is a strain on personal and family finances and a drag on the broader economy. A resulting concern is that health care will become less and less affordable for Americans unless steps are taken to curb current cost trends. As policymakers and payers seek ways to assure the best use of limited resources, they are appropriately turning to physician experts for a better understanding—and definition—of value. ASCO has dedicated significant volunteer time and resources to the issue of cost and has now turned its attention to a formal definition of and strategy for assessing value in cancer care.

In 2013, the ASCO Board of Directors charged the Task Force, now renamed the Value in Cancer Care Task Force, with developing a framework for comparing the relative clinical benefit, toxicity, and cost of treatment in the medical oncology setting. At the clinical level, the goal of the ASCO framework is to provide a standardized approach to assist physicians and patients in assessing the value of a new drug treatment for cancer as compared with one or several prevailing standards of care. From this framework, it is possible to provide medical oncologists with the information and physician-guided tools necessary to assess the relative value of cancer therapies as an element of shared decision making with their patients. At the societal level, the assumption underlying this effort is that the cost of a given intervention should bear a relationship to the beneficial impact it has for the patients who receive that treatment.

The work of the ASCO Value in Cancer Care Task Force has been guided by the following core principles:

- The physician-patient relationship is of central importance in defining management options for the patient. It is the view of ASCO that the oncologist is the patient's best advocate and resource for guidance in assessing the value of treatment options. To accomplish this, the oncologist must have the knowledge and tools necessary to assess the relative value of therapies for specific clinical scenarios and use these in discussing treatment options with the patient.
- To ensure informed decision making, patients need access to both clinical and cost information about their treatment options. Patients need a clear understanding of the possible clinical benefits and harms of treatment options available to them, along with an appreciation of how these options differ with respect to the relative financial consequences they will face.
- As a physician performs his or her primary role as the patient's trusted advocate, he or she also has a responsibility to be a good steward of health care resources. It is the position of ASCO that oncologists should make informed decisions regarding the value of care, understanding both the most accurate and up-to-date information on benefits and costs to patients and society. This is consistent with the statement in the Ethics Manual of the American College of Physicians: "As a physician performs his or her primary role as a patient's trusted advocate, he or she has a responsibility to use all health-related resources in a technically appropriate and efficient manner."[19(p86)] Furthermore, ASCO believes that these goals are not in conflict.
- Working from these principles, ASCO presents herein a proposed framework for assessing the value of treatment options. The framework is designed to eventually assist in facilitating shared decision making with patients about clinical benefits and costs. The framework has benefitted from input from representatives of four major stakeholder constituencies, including oncologists, patients, payers, and manufacturers. The framework should not be viewed as final in concept, and it is not yet suitable for use during a routine clinical encounter. It is designed to be used with the highest quality evidence available, but its development reveals significant gaps in the evidence base that, ideally, will be filled to more fully address the need for comparative information on the relative value of treatments assessed. It is presented now to demonstrate an initial approach to the challenge and to stimulate further discussion toward the goal of developing a clinically useful tool. We seek feedback from all stakeholders, and we plan to use this feedback to further refine the framework and ensure its eventual usefulness to the oncology provider community.
- As this framework and its accompanying scenarios show, health benefits and costs can differ substantially among therapies. Although not its underlying intent, ASCO recognizes that this work has the potential to influence policymakers and payers as they consider preferred management options and evaluate the relative value of new treatments introduced into the cancer marketplace. As it evolves, ASCO anticipates that the framework will play an increasingly important role in

determining the value of new approaches to the treatment of cancer. All of this makes it critically important for all voices to be heard, that a flexible and transparent approach is used, and that the overall goals of the project are understood.

ASSESSING VALUE IN HEALTH CARE

Defining Value

Although the methods of assessing value vary depending on the country, health care system, disease, and patient population, the definition of value is generally accepted as a measure of outcomes achieved per monetary expenditure.[20] The Institute of Medicine (IOM) has identified six elements of quality health care delivery: safety, effectiveness, patient centeredness, timeliness, efficiency, and equity.[21,22] ASCO, through the Value in Cancer Care Task Force, has chosen to define value in cancer care by emphasizing three critical elements articulated by the IOM: clinical benefit (efficacy), toxicity (safety), and cost (efficiency). These three elements are readily measured, ascertainable from high-quality medical evidence, and central to the mission of the clinical oncologist. Patient centeredness, timeliness of therapy, and equity in access to cancer care are also essential elements of quality care; however, they are not as easily measured and are only rarely reported as outcomes of clinical trials. The health and individual needs of the patient are paramount, and the intent of ASCO in developing the framework is that it will encourage the development of more patient-centered care.

Patient Perspective

The perspective of the patient is of central importance in defining value. Patient perception of value is highly individualized, can be subjective, and may change over time. It is aligned with efficacy and toxicity of an intervention, dynamic throughout the course of the disease process, and dependent on variables such as age, comorbidities, life circumstances, insurance coverage, personal finances, and individual goals, religious beliefs, and values. When making treatment decisions, patients often consider not only efficacy (chance of cure or disease response) but also quality of life, toxicity, convenience, and cost.[23,24]

Patients often face uncertainty about what a treatment will cost and where to obtain financial information and assistance. Differences in insurance coverage and reimbursement or cost-sharing structures also make it exceedingly difficult for providers to understand the direct, out-of-pocket cost of care faced by individual patients, especially for new drugs.[25] Information on indirect costs to patients is also difficult to obtain and can vary significantly from patient to patient. To address this issue, there is increasing emphasis on providing clear and objective information not only on the clinical benefits and risks of treatment options but also on cost. Doing so can help patients make informed treatment decisions that are best for their health, while potentially incurring less of a financial burden when there are alternative approaches with little or no difference in overall effectiveness or toxicity.

Because patient perception of value is so individualized, it is crucial that discussions with patients include an assessment of which treatments are most likely to support their needs, goals, and preferences, and that information that could affect their treatment decision making be provided as transparently as possible.

Role of the Oncologist

Oncologists play a crucial role in ensuring that the care patients receive is appropriate for the clinical indication, evidence based whenever possible, and consistent with each person's individual values and preferences. Shared decision making requires sharing comprehensive information about prognosis and treatment options, with the level of detail tailored to the health literacy of the individual patient.[26]

A routine and reliable mechanism for assessing and informing patients of the financial impact of treatment in the context of expected benefits remains an unmet need and was part of the first two recommendations of the recent IOM report on delivery of high-quality care.[22] That said, discussions with patients with cancer about treatment recommendations and their cost are complicated by the emotional distress experienced by patients after a cancer diagnosis.

Metrics to Assess Value in Health Care

A number of methodologies have been employed by health economists to assess the value of medical therapies. Two commonly used metrics are quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs).

QALY. A QALY is a measure of disease burden, including both the quality and quantity of life lived. QALYs can provide an indication of the benefits obtained from medical procedures in terms of quality of life and survival. The QALY is often used in cost-effectiveness analyses to evaluate and compare the value of specific treatments for purposes of allocating resources across a health care system or systems.[27] An intervention with a lower cost-to-QALY ratio would be preferred over an intervention with a higher ratio. Although the QALY can be adapted for individual decision making, it is not the purpose for which it is most commonly used. There are significant limitations to the application of QALYs, because individuals with the same illness may have different preferences for a health state. For example, one individual with advanced cancer may prefer length of overall survival (OS) above all else, whereas another might view minimization of symptoms as the highest priority.

ICER. The ICER is the basis of cost-effectiveness analysis. The ICER is the ratio between the difference in cost and the difference in benefit of two interventions. QALYs are commonly used in assessing benefits when deriving an ICER, which is commonly expressed as incremental cost per QALY. Researchers are increasingly integrating ICER analyses into the results of clinical trials as a means of providing a more complete assessment of benefit relative to cost. Defining an acceptable threshold for cost effectiveness has been a major focus of public policy worldwide. Currently, no uniform threshold exists across health care systems; however, in many countries, such thresholds are being established, which raises concerns about limiting patient choice and health care rationing.

Global Context for Assessing Value

The creation of new and increasingly expensive therapeutic agents has made it difficult for governments and pharmaceutical benefit providers to plan or know how to effectively and efficiently spend limited resources.[28,29] Many Western European nations, as well as others, including Australia and Canada, rely on health technology assessments provided by a government-sanctioned entity to determine the value of a new therapeutic option and use this assessment to help determine whether the drug in question should be purchased for the pharmacopeia of that nation. The United Kingdom has formalized

a process that integrates clinical and econometric analyses to determine whether the value of a new agent is great enough that it should be available to patients through the National Health Service. The review processes of the United Kingdom, Canada, Australia, France, and Germany have been well described in the literature and are summarized in Table 1. Notably, each considers measures of efficacy, toxicity, and cost, often in the context of disease prevalence, medical need, and prevailing alternatives.

In the United States, although there have long been concerns with high costs of health care at the individual and societal levels, there has been reluctance to accept constraints on spending on the basis of cost-effectiveness analysis.[39] Policy discussions have evolved from an emphasis on cost containment to quality and now to value over the course of the last few decades. Absent clear and universally accepted value standards, and stimulated by significant fiscal pressures, federal programs, health plans, professional societies, and others have undertaken efforts to define, assess, and implement value in health care delivery. Benefit structures, adjustment of insurance premiums, and implementation of clinical pathways and administrative controls have all been employed as means of controlling cost while emphasizing value. It is in this arena that the ASCO Value in Cancer Care Task Force seeks to contribute to the effort to ensure value for patients while preserving and enhancing quality and sustaining innovation.

In addition to ASCO, other provider organizations are beginning to address the issue of value within their medical communities. Recently, the American College of Cardiology and American Heart Association issued the "Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures,"[40] which argues for a transparent and consistent approach to considering value when making health care decisions and proposes a schema for value categories, based on QALYs gained by an intervention.

ASCO VALUE FRAMEWORK

Methodology

To develop the framework, ASCO established a steering group of the Value in Cancer Care Task Force, co-chaired by Drs Nancy E. Davidson and Lowell E. Schnipper, to oversee the initiative. The steering group organized the Task Force into three work groups, each charged with defining a key parameter of the value framework: clinical benefit, toxicity, and cost. Each work group met via conference calls to define its assigned domain and consider relevant metrics. Decisions were reached by consensus and anchored in the results of prospective, randomized trials comparing a new treatment with a prevailing standard of care. Once the parameters of the framework were established, the Task Force developed a set of clinical case scenarios to assess the utility of the framework. Earlier versions of the framework and scenarios were shared with key stakeholders at meetings with oncologists, patient advocates, payers, and leaders from the pharmaceutical industry. The input received was carefully considered in the version of the framework that is presented herein.

Framework Overview

The ASCO value framework has been developed as a physician-guided tool to assist the physician and patient in shared decision making. It has been constructed to enable comparisons of a new treatment regimen with the prevailing standard of care for a specific clinical cancer indication using data derived from a prospective randomized trial. Two versions of the framework have been developed—one for advanced cancer and another for potentially curative treatment (adjuvant or neoadjuvant therapy), recognizing the unique clinical concerns associated with these diverse treatment settings.

In both the advanced disease and curative frameworks, points are awarded (or subtracted) in the categories of clinical benefit and toxicity. In the advanced disease framework, bonus points can be earned if a regimen shows statistically significant improvement in palliation of symptoms and/or treatment-free interval compared with the control treatment in a clinical trial. Clinical benefit and toxicity (and bonus points, in the advanced disease framework) are combined to generate a net health benefit (NHB) score, which is then juxtaposed against the direct cost of the treatment, to provide an overall summary assessment. These components are further described herein, and the frameworks are summarized in Figures 1 and 2.

Clinical benefit. In the advanced disease framework, clinical benefit is assigned a categorical score (1 to 5) based on the fractional improvement in median OS when comparing a new regimen or agent with a standard-of-care regimen for a specific clinical scenario. If data on median OS are not available, median progression-free survival (PFS) data are to be used instead. If neither OS nor PFS data are available, or the regimen has been evaluated in a single-arm trial only, response rate (RR) should be used. The categorical score for OS is weighted (ie, multiplied) by 16 (this multiple was chosen to indicate that maximum of 80 [16 × 5] of 100 points can be attributed to improvement in survival), PFS is weighted by 11 (because it is a less clinically meaningful end point and is not always a surrogate for OS), and RR is weighted by eight, reflecting the fact that this end point represents a clinical benefit that might not translate to improvement in OS. For the curative framework, a categorical score (1 to 5) for OS is assigned based on the hazard ratio (HR) when comparing the test therapy with a standard of care. If OS data are not reported, the HR for disease-free survival (DFS) is used instead. The categorical score is weighted by 16 for OS and 15 for DFS. Here as well, the weight of the survival benefit is 80 of a possible score of 100, reflecting the view of the Task Force that improvement in OS represents the most important component of the value assessment.

Toxicity. In both the advanced disease and curative frameworks, toxicity is calculated as the relative toxicity of the new agent against the comparator regimen. This option awards (or subtracts) a categorical value (−20 to +20) ranging from substantially less well tolerated to substantially better tolerated when comparing the frequency of grade 3 to 5 toxicities as defined by the Common Terminology Criteria for Adverse Events for the new regimen against the comparator.

Bonus points. As noted, regimens scored using the advanced disease framework have an opportunity to gain bonus points in two ways: Palliation bonus points should be awarded if a statistically significant improvement in any cancer-related symptom is reported in a randomized trial of the new treatment; treatment-free interval bonus points should be awarded if a statistically significant improvement in treatment-free interval is reported in a randomized trial of the new treatment versus the comparator. This option is included because a period off all therapy for patients with cancer implies that their disease is not progressing and that they can be spared the treatment-related toxicities (or at least are dealing with resolution of those previous experienced) of continuing therapy.

Table 1. Summary of International Value Determination Frameworks

Country	Reviewing Body	Criteria for Value Assessment	Evidence	Outcome Variables	Cost Metrics	Type of Economic Assessment	Use of Results	Source
United Kingdom	NICE, SMC, AWMSG	Strength of available evidence, importance of outcomes, health impact, cost effectiveness, budget impact, inequalities, feasibility of implementation, impact on NHS, acceptability, broad clinical and government policy priorities, health needs	Burden of disease (population affected, morbidity, mortality); resource impact (cost impact on NHS or public sector); clinical and policy importance (whether topic is within government priority area); presence of inappropriate variations in practice; potential factors affecting timeliness of guidance to be produced (degree of urgency, relevance of guideline at expected date of delivery); likelihood of guidance having impact on public health and quality of life, reduction in health inequalities, or delivery of quality programs or interventions; appropriateness and ability of NICE to commence development of guideline. (source: manufacturer data, RCTs, systematic literature reviews)	Mortality, morbidity, quality of life, cost per QALY	Direct costs for NHS and PSS; may also add travel and other public sector costs but typically does not include productivity costs; some consideration for indirect costs	Cost-effectivness or cost-utility analysis; cost-benefit analysis may be used in specific situations; in addition, cost-consequence approach may be adopted to take account of complex and multidimensional character of public health interventions and programs; other issues (eg, equity, distribution) can also inform analysis; budget impact model (template specific to SMC) or cost minimization where clinical equivalence is statistically demonstrated	To develop standards, guide patient-care decisions, inform strategies to meet government indicators and targets, support decision making on NHS funding and resource allocation, guide education and training of health professionals; health authorities are unlikely to accept (reimburse or fund) products that are not recommended (although they can) and are mandated (in England) to reimburse products that are recommended	NICE,[30] SMC,[31] AWMSG[32]
Canada	pCODR, INESSS	Overall clinical benefit, cost effectiveness, alignment with patient values, feasibility of adoption into health system	Effectiveness, measured in terms of relevant patient outcomes (eg, mortality, morbidity, quality of life) with magnitude, direction, and uncertainty of effect also considered; safety; burden of illness; need (availability of effective alternative); patient values; cost effectiveness; economic feasibility (net budget impact of new drug, including companion testing); organization feasibility (source: manufacturer data, RCTs, systematic literature review, clinical guidance report, patient advocacy data, other unpublished data)	Mortality, morbidity, safety, quality of life	Direct costs from public payer perspective (usually Ontario MOHTL)	Cost, cost-effectiveness analysis, cost-utility analysis, budget impact assessment; uncertainty of results must be assessed (range for worst-case scenario)	Evaluate clinical data, assess cost effectiveness, make recommendations to guide drug reimbursement decisions at provincial level; decisions can include: list, list with conditions upon clinical criteria or lower ICER, or not list	pCODR,[33] INESSS[34]

(continued on following page)

Table 1. Summary of International Value Determination Frameworks (continued)

Country	Reviewing Body	Criteria for Value Assessment	Evidence	Outcome Variables	Cost Metrics	Type of Economic Assessment	Use of Results	Source
Australia	PBAC	Clinical efficacy and costs compared with other medications already in PBS for corresponding indications; cost-effectiveness and cost-utility analyses	Meta-analysis of manufacturer data against available comparator data, including benefits and costs; assessment of direct randomized trials to give superior therapeutic conclusion; translation of these direct trial issues using premodeling provide trial-based or stepped economic evaluation (ie, cost effectiveness); epidemiologic analysis of budgetary implications (source: manufacturer data, RCTs, indirect comparisons of several trials with applicable comparator)	Efficacy (ICERs, QALYs, LYGs), morbidity, mortality, maximum health outcome per dollar spent	Direct and indirect costs; process takes national health budget perspective, looks at costs and offsets to health care system as whole, as well as patient copay amounts	Comparative-effectiveness analysis, relative comparative effectiveness, cost-minimization analysis where clinical equivalence is statistically demonstrated	Recommendations for state subsidization of new pharmaceutical agents	PBAC[35]
France	HAS Transparency Commission and Public Health and Economic Evaluation Committee, CEPS	Clinical effectiveness of drug and possible side effects, position in therapeutic spectrum relative to other available treatments, disease or condition severity, clinical profile of drug, public health impact, cost-effectiveness for innovative drugs (ASMR I, II, III) expected to have significant budget impact on system	Clinical, epidemiologic, and economic data; financial and public health impact (source: manufacturer data, RCTs, systematic literature reviews, indirect comparisons)	Mortality, morbidity, quality of life	Depends on aim of study or assessment; all relevant costs must be reported and presented in detail; indirect costs must be reported separately	Budget impact models; cost-minimization, cost-effectiveness, cost-utility, or cost-benefit analysis	Reimbursement and pricing decisions	HAS,[36] Ministère des Affaires Sociales de la Santé[37]
Germany	Federal Joint Committee; Institute for Quality and Efficiency in Health Care	Nature and severity of disease, magnitude of additional therapeutic benefit, availability of treatment alternatives, adverse-effect profile	Clinical benefit with respect to patient-relevant outcomes, medical need, efficiency (source: RCTs, systematic literature reviews, indirect comparisons [in special cases])	Mortality, morbidity, quality of life	All direct and, in some cases, indirect costs	For early benefit only, direct cost comparison; no health economic assessments unless pricing negotiation sent to arbitrage	Supports reimbursement, pricing decisions, guideline development	Bundesministerium für Gesundheit[38]

Abbreviations: ASMR, Amélioration du Service Médical Rendu; AWMSG, All Wales Medicines Strategy Group; CEPS, Comité Économique des Produits de Santé; HAS, Haute Autorité de Santé; ICER, incremental cost-effectiveness ratio; INESSS, Institut National d'Excellence Santé et en Services Sociaux; LYG, life-year gained; MOHTL, Ministry of Health and Long-Term Care; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PBS, Pharmaceutical Benefits Scheme; pCODR, Pan-Canadian Oncology Drug Review; PSS, Personal Social Services; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SMC, Scottish Medicines Consortium.

THE ASCO VALUE FRAMEWORK: ADVANCED DISEASE

Step 1: Determine the regimen's CLINICAL BENEFIT

1.A. Is Overall Survival (OS) reported?	**YES.** Assign an OS Score (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.D.**						**OS Score**
	OS Score	1	2	3	4	5	
	Improvement in median OS (% change in median OS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median OS of new regimen, there is a 50% improvement in the fraction of patients surviving	
	NO. Proceed to 1.B.						
1.B. If OS is not reported, is Progression-Free Survival (PFS) reported?	**YES.** Assign a PFS Score (1 through 5 as shown below) and multiply by 11. Write this number in the box labeled, "PFS Score." **Proceed to 1.D.**						**PFS Score**
	PFS Score	1	2	3	4	5	
	Improvement in median PFS (% change in median PFS)	> 0%-24%	25%-49%	50%-75%	76%-100%	At double the median PFS of new regimen, there is a 50% improvement in the fraction of patients without progression or death	
	NO. **Proceed to 1.C.**						
1.C. If neither OS nor PFS is reported, is Response Rate (RR) reported?	**YES.** Assign an RR Score (1 through 5 as shown below) and multiply by 8. RR should be calculated by adding the complete response (CR) and partial response (PR) rates. Write this number in the box labeled, "RR Score." Proceed to 1.D.						**RR Score**
	RR Score	1	2	3	4	5	
	What was the reported response rate (CR + PR)?	> 0%-20%	21%-40%	41%-60%	61%-80%	81%-100%	
1.D. Calculate the Clinical Benefit Score	Insert the OS, PFS, or RR Score. **Note: You should have EITHER an OS Score OR a PFS score OR an RR score, NOT MORE THAN ONE.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**

Step 2: Determine the regimen's TOXICITY

Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities (ie, calculate the sum of toxicities of grade 3-5 reported for each regimen) and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. Write this number in the box labeled, "Toxicity Score." The maximum allowable toxicity points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Less well tolerated (50%-74% increase in the number of grade 3-5 toxicities reported for the new regimen.)	Toxicity is the same (less than 49% increase and up to 49% fewer toxicities are reported for the new regimen.)	Better tolerated (50%-74% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	Substantially better tolerated (75%-100% decrease in the number of grade 3-5 toxicities reported for the new regimen.)	

Step 3: Determine Bonus Points

3.A. PALLIATION BONUS. Are data related to the palliation of symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported, award 10 points, and place this in the box labeled "Palliation Bonus Points." **Proceed to Step 3.B.**						**Palliation Bonus Points**
	NO. No bonus points are awarded. **Proceed to Step 3.B.**						
3. B. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported, award points based on the table below, and place this in the box labeled "Clinical Benefit Bonus Points." This is the interval from completion of study treatment to initiation of next treatment. **Proceed to 3.C.**						**Treatment-Free Interval Bonus**
	Bonus Points	0	5	10	15	20	
	% Change	> 0%-19%	20%-35%	36%-49%	50%-74%	≥ 75%	
	NO. No bonus points are awarded. **Proceed to Step 3.C.**						
3.C. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A) and the Treatment-Free Interval Bonus Points (Step 3.B). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 30. **Proceed to Step 4.**						**Total Bonus Points**

Step 4: Determine the regimen's NET HEALTH BENEFIT

Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1), Toxicity Score (Step 2), and Bonus Points (Step 3). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for Net Health Benefit are 130 (100 + 30 bonus points). Proceed to **Step 5.**	Net Health Benefit

Step 5: Determine the regimen's COST

Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs per month.	**Cost Per Month:** **DAC:** _____ **Patient Co-Pay:** _____

Step 6: Summary Assessment – Advanced Disease Framework

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
/80	/20	/30	/130	DAC: _____ Patient Payment: _____

Fig 1. ASCO Value Framework: advanced disease. Future versions of the framework will allow for patients weighting their preferences such that the fractional contribution of each element (clinical benefit, toxicity) to the overall score can be modified, thereby individualizing the net health benefit. ASCO, American Society of Clinical Oncology; CR, complete response; DAC, drug acquisition cost; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

NHB. The clinical benefit and toxicity scores (plus bonus points in advanced disease framework only) are combined to yield an NHB score. The maximum NHB score is 130 for the advanced disease framework and 100 for the curative framework.

Cost. Two types of cost estimates are to be presented when the value of an intervention is being considered. One is the drug acquisition cost (DAC), and the other is the patient cost, which directly affects the patient but is highly variable depending on the patient's insurance

THE ASCO VALUE FRAMEWORK: ADJUVANT SETTING

Step 1: Determine the regimen's CLINICAL BENEFIT							
1.A. Is a Hazard Ratio (HR) for death reported?	**YES.** Assign score for HR (1 through 5 as shown below) and multiply by 16. Write this number in the box labeled, "OS Score." **Proceed to 1.C.**						**OS Score**
	Score	1	2	3	4	5	
	HR for death	> 0.85	0.84-0.71	0.70-0.55	0.54-0.21	< 0.20	
	NO. Proceed to 1.B.						
1.B. If an HR for death is not reported, is Disease-Free Survival reported?	**YES.** Assign a Disease-Free Survival Score (0 through 4 as shown below) and multiply by 15. Write this number in the box labeled, "DFS Score." **Proceed to 1.C.**						**DFS Score**
	DFS Score	0	1	2	3	4	
	Improvement in median DFS (% change in DFS) **OR use HR as above**	> 0%-10% or HR > 0.85	11%-24% or HR 0.84-0.71	25%-49% or HR 0.70-0.55	50%-75% or HR 0.54-0.21	76%-≥ 100% or HR < 0.20	
1.C. Calculate the Clinical Benefit Score	Insert the OS or DFS Score. **Note: You should have EITHER an OS Score OR a DFS score, NOT BOTH.** Write the total in the box labeled "Clinical Benefit Score." The maximum allowable Clinical Benefit points are 80. **Proceed to Step 2.**						**Clinical Benefit Score**
Step 2: Determine the regimen's TOXICITY							
Calculate the Toxicity Score	For the regimens being assessed, compare the number of grade 3-5 toxicities and assign a Toxicity Score (-20 through +20 as shown below). The score will be based on the difference in toxicity between the two regimens. **If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment, subtract 5 points.** The maximum allowable Toxicity Points are 20. **Proceed to Step 3.**						**Toxicity Score**
	Toxicity Score	-20	-10	0	+10	+20	
	Does the new regimen represent an improvement in toxicity over the standard of care/comparator?	Substantially less well tolerated (75%-100% MORE grade 3-5 toxicities are reported for the new regimen.)	Less well tolerated (50%-74% MORE grade 3-5 toxicities are reported for the new regimen.)	Toxicity is the same (less than 49% MORE and up to 49% FEWER toxicities are reported for the new regimen.)	Better tolerated (50%-74% fewer grade 3-5 toxicities are reported for the new regimen.)	Substantially better tolerated (75%-100% fewer grade 3-5 toxicities are reported for the new regimen.)	
Step 3: Determine the regimen's NET HEALTH BENEFIT							
Calculate the Net Health Benefit	Add the Clinical Benefit Score (Step 1) and the Toxicity Score (Step 2). This yields a Net Health Benefit Score. Write this number in the box labeled "Net Health Benefit." The maximum points available for this score are 100. Proceed to **Step 4.**						**Net Health Benefit**
Step 4: Determine the regimen's COST							
Insert the drug acquisition cost (DAC) and patient co-pay based on how much the treatment regimen costs in total (cost per cycle × number of cycles).							**Cost of entire course of regimen:** **DAC:**_____ **Patient Co-Pay:**_____

Step 5: Summary Assessment			
Clinical Benefit	Toxicity	Net Health Benefit	Cost
/80	/20	/100	DAC:_____ Patient Payment: _____

Fig 2. ASCO Value Framework: adjuvant setting. Future versions of the framework will allow for patients weighting their preferences such that the fractional contribution of each element (clinical benefit, toxicity) can be modified, thereby individualizing the net health benefit. ASCO, American Society of Clinical Oncology; DAC, drug acquisition cost; DFS, disease-free survival; HR, hazard ratio.

benefits. For the advanced treatment (adjuvant) framework, cost information will be provided as a monthly cost of the regimen (in both DAC and patient cost). For the curative treatment (adjuvant) framework, cost information will be provided as the total cost of the treatment regimen (in both DAC and patient cost) for the standard duration of therapy. Costs for supportive care drugs required to administer the anticancer treatment (eg, antiemetics) are included in these calculations.

Summary assessment. The NHB and cost information are provided at the end of each framework as the summary assessment, with value being inferred through the relationship between NHB and the cost incurred to achieve that degree of benefit.

Application of Framework in Clinical Scenarios

We applied the framework to four clinical scenarios in which multiple trials have compared new treatment options with current standards of care: first-line treatment for metastatic non–small-cell lung cancer, treatment of advanced multiple myeloma, treatment of metastatic castration-resistant prostate cancer, and adjuvant therapy for women with human epidermal growth factor receptor 2–positive breast cancer. These scenarios were selected to demonstrate the potential utility of the approach for diverse clinical circumstances and to inform refinements to the framework. The results of our analyses are shown in Figures 3 to 6, where, for each test regimen evaluated in a prospective randomized clinical trial, the clinical benefit, relative toxicity, and magnitude of improvement in NHB for the new regimen are depicted along with the cost of the new regimen compared with that of delivering the standard-of-care treatment. Table 2 summarizes information shown in Figure 3. Similar data can be found in Appendix Tables A1 to A15 (online only).

After publication of the article, we recognized the need to acknowledge nuances in the concept of NHB. To better illustrate the derivation and utility of NHB, we analyzed a subset of the patient population reported by Scagliotti et al[42] that represents the patient population for whom the drug is intended to be used according to the drug label. This noninferiority trial that compared cisplatin/gemcitabine with cisplatin/pemetrexed included a prespecified subset analysis by histologic type. This analysis revealed an OS benefit for the pemetrexed-containing regimen in patients with nonsquamous histology. Although the analysis of the entire study population demonstrated no NHB for the test regimen (Figures 3B), the NHB of the test regimen among the patients with non-squamous disease

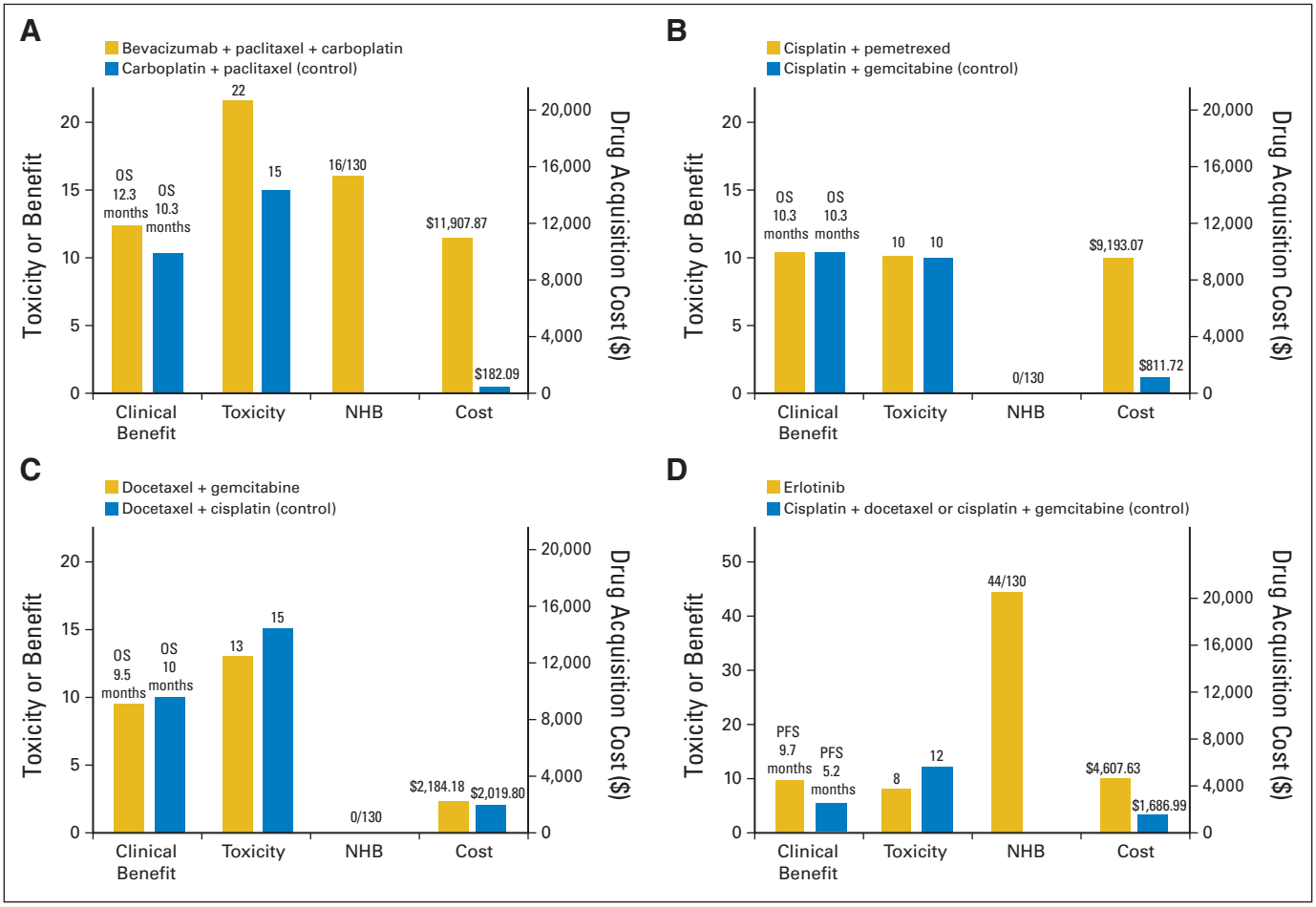

Fig 3. Clinical benefit, toxicity, net health benefit (NHB), and cost of four regimens when compared with standard-of-care regimen used in clinical trials for first-line treatment of metastatic non–small-cell lung cancer: (A) bevacizumab, paclitaxel, and carboplatin versus carboplatin plus paclitaxel (control)[41]; (B) cisplatin plus pemetrexed versus cisplatin plus gemcitabine (control)[42]; (C) docetaxel plus gemcitabine versus docetaxel plus cisplatin (control)[43]; and (D) erlotinib versus cisplatin plus docetaxel or cisplatin plus gemcitabine (control) in patients with *EGFR* mutation–positive advanced NSCLC.[44] Raw data for each parameter shown above each bar. Costs based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs[45]; shown per month of treatment. Table 2 summarizes information shown in figure. Similar data can be found in Appendix Tables A1 to A15 (online only). (A) Bevacizumab, paclitaxel, and carboplatin has overall survival (OS) of 12.3 months versus 10.3-month OS for carboplatin plus paclitaxel (control), 15 grade 3 to 5 toxicities versus 22 for control, NHB of 16 of maximum 130, and cost of $11,907.87 per month versus $182.09 per month for control. (B) Cisplatin plus pemetrexed has OS of 10.3 months versus 10.3-month OS for cisplatin plus gemcitabine (control), 10 grade 3 to 5 toxicities versus 10 for control, NHB of zero of maximum 130, and cost of $9,193.07 per month versus $811.72 per month for control. (C) Docetaxel plus gemcitabine has OS of 9.5 months versus 10.0-month OS for docetaxel plus cisplatin (control), 13 grade 3 to 5 toxicities versus 15 for control, NHB of zero of maximum 130, and cost of $2,184.18 per month versus $2,019.80 per month for control. (D) Oral erlotinib has median progression-free survival (PFS) of 9.7 months versus 5.2 months for cisplatin plus docetaxel or cisplatin plus gemcitabine (control), eight grade 3 to 5 toxicities versus 12 for control, NHB of 44 of maximum 130, and cost of $4,607.63 per month versus $1,686.99 per month for cisplatin plus docetaxel and $903.31 per month for cisplatin plus gemcitabine.

revealed an NHB of 16. This additional analysis has been included at the end of the article as an Addendum.

In keeping with the patient-specific focus of this approach to assessing value, ASCO anticipates that cost will be interpreted by the patient in the context of the NHB offered by each treatment option. ASCO acknowledges that this method of calculating the NHB does not permit assessment of the relative value of regimens that were not directly compared in clinical trials and that the observed improvement in NHB for a new regimen might be influenced by whether the comparator was best supportive care or active treatment. Nevertheless, ASCO believes this method to be one that is well grounded in the available medical evidence and provides the most objective assessment of NHB. Furthermore, it can be iterative and adaptive as new data are introduced into the clinic. Importantly, it provides physicians with a new approach for assessing the results of clinical trials: a single, standardized NHB score that takes into consideration not only the primary end point of the trial but also the relative clinical benefit and toxicity of the regimen under evaluation.

DISCUSSION

The highest priority of ASCO is making clinically meaningful progress against cancer through research and the delivery of high-quality care to all patients with cancer. As we strive to reach this goal, an essential prerequisite is achieving a rational relationship between the health benefit of an intervention and its cost (ie, its value to patient and,

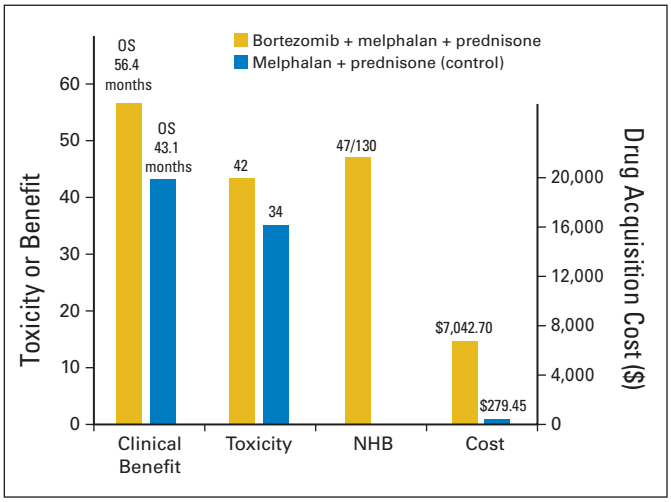

Fig 4. Clinical benefit, toxicity, net health benefit (NHB), and cost of bortezomib, melphalan, and prednisone when compared with melphalan plus prednisone (control) in clinical trial for first-line treatment of advanced multiple myeloma.[46,47] Bortezomib, melphalan, and prednisone has overall survival (OS) of 56.4 months versus 43.1-month OS for melphalan plus prednisone (control), 42 grade 3 to 5 toxicities versus 34 for control, NHB of 47 of maximum 130, and cost of $7,042.70 per month versus $279.45 per month for control. Raw data for each parameter shown above each bar. Costs based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs[45]; shown per month of treatment.

secondarily, to health care system). The value framework presented herein has been developed to assist the physician and patient in shared decision making as they work toward defining value and identifying an appropriate intervention for that individual patient. To accomplish this goal, the following issues were considered:

Importance of High-Quality Evidence

Value must be assessed using only the highest-quality evidence available. Such evidence is usually derived from prospective randomized trials published in peer-reviewed journals. The clinical end points used to assess benefit (ie, OS, PFS, DFS) and toxicity (grade) within the ASCO framework were selected because they represent those data most commonly collected in clinical trials. There is additional information that is important to patients that cannot easily be incorporated into the framework because of the lack of complete and easily accessible data, such as quality of life or patient-reported outcomes. Developing the framework illuminated how important it is that these variables be more consistently collected and reported in the future so they might be incorporated into future value assessments.

Measuring Clinical Benefit and Toxicity

Optimally, a metric reflecting clinical benefit should be transparent and easy to interpret by all stakeholders, including physicians and patients.[25] In the advanced disease framework, we chose to measure effectiveness as the incremental benefit in OS or PFS demonstrated by a new treatment compared with a prevailing standard of care in a prospective clinical trial. When survival data are not available and/or only noncomparative trials have been performed, as is increasingly the case with drugs approved under the Breakthrough Therapy designation, RR should be used to determine effectiveness until survival data become available. For the curative framework, we rely on the HR for

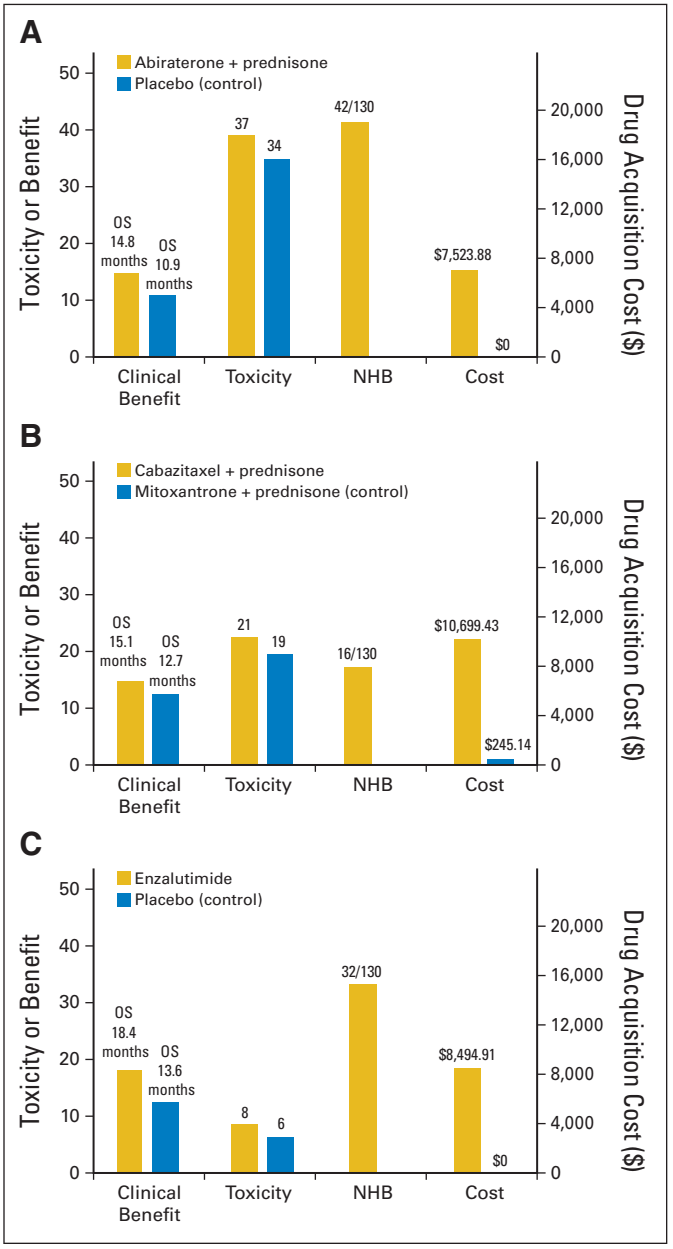

Fig 5. Clinical benefit, toxicity, net health benefit (NHB), and cost of three regimens when compared with standard-of-care regimen used in clinical trial for first-line treatment of metastatic castration-resistant prostate cancer: (A) abiraterone plus prednisone versus placebo (control),[48,49] (B) cabazitaxel plus prednisone versus mitoxantrone plus prednisone (control),[50] and (C) enzalutamide versus placebo (control).[51] Raw data for each parameter shown above each bar. Costs based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs[45]; shown per month of treatment. (A) Abiraterone plus prednisone has overall survival (OS) of 14.8 months versus 10.9-month OS for placebo (control), 37 grade 3 to 5 toxicities versus 34 for control, NHB of 42 of maximum 130, and cost of $7,523.88 per month versus $0 per month for control. (B) Cabazitaxel plus prednisone has OS of 15.1 months versus 12.7-month OS for mitoxantrone plus prednisone (control), 21 grade 3 to 5 toxicities versus 19 for control, NHB of 16 of maximum 130, and cost of $10,699.43 per month versus $245.14 per month for control. (C) Enzalutamide has overall survival (OS) of 18.4 months versus 13.6-month OS for placebo (control), eight grade 3 to 5 toxicities versus six for control, NHB of 32 of maximum 130, and cost of $8,494.91 per month versus $0 per month for control.

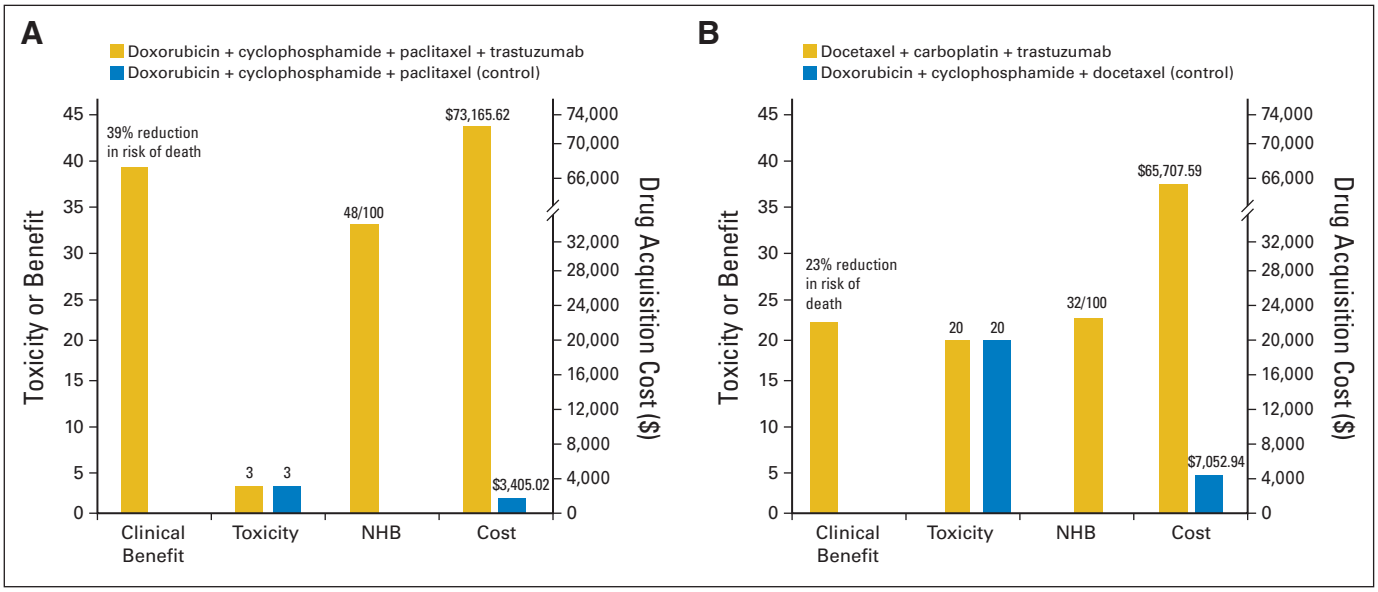

Fig 6. Clinical benefit, toxicity, net health benefit (NHB), and cost of two regimens when compared with standard-of-care regimen used in clinical trial for adjuvant treatment of human epidermal growth factor receptor 2–positive breast cancer: (A) doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab and total of 1 year of trastuzumab versus doxorubicin, cyclophosphamide, and paclitaxel (control)[52,53] and (B) docetaxel, carboplatin, and trastuzumab followed by total of 1 year of trastuzumab versus doxorubicin, cyclophosphamide, and docetaxel (control).[54] Raw data for each parameter shown above each bar. Costs based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs[45]; shown as cost of delivering entire course of regimen. (A) Doxorubicin, cyclophosphamide, and paclitaxel plus trastuzumab versus doxorubicin, cyclophosphamide, and paclitaxel (control) has hazard ratio (HR) of 0.61, or 39% reduction in risk of death, when compared with control, three grade 3 to 5 toxicities versus three for control; NHB of 48 of maximum 100, and cost of $73,165.62 versus $3,405.02 for control. (B) Docetaxel, carboplatin, and trastuzumab versus doxorubicin, cyclophosphamide, and docetaxel (control) has HR of 0.77, or 23% reduction in risk of death, when compared with control, 20 grade 3 to 5 toxicities versus 20 for control, NHB of 32 of maximum 100, and cost of $65,707.59 versus $7,052.94 for control.

OS for the comparison of the test therapy with a standard of care. If OS data are not reported, the HR for DFS is used instead.

In devising the categorical scores and weights for the clinical benefit component of the framework, the Task Force was informed by the prior work of ASCO in defining clinically meaningful outcomes for clinical trials.[55] In this effort, the ASCO Cancer Research Committee assembled working groups for four main cancer types that included patient advocates, biostatisticians, US Food and Drug Administration oncologists, and industry oncologists. It was generally agreed that relative improvements in median OS of at least 20% are necessary to define a clinically meaningful improvement in outcome. Each group identified an HR of 0.6 to 0.8, corresponding to an improvement in median OS ranging from 2.5 to 6 months, depending on the clinical context (metastatic pancreatic, non–small-cell lung, triple-negative breast, and colorectal cancers), as the minimum incremental improvement over standard therapy that would define a clinically meaningful outcome. New regimens that are substantially more toxic than current standards should be expected to produce greater increments to be meaningful. Thus, in the current framework, a point score of 3 of 5 (which would be multiplied by 16) was given to a 50% improvement in median OS.

Table 2. Bevacizumab, Carboplatin, and Paclitaxel Versus Carboplatin Versus Carboplatin Plus Paclitaxel (control; Fig 3)

Measure	Score/Result
Clinical benefit score (maximum, 180 points)	
Improvement ([12.3 − 10.3]/10.3 = 19%)	
OS score (1 × 16)	16
Toxicity score (maximum, 20 points)	
Carboplatin plus paclitaxel (control)	15 (grade 3 to 5)
Bevacizumab, carboplatin, and paclitaxel	22 (grade 3 to 5)
Toxicity score ([22 − 15]/15 = 46%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	16
Drug cost (monthly)	
Drug acquisition cost	$11,907.87
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Clinical benefit integrates assessments of quality of life as well as disease-specific treatment effectiveness. As stated, we did not find quality-of-life data or patient-reported outcomes to be end points reported in clinical trials with enough consistency or reliability to be informative in our assessment of clinical benefit. Thus, we relied on a comparison of high-grade, acute toxicity, including rates of treatment-related death, to assess the negative physical effects of treatment that detract from overall health benefit. We acknowledge that certain chronic, low-grade toxicities can be troubling to patients as well and should be incorporated into future versions of the framework if the relevant data are available.

Importantly, the weights given to clinical benefit and toxicity are based on the consensus of the framework developers and are intended to serve as a starting point. With further development and when used in shared decision making, the Task Force recommends that the patient be able to modify the importance of both clinical benefit and/or toxicity based on his or her personal values and goals. Doing so will

enable modification of the fractional contribution of each to a possible total score of 100, thereby individualizing NHB.

Palliation of Symptoms and Treatment-Free Intervals

In the advanced disease framework, the Task Force identified palliation of symptoms and treatment-free interval as two additional factors that are important in assessing treatment options. Bonus points should be offered for a regimen that has provided measureable impact on symptom palliation in the advanced disease setting and/or a significant prolongation of the treatment-free interval. The latter is presumed to be a surrogate for good health, because the disease is clinically stable, and the patient is not subject to the toxicity of therapy during the treatment-free interval.

NHB

NHB is a term that has been described in the health economics literature as the difference in mean effectiveness of a new treatment compared with a standard, adjusted for cost difference.[56] More recently, it has been defined by the Institute for Clinical and Economic Review as the balance between clinical benefits and risks and/or adverse effects and used to assess the magnitude of the difference between a therapeutic agent and its comparator.[57] We used the NHB of a treatment to express the positive impact on a disease state and the amount of toxicity a patient might experience to achieve that benefit. The Task Force elected to display the NHB as a separate calculation so that the physician and patient could view the clinical information independent of cost considerations as part of the decision-making process.

In this formulation of the framework, the NHB is derived from randomized clinical trials directly comparing two or more chemotherapy regimens studied in a clinical trial. There are at least two limitations imposed by this approach. First, the calculation of the NHB of a given regimen is valid for the therapies compared within the context of the clinical trial and not readily comparable to the NHB of other regimens determined on the basis of a different comparator regimen used in another trial. Specifically, this framework does not permit intertrial comparisons. Failure to recognize this could lead to an erroneous conclusion that a regimen with a large NHB is superior to one with a small NHB, when, in fact, the regimen with the large NHB is simply one compared with best supportive care instead of an active treatment regimen. Second, the study populations are defined by the clinical trial eligibility requirements and are unlikely to represent the general cancer population. Consequently, the patient may be basing his or her decision on the NHB calculated for patients who are not like him or her.

There is currently no valid way to compare regimens that have not been compared head to head in clinical trials. In undertaking its charge, the Task Force considered other approaches to deriving NHB, such as examining the absolute benefit of a given therapy (eg, assigning score based on absolute months of DFS or OS) instead of the relative benefit within a given trial. This approach would encourage cross-trial comparisons that could lead to spurious conclusions if the patient populations compared had different prognoses. For example, posit that treatment regimen A was administered as adjuvant chemotherapy to patients with breast cancer with zero involved axillary nodes and produced a median DFS of 92% at 5 years, whereas treatment B, administered as adjuvant chemotherapy to patients with breast cancer four to nine involved axillary nodes, produced a median DFS of 72% at 5 years. Using an absolute grading scale, regimen A is assigned a score of 4, and regimen B receives a score of 3, leading to the conclusion that regimen A produces greater clinical benefit, when, in fact, its superior outcomes might be accounted for by the better prognosis of the patient population treated.

The Task Force elected to use the relative NHB of a new treatment compared with the standard against which it was tested in a clinical trial because of the strong evidence base for such comparisons and because it will allow useful conversations between physician and patient about the value of a new therapy over an accepted standard. In the relatively near future, using aggregation of large amounts of data, it should be possible to assess the absolute benefit of different therapies based on the clinical experiences of real-world patients. One could envision an NHB calculated by measurement of patient OS, PFS, RR, and toxicities, derived from collation of data from real-world patient experiences, with these parameters measured in absolute values and not relative to a comparator arm (eg, SEER program). Assuming a large-enough database, patients could also search to match their characteristics to those of other patients as a way of predicting their personal NHB with a specific therapy. Such a model will require maintaining a large database of medical records of patients with cancer, with advanced search capability, such as that being developed for the ASCO CancerLinQ, a rapid learning system for oncology.

Calculating Cost

Cost is a key component of the value assessment. Although cost serves as the denominator of most value equations, universal agreement on the elements of cost to be included in value assessments is often a point of debate. Obtaining reliable data for all the potential dimensions of cost (eg, hospital use, emergency department use, earnings lost, travel time, childcare costs) is extremely challenging from the standpoint of data collection. In addition, many costs are difficult to anticipate when treatment decisions are being made. Therefore, we have chosen to use the cost of the drugs themselves as a readily available, although admittedly incomplete, estimate of cost. We also propose that patients receive a full explanation of their likely out-of-pocket costs based on the features of their health insurance program.

In clinical decision making between physician and patient, the direct cost to the patient is clearly paramount. ASCO also feels that oncologists should be aware of the value of an intervention in terms of societal cost. Clearly, increasing health care costs are eventually transferred to the consumers of health care, if not in the form of out-of-pocket costs, then in the form of higher insurance premiums, higher taxes, or limited wage increases as employers confront the escalating costs of providing health care to their employees.

Value Assessment

In the ASCO value framework, the cost of the treatment and the NHB are illustrated side by side to facilitate an assessment of value. ASCO believes that an understanding of the NHB and costs associated with new treatments is what our patients want and need. When considering the NHB of a treatment, patients may consider the cost they must incur to receive that treatment and make decisions in accordance with their personal goals for their health and their financial realities.

The ultimate purpose of this process is for patients to have transparent information about their treatment options so that they make more fully informed decisions. If fully realized, this would represent an individualized approach to cancer care that is consistent with provision of the best available therapy at the lowest achievable cost (ie, high-value care for each person).

Additional Considerations

In developing the framework, the Task Force elected to focus on the medical oncology setting, creating a way to assess the value of drug regimens. Ultimately, a framework such as this one could be used to assess any cancer treatment modality, and we believe such frameworks should be developed in the future.

The Task Force also chose to use an analytic method for assessing NHB using those data elements commonly collected in clinical trials and reported in the medical literature. These clinical end points were used in lieu of certain commonly employed metrics of cost effectiveness, such as QALYs, because of the limitations associated with this approach, as discussed earlier in this statement. Other methodologic limitations of using QALYs related to cancer care have been reported elsewhere.[58] A limitation of the ASCO methodology is the use of a consensus process and the somewhat arbitrary assignment of scoring categories for OS, PFS, and RR (as shown in framework) and weights based largely on expert clinical opinions. Our reliance on data derived from clinical trials, while providing a high level of evidence to our analyses, may limit their applicability to individuals who would not have qualified for trial participation. Ultimately, the framework and the methods underlying its development will need to be tested further to confirm acceptance by the oncology community, including patients.

The complexity of the value framework makes it clear that for it to eventually be used effectively in a practice setting, the information must be presented in a visually appealing, user-friendly way and acquired almost immediately. Thus, our vision entails preloading data for all regimens to be evaluated, and that of their comparators, into user-friendly software that can be used on a smart phone, tablet, or computer and integrated into the electronic medical record. The tool that is envisioned will include the key elements discussed here for clinical benefit and toxicity for the majority of commonly used cancer regimens in a variety of clinical scenarios and will permit incorporation of patient weighting preferences. For example, if, in the advanced disease setting, longevity is less important to a patient than freedom from toxicity, the tool should be able to adjust the clinical benefit and toxicity parameters to reduce the impact of clinical benefit and enhance the impact of toxicity, thereby producing a personalized NHB. The ability to modify the framework at the point of care would facilitate decision making by enabling patients to create a personalized NHB score that takes into account not only the specific clinical problem but also existing comorbidities, personal preferences, and values. In addition, access to the cost of the regimen in question and the patient's out-of-pocket costs will provide additional context to the physician and patient in determining the relative value of treatment options.

Finally, an important assumption used in developing the ASCO framework is that the relative value of a given cancer treatment is likely to change over its lifetime. It is understood that novel regimens or single agents are generally first brought into the clinic for treatment of patients with advanced-stage disease. In this context, a novel agent may provide a statistically significant improvement when compared with the standard of care, but the improvement is often measured in months, rarely in years. Thus, the NHB may be modest when a product is first introduced. However, the impact of many agents is often appreciably greater when used in an adjuvant or curative setting or when a biomarker can identify patients most likely to benefit from the treatment. In such a circumstance, the NHB associated with the agent or regimen will be enhanced greatly, and in all likelihood, its value will as well, because the cost of treatment will be juxtaposed against a far greater NHB. Clearly, the assessment of the value of any treatment

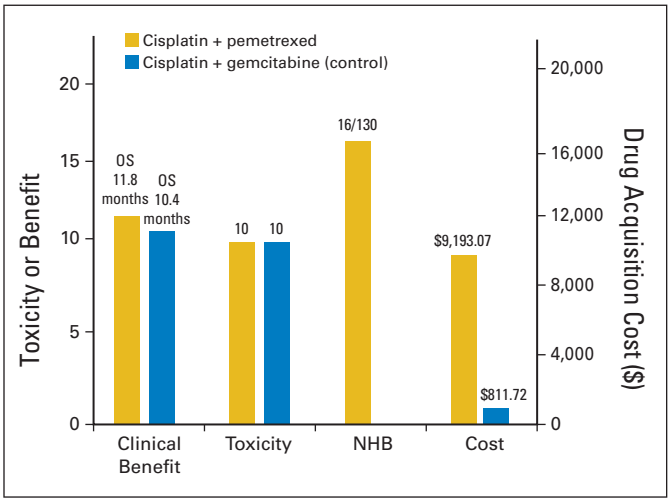

Fig 7. Clinical benefit, toxicity, net health benefit (NHB), and cost using cisplatin/pemetrexed versus cisplatin/gemcitabine (control) for first-line treatment of metastatic non–small-cell lung cancer in patients with nonsquamous histology.[42] Raw data for each parameter are shown above each bar. Cost is based on average sales price as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs[45]; shown per month of treatment. Table 3 summarizes information shown in the figure. Cisplatin/pemetrexed has an overall survival (OS) of 11.8 months versus 10.4 months for cisplatin/gemcitabine (control), 10 grade 3 to 5 toxicities versus 10 for control, NHB of 16 of a maximum of 130, and cost of $9,193.07/month versus $811.72/month for control.

Table 3. Cisplatin/Pemetrexed Versus Cisplatin/Gemcitabine (control): Nonsquamous Subgroup

Measure	Score/Result
Clinical benefit score (maximum = 80 points)	
Improvement ([11.8 − 10.4]/10.4 = 13%)	
OS score (1 × 16)	16
Toxicity score (maximum = 20 points)	
Carboplatin + paclitaxel	10 (grade 3 to 5)
Cisplatin + pemetrexed	10 (grade 3 to 5)
Toxicity score ([10 − 10]/10 = 0%)	0
Bonus points (maximum = 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
NHB (maximum = 130 points)	16
Drug cost (monthly)	
DAC	$9,193.07
Patient copay	Calculated per patient

Abbreviations: DAC, drug acquisition cost; NHB, net health benefit; OS, overall survival.

must be dynamic and adapt to new medical information that may better inform its use, mitigate its toxicity, or modify its place in the treatment landscape.

CALL FOR COMMUNITY COMMENT

We appreciate that developing a method for establishing value of specific cancer treatment regimens is a daunting task. ASCO views this as an iterative process and encourages comments from all interested parties regarding the elements we have included in the value framework and its utility in facilitating discussion between providers and patients on the value of available treatment options. Comments may be submitted through August 21, 2015, at www.asco.org/value.

On the basis of these comments, ASCO envisions publishing additional iterations of the framework, practical applications, recommendations regarding the additional evidence needed to develop the most useful value tools, and more detailed examinations of value in these and other disease states.

Addendum

As noted in the Application of Framework in Clinical Scenarios section, after publication, we recognized the need to acknowledge nuances in the concept of NHB. To better illustrate the derivation and utility of NHB, we analyzed a subset of the patient population reported by Scagliotti et al[42] that represents the patient population for whom the drug is intended to be used according to the drug label. These investigators reported results of a prospective, randomized, phase III clinical trial designed as a noninferiority study to compare cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with locally advanced or metastatic NSCLC. The design included a prespecified test for a treatment-by-histology interaction. The study results demonstrated that cisplatin/pemetrexed was, in fact, not inferior to cisplatin/gemcitabine in the overall study population. However, in the analysis of treatment-by-histology, OS was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients in the nonsquamous subgroup (n = 1,000; 11.8 v 10.4 months, respectively). Accordingly, the US Food and Drug Administration–approved product label for pemetrexed prescribing in NSCLC is for use in patients with nonsquamous histology.

The results of our analysis for this group of patients are shown in Figure 7 and Table 3. For this intended-use population, the pemetrexed/cisplatin regimen received an NHB score of 16. This analysis demonstrates several important features of the framework. First, it identified a treatment that was demonstrated to be noninferior to an existing standard and with similar toxicity as having an NHB of 0, meaning that no incremental benefit could be identified for this regimen over the standard regimen to which it was compared in the overall study population. Second, the framework is intended to be used as a discussion guide between doctors and patients and not as a substitute for physician knowledge or judgment. Indeed, experienced oncologists are well aware of the approved use of pemetrexed only in patients with nonsquamous histology NSCLC, and would likely realize its value in this patient population. Limiting our analysis of the trial by Scagliotti et al[42] to this patient population clearly indicates the NHB associated with this regimen.

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Disclosures provided by the authors are available with this article at www.jco.org.

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Appendix

Table A1. First-Line Systemic Therapy for Metastatic Non–Small-Cell Lung Cancer (Fig 3)

Regimen	OS (months)	PFS (months)	RR (CR plus PR)	Palliation Data	Time to Next Treatment (months)	Reported Toxicity	Monthly Cost of Treatment (drug only)
Fig 3A							
Carboplatin plus paclitaxel (standard of care)[41]*	10.3	4.5	15% (separate CR and PR data not reported)	—	—	Grade 3: epistaxis, 0.2%; febrile neutropenia, 1.8%; headache, 0.5%; hemoptysis, 0.2%; hypertension, 0.5%; hyponatremia, 0.9%; melena/GI bleeding, 0.2%; rash/desquamation, 0.5% Grade 4: anemia, 0.9%; hypertension, 0.2%; hyponatremia, 0.2%; neutropenia, 16.8%; thrombocytopenia, 0.2% Grade 5: febrile neutropenia, 0.2%; melena/GI bleeding, 0.2%	Carboplatin plus paclitaxel, $161.50; antiemetics, $20.59; regimen cost, $182.09
Bevacizumab, carboplatin, and paclitaxel[41]†	12.3	6.2	35% (separate CR and PR data not reported)	—	—	Grade 3: epistaxis, 0.7%; febrile neutropenia, 4.0%; headache, 3.0%; hemoptysis, 0.5%; hypertension, 6.8%; hyponatremia, 2.6%; proteinuria, 2.6%; melena/GI bleeding, 0.7%; other hemorrhage, 0.2%; rash/desquamation, 2.3% Grade 4: CNS hemorrhage, 0.7%; hemoptysis, 0.2%; hypertension, 0.2%; hyponatremia, 0.9%; melena/GI bleeding, 0.2%; neutropenia, 25.5%; other hemorrhage, 0.2%; proteinuria, 0.5%; thrombocytopenia, 1.6% Grade 5: febrile neutropenia, 1.2%; hematemesis, 0.5%; hemoptysis, 1.2%	Bevacizumab, carboplatin, and paclitaxel, $11,887.28; antiemetics, $20.59; regimen cost, $11,907.87
Fig 3B							
Cisplatin plus gemcitabine (standard of care)[42]‡	10.3	5.1	—	—	—	Grade 3/4: alopecia (any grade), 21.4%; anemia, 9.9%; dehydration (any grade), 2.0%; fatigue, 4.9%; febrile neutropenia, 3.7%; leukopenia, 7.6%; nausea, 3.9%; neutropenia, 26.7%; thrombocytopenia, 12.7%; vomiting, 6.1%	Cisplatin plus gemcitabine, $158.32; antiemetics, $653.40; regimen cost, $811.72
Cisplatin plus pemetrexed[42]§	10.3	4.8	—	—	—	Grade 3/4: alopecia (any grade), 11.9%; anemia, 5.6%; dehydration (any grade), 3.6%: fatigue, 6.7%; leukopenia, 4.8%; febrile neutropenia, 1.3%; nausea, 7.2%; neutropenia, 15.1%; thrombocytopenia, 4.1%; vomiting, 6.1%	Cisplatin plus pemetrexed, $8,539.68; antiemetics, $653.40; regimen cost, $9,193.07

(continued on following page)

Table A1. First-Line Systemic Therapy for Metastatic Non–Small-Cell Lung Cancer (Fig 3) (continued)

Regimen	OS (months)	PFS (months)	RR (CR plus PR)	Palliation Data	Time to Next Treatment (months)	Reported Toxicity	Monthly Cost of Treatment (drug only)
Fig 3C							
Docetaxel plus cisplatin (control)[43]‖	10.0	8.0	ORR, 35%	—	—	Grade 3: anemia, 5.0%; asthenia, 6.0%; constipation, 1.0%; diarrhea, 8.0%; neutropenia, 13.0%; thrombocytopenia, 2.0%; mucositis, 1.0%; nausea/vomiting, 10.0%; neurotoxicity, 1.0% Grade 4: asthenia, 1.0%; constipation, 1.0%; diarrhea, 2.0%; mucositis, 1.0%; neurotoxicity, 1.0%; neutropenia, 21.0%	Docetaxel plus cisplatin, $1,366.40; antiemetics, $653.40; regimen cost, $2,019.80
Docetaxel plus gemcitabine[43]¶	9.5	9.0	ORR, 33%	—	—	Grade 3: anemia, 1.0%; asthenia, 5.0%; diarrhea, 2.0%; nausea/vomiting, 2.0%; neurotoxicity, 2.0%; neutropenia, 11.0%; thrombycytopenia, 2.0% Grade 4: anemia, 1.0%; asthenia, 1.0%; diarrhea, 1.0%; neurotoxicity, 1.0%; neutropenia, 11.0%; thrombocytopenia, 2.0%	Gemcitabine plus docetaxel, $1,530.78; antiemetics, $653.40; regimen cost, $2,184.18
Fig 3D							
Cisplatin plus docetaxel or cisplatin plus gemcitabine (control)[44]#	—	5.2	—	—	—	Grade 3: alopecia, 2%; anemia, 4%; appetite loss, 2%; arthralgia, 1%; fatigue, 20%; febrile neutropenia, 1%; neuropathy, 1%; neutropenia, 15%; pneumonitis, 1%; thrombocytopenia, 7% Grade 4: febrile neutropenia, 2%; neutropenia, 7%; thrombocytopenia, 7%	Cisplatin plus docetaxel, $1,033.61; antiemetics, $653.38; regimen cost, $1,686.99 Cisplatin plus gemcitabine, $249.93; antiemetics, $653.38; regimen cost, $903.31
Oral erlotinib (150 mg per day)[44]	—	9.7	—	—	—	Grade 3: aminotransferase rise, 2%; arthralgia, 1%; diarrhea, 5%; fatigue, 6%; pneumonitis, 1%; rash, 13% Grade 4: anemia, 1%; neuropathy, 1%	Erlotinib: $4,607.63; antiemetics, $0; regimen cost, $4,607.63

Abbreviations: AUC, area under the curve; CR, complete response; IV, intravenous; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

*Carboplatin AUC 6 IV over 30 minutes after paclitaxel on day 1 every 21 days; paclitaxel 200 mg/m^2 IV over 3 hours on day 1 every 21 days.

†Bevacizumab 15 mg/kg on day 1 every 21 days; carboplatin AUC 6 IV over 30 minutes after paclitaxel on day 1 every 21 days; paclitaxel 200 mg/m^2 IV over 3 hours on day 1 every 21 days.

‡Cisplatin 75 mg/m^2 on day 1; gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks.

§Cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 on day 1 every 3 weeks for up to six cycles.

‖Docetaxel 100 mg/m^2 on day 1 and cisplatin 80 mg/m^2 on day 2 for 3 weeks.

¶Gemcitabine 1,100 mg/m^2 on days 1 and 8 and docetaxel 100 g/m^2 on day 8 for 3 weeks.

#Three-week cycles of standard IV chemotherapy consisting of cisplatin 75 mg/m^2 on day 1 plus docetaxel 75 mg/m^2 on day 1 or gemcitabine 1,250 mg/m^2 on days 1 and 8.

Table A2. Carboplatin Plus Paclitaxel (standard of care) Versus Bevacizumab, Carboplatin, and Paclitaxel (Fig 3A)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([12.3 − 10.3]/10.3 = 19%	
OS score (1 × 16)	16
Toxicity score (maximum, 20 points)	
Carboplatin plus paclitaxel (control)	15 (grade 3 to 5)
Bevacizumab, carboplatin, and paclitaxel	22 (grade 3 to 5)
Toxicity score ([22 − 15]/15 = 47%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	16
Drug cost (monthly)	
Drug acquisition cost	$11,907.87
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A3. Cisplatin Pemetrexed Versus Cisplatin Gemcitabine (control; Fig 3B)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([10.3 − 10.3]/10.3 = 0%)	
OS score (0 × 16)	0
Toxicity score (maximum, 20 points)	
Cisplatin plus gemcitabine	10 (grade 3 to 5)
Cisplatin plus pemetrexed	10 (grade 3 to 5)
Toxicity score ([10 − 10]/10 = 0%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	0
Drug cost (monthly)	
Drug acquisition cost	$9,193.07
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A4. Docetaxel Plus Gemcitabine Versus Docetaxel Plus Cisplatin (control; Fig 3C)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([9.5 − 10]/10 = −5%)	
OS score (0 × 16)	0
Toxicity score (maximum, 20 points)	
Docetaxel plus cisplatin	15 (grade 3 to 5)
Docetaxel plus gemcitabine	13 (grade 3 to 5)
Toxicity score ([15 − 13]/15 = 13%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	0
Drug cost (monthly)	
Drug acquisition cost	$2,184.18
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A5. Oral Erlotinib Versus Cisplatin Plus Docetaxel or Cisplatin Plus Gemcitabine (control; Fig 3D)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([9.7 − 5.2]/5.2 = 87%)	
PFS score (4 × 11)	44
Toxicity score (maximum, 20 points)	
Erlotinib	8 (grade 3 to 5)
Cisplatin, docetaxel, and gemcitabine	12 (grade 3 to 5)
Toxicity score ([12 − 8]/8 = 33%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	44
Drug cost (monthly)	
Drug acquisition cost	$4,607.63
Patient copay	Calculated per patient

Abbreviation: PFS, progression-free survival.

Table A6. Advanced Multiple Myeloma (Fig 4)

Regimen	Median OS (months)	PFS (months)	RR (CR plus PR)	Palliation Data	Time to Next Treatment (months)	Reported Toxicity	Monthly Cost of Treatment (drug only)
Melphalan plus prednisone (control)[46,47]*	43.1	16.6 (reported as time to progression)[46]	35%	—	20.5	Grade 3: anemia, 20.0%; anorexia, 1.0%; arthralgia, 1.0%; asthenia, 3.0%; back pain, 3.0%; cough, 1.0%; diarrhea, 1.0%; dizziness, < 1.0%; DVT, 1.0%; dyspnea, 1.0%; fatigue, 2.0%; herpes zoster, 2.0%; hypokalemia, 2.0%; leukopenia, 16.0%; lymphopenia, 9.0%; nausea, < 1.0%; neuralgia, < 1.0%; neutropenia, 23.0%; pneumonia, 4.0%; pyrexia, 2.0%; rash, < 1.0%; thrombocytopenia, 16.0%; vomiting, 1.0% Grade 4: anemia, 8.0%; arthralgia, < 1.0%; back pain, < 1.0%; dyspnea, 1.0%; hypokalemia, 1.0%; leukopenia, 4.0%; lymphopenia, 2.0%; neutropenia, 15.0%; pneumonia, 1.0%; pyrexia, 1.0%; thrombocytopenia, 14.0%	Melphalan plus prednisone, $279.45; antiemetics, $0; regimen cost, $279.45
Bortezomib, melphalan, and prednisone[46,47]†	56.4	24 (reported as time to progression)	71%	—	30.7; HR, 0.557	Grade 3: anemia, 16.0%; anorexia, 3.0%; arthralgia, 1.0%; asthenia, 6.0%; DVT, 1.0%; back pain, 3.0%; constipation, 1.0%; diarrhea, 7.0%; dizziness, 2.0%; dyspnea, 3.0%; fatigue, 7.0%; herpes zoster, 3.0%; hypokalemia, 6.0%; insomnia, < 1.0%; leukopenia, 20.0%; lymphopenia, 14.0%; nausea, 4.0%; neuralgia, 8.0%; neutropenia, 30.0%; peripheral edema, 1.0%; peripheral sensory neuropathy, 13.0%; pneumonia, 5.0%; pyrexia, 2.0%; rash, 1.0%; thrombocytopenia, 20.0%; vomiting, 4.0% Grade 4: anemia, 3.0%; anorexia, < 1.0%; asthenia, < 1.0%; back pain, < 1.0%; diarrhea, 1.0%; dyspnea, 1.0%; fatigue, 1.0%; hypokalemia, 1.0%; leukopenia, 3.0%; lymphopenia, 5.0%; neuralgia, 1.0%; neutropenia, 10.0%; peripheral sensory neuropathy, < 1.0%; pneumonia, 2.0%; pyrexia, 1.0%; thrombocytopenia, 17.0%[46]	Bortezomib, melphalan, and prednisone, $7,042.70; antiemetics, $0; regimen cost, $7,042.70

Abbreviations: CR, complete response; DVT, deep vein thrombosis; HR, hazard ratio; IV, intravenous; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.

*Melphalan 9 mg/m^2 of body-surface area orally on days 1 to 4 every 6 weeks; prednisone 60 mg/m^2 orally on days 1 to 4 every 6 weeks.

†Melphalan 9 mg/m^2 orally on days 1 to 4 every 6 weeks; prednisone 60 mg/m^2 orally on days 1 to 4 every 6 weeks; bortezomib 1.3 mg/m^2 IV bolus on day 8 for first four cycles and day 5 for cycles five to nine.

Table A7. Bortezomib, Melphalan, and Prednisone Versus Melphalan Plus Prednisone (control; Fig 4)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([56.4 − 43.1]/43.1 = 31%)	
OS score (2 × 16)	32
Toxicity score (maximum, 20 points)	
Melphalan plus prednisone	34 (grade 3 to 5)
Bortezomib, melphalan, and prednisone	42 (grade 3 to 5)
Toxicity score (42 − 34/34 = 24%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	15
Total bonus points	15
Net health benefit (maximum, 130 points)	47
Drug cost (monthly)	
Drug acquisition cost	$7,042.70
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A8. Metastatic Castration-Resistant Prostate Cancer (Fig 5)

Regimen	OS (months)	PFS (months)	Response Rate (CR + PR)	Palliation Data	Time to Next Treatment (months)	Reported Toxicity	Monthly Cost of Treatment (drug only)
Fig 5A							
Placebo (control)[48,49]	10.9	3.6	3%	28.8% of patients experienced palliation of pain; 38% experienced palliation of pain interference[49]	—	Grade 3: abdominal pain, 2.0%; anemia, 6.0%; arthralgia, 4.0%; asthenia, 2.0%; back pain, 9.0%; bone pain, 6.0%; cardiac disorder, 2.0%; constipation, 1.0%; diarrhea, 1.0%; dyspnea, 2.0%; fatigue, 9.0%; fluid retention/edema, 1.0%; hematuria, 2.0%; hypertension, < 1.0%; hypokalemia, 1.0%; liver function test abnormality, 3.0%; nausea, 3.0%; pain, 2.0%; neutropenia, < 1.0%; pain in arm or leg, 5.0%; pyrexia, 1.0%; thrombocytopenia, < 1.0%; urinary tract infection, < 1.0%; vomiting, 3.0% Grade 4: anemia, 2.0%; asthenia, < 1.0%; back pain, < 1.0%; bone pain, 1.0%; cardiac disorder, < 1.0%; dyspnea, < 1.0%; fatigue, 1.0%; liver function test abnormality, < 1.0%; pain, < 1.0%; thrombocytopenia, < 1.0%	$0
Abiraterone plus prednisone[48,49*]	14.8	5.6	14%	45% of patients experienced palliation of pain; 60% experienced palliation of pain interference[49]	—	Grade 3: abdominal pain, 2.0%; anemia, 6.0%; arthralgia, 4.0%; asthenia, 2.0%; back pain, 6.0%; bone pain, 5.0%; cardiac disorder, 3.0%; constipation, 1.0%; diarrhea, 1.0%; dyspnea, 1.0%; fatigue, 8.0%; fluid retention/edema, 2.0%; hematuria, 1.0%; hypertension, 1.0%; hypokalemia, 3.0%; liver function test abnormality, 3.0%; nausea, 2.0%; neutropenia, < 1.0%; pain, 1.0%; pain in arm or leg, 2.0%; pyrexia, < 1.0%; thrombocytopenia, 1.0%; urinary tract infection, 2.0%; vomiting, 2.0% Grade 4: anemia, 1.0%; back pain, < 1.0%; bone pain, < 1.0%; cardiac disorder, 1.0%; dyspnea, < 1.0%; fatigue, < 1.0%; fluid retention/edema, < 1.0%; hypokalemia, < 1.0%; liver function test abnormality, < 1.0%; nausea, < 1.0%; pain in arm or leg, < 1.0%; thrombocytopenia, < 1.0%; vomiting, < 1.0%	Abiraterone plus prednisone, $7,523.88; antiemetics, $0; regimen cost, $7,523.88

(continued on following page)

Table A8. Metastatic Castration-Resistant Prostate Cancer (Fig 5) (continued)

Regimen	OS (months)	PFS (months)	Response Rate (CR + PR)	Palliation Data	Time to Next Treatment (months)	Reported Toxicity	Monthly Cost of Treatment (drug only)
Fig 5B							
Mitoxantrone plus prednisone (control)[50]†	12.7	1.4	4.4% (CR, PR not defined)	—	—	Grade 3 to 5: anemia, 5.0%; arthralgia, 1.0%; asthenia, 2.0%; back pain, 3.0%; bone pain, 2.0%; constipation, 1.0%; diarrhea, < 1.0%; dyspnea, 1.0%; fatigue, 3.0%; febrile neutropenia, 1.0%; hematuria, 1.0%; leukopenia, 42.0%; nausea, < 1.0%; neutropenia, 58.0%; pain, 2.0%; pain in extremeity, 1.0%; pyrexia, < 1.0%; thrombocytopenia, 2.0%; urinary tract infection, 1.0%	Mitoxantrone plus prednisone, $243.03; antiemetics, $2.11; regimen cost, $245.14
Cabazitaxel plus prednisone[50]‡	15.1	2.8	14.4% (CR, PR not defined)	—	—	Grade 3 to 5: abdominal pain, 2.0%; anemia, 11.0%; arthralgia, 1.0%; asthenia, 5.0%; back pain, 4.0%; bone pain, 1.0%; constipation, 1.0%; diarrhea, 6.0%; dyspnea, 1.0%; fatigue, 5.0%; febrile neutropenia, 8.0%; hematuria, 2.0%; leukopenia, 68.0%; nausea, 2.0%; neutropenia, 82.0%; pain, 1.0%; pain in extremity, 2.0%; pyrexia, 1.0%; thrombocytopenia, 4.0%; urinary tract infection, 1.0%; vomiting, 2.0%	Cabazitaxel plus prednisone, $10,697.32; antiemetics, $2.11; regimen cost, $10,699.43
Fig 5C							
Placebo (control)[51]	13.6	2.9	4% (soft tissue RR)	—	—	Grade 3/4: abnormal liver function testing, < 1.0%; cardiac disorder, 2.0%; diarrhea, < 1.0%; fatigue, 7.0%; musculoskeletal pain, < 1.0%; myocardial infarction, < 1.0%	$0
Enzalutamide (160 mg per day orally)[51]	18.4	8.3	29% (soft tissue RR)	—	—	Grade 3/4: abnormal liver function testing, < 1.0%; cardiac disorder, 1.0%; diarrhea, 1.0%; fatigue, 6.0%; headache, < 1.0%; musculoskeletal pain, 1.0%; myocardial infarction, < 1.0%; seizure, < 1.0%	Enzalutamide: $8493.33; antiemetics, $1.58; regimen cost, $8,494.91

Abbreviations: CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; RR, response rate.
*Abiraterone 1,000 mg orally daily for 28 days; prednisone 5 mg orally twice per day for 28 days.
†Mitoxantrone 12 mg/m^2 and prednisone 10 mg orally once per day for 3 weeks.
‡Cabazitaxel 25 mg/m^2 once every 3 weeks (1-hour infusion on day 1 every 21 days); prednisone 10 mg orally once per day.

Table A9. Abiraterone Plus Prednisone Versus Placebo (control; Fig 5A)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([14.8 − 10.9]/10.9 = 36%)	
OS score (2 × 16)	32
Toxicity score (maximum, 20 points)	
Placebo	34 (grade 3 to 5)
Abiraterone plus prednisone	37 (grade 3 to 5)
Toxicity score ([37 − 34]/34 = 9%)	0
Bonus points (maximum, 30 points)	
Palliation	10
Treatment-free interval	0
Total bonus points	10
Net health benefit (maximum, 130 points)	42
Drug cost (monthly)	
Drug acquisition cost	$7,523.88
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A10. Cabazitaxel Plus Prednisone Versus Mitoxantrone Plus Prednisone (control; Fig 5B)

Measure	Score/Result
Clinical benefit score (maximum, 80 patients)	
Improvement ([15.1 − 12.7]/12.7 = 19%)	
OS score (1 × 6)	16
Toxicity score (maximum, 20 points)	
Mitoxantrone plus prednisone	19 (grade 3 to 5)
Cabazitaxel plus prednisone	21 (grade 3 to 5)
Toxicity score ([21 − 19]/19 = 11%)	0
Bonus points (maximum, 80 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	16
Drug cost (monthly)	
Drug acquisition cost	$10,699.43
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A11. Enzalutamide Versus Placebo (control; Fig 5C)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Improvement ([18.4 − 13.6]/13.6 = 35%)	
OS score (2 × 16)	32
Toxicity score (maximum, 20 points)	
Placebo	6 (grade 3 to 5)
Enzalutamide	8 (grade 3 to 5)
Toxicity score ([8 − 6]/6 = 33%)	0
Bonus points (maximum, 30 points)	
Palliation	0
Treatment-free interval	0
Total bonus points	0
Net health benefit (maximum, 130 points)	32
Drug cost (monthly)	
Drug acquisition cost	$8,494.91
Patient copay	Calculated per patient

Abbreviation: OS, overall survival.

Table A12. Adjuvant Treatment of HER2-Positive Breast Cancer (Fig 6)

Regimen	Median OS (months)	DFS (months)	Reported Toxicity	Total Regimen Cost (drug only)
Fig 6A				
Doxorubicin, cyclophosphamide, and paclitaxel (control)[52]*	Not reached	—	NYHA class III or IV CHF or death resulting from cardiac causes, 0.8%[52]; severe CHF, 0.0%; symptomatic CHF, 0.1%[53]	Doxorubicin plus cyclophosphamide, $3,175.82; paclitaxel, $229.20; antiemetics, $0; regimen cost, $3,405.02
Doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab[52,53]†	Not reached; HR, 0.61	HR, 0.52	NYHA class III or IV CHF or death resulting from cardiac causes, 4.1%; severe CHF, 0.8%; symptomatic CHF, 1.9%	Doxorubicin plus cyclophosphamide, $3,175.82; paclitaxel plus trastuzumab, $17,103.00; trastuzumab, $52,546.13; antiemetics, $340.66; regimen cost, $73,165.62
Fig 6B				
Doxorubicin, cyclophosphamide, and docetaxel (control)[54]‡	Not reached	75%	Grade 3/4: anemia, 2.4%; arthralgia, 3.2%; creatinine elevation, 0.6%; diarrhea, 3.0%; fatigue, 7.0%; febrile neutropenia, 9.3%; hand-foot syndrome, 1.9%; irregular menses, 27.0%; leukemia, 0.6%; leukopenia, 51.8%; motor neuropathy, 5.2%; myalgia, 5.2%; nail changes (any grade), 49.3%; nausea, 5.9%; neutropenia, 63.3%; neutropenic infection, 11.1%; sensory neuropathy, 48.6%; stomatitis, 3.5%; thrombocytopenia, 1.6%; vomiting, 6.2%	Doxorubicin, cyclophosphamide, $3,175.82; docetaxel, $3,877.63; antiemetics, $0; regimen cost, $7,052.94
Carboplatin, docetaxel, and trastuzumab[54]§	Not reached; HR, 0.77	81% (control); HR, 75%	Grade 3/4: anemia, 5.8%; arthralgia, 1.4%; creatinine elevation, 0.1%; diarrhea, 5.4%; fatigue, 7.2%; febrile neutropenia, 9.6%; irregular menses, 26.5%; leukemia, 0.1%; leukopenia, 48.2%; motor neuropathy, 4.3%; myalgia, 1.8%; nail changes (any grade), 28.7%; nausea, 4.8%; neutropenia, 65.9%; neutropenic infection, 11.2%; renal failure, 0.1%; sensory neuropathy, 36.0%; stomatitis, 1.4%; thrombocytopenia, 6.1%; vomiting, 3.5%	Carboplatin, docetaxel, and trastuzumab, $21,228.22; trastuzumab, $44,462.11; antiemetics, $17.27; regimen cost, $65,707.59

Abbreviations: AUC, area under the curve; CHF, congestive heart failure; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IV, intravenous; NYHA, New York Heart Association; OS, overall survival.

*Doxorubicin 60 mg/m^2 via IV push and cyclophosphamide 600 mg/m^2 over 30 to 45 minutes every 21 days for four cycles, followed by 12 weekly doses of paclitaxel 80 mg/m^2 over 60 minutes.

†Same as (*) dosing, followed by trastuzumab (loading dose of 4 mg/kg over 90 minutes, then 12 weekly doses of 2 mg/kg over 30 minutes, then 6 mg/kg every 3 weeks for 39 weeks).

‡Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles, followed by docetaxel 100 mg/m^2 every 3 weeks for four doses.

§Docetaxel 75 mg/m^2 over 60 minutes plus carboplatin 6 AUC over 60 minutes, followed by trastuzumab (loading dose of 4 mg/m^2 over 90 minutes, then 2 mg/m^2 over 30 minutes on days 8 and 15), followed by trastuzumab (6 mg/kg over 30 minutes) every 3 weeks for 13 weeks.

Table A13. Doxorubicin, Cyclophosphamide, Paclitaxel, and Trastuzumab Versus Doxorubicin, Cyclophosphamide, and Paclitaxel (control; Fig 6A)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Hazard ratio	0.61
Hazard ratio score	3
Benefit score (3 × 16)	48
Toxicity score (maximum, 20 points)	
Doxorubicin, cyclophosphamide, and paclitaxel	3 (grade 3 to 5)
Doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab	3 (grade 3 to 5)
Toxicity score ([3 − 3]/3 = 0%)	0
Net health benefit (maximum, 100 points)	48
Drug cost (regimen)	
Drug acquisition cost	$73,165.62
Patient copay	Calculated per patient

Table A14. Carboplatin, Docetaxel, and Trastuzumab Versus Doxorubicin, Cyclophosphamide, and Docetaxel (control; Fig 6B)

Measure	Score/Result
Clinical benefit score (maximum, 80 points)	
Hazard ratio	0.77
Hazard ratio score	2
Benefit score (2 × 16)	32
Toxicity score (maximum, 20 points)	
Doxorubicin, cyclophosphamide, and docetaxel	20 (grade 3 to 5)
Carboplatin, docetaxel, and trastuzumab	20 (grade 3 to 5)
Toxicity score ([20 − 20]/20 = 0%)	0
Net health benefit (maximum, 100 points)	32
Drug cost (regimen)	
Drug acquisition cost	$65,707.59
Patient copay	Calculated per patient

Table A15. Average Body-Surface Area Measurements

Sex	Body-Surface Area (m^2)	Weight (kg)	Height (cm)
Men	2.08		
Women	1.83		
Average of men and women	1.96	81.5	169.25

NOTE. Dosing information for each clinical case scenario was calculated based on average body-surface area measurements as defined by National Center for Health Statistics mean weight and height for men and women age ≥ 20 years.