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ASCO SPECIAL ARTICLE

Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received

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INTRODUCTION

The mission of American Society of Clinical Oncology (ASCO) is to conquer cancer through research, education, and promotion of the highest quality patient care. Toward fulfillment of this goal and at the direction of its board of directors, the ASCO Value in Cancer Care Task Force set out to develop a framework that would enable a physician and patient to assess the value of a particular cancer treatment regimen given the patient's individual preferences and circumstances. The rationale that served as the impetus for this initiative is many faceted.

Substantial progress has been made in translating our knowledge of the biologic characteristics of cancer into novel therapies. Some of these therapies have led to major improvements in outcomes for specific diseases, and others have produced only modest advances. There is now a wide array of choices for treating many cancer types, and these treatment choices often differ by only small degrees in clinical effectiveness and toxicity. Yet, there is often a wide disparity in cost to patients and payers. Because patients are often confronted with enormous expenses when receiving cancer care, the goal of describing a relationship between the cost of an agent or regimen and the clinical benefits it delivers takes on great importance. As the primary advisor to the patient, the oncologist has an important role in providing a comparative assessment of the various treatment options available; in the spirit of shared decision making, the patient should have transparent information about the clinical impact that can be expected from the different options presented and their relative financial implications.

The value framework[1] has been constructed as a conceptual model that incorporates the elements of clinical benefit, toxicity, and symptom palliation as derived from a comparative clinical trial and combines these elements into a score termed the net health benefit (NHB). Ultimately, deployment of the framework as a software application is planned, enabling a patient to modify the weight attributed to any of the elements included in the NHB depending on his or her personal preferences and circumstances. The final NHB will therefore reflect the priorities that are most important to the patient and will be arrived at through guidance from the physician. Information on the cost of the regimens will also be presented so the patient can consider the relative financial impact of his or her treatment options. Two versions of the framework have been created: one for advanced disease and the other for potentially curable (adjuvant therapy) clinical presentations. The original framework versions are shown in Appendix Tables A1 and A2 (online only).

The key elements included in the framework—namely, clinical benefit and toxicity—are also those that are regularly reported in the scientific literature when discussing the outcome of a clinical trial that compares two or more therapies. The importance of relying on high-quality, quantifiable evidence cannot be overstated, and this is most often provided by a well-designed, well-conducted prospective randomized trial. The task force recognizes that a limitation of this approach is that it does not readily permit cross-trial comparisons. Such analyses are important to patients and remain a goal for future versions of the value framework.

The task force is well aware that there are many elements that might be important to individual patients in assessing the relative value of their treatment options that are not taken into account in our model. These include the convenience of receiving therapy, the avoidance of interrupting the flow of activities of daily living, and the impact of a treatment on quality of life

(QoL) and the ability to achieve personal and professional goals. These are domains that could be measured under the broad rubric of patient-reported outcomes (PROs). Much work is needed to develop reliable assessments and consistent use of PROs, both within clinical trials and as part of routine clinical care. Future versions of the framework will recognize these when they are evidence based and thereby facilitate incorporation of PROs into the determination of the NHB of a treatment.

ASCO sought feedback on the conceptual value framework from a wide array of stakeholders to ensure that future iterations would more effectively meet the needs of practicing oncologists and their patients. After publication of the framework in June 2015 in *Journal of Clinical Oncology*,[1] ASCO received more than 400 responses during the 60-day public comment period that followed. The majority of feedback was submitted via a Web-based survey. Individual physicians and scientists responded, as did a variety of stakeholders, with the majority being patient advocacy groups, individual health care providers, and members of the pharmaceutical industry. The majority of respondents agreed with the need for a formal approach to define the value of cancer treatments and supported the development of a tool to facilitate one-on-one discussions with patients regarding the relative value of various treatment options. Respondents also provided specific suggestions for strengthening the framework or identified concerns with the approach. The issues that were raised and the suggestions offered can be aggregated by themes. Here we summarize these themes and present a number of revisions we have made to the framework based on the input received. The revised versions of the framework can be found in Figures 1 (advanced disease setting) and 2 (adjuvant setting).

Step 1: Determine the regimen's CLINICAL BENEFIT		
1.A. Is hazard ratio (HR) for death reported?	**YES.** Assign an HR Score for death by subtracting the HR from 1, and then multiplying the result by 100. Write this number in the box labeled "HR Score (death)." **Proceed to 1.F.**	**HR Score (death)**
	No. Proceed to 1B.	
1.B. If HR for death is not reported, is median overall survival (OS) reported?	**YES.** Assign an OS Score by calculating the percentage (ie, fractional) difference in median overall survival between the two regimens and multiply the result by 100. Write this number in the box labeled "OS Score." **Proceed to 1.F.**	**OS Score**
	NO. Proceed to 1.C.	
1.C. If OS data are not reported, is hazard ratio (HR) for disease progression reported?	**YES.** Assign an HR Score for disease progression by subtracting the HR from 1, multiplying the result by 100, and then multiplying this number by 0.8. Write this number in the box labeled "HR Score (progression)." **Proceed to 1.F.**	**HR Score (progression)**
	NO. Proceed to 1.D.	
1.D. If HR for disease progression is not reported, is median progression-free survival (PFS) reported?	**YES.** Assign a PFS Score by calculating the percentage (ie, fractional) difference in median progression-free survival between the two regimens and multiply the result by 100. Multiply this number by 0.8. Write this number in the box labeled "PFS Score." **Proceed to 1.F.**	**PFS Score**
	NO. Proceed to 1.E.	
1.E. If median PFS is not reported, is response rate (RR) reported?	**YES.** Assign an RR Score by adding the complete response (CR) and partial response (PR) rates, multiply by 100, then multiply this number by 0.7. Write this number in the box labeled "RR Score." **Proceed to 1.F.**	**RR Score**
1.F. Calculate the Clinical Benefit Score	Insert the score for HR death, HR PFS, median OS, or median PFS. **Note: You should have a score for only 1 of the clinical benefit scales above.** Write the total in the box labeled "Clinical Benefit Score." **Proceed to Step 2.**	**Clinical Benefit Score**
Step 2: Determine the regimen's TOXICITY		
Does the new regimen represent an improvement in toxicity over the standard of care/ comparator?	For each of the regimens being assessed, compare the number and frequency of clinically relevant toxicities, and assign a Toxicity Score) as shown below. Each clinically meaningful toxicity (ie, exclude laboratory results only) is assigned a score between 0.5 and 2.0 based on grade and frequency: For every grade 1 or 2 toxicity with a frequency < 10%, record 0.5 points. For every grade 1 or 2 toxicity with a frequency ≥ 10%, record 1.0 points. For every grade 3 or 4 toxicity with a frequency < 5%, record 1.5 points. For every grade 3 or 4 toxicity with a frequency ≥ 5%, record 2.0 points. Calculate the total number of toxicity points for each regimen. Calculate the percentage difference in total toxicity points between the two regimens, then multiply by 20 to obtain a toxicity score. If the regimen being evaluated is more toxic than the comparator, subtract the toxicity score of the regimen from the clinical benefit score. If the regimen is less toxic than the comparator, add the toxicity score of the regimen to the clinical benefit score. **If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment, subtract 5 additional points from the clinical benefit score.** The maximum points that can be awarded is 20. **Proceed to Step 3.**	**Toxicity Score**
Step 3: Determine Bonus Points		

Fig 1. Revised value framework: advanced disease. QoL, quality of life.

3.A. TAIL OF THE CURVE. Identify the time point on the survival curve that is 2X the median OS (or PFS) of the comparator regimen. Is there a 50% or greater improvement in proportion of patients alive with the test regimen at this time point (assuming ≥ 20% surviving with standard)?	**YES.** If yes, award 20 points if the improvement is in OS, and 16 points (0.8 x 20) if the improvement is in PFS, and place this number in the box labeled "Tail of the Curve Bonus Points." **Proceed to Step 3.B.**	**Tail of the Curve Bonus Points**
	NO. No bonus points are awarded. **Proceed to Step 3.B.**	
3.B. PALLIATION BONUS. Is an improvement in cancer-related symptoms reported?	**YES.** If a statistically significant improvement in cancer-related symptoms is reported for the regimen being evaluated, award 10 points, and place this number in the box labeled "Palliation Bonus." **Proceed to Step 3.C.**	**Palliation Bonus**
	NO. No bonus points are awarded. **Proceed to Step 3.C.**	
3.C. QoL BONUS. Is an improvement in QoL reported?	**YES.** If a statistically significant improvement in QoL is reported for the regimen being evaluated, award 10 points, and place this number in the box labeled "QoL Bonus." **Proceed to Step 3.D.**	**QoL Bonus**
	NO. No bonus points are awarded. **Proceed to Step 3.D.**	
3.D. TREATMENT-FREE INTERVAL BONUS. Are data related to treatment-free interval reported?	**YES.** If a statistically significant improvement in treatment-free interval is reported for the regimen being evaluated, multiply the percentage improvement by 20 and award points. **Proceed to 3.E.**	**Treatment-Free Interval Bonus**
	NO. No bonus points are awarded. **Proceed to Step 3.E.**	
3.E. Calculate Total Bonus Points	Add the Palliation Bonus Points (Step 3.A), the Treatment-Free Interval Bonus Points (Step 3.B), and the QoL Bonus Points (Step 3.C.). Write this number in the box labeled "Total Bonus Points." The maximum points available for Bonus Points is 60. **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." 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 Payment:** _____
Step 6: Summary Assessment: Advanced Disease Framework		

Clinical Benefit	Toxicity	Bonus Points	Net Health Benefit	Cost (per month)
				DAC: _____ Patient Payment: _____

Fig 1. (continued).

DOMAINS ADDRESSED AND REVISIONS MADE

NHB Score

The NHB score was perceived by some readers as arbitrary, not intuitive, and therefore lacking the meaning that an absolute value for either clinical benefit or toxicity would have. We concur that NHB is an artificial construct. However, it is derived from the key efficacy elements of overall survival (OS), progression-free survival (PFS), response rate (RR), symptom palliation, time off treatment, and QoL, along with the comparative toxicity of the regimen. In the advanced disease setting, the framework reflects the importance of these by attributing the greatest weight to OS, with less weight given to a trial reporting only PFS and still less to one reporting only RR. Thus, the NHB represents the very elements that patients seek to understand as they consider treatment options and that most oncologists use to make treatment recommendations.

Step 1: Determine the regimen's CLINICAL BENEFIT		
1.A. Is hazard ratio (HR) for death reported?	**YES.** Assign an HR Score for death by subtracting the HR from 1, and multiplying the result by 100. Write this number in the box labeled "HR Score (death)." **Proceed to 1.E.**	**HR Score (death)**
	NO. Proceed to 1.B.	
1.B. If HR for death is not reported, is median overall survival (OS) reported?	**YES.** Assign an OS Score by calculating the percentage (ie, fractional) difference in median OS between the two regimens and multiplying the result by 100. Write this number in the box labeled "OS Score." **Proceed to 1.E.**	**OS Score**
	NO. Proceed to 1.C.	
1.C. If OS data are not reported, is HR for disease-free survival (DFS) reported?	**YES.** Assign an HR score for DFS Score by subtracting the HR from 1, and multiplying the result by 100. Write this number in the box labeled "DFS Score." **Proceed to 1.E. NO. Proceed to 1.D.**	**HR Score (DFS)**
1.D. If HR for DFS is not reported, is median DFS reported?	**YES.** Assign a DFS Score by calculating the percentage (i.e., fractional) difference in median DFS between the two regimens and multiplying the result by 100. Write this number in the box labeled "Median DFS Score." **Proceed to 1.E.**	**Median DFS Score**
	NO. Proceed to 1.E.	
1.E. Calculate the Clinical Benefit Score	Insert the score for HR death, HR DFS, median OS, or median DFS. **Note: You should have a score for only 1 of the clinical benefit scales above.** Write the total in the box labeled "Clinical Benefit Score." **Proceed to Step 2.**	**Clinical Benefit Score**
Step 2: Determine the regimen's TOXICITY		
Does the new regimen represent an improvement in toxicity over the standard of care/ comparator?	For each of the regimens being assessed, compare the number and frequency of clinically relevant toxicities, and assign a Toxicity Score as shown below. Each clinically meaningful toxicity (ie, exclude laboratory results only) is assigned a score between 0.5 and 2.0 based on grade and frequency: For every grade 1 or 2 toxicity with a frequency < 10%, record 0.5 points. For every grade 1 or 2 toxicity with a frequency ≥ 10%, record 1.0 points. For every grade 3 or 4 toxicity with a frequency < 5%, record 1.5 points. For every grade 3 or 4 toxicity with a frequency ≥ 5%, record 2.0 points. Calculate the total number of toxicity points for each regimen. Calculate the percentage difference in total toxicity score between the two regimens, then multiply by 20 to obtain a toxicity score. If the regimen being evaluated is more toxic than the comparator, subtract the toxicity score of the regimen from the clinical benefit score. If the regimen being evaluated is less toxic than the comparator, add the toxicity score of the regimen to the clinical benefit score. **If there are unresolved symptomatic treatment-related toxicities at 1 year after completion of treatment, subtract 5 additional points from the clinical benefit score. Proceed to Step 3.** The maximum points that can be awarded is 20.	**Toxicity Score**
Step 3: Determine Bonus Points		
TAIL OF THE CURVE. Identify the time point on the survival curve that is 2X the median OS (or DFS) of the comparator regimen. Is there a 50% or greater improvement in proportion of patients alive with the test regimen at this time point (assuming > 20% surviving with standard)?	**YES.** If yes, award 20 points. Write this number in the box labeled "Bonus Points." **Proceed to Step 4.**	**Bonus Points**
	NO. No bonus points are awarded. **Proceed to Step 4.**	
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." 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 in total (cost per cycle × number of cycles). Proceed to **Step 6.**		**Cost (for entire treatment regimen)** **DAC:** _____ **Patient Payment:** _____

Step 6: Summary Assessment: Adjuvant Setting				
Clinical Benefit	**Toxicity**	**Bonus Points**	**Net Health Benefit**	**Cost (for entire treatment regimen)**
				DAC: _____ Patient Payment: _____

Fig 2. Revised value framework: adjuvant setting.

We have made several revisions to the framework to make the comparisons within a trial more reflective of the actual differences observed. Because hazard ratios (HRs) provide a more complete assessment of relative efficacy, the HR is now the preferred variable in the value framework instead of median OS or PFS to establish efficacy, unless the HR is not reported. When using the HR, it is

critically important to interpret it in the context of the actual magnitude of difference between the two treatments (ie, because an HR expresses a relative difference in risk, a similar HR could be derived for a modest improvement in survival that is measured in weeks or months for a tumor type with a poor prognosis or for a larger absolute gain that is produced by a highly effective therapy in a tumor type more amenable to treatment). To avoid the misinterpretation that a favorable HR necessarily represents a large absolute gain in OS or PFS, it is incumbent upon the physician, at the point of care, to explain the absolute difference in survival (eg, "on average, a patient can expect an improvement of X weeks or months") with the test regimen when compared with the standard of care. It is anticipated that the software tool to be developed for use at the patient–physician interface will demonstrate the absolute difference in outcome for the regimens being compared, along with the clinical benefit and NHB scores that are derived using the value framework.

In addition, the percent change in median OS or PFS is no longer assigned a score of 1 to 5 on the basis of magnitude of difference between the test regimen and comparator. Instead, a continuous scoring system is used to avoid arbitrary cutoffs. As stated, we have retained the primary importance of OS as compared with PFS or RR, because patients are often most interested in length of survival. If the OS determination is obscured by trial design (eg, crossover from comparator to test arm), the PFS determination will be used to score clinical benefit. It also is acknowledged that symptom control and comfort may be higher priorities for some patients with advanced cancer and their families. In this case, a tool capable of supporting the framework will allow for increasing the relative weight attributed to either freedom from toxicity or length of life, based on patient preference.

The revised framework emphasizes the importance of achieving improved survival or long-term disease control (PFS) by awarding bonus points if certain criteria are met. As a study matures, the tail of the survival curve can reflect a noteworthy change for a significant minority of patients receiving a new regimen, assuming the difference between comparator and test regimen is statistically significant. Thus, bonus points are awarded if the test regimen results in at least a 50% relative improvement in percentage of patients alive at a time point that is at twice the median OS or PFS point for the control regimen and if at least 20% of patients receiving the control regimen are alive at this time. Although the absolute time in months or years will vary for illnesses that differ in natural history and are more or less sensitive to therapy, the task force believes this approach of rewarding an outcome of long-term disease control is meritorious. As in the original framework, statistically significant improvements in symptom palliation are awarded bonus points; however, in the revised framework, bonus points are also given for improvement in QoL.

The revision of the framework also modifies the way toxicities are compared. Rather than focus exclusively on high-grade toxicities, the revised framework incudes all adverse effects experienced by patients and attributes different scores for the frequencies of toxicities depending on their grade. In the revised version, the total points for toxicities associated with the test regimen and the control are expressed as fractions, which are then multiplied by 20 (ie, toxicity points attributed to the test regimen divided by toxicity points of the control, multiplied by 20). If the regimen being evaluated is more toxic than the comparator, the toxicity score is subtracted from the clinical benefit score. If the regimen is less toxic than the comparator, the toxicity score is added to the clinical benefit score. Thus, a regimen less toxic than the control may be awarded up to 20 points, and if the toxicity is doubled, 20 points will be subtracted from the clinical benefit score of the test regimen. Ultimately, as in the original framework, the NHB is derived by combining the clinical benefit, toxicity, and bonus points awarded.

Table 1. Enzalutamide Versus Placebo After Chemotherapy in Metastatic Adenocarcinoma of Prostate: Calculations for Clinical Benefit, Toxicity, Bonus Points, NHB, and Cost

Measure	Result/Score
Clinical benefit score	
HR (death), 0.63	
Clinical benefit, (1 − 0.63) × 100 × 1 = 37	37
Toxicity score	
Placebo	
Enzalutamide, 15/13.5 − 1 = 0.11	
0.11* × −20 = −2.2	−2.2
Bonus points	
Tail of the curve	16
Palliation	10
Treatment-free interval	0
Health-related QoL	10
Total bonus points	36
NHB	70.8
DAC (per month)	$8,495

Abbreviations: DAC, drug acquisition cost; HR, hazard ratio; NHB, net health benefit; QoL, quality of life.
*Only grade 3 and higher toxicities have been counted, because the lower-grade toxicities are not clearly described in the reports.[2,3] Those toxicities included in calculation are any serious adverse event, drug discontinuation, adverse event leading to death, fatigue, diarrhea, hot flashes, musculoskeletal pain, headache, and any cardiac and myocardial infarction.

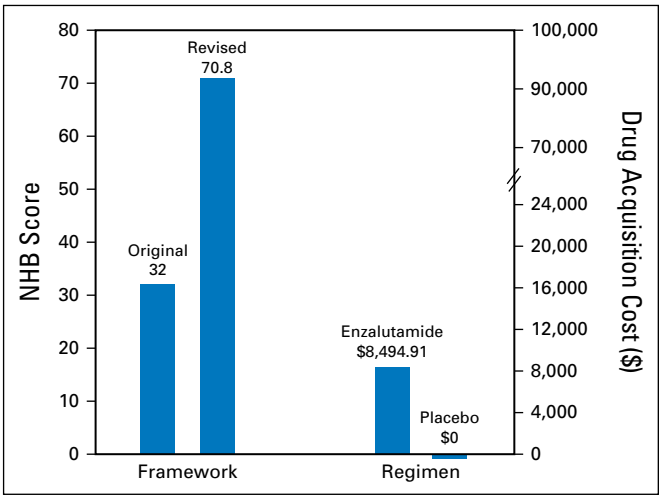

Fig 3. Net health benefit (NHB) scores for the randomized placebo-controlled trial of enzalutamide versus placebo in metastatic adenocarcinoma of the prostate[1] calculated using the original and revised frameworks. Costs are shown per month of therapy for each regimen, using calculations from the original value framework publication,[1] which were based on average sales prices as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs.

In this revised version, the value framework continues to be presented for two distinct scenarios: advanced disease and potentially curable (adjuvant therapy) clinical presentations. This reflects our recognition that assessments of value must reflect the different clinical circumstances in which an agent will be used. In addition, the task force acknowledges that the value of a new agent will most likely change as it moves from use in advanced disease to the adjuvant setting.

The NHB score was criticized for not taking into account details of study design (eg, choice of standard therapy against which a test agent is compared). Thus, a new drug may have a greater NHB if the comparator is a minimally active regimen or placebo than if it is a more active regimen. This is the reason NHB scores cannot be compared among trials. The NHB serves as an indicator of the clinical impact of a therapy as compared with a control regimen. Likewise, it is a measure of the relative toxicity between comparator and test regimens. The NHB, as constructed, can help a physician and patient assess the relative improvement in benefit that has been found when using one regimen compared with another. As stated, it is important for the clinician to make clear the absolute magnitude of benefit that the patient might expect from the therapy under consideration, to minimize the chance for misinterpretation.

Focus on Prescription Drug Costs

The concern was raised that by focusing solely on the cost of prescription drugs, the framework fails to provide a complete picture of the costs associated with caring for a patient with cancer. The task force recognizes the fact that costs of antineoplastic drugs and the supportive care agents administered with them are only a fraction of the total expenditures in cancer care. There are costs incurred by work missed by the patient and spouse or significant other, emergency department visits, hospitalizations, and physician visits, all of which are often substantial. However, these costs are not readily available, nor are they easily quantified for any given group of patients. The high and rapidly rising cost of specialty drugs to the health care system and to the patient through copays are of great importance to patients, providers, and payers and has therefore been retained as the primary focus of the current version of the framework. As noted in our original value framework publication, cost incurred during catastrophic illness is among the most frequent causes of personal bankruptcy.[1] By discussing several alternative regimens, a patient can judge the clinical benefit he or she might derive and at what cost, both physically and financially. This should facilitate the generation of a sound, personalized treatment plan that takes into account goals of care and financial realities.

Lack of QoL and PRO Information

A substantial number of respondents commented on the lack of inclusion of PROs in the value framework. The concern expressed was that the framework is insensitive to palliative care benefits of the therapies being considered and their impact on QoL. We concur that the absence of PROs is an important deficiency in the framework. However, their omission reflects the absence of such data in many clinical trials. One hope of the value task force is that PRO end points will be included in a larger number of cancer clinical trials in the future. In the ASCO framework, clinical trials that demonstrate improvement in duration of treatment-free interval, QoL, or symptom palliation are eligible for bonus points that add to the NHB. There is no substitute for rigorously measured PROs; the task force believes it is important to measure and report such variables and looks forward to amending the framework in the future to incorporate PROs when they are regularly reported as clinical trial end points.

Table 2. Doxorubicin Plus Cyclophosphamide Followed by Paclitaxel Plus Trastuzumab Versus Doxorubicin, Cyclophosphamide, and Paclitaxel (control) in Adjuvant Treatment of HER2-Positive Breast Cancer: Calculations for Clinical Benefit, Toxicity, Bonus Points, NHB, and Cost

Measure	Result/Score
Clinical benefit score	
HR (death), 0.59	
Clinical benefit, (1 − 0.59) × 100 × 1 = 41	41
Toxicity score	
Doxorubicin, cyclophosphamide, paclitaxel, and trastuzumab	
Doxorubicin, cyclophosphamide, and paclitaxel	0
Bonus points	
Tail of the curve	0
Total bonus points	0
NHB	41
DAC (total course of therapy)	$73,166

Abbreviations: DAC, drug acquisition cost; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NHB, net health benefit.

Only Head-to-Head Comparisons of Regimens

The fact that only drug regimens that have been compared head to head in a clinical trial can be used in the framework was cited as a serious limitation that will limit its utility as a decision-

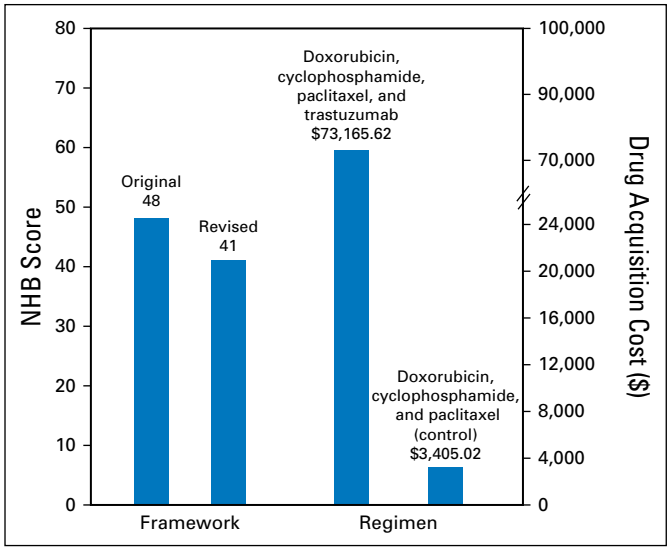

Fig 4. Net health benefit (NHB) scores for doxorubicin plus cyclophosphamide followed by paclitaxel plus trastuzumab versus doxorubicin, cyclophosphamide, and paclitaxel (control) in the adjuvant treatment of human epidermal growth factor receptor 2–positive breast cancer. NHB scores were calculated using the original and revised frameworks. Costs are shown for the total course of therapy for each regimen, using calculations from the original value framework publication,[1] which were based on average sales prices as of October 2014 for intravenous therapies and on information from UnitedHealthcare for oral drugs.

Table 3. Ipilimumab Versus Placebo After Primary Treatment of Stage III Melanoma: Calculations for Clinical Benefit, Toxicity, Bonus Points, NHB, and Cost

Measure	Result/Score
Clinical benefit score	
HR (DFS), 0.75	
Clinical benefit, (1 − 0.75) × 100 × 1 = 25	25
Toxicity score	
Placebo	
Ipilimumab, 38.5/28 − 1 = 0.38	
0.38 × −20 = −7.6	−7.6
Bonus points	
Tail of the curve	0
Total bonus points	0
NHB	17.4
DAC (total course of therapy)	$458,858

Abbreviations: DAC, drug acquisition cost; DFS, disease-free survival; HR, hazard ratio; NHB, net health benefit.

making aid. The task force believes that cross-trial comparisons are not justified, because the methodology for making such comparisons is not well validated, and there is a risk that such comparisons will lead to inappropriate conclusions as a result of bias or noncomparable patient populations. Instead, we envision a framework tool that will be prepopulated with data that include clinical benefits, toxicities, and NHBs for trials that support use of the treatment options being considered for a patient. The physician's guidance will be supported by having the data available at the click of a button so that each relevant trial can be considered on its own merits in the same clinical scenario.

Dual Intent of the Framework

A number of commentators questioned whether the value framework is intended to drive public policy discussions about drug pricing in addition to helping with shared decision making between patients and their oncologists. Concern was expressed that these dual objectives are fundamentally different and cannot be accomplished using the same model.

As currently configured, the framework is not meant to be a policy tool. It is intended for use in the clinical setting between physicians and their patients and is meant to serve as a catalyst and facilitator of individual treatment discussions. Once converted to a software application, the value framework will contain scales of clinical benefit, toxicity, and symptom palliation that can be adjusted to give differential weight to any of the elements included in the NHB. It is essential to understand that the framework is meant to be modified at the point of care, as a physician and patient finalize a regimen to be used.

The task force fully acknowledges that value assessments supported by such a framework could be generated for use in the development of health care policy. Such an adaptation of the original intent of the framework would require further discussion with physicians, health economists, and key stakeholder groups, including patients, the pharmaceutical industry, and payers.

Practicality

A number of commentators asserted that the framework is impractical and that its utility in the clinician's office is uncertain and must be tested. The task force agrees that the utility of the planned software application will depend on its ability to provide fast access to the relevant information and permit easy incorporation into the physician's workflow. The model framework is just that: a conceptual model that will need to be converted to a user-friendly software application, tested, and refined for it to be useful in a clinical encounter.

Personalized Decision Making Not Permitted

A number of commentators expressed concern that judgments about the value of specific drugs or regimens would be made using a one-size-fits-all set of assumptions. The intent of the framework is just the opposite. Once deployed as a software application, the categories that are scored (ie, clinical benefit and toxicity) will be subject to weighting by the individual patient, so each person can determine the extent to which he or she wishes to emphasize length of survival over avoidance of adverse effects, or the reverse. If a patient values avoidance of toxicity over length of life, as we know some with advanced cancer do, the software tool developed from the framework can be adjusted so that toxicity is given greater overall weight compared with OS.

APPLICATION OF REVISED FRAMEWORK IN CLINICAL SCENARIOS

In our original framework publication, we applied the framework to four clinical scenarios: first-line treatment of 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.[1] These scenarios were selected to demonstrate the potential utility of the approach in diverse clinical scenarios and to inform refinements of the framework. To demonstrate the differences in NHB calculations that emerge from use of the original and revised frameworks, here we present two of the original scenarios: enzalutamide versus placebo (control) for first-line treatment of metastatic castration-resistant prostate cancer[2,3] (Table 1; Fig 3) and doxorubicin plus

Table 4. Ibrutinib Versus Chlorambucil As Initial Therapy for Patients With Chronic Lymphocytic Leukemia: Calculations for Clinical Benefit, Toxicity, Bonus Points, NHB, and Cost

Measure	Result/Score
Clinical benefit score	
HR (death), 0.16	
Clinical benefit, (1 − 0.16) × 100 × 1 = 84	84
Toxicity score	
Chlorambucil	
Ibrutinib, 27.5/20.5 − 1 = 0.34	
0.34 × −20 = −6.8	−6.8
Bonus points	
Tail of the curve	0
Palliation	0
Treatment-free interval	0
Health-related QoL	0
Total bonus points	0
NHB	77.2
DAC (per 4 months)	$35,770

Abbreviations: DAC, drug acquisition cost; HR, hazard ratio; NHB, net health benefit; QoL, quality of life.

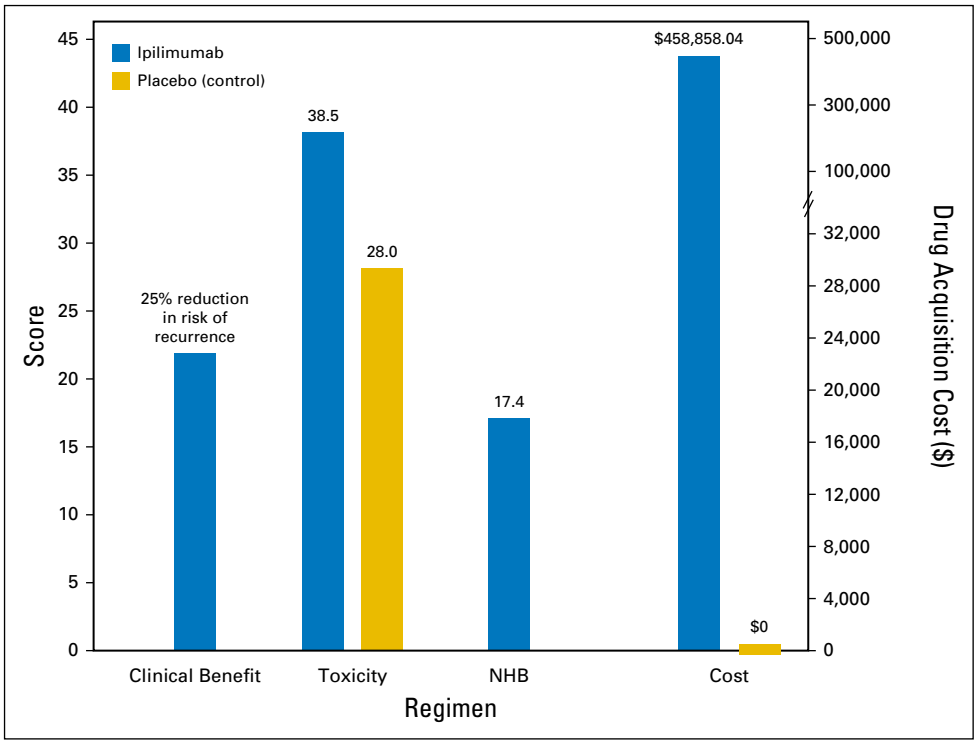

Fig 5. Clinical benefit, toxicity, net health benefit (NHB), and cost of ipilimumab versus placebo as derived from the prospective randomized trial comparing ipilimumab against placebo after primary treatment of stage III melanoma. Raw data for each parameter are shown above each bar. Costs are shown for the total course of therapy for each regimen, on the basis of average sales prices for intravenous therapies[8] and on wholesaler acquisition cost (WAC) information for oral drugs from AnalySource Monthly data, adapted with permission.[9] Ipilimumab has a hazard ratio of 0.75, or 25% reduction in risk of recurrence, when compared with control; a toxicity score of 38.5 versus 28.0 for control; NHB of 17.4; and cost of $458,858 versus $0 for control. The cost of ipilimumab is based on administration of four 3-week induction cycles at a dose of 10 mg/kg per dose, and this cost could be significantly higher for a patient who received the entire protocol-specified, 3-year course of treatment. NOTE. The WAC indicates the manufacturer's published price to wholesalers; WACs represent published catalog or list prices and may not represent actual transactional prices. A detailed explanation of the First Databank pricing methodology can be found on the First Databank Web site.[10]

cyclophosphamide followed by paclitaxel plus trastuzumab (and total of 1 year of trastuzumab) versus doxorubicin, cyclophosphamide, and paclitaxel (control) for adjuvant treatment of human epidermal growth factor receptor 2–positive breast cancer[4,5] (Table 2; Fig 4). In the enzalutamide example, the NHB in the revised framework is substantially improved because of the awarding of bonus points for improvement in the tail of the PFS curve and a statistically significant improvement in the QoL and pain scores[3] in the test arm (Fig 3). In the adjuvant breast cancer study, there was only a small change in the NHB with the revised framework (Fig 4).

We have also applied the revised framework to two new scenarios: ibrutinib compared with chlorambucil as initial therapy for the treatment of chronic lymphocytic leukemia[6] and adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma.[7] The results of these analyses are summarized in Tables 3 and 4 and Figures 5 and 6. Data used to generate the calculations shown can be found in Appendix Tables A3 and A4 (online only). As in our original publication, these scenarios are shown as an example of how the Value Framework operates in different clinical scenarios. They are not intended to provide a comprehensive assessment of a specific drug or treatment regimen, and they may not encompass the full range of data that have been reported for the regimens in question.

DISCUSSION

The ASCO value framework is one of several attempts to assess the value of cancer treatment regimens. The European Society of Medical Oncology has also developed a tool that evaluates the clinical utility of agents in the advanced disease and adjuvant settings based on efficacy, toxicity, QoL, and survival.[11] The National Comprehensive Cancer Network recently introduced its evidence blocks, which include efficacy, toxicity, quality of evidence, and affordability, to assess value of drug treatments.[12] In addition, Memorial Sloan Kettering Cancer Center has published the Drug Abacus.[13] Finally, the Institute for Clinical and Economic Review, which develops reports analyzing the evidence on the effectiveness and value of drugs and other medical services, has begun to expand its focus to include cancer treatments, beginning with multiple myeloma.[14] Any value assessment that is dependent on a growing evidence base must be regarded as dynamic. As clinical trials mature, results may change in ways that justify modification of an earlier value assessment.

There are common themes among these efforts, because the basic elements of clinical benefit, toxicity, and quality of evidence contributing to a value assessment are important in each. The urgency of arriving at a value framework that can be used in the conversation between a physician and patient takes on added importance in an environment in which patients are increasingly exposed to sharing the rapidly rising costs of cancer treatments by third-party payers, as is the case in the United States. In publishing this revision to the ASCO value framework, we have tried to respond to the many constructive suggestions we received. In doing so, we are adhering to our goals of stimulating debate and forging a broad consensus on how to define the value of a cancer treatment—putting the patient at the center. Once prepopulated with data from high-quality clinical trials, the framework tool can assist in shared decision making regarding the options available to oncologist and patient, provide comprehensible information in a rapidly accessible fashion, and thereby facilitate treatment choices that are tailored to each patient's preferences, goals, and financial circumstances.

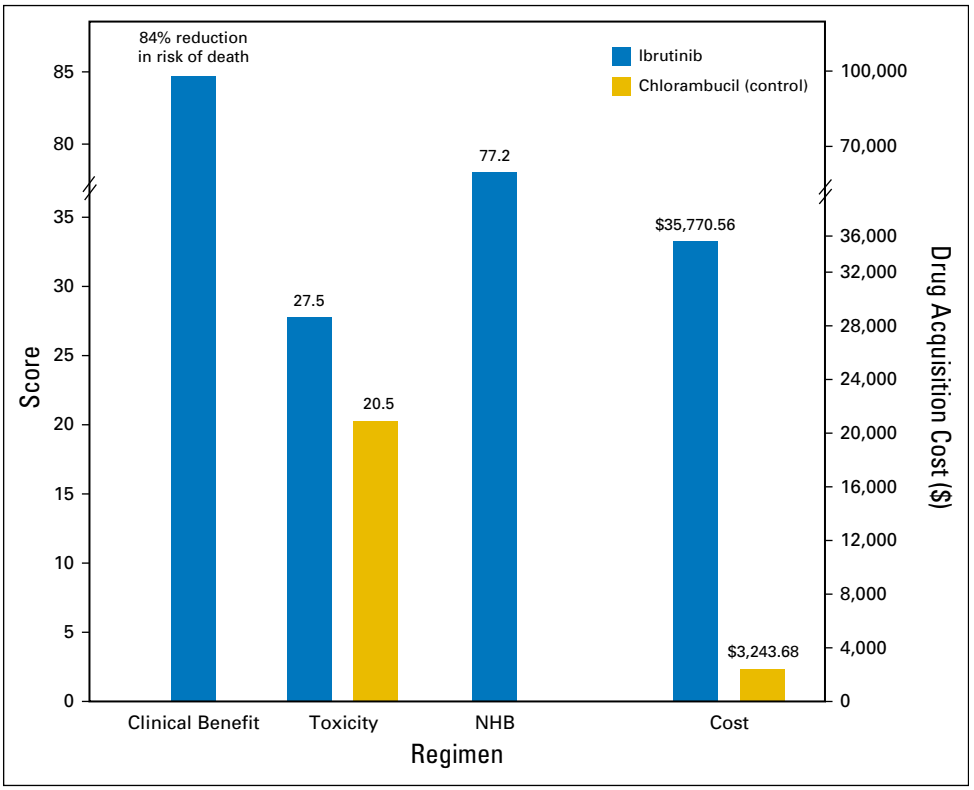

Fig 6. Clinical benefit, toxicity, net health benefit (NHB), and cost from a randomized phase III trial of ibrutinib versus chlorambucil for treatment of chronic lymphocytic leukemia. Raw data for each parameter are shown above each bar. Costs are shown for four monthly cycles of therapy, on the basis of average sales prices for intravenous therapies,[8] and on wholesaler acquisition cost (WAC) information for oral drugs from AnalySource Monthly, adapted with permission.[9] Ibrutinib has a hazard ratio of 0.16, or 84% reduction in risk of death, when compared with control; a toxicity score of 27.5 versus 20.5 for control; NHB of 77.2; and cost of $35,770.56 versus $3,243.68 for control. NOTE. The WAC indicates the manufacturer's published price to wholesalers; WACs represent published catalog or list prices and may not represent actual transactional prices. A detailed explanation of the First Databank pricing methodology can be found on the First Databank Web site.[10]

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Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received

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Appendix

Table A1. ASCO Value Framework: Advanced Disease

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: _____

NOTE. 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.

Table A2. ASCO Value Framework: Adjuvant Setting

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: _____

NOTE. 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.

Table A3. Ipilimumab Versus Placebo After Primary Treatment of Stage III Melanoma

Regimen	HR (death)	mRFS	Tail of the Curve	Reported Toxicity	Regimen Cost
Ipilimumab*	—	26.1 (HR, 0.75; $P = .0013$)	—	Grade 1 to 2 < 10%, 1 Grade 1 to 2 > 10%, 14 Grade 3 to 4 < 5%, 12 Grade 3 to 4 > 5%, 3	$458,858
Placebo	—	17.1	—	Grade 1 to 2 < 10%, 7 Grade 1 to 2 > 10%, 8 Grade 3 to 4 < 5%, 11 Grade 3 to 4 > 5%, 0	$0

NOTE. Dashes indicate data not available.
Abbreviations: HR, hazard ratio; mRFS, median recurrence-free survival.
*Ipilimumab 10 mg/kg every 3 weeks for four cycles, using an average weight of 81.5 kg, as defined by the National Center for Health Statistics.

Table A4. Ibrutinib Versus Chlorambucil As Initial Therapy for Patients With Chronic Lymphocytic Leukemia

Regimen	HR (death)	mOS (months)	HR (progression)	mPFS (months)	RR (CR + PR)	Tail of the Curve	Palliation Data	Treatment-Free Interval	Reported Toxicity	Regimen Cost
Ibrutinib*	0.16	—	0.16	NR	81%	—	—	—	Grade 1 to 2 < 10%, 0 Grade 1 to 2 > 10%, 8 Grade 3 to 4 < 5%, 13 Grade 3 to 4 > 5%, 0	$35,770.56
Chlorambucil†	—	—	—	18.9	36%	—	—	—	Grade 1 to 2 < 10%, 3 Grade 1 to 2 > 10%, 5 Grade 3 to 4 < 5%, 8 Grade 3 to 4 > 5%, 1	$3,243.68

NOTE. Dashes indicate data not available.
Abbreviations: CR, complete response; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; PR, partial response; RR, response rate.
*Cost estimate for ibrutinib based on a dose of 420 mg orally once daily for four cycles, using an average weight of 81.5 kg, as defined by the National Center for Health Statistics.
†Cost estimate for chlorambucil based on a dose of 0.5 mg/kg on days 1 and 15 of a 28-day cycle for four cycles, using an average weight of 81.5 kg, as defined by the National Center for Health Statistics.