Comparative Assessment of Clinical Benefit Using the ESMO-Magnitude of Clinical Benefit Scale Version 1.1 and the ASCO Value Framework Net Health Benefit Score

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PURPOSE To better understand the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS v1.1) and the ASCO Value Framework Net Health Benefit score version 2 (ASCO-NHB v2), ESMO and ASCO collaborated to evaluate the concordance between the frameworks when used to assess clinical benefit attributable to new therapies.

METHODS The 102 randomized controlled trials in the noncurative setting already evaluated in the field testing of ESMO-MCBS v1.1 were scored using ASCO-NHB v2 by its developers. Measures of agreement between the frameworks were calculated and receiver operating characteristic curves used to define thresholds for the ASCO-NHB v2 corresponding to ESMO-MCBS v1.1 categories. Studies with discordant scoring were identified and evaluated to understand the reasons for discordance.

RESULTS The correlation of the 102 pairs of scores for studies in the noncurative setting is estimated to be 0.68 (Spearman’s rank correlation coefficient; overall survival, 0.71; progression-free survival, 0.67). Receiver operating characteristic curves identified thresholds for ASCO-NHB v2 for facilitating comparisons with ESMO-MCBS v1.1 categories. After applying pragmatic threshold scores of 40 or less (ASCO-NHB v2) and 2 or less (ESMO-MCBS v1.1) for low benefit and 45 or greater (ASCO-NHB v2) and 4 to 5 (ESMO-MCBS v1.1) for substantial benefit, 37 discordant studies were identified. Major factors that contributed to discordance were different approaches to evaluation of relative and absolute gain for overall survival and progression-free survival, crediting tail of the curve gains, and assessing toxicity.

CONCLUSION The agreement between the frameworks was higher than observed in other studies that sought to compare them. The factors that contributed to discordant scores suggest potential approaches to improve convergence between the scales.

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INTRODUCTION

Evaluation of the clinical benefit of any anticancer therapy depends on an objective assessment of the magnitude of improvement in meaningful clinical outcomes in the face of toxicity associated with the treatment. Both the European Society for Medical Oncology (ESMO)\textsuperscript{1,2} and the American Society of Clinical Oncology (ASCO)\textsuperscript{3,4} have developed algorithmic scales to evaluate benefit of cancer therapies. The ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) was developed to generate clear, valid, and unbiased grading of the magnitude of clinical benefit demonstrated in therapeutic studies that could be used for a number of purposes, including public health policy and health technology assessment, clinical decision making, medical publication, and journalism.\textsuperscript{1,2} The ASCO Value Framework was developed primarily as a physician-guided tool to facilitate shared decision making by patients and oncologists in selecting a high-value treatment (clinical benefit vs toxicity) for an individual patient.\textsuperscript{3,4}

The ESMO-MCBS version 1.0 was published in 2015\textsuperscript{1} and was revised in version 1.1 in 2017.\textsuperscript{2} The ASCO Value Framework was published in 2015\textsuperscript{3} and was revised in version 2 in 2016.\textsuperscript{4}

Although the frameworks were developed for different purposes, they share the aspiration to provide an assessment of clinical benefit using a valid, clear, unbiased, and reliable approach to data analysis. Both assign lesser weight to outcome measures derived from surrogates for survival and incorporate in the benefit evaluation other outcome measures, including
long-term survival, quality of life (QoL), and adverse effects. Despite these similarities, a number of distinguishing characteristics exist in the approaches taken to develop a clinical benefit or net health benefit (NHB) score (Table 1).

The two frameworks have been developed with different internal controls and are at different stages of development. The ESMO-MCBS assigns categorical benefit scores to positive randomized clinical trials, that is, superiority trials that have demonstrated a statistically significant result for the primary end point of the study or secondary in case of overall survival (OS) and noninferiority trials that reach a conclusion of noninferiority. Primary or secondary end points included in the scoring system are OS, progression-free survival (PFS), QoL, and treatment toxicity. In developing the MCBS, ESMO aspired to meet standards for accountability for reasonableness by incorporating extensive field testing, statistical modeling, and peer review of the reasonableness of the generated results into the development process. The ESMO-MCBS currently is incorporated in ESMO’s clinical practice guidelines and is being used as part of health technology assessment processes. The ASCO Value Framework uses the construct of an NHB score (ASCO-NHB), which is intended to be applied to randomized trials but not specifically to trials that demonstrate statistical significance in superiority trials. Discussions between ESMO and ASCO about the two frameworks and ESMO’s assessment of a large number of trials using the ESMO-MCBS served as a stimulus for both organizations to evaluate the same set of trials to understand the extent of concordance or discordance between the respective frameworks. Moreover, publications not associated with either organization reported evaluations of the degrees of association between the scores generated by both (Table 2). Four of five analyses found a limited association, with low to modest correlation (Spearman rank correlation coefficient, 0.17 and 0.36, respectively; Pearson’s correlation coefficient, 0.36 and 0.40, respectively) or agreement ($\kappa = 0.33$ and 0.40, respectively), which suggests that the two frameworks do not consistently agree with respect to what constitutes substantial or low benefit.

Thus, ESMO and ASCO undertook this cooperative project to better understand the performance characteristics of the ESMO-MCBS version 1.1 (ESMO-MCBS v1.1) and the

| Table 1. Shared and Unique Characteristics of ESMO-MCBS v1.1 and ASCO-NHB v2 Scales |
|---------------------------------|---------------------------------|---------------------------------|
| Characteristic                  | ESMO-MCBS v1.1                  | ASCO-NHB v2                     |
| Separate scaling for curative and noncurative disease | Yes                             | Yes                             |
| Descending weighting for OS, PFS, and RR | Yes                             | Yes                             |
| Tail of curve credits OS       | Yes                             | Yes                             |
| Tail of curve credits PFS      | Yes                             | Yes                             |
| Toxicity assessment            | Yes                             | Yes                             |
| Credits QoL gains              | Yes                             | Yes                             |
| Scoring metric                 | Categorical                     | Continuous                      |
| Relative benefit assessment using HR | LL95%CI                        | Point estimate                  |
| Bonus for both QoL and symptom palliation | No                             | Yes                             |
| Toxicity assessment incorporates penalty for low-grade toxicity | No                             | Yes                             |
| Bonus for treatment-free interval | No                             | Yes                             |
| Prognostically stratified scoring for OS and PFS | Yes                             | No                              |
| Considers relative and absolute gain thresholds | Yes                             | No                              |
| Downgrades for PFS scores not associated with improvement in OS or QoL | Yes                             | No                              |
| Separate scale for single-arm studies | Yes                             | No                              |
| Applicable to pCR neoadjuvant studies | Yes                             | Yes                             |
| Separate scale for QoL studies | Yes                             | No                              |
| Stratified approach to toxicity penalties according to primary outcomes (less toxicity penalty when outcome is cure or OS instead of PFS) | Yes                             | No                              |
| Differential toxicity weighting for curative/noncurative disease | Yes                             | No                              |

Abbreviations: ASCO-NHB v2, ASCO Value Framework Net Health Benefit score version 2; ESMO-MCBS v1.1, ESMO-Magnitude of Clinical Benefit Scale version 1.1; HR, hazard ratio; LL95%CI, lower limit of the 95% CI; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; QoL, quality of life; RR, relative risk.
ASCO-NHB version 2 (ASCO-NHB v2) and to identify reasons for discordant scoring. The initial step in this process addressed the noncurative setting and was undertaken to evaluate the association between the frameworks to scaling clinical benefit, to identify the factors that contribute to discordant evaluations and, to identify ways to improve each framework.

**METHODS**

Because the ESMO-MCBS framework was designed to be applicable only to positive trials, all clinical studies included in this evaluation demonstrated either a statistically significant result for the outcome under evaluation (in superiority trials) or a conclusion that supported noninferiority (in noninferiority trials). In the original field testing for ESMO-MCBS v1.1, 109 studies were evaluated.

The published articles for these 109 randomized clinical studies were submitted to the ASCO-NHB development team for independent scoring using the ASCO-NHB v2. One was listed twice, and four were identified as not suitable for scoring with ASCO-NHB v2 for the following reasons: nonrandomized study (n = 1),15 noninferiority study with benefit not evaluable by ASCO (n = 1),16 and unconventional designs in a curative setting (n = 2).17,18

Among the 104 trials evaluated, seven were in a curative setting and 97 in a noncurative setting, including one that was scoreable in both settings. Because the ESMO-MCBS uses a different scale for studies in the curative and noncurative setting, these seven studies were excluded from this evaluation, and the results are based on evaluation of clinical benefit from the 97 studies in the noncurative setting. The 97 studies included two with two experimental arms,19,20 and two with preplanned subgroup comparisons,21-23 which yielded 102 comparisons graded using each framework (Fig 1).

The ESMO-MCBS v1.1 scoring has been published previously.2 The scoring was performed as a team process, not by any single evaluator. All abstracted data were verified from the cited primary sources for accuracy. Scoring was reviewed by multiple members of the development team and by biostatisticians and has been subjected to peer review for accuracy and reasonableness by ESMO faculty. ASCO-NHB v2 scores were derived through a similar process by the ASCO-NHB v2 development team.

Spearman rank correlation coefficient was calculated for the ESMO and ASCO grading for the 102 pairs of comparisons in the noncurative setting. ASCO-NHB v2 threshold scores that correspond to substantial and low benefit were derived from the evaluation of receiver operating characteristic curves.24 These thresholds were estimated only to facilitate comparison between the frameworks because ESMO-MCBS v1.1 uses categorical scoring and ASCO-NHB v2 uses continuous scoring. The aim of this comparative process was to identify studies with discordant scores without suggesting that either scoring system be changed. ASCO-NHB v2 was benchmarked against ESMO-MCBS v1.1 substantial benefit scores of 4 to 5 versus scores of 1 to 3 and separately for low benefit scores of 1 to 2 versus scores of 3 to 5. In addition, optimal thresholds on the basis of weighted κ optimization25,26 and results of the Svensson method27,28 for the comparison of a continuous to a discrete scale were explored as sensitivity analyses (Data Supplement).

### Table 2. Publications That Examined the Association of ESMO-MCBS Version 1.1 and ASCO-NHB Version 2 Scores in the Noncurative Setting

<table>
<thead>
<tr>
<th>First author</th>
<th>Studies evaluated</th>
<th>ESMO-MCBS version</th>
<th>ASCO-NHB version</th>
<th>Association measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheng10</td>
<td>83 RCTs of oncology drug approvals by FDA, EMA, and Health Canada between 2006 and 2015</td>
<td>1.0</td>
<td>1</td>
<td>0.36 (Spearman rank correlation coefficient)</td>
</tr>
<tr>
<td>Becker13</td>
<td>55 drug approval studies from 2004 to 2015</td>
<td>1.0</td>
<td>1</td>
<td>0.36 (Pearson’s correlation coefficient)</td>
</tr>
<tr>
<td>Del Paggio11,12</td>
<td>109* RCTs in NSCLC and breast, colorectal, and pancreatic cancer from 2011 to 2015</td>
<td>1.0</td>
<td>2</td>
<td>0.398† (Cohen’s κ)</td>
</tr>
<tr>
<td>Del Paggio12</td>
<td>109* RCTs in NSCLC and breast, colorectal, and pancreatic cancer from 2011 to 2015</td>
<td>1.1</td>
<td>2</td>
<td>0.40 (Cohen’s κ)</td>
</tr>
<tr>
<td>Bentley14</td>
<td>5 advanced lung cancer drugs</td>
<td>1.0</td>
<td>2</td>
<td>0.80 (Kendall’s W)</td>
</tr>
</tbody>
</table>

Abbreviations: ASCO-NHB, ASCO Value Framework Net Health Benefit score; EMA, European Medicines Agency; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FDA, Food and Drug Administration; NSCLC, non–small-cell lung cancer; RCT, randomized controlled trial.

*The Del Paggio data referred to the full cohort of 109 studies, which included 19 curative and 90 palliative studies. Within the palliative setting, †In the initial 2017 publication, this was 0.33, but the authors corrected it to 0.398 in their later (2018) publication.12
Studies with discordant categorical grades between the two frameworks, on the basis of the proposed thresholds, were evaluated in detail to identify the responsible factors. Analyses were performed using R-3.4.0 language for statistical computing.

RESULTS

Association of ESMO-MCBS v1.1 and ASCO-NHB v2 Scoring in the Noncurative Setting

Figure 2 presents the distribution of scores for ESMO-MCBS v1.1 and ASCO-NHB v2 by distinguishing between studies that evaluated OS (blue circle) or PFS (green circle). Two studies had discrepant evaluated end points between the two frameworks (red circles). In one, the ESMO-MCBS v1.1 grade 3 was based on OS, whereas the ASCO-NHB v2 grade 8.7 was based on PFS because ASCO assessed the OS results as exploratory. In the other, the ESMO-MCBS v1.1 grade 4 was based on evidence of noninferiority and reduced toxicity, whereas the ASCO-NHB v2 score 45.36 was based on the point estimate of the hazard ratio (HR) of OS and toxicity. After excluding these two studies, the Spearman rank correlation coefficient of the 54 studies that evaluated OS is 0.71 and for the 46 studies that evaluated PFS, 0.67 (Fig 2). Overall, the correlation coefficient for the 102 pairs of scores is 0.68.

Defining ASCO-NHB v2 Threshold Scores for Substantial and Low Benefit Consistent With ESMO-MCBS v1.1 Scoring

The optimal threshold scores found by receiver operating characteristic curves for the ASCO-NHB v2 were 46 or greater and 41 or less to define studies with substantial benefit and low benefit, respectively (see Data Supplement for details of threshold derivation). Similar thresholds and results were derived when using the optimization of weighted $\kappa$ coefficient and the Svensson method.

For consistency, common rounded thresholds (multiples of five) are used for all studies. The threshold score of 45 or greater is proposed for recognizing substantial benefit and of 40 or less for recognizing low benefit (instead of the optimal 46 or greater and 41 or less, respectively). These thresholds correspond to a minor gain or loss in specificity and sensitivity of less than 5% relative to the optimal thresholds.

Discordant Studies and Mechanisms That Generate Discordance Between the Frameworks

By applying the proposed thresholds, 37 discordant studies are identified: 19 in which the ASCO-NHB v2 category is higher than the ESMO-MCBS v1.1 category (ASCO-NHB v2 high cluster; Table 3) and 18 in which the ASCO-NHB v2 category is lower than the ESMO-MCBS v1.1 category (ASCO-NHB v2 low cluster; Table 4). If the optimal common thresholds were used instead of the proposed thresholds, one less study would be identified as discordant.

ASCO-NHB v2 higher than the ESMO-MCBS v1.1 category.

Among the 19 discordant studies in the ASCO-NHB v2 high cluster, the evaluated outcome reported in the published studies was OS in six and PFS in 13 (Table 3). Of these, one had a stated primary end point of PFS, but because mature OS results were available and no crossover existed in
assigned treatment, OS was the end point evaluated. 40, 41
Two mechanisms account for this discordance.

1. In 11 studies, 19, 21, 33-39 discordantly high ASCO-NHB v2 scores were derived on the basis of PFS results in settings where the median control PFS was less than 6 months (sometimes as low as several weeks), with the point estimate for HR ranging from 0.18 to 0.45 (ie, low or very low point estimate) and without mature OS data. Because the highest possible ESMO-MCBS v1.1 grade for PFS is 3, except in cases of reduced toxicity, tail of curve, or QoL upgrade, the ESMO-MCBS v1.1 scores remained below the ASCO-NHB v2 scores.

2. In eight studies, 20, 40-47 discordantly high ASCO-NHB v2 scores were generated by tail of curve bonuses awarded on the basis of relative OS or PFS data assessed at twice the median OS or PFS of the control arm. In one study, the clinical benefit score was based on OS gain, and the tail of the curve bonus was awarded for improvement in the tail of the PFS curve despite it not being observed in the OS curve. 41, 42 In one study graded on the basis of OS, 43 this discrepancy generated scores using the two frameworks that were two categories apart (Table 3 [asterisk]).

ASCO-NHB v2 lower than the ESMO-MCBS v1.1 category. Among the 18 discordant studies in the ASCO-NHB v2 low cluster, the evaluated end point was OS in eight studies and PFS in nine (Table 4). There was one study 30, 31 for which the ESMO-MCBS v1.1 evaluated end point was OS and the ASCO-NHB v2 evaluated end point was PFS. In four studies 38, 61-63 that evaluated OS, there was a two-grade discordance between the two frameworks (Table 4 [asterisks]). Two dominant mechanisms or a combination of them account for most of these discordant results.

1. In six studies, the discordantly low ASCO-NHB v2 scores were generated by a high HR point estimate for OS or PFS. In four studies 48-51, low ASCO-NHB v2 scores were based on OS results calculated using the point estimate of HR greater than or equal to 0.60 (range, 0.62 to 0.77). These included one study with extreme discordance. 48 In two additional studies, the low score was derived from a PFS result where the point estimate was 0.50 52 and 0.73. 53

2. In six studies, 54-60 discordantly low ASCO-NHB v2 scores were derived from high-toxicity penalties applied by the ASCO-NHB v2 but not by ESMO-MCBS v1.1. In one study, ESMO-MCBS v1.1 awarded a toxicity credit on the basis of a 12% reduction in skin cancer, whereas the ASCO-NHB v2 applied a penalty on the basis of an increase in frequency or severity of other adverse effects. 54

3. In four studies, 61-65 discordantly low ASCO-NHB v2 scores were derived from both of the aforementioned reasons. These included three studies with extreme discordance. 50-62

In one study, 30, 31 the two scales generated scores using different evaluated end points. Low ASCO-NHB v2 score was generated by a high HR point estimate for PFS and toxicity penalty, and in contrast, the higher ESMO-MCBS v1.1 score was generated by the lower limit of the 95% CI (LL95% CI) for HR of the OS and substantial gain in median survival (that met the defined thresholds for relative and absolute benefit credit) with no toxicity penalty. In one outlying study, the discrepancy was driven by a relatively low ASCO-NHB v2 score that was based on a high HR point estimate for PFS and a relatively small bonus for reduced toxicity. 19

DISCUSSION

The association between the ESMO-MCBS v1.1 and ASCO-NHB v2 scores generated by experts in the use of each framework for studies in a noncurative setting is at least moderate. It is substantially better than reported by others 10-12 with only one exception being the high Kendall’s W (0.80) reported by Bentley et al, 14 albeit they used only a small number of studies (n = 5). Our comparison of the scales is made with scores derived by expert groups using stringent methodological criteria. A learning curve exists in the correct application of these frameworks as well as many nuances to analysis and interpretation of clinical trial results that we suspect contributed to the low association observed in other publications. 10-14 This hypothesis is supported by the relatively high inter-rater variability in scoring reported by Cheng et al 19 who used both frameworks as well as by the results of the quantitative exploration on the other publications presented in the Data Supplement.

This is the first time that the developers of ASCO-NHB v2 have applied the scale to a large cohort of studies. Hitherto, there were insufficient objective data to determine which
<table>
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<tr>
<th>Reason for discrepancy, medication</th>
<th>Setting</th>
<th>Primary outcome</th>
<th>Evaluated end point</th>
<th>PFS</th>
<th>OS</th>
<th>ESMO-MCBS</th>
<th>ASCO-NHB</th>
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<tr>
<td>Nitaparib vs placebo³²</td>
<td>Platinum-sensitive relapsed ovarian cancer, planned cohorts gBRCA, non-gBRCA HRD positive, non-gBRCA</td>
<td>PFS gBRCA</td>
<td>PFS</td>
<td>5.5</td>
<td>15.5</td>
<td>0.27 (0.17 to 0.41)</td>
<td>3 39.90</td>
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<td></td>
<td>PFS non-gBRCA HRD positive</td>
<td>PFS</td>
<td></td>
<td>3.8</td>
<td>9.1</td>
<td>0.38 (0.24 to 0.59)</td>
<td>3 51.03</td>
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<td>PFS, non-gBRCA</td>
<td>PFS</td>
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<td>3.9</td>
<td>5.4</td>
<td>0.45 (0.34 to 0.61)</td>
<td>3 45.43</td>
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<td>Cabozantinib vs placebo (no crossover)³³</td>
<td>Progressive unresectable locally advanced or metastatic medullary thyroid carcinoma</td>
<td>PFS</td>
<td>PFS</td>
<td>4</td>
<td>7.2</td>
<td>0.28 (0.19 to 0.40)</td>
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<td>Regorafenib vs placebo³⁴</td>
<td>Third line after imatinib and sunitinib</td>
<td>PFS crossover allowed</td>
<td>PFS</td>
<td>0.9</td>
<td>3.9</td>
<td>0.27 (0.19 to 0.39)</td>
<td>3 54.40</td>
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<tr>
<td>Nivolumab plus or minus ipilimumab³⁵</td>
<td>First-line advanced or metastatic melanoma</td>
<td>PFS</td>
<td>PFS</td>
<td>2.9</td>
<td>8.6</td>
<td>0.42 (0.31 to 0.57), p=0.05, v=0.40</td>
<td>3 53.62</td>
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<td>Sunitinib vs placebo³⁶</td>
<td>Advanced GIST second line after imatinib</td>
<td>PFS crossover allowed</td>
<td>PFS</td>
<td>6.4 weeks</td>
<td>20.9 weeks</td>
<td>0.33 (0.23 to 0.47)</td>
<td>3 51.54</td>
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<tr>
<td>Exemestane plus or minus everolimus³⁷</td>
<td>Metastatic after failure of aromatase inhibitor (with PFS &gt; 6 months; no crossover)</td>
<td>PFS</td>
<td>PFS</td>
<td>4.1</td>
<td>6.5</td>
<td>0.36 (0.27 to 0.47)</td>
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<td>Olaparib vs placebo³⁸</td>
<td>BRCA mutated ovarian in remission</td>
<td>PFS</td>
<td>PFS</td>
<td>4.3</td>
<td>6.9</td>
<td>0.18 (0.10 to 0.31)</td>
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<tr>
<td>Pazopanib vs placebo³⁹</td>
<td>Previously treated non-GIST metastatic soft tissue sarcoma</td>
<td>PFS</td>
<td>PFS</td>
<td>1.6</td>
<td>3</td>
<td>0.31 (0.24 to 0.40)</td>
<td>3 46.79</td>
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<tr>
<td>Pemetrexed vs best supportive care⁴⁰</td>
<td>Third-line metastatic, stratified for KRAS</td>
<td>PFS</td>
<td>PFS</td>
<td>7.3 weeks</td>
<td>5 weeks</td>
<td>0.45 (0.34 to 0.59)</td>
<td>2 44.00</td>
</tr>
</tbody>
</table>

(continued on following page)
### TABLE 3. Discordant Studies When the Corresponding ESMO-MCBS Version 1.1 Category Derived From ASCO-NHB Version 2 Is Higher Than the ESMO-MCBS Version 1.1 Category (ASCO-NHB High Cluster) (continued)

<table>
<thead>
<tr>
<th>Reason for discrepancy, medication</th>
<th>Setting</th>
<th>Primary outcome</th>
<th>Evaluated end point</th>
<th>Control (months)</th>
<th>Gain (months)</th>
<th>HR (95% CI)</th>
<th>QoL</th>
<th>Toxicity</th>
<th>ESMO-MCBS</th>
<th>ASCO-NHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 2 mg/kg v docetaxel</td>
<td>Second line after platinum-based therapy or TKI (for EGFR/ALK-mutated) advanced NSCLC &gt; 1% tumor cell PD-L1 expressing</td>
<td>OS</td>
<td>OS</td>
<td>8.5</td>
<td>1.9</td>
<td>0.71 (0.58 to 0.88)</td>
<td>Reduced</td>
<td>3</td>
<td>53.14</td>
<td></td>
</tr>
<tr>
<td>Docetaxel (every 21 days) prednisone v mitoxantrone plus prednisone</td>
<td>Castration refractory</td>
<td>OS</td>
<td>OS</td>
<td>16.5</td>
<td>2.4</td>
<td>0.76 (0.62 to 0.94)</td>
<td>Improved</td>
<td>3</td>
<td>52.93</td>
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<tr>
<td>Cabozantinib v everolimus</td>
<td>Clear cell RCC second line after progression on TKI</td>
<td>PFS</td>
<td>OS</td>
<td>3.8</td>
<td>3.6</td>
<td>0.58 (0.45 to 0.75)</td>
<td>16.5</td>
<td>4.9</td>
<td>0.66 (0.53 to 0.83)</td>
<td>3</td>
</tr>
<tr>
<td>Afatinib v erlotinib</td>
<td>Squamous cell NSCLC progressed on platinum-based doublet chemotherapy</td>
<td>OS</td>
<td>OS</td>
<td>6.8</td>
<td>1.1</td>
<td>0.81 (0.69 to 0.95)</td>
<td>Improved QoL</td>
<td>2</td>
<td>43.63</td>
<td></td>
</tr>
<tr>
<td>Trifluridine/tipiracil v placebo</td>
<td>Metastatic CRC third-line therapy</td>
<td>OS</td>
<td>OS</td>
<td>5.53</td>
<td>1.8</td>
<td>0.68 (0.58 to 0.81)</td>
<td>2</td>
<td>49.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gemcitabine plus or minus nab-paclitaxel</td>
<td>First-line advanced or metastatic Good performance status</td>
<td>OS</td>
<td>OS</td>
<td>6.7</td>
<td>1.8</td>
<td>0.72 (0.62 to 0.83)</td>
<td>2</td>
<td>41.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine plus or minus lapatinib</td>
<td>Second-line metastatic after trastuzumab failure</td>
<td>PFS</td>
<td>PFS</td>
<td>4.4</td>
<td>4</td>
<td>0.49 (0.34 to 0.71)</td>
<td>NS</td>
<td>3</td>
<td>61.35</td>
<td></td>
</tr>
<tr>
<td>Erlotinib plus or minus bevacizumab</td>
<td>Advanced metastatic or recurrent nonsquamous NSCLC with EGFR-activating mutations Either exon 19 deletion or the L858R mutation</td>
<td>PFS</td>
<td>PFS</td>
<td>0.7</td>
<td>6.3</td>
<td>0.54 (0.36 to 0.79)</td>
<td>Immature QoL NS</td>
<td>3</td>
<td>47.43</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** The evaluated end point results are indicated with boldface.

**Abbreviations:** ASCO-NHB, ASCO Value Framework Net Health Benefit score; CRC, colorectal cancer; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; gBRCA, germline BRCA; GIST, GI stromal tumor; HR, hazard ratio; HRD, homologous recombination deficiency; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; QoL, quality of life; RCC, renal cell cancer; TKI, tyrosine kinase inhibitor; TTP, time to progression.

* Large discrepancy (difference greater than one level) between the two scales.
**TABLE 4.** Discordant Studies When the Corresponding ESMO-MCBS Version 1.1 Category Derived From ASCO-NHB Version 2 Score Is Lower Than the ESMO-MCBS Version 1.1 Category (ASCO-NHB Low Cluster)

<table>
<thead>
<tr>
<th>Reason for discrepancy, medication</th>
<th>Setting</th>
<th>Primary outcome</th>
<th>Evaluated end point</th>
<th>Control (months)</th>
<th>Gain (months)</th>
<th>HR (95% CI)</th>
<th>QoL</th>
<th>Toxicity</th>
<th>ESMO-MCBS</th>
<th>ASCO-NHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panitumumab plus mFOLFOX6 v bevacizumab plus mFOLFOX61,2</td>
<td>First-line metastatic CRC (KRAS WT)</td>
<td>PFS</td>
<td>OS</td>
<td>NS</td>
<td>24.3</td>
<td>9.9</td>
<td>0.62 (0.44 to 0.89)</td>
<td>4</td>
<td>37.33</td>
<td></td>
</tr>
<tr>
<td>ILF plus or minus bevacizumab12</td>
<td>First-line metastatic</td>
<td>OS</td>
<td>OS</td>
<td>15.6</td>
<td>4.7</td>
<td>0.66 (0.54 to 0.81)</td>
<td>3</td>
<td>34.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX plus or minus bevacizumab v bevacizumab alone12</td>
<td>Second-line metastatic after FOLFI</td>
<td>OS</td>
<td>OS</td>
<td>10.8</td>
<td>2.1</td>
<td>0.75 (0.63 to 0.89)</td>
<td>3</td>
<td>21.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sorafenib v placebo12,13</td>
<td>Second-line locally advanced or metastatic RCC</td>
<td>OS</td>
<td>OS</td>
<td>15.9</td>
<td>3.4</td>
<td>0.77 (0.63 to 0.90)</td>
<td>3</td>
<td>18.75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab v platinum-based chemotherapy12</td>
<td>First-line metastatic and PFS advanced NSCLC with PD-L1 &gt; 50%, EGFR and ALK WT</td>
<td>PFS</td>
<td>6</td>
<td>4.3</td>
<td>0.50 (0.37 to 0.68)</td>
<td>12% reduction in skin cancer</td>
<td>4</td>
<td>44.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI plus or minus panitumumab12</td>
<td>Second-line metastatic PFS KRAS WT</td>
<td>PFS</td>
<td>3.9</td>
<td>2</td>
<td>0.73 (0.59 to 0.90)</td>
<td>NS but immature</td>
<td>No benefit</td>
<td>3</td>
<td>37.60</td>
<td></td>
</tr>
</tbody>
</table>

**ESMO high: OS or PFS, low LL95%CI; ASCO low: OS or PFS, high point estimate HR**

(continued on following page)
TABLE 4. Discordant Studies When the Corresponding ESMO-MCBS Version 1.1 Category Derived From ASCO-NHB Version 2 Score Is Lower Than the ESMO-MCBS Version 1.1 Category (ASCO-NHB Low Cluster) (continued)

<table>
<thead>
<tr>
<th>Reason for discrepancy, medication</th>
<th>Setting</th>
<th>Primary outcome</th>
<th>Evaluated end point</th>
<th>Control (months)</th>
<th>Gain (months)</th>
<th>HR (95% CI)</th>
<th>QoL</th>
<th>Toxicity</th>
<th>ESMO-MCBS</th>
<th>ASCO-NHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temsirolimus v interferon v combined*</td>
<td>First-line poor-prognosis metastatic RCC</td>
<td>OS</td>
<td>7.3</td>
<td>Temsirolimus alone</td>
<td>3.6</td>
<td>0.73 (0.58 to 0.92)</td>
<td>4</td>
<td>22.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFIRI plus or minus cetuximab*</td>
<td>First-line metastatic stratified for KRAS WT (post hoc KRAS, MRAS WT)</td>
<td>PFS</td>
<td>OS</td>
<td>8.4</td>
<td>3</td>
<td>0.56 (0.41 to 0.76)</td>
<td>20.2</td>
<td>8.2</td>
<td>0.69 (0.54 to 0.88)</td>
<td>4</td>
</tr>
<tr>
<td>Pemetrexed v placebo**</td>
<td>Stage IIIB or IV disease maintenance after responding to four cycles platinum doublet</td>
<td>PFS stratified for histology (nonsquamous)</td>
<td>OS</td>
<td>2.6</td>
<td>1.7</td>
<td>0.50 (0.42 to 0.61)</td>
<td>10.3</td>
<td>5.2</td>
<td>0.70 (0.56 to 0.88)</td>
<td>4</td>
</tr>
<tr>
<td>FOLFIRI plus or minus cetuximab***</td>
<td>First-line metastatic stratified for KRAS WT</td>
<td>PFS</td>
<td>OS</td>
<td>8.4</td>
<td>1.5</td>
<td>0.70 (0.56 to 0.87)</td>
<td>20</td>
<td>3.5</td>
<td>0.80 (0.67 to 0.95)</td>
<td>3</td>
</tr>
</tbody>
</table>

ESMO high: OS or PFS, low LL95%CI; ASCO low: OS or PFS, high point estimate HR and toxicity penalty

NOTE. The evaluated end point results are indicated with boldface.

Abbreviations: ASCO-NHB, ASCO Value Framework Net Health Benefit score; CRC, colorectal cancer; ER, estrogen receptor; ESMO-MCBS, European Society for Medical Oncology-Magnitude of Clinical Benefit Scale; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ILF, irinotecan, leucovorin, and fluorouracil; LL95%CI, lower limit of the 95% CI; mFOLFOX, modified fluorouracil, leucovorin, and oxaliplatin; NSCLC, non–small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, progesterone receptor; QoL, quality of life; RCC, renal cell cancer; TKI, tyrosine kinase inhibitor; WT, wild type.

*Large discrepancy (difference greater than one level) between the two scales.
ASCO-NHB v2 scores correlated with thresholds for low, intermediate, or substantial benefit. Indeed, in one previous study, researchers had proposed the arbitrary threshold for ASCO-NHB v2 score for substantial benefit to be at 26, the median value. Because ESMO-MCBS v1.1 had undergone prior extensive field testing and statistical modeling and provides ordered benefit categories, it was used to derive corresponding optimal categorical thresholds for ASCO-NHB v2 scores to facilitate comparison. The analysis reported here demonstrates that ASCO-NHB v2 scores of 40 or less correspond reasonably well to ESMO-MCBS v1.1 scores 1 to 2, those greater than 40 and less than 45 to ESMO score 3, and those 45 or greater to ESMO scores 4 to 5, which represent low, intermediate, and substantial benefit categories, respectively.

When applying the derived three-level categorical scale for purposes of comparison, significant discordance remains between the grading generated by the two systems in more than 35% of the studies. Major factors that contribute to nonconvergence are different approaches to evaluation of relative and absolute gain for OS and PFS, crediting tail of the curve gains, and application of toxicity penalties. These three factors alone accounted for 34 of the 37 discordant scores (Data Supplement).

**Different Approaches to Evaluation of HR and Absolute Gain**

The use of different approaches to the evaluation of HR and absolute gain was the most common cause of divergent scoring, which contributed to 23 of the 37 discordant evaluations. The divergent scoring generated by the different approaches to evaluation of HR and absolute gain was bidirectional.

The ASCO-NHB v2 approach to scoring of PFS and OS is based on evaluation of relative benefit using the point estimate of the HR without consideration of absolute benefit; scores calculated on the basis of PFS incur a 20% penalty relative to OS scoring. Even with the penalties currently applied for scores derived from PFS in ASCO-NHB v2, this approach tends to generate high scores on the basis of PFS, especially when the control PFS is very short (Table 3). PFS often is an unreliable surrogate for improved OS, and this limitation of PFS surrogacy is not well reflected in these high scores.

Among studies that generate scores on the basis of OS, the point estimate of HR tends to be higher than for PFS, and the use of the point estimate for HR in ASCO-NHB v2 tends to generate lower scores relative to ESMO-MCBS v1.1. Consequently, when the point estimate of HR is greater than 0.6 but the absolute difference in median survival is relatively large, the ASCO-NHB v2 scores are low compared with the ESMO-MCBS v1.1 scores. This is perhaps best illustrated in the scoring of two studies of epidermal growth factor receptor antibody therapies as first-line therapy of wild-type metastatic colorectal cancer. The clinical benefit score of cetuximab in ASCO-NHB v2 is 31 on the basis of the point estimate of the HR of 0.69 (0.54 to 0.88) and for panitumumab, this score is 38 on the basis of an HR of 0.62 (0.44 to 0.89). These scores assign relatively low benefit to these treatments, even though these studies generated absolute benefit improvements in OS of 8 to 10 months (from 20.2 to 28.4 months for cetuximab and 24.3 to 34.2 months for panitumumab), which are among the largest gains observed in metastatic colorectal cancer. The ASCO-NHB v2 numeric scoring on the basis of the point estimate of the HR could penalize studies of substantial benefit by ignoring the precision of the estimate.

The ESMO-MCBS v1.1 dual rule evaluates the observed relative benefit as well as the absolute benefit in the preliminary grading of OS and PFS. The dual rule consists of the relative benefit rule whereby the LL95%CI for the HR is compared with specified threshold values (PFS: LL of 0.65 or less; OS: LL of 0.65 or less for median control of 12 months or fewer or LL of 0.70 or less for more than 12 months) and the absolute benefit rule whereby the observed absolute difference in median treatment outcome is compared with the minimum clinically significant absolute benefit. The use of the LL95%CI for the HR takes into account the variability of the estimate, which the point estimate does not. The apparent leniency to credit studies with wide CIs around the point estimate of the HR, as long as they do not cross 1, is acknowledged, but it is mitigated by the required absolute benefit thresholds.

According to the ESMO-MCBS Working Group, the validity of this approach is supported by simulations that demonstrate that a dual rule using the LL95%CI addresses both goals of inclusiveness and discernment more effectively than a dual rule using point estimate thresholds in relative benefit assessment. The simulations showed that the relative benefit assessment using the LL95%CI for HR rather than a point estimate threshold avoids exclusion of a substantial proportion of big-benefit–positive studies from achieving due credit. Moreover, it downgrades more trials with a statistically significant but clinically insignificant observed benefit than when using the point estimate (stricter discernment when the study power is 90% v 80%).

The use of both relative benefit and absolute benefit was considered by the ASCO Task Force as it developed the Value Framework. It was determined that the tool, designed for shared decision making between physicians and patients, should enable the patient to decide how much of an absolute benefit he or she would choose in the context of receiving a therapy that will have predictable toxicities.

**Different Approaches to Crediting Tail of the Curve Gains**

This factor accounted for eight of the 37 discordant studies. This discordance was unidirectional, with extra credits awarded by ASCO-NHB v2 but not by ESMO-MCBS v1.1. The frameworks differ in their criteria for awarding bonus credits for long-term survival gain. The ASCO-NHB v2 criteria award bonus points on the basis of outcomes at an evaluation point at twice the median survival of the control arm with the requirement that the survival at that point in
20% or greater in the control arm and the survival of the study arm is improved by 50% or more. Scrutiny of relevant survival curves indicates that these criteria may reward benefits on the basis of outcome differences that occur at earlier time points than the true tail of the curve. ESMO-MCBS v1.1 credits long-term PFS and OS gain for a 10% or greater absolute gain at prognostically weighted specified time points that approximate the tail of the curve; in studies where the primary outcome is OS and with a control arm median OS of less than 12 months, 12 to 24 months, and greater than 24 months, the time points for evaluation of tail of curve benefit are 2 years, 3 years, and 5 years, respectively. In addition, when there is very long-term plateauing of OS in conditions not normally treated with a curative intent, a secondary grade that acknowledges and credits the potential for long-term disease control is credited. Thus far, the only immunotherapy study to fulfill this criterion is the study of dacarbazine plus or minus ipilimumab in metastatic melanoma.

**Different Approaches to Toxicity Assessment**

This factor contributed to 12 of the 37 discordant studies. This discordance was unidirectional, with high penalties for toxicity applied by ASCO-NHB v2 but not by ESMO-MCBS v1.1. Although both frameworks award bonus scores for treatment that demonstrates reduced toxicity, their approaches differ. ASCO-NHB v2 applies penalties of up to 20 points on the basis of the number and frequency of both low-grade and high-grade adverse effects (other than laboratory parameters). The inclusion of a toxicity penalty for low-grade adverse events on the basis of input from patient groups that expressed concern that toxicity penalties based only on high-grade toxicities would exclude many low-grade events that are troubling for patients and negatively affect their activities of daily living.

In contrast, the ESMO-MCBS v1.1 only applies a toxicity penalty when the scoreable outcome is PFS and only for high-grade adverse events where there are compelling data that they compromise global QoL. This difference in approach is illustrated in the study of dabrafenib plus or minus trametinib in the treatment of unresectable or metastatic melanoma with the *BRAF* V600E mutation, where ESMO-MCBS v1.1 awarded a 1-point upgrade on the basis of the 12% reduction in skin cancers and ASCO-NHB v2 awarded a 4-point toxicity penalty largely on the basis of differences in grade 3 to 4 toxicities with frequency of less than 5%.

**Steps to Improve Convergence**

Because the ESMO and ASCO frameworks were developed with different goals, that they do not agree in the scoring of every study is not surprising. It is gratifying that there is convergence in approximately two thirds of the trials assessed using both frameworks. To improve convergence of the two frameworks, our findings suggest four issues to be addressed.

1. With regard to absolute and relative benefit, the authors of ASCO-NHB v2 have written that an ideal scale takes into consideration both absolute benefit and relative benefit gains. The current approach that is based on a numeric score derived from the HR, although practical in its simplicity, ignores the variability of the estimate and was not developed using a data-driven or statistically based approach. Future iterations of the ASCO-NHB should consider more rigorous evaluation of the scoring system.

2. With regard to scores derived from PFS, the approach to the scoring of studies on the basis of PFS data must incorporate adequate adjustments to ensure that the limitations of PFS as a surrogate for improved OS are duly expressed in the generated grades.

3. With regard to tail of the curve credits, if long-term benefit is to be called tail of the curve, the criteria should reflect the true tail, or a different term should be used to avoid confusion.

4. With regard to toxicity penalties, there is not yet an optimal approach to toxicity scoring, and both frameworks have advantages and disadvantages. The ASCO approach accounts for low-grade toxicities that often affect patient activities of daily living, but the approach requires a more complicated adjudication of reported toxicities. In this context, recognition of the initial intent of the ASCO Value Framework as a tool to assist physicians and patients as they decide on a course of cancer treatment is appropriate. The ESMO approach is simpler and accounts for important high-grade toxicities but may underestimate the effect of persistent, low-grade adverse events. The opportunity exists for the ESMO-MCBS Working Group to consider the introduction of toxicity penalties for OS studies and for the ASCO-NHB developers to reconsider the severity of the penalties applied.

In conclusion, both ESMO and ASCO recognize the importance of developing robust, valid tools for assessment of clinical benefit that are anchored in standards for accountability for reasonableness. This joint initiative is an important first step by the two organizations to develop their respective frameworks to meet the shared standards to which they aspire.

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Comparative Assessment of Clinical Benefit Using the ESMO-Magnitude of Clinical Benefit Scale Version 1.1 and the ASCO Value Framework Net Health Benefit Score

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