Appraisal of Innovative Anticancer Agents: Do the Scores of European Society for Medical Oncology–Magnitude of Clinical Benefit Scale and American Society of Clinical Oncology Task Force Correlate With Survival Gains?

TO THE EDITOR: In 2015, a task force of oncologists coordinated by ASCO developed a complex consensus document that examined the main determinants of effectiveness for current anticancer treatments along with data on treatment costs.1,2 In particular, data on effectiveness and cost were combined to produce a series of information that patients can use—together with oncologists—to select their treatment from available options. In the same year, another project with similar characteristics was carried out by the European Society for Medical Oncology (ESMO). The ESMO report3 was aimed at determining the magnitude of clinical benefit from anticancer therapies by using a standardized approach. This report showed an important difference because costs were not included in the analysis. Overall, the degree of technicality of both these documents was kept to a minimum, and one important reason for this choice is that the scores—and especially the ASCO score—were designed to also be used by patients.

The ASCO task force document and the ESMO report share an important characteristic as both generate a score that quantifies the incremental clinical benefit that is associated with a new treatment compared with the standard of care. These scores are denoted as net health benefit score in the ASCO tool and magnitude of clinical benefit score in the ESMO tool.

Before the availability of these two tools, determining the incremental benefit in the health care decision process had been a task typically given to health technology assessment (HTA) evaluations.4,5 In fact, for many decades, gain in survival or in quality-adjusted survival has been the mainstay of the decision process of HTA, and there is worldwide experience surrounding this point.4,6

In the current context, where these two new tools have been made available, an essential question is to determine whether the scores generated by the two methods correlate with the values of survival gain. The analyses described herein, which are aimed at this objective, have been focused on the ESMO method—and not the ASCO method—mainly because the documentation needed to test a series of real examples was available for the former method and not for the latter.

Hence, to test the correlation between survival gains and ESMO scores, we analyzed the data reported in Tables 3 to 12 in the study by Cherny et al.7 Information on overall survival (OS) and progression-free survival (PFS) was evaluated in two separate analyses. All statistical calculations were carried out by using SPSS for Windows version 22 (SPSS, Chicago, IL).

The results of our analyses are summarized in Fig 1 (Panel A: information on OS, 40 examples; Panel B: information on PFS, 49 examples). Quite surprisingly, the correlation between survival gains and ESMO scores proved to be extremely poor in both analyses (determination coefficient: 0.0626 for OS data and 0.0171 for PFS data). Corresponding correlation coefficients were 0.25 and 0.13, respectively.

![Fig 1](https://ascopubs.org)
These results raise some concern mainly because ESMO scores seem to reflect a decision criterion that is different from that which has been used for more than 20 years in all HTA analyses. Regarding the ASCO task force method, the original paper that describes this new evaluation approach\textsuperscript{1,2} did not include a detailed description of a series of examples, and so we could not carry out statistical analysis to test whether scores, that is, the net health benefit score, correlated with gains; however, such an analysis could easily be performed by the task force group.

Andrea Messori, Sabrina Trippoli, and Claudio Marinai
Ente di Supporto Tecnico Amministrativo Regionale, Regional Health Service, Firenze, Italy

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

REFERENCES
4. Tufts Medical Center; Center for the Evaluation of Value and Risk in Health: Cost-effectiveness analysis registry. www.cearegistry.org

DOI: 10.1200/JCO.2016.69.2731; published at ascopubs.org/journal/jco on February 6, 2017.
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Appraisal of Innovative Anticancer Agents: Do the Scores of European Society for Medical Oncology–Magnitude of Clinical Benefit Scale and American Society of Clinical Oncology Task Force Correlate With Survival Gains?

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Andrea Messori
No relationship to disclose

Sabrina Trippoli
No relationship to disclose

Claudio Marinai
No relationship to disclose
Relevance of American Society of Clinical Oncology Value Framework Will Be Improved if It Is Based on Network Meta-Analyses

TO THE EDITOR: Value frameworks can be relevant for clinical decision-making. For many disease states, there are multiple competing interventions from which to choose, and the value of an intervention cannot be judged independently of available alternatives. For example, a significant hazard ratio for survival of 0.8 with a certain treatment compared with placebo has a different implication in a situation when no other treatments are available than it does in a situation in which several other treatments exist with similar hazard ratios. Randomized controlled trials (RCTs) are considered to provide the most credible evidence for the efficacy of an intervention, which is an essential aspect in the value assessment. However, an RCT will rarely include all competing interventions of interest for a particular disease state when there are more than two relevant treatment options available.1-4 The main reason is that many RCTs are designed for regulatory purposes to demonstrate efficacy rather than to identify the most efficacious intervention available. As such, an individual trial rarely provides all information needed to guide evidence-based treatment selection. The ASCO value framework 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.”5 This statement is ignorant of a plethora of methods research, but more worrying is that it ignores the reality of available evidence and fundamentally undermines evidence-based decision-making with the aim to identify the preferred intervention among alternatives on the basis of all and only relevant evidence.1-4

Rather than judging each RCT on its own merit, as ASCO states, one should consider each study as a piece of a larger evidence base and interpret the findings as such. Each RCT evaluates a subset of all competing interventions of interest, and by considering the findings of all relevant trials simultaneously we have a lot more information that can help inform clinical decision-making. This concept has been formalized in a network meta-analysis.1-4 A network meta-analysis of RCTs can be considered an extension of traditional meta-analysis where we no longer include only trials that evaluate the same intervention relative to the same control, but we now include all relevant RCTs where each trial compares a subset of competing interventions of interest. As a result, we get not only pooled results of available treatment comparisons studied in a head-to-head fashion but also relative treatment effects between interventions that were not compared directly.

In principle, network meta-analysis relies on the same assumptions as a traditional meta-analysis.6 The findings of a meta-analysis are only relevant if the study population of each trial included in the meta-analysis is not meaningfully different from the target population for which a treatment decision needs to be made. For example, if we are interested in the efficacy of an intervention as first-line therapy of advanced unresectable melanoma, it is not of interest to include RCTs in the analysis where results are only reported for an all-comer population that is a mix of first-line and second-line patients. The pooled result is not applicable to our target population of first-line patients—assuming the treatment has a different efficacy in the first-line setting than in the second-line setting. One could even say that the pooled result obtained with the meta-analysis is biased given our decision problem. Similarly, in a network meta-analysis, we only want to consider relevant trials. If the trial populations of the different studies included in the analysis are in line with the target population of interest—that is, none of the individual trials is biased given our treatment effect estimation of interest—then the network meta-analysis results are not biased either and are equally as valid as traditional meta-analysis results.

The recommendation by ASCO to focus on individual trials means that only subsets of all available treatments can be compared as determined by available head-to-head trials. Given the reality of clinical decision-making, it would be naïve to think that health benefit scores of competing interventions that were not studied head-to-head will not be compared. The impact of between-trial differences in those implicit between-trial comparisons is likely ignored—just what the ASCO task force is worried about. Their ambitions of a relevant tool that helps to guide treatment selection can only be achieved when it is grounded in network meta-analysis. Network meta-analysis is the only transparent framework to get efficacy estimates of all competing interventions relative to one and the same treatment of reference, thereby providing coherent information to help answer the treatment selection question.

Jeroen P. Jansen
Precision Health Economics, Oakland, CA, and Tufts University School of Medicine, Boston, MA

AUTHOR’S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascpubs.org/journal/jco.

REFERENCES


© 2017 by American Society of Clinical Oncology


DOI: 10.1200/JCO.2016.69.4612; published at ascopubs.org/journal/jco on February 6, 2017.
AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Relevance of American Society of Clinical Oncology Value Framework Will Be Improved if It Is Based on Network Meta-Analyses

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rcwc or ascopubs.org/jco/site/lic.

Jeroen P. Jansen
Employment: Precision Health Economics
Reply to J.P. Jansen, A. Messori et al, and H.S.L. Jim et al

In their letter, Jim and McLeod\(^1\) address the importance of the toxicity score in determining the net health benefit (NHB) of a test regimen that has been arrived at by using the ASCO value framework. They point out that toxicity experienced by patients in clinical trials may be under-reported in the published literature as it typically represents physician interpretation of patient experience. We agree and acknowledge that widespread use of the patient-reported outcome version of the Common Terminology Criteria for Adverse Events as part of the data collected in clinical trials will provide valuable additional information in the assessment of toxicity. Doing so will contribute to a more precise and patient-centric assessment of NHB when using the ASCO value framework.

Messori et al\(^2\) raise the question of whether the NHB score derived by using the ASCO value framework and the magnitude of clinical benefit (MCB) score derived by using the European Society for Medical Oncology (ESMO) framework correlate with established methods for determining incremental benefit of a particular intervention. When these authors compared many of the trials included in the ESMO analysis, they observed a poor correlation between survival gains determined by established methodologies and reported MCB score as published by Cherny et al.\(^3\) Because the ESMO MCB framework was derived independently, we cannot address the differences that were observed and suggest communicating with those authors.

The ASCO value framework has been developed to support shared decision-making between physicians and patients when deciding on a course of therapy. The framework enables calculation of an NHB score that is derived from assessment of relative clinical benefit—overall survival or progression-free survival advantage—and toxicity—number of toxic events and their severity—of a new treatment compared with a comparator in a clinical trial and presentation of this information to patients along with the anticipated cost of the treatment options. This approach differs from a formal health technology assessment that the authors allude to and is more suited to shared decision-making. ASCO does envision adaptations of the framework for broader policy purposes and, in that context, recognizes the importance of incorporating conventional methodologies that are suitable for health technology assessments.

Jansen\(^4\) makes a strong argument for use of network meta-analyses as a means of performing cross-trial comparisons when multiple trials use different control treatments for the same clinical intervention. The ASCO Value in Cancer Care Task Force is well aware of the legitimacy of this concern and we appreciate the recommendation to incorporate this methodologic approach in future refinements of the value framework.

Lowell E. Schnipper
Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

Richard L. Schilsky
American Society of Clinical Oncology, Alexandria, VA

AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

REFERENCES

DOI: 10.1200/JCO.2016.70.9246; published at ascopubs.org/journal/jco on February 6, 2017.
Correspondence

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reply to J.P. Jansen, A. Messori et al, and H.S.L. Jim et al

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/misc/ic.

Lowell E. Schnipper  Richard L. Schilsky
Leadership: NanteHealth  No relationship to disclose
Consulting or Advisory Role: Merck
Patents, Royalties, Other Intellectual Property: Coeditor-in-chief,
UpToDate, Oncology