

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

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INTRODUCTION

Cancer clinical trials have typically investigated agents or regimens in patients selected for study based primarily on tumor histology and clinical characteristics. This approach, when successful, has too often resulted in only small incremental improvements in overall survival (OS) that likely reflect the impact of agents with modest efficacy in a subset of the study population that is not readily identifiable. Although this work has improved the lives of countless patients with cancer, it has been slow, costly, and empiric.

More recently, targeted therapies administered to patients selected by reliable and biologically relevant biomarkers have produced substantial improvements in outcomes that have rapidly transformed patient care for several cancer types.¹⁻⁵ As we improve our ability to identify the molecular drivers of cancer, it is reasonable to anticipate that highly effective, molecularly targeted regimens will continue to be introduced for use in patients who can be identified prospectively as likely to benefit from treatment.⁶ In addition, newer treatment modalities such as immune therapy and antibody-drug conjugates are emerging as highly effective therapies that are providing improvements in patient outcomes far beyond what was achieved in the past.^{7,8}

In this evolving paradigm, patients and physicians should expect that clinical trials will be designed to seek larger gains in selected groups of patients than have been achieved in the past. As articulated in the American Society of Clinical Oncology (ASCO) research blueprint,⁹ these advances should allow us to implement clinical trials where meaningful advances in patient outcomes can be achieved with smaller numbers of trial participants (ie, smaller and smarter trials). On the basis of the rapid advances made in technology to interrogate the genome, we expect that the genomic tests used to guide cancer treatment will not only improve in sensitivity and specificity but also decrease the

amount of biologic sample necessary and lower the cost and turnaround time to enable widespread use.

To examine these goals and opportunities, ASCO, via the ASCO Cancer Research Committee, convened four disease-specific working groups to consider the design of future clinical trials that would produce results that are clinically meaningful to patients (ie, significantly improved survival, quality of life [QOL], or both). Although the working groups did not restrict discussion to biomarker-driven clinical trials, the goals established will likely require enrichment strategies to achieve them. In the particular examples considered by the working groups, validated biomarkers are not currently available to select patients for treatment with specific drugs. However, we expect that over time, such biomarkers will be identified and that the goals set forth by these working groups will be achievable.

The conclusions reached by the working groups are not intended to set standards for regulatory approval or insurance coverage but rather to encourage patients and investigators to demand more from clinical trials. We recognize that the descriptions of clinically meaningful outcomes derived by the working groups are highly nuanced and influenced by clinical context, effectiveness and toxicity of available therapies, and patient goals and preferences and that they will likely change as the standard of care evolves in cancer treatment. Although OS was selected as the primary end point by all working groups, this does not diminish the value of progression-free survival (PFS) and other surrogate end points as valid end points in certain clinical situations. This is especially true in cancer types that often produce symptoms related to progressive disease, for example, painful bone metastases, where a significant prolongation in PFS may provide meaningful palliation and improved QOL.

The primary goal of the working groups was to help guide the development of definitive, randomized phase III trials, although each group recognized that it is imperative for investigators to obtain data

from well-conducted early-phase trials that will provide a strong foundation for the development of ambitious phase III studies. It is necessary to observe extremely strong signals in phase II studies if we are to expect clinically meaningful outcomes to be achieved in subsequent phase III studies. Although this statement may be obvious, we sometimes are more optimistic about results from phase II trials than is warranted.¹⁰ It is even possible that phase III studies will not be necessary if results from well-conducted phase II trials demonstrate exceptional activity that clearly benefits patients.¹¹ A recent example is the development of crizotinib for treatment of *ALK*-translocated non-small-cell lung cancer, where phase II studies were sufficient to convince patients, oncologists, and the US Food and Drug Administration that accelerated approval was warranted because phase III studies were in progress.¹² Unfortunately, however, in many cases, targeted agents continue to be developed without a complete understanding of the drug target and therefore without development of a companion diagnostic to aid in patient selection. Thus, it is imperative that trial sponsors develop comprehensive biospecimen banks for each trial with informed consent from patients that will allow investigators to ask scientific questions before and after trials are completed to facilitate biomarker discovery and validation.¹³

WORKING GROUP DELIBERATIONS

The ASCO Cancer Research Committee convened four working groups composed of experts in carcinomas of the pancreas, breast, lung, and colon. An effort was undertaken to ensure broad stakeholder input and diverse points of view. Each working group included clinical investigators, patient advocates, biostatisticians, US Food and Drug Administration oncologists, and industry oncologists. Each working group met four to nine times over a 12-month period. Preliminary conclusions were posted for public comment on April 19, 2013, and more than 100 responses were obtained. This input was then considered by the working groups and integrated into the final conclusions presented here.

Each working group first selected a patient population as the focus of its deliberations and then selected primary and secondary end points for potential trials that would reflect clinically meaningful benefits to patients. Issues frequently discussed with respect to primary end point selection included the relationship of PFS to OS in a given clinical context. Although PFS is a commonly used end point, the working groups each preferred to use OS as the primary measure of clinically meaningful outcome. The groups acknowledged the challenges with OS, such as the need for longer follow-up and the potential confounding effect of poststudy therapies on assessment of the OS end point. The magnitude of the benefit that would be considered clinically meaningful engendered lengthy discussion, particularly in the breast cancer group, where consensus was not achieved. The groups discussed the need to balance the risks and benefits of therapy to define a clinically meaningful outcome in each clinical setting.

The working groups acknowledged that crossover in clinical trials is increasingly common, because it offers patients a greater chance to receive the experimental treatment than fixed-arm trials. Clearly, trials can be designed that demonstrate clinically meaningful outcomes without affecting OS, such as trials that demonstrate noninferiority compared with existing therapies with significantly less toxicity.

In addition, we are now able to identify secondary mutations that drive tumor growth after progression during first-line targeted therapies.¹⁴ Although this information provides an opportunity for success in second-line therapies, it also makes OS a more difficult end point to attain. Thus, the use of PFS as a clinically meaningful end point may be appropriate in particular disease settings and has, in fact, been accepted by regulatory authorities on many occasions already.¹⁵⁻¹⁷

A common theme that arose in all working group discussions was the issue of QOL, and all agreed that QOL is difficult to measure and interpret, even when using validated instruments. In particular, the challenge in defining a clinically meaningful change score in global QOL measures was noted. In more recent years, interest has therefore shifted to focus on a patient's specific symptom burden and engaging the patient in reporting directly on his or her symptoms. The working groups expressed the view that serial assessment of specific cancer-related symptoms, using validated instruments and shorter, more cancer-specific surveys, can define a clinically meaningful outcome for patients, as evidenced by the 2011 approval of ruxolitinib for treatment of myelofibrosis.¹⁸

Patient symptoms resulting from cancer progression and tolerability of treatment-related toxicities are of critical importance when considering whether a new treatment produces a clinically meaningful outcome for patients. For the most part, the working groups agreed that if a therapy is less toxic than prevailing treatments, a smaller improvement in efficacy is acceptable. Conversely, a highly toxic therapy should be accompanied by an expectation of substantially greater benefit to provide a clinically meaningful outcome to patients.

To address the nuances of balancing toxicity with efficacy as well as QOL outcomes, working groups used ranges of time and hazard ratios (HRs) to describe clinically meaningful outcomes in each disease setting. However, it was generally agreed that relative improvements in median OS of at least 20% are necessary to define a clinically meaningful improvement in outcome.

OUTCOME OF THE WORKING GROUP DISCUSSIONS

The conclusions of the working groups are summarized in Table 1. All but the colon cancer group focused on patients with metastatic disease receiving first-line systemic treatment, and all groups selected OS as the primary clinical end point of interest. Each group identified an $HR \leq 0.8$ corresponding to an improvement in median OS within a range of 2.5 to 6 months, depending on the clinical context, as the minimum incremental improvement over standard therapy that would define a clinically meaningful outcome. Secondary efficacy end points of interest are summarized in Table 1 as well. Each working group felt that the incremental gains shown in Table 1 should be accompanied by little to no increase in toxicity compared with prevailing therapies and that new regimens that are substantially more toxic than current standards should also produce the greatest increments in OS to be considered as having achieved a clinically meaningful outcome. Statisticians in each group provided information regarding the number of patients necessary for study based on the ranges for OS improvement (and HRs) provided by each working group (Appendix, online only).

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point		Secondary End Point	
			Improvement Over Current OS That Would Be Clinically Meaningful (months)	Target HRs	Improvement in 1-Year Survival Rate (%)*	Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11 ¹⁹	4 to 5	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel-eligible patients	8 to 9 ^{20,21}	3 to 4	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13 ²²	3.25 to 4	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10 ²³	2.5 to 3	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18 ^{24,25}	4.5 to 6	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6 ²⁶	3 to 5	0.67 to 0.67	25 → 35	3 to 5

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival. *Current → target.

DISCUSSION

This project undertaken by four groups of experts to define clinically meaningful outcomes for cancer clinical trials provides an example of the deliberations that we believe clinical trial sponsors and investigators should undertake in developing new therapies for patients with advanced cancer. We are calling on the community of patients, patient advocates, and clinical investigators to collectively raise the bar in our expectations of the benefits of new therapies. The benchmarks we propose highlight the promise of predictive biomarkers and their associated targeted therapeutics to achieve these goals. We recognize that at present, no validated biomarkers exist to guide patient selection for clinical trials in any of the clinical scenarios described here. Thus, the outcomes discussed here can only be considered aspirational at this time. The goals put forth are the result of extensive discussion and compromise among working group members, input from the public, and insight from ASCO committees and leaders. Consensus was hard to come by, as expected. Nearly all of the working groups and stakeholders agreed that we are now in a new era, where molecular tools can be used to identify specific patient subpopulations likely to benefit from targeted therapies that in turn will lead to substantially improved treatment outcomes. Unfortunately, even with these tools already in hand for some cancers, incremental gains are still small, measured in weeks, not months or years, and often transient. Thus, much work remains to be done to optimize treatment regimens and suppress or circumvent drug resistance. Even so, the recent development of crizotinib and vemurafenib,^{2-4,7} each with a companion diagnostic, provides tangible evidence that the approaches and goals laid out here are achievable and encourages us to seek even more effective therapies for common cancers.

A focus on defining meaningful outcomes for patients will also contribute important information and perspective to ongoing discussions in many venues about improving the value of health care in general and cancer care in particular. Value can be defined in various ways, although a patient-centric definition considers patient outcomes in the context of the cost of delivering those outcomes.²⁷ Because clinical trial results provide the gold standard for defining treatment efficacy, the deliberations of the working groups around the concept of clinically meaningful outcomes will help inform discus-

sions about optimizing value in cancer care. Indeed, the ASCO Value of Cancer Care Task Force has been formed to consider how efficacy, toxicity, and cost can be weighted to best describe the value of specific treatment interventions.

We hope that the exercise described here will inspire investigators to raise the bar in an effort to significantly advance cancer care. We encourage physicians who are considering implementing trials to select those trials that are designed to deliver the most benefit to patients. We anticipate that patient advocates who are participating in peer-review programs, institutional review boards, and protocol design committees will also begin to demand more from trials. We hope that clinical trial sponsors will have a better understanding of patients' and investigators' expectations when weighing research and funding priorities for their pipeline molecules. Trials that are designed with less ambitious goals than described here may still be of benefit to individual patients if trial end points are met. However, we believe that investigators and sponsors who accept the challenges laid out here are more likely to make true advances in drug and device development that will change paradigms in cancer care and, in so doing, provide clinically meaningful outcomes for our patients. As always, discussing the value of clinical trials with patients and explaining the goals of such trials are essential in the comprehensive care of those with cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

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General Overview of Design Considerations for All Disease Types

The following assumptions are true of all designs considered:

- Two-arm trial with 1:1 randomization
- Two-sided α level of 0.05
- No interim analyses were included in the sample size projections
- Power of 80% or 90% to detect target hazard ratio on overall survival (OS) end point

Although interim analyses are not part of these calculations, it is widely supported that interim analyses for futility and efficacy should be considered when planning randomized phase III trials. Including one or more interim analyses would modestly affect these required sample sizes (< 5% impact on total sample size). It is also often appropriate to perform one-sided testing or opt for unbalanced randomization. Switching to one-sided testing would reduce the required sample size by approximately 20%. Switching to a 2:1 randomization would require an increase in sample size of approximately 15%. Because of differences in patient populations and median OS, individual disease working groups have chosen different expected times of accrual and follow-up times.

Design Considerations for Metastatic Pancreatic Cancer Phase III Trial

Assumptions:

- Accrual of 18 months
- Minimum 12-month follow-up for all patients

Scenarios considered (Appendix Table A1, online only):

- Median survival in control group, 6 months (gemcitabine population); goal: increase median survival 10 to months (hazard ratio [HR] of 0.60, assuming exponential survival function)
- Median survival in control group, 10 months (FOLFIRINOX [leucovorin, fluorouracil, irinotecan, and oxaliplatin] –eligible population); goal: increase median survival 15 to months (HR of 0.67, assuming exponential survival function)

Design Considerations for Metastatic/Stage IV Lung Cancer Phase III Trial

Assumptions:

- Accrual of 18 months
- Minimum 18-month follow-up for all patients

Scenarios considered (Appendix Table A2, online only):

- For patients with nonsquamous cell carcinoma: median survival in control group, 13 months; goal: increase median survival to 17 months (HR of 1.3, assuming exponential survival function)
- For patients with squamous cell carcinoma: median survival in control group, 10 months; goal: increase median survival to 13 months (HR of 1.3, assuming exponential survival function)

Design Considerations for Metastatic Triple-Negative Breast Cancer Phase III Trial

Assumptions:

- Accrual of 24 months
 - Minimum 36-month follow-up for all patients
- Scenario considered (Appendix Table A3, online only):
- Two-arm study designs for selected median survivals and improvements in median survivals for patients with metastatic triple-negative breast cancer

Design Considerations for Metastatic Colorectal Cancer Phase III Trial

Assumptions:

- Accrual of 12 months
 - Minimum 12-month follow-up for all patients
- Scenarios considered (Appendix Table A4, online only):
- Median survival in control group, 4 months; goal: increase median survival by 5 to 9 months (HR of 0.44, assuming exponential survival function)
 - Median survival in control group, 4 months; goal: increase median survival by 3 to 7 months (HR, 0.57); also approximately applicable to increasing median survival from 6 to 11 months (HR, 0.55)
 - Median survival in control group, 6 months; goal: increase median survival by 3 to 9 months (HR, 0.67); also corresponds to increasing 1-year survival from 25% to 40%
 - One-year survival in control group, 25%; goal: increase 1-year survival by 10% to 35% (HR, 0.76)

Table A1. Metastatic Pancreatic Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required per Arm
6	10	0.60	0.80	120	73
			0.90	160	97
8.5	12.5	0.68	0.80	211	143
			0.90	284	192
10	15	0.67	0.80	191	140
			0.90	256	188

Abbreviation: HR, hazard ratio.

Table A2. Metastatic/Stage IV Lung Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required per Arm
13	17	0.76	0.80	438	306 (612 total)
			0.90	587	414 (828 total)
10	13	0.77	0.80	457	288 (576 total)
			0.90	612	387 (774 total)

Abbreviation: HR, hazard ratio.

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Table A3. Metastatic Triple-Negative Breast Cancer Phase III Trial

Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	No. of Events Required (total)	Sample Size Required
12	18	0.67	0.80	196	220
			0.90	262	290
15	21	0.71	0.80	268	330
			0.90	358	440
18	24	0.75	0.80	380	480
			0.90	508	640
21	27	0.78	0.80	509	660
			0.90	681	880
12	16	0.75	0.80	380	420
			0.90	505	560
15	19	0.79	0.80	566	660
			0.90	756	870
18	22	0.82	0.80	789	960
			0.90	1,067	1,280
21	25	0.84	0.80	1,033	1,360
			0.90	1,382	1,790

Abbreviation: HR, hazard ratio.

Table A4. Metastatic Colorectal Cancer Phase III Trial

Scenario	Median Survival in Control Group (months)	Target Median Survival in Experimental Group (months)	HR	Power	Sample Size Required per Arm
1	4	9	0.44	0.80	30
				0.90	40
2	4	7	0.57	0.80	60
				0.90	80
3	6	9	0.67	0.80	120
				0.90	160
4	1-year OS, 25%	1-year OS, 35%	0.76	0.80	250
				0.90	340

Abbreviations: HR, hazard ratio; OS, overall survival.