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Defining Clinically Meaningful Outcomes: ASCO Recommendations to Raise the Bar for Clinical Trials

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The following does not represent a position of, or recommendations from, ASCO, its members, or the consensus of all of the authors of this draft. This document is a summary of draft recommendations generated by the ASCO Cancer Research Committee for public comment. ASCO is releasing these draft recommendations to gather feedback from the investigator, patient, and trial sponsor communities. Comments will be collected until May 1st 2013, although feedback is always welcome.

Goals for Defining Clinically Meaningful Outcomes

These recommendations are intended to provide a framework for the design of future clinical trials that would be clinically meaningful to patients and improve both their duration and quality of life. The ASCO Cancer Research Committee hopes that all parties involved in clinical trials, including trial participants, investigators, and sponsors (both government and industry) will use these guidelines as benchmarks for trial development. Having such guidelines will provide stakeholders a starting point in determining clinical trial design that focuses on clinically meaningful endpoints and the impact of therapy and disease on quality of life. Importantly, investigators, patient advocacy groups, and patients will now have more clearly defined expectations when considering clinical trials. If clinical trials with new drugs or regimens based on molecular or biologic markers have the potential to significantly improve the lives of patients and lead to advances in therapy, patients and investigators are more likely to participate in these trials, accelerating accrual and shortening the time to reach trial endpoints. This will lead to “smaller and smarter” trials, necessary to accelerate cancer research and work within a reasonable economic structure.

These guidelines are not intended to set the bar for Food and Drug Administration (FDA) approvals, but to inspire patients and investigators to demand more from clinical trials and “vote with their feet” - to participate in trials that meet these recommendations. These guidelines should serve as suggestions for the design of clinical trials based on input from our committee composed of various stakeholders in cancer therapy. We have set a high “bar” for these clinical trial endpoints in an effort to inspire all stakeholders. If we are expected to achieve the goals set forth here, we

must be able to identify driver mutations and/or pathways that are targetable by current or future drugs. Although these recommendations are intended to help guide the clinical development of definitive, randomized Phase 3 trials, it is imperative for investigators to obtain data from Phase 2 trials that will provide a strong signal for the foundation for ambitious Phase 3 studies.

A New Era of Clinical Trials

Progress in cancer therapy has traditionally been based on empiric observations of drug activity in a particular tumor type in phase I clinical trials, and then advanced through phase II and III clinical trials with little consideration in regards to molecular markers and patient selection. In the majority of cases, activity observed in early phase trials resulted in less than optimal results in Phase III studies.¹ Typically, large numbers of patients were enrolled on clinical trials in order to achieve small incremental gains that were nonetheless statistically significant²⁻⁵. Therapy that targeted the mutations specific to the cancer cell were rarely integral to clinical trials.

Work over the last two decades has revealed that genetic alterations in a patient's tumor are frequently important driving factors in the development and growth of cancer and resistance to therapy. Identification of (a) molecular "driver(s)" of the cancer and an agent that targets the mutation(s) will allow oncologists to enroll patients who are most likely to respond on the trial. The therapy is also likely to have a larger effect on the cancer. As articulated in ASCO's research blueprint⁶, these advances should allow us to implement smarter clinical trials where meaningful advances in patient outcomes can be achieved with smaller numbers of trial participants.

ASCO is developing these recommendations to challenge the research community to *raise the bar* for the design of clinical trials in an attempt to develop new treatments that will include the use of integral molecular markers in an effort to maximize patient benefit. While incremental advances have laid the foundation for today's cancer care, many of these incremental advances have not been clinically meaningful, especially if a regimen is associated with increased toxicity (as is often the case when adding a drug to a standard regimen). Although FDA approval and the cost of drugs are, of course, important issues in drug development and trial design, there are times when these issues have taken priority over the issues that patients face: longevity and quality of life. Thus, these recommendations and guidelines are solely focused on what would be clinically meaningful to patients and their families.

Developing the Recommendations

Providing guidelines and benchmarks for clinical trial outcomes across all cancers is a daunting task. The ASCO Cancer Research Committee piloted the process in four

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cancer types: pancreatic cancer, breast cancer, lung cancer, and colon cancer. A working group on each disease included investigators, patient advocates, biostatisticians, Food and Drug Administration (FDA) staff, and industry.

Each working group began by determining the patient population to study. This included discussions focused on the line of therapy (chemotherapy naïve, refractory, etc) as well as subsets of patients, such as triple negative breast cancer, or non-small cell lung cancer (NSCLC) patients with tumors with mutations not associated with particular treatments (specifically excluding EML-ALK and EGFR kinase mutations).

The working groups then selected primary and secondary endpoints of a trial. FDA staff on the working groups provided insight about prior approvals. Issues arising with primary endpoint selection included the association between progression free survival (PFS) and overall survival (OS), and the regulatory preference of OS as an endpoint. The breast and colon working groups also discussed the difficulty in obtaining an OS endpoint when patients live for a prolonged period after first line therapy and may receive subsequent therapy at progression. This was reflected by the lengthy discussion by the breast cancer group, where consensus of the entire subcommittee was not achieved. In contrast, the colon subcommittee chose to propose studies in the refractory setting, where OS was a more achievable endpoint. These examples highlight the challenges of obtaining consensus among experts and stakeholders in the field.

General Considerations

A common theme that arose in all working group discussions was the issue of quality of life (QOL). All working groups noted the challenges of the standard QOL surveys and concluded that an assessment of QOL needs to be disease specific. For example, the impact of pain and anorexia associated with pancreatic cancer is quite distinct from respiratory distress and comorbidities of patients with unresectable and/or metastatic lung cancer. Patient symptoms and toxicities of therapy are of critical importance when determining the benchmarks for clinically meaningful outcomes in all cancers discussed. For the most part, working groups agreed that if a therapy is relatively non-toxic, then a smaller improvement in survival is acceptable. Low toxicity may be achievable with some endocrine therapies such as is utilized in breast cancer, but for most other therapies, including cytotoxic therapies or kinase inhibitors, toxicity can be significant. Toxicity associated with monoclonal antibodies depends upon the individual agent. The risk/benefit tradeoff for an improvement in OS was viewed from different perspectives in different subcommittees. For example, patients with breast cancer may accept a lesser improvement in OS if the regimen of drug was not toxic, based on the fact, that in the past, many therapies for breast cancer have been well tolerated. However, advances in patients with pancreatic

cancer has been associated with associated with more pronounced toxicity with minimal gain in OS, so the bar was set somewhat higher in pancreatic cancer than in breast cancer. Overall, there was general agreement among the subcommittees that a more toxic drug or regimen would require a longer PFS or OS.

To address the issue of the balance of toxicity and QOL with efficacy/survival outcomes, working groups encouraged use of ranges of time for desirable endpoints, rather than a fixed threshold for improvements in OS (the primary endpoint chosen by all committees). All committees supported the concept of increasing median survival by a significant amount as measured in time (months), as opposed to targeting pre-defined hazard ratios (HRs) that are dependent on multiple factors. However, it was generally agreed that improvements in overall survival of a minimum of 20% is critical in establishing clinically meaningful outcomes. These recommendations must be updated and modified as the current standard of care for each disease evolves. The working groups discussed FDA regulatory issues and pricing of drugs, but these considerations were not incorporated into the CMOs for each cancer type and are beyond the scope of the charge of each committee.

Each working group summarizes their results and discussions below. Each section also includes distinct and interesting issues that arose during discussions within each working group.

Pancreatic Cancer

Recommendation: Clinical trials should aim to improve overall survival (OS) by a minimum of 50%, or 3-5 months, while considering the trade-off of toxicity and quality of life that are specific to pancreatic cancer. Table 1 details recommendations for two subgroups of pancreatic cancer patients.

Patient Population

The working group decided to focus on patients with metastatic or locally advanced pancreatic cancer because of the need for significant advances in treatment in this area. The standard of care for patients with metastatic pancreatic cancer is the FOLFIRINOX regimen (5FU, irinotecan, and oxaliplatin).⁷ Patients with unresectable, locally advanced disease or metastatic pancreatic cancer not fulfilling the criteria for FOLFIRINOX are generally treated with gemcitabine-based therapy. These two patient populations were chosen for discussion: FOLFIRINOX eligible and gemcitabine eligible.

Overall Survival as a Meaningful Endpoint

The primary endpoint chosen was overall survival (OS), which is commonly used in pancreatic cancer studies. Measurement of OS is feasible in pancreatic cancer due to the short duration of patient survival and limits on the number of lines of therapy received because of morbidity.

Median overall survival for patients receiving “FOLFIRINOX” is approximately 10-11 months, whereas the “Gemcitabine” population has an expected median overall survival of 6-8 months.^{7,8} Although hazard ratios are used commonly to determine clinical benefit, patient advocates and investigators on the working group indicated that an absolute gain of 4 to 5 months beyond the current median overall survival would be a meaningful and exciting advance. If treatment had limited side effects a gain in OS of 3-4 months was considered acceptable. With the advancement of novel therapies in the foreseen future, the 1- and 2- year survival rates may serve as valuable secondary endpoints. As a secondary endpoint, and one of great interest to patients, an increase of 10-20% in 12-month survival rates is considered a meaningful indication of potential benefit.

Quality of Life Considerations

The group concluded that improvement in quality of life, while important, would not be sufficiently exciting to pursue as the *primary* objective of a clinical trial. Current global quality of life questionnaires are not considered to be useful. Future trials should focus on specific symptoms that are relevant to patients with pancreatic cancer. The most clinically relevant symptoms are: pain, weight loss, anorexia, and fatigue.

Lung Cancer

Recommendation: Clinical trials should aim to improve overall survival (OS) by a minimum of 25% with only a minor increase in toxicity, as compared with standard therapy. Table 1 details recommendations for two subgroups of non-small cell lung cancer patients.

Patient Population

Lung cancer is a heterogenous disease comprised of various histologic subsets, but more importantly, molecularly distinct populations.⁹⁻¹¹ In order to provide meaningful recommendations, patient subpopulations must be considered individually. Advanced metastatic (stage IV) non-small cell lung cancer in the frontline/untreated setting provides two distinct subpopulations (non-squamous and squamous) for discussion. For purposes of the recommendations, patients whose tumors have EGFR mutations, ALK translocations, and ROS translocations, are excluded, as targeted agents currently provide significantly better treatment than therapies for patients without these genetic alterations.

Overall Survival as a Meaningful Endpoint

After considering a variety of clinical trial endpoints, the group chose overall survival (OS) as the primary endpoint for future trials. Although the effects of the experimental drug on OS can be clouded by treatments administered after the period

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of therapy, survival after first line therapy is, unfortunately, relatively short and OS survival is a feasible endpoint.

The working group reviewed historical data to assess a baseline median survival rate for each subpopulation. This represents the estimate median survival of patients receiving the current standard of care. In the untreated setting, median survival for patients with non-squamous is approximately 13 months while in the patients with squamous cell carcinoma, the median survival is approximately 10 months.^{12,13}

Breast Cancer

Recommendation: Clinical trials should aim to improve overall survival (OS) by a minimum of 20% if involving minimal to modest increases in toxicity. Table 1 details recommendations for patients with metastatic triple negative breast cancer who are previously untreated for metastatic disease.

Patient Population

The realization that breast cancer is heterogeneous even within a broad genotypic and phenotypic category (e.g., Her 2 amplified and ER positive as opposed to ER negative) stimulated the group to identify a relatively homogeneous population within the limits of current understanding. The group decided to focus on triple negative breast cancer and to place this trial in a population of women who had not received prior therapy for metastatic disease. The justification for this decision is the poor survival of this group of patients, the absence of validated targeted therapies, and the urgent need for improved treatment options.

Overall Survival as a Meaningful Endpoint

Overall survival was selected as a meaningful endpoint since this is of obvious importance to patients and is the preferred endpoint of the FDA when considering approval of a new agent or regimen. There are very few studies that report OS exclusively in the triple negative breast cancer subgroup. The meta-analysis reported by O'Shaugnessey, et al. was thought to represent the clearest articulation of this endpoint following first line therapy for metastatic disease in women with triple negative breast cancer.^{14,15} The median OS in this report was 18 months.

Discussions on the magnitude of improvement in OS considered to provide a clinically meaningful outcome reflected widely divergent views within the working group; each well-reasoned and carefully thought out. A proposed six-month improvement in OS produced two different views. On one hand, currently available agents have not met this magnitude of improvement in OS. Following approval,

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many of these agents have been incorporated into adjuvant or neo-adjuvant treatment regimens with notable clinical benefit for patients. On the other hand, classical cytotoxic drugs typically improve OS by 2-3 months, and we should expect better from molecularly targeted agents based on the identification of driver mutations and/or alterations^{16,17}. Consensus was reached on a ≥ 4.5 month improvement in median OS with a favorable benefit risk profile as being clinically meaningful. Higher toxicities would require a greater benefit in OS. Lower (3 to 4 months) improvement in median OS can be considered clinically meaningful if the benefit outweighs the risk.

Quality of Life Considerations

Quality of life considerations were repeatedly emphasized as being critical to the decision about the clinical importance of a result. Patient advocates who participated in this exercise reflected a consensus that, in the context of metastatic breast cancer, quality of life is as important, if not more important, than longevity. We decided to be ambitious in our thinking about OS, but not at the expense of enhanced treatment morbidity.

Colon Cancer

Recommendation: Clinical trials should aim to improve overall survival (OS) by approximately 3-5 months with minimal increases in toxicity compared to current regimens/drugs utilized in this setting. Table 1 details recommendations for patients who have progressed on all standard therapies.

Patient Population

Given the many different chemotherapeutic options, the paradigm for treating metastatic colorectal cancer patients is considered more of a continuum than an orderly progression from first to subsequent lines. Selecting the patient population to be targeted is further challenged by the frequent use of local / regional approaches to potentially resectable disease, which confounds the analysis of many common endpoints such as OS and PFS. Furthermore, there is evolving data that patients whose tumors harbor *Braf* mutations have a poorer prognosis than others¹⁸. The working group spent considerable time discussing this population and decided to exclude such patients from studies being considered for this exercise.

With these concerns, the working group considered a variety of patient populations for the identification of clinically meaningful outcomes, but felt that the many nuances and collateral options for untreated patients or those who were progressing after initial therapies would make interpretation of results difficult. For these many reasons, the group identified patients who demonstrated progression of disease on

prior therapies or who were not candidates for all currently available standard therapies.

Overall Survival as a Meaningful Endpoint

The primary endpoint chosen was overall survival, which is relatively predictable in patients who have progressed after receiving the common range of treatment options.

To put this issue in context, regorafenib was granted FDA approval for this population of patients on the basis of a 1.4-month median improvement in overall survival¹⁹. The median overall survival benefit for patients that we would consider clinically meaningful is 3-5 months and, as stated above, one must take into account the possible increase in efficacy obtained balanced with the toxicity associated with a drug or regimen.

Quality of Life Considerations

Many patients with metastatic colorectal cancer maintain an excellent performance status even as they progress through multiple lines of treatment. Regorafenib improves OS by 1.4 months, and more than half of all patients have substantial toxicity. In the absence of a significant improvement in objective responses, the clinician must weigh the risk:benefit ratio carefully to continue this therapy with significant toxicity in patients with refractory disease. Therefore, trials in patients with mCRC who are refractory to standard therapy can use regorafenib or best supportive care as the control arm.

For these reasons, the therapy should be without major toxicities such as skin or alopecia, and cumulative or chronic toxicities should be minimal. Also, this treatment should be well tolerated in patients with mild neuropathy (considered a reasonable likelihood in patients who had seen prior oxaliplatin).

Summary:

These efforts by the ASCO Cancer Research Committee and stakeholders in cancer care provide a framework for the development of clinical trials that hopefully will significantly improve the lives of patients with advanced stage malignancies. These guidelines were the outcome of compromise among committee members. Consensus was hard to come by, but nearly all of the working groups agreed that we are now in a new era where molecular tools can provide for the identification of new targets that, in turn, will lead to the development of new drugs.

We can no longer view metastasis or unresectable tumors that originate from an organ as homogenous, and thus treat with one standard regimen. There are distinct molecular subsets within each cancer type; understanding the molecular drivers of

cancer, and developing drugs to target these drivers will likely lead to significant increases in survival. In addition, understanding how cancer cells adapt through the emergence additional molecular alterations after first line therapy will likewise provide new/emerging targets for therapy. These approaches, if successful, will allow us to “raise the bar” for cancer therapy that includes both first line therapy and adaptive second line therapies. Thus, the incorporation of integral molecular markers and advances in the understanding of drivers of cancer growth into clinical trial design should lead to “smaller and smarter trials” that we hope will accelerate clinical cancer research and, more importantly, improve outcomes for our patients. These outcomes should be measured in months, and not be percentages that, at times, can be deceiving.

These guidelines that we have provided are not rules; *these are in fact guidelines* that we hope will inspire investigators to push the edge of the envelope in an effort to significantly advance cancer care. Trials that are designed with lessor goals may still be of benefit to individual patients if trial endpoints are met. However, we believe that trials that adhere to our recommendations are more likely to lead to innovation in marker, drug, and trial design that will change paradigms in cancer care.

Table 1: Summary of recommended targets for meaningful clinical trial goals.

Cancer Type	Patient Population	Current Baseline Median OS	Improvement Over Current OS That Would be Clinically Meaningful	Target Hazard Ratios	1 Yr Survival Rate (Current/ Target)
Pancreatic Cancer	FOLFIRONOX Eligible Patients	10 – 11 months	4-5 months	0.67 – 0.69	48% / 56%
Pancreatic Cancer	Gemcitabine Eligible Patients	6 - 8 months	3-4 months	0.6 – 0.679	21% / 24%
Lung Cancer	Non-squamous cell carcinoma	13 months	3.25-4 months	0.76-0.8	53% / 61%
Lung Cancer	Squamous cell carcinoma	10 months	2.5-3 months	0.77-0.8	44% / 53%
Breast Cancer	Metastatic triple negative, previously untreated for metastatic disease	18 months	4.5-6 months	0.75-0.8	63% / 69%
Colon Cancer	disease progression on all prior therapies (or not a candidate for standard 2 nd or 3 rd line options)	4-6 months	3-5 months	0.44 – 0.67*	N/A

*Hazard ratios represent a 5 month improvement on a baseline of 4 month median OS and a 3 month improvement on a baseline of 6 month median OS

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