FRIENDS OF CANCER RESEARCH ANNUAL MEETING

November 2016 - Washington DC

Supported by:

American Association for Cancer Research

American Society of Clinical Oncology

Susan G. Komen

Friends of Cancer Research Annual Meeting

November 16, 2016
8:30 AM – 4:00 PM
Hyatt Regency Washington on Capitol Hill

AGENDA

8:00 am **Breakfast**

8:30 am **Welcome** – **Jeff Allen**, President & CEO, Friends of Cancer Research
Ellen Sigal, Chair & Founder, Friends of Cancer Research

8:35 am **Keynote** – **Rob Califf**, Commissioner, U.S. FDA
Doug Lowy, Acting Director, NCI

9:00 am **Panel One – Modernization of Eligibility Criteria**
- *Moderator:* Edward Kim, Carolinas HealthCare
- Andrea Denicoff, NCI
- Elizabeth Garrett-Mayer, Medical University of South Carolina
- Paul J. Hesketh, Lahey Health Cancer Institute
- Gwynn Ison, U.S. FDA
- Pratik Multani, Ignyta
- Nancy Roach, Fight Colorectal Cancer
- Eric Rubin, Merck
- Rajeshwari Sridhara, U.S. FDA

10:45 am **Break**

11:00 am **Panel Two – Examining the Feasibility of Real World Evidence Through Pilot Studies**
- *Moderator:* Gideon Blumenthal, U.S. FDA
- Amy Abernethy, FlatIron
- Lisa LaVange, U.S. FDA
- Jane Perlmutter, Gemini Group
- Michael Taylor, Genentech

12:45 pm **Break**

1:00 pm **Lunch and Discussion – Global Harmonization of Drug Development**
- Richard Pazdur, U.S. FDA
- Francesco Pignatti, European Medicines Agency
- Prudence Scott, Medex Consulting

2:15 pm **Panel Three – Optimization of Exploratory Randomized Trials**
- *Moderator:* Lisa LaVange, U.S. FDA
- Jonathan Denne, Eli Lilly & Co.
- Eric Kowack, Ignyta
- Amy McKee, U.S. FDA
- Cyrus Mehta, Cytel Corporation
- Richard Simon, NCI
- Rajeshwari Sridhara, U.S. FDA

4:00 pm **Summary and Closing Remarks** – Samantha Roberts, Friends of Cancer Research

FRIENDS of CANCER RESEARCH

PARTNERSHIPS ***SCIENCE SOLUTIONS***

Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients.

The Power of Collaboration

During the past 20 years, Friends of Cancer Research (Friends) has been instrumental in the creation and implementation of policies ensuring patients receive the best treatments in the fastest and safest way possible. We've been successful due to our ability to convene the right people at the right time and put forth revolutionary, yet realistic ideas. Now, in our 20th year, we are energized more than ever to continue this critical work with our trusted partners, creating innovative solutions to overcome barriers standing in the way of conquering cancer. Below are highlights of our collaborations and active initiatives.

Breakthrough Therapy: *A Pathway that Rewards Innovation*

When new drugs aimed to treat serious and life-threatening conditions show unprecedented effect in early clinical testing, patients shouldn't have to wait to receive treatment. To address this complex problem, Friends worked with partners in advocacy, regulation, drug development and bipartisan Congressional champions to take the Breakthrough Therapy Designation from an innovative concept, to scientific whitepaper, to federal law in just 13 months. This resulted in the passage of an expedited FDA development program that ensures patient access to revolutionary drugs as quickly and effectively as possible.

- The concept was initiated at our Annual Meeting, with an expert working group which proposed strategies to expedite FDA approval of exceptional drugs intended to treat a serious or life-threatening disease and preliminary clinical evidence suggests it provides a substantial improvement over existing therapies, without sacrificing safety and efficacy standards
- The program has seen upwards of 400 requests, over 100 designations with more than 40 of those drugs now approved.

Lung-Map: *A Revolutionary Precision Medicine Clinical Trial Design*

Taking a new drug from the initial discovery stage through clinical testing and regulatory review is complicated, expensive and often inefficient. This is compounded by the fact that trials for new drugs are almost always conducted separately, even when multiple drugs are being developed to treat the same condition. To address these hurdles, Friends developed a first-of-its kind collaborative clinical trial.

- The approach, initiated at our Annual Meeting, is a multi-stakeholder partnership with leadership from the FDA, NCI, Foundation for the NIH, research institutions, patient advocacy groups and industry collaborating together to develop a new and more efficient protocol for how future clinical trials could be conducted.
- The trial, a biomarker driven multi-drug study in squamous cell non-small cell lung cancer launched in June, 2014, now enrolling over 1,000 patients, is open at more than 700 sites across the U.S. with 5 pharmaceutical companies collaborating on a single trial.

Creating a Blueprint *for Drug/Diagnostic Co-Development*

While cutting-edge drugs have access to special FDA pathways and approval mechanisms, the addition of companion diagnostics that enable their use can complicate the regulatory process. Through our annual "Blueprint" forum, we develop innovative solutions and approaches to address the challenges of drug/diagnostic co-development. Major outcomes of this forum include:

- Identifying ways to overcome the challenges associated with biomarker development;
- Facilitate optimal development of diagnostics with breakthrough therapies;
- Developed a regulatory framework for next-generation sequencing as a companion diagnostic;
- Develop standardized approach to increase utilization and sharing of large-scale genetic databases.

The Future of Treating Cancer: *Immunotherapies*

Friends is working to further the field of immuno-oncology through the development of a Policy Advisory Group consisting of a small, but representative group of scientific, clinical, patient, policy and industry thought leaders. These thought leaders will shape a multi-stakeholder process to pave the way for this exciting new science. In April of 2016, Friends became a launch partner of The Parker Institute for Immunotherapy, with Friends Chair, Ellen Sigal, serving on the institute's advisory committee.

Patient & Advocate *Regulatory Education*

Patient input in the regulatory process is a vital part of the evaluation and approval of new therapies. The FDA structure and process for potential new therapies is complicated and not commonly understood. To best equip advocates to engage with researchers, regulators and scientists, Friends is developing an online-based advocacy education and training program. This will provide a strong foundation of knowledge and act as a venue to connect patients with opportunities to impact drug development.

Policy Priorities

21st Century Policies *for 21st Century Science & Innovation*

- Friends was a primary driver of one of the most significant health-related legislative actions of 2014 and 2015, the House Energy and Commerce Committee's "21st Century Cures Initiative." The final bill passed the House with overwhelming bipartisan support.
- Friends developed key sections of the bill that represent substantive changes that will improve outcomes for patients. These sections focus on: creating a framework for patient-focused drug development, improving tools to evaluate and advance precision medicine, expanding FDA flexibility and enhancing the ability for the agency to attract the best and brightest talent.

Centers of Excellence: *Cross-Center Coordinating at the FDA to Reflect Current Patient Care*

Congress has not modernized FDA's organizational structure for medical products since the 1970s. The existing regulatory framework has been defined by a "divide and conquer" approach to oversight; separate centers within FDA regulate three major categories of medical products: drugs, devices and biologics. In order to take advantage of today's advancements in science, drug development and patient treatment, the FDA's structure needs reorganization to focus its resources and ensure the best outcomes for patients.

- Friends put forth a proposal to enhance coordination at the FDA based on specific diseases to reflect 21st Century science and modern medical care.
- Centers of Excellence will build on previous efforts to develop a more disease-oriented approach to product regulation that have demonstrated the positive effect of this type of organizational structure. They will also allow the agency to develop regular cross-center processes to align with and support employee motivation for regulating and delivering safe and effective medical products to treat major diseases.
- Our proposal was adopted by the White House as part of Vice President Biden's National Cancer Moonshot Initiative, and is included in the bipartisan Senate "Innovation for Healthier Americans Act," which is currently being finalized in the Senate.

Supported by:

American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 37,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 108 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting with nearly 19,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.

ASCO – American Society of Clinical Oncology – Making a world of difference in cancer care.

Our Mission – Conquering cancer through research, education, and promotion of the highest quality patient care. Our vision is a world where cancer is prevented or cured, and every survivor is healthy. ASCO promotes and provides for: lifelong learning for oncology professionals; cancer research; an improved environment for oncology practice; access to quality cancer care; a global network of oncology expertise; and educated and informed patients with cancer. ASCO is supported by its affiliate organization, the Conquer Cancer Foundation, which funds ground-breaking research and programs to make a tangible difference in the lives of people with cancer. ASCO's diverse network of more than 40,000 oncology professionals recognizes ASCO's dedication to provide the highest-quality resources in education, policy, the pioneering of clinical research, and above all, advancing the care of patients with cancer. ASCO is unique in that we are the only organization that encompasses all oncology subspecialties, allowing our members to grow from the professional and personal expertise of their colleagues worldwide and across disciplines. International members make up approximately 30% of the Society's total membership and represent more than 120 countries. Please visit ASCO at www.asco.org.

Susan G. Komen

Susan G. Komen is the boldest community fueling the best science and making the biggest impact in the fight against breast cancer. In 1980, Nancy G. Brinker promised her dying sister, Susan G. Komen, she would do everything in her power to end breast cancer forever. In 1982, that promise became Susan G. Komen and launched the global breast cancer movement. Our promise is to save lives and end breast cancer forever. Our motivation is that every 60 seconds, somewhere in the world, someone dies from breast cancer. We have global headquarters in Dallas, Texas, 114 affiliates in the United States and three international affiliates (Germany, Italy and Puerto Rico). We are active through partnerships in more than 30 countries around the world.

We've transformed how the world treats and talks about this disease and have helped turn millions of breast cancer patients into breast cancer survivors. Since 1982, we've funded more than $889 million in research, more than $1.95 billion in medical care, community and provider education, and psychosocial support, serving millions in over 60 countries worldwide. Visit komen.org or call 1-877 GO KOMEN. Connect with us on social at ww5.komen.org/social.

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Modernization of Eligibility Criteria

CONTRIBUTORS

Suanna Bruinooge
American Society of Clinical Oncology

Andrea Denicoff
National Cancer Institute

Elizabeth Garrett-Mayer
Medical University of South Carolina

Paul J. Hesketh
Lahey Health Cancer Institute

Gwynn Ison
U.S. FDA

Edward Kim
Levine Cancer Institute, Carolinas Healthcare System

Marina Kozak
Friends of Cancer Research

Pratik Multani
Ignyta, Inc.

Nancy Roach
Fight Colorectal Cancer

Samantha Roberts
Friends of Cancer Research

Eric Rubin
Merck Research Laboratories

Caroline Schenkel
American Society of Clinical Oncology

Rajeshwari Sridhara
U.S. FDA

Summary

Eligibility criteria are a critical component of clinical trials and serve to define the patient population under study. They can be inclusionary, perhaps by specifying a tumor type or molecular alteration needed for study entry, or exclusionary by specifying certain characteristics such as comorbidities that would render a patient ineligible for enrollment. While restricting trial eligibility to a homogenous patient group improves the ability of a trial to detect a treatment effect, should one exist, a primary purpose of eligibility criteria is to protect the safety of those patients who are thought to be at increased risk of experiencing a treatment-related adverse effect. However, excessive or overly restrictive eligibility criteria can impair clinical trial accrual and the applicability of trial results to heterogeneous "real-world" patients who ultimately may receive the drug in the post-market setting. It also delays access to investigational agents for patients who may in fact stand to benefit. In 2016, the American Society of Clinical Oncology (ASCO), Food and Drug Administration (FDA), and Friends of Cancer Research (Friends), launched an initiative to re-assess the current approach to determining clinical trial eligibility. We will build on these and other efforts and provide recommendations for how sponsors, investigators, and regulators can work together to implement expanded clinical trial eligibility where appropriate.

Background

Common exclusion/inclusion criteria have developed over time, primarily through experience with cytotoxic chemotherapeutics. Many of these are grandfathered from prior trial protocols, with little consideration as to whether they are truly appropriate for the specific clinical question being asked. Given the increase in complexity of cancer treatment, and the advent of novel therapeutic modalities, many have called for simplified, rational eligibility criteria.[1,2] Newer, molecularly targeted agents generally do not have the same safety profiles as chemotherapies and often require additional biomarker-driven patient selection parameters that may severely limit the number of patients eligible for a trial; therefore, identifying opportunities to safely broaden eligibility has been recognized as a priority.[3]

Recent cooperative group studies of the impact of different eligibility criteria on trial and patient outcomes support the need for a re-evaluation of clinical trial eligibility. Gerber *et al* reviewed lung cancer trials sponsored by the Eastern Cooperative Oncology Group (ECOG) between 1986 and 2013 and determined that patients with prior malignancies were excluded from 94% of trials that used survival as a primary endpoint and 73% of trials that used other primary endpoints.[4] This study also analyzed the SEER-Medicare database and determined that up to 18% of lung cancer patients have prior cancer diagnoses, and therefore a substantial portion of patients are potentially excluded from trials for this reason alone. Subsequent work by this group showed that prior malignancies did not impact survival outcomes in patients with stage IV lung cancer or locally advanced lung cancer, suggesting that clinical trial outcomes would not be adversely impacted by inclusion of patients with a history of prior cancer.[5,6] A similar case-by-case, evidence-based approach to assessing other common eligibility criteria will be useful to determine when they can be safely relaxed.

[1] George SL. "Reducing patient eligibility criteria in cancer clinical trials." J Clin Oncol. 1996 Apr;14(4):1364-70."

[2] Fuks A, Weijer C, Freedman B, Shapiro S, Skrutkowska M, Riaz A." A study in contrasts: eligibility criteria in a twenty-year sample of NSABP and POG clinical trials. National Surgical Adjuvant Breast and Bowel Program. Pediatric Oncology Group." J Clin Epidemiol. 1998 Feb;51(2):69-79.

[3] Kim ES, Bernstein D, Hilsenbeck SG, Chung CH, Dicker AP, Ersek JL, et al. "Modernizing Eligibility Criteria for Molecularly Driven Trials." J Clin Oncol. 2015 Sep 1;33(25):2815-20.

[4] Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. "Impact of prior cancer on eligibility for lung cancer clinical trials." J Natl Cancer Inst. 2014 Sep 24;106(11).

[5] Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. "Effect of prior cancer on outcomes in advanced lung cancer: implications for clinical trial eligibility and accrual." J Natl Cancer Inst. 2015 Feb 9;107(4).

[6] Laccetti AL, Pruitt SL, Xuan L, Halm EA, Gerber DE. "Prior cancer does not adversely affect survival in locally advanced lung cancer: A national SEER-medicare analysis." Lung Cancer. 2016 Aug;98:106-13.

ASCO-FDA-Friends Eligibility Criteria Initiative

In an effort to modernize clinical trial eligibility criteria to better reflect intended-to-treat populations and allow broader and more representative enrollment of patients in trials, four working groups composed of multiple stakeholders, including sponsors, investigators, biostatisticians, pharmacologists, regulators, and patient representatives, developed detailed consensus-driven recommendations regarding where it is scientifically and clinically appropriate to expand eligibility criteria. The four working groups considered: 1) patients who have brain metastases, 2) the minimum age of patients eligible for enrollment, 3) patients who are HIV positive, and 4) patients with organ dysfunction. In developing these recommendations, the working groups reviewed the state of the science, any existing case studies, and attempted to balance the needs of protecting patient safety, facilitating access to investigational therapies, and protecting trial integrity (including safety, efficacy, and statistical considerations). To maximize the generalizability of results, clinical trial enrollment criteria should strive for inclusiveness and provide justification for the selected inclusion and exclusion criteria if compelling safety or efficacy concerns mandate the exclusion of specific populations. Recommendations were presented at a public workshop on May 12th, 2016, and are summarized below.

Brain Metastases[7]

Broad exclusion of patients with brain metastases is common despite the very high incidence of brain metastases in some tumor types. Although life expectancy may be reduced for some patients with brain metastases, and there may be greater risk of neurological toxicity, existing literature does not indicate that these patients experience higher rates of serious adverse events. This working group developed recommendations specific to: 1) patients with treated or stable brain metastases, 2) patients with new/active/progressive brain metastases, and 3) patients with leptomeningeal disease. For patients with treated or stable brain metastases, the working group concluded that, without a compelling rationale for exclusion, these patients should be routinely included in prospective clinical trials of all phases. If there are specific safety concerns, then tailoring specific criteria to the concern is preferable to blanket exclusion of all brain metastasis patients. For patients with active brain metastases, the working group concluded that a one-size-fits-all approach is not appropriate, and factors such as natural history of the disease, trial phase and design, and the drug mechanism and potential for CNS penetration should determine whether such patients are included in a trial. If patients with active brain metastases are included, additional prospective planning may be required to better define safety and response. Early stopping rules may be appropriate should excessive toxicity be observed. Finally, the working group concluded that in most trials, it remains appropriate to exclude patients with leptomeningeal disease due to their poor prognosis, although there may be situations that warrant a cohort of such patients in early phase trials – for example, when CNS activity is anticipated.

Minimum Age[8]

Children and adolescents under the age of 18 years are often excluded from participating in clinical trials with novel agents until extensive adult data are available, sometimes many years after the introduction of an agent. Because pediatric patients have historically been considered

[7] Recommendations of the 2016 ASCO-Friends Brain Metastases Eligibility Criteria Working Group (N Lin, E Kim, A Tan, K Beal, J White, J Sul, T Prowell, LA Kordestani, L Perkins, O Rosen). In preparation for publication.

[8] Recommendations of the 2016 ASCO-Friends Minimum Age Eligibility Criteria Working Group (L Gore, F Balis, M Donoghue, N Goodman, P Ivy, G Reaman, E Rubin, K Thornton). In preparation for publication.

a vulnerable population, there is concern that a high profile adverse event in a child could endanger the entire drug development program. However, there is no evidence to support this concern. The main scientific barriers that preclude enrollment of pediatric patients in most "adult" clinical trials are the lack of overlap between some types of cancers that adult and pediatric patients develop, the potential for developmental toxicity, as well as differences in metabolism between the age groups. The working group developed recommendations for inclusion of pediatric patients in early and late phase trials. In initial dose-finding trials, the group recommended the inclusion of pediatric-specific cohorts when there is a strong scientific rationale, based on molecular pathways or histology as well as preclinical data, to believe that a specific pediatric population could benefit from a drug under study. These cohorts would assess dose and pharmacokinetics separately in the pediatric population. Staggered enrollment starting with older children followed by younger children could be considered to address potential concerns specific to younger pediatric patients, including not only metabolic differences but also challenges related to the availability of appropriate formulations for young children. The working group also recommended that later phase trials in diseases which span adult and pediatric populations include pediatric patients with the specific disease under study. Based on the similarity in metabolism between adults and adolescents, the working group recommended that patients aged 12 years and above be enrolled in such trials.

HIV/AIDS[9]

Many people infected with HIV have a near normal life expectancy due to substantial improvements in HIV therapeutics over the past 20 years. Cancer is now a leading cause of mortality in people with HIV, however most oncology studies exclude this population. This working group recommended that HIV-infected patients who are healthy and have a low risk of AIDS-related outcomes should be included in cancer clinical trials unless there is a specific rationale to exclude such patients – for example, if there is reason to believe that the investigational drug might interfere with control of HIV infection, which may be the case with some immunomodulating agents. In the absence of a rationale for exclusion, HIV-related eligibility criteria should be straight-forward and focus on current and past CD4 and T-cell counts, history (if any) of AIDS-defining conditions such as opportunistic infections other than historically low CD4 and T cell counts, and status of HIV treatment. Healthy HIV-positive patients that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication.

Organ Dysfunction[10]

This working group began by discussing the types of organ dysfunction that were likely to drive most clinical trial exclusion criteria. They decided to focus on kidney, heart, and liver dysfunction, as well as exclusion based on a prior, alternate cancer history. The group conducted analysis of these criteria from a large, representative dataset that included a cohort of nearly 13,000 patients newly diagnosed with breast, colon, lung, and bladder cancers from 2013-2014. The analysis, as well as review of the literature, helped the group determine which of the organ dysfunction criteria to prioritize for development of recommendations. Because the dataset included only newly diagnosed patients, it is possible that other exclusionary criteria should also be considered,

[9] Recommendations of the 2016 ASCO-Friends HIV/AIDS Eligibility Criteria Working Group (K Dunleavy, G Ison, RF Little, BW Miller, A Noy, M Rudek, K Schwartz, TS Uldrick, J Wang, J Zeldis,). In preparation for publication.

[10] Recommendations of the 2016 ASCO-Friends Organ Dysfunction Eligibility Criteria Working Group (SM Lichtman, P Cortazar, L Fehrenbacher, RD Harvey, NA Rahman, N Roach, D Smit, M Thompson, D Walker). In preparation for publication.

but the group decided to focus on the organ performance status that raised the most challenge for patient participation. The group prioritized a focus on renal function because the rates of exclusion based on typical hepatic and cardiac function tests would not have raised a problem with participation in the newly diagnosed patients. The group concluded that renal function criteria should be based on creatinine clearance rather than serum creatinine levels. The group also proposed liberal creatinine clearance criteria in situations where renal excretion is not a significant component of a drug's pharmacokinetics or when known dose modification strategies can allow safe and effective administration. Conservative criteria remain appropriate for nephrotoxic drugs. Although the group did not recommend changes to the current criteria for hepatic or cardiac function, they did propose that future studies include cohorts of patients with organ dysfunction as well as geriatric patients when appropriate to better define the spectrum of toxicity. This would aid clinicians in decision-making and allow a more realistic description of patient outcomes. The group agreed that exclusions based on prior malignancies should be liberalized – both in terms of the timing and types of prior malignancies, as well as current malignancies that are not life-threatening in the short term.

Implementation

Through the course of working group discussions, potential benefits and risks of expanding eligibility criteria were identified (Table 1). As previously stated, the primary purpose of eligibility criteria is to protect the safety of patients presumed to be at a higher risk of experiencing an adverse event. Thus, significant concerns are that use of broader criteria may put some patients at risk, and that the development of an effective drug could be jeopardized if a serious adverse event occurs in a patient population that is inherently sicker. Inclusion of some patients may require additional screening/monitoring or the engagement of additional expertise to manage safety issues specific to that patient population. This would help to mitigate risk in these patients but would also increase trial cost and complexity. In some cases, working groups concluded that it would be appropriate to include a traditionally excluded patient population as a part of the general trial population, while in other situations, working groups recommended that certain patient groups be included as a separate cohort within a trial or analyzed separately from the general trial population. Either of these options would again present additional operational considerations and cost to drug sponsors; however, they may also provide data in an underrepresented population that could potentially be included in a drug label and used to differentiate a drug from others in its class. Potential study design options that can be considered to address these concerns and potentially mitigate risk are provided in Table 2. Some options are similar to biomarker-based stratification designs that have been used to evaluate efficacy and toxicity in biomarker-positive and -negative patients. These designs may facilitate label inclusion of safety or efficacy information in the expanded population if sufficient data is collected to draw meaningful conclusions; however, discussion with regulators will be necessary to determine the best approach for each situation. We anticipate that current efforts to expand eligibility in several clinical trials will help to demonstrate the feasibility and that future FDA guidance, particularly with regards to safety reporting, will assist sponsors in designing more representative trials.

Following publication of the current working group recommendations, future efforts will include data-driven efforts to identify other opportunities to safely broaden clinical trials, including evaluation of potential opportunities to adjust requirements around drug washout periods, use of concomitant medications, and inclusion of geriatric patients. One goal will be to create

standardized and consistent language for trial protocols to facilitate electronic data collection and searches of clinical trials. Another goal will be to develop metrics to monitor uptake of these recommendations. Outreach to institutional review boards will be critical to ensure that patient safety is appropriately balanced with access to investigational therapies. Ultimately, the goal of this initiative is to change the culture such that sponsors and investigators include patients unless there is a compelling rationale not to, rather than the current default to exclusion. Given the significant interest in and enthusiasm for this effort from many in the cancer community, we believe this goal can be achieved for the benefit of all stakeholders.

Table 1: Benefits and Risks of Expanded Eligibility Criteria

	Patients and Physicians	Sponsors/Investigators
Benefits	Earlier access to investigational agents, expanded trial and treatment options	Ability to generalize to "real-world" patients, and may reduce post-marketing requirements.
	More complete safety data, which can inform clinical use and enable safe delivery if/once investigational agent becomes commercially available	Faster accrual
		Identification of potential safety issues during clinical trials may facilitate early development of mitigation strategies, enabling broader uptake after approval
	Availability of efficacy data can inform weighing of commercially available treatment options	Efficacy in traditionally understudied population could potentially be included in drug label and provide a differentiating factor between drugs of same class
Risks	Limited data from small cohorts may not be adequate for clinical decision-making	More variability in outcomes – may require larger sample sizes and inferences may not be as precise
	Patients that are inherently sicker may have higher risk of experiencing an adverse event due to the drug or disease	Potential safety concerns – may require separate cohorts or analysis plans and early stopping rules for excess toxicity
		May complicate attribution of adverse events - consider randomization and data from other drugs in class
	Additional screening or imaging needs in some situations may incur additional costs to patients	Increased costs associated with additional cohorts, statistical requirements, additional testing or special expertise to manage specific patient needs

Table 2: Potential Trial Designs and Considerations

Early Phase Trials

Add an expansion cohort restricted to a specific patient population (e.g., a pediatric population, patients with poor performance status, or patients with active brain metastases).

- Maximum tolerated dose, dose-limiting toxicities, pharmacokinetics may be assessed separately in that population
- Serious safety issues could prompt the cohort to be closed without compromising the entire drug development program.
- Results in early phase can inform the decision as to whether and how to include (or not) the patient population in later phase trials

Later Phase Trials

Expand eligibility criteria to include a specific patient population (may be appropriate for prior malignancies or patients with HIV) and include these patients in primary analysis

Allow broad enrollment while restricting primary analysis to narrower patient population

- Protects integrity of trial while enabling data collection in broader populations
- Data may be helpful to inform safe clinical use in "real-world" patients

Expand trial eligibility to include a specific patient group but stratify randomization where one strata includes patients who would not meet traditional eligibility to ensure balance of these patients across treatment arms.

- May be appropriate when early-phase data shows that special subset can tolerate drug but only at a lower dose, or when life expectancy is shorter in special subset

Consider adaptive designs where trial is expanded or restricted based on data collection early in the trial and recommendations from a Data Safety Monitoring Board

Initiate a separate cohort or companion protocol restricted to a specific patient population

- Similar to expanded access protocols and may only include safety monitoring

ISSUE BRIEF

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Examining the Feasibility of Real World Evidence Through Pilot Studies

CONTRIBUTORS

Amy Abernethy
Flatiron

Gideon Blumenthal
U.S. FDA

Marina Kozak
Friends of Cancer Research

Grazyna Lieberman
Genentech

Lisa LaVange
U.S. FDA

Jane Perlmutter
Gemini Group

Michael Taylor
Genentech

Summary

Technological advances in data capture are raising the potential that information collected as part of broad care delivery can be used to support the observed clinical benefit of a new drug and supplement post-marketing commitments or label claims for additional indications in rare cancers, where few treatment options exist.

Introduction

Traditional evidence generation for the development of new treatments follows well-established pathways beginning with defining safety profiles, establishing initial efficacy, and expanding to pivotal trials to support regulatory approval. Often pivotal trials rely on randomized controlled clinical trials (RCTs) that provide the most reliable information, through comprehensive designs to control for most sources of bias, regarding the effects of therapeutic interventions. In recent years, biomedical advances have facilitated broader use of alternative evidence collection models, including non-randomized approaches, where RCTs may not be feasible or ethical.[1]

While providing mechanisms to comprehensively address the safety and efficacy of novel therapies, these traditional approaches to evidence generation only provide information of relatively homogeneous populations found in clinical trials and needed for regulatory approval, yet, leave many questions unanswered regarding drug effectiveness, tolerability, and treatment heterogeneity in real-world populations. While many new drugs continue to be monitored through systemic post-market evaluation to address certain practical aspects of drug applications, the systemic monitoring of clinical practice has yet to be more broadly applied to other stages of drug development, particularly in oncology.

Additionally, new scientific advancements in drug development have led to the increase in molecularly targeted therapies, which target "subgroups of patients (within the larger population with a given disease) who are predicted to benefit from them."[2] The increased specificity and potential for substantially greater benefits over other therapies provide great promise, but also may lead to tension between the regulatory requirements and development resources, including ethics, time, costs, and patients. The Breakthrough Therapy Designation (BTD) program, for example, seek to mitigate some of these tensions by expediting the clinical development of drugs that are intended to treat serious and life-threatening diseases and for which preliminary clinical data indicate that the drug may provide a substantial benefit over available therapies, while minimizing valuable resources. While BTD and Accelerated Approval programs have contributed to the expedited development of many novel therapies, they rely on the need to expand the safety profile and confirm clinical benefit of the drug in other disease settings and/or in the post-market setting.

Real-World Evidence

The growing use of electronic health records (EHRs) have facilitated collection of patient data outside of clinical trial settings, and hold potential to further inform patient care, supplement current clinical trial methodologies, and speed drug development; in general, EHR-derived clinical data, which is a comprehensive collection of a patient's medical and clinical history, is referred to as "real world data" (RWD). EHRs, along with numerous other data sources including, randomized trial supplements, pragmatic trials, patient registries, administrative claims, surveys, pre-approval access programs, and mobile health-generated data (e.g., smartphones, wearables, social media)

[1] The role of Non-Randomized Trials for the Evaluation of Oncology Drugs. November 2014. http://www.focr.org/sites/default/files/pdf/Non-Randomized%2BTrials.pdf 2

[2] Sherman RE, Li J, Shapley S, Robb M, and Janet Woodcock. Expediting Drug Development—The FDA's New "Breakthrough Therapy" Designation, NEJM. 2013. 369:1877–1880.

all contribute to the broader concept of Real-World Evidence (RWE), referring to evidence generated from data collected outside the traditional clinical trial setting including use of data that is routinely collected in the daily practice of medicine, and thus reflective of the heterogeneous patients seen in real world practice. RWE may better reflect the general population and the care they receive, given that enrollment in clinical trials is often limited to patients with specific baseline characteristics. Therefore, high quality RWE can potentially enable a more generalizable estimate of the safety and effectiveness of therapies than well-controlled clinical trials with narrow eligibility criteria.

RWE may be particularly useful in the case of a drug with a large effect size, such as a BTD, where confidence in the original efficacy data is relatively high. While concerns regarding data quality, owing to factors such as missing information and non-systematic data collection, are substantial, information gathered from EHRs holds the promise of allowing data to be collected on more patients and more rapidly than traditional phase 4 trials, or phase 2/3 trials designed to provide evidence for new indications. Thus, in cases of transformative treatments, the question under what conditions would it be feasible to confirm clinical benefit in new indications in the real world setting and use this evidence to support new label claim, warrants serious consideration.

Real-World Evidence Applications

There are numerous uses and advantages to collecting RWD and applying it as a source of RWE to extend our understanding of the safety and effectiveness of a therapeutic.[3] The challenge for studies utilizing RWE, will be to balance the need to ease access to new promising therapies and at the same time provide strong convincing evidence of clinical benefit.

Thus, an opportunity exists to outline approaches and considerations for developing and testing pilot studies that aid in determining the feasibility of collecting and using RWE to provide strong clinical evidence to support regulatory decisions. Pilot projects have opportunities to 1) test data collection systems and identify reliable sources of RWD, 2) assess the feasibility and utility of real-world data, 3) identify novel endpoints that correlate with clinical benefit and reflect correlations between clinical practice and trial settings, and 4) determine other study criterion, such as biomarkers and study size, important for meeting study objectives. Ultimately, such studies can inform regulatory practices, including identifying criterion for label expansion, and improving our understanding of drug performance and clinical trial generalizability.

Exploring RWE Collection: Hypothetical Case Studies

We explore three potential uses for RWE using a hypothetical scenario. In this scenario, the original approval of "Therapy A" was based on a single arm study, which displayed activity similar to a Breakthrough-like product. The drug received either full approval in an indication with a small overall patient population or accelerated approval that was later converted to full approval based on a randomized study in a less sick population. The drug has been available on the market for 1+ years and additional data, including phase 4, investigator initiated studies and RWD, confirms the positive risk/benefit in the approved indication.

Based on this scenario, three case studies are considered below for using RWD could be used to support and expand the safety and efficacy dataset for hypothetical Therapy A. The goal of these approaches is to learn about the utility of collecting real-world data in the specific cases described and determine if the generated evidence that meets a pre-specified data quality

[3] Blueprint for Breakthrough: Exploring the Utility of Real World Evidence (RWE). June 2016. http://www.focr.org/sites/default/files/pdf/RWE%20-%20Project%20PRE-MEETING%20DRAFT.pdf

standard, could support a label claim for an additional indication or an update to the label considering dosage and/or schedule of approved treatment regimen. Thus, each approach requires a discussion, between the sponsor/investigator and the FDA around determining the appropriate standard for collecting real-world data, which may include observational data, as well as best approaches for combining data from multiple sources, determining the appropriate study sample size, analysis approaches, and data quality expectations.

1. Prospectively-defined collection and review of patient experiences on off-label use (i.e., observational data) for approved agents.

   Application: *Early phase 1 trials and evidence from a "basket" phase 4 trials, based on 10-15 treated patients, indicates the Therapy A maybe very active in a rare cancer, where no other treatment options are available. To gain access to this drug (off-label), the sponsor requests a meeting with the FDA to review and discuss existing evidence and the ability to collect observational data to supplement the existing limited data obtained in clinical trials.*

   Determining the feasibility of using observational data as the basis to update the label of Therapy A, will depend on an agreement around the assurance of data quality and necessary documentation, the necessity of conducting an observational study over a traditional single-arm approach, and the ability to define and meet study objectives.

   Based on the feedback received, the sponsor conducts analyses using the most relevant endpoints (e.g., physician defined response, time on current therapy, compared to time on previous therapy and/or decrease of pain medication use on current therapy, compared to previous 6 months). If significant activity is observed, sponsors may consider requesting a FDA meeting to discuss the submission of reports and data.

2. Phase 2 randomized trial approach to assess or confirm a robust response rate and continue long-term follow-up in the real-world setting.

   Application: *In a narrow disease setting, patients have limited treatment options once they exhaust the 3-4 available therapies resulting in unfavorable outcomes. A strong scientific rational exists that Therapy A could be active in a specific indication (e.g., biomarker defined). A detailed assessment of the activity of Therapy A could be done using a relatively small, approximately 60-80 patients, randomized (2:1) phase 2 study of Therapy A vs. physician's choice. If the patients on Therapy A experience significant response compared to patients on the control arm, who are progressing rapidly, then crossover at the time of progression would be allowed.*

   Concurrent to the phase 2 study, an observational data collection strategy for the same indication, matching patients on a set of pre-specified baseline characteristics and number of prior therapies, could be employed. The collection of observational data could also be used as a control arm to the phase 2 trial to assess and compare longer-term outcomes (e.g., time on the most current therapy, and even overall survival). The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study design.

3. Pragmatic randomized trial approach leveraging existing clinical infrastructure to test interventions in everyday clinical settings.

   Application: *Following initial approval of Therapy A, additional clinical experience suggests*

that a lower dose given more frequently could be just as efficacious and possibly safer than the original dose studied and included in the product label.

Efficacy and safety of the new dose could be assessed by conducting a non-inferiority pragmatic randomized study comparing the two treatment regimens. Following randomization, the data for the study (including patient characteristics, treatment, and outcomes) could be obtained from electronic health records. The feasibility of this approach would depend on sponsor/FDA agreed upon criteria for collecting, analyzing, and assuring appropriateness of data quality and study design. This approach would allow for assessment of feasibility of both obtaining consent and randomizing patients at sites beyond those typically conducting randomized controlled trials. Given the pre-specified criteria are met, the generated evidence could be used to update the label with information on the new regimen.

The success of these three approaches depends on a rigorous assessment of outcomes within the RWD setting. The assessment process needs to assure reliability, consistency and validity of the outcomes. It maybe also be required that real world data outcomes in the original indication are consistent with the results from the clinical trials in the original indication.

While not captured in the above approaches, RWD collection for Therapy A post-approval may additionally provide information on the safety profile of the drug including: dose interruptions, dose modifications, concomitant medications, additional toxicity and other adverse events, therapy duration, and may contribute to the enhanced evaluation of an appropriate dose of the drug in the post-market setting. Thus, data around patient characteristics, safety, and mortality in patients receiving treatment with Therapy A, in any treatment setting using even a limited patient pool that meet the criteria of the study population, may facilitate determination of appropriate treatment safety, dosing, and sequencing.

Real-World Evidence Considerations

Each approach will require additional considerations and questions to be addressed to determine the appropriate study mechanism. These are summarized in the below table.

Considerations	Questions
Disease setting	■ Is randomization feasible? ■ Should rarity be a factor? ■ Could study enrollment and completion be effected (i.e., inability to accrue patients)?
Efficacy experience	■ What efficacy data is available? ■ Is it consistent with a BTD? ■ Does preliminary information on the activity of the BTD in this specific indication exist?
Safety profile	■ Is there a well-described safety profile on this therapy? ■ Are adverse events well described? ■ Has appropriate dosing and sequencing been determined?
Existing treatment options	■ Could these serve as a control? ■ Could alternative treatment options effect study accrual or analysis?

Study outcomes	■ Which outcomes are appropriate for the study? • Physician assessed response rate • Duration of physician assessed response • Decrease in pain medication use as compared to patients previous 6 – 8 months • Decrease in medication use to control other disease specific symptoms • Duration on previous anti-tumor therapy as compared to duration on the most recent breakthrough therapy • Time to switch in therapy (versus control) • Overall Survival (versus control) • Physician assessed PFS (versus control)
Sample size	■ What data is already available? ■ What is the expected sample size, based on factors such as response rate?
Feasibility	■ Given the above, is the study feasible? • Can it be enrolled considering disease rarity? • What will it take to complete the study (time and resources)? • Will control patients agree to be part of this study, or will they look for other treatment options? • Where appropriate, is crossover possible? How will the point of cross-over be determined?
Data collection and use	■ What approaches can be used to minimize bias? • Data is collected from multiple medical institutions with varying standard practice • Gather data for same indication for patients treated with any other therapy as a control arm ■ Can patient level data be submitted to FDA? ■ What documentation is available for these data and can any of the source documents be audited?
Benefit/Risk	■ What are the benefits of this approach compared to other approaches? ■ Under what conditions would it be preferable to other approaches for labeling claims, i.e., additional indications for BTD? ■ Are there any legal ethical concerns with the approach? i.e., off-label promotion? ■ How can the risks for sponsors and the FDA be mitigated? ■ Can a clinical trial, or pragmatic trial be initiated in the same indication, but in earlier lines of therapy? ■ Are there conditions under which this approach would be able to support label claim for an additional indication for BTD? • Outside BTD? • Under-represented groups? (e.g. patients with brain metastases, leptomeningeal carcinomatosis) • Biomarker selected studies (e.g. selection based on liquid biopsy rather than tissue testing)?

Conclusions

As real-world evidence is increasingly used to support drug development, more research, collaboration, and transparency is needed to improve data capture, quality, and analytics. Already advancements in data capture have expanded opportunities to better incorporate patient experiences and outcomes from routine clinical care into a range of drug development processes that can improve evidence quality used to support decision making. Additional efforts, including legislative proposals and Prescription Drug User Fee Act VI (PDUFA)[4] negotiations have highlighted these issues as a priority.

The first step in realizing the numerous opportunities offered by real-world data, will be to begin testing the ability of such data to address outstanding questions in drug development. This work group considered possible approaches for designing prospective pilot studies to assess the ability of using RWE to support regulatory decisions. The three approaches outlined above for developing pilot studies are intended guide developers in considering broader data collection to inform the totality of evidence during drug development; however, careful consideration and discussions between sponsors and regulatory agencies will be needed including an agreed upon pre-specified approach, data standards, and considerations that account for any observed outcomes, such as loss of efficacy, within the real-world.

[4] PDUFA VI Commitment Letter http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf

ISSUE BRIEF

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Optimization of Exploratory Randomized Trials

CONTRIBUTORS

Eric Kowack
Ignyta

Lisa LaVange
U.S. FDA

Amy McKee
U.S. FDA

Cyrus Mehta
Cytel Corporation; Harvard University

Samantha Roberts
Friends of Cancer Research

Richard Simon
National Cancer Institute

Rajeshwari Sridhara
U.S. FDA

Mark Stewart
Friends of Cancer Research

Summary

In recent years, the field of oncology has benefitted from the development of several highly effective new therapies for some forms of cancer. These therapies may demonstrate profound treatment effects that are apparent in early phase clinical trials, necessitating expedient clinical trial approaches that move beyond the traditional stepwise drug development paradigm. These approaches must maintain rigor while improving efficiency to ensure that truly effective drugs can quickly reach patients in need without compromising patient safety. Different approaches may be needed for different scenarios. This panel will address potential paths forward when unexpectedly large improvements in overall survival (usually included as a secondary endpoint) are observed in early phase randomized studies, a scenario that is occurring with increasing frequency. Because these are exploratory trials, primarily initiated to guide "go/no-go" decisions in product development, they are typically not designed with the necessary statistical rigor for definitive assessments of clinical benefit. Therefore, using these trials as the basis of a regulatory decision without further study may present challenges. However, only using the data for a "go/no go" decision and initiating a separate randomized phase 3 trial may also be problematic depending on how compelling the exploratory trial results were as well as the level of unmet need in the disease under study. We will provide recommendations for the optimal conduct of early phase randomized trials, potential frameworks that can be put in place prospectively for the controlled expansion of exploratory trials, and statistical approaches that can be used by sponsors or FDA reviewers to help interpret the results in the absence of pre-specification and determine how to proceed in the event of unexpected but promising survival signals.

Exploratory Randomized Trials

Although exploratory trials are often single-arm studies, in some cases randomized trials are employed early in development with the objectives of providing proof-of-concept or generating hypotheses. In these trials, the patient population under study may be limited for safety reasons or to improve the chance of detecting an efficacy signal. The requirements for the trial's operating characteristics such as power and Type I error (concluding that a drug has a certain effect, when it, in fact, does not) may also be less restrictive than in later stage trials, or may not even be pre-specified. There may be multiple looks at the data, potentially introducing bias, and informal interim analyses with no planned adjustments to avoid inflation of the Type I error rate. In our scenario, compelling survival outcomes may be observed, but survival is not the primary endpoint and is rather a secondary endpoint. In fact, a variety of endpoints may be specified to assess pharmacological activity and tolerability and to provide early evidence of efficacy with respect to clinical or patient reported outcomes, typically with no plans to account for multiplicity due to the numerous outcomes in place. In general, these "looser" operating characteristics are accepted for exploratory trials, with the assumption that clinical benefit will be rigorously assessed in later phase trials.

Consequently, if unexpected and potentially exceptional survival signals are observed in an exploratory randomized study, these issues can lead to difficult decisions about whether to expand the ongoing trial, initiate a subsequent phase 3 trial, or seek regulatory approval. Options available to sponsors could include:

Traditional approach:

1. Use the exploratory data results solely for a "go/no go" decision and initiate confirmatory trials.

Alternative approaches:

2. Expand the exploratory randomized trial, and if the survival benefit is maintained, seek regulatory approval.

3. For exceptional survival data in exploratory randomized trial, submit for regulatory approval, and potentially initiate a phase 3 confirmatory study at the same time.

There are many factors to consider as sponsors determine how best to proceed with unexpected data that includes both statistical and non-statistical issues.

Statistical Approaches for Interpretation of Unexpected Findings

In instances where there is little to no pre-specification in the exploratory randomized trial and an unexpectedly large improvement in overall survival is observed, sponsors and the FDA can be faced with the challenging scenario of interpreting the results. We will discuss a potential statistical model that can be useful in these scenarios. This is an adaptation of a previously published Bayesian approach which accounts for the clinical significance of the results and for the fact that the survival results were unexpected in a phase 2 trial and often not specified as the primary endpoint for analysis.[1] Bayesian approaches can be very useful in looking across multiple endpoints, analysis times, or studies. These factors are not accounted for in the calculation of a "p value".

Instead of a p value, the tool described here provides a posterior probability that the treatment effect (treatment relative to control) exceeds a minimal clinically significant threshold. For survival in oncology studies that threshold might be a 20% to 30% relative reduction in the hazard of death but will depend on the disease and line of therapy. The posterior probability depends on the observed treatment effect in the clinical trial, the size of the trial, and on the prior probability distribution of the treatment effect (i.e., the likelihood of different treatment effect sizes one would expect before seeing the results of the clinical trial). It is the prior distribution which enables one to express the fact that an extreme treatment effect on survival is unexpected for a phase 2 trial with a PFS or response endpoint. The prior distributions have decreasing effect on the posterior probabilities as the sample size of the trial increases, and in the example case studies discussed below, the results are not critically dependent of the prior distribution.

The model we have investigated is based on the estimation of an unknown hazard ratio (HR) for treatment on survival. An HR of 1.0 means no treatment effect on survival and an HR of 0.75 represents a 25% reduction in the hazard of death by treatment. The prior probability of the null hypothesis of no treatment effect on survival is denoted by $1-\theta$. For an early phase 2 trial of a drug of unknown efficacy, one would generally set this null prior probability to be .90 or some suitably large figure. The prior distribution when the null hypothesis is false is based on a standard deviation parameter τ as described in the Appendix.

[1] Simon R. "[Clinical Trials and Sample Size Considerations: Another Perspective]: Comment." Statistical Science. 2000 15(2): 103-5.

To compute the posterior probability that an observed difference in survival is clinically significant, one must specify the survival results of the trial, θ, τ, and the threshold for clinical significance (e.g. 25% reduction in hazard of death). In our simulations, we have summarized the trial results for survival by indicating the observed HR and the total number of deaths observed in the trial. For details on computing the posterior probability of a clinically significant treatment effect, see the Appendix.

It is important to note that this model helps to interpret the level and confidence of evidence in trials with unexpected results, but it does not alleviate issues related to robustness of results, sensitivity analyses, uncontrolled interim looks, and trial conduct.

Application of the Bayesian Statistical Approach to Real-World Case Studies

Iniparib is an inhibitor of the enzyme poly ADP-ribose polymerase (PARP). This example is chosen because it is a well-known example where preliminary trial results indicated a significant survival advantage which generated considerable enthusiasm. However, follow-up studies failed to confirm this effect and, in fact, demonstrated that iniparib did not inhibit PARP at clinically relevant doses. Early approval based on the initial phase 2 results would have put patients at risk by exposing them to an ineffective drug.

In a phase 2 open-label, randomized study of patients with metastatic triple negative breast cancer iniparib combined with chemotherapy improved the rate of clinical benefit from 34% to 56% (P=0.01) and the rate of overall response from 32% to 52% (P=0.02).[2] The addition of iniparib also prolonged the median progression-free survival from 3.6 months to 5.9 months (HR for progression, 0.59; P=0.01) and the median overall survival from 7.7 months to 12.3 months (HR for death, 0.57; P=0.01). A subsequent randomized phase 3 trial enrolled 519 women who had previously received at least two rounds of chemotherapy. This trial was designed with overall survival and progression-free survival as co-primary endpoints and was unable to demonstrate significant improvements in these endpoints.

We applied the statistical model described above to determine how it might have influenced decision making based on the phase 2 results. The total number of deaths was not reported but was estimated to be approximately 73 from the confidence interval given for the HR. From that value and the reported HR, the Bayesian analysis was performed using θ=.9 and τ=1. The resulting posterior probability distribution for the true HR for survival is shown in Figure 1. For any HR on the x axis, the y axis shows the posterior probability that the x-axis value is the true HR. An HR value of 1.0 corresponds to no treatment benefit on survival. A vertical line is drawn at 0.70 as a potential threshold for clinical significance; that is an HR < 0.70 would represent a clinically significant treatment effect on survival. The area under the curve to the left of the vertical line is the posterior probability that the treatment effect is clinically significant. In this case that area is 0.71; and may indicate that additional data is needed to ensurethe treatment effect on survival is clinically significant. If we use a threshold of clinical significance of 0.75, the area under the curve to the left of the x-axis point HR=0.75 is 0.82. Thus, even with a threshold of clinical significance of 0.75, the data is not strongly convincing that there is a clinically significant treatment effect on survival. The posterior probability of the null hypothesis that iniparib has no effect on survival was 0.044 as can be seen by the point at an x-axis value of 1.0. The posterior probability of the null hypothesis is however not very robust to changes in the model parameters, and we do not recommend using it for decision making in this context. A posterior probability of .82 that the HR for survival is less than .75 may not be sufficiently strong to support the conclusion that the

[2] SO'Shaughnessy J, Osborne C, Pippen JE, et al. "Iniparib plus chemotherapy in metastatic triple-negative breast cancer." N Engl J Med. 2011 364:205-14.

treatment is effective to a clinically significant degree. Consequently, this approach as part of the evaluation of the study would not have suggested consideration of approval of the drug without a follow-up phase 3 trial. This use of this approach would have been appropriate to guide decision making in this example.

Olaratumab is a platelet-derived growth factor (PDGF) receptor alpha blocking antibody. Olaratumab received fast track and breakthrough therapy designation, priority review status, and accelerated approval for its use in soft tissue sarcoma (STS). This example illustrates a study where there was highly significant improvement in survival outcomes, a secondary endpoint, in an early phase trial when progression-free survival was the primary endpoint. Though the study was not necessarily designed to be a pivotal trial, it did lead to its approval.

Data came from a randomized phase 2 trial involving 133 patients with multiple subtypes of metastatic STS.[3] Patients were randomized in a 1:1 ratio to receive either combination therapy comprising of olaratumab and doxorubicin, or the standard of care treatment of doxorubicin monotherapy. Patients in the combination treatment arm had a median overall survival of 26.5 months, compared with 14.7 months for those treated with doxorubicin monotherapy (HR 0.46; P=0.0003). In contrast, progression-free survival was extended by only 2.5 months in the olaratumab arm (6.6 months versus 4.1 months). Though the primary endpoint of the study, a 50% increase in progression-free survival, was met, it was not significant by investigator assessment (HR 0.67; P=0.0615) or independent radiological review (HR ratio 0.67; P=0.1208).

To evaluate how the statistical model described above might have influenced decision making, data from the phase 2 trial were evaluated using an HR of 0.46 and 91 observed deaths (Figure 1). A vertical line is drawn at a true HR of 0.70 which might correspond to a minimal clinically significant effect. The Bayesian analysis was performed and the posterior distribution of HR for survival is shown in Figure 1. The area under the curve to the left of 0.70 is approximately 0.95. This means that there is a 95% posterior probability that the true HR is 0.70 or less indicating that the evidence is convincing and supports the FDA decision. If the line were drawn at 0.75, representing a lesser reduction in survival, the posterior probability to the left of that would be 0.98.

The posterior distribution was computed based on an assumption that the prior probability of no treatment benefit was 0.90; so the survival effect was unexpected. However, the data was sufficiently strong that with 91 deaths the high prior probability of no treatment effect is overridden by the data. We also used the parameter τ=1 for the standard deviation of the treatment effect under the alternative. The results were little changed however if we used τ=2 or 0.5.

[3] Tap WD, Jones RL, Van Tine BA, et al. "Olaratumab and doxorubicin versus doxorubicin alone for treatment of soft-tissue sarcoma: an open-label phase 1b and randomized phase 2 trial." Lancet. 2016 388:488-97.

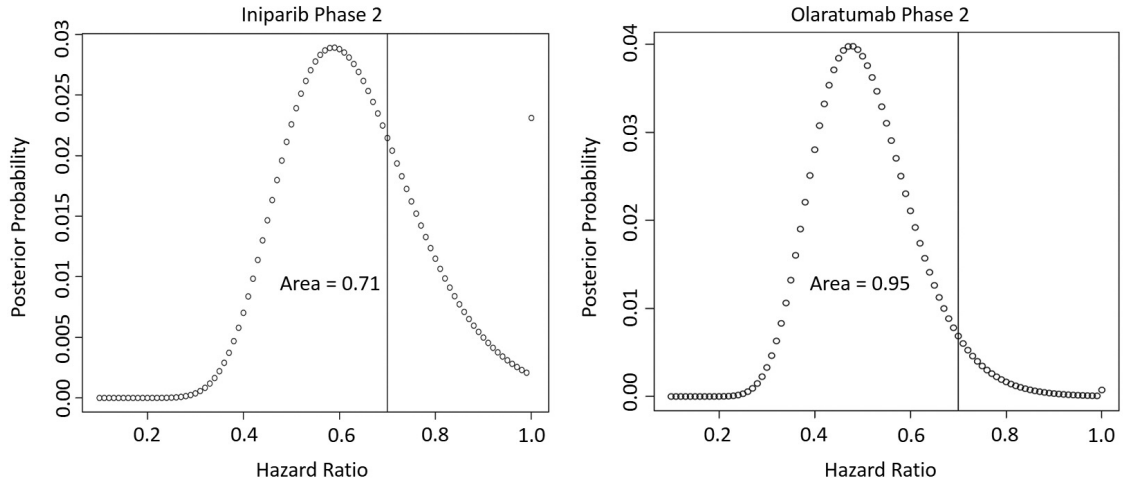

Figure 1. Statistical model evaluating data from phase 2 trial data of iniparib and olaratumab. *For any HR on the x-axis, the y-axis shows the posterior probability that the x-axis value is the true HR. An HR value of 1.0 corresponds to no treatment benefit on survival. A vertical line is drawn at 0.70 as a potential threshold for clinical significance; that is an HR < 0.70 would represent a clinically significant treatment effect on survival. The Bayesian analysis was performed and the posterior probability calculated as the area under the curve. For iniparib, there is a 71% posterior probability that the true HR is 0.70 or less indicating that additional evidence may be needed to sufficiently support the conclusion that the treatment is effective to a clinically significant degree. For Olaratumab, there is a 95% posterior probability that the true HR is 0.70 or less indicating that the evidence is convincing, but would need to be considered as part of the evaluation of the entire study.*

Additional Factors to Consider When Interpreting Findings from an Exploratory Trial

As sponsors navigate these various options, factors other than statistical analyses will also need to be considered, such as the strength of evidence from the phase 2 study, the feasibility of restarting enrollment once preliminary results are known, the role of an independent monitoring committee in triggering further enrollment, and potential drifts in patient population due to expanding the number or location of study sites.

Additionally, recruitment for a subsequent study may be difficult, once the early trial's results are publicly available. Other issues critically important include chemistry, manufacturing, and controls (CMC) readiness and the adequacy of the safety database

Standard considerations around the interpretation of results from any randomized clinical trial, such as those described in ICH E9, apply across all trials in general.[4] Several considerations are highlighted here as particularly relevant in the context of observing an unexpectedly large benefit in survival in an exploratory randomized study. The extent to which many of these can be adequately addressed will help determine the interpretation of the strength of the results, and hence help determine the best appropriate path forward.

[4] Guidance for Industry: E9 Statistical Principles for Clinical Trials.
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073137.pdf (accessed Oct. 31, 2016)

Potential sources of concern in the design, conduct, analysis, and interpretation of the results include:

- Multiplicity due to overall survival typically being a secondary endpoint, multiple interim analyses; other possible sources of multiplicity such as multiple arms, statistical methods for analyzing the data, and the primary analysis population
- The robustness of the survival results, in view of the likely small sample size of an exploratory study, especially as it relates to potential imbalances in important prognostic factors, the impact of post-discontinuation anti-cancer therapy, and the ability to evaluate consistency across subgroups
- The conduct of the study, including the level of blinding, the sufficiency of the description of the process and procedures for examining data, including informal and formal analyses, and whether crossover to the experimental therapy has been allowed

In contrast to confirmatory trials, exploratory trials often have less pre-specification allowing for more flexibility in the design and conduct of the study. This is often appropriate depending on the specific objectives of the study, the extent to which the safety and efficacy of the experimental treatment is understood, and the extent of ongoing biomarker evaluation. However, flexibility in the design and conduct of these studies can pose challenges to evaluating the results in a regulatory approval setting.

There is benefit in sponsors considering the incorporation of some standard features found in confirmatory trials when designing, conducting, and analyzing exploratory randomized studies. The addition of some pre-specification and rigor around the timing and assessment of interim analyses or the planned timing of the final overall survival analysis can often bring additional scientific rigor with little downside. Furthermore, recently observed faster-than-expected enrollment in studies (e.g., checkpoint inhibitor trials) coupled with the time lag on obtaining survival data may make it necessary to add language that allows extended enrollment if early efficacy results are quite favorable to help reduce delays in global protocol amendment.

Opportunities for Prospective Planning and Trial Expansions

In instances where there is a promising benefit in overall survival but the data is not quite strong enough or requires additional patient populations before submission for regulatory approval, a trial expansion may be one approach to efficiently collect more evidence and data. The points to consider in the section on "Additional Factors to Consider When Interpreting Findings from an Exploratory Trial" are applicable both to the original study (in terms of whether it provides a solid basis for expansion) as well as to the design of the expansion. It is also important to note that having a prospective plan in place does not guarantee positive data; it simply improves the ability to appropriately interpret the data.

Adaptive designs that prospectively incorporate a trial expansion, using appropriate statistical methods to control the Type I error rate are available and are described in the extensive literature on this topic. These designs are valuable in the context of designing a Phase 2/3 study. Few exploratory studies are designed in this way, and it would not be desirable or feasible to design all randomized phase 2 exploratory studies in this manner. However, trials for new classes of drugs that have shown exceptional promise in early exploratory settings in terms of objective

tumor response (e.g., immune checkpoint inhibitors), may warrant greater consideration for provisions to be in place at the start of the trial.

Some pre-planning around potential outcomes, associated decisions, and resultant actions into the protocol can be beneficial in terms of reducing the need for protocol amendments and improving the understanding of the operating characteristics of the study. At this stage of development though, maintaining the ability of the sponsor to also incorporate ongoing, and maybe unexpected, learnings from this trial and external data will continue to be important.

A major concern in regards to unplanned adaptations in clinical trial design or conduct during the trial is the loss of control over Type I error rates. As a starting point, it is worthwhile to consider the simplest case of expanding the trial (either in terms of number of patients or number of events) to collect additional overall survival data in the same patient population as defined by the protocol. In the context of this paper, it is assumed that a large overall survival has been observed in the original (unexpanded) study, and what might be defined as an unexpectedly large effect, is also likely to be statistically significant at the 5% level. With a statistically significant effect on overall survival acting as a gate-keeper, a study expansion in the same population would not inflate the Type I error rate above the standard 5%. Methods to assess the evidence, such as the interpretation of the p-value (and point estimate), from the expanded trial with reference to an even higher bar for remarkable results (such as that outlined in the Bayesian statistical approach above as guidance) will then need to be evaluated.[5] In instances where the threshold for statistical significance is not met, it may be desirable to increase patient follow-up time or recruit additional patients. However, in scenarios where statistical significance is not met but is still promising, it may be necessary for sponsors to have some pre-specification in place prior to unblinding (e.g., number of overall survival events to collect if the trial were to proceed) and to utilize adaptive methods to ensure statistical validity is maintained.[6,7]

Expansion from a study that made significant alterations to the patient population based on results might be more challenging and could lead to significant bias. This could be somewhat mitigated if the study was originally designed to evaluate the populations—for instance, a study designed to evaluate in a specific biomarker positive and negative population, and subsequently dropping the biomarker negative population for the expansion.

Further, expansion based on data collected from a study with insufficient quality is also a concern. Making alterations to the choice of study endpoints, patient populations, or treatment allocations based on unblinded interim results may lead to biases toward favorable study outcomes or add unwanted variability to the study characteristics. A framework designed with operating characteristics that permit trial expansion or potential drug approval depending on the outcome of the exploratory trial may help minimize uncertainty in the assessment of the results of these types of trials.

A template for pre-specified expansion could include options to modify inclusion/exclusion criteria to increase generalizability of data within a single trial, or the template could allow for adaption of specific trial features, if warranted based on accumulating data, without starting a new trial. Additionally, it could include options to increase the follow-up time and the sample size possibly through expanding the number and geographic spread of trial sites. This framework could guide the development and use of pre-specified triggers for expansion in the event of

[5] Gao P, Liu L, Mehta C. "Exact inference for adaptive group sequential designs." Stat Med. 2013 Oct;32(23):3991-4005.

[6] Denne JS. "Sample size recalculation using conditional power." Stat Med. 2001 Sep;20(17-18):2645-60.

[7] Müller HH, Schäfer H. "Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches." Biometrics. 2001 Sep;57(3):886-91.

observing a surprising survival benefit, the statistical considerations necessary for a robust analysis, and the operating characteristics necessary to minimize uncertainty in the results in these types of trials.

Conclusions

Oncology drug development is benefiting from improved research capabilities and techniques that help to better identify appropriate patient populations for clinical trials. Thus, scenarios where unexpectedly large improvements in overall survival observed in exploratory randomized studies are becoming more frequent as our scientific understanding continues to advance. New therapies have necessitated the need for innovative clinical trial designs and expedient pathways for drug approval. It is clear that full pre-planning for registration for every early phase trial is not feasible or even possible because exploratory trials need to be able to have a reasonable sample size for the phase of development; be able to address multiple exploratory objectives; and if needed, evolve in response to the data being generated. However, both sponsors and the FDA can be better equipped to handle and evaluate trials with unexpectedly large improvements in overall survival. It is important to get the most information from data collected in these trials. Therefore, we have provided considerations for sponsors to consider at the design and conduct stages and for both sponsors and the FDA to use to help evaluate these types of results, which include a Bayesian analysis approach to assist with decision-making.

Appendix

Proposed Model:

- δ = log hazard ratio for survival
- δ takes any value ≤ 0
- Prior probability $\delta=0$ is $1-\theta$
- Prior probability density for any value $\delta<0$ is θ times a folded normal $N(0,\tau)$ distribution
- Trial survival results summarized by the maximum likelihood estimate of δ denoted δ' and by the total number of deaths, D, observed in the trial.
- The standard error of δ' is approximately $s=2/\sqrt{D}$
- The posterior probability that $\delta=0$ can be written $Pr[\delta=0|\delta']=c\ (1-\theta)\phi(\delta'; mean=0, sd=s)$ where c is a normalizing constant and ϕ denotes the density function for the standard normal distribution.
- For any $\delta< 0$, the posterior probability that the log hazard ratio is δ can be written $c\ \phi(\delta'; mean=\delta, sd=s)\ \theta\ 2\phi(\delta; mean=0, sd=\tau)$
- The normalizing constant c is determined by computing the posterior over a grid and forcing the posterior values to sum to 1.
- We considered a result to be conclusively clinically significant if the posterior probability that δ is less than the threshold for clinical significance was at least 0.90
- We found that for studies of 25 total deaths or more, the results were rather insensitive to θ
- With 25 or 50 total deaths, results are convincing for clinically significant treatment effect on survival if the nominal p value for survival p <=.001
- With 100 total deaths, a nominal p<=.0001 is necessary for the results to be convincing for a clinically significant treatment effect on survival. A given p value corresponds to a smaller treatment effect as the sample size increases. Hence, larger studies require smaller p values to be clinically significant.

Friends of Cancer Research 1800 M St NW Washington, DC 20036 202.944.6708 www.focr.org