American Association for Cancer Research

615 Chestnut Street • 17th Floor • Philadelphia, PA 19106-4404
Telephone: (215) 440-9300 • Fax: (215) 440-9313 • www.aacr.org

Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

September 7, 2010

Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-N-0247

Dear Sir or Madam:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication, and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the Federal Register Notice on the Co-development of Investigational Drugs. We commend the FDA for its effort to develop guidance in this critical area that holds great promise to dramatically improve cancer therapy.

The rapid advancement of our understanding of cancer biology combined with the continuous innovation in technology is fueling novel approaches with true potential to revolutionize the treatment of cancer. The drug development enterprise is primed for a quantum leap in which new methods, approaches, and therapies must be explored without sacrificing the high standards for safety and efficacy. This new era in science challenges all stakeholders to come to the table to identify solutions to extremely difficult problems, and AACR is proud to be partner in this process.

The issues surrounding co-development of investigational agents, in particular, are complex and warrant extensive stakeholder discussions. Ultimately, the key to speeding safe and effective therapies to patients will be a flexible regulatory framework that provides drug developers with confidence in their methodologies, regulators with assurance in their ability to efficiently assess new therapies, and all parties with the motivation to rationally and reasonably pursue the best science without administrative delay.

Below, we share our perspective on alternative strategies to the current regulatory scheme for consideration by the FDA and we specify what would be most useful to learn from the FDA with regard to the agency's requirements for types and levels of evidence at the different stages of co-development.

Combination Therapy is Critical to Effective Treatments in Oncology

Combination therapy is not a new concept in oncology. For decades, clinicians have combined multiple therapeutic agents to attack cancer. Older anticancer drugs block broad biological functions

of the cell, such as cellular structure or maintenance functions, and work primarily by killing dividing cells. Toxicities are typically high for these drugs and cells rapidly develop resistance. Combinations have been used to help prevent or overcome resistance to a therapeutic agent, as well as to lower the necessary dose below the maximum tolerated dose (MTD), thereby reducing toxicities while maintaining clinical effect. With an improved understanding of the mechanisms that contribute to resistance, clinical researchers are now able to apply this knowledge through a more accurate use of combination therapies, including innovative approaches to scheduling and dosing.

Even more exciting—and more promising—is the growing wealth of information about the underlying biological mechanisms of the cancer cell and its microenvironment, which is allowing researchers to identify specific molecules and functions that can be targeted by rational drug design. Targeted therapies tend to have lower toxicity and reduced harmful side effects because the impact on ancillary cellular systems is limited.

Clinical experience with targeted therapies, however, has revealed they are not the proverbial silver bullet. We now know that this is because complex signaling networks, not simple linear pathways, control cell behaviors from cell division to invasion of tissues. Researchers are investigating how to interrupt these signaling networks in order to thwart cancer cells' ability to proliferate and metastasize. It has become clear that these networks have numerous redundancy, crosstalk and feedback mechanisms that compensate for the loss of single components. Thus, unless an agent targets the specific molecular event that is causative of that cancer, a single agent is unlikely to have a pronounced and long-lasting antitumor effect. In situations where the goal of therapy is to inhibit overlapping or redundant, dysregulated pathways, it is likely that two or more agents will be required to effectively control or cure the cancer.

New high-throughput technologies allow the examination of very large numbers of genes, proteins, and other molecules, such as the so-called "omics" approaches that analyze activities across the full genome, proteome, metabolome, etc. These types of experiments can be used to identify relevant cellular targets and, importantly, to identify multiple pathways essential to the growth and spread of cancer. These advances allow researchers to identify and evaluate promising combinations not by trial and error but by objective scientific evidence. Furthermore, technological advances also allow rapid evaluation of a large number of small molecules or other agents that may enhance the effects of an agent already being studied. As these experimental approaches mature and new technologies are created, researchers will have an even greater ability to detect vulnerable molecules and pathways and devise a rational approach to attacking the cancer cells.

As molecularly targeted cancer treatment becomes more common, we must learn from our long history with combination therapies, examine our present experience with first generation targeted therapies, and plan for a future in which combinations are the rule instead of the exception.

Biology Reveals Why Targeting Multiple Components is Necessary

- **Redundant Pathways**—In some cancers, more than one pathway can drive tumor growth and malignancy. For example, a particular tumor may receive proliferation signals from both the PI3K pathway and the Ras pathway. In this situation, neither a PI3K inhibitor nor a Ras inhibitor would be effective alone; two targeted therapies would be needed to block the drive for cancer cell proliferation.

- **Feedback and Crosstalk**—The interplay between signaling pathways is complex, and modifications to one pathway often affect the activity of other pathways. For example, the mTOR and AKT pathways control different aspects of cellular proliferation, but components of the pathways interact with each other. Inhibition of mTOR results in an increase in AKT pathway activity. If cancers with increased activity of mTOR are treated with an mTOR inhibitor, the resulting increase in AKT activity may result in continued tumor growth; in this case, one might observe an mTOR inhibitor to be effective for only a short period (before AKT activity begins to drive cancer progression), while an AKT inhibitor alone would be ineffective (because increased mTOR activity was the primary driver of the cancer).

- **Robust Pathways**—Cellular signaling pathways often create a network of interactions in which components are wholly or partially redundant. In some cancers, targeting one component of a pathway is not sufficient. For example, Merck has completed a phase I clinical trial for the two-drug combination of an IGF1R inhibitor and an mTOR inhibitor in luminal B-type breast cancer patients. Initial results show a greater than 50% response to the combination, indicating that two components of the signaling pathway must be targeted to overcome the robust signaling of the cancer cell.

The Current Regulatory Framework Falls Short

As discussed above, compounds that are highly effective in targeting specific cancer-related pathways may not yield significant clinical benefit as monotherapy, yet based on strong biology, may be highly active in combination with another compound. Moreover, with the ability today to objectively identify the most promising combinations of agents *a priori*, it will be increasingly common that the most promising therapy to test is a rational combination of two agents that have never before been tested in humans. At present, this is uncharted territory and the barriers to co-development are high and include a lack of regulatory guidance.

Under the current regulatory framework, the typical path to gain market approval of a combination therapy requires that one agent of the combination is already FDA-approved. The second agent is added to the approved drug in a subsequent clinical study, and each individual therapy and the combination must be tested in independent arms of a phase III clinical trial (A vs. B vs. A+B vs. SOC) to demonstrate the contribution of the individual components to the combination therapy.

It does not make sense to laboriously test individual drugs through all phases of human studies when strong biological rationale indicates that the combinations are highly likely to be significantly more effective than the single agents alone. Moreover, in some cases one agent may be expected, based on mechanistic and preclinical data, to have no clinical benefit on its own. Testing such an agent in the large number of patients required for a phase III trial raises serious ethical considerations. Thus, conducting a four-arm phase III trial may not be necessary, or even ethical, in some cases. A primary objective of FDA guidance for the co-development of investigational agents should be to limit, as much as possible, patient exposure to treatments that are not expected to be effective. This is an ethical imperative to both the patients on trial and to those who would benefit from resources allocated to trials intended to prove efficacy, rather than inefficacy.

The lack of clarity surrounding trial requirements is stymieing innovation. The high cost of clinical trials poses too great a risk for co-development without clear regulatory pathways. We support the use of new trial designs that generate adequate safety and efficacy information for combinations with strong biological rationale. For example, we support a phase II adaptive design that would eliminate underperforming monotherapy arms during the course of the trial and rapidly move the active combination to a phase III trial. The ultimate goal would be to do a two-arm phase III trial comparing the combination targeted therapy to standard of care and have no monotherapy arms.

We urge the FDA to adopt flexible approaches because no standard set of criteria will be applicable to every combination seeking market approval. Nevertheless, it is important that the FDA provide a qualitative description of what the agency will consider acceptable. Having working definitions for what constitutes a "strong biological rationale" is key, as is learning what the agency feels is the appropriate amount of evidence required to obviate the need for the standard four arms of a phase III trial.

A "Strong Biological Rationale" is the Driving Force behind Combination Therapy

Development of drugs for use in combination relies on a strong biological rationale, or a hypothesis supported by data showing that the drugs work in concert to achieve a therapeutic result. As the basic understanding of cancer biology grows and the ability to target specific molecules or pathways increases, biological rationale may allow for steps in the traditional drug development pathway to be omitted.

Discovery, preclinical and clinical data collectively contribute to biological rationale, and the totality of data must be considered at each step of development. Although the supporting data and strength of the hypothesis will be specific to the stage of research and affected by the specific project, FDA's characterization of these data is vital for drug developers to design protocols that will adequately demonstrate safety and efficacy at key stages of development.

In developing guidance, it would be most helpful for FDA to provide clarity on what would be considered significant data at each stage. Specifically, FDA should:

- Describe the characteristics of discovery data (e.g., genetic relationship, biologic data, etc.) and preclinical data (i.e., pharmacodynamics) that would be sufficient to warrant human trials of a drug combination in which one or both of the drugs is expected to be ineffective or minimally effective alone.
- Describe the characteristics of preclinical and phase I safety data that would allow alternative phase II and/or phase III trial designs.

Adaptive Designs for Phase IIb Trials Will Facilitate Co-Development

To speed development of safe and effective drug combinations for patients, AACR requests that the FDA provide guidance concerning data requirements for the use of adaptive randomized phase IIb trial designs that aim to rapidly eliminate underperforming monotherapy arms. Specifically, FDA can define a "formula" that describes when single therapies can be considered ineffective and when activity of the combination is considered significant. Although these parameters cannot be presented as simple rules, qualitative characterization would allow developers to better address FDA data requirements.

In developing parameters for the use of adaptive phase IIb trials for combinations of investigational agents, FDA should:

- Define the required statistical rigor for the data. For example, what is required to demonstrate that a single agent is ineffective if there is a strong biological rationale suggesting it will only be effective in combination?
- Comment on the use of clinical endpoints, such as tumor shrinkage on CT scans (measured by RECIST or other criteria), in assessing clinical activity of the combination and each monotherapy component.
- Consider assessment of absolute response and differential response. For example, define the threshold for significance of clinical benefit if a combination provides a 30% response rate while individual drugs provide a 0% response rate, or in the case when a combination provides a 70% response rate while individual drugs provide a 40% response rate.
- Characterize acceptable surrogate endpoints, recognizing that multiple endpoints are informative for different purposes. FDA could clarify whether endpoints for determining activity of single agent versus combination can be different from endpoints for determining clinical benefit.
- Reconcile cases in which clinically meaningful data are not acceptable to the FDA for safety and efficacy determinations.

The AACR hopes that the FDA will continue to seek stakeholder involvement and offers its resources to assist in development of reference cases, collection of data, and/or discussion of issues that FDA would find useful for its deliberations.

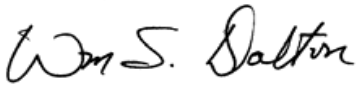
Concluding Remarks

Clarity on the regulatory requirements for co-development of investigational drugs is complicated by the fact that the issue intersects with many other complex issues facing drug development more broadly, including appropriate use of adaptive designs, biomarkers, surrogate endpoints, and multiple, flexible endpoints. We strongly urge the FDA to provide leadership on these related issues to expedite not only co-development of combinations but drug development more generally. These issues should be considered concomitantly to move the entire drug development enterprise forward as rapidly as possible.

We cannot underscore enough our appreciation that the FDA is pursuing this complex and challenging issue. The fast pace of progress in science and technology drives a continual evolution of our understanding of cancer biology and innovation in our approaches to cancer treatment. Such rapid change necessitates flexible modernization of regulatory approaches. We are confident the FDA can develop guidance on co-development that will expedite the development of the most effective drug combinations, while maintaining the agency's high standard of safety. Providing clear metrics by which the FDA will evaluate combinations will foster co-development of combinations and will undoubtedly have a dramatic impact on the speed with which patients gain access to novel life-saving therapies.

Representing cancer researchers across the discovery and development continuum, the AACR again thanks the FDA for the opportunity to comment and looks forward to contributing its collective expertise in further considerations of these and other issues.

Sincerely,



William S. Dalton, Ph.D., M.D.
Chair, Science Policy and Legislative Affairs Committee

Margaret Foti, Ph.D., M.D. (h.c.)
Chief Executive Officer

The mission of the American Association for Cancer Research is to prevent and cure cancer. Founded in 1907, the AACR is the world's oldest and largest professional organization dedicated to advancing cancer research. The membership includes 32,000 basic, translational and clinical researchers; health care professionals; and cancer survivors and advocates in the United States and more than 90 other countries. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, diagnosis and treatment of cancer through high-quality scientific and educational programs. It funds innovative, meritorious research grants, research fellowship and career development awards. The AACR Annual Meeting attracts more than 18,000 participants who share the latest discoveries and developments in the field. Special focused conferences throughout the year present novel data across a wide variety of topics in cancer research, treatment and prevention. The AACR publishes six major peer-reviewed journals: *Cancer Research; Clinical Cancer Research; Molecular Cancer Therapeutics; Molecular Cancer Research; Cancer Epidemiology, Biomarkers & Prevention; and Cancer Prevention Research*. The AACR also publishes CR, a magazine for cancer survivors and their families, patient advocates, physicians and scientists. CR provides a forum for sharing essential, evidence-based information and perspectives on progress in cancer research, survivorship and advocacy.