



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, “Investigational New Drug Applications; Co-development of Investigational Drugs”

Dear Sir or Madam:

The Melanoma Research Alliance (MRA) welcomes the opportunity to provide comments in response to the FDA request for information about methodologic and regulatory issues in the development of combinatorial therapies. MRA appreciates the FDA’s efforts to seek information to improve treatment options for patients, particularly those with cancer, from which more than 1,500 Americans die each day. More than 8,000 Americans die each year from melanoma, the deadliest of skin cancers.

Founded in 2007, MRA is a public charity focused on accelerating the pace of scientific discovery and its translation into effective options for patients. MRA has awarded almost \$22 million to 50 innovative research programs worldwide aiming to improve melanoma prevention, diagnosis, and treatment, in order to eliminate suffering and death due to melanoma.

It is becoming increasingly evident that cancers such as melanoma are dependent on a number of altered molecular and immunological pathways and that single agent therapies alone may not provide long-lasting benefit for most patients. Even dramatic objective responses to single agents are commonly short-lived as evolving mutations in the agent’s primary target or changes in a downstream effector lead to drug resistance and cancer progression. For example, the median duration of response to PLX4032/RO5185426, a highly selective mutant BRAF inhibitor under development for metastatic melanoma, is approximately 9 months despite an initial response rate of 70%.

The urgency for developing new effective treatments for patients with melanoma is underscored by the fact that melanoma ranks among the top 10 causes of new U.S. cancer cases annually, and its incidence has tripled in the last 3 decades. Although melanoma is highly curable in its earliest stages, patients with advanced metastatic disease have a median survival measured in months. Conventional treatment options for patients with end-stage disease are limited to high-dose interleukin-2 or dacarbazine chemotherapy, which have objective response rates of only 10-15%. Issues concerning combinatorial therapies are generic to oncology. However, the paucity of FDA-approved agents for treating melanoma, coupled with recent scientific advances and the

emergence of very promising new drugs targeting immunologic or signaling pathways, suggest that melanoma could be the ideal model system in which to draft new FDA guidelines for combinatorial therapies.

Compelling evidence from animal tumor models indicates that certain drug combinations may provide synergistic therapeutic effects exceeding the impact of monotherapies. Despite ample preclinical data to support this notion and guide the design of combinatorial strategies, there are many challenges to their research and development, and regulatory considerations are of paramount importance. Mechanisms are needed to implement clinical development of high priority combinations efficiently. The expense, complexity, and time needed to prove that a combination product is both superior to standard care and to monotherapy with each agent are major barriers to development.

A major issue that the FDA should address stems from the fact that sponsors considering development of combinations of multiple agents are often in the process of developing one or more of the components as single agents. Under these circumstances, there is commonly concern that unexpected toxicities associated with the combination will either slow the concurrent development of the single agent or create new liability. FDA does not currently have a mechanism for single agent “indemnification,” i.e., attributing an adverse event (toxicity) to one component of a combinatorial treatment regimen but not the other. Furthermore, the FDA has not yet clearly articulated policies of toxicity review and drug labeling that would allow single agent development pathways to proceed unfettered by toxicities that only arise when the agent is used in a novel combination.

Clinical trial design for combinations is complex, and there is no one-size-fits-all approach; however, new and more flexible development models may serve to inform this process. Clinical trial design for a combination must be driven by preclinical studies, the characteristics of the individual compounds, and the patient population of interest. Given that combinatorial strategies will always be easier to develop when one of the components is already approved as a single agent, accelerated approval of single agents would dramatically enhance the development of combinatorial approaches to cancer. This is an important consideration apart from the conventional focus on making promising agents more available to cancer patients. Enhancements of the accelerated review process that allows for market approval contingent on a post-marketing Phase III study would therefore have important benefits for the combinatorial therapies.

We applaud the FDA for its efforts to improve the development and approval of combinatorial therapies for cancer. We welcome opportunities to work with FDA to advance the pace of scientific discovery to benefit patients.

Sincerely,

A handwritten signature in cursive script that reads "Wendy Selig".

Wendy K.D. Selig
MRA President and Chief Executive Officer