Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee Meeting
November 5, 2013

Location: FDA White Oak Campus, Building 31, The Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland

Issue: During the morning session, there was a presentation and general discussion of the potential applicability of pharmacological and cellular manipulation of the immune system, as a potential therapeutic intervention in various pediatric cancers. The recent, dramatic results of inhibition of the PD-1/PD-L1 axis and checkpoint inhibitors on normal T cells in melanoma and other adult cancers strongly suggest a potential role for such agents in the management of childhood cancer. Information was presented regarding pediatric development plans for two products that are in late stage development for various adult oncology indications. The subcommittee considered and discussed issues relating to the development of each product for potential pediatric use and provided guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The two products under consideration were: (1) nivolumab, application submitted by Bristol Myers Squibb Co.; (2) MK-3475, application submitted by Merck Sharp and Dohme.

During the afternoon session, information was presented regarding pediatric development plans for LEE011, application submitted by Novartis Pharmaceuticals Corporation, a product in late stage development for an adult oncology indication. The subcommittee considered and discussed issues relating to the development of this product for possible pediatric use and provided guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate.

These summary minutes for the November 5, 2013 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee were approved on 12/10/13.

I certify that I attended the November 5, 2013 meeting of the Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/S/
Caleb Briggs, PharmD
Designated Federal Officer, ODAC

/S/
Malcolm Smith, MD, PhD
Acting Chairperson, pedsODAC

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Center for Drug Evaluation and Research met on November 5, 2013 from 8 a.m. to 12 noon at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsors, Bristol-Myers Squibb Co. and Merck Sharp and Dohme. The meeting was called to order by Malcolm Smith, MD, PhD (Acting Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 50 persons in attendance. There was one speaker for the Open Public Hearing session.

Issue: During the morning session, there was a presentation and general discussion of the potential applicability of pharmacological and cellular manipulation of the immune system, as a potential therapeutic intervention in various pediatric cancers. The recent, dramatic results of inhibition of the PD-1/PD-L1 axis and checkpoint inhibitors on normal T cells in melanoma and other adult cancers strongly suggest a potential role for such agents in the management of childhood cancer. Information was presented regarding pediatric development plans for two products that are in late stage development for various adult oncology indications. The subcommittee considered and discussed issues relating to the development of each product for potential pediatric use and provided guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The two products under consideration were: (1) nivolumab, application submitted by Bristol Myers Squibb Co.; (2) MK-3475, application submitted by Merck Sharp and Dohme.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):
Mikkael Sekeres, MD, MS, MD, Jane Zones, PhD (*Consumer Representative*)

Temporary Members Present (Voting):
F. Daniel Armstrong, PhD, Stewart Goldman, MD, Nancy Goodman (*Patient Representative*), Nita Seibel, MD, Malcolm Smith, MD, PhD (*Acting Chairperson)*, Kathy Warren, MD, Brigitte Widemann, MD

Oncologic Drugs Advisory Committee Member Present (Non-Voting):
Howard Fingert, MD, FACP (*Industry Representative*)

Guest Speaker (Non-Voting, Presenting Only):
Paul Sondel, MD, PhD

FDA Participants (Non-Voting):
Richard Pazdur, MD, Lynne Yao, MD, Gregory Reaman, MD, Suzanne Demko, PA-C, Sandra Casak, MD

Designated Federal Officer:
Caleb Briggs, PharmD

Open Public Hearing Speakers:
Anna E. Mazzucco, PhD – Cancer Prevention and Treatment Fund

The agenda was as follows:

Call to Order Introduction of Subcommittee	**Malcolm Smith, MD, PhD** Acting Chairperson, pedsODAC
Conflict of Interest Statement	**Caleb Briggs, PharmD** Designated Federal Officer, pedsODAC
Introductory Remarks	**Gregory Reaman, MD** Associate Director for Oncology Sciences, Office of Hematology and Oncology Products (OHOP), Office of New Drugs (OND), CDER, FDA
Guest Speaker Presentation Biologic Rationale for Immunotherapy of Childhood Cancer	**Paul Sondel, MD, PhD (Guest Speaker)** Professor Pediatric Oncology University of Wisconsin-Madison
Clarifying Questions from Subcommittee	
Industry Presentation MK-3475 Pediatric Development Plan	**Merck Sharp and Dohme** **Robert Iannone, MD, MSCE** Executive Director Clinical Research – Oncology Merck Research Laboratories
Clarifying Questions from Subcommittee	
Industry Presentation Introduction	**Bristol-Myers Squibb Co.** **Mark Moyer, MS** Vice President, Global Regulatory Sciences Oncology
Industry Presentation (cont.)	
Proposal and Data to Support Nivolumab Pediatric Development Plan	**Renzo Canetta, MD** Vice President, Oncology, Global Clinical Research
Clarifying Questions from Subcommittee	
Open Public Hearing	
Questions to the Subcommittee and Subcommittee Discussion	
Adjournment of Morning Session	

Questions to the Committee:

Although several drugs and biologic agents have been developed in the last few years which target specific key pathways and functions, in some pediatric cancers, the backbone of treatment is still made up of compounds which rely on DNA damage to accomplish their role.

DNA damage response and checkpoint pathways are intertwined signaling networks that arrest cell cycle, recognize and repair genetic mistakes which arise during DNA replication and transcription, as well as through the exposure to chemical and physical agents that interact with nucleic acids.

1. **DISCUSSION:** Please consider the potential role of the checkpoints in immunoregulatory T-cells in children and how their pharmacological manipulation might be applicable in the treatment of pediatric cancer and possibly lead to synergism with currently used drugs.

In regards to the role of checkpoints in this area, subcommittee members agreed generally that this is an area with significant potential for treatment of pediatric cancers. In regards to synergism with currently used drugs, several subcommittee members encouraged caution in proceeding directly to combination therapy without first having additional information on safety and efficacy as single-agent treatment. A few members referenced the expected effect of immune boosting or suppressing agents and the resulting impact on the efficacy of these agents positively or negatively, respectively.

2. **DISCUSSION**: Please describe the potential role of multiple checkpoint pathway inhibitions.

Several members of the subcommittee reiterated a desire to gather additional information about these agents by continuing to study each product as a single-agent, before proceeding to combination therapy with multiple checkpoint pathway inhibitors. Another member agreed that, in the long term, it is important to fully characterize these products with further study as single-agents, but stated that it is also important that patients have access to the most effective treatments that are available. This subcommittee member stated that, if combination therapy is understood to be more effective than single-agent treatment, patients should not be restricted to single-agent therapy.

3. **DISCUSSION**: Please discuss the potential impact of the different stages of immune maturation as a factor influencing tumor response when using immune cell checkpoint inhibitors.

Members of the subcommittee described some uncertainty with regards to the particular degree of impact of immune maturation as a factor influencing tumor response with these agents, but an expectation that most pediatric patients would have an adequate immune response to allow treatment with these agents. Several members of the subcommittee stated that the experience with immunizations in infants and young children provided some

assurance that adequate immune function could be expected in this age group, which would encourage investigation of immune system manipulation as anti-cancer therapy in children. This question was addressed further in discussion of previous questions.

4. **DISCUSSION**: Please discuss any concerns about the potential for long-term modulation of the immune system and sequelae and consider possible monitoring strategies.

Members of the subcommittee highlighted the importance of collecting information about adverse effects, over both the short and long term. Several members explained that long term safety is not as important to monitor in Phase I and II trials, given that these refractory patient populations are not expected to have long-term outcomes. These members stated that, as development progresses and these agents are administered in more front line settings, monitoring of long-term adverse events becomes more important. Another subcommittee member highlighted a need to consider safety of the product, even in early phase trials to insure that any safety signal which may be present is not missed. Other suggestions that were raised by subcommittee members include ensuring that investigators are specifically knowledgeable about immune adverse events, being particularly observant for autoimmune disorders and pneumonitis, and adapting information learned from adult ipilimumab trials.

5. **DISCUSSION**: Please consider the importance of evaluating the correlation of tumor cell PD-L1 expression by various pediatric tumor cells with activity and if the combined use of multiple checkpoint inhibitors may prove useful in tumors with lower expression levels.

In regards to the correlation of tumor cell PD-L1 expression, some subcommittee members expressed that additional information will need to be gathered before treatment can be guided based on PD-L1 expression. One subcommittee member stated that it may be most appropriate to initially enroll a more general patient population, one that is not specifically enriched for greater tumor cell PD-L1 expression, and use the experiences with this patient population to inform what may be the most appropriate patients for future study. Some subcommittee members did state that there may be value in enriching the patient population with patients who have greater tumor cell PD-L1 expression, but that information should be gathered to inform future treatment and study approaches. In regards to combined use of multiple checkpoint inhibitors, several subcommittee members urged caution in proceeding to combination therapy before additional information is known to resolve uncertainty about safety and efficacy of single-agent therapy. Another member of the subcommittee emphasized that patients should be treated with the best available therapy that is known, and that combination therapy should be available to patients if it is demonstrated to be beneficial. Several subcommittee members stated that information should be utilized from studies evaluating multiple checkpoint therapy in adults.

(Please see official transcript for details.)

Morning session adjourned at approximately 12 noon

========== Lunch Break ==========

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) of the Center for Drug Evaluation and Research met on November 5, 2013 from 12:45 p.m. to 3:00 p.m. at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), Silver Spring, MD. Prior to the meeting, members and temporary voting members were provided copies of the background material from the FDA and the Sponsor, Novartis Pharmaceuticals Corp. The meeting was called to order by Malcolm Smith, MD, PhD (Acting Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, PharmD (Designated Federal Officer). There were approximately 25 persons in attendance. There were no speakers for the Open Public Hearing session.

Issue: During the afternoon session, information was presented regarding pediatric development plans for LEE011, application submitted by Novartis Pharmaceuticals Corporation, a product in late stage development for an adult oncology indication. The subcommittee considered and discussed issues relating to the development of this product for possible pediatric use and provided guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):
Mikkael Sekeres, MD, MS, MD, Jane Zones, PhD (*Consumer Representative*)

Temporary Members Present (Voting):
F. Daniel Armstrong, PhD, Ira Dunkel, MD, Stewart Goldman, MD, Nancy Goodman (*Patient Representative*), Nita Seibel, MD, Malcolm Smith, MD, PhD *(Acting Chairperson)*, Kathy Warren, MD, Brigitte Widemann, MD

Oncologic Drugs Advisory Committee Member Present (Non-Voting):
Howard Fingert, MD, FACP (*Industry Representative*)

FDA Participants (Non-Voting):
Lynne Yao, MD, Gregory Reaman, MD, Suzanne Demko, PA-C, Martha Donoghue, MD

Designated Federal Officer:
Caleb Briggs, PharmD

The agenda was as follows:

Call to Order Introduction of Subcommittee	**Malcolm Smith, MD, PhD** Acting Chairperson, pedsODAC
Conflict of Interest Statement	**Caleb Briggs, PharmD** Designated Federal Officer, pedsODAC
Industry Presentation Development of LEE011 in pediatric neuroblastoma and rhabdoid tumors	**Novartis Pharmaceuticals Corporation** **Samit Hirawat, MD** Senior Vice-President, Global Program Head
Clarifying Questions from Subcommittee	

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

Closing Remarks **Gregory Reaman, MD**

Adjournment

Questions to the Committee:

1. **DISCUSSION:** Does the panel consider LEE011 a good candidate for study in pediatric patients with malignant rhabdoid tumors and neuroblastoma? Are there concerns regarding the design of the ongoing pediatric study?

Several members of the subcommittee expressed the sentiment that LEE011 is a reasonable candidate for study in these patient populations, although several cited the cytostatic mechanism of action as a factor that requires some consideration. One subcommittee member had questions about the preclinical data package, including the extent to which drug exposures tolerated in humans are reflected by drug exposures in the mouse xenograft experiments and the extent to which the single xenograft models for rhabdoid tumor and neuroblastoma that were presented are representative of what would be observed if more models were tested. One subcommittee member described the heterogeneity of neuroblastoma as an important consideration when evaluating the ongoing pediatric study. This member expressed that stable disease may represent differing levels of clinical benefit depending on the expected disease course for a given patient. In regards to concerns about the ongoing study, one member noted that a minimally therapeutic dose that is determined from a Phase I trial, in patients that are heavily pre-treated and may have low bone marrow reserves, could end up being suboptimal for the proposed treatment of patients in earlier lines of therapy.

2. **DISCUSSION:** Please provide recommendations regarding the design of future studies to evaluate the efficacy and safety of LEE011 in pediatric patients with malignant rhabdoid tumors and neuroblastoma, if the results of the ongoing study indicate that there is sufficient activity to warrant future pediatric development for these indications.

In general, members of the subcommittee agreed that the design of future pediatric trials would be very much dependent on the results of the ongoing trial, and that it is likely too early to provide specific recommendations for these future trials. One subcommittee member stated that the primary focus for pediatric drug development should be on finding a "pathway to cure," and questioned what that pathway might be for a cytostatic agent that is difficult to combine with standard chemotherapy drugs and is not expected to induce tumor regression as a single agent. This member further stated that it may be appropriate to conduct additional preclinical studies to attempt to identify an appropriate agent or agents to combine with LEE011.

(Please see official transcript for details.)

Meeting adjourned at approximately 2:50 p.m.