

The Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on November 1, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsors. The meeting was called to order by Frank Balis, M.D. (Acting Chairperson); the conflict of interest statement was read into the record by Caleb Briggs, Pharm.D. (Designated Federal Officer). There were approximately 20 persons in attendance. There were two (2) speakers for the Open Public Hearing session.

Issue: Information was presented regarding pediatric development plans for four products that were either recently approved by FDA, are in late stage development for an adult oncology indication, or in late stage development in pediatric patients with cancer. The subcommittee considered and discussed issues relating to the development of each product for pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The four products under consideration were: (1) sodium thiosulfate injection, application submitted by Adherex Technologies, Inc.; (2) vismodegib (GDC-0449), application submitted by Genentech, Inc.; (3) pazopanib, application submitted by Glaxo Wellcome Manufacturing Pte Ltd, Singapore doing business as GlaxoSmithKline; and (4) Medi-573 (fully human antibody to IGF-I and IGF-II), application submitted by MedImmune, LLC.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):

Frank Balis, M.D. (Acting Chairperson), Ralph Freedman, M.D., Ph.D., Mikkael Sekeres, M.D., M.S.

Special Government Employee Consultants (Temporary Voting Members):

Carola Arndt, M.D. (Sessions 2, 3 & 4 only), Richard Gorlick, M.D., Craig Lustig (Patient Representative), Leo Mascarenhas, M.D., M.S. (Sessions 2, 3 & 4 only), Kathleen Neville, M.D., M.S., Patricia Shearer, M.D., M.S.

Regular Government Employee Consultants (Temporary Voting Members):

Nita Seibel, M.D. (Sessions 1 & 2 only), Susan Shurin, M.D., Malcolm Smith, M.D., Ph.D. (Sessions 1 & 2 only)

Acting Industry Representative to the Subcommittee (Non-Voting):

Gregory Curt, M.D. (Acting Industry Representative) (Sessions 1, 2, & 3 only)

FDA Participants (Non-Voting):

Richard Pazdur, M.D., Melissa S. Tassinari, Ph.D. DABT, Greg Reaman, M.D., Kristen Snyder, M.D. (Session 1 Only), Amy McKee, M.D. (Session 2 Only), Amir Shahlaee, M.D. (Sessions 3 & 4 only)

Designated Federal Officer:

Caleb Briggs, Pharm.D.

Open Public Hearing Speakers:

Joshua Hofmeister

Mary Beth Collins

The agenda was as follows:

Call to Order
Introduction of Subcommittee

Frank Balis, M.D.
Acting Chairperson, Pediatric Oncology
Subcommittee of the Oncologic Drugs Advisory
Committee

FDA Presentation
Overview of Pediatric Regulations

Melissa S. Tassinari, Ph.D., DABT
Senior Clinical Analyst
Pediatric and Maternal Health Staff
Office of New Drugs, FDA

Clarifying Questions from Subcommittee

Topic 1: Sodium thiosulfate- Adherex Technologies, Inc.

Conflict of Interest Statement

Caleb Briggs, Pharm.D.

Designated Federal Officer, Oncologic Drugs
Advisory Committee (ODAC)

Introduction of New Participants

Frank Balis, M.D.

Industry Presentation

**Adherex Technologies, Inc. – sodium
thiosulfate**

Introduction

Franck Rousseau, M.D.

Consultant, Medical Affairs
Adherex Technologies, Inc.

Pediatric Ototoxicity

Kristin Knight, M.S., CCC-A

Assistant Professor, Director of Pediatric
Audiology
Oregon Health and Science University

STS Data Demonstrating Lack
of Tumor Protection

Edward Neuwelt, M.D.

Director of the Blood Brain Barrier
Program,
and Director of the Head and Spinal
Cord Injury Prevention Program
Professor Neurology and Neurosurgery
Oregon Health and Science University

COG and SIOPEL Clinical
Studies

David R. Freyer, D.O., M.S.

Chair of the ACCL0431 Study,
Director, LIFE Cancer Survivorship &
Transition Program
Children's Center for Cancer & Blood Diseases
Children's Hospital Los Angeles
University of Southern California Keck School of
Medicine

Challenges in Development
and Q&A

Franck Rousseau, M.D.

Clarifying Questions from Subcommittee

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

Topic 2: Vismodegib-Genentech, Inc.

Conflict of Interest Statement

Caleb Briggs, Pharm.D.

Introduction of New Participants

Frank Balis, M.D.

Industry Presentation

Vismodegib Hedgehog Pathway Inhibitor

Genentech, Inc. - vismodegib

Jennifer Low, M.D., Ph.D.

Group Medical Director and Global
Development Leader, Product
Development Oncology
Genentech, Inc.

Clarifying Questions from Subcommittee

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

Topic 3: Pazopanib-GlaxoSmithKline

Conflict of Interest Statement

Caleb Briggs, Pharm.D.

Introduction of New Participants

Frank Balis, M.D.

Industry Presentation

Development of Votrient™ (pazopanib)
In Pediatric Oncology

GlaxoSmithKline - pazopanib

Christopher Carpenter, M.D.

Clinical Development
GlaxoSmithKline

Clarifying Questions from Subcommittee

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

Topic 4: Medi-573-MedImmune, LLC

Conflict of Interest Statement

Caleb Briggs, Pharm.D.

Introduction of New Participants

Frank Balis, M.D.

Industry Presentation

MEDI-573

MedImmune, LLC. – Medi-573

Bob Sikorski, M.D., Ph.D.

Senior Director, Clinical Development
MedImmune, LLC.

Jaye Viner, M.D., M.P.H.

Associate Director, Clinical
Development
MedImmune, LLC.

Clarifying Questions from Subcommittee

Open Public Hearing

Questions to the Subcommittee and Subcommittee Discussion

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Questions to Committee:

Session 1: SODIUM THIOSULFATE

APPLICANT: Adherex Technologies, Inc.

Discussion Questions:

1. What study design will be required to definitively demonstrate the efficacy of sodium thiosulfate in preventing cisplatin-induced ototoxicity?

Members discussed that the ongoing Phase 3 Children's Oncology Group (COG) study was intended to serve as a "proof of principle" and is a "good start" toward demonstrating efficacy of sodium thiosulfate in the prevention of platinum-induced ototoxicity. Some members questioned whether the one year follow up duration of this study would be adequate to properly assess prevention of ototoxicity, but the subcommittee generally agreed that it was sufficient to assess the large majority of this effect. One member described the need for careful consideration of dosing in efficacy studies, citing the pharmacokinetics of sodium thiosulfate together with cisplatin.

Please see the transcript for detailed discussions

2. What type of trial design would be required to confidently demonstrate that sodium thiosulfate does not provide tumor protection? Please also comment on the appropriate patient population(s) for study.

The subcommittee discussed several considerations for the design of a study to investigate tumor protection. Multiple members described the need for a randomized trial to properly assess the impact of sodium thiosulfate on cisplatin efficacy, though one member cited the low number of available pediatric subjects as a possible argument for a historically-controlled study. One member pointed out the difficulties of conducting a randomized trial in the adult cancer populations since the risk of ototoxicity to adults, having already developed language skills, is not as great as it is for young children, while the risk of possible tumor protection remains a larger issue for adult cancer populations with poorer prognoses in general. Another member suggested a randomized controlled trial with a factorial study design in a patient population which typically receives intensive doses of cisplatin and suffers from frequent ototoxicity. Another member suggested that potential studies should investigate the degree of benefit that sodium thiosulfate may offer over the large variety of cisplatin-receiving patients. Some members discussed the possibility that prevention of ototoxicity could allow for larger doses of cisplatin, potentially leading to greater cancer treatment effect, and highlighted this as an important topic for investigation. Nearly all members agreed that possible tumor protection is a critical component of the safety profile of sodium thiosulfate, and that it should be thoroughly investigated prior to drug approval.

Please see the transcript for detailed discussions.

Session 2: VISMODEGIB

APPLICANT: Genentech, Inc.

Discussion Questions:

1. Given the potential for increased development-related toxicity in children and the lack of scientific rationale for testing vismodegib in pediatric patients without activated Hh pathway medulloblastoma, does the committee have concerns if the negative predictive value of the diagnostic assay is not tested in Hh diagnostic-negative patients?

Most members agreed that there was some level of concern with using vismodegib in these patients if the diagnostic assay had not been tested in Hh diagnostic-negative patients. Members discussed the need to further confirm the negative predictive value of the diagnostic assay by testing in more Hh diagnostic-negative patients. Concern was expressed over the potential to expose patients without an activated Hh pathway to drug side effects without the benefit of drug efficacy.

Please see transcript for detailed discussions.

2. If the current Pediatric Brain Tumor Consortium Phase II study evaluating vismodegib treatment shows promising tumor response rates in children with medulloblastoma, does the committee have comments on the most appropriate primary endpoint to establish efficacy in a confirmatory study? Does the committee have comments on the appropriateness of using a historical control or single-arm study?

Members of the subcommittee discussed some potential difficulty in designing a trial due to the excellent prognosis of these patients after treatment with chemotherapy alone. One member suggested that the drug may have efficacy in anaplastic large cell medulloblastoma, which are known to have a poorer outcome. Members also described challenges in study design due to the limited number of refractory patients available to study, which may necessitate a single-arm study. One member discussed several challenges with using a historical control group, due to the limited study of this specific population in the past.

Please see transcript for detailed discussions.

3. Please identify any other pediatric cancers and pediatric subpopulations (e.g., ages, degree of refractoriness to therapy) that should be targeted for drug development with vismodegib.

Members were clear in stating that they did not feel that there was any potential for development in diseases that do not have hedgehog pathway activation. One member discussed that animal models are often not a good predictor of toxicities in human pediatric patients, and that those animal studies should not discourage development in pediatrics, though those potential late effects should be carefully monitored. Multiple members expressed comfort with the degree of toxicity for the refractory population, with potential to further investigate in earlier stages if results are promising in refractory patients.

Please see transcript for detailed discussions.

Session 3: PAZOPANIB

APPLICANT: GlaxoSmithKline

Discussion Questions:

Non-rhabdomyosarcoma soft tissue sarcomas (NRSTS) comprise 4% of pediatric malignancies and affect approximately 500 patients younger than 20 years old in the US each year. Despite advances in other areas of pediatric oncology, the cure rate for this subset of patients has remained unchanged in more than 2 decades with little change in traditional chemotherapy approaches. Studies in these patients are usually complicated by the rarity of individual subtypes of NRSTS and inadequate response to chemotherapy consisting of anthracyclines and alkylators. Development of novel approaches to treatment of NRSTS is critical to improving the outcomes for this patient population.

1. Does the panel consider pazopanib a viable drug candidate for further study in pediatric and young adult patients with non-rhabdomyosarcoma soft tissue sarcomas (NRSTS)?
 - a. Please comment on potential study designs.

Many members expressed discomfort with the prospect of study in this patient population as a single agent, citing ethics concerns with randomizing patients away from chemotherapy. Some members suggested the possibility of investigating use as maintenance therapy following chemotherapy, or in subtypes that are refractory to chemotherapy. Some members suggested a trial which randomizes patients between standard chemotherapy with or without pazopanib, with one member suggesting PET scan response as a possible surrogate endpoint, if it could be shown to be an adequate surrogate endpoint. Other members discussed the need to examine the safety of pazopanib in combination with chemotherapy in pediatrics, stating that this could be different than in adults. One member expressed concern with the safety of pazopanib combined with radiation due to the drug's mechanism of action. One member suggested that the adult study could be repeated in pediatric patients to assess the drug activity. Another member expressed a desire for progression-free survival data to be gathered in pediatric trials, to allow more effective comparison with the adult data. Some members agreed that current data would suggest a phase 1 trial of combination therapy, rather than a phase 2 study.

Please see transcript for detailed discussions.

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and adolescents affecting nearly 350 patients in the US annually. Although cure rates for most subtypes of

rhabdomyosarcoma have drastically improved with multimodal therapy, patients with relapsed and metastatic disease continue to fare poorly despite attempts at treatment intensification with cytotoxic chemotherapy. Up-front window approaches for testing new agents in rhabdomyosarcoma have in the past helped identify active agents and agent combinations. This approach however has not led to any improvements in survival rates of patients with high risk disease. Novel therapeutic approaches with targeted agents may offer an alternative approach worthy of further exploration in this patient population.

2. Does the panel consider pazopanib a viable drug candidate for further study in pediatric and young adult patients with rhabdomyosarcoma?

a. Please comment on potential study designs.

Several members expressed concern over the lack of data from adult trials in this patient population. One member stated that, if further study were to be done, it should start with phase 1 multi-agent studies, as single agent treatment would likely not meet RECIST criteria. Some members discussed that the lack of existing data in this disease state would discourage use of limited pediatric patient resources to initiate studies at this time. One member suggested possible investigation as maintenance therapy in patients who are at very high risk of relapse, and another suggested study as a single agent in the relapsed setting. While one member expressed desire for a randomized study with stratification of patients to address the heterogeneity of the population, other members voiced doubt that there was an adequate number of patients to make this feasible.

Please see transcript for detailed discussions.

Session 4: MEDI-573

APPLICANT: MedImmune, LLC.

Discussion Questions:

1. Do you consider the modest activity of IGF1R inhibitors seen to date sufficiently compelling to warrant more definitive evaluation in children, adolescents, and young adults with specific sarcoma subtypes? Specifically, how do you think the different mechanism of action of MEDI-573 impacts further investigation of this agent in bone and soft tissue sarcomas in children, adolescents, and young adults?

Many members expressed interest in further investigation of IGF1R inhibitors in pediatrics. One member described “significant interest” in agents that target this pathway for treatment of bone sarcomas, either in the metastatic setting, or potentially as front-line therapy, likely in combination with chemotherapy. One member discussed that a high expression of the target pathway in pediatrics offers promise for development. In discussing potential considerations for study design, one member stated that the 10% response rate presents challenges, as the drug would likely require combination with chemotherapy. This member stated that the side effects seem to be a class effect for these drugs, and questioned the

possibility to begin study in phase 2 for adolescents. Another member stated that this may be possible in bone sarcomas by adapting the adult dose in these patients, but that a phase 1 trial would be necessary in rhabdomyosarcoma. One member mentioned the possibility of phase 1 study in combination with other non-chemotherapeutic agents, such as mTOR inhibitors. However, another member described difficulty with assessing the action of two unproven entities in this way.

Please see transcript for detailed discussions.

2. What recommendations do you have regarding the most appropriate pediatric patient population(s) in which to study these agents?

Members suggested that it may be appropriate to divide study between bone sarcomas and soft tissue sarcomas, such as rhabdomyosarcoma, due to their different characteristics. One member discussed that it may be possible to include adolescent bone sarcoma patients in adult trials, while rhabdomyosarcoma would require separate pediatric studies. Another member reiterated the possibility that phase 1 trials could be foregone in adolescent and young adults by adapting the adult dose, while separate pediatric trials would be required for younger patients.

Please see transcript for detailed discussions.

3. What recommendations do you have regarding the appropriate study design to efficiently evaluate the safety and activity of this class of agents in this pediatric population?

Several members described challenges in conducting trials in this population due to the rarity of the disease. One member stated that phase 3 trials would likely need to be conducted in recurrent disease or up-front with other agents, but that either population would require several years for accrual and possible international study sites. Another member suggested that an up-front trial in osteosarcoma may offer better accrual, due to a lack of “other questions” under study in this group. However, this member discussed that frequent use of doxorubicin in this group would require comfort with the cardiac toxicity of the drug. One member described a general focus in pediatrics on finding curative therapies rather than second-line agents, and encouraged investigation in front line settings. Another member suggested that a phase 2 trial may successfully accrue sufficient patients for randomization in Ewings Sarcoma, but that any agent to be studied would need to be very nontoxic, to avoid compromising the timing and effectiveness of standard therapies.

Please see transcript for detailed discussions.

Meeting adjourned at approximately 3:00 p.m.