



June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

*Summary Minutes*  
**Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting**  
**June 21-22, 2017**

The following is the final report of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting held on June 21-22, 2017. A verbatim transcript will be available in approximately six weeks, sent to the Office of Hematology and Oncology Products and posted on the FDA website at:

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm547155.htm>

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

---

The Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on June 21-22, 2017 at the FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, Maryland. Prior to the meeting, members and temporary voting members were provided copies of the briefing materials from the FDA, and Industry Presenters (Apexigen Inc., PharmaMar USA Inc., Estella's Pharma Global Development Inc., and Eli Lilly and Company). The meeting was called to order by Alberto S. Pappo, MD, (Chairperson). The conflict of interest statement was read into the record by Lauren D. Tesh, PharmD, BCPS (Designated Federal Officer). There were approximately 65 people in attendance on both days. There was one Open Public Hearing (OPH) speaker for June 21, 2017 Topic 1. There were no OPH speakers for June 21, 2017 Topics 2 and 3, or June 22, 2017.

**Issue:** On June 21, 2017, information was presented to gauge investigator interest in exploring potential pediatric development plans for three products in various stages of development for adult cancer indications. The subcommittee considered and discussed issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) APX-005M, presentation by Apexigen, Inc.; (2) PM01183 (lurbinectedin), presentation by PharmaMar USA Inc.; and (3) ASP2215 (gilteritinib), presentation by Astellas Pharma Global Development, Inc.

On June 22, 2017, information was presented to gauge investigator interest in exploring potential pediatric development plans for two products in various stages of development for adult cancer indications. The subcommittee considered and discussed issues concerning diseases to be studied, patient populations to be included, and possible study designs in the development of these products for pediatric use. The discussion provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) olaratumab, presentation by Eli Lilly and Company and (2) prexasertib, presentation by Eli Lilly and Company.

June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

**Attendance:**

**ODAC Members Present (Voting):** Alberto S. Pappo, MD (pedsODAC Chairperson); Courtney J. Preusse, MA (Consumer Representative); Bruce J. Roth, MD

**ODAC Members Not Present (Voting):** Harold J. Burstein, MD, PhD; Bernard F. Cole, PhD; Philip C. Hoffman, MD; Heidi D. Klepin, MD, MS; Grzegorz S. Nowakowski, MD; Vassiliki A. Papadimitrakopoulou, MD; Gregory J. Riley, MD, PhD; Brian I. Rini, MD, FACP; Alice T. Shaw, MD, PhD; Thomas S. Uldrick, MD, MS

**ODAC Member Present (Non-Voting):** Phuong Khanh (P.K.) Morrow, MD, FACP

**Temporary Members (Voting):** Anne L. Angiolillo, MD (Participation in Day 1 Topic 3 and Day 2); Carola A. S. Arndt, MD; Steven G. DuBois, MD (Participation in Day 1); Lia Gore, MD (Participation in Day 1 Topics 1 and 3); Richard G. Gorlick, MD; Donna M. Ludwinski (Patient Representative); Tobey J. MacDonald, MD; Leo Mascarenhas, MD, MS; Elizabeth A. Raetz, MD; Brenda J. Weigel, MD, MSc

**FDA Participants (Non-Voting):** Leslie Doros, MD (Participation in Day 2 Topic 1); Nicole Drezner, MD (Participation in Day 1 Topic 1); Aviva Krauss, MD (Participation in Day 1 Topic 2); Christy Osgood, MD (Participation in Day 2 Topic 2); Gregory Reaman, MD; Ashley Ward, MD (Participation in Day 1 Topic 3)

**Designated Federal Officer (Non-Voting):** Lauren D. Tesh, PharmD, BCPS

**Open Public Hearing Speakers:** Megan Polanin, Ph.D. (National Center for Health Research)

*The Agenda proceeded as follows:*

*June 21, 2017*

Call to Order  
Introduction of Subcommittee

**Alberto Pappo, MD**  
Chairperson, Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC)

FDA Introductory  
Remarks/Presentation

**Gregory Reaman, MD**  
**Associate Office Director**  
**Office of Hematology and Oncology Products(OHOP)**  
Associate Director for Pediatric Oncology Acting  
Oncology Center of Excellence

Office of New Drugs (OND), CDER, FDA

**Topic 1: Topic 1: APX-005M – Apexigen, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Apexigen, Inc.**

APX005M, A CD40 Agonistic Monoclonal  
Antibody

**Ovidiu C. Trifan, MD, PhD**  
Chief Medical Officer  
Apexigen, Inc.

Clarifying Questions from Subcommittee

June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**BREAK**

**Topic 2: PM01183 (lurbinectedin) – PharmaMar USA, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Pharma Mar, USA, Inc.**

Lurbinectedin (PM01183) for the treatment of  
Ewing Sarcoma and Neuroblastoma

**Arturo Soto, MD**  
Clinical Department Director  
Oncology Business Unit  
Pharma Mar, S.A.

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**LUNCH**

**Topic 3: ASP2215 (Gilteritinib) – Astellas Pharma Global Development, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Astellas Pharma Global Development, Inc.**

Gilteritinib for Treatment of Pediatric Patients  
with FLT3/ITD AML

**Andrew Krivoschik, MD, PhD**  
Vice President of Medical Sciences Oncology  
Astellas

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

**ADJOURNMENT**

June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

**June 22, 2017**

Call to Order

Introduction of Subcommittee

**Alberto Pappo, MD**

Chairperson, Pediatric Subcommittee of the Oncologic  
Drugs Advisory Committee (pedsODAC)

FDA Introductory Remarks/Presentation

**Gregory Reaman, MD**

Associate Director for Oncology Sciences,  
Office of Hematology and Oncology Products  
(OHOP), Office of New Drugs (OND)  
CDER, FDA

**Topic 1: Olaratumab – Eli Lilly and Company**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

Designated Federal Officer, ODAC

**INDUSTRY PRESENTATION**

**Eli Lilly and Company**

LARTRUVO™ (Olaratumab) in Advanced  
Soft Tissue Sarcoma

Introduction

**Allen Melemed, MD, MBA**

Distinguished Medical Fellow & Senior Director,  
Global Regulatory Affairs  
Eli Lilly and Company

Olaratumab Development in Adults &  
Pediatrics

**Volker Wacheck, MD**

Senior Medical Director, Olaratumab  
Eli Lilly and Company

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**BREAK**

**Topic 2: Prexasertib – Eli Lilly and Company**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Eli Lilly and Company**

Prexasertib (LY2606368), A CHK1 Inhibitor

**Allen Melemed, MD**

Distinguished Medical Fellow and Sr. Director  
Global Regulatory Affairs

June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

Eli Lilly and Company

**Aimee Bence Lin, PhD**

Research Advisor, Prexasertib

Eli Lilly and Company

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**ADJOURNMENT**

*June 21, 2017*

*Questions to the Committee:*

---

**Day 1, Topic 1: APX005M, Apexigen, Inc.**

---

1. **DISCUSSION:** Please comment on the unique safety concerns that arise from the use of immune activator agents, in particular with CD40 agonistic antibodies in pediatric patients, and on methods to mitigate these safety issues in clinical trials.

*Committee Discussion:* The subcommittee members stated that it is not clear what mitigation strategies will be implemented for this agent such as cytokine release syndrome. The members noted that there are a number of biologic issues to address including whether the molecule crosses the blood- brain barrier. The subcommittee members highlighted that antibodies are normally large in size, and patients with brain tumors commonly do not have an intact blood brain barrier but also, that it is not clear that the immune mediated anti-tumor effects of activated T cells depend on something actually penetrating the blood- brain barrier. Moreover, it is not clear what the overall mechanism of action might be, and the members would like to better understand Apexigen's strategies for evaluation. There was considerable discussion as to why primary CNS tumors were selected as the first target pediatric solid tumor to evaluate this agent. It was highlighted that the peak of action would be within the first 24 hours, thus, the subcommittee members believe it would be helpful to know the logistic strategy for that time period, as in whether these patients would be treated as inpatients or outpatients. The subcommittee members also wanted clarification on the inclusion and exclusion criteria specifically in regards to previous allogeneic stem cell and solid organ transplants, the role of immunizations while on this therapy, the short and long term management of autoimmune diseases, corticosteroid use and concurrent brain radiation. Please see the transcript for details of the subcommittee discussion.

2. **DISCUSSION:** Please consider the way in which CD40-agonistic antibodies can be used synergistically with current pediatric cancer treatment modalities, including cancer vaccines, given their immunomodulatory effects.

***Committee Discussion:** The subcommittee members encouraged leveraging of the data that currently exists with checkpoint inhibition for therapy in children to quickly move to a combination strategy (after first identifying the dose of the single agent needed) due to significant enhancement of efficacy with combination therapy in preclinical studies. The subcommittee members highlighted that this is a population that can often only pursue one novel therapy at relapse or for DIPG at the frontline. The data presented suggests limited potential benefit of single agent activity; therefore the members encourage moving rapidly onto combination strategies. However, the subcommittee members list that one of the concerns with progressing to combination therapy soon would be pseudo-progression in DIPG. Therefore, the members recommended developing a plan on how to determine and act on this. The subcommittee members also encouraged considering other histologies, particularly solid tumors. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please consider the importance of evaluating the correlation of tumor cell CD40 expression and antigen burden in various pediatric solid tumors with the activity of CD40-agonistic antibodies, and whether the combined use of CD40-agonistic antibodies with immune checkpoint inhibitors may prove to be useful in tumors with lower CD40 expression and/or antigen burden.

***Committee Discussion:** The subcommittee members stated that the ultimate success or failure would be dependent on the strength of the biologic correlative studies. The members noted that it is important to understand why this does or does not work to identify potential responders. The subcommittee members suggested focusing on non-brain tumors prior to exploring the brain, and stated that they would be interested in learning the correlation between CD40 status and the response. The subcommittee members suggested using the combination approach in other pediatric solid tumors such as neuroblastoma, osteosarcoma and recommended a detailed exploration of toxicities. Finally, the subcommittee members asked whether this could be an opportunity to better define the role of T cell exhaustion along with checkpoint inhibitors and CD40 agonists. Please see the transcript for details of the subcommittee discussion.*

**Day 1, Topic 2: PM01183 (Lurbinectedin), Pharma Mar USA, Inc.**

---

1. **DISCUSSION:** Please discuss the preliminary pediatric development plan, including the tumor types proposed for further study. In addition, please include considerations regarding a targeted approach based on bio- or other markers versus one that is broader in scope.

***Committee Discussion:** The subcommittee members encouraged generation of more preclinical efficacy data in regards to specific pediatric tumors. The members expressed concern for the need for a second phase II study limited to pediatric patients, considering at that point there will already be a completed adult study featuring the same regimen. The members encouraged the sponsor to consider lowering the age on the adult trial Ewing trial to age 12 or a new combination regimen for the pediatric trial, since most likely this medication will not be used as a single agent. The subcommittee members recommended tumor or germline sequencing panels to address histology and molecular profiles to identify those that are more likely to respond to the medication. The members highlighted that it is clear that this class of drugs has activity in certain malignancies, and that the question lies in understanding from the mechanism of action whether this is a non-specific cytotoxic or a targeted agent for tumors with specific transcription factor fusions. The subcommittee members encouraged the sponsor to identify the spectrum that defines activity. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Given the mechanism of action of lurbinectedin, please consider other pediatric tumor types for which there is a biologic rationale for evaluation of its activity. Address any differences in biology between adult and pediatric hematologic malignancies that might support its evaluation in pediatric diseases for which its activity in adults has been limited.

***Committee Discussion:** The subcommittee members encouraged investigation of potentially translocation driven malignancies in a variety of sarcomas. The members stated that in the hematologic malignancies there have not been many successful single agent trials and therefore, combination studies should be designed pre-clinically. However, the subcommittee members highlighted that this combination of agents could be problematic due to overlapping hematologic toxicity. Therefore, the members recommended considering combination therapy with other targeted agents if pursuing a leukemia trial. The subcommittee members also noted another clinical and scientific question as related to Ewing sarcoma breakpoint region 1 translocated tumors such as clear cell sarcoma, in that it is necessary to consider how to evaluate those other areas of significant unmet clinical need. Lastly, the members noted the need to understand the pharmacokinetic profile of the medication to see what defines activity be it peak dose, duration of exposure, or half-life. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please discuss the impact of low CNS and testicular penetration of lurbinectedin in tissue distribution studies on potential areas of study in the pediatric population.

***Committee Discussion:** The subcommittee members stated that this would be potentially relevant for hematologic malignancies. However, the members highlighted that there is no compelling evidence of a lack of CNS penetration given there has been a documented response, meaning there needs to be a clarification as to what “low” means. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please address any potential safety concerns unique to the pediatric population, including consideration as to whether any pediatric age groups should be excluded from study.

***Committee Discussion:** The subcommittee members stated that the data as presented demonstrated that as a single agent this is a myelotoxic drug, and encouraged thoughtful consideration in regards to extended exposure studies for both combination regimens and use of it as a single agent due to variable pharmacokinetics. The members encouraged designing the studies not to exclude certain patient populations, but rather to learn as much as possible about metabolism and exposure necessary to gain desired effects. The subcommittee members stated that there are no concerns about formulation issues, since 100 mL of the drug is to be infused over one hour and no pediatric volume constraints exist for the patient population at risk. The members stated that this does not account for any concerns, and that the only potential concern would be the lactate content in the diluent causing metabolic acidosis in very small infants. However, this was countered with the indication only covering children older than 2 years of age. Please see the transcript for details of the subcommittee discussion.*

---

### Day 1, Topic 3: ASP2215 (Gilteritinib), Astellas Pharma Global Development

---

1. **DISCUSSION:** Please discuss the preliminary pediatric development plan, including the indications proposed for further study and, in particular, the proposal to study gilteritinib only in children with Acute Myeloid Leukemia and FLT3 Internal Tandem Duplication.

***Committee Discussion:** The subcommittee members stated that it appropriate to study the drug in patients with a specific mutation, specifically FLT3 Internal Tandem Duplications. The members agreed that as additional data emerges regarding the activity of gilteritinib in adult patients with other mutations, such as point mutations in the tyrosine kinase domain of FLT3, the corresponding pediatric population could also be studied. The subcommittee members stated that investigation of this product in Mixed-Lineage Leukemia (MLL)-rearranged leukemia is not recommended at this time as currently available data suggests that FLT3 inhibition may be ineffective in this disease. The subcommittee further stated that plans for the pediatric study should be contingent upon pediatric oral formulation availability, which is currently being addressed by the Astellas. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please discuss any potential safety concerns unique to the pediatric population, including toxicities that may be seen when gilteritinib is added to multi-agent chemotherapy. Consider whether any pediatric age groups should be excluded from study and mechanisms to minimize risk on the proposed clinical trials.

***Committee Discussion:** The subcommittee members noted that DaunoXome is not available in the US, and thus recommended that a trial using a liposomal daunorubicin formulation be conducted internationally. The members also noted the need to monitor for long term effects in the pediatric population, but see no reason to restrict the study of gilteritinib to children of specific ages. As most pediatric trials allow administration of intrathecal chemotherapy to reduce the risk of CNS recurrence, the subcommittee members encouraged standardizing the use and dosage of intrathecal chemotherapy across the treatment protocols to avoid confounding the assessment of the incidence of PRES (posterior reversible encephalopathy syndrome). The subcommittee members also highlighted*

June 21-22, 2017

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee Meeting

*that there should be clear guidelines in both the relapsed and up-front trials regarding the prior use of anthracyclines, and suggested careful assessment of potential cardiac toxicity. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please comment on the sponsor's proposal to include one year of maintenance therapy with gilteritinib monotherapy after Intensification II or hematopoietic stem cell transplantation in Study 0604.

***Committee Discussion:** The subcommittee members stated that the toxicity profile of gilteritinib monotherapy might be different for patients receiving maintenance therapy after stem cell transplant compared to those receiving it after Intensification II. The members encouraged reaching an agreement among transplant advisors as to when therapy should be started after transplantation, and suggested consideration of a randomized trial design that may allow confirmation of the utility of maintenance therapy in these settings. Please see the transcript for details of the subcommittee discussion.*

**June 22, 2017**

**Questions to the Committee:**

---

**Day 2, Topic 1: Olaratumab, Eli Lilly and Company**

---

1. **DISCUSSION:** Based on the non-clinical and clinical data presented, please comment on the relevant cancers that should be studied and potential endpoints that could be used in future clinical trials designed to evaluate the efficacy of olaratumab in pediatric patients.

***Committee Discussion:** The subcommittee members considered it critical to evaluate in more detail the spectrum of pediatric tumors that have Platelet-derived growth factor receptor (PDGFR) expression. The members stated that the challenge would be the fact that, with rare exceptions, every sarcoma patient that has a chemo-sensitive disease will have already received anthracyclines. The members expressed concern that the rare exceptions would not yield a sufficient number of patients to answer a meaningful question. The subcommittee members pointed out that it is critical to ultimately use this product in combination with doxorubicin or as a single agent after doxorubicin. The members raised concern that as a single agent it would be a challenge, therefore suggesting that it was necessary to define a combination to appropriately evaluate activity. The subcommittee members encouraged generation of more preclinical data particularly with rhabdomyosarcoma. The members highlighted that given the mechanism of action and history with other tumors, there are other potential areas of interest, such as hepatic tumors and a subset of renal tumors. The members clarified that PDGFR expression is necessary but may not be sufficient as a predictive biomarker. Furthermore, the subcommittee members advised against a placebo controlled double blind clinical trial design, and encouraged considering a trial in rhabdomyosarcoma with progression free survival as the primary endpoint. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please comment on the safety profile of single-agent olaratumab and possible toxicities that may be seen when olaratumab is added to multi-agent combination therapy in pediatric patients.

***Committee Discussion:** The subcommittee members highlighted that one of the challenges with olaratumab is that it appears to be predominantly targeted for development in combination with doxorubicin and doxorubicin is part of most upfront regimens for the vast majority of pediatric solid tumors. Since in the adult data thus far, this medication was only used in doxorubicin and anthracycline naïve adults, the subcommittee members encourage two potential strategies – either taking the combination in very high risk newly diagnosed pediatric patients or obtaining data in adults with prior anthracycline exposure and then designing an early phase trial in children with clear historically defined safe cut offs of anthracycline exposures and mandated cardioprotective strategies. The members noted that it was well tolerated but many patients experienced greater than grade 3 neutropenia and therefore encourage close monitoring. The subcommittee members stressed the need to optimize the dose of antibody distinctly with each of the combinations, and to specifically look at the different microenvironments in the bone marrow. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please comment on the feasibility of or requirement for international cooperative group collaboration in a future efficacy study.

***Committee Discussion:** The subcommittee members highlighted that in the context of osteosarcoma there was an international European and North American study and such international collaborations were encouraged. The need for international collaboration was driven by the use of a biological stratification, and the subcommittee members stated that if the concern is surrounding the assessment of a single agent then it may not require international collaboration. The members stated that international studies are difficult due to the fact that they are controlled by multiple regulatory groups. Nonetheless, the members clarified that studies are feasible if the question demands that sample size. The subcommittee offered an alternative to increase sample size by lowering the age of eligibility of the planned adult study and making it 12 years of age and older study rather than just limiting it to adults. The members emphasized that larger studies require cooperative group collaboration with rare subtypes of tumors, and that the Children's Oncology Group successfully demonstrated the ability to conduct randomized phase two trials in rhabdomyosarcoma. The subcommittee members stated that such a trial could be completed if an appropriate comparator is found. However, the members highlighted that a randomized trial would have to be an international collaboration because of the number of patients needed. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please comment on the sponsor's plan to evaluate platelet-derived growth factor receptor expression in pediatric cancers during their proposed development program.

***Committee Discussion:** The subcommittee members expressed that requesting archived tissue of newly diagnosed patients to assess platelet-derived growth factor receptor expression in pediatric cancers is not going to be an issue. The members further noted that pharmacodynamics studies*

*looking at signaling post exposure; could be undertaken if olaratumab is administered up front in of high risk patients, since delayed surgery is often part of plan and there is an opportunity to evaluate tumor post-therapy. However, the subcommittee members highlighted that biopsies cannot be mandated solely for research purposes without prospect for providing any clinical benefit in pediatric patients. Furthermore, the members discussed the ethical considerations of mandating archival tissue. Please see the transcript for details of the subcommittee discussion.*

5. **DISCUSSION:** Given the recent approval of this product in adults with soft tissue sarcoma, please discuss whether evaluation of olaratumab in pediatric non-rhabdomyosarcoma soft tissue sarcoma should be considered.

***Committee Discussion:** The subcommittee members agreed that evaluation of olaratumab in pediatric non-rhabdomyosarcoma soft tissue sarcoma should be considered, because the spectrums of the non-rhabdomyosarcoma soft tissue sarcomas are very different in children compared to adults seeing that the adult trials mainly have liposarcomas and children mainly have synovial sarcomas. The members offered several strategies to address this such as creating a separate cohort in an adult trial or considering an expansion of adult trials to lower ages. The subcommittee members highlighted that all the non-rhabdo soft tissue sarcomas cannot be grouped together. However, the subcommittee members suggested that a non-rhabdo pediatric trial would be better designed with histology-specific cohorts. Please see the transcript for details of the subcommittee discussion.*

---

## Day 2, Topic 2: Prexasertib, Eli Lilly and Company

---

1. **DISCUSSION:** Please consider the preclinical data and rationale for the development of prexasertib in neuroblastoma and rhabdomyosarcoma. Additionally, please discuss other tumor types that may benefit from the development of prexasertib.

***Committee Discussion:** The subcommittee members stated that getting combination data and developing a plan incorporating this agent with the current mainstays of treatment, chemotherapy and radiation, is desirable and should inform every potential clinical trial design. However, it was noted to pay close attention to the combinations being used, especially due to the added hematologic toxicities. To address this concern, the subcommittee members suggested using agents such as irinotecan, since its main adverse event is diarrhea and thus does not provide an additive toxicity. In terms of other types of cancers that may benefit from the development of this medication, the subcommittee members stated that they believe the Applicant is right in selecting neuroblastoma and rhabdomyosarcoma for the time being. However, the members encouraged them to look into a variety of other diseases, such as desmoplastic small round cell tumor, osteosarcoma, Ewing sarcoma and hematologic malignancies, in the future. The subcommittee members highlighted that some of these would require a separate development strategy and separate studies due to different patient populations and toxicity profiles. Furthermore, the members encouraged expanding of the preclinical evaluation of this agent in combination with others. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please consider the planned pediatric study of prexasertib in neuroblastoma and rhabdomyosarcoma and provide an opinion regarding the overall study design, including the patient population eligible for enrollment and the tumor types that are planned to be evaluated.

**Committee Discussion:** *The subcommittee members strongly support the evaluation of these two populations, but encourage a smaller study. The members suggest that one way to make the study smaller would be to calculate the necessary study population using a greater effect size. The subcommittee members caution that initial response rates in rhabdomyosarcoma have not always predicted long term outcomes. Nonetheless, the members highlight that in general pediatric tumors are chemo-sensitive, assuming the response rate is sufficient. The members suggest adding another cohort to look at the more rare histologies, to see if there is any activity in those patients. Finally, the subcommittee members encourage using time to progression or duration of response as other endpoints in these studies. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please address the plans for administering prexasertib in combination with cytotoxic chemotherapy regimens. Please address plans for administering prexasertib in combination with other targeted therapies.

**Committee Discussion:** *The subcommittee members stated that neutropenia in pediatrics is easily addressable with the use of growth factors and potentially with the timing and sequencing strategies of the specific agent. The members further noted that a key challenge would be the multitude of different strategies to combination therapy based on what agent is used. The subcommittee members specified that careful consideration should be given to prioritization of the tumor types and the most relevant medications. The members encouraged that radiation therapy and the timing of that radiation should also be considered an important factor in treatment combination. Finally, the subcommittee members noted that the sequence is very important, and it should be tested whether giving the agent 24 hours prior to cytotoxic chemotherapy actually leads to potentiation in the leukemic population and others. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please comment on whether rhabdomyosarcoma should be considered one disease or divided into two disease entities for embryonal and alveolar rhabdomyosarcoma given the different pathology and clinical courses of these tumors.

**Committee Discussion:** *The subcommittee members stated that in the perfect environment they would be divided into two disease entities. However, it was further stated, given the challenges with patient numbers this is not realistic. The subcommittee members suggested addressing this in a larger population including adults to get more patients. The members encouraged creating two separate cohorts as the trial continues if specific differences are identified. Please see the transcript for details of the subcommittee discussion.*

5. **DISCUSSION:** Please address any short-term and potential long-term or late toxicities that may be associated with the use of this drug in children.

**Committee Discussion:** *The subcommittee members stated that there is current information of long term toxicities, but it is only applicable to adults as of now. It was further stated that the initial studies in younger patients will be conducted in patients with relapsed disease and it will be unlikely to see any secondary effects such as secondary malignancies and infertility given the patient population. However, if in the long term, the applicant decides to do observe the medication in newly diagnosed patients, the subcommittee members urge the need for a plan observe long term toxicities. Please see the transcript for details of the subcommittee discussion.*

*The meeting was adjourned at approximately 2:30 p.m. on June 21, 2017 and at 11:45 a.m. on June 22, 2017.*