

**Food and Drug Administration  
Center for Drug Evaluation and Research**

**Summary Minutes of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee  
June 28-29, 2016**

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

**Topic:** On June 28, 2016, information was presented for expert assessments related to 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 also provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) venetoclax, presentation by AbbVie, Inc. (2) tazemetostat, presentation by Epizyme, Inc., and (3) atezolizumab, presentation by Roche/Genentech.

On June 29, 2016, during the morning session, information was presented for expert assessments related to 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 also provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) LOXO-101, presentation by Loxo Oncology, Inc., and (2) entrectinib, presentation by Ignyta, Inc.

During the afternoon session, information was presented on the current unmet clinical need in the nearly uniformly fatal brain tumor, diffuse intrinsic pontine glioma (DIPG) which occurs predominantly in the pediatric age group. The diagnosis of DIPG is typically based on characteristic radiographic and clinical features in lieu of brain biopsy, and histological confirmation. Recent data has demonstrated that the biology and pathophysiology of these tumors differ. There are no approved drugs for this disease. Clinical investigators seek to exploit precision medicine approaches to DIPG and use potentially predictive information from the genomic signature of tumors at either diagnosis or relapse. This information can be used to select specific molecularly targeted drugs based on the genetic aberrations of an individual patient's tumor. The Agency sought the input of the subcommittee, including an assessment of benefit/risk given the potential for an adverse event associated with a surgical intervention in the brainstem.

These summary minutes for the June 28-29, 2016 meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on July 28, 2016.

I certify that I attended the June 28-29, 2016, meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Lauren D. Tesh, PharmD, BCPS  
*Designated Federal Officer, ODAC*

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Alberto S. Pappo, MD  
*Chairperson, pedsODAC*

June 28-29, 2016

Meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee

*Summary Minutes*  
**Meeting of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee**  
**June 28-29, 2016**

The following is the final report of the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting held on June 28-29, 2016. 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:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm486395.htm>

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

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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 28-29, 2016 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 (AbbVie, Inc., Epizyme, Inc., Roche/Genentech, Loxo Oncology, Inc. and Ignyta, Inc.). 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). On June 28, 2016 there were approximately 75 people in attendance. On June 29, 2016 there were approximately 60 people in attendance. There were no Open Public Hearing (OPH) speakers for June 28, 2016 or June 29, 2016 Topic 1. There was 1 OPH speaker for June 29, 2016 Topic 2 and 5 OPH speakers for Topic 3.

**Issue:** On June 28, 2016, information was presented for expert assessments related to 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 also provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) venetoclax, presentation by AbbVie, Inc. (2) tazemetostat, presentation by Epizyme, Inc., and (3) atezolizumab, presentation by Roche/Genentech.

On June 29, 2016, during the morning session, information was presented for expert assessments related to 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 also provided information to the Agency pertinent to the formulation of written requests for pediatric studies, if appropriate. The products under consideration were: (1) LOXO-101, presentation by Loxo Oncology, Inc., and (2) entrectinib, presentation by Ignyta, Inc.

During the afternoon session, information was presented on the current unmet clinical need in the nearly uniformly fatal brain tumor, diffuse intrinsic pontine glioma (DIPG) which occurs predominantly in the pediatric age group. The diagnosis of DIPG is typically based on characteristic radiographic and clinical features in lieu of brain biopsy and histological confirmation. Recent data has demonstrated that the biology and pathophysiology of these tumors differ. There are no approved drugs for this disease. Clinical investigators seek to exploit precision medicine approaches to DIPG and use potentially predictive information from the genomic signature of tumors at either diagnosis or relapse. This information can be

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used to select specific molecularly targeted drugs based on the genetic aberrations of an individual patient's tumor. The Agency sought the input of the subcommittee, including an assessment of benefit/risk given the potential for an adverse event associated with a surgical intervention in the brainstem.

**Attendance:**

**ODAC Members Present (Voting):** Deborah K. Armstrong, MD; Alberto S. Pappo, MD (pedODAC Chairperson)

**ODAC Members Not Present (Voting)** Harold J. Burstein, MD, PhD; Bernard F. Cole, PhD; Louis F. Diehl, MD; Tito Fojo, MD, PhD; Jeffrey E. Lancet, MD; Michael Menefee, MD; Grzegorz S. Nowakowski, MD; Vassiliki A. Papadimitrakopoulou, MD; Brian I. Rini, MD, FACP; Bruce J. Roth, MD

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

**Temporary Members (Voting):** Peter C. Adamson, MD (Day 1 Only); Patrick Brown, MD; Steven G. DuBois, MD, MS (Day 2, Topics 2 and 3 Only); Ira J. Dunkel, MD; Julia Glade Bender, MD; Pamela Haylock (Acting Consumer Representative); Tobey J. MacDonald, MD; Gigi McMillan (Patient Representative); Kathleen A. Neville, MD, Elizabeth A. Raetz, MD; Nita L. Seibel, MD; Katherine E. Warren, MD; Brenda Weigel, MD, MSc

**FDA Participants (Non-Voting):** Amy Barone, MD (Day 1 Morning Session and Day 2 Afternoon Session Only); Martha Donoghue, MD (Day 1 Afternoon Session Only); Lori Ehrlich, MD, PhD (Day 1 Morning Session Only); Rachel Ershler, MD (Day 2 Morning Session Only); Edvardas Kaminskas, MD (Day 2 Morning Session Only); Robert (Skip) Nelson, MD (Day 2 Afternoon Session Only); Christy Osgood, MD (Day 2 Morning Session Only); Richard Pazdur, MD; Gregory Reaman, MD; Jeffrey D. Seidman, MD (Day 2 Afternoon Session Only); Joohee Sul, MD (Day 2 Afternoon Session Only)

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

**Open Public Hearing Speakers:** Jonathan Eric Agin, JD (The Children's Cancer Therapy Development Institute, The Max Cure Foundation); Laura Gottschalk, PhD (National Center for Health Research); Jenny Mosier (National Brain Tumor Society); Lisa Peabody (National Brain Tumor Society); Mr. Cord Schlobohm, DMD (National Brain Tumor Society); Jesse Shumaker (The Cure Starts Now)

***The Agenda proceeded as follows:***

***June 28, 2016***

Call to Order

**Alberto Pappo, MD**

Introduction of Subcommittee

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

FDA Introductory

**Gregory Reaman, MD**

Remarks/Presentation

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

**Topic 1: ABT-199 (Venetoclax) – AbbVie, Inc.**

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Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**AbbVie, Inc.**

Venetoclax for the Treatment of Pediatric Patients with Relapsed/Refractory Cancers

**Su Young Kim, MD, PhD**  
Medical Director, Oncology Development  
AbbVie, Inc.

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**BREAK**

**Topic 2: Tazemetostat – Epizyme, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Epizyme, Inc.**

Tazemetostat for the Treatment of Pediatric Subjects with Malignant Rhabdoid Tumors and Other INI1-Negative Tumors

**Peter Ho, MD, PhD**  
Chief Medical Officer  
Epizyme, Inc.

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

**LUNCH**

**Topic 3: Atezolizumab- Roche/Genentech**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

**Roche/Genentech**

Atezolizumab Oncology Development

**Raphaël Rousseau, MD, PhD**  
Global Head, Pediatric Oncology Drug Development Group  
Genentech, a member of the Roche Group

Clarifying Questions from Subcommittee

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**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

**ADJOURNMENT**

*June 29, 2016*

Call to Order  
Introduction of Subcommittee

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

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: LOXO-101- Loxo Oncology, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**  
Designated Federal Officer, ODAC

**INDUSTRY PRESENTATION**

Developing LOXO-101 in Children with  
NTRK Gene Fusion Cancers

**Josh Bilenker, MD**  
Chief Executive Officer  
Loxo Oncology, Inc.

Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

**BREAK**

**Topic 2: Entrectinib – Ignyta, Inc.**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

**INDUSTRY PRESENTATION**

Entrectinib for the Treatment of Pediatric Cancers  
Harboring an Activating Alteration  
of *NTRK1/2/3*, *ROS1*, or *ALK*

**Pratik S. Multani, MD, MS**  
Chief Medical Officer at Ignyta, Inc.

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Clarifying Questions from Subcommittee

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and  
Subcommittee Discussion

**LUNCH**

**Topic 3: Diffuse Intrinsic Pontine Glioma (DIPG)**

Conflict of Interest Statement

**Lauren Tesh, PharmD, BCPS**

FDA Introductory Remarks

**Joohee Sul, PhD**  
Medical Officer  
Division of Oncology Products II (DOPII)  
OHOP, OND, CDER, FDA

**FDA PRESENTATIONS**

To Biopsy or Not to Biopsy – That is the  
Question.

**Robert (Skip) Nelson, MD**  
Deputy Director and Senior Pediatric Ethicist  
Office of Pediatric Therapeutics  
Office of the Commissioner, FDA

Biopsy Risks for Investigational in vitro  
Diagnostic Devices

**Jeffrey D. Seidman, MD**  
Medical Officer/Pathologist  
Molecular Pathology and Cytology Branch  
Division of Molecular Genetics and Pathology  
Office of In Vitro Diagnostics and Radiological Health  
Center for Devices and Radiological Health FDA

**SPEAKER PRESENTATION**

Treatment Opportunities in Diffuse Intrinsic  
Pontine Glioma (DIPG)

**Mark W. Kieran, MD, PhD**  
Director, Pediatric Medical Neuro-Oncology  
Dana-Farber Cancer Institute/Boston Children's  
Hospital  
Director, Pediatric Brain Tumor Clinic  
Dana-Farber Cancer Institute/Boston Children's  
Hospital  
Associate Professor of Pediatrics  
Harvard Medical School

**GUEST SPEAKER PRESENTATIONS**

DIPG: The Role of Neurosurgery

**Jeffrey R. Leonard, MD**  
Pediatric Neurosurgeon  
Chief of Neurosurgery

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Nationwide Children's Hospital  
Professor, Department of Neurological Surgery  
The Ohio State University

Surgical Experience with Biopsy of Brainstem Tumors

**Nalin Gupta, MD, PhD**  
Professor in Residence of Neurological Surgery and Pediatrics  
Dennis Bruce Dettmer Endowed Chair in Pediatric Neurosurgery  
Director, Pediatric Neurological Surgery Program  
Principal Investigator, Brain Tumor Research Center  
University of California, San Francisco

Clarifying Questions from Subcommittee

**BREAK**

**OPEN PUBLIC HEARING**

Questions to the Subcommittee and Subcommittee Discussion

Closing Remarks

**Gregory Reaman, MD**

**ADJOURNMENT**

*June 28, 2016*

*Questions to the Committee:*

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**Topic 1: Venetoclax**

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1. **DISCUSSION:** Please address the biologic significance of BCL-2 inhibition as a treatment strategy in malignancies of children.

*Committee Discussion:* The subcommittee members stated their interest in BCL-2 inhibition as a treatment strategy in a number of pediatric cancers based on pre-clinical data associated with venetoclax, especially in neuroblastoma. The subcommittee suggested identifying relevant subtypes of AML that can be targeted with this drug. Please see the transcript for details of the subcommittee discussion.

2. **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 recommended that there should be a separate phase 1 study for leukemia and for solid tumors, and to consider a design that has been used in the past for solid tumors that is to give single agent during cycle one and after the dose has been determined to combine this with a series of agents or several agents during cycle two. Also, the subcommittee recommended avoiding a pure dose finding study in hematological malignancies, and to develop a trial that uses combination therapy based on the dose that was determined in the phase 1 study of solid tumors. The subcommittee suggested doing an evaluation during phase 1 to determine the short-term toxicities, and the subcommittee stated their interest in learning about the long-term toxicity of this agent. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please address whether sufficient relapsed/refractory patients would be available for evaluation of this drug given the numerous salvage therapy trials in progress.

**Committee Discussion:** *The subcommittee commented that there may be a low accrual in the lymphoid leukemia population as a single agent but this particular population is not limited in numbers. However, the numbers may be limited within the lymphoma population. Members of the subcommittee suggested that the combination therapy choices should be reconsidered and the study should include a single agent window therapy followed by a combination therapy specifically for solid tumors, and a combination study for leukemias. Other recommendations included considering an international collaborative study to increase the number of patients. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please discuss the design of the proposed phase 1 trial in children including disease types and minimum tumor activity required for cohort expansion.

**Committee Discussion:** *The subcommittee suggested that there should be separate phase 1 studies for leukemia and for solid tumors with different definitions of toxicity for each; however one member commented that it may be a wrong approach to separate the diseases based on bone marrow infiltration. The subcommittee recommended that the sponsor consider a design done from the past for solid tumors where single agent is given during cycle one and when the dose is determined, series of agents are combined to the agent during cycle two. Also, the members recommended avoiding dose finding studies for single agents and the ramp-up phase for all types of tumors. The subcommittee mostly agreed that 20% is reasonable design for cohort expansion in phase 2 based on the disease being evaluated. Please see the transcript for details of the subcommittee discussion.*

5. **DISCUSSION:** Please address the plans for administering venetoclax in combination with other chemotherapy regimens.

**Committee Discussion:** *Members of the subcommittee suggested that the sponsor should develop a more robust backbone to combine venetoclax with chemotherapy that will be moved to a phase 2 or upfront regimen. The subcommittee encouraged the sponsor to consider combination regimens for upfront care for patients and to reconsider drug combinations to determine the tolerability and efficacy data in that context. Please see the transcript for details of the subcommittee discussion.*

6. **DISCUSSION:** Discuss other relevant pediatric cancers (including clear cell sarcoma of the kidney and Wilms tumor) for which a biologic rationale for the evaluation of venetoclax exists with high BCL-2 expression in the absence of xenograft animal models.

**Committee Discussion:** *The subcommittee members recommended considering expanding the number of histologies included in the solid tumors cohort, including patients for example with clear cell sarcoma. Please see the transcript for details of the subcommittee discussion.*

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## Topic 2: Tazemetostat

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1. **DISCUSSION:** Please consider the relevant pediatric cancers (including non-Hodgkin lymphoma) for which a biologic rationale for the evaluation of tazemetostat exists.

**Committee Discussion:** *The subcommittee members encouraged the sponsor to consider neuroblastoma as a potential indication as well as to consider investigating alternate modes of delivery to the CNS for CNS tumors given its poor penetration. Also, the subcommittee suggested that the sponsor consider subsets of patients that have rare EZH2 mutations be included in small efficacy studies at later stages of the studies. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please comment on a trial design considered to be adequate and well controlled in order to demonstrate efficacy and safety in this pediatric population given the rarity of the disease.

**Committee Discussion:** *The subcommittee recommended optimization of exposure and reconsideration of dose escalation to beyond the dose limiting toxicity. Also, members of the subcommittee noted concerns that the dose escalation may be too cautious and that the doses should be pushed to get the exposure that is associated with activity. However, the subcommittee noted concerns about whether increasing the dose will overcome the poor CNS penetration. The subcommittee also noted dose optimization and inclusion of infants to optimize clinical findings in phase I studies. A member of the subcommittee suggested that another way to gather tumor penetration data would be to allow a very short window of drug and consider resection for those who are newly diagnosed with potentially resectable tumors and to obtain tissues that could serve as biomarker verification of CNS penetration. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please consider the necessity for an international collaborative study given the very rare cancers for which this drug might prove relevant.

**Committee Discussion:** *The subcommittee agreed that it is necessary to continue to conduct international collaborative studies if there is activity, that is promising, in specific subsets of populations. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please comment on any safety concerns relating to the use of tazemetostat in pediatric patients. In addition, please comment on combining safety data across multiple mutation types.

**Committee Discussion:** *The subcommittee recommended that the inclusion and exclusion criteria be should be limited since the population is very small. Additionally, the subcommittee suggested identifying toxicities in patients that are on steroids and those who are not, as well as, taking into consideration the host factors in young patients and incorporating into the studies. The subcommittee suggested differentiating the safety patterns for germline versus acquired INI1 mutations. Another*

*member suggested that it would be important to follow-up growth and endocrine development outcomes data early on since it is expected that it would be a long-term therapy. Please see the transcript for details of the subcommittee discussion.*

5. **DISCUSSION:** Please comment on the adequacy of the current pediatric formulation and any future plans.

*Committee Discussion: The subcommittee recommended further development of this oral formulation and providing a formulation with less sugar. Please see the transcript for details of the subcommittee discussion.*

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### Topic 3: Atezolizumab

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1. **DISCUSSION:** Please discuss the relative expression of tumor neoantigens in specific pediatric cancers in comparison to that in adult tumors and the resulting biological rationale for evaluating atezolizumab in pediatric patients.

*Committee Discussion: The subcommittee recommended that the sponsor continue to assess and develop robust biomarkers given that there is not a clear understanding of the prevalence and role of PDL-1 expression in pediatric tumors and the relationship between PDL-1 expression and potential antitumor activity with atezolizumab. The subcommittee also suggested that the sponsor explore the correlation between mutational burden and neoantigen expression in pediatric tumors. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please consider which specific pediatric cancers might be ideal candidates for evaluation of atezolizumab based upon available non-clinical and clinical data for this class of drugs and the current needs of the pediatric oncology community. Please comment regarding whether level of PDL-1 expression should be considered when selecting tumor types for future pediatric studies of atezolizumab.

*Committee Discussion: The subcommittee noted that not using PDL-1 expression to stratify patients and restrict trial eligibility was a good approach given the currently incomplete understanding of the prevalence and role of PDL-1 expression in pediatric cancers. Also, the subcommittee recommended that the sponsor analyze the tumor biomarker and efficacy data generated in the ongoing pediatric trial to assist with identification of a predictive biomarker that can help identify the subpopulations of pediatric cancers that are most likely to respond to atezolizumab. The subcommittee recommended that the sponsor explore other factors that could impact the antitumor activity of atezolizumab, such as tumor burden, immune status including absolute lymphocyte count, and concomitant use of immunosuppressive therapies such as corticosteroids. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please consider the ongoing pediatric study and provide an opinion regarding the overall study design, including the patient population eligible for enrollment and the ability of the gated design to identify the tumor types that should be further studied.

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**Committee Discussion:** *The subcommittee expressed concern that the thresholds for response rate may be set too high and could result in a premature and erroneous conclusion that atezolizumab should not be developed further in pediatric cancers. Also, the subcommittee recommended considering combination studies once the atezolizumab dose and subset of patients that may benefit from atezolizumab are identified. The subcommittee suggested that the sponsor explore immune competency, age, and other factors given the unclear correlation between histology and response in pediatric tumors. Additionally, the subcommittee recommended expanding objectives to collect quality of life data to better assess the potential benefits of atezolizumab. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please consider the toxicity profile of atezolizumab in the adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of PDL-1 inhibitors in pediatric patients. Also discuss potential ways to mitigate these risks.

**Committee Discussion:** *The subcommittee suggested that the side effects or safety concerns can be mitigated by close observation and implementation of appropriate medical interventions in a timely fashion given that atezolizumab has a very similar toxicity profile as other PDL-1 inhibitors. Also, the subcommittee noted that predicting the impact on autoimmunity may be difficult and suggested proceeding with the development of the drug given that there are no significant concerns for unique toxicities in pediatric patients. Additionally, the subcommittee recommended that the sponsor provide clear guidance on how to mitigate side effects and the approach to use of corticosteroids. Please see the transcript for details of the subcommittee discussion.*

The meeting on June 28, 2016 was adjourned at approximately 2:45 p.m.

**June 29, 2016**

**Questions to the Committee:**

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### Topic 1: LOXO-101

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1. **DISCUSSION:** Please consider the ongoing pediatric study and provide an opinion regarding the overall study design.

**Committee Discussion:** *There was significant interest, enthusiasm, and support from subcommittee members in conducting phase 1 studies in pediatrics early on. The subcommittee struggled with how to best define optimal dose and how to identify the optimal biological dose for these patients. One suggestion was to do intra-patient dose escalation and get dose and pharmacokinetic information based on an individual basis instead of cohort analysis. One panel member cautioned this approach. It is unclear whether real time pharmacokinetics is useful because responses have been observed with various doses and exposures. In addition, it was stated that it is unclear if increasing dose will increase efficacy and potentially increase toxicity. The subcommittee agreed that chronic toxicity and neurological toxicity concerns were addressed very clearly by the industry presentation. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please consider the toxicity profile of LOXO-101 in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of LOXO-101 in pediatric patients. Also, discuss potential ways to mitigate these risks.

**Committee Discussion:** *The subcommittee agreed that the safety profile of LOXO-101 appears to be favorable and the ongoing phase 1 study offers a unique opportunity to study the activity, pharmacokinetics, short and long-term toxicity in this unique group of patients (young children afflicted with tumors such as infantile fibrosarcoma, and, hemangiopericytoma). The subcommittee recommended that the sponsor continue monitoring long-term toxicity (especially neurotoxicity) and consider further the issue of how to better define the dose of this drug for this group of patients. The subcommittee also recommended that the sponsor continue exploring using maximum tolerable dose versus biological dose in this group of patients. Please see the transcript for details of the subcommittee discussion.*

3. **DISCUSSION:** Please consider the necessity for an international collaborative study given the very rare cancers for which LOXO-101 may prove relevant.

**Committee Discussion:** *The subcommittee supported international collaboration especially with this subgroup of patients with rare tumors. The subcommittee recommended that the sponsor continue to explore the availability of genomic testing in specific sites (especially in Europe) and consider centralized testing. Please see the transcript for details of the subcommittee discussion.*

4. **DISCUSSION:** Please comment on the adequacy of the current pediatric formulation and any plans for evaluation of the pediatric formulation.

**Committee Discussion:** *The subcommittee agreed that this liquid formulation is appropriate and advantageous to give to young patients. Please see the transcript for details of the subcommittee discussion.*

5. **DISCUSSION:** Please comment on the clinical availability and utility of NTRK fusion identification in current pediatric oncology practice.

**Committee Discussion:** *The subcommittee generally agreed that if tumors with a certain histology are expected to have an NTRK alteration then genomic testing should be pursued. The subcommittee further agreed that this condition of testing should be diagnosis-specific and testing must be done in a CLIA-certified laboratory and potentially a second laboratory for validation. Please see the transcript for details of the subcommittee discussion.*

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## Topic 2: Entrectinib

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1. **DISCUSSION:** Please consider whether NTRK1 and 2 and ALK overexpression provides an appropriate biological rationale for the proposed target tumors. Please address the role of ROS1 inhibition in pediatric tumors.

**Committee Discussion:** *The subcommittee agreed that expression profiling in this study could offer the opportunity to capture data whether overexpression of these genes are appropriate biological targets for inhibition by entrectinib. It was further stated that this might have a role for a very small subset of pediatric tumors in which ROS1 is rearranged such as IMT or a subset patients with leukemia that can benefit from this drug. Please see the transcript for details of the subcommittee discussion.*

2. **DISCUSSION:** Please comment on the clinical availability and feasibility of *NTRK1/2/3* and *ROSI* evaluation in current pediatric oncology practice.

*Committee Discussion:* The subcommittee stated that it might be difficult to evaluate *NTRK* expression particularly in brain tumors. It would be worthwhile to proceed with extensive genomic testing of *NTRK* and *ALK* if given availability and feasibility of histology evaluation. The subcommittee recommended that sponsor should track and validate tissues and studies outside of the company and make sure rearrangement, expression, or histology is actually present. Please see the transcript for details of the subcommittee discussion.

3. **DISCUSSION:** Please consider the ongoing pediatric study and discuss the overall study design.

*Committee Discussion:* The subcommittee appreciated the design of this study starting at what was thought to be an effective dose in adults. The subcommittee recommended careful consideration of dose escalation especially if toxicity is not the endpoint and clarifying the criteria for defining an optimal dose. The subcommittee agreed not to de-escalate the dose a-priori in patients with CNS tumors to avoid jeopardizing CNS penetration and dose adjust based on toxicity. The subcommittee also mentioned to encourage biopsy at the time of recurrence while considering risk: benefit. The subcommittee agreed that the sponsor should work on clearly defining the criteria of toxicity and defining the optimal dose. Please see the transcript for details of the subcommittee discussion.

4. **DISCUSSION:** Please consider the toxicity profile of entrectinib in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of entrectinib in pediatric patients. Also discuss potential ways to mitigate these risks.

*Committee Discussion:* The subcommittee agreed that the sponsor has to be vigilant in monitoring for any long-term toxicity and be aware of off-target effects. The subcommittee further noted that sponsor should also monitor survivors for long-term toxicity in addition to the expected renal toxicity. Please see the transcript for details of the subcommittee discussion.

5. **DISCUSSION:** Please address whether evaluation of this drug in pediatrics would require international collaboration.

*Committee Discussion:* The subcommittee encouraged international collaboration, but stated that it might not be necessary for neuroblastoma. However, it would be worth pursuing collaboration between sponsors due to the small subset of patients. These agents nevertheless aren't identical and might have different indications for select subsets of patients. Please see the transcript for details of the subcommittee discussion.

6. **DISCUSSION:** Please comment on the adequacy of the current pediatric formulation and any future plans for the pediatric formulation.

*Committee Discussion:* The subcommittee encouraged the development of the granule/sprinkle formulation. The subcommittee stated that the bioavailability studies should be done since the interim alternative is to open the capsule and sprinkle its contents into food. The subcommittee further commented that bioavailability studies would optimize the use of this drug and to better define what factors affect bioavailability. The subcommittee also suggested the sponsor to provide adequate instructions to family regarding how much of the capsule's contents are sprinkled, specify what

*food(s) it can be sprinkled on, and how to handle leftover medications regarding disposal. Please see the transcript for details of the subcommittee discussion.*

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### Topic 3: DIFFUSE INTRINSIC PONTINE GLIOMA (DIPG)

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1. **DISCUSSION:** Consider changes over time in the adverse event rate associated with surgical biopsy of the brainstem to obtain DIPG tissue for biology studies and more recently to select molecularly targeted drugs for therapy.

*Committee Discussion:* The subcommittee stated that the applicability and safety of this procedure has changed and will continue to change over time. The subcommittee supported moving forward with biopsy in context of clinical trials and discussed expanding education on how to perform these biopsies in other institutions in the future. The subcommittee further commented that this would have a positive impact on knowledge and the applicability of precision medicine in the future. Please see the transcript for details of the subcommittee discussion.

2. **DISCUSSION:** Consider the benefit: risk assessment of surgical biopsy of DIPG for molecular analysis of both newly diagnosed and progressive (on current therapy) tumors for the purpose of selecting an appropriate phenotype-directed targeted therapeutic agent for patients with this disease.

*Committee Discussion:* The subcommittee was supportive of continuing to explore the role of surgical biopsy in patients with DIPG and agreed that the benefit: risk ratio needs to be further defined since results of biopsy-directed treatment assignment are limited currently. The subcommittee further stated that surgical biopsy is best performed in the context of clinical trials in order to systematically study to and better understand the benefits and complications of this procedure. Biopsies of DIPG have a role in confirming DIPG diagnosis and relapse, and are needed in order to better understand the molecular signatures and heterogeneity of DIPG and enable development of effective targeted therapies for this disease. The subcommittee also noted that incorporating biopsies into clinical trials will help guide parents to academic centers that have expertise in performing this procedure and supported the idea of expanding availability of DIPG biopsies to more centers in the future. Please see the transcript for details of the subcommittee discussion.

3. **DISCUSSION:** Please discuss whether the benefit: risk assessment is favorable.

*Committee Discussion:* The subcommittee agreed that benefit: risk ratio for surgical biopsy is favorable. However, it was stated that in light of the current therapeutic landscape and emerging understanding of the molecular drivers in DIPG, substantial improvement are needed and biopsy of DIPG certainly has a role in clinical trials of targeted therapies in this disease. The subcommittee commented that the purpose of biopsy at this point is to obtain more knowledge about DIPG and help guide choice of specific drugs and the potential role for precision medicine in the management of DIPG. Please see the transcript for details of the subcommittee discussion.

The meeting on June 29, 2016 was adjourned at approximately 4:15 p.m.