FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (pedsODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
June 28 - 29, 2016

QUESTIONS

Day 1, Topic 1: venetoclax, AbbVie, Inc.

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

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.

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.

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.

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

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.

QUESTIONS (cont.)

Day 1, Topic 2: tazemetostat, Epizyme, Inc.

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

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.

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

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.

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

QUESTIONS (cont.)

Day 1, Topic 3: atezolizumab, Roche/Genentech

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.

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.

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.

4. **DISCUSSION:** Please consider the toxicity profile of atezolizumab in adults and discuss whether there are unique safety concerns related to potential short and long-term toxicities from the use of PD-L1 inhibitors in pediatric patients. Also discuss potential ways to mitigate these risks.

QUESTIONS (cont.)

Day 2, Topic 1: LOXO-101, Loxo Oncology, Inc.

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

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.

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

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

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

QUESTIONS (cont.)

Day 2, Topic 2: entrectinib, Ignyta, Inc.

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.
2. **DISCUSSION:** Please comment on the clinical availability and feasibility of *NTRK1/2/3* and *ROS1* evaluation in current pediatric oncology practice.
3. **DISCUSSION:** Please consider the ongoing pediatric study and discuss the overall study design.
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.
5. **DISCUSSION:** Please address whether evaluation of this drug in pediatrics would require international collaboration.
6. **DISCUSSION:** Please comment on the adequacy of the current pediatric formulation and any future plans for the pediatric formulation.

QUESTIONS (cont.)

Day 2, Topic 3: Diffuse Intrinsic Pontine Glioma (DIPG)

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.

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 molecular phenotype-directed targeted therapeutic agent for patients with this disease.

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