



## **FDA Briefing Document**

### **Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)**

**June 28, 2016**

#### **DISCLAIMER STATEMENT**

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office.

We have brought the following issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee.

Information will be 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 will consider and discuss 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 will also provide information to the Agency pertinent to the formulation of Written Requests for pediatric studies, if appropriate. The products under consideration are: (1) venetoclax, presentation by AbbVie, (2) tazemetostat, presentation by Epizyme, Inc., and (3) atezolizumab, presentation by Roche/Genentech.

The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.



## Memorandum

Date: June 3, 2016

To: Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) Members, Consultants, and Guests

From: Gregory Reaman, MD  
Associate Director for Oncology Sciences, Office of Hematology and Oncology Products (OHOP), CDER, FDA

Subject: FDA Background Package for June 28, 2016 Meeting

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Thank you for agreeing to participate in the upcoming Pediatric Oncology Subcommittee of the ODAC. The Subcommittee will hear about pediatric development plans for three products that are under development for one or more oncology indications. We believe that this focused discussion will utilize the expertise of the Pediatric Oncology Subcommittee in guiding the Agency's decisions related to the issuance of Written Requests in accordance with current legislative initiatives enacted to accelerate drug development in the pediatric population. The Subcommittee will consider and discuss issues relating to the development of each product for potential pediatric use and provide guidance to facilitate the formulation of Written Requests for pediatric studies, if appropriate. The products under consideration are: (1) venetoclax, presentation by AbbVie, Inc. (2) tazemetostat, presentation by Epizyme, Inc., and (3) atezolizumab, presentation by Roche/Genentech.

As always, we appreciate your time and commitment and look forward to an informative meeting on June 28, 2016.

### REFERENCE:

1. **Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA):**  
Title V – Pediatric Drugs and Devices (pages 47-58).

FDASIA legislation is available at: <http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>

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## Pediatric Legislative Initiatives

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Pediatric legislation, including a combination of incentives and requirements, has significantly increased pediatric drug research and development and led to a substantial increase in products with new pediatric information in labeling.

Relevant pediatric legislative initiatives are listed below:

- 1997 The Pediatric Exclusivity provision - created in the Food and Drug Administration Modernization Act (FDAMA)
- 2002 Best Pharmaceuticals for Children Act (BPCA) – reauthorization of the Pediatric Exclusivity provision
- 2003 The Pediatric Research Equity Act (PREA - a requirement which allows the FDA to require pediatric studies in drugs and biologics for certain applications
- 2007 Re-authorization of BPCA and PREA in the Food and Drug Administration Amendments Act (FDAAA)
- 2010 The Biologics Price Competition and Innovation Act of 2009 (BPCI) was included in the Patient Protection and Affordable Care Act – created a framework for the approval of follow-on biologics and made biologics, including follow-on biologics, eligible for Pediatric Exclusivity through amendment of section 351 of the Public Health Services Act. BPCI sunsets in March 2015
- 2012 BPCA and PREA made permanent in the Food and Drug Administration Safety and Innovation Act (FDASIA)

Each one of these pediatric milestones has expanded and improved consistency and transparency of the pediatric information available for product use. For example, FDAAA requires that study data, both positive and negative, conducted under BPCA and PREA be described in product labeling. Also, a labeling statement of the FDA's determination whether or not the studies demonstrate safety or efficacy or if the studies were inconclusive in pediatric populations must also be included. Another important milestone with the recent passage of FDASIA was the permanent reauthorization of BPCA and PREA. Other important changes to pediatric drug development were included in this legislation. One such change was the new requirement for drug developers to submit more detailed plans to perform pediatric studies earlier during drug development. Traditionally, drug developers were not required to provide plans for pediatric studies until relatively late the development of a product. New legislation under PREA requires that drug developers submit plans for pediatric drug development earlier during the development of the product (i.e., at the end of phase 2). The intent of this legislation is to promote earlier development of products for pediatric use.

The following is a brief review of the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act, two laws that support pediatric drug development, and recent changes to these laws under the Food and Drug Administration Safety and Innovation Act.

## **Best Pharmaceuticals for Children Act**

The intent of BPCA is to provide an incentive to drug developers to perform pediatric studies in order to improve the efficacy and safety data available for products used in children and infants. This incentive allows sponsors to qualify for an additional six months of marketing exclusivity for the entire moiety (molecule responsible for the pharmacological action of the drug), if specific studies addressing relevant pediatric indications are completed and submitted to FDA. A Written Request is a document issued by the FDA which outlines the type of studies to be conducted, study design and objectives, and the age groups to be studied. Because the pediatric exclusivity provision is voluntary, the sponsor may decline a Written Request. Thus, FDA has the ability to request that the sponsor perform pediatric studies under a Written Request that can lead to additional marketing exclusivity for the product.

This process can be initiated by either the sponsor or the FDA. A sponsor may submit a proposal to the FDA to conduct pediatric studies. If the FDA determines there is a public health need, the Agency will issue a Written Request for pediatric studies. These studies may or may not include the studies proposed by the sponsor. FDA may issue a Written Request on its own initiative when it identifies a need for pediatric data.

Of note, prior to 2010, the Written Request process only applied to drugs, and not to biological products. However, under BPCI, biological products became eligible for additional marketing exclusivity through the Written Request process. To date, no Written Requests have been issued for biologic products.

## **Pediatric Research Equity Act**

PREA works in concert with BPCA. In contrast to BPCA, which is based on incentives for drug developers to voluntarily perform needed pediatric studies, PREA requires that pediatric studies must be performed. However, this requirement only applies to the specific indications for which the sponsor is seeking approval for their product. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. Under PREA, the FDA may require that the sponsor develop age appropriate formulations for use in required pediatric studies and that the required pediatric studies must include data to support pediatric dosing and administration. Additionally under PREA, pediatric studies of currently marketed drugs and biologics may be required if the product is used by a “substantial” number of children, if adequate pediatric labeling would provide “meaningful” therapeutic benefit compared with existing treatments for children for the claimed indication, or if the lack of “adequate” labeling poses a risk for the pediatric population.

Pediatric studies may be deferred (postponed until a later date) by the FDA in certain situations including if the application is ready for approval for use in adults before pediatric studies are complete, or when additional safety or effectiveness data needs to be collected before studying in the pediatric population. Studies may be waived in full or in part in certain situations, including when a clinical condition or disease entity does not occur in the

pediatric population, when necessary studies are impossible or highly impracticable, there is evidence strongly suggesting that the product would be ineffective or unsafe in all or some pediatric age groups or the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients.

It should be noted that PREA does not apply to products granted orphan designation. PREA has limited applicability for drugs and biologics being developed for oncology as the tumors being treated in adults rarely occur in children. Therefore pediatric tumors are considered as distinct indications and are studied by a Written Request under BPCA.

### **Pediatric Study Plan (PSP)**

With passage of FDASIA in July 2012, both BPCA and PREA have been permanently reauthorized precluding the necessity of periodic (every 5 years) justification for reauthorization. Among the changes brought by this legislation is the requirement under PREA for earlier initiation of discussion of the proposed studies to be conducted in the appropriate pediatric populations. Sponsors are now required to submit an initial PSP within 60 days of the End of Phase 2 (EOP2) meeting with the FDA. The content of the PSP includes an outline of the sponsor's proposed study(ies): objectives, design, age groups evaluated, relevant endpoints, and statistical approach. Requests for deferral or waiver may be made with supporting information. Relevant information to understand the rationale for the PSP should be included to describe, as appropriate, a disease overview in the pediatric population and the product under development, potential plans and justification for the use of extrapolation of data generated in other patient populations, nonclinical data both existing and planned to support pediatric studies, plans for pediatric specific formulation when appropriate, synopsis/summary of proposed study(ies) and timelines for completion, information with respect to agreements with other Health Authorities, e.g. Pediatric Investigation Plan( PIP) for EMA. PSPs will be required for all products (drugs and biologics) that trigger PREA if an EOP2 meeting is held as of January 5, 2013.

### **Additional Provisions of Food and Drug Administration Safety and Innovation Act (FDASIA)**

In recognition of the particular need for clinically evaluated drugs in neonates, specific justification for the inclusion or exclusion of neonatal patients in the proposed studies must be provided in the PSP. This information is to be explicitly stated in any Written Request.

Studies that are required under PREA include specific deadlines for completion. Under FDASIA, a new provision allows for an extension of the deadline for submission of these deferred studies. However, the requests for deferral must be reviewed by the Pediatric Review Committee within FDA and recommendations regarding whether the deferral extension should be granted. For studies that have not been submitted prior to the established deadline, FDASIA has provided increased enforcement mechanisms including the public posting of non-compliance letters for overdue PREA post-marketing requirements and a process for misbranding products, if applicable.

Difficulties in development of drugs for pediatric use in rare diseases have long been an important issue. FDASIA includes a new provision known as the Pediatric Priority Review Voucher. This program awards developers of products for a rare pediatric disease a voucher for 'priority review' of a subsequent human drug application. To qualify for this voucher program, the product and its development program must meet three requirements:

- Definition of a pediatric rare disease; a “disease that primarily affects individuals aged from birth to 18 years, including age groups often called neonates, infants, children and adolescents” and that meets the definition of a “rare disease or condition” set forth under the Orphan Drug Act.
- The application for the voucher “relies on clinical data derived from studies examining a pediatric population and dosages of the drug intended for that population” and
- The applicant “does not seek approval for an adult indication in the original rare disease product application”.

Additionally, within 18 months of the passing of FDASIA, FDA held an open public meeting on the development of new therapies for pediatric rare diseases, including cancer and subsequently sent a Report to Congress on the status of pediatric drug development.

The various pediatric initiatives have led to a dramatic increase in pediatric studies submitted to the FDA and resulted in new pediatric information in labeling. There have been 466 pediatric labeling changes for drugs and biologics between 1998 and October 2012. Of these, 15 labeling changes, including 4 approvals for pediatric use, were for drugs used in oncology.

## First Session

**PRODUCT:** Venetoclax

**COMPANY:** AbbVie, Inc.

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### I. Regulatory history

Venetoclax is an oral, small molecule, selective inhibitor of BCL-2, a regulator of apoptosis. BCL-2 family proteins include both anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1) and pro-apoptotic proteins (BIM, BAD, BID, NOXA, BAK, and BAX). The anti-apoptotic proteins bind to and sequester the pro-apoptotic proteins to inhibit programmed cell death. BCL-2 is overexpressed in some malignancies, tipping the balance in favor of cell survival, and is associated with increased resistance to chemotherapy. Venetoclax binds to BCL-2 with high affinity which releases the pro-apoptotic proteins to initiate apoptosis.

Beginning in 2010, venetoclax has been studied in a variety of hematologic malignancies. In April 2016, venetoclax was granted accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) with 17p deletion who had received at least one prior therapy. Venetoclax has shown preliminary clinical activity in acute myeloid leukemia (AML) in combination with a hypomethylating agent, and has received breakthrough therapy designation for this indication in adults. Venetoclax also has shown preliminary anti-tumor activity in adults with Non-Hodgkin Lymphoma (NHL), including Diffuse Large B-Cell Lymphoma (DLBCL). Venetoclax is not being studied in any trials in pediatric patients.

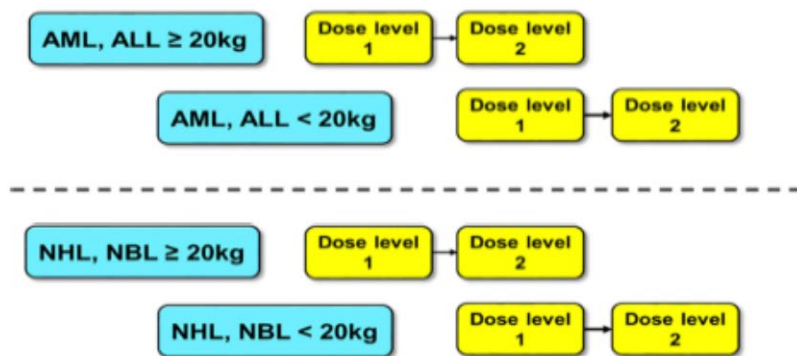
As of November 2015, more than 1400 adult patients have been exposed to at least 1 dose of venetoclax; 560 as monotherapy and 933 in combination with other therapies. The most common treatment-emergent adverse events include grade 3-4 hematologic toxicities (neutropenia/febrile neutropenia, thrombocytopenia, and anemia) and grade 1-2 GI toxicities (nausea, diarrhea). Tumor lysis syndrome has occurred, including fatal events and renal failure, in patients with high tumor burden. TLS risk has been largely mitigated by risk stratification, gradual ramp-up dosing, and TLS prophylaxis including electrolyte monitoring, hydration, and anti-hyperuricemics. Neutropenia is also an important risk and occurs commonly. Supportive measures include monitoring of blood counts, myeloid growth factors, or antimicrobials as indicated.

The rationale for selection of pediatric tumor types for evaluation was based on tumors that have high levels of BCL-2 expression, pre-clinical activity in mouse xenograft models, and preliminary clinical data in adult malignancies if they occur in children. This process identified AML, acute lymphocytic leukemia (ALL), non-Hodgkin Lymphoma (NHL), and neuroblastoma (NBL) as the tumor types for initial pediatric development. BCL-2 mRNA expression was high relative to BCL-XL in a variety of pediatric tumors including NBL, AML,



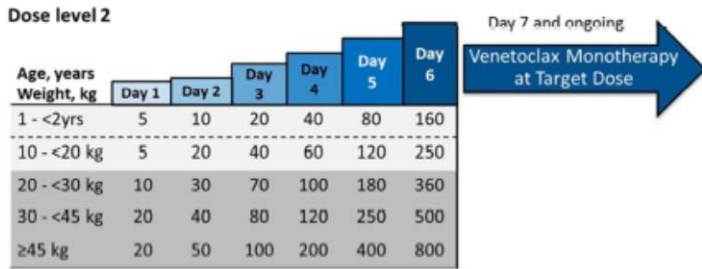
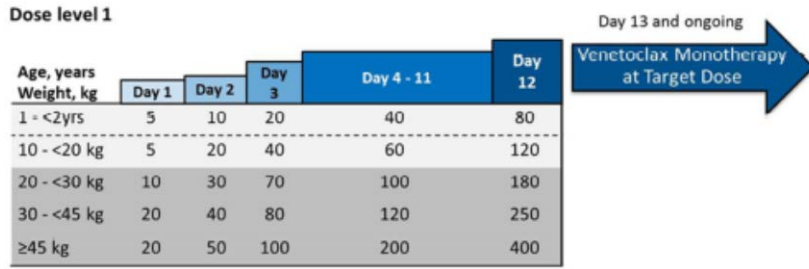
ALL, Wilms tumor, osteosarcoma, clear cell sarcoma of the kidney, and rhabdoid tumors. However, venetoclax did not show activity in preclinical models of pediatric solid tumors (Ewings, osteosarcoma, rhabdomyosarcoma, and medulloblastoma), or had no preclinical data available for clear cell sarcoma or Wilms tumors of the kidney. Venetoclax did show activity in patient-derived xenograft models of AML, ALL, NHL (except Burkitt's lymphoma), and NBL.

The proposed phase 1 study in children will consist of a dose escalation phase followed by a cohort expansion phase in approximately 150 patients with relapsed or refractory AML, ALL, NHL, and NBL. The dose escalation phase, shown in Figure 1, will use a 3+3+3 design with 4 groups based on disease type and weight. AML and ALL will be escalated independently of NHL and NBL due to the different dose limiting toxicity (DLT) criteria for bone marrow involvement in the former. If patients with NHL or NBL have significant marrow involvement, they will use the DLT criteria of AML and ALL patients.



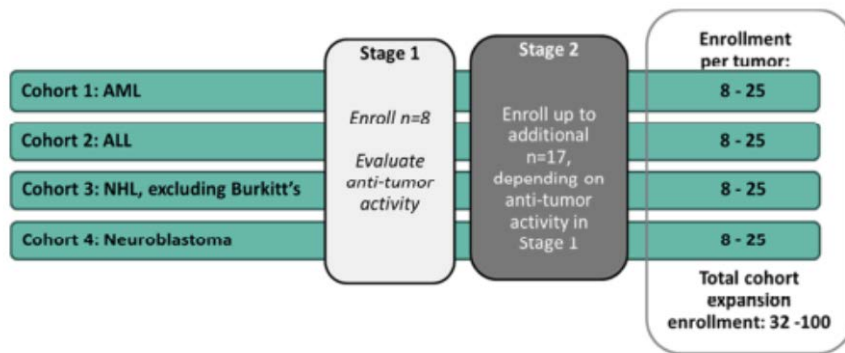
**Figure 1: Dose Escalation Scheme; copied from AbbVie/Genentech Briefing Package**

Doses will be age or weight-adjusted to match adult equivalent target doses of 400 mg (dose level 1) or 800 mg (dose level 2) with actual doses shown in Figure 2. Patients 1-<2 years old will have a fixed dose due to immature CYP3A metabolism which is expected to impact bioavailability. Patients  $\geq 2$  years old will have weight-based dosing with patients  $\geq 45$  kg receiving adult dosing based on population PK data in prior adult studies. A daily ramp-up will occur until the target dose is reached. The dose ramp up will pause on days 4-11 in dose level 1 to allow for steady state PK evaluation.



**Figure 2: Dosing Schedule; copied from AbbVie/Genentech Briefing Package**

After the dose escalation is completed for each group, cohort expansion will proceed as shown in Figure 3. Dose escalation will proceed using the Gehan 2-stage design with a threshold of success of 20%. Each cohort will initially enroll 8 patients at least 1 response must occur to continue enrollment in that cohort. If anti-tumor activity is seen, then up to 17 additional patients will be enrolled. Additional patients may be added if required, particularly in the ALL cohort due to disease heterogeneity, to pursue potential signals in different subtypes.



**Figure 3: Cohort Expansion; copied from AbbVie/Genentech Briefing Package**

After completion of the DLT period (21 days), patients may receive venetoclax in combination with chemotherapy for any of the following responses:

- Patients with complete remission (CR) and cannot proceed to stem cell transplantation
- Patients with partial remission (PR) and no evidence of further response at the second response assessment
- Patients with stable disease (SD) after 3 stable assessments in the AML and ALL cohorts or after 2 stable assessments in the NHL and neuroblastoma cohorts
- Patients with progressive disease (PD)

The following combination regimens will be assessed:

- AML: low-dose cytarabine
- ALL: dexamethasone and vincristine (imatinib if Philadelphia chromosome positive)
- NHL: rituximab
- Neuroblastoma: cyclophosphamide

## **II. Issues Relating to the Development of Venetoclax in Pediatrics**

1. Please address the biologic significance of BCL-2 inhibition as a treatment strategy in malignancies of children.
2. 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. Please address whether sufficient relapsed/refractory patients would be available for evaluation of this drug given the numerous salvage therapy trials in progress.
4. Please discuss the design of the proposed phase 1 trial in children including disease types and minimum tumor activity required for cohort expansion.
5. Please address the plans for administering venetoclax in combination with other chemotherapy regimens.
6. 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.

## Second Session

**PRODUCT: Tazemetostat**  
**COMPANY: Epizyme, Inc.**

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### I. Regulatory History

Tazemetostat is a selective, reversible small molecule inhibitor of the histone lysine methyltransferase enhancer of zeste homolog 2 (EZH2).

- EZH2 is the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and trimethylation of lysine 27 of histone H3 (H3K27). EZH2 mutation and/or over-expression have been observed in several cancer types, leading to an aberrant H3K27 trimethylation (H3K27Me3) state which is oncogenic.
- In addition to genetic alterations in EZH2 itself, distal genetic changes in other proteins can lead to an oncogenic dependency on EZH2 activity, specifically those affecting proteins of the SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeling complex. If components of the SWI/SNF complex, such as INI1 or SMARCA4, are mutated or deleted, the normal counterbalance between PRC2 and SWI/SNF activities is disrupted, leading to hyper-repression of PRC2 targets, potentiation of stem cell programs and oncogenic transformation.
- Epizyme hypothesizes that EZH2 inhibition will release this aberrant repression leading to anti-proliferative effects.

Genetic loss of INI1 has been described in many human malignancies including malignant rhabdoid tumors (MRTs). MRTs are extremely rare and highly aggressive tumors that arise in the brain (atypical teratoid rhabdoid tumor [ATRT]), kidney (rhabdoid tumor of kidney [RTK]), soft tissues, and solid organs (e.g. MRT of ovary [MRTO]). Rhabdoid tumors in children are characterized by bi-allelic loss of INI1 in up to 98% of tumors and often present in infancy. In the US, the annual incidence among children less than 15 is 0.19 per million for renal tumors, 0.89 per million for ATRT and 0.32 per million for tumors of other sites (approximately 450 patients per year). Standard of care treatment consists of surgical resection, intensive chemotherapy and radiotherapy, however the use of radiotherapy is limited in younger patients. Cooperative group protocols that included children younger than 36 months demonstrated a 2-year event free-survival rate of 14% in pediatric patients receiving chemotherapy alone. Undifferentiated thoracic sarcomas with loss of SMARCA4 have a highly aggressive clinical presentation characterized by a young age of onset, limited response to therapy and a median overall survival of seven months. Current regimens of high-intensity chemotherapy and irradiation have anecdotal cases of long-term survivors, but are typically associated with significant treatment morbidity. There are no FDA approved therapies for the treatment of MRTs. Patients who experience disease recurrence or progression are typically referred to clinical trials and have extremely poor overall survival.

Tazemetostat is currently being assessed in three ongoing studies in adult patients and one in pediatric patients. The studies in adults focus on patients with non-Hodgkin lymphoma (NHL), solid tumors and mesothelioma. In the first-in-human, single-agent, dose-escalation

trial of tazemetostat, the recommended phase 2 dose (RP2D) was determined to be 800 mg orally twice a day (BID) based on a dose-limiting toxicity (DLT) of Grade 4 thrombocytopenia in a patient treated at 1600 mg orally BID . Four objective responses were reported in patients with INI1- and SMARCA4-negative cancers (1 complete response, 3 partial responses). As of January 15, 2016, 89 patients have been treated with tazemetostat. Of those 89 patients, 78 (88%) patients experienced at least one treatment-emergent adverse event (TEAE). The majority of the TEAEs were Grade 1 or 2 (92%) with 7 patients (8%) experiencing Grade 3 or 4 TEAEs. No clear pattern of dose-related increase in toxicity (all Grades and Grade 3 or 4) has been identified.

A pediatric escalation safety and tolerability study (n=24) with three expansion cohorts (n=20 per cohort) to determine preliminary anti-tumor activity in INI1-negative tumors is ongoing (EZH-102 “A Phase 1 Study of Tazemetostat in Pediatric Subjects with Relapsed/Refractory INI1-negative Tumors or Synovial Sarcomas”). Patients receive tazemetostat as an oral agent BID daily in a continuous 28-day cycle for a maximum duration of 2 years. Tazemetostat is available for pediatric administration as an oral suspension and the amount of suspension per dose is calculated based on the subject’s body surface area (BSA) and the assigned dose level. The primary objective of the dose-escalation study is to determine the maximum tolerated dose (MTD) or RP2D of tazemetostat when administered as an oral suspension BID. The primary objective of the dose expansion cohort is to evaluate the anti-tumor activity of tazemetostat as assessed by overall response rate (ORR) in pediatric patients with relapsed/refractory atypical teratoid rhabdoid tumor (ATRT) (Cohort 1), non-ATRT rhabdoid tumors (Cohort 2), and INI1-negative tumors or synovial sarcoma (Cohort 3) using disease appropriate standardized response criteria (e.g. RECIST 1.1, RANO). Epizyme proposes that this trial can be used as the basis for a Written Request from the FDA.

Additionally, Epizyme plans to participate in the NCI-sponsored Pediatric MATCH multi-center trial in collaboration with NCI. This pediatric counterpart to the NCI-MATCH trial in adults will evaluate molecularly targeted therapies such as tazemetostat in children with advanced cancers who have few other treatment options. Pediatric MATCH which will be led by the Children’s Oncology Group is under currently under development and expected to start dosing in 2016. Tazemetostat will be incorporated into Pediatric MATCH as one of the initial investigational agents to be tested.

## **II. Issues Relating to the Development of Tazemetostat in Pediatrics**

1. Please consider the relevant pediatric cancers (including non-Hodgkin lymphoma) for which a biologic rationale for the evaluation of tazemetostat exists,
2. 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. Please consider the necessity for an international collaborative study given the very rare cancers for which this drug might prove relevant
4. 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. Please comment on the adequacy of the current pediatric formulation and any future plans.

## Third Session

**PRODUCT: Atezolizumab**  
**COMPANY: Genentech, Inc.**

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### I. Regulatory History

Programmed death ligand-1 (PD-L1) may be expressed on tumor cells and tumor-infiltrating immune cells and can contribute to inhibition of the antitumor immune response in the tumor microenvironment. Atezolizumab is an Fc-engineered, humanized, monoclonal IgG1 kappa antibody that binds to PD-L1 and blocks interactions with PD-1 and B7.1 receptors. This releases PD-L1/PD-1 mediated inhibition of the immune response, including activation of the antitumor immune response, without inducing antibody-dependent cellular cytotoxicity. In syngeneic mouse tumor models, blocking PD-L1 activity resulted in decreased tumor growth.

On May 18, 2016, the U.S. Food and Drug Administration (FDA) granted accelerated approval to atezolizumab (trade name: Tecentriq™) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Accelerated approval was based upon confirmed objective response rate (ORR) and duration of response (DoR) according to independent reviewer assessment using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) in a study of 310 patients with locally advanced or metastatic urothelial carcinoma. A total of 46 of the 310 patients (14.8% [95% CI: 11.1, 19.3]) had an objective response and the median duration of response was not reached at the time of the analysis (range: 2.1+, 13.8+ months). Tumor specimens were evaluated prospectively using the Ventana PD-L1 (SP142) assay at a central laboratory, and the results were used to define subgroups for pre-specified analyses. Of the 310 patients, 100 (32%) were classified as having PD-L1 expression of  $\geq 5\%$  (defined as PD-L1 stained tumor-infiltrating immune cells [TICs] covering  $\geq 5\%$  of the tumor area). The remaining 210 patients (68%) were classified as having PD-L1 expression of  $< 5\%$  (PD-L1 stained TICs covering  $< 5\%$  of tumor area). ORR was higher in patients whose tumors had PD-L1 expression of  $\geq 5\%$  compared to those whose tumors had PD-L1 expression of  $< 5\%$  (Table 1). Therefore, FDA also approved the Ventana PD-L1 (SP42) assay to detect PD-L1 protein expression levels on patient TICs to help physicians determine which patients may benefit most from treatment with atezolizumab. The approved dose of atezolizumab is 1200 mg administered as an intravenous infusion over 60 minutes every 3 weeks.

**Table 1: Summary of Efficacy in Patients with Progressive Locally Advanced or Metastatic Urothelial Carcinoma**

	All Patients	PD-L1 Expression Subgroups	
	N=310	PD-L1 Expression of < 5% in ICs <sup>1</sup> (N=210)	PD-L1 Expression of ≥ 5% in ICs <sup>1</sup> (N=100)
Number of IRF-assessed Confirmed Responders	46	20	26
ORR % (95% CI)	14.8% (11.1, 19.3)	9.5% (5.9, 14.3)	26.0% (17.7, 35.7)
Complete Response (CR) (%)	5.5%	2.4%	12.0%
Partial Response (PR) (%)	9.4%	7.1%	14.0%
Median DoR, months (range)	NR (2.1+, 13.8+)	12.7 (2.1+, 12.7)	NR (4.2, 13.8+)
NR = Not reached + Denotes a censored value <sup>1</sup> PD-L1 expression in tumor-infiltrating immune cells (ICs)			

Source: Tecentriq™ product labeling

The most common adverse reactions (≥ 20% of patients) included: fatigue, decreased appetite, nausea, urinary tract infection, pyrexia, and constipation. Other serious adverse reactions to atezolizumab include immune-related adverse reactions (such as pneumonitis, colitis, endocrinopathies, motor and sensory neuropathies [myasthenic syndrome/myasthenia gravis, Guillan-Barre, meningoencephalitis], ocular inflammatory toxicity, and pancreatitis), infection, and infusion-related reactions. Based on its mechanism of action, atezolizumab can cause fetal harm when administered to pregnant women.

PD-L1 expression has been reported in many pediatric tumor types, including high-grade gliomas, rhabdomyosarcoma, lymphomas, soft tissue sarcomas, osteosarcoma, Ewing sarcoma, neuroblastoma, and Wilms tumor. The presence of CD8+ tumor-infiltrating lymphocytes has also been documented in a variety of pediatric tumor samples.

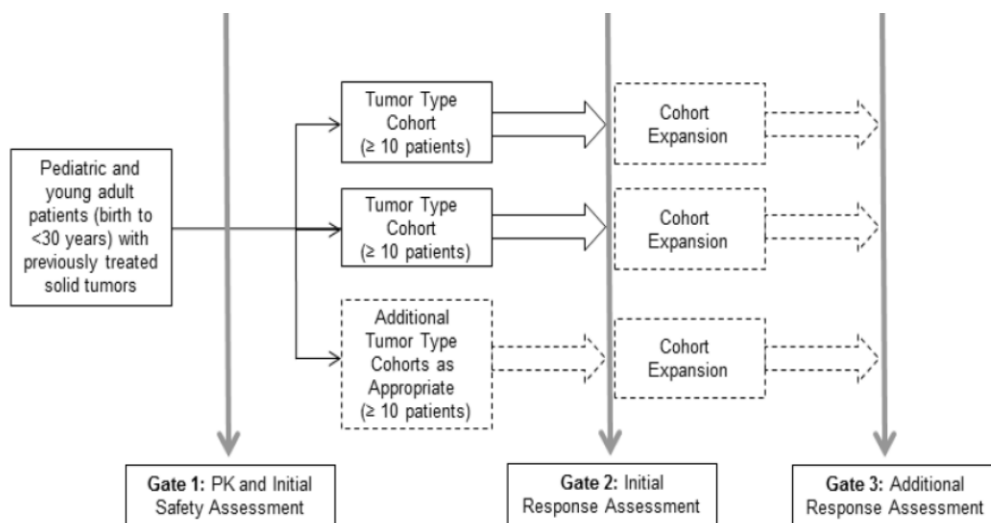
Atezolizumab is exempt from the requirement to conduct pediatric studies under the Pediatric Research Equity Act (PREA). On April 1, 2015, the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) provided agreement with a Pediatric Investigation Plan (PIP) for study of atezolizumab in pediatric patients with malignant neoplasms except for central nervous system tumors, hematopoietic, and lymphoid tissue neoplasms.

Genentech Inc.'s pediatric development plan for atezolizumab consists of up to two clinical studies and a nonclinical biomarker study. The biomarker study will assess PD-L1 expression, the presence of CD8+ T cells, and other immune markers in 100 tumor samples collected in pediatric patients with Ewing sarcoma, medulloblastoma, neuroblastoma, osteosarcoma, and rhabdomyosarcoma. The first clinical study, Study G029664, is an ongoing multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary efficacy of atezolizumab in approximately 40 to 100



pediatric and young adult patients < 30 years of age with relapsed or refractory solid tumors with known or expected PD-L1 pathway involvement (Figure 1). Patients with the following tumor types are eligible for enrollment: neuroblastoma, rhabdomyosarcoma, non-rhabdomyosarcoma soft tissue sarcoma, osteosarcoma, Ewing sarcoma, Wilms tumor, Hodgkin lymphoma, and non-Hodgkin lymphoma; patients with other tumor types may also be eligible, including a limited number of patients with tumors that do not have documented PD-L1 expression. The dose of atezolizumab is 15 mg/kg (maximum 1200 mg) for patients < 18 years of age and 1200 mg for patients  $\geq 18$  years of age. Atezolizumab is administered on Day 1 of each 3 week cycle (Q3W).

**Figure 1: Schema for Study GO29664**



Source: copied from Genentech, Inc. Briefing Package

Genentech Inc. (Genentech) plans to assess response for each tumor type cohort after a minimum of 10 patients have been treated with atezolizumab and followed for 6 months or longer (“Gate 2”). Based upon the number of responders in the initial cohort, enrollment feasibility, biomarker analyses, and other relevant considerations, Genentech will determine whether to enroll an expansion cohort to further study the antitumor activity of atezolizumab for each specific tumor type, with a maximum of 40 patients studied for each specific tumor type. After the results of Study GO29664 are available, Genentech will determine whether to conduct a second study to further assess the efficacy and safety of atezolizumab in a tumor type selected based on the results of Study G029664.

As of April 18, 2016, 62 patients have enrolled in Study GO29664. Analyses of interim PK data from the first 20 patients suggest that exposure in pediatric patients receiving 15 mg/kg atezolizumab IV Q3W is similar to that observed in adults receiving the approved dose of 1200 mg IV Q3W.

### **III. Issues Relating to the Development of Atezolizumab in Pediatrics**

1. 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. 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. 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. 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.