ATEZOLIZUMAB
(MPDL3280A)

BRIEFING PACKAGE

PEDIATRIC ONCOLOGY SUBCOMMITTEE OF THE ONCOLOGIC DRUGS ADVISORY COMMITTEE MEETING

GENENTECH, INC.,
A MEMBER OF THE ROCHE GROUP

JUNE 2016

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

1L	first-line treatment
2L	second-line treatment
ALK	anaplastic lymphoma kinase
BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
BTD	Breakthrough Therapy Designation
CHOP	cyclophosphamide + hydroxydaunorubicin + vincristine + prednisolone
CI	confidence interval
CNS	central nervous system
CTA	Clinical Trial Application
DOR	duration of response
EC	European Commission
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
GBM	glioblastoma multiforme
HR	hazard ratio
IC	immune cells
iDMC	independent Data Monitoring Committee
IFNγ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IND	Investigational New Drug
IRF	Independent Review Facility
ITCC	Innovative Therapies for Children with Cancer European Consortium
ITT	intent-to-treat
IV	intravenous
MAA	Marketing Authorisation Application
MOA	mechanism of action
MPDL3280A	atezolizumab
mUC	metastatic urothelial carcinoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non–small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee

ORR	objective response rate
OS	overall survival
PDCO	Paediatric Committee (EMA)
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PFS	progression-free survival
PIP	Paediatric Investigation Plan
PK	pharmacokinetic
POETIC	Pediatric Oncology Experimental Therapeutics Investigators' Consortium
popPK	population PK
PREA	Pediatric Research Equity Act
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RCC	renal cell carcinoma
SEER	Surveillance Epidemiology and End Results
TC	tumor cells
TIL	tumor-infiltrating lymphocytes
UC	urothelial carcinoma

1. EXECUTIVE SUMMARY

Cancer immunotherapies are some of the most exciting developments seen in the history of cancer research. The ability to harness the body's immune system with the goal of long-lasting response to treatment holds significant promise for a variety of cancer types, including rare pediatric cancers.

The cancer immunotherapy, atezolizumab (also known as MPDL3280A), is an investigational monoclonal antibody designed to bind with a protein called programmed death ligand–1 (PD-L1). Atezolizumab is designed to directly bind to PD-L1 expressed on tumor cells and tumor-infiltrating immune cells, blocking its interactions with programmed death–1 (PD-1) and B7.1 receptors. By inhibiting PD-L1, atezolizumab may enable the activation of anti-tumor T cells, which play an important role in helping the immune system fight cancer.

The ongoing clinical development program of atezolizumab is focused on the use of the medicine alone, or in combination with other medicines, in adult cancers for a variety of blood cancers and solid tumors such as bladder and lung cancers. Atezolizumab is currently exempt from all pediatric obligations under the Pediatric Research Equity Act (PREA) in the United States and under the Paediatric Regulation in the European Union. However, the Sponsor believes children with cancer should be offered earlier access to innovative medicines and have options that are developed specifically for them. To this end, the Sponsor is pursuing voluntary pediatric development of atezolizumab in certain types of cancer as part of a broader approach to evaluate medicines based on their mechanism of action (MOA) and the underlying biology of the disease.

Childhood cancer is rare, with an overall incidence rate of 17.6 per 100,000 in the United States, compared with approximately 631 per 100,000 in adults. The low incidence of childhood cancers make it difficult to enroll and conduct clinical trials and can create challenges in recruiting the necessary number of patients for clinical trials to determine the efficacy and safety of a medicine. Furthermore, with an increasing focus on molecular profiling and driver mutations, these exceedingly rare populations may be even further segmented. In approximately 20%–30% of pediatric cancers, the disease will recur after treatment, leading to poorer prognoses with few curative options.

To help address some of these issues, the Sponsor is proposing a broad MOA-based approach to the development of atezolizumab in the pediatric population across a range of age groups and cancer types. The Sponsor has partnered with several pediatric oncology cooperatives, including the Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) and Innovative Therapies for Children with Cancer European Consortium (ITCC), to develop the concept, design, and implementation of pediatric development plans for a gated, early-phase iMATRIX trial platform. This platform concurrently studies multiple molecules, including atezolizumab, across a range

of relevant pediatric tumor types on the basis of MOA-guided drug development. The gated assessment of safety and preliminary efficacy will allow rapid prioritization of the most promising molecule–tumor type pairs to pursue further development specifically for pediatric cancers.

As we increase our understanding of the underlying biology of different types of cancers, our drug development models need to evolve. Private industry, regulatory authorities, academia, healthcare professionals, and families have to work together to prioritize advancing these medicines. This iMATRIX trial platform utilizes an MOA-based approach to place an increased focus on the targets and pathways of new molecules rather than their initial adult indications to help accelerate the development of new drugs for children with high unmet medical need, and without compromising the need for adequate assessment of safety and efficacy.

This briefing document describes the mechanism of action of atezolizumab and provides safety, efficacy, and biomarker data from nonclinical and clinical adult studies. The framework of the proposed iMATRIX trial platform is also included as a proposal for developing medicines for rare types of cancers.

2. MECHANISM OF ACTION OF ATEZOLIZUMAB AND PD-L1 PATHWAY INVOLVEMENT IN PEDIATRIC SOLID TUMORS

Atezolizumab is a humanized kappa immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function and depletion of cells expressing programmed death–ligand 1 (PD-L1) in humans. Atezolizumab targets human PD-L1 and inhibits its interaction with its receptors, programmed death–1 (PD-1) and B7.1, both of which can provide inhibitory signals to T cells.

Tumor and immune cell PD-L1 expression mediates cancer immune evasion, and the blockade of PD-L1 binding is an attractive strategy for restoring tumor-specific T-cell immunity. Tumor responses have been obtained both with anti-PD-1 and anti-PD-L1 therapies in adult patients with several forms of cancer (Brahmer et al. 2015; Motzer et al. 2015; Ribas et al. 2015; Robert et al. 2015; Fehrenbacher et al. 2016; Herbst et al. 2016; Rosenberg et al. 2016).

Studies in adult cancers have shown that PD-L1 expression on tumor cells (TC) and immune cells (IC) is differentially regulated via tumor-intrinsic mechanisms such as genomic amplification on TC or adaptive regulation of PD-L1 via IFNγ on IC

(Besse et al. 2015; Schmid et al. 2015). Association of PD-L1 expression with outcomes to atezolizumab has shown that PD-L1 on immune cells is associated with clinical benefit in bladder cancer (Rosenberg et al. 2016), and PD-L1 expression on both TC and IC is associated with clinical benefit in non–small cell lung cancer (NSCLC) (Fehrenbacher et al. 2016). Remarkably, the underlying biology of pre-existing immunity, as defined by the tumor IFNγ gene signature in both NSCLC and bladder cancer, appears to correlate well with clinical benefit (Fehrenbacher et al. 2016; Rosenberg et al. 2016).

The expression of PD-L1 by malignant cells has been reported in many pediatric tumor types, including high-grade glioma (Wintterle et al. 2003; Wilmotte et al. 2005; Parsa et al. 2007), rhabdomyosarcoma (Kim et al. 2008; Wiendl et al. 2003; Chowdhury et al. 2015), non-Hodgkin's lymphoma (Yamamoto et al. 2009; Green et al. 2010; Andorsky et al. 2011), Hodgkin's lymphoma (Yamamoto et al. 2008; 2009; Green et al. 2010), soft tissue sarcoma (Kim et al. 2008), osteosarcoma (Lussier et al. 2013; Chowdhury et al. 2015), Ewing sarcoma (Kim et al. 2008; Chowdhury et al. 2015), neuroblastoma (Chowdhury et al. 2015), and Wilms' tumor (Routh et al. 2008; 2013).

The presence of CD8+ tumor-infiltrating lymphocytes (TIL) has also been evaluated in pediatric tumors (Chowdhury et al. 2015). Immunohistochemistry evaluations of patient tumor samples of neuroblastoma, Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma (both embryonal and alveolar) revealed the presence of CD8+ TIL in many samples. In addition, patient tumor tissue with higher levels of CD8+ TILs showed better survival than those with no or low CD8+ TILs suggesting that a pre-existing immune response to the tumor may be present for many pediatric tumor types. Blockade of the PD-1/PD-L1 pathway may augment this inherent immunity (Hegde et al. 2016).

These published nonclinical data suggest that pediatric and young adult patients diagnosed with relapsed and refractory solid tumors may benefit from the addition of an immune checkpoint inhibitor such as atezolizumab. Additional nonclinical evaluations are ongoing for further tumor types, specifically leukemias. In addition, atezolizumab has an acceptable toxicity profile in adults. Given the poor long-term survival of children and young adults diagnosed with relapsed and refractory solid tumors, the potential benefit of atezolizumab is expected to outweigh the risk in this population. On the basis of the preliminary evidence outlined above, the Sponsor proposes a broad MOA-based approach to the development of atezolizumab in the pediatric population, with the aim of determining dosing, pharmacokinetics, safety, and preliminary anticancer activity across a range of age groups and tumor types.

3. REGULATORY HISTORY

An initial Investigational New Drug (IND) application for atezolizumab was approved on 11 May 2011 for the treatment of patients with locally advanced or metastatic malignancies. Additional INDs have subsequently been submitted to study atezolizumab as both a single agent and in combination with other agents for the treatment of solid tumors and hematologic malignancies (see Section 7).

Atezolizumab (TECENTRIQ™) is approved in the United States for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) who have progressed during or following platinum-containing chemotherapy. Additional marketing applications for atezolizumab are under review with the Food and Drug Administration (FDA) for the treatment of NSCLC, and with the European Medicines Agency (EMA) for both metastatic urothelial carcinoma (mUC) and NSCLC. Breakthrough Therapy Designation (BTD) was previously granted by the FDA for the corresponding indications on 22 May 2014 and 28 January 2015, respectively.

Atezolizumab is currently exempt from all pediatric obligations under the Pediatric Research Equity Act (PREA) in the United States and under the Paediatric Regulation in the European Union. However, the Sponsor is pursuing voluntary pediatric development of atezolizumab in patients with pediatric solid tumors to address the unmet need of children, adolescents, and young adults with cancer. An IND in the United States and a Clinical Trial Application (CTA) in the European Union were approved on 13 March 2015 and 15 April 2015, respectively, for the treatment of pediatric and young adult patients with relapsed and refractory pediatric solid tumors with known or expected PD-L1 pathway involvement. Global study enrollment began on 5 November 2015.

In the European Union, a Paediatric Investigation Plan (PIP) for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumors, hematopoietic, and lymphoid tissue neoplasms) was agreed with the Paediatric Committee (PDCO) of the EMA on 1 April 2015.

4. CHALLENGES IN PEDIATRIC DRUG DEVELOPMENT

4.1 EPIDEMIOLOGY OF PEDIATRIC CANCER

Childhood cancer is rare, with an overall incidence rate of 17.6 per 100,000 in the United States, compared with approximately 631 per 100,000 in adults (SEER 2014). In the United States in 2014, an estimated 10,450 new cases and 1,350 cancer deaths were expected to occur among children, and 5,330 new cases and 610 cancer deaths were expected to occur among adolescents (ages 15–19) (ACS 2014).

Tumor type–specific incidence rates highlight the extreme rarity of many of these tumor types. For example, in the United States, the incidence rate of neuroblastoma is

7.7 cases per million children (aged 0–19 years) and the incidence rate of Ewing sarcoma is 4.0 cases per million children (aged 0–19 years). On average, approximately 20%–30% of pediatric tumors will recur, and it is this relapsed population which is eligible for enrollment in most traditional pediatric trials. Furthermore, with an increasing focus on molecular profiling and driver mutations, these exceedingly rare populations may be even further segmented. For example, only 10% of high-grade gliomas and 10% of neuroblastomas have BRAF V600 or ALK mutations, respectively.

4.2 FEASIBILITY CHALLENGES WITH PEDIATRIC ONCOLOGY CLINICAL TRIALS

Pediatric trials are inherently difficult because of the rarity of childhood cancer in the United States and Europe (Vassal et al. 2013; Adamson et al. 2014). Typical clinical trial considerations such as country and investigator selection, regional disease-specific treatment patterns, and patient catchment areas continue to challenge operational planning and remain a learning experience for sponsors, particularly given a relative paucity of pediatric registry data. Outcome trials in children with relapsed or refractory malignancies—the usual population offered participation in early-phase clinical trials—are even more difficult because of the limited number of such patients among an already rare patient population. This has a negative effect on enrollment feasibility and prevents conclusive outcomes of adequately powered studies. Further exacerbating the problem, multiple sponsors are seeking to enroll study patients from the same limited patient pool and are therefore severely constrained in the ability to accurately project and successfully enroll patients according to agreed timelines.

To help address some of these issues, the Sponsor has partnered with several pediatric oncology cooperative groups, including the Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) and Innovative Therapies for Children with Cancer European Consortium (ITCC), to develop the concept, design, and implementation of pediatric development plans. Together, these prominent pediatric oncology groups have the global potential to reach a much greater number of pediatric patients and academic collaborators. These partnerships between academia and industry are critical for sharing scientific and clinical information across geographic regions, obtaining comprehensive feasibility information to inform study design and initial enrollment projections, and to provide ongoing access to patient communities in order to conduct clinical research.

4.3 REGULATORY CHALLENGES FOR PEDIATRIC ONCOLOGY DRUG DEVELOPMENT

In the United States, the enactment of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), which were made permanent under the Food and Drug Administration Safety and Innovation Act in 2012, has enabled significant progress in pediatric drug development (Addy 2015; FDA 2016). Similarly, the number

of industry-sponsored pediatric studies increased substantially since the adoption of the European pediatric medicine regulation (Regulation [EC] No 1901/2006; EMA 2006) that came into force on 26 January 2007 (as cited in a 5-year interim report on the implementation of the regulation [EC 2013a, 2013b; EMA 2012]).

It was anticipated that the introduction of these legislative measures would also benefit children with cancer. However, the number of approved drugs for pediatric oncology remains low (Adamson et al. 2014; Vassal et al. 2013). Although the reason for this is multifactorial, a key issue is that the regulatory legislations governing the obligations for pediatric development typically mandate that sponsors develop each drug in conditions that correspond to the adult indications. In the United States under PREA, a vast majority of oncology drugs therefore receive waivers from the mandatory requirement for pediatric studies because of the absence or extreme rarity of the equivalent disease in the pediatric setting. Further, drugs with orphan designation are exempt from PREA obligations. Although studies may be conducted voluntarily under BPCA, to date only a small number of molecules have been investigated or approved for use in children with cancer. These limitations have similarly been described in European Union (EMA 2012). The unintended consequence has been lack of access to innovative drugs for children with pediatric-specific malignancies.

A further challenge resulting from this legislative framework is the competition across sponsors for patients in a defined tumor type that is not covered by a waiver, when molecules with a similar mechanism of action are being developed in parallel in the pediatric population (e.g., melanoma). This produces an inability to recruit the planned number of patients and obtain sufficient information to determine the efficacy and safety of these drugs to inform patient care for children with cancer.

One approach to addressing this key challenge in pediatric oncology is using MOA–based approaches to enlarge the scope of pediatric investigations that are currently narrowly defined within the existing legislations. As such, many pediatric diseases for which there is no adult counterpart may be voluntarily investigated by following the science and leveraging the best available evidence based on tumor biology and molecule mechanism established in the literature or, where possible, generated using relevant in vitro and in vivo nonclinical models. Section 5 outlines the Sponsor's MOA-based pediatric oncology iMATRIX Trial approach for identifying the optimal molecule–tumor type match for further investigation in confirmatory trials.

5. OPPORTUNITY TO ADDRESS UNMET MEDICAL NEED IN PEDIATRICS

Consistent with guidance from academic experts and parents, the Sponsor believes that first-in-children trials should be initiated upon careful assessment of risk and benefit to maximize therapeutic intent in this vulnerable population. The Sponsor has developed a

gated, early-phase iMATRIX trial platform for concurrently studying multiple molecules across a range of relevant pediatric tumor types on the basis of MOA–guided drug development. The gated assessment of safety and preliminary efficacy will allow rapid prioritization of the most promising molecule–tumor type pairs to pursue further development. This iMATRIX trial platform involves an increased focus on the targets and pathways of new molecules rather than adult indications. It further proposes to limit initial pediatric study proposals to Phase I/II clinical research, and to defer the design of confirmatory trials until early-phase pediatric data is available. Atezolizumab is the first molecule of the Sponsor's oncology portfolio to employ the gated assessment design of the iMATRIX trial platform for early-phase pediatric development.

The iMATRIX concept is designed to direct these rare pediatric patients to receive the most promising therapies while optimizing the ability to gain clinical trial information. Although individual molecules may demonstrate efficacy trends in multiple tumor types, or multiple molecules may demonstrate efficacy for the same tumor type, it may not be feasible to conduct multiple confirmatory trials in several pediatric tumor types for each active molecule identified in the iMATRIX trial platform. The selection of molecules and pediatric tumor types for confirmatory trials will be based on the totality of early-phase data observed in the iMATRIX Trial (pharmacokinetics, safety, and efficacy) and other prioritization considerations, such as unmet medical need, disease prevalence, line of treatment, potential combination partners, development status in pediatrics of other drugs in the same class, and operational feasibility.

The ultimate decision to advance development of a molecule for the treatment of a particular tumor type or disease state into a confirmatory trial will be made by the Sponsor in consultation with health authorities and academic collaborators on the basis of all relevant considerations, including regulatory obligations. Irrespective of whether a molecule–tumor type pair is selected for advancement to a confirmatory trial, the comprehensive early-phase pediatric data that is generated in the iMATRIX trial platform, and any additional data obtained through Sponsor-supported, investigator-initiated trials following the iMATRIX Trial, is aimed to inform product labelling for marketed products.

Overall, the iMATRIX trial platform is designed to accelerate the development of new drugs for children with high unmet medical need without compromising the need for adequate assessment of safety and efficacy. The platform provides treatment allocation rules, tumor type–specific endpoints, and response criteria that may ultimately allow multiple manufacturers to preserve and match rare pediatric patients to the best available therapies across the industry's portfolio. It is the Sponsor's position that the iMATRIX trial platform and its MOA–based approach to pediatric drug development is an important first step to allow the prioritization of molecules to be further explored through adequate confirmatory trials—with the overall goal of updating product labels to provide prescribers with relevant information for the safe and efficacious administration of new

drugs in children. As such, the iMATRIX trial platform is fully aligned with the spirit of the pediatric regulations and its intention to protect children *through* research as opposed to *from* research (FDA 2014; EC 2013a).

6. SUMMARY OF NONCLINICAL DATA SUPPORTING PEDIATRIC CLINICAL STUDIES

The pharmacology, pharmacokinetics, and toxicology of atezolizumab have been investigated in several nonclinical studies. The currently available nonclinical data are considered to be sufficient to support the initiation of pediatric development of atezolizumab. The nonclinical safety findings observed for atezolizumab are consistent with PD-L1/PD-1 pathway inhibition and identify heightened immune responses and the potential to increase immune-associated inflammatory lesions as possible safety risks to patients. Neither of these safety risks is excluded from, or specific to, pediatric patients, and no toxicities have been identified in developmentally sensitive tissues in nonclinical studies, such as the musculoskeletal system, reproductive system, or central nervous system.

No specific toxicities have been identified in completed nonclinical studies that highlight concerns for pediatric patients that could be further informed by juvenile animal studies. The safety profile in adult patients has been consistent with immune-system activation, and largely manageable and reversible.

On the basis of MOA and the established nonclinical and clinical safety profiles, the risk of direct effects of atezolizumab that are specific to pediatric patients is low, and does not warrant the generation of additional nonclinical safety data.

7. CLINICAL TRIAL EXPERIENCE IN ADULT PATIENTS

7.1 OVERVIEW

Clinical studies with atezolizumab in adult patients are currently ongoing for a variety of solid tumors and hematologic malignancies. As of April 2016, there are 42 ongoing trials with atezolizumab either as monotherapy or in combination with other agents (e.g., bevacizumab, cobimetinib, obinutuzumab, CHOP, bendamustine, ipilimumab, interferon alfa). Clinical indications under investigation include non-small cell lung cancer (NSCLC), urothelial carcinoma (UC), renal cell carcinoma (RCC), hepatocellular carcinoma, triple negative breast cancer, colorectal cancer, hematologic malignancies in addition to other tumor types (Appendix 1).

Atezolizumab monotherapy has demonstrated anti-tumor activity in NSCLC (Besse et al. 2015; Spigel et al. 2015; Horn et al. 2015; Fehrenbacher et al. 2016), UC (Rosenberg et al. 2016; Petrylak et al. 2015) glioblastoma multiforme (GBM; Lukas et al. 2015) and RCC (McDermott et al. 2016) with the majority of responses

being partial (by RECIST v1.1 or immune-modified RECIST). In a randomized Phase II study in patients with NSCLC, atezolizumab monotherapy has demonstrated an overall survival benefit compared with docetaxel (Fehrenbacher et al. 2016). Data across various tumor types suggest that the PD-L1 expression on TCs and/or tumor-infiltrating immune cells may predict clinical benefit.

As of February 2016, approximately 5000 patients have received atezolizumab, in clinical trials; of these, more than 2000 patients have received atezolizumab as monotherapy. Atezolizumab monotherapy has an acceptable safety profile and is generally well tolerated. The safety profile appears similar between tumor types and suggests independence from the level of PD-L1 expression. The key safety risks associated with atezolizumab monotherapy are immune-related events; these events have been generally manageable with dose interruption and supportive care, including the use of systemic corticosteroids, where appropriate.

7.2 PHARMACOKINETICS OF ATEZOLIZUMAB

The pharmacokinetics of atezolizumab have been characterised in adult patients in multiple clinical trials at doses 0.01 mg/kg to 20 mg/kg administered every 3 weeks including the fixed dose of 1200 mg. Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. With an estimated terminal half-life of 27 days, the pharmacokinetics of atezolizumab are consistent with the expected profile of an IgG1 antibody in humans.

7.3 CLINICAL EFFICACY OF ATEZOLIZUMAB

Although there are several ongoing trials with atezolizumab in a variety of solid tumors and hematologic malignancies, the most advanced programs are those for UC and NSCLC. Clinical efficacy data from these two programs as well as recently published data from RCC are presented below. Clinical safety data are presented based on pooled data from the UC and NSCLC studies.

7.3.1 Urothelial Carcinoma

The efficacy and safety of atezolizumab as monotherapy in patients with UC has been evaluated in one Phase II study (IMvigor 210) and one Phase Ia study (PCD4989g). Both studies are single arm, multi-center trials and enrolled patients being treated in the second-line or beyond (2L+) setting. In addition, Study IMvigor 210 included a cohort of patients composed of previously untreated patients who were ineligible for cisplatin. In IMvigor 210, the co-primary endpoints were Independent Review Facility (IRF)-assessed objective response rate (ORR by RECIST v1.1) and investigator-assessed ORR according to by immune-modified RECIST (Cohort 2 only). In Study PCD4989g, the primary objective was safety and tolerability and a secondary objective was clinical activity (investigator-assessed ORR by RECIST v1.1). Key features of these two trials are shown in Table 1. Although both studies allowed recruitment of patients unselected

for PD-L1 status (i.e., all-comers), Study IMvigor 210 mandated that approximately 30% of the patient population be PD-L1 selected (i.e., express PD-L1 on at least 5% of ICs (IC2/3) [Table 2]).

Table 1 Key Design Features of Studies IMvigor 210 and PCD4989g (UC Cohort)

Study	IMvigor 210		PCD4989g
Cohort	Cohort 1	Cohort 2	UC Cohort
Patient population	Locally advanced or metastatic UC	Locally advanced or metastatic UC	Locally advanced or metastatic UC
Line of therapy	1L cisplatin ineligible	2L+	2L+
No of treated patients	119	310	92
PD-L1 status	Unselected[a]	Unselected[a]	Selected (IC2/3)[b]
Atezolizumab dose	1200 mg IV q3w		0.1-20 mg/kg IV q3w

1L = first-line; 2L+ = second-line and beyond; UC = urothelial carcinoma.

[a] Approximately 30% of patients were required to be PD-L1 selected (IC2/3).

[b] The study protocol was amended during the course of the trial, however, the final enrolled population was enriched for PD-L1 selected (IC2/3) patients.

Table 2 Criteria for PD-L1 Expression Assessment in Atezolizumab Studies

Description of IHC Scoring Algorithm	PD-L1 Expression Level [a]
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in ICs covering **<1%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC0
Presence of discernible PD-L1 staining of any intensity in ICs covering between **≥1% and <5%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC1
Presence of discernible PD-L1 staining of any intensity in ICs covering between **≥5% and <10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC2
Presence of discernible PD-L1 staining of any intensity in ICs covering **≥10%** of tumor area occupied by tumor cells, associated intratumoral, and contiguous peri-tumoral desmoplastic stroma	IC3
Absence of any discernible PD-L1 staining OR presence of discernible PD-L1 staining of any intensity in **<1%** TCs	TC0
Presence of discernible PD-L1 staining of any intensity in **≥1% and <5%** TCs	TC1
Presence of discernible PD-L1 staining of any intensity in **≥ 5% and <50%** TCs	TC2
Presence of discernible PD-L1 staining of any intensity in **≥ 50%** TCs	TC3

IC = tumor-infiltrating immune cell; IHC = immunohistochemistry; PD-L1 = programmed death–ligand 1; TC = tumor cell.

Note: Cutoffs for PD-L1 positivity are being evaluated in ongoing trials.

[a] TC scoring (in addition to IC) was used in Study PCD4989g and NSCLC studies only.

In the primary analysis of Cohort 2 (2L+) of Study IMvigor 210, the IRF-assessed ORR was 15% in the intent-to-treat (ITT) population (N=310) and 27% in the IC2/3 subgroup (N=100) (Rosenberg et al. 2016). Overall, increased levels of PD-L1 expression on immune cells were associated with increased response. Responses appeared to be durable and the median duration of response (DOR) had not been reached at the time of data cutoff (14 September 2015). Data from Cohort 1 are immature and require longer follow-up.

In the UC cohort of PCD4989g, after a minimum follow-up of 12 weeks, the investigator-assessed (unconfirmed) ORRs (by RECIST v1.1) were 50% (23/46 patients) in the IC 2/3 subgroup (including 20% complete response [9/46]) and 17% (7/41 patients) in the IC0/1 subgroup (Petrylak et al. 2015). At the time of data cut-off (2 December 2014), the median duration of response had not been reached in either IC subgroup (range 0+ to 43 months).

7.3.2 Non-Small Cell Lung Cancer

The efficacy and safety of atezolizumab as monotherapy in patients with NSCLC has been evaluated in three Phase II studies (FIR, POPLAR and BIRCH) and one Phase Ia study (PCD4989g). All studies were single arm, except for POPLAR which included a docetaxel control arm. The primary endpoint in all studies was ORR except for POPLAR, which was overall survival (OS).

All studies enrolled patients with recurrent Stage IIIB and IV NSCLC being treated in the 2L+ setting (Table 3). In addition, Studies BIRCH, FIR, and PCD4989g also enrolled previously untreated patients (1L). Studies BIRCH and FIR enrolled patients who were PD-L1–selected (i.e., expressing PD-L1 on at least 5% of TC or IC cells [TC2/3 or IC2/3]), whereas POPLAR and PCD4989g enrolled both PD-L1–selected and unselected patients. Atezolizumab was administered in all studies at a dose of 1200 mg intravenously every 3 weeks, except for Study PCD4989g where, in addition, patients received body-weight adjusted dosing (1, 10, 15, and 20 mg/kg).

Table 3 Key Study Design Features of Studies BIRCH, POPLAR, FIR, and PCD4989g (NSCLC Cohort)

Study	BIRCH			POPLAR		FIR			PCD4989g
Cohort	Cohort 1	Cohort 2	Cohort 3	Docetaxel	ATZ	Cohort 1	Cohort 2	Cohort 3	NSCLC Cohort
Patient population	Stage IIIB, IV and recurrent NSCLC			Stage IIIB, IV and recurrent NSCLC		Stage IIIB, IV and recurrent NSCLC			advanced, metastatic, recurrent
Line of therapy	1L	2L	3L+	2L/3L		1L	2L+	2L+ with previously treated brain metastasis	All lines
No of Treated Patients	139	267	253	135	142	31	93	13	88
Dose	1200 mg atezolizumab IV q3w			75 mg/m^2 q3w	1200 mg IV q3w	1200 mg atezolizumab IV q3w			1-20 mg/kg IV q3w
PD-L1 status	PD-L1 selected (TC2/3 or IC2/3)			All comers		PD-L1 selected (TC2/3 or IC 2/3)			PD-L1–selected and unselected

ATZ = atezolizumab; IC = infiltrating cells; NSCLC = non-small cell lung cancer; q3w = every 3 weeks; TC = tumor cells.

In BIRCH, among the 659 evaluable patients, the IRF-assessed ORR in the TC2/3 or IC2/3 subgroup ranged from 17% to 19% across the different lines of treatment and was higher in the TC3/IC3 subgroup (range: 24% to 27%) (Besse et al. 2015).

In POPLAR, treatment with atezolizumab compared with docetaxel led to significant improvement in OS in the ITT population (overall n=287 patients, hazard ratio [HR] 0·73 [95% confidence interval, CI: 0·53, 0·99]) (Fehrenbacher et al. 2016). After a median

follow-up of 14.8 months and 15.7 months in the atezolizumab and docetaxel arms, respectively, the median OS was 12.6 months vs. 9.7 months, respectively. Investigator-assessed ORR (as determined by immune-modified RECIST in the atezolizumab arm and RECIST v1.1 in the docetaxel arm) was comparable between the arms (17% atezolizumab vs 15% docetaxel); however, responses were more durable with atezolizumab (14.3 months vs. 7.2 months). OS and ORR improved with increasing levels of PD-L1 expression.

In FIR, among the 136 evaluable patients, the investigator-assessed ORR in PD-L1 selected patients (TC2/3 or IC2/3) ranged from 17% to 29% across the different lines of treatment by immune-modified RECIST criteria and from 16% to 26% by RECIST v1.1 (Spigel et al. 2015). The median DOR per immune-modified RECIST was 9 months in the 1L cohort and was not reached in the other cohorts, and the median DOR per RECIST v1.1 was not reached for all cohorts.

In the NSCLC cohort of Study PCD4989g, the investigator-assessed ORR in the ITT population, comprising 88 evaluable patients, was 23%, and the median DOR was 17 months (Horn et al. 2015).

7.3.3 Renal Cell Carcinoma

The safety, tolerability, and clinical activity of atezolizumab as monotherapy in patients with RCC have been evaluated in one single-arm Phase Ia study, PCD4989g. Patients received atezolizumab in the dose range of 3–20 mg/kg or a 1200 mg flat dose every 3 weeks. The population included patients with either metastatic clear-cell or non–clear-cell RCC. Patients were initially enrolled irrespective of PD-L1 status; enrollment was later limited to patients whose tumors expressed PD-L1 at IC2 or IC3 (≥5% of ICs stained positive for PD-L1). A secondary study objective was clinical activity of atezolizumab which included ORR, progression-free survival (PFS), and OS.

After a median duration of survival follow-up of 23.9 months, the median PFS was 5.6 months and the median OS was 28.9 months among the 63 evaluable patients (McDermott et al. 2016). Among the 62 patients assessed for response, the investigator-assessed ORR (determined by RECIST v1.1) was 15%.

7.4 CLINICAL SAFETY OF ATEZOLIZUMAB

As of February 2016, approximately 5000 patients with various tumor types have received atezolizumab, alone or in combination, in clinical trials. Overall, atezolizumab monotherapy has been well tolerated even among patients of advanced age and multiple comorbidities; the observed adverse events have been largely consistent across studies and with mechanism of action or the underlying disease.

The most common adverse events reported in patients with UC and NSCLC during treatment with atezolizumab include fatigue, decreased appetite, nausea, dyspnea, cough, diarrhea, pyrexia, constipation, vomiting, back pain, arthralgia, anemia, pruritus, and asthenia; most of these were Grade 1 or 2 in intensity. These events were consistent with those reported in other clinical trials in this patient population that included cancer patients of advanced age who were heavily pre-treated and had multiple comorbidities. Adverse events were generally manageable with dose interruption and/or supportive care, including the use of corticosteroids, where appropriate.

The immune-related risks associated with atezolizumab include pneumonitis, meningitis, encephalitis, pancreatitis colitis, endocrinopathies (thyroid disorders, diabetes mellitus, adrenal insufficiency), hepatitis, and dermatologic reactions. These immune-related events are generally manageable by withholding atezolizumab administration, and with appropriate medical management (e.g. steroid treatment, hormone replacement).

8. PEDIATRIC DEVELOPMENT PLAN

8.1 OVERVIEW

Despite the absence of any current regulatory obligation in any region to pursue the development of atezolizumab in the pediatric population, the Sponsor has proactively initiated the development of atezolizumab in pediatric and young adult patients with relapsed or refractory pediatric solid tumors with known or expected PD-L1 pathway involvement. Additional tumor types (including leukemias) may be considered for future inclusion in the trial.

The pediatric development plan for atezolizumab comprises two clinical studies (Table 4), as well as a nonclinical biomarker study of PD-L1 prevalence. The Sponsor initiated the early-phase trial in pediatric and young adult patients with relapsed and refractory pediatric solid tumors (Study GO29664) in November 2015. Although premature to propose a definitive design, the Sponsor proposes to perform a subsequent confirmatory study (see Section 8.4) in a specific tumor type, if supported by the clinical evidence gathered in Study GO29664.

Table 4 Overview of Planned and Ongoing Clinical Studies in the Pediatric Development of Atezolizumab

Study Identifier	Type of Study / Design Features	Study Population	Dosage, Regimen	Primary Endpoint(s)
Study GO29664 (IND 124,026)	Early-phase, multicenter, open-label, single-arm, single agent study to assess safety, tolerability, pharmacokinetics, immunogenicity, and anti-cancer activity of atezolizumab in the treatment of relapsed and refractory pediatric solid tumors with known or expected PD-L1 pathway activation.[a] After initial enrollment of at least 10 patients in a tumor type cohort, further enrollment within that cohort will take into account the number of responders.	Age: children and young adults < 30 years. In total, a minimum of 40 patients will be enrolled	Atezolizumab: patients <18 years 15 mg/kg IV Q3W (maximum 1200 mg); patients ≥18 years, 1200 mg IV Q3W.	The primary endpoints are safety, tolerability, and pharmacokinetics of atezolizumab.
Confirmatory Study Protocol number to be determined	Confirmatory study to assess the efficacy and safety of atezolizumab in a tumor type selected on the basis of the results of Study GO29664.	Age: children and young adults. Study population will be defined on the basis of the tumor type to be included.	Dose to be confirmed on the basis of Study GO29664.	TBD

IV = intravenous; Q3W = every 3 weeks; TBD = to be determined.

[a] Specific tumor types eligible for enrolment are outlined in Section 8.3.4.

8.2 NONCLINICAL BIOMARKER STUDY OF PD-L1 PREVALENCE

Although published literature has reported PD-L1 expression in tumor and immune cells (reviewed in Section 2), the immunohistochemistry (IHC) assays and quantification were conducted by unvalidated methods. The Sponsor has undertaken a nonclinical study of PD-L1 expression in 100 pediatric tumor samples, representing five tumor types (Ewing sarcoma, medulloblastoma, neuroblastoma, osteosarcoma, and rhabdomyosarcoma), using a validated IHC assay (Clone SP142; Spring BioSciences, Pleasanton, CA). In addition to PD-L1 expression, the presence of CD8+ T cells and other immune markers are also being evaluated in these patient samples. The Sponsor is still evaluating the

significance of these data in conjunction with PD-L1 expression and immune marker data from the ongoing pediatric clinical trial.

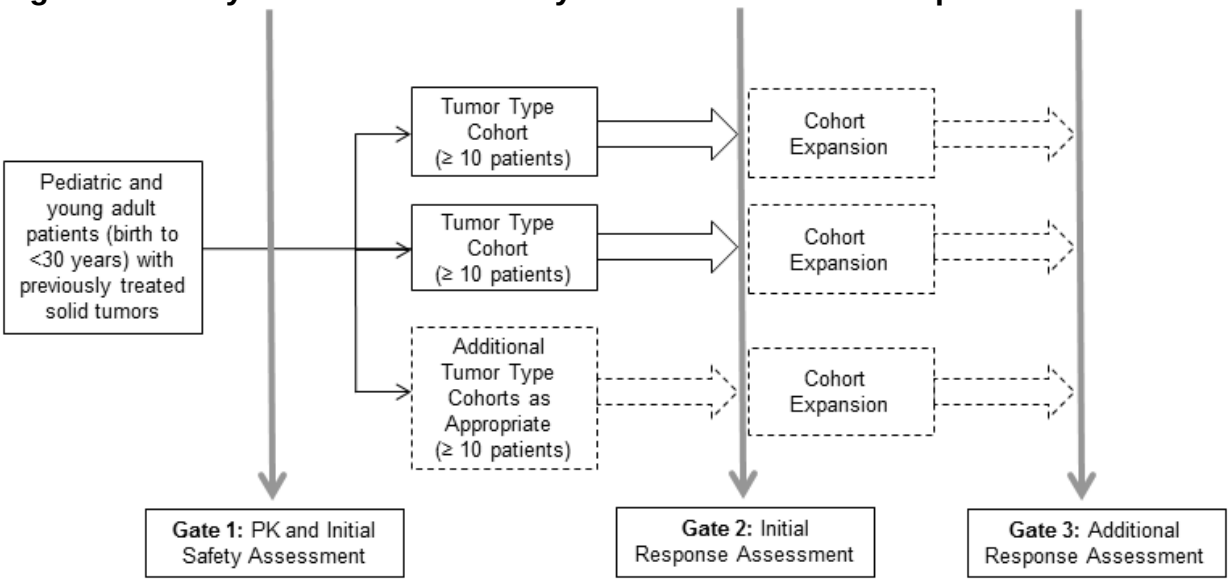
8.3 STUDY GO29664

8.3.1 Study Design

Study GO29664 (IND 124,026 approved on 13 March 2015) is an early-phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients with solid tumors for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard of care treatment options exist.

Study GO29664 follows the gated assessment design of the iMATRIX Trial. The development stages and gates are outlined in Figure 1.

Figure 1 Study Schema: Gated Early-Phase Pediatric Development



Interim pharmacokinetic (PK) analyses were conducted after the first 5 patients and the first 20 patients completed Cycle 1, along with an ongoing evaluation of safety. An additional interim PK analysis was conducted after the first 5 patients less than 6 years of age completed Cycle 1 (see Section 8.3.6).

An initial, tumor type–specific response assessment will be performed after a minimum of 10 patients have been enrolled in a tumor type cohort and followed for approximately 6 months, to determine whether further enrollment is warranted within that tumor type cohort (cohort expansion) for additional response assessment. A minimum number of responders will be needed for cohort expansion and advancement to the additional expansion phase (see Table 5). The number of patients required for cohort expansion

will take into account practical considerations (e.g., enrollment feasibility), biomarker analysis, safety profiles, and any other relevant information. No tumor type cohort will enroll more than 40 patients. Approximately 40-100 patients are expected to be enrolled throughout the study.

Table 5 Sample Size Requirements for Initial Response Assessment

Disease	Control Response Rate	Minimum No. of Patients Required for Initial Response Assessment	Minimum No. of Responders Required for Cohort Expansion	Response Assessment Tool
Hodgkin's disease	60% combination therapy	14	10	Cheson
Wilms' tumor	10%	10	2	RECIST
Neuroblastoma	18%	10	3	INRC
Non-Hodgkin's Lymphoma (NHL)	40% combination therapy	12	6	Cheson
High-grade Osteosarcoma	10%	10	2	RECIST
Rhabdomyosarcoma	10%	10	2	RECIST
Non-rhabdomyosarcoma soft tissue sarcoma (NRSTS)	10%	10	2	RECIST
Ewing's sarcoma	10%	10	2	RECIST

Cheson = Cheson Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007); INRC = International Neuroblastoma Response Criteria; RECIST = Response Evaluation Criteria in Solid Tumors, Version 1.1.

Enrollment to a tumor type cohort and/or to the study drug will be stopped at any point if there is a safety concern that warrants the study discontinuation. In addition, enrollment in a tumor type cohort may be stopped if any one of the following criteria is met:

- The number of patients needed for initial response assessment is reached and the number of responders does not meet the requirement for additional tumor type cohort expansion
- The number of patients needed for additional response assessment is reached
- The Sponsor has stopped the study

Enrollment to the study drug may be stopped if both of the following criteria are met:

- At least 20 patients of <18 years of age have been treated with the study drug.

- At least 2 tumor type cohorts and a minimum of 40 patients have completed response assessment (either initial response assessment or additional response assessment).

All patients in Study GO29664 are required to submit archival tumor tissue. A retrospective analysis of PD-L1 and CD8 expression and their correlation with response will be performed. The findings of this retrospective biomarker analysis will help inform which, if any, of the tumor type cohorts should expand beyond Gate 2. It will also guide the design of the confirmatory trial.

8.3.2 Dosing

The dose of atezolizumab is 15 mg/kg (maximum, 1200 mg) for patients <18 years of age. Patients aged ≥18 years will receive a flat dose of 1200 mg of atezolizumab. Atezolizumab will be administered by IV infusion once every 3 weeks (Q3W). Patients are weighed at the beginning of each cycle (within 3 days of the Day 1 dose), and the dose is adjusted as needed.

The recommended starting dose in pediatric patients was selected on the basis of PK predictions derived from an adult population PK (popPK) model assuming allometric scaling. At this proposed starting dose, the predicted PK exposures in pediatric patients ≥6 years of age are generally similar to that achieved in a typical adult following 1200 mg Q3W doses. The predicted PK exposures in pediatric patients <6 years of age are moderately lower, but within the range of adult PK exposure (following 1200 mg given every 3 weeks) at which safety and efficacy have been demonstrated in clinical trials of adult patients. The popPK model will be updated on the basis of interim pediatric PK data and used to inform dose modifications for pediatric patients, as appropriate, along with the emerging safety profile.

8.3.3 Study Population

The selected pediatric population includes all pediatric and young adult patients <30 years of age with relapsed or refractory non-central nervous system (CNS) pediatric solid tumors, including Hodgkins and non-Hodgkins lymphoma with known or expected PD-L1 pathway involvement (see Section 8.3.4). Given the rarity of relapsed and refractory solid tumors in younger children, numbers of patients in each age subgroup are not specified. However, the totality of the atezolizumab pediatric program should provide information on pharmacokinetics, safety, and efficacy across age ranges.

8.3.4 Enrollment Strategy

Study GO29664 will enroll patients with a histologically or cytologically confirmed solid tumor of a type with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective and for which there are no curative treatment options. Pediatric tumor types with some evidence of PD-L1 expression on either

immune cells or tumor cells were identified in the available literature. These tumor types are included for enrollment in Study GO29664:

- Neuroblastoma
- Rhabdomyosarcoma
- Non-rhabdomyosarcoma soft tissue sarcoma
- Osteosarcoma
- Ewing's sarcoma
- Wilms' tumor
- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma

In addition, patients with tumor types not listed above, but with documented expression of PD-L1 on either tumor cells or immune infiltrating cells, can enroll with approval of the Medical Monitor. Patients with tumor types not listed above and without documented PD-L1 expression can also be enrolled with approval of the Medical Monitor; however, this total population should not exceed 20%.

This enrollment strategy was designed to acknowledge the possible role of PD-L1 expression as a predictive biomarker of response in adult patients. Although this relationship is not fully elucidated, preliminary evidence in studies of adult patients suggests that PD-L1 expression may be associated with more favorable outcomes in some tumor types (see Section 7.3). Given this, those pediatric tumor types with some evidence of PD-L1 expression on either tumor cells or immune infiltrating cells were identified and included for enrollment. The Sponsor acknowledges that the data for many of the proposed pediatric tumor types are limited and based on small sample sizes. However, given the limited understanding of the underlying relationship between PD-L1 expression and efficacy in pediatric patients, and the relapsed/refractory nature of the patient population, the risk-benefit assessment favors inclusion even with limited nonclinical evidence. Additionally, some adult patients with urothelial bladder cancer or renal cell carcinoma who did not exhibit PD-L1 expression (IC0/TC0) have experienced clinical benefit (Herbst et al. 2014; McDermott et al. 2016). As such, a small percentage of patients who do not have a prespecified tumor type or do not have known PD-L1 expression will also be allowed to enroll.

Rationale for Unselected PD-L1 Population

Biomarker characterization is crucial to the successful development of atezolizumab for the treatment of pediatric patients. Although studies of adult patients have shown that higher PD-L1 expression is associated with higher overall response rate following treatment with atezolizumab (Herbst et al. 2014), the clinically meaningful cutoff and definition for PD-L1 expression appears to vary by patient population or tumor type, and

responses also occur in patients without detectable PD-L1 expression. In the pediatric setting, the ability to extrapolate the clinically meaningful cutoff for PD-L1 expression is currently limited.

In addition, the current understanding of the prevalence and predictive value of PD-L1 expression in pediatric tumors is limited. Moreover, most of the published literature regarding PD-L1 expression in children has been performed using unvalidated assays on archival tissue from initial diagnosis. These data are difficult to interpret in the context of a relapsed and refractory patient population, and may not be directly comparable to the SP142 PD-L1 diagnostic assay. The Sponsor is therefore evaluating PD-L1 expression in 100 pediatric tumor samples to further explore PD-L1 prevalence and the immune environment in common pediatric tumor types (see Section 8.2).

Given the limited data available on baseline prevalence of PD-L1 expression in pediatric patients and the uncertainty regarding a clinically meaningful definition of PD-L1 expression, the Sponsor believes that it would be premature to limit enrollment in Study GO29664 to patients with documented expression of PD-L1. As PD-L1 expression is retrospectively evaluated in Study GO29664, the relevance of the IHC scoring algorithm in TCs and ICs (Table 2) will be determined for pediatric tumor types. The results of Study GO29664 will further inform whether the IHC ranking correlates with treatment benefit in pediatric solid tumors. If the data gathered in Study GO29664 demonstrates that PD-L1 or other predictive biomarkers are clinically meaningful predictors of response, the Sponsor will implement a patient selection strategy in the future confirmatory study (see Section 8.4).

8.3.5 Safety Monitoring and Guidelines

The immune-related risks associated with atezolizumab include pneumonitis, meningitis, encephalitis, pancreatitis colitis, endocrinopathies (thyroid disorders, diabetes mellitus, adrenal insufficiency), hepatitis, and dermatologic reactions. Toxicities possibly associated with atezolizumab treatment should be managed according to management guidelines described in the Atezolizumab Investigator's Brochure in conjunction with standard medical practice. Hypothyroidism is a safety concern with atezolizumab use that is not unique to the pediatric patient population, but is more clinically significant in this population. Careful monitoring of thyroid function in the pediatric age groups is of vital importance because thyroid hormone actions vary with age, with maximal effects on somatic growth, skeletal growth and maturation, and brain growth and development in infancy and childhood. Thyroid function also influences the onset and progress of normal sexual maturation. Thyroid dysfunction has more significant developmental consequences in children than in adults. Therefore, patients will be carefully monitored for immune-related events, such as thyroid abnormalities with frequent monitoring of thyroid function tests throughout the study.

Measures will be taken to support the safety of the pediatric and young adult patients participating in this trial. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. In addition, patients will undergo rigorous safety monitoring during the study. The evaluation of safety will include the reporting of adverse events and the assessment of routine laboratory values (blood counts and differential, serum chemistries, urinalysis), physical exam, and vital signs. All adverse events (related and unrelated to study treatment) occurring during the study and up to 90 days after the last dose of study medication must be reported; treatment-related adverse events must be reported beyond this date. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 will be used to quantify the severity of adverse events occurring in this study. Children will be assessed for adverse events at each clinic visit and as necessary throughout the study.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies. The Sponsor will monitor patient safety throughout the study. An independent data monitoring committee (iDMC) is established to monitor safety during the study. The iDMC includes two pediatric oncologists and an independent statistician and meets to evaluate the safety of the study approximately every 6 months. In addition to safety review, the iDMC may also contribute to the selection of tumor types to be included in the cohort expansion.

8.3.6 Study Status

The Sponsor initiated the initial early-phase trial in pediatric and young adult patients with relapsed and refractory pediatric solid tumors (Study GO29664) in November 2015. As of 18 April 2016, 62 patients have been enrolled across tumor type cohorts.

The iDMC has met twice to review ongoing trial data, and has recommended that the study continue without modification.

Interim PK analyses have been completed on the first 20 patients to complete Cycle 1. Preliminary PK data suggest that exposure in pediatric patients administered 15 mg/kg (or 1200 mg for patients ≥18 years of age) have similar exposure (within the 90% exposure prediction interval based on data from adult patients) to atezolizumab as that observed in adult patients administered 1200 mg atezolizumab.

8.4 CONFIRMATORY STUDY

If preliminary evidence for the efficacy of atezolizumab is observed in some or all assessed pediatric tumor cohorts, and if the overall safety profile of the drug is acceptable, the Sponsor proposes to perform a confirmatory study in a specific tumor type. Patient selection based on an established biomarker profile may be considered if indicated by retrospective analyses in Study GO29664. The primary and secondary

endpoints will be selected on the basis of the tumor type to be studied. Secondary endpoints will include safety and pharmacokinetics of atezolizumab in pediatric patients. Combinations of atezolizumab with other agents may be considered in this trial. A number of factors will be considered when making this decision, including:

- The tumor type that demonstrates a response to single-agent atezolizumab in Study GO29664
- The pharmacokinetics and recommended therapeutic dose of atezolizumab
- The safety profile of atezolizumab as a single agent in children
- Safety and PK data from other targeted agents that may be used in combination with atezolizumab
- Efficacy data generated by the Sponsor, collaborators, or in published literature from pediatric nonclinical models with combination therapies

The Sponsor plans to discuss the proposed design for a confirmatory study of registration potential with the appropriate health authorities and academic collaborators prior to implementation.

9. REFERENCES

[ACS] American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society, 2014.

Adamson PC, Houghton PJ, Perilongo G, Pritchard-Jones K. Drug discovery in paediatric oncology: roadblocks to progress. Nat Rev Clin Oncol 2014;11:732–9.

Addy, R. DIA 2015: The State of Pediatric Research in the United States: Successes Under BPCA and PREA [resource on the Internet; cited 9 March 2016]. Available from: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM452231.pdf

Andorsky DJ, Yamada RE, Said J, et al. Programmed death ligand 1 is expressed by non-Hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res 2011;17:4232–44.

Besse B, Johnson ML, Jänne PA, et al. Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1–selected non-small cell lung cancer (NSCLC). Eur J Cancer 2015;51(Suppl 3):S717–8.

Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123–35.

Cheson BD, Pfistner B, Juweid ME, et al. and the International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579–86.

Chowdhury F, Dunn S, Mitchell S, et al. PD-L1 and CD8+PD1+ lymphocytes exist as targets in the pediatric tumor microenvironment for immunomodulatory therapy. Oncoimmunology 2015; 4:e1029701.

[EC] Commission to the European Parliament and Council. Better Medicines for Children — From Concept to Reality. General Report on experience acquired as a result of the application of Regulation (EC) No 1901/2006 on medicinal products for paediatric use. 2013a. Available from: http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf

[EC] Commission to the European Parliament and Council. General Report on experience acquired as a result of the application of the Paediatric Regulation (Article 50(2) of regulation (EC) NO1901/2006: summary of the replies to the public consultation. 2013b. Available from: http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/2013_paediatric_report_summary.pdf

[EMA] European Medicines Agency. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Direction 2001/83/EC and Regulation (EC) No 726/2004. 2006. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

[EMA] European Medicines Agency. 5-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation [EMA/428172/2012]. 2012. Available from: http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

[FDA] Food and Drug Administration. Third Annual Patient Network Meeting; Under the Microscope: Pediatric Drug Development. 10 September 2014.

[FDA] Food and Drug Administration. New Pediatric Labeling Information Database [resource on the Internet].[updated 31 January 2016; cited 9 March 2016]. Available from: http://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase

Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet 2016;387:1837–46.

Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010;116:3268–77.

Hegde PS, Karanikas V, Evers S. The Where, the When, and the How of Immune Monitoring for Cancer Immunotherapies in the Era of Checkpoint Inhibition. Clin Cancer Res 2016;22:1865–74.

Herbst RS, Soria J-C, Kowanetz M, et al. Predictive correlates of response to anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–7.

Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-postiive, advanced non-small-cell lunch cancer (KEYNOTE-010): a randomized controlled trial. Lancet 2016;387:1540–50.

Horn L, Spigel DR, Gettinger S, et al. Clinical activity, safety and predictive biomarkers of the engineered antibody MPDL3280A (anti-PDL1) in non-small cell lung cancer (NSCLC): update from a phase Ia study. J Clin Oncol 2015;33(suppl):A8029.

Kim A, Fox E, Warren K, et al. Characteristics and outcome of pediatric patients enrolled in phase I oncology trials. Oncologist 2008;13:679–89.

Lukas RV, Rodon J, Shih K, et al. Clinical activity and safety of atezolizumab (anti-PDL1) in patients with glioblastoma (GBM). Society for Neuro-Oncology – 20th Annual Meeting. 2015; abstract IMCT-24.

Lussier DM, Nieves LM, McAfee MS, et al. Enhancement of T cell immunity to osteosarcoma through modulation of PD-1/PD-L1 interactions. J Immunother Cancer 2013;1(Suppl 1):P162.

McDermott DF, Sosman JA, Sznol M, et al. Atezolizumab, an Anti-Programmed Death-Ligand 1 Antibody, in Metastatic Renal Cell Carcinoma: Long-Term Safety, Clinical Activity, and Immune Correlates From a Phase Ia Study. J Clin Oncol. 2016;34(8):833–42.

Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. New Engl J Med 2015;373:1803–13.

Parsa AT, Waldron JS, Panner A, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nat Med 2007;13:84–8.

Petrylak D, Powles T, Bellmunt J, et al. A phase Ia study of MPDL3280A (anti-PDL1): updated response and survival data in urothelial bladder cancer (UBC). J Clin Oncol 2015;33(Suppl):A4501.

Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomized, controlled, phase 2 trial. Lancet Oncol 2015;16:908–18.

Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521–32.

Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

Routh JC, Ashley RA, Sebo TJ, et al. B7-H1 expression in Wilms' tumor: correlation with tumor biology and disease recurrence. J Urol 2008;179:1954–60.

Routh JC, Grundy PE, Anderson JR, Retik AB, Kurek KC. B7-H1 as a biomarker for therapy failure in patients with favorable histology Wilms' tumor. J Urol 2013;189:1487–92.

Schmid P, Kowanetz M, Koeppen H, et al. NSCLC with high PD-L1 expression on tumor cells or tumor-infiltrating immune cells represents distinct cancer subtypes. Eur J Cancer 2015;51(Suppl 3):S602.

SEER (Surveillance, Epidemiology, and End Results) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence—SEER 9 Regs Research Data, Nov 2012 Sub (1973-2010) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013, based on the November 2012 submission.

Spigel DR, Chaft JE, Gettinger S, et al. Clinical activity and safety from a phase II study (FIR) of MPDL3280A (anti-PDL1) in PD-L1 selected patients with non-small cell lung cancer (NSCLC). J Clin Oncol 2015;33(Suppl):A8028.

Vassal G, Zwaan CM, Ashley D, et al. New drugs for children and adolescents with cancer: the need for novel development pathways. Lancet Oncol 2013;14:e117–24.

Wiendl H, Mitsdoerffer M, Schneider D, et al. Human muscle cells express a B7-related molecule, B7-H1, with strong negative immune regulatory potential: a novel mechanism of counterbalancing the immune attack in idiopathic inflammatory myopathies. FASEB J 2003;17:1892–4.

Wilmotte R, Burkhardt K, Kindler V, et al. B7-homolog 1 expression by human glioma: a new mechanism of immune evasion. Neuroreport 2005;16:1081–5.

Wintterle S, Schreiner B, Mitsdoerffer M, et al. Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. Cancer Res 2003;63:7462–7.

Yamamoto R, Nishikori M, Kitawaki T, et al. PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. Blood 2008;111:3220–4.

Yamamoto R, Nishikori M, Tashima M, et al. B7-H1 expression is regulated by MEK/ERK signaling pathway in anaplastic large cell lymphoma and Hodgkin lymphoma. Cancer Sci 2009;100:2093–100.

Appendix 1
List of Ongoing Studies with Atezolizumab

Study	Study Title
BO29562 C	A Phase Ib/II study evaluating the safety and efficacy of atezolizumab in combination with obinutuzumab plus lenalidomide in patients with relapsed or refractory follicular lymphoma
BO29563 C	A Phase Ib/II study evaluating the safety and efficacy of MPDL3280A in combination with either obinutuzumab plus bendamustine or obinutuzumab plus chop in patients with follicular lymphoma or diffuse large b-cell lymphoma
BP28179 C	An open-label, multi-center, dose escalation Phase I study of single agent RO5520985, administered as an intravenous infusion in patients with locally advanced or metastatic solid tumors.
BP29392 C	An open-label, multicenter, dose-escalation Phase Ib study to investigate the safety, pharmacokinetics, pharmacodynamics, and therapeutic activity of RO7009789 (CD40 agonist) in combination with MPDL3280A (anti−PD-L1) in patients with locally advanced and/or metastatic solid tumors
BP29428 C	Open-label, multicenter, dose escalation Phase Ib study with expansion phase to evaluate the safety, pharmacokinetics and activity of RO5509554 and MPDL3280A administered in combination in patients with advanced solid tumors
BP29435 C	A Phase 1b, open-label, multi-center, dose-escalation study of the safety, pharmacokinetics, and therapeutic activity of RO6895882, an immunocytokine, which consists of a variant of interleukin-2 (IL-2v), that targets carcinoembryonic antigen (CEA), and MPDL3280A, an antibody that targets programmed death-ligand 1 (PD-L1), administered in combination intravenously, in patients with locally advanced and/or metastatic solid tumors.
GO27831 - PCD4989G M	A Phase I, open label, dose escalation study of the safety and pharmacokinetics of atezolizumab administered intravenously as a single agent to patients with locally advanced or metastatic solid tumors or hematologic malignancies
GO28625 M	A Phase II, multicenter, single-arm study of atezolizumab in patients with PD-L1-positive locally advanced or metastatic non-small cell lung cancer [FIR]
GO28753 M	A Phase II, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after platinum failure
GO28754 M	A Phase II, multicenter, single-arm study of MPDL3280A in patients with pd l1-positive locally advanced or metastatic non-small cell lung cancer
GO28915 M	A Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PD-L1 antibody) compared with docetaxel in patients with non-small cell lung cancer after failure with platinum-containing chemotherapy
GO29293 M	A Phase II, multicentre, single-arm study of atezolizumab in patients with locally advanced or metastatic urothelial bladder cancer
GO29294 M	A Phase III, open-label, multicenter, randomized study to investigate the efficacy and safety of atezolizumab (anti-PD-L1 antibody) compared with chemotherapy in patients with locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy [IMvigor211]
GO29322 C	A Phase Ib study of the safety and pharmacology of MPDL3280A administered with ipilimumab or interferon-alpha in patients with locally advanced or metastatic solid tumors
GO29383 C	A Phase Ib study of the safety and pharmacology of atezolizumab (MPDL3280A) administered with obinutuzumab in patients with relapsed/refractory follicular lymphoma and diffuse large b-cell lymphoma

Study	Study Title
GO29431 M	A Phase III, open-label, randomized study of MPDL3280A (anti-PD-L1 ant body) compared with cisplatin or carboplatin + pemetrexed for pd-l1-selected chemotherapy naive patients with stage IV non-squamous non-small cell lung cancer patients with stage IV non-squamous non-small cell lung cancer
GO29432 M	A Phase III, open-label, randomized study of MPDL3280A (anti-PD-L1 ant body) compared with gemcitabine + cisplatin or carboplatin for PD-L1-selected, chemotherapy naïve patients with stage IV squamous non-small cell lung cancer
GO29436 C	A Phase III, open-label, randomized study of MPDL3280A (anti-PDL-1 ant body) in combination with carboplatin + paclitaxel with or without bevacizumab compared with carboplatin + paclitaxel + bevacizumab in chemotherapy-naive patients with stage IV non-squamous non-small cell lung cancer
GO29437 C	A Phase III, open-label, multicenter, randomized study evaluating the efficacy and safety of MPDL3208A (anti-PDL-1 antibody) in combination with carboplatin + paclitaxel or MPDL3208A in combination with carboplatin + nab-paclitaxel versus carboplatin + nab-paclitaxel in chemotherapy-naive patients with stage IV squamous non-small cell lung cancer
GO29527 M	A Phase III, open-label, randomized study to investigate the efficacy and safety of MPDL3280A (anti-PDL-1 antibody) compared with best supportive care following adjuvant cisplatin-based chemotherapy in PD-L1-selected patients with completely resected stage IB-IIIA non-small cell lung cancer
GO29537 C	A Phase III, multicenter, randomized, open-label study evaluating the efficacy and safety of MPDL3280A (anti-PDL-1 antibody) in combination with carboplatin + nab-paclitaxel for chemotherapy-naive patients with stage IV non-squamous non-small cell lung cancer
GO29664 M	A Phase I/II, open-label study of the safety and pharmacokinetics of MPDL3208A administered intravenously as a single agent to pediatric patients with relapsed/refractory solid tumors - iMATRIX atezo
GO29674 C	A Phase Ib, open-label, dose-escalation study of the safety and pharmacokinetics of MOXR0916 and MPDL3280A in patients with locally advanced or metastatic solid tumors
GO29695 C/M	A Phase Ib study of the safety and pharmacokinetics of MPDL3280A (anti-PDL-1 antibody) alone or in combination with lenalidomide in patients with multiple myeloma (relapsed and post-autologous stem cell transplantation)
GO29754 C/M	A Phase Ib study of the safety and pharmacology of MPDL3280A administered alone or in combination with azacitidine in patients with myelodysplastic syndromes
GO29779 C	A Phase Ib, open-label, dose-escalation study of the safety and pharmacology of GDC-0919 administered with atezolizumab in patients with locally advanced or metastatic solid tumors
GO29831 C	A Phase Ib, open-label, two-arm study evaluating the safety and pharmacokinetics of atezolizumab (anti-PD-L1 antibody) in combination with trastuzumab emtansine or with trastuzumab and pertuzumab in patients with HER2 positive breast cancer
GP28328 C	A Phase Ib study of the safety and pharmacology of atezolizumab (anti−PD-L1 antibody) administered with bevacizumab and/or chemotherapy in patients with advanced solid tumors
GP28363 C	A Phase 1b Study of the safety and pharmacology of atezolizumab administered with cobimetinib in patients with locally advanced or metastatic solid tumors
GP28384 C	A Phase 1b, open-label study of the safety and pharmacology of atezolizumab (anti-PD-L1 antibody) administered in combination with vemurafenib or vemurafenib plus cobimetin b in patients with BRAFV600 mutation-positive metastatic melanoma

Study	Study Title
ML29725 M	An open-label, multicenter, expanded access program for MPDL3280A in patients with PD-L1-positive locally advanced or metastatic urothelial bladder cancer after failure with platinum-containing chemotherapy
MO29112 C	A multi-center, randomized clinical trial of biomarker-driven maintenance treatment for first-line metastatic colorectal cancer
MO29518 M	An open-label, multi-cohort, Phase II study of atezolizumab in advanced solid tumors
WO29074 C/M	A randomized Phase II study in MPDL3280A administered in combination with Bevacizumab or alone versus sunitin b in patients with untreated advanced renal cell carcinoma
WO29522 C	A Phase III, multicenter, randomized, placebo-controlled study of atezolizumab (anti PD-L1 antibody) in combination with nab paclitaxel compared with placebo with nab paclitaxel for patients with previously untreated metastatic triple negative breast cancer
WO29636 M	A Phase III, open-label, multicenter, randomized study of atezolizumab (anti-PD-L1 antibody) versus observation as adjuvant therapy in patients with PD-L1-selected, high-risk muscle-invasive bladder cancer after cystectomy.
WO29637 C	A Phase III, open-label, randomized study of atezolizumab (anti PD-L1 antibody) in combination with bevacizumab versus sunitinib in patients with untreated advanced renal cell carcinoma (IMmotion151)
WP29158 C	A Phase Ib study of the safety and pharmacology of MPDL3280A administered with erlotinib or alectinib in patients with advanced non-small cell lung cancer.
WP29945 C	An open-label, multicenter, dose escalation and expansion Phase Ib study to evaluate the safety, pharmacokinetics, and therapeutic activity of RO6958688 in combination with atezolizumab in patients with locally advanced and/or metastatic CEA-positive solid tumors
GO29438 C	A Phase III, open-label, randomized study of atezolizumab (MPDL3280A, anti-PD-L1 Antibody) in combination with carboplatin or cisplatin + pemetrexed compared with carboplatin or cisplatin + pemetrexed in patients who are chemotherapy-naive and have stage iv non-squamous non-small cell lung cancer
GO29664	A single-arm study to evaluate the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of MPDL3280A (anti-PD-L1 antibody) in pediatric and young adult participants with solid tumors
GO30140 C	An open-label, multicenter Phase Ib study of the safety and tolerability of atezolizumab (anti-PD-L1 antibody) administered in combination with bevacizumab and/or other treatments in patients with solid tumors