DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 124026

WRITTEN REQUEST

Genentech, Inc.
Attention: Ruchi Gupta, M.S.
Regulatory Program Management
1 DNA Way
South San Francisco, CA 94080

Dear Ms. Gupta:

Reference is made to your Proposed Pediatric Study Request, submitted April 11, 2016, received April 11, 2016 for atezolizumab (MPDL3280A). We also refer to the teleconference between representatives of FDA and representatives of Genentech on June 21, 2016, to discuss the draft Written Request, and to Genentech's comments on the draft Written Request, sent via electronic mail (email) on July 20, 2016.

Included are studies to investigate the potential use of atezolizumab in the treatment of pediatric and young adult patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care (SOC) treatment options exist.

Background

Immune checkpoint inhibitors are therapeutic agents designed to target the same pathways tumor cells use to evade recognition and destruction by the immune system, increasing the immune system's capability to attack tumor cells.

Atezolizumab (MPDL3280A) is a human monoclonal antibody, a type of checkpoint inhibitor, that targets human programmed death ligand 1(PD-L1) thereby disrupting the PD-1/ PD-L1 pathway, a critical immune checkpoint in regulating cytotoxic T cell function. It is currently being investigated in adult patients with multiple solid tumors and hematologic malignancies.

Despite the progress made after 40 years of clinical research using combinations of chemotherapy, radiotherapy, and surgery, disease-free survival and overall survival rates have not significantly improved for children, adolescents and young adults with relapsed or refractory tumors most commonly observed in the pediatric population. Given the low accrual rates of young adults and adolescents on clinical trials, enrollment will include patients up to 30 years of age.

The expression of PD-L1 by malignant cells has been reported in many pediatric tumor types, including high-grade glioma, rhabdomyosarcoma, non-Hodgkin lymphoma, Hodgkin lymphoma, soft tissue sarcoma, osteosarcoma, Ewing sarcoma, and Wilms' tumor. PD-L1 is highly expressed on tumor-infiltrating leukocytes and tumor-associated macrophages (TAMs). TAMs are reported to have a prognostic role in pediatric tumors, including malignant glioma, neuroblastoma, Ewing sarcoma, Hodgkin lymphoma, and high-grade osteosarcoma.

The atezolizumab formulation (concentrate for solution for IV infusion) and dosage(s) used in studies in adult patients will also be used in the planned pediatric studies. This formulation is suitable for use in pediatric patients.

To obtain needed pediatric information on atezolizumab, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

FDA is not requesting studies in neonates because solid tumors are diagnosed infrequently in the neonatal period. Additionally, tumors diagnosed in neonates are generally not relapsed or refractory to standard treatments during the neonatal period.

- *Nonclinical studies:*

Based on review of the available non-clinical toxicology data, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Biomarker studies:*

Patients are required to either submit archival tissue or undergo biopsy to be eligible for Study 1. Results of biomarkers studies and initial clinical activity data may be used to prioritize pediatric tumor types for future clinical evaluation. Expression of PD-L1 on tumor cells or immune cells may predict clinical responses to atezolizumab; however, current understanding of the prevalence of PD-L1 expression in pediatric tumors is limited. Paraffin-embedded archival tissue will be submitted for participation in Study 1. In addition, optional on-study tumor specimens will be collected and analyzed. A retrospective biomarker analysis will be conducted using the same approach for PD-L1 expression analysis used in the adult studies to assess the underlying prevalence of PD-L1 expression in all enrolled pediatric patients and to assess whether antitumor activity of atezolizumab is higher in patients with PD-L1−positive tumors compared to patients with PD-L1−negative tumors. If the data gathered in Study 1 demonstrate that PD-L1 or other potential biomarkers are a clinically meaningful predictor of response, a biomarker-selected patient strategy will be implemented in Study 2.

- *Clinical studies:*

Study 1

A multicenter, open-label, single agent dose-finding and activity-estimating study to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and preliminary efficacy of atezolizumab in pediatric and young adult patients < 30 years of age with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care (SOC) treatment options exist.

This study is ongoing and will enroll patients into a minimum of five cohorts of 10 or more patients each with a specific histologically-defined tumor type, including neuroblastoma, rhabdomyosarcoma, soft tissue sarcoma, osteosarcoma, and Ewing sarcoma. Patients with Hodgkin lymphoma, non-Hodgkin lymphoma, Wilms' Tumor, and other PD-L1+ tumors will also be enrolled

Each tumor type will be considered a distinct tumor type cohort for assessment of anti-tumor activity.

Study 2

One or more randomized, multicenter, open label, active-control trials of atezolizumab in patients 0 to <18 years of age with solid tumors. Specific tumor type(s) to be studied will be selected based on the results of Study 1, including the retrospective analysis of PD-L1 expression in tumors from patients enrolled on Study 1 and will be mutually agreed upon by FDA and Genentech. Elements of study design such as endpoints, choice of comparator, dosage, sample size, and eligibility criteria will depend on the specific tumors to be studied. The final protocol and statistical analysis plan for Study 2 must be submitted to and agreed upon by the FDA prior to enrollment of any study subjects, and the WR will be amended accordingly. If the results of Study 1 show that further studies are not warranted, Genentech will submit a request for an amendment to the WR.

- *Objectives of each study:*

Study 1 Primary Objectives

- To evaluate the safety, tolerability, pharmacokinetic (PK) profile, immunogenicity, of atezolizumab in pediatric and young adult patients.
- To make a preliminary assessment of the anti-tumor activity of atezolizumab in specific tumor types through assessment of objective response rate (ORR) and progression-free survival (PFS).

Study 1 Secondary Efficacy Objectives

- To assess the duration of response (DOR) to atezolizumab.
- To evaluate overall survival (OS) for all tumor types except osteosarcoma.

  To evaluate clinical benefit response (objective response or stable disease for at least 6 months, as determined by RECIST v. 1.1) in osteosarcoma.

Study 1 Exploratory Objectives

- To explore if PD-L1 expression on tumor and/or tumor-infiltrating cells at baseline is predictive of response to atezolizumab
- To explore the relationship between atezolizumab exposure and changes in levels of pharmacodynamic (PD) biomarkers including but not limited to cytokines, circulating tumor DNA (ctDNA) concentration and T-cell subpopulations
- To explore non-inherited biomarkers that may be predictive of response to atezolizumab (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events, may provide evidence of atezolizumab activity, or may increase the knowledge and understanding of disease biology
- To explore inherited biomarkers (i.e., variants in germline DNA) that may be predictive of response to atezolizumab (i.e., predictive biomarkers), may be associated with progression to a more severe disease state (i.e., prognostic biomarkers), acquired resistance to atezolizumab, or susceptibility to developing adverse events, or may increase the knowledge and understanding of disease biology
- To evaluate potential relationships between anti-therapeutic antibodies (ATAs) and other outcome measures (e.g., PK, safety, and efficacy)

Study 1 Pharmacokinetic Objective:

- To assess the PK of atezolizumab in pediatric patients with solid tumors with known or expected PD-L1 pathway involvement

Study 2 Primary Objectives:

- To assess the efficacy and safety of atezolizumab in one or more solid tumor types selected on the basis of the results of Study 1
- To assess a time-to-event primary endpoint [event-free survival (EFS), PFS, or OS], selected based on the tumor type(s) and patient population(s) studied

- *Patients to be studied:*

    - *Age group in which studies will be performed:*

    Study 1 will enroll patients whose age at study entry is <30 years of age. 48 patients (2 years of age and older) have enrolled into Study 1 to date:

    - *Number of patients studied:*

    Study 1 will enroll between 50 and 100 patients, at least 75% of whom should be <18 years of age across all tumor types. In addition, at least five tumor type cohorts must enroll a minimum of 10 patients.

Study 2 will enroll patients in appropriate age ranges based upon the epidemiology of the disease(s) to be studied and in numbers as discussed and agreed upon with FDA prior to initiating the study(ies).

- *Representation of Ethnic and Racial Minorities:*

  The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - *Efficacy Endpoints:*

    Study 1: Efficacy objectives are exploratory in nature, and will serve to inform future studies (i.e. Study 2) in a specific tumor population.

    Primary endpoints for Study 1:

    - Safety
    - PK
    - Preliminary antitumor activity (ORR, PFS)

    Secondary endpoints Study 1:

    - DOR
    - OS

    Study 2: Efficacy endpoints will be among the elements of study design that will depend on the specific tumors to be studied. The final protocol and statistical analysis plan for Study 2 must be submitted to and agreed upon by the FDA prior to enrollment of any study subjects.

    Primary endpoints Study 2:

    - Safety
    - Efficacy: A Time-to-event primary endpoint (EFS, PFS, or OS), selected based on tumor type and patient population studied
    - PK

  - *Safety Endpoints:*

    Study 1 and Study 2:

    The primary safety endpoints will be evaluation of adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), vital signs, and changes in growth and development patterns.

- *Pharmacokinetic Endpoints:*

Study 1: The PK objective of Study 1 is to achieve similar systemic exposures as that observed in adults. Interim PK analyses will be performed after 5 patients of <6 years of age have completed the first cycle and after the first 20 patients (regardless of age) have completed the first cycle. Dose adjustments will be determined on the basis of the available information (i.e., systemic exposure based on interim PK analyses and the emerging safety profile).

- *Known safety concerns and monitoring:*

Pneumonitis, colitis, endocrine disorders (e.g., adrenal insufficiency, hypothyroidism, and hyperthyroidism), hepatitis, neurologic disorders (e.g., Guillain-Barre syndrome, myasthenia gravis, and meningoencephalitis), events suggestive of hypersensitivity, influenza-like illness, infusion related reactions, and dermatologic reactions are known safety concerns of atezolizumab. Additional potential safety concerns include myopathies (e.g., myositis, myopathy), nephritis, and other endocrinopathies (e.g., diabetes and pancreatitis). Systemic immune activation (SIA) is an additional safety concern when used in combination with another immune-modulating compound.

Immune-mediated adverse reactions associated with atezolizumab include dermatologic, hepatic, endocrine, and respiratory events, as well as events of hepatitis/elevated liver function tests and influenza-like illness. In addition, systemic immune activation (SIA), characterized by an excessive immune response, is a potential risk associated with atezolizumab when used in combination with another immune modulating compound. In Study 1, thyroid tests will be performed at baseline and then every two cycles, as thyroid toxicities are a known safety risk. Additionally, management guidelines will be used for interruption or discontinuation of atezolizumab for occurrence of endocrine and other immune-related adverse events. Other laboratory assessments such as serum chemistries, amylase, and lipase will also be assessed with the aim of early detection and management of other possible immune related adverse events.

An independent Data Monitoring Committee (iDMC) is required for Study 1 and Study 2. See FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Biological product information:*

  - *Dosage form:* The atezolizumab drug product is formulated as (b) (4)

  - *Route of administration:* intravenous administration

  - *Regimen:* The dose of atezolizumab is 15 mg/kg (maximum, 1200 mg) every 3 weeks for patients aged <18 years. Patients aged ≥ 18 years will receive a flat dose of 1200 mg of atezolizumab. Dose adjustments will be determined based on PK and safety data obtained at the planned interim analysis.

- *Statistical information, including power of studies and statistical assessments:*

  Study 1:

  No formal hypothesis testing is planned because statistics will be descriptive. The efficacy analyses will be performed on the safety evaluable population.

  For Study 1, the ORR along with 95% confidence intervals (CIs) (using the Blyth-Still-Casella method) will be calculated for each tumor type cohort, except osteosarcoma, for which CBR will be calculated. The Kaplan-Meier approach will be used to estimate median PFS, DOR, and OS, as appropriate. There will be interim PK analyses.

  A minimum of 50 patients will be enrolled in this study across all tumor types. In addition, at least five tumor type cohorts must enroll a minimum of 10 patients. To make a preliminary assessment of the efficacy of the study drug, two response assessments are planned: an initial response assessment and an additional response assessment. Taking into account historical control ORRs for each pediatric tumor type, the minimum number of patients in the initial response assessment and the minimum number of responders needed for cohort expansion and advancement to the additional response assessment will be calculated.

  Study 2: The statistical analysis plan(s) will be presented and agreed upon with the FDA before enrollment of the first patient in this study(ies).

- *Pharmacokinetic/pharmacodynamic analysis*

  Estimated atezolizumab clearance (CL) and volume of distribution (Vd) from PK samples obtained across all studies with a minimum of 7 patients in each of the following age groups: < 6 years, 6 to < 12 years, and 12 to < 18 years of age. Population PK analysis should be performed using atezolizumab concentration data obtained from all studies. Effect of age, weight, and other relevant covariates on atezolizumab PK should be assessed. Combine data from all completed studies to develop PK/PD models to explore exposure-response relationships for measures of safety and efficacy/activity as the data allow.

Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate that atezolizumab is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted:* You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. The Sponsor should collect this information when permissible by individual country law. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the FD&C Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 600.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):*

  Reports of Study 1 must be submitted to the Agency on or before June 30, 2019 followed by the submission of the protocol / amendment to this WR for Study 2. The CSR for Study 2 should be submitted by December 31, 2025. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, that would otherwise expire

nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, if there is unexpired exclusivity that is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such exclusivity is otherwise due to expire.

If FDA has not determined whether atezolizumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this formal pediatric Written Request, nor any request for exclusivity made by you confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC WRITTEN REQUEST STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Claire Myers, Ph.D., Regulatory Project Manager, at (240) 402-6612.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GREGORY H REAMAN
08/10/2016