Clinical Review of Efficacy Supplement

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I. Executive Summary

This is an efficacy supplement containing a final Clinical Study Report (CSR) for Study GO29664, a multicenter, open-label, single-arm activity-estimating study of atezolizumab in 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 treatment options exist. The study was designed with tumor-specific cohorts which would be expanded if a pre-defined efficacy threshold was met. Ninety patients were enrolled including patients 0 – 29 years of age. No cohorts demonstrated sufficient efficacy to trigger additional expansion and enrollment of additional patients with that tumor type. The safety profile of atezolizumab in pediatric patients did not present new safety signals compared to the safety profile demonstrated in adults.

FDA issued a Written Request (WR) for the conduct of pediatric studies including Study GO29664 on August 10, 2016. Based on the submission of the primary CSR on September 27, 2018, FDA amended the WR to remove the requirement for additional studies beyond Study GO29664 (Study 1 in the WR) given the demonstrated lack of anti-tumor activity in this study. The amended WR was issued April 29, 2019. This efficacy supplement is intended to provide information to support revision of the atezolizumab label and to support an application for pediatric exclusivity on the basis of the completed WR. The Division assessed that the terms of the Written Request had been met by submission of the clinical study report. The Pediatric Exclusivity Board agreed with granting exclusivity based on fulfillment of the terms of the Written Request. The Annotated Written Request Template and Pediatric Exclusivity Board comments are included in Appendix 1 of this review

II. Description of Trial

Study Title: A Phase I Trial of atezolizumab in pediatrics and young adult patients with previously treated solid tumors

Study GO29664 is a multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of atezolizumab in 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 treatment options exist. The agreed upon population for Study 1 included patients < 30 years of age. Study 1 was planned to enroll 50 – 100 patients, with at least 75% of patients to be < 18 years of age across all tumor types. At least five tumor type cohorts were to enroll a minimum of 10 patients.

Atezolizumab was administered by IV infusion every 3 weeks to pediatric and young adult patients with previously treated solid tumors. Children aged < 18 years received the weight-based equivalent of the approved adult dose and recommended Phase II/III adult dose (15 mg/kg atezolizumab every 3 weeks, with a maximum of 1200 mg). Patients who are ≥ 18 years old will receive the approved adult dose of 1200 mg. Specific objectives for the study are outlined below.

Safety Objective: To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on nature, frequency, and severity of serious and non-serious adverse-events (AEs), as well as effects on laboratory test values and vital signs.

Pharmacokinetic Objective: To characterize the pharmacokinetics of atezolizumab in pediatric and young adult patients.

Efficacy Objectives:

- To evaluate the anti-cancer activity of atezolizumab in pediatric and young adult patients, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and clinical benefit response rate (CBRR; only for patients with osteosarcoma).
- To evaluate the anti-cancer activity of atezolizumab in pediatric and young adult patients, as measured by overall survival (OS).

Pharmacokinetic Objective: To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures.

III. Trial Results:

Efficacy

The trial enrolled 90 patients and 87 received treatment. All patients who received atezolizumab had received prior systemic therapy, 66% had received prior radiation therapy, 86% had received prior surgery and 24% had received prior stem cell transplant.

Two patients < 2 years of age received treatment. Among the 90 patients enrolled, 20% were 18 years of age or older, in agreement with the Agency's stipulation that at least 75% of patients be <18 years of age. The cohorts of patients with Ewing's sarcoma, neuroblastoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma, osteosarcoma and Wilms tumor each enrolled at least 10 patients.

The primary efficacy outcome measures were ORR and PFS. Clinical benefit rate was a primary efficacy measure for the osteosarcoma cohort only. The secondary efficacy outcome measures were DOR and OS. None of the cohorts met the pre-specified minimum number of responders (best overall response of complete or partial response) needed for tumor type cohort expansion after treatment with single-agent atezolizumab, therefore Study GO29664 did not proceed to the additional response assessment stage. Efficacy data for the overall study, copied from the CSR, is included below:

Table 3 Overview of Efficacy Results (Safety-Evaluable Population)

	All Patients (n=87)
Primary Efficacy Parameters	
Objective Response Rate (ORR) [a]	n=87
Responders (%)	4 (4.6%)
95% CI (Blyth-Still-Casella)	1.59, 10.89
Progression-Free Survival (PFS)	n=87
Patients with event (%)	84 (96.6%)
Median duration of PFS (months)	1.3
95% CI (Brookmeyer and Crowley)	1.2, 1.4
25% and 75%-ile	1.1, 2.6
Range	0–24 [b]
Secondary Efficacy Parameters	
Duration of Response (DOR)	n=4
Patients with event (%)	2 (50.0%)
Median DOR (months)	13.2
95% CI (Brookmeyer and Crowley)	4.1, NE
25% and 75%-ile	8.7, NE
Range	4–22 [b]
Overall Survival (OS)	n=87
Patients with event (%)	64 (73.6%)
Median OS (months)	7.4
95% CI (Brookmeyer and Crowley)	5.3, 9.7
25% and 75%-ile	3.1, 14.7
Range	0–27 [b]

CBR=clinical benefit response; CI=confidence interval; DOR=duration of response; NE=not evaluable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

[a] Includes patients with osteosarcoma, because no patients in the osteosarcoma cohort experienced stable disease for ≥6 months and therefore did not qualify for CBR.

[b] Censored observation. Censor is defined as no progression of disease or death up to clinical cutoff date.

Safety

Most patients (60.9%) received atezolizumab for <2 months; 7 (8%) patients received atezolizumab for 6 months or longer. The median number of doses received was 2 (range 1 – 32).

Three patients (3.4%) withdrew from treatment with study drug due to AEs: one patient with Grade 4 diabetic ketoacidosis and Grade 3 Fanconi syndrome, one patient with Grade 3 transaminases increased, and one patient with a Grade 3 lung infection. Thirty-one patients (35.6%) experienced SAEs with no notable trend across cohort or age group. Pyrexia was the most frequently reported SAE (4.6%). The incidence of Grade 3 – 4 AEs was similar across age groups and cohorts. The most frequently reported Grade 3 – 4 AE was anemia (21.8%). No patients experienced a Grade 5 AE. Fifty-seven patients (65.5%) were reported to have an AE considered by the investigator to be related to the study drug, with fatigue as the most frequently reported study drug-related AE (19.5%].

Per the sponsor, there was no apparent difference in the PK of atezolizumab between the 2 to <12 and 12 to <18-year-old age groups. Exposures of the two younger age groups were trending slightly lower in comparison to the ≥ 18-year age group, as expected, based on the body weight ranges in each age group and respective dosing regimens (15 mg/kg body weight-based dosing of patients <18 years of age and 1200 mg flat dose received by patients ≥ 18 years of age).

A summary of AESI data from the CSR is provided below:

Table 21 Overall Summary of AESIs (Safety-Evaluable Population)

	All (n = 87)
Total number of patients with at least one AESI	40 (46.0%)
Grade 1–2	30 (34.5%)
Grade 3–4	10 (11.5%)
Grade 5	0
Total number of patients with at least one AESI by medical concept (all grades)	
Important AESIs	
Immune-related hepatitis (diagnosis and laboratory abnormalities)	16 (18.4%)
Immune-related hepatitis (laboratory abnormalities)	16 (18.4%)
Immune-related hepatitis (diagnosis)	1 (1.1%)
Infusion-related reactions	10 (11.5%)
Immune-related hypothyroidism	6 (6.9%)
Immune-related pancreatitis	4 (4.6%)
Immune-related pneumonitis	2 (2.3%)
Immune-related hyperthyroidism	1 (1.1%)
Immune-related colitis	1 (1.1%)
Immune-related meningoencephalitis	1 (1.1%)
Immune-related diabetes mellitus	1 (1.1%)
Other AESIs	
Immune-related rash	11 (12.6%)
Immune-related severe cutaneous reaction	1 (1.1%)
Total number of patients, with at least one AESI, who received systemic corticosteroid [a] within 30 days of AESI onset	10 (11.5%)
Grade 1–2	6 (6.9%)
Grade 3–4	4 (4.6%)
Grade 5	0

AESI = adverse event of special interest.

[a] Per the programmatic derivation used, if a corticosteroid was available in multiple formulations and the formulation or route was not specified, it was assumed to be systemic.

Sources: t_ae_si_overall_SE; t_ae_si_ctc_3cat_SE_BYCHRT; t_ae_im_ctc_3cat_SE_BYCHRT.

IV. Proposed Labeling

The following text represents the sponsor's proposed addition to Section 8.4, Pediatric Use (new text in blue).

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients. (b) (4) [redacted]

Reviewer Comments:

(b) (4) [redacted]

Negative studies and inconclusive studies should be briefly summarized in this subsection... Furthermore, when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the Pediatric Use subsection." Therefore, DO2 agrees a description of the inconclusive or negative study should be included in Subsection 8.4.

As per 21 CFR 201.57(c)(9)(iv)(E)): When substantial evidence does not exist to support an indication in a particular pediatric population, or the drug has not been studied in a particular pediatric population, an appropriate statement must be included, such as "Safety and effectiveness in pediatric patients have not been established." Given the lack of evidence to support an indication of TECENTRIQ in pediatric patients, DO2 agrees with the inclusion of this language in section 8.4.

According to 21 CFR 201.57(c)(9)(iv)(A): The terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents. Therefore, the text was modified to include only patients < 17 years enrolled in the study. The description of the study was modified to provide a more clinically useful description of the study design.

The Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019 states, "when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients compared with adults, a summary of this information should be included in the Pediatric Use subsection." Although no clinically significant differences were observed, it is recommended to include a statement that no new adverse reactions were observed to provide additional information to healthcare providers It is recommended to modify the

proposed statement describing the safety profile [redacted] (b) (4) .

FDA's *Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling* recommends including pharmacokinetic data when data reflect safety concern related to dosing (e.g., the clearance of the drug is low, resulting in higher exposure).

If the number of pediatric patients or age range for the pediatric patients in the pharmacokinetic assessment is different than those of the study, it is recommended to include the number of pediatric patients and their age range in these statements.

The agreed-upon labeling is as follows:

The safety and effectiveness of TECENTRIQ have not been established in pediatric patients.

The safety and antitumor activity of TECENTRIQ were assessed but not established in a single-arm, multi-center, multi-cohort trial (NCT02541604) in 60 pediatric patients aged 7 months to <17 years with relapsed or progressive solid tumors and lymphomas. No new safety signals were observed in pediatric patients in this study.

In pediatric patients who received TECENTRIQ 15 mg/kg with a maximum dose of 1200 mg every 3 weeks, the steady-state exposure (AUC) of atezolizumab in pediatric patients aged 12 years or older was comparable to that in adult patients who received TECENTRIQ 1200 mg every 3 weeks, while the exposure trended lower in pediatric patients less than 12 years old.

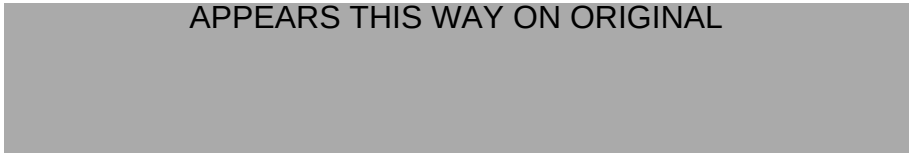
V. Fulfillment of Written Request

The Division of Oncology 2 reviewed the primary Clinical Study Report (CSR) submitted to IND 124026 on September 27, 2018 in addition to the labeling supplement submitted to the BLA on March 31, 2020. The Division assessed that the terms of the Written Request had been met based on the information in the primary CSR. The Pediatric Exclusivity Board determined that exclusivity could be granted. The Annotated Written Request Template, which includes comments from the board regarding the timing of submission of the CSR and efficacy supplement, is provided as an appendix to this review.

VI. Conclusions and Regulatory Action

The Division agrees with approval of the supplement with the agreed-upon labeling and with the Pediatric Exclusivity Board's recommendation that pediatric exclusivity be granted based upon fulfillment of the terms of the Written Request.

Appendix 1: Annotated Written Request Template



Written Request Items	Information Submitted/ Sponsor's Response	Division's Comments
Types of studies/ Study Design: Revised 24 April 2019 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 refracto1y) 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-LI +tumors will also be enrolled. Each tumor type will be considered a distinct tumor type cohort for assessment of anti-tumor activity.	Type of study: The Phase I was performed in accordance with the terms of the Written Request agreement, Amendment 1 (revised 24 April 2019). Details of the studies are provided below: Phase I Study: CSR NO1095866 A Phase I Trial of atezollizumab in pediatrics and young adult patients with previously treated solid tumors. Number of patients enrolled: 90 Number of patients treated: 87 Target Population: Patients aged 2-30 years with previously treated solid tumors. This study evaluated the safety, tolerability, PK, pharmacodynamics, immunogenicity, and preliminary efficacy of atezolizumab administered by IV infusion every 3 weeks to pediatric and young adult patients with previously treated solid tumors. Specific objectives for the study are outlined below: Safety Objective: To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on nature, frequency, and severity of serious and non-serious adverse-events (AEs), as well as effects on laboratory test values and vital signs. Pharmacokinetic Objective: To characterize the pharmacokinetics of atezolizumab in pediatric and young adult patients. Immunogenicity Objective: To evaluate the immune response to atezolizumab in pediatric and young adult patients on the basis of the incidence of anti-drug antibodies (ADAs; referred to as anti-therapeutic antibodies or ATAs in previous submissions). Efficacy Objectives:	The sponsor met the exact terms of the WR. The study was a multi-center, open-label study designed to evaluate the safety and preliminary efficacy of atezolizumab in patients < 30 years of age and is consistent with the design described in the WR. The cohorts of patients with Ewing sarcoma, neuroblastoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma, osteosarcoma and Wilms tumor each enrolled at least 10 patients, in accordance with the Agency's stipulation.

Written Request Items	Information Submitted/ Sponsor's Response	Division's Comments
Study 1 concluded enrollment and results from the primary analysis were included in the Clinical Study Report (submitted on September 27, 2018 as Serial No. 0099)	• To evaluate the anti-cancer activity of atezolizumab in pediatric and young adult patients, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR), and clinical benefit response rate (CBRR; only for patients with osteosarcoma). • To evaluate the anti-cancer activity of atezolizumab in pediatric and young adult patients, as measured by overall survival (OS). Dose-Assessment Objective: To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures. 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 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	The Division agrees with the description of the efficacy objectives, though notes that the interpretation of PFS and OS are limited in a single arm trial.

Written Request Items	Information Submitted/ Sponsor's Response	Division's Comments
	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 detectable ADAs and other clinically relevant outcome measures (e.g., PK, safety, and efficacy)	
Indication(s) to be studied: Revised 24 April 2019 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 there is no effective standard treatment available. *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.	Indication(s) studied: Per the Written Request, Amendment 1 (revised 24 April 2019), studies were conducted in pediatric and young adult patients with previously treated solid tumors. As outlined in the FDA's Written Request, the Phase I objectives were independent of tumor type. Therefore, in the Phase I study GO29664, patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment has proven to be ineffective or intolerable and for whom no curative standard-of-care treatment options exist were included. The intent-to-treat (ITT) population (safety and efficacy) consisted of 87 patients treated with similar atezolizumab exposures in children and adolescents to adult patients receiving the recommended Phase II/III dose of 1200 mg every 3 weeks.	The sponsor met the exact terms of the WR. See "Entry Criteria" below. The Division agrees that the study was conducted in the intended population. Data on race and ethnicity was submitted. See "Format of reports to be submitted."

Written Request Items	Information Submitted/ Sponsor's Response	Division's Comments
Age group and population in which study will be performed: Revised 24 April 2019 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 there is no effective standard treatment available. Study 1 will enroll patients whose age at study entry is <30 years of age. 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 coho1is must enroll a minimum of 10 patients.	Age group and population in which study was performed: <u>Phase I Study GO29664</u> During the study, patients were enrolled into a total of 12 cohorts by tumor types: Ewing sarcoma (Cohort 1, N=11); Hodgkin lymphoma (Cohort 2, N=9); Neuroblastoma (Cohort 3, N=11); Non-Hodgkin lymphoma (Cohort 4, N=3); Non-rhabdomyosarcoma soft tissue sarcoma (Cohort 5, N=10); Osteosarcoma (Cohort 6, N=12); Rhabdomysosarcoma (Cohort 7, N=10); Wilms tumor (Cohort 8, N=10); Other tumor types with documented PD-L1 expression (Cohort 9, N=4); Other tumor types without documented PD-L1 expression (Cohort 10, N= 5); Rhabdoid tumor (Cohort 11, N=2); Atypcial teratoid rhabdoid tumor (Cohort 12, N=3). Age Group and Population: The 87 patients treated in the Phase I Study were between the ages of ≥ 2yrs to ≤ 30 years of age, males and females and were distributed among the following age groups: <2 years: 2 patients 2 years to <12: 29 patients 12 to <18 years: 38 patients ≥ 18 years: 18 patients For details please see the final CSR NO1095866:	The sponsor met the exact terms of the WR. The Division agrees that the age group and population studied was consistent with that outlined in the WR. The cohorts of patients with Ewing sarcoma, neuroblastoma, non-rhabdomyosarcoma soft tissue sarcoma, rhabdomyosarcoma, osteosarcoma and Wilms tumor each enrolled at least 10 patients, in accordance with the Agency's stipulation. Study 1 was planned to enroll 50 – 100 patients, with at least 75% of patients to be < 18 years of age across all tumor types. At least five tumor type cohorts were to enroll a minimum of 10 patients. Two patients < 2 years of age received treatment. In addition to those listed, 3 patients aged 12 to < 18 years were enrolled but not treated. Among the 90 patients enrolled, 20% were 18 years or older, in agreement with the

Written Request Items	Information Submitted/ Sponsor's Response	Division's Comments
		Agency's stipulation that at least 75% of patients be < 18 years of age (and therefore that no more than 25% of patients be 18 years or older).

Entry criteria: Pediatric and young adult patients< 30 years of age with solid tumors with known or expected PD-Ll 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 coho1ts 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-LI +tumors will also be enrolled.	Entry criteria used: Inclusion criteria for patients can be referenced in study protocol GO29664 Section 4.1 and is outlined below: Histologically or cytologically confirmed solid tumor of a type listed below (tumor types with known or expected PD-L1 pathway involvement) (including Hodgkin and non-Hodgkin lymphoma), for which prior treatment had proven to be ineffective (i.e., relapsed or refractory disease) or intolerable. Patients had to have histologic or cytologic confirmation of malignancy at the time of diagnosis or relapse. Neuroblastoma Rhabdomyosarcoma (RMS) Non-RMS soft tissue sarcoma Osteosarcoma Ewing sarcoma Wilms tumor	The sponsor met the exact terms of the WR. The Division agrees that the study population reflects the population outlined in the WR.

	Hodgkin lymphoma • Non-Hodgkin's lymphoma *Rhabdoid tumor* *Note: Patients who have synchronous rhabdoid tumor and ATRT with no clear primary should be enrolled into the rhabdoid tumor cohort, and they should complete the additional assessments scheduled for patients with ATRT.* *ATRT* Other tumor types not included in the list above with documented expression of PD-L1 on either tumor cells or immune infiltrating cells with approval of the Medical Monitor • Disease that is measurable as defined by RECIST v1.1, *m*INRC, Revised Response Criteria for Malignant Lymphoma, *or RANO criteria* (as appropriate) or evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, or other reliable measures • Archival tumor tissue block or 15 freshly cut, unstained, serial slides available for submission or willingness to undergo a core or excisional biopsy prior to enrollment (fine-needle aspiration, brush biopsy and lavage samples are not acceptable) • For patients of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least *months* after the last dose of study drug	

Clinical endpoints: Revised 24 April 2019 Study 1 Primary Objectives: • To evaluate the safety, tolerability, pharmacokinetic (PK) profile, and 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). Secondary objectives: • To assess the duration of response (DOR) to atezolizumab, to evaluate the overall survival (OS) for all tumor types except osteosarcoma, and to evaluate clinical benefit response (objective response or stable disease for at least 6 months, as determined by RECIST v. 1.1) in osteosarcoma. Explorary Objectives: • To explore if PD-LI 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	Clinical endpoints used: <u>1. Phase I Study GO29664</u> The Primary Objectives studied are outlined below: To evaluate the safety and tolerability of atezolizumab in pediatric and young adult patients, focusing on the nature, frequency, and severity of serious and non-serious adverse events, as well as effects on laboratory test values and vital signs to characterize the pharmacokinetics of atezolizumab The Secondary Objectives studied are outlined below: • To evaluate the immune response to atezolizumab on the basis of the incidence of anti-therapeutic antibodies (ATAs) • To evaluate the anti-cancer activity of atezolizumab, as measured by objective response rate (ORR), progression-free survival (PFS), duration of objective response (DOR) and clinical benefit response rate (CBRR) • To evaluate the anti-cancer activity of atezolizumab, as measured by overall survival (OS) • To assess the optimal dose of atezolizumab in pediatric and young adult patients on the basis of safety, PK, and efficacy outcome measures 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	The sponsor met the exact terms of the WR. The Division agrees that the objectives of the study are consistent with those in the WR. The CSR contains analyses of the safety and pharmacokinetic profile of atezolizumab in pediatric patients with relapsed/refractory solid tumors and lymphomas as well as analyses of ORR, DOR, OS and PFS. The CSR contains brief descriptions of analyses or tables of data related to the exploratory objectives.

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	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 *detectable* ATAs and other *clinically relevant* outcome measures (e.g., pharmacokinetics, safety, and efficacy) The details surrounding the Primary Objectives for study GO29664 can be found in Module 5 CSR No. 1095866, Synopsis (page 11); Section 2 Objectives (Section 2 1 Safety Objective; Section 2.2 Pharmacokinetic Objective; Section 2.3 Immunogenicity Objective; Section 2.4 Efficacy Objectives; Section 2.5 Dose-Assessment Objective; Section 2.6 Exploratory Objectives). The results from Study GO29664 can be found in the final CSR No.1095866, Section 5.1 Overview of Safety and Section 6.1 Overview of Efficacy.	

Drug information: Revised 24 April 2019 Biological product information: • Dosage from: The atezolizumab drug product is formulated as (b) (4) [redacted] • 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 ≥ 18 years will receive a flat dose of 1200 mg of atezolizumab. Dose adjustements will be determined based on PK and safety data obtained at the planned interim analysis.	Drug information: Dosage Form: The atezolizumab drug product is formulated as (b) (4) [redacted] Route of administration: Intravenous injection Regimen: The dose of atezolizumab is 15 mg/kg (maximum, 1200 mg) every 3 weeks for patients aged <18 years. Patients ≥ 18 years will receive a flat dose of 1200 mg of atezolizumab. Dose adjustements will be determined based on PK and safety data obtained at the planned interim analysis. The pharmacokinetic results show that the clearance and volume of distribution of atezolizumab were comparable between pediatric patients receiving 15 mg/kg and young adult patients receiving 1200 mg of atezolizumab every 3 weeks when normalized by body weight, with exposure trending lower in pediatric patients as body weight decreased. These differences were not associated with a decrease in atezolizumab concentrations below the therapeutic target exposure. Data for children ≥ 2 years is limited thus no definitive conclusions can be made. Population PK Report – GO29664. Population Pharmacokinetics of Atezolizumab in Pediatric and Young Adult Patients with Previously Treated Solid Tumors. Report No. 1090147.	The sponsor met the exact terms of the WR. The Division agrees with the description of the product and doses administered in the study.

Drug specific safety concerns: Revised: 24 April 2019 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	Drug specific safety concerns: The safety of atezolizumab in pediatric patients and young adults with previously treated pediatric solid tumors was evaluated as outlined in the FDA's Written Request Agreement, Amendment 1 (24 April, 2019) Safety analyses were performed on the safety-evaluable population, with sub-group safety analyses by tumor type cohort, by age, and by ADA conducted as appropriate (please refer to Sections 5 and 7.3 of the primary CSR). Safety assessments included AEs, standard laboratory assessments, and vital signs. AEs and laboratory data were graded by the investigator in accordance with the NCI CTCAE v4.0. AESIs were pre-defined in the protocol (please refer to Section 5.2.3 of the protocol) and analyzed in the CSR based on the known mechanism of action for atezolizumab and consistent with adult atezolizumab studies (please refer to Section 5.9 of the primary and final CSRs). A review of the safety results as reported in the final CSR indicated that atezolizumab was well-tolerated and its safety profile in pediatric patients in Study GO29664 was consistent with its known safety profile in adult patients. There were no new safety signals identified.	The sponsor met the exact terms of the WR. Safety data appears to have been collected and analyzed in an acceptable manner. There were no new safety signals identified in Study 1. Ten patients (11.5%) developed an immune-mediated AE, 46% of patients had an adverse event of special interest (AESI) and 58.6% of patients had at least one Grade 3 – 4 AE. Thirty-six percent (35.6%) of patients had at least one serious AE. There were no AEs with a fatal outcome. The most frequently reported AEs were pyrexia (41.4%), fatigue (35.6%), constipation (33.3%), anemia (28.7%), cough (25.3%), vomiting (24.1%), and diarrhea (21.8%). An independent Data Monitoring Committee

managements of other possible immune related adverse events. ndependent Data Monitoring Committee (iDMC) is required for Study 1. See FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees //www.fda.gov/downloads/Regulat01 yinf01mation/Guidances/UCM126578.pdf		(iDMC) was required for Study 1 per the Written Request and oversaw the study according to the CSR.
Statistical information, including power of study and statistical assessments: Revised 24 April 2019 For 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 internals (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	Statistical information, including power of study and statistical assessments: Statistical information was provided as outlined in the FDA's Written Request, Amendment 1 (revised 24 April 2019): A total of 90 patients were enrolled in the study, and a total of 87 patients were treated in the study. Six cohorts enrolled 10 or more patients: • Cohort 1: Ewing sarcoma • Cohort 3: Neuroblastoma • Cohort 5: Non-Rhabdomyosarcoma soft tissue sarcoma • Cohort 6: Osteosarcoma • Cohort 7: Rhabdomyosarcoma • Cohort 8: Wilms tumor No tumor type cohort met the protocol-specified response criteria at the initial response assessment, and therefore no cohort advanced to further expansion for additional response assessment. No formal statistical hypothesis testing was planned for this study. The efficacy analyses were performed on the safety evaluable population.	The sponsor met the exact terms of the WR.

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.	The primary efficacy endpoints were ORR, CBRR (for osteosarcoma), and PFS. The ORR by cohort were as follows, Cohort 1 : EWING SARCOMA (N=11), ORR (CI): 0 (0.00, 24.95); Cohort 2 : HODGKIN LYMPHOMA (N=9), ORR (CI): 2 (4.10, 55.83); Cohort 3 : NEUROBLASTOMA (N=11), ORR (CI): 0 (0.00, 24.95); Cohort 4 : NON HODGKIN LYMPHOMA, (N=3), ORR (CI): 1 (1.70, 86.46); Cohort 5 : NON-RHABDOMYOSARCOMA SOFT TISSUE SARCOMA, , (N=10), ORR (CI): 1 (0.51, 44.39); Cohort 6 : OSTEOSARCOMA; (N=10), ORR (CI): 0 (0.00, 26.70) , Objective Response (OR) was used for cohort 6, because no patients qualified for Clinical Benefit Response (CBR) with SD for more than 6 month. Cohort 7 : RHABDOMYOSARCOMA, (N=10), ORR (CI): 0 (0.00, 26.70) ; Cohort 8 : WILMS TUMOR, (N=10), ORR (CI): 0 (0.00, 26.70); Cohort 9 : OTHER TUMOR TYPES WITH DOCUMENTED PD-L1 EXPRESSION, (N=4), ORR (CI): 0 (0.00, 52.71); Cohort 10 : OTHER TUMOR TYPES WITHOUT DOCUMENTED PD-L1 EXPRESSION, (N=4), ORR (CI): 0 (0.00, 52.71); Cohort 11 : RHABOID TUMOR, (N=2), ORR (CI): 0 (0.00, 77.64); Cohort 12 : ATYPICAL TERATOID RHABOID TUMOR, (N=3), ORR (CI): 0 (0.00, 63.16). At the clinical cutoff, 84 PFS events occurred across all cohorts in the safety-evaluable population. Of the 84 PFS events, disease progression was experienced by 73 patients and 11 patients died. The median duration of PFS across all cohorts was 1.3 months (95% confidence interval [CI]: 1.2,1.4). (Please refer to Section 6.1 in the final CSR) Duration of response was analyses for only patient who had response, Of the 4 patients with objective responses, two patients had experienced an event of disease progression (1 patient in Cohort 2) or death (1 patient in Cohort 5), with a DOR of 4 months and 13.2 months, respectively. Another patient in Cohort 2 and 1 patient in Cohort 4 had not had an event, with a DOR of 22 months and 6 months (censored), respectively(Please refer to Section 6.3.1 in the final CSR). Overall, a total of 67 patients died during the study. The median OS across all treatment cohorts was 7.4 months (95% CI: 5.3, 9.6).	The Division did not independently calculate overall response rate or other efficacy endpoints based on the submitted datasets. The minimum response rate needed to trigger further cohort expansion was set separately for each disease type. Overall, no cohorts met the required threshold to trigger additional study in that tumor type and four patients of 87 (4.6%) demonstrated a partial response.

Pharmacokinetic/pharmacodynamics analysis: Estimated atezolizumab clearance (CL) and volume 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.	PK results of atezolizumab for 87 pediatric and young adult patients with relapsed or refractory disease were assessed. Individual and mean maximum serum concentration (C_{max}) of atezolizumab on Day 1 of Cycle 1 and Day 1 of Cycle 4 in addition to minimum serum concentration (C_{min}) of atezolizumab on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 and every 8 cycles thereafter, at study drug discontinuation, and after washout were summarized. Atezolizumab area under the serum concentration-time profile in Cycle 1 (AUC) was estimated using a population PK model. Further comparisons between atezolizumab PK in pediatric patients and young adults were also explored using population PK modeling approaches. Based on the PK analysis: • PK parameters and covariate effects were generally similar between the pediatric and young adult population. Clearance (CL) and volume of distribution of atezolizumab were comparable between pediatric patients receiving 15 mg/kg and young adult patients receiving 1200 mg of atezolizumab every 3 weeks (q3w) when normalized by body weight. • Exposure distributions of atezolizumab largely overlapped between age groups, and minimum serum concentration (C_{min}) trough values were above the target serum concentration of 6 μg/mL, suggesting minimal potential for under-dosing. • The half-life in pediatric patients was 2-3 weeks, also consistent with adults. • Variability in exposure was lower in pediatric patients relative to the young adults despite the greater weight range, showing the appropriateness of weight-adjusted dosing in the pediatric population. PK results of atezolizumab for 87 pediatric and young adult patients with relapsed or refractory disease were assessed. Individual and mean maximum serum concentration (C_{max}) of atezolizumab on Day 1 of Cycle 1 and Day 1 of Cycle 4 in addition to minimum serum concentration	According to the Primary CSR, Serum samples were collected from a total of 84 patients receiving atezolizumab therapy. Among the 84 patients who contributed PK samples, 2 patients were <2 years old, 29 patients were 2 to <12 years old, 37 patients were 12 to <18 years, and 18 patients were 18 years old or greater. According to review of the dataset, there are 14 patients < 6 years old, 17 patients 6 to < 12 years old, 38 patients 12 to <18 years old, and 18 patients 18 years or older. Atezolizumab PK profiles were similar between pediatrics and adults after adjustment of body weight.

	(C_{min}) of atezolizumab on Day 1 of Cycles 2, 3, 4, 8, 12, and 16 and every 8 cycles thereafter, at study drug discontinuation, and after washout were summarized. Atezolizumab area under the serum concentration-time profile in Cycle 1 (AUC) was estimated using a population PK model. Further comparisons between atezolizumab PK in pediatric patients and young adults were also explored using population PK modeling approaches.	Following multiple doses of 15 mg /kg atezolizumab up to 1200 mg q3w, exposure (AUC) overlapped between pediatrics aged 12 years or older and adults receiving 1200 mg atezolizumab q3w; and trended lower in pediatrics <12 years.
Labeling that may result from the studies: Revised 24 April 2019 u 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).	Labeling that may result from the studies: Based upon the results of the pediatric Phase I Study GO29664, the proposed labeling changes are being submitted in Module 1, Section 1.14.1.2 of the application. An update for Pediatric Use was proposed in Section 8.4, of the TECENTRIQ label.	Proposed labeling with revisions to section 8.4 describing the study was submitted as part of supplement 29.
Format of reports to be submitted: Revised 24 April 2019 Full study reports not previously submitted to the Agency addressing the issues outlined in this request, with full analysis, assessment, and interpretation.	Format of reports submitted: Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted. The reports included information on the representation of pediatric	Submitted full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted.

In addition, reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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, one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino. Under section 505A(d)(2)(B) of the 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 314.80 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/FormsSubmissionRequire	patients of ethnic and racial minorities according to the categories and designations in the FDA's Written Request. <u>Post-Marketing Adverse event reports:</u> The latest Periodic Benefit-Risk Evaluation Report (PBRER) covering the period 18 May 2019 to 17 November 2019 was submitted to the FDA on 25 July 2019. This PBRER is the most recent post-marketing adverse event report available at this time. <u>Study Data Format:</u> • Although not required per the Written Request agreement, Genentech acknowledges the Agency's request for the data to be submitted electronically according to the SDTM standard. As per the FDA Guidance for Industry on Regulatory Submissions in Electronic Format, issued in December 2014 (https://www.fda.gov/media/88120/download), it is our understanding that studies are required to submit CDISC data	Demographic data included in the submission includes a description of the race and ethnicity of the ITT population. The majority of patients were White (57.8%), followed by unknown (30%), Black or African American (6.7%), Asian (3.3%), and multiple (2.2%). Hispanic or Latino patients comprised 17.8% of patients, 58.9% were not Hispanic or Latino, 15.6% had no stated ethnicity and 7.8% had unknown ethnicity. The Division confirms that a post-marketing safety report was submitted July 25, 2019; since the submission of this supplement, a new post-marketing report has been submitted (July 21, 2020).

ments/ElectronicSubmissions/UCMI99759.pdf and referenced in the FDA Guidance for Industry	if their start date is 24 months after the issuance, and therefore the CDISC compliance requirement should not be applicable in the requested Tecentriq sBLA submission, where study GO29664 will be included as the sole clinical study and enrolled its first patient on November 5, 2015. However Genentech proposes to provide the pediatric study CDISC-compliant format. For details on agreement, see Agency's correspondence dated 5 August 2019 (Reference ID: 4472530) and 17 September 2019 Reference ID: 4493108 (Section 1.9.6).	The Division confirms that datasets were submitted as part of the submission.
Timeframe for submitting reports of the studies: Revised 24 April 2019 The study reports of the above studies must be submitted to the Agency on or before June 30, 2019.	Timeframe for submitting reports of the studies: The primary CSR for study GO29664 was submitted to the FDA on 27 September 2018.	The Division verifies the primary CSR was submitted to IND 124026 on September 27, 2018. See additional comment below.

Additional Comments from Pediatric Exclusivity Board:

The sponsor sought "alignment with the Agency on requirements for fulfilling the Written Request" through a series of communications before and after June 30, 2019. For example:

--June 10, 2019, letter from Genentech to FDA;

--series of emails from May 2019 through July 2019 (entered into DARTS July 23, 2019);

--August 25, 2019, Letter from FDA to Genentech,

--September 12, 2019, Letter from Genentech to FDA;

--September 17, 2019, Letter from FDA to Genentech.

The sponsor submitted its BLA supplement on March 31, 2019. The communications between the Division and the sponsor reflect that the Division was aware of the sponsor's proposed approach to fulfill the WR regarding submission of the primary study report in 2018, and the final study report in Q4 2019, followed by a labeling supplement . Despite the sponsor's repeated inquiries before and after June 30, 2019, the Division did not communicate any concerns with the sponsor's proposed approach. Rather, the Division's communications conveyed the

impression that submission of the primary study report to the IND satisfied the timeframe for submitting reports of studies as outlined in the WR. If not for these communications, the sponsor may have taken further action, such as seeking an amendment to the WR with respect to timing.

In light of these considerations, we conclude the following:

(1) It is appropriate to correct for the above-referenced communications; and
(2) conclude the sponsor fairly responded to the WR in this regard (to the extent the timeframe could be considered an element of the WR).

Appendix 2
Financial Disclosure Information

Genentech submitted an amendment to the SBLA on 9/4/2020 providing information regarding financial disclosures that had inadvertently not been provided. The information is summarized below:

Study Protocol Number	Clinical Site Number	Investigator Name	Patients Enrolled at Site	Disclosure (Payment Amount)
GO29664	[redacted]	(b) (6)		$27,965 for consulting fees paid between May 2014 to March 2018
GO29664				$50,000 for a grant, paid June 2018

Given the limited number of patients at this site and the negative study results, this reviewer concludes that the payments are unlikely to have unduly influenced study conduct or results.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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