NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated December 9, 2022.

Application Type	Supplemental Biologic License Application
Application Number(s)	761034/47
Priority or Standard	Priority
Submit Date(s)	June 30, 2022
Received Date(s)	June 30, 2022
PDUFA Goal Date	December 30, 2022
Division/Office	Division of Oncology 3
Review Completion Date	December 8, 2022
Established Name	Atezolizumab
(Proposed) Trade Name	Tecentriq
Pharmacologic Class	Anti-PD-L1 monoclonal antibody
Code name	MPDL3280A, RG7446
Applicant	Genentech, Inc
Formulation(s)	Injection, for intravenous use
Dosing Regimen	Adults: Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks Pediatric: Atezolizumab 15 mg/kg once every 21 days (up to a maximum of 1200 mg)
Applicant Proposed Indication(s)/Population(s)	Adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
RBPM= Regulatory Business Process Manager

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Glossary

ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ALK	anaplastic lymphoma kinase
ASPS	alveolar soft part sarcoma
BTD	Breakthrough Therapy Designation
CCOD	clinical cut-off date
CI	confidence interval
Cmin	minimum concentration
CNS	central nervous system
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
EGRF	epidermal growth factor receptor
ER	Exposure response
HCC	Hepatocellular Carcinoma
IC	immune cell
IND	investigational new drug
INV	Investigator
IRC	Independent Review Committee
IV	intravenous
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-CTEP	National Cancer Institute, Cancer Therapy Evaluation Program
NSCLC	non-small cell lung cancer
ORR	objective response rate
PD	pharmacodynamic
PK	pharmacokinetic
popPK	population pharmacokinetic
PD-L1	programmed death-ligand 1
PFS	progression free survival
PR	partial response
PT	preferred term
Q3W	every 3 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
sBLA	supplemental biologics license application

SCLC	small cell lung cancer
STS	soft tissue sarcoma
TC	tumor cells

1 Executive Summary

1.1. Product Introduction

Atezolizumab (Tecentriq®) is an anti-PD-L1 monoclonal antibody. It is FDA approved as a single agent or in combination for the adjuvant and neoadjuvant treatment of patients with non-small cell lung cancer, in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC), in combination with bevacizumab for patients with unresectable or metastatic hepatocellular carcinoma (HCC) who have not received prior systemic therapy, and in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The Applicant's proposed indication is for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has submitted data that provide substantial evidence of the effectiveness of atezolizumab for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic alveolar soft part sarcoma (ASPS; for 1200 mg administered every 3 weeks and for pediatric patients (ages 2-17) 15 mg/kg once every 21 days (up to a maximum of 1200 mg).

This conclusion is based on the results of a clinical study, ML39345. Study ML39345 is an open-label, single-arm study conducted in patients greater than 2 years of age. The study enrolled 47 adult patients and 2 pediatric patients with unresectable or metastatic ASPS not curable by surgery. The primary efficacy endpoint was overall response rate (ORR) assessed by independent review committee according to RECIST v1.1. guidelines. Adult patients received a fixed dose of 1200 mg intravenously (IV) and pediatric patients received 15 mg/kg (up to a maximum of 1200 mg) IV once every 21 days until disease progression or unacceptable toxicity. The ORR was 24.5% (n=12/49) (95% confidence interval [CI]: 13, 39) with all responders achieving a partial response. Of the 12 patients who experienced an objective response, duration of response (DOR) was ≥6 months for 67% of patients and ≥12 months for 42% of patients.

The safety of atezolizumab has been well characterized by across solid tumors including data submitted in this application. The safety profile in ASPS based on data from study ML39245 is generally consistent with the known safety profile of atezolizumab. Additional safety data to characterize the safety of atezolizumab in pediatric patients is derived from Study GO29664. Study GO29664 enrolled 60 pediatric patients ages 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. There are no FDA approved therapies indicated for the treatment of patients with ASPS which is a rare subtype of soft tissue sarcoma. The review team determined that the ORR and DOR provides a benefit that outweighs the risks associated with treatment with atezolizumab for this patient population. Given the rarity of ASPS in the pediatric population, the high unmet medical need for treatments for this disease, and the reported similarities across age groups on the basis of diagnostic features, disease management, and clinical course, the efficacy data from adult patients as well as two adolescent patients in study ML39345 are used to extrapolate efficacy to pediatric patients.

Therefore, the review team recommends granting traditional approval to atezolizumab for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Alveolar soft part sarcoma (ASPS) is a rare subtype of soft tissue sarcoma (STS) representing less than 1% of all STSs (i.e., less than 100 cases per year in the US) (SEER data). ASPS is characterized by an unbalanced recurrent translocation (t(x;17)(p11,q25) resulting in the ASPSCR1-transcription factor E3 (TFE3) fusion gene. Tumors are typically slow-growing, indolent soft tissue masses most commonly found in the lower extremity (Paoluzzi et al). ASPS predominantly affects young adults with a median age of 25 years and a female predominance (2:1) (Chang et al). There are no known differences in the biology, molecular alterations, clinical course, or treatment, among pediatric and adolescents or adult patients with ASPS although in general, tumors in the pediatric population tend to be completely resectable tumors as they are identified earlier..(Casanova et al). Metastatic disease typically presents late in the course of the disease. Complete surgical resection with or without radiation is the mainstay of treatment for localized disease. For patients with unresectable or metastatic disease, the 5-year overall survival is approximately 20% (Kummar et al). Historically, patients were treated with an anthracycline with response rates ranging between 8-19%. Following treatment with an anthracycline such as doxorubicin, pazopanib is approved for the broader STS population based on an improvement in median progression free survival of 4.6 months versus 1.6 months for placebo. The overall response rate (ORR) was 4.5%. According to the National Comprehensive Cancer Network (NCCN) guidelines version 2.2022 for sarcoma, the preferred systemic regimens for ASPS are pazopanib, sunitinib, pembrolizumab, and pembrolizumab in combination with axitinib. Pazopanib has shown activity in patients with ASPS showing response rates of 17% (95% confidence interval [CI]: 0.4, 64) (Kim et al) and 28% (95% CI: 13, 49) (Stacchiotti et al). In small, retrospective studies evaluating sunitinib in patients with ASPS, response rate ranged from 29-56% (Li et al and Stacchiotti et al). Pembrolizumab in combination with axitinib showed an ORR of 55% but this was in a limited patient population (n=12) (Wilky, et al).

The effectiveness of atezolizumab for the proposed indication is demonstrated by results from study ML39345, an open-label, single arm study evaluating single agent atezolizumab in 47 adult and 2 pediatric patients with unresectable to metastatic ASPS. The ORR as assessed by independent review was 24.5% (95% confidence interval [CI]: 13, 39). Duration of response was ≥6 months for 67% of responding patients, ≥12 months for 42% of responding patients, and >36 months for 25% of responding patients.

Safety data supporting the indication reflected exposure to atezolizumab in 47 adult patients and in 2 pediatric patients treated on study ML39345 and, 60 pediatric patients ages 7 months to <17 years in study GO29664. The safety of single agent atezolizumab has been well-

characterized in the treatment of adult patients with non-small cell lung cancer (NSCLC) and urothelial cancer, and in pediatric patients enrolled on study GO29664. In general, the safety profile of atezolizumab in patients with ASPS was consistent with the known safety profile in the other approved indications in adult. FDA noted a higher incidence of hypertension in study ML39345 than has been previously reported with single agent atezolizumab. The majority of cases were Grade 1-2, required no intervention, and were transient.

A favorable benefit:risk has been established for atezolizumab for the treatment of adult and pediatric patients 2 year of age and older with unresectable or metastatic ASPS based on the results of a single study, Study ML39345. Given the rarity of ASPS and small sample size, there are limited data to draw conclusions regarding subgroup analyses (i.e., race, age, sex, etc.) from this application. Due to the rarity of the population, large randomized clinical studies are infeasible. Therefore, regulatory flexibility is applied in accepting Study ML39345 to support approval as the demonstrated ORR is clinically meaningful in its magnitude and durability for an indication with no approved therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ASPS represents a small subset of STS. • Approximately <1% (<100 cases) are diagnosed in the US annually. • ASPS is characterized by ASPSCR1-TFE3 fusion gene. • Patients with metastatic disease have approximately 20% 5-year survival.	**Patients with unresectable or metastatic ASPS represent a rare population with a serious disease.**
Current Treatment Options	• Complete surgical resection is the treatment of choice for localized disease. • NCCN guidelines for sarcoma recommend pazopanib (response rates of 17% and 28%), sunitinib (response rates range from 29-56%), pembrolizumab (ORR of 50% in 4 patients) as a single agent or in combination with axitinib (ORR of 55% in 12 patients) as preferred regimens for unresectable or metastatic STS. • There are no FDA-approved therapies specifically for patients with ASPS.	**Unresectable or metastatic ASPS represents a disease with an unmet need for therapies with a positive benefit:risk assessment.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• There are no clinically significant differences between adult patients versus pediatric patients with ASPS.	
Benefit	• Study ML39345 demonstrated a clinically meaningful ORR. • The ORR was 24.5% (95% CI: 13, 39). The response rate was durable with 67% of responding patience maintaining the response for ≥6 months, 42% of responding patients maintaining response for ≥ 12 months, and >36 months for 25% of responding patients.	**The magnitude and duration of response demonstrated in Study ML39345 Was clinically meaningful in a rare disease with unmet medical need.** **A clinically meaningful and durable ORR has been used to support traditional approval in select malignancies.**
Risk and Risk Management	• The safety profile of atezolizumab appears acceptable for a therapy used to treat a serious and life-threatening condition. • Single agent atezolizumab has a well-characterized safety profile based on safety data in adult patients with SCLC and urothelial cancer. Study GO29664 which evaluated atezolizumab in pediatric patients provided supportive safety data for this population. • Hypertension is not a known adverse reaction for atezolizumab. The data demonstrated a higher rate than has been identified in other clinical studies evaluating single agent atezolizumab.	**The overall safety profile of atezolizumab is acceptable for the treatment of a serious and life-threatening condition. Although hypertension was reported at a higher incidence in study ML39345, 89% of cases were Grade 1-2, resolved without intervention and were transient.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:	Not Applicable; No COA data was submitted.
□	Clinical outcome assessment (COA) data, such as	
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
□	Patient-focused drug development or other stakeholder meeting summary reports	
	Observational survey studies designed to capture patient experience data	
□	Natural history studies	
□	Patient preference studies (e.g., submitted studies or scientific publications)	
□	Other: (Please specify)	
□	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Leslie Doros
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Alveolar soft part sarcoma (ASPS) is a very rare sarcoma subtype (less than 1% of all soft tissue sarcomas). The disease is characterized by the unbalanced recurrent t(X;17)(p11;q25) translocation, which leads to a chimeric ASPSCR1 transcription factor E3 (TFE3) gene (Ladanyi et al. 2001). ASPS occurs most commonly in the deep soft tissues. The most common metastatic sites are lung, bone, and brain; metastases to lymph nodes are uncommon.

ASPS occurs most frequently in patients between 15 and 35 years of age with a median age at presentation of 25 years (Wang et al. 2016). It can also occur in patients as young as 1.5 years of age (Flores et al. 2018). A Surveillance, Epidemiology and End Results (SEER) database of the US population between 1975 and 2018 identified 320 patients with ASPS and 141 patients diagnosed in the metastatic setting (Sankaran et al. 2021).

In the poster publication (Sankaran et al. 2021), of the 320 patients identified, 6 (2%) patients were identified as American Indian/Alaskan Native, 48 (15%) Asian/Pacific Islander, 76 (24%) Black, 185 (58%) White and 5 (1.6%) unknown. Due to the rarity of the disease and lack of large epidemiologic data, there is not much known about differences in prevalence or disease characteristics between racial and ethnic subgroups. This publication did touch upon metastatic presentation at diagnosis being more common in the black population when compared to other racial groups. The reasoning behind this is unknown at this time and may suggest larger socioeconomic issues, which lead to delayed screening and diagnosis.

Given the rarity of the disease, reports regarding overall prognosis are limited. One of the largest series is a retrospective review of 74 patients with ASPS treated at MD Anderson Cancer Center (Portera et al. 2001). The majority (n = 48) of these patients presented with advanced, metastatic disease; 33 patients received treatment, of which 26 patients with metastatic disease and 3 patients with localized disease received systemic chemotherapy. Only one of the 33 patients responded to systemic therapy. The 5-year overall survival (OS) rate for the 33 patients with metastatic ASPS was 20%. Median survival was 40 months. Overall, review of the literature revealed lack of observed objective responses to standard chemotherapies and an overall poor prognosis of 20% OS at 5 years for patients with advanced metastatic ASPS.

Pediatric data is limited with one of the largest series having 51 children and adolescents from 7 European Cooperative groups (Orbach at al. 2013).The median age was 13 years (range: 2-21). Primary sites were mostly limbs (63% of patients). Metastatic disease was observed in 27% of patients (14 patients). In 13 out of the 14 patients with metastatic disease (93% of patients), the lung was the site of metastases (associated with bone metastases in two cases and liver metastases in one case). In the entire dataset, only 3 of the 18 evaluable patients (17% of patients) had a response to conventional chemotherapy. Ten-year OS and event-free survival (EFS) was 78.0±7% and 62.8±7% respectively, which lowered to 44.8 ±17% and 14.3 ±9% in patients with metastatic disease (intergroup rhabdomyosarcoma IV [IRS-IV]). A similar retrospective analysis of 69 children and young adults less than 30 years old with ASPS diagnosed from 1980 to 2014 in 4 major institutions, showed a similar range of age at diagnosis (range: 1.5–30) with 32 out of 69 patients <17 years of age. Of the 69 patients, 38 patients had metastatic tumors (IRS-IV), of which the observed 5-year EFS and OS were of 7% and 61%, respectively (Flores et al. 2018). Another report of 22 patients with ASPS enrolled in the European Pediatric Soft Tissue Sarcoma study group trial (Brennan et al. 2018), had a median age at diagnosis of 11.5 years (range 2.7–17.5 years).

Overall, data from three pediatric and young adult studies (Orbach at al. 2013; Flores et al. 2018; Brennan et al. 2018) consistently showed similar primary sites, rate of metastatic disease, prognosis, and range of ages at diagnosis spanning from very early age (~2 years of age) to the respective upper limit of age inclusion for young adults of the examined studies. While very rare in patients <12 years of age, isolated cases of ASPS diagnosis at early age are to be expected and considered an area of high unmet medical need particularly in the unresectable metastatic setting.

The FDA's Assessment:

The FDA agrees with the overall analysis of ASPS presented by the Applicant. Given the rarity of ASPS, a true estimate of the incidence is difficult to ascertain; however, most literature reports support an incidence of <1% of all STS. ASPS is a disease of young adults. There have been no identified differences between adults and pediatric patients with ASPS on the basis of histology and biology, presentation, and disease. However, data from Casanova et al, suggest that pediatric patients with ASPS may have a more favorable prognosis than adults given that pediatric patients tend have more complete surgical resection than adult patients. However, no specific conclusion of differences in clinical benefit may be made given the limited data to support this. Outcomes for patients with metastatic disease is poor and there are no curative therapies.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are no approved treatments for unresectable or metastatic ASPS. Pazopanib is approved for the treatment of advanced soft tissue sarcoma (STS); however, as the study supporting approval focused on a broad population of which patients with ASPS represent a small subset, there is limited information on the efficacy of pazopanib specifically in these patients (van der Graaf et al. 2012). Surgical excision may be curative for primary tumors, but conventional chemotherapy is not effective for unresectable or metastatic disease. Current National Comprehensive Cancer Network guidelines (V1.2022) list preferred regimens with limited efficacy and safety data. These include sunitinib, pazopanib, pembrolizumab and pembrolizumab in combination with axitinib and are summarized in Table 1.

Table 1 Current Preferred Treatments Options for Patients with ASPS

Regimen	Pembrolizumab + axitinib[a]	Sunitinib[b,c]		Pazopanib[d]	Pembrolizumab
Dosing	Pembrolizumab 200 mg IV q3w + axitinib 5 mg PO BID	37.5 mg PO daily		600-800 mg PO daily *or* 400 mg PO BID	Not specified in reference
Study Type	Phase 2 Trial	Retrospective case series	Case series	Retrospective chart review	Retrospective chart review
N	Any sarcoma: 33 ASPS: 12	9	7 (5 treated with sunitinib)	30	Any sarcoma: 50 ASPS: 4
Pt Pop	Advanced or metastatic sarcomas, including ASPS Progressive disease after prior treatment with ≥ 1 systemic therapy	Advanced translocated ASPS evidence of progression during previous 3 months adequate bone marrow and organ function	Unresectable progressive ASPS during previous 3 months (per RECIST) resistant to interferon treatment heavily pre-treated with 1+ surgical procedures, radiotherapy, and medical therapy	Metastatic ASPS 60% (18/30) patients received prior treatment (13 of these received other anti-angiogenic agents)	Advanced STS, including ASPS received an immunotherapy (not specific to pembrolizumab or even anti-PD(L)-1) 2 ASPS patients received anti-PD-L1-based therapy
Efficacy	Median follow-up: 14.7 months Best ORR (ASPS): 60.0% Median PFS (ASPS): 12.4 months Median OS (ASPS): not reached 3-month PFS: 72.7% PR: 55% (6/11) SD: 18% (2/11)	Median tx duration: 10 months 3-month PR: 56% (5/9) 3-month SD: 33% (3/9) 6-month PR/SD: 89% (8/9) Median OS: 19 months Median PFS: 17 months	Mean tx duration: 5 months 3-month PR: 40% (2/5) 3-month SD: 20% (1/5) 2 patients reported improvement in symptoms	Median follow-up: 19 months ORR: 27% Median PFS: 13.6 months 1-year PFS: 59% Median OS: not reached Best responses: 1 CR, 7 PR, 17 SD and 4 PD	ASPS patients PR: 50% (2/4) SD: 50% (2/4)

Safety	• Grade 3-4 TRAEs: 13 (39%) • Grade 3-4 irAEs: 5 (15%) • Serious TRAEs: 7 (21%) • Pembrolizumab-related autoimmune toxic effects occurred in eight (24%) of 33 patients, with five Grade 3 or 4 adverse events. Of 31 patients received axitinib, one patient discontinued study therapy due to axitinib-related hepatotoxicity. 18 (58%) patients required dose reduction and 15 (48%) required one or more dose interruptions	• 8 patients (53%; n=15) had Grade 3/4 toxicity • 7 patients required dose reduction • The most common toxicities were neutropenia thrombocytopenia, hypothyroidism, arterial hypertension, and hand-foot syndrome • Treatment related sepsis and shock occurred in 1 patient[c]	• Four patients discontinued pazopanib due to side effects • Grade ≥ 3 non-hematologic toxicity were reported in 6 patients	• Not available

q3w = every 3 weeks; ASPS = alveolar soft part sarcoma; BID = twice a day; CR = complete response; irAE= immune related adverse event; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD(L)-1 = programmed death-ligand 1; PFS = progression free survival; PO = oral; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; STS = soft tissue sarcoma; TRAE = treatment related adverse events; tx = treatment

[a] Wilky et al. 2019

[b] Stacchiotti et al. 2011

[c] Jagodzinska-Mucha et al. 2017

[d] Stacchiotti et al 2018

[e] Groisberg et al 2017

The FDA's Assessment:
FDA agrees with the Applicant's assessment of potential treatment options for STS. Although doxorubicin and pazopanib are FDA approved for the broader STS patient population, there is limited data regarding specific outcomes in patients with unresectable or metastatic ASPS from the clinical studies that supported the respective approvals.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:
Tecentriq is currently approved in the U.S. under accelerated approval for the following indications:

- Patients with locally advanced or metastatic Urothelial Carcinoma who:
  - are not eligible for cisplatin-containing chemotherapy, and whose tumors express programmed death-ligand 1 (PD-L1 [PD-L1 stained tumor-infiltrating immune cell (IC) covering ≥ 5% of the tumor area]), as determined by an FDA-approved test, or
  - are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status

Tecentriq is also currently approved in the US for the following indications:

- Non-Small Cell Lung Cancer (NSCLC):
  - for the 1L treatment of adult patients with metastatic NSCLC whose tumors have high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cell (TC) [TC ≥ 50%] or PD-L1 stained tumor-infiltrating IC covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
  - in combination with bevacizumab, paclitaxel, and carboplatin, for the 1L treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
  - in combination with paclitaxel protein-bound and carboplatin for the 1L treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumor aberrations.
  - for the treatment of adult patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Tecentriq.

  - as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage II to IIIA non-small cell lung cancer (NSCLC) whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test

- Small Cell Lung Cancer (SCLC):
  - in combination with carboplatin and etoposide, for the 1L treatment of adult patients with extensive-stage SCLC.
- Hepatocellular Carcinoma (HCC):
  - in combination with bevacizumab for the treatment of patients with unresectable or metastatic HCC who have not received prior systemic therapy.
- Melanoma:
  - in combination with cobimetinib and vemurafenib for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of prior approvals for atezolizumab; however, the indication in urothelial carcinoma was withdrawn on December 2, 2022 after the submission of this sBLA.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
FDA interactions and submissions that are relevant to this sBLA are described below.

- On 30 September 2020, atezolizumab received approval for the sBLA (BLA 761034/S-029) that provided updates to the 'Use in Specific Populations, Pediatric Use' subsection of the Package Insert to include the results and pharmacokinetic data from the pediatric Study GO29664 conducted as part of the 10 August 2016, original Written Request for pediatric studies for atezolizumab and subsequent 29 April 2019, amended Written Request letter.
- Study ML39345, A Phase II Study of Anti-PD-L1 Antibody (atezolizumab) in ASPS, is conducted by the National Cancer Institute, Cancer Therapy Evaluation Program (NCI-CTEP) under IND 131,853.
- On 15 November 2019, a preliminary Breakthrough Therapy Designation (BTD) request for advice was submitted to Genentech IND 111,271 to discuss results from Study ML39345. A preliminary BTD request teleconference was held with the Agency on 10 December 2019. At this informal teleconference, FDA encouraged Genentech to submit a full BTD based on the data presented in the preliminary request. A full BTD was submitted to the FDA under IND 111,271 on 19 March 2020 for atezolizumab for the treatment of patients with

unresectable or metastatic ASPS. On 20 May 2020, FDA granted BTD for atezolizumab for treatment of patients with unresectable or metastatic ASPS.

- A Type C meeting to discuss the proposed content and format of the planned sBLA for atezolizumab for the treatment of patients with unresectable and metastatic ASPS was held on 15 October 2020. Key outcomes from that meeting were as follows:
  - FDA considered the results presented in the pre-meeting package (24 patients total, clinical cut-off date [CCOD]: May 2019) to be preliminary and requested updated safety and efficacy results be presented in a pre-sBLA briefing package. FDA agreed that the Applicant's proposal to provide updated safety and efficacy results for Study ML39345 seemed feasible, with a revised data cutoff which would include approximately 40 patients having >6 months of follow-up (if death or study withdrawal did not occur first).
  - FDA requested that the topline efficacy results included in the pre-sBLA meeting package be independently reviewed.
  - FDA stated that while the pharmacokinetic (PK) data from Study GO29664 suggests that atezolizumab exposure in patients >12 appear comparable to the approved 1200 mg dose in adults, based on the PK data reviewed, exposure appears lower in patients <12 years of age. FDA noted that this trend may lead to suboptimal exposure from an efficacy perspective in the current proposed indication. FDA recommended that Genentech provide adequate justification that the proposed 15 mg/kg dose in patients <12 years of age leads to adequate exposure.
- A Type B pre-submission meeting to present the results from Study ML39345 and discuss the acceptability of the results to form the basis of a sBLA for the approval of atezolizumab for the treatment of ASPS was held on 17 May 2022. Key outcomes from the meeting were as follows:
  - FDA stated that the collection of steady state PK from any remaining patient and any available anti-drug antibody (ADA) data (b) (4) The Sponsor agreed to assess the feasibility of obtaining such data and providing an update containing the requested information to FDA during the course of review of the sBLA.
  - FDA clarified that the additional PK data is not required for submitting the application, but may impact the indication that is approved.
  - In the preliminary comments, FDA provided feedback that in the proposed sBLA submission, as part of the description of the epidemiology and other disease characteristics of ASPS, include an assessment of the disease among all racial and ethnic populations that have historically been underrepresented in clinical research.

The FDA's Assessment:
FDA agrees with the Applicant's description of the key regulatory activities. Given the small sample size to support approval in the proposed indication, FDA requests that the Applicant provide complete sBLA data package, include any available data and information that can address the residual uncertainties regarding atezolizumab's effect on ORR and the durability of response, to support the benefit:risk assessment. This may include real world data, literature evidence, case reports using atezolizumab or other immune checkpoint inhibitors in patients with ASPS during the pre-sBLA meeting held on May 17, 2020. The Applicant stated that they would include a discussion of the available data from the current recommended treatment of patients for the proposed indication based on current NCCN guidelines, using information from literature evidence and case reports. Moreover, safety and efficacy data for the one pediatric patient that had received atezolizumab as a single agent under compassionate use would be summarized. FDA reviewed the data for this one pediatric patient. This patient had stable disease at week 8 and then progressed.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Applicant submitted clinical data from study ML39345 to support an sBLA for atezolizumab. The imaging contract research organization (CRO), (b) (4) was chosen for inspection by FDA because the study is small and the management of the primary endpoint data for all patients can be verified at the central imaging CRO.

The central imaging reads by the Applicant were conducted in compliance with the independent review charter and the study specific imaging manual. There was no evidence of unblinding of the radiologist readers to patients information or alternate reader assessments. Imaging data were reviewed for primary endpoint measurements and responses in 4 out of 50 patients and there were no discrepancies between the patient level data listings and the measurements/RECIST report in the source data.

The conducted onsite inspection of (b) (4) was completed. Based on the results of this inspection, the data generated for the primary endpoint appear acceptable in support of the proposed indication for the sBLA.

4.2. Product Quality

The submission did not contain any new product quality information.

4.3. Clinical Microbiology

The submission did not contain any new microbiology information.

4.4. Devices and Companion Diagnostic Issues

The submission for the proposed indication did not require a companion diagnostic.

5 Nonclinical Pharmacology/Toxicology

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
The submission did not contain new nonclinical information.

6 Clinical Pharmacology

6.1. Executive Summary

Genentech submitted this efficacy supplement to BLA 761034 for Tecentriq® (Atezolizumab), as a single agent, for the treatment of unresectable or metastatic alveolar soft part sarcoma (ASPS) in patients aged 2 years and older. Data to support this efficacy supplement are derived from one ongoing single arm, open-label study (ML39345) of atezolizumab that enrolled 47 adults patients and 2 adolescent pediatric patients (≥12 years of age) with unresectable or metastatic ASPS not curable by surgery. Additional pharmacokinetic (PK) and safety data from Study GO29664 provided supportive evidence of effectiveness in pediatric patients 2 years to < 12 years of age.

Study GO29664 is a multicenter, open-label, single-arm study in patients aged 7 months and older with relapsed or progressive solid tumors and lymphomas. In this study, a dosing regimen of 15 mg/kg Q3W (capped to 1200 mg) was selected for pediatric patients with the assumption that this dosage would provide a similar exposure to that in adults. PopPK analyses and simulations suggest that exposure distributions of atezolizumab in pediatric patients largely overlapped with that observed for adult patients with comparable inter-subject variability. The geometric mean Cycle 1 Cmin was for pediatric patients 6 to < 17 years was within range of that in adults, but slightly lower for pediatric patients 2 to < 6 years. No pediatric patients with either observed or simulated Cycle 1 Cmin had concentrations below 6 μg/mL, the target needed to achieve 95% receptor occupancy. There was also a trend for lower median AUC in pediatric patients aged 2 to 12 years old. Given the broad therapeutic window and flat exposure-response relationship for efficacy observed in adult patients across other tumor types, the lower median exposure in pediatric patients is not clinically meaningful.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:
The clinical pharmacology properties of atezolizumab in pediatric patients have been summarized previously for Study GO29664/iMATRIX submitted to BLA 761034 on March 31, 2020.

The FDA's Assessment:
The FDA agrees with the Applicant's position. In brief, a cross comparison of observed atezolizumab Cycle 1 Cmin in pediatric patients aged 2 to <6 years, 6 to <12 years, and 12 to 17 years, and adult patients suggested that observed pediatric concentrations in Study GO29664 were comparable with the distributions seen in adults. The geometric mean Cycle 1 Cmin observed in adults ranged from 56 to 88 μg/mL across studies. The observed geometric mean Cmin for pediatric patients 6 to <12 years was 63 μg/mL and for pediatric patients 12 to <17

years was 58 μg/mL, which are within the range of that in adults. The geometric mean Cycle 1 Cmin was 53 μg/mL for pediatric patients 2 to <6 years which is slightly lower than that observed for adults; however, this difference is not expected to be clinically significant given the broad therapeutic window and flat E-R relationship for efficacy.

Although there was a trend for lower median AUC in pediatric patients aged 2 to <12 years old, exposure distributions of atezolizumab largely overlapped across age groups with comparable inter-subject variability. The exposure of pediatric patients was within the exposure range demonstrated efficacy in adults with other tumor types. All exposures in pediatric patients were above the target of 6 mg/mL needed to achieve 95% receptor occupancy. In addition, there were a limited number of responders across patients (4/87) including two pediatric patients aged 2 to <12 years of age. Cycle 1 Cmin for these four patients was 28 mg/mL (17 year old), 40 mg/mL (4 years old), 80 μg/mL (26 years old), and 88 μg/mL (9 years old).

6.2 General Dosing and Therapeutic Individualization

6.2.1.1 General Dosing

Data:

Patients received atezolizumab at a fixed dose of 1200 mg intravenous (IV) for adults (≥18 years of age) and 15 mg/kg for pediatric patients (≥ 2 years of age) up to 1200 mg once every 21 days, in 21-day cycles.

The fixed dose of atezolizumab 1200 mg Q3W is an approved dosing regimen in adults (Tecentriq USPI).

Details to support the pediatric dosing of atezolizumab are provided below.

The 15 mg/kg Q3W regimen of atezolizumab is considered equivalent to the 1200 mg flat dose for a patient with a typical body weight of 80 kg, which is an approved regimen in several adult indications (Chiang et al. 2020).

Studies of atezolizumab in preclinical models predict that atezolizumab trough concentrations (C_{min}) of 6 μg/mL are needed to achieve maximal tumor growth inhibition (Deng et al. 2016). In clinical studies in adults, clinical activity was observed at doses ranging from 1 to 20 mg/kg (Herbst et al. 2014).

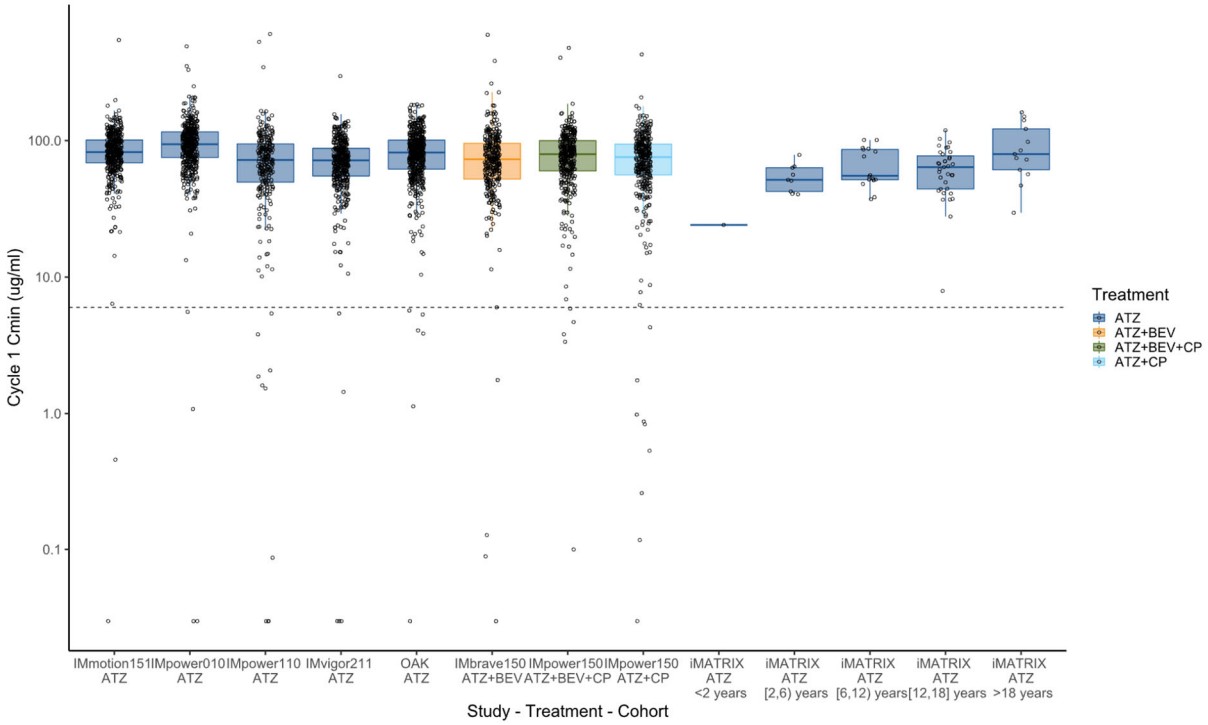
Clinical pharmacology data were not available for pediatric patients with ASPS receiving atezolizumab in Study ML39345. As such, data from the early phase pediatric Study GO29664 were used to support the pediatric dosing rationale. In Study GO29664, the 15 mg/kg Q3W regimen of atezolizumab (capped to 1200 mg) was chosen for pediatric patients due to

expected similar associated exposure to that in adults where a broad therapeutic window and flat exposure-efficacy/safety relationships for atezolizumab is observed (Morrissey et al. 2019, Shemesh et al. 2020, Stroh et al. 2017). Such similar associated exposure in pediatric patients aged 2 years and above is expected to achieve a comparable efficacy and safety profile to that observed in adults (Shemesh et al. 2019).

In Study GO29664 despite a trend for lower median exposure in the 2-12 year old age group, exposure distributions of atezolizumab largely overlapped across age groups with comparable inter-subject variability. The exposure of pediatric patients was within the exposure-efficacy range previously demonstrated in adult dose-ranging trials.

A cross comparison of observed atezolizumab Cycle 1 C_{min} in pediatric patients aged 2-6 years old, 6-12 years old, 12-18 years old, and >18 years old further confirmed that observed pediatric exposures in GO29664 were comparable with the distributions seen in adults. When compared to observed adult exposures, observed pediatric subjects achieved exposures in the range shown to be efficacious in adult Phase 3 trials. The geometric mean C_{min} in observed adults ranged from 56.4 to 87.8 μg/mL across studies, and the geometric mean C_{min} for pediatric patients older than 2 years of age was very close to/within that range for all age groups: 53.0 μg/mL for subjects to 2 to 6 years of age, 63.2 μg/mL for subjects 6 to 12 years, and 57.8 μg/mL for subjects 12 to 18 years. Incidence rate of post-baseline ADA-positive patients who had at least one post-baseline result was 11/77 patients (14.3%). Generally comparable PK of atezolizumab were observed between ADA-positive and ADA-negative patients.

Figure 1 Cross Comparison of Observed Atezolizumab Cycle 1 C_{min} in Pediatric Patients Receiving 15 mg/kg (Capped to 1200 mg) and Adult Patients Receiving 1200 mg



ATZ=atezolizumab; BEV=bevacizumab; C_{min}=minimum concentration; CP=carboplatin

Notes: Only one out of two infants (<2 years) had observed Cycle 1 data in iMATRIX.

The 5 rightmost columns represent pediatric data from iMATRIX in pediatric subjects <2 years, 2 to <6 years, 6 to <12 years, 12 to 18 years, and >18 years old. The boxplot represents first and third quartiles, the center line represents the median, whiskers extend to the minimum and maximum, excluding outliers that are defined as >1.5-fold of the interquartile range, and circles represent individual subjects. The dashed line represents the target Cmin of 6 µg/mL.

Source: sBLA 761034/S-047

Table 2 Cross Comparison Summary of Observed Atezolizumab Cycle 1 C_{min} in Pediatric Patients Receiving 15 mg/kg (Capped to 1200 mg) and Adult Patients Receiving 1200 mg

Study	Treatment	Age	N	Geometric Mean (μg/mL)	Geometric Mean (CV%)	Min	Max
IMmotion151	ATZ	>18 years	426	78.1	65.0	0.03	545.0
IMpower010	ATZ	>18 years	446	87.8	79.3	0.03	491.0
IMpower110	ATZ	>18 years	256	56.4	175.3	0.03	604.0
IMvigor211	ATZ	>18 years	402	63.7	97.9	0.03	297.0
OAK	ATZ	>18 years	534	74.9	66.9	0.03	184.0
IMbrave150	ATZ+BEV	>18 years	294	65.4	109.0	0.03	596.0
IMpower150	ATZ+BEV+CP	>18 years	345	70.1	75.4	0.1	478.0
IMpower150	ATZ+CP	>18 years	354	62.2	120.4	0.03	428.0
iMATRIX	ATZ	<2 years	1	24.1	NA	24.1	24.1
iMATRIX	ATZ	2-6 years	9	53.0	23.4	40.4	78.6
iMATRIX	ATZ	6-12 years	16	63.2	34.2	37.2	101.0
iMATRIX	ATZ	12 - 18 years	35	57.8	51.3	7.92	119.0
iMATRIX	ATZ	>18 years	13	81.6	52.3	29.6	161.0

ATZ =atezolizumab; BEV =bevacizumab; CP = carboplatin; CV% = coefficient of variation; N = number of patients; NA = not applicable.
Source: sBLA 761034/S-047

Additional popPK model-based simulations of 15 mg/kg capped to 1200 mg Q3W were performed based on a large (N=2000) virtual pediatric population build from the National Health and Nutrition Examination Survey database and GO29664 data. Results are shown in Table 3 the geometric mean Cycle 1 C_{min} (5^{th}, 95^{th} percentiles) concentration of atezolizumab

was 44.6 μg/mL (24.3–76.5) in pediatric patients aged 2 to 6 years, and 55.2 μg/mL (28.9–96.6) in pediatric patients aged 6 to 12 years, levels that were >7-fold higher than the target C_{min} concentration of 6 μg/mL. The exposure was also considered to be adequate comparing to that of older pediatric patients (12 to 18 years) with 61.0 μg/mL (32.0–104) and adults (≥18 years) with 75.9 μg/mL (40.3–132) for achieving tumor inhibition. There were no patients with either observed or simulated Cycle 1 C_{min} concentrations below 6 μg/mL. Therefore, a difference in efficacy in patients 2 to 6 years, or 6 to 12 years of age is not expected.
Furthermore, the 15 mg/kg Q3W atezolizumab dosing regimen in pediatric patients has been generally well tolerated with manageable toxicities consistent with the known safety profile of atezolizumab in other approved adult indications (Geoerger et al. 2020).

There were a limited number of responders across patients in GO29664 (4/87) including two pediatric patients aged 2 to <12 years of age. Cycle 1 atezolizumab C_{min} for responding patients was 27.8 μg/mL (17 years old), 40.4 μg/mL (4 years old), 79.6 μg/mL (26 years old), and 88.4 μg/mL (9 years old). All exposures in pediatric patients were above the target of 6 μg/mL needed to achieve 95% receptor occupancy (Deng et al. 2016). Pediatric outcome data in ML39345 was limited to 2 patients (aged 12 and 15 years) with ASPS, while 1 patient aged 15 was a non-responder per RECIST v1.1, the other patient aged 12 achieved a PR to treatment with the 15 mg/kg Q3W regimen of atezolizumab with a DOR of 9.9 months per IRC or 25.9 months per investigator (INV) and was censored.

Table 3: Summary of Model-Simulated Atezolizumab Pharmacokinetic Exposures after 15 mg/kg (up to 1200 mg) Q3W Dosing across Age Groups

	Geometric Mean (%CV) [5th and 95th percentiles]			
	Patients Aged 2 to 6 Years n=1000	**Patients Aged 6 to 12 Years n=1000**	**Patients Aged 12 to 18 Years n=1000**	**Patients Aged ≥18 Years n=500, 100 replicates***
C_{min} Cycle 1 (μg/mL)	44.6 (36.7%) [24.3, 76.5]	55.2 (37.9%) [28.9, 96.6]	61.0 (39.8%) [32.0, 104]	75.9 (38.0%) [40.3, 132]
AUC Cycle 1 (μg*day/mL)	1830 (24.1%) [1240, 2680]	2460 (23.4%) [1670, 3520]	2960 (21.2%) [2080, 4070]	2990 (24.1%) [2020, 4420]
C_{min} steady state (μg/mL)	104 (44.6%) [50.3, 198]	109 (46.6%) [48.1, 213]	106 (51.8%) [45.2, 216]	168 (61.1%) [62.7, 390]
AUC steady state (μg*day/mL)	3600 (32.1%) [2100, 5860]	4160 (31.5%) [2400, 6830]	4510 (31.6%) [2640, 7330]	5750 (40.9%) [2970, 10800]

AUC=area under the plasma concentration-time curve during the dosing duration; C_{min} = minimum concentration; CV=coefficient of variation; n=number of patients; Q3W=every three weeks

Note: Population PK model simulation for patients aged 2 to 18 years were based on NHANES growth chart for age-matched body weights and 70% ADA negative treatment-emergent status.

*Simulated patients aged ≥18 years refer to simulations performed using the adult popPK model with N=500, replicated 100 times.

The Applicant's Position:
Based on the results of the popPK analysis and simulations presented above along with the totality of clinical pharmacology evidence to date, and the favorable benefit-risk of this dosing regimen, 15 mg/kg weight-based dosing regimen, capped at 1200 mg, is supported as an appropriate weight-based dosing regimen in pediatric patients aged 2 and above.

The FDA's Assessment:
FDA agrees with the Applicant's position. Based upon popPK results and simulated atezolizumab exposures after a dosage of 15 mg/kg Q3W, despite a trend for lower median AUC in patients aged 2 to 12 year old, exposure distributions of atezolizumab largely overlapped across age groups with comparable inter-subject variability. The exposure in pediatric patients was within the range of the exposure that demonstrated the efficacy in adults across other tumor types. Refer to Section 17.4.

Therapeutic Individualization

Data:
See Section 6.2.2.1.

The Applicant's Position:
No dose individualization is needed for intrinsic or extrinsic factors other than dose base on body weight (15 mg/kg) capped at 1200 mg.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.1.1. Outstanding Issues

The Applicant's Position:
None

The FDA's Assessment:

FDA agrees with the Applicant's position.

Comprehensive Clinical Pharmacology Review

6.2.2. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.2.3. Clinical Pharmacology Questions

6.2.3.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

A cross comparison of observed atezolizumab Cycle 1 Cmin in pediatric patients aged 2 to 6 years, 6 to 12 years, and 12 to 18 years receiving 15 mg/kg (capped to 1200 mg) and adult patients receiving 1200 mg further confirmed that observed pediatric exposures in Study GO29664 were comparable with the distributions seen in adults. When compared to observed adult data it was shown that simulated pediatric subjects across both age groups achieved exposures within the observed exposure range shown to be efficacious in adult Phase 3 trials.

The Applicant's Position:
Yes, the data provides supportive evidence of effectiveness of the proposed regimen.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.1 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:
See Section **Error! Reference source not found.**.

The FDA's Assessment:
FDA agrees with the Applicant's position. Given that no PK data are available from patients with ASPS, the similarity in PK between other tumor types and the lack of significant E-R relationships for efficacy in adults, the proposed dosing regimen of 15 mg/kg, (capped at 1200 mg) Q3W is acceptable for pediatric patients aged 2 years of age and older with ASPS.

6.3.2.2 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:
See Section **Error! Reference source not found.**.

The Applicant's Position:
No intrinsic factors have been identified. Proposed dose regimen in pediatric patients aged 2

years and above is body weight based (15 mg/kg capped at 1200 mg) which provides comparable exposure across pediatric populations to adult exposure at 1200 mg.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.3 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:
Atezolizumab is given by IV infusion thus there are no anticipated absorption issues regarding food or beverage effects. No drug-drug interactions have been identified. Atezolizumab is not metabolized via CYP enzymes but rather is eliminated via catabolysis.

The Applicant's Position:
Not relevant for monoclonal antibody drug given by IV infusion.

The FDA's Assessment:
FDA agrees with the Applicant's position.

X _____ X

Christy John
Primary Reviewer

Hong Zhao
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

APPEARS THIS WAY ON ORIGINAL

Table 4 Listing of Clinical Trials included with this sBLA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Primary Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
ML39345	NCT03141684	Open-label, single arm, Phase II study	**Atezolizumab Monotherapy Arm** Atezolizumab Adults ≥18 yrs Atezolizumab 1200 mg IV q3w Atezolizumab Pediatrics ≥2 yrs Atezolizumab 15mg/kg (1200mg max) IV q3w	ORR by IRC	Treatment Duration: 21-day cycles Follow Up: 30 days after the last dose or until the patient enrolls on another study or death, whichever comes first	50	Patients with histologically or cytologically confirmed ASPS that was not curable by surgery	16 centers in 1 country (US)
		Studies to Support Safety and PK						
GO29664	NCT02541604	Early phase, multicenter, open-label, single-arm study	Patients <18 years Atezolizumab (IV), 15 mg/kg (1200 mg max) Patients ≥18 yrs Atezolizumab 1200 mg IV q3w	ORR, CBRR, PFS	Until loss of clinical benefit	90	Pediatric or young adult patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment had proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options existed	20 centers in 10 countries

ASPS= alveolar soft part sarcoma; CBRR=clinical benefit rate; IV=intravenous; ORR= overall response rate; PD-L1= programmed death-ligand 1; PFS= progression free survival; pk=pharmacokinetic; q3w=every 3 weeks

The Applicant's Position:
Applicable data from Study GO29664 were used only to provide safety and PK data to support the appropriate dosing of atezolizumab in the pediatric patient population.

The FDA's Assessment:
FDA agrees with the Applicant's summary of clinical studies relevant to the application. For this sBLA, FDA's analysis of efficacy was based on data from Study ML39345 that included 47 adults patients and 2 pediatric patients. Safety was assessed from the results of Study ML39345 and Study GO29664 which enrolled 90 pediatric patients with various tumor types. FDA agrees with the Applicant that data from Study GO29664 were the basis for characterizing atezolizumab pharmacokinetics in pediatric patients.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study ML39345

Trial Design

The Applicant's Description:

Basic Study Design: Study ML39345 is an open-label, single arm, Phase II study of atezolizumab in patients with advanced ASPS in adult subjects ≥18 years of age and in pediatric/adolescent subjects ≥2 years of age. The study design is depicted in Table 5. Since the protocol amendment dated 07 January 2021, this study is also evaluating the combination of atezolizumab plus bevacizumab in adult subjects with advanced ASPS that progressed (definitive clinical progression or immune confirmed progression of disease) on ML39345 atezolizumab monotherapy. Combination treatment of atezolizumab plus bevacizumab was not analyzed for this submission as the sBLA is to support atezolizumab monotherapy. In addition, 4 patients were on combination treatment at CCOD, which is not sufficient to assess the benefit/risk of the combination of atezolizumab plus bevacizumab.

Although the protocol defined the adult cutoff as 18 years, the efficacy data were analyzed using the age cutoff of 17 years as per 21 CFR 201.57.

Table 5 Study design for Study ML39345

Study No (Phase)	Population	Study Design	Number of Patients	Dose, Route, and Regimen	CCOD	Median observation time
ML39345	Patients with histologically or cytologically confirmed ASPS that was not curable by surgery.	Open-label, single arm, phase II study	Enrolled: 50 patients Treated: 49 patients	**Atezolizumab Monotherapy Arm** Atezolizumab Adults ≥18 yrs Atezolizumab 1200 mg IV q3w Atezolizumab Pediatrics ≥2 yrs Atezolizumab 15mg/kg (1200mg max) IV q3w	01 Sep 2021	9.9 months (range: 1 – 43 months).

ASPS= alveolar soft part sarcoma; CCOD= clinical cut-off date; IV=intravenous

Trial Location: Patients were enrolled from 18 investigators across 16 centers in the USA.
Choice of Control Group: This was a single arm, monotherapy study.

Diagnostic Criteria Key inclusion/exclusion criteria: Patients with histologically or cytologically confirmed ASPS that was not curable by surgery were enrolled in Study ML39345. Key eligibility

criteria are provided below.

Key Inclusion criteria:

- Histologically or cytologically confirmed ASPS with measurable disease that was not curable by surgery.
- Patients had to be ≥2 years of age at the national cancer institute (NCI) site and ≥14 years of age at other sites.
- Eastern Cooperative Oncology Group performance status ≤2 (Karnofsky or Lansky ≥70%).
- Life expectancy of more than 3 months.
- Normal marrow and organ function.
- Agreement to use adequate contraception prior to and during the study and for 5 months after the last dose (as indicated).

Key Exclusion criteria:

- Any prior therapy had to be completed ≥4 weeks or, if known, ≥5 half-lives of the prior agent (whichever is shorter).
- Prior treatment with ant-PD-1, or anti-PD-L1 antibodies or pathway targeting agents.
  - Patients who received prior therapy with anti-CTLA-4 may have enrolled if a minimum of 12 weeks from first dose and >6 weeks from last dose had occurred and there was no history of severe immune-related AEs from anti-CTLA-4.
- Treatment with systemic immunosuppressive medications within 2 weeks prior to Cycle 1, Day 1.
- Patients who took bisphosphonate therapy for symptomatic hypercalcemia.
- Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases were excluded, with the following exceptions:
  - Patients with asymptomatic untreated CNS disease may have enrolled, if evaluable disease was present outside of the CNS, there were no metastases to brain stem, midbrain, pons, medulla, or cerebellum, no history of intracranial or spinal cord hemorrhage, no ongoing requirement for dexamethasone for CNS disease and no neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1
  - Patients with asymptomatic treated CNS metastases may have enrolled if there was radiographic demonstration of improvement upon completion of CNS directed therapy and no evidence of interim progression between the completion of this therapy and radiographic screening for the current study, no stereotactic or whole-brain radiation within 28 days prior to Cycle 1, Day 1 and screening CNS radiographic study ≥4 weeks from completion of radiotherapy and ≥2 weeks from discontinuation of corticosteroids

Dose selection: Patients received atezolizumab at a fixed dose of 1200 mg IV for adults (≥18 years of age) and 15 mg/kg for pediatric patients (≥ 2 years of age) up to 1200 mg once every 21 days, in 21-day cycles.

The fixed dose of atezolizumab 1200 Q3W is an approved dosing regimen in adults (Tecentriq USPI).

The 15 mg/kg Q3W regimen of atezolizumab is considered equivalent to the 1200 mg flat dose for a patient with a typical body weight of 80 kg, which is an approved regimen in several adult indications (Chiang et al. 2020).

Clinical pharmacology data were not available for pediatric patients with ASPS receiving atezolizumab in Study ML39345. As such, data from the early phase pediatric Study GO29664 were used to support the pediatric dosing rationale. In Study GO29664, the 15 mg/kg Q3W regimen of atezolizumab (capped to 1200 mg) was chosen for pediatric patients due to expected similar associated exposure to that in adults. See Section **Error! Reference source not found.** for more details.

Study treatments: Atezolizumab was administered as an IV infusion over 60 minutes (±15 minutes). If the first infusion was tolerated without infusion-associated adverse events (AE), all subsequent infusions were to be delivered over 30 minutes (±10 minutes). No premedication was indicated for administration of Cycle 1 of atezolizumab. Patients who experienced an infusion-related reaction with Cycle 1 of atezolizumab may have received premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Assignment to treatment: Patients received atezolizumab monotherapy once enrolled.

Blinding: This was an open-label study, however the primary endpoint was assessed by an Independent Review Committee (IRC).

Dose Modification/Dose Discontinuation: There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced

Administrative Structure: An Independent Review Committee (IRC) was established to provide an independent assessment of tumor response based on the RECIST 1.1 guideline for each enrolled patient with minimum imaging/clinical data necessary for independent review. Members of the IRC were external to the Sponsor.

Procedures and Schedule:

Patients received atezolizumab at a fixed dose of 1200 mg IV for adults (≥18 years of age) and 15 mg/kg (1200 mg max) for pediatric patients (≥ 2 years) once every 21 days, in 21-day cycles.

Tumor biopsies (mandatory at all sites after February 2019) were collected from adult patients (≥18 years of age) at baseline and prior to Cycle 3 Day 1 (±3 days), or at any point where there was clinical evidence that the patient was responding to drug, to evaluate any changes in either tumor or blood targets of immune checkpoint blockade.

The study was to be halted unless there was at least one response in the initial 9 patients accrued to the monotherapy arm. At the time of protocol amendment dated 14 November 2017, a partial response was observed in the initial 9 patients, therefore the study continued to enroll to meet accrual goals.

Patients on treatment for >2 years were given the option of going on a treatment holiday for up to 2 years.

The monotherapy arm remains open to pediatric patients for as long as that arm is accruing.

Concurrent Medications: A summary of the drugs to be avoided is below:

- Chronic daily treatment with a non-steroidal anti-inflammatory drug, clopidogrel, dypiridamole, or aspirin therapy >81 mg/day.
- Traditional herbal or homeopathic or natural medicines should be limited and used at the discretion of the investigator
- Ingredients for such medicines have not been fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity.
- Immunostimulatory agents, including but not limited to interferon (IFN)-α, IFN-γ, anti-TNF-α, or IL-2 (aldesleukin) (prohibited prior to and during the study and for 10 weeks after the last dose of atezolizumab). These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.
- Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab.
- Live vaccines and live, attenuated vaccines (prohibited during the study and for 100 days after the last dose of study drug).
- Initiation of granulocyte colony-stimulating factors (e.g., filgrastim and biosimilar products, sargramostim, and/or pegfilgrastim) should be discussed with the Medical Monitor.

Treatment Compliance: Trained study personnel administered the scheduled infusions of atezolizumab. Doses of atezolizumab received were recorded on a Case Report Form. Data regarding dose modifications and cycle delays were also collected.

Subject completion, discontinuation, or withdrawal: The specific criteria and procedures for early discontinuation from study treatment(s) or withdrawal from the study are described

below:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

Patients who show evidence of clinical benefit may be permitted to continue study treatment after disease progression, if they meet the criteria outlined below.

- Evidence of clinical benefit as assessed by the investigator and agreed upon by the Medical Monitor
- Absence of symptoms or signs (including worsening laboratory values) indicating unequivocal progression of disease
- No significant decline in performance status that can be attributed to disease progression
- Absence of tumor progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions

The FDA's Assessment:

FDA agrees with the Applicant's summary of Study ML39345.

Study Endpoints

The Applicant's Description:

Primary Efficacy Endpoint

- To evaluate efficacy of atezolizumab monotherapy in patients with advanced Alveolar Soft Part Sarcoma (ASPS) in adult subjects ≥17 years and in pediatric/adolescent subjects ≥ 2 years as response rate using RECIST v 1.1: Objective Response Rate (ORR) by IRC

Secondary Efficacy Endpoints

- To evaluate efficacy of atezolizumab monotherapy in patients with ASPS in adult subjects ≥17 years and in pediatric/adolescent subjects ≥2 years as response rate using RECIST v 1.1: ORR by investigator
- To evaluate duration of response (DOR) to atezolizumab monotherapy using RECIST v 1.1 and/or change in clinical symptoms: DOR by IRC/investigator
- To evaluate progression-free survival (PFS) time for patients receiving atezolizumab monotherapy as determined by investigator using RECIST v 1.1: PFS by IRC/investigator

The FDA's Assessment:

FDA agrees with the Applicant's summary of the primary and secondary efficacy endpoints.

DOR is considered supportive of the ORR endpoint. These endpoints are standard endpoints used to assess efficacy and also to evaluate tumor size (i.e., response was per RECIST v1.1 criteria). However, FDA notes that time-to-event endpoints such as PFS are not interpretable in single arm studies.

Statistical Analysis Plan and Amendments

The Applicant's Description:
All changes in the planned analyses for the study are described below.

- Among the protocol defined objectives/endpoints, the endpoints related to atezolizumab and bevacizumab combination therapy and biomarkers, as well as exploratory objectives were not analyzed for the sBLA for atezolizumab monotherapy.
- The protocol defined adult and pediatric/adolescent age cutoff as 18 years old in the primary objectives. As per 21 CFR 201.57, efficacy data were summarized using age cutoff of 17 years (i.e., younger than 17 years old as pediatrics).
- IRC was applied after the meeting with U.S. Food and Drug Administration on 15 October 2020. The primary endpoint was updated as ORR by IRC per FDA request and ORR by investigator was moved to the secondary endpoint. The summaries of DOR and PFS by IRC were also provided in addition to the investigator. The efficacy analysis was done for efficacy evaluable population, which was defined as patients who received at least one proposed recommended dose of atezolizumab in the monotherapy arm.

Analysis Populations: There were three populations:

- Enrolled: All enrolled patients in the monotherapy arm, whether or not atezolizumab was received.
- Safety: Patients who received any amount of atezolizumab in the monotherapy arm.
- Efficacy evaluable: Patients who received at least one proposed recommended dose of atezolizumab in the monotherapy arm

Methods for Handling Missing Data: No imputations will be made in case of missing data.

Statistical Methodology: The primary efficacy endpoint is objective response rate (ORR, confirmation required), defined as the proportion of patients with a confirmed objective response, either complete response (CR) or partial response (PR) as determined by the IRC, observed on two consecutive assessments 28 days apart with the use of RECIST v1.1, based on IRC assessment. Patients without any post-baseline tumor assessments will be considered non-responders. An estimate of ORR and its 95% confidence interval (CI) will be calculated for each treatment arm using the Clopper-Pearson method (Clopper and Pearson 1934). In order to characterize responders, descriptive statistics (e.g., median, range) will be provided for time from enrollment to response for patients with an objective response.

The FDA's Assessment:
FDA agrees with the Applicant's summary of changes from planned analysis per protocol, analysis population and the primary efficacy endpoint analysis method. The secondary endpoint of DOR provided supportive evidence of the efficacy of atezolizumab. DOR was analyzed descriptively using the Kaplan-Meier method; median DOR along with the corresponding 2-sided 95% CI were estimated. In addition, the response durations observed up to a specific time-point (e.g., 3, 6, 9 , 12, 24 and 36 months) were calculated.

The secondary endpoint of ORR by investigator was analyzed using the same analysis method used for the primary endpoint of ORR by IRC. The concordance between ORR per IRC and investigator were also reported.

Sample Size assumptions:
A Simon's two-stage design was used to calculate an initial sample size of 24 evaluable patients. The null hypothesis of an ORR of 5% was tested against a one-sided alternative of at least an ORR of 24.5%. In the first stage, if at least one response was observed among the initial 9 patients, the study was planned to continue and enroll up to 24 evaluable patients. If at least 3 responses (at least 12.5%) were observed among the initial 24 evaluable patients, this regimen would be considered as efficacious. This design yields at least 90% power to detect a true response rate of at least 25%. Twenty-six patients was planned to be accrued to obtain 24 evaluable patients.

Based on protocol amendment Serial 0024 submitted to FDA on February 8, 2019 and amendment serial 0052 submitted on January 7, 2021:, the accrual ceiling was raised to 53 patients. (Refer to subsection Protocol Amendments for more details on the protocol amendments).

Protocol Amendments
The protocol for this study was approved on 17 November 2016 and was subsequently amended during the study conduct. Seventeen protocol amendments were submitted to the Ethics Committees of the investigational sites and were implemented. A brief summary of the rationale for the significant changes to the protocols are described below. Detailed information is provided below.

- Protocol Amendment Serial 004. Version date; 30 March 2017:
    - Clarifications were made to the study calendar and consent process prior to the study opening at participating sites.
    - Changes were made to the protocol based on CTEP recommendations from initial protocol approval and the new atezolizumab template.

- Protocol Amendment Serial 005. Version date; 26 May 2017:

- Revised Comprehensive Adverse Events and Potential Risks list was inserted.

- Protocol Amendment Serial 0010. Version date; 27 June 2017:
  - CTEP recommendations were addressed.

- Protocol Amendment Serial 0011. Version date; 23 August 2017:
  - Changes to the schedule for labs were made, as weekly tests of thyroid-stimulating hormone (TSH) during Cycles 1 and 2 were imposing a financial burden on participating sites.
  - Clarifications to the timing for screening and baseline evaluations and the process for PD sample collection was updated.

- Protocol Amendment Serial 0012. Version date; 14 November 2017:
  - Common Terminology Criteria for Adverse Events (CTCAE) was updated from version 4.0 to version 5.0.

- Protocol Amendment Serial 0013. Version date; 26 February 2018:
  - Update was made to make research biopsies mandatory at the NCI Clinical Center and optional at external participating sites.

- Protocol Amendment Serial 0023. Version date; 19 September 2018:
  - Revised CAEPR was inserted.

- Protocol Amendment Serial 0024. Version date; 08 February 2019:
  - Eligibility criteria was updated

- Protocol Amendment Serial 0031. Version date; 08 July 2019:
  - Amendment was made to primarily allow a treatment holiday for patients on study treatment for over 2 years.

- Protocol Amendment Serial 0039. Version date; 14 January 2020:
  - Amendment was made to correct the criteria for patients to resume treatment after taking a treatment holiday, such that patients on holiday did not need to have measurable disease to resume treatment. Given the slow-growing nature of this disease, the maximum duration of the treatment holiday was extended from 1 to 2 years, provided scans continued to show no sign of disease progression.

- Protocol Amendment Serial 0041. Version date; 19 March 2020:
  - Amendment was made to make the study an Early Drug Development Opportunity Program study. This was an effort to increase the number of eligible

participating sites in order to facilitate the transfer of some enrolled patients to a local site for treatment during the COVID-19 pandemic.

- Protocol Amendment Serial 0044. Version date; 28 July 2020:
    - Amendment was made to remove the exclusion criterion that prohibits the use of a RANKL inhibitor on this study.

- Protocol Amendment Serial 0052. Version date; 07 January 2021:
    - Amendment was made to add a treatment arm combining the VEGF inhibitor bevacizumab with atezolizumab for adult patients who have progressed on ML39345 atezolizumab monotherapy.
    - New correlative studies were incorporated to analyze the genomic and immune profiles of tumors expressing the distinct Type 1 and Type 2 ASPL-TFE3 chimeric fusion proteins that are characteristic of ASPS and implicated its pathogenesis.

- Protocol Amendment Serial 0053. Version date; 11 March 2021:
    - Deleted language referring to the return of incidental genetic findings, per CTEP's policy that incidental findings will not be returned for research tests not conducted in a Clinical Laboratory Improvement Amendments setting.

- Protocol Amendment Serial 0054. Version date; 06 April 2021:
    - Amendment was made to primarily specify lab monitoring evaluations, revise the guidelines for vital sign monitoring after atezolizumab infusion, and clarify the clinical specimen collection and shipping instructions.

- Protocol Amendment Serial 0055. Version date; 17 May 2021:
    - Revised CAEPR was inserted.

- Protocol Amendment Serial 0060. Version date; 13 July 2021:
    - Amendment was made to the protocol based on CTEP recommendations including to alignment to the NCI protocol template, updated exclusion and inclusion criteria, added adverse events of special interest (AESI) information for atezolizumab and bevacizumab, updated information related to immune-related adverse events associated with atezolizumab, added guidelines for managing bevacizumab-specific AEs, provided more specific guidance on immune-related AEs, added new information on management of infusion-related reactions, hemophagocytic lymphohistiocytosis, and macrophage activation syndrome, and increased the window to 21 days for electrocardiogram cardiac monitoring.

The FDA's Assessment:

In general, FDA agrees with Applicant's summary of protocol amendments. FDA notes that the

stated amendments by the Applicant for Protocol Amendment Serial 0012 and protocol Amendment Serial 0013 are incorrect. CTCAE was updated from version 4.0 to version 5.0 in amendment 0013, not 0012, and requiring mandatory biopsies at the NCI site occurred under amendment 0012, not 0013. Additional relevant clinical and statistical comments are listed below.

- Protocol Amendment Serial 0012. Version date; 14 November 2017
  - The schedule for confirmatory scans after observing a response was corrected.
  - An update regarding the number of responses observed in the initial 9 patients (Stage-1 of Simon's Two-Stage design) was added to the protocol that allowed to initiate Stage-2 of the study
  - Added text referring to the increase in the sample size (additional 9 patients) to obtain the required number of biopsies.

- Protocol Amendment Serial 0024. Version date; 08 February 2019
  - The Applicant states that protocol amendment serial 0024 updated the eligibility criteria. More specifically, this amendment decreased the minimum age of enrollment from ≥18 years to ≥14 years at sties outside of the NCI and decreased the minimum age for eligibility at the NCI site from ≥6 years to ≥2 years of age.
  - The accrual ceiling was increased by 20 patients (initial accrual ceiling 26; new accrual ceiling: 46) to allow for collection of additional research biopsies. These additional patients, if ≥18 years of age, were required to give research biopsies to support the collection of pharmacodynamic endpoints.

- Protocol Amendment Serial 0052. Version date; 07 January 2021:
  - Additional seven patients were added to the sample size. The accrual ceiling for the monotherapy arm was increased from 26 patients to 53 patients to successfully obtain biopsies from 15 adult participants, and to allow patient slots for the enrollment of pediatric participants. In addition, a maximum of 9 patients will be enrolled to the combination arm (all of whom were previously enrolled to the monotherapy arm). Thus, the anticipated maximum combined sample size is 62, comprised of a maximum of 53 unique patients.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

NCI-CTEP conducted audits at 16 investigator sites across the United States. No critical audit findings were identified during the investigator audit. For all audit findings, appropriate corrective and preventive actions were undertaken.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. A statement was provided that the trial was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct. There is no evidence that compliance with GCP was violated during conduct of Study ML39345.

Financial Disclosure

The Applicant's Position:
There are no investigators with positive disclosable interests from study P10005.

The FDA's Assessment:
The Applicant's financial disclosure information was reviewed by FDA. FDA agrees there are no financial interests to disclose. Additional information is provided in Section 17.2.

Patient Disposition

The Applicant's Position:
Patients were enrolled from 18 investigators across 16 centers in the United States. The majority of centers each recruited between 1–2 patients; the 5 highest enrolling sites each recruited between 4–13 patients.

Overall, 50 patients were enrolled in the study. One enrolled adult patient did not receive treatment prior to CCOD and was not included in the efficacy- and safety-evaluable populations. Forty-seven adult (≥17 years) and 2 pediatric patients (2 to <17 years of age) were included in the efficacy- and safety-evaluable population.

As of CCOD, 33 patients were discontinued from the study. All of the patients that discontinued were adults and were discontinued for non-safety reasons, with most patients discontinuing

due to disease progression (28.0% [14 patients]). Patients with disease progression aged ≥18 years were eligible to crossover to combination therapy of atezolizumab with bevacizumab. Four patients (8.0%) crossed over to combination therapy of atezolizumab with bevacizumab, and although they continue in the study, they were treated as discontinued for the analyses done for this filing. Three patients discontinued due to 'other' reasons including one patient that was not dosed.

As of CCOD, 17 patients (34.0%) were continuing study treatment.

The FDA's Assessment:
FDA agrees with the Applicant's summary of patient enrollment and patient disposition as of the CCOD.

Protocol Violations/Deviations

Data:

Table 6 Major and COVID-19 Related Protocol Deviations (Enrolled Patients)

Deviation Category Types of Deviation	**Atezolizumab** **N=50** **n (%)**
Total number of patients with at least one deviation	**27 (54.0)**
Overall total number of deviations	**62**
Adverse event details	
Total number of patients with at least one deviation	9 (18.0)
Total number of events	9
Failure to report or delayed reporting of an adverse event that would require filing an expedited adverse event report or reporting to the group	9 (18.0)
COVID-19 study interrupt	
Total number of patients with at least one deviation	10 (20.0)
Total number of events	20
Cycle treatment given early or late	6 (12.0)
Late or missed study lab	1 (2.0)
Missed study visit	2 (4.0)
Phone or virtual visit	1 (2.0)
General data management quality details	
Total number of patients with at least one deviation	8 (16.0)
Total number of events	20
Delinquent data submission [a]	6 (12.0)
Errors in submitted data	6 (12.0)
Frequent data inaccuracies	2 (4.0)
Other deficiencies	2 (4.0)
Protocol-specified diagnostic studies including baseline assessments not done, not reported or not documented	1 (2.0)

Deviation Category Types of Deviation	**Atezolizumab** **N=50** **n (%)**
Protocol-specified research/advanced imaging studies not done or submitted appropriately	1 (2.0)
Informed consent details	
Total number of patients with at least one deviation	2 (4.0)
Total number of events	2
Consent form used was not the most current irb-approved version at the time of patient registration	1 (2.0)
Other deficiencies	1 (2.0)
Treatment details	
Total number of patients with at least one deviation	8 (16.0)
Total number of events	11
Dose deviations, modifications, or incorrect calculations (error greater than +/- 10%)	1 (2.0)
Other deficiencies	1 (2.0)
Timing and sequencing of treatment/intervention not per protocol	1 (2.0)
Treatment/intervention incorrect or not administered correctly, incorrectly calculated, or not adequately documented	5 (10.0%)
Treatment/intervention incorrect, not administered correctly, or not adequately documented	1 (2.0%)

[a] More than 6 months delinquent is considered a major deficiency; a 3-6 month delinquency is considered a lesser deficiency.

Notes:

A patient will be only counted once if received more than one deviation of the same type.
A patient will be counted more than once if received more than one type of deviation.
Clinical Data Cutoff Date: 1 September 2021.

Source: Study ML39345.

The Applicant's Position:

The majority of major protocol deviation events were COVID-19 study interrupt (20.0% [10 patients]) and adverse event (AE) details (18.0% [9 patients]). These protocol deviations did not have an impact overall quality of the study or the outcome of the study.

Major protocol deviations related to the COVID-19 pandemic did not have an impact on the overall quality of the study or the outcome of the study.

The FDA's Assessment:

FDA agrees that the identified protocol deviations did not significantly impact the interpretation of the study results. Furthermore, the overall study results were supported/verified by independent central review of imaging.

Table of Demographic Characteristics

Data:

Table 7 Demographic and Baseline Characteristics (Safety-Evaluable Patients)

Demographic Parameters	Atezolizumab N=49 n (%)
Sex	
Male	24 (49.0)
Female	25 (51.0)
Age (years)	
Mean (SD)	32.1 (11.3)
Median	31.0
Min, max	12, 70
Age Group	
< 65 years	48 (98.0)
≥ 65 years	1 (2.0)
Age Group- Pediatrics	
2 to < 17 years	2 (4.1)
≥ 17 years	47 (95.9)
Race	
White	27 (55.1)
Black or African American	14 (28.6)
Asian	5 (10.2)
Unknown	2 (4.1)
Not reported	1 (2.0)
Ethnicity	
Hispanic or Latino	5 (10.2)
Not Hispanic or Latino	42 (85.7)
Not stated	2 (4.1)
Weight (kg) at Baseline	
Mean (SD)	75.61 (26.48)
Median	73.0
Min, max	29.5, 190.7
Body Mass Index (kg/m^2) at Baseline	
< 25	24 (49.0)
25 to < 30	18 (36.7)
≥ 30	7 (14.3)
Baseline ECOG Performance Status	
0	26 (53.1)
1	22 (44.9)
2	1 (2.0)

ECOG = Eastern Cooperative Oncology Group.

Notes:

For pediatric patients, Karnofsky is recalculated to ECOG Performance Status.

Clinical Data Cutoff Date: 1 September 2021.

Source: Study ML39345.

The Applicant's Position:
Both the efficacy- and safety-evaluable populations were the same. The median age of patients was 31.0 (range: 12 – 70 years) with a mean age of 32.1 years. Overall, 95.9% of patients were adult (≥17 years [47 patients]) and 4.1% were pediatric (2 to <17 years [2 patients]). Of the adult patients, 2.0% were elderly (≥65 years, [1 patient]) and the pediatric patients were both adolescents (≥ 12 years). Patients were evenly split between males (49.0% [24 patients]) and females (51.0% [25 patients]). The majority of the patients were White (55.1% [27 patients]) or Black or African American (28.6% [14 patients]), with 10.2% (5 patients) being Asian.

The FDA's Assessment:
FDA agrees with Applicant's summary of patient's baseline demographic characteristics. The two pediatric patients treated on Study ML39345 were 12 and 15 years of age. Given the rarity of ASPS, there is limited published data on the incidence of ASPS by race. However, the racial breakdown of patients enrolled on Study ML39345 appears consistent with the data from the poster publication (Sankaran et al. 2021).

Table 8 Racial Breakdown of ASPS

	Sankaran Poster N=320	**ML39345 N=49**
White	58%	55%
Black/African American	24%	29%
Asian/Pacific Islander	15%	10%
American Indian/Alaskan Native	2%	0
Unknown	1.6%	4%

Source: Reviewer generated table from Sankaran poster and CSR.

During review of the proposed labeling, FDA asked the Applicant if there was any information for the two patients classified as unknown race. The Applicant stated that that information was not available.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:
All patients (100% [49 patients]) had prior surgery for ASPS. The majority of patients (55.1% [27 patients]) received at least one prior line of treatment for ASPS, with 53.1% (26 patients) receiving chemotherapy and 55.1% (27 patients) receiving radiotherapy.

At initial diagnosis, the majority of patients (97.8% [44 patients]) were at Stage IV and 2.2% of patients (1 patient) was at Stage IVA.

Per INV assessment at baseline, the median number of all lesions per patient was 4.0 (range: 1 – 9) and the median number of target lesions was 3.0 (range: 1 – 5). For all lesions at baseline, the majority of patients had lesions in the lung (95.9% [47 patients]), followed by bone (16.3% [8 patients]), lymph node (16.3% [8 patients]), liver (14.3% [7 patients]) and muscle (12.2% [6 patients]). This was similar to the location of target lesions at baseline as the majority of patients had target lesions in the lung (89.8% [44 patients]) followed by lymph node (14.3% [7 patients]), muscle (12.2% [6 patients]), liver (10.2% [5 patients]), and soft tissue (10.2 [5 patients]).

The FDA's Assessment:
FDA agrees with Applicant's summary of other baseline patient characteristics. During the review of the proposed label, FDA requested that the Applicant define the difference between Stage IV and Stage IVA ASPS. The Applicant stated that Stage IVA was a subset of Stage IV, but is no longer commonly used as a staging criterion in current guidelines. Therefore, all patients had Stage IV disease.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:
Treatment Compliance: A total of 49 patients in the study received at least one dose of atezolizumab. The median cumulative dose was 13,200.00 mg (range: 2400.0 – 69,600.0 mg) and median treatment duration was 8.9 months (range: 1 – 40 months).

Concomitant Medication: After study start, the most frequently reported classes of concomitant medications were ophthalmologicals (69.4% [34 patients]), analgesics (59.2% [29 patients]), stomatological preparations (46.9% [23 patients]), anti-acne preparations (44.9% [22 patients]), antibacterials for systemic use (44.9% [22 patients]), antidiarrheals, intestinal anti-inflammatory/anti-infective agents (42.9% [21 patients]), and antiemetics and antinauseants (42.9% [21 patients]).

The FDA's Assessment:
FDA agrees with the Applicant's summary of treatment compliance and concomitant medications.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 9 Best Confirmed Overall Response by Independent Review Committee by RECIST1.1 (Efficacy Evaluable Patients)

	Atezolizumab	
	Age ≥ 17 years N=47	**All Patients N=49**
Responders 95% CI	11 (23.4%) (12.30, 38.03)	12 (24.5%) (13.34, 38.87)
Complete Response (CR) 95% CI	0 (0.00, 7.55)	0 (0.00, 7.25)
Partial Response (PR) 95% CI	11 (23.4%) (12.30, 38.03)	12 (24.5%) (13.34, 38.87)
Stable Disease (SD) 95% CI	23 (48.9%) (34.08, 63.94)	24 (49.0%) (34.42, 63.66)
Progressive Disease (PD) 95% CI	10 (21.3%) (10.70, 35.66)	10 (20.4%) (10.24, 34.34)
Not Evaluable (NE) Missing	3 (6.4%) 0	3 (6.1%) 0

Notes:
Patients were classified as missing or not evaluable if no post-baseline response assessments were available or all post-baseline response baseline assessments were unevaluable.
Responders include patients with confirmed best overall response of Complete Response and Partial Response.
The 95% CI for rates were constructed using the Clopper Pearson method.
The pediatric patients are not summarized due to the small sample size but refer to the efficacy listings.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

The Applicant's Position:

Primary Endpoint: The primary endpoint of ORR by IRC assessment demonstrated clinically meaningful responses in ASPS adult and pediatric patients treated with atezolizumab.

The FDA's Assessment:

FDA agrees with Applicant's summary of ORR by IRC results; ORR by IRC was 24.49% (95% CI: 13.34, 38.87) in the overall population. Of note, there was one partial response observed among the 2 pediatric patients (age <17 years). As of the CCOD of September 1 2021, the response duration for this responding patient lasted for approximately 10 months, at which time the patient's DOR data was censored due to ongoing response. The other pediatric patient had disease progression.

ORR Subgroup Analysis:

The ORR results for all the subgroups were not reported by the FDA review team due to the small sample size of the subgroups. The table below includes the ORR subgroup results for a few selected subgroups. In general, it appears that the ORR was consistent across these

subgroups. Note that all subgroup analyses were considered exploratory. Subgroup results should be interpreted with caution, particularly for the subgroups with very few patients,.

Table 10 ORR Subgroup Results for Selected Subgroups

Subgroup	#Responders/N	ORR (95% exact CI)
Sex		
Male	6/24	25% (10, 47)
Female	6/25	24% (9, 45)
Race		
White	9/27	33% (17, 54)
Asian	0/ 5	-
Black/African American	3/14	21% (5, 51)
Unknown/Not Reported	0/ 3	-
ECOG		
0	8/26	31% (14, 52)
1	4/22	18% (5, 40)
2	0/1	-

+: censored
Source: FDA Analysis; CCOD September 1, 2021

Data Quality and Integrity

The Applicant's Position:

There were no data quality or integrity issues identified in Study ML39345.

The FDA's Assessment:

No issues were identified that could potentially impact data integrity or data quality.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 11 Summary of Efficacy Endpoints

Parameter	Adults (Age ≥ 17)	All Patients
Secondary Endpoint: Best Confirmed ORR by INV		
Efficacy-Evaluable Patients		
Number of evaluable patients (N)	47	49
ORR, N (%)	16 (34.0%)	17 (34.7%)
95% CI	(20.86, 49.31)	(21.67, 49.64)
Median time to confirmed response, months	3.8	3.6
95% CI	(3.4, 5.1)	(3.4, 5.1)
Secondary Endpoint: Duration of Confirmed Response by IRC		
Efficacy-Evaluable Patients		
Number of evaluable patients (N)	47	49
Number of responders	11	12

Parameter	Adults (Age ≥ 17)	All Patients
Number (%) of responders with event	3 (27.3%)	3 (25.0%)
Median, month	NE	NE
95% CI	(9.2, NE)	(17.0, NE)
Event free (%) at one year	75.00	77.78
95% CI	(44.99, 100.00)	(50.62, 100.00)
Secondary Endpoint: Duration of Confirmed Response by INV		
Efficacy-Evaluable Patients		
Number of patients (N)	47	49
Number of responders	16	17
Number (%) of responders with event	5 (31.3%)	5 (29.4%)
Median, months	35.3	35.3
95% CI	(19.2, NE)	(19.2, NE)
Event free (%) at one year	100.00	100.00
95% CI	(100.00, 100.00)	(100.00, 100.00)
Secondary Endpoint: PFS by IRC		
Efficacy-Evaluable Patients		
Number of patients (N)	47	49
Number (%) of patients with event	31 (66.0%)	31 (63.3%)
Median, months	6.4	7.2
95% CI	(3.6, 9.9)	(3.7, 9.9)
Secondary Endpoint: PFS by INV		
Efficacy-Evaluable Patients		
Number of patients (N)	47	49
Number (%) of patients with event	24 (51.1%)	24 (49.0%)
Median, months	19.9	19.9
95% CI	(7.8, 28.3)	(7.8, 40.0)

CI=confidence interval; INV=investigator; IRC= Independent Review Committee; NE=not evaluable; ORR=Objective Response Rate; PFS=progression-free survival

Note: The pediatric patients are not summarized in this table due to the small sample size

The Applicant's Position:

The secondary endpoint of ORR by INV assessment demonstrated clinically meaningful responses in ASPS adult and pediatric patients treated with atezolizumab. The secondary IRC-assessed endpoint of median DOR was not reached, but a prolonged DOR was observed in INV-assessed responders. The IRC-assessed median PFS was numerically shorter than INV-assessed median PFS.

The FDA's Assessment:

FDA agrees with the Applicant's summary of secondary endpoint results. Although the Applicant provided PFS results, the results of this analysis are not interpretable in a single-arm study and are therefore not included in product labeling.

Concordance between IRC-assessed and INV-assessed ORR:

The ORR by IRC was 24.5% (95% CI: 13, 39)with no complete responses. ORR by Investigator

was 34.7% (95% CI: 22, 50) with one complete response. Due to the differences noted, FDA performed an additional analysis to assess the difference in assessments. The table below provides a cross-tabulation of best overall response by IRC and Investigator. The inconsistency was noted in a total of 13 patient's best overall response (BOR) assessment, out of which 5 patients' assessment by Investigator (as PR) differed from the IRC's assessment, resulting in a higher ORR of 34.7% per Investigator assessment.

Table 12 Comparison of IRC-assessed and INV-assessed ORR

BOR IRC	BOR INV			
	CR	PR	SD	PD
PR	1	0	0	0
SD	0	3	0	2
PD	0	2	4	0
NE	0	0	0	1

Source: FDA analysis; CCOD September 1, 2021

Duration of Response (DOR) Analysis:
In addition to the median DOR reported by the Applicant, FDA calculated the durability of response at specific time-points (e.g., 3, 6, 9 , 12, 24 and 36 months) using the observed DOR values rather than KM estimates. The minimum and maximum observed durations as of the CCOD are also presented in the table below.

Table 13 DOR Results in Responders

	Atezolizumab N=49
Duration of Response (DOR)	
#PDs/#Responders	3/12
Median (95% CI)	NR (17, NR)
Min, Max	1+, 41+
Responders with DOR	
≥3 mons	9 (75%)
≥6, 9 mons	8 (67%)
≥12 mons	5 (42%)
≥24, 36 mons	3 (25%)

PD: progressive disease; NR: Not reached; mons: months; +: Censored/Ongoing
Source: FDA analysis; CCOD September 1, 2021

As part of the DOR analysis, the Applicant presented the percentage of patients who were

event free at one year. Note that these estimates were calculated using the KM method. However, FDA's analysis of DOR milestone rates, presented in the table above, are calculated using observed DOR.

Dose/Dose Response

The Applicant's Position:
The exposure response (ER) relationship has been previously characterized. Exposure-response (E-R) analyses for atezolizumab in both monotherapy and combination settings have been conducted in over 8 studies including PCD4989g, IMvigor211, OAK, IMpower130, IMpower150, IMpower133, IMpassion130, and IMbrave150 from 5 distinct indications including MUC, NSCLC, ES-SCLC, TNBC, and HCC. All the analyses have come to the same conclusion that atezolizumab has flat exposure-efficacy and exposure-safety relationships. No clinically meaningful E-R relationships using clinical efficacy and safety endpoints have been observed for atezolizumab across numerous diverse indications. No new ER analyses have been conducted in Study ML39345.

The FDA's Assessment:
Based on the results of the popPK analysis and simulations presented above along with the totality of clinical pharmacology evidence to date, and the favorable benefit-risk of this dosing regimen, 15 mg/kg weight-based dosing regimen, capped at 1200 mg, is supported as an appropriate weight-based dosing regimen in pediatric patients aged 2 and above.

FDA agrees with the Applicant that atezolizumab has a flat exposure-efficacy and exposure-safety relationship as shown in previous studies. No new ER analyses were conducted in Study ML39345.

Durability of Response

The Applicant's Position:
See text above on Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
Refer to FDA's DOR analysis presented above.

Persistence of Effect

The Applicant's Position:
See text above on Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
The median DOR was not reached. Five (42%) of responders had DOR ≥12 months indicating

persistence of effect.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:
Not applicable as PRO endpoints were not assessed in the ML39345 study.

The FDA's Assessment:
FDA agrees.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
No additional analyses were conducted.

The FDA's Assessment:
FDA conducted subgroup analysis based on some of the demographics characteristics at baseline in the efficacy-evaluable population. Due to small overall study sample size and consequently small sample size for the subgroups, the results should be interpreted with caution. The ORR in sex based subgroups was similar to the ORR in overall population (~24% – 25%). ORR in Black/African Americans appeared lower compared to Whites (21% vs 33%); however, due to the small number of patients and wide and overlapping confidence intervals (as shown in the table below), no conclusive statements regarding the ORR point estimates across these 2 race groups can be made. The ORR in the subgroup of patients with ECOG PS 0 is numerically higher compared to ECOG PS 1 (31% vs 18%).

Table 14 ORR Results for Selected Subgroups

Subgroup	#Responders/N	ORR (95% exact CI)
Sex		
Male	6/24	25% (10, 47)
Female	6/25	24% (9, 45)
Race		
White	9/27	33% (17, 54)
Asian	0/ 5	-
Black/African American	3/14	21% (5, 51)
Unknown/Not Reported	0/ 3	-
ECOG		
0	8/26	31% (14, 52)
1	4/22	18% (5, 40)
2	0/1	-

+: censored
Source: FDA Analysis; CCOD September 1, 2021

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:
Study ML39345 is the only pivotal study supporting the efficacy claim for this sBLA and results demonstrated evidence of clinically meaningful activity in the proposed patient population. Study GO29664 was submitted as a supportive study to assess safety in the pediatric population. Therefore, no integrated review of effectiveness was performed.

8.1.4. Assessment of Efficacy Across Trials

The Applicant's Position:
Not applicable as efficacy data in the submitted dossier is based on a single Phase II study.

The FDA's Assessment:
FDA agrees with Applicant's position stated above.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:
The primary endpoint of ORR by IRC assessment demonstrated clinically meaningful responses in ASPS adult and pediatric patients treated with atezolizumab.

The secondary endpoint of ORR by INV assessment demonstrated clinically meaningful responses in ASPS adult and pediatric patients. The concordance for IRC–assessed and INV–assessed ORR was high (89.8%) for confirmed responder versus non-responder, demonstrating that there was limited bias of assessment.

A median DOR by IRC assessment was not reached in ASPS adult and pediatric patients treated with atezolizumab, however a prolonged DOR by INV assessment was observed in adult and pediatric patients treated with atezolizumab.

The secondary endpoint of median PFS by IRC assessment was 7.2 months (95% CI: 3.7, 9.9), which was numerically shorter than the median PFS by INV assessment of 19.9 months (95% CI: 7.8, 40.0) in ASPS adult and pediatric patients treated with atezolizumab.

The FDA's Assessment:
The efficacy of atezolizumab in pediatric and adult patients is based on Study ML39345, an open-label, single-arm study in 49 adult and pediatric patients aged 2 years and older with unresectable or metastatic ASPS.

The FDA agrees with the Applicant's assessment that the results of Study ML39345 provide

clinically meaningful evidence of activity of atezolizumab in patients ≥2 years of age with unresectable or metastatic ASPS where no approved therapies exist. However, FDA reiterates that PFS is not interpretable in a single arm study and results would not be included in labeling.

8.2. Review of Safety

The Applicant's Position:
The clinical safety data are based on the primary analysis of Study ML39345, an open-label, single arm, phase II study of atezolizumab in patients with ASPS in adult subjects ≥18 years of age and in pediatric/adolescent subjects ≥2 years of age. Overall, the safety data from ML39345 were consistent with the well-established safety profile of atezolizumab and no new clinically meaningful safety concerns were identified. The safety profile of atezolizumab in pediatrics is further supported from Study GO29664; an early phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, PK, pharmacodynamics (PD), 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 had proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options existed. Atezolizumab was well-tolerated and its safety profile in pediatric patients was consistent with its known safety profile in adult patients. Safety data from study GO29664 is presented in Section **Error! Reference source not found.**.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. The 2 pediatric patients treated on study ML39345 also contributed to the overall assessment of safety in the pediatric population.

Safety Review Approach

The Applicant's Position:
The safety and tolerability assessment was based on the frequency of AEs, serious adverse events (SAE), severe AEs (Grade≥ 3), fatal AEs, AEs leading to discontinuation, AEs leading to dose reduction or interruption, AESIs, and clinical laboratory assessments and vital sign measurements.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of the approach to the review of safety. In Study ML39345, verbatim description of adverse events (AEs) were mapped to Medical Dictionary for Regulatory Activities (MedDRA) version 24.0 for AEs. AE terms were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 until March 31, 2018. Protocol amendment 0012 updated AE grading from CTCAE v4.0 to CTCAE v5.0 beginning April 1, 2018. Laboratory data were classified according to NCI CTCAE

During FDA review of the proposed labeling, the Applicant was asked to group terms for adverse events for study ML39345. These group terms were as follows:

Table 15 FDA Group Terms

Group Term	Preferred Terms
Abdominal Pain	abdominal pain and abdominal pain upper
Cough	cough, upper-airway cough syndrome, and productive cough
Musculoskeletal pain	arthralgia, pain in extremity, myalgia, non-cardiac chest pain, neck pain, musculoskeletal chest pain, and back pain
Rash	rash maculo-papular, rash, dermatitis acneiform, eczema, skin exfoliation, and drug eruption
Dizziness	vertigo and dizziness
Hemorrhage	pulmonary hemorrhage, hemoptysis, conjunctival hemorrhage, epistaxis, hematuria, rectal hemorrhage, and laryngeal hemorrhage
Arrhythmia	atrial fibrillation, sinus bradycardia, ventricular tachycardia, and sinus tachycardia
Hypothyroidism	hypothyroidism and blood thyroid stimulating hormone increased

Source: FDA generated table from label

AEs were collected for 30 days after the last administration of atezolizumab.

Data:
Information on the safety database and analysis subsets relevant to the evaluation of the safety of single agent atezolizumab is summarized in Table 16.

Table 16 Safety Population

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review N=49			
Clinical Trial Groups	Number of Patients Evaluable for Safety	Dose, Route, and Regimen	Data Cutoff Date
Open-label trials conducted for this indication	49	Atezolizumab Monotherapy Arm Atezolizumab Adults ≥18 yrs Atezolizumab 1200 mg IV q3w Atezolizumab Pediatrics ≥2 yrs	01 Sep 2021

Safety Database for the Study Drug Individuals exposed to the study drug in this development program for the indication under review N=49			
		Atezolizumab 15mg/kg (1200mg max) IV q3w	

IV=intravenous; q3w= every 3 weeks

The Applicant's Position:
A total of 49 patients in the study received at least one dose of atezolizumab. The median cumulative dose was 13,200.00 mg (range: 2400.0 – 69,600.0 mg) and median treatment duration was 8.9 months (range: 1 – 40 months).

The FDA's Assessment:
In addition to safety data from study ML39345, the Applicant submitted data from Study GO29664 to provide supportive safety data for the pediatric population (Refer to Section 10 for more details).

FDA analyzed the exposure data for atezolizumab and agrees with the Applicant's assessment..

Relevant characteristics of the safety population:

The Applicant's Position:
The safety and efficacy populations are the same and the demographic and baseline characteristics are summarized in Section 8.1.2.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. (Refer to Table 7)

Adequacy of the safety database:

The Applicant's Position:
The safety profile of atezolizumab is now established, with an estimated cumulative total exposure of 27,282 patients in clinical trials and 198,582 patients in the postmarketing setting as of 17 May 2021. The size of the safety database for Study ML39345, supported by supplemental data from the Study GO29664 is considered adequate to support the benefit-risk assessment for the proposed indication in ASPS, which is a serious, life-threatening condition.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.1. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues relating to data integrity or quality were identified for the studies included in this submission.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of data integrity and submission quality.

Categorization of Adverse Event

The Applicant's Position:
Verbatim description of adverse events were mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms. AEs were graded by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 until 31 March 2018. CTCAE Version 5.0 was utilized for AE reporting beginning 1 April 2018. Multiple occurrences of the same event were counted once at the maximum grade. All reported AEs, SAEs, Grade 5 AEs, treatment-related AEs (as assessed by the investigator), severe AEs (Grade≥ 3), AESIs, immune-mediated adverse events (defined as AEs requiring the use of systemic corticosteroids with no clear alternate etiology), AEs leading to study drug discontinuation, and AEs leading to interruption were summarized.

The FDA's Assessment:
The overall approach to evaluate the safety data in study ML39345 was adequate and consistent
with standards used with other clinical study. MedDRA version 24.0 was used for AEs. The AEs for atezolizumab were listed in the protocol. The Applicant provided appropriate definitions and reporting requirements for serious AEs (SAEs), and AE of special interest (AESI). AE evaluation was performed at baseline and every cycle weeks 1, 2, and 3.

Routine Clinical Tests

The Applicant's Position:
All patients were closely monitored for safety and tolerability during all cycles of therapy. During treatment patients had the following assessments per the schedule of assessment:

- Concurrent meds
- Physical examination
- Vital signs
- Weight
- Performance status
- Adverse event reporting

- Laboratory assessments (CBC w/diff, plts, serum chemistry, TSH, urinalysis, pregnancy)
- Tumor measurements (repeated every 6 weeks)
- Biopsy (Adult patients (≥18 years of age; mandatory at all sites), at baseline and prior to cycle 3 day 1 (±3 days))
- Blood for PD and genetic sequencing
- EKG and echocardiogram at baseline

The FDA's Assessment:
FDA agrees with the routine clinical tests that were monitored. Specifically, concurrent meds, physical examination, vital signs, weight, performance status, adverse event reporting and laboratory assessments were performed at baseline and on day one of every treatment cycle. Per the study calendar, EKG and ECHOs were performed at baseline and as clinically indicated.

8.2.2. Safety Results

Deaths

The Applicant's Position:
Two patients (4.1%) died during the study. In both patients, the primary cause of death was malignant disease and occurred at least 30 days from the last atezolizumab administration.

The FDA's Assessment:
FDA reviewed the submitted narratives for the two patients who died. FDA agrees that both patients died from disease progression with clinical deterioration. AEs reported leading up to the patient's death included one patient with a pulmonary embolism which led to complete collapse of the left lung and the other patient experienced spinal cord compression due to widely metastatic disease in the spine.

Serious Adverse Events

Data:

Table 17 Serious Adverse Events by System Organ Class and Preferred Term Reported in at least 2 Patients (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**20 (40.8)**
Respiratory, thoracic and mediastinal disorders	
Total number of patients with at least one adverse event	6 (12.2)
Pulmonary haemorrhage	2 (4.1)
Injury, poisoning and procedural complications [a]	
Total number of patients with at least one adverse event	4 (8.2)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
General disorders and administration site conditions	
Total number of patients with at least one adverse event	3 (6.1)
Fatigue	2 (4.1)
Infections and infestations	
Total number of patients with at least one adverse event	3 (6.1)
Pneumonia	2 (4.1)
Nervous system disorders [a]	
Total number of patients with at least one adverse event	3 (6.1)
Gastrointestinal disorders [a]	
Total number of patients with at least one adverse event	2 (4.1)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	2 (4.1)
Pain in extremity	2 (4.1)
Vascular disorders [a]	
Total number of patients with at least one adverse event	2 (4.1)

[a] None of the individual Preferred Terms under this System Organ Class were reported in at least 2 patients.

Notes:
Percentages are based on N in the column headings.
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.

Source: Study ML39345.

The Applicant's Position:

Twenty patients (40.8%) experienced at least one SAE. Of the patients that experienced SAEs, 4 patients (8.2%) reported treatment-related SAEs. One pediatric patient experienced a SAE of fatigue.

Of the SAEs reported, 3 patients reported treatment-related Grade 3 SAEs. These treatment-related Grade 3 SAEs included preferred terms (PT) of vertigo (2.0% [1 patient]), upper limb fracture (2.0% [1 patient]), and pneumonitis (2.0% [1 patient]).

The FDA's Assessment:

FDA reviewed all narratives provided by the Applicant for SAEs and agrees with the Applicant's assessment. The Applicant points out AEs that were considered treatment-related; however, FDA's safety analysis is evaluated based on all-cause events because attribution of AEs is difficult in single arm studies. The reported SAEs are consistent with the known safety profile for atezolizumab.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 18 Adverse Events by System Organ Class and Preferred Term, Adverse Events Leading to Study Treatment Discontinuation (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**2 (4.1)**
Injury, poisoning and procedural complications	
Total number of patients with at least one adverse event	1 (2.0)
Fracture	1 (2.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Total number of patients with at least one adverse event	1 (2.0)
Tumour pain	1 (2.0)
Pregnancy, puerperium and perinatal conditions	
Total number of patients with at least one adverse event	1 (2.0)
Pregnancy	1 (2.0)

Notes:
Percentages are based on N in the column headings.
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

The Applicant's Position:

Two patients (4.1%) experienced 3 AEs leading to withdrawal of study treatment. None of the AEs were related to study treatment.

One patient had fracture (2.0%) and tumour pain (2.0%), both leading to withdrawal of treatment. One patient had a pregnancy (2.0%) and was withdrawn from study treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of discontinuations. Although the two patients discontinued study treatment due to an AE, these events were not placed in the label.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 19 Adverse Events Leading to Dose Interruption, by System Organ Class and Preferred Term (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**15 (30.6)**
Respiratory, thoracic and mediastinal disorders	
Total number of patients with at least one adverse event	6 (12.2)
Pneumonitis	2 (4.1)
Cough	1 (2.0)
Obstructive airways disorder	1 (2.0)
Pneumothorax	1 (2.0)
Pulmonary embolism	1 (2.0)
Pulmonary haemorrhage	1 (2.0)
Rhinitis allergic	1 (2.0)
Infections and infestations	
Total number of patients with at least one adverse event	3 (6.1)
Influenza	1 (2.0)
Sinusitis	1 (2.0)
Upper respiratory tract infection	1 (2.0)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	3 (6.1)
Pain in extremity	2 (4.1)
Muscular weakness	1 (2.0)
General disorders and administration site conditions	
Total number of patients with at least one adverse event	2 (4.1)
Influenza like illness	1 (2.0)
Non-cardiac chest pain	1 (2.0)
Vaccination site reaction	1 (2.0)
Injury, poisoning and procedural complications	
Total number of patients with at least one adverse event	2 (4.1)
Lower limb fracture	1 (2.0)
Upper limb fracture	1 (2.0)
Nervous system disorders	
Total number of patients with at least one adverse event	2 (4.1)
Cerebrovascular accident	1 (2.0)
Hemiparesis	1 (2.0)
Ear and labyrinth disorders	
Total number of patients with at least one adverse event	1 (2.0)
Vertigo	1 (2.0)
Endocrine disorders	
Total number of patients with at least one adverse event	1 (2.0)
Adrenal insufficiency	1 (2.0)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Gastrointestinal disorders	
Total number of patients with at least one adverse event	1 (2.0)
Nausea	1 (2.0)
Vomiting	1 (2.0)
Investigations	
Total number of patients with at least one adverse event	1 (2.0)
Amylase increased	1 (2.0)
Lipase increased	1 (2.0)
Psychiatric disorders	
Total number of patients with at least one adverse event	1 (2.0)
Mental status changes	1 (2.0)
Skin and subcutaneous tissue disorders	
Total number of patients with at least one adverse event	1 (2.0)
Pruritus	1 (2.0)
Surgical and medical procedures	
Total number of patients with at least one adverse event	1 (2.0)
Medical procedure	1 (2.0)
Vascular disorders	
Total number of patients with at least one adverse event	1 (2.0)
Haematoma	1 (2.0)

Notes:
Percentages are based on N in the column headings.
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

Table 20 Adverse Events Leading to Dose Modification, by System Organ Class and Preferred Term (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**2 (4.1)**
Infections and infestations	
Total number of patients with at least one adverse event	1 (2.0)
Pneumonia	1 (2.0)
Investigations	
Total number of patients with at least one adverse event	1 (2.0)
Blood thyroid stimulating hormone decreased	1 (2.0)

Notes:
Adverse events leading to dose interruption and change are considered as adverse events leading to dose modification as doses are interrupted then changed.
Percentages are based on N in the column headings.

Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

The Applicant's Position:

A total of 17 patients (34.7%) experienced AEs that led to dose modification (5 patients [30.6%]) or dose interruption- (2 patients [4.1%]). Of these, 7 patients (14.3%) experienced AEs that were related to study treatment.

The FDA's Assessment:

FDA agrees with the Applicant's assessment for dose modifications.

Significant Adverse Events

Table 21 Adverse Events Grade 3-5, with an Incidence Rate of at Least 2 patients, by System Organ Class and Preferred Term (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**16 (32.7)**
Overall total number of events	**28**
Investigations	
Total number of patients with at least one adverse event	5 (10.2)
Total number of events	5
Weight increased	3 (6.1)
Lymphocyte count decreased	2 (4.1)
Musculoskeletal and connective tissue disorders	
Total number of patients with at least one adverse event	5 (10.2)
Total number of events	7
Pain in extremity	3 (6.1)
Muscular weakness	2 (4.1)
Vascular disorders	
Total number of patients with at least one adverse event	3 (6.1)
Total number of events	5
Hypertension	3 (6.1)
Blood and lymphatic system disorders	
Total number of patients with at least one adverse event	2 (4.1)
Total number of events	2
Anaemia	2 (4.1)
Ear and labyrinth disorders	
Total number of patients with at least one adverse event	2 (4.1)
Total number of events	3
Vertigo	2 (4.1)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Infections and infestations	
Total number of patients with at least one adverse event	2 (4.1)
Total number of events	2
Pneumonia	2 (4.1)
Metabolism and nutrition disorders	
Total number of patients with at least one adverse event	2 (4.1)
Total number of events	2
Hyperglycaemia	2 (4.1)
Nervous system disorders	
Total number of patients with at least one adverse event	2 (4.1)
Total number of events	2
Headache	2 (4.1)

Notes:
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by System Organ Class, all events are being counted (not just the ones fulfilling the incidence rate criterion).
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

The Applicant's Position:

A total of 27 patients (55.1%) experienced AEs of Grade 3 intensity (Table 22), 19 patients (38.8%) had AEs of Grade 2 intensity, and 3 patients (6.1%) had AEs of Grade 1 intensity. There were no patients with Grade 4 or 5 AEs in the study.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of significant AEs.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 22 Summary of Adverse Events (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one AE	**49 (100)**
Total number of events	**1417**
Total number of patients discontinued from study due to an AE	**0**
Total number of patients with at least one	
AE with fatal outcome	0
Serious AE	20 (40.8)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Serious AE leading to withdrawal from treatment	1 (2.0)
Serious AE leading to dose modification/interruption	10 (20.4)
Related Serious AE	4 (8.2)
AE leading to withdrawal from treatment	2 (4.1)
AE leading to dose modification/interruption	17 (34.7)
AE leading to dose modification	2 (4.1)
AE leading to dose interruption	15 (30.6)
Related AE	47 (95.9)
Related AE leading to withdrawal from treatment	0
Related AE leading to dose modification/interruption	7 (14.3)
Grade 3-5 AE	27 (55.1)
Grade 3-4 AE	27 (55.1%)
Grade 3	27 (55.1%)
Grade 4	0
Grade 5 AE (death due to AE)	0

Notes:
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

Table 23 Adverse Events with an Incidence Rate of at Least 10%, by System Organ Class and Preferred Term (Safety-Evaluable Patients)

MedDRA System Organ Class MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**	
	All Grades [a]	**Grade 3**
Any adverse events	**49 (100)**	**27 (55.1)**
Investigations		
- Overall -	42 (85.7)	8 (16.3)
Lymphocyte count decreased	22 (44.9)	2 (4.1)
White blood cell count decrease	15 (30.6)	0
Blood alkaline phosphatase increased	11 (22.4)	0
Aspartate aminotransferase increased	10 (20.4)	1 (2.0)
Blood lactate dehydrogenase increased	9 (18.4)	0
Weight decreased	9 (18.4)	0
Blood thyroid stimulating hormone increased	8 (16.3)	0
Weight increased	8 (16.3)	3 (6.1)
Alanine aminotransferase increased	6 (12.2)	1 (2.0)
Neutrophil count decreased	6 (12.2)	0
Platelet count decreased	6 (12.2)	0
Blood bilirubin increased	5 (10.2)	0
General disorders and administration site conditions		
- Overall -	39 (79.6)	2 (4.1)

MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab N=49 n (%)	
	All Grades [a]	Grade 3
Fatigue	27 (55.1)	1 (2.0)
Pyrexia	12 (24.5)	1 (2.0)
Influenza like illness	9 (18.4)	0
Chills	6 (12.2)	0
Non-cardiac chest pain	6 (12.2)	0
Pain	5 (10.2)	0
Gastrointestinal disorders		
- Overall -	38 (77.6)	2 (4.1)
Nausea	21 (42.9)	0
Vomiting	18 (36.7)	0
Constipation	16 (32.7)	0
Diarrhoea	13 (26.5)	1 (2.0)
Abdominal pain	10 (20.4)	0
Metabolism and nutrition disorders		
- Overall -	37 (75.5)	4 (8.2)
Hyperglycaemia	26 (53.1)	2 (4.1)
Hyponatraemia	12 (24.5)	0
Decreased appetite	11 (22.4)	1 (2.0)
Hypoglycaemia	8 (16.3)	0
Hypokalaemia	7 (14.3)	0
Hypophosphataemia	7 (14.3)	1 (2.0)
Hypocalcaemia	6 (12.2)	0
Dehydration	5 (10.2%)	0
Hyperkalaemia	5 (10.2%)	0
Respiratory, thoracic and mediastinal disorders		
- Overall -	35 (71.4)	6 (12.2)
Cough	20 (40.8)	0
Dyspnoea	16 (32.7)	0
Rhinitis allergic	8 (16.3)	0
Nasal congestion	6 (12.2)	0
Oropharyngeal pain	6 (12.2)	0
Musculoskeletal and connective tissue disorders		
- Overall -	33 (67.3)	5 (10.2)
Arthralgia	14 (28.6)	1 (2.0)
Pain in extremity	14 (28.6)	3 (6.1)
Back pain	11 (22.4)	0
Myalgia	8 (16.3)	0
Skin and subcutaneous tissue disorders		
- Overall -	27 (55.1)	1 (2.0)
Rash	14 (28.6)	0
Dry skin	7 (14.3)	0
Dermatitis acneiform	6 (12.2)	0
Pruritus	6 (12.2)	0
Rash maculo-papula	6 (12.2)	1 (2.0)

MedDRA System Organ Class MedDRA Preferred Term	Atezolizumab N=49 n (%)	
	All Grades [a]	Grade 3
Infections and infestations		
- Overall -	25 (51.0)	3 (6.1)
Upper respiratory tract infection	6 (12.2)	0
Sinusitis	5 (10.2)	0
Nervous system disorders		
- Overall -	25 (51.0)	6 (12.2)
Headache	21 (42.9)	2 (4.1)
Dizziness	11 (22.4)	0
Vascular disorders		
- Overall -	23 (46.9)	3 (6.1)
Hypertension	21 (42.9)	3 (6.1)
Hot flush	5 (10.2)	0
Psychiatric disorders		
- Overall -	21 (42.9)	1 (2.0)
Insomnia	13 (26.5)	0
Anxiety	12 (24.5)	0
Depression	7 (14.3)	0
Blood and lymphatic system disorders		
- Overall -	20 (40.8)	2 (4.1)
Anaemia	18 (36.7)	2 (4.1)
Cardiac disorders		
- Overall -	16 (32.7)	1 (2.0)
Sinus tachycardia	6 (12.2)	0
Sinus bradycardia	5 (10.2)	0
Tachycardia	5 (10.2)	0
Endocrine disorders		
- Overall -	12 (24.5)	0
Hyperthyroidism	6 (12.2)	0
Hypothyroidism	5 (10.2)	0

[a] There were no Grade 4 or Grade 5 adverse events reported in Study ML39345.

Notes:
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
The adverse event system organ class (AESOC) overall total number and percent reflects the full population, not the reduced set of adverse event preferred terms (AEPTs) obtained after selecting for the incidence percentage.
Clinical Data Cutoff Date: 1 September 2021.
Source:

The Applicant's Position:

The majority of patients (95.9% [47 patients]) experienced treatment–related AEs. Of the patients that experienced treatment-related AEs, 41 patients (83.7%) experienced

treatment–related AEs that were Grade 1–2 in intensity, 6 patients (12.2%) experienced treatment-related AEs that were Grade 3 in intensity, and no patients experienced treatment-related AEs that were Grade 4-5 in intensity. No treatment–related AEs led to withdrawal of study treatment.

The FDA's Assessment:

FDA agrees with the Applicant's overview of adverse events in study Ml39345. For labeling and review purposes, all adverse reactions regardless of "relatedness" are considered, because assessment of attribution is difficult in single-arm studies.

During review of Adverse Reactions section of the proposed labeling, FDA did not agree with the grouping of AE terms. FDA informed the Applicant and requested the Applicant run the analysis based on FDA group terms. Results of adverse reactions based on FDA group terms was included in the label.

Table 24 Adverse Events Using FDA Group Terms Occurring in ≥15% of Patients with ASPS Receiving Atezolizumab in ML39345

Adverse Events	Atezolizumab N = 49	
	All Grades (%)	Grades 3–4 (%)
General disorders and administration site conditions		
Fatigue	55	2
Pyrexia	25	2
Influenza like illness	18	0
Gastrointestinal disorders		
Nausea	43	0
Vomiting	37	0
Constipation	33	0
Diarrhea	27	2
Abdominal pain[1]	25	0
Metabolism and nutrition disorders		
Decreased appetite	22	2
Respiratory, Thoracic and Mediastinal		
Cough[2]	45	0
Dyspnea	33	0
Rhinitis allergic	16	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[3]	67	8
Skin and subcutaneous tissue disorders		
Rash[4]	47	2
Nervous system disorders		
Headache	43	4
Dizziness[5]	29	4
Vascular disorders		
Hypertension	43	6

Adverse Events	Atezolizumab N = 49	
	All Grades (%)	Grades 3–4 (%)
Hemorrhage[6]	29	2
Psychiatric disorders		
Insomnia	27	0
Anxiety	25	0
Cardiac Disorders		
Arrhythmia[7]	22	2
Endocrine disorders		
Hypothyroidism[8]	25	0
Investigations		
Weight decreased	18	0
Weight increased	16	6

Source: FDA table based on group terms
[1]Includes abdominal pain and abdominal pain upper
[2]Includes cough, upper-airway cough syndrome, and productive cough
[3]Includes arthralgia, pain in extremity, myalgia, non-cardiac chest pain, neck pain, musculoskeletal chest pain, and back pain
[4]Includes rash maculo-papular, rash, dermatitis acneiform, eczema, skin exfoliation, and drug eruption
[5]Includes vertigo and dizziness
[6]Includes pulmonary hemorrhage, hemoptysis, conjunctival hemorrhage, epistaxis, hematuria, rectal hemorrhage, and laryngeal hemorrhage
[7]Includes atrial fibrillation, sinus bradycardia, ventricular tachycardia, and sinus tachycardia
[8]Includes hypothyroidism and blood thyroid stimulating hormone increased

Laboratory Findings

Data:
Laboratory data were categorized according to NCI-CTCAE v5.0 and summarized as clinically relevant shifts from baseline per treatment arm (defined as shift from Grade 0, 1, or 2 at baseline to Grade 3 or 4 post-baseline).

Heamatology: The only common (≥ 5%) clinically relevant shift in Hematology was low counts for absolute lymphocytes in 5 patients (10.9%), but none of these were clinically important.

Chemistry: The most common (≥ 5%) clinically relevant shifts were elevated amylase, calcium, triacylglycerol lipase, magnesium, and uric acid. Overall, these shifts do not represent a new safety concern for atezolizumab. No patients met laboratory or clinical criteria for Hy's Law.

Coagulation: The only common (≥ 5%) clinically relevant shift was elevated activated partial thromboplastin time

The Applicant's Position:
The clinical laboratory results showed no unexpected safety findings.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of laboratories. Table XX displays the laboratory abnormalities that worsened from baseline occurring in ≥20% of patients.

Table 25 Laboratory Abnormalities Worsening from Baseline Occurring in 20% of Patients with ASPS Receiving Atezolizumab in Study ML39345

Laboratory Abnormality [1]	**Atezolizumab[2]**	
	All Grades (%)	**Grades 3–4 (%)**
Hematology		
Decreased Hemoglobin	63	0
Decreased Platelets	27	0
Increased Platelets	29	0
Chemistry		
Increased Alkaline Phosphatase	29	0
Decreased Amylase	40	0
Increased Amylase	20	20
Decreased Bilirubin	49	0
Decreased Calcium	47	0
Increased Calcium	25	14
Decreased Glucose	33	0
Increased Glucose	78	0
Decreased Glucose (fasting)	25	0
Decreased Magnesium	21	0
Increased Magnesium	26	26
Increased AST	39	2
Increased ALT	33	2
Decreased Sodium	43	0
Increased Lipase	25	25

Source: FDA reviewer generated table

[1]Laboratory tests which do not have NCI CTCAE grading criteria are also included for All Grade assessments, which were performed by comparing to respective lab normal ranges.

[2]The denominators used to calculate the rate varied from 4-49 for all tests of interest based on the number of patients with a baseline value and at least one on-study laboratory measurement available.

Vital Signs

Data:
There was a high incidence of hypertension in the study with 21 patients (42.9%) experiencing hypertension. A total of 21 patients (42.9%) experienced hypertension and none of the events were considered to be treatment-related by the investigator. Eighteen patients (36.7%) experienced hypertension that was Grade 1-2 in intensity. The remaining 3 patients (6.1%) experienced Grade 3 hypertension, of which 1 patient (2.0%) experienced serious Grade 3 hypertension. The one patient that experienced the unrelated Grade 3 SAE hypertension on Study Day 94, also experienced SAEs of fracture and pain in extremity at the same time. This subject had pre-existing hypertension at baseline. All of these Grade 3 events resolved. No patients experienced Grade 4-5 hypertension. The study treatment was not interrupted or discontinued due to the event of hypertension in any patient.

The Applicant's Position:
The observed rates of hypertension were not related to the study treatment and were likely due to pre-existing baseline medical conditions. Most of the hypertension cases were transient and resolved without treatment.

The FDA's Assessment:
For the AE of hypertension, FDA noted that there were no eligibility criteria for diastolic or systolic blood pressure parameters to enroll for patients receiving single agent atezolizumab in the protocol. Management guidelines were provided for hypertension for patients receiving bevacizumab in combiantion with atezolizumab.

FDA reviewed all the patient narratives and vital signs to identify a cause for the increased incidence of hypertension in study ML39345. FDA identified a total of 18 (36%) patients that had baseline hypertension. In addition to baseline hypertension, patients also had other comorbidities (i.e., cardiac disease) that may confound the attribution of hypertension to atezolizumab. FDA reviewed the narrative for the patients that had the SAE of hypertension and agrees with the Applicant's assessment that the hypertension was likely a result of the pain and fracture.

Blood pressure measurements that were outside the normal limits among patients without an abnormal diastolic or systolic measurement were reviewed. A total of 18 (45%) of 40 of patients had an elevated diastolic blood pressure from baseline and 28 (67%) of 42 patients had an elevated systolic blood pressure from baseline. As noted, the majority of patients (86%) had Grade 1-2 hypertension reported as an AE. These events were transient in nature. Only 3 (6%) of patients required medication for hypertension; hypertension resolved without intervention in all other cases.

FDA performed a review of the literature to determine if there was a relationship between patients with ASPS and having hypertension. FDA was unable to identify any supporting evidence for this association. FDA also reviewed other anti-PD-L1 drugs to look for any notable increase in the incidence of hypertension based on the individual drug or by tumor type. No increases were noted.

FDA was unable to identify a root cause for the increased incidence of hypertension noted in study ML39345 as compared to other single agent studies evaluating atezolizumab. The majority of cases were Grade 1-2 and resolved without intervention and therefor hypertension does not appear to be a clinically relevant AE.

Electrocardiograms (ECGs)

The Applicant's Position:
No ECG data after baseline/screening assessments were reported in this study.

The FDA's Assessment:
FDA note that ECG evaluation was performed at baseline and then only when clinically indicated. A total of 11 (22%) patients had atrial fibrillation, sinus bradycardia, ventricular tachycardia, or sinus tachycardia The patient with atrial fibrillation was the only patient with a Grade 3 event, all other events were Grade 1-2. This patient experienced atrial fibrillation on study day 490. He received treatment with diltiazem, apixaban, and scopolamine patch. On Study Day 493, the events atrial fibrillation and sinus tachycardia (pulse rate 63 beats/min) were considered resolved

QT

The Applicant's Position:
QT were not reported in Study ML39345.

The FDA's Assessment:
FDA agrees. There were no reported AEs of QT prolongation.

Immunogenicity

The Applicant's Position:
Immunogenicity were not reported in Study ML39345.

The FDA's Assessment:
FDA agrees.

8.2.3. Analysis of Submission-Specific Safety Issues

8.2.5.1 Adverse Events of Special Interest

Data:

Table 26 Adverse Events of Special Interest with an Incidence Rate of at Least 20%, by Medical Concept Category and Preferred Term (Safety-Evaluable Patients)

MedDRA Medical Concept Category MedDRA Preferred Term	**Atezolizumab** **N=49** **n (%)**
Total number of patients with at least one adverse event	**37 (75.5)**
Immune-mediated rash	
Total number of patients with at least one adverse event	24 (49.0)
Rash	14 (28.6)
Immune-mediated hypothyroidism [a]	
Total number of patients with at least one adverse event	16 (32.7)
Immune-mediated hepatitis (diagnosis and lab abnormalities)	
Total number of patients with at least one adverse event	12 (24.5)
Aspartate aminotransferase increased	10 (20.4)

[a] None of the Preferred Terms under the immune-mediated hypothyroidism medical concept category was reported in ≥20% of patients.

Notes:
Investigator text for adverse events encoded using MedDRA version 24.0.
Includes adverse events occurring on or after the start of treatment and up to 30 days post last treatment.
For frequency counts by Preferred Term, multiple occurrences of the same adverse event in an individual are counted only once.
Clinical Data Cutoff Date: 1 September 2021.
Source: Study ML39345.

The Applicant's Position:

Overall, 37 patients (75.5%) experienced 175 AESIs. Among patients who experienced AESIs, the majority (69.4% [34 patients]) had AESIs that were Grade 1–2 in intensity. Three patients (6.1%) experienced AESIs that were Grade 3 in intensity, of which 2 patients (4.1%) experienced 4 Grade 3 AESIs that were treatment–related (PTs: rash maculo-papular, amylase increased, lipase increased, and pneumonitis). No patients experienced Grade 4 or 5 AESIs.

One patient (2.0%) experienced a serious AESI of immune–mediated pneumonitis, which was treatment–related, but did not lead to dose modification or dose interruption or treatment discontinuation. Four patients (8.2%) experienced AESIs that led to dose modification or dose interruption. None of the AESIs led to treatment discontinuation. Five patients (10.2%) required treatment with systemic corticosteroids.

No patient experienced events under the AESI medical concepts of immune–mediated hypophysitis, immune–mediated Guillain–Barre syndrome, immune–mediated myasthenic

syndrome, immune-mediated diabetes, immune–mediated nephritis, immune–mediated colitis, immune–mediated myocarditis, immune–mediated myositis, or rhabdomyolysis, immune-mediated severe cutaneous reactions, immune-mediated vasculitis, immune-mediated ocular inflammatory toxicity, and haemophagocytic lymphohistiocytosis.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of AESIs. Atezolizumab has a well characterized AESI profile. Based on the data presented by the Applicant, there were no new AESIs.

8.2.4. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA agrees.

8.2.5. Safety Analyses by Demographic Subgroups

The Applicant's Position:
Not applicable

The FDA's Assessment:
FDA performed an analysis of AEs for the effects of age, gender and race on atezolizumab. No significant differences were noted; however, the limited number of patients enrolled does not allow for meaningful conclusions to be drawn based on age, sex, or race/ethnicity.

8.2.6. Specific Safety Studies/Clinical Trials

The Applicant's Position:
No studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
FDA agrees.

8.2.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:

FDA agrees.

Human Reproduction and Pregnancy

The Applicant's Position:

Pregnancy was reported in one patient (2.0%) during the study. The pregnancy was reported on Study Day 422 and the patient was discontinued from the study due to pregnancy. On Study Day 612, the patient delivered a female baby via vaginal delivery.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

The Office of Orphan Products Development granted Tecentriq Orphan Drug Designation on October 08, 2020 for the treatment of patients with soft tissue sarcoma (Designation 2020-7693). Therefore, this sBLA is exempt from requirements for the PDUFA user fee and compliance with the Pediatric Research Equity Act.

Given the extreme rarity of ASPS patients in the pediatric population, the high unmet medical need, the reported similarities across ages at diagnosis in diagnostic features, disease management, prognosis and related prognostic factors of ASPS patients, the efficacy data from adult patients as well as two adolescent patients in ML39345 will be used to extrapolate efficacy to pediatric patients.

The safety profile of atezolizumab in pediatrics is further supported from Study GO29664; an early phase, multicenter, open-label, single-arm study designed to evaluate the safety, tolerability, PK, PD, 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 had proven to be ineffective (i.e., relapsed or refractory) or intolerable and for whom no curative standard-of-care treatment options existed. Atezolizumab was well-tolerated and its safety profile in pediatric patients was consistent with its known safety profile in adult patients. Safety data from study GO29664 is presented in Section **Error! Reference source not found.**.

The impact of atezolizumab treatment on patients' growth and development were assessed by evaluation of anthropometric measures in relative to age-specific standards in the healthy reference population, and the onset of puberty by Tanner stage classification, respectively in Study GO29664 (BLA761034/S-029).

No clinically meaningful trends were seen regarding the absolute changes of body measurement of weight, height, or body mass index (BMI) in safety evaluable patients during the study. A patient's standard deviation score (SDS) was calculated for each body

measurement at each study visit, which indicates to what extent the patient's value deviated from the median of the reference healthy population. At baseline, the mean SDS value in evaluable patients was slightly below zero for each body measurement (i.e., weight, height, and BMI). The values of body measurements in relation to the reference healthy population maintained at a similar level throughout the study. No clinical meaningful impact of atezolizumab on the growth pattern of evaluable patients in the study was observed. Head circumference was assessed in patients <3 years of age. Head circumference data were available for 3 patients in the study, of whom two patients only had baseline results. Therefore, a meaningful evaluation of changes in head circumference for patients in the study could not be conducted.

Patients with delayed puberty were defined as any girls ≥13 years old or any boys ≥ 14 years old who had a Tanner stage of 1. Among the 76 patients in the safety-evaluable population with Tanner stage data at baseline, 20 patients had a baseline Tanner stage of 1, 14 of these 20 patients had at least one post-baseline Tanner stage assessment reported. No delayed puberty was observed during the study in these 14 patients. Given the limited patient data and a limited duration of patient follow-up in study (median: 6.9 months), no definitive conclusion can be made regarding the impact of atezolizumab on patients' development.

The FDA's Assessment:
FDA did not formally review this data. The Applicant's conclusion is based on a small sample size of pediatric patients. Although no growth plate abnormalities were identified, data are limited and absolute conclusions may be challenging to draw.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:
Since the International Birth Date (18 May 2016) through 17 May 2021, an estimated cumulative total of 198,582 patients have received atezolizumab from marketing experience (U.S. n=84,796; EU n=54,754; Japan n=20,092; Rest of the World n=38,939). No new or unexpected safety findings were identified in the post-marketing setting for atezolizumab when used as monotherapy.

The FDA's Assessment:

Atezolizumab has not previously been approved for the treatment of pediatric patients. Postmarketing experience is mainly in adult patients.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:
Not applicable.

The FDA's Assessment:
Safety in the postmarket setting is expected to be similar to that observed on the clinical study reviewed in this application.

8.2.9. Integrated Assessment of Safety

The Applicant's Position:
The overall safety experience with atezolizumab in ML39345 is consistent with its well-established safety profile in the monotherapy setting across multiple indications. Atezolizumab was well tolerated and no new safety signals were identified. The main safety risks associated with atezolizumab are immune-mediated events, a checkpoint inhibitor class-effect. The most common AESIs were low-grade dermatologic reactions, liver function test abnormalities, and thyroid dysfunction. Overall, these events were manageable. The current labeling information provides adequate guidance to physicians on the management of immune-mediated AEs, which are monitored through routine pharmacovigilance activities.

The FDA's Assessment:
In general, FDA agrees with the Applicant's integrated assessment of safety. Overall, the safety profile for atezolizumab is consistent with the types of AEs/AESIs expected from previous clinical studies in adults patients. Atezolizumab has not previously been approved for pediatric patients. Study GO29664 evaluated 60 pediatric patients across tumor types who received single agent atezolizumab and no new safety signals were identified. There was a higher incidence of hypertension than has been previously reported in other studies with single agent atezolizumab. A rationale for this has not been established. Oncologists are well versed in the management of AEs related to other in class drugs.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
No major statistical issues were identified while reviewing the data and results submitted in this application. No inferential procedures were used to evaluate results from this single arm study. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response.

8.4. Conclusions and Recommendations

The FDA's Assessment:

FDA agrees that the results of Study ML39345 in pediatric and adult patients ≥2 years of age with unresectable or metastatic ASPS demonstrate that atezolizumab provides clinically meaningful responses and durability of responses for patients who have no satisfactory alterative treatment options. Due to the rarity of ASPS and the small sample size enrolled, meaningful conclusions regarding subgroup analyses could not be made. It may be important to note that the majority of the patients with ASPS were White and this may not represent the racial diversity of patients with ASPS but is consistent with the largest study to date that described racial distribution among patients with ASPS.

The primary safety review consisted of data based on the results from Study ML39345 with supportive data from Study GO29664. The safety profile in both adult and pediatric patients who received atezolizumab is generally consistent with the established safety profile. Atezolizumab has a clinically manageable safety profile that is acceptable given the effects on response rate.

Approval is justified based on clinically meaningful responses rates observed in patients with unresectable or metastatic ASPS that were durable in a patient population with no currently approved therapies for a rare and life-threatening disease. Due to the rarity of the population, large randomized clinical studies are infeasible. Therefore, regulatory flexibility is applied in accepting Study ML39345 to support approval as the demonstrated ORR is clinically meaningful in its magnitude and durability for an indication with no approved therapies.

X _____ X

Sirisha Mushti
Primary Statistical Reviewer

Joyce Cheng
Statistical Team Leader

X _____ X

Leslie Doros
Primary Clinical Reviewer

Leslie Doros
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants, as it did not raise significant efficacy concerns or new safety concerns.

10 Pediatrics

The Applicant's Position:

ASPS is a rare, malignant, mesenchymal tumor diagnosed most frequently in patients between 15 and 35 years of age, but has been observed in patients as young as 1.5 years of age, and one third of ASPS diagnoses occur in children and adolescents (Flores et al. 2018).

In accordance with the 2020 World Health Organization classification of STS, no differentiation is made on ASPS diagnosis based on the age of onset or diagnosis, with ASPS categorized under Tumors of Uncertain Differentiation (Sbaraglia et al. 2021). Based on data from the SEER database collected between 2000 and 2015, ASPS accounts for 1.4% of STS in patients younger than 20 years.

Patients diagnosed with ASPS show similar characteristics regardless of the age at diagnosis. The histopathological characteristics are distinct organoid or nesting patterns separated by delicate partitions of connective tissue containing sinusoidal vessels, and cytogenetically, both adults and pediatric patients share an unbalanced recurrent t(X;17)(p11;q25) translocation, which leads to a chimeric ASPSCR1-transcription factor E3 (TFE3) transcription factor (Paoluzzi et al. 2018).

Management of ASPS is similar across the whole age range of presentation including surgical resection and systemic treatment for metastatic disease. Children, young adults, and adult ASPS patients are generally chemotherapy insensitive with only a very limited fraction of patients responding to chemotherapy (Orbach et al 2013). Similar to older patients, after recurrence of disease, treatment options for these rare cases diagnosed under the age of 12 years are extremely limited. There is still an unmet need for younger pediatric patients and thus the proposal to extend the indication to this underrepresented population.

The largest published series of pediatric and young adult patients are summarized in Section 2.1 of the Assessment Aid, and reported in Table 27 The Largest Published Series of Pediatric and Young Adult Alveolar Soft Part Sarcoma Patients. These series are primarily retrospective, as it is unfeasible to run prospective experimental controlled studies in the pediatric population due to the extreme rarity of ASPS in the pediatric populations. The three studies showed the broad range of ages at diagnosis for pediatric and young adult patients diagnosed with ASPS, with general higher prevalence in the adolescent and young adult group.

Table 27 The Largest Published Series of Pediatric and Young Adult Alveolar Soft Part Sarcoma Patients

Author	Median age at diagnosis (years)	Inclusion criteria for enrollment (years)	Enrollment Age Range (years)	Number of Patients included in the Analysis	Age break down
Flores et al. 2017	17	<30	1.5 - 30	69	<17 years - 32/69 patients [46%] >17 years - 37/69 patients [54%]
Brennan et al. 2018	11.5	<21	2.7-17.5	22	1-9 years - 8/22 patients [37%], 10-17 years - 14/22 patients [63%]
Orbach et al. 2013	13	0-21	2-21	51	<12 years - 25/51 patients [49%] >13 years - 26/51 patients [51%]

A comparison of pediatric series with published adult series of ASPS did not demonstrate any major differences between the two series, with similar chemotherapy insensitivity, a high rate of resectability and the development delayed pulmonary or cerebral metastasis (Orbach et al. 2013). Poorer overall prognosis in the adult population is thought to be associated to a higher percentage of metastases at diagnosis and larger tumors. Both in adult and pediatric patients, tumor sizes larger than 5 cm and presence of metastasis were correlated to a worse prognosis.

Given the extreme rarity of ASPS patients in the pediatric population, the high unmet medical need, the similarities across ages at diagnosis in diagnostic features, disease management, prognosis and related prognostic factors of ASPS patients, and the durable response observed in a 12 year old patient enrolled in ML39345, the Sponsor believes that efficacy data from adult patients with atezolizumab in ASPS may be used to extrapolate to pediatric patients.

Additionally, study GO29664 provided safety and PK data to support the appropriate dosing of atezolizumab in the pediatric patient population (Section 6.2.2.1 of the Assessment Aid). While no patients with ASPS were enrolled in Study GO29664, safety and PK information were collected across a wide variety of pediatric tumor types (including other STS sub-types), and notably the same dosing regimen and frequency was used for pediatric patients across the two studies (i.e., 15 mg/kg for pediatric patients once every 21 days capped at 1200 mg as for adult patients). Thereby, the data from Study GO29664 supports the atezolizumab dosing of pediatric patients in the ASPS indication.

Atezolizumab was well-tolerated and its safety profile in pediatric patients (N=87 [age group: 0-30 years]) in Study GO29664 was consistent with its known safety profile in adult patients. There were no new safety signals identified. The safety profile was similar across age groups and also across cohorts, though analysis of the safety profile in the <2-year-old age group was limited by the small number of patients (N=2). Furthermore, the interpretation of any numerical differences between cohorts was limited by the small number of patients enrolled in each cohort (ranging from N=2 to N=11).

- The incidence of AEs was similar across age groups and cohorts; nearly all patients (97.7%) experienced at least one AE.
- Four patients (4.6%) withdrew from study treatment due to AEs: 1 patient with Grade 4 dyspnea, 1 patient with Grade 3 transaminases increased, 1 patient with a Grade 3 lung infection, and 1 patient with Grade 4 diabetic ketoacidosis and Grade 3 Fanconi syndrome.
- Thirty-three patients (37.9%) experienced SAEs with no notable trend across age group or cohort. Pyrexia was the most common SAE (4 patients [4.6%]).
- The incidence of Grade 3–4 AEs was similar across age groups and cohorts. The most common Grade 3–4 AE was anemia (19 patients [21.8%]).
- One patient experienced a fatal (Grade 5) AE of graft versus host disease. This event occurred 90 days since the last dose of atezolizumab. Although this event was considered related to study drug, it was confounded by (and also reported as related to) allograft transplant, as well as the more recent use of follow-up anti-cancer therapy (nivolumab).
- 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 common study drug–related AE (17 patients [19.5%]).
- The incidence of AESIs for atezolizumab was consistent with the known safety profile of atezolizumab in adults. The most common AESIs were reported under the medical concepts of immune-related hepatitis, immune-related rash, and infusion-related reactions. The majority of AESI events were of Grade 1 or 2 intensity.
- No clinically meaningful impact of atezolizumab on the growth pattern of safety evaluable patients in the study was observed. No delayed puberty was observed during the study.

Despite the limited number of pediatric patients enrolled in Study ML39345, the safety findings of pediatrics in Study ML39345 are consistent with the findings in Study GO29664.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of atezolizumab in the pediatric population. ASPS is a disease that most commonly affects patients ages 15-35 years of age. There does not appear to be a difference between adult and pediatric patients with ASPS regarding the histopathological and cytogenetic characteristics, or management. There were no newly identified safety signals identified in pediatric patients.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
1.6 Alveolar Soft Part Sarcoma (ASPS)	Extended the indication to include the use of TECENTRIQ, as a single agent, for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS.	FDA agrees with proposed indication and no changes were made.
2.2 Recommended Doses and Schedules	Included posology of TECENTRIQ in adult and pediatric patients with ASPS.	FDA agreed with the proposed dose and schedule of atezolizumab.
6.1 Clinical Trials Experience	Included information from Study ML39345	Changes were made for brevity, clarity and within the guidelines of FDA labeling practices. FDA removed (b) (4) FDA provided the Applicant with group terms to calculate the incidence of AEs. The Applicant revised Table 22 accordingly. The laboratory abnormalities were edited to denote if an lab abnormality was increased or decreased.
8.4 Pediatric Use	- Included information from Study ML39345 - Included information from Study GO29664, a single-arm, multi-center, multi-cohort trial in 60 pediatric patients aged 7 months to <17 years with	This section was edited for brevity and clarity. Two subsections were added for ASPS and Solid Tumors and Lymphomas. The discussion. The results for Study GO29664 were moved under the new subheading

	relapsed or progressive solid tumors and lymphomas.	Solid Tumors and Lymphomas.
12.3 Pharmacokinetics	Included statements for Pediatric Patients (ASPS)	The proposed statements were accepted with minor modifications.
12.6 Immunogenicity	Immunogenicity Section 6.2 from previously approved PI was moved to 12.6.	The proposed statements were accepted with modifications.
14.6 Alveolar soft part sarcoma (ASPS)	Included information from Study ML39345	Revised to condense and reorganize for brevity, precision, and readability. Revised efficacy results to (b) (4) Revised the presentation for DOR.

The Applicant's Position:

The results presented in the dossier from study ML39345 demonstrate a positive benefit-risk balance of TECENTRIQ, as a single agent, for the treatment of adult and pediatric patients 2 years of age and older with unresectable or metastatic ASPS. The primary endpoint of IRC-assessed ORR demonstrated clinically meaningful responses in adult and pediatric patients with ASPS. Atezolizumab was well-tolerated and no new clinically meaningful safety concerns were identified. The Applicant recommends that TECENTRIQ should be made available to patients with ASPS according to the following proposed indication:

> *"Tecentriq, as a single agent, is indicated for the treatment of unresectable or metastatic alveolar soft part sarcoma (ASPS) in patients aged 2 years and older."*

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Clinical pharmacology sections were revised/edited as follows:

Proposed Language by Applicant Section 8.4	Alveolar Soft Part Sarcoma The safety and effectiveness of TECENTRIQ for unresectable or metastatic ASPS have been established in pediatric patients aged 2 years and older. Use of TECENTRIQ for this indication is supported by evidence from an adequate and well-controlled study of TECENTRIQ in adults and 2 adolescent pediatric patients (≥12 years of age) with

	ASPS with additional pharmacokinetic data in pediatric patients 2 years to 17 years (b) (4). These data suggest that TECENTRIQ exposure in pediatric patients aged 2 years and older is comparable with that of adults and is expected to result in similar safety and efficacy to that of adults *[see Adverse Reactions (6.1), Pharmacokinetics (12.3), Clinical Studies (14.6)]*. The course of unresectable or metastatic ASPS is sufficiently similar between (b) (4) pediatric patients 2 to 11 years (b) (4) The safety and (b) (4) of TECENTRIQ have not been established in pediatric patients younger than 2 years (b) (4)
FDA Proposed modifications Section 8.4	<u>Alveolar Soft Part Sarcoma</u> The safety and effectiveness of TECENTRIQ for unresectable or metastatic ASPS have been established in pediatric patients aged 2 years and older. Use of TECENTRIQ for this indication is supported by evidence from an adequate and well-controlled study of TECENTRIQ in adults and 2 adolescent pediatric patients (≥12 years of age) with ASPS with additional pharmacokinetic data in pediatric patients 2 years to <17 years. These data suggest that atezolizumab exposure in pediatric patients aged 2 years and older is comparable with that of adults and is expected to result in similar safety and efficacy to that of adults *[see Adverse Reactions (6.1), Pharmacokinetics (12.3), Clinical Studies (14.6)]*. The course of unresectable or metastatic ASPS is sufficiently similar between pediatric patients 2 to 11 years old and that of adults and adolescent patients to allow extrapolation of efficacy and safety to pediatric patients 2 years and older. The safety and effectiveness of TECENTRIQ for ASPS have not been established in pediatric patients younger than 2 years of age.
Rationale for Changes to Section 8.4	API used when parameters are described. Revised for clarity. Retain previous language. Source of data supporting the safety and effectiveness for the pediatric indication is described in the second sentence of the paragraph.
FDA Proposed Addition to Section 12.2	**12.2 Pharmacodynamics** The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of atezolizumab have not been fully characterized.
Applicant's Proposal	

FDA's Response:	The Applicant proposed [redacted] (b) (4) FDA deleted this proposed statement [redacted] (b) (4), this subsection must contain a statement indicating this lack of information. See *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance*
Applicant's Proposed	**12.3 Pharmacokinetics**
FDA's proposed modifications	[redacted] (b) (4) exposure [redacted] (b) (4) increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg, including a dose of 1200 mg administered every 3 weeks. The clearance (CV%) was 0.20 L/day (29%), the volume of distribution at steady state was 6.9 L, and the terminal half-life was 27 days. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration [redacted] (b) (4) 3.3- and 1.9- fold, respectively. Atezolizumab clearance was found to decrease over time, with a mean maximal reduction (CV%) from baseline value of approximately 17% (41%); however, the decrease in clearance was not considered clinically relevant. Atezolizumab exposure increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg (0.07 to 1.33 times of the approved recommended doses), including a dose of 1200 mg administered every 3 weeks. Steady state was achieved after 6 to 9 weeks following multiple doses. The systemic accumulation ratio for every 2 weeks administration and every 3 weeks administration is 3.3- and 1.9- fold, respectively. <u>Distribution</u> The volume of distribution at steady state is 6.9 L. <u>Elimination</u> The clearance (CV%) is 0.2 L/day (29%) and the terminal half-life is 27 days. Atezolizumab clearance was found to decrease over time, with a mean maximal

Rationale for changes to 12.3	reduction (CV%) from baseline value of 17% (41%); however, the decrease in clearance was not considered clinically relevant. Revised this section to be consistent with recommendations in clin pharm labeling guidance found here: https://www.fda.gov/media/74346/download. (b) (4)
FDA's Proposed addition to Section 12.3	<u>Specific Populations</u> Pediatric Patients Atezolizumab serum concentrations with weight-based dosing at 15 mg/kg up to a maximum of 1200 mg every 3 weeks, in pediatric patients (2 years to <17 years) with relapsed or progressive solid tumors and lymphomas, are comparable to those of adult patients receiving 1200 mg every 3 weeks; while the exposure tended to be lower in pediatric patients less than 12 years old, this is not considered to be clinically relevant. See revision to align with current labeling practices and guidance cited above
Moved Immunogenicity from 6.2 to 12.6 and modified accordingly per FDA's request	**12.6 Immunogenicity** The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA (b) (4) other products. During the first year of treatment across (b) (4) clinical studies, (b) (4) median atezolizumab clearance in patients who tested positive for ADA was 19% ((b) (4) 18% (b) (4) 49%) higher as compared to atezolizumab clearance in patients who tested negative for ADA. (b) (4) clearance is not expected to be clinically significant, (b) (4) The presence of ADA did not have a clinically significant impact on the incidence or severity of adverse reactions. (b) (4) IMpower150, (b) (4) the impact of ADA on efficacy did not appear to be clinically significant. (b) (4)

	(b) (4) [redacted]
Applicant's rationale for addition of Section 12.6	The Applicant has added this per FDA's request and draft guidance, *Immunogenicity Information in Human Prescription Therapeutic Protein and Select Drug Product Labeling.* For ease of readability, the Applicant has streamlined and summarized the immunogenicity information previously presented in Section 6.2 here. Relative to the information presented in previous Section 6.2, the following updates were made for completeness and accuracy: (b) (4) [redacted]

	(b) (4)
FDA's proposed modifications	12.6 Immunogenicity The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other (b) (4) During the first year of treatment with TECENTRIQ across (b) (4) clinical studies, 13% to (b) (4)% of patients developed anti-atezolizumab antibodies. Median atezolizumab clearance in patients who tested positive for ADA was 19% ((b) (4) minimum 18%, maximum (b) (4) 49%) higher as compared to atezolizumab clearance in patients who tested negative for ADA. This change in clearance is not expected to be clinically significant. In study OAK and IMbrave150, exploratory analyses showed that the subset of patients who were ADA-positive appeared to have less efficacy (effect on overall survival) as compared to patients who tested negative for ADA [see Clinical Studies (14.2, 14.4)]. In the remaining studies there is insufficient information to characterize the effect of the ADA on efficacy. The presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions. Across clinical studies, 4.3% to 27.5% of neutralizing antibody (NAb)-evaluable patients had a positive NAb status at any timepoint post-treatment. The effect of NAb on atezolizumab exposure and safety did not appear to be clinically significant. The effect of NAb on key efficacy endpoints is uncertain due to small sample sizes
FDA's Rationale for the proposed changes	Revised to be consistent with language found in the immunogenicity labeling guidance. The statement regarding neutralizing antibody has been added as it describes the results of a PMC (neutralizing antibody report November 2019) submitted by Applicant (SDN 836).

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The safe use of atezolizumab can be adequately implemented in the postmarketing setting without issuing a REMS for this drug product. The product label for atezolizumab includes information on common and clinically significant adverse reactions that have been observed across the drug class. Product labeling also includes dose modification and management guidelines for these events. Risk management based on labeling and routine pharmacovigilance is expected to ensure the safe use of atezolizumab.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

There are no Postmarketing Requirements or Commitments for this application. Given the limited number of patients enrolled in Study ML39345, no meaningful conclusion can be made about differences in the safety or efficacy by demographics. Given the rarity of ASPS, there is limited published data on the incidence of ASPS by race. However, the racial breakdown of patients enrolled on study ML39345 appears consistent with the data from the poster publication (Sankaran et al. 2021)

FDA PMC/PMR Checklist for Trial Diversity and U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
□	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	X Yes __ No
□	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	__ Yes X No
□	Other considerations (e.g.: PK/PD), if applicable:	__ Yes X No

14 Division Director (OCP)

X

Stacy Shord

15 Division Director (Clinical)

I concur with the review team's evaluation of this application and with the recommendation to approve to approve it based on a demonstration of substantial evidence of effectiveness. ASPS is a rare soft tissue sarcoma comprising less than 1% of cases. The magnitude and durability of ORR in the Study ML39345 in the context of an acceptable safety profile, is clinically meaningful for a serious condition with an unmet need for effective therapies wherein conducting a randomized controlled trial is infeasible due to the rarity of the disease.

X

'Lola Fashoyin-Aje

16 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Not applicable. See Division Director Section.

X

17 Appendices

17.1. References

The Applicant's References:

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17.2. Financial Disclosure

The Applicant's Position:
There are no investigators with positive disclosable interests from study P10005.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Covered Clinical Study (Name and/or Number):* ML39345

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 71		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

17.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:
Not applicable.

The FDA's Assessment:
No new nonclinical data were submitted with this application.

17.4. OCP Appendices (Technical documents supporting OCP recommendations)

17.4.0. Population PK Analysis

17.4.0.1. Executive Summary

The FDA's Assessment: Population PK simulation in virtual pediatric patients was conducted by the Applicant to support the proposed dosing regimen (15 mg/kg once every 21 days [up to a maximum of 1200 mg], for each 21-day cycle) for atezolizumab in treatment of ASPS. In the current analysis, no PK data from patients with ASPS were available given the rarity of the disease but population PK model suggested no difference in exposure across other solid tumors. Population PK model developed with pediatric and young adult patients from Study GO29664 was used for pediatric exposure simulation. Simulation results showed that the range of Cmin and AUC largely overlapped for pediatric patients aged 2 to <12 years and 12 to 17 years at Cycle 1 and at steady state. The median exposure in younger pediatric patients (2 to <12 years) were slightly lower compared to adult exposure, but still within exposure range for adults receiving 1200 mg, which would be expected to provide an adequate response in pediatric patients due to the flat atezolizumab exposure-response relationship for efficacy observed in adult patients across other tumor types. Cmin at Cycle 1 and at steady state across all age groups of the simulated pediatric patients were also above the target of 6 μg/mL needed to achieve 95% tumor receptor saturation for efficacy.

17.4.0.2. PPK Assessment Summary

Population PK simulations of atezolizumab in pediatric patients were based on the previously developed pediatric and young adult population PK model. The pediatric and young adult population PK model was established using PK data obtained from 87 patients (< 2 years:n=2. 2-11 years: n=29, 12-17 years:n=38, >17 years: n=18) with solid tumor from Study GO29664, following the same structure as the adult model in the previous report. The pediatric and young adult population PK model was a two-compartment model. Final covariates included body

weight and albumin on clearance and volume of the central compartment, and baseline tumor burden and treatment -emergent ADA on CL. The parameter estimates and derived exposure metrics are presented in **Error! Reference source not found.** and Table 29.

Table 28. The Parameter Estimates in Pediatric and Young Adult Population PK Model

Parameter	Estimate	%RSE
CL (L/day)	0.217	4.93
V1 (L)	3.01	4.0
V2 (L)	1.36	11.3
Q (L/day)	0.183	18.1
Weight on CL	0.795	7.68
Albumin on CL	-1.18	20.0
Tumor burden on CL	0.122	34.5
Positive ADA on CL	1.23	7.96
Weight on V1	0.766	7.63
Albumin on V1	-0.566	28.7
BSV for CL	0.0458	32.8
BSV for V1	0.0140	64.7
BSV for V2	0.311	62.6
Covariance of BSVs for CL, V1	0.0129	65.6
Proportional residual variance	0.0509	32.3
Additive residual variance	68.9	109
Proportional residual SD	0.226	
Additive residual SD	8.30	
Objective function	3637	

Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 20-21, Table 3.

Table 29. Model-based Atezolizumab Exposure Parameters in Pediatric and Young Adult Subjects in Study GO29664

Parameter	Day	< 2 Years Old (N=2[a])	2 to < 12 Years Old (N=29)	12 to 17 Years Old (N=38)	≥18 Years Old (N=18)
Cmax (µg/mL)	Cycle 1	190 (5.87)	292 (13.7)	338 (10.5)	414 (24.5)
	Steady-State	280 (1.83)	417 (16.9)	457 (15.0)	549 (30.1)
Cmin (µg/mL)	Cycle 1	11.7 (259)	55.6 (30.1)	60.9 (28.5)	73.4 (44.7)
	Steady-State	84.3 (3.61)	119 (44.9)	116 (36.3)	125 (64.3)
AUC (day.µg/mL)	Cycle 1	1130 (5.28)	2209 (21.3)	2816 (17.7)	3579 (28.4)
	Steady-State	2590 (2.97)	4140 (27.6)	4562 (23.7)	5363 (41.1)

Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 21, Table 4.

Population PK simulations were performed with virtual pediatric patients' dataset (N=2000) with equal number of male and female subjects in children (2 to < 12 years) and adolescents (12 to <17 years) including a mixture of 30% subjects with ADA positive and 70% with ADA negative. Baseline tumor burden and albumin were generated by sampling jointly with replacement from Study GO29664. The comparison of continuous covariates between virtual population, observed adults and simulated adults is shown in Table 30.

Table 30. Summary Statistics of Continuous Covariates in the Pediatric Simulated Dataset

	Simulated 2 to <12 Years Old (N=1000)	Simulated 12 to 17 Years Old (N=1000)	Observed Adults (N=3408)	Simulated Adults (N=500, 100 replicates)[a]	Overall (N=5908)
Age (years)					
Mean (SD)	6.98 (2.90)	14.5 (1.44)	62.7 (9.78)		43.5 (26.4)
Median [min, max]	6.97 [2.00, 12.0]	14.6 [12.0, 17.0]	63.0 [24.0, 89.0]		55.0 [2.00, 89.0]
Baseline body weight (kg)					
Mean (SD)	28.6 (11.9)	61.8 (13.8)	73.5 (17.1)	75.6 (17.4)	64.1 (23.0)
Median [min, max]	26.8 [10.0, 80.5]	59.7 [34.5, 118]	72.0 [34.3, 196]	75.0 [39.1, 141]	65.0 [10.0, 196]
Albumin (g/L)					
Mean (SD)	40.5 (5.35)	41.6 (5.03)	39.6 (5.31)	39.0 (5.18)	40.0 (5.32)
Median [min, max]	41.0 [23.0, 46.0]	42.0 [29.0, 49.0]	40.0 [3.20, 56.8]	39.0 [18.0, 56.6]	41.0 [3.20, 56.8]
Missing	0 (0%)	0 (0%)	14 (0.4%)	0 (0%)	14 (0.2%)
Baseline tumor burden, sum of longest diameter (mm)					
Mean (SD)	75.5 (61.0)	80.7 (44.8)	79.1 (58.9)	75.5 (49.3)	78.4 (56.1)
Median [min, max]	57.0 [15.0, 301]	63.7 [11.0, 208]	67.0 [10.0, 1490]	64.0 [10.0, 293]	63.0 [10.0, 1490]
Missing	0 (0%)	0 (0%)	495 (14.5%)	0 (0%)	495 (8.4%)
Absolute dose (mg)					
Mean (SD)	429 (179)	910 (174)	1200 (0)	1200 (0)	1020 (305)
Median [min, max]	403 [150, 1200]	895 [518, 1200]	1200 [1200, 1200]	1200 [1200, 1200]	1200 [150, 1200]

Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 28, Table 7.

The comparison of atezolizumab exposure (AUC, C_{max} and C_{min} at Cycle 1 and steady-state) in simulated pediatric subjects and adult subjects are summarized in Table 31, Table 32 and **Error! Reference source not found.**. All exposures in simulated pediatric subjects were above the target of 6 µg/mL needed to achieve 95% tumor receptor saturation for efficacy. Median exposure of atezolizumab increased by age for all exposure values. The range of AUC and C_{min} of atezolizumab at Cycle 1 and steady state in subjects aged 2 to <12 years are largely overlapped with subjects aged 12 to <17 years. (Figure 3 and Table 33)

Table 31. Summary of Cycle 1 Exposures in Pediatric and Adult Subjects

	Simulated 2 to <12 Years Old (N=1000)	Simulated 12 to 17 Years Old (N=1000)	Simulated 2 to 17 Years Old (N=2000)	Observed Adults (N=3408)	Simulated Adults[b] (N=500, 100 replicates)
Cmax Cycle 1 (µg/mL)					
Median [min, max]	297 [145, 554]	362 [244, 537]	331 [145, 554]	387 [0.03, 1950]	386 [131, 1250]
Geo. mean (Geo. CV%)	295 (17.9%)	361 (14.3%)	326 (19.2%)	334 (175.7%)	388 (25.1%)
5th percentile	219	283	234	233	261
95th percentile	389	452	435	603	589
Missing	0 (0%)	0 (0%)	0 (0%)	228 (6.7%)	166 (0.3%)
Cmin Cycle 1 (µg/mL)					
Median [min, max]	53.7 [11.5, 140]	66.9 [19.2, 180]	60.1 [11.5, 180]	79.7 [0.03, 604]	77.7 [4.18, 342]
Geo. mean (Geo. CV%)	51.7 (41.3%)	65.7 (36.0%)	58.3 (40.8%)	70.7 (94.3%)	75.9 (38.0%)
5th percentile	26.1	35.3	29.4	29.9	40.3
95th percentile	93.9	110	105	137	132
Missing	0 (0%)	0 (0%)	0 (0%)	351 (10.3%)	34 (0.1%)
AUC Cycle 1 (day.µg/mL)					
Median [min, max]	2260 [803, 4820]	3090 [1640, 5740]	2700 [803, 5740]	NA	2980 [802, 8710]
Geo. mean (Geo. CV%)	2210 (28.6%)	3080 (19.5%)	2610 (29.9%)	NA	2990 (24.1%)
5th percentile	1380	2230	1530	NA	2020
95th percentile	3460	4170	3970	NA	4420
Missing	0 (0%)	0 (0%)	0 (0%)	3408 (100%)	0 (0%)

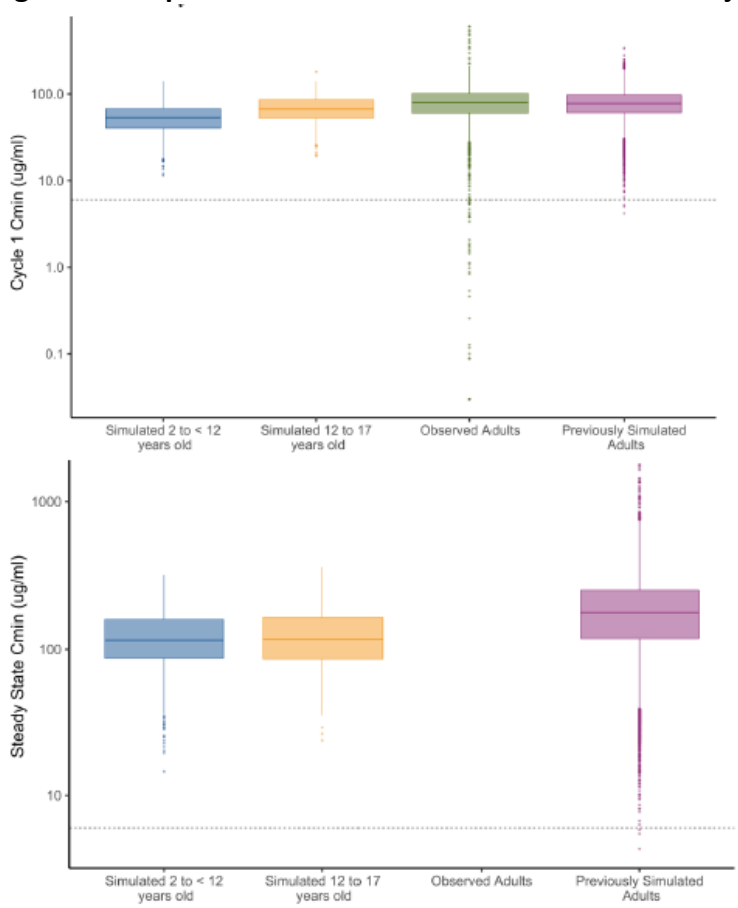
Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 33-35, Table 9.

Table 32. Summary of Steady-State Exposures in Pediatric and Adult Subjects

	Simulated 2 to <12 Years Old (N=1000)	Simulated 12 to 17 Years Old (N=1000)	Simulated 2 to 17 Years Old (N=2000)	Observed Adults (N=3408)	Simulated Adults[b] (N=500, 100 replicates)
Cmax steady state (µg/mL)					
Median [min, max]	417 [167, 783]	484 [285, 813]	452 [167, 813]	NA	568 [178, 2960]
Geo. mean (Geo. CV%)	412 (22.3%)	484 (18.3%)	446 (22.0%)	NA	570 (29.1%)
5th percentile	278	354	308	NA	360
95th percentile	580	648	623	NA	916
Missing	0 (0%)	0 (0%)	0 (0%)	3408 (100%)	44 (0.1%)
Cmin steady state (µg/mL)					
Median [min, max]	116 [14.6, 315]	117 [23.8, 359]	116 [14.6, 359]	NA	174 [4.30, 1790]
Geo. mean (Geo. CV%)	111 (49.7%)	116 (46.1%)	113 (48.0%)	NA	168 (61.1%)
5th percentile	44.9	54.8	49.5	NA	62.7
95th percentile	213	227	222	NA	390
Missing	0 (0%)	0 (0%)	0 (0%)	3408 (100%)	210 (0.4%)
AUC steady state (day.µg/mL)					
Median [min, max]	4080 [1200, 9540]	4770 [1980, 11000]	4390 [1200, 11000]	NA	5790 [856, 41600]
Geo. mean (Geo. CV%)	4020 (34.3%)	4780 (28.8%)	4390 (32.9%)	NA	5750 (40.9%)
5th percentile	2200	3020	2520	NA	2970
95th percentile	6730	7620	7260	NA	10800
Missing	0 (0%)	0 (0%)	0 (0%)	3408 (100%)	0 (0%)

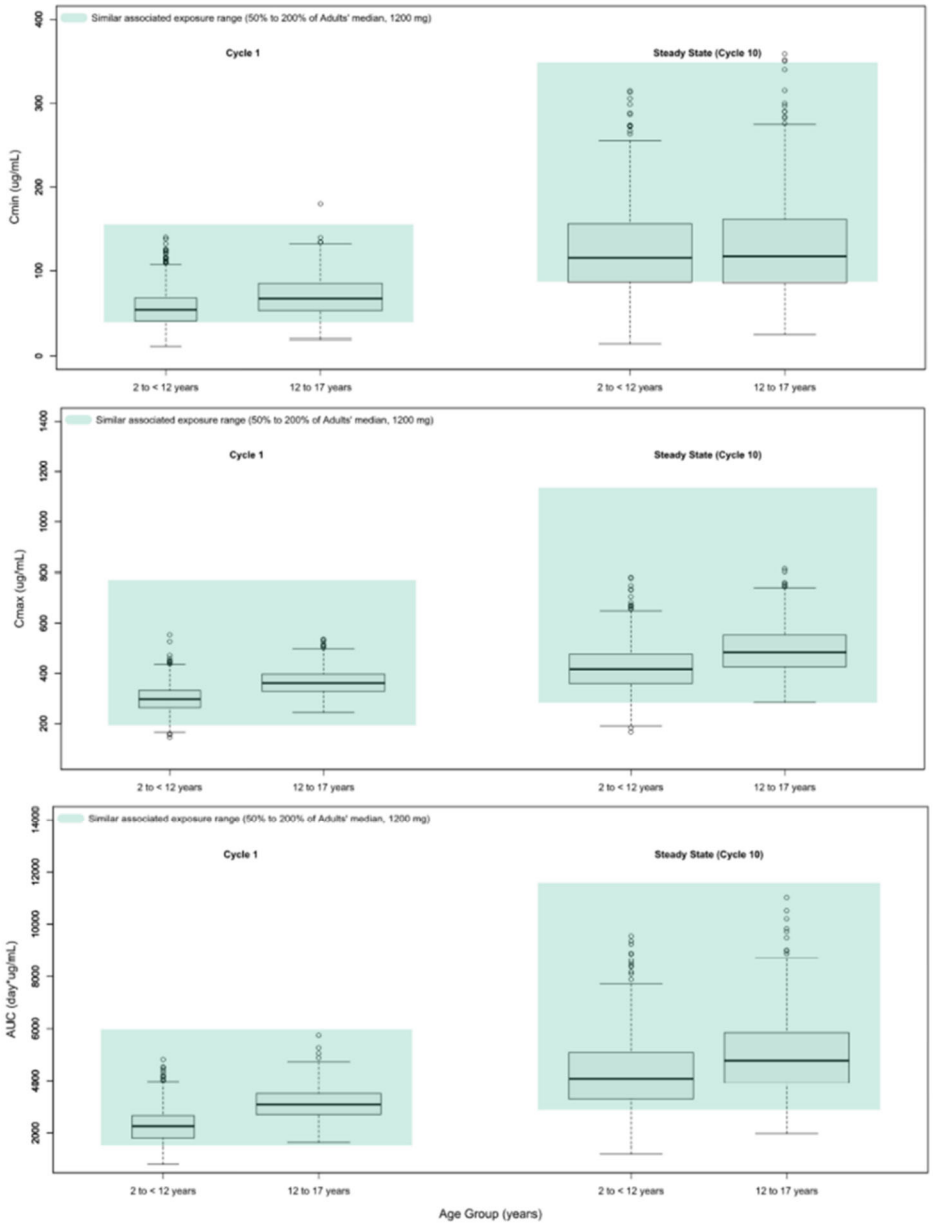
Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 33-35, Table 9.

Figure 2 Comparison of Cmin in Pediatric and Adult Subjects at Cycle 1 and Steady State



Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 37, Figure 9.

Figure 3. Simulated Virtual Pediatric Exposures and Adult Simulated Exposure Range, Stratified by Age Group and Dosing Day.



Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 40-41, Figure 12.

Table 33. Comparison of Simulated Exposures of Virtual Pediatric Subjects and Previously Simulated Adults

	Age Group	Above Adult Maximum (%)	Between 5th and 95th Percentiles (%)	Above Adult 95th Percentiles (%)	Below Adult 5th Percentiles (%)	Below Adult Minimum (%)	Below 50% Adult Median (%)	Above 200% Adult Median (%)	Below 6 µg/mL (%)
Cycle 1									
AUC	2 to <12 years old	0	62.3	0.3	37.4	0	8.4	0.0	0
	12 to 17 years old	0	95.8	2.4	1.8	0	0.0	0.0	0
Cmax	2 to <12 years old	0	76.9	0.0	23.1	0	1.3	0.0	0
	12 to 17 years old	0	98.8	0.0	1.2	0	0.0	0.0	0
Cmin	2 to <12 years old	0	74.3	0.3	25.4	0	23.1	0.0	0
	12 to 17 years old	0	89.8	0.5	9.7	0	7.9	0.1	0
Steady state									
AUC	2 to <12 years old	0	83.4	0.0	16.6	0.0	15.0	0.0	0
	12 to 17 years old	0	95.6	0.1	4.3	0.0	3.6	0.0	0
Cmax	2 to <12 years old	0	74.9	0.0	25.1	0.1	5.6	0.0	0
	12 to 17 years old	0	93.9	0.0	6.1	0.0	0.0	0.0	0
Cmin	2 to <12 years old	0	88.8	0.0	11.2	0.0	25.3	0.0	0
	12 to 17 years old	0	92.1	0.0	7.9	0.0	26.3	0.3	0

Source: Pediatric simulation report: population PK simulations of atezolizumab in pediatric patients, Page 43, Table 10.

The FDA's Assessment:

Applicant's population PK analysis and simulation were verified by the reviewer's independent analysis. In general, the results of the population PK simulation for pediatric patients are consistent with applicant's results. While it's noticed that ADA ratio and median body weight are higher in the virtual pediatric population than the pediatric subjects in Study GO29664, (Table 34) the predicted exposures of atezolizumab in pediatric subjects at 15 mg/kg weight-based dosing regimen, capped at 1200 mg are slightly lower than adult subjects at 1200 mg dosing regimen. In particular, the predicted median exposure in younger pediatric patients (2 to <6 and 6 to <12 years) were slightly lower compared to adult exposure, especially for subjects with lower body weight. (Figure 4 and **Error! Reference source not found.**) While the exposures

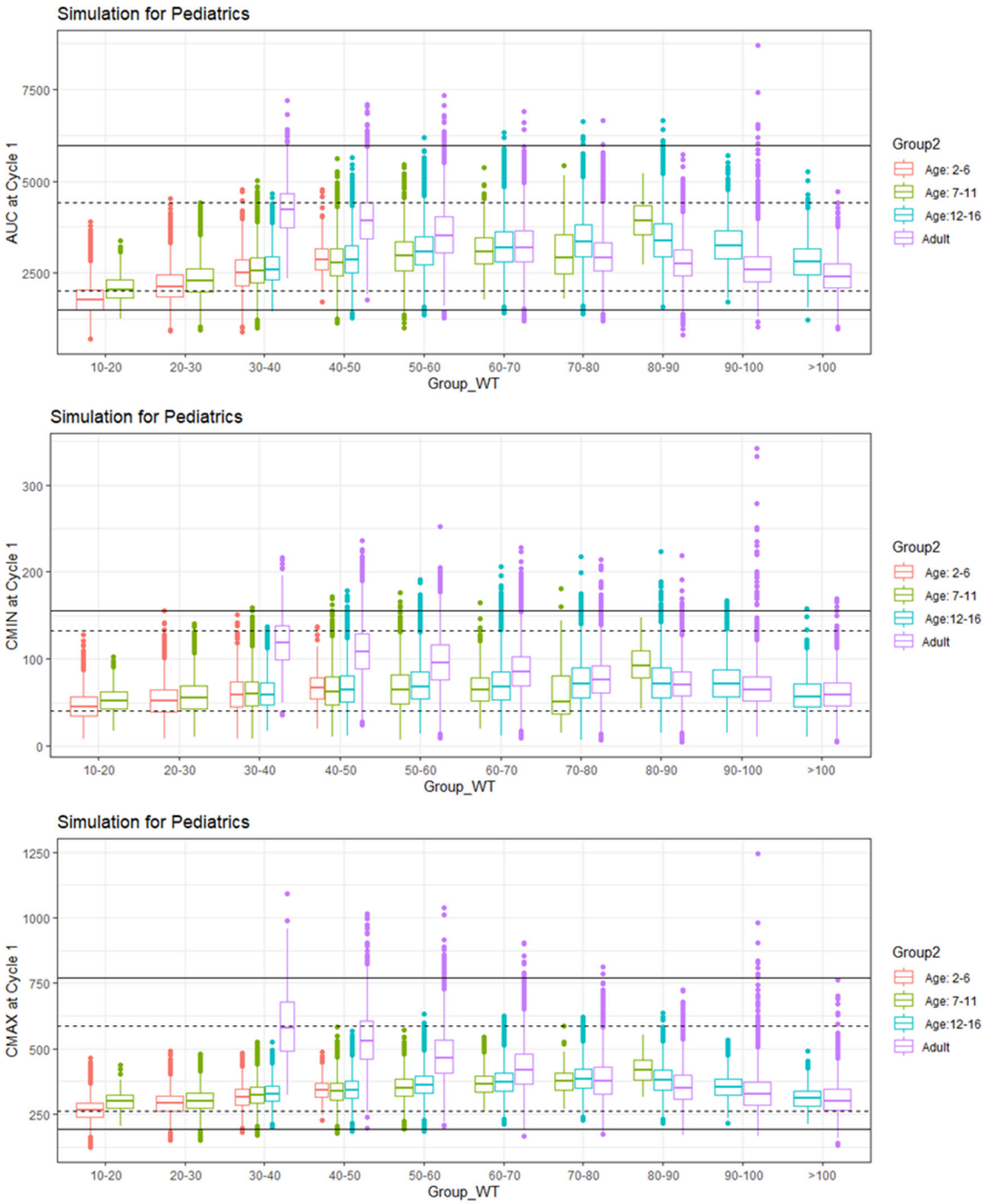
in both age groups are lower than the exposures in adult subjects, the simulated exposure for pediatric subjects were still within the range of simulated median exposure in adults receiving 1200 mg, which would be expected to provide an adequate response in pediatric subjects due to the flat atezolizumab exposure-response relationship for efficacy observed in adult patients across other tumor types.

Table 34. Comparison of Baseline Characteristics Among Virtual Pediatric Population, Pediatric Subjects in Study GO29664and Adult Population

	Pediatrics				Adults
	popPK (Study: iMatrix)		Simulation		Simulation
Age_group	2-11	12-17	2-11	12-17	>=18
N	29	38	1000	1000	50000
Age (year)	7 (2-11)	14.5 (12-17)	7 (2-11)	14.6 (12-17)	-
BW (kg)	22.5 (12-74.4)	51.1 (28.2-105)	26.8 (10 -80.5)	59.7 (34.5 -118)	74 (34.9-163)
ALB (g/mL)	41 (23 -46)	41 (29- 49)	41 (23-46)	42 (29-49)	39 (17-270)
BSLD (mm)	57 (15-301)	63 (11-208)	57 (15-301)	64 (11-208)	63 (10 -329)
SEX (Female)	14 (48%)	16 (42%)	500 (50%)	500 (50%)	67%
ADA	5 (17%)	4 (11%)	300 (30%)	300 (30%)	36%

Source: Reviewer's analysis.

Figure 4. Simulated Virtual Pediatric Exposures and Adult Simulated Exposure Range, Stratified by Age and Bodyweight Groups at Cycle 1.



Source: Reviewer's analysis.

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