CLINICAL REVIEW

Application Type	sBLA
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Priority or Standard	Priority
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Denise Casey, MD Suzanne Demko, PA-C (CDTL)
Review Completion Date	July 14, 2017
Established Name	Ipilimumab
Trade Name	Yervoy®
Therapeutic Class	CTLA-4 monoclonal antibody
Applicant	Bristol Meyers Squibb (BMS)
Formulation(s)	Intravenous infusion
Dosing Regimen	3 mg/kg every three weeks x 4 doses
Indication(s)	Pediatric patients 12 and older with unresectable or metastatic melanoma

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1 Recommendations/Executive Summary

1.1 Recommendation on Regulatory Action

The reviewer recommends approval of ipilimumab at a dose of 3 mg/kg given as an intravenous (IV) infusion over 90 minutes every three weeks for four doses for the treatment of pediatric patients 12 and older with unresectable or metastatic melanoma.

- Efficacy was established in pediatric patients 12 and older through extrapolation from adult data demonstrating an improvement in overall survival in patients with advanced melanoma treated with ipilimumab as compared to the gp100 melanoma peptide vaccine [1].

- Safety was established in pediatric patients 12 and older based on 45 pediatric patients between the ages of two and 20 years old treated across two clinical trials of single-agent ipilimumab. The safety profile of ipilimumab in the pediatric population studied is similar to that of the adult population.

I additionally recommend that Pediatric Exclusivity be granted for Yervoy (ipilimumab) and that the relevant information obtained from pediatric studies of ipilimumab be incorporated into the Yervoy package insert. This recommendation is based on the review findings that the Application Holder fairly responded to the elements outlined in the Pediatric Written Request (PWR) including providing adequate justification for any missing information.

1.2 Executive Summary

Data from two pediatric clinical trials including a total of 45 patients were submitted as the support for this supplemental Biologic License Application (sBLA). Study CA184070 was a multi-center, open-label, 3 + 3 dose-escalation with expansion trial of ipilimumab in 33 patients less than or equal to 21 years of age with various advanced solid tumors including melanoma. Study CA184178 was a multicenter, single-arm, open label study of ipilimumab in 12 pediatric patients 12 to < 18 years of age with previously treated or untreated, unresectable Stage III or Stage IV advanced or metastatic melanoma. Study CA184178 closed early due to poor accrual in the context of emerging adult data demonstrating increased clinical benefit in adult patients treated with ipilimumab in combination with nivolumab as compared to single-agent ipilimumab and the opening of pediatric trials of the combination regimen.

Melanoma in the pediatric population is rare, accounting for 1-4% of all cases of melanoma and approximately 3% of all pediatric cancers [2]. Approximately 75% of

pediatric cases of melanoma occur in patients 15 to 19 years old [3]. Outcomes for pediatric patients with advanced melanoma remain poor with no available treatment shown to improve survival. Furthermore, given the rarity of pediatric melanoma, conducting randomized trials in adequate numbers of patients to reliably investigate new treatments is usually not feasible.

Ipilimumab was approved in 2011 for the treatment of adult patients with unresectable or metastatic melanoma based on a randomized trial demonstrating an improved overall survival in patients treated with ipilimumab as compared to patients treated with a melanoma peptide vaccine. The pediatric trials of ipilimumab were not designed to show a survival effect and in fact did not demonstrate evidence of substantial antitumor activity in pediatric patients with various advanced solid tumors including melanoma. However, based on the similarity in disease characteristics and response to treatment for adolescent and adult patients with melanoma and pharmacokinetic (PK) evidence showing that a dosing regimen of 3 mg/kg every three weeks produces similar exposures in adult and pediatric patients, it is reasonable to extrapolate adult efficacy data to pediatric patients 12 years and older.

Studies CA184070 and 184178 assessed antitumor activity via radiologic response rates in pediatric patients treated with a range of ipilimumab doses. Of the 17 patients 12 years and older with advanced melanoma treated, there were two partial responses (ORR=12%), one of which was durable for more than 15 months. One additional patient had a prolonged stable disease (> 22 months). In the primary trial supporting licensure, the ORR for adult patients receiving single-agent ipilimumab was 11% [1]. These results indicate that the antitumor activity in pediatric patients as measured by ORR is similar to that in adults. It is anticipated that adolescent patients will experience similar improvements in survival despite the modest response rates observed in the pediatric trials.

The safety results of ipilimumab in pediatric patients treated across Studies CA184070 and CA184178 did not identify any unique or exaggerated adverse reactions and was overall consistent with the known toxicity profile in adults. There were a limited number of pediatric patients under the age of 12 treated with ipilimumab in these trials (n=13), but the safety findings in this group, including the incidence and severity of immune-mediated adverse reactions (imARs), were similar to those for adolescents and adults.

In summary, the benefit-risk assessment of pediatric patients 12 years and older with advanced melanoma treated with ipilimumab is considered favorable, and the reviewer recommends extending the adult melanoma indication for the treatment of unresectable or metastatic melanoma to pediatric patients 12 and older.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Ipilimumab

Proprietary Name: Yervoy®

Applicant: Bristol Meyers Squibb (BMS)

Pharmacological Class: Human monoclonal antibody

Mechanism of Action: Antibody to of cytotoxic T-lymphocyte antigen 4 (CTLA-4)

Proposed Indication: Treatment of unresectable or metastatic melanoma in adult and pediatric patients

2.2 Rationale for Pediatric Studies of Ipilimumab

Despite the dramatic improvement in survival observed in the last four decades as a result of the multidisciplinary approach applied to the management of pediatric solid malignancies, the outcomes for patients with recurrent or metastatic tumors remain poor. Investigation of ipilimumab activity in melanoma and non-melanoma pediatric solid tumors was warranted when the initial PWR was issued. The effectiveness of immunologically-directed treatments had not been explored as extensively in pediatric cancers as for many adult tumors, and at least some childhood cancers may benefit from drugs that augment host anti-tumor immune responses. The PWR outlined a pediatric development program aimed toward establishing a safety and pharmacokinetic profile for ipilimumab in pediatric patients and identifying tumor subtypes in which ipilimumab could be of potential benefit with a focus on pediatric metastatic melanoma given the adult clinical experience.

Melanoma in the pediatric and adolescent populations is rare; however, the incidence across all age groups continues to increase at a rate of approximately 3% per year in individuals < 20 years of age [3]. The estimated incidence of melanoma (all stages) reported in 2008 among children age 0 to 14 years was 2 cases per million in North America. Patients < 20 years of age account for approximately 2% of all melanoma diagnoses, and 15 to19 year old patients account for the vast majority of these cases [4-6]. There is no approved treatment for pediatric patients with metastatic melanoma. Similar to adult patients, surgical resection, if feasible, for limited metastatic disease is recommended. For the small subset of patients with distant metastatic disease, prognosis remains poor, and various agents such as interferon, dacarbazine, temozolomide, sorafenib, or interleukin-2 have been utilized [7]. Studies are limited due to very small numbers of children and adolescents with melanoma to conduct pediatric

clinical trials. In addition, age restrictions of current melanoma clinical trials have often precluded the enrollment of pediatric patients.

Prepubescent patients appear to have different risk factors and disease characteristics as compared to adult melanoma patients including higher likelihood of predisposition syndromes, nodal metastases at diagnosis, nodular or spitzoid histology, thicker lesions and head/face/neck primaries. Adolescents, however, appear to be comparable to adult patients with regard to key primary tumor characteristics (site, histology, stage at diagnosis, specific genetic mutations, thickness, and level of invasion) [5, 8]. An extrapolation approach for establishing efficacy in pediatric patients 12 and older, as outlined in the PWR, was supported by the knowledge that adolescents have sufficiently similar disease characteristics and prognoses as adults with melanoma, and the presumption that the pediatric studies of ipilimumab would provide evidence of similar drug exposures between children and adults.

2.3 Summary of Presubmission Regulatory Activities

Ipilimumab is approved for the following indications in adults:

- Treatment of unresectable or metastatic melanoma
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy

Pediatric Regulatory History

July 20, 2012: The Applicant submitted a draft PPSR and requested a Type C meeting to discuss the pediatric development plan for ipilimumab.

August 28, 2012: Type C meeting was held to discuss the two clinical studies included in the draft PPSR:

(1) The NCI sponsored, dose-escalation study in patients 1 to 21 years of age with refractory solid tumors (CA184070/NCI 7458/Study 1)
(2) A BMS sponsored, single-arm, study in adolescents age 12 to $\leq$ 18 years with previously treated or untreated, unresectable Stage III or IV malignant melanoma (CA184178/Study 2).

During this meeting, FDA agreed that the inclusion of the dose-finding Study 1 trial in the PPSR was appropriate, but did not agree that the proposed design of CA184178 (Study 2) was adequate to support issuance of a Written Request. FDA specifically advised BMS that the primary endpoint of an efficacy study should be a time to event endpoint analysis of OS evaluated in a randomized trial. FDA and

BMS discussed the potential option of an extrapolation approach versus directly establishing efficacy through a randomized study.

Other issues discussed during this meeting were the submission timelines for the final study reports, the adequacy of the PK and safety data for the children 12-17 years of age and inadequacy of the PK and safety data for the children 2-11 years of age to support claims for this age group.

October 8, 2012: The Applicant submitted a communication that stated its intent to submit a formal PPSR with plans to extrapolate safety and efficacy data from adults with advanced melanoma in lieu of evaluating efficacy in a separate study. BMS clarified that it did not intend to pursue labeling claims for children less than 12 years of age.

January 18, 2013: The Applicant submitted a PPSR and a background document which provided rationale for extrapolating efficacy from the approved adult melanoma indication. Although the rationale for extrapolation was reasonable, BMS did not modify the study design or treatment plan for CA184178 (Study 2); the primary endpoint was one year survival rates evaluated in a single arm study, and the treatment plan called for a 10 mg/kg dose every 3 weeks for 4 doses followed by infusions once every 12 weeks until disease progression or intolerable toxicity.

March 11, 2013: FDA issued an Inadequate Study Request letter and recommended that BMS resubmit the PPSR addressing the following comment:

You propose that the efficacy of ipilimumab for the treatment of melanoma in pediatric patients will be based on the extrapolation of adult data. In the absence of data from adult efficacy studies demonstrating that the selected dose of 10 mg/kg intravenously every three weeks for four infusions and then every 12 weeks ("retreatment") in Study CA184178 is an active and safe dose and dosing schedule, the proposed pediatric study will not be adequate to support extrapolation of the efficacy data.

February 4, 2014: The Applicant submitted a revised PPSR and stated its intent to seek a PWR for ipilimumab using the approved adult indication in adolescents, supported by the conduct of the two ongoing clinical studies (NCI 7458/Study 1 and CA184178/Study 2) and extrapolation of efficacy established in adults with advanced melanoma. BMS also submitted a protocol amendment to CA184178/Study 2 to address FDA's comment regarding the selected dosing regimen in the Inadequate Study Request letter. The protocol for Study 2 (CA184178) was amended to administer the approved dose of 3 mg/kg every three weeks for a total of 4 doses, and to remove the every 12 week treatment administration. Patients were still permitted one course of retreatment therapy of 4 infusions (one dose of 3mg/kg every 3 weeks) if they experienced disease progression after previously having an objective response or stable disease $\geq$ 24 weeks when treated with ipilimumab.

July 7, 2014: FDA issued a PWR for the investigation of the use of ipilimumab in the treatment of adolescent patients with malignant melanoma. The original WR included the following clinical studies:

Study 1:
An open label, dose-escalation study of ipilimumab in pediatric patients (aged 1 to 21 years) with refractory cancers .

Study 2:
A clinical study of ipilimumab in pediatric patients (12 to < 18 years) with unresectable or metastatic melanoma to evaluate PK and safety.

- Efficacy in adolescent patients (12 to < 18 years) will be determined by extrapolation from results observed in adult patients treated with ipilimumab for unresectable or metastatic melanoma.

Study 3:
A clinical study of ipilimumab in pediatric patients evaluating the anti-tumor activity (i.e., durable objective response rate) of ipilimumab in specified relapsed or treatment-refractory solid tumors other than melanoma. Primary tumors in which ipilimumab activity may be evaluated in this study include, but are not limited to, rhabdomyosarcoma and other soft tissue sarcomas, Ewing sarcoma, osteosarcoma, neuroblastoma, Wilms tumor, Hodgkin's or non- Hodgkin's lymphoma.

Study 4:
If further evaluation of ipilimumab is warranted based on results of Studies 1, 2, or 3, one or more studies will be conducted to establish the safety and efficacy of ipilimumab in specific pediatric indications.

July 20, 2015: The Applicant submitted a proposed amendment to the WR to BLA 125377 deleting Study 3. BMS stated that there was a lack of efficacy signal with ipilimumab monotherapy in pediatric non-melanoma solid tumors and that an expert panel recommended not evaluating single-agent ipilimumab in pediatric cancers any further, and that ipilimumab should be investigated in the pediatric population in combination with nivolumab. FDA and BMS had two teleconferences discussing the proposed amendment and BMS's rationale.

April 11, 2016: FDA issued an amended WR deleting Study 3 and revising the study completion deadlines. In the cover letter, FDA stated that it did not agree with BMS's rationale for the amendment because ipilimumab was not evaluated in a population with adequate representation of pediatric solid tumors other than melanoma and osteosarcoma. FDA agreed to remove Study 3 from the WR because of expected

accrual challenges with the ongoing pediatric nivolumab/ipilimumab combination study under the nivolumab PWR.

May 6, 2016: The Applicant submitted a Type C meeting request to discuss the available pediatric data to support a labeling claim for a sBLA and to obtain guidance with respect to amending the ipilimumab WR. BMS stated that members of DMC communicated that due to current accrual and evolutions in scientific opportunities, CA184178/Study 2 would not complete its endpoints, and that further accrual appeared futile. BMS stated that further feedback from providers indicated that the availability of new immuno-oncology treatments has reduced the pool of eligible subjects further, leading to no enrollment since April 2015. BMS proposed to develop a population pharmacokinetic (PPK) model using pooled pediatric data from Studies 1 and 2, as well as adult PK data to define a recommended dosing regimen for ipilimumab for the treatment of adolescents (12 – ≤ 18 years of age) with advanced and metastatic melanoma. The proposed PK-based extrapolation would be performed by:

- characterizing the PK of ipilimumab in pediatric subjects using a PPK modelling approach, and
- applying the PPK model to simulate ipilimumab exposure to determine an ipilimumab dose for adolescents that achieves exposures similar to that in adults treated with the approved adult dose of 3 mg/kg Q3W for a total of 4 doses.

FDA stated that the proposed approach of using population pharmacokinetic analysis through exposure matching to determine the recommended dosing regimen appeared reasonable. The adequacy of the modeling and simulation analyses to support the recommended dosing regimen and labeling claims of ipilimumab for the treatment of adolescents (12 to ≤ 18 years) with advanced and metastatic melanoma would be assessed during the review of the sBLA.

With regard to amending the PWR, FDA stated that if BMS concluded that the study was complete, all study data collected to date should formally be submitted to the sBLA for review. The submission should include a cover letter providing justification for any missing information outlined in the PWR, such as early closure of Study 2 and omission of Study 4.

January 23, 2017: The Applicant submitted the sBLA containing pediatric data and revised labeling based on these data.

April 14, 201: A teleconference between FDA and the Applicant was held to discuss extension of the adult melanoma indication to pediatric patients 12 years and older based on extrapolation of efficacy from adult data (as was outlined in the PWR). BMS agreed that the indication should be revised to include pediatric patients 12 and older and stated plans to submit modified labelling to the BLA.

April 27, 2017: BMS submitted revised labelling including the pediatric indication to the BLA as an amendment. Additional revisions were proposed for Sections 8 and 12 of the product label.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contained the debarment certificate, sufficient datasets and relevant case report forms. The quality and integrity of the submission were adequate to permit a comprehensive review.

3.2 Compliance with Good Clinical Practices

The Clinical Study Reports (CSRs) for Studies CA184070 and CA184178 state that the trials were conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

3.3 Financial Disclosures

This submission contained the required financial disclosure information for clinical investigators who participated in Studies CA184070 and CA184178. There were no disclosable financial interests evident for Study 184070. For Study 184178, one of the 74 investigators, Dr. Wolchok from Memorial Sloan Kettering Cancer Center, reported disclosable financial interest in the category of significant payments of other sorts due to his participation in the Bristol- Myers Squibb II-ON network and his institution's receipt of funding from the following IION research grants during the conduct of this clinical trial. The stated payment to the institution across these research grants was (b) (4). The potential bias introduced by Dr. Wolchok's disclosed financial interest should have minimal impact on the results of the study given the number of investigators, the objective primary endpoint of survival at 12 months and the presence of an external Data Monitoring Committee.

4 Sources of Clinical Data

4.1 Tables of Clinical Trials

This submission contains the results of two clinical trials conducted in response to the PWR: Studies CA184070 (Study 1 in the PWR) and CA184178 (Study 2 in the PWR).

Table 1: Clinical Trials of Ipilimumab Conducted in Response to the PWR

Study Number	Title	Study Objectives	Design	Number of Patients and Doses Evaluated
CA184070/ NCI7458	A phase 1 study of ipilimumab (anti-CTLA-4) in children, adolescents, and young adults with treatment refractory cancer	To determine the tolerance and toxicity profile of ipilimumab at a range of doses up to, but not exceeding, the highest dose tolerated in adults in patients ≤ 21 years To assess the PK of ipilimumab administered IV in patients ≤ 21 years	Open label, multicenter dose-finding study. Treatment phase: IV ipilimumab administered on day 1 of each 21-day cycle for four cycles. Maintenance Phase: IV ipilimumab administered every 12 weeks.	A total of 33 patients 3-21 years of age 3 at 1 mg/kg; 3 at 3 mg/kg; 14 at 5 mg/kg; 13 at 10 mg/kg
CA184178	A phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated, unresectable stage III or stage IV malignant melanoma	To estimate the survival rate at 1 year To assess safety and tolerability, specifically the frequency of severe (Grade 3–5) immune-mediated adverse reactions of ipilimumab in adolescent patients	Open label, multicenter study Treatment phase: Ipilimumab 3 or 10 mg/kg* IV every three weeks for four doses. Retreatment: Patients who experienced objective response or stable disease for ≥ 3 months beginning at week 12 were eligible for one course of retreatment therapy consisting of another four infusions)given as one infusion every three weeks).	12 total: 8 at 10 mg/kg; 4 at 3 mg/kg*

*Protocol was amended to revise treatment dose to that recommended in the approved product label for the treatment of melanoma in adult patients

4.2 Review Strategy

The objectives of this review were two-fold: to determine if the Applicant fairly responded to the elements outlined in Amendment #1 of the PWR; and provide recommendations for incorporation of relevant pediatric information derived from the conduct of the studies outlined in the PWR into the Yervoy package insert. It should be noted that the PWR outlined rationale for an extrapolation of adult efficacy data to pediatric patients 12 years of age and older for the melanoma indication; therefore, the pediatric safety and PK results were the primary sources of data to support the proposed modifications to the indication statement and Section 8.4 of the product label for Yervoy. The CSRs for the clinical trials submitted with this supplement and the corresponding datasets were reviewed. Documentation from previous interactions with FDA regarding the pediatric development plan for ipilimumab, the PWR, and relevant published literature were also reviewed.

4.3 Discussion of Individual Clinical Trials

4.3.1 Study CA184070

Study Title: A Phase I Study of Ipilimumab (Anti-CTLA-4) in Children, Adolescents, and Young Adults with Treatment Refractory Cancer

Protocol Milestones
This clinical trial was conducted by three investigators at three sites in the U.S. from September 8, 2008 through April 13, 2014.

Study Objectives
The primary objective was to determine the tolerance and toxicity profile and assess the pharmacokinetics (PK) of ipilimumab administered intravenously (IV) in patients less than 21 years of age. The secondary objectives were to assess antitumor effects and immunomodulatory activity of ipilimumab in pediatric patients.

Study Design
Study CA184070 was a multi-center, open-label, 3 + 3 dose-escalation trial in 33 patients less than or equal to 21 years of age.

Eligibility Criteria

Patients were required to meet the following key inclusion criteria:

- $\geq$ 1 year to $\leq$ 21 years of age
- Evaluable disease

- Histologically confirmed, refractory, relapsed solid malignant tumors including rhabdomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's or non-Hodgkin's lymphoma, and melanoma
- No known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
- Karnofsky/Lansky Score of ≥50

Patients were excluded based on the following key exclusion criteria:

- Diagnosis of primary brain tumors or brain metastasis (unless the metastasis was previously treated and the subject was off steroids for at least 4 weeks and considered stable)
- Unrelated systemic illness as judged by the investigators that would compromise the patient's ability to tolerate the agents, were
- Critically-ill or medically unstable, autoimmune disease, history of allogeneic bone marrow transplantation
- Active diarrhea, history of intermittent bowel obstruction, active eye inflammation or uveitis, symptomatic pleural effusion
- Treatment with immunomodulatory agents within 14 days prior to study entry
- Treatment with myeloid growth factors within 72 hours prior to study entry
- Pregnancy or breastfeeding

Treatment Plan
Ipilimumab at doses of 1, 3, 5 or 10 mg/kg according to the 3+3 dose escalation plan was administered IV over 90 minutes on Day 1 of each 21-day cycle for four cycles. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing). No intra-patient dose escalation was allowed. The DLT monitoring period was six weeks.

The protocol stated that the cohort of the MTD was to be expanded to enroll a total of 12 patients to obtain sufficient data for pediatric PK and for tolerability within each age group of < 12 years and ≥ 12 years. Because there appeared to be a different toxicity profile in patients <12 years old, the expansion cohort of 10 mg/kg was divided into 2 cohorts in 2011. As a result, the 5 mg/kg dose cohort was expanded to a total of 14 patients that included 6 patients <12 years, and the 10 mg/kg dose cohort was expanded to include more patients ≥ 12 years old. Patients continued treatment until the occurrence of unacceptable toxicity or disease progression.

Re-induction therapy (ipilimumab at the previously assigned dose administered every three weeks for four cycles) was permitted for patients who developed progressive disease (PD) during maintenance, for patients who stopped maintenance treatment because of a complete response (CR) and then experienced PD and for patients who had an initial partial response (PR), CR or stable disease (SD) for at least three months with a subsequent PD. Patients who experienced pre-specified drug-related AEs or delayed dosing beyond 35 days due to immune-related AEs (irAEs) or who had been discontinued for an AE were not eligible for re-induction.

Dose Modifications for Adverse Events

Toxicity monitoring was according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 until July 2010 and Version 4.0 from August 2010 onward. The following definition was used for DLT:

- *Non-hematologic DLT*: any non-hematologic Grade 3 or 4 toxicity or Grade 2 toxicity requiring immunosuppressive or hormone replacement therapy judged to be at least possibly related to ipilimumab.
- *Hematologic DLT:* Grade 4 neutropenia or thrombocytopenia, which persisted for 5 days at any time during the treatment cycle or any grade 5 toxicity at least possibly attributable to ipilimumab. Grade 3 hematologic toxicity was not considered dose limiting.

Patients who experienced the following AEs were removed from study treatment:

- Occurrence of DLT
- Grade 1 diarrhea/colitis which is not clearly ascribed to another etiology
- Grade 2 endocrine dysfunction (e.g. hypothyroidism, hypophysitis)
- Grade 2 or greater autoimmunity of critical organs including lung, heart, bowel, kidney or CNS (including eye).

Patients who experienced a grade 2 liver toxicity which resolved to Grade 1 by the end of the treatment cycle were allowed to continue receiving ipilimumab at full dose. Patients who developed Grade 2 or 3 hematologic toxicity, but were benefiting from the therapy as evidenced by a tumor response or stable disease with improvement in clinical symptoms could elect to continue to receive ipilimumab but the dose was reduced by 50%. If toxicity persisted after one dose reduction, ipilimumab was permanently discontinued.

Discontinuation Criteria

Patients were discontinued from study therapy for any of the following conditions:

- unacceptable toxicity
- progressive disease (if criteria for re-induction were not met; patients also were permitted one additional dose of ipilimumab if the PD was up to 50% and there had been no DLTs)

- completion of protocol-defined therapy (up to 2 years of treatment)
- pregnancy.

Patients were withdrawn from the study for any of the following reasons:

- if deemed in best interest of patient
- withdrawal of consent/patient refusal of further treatment
- death
- completion of the two year follow-up period from the initiation of therapy.

Study Schedule

Table 2, copied from the Applicant's submission, outlines the schedule of assessments for Study CA184070.

Table 2: Schedule of Assessments for Study CA184070

PROCEDURE	VOL (CC) TUBE[15]	ENTRY (WITHIN 72 HRS OF C1D1)	C1D1 OR D0	C1 D1	C1 D2	C1 D4	C1 D8	C1 D15	PREDOSE C2D1	C2D1	C2,3,4	PREDOSE C3D1	C3D1	PREDOSE C4D1	C4D1	PREDOSE C5-8	C5-8 D1	C5-8	OFF STUDY
Ipilimumab[1]				X						X			X		X		X		
Physical Exam		X	X	X	X	X	X	X	X	X	wkly	X	X	X	X	X	X	bi-wkly	X
Weight, Vitals[2]		X	X	X[2]	X	X	X	X	X	X[2]	wkly	X	X[2]	X	X[2]	X	X[2]	bi-wkly	X
CBC/diff, Plts, retic	2ml LTT	X	X		X	X	X	X	X		wkly	X		X		X		bi-wkly	X
Direct Coombs	6ml LTT	X							X			X		X		X			X
PT/PTT, Fibrinogen	3.5mlBTT	X	X		X	X	X	X	X			X		X		X			X
C-Reactive Protein		X							X			X		X		X			
Chemistries[3]	10ml SST	X	X		X	X	X	X	X		wkly	X		X		X		bi-wkly	X
Trigly,amylase,lipase	3ml SST	X							X			X		X		X			
Endocrine[4]	see below	X							X			X		X		X			X
Urinalysis, with micro		X	X		X	X	X	X	X		wkly	X		X		X		bi-wkly	X
Urine B-HCG[14]		X	X						X			X		X		X			
Autoimmune Profile[5]	5ml SST	X							X			X		X		X			X
HLA typing	2ACD-8mL	X																	
FACS Analysis[6]	5ml LTT		X						X			X							
Serum cytokine[6]	8.5mlSST		X						X			X		X		X			X
Ipilimumab PK[7]	4ml STT			X[7]	C1,3	C1,3	C1,3	C1,3	X			X	X	X	X	X			
HAHA[8]	4ml STT	X							X			X		X		X			X
Lymphocyte Functional Studies[9]	GTT:1cc/kg (max 50 cc)		X						X										
Bone Marrow, Urine[10]		X										X				X			X
EKG/Echo		X										X				X			X
CXR/CT/MRI[11]		X										X				X			X
Nuclear Med[12]		X										X				X			X
Eye Examination[13]		X										X							X

[1] Ipilimumab will be administered intravenously over 90 minutes on day 1 of each treatment cycle.

[2] Vitals will be obtained at every 30 minutes during the infusion and at hours 1, 2, 4, and 6 post completion for initial the cycle .Subsequent cycle vitals dictated by patient tolerance, but obtained no less than just prior to Ipilimumab administration every 30 minutes during infusion and 1 hour post dose, and at all clinic visits. Adjustments to these guidelines may be required based on practical clinical considerations.

[3] Chemistries: electrolytes, glucose, BUN, creatinine, albumin, total protein, calcium, magnesium, phosphorus, uric acid, CPK, LDH, alkaline, phosphatase, SGOT, SGPT, total bilirubin.

[4] Endocrine: Run from 4ml in a single SST: T3, T4, Thyroid binding globulin, free T4, Thyroid Stimulating Hormone, **AM cortisol**, Growth Hormone. Run from a second SST: anti-Thyroid antibody. In a third 4 mL SST: Insulin like growth factor-1. In a plain RTT Insulin like growth factor Binding protein-3 and anti-21-hydroxylase (send out to Mayo). In a LTT AM cortisol which must be kept on ice to lab.

[5] Autoimmune Profile: Rheumatoid factor (RF), ANA. **If after C1D1, ANA positive (>2)**: anticardiolipin antibody (ACA), anti-neutrophil cytoplasmic antibody (ANCA), C3, C4, anti-DNA, anti-SSA, anti-SSB.

[6] FACS analysis and Serum Cytokine analysis: immediately prior to ipilimumab administration (hour 0, day 1) Cycle 1 ,2 and prior to Cycle 3.

[7] Ipilimumab Pharmacokinetics: Cycles 1&3: Just prior to ipilimumab administration (ie hour 0), 2 hours post ipilimumab infusion, days 2, 4, 8, and 15. Just prior to subsequent doses, and off study.

[8] HAHA (anti-idiotype, human anti-human antibody): Baseline immediately prior to ipilimumab administration (same SST as PK when drawn at same timepoint), prior to all subsequent doses, and off study.

[9] Lymphocyte for functional studies: Immediately prior to ipilimumab administration (hour 0, day 1) Cycle 1 and prior to Cycle 2.

[10] Bone Marrow for patients with bone marrow only evidence of neuroblastoma. Urine Vanillymandellic acid (VMA) and homovanillyc acid (HVA) at entry and subsequently if positive.

[11] XR: To be done if CT of the chest not performed as part of disease evaluation to evaluate for pulmonary lesions/infiltrates/sarcoidosis

[12] If appropriate, Nuclear Medicine: Bone scan, PET Scan, or MIBG scan (neuroblastoma patients only)

[13] Eye examination to include but not be limited to normal and dilated slit lamp examination.

[14] For females of childbearing potential only.

[15] BTT = blue top tube (sodium citrate), LTT = lavender top tube (potassium edta), GTT = green top tube (sodium heparin), RTT = red top tube (no additives SST = serum separator tube (ours are red/yellow top)

Source: CSR for Study CA184070

Statistical Plan
The protocol specified that descriptive statistics would be used to summarize safety, efficacy and PK findings by dose cohort. No formal statistical testing was performed.

4.3.2 Study CA184178

Study Title
A phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated, unresectable stage III or stage IV malignant melanoma

Protocol Milestones
This clinical trial was conducted by 10 investigators at 10 sites globally from April 23, 2013 to June 22, 2016.

Study Objectives
The primary objectives were to assess safety and tolerability, specifically the frequency of severe immune-mediated adverse reactions (imARs) with ipilimumab and to estimate the survival rate at one year in adolescent patients (12 to < 18 years). The key secondary objectives were to estimate disease control rate (DCR), PFS, BORR and OS.

Study Design
Study CA184178 was a non-randomized, multicenter, single-arm, open label study of ipilimumab in pediatric patients 12 to < 18 years of age with previously treated or untreated, unresectable Stage III or Stage IV advanced or metastatic melanoma.

In the original protocol, 40 patients were planned to be enrolled in order to treat approximately 30 patients at the 10 mg/kg dose level (the MTD established in Study CA184070 for patients 12 and older). The protocol was subsequently amended to include at least 20 patients treated at the 3 mg/kg dose level based on the approved adult dose. Study closure was recommended by the DMC in 2016 based on poor enrollment due to the rarity of the disease and the availability of competing therapies. At the time of study closure, 14 patients were enrolled and 12 were treated with ipilimumab: four patients received the 3 mg/kg dose and eight received the 10 mg/kg dose.

Eligibility Criteria

Patients were required to meet the following key inclusion criteria:

- ≥ 12 to < 18 years of age
- Evaluable disease
- Histologically confirmed malignant melanoma

- Presence of brain metastases was permitted if the patient was free of neurologic symptoms related to the brain lesions and did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab
- Karnofsky Score of ≥50

Patients were excluded based on the following key exclusion criteria:

- Primary ocular melanoma
- Active brain metastases requiring corticosteroids
- History of or active autoimmune disease or immunodeficiency or history of allogeneic bone marrow transplantation
- Use of systemic immunosuppressive agents within four weeks of study entry
- History of allergic reaction to a recombinant protein
- Treatment with cytotoxic or any other investigational agents within four weeks of study entry

Treatment Plan
Patients were treated with ipilimumab (10 or 3 mg/kg) every three weeks for four doses (weeks 1, 4, 7, and 10). After completion of the 4 infusions, a safety and tumor assessment at Week 12 was performed. Patients with an initial PR or CR or stable disease of at least 3 months who subsequently experienced a confirmed PD per immune-related Response Criteria (irRC) were eligible to enter one Re-Treatment phase. Patients were followed for toxicity and survival every 12 weeks after completion of study treatment.

Toxicity Monitoring
Toxicities were graded using NCI CTCAE Version 4.0. Patients were followed for 90 days following AEs.The protocol included diagnostic and management guidelines for infusion reactions and imARs.

Dose Modifications for Adverse Events
Dose reduction was not permitted. Dose delays were required for any ≥ Grade 3 skin-related adverse event or any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the Investigator, warranted delaying the dose. A dose delay longer than 60 days after the scheduled dose led to permanent discontinuation.

Protocol-Specified Discontinuation Criteria
Patients were discontinued from study therapy for occurrence of any of the following:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment

- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction
- Any other ≥ Grade 3 non-skin related adverse event with the exception of laboratory abnormalities;
- Any Grade 4 laboratory abnormalities
- AST or ALT > 8 x ULN
- Total bilirubin > 5 x ULN
- Any other Grade 4 adverse event
- Allergic/infusion reaction while receiving study drug at a slower infusion rate due to a prior allergic/infusion reaction
- Any motor neurologic toxicity ≥ Grade 3 regardless of causality
- Any ≥ Grade 3 treatment-related sensory neurologic toxicity
- Dose delay of > 60 days from the scheduled dose due to toxicity
- Disease progression

Tumor Response Criteria

Tumor response-based endpoints were measured using both modified World Health Organization (mWHO) criteria and ifRC for treatment decisions.

Study Schedule

Table 3, copied from the Applicant's submission, outlines the schedule of assessments for Study CA184178.

Table 3: Schedule of Assessments for Study CA184178

Phase	Screening	Treatment / Retreatment			Tumor Assessments	EOT	Tox/PD Follow-up	Survival Follow-up	
Procedure	(within 14 days prior to dosing)	Wk 1, Day 1	Wk 4, 7, 10 Day 22, 43, 64 (± 3 days)	Wk 12 Day 78 (± 3 days)	Wk 24 Day 162, (± 3 days)		(± 14 days)	(± 14 days)	Notes
Inclusion/Exclusion Criteria	X								Section 3.3.1
Medical History	X								Section 5.3.1
Physical Examination	X								Section 5.3.1
Targeted Physical Examination		X	X	X		X			Section 5.3.1
Vital Signs	X	X	X	X		X			Section 5.3.2
Pre-treatment Events	X								Record findings within 14 days of first dose
Adverse Events Assessment		X	X	X	X	X	X		Section 3.1.1.5, Section 6. Collect up to 90 days after last dose.
Prior & concomitant medications, procedures & therapies	X	X	X	X	X	X			Section 3.4, Section 5.3.6
ECG (12-lead)	X								At screening and as clinically indicated (Section 5.3.3)
Karnofsky/Lansky PS	X	X	X	X		X			Section 5.3.5, Appendix 1
Pregnancy test (FOCBP)	X	X	X			X			≤ 24 hr pre-dose, Section 3.3.4, Section 5.3.3 and Section 6.4

Hematology (CBC/diff)	X	X	X	X		X			Obtain ≤ 72 hr pre-dose. Section 5.3.7
Chemistry (including electrolytes)	X	X	X	X		X			Obtain ≤ 72 hr pre-dose. Review LFT results prior to drug administration. Section 5.3.7
Endocrine (TSH, Free T3/T4, ACTH)	X		TSH sample collection to be done prior to each Treatment/Retreatment dose; all others as clinically indicated.						Section 5.3.7.3
Pharmacokinetic		X	X	X		X			Section 5.5 (Table 5.5-1) for detailed instructions and sampling time points
Anti-Drug Antibody		X	X	X		X			Section 5.5 (Table 5.5-1) and Section 5.8 for detailed instructions and sampling time points
Biomarkers		X	Day 22	X					Treatment phase only. Section5.6
Radiographic Tumor Assessment (CT or MRI)	X (within 28 days prior to dosing)			X	X[a]		X[a]		a: At Week 24 and then every 12 weeks for the first 2 years and then every 6 months until confirmed and documented irPD
Survival	X	X	X	X	X	X[b]	X[b]	X[b]	b: Every 12 weeks from end of treatment until 1° endpoint analysis has been conducted, then every 24 weeks. Section 3.1.1.6
Subsequent anti-cancer tx						X	X	X	Section 5.3.6
Study Drug		X	X			X[c]			c: Eligible subjects can receive one retreatment upon progression. Section 3.1.1.3

Source: Clinical Study Report for Study CA184178.

Statistical Plan

The primary endpoints of this study were overall survival rate at 1 year and the frequency of severe imARs. The 1-year overall survival rate was based on a Kaplan-Meier estimate. The protocol stated that with 20 3 patients treated at the 3 mg/kg dose, the lower boundary of the two-sided exact 95% confidence interval (CI) for the 1-year survival rate will be at least 27.2% if 10 or more are alive after 1-year. The maximum width of the CI is 46%. Assuming that the incidence of high-grade imARs is at least 15%, a sample size of 20 patients would provide a two-sided exact 95% CI of 3.2 to 37.9%.

5 Evaluation of the Applicant's Fulfillment of the Requirements of the Pediatric Written Request

The Applicant requested a Type C meeting on May 6, 2016 to discuss the available pediatric data to support a labeling claim in a supplemental BLA and to obtain guidance with respect to amending the ipilimumab WR. BMS stated that members of the DMC determined that due to the current accrual times and other scientific opportunities that were evolving with regard to combination regimens for the treatment of advanced melanoma (e.g., ipilimumab plus nivolumab), completion of Study CA184178 (Study 2) was unlikely to be feasible, and further accrual appeared futile. BMS stated that further feedback from providers indicated that the availability of new immuno-oncology treatments had reduced the pool of eligible patients leading to poor enrollment despite enhanced recruitment efforts. In the preliminary comments issued on July 8, 2016, FDA advised the Applicant to submit all available study data to the sBLA for review and to include a cover letter providing justification for any missing information from that outlined in the PWR, such as early closure of Study 2 and omission of Study 4.

Key points made in the Applicant's justification provided in the cover letter for the sBLA are as follows:

- There were considerable enrollment challenges for Study CA184178.
- Members of the DMC communicated to BMS that due to the changing landscape for immunotherapies, further accrual to Study 2 appeared to be futile (official DMC meeting minutes also submitted).
- Although study CA184178 did not meet its original planned enrollment as described in the PWR, sufficient data from study CA184178 in addition to data from study CA184070 (Study 1) was collected to perform modeling and simulation analyses to inform a labeling update for pediatric information.
- Study 4 of the PWR was intended to establish the safety and efficacy of single agent ipilimumab in specific pediatric indications if further evaluation of ipilimumab was warranted based on the outcomes of Studies 1 and 2. Since the outcome of Studies 1 and 2 do not support further evaluations of single-agent ipilimumab in pediatric patients, BMS had recommended removal of Study 4 from the PWR in the Briefing Document submitted to FDA on June 16, 2016.
- As advised by FDA in the preliminary comments received on July 8, 2016, the PWR was not amended.
- The Applicant has complied with the PWR, with the exception of Study 2 and Study 4 for the reasons described above. Based on this, the Applicant requests the determination of Pediatric Exclusivity.

After conducting a thorough interdisciplinary review of the data submitted, the clinical, clinical pharmacology, and statistical reviewers concluded that the Applicant fulfilled the majority of requirements of the PWR and provided adequate justification for any missing information. Table 4, adapted from the Applicant's submission, outlines the items

contained in the PWR Amendment 1 issued on April 11, 2016 and the information and responses submitted by the Applicant in this sBLA.

The review team recommends that pediatric exclusivity be awarded to the Applicant. The Pediatric Exclusivity Board provided concurrence with this recommendation on July 14, 2017. DOP2 will issue a letter notifying the Applicant that exclusivity was granted for pediatric studies of ipilimumab conducted in response to the PWR under section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a).

Table 4: Summary of the Applicant's Response to the Pediatric Written Request

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Nonclinical Study(ies) The nonclinical studies have been completed and results have been reported to FDA prior to the initiation of clinical studies. Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.	**Nonclinical Studies/Study Design** In alignment with the PWR, no additional animal studies have been conducted.	The response fulfills the requirements of the PWR.
Clinical Studies *Study 1*: An open label, dose-escalation study of ipilimumab in pediatric patients (aged 1 to 21 years) with refractory cancers. *Study 2*: A clinical study of ipilimumab in pediatric patients (12 to ≤ 18 years) with unresectable or metastatic melanoma to evaluate PK and safety.	**Clinical Studies/Study Design** *Study 1:* In alignment with the PWR, study CA184070 is a completed multi-center, Phase 1, open-label, dose-escalation study of ipilimumab in pediatric patients with untreatable, relapsed or refractory solid malignant tumors who did not have a curative option with standard therapy *Study 2*: In alignment with the PWR, study CA184178 is a completed Phase 2 study of ipilimumab in children and adolescents (12 to	The response fulfills the requirements of the PWR. The Applicant informed DOP2 that Study 2 was to be closed due to poor accrual and therefore would not enroll the

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
	<18 years) with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma. Note, because the study population seen at participating sites was more rare than anticipated, as well as the availability of competition from more recent emerging therapies (eg, anti-PD-1), the majority of sites were unable to enroll a participant over the 3.5-year period, and study closure was recommended by the Data Monitoring Committee (DMC).	30 patients as stated in the PWR. Members of the DMC communicated to BMS that due to the changing landscape for immunotherapies and combination regimens (e.g., ongoing adult studies of nivolumab plus ipilimumab with encouraging results in melanoma), further accrual to Study 2 appeared to be futile. The December 11, 2015 Official DMC meeting minutes were submitted with the application. As a result, BMS decided to close Study CA184178. BMS requested a teleconference with FDA to discuss the implications of study closure for the PWR and whether or not an amendment was required. DOP2 advised BMS to submit the available data in the sBLA with justification for not completing

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
		specific requirements outlined in the PWR, and BMS provided this justification. DOP2 determined that the justification was acceptable.
Efficacy in adolescent patients (12 to ≤ 18 years) will be determined by extrapolation from results observed in adult patients treated with ipilimumab for unresectable or metastatic melanoma.	In alignment with the PWR, efficacy results from adult patients treated with ipilimumab for unresectable or metastatic melanoma were extrapolated to adolescent patients, as described in the Pop PK document.	DOP2 had agreed, prior to issuing the PWR, to the extrapolation approach for efficacy in adolescent patients with advanced melanoma based on the similar biology and natural history of melanoma in adolescent and adult patients and evidence of similar exposures using popPK data.
Study 4: If further evaluation of ipilimumab is warranted based on results of Studies 1 or 2, one or more studies will be conducted to establish the safety and efficacy of ipilimumab in specific pediatric indications.	*Study 4:* Not conducted based on communication to FDA in the briefing document in 16-June-2016 sequence # 1157. As a result, further entries for Study 4 are not included in subsequent Sponsor sections.	DOP2 was aware that Study 4 would not be conducted and did not require BMS to submit an amendment to the PWR after discussion with BMS on July 14, 2016.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Objectives of each study *Study 1:* • To determine the safety and tolerability of ipilimumab in pediatric patients with solid tumors that are refractory to standard therapy over a range of doses. • To assess the pharmacokinetics (PK) of ipilimumab, administered intravenously, in pediatric patients with solid tumors that are refractory to standard therapy. • To obtain preliminary evidence of the antitumor activity of ipilimumab in pediatric patients with solid tumors that are refractory to standard therapy.	**Study Objectives** *Study 1:* In alignment with the PWR, study CA184070 included the following: • Primary Objective – To determine the tolerance and toxicity profile of ipilimumab at a range of doses up to, but not exceeding, the highest dose tolerated in adults in patients ≤21 years of age with untreatable, refractory or relapsed solid malignant tumors. – To assess the pharmacokinetics (PK) of ipilimumab administered intravenously (IV) in patients ≤21 years of age with solid tumors refractory to standard therapy. • Secondary Objective(s) – To quantify antitumor effects of ipilimumab in patients ≤21 years of age with solid tumors refractory to standard therapy. – To evaluate the immunomodulatory	The response fulfills the requirements of the PWR.

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	(pharmacodynamic) activity of ipilimumab in patients ≤ 21 years of age with solid tumors refractory to standard therapy.	
Study 2: • To estimate ipilimumab clearance (CL) and volume of distribution (Vd) in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma. • To assess the safety and tolerability, of ipilimumab in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma • To estimate the best overall response rate (BORR) and the response duration in patients age 12 to ≤ 18 years with unresectable or metastatic melanoma.	*Study 2:* In alignment with the PWR, study CA184178 included the following: • Primary Objective – To estimate the survival rate at 1 year in adolescent patients (12 to < 18 years) with previously treated or untreated, unresectable Stage III or Stage IV malignant melanoma at the 3 mg/kg dose level. – To assess safety and tolerability, specifically the frequency of severe (Grade 3–5) immune mediated adverse reactions of ipilimumab in adolescent patients (12 to < 18 years) at the 3 mg/kg dose level. • Secondary Objectives – To estimate the disease control rate (DCR) by mWHO criteria at the 3	The response fulfills the requirements of the PWR in that the study objectives included a determination of safety, PK and BORR per protocol; however, Study 2 was closed after the accrual of 12 patients including the four patients treated at the 3 mg/kg dose level. Safety and efficacy data were limited in this Study but contributed to the review of safety and preliminary activity across the 45 patients enrolled in Studies 1 and 2. DOP2 was aware of the early closure of Study 2. See above discussion under the "Clinical Studies" section of this table.

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	mg/kg dose level. – To estimate progression free survival (PFS) by mWHO criteria at the 3 mg/kg dose level. – To estimate best overall response rate (BORR) by mWHO criteria at the 3 mg/kg dose level. – To assess overall survival at the 3 mg/kg dose level. • Exploratory Objectives – To characterize pharmacokinetics of ipilimumab, the immunogenic potential, and to explore exposure- response relationship with selected exposure measure, safety, and efficacy endpoints. – To explore serum soluble factors and peripheral T cell activation as predictive or pharmacodynamic biomarkers of ipilimumab's clinical activity or safety in this patient population. In addition, Ipilimumab CL and Vd in patients 12 to < 18 years with unresectable or metastatic melanoma were determined in the	

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Study 4: • To establish the effectiveness of ipilimumab in the proposed study population. • To assess safety and tolerability in patients age 1 to ≤ 18 years with specific primary cancer(s) based on the results of Study 3, To assess the PK of ipilimumab in patients age 1 to ≤ 18 years with specific primary cancer(s), including assessment of drug interactions if appropriate.	study and we have estimated the clearance and volume of distribution for each individual including pediatric patients. *Study 4:* N/A	
Patients to be Studied: *Age group in which studies will be performed:* • **Study 1:** Patients 1 to 21 years of age. • **Study 2:** Patients 12 to ≤ 18 years of age. • **Study 4:** Patients 1 to ≤ 18 years of age, if appropriate	**Patient population and number of patients studied:** *Age group in which studies will be performed:* *Study 1:* In alignment with the PWR, the population of CA184070 included male and female patients ≥ 1 year to ≤ 21 years of age. *Study 2*: In alignment with the PWR, the population of CA184178 included male and	The response fulfills the requirements of the PWR with regard to age groups that were evaluated. Study 1 enrolled 33 patients. Study 2 enrolled 12 patients (minimum requirement was 30 in the PWR) and Study 4 was not conducted. Rationale

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Number of patients to be studied: • **Study 1:** At least 30 patients, including at least 6 patients enrolled at the highest dose tolerable for each of the following age groups: children 1 to 12 years of age and adolescents 12 to ≤ 18 years of age • **Study 2:** At least 30 patients, with at least 20 patients treated at approved dosing regimen for ipilimumab (3 mg/kg as an intravenous infusion every 21 days for up to 4 cycles). • **Study 4:** A sufficient number of patients to establish the safety and effectiveness of ipilimumab for the treatment of one or more specific pediatric primary solid tumors.	female adolescent patients 12 to < 18 years of age. *Number of patients to be studied:* *Study 1:* In alignment with the PWR, all 33 enrolled patients in study CA184070 were treated at one of the 4 dose levels in the study. In the < 12 years of age group, 6 patients were enrolled at the highest dose tolerable, 5mg/kg. In the ≥ 12 years of age group, 9 patients were enrolled at the highest dose tolerable, 10mg/kg. *Study 2:* In study CA184178, 14 patients were enrolled in this study. Of these, 12 were treated: 4 patients at 3 mg/kg and 8 at 10 mg/kg. As noted in the Clinical Studies section of this document, study CA184178 was closed early after recommendation from the DMC. *Study 4:* N/A	for Study 2 early closure prior to enrolling 30 patients is discussed above.

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Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.	*Representation of Ethnic and Racial Minorities:* In alignment with the PWR, the patient population studied in Studies 1 (CA184070) and 2 (CA184178) is representative of the overall disease population, in being mostly Caucasian. An appropriate proportion of patients of ethnic and racial minorities were enrolled. *Study 1:* Of the 33 patients treated in study CA184070, there were 2 Black or African American patients, 5 Asian patients, and 2 American Indian or Alaska native patients. Of the remaining 24 patients, 23 were White and 1 Unknown. *Study 2:* Of the 12 patients treated in study CA184178, there was 1 Black or African American patient. The remaining 11 patients were White. *Study 4: N/A*	The response fulfills the requirements of the WR. DOP2 agrees that the mostly Caucasian study population is representative of the general melanoma population.

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Study endpoints: ***Pharmacokinetic/Pharmacodynamic Endpoints:*** • **All studies:** Ipilimumab trough concentrations obtained from samples collected in a minimum of 8 patients in each of the following age groups: 1 to < 12 years and 12 to < 18 years from the start of ipilimumab treatment through the last dose. The age groups are based on the identification of an apparent age-dependent maximum tolerated dose identified in Study 1. • **Study 2:** Estimated ipilimumab CL and Vd from samples collected from an adequate number of adolescents age 12 to < 18 years old with unresectable or metastatic melanoma to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of CL and Vd of ipilimumab with 80% power.	**Clinical endpoints used:** ***Pharmacokinetic/Pharmacodynamic Endpoints:*** *All Studies:* In alignment with the PWR, all ipilimumab pediatric PK data (including trough concentrations) were obtained from 9 patients in 2 to 12 years, and 26 patients in 12 to 18 years from the pooled dataset including the CA184070 and CA184178 studies. The population PK analysis predicted the peak and trough concentrations after the first and fourth dose of Ipilimumab and presented in the Summary of clinical pharmacology and Pop PK report. *Study 2:* Ipilimumab trough concentrations were available in 11 patients 12 to < 18 years of age. This provided sufficient power to estimate ipilimumab CL and Vd within 95% CIs within 60% and 140% of the point estimate for the geometric mean estimates of CL and Vd of ipilimumab with 90% power.	The response fulfills the requirements of the WR.

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Efficacy Endpoints • **Study 1:** Best objective response rate (ORR) and duration of responses using RECIST 1.1 criteria. • **Study 2:** ORR and duration of responses using RECIST 1.1 criteria. • **Study 4:** Evidence of clinical benefit, including overall survival, event-free survival, and/or progression-free survival.	*Study 4:* N/A ***Efficacy Endpoints*** *Study 1:* In alignment with the PWR, best objective response rate (BORR) and duration of responses (DoR) were included as endpoints in study CA184070. However, none of the patients reached an objective response (PR or CR) per RECIST criteria, so DoR could not be calculated. *Study 2:* In alignment with the PWR, BORR and DoR were determined in study CA184178. In addition, overall survival rate (OSR), overall survival (OS), progression free survival (PFS) and disease control rate (DCR) are also presented in the CSR.	The response fulfills the requirements of the WR.
Safety endpoints • **Study 1:** The key endpoint for Study 1 will be defining the age appropriate MTD and recommended phase 2 dose of ipilimumab in pediatric patients based on the frequency of	***Safety Endpoints:*** *Study 1:* In alignment with the PWR, BMS determined the MTD of ipilimumab in study CA184070 to be 5 mg/kg for <12 years and 10mg/kg in ≥12 years by evaluating dose-limiting toxicities, including immune-related	The response fulfills the requirements of the WR.

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observed dose-limiting toxicities. The rate and clinical course of adverse events including, but not limited to, ipilimumab-induced immune-related AEs, will be evaluated. The type, frequency, duration, and severity of laboratory abnormalities will also be analyzed. • **Study 2:** Characterization of safety will include descriptive analyses of adverse events, including the incidence, severity, and clinical outcomes of all adverse events, and the incidence, severity, and clinical outcomes of severe, serious and fatal adverse events. Type, frequency, duration, and severity of laboratory abnormalities will also be analyzed using descriptive statistics. • **Study 4:** Characterization of safety, by primary cancer type if appropriate and by overall study population, will include descriptive analyses of adverse events, including the	AEs. The frequency, duration and severity of laboratory abnormalities are provided in the CSR. o *Final CA184070 CSR, Section 8.5.2 Dose-Limiting Toxicities* *Study 2:* In alignment with the PWR, descriptive statistics of safety in study CA184178 are presented as indicated in the CSR. *Study 4:* N/A	

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incidence, severity, and clinical outcomes of all adverse events, and the incidence, severity, and clinical outcomes of severe, serious and fatal adverse events. The type, frequency, duration, and severity of laboratory abnormalities will also be analyzed using descriptive statistics.		

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Known Drug Safety concerns and monitoring: For adults treated with ipilimumab at doses of 3 mg/kg administered intravenously every 3 weeks, the most frequently reported adverse reactions are fatigue, diarrhea, pruritus, rash, and colitis. Ipilimumab has also resulted in severe and fatal immune-mediated reactions due to T-cell activation and proliferation in adults. Therefore, the eligibility criteria for all studies will exclude patients with chronic autoimmune disorders and patients with known liver and/or endocrine dysfunction. Study 1 will incorporated a stopping rule in the event that 2 of 6 patients experience grade 4 non- hematologic toxicity or grade 5 toxicity that is at least possibly related to ipilimumab and occurs within one month of receiving any dose of ipilimumab. All clinical study protocols will incorporate surveillance for such immune-mediated events, close monitoring of patients, and an algorithm for medical management of anticipated adverse reactions.	**Drug specific safety concerns evaluated** *Study 1 and 2*: CA184070 and CA184178 In alignment with the PWR, the inclusion/exclusion criteria for both studies were compliant with the proposed eligibility criteria and are provided in the study protocols. In alignment with the PWR, the stopping rules for Study 1, CA184070, were included as indicated in the PWR and are provided in the study protocol. In alignment with the PWR, surveillance of immune related AEs, as well as an algorithm for the management of anticipated immune related AEs, were included in both studies as indicated and are included in the study protocols.	The response fulfills the requirements of the WR.

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The safety and efficacy of ipilimumab in pregnant women has not been established. Animal toxicology studies demonstrate an increased incidence of abortion, stillbirths and postnatal deaths in monkeys who received ipilimumab during pregnancy and developmental abnormalities in infant monkeys exposed to ipilimumab in utero. All patients of childbearing potential enrolled in the above studies must therefore use highly effective contraception during treatment and for 5 months after the end of treatment. Pregnancy tests for women of childbearing potential will be conducted at screening, at defined time points while on study, and during safety follow-up. Patients on the above studies will be followed for toxicity for a minimum of 90 days following the last dose of ipilimumab and until any related adverse event resolves, returns to baseline or is deemed irreversible. Patients will be followed for long-term survival information.	In alignment with the PWR, BMS has met the criteria for child bearing criteria as indicated in the PWR for both Studies 1 and 2 (CA184070 and CA184178, respectively). Subjects were required to use appropriate highly effective methods of contraception The current ICF for CA184070 indicates to use highly effective contraception for at least 3 months after the last dose of Ipilimumab as this study was already completed by the time of PWR issuance. In addition, please note that CA184070 is a NCI/COG study, not sponsored by BMS. *Study 1:* In study CA184070, patients were followed for toxicity following the last dose of ipilimumab for a minimum of 30 days. As this is a NCI/COG sponsored study initiated prior to FDA's request to have a 90 day safety follow up, the follow up period for this older study, CA184070 remained at 30 days. FDA's request for 90 day follow up period was mainly for Study 2,	

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Specific monitoring for immune-induced endocrinopathies and other auto-immune reactions will occur at regular, protocol specified timepoints. Guidelines for mitigation and/or management of such provided in the protocol. All studies will be conducted under the oversight of a Data and Safety Monitoring Committee.	which has been implemented. ***Study 2:*** In alignment with the PWR, patients in study CA 184178 were followed for toxicity city following the last dose of ipilimumab for a minimum of 90 days. *Study 1*: Study CA184070 contained specific monitoring for autoimmune reactions and guidelines were provided in the protocol. This study was sponsored children's oncology group (COG/NCI). Although there was no external DMC, the study was conducted by pediatric oncologists with extensive experience in performing investigational drug studies in children, at centers with routine measures to minimize risk and distress in pediatric participants. *Study 2:* In alignment with the PWR, study CA184178 contained specific monitoring for autoimmune reactions and guidelines were provided in the IB. Additionally, the study was conducted under the oversight of a DMC. *Study 4:* N/A	

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Drug information *Drug information:* • *Dosage form:* Solution for injection (200 mg/40 mL vial and 50 mg/10 mL vial) • Route *of administration: Intravenous*	**Study drug used** In alignment with the PWR, Studies 1 and 2 (CA184070 and CA184178, respectively), dosed patients with intravenous ipilimumab. The investigational product was supplied in single- use vials containing 50mg ipilimumab in a 10mL vial or 200mg ipilimumab in a 40 mL vial, either containing 5mg/mL.	The response fulfills the requirements of the WR.
Statistical information *Study 1:* This trial will use a 3+3 dose escalation design to study the toxicity profile of ipilimumab at doses tolerable in adult trials. All statistics will be descriptive. The highest dose tolerated will be defined as the dose level immediately below the level at which ≥ 2 patients in a cohort of 2 to 6 patients experienced a DLT attributable to ipilimumab. Safety outcomes will include an analysis of adverse events, including the incidence of adverse events, severe adverse events, serious adverse events, and fatal adverse	**Statistical analyses** *Study 1:* In alignment with the PWR, study CA184070 used an appropriate study design and incorporated the appropriate statistical analyses, as indicated in the CSR.	

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
events. The rate of severe immune-related adverse events including, but not limited to, enterocolitis, dermatitis, hepatitis, endocrinopathies and neuropathies will be evaluated. Type, frequency, and severity of laboratory abnormalities will also be analyzed for each cohort. Safety analyses will be performed in aggregate, by dosing cohort, and by age group (< 12 years of age and 12 to < 21 years of age). Tumor response will be assessed using the RECIST 1.1 criteria. Patients will be considered evaluable for tumor response if they complete at least one cycle of therapy, or if they experienced progressive disease prior to that time. *Study 2:* The primary safety endpoints will be reported using descriptive statistics. ORR will be assessed using RECIST 1.1 criteria and 95% exact CI will be provided; however, an extrapolation approach will be utilized for determining efficacy in adolescent melanoma patients.	*Study 2:* In alignment with the PWR, study CA184178 used the appropriate statistical analyses to report the safety and efficacy endpoints. Additionally, in alignment with the PWR, the extrapolation approach has been utilized as	

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
With regard to PK collection, Study 2 must be prospectively powered to target a 95% confidence interval (CI) within 60% and 140% of the point estimate for the geometric mean estimates of CL and Vd of ipilimumab with 80% power in pediatrics aged 12 to ≤ 18 years administered a dose of 3 mg/kg. The choice of the sample size and sampling scheme for the study must be justified. Either non-compartmental analysis (NCA) based on rich pharmacokinetics sampling or population pharmacokinetic modeling analysis based on sparse PK sampling can be applied to achieve this precision standard. After initial data from the study are evaluated, if the goals for characterizing pharmacokinetics across the intended age range are not achieved, the sample size must be increased as necessary to meet the goals of the study. **Study 4:** A statistical analysis plan with the protocol will be submitted to the Agency for review prior to enrolling patients onto Study 4.	described in the Pop PK report. *Study 4:* N/A	

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Labeling that may result from the studies You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that ipilimumab is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.	**Labeling submitted** In alignment with the PWR, proposed labeling is included in Module 1.14 of this supplement to BLA 125377 (Sequence 0253) based upon the final results from completed Studies 1 (CA184070) and 2 (CA184178).	The response fulfills the requirements of the WR.
Format of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in	**Reports submitted** In alignment with the PWR, full study reports for completed Studies 1 (CA184070), 2 (CA184178), are included in Module 5 of this supplement to	The response fulfills the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study (ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency a greement. Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post- market	BLA 125377 (Sequence 0253). All pediatric patients enrolled in the studies above were categorized using one of the following designations for race: • American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White or Other. For ethnicity, following designations were utilized (note, ethnicity was collected only for the United States): • Hispanic/Latino or Not Hispanic/Latino.	

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD*		

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm.		
Timeframe for submitting reports of the study(ies) Reports of the above studies must be submitted to the Agency on or before the following dates: • Study 1: February 1, 2015 • Study 2: December, 2018 • Study 4: To be determined upon discussion with the Division of Oncology Products 2 and review of results of study 3.	**Timeframe for submitting reports of the study(ies)** *In alignment with the PWR, the full study reports for completed Studies 1 (CA184070) and 2 (CA184178) were submitted before the indicated dates.*	The response fulfills the requirements of the WR. Study 1 CSR submitted on December 14, 2014 and Study 2 submitted in the sBLA on January 23, 2017.

Source: Adapted from the Applicant's sBLA submission

6 Review of Efficacy

Efficacy Summary

The pediatric data submitted with this application did not provide evidence of a treatment benefit from the administration of ipilimumab to the limited number of pediatric patients with various solid tumors including metastatic melanoma treated across Studies CA184070 and 184178. However, it was determined that an extrapolation approach could be used to establish efficacy in pediatric patients 12 years of age and older with advanced melanoma. The original ipilimumab approval was based on demonstration of a survival advantage in adult patients with advanced melanoma [9].

According to the Pediatric Research Equity Act (PREA), "Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies." In order to permit extrapolation from adult efficacy data in the melanoma indication to pediatric patients with melanoma, FDA reviewed several factors to assume disease similarity across age groups including disease pathogenesis, criteria for disease definition, clinical classification, measures of disease progression, and pathophysiologic characteristics. Additionally, it had to be determined that the disease course and response to treatment are sufficiently similar and that there is adequate evidence of similar exposure-response relationships in pediatric patients and adults. [10].

Although prepubescent patients appear to have different disease characteristics as compared to adult melanoma patients, adolescents are considered to be comparable to adult patients with regard to key tumor characteristics (primary site, histology, stage at diagnosis, specific genetic mutations, thickness, and level of invasion). Survival data from adult melanoma patients demonstrate a disease stage-dependent outcome that appears to be independent of age in subgroup analyses. Similarly, overall survival in pediatric patients is predicted by melanoma characteristics (e.g., primary site, histology, stage at diagnosis, thickness, and level of invasion) but not age [8].

With regard to ipilimumab metabolism in children and adults, the Applicant submitted population PK data and analyses in the sBLA to support the recommended dose of 3 mg/kg every three weeks. These were reviewed by the FDA clinical pharmacology team who concluded that a dose regimen of ipilimumab 3 mg/kg every three weeks is predicted to achieve similar exposures in pediatric patients $\geq$ 2 and < 18 years old and adult patients with metastatic melanoma (refer to the primary clinical pharmacology review for details).

In summary, in the setting of a rare and life-threatening disease with lack of alternative therapies, evidence of sufficiently similar disease characteristics and prognosis between adolescents and adults with melanoma, and PK evidence of similar drug exposures

between children and adults support extrapolation of adult efficacy data to support the extension of the ipilimumab indication in adult unresectable or metastatic melanoma to adolescent patients with advanced melanoma.

6.1 Methods

The efficacy review was based primarily upon the clinical study reports for Studies CA184070 and CA184178 and primary datasets submitted by the Applicant. Tumor response assessments were reviewed for the 17 patients between 12 and 21 years of age treated across both trials.

6.2 Baseline Demographic and Disease Characteristics

Demographic characteristics of pediatric patients treated with ipilimumab across Studies CA184070 and 184178 are summarized in Table 5.

Table 5: Demographic Characteristics for Study CA184070 and Study 184178

Demographic Characteristic	CA184070 N = 33 n (%)	CA184178 N = 12 n (%)
Gender		
Male	14 (42)	7 (58)
Female	19 (58)	5 (42)
Race		
White	23 (70)	11 (92)
Black or African American	2 (6)	1 (8)
American Indian or Alaskan Native	2 (6)	0
Asian	5 (15)	0
Unknown	1 (3)	0
Age (years)		
Mean (Standard deviation)	13 (5.49)	14.3 (1.37)
Median (Min, Max)	13 (2.4 – 21.8)	15 (12-16)
Age subgroup (years)		
< 12	13 (39)	0
≥12 to <21	20 (61)	12 (100)
Weight (kg)		
Mean	47	65
Median (min, max)	45 (12-153)	65 (46-91)

Demographic Characteristic	CA184070 N = 33 n (%)	CA184178 N = 12 n (%)
Disease Stage and Prior Therapy (for patients with melanoma)		
Stage III	1 (3)	2 (17)
Stage IV	7 (21)	10 (83)
Missing data	5 (15)	
Prior surgery	33 (100)	12 (100)
Prior radiotherapy	18 (55)	1 (8)
Prior systemic therapy	21 (64)	7 (58)

Source: CSRs for CA184070 and 184178; ADSL.xpt databases

6.3 Concomitant Medications

Prior or concomitant treatment with any other CTLA-4, PD-1, PD-L1, or CD137 targeted therapies was not permitted. Analgesics and systemic antihistamines were classes of concomitant medications used most commonly in both trials. In Study CA184070, corticosteroids were administered to four (12%) of patients during treatment with ipilimumab as an immunosuppressant. The patients requiring steroid treatment were receiving either the 5 or 10 mg/kg dosing regimen. In Study CA184178, corticosteroids were used concomitantly with ipilimumab treatment in eight patients (67%) for the treatment for an adverse event.

Reviewer: *The increased use of corticosteroids in Study CA184178 may be attributed to increased provider recognition of immune-mediated adverse events given the more well-known toxicity profile of ipilimumab at the time when the second trial was conducted as compared to 2008 when Study CA184070 was initiated. The sample sizes are too small to make reliable comparisons.*

6.4 Patient Disposition

Study CA184070

All 33 patients enrolled were treated with at least one dose of ipilimumab. Eight patients (24%) completed the four induction doses of ipilimumab. All patients eventually discontinued study treatment for the following reasons: development of PD (n=23), AE occurrence (n=8), death (n=1) and complicating intercurrent illness (n=1).

Study CA184178
Fourteen patients enrolled and 12 patients were treated. Two patients no longer met eligibility criteria after screening and did not receive ipilimumab. Two patients completed the treatment phase of the trial (received four infusions), four patients experienced

disease progression, and six patients (50%) discontinued ipilimumab due to a treatment-related AE (see Section 7 of the review).

6.5 Analysis of Efficacy Endpoints

Both pediatric trials of ipilimumab evaluated antitumor activity in addition to assessing the safety and PK profile of ipilimumab in pediatric patients. Neither trial was randomized, and the sample sizes were limited such that any potential survival effect could not be reliably detected. Radiologic objective response rates were collected as secondary endpoints in both trials.

A total of 13 children less than 12 years old with various solid tumors including seven patients with advanced melanoma were treated with ipilimumab in Study CA184070, and no objective responses were observed.

Across Studies CA184070 and CA184178, there were 17 patients of at least 12 years of age with advanced melanoma who received ipilimumab treatment. Two of the 17 patients (12%) experienced a PR. One additional patient had a prolonged SD (> 22 months) and received 15 doses of ipilimumab prior to developing PD. See the following tables 6 and 7 for summary efficacy results in patients with melanoma greater than 12 years of age during treatment on studies CA184070 and CA184178.

Table 6: Best Overall Response in Patients with Melanoma, CA184070

Dose Level [mg/kg]	No. of Ipilimumab Infusions	BOR	Response Study Day	Progression Study Day	Death Study Day
5	15	SD	39	732	NA
5	4	SD	61	104	NA
5	1	NE	–	-	93
10	2	PD	–	41	–
10	2	PD	–	41	–

Source: Adapted from Summary of Clinical Efficacy, Module 2.7.3, p 25

Table 7: Efficacy Results in Patients with Melanoma, CA184070 and CA184178

NCI7458/CA184070	
5 mg/kg (n=3)	**10 mg/kg (n=2)**
Participants with Stable Disease, RECIST Criteria	
2/3[a]	0/2
Participants with Objective Response (PR or CR), RECIST Criteria	
0/3	0/2
CA184178	
3 mg/kg (n=4)	**10 mg/kg (n=8)**
1-year Survival Rate, mWHO Criteria	
75.0% (95% CI: 12.8, 96.1)	62.5% (95% CI: 22.9, 86.1)
Participants with Stable Disease, mWHO Criteria[b]	
1/4	1/8
Participants with Objective Response (PR or CR), mWHO Criteria	
0/4	2/8[c]
BORR, mWHO Criteria	
0% (95% CI: 0, 60.2)	25% (95% CI: 3.2, 65.1)
DCR, mWHO Criteria	
25% (95% CI: 0.6, 80.6)	37.5% (95% CI: 8.5, 75.5)
Median PFS, mWHO Criteria	
2.6 months (95% CI: 2.3, 8.5)	2.9 months (95% CI: 0.7, -)
Median OS	
18.2 months (95% CI: 8.9, 18.2)	not reached (95% CI: 5.2, -)

[a] One with a duration of nearly 2 years (> 22 months).

[b] Stable disease (SD) was observed in 1/4 participants treated with ipilimumab 3 mg/kg for 260 days, and 1/8 participants treated with ipilimumab 10 mg/kg for ~14 months.

[c] One was durable (ongoing for ~ 15 months).

Source: Adapted from Table 4 provided in *Clinical Overview, sBLA submission*

Reviewer: *The ORR findings across the two pediatric trials are similar to the response rates shown in adult melanoma trials that demonstrated a survival advantage despite modest response rate findings of 6 and 11% ORRs for patients on the ipilimumab arms in the trial supporting licensure [1]. However, as discussed above, based on adolescent patients with melanoma having a similar disease and disease course as adult patients and adequate PK data supporting similar exposures in pediatric patients, it is reasonable to assume that adolescent patients would experience a similar improvement in survival with ipilimumab treatment despite the 12% ORR in the limited sample size evaluated across the two pediatric trials.*

7 Review of Safety

Safety Summary

The safety of ipilimumab in pediatric patients was supported by the results of Studies CA184070 and CA184178. In total, 45 pediatric patients enrolled in these trials were treated with ipilimumab administered at doses of 1, 3, 5 or 10 mg/kg every three weeks. Forty-two of the 45 patients received ipilimumab at a dose of $\geq$ 3 mg/kg, and the other three patients received the 1 mg/kg dose.

There were no ipilimumab-related deaths reported in pediatric patients. Nonfatal serious adverse events (SAEs) considered related to study drug occurred in 13 (39%) of patients in Study CA184070 and included abdominal pain, nausea, vomiting, pyrexia, amylase and lipase increased, autoimmune disorder, anaphylactic reaction, skin infection, musculoskeletal pain, headache, vision blurred, diarrhea, blood creatine phosphokinase increased, pleural effusion, and upper respiratory tract infection. Nonfatal SAEs related to ipilimumab occurred in six patients (50%) treated in Study CA184178 and included hepatitis, pancreatitis, chlolestatis/cholecystitis, pleural effusion, hypokalemia, and infusion related reaction.

The most common AEs occurring in pediatric patients treated with ipilimumab across both trials included nausea, abdominal pain, diarrhea, fatigue, pyrexia, headache, vomiting, decreased appetite, rash, constipation, cough, decreased appetite. Common laboratory abnormalities reported as AEs included anemia, lymphopenia, elevated activated partial thromboplastin time (aPTT), hyponatremia, increased alanine and aspartate aminotransferases, low magnesium and low albumin.

Immune-mediated adverse reactions (imARs) pose a serious risk to patients treated with ipilimumab and can occur in any organ system. The most common classes of imARs to ipilimumab in pediatric studies were gastrointestinal (colitis/diarrhea), hepatic (transaminitis, hepatitis, cholestasis) and dermatologic (various skin rashes). No new or more severe imARs were identified in the pediatric development program as compared

to what has been observed in the adult experience. Diagnosis and management guidelines were similar for pediatric and adult patients.

Overall, the adverse reaction profile of ipilimumab in pediatric patients was consistent with the known adverse reaction profile in adults.

7.1 Methods

The safety review was based primarily upon the clinical study reports for Studies CA184070 and CA184178 and primary datasets and narratives submitted by the Applicant. The results are presented by study. The key safety analyses conducted were for ipilimumab-related deaths, nonfatal SAEs, AEs leading to discontinuation, common AEs and imARs.

The Summary of Clinical Safety included in the application focused on the findings for the 30 patients 12 years of age or older who were treated with ipilimumab at doses at or above the recommended 3 mg/kg dose in order to support a labeled indication in adolescent patients with unresectable or metastatic melanoma. For some analyses, a side-by-side comparison of the data collected in this subgroup of 30 adolescent patients and adult safety data from a pooled analysis of four trials of single-agent ipilimumab in advanced melanoma (Studies CA184004, CA184007, CA184008, and CA184022) was provided to provide context. The pooled adult safety population included 111 patients treated at 3 mg/kg and 325 patients treated at 10 mg/kg. Datasets for the adult studies were not requested or submitted.

7.2 Ipilimumab Exposure

Table 8 provides a summary of ipilimumab exposure for all patients enrolled in Studies CA18470 (N=33) and CA184178 (N=12). Eight patients (24%) completed at least four infusions in Study CA184070 and six patients (50%) completed at least four infusions in Study CA184178.

Table 8: Summary of Ipilimumab Exposure across pediatric trials

Exposure Parameter	1 mg/kg	3 mg/kg	5 mg/kg	10 mg/kg	Total
Study CA18470					
Number of patients	3	3	14	13	33
Median number of doses (range)	2 (1-2)	2 (1-4)	2 (1-15)	2 (1-6)	2 (1-15)

Number of patients who received 4 doses	0	1	3	4	8
Study 184178					
Number of patients	0	4	0	8	12
Median number of doses (range)	NA	4 (2-4)	NA	3 (1-4)	3.5 (1-4)
Number of patients who received 4 doses	NA	3	NA	3	6

Source: CSRs and ADEX.xpt datasets for both studies

Summary exposure data for all patients over the age of 12 who received at least 3 mg/kg of ipilimumab as compared to adult exposure data is presented in the following table copied from the SCS:

Table 9: Exposure in Pediatric Patients ≥ 12 years old as compared to adults

	NCI7458/CA184070 ≥ 12 to 21 years			CA184178 12 to < 18years		Adult Safety Pool	
	3 mg/kg N = 1	5 mg/kg N = 8	10 mg/kg N = 9	3 mg/kg N = 4	10 mg/kg N = 8	CA184004/ 022 3 mg/kg N = 111	CA184004/ 007/008/022 10 mg/kg N = 325
Median Doses	4.0	2.5	2.0	4.0	3.0	4.0	4.0
Participants with 4 Doses (%)	1 (33.3)	3 (37.5)	4 (44.4)	3 (75.0)	3 (37.5)	78 (70.3)	189 (58.2)
Median Cumulative (mg)	NA	NA	NA	691.25	1896.0	894.0	2710.0
Median Cumulative (mg/kg)[a]	NA	NA	NA	11.95	29.75	12.0	39.9

Source: Summary of Clinical Safety, page 15

Reviewer comment: *Overall, the level of exposure to ipilimumab with regard to the number of patients completing at least four doses was slightly less in adolescent patients (47%) as compared to adult patients (61%). The cumulative doses received are accordingly less in the adolescent group. The lower completion rate in Study CA184070 could be attributed to the dose-escalation design with discontinuations based on DLT occurrences and the study population including patients with various non-melanoma*

solid tumors having received multiple prior cytotoxic chemotherapy regimens at study entry. The completion rate for adolescents with melanoma receiving the 3 mg/kg dose in Study CA184178 (75%) was similar to the adult group receiving 3 mg/kg (70%). The exposure in pediatric patients appears adequate to evaluate safety. Although the pediatric sample size is small, the PK data collected during the trials across age groups and the population PK analyses and simulations conducted by the Applicant were deemed sufficient to provide evidence of similar exposures in pediatric and adult patients (see primary clinical pharmacology review for details).

7.3 Analysis of Adverse Events

7.3.1 Deaths

Study CA18470
At the time of data analysis, 15 of 33 patients had died, and two of the 15 within 30 days of the last dose of ipilimumab. All deaths were attributed to disease progression.

Study CA18478
At the time of data analysis, five of 12 patients had died. All deaths occurred more than 90 days following the last dose of ipilimumab and were attributed to disease progression.

7.3.2 Nonfatal Serious Adverse Events

Study CA18470
Seventeen patients (52%) had at least one SAE while on study. Thirteen of these patients (39%) had an SAE that was considered at least possibly related to study drug. Thirteen patients (39%) had a Gr 3 or 4 SAE on study. No single event occurred in more than 2 patients.

Of the 20 patients > 12 years old treated in Study CA184070, 12 (60%) had an SAE. One patient treated with 3 mg/kg iplimumab had a device-related infection with associated chills, pain and fever. Seven patients in the 5 mg/kg group experienced at least one SAE, and five patients experienced SAEs that were $\geq$ Grade 3 in severity and considered related to ipilimumab (amylase and lipase increased, autoimmune disorder, abdominal pain, skin infection, musculoskeletal pain, headache, and vision blurred). Four patients receiving 10 mg/kg experienced at least one drug-related SAE (diarrhea, elevated creatine kinase, pleural effusion, and upper respiratory tract infection).

Table 10: Serious Adverse Events in Study CA184070

Preferred Term	Ipilimumab Safety Population N=33 n (%)
Pyrexia	3 (9)
Abdominal pain	2 (6)
Anemia	2 (6)
Autoimmune disorder	2 (6)
Cough	2 (6)
Diarrhea	2 (6)
Vomiting	2 (6)
Amylase increased	1 (3)
Anaphylactic reaction	1 (3)
Blood creatine phosphokinase increased	1 (3)
Chills	1 (3)
Device related infection	1 (3)
Dyspnoea	1 (3)
Headache	1 (3)
Hypoxia	1 (3)
Large intestine perforation	1 (3)
Lipase increased	1 (3)
Lymphocyte count decreased	1 (3)
Musculoskeletal pain	1 (3)
Nausea	1 (3)
Pain	1 (3)
Photophobia	1 (3)
Pleural effusion	1 (3)
Pneumonitis	1 (3)
Skin infection	1 (3)
Upper respiratory tract infection	1 (3)
Vision blurred	1 (3)

Source: ADAE.xpt, Study CA184070

Study CA18478

Seven patients (58%) had at least one SAE on study including one patient in the 3mg group and six patients in the 10 mg/kg group. Six of the patients experienced at least one treatment-related SAE (hepatitis, pancreatitis, chlolestatis/cholecystitis, pleural effusion, hypokalemia, and infusion related reaction).Two patients had a pleural effusion. All other SAEs occurred in one patient.

Table 11 provides a listing by preferred term of serious adverse events that occurred in patients treated during Study CA184178.

Table 11: Serious Adverse Events in Study CA184178

Preferred Term	Ipilimumab Safety Population N=12 n (%)
Hepatitis	2 (17)
Pleural effusion	2 (17)
Cholecystitis acute	1 (8)
Cholestasis	1 (8)
Hepatic enzyme increased	1 (8)
Hypokalaemia	1 (8)
Hyponatraemia	1 (8)
Infusion related reaction	1 (8)
Metastatic malignant melanoma	1 (8)
Pancreatitis	1 (8)
Transaminases increased	1 (8)
Tumor pain	1 (8)

Source: ADAE.xpt, Study CA184178

Adult Safety Pool
In the pooled data from adults treated with 3 mg/kg, the Applicant reports that 45% of patients had at least one SAE and 17% experienced at least one treatment-related SAE. Five percent of patients had an SAE of colitis and diarrhea and the majority of other types of SAEs occurred in one patient. Similarly, in the 10 mg/kg pooled group, the most frequent SAEs were diarrhea (11%) and colitis (7%).

Reviewer: *Across pediatric and adult data, patients treated at the 10 mg/kg dose appeared to experience a greater number of SAEs. Review of the types of SAEs experienced by patients enrolled in Studies CA184070 and 184178 did not identify any new or exaggerated safety signals in pediatric patients as compared to the known safety profile of ipilimumab in adult patients.*

7.3.3 Dose-limiting Toxicity

Based on the DLT criteria in the CA184070 protocol, children older than 12 years of age (N=20) tolerated higher doses of ipilimumab as compared to children <12 years old (n=13). Two of the initial 3 patients <12 years old that were treated with 10 mg/kg

experienced a DLT within the pre-specified 6-week timeframe (Grade 3 diarrhea and grade 3 transaminitis). The MTD for patients less than 12 years of age was determined to be 5 mg/kg whereas the MTD for patients 12 years and older was determined to be 10 mg/kg. The following table from the CSR summarizes the DLTs by age and dose in Study CA184070.

Table 12: Dose-limiting Toxicities by Age and Dose, Study CA184070

Subject	Age	Dose (mg/kg)	CTC Grade	DLT	Clinical Diagnosis	Study Day	Timing from 1st dose of ipi
7458-DFCI-202	<12	5	3	anaphylactic reaction	–	1	<6 weeks
7458-NCI-15	<12	10	3	diarrhoea	colitis	8	<6 weeks
7458-NCI-17	<12	10	3	increased ALT	transaminitis	28	<6 weeks
			3	increased AST	–	28	<6 weeks
7458-NCI-10	≥12	5	4	increased amylase	pancreatitis	11	<6 weeks
			3	abdominal pain	transaminitis	17	<6 weeks
7458-DFCI-201	≥12	5	3	autoimmune disorder	–	49	≥6 weeks
7458-NCI-19	≥12	10	3	pleural effusion	–	12	<6 weeks
7458-NY016-102	≥12	10	3	diarrhoea	–	122	≥6 weeks

Source: CSR CA184070, p. 90

7.3.4 AEs Leading to Discontinuation

Study CA184070
Eight patients (24%) discontinued ipilimumab for a drug-related AE. The PTs for events leading to discontinuation were autoimmune disorder, abdominal pain, amylase increased, lipase increased, and headache, diarrhea, pleural effusion, anaphylactic reaction, vomiting and AST/ALT elevation. All of the patients who discontinued ipilimumab for an AE were receiving either 5 or 10 mg/kg dose regimens.

Study CA184178
Six patients (50%) discontinued ipilimumab for a drug-related AE; one received 3 mg/kg, and the rest received 10 mg/kg. The PTs for events leading to discontinuation were hypokalemia, hepatitis, pancreatitis, fever, liver enzyme increase elevation, and pleural effusion.

Adult Safety Pool
In the pooled safety data for adults receiving 3 mg/kg ipilimumab, the rate of discontinuation due to treatment-related AEs was 7%. The most common treatment-related AEs leading to discontinuation were hypopituitarism and colitis/diarrhea, each leading to discontinuation in 3% of patients. Discontinuation due to treatment-related AEs occurred in 19% of patients in the pooled 10 mg/kg group. The most common treatment-related AEs leading to discontinuation in the pooled 10 mg/kg group were diarrhea or colitis in 11% of the patients. Other common AEs leading to discontinuation of ipilimumab in the adult database included elevated transaminases (3%) and hepatobiliary disorders (3%).

Reviewer: *Similar to the overall incidence of treatment-related AEs and SAEs, the rate of discontinuation for treatment-related toxicity was higher in the pediatric patients receiving higher doses of ipilimumab. Only one pediatric patient treated with 3 mg/kg was discontinued for an AE; however, the total number of patients treated at the 3 mg/kg dose across both studies was small (n=7). This dose-related trend is also present in the adult pooled data.*

7.3.5 Severe and Common Adverse Events
In the current product label for Yervoy, the most common adverse reactions (≥5%) experienced by adult patients in clinical trials of ipilimumab dosed at 3 mg/kg or 10 mg/kg are fatigue, diarrhea, pruritus, rash, and colitis, nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. Lab abnormalities that occurred in more than 20% of adult patients treated with ipilimumab at 10 mg/kg included Increased ALT Increased AST, increased lipase, and anemia.

Study CA184070
All patients treated with ipilimumab experienced at least one treatment emergent AE including laboratory abnormalities reported as AEs. The most common AEs across all dose levels included anemia, lymphopenia, elevated activated partial thromboplastin time (aPTT), hyponatremia, increased alanine aminotransferase and aspartate anminotransferase , nausea, abdominal pain, diarrhea, fatigue, pyrexia, headache, vomiting, low magnesium and low albumin. Twenty-two patients (67%) experienced at least one Grade 3 or 4 AE. The most common (≥ 3 patients) severe (≥ Grade 3) adverse events were anemia and prolonged aPTT.

Study CA184178 (N=12)
All patients treated with ipilimumab experienced at least one adverse event. The most common AEs (occurring in at least 3 patients) included vomiting, headache, nausea, decreased appetite, diarrhoea, fatigue, pyrexia, rash, weight decreased, abdominal pain, constipation, cough, hyponatraemia, and pruritus. Seven patients (58%) experienced at least one Grade 3 or 4 AE. In the 3 mg/kg group, one patient

experienced Grade 3 hepatitis. In the 10 mg/kg group, two patients experienced multiple Grade 3 events (vomiting, ascites, constipation, decreased appetite, urinary tract infection, rhinitis, pleural effusion, cholecystitis, hepatitis, infusion reaction, lab abnormalities), and four patients experienced Grade 4 events (decreased appetite and electrolyte abnormalities). The incidence rates of all grade and severe AEs were higher among the ipilimumab 10 mg/kg group as compared to the 3 mg/kg group; however, the limited number of patients in each group makes safety comparisons less reliable.

Adult Safety Pool
Across all doses in the pooled adult safety data, 97% of patients experienced at least one AE during treatment with ipilimumab. Common AEs were similar to those observed in the pediatric population. In the pooled safety data for adults receiving 3 mg/kg ipilimumab, 27% of patients experienced Grade 3 or 4 AEs, the most common of which was fatigue (6%). In the pooled 10 mg/kg group, 38% of patients experienced Grade 3–4 AEs, the most common being diarrhea (11%).

Tables 13 and 14 list the adverse events with a per-patient incidence of ≥10% overall and includes the proportion of common AEs that were ≥ Grade 3 severity for Studies CA184070 and CA184178.

Table 13: Summary of Common (> 10%) and Severe AEs for Study CA184070

Preferred Term	Ipilimumab, N=33	
	Any Grade n (%)	Grade 3-4 n (%)
Anemia	18 (55)	3 (9)
Lymphocyte count decreased	16 (48)	2 (6)
Activated partial thromboplastin time prolonged	15 (45)	3 (9)
Hyponatremia	13 (39)	0
Alanine aminotransferase increased	12 (36)	2 (6)
Nausea	12 (36)	0
Abdominal pain	11 (33)	1 (3)
Aspartate aminotransferase increased	11 (33)	2 (6)
Diarrhea	11 (33)	2 (6)
Fatigue	11 (33)	1 (3)
Pyrexia	11 (33)	0

Preferred Term	Ipilimumab, N=33	
	Any Grade n (%)	Grade 3-4 n (%)
Headache	10 (30)	1 (3)
Hypomagnesaemia	10 (30)	0
Hypoalbuminemia	10 (30)	0
Vomiting	10 (30)	0
Hypophosphatemia	8 (24)	2 (6)
White blood cell count decreased	8 (24)	1 (3)
Blood alkaline phosphatase increased	7 (21)	1 (3)
Hyperglycemia	7 (21)	1 (3)
Hypokalemia	7 (21)	2 (6)
Cough	6 (18)	1 (3)
Neutrophil count decreased	6 (18)	1 (3)
Pain	6 (18)	0
Platelet count decreased	6 (18)	0
Autoimmune disorder	5 (15)	1 (3)
Constipation	5 (15)	0
Decreased appetite	5 (15)	0
Hypomagnesaemia	5 (15)	0
Pain in extremity	5 (15)	0
Pruritus	5 (15)	0
Back pain	4 (12)	0
Dyspnea	4 (12)	2 (6)
Myalgia	4 (12)	0
Proteinuria	4 (12)	0
Rash maculo-papular	4 (12)	0

Source: ADAE.xpt, Study CA184070

Table 14: Summary of Common (> 10%) and Severe AEs for Study CA184178

Preferred Term	Ipilimumab, N=12	
	All Grades n (%)	Grade 3-4 n (%)
Vomiting	8 (67)	1 (8)
Headache	7 (58)	0
Nausea	7 (58)	0
Decreased appetite	4 (33)	1 (8)
Diarrhea	4 (33)	1 (8)
Fatigue	4 (33)	0
Pyrexia	4 (33)	1 (8)
Rash	4 (33)	0
Weight decreased	4 (33)	0
Abdominal pain	3 (25)	0
Constipation	3 (25)	0
Cough	3 (25)	0
Hyponatremia	3 (25)	2 (17)
Pruritus	3 (25)	0
Alanine aminotransferase increased	2 (17)	1 (8)
Aspartate aminotransferase increased	2 (17)	1 (8)
Dehydration	2 (17)	0
Epistaxis	2 (17)	0
Hepatitis	2 (17)	2 (17)
Hyperglycemia	2 (17)	1 (8)
Hyperhidrosis	2 (17)	0
Hypokalemia	2 (17)	2 (17)
Myalgia	2 (17)	0

Preferred Term	Ipilimumab, N=12	
	All Grades n (%)	Grade 3-4 n (%)
Pleural effusion	2 (17)	2 (17)

Source: ADAE.xpt, Study CA184178

7.3.6 Immune-mediated adverse reactions (imARs)

The current Yervoy product label includes a boxed warning for imARs [9]:

> *YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.*
>
> *Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. (2.3)*
>
> *Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. (5.1, 5.2, 5.3, 5.4, 5.5)*

The following case definitions were used in the Applicant's safety analysis (definitions adapted from the SCS):

- ***Immune-related AEs (irAEs):*** AEs of unknown etiology, associated with drug exposure and consistent with an immune phenomenon that were reported by the investigator to be related to treatment with study drug or with an unknown causality. The irAEs were programmatically determined from a predefined list of MedDRA PTs representing AEs potentially associated with inflammation and based on program-wide experience with ipilimumab considered to be causally related to study drug exposure by the investigator. These terms were grouped into the following organ-specific subcategories: GI, skin, liver, endocrine, neurological, and other. Formal exclusion of a noninflammatory etiology was not required for identifying irAEs.

- ***Immune-mediated adverse reactions (imARs):*** the subset of AEs for which a non-immune etiology could not be established, and included the following specific events of clinical interest: enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and other. imARs were not collected or analyzed for CA184070

or the adult safety data pool as these studies were initiated prior to the development of the specific definition of imARs.

Both pediatric protocols included treatment guidelines recommending administration of immunosuppressants for the treatment of irAEs. These events were generally managed with either symptomatic therapy for Grade 1–2 events, systemic corticosteroids for Grade 3–4 events, or other immunosuppressants for steroid unresponsive GI or hepatic irAEs, as appropriate.

Study CA184070
Immune-related AEs occurred in 25 patients (76%) treated at all dose levels. No fatal irAEs were observed. The most commonly observed classes of irAEs (any grade) were GI (12/33 patients; 36%), liver (11/33 patients; 33%) and skin disorders (9/33 patients; 27%). Six patients (18%) experienced at least one $\geq$ Grade 3 irAE. Grade 3 and 4 irAEs included transaminase elevations, diarrhea, autoimmune disorder, anaphylactic reaction and amylase and lipase elevation. All Grade 3 and 4 irAEs occurred at the 5 or 10 mg/kg dose levels.

GI irAEs were relatively common and mostly mild to moderate in severity; nine patients had Grade 1 or 2 diarrhea, one patient had a Grade 1 lower GI hemorrhage, and one patient had Grade 2 pancreatitis. Grade 3 or 4 diarrhea occurred in three patients; all in the 10 mg/kg dose group.

GI perforation, a rare complication of colitis that has been observed in adult patients, occurred in one patient treated in this study. The patient was 20.8 years old and treated in the 5 mg/kg dose group. Before this event, she experienced Grade 1 elevation of ALT on Days 22 and 42 and Grade 1 diarrhea on Day 34. She also had a Grade 3 skin infection on Day 34. She was discontinued from the study on Day 49 for an autoimmune disorder which was not specified, but she did experience Grade 3 elevations of AST and ALT on the same day. She had received two dose of ipilimumab. The patient experienced Grade 1-2 diarrhea on Day 63 and was started on methylprednisolone. On Day 83, the dose of methylprednisone was increased and budesonide added for persistent diarrhea. On Day 88, she was positive for C. dificile infection and metronidazole was started and steroids continued. On Day 107, 85 days following the last dose of ipilimumab, the patient presented with severe abdominal pain and a CT confirmed colonic perforation. She had surgical repair and was discharged eight days later and was weaned off budesonide and methylprednisolone as an outpatient.

Reviewer: *The current product label describes immune-mediated enterocolitis and states that 1% of patients developed intestinal perforation and 0.8% of patients had fatal perforations.*

Hepatic irAEs of AST and ALT increased were observed in eight patients (24%), two of which were Grade 3 in severity.

Endocrine irAEs occurred in two patients treated at the 5 mg/kg dose, one Grade 2 hypophysitis and one Grade 1 blood prolactin abnormality. The patient with hypophysitis also experienced a Grade 2 diabetes insipidus and a Grade 3 SAE of headache prior to the diagnosis of hypopysitis.

Skin irAEs occurred in 9 patients (27%). All were ≤ Grade 2 and these included rash pruritis, urticarial, dermatitis acneiform, and erythema multiforme.

Other irAEs that occurred were one Grade 1 peripheral sensory neuropathy, two Grade 1-2 autoimmune disorders with the clinical diagnosis of autoimmune thyroiditis, one Grade 3 autoimmune disorder in the patient who experienced transaminitis and a later colonic perforation and one unspecified low grade autoimmune disorder.

CA184178

Immune-related AEs occurred in six patients (50%). No fatal irAEs were observed. Four of the patients were discontinued from study drug based on the irAE. The most commonly observed classes of irAEs (any grade) were liver (4/12 patients; 33%), skin (4/12 patients; 33%). GI (2/12 patients; 17%) and endocrine (2/12; 17%). Four patients (18%) experienced at least one ≥ Grade 3 irAE. Grade 3 and 4 irAEs included transaminase elevations, cholestasis, hyperglycemia and amylase and lipase elevations. All Grade 3 and 4 irAEs occurred at the 10 mg/kg dose except one Grade 3 hepatitis which occurred in a patient receiving 3 mg/kg ipilimumab.

Liver irAEs of any grade occurred in four patients who experienced hepatitis, cholestasis, and hepatic enzyme increases. Four patients experienced Grade 1 rash or pruritis. Two patients experienced hyperglycemia (Grade 1 and 3). Two patients experienced GI events including a grade 2 diarrhea and a grade 2 hematochezia. Grade 2 drug hypersensitivity occurred in one patient and Grade 1 pancreatitis with an associated Grade 4 lipase elevation occurred in one patient.

Reviewer: *For the most part in Study CA184178, there was overlap between the events that were categorized as irAEs and those that were flagged as imARs. One additional patient was included in the group of patients who experienced at least one imAR. This patient experienced Grade 1-2 events including hot flashes, rash, fever and a pleural effusion. Ipilimumab was discontinued for the Grade 2 pleural effusion.*

Adult Safety Pool

The incidence of irAEs of any grade was 61% in the 3 mg/kg group with 6% of patients experiencing Grade 3–4 irAEs. One patient (0.9%) had a fatal irAE. In the 10 mg/kg

group, the incidence of irAEs of any grade was 72%. Three patients (0.9%) had fatal irAEs. The most common irAEs at both dose levels were GI and skin related toxicities. Two patients in the adult safety pool, one in each dose group, had fatal colonic perforations that were considered irAEs.

Reviewer: *No new or unexpected irAEs were observed in pediatric patients treated in Studies CA184070 and CA184070. irAEs appeared to be more common in patients treated at higher doses of ipilimumab in both adults and pediatric patients. The observed irAEs in children and adolescents were similar in frequency and severity to what has been reported in adult studies.*

8 Overall Conclusions

Melanoma in the pediatric population is a rare and serious disease with an increasing annual incidence. Pediatric patients with unresectable or metastatic melanoma have a poor prognosis and no available treatments known to improve survival.

The efficacy of ipilimumab in pediatric patients was not established in Studies CA184070 and 184178. An extrapolation of efficacy from adult data for pediatric patients 12 and older is reasonable based on disease similarity between the adult and adolescent populations and population PK analyses demonstrating that a dosing regimen of 3 mg/kg ipilimumab every 3 weeks produces similar exposures in children and adults.

The overall safety profile of ipilimumab in children and adolescents 12 years of age and older with advanced melanoma was consistent with the known safety profile in adults.

Based on review of this sBLA, FDA recommends approval of ipilimumab for the treatment of pediatric patients 12 and older with unresectable or metastatic melanoma.

9 Labeling Recommendations

Labeling negotiations were ongoing at the time of completing this review. A discussion of labeling recommendations will be provided as an addendum to the clinical review at a later date.

10 References

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/s/

DENISE A CASEY
07/14/2017

SUZANNE G DEMKO
07/17/2017

I concur with the findings in this review and the recommended regulatory decision to grant approval to this supplemental BLA. I also concur in the opinion that the applicant has fairly responded to the elements outlined in the Pediatric Written Request for ipilimumab issued on July 7, 2014