20 July 2017
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Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Yervoy

ipilimumab

Procedure no: EMEA/H/C/002213/P46/034.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BOR	Best Overall Response
CI	Confidence Interval
Cminss	Minimum concentration at steady state
CR	Complete Response
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DCR	Disease Control Rate
DMC	Data Monitoring Committee
DOR	Duration of Response
FPFV	First Patient First Visit
GCP	Good Clinical Practice
H	Hour
HLA	Human Leukocyte Antigen
ICF	Informed Consent Form
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
imAR	Immune-mediated Adverse Events
irAE	Immune-related Adverse Events
IRB	Independent Review Board
irRC	Immune-related response criteria
IV	Intravenous
LFT	Liver Function Tests
LLN	Lower Limit of Normal
min	Minute
mL	Milliliter
mWHO	Modified World Health Organization Criteria
NA	Not Applicable
NCI	CTCAE National Cancer Institute Common Terminology Criteria for Adverse events
OR	Overall Response
OS	Overall Survival
PD	Pharmacodynamics
PD	Progressive Disease
PD-1	Programmed Death-1
PFS	Progression-Free Survival
PK	Pharmacokinetics
PR	Partial Response
PS	Performance Status
PT	Preferred Term
PY	Person-year
SAE	Serious Adverse Event
SD	Stable Disease
SOC	System Organ Class
ULN	Upper Limit of Normal

Introduction

On 28 December 2016, the MAH submitted a completed paediatric study for Yervoy, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measures

A short critical expert overview has also been provided.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study CA184178 ("A phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated, unresectable stage III of stage IV malignant melanoma") is part of a clinical development program (see below and Table 1). The variation application consisting of the full relevant data package (i.e. containing several studies) is expected to be submitted by 25 March 2017.

1.2. Information on the pharmaceutical formulation used in the study

Ipilimumab was supplied as a clear, colourless solution in single-use vials, containing 50 mg ipilimumab in a 10 mL vial or 200 mg ipilimumab in a 40 mL vial, either containing 5 mg/mL.

1.3. Clinical aspects

1.3.1. Introduction

Regulatory background

This PAM concerns the assessment of the final study report of study CA184178 (submitted in accordance of Article 46 of Regulation (EC) No. 1901/2006), a non-randomised, multicenter, open-label, phase 2 study of ipilimumab for children and adolescents 12 to <18 years with previously treated or untreated, unresectable stage III or stage IV malignant melanoma. The MAH proposed no labelling changes on this Article 46 submission.

Two paediatric studies in advanced metastatic melanoma have been completed: NCI7458/CA184070 and CA184178 (Table 1). A third paediatric study, E1609 (also known as CA184116), a phase 3 randomised study of adjuvant ipilimumab anti-CTLA-4 therapy vs high-dose interferon α-2b for resected high-risk melanoma, is being conducted with the cooperation of the Eastern Cooperative Oncology Group (ECOG), primarily in high-risk surgically-resected melanoma in the adjuvant setting. The amendment to add a paediatric/adolescent cohort to study CA184116/E1609 was activated on 23-Sep-2014. The primary endpoint for adolescents is safety. Of the originally planned 45 adolescent subjects, 3 were enrolled over 15 months up to November 2016 and 2 patients were treated.

Table 1. Ipilimumab paediatric clinical development program in advanced melanoma

Study identifier Sponsor/Collaborator	Type of study/ design features	Study population/ Planned/Enrolled	Dosage, regimen	Primary Objectives
NCI7458/CA184070 National Cancer Institute (NCI)	Phase 1, open-label, dose-escalation clinical study of IV ipilimumab in subjects with untreatable, refractory or relapsed solid malignant tumors to evaluate PK and safety.	Children and adolescents 1 to < 18 y (+ young adults up to 21 years) with advanced and/or refractory solid malignant tumors. Actual age range: 2.4 to 21.8 years Planned: 30 total Actual: 33 total; 3 at 1 mg/kg; 3 at 3 mg/kg; 14 at 5 mg/kg; 13 at 10 mg/kg.	4 planned dose levels (1, 3, 5, and 10 mg/kg. Ipilimumab IV Treatment Phase: Day 1 of q21-day cycle for 4 cycles. Maintenance Phase: From Cycle 5 onward, ~q12wks	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 subjects ≤ 21 years of age with untreatable, refractory or relapsed solid malignant tumors. To assess the pharmacokinetics (PK) of ipilimumab administered intravenously (IV) in subjects ≤ 21 years of age with solid tumors refractory to standard therapy.
CA184178 Bristol-Myers Squibb (BMS)	Phase 2, open-label, multi-center, single-arm efficacy and safety clinical study of ipilimumab in subjects with untreated or previously treated advanced/metastatic melanoma	Children age 12 to < 18 y with untreated or previously treated advanced/metastatic melanoma. Actual age range: 12 to 16 years Planned: 30 total; up to 10 at 10 mg/kg; at least 20 at 3 mg/kg Actual: 12 total 8 at 10 mg/kg; 4 at 3 mg/kg	Ipilimumab 3 or 10 mg/kg IV Treatment Phase: ipilimumab q3wks (Week 1, 4, 7, 10). Eligible subjects with a PR or CR or SD of ≥3 months (beginning at Week 12 with SD at Week 24) with subsequent confirmed PD are eligible for one course of retreatment therapy consisting of 4 infusions (each dose of ipilimumab 3or 10 mg/kg q3wks).	To estimate the survival rate at 1 year in adolescent subjects (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 subjects (12 to < 18 years) at the 3 mg/kg dose level.

CR = complete response; IV = intravenous; NCI = National Cancer Institute; OS = overall survival; PD = progressive disease; PK = pharmacokinetics; PR = partial response; q = every; SD = stable disease; TBD= to be decided; wks = weeks.

A Paediatric Investigation Plan (PIP) for ipilimumab in all conditions in the category of malignant neoplasms except melanoma, nervous system, haematopoietic and lymphoid tissue (EMEA-000117-PIP01-07), and another one for the treatment of the condition of melanoma (EMEA-000117-PIP02-10) were initially approved by the EMA in November 2008 (EMA Decision P/95/2008) and June 2011 (EMA Decision P/128/2011), respectively. Subsequently, several requests for modification for both PIPs have been submitted.

Clinical study NCI7458/CA184070, which was included in both PIPs, was submitted under Article 46 in December 2014.

Ipilimumab

Ipilimumab (BMS-734016, MDX-010, YERVOY®) is a fully human monoclonal immunoglobulin specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4). Ipilimumab is approved as monotherapy in the United States (March 2011), European Union (July 2011), and other countries for the treatment of advanced (unresectable or metastatic) melanoma in adults at a dose of 3 mg/kg administered intravenously (IV) once every 3 weeks for a total of 4 doses.

1.3.2. Clinical study

Study CA184178: A phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated, unresectable stage III of stage IV malignant melanoma

Description

Study CA184178 is a non-randomised, multicenter, open-label, phase 2 study of ipilimumab for children and adolescents 12 to <18 years with previously treated or untreated, unresectable stage III or stage IV malignant melanoma.

Methods

Objective(s)

In Table 2 the study objectives and a description of corresponding endpoints are presented.

Table 2. Study objectives and endpoints

Objective	Endpoint	Endpoint Description
PRIMARY		
To estimate the overall 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	OSR	The overall survival rate was estimated in two ways: Kaplan-Meier (KM) estimate at 1-year Proportion of treated subjects that were alive for 1-year or longer. The survival rate at one year was defined as the probability that a participant was alive at one year following start of treatment. .
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	Deaths, AEs, SAEs, AEs leading to DC & dose delay, vital signs, specific lab abnormalities	The assessment of safety was based on AEs, SAEs, irAEs, imARs, deaths and the results of vital sign measurements, physical measurements, clinical laboratory tests and exposure to study therapy for participants who received at least 1 dose of study treatment and within 90 days of last dose of ipilimumab administration. AEs were coded using the MedDRA Version 19.0. AEs and laboratory values were graded for severity according to the NCI CTCAE version 3.0.
SECONDARY		
To estimate the disease control rate by mWHO criteria at the 3 mg/kg dose level.	DCR	The primary definition of DCR was the total number of treated subjects with a best overall response of CR, PR, or SD, divided by the total number of treated subjects. Any participant who was unevaluable for disease control, eg, on account of missing or "not evaluable" assessments, was included in the denominator of the calculation, ie, was considered a non-responder with respect to the DCR endpoint. The time frame for this endpoint was from Day 1 of first participant first treatment to Day 365 from the last participant first visit.
To estimate progression free survival (PFS) by mWHO criteria at the 3 mg/kg dose level.	PFS	PFS was defined as the time from the start of ipilimumab treatment to progression or death, whichever occurs first. A participant who died without reported progression were considered to have progressed on their date of death. For subjects who remained alive and had not progressed, PFS was censored on the date of the last tumor assessment.

•To estimate best overall response rate (BORR) by mWHO criteria at the 3 mg/kg dose level.	BORR	BORR was defined as the total number of treated subjects with the best overall response of CR or PR, divided by the total number of treated subjects. The time frame for this endpoint was from Day 1 of first participant treatment to Day 365 from the last participant first treatment.
•To assess overall survival at the 3 mg/kg dose level	OS	OS was defined as the time from the start of ipilimumab treatment date to death. If a participant had not died, the participant was censored at the time of last contact (last known alive date.)
EXPLORATORY		
To characterize pharmacokinetics of ipilimumab, the immunogenic potential, and to explore exposure-response relationship with selected exposure measure, safety, and efficacy endpoints[a]	Pharmacokinetics	Minimum serum concentration- Cmin Maximum serum concentration -Cmax Total body clearance- CLT Area under the serum concentration time curve from time zero to time of the last quantifiable concentration - AUC (0-T)[b] Area under the serum concentration time curve from time zero to 21 day- AUC (0-21)
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[c]	Immunomodulating activity	The immunomodulating activity was to be derived from ALC and the T cell subsets, activated CD4 and CD8 T cells.

[a] The exposure-response relationship was not explored in this report. A PPK model will be developed to characterize the concentration-time profile of ipilimumab in pediatric subjects receiving ipilimumab using pooled data from adult and pediatric in multiple clinical studies including the assessment of covariate effects on the PK model parameters.

[b] AUC (0-T) was not performed.

[c] There were too few patients per dose group to perform lymphocyte phenotyping and determine circulating levels of selected cytokines. In addition, there were issues with peripheral blood mononuclear cell viability for some of the samples to derive the activated CD4 and CD8 T-cell data. Given the inherent variability in these measures and the lower than expected sample size, it would be too difficult to draw conclusions from the data.

As part of the safety analyses, the MAH evaluated the incidence of immune-related adverse events (irAEs) and immune-mediated adverse events (imARs):

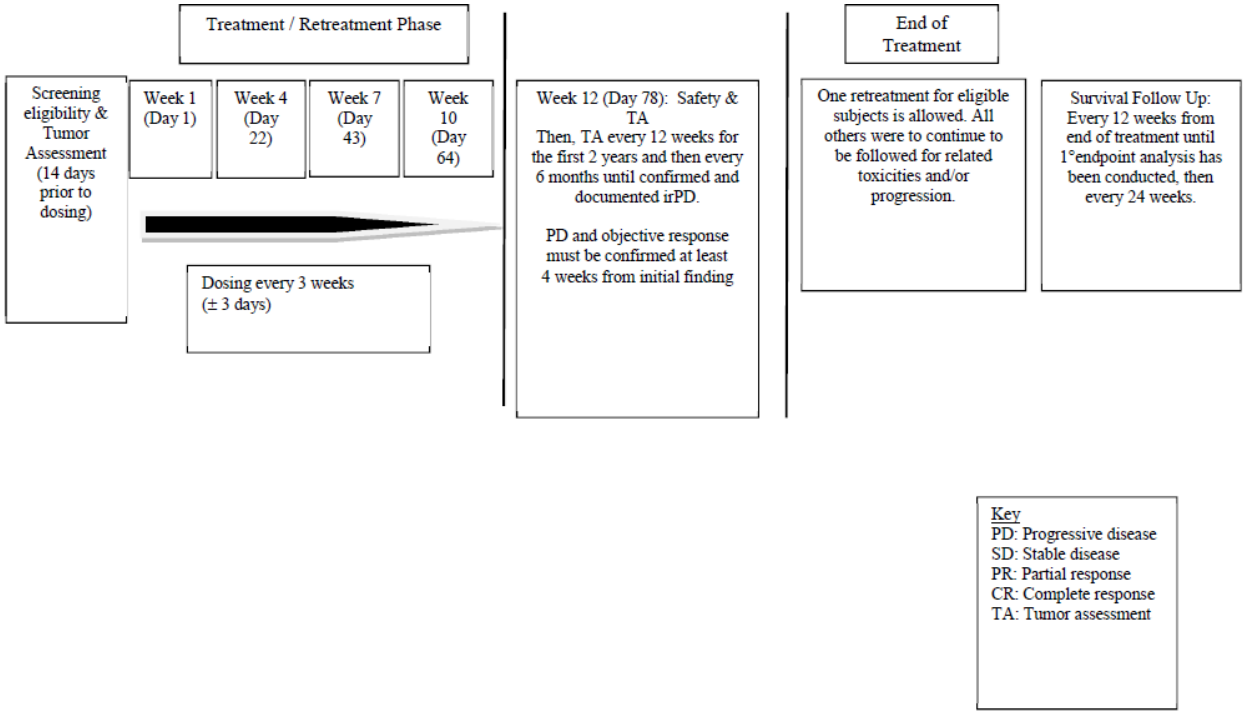
- **irAEs** are AEs of unknown aetiology, which are consistent with an immune phenomenon and identified by the investigator as related to study treatment. The irAEs were programmatically determined from a predefined list of MedDRA high-level group terms, high-level terms and preferred terms; changes may be made to this list with each new version of MedDRA. Six subcategories of irAEs were reported: gastrointestinal, liver, skin, endocrine, neurological, and other irAE summaries were also produced on diarrhoea as a separate grouped term.
- **imARs** are AEs determined by the investigator to have an immune-mediate aetiology. imARs were likely to be inflammatory events associated with ipilimumab treatment.

Study design

CA184178 was a non-randomised, multicenter, single-arm open-label phase 2 study in adolescent patients (12 to <18 years of age) with previously treated or untreated, unresectable stage III or stage IV advanced or metastatic melanoma. This study was divided into the following phases: screening, induction (hereafter referred to as the treatment phase), retreatment, toxicity/progression follow-up, and survival follow-up.

Patients were treated with 4 infusions of ipilimumab (10 or 3 mg/kg) at weeks 1, 4, 7, and 10. After completion of the 4 infusions a thorough safety and tumour assessment at week 12 was performed. Patients with stable or responding disease were to have tumour assessments performed every 12 weeks for the first 2 years, followed by every 6 months until confirmed and documented immune-related Progressive Disease (irPD) (Figure 1).

Figure 1. Study scheme



Source: Appendix 1.1: CA184178 Revised Protocol 01[2]

Tumour response-based endpoints were assessed by the investigator using both modified World Health Organization (mWHO) criteria for secondary efficacy endpoints, and immune-related response criteria (irRC) for study treatment decisions.

Patients with an initial partial response (PR) or complete response (CR) or stable disease of ≥3 months (beginning at week 12 with SD at week 24) who subsequently experienced confirmed PD per irRC were eligible to enter the retreatment phase. Eligible patients could receive up to 4 doses of ipilimumab during retreatment (one dose every 3 weeks as was done during the initial treatment phase). Retreatment had to begin within 14 days of the confirmed PD and the phase ended with discontinuation of ipilimumab at study closure or when the patient entered the toxicity/progression follow-up phase.

Patients who discontinued study treatment due to toxicity or PD prior to completing the treatment phase were to have an end of treatment assessment. A strict stopping rule based upon the occurrence of drug-related, life threatening toxicities, irAEs (immune-related adverse events) which occur beyond first dose of study drug was employed. In addition, stopping rules were in place for any AE, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presented a substantial clinical risk to the patient.

Follow-up for progression/toxicity started after the last dose of study treatment and continued every 12 weeks (±14 days) until documented and confirmed disease progression or AE resolution. Patients were followed for related AEs for a minimum of 90 days following the last dose of study treatment. Adverse events collection was to resume if the patient started retreatment and continue for a minimum of 90 days following the last dose of study treatment. Patients who completed the toxicity follow-up period and had PD per irRC during the treatment or retreatment phase then entered the overall survival follow-up phase. Adverse event assessments continued until all related AEs were resolved, returned to baseline, or were deemed irreversible.

For patients who did not experience PD per irRC, tumour assessments were performed at week 12, 24 and every 12 weeks for the first 2 years and then every 6 months until confirmed and documented irPD.

Patients were followed for long-term survival information until study closure. The survival follow-up phase began after progression per irRC for patients who did not enter the retreatment phase.

Patients continued study treatment until they either experienced intolerable toxicity, confirmed disease progression or the patient requested to stop study treatment.

Corticosteroids (oral or intravenous) were permitted to be used for treatment of irAEs. Alternative immunosuppressive therapies were also permitted to treat irAEs that did not respond to initial steroid therapy.

Study population /Sample size

In- and exclusion criteria

The study enrolled male and female adolescent patients (12 to <18 years of age) who met the following key target disease criteria:

- Histologically or cytologically confirmed malignant melanoma.
- Previously treated or untreated, unresectable stage III or stage IV malignant melanoma.
- Measurable and/or evaluable disease within 28 days prior to first dose of study treatment.
- Karnofsky or Lansky Score ≥50.
- Adequate hematologic, renal and hepatic function.

Key exclusion criteria included:

- Patients with primary ocular melanoma.
- Active brain metastases. Patients with brain metastases who were free of neurologic symptoms and who did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy were eligible.
- History of or current active autoimmune disease.
- Prior therapy with a CTLA-4, PD-1, PD-L1, or CD137 targeted agents.
- Prior therapy with systemic immunosuppressive doses of agents such as cyclosporine or high dose steroid treatment within 4 weeks.

Treatments

Ipilimumab was administered intravenously (IV) at doses of 3 or 10 mg/kg over 90 minutes on day 1 of each 21-day cycle for 4 cycles unless there was confirmed disease progression (per irRC), unacceptable toxicity, or patient request to stop study treatment. Patients eligible for retreatment could receive up to 4 additional doses of ipilimumab during retreatment: one dose every 3 weeks as was done during the initial treatment phase. Alternative therapy such as both anti-PD1 and ipilimumab were to be offered to the patient if their disease were to progress outside of the study.

Ipilimumab at 10 mg/kg was initially chosen for the CA184178 study based on the observations that 10 mg/kg was tolerated in adolescent patients in the study NCI7458 (CA184070) and 10 mg/kg was potentially more active in a randomised phase 2 study (CA184022) of ipilimumab in adult melanoma, with a tolerable safety profile. Ipilimumab 10 mg/kg was also used in a second registrational study in adult patients with previously untreated advanced melanoma and prolonged overall survival when combined with dacarbazine, versus dacarbazine alone (CA184024).

Given that ipilimumab 3 mg/kg was broadly approved across treatment lines in Europe, the United States, and other countries throughout the world, the MAH amended the protocol in 2014 (amendment 04; see paragraph “Changes in the conduct of the study” for more information) to change the dose of ipilimumab from 10 to 3 mg/kg to ensure consistency with the approved adult dose. Inclusion of the 3 mg/kg dose in this study was further supported by similarities between adults and adolescents with advanced melanoma, based upon comparable general clinical characteristics as well as maturation of the immune system for the two populations.

Patients who started at 10 mg/kg stayed on 10 mg/kg and no dose reduction was allowed, as amendment 04 was not driven by safety concerns associated with 10 mg/kg and no experience exists with dose reductions in the ipilimumab program.

Statistical Methods

Sample size

The sample size for this study was not based upon a comparative objective. Initially, the study was designed to enrol approximately 30 patients, from age 12 to <18 years of age, with previously treated or untreated unresectable stage III or IV metastatic melanoma to be treated with 10 mg/kg or 3 mg/kg of ipilimumab. In case not more than 10 patients were treated with 10 mg/kg, this sample size of approximately 30 patients ensured that at least 20 patients would have been treated with 3 mg/kg. If, however, more than 10 patients were treated with 10 mg/kg, the total sample size would have been increased to ensure that at least 20 patients would be treated with 3 mg/kg. With 20 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 would have been at least 27.2% if 10 or more patients are alive after 1 year. The maximum width of the CI would have been 46%. Assuming that the incidence of high-grade imARs was at least 15%, a sample size of 20 patients treated at 3 mg/kg would have provided a two-sided exact 95% CI of 3.2% to 37.9.

Statistical analyses

Discrete variables were summarised with the number and proportion of patients falling into each category, grouped by treatment group (3 mg/kg or 10 mg/kg total, unless otherwise noted). Unless otherwise indicated, percentages in the tables were column percentages, using all observations that belong in the column as the denominator. Percentages were rounded to the first decimal place and therefore may not always add up to 100. Continuous variables were summarised using descriptive statistics (mean, standard deviation, median, minimum and maximum values). Patient listings were produced to accompany the tabulations. Summary statistics were presented for each treatment group (ipilimumab 3 mg/kg or 10 mg/kg) and for all treated patients unless otherwise noted. No formal statistical testing was performed, only summary statistics are provided

Exposure analyses

Ipilimumab dose in mg/kg was calculated as the dose in mg divided by the most recent weight prior to infusion. Cumulative dose was defined as the sum of all calculated doses (mg). Cumulative dose of ipilimumab in mg/kg was defined as the sum of all doses (in mg/kg) received by the subject.

Efficacy analyses

Due to the limited number of subjects enrolled in this study, only key analyses were performed for each treatment group (3mg/kg or 10 mg/kg of ipilimumab [primary objective analyses descriptive by dose level]). The 1-year OS rate was based on a Kaplan-Meier estimate along with their corresponding log-log transformed 95% confidence interval. The OS probabilities were estimated using the Kaplan-Meier product-limit method. The estimates of the median and corresponding two-sided 95% confidence intervals were calculated using the Brookmeyer and Crowley method. In addition, the 1-year survival rate was calculated as the proportion of patients alive at one year divided by the total number of treated patients along with the Clopper-Pearson exact two-sided 95% confidence interval.

The PFS probabilities were estimated using the Kaplan-Meier product-limit method. The estimates of the median and corresponding two-sided 95% confidence intervals were calculated using the Brookmeyer and Crowley method. For both the DCR and BORR, each rate was presented together with its Clopper-Pearson exact two-sided 95% confidence interval. Subjects were considered evaluable for tumour response if they completed at least one cycle of therapy, or if they experienced progressive disease prior to that time.

Safety analyses

All analyses are presented by dose cohort (3 mg/kg and 10 mg/kg). No formal comparisons are made between dose cohorts with the exception of the primary endpoint of imARs. Otherwise, no formal statistical testing was performed, only summary statistics are provided.

The on-study reporting period for safety data was from the first dose of study medication to 90 days (> 5 half lives) after the last dose was received.

The primary assessment of safety was severe imARs. The rate of severe imAR was calculated as a proportion of patients having a grade 3 or worse immune mediated adverse reaction divided by the total number of treated patients along with its Clopper-Pearson exact two-sided 95% confidence interval to support the primary safety endpoint

Descriptive statistics of safety were presented for treated patients in each treatment group (3 or 10 mg/kg ipilimumab). All on-study AEs, drug-related AEs, immune-related AEs, SAEs, drug-related

SAEs, irAEs, and imARs were tabulated using worst grade per NCI CTCAE by MedDRA version 19.0 system organ class (SOC) and by preferred term (PT).

Summary tables of multiple occurrences of AEs were presented for each treatment group showing the total number and rate (exposure adjusted) of occurrences for all on-study AEs as well as the number of patients experiencing an irAE once or multiple times during on-study period.

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 (identified by the safety and medical representatives from) that were considered as causally related to study drug exposure by the investigator. These terms were grouped into the following organ-specific subcategories: gastrointestinal, skin, liver, endocrine, neurological, and other. Formal exclusion of a non-inflammatory aetiology was not required for identifying irAEs.

On-study laboratory parameters, including haematology, serum chemistry, liver function, and renal function were summarised using worst CTC grade.

Study conduct

Ethics

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council on Harmonization 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).

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. Specific measures that were taken to minimise risk in this clinical study, consistent with ICH guidelines E11 (ICH Technical Requirements for Registration of Pharmaceuticals for Human Use, 20-July-2000), include minimisation of the frequency and volume of blood drawn. Consistent with the Ethical Considerations for Clinical Trials Performed in Children: Recommendations of the Ad Hoc group for the development of implementing guidelines for Directive 2001/20/EC, 2008, throughout the design and conduct of the study, investigations/interventions were limited to the minimum required for obtaining valid data and were performed using size-/age-appropriate material and devices, including limiting the number of attempts for sampling.

Institutional Review Board/Independent Ethics Committee

The protocol, amendments, and patient informed consent received appropriate approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) prior to initiation of study at the site.

Informed consent

Investigators were to ensure that patients, or, in those situations where consent could not be given by patients, their legally acceptable representatives, were clearly informed about the purpose, potential risks, and other critical issues regarding this study. This study was conducted in adolescent patients, therefore, for all minors, according to local legislation, one or both parents or a legally acceptable representative was informed of the study procedures and signed the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who was capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time was to be considered by the investigator. Study patients who were judged to be of an age of reason also gave their written assent, unless otherwise specified by local regulations. Prior to the beginning of the study, the investigator must have had the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other information to be provided to the patients. Freely given written informed consent was obtained from each patient, prior to study participation, including informed consent for any screening procedures conducted to establish patient eligibility in the study.

Protocol deviations

Two subjects had a significant protocol deviation. One patient in the 10 mg/kg group was diagnosed with Stage 3, M0 metastatic melanoma and underwent surgical excision prior to enrolling in the study, and had no evaluable/measurable lesions at baseline. Despite the resection, her baseline CT scan showed anomalies in the parotid area that were sufficient to indicate that some tumour may have remained, and because the anatomy in the surgical area was distorted, it was impossible to confirm complete surgical excision of the tumour nor perform measurements. Because of this observation and because she was a member of the analysis population, i.e., the treated population, she was, therefore, included in the efficacy, safety and PK analyses. As the anatomy in the surgical area was similarly distorted during subsequent evaluations and the presence of tumour could not be confirmed or ruled out, she was considered to have stable disease through the end of the study.

The second patient was not re-consented in a timely fashion during the follow-up phase.

Changes in the conduct of the study

Four amendments were made to this study (Table 3). The rationale for removing the maintenance phase of ipilimumab treatment with Amendment 04 was that maintenance treatment has not been proven to add additional benefit in previous studies in adults and the potential risk for severe immune-related adverse events with prolonged treatment. Regarding retreatment, as there were indications for clinical benefit of retreatment after progression, this option was added to the study protocol.

Table 3. Summary of changes to protocol CA184178

Designation/ Date	Centers	Changes
01 28-Feb-2013	Country Specific (United Kingdom)	Inclusion of exclusionary criteria for participants unwilling to notify their general practitioner or referring physician (if applicable) of study participation Provision of further guidance on the length of time participants should be monitored following study treatment infusion Updating of the requirements for review of TSH results.
02 23-Apr-2013	Country Specific (France)	Inclusion of recommended management algorithms for suspected GI toxicity, diarrhea/colitis, suspected hepatotoxicity, suspected skin toxicity, suspected, endocrinopathy and suspected neurotoxicity as an appendix to the protocol
03 02-Jul-2013	Country Specific (Germany)	Specification of MRI as the standard for tumor assessments Clarification of the use of condoms in combination with spermicides Specification of exclusion criteria for participants with a history of allergic reactions to parental administration of recombinant protein
04 21-May-2014	All	Change in dose of study medication dose from 10 mg/kg to 3 mg/kg based on the approved adult ipilimumab dose for the advanced melanoma indication Removal of the maintenance phase due to lack of added benefit Addition of one reinduction/retreatment for eligible participants Revision of the definition and guidance for WOCBP Revision of ipilimumab program-specific language for defining imARs Revision of the maximum number of index, non-index and new lesions for follow up Clarification of the pre-dose window time frame for PK Provision for re-enrollment of eligible participants Provision for additional TSH testing at Week 24

Abbreviations: TSH = thyroid stimulating hormone; MRI = magnetic resonance imaging; WOCBP = Women of Child Bearing Potential; imARs = immune-mediated adverse reactions; PK = pharmacokinetics.

Source: Appendix 1.1

Results

Recruitment / Number analysed

Enrolment in 32 sites across 10 countries was planned (Table 5), and 80% of sites were activated as of December 2013. Because the rarity of the patient population was greater than anticipated, as well as the availability of competing new emerging therapies (e.g., anti-PD-L1), the majority of sites were unable to enrol a patient over the 3.5-year period, and study closure was recommended by the DMC. At the time of study closure (April 2016), 14 patients were enrolled and 12 were treated in the study:8 subjects in the 10 mg/kg and 4 of the 20 planned subjects in the 3 mg/kg cohort (Table 4). All treated subjects completed 1-year survival follow-up. No additional subjects were enrolled after April 2015. The number of treated subjects per country are presented in Table 5.

Table 4. Patient disposition of all enrolled patients

	Number of Subjects (%)		
	3 mg/kg Ipilimumab	10 mg/kg Ipilimumab	Total
NUMBER OF ENROLLED SUBJECTS	5	9	14
NUMBER TREATED	4 (80.0)	8 (88.9)	12 (85.7)
NUMBER NOT TREATED	1 (20.0)	1 (11.1)	2 (14.3)
REASON NOT TREATED			
SUBJECT NO LONGER MEETS STUDY CRITERIA	1 (20.0)	1 (11.1)	2 (14.3)
ADMINISTRATIVE REASON BY SPONSOR	0	0	0
ADVERSE EVENT	0	0	0
DEATH	0	0	0
LOST TO FOLLOW-UP	0	0	0
OTHER	0	0	0
POOR/NON-COMPLIANCE	0	0	0
PREGNANCY	0	0	0
SUBJECT WITHDREW CONSENT	0	0	0

Re-enrollment was permitted for subjects who discontinued study as a pretreatment failure. Subjects re-enrolled and subsequently treated are only counted once as "treated".

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-DS-DISP.SAS Run Date: 13SEP2016:04:02:39

Table 5. Accrual by country

Country	Number of Sites	Number Treated
Belgium	1	1
Denmark	1	1
France	2	3
Spain	1	1
United States	5	6

Source: Supplemental Table S.2.2

The following populations were defined for analyses:

- Enrolled Subjects: All 14 subjects who signed the ICF and who were registered in the IVRS.
- Treated subjects: All 12 treated subjects who received at least 1 dose of 3 mg/kg or 10 mg/kg ipilimumab.
- Pharmacokinetic Subjects: 12 treated subjects who had any available serum time-concentration data.
- ADA Subjects: 12 treated subjects who had at least 1 ADA sample collected at screening and on-study.

Baseline data

Overall, most subjects were male (58.3%) and white (91.7%) (Table 6). Median overall age was 15.0 years, with a range of 12 to 16 years. Baseline Lansky/Karnofsky scores ranged from 90 to 100 overall. Baseline LDH was normal for 83.3% of patients. Median time from pathological diagnosis to first dose of ipilimumab was 10.45 months, and from diagnosis of advanced melanoma to first dose of ipilimumab was 2.35 months. Consistent with the inclusion criteria, all subjects were stage III or IV at study entry.

One patient in the 10 mg/kg group was not evaluable because baseline tumour assessment of the target lesion was made using MRI and the follow-up evaluation was made using PET, and thus, a comparison of the size of the target lesions could not be made. A second patient in the 10 mg/kg group was diagnosed with stage III, M0 metastatic melanoma and underwent surgical excision prior to enrolling in the study, and had no evaluable/measurable lesions at baseline. As the anatomy in the surgical area was similarly distorted during subsequent evaluations and the

presence of tumour could not be confirmed or ruled out, she was considered to have stable disease through the end of the study (see also paragraph about protocol deviation).

Table 6. Baseline demographics and patient characteristics

	Number of Subjects (%)		
	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8	Total N = 12
AGE (YEARS)			
N	4	8	12
MEAN (SD)	13.3 (1.89)	14.9 (0.64)	14.3 (1.37)
MEDIAN	12.5	15.0	15.0
MIN - MAX	12 - 16	14 - 16	12 - 16
GENDER			
FEMALE	2 (50.0)	3 (37.5)	5 (41.7)
MALE	2 (50.0)	5 (62.5)	7 (58.3)
RACE			
WHITE	3 (75.0)	8 (100.0)	11 (91.7)
BLACK OR AFRICAN AMERICAN	1 (25.0)	0	1 (8.3)
ASIAN	0	0	0
AMERICAN INDIAN OR ALASKA NATIVE	0	0	0
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	0	0	0
OTHER	0	0	0
REGION			
EUROPE	3 (75.0)	3 (37.5)	6 (50.0)
NORTH AMERICA	1 (25.0)	5 (62.5)	6 (50.0)
BASELINE HEIGHT (CM)			
N	4	8	12
MEAN (SD)	154.18 (8.321)	170.48 (12.336)	165.04 (13.422)
MEDIAN	155.40	177.10	160.60
MIN - MAX	143.5 - 162.4	154.0 - 182.3	143.5 - 182.3
BASELINE WEIGHT (KG)			
N	4	8	12
MEAN (SD)	65.55 (19.655)	64.28 (4.869)	64.70 (10.993)
MEDIAN	62.60	64.85	64.85
MIN - MAX	45.7 - 91.3	57.1 - 71.6	45.7 - 91.3
BASELINE LACTATE DEHYDROGENASE (ELEVATION DEFINED AS > UPPER NORMAL LIMIT)			
ELEVATED	1 (25.0)	1 (12.5)	2 (16.7)
NORMAL	3 (75.0)	7 (87.5)	10 (83.3)
NOT REPORTED	0	0	0
BASELINE KARNOFSKY/LANSKY PERFORMANCE STATUS			
100	4 (100.0)	5 (62.5)	9 (75.0)
90	0	3 (37.5)	3 (25.0)
NOT REPORTED	0	0	0
TIME FROM INITIAL PATHOLOGICAL DIAGNOSIS OF MALIGNANT MELANOMA TO 1ST DOSE OF IPILIMUMAB (MONTHS)			
N	4	8	12
MEAN (SD)	20.35 (18.461)	11.58 (7.792)	14.50 (12.258)
MEDIAN	12.55	10.45	10.45
MIN - MAX	8.7 - 47.6	2.8 - 27.2	2.8 - 47.6
TIME FROM DIAGNOSIS OF ADVANCED METASTATIC MELANOMA TO 1ST DOSE OF IPILIMUMAB (MONTHS)			
N	4	8	12
MEAN (SD)	3.80 (3.403)	2.21 (1.808)	2.74 (2.419)
MEDIAN	3.20	1.75	2.35
MIN - MAX	0.5 - 8.3	0.5 - 5.3	0.5 - 8.3
DISEASE STAGE AT INITIAL DIAGNOSIS OF MALIGNANT MELANOMA			
I	0	0	0
II	3 (75.0)	0	3 (25.0)
III	0	6 (75.0)	6 (50.0)
IV	1 (25.0)	2 (25.0)	3 (25.0)
DISEASE STAGE AT STUDY ENTRY			
III	0	2 (25.0)	2 (16.7)
IV	4 (100.0)	6 (75.0)	10 (83.3)

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Overall, 91.7% of the patients treated had at least one lesion, and 41.7% had lesions at ≥5 sites (see Supplemental Table S.3.2 in CSR). Ten out of 12 patients (83.3%) had at least one index lesion (see Supplemental Table S.3.3 in CSR).

Prior anti-cancer therapies

All treated patients had prior surgery, with 58.3% also receiving systemic therapy and 1 (8.3%) receiving radiotherapy (Table 7).

Table 7. Prior anti-cancer therapies

	Number of Subjects (%)		
	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8	Total N = 12
NUMBER OF SUBJECTS WITH ANY PRIOR SYSTEMIC THERAPY	3 (75.0)	4 (50.0)	7 (58.3)
NUMBER OF SYSTEMIC THERAPY REGIMENS RECEIVED			
1	1 (25.0)	1 (12.5)	2 (16.7)
2	2 (50.0)	1 (12.5)	3 (25.0)
3	0	1 (12.5)	1 (8.3)
4	0	0	0
>4	0	1 (12.5)	1 (8.3)
NUMBER OF SUBJECTS WITH ANY PRIOR RADIOTHERAPY	0	1 (12.5)	1 (8.3)
NUMBER OF RADIOTHERAPY REGIMENS RECEIVED			
1	0	1 (12.5)	1 (8.3)
2	0	0	0
3	0	0	0
4	0	0	0
>4	0	0	0
NUMBER OF SUBJECTS WITH ANY PRIOR SURGERY RELATED TO CANCER	4 (100.0)	8 (100.0)	12 (100.0)
NUMBER OF PRIOR SURGERIES RELATED TO CANCER			
1	0	0	0
2	1 (25.0)	2 (25.0)	3 (25.0)
3	0	1 (12.5)	1 (8.3)
4	0	2 (25.0)	2 (16.7)
>4	3 (75.0)	3 (37.5)	6 (50.0)

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Concomitant therapies

All patients received non-study medications between first dose date and 90 days after last dose of study therapy. These medications were primarily given for the ongoing clinical management of disease symptoms or the treatment of AEs. The classes of concomitant medications used by most patients were analgesics and systemic antihistamines. No patient received anti-cancer therapy during ipilimumab treatment. Two patients received anti-cancer treatment within the reporting period of 90 days. Patient received temozolomide approximately one month after the last ipilimumab 10 mg/kg dose. Patient received dabrafenib and trametinib almost one month after the last and only dose of ipilimumab 10 mg/kg.

Subsequent therapies

In study CA184178, subsequent therapy could be initiated for progressive disease, the need for surgical excision, or maintenance therapy after discontinuation due to an AE related to ipilimumab or to maintain response after treatment with another agent subsequent to failing ipilimumab treatment. Collection of information about subsequent therapy for treatment of melanoma was an essential component of subject follow-up, and subjects were followed for 90 days or more. All subjects in the 3 mg/kg group and 6/8 subjects received some type of subsequent therapy. Treatments included chemotherapy (dabrafenib, trametinib, aldesleukin, temozolomide, paclitaxel), immunotherapy (pembrolizumab, nivolumab, MK-3475 [MEKPD]), radiotherapy, surgery, and other (fomustine [chemoembolisation]).

Extent of exposure

Overall, 8 patients received 10 mg/kg and 4 patients received 3 mg/kg. Of the 8 patients who received 10 mg/kg, 3 patients received the 4 planned infusions of ipilimumab. Of the 4 patients who received 3mg/kg, three of the patients received the 4 planned infusions (Table 8). In the 3 mg/kg group the median cumulative dose (mg) was 691.25 mg with the min-max 336.6 to 1103.7 mg and in the 10 mg/kg group, the median cumulative dose was 1896.00 mg with the min-max 617 to 2965.0 mg. The cumulative dose median dose (mg/kg) in the 3 mg/kg group was 11.95 mg/kg with a min-max of 6.0 to 12.0 mg/kg and in the 10 mg/kg group the median cumulative dose was 29.75 mg/kg with a min-max of 10.0 to 39.8 mg/kg.

No patients entered the re-treatment phase. Two adolescents in study CA184178 were eligible for retreatment, but did not receive it. One patient was treated in the next line with pembrolizumab and for the other patient the investigator decided to not retreat based on continued PR.

Table 8. Number of doses of ipilimumab during the study

	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8	Total N = 12
NUMBER OF DOSES PER SUBJECT			
NUMBER OF SUBJECTS	4	8	12
MEAN (SD)	3.5 (1.00)	2.8 (1.28)	3.0 (1.21)
MEDIAN	4.0	3.0	3.5
MIN - MAX	2 - 4	1 - 4	1 - 4
NUMBER OF DOSES PER SUBJECT			
1	0	2 (25.0)	2 (16.7)
2	1 (25.0)	1 (12.5)	2 (16.7)
3	0	2 (25.0)	2 (16.7)
4	3 (75.0)	3 (37.5)	6 (50.0)
5	0	0	0
6	0	0	0
7	0	0	0
8	0	0	0
9	0	0	0
10	0	0	0
>10	0	0	0

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Discontinuation of study therapy

Most patients (50%) in the study were discontinued from treatment due to study drug toxicity. Four patients (33.3%) were discontinued due to disease progression (Table 6.2-1). Six patients were discontinued due to study drug toxicity which was considered to be drug-related by the investigator (see safety part for more information on discontinuation due to toxicity). Of these 6 patients, 2 were discontinued after 1 dose, 2 after 2 doses, and 2 after 3 doses.

Table 9. Discontinuation of study therapy

	Number of Subjects (%)		
	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8	Total N = 12
SUBJECTS TREATED IN THE TREATMENT PHASE	4	8	12
COMPLETED PHASE	1 (25.0)	1 (12.5)	2(16.7)
DID NOT COMPLETE PHASE	3 (75.0)	7 (87.5)	10 (83.3)
REASON FOR NON-COMPLETION (a):			
STUDY DRUG TOXICITY	1 (25.0)	5 (62.5)	6 (50.0)
DISEASE PROGRESSION	2 (50.0)	2 (25.0)	4 (33.3)

(a) The percentage is based on the number of subjects treated in the study.
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Interruption or delay of study therapy

Four patients required interruption of study drug due to AEs; one in the 3 mg/kg group and 3 patients in the 10mg/kg group:

- Treatment was interrupted for in the 3 mg/kg group due to a hypersensitivity reaction (drug fever to 38.3 degrees) on day 22. Ipilimumab was then given at half the infusion rate without complication.
- Treatment was interrupted for in the 10 mg/kg group due to hypersensitivity reaction (chills) on day 1. The patient continued with treatment cycles 2 and 3 without reoccurrence of the event.

- Treatment was interrupted for in the 10 mg/kg group due to complaints of burning sensation beside the new infusion port on day 1. The rate of the infusion was decreased and the burning sensation did not return.
- Treatment was interrupted for in the 10 mg/kg group due to hypersensitivity reaction of mild nausea and a strange feeling inside on day 1. The rate of the infusion was decreased for the duration of the day 1 treatment.

Efficacy results

All 12 treated patients have been followed for survival for more than 1 year. The survival rate at 1 year was 75.0% (95% CI: 12.8, 96.1) in the ipilimumab 3 mg/kg group and 62.5% (95% CI: 22.9, 86.1) in the ipilimumab 10 mg/kg group (Table 10).

Table 10. 1-year overall survival rate

	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8
OS RATE AT 1 YEAR (%) (a)	75.0	62.5
95% CI	(12.8, 96.1)	(22.9, 86.1)
OS RATE AT 1 YEAR (%) (b)	75.0	62.5
95% CI	(19.4, 99.4)	(24.5, 91.5)

(a) Based on Kaplan-Meier estimation and log-log transformed confidence intervals.
(b) Proportion of subjects alive at one year following start of treatment divided by the total number of treated subjects and Clopper-Pearson exact two-sided 95% confidence interval.
Program Source: BMS BMSCA184178\TRUNK\TLF\RT-EF-OSRATEMITT.SAS Run Date: 14SEP2016:03:16:42

All treated patients (having received at least one dose of ipilimumab) were included in the efficacy analysis, see also paragraph about baseline characteristics for more information on two patients with difficulties in tumour evaluation analyses. Efficacy assessments showed stable disease (SD) in 1/4 patients treated with ipilimumab 3 mg/kg, and 1/8 patients treated with ipilimumab 10 mg/kg. None of the patients treated with ipilimumab 3 mg/kg experienced a partial response (PR). Two patients treated with ipilimumab 10 mg/kg experienced a partial response (PR), and the PR for one patient was durable (ongoing for more than 1 year, at time of study closure). BORR was 0% (95% CI: 0, 60.2) in the 3 mg/kg group and 25% (95% CI: 3.2, 65.1) in the 10 mg/kg group. DCR was 25% (95% CI: 0.6, 80.6) in the 3 mg/kg group and 37.5% (95% CI: 8.5, 75.5) in the 10 mg/kg group (Table 11).

Table 11. BOR and DCR by mWHO criteria

	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8
Best Overall Response (BOR)	Number of Subjects (%)	Number of Subjects (%)
COMPLETE RESPONSE (CR)	0	0
PARTIAL RESPONSE (PR)	0	2 (25.0)
STABLE DISEASE (SD)	1 (25.0)	1 (12.5)
PROGRESSIVE DISEASE (PD)	3 (75.0)	4 (50.0)
UNKNOWN	0	1 (12.5)
	Number of Subjects (%) 95% CI	Number of Subjects (%) 95% CI
BEST OVERALL RESPONSE RATE (%) (a) (b)	0 (0.0, 60.2)	2 (25.0) (3.2, 65.1)
DISEASE CONTROL RATE (%) (c) (b)	1 (25.0) (0.6, 80.6)	3 (37.5) (8.5, 75.5)

(a) Number of subjects with CR or PR / Number of treated subjects.
(b) 2-sided 95% exact confidence intervals (CI) are computed using the method of Clopper and Pearson.
(c) Number of subjects with CR, PR or SD / Number of treated subjects.
Responses are based only on assessments taken during the treatment phase and first progression follow-up phase.
Program Source: BMS BMSCA184178\TRUNK\TLF\RT-EF-BORMITT.SAS Run Date: 13SEP2016:04:05:56

Median PFS was 2.6 months (95% CI: 2.3, 8.5) in the 3 mg/kg group and 2.9 months (95% CI:0.7, NA) in the 10 mg/kg group (Table 12).

Table 12. PFS by mWHO criteria

Variable	No. of Events/No. of Subjects (%) Median (Months) (95% CI) (a) 3 mg/kg Ipilimumab	10 mg/kg Ipilimumab
PROGRESSION-FREE SURVIVAL	4/4 (100.0) 2.6 (2.3, 8.5)	5/8 (62.5) 2.9 (0.7, ---)

(a) Median and associated 2-sided 95% confidence intervals calculated using the Brookmeyer and Crowley method.
(---) indicates statistic was not reached or could not be calculated.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-EF-PFSMITT.SAS Run Date: 13SEP2016:04:05:50

Median OS was 18.2 months (95% CI:8.9, 18.2) in the 3 mg/kg group and not reached (95% CI: 5.2, NA) in the 10 mg/kg group (Table 13).

Table 13. OS

Variable	No. of Events/No. of Subjects (%) Median (Months) (95% CI) (a) 3 mg/kg Ipilimumab	10 mg/Kg Ipilimumab
OVERALL SURVIVAL	2/4 (50.0) 18.2 (8.9, 18.2)	3/8 (37.5) --- (5.2, ---)

(a) Median and associated 2-sided 95% confidence intervals calculated using the Brookmeyer and Crowley method.
(---) indicates statistic was not reached or could not be calculated.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-EF-OSMITT.SAS Run Date: 13SEP2016:04:05:42

Safety results

According to the MAH no new safety signals were identified, the safety profile of ipilimumab was consistent with that observed in the adult population.

Among the 12 treated patients, a total of 2/4 (50.0%) and 3/8 (37.5%) deaths were reported in the study with ipilimumab 3 mg/kg and ipilimumab 10 mg/kg, respectively. All deaths were due to disease progression (Table 14).

The rates of all-causality SAEs (Any Grade) were 1/4 (25.0%) in the 3 mg/kg group and 6/8 (75.0 %) in the 10 mg/kg group. The rate of drug-related SAEs (any grade) were 1/4 (25.0%) in the 3 mg/kg group and 5/8 (62.5%) in the 10 mg/kg group. No Grade 5 drug-related SAEs were reported (Table 14).

The rates of all-causality AEs (any Grade and Grade 3-5) were higher among the ipilimumab 10 mg/kg group. Drug-related AEs were reported less frequently for ipilimumab 3 mg/kg (50.0% any Grade, 25.0% Grade 3-5) vs ipilimumab 10 mg/kg (87.5% any Grade, 62.5% Grade 3-5) (Table 14).

The rates of all-causality AEs leading to discontinuation were lower in ipilimumab 3 mg/kg (1/4 [25.0%]) compared to ipilimumab 10 mg/kg (5/8 [62.5%]). Grade 3-4 AEs leading to

discontinuation were 1/4 (25.0%) in ipilimumab 3 mg/kg compared to 4/8 (50.0%) in ipilimumab 10 mg/kg group. No Grade 5 AEs were reported (Table 14).

The frequency of severe (Grade 3–5) immune mediated adverse reactions was the primary safety objective. The proportion of patients who experienced a Grade 3-5 imAR was 1/4 (25.0%; 95% CI: 0.6, 80.6) in the 3 mg/kg group hand 5/8 (62.5%; 95% CI: 24.5, 91.5) in the ipilimumab 10 mg/kg group. There were no Grade 5 events in either treatment group (Table 14).

Patients were analysed for multiple occurrences of unique events and irAEs, i.e., more than 1 occurrence of the same AE or irAE in a single subject. The rate of exposure adjusted, multiple occurrences of unique irAEs was higher in the 10 mg/kg treatment group compared to the 3 mg/kg treatment group. All events were well-known irAEs associated with ipilimumab treatment.

Table 14. Summary of AEs

	Number of Subjects (%)	
	Dose Cohort N= 12	
	3 mg/kg n = 4	10 mg/kg n = 8
Deaths, n (%)[a]	2 (50.0)	3 (37.5)
SAEs, n (%)	1 (25.0)	6 (75.0)
SAEs, drug-related, n (%)	1 (25.0)	5 (62.5)
AEs leading to study drug discontinuation, n (%)	1 (25.0)	5 (62.5)
Drug-related AEs leading to study drug discontinuation, n (%)	1 (25.0)	5 (62.5)
irAEs, n (%)	2 (50.0)	4 (50.0)
imARS, n (%)	1 (25.0)	5 (62.5)
AE, n (%)	4 (100.0)	8 (100.0)
Drug-related AEs, n (%)	2 (50.0)	7 (87.5)

[a] All deaths were due to progressive disease and occurred > 90days after the last dose.
Abbreviations: N=total number of subjects treated; n=number within a group; SAE=serious adverse event; AE=adverse event; irAE=immune-related adverse event.

Source: Tables 8.3.1-1, 8.4-1, 8.5.1-1, 8.5.2-1; Supplemental Tables S.6.5, S.6.7, S.6.10, S.6.1, S.6.2.

Deaths

Among 12 treated patients, a total of 2/4 (50.0%) and 3/8 (37.5%) deaths were reported in the study with ipilimumab 3 mg/kg and ipilimumab 10 mg/kg, respectively. All deaths were due to disease progression. No patients died within 90 days of the last dose. Full safety narratives are provided in Supplemental Table S.6.0 of the CSR.

Serious adverse events

The rates of all-causality SAEs (any Grade) were 1/4 (25.0%) in ipilimumab 3 mg/kg and 6/8 (75.0 %) in ipilimumab 10 mg/kg (Table 15). No Grade 5 (fatal) events were reported. The most common SAEs by SOC were Hepatobiliary disorders, Metabolism and Nutrition disorders, and Respiratory, Thoracic and Mediastinal disorders (Table 15). All SAEs were considered to be drug-related by the investigator except for 4 events in 2 subjects in the 10 mg/kg group. One subject

experienced Grade 3 events of hyponatraemia and pleural effusion, the second subject reported Grade 3 tumour pain.

Table 15. On-study SAEs

Treatment Group: 3 mg/kg Ipilimumab N = 4

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	0	0	1 (25.0)	0	0	0	1 (25.0)
HEPATOBILIARY DISORDERS	0	0	1 (25.0)	0	0	0	1 (25.0)
HEPATITIS	0	0	1 (25.0)	0	0	0	1 (25.0)

Treatment Group: 10 mg/kg Ipilimumab N = 8

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	1 (12.5)	0	3 (37.5)	2 (25.0)	0	0	6 (75.0)
HEPATOBILIARY DISORDERS	0	0	2 (25.0)	0	0	0	2 (25.0)
CHOLECYSTITIS ACUTE	0	0	1 (12.5)	0	0	0	1 (12.5)
CHOLESTASIS	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATITIS	0	0	1 (12.5)	0	0	0	1 (12.5)
METABOLISM AND NUTRITION DISORDERS	0	0	1 (12.5)	1 (12.5)	0	0	2 (25.0)
HYPOKALAEMIA	0	0	0	1 (12.5)	0	0	1 (12.5)
HYPONATRAEMIA	0	0	1 (12.5)	0	0	0	1 (12.5)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	0	1 (12.5)	1 (12.5)	0	0	2 (25.0)
METASTATIC MALIGNANT MELANOMA	0	0	0	1 (12.5)	0	0	1 (12.5)
TUMOUR PAIN	0	0	1 (12.5)	0	0	0	1 (12.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	2 (25.0)	0	0	0	2 (25.0)
PLEURAL EFFUSION	0	0	2 (25.0)	0	0	0	2 (25.0)
GASTROINTESTINAL DISORDERS	1 (12.5)	0	0	0	0	0	1 (12.5)
PANCREATITIS	1 (12.5)	0	0	0	0	0	1 (12.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	1 (12.5)	0	0	0	0	0	1 (12.5)
INFUSION RELATED REACTION	1 (12.5)	0	0	0	0	0	1 (12.5)
INVESTIGATIONS	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATIC ENZYME INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
TRANSAMINASES INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)

Events are coded according to MedDRA v.19.0 and graded according to NCI CTCAE 3.0.
Subjects may have more than one event.
On-study event is defined as any event with onset on or after Day 1 of study therapy and no later than 90 days following the last day of study therapy.

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Adverse events leading to discontinuation

The rates of all-causality AEs leading to discontinuation were lower in ipilimumab 3 mg/kg (1/4 [25.0%]) compared to ipilimumab 10 mg/kg (5/8 [62.5%]) (Table 16). Grade 3-4 AEs leading to discontinuation were 1/4 (25.0%) in the ipilimumab 3 mg/kg group compared to 4/8 (50.0%) in ipilimumab 10 mg/kg group. No Grade 5 AEs were reported. All AEs leading to discontinuation were considered to be related to study drug by the investigator.

Table 16. On-study AEs leading to discontinuation of study drug

Treatment Group: 3 mg/kg Ipilimumab N = 4

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	0	0	1 (25.0)	0	0	0	1 (25.0)
HEPATOBILIARY DISORDERS	0	0	1 (25.0)	0	0	0	1 (25.0)
HEPATITIS	0	0	1 (25.0)	0	0	0	1 (25.0)

Treatment Group: 10 mg/kg Ipilimumab N = 8

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	1 (12.5)	0	3 (37.5)	1 (12.5)	0	0	5 (62.5)
INVESTIGATIONS	0	0	2 (25.0)	0	0	0	2 (25.0)
ALANINE AMINOTRANSFERASE INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
ASPARTATE AMINOTRANSFERASE INCREASED	0	1 (12.5)	0	0	0	0	1 (12.5)
BLOOD POTASSIUM DECREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
GASTROINTESTINAL DISORDERS	1 (12.5)	0	0	0	0	0	1 (12.5)
PANCREATITIS	1 (12.5)	0	0	0	0	0	1 (12.5)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	1 (12.5)	0	0	0	0	1 (12.5)
PYREXIA	0	1 (12.5)	0	0	0	0	1 (12.5)
HEPATOBILIARY DISORDERS	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATITIS	0	0	1 (12.5)	0	0	0	1 (12.5)
METABOLISM AND NUTRITION DISORDERS	0	0	0	1 (12.5)	0	0	1 (12.5)
HYPOKALAEMIA	0	0	0	1 (12.5)	0	0	1 (12.5)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	0	1 (12.5)	0	0	0	1 (12.5)
PLEURAL EFFUSION	0	0	1 (12.5)	0	0	0	1 (12.5)

Events are coded according to MedDRA v.19.0 and graded according to NCI CTCAE 3.0.
Subjects may have more than one event.
On-study event is defined as any event with onset on or after Day 1 of study therapy and no later than 90 days following the last day of study therapy.
AEs leading to discontinuation are events with an action indicating discontinuation of study medication.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-AE-AEDISCMITT.SAS Run Date: 13SEP2016:04:07:34

Immune-related adverse events (irAEs)

No new or unexpected irAEs were observed in this study. The observed irAEs were similar in frequency, intensity and organ site to what has been reported in adult studies.

Ipilimumab 3 mg/kg had 2/4 (50.0%) any Grade and 1/4 (25.0%) Grade 3-5 irAEs compared to 4/8 (50.0%) any Grade and 3/8 (37.5%) Grade 3-5 in the ipilimumab 10 mg/kg group (Table 17). No Grade 5 events were reported in either treatment group. In the 3 mg/kg group the most common irAEs by SOC were Immune system disorders 2/4 (50%) and Skin and subcutaneous tissue disorders 2/4 (50%). In the 10 mg/kg group the most common irAEs by SOC were Gastrointestinal disorders 3/8 (37.5%) and Investigations 3/8 (37.5%). On-study liver irAEs of any grade across all dose levels occurred in 4 patients who experienced hepatitis, cholestasis, ALT increased, AST increased, hepatic enzyme increased, and transaminases increased. On-study skin irAEs of any grade across all dose levels occurred in 2 patienta in the 3 mg/kg treatment group and 2 patients in the 10 mg/kg group who experienced Grade 1 rash and pruritus.

There were 2 patients in the 10 mg/kg group who experienced a Grade 1 and Grade 3 on study endocrine irAE of hyperglycaemia. There were no-on study neurological irAEs in any treatment group. There were 2 patients in the 10 mg/kg group who experienced a Grade 2 diarrhoea and Grade 2 haematochezia on-study gastrointestinal irAEs. On-study other irAEs of any grade occurred in 2 patients in the 3 mg/kg group who experienced Grade 2 drug hypersensitivity and Grade 1

hypersensitivity. In the 10 mg/kg group 1 patient experienced Grade 1 pancreatitis, Grade 2 amylase increased, and Grade 4 lipase increased.

Table 17. On-study irAEs

Treatment Group: 3 mg/kg Ipilimumab N = 4

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	1 (25.0)	0	1 (25.0)	0	0	0	2 (50.0)
IMMUNE SYSTEM DISORDERS	1 (25.0)	1 (25.0)	0	0	0	0	2 (50.0)
DRUG HYPERSENSITIVITY	0	1 (25.0)	0	0	0	0	1 (25.0)
HYPERSENSITIVITY	1 (25.0)	0	0	0	0	0	1 (25.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (50.0)	0	0	0	0	0	2 (50.0)
PRURITUS	1 (25.0)	0	0	0	0	0	1 (25.0)
RASH	1 (25.0)	0	0	0	0	0	1 (25.0)
HEPATOBILIARY DISORDERS	0	0	1 (25.0)	0	0	0	1 (25.0)
HEPATITIS	0	0	1 (25.0)	0	0	0	1 (25.0)

Treatment Group: 10 mg/kg Ipilimumab N = 8

System Organ Class (%) Preferred Term (%)	Number of Subjects (%) Worst CTCAE Grade 1	2	3	4	5	Unknown	Any Grade
TOTAL SUBJECTS WITH AN EVENT	0	1 (12.5)	1 (12.5)	2 (25.0)	0	0	4 (50.0)
GASTROINTESTINAL DISORDERS	1 (12.5)	2 (25.0)	0	0	0	0	3 (37.5)
DIARRHOEA	0	1 (12.5)	0	0	0	0	1 (12.5)
HAEMATOCHEZIA	0	1 (12.5)	0	0	0	0	1 (12.5)
PANCREATITIS	1 (12.5)	0	0	0	0	0	1 (12.5)
INVESTIGATIONS	0	1 (12.5)	0	2 (25.0)	0	0	3 (37.5)
ALANINE AMINOTRANSFERASE INCREASED	0	1 (12.5)	0	1 (12.5)	0	0	2 (25.0)
ASPARTATE AMINOTRANSFERASE INCREASED	1 (12.5)	0	0	1 (12.5)	0	0	2 (25.0)
AMYLASE INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATIC ENZYME INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
LIPASE INCREASED	0	0	0	1 (12.5)	0	0	1 (12.5)
TRANSAMINASES INCREASED	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATOBILIARY DISORDERS	0	0	2 (25.0)	0	0	0	2 (25.0)
CHOLESTASIS	0	0	1 (12.5)	0	0	0	1 (12.5)
HEPATITIS	0	0	1 (12.5)	0	0	0	1 (12.5)
METABOLISM AND NUTRITION DISORDERS	1 (12.5)	0	1 (12.5)	0	0	0	2 (25.0)
HYPERGLYCAEMIA	1 (12.5)	0	1 (12.5)	0	0	0	2 (25.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (25.0)	0	0	0	0	0	2 (25.0)
RASH	2 (25.0)	0	0	0	0	0	2 (25.0)
PRURITUS	1 (12.5)	0	0	0	0	0	1 (12.5)

Events are coded according to MedDRA v.19.0 and graded according to NCI CTCAE 3.0.
Subjects may have more than one event.
On-study events are events reported between first dose date of study therapy and 90 days after last dose of study therapy.
Unknown intensities are included in "Any Grade" column.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-AE-IRAESI.SAS Run Date: 13SEP2016:04:07:58

Analyses were performed to determine the frequency of unique multiple occurrences of irAEs, i.e., more than 1 occurrence of the same irAE in a single subject. A total of 4 patients experienced a unique irAE more than once. Most patients in the ipilimumab 3 mg/kg group did not experience an individual irAE more than one time. One patient in this group experienced rash 2 to 3 times.

In the 10 mg/kg group, multiple occurrences of irAEs were reported for events of increased ALT (2-3x), increased AST (2-3x), hyperglycaemia (≥4x), and rash (2-3x). All 4 events are well-known irAEs associated with ipilimumab treatment.

Immune-mediated adverse reactions (imARs)

The frequency of severe (Grade 3–5) imARs of ipilimumab was the primary safety objective. The proportion of patients treated with ipilimumab 3 mg/kg who experienced Grade 3-5 imARs was 1/4 (25.0%; 95% CI: 0.6, 80.6), compared to the ipilimumab 10 mg/kg group where 5/8 (62.5%;

95% CI: 24.5, 91.5) patients experienced Grade 3-5 imARs (Table 18). No Grade 5 events were reported in either treatment group.

No patients in the 3 mg/ kg treatment group experienced a Grade 2 imAR, while in the 10 mg/kg group 2/8 (25.0%; 1 with diarrhoea and 1 with haematochezia) patients experienced Grade 2 events. There was 1 Grade 3-4 imAR of hepatitis in the 3 mg/kg group. The most common Grade 3-4 imARs in the 10 mg/kg group were hepatitis (2/8, 25.0%) and pyrexia (2/8, 25.0%).

Table 18. Severe (Grade 3-5) imARs

	3 mg/kg Ipilimumab N = 4	10 mg/kg Ipilimumab N = 8
RATE OF SEVERE IMAR (%) (a)	1/4 (25.0)	5/8 (62.5)
95% CI (b)	(0.6 , 80.6)	(24.5 , 91.5)

Events are coded according to MedDRA v.19.0 and graded according to NCI CTCAE 3.0.
(a) Number of subjects with a grade 3 or worse imAR / Number of treated subjects.
(b) 2-sided 95% exact confidence intervals (CI) are computed using the method of Clopper and Pearson.
Includes events with an onset date on or after the first study therapy dose date and no later than 90 days after the last dose date of study therapy. On-study events also include
those with an onset >90 days after the last dose of study therapy if they were a continuation of events with onset during the on-study period within the same class.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-AE-RATESEVIMAR.SAS Run Date: 13SEP2016:04:09:00

Overall adverse events

All adverse events

Adverse events were reported for all patients in both the 3 and 10 mg/kg groups. In the 3 mg/kg group most events were Grade 1 or 2 in intensity, in the 10 mg/kg group most events were Grade 3 or 4 in intensity. In the 3 mg/kg group one patient experienced a Grade 3 event. In the 10 mg/kg group, 2 patients experienced Grade-3 events and 4 patients experienced Grade 4 events. The rates of all-causality AEs (any Grade and Grade 3-5) were higher among the ipilimumab 10 mg/kg group compared to the 3 mg/kg group (see also Supplemental Table S.6.1 CSR).

Drug-related adverse events

Drug-related AEs were reported less frequently for ipilimumab 3 mg/kg (50.0%) any Grade, [25.0% Grade 3-5]) vs ipilimumab 10 mg/kg (87.5% any Grade, [62.5% Grade 3-5]) (see also Supplemental Table S.6.2 CSR).

Multiple occurrences of adverse events

Patients were analysed for multiple occurrences of AEs, i.e., more than 5 occurrences of the same AE in a single subject, and adjusted for exposure (Table 19).

Table 19. Exposure-adjusted summary of on-study AEs, including multiple occurences of unique events

System Organ Class Preferred Term	3 mg/kg Ipilimumab (N = 4) (P-Y = 1.5) Event Count	3 mg/kg Ipilimumab (N = 4) (P-Y = 1.5) Rate: (IR/100 P-Y)	10 mg/kg Ipilimumab (N = 8) (P-Y = 2.8) Event Count	10 mg/kg Ipilimumab (N = 8) (P-Y = 2.8) Rate: (IR/100 P-Y)
TOTAL EVENTS	21	1400.0	180	6428.6
NAUSEA	3	200.0	8	285.7
PANCREATITIS	0	0	1	35.7
VOMITING	3	200.0	15	535.7
PYREXIA	1	66.7	10	357.1
DECREASED APPETITE	0	0	6	214.3
HYPERGLYCAEMIA	0	0	5	178.6

P-Y = Person-years of exposure
Incidence rate per 100 person-years of exposure (IR/100 P-Y) = event count * 100 /person-years of exposure
Events are coded according to MedDRA v.19.0 and graded according to NCI CTCAE 3.0.
On-study event is defined as any events occurring on or after Day 1 of study treatment and no later than 90 days following the last day of study treatment.

Program Source: BMS BMSCA184178\TRUNK\TLF\RT-AE-EXPADJMITT.SAS Run Date: 13SEP2016:04:09:38

Patients in the ipilimumab 3 mg/kg group had 1.5 person-years (P-Y) of exposure, and 21 multiple occurrences of on-study unique AEs adjusted for exposure were reported among all patients at an incidence rate per 100 person-years of exposure (IR/100 P-Y) of 1400.0.

Patients in the ipilimumab 10 mg/kg group had 2.8 P-Y of exposure and 180 multiple occurrences of on-study unique AEs adjusted for exposure were reported among all patients at an IR/100 P-Y of 6428.6. The rate of exposure-adjusted, multiple occurrences of unique irAEs was higher in the 10 mg/kg treatment group compared to the 3 mg/kg treatment group.

Clinical laboratory evaluations

Haematology

Decreases in haematological parameters during treatment were ≤Grade 2 for most patients. One patient in the 10 mg/kg group experienced a Grade 4 decreased platelet count and Grade 4 decreased white blood cell count from Grade 0 at baseline.

Liver function tests

Grade 3 or 4 increases in LFT values occurred in a few patients during treatment. Increases from baseline CTC Grade to Grade 4 were observed for ALT and AST. There were no abnormal elevations (≥Grade 1) in ALP for any patient.

ALT:

- Increased to Grade 3 from baseline 0 for 1 patient in the 3 mg/kg group and 1 patient in the 10 mg/kg group
- Increased to Grade 4 from baseline 0 for 1 patient in the 10 mg/kg group

AST:

- Increased to Grade 3 from baseline 0 for 1 patient in the 3 mg/kg group
- Increased to Grade 4 from baseline 0 for 1 patient in the 10 mg/kg group
-

Bilirubin:

- Increased to Grade 3 bilirubin increased from baseline Grade 0 for 2 patients in the 10 mg/kg group

Adverse events of increased ALT and AST and total bilirubin which led to discontinuation were reported for 3 patients with Grade 3/4 shifts from baseline in ALT, AST or Total Bilirubin values.

Patients and each experienced a serious AE of hepatitis resulting in discontinuation of study therapy. Subject discontinued therapy due non serious events of Grade 3 elevated AST and Grade 2 elevated ALT.

Renal function tests

No Grade 3 or 4 increases in creatinine values were reported for any patient during treatment.

Endocrine function tests

The majority of patients had normal TSH, free T3, free T4, and adrenocorticotropic hormone (ACTH) levels at baseline and throughout the treatment period. Two patients in the 3 mg/kg group and 2 patients in the 10 mg/kg group had elevated free T3 at baseline, which remained elevated throughout treatment. The clinical relevance of these findings is unclear.

Serum chemistry

Grade 3 or 4 increases in serum chemistry values occurred in 2 patients in the 10 mg/kg treatment group during treatment.

Amylase:

- Increased to Grade 3 from baseline 0 for 1 patient in the10 mg/kg group

Lipase:

- Increased to Grade 3 from baseline 0 for 1 patient in the10 mg/kg group
- Increased to Grade 4 from baseline 0 for 1 patient in the10 mg/kg group

Adverse events of increased amylase and lipase which led to discontinuation were reported for 2 patients with Grade 3/4 shifts from baseline in amylase and lipase values. Patient discontinued due a Grade 1 non serious AE of pancreatitis and patient discontinued due to a serious AE of Grade 3 hepatitis.

Electrocardiograms

ECGs were not collected or analysed.

Vital signs and physical findings

No clinically relevant changes form baseline in vital signs was observed.

Other observations related to safety

No patients became pregnant.

Pharmacokinetics and immunogenicity

Pharmacokinetic sample collection and processing

A pre-dose sample was to be drawn within 3 days of treatment on study dosing days during the treatment and retreatment phase for all treated participants: at Day 1, Day 22, Day 43, between Days 46 and 50 (treatment phase only), between Days 53 and 58 (treatment phase only), Day 64, Day 78 and at the end of treatment visit(s).

Quantification of ipilimumab in human serum was performed using a validated enzyme linked immunosorbent assay (ELISA). The assay provides a quantitative measurement of ipilimumab in human serum using CTLA4/Fc chimera as the capture reagent and an alkaline phosphatase-labeled

goat anti-human IgG F(ab')2 for detection. The validated range for this method in human serum is from 0.800 to 25.6 µg/ml.

Pharmacokinetics of ipilimumab were derived from serum concentration versus time data. Individual participant PK parameter values were calculated by noncompartmental methods by a validated PK analysis program, Phoenix® WinNonlin® Version 6.2.1 (Pharsight Corporation, St Louis, MO).

Antibodies against ipilimumab were analysed by a drug-tolerant electrochemiluminescent (ECL) immunoassay, ICDIM 14 V 2.02. A 3-tiered approach was used: screening, confirmation and quantification of the anti-ipilimumab antibodies.

Pharmacokinetics results

Ipilimumab was administered intravenously (IV) at doses of 3 or 10 mg/kg over 90 minutes on Day 1 of each 21-day cycle for 4 cycles. Pharmacokinetics of ipilimumab was evaluated following the 3rd administration. By that time 3 out of 8 participants receiving 10 mg/kg and 1 out of 4 participants receiving 3 mg/kg ipilimumab had discontinued treatment due to AEs. Hence, pharmacokinetic data were available from 4 subjects receiving 10 mg/kg and 3 subjects receiving 3 mg/kg. The individual pharmacokinetic parameters are listed in Table 20. Based on the results of this study, the pediatric data suggest that the exposure of ipilimumab (e.g., AUC, Cmax, and Cmin) increased approximately in proportion with doses ranging from 3 to 10 mg/kg, although the data are limited.

Table 20. Individual pharmacokinetic parameters of ipilimumab after the third dose, all pharmacokinetic eligible patients

Treatment Group = 3 mg/kg Ipilimumab

Subject	Cycle	Cmin (ug/mL)	Cmax (ug/mL)	AUC(0-21d) (h*ug/mL)	CL/F (mL/hr)
[redacted]	TRT CYCLE 3	36.4	159	32385.6	8.5
[redacted]	TRT CYCLE 3	16.8	106	29301.1	7.1
[redacted]	TRT CYCLE 3	29.4	84.1	32823.5	4.2

Treatment Group = 10 mg/kg Ipilimumab

Subject	Cycle	Cmin (ug/mL)	Cmax (ug/mL)	AUC(0-21d) (h*ug/mL)	CL/F (mL/hr)
[redacted]	TRT CYCLE 3	130	435		
[redacted]	TRT CYCLE 3	78.4	292	71585.1	10.5
[redacted]	TRT CYCLE 3	89.4	297	79258.8	8.1
[redacted]	TRT CYCLE 3	67.3	210	63868.4	9.9

Program Source: BMS BMSCA184178\TRUNK\TLF\RL-PK-SUM.SAS Run Date: 23SEP2016:08:43:55

Ipilimum ab exposure of adolescents in study CA184178 seemed slightly higher than previously observed in adolescents (study CA184070, EMEA/H/C/002213-EU/1/11/698/001-002) and in adults (studies CA184007 & CA184008); clearance of ipilimumab appeared to be half of that observed in adults (see Table 21).

Table 21. Ipilimumab PK parameters in adolescents (studies CA184178 and CA184070 and adults (studies CA184007 and CA184008, marketing application dossier)

	Age ≥ 12 < 18 years Study CA184178		Adults[$] Study CA184007 & CA184008		Age ≥ 12 < 21 years Study CA184070*
Dose (number) PK parameter (CV%)	3 mg/kg N=3	10 mg/kg N=4	3 mg/kg	10 mg/kg N=15	10 mg/kg N=8
Cmax (µg/ml)	116 (33%)	309 (30%)		223 (24%)	203 (22%)

AUC_{0-21} (mg.h/ml)	31.5 (6%)	71.6 (11%)		48.9 (24%)	36.8 (14%)
Cl (ml/h)^	6.6 (33%)	9.5 (13%)	15.3 (38.5%)	18.3 (32%)	13.3 (24%)
Ctrough (µg/ml)#	27.5 (36%)	91.3 (30%)	21.8 (51%)	57.4	33 N=7

$ Adult data for 3 and 10 mg/kg ipilimumab as reported in EPAR

*Adolescents following 1st dose of 10 mg/kg ipilimumab

^ Cl in adolescents from study CA184070 was calculated for a 70 kg subject

Ctrough was determined at cycle 3.

Immunogenicity results

Among available data for the 12 treated participants in CA184178, all participants were negative for anti-drug antibodies at any time after initiation of treatment.

1.3.3. Discussion on clinical aspects

In accordance with the Article 46 regulation, the MAH submitted the final study report of CA184178, a non-randomised, multicentre, open-label, phase 2 study investigating ipilimumab in children and adolescents 12 to 18 years of age with previously treated or untreated, unresectable stage III or stage IV malignant melanoma. Ipilimumab is a fully human immunoglobulin specific for human CTLA-4 and is approved as monotherapy for the treatment of advanced melanoma in adults at a dose of 3 mg/kg intravenously once every 3 weeks for a total of 4 doses.

Study CA184178 is part of a paediatric clinical development program. The results of the phase 1 dose-escalation study NCI7458/CA184070 have been submitted in 2014 and determined the tolerance and toxicity of ipilimumab in patients below 21 years of age with untreatable, refractory or relapsed solid malignant tumours. The third study, CA184116 is a phase 3 study randomising between ipilimumab or interferon α-2b for resected high-risk melanoma. In November 2016, 3 patients were enrolled and 2 were treated.

Methods- For study CA184178, primary objectives were to estimate the survival rate at 1 year and to assess the safety and tolerability, specifically the frequency of severe (Grade 3-5) immune-mediated adverse reactions. Patients were treated with 3 or 10 mg/kg intravenously on day 1 of each 21-day cycle for 4 cycles unless there was confirmed disease progression, unacceptable toxicity, or patient request to stop study treatment. Given that ipilimumab 3 mg/kg was approved, the MAH amended the protocol in 2014 (Amendment 04) to change the dose of ipilimumab from 10 to 3 mg/kg to ensure consistency with the approved adult dose. Patients who started at 10 mg/kg stayed at that dose and no dose reduction was allowed. With this Amendment the maintenance phase of ipilimumab treatment was also removed, because maintenance treatment has not been proven to add additional benefit in previous studies in adults and the potential risk for severe immune-related adverse events with prolonged treatment. Moreover, as there were indications for clinical benefit of retreatment after progression, this option was added to the study protocol. The sample size was not aimed to allow for a comparative analysis. Initially, the study was designed to enrol approximately 30 patients with at least 20 patients treated with the 3 mg/kg dose.

Study population- Due to the rarity of the patient population and the availability of other therapies, such as anti-PD-(L)1 therapies, enrolment was lower than anticipated and study closure was recommended by the DMC. At the time of study closure in April 2016, 14 patients were enrolled and 12 patients treated: 4 in the 3 mg/kg group and 8 in the 10 mg/kg group. Overall, median age was 15.0 years (range 12-16 years), 58.3% were male and 91.7% white. Baseline Lansky/Karnofsky scores ranged from 90 to 100 and 83.3% had normal LDH at baseline. Median time from diagnosis of advanced melanoma to treatment with ipilimumab was 2.35 months.

Two patients were not evaluable, both in the 10 mg/kg group. One patient was not evaluable because of different tumour evaluation techniques used at baseline and follow-up. Another patient had no measurable disease at baseline since surgery was performed prior to enrolment. The MAH considered this patient to have stable disease, since the anatomy of the surgical area was similarly distorted during subsequent evaluations.

Two adolescents in study CA184178 were eligible for retreatment, but did not receive it. One patient was treated with pembrolizumab as next line treatment and for the other patient the investigator decided to not retreat based on continued PR.

Exposure- Of the 4 patients in the 3 mg/kg group, 3 received the 4 planned infusions. Of the 8 patients who received 10 mg/kg, 3 patients received the 4 planned infusions. Half of the patients discontinued from study treatment due to toxicity and 33.3% due to disease progression. For 6 patients that discontinued because of toxicity, this was considered to be drug-related. Four patients required interruption of the infusions: one in the 3 mg/kg group and 3 in the 10 mg/kg group.

Efficacy- The survival rate at 1 year was 75.0% (95% CI: 12.8, 96.1) in the ipilimumab 3 mg/kg group and 62.5% (95% CI: 22.9, 86.1) in the ipilimumab 10 mg/kg group. Tumour assessments showed SD in 1/4 patients treated with ipilimumab 3 mg/kg, and 1/8 patients treated with ipilimumab 10 mg/kg. Two patients treated with ipilimumab 10 mg/kg experienced PR, and the PR for one patient was durable (ongoing for more than 1 year, at time of study closure). BORR was 0% (95% CI: 0, 60.2) in the 3 mg/kg group and 25% (95% CI: 3.2, 65.1) in the 10 mg/kg group. DCR was 25% (95% CI: 0.6, 80.6) in the 3 mg/kg group and 37.5% (95% CI: 8.5, 75.5) in the 10 mg/kg group. Median PFS was 2.6 months (95% CI: 2.3, 8.5) in the 3 mg/kg group and 2.9 months (95% CI: 0.7, NA) in the 10 mg/kg group. Median OS was 18.2 months (95% CI: 8.9, 18.2) in the 3 mg/kg group and not reached (95% CI: 5.2, NA) in the 10 mg/kg group. All subjects in the 3 mg/kg group and 6/8 subjects received some type of subsequent anticancer therapy.

Safety- The frequency of severe (Grade 3–5) immune mediated adverse reactions was the primary safety objective. The proportion of patients who experienced a Grade 3-5 imAR was 1/4 (25.0%; 95% CI: 0.6, 80.6) in the 3 mg/kg group hand 5/8 (62.5%; 95% CI: 24.5, 91.5) in the ipilimumab 10 mg/kg group.
Among the 12 treated patients, a total of 2/4 (50.0%) and 3/8 (37.5%) deaths were reported in the study with ipilimumab 3 mg/kg and ipilimumab 10 mg/kg, respectively. All deaths were due to disease progression.
The rates of all-causality SAEs (any Grade) were 1/4 (25.0%) in the 3 mg/kg group and 6/8 (75.0%) in the 10 mg/kg group. The rate of drug-related SAEs (any grade) were 1/4 (25.0%) in the 3 mg/kg group and 5/8 (62.5%) in the 10 mg/kg group. No Grade 5 drug-related SAEs were reported.
The rates of all-causality AEs (any Grade and Grade 3-5) were higher among the ipilimumab 10 mg/kg group. Drug-related AEs were reported less frequently for ipilimumab 3 mg/kg (50.0% any Grade, 25.0% Grade 3-5) vs ipilimumab 10 mg/kg (87.5% any Grade, 62.5% Grade 3-5).
The rates of all-causality AEs leading to discontinuation were lower in ipilimumab 3 mg/kg (1/4 [25.0%]) compared to ipilimumab 10 mg/kg (5/8 [62.5%]). Grade 3-4 AEs leading to discontinuation were 1/4 (25.0%) in ipilimumab 3 mg/kg compared to 4/8 (50.0%) in ipilimumab 10 mg/kg group. No Grade 5 AEs were reported.
Patients were analysed for multiple occurrences of unique events and irAEs, i.e., more than 1 occurrence of the same AE or irAE in a single subject. The rate of exposure adjusted, multiple occurrences of unique irAEs was higher in the 10 mg/kg treatment group compared to the 3 mg/kg treatment group.

Pharmacokinetics and immunogenicity- The bioanalytical methods for ipilimumab and anti-ipilimumab antibodies have been described in earlier applications as ipilimumab monotherapy or in combination with nivolumab (EMEA/H/C/003985/II/0003). Bioanalysis of ipilimumab and anti-ipilimumab antibodies in study CA184178 was adequate; QC samples, dilution integrity and ISR samples met acceptance criteria. The assay for neutralising antibodies was not provided but as none of the samples scored positive for anti-ipilimumab antibodies post treatment, this can be accepted.

Ipilimumab exposure of adolescents in study CA184178 seemed slightly higher than previously observed in adolescents (study CA184070, EMEA/H/C/002213-EU/1/11/698/001-002) and in adults (studies CA184007 & CA184008). This might be due to the small dataset (N=3, 4 per dose group), and the less applied frequent sampling schedule in study CA184178 compared to studies CA184070, CA184007 and CA184008. The results from this study imply that compared to the approved 3mg/kg ipilimumab in adults, adolescents will obtain an adequate ipilimumab exposure.

None of the subjects scored positive for anti-drug antibodies. This is in line with the low incidence of anti-drug antibodies in adults.

Discussion- The sample size of study CA184178 is limited with in total 12 patients treated with ipilimumab. With Amendment 04 the posology was changed from 10 to 3 mg/kg based on results in the adult population. The enrolment was stopped preliminary since not enough patients could be recruited in this trial, which is understandable due to the availability of other anti-cancer immunotherapies such as anti-PD-(L)1 therapies. In the final study report the results are described of 4 patients treated with 3 mg/kg and 8 patients with 10 mg/kg. With this low number of patients included, it is difficult to draw definitive conclusions. Key analyses were performed to determine 1-year OS rate and the incidence of immune-mediated ARs. Two patients were not evaluable, however this would not influence the interpretation of the primary endpoints.

In the adult population median OS after ipilimumab monotherapy (3 mg/kg) was 10.12 months (CI 95%: 8.02, 13.80) with a 1-year OS rate of 46% (CI 95%: 37.0, 54.1). Median PFS was 2.86 months (CI 95%: 2.76, 3.02). In 137 treated patients, tumour evaluation showed CR in 1.5%, PR in 9.5%, SD in 17.5%, PD in 51.1% of patients respectively, and 20.4% was not evaluable. BORR was 10.9% (CI 95: 6.3, 17.4) [EPAR Ipilimumab; SmPC Ipilimumab]. Although interpretation of the paediatric phase 2 data is difficult, the primary endpoint of 1-year OS rate is numerically higher than in adults, as is median OS. The higher survival is in line with a retrospective cohort study conducted in melanoma patients from 1998 to 2011 using the National Cancer Data Base (NCDB; n = 420,416), although these patients had non-metastatic disease. Three age-based cohorts were analysed: 1–10 years (paediatric), 11–20 years (adolescent), and ≥21 years (adult). Adolescents had longer survival when compared with adults (HR 0.22, CI 95%: 0.19, 0.26) [Lorimer et al. Ann Surg Oncol (2016) 23:4058–4066]. Responses are lower in after ipilimumab in adolescents compared to adults, and PFS seems comparable. The number of treated patients between the age of 12 and 18 years is small, but there are no indications of significant worse efficacy in this age group. It should be noted that many patients received subsequent anticancer therapy.

Toxicity in children and adolescents is significant, especially in the 10 mg/kg group with discontinuation in half of the patients due to study drug toxicity. Also the number of SAEs and immune-related AEs was higher in the 10 mg/kg group, although no formal comparisons can be made due to the small number of patients treated. According to the MAH, no new safety signals were identified and the safety profile was considered consistent with the adult population. Also in adults patients treated with ipilimumab 3 mg/kg monotherapy the incidence of treatment-related AEs is reported to be high. Most of the SAEs in adults are immune-related, as can be expected based on the mechanism of action. In adults a 3.1% risk of treatment-related death associated with ipilimumab therapy is reported, with half of these deaths occurring within the first month after start of treatment. The percentage of Grade 3-4 AEs is 20.6% and the number of patients discontinuing study therapy due to drug toxicity 9.9% in the population >18 years [EPAR Ipilimumab]. It is agreed that there are no new safety signals, but also in the paediatric population toxicity is considerable, as also shown in the phase 1 dose escalation study NCI7458/CA184070 submitted in 2014.

Ipilimumab is at this time only indicated for adults (section 4.1 SmPC ipilimumab). In section 4.2 it is written that the safety and efficacy of ipilimumab in children and adolescents below 18 years have not been established and that it should not be used in this age group. Given that the ongoing type II variation (EMEA/H/C/002213/II/0044) to extend the indication to patients of 12-18 years old, currently no labelling changes are planned by the MAH based on this Article 46 submission. This is agreed by the Rapporteur for this procedure. The benefit/risk assessment of ipilimumab for the treatment of advanced melanoma in children and adolescents of 12 years and older will be further discussed in the extension of indication procedure.

2. CHMP overall conclusion and recommendation

In conclusion, the Rapporteur considers that the data presented do not affect the positive benefit/risk of ipilimumab and there is no need for modification of the SmPC at this time, but has additional questions.

☒ Not fulfilled:
Based on the data submitted, the MAH should provide description of the additional clarifications requested per study as part of this procedure (see section “Additional clarification requested”).

3. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. With Amendment 04, more than 1 year after the original study protocol, the MAH introduced addition of one reinduction/retreatment for eligible participants. The maintenance phase was removed due to lack of added benefit. According to the CSR one patient was eligible for retreatment, but did not enter the retreatment phase.

The MAH is asked to elaborate on the rationale of this change in the study protocol, on the criteria for a patient to be eligible for reinduction/retreatment and how many patients would have been eligible for reinduction/retreatment if this option would have been part of the initial study protocol. Furthermore, the reason for not entering the retreatment phase of the one eligible patient should be given.

2. The accrual rate in the submitted phase 2 CA184178 and in the phase 1 NCI7458/CA184070 was low and in total the sample size of patients at the age of 12 to 18 years treated with the approved dose of 3 mg/kg is very small. Therefore, the Applicant is asked to elaborate on the progress of the clinical development of ipilimumab in the paediatric population with melanoma and discuss future plans, in particular for the combination with other immunotherapies.

4. MAH responses to Request for supplementary information

Question 1

With Amendment 04, more than 1 year after the original study protocol, the MAH introduced addition of one reinduction/retreatment for eligible participants. The maintenance phase was removed due to lack of added benefit. According to the CSR one patient was eligible for retreatment, but did not enter the retreatment phase.

The MAH is asked to elaborate on the rationale of this change in the study protocol, on the criteria for a patient to be eligible for reinduction/retreatment and how many patients would have been eligible for reinduction/retreatment if this option would have been part of the initial study protocol. Furthermore, the reason for not entering the retreatment phase of the one eligible patient should be given.

MAH's response

The currently approved administration regimen for ipilimumab (IPI) is limited to 4 IPI doses (administered as 1 dose every 3 weeks [Q3W]). The approved regimen for IPI in advanced melanoma in adults is limited to induction only, based on the pivotal randomized Phase 3 study MDX010-20 in metastatic melanoma. A large meta-analysis of IPI-treated patients with advanced melanoma (n=1861) from 10 prospective and 2 retrospective, observational studies demonstrated a plateau in overall survival (OS) Kaplan-Meier curve starting at Year 3 that appeared flat up to Year 10 in some patients. The plateau in the OS Kaplan-Meier curve was independent of patient population (treatment-naive or pre-treated), IPI dose (3 or 10 mg/kg), or use of maintenance therapy. Furthermore, it is possible that additional IPI treatment after the induction phase could theoretically put a patient at risk for severe immune-related adverse events. Based on these considerations, induction with 4 doses of IPI at 3 mg/kg without maintenance represents the most appropriate choice for adolescent patients with advanced melanoma, consistent with the recommendations for adults.

There are some clinical data that indicate that retreatment after previous progression may have clinical benefit. In study MDX010-20, up to 67% of the 40 adult subjects who received retreatment with IPI (3 mg/kg Q3W x 4) at the time of progression achieved disease control (stable disease [SD] or better) with the first course of retreatment, potentially prolonging life in those subjects.

Based on the results of MDX010-20 in adult patients, one retreatment with IPI was originally allowed for eligible patients in CA184178. Eligibility for entering one retreatment phase in CA184178 required patients to have an initial partial response (PR), complete response (CR), or SD of ≥3 months (beginning at Week 12 with SD at Week 24) and subsequent confirmed progressive disease (PD) (per immune-related Response Criteria). Amendment 04 of the CA184178 protocol, implemented on 21-May-2014, removed the maintenance phase since maintenance treatment has not been proven to add additional benefit based on previous IPI studies in adults, and the approved schedule of IPI for adults does not include maintenance treatment, as previously described.

Two subjects were eligible for re-induction/retreatment over the duration of Study CA184178, with >SD after Week 12 and Week 24 tumour assessments:

- Subject progressed in Oct-2015 and initiated treatment with pembrolizumab and, therefore, was no longer eligible for retreatment at the time of the Final CSR.

- Subject had a continued PR at the time of the Final CSR. The principal investigator last indicated the subject was still doing well in remission. The investigator hoped this would continue, but should the need arise in the future, would treat the patient outside of the CA184178 protocol.

Rapporteur's assessment

The MAH explained that the rationale for removing the maintenance phase of ipilimumab treatment was that maintenance treatment has not been proven to add additional benefit in previous studies in adults and the potential risk for severe immune-related adverse events with prolonged treatment. Moreover, as there were indications for clinical benefit of retreatment after progression, this option was added in the study protocol.

Two adolescents in study CA184178 were eligible for retreatment, but did not receive it. One patient was treated with pembrolizumab as next line treatment and for the other patient the investigator decided to not retreat based on continued PR.

Issue resolved.

Question 2

The accrual rate in the submitted phase 2 CA184178 and in the phase 1 NCI7458/CA184070 was low and in total the sample size of patients at the age of 12 to 18 years treated with the approved dose of 3 mg/kg is very small. Therefore, the Applicant is asked to elaborate on the progress of the clinical development of ipilimumab in the paediatric population with melanoma and discuss future plans, in particular for the combination with other immunotherapies.

MAH's response

Along with the well-established benefit/risk profile for IPI use in adults, based on disease similarity between the adult and paediatric populations, modelling and simulation analyses combined with extrapolation activities, demonstrated a similar exposure-response (E-R) between adolescent and adult subjects. Therefore, in the Type II variation (EMEA/H/C/002213/II/0044) currently under review, BMS proposed that modelling and extrapolation from the available paediatric and adult data, along with the data available from 2 paediatric studies, would provide clinically relevant information to support potential labelling statements and guide physicians in the safe and effective use of IPI in younger patients.

Section 1.3 of this AR summarises the studies in the paediatric clinical development program in advanced melanoma. Two IPI paediatric studies in advanced metastatic melanoma, included within the IPI melanoma PIP, have been completed: the dose-escalation NCI7458/CA184070 study (Study 2 in IPI PIP02) and another in treated and untreated subjects in the advanced metastatic setting (CA184178, Study 3 in IPI PIP02).

A third paediatric study, E1609 (also known as CA184116), a Phase 3 randomized study of adjuvant IPI anti-CTLA-4 therapy vs high-dose interferon α-2b for resected high-risk melanoma, is being conducted with the cooperation of the Eastern Cooperative Oncology Group (ECOG), primarily in high-risk surgically-resected melanoma in the adjuvant setting. An amendment to add a paediatric/adolescent (≥12 to 17 years of age) cohort to study CA184116/E1609 was activated Sep-2014. Of the originally planned 45 adolescent subjects, 3 were enrolled over 15 months up to Nov-2016 and 2 patients were treated (1 subject with IPI 10 mg/kg and 1 subject with IPI 3 mg/kg).

The paediatric arm of CA184116/E1609 was closed to recruitment in Dec-2016 and has been removed from the PIP in agreement with the PDCO: EMA decision P/0003/2017 dated 12-Jan-2017. In view of the increasing availability of new treatments, the PDCO agreed to remove this study from the melanoma PIP, which has no impact on the development of a dose recommendation for adolescents with advanced metastatic melanoma, given the different disease settings. Furthermore, the analyses conducted on data for these participants are unlikely to considerably contribute towards the assessment of benefit/risk in the small population of high-risk, surgically resectable melanoma patients. Details of these 2 patients were included in the Type II variation (EMEA/H/C/002213/II/0044) currently under review.

CTLA-4 and PD-1 inhibit antitumor immunity through complementary and non-redundant mechanisms, and have been shown to have complementary activity in metastatic melanoma. Studies have demonstrated that there is greater efficacy with the combination (administered sequentially) than that of either nivolumab (NIVO) or IPI monotherapy.

There is currently one ongoing study (Table 22) investigating the safety and efficacy of combination administration of NIVO with IPI in a broad range of paediatric solid tumours, including advanced and metastatic melanoma (ADVL1412/CA209070, included in the NIVO PIP). This study will include paediatric patients (from 1 to <18 years of age) with refractory or relapsed solid malignant tumours, and provide PK data from approximately 15 subjects with combination therapy and approximately 12 subjects with NIVO monotherapy. No data are currently available in any paediatric subset.

Table 22. Study ADVL1412/CA209070

Study identifier Sponsor/Collaborator	Type of study/design features	Study population/ Planned/Enrolled	Dosage, regimen	Primary Objectives
Ipilimumab and Nivolumab Combination Therapy				
ADVL1412/CA209070 Children's Oncology Group (COG)	Phase 1/2, multicenter, open-label study of NIVO and the combination of NIVO and IPI in patients from 1 to <18 years of age (and young adults) with refractory or relapsed solid malignant tumors to evaluate safety, PK, and anti-tumor activity	Children and adolescents 1 to <18 years of age (+ young adults up to 30 years of age) with refractory or relapsed solid malignant tumors including advanced and metastatic melanoma. Actual age range: 1.4 to 27 years Planned: 352 total Actual: 110 total: 36 subjects <12 years of age, 74 subjects >12 years of age; Nivolumab monotherapy: 78 subjects at 3 mg/kg; Combination therapy: 6 subjects at NIVO 1 mg/kg + IPI at 1 mg/kg; 26 subjects at NIVO 1 mg/kg + IPI at 3 mg/kg with subsequent NIVO at 3 mg/kg	Nivolumab monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or Nivolumab administered IV over 60 minutes at 1 mg/kg combined with IPI administered IV over 90 minutes at 1 or 3 mg/kg every 3 weeks for 4 doses followed by NIVO administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression	Safety and anti-tumor activity

Plans for IPI in combination with NIVO were described above in the discussion for ADVL1412/CA209070. The NIVO solid tumour PIP also sets out further plans for a randomised, controlled trial to evaluate PK, efficacy, and safety of NIVO in combination with a rationally selected other medicine, and compared to standard anti-cancer care in patients from birth to <18 years of age with a paediatric solid malignant tumour type. Furthermore, a modelling and simulation approach has been proposed within the PIP for determination of a recommended paediatric combination dose.

At this time, there are no future plans for studies with IPI in combination with other immunotherapies.

Rapporteur's assessment

Besides the three paediatric studies with ipilimumab described in the introduction in section 1.3 of this AR, there is one ongoing study investigating ipilimumab in children. In this study ADVL1412/CA209070 ipilimumab is combined with nivolumab in a paediatric population with solid tumours. No data are currently available in any paediatric subset. Furthermore, the MAH has no future plans for other studies with ipilimumab in the paediatric population. Efficacy data of ipilimumab after progression of disease on nivolumab treatment are not expected.

Issue resolved, the benefit/risk of ipilimumab monotherapy in the adolescent population with advanced metastatic melanoma will be further discussed in the ongoing Type II variation (EMEA/H/C/002213/II/0044).

5. Updated CHMP overall conclusion and recommendation

In conclusion, the Rapporteur considers that the data presented do not affect the positive benefit/risk of ipilimumab and there is no need for modification of the SmPC at this time. The benefit/risk assessment of ipilimumab for the treatment of advanced melanoma in children and adolescents of 12 years and older will be further discussed in the extension of indication procedure.

☒ Fulfilled:
No regulatory action required.

☐ Not fulfilled: