26 February 2015
EMA/CHMP/195973/2015
Committee for Medicinal Products for Human Use (CHMP)

Yervoy

(Ipilimumab)

Procedure No. EMEA/H/C/002213/P46 032

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

Assessment report as adopted by the CHMP with all commercially confidential information deleted

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1. Introduction

This report covers the following post-authorisation commitments undertaken by the MAH:

Submission of final study report in accordance with Article 46 of regulation (EC) N0 1901/2006 of study NCI7458-CA184070: Open label, dose escalation clinical trial of intravenously administered ipilimumab in patients with untreatable, refractory or relapsed solid malignant tumours.

After review of the submitted data, the CHMP is of the opinion that the data do not support the requirement for a variation of the SmPC. However, a variation of the currently approved Paediatric Investigational Program (PIP) after consultation with the PDCO is recommended.

1.1. Steps taken for the assessment

Submission date:	08 December 2014
Start of procedure:	December 2014
CHMP Rapporteur's preliminary assessment report circulated on:	27 January 2015
CHMP Rapporteur's updated assessment report circulated on:	16 February 2015
CHMP opinion:	26 February 2015

2. Assessment of the post-authorisation measure PAM EMEA/H/C/002213-EU/1/11/698/001-002

Ipilimumab (BMS-734016, MDX-010, YERVOY®) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human cytotoxic T lymphocyte antigen 4 (CTLA-4). CTLA-4 is a key regulator of T-cell activity. Ipilimumab is a CTLA-4 immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of tumor reactive T-effector cells, which mobilize to mount a direct T-cell immune attack against tumor cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may lead to an increase in anti-tumor immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumor site, leading to an increase in the intratumoral T-effector/T-regulatory cell ratio, which drives tumor cell death.

Ipilimumab is currently approved for adults in European Union (EU), the United States (US) and other countries for the treatment of advanced (unresectable or metastatic) melanoma at a dose of 3 mg/kg administered intravenously (IV) once every 3 weeks for a total of 4 doses.

This PAM concerns the assessment of the final report of the NCI7458-CA184070 (submitted in accordance of Article 46 of Regulation (EC) N 1901/2006), a dose escalation study performed with ipilimumab in children, adolescents, and young adults affected by untreatable, relapsed or refractory solid tumors.

According to the Ipilimumab Pediatric Development Program, other two studies in melanoma patients are currently ongoing:

-Study CA184178: a Phase 2 study of ipilimumab in children and adolescents (12 to <18 years) with previously treated or untreated Stage III or Stage IV malignant melanoma, being conducted by the MAH.

-Study E1609 (also known as CA184116): a Phase 3 randomized study of adjuvant ipilimumab anti-CTLA-4 therapy vs high-dose interferon α-2b for resected high-risk melanoma, with the cooperation of the Eastern Cooperative Oncology Group (ECOG).

One other study is planned:

- A Phase 2 study of ipilimumab in pediatric subjects, 0 to <18 years with solid malignant tumors, based on the results of study NCI7458/CA184070.

Table 1: Ipilimumab Pediatric Development Program

Study identifier Sponsor/Collaborator	Type of study/ design features	Study population/ Planned/Enrolled	Dosage, regimen	Primary Objectives
Complete				
NCI 7458 (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.	Subjects aged from 1 - <18 y (+ young adults up to 21 years) with advanced and/or refractory solid malignant tumors. 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 Induction 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.
Ongoing				
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 from age 12 - <18 years with untreated or previously treated advanced/metastatic melanoma. Planned: 30 total; up to 10 at 10 mg/kg; at least 20 at 3 mg/kg Current: 8 at 10 mg/kg; 1 at 3 mg/kg	Ipilimumab 3 or 10 mg/kg IV Induction Phase: ipilimumab q3wks (Week 1, 4, 7, 10). Subjects in the 3 mg/kg group 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 (one dose of ipilimumab 3 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 subjectss (12 to < 18 years) at the 3 mg/kg dose level.
Amendment to E1609 (CA184116) Eastern Cooperative Oncology Group (ECOG)	Phase 3, randomized active-controlled study of adjuvant ipilimumab anti-CTLA-4 therapy vs high-dose interferon α-2b for resected high-risk melanoma to evaluate efficacy, safety and tolerability.	Adults and children from 12 – <18 years with resected high-risk melanoma, stratified by the AJCC stage (IIIB, IIIC, M1a, M1b) and by age (less than 18 years vs greater than or equal to 18 years). Planned:~1545 total at least 45 adolescents, 15/group; ~1500 adults Current: 1	Ipilimumab 3 or 10 mg/kg IV Induction Phase: Every 3 weeks for a total of 4 doses. Maintenance Phase: Ipilimumab 3 or 10 mg/kg, administered by IV infusion every 12 weeks (3 months), beginning at week 24, then at Weeks 36, 48, and 60 for a total of 4 doses.	Adolescent Subgroup: • To evaluate safety and tolerability of post-operative adjuvant ipilimumab therapy given at either 10 mg/kg or 3 mg/kg.
Planned				
Solid tumor TBD	Phase 2 study of ipilimumab in pediatric subjects aged from 0 to less than 18 years with solid malignant tumors based on the results of the Phase 1 study NCI7458	Subjects 0 to < 18 years with solid malignant tumors including advanced and metastatic melanoma selected on the basis of results of Phase 1 study Number TBD	To be agreed upon by the PDCO prior to initiation of the study	Efficacy and Safety

AJCC = American Joint Committee on Cancer; CR = complete response; CTLA-4 = cytotoxic T-lymphocyte antigen 4; HAHA = human anti-human antibodies; IV = intravenous; NCI = National Cancer Institute; OS = overall survival; PD = progressive disease; PDCO = Paediatric Committee; PK = pharmacokinetics; PR = partial response; q = every; RECIST = Response Evaluation Criteria in Solid Tumors; RFS = recurrence-free survival; SD = stable disease; TBD= to be decided; wks = weeks.

An initial Pediatric Investigation Plan (PIP) for all conditions in the category of malignant neoplasms except melanoma, nervous system, haematopoietic and lymphoid tissue (EMEA-000117-PIP01-07),

and one for the treatment of the condition of melanoma (EMEA-000117-PIP02-10) was provided to the European Medicines Agency's (EMA) Paediatric Committee (PDCO) in 2007 and 2010, respectively. Feedback on the pediatric development program for ipilimumab was provided by the PDCO in the decisions after submission of the initial PIPs and in opinions and decisions rendered for Requests for Modification (RfM) to the initial PIP for the category of malignant neoplasms (except melanoma, nervous system, haematopoietic and lymphoid tissue) and for the PIP for melanoma.

BMS was initially granted a waiver by the US Food & Drug Administration (FDA) based on 21CFR314.55, which states that any drug for an indication or indications for which orphan product designation has been granted are exempt from pediatric studies typically required under the Pediatric Research Equity Act. The FDA granted ipilimumab orphan-product designation (03-1777) on 03-June-2004 for "treatment of high-risk Stage II, Stage III, and Stage IV melanoma." BMS had a subsequent meeting with the FDA on 28-Aug-2012 to discuss a pediatric development plan for ipilimumab and to obtain guidance on the content of a Proposed Pediatric Study Request (PPSR). At FDA's request, BMS provided a revised PPSR in 2013 to provide additional information to support extrapolation of adult efficacy data for the development of ipilimumab in advanced melanoma in the adolescent population (ages 12 to 18), which would be supported by data from studies NCI7458/CA184070 and CA184178. Based on FDA feedback on the 2013 PPSR, BMS submitted a new PPSR in 2014, in which a change in dose from 10 to 3 mg/kg and removal of maintenance treatment (every 12-weeks) were introduced for study CA184178.

STUDY NCI7458 (or CA184070)

Study NCI7458 (or CA1840701) was a Phase 1, multi-center, open-label, dose-escalation (doses of 1, 3, 5 and 10 mg/kg) study conducted with ipilimumab in children, adolescents, and young adults, ranging in age from 1 to 21 year with untreatable, relapsed or refractory solid malignant tumors (including melanoma) without a curative option with standard therapy. The rationale for studying ipilimumab in pediatric solid tumors was based on the hypothesis that 1) existent immune responses are present in pediatric patients with tumors, but tumor immune escape diminishes the potency of such responses leading to inadequate control, and that 2) the anti-CTLA-4 activity provided by ipilimumab would augment immune responses to tumors in the pediatric population, thereby improving clinical outcomes. Based on the activity of ipilimumab against melanoma in adults, similar activity was hypothesized in the pediatric population, given the similarity of the immune system in adults and pediatric subjects. The study was conducted under the supervision of the Pediatric Oncology Branch (POB) of the National Cancer Institute (NCI).

Study Design

The primary objective was to determine the toxicity profile and the maximum tolerated dose 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. The pharmacokinetics (PK) of ipilimumab was also evaluated.

Secondary objectives included evaluation of antitumor activity (in terms of ORR) and of the immunomodulatory (pharmacodynamics) activity of ipilimumab.

Ipilimumab was administered intravenously (IV) over 90 minutes on Day 1 of each 21-day cycle for 4 cycles in the absence of dose-limiting toxicity (DLT) or disease progression. From Cycle 5 onward (with Cycle 5 at Week 12), ipilimumab was administered approximately every 12 weeks (maintenance dosing). Ipilimumab doses ranging from 1 mg/kg to 10 mg/kg in 4 dose levels (1, 3, 5, or 10 mg/kg)

were planned. Three to 6 subjects were to be enrolled at each dose level. If none of the first 3 subjects who were evaluable for toxicity at a given dose level had a DLT within 6 weeks following the first dose date, dose escalation was performed. No intra-subject dose escalation was allowed. If a DLT related to ipilimumab was observed in 1 subject from a cohort of 3 subjects at a given dose level, an additional 3 subjects were to be entered at that dose level. If none of these additional subjects experienced a DLT(≤1/6 with DLT), the dose of ipilimumab was to be escalated. However, if ≥1 of the additional subjects experienced a DLT (≥2/6 with DLT), the highest dose tolerated was determined to be exceeded, and the next lower dose level would be considered the highest tolerated dose for ipilimumab. The cohort of the maximum tolerated dose (MTD) was to be expanded to enroll a total of 12 patients.

Because there appeared to be a different toxicity profile in subjects <12 years old, the expansion cohort of 10 mg/kg was divided into 2 cohorts in 2011. As a result, the 5 mg/kg dose cohort was expanded to a total of 14 subjects that included 6 subjects <12 years, and the 10 mg/kg dose cohort was expanded to include more subjects ≥12 years old.

Re-induction therapy (ipilimumab every 3 weeks for 4 cycles) was allowed: a) in patients experiencing disease progression during the maintenance phase; b) in patients who stopped the maintenance phase due to complete response and subsequently experienced disease progression; c) in patients with an initial partial response (PR), CR, or stable disease (SD) for at least 3 months with subsequent progression.

All subjects who received at least 1 dose of ipilimumab were considered evaluable for safety. The maximum study duration was 2 years total duration of therapy.

Dose-limiting toxicity (DLT) was defined as a drug-related AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 until 31-July-2010 and Version 4.0 from 1-August-2010, that occurred during induction with ipilimumab:

☐ Non-hematologic DLT: any non-hematologic Grade 3 or 4 toxicity or Grade 2 toxicity requiring immunosuppressive or hormone replacement therapy judged to be at least possibly related to ipilimumab.

☐ Hematologic DLT: Grade 4 neutropenia or thrombocytopenia, which persisted for 5 days at any time during the treatment cycle or any grade 5 toxicity at least possibly attributable to ipilimumab. Grade 3 hematologic toxicity was not considered dose limiting.

The MTD of ipilimumab was defined as the dose level immediately below the dose level at which ≥2 subjects in a cohort (dose level) of two to 6 patients experienced a DLT attributable to ipilimumab.

Immune-related AEs were defined using a predefined list of Medical Dictionary for Regulatory Activities (MedDRA) high-level group terms, high-level terms, and preferred terms (PTs).

The development of immune function was to be evaluated prior to all cycles, based on the following laboratory tests: Rheumatoid factor, anti-nuclear antibody (ANA). If ANA values were positive (>2) subsequent to baseline evaluation, the following tests were also to be performed prior to all cycles of ipilimumab treatment: anticardiolipin antibody (ACA), anti-neutrophil cytoplasmic antibody (ANCA), complement 3 (C3), C4, anti-deoxyribonucleic acid (DNA), anti-Sjögren's syndrome (SS)A, and anti-SSB.

Corticosteroids (oral or IV) could be used for treatment of immune-related adverse events (irAEs). In addition, alternative immunosuppressive therapies (e.g., infliximab, mycophenolate mofetil, tacrolimus) could be used to treat irAEs that do not respond to initial steroid therapy.

Results

Disposition and Baseline/Demographic Characteristics

A total of 33 patients were enrolled: 13 (39.4%) of the 33 subjects in the study were <12 years old and 20 (60.6%) were ≥12 years. No subjects were ≥1 and <2 years old. All patients were treated at 3 study sites in the United States.

Overall, 57.6% of subjects were female and 69.7% Whites. Most (92.9% of subjects in the 5 mg/kg group were female, and in the 10 mg/kg group, most were male (76.9%). Overall, 39.4% were <12 years old and 60.6% were ≥12 years. The minimum age was 2.4 years; one subject in the 3 mg/kg group was 21.8 years old. All subjects had baseline Lansky/Karnofsky scores ≥50, as required by the inclusion criteria.

Table 2. Demographic and baseline characteristics by dose level.

	Number of Subjects (%)				
	1 mg/kg Ipilimmab N = 3	3 mg/kg Ipilimmab N = 3	5 mg/kg Ipilimmab N = 14	10 mg/kg Ipilimmab N = 13	Total N = 33
GENDER, n(%)					
FEMALES	2 (66.7)	1 (33.3)	13 (92.9)	3 (23.1)	19 (57.6)
MALES	1 (33.3)	2 (66.7)	1 (7.1)	10 (76.9)	14 (42.4)
RACE, n(%)					
WHITE	3 (100.0)	2 (66.7)	10 (71.4)	8 (61.5)	23 (69.7)
BLACK OR AFRICAN AMERICAN	0	0	0	2 (15.4)	2 (6.1)
ASIAN	0	0	2 (14.3)	3 (23.1)	5 (15.2)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (33.3)	1 (7.1)	0	2 (6.1)
UNKNOWN	0	0	1 (7.1)	0	1 (3.0)
AGE (YEARS)					
N	3	3	14	13	33
MEAN (STD)	14.57 (10.542)	12.57 (8.832)	12.76 (5.667)	14.18 (3.527)	13.47 (5.490)
MEDIAN	20.30	11.70	13.50	13.40	13.40
MIN-MAX	2.4 - 21.0	4.2 - 21.8	3.3 - 20.8	7.5 - 19.4	2.4 - 21.8
AGE, n(%)					
< 12 YEARS	1 (33.3)	2 (66.7)	6 (42.9)	4 (30.8)	13 (39.4)
>= 12 YEARS	2 (66.7)	1 (33.3)	8 (57.1)	9 (69.2)	20 (60.6)

Melanoma was the most common tumor type (12/33 subjects), followed by osteosarcoma (n=8), soft tissue sarcoma (n=7), renal cell of the kidney (n=1), clear cell of the kidney (n=1), neuroblastoma (n=1), and solid tumor not otherwise specified (NOS) (n=3). all subjects had received anti-cancer treatment prior to enrollment. All subjects had prior surgery. Among subjects with prior radiation, 1 had extensive radiation, 4 limited radiation, and 13 radiation (NOS). All 12 melanoma subjects were treated with IL-2 or interferon (IFN) alpha prior to enrollment, and most of the subjects with other tumor types (63.6%) were treated with standard multi-agent chemotherapy regimens for their particular tumor type. The subject with a neuroblastoma was enrolled and treated following an autologous stem cell rescue.

Table 3. Tumor type by age-groups

Age Group	Tumor Type	1 mg/kg	3 mg/kg	5 mg/kg	10 mg/kg	Total
< 12 years old	Melanoma	1	1	4	1	7
	Non-melanoma	0	1	2	3	6
≥ 12 years old	Melanoma	0	0	3	2	5
	Non-melanoma	2	1	5	7	15

CHMP's comment

According to the demographic baseline characteristics, no patients were enrolled in the study with age < 2.4 years.

Safety

Dose escalation

At doses of 1 and 3 mg/kg, 3 subjects each were enrolled, regardless of age group. Since no DLTs were observed, the dose was escalated to 5 mg/kg.

At 5 mg/kg, the first cohort of subjects to assess DLT's was 4 instead of 3. The second subject enrolled died of progressive disease before 6 weeks on study and was not evaluable. Therefore, the subject was replaced by another subject at this dose level. Since only the 4th subject treated at 5 mg/kg experienced a DLT, an additional 3 subjects were enrolled at this dose; however, as none of these experienced a DLT, the dose was escalated to 10 mg/kg.

At 10 mg/kg, one of the first 3 subjects enrolled experienced a DLT within 6 weeks of first dose; this subject was <12 year old. Since a DLT was reported for <2 of the 3 subjects enrolled and treated at 10 mg/kg, additional subjects were enrolled into the 10 mg/kg dose group. A second subject <12 year old experienced at 10 mg/kg, as enrolment continued into this dose cohort. Therefore, the protocol was amended to limit further treatment of subjects <12 year old to the 5 mg/kg dose, thereby limiting expansion of treatment at 10 mg/kg to subjects ≥12 years old. Shortly thereafter, the first DLT in a subject ≥12 years old was reported.

Dose expansion phase by age

Since no young children had been enrolled in the 5 mg/kg dose cohort, after escalation to 10 mg/kg, an amendment was put in place to enroll 6 additional subjects <12 years at the 5 mg/kg dose. This expansion allowed further exploration of safety and PK at these age group to determine if 5 mg/kg was a tolerated dose for <12-year-old age group. By the time the MTD for subjects <12 years old was established, and further treatment had been separated by age groups, and the 10 mg/kg dose level was expanded to enroll additional subjects ≥12 years old, besides the initial 3 subjects need to establish the highest tolerated dose tested, 4 subjects <12 years old had been treated at 10 mg/kg.

Additional subjects ≥12 years old were needed to allow further exploration at this dose, and therefore, 6 additional subjects ≥12 years old were enrolled into the 10 mg/kg group for a total of additional 9 subjects during the dose expansion phase.

CHMP's comment

The applied dose escalation and expansion schema is considered acceptable. However, in view of the PK results of the CA184070 study and the observed activity of ipilimumab in adults at 3 mg/kg dose (currently recommended dose regimen in adults) an expansion cohort at 3 mg/kg dose would have been appropriate too, in order to allow a better evaluation of tolerability and potential activity signals of the drug at this dose.

Safety results

Ipilimumab was reasonably well tolerated in CA184070 study. The safety profile observed in patients ≤21 years of age appears in line with the known safety profile of ipilimumab as reported in adults. No new safety signals were identified in paediatric patients.

No DLTs were identified in the 1 and 3 mg/kg dose cohorts. The MTD was determined to be 5 mg/kg in subjects ≥1 to <12 years old, and 10 mg/kg was the highest tolerated dose tested for subjects ≥12 to ≤21 years old in this study.

Adverse Events (AEs)

Ipilimumab treatment was tolerated and the AE profile in this study was similar to that seen in the adult studies. Serious AEs were reported for 9 (64.3%) of 14 subjects in the 5 mg/kg group and 5 (38.5%) of 13 subjects in the 10 mg/kg group. Immune-related AEs (irAEs) of any grade in subjects who received at least one dose of ipilimumab were reported in 25 (76%) of the 33 subjects treated at all dose levels. Most were low grade.

Most of the subjects in all treatment groups were discontinued due to progressive disease. A total of 8 (24%) subjects (4 in the 5 mg/kg dose group and 4 in the 10 mg/kg dose group) were discontinued from the study because of a drug related AE (Grade 3 – 4). The AEs leading to discontinuation included anaphylactic reaction, autoimmune disorder, increased amylase/lipase (pancreatitis), headache, diarrhoea, and pleural effusion with no single event occurring in more than 2 subjects.

AEs reported at different dose levels were the following:

-1 mg/kg and the 3 mg/kg dose cohorts: no AEs leading to discontinuation or severe (Grade 3-4) irAEs were reported in the

- *5 mg/kg dose cohort (14 pts)*:

o Related AEs were reported for most subjects (12/14), and half of them were severe (6/14);

o Severe irAEs were reported for 3 subjects (1/6 <12years old, 2/8 ≥12 years old) and included anaphylactic reaction, amylase increased, lipase increased, ALT increased, and AST increased;

o Four subjects had AEs leading to discontinuation (1/6 subject <12 years old, 3/8 subjects ≥12 years old): all but one of the events (vomiting) was considered a DLT. Events leading to discontinuation were anaphylactic reaction, diarrhoea, vomiting, ALT increased, and AST increased.

- *10 mg/kg dose cohort (13 pts):*

o Related AEs were reported for most subjects (12/13), and half of them were severe (6/13);

o Severe irAEs were reported for 3 subjects (2/4 < 12years old, 1/9 ≥12 years old) and included diarrhoea, ALT increased, and AST increased;

o Four subjects had AEs leading to discontinuation (2/4 subjects <12 years old, 2/9 subjects ≥12 years old): all of these events were considered a DLT, except for the event of headache. Events

leading to discontinuation were autoimmune disorder, abdominal pain, amylase increased, lipase increased, headache, diarrhoea, and pleural effusion.

Table 4. Adverse Events by age groups.

	Number of Subjects (%)[a]							
	Dose Cohort N= 33							
	Age <12 years				Age ≥12 years			
	1 mg/kg n = 1	3 mg/kg n = 2	5 mg/kg n = 6	10 mg/kg n = 4	1 mg/kg n = 2	3 mg/kg n = 1	5 mg/kg n = 8	10 mg/kg n = 9
Deaths, n (%)[b]	0	0	0	1 (25.0)	0	0	1 (12.5)	0
All Deaths, n (%)[a,b]	1 (100.0)	2 (100.0)	1 (16.7)	2 (50.0)	2 (100)	1 (100.0)	4 (50.0)	2 (22.2)
SAEs, n (%)	0	1 (50.0)	2 (33.3)	1 (25.0)	0	1 (100.0)	7 (87.5)	4 (44.4)
SAEs, drug-related, n (%)[c]	0	1 (50.0)	1 (16.7)	1 (25.0)	0	1 (100.0)	5 (62.5)	4 (44.4)
AEs leading to study drug discontinuation, n (%)	0	0	1 (16.7)	2 (50.0)	0	0	3 (37.5)	2 (22.2)
Drug-related AEs leading to study drug discontinuation, n (%)[c]	0	0	1 (16.7)	2 (50.0)	0	0	3 (37.5)	2 (22.2)
irAEs, n (%)	1 (100.0)	2 (100.0)	3 (50.0)	3 (75.0)	1 (50.0)	1 (100.0)	7 (87.5)	7 (77.8)
AE, n (%)	1 (100.0)	2 (100.0)	6 (100.0)	4 (100.0)	2 (100.0)	2 (100.0)	8 (100.0)	9 (100.0)
Drug-related AEs, n (%)[c]	1 (100.0)	2 (100.0)	5 (83.3)	3 (75.0)	2 (100.0)	2 (100.0)	7 (87.5)	9 (100.0)
Dose-limiting Toxicities	0	0	1 (16.7)	2 (50%)	0	0	2 (25.0)	2 (22.2)

[a] Subjects with on-study events within 30 days of the last dose, except for "All Deaths," which were >30 days after the last dose.

[b] All cause of death due to malignant disease. Additional subjects may have died after the database lock due to malignant disease (off study).

[c] Attribution to ipilimumab reported as "Possible," "Probable," "Definite," or Missing.

Note: In the age cohort ≥12 years old, one of the 2 DLTs in each of the 5 and 10 mg/kg dose cohorts were reported >6 weeks after the first dose and did not contribute toward the MTD.

Abbreviations: N=total number of subjects treated; n=number within a group; SAE=serious adverse event; AE=adverse event; irAE=immune-related adverse event.

CHMP's comment

The number of patients treated with ipilimumab 1mg/kg and 3 mg/kg is too low to allow any conclusion on the safety profile of the drug in the paediatric population at such doses administered. The absence of DLTs clearly suggests tolerability. Moreover overall the safety profile of ipilimumab as observed in this study appears in line with the known toxicity of the drug in adults. No new safety signals are observed in the paediatric population also in terms of irAEs. Nevertheless, as already observed in adults, the toxicity of the drug is substantial with several severe and life threatening AEs.

DLT

A total of thirteen subjects <12 years of age and 20 subjects ≥12 years were treated with ipilimumab. The highest tolerated dose tested was different between subjects <12 years old and ≥12 years old.

o For subjects ≥1 to <12 years old, the MTD was determined to be 5 mg/kg. Tolerability of the 5 mg/kg dose in this age group was confirmed by expansion of the cohort to a total of 13 subjects. DLTs were observed in:

- 1 of a total of 6 subjects in this age group treated with 5 mg/kg (anaphylactic reaction);

- 2 of a total of 4 subjects in this age group treated with 10 mg/kg cohort (diarrhoea; increased ALT/AST).

o The highest tolerated dose tested for subjects ≥12 to ≤21 years old was 10 mg/kg. DLTs were observed in:

- 2 of a total of 8 subjects in this age group treated with 5 mg/kg (amylase increased and abdominal pain; autoimmune disorder);

- 2 of a total of 9 subjects in this age group treated with 10 mg/kg (pleural effusion; diarrhoea).

For older children (>12 years of age), 10 mg/kg was established in this study as the highest tested tolerated dose and the dose cohort of 10 mg/kg was therefore further expanded for this older age group.

CHMP's comment

The results of the study suggest different maximum tolerated doses of ipilimumab at different ages. In particular, in patients <12 years old the MTD of ipilimumab appears to be 5 mg/kg, whereas in patients ≥12 to ≤21 years old the maximum evaluated ipilimumab dose and reported to be tolerable is 10 mg/kg. However, the PK data show adequate levels of drug exposure at 3 mg/kg dose already and a signal of activity was observed in a patient >12 years old treated with ipilimumab 5 mg/kg. These raise discussion over the appropriate dose to be used for further clinical testing in the paediatric population. Unfortunately the results of the CA184169 and CA184178 studies (comparing efficacy and safety of ipilimumab 3mg/kg vs 10 mg/kg in adults and paediatric (≥ 12 -≤ 18 years old) melanoma patients, respectively, are currently not available.

Immune-related AEs (irAEs) and

Immune-related AEs of any grade in subjects who received at least one dose of ipilimumab were reported in 25 (76%) of 33 of subjects treated at all dose levels. No irAEs ≥Grade 3 were reported for any subject treated with 1 or 3 mg/kg dose group, and 3 (21%) of 14 subjects treated with 5 mg/kg and 3 (23%) of 13 subjects treated with 10 mg/kg reported Grade 3 to 4 events. None were fatal.

The types of irAEs were also consistent with the adult experience, with the most commonly reported irAEs across all groups being in the categories of gastrointestinal (n=12/33 pts, including 2 severe events of which 1 GI perforation), liver (n=11/33 pts, including 2 Grade 3 increase AST/ALT), and skin (n=9/33 pts, all low grade) events. Grade 3 or 4 increase in serum lipase and amylase laboratory values were reported for 2 of 33 pts and were consistent with clinical diagnosis of pancreatitis.No new or unexpected irAEs were observed in pediatric subjects. Similar to the results of studies in adults, while the proportion of subjects with irAEs increased with higher doses, there was no difference in the spectrum of irAEs reported. While 10 mg/kg did not appear to be tolerable in the younger age group, the safety profile at lower doses, including 5 mg/kg, was consistent with the known safety profile of ipilimumab, including the frequency and types of irAEs. Immune-related adverse events in this study were managed using treatment algorithms previously established for adult subjects.

Immune and Endocrine Function

Three of the 33 subjects in the study had ANA values >2 and 2 of the 33 subjects had elevations of rheumatoid factor. None appeared to be clinically relevant.

Three of 33 subjects treated in this study reported abnormal endocrine laboratory values that were diagnostic for an endocrine disorder.

Deaths

Overall, death due to malignant disease was reported for 15 subjects in this study as of the database lock. Two deaths occurred within 30 days of last dose. No subjects died from study drug toxicity and no deaths were attributed as related to study drug toxicity by the investigator.

CHMP's Comment

The data regarding irAEs and deaths appears in line with what reported in the adult population. No new safety signal is observed.

Pharmacokinetics

In Study CA184070, ipilimumab IV was rapidly absorbed and there appeared to be little difference observed in mean Tmax values between either the age or dose cohorts in pediatric subjects. There were also no apparent differences in concentration-time profiles in this study between the paediatric age cohorts of <12 (N=13) and ≥12 years old (N=20), regardless of dose level (see

Figure 1 and Figure 2). Mean serum T-half values ranged from 7 to 15 days.

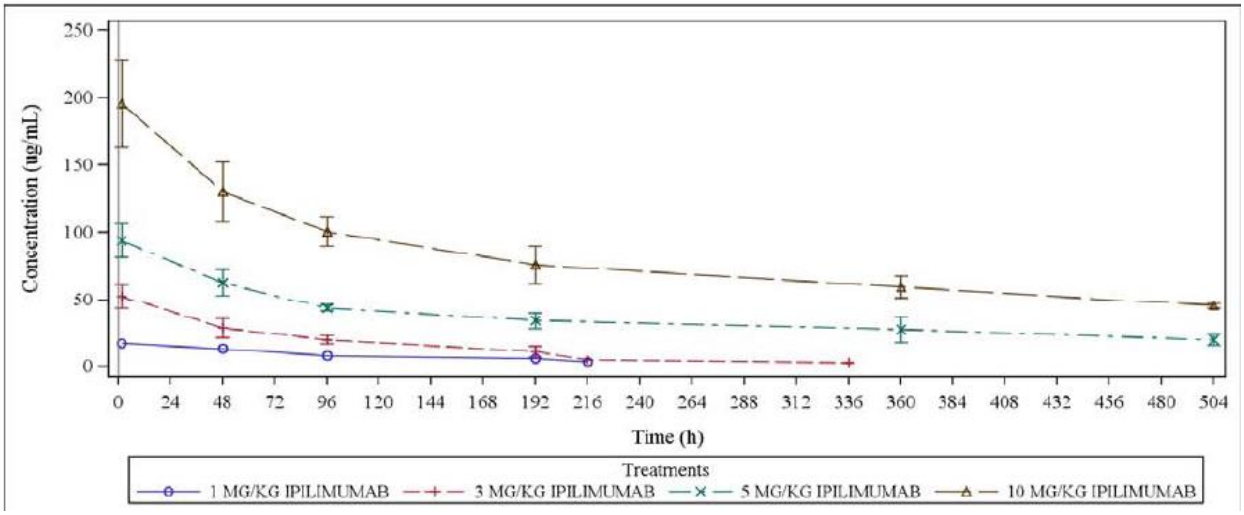

Figure 1 Mean Concentration-Time Profiles of Ipilimumab, Cycle 1, Age(2 and <12 Years Old - Linear Scale (CA184070)

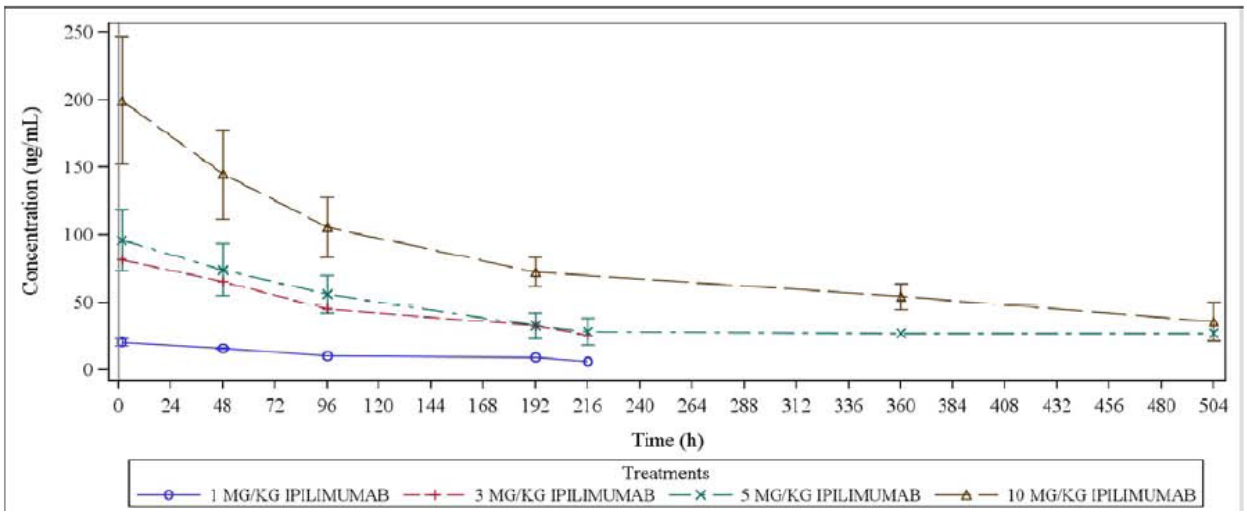

Figure 2 Mean Concentration-Time Profiles of Ipilimumab, Cycle 1, Age ≥12 Years and <21 Years Old - Linear Scale (CA184070)

Based on the results of this study, the pediatric data suggest that the exposure of ipilimumab (eg, AUC, Cmax, and Cmin) increased approximately in proportion with doses ranging from 3 to 10 mg/kg, although the data with the 3mg/kg are limited (N=3).

Ipilimumab exposure of pediatric subjects in study CA184070 appeared to be consistent with exposure in adults, based on comparison with pharmacokinetics of ipilimumab 10 mg/kg in adults from studies CA184007 & CA184008 in the application dossier (Table 1). There was no apparent difference in Cmax, AUC0-21, Ctrough between children (≥2 and <12 years), adolescents (≥12 and <18 years), and adults.

Table 1 Ipilimumab PK Parameters by Age during Cycle 1 (patients <12 and ≥ 12 < 21 years study CA184070, adults studies CA184007 and CA184008 (application dossier))

	Age < 12 years Study CA184070		Age ≥ 12 < 21 years Study CA184070		Adults[$] Study CA184007 & CA184008
Dose (number) PK parameter (CV%)	5 mg/kg N=5	10 mg/kg N=3-4*	5 mg/kg N=5-7*	10 mg/kg N=8	10 mg/kg N=15
Cmax (µg/ml)	93 (13%)	193* (17%)	91* (25%)	203 (22%)	205 (19%)
AUC_{0-21} (µg.h/ml)	16318 (20%)	37053 (18%)	12681* (73%)	36751 (14%)	34176 (19%)
Cl (ml/h/kg)^	0.20	0.18	0.22	0.19	0.24

	(39%)	(27%)	(53%)	(24%)	
Vss (L/kg)	0.095 (5%)	0.085 (6%)	0.065 (17%)	0.079 (24%)	0.077
T1/2 (days)	14.3 (5%)	14.1 (3%)	9.8 (5%)	12.7 (5%)	9.5
Ctrough (µg/ml)#	19 N=4	45 N=2	28 N=4	33 N=7	57

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

^ Cl in adults was calculated for a 75 kg subject

In patients<12 years of age Ctrough was determined at the end of the second cycle for patients ≥12 years and adults at the end of cycle 3.

CHMP's comment

Bioanalysis of ipilimumab is adequate, 93.5% of the ISR samples met acceptance criteria.

Results from pediatric study CA184070 indicated that pharmacokinetics of ipilimumab is comparable in pediatric patients and adults when dosed by mg/kg. The elimination half-life seemed somewhat longer in pediatric patients<12 years compared to older patients but in the application dossier a half-life of ipilimumab between 10 and 17 days was reported for adults. The results from this study imply that compared to the approved 3mg/kg ipilimumab in adults, the pediatric patients will likely obtainan adequate ipilimumab exposure to allow for interpretation of safety and efficacy data. Safety differences observed for the <12 year old subjects do not appear to be due to differences in PK.

Pharmacodynamics

In Study CA184070, pre-treatment and on-treatment measurements of ALC and activated CD4+ and CD8+ T-cells from whole blood were analyzed to demonstrate immunomodulating pharmacodynamic effects of ipilimumab treatment. Samples were taken from all 33 subjects in the study, but due to the limited number of subjects in the 1 and 3 mg/kg dose cohorts, summaries and figures were only provided for subjects in the 5 and 10 mg/kg dose cohorts. Data for ALC for the first 3 cycles are presented in Table 2.

Table 2 Effect of ipilimumab on Absolute Lymphocyte Counts in pediatric patients treated with 5 mg/kg upper panel or 10 mg/kg lower panel (study CA184070)

Dose Cohort = 5 mg/kg Ipilimumab

Biomarker	Study Day	Statistics	Absolute Value (K/MICROL)	Change from BL (K/MICROL)	Percent Change from Baseline (%)
ABSOLUTE LYMPHOCYTE COUNT	CYCLE1 D1	N	11		
		MEAN (STD)	1.516 (1.1285)		
		MEDIAN	1.180		
		MIN - MAX	0.00 - 3.87		
	CYCLE1 D8	N	11	10	10
		MEAN (STD)	1.157 (0.8967)	-0.232 (0.2298)	-15.3 (13.37)
		MEDIAN	0.810	-0.210	-17.2
		MIN - MAX	0.00 - 3.15	-0.72 - 0.10	-31 - 19
	CYCLE1 D15	N	5	5	5
		MEAN (STD)	1.168 (1.0882)	0.032 (0.1143)	2.1 (19.04)
		MEDIAN	0.700	0.050	2.8
		MIN - MAX	0.00 - 2.72	-0.14 - 0.17	-19 - 32
	CYCLE2 D1	N	10	9	9
		MEAN (STD)	1.705 (1.1923)	0.122 (0.2547)	8.5 (16.84)
		MEDIAN	1.560	0.060	3.4
		MIN - MAX	0.00 - 3.94	-0.31 - 0.58	-13 - 45
	CYCLE2 D8	N	5	4	4
		MEAN (STD)	1.114 (0.7596)	0.035 (0.0351)	4.0 (3.11)
		MEDIAN	1.147	0.035	3.7
		MIN - MAX	0.00 - 1.84	0.00 - 0.07	1 - 8
	CYCLE2 D15	N	8	7	7
		MEAN (STD)	1.591 (1.1455)	-0.097 (0.7127)	-3.9 (25.46)
		MEDIAN	1.510	0.000	-5.4
		MIN - MAX	0.00 - 3.60	-1.35 - 0.96	-35 - 36
	CYCLE3 D1	N	3	3	3
		MEAN (STD)	1.363 (0.6730)	0.257 (0.1704)	25.0 (20.35)
		MEDIAN	1.090	0.350	20.3
		MIN - MAX	0.87 - 2.13	0.06 - 0.36	7 - 47

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Dose Cohort = 10 mg/kg Ipilimumab

Biomarker	Study Day	Statistics	Absolute Value (K/MICROL)	Change from BL (K/MICROL)	Percent Change from Baseline (%)
ABSOLUTE LYMPHOCYTE COUNT	CYCLE1 D1	N	13		
		MEAN (STD)	1.432 (0.7795)		
		MEDIAN	1.390		
		MIN - MAX	0.23 - 3.08		
	CYCLE1 D8	N	13	13	13
		MEAN (STD)	1.398 (0.8837)	-0.035 (0.1995)	-0.1 (30.59)
		MEDIAN	1.040	-0.050	-4.1
		MIN - MAX	0.44 - 3.43	-0.35 - 0.35	-37 - 91
	CYCLE1 D15	N	4	4	4
		MEAN (STD)	1.218 (1.0503)	0.155 (0.2170)	15.6 (19.55)
		MEDIAN	0.935	0.160	22.3
		MIN - MAX	0.30 - 2.70	-0.10 - 0.40	-13 - 30
	CYCLE2 D1	N	9	9	9
		MEAN (STD)	1.670 (0.7522)	-0.008 (0.4868)	15.6 (52.15)
		MEDIAN	1.490	0.000	0.0
		MIN - MAX	0.55 - 2.63	-0.80 - 0.70	-36 - 139
	CYCLE2 D8	N	4	4	4
		MEAN (STD)	1.450 (1.0472)	0.213 (0.5294)	56.9 (102.27)
		MEDIAN	1.050	0.335	27.7
		MIN - MAX	0.70 - 3.00	-0.52 - 0.70	-32 - 204
	CYCLE2 D15	N	7	7	7
		MEAN (STD)	2.020 (1.0095)	0.293 (0.5263)	26.5 (29.32)
		MEDIAN	2.380	0.450	25.9
		MIN - MAX	0.40 - 3.30	-0.70 - 1.00	-23 - 74
	CYCLE3 D1	N	4	4	4
		MEAN (STD)	1.873 (1.1349)	0.345 (0.6344)	18.7 (35.92)
		MEDIAN	1.635	0.425	32.6
		MIN - MAX	0.92 - 3.30	-0.47 - 1.00	-34 - 43

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Mean ALC increased following 2 doses of ipilimumab treatment in the 3, 5 and 10 mg/kg groups in this study, with a more pronounced increase in the 10 mg/kg group. This increase is indicative of a pharmacodynamic effect of ipilimumab; however, interpretation of dose dependency is limited by the small numbers of subjects with ALC measurements at Day 1 of Cycle 3 in all dose groups. Likewise,

results for correlation of ALC with Grade 3 to 5 irAEs were inconclusive for both the 5 and 10 mg/kg cohorts, based on the low number of subjects experiencing a severe irAE.

In clinical studies in adults with advanced melanoma, the majority of treated subjects experienced a rise in ALC during the induction dosing period. This observed increase was dose-dependent, was not observed in the control group (gp100 vaccine) of the pivotal Phase 3 study (MDX010-20[1]), was positively and significantly associated with overall survival in adults.

Assessments of the absolute number of activated CD4+ and CD8+ T cells in peripheral blood and change from baseline by study day were made on Day 1 of Cycle 1, and Day 1 of Cycle 2. The activated CD4+ T cells increased from baseline in both the 5 and 10 mg/kg dose cohorts (Table 3). No meaningful change in activated CD8+ T cells was observed. Due to the limited number of subjects per cohort (3 subject in each), summaries of peripheral CD4+ and CD8+ T cells in the 1 and 3 mg/kg dose cohorts are not presented.

Due to the limited number of subjects per cohort (3 subject in each), summaries of peripheral CD4+ and CD8+ T cells in the 1 and 3 mg/kg dose cohorts are not presented (refer to Appendix 9.1 of the Final CSR for NCI7458/CA184070).

Table 3 Effect of ipilimumab 5 mg/kg and 10 mg/kg on T cell subsets

Dose Cohort = 5 mg/kg Ipilimumab					
Biomarker	Study Day	Statistics	Absolute Value (MICROL)	Change from BL (MICROL)	Percent Change from Baseline (%)
ACTIVATED CD4 T CELLS	CYCLE1 D1	N	11		
		MEAN (STD)	641.7 (680.14)		
		MEDIAN	451.0		
		MIN - MAX	37 - 2411		
	CYCLE2 D1	N	9	9	9
		MEAN (STD)	742.2 (724.82)	54.0 (103.18)	22.0 (36.82)
		MEDIAN	571.0	32.0	26.6
		MIN - MAX	66 - 2352	-59 - 269	-37 - 86
ACTIVATED CD8 T CELLS	CYCLE1 D1	N	11		
		MEAN (STD)	413.8 (261.17)		
		MEDIAN	401.0		
		MIN - MAX	63 - 848		
	CYCLE2 D1	N	9	9	9
		MEAN (STD)	412.8 (274.40)	-20.1 (76.54)	1.6 (48.02)
		MEDIAN	489.0	-12.0	-1.9
		MIN - MAX	35 - 729	-119 - 106	-72 - 110
Dose Cohort = 10 mg/kg Ipilimumab					
Biomarker	Study Day	Statistics	Absolute Value (MICROL)	Change from BL (MICROL)	Percent Change from Baseline (%)
ACTIVATED CD4 T CELLS	CYCLE1 D1	N	10		
		MEAN (STD)	622.2 (365.40)		
		MEDIAN	623.5		
		MIN - MAX	80 - 1429		
	CYCLE2 D1	N	9	8	8
		MEAN (STD)	610.1 (261.06)	-3.3 (203.27)	27.0 (63.21)
		MEDIAN	577.0	86.0	20.4
		MIN - MAX	216 - 1064	-365 - 234	-27 - 170
ACTIVATED CD8 T CELLS	CYCLE1 D1	N	10		
		MEAN (STD)	591.8 (413.33)		
		MEDIAN	505.5		
		MIN - MAX	61 - 1362		
	CYCLE2 D1	N	9	8	8
		MEAN (STD)	424.2 (277.92)	-220.6 (205.46)	-10.5 (65.03)
		MEDIAN	389.0	-249.0	-30.8
		MIN - MAX	148 - 1054	-557 - 87	-59 - 143

[1] Final Clinical Study Report for MDX010-20: A Randomized, Double-blind, Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201-Positive Patients with Previously Treated Unresectable Stage III or IV Melanoma. Bristol-Myers Squibb Company, 2010. Document Control No. 930041541.

CHMP's comment

In the 10 mg/kg group, mean ALC increased following 2 doses of ipilimumab treatment, however, there was no consistent increase in ALC in the 5 mg/kg group.

As can be seen in Table 3 , the intersubject variability for the absolute values for CD4+ and CD8+ T cells was very high with ranges of 37-2411 and 61-1362, respectively. It is not known if the effect of ipilimumab is influenced by the absolute value of T cells. In this study, an increase in activated CD4+ T cells but no increase in activated CD8+ T cells from baseline was observed in pediatric subjects in both the 5 and 10 mg/kg dose cohorts. Comparison with adult data is hampered because in this pediatric study the absolute values of T cell subsets were evaluated rather than the relative expression as was the case in adults. In adult subjects treated with ipilimumab, a more pronounced pharmacodynamic effect on activated CD4+ T cells relative to activated CD8+ T cells has been observed.

Pharmacodynamic markers in this study in pediatric patients were in line with observations in adults. However, the number (N=3) of pediatric patients treated data with the approved 3 mg/kg is too small to draw any conclusion with regards to similar dose response in pediatric patients as in adults.

Immunogenicity

Among available data for 33 subjects in the study, 1 subject (7458-NCI-16) in the 10 mg/kg group had a HAHA positive result at baseline and 1 subject (7458-NCI-27) in the 5 mg/kg group had a HAHA positive results on Day 1 (sample collected 15 minutes into the infusion). No subjects were considered to be positive up to 26 weeks after ipilimumab treatment. Based on these results, no summaries for neutralizing antibodies were presented.

CHMP's comment

No subjects are considered to be positive for an anti-ipilimumab antibody (human anti-human antibody [HAHA]) response up to 26 weeks after ipilimumab treatment.

Efficacy

Subjects were considered evaluable for tumor response if they completed at least one cycle of therapy, or if they experienced progressive disease prior to that time. Results must be interpreted with caution based on the small sample size, heterogeneity of the tumors included, and limited follow up in subjects who discontinued for AEs. However, exposure was adequate based on PK.

None of the subjects reached an objective response (PR or CR) per RECIST criteria. Eleven subjects had SD as the best overall response (BOR). All subjects with SD were treated at doses >1 mg/kg (the minimum dose established to be effective for advanced melanoma in adults). Only 1 of the 13 subjects <12 years old achieved SD. Stable disease was achieved in 2 of 12 subjects with melanoma, and 9 of the 21 subjects with other types of solid tumors. Of 9 subjects with SD in subjects with non-melanoma solid tumors, 2 were unconfirmed.

Overall, stable disease was of short duration for most subjects. Stable disease >6 months duration was observed in 2 subjects. One subject with melanoma (7458-NCI-9) achieved a duration of SD for nearly 2 years (>22 months). The other subject had an unspecified solid tumor (7458-NCI-14) and although SD was achieved, disease progressed within 7 months.

In most cases of non-melanoma patients that achieved SD, SD was maintained for about 3 months or less, and for 3 of the 9 patients the duration of SD was < 2 months. For 4 of the 9 non-melanoma

subjects with SD, all 4 were discontinued due to an AE rather than disease progression and did not continue tumor assessment. Therefore, duration of SD could not be assessed for these subjects. Of note, many of the non-melanoma patients enrolled in the study were known with protracted disease course regardless of treatment.

Best overall responses other than SD were:

☐ PD (16 subjects; 7 of 13 subjects with melanoma, 9 of 21 subjects with non-melanoma, with study day of progression between Day 22 and Day 51);

☐ assessment not evaluable/performed (subjects had only 1 infusion); one melanoma patient died due to disease progression on Day 7 after start of treatment.

Conclusion according to the MAH: although no objective response was reported in any of the patients treated, 1 of 12 melanoma patients achieved durable stable disease, consistent with observation in adults. This supports further evaluation of ipilimumab in paediatric and adolescent melanoma patients. In view of the very limited activity observed in non-melanoma patients, considering also that drug exposure was adequate based on PK, no further evaluation of ipilimumab in this subsgroup of the population is warranted.

CHMP's comment

According to the data provided, no significant activity has been observed in patients with non-melanoma tumors. The limitations of the efficacy data presented, essentially related to the very limited number of patients enrolled in the different age groups, the heterogeneity of the cancer types and the different doses of ipilimumab administered, are acknowledged. However, we agree with the conclusion of the MAH that in absence of an efficacy signal despite the adequate PK exposure to study drug, further investigation of ipilimumab as monotherapy in paediatric non-melanoma patients should not be performed at this time.

Regarding the melanoma population, we agree that a signal of potential activity has been observed, as one melanoma patient (7458-NCI-9) achieved a duration of SD for nearly 2 years (>22 months). It should be noted that according to the data presented, this patient had age > 12 years and was treated with an ipilimumab dose of 5 mg/kg. According to the results of the CA184070 study the maximum ipilimumab dose tested in patients > 12 years old and considered to be tolerable was 10 mg/kg. The activity observed in the patient treated with 5 mg/kg, and therefore suggesting anti-tumor efficacy already at this dose, raises concerns over the appropriate dose to be use for further clinical testing in this patient subgroup, considering also that PK exposure was adequate also at ipilimumab doses < 10 mg/kg and that incidence and severity of adverse events appears to increase at higher dose of the drug.

It should be noted that in adult patients the currently recommended dose of ipilimumab is 3 mg/kg. Study CA184169 comparing efficacy and safety of ipilimumab 3 mg/kg vs 10 mg/kg in adult melanoma patients is currently ongoing. According to clinicaltrial.gov website the study has reached the planned accrual. The results of this study should be provided by the MAH as soon as available.

Similarly, the results of the CA184178 study (comparing efficacy and safety of ipilimumab 3mg/kg vs 10 mg/kg in paediatric (≥ 12 -≤ 18 years old) melanoma patients) are currently not available.

3. CHMP's overall conclusion

Study CA184070 (NCI7458) was a phase I, multi-center, dose escalation study, in order to evaluate safety, maximum tolerated dose and PK of ipilimumab in children and young adults (≤21 years old) with advanced solid tumors. Efficacy was evaluated as secondary endpoint. Of note, no children <2.4 years old were enrolled, therefore no data over efficacy and safety of ipilimumab are currently available in this subgroup of the paediatric population.

Overall, despite the limitations related to the low number of patients enrolled, the safety profile of ipilimumab as observed in this study appears in line with the known toxicity of the drug in adults. No new safety signals are observed in the paediatric population also in terms of irAEs. Nevertheless, as already observed in adults, the toxicity of the drug is substantial with several severe and life threatening AEs.

Moreover, the results of the study suggest different maximum tolerated doses of ipilimumab at different ages. In particular, in patients <12 years old the MTD of ipilimumab appears to be 5 mg/kg, whereas in patients ≥12 to ≤21 years old the maximum evaluated ipilimumab dose and reported to be tolerable is 10 mg/kg. However, the PK data show comparable drug exposure between the age cohorts of <12 and ≥12 years old, regardless of dose level and there is a signal of activity observed in a patient >12 years old treated with ipilimumab 5 mg/kg. These findings raise discussion over the appropriate dose to be used for further clinical testing in the melanoma paediatric population. Considering that in adult patients the currently recommended dose of ipilimumab is 3 mg/kg, it is regrettable that the results of the CA184169 and CA184178 studies (comparing efficacy and safety of ipilimumab 3 mg/kg vs 10 mg/kg in adults and paediatric (≥ 12 -≤ 18 years old) melanoma patients, respectively, are currently not available. The MAH should discuss when the results of these studies can be expected.

Finally, although the limitations of the efficacy data presented are acknowledged, the CHMP agreed with the MAH that, in absence of an efficacy signal despite the adequate PK exposure to study drug, further investigation of ipilimumab as monotherapy in paediatric non-melanoma patients seems not to be reasonable, at this time. If the MAH decides not to continue studying ipilimumab use in children below the age of 12 years, a modification of the currently approved Paediatric Investigational Program (PIP) should be applied with the PDCO.

A variation of the currently approved PIP after consultation with the PDCO is also recommended before continuing on other studies in paediatric population. At the time of the discussion with the PDCO (and within the following PSUR), the MAH should also present the results of studies CA184169 and/or CA184178 (comparing efficacy and safety of ipilimumab 3mg/kg vs 10 mg/kg in adults and paediatric (≥ 12 -≤ 18 years old) melanoma patients, respectively, or state the date when such results will be available.

In conclusion, the CHMP considered that the data presented do not affect the positive benefit/risk of ipilimumab and there is no need for modification of the SmPC at the time of this report.