Amsterdam, 20 May 2021
EMA/CHMP/125573/2021
Committee for Medicinal Products for Human Use (CHMP)

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

OPDIVO

nivolumab

Procedure no: EMEA/H/C/003985/P46/043

Yervoy

ipilimumab

Procedure no: EMEA/H/C/002213/P46/042

Note

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

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1. Introduction

On 18.12.2020 the MAH submitted a completed paediatric study for Opdivo (nivolumab) and Yervoy (ipilimumab), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study CA209915 encompass both products and therefore a single (integrated) assessment report for Opdivo/Yervoy is written.

2. Scientific discussion

2.1. Information on the development program

The approval of nivolumab for the adjuvant melanoma indication was based on the results of the CA209238 study, a Phase 3 randomized, double-blind study of nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV melanoma.

Based on data from Study CA209067, combination of nivolumab plus ipilimumab was approved as a first-line treatment option for patients with advanced melanoma.

As a result, Study CA209915 was designed to investigate whether nivolumab and ipilimumab combination treatment will improve RFS compared to nivolumab monotherapy (primary outcome) as adjuvant treatment in patients with completely resected Stage IIIb/c/d or Stage IV no evidence of disease (NED) melanoma. A total of 1844 adults and adolescents between 12 to <18 years of age were randomized to nivolumab + ipilimumab or nivolumab monotherapy in Study CA209915. Of these, 3 adolescent subjects were randomized and treated; 2 adolescents were treated with nivolumab monotherapy and 1 adolescent was treated with nivolumab + ipilimumab combination therapy.

In the overall population in Study CA209915, there was no evidence of improved efficacy for nivolumab + ipilimumab compared with nivolumab monotherapy in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma. No new safety signals were detected in this study.

No definitive conclusions can be drawn about the efficacy and safety of nivolumab + ipilimumab compared with nivolumab monotherapy in the population of adolescents (< 18 years) with completely resected Stage IIIb/c/d or Stage IV NED melanoma due to the small sample size (n=3). Therefore, no updates to the Product Information of OPDIVO or YERVOY are being proposed.

2.2. Information on the pharmaceutical formulation used in the study

Study participants were treated with one of the following:

- Arm A: nivolumab 240 mg IV Q2W plus ipilimumab 1 mg/kg IV Q6W (for 1 year of study drug treatment)
- Arm B: nivolumab 480 mg IV Q4W (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49

The original study design included an ipilimumab monotherapy treatment arm (Arm C). Randomization into Arm C was discontinued upon implementation of Amendment 06, after 99 subjects had been enrolled. No adolescent patient was treated with ipilimumab monotherapy.

For adolescents between 12 to <18 years of age, the dosing of nivolumab was based on body weight as follows: Q2W dosing - 3 mg/kg IV Q2W up to a maximum of 240 mg; Q4W dosing - 6 mg/kg Q4W up to a maximum of 480 mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study CA209915: a phase 3, randomized, double-blind study of nivolumab plus ipilimumab vs nivolumab monotherapy in participants (≥ 12 years) with completely resected Stage IIIb/c/d or Stage IV NED melanoma.

2.3.2. Clinical study

Study CA209915

A phase 3, randomized, double-blind study of nivolumab plus ipilimumab vs nivolumab monotherapy in participants (≥ 12 years) with completely resected Stage IIIb/c/d or Stage IV NED melanoma.

Description

Methods

Objectives

The primary objective of Study CA20915 was to compare the efficacy, as measured by recurrence-free survival (RFS), provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV NED melanoma (in all randomized participants with tumor PD-L1 expression level < 1% and all randomized participants).

Secondary objectives included:

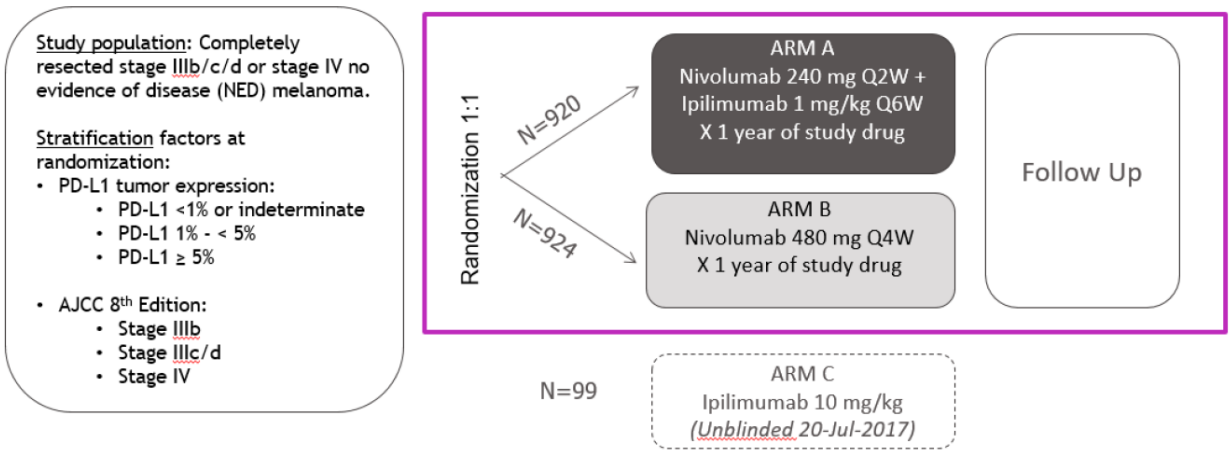
- To compare the OS provided by nivolumab plus ipilimumab versus nivolumab monotherapy in participants with completely resected stage IIIb/c/d or stage IV NED melanoma (in all randomized participants with tumor PD-L1 expression level < 1% and all randomized participants).
- To evaluate the association between PD-L1 expression and RFS.
- To evaluate investigator-assessed outcomes on next-line therapies.

Exploratory objectives include assessment of safety and tolerability, evaluation of distant metastasis-free survival (DMFS), Health Related Quality of Life, changes in health status and work productivity, associations between BRAF mutation status and clinical efficacy, the potential association of biomarkers with clinical efficacy and/or incidence of adverse events (AEs), assessment of effect of natural genetic variation in select genes on clinical endpoints and/or incidence of AEs, characterization of the pharmacokinetics and immunogenicity of nivolumab and ipilimumab, and exploration of exposure-response relationships with respect to safety and efficacy.

Study design

Study CA20915 was a randomized, double-blind study. The study design is outlined below.

The original study design included an ipilimumab monotherapy treatment arm (Arm C). Randomization into Arm C was discontinued upon implementation of Amendment 06, after 99 subjects had been enrolled. No adolescents were treated with ipilimumab monotherapy.



Study population /Sample size

A total of 1844 adults and adolescents between 12 to <18 years of age were randomized to nivolumab + ipilimumab or nivolumab monotherapy in Study CA209915. Of these, 3 adolescent subjects were randomized and treated.

Treatments

Study participants were treated with one of the following:

- Arm A: nivolumab 240 mg IV Q2W plus ipilimumab 1 mg/kg IV Q6W (for 1 year of study drug treatment)
- Arm B: nivolumab 480 mg IV Q4W (for 1 year of study drug treatment) with nivolumab placebo on Weeks 3, 7, 11, 15, 19, 23, 27, 31, 35, 39, 43, & 47 and ipilimumab placebo on Weeks 1, 7, 13, 19, 25, 31, 37, 43, & 49

For the 3 included adolescents between 12 to <18 years of age, the dosing of nivolumab was based on body weight as follows: Q2W dosing - 3 mg/kg IV Q2W up to a maximum of 240 mg; Q4W dosing - 6 mg/kg Q4W up to a maximum of 480 mg.

Outcomes/endpoints

The primary endpoint was recurrence free survival, in all randomized subjects and in all randomized subjects with tumor PD-L1 <1%.

Key secondary endpoint was OS.

Statistical Methods

The sample size of the study was based on a comparison of the RFS distribution between subjects randomized to nivolumab + ipilimumab and subjects randomized to nivolumab. RFS was evaluated for treatment effect using the following testing strategy: RFS was compared first in the all randomized subjects with tumor PD-L1 expression level < 1% subgroup with an alpha allocation of 0.03 (two-sided); and if significant (which was not considered to be the case per DMC recommendation in Nov-2019), the alpha allocated to this subgroup was to be recycled to the treatment comparison in the

overall population (all randomized subjects). For the comparison of RFS between nivolumab + ipilimumab and nivolumab in all randomized subjects with tumour PD-L1 expression level < 1%, at least 257 RFS events were required in the 2 treatment arms for a two-sided experiment-wise $\alpha = 0.03$ log-rank test to show a statistically significant difference in RFS between the treatment arms with at least 90.0% power when the average hazard ratio (HR) of the nivolumab + ipilimumab arm to the nivolumab arm was 0.65. Approximately 600 subjects with tumour PD-L1 expression level < 1% were planned to be randomized in a 1:1 ratio to nivolumab + ipilimumab and nivolumab monotherapy.

Results

Recruitment/ Number analysed

Of the 1844 subjects randomized to nivolumab + ipilimumab or nivolumab, 1833 (99.4%) were treated (916 with nivolumab + ipilimumab, 917 with nivolumab).

Baseline data

The demographic characteristics of the overall population are summarized in Table 1.

Table 1: Demographic characteristics of all randomized subjects

	Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W N = 920	Nivo 480 mg Q4W N = 924	Total N = 1844
AGE (YEARS)			
N	920	924	1844
MEAN	53.8	54.6	54.2
MEDIAN	55.0	55.0	55.0
MIN , MAX	16 , 89	15 , 88	15 , 89
Q1 , Q3	44.0 , 66.0	45.0 , 65.0	44.0 , 65.5
SD	14.6	13.7	14.2
AGE CATEGORIZATION (%)			
< 65	662 (72.0)	674 (72.9)	1336 (72.5)
>= 65 AND < 75	202 (22.0)	186 (20.1)	388 (21.0)
>= 75	56 (6.1)	64 (6.9)	120 (6.5)
>= 65	258 (28.0)	250 (27.1)	508 (27.5)
SEX (%)			
MALE	515 (56.0)	537 (58.1)	1052 (57.0)
FEMALE	405 (44.0)	387 (41.9)	792 (43.0)
RACE (%)			
WHITE	907 (98.6)	911 (98.6)	1818 (98.6)
BLACK OR AFRICAN AMERICAN	4 (0.4)	1 (0.1)	5 (0.3)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (0.1)	1 (<0.1)
ASIAN	3 (0.3)	5 (0.5)	8 (0.4)
OTHER	6 (0.7)	6 (0.6)	12 (0.7)
ETHNICITY (%)			
HISPANIC OR LATINO	22 (2.4)	22 (2.4)	44 (2.4)
NOT HISPANIC OR LATINO	359 (39.0)	376 (40.7)	735 (39.9)
NOT REPORTED	539 (58.6)	526 (56.9)	1065 (57.8)

Source: Table S.3.1.1 of the CA209915 CSR[1]

Of the overall population, 3 adolescent subjects were randomized and treated.

- Subject CA209-915-xx-xx, a 15-year old white male with PD-L1 status ≥ 5%, was randomized to nivolumab (nivo) at a site in Australia. This subject had been treated with wide local excision, resective surgery, and complete lymph node dissection prior to the study. This subject completed the treatment period.

- Subject CA209-915-xx-xx, a 16-year old white male with PD-L1 status < 1%, was randomized to nivolumab + ipilimumab (nivo+ipi) at a site in Italy. The subject had been treated with resective surgery and complete lymph node dissection prior to the study. This subject died of disease progression.
- Subject CA209-915-xx-xx, a 16-year old white female with PD-L1 status < 1%, was randomized to nivolumab (nivo) at a site in the UK. The subject had been treated with resective surgery and complete lymph node dissection prior to the study. This subject experienced disease recurrence after RFS of 11.2 months.

None of the adolescent subjects had received systemic cancer treatment or radiotherapy prior to the study.

The baseline disease characteristics of the 3 adolescent subjects are presented in Table 2.

Table 2: Baseline disease characteristics of adolescent subjects in Study CA209915

Unique Subject ID (Age/Sex/Race)	Time from Surgical Resection to Randomization (Weeks)	Completion Lymph Node Dissection	Equivocal Lymph Nodes Present	Tumor Origin	Location of Primary Tumor	Melanoma Subtype
CA209915-xx-xx (15/M/C)	6.4	YES	NO	RECURRENT	SKIN	CUTANEOUS
CA209915-xx-xx (16/M/C)	8.1	YES	NO	PRIMARY	LYMPH NODE	OTHER
CA209915-xx-xx (16/F/C)	10.1	YES	NO	PRIMARY	SKIN	CUTANEOUS

Unique Subject ID (Age/Sex/Race)	Disease Stage at Study Entry According to: IRT	Disease Stage at Study Entry According to: CRF (M-Status)	Tumor Thickness (mm)	Tumor Ulceration Status	Lymph Node Involvement	Total Number of Tumor-Involved Regional Lymph Nodes	Number of Clinically Occult Nodes/ Clinically Detected Nodes	Presence of In-Transit Satellite and/or Microsatellite Metastases
CA209915-xx-xx (15/M/C)	STAGE IIIB	STAGE IIIC	NO EVIDENCE OF PRIMARY MELANOMA	UNKNOWN	NOT REPORTED	2 - 3	NOT REPORTED/ 2 - 3	NOT APPLICABLE
CA209915-xx-xx (16/M/C)	STAGE IIIC/IIID	STAGE IIIC	>2.0-4.0	ABSENT	CLINICALLY DETECTED AND CLINICALLY OCCULT	>= 4	>= 4/ 1	NOT APPLICABLE
CA209915-xx-xx (16/F/C)	STAGE IIIC/IIID	STAGE IIIC	>2.0-4.0	PRESENT	CLINICALLY DETECTED ONLY	1	0/ 1	NOT APPLICABLE

Efficacy results

The primary study objectives of demonstrating improved RFS with nivolumab + ipilimumab vs nivolumab as adjuvant therapy in all randomized subjects or in all randomized subjects with tumour PD-L1 < 1% with completely resected stage IIIb/c/d or stage IV NED melanoma was not met. At this analysis, subjects were followed for a minimum of approximately 24 months (from 22-Jun-2018 [last subject randomization] to 12-Jun-2020 [data cutoff]).

<u>All randomized subjects:</u>

- Nivolumab + ipilimumab did not demonstrate a statistically significant and clinically meaningful improvement in the primary endpoint of RFS vs nivolumab (HR = 0.92 [97.295% CI: 0.77, 1.09]); stratified log-rank p = 0.26861).
- RFS results for nivolumab + ipilimumab vs nivolumab were similar across the baseline tumor PD-L1 expression level subgroups.
- There was no improvement in DMFS with nivolumab + ipilimumab vs nivolumab.

<u>All randomized subjects with tumor PD-L1 expression < 1%:</u>

- As per the 24 months exploratory follow-up RFS data analysis, the results in the PD-L1 < 1% population were consistent with those in the overall population (all randomized subjects). There was no improvement in RFS with nivolumab + ipilimumab vs nivolumab (HR = 0.91 [95% CI: 0.73, 1.14]).
- As per the DMC recommendation in Nov-2019, nivolumab + ipilimumab did not demonstrate a statistically significant improvement in the primary endpoint of RFS vs nivolumab.
- There was no improvement in DMFS with nivolumab + ipilimumab vs nivolumab.

Results for the primary and secondary efficacy endpoints for the overall population are summarized in Table 3.

Table 3: Summary of key efficacy results in all randomized subjects in CA209915

Efficacy Parameter	All Randomized		All Randomized with Tumor PD-L1 < 1%[a]	
	Nivolumab + Ipilimumab	Nivolumab	Nivolumab + Ipilimumab	Nivolumab
PRIMARY ENDPOINT				
Recurrence-free Survival (RFS)				
Events/number of subjects, (%)	327/920 (35.5)	347/924 (37.6)	159/349 (45.6)	166/351 (47.3)
Median RFS (95% CI)[b], months	N.A.	N.A.	33.18 (22.21, N.A.)	25.33 (19.81, N.A.)
HR (97.295% CI)[c]	0.92 (0.77, 1.09)		N.A.	
HR (95% CI)[c]	N.A.		0.91 (0.73, 1.14)	
Stratified log-rank p-value[d]	0.26861		-	
Rate at 12 months (95% CI)[b], %	74.3 (71.3, 77.1)	73.0 (69.9, 75.8)	66.6 (61.3, 71.4)	62.6 (57.2, 67.6)
Rate at 24 months (95% CI)[b], %	64.6 (61.3, 67.7)	63.2 (59.9, 66.4)	53.6 (48.0, 58.8)	52.4 (46.8, 57.7)
SECONDARY ENDPOINTS				
RFS by Baseline Tumor PD-L1 Expression[e]				
Subjects with < 1% Tumor PD-L1 Expression				
Events/number of subjects, (%)	159/350 (45.4)	166/350 (47.4)	N.A.	
Unstratified HR (95% CI)[f]	0.91 (0.73, 1.14).			
Median (95% CI)[b], months	33.18 (22.21, N.A.)	25.33 (19.81, N.A.)		
Subjects with ≥ 1% Tumor PD-L1 Expression				
Events/number of subjects, (%)	153/527 (29.0)	164/534 (30.7)	N.A.	
Unstratified HR (95% CI)[f]	0.95 (0.76, 1.18).			
Median (95% CI)[b], months	N.A.	N.A.		
Subjects with ≥ 5% Tumor PD-L1 Expression				
Events/number of subjects, (%)	76/300 (25.3)	79/303 (26.1)	N.A.	
Unstratified HR (95% CI)[f]	0.98 (0.71, 1.34)			
Median (95% CI)[b], months	N.A.	N.A.		
Subjects with < 5% Tumor PD-L1 Expression				
Events/number of subjects	236/577 (40.9)	251/581 (43.2)	N.A.	

Efficacy Parameter	All Randomized		All Randomized with Tumor PD-L1 < 1%[a]	
	Nivolumab + Ipilimumab	Nivolumab	Nivolumab + Ipilimumab	Nivolumab
Unstratified HR (95% CI)[f]	0.92 (0.77, 1.10)		N.A.	
Median (95% CI)[b], months	N.A. (31.18, N.A.)	N.A. (27.63, N.A.)	N.A.	
Subjects with Non-quantifiable Tumor PD-L1 Expression				
Events/number of subjects (%)	15/43 (34.9)	17/40 (42.5)	N.A.	
Unstratified HR (95% CI)[f]	0.76 (0.38, 1.51)			
Median (95% CI)[b], months	N.A. (22.41, N.A.)	N.A. (10.87, N.A.)		
PFS on Next Line Therapy (PFS2)				
Events/number of subjects (%)	185/920 (20.1)	185/924 (20.0)	89/349 (25.5)	92/351 (26.2)
Median (95% CI), months	N.A.	N.A.	N.A.	N.A. (35.94, N.A.)
Time to Next Therapy				
Events/number of subjects (%)	187/920 (20.3)	215/924 (23.3)	86/349 (24.6)	102/351 (29.1)
Median (95% CI), months	N.A.	N.A.	N.A.	N.A.
Time to Second Next Therapy				
Events/number of subjects (%)	81/920 (8.8)	81/924 (8.8)	35/349 (10.0)	46/351 (13.1)
Median (95% CI), months	N.A.	N.A.	N.A.	N.A.
Time from Next Therapy to Second Next Therapy				
Number of subjects	81	81	35	46
Median (min, max), months	4.60 (0.8, 23.7)	4.80 (0.0, 27.7)	4.44 (0.8 , 23.7)	5.04 (0.9 , 27.7)
EXPLORATORY ENDPOINTS **Distant Metastasis-free Survival (DMFS)** in subjects with Stage III disease at study entry				
Events/number of subjects (%)	195/797 (24.5)	194/798 (24.3)	92/305 (30.2)	96/307 (31.3)
Median DMFS (95% CI)[b], months	N.A.	N.A.	N.A. (33.18, N.A.)	N.A. (33.35, N.A.)
HR (95% CI)[c]	1.01 (0.83, 1.23)		0.94 (0.70, 1.25)	
Rate at 12 months % (95% CI)	83.9 (81.1, 86.4)	87.2 (84.5, 89.3)	81.5 (76.4, 85.5)	81.2 (76.1, 85.3)
Rate at 24 months % (95% CI)	75.4 (72.1, 78.4)	77.4 (74.1, 80.3)	67.9 (61.9, 73.1)	68.4 (62.5, 73.7)

[a] PD-L1 tumor expression based on IRT.

[b] Based on Kaplan-Meier estimates.

[c] Stratified Cox proportional hazards model. HR is nivolumab over ipilimumab.

[d] Log-rank test stratified by tumor PD-L1 status and disease stage at study entry as entered into the IRT.

[e] PD-L1 tumor expression based on clinical database.

[f] Nivolumab over ipilimumab.

The efficacy results in the adolescent subjects are summarized briefly below.

- Subject **CA209-915-xx-xx**, who was randomized to nivolumab, was censored at 30.4 months in the follow-up period (data cutoff) and had no recurrence of disease.
- Subject **CA209-915-xx-xx**, who was randomized to nivolumab + ipilimumab, had a RFS of 16.9 months, and a PFS2 of 17.2 months.
- Subject **CA209-915-xx-xx**, who was randomized to nivolumab, had a RFS of 11.2 months, and a PFS2 of 27.2 months.

The data on RFS (Table 4), PD-L1 expression (Table 5), PFS on next-line systemic therapy (Table 6) and subsequent anticancer therapies (Table 7) in the 3 included adolescents are listed below.

Table 4: Recurrence-free survival in adolescent subjects in study CA209915

Unique Subject ID (Age/Sex/Race)	Randomization Date	First/Last Dose Date	Event/Censored Date	Event Occurred	Event/Censoring Status	RFS (Months)	Subsequent Therapy Date	Second Non-Melanoma Primary Cancer Date
CA209915-xx-xx (15/M/C)	23OCT2017	24OCT2017/ 25SEP2018	05MAY2020	NO	IN FOLLOW-UP	30.4		
CA209915-xx-xx (16/M/C)	05MAR2018	06MAR2018/ 11DEC2018	01AUG2019	YES	DISTANT METASTASIS	16.9	07AUG2019	
CA209915-xx-xx (16/F/C)	02MAR2018	05MAR2018/ 11FEB2019	06FEB2019	YES	REGIONAL RECURRENCE	11.2	13MAR2019	

Table 5: All PD-L1 IHC data in adolescent subjects in study CA209915

Unique Subject ID (Age/Sex/Race)	Tumor Specimen Collection Date/ Time	Collection Method	Tumor Specimen Site	Metastasis Site	Assessment Date/ Time	Number of Viable Tumor Cells	PD-L1 Expression Result (%)	Immune Cells Present
CA209915-xx-xx (15/M/C)	08SEP2017		METASTATIC	OTHER	12OCT2017/ 22:50	>=100	20(*)	YES
CA209915-xx-xx (16/M/C)	27NOV2017		METASTATIC	OTHER	08FEB2018/ 15:53	>=100	0(*)	YES
CA209915-xx-x (16/F/C)	22DEC2017		METASTATIC	LYMPH NODE	13FEB2018/ 12:45	>=100	0(*)	YES

Table 6: Progression-free survival on next-line systemic therapy in adolescent subjects in study CA209915

			Primary Definition			Secondary Definition		
Unique Subject ID (Age/Sex/Race)	Randomization Date	First/Last Dose Date	PFS (Months)	Event or Censored/ Date	Event or Censoring Status	PFS (Months)	Event or Censored/ Date	Event or Censoring Status
CA209915-xx-xx (15/M/C)	23OCT2017	24OCT2017/ 25SEP2018	30.4	CENSORED/ 05MAY2020	NO NEXT-LINE SYSTEMIC THERAPY AND NO DEATH	30.4	CENSORED/ 05MAY2020	NO NEXT-LINE SYSTEMIC THERAPY AND NO DEATH
CA209915-xx-xx (16/M/C)	05MAR2018	06MAR2018/ 11DEC2018	17.2	EVENT/ 11AUG2019	END OF NEXT-LINE SYSTEMIC THERAPY	17.2	EVENT/ 11AUG2019	END OF NEXT-LINE SYSTEMIC THERAPY
CA209915-xx-xx (16/F/C)	02MAR2018	05MAR2018/ 11FEB2019	27.2	EVENT/ 05JUN2020	END OF NEXT-LINE SYSTEMIC THERAPY	27.2	EVENT/ 05JUN2020	END OF NEXT-LINE SYSTEMIC THERAPY

Table 7: Subsequent systemic cancer therapy in adolescent subjects in study CA209915

Unique Subject ID (Age/Sex/Race)	First/Last Dose	Visit	Regimen Number / Regimen Setting / Line of Therapy	Start/Stop FU Therapy	FU Therapy Specification	Best Response / Progression (Y/N) - Date / Reason for Discontinuation
CA209915-xx-xx (16/M/C)	06MAR2018/ 11DEC2018	OFF-TREATMENT	1 METASTATIC FIRST LINE	07AUG2019/ 11AUG2019	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS TEMOZOLOMIDE TEMOZOLOMIDE	UNABLE TO DETERMINE DEATH
CA209915-xx-xx (16/F/C)	05MAR2018/ 11FEB2019	FOLLOW-UP 1	1 ADJUVANT NOT APPLICABLE	29APR2019/ 05JUN2020	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS DABRAFENIB DABRAFENIB	COMPLETE RESPONSE COMPLETED TREATMENT
	05MAR2018/ 11FEB2019		1 ADJUVANT NOT APPLICABLE	29APR2019/ 05JUN2020	ANTINEOPLASTIC & IMMUNOMODULATING AGENT ANTINEOPLASTIC AGENTS TRAMETINIB TRAMETINIB	COMPLETE RESPONSE COMPLETED TREATMENT

Safety results

As of the 08-Sep-2020 database lock (minimum follow-up: ~24 months), the safety profiles of nivolumab 240 mg Q2W + ipilimumab 1 mg/kg Q6W and nivolumab monotherapy (480 mg Q4W) in all treated subjects with completely resected Stage IIIb/c or Stage IV melanoma (Table 8) were consistent with those in other tumor types, with no new safety signals. In summary:

- In total, 4 deaths were attributed to study drug toxicity (liver failure, myasthenia gravis, respiratory distress syndrome and pneumonitis) by the investigator, all in the nivolumab + ipilimumab group.
- The overall frequencies of all-causality SAEs and drug-related SAEs (any grade and Grade 3-4) were higher in the nivolumab + ipilimumab group than in the nivolumab group.
- The overall frequencies of all-causality and drug-related AEs leading to discontinuation (any grade and Grade 3-4) were higher in the nivolumab + ipilimumab group than in the nivolumab group.
- The overall frequencies of any-grade AEs were similar in the nivolumab + ipilimumab and nivolumab treatment groups. The frequencies of Grade 3-4 AEs and drug-related AEs were higher in the nivolumab + ipilimumab group than in the nivolumab group. However, Grade 3-4 events were uncommon.
- In both treatment groups, most subjects with immune-mediated AEs (IMAEs) within the categories of rash, pneumonitis, hypersensitivity, nephritis and renal dysfunction, and endocrine, experienced Grade 1-2 events. However, there was more Grade 3-4 vs Grade 1-2 immune related diarrhea/colitis and hepatitis in the nivolumab + ipilimumab group. The majority of IMAEs resolved and were manageable using the recommended treatment guidelines for early work-up and intervention.
- In both treatment groups, most subjects with select AEs experienced Grade 1-2 events. Select AEs, including those that were severe (Grade 3-4), were manageable using the established algorithms. Except for endocrine events, most drug-related select AEs in both treatment groups had resolved at the time of database lock. Some endocrine AEs were not considered resolved due to the continuing need for hormone replacement therapy.
- Abnormalities in hematology laboratory results, liver tests, kidney function tests, and electrolytes in subjects treated with nivolumab + ipilimumab or nivolumab were primarily Grade 1 or 2.
- Nivolumab and ipilimumab ADA development did not appear to have an effect on the safety or

efficacy of nivolumab + ipilimumab combination treatment or nivolumab monotherapy treatment.

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Table 8: Summary of safety results - all treated subjects

	Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W N = 916		Nivo 480 mg Q4W N = 917	
DEATHS	101 (11.0)		99 (10.8)	
WITHIN 30 DAYS OF LAST DOSE	5 (0.5)		3 (0.3)	
WITHIN 100 DAYS OF LAST DOSE	13 (1.4)		4 (0.4)	
DUE TO STUDY DRUG TOXICITY	4 (0.4)		0	
	Any Grade	**Grade 3-4**	**Any Grade**	**Grade 3-4**
ALL CAUSALITY SAEs	308 (33.6)	208 (22.7)	185 (20.2)	109 (11.9)
DRUG-RELATED SAEs	198 (21.6)	145 (15.8)	66 (7.2)	46 (5.0)
ALL CAUSALITY AEs LEADING TO DC	310 (33.8)	185 (20.2)	108 (11.8)	62 (6.8)
DRUG-RELATED AEs LEADING TO DC	289 (31.6)	173 (18.9)	95 (10.4)	54 (5.9)
ALL-CAUSALITY AEs	903 (98.6)	391 (42.7)	888 (96.8)	211 (23.0)
Most Frequent AEs (≥ 20% of Any Grade in either treatment group)				
FATIGUE	339 (37.0)	11 (1.2)	334 (36.4)	3 (0.3)
PRURITUS	336 (36.7)	2 (0.2)	236 (25.7)	1 (0.1)
DIARRHOEA	333 (36.4)	24 (2.6)	300 (32.7)	8 (0.9)
HEADACHE	266 (29.0)	3 (0.3)	207 (22.6)	1 (0.1)
RASH	256 (27.9)	8 (0.9)	231 (25.2)	9 (1.0)
NAUSEA	214 (23.4)	2 (0.2)	180 (19.6)	1 (0.1)
HYPOTHYROIDISM	209 (22.8)	2 (0.2)	136 (14.8)	1 (0.1)
HYPERTHYROIDISM	183 (20.0)	4 (0.4)	98 (10.7)	0
ARTHRALGIA	142 (15.5)	8 (0.9)	186 (20.3)	5 (0.5)
DRUG-RELATED AEs	863 (94.2)	299 (32.6)	788 (85.9)	117 (12.8)
Most Frequent Drug-related AEs (≥15% of Any Grade in either treatment group)				
PRURITUS	303 (33.1)	2 (0.2)	194 (21.2)	0
FATIGUE	279 (30.5)	10 (1.1)	276 (30.1)	2 (0.2)
DIARRHOEA	248 (27.1)	22 (2.4)	187 (20.4)	5 (0.5)
RASH	222 (24.2)	5 (0.5)	192 (20.9)	6 (0.7)
HYPOTHYROIDISM	202 (22.1)	2 (0.2)	133 (14.5)	1 (0.1)
HYPERTHYROIDISM	178 (19.4)	4 (0.4)	93 (10.1)	0
ALL-CAUSALITY SELECT AEs, BY CATEGORY				
SKIN	543 (59.3)	15 (1.6)	482 (52.6)	20 (2.2)
ENDOCRINE	416 (45.4)	40 (4.4)	244 (26.6)	14 (1.5)
GASTROINTESTINAL	366 (40.0)	65 (7.1)	313 (34.1)	17 (1.9)
HEPATIC	217 (23.7)	75 (8.2)	125 (13.6)	15 (1.6)
HYPERSENSITIVITY/INFUSION REACTIONS	77 (8.4)	2 (0.2)	59 (6.4)	2 (0.2)
RENAL	45 (4.9)	5 (0.5)	48 (5.2)	4 (0.4)
PULMONARY	35 (3.8)	6 (0.7)	14 (1.5)	1 (0.1)
DRUG-RELATED SELECT AEs, BY CATEGORY				
SKIN	489 (53.4)	12 (1.3)	402 (43.8)	13 (1.4)
ENDOCRINE	408 (44.5)	40 (4.4)	233 (25.4)	14 (1.5)
GASTROINTESTINAL	284 (31.0)	63 (6.9)	201 (21.9)	13 (1.4)
HEPATIC	190 (20.7)	72 (7.9)	109 (11.9)	13 (1.4)
HYPERSENSITIVITY/INFUSION REACTIONS	73 (8.0)	2 (0.2)	51 (5.6)	2 (0.2)
RENAL	21 (2.3)	3 (0.3)	22 (2.4)	2 (0.2)
PULMONARY	33 (3.6)	6 (0.7)	13 (1.4)	1 (0.1)
ALL-CAUSALITY IMMUNE-MEDIATED ADVERSE EVENTS WITHIN 100 DAYS OF LAST DOSE, BY CATEGORY				
Immune-mediated AEs Treated with Immune-modulating medication				
RASH	179 (19.5)	12 (1.3)	135 (14.7)	13 (1.4)
DIARRHEA/COLITIS	131 (14.3)	73 (8.0)	55 (6.0)	24 (2.6)
HEPATITIS	91 (9.9)	69 (7.5)	25 (2.7)	13 (1.4)
PNEUMONITIS	33 (3.6)	7 (0.8)	15 (1.6)	2 (0.2)
HYPERSENSITIVITY	27 (2.9)	2 (0.2)	16 (1.7)	2 (0.2)
NEPHRITIS AND RENAL DYSFUNCTION	8 (0.9)	4 (0.4)	11 (1.2)	4 (0.4)

	Nivo 240 mg Q2W + Ipi 1 mg/kg Q6W N = 916		Nivo 480 mg Q4W N = 917	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Immune-Mediated Endocrine AEs Treated with or without Immune-Modulating Medications				
HYPOTHYROIDISM/THYROIDITIS	231 (25.2)	6 (0.7)	146 (15.9)	2 (0.2)
HYPERTHYROIDISM	170 (18.6)	4 (0.4)	97 (10.6)	0
HYPOPHYSITIS	119 (13.0)	29 (3.2)	20 (2.2)	7 (0.8)
ADRENAL INSUFFICIENCY	59 (6.4)	10 (1.1)	9 (1.0)	0
DIABETES MELLITUS	7 (0.8)	2 (0.2)	9 (1.0)	8 (0.9)
ALL-CAUSALITY OESI Within 100 Days of LAST DOSE WITH OR WITHOUT IMMUNE MODULATING MEDICATION				
PANCREATITIS	18 (2.0)	5 (0.5)	9 (1.0)	6 (0.7)
ENCEPHALITIS	6 (0.7)	4 (0.4)	2 (0.2)	2 (0.2)
MYOSITIS/RHABDOMYOLYSIS	5 (0.5)	0	2 (0.2)	1 (0.1)
MYASTHENIC SYNDROME	3 (0.3)	2 (0.2)	1 (0.1)	1 (0.1)
DEMYELINATION	0	0	0	0
GUILLAIN-BARRE SYNDROME	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)
UVEITIS	3 (0.3)	1 (0.1)	5 (0.5)	0
MYOCARDITIS	4 (0.4)	3 (0.3)	0	0
GRAFT VERSUS HOST DISEASE	0	0	0	0

MedDRA Version: 23.0 CTC Version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Safety in the 3 adolescent subjects is summarized below. By-subjects listings of death and SAEs are included in Table 9 and Table 10, respectively.

- Subject **CA209-915-xx-xx**, who was randomized to nivolumab, reported few AEs and no SAEs. All reported AEs were CTC Grade 1, and only 1 AE of nausea was considered related to study treatment.
- Subject **CA209-915-xx-xx**, who was randomized to nivolumab + ipilimumab, reported SAEs of thrombocytopenia on day 364 and Pneumocystis Jirovecii pneumonia on day 417. None of these SAEs was considered related to study treatment. This subject received 16 doses of nivolumab and 6 doses of ipilimumab. The subject died from disease progression on 26-Aug-2019.
- Subject **CA209-915-xx-xx**, who was randomized to nivolumab, reported the following AEs that were assessed as being related to study treatment: anorexia, fatigue, low TSH, weight loss, alopecia, and lipase increased. Two AEs (wound infection and wound dehiscence) were CTC Grade 3. All other AEs were CTC Grade 1 or 2. The subject reported no SAEs.

Table 9: Deaths in adolescent subjects in study CA209915

Unique Subject ID (Age/Sex/Race)	Randomization Date	First Dose Date	Last Dose Date	Death Date	Days Since Last Dose	CRF Source	Cause of Death	Specify
CA209915-xx-xx (16/M/C)	05MAR2018	06MAR2018	11DEC2018	26AUG2019	259	DEATH	DISEASE	

Deaths may be captured on death, adverse event, ECOG performance status, status and follow-up case report form pages. The primary source of Death date is the death case report form. If the date is missing, the death date reported on the adverse event case report form is reported.
A=Asian; B=Black/African American; C=White; I=American Indian/Alaska Native; O=Other; P=Native Hawaiian/Other Pacific Islander.

Table 10: Serious adverse events in adolescent subjects in study CA209915

Unique Subject ID (Age/Sex/Race)	Current Trt Period Visit	Onset D/T Resolution D/T Study Day	Dur TRD Type	System Organ Class Preferred Term	REL CTC	TRT ACT
CA209915-xx-xx (16/M/C)	ENDED TREATMENT 30-100 DAYS FOLLOW-UP ON TREATMENT WEEK 31	04MAR2019/16:00 07MAR2019 364	3D 83D SAE	Blood and lymphatic system disorders Thrombocytopenia THROMBOCYTOPENIA	5 3	1 1
	ENDED TREATMENT POST 100 DAYS FOLLOW-UP ON TREATMENT WEEK 31	26APR2019 02MAY2019 417	7D 136D SAE	Infections and infestations Pneumocystis jirovecii pneumonia PNEUMOCISTIS JIROVECII PNEUMONIA	5 2	1 1

REL (RELATIONSHIP): 5 = NOT RELATED 6 = RELATED; TRT (TREATMENT REQUIRED): 0 = NO 1 = YES
CTC (COMMON TERMINOLOGY CRITERIA): 1 = GRADE 1 2 = GRADE 2 3 = GRADE 3 4 = GRADE 4 5 = GRADE 5
ACT (ACTION): 1 = DOSE NOT CHANGED 2 = DOSE REDUCED 3 = DOSE INCREASED 4 = DOSE DELAYED 5= DRUG INTERRUPTED 6 = DRUG WITHDRAWN
DUR (DURATION OF EVENT)/ TRD (TIME RELATIVE TO MOST RECENT DOSE): D = DAYS H = HOURS M = MINUTES S = SECONDS
MedDRA Version: 23.0 ; CTC Version 4.0

2.3.3. Discussion on clinical aspects

The MAH submitted the final CSR for study CA209915 as part of this Article 46 procedure, because 3 adolescent patients were included in this phase 3 study. These adolescent patients were treated with nivolumab monotherapy (n=2) or nivolumab + ipilimumab combination therapy (n=1) in the adjuvant setting for melanoma.

Nivolumab as monotherapy is currently indicated for the adjuvant treatment of completely resected stage IIIb/c or IV melanoma in adults. It is also indicated in adults for treatment of inoperable or metastatic disease, as monotherapy or in combination with ipilimumab. Nivolumab is not indicated for patients <18 years of age in any setting.

Ipilimumab as monotherapy is indicated for treatment of inoperable or metastatic melanoma in patients from 12 years of age.

The phase 3 study CA209915 did not meet its primary endpoint, with no statistically significant difference in RFS between the control arm of nivolumab monotherapy and the intervention arm of nivolumab + ipilimumab combination therapy. Therefore, an indication for nivolumab + ipilimumab as adjuvant melanoma treatment, either in adults or children >12 years of age, has not been applied for and is not foreseen.

Nivolumab currently is not indicated in the paediatric population and it is not expected that it is currently used in clinical practice in the adjuvant setting of melanoma treatment in paediatric patients. No firm conclusion on (lack of) efficacy can be drawn from the data submitted in the current procedure, because only 3 adolescent patients were included in study CA209915. Inclusion of the data of these 3 patients in the SmPC is not considered clinically relevant nor informative for the prescriber, from an efficacy point of view, at this time.

Of note, the indication for ipilimumab in adolescents with advanced melanoma was based on extrapolation of data in the adult population and the result of PK-studies. The MAH has provided information on the development plan and the ongoing activities for nivolumab in the paediatric population with advanced melanoma. One clinical study studying nivolumab monotherapy or nivolumab+ipilimumab combination therapy has completed accrual and study completion is expected in December 2021. A PK modelling and simulation study will use data from this clinical study to propose dosing recommendations for nivolumab monotherapy and nivolumab+ipilimumab combination therapy in adolescents with advanced melanoma (expected completion date February 2022). If the MAH intends (in the future) to submit an application for nivolumab monotherapy or nivolumab+ipilimumab combination therapy in the paediatric population, the company is strongly recommended to request CHMP Scientific Advice before submission.

In the event an application for nivolumab monotherapy or nivolumab+ipilimumab combination therapy in the paediatric population would be submitted, the relevance of the currently submitted study for the

applied indication, and by that inclusion of the obtained (PK, efficacy or safety) results into the SmPC should be reconsidered.

No new safety signals were reported from study CA209915, for the included population as a whole or for the 3 adolescent subjects. Therefore, also from a safety perspective, inclusion of the data in the SmPC is also not considered necessary at this time.

The MAH proposes not to amend the SmPC of Opdivo or Yervoy based on the submitted results, this is supported.

3. Overall conclusion and recommendation

It is agreed with the MAH that no efficacy conclusion for the paediatric population can be drawn from the results of the 3 adolescents subjects included in study CA209915, and also that no new safety concerns arise.

Nivolumab is not indicated in the paediatric population, and ipilimumab is not indicated in the adjuvant melanoma setting. Either nivolumab as monotherapy or nivolumab+ipilimumab as combination therapy are not registered, recommended or expected to be used as adjuvant melanoma treatment in clinical practice in paediatric patients.

Therefore, inclusion of the submitted data in the SmPC is not considered informative nor necessary at this time.

In the future, interaction with regulatory authorities on the dossier before an application for nivolumab monotherapy or nivolumab+ipilimumab combination therapy in the paediatric population is submitted, is strongly encouraged. If such an application would take place, the inclusion of the data submitted as part of the current procedure should be reconsidered.

☒ Fulfilled:

No regulatory action required.

MAH responses to Request for supplementary information

QUESTION 1

The MAH is asked to provide information on the development plan and the ongoing activities for nivolumab in the paediatric population with advanced melanoma.

RESPONSE

BMS is fully committed to the paediatric development of nivolumab, including for advanced melanoma. As part of the agreed nivolumab Paediatric Investigation Plan (PIP) for the treatment of all conditions included in the category of malignant neoplasms, except nervous system, haematopoietic and lymphoid tissue, (PIP ref. EMEA-001407-PIP01-12-M03, latest EMA decision P/0432/2020, dated 05 November 2020), the 2 following studies are ongoing:

- **Study 2 (CA209070**): Open-label, multi-centre trial to evaluate pharmacokinetics, pharmacodynamics, toxicity, safety, and anti-cancer activity of nivolumab and of nivolumab in combination with ipilimumab in paediatric patients from 1 year to < 18 years of age with a refractory or relapsed malignant solid tumour, including advanced melanoma. This study has an expansion phase evaluating nivolumab in paediatric patients from 1 year to < 18 years of

age (and adults) with a refractory or relapsed malignant solid tumour such as Ewing sarcoma, osteosarcoma, rhabdomyosarcoma, and neuroblastoma. In this study and in the expansion phase, patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

Estimated date of completion: December 2021.

- **Study 4**: Study to generate paediatric dosing recommendation for nivolumab alone and in combination with ipilimumab.

  Date of completion: February 2022.

Study 2 (CA209070) completed accrual in March 2020. Available data from nivolumab monotherapy cohorts have been published.[1] BMS is actively working with the Sponsor of Study CA209070 to obtain the full data from the trial in order to conduct a complete assessment of the results and prepare the corresponding Clinical Study Report.

With regards to Study 4 (modelling and simulation measure), BMS will work on the model once the data from CA209070 are available, and a report will be prepared according to the agreed completion date indicated in the PIP.

The applicant wants to bring to your attention that a consensus review conference on checkpoint inhibition in paediatric patients consisting of academics, family/foundation representatives, industry and members from both the EMA and FDA was recently published.[2] Based on the limited activity identified to date, there was "collective agreement that there is no scientific rationale for children to be enrolled in new monotherapy trials of additional checkpoint inhibitors with the same mechanism of action of agents already studied (eg, anti-PD1, anti-PDL1, anti- CTLA-4) unless additional scientific knowledge supporting a different approach becomes available. This shared perspective, based on scientific evidence and supported by paediatric oncology cooperative groups, should inform companies on whether a paediatric development plan is justified."

Therefore, once the totality of data is available, any potential new indication in the paediatric population will be subject to a health authority interaction to agree on the dossier content to support a benefit/risk evaluation of nivolumab and/or nivolumab in combination with ipilimumab in the treatment of paediatric patients with advanced melanoma.

REFERENCES

1. Davis KL, Fox E, Merchant MS, et al. Nivolumab in children and young adults with relapsed or refractory solid tumours or lymphoma (ADVL1412): a multicentre, open-label, single-arm, phase 1–2 trial. Lancet Oncol 2020;21:541-50.

2. Pearson ADJ, Rossig C, Lesa G, et al. ACCELERATE and European Medicines Agency Paediatric Strategy Forum for medicinal product development of checkpoint inhibitors for use in combination therapy in paediatric patients. European Journal of Cancer 2020;127:52-66.

Assessor's comment

The Applicant has provided information on the development plan for nivolumab in the paediatric population. One clinical study of nivolumab monotherapy or nivolumab+ipilimumab combination therapy has completed accrual and study completion is expected in December 2021. The second study is a modelling and simulation study that will use the data from the clinical study to (as one of the objectives) provide dosing recommendations for nivolumab monotherapy and nivolumab+ipilimumab combination therapy in adolescents.

The recent consensus document on immunotherapy trials in the paediatric population is acknowledged – and interaction with regulatory authorities on the dossier before an application for nivolumab monotherapy or nivolumab+ipilimumab combination therapy in the paediatric population is submitted, is strongly encouraged.

The provided information on the development plan for nivolumab in the paediatric population does not change the conclusion of the current assessment – no changes to the SmPC of Opdivo or Yervoy are currently warranted.

In the future, if there would be an application for an indication for nivolumab monotherapy or nivolumab+ipilimumab combination therapy in the paediatric population, the inclusion of the data submitted as part of the current procedure should be reconsidered.