![European Medicines Agency — Science Medicines Health]

24 June 2021
EMA/400368/2021
Human Medicines Division

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

Opdivo

nivolumab

EMEA/H/C/003985/P46/045

Yervoy

ipilimumab

EMEA/H/C/002213/P46/043

Note

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

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1. Introduction

On 8 April 2021 the MAH submitted a completed paediatric study for nivolumab and ipilimumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study CA209908 is part of the agreed nivolumab Paediatric Investigation Plan (PIP) covering the conditions of treatment of malignant neoplasms of lymphoid tissue and treatment of malignant neoplasms of the CNS (PIP number EMEA-001407-PIP02-15-M05; latest EMA Decision P/0237/2021, dated 14-Jun-2021).

Study CA209908 is also part of the ipilimumab Risk Management Plan (RMP) to report long-term safety data in paediatric patients in studies of nivolumab and ipilimumab combination therapy.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study CA209908 is a stand-alone study.

At the time of study design and initiation for CA209908, nivolumab and nivolumab in combination with ipilimumab were being investigated in adult patients with glioblastoma multiforme (GBM) in Studies CA209143, CA209498, and CA209548 (results not yet published) although no survival benefit has been observed.

Neither nivolumab nor ipilimumab are presently approved for adult or paediatric patients in malignancies of the CNS. Ipilimumab is approved for paediatric use in the following indication: as monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults, and adolescents 12 years of age and older.

At the time of study design and initiation of CA209908, there was limited data available regarding the use of immune-checkpoint inhibitors (ICIs) in paediatric subjects, although preliminary phase 1/2 studies had demonstrated acceptable safety and tolerability of nivolumab and ipilimumab in childhood malignancies other than CNS. The research hypothesis for Study CA209908, therefore, aimed to investigate whether treatment with nivolumab monotherapy or nivolumab combined with ipilimumab would be safe and have clinical activity in paediatric subjects with primary high grade CNS tumours, which are almost uniformly fatal, with limited therapeutic options, and pose a high unmet medical need.

2.2. Information on the pharmaceutical formulation used in the study

The selection of the monotherapy dose of 3 mg/kg nivolumab and combination dose of 3mg/kg nivolumab + 1 mg/kg ipilimumab was primarily justified by the benefit/risk profile obtained with these regimens in adult clinical studies. Nivolumab and ipilimumab are both administered as intravenous infusion.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

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- Study CA209908: an open-label, sequential-arm, Phase 1b/2 clinical study of nivolumab monotherapy and nivolumab + ipilimumab in paediatric subjects with high-grade primary central nervous system (CNS) malignancies.

2.3.2. Clinical study

Study CA209908: an open-label, sequential-arm, Phase 1b/2 clinical study of nivolumab monotherapy and nivolumab + ipilimumab in paediatric subjects with high-grade primary central nervous system (CNS) malignancies.

Description

CA209908 is an open-label, sequential-arm, Phase 1b/2 clinical study of nivolumab monotherapy and nivolumab + ipilimumab combination therapy in paediatric subjects with high-grade primary CNS malignancies, including diffuse intrinsic pontine glioma (DIPG), high-grade glioma (HGG), medulloblastoma, ependymoma, and uncommon malignant tumours (pineoblastoma, atypical teratoid/rhabdoid tumour [AT/RT], and embryonal CNS tumours).

This study includes 5 cohorts (Cohorts 1-5) and 2 modules (Modules A and B) in each cohort.

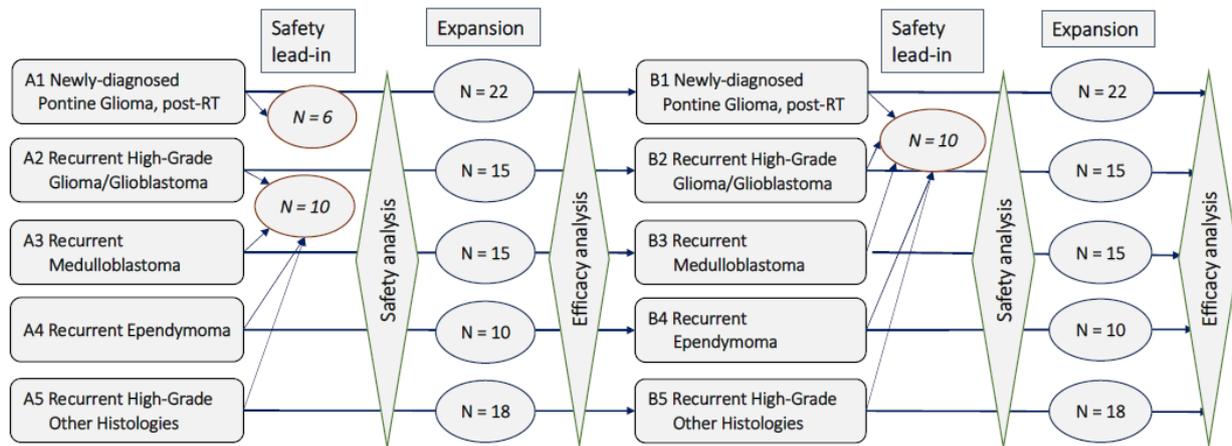The study design is visualized in Figure 1.

Cohorts are defined by tumour type (histology):

- Cohort 1: subjects with newly-diagnosed DIPG, including midline glioma with H3K27M mutation

- Cohort 2: subjects with recurrent or progressive non-brainstem HGG, regardless of mutation status, including glioblastoma

- Cohort 3: subjects with relapsed or resistant medulloblastoma

- Cohort 4: subjects with relapsed or resistant ependymoma

- Cohort 5: subjects with other recurrent or progressive subtypes of high-grade CNS malignancy (eg, pineoblastoma, AT/RT, germ cell tumour, and others)

Treatments are defined by Module:

- Module A: nivolumab monotherapy

- Module B: nivolumab + ipilimumab

Figure 1: Study design for CA209908

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Notes:
- Cohorts are indicated by tumor type; Study Treatments are indicated as A = nivolumab and B = nivolumab + ipilimumab
- Safety is evaluated *across* cohorts (indicated as "lead-in"), prior to expansion
- Efficacy is evaluated *by* cohort (indicated as Expansion), including lead-in population
- Module B opens, by cohort, when corresponding Module A is completed or upon decision of Steering Committee

The primary CSR for CA209908 provides results from the pre-specified final analyses of the primary endpoints, secondary endpoints, and a subset of exploratory endpoints, at a database lock (DBL) of 13-Jan-2021.

Study CA209908 remains ongoing until completion of the follow-up phase for all subjects, including observations at least 100 days after the last dose for safety and a minimum of 3 years for survival; final analysis will be planned upon study completion.

There were 4 subjects < 18 years old remaining on study treatment at the time of the DBL.

Methods

Objective(s)

The primary objectives of the study include the estimation of the safety and tolerability of study treatment in a safety lead-in phase across cohorts, overall survival (OS) in Cohort 1, and progression-free survival (PFS) in Cohorts 2-5.

Study design

The study had an open-label, sequential arm design.

CA209908 consisted of a safety lead-in phase and expansion phase. A safety lead-in phase across cohorts was implemented prior to the expansion phase, because nivolumab, as monotherapy or immediately after radiation therapy (RT) or in combination with ipilimumab, had not been previously studied in paediatric subjects with CNS tumours.

Enrolment to Module A (nivolumab monotherapy) opened in parallel for all cohorts. The first 6 subjects in Cohort 1 treated and dose-limiting toxicity (DLT)-evaluable were to be evaluated for safety before additional subjects would be treated in that cohort. Separately, the first 10 subjects treated and DLT-evaluable in the recurrent disease Cohorts 2-5 were to be evaluated for safety before additional subjects would be treated in those cohorts.

Based on determination of adequate safety, enrolment re-opened for evaluation of efficacy to complete the planned number of subjects for each cohort in Module A (nivolumab monotherapy) expansion. Subjects evaluated in the safety lead-in were included for evaluation of efficacy.

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Enrolment began in Module B (nivolumab + ipilimumab), by cohort, based on completion of planned accrual in Module A or a decision of the Study Steering Committee (SSC). For Module B, the first 10 subjects treated and DLT-evaluable in all cohorts combined were to be evaluated for safety by the SCC before additional subjects would be enrolled, after which cohorts were to be re-opened for full accrual in the expansion. An individual participant was not permitted to enrol in more than one module.

Study population /Sample size

In the expansion phase of CA209908, the population for evaluation was **overall, all-treated subjects** for both safety and efficacy endpoints. Although not a pre-specified population for analysis in the CA209908 statistical analysis plan (SAP), selected key analyses were performed based on **all-treated subjects < 18 years of age** for the purposes of the current procedure, in order to present results specifically for paediatric subjects defined as < 18 years of age at the time of study enrolment.

Treatments

- **Nivolumab monotherapy (Module A)**: nivolumab 3 mg/kg as a 30-minute intravenous (IV) infusion on Day 1 of each treatment cycle Q2W, as monotherapy

- **Nivolumab + ipilimumab (Module B)**: nivolumab 3 mg/kg as a 30-minute IV infusion, followed 30 minutes later by ipilimumab 1 mg/kg as a 30-minute IV infusion on Day 1 of each treatment cycle Q3W for 4 doses. Starting 3 weeks after the fourth dose of the combination, nivolumab was administered at a dose of 3 mg/kg as a 30-minute IV infusion on Day 1 of each treatment cycle Q2W, as monotherapy.

For both modules, treatment was to begin within 3 calendar days of treatment assignment and subjects in Cohort 1 (newly diagnosed pontine glioma, post-radiotherapy) began treatment within 6 weeks after the end of RT. For both modules, treatment was to continue until progression, unacceptable toxicity, withdrawal of consent, or end of study, whichever occurred first.

Outcomes/endpoints

Table 1: Study objectives and endpoints

Objectives	Endpoints	Included in Primary CSR
PRIMARY		
Safety Lead In		
To estimate the safety and tolerability of study treatment in paediatric subjects with primary high-grade CNS tumours.	Incidence of DLTs, SAEs, and AEs leading to discontinuation.	Yes
Expansion		
To estimate the OS in paediatric subjects with newly diagnosed DIPG. (Cohort 1)	OS	Yes

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Objectives	Endpoints	Included in Primary CSR
To estimate the PFS in paediatric subjects with recurrent or progressive HGG. (Cohort 2)	PFS	Yes
To estimate the PFS in paediatric subjects with relapsed or resistant medulloblastoma. (Cohort 3)	PFS	Yes
To estimate the PFS in paediatric subjects with relapsed or resistant ependymoma. (Cohort 4)	PFS	Yes
To estimate the PFS in paediatric subjects with recurrent or progressive other rare CNS tumours (including pineoblastoma, AT/RT, embryonic CNS tumours) (Cohort 5)	PFS	Yes
SECONDARY		
Safety Lead In		
To describe any observed anti-tumour activity of study treatment in paediatric primary high-grade CNS tumours.	Secondary endpoints are the same as in the expansion phase.	Yes
Expansion		
To estimate the safety of study therapy in paediatric subjects with newly diagnosed primary DIPG, recurrent or progressive HGG, relapsed or resistant primary medulloblastoma, relapsed or resistant primary ependymoma and recurrent or progressive other primary rare CNS tumours.	Incidence of death, AEs, SAEs, drug-related AEs, AEs leading to discontinuation, and laboratory abnormalities.	Yes
To estimate the PFS and OS rate in paediatric subjects with newly diagnosed DIPG. (Cohort 1)	PFS and OS at 12 months	Yes
To estimate the PFS rate, OS, and OS rate and in paediatric subjects with recurrent or progressive HGG. (Cohort 2)	PFS at 6 months, OS, and OS at 12 months	Yes
To estimate the PFS rate, OS, and OS rate in paediatric subjects with relapsed or resistant medulloblastoma. (Cohort 3)	PFS at 6 months, OS, and OS at 12 months	Yes
To estimate the PFS rate, OS, and OS rate in paediatric subjects with relapsed or resistant ependymoma. (Cohort 4)	PFS at 6 months, OS, and OS at 12 months	Yes
To estimate the PFS rate and OS and in paediatric subjects with recurrent or progressive other rare CNS tumours (including pineoblastoma, AT/RT, other embryonic CNS tumours). (Cohort 5)	PFS at 6 months and OS	Yes
EXPLORATORY		
To investigate ORR and DOR in subjects with measureable disease at baseline (Cohorts 1-5).	ORR and DOR	Yes
To investigate biomarker expression in clinical tumour specimens of paediatric subjects with CNS tumours.	To assess biomarkers such as PD-L1 expression, MHC I/II	Yes Tumour PD-L1

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Objectives	Endpoints	Included in Primary CSR
	expression, mutational burden, and immune-related gene expression.	expression only
To estimate the PD activity of nivolumab monotherapy and nivolumab + ipilimumab combination therapy in the peripheral blood, cerebrospinal fluid and tumour tissue as measured by flow cytometry, immunohistochemistry, soluble factor analysis, and gene expression analysis.	To summarize changes in biomarker levels over time.	No
To investigate the association between biomarkers in the peripheral blood, tumour tissue and cerebrospinal fluid with safety and efficacy in paediatric subjects with CNS tumours.	To assess association of biomarkers with safety, ORR, PFS and OS.	Yes Association of Tumour PD-L1 expression with safety and OS only
To characterize the pharmacokinetics (PK) of nivolumab and ipilimumab in paediatric subjects with recurrent or progressive CNS tumours	PK parameters	No
To characterize the immunogenicity of nivolumab and ipilimumab in this setting.	Anti-nivolumab and anti-ipilimumab antibody levels and their relationship with efficacy and safety.	Yes

Abbreviations: AE=adverse event; AT/RT=atypical teratoid/rhabdoid tumour; CNS=central nervous system; CSR=Clinical Study Report; DIPG=diffuse intrinsic pontine glioma; DLT=dose-limiting toxicity; DOR=duration of response; HGG=high-grade glioma; MHC= Major histocompatibility complex; ORR=objective response rate; OS=overall survival; PD=pharmacodynamics; PD-L1=programmed death ligand 1; PFS=progression-free survival; PK=pharmacokinetics; SAE=serious adverse event.

Statistical Methods

Sample size

Sample sizes for Cohorts 1-4 were calculated assuming exponential survival and the standard formula adapted for a single arm as described in Section 10.1 of the study protocol. By applying this methodology, the intended target numbers of subjects for Cohorts 1-4 were obtained as follows:

Cohort 1: N = 22 for each of the expansion Cohorts 1A and 1B. This assumes 80% power with a one sided Type 1 error of 10%, a historical median OS of 9 months, 1-year accrual, 2-year follow-up, and a target effect size of median OS of 15 months.

Cohort 2: N = 15 for each of the expansion Cohorts 2A and 2B. This assumes 80% power with a one-sided Type 1 error of 10%, a historical 6-months PFS rate of 18%, 1-year accrual, one-year follow-up, and a target 6-month PFS rate of 38%.

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Cohort 3: N = 15 for each of the expansion Cohorts 3A and 3B. This assumes 80% power with a one-sided Type 1 error of 10%, 1-year accrual and 1-year follow-up, a historical 4-month PFS rate of 18% and a target 4-month PFS rate of 38%, equivalent to 6-month PFS rate of 23%.

Cohort 4: N = 10 for each of the expansion Cohorts 4A and 4B. This assumes at least 80% power with a one-sided Type 1 error of 10%, a historical median PFS of 2.1 months, 1-year accrual, 1-year follow-up, and a target median PFS of 4.4 months.

Cohort 5: N = 18 for each of the expansion Cohorts A5 and B5. This was not based on statistical considerations as these cohorts contain various tumor types. However, if the disease control rate at 12 months is 30%, 18 subjects provides 21% precision for the estimate.

Primary efficacy analyses

Results for OS and PFS were intended to be compared with the available historical controls (median OS of 9 months for DIPG, median PFS of 2.25 months for HGG, 4-month PFS rate of 18% for medulloblastoma, and median PFS of 2.1 months for ependymoma).

The primary efficacy analyses were performed on the all-treated population for the final analysis. Efficacy analysis of nivolumab monotherapy and nivolumab + ipilimumab was performed for each cohort separately; however, treated subjects in the safety lead-in phase who met the inclusion criteria for the corresponding cohort were also included in the cohort efficacy analysis.

Time to event distribution (ie, PFS, OS and duration of response [DOR]) were estimated using the Kaplan-Meier (KM) product limit method. Median time along with 95% (or 80%) confidence interval (CI) was constructed based on a log-log transformed CI for the survivor function S(t). Rates at fixed timepoints (eg, OS at 12 months) were derived from the KM estimate and corresponding CIs were derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t). CIs for binomial proportions (objective response rate [ORR]) were derived using the Clopper-Pearson method.

Overall Survival (OS)

- Cohort 1

The OS curve for each treatment group was estimated using the KM method. Median OS and the corresponding two-sided 80% CIs using the log-log transformation were computed. The distribution of OS for each treatment group was also compared against the historical control of an exponential distribution with median OS of 9 months, using a one-sided one-sample log rank test when approximately 17 events had occurred or after each subject had been followed for at least 24 months. At the time of DBL, all subjects were followed for at least 24 months for OS. As one of the secondary endpoints, OS rate at 12 months for each treatment group was estimated using KM estimates on the OS curve and its corresponding 95% CI was derived based on Greenwood formula.

- Cohorts 2-4

As secondary endpoints for Cohorts 2-4, the OS curve for each treatment group was estimated using the KM method. Median OS and the corresponding two-sided 95% CIs using the log-log transformation were computed. OS rate at 12 month for each treatment group was estimated using KM estimates on the OS curve and its corresponding 95% CI was derived based on Greenwood formula.

- Cohort 5

OS (secondary endpoint) was listed. OS curves were computed using KM method for pooled indications and selected individual indications. The corresponding 95% CI for median OS was calculated via Brookmeyer and Crowley methodology using log-log transformation.

Progression Free Survival (PFS)

- Cohort 1

As one of the secondary endpoints of Cohort 1, PFS for each treatment group was estimated by KM method and the corresponding 95% CI for median PFS were calculated via Brookmeyer and Crowley methodology using log-log transformation.

- Cohorts 2-4

As the primary efficacy endpoints of Cohorts 2 to 4, the PFS curve for each treatment group was estimated using the KM method. Median PFS and the corresponding two-sided 80% CIs using the log-log transformation were computed.

The distribution of PFS for Cohort 2 for each treatment group was compared against the historical control of an exponential distribution with median PFS of 2.25 months, using a one-sided one-sample log rank test when each subject had been followed for at least 12 months.

The distribution of PFS for Cohort 3 for each treatment group was compared against the historical control of an exponential distribution with PFS at 4 months equal to 18%, using a one-sided one-sample log rank test when either 15 events had occurred or each subject had been followed for at least 12 months.

The distribution of PFS for Cohort 4 for each treatment group was compared against the historical control of an exponential distribution with median PFS equal to 2.1 months, using a one-sided one-sample log rank test when either 10 events have occurred or each subject has been followed for at least 12 months.

In addition, as one of the secondary endpoints for Cohorts 2-4, PFS rate at 6 months for each treatment group was estimated using KM estimates on the PFS curve, and its corresponding 95% CI was derived based on Greenwood formula.

- Cohort 5

As a secondary endpoint, the PFS curve for each treatment group was estimated using the KM method for all tumour types (pooled) and selected individual tumour types, if there was enough data. For each treatment group separately individual PFS was listed by tumour type after each subject reached 12 months follow-up. In addition, as one of the secondary endpoints for Cohort 5, PFS rate at 6 months for each treatment group was estimated using KM estimates on the PFS curve, and its corresponding 95% CI was derived based on Greenwood formula.

Safety analyses

Primary safety analyses were performed for safety lead-in subjects, which included 3 groups: in Module A, the first 15 DLT-evaluable subjects in Cohort 1 (increased from 6 planned originally), and the first 10 DLT-evaluable subjects in Cohorts 2-5; in Module B, the first 16 DLT-evaluable subjects (increased from 10 planned originally).

Secondary safety analyses were performed for all treated subjects and summarized by cohort and treatment. Safety analyses were performed for individual cohorts and for combined cohorts by treatment module. The safety population included all treated subjects.

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Descriptive statistics of safety (both primary and secondary) are presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All on-study AEs, drug-related AEs, AEs leading to discontinuation, drug-related AEs leading to discontinuation, serious adverse events (SAEs), and drug-related SAEs are tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class (SOC) and PT. On-study lab parameters including hematology, chemistry, liver function, and renal function are summarized using worst grade per NCI CTCAE v 4.0 criteria, and reported using International system of units (SI) and repeated using US conventional units. All on-study AEs and lab parameters were summarized for the entire treatment period from the first dosing date to the last dosing date plus 30 days (30-day window).

Results

Recruitment/ Number analysed

This study was conducted at 51 sites in 15 countries. Across all cohorts in Modules A and B, a total of 204 subjects were enrolled, of whom 166 (81.4%) subjects entered the treatment period.

For the primary CSR, the clinical cut-off (last patient's last visit [LPLV]) occurred on 19-Oct-2020 and the database lock (DBL) took place on 13-Jan-2021. For the purpose of the primary CSR, study results were assessed after a minimum of 24 months follow-up for all subjects for the assessment of the primary endpoint of OS (Cohort 1) and after a minimum of 12 months follow-up for all subjects for the assessment of the primary endpoint of PFS (Cohorts 2-5).

A total of 85 and 81 subjects ≥ 6 months and < 22 years of age were treated with nivolumab monotherapy (Module A, Cohorts 1-5) or nivolumab in combination with ipilimumab (Module B, Cohorts 1-5), respectively, in the overall, all-treated population of Study CA209908, based on a database lock (DBL) of 13-Jan-2021. Of these, 77 (90.6%) (Module A) and 74 (91.4%) (Module B) were < 18 years of age at the time of study enrolment.

The numbers of subjects actually evaluated for DLTs were 15 in Cohort 1 (Module A), 10 in Cohorts 2-5 (Module A), and 17 in Cohorts 2-5 (Module B), with 16 in the safety lead-in phase and 1 in the expansion phase. These changes from the planned numbers were implemented per recommendation of the SSC.

Baseline data

Demographic characteristics

As per protocol, at study entry, all subjects in Cohort 1 had newly diagnosed DIPG, all subjects in Cohorts 2, 3, and 4 had a diagnosis of recurrent or progressive HGG, relapsed or resistant medulloblastoma, and relapsed or resistant ependymoma, respectively, and Cohort 5 had subjects with other recurrent or progressive CNS tumours. Demographics and baseline characteristics were generally similar across individual cohorts and between the modules. The majority of subjects in both modules, in both the overall and < 18 year populations, were white and male, and from the US/Canada or Europe.

In combined cohorts treated with **nivolumab monotherapy**:

- The median age was 10.0 years (range: 1 - 21 years) with 90.6% of subjects < 18 years.

- The majority of subjects were white (83.5%) and male (61.2%).

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- 60.0% of subjects were from Europe, 28.2% were from US/Canada, and 11.8% were from the rest of the world (ROW).

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In combined cohorts treated with **nivolumab + ipilimumab**:

- The median age was 11.0 years (range: 1 - 21) with 91.4% of subjects < 18 years.

- The majority of subjects were white (75.3%) and male (54.3%).

- 39.5% of subjects were from Europe, 28.4% were from US/Canada, and 32.1% were from the ROW.

Baseline demographic characteristics for all-treated subjects and all-treated subjects <18 years of age are shown in Table 2 and Table 3.

Table 2: Demographic Characteristics Summary - All Treated Subjects (Modules A and B)

	MODULE A ALL COHORTS N = 85	MODULE B ALL COHORTS N = 81
AGE (YEARS)		
MEAN	10.1	10.6
MEDIAN	10.0	11.0
MIN, MAX	1 , 21	1 , 21
SD	5.5	5.2
AGE CATEGORIZATION (%)		
< 2	1 (1.2)	2 (2.5)
>= 2 AND < 12	46 (54.1)	41 (50.6)
>= 12 AND < 18	30 (35.3)	31 (38.3)
>= 18	8 (9.4)	7 (8.6)
SEX (%)		
MALE	52 (61.2)	44 (54.3)
FEMALE	33 (38.8)	37 (45.7)
RACE (%)		
WHITE	71 (83.5)	61 (75.3)
BLACK OR AFRICAN AMERICAN	4 (4.7)	5 (6.2)
ASIAN	4 (4.7)	6 (7.4)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (1.2)
NATIVE HAWAIIAN OR OTHER PI	0	0
OTHER	6 (7.1)	8 (9.9)
COUNTRY BY GEOGRAPHIC REGION (%)		
US/CANADA	24 (28.2)	23 (28.4)
EUROPE	51 (60.0)	32 (39.5)
REST OF THE WORLD	10 (11.8)	26 (32.1)
AUSTRALIA	8 (9.4)	4 (4.9)
BRAZIL	1 (1.2)	19 (23.5)
ISRAEL	1 (1.2)	1 (1.2)
HONG KONG	0	2 (2.5)

Percentages based on subjects entering treatment period.
Abbreviations: MAX=maximum; MIN=minimum; PI=Pacific Islander; SD=standard deviation; US=United States.

Table 3: Demographic Characteristics Summary - All Treated Subjects < 18 Years (Modules A and B)

	MODULE A ALL COHORTS N = 77	MODULE B ALL COHORTS N = 74
AGE (YEARS)		
MEAN	9.1	9.7
MEDIAN	9.0	10.0
MIN, MAX	1 , 17	1 , 17
SD	4.7	4.7
AGE CATEGORIZATION (%)		
< 2	1 (1.3)	2 (2.7)
>= 2 AND < 12	46 (59.7)	41 (55.4)
>= 12 AND < 18	30 (39.0)	31 (41.9)
SEX (%)		
MALE	45 (58.4)	39 (52.7)
FEMALE	32 (41.6)	35 (47.3)
RACE (%)		
WHITE	66 (85.7)	55 (74.3)
BLACK OR AFRICAN AMERICAN	3 (3.9)	4 (5.4)
ASIAN	3 (3.9)	6 (8.1)
AMERICAN INDIAN OR ALASKA NATIVE	0	1 (1.4)
NATIVE HAWAIIAN OR OTHER PI	0	0
OTHER	5 (6.5)	8 (10.8)
COUNTRY BY GEOGRAPHIC REGION (%)		
US/CANADA	19 (24.7)	21 (28.4)
EUROPE	48 (62.3)	29 (39.2)
REST OF THE WORLD	10 (13.0)	24 (32.4)
AUSTRALIA	8 (10.4)	4 (5.4)
BRAZIL	1 (1.3)	17 (23.0)
ISRAEL	1 (1.3)	1 (1.4)
HONG KONG	0	2 (2.7)

Percentages based on subjects entering treatment period.
Abbreviations: MAX=maximum; MIN=minimum; PI=Pacific Islander; SD=standard deviation; US=United States
Source: Table S.3.2.1p.1 of Appendix 1.

Disease characteristics

Baseline characteristics of the overall and < 18 year populations, by module, are summarized in Table 4 and Table 5, respectively. The majority of subjects in both modules, in both the overall (80.0% [nivolumab]; 82.7% [nivolumab + ipilimumab]) and < 18 year (81.8% [nivolumab]; 82.4% [nivolumab + ipilimumab]) populations, had Karnofsky Performance Score (KPS)/ Lansky Play Score (LPS) of ≥ 80.0%.

In both Module A and B, per protocol, all subjects in Cohort 1 treated with nivolumab monotherapy and nivolumab plus ipilimumab, respectively, received prior radiotherapy but none received prior systemic cancer therapy. In Cohorts 2-5, most subjects received all 3 forms of prior therapy: radiotherapy, surgery related to cancer, and systemic anticancer therapy. This was also observed in the < 18 year population.

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Table 4: Baseline Characteristics - All Treated Subjects (Modules A and B)

	MODULE A ALL COHORTS N = 85	MODULE B ALL COHORTS N = 81
CURRENT DISEASE DIAGNOSIS		
ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA	1 (1.2)	1 (1.2)
ATYPICAL TERATOID RHABDOID TUMOUR	4 (4.7)	3 (3.7)
CHOROID PLEXUS CARCINOMA	0	4 (4.9)
DIFFUSE INTRINSIC PONTINE GLIOMA	18 (21.2)	18 (22.2)
DIFFUSE MIDLINE GLIOMA	6 (7.1)	4 (4.9)
EMBRYONAL TUMOUR W MULTILAYERED ROSETTES	1 (1.2)	1 (1.2)
EPENDYMOMA	12 (14.1)	10 (12.3)
GLIOMA - HIGH GRADE	18 (21.2)	16 (19.8)
MALIGNANT GERM CELL TUMOUR	1 (1.2)	1 (1.2)
MEDULLOBLASTOMA	15 (17.6)	15 (18.5)
PINEOBLASTOMA	4 (4.7)	0
OTHER	5 (5.9)	8 (9.9)
CURRENT DISEASE STAGE		
LOCALIZED	54 (63.5)	60 (74.1)
METASTATIC	31 (36.5)	21 (25.9)
LPS/KPS (A)		
< 80	17 (20.0)	14 (17.3)
>= 80	68 (80.0)	67 (82.7)
PD-L1 CATEGORY		
< 1%	41 (48.2)	42 (51.9)
>= 1%	21 (24.7)	15 (18.5)
< 5%	46 (54.1)	46 (56.8)
>= 5%	16 (18.8)	11 (13.6)
INDETERMINATE/NOT EVALUABLE	1 (1.2)	2 (2.5)
NOT REPORTED (B)	22 (25.9)	22 (27.2)

(A) Lansky play score (LPS) for <=16 years or Karnofsky performance scale (KPS) for > 16 years.

(B) All but 2 subjects in Module A and 1 subject in Module B of the "not reported" were from Cohort 1 for which tissue sample collection was not required

Abbreviations: KPS = Karnofsky performance scale; LPS = Lansky play score; PD-L1 = programmed death-ligand 1

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Table 5: Baseline Characteristics - All Treated Subjects < 18 Years (Modules A and B)

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-----------------------------------------------------------------------------
                                              MODULE A              MODULE B
                                             ALL COHORTS           ALL COHORTS
                                              N = 77                N = 74
-----------------------------------------------------------------------------
CURRENT DISEASE DIAGNOSIS
  ANAPLASTIC PLEOMORPHIC XANTHOASTROCYTOMA    1 (  1.3)             1 (  1.4)
  ATYPICAL TERATOID RHABDOID TUMOUR           4 (  5.2)             3 (  4.1)
  CHOROID PLEXUS CARCINOMA                    0                     4 (  5.4)
  DIFFUSE INTRINSIC PONTINE GLIOMA           17 ( 22.1)            17 ( 23.0)
  DIFFUSE MIDLINE GLIOMA                       5 (  6.5)             4 (  5.4)
  EMBRYONAL TUMOUR W MULTILAYERED ROSETTES     1 (  1.3)             1 (  1.4)
  EPENDYMOMA                                  11 ( 14.3)             8 ( 10.8)
  GLIOMA - HIGH GRADE                         14 ( 18.2)            14 ( 18.9)
  MALIGNANT GERM CELL TUMOUR                   1 (  1.3)             1 (  1.4)
  MEDULLOBLASTOMA                             15 ( 19.5)            13 ( 17.6)
  PINEOBLASTOMA                                3 (  3.9)             0
  OTHER                                        5 (  6.5)             8 ( 10.8)

CURRENT DISEASE STAGE
  LOCALIZED                                   48 ( 62.3)            55 ( 74.3)
  METASTATIC                                  29 ( 37.7)            19 ( 25.7)

LPS/KPS (A)
  < 80                                        14 ( 18.2)            13 ( 17.6)
  >= 80                                       63 ( 81.8)            61 ( 82.4)

PD-L1 CATEGORY
  < 1%                                        37 ( 48.1)            37 ( 50.0)
  >= 1%                                       18 ( 23.4)            14 ( 18.9)
  < 5%                                        42 ( 54.5)            41 ( 55.4)
  >= 5%                                       13 ( 16.9)            10 ( 13.5)
  INDETERMINATE/NOT EVALUABLE                  1 (  1.3)             2 (  2.7)
  NOT REPORTED (B)                            21 ( 27.3)            21 ( 28.4)
-----------------------------------------------------------------------------
```

(A) Lansky play score (LPS) for <=16 years or Karnofsky performance scale (KPS) for > 16 years.

(B) All but 2 subjects in Module A and 1 subject in Module B of the "not reported" were from Cohort 1 for which tissue sample collection was not required

Abbreviations: KPS = Karnofsky performance scale; LPS = Lansky play score; PD-L1 = programmed death-ligand 1

Efficacy results

Exposure to study therapy

In the all-treated <18 year population, in combined cohorts, for nivolumab monotherapy treated subjects, the proportion of subjects who received 90% to < 110% of the planned dose intensity was 88.6% and the median number of doses received was 5 (range 1-87). For nivolumab/ipilimumab combination therapy treated subjects, the proportion of subjects who received 90% to < 110% of the planned dose intensity was 86.5% and the median number of doses received was 4 (range 1-63).These parameters were comparable to the overall population.

For nivolumab monotherapy-treated subjects, based on KM analysis, the median time to treatment discontinuation was 2.10 months in the combined cohorts (cohort 1: 4.17 months; cohort 2: 2.12 months; cohort 3: 1.41 months; cohort 4: 1.87 months; cohort 5: 0.95 months).

For nivolumab + ipilimumab-treated subjects, based on KM analysis, the median time to treatment discontinuation was 2.12 in the combined cohorts (cohort 1: 3.68 months; cohort 2: 1.41 months; cohort 3: 4.63 months; cohort 4: 4.06 months; cohort 5: 1.45 months).

Primary efficacy outcomes

Overall, all-treated population

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The primary endpoints of OS in cohort 1 and PFS (by Investigator) in Cohorts 2-5 were short, indicating no meaningful benefit:

- Median OS of 11.66 months (80% CI: 10.32, 16.46) with nivolumab monotherapy and 10.78 months (80% CI: 9.13, 15.77) with nivolumab + ipilimumab in subjects with newly diagnosed DIPG (Cohort 1)

- Median PFS of 1.74 months (80% CI: 1.35, 2.73) with nivolumab monotherapy and 1.31 months (80% CI: 1.18, 1.45) with nivolumab + ipilimumab in subjects with recurrent or progressive HGG (Cohort 2)

- Median PFS of 1.38 months (80% CI: 1.22, 1.38) with nivolumab monotherapy and 2.76 months (80% CI: 1.48, 4.53) with nivolumab + ipilimumab in subjects with recurrent or progressive medulloblastoma (Cohort 3)

- Median PFS of 1.41 months (80% CI: 1.41, 2.60) with nivolumab monotherapy and 4.60 months (80% CI: 1.41, 5.39) with nivolumab + ipilimumab in subjects with recurrent or progressive ependymoma (Cohort 4)

- Median PFS of 1.22 months (95% CI: 1.08, 1.31) with nivolumab monotherapy and 1.61 months (95% CI: 1.31, 3.45) with nivolumab + ipilimumab in subjects with all other recurrent or progressive CNS tumours (Cohort 5).

Efficacy by baseline PD-L1 expression

Exploratory analyses for tumour PD-L1 were based on baseline PD-L1 positive status using 1% and 5% cutoffs. Of the 85 subjects treated with nivolumab monotherapy (Module A), 62 had evaluable PD-L1 IHC results; of the 81 subjects treated with nivolumab + ipilimumab (Module B), 57 had evaluable PD-L1 IHC results. Data suggest that tumour PD-L1 ≥ 1% or ≥ 5% was not associated with improved OS relative to tumour PD-L1 < 1% or < 5%, respectively, for either nivolumab monotherapy or nivolumab + ipilimumab. In combined cohorts, for both treatment regimens, CIs of both OS hazard ratios (HRs) (PD-L1 ≥ 1% vs PD-L1 < 1% and PD-L1 ≥ 5% vs PD-L1 < 5%) included 1, indicating no significant difference; however, small subgroup sizes preclude definitive conclusions

All-treated (<18 year) population

Efficacy results are summarized by cohort for nivolumab monotherapy (Module A) in Table 6 and nivolumab + ipilimumab (Module B), for the all-treated <18 year population, in Table 7.

As noted for the overall, all-treated population, the primary endpoints of OS in Cohort 1 and PFS (by Investigator) in Cohorts 2-5 were short, indicating no meaningful benefit:

- Median OS of 10.97 months (80% CI: 9.92, 12.16) with nivolumab monotherapy and 10.50 months (80% CI: 9.10, 12.32) with nivolumab + ipilimumab in subjects < 18 years of age with newly diagnosed DIPG (Cohort 1)

- Median PFS of 2.35 months (80% CI: 1.35, 2.76) with nivolumab monotherapy and 1.45 months (80% CI: 1.22, 1.48) with nivolumab + ipilimumab in subjects < 18 years of age with recurrent or progressive HGG (Cohort 2)

- Median PFS of 1.38 months (80% CI: 1.22, 1.38) with nivolumab monotherapy and 2.76 months (80% CI: 1.48, 4.53) with nivolumab + ipilimumab in subjects < 18 years of age with recurrent or progressive medulloblastoma (Cohort 3)

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- Median PFS of 1.41 months (80% CI: 1.38, 2.60) with nivolumab monotherapy and 3.09 months (80% CI: 1.18, 4.63) with nivolumab + ipilimumab in subjects < 18 years of age with recurrent or progressive ependymoma (Cohort 4)

- Median PFS of 1.23 months (95% CI: 1.08, 1.31) with nivolumab monotherapy and 1.61 months (95% CI: 1.31, 3.45) with nivolumab + ipilimumab in subjects < 18 years of age with all other recurrent or progressive CNS tumours (Cohort 5).

Table 6: Efficacy Summary - Nivolumab Monotherapy - All Treated Subjects < 18 Years (Module A)

	Nivolumab (Module A)				
	Cohort 1 (DIPG) N = 21	Cohort 2 (HGG) N =12	Cohort 3 (Medulloblastoma) N =15	Cohort 4 (Ependymoma) N = 11	Cohort 5 (Other high-grade tumours) N = 18
OS (Primary Endpoint in Cohort 1 and Secondary Endpoint in Cohorts 2-5)					
Median (80% CI), Months	10.97 (9.92, 12.16)	N.A.	N.A.	N.A.	N.A.
Median (95% CI), Months	N.A.	8.72 (2.99, N.E.)	7.36 (2.46, 30.23)	4.83 (1.81, 27.07)	6.00 (1.97, 7.98)
12-month Rate (95% CI), %	42.2 (19.8, 63.2)	41.7 (15.2, 66.5)	38.9 (14.3, 63.2)	36.4 (11.2, 62.7)	N.A.
PFS (Primary Endpoint in Cohort 2-5 and Secondary Endpoint in Cohort 1)					
Median (80% CI), Months	N.A.	2.35 (1.35, 2.76)	1.38 (1.22, 1.38)	1.41 (1.38, 2.60)	N.A.
Median (95% CI), Months	4.76 (3.25, 6.47)	N.A.	N.A.	N.A.	1.23 (1.08, 1.31)
6-month Rate (95% CI), %	N.A.	12.5 (0.9, 39.9)	0	20.0 (3.1, 47.5)	5.6 (0.4, 22.4)
12-month Rate (95% CI), %	N.A	N.A	N.A	N.A	5.6 (0.4, 22.4)
ORR (Exploratory Endpoint in Cohorts 1-5)					
Response-evaluable Subjects	2 [a]	9	13	9	11
ORR (%)	0	0	0	1 (11.1)[b]	0
(95% CI)	(0.0, 84.2)	(0.0, 33.6)	(0.0, 24.7)	(0.3, 48.2)	(0.0, 28.5)
DOR (Exploratory Endpoint in Cohorts 1-5)					
Median (95% CI), Months[c]	Not applicable	Not applicable	Not applicable	31.21 (N.A., N.A.)	Not applicable

[a]Subjects in Cohort 1 were considered to have non-measurable disease and therefore considered to be non-evaluable for response. Two subjects were incorrectly entered as having measurable disease at baseline in the database. These subjects' CRF pages will be updated for final analysis.

[b]Partial response

[c]Computed using the Kaplan-Meier (KM) method

Medians and rates of OS and PFS were computed using the KM method. Two-sided exact 95% CIs for ORR were computed using the Clopper-Pearson method. Abbreviations: CI=confidence interval; NA=not available; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Table 7: Efficacy Summary - Nivolumab + Ipilimumab - All Treated Subjects < 18 Years (Module B)

	Nivolumab + Ipilimumab (Module B)				
	Cohort 1 (DIPG) N = 21	Cohort 2 (HGG) N =13	Cohort 3 (Medulloblastoma) N = 13	Cohort 4 (Ependymoma) N = 8	Cohort 5 (Other high-grade tumours) N = 19
OS (Primary Endpoint in Cohort 1 and Secondary Endpoint in Cohorts 2-5)					
Median (80% CI), Months	10.50 (9.10, 12.32)	N.A.	N.A.	N.A.	N.A.
Median (95% CI), Months	N.A.	11.01 (1.41, 13.63)	20.76 (13.77, N.A.)	13.16 (2.50, N.E.)	8.48 (3.45, 24.34)
12-month Rate (95% CI), %	40.0 (19.3, 60.0)	42.8 (13.9, 69.4)	84.6 (51.2, 95.9)	50.0 (15.2, 77.5)	N.A.
PFS (Primary Endpoint in Cohort 2-5 and Secondary Endpoint in Cohort 1)					
Median (80% CI), Months	N.A.	1.45 (1.22, 1.48)	2.76 (1.48, 4.53)	3.09 (1.18, 4.63)	N.A.
Median (95% CI), Months	4.11 (2.76, 6.44)	N.A.	N.A.	N.A.	1.61 (1.31, 3.45)
6-month Rate (95% CI), %	N.A.	18.2 (2.9, 44.2)	23.1 (5.6, 47.5)	12.5 (0.7, 42.3)	14.0 (2.8, 34.1)
12-month Rate (95% CI), %	N.A.	N.A.	N.A.	N.A.	7.0 (0.5, 26.2)
ORR (Exploratory Endpoint in Cohorts 1-5)					
Response-evaluable Subjects	1[a]	7	7	4	13
ORR (%)	0	0	0	0	0
(95% CI)	(0.0, 97.5)	(0.0, 41.0)	(0.0, 41.0)	(0.0, 60.2)	(0.0, 24.7)
DOR (Exploratory Endpoint in Cohorts 1-5)					
Median (95% CI), Months[b]	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

[a]Subjects in Cohort 1 were considered to have non-measurable disease and therefore considered to be non-evaluable for response. One subject was incorrectly entered as having measurable disease at baseline in the database. These subject's CRF pages will be updated for final analysis.

[b]Computed using the Kaplan-Meier (KM) method
Medians and rates of OS and PFS were computed using the KM method. Two-sided exact 95% CIs for ORR were computed using the Clopper-Pearson method.
Abbreviations: CI=confidence interval; NA=not available; NE=not estimable; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

Exploratory endpoints of Objective Response Rate and Duration of Response

Nivolumab monotherapy

Across 5 cohorts treated with nivolumab monotherapy, 1 patient with ependymoma had a BOR of PR (Cohort 4) and 9 had a BOR of SD (2 in Cohort 1, 4 in Cohort 2, and 1 each in Cohorts 3, 4, and 5), see Table 8. No subjects had a BOR of CR. The time to response was 2.83 months and, as of the data cutoff, the DOR was 31.2 months with the response still ongoing.

Table 8: Best Overall Response per Investigator - All Response-evaluable Subjects - Nivolumab Monotherapy Treated Subjects (Module A)

	Nivolumab Monotherapy				
	COHORT 1 (DIPG) N = 2	COHORT 2 (HGG) N = 11	CPHORT 3 (Medulloblastoma) N = 13	COHORT 4 (Ependymoma) N = 9	COHORT 5 (Others) N = 12
BEST OVERALL RESPONSE					
COMPLETE RESPONSE (CR)	0	0	0	0	0
PARTIAL RESPONSE (PR)	0	0	0	1 (11.1)	0
STABLE DISEASE (SD)	2 (100.0)	4 (36.4)	1 (7.7)	1 (11.1)	1 (8.3)
PROGRESSIVE DISEASE (PD)	0	7 (63.6)	12 (92.3)	7 (77.8)	11 (91.7)
UNABLE TO DETERMINE (UTD)	0	0	0	0	0
OBJECTIVE RESPONSE RATE(1)	0/2 (0.0%)	0/11 (0.0%)	0/13 (0.0%)	1/9 (11.1%)	0/12 (0.0%)
(95% CI)	(0.0, 84.2)	(0.0, 28.5)	(0.0, 24.7)	(0.3, 48.2)	(0.0, 26.5)

Per RANO criteria where confirmation of response is required.
(1) CR+PR/Number of Response Evaluable Subjects, confidence interval based on the Clopper and Pearson method.
Source: Table S.5.5

Nivolumab + Ipilimumab

Across 5 cohorts treated with nivolumab + ipilimumab, none of the subjects had a BOR of PR or CR and 9 had a BOR of SD (1 in Cohort 2, 4 in Cohort 3, 3 in Cohort 4, and 1 in Cohort 5), see Table 9.

Table 9: Best Overall Response per Investigator - All Response-evaluable Subjects-Nivolumab + Ipilimumab Treated Subjects (Module B)

```
-------------------------------------------------------------------------------------------------
                                              Nivolumab + Ipilimumab
                              -------------------------------------------------------------------
                              COHORT 1      COHORT 2       COHORT 3         COHORT 4        COHORT 5
                              (DIPG)        (HGG)          (Medulloblastoma) (Ependymoma)   (Others)
                              N = 1         N = 9          N = 8            N = 5           N = 13
-------------------------------------------------------------------------------------------------

BEST OVERALL RESPONSE

   COMPLETE RESPONSE  (CR)     0            0              0                0               0
   PARTIAL RESPONSE   (PR)     0            0              0                0               0
   STABLE DISEASE     (SD)     0            1 ( 11.1)      4 ( 50.0)        3 ( 60.0)       1 (  7.7)
   PROGRESSIVE DISEASE (PD)    0            8 ( 88.9)      4 ( 50.0)        2 ( 40.0)       11 ( 84.6)
   UNABLE TO DETERMINE (UTD)   1 (100.0)    0              0                0               1 (  7.7)

OBJECTIVE RESPONSE RATE(1)     0/1 (  0.0%) 0/9 (  0.0%)   0/8 (  0.0%)     0/5 (  0.0%)    0/13 (  0.0%)
   (95% CI)                    (0.0, 97.5)  (0.0, 33.6)    (0.0, 36.9)      (0.0, 52.2)     (0.0, 24.7)

-------------------------------------------------------------------------------------------------
Per RANO criteria where confirmation of response is required.
(1) CR+PR/Number of Response Evaluable Subjects, confidence interval based on the Clopper and Pearson method.
```

Safety results

As of the 13-Jan-2021 DBL (minimum follow-up: at least 24 months for OS; at least 12 months for PFS, where applicable), the safety profiles of nivolumab monotherapy and nivolumab + ipilimumab) in all treated subjects with high grade primary CNS malignancies were consistent with those in other tumour types in adults, with no new safety signals observed. Safety results are presented for the all-treated <18 year population only (n=77 nivolumab monotherapy and n=74 nivolumab + ipilimumab), but results were comparable to the all-treated population (n=85 for nivolumab monotherapy and n=81 for nivolumab + ipilimumab).

All-treated <18 year) population

The median follow-up in combined cohorts was 8.08 months (range: 0.2 - 41.7) and 10.89 months (range: 0.7 - 34.7) for nivolumab monotherapy and nivolumab + ipilimumab treated subjects, respectively.

Safety Lead-in Phase

As noted for the overall, all-treated population, no DLTs of any grade were reported in the lead-in phase in subjects < 18 years of age.

Expansion Phase

As was observed for the overall, all-treated population, the overall safety profile of nivolumab monotherapy and nivolumab + ipilimumab in subjects < 18 years of age was acceptable and consistent with the respective known safety profiles in the adult population. No meaningful differences were observed in safety results in paediatric (< 18 year old) subjects in Study CA209908 as compared with the overall, all-treated population; however, 1 DLT (treatment-related Grade 3 pancreatitis and Grade 2 colitis) was noted for nivolumab + ipilimumab during extended safety monitoring in the expansion phase in 1 subject in Cohort 5 (the subject was 13 years old).

Nivolumab Monotherapy (Module A)

In combined cohorts treated with nivolumab monotherapy, among subjects < 18 years of age:

- 61 (79.2%) subjects had died. No deaths were attributed to study drug toxicity.

- The frequency of drug-related SAEs was 11.7%.

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- Drug-related AEs leading to discontinuation were reported in 11.7% of subjects.

- The frequency of drug-related AEs was 55.8%; 14.3% of subjects had Grade 3-4 drug-related AEs.

- Grade 3-4 drug-related AEs reported in ≥ 2 subjects were neutrophil count decreased (3.9%), rash (2.6%), and platelet count decreased (2.6%).

Nivolumab + Ipilimumab (Module B)

In combined cohorts treated nivolumab + ipilimumab, among subjects < 18 years of age:

- 55 (74.3%) subjects had died. No deaths were attributed to study drug toxicity.

- The frequency of drug-related SAEs was 27.0%.

- Drug-related AEs leading to discontinuation were reported in 18.9% of subjects.

- The frequency of drug-related AEs was 67.6%; 29.7% of subjects had Grade 3-4 drug-related AEs.

- Grade 3-4 drug-related AEs reported in ≥ 2 subjects were alanine aminotransferase (ALT) increased (6.8%), aspartate aminotransferase (AST) increased (5.4%), weight decreased (2.7%), and tumour flare (2.7%).

Most select AEs and immune-mediated AEs (IMAEs) were Grade 1-2 in the < 18 year population were consistent with the overall, all-treated population. A summary of safety results in the treated patients <18 year of age is presented in Table 8.

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Table 10: Overall Safety Summary - All Treated Subjects < 18 Years (Modules A and B)

Safety Parameters	No. of Subjects (%)			
	Nivolumab (N = 77)		Nivolumab + Ipilimumab (N = 74)	
Deaths	61 (79.2)		55 (74.3)	
Primary Reason for Death				
Disease	60 (77.9)		54 (73.0)	
Study Drug Toxicity	0		0	
Unknown	0		0	
Other Reasons[a]	1 (1.3)		1 (1.4)	
Subjects who died within 30 days of last dose	12 (15.6)		5 (6.8)	
Subjects who died within 100 days of last dose	30 (39.0)		17 (23.0)	

Preferred Term	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All-causality SAEs	40 (51.9)	22 (28.6)	45 (60.8)	34 (45.9)
Drug-related SAEs	9 (11.7)	4 (5.2)	20 (27.0)	13 (17.6)
All-causality AEs leading to DC	20 (26.0)	14 (18.2)	25 (33.8)	21 (28.4)
Drug-related AEs leading to DC	9 (11.7)	6 (7.8)	14 (18.9)	12 (16.2)
All-causality AEs	74 (96.1)	30 (39.0)	71 (95.9)	47 (63.5)
≥ 20% of Subjects in any Treatment Group				
Headache	34 (44.2)	2 (2.6)	24 (32.4)	6 (8.1)
Vomiting	28 (36.4)	3 (3.9)	32 (43.2)	5 (6.8)
Fatigue	19 (24.7)	3 (3.9)	16 (21.6)	2 (2.7)
Diarrhea	18 (23.4)	1 (1.3)	18 (24.3)	1 (1.4)
Pyrexia	12 (15.6)	1 (1.3)	16 (21.6)	1 (1.4)
Constipation	11 (14.3)	1 (1.3)	16 (21.6)	0
Nausea	14 (18.2)	2 (2.6)	15 (20.3)	0
Cough	12 (15.6)	0	15 (20.3)	0
Drug-related AEs	43 (55.8)	11 (14.3)	50 (67.6)	22 (29.7)
≥ 5% of Subjects in any Treatment Group				
AST increased	6 (7.8)	1 (1.3)	10 (13.5)	4 (5.4)
ALT increased	7 (9.1)	1 (1.3)	9 (12.2)	5 (6.8)
Fatigue	8 (10.4)	1 (1.3)	6 (8.1)	0
Decreased appetite	7 (9.1)	1 (1.3)	4 (5.4)	0
Vomiting	5 (6.5)	0	7 (9.5)	0
Abdominal pain	6 (7.8)	0	3 (4.1)	0
Weight decreased	2 (2.6)	0	6 (8.1)	2 (2.7)
Diarrhea	5 (6.5)	0	5 (6.8)	1 (1.4)
Headache	4 (5.2)	0	5 (6.8)	0
Neutrophil count decreased	5 (6.5)	3 (3.9)	1 (1.4)	1 (1.4)
White blood cell count decreased	4 (5.2)	0	2 (2.7)	0
Rash	5 (6.5)	2 (2.6)	2 (2.7)	1 (1.4)
Tumour flare	1 (1.3)	0	4 (5.4)	2 (2.7)
Platelet count decreased	3 (3.9)	2 (2.6)	4 (5.4)	1 (1.4)

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Safety Parameters Preferred Term	Nivolumab (N = 77)		Nivolumab + Ipilimumab (N = 74)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Dry skin	1 (1.3)	0	4 (5.4)	0
Pyrexia	3 (3.9)	0	4 (5.4)	0
Hypothyroidism	4 (5.2)	0	4 (5.4)	0
Hyperthyroidism	0	0	4 (5.4)	0
All-causality Select AEs				
Skin	24 (31.2)	3 (3.9)	18 (24.3)	1 (1.4)
Gastrointestinal	19 (24.7)	1 (1.3)	22 (29.7)	6 (8.1)
Endocrine	6 (7.8)	0	10 (13.5)	0
Hepatic	14 (18.2)	6 (7.8)	17 (23.0)	9 (12.2)
Pulmonary	0	0	1 (1.4)	1 (1.4)
Hypersensitivity/Infusion Reactions	1 (1.3)	0	8 (10.8)	1 (1.4)
Renal	6 (7.8)	0	3 (4.1)	0
Drug-Related Select AEs				
Skin	11 (14.3)	3 (3.9)	9 (12.2)	1 (1.4)
Endocrine	5 (6.5)	0	8 (10.8)	0
Gastrointestinal	6 (7.8)	0	10 (13.5)	6 (8.1)
Hepatic	11 (14.3)	5 (6.5)	15 (20.3)	8 (10.8)
Pulmonary	0	0	1 (1.4)	1 (1.4)
Hypersensitivity/Infusion Reactions	0	0	6 (8.1)	0
Renal	3 (3.9)	0	1 (1.4)	0
All-causality non-endocrine IMAEs within 100 days of last dose				
Treated with immune modulating medication[b]				
Rash	2 (2.6)	1 (1.3)	4 (5.4)	1 (1.4)
Diarrhea/Colitis	2 (2.6)	0	8 (10.8)	6 (8.1)
Hepatitis	4 (5.2)	4 (5.2)	7 (9.5)	6 (8.1)
Hypersensitivity	0	0	1 (1.4)	0
All-causality endocrine IMAEs within 100 days of last dose				
With or Without Immune Modulating Medication[c]				
Hypothyroidism/ Thyroiditis	4 (5.2)	0	6 (8.1)	1 (1.4)
Hyperthyroidism	0	0	4 (5.4)	0
All-causality OESIs within 100 days of last dose[d]				
Pancreatitis	0	0	1 (1.4)	1 (1.4)

[a]Other' reasons reported as: cardiorespiratory arrest in Module A and unexpected death in Module B.

[b]No events were reported in the following non-endocrine IMAE categories in both treatment modules: pneumonitis and nephritis/renal dysfunction

[c]No events were reported in the following endocrine IMAE categories in both treatment modules: adrenal insufficiency, diabetes mellitus, and hypophysitis

[d]No events were reported in the following OESI categories: myocarditis, myasthenic syndrome, demyelination, encephalitis, uveitis, myositis/rhabdomyolysis, graft versus host disease, and Guillain-Barré syndrome

MedDRA version 23.1 CTCAE version 4.0. All events are within 30 days of the last dose of study drug, unless otherwise indicated.

Abbreviations: AE = adverse event, ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTC = Common Toxicity Criteria, DC = discontinuation, IMAE = immune-mediated adverse event; MedDRA = Medical Dictionary for Regulatory Activities, OESI = other event of special interest, SAE = serious adverse event

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2.3.3. Discussion on clinical aspects

The MAH submitted the final CSR for study CA209908 as part of this Article 46 procedure. In this open-label, uncontrolled study, 152 paediatric patients were treated with nivolumab monotherapy (n=77) or nivolumab + ipilimumab combination therapy (n=74) in five cohorts based on different CNS tumour types.

The primary endpoints of OS in Cohort 1 (DIPG) and PFS in Cohorts 2-5 (other high-grade primary CNS malignancies) showed short survival. Results for OS and PFS were intended to be compared with the available historical controls (median OS of 9 months for DIPG, median PFS of 2.25 months for HGG, 4-month PFS rate of 18% for medulloblastoma and median PFS of 2.1 months for ependymoma). However, given the limitations associated with the available historical controls (eg, single studies and small sample sizes) and the small precision on point estimates and CIs, no meaningful conclusions could be drawn based on comparison against the historical values.

Across the 5 cohorts treated with nivolumab monotherapy, 1 patient with ependymoma had a partial response. The time to response was 2.83 months and, as of the data cut off, the DOR was 31.2 months with the response still ongoing. There were no other responses on nivolumab monotherapy, and there were no responses in patients treated with nivolumab + ipilimumab.

It is agreed with the Applicant that, overall, results for OS, PFS, and objective response rate observed in Study CA209908 did not demonstrate clinically meaningful improvement over what is expected in these patient populations. These data therefore do not warrant further investigation of nivolumab or nivolumab + ipilimumab in these tumour types. It is stated that no new indication will be pursued for these medicinal products in paediatric patients with CNS malignancies.

The safety profiles of nivolumab monotherapy and nivolumab + ipilimumab combination therapy in the evaluated overall, all-treated patient population with high-grade primary CNS malignancies were acceptable, and consistent with previously reported studies in the adult population. Low rates of treatment discontinuation due to drug toxicity were observed. As expected, drug-related AEs, SAEs, select AEs, and IMAEs were more frequent with nivolumab + ipilimumab relative to nivolumab monotherapy. One DLT was observed in 1 subject treated with nivolumab + ipilimumab in Cohort 5 during extended safety monitoring (treatment-related grade 3 pancreatitis and grade 2 colitis). There were no new safety signals identified. Safety in paediatric subjects (<18 year population, n=151) was similar to that observed in the overall, all-treated patient population (n=166).

In summary, in the overall population in Study CA209908, there was no evidence of efficacy with nivolumab alone or with nivolumab + ipilimumab in subjects with high-grade primary CNS tumours (of whom 91% were paediatric patients) based on the primary and key efficacy endpoints specified. No new safety signals were detected in the study. No updates to the Product Information of Opdivo or Yervoy are being proposed by the Applicant. This is not agreed, as the results from Study CA209908 could be relevant for the prescriber.

Currently, in section 5.1 of the Yervoy SmPC, only the results of 25 paediatric patients treated in studies CA184070 and CA184078 are described. This includes data on 17 melanoma patients, currently the only indication for Yervoy in the paediatric population. As concluded, the CA209908 study results do not support efficacy of either nivolumab monotherapy or nivolumab + ipilimumab combination therapy in paediatric CNS tumours, there is no approval for this indication in adults, these treatments are not included in guidelines nor suggested by literature. However, considering the dismal prognosis of paediatric CNS tumours and the high unmet medical need in this population, treating physicians might consider immunotherapy as a treatment option. In this light, the lack of efficacy in

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Study CA209908 should be described in section 5.1 of the SmPC of Opdivo and Yervoy, as the reported study does provide new information.

On the safety data, section 4.8 of the Yervoy SmPC contains safety data on 12 patients from 12-18 years of age. The current study includes a much larger cohort of paediatric patients and a short study description including the primary efficacy and safety findings should be included in the SmPC.

Section 4.8 of the Opdivo SmPC does not include a subsection on the safety in the paediatric population. This section should be added to the SmPC with a description of the safety data from Study CA209908.

Regarding posology, for Opdivo, which is not indicated in the paediatric population, the following statement is included in section 4.2 of the SmPC:

Paediatric population

The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available.

For Yervoy, the following is stated in section 4.2 of the SmPC:

Paediatric population

The safety and efficacy of YERVOY in children younger than 12 years of age have not been established. Very limited data are available. YERVOY should not be used in children younger than 12 years of age.

Also this section should be updated for both the Opdivo and Yervoy SmPC's, based on the results of study CA209908 submitted in the current procedure and in line with the SmPC guideline.

3. Overall conclusion and recommendation

It is agreed with the Applicant that the results of Study CA209908 showed no evidence of efficacy with nivolumab alone or with nivolumab + ipilimumab in subjects with high-grade primary CNS tumours (of whom 91% were paediatric patients), and that no new safety signals were detected in the study. However, as this concerns new information which is of relevance to the prescriber, the efficacy and safety results for Study CA209908 should be described in both the Yervoy and Opdivo SmPC's. An update of sections 4.2, 4.8 and 5.1 is warranted for Yervoy, and an update of sections 4.2, 4.8 and 5.1 is warranted for Opdivo. The Applicant should propose and update of both SmPC's via a separate type II variation procedure in line with the Paediatric Regulation.

☒ **Fulfilled:** However, to improve the information available on the use of medicinal products in the paediatric population, relevant information on use in paediatric populations should be included in the authorised product information in line with the Paediatric regulation. The MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and no later than 60 days after the receipt of these conclusions.

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