Neuro-Oncology

Nivolumab with or without ipilimumab in pediatric patients with high-grade CNS malignancies: Safety, efficacy, biomarker, and pharmacokinetics—CheckMate 908

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Abstract

Background. Therapeutic options are limited in pediatric CNS malignancies. CheckMate 908 (NCT03130959) is an open-label, sequential-arm, phase 1b/2 study investigating nivolumab (NIVO) and NIVO + ipilimumab (IPI) in pediatric patients with high-grade CNS malignancies.

Methods. Patients (N = 166) in 5 cohorts received NIVO 3 mg/kg every 2 weeks (Q2W) or NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks (4 doses) followed by NIVO 3 mg/kg Q2W. Primary endpoints included overall survival (OS; newly diagnosed diffuse intrinsic pontine glioma [DIPG]) and progression-free survival (PFS; other recurrent/progressive or relapsed/resistant CNS cohorts). Secondary endpoints included other efficacy metrics and safety. Exploratory endpoints included pharmacokinetics and biomarker analyses.

Results. As of January 13, 2021, median OS (80% CI) was 11.7 (10.3–16.5) and 10.8 (9.1–15.8) months with NIVO and NIVO + IPI, respectively, in newly diagnosed DIPG. Median PFS (80% CI) with NIVO and NIVO + IPI was 1.7 (1.4–2.7) and 1.3 (1.2–1.5) months, respectively, in recurrent/progressive high-grade glioma; 1.4 (1.2–1.4) and 2.8 (1.5–4.5) months in relapsed/resistant medulloblastoma; and 1.4 (1.4–2.6) and 4.6 (1.4–5.4) months in relapsed/resistant ependymoma. In patients with other recurrent/progressive CNS tumors, median PFS (95% CI) was 1.2 (1.1–1.3) and 1.6 (1.3–3.5) months, respectively. Grade 3/4 treatment-related adverse-event rates were 14.1% (NIVO) and 27.2% (NIVO + IPI). NIVO and IPI first-dose trough concentrations were lower in youngest and lowest-weight patients. Baseline tumor programmed death ligand 1 expression was not associated with survival.

Conclusions. NIVO ± IPI did not demonstrate clinical benefit relative to historical data. The overall safety profiles were manageable with no new safety signals.

Key Points

- NIVO ± IPI did not improve survival in pediatric patients with CNS malignancies.
- The safety profiles of NIVO ± IPI were manageable in the pediatric population.
- Baseline tumor PD-L1 expression was not associated with survival with NIVO ± IPI.

Primary CNS tumors are heterogeneous and are collectively the most common malignancy in children and the most common cause of cancer-related mortality and morbidity (aged 0–19 years).[1] Patients with CNS tumors (eg, diffuse intrinsic pontine glioma [DIPG], high-grade glioma [HGG]) have poor prognoses at diagnosis;[2,3] others (eg, medulloblastoma,

Importance of the Study

An urgent need exists for novel therapeutics for pediatric patients with CNS malignancies, the most common cause of cancer-related mortality in children. Immune checkpoint inhibitors were evaluated in CheckMate 908. Nivolumab (NIVO) and NIVO + ipilimumab (IPI) did not improve survival in patients with newly diagnosed diffuse intrinsic pontine glioma following upfront irradiation or with other high-grade CNS malignancies (recurrent/progressive high-grade glioma, relapsed/resistant medulloblastoma, relapsed/resistant ependymoma, and other recurrent/progressive CNS tumors), consistent with historical data. The safety profiles of NIVO ± IPI were manageable. Although use of NIVO ± IPI in pediatric CNS malignancies is not currently warranted, further investigation with combination strategies should be considered.

ependymoma) have fair prognoses at diagnosis but poor long-term prognoses for recurrent disease.[4,5]

Immunotherapy represents a promising option in several non-CNS solid tumors in adults. Various immunotherapy agents are under investigation in pediatric brain tumors.[6] Immune cells can enter and function within the tumor microenvironment of CNS malignancies, including pediatric brain tumors.[7–9] Lymphocyte infiltration has been found in pediatric glioblastoma (GBM), medulloblastoma, ependymoma, and atypical teratoid/rhabdoid tumors, with higher lymphocyte numbers in ependymoma tissue vs non-tumor-bearing brain tissue, GBM, and medulloblastoma samples.[8,10,11] Microglia may also contribute to the immunosuppressive tumor microenvironment of various CNS tumors.[12–16]

The immune checkpoint inhibitors (ICIs) nivolumab (NIVO) and ipilimumab (IPI) are fully humanized IgG monoclonal antibodies targeting programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated protein (CLTA-4), respectively, and are approved to treat multiple advanced cancers both as monotherapy and in combination,[17,18] including for pediatric patients ≥12 years with unresectable or metastatic melanoma (IPI) and microsatellite instability-high (MSI-H) or mismatch repair–deficient metastatic colorectal cancer (NIVO ± IPI).[17,18]

Investigation of ICIs in brain tumors has focused on adults with GBM, although none are approved. Ongoing trials of NIVO in adult GBM at the start of this trial included CheckMate 143 and 548 and the recently concluded CheckMate 498. Phase 1 exploratory cohorts of CheckMate 143 reported that NIVO ± IPI was tolerable in adults with recurrent GBM with some antitumor activity signals; however, median overall survival (OS) was consistent with historical controls.[19] NIVO was also evaluated in adults with newly diagnosed GBM in additional exploratory phase 1 cohorts from CheckMate 143 and in the phase 3 CheckMate 498 and CheckMate 548 trials.[19–22] Although no new safety signals were detected with NIVO, primary endpoints of improved survival were not achieved in CheckMate 498 and Checkmate 548.[19–22]

Good tolerability of both NIVO and IPI has been reported in pediatric patients with relapsed/refractory non-CNS solid tumors and lymphoma[23] and recurrent/progressive solid tumors.[24] Clinical activity was observed in pediatric patients with unresectable melanoma treated with IPI, but the trial was terminated due to slow accrual.[25]

Here, we report efficacy, safety, biomarker, and pharmacokinetic results from CheckMate 908 (NCT03130959), an open-label, sequential-arm, phase 1b/2 trial of NIVO monotherapy and NIVO + IPI in pediatric patients with high-grade recurrent/progressive or relapsed/resistant CNS malignancies, and newly diagnosed DIPG treated within 6 weeks from completion of upfront radiotherapy (RT).

Methods

Patients

Patients were enrolled in 5 cohorts. Cohort 1 included patients with newly diagnosed DIPG (including diffuse midline glioma with *H3K27M* mutation) confirmed by MRI or histology who were within 4 weeks from the completion of upfront RT only. Cohort 2 included patients with histologically confirmed recurrent/progressive non-brain stem HGG (including GBM) previously treated with surgical resection and RT (with or without chemotherapy). Cohort 3 included patients with histologically confirmed medulloblastoma with relapse/resistance to ≥1 line of therapy, including surgery, RT, or chemotherapy. Cohort 4 included patients with histologically confirmed ependymoma with relapse/resistance to ≥1 line of therapy including surgical resection and RT. Cohort 5 included patients agreed upon by the clinical team with a diverse array of complex and rare histologically confirmed high-grade CNS malignancies not included in cohorts 1 to 4 that were recurrent/progressive after ≥1 line of therapy (Supplementary Table S1 details individual cases). Patients in cohorts 2 to 5 were required to submit a tumor sample (from surgery following recurrence prior to baseline or from archival tissue). Patients in cohort 1 were not required to submit tumor samples.

All patients previously received standard-of-care therapy or had no available potentially curative treatment. Patients were aged ≥0.5 to <22 years at enrollment with a Lansky performance score (age ≤16 years) or a Karnofsky performance score (age >16 years) of ≥60 within 2 weeks of enrollment. An interval of ≥12 weeks was required after prior RT termination unless histopathologic confirmation of recurrent tumor or a new enhancement on MRI outside the RT treatment field occurred (cohorts 2–5). A 4-week interval (or 5 half-lives of a targeted therapy with short half-life) was required after last administration of other treatment for CNS malignancies (6 weeks for nitrosoureas). The interval from most recent bevacizumab infusion had to be 5 weeks, and 7 days or 5 half-lives for other biological agents, whichever was longer.

Patients were requested to taper corticosteroids at a clinically appropriate pace and discontinue use, if possible, prior to study treatment. Eligible patients could receive dexamethasone ≤0.05 mg/kg daily (or equivalent) for tumor-associated intracranial mass effect at study entry. In the absence of active autoimmune disease, patients were permitted inhaled or topical steroids and adrenal replacement steroid doses of >0.25 mg/kg daily prednisone equivalent for concurrent conditions other than brain tumors. Patients who had received high-dose chemotherapy must have been ≥6 months post-autologous hematopoietic cell transplant with a CD4 count of ≥200/mm³. Baseline steroid use was recorded within 5 days before first dose for consistency with prior studies; this window was not used to determine eligibility.

Patients were excluded for prior allogeneic bone marrow transplant; anti-PD-1, anti-programmed death ligand 1 (PD-L1), anti-PD-L2, anti-CTLA-4, or other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways; receiving any anti-cancer therapy, investigational therapy, or non-palliative RT; low-grade gliomas; tumors of unknown malignant potential; bulky tumors (imaging >6 cm); grade >1 recent CNS hemorrhage (baseline MRI); active, known, or suspected autoimmune disease; or inability to undergo contrast MRI.

Study Design and Treatment

Patients were enrolled into 2 modules (Module A; Module B). Patients in Module A received NIVO 3 mg/kg i.v. Q2W (NIVO3), and patients in Module B received NIVO 3 mg/kg i.v. + IPI 1 mg/kg i.v. once every 3 weeks (IPI1) for 4 doses then NIVO3 Q2W (NIVO3 + IPI1; Supplementary Figure S1). This study made no direct comparisons between treatments or among cohorts.

The study included safety lead-in and expansion phases. The safety lead-in population was evaluated for safety and tolerability following 3 doses and ≥6 weeks on study based on a dose-limiting toxicity assessment. Patients in the safety lead-in were included for evaluation of efficacy in the expansion phase. Module A enrolled in parallel for all cohorts. Module B opened by cohort when planned accrual to respective Module A cohort was completed or by decision of the Study Steering Committee.

Primary endpoints were safety/tolerability in the safety lead-in phase, OS in cohort 1, and progression-free survival (PFS) in cohorts 2 to 5 in the expansion phase. Secondary endpoints included safety/tolerability in the expansion phase; PFS and 12-month OS rate in cohort 1; OS, 6-month PFS rate, and 12-month OS rate in cohorts 2 to 4; and OS and 6-month PFS rate in cohort 5. Exploratory endpoints included pharmacokinetics and biomarkers.

Assessments

Disease status (ie, best overall response) was assessed using contrast-enhanced MRI after 6 and 12 weeks (±1 week), then every 8 weeks (±1 week) (×4), then every 12 weeks (±1 week) until progressive disease (PD) according to Radiologic Assessment in Neuro-Oncology (RANO).

OS was defined as the time between diagnosis date and death or last known alive date (cohort 1) and time from date of first dose and death or last known alive date (cohorts 2–5). The cohort 1 OS definition was selected to discuss results in the context of historical studies that enrolled patients with DIPG prior to RT. Date of first dose to death was determined to be the most robust OS measure for relapsed/refractory disease groups. OS was documented continuously while on study and at 3-month intervals during the survival follow-up beginning at the second follow-up visit (≈100 days after last study treatment dose).

Across all cohorts, PFS was defined as time from first dose to first documented tumor progression or death (any cause) and determined by investigators using RANO criteria.[26]

In cohort 1, suspected PD within ≤12 weeks after RT completion was confirmed per RANO, when potential pseudoprogression is thought to be most prevalent.[27] PD was assessed by subsequent MRI ≈6 to 8 weeks after initial radiological assessment of progression. PD was confirmed if most of the new enhancement was outside the radiation field (beyond the high-dose region or 80% isodose line) or if pathological evidence of PD existed. To differentiate between pseudoprogression and confirmed PD, pseudoprogression was defined as absence of clinical progression and clear worsening of lesions in the first follow-up ≥3 months after the date of reported PD (including death from study disease). Patients who initially met radiologic criteria for disease progression but were tolerating NIVO ± IPI were permitted to continue until progression was confirmed. Imaging was not transmitted for centralized review.

Adverse events (AEs) were assessed continually per National Cancer Institute Common Terminology Criteria for Adverse Events version 4. A serious AE was defined as any treatment-emergent event that resulted in death, was life-threatening, required inpatient hospitalization or resulted in prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was deemed an important medical event.

Pharmacokinetics

The pharmacokinetic sample collection schedule for NIVO ± IPI is presented in the Supplementary Materials. NIVO and IPI trough serum concentrations (pre-infusion dose) on cycle 2 day 1 (C_{min1}) were determined from monotherapy or combination treatment and evaluated according to age and weight.

Biomarkers

Tumor PD-L1 expression was assessed by immunohistochemistry on formalin-fixed, paraffin-embedded tumor tissue obtained before first study dose (fresh or archival). PD-L1 expression was defined as the percentage of tumor cells with membrane staining in ≥100 evaluable tumor cells per validated Dako PD-L1 immunohistochemistry assay (Mosaic Laboratories; MOS785-APD). Analyses for tumor PD-L1 were based on baseline PD-L1-positive status (1% and

Table 1. Patient Demographics and Baseline Characteristics, All Treated

Variable	NIVO3 *n* = 85 No. (%)	NIVO3 + IPI1 *n* = 81 No. (%)
Age		
Median (range), years	10.0 (1–21)	11.0 (1–21)
Age, years		
<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)
Disease diagnosis		
Cohort 1:		
DIPG	18 (21.2)	18 (22.2)
Diffuse midline glioma[a]	5 (5.9)	4 (4.9)
Cohort 2:		
HGG[b]	16 (18.8)	15 (18.5)
Cohort 3:		
Medulloblastoma	15 (17.6)	15 (18.5)
Cohort 4:		
Ependymoma	12 (14.1)	10 (12.3)
Cohort 5 (other diagnoses)[c]:		
Atypical teratoid rhabdoid tumor	4 (4.7)	3 (3.7)
Pineoblastoma	4 (4.7)	0
Choroid plexus carcinoma	0	4 (4.9)
HGG	2 (2.4)	1 (1.2)
Anaplastic pleomorphic xanthoastrocytoma	1 (1.2)	1 (1.2)
Embryonal tumor with multilayered rosettes	1 (1.2)	1 (1.2)
Malignant germ cell tumor	1 (1.2)	1 (1.2)
Diffuse midline glioma	1 (1.2)	0
Other[d]	5 (5.9)	8 (9.9)
Disease stage		
Localized	54 (63.5)	60 (74.1)
Metastatic	31 (36.5)	21 (25.9)
LPS/KPS		
<80	17 (20.0)	14 (17.3)
≥80	68 (80.0)	67 (82.7)
Time from initial diagnosis to first dose[e]		
<6 months	1 (1.2)	2 (2.5)
6 to <12 months	7 (8.2)	6 (7.4)
12 to <18 months	10 (11.8)	11 (13.6)
18 to <24 months	5 (5.9)	6 (7.4)
≥24 months	38 (44.7)	34 (42.0)
Not reported	1 (1.2)	0
Steroid use[f]		
Yes	17 (20.0)	10 (12.3)
No	68 (80.0)	71 (87.7)

Table 1. Continued

Variable	NIVO3 n = 85 No. (%)	NIVO3 + IPI1 n = 81 No. (%)
PD-L1 expression level		
Quantifiable	62 (72.9)	57 (70.4)
<1%	41 (66.1)	42 (73.7)
≥1%	21 (33.9)	15 (26.3)
<5%	46 (74.2)	46 (80.7)
≥5%	16 (25.8)	11 (19.3)
Indeterminate/not evaluable	1 (1.2)	2 (2.5)
Not reported[g]	22 (25.9)	22 (27.2)
DIPG (biopsy not required), n	20	21
Not reported, n	2	1
Prior RT	80 (94.1)	76 (83.8)
Prior systemic therapy[e]	56 (65.9)	56 (69.1)
Prior surgery related to cancer	66 (77.6)	62 (76.5)

Abbreviations: DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; IPI, ipilimumab; KPS, Karnofsky performance status; LPS, Lansky performance status; NIVO, nivolumab; NOS, not otherwise specified; PD-L1, programmed death ligand 1; PNET, primitive neuroectodermal tumor; RT, radiotherapy.
[a]Cohort 1 eligibility included diffuse midline glioma with demonstrated H3K27M mutation.
[b]Cohort 2 included patients with non-brain stem HGG.
[c]Several of these patients had complex diagnoses that could have placed them in more than one cohort; however, after discussion and agreement by the clinical team, the patients were ultimately placed into cohort 5 on a case-by-case basis.
[d]Cohort 5 "other" diagnoses at study entry: NIVO3: isolated spine lesion (n = 1), CNS embryonal tumor, NOS group, WHO grade 4 (n = 1); disseminated oligodendroglial-like leptomeningeal tumor (n = 1); PNET (n = 1); high-grade neuroepithelial tumor (n = 1); NIVO3 + IPI1: PNET (n = 2); CNS embryonal tumor NOS (n = 1); ependymoblastoma (n = 1); cribriform neuroepithelial tumor (n = 1); atypical meningioma WHO grade 2 (n = 1); supratentorial PNET (n = 1); anaplastic astrocytoma grade 3 (n = 1).
[e]Excluding DIPG and diffuse midline glioma.
[f]Baseline corticosteroid use is based on corticosteroid use within 5 days prior to first dose date. Patients receiving corticosteroids for tumor-associated intracranial mass effect at the time of screening were required to discontinue or taper use to ≤0.05 mg/kg of dexamethasone daily (or equivalent) at study entry.
[g]DIPG cohort included in total output. Tissue collection was not required for DIPG cohort.

5% cutoffs). See Supplementary Methods for whole exome sequencing (WES) for tumor mutational burden (TMB) methods. Genetic or molecular analyses (eg, H3K27M mutation, *BRAF* mutation, RELA-fusion, etc.) were performed according to institutional standards.

Statistical Analysis

Primary endpoints: OS (cohort 1) and PFS (cohorts 2–5) curves were estimated using Kaplan–Meier methodology. Median OS, median PFS, and corresponding 2-sided 80% CIs (OS, cohort 1; PFS, cohorts 2–4) and 95% CIs (PFS, cohort 5) were computed using Greenwood's formula with log–log transformation.

Secondary endpoints: OS (cohort 2–5) and PFS (cohort 1) curves were estimated using Kaplan–Meier methodology. Median OS, median PFS, and corresponding 2-sided 95% CIs (OS, cohorts 2–5; PFS, cohort 1) were computed using log–log transformation. 95% CIs were computed for 12-month OS and 6-month PFS rate.

Exploratory endpoints: Summary statistics, including geometric means and coefficients of variation, were reported for pharmacokinetics data. PD-L1 expression was summarized using descriptive statistics.

Study Oversight

The study was conducted in accordance with Good Clinical Practice guidelines per the International Conference on Harmonisation ethical principles of the European Union Directive and US Code of Federal Regulations and registered at ClinicalTrials.gov (NCT03130959). The protocol was approved by institutional review boards and/or independent ethics committees at each site. All patients or their parents/legal guardians provided written informed consent in accordance with the Declaration of Helsinki.

Results

Patients

Overall, 204 patients were enrolled, and 166 patients were treated (NIVO3, n = 85; NIVO3 + IPI1, n = 81) at 51 sites
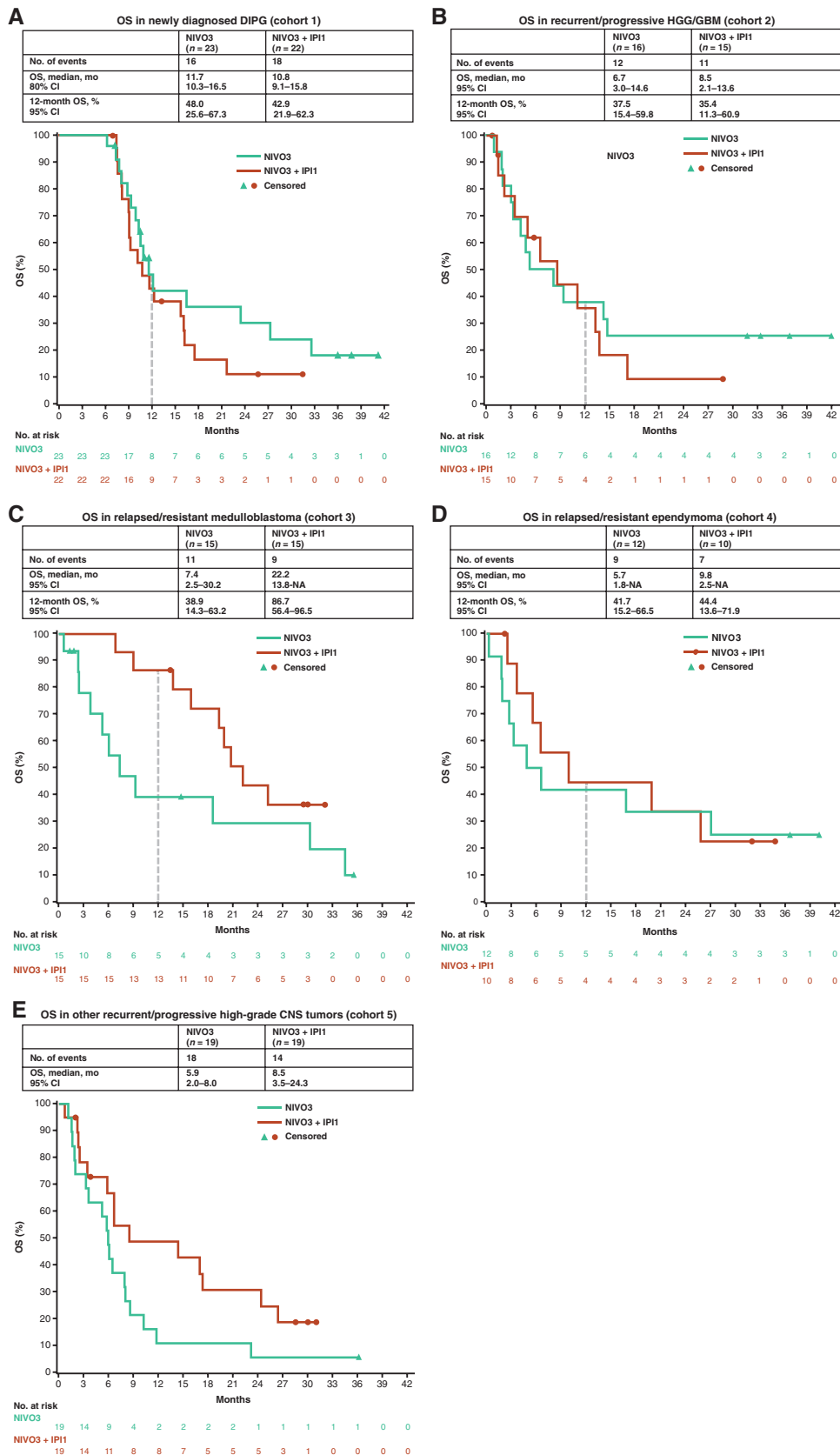
Figure 1. Overall survival. Number of events, median OS, and Kaplan–Meier curve for OS in cohort 1 (newly diagnosed DIPG) (A), cohort 2 (recurrent/progressive HGG) (B), cohort 3 (relapsed/resistant medulloblastoma) (C), cohort 4 (relapsed/resistant ependymoma) (D), and cohort

across 15 countries. Baseline characteristics were balanced between modules and were representative of the diseases studied (Table 1). Median ages in the NIVO3 and NIVO3 + IPI1 groups were 10.0 (range, 1–21) and 11.0 (range, 1–21) years, respectively. Among treated patients with baseline PD-L1 positivity, tumor PD-L1 expression was ≥1% in 33.9% (NIVO3) and 26.3% (NIVO3 + IPI1). Eighty percent and 87.7% of patients treated with NIVO3 and NIVO3 + IPI1, respectively, had no baseline corticosteroid use. Among patients treated with NIVO3 with baseline corticosteroid use (presented in dexamethasone equivalent doses) within 5 days of first treatment dose, 14 (16.5%) received ≤0.04 mg/kg/day, 2 (2.4%) received >0.04 to 0.05 mg/kg/day, and 1 (1.2%) received >0.05 mg/kg/day. In the NIVO3 + IPI1 group, corticosteroids were used by 5 (6.2%) patients at ≤0.04 mg/kg/day, 2 (2.5%) patients at >0.04 to 0.05 mg/kg/day, and 3 (3.7%) patients at >0.05 mg/kg/day. Upon analysis after study completion, 4 enrolled patients (cohort 1; NIVO3, n = 1; NIVO3 + IPI1, n = 3) appeared to exceed the 0.05 mg/kg/day corticosteroid use criterion at study entry. Of these 4 patients, 2 were confirmed eligible, and 2 were recorded as exceeding the maximum dose by weight. Supplementary Table S2 details baseline corticosteroid use by cohort and module.

Most Patients Discontinued Treatment

At data cutoff (January 13, 2021), the NIVO3 group received a median of 5 NIVO doses (range, 1–87). The NIVO3 + IPI1 group received a median of 4 NIVO (range, 1–63) and 4 IPI doses (range, 1–4).

Most patients discontinued treatment by data cutoff (NIVO3, 96.5%; NIVO3 + IPI1, 97.5%) (Supplementary Figure S2), most commonly due to PD (NIVO3, 74.1%; NIVO3 + IPI1, 64.2%) and treatment-related toxicity (NIVO3, 11.8%; NIVO3 + IPI1, 13.6%). Time to treatment discontinuation was similar between modules (Supplementary Table S3). Median durations of follow-up were 8.1 (range, 0.2–41.7) months with NIVO3 and 10.8 (range, 0.7–34.7) months with NIVO3 + IPI1.

No Survival Benefit Was Observed Across Cohorts

In newly diagnosed DIPG (cohort 1) median OS was 11.7 (80% CI, 10.3–16.5) months with NIVO3 (n = 23) and 10.8 (80% CI, 9.1–15.8) months with NIVO3 + IPI1 (n = 22); 12-month OS rates were 48.0% (95% CI, 25.6%–67.3%) with NIVO3 and 42.9% (95% CI, 21.9%–62.3%) with NIVO3 + IPI1 (Figure 1A). Median PFS was 6.2 (95% CI, 3.8–6.5) months with NIVO3 and 4.5 (95% CI, 2.8–6.4) months with NIVO3 + IPI1 (Figure 2A).

In recurrent/progressive HGG/GBM (cohort 2), median OS was 6.7 (95% CI, 3.0–14.6) months with NIVO3 (n = 16) and 8.5 (95% CI, 2.1–13.6) months with NIVO3 + IPI1 (n = 15); 12-month OS rates were 37.5% (95% CI, 15.4%–59.8%) with NIVO3 and 35.4% (95% CI, 11.3%–60.9%) with NIVO3 + IPI1 (Figure 1B). Median PFS was 1.7 (80% CI, 1.4–2.7) months with NIVO3 and 1.3 (80% CI, 1.2–1.5) months with NIVO3 + IPI1; 6-month PFS rates were 9.4% (95% CI, 0.7%–31.8%) and 15.4% (95% CI, 2.5%–38.8%), respectively (Figure 2B).

In relapsed/resistant medulloblastoma (cohort 3), median OS was 7.4 (95% CI, 2.5–30.2) months with NIVO3 (n = 15) and 22.2 (95% CI, 13.8-not available [N.A.]) months with NIVO3 + IPI1 (n = 15); 12-month OS rates were 38.9% (95% CI, 14.3%–63.2%) with NIVO3 and 86.7% (95% CI, 56.4%–96.5%) with NIVO3 + IPI1 (Figure 1C). Median PFS was 1.4 (80% CI, 1.2–1.4) months with NIVO3 and 2.8 (80% CI, 1.5–4.5) months with NIVO3 + IPI1; 6-month PFS rates were 0% and 20.0% (95% CI, 4.9%–42.4%), respectively (Figure 2C).

In relapsed/resistant ependymoma (cohort 4), median OS was 5.7 (95% CI, 1.8-N.A.) months with NIVO3 (n = 12) and 9.8 (95% CI, 2.5-N.A.) months with NIVO3 + IPI1 (n = 10); 12-month OS rates were 41.7% (95% CI, 15.2%–66.5%) with NIVO3 and 44.4% (95% CI, 13.6%–71.9%) with NIVO3 + IPI1 (Figure 1D). Median PFS was 1.4 (80% CI, 1.4–2.6) months with NIVO3 and 4.6 (80% CI, 1.4–5.4) months with NIVO3 + IPI1; 6-month PFS rates were 27.3% (95% CI, 6.5%–53.9%) and 11.4% (95% CI, 0.6%–39.5%), respectively (Figure 2D).

In recurrent/progressive other high-grade CNS tumors (cohort 5), median OS was 5.9 (95% CI, 2.0–8.0) months with NIVO3 (n = 19) and 8.5 (95% CI, 3.5–24.3) months with NIVO3 + IPI1 (n = 19) (Figure 1E). Median PFS was 1.2 (95% CI, 1.1–1.3) months with NIVO3 and 1.6 (95% CI, 1.3–3.5) months with NIVO3 + IPI1; 6-month PFS rates were 5.3% (95% CI, 0.4%–21.4%) and 14.0% (95% CI, 2.8%–34.1%), respectively (Figure 2E).
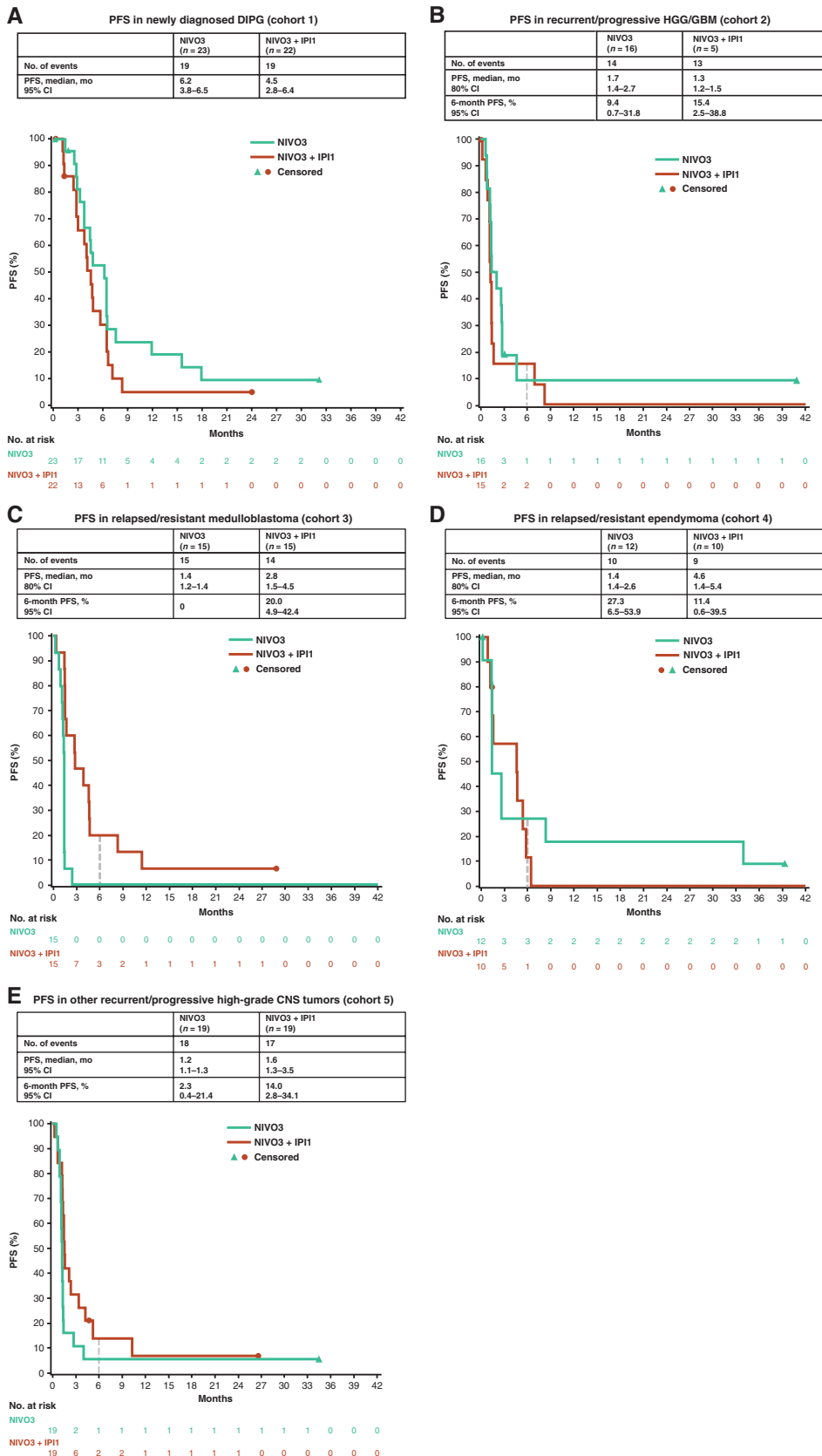
Pseudoprogression was identified in 2 patients treated with NIVO3 (cohort 2, n = 1; cohort 3, n = 1). Overall, 88.6% of patients had investigator-assessed PD, including 75.3% of patients with PD ≤6 months since treatment initiation. The median time from PD to death across modules was 4.04 months and was calculated to understand whether pseudoprogression played a role in the relatively rapid PD observed. The median (range) time from PD to death in months was 3.59 (0.13–12.19) in cohort 1, 2.96 (0.03–12.45) in cohort 2, 7.95 (0.43–33.22) in cohort 3, 3.11 (0.07–24.51) in cohort 4, and 3.96 (0.20–25.13) in cohort 5.

NIVO ± IPI Safety Profiles Were Manageable With No New Safety Signals

Supplementary Table S4 details the most frequent (>5%) AEs. Treatment-related adverse events (TRAEs) occurred in 57.6% (NIVO3) and 64.2% (NIVO3 + IPI1) of patients; grade

Figure 1. Continued

5 (other recurrent/progressive high-grade CNS tumors) (E). Symbols indicate censored observations. Overlay of Module A and Module B is not intended to provide statistical comparison between the treatment modules. DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; IPI, ipilimumab; NA, not available; NIVO, nivolumab; OS, overall survival.

A   PFS in newly diagnosed DIPG (cohort 1)

	NIVO3 (n = 23)	NIVO3 + IPI1 (n = 22)
No. of events	19	19
PFS, median, mo 95% CI	6.2 3.8–6.5	4.5 2.8–6.4

B   PFS in recurrent/progressive HGG/GBM (cohort 2)

	NIVO3 (n = 16)	NIVO3 + IPI1 (n = 5)
No. of events	14	13
PFS, median, mo 80% CI	1.7 1.4–2.7	1.3 1.2–1.5
6-month PFS, % 95% CI	9.4 0.7–31.8	15.4 2.5–38.8

C   PFS in relapsed/resistant medulloblastoma (cohort 3)

	NIVO3 (n = 15)	NIVO3 + IPI1 (n = 15)
No. of events	15	14
PFS, median, mo 80% CI	1.4 1.2–1.4	2.8 1.5–4.5
6-month PFS, % 95% CI	0	20.0 4.9–42.4

D   PFS in relapsed/resistant ependymoma (cohort 4)

	NIVO3 (n = 12)	NIVO3 + IPI1 (n = 10)
No. of events	10	9
PFS, median, mo 80% CI	1.4 1.4–2.6	4.6 1.4–5.4
6-month PFS, % 95% CI	27.3 6.5–53.9	11.4 0.6–39.5

E   PFS in other recurrent/progressive high-grade CNS tumors (cohort 5)

	NIVO3 (n = 19)	NIVO3 + IPI1 (n = 19)
No. of events	18	17
PFS, median, mo 95% CI	1.2 1.1–1.3	1.6 1.3–3.5
6-month PFS, % 95% CI	2.3 0.4–21.4	14.0 2.8–34.1

Figure 2. Progression-free survival. Number of events, median PFS, and Kaplan–Meier curve for PFS per investigator in cohort 1 (newly diagnosed DIPG), cohort 2 (recurrent/progressive HGG) (B), cohort 3 (relapsed/resistant medulloblastoma) (C), cohort 4 (relapsed/resistant

3/4 TRAEs were reported in 14.1% (NIVO3) and 27.2% (NIVO3 + IPI1) of patients (Table 2). The most common (>10% in either module) any-grade TRAEs were fatigue (10.6% and 8.6%), increased alanine aminotransferase (ALT; 8.2% and 11.1%), and increased aspartate aminotransferase (AST; 7.1% and 12.3%), with NIVO3 and NIVO3 + IPI1, respectively. Any-grade neurological TRAEs occurred in 16.5% of patients with NIVO3 and 13.6% of patients with NIVO3 + IPI1. The most frequent (>5%) neurological TRAE was headache (NIVO3, 7.1%; NIVO3 + IPI1, 6.2%). Severe (grade 3/4) AEs occurred in 38.8% (NIVO3) and 61.7% (NIVO3 + IPI1) of patients. The most frequent severe AEs included neutrophil count decreased (5.9%) and malignant neoplasm progression (4.7%) with NIVO3 and vomiting (8.6%) and headache (8.6%) with NIVO3 + IPI1. Serious TRAEs occurred in 11.8% (NIVO3) and 24.7% (NIVO3 + IPI1) of patients. No grade 5 TRAEs were observed.

TRAEs leading to discontinuation occurred in 10 patients (11.8%) with NIVO3 and 14 patients (17.3%) with NIVO3 + IPI1. TRAEs that led to discontinuation in ≥1 patient included hepatitis and rash with NIVO3 and colitis, increased ALT, and increased AST with NIVO3 + IPI1 (Supplementary Table S5). One dose-limiting toxicity occurred in cohort 5 (with NIVO3 + IPI1: atypical meningioma World Health Organization [WHO] grade 2, grade 3 pancreatitis, and grade 2 colitis).

In the NIVO3 and NIVO3 + IPI1 modules, 66 and 59 patients died, respectively; of these, 34 and 19 died ≤100 days after their last dose of study drug. The primary cause of death was PD (NIVO3, $n = 64/85$ [75.3%]; NIVO3 + IPI1, $n = 58/81$ [71.6%]). No deaths were attributed to study drug. Three patients died following PD for reasons considered unrelated to the study drug (NIVO3: $n = 1$, tumoral hemorrhage; $n = 1$ cardiorespiratory arrest; NIVO3 + IPI1: $n = 1$, unknown cause).

Age and Weight Impacted NIVO ± IPI Pharmacokinetics

Observed NIVO and IPI trough concentrations after first dose (C_{min1}) appeared lower in the youngest (<2 years of age) and lowest-weight (<20 kg) patients treated with NIVO3 and NIVO3 + IPI1 (Figure 3). NIVO C_{min1} values were similar when given as monotherapy or in combination with IPI.

Biomarker Profiles

Baseline PD-L1 positivity was quantifiable in 62 of 85 (72.9%) patients treated with NIVO3 (cohort 1, $n = 3$; cohort 2, $n = 14$; cohort 3, $n = 15$; cohort 4, $n = 12$; cohort 5, $n = 18$) and 57 of 81 (70.4%) patients treated with NIVO3 + IPI1 (cohort 2, $n = 15$; cohort 3, $n = 15$; cohort 4, $n = 10$; cohort 5, $n = 17$). Remaining samples were not evaluable or unavailable.

Cohort 1 was not required to submit a tumor sample, which accounted for most missing data. Supplementary Figure S3 contains representative PD-L1-positive staining images. There were no associations of OS or PFS in patients with evaluable tumor PD-L1 expression in either module (≥1% vs <1% and ≥5% vs <5%; Figure 4). Among 38 patients with available TMB data (NIVO3, $n = 15$; NIVO3 + IPI1, $n = 23$), 1 with recurrent/progressive HGG (NIVO3 + IPI1) had high TMB (7802 somatic mutations in exome), while remaining patients had <100 somatic mutations (Supplementary Figure S4). This patient demonstrated 5% tumor PD-L1 expression but did not respond to therapy (eg, an 11-month OS). One partial response was observed with NIVO3 in a patient with relapsed/resistant ependymoma with MSI-H and 13.6-month OS, as determined by WES using an exploratory MSI scoring algorithm (Supplementary Figure S5). Notably, 1 patient with recurrent/progressive non-brain stem HGG treated with NIVO3 demonstrated 40% PD-L1 expression and an OS of 41.7 months.

Medulloblastoma genetic subtyping was analyzed per available WHO guidelines at the time of the study for the 4 historically reported molecular subtypes[28,29] (Supplementary Table S6 and Figure S6). Low/absent CD8+ tumor-infiltrating lymphocytes were observed across recurrent/progressive and relapsed/resistant pediatric CNS tumors in all cohorts (data not shown). These tumors are considered immunologically "cold," as has been described previously in DIPG and pediatric low- and high-grade gliomas.[30,31] Only 4 HGG tumors in this study had CD8+ expression >1%.

Post-Checkmate 908 Treatment

Across all cohorts, 38 (44.7%) patients treated with NIVO3 and 34 (42.0%) treated with NIVO3 + IPI1 received ≥1 subsequent therapies on or after the first dosing date of the study drug (eg, new anticancer therapy, tumor-directed RT, or tumor-directed surgery prior to progression). Subsequent systemic therapy was the most frequent across modules (NIVO3: 35.3%; NIVO3 + IPI1: 34.6%).

Discussion

CheckMate 908 evaluated primary endpoints of safety and efficacy, including OS with NIVO ± IPI in pediatric patients with newly diagnosed DIPG (cohort 1) and PFS with NIVO ± IPI in pediatric patients with high-grade recurrent/relapsed CNS malignancies (cohorts 2–5). Although no potentially meaningful clinical OS or PFS benefit was observed, NIVO3 and NIVO3 + IPI1 were well tolerated with no new or unexpected treatment-related safety signals.

Despite NIVO and IPI showing efficacy in other cancer types,[17,18] and enhanced survival with the addition of

Figure 2. Continued

ependymoma) (D), and cohort 5 (other recurrent/progressive high-grade CNS tumors) (E). Symbols indicate censored observations. Overlay of Module A and Module B is not intended to provide statistical comparison between the treatment modules. DIPG, diffuse intrinsic pontine glioma; HGG, high-grade glioma; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival.

Table 2. Treatment-related Adverse Events, All Treated

Treatment-related adverse events	NIVO3 *n* = 85 No. (%)		NIVO3 + IPI1 *n* = 81 No. (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Patients with any TRAE	49 (57.6)[a]	12 (14.1)	52 (64.2)[a]	22 (27.2)
TRAEs in ≥5% of patients in either module[b]				
Fatigue	9 (10.6)	1 (1.2)	7 (8.6)	0
Decreased appetite	8 (9.4)	1 (1.2)	4 (4.9)	0
ALT increased	7 (8.2)	1 (1.2)	9 (11.1)	5 (6.2)
Abdominal pain	7 (8.2)	0	3 (3.7)	0
AST increased	6 (7.1)	1 (1.2)	10 (12.3)	4 (4.9)
Neutrophil count decreased	6 (7.1)	3 (3.5)	1 (1.2)	1 (1.2)
Headache	6 (7.1)	0	5 (6.2)	0
Diarrhea	6 (7.1)	0	5 (6.2)	1 (1.2)
WBC count decreased	6 (7.1)	0	2 (2.5)	0
Vomiting	5 (5.9)	0	7 (8.6)	0
Nausea	5 (5.9)	0	4 (4.9)	0
Rash	5 (5.9)	2 (2.4)	2 (2.5)	1 (1.2)
Weight decreased	2 (2.4)	0	6 (7.4)	2 (2.5)
Neurological disorders	14 (16.5)	1 (1.2)	11 (13.6)	1 (1.2)
Serious TRAEs	10 (11.8)[a]	5 (5.9)	20 (24.7)	13 (16.0)
TRAEs leading to discontinuation	10 (11.8)[a]	6 (7.1)	14 (17.3)	12 (14.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; TRAE, treatment-related adverse event; WBC, white blood cell.
[a]No treatment-related deaths were reported.
[b]Order based on NIVO3 mg/kg treatment group.

neoadjuvant anti-PD-1 prior to salvage surgery followed by continued adjuvant therapy in adult patients with recurrent GBM,[32] no survival benefit was observed in pediatric patients with high-grade relapsed/resistant CNS malignancies or newly diagnosed DIPG. As this study was not designed for comparisons between modules or across cohorts, OS (cohort 1, primary endpoint; cohorts 2–5, secondary endpoint) and PFS (cohort 1, secondary endpoint; cohorts 2–5, primary endpoint) were interpreted relative to historical benchmarks. Previous studies reported median OS as 9.6 months[2] in newly diagnosed DIPG, and median PFS as 2.25 months[33] and 2.1 months[34] in recurrent/progressive pediatric HGG and relapsed/resistant ependymoma, respectively. A 4-month PFS rate of 18% was reported in relapsed/resistant medulloblastoma.[35] Primary endpoint findings of a median OS of 11.7 months (NIVO3)/10.8 months (NIVO3 + IPI1) in newly diagnosed DIPG, median PFS of 1.7 months (NIVO3)/1.3 months (NIVO3 + IPI1) in recurrent/progressive HGG, and 1.4 months (NIVO3)/4.6 months (NIVO3 + IPI1) in relapsed/resistant ependymoma suggest that NIVO ± IPI did not improve outcomes over historical data. In relapsed/resistant medulloblastoma, clinical benefit was not observed with NIVO3 (4-month PFS rate, 0%); despite small sample size and lack of statistical power, a potential survival trend was observed with NIVO3 + IPI1 (4-month PFS rate, 40%). No

comparisons to historical controls could be made for the cohort of patients with other rare high-grade CNS tumors. Results align with prior reports in pediatric recurrent/refractory non-CNS solid tumors demonstrating a lack of NIVO single-agent activity in a phase 1/2 study.[23]
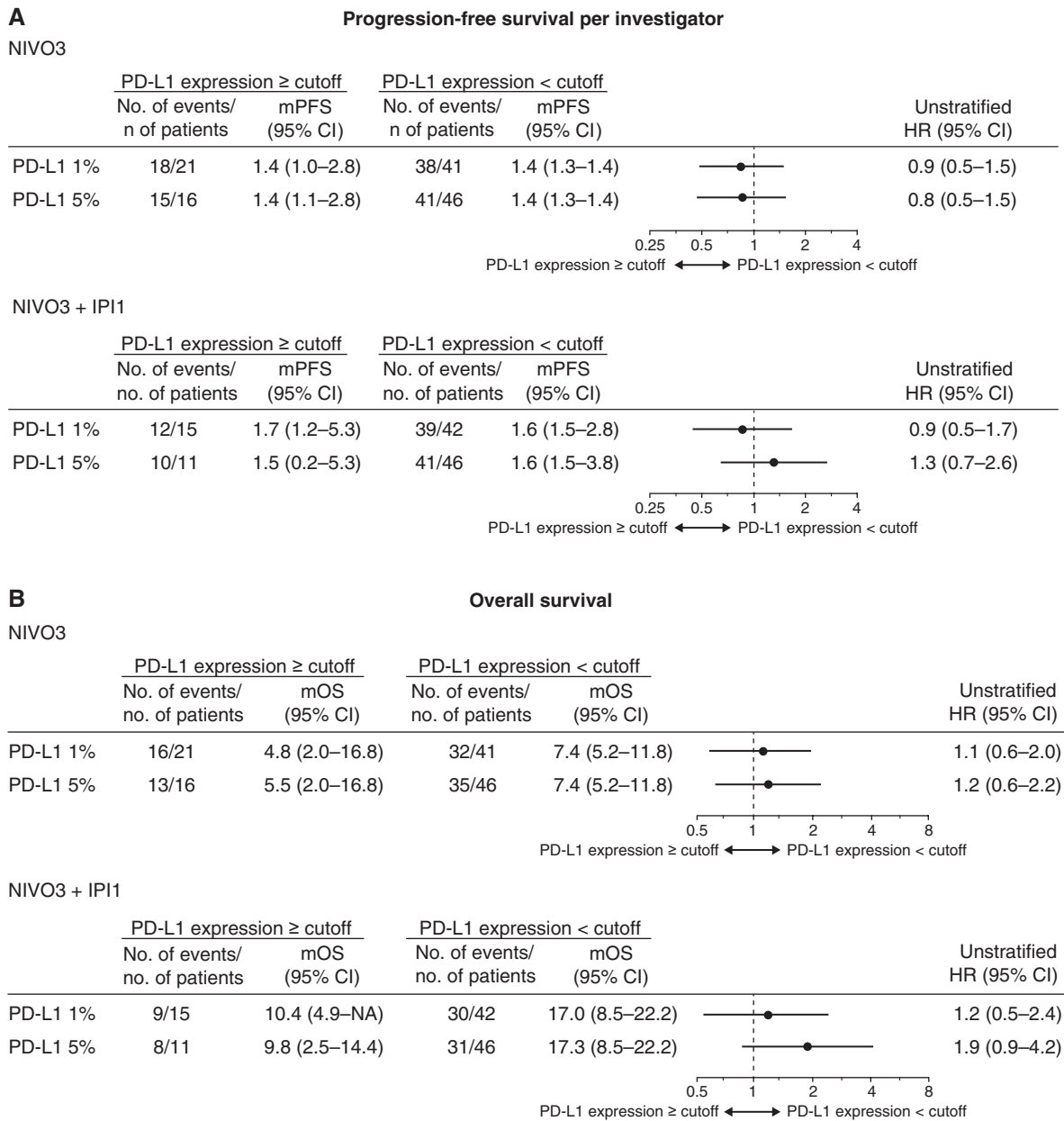
Although increased sensitivity to anti-PD-1 therapy may result from enhanced PD-L1 expression, as suggested in supratentorial *RELA* fusion ependymoma,[36,37] exploratory analyses demonstrated that baseline tumor PD-L1 expression ≥1% or ≥5% was not associated with improved PFS or OS, although small subgroup sizes preclude a firm conclusion. ICIs have generally been less effective in pediatric patients, in part due to infrequent detectable PD-L1 expression in pediatric tumors,[8] which tend to have fewer infiltrating T cells and low TMB.[38] Indeed, the KEYNOTE-051 phase 1/2 trial investigated the anti-PD-1 antibody pembrolizumab in PD-L1-positive pediatric patients with relapsed/refractory lymphoma or solid tumors.[39] Low antitumor activity was reported in most tumor types.[39] Current findings corroborate these reports. Taken together, PD-L1 appears insufficient as a standalone marker to predict treatment response in most pediatric patients and tumor types.[38,39] In the future, tailoring combination therapies through targeted approaches may improve treatment response. For example, radiotherapy, chemotherapy, or other drugs that convert pediatric tumors from immune-cold to immune-hot could
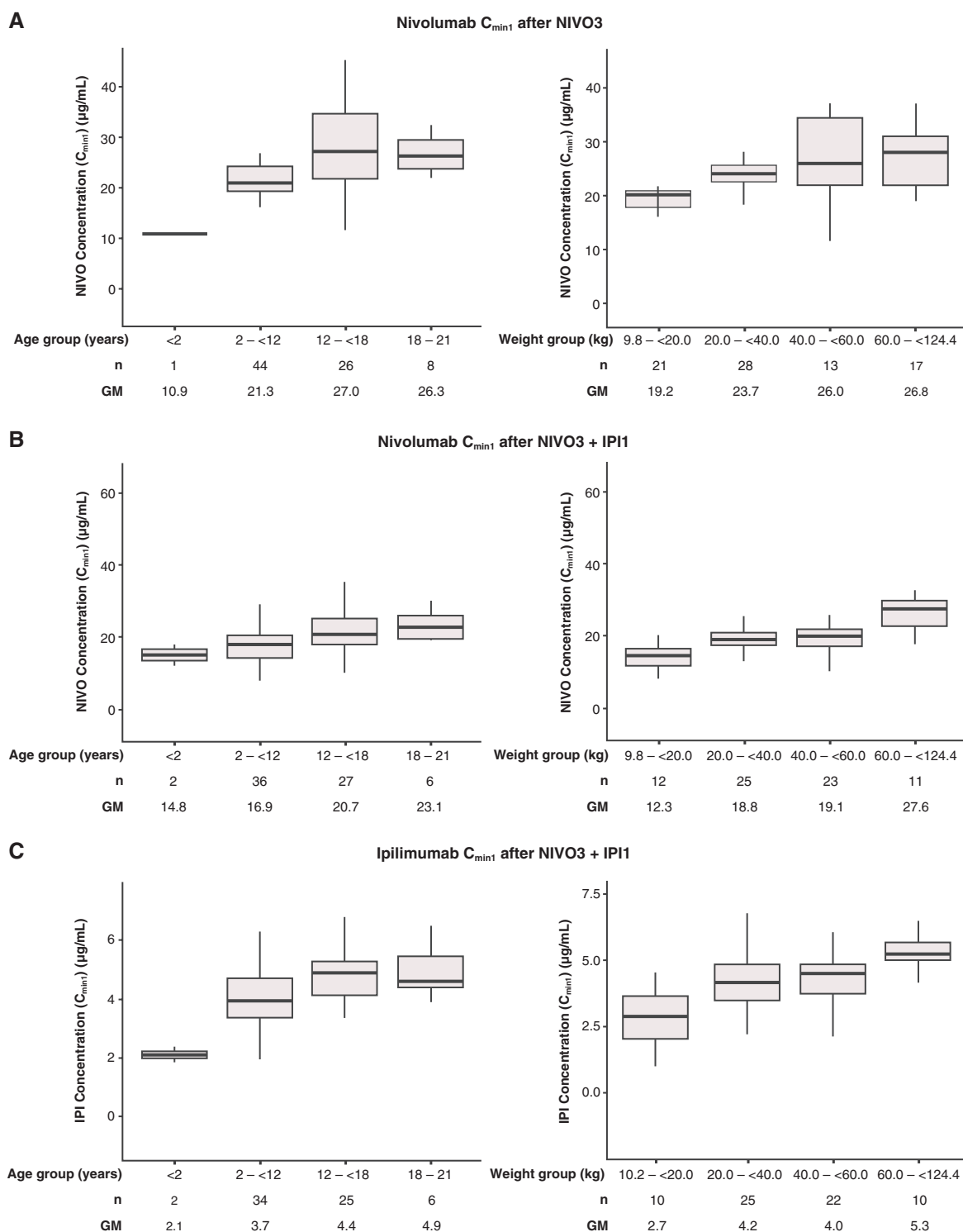
Figure 3. Nivolumab and ipilimumab exposures by age and weight. Observed NIVO and IPI trough (C_{min1}) concentrations after first dose by patient age and weight. GM, geometric mean; IPI, ipilimumab; NIVO, nivolumab.

be used to improve immunotherapeutic effectiveness. Novel biomarkers may identify patients who respond optimally to immunotherapy. Biological samples and data from the current study can help inform future research to assess the probability of success with targeted interventions.

Despite overall negative results, 1 partial response was observed in a patient with relapsed/resistant ependymoma with MSI-H, consistent with the previously reported unconfirmed partial response in a patient with relapsed/refractory ependymoma treated with NIVO combined with

A — Progression-free survival per investigator

NIVO3

| | PD-L1 expression ≥ cutoff | | PD-L1 expression < cutoff | | | Unstratified |
	No. of events/ n of patients	mPFS (95% CI)	No. of events/ n of patients	mPFS (95% CI)		HR (95% CI)
PD-L1 1%	18/21	1.4 (1.0–2.8)	38/41	1.4 (1.3–1.4)		0.9 (0.5–1.5)
PD-L1 5%	15/16	1.4 (1.1–2.8)	41/46	1.4 (1.3–1.4)		0.8 (0.5–1.5)

0.25 0.5 1 2 4
PD-L1 expression ≥ cutoff ⟵⟶ PD-L1 expression < cutoff

NIVO3 + IPI1

| | PD-L1 expression ≥ cutoff | | PD-L1 expression < cutoff | | | Unstratified |
	No. of events/ no. of patients	mPFS (95% CI)	No. of events/ no. of patients	mPFS (95% CI)		HR (95% CI)
PD-L1 1%	12/15	1.7 (1.2–5.3)	39/42	1.6 (1.5–2.8)		0.9 (0.5–1.7)
PD-L1 5%	10/11	1.5 (0.2–5.3)	41/46	1.6 (1.5–3.8)		1.3 (0.7–2.6)

0.25 0.5 1 2 4
PD-L1 expression ≥ cutoff ⟵⟶ PD-L1 expression < cutoff

B — Overall survival

NIVO3

| | PD-L1 expression ≥ cutoff | | PD-L1 expression < cutoff | | | Unstratified |
	No. of events/ no. of patients	mOS (95% CI)	No. of events/ no. of patients	mOS (95% CI)		HR (95% CI)
PD-L1 1%	16/21	4.8 (2.0–16.8)	32/41	7.4 (5.2–11.8)		1.1 (0.6–2.0)
PD-L1 5%	13/16	5.5 (2.0–16.8)	35/46	7.4 (5.2–11.8)		1.2 (0.6–2.2)

0.5 1 2 4 8
PD-L1 expression ≥ cutoff ⟵⟶ PD-L1 expression < cutoff

NIVO3 + IPI1

| | PD-L1 expression ≥ cutoff | | PD-L1 expression < cutoff | | | Unstratified |
	No. of events/ no. of patients	mOS (95% CI)	No. of events/ no. of patients	mOS (95% CI)		HR (95% CI)
PD-L1 1%	9/15	10.4 (4.9–NA)	30/42	17.0 (8.5–22.2)		1.2 (0.5–2.4)
PD-L1 5%	8/11	9.8 (2.5–14.4)	31/46	17.3 (8.5–22.2)		1.9 (0.9–4.2)

0.5 1 2 4 8
PD-L1 expression ≥ cutoff ⟵⟶ PD-L1 expression < cutoff

Figure 4. Survival in prespecified patient subgroups defined by baseline PD-L1 expression. Forest plots of unstratified HRs for progression per investigator (A) and overall survival (B) based on baseline PD-L1 expression. HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; PD-L1, programmed death ligand 1.

metronomic cyclophosphamide.[40] Additionally, 1 patient with HGG had high TMB (based on 199 mutations/Mb cutoff[41]) and an OS of 11 months. Prior studies of PD-1 inhibitors suggest TMB as an important factor for efficacy in various tumors, including mismatch repair deficiency recurrent GBMs[42–45]. Furthermore, higher MSI has been reported in pediatric vs adult gliomas.[46] Although promising, a separate cohort for this patient population was not included in this study.

Additional exploration of baseline characteristics that may be associated with OS revealed 4 patients with predisposing cancer conditions, including a constitutional mismatch repair deficiency mutation and a prior history of T-cell acute lymphoblastic leukemia in 1 patient with recurrent/progressive HGG (cohort 2; OS 41.7 months, PFS, 40.8 months), Lynch syndrome in 1 patient with recurrent/progressive HGG (cohort 2; OS 8.5 months, PFS 1.3 months), and Li-Fraumeni syndrome in 2 patients with recurrent/progressive choroid plexus carcinoma (cohort 5; OS 36.2 months and PFS 34.5 months; OS 8.0 months and PFS 1.2 months). Notably, the cohort 2 patient with a prior history of T-cell acute lymphoblastic leukemia and constitutional mismatch repair deficiency mutation had high PD-L1 expression (>40%) and was in

complete remission with continued NIVO at the censored date. Taken together, these exploratory analyses provide novel insights for future trials. Expanding the definition of clinically meaningful outcomes is an important consideration in the context of high-grade and recurrent/progressive pediatric tumors. For example, improving tumor characterization could result in immunotherapy extending survival or progression-free intervals or improving quality of life despite a lack of response per RANO criteria.

Safety profiles of NIVO ± IPI were manageable and consistent with previous reports in adults.[17,18] Most TRAEs were mild and few serious TRAEs were observed. Additionally, low rates of discontinuation due to study drug toxicity were observed. While no new or unexpected treatment-related safety signals or toxicities specific to a given disease cohort were identified, TRAEs, serious TRAEs, and TRAEs leading to discontinuation appeared more frequent with NIVO3 + IPI1, as expected. One patient in the other high-grade CNS tumors cohort 5 (atypical meningioma, WHO grade 2) treated with NIVO3 + IPI1 met the criteria for a dose-limiting toxicity (grade 3 pancreatitis and grade 2 colitis in the same patient).

Medulloblastoma has been subject to significant molecular analyses. The WHO classification subdivides medulloblastoma into 4 distinct subtypes: wingless/WNT; sonic hedgehog/SHH, which may be further subdivided by *P53* wild-type or mutant status; group 3 (group C); and group 4 (group D).[28,29] Several reviews describe the increasing number of medulloblastoma subgroups and their implications for diagnosis and treatment.[29,47–49] Current results confirmed similar prevalence of the 4 subgroups and revealed 5 of 19 (26%) medulloblastoma cases without any subtype-specific genetic variances.

Pharmacokinetic analyses indicated that NIVO and IPI trough concentrations after first dose appeared lower in younger and lower-weight patient groups. This was consistent with the known relationship of less-than-proportional increase in NIVO and IPI clearance with body weight. Lower NIVO and IPI exposures observed in the youngest patients were likely attributable to the associated lower body weight. Of note, NIVO and IPI exposures were largely similar between adolescents (12 to <18 years) and young adults (18 to <21 years).

This study's limitations included that imaging and neuropathology data were not reviewed centrally, and immunotherapy (iRANO) criteria were not considered since they were not standardized at the time of the study. Given the aggressive nature of DIPG, relapsed status of other cohorts, and low incidence of confirmed pseudoprogression in this study population, these factors likely did not impact overall outcomes. Additional limitations include those associated with interpretations relative to historical data (eg, small sample sizes in single-arm studies, low precision in estimated treatment effects with small sample sizes in this study), as no meaningful conclusions could be drawn based on external benchmarks. Furthermore, after study and analysis completion, 4 patients from cohort 1 were identified as having baseline corticosteroid use >0.05 mg/kg/day at study entry. Upon further investigation, it was determined that the study site(s) may not have entered the correct dose for 2

patients treated with NIVO3 + IPI1. This occurred after database lock; therefore, they were retained in the current analysis. Remaining patients (NIVO3, n = 1; NIVO3 + IPI1, n = 1) were confirmed eligible based on internal system reporting.

CheckMate 908 evaluated primary and secondary endpoints including safety and efficacy associated with NIVO ± IPI in pediatric patients with high-grade primary CNS malignancies. Overall outcomes did not demonstrate clinically meaningful improvements relative to historical data. Safety profiles of NIVO ± IPI were manageable in each pediatric population evaluated. Efficacy results do not currently warrant further investigation of NIVO ± IPI in pediatric CNS malignancies. Nonetheless, these results do not signify the end of prospects for immunotherapy in pediatric neuro-oncology. Rather, the low response rate to PD-1- and CLTA-4-targeted treatments together with low TMB and immunologically "cold" tumor profiles provide insight for developing novel hypotheses unique to CNS malignancies to use in future trials. Acknowledging the obstacles to establishing appropriate translational preclinical models for CNS-specific malignancies, an urgent need remains for continued collaboration between preclinical researchers and clinicians to build on the rationale for immunotherapeutic combinations, including ICI approaches, for pediatric CNS malignancies. Such efforts will enhance the discovery and understanding of novel targets and combinational strategies with ICIs for tumors with appropriate immune, genetic, or mutational profiles, with the ultimate goal of improving patient outcomes.[38,50]

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Keywords:

checkpoint inhibitors | DIPG | ependymoma | HGG | medulloblastoma

Conflict of interest statement

I.J.D. received grant funding from Genentech/Roche and Novartis; personal fees from AstraZeneca, Bristol Myers Squibb, Celgene, a Bristol-Myers Squibb company, Day One, Fennec, Pyramid, QED, Roche. F.D. received fees for advisory board roles from Bayer, Bristol Myers Squibb, Roche, Celgene, a Bristol-Myers Squibb company, LOXO Oncology, Servier, Tesaro; travel expenses from Bayer, Bristol Myers Squibb, Roche; and consultancy roles from Servier. (Note: all honoraria were contributed to an account at Institut Curie, not his personal funds). D.H. received funding from the National Institute for Health and Care Research Great Ormond Street Hospital Biomedical Research Centre; consultancy fees from AstraZeneca, Bayer, Roche, LOXO Oncology, Novartis. His views are his own and not necessarily those of the NHS, the NIHR or the Department of Health, London, UK. A.L. received fees from Servier and Gilead; served on advisory boards for Jazz Pharmaceuticals and Servier. N.A. received grant funding from Bristol Myers Squibb; fees from Bristol Myers Squibb, Ankira, Bayer, Roche. M.E. received fees from and served on an advisory board for Bristol Myers Squibb. A.G. served on an advisory board for Day One Therapeutics. D.W., R.T., and L.Z. are employees of and received stock from Bristol Myers Squibb. Y.W. is an employee of Bristol Myers Squibb. K.C. received grant funding from Regeneron and Novartis; fees from DNAtrix, CRICO, Roetzel & Andres; DMSC member for Y-mAbs. J.R.H. received honoraria for consultation from Bayer Australia, Alexion Pharmaceuticals, Boxer Capital; N.K.F., L.H., T.H., S.G., U.B., and M.P. have nothing to disclose.

Authorship statement

Study conception and design: I.J.D., N.K.F., K.C. Data acquisition: I.J.D., F.D., N.K.F., D.H., A.L., N.A., J.R.H., T.H., M.E., S.G., U.B., A.G., L.H. Data analyses: D.W., M.P., R.T., Y.W., L.Z. Data interpretation: all authors; contribution to and approval of manuscript: all authors.

Data Sharing

Bristol Myers Squibb's policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html

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