ORIGINAL ARTICLE

Systemic and Intracranial Outcomes With First-Line Nivolumab Plus Ipilimumab in Patients With Metastatic NSCLC and Baseline Brain Metastases From CheckMate 227 Part 1

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ABSTRACT

Introduction: In CheckMate 227 Part 1, nivolumab plus ipilimumab prolonged overall survival (OS) versus chemotherapy in patients with metastatic NSCLC, regardless of tumor programmed death-ligand 1 (PD-L1) expression. Here, we report post hoc exploratory systemic and intracranial efficacy outcomes and safety by baseline brain metastasis status at 5 years' minimum follow-up.

Methods: Treatment-naive adults with stage IV or recurrent NSCLC without *EGFR* or *ALK* alterations, including asymptomatic patients with treated brain metastases, were enrolled. Patients with tumor PD-L1 greater than or equal to 1% were randomized to nivolumab plus ipilimumab, nivolumab, or chemotherapy; patients with tumor PD-L1 less than 1% were randomized to nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy groups. Assessments included OS, systemic and intracranial progression-free survival per blinded independent central review, new brain lesion development, and safety. Brain imaging was performed at baseline (all randomized patients) and approximately every 12 weeks thereafter (patients with baseline brain metastases only).

Results: Overall, 202 of 1739 randomized patients had baseline brain metastases (nivolumab plus ipilimumab: 68; chemotherapy: 66). At 61.3 months' minimum follow-up, nivolumab plus ipilimumab prolonged OS versus chemotherapy in patients with baseline brain metastases (hazard ratio = 0.63; 95% confidence interval: 0.43–0.92) and in those without (hazard ratio = 0.76; 95% confidence interval: 0.66–0.87). In patients with baseline brain metastases, 5-year systemic and intracranial progression-free survival rates were higher with nivolumab plus ipilimumab (12% and 16%, respectively) than chemotherapy (0% and 6%). Fewer patients with baseline brain metastases developed new brain lesions with nivolumab plus ipilimumab (4%) versus chemotherapy (20%). No new safety signals were observed.

Conclusions: With all patients off immunotherapy for more than or equal to 3 years, nivolumab plus ipilimumab continued to provide a long-term, durable survival benefit in patients with or without brain metastases. Intracranial efficacy outcomes favored nivolumab plus ipilimumab versus chemotherapy. These results further support nivolumab plus ipilimumab as an efficacious first-line treatment for patients with metastatic NSCLC, regardless of baseline brain metastasis status.

Keywords: NSCLC; Nivolumab; Ipilimumab; Brain metastases; Intracranial outcomes

Introduction

Brain metastasis is a common manifestation of NSCLC that is associated with a poor prognosis.[1,2] It is estimated that 10% to 25% of patients with NSCLC have brain metastases at diagnosis, with up to 40% developing brain metastases over the course of the disease.[1–4] Although substantial advances in the treatment of NSCLC have been made in the past 20 years, survival outcomes remain relatively poor among patients with brain metastases,[2,5] indicating a high unmet need. Standard-of-care local treatments for brain metastases include whole-brain radiotherapy and stereotactic radiosurgery; however, median overall survival (OS) in patients receiving these treatments is only approximately 12 months.[2] Systemic treatment options are even more limited owing to poor penetration of the blood-brain barrier (BBB), which limits the efficacy of treatments such as chemotherapy.[5,6]

During the last several years, the clinical activity of immunotherapy in patients with brain metastases has been reported across a variety of primary tumor types.[7–18] Findings from phase 1 and 2 studies suggested that immunotherapy (as monotherapy or in combination with chemotherapy) was well tolerated and provided favorable efficacy outcomes in patients with melanoma, NSCLC, or renal cell carcinoma who had untreated or progressive brain metastases.[7–10,16,18] Moreover, pooled analyses also suggested clinical benefit with immunotherapy in patients with NSCLC and treated brain metastases.[11,13] However, reports of intracranial analyses from phase 3 NSCLC studies evaluating the efficacy of immunotherapy are limited.[12,17]

In CheckMate 227 Part 1, first-line nivolumab plus ipilimumab demonstrated significantly improved independent primary end points of progression-free survival (PFS) in patients with high tumor mutational burden (≥10 mutations per megabase) and OS in patients with tumor programmed death-ligand 1 (PD-L1) greater than or equal to 1% versus chemotherapy in patients with metastatic NSCLC (mNSCLC).[19,20] In a prespecified descriptive analysis, OS was also prolonged in patients with tumor PD-L1 less than 1%.[20] On the basis of these findings, first-line nivolumab plus ipilimumab was approved in the United States and other countries for the treatment of adults with mNSCLC (lacking *EGFR* or *ALK* alterations) and tumor PD-L1 greater than or equal to 1%,[21–23] with some countries approving the regimen regardless of tumor PD-L1 expression.[24,25] Furthermore, nivolumab plus ipilimumab is recommended as a first-line treatment option by National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) for patients with mNSCLC and tumor PD-L1 greater than or equal to 1% or less than 1%[26] and

by European Society for Medical Oncology guidelines for patients with mNSCLC and tumor PD-L1 greater than or equal to 1%.[27] Long-term, durable OS benefit with nivolumab plus ipilimumab versus chemotherapy was seen in patients with tumor PD-L1 greater than or equal to 1% or less than 1% in CheckMate 227 Part 1 at 5 years' follow-up.[28] Here, we report post hoc exploratory analyses of systemic and intracranial efficacy and safety outcomes from CheckMate 227 Part 1 at 5 years' minimum follow-up in patients with or without baseline brain metastases.

Materials and Methods

Patients and Study Design

The eligibility criteria and study design of CheckMate 227 Part 1 have been previously reported.[19,20,28,29] Briefly, CheckMate 227 (NCT02477826) was a randomized, open-label, two-part, global phase 3 study in adult patients with histologically confirmed stage IV or recurrent NSCLC and Eastern Cooperative Oncology Group performance status less than or equal to 1 (Supplementary Fig. 1). Patients who received previous systemic therapy for metastatic disease, had known *EGFR* or *ALK* alterations, or had untreated brain metastases (identified at screening using magnetic resonance imaging) were excluded. Patients with treated brain metastases were eligible for enrollment if they remained asymptomatic for more than or equal to 2 weeks before randomization; additional confirmatory brain imaging scans were not required. Palliative radiotherapy targeting non–central nervous system (CNS) lesions must have been completed more than or equal to 2 weeks before randomization. Patients were permitted to receive corticosteroid treatment with prednisone less than or equal to 10 mg daily (or its equivalent) if doses remained stable or were being tapered more than or equal to 2 weeks before randomization. Palliative locoregional therapy, including radiotherapy, targeting bone, skin, or CNS lesions, was permitted for patients without evidence of overall clinical or radiographic disease progression.

Patients were randomized to receive nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks, nivolumab 240 mg every 2 weeks alone (tumor PD-L1 $\geq$1% only) or nivolumab 360 mg plus platinum-doublet chemotherapy every 3 weeks (tumor PD-L1 $<$1% only), or platinum-doublet chemotherapy every 3 weeks (Supplementary Fig. 1). Randomization was stratified by tumor histology (squamous or nonsquamous). Treatment continued until disease progression, unacceptable toxicity, or 2 years of immunotherapy administration.

This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice as outlined by the International Conference on Harmonisation. The protocol and all amendments were approved by the institutional review board or independent ethics committee at each participating study site. All enrolled patients provided written informed consent. The Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

Outcomes

Independent primary end points, hierarchical secondary end points, and prespecified descriptive analyses from CheckMate 227 Part 1 have been reported previously.[19,20,28,29] Post hoc exploratory end points on the basis of baseline brain metastasis status included OS; blinded independent central review (BICR)–assessed PFS (systemic and intracranial), objective response rate (ORR; systemic), and development of new brain lesions; and safety. Systemic response was assessed using Response Evaluation Criteria in Solid Tumors version 1.1, whereas intracranial outcomes were assessed using modified Response Evaluation Criteria in Solid Tumors version 1.1 guidelines adapted for brain metastases.[30,31] Contrast-enhanced magnetic resonance imaging was the preferred imaging method for intracranial assessments and was performed in all randomized patients at baseline and approximately every 12 weeks thereafter until disease progression in patients with baseline brain metastases. After the baseline assessment, brain imaging scans were only performed in patients without baseline brain metastases if symptoms that warranted such scans arose. Information regarding prior locoregional therapy for brain metastases (including surgery and radiotherapy) and posttreatment progression status was not provided to the BICR committee. Adverse events were classified per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Treatment-related adverse events (TRAEs), including neurologic TRAEs, occurring between the first dose of study treatment and 30 days after the last dose of study treatment were reported. Immune-mediated adverse events (IMAEs; specific events that required treatment with immunosuppressive medication, except for particular endocrine events) occurring between the first dose of study treatment and 100 days after the last dose of study treatment, regardless of causality, were also reported.

Statistical Analyses

Post hoc exploratory analyses were performed in all randomized patients and subgroups defined by tumor PD-L1 expression and baseline brain metastasis status. OS and BICR-assessed PFS and duration of response (DOR) were estimated using Kaplan-Meier methodology; hazard ratios (HRs) and associated two-sided 95% confidence intervals

(CIs) were calculated using an unstratified Cox proportional hazards model with treatment arm as a single covariate. Two-sided exact 95% CIs for ORRs were calculated using the Clopper-Pearson method. Safety outcomes were evaluated in patients who received at least one dose of study treatment.

Results

Patient Demographics and Treatment

As reported previously,[19,20,28,29] 2867 patients were enrolled between August 2015 and November 2016. Of these patients, 1739 were randomized in CheckMate 227 Part 1, including 202 with baseline treated brain metastases in the nivolumab plus ipilimumab (n = 68; combined population from Parts 1a [tumor PD-L1 ≥1%] and 1b [tumor PD-L1 <1%]), nivolumab (n = 48; tumor PD-L1 ≥1%), nivolumab plus chemotherapy (n = 20; tumor PD-L1 <1%), or chemotherapy arms (n = 66; combined populations from Parts 1a and 1b; Supplementary Fig. 2). Baseline characteristics were generally similar between treatment arms, regardless of baseline brain metastasis status (Table 1). A lower proportion of patients with baseline brain metastases in the nivolumab plus ipilimumab arm had liver metastases at baseline than those in the chemotherapy arm (16% versus 29%). Prior brain radiotherapy use was comparable between patients with baseline brain metastases in the nivolumab plus ipilimumab and chemotherapy arms (79% versus 80%).

At the data cutoff date (February 15, 2022), the minimum OS follow-up was 61.3 months (median = 66.7 mo), and all patients with or without baseline brain metastases who received nivolumab plus ipilimumab or chemotherapy had discontinued study treatment, except for one patient without baseline brain metastases treated with chemotherapy who continued to receive maintenance pemetrexed. The median duration of treatment with nivolumab plus ipilimumab was 4.2 (range: 0–24.4) and 4.2 months (range: 0–25.5) in patients with and without baseline brain metastases, respectively, and the median duration of treatment with chemotherapy was 3.6 (range: 0–49.4) and 2.6 months (range: 0–56.7 + [plus symbol indicates a censored value]). Exposure to nivolumab and ipilimumab was comparable between groups, regardless of baseline brain metastasis status (Supplementary Table 1); the median number of nivolumab doses was 9 (range: 1–53) and 9 (range: 1–55) in patients with and without baseline brain metastases, respectively, and the median number of ipilimumab doses was 3 (range: 1–18) and 3 (range: 1–19). Chemotherapy exposure is described in Supplementary Table 1.

In patients with baseline brain metastases, 44% and 68% of patients in the nivolumab plus ipilimumab and chemotherapy arms, respectively, received subsequent therapy of any type, including 38% and 59% who received subsequent systemic therapy, 9% and 44% who received subsequent immunotherapy, and 24% and 5% who received subsequent platinum-doublet chemotherapy (Supplementary Table 2). Among those without baseline brain metastases, 50% and 61% of patients in the nivolumab plus ipilimumab and chemotherapy arms, respectively, received subsequent therapy of any type, including 41% and 54% who received subsequent systemic therapy, 8% and 42% who received subsequent immunotherapy, and 33% and 8% who received subsequent platinum-doublet chemotherapy.

Efficacy

Systemic Outcomes. In patients with baseline brain metastases, the median OS was 17.4 months (95% CI: 9.2–29.4) with nivolumab plus ipilimumab and 13.7 months (95% CI: 10.5–16.2) with chemotherapy (HR = 0.63, 95% CI: 0.43–0.92); 5-year OS rates were 20% (95% CI: 12–31) and 6% (95% CI: 2–14), respectively (Fig. 1*A*). Similar outcomes were observed in patients without baseline brain metastases: the median OS was 17.2 months (95% CI: 15.3–20.0) with nivolumab plus ipilimumab and 13.9 months (95% CI: 11.8–15.3) with chemotherapy (HR = 0.76, 95% CI: 0.66–0.87), and 5-year OS rates were 23% (95% CI: 19–26) and 13% (95% CI: 10–16), respectively (Fig. 1*B*). Among patients with tumor PD-L1 greater than or equal to 1%, OS was improved with nivolumab plus ipilimumab versus chemotherapy in patients with baseline brain metastases (HR = 0.61, 95% CI: 0.39–0.95; Supplementary Fig. 3*A*) and in those without (HR = 0.82, 95% CI: 0.69–0.97; Supplementary Fig. 3*B*); HRs for OS with nivolumab versus chemotherapy were 0.89 (95% CI: 0.58–1.38) and 0.93 (95% CI: 0.79–1.10) in patients with and without baseline brain metastases, respectively. Five-year OS rates with nivolumab plus ipilimumab, nivolumab, and chemotherapy among patients with tumor PD-L1 greater than or equal to 1%, respectively, were 27% (95% CI: 15–40), 14% (95% CI: 6–27), and 8% (95% CI: 3–18) in patients with baseline brain metastases and 24% (95% CI: 19–28), 17% (95% CI: 14–22), and 15% (95% CI: 12–19) in patients without baseline brain metastases. Among patients with tumor PD-L1 less than 1% (Supplementary Table 3), OS seemed to favor nivolumab plus ipilimumab versus chemotherapy in patients with baseline brain metastases (HR = 0.63, 95% CI: 0.30–1.33) and those without (HR = 0.65, 95% CI: 0.51–0.82); HRs for OS with nivolumab plus chemotherapy versus chemotherapy were 0.92 (95% CI: 0.47–1.80) and 0.78 (95% CI: 0.62–0.99) in patients with and without brain metastases, respectively.

Table 1. Baseline Characteristics by Baseline Brain Metastasis Status in All Randomized Patients

Characteristics	With Baseline Brain Metastases				Without Baseline Brain Metastases			
	Nivolumab Plus Ipilimumab (n = 68)	Nivolumab (n = 48)	Nivolumab Plus Chemotherapy (n = 20)	Chemotherapy (n = 66)	Nivolumab Plus Ipilimumab (n = 515)	Nivolumab (n = 348)	Nivolumab Plus Chemotherapy (n = 157)	Chemotherapy (n = 517)
Median age (range), y	60 (31-77)	64 (27-79)	62 (30-74)	61 (31-76)	64 (26-87)	64 (32-85)	65 (33-89)	65 (29-87)
Female	25 (37)	19 (40)	8 (40)	26 (39)	165 (32)	105 (30)	39 (25)	172 (33)
ECOG PS								
0	18 (26)	11 (23)	9 (45)	18 (27)	186 (36)	131 (38)	50 (32)	173 (34)
1	49 (72)	36 (75)	10 (50)	46 (70)	328 (64)	216 (62)	106 (68)	340 (66)
≥2	1 (2)	0	0	2 (3)	1 (<1)	0	1 (<1)	2 (<1)
Not reported	0	1 (2)	1 (5)	0	0	1 (<1)	0	2 (<1)
Smoking status								
Current or former	59 (87)	41 (85)	16 (80)	53 (80)	438 (85)	301 (86)	131 (83)	446 (86)
Never smoked	9 (13)	6 (12)	3 (15)	12 (18)	70 (14)	44 (12)	24 (15)	66 (13)
Unknown	0	1 (2)	0	1 (2)	7 (1)	3 (1)	2 (1)	5 (1)
Not reported	0	0	1 (5)	0	0	0	0	0
Histology								
Squamous	9 (13)	8 (17)	4 (20)	10 (15)	155 (30)	110 (32)	39 (25)	154 (30)
Nonsquamous	59 (87)	40 (83)	16 (80)	56 (85)	360 (70)	238 (68)	118 (75)	363 (70)
Metastases								
Liver	11 (16)	17 (35)	6 (30)	19 (29)	111 (22)	75 (22)	33 (21)	111 (22)
Bone	21 (31)	20 (42)	9 (45)	21 (32)	142 (28)	87 (25)	43 (27)	132 (26)
Tumor PD-L1 expression								
<1%	19 (28)	0	19 (95)	18 (27)	168 (33)	0	157 (100)	168 (32)
≥1%	49 (72)	48 (100)	1 (5)[a]	48 (73)	347 (67)	348 (100)	0	349 (68)
Corticosteroid use at baseline	10 (15)	5 (10)	2 (10)	9 (14)	9 (2)	3 (1)	3 (2)	9 (2)
Prior radiotherapy	61 (90)	40 (83)	14 (70)	58 (88)	118 (23)	65 (19)	41 (26)	125 (24)
Prior brain radiotherapy	54 (79)[b]	39 (81)[b]	14 (70)[b]	53 (80)[b]	37 (7)[c]	23 (7)[c]	11 (7)[c]	27 (5)[c]
Median brain tumor burden (range), mm	29 (10-167)	22 (10-100)	20 (10-119)	23 (10-91)	-	-	-	-

Note: Data are n (%) unless otherwise stated. Percentages may not total 100 owing to rounding.
[a]One patient with tumor PD-L1 1% to 49% was randomized to nivolumab plus chemotherapy (protocol deviation).
[b]Patients not receiving prior brain radiotherapy had prior brain surgery, brain metastases not confirmed per investigator assessment, or unreported prior treatment for brain metastases.
[c]Patients receiving prior brain radiotherapy had brain metastases confirmed per investigator assessment but not by BICR.
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

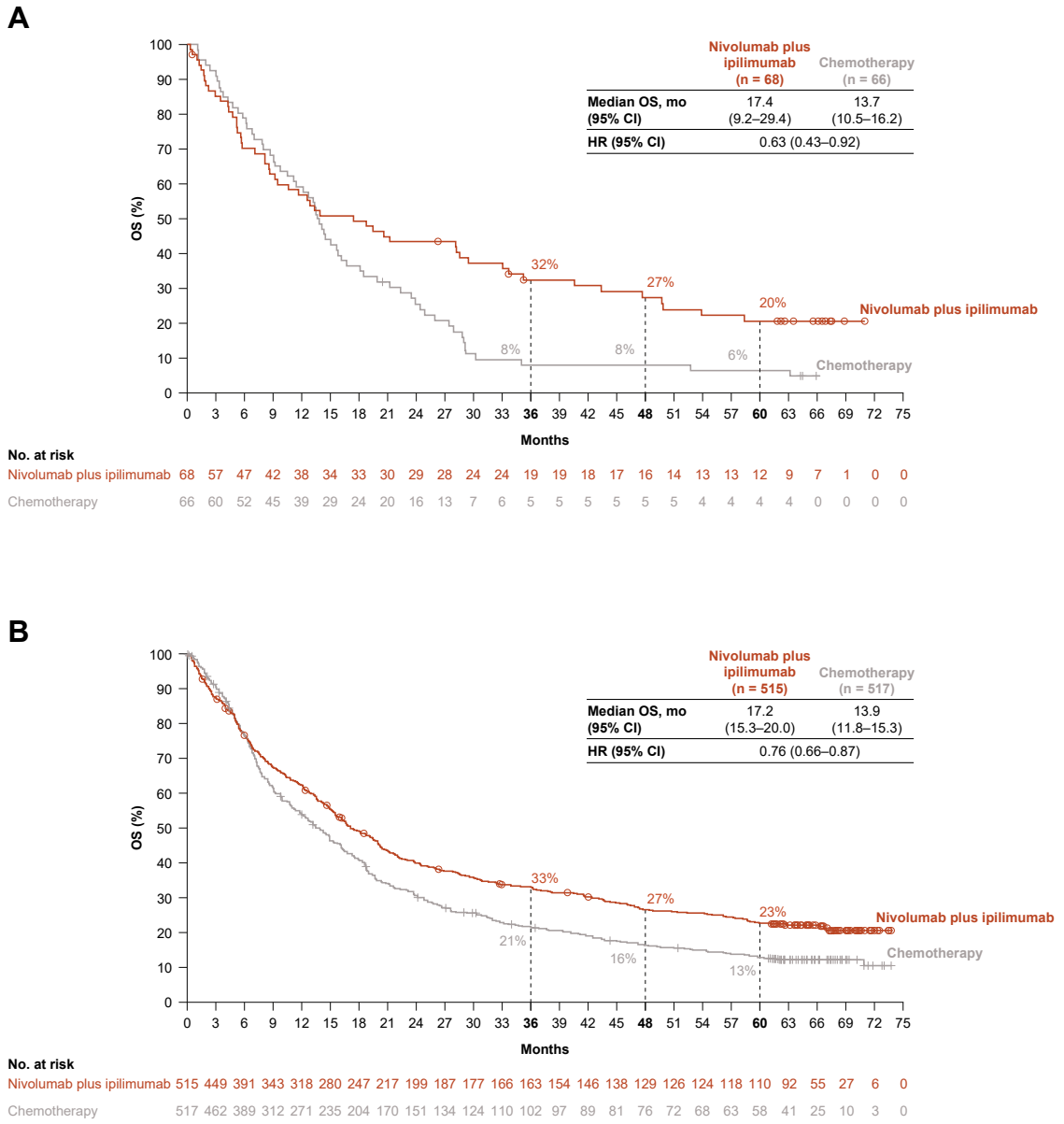

Figure 1. OS in randomized patients (*A*) with or (*B*) without baseline brain metastases: nivolumab plus ipilimumab versus chemotherapy. The 95% CIs for 5-year rates with nivolumab plus ipilimumab and chemotherapy, respectively, are as follows: (*A*) 12–31 and 2–14, and (*B*) 19–26 and 10–16. CI, confidence interval; HR, hazard ratio; OS, overall survival.

With respect to systemic PFS, trends favoring treatment with nivolumab plus ipilimumab versus chemotherapy were observed in patients with baseline brain metastases (HR = 0.77, 95% CI: 0.51–1.15; Fig. 2*A*). Five-year systemic PFS rates in these patients were 12% (95% CI: 5–23) and 0% (95% CI: not available), respectively. In patients without baseline brain metastases, systemic PFS was improved with nivolumab plus ipilimumab versus chemotherapy (HR = 0.79, 95% CI: 0.68–0.91); 5-year systemic PFS rates were 11% (95% CI: 8–15) and 2% (95% CI: 1–5), respectively (Fig. 2*B*). In patients with tumor PD-L1 greater than or equal to 1%, nivolumab plus ipilimumab showed trends toward improved systemic PFS versus chemotherapy in patients with (HR = 0.85, 95% CI: 0.53–1.36; Supplementary Fig. 4*A*) or without baseline brain metastases (HR = 0.81, 95% CI: 0.68–0.96; Supplementary Fig. 4*B*); similar trends toward improved systemic PFS were observed with nivolumab versus chemotherapy, regardless of baseline brain metastasis status. Five-year systemic PFS rates with nivolumab plus ipilimumab, nivolumab, and chemotherapy among patients with tumor PD-L1 greater than or equal to 1%, respectively, were 16% (95% CI: 7–29), 11% (95% CI: 3–24), and 0% (95% CI: not available) in patients with baseline brain metastases and 12% (95% CI: 8–16), 9% (95% CI: 6–13), and 2% (95% CI: 1–6) in patients

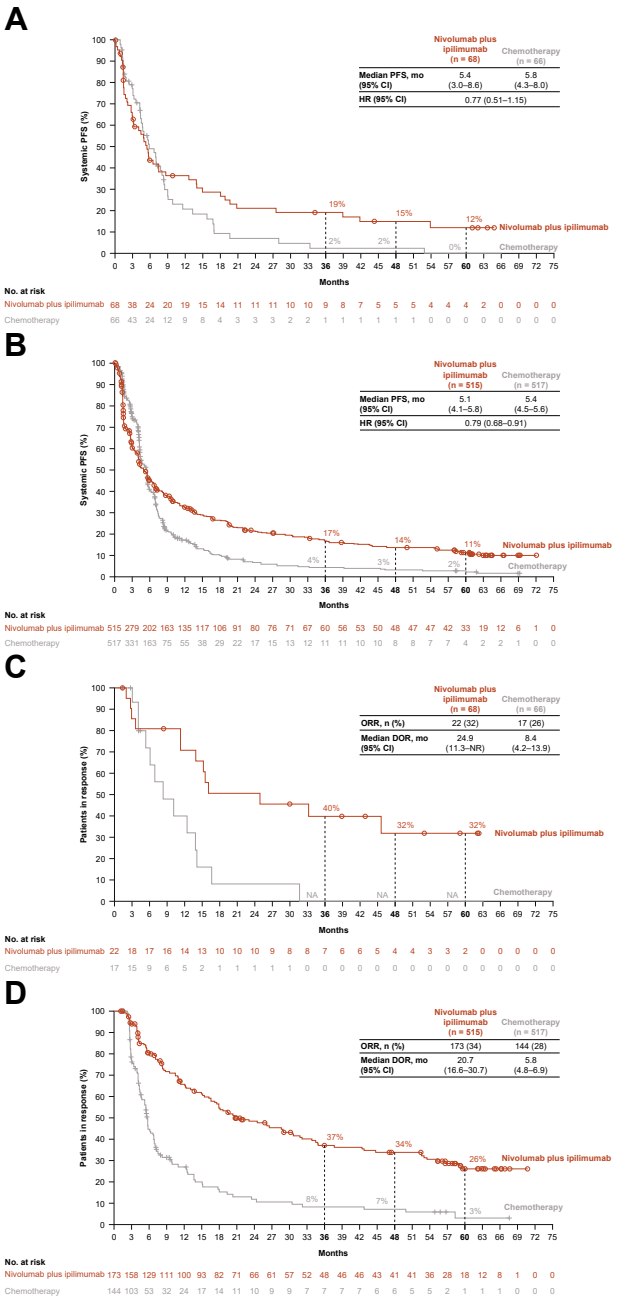

Figure 2. Systemic PFS in patients (*A*) with or (*B*) without baseline brain metastases, and systemic ORR and DOR in randomized patients (*C*) with or (*D*) without baseline brain metastases: nivolumab plus ipilimumab versus chemotherapy. The 95% CIs for 5-year rates with nivolumab plus ipilimumab and chemotherapy, respectively, are as follows: (*A*) 5-23 and NA, (*B*) 8-15 and 1-5, (*C*) 12-54 and NA, and (*D*) 19-34 and 0-11. CI, confidence interval; DOR, duration of response; HR, hazard ratio; NA, not available; NR, not reached; ORR, objective response rate; PFS, progression-free survival.

without baseline brain metastases. Among patients with tumor PD-L1 less than 1% (Supplementary Table 3), trends toward improved systemic PFS were observed with nivolumab plus ipilimumab versus chemotherapy in patients with baseline brain metastases (HR = 0.63, 95% CI: 0.29–1.38) or without (HR = 0.76, 95% CI: 0.59–0.98); similar trends toward improved systemic PFS were observed with nivolumab plus chemotherapy versus chemotherapy in patients with baseline brain metastases (HR = 0.61, 95% CI: 0.31–1.22) or without (HR = 0.73, 95% CI: 0.57–0.93).

Systemic ORR was 32% (95% CI: 22–45) and 26% (95% CI: 16–38) with nivolumab plus ipilimumab and chemotherapy, respectively, in patients who had baseline brain metastases (Fig. 2*C*), with one patient in each treatment arm achieving a complete response (Supplementary Table 4). Median DOR in patients with baseline brain metastases was 24.9 months (95% CI: 11.3–not reached) with nivolumab plus ipilimumab and 8.4 months (95% CI: 4.2–13.9) with chemotherapy. The proportion of patients with baseline brain metastases with DOR more than or equal to 5 years was 32% (95% CI: 12–54) in the nivolumab plus ipilimumab arm; there were no responding patients with baseline brain metastases in the chemotherapy arm at 5 years. In patients without baseline brain metastases, systemic ORRs were 34% (95% CI: 30–38) and 28% (95% CI: 24–32) with nivolumab plus ipilimumab and chemotherapy, respectively (Fig. 2*D*); complete response rates were 6% and 2%, median DOR was 20.7 (95% CI: 16.6–30.7) and 5.8 months (95% CI: 4.8–6.9) and proportions of patients with DOR more than or equal to 5 years were 26% (95% CI: 19–34) and 3% (95% CI: 0–11; Supplementary Table 4). Systemic response with other nivolumab-based regimens is summarized in Supplementary Table 4.

Intracranial PFS and Development of New Brain Lesions. Nivolumab plus ipilimumab was associated with a trend toward improved intracranial PFS versus chemotherapy (HR = 0.82, 95% CI: 0.52–1.30); 5-year intracranial PFS rates were 16% (95% CI: 5–33) and 6% (95% CI: 1–22), respectively (Fig. 3). Median intracranial PFS with nivolumab plus ipilimumab and chemotherapy, respectively, was 8.6 (95% CI: 5.7–19.5) and 11.5 months (95% CI: 6.6–24.4) in patients with tumor PD-L1 greater than or equal to 1%, and 12.6 (95% CI: 4.1–53.8) and 7.1 months (95% CI: 3.1–8.4) in those with tumor PD-L1 less than 1% (Supplementary Table 5).

Fewer patients with baseline brain metastases in the nivolumab plus ipilimumab arm developed new brain lesions (4%) than those in the chemotherapy arm (20%; Table 2). In patients without baseline brain metastases, the incidence of new brain lesions was similar among patients in the nivolumab plus ipilimumab (5%) and chemotherapy arms (2%). The median time to development of new brain lesions in the nivolumab plus ipilimumab and chemotherapy arms was 4.0 and 7.1 months, respectively, among patients with baseline brain metastases, and 5.1 and 5.8

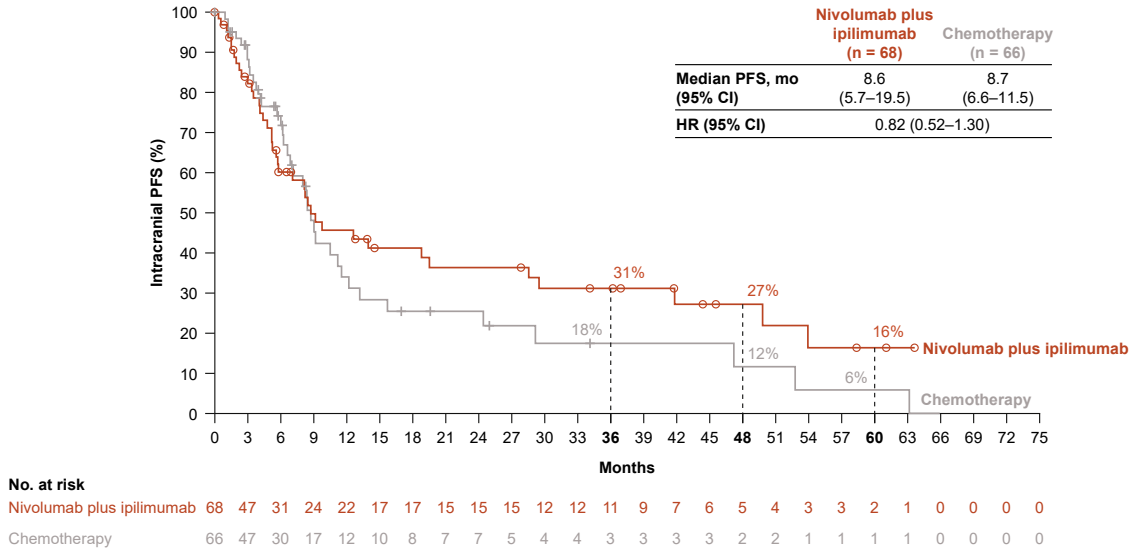

Figure 3. Intracranial PFS in patients with baseline brain metastases: nivolumab plus ipilimumab versus chemotherapy. The 95% CIs for 5-year rates with nivolumab plus ipilimumab and chemotherapy were 5-33 and 1-22, respectively. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

months among patients without brain metastases (Table 2). In patients with tumor PD-L1 greater than or equal to 1%, fewer patients with baseline brain metastases in the nivolumab plus ipilimumab arm (6%) developed new brain lesions than those in the chemotherapy arm (17%), whereas the incidence of new brain lesions was similar between these treatment arms (5% and 2%, respectively) among patients without baseline brain lesions (Supplementary Table 6). In patients with tumor PD-L1 less than 1% and baseline brain metastases, no patient in the nivolumab plus ipilimumab arm, and 28% of those in the chemotherapy arm developed new brain lesions. The development of new brain lesions in patients in other groups (including other nivolumab-containing treatment arms) is summarized in Supplementary Table 6.

Safety

At 61.3 months' minimum follow-up, safety outcomes in patients with or without baseline brain metastases were consistent with those in the all-randomized population,[28] and no new safety signals were identified. Among patients with baseline brain metastases who received at least one dose of study treatment, 77% and 76% of patients treated with nivolumab plus ipilimumab or chemotherapy alone, respectively, reported any-grade TRAEs, and 30% and 27% reported grade 3 or 4 TRAEs (Table 3). Similarly, 77% and 83% of patients without baseline brain metastases treated with nivolumab plus ipilimumab or chemotherapy alone, respectively, reported any-grade TRAEs, and 33% and 37% reported grade 3 or 4 TRAEs. Among patients treated with nivolumab plus ipilimumab or chemotherapy alone, respectively, 9% and 3% of those with baseline brain metastases and 19% and 10% of those without baseline brain metastases discontinued treatment owing to TRAEs (Table 3). The most common any-grade IMAEs with nivolumab plus ipilimumab were hypothyroidism or thyroiditis (23%), hyperthyroidism (11%), hepatitis (9%), and rash (9%) among patients with baseline brain

Table 2. Development of New Brain Lesions by Baseline Brain Metastasis Status in patients in the Nivolumab Plus Ipilimumab or Chemotherapy Arms

	With Baseline Brain Metastases		Without Baseline Brain Metastases	
Development of New Brain Lesions	Nivolumab Plus Ipilimumab (n = 68)	Chemotherapy (n = 66)	Nivolumab Plus Ipilimumab (n = 515)	Chemotherapy (n = 517)
Patients who developed new brain lesions, n (%)	3 (4)	13 (20)	27 (5)	13 (2)
Median time to develop new brain lesions (range), mo	4.0 (2.4-9.8)	7.1 (3.0-47.1)	5.1 (0.3-59.0)	5.8 (0.1-28.0)

Note: Patients may have developed more than or equal to one new brain lesions.

Table 3. Safety Summary by Baseline Brain Metastasis Status in Patients Treated with Nivolumab Plus Ipilimumab or Chemotherapy

	With Baseline Brain Metastases				Without Baseline Brain Metastases			
	Nivolumab Plus Ipilimumab (n = 64)		Chemotherapy (n = 66)		Nivolumab Plus Ipilimumab (n = 512)		Chemotherapy (n = 504)	
Adverse Events	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
TRAEs[a]	49 (77)	19 (30)	50 (76)	18 (27)	393 (77)	170 (33)	419 (83)	187 (37)
Most frequent TRAEs[a,b]								
Rash	12 (19)	0	4 (6)	0	86 (17)	9 (2)	25 (5)	0
Hypothyroidism	12 (19)	1 (2)	0	0	60 (12)	1 (<1)	1 (<1)	0
Nausea	11 (17)	0	21 (32)	0	46 (9)	3 (1)	185 (37)	12 (2)
Pruritus	10 (16)	1 (2)	0	0	73 (14)	2 (<1)	6 (1)	0
Decreased appetite	9 (14)	1 (2)	18 (27)	2 (3)	67 (13)	3 (1)	94 (19)	5 (1)
Fatigue	7 (11)	1 (2)	12 (18)	3 (4)	76 (15)	9 (2)	96 (19)	5 (1)
Diarrhea	7 (11)	0	8 (12)	2 (3)	92 (18)	10 (2)	47 (9)	2 (<1)
Constipation	4 (6)	0	6 (9)	0	22 (4)	0	80 (16)	2 (<1)
Vomiting	2 (3)	0	13 (20)	1 (2)	26 (5)	2 (<1)	64 (13)	12 (2)
Anemia	2 (3)	2 (3)	20 (30)	9 (14)	20 (4)	6 (1)	171 (34)	57 (11)
Neutropenia	0	0	10 (15)	4 (6)	1 (<1)	0	89 (18)	51 (10)
TRAEs leading to discontinuation of any component of the regimen[a]	6 (9)	4 (6)	2 (3)	1 (2)	98 (19)	68 (13)	51 (10)	27 (5)
Neurologic TRAEs[a]	10 (16)	0	11 (17)	0	41 (8)	5 (1)	72 (14)	2 (<1)
Most frequent neurologic TRAEs[a,c]								
Headache	3 (5)	0	1 (2)	0	8 (2)	0	7 (1)	0
Paresthesia	2 (3)	0	1 (2)	0	6 (1)	0	10 (2)	0
Taste disorder	2 (3)	0	1 (2)	0	3 (1)	0	3 (1)	0
Somnolence	2 (3)	0	0	0	0	0	1 (<1)	0
Dysgeusia	0	0	4 (6)	0	12 (2)	0	25 (5)	0
Dizziness	0	0	1 (2)	0	3 (1)	0	12 (2)	0
Peripheral sensory neuropathy	0	0	2 (3)	0	3 (1)	0	7 (1)	0
Peripheral neuropathy	0	0	2 (3)	0	1 (<1)	1 (<1)	7 (1)	0
Neurologic TRAEs leading to discontinuation of any component of the regimen[a]	0	0	0	0	2 (<1)	2 (<1)	3 (1)	0
Treatment-related SAEs[a]	12 (19)	9 (14)	6 (9)	3 (4)	129 (25)	97 (19)	73 (14)	58 (12)

Note: Data are n (%). Treatment-related deaths: thrombocytopenia (n = 1) with chemotherapy in patients with baseline brain metastases; pneumonitis (n = 4) and myocarditis, acute tubular necrosis, shock, and cardiac tamponade (n = 1 each) with nivolumab plus ipilimumab in patients without baseline brain metastases; sepsis (n = 2) and multiple brain infarctions, interstitial pneumonia, and febrile neutropenia with sepsis (n = 1 each) with chemotherapy in patients without baseline brain metastases.

[a]Reported between the first dose and 30 days after the last dose of study drug.

[b]TRAEs that occurred in more than or equal to 15% of patients in either treatment arm.

[c]Neurologic TRAEs that occurred in more than or equal to 2% of patients in either treatment arm.

SAE, serious adverse event; TRAE, treatment-related adverse event.

metastases and rash (21%), hypothyroidism or thyroiditis (13%), pneumonitis (9%) and diarrhea or colitis (9%) among patients without baseline brain metastases (Supplementary Table 7). Grade 3 or 4 IMAEs were rare in patients with or without baseline brain metastases, except for hepatitis (9% and 6%, respectively). Treatment-related deaths with nivolumab plus ipilimumab and chemotherapy, respectively, occurred in 0% and 2% of patients with baseline brain metastases, and 2% and 1% of those without baseline brain metastases (Table 3). Supplementary Tables 8 and 9 describe overall safety and IMAEs, respectively, with other nivolumab-based regimens.

Overall, 16% and 17% of patients with baseline brain metastases treated with nivolumab plus ipilimumab or chemotherapy alone, respectively, reported neurologic TRAEs, with all events being grade 1 or 2 in severity (Table 3). The most common any-grade neurologic TRAEs in either the nivolumab plus ipilimumab or chemotherapy arms were headache (nivolumab plus ipilimumab: 5%; chemotherapy: 2%), paresthesia (3%; 2%), taste disorder (3%; 2%), and dysgeusia (0%; 6%). No neurologic TRAEs resulted in treatment discontinuation or death among patients with baseline brain metastases treated with nivolumab plus ipilimumab or chemotherapy alone. The incidence of neurologic TRAEs with nivolumab plus ipilimumab versus chemotherapy was comparable in patients without baseline brain metastases (Table 3). Neurologic TRAEs with other nivolumab-based regimens are summarized in Supplementary Table 8.

Discussion

The present post hoc analysis of CheckMate 227 Part 1 reports efficacy and safety outcomes in patients with or without brain metastases at 5 years' minimum follow-up. To our knowledge, this is the longest follow-up reported so far from a phase 3 study evaluating dual immunotherapy in patients with NSCLC and brain metastases and including intracranial efficacy. Overall, nivolumab plus ipilimumab demonstrated durable improvements in OS and ORR, and longer DOR versus chemotherapy, regardless of baseline brain metastasis status. Trends favoring treatment with nivolumab plus ipilimumab over chemotherapy were also observed with respect to systemic PFS (regardless of baseline brain metastasis status) and intracranial PFS (in patients with baseline brain metastases) as evidenced by improved landmark rates, a metric that is considered to be better suited to evaluate long-term survival benefits with immunotherapy.[32,33] Furthermore, fewer patients in the nivolumab plus ipilimumab arm developed new brain lesions than those in the chemotherapy arm. Safety outcomes in patients with or without baseline brain metastases were consistent with the known safety profile of nivolumab plus ipilimumab.

At 5 years' follow-up in the current analysis, long-term, durable clinical benefit was demonstrated with nivolumab plus ipilimumab both in patients with or without baseline brain metastases, consistent with results reported for the all-randomized population.[28] In patients with baseline brain metastases, clinical benefit with nivolumab plus ipilimumab was indicated by higher 5-year intracranial PFS rates (16% versus 6% with chemotherapy) and fewer patients with new brain lesions (4% versus 20% in the chemotherapy arm). Among the few patients who developed new brain lesions, the median time to develop new lesions seemed to be shorter with nivolumab plus ipilimumab versus chemotherapy alone. Nevertheless, prolonged OS was observed in patients with baseline brain metastases in the nivolumab plus ipilimumab arm versus the chemotherapy arm despite greater than or equal to 40% of patients in the chemotherapy arm receiving subsequent immunotherapy. Given the limited reports of intracranial efficacy of immunotherapy in patients with mNSCLC and brain metastases,[12,17] these results are particularly encouraging and may help guide the management of this difficult-to-treat subpopulation[2,5] in the clinic.

Findings from this 5-year systemic and intracranial efficacy analysis in patients with brain metastases are consistent with reports of other studies evaluating immunotherapy in similar populations. For example, recently published results revealed that nivolumab plus ipilimumab with two cycles of chemotherapy prolonged OS, systemic PFS and DOR, and intracranial PFS versus chemotherapy in patients with mNSCLC and treated brain metastases in the phase 3 CheckMate 9LA study at 3 years' minimum follow-up.[12] The consistent systemic and intracranial outcomes from CheckMate 9LA and CheckMate 227 indicate the clinical benefit of the nivolumab plus ipilimumab–based dual immunotherapy regimen in patients with mNSCLC and treated brain metastases. In addition, systemic outcomes with nivolumab plus ipilimumab reported here were broadly similar to those in pooled analyses evaluating pembrolizumab in a similar patient population with treated brain metastases.[11,13] Improved clinical outcomes with dual immunotherapy and combination immunotherapy plus chemotherapy were also observed in patients with mNSCLC and untreated brain metastases, as reported in the phase 3b CheckMate 817 and the phase 2 ATEZOBRAIN studies, respectively,[16,34] although cross-trial comparisons should be made with caution owing to differences in patient characteristics and study designs. Taken together, our findings further highlight the clinical benefit

of immunotherapy in patients with NSCLC and treated brain metastases, a population of high unmet needs.

The clinical benefit of systemic therapy in patients with brain metastases is thought to be limited owing to the BBB.[6,35] The intracranial activity of chemotherapy may be attenuated owing to the BBB impeding the delivery of these large molecules and the rapid efflux of these agents out of the CNS.[6,35,36] Although immune checkpoint inhibitors also have relatively low BBB penetrability,[37,38] the activation of extracranial lymphocytes and their subsequent transport into the CNS is thought to be a potential mechanism of action against brain metastases.[39,40] In addition, the distinct but complementary mechanisms of action of nivolumab and ipilimumab in inducing antitumor T-cell activity may be particularly beneficial in producing long-term clinical benefit,[6,41,42] as suggested by longer median OS (20.6 versus 12.0 mo) and higher 5-year OS rates (27% versus 14%) observed with nivolumab plus ipilimumab versus nivolumab in patients with baseline brain metastases and tumor PD-L1 greater than or equal to 1% in the present analysis. Considering growing evidence supporting the clinical benefit of immunotherapy-based regimens, NCCN Guidelines, and European Association of Neuro-Oncology–European Society for Medical Oncology guidelines now recommend the use of first-line immune checkpoint inhibitors as alternatives to local treatment options for the management of certain patients with brain metastases and PD-L1–positive mNSCLC.[43,44]

Patients with baseline brain metastases treated with nivolumab plus ipilimumab had similar safety outcomes compared with those without baseline brain metastases in this 5-year post hoc analysis. With all patients off treatment, there were no notable differences in TRAEs overall or neurologic TRAEs among patients with versus without baseline brain metastases. The incidence of IMAEs in patients with baseline brain metastases treated with nivolumab plus ipilimumab was generally similar to that observed in all randomized patients.[28]

Although the present analysis characterized long-term outcomes with nivolumab-based regimens in patients with NSCLC by baseline brain metastasis status, the relatively small sample sizes of certain subgroups of patients with brain metastases (e.g., patients with tumor PD-L1 $<1\%$ or those receiving nivolumab or nivolumab plus chemotherapy) and the nature of post hoc exploratory analyses limit data interpretation. The small sample size also precludes the generation of clinically meaningful data from an intracranial analysis by histology, although it is known that chemotherapy regimens selected on the basis of tumor histology may differ with respect to CNS penetration and intracranial efficacy.[45,46] In addition, a robust analysis of the development of new brain lesions was precluded by a lack of routine brain imaging in patients without baseline brain metastases (per protocol). Although the use of prior brain radiotherapy for the treatment of brain metastases was generally similar across the treatment arms, the potential impact of this treatment on intracranial outcomes observed in this post hoc analysis cannot be ruled out definitively. Imbalances in other confounding factors among patients with versus without baseline brain metastases in this analysis, such as baseline characteristics and subsequent therapy, also suggest that caution be exercised when interpreting these findings. Additional data from larger populations of patients with brain metastases are needed to guide the management of patients with NSCLC, brain metastases, and tumor PD-L1 less than 1%.

In summary, this post hoc exploratory systemic and intracranial analysis of CheckMate 227 Part 1 demonstrated that first-line nivolumab plus ipilimumab provided durable, long-term clinical benefit, including intracranial benefit, versus chemotherapy in patients with mNSCLC at 5-years' minimum follow-up. No new safety signals were observed in patients with or without baseline brain metastases treated with nivolumab plus ipilimumab. These data further support first-line nivolumab plus ipilimumab as an efficacious treatment option in patients with mNSCLC, regardless of baseline brain metastasis status.

CRediT Authorship Contribution Statement

Martin Reck: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

Tudor-Eliade Ciuleanu: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Jong-Seok Lee: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Michael Schenker: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Bogdan Zurawski: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Sang-We Kim: Validation, Investigation, Resources, Data curation, Writing - review & editing.

Mauricio Mahave: Validation, Investigation, Resources, Data curation, Writing - review & editing.

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Koichi Azuma: Validation, Investigation, Resources, Data curation, Writing - review & editing.

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Suresh S. Ramalingam: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

Hossein Borghaei: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

Kenneth J. O'Byrne: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

Li Li: Software, Formal Analysis, Data curation, Writing - review & editing, Visualization.

Judith Bushong: Validation, Data curation, Writing - review & editing, Visualization, Project administration, Funding acquisition.

Ravi G. Gupta: Validation, Data curation, Writing - review & editing, Visualization, Project administration, Funding acquisition.

Diederik J. Grootendorst: Validation, Data curation, Writing - review & editing, Visualization.

Laura J. Eccles: Writing - review & editing, Visualization.

Julie R. Brahmer: Conceptualization, Methodology, Validation, Investigation, Resources, Data curation, Writing - review & editing, Supervision.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2023.04.021.

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