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First-line nivolumab plus ipilimumab for metastatic non-small cell lung cancer, including patients with ECOG performance status 2 and other special populations: CheckMate 817

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ABSTRACT

Background CheckMate 817, a phase 3B study, evaluated flat-dose nivolumab plus weight-based ipilimumab in patients with metastatic non-small cell lung cancer (NSCLC). Here, in this research, we report on first-line treatment in patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1 (cohort A) and special populations (cohort A1: ECOG PS 2; or ECOG PS 0–1 with untreated brain metastases, renal impairment, hepatic impairment, or controlled HIV infection).

Methods Cohorts A and A1 received nivolumab 240 mg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks. The primary endpoint was the incidence of grade 3–4 and grade 5 immune-mediated adverse events (IMAEs; adverse events (AEs) deemed potentially immune-related, occurring <100 days of last dose, and treated with immune-modulating medication (except endocrine events)) and treatment-related select AEs (treatment-related AEs with potential immunological etiology requiring frequent monitoring/intervention, reported between first dose and 30 days after the last dose) in cohort A; efficacy endpoints were secondary/exploratory. In cohort A1, safety/efficacy assessment was exploratory.

Results The most common grade 3–4 IMAEs were pneumonitis (5.1%), diarrhea/colitis (4.9%), and hepatitis (4.6%) in cohort A (N=391) and diarrhea/colitis (3.5%), hepatitis (3.5%), and rash (3.0%) in cohort A1 (N=198). The most common grade 3–4 treatment-related select AEs were hepatic (5.9%), gastrointestinal (4.9%), and pulmonary (4.6%) events in cohort A and gastrointestinal (4.0%), skin (3.5%), and endocrine (3.0%) events in cohort A1. No grade 5 IMAEs or treatment-related select AEs occurred. Treatment-related deaths occurred in 4 (1.0%) and 3 (1.5%) patients in cohorts A and A1, respectively. Three-year overall survival (OS) rates were 33.7% and 20.5%, respectively.

Conclusions Flat-dose nivolumab plus weight-based ipilimumab was associated with manageable safety and durable efficacy in cohort A, consistent with data from phase 3 metastatic NSCLC studies. Special populations of cohort A1 including patients with ECOG PS 2 or ECOG PS 0–1 with untreated brain metastases had manageable treatment-related toxicity and clinically meaningful 3-year OS rate.

Trial registration number NCT02869789.

INTRODUCTION

First-line immunotherapy targeting programmed death-1 (PD-1) or its ligand (PD-L1) alone or in combination with other treatment modalities has improved overall survival (OS) for patients with metastatic non-small cell lung cancer (NSCLC) having no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations.[1] Nivolumab (a PD-1 inhibitor) and ipilimumab (a cytotoxic T-lymphocyte antigen-4 inhibitor) are immune checkpoint inhibitors with distinct, but complementary mechanisms of action.[2 3] Nivolumab restores antitumor T-cell function while ipilimumab induces de novo antitumor T-cell responses, including an increase in memory T cells.[4–7] In the randomized, open-label, phase 3 CheckMate 227 study, first-line, weight-based nivolumab plus ipilimumab provided durable OS benefit versus chemotherapy in patients with metastatic NSCLC and tumor PD-L1 expression ≥1% or <1%, regardless of histology.[8] Four-year OS

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immunotherapy regimens, including programmed death-1/programmed death ligand 1 regimens alone or in combination with other immune checkpoint inhibitors and/or chemotherapy, have improved survival outcomes for patients with metastatic non-small cell lung cancer (NSCLC). Combination nivolumab and ipilimumab treatment has shown promising benefit in patients with metastatic NSCLC, but there are limited prospective studies that evaluate the safety and efficacy of this combination in patients with poorer prognosis, including those with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, or those with ECOG PS 0–1 plus untreated brain metastases, organ dysfunction, or positive HIV status.

WHAT THIS STUDY ADDS

⇒ The CheckMate 817 trial is the first to show that first-line combination flat-dose nivolumab plus weight-based ipilimumab has a tolerable safety profile and durable efficacy in patients with metastatic NSCLC. Additionally, CheckMate 817 is the first prospective study to evaluate patients with metastatic NSCLC and patient subgroups that are typically excluded from phase 3 randomized controlled trials: those with ECOG PS 2, or ECOG PS 0–1 plus untreated brain metastases, renal or hepatic impairment, or positive HIV status.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results support the use of combination nivolumab and ipilimumab as a first-line treatment for patients with metastatic NSCLC, including patients who were ECOG PS 2, or ECOG PS 0–1 and had untreated brain metastases, renal or hepatic impairment, or positive HIV status.

rates with nivolumab plus ipilimumab were 29% and 24% in patients with tumor PD-L1 expression ≥1% and <1%, respectively.[8] Nivolumab plus ipilimumab has been approved in the USA and other countries for the first-line treatment of adults with metastatic NSCLC expressing PD-L1 ≥1% and no sensitizing targetable *EGFR* or *ALK* aberrations, and is recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) and European Society for Medical Oncology Guidelines as first-line treatment regardless of PD-L1 expression or histology.[2 3 9–12]

Nivolumab plus ipilimumab combination therapy underwent additional dose optimization for NSCLC indications in order to improve the safety profile seen particularly with the ipilimumab 3 mg/kg every 3-week (Q3W) dose that was developed to treat malignant melanoma.[13] CheckMate 012 was a phase 1 trial with multiple treatment arms designed to identify an optimal dose and schedule of nivolumab plus ipilimumab for metastatic NSCLC. In CheckMate 012, nivolumab 1 mg/kg Q3W plus ipilimumab 3 mg/kg Q3W and nivolumab 3 mg/kg Q3W plus ipilimumab 1 mg/kg Q3W dosing regimens had poor tolerability, while nivolumab 3 mg/kg every 2 weeks (Q2W) plus ipilimumab 1 mg/kg every 6 weeks (Q6W) was tolerable with promising clinical benefit.[14] Therefore, to assess the clinical safety of flat-dose nivolumab in combination with ipilimumab, nivolumab (240 mg Q2W) plus ipilimumab (1 mg/kg Q6W) was evaluated in CheckMate 817. A fixed-dosing regimen increases convenience to patients while minimizing dosing errors and dosage preparation time and reducing overall healthcare burden.[15] Another key unmet need is to improve clinical outcomes in patients with metastatic NSCLC and poorer prognosis, such as those with Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, or those with ECOG PS 0–1 and either untreated brain metastases, organ dysfunction, or positive HIV status, who are often excluded from prospective clinical trials.[16 17] Data on safety and efficacy of immunotherapy in these patient populations are limited, and effective therapeutic options for these patients are a high unmet need. Reported herein are safety and efficacy findings with flat-dose nivolumab plus weight-based ipilimumab in patients with metastatic NSCLC in cohorts A (ECOG PS 0–1) and A1 (ECOG PS 2; or ECOG PS 0–1 with untreated brain metastases, renal or hepatic impairment, or positive HIV status) of CheckMate 817.

METHODS

Patients

Detailed eligibility criteria are summarized in online supplemental table S1. Briefly, eligible patients in cohorts A and A1 had histologically confirmed stage IV or recurrent NSCLC (per the seventh edition of the International Association for the Study of Lung Cancer Classification) with no prior systemic therapy for advanced or metastatic disease. Following a protocol amendment in November 2016, patients with *EGFR* mutations or *ALK* translocations sensitive to available therapy were excluded. In cohort A, eligible patients had ECOG PS 0–1, adequate renal and hepatic function, negative HIV status, and no active or untreated brain metastases. In cohort A1, eligible patients either had ECOG PS 2 or ECOG PS 0–1 with one of the following: untreated asymptomatic brain metastases, renal impairment (creatinine clearance: 20–39 mL/min), hepatic impairment (aspartate aminotransferase/alanine aminotransferase: 3.0–5.0×upper limit of normal and/or total bilirubin 1.5–3.0×upper limit of normal), or controlled HIV infection.

Study design and treatment

CheckMate 817 is a phase 3B, multicenter, open-label, single-arm, multicohort, safety study conducted at 135 study sites across North America, Europe, and South America. Patients in cohorts A and A1 received nivolumab (240 mg Q2W) plus ipilimumab (1 mg/kg Q6W) intravenously until disease progression, unacceptable toxicity, withdrawal of consent, or for up to 2 years (online supplemental figure S1). Dose delay criteria are summarized in online supplemental table S2.

Endpoints and assessments

The primary endpoint was the proportion of patients with grade 3–4 and grade 5 immune-mediated adverse events (IMAEs) and treatment-related select adverse events (AEs) in cohort A. Secondary endpoints included efficacy

in cohort A: OS, and Response Evaluation Criteria in Solid Tumors V.1.1-defined investigator-assessed progression-free survival (PFS), objective response rate (ORR), and duration of response (DOR); efficacy by tumor PD-L1 expression (≥1% and <1%) was exploratory. In cohort A1, efficacy and safety assessments were exploratory.

IMAEs were AEs deemed potentially immune-related by the investigator (regardless of causality), occurring within 100 days of the last dose, and treated with immune-modulating medication, except for endocrine events, which were included in the analysis regardless of method of treatment. Treatment-related select AEs were treatment-related AEs (TRAEs) with a potential immunological etiology requiring frequent monitoring/intervention, and included events reported between first dose and 30 days after last dose of study drug. Grade 3–4 and grade 5 IMAEs and treatment-related select AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0. Events leading to death ≤24 hours from onset were documented as grade 5. Events leading to death >24 hours after onset were reported with the worst grade before death. Additional details are included in online supplemental methods.

Statistical analysis

Based on previous reports on the incidence of grade 3–4 treatment-related select AEs (≤5% per category) with weight-based dosing of nivolumab (3 mg/kg Q2W) plus ipilimumab (1 mg/kg Q6W),[14] a sample size of approximately 400 patients in cohort A was estimated to allow detection of safety events with incidence rates of 1% and 0.5% with >98% and >86% probability, respectively. In cohort A1, a sample size of 30 patients for each special population subgroup was estimated to allow detection of safety events with an incidence rate of 5% with a probability of approximately 79%.

Safety and efficacy were analyzed in all patients who received ≥1 dose of study drug. OS, PFS, and DOR were summarized by Kaplan-Meier methodology and reported as medians with two-sided 95% CIs, per the Brookmeyer and Crowley method. Survival rates were estimated using the Kaplan-Meier method and expressed with two-sided 95% CIs per the Greenwood formula. Confirmed ORRs were summarized by binomial response rates with corresponding two-sided 95% exact CIs, per the Clopper-Pearson method. Statistical analyses were conducted using SAS software V.9.4 (SAS Institute).

RESULTS

Patients and treatment

Starting November 2016, 391 (cohort A) and 198 (cohort A1) patients received ≥1 dose of treatment (online supplemental figure S2). Cohort A1 included 139 patients with baseline ECOG PS 2, and 68 patients with ECOG PS 0–1 plus one of the following: untreated brain metastases (n=49), renal impairment (n=9), hepatic impairment (n=7), or positive HIV status (n=4). One patient had both untreated brain metastases and positive HIV status; 9 patients with untreated brain metastases or comorbidities in cohort A1 also had ECOG PS 2. Of these 10 patients, 5 were enrolled when study eligibility criteria allowed inclusion of patients with ≥1 special population criteria; 5 patients had protocol deviations. Patients belonging to multiple subgroups were included in each of the subgroups for all analyses. At database lock (February 19, 2021), all patients in both cohorts had discontinued or completed treatment; treatment discontinuation was mainly due to disease progression or study drug toxicity (online supplemental table S3). Median (range) duration of treatment was 4.0 (<0.1–25.8) months in cohort A and 2.8 (<0.1–25.4) months in cohort A1 (online supplemental table S4). Subsequent systemic therapy was received by 139 (35.5%) and 53 (26.8%) patients in cohorts A and A1, subsequent chemotherapy by 120 (30.7%) and 43 (21.7%), and subsequent immunotherapy by 32 (8.2%) and 14 (7.1%) patients, respectively, (online supplemental table S5). The minimum and median follow-up in cohorts A and A1 were 40.9/43.9 months and 33.9/38.1 months, respectively.

In cohort A, most patients had stage IV disease (88.0%) and non-squamous histology (71.9%); 55.5% had ECOG PS 1, and 49.3% had tumor PD-L1 expression ≥1% (table 1). Of eight patients (2.0%) with *EGFR*-positive mutation status, three had sensitizing mutations (two patients were enrolled before protocol amendment exclusion; one was protocol deviation). In cohort A1, 93.4% of the patients had stage IV disease and 70.2% had non-squamous histology, and 44.4% had tumor PD-L1 expression ≥1%; neither of the two patients with *EGFR*-positive mutation status had a sensitizing mutation. In cohort A1 subgroups, baseline characteristics, excluding protocol-defined differences, were largely similar to those in cohort A1 overall (table 1).

Cohort A

Safety

In patients with ECOG PS 0–1, any-grade TRAEs were reported in 301 (77.0%), grade 3–4 TRAEs in 138 (35.3%), and any-grade TRAEs leading to treatment discontinuation of at least one study drug in 93 (23.8%) patients (table 2). Four treatment-related deaths (1.0%) occurred (cardiac failure secondary to immune-mediated rhabdomyolysis of heart and other muscles (n=1), autoimmune esophagitis (n=1), autoimmune hepatitis (n=1), and Guillain–Barré syndrome (n=1)). The most common grade 3–4 IMAEs were pneumonitis (5.1%), diarrhea/colitis (4.9%), and hepatitis (4.6%) (table 2). The most common grade 3–4 treatment-related select AEs were hepatic (5.9%), gastrointestinal (4.9%), and pulmonary (4.6%) events. No grade 5 IMAEs or treatment-related select AEs were reported. Times to onset and resolution of IMAEs are shown in figure 1. Systemic corticosteroids were primarily used for the management of IMAEs, with treatment lasting <1 week to 1.5 months (online

Table 1 Patient demographics and baseline characteristics

	Cohort A1*			
	Cohort A	Overall	ECOG PS 2	Asymptomatic untreated brain metastases
	(N=391)	(N=198)†	(n=139)‡	(n=49)§
Age, years				
Median (range)	65.0 (26–89)	67.0 (39–90)	67.0 (39–90)	64.0 (40–78)
<75 years, n (%)	331 (84.7)	157 (79.3)	108 (77.7)	48 (98.0)
≥75 years, n (%)	60 (15.3)	41 (20.7)	31 (22.3)	1 (2.0)
Sex, n (%)				
Male	236 (60.4)	127 (64.1)	90 (64.7)	28 (57.1)
Female	155 (39.6)	71 (35.9)	49 (35.3)	21 (42.9)
Race, n (%)				
White	379 (96.9)	194 (98.0)	138 (99.3)	46 (93.9)
Black	6 (1.5)	3 (1.5)	1 (0.7)	3 (6.1)
Other	5 (1.3)	1 (0.5)	0	0
Not reported	1 (0.3)	0	0	0
Region, n (%)				
North America	121 (30.9)	24 (12.1)	17 (12.2)	5 (10.2)
Europe	270 (69.1)	144 (72.7)	100 (71.9)	41 (83.7)
Other	0	30 (15.2)	22 (15.8)	3 (6.1)
ECOG PS, n (%)				
0	171 (43.7)	18 (9.1)	0 (0)	15 (30.6)
1	217 (55.5)	50 (25.3)	10 (7.2)	30 (61.2)
2	3 (0.8)	130 (65.7)	129 (92.8)	4 (8.2)
Smoking status, n (%)				
Never smoker	32 (8.2)	17 (8.6)	13 (9.4)	6 (12.2)
Former/current smoker	357 (91.3)	177 (89.4)	123 (88.5)	42 (85.7)
Unknown	2 (0.5)	4 (2.0)	3 (2.2)	1 (2.0)
Disease stage, n (%)				
IV	344 (88.0)	185 (93.4)	130 (93.5)	49 (100.0)
Recurrent	47 (12.0)	13 (6.6)	9 (6.5)	0
Histology, n (%)				
Non-squamous	281 (71.9)	139 (70.2)	88 (63.3)	45 (91.8)
Adenocarcinoma	268 (68.5)	127 (64.1)	80 (57.6)	41 (83.7)
Large cell	6 (1.5)	5 (2.5)	4 (2.9)	0
Bronchoalveolar	1 (0.3)	0	0	0
Other	6 (1.5)	7 (3.5)	4 (2.9)	4 (8.2)
Squamous	110 (28.1)	59 (29.8)	51 (36.7)	4 (8.2)
Tumor PD-L1 expression, n (%)¶				
Evaluable	357 (91.3)	171 (86.4)	119 (85.6)	43 (87.8)
≥1%	176 (49.3)	76 (44.4)	52 (43.7)	20 (46.5)
<1%	181 (50.7)	95 (55.6)	67 (56.3)	23 (53.5)
≥50%	65 (18.2)	32 (18.7)	22 (18.5)	8 (18.6)
EGFR mutation status, n (%)				
Positive	8 (2.0)**	2 (1.0)**	1 (0.7)**	1 (2.0)**
Not detected	279 (71.4)	129 (65.2)	83 (59.7)	40 (81.6)
Not reported	104 (26.6)	67 (33.8)	55 (39.6)	8 (16.3)

*Patients belonging to multiple subgroups are included in each of the subgroups.
†Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.
‡Includes five patients with untreated brain metastases, one with renal impairment, and three with hepatic impairment.
§Includes five patients with ECOG PS 2 and one patient with positive HIV status.
¶Assessed on tumor tissue collected prior to treatment initiation, as described in the online supplemental methods, and calculated as a percentage of evaluable patients.
**Of the eight *EGFR* mutations in cohort A, three were sensitizing; neither of the two *EGFR* mutations in cohort A1 was sensitizing.
ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; PD-L1, programmed death ligand 1.

Table 2 Safety summary for patients treated with nivolumab plus ipilimumab in cohort A

Adverse events, n (%)	Cohort A (N=391)	
	Any grade	Grade 3–4
TRAEs	301 (77.0)	138 (35.3)
TRAEs reported by ≥10% of the patients in any group		
Diarrhea	80 (20.5)	8 (2.0)
Pruritus	71 (18.2)	2 (0.5)
Fatigue	58 (14.8)	7 (1.8)
Hypothyroidism	50 (12.8)	2 (0.5)
Rash	47 (12.0)	4 (1.0)
TRAEs leading to discontinuation*	93 (23.8)	65 (16.6)
Treatment-related serious AEs	88 (22.5)	69 (17.6)
Treatment-related deaths	4 (1.0)†	
IMAEs by category including preferred terms in ≥1% of the patients‡		
Hypothyroidism/thyroiditis	55 (14.1)	3 (0.8)
Hypothyroidism	52 (13.3)	2 (0.5)
Thyroiditis	5 (1.3)	1 (0.3)
Thyroiditis acute	1 (0.3)	0
Rash	52 (13.3)	14 (3.6)
Rash	30 (7.7)	5 (1.3)
Rash maculopapular	15 (3.8)	5 (1.3)
Dermatitis acneiform	5 (1.3)	1 (0.3)
Diarrhea/colitis	40 (10.2)	19 (4.9)
Diarrhea	28 (7.2)	7 (1.8)
Colitis	11 (2.8)	8 (2.0)
Immune-mediated enterocolitis	8 (2.0)	4 (1.0)
Pneumonitis	39 (10.0)	20 (5.1)
Pneumonitis	35 (10.0)	17 (4.3)
Hyperthyroidism	28 (7.2)	1 (0.3)
Hepatitis	22 (5.6)	18 (4.6)
Hepatotoxicity	9 (2.3)	8 (2.0)
Alanine aminotransferase increased	6 (1.5)	4 (1.0)
Aspartate aminotransferase increased	6 (1.5)	4 (1.0)
Transaminases increased	4 (1.0)	3 (0.8)
Hypersensitivity	11 (2.8)	4 (1.0)
Infusion-related reaction	7 (1.8)	3 (0.8)
Adrenal insufficiency	10 (2.6)	5 (1.3)
Hypophysitis	7 (1.8)	3 (0.8)
Hypophysitis	4 (1.0)	2 (0.5)
Nephritis and renal dysfunction	3 (0.8)	2 (0.5)
Diabetes mellitus	3 (0.8)	3 (0.8)
Treatment-related select AEs		
Skin events	128 (32.7)	14 (3.6)
Endocrine events	93 (23.8)	16 (4.1)
Gastrointestinal events	88 (22.5)	19 (4.9)
Pulmonary events	42 (10.7)	18 (4.6)
Hepatic events	40 (10.2)	23 (5.9)
Hypersensitivity/infusion reactions	34 (8.7)	6 (1.5)
Renal events	8 (2.0)	2 (0.5)

*In the event of discontinuation of ipilimumab treatment, nivolumab treatment could continue; however, continuation of ipilimumab after discontinuation of nivolumab was not allowed.
†Due to grade 5 cardiac failure secondary to immune-mediated grade 3 rhabdomyolysis of heart and other muscles (n=1), autoimmune esophagitis (n=1), autoimmune hepatitis (n=1), and Guillain–Barré syndrome (n=1).
‡Included IMAEs that were treated using immune-modulating medications, except for endocrine events, which were included regardless of treatment.
AE, adverse event; IMAE, immune-mediated adverse event; TRAE, treatment-related adverse event.

supplemental table S6). Most patients did not require any other immune-modulating medications for IMAE management.

Efficacy

In cohort A, median (95% CI) OS was 16.8 months (14.6 to 22.4), with a 3-year OS rate (95% CI) of 33.7% (29.0% to 38.5%) (figure 2A); median (95% CI) PFS was 5.8 months (4.5 to 7.6) with a 3-year PFS rate (95% CI) of 20.1% (15.9% to 24.7%) (figure 2B). ORR (95% CI) was 37.3% (32.5% to 42.3%) and median (95% CI) DOR was 27.6 months (20.4 to 34.3); 41% (32% to 50%) of responders had an ongoing response at 3 years (online supplemental table S7).

In patients with tumor PD-L1 expression ≥1% and <1%, respectively, median (95% CI) OS was 21.0 months (14.2 to 30.8) and 15.3 months (12.5 to 19.2) (figure 2A); median (95% CI) PFS was 7.1 months (4.2 to 9.3) and 5.3 months (4.1 to 6.3) (figure 2B). ORR (95% CI) was 43.8% (36.3% to 51.4%) and 30.9% (24.3% to 38.2%) (online supplemental table S7); median (95% CI) DOR was 29.9 months (15.2 to 39.8) and 25.8 months (16.8 to 34.3); and 45% (32% to 56%) and 35% (22% to 49%) of responders had an ongoing response at 3 years. Data trends were generally similar in patients with tumor PD-L1 ≥50% with median (95% CI) OS of 21.4 months (11.8 to 41.1) and median (95% CI) PFS was 8.4 months (5.4 to 14.8); however the sample size for patients with tumor PD-L1 ≥50% was small (online supplemental table S7).

In patients with non-squamous and squamous histology, respectively, median (95% CI) OS was 20.1 months (15.4 to 27.3) and 13.7 months (9.4 to 21.4) (figure 2C); median (95% CI) PFS was 5.8 months (4.2 to 8.3) and 5.5 months

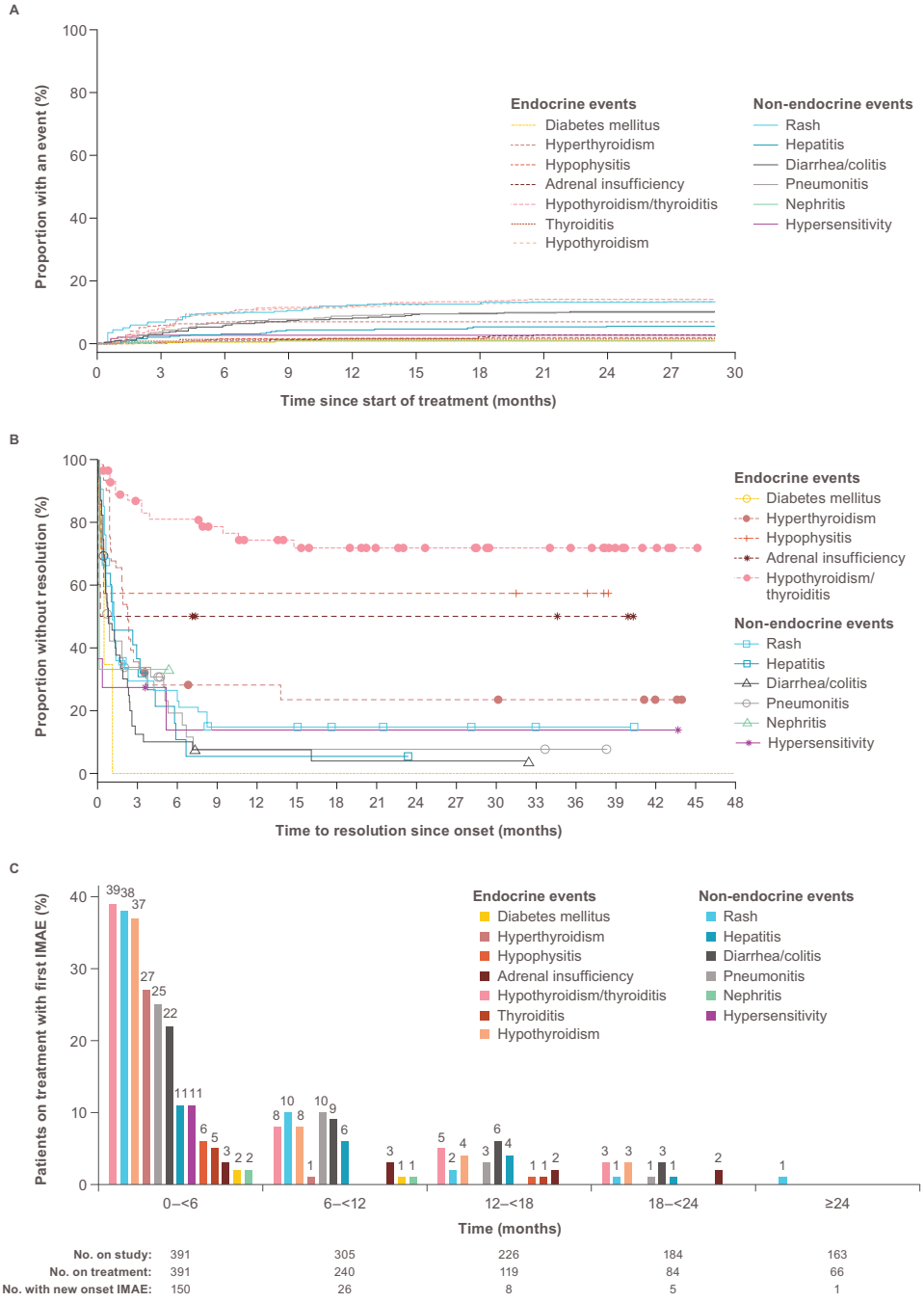

Figure 1 Cumulative time to onset of immune-mediated adverse events (IMAEs) (A), cumulative time to resolution of IMAEs (B), and IMAEs over time (C) in cohort A.

(4.1 to 8.2). ORR (95% CI) was 38.1% (32.4% to 44.0%) and 35.5% (26.6% to 45.1%); and median (95% CI) DOR was 27.6 months (18.9 to 39.8) and 29.9 months (13.7 to 37.2).

Cohort A1 (special populations)

Safety

In cohort A1, any-grade TRAEs were reported in 135 (68.2%), grade 3–4 TRAEs in 58 (29.3%), and TRAEs leading to treatment discontinuation of at least one study drug in 32 (16.2%) patients (table 3). Three treatment-related deaths (1.5%) were reported, all in patients with ECOG PS 2 (myasthenic syndrome secondary to immunotherapy (n=1), interstitial diffuse pneumonitis (n=1), and polymyositis (n=1)). The most common grade 3–4 IMAEs were diarrhea/colitis (3.5%), hepatitis (3.5%), and rash (3.0%). The most common grade 3–4 treatment-related select AEs were gastrointestinal (4.0%), skin (3.5%), and endocrine (3.0%) events. No grade 5 IMAEs or treatment-related select AEs were reported. Times to onset and resolution of IMAEs are reported in figure 3. Use of systemic corticosteroids for IMAE management was overall similar to that reported in cohort A (online supplemental table S6).

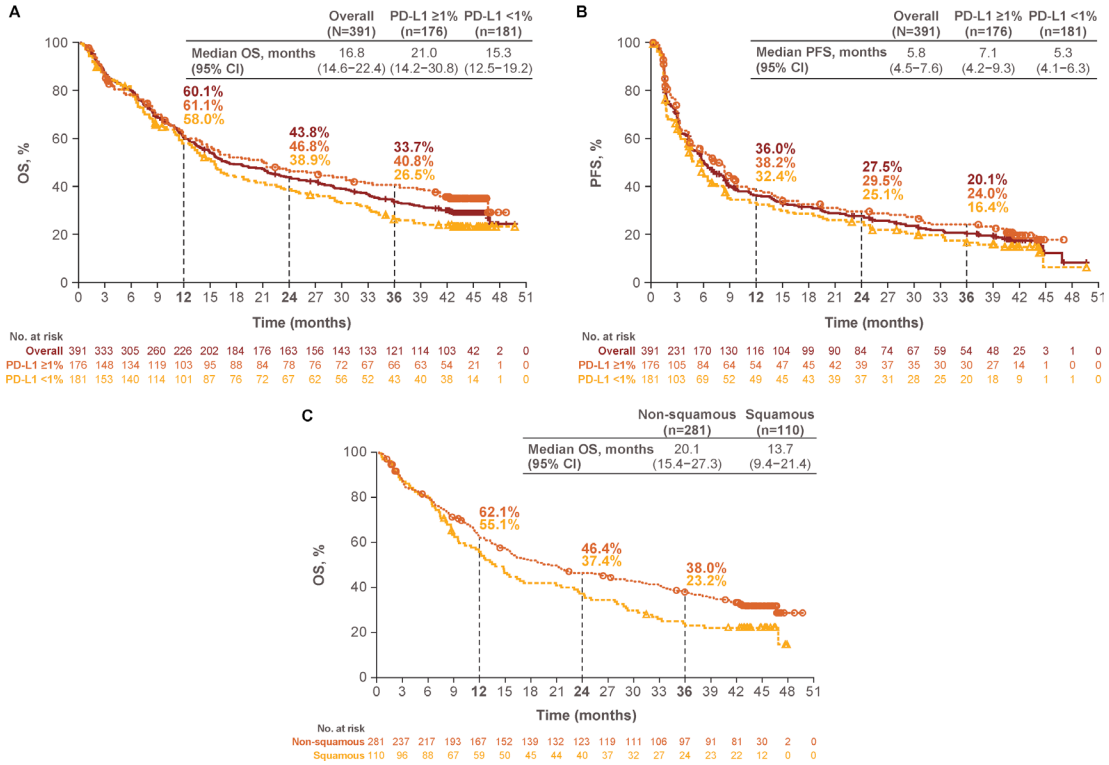

Figure 2 Overall survival (OS) and progression-free survival (PFS) in cohort A. (A) OS and (B) PFS, overall and by tumor programmed death ligand 1 (PD-L1) expression, and (C) OS by tumor histology.

Among patients with ECOG PS 2, any-grade and grade 3–4 TRAEs were reported in 89 (64.0%) and 38 (27.3%) patients, respectively; 20 (14.4%) patients discontinued treatment due to TRAEs (table 3). The most common grade 3–4 IMAEs were rash (3.6%), hepatitis (3.6%), diarrhea/colitis (2.2%) and pneumonitis (2.2%). The most common grade 3–4 treatment-related select AEs were skin (4.3%), endocrine (3.6%), hepatic (2.9%), and gastrointestinal (2.9%) events (table 3).

Safety profile for patients with ECOG PS 0–1 and untreated brain metastases, organ impairment, or positive HIV status is reported in table 3. Among patients with untreated brain metastases, any-grade or grade 3–4 TRAEs were reported in 38 (77.6%) and 18 (36.7%) patients, respectively; 11 (22.4%) discontinued treatment due to TRAEs. The most common grade 3–4 IMAEs were diarrhea/colitis (6.1%), hepatitis (4.1%), and pneumonitis (4.1%); the most common grade 3–4 treatment-related select AEs were gastrointestinal (6.1%) and pulmonary (4.1%) events (table 3). Of nine patients with baseline renal impairment, two had grade 2 increased blood creatinine during the study; one was treatment-related and led to treatment discontinuation, while the other was not treatment-related. Among seven patients with baseline hepatic impairment, one experienced grade 3 treatment-related hepatotoxicity, which led to treatment discontinuation. Another patient with bilirubin elevated at baseline and a history of toxic liver cirrhosis experienced grade 3 increased bilirubin and grade 5 aggravated biliary cirrhosis, both of which were deemed unrelated to study treatment by the investigator. All four patients with HIV-positive status remained on concomitant antiretroviral medications throughout the study.

Efficacy

In cohort A1, median (95% CI) OS was 9.9 months (7.0 to 13.7) with a 3-year OS rate (95% CI) of 20.5% (15.0% to 26.6%) (figure 4A); median (95% CI) PFS was 3.9 months (2.8 to 5.4) with a 3-year PFS rate (95% CI) of 9.4% (5.2% to 15.3%) (figure 4B). Specifically, in patients with ECOG PS 2, median (95% CI) OS was 9.0 months (5.5 to 12.9) with a 3-year OS rate (95% CI) of 18.7% (12.4% to 26.0%) (figure 4C); median (95% CI) PFS was 3.6 months (2.8 to 5.4) and the 3-year PFS rate (95% CI) was 6.3% (1.9% to 14.4%) (figure 4D). ORR (95% CI) was 20.9% (14.4% to 28.6%) and median (95% CI) DOR was 15.5 months (9.8 to 29.3); 28% (12% to 47%) of responders had an ongoing response at 30 months (table 4). In patients with untreated brain metastases, median (95% CI) OS was 12.8 months (7.7 to 25.9) with a 3-year OS rate (95% CI) of 21.0% (10.9% to 33.4%) (figure 4C). Median (95% CI) PFS was 2.8 months (1.7 to 8.0); the 3-year PFS rate (95% CI) was 14.2% (5.4% to 27.1%) (figure 4D). ORR (95% CI) was 32.7% (19.9% to 47.5%) and median (95% CI) DOR was 12.6 months (6.7 to not reached); 39% (15% to 64%) of responders had an ongoing response at 3 years (table 4). For the nine patients with renal impairment, OS ranged from 1.4 to 45.3+ months; five patients experienced a partial response. For the seven patients with hepatic impairment, OS ranged from 0.4 to 35.5+ months; one patient experienced a partial response. OS in the four patients with HIV-positive status ranged from

Table 3 Safety summary for patients treated with nivolumab plus ipilimumab in cohort A1

	Cohort A1*					
	Overall (N=198)†		ECOG PS 2 (n=139)‡		Asymptomatic untreated brain metastases (n=49)§	
AEs, n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs	135 (68.2)	58 (29.3)	89 (64.0)	38 (27.3)	38 (77.6)	18 (36.7)
TRAEs reported by ≥10% of the patients in any group						
Pruritus	30 (15.2)	1 (0.5)	23 (16.5)	1 (0.7)	8 (16.3)	0
Diarrhea	29 (14.6)	1 (0.5)	16 (11.5)	1 (0.7)	9 (18.4)	0
Rash	28 (14.1)	3 (1.5)	19 (13.7)	2 (1.4)	8 (16.3)	1 (2.0)
Fatigue	26 (13.1)	2 (1.0)	16 (11.5)	1 (0.7)	8 (16.3)	0
Asthenia	20 (10.1)	2 (1.0)	10 (7.2)	2 (1.4)	9 (18.4)	0
TRAEs leading to discontinuation¶	32 (16.2)	24 (12.1)	20 (14.4)	16 (11.5)	11 (22.4)	8 (16.3)
Treatment-related serious AEs	33 (16.7)	24 (12.1)	22 (15.8)	15 (10.8)	10 (20.4)	8 (16.3)
Treatment-related deaths	3 (1.5)**		3 (2.2)**		0	
IMAEs by category including preferred terms in ≥1% of the patients in cohort A1 overall††						
Rash	20 (10.1)	6 (3.0)	15 (10.8)	5 (3.6)	4 (8.2)	1 (2.0)
Rash	14 (7.1)	4 (2.0)	9 (6.5)	3 (2.2)	4 (8.2)	1 (2.0)
Rash maculopapular	4 (2.0)	2 (1.0)	3 (2.2)	2 (1.4)	1 (2.0)	0
Rash pruritic	2 (1.0)	0	2 (1.4)	0	0	0
Diarrhea/colitis	18 (9.1)	7 (3.5)	11 (7.9)	3 (2.2)	6 (12.2)	3 (6.1)
Colitis	7 (3.5)	4 (2.0)	3 (2.2)	1 (0.7)	3 (6.1)	2 (4.1)
Immune-mediated enterocolitis	7 (3.5)	2 (1.0)	5 (3.6)	1 (0.7)	2 (4.1)	1 (2.0)
Diarrhea	5 (2.5)	0	3 (2.2)	0	2 (4.1)	0
Hyperthyroidism	17 (8.6)	0	8 (5.8)	0	9 (18.4)	0
Hypothyroidism/thyroiditis	14 (7.1)	2 (1.0)	10 (7.2)	1 (0.7)	5 (10.2)	1 (2.0)
Hypothyroidism	14 (7.1)	1 (0.5)	10 (7.2)	0	5 (10.2)	1 (2.0)
Autoimmune thyroiditis	1 (0.5)	1 (0.5)	1 (0.7)	1 (0.7)	0	0
Hepatitis	10 (5.1)	7 (3.5)	7 (5.0)	5 (3.6)	3 (6.1)	2 (4.1)
Hepatitis	3 (1.5)	2 (1.0)	1 (0.7)	1 (0.7)	2 (4.1)	1 (2.0)
Hepatotoxicity	3 (1.5)	2 (1.0)	3 (2.2)	2 (1.4)	0	0
Alanine aminotransferase increased	2 (1.0)	1 (0.5)	1 (0.7)	1 (0.7)	1 (2.0)	0
Aspartate aminotransferase increased	2 (1.0)	1 (0.5)	1 (0.7)	1 (0.7)	1 (2.0)	0
Autoimmune hepatitis	2 (1.0)	1 (0.5)	2 (1.4)	1 (0.7)	0	0
Pneumonitis	6 (3.0)	5 (2.5)	4 (2.9)	3 (2.2)	2 (4.1)	2 (4.1)
Pneumonitis	4 (2.0)	2 (1.0)	3 (2.2)	1 (0.7)	1 (2.0)	1 (2.0)
Adrenal insufficiency	5 (2.5)	2 (1.0)	3 (2.2)	2 (1.4)	2 (4.1)	0
Hypophysitis	4 (2.0)	2 (1.0)	2 (1.4)	2 (1.4)	2 (4.1)	0
Hypophysitis	3 (1.5)	2 (1.0)	2 (1.4)	2 (1.4)	1 (2.0)	0

Continued

Table 3 Continued

AEs, n (%)	Cohort A1*					
	Overall (N=198)†		ECOG PS 2 (n=139)‡		Asymptomatic untreated brain metastases (n=49)§	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Nephritis and renal function	3 (1.5)	2 (1.0)	1 (0.7)	1 (0.7)	1 (2.0)	1 (2.0)
Hypersensitivity	2 (1.0)	0	2 (1.4)	0	0	0
Diabetes mellitus	1 (0.5)	1 (0.5)	1 (0.7)	1 (0.7)	0	0
Treatment-related select AEs						
Skin events	58 (29.3)	7 (3.5)	43 (30.9)	6 (4.3)	14 (28.6)	1 (2.0)
Endocrine events	37 (18.7)	6 (3.0)	23 (16.5)	5 (3.6)	15 (30.6)	1 (2.0)
Gastrointestinal events	37 (18.7)	8 (4.0)	22 (15.8)	4 (2.9)	11 (22.4)	3 (6.1)
Pulmonary events	6 (3.0)	4 (2.0)	4 (2.9)	2 (1.4)	2 (4.1)	2 (4.1)
Hepatic events	21 (10.6)	5 (2.5)	16 (11.5)	4 (2.9)	5 (10.2)	1 (2.0)
Hypersensitivity/infusion reactions	6 (3.0)	2 (1.0)	5 (3.6)	2 (1.4)	1 (2.0)	0
Renal events	7 (3.5)	2 (1.0)	5 (3.6)	1 (0.7)	2 (4.1)	1 (2.0)

*Patients belonging to multiple subgroups are included in each of the subgroups.
†Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.
‡Includes five patients with untreated brain metastases, one with renal impairment, and three with hepatic impairment.
§Includes five patients with ECOG PS 2 and one patient with positive HIV status.
¶In the event of discontinuation of ipilimumab treatment, nivolumab treatment could continue; however, continuation of ipilimumab after discontinuation of nivolumab was not allowed.
**Due to myasthenic syndrome secondary to immunotherapy (n=1), interstitial diffuse pneumonitis (n=1), and polymyositis (n=1).
††Included IMAEs that were treated using immune-modulating medications, except for endocrine events, which were included regardless of treatment.
AE, adverse event; ECOG PS, Eastern Cooperative Oncology Group performance status; IMAE, immune-mediated adverse event; TRAE, treatment-related adverse event.

7.0 to 41.4+months; two patients experienced a partial response.

Median (95% CI) OS by tumor PD-L1 expression levels were 6.9 months (3.6 to 12.8), 10.5 (7.0 to 15.6), and 13.3 (7.9 to 30.1) for tumor PD-L1 ≥1%, tumor PD-L1 <1%, and tumor PD-L1 ≥50%, respectively, (figure 4A for tumor PD-L1 ≥1% and <1%). Median (95% CI) for PFS were 3.3 months (2.8 to 6.0), 3.9 (2.6 to 6.2), and 9.6 (2.8 to 16.4) for tumor PD-L1 ≥1%, tumor PD-L1 <1%, and tumor PD-L1 ≥50%, respectively, (figure 4B for tumor PD-L1 ≥1% and <1%). ORR was similar in patients with tumor PD-L1 ≥1% and those with tumor PD-L1 <1% (27.6% and 24.2%, respectively; table 4). In patients with tumor PD-L1 ≥50%, responses were generally similar except for ORR (40.6%; online supplemental table S8).

DISCUSSION

Concerns regarding excess treatment-related immune toxicity have influenced the use of combination nivolumab plus ipilimumab for metastatic NSCLC in clinical practice; therefore, clinical trials optimizing dosing and schedule are important. In CheckMate 817, the safety and efficacy of flat-dose nivolumab plus weight-based ipilimumab in cohort A (patients with metastatic NSCLC and ECOG PS 0–1) was consistent with that reported for weight-based nivolumab plus weight-based ipilimumab.[14 18 19]

Clinical trials usually exclude patients from special populations, including patients with ECOG PS 0–1 and untreated brain metastases, organ dysfunction, or chronic viral infections; there is a paucity of prospective clinical trial data to guide clinicians in treating patients with metastatic NSCLC from special populations. We report some of the first prospective safety and efficacy data for patients from special populations receiving any type of combination immunotherapy. Of particular interest, fixed-dose nivolumab plus weight-based ipilimumab had a tolerable safety profile and clinically meaningful 3-year OS in special populations of patients with metastatic NSCLC, including in patients with ECOG PS 2, untreated asymptomatic brain metastases, renal impairment, hepatic impairment, or controlled HIV infection.

Since the approval of nivolumab plus ipilimumab for advanced melanoma, optimization of dose and administration schedule of these agents for the treatment of various cancers has enabled clinicians to appropriately manage TRAEs. In metastatic NSCLC, nivolumab 3 mg/kg Q2W plus

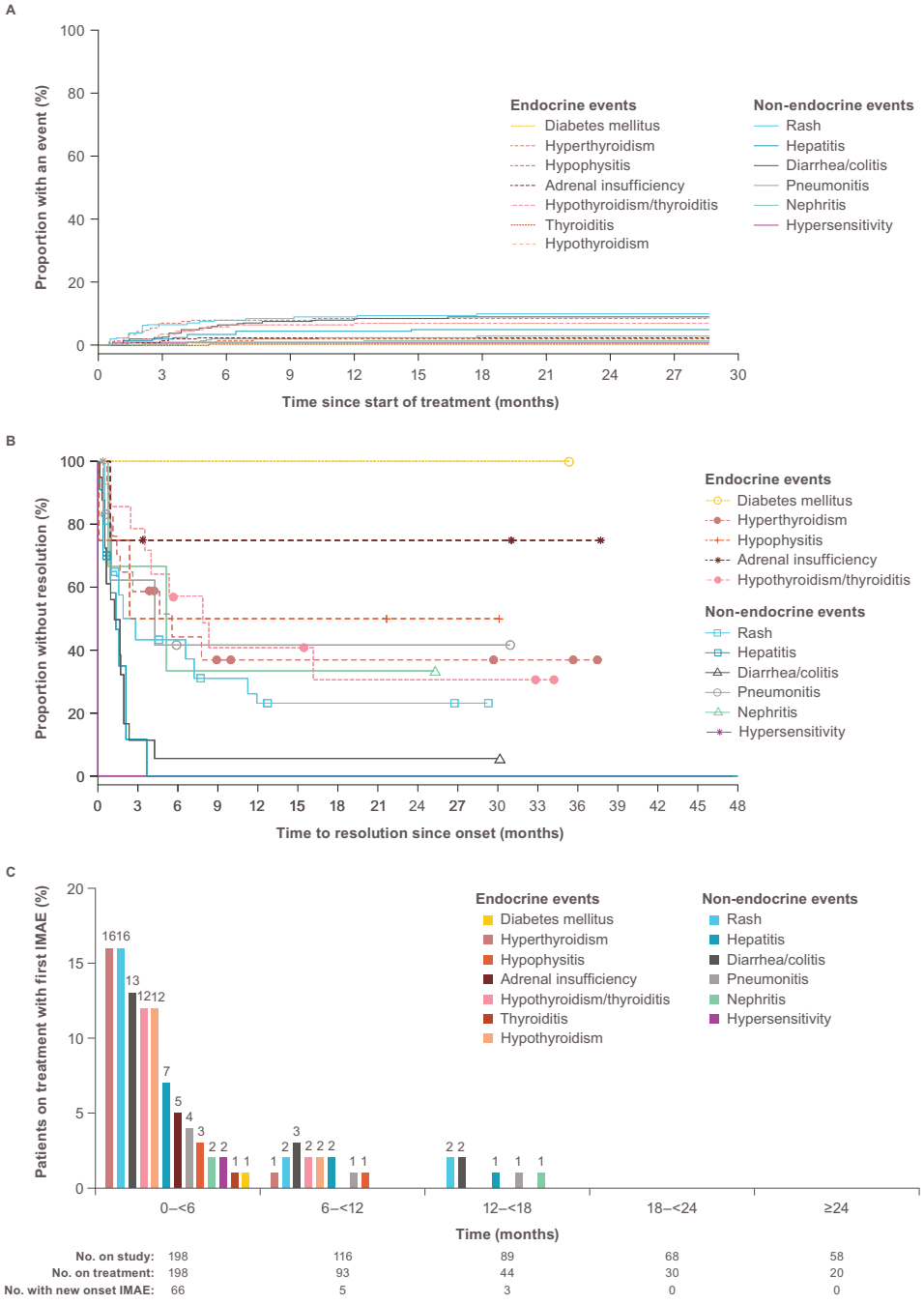

Figure 3 Cumulative time to onset of immune-mediated adverse events (IMAEs) (A), cumulative time to resolution of IMAEs (B), and IMAEs over time (C) in cohort A1.

ipilimumab 1 mg/kg Q6W demonstrated a more favorable safety profile with similar efficacy benefits compared with regimens incorporating higher dosing of ipilimumab.[14 18 19] In the present study, no new safety signals were identified. IMAEs and treatment-related select AEs were primarily grade 1–2 with no grade 5 events reported. IMAEs occurred early after treatment initiation and resolved quickly with management based on guidelines that have been developed using data from various clinical studies.[20]

Immunotherapy-based regimens have shown long-term clinical benefit across numerous studies and have become the standard of care for the first-line treatment of patients with metastatic NSCLC without targetable mutations, with treatment choice influenced by tumor PD-L1 expression.[10 11] Anti-PD-(L)1 monotherapy has demonstrated OS benefit versus standard chemotherapy in patients with tumor PD-L1 expression ≥50%,[21–23] whereas immunotherapy plus chemotherapy or dual immunotherapy with nivolumab plus ipilimumab[18 24–29] have shown benefit regardless of tumor PD-L1 expression or histology. Although efficacy endpoints were secondary in cohort A of CheckMate 817, nivolumab plus ipilimumab resulted in long-term OS benefit (with one-third of the patients alive at 3 years) and durable responses (with over

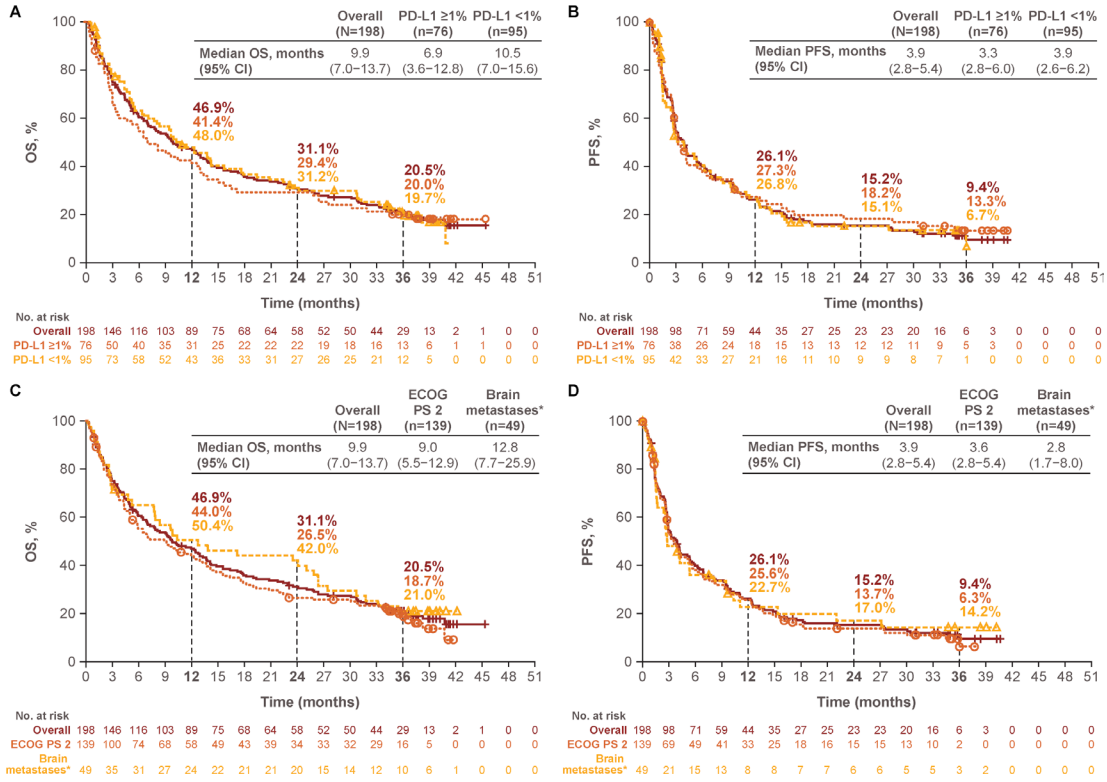

Figure 4 Overall survival (OS) and progression-free survival (PFS) in cohort A1. (A) OS and (B) PFS, overall and by tumor programmed death ligand 1 (PD-L1) expression, (C) OS and (D) PFS, overall and in patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 2 and untreated brain metastases. *Asymptomatic, untreated.

40% of the responders maintaining response at 3 years) across tumor PD-L1 expression and histology subgroups, consistent with the results of the CheckMate 227 study at similar follow-up times.[8] It is worth noting that in patients with high unmet needs, that is, those with tumor PD-L1 expression <1% or with squamous histology, 3-year OS rates remained above 20%, as seen with this regimen in the CheckMate 227 study. Furthermore, in CheckMate 227, response with nivolumab plus ipilimumab at 6 months was associated with long-term OS benefit: 70% and 82% of the patients with ≥1% and <1% tumor PD-L1 expression who were in response at 6 months were alive at 3 years, supporting the durability of efficacy benefit with this immunotherapy combination regimen.[30]

CheckMate 817 is the first prospective study to evaluate the clinical profile of dual immunotherapy in patient populations that have poor prognosis[31] and are often excluded from clinical trials.[17] Safety in the overall cohort A1, as well as in the ECOG PS 2 and untreated brain metastases subgroups, was comparable with that in cohort A. Most patients with renal and hepatic impairment did not experience worsening of renal and hepatic functions, respectively. All four patients with HIV-positive status could continue treatment with antiretroviral medications throughout the study. Although efficacy was lower in cohort A1 than in cohort A, likely due to the prognostic impact of ECOG PS 2 and brain metastases, encouraging clinical activity was observed regardless of tumor PD-L1 expression in cohort A1 overall as well as in subgroups. Limited data sets in patients with ECOG PS 2 have shown median OS ranging from 3.0 to 9.8 months with single-agent PD-1 inhibitor therapy in the first-line or later-line settings.[32–38] Despite 56% of the patients with ECOG PS 2 having tumor PD-L1 expression <1% in this study, these patients, who received dual immunotherapy with a minimum follow-up of 3 years, had a median OS of 9.0 months, 6% PFS rate, median DOR of 15.5 months (9.8–29.3), and approximately 20% of the patients had a clinically meaningful 3-year OS rate. Taken together, these findings for the first time prospectively demonstrate promising efficacy in these patient populations of high unmet need.

Immunotherapy has shown promise in the treatment of NSCLC among patients with brain metastases; however, most of the data relate to patients with treated brain metastases or are based on non-prospective analyses.[39–45] Median OS with anti-PD-(L)1 agents as monotherapy, dual immunotherapy, or dual immunotherapy plus chemotherapy in this patient population ranges from 8.6 to 19.9 months.[39–43 45] Exploratory analyses in patients with metastatic NSCLC and previously treated brain metastases from the phase 3 CheckMate 227 and CheckMate 9LA studies have shown durable and long-term survival benefits with the nivolumab plus ipilimumab combination with or without chemotherapy. In CheckMate 227, over one-third of the patients with treated brain metastases were alive at 3 years[46]; similarly in CheckMate 9LA, 35% of the patients with treated brain metastases were alive at

Table 4 Tumor response in cohort A1

	Cohort A1*			Cohort A1 by tumor PD-L1 expression†	
	Overall (N=198‡)	ECOG PS 2 (n=139§)	Asymptomatic untreated brain metastases (n=49¶)	PD-L1 ≥1% (n=76)	PD-L1 <1% (n=95)
Objective response rate, n (%)** 95% CI	51 (25.8) 19.8 to 32.4	29 (20.9) 14.4 to 28.6	16 (32.7) 19.9 to 47.5	21 (27.6) 18.0 to 39.1	23 (24.2) 16.0 to 34.1
Complete response, n (%)	0	0	0	0	0
Partial response, n (%)	51 (25.8)	29 (20.9)	16 (32.7)	21 (27.6)	23 (24.2)
Stable disease, n (%)	73 (36.9)	55 (39.6)	14 (28.6)	27 (35.5)	34 (35.8)
Progressive disease, n (%)	37 (18.7)	26 (18.7)	12 (24.5)	10 (13.2)	23 (24.2)
Not evaluable, n (%)	37 (18.7)	29 (20.9)	7 (14.3)	18 (23.7)	15 (15.8)
Time to objective response, median (range), months	2.6 (1.1–13.8)	2.6 (1.1–10.0)	2.6 (1.2–13.8)	1.4 (1.2–5.6)	2.6 (1.1–13.8)
Duration of objective response, median (95% CI), months	13.5 (9.6 to 27.4)	15.5 (9.8 to 29.3)	12.6 (6.7 to NR)	24.8 (10.0 to NR)	12.4 (4.3 to 34.6)
Patients with duration of response of at least, % (95% CI)					
6 months	79 (65 to 88)	79 (60 to 90)	86 (54 to 96)	95 (71 to 99)	68 (44 to 83)
12 months	55 (40 to 68)	61 (41 to 76)	55 (26 to 77)	69 (43 to 85)	52 (29 to 71)
18 months	39 (25 to 53)	43 (24 to 60)	39 (15 to 64)	53 (29 to 72)	36 (16 to 56)
24 months	39 (25 to 53)	43 (24 to 60)	39 (15 to 64)	53 (29 to 72)	36 (16 to 56)
30 months	29 (16 to 43)	28 (12 to 47)	39 (15 to 64)	37 (17 to 58)	36 (16 to 56)
36 months	23 (10 to 39)	NA	39 (15 to 64)	37 (17 to 58)	NA

*Patients belonging to multiple subgroups are included in each of the subgroups.
†Tumor PD-L1 expression was not evaluable in 27 patients in cohort A1.
‡Includes all special populations: ECOG PS 2, untreated brain metastases, renal impairment, hepatic impairment, and positive HIV status.
§Includes five patients with untreated brain metastases, one with renal impairment, and three with hepatic impairment.
¶Includes five patients with ECOG PS 2 and one patient with positive HIV status.
**Defined as the sum of complete and partial responses per Response Evaluation Criteria in Solid Tumors V.1.1.
ECOG PS, Eastern Cooperative Oncology Group performance status; NA, not achieved; NR, not reached; PD-L1, programmed death ligand 1.

2 years.[47] Importantly, of the responders in these studies, nearly 40% maintained their response at the indicated landmarks. In contrast, data on untreated brain metastases in NSCLC are limited. In a small phase 2 study with single-agent pembrolizumab, median OS of 9.9 months and a 2-year OS rate of 34% were reported.[48 49] Although findings across studies should be interpreted with caution due to different study designs and patient populations, the long-term OS benefit and durability of responses (39% of responders maintaining response at 3 years) reported with nivolumab plus ipilimumab in patients with asymptomatic untreated brain metastases in CheckMate 817 are promising and continue to reflect the biologic effect of ipilimumab on the immune system. Encouraging clinical activity was also noted in patients with renal and hepatic impairment and HIV-positive status, although these subgroups had small patient numbers.

Although CheckMate 817 was a prospective study, conclusions were limited by its single-arm design. Additionally, intracranial benefit among patients with brain metastases could not be assessed given data collection limitations. Furthermore, the subgroups of renal impairment, hepatic impairment, and HIV-positive status had limited patient numbers and provide descriptive analysis only.

In conclusion, flat-dose nivolumab plus weight-based ipilimumab among patients with ECOG PS 0–1 was associated with manageable safety and durable efficacy, consistent with outcomes with weight-based nivolumab plus weight-based ipilimumab in metastatic NSCLC.[14 18 19] Among patients with ECOG PS 2 or with ECOG PS 0–1 and untreated brain metastases, organ impairment, or positive HIV status, safety was comparable with that in patients with ECOG PS 0–1 and encouraging long-term durable clinical activity was reported. These results support the use of flat-dose nivolumab plus weight-based ipilimumab for the first-line treatment of patients with metastatic NSCLC, including those with ECOG PS 2, or with ECOG PS 0–1 and asymptomatic untreated brain metastases, renal impairment, hepatic impairment, or HIV-positive status.

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