original reports

Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451

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abstract

PURPOSE In extensive-disease small-cell lung cancer (ED-SCLC), response rates to first-line platinum-based chemotherapy are robust, but responses lack durability. CheckMate 451, a double-blind phase III trial, evaluated nivolumab plus ipilimumab and nivolumab monotherapy as maintenance therapy following first-line chemotherapy for ED-SCLC.

METHODS Patients with ED-SCLC, Eastern Cooperative Oncology Group performance status 0-1, and no progression after ≤ 4 cycles of first-line chemotherapy were randomly assigned (1:1:1) to nivolumab 1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for 12 weeks followed by nivolumab 240 mg once every 2 weeks, nivolumab 240 mg once every 2 weeks, or placebo for ≤ 2 years or until progression or unacceptable toxicity. Primary end point was overall survival (OS) with nivolumab plus ipilimumab versus placebo. Secondary end points were hierarchically tested.

RESULTS Overall, 834 patients were randomly assigned. The minimum follow-up was 8.9 months. OS was not significantly prolonged with nivolumab plus ipilimumab versus placebo (hazard ratio [HR], 0.92; 95% CI, 0.75 to 1.12; $P = .37$; median, 9.2 *v* 9.6 months). The HR for OS with nivolumab versus placebo was 0.84 (95% CI, 0.69 to 1.02); the median OS for nivolumab was 10.4 months. Progression-free survival HRs versus placebo were 0.72 for nivolumab plus ipilimumab (95% CI, 0.60 to 0.87) and 0.67 for nivolumab (95% CI, 0.56 to 0.81). A trend toward OS benefit with nivolumab plus ipilimumab was observed in patients with tumor mutational burden ≥ 13 mutations per megabase. Rates of grade 3-4 treatment-related adverse events were nivolumab plus ipilimumab (52.2%), nivolumab (11.5%), and placebo (8.4%).

CONCLUSION Maintenance therapy with nivolumab plus ipilimumab did not prolong OS for patients with ED-SCLC who did not progress on first-line chemotherapy. There were no new safety signals.

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INTRODUCTION

Most patients with extensive-disease small-cell lung cancer (ED-SCLC) respond to first-line platinum-based chemotherapy; however, responses are not durable and patients with recurrent disease have limited treatment options and poor prognosis.[1,2] Maintenance therapies have improved outcomes for non–small-cell lung cancer[3]; however, trials of cytotoxic or targeted maintenance therapy following first-line chemotherapy in small-cell lung cancer (SCLC) have not demonstrated durable benefits.[4-7]

Antiprogrammed death-1 (PD-1) or antiprogrammed death ligand-1 (PD-L1) antibodies have clinical benefit in SCLC when added to first-line chemotherapy[8-10] and as monotherapy in third- or later-line settings.[11-15] Nivolumab, a fully human anti–PD-1 antibody, is approved for several types of cancer. In the phase I or II CheckMate 032 trial, clinical activity with nivolumab and nivolumab plus ipilimumab was observed for relapsed SCLC.[11-13] However, nivolumab did not improve survival over chemotherapy as second-line treatment for relapsed SCLC in the phase III CheckMate 331 trial.[16] Nivolumab improves the function of existing antitumor T cells, whereas ipilimumab, a fully human anticytotoxic T lymphocyte antigen-4 antibody, induces T-cell proliferation and de novo antitumor T-cell responses, thereby offering a complementary mechanism of action.[17,18]

CheckMate 451 (ClinicalTrials.gov identifier: NCT02538666) evaluated nivolumab plus ipilimumab (combination therapy) and nivolumab monotherapy as

ASSOCIATED CONTENT

Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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maintenance therapy in patients with ED-SCLC without progression after first-line chemotherapy. We report efficacy and safety, including efficacy in biomarker-defined subsets using tumor mutational burden (TMB) and PD-L1 combined positive score (CPS), the latter allowing for evaluation of tumor cells and tumor-associated immune cells, with a potentially stronger association with clinical outcome.[19]

METHODS

Patients

Adults with histologically or cytologically confirmed ED-SCLC[20] and an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1 were eligible if they had received three to four cycles of first-line platinum-based chemotherapy and had an ongoing complete or partial response; patients with stable disease after four cycles of first-line chemotherapy were also eligible (Data Supplement, online only). Random assignment occurred ≤ 9 weeks from the last dose of chemotherapy or ≤ 11 weeks for patients receiving prophylactic cranial irradiation (PCI) or brain radiation therapy. Study treatment was administered ≥ 3 weeks and ≥ 2 weeks from the last dose of chemotherapy and radiotherapy, respectively.

Trial Design and Treatment

CheckMate 451 was a randomized, double-blind, three-arm, phase III trial conducted across 168 sites in 32 countries (Data Supplement). Patients were randomly assigned (1:1:1) to nivolumab (1 mg/kg plus ipilimumab 3 mg/kg once every 3 weeks for 12 weeks followed by nivolumab 240 mg once every 2 weeks), nivolumab (240 mg once every 2 weeks), or matching placebo. Treatment continued for ≤ 2 years or until disease progression or unacceptable toxicity (Data Supplement). Crossover was not permitted. Random assignment was stratified by ECOG PS (0 *v* 1), sex (male *v* female), and PCI (yes *v* no) (Data Supplement). The study included a separate China extension cohort, allowing enrollment of patients after the global study had reached the prespecified sample size; two patients from China, randomly assigned before conclusion of the global study accrual, were included in both the intent-to-treat (ITT) population and China cohort. The ITT population reported here excludes all other patients from China.

An institutional review board or independent ethics committee at each site approved all versions of the Protocol (online only). An independent data monitoring committee provided safety and efficacy oversight. The trial was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent.

End Points and Assessments

The primary end point was overall survival (OS) with combination therapy versus placebo after completion of first-line chemotherapy, assessed from random assignment. Hierarchical secondary end points were, in order of testing, OS with nivolumab versus placebo, progression-free survival (PFS) with combination therapy versus placebo, and PFS with nivolumab versus placebo. Other secondary end points were OS and PFS with combination therapy versus nivolumab and OS and PFS by TMB status with nivolumab and combination therapy. OS subgroup and multivariate analyses, objective response rate (ORR), duration of response (DOR), tumor PD-L1 expression (measured by CPS) as an independent predictive biomarker, and safety and tolerability were exploratory.

The schedule of tumor assessments is described in the Data Supplement. PFS and ORR were determined according to RECIST v1.1[21] by blinded independent central review. Safety and tolerability were continuously monitored. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Follow-up visits occurred 35 days after last dose and 80 days after first follow-up.

TMB was assessed using the FoundationOne CDx assay,[22] reported as the number of mutations per megabase (mut/Mb). PD-L1 expression level was determined using the Dako PD-L1 IHC 28-8 pharmDx assay.[23] CPS was defined as the total number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) divided by total viable tumor cells and multiplied by 100.[19] OS and PFS were assessed in TMB- and CPS-evaluable populations and compared for patients with high or low TMB (10 and 13 mut/Mb cutoffs) and CPS ≥ 1% or < 1%. TMB cutoffs were prespecified and selected based on estimated sample sizes of the resulting TMB-high and TMB-low populations.

Statistical Analysis

Approximately 810 patients were planned for random assignment. The primary end point was analyzed when ≥ 386 deaths were observed across the arms. This was estimated to provide approximately 90% power to detect a hazard ratio (HR) of 0.72, favoring combination therapy over placebo with a two-sided type I error of 0.05, by log-rank test (Data Supplement).

A hierarchical procedure was used to control the overall type I error rate at 0.05; the secondary end point of OS with nivolumab versus placebo was tested if the primary end point was statistically significant; PFS was tested if OS with nivolumab versus placebo was statistically significant. OS and PFS curves were estimated using Kaplan–Meier methodology. HRs and two-sided CIs were estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by ECOG PS, sex, and PCI (Data Supplement). This report is based on final efficacy and safety analyses in the ITT population (database lock, November 12, 2018).

RESULTS

Patients and Treatment

Of 1,212 enrolled patients, 834 were randomly assigned to combination therapy (n = 279), nivolumab (n = 280), or

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	Nivolumab Plus Ipilimumab (n = 279)	Nivolumab (n = 280)	Placebo (n = 275)
Age, years			
Median (range)	64.0 (39-85)	65.0 (32-84)	64.0 (44-84)
< 65	140 (50.2)	135 (48.2)	148 (53.8)
≥ 65	139 (49.8)	145 (51.8)	127 (46.2)
Female	99 (35.5)	103 (36.8)	100 (36.4)
Race			
White	216 (77.4)	213 (76.1)	198 (72.0)
Black or African American	1 (0.4)	6 (2.1)	2 (0.7)
Asian	58 (20.8)	58 (20.7)	69 (25.1)
Others	3 (1.1)	3 (1.1)	6 (2.2)
Not reported	1 (0.4)	0 (0.0)	0 (0.0)
Region			
United States or Canada	64 (22.9)	59 (21.1)	57 (20.7)
Europe	115 (41.2)	123 (43.9)	103 (37.5)
Asia[a]	57 (20.4)	55 (19.6)	68 (24.7)
Rest of the world	43 (15.4)	43 (15.4)	47 (17.1)
ECOG PS			
0	111 (39.8)	118 (42.1)	103 (37.5)
1	168 (60.2)	162 (57.9)	172 (62.5)
Smoking status			
Current or former	257 (92.1)	257 (91.8)	259 (94.2)
Never	20 (7.2)	20 (7.1)	13 (4.7)
Unknown	2 (0.7)	3 (1.1)	3 (1.1)
Lactate dehydrogenase			
≤ ULN	210 (75.3)	207 (73.9)	203 (73.8)
> ULN	66 (23.7)	69 (24.6)	69 (25.1)
Not reported	3 (1.1)	4 (1.4)	3 (1.1)
Liver metastases			
Yes	110 (39.4)	106 (37.9)	109 (39.6)
No	169 (60.6)	174 (62.1)	166 (60.4)
CNS metastases			
Yes	38 (13.6)	46 (16.4)	32 (11.6)
No	241 (86.4)	234 (83.6)	243 (88.4)
Prior PCI	64 (22.9)	61 (21.8)	61 (22.2)
Prior first-line platinum-based chemotherapy[b]			
Carboplatin	175 (62.7)	184 (65.7)	160 (58.2)
Cisplatin	116 (41.6)	105 (37.5)	124 (45.1)
Best response to first-line chemotherapy[c]			
Complete response	9 (3.2)	7 (2.5)	5 (1.8)
Partial response	200 (71.7)	193 (68.9)	193 (70.2)
Stable disease	70 (25.1)	80 (28.6)	76 (27.6)
Time (weeks) from last dose of first-line chemotherapy to random assignment[d]			
Median (range)	5.6 (2.9-15.7)	5.7 (0.6-13.0)	5.4 (3.0-17.0)
≤ 5	116 (41.6)	107 (38.2)	118 (42.9)
> 5	163 (58.4)	173 (61.8)	157 (57.1)
> 5-9	142 (50.9)	149 (53.2)	132 (48.0)
> 9	21 (7.5)	24 (8.6)	25 (9.1)
TMB			
Patients evaluated	192 (68.8)	196 (70.0)	192 (69.8)
Median (range)	8.8 (1.3-35.3)	9.5 (0.0-118.5)	8.8 (1.3-37.8)
< 10 mut/Mb	102 (53.1)	98 (50.0)	104 (54.2)
≥ 10 mut/Mb	90 (46.9)	98 (50.0)	88 (45.8)
< 13 mut/Mb	131 (68.2)	125 (63.8)	133 (69.3)
≥ 13 mut/Mb	61 (31.8)	71 (36.2)	59 (30.7)
PD-L1 CPS			
Patients evaluated	116 (41.6)	124 (44.3)	114 (41.5)
< 1%	64 (55.2)	69 (55.6)	58 (50.9)
≥ 1%	52 (44.8)	55 (44.4)	56 (49.1)

NOTE. Data presented as no. (%) unless otherwise indicated.

Abbreviations: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; mut/Mb, mutations per megabase; PCI, prophylactic cranial irradiation; PD-L1, programmed death ligand-1; TMB, tumor mutational burden; ULN, upper limit of normal.

[a]The intent-to-treat population excluded patients from China, except for two patients who were randomly assigned on or before the end of the global study accrual and were included in both the intent-to-treat and China cohorts.

[b]Patients might have received more than one type of platinum compound.

[c]Response was not applicable for one patient in the placebo group who was randomly assigned but not treated.

[d]Study drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

placebo (n = 275) between October 26, 2015, and January 3, 2018 (Data Supplement). The main reason for not being randomly assigned was no longer meeting study criteria (n = 334). Of patients randomly assigned to combination therapy, nivolumab, or placebo, respectively, 278, 279, and 273 received ≥ 1 dose of study treatment; 8, 17, and 9 remained on treatment at database lock. Baseline characteristics were generally balanced across treatments (Table 1), including

liver and brain metastases. Approximately 70% of patients in each arm responded to first-line chemotherapy; approximately 22% received prior PCI.

The minimum follow-up for OS (from last patient's random assignment to last visit) was 8.9 months, with 96% of patients having ≥ 12 months' follow-up. The median follow-up was 8.4, 9.9, and 9.1 months in the combination, nivolumab, and placebo arms, respectively. Patients received a median (range) of 2.0 (1-45) nivolumab doses and 2.0 (1-4) ipilimumab doses in the combination arm, 5.0 (1-54) nivolumab doses in the nivolumab arm, and 5.0 (1-67) nivolumab-placebo doses and 3.0 (1-4) ipilimumab-placebo doses in the placebo arm. The median cumulative doses of nivolumab were 2.0 mg/kg and 16.5 mg/kg in the combination and nivolumab arm, respectively. Subsequent immunotherapy was received by 2.2% of patients in the combination arm, 2.1% in the nivolumab arm, and 2.9% in the placebo arm; subsequent systemic cancer therapy was received by 32.6%, 38.9%, and 46.5%, respectively (Data Supplement).

Efficacy

The median (95% CI) OS was 9.2 (8.2 to 10.2) months with combination therapy, 10.4 (9.5 to 12.1) months with nivolumab, and 9.6 (8.2 to 11.0) months with placebo. The primary end point of OS with combination therapy versus placebo was not met (HR, 0.92; 95% CI, 0.75 to 1.12; $P = .37$; Fig 1A). Although not formally tested, nivolumab monotherapy did not prolong OS versus placebo (HR, 0.84; 95% CI, 0.69 to 1.02; Fig 1B).

The median PFS (95% CI) by blinded independent central review was 1.7 (1.5 to 2.6) months with combination therapy, 1.9 (1.6 to 2.6) months with nivolumab, and 1.4 (1.4 to 1.5) months with placebo. PFS favored combination therapy over placebo (HR, 0.72; 95% CI, 0.60 to 0.87; Fig 1C) and nivolumab over placebo (HR, 0.67; 95% CI, 0.56 to 0.81; Fig 1D). Tumor responses and DOR for patients with ≥ 1 baseline lesion are summarized in Table 2. ORR favored combination therapy (9.1%; 95% CI, 5.9 to 13.2) and nivolumab (11.5%; 95% CI, 7.9 to 16.0) compared with placebo (4.2%; 95% CI, 2.1 to 7.4). The median DOR (95% CI) was 10.2 (3.5 to 16.1) months with combination therapy, 11.2 (7.3 to not reached) months with nivolumab, and 8.1 (2.1 to not reached) months with placebo.

Exploratory analyses by baseline characteristics showed that OS was similar with combination therapy and nivolumab versus placebo across most patient subgroups (Fig 2). There was a trend toward survival benefit with combination therapy versus placebo in patients of age < 65 years (HR, 0.72; 95% CI, 0.54 to 0.95). Trends toward survival benefit with nivolumab versus placebo were seen in patients of age < 65 years (HR, 0.74; 95% CI, 0.56 to 0.97), those with baseline lactate dehydrogenase ≤ upper limit of normal (HR, 0.79; 95% CI, 0.63 to 0.99), and those who had the last dose of first-line chemotherapy ≤ 5 weeks before random assignment (HR, 0.66; 95% CI, 0.49 to 0.91). Exploratory multivariate analyses adjusting for prognostic factors provided further evidence that time from last dose of first-line chemotherapy was predictive of OS benefit with nivolumab versus placebo, but did not support other predictive factors (Data Supplement).

Biomarker Analyses

TMB. Of 834 randomly assigned patients, 580 (69.5%) were evaluable for baseline TMB. Among them, 276 (47.6%) had TMB ≥ 10 mut/Mb and 191 (32.9%) TMB ≥ 13 mut/Mb (Data Supplement). Baseline characteristics were generally balanced between the TMB-evaluable, nonevaluable, and ITT populations (Data Supplement) and across treatments in the TMB-evaluable population (Data Supplement); however, within the TMB-evaluable population, the combination arm included a higher proportion of White (79.7% *v* 69.3%) and lower proportion of Asian (18.2% *v* 27.1%) patients versus placebo. OS for combination therapy versus placebo was similar in the TMB-evaluable (HR, 0.86; 95% CI, 0.68 to 1.09) and nonevaluable (HR, 1.06; 95% CI, 0.74 to 1.52) groups. In the TMB-evaluable population, OS was improved with combination therapy versus placebo in patients with TMB ≥ 13 mut/Mb (HR, 0.61; 95% CI, 0.39 to 0.94; Fig 3A) but not in those with TMB < 13 mut/Mb (HR, 1.04; 95% CI, 0.79 to 1.37; Fig 3B). For nivolumab versus placebo, OS was similar in the TMB-evaluable (HR, 0.82; 95% CI, 0.65 to 1.03) and nonevaluable (HR, 0.87; 95% CI, 0.60 to 1.26) groups. A trend toward OS benefit with nivolumab versus placebo was seen in patients with TMB ≥ 13 mut/Mb (HR, 0.67; 95% CI, 0.45 to 1.01; Fig 3A), but not in those with TMB < 13 mut/Mb (HR, 0.92; 95% CI, 0.70 to 1.22; Fig 3B). A TMB cutoff of 10 mut/Mb was not predictive of OS benefit with combination or monotherapy versus placebo (Data Supplement). Data on PFS and ORRs by TMB were largely consistent with the OS results (Data Supplement).

CPS. Of 834 randomly assigned patients, 354 (42.4%) had evaluable baseline CPS data. Among them, 163 (46.0%) had CPS ≥ 1% (Data Supplement). Baseline characteristics were generally balanced between CPS-evaluable and ITT populations (Data Supplement) and across treatments in the CPS-evaluable population (Data Supplement). OS with combination therapy versus placebo was comparable between CPS-evaluable (HR, 0.85; 95% CI, 0.63 to 1.14) and nonevaluable (HR, 0.99; 95% CI, 0.76 to 1.29) groups; similarly, OS with nivolumab versus placebo was comparable between CPS-evaluable (HR, 0.81; 95% CI, 0.60 to 1.08) and nonevaluable (HR, 0.85; 95% CI, 0.65 to 1.11) groups. Median OS (95% CI) was greater in the CPS ≥ 1% versus CPS < 1% population within the combination (11.9 [6.9 to 15.2] months *v* 8.6 [7.1 to 12.4] months), nivolumab (14.1 [9.9 to 21.6] months *v* 9.4 [5.8 to 11.3] months), and placebo arms (13.9 [8.9 to 16.5] months *v* 6.1 [4.8 to 8.1] months) (Figs 3C and 3D). In patients with CPS ≥ 1%, no survival benefit was seen for either combination or monotherapy versus placebo; however, in

patients with CPS < 1%, both combination therapy and monotherapy trended toward an OS benefit versus placebo. There was no clear PFS or ORR benefit with combination or monotherapy versus placebo in patients with CPS ≥ 1% (Data Supplement).

Safety

Safety is summarized in Table 3. Any-grade and grade 3-4 treatment-related AEs (TRAEs) were reported in 85.6% and 52.2% of the combination arm, 60.9% and 11.5% of the nivolumab arm, and 50.2% and 8.4% of the placebo arm, respectively. Any-grade treatment-related serious AEs were more common with combination therapy versus monotherapy or placebo (37.4% *v* 6.1% or 2.9%, respectively), as were any-grade TRAEs leading to discontinuation (28.8% *v* 7.9% or 0.4%, respectively). The most common any-grade treatment-related select AEs (with potential immunologic cause) for combination therapy were skin (47.5%), GI (27.3%), and hepatic (18.3%) events; for monotherapy, these were skin (22.6%), GI (14.7%), and endocrine (12.5%).

Seven treatment-related deaths occurred in the combination arm (one each from rhabdomyolysis, myocarditis, hepatic failure, limbic encephalopathy, myasthenia gravis, encephalitis, and immune colitis complicated by bowel perforation, leading to bacterial peritonitis, sepsis, and end-organ failure), one in the monotherapy arm (encephalitis), and one in the placebo arm (pneumonitis).

DISCUSSION

CheckMate 451 did not meet its primary end point of prolonged OS with combination therapy versus placebo as maintenance therapy after first-line platinum-based

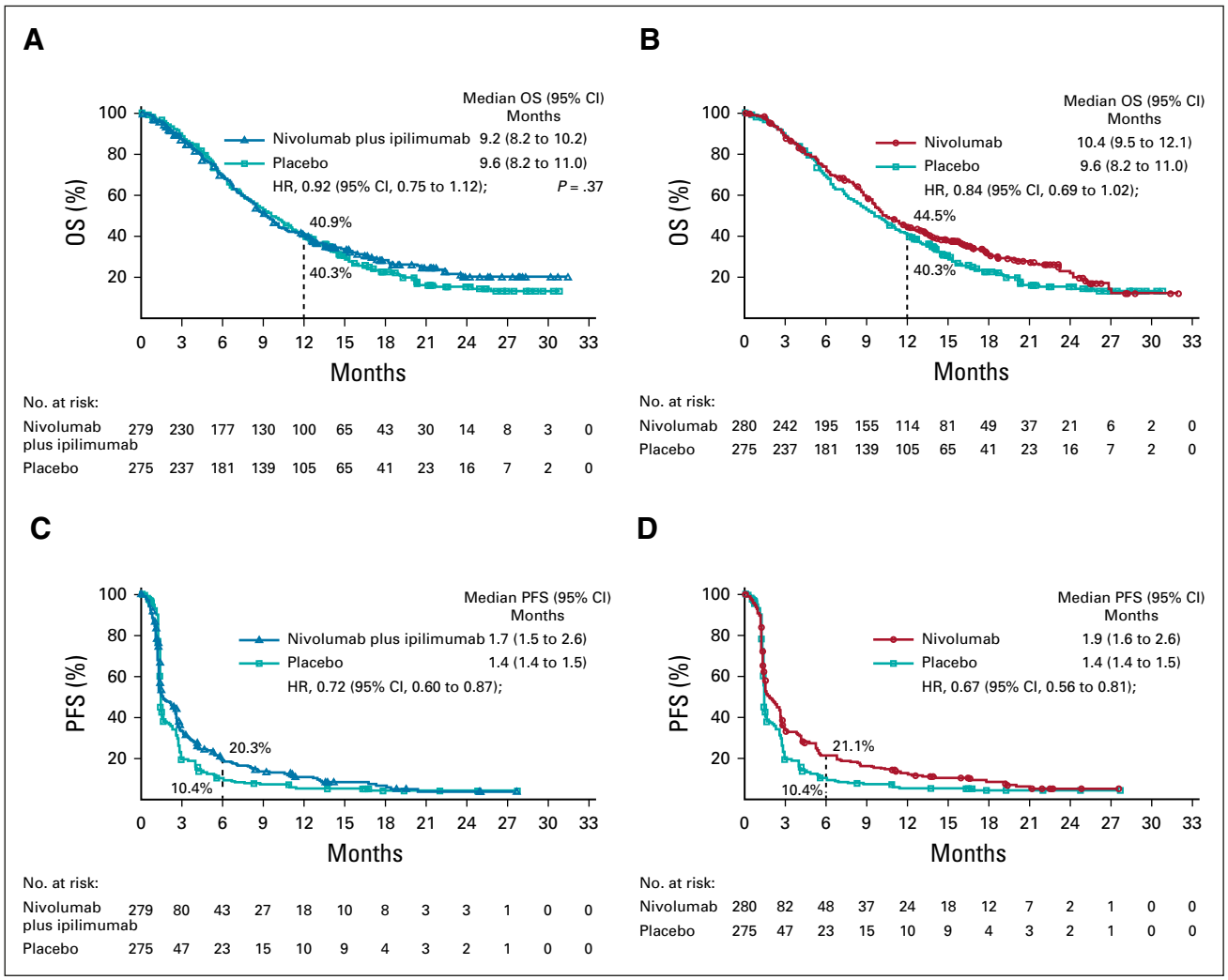

FIG 1. (A) OS with nivolumab plus ipilimumab versus placebo, (B) nivolumab monotherapy versus placebo, (C) PFS per blinded independent central review with nivolumab plus ipilimumab versus placebo, and (D) nivolumab monotherapy versus placebo. HRs were based on a stratified three-arm Cox proportional hazards model, and the *P* value for the primary end point was calculated from a stratified log-rank test. HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

TABLE 2. Summary of Tumor Response During the Maintenance Phase: Patients With At Least One Target Lesion at Baseline

End Point	Nivolumab Plus Ipilimumab (n = 265)[a]	Nivolumab (n = 261)[a]	Placebo (n = 263)[a]
Objective response[b]			
Patients with response, n	24	30	11
% of patients (95% CI)	9.1 (5.9 to 13.2)	11.5 (7.9 to 16.0)	4.2 (2.1 to 7.4)
Odds ratio[c] (95% CI)	2.33 (1.11 to 4.91)	2.93 (1.44 to 5.93)	
DOR, months[d]			
Median (95% CI)	10.2 (3.5 to 16.1)	11.2 (7.3 to NR)	8.1 (2.1 to NR)
Range	1.3+ to 16.6+	1.4+ to 26.3+	1.4+ to 16.6+
Best overall response, n (%)			
Complete response	5 (1.9)	5 (1.9)	3 (1.1)
Partial response	19 (7.2)	25 (9.6)	8 (3.0)
Stable disease	94 (35.5)	92 (35.2)	82 (31.2)
Progressive disease	122 (46.0)	120 (46.0)	151 (57.4)
Could not be determined	25 (9.4)	19 (7.3)	19 (7.2)

NOTE. + indicates ongoing status at database lock.

Abbreviations: DOR, duration of response; NR, not reached.

[a]Excludes patients with nonmeasurable disease at baseline: nivolumab plus ipilimumab (n = 14), nivolumab (n = 19), and placebo (n = 12).

[b]Objective response was defined as the number of patients with a best overall response of complete or partial response, as determined by blinded independent central review. 95% CIs were calculated using the Clopper–Pearson method.

[c]The odds ratio versus placebo was estimated using the Cochran–Mantel–Haenszel method and adjusted by Eastern Cooperative Oncology Group performance status score (0 *v* 1), sex (male *v* female), and prophylactic cranial irradiation (yes *v* no) as entered into the interactive voice response system at random assignment.

[d]Duration of objective response was defined as the time between the date of first confirmed response and the date of the first documented tumor progression as assessed by blinded independent central review or death because of any cause.

chemotherapy. Although not formally tested, nivolumab monotherapy did not improve OS versus placebo; however, trends toward greater improvement in PFS, ORR, and DOR were observed. Safety profiles were consistent with previous reports at equivalent doses and schedules in SCLC[11,12]; no new safety concerns were observed.[24]

Compromised nivolumab exposure because of increased toxicity with combination therapy might have contributed to the negative study outcome. Of note, patients in this arm received a median of two (of four planned) treatment cycles, whereas patients on monotherapy received an eight-fold higher median cumulative nivolumab dose (240 mg). This disparity in nivolumab exposure could explain the trend toward greater efficacy with monotherapy. These exposure differences might have been the result of different dosages (1 mg/kg *v* a 240 mg flat dose equivalent to 3 mg/kg), dosing schedules, and increased TRAEs leading to discontinuation at a 3.6-fold higher rate in the combination arm. However, the primary progression rate was similar between arms. Doses of immunotherapy were selected based on the results from the phase I or II CheckMate 032 trial, which suggested improved efficacy with combination therapy (at varying doses) versus nivolumab alone in SCLC.[12,13] These dosages notably differ from those indicated in non–small-cell lung cancer[25-27]; however, tumor-specific factors may affect optimal dosing.

The delay between patients' last dose of chemotherapy and random assignment might have also affected the results. To ensure that all patients who completed first-line chemotherapy did not progress at the end of treatment, a window of ≥ 3 weeks from the last chemotherapy dose to first dose of study drug was chosen; the median of this window was 5.6 weeks for the total study (5.4-5.7 across study arms). Given the high risk of tumor regrowth in SCLC, some patients might have experienced disease progression before initiating maintenance treatment. In line with this, OS appeared to be improved with nivolumab monotherapy versus placebo when maintenance treatment was initiated sooner after the last dose of first-line chemotherapy. Consistent with the results from this study, several other trials have shown no benefit of chemotherapy or targeted agents as maintenance therapy for ED-SCLC after first-line chemotherapy.[4-7] By contrast, studies have shown modest but significant efficacy of first-line platinum-doublet chemotherapy plus immunotherapy, followed by a median of three maintenance immunotherapy cycles, in ED-SCLC; in these studies, immunotherapy was delivered without delay following the last cycle of chemotherapy.[8,10] Concurrent administration of chemotherapy and immunotherapy might have also contributed to these positive results, as previously reported.[28] The CASPIAN study demonstrated a survival benefit for durvalumab plus chemotherapy versus chemotherapy as first-line treatment for SCLC, but not for

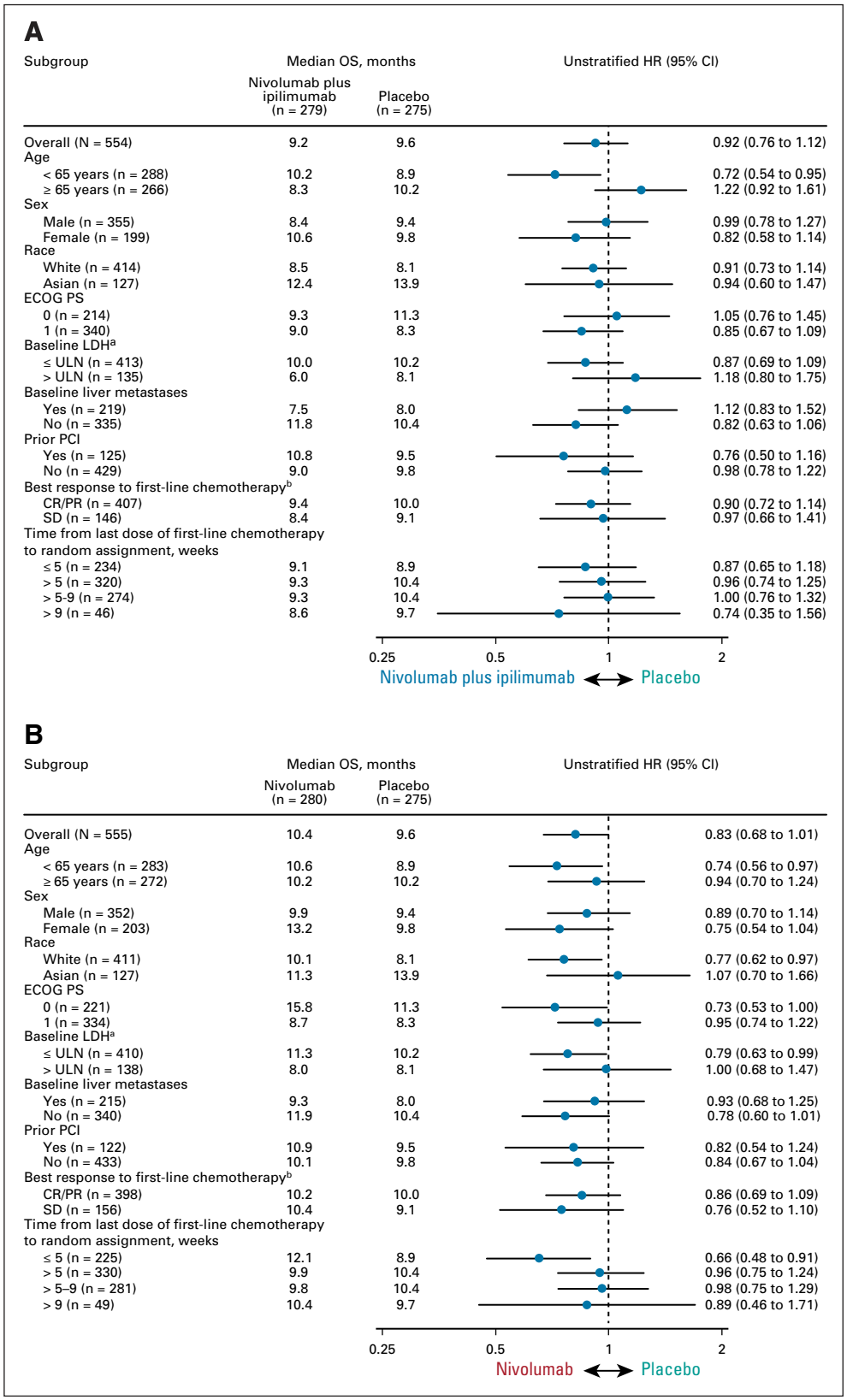

FIG 2. (A) OS by predefined subgroups with nivolumab plus ipilimumab versus placebo and (B) nivolumab monotherapy versus placebo. [a]Not reported for three patients in the nivolumab plus ipilimumab arm, four patients in the nivolumab arm, and three patients in the placebo arm. [b]Not evaluated for one patient in the placebo arm. CR, complete response; ECOG PS, Eastern Cooperative Oncology (continued on following page)

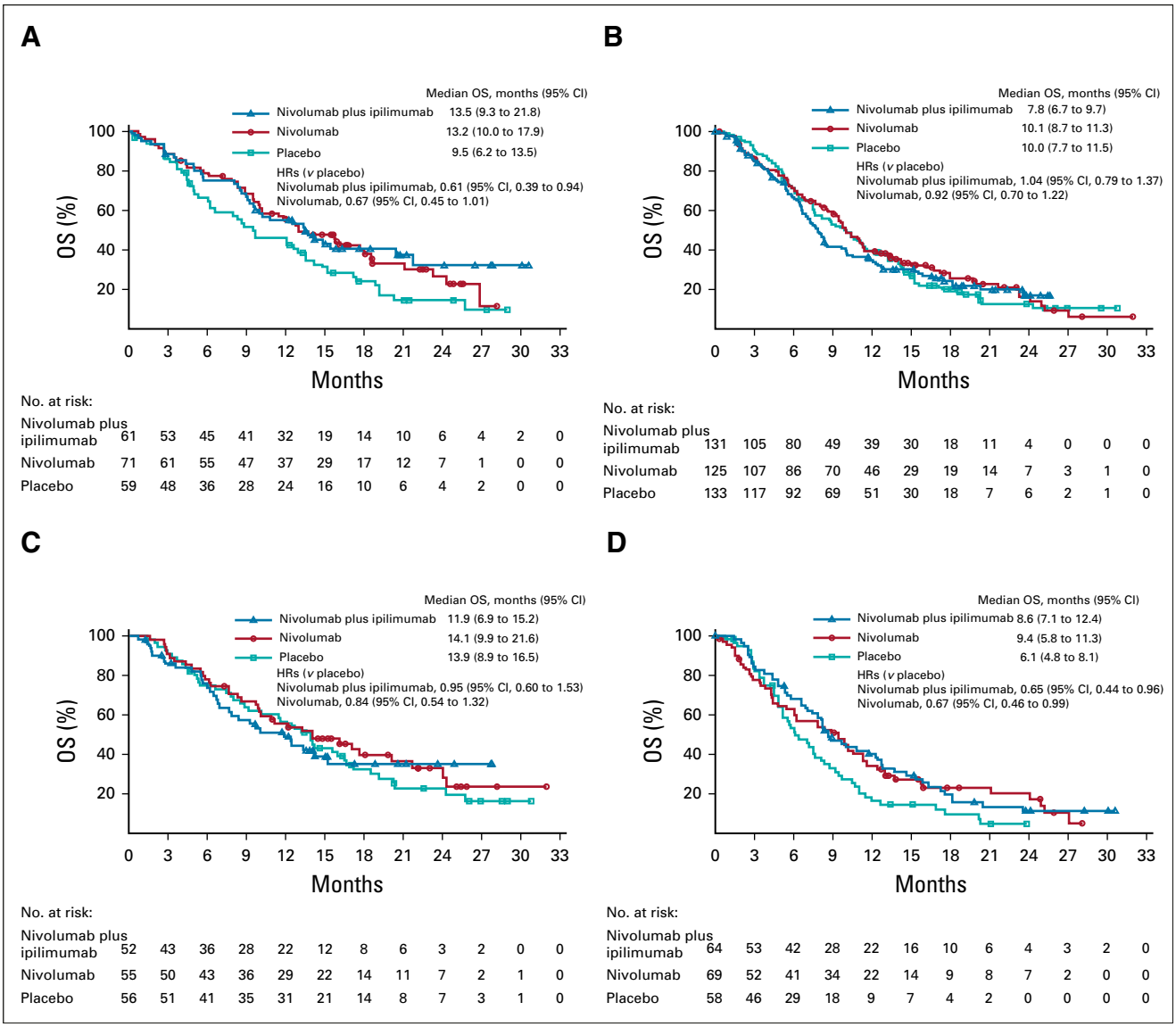

FIG 3. OS with nivolumab plus ipilimumab versus nivolumab versus placebo by (A) TMB ≥ 13 mut/Mb and (B) < 13 mut/Mb and by programmed death ligand-1 (C) CPS ≥ 1% and (D) < 1%. CPS, combined positive score; HR, hazard ratio; mut/Mb, mutations per megabase; OS, overall survival; TMB, tumor mutational burden.

durvalumab plus tremelimumab versus chemotherapy.[29] Rates of all-cause grade 3-4 AEs were 62% and 70% for durvalumab with chemotherapy and durvalumab plus tremelimumab with chemotherapy, respectively; rates of AEs leading to discontinuation were 10% and 21%, respectively. The increased rate of toxicity observed with the nivolumab plus ipilimumab combination in the current study and the durvalumab plus tremelimumab arm of the CASPIAN trial, along with lack of efficacy improvement, raises a legitimate question about the clinical relevance of this strategy of combined targeting of cytotoxic T-cell lymphocyte-4/PD-1 in an unselected patient population.

The delayed effect of immunotherapy and patient selection factors might have also affected study outcomes. Without a validated biomarker, an optimal patient subset to enroll could not be defined prospectively. Although exploratory analyses suggested a survival benefit of both experimental arms versus placebo in certain prognostic subgroups, an exploratory multivariate analysis only supported time from last dose of chemotherapy as predictive.

FIG 2. (Continued). Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PCI, prophylactic cranial irradiation; PR, partial response; SD, stable disease; ULN, upper limit of normal.

TABLE 3. Treatment-Related Adverse Events[a]

	Nivolumab Plus Ipilimumab (n = 278)		Nivolumab (n = 279)		Placebo (n = 273)	
Event	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**	**Any Grade**	**Grades 3-4**
Any	238 (85.6)	145 (52.2)	170 (60.9)	32 (11.5)	137 (50.2)	23 (8.4)
Serious	104 (37.4)	87 (31.3)	17 (6.1)	10 (3.6)	8 (2.9)	8 (2.9)
Led to discontinuation	80 (28.8)	69 (24.8)	22 (7.9)	12 (4.3)	1 (0.4)	1 (0.4)
Occurred in ≥ 15% of patients in either group (by preferred term)						
Diarrhea	67 (24.1)	15 (5.4)	40 (14.3)	3 (1.1)	19 (7.0)	0 (0.0)
Pruritus	66 (23.7)	3 (1.1)	31 (11.1)	0	22 (8.1)	0 (0.0)
Rash	65 (23.4)	5 (1.8)	17 (6.1)	1 (0.4)	11 (4.0)	1 (0.4)
Fatigue	59 (21.2)	8 (2.9)	55 (19.7)	6 (2.2)	40 (14.7)	1 (0.4)
Decreased appetite	54 (19.4)	6 (2.2)	27 (9.7)	1 (0.4)	22 (8.1)	1 (0.4)
Select (by system organ class)[b]						
Skin	132 (47.5)	14 (5.0)	63 (22.6)	2 (0.7)	36 (13.2)	2 (0.7)
GI	76 (27.3)	31 (11.2)	41 (14.7)	3 (1.1)	19 (7.0)	0 (0.0)
Hepatic	51 (18.3)	32 (11.5)	16 (5.7)	5 (1.8)	8 (2.9)	3 (1.1)
Endocrine	47 (16.9)	10 (3.6)	35 (12.5)	1 (0.4)	10 (3.7)	0 (0.0)
Pulmonary	19 (6.8)	8 (2.9)	10 (3.6)	4 (1.4)	4 (1.5)	1 (0.4)
Hypersensitivity or infusion reaction	16 (5.8)	1 (0.4)	13 (4.7)	2 (0.7)	4 (1.5)	0 (0.0)
Renal	10 (3.6)	3 (1.1)	2 (0.7)	0 (0.0)	1 (0.4)	0 (0.0)
Treatment-related deaths[c]	7 (2.5)		1 (0.4)		1 (0.4)	

NOTE. Data presented as no. of patients with an event (%).

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

[b]Treatment-related select adverse events are those with potential immunologic etiology that require frequent monitoring or intervention.

[c]Treatment-related deaths were due to rhabdomyolysis (n = 1), myocarditis (n = 1), immune colitis and bowel perforation, leading to bacterial peritonitis, sepsis, and end-organ failure (n = 1), liver dysfunction and hepatic failure (n = 1), limbic encephalopathy (n = 1), myasthenia gravis (n = 1), and encephalitis (n = 1) in the nivolumab plus ipilimumab group, encephalitis (n = 1) in the nivolumab group, and pneumonitis (n = 1) in the placebo group.

Of note, TMB has previously been suggested as predictive of outcomes with nivolumab-based therapies in SCLC. In CheckMate 032, patients with high TMB derived greater benefit from combination therapy and nivolumab than those with medium or low TMB.[30] In the current study, post hoc analysis of patients with TMB ≥ 13 mut/Mb suggested improved OS with combination therapy and monotherapy versus placebo, whereas a less stringent TMB cutoff (≥ 10 mut/Mb) failed to show a survival benefit in either group. The role of TMB in SCLC is still unclear; further investigation is warranted in prospective phase III trials. Exploratory analysis of CPS-evaluable patients suggested that baseline tumor PD-L1 expression ≥ 1% was not associated with efficacy of combination therapy or monotherapy versus placebo. However, patients with CPS ≥ 1% achieved better OS than patients with CPS < 1% across all treatment groups including placebo, suggesting that PD-L1 expression may be a prognostic marker independent of treatment for SCLC. Similar findings regarding the prognostic nature of PD-L1 have been observed in other tumor types; however, the data are inconsistent and the relationship between PD-L1 expression and patient prognosis is generally unclear.[31-35]

In conclusion, maintenance with combination therapy in the current dosing regimen did not prolong OS in patients with ED-SCLC after first-line platinum-based chemotherapy. Investigation into alternative dosing regimens for either experimental arm explored in this study or alternative combination therapies for maintenance treatment that reflect the unique histology and natural history of SCLC or offer improved tolerability may be warranted.

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REFERENCES

1. Farago AF, Keane FK: Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res 7:69-79, 2018
2. Hurwitz JL, McCoy F, Scullin P, et al: New advances in the second-line treatment of small cell lung cancer. Oncologist 14:986-994, 2009
3. Ramalingam SS, Dahlberg SE, Belani CP, et al: Pemetrexed, bevacizumab, or the combination as maintenance therapy for advanced nonsquamous non-small-cell lung cancer: ECOG-ACRIN 5508. J Clin Oncol 37:2360-2367, 2019
4. Rossi A, Garassino MC, Cinquini M, et al: Maintenance or consolidation therapy in small-cell lung cancer: A systematic review and meta-analysis. Lung Cancer 70:119-128, 2010
5. Schiller JH, Adak S, Cella D, et al: Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593—A phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 19:2114-2122, 2001
6. Ready NE, Pang HH, Gu L, et al: Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: A randomized, double-blind, placebo-controlled phase II study—CALGB 30504 (Alliance). J Clin Oncol 33:1660-1665, 2015
7. Gadgeel SM, Pennell NA, Fidler MJ, et al: Phase II study of maintenance pembrolizumab in patients with extensive-stage small cell lung cancer (SCLC). J Thorac Oncol 13:1393-1399, 2018
8. Horn L, Mansfield AS, Szczesna A, et al: First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 379:2220-2229, 2018
9. Leal T, Wang Y, Dowlati A, et al: Randomized phase II clinical trial of cisplatin/carboplatin and etoposide (CE) alone or in combination with nivolumab as frontline therapy for extensive-stage small cell lung cancer (ES-SCLC): ECOG-ACRIN EA5161. J Clin Oncol 38, 2020 (suppl 15; abstr 9000)
10. Paz-Ares L, Dvorkin M, Chen Y, et al: Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): A randomised, controlled, open-label, phase 3 trial. Lancet 394:1929-1939, 2019

11. Ready N, Farago AF, de Braud F, et al: Third-line nivolumab monotherapy in recurrent SCLC: CheckMate 032. J Thorac Oncol 14:237-244, 2018
12. Antonia SJ, Lopez-Martin JA, Bendell J, et al: Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial. Lancet Oncol 17:883-895, 2016
13. Ready NE, Ott PA, Hellmann MD, et al: Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: Results from the CheckMate 032 randomized cohort. J Thorac Oncol 15:426-435, 2020
14. Brahmer JR, Rodríguez-Abreu D, Robinson AG, et al: Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): A multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol 18:1600-1609, 2017
15. Chung HC, Piha-Paul SA, Lopez-Martin J, et al: Pembrolizumab after two or more lines of prior therapy in patients with advanced small-cell lung cancer (SCLC): Results from the KEYNOTE-028 and KEYNOTE-158 studies. Cancer Res 79, 2019 (suppl 13; abstr CT073)
16. Reck M, Vicente D, Ciuleanu T, et al: Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331. Ann Oncol 29:LBA5, 2018
17. Sharma P, Allison JP: Dissecting the mechanisms of immune checkpoint therapy. Nat Rev Immunol 20:75-76, 2020
18. Das R, Verma R, Sznol M, et al: Combination therapy with anti-CTLA-4 and anti-PD-1 leads to distinct immunologic changes in vivo. J Immunol 194:950-959, 2015
19. Kulangara K, Zhang N, Corigliano E, et al: Clinical utility of the combined positive score for programmed death ligand-1 expression and the approval of pembrolizumab for treatment of gastric cancer. Arch Pathol Lab Med 143:330-337, 2019
20. American Joint Committee on Cancer: AJCC Cancer Staging Manual (ed 7). New York, NY, Springer, 2010
21. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247, 2009
22. Foundation Medicine: Foundation One CDx™, 2017
23. Dako North America: Labeling: PD-L1 IHC 28-8 pharmDx, 2016
24. Bristol-Myers Squibb: Opdivo® (Nivolumab) Prescribing Information, October 2020
25. Hellmann MD, Ciuleanu TE, Pluzanski A, et al: Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. N Engl J Med 378:2093-2104, 2018
26. Hellmann MD, Rizvi NA, Goldman JW, et al: Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncol 18:31-41, 2017
27. Bristol-Myers Squibb: Yervoy® (Ipilimumab) Prescribing Information, October 2020
28. Rudin CM, Awad MM, Navarro A, et al: Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: Randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol 38:2369-2379, 2020
29. Paz-Ares LG, Dvorkin M, Chen Y, et al: Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): Updated results from the phase III CASPIAN study. J Clin Oncol 38, 2020 (suppl 15; abstr 9002)
30. Hellmann MD, Callahan MK, Awad MM, et al: Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. Cancer Cell 33:853-861, 2018
31. Kim HR, Ha SJ, Hong MH, et al: PD-L1 expression on immune cells, but not on tumor cells, is a favorable prognostic factor for head and neck cancer patients. Sci Rep 6:36956, 2016
32. Sun JM, Zhou W, Choi YL, et al: Prognostic significance of PD-L1 in patients with non-small cell lung cancer: A large cohort study of surgically resected cases. J Thorac Oncol 11:1003-1011, 2016
33. Hatogai K, Fujii S, Kojima T, et al: Large-scale comprehensive immunohistochemical biomarker analyses in esophageal squamous cell carcinoma. J Cancer Res Clin Oncol 143:2351-2361, 2017
34. Ito S, Okano S, Morita M, et al: Expression of PD-L1 and HLA class I in esophageal squamous cell carcinoma: Prognostic factors for patient outcome. Ann Surg Oncol 23:508-515, 2016
35. Yu H, Chen Z, Ballman KV, et al: Correlation of PD-L1 expression with tumor mutation burden and gene signatures for prognosis in early-stage squamous cell lung carcinoma. J Thorac Oncol 14:25-36, 2019

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