

SUPPLEMENTARY APPENDIX

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METHODS

A. Additional Eligibility Criteria

Extensive-disease small-cell lung cancer was defined per National Comprehensive Cancer Network (NCCN) guidelines.¹ First-line chemotherapy must have been in accordance with the NCCN Clinical Practice Guidelines for small-cell lung cancer²; acceptable combinations included cisplatin or carboplatin with either etoposide or irinotecan. Patients were required to be naive to immuno-oncology treatments targeting T-cell co-stimulation or checkpoint pathways, including anti-programmed death-1, anti-programmed death ligand 1 (PD-L1), or anti-cytotoxic T-lymphocyte antigen-4 antibodies. A formalin-fixed paraffin-embedded archival or fresh tumor sample (tissue block or 10 unstained slides) for biomarker evaluation had to be available prior to randomization. Re-enrollment was permitted for patients who were initially enrolled but not randomized and/or treated. All toxicities attributed to prior anti-cancer therapy must have been resolved to grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0) or baseline before administration of blinded study drug(s). However, patients with AEs related to first-line treatment that were not expected to resolve and/or result in long-lasting sequelae, or not expected to interfere with study treatment, as well as those with grade 2 anemia if presenting a hemoglobin level of ≥ 8.0 g/dL, were included. Those with the following autoimmune conditions were permitted: type I diabetes mellitus, hypothyroidism controlled with hormone replacement therapy, skin disorders not requiring systemic treatment, and conditions not expected to recur in the absence of an external trigger.

Patients with symptomatic central nervous system metastases were excluded, but those with asymptomatic brain metastases were eligible if they had stable disease at

screening and did not require treatment with radiation therapy, anticonvulsants, or corticosteroids (a stable or decreasing dose of ≤ 10 mg daily prednisone equivalent was permitted). Patients experiencing first-line treatment-related AEs of grade 2 or higher, receiving consolidative chest radiation therapy or systemic treatment with immunosuppressive agents including corticosteroids (> 10 mg daily prednisone equivalent), and those with carcinomatous meningitis, inadequately controlled pleural effusion, active (known or suspected) autoimmune disease, or symptomatic interstitial lung disease were excluded. Patients with previously diagnosed malignancies (except for non-melanoma skin cancers and bladder, gastric, colon, endometrial, cervical [or cervical dysplasia], melanoma, or breast in situ cancers) were also excluded unless a complete remission had been achieved ≥ 2 years prior to study entry and no additional therapy was required during the study period. Other exclusion criteria were positive testing for hepatitis B, hepatitis C, or human immunodeficiency virus, and an inadequate hematological function (defined as absolute neutrophil count of $< 1000/\text{mm}^3$ or platelet count of $< 100,000/\text{mm}^3$ or hemoglobin level of < 8.0 g/dL), hepatic function (defined as total bilirubin level of ≥ 1.5 times the upper limit of normal [ULN] or aspartate aminotransferase and alanine aminotransferase levels of ≥ 2.5 times ULN) or pancreatic function (defined as lipase or amylase > 1.5 ULN).

All patients (excluding those in China) were required to provide a formalin-fixed, paraffin-embedded tumor tissue block (preferred) or 10 unstained slides of tumor sample (archival or recent) for biomarker evaluation that was received by a central laboratory prior to randomization (patients in China had tissue submitted to a separate central laboratory within China; these samples were not included in the ITT analysis). Excisional, incisional, or core needle biopsies were strongly preferred;

however, samples collected via endobronchial ultrasound-guided biopsy and transbronchial lung biopsy were acceptable.

B. Randomization and Blinding

Enrollment and randomization were facilitated by an interactive voice response system; randomization was conducted using the permuted blocks within each stratum.

Unblinding to study treatment was permitted in cases of disease progression, treatment discontinuation, medical emergency, or when this knowledge was critical to patient management.

C. Dose Modification

Dose reductions for individual patient management of toxicities were not permitted. Dose delay of blinded study therapy was indicated for grade 2 non-skin, drug-related AEs, with the exception of fatigue; grade 2 drug-related creatinine, AST, ALT, and/or bilirubin abnormalities; any grade 3 skin, drug-related AE; any grade 3, drug-related laboratory abnormality, except for grade 3 lymphopenia or grade ≥ 3 drug-related amylase or lipase abnormality not associated with symptoms of pancreatitis; and any AE, laboratory abnormality, or intercurrent illness that warrants dose delay as judged by the investigator.

D. Treatment Beyond Progression

Treatment with nivolumab plus ipilimumab and nivolumab was permitted to continue beyond disease progression if the patient was unblinded to study therapy and had investigator-assessed clinical benefit without rapid disease progression, continued to tolerate the treatment, had a stable Eastern Cooperative Oncology Group performance status, and if the treatment would not delay an imminent intervention to

prevent serious complications of disease progression. A radiographic assessment was performed within 6 weeks of the original progression to determine if there had been a decrease in tumor size or continued progression. For patients who continued study therapy beyond progression, further progression was defined as an additional 10% increase in tumor size from time of initial progression. Treatment was discontinued upon further disease progression.

D. Concomitant Treatment

Palliative radiotherapy during the trial was permitted to treat bone lesions or single metastatic non-bone lesion excluding lung tissue, although the study treatment had to be ceased during and for 2 weeks after completion of radiotherapy.

E. Blinding

The sponsor, patients, investigators, and site staff were blinded to the trial therapy. In order to maintain a blinded trial, the schedule of all treatments consisted of two 6-week cycles at the start of therapy, followed by 2-week cycles for the duration of therapy, so that matched placebos could be administered. Treatment was therefore administered in all arms on days 1, 15, 22, and 29 of cycles 1 and 2 (42-day cycles), and day 1 of every cycle (14-day cycles) thereafter.

F. Tumor Assessment Schedule

Radiographic tumor assessments were performed using computed tomography or magnetic resonance imaging at baseline, every 6 weeks (± 5 days) up to week 36, and every 12 weeks (± 5 days) thereafter, or as clinically indicated, until disease progression (or discontinuation of study therapy in patients treated beyond progression).

G. Sample Size Calculation

Power calculations were performed using EAST® Software (Version 6.4.1). Survival function modeling was performed for the placebo arm using four hazard pieces based on published data and adjusted for induction phase (3 months, 90%; 9 months, 47%; 18 months, 15%; 26 months, 9%).³ For nivolumab plus ipilimumab, the overall HR of 0.72 was based on an HR of 1 for the first 3 months⁴ and an HR of 0.68 thereafter to allow for a delayed effect versus placebo; median OS derived from the survival functions were 11.0 months and 8.8 months for the nivolumab plus ipilimumab and placebo arms, respectively.

H. Statistical Analysis of Tumor Response

ORRs were compared using a two-sided stratified Cochran–Mantel–Haenszel test, with exact two-sided 95% CIs calculated using the Clopper–Pearson method. DOR was estimated using Kaplan–Meier methodology.

I. Assessment of the Predictive Effect of Select Baseline Characteristics on OS

Univariate analyses of OS by baseline characteristics were conducted by estimating the unstratified HR and 95% CI for select prespecified patient subgroups. The predictive effect of baseline characteristics on OS was assessed using multivariate Cox proportional hazards model with interaction with treatment analyses. HRs and 95% CIs were calculated using unstratified Cox proportional hazards models with treatment, subgroup, and treatment by subgroup interaction as terms. Analyses were carried out with and without adjustment for the following prognostic factors: baseline Eastern Cooperative Oncology Group performance status (1 v 0), lactate dehydrogenase (ULN v other), liver metastases (yes v other), and time from last

dose of first-line chemotherapy to randomization (≤ 5 weeks v other [only for OS by time from last dose of first-line chemotherapy to randomization]).

J. Selection of Prognostic Factors for Multivariate Analysis

The prognostic variables included in multivariate analysis for OS were selected based on best subset Cox proportional hazards models to evaluate the influence of factors other than treatment on OS. The following baseline variables were assessed as prognostic factors: prophylactic cranial irradiation following chemotherapy (yes v other), baseline lactate dehydrogenase ($>ULN$ v other), baseline liver metastases (yes v other), baseline central nervous system metastases per case report form (yes v other), best response to first-line chemotherapy (CR/PR v other), baseline ECOG PS (≥ 1 v other), time from initial disease diagnosis to randomization (< 1 year v other), time from last dose of first-line chemotherapy to randomization (≤ 5 weeks v other), and sex (female v male). A model with 3 variables accounted for a majority of the variability in OS; these variables were therefore included as prognostic variables in the multivariate analyses: baseline ECOG PS, baseline liver metastases, and baseline lactate dehydrogenase.

Table A1. Subsequent Cancer Therapy^a

	Nivolumab Plus Ipilimumab	Nivolumab	Placebo
n (%)	(n = 279)	(n = 280)	(n = 275)
Any	117 (41.9)	132 (47.1)	148 (53.8)
Radiotherapy	52 (18.6)	64 (22.9)	61 (22.2)
Surgery	0	1 (0.4)	2 (0.7)
Systemic therapy	91 (32.6)	109 (38.9)	128 (46.5)
Immunotherapy	6 (2.2)	6 (2.1)	8 (2.9)
Anti-PD-1/PD-L1			
Nivolumab	6 (2.2)	5 (1.8)	6 (2.2)
Pembrolizumab	0	0	2 (0.7)
Atezolizumab	0	1 (0.4)	0
Anti-CTLA-4			
Ipilimumab	3 (1.1)	3 (1.1)	1 (0.4)
Targeted therapy	1 (0.4)	1 (0.4)	0
Experimental drugs	4 (1.4)	7 (2.5)	8 (2.9)
Chemotherapy	86 (30.8)	103 (36.8)	124 (45.1)

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

^aPatients may have received more than one type of subsequent therapy.

Table A2. Multivariate Analysis for Overall Survival^a

Baseline Characteristic	Unstratified HR (95% CI) Nivolumab v Placebo	Interaction P-value^b
Baseline LDH		
> ULN	0.94 (0.64 to 1.38)	0.6515
≤ ULN	0.84 (0.67–1.06)	
Baseline ECOG PS		
1	0.91 (0.71 to 1.17)	0.4918
0	0.79 (0.57 to 1.10)	
Time from last dose of first-line chemotherapy		
≤ 5 weeks	0.68 (0.50 to 0.93)	0.0462
> 5 weeks	1.02 (0.79 to 1.31)	
Baseline liver metastases		
Yes	0.91 (0.67 to 1.22)	0.7152
No	0.84 (0.65 to 1.09)	

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal.

^aUnstratified Cox proportional hazards models including treatment, subgroup, and treatment by subgroup interaction, adjusted for baseline LDH, baseline ECOG PS, and baseline liver metastases.

^bFor descriptive purposes only; there was no correction for multiplicity.

Table A3. Distribution of Patients by TMB Cutoff in the TMB-Evaluable Population

	Nivolumab Plus Ipilimumab	Nivolumab	Placebo
n (%)	(n = 192)	(n = 196)	(n = 192)
≥ 10 mut/Mb	90 (46.9)	98 (50.0)	88 (45.8)
≥ 13 mut/Mb	61 (31.8)	71 (36.2)	59 (30.7)

Abbreviations: mut/Mb, mutations per megabase; TMB, tumor mutational burden.

Table A4. Patient Demographics and Baseline Characteristics of Patients Evaluable and Non-evaluable for TMB and the ITT Population

	TMB Evaluable (n = 580)	TMB Non-evaluable (n = 254)	ITT Population (n = 834)
Age, years			
Median (range)	64.0 (32 to 84)	64.0 (37 to 85)	64.0 (32 to 85)
< 65	295 (50.9)	128 (50.4)	423 (50.7)
≥ 65	285 (49.1)	126 (49.6)	411 (49.3)
Female	210 (36.2)	92 (36.2)	302 (36.2)
Race			
White	433 (74.7)	194 (76.4)	627 (75.2)
Black or African American	7 (1.2)	2 (0.8)	9 (1.1)
Asian	130 (22.4)	55 (21.7)	185 (22.2)
Other	9 (1.6)	3 (1.2)	12 (1.4)
Not reported	1 (0.2)	0	1 (0.1)
Region			
United States / Canada	116 (20.0)	64 (25.2)	180 (21.6)
Europe	244 (42.1)	97 (38.2)	341 (40.9)
Asia	125 (21.6)	55 (21.7)	180 (21.6)
Rest of world	95 (16.4)	38 (15.0)	133 (15.9)
ECOG PS			
0	234 (40.3)	98 (38.6)	332 (39.8)
1	346 (59.7)	156 (61.4)	502 (60.2)
Smoking status			
Current or former	542 (93.4)	231 (90.9)	773 (92.7)
Never	33 (5.7)	20 (7.9)	53 (6.4)
Unknown	5 (0.9)	3 (1.2)	8 (1.0)
Lactate dehydrogenase			
≤ ULN	434 (74.8)	186 (73.2)	620 (74.3)

> ULN	139 (24.0)	65 (25.6)	204 (24.5)
Not reported	7 (1.2)	3 (1.2)	10 (1.2)
Liver metastases			
Yes	217 (37.4)	108 (42.5)	325 (39.0)
No	363 (62.6)	146 (57.5)	509 (61.0)
CNS metastases			
Yes	81 (14.0)	35 (13.8)	116 (13.9)
No	499 (86.0)	219 (86.2)	718 (86.1)
Prior PCI	129 (22.2)	57 (22.4)	186 (22.3)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	364 (62.8)	155 (61.0)	519 (62.2)
Cisplatin	236 (40.7)	109 (42.9)	345 (41.4)
Best response to first-line chemotherapy ^b			
Complete response	13 (2.2)	8 (3.1)	21 (2.5)
Partial response	411 (70.9)	175 (68.9)	586 (70.3)
Stable disease	156 (26.9)	70 (27.6)	226 (27.1)
Time (weeks) from last dose of first-line chemotherapy to randomization ^c			
≤ 5	227 (39.1)	114 (44.9)	341 (40.9)
> 5	353 (60.9)	140 (55.1)	493 (59.1)
> 5–9	308 (53.1)	115 (45.3)	423 (50.7)
> 9	45 (7.8)	25 (9.8)	70 (8.4)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; PCI, prophylactic cranial irradiation; TMB, tumor mutational burden; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bResponse was not applicable for one patient in the TMB non-evaluable group who was randomized but not treated.

^cStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A5. Patient Demographics and Baseline Characteristics of Patients Evaluable for Tumor Mutational Burden by Treatment Group

	Nivolumab Plus Ipilimumab (n = 192)	Nivolumab (n = 196)	Placebo (n = 192)
Age, years			
Median (range)	64.0 (39 to 84)	64.5 (32 to 84)	64.0 (44 to 80)
< 65	97 (50.5)	98 (50.0)	100 (52.1)
≥ 65	95 (49.5)	98 (50.0)	92 (47.9)
Female	67 (34.9)	74 (37.8)	69 (35.9)
Race			
White	153 (79.7)	147 (75.0)	133 (69.3)
Black or African American	1 (0.5)	4 (2.0)	2 (1.0)
Asian	35 (18.2)	43 (21.9)	52 (27.1)
Other	2 (1.0)	2 (1.0)	5 (2.6)
Not reported	1 (0.5)	0	0
Region			
United States / Canada	43 (22.4)	38 (19.4)	35 (18.2)
Europe	84 (43.8)	87 (44.4)	73 (38.0)
Asia	34 (17.7)	40 (20.4)	51 (26.6)
Rest of world	31 (16.1)	31 (15.8)	33 (17.2)
ECOG PS			
0	78 (40.6)	79 (40.3)	69 (35.9)
1	114 (59.4)	117 (59.7)	123 (64.1)
Smoking status			
Current or former	177 (92.2)	184 (93.9)	181 (94.3)
Never	13 (6.8)	11 (5.6)	9 (4.7)
Unknown	2 (1.0)	1 (0.5)	2 (1.0)
Lactate dehydrogenase			

≤ ULN	144 (75.0)	147 (75.0)	143 (74.5)
> ULN	45 (23.4)	46 (23.5)	48 (25.0)
Not reported	3 (1.6)	3 (1.5)	1 (0.5)
Liver metastases			
Yes	75 (39.1)	66 (33.7)	76 (39.6)
No	117 (60.9)	130 (66.3)	116 (60.4)
CNS metastases			
Yes	25 (13.0)	33 (16.8)	23 (12.0)
No	167 (87.0)	163 (83.2)	169 (88.0)
Prior PCI	43 (22.4)	43 (21.9)	43 (22.4)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	122 (63.5)	126 (64.3)	116 (60.4)
Cisplatin	78 (40.6)	75 (38.3)	83 (43.2)
Best response to first-line chemotherapy			
Complete response	6 (3.1)	5 (2.6)	2 (1.0)
Partial response	140 (72.9)	133 (67.9)	138 (71.9)
Stable disease	46 (24.0)	58 (29.6)	52 (27.1)
Time (weeks) from last dose of first-line chemotherapy to randomization ^b			
≤ 5	76 (39.6)	70 (35.7)	81 (42.2)
> 5	116 (60.4)	126 (64.3)	111 (57.8)
> 5–9	103 (53.6)	111 (56.6)	94 (49.0)
> 9	13 (6.8)	15 (7.7)	17 (8.9)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A6. Patient Demographics and Baseline Characteristics of Patients Evaluable for TMB, by TMB Cutoff

	TMB < 13 mut/Mb	TMB ≥ 13 mut/Mb
	(n = 389)	(n = 191)
Age, years		
Median (range)	64 (32 to 84)	64 (44 to 82)
< 65	197 (50.0)	98 (51.3)
≥ 65	192 (49.4)	93 (48.7)
Female	130 (33.4)	80 (41.9)
Race		
White	283 (72.8)	150 (78.5)
Black or African American	5 (1.3)	2 (1.0)
Asian	93 (23.9)	37 (19.4)
Other	7 (1.8)	2 (1.0)
Not reported	1 (0.3)	0
Region		
United States / Canada	69 (17.7)	47 (24.6)
Europe	164 (42.2)	80 (41.9)
Asia	90 (23.1)	35 (18.3)
Rest of world	66 (17.0)	29 (15.2)
ECOG PS		
0	168 (43.2)	66 (34.6)
1	221 (56.8)	125 (65.4)
Smoking status		
Current or former	363 (93.3)	179 (93.7)
Never	23 (5.9)	10 (5.2)

Unknown	3 (0.8)	2 (1.0)
Lactate dehydrogenase		
≤ ULN	288 (74.0)	146 (76.4)
> ULN	98 (25.2)	41 (21.5)
Not reported	3 (0.8)	4 (2.1)
Liver metastases		
Yes	148 (38.0)	69 (36.1)
No	365 (93.8)	182 (95.3)
CNS metastases		
Yes	50 (12.9)	31 (16.2)
No	339 (87.1)	160 (83.8)
Prior PCI	129 (33.2)	65 (34.0)
Prior first-line platinum-based chemotherapy ^a		
Carboplatin	389 (100)	191 (100)
Cisplatin	243 (62.5)	121 (63.4)
	50 (38.2)	75 (39.3)
Best response to first-line chemotherapy		
Complete response	7 (1.8)	6 (3.1)
Partial response	284 (73.0)	127 (66.5)
Stable disease	98 (25.2)	58 (30.4)
Time (weeks) from last dose of first-line chemotherapy to randomization ^b		
≤ 5	83 (43.5)	83 (43.5)
> 5	108 (56.6)	108 (56.6)
> 5–9	93 (48.7)	93 (48.7)

> 9

15 (7.9)

15 (7.9)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; TMB, tumor mutational burden; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A7. Patient Demographics and Baseline Characteristics of Patients With Tumor Mutational Burden < 13 mut/Mb by Treatment Group

	Nivolumab Plus Ipilimumab (n = 131)	Nivolumab (n = 125)	Placebo (n = 133)
Age, years			
Median (range)	65 (39 to 84)	65 (32 to 84)	64 (44 to 80)
< 65	63 (48.1)	61 (48.8)	73 (54.9)
≥ 65	68 (51.9)	64 (51.2)	60 (45.1)
Female	43 (32.8)	45 (36.0)	42 (31.6)
Race			
White	102 (77.9)	91 (72.8)	90 (67.7)
Black or African American	1 (0.8)	4 (3.2)	0
Asian	26 (19.8)	28 (22.4)	39 (29.3)
Other	1 (0.8)	2 (1.6)	4 (3.0)
Not reported	1 (0.8)	0	0
Region			
United States / Canada	27 (20.6)	17 (13.6)	25 (18.8)
Europe	57 (43.5)	60 (48.0)	47 (35.3)
Asia	25 (19.1)	26 (20.8)	39 (29.3)
Rest of world	22 (16.8)	22 (17.6)	22 (16.5)
ECOG PS			
0	61 (46.6)	52 (41.6)	55 (41.4)
1	70 (53.4)	73 (58.4)	78 (58.6)
Smoking status			
Current or former	123 (93.9)	114 (91.2)	126 (94.7)
Never	7 (5.3)	10 (8.0)	6 (4.5)
Unknown	1 (0.8)	1 (0.8)	1 (0.8)
Lactate dehydrogenase			

≤ ULN	97 (74.0)	93 (74.0)	98 (73.7)
> ULN	33 (25.2)	33 (25.2)	34 (25.6)
Not reported	1 (0.8)	1 (0.8)	1 (0.8)
Liver metastases			
Yes	51 (38.9)	40 (32.0)	57 (42.9)
No	80 (61.1)	85 (68.0)	76 (57.1)
CNS metastases			
Yes	7 (5.3)	8 (6.4)	14 (10.5)
No	124 (94.7)	117 (93.6)	124 (93.2)
Prior PCI	40 (30.5)	44 (35.2)	45 (33.8)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	86 (65.6)	78 (2.4)	79 (59.4)
Cisplatin	50 (38.2)	52 (41.6)	59 (44.4)
Best response to first-line chemotherapy			
Complete response	2 (1.5)	4 (3.2)	1 (0.8)
Partial response	98 (74.8)	86 (68.8)	100 (75.2)
Stable disease	31 (23.7)	35 (28.0)	32 (24.1)
Time (weeks) from last dose of first-line chemotherapy to randomization ^b			
≤ 5	51 (38.9)	41 (32.8)	52 (39.1)
> 5	80 (61.1)	84 (67.2)	81 (60.9)
> 5–9	69 (52.7)	76 (60.8)	70 (52.6)
> 9	11 (8.4)	8 (6.4)	11 (8.3)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A8. Patient Demographics and Baseline Characteristics of Patients With Tumor Mutational Burden ≥ 13 mut/Mb by Treatment Group

	Nivolumab Plus Ipilimumab (n = 61)	Nivolumab (n = 71)	Placebo (n = 59)
Age, years			
Median (range)	63 (44 to 81)	64 (51 to 82)	65 (45 to 78)
< 65	34 (55.7)	37 (52.1)	27 (45.8)
≥ 65	27 (44.3)	34 (47.9)	32 (54.2)
Female	24 (39.3)	29 (40.8)	27 (45.8)
Race			
White	51 (83.6)	56 (78.9)	43 (72.9)
Black or African American	0	0	2 (3.4)
Asian	9 (14.8)	15 (21.1)	13 (22.0)
Other	1 (1.7)	0	1 (1.7)
Region			
United States / Canada	16 (26.2)	21 (29.6)	10 (16.9)
Europe	27 (44.3)	27 (38.0)	26 (44.1)
Asia	9 (14.8)	14 (19.7)	12 (20.3)
Rest of world	9 (14.8)	9 (12.7)	11 (18.6)
ECOG PS			
0	19 (31.1)	34 (47.9)	13 (22.0)
1	42 (68.9)	37 (52.1)	46 (78.0)
Smoking status			
Current or former	54 (88.5)	70 (98.6)	55 (93.2)
Never	6 (9.8)	1 (1.4)	3 (5.1)
Unknown	1 (1.6)	0	1 (1.7)
Lactate dehydrogenase			
\leq ULN	47 (77.0)	54 (76.1)	45 (76.3)

> ULN	12 (19.7)	15 (21.1)	14 (23.7)
Not reported	2 (3.3)	2 (2.8)	0
Liver metastases			
Yes	24 (39.3)	26 (36.6)	19 (32.2)
No	37 (60.7)	69 (97.2)	40 (67.8)
CNS metastases			
Yes	11 (18.0)	11 (15.5)	9 (15.3)
No	50 (82.0)	45 (63.4)	50 (84.7)
Prior PCI	21 (34.4)	25 (35.2)	19 (32.2)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	61 (100.0)	71 (100.0)	59 (100.0)
Cisplatin	36 (59.0)	48 (67.6)	37 (62.7)
	28 (45.9)	23 (32.4)	24 (40.7)
Best response to first-line chemotherapy			
Complete response	4 (6.6)	1 (1.4)	1 (1.7)
Partial response	42 (68.9)	47 (66.2)	38 (64.4)
Stable disease	15 (24.6)	23 (32.4)	20 (33.9)
Time (weeks) from last dose of first-line chemotherapy to randomization ^b			
≤ 5	25 (41.0)	29 (40.8)	29 (49.2)
> 5	36 (59.0)	42 (59.2)	30 (50.8)
> 5–9	34 (55.7)	35 (49.3)	24 (40.7)
> 9	2 (3.3)	7 (9.9)	6 (10.2)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A9. Progression-Free Survival and Objective Response Rates With Nivolumab Plus Ipilimumab Versus Nivolumab Versus Placebo by Tumor Mutational Burden (10 mut/Mb and 13 mut/Mb Cutoffs)

	TMB ≥ 10 mut/Mb			TMB < 10 mut/Mb		
	Nivolumab Plus Ipilimumab (n = 90)	Nivolumab (n = 98)	Placebo (n = 88)	Nivolumab Plus Ipilimumab (n = 102)	Nivolumab (n = 98)	Placebo (n = 104)
Median PFS (95% CI), mo	2.3 (1.5 to 2.8)	2.8 (2.1 to 4.2)	1.6 (1.4 to 2.6)	1.5 (1.4 to 2.0)	1.6 (1.4 to 2.3)	1.4 (1.4 to 1.4)
PFS HR (95% CI) ^a	0.76 (0.56 to 1.05)	0.70 (0.51 to 0.95)	–	0.72 (0.53 to 0.97)	0.68 (0.50 to 0.92)	–
ORR (95% CI), %	10.8 (5.1 to 19.6)	12.5 (6.6 to 20.8)	6.0 (2.0 to 13.5)	7.2 (3.0 to 14.3)	10.0 (4.7 to 18.1)	3.0 (0.6 to 8.5)
	TMB ≥ 13 mut/Mb			TMB < 13 mut/Mb		
	Nivolumab Plus Ipilimumab (n = 61)	Nivolumab (n = 71)	Placebo (n = 59)	Nivolumab Plus Ipilimumab (n = 131)	Nivolumab (n = 125)	Placebo (n = 133)
Median PFS (95% CI), mo	2.7 (1.5 to 3.6)	2.8 (1.6 to 4.1)	1.6 (1.4 to 2.6)	1.5 (1.4 to 2.0)	1.6 (1.4 to 2.6)	1.4 (1.4 to 1.4)

PFS HR (95% CI) ^a	0.69 (0.47 to 1.03)	0.68 (0.47 to 0.99)	–	0.78 (0.60 to 1.01)	0.69 (0.53 to 0.90)	–
ORR (95% CI), %	14.0 (6.3 to 25.8)	14.3 (7.1 to 24.7)	5.3 (1.1 to 14.6)	6.5 (2.8 to 12.4)	9.5 (4.8 to 16.3)	4.0 (1.3 to 9.0)

Abbreviations: CI, confidence interval; HR, hazard ratio; ORR, objective response rate; mo, months; mut/Mb, mutations per megabase; PFS, progression-free survival; TMB, tumor mutational burden.

^aVersus placebo.

Table A10. Distribution of Patients by CPS in the CPS-Evaluable Population

	Nivolumab Plus Ipilimumab	Nivolumab	Placebo
n (%)	(n = 116)	(n = 124)	(n = 114)
CPS \geq 1%	52 (44.8)	55 (44.4)	56 (49.1)
CPS < 1%	64 (55.2)	69 (55.6)	58 (50.9)

Abbreviation: CPS, combined positive score.

Table A11. Patient Demographics and Baseline Characteristics of Patients

Evaluable and Non-evaluable for Programmed Death Ligand 1 CPS and the ITT

Population

	CPS Evaluable (n = 354)	CPS Non-evaluable (n = 480)	ITT Population (n = 834)
Age, years			
Median (range)	65.0 (34 to 85)	64.0 (32 to 84)	64.0 (32 to 85)
< 65	172 (48.6)	251 (52.3)	423 (50.7)
≥ 65	182 (51.4)	229 (47.7)	411 (49.3)
Female	128 (36.2)	174 (36.3)	302 (36.2)
Race			
White	284 (80.2)	343 (71.5)	627 (75.2)
Black or African American	5 (1.4)	4 (0.8)	9 (1.1)
Asian	59 (16.7)	126 (26.3)	185 (22.2)
Other	6 (1.7)	6 (1.3)	12 (1.4)
Not reported	0	1 (0.2)	1 (0.1)
Region			
United States / Canada	76 (21.5)	104 (21.7)	180 (21.6)
Europe	154 (43.5)	187 (39.0)	341 (40.9)
Asia	57 (16.1)	123 (25.6)	180 (21.6)
Rest of world	67 (18.9)	66 (13.8)	133 (15.9)
ECOG PS			
0	143 (40.4)	189 (39.4)	332 (39.8)
1	211 (59.6)	291 (60.6)	502 (60.2)
Smoking status			
Current or former	329 (92.9)	444 (92.5)	773 (92.7)
Never	21 (5.9)	32 (6.7)	53 (6.4)
Unknown	4 (1.1)	4 (0.8)	8 (1.0)
Lactate dehydrogenase			

≤ ULN	261 (73.7)	359 (74.8)	620 (74.3)
> ULN	89 (25.1)	115 (24.0)	204 (24.5)
Not reported	4 (1.1)	6 (1.3)	10 (1.2)
Liver metastases			
Yes	144 (40.7)	181 (37.7)	325 (39.0)
No	210 (59.3)	299 (62.3)	509 (61.0)
CNS metastases			
Yes	56 (15.8)	60 (12.5)	116 (13.9)
No	298 (84.2)	420 (87.5)	718 (86.1)
Prior PCI	77 (21.8)	109 (22.7)	186 (22.3)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	225 (63.6)	294 (61.3)	519 (62.2)
Cisplatin	142 (40.1)	203 (42.3)	345 (41.4)
Best response to first-line chemotherapy ^b			
Complete response	8 (2.3)	13 (2.7)	21 (2.5)
Partial response	240 (67.8)	346 (72.1)	586 (70.3)
Stable disease	106 (29.9)	120 (25.0)	226 (27.1)
Time (weeks) from last dose of first-line chemotherapy to randomization ^c			
≤ 5	137 (38.7)	204 (42.5)	341 (40.9)
> 5	217 (61.3)	276 (57.5)	493 (59.1)
> 5–9	190 (53.7)	233 (48.5)	423 (50.7)
> 9	27 (7.6)	43 (9.0)	70 (8.4)

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

Abbreviations: CNS, central nervous system; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intent-to-treat; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

^bResponse was not applicable for one patient in the CPS non-evaluable group who was randomized but not treated.

^cStudy drug could not be administered < 3 weeks from the last dose of first-line chemotherapy.

Table A12. Patient Demographics and Baseline Characteristics of Patients

Evaluable for Programmed Death Ligand 1 Combined Positive Score by Treatment

Group

	Nivolumab Plus Ipilimumab (n = 116)	Nivolumab (n = 124)	Placebo (n = 114)
Age, years			
Median (range)	65.0 (39 to 85)	64.0 (34 to 83)	65.0 (45 to 84)
< 65	56 (48.3)	63 (50.8)	53 (46.5)
≥ 65	60 (51.7)	61 (49.2)	61 (53.5)
Female	41 (35.3)	47 (37.9)	40 (35.1)
Race			
White	95 (81.9)	98 (79.0)	91 (79.8)
Black or African American	1 (0.9)	3 (2.4)	1 (0.9)
Asian	18 (15.5)	21 (16.9)	20 (17.5)
Other	2 (1.7)	2 (1.6)	2 (1.8)
Region			
United States / Canada	29 (25.0)	22 (17.7)	25 (21.9)
Europe	51 (44.0)	55 (44.4)	48 (42.1)
Asia	17 (14.7)	20 (16.1)	20 (17.5)
Rest of world	19 (16.4)	27 (21.8)	21 (18.4)
ECOG PS			
0	53 (45.7)	49 (39.5)	41 (36.0)
1	63 (54.3)	75 (60.5)	73 (64.0)
Smoking status			
Current or former	104 (89.7)	116 (93.5)	109 (95.6)
Never	11 (9.5)	7 (5.6)	3 (2.6)
Unknown	1 (0.9)	1 (0.8)	2 (1.8)
Lactate dehydrogenase			

≤ ULN	85 (73.3)	89 (71.8)	87 (76.3)
> ULN	30 (25.9)	32 (25.8)	27 (23.7)
Not reported	1 (0.9)	3 (2.4)	0
Liver metastases			
Yes	44 (37.9)	50 (40.3)	50 (43.9)
No	72 (62.1)	74 (59.7)	64 (56.1)
CNS metastases			
Yes	20 (17.2)	22 (17.7)	14 (12.3)
No	96 (82.8)	102 (82.3)	100 (87.7)
Prior PCI	25 (21.6)	22 (17.7)	30 (26.3)
Prior first-line platinum-based chemotherapy ^a			
Carboplatin	74 (63.8)	82 (66.1)	69 (60.5)
Cisplatin	46 (39.7)	48 (38.7)	48 (42.1)
Best response to first-line chemotherapy			
Complete response	3 (2.6)	2 (1.6)	3 (2.6)
Partial response	81 (69.8)	81 (65.3)	78 (68.4)
Stable disease	32 (27.6)	41 (33.1)	33 (28.9)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

Table A13. Patient Demographics and Baseline Characteristics of Patients
Evaluable for Programmed Death Ligand 1 CPS by CPS Cutoff

	CPS < 1% (n = 191)	CPS ≥ 1% (n = 163)
Age, years		
Median (range)	64 (34 to 84)	66 (42 to 85)
< 65	102 (53.4)	70 (42.9)
≥ 65	89 (46.6)	93 (57.1)
Female	72 (37.7)	56 (34.4)
Race		
White	157 (82.2)	127 (77.9)
Black or African American	3 (1.6)	2 (1.2)
Asian	28 (14.7)	31 (19.0)
Other	3 (1.6)	3 (1.8)
Region		
United States / Canada	42 (22.0)	34 (20.9)
Europe	89 (46.6)	65 (39.9)
Asia	27 (14.1)	30 (18.4)
Rest of world	33 (17.3)	34 (20.9)
ECOG PS		
0	66 (34.6)	77 (47.2)
1	125 (65.4)	86 (52.8)
Smoking status		
Current or former	173 (90.6)	156 (95.7)
Never	17 (8.9)	4 (2.5)
Unknown	1 (0.5)	3 (1.8)
Lactate dehydrogenase		
≤ ULN	147 (77.0)	114 (69.9)
> ULN	42 (22.0)	47 (28.8)
Not reported	2 (1.0)	2 (1.2)

Liver metastases		
Yes	92 (48.2)	52 (31.9)
No	99 (51.8)	111 (68.1)
CNS metastases		
Yes	30 (15.7)	26 (16.0)
No	161 (84.3)	137 (84.0)
Prior PCI	60 (31.4)	63 (38.7)
Prior first-line platinum-based chemotherapy ^a		
Carboplatin	128 (67.0)	97 (59.5)
Cisplatin	70 (36.6)	72 (44.2)
Best response to first-line chemotherapy		
Complete response	3 (1.6)	5 (3.1)
Partial response	138 (72.3)	102 (62.6)
Stable disease	50 (26.2)	56 (34.4)

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

Abbreviations: CNS, central nervous system; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

Table A14. Patient Demographics and Baseline Characteristics of Patients With Programmed Death Ligand 1 Combined Positive Score < 1% by Treatment Group

	Nivolumab Plus Ipilimumab (n = 64)	Nivolumab (n = 69)	Placebo (n = 58)
Age, years			
Median (range)	64.0 (39 to 84)	62.0 (34 to 81)	65.0 (45 to 84)
< 65	32 (50.0)	43 (62.3)	27 (46.6)
≥ 65	32 (50.0)	26 (37.7)	31 (53.4)
Female	25 (39.1)	26 (37.7)	31 (53.4)
Race			
White	54 (84.4)	54 (78.3)	49 (84.5)
Black or African American	1 (1.6)	2 (2.9)	0
Asian	8 (12.5)	12 (17.4)	8 (13.8)
Other	1 (1.6)	1 (1.4)	1 (1.7)
Region			
United States / Canada	17 (26.6)	13 (18.8)	12 (20.7)
Europe	29 (45.3)	32 (46.4)	28 (48.3)
Asia	8 (12.5)	11 (15.9)	8 (13.8)
Rest of world	10 (15.6)	13 (18.8)	10 (17.2)
ECOG PS			
0	26 (40.6)	21 (30.4)	19 (32.8)
1	38 (59.4)	48 (69.6)	39 (67.2)
Smoking status			
Current or former	55 (85.9)	62 (89.9)	56 (96.6)
Never	9 (14.1)	7 (10.1)	1 (1.7)
Unknown	0	0	1 (1.7)
Lactate dehydrogenase			
≤ ULN	51 (79.7)	50 (72.5)	46 (79.3)

➤ ULN	12 (18.8)	18 (26.1)	12 (20.7)
Not reported	1 (1.6)	1 (1.4)	0
Liver metastases	28 (43.8)	32 (46.4)	32 (55.2)
Yes	36 (56.3)	37 (53.6)	26 (44.8)
No			
CNS metastases			
Yes	14 (21.9)	11 (15.9)	5 (8.6)
No	50 (78.1)	58 (84.1)	53 (91.4)
Prior PCI	19 (29.7)	20 (29.0)	21 (36.2)
Prior first-line platinum-based chemotherapy ^a	64 (100.0)	69 (100.0)	58 (100.0)
Carboplatin	42 (65.6)	52 (75.4)	34 (58.6)
Cisplatin	25 (39.1)	21 (30.4)	24 (41.4)
Best response to first-line chemotherapy			
Complete response	1 (1.6)	0	2 (3.4)
Partial response	46 (71.9)	49 (71.0)	43 (74.1)
Stable disease	17 (26.6)	20 (29.0)	13 (22.4)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

Table A15. Patient Demographics and Baseline Characteristics of Patients With Programmed Death Ligand 1 Combined Positive Score \geq 1% by Treatment Group

	Nivolumab Plus Ipilimumab (n = 56)	Nivolumab (n = 55)	Placebo (n = 52)
Age, years			
Median (range)	66.0 (44 to 85)	67.0 (42 to 83)	66.0 (45 to 81)
< 65	24 (46.2)	20 (36.4)	26 (46.4)
\geq 65	28 (53.8)	35 (63.6)	30 (53.6)
Female	16 (30.8)	21 (38.2)	19 (33.9)
Race			
White	41 (78.8)	44 (80.0)	42 (75.0)
Black or African American	0 (0)	1 (1.8)	1 (1.8)
Asian	10 (19.2)	9 (16.4)	12 (21.4)
Other	1 (1.9)	1 (1.8)	1 (1.8)
Region			
United States / Canada	12 (23.1)	9 (16.4)	13 (23.2)
Europe	22 (42.3)	23 (41.8)	20 (35.7)
Asia	9 (17.3)	9 (16.4)	12 (21.4)
Rest of world	9 (17.3)	14 (25.5)	11 (19.6)
ECOG PS			
0	27 (51.9)	28 (50.9)	22 (39.3)
1	25 (48.1)	27 (49.1)	34 (60.7)
Smoking status			
Current or former	49 (94.2)	54 (98.2)	53 (94.6)
Never	2 (3.8)	0	2 (3.6)
Unknown	1 (1.9)	1 (1.8)	1 (1.8)
Lactate dehydrogenase			
\leq ULN	34 (65.4)	39 (70.9)	41 (73.2)

> ULN	18 (34.6)	14 (25.5)	15 (26.8)
Not reported	0	2 (3.6)	0
Liver metastases			
Yes	16 (30.8)	18 (32.7)	18 (32.1)
No	36 (69.2)	37 (67.3)	38 (67.9)
CNS metastases			
Yes	6 (11.5)	11 (20.0)	9 (16.1)
No	46 (88.5)	44 (80.0)	47 (83.9)
Prior PCI	18 (34.6)	22 (40.0)	23 (41.1)
Prior first-line platinum-based chemotherapy ^a	52 (100.0)	55 (100.0)	56 (100.0)
Carboplatin	32 (61.5)	30 (54.5)	35 (62.5)
Cisplatin	21 (40.4)	27 (49.1)	24 (42.9)
Best response to first-line chemotherapy			
Complete response	2 (3.8)	2 (3.6)	1 (1.8)
Partial response	35 (67.3)	32 (58.2)	35 (62.5)
Stable disease	15 (28.8)	21 (38.2)	20 (35.7)

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

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PCI, prophylactic cranial irradiation; ULN, upper limit of normal.

^aPatients may have received more than one type of platinum compound.

Table A16. Progression-Free Survival and Objective Response Rates With Nivolumab Plus Ipilimumab Versus Nivolumab Versus Placebo by Programmed Death Ligand 1 CPS ($\geq 1\%$ and $< 1\%$)

	CPS $\geq 1\%$			CPS $< 1\%$		
	Nivolumab Plus Ipilimumab (n = 52)	Nivolumab (n = 55)	Placebo (n = 56)	Nivolumab Plus Ipilimumab (n = 64)	Nivolumab (n = 69)	Placebo (n = 58)
Median PFS (95% CI), mo	2.8 (1.5 to 3.7)	1.9 (1.4 to 4.1)	1.4 (1.4 to 1.5)	1.5 (1.4 to 2.5)	1.6 (1.4 to 2.6)	1.4 (1.4 to 1.5)
PFS HR (95% CI)*	0.65 (0.43 to 0.99)	0.67 (0.45 to 1.01)	–	0.72 (0.50 to 1.05)	0.63 (0.44 to 0.91)	–
ORR (95% CI), %	8.0 (2.2 to 19.2)	9.8 (3.3 to 21.4)	5.6 (1.2 to 15.4)	11.5 (4.7 to 22.2)	13.2 (6.2 to 23.6)	0.0 (0.0 to 6.6)

Abbreviations: CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ORR, objective response rate; mo, months; PFS, progression-free survival.

^aVersus placebo.

Fig A1. Study design.

*Patients receiving only three cycles of chemotherapy due to toxicity were eligible if they had an ongoing complete response (CR) or partial response (PR) after the third cycle.

†All patients were randomized ≤ 9 weeks from the last dose of first-line chemotherapy, or ≤ 11 weeks for those receiving prophylactic cranial irradiation (PCI) or whole brain radiotherapy.

‡Patients could be treated beyond progression under protocol-defined circumstances.

§Secondary endpoints to be tested hierarchically if the primary endpoint was met.

||Per blinded independent central review.

Abbreviations: 1L, first-line; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ED-SCLC, extensive-disease small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomization; SD, stable disease; TMB, tumor mutational burden.

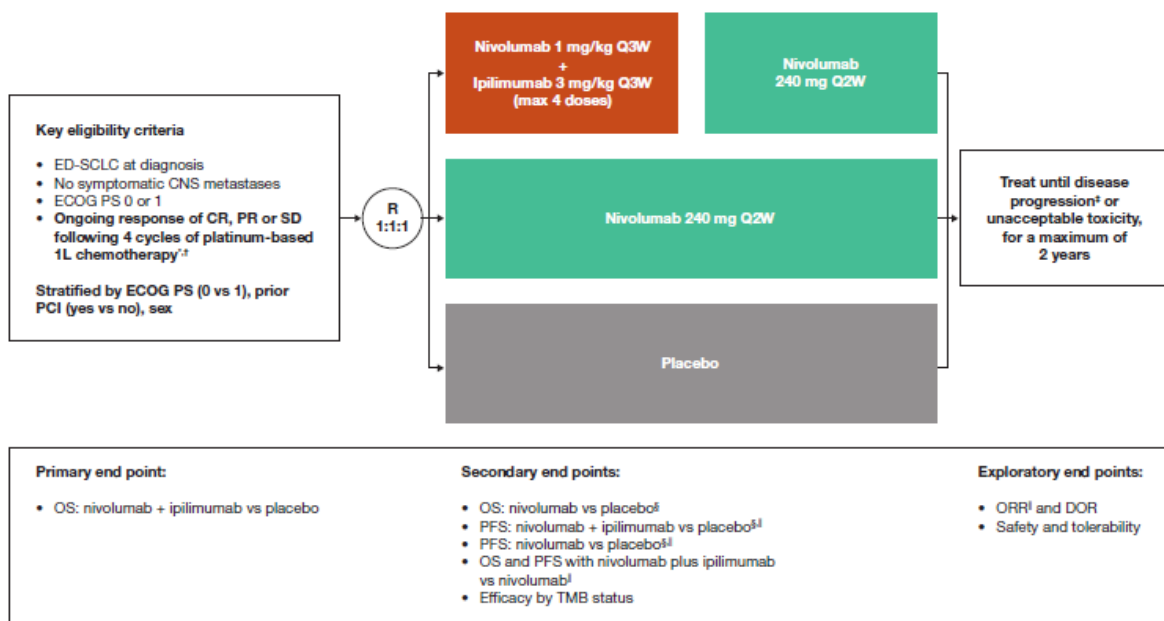


Fig A2. Consolidated standards of reporting trials (CONSORT) flow chart of patient disposition.

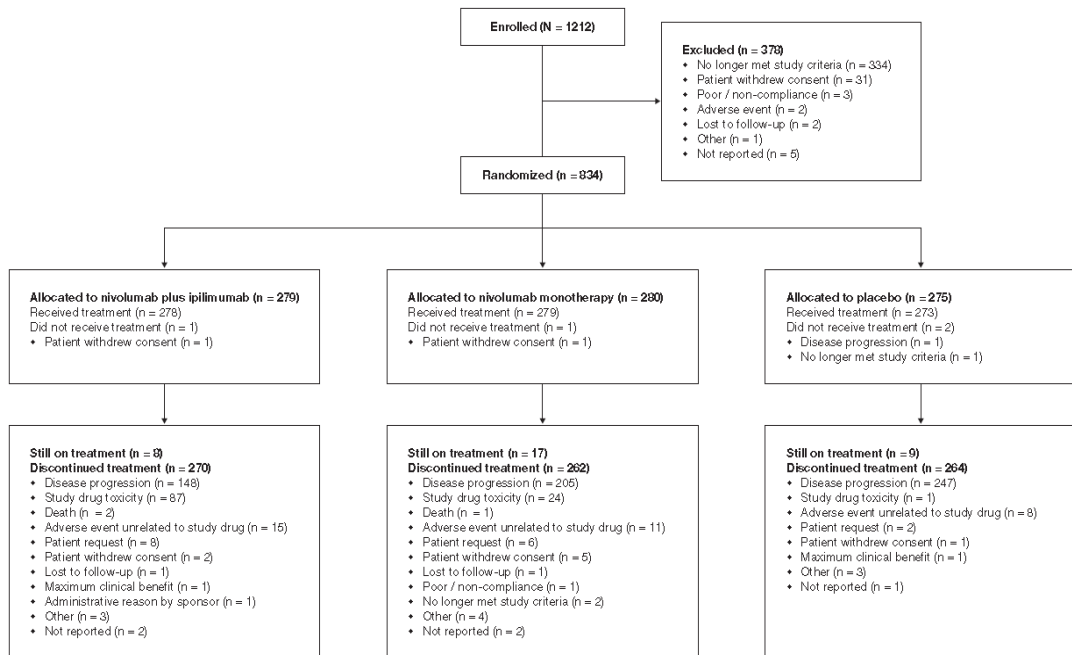
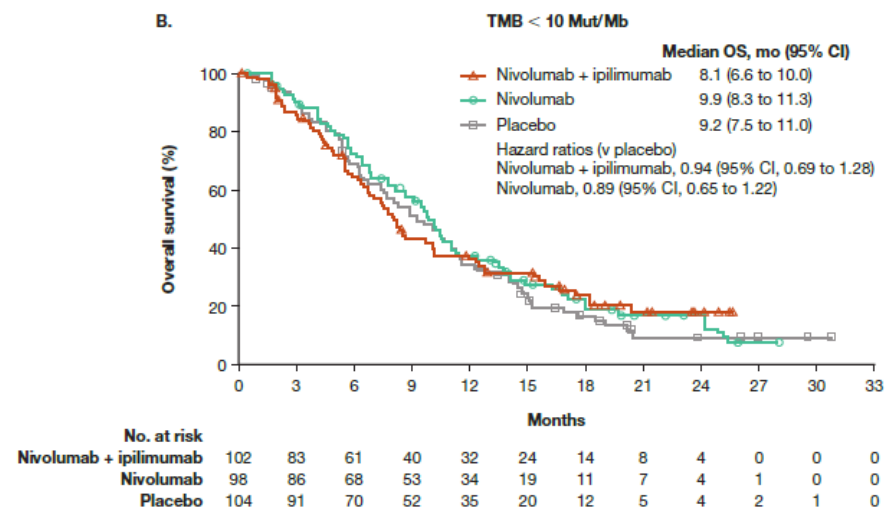
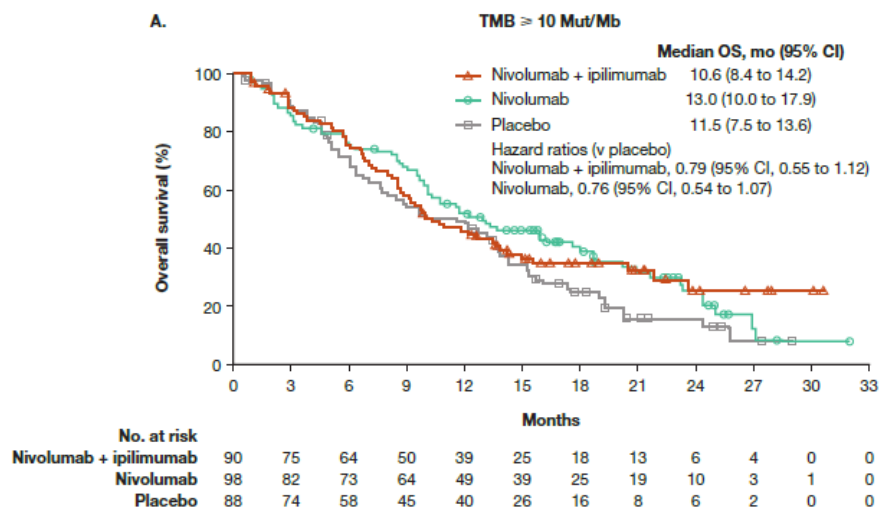
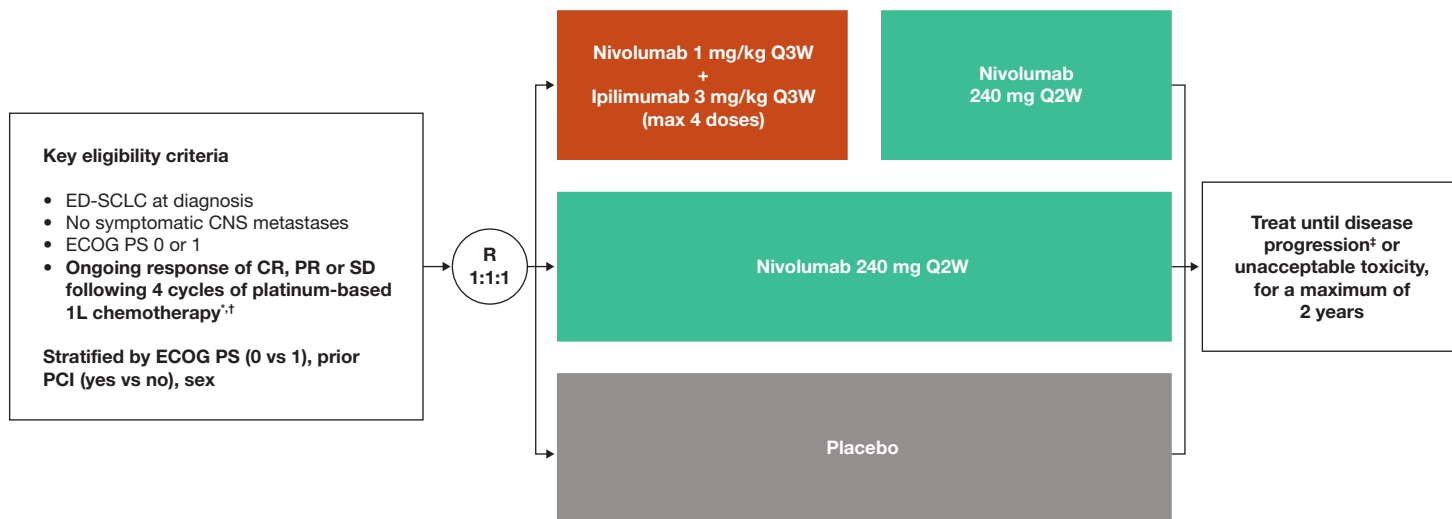


Fig A3. Overall survival (OS) with nivolumab plus ipilimumab versus nivolumab versus placebo by tumor mutational burden (TMB) ≥ 10 mut/Mb (A) and < 10 mut/Mb (B).



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**Primary end point:**

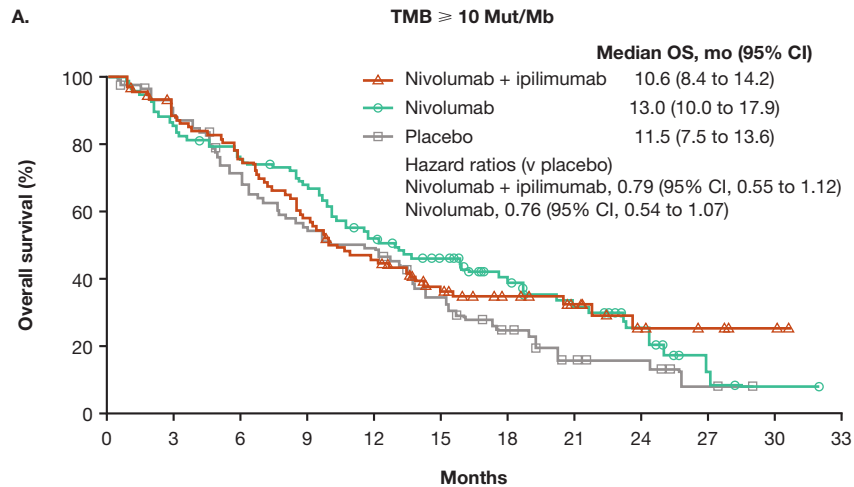
- OS: nivolumab + ipilimumab vs placebo

Secondary end points:

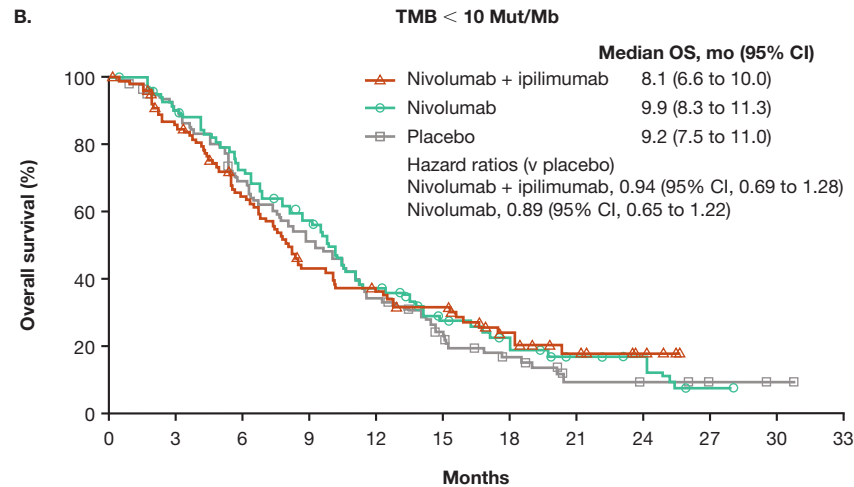
- OS: nivolumab vs placebo[§]
- PFS: nivolumab + ipilimumab vs placebo^{§,||}
- PFS: nivolumab vs placebo^{§,||}
- OS and PFS with nivolumab plus ipilimumab vs nivolumab^{||}
- Efficacy by TMB status

Exploratory end points:

- ORR^{||} and DOR
- Safety and tolerability



	No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Nivolumab + ipilimumab	90	75	64	50	39	25	18	13	6	4	0	0	0
Nivolumab	98	82	73	64	49	39	25	19	10	3	1	0	0
Placebo	88	74	58	45	40	26	16	8	6	2	0	0	0



	No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Nivolumab + ipilimumab	102	83	61	40	32	24	14	8	4	0	0	0	0
Nivolumab	98	86	68	53	34	19	11	7	4	1	0	0	0
Placebo	104	91	70	52	35	20	12	5	4	2	1	0	0