Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Carbone DP, Reck M, Paz-Ares L, et al. First-line nivolumab in stage IV or recurrent non–small-cell lung cancer. N Engl J Med 2017;376:2415-26. DOI: 10.1056/NEJMoa1613493

Supplementary Appendix

First-line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

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Supplemental Text

Analyses of tumor mutation burden

RNA and DNA isolation

DNA and RNA was co-isolated from archival tumor tissue using the Allprep DNA/RNA FFPE kit (Qiagen, Hilden, Germany). DNA from whole blood (germline DNA) was isolated using the QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany) following the manufacturer's instructions.

Whole exome capture and sequencing

Genomic DNA (150 ng) was used for library preparation using the Agilent SureSelectXT reagent kit (Agilent Technologies, Santa Clara, USA) with the on-bead modifications of Fisher et al, 2011.[1] A total of 500 ng of enriched library was used in the hybridization and captured with the SureSelect All Exon v5 (Agilent Technologies, Santa Clara, USA) bait. Following hybridization, the captured libraries were purified according to the manufacturer's recommendations and amplified by polymerase chain reaction (11 cycles). Normalized libraries were pooled and DNA was sequenced on the Illumina HiSeq 2500 using 2 x 100-bp paired-end reads; an average of 84 million reads were sequenced per tumor sample (average 84.6 x the mean tumor target coverage), and an average of 89 million reads were sequenced per germline sample (average 93 x the mean germline target coverage).

Tumor mutation burden determination

Whole exome sequencing data were used to generate tumor mutation burden (total number of missense mutations) for each patient. Missense mutations were identified from paired tumor-

germline whole exome sequencing data using two mutation callers.[2, 3] The union of the two callers was used to calculate the tumor mutation burden.

Figure S1A. Consolidated Standards of Reporting Trials (CONSORT) Diagram of Patient Disposition.

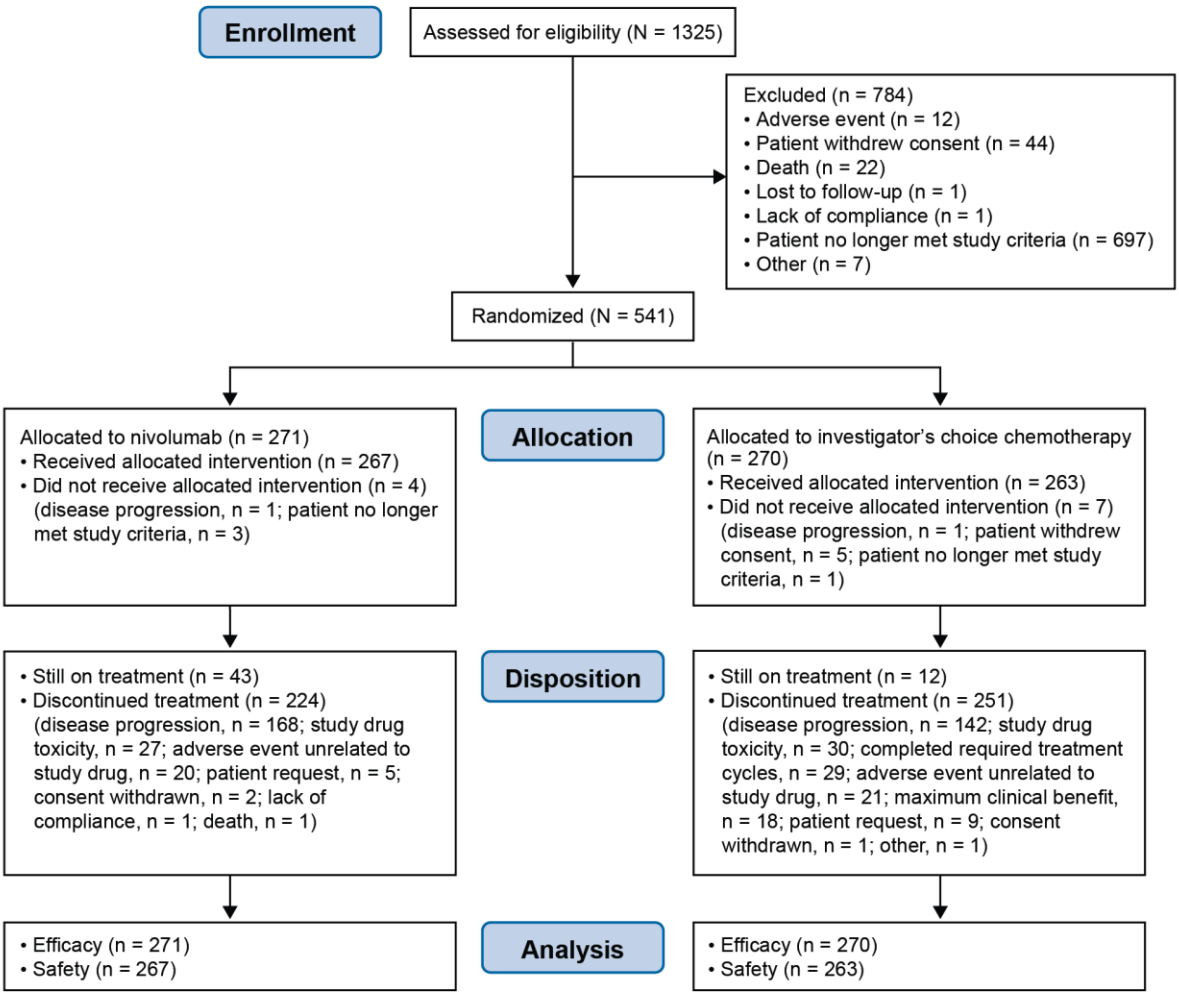
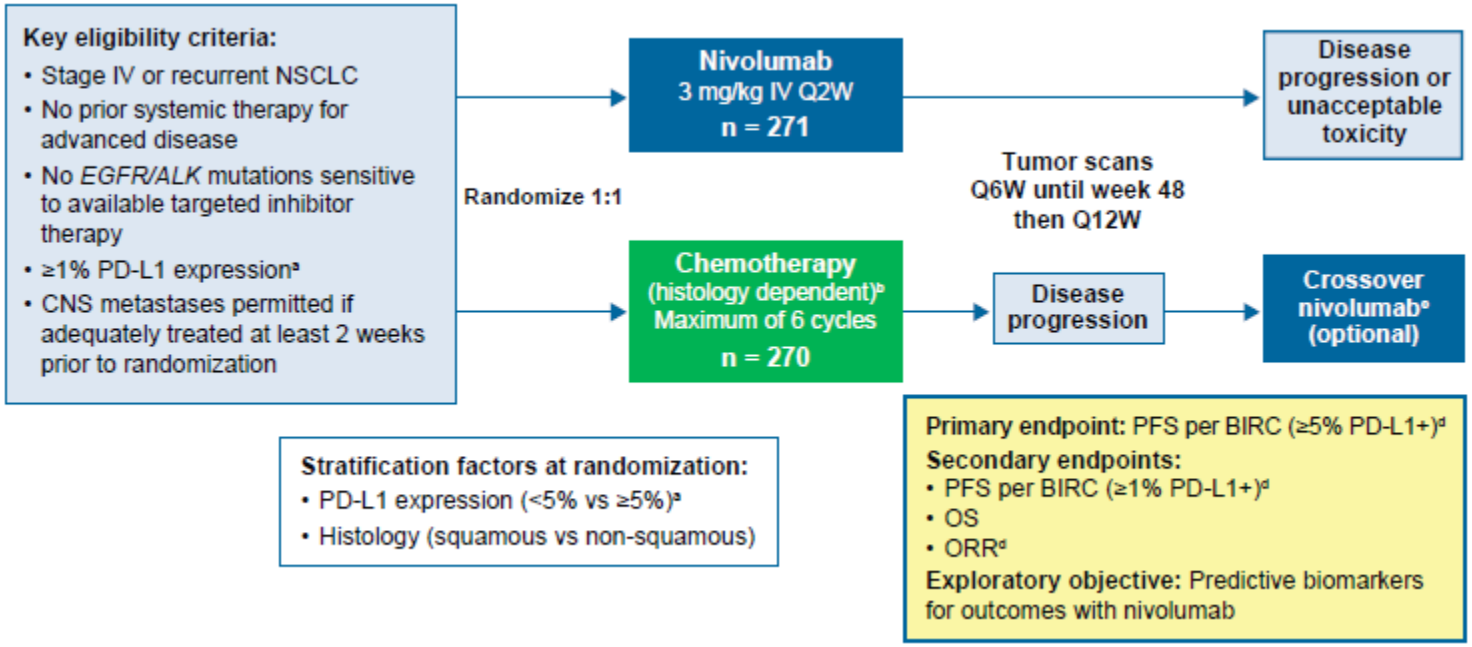


Figure S1B. Study Design.



[a]Dako 28-8 validated; archival tumor samples obtained ≤6 months before enrollment were permitted; PD-L1 testing was centralized.

[b]Squamous: gemcitabine 1250 mg/m^2 + cisplatin 75 mg/m^2; gemcitabine 1000 mg/m^2 + carboplatin AUC 5; paclitaxel 200 mg/m^2 + carboplatin AUC 6; nonsquamous: pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2; pemetrexed 500 mg/m^2 + carboplatin AUC 6; option for pemetrexed maintenance therapy.

[c]Permitted if crossover eligibility criteria met, including progression confirmed by independent radiology review.

[d]Tumor response assessment for PFS and ORR per RECIST v1.1 as determined by independent central review.

ALK = anaplastic lymphoma kinase; CNS = central nervous system; *EGFR* = epidermal growth factor receptor; *IV* = intravenous; *NSCLC* = non-small cell lung cancer; *OS* = overall survival; *ORR* = objective response rate; *PD-L1* = programmed death-1 ligand 1; *PFS* = progression-free survival; *Q2W* = every 2 weeks; *Q6W* = every 6 weeks; *Q12W* = every 12 weeks; *RECIST* = response evaluation criteria in solid tumors.

Figure S2. Kaplan–Meier Plot of Progression-free Survival in All Randomized Patients.

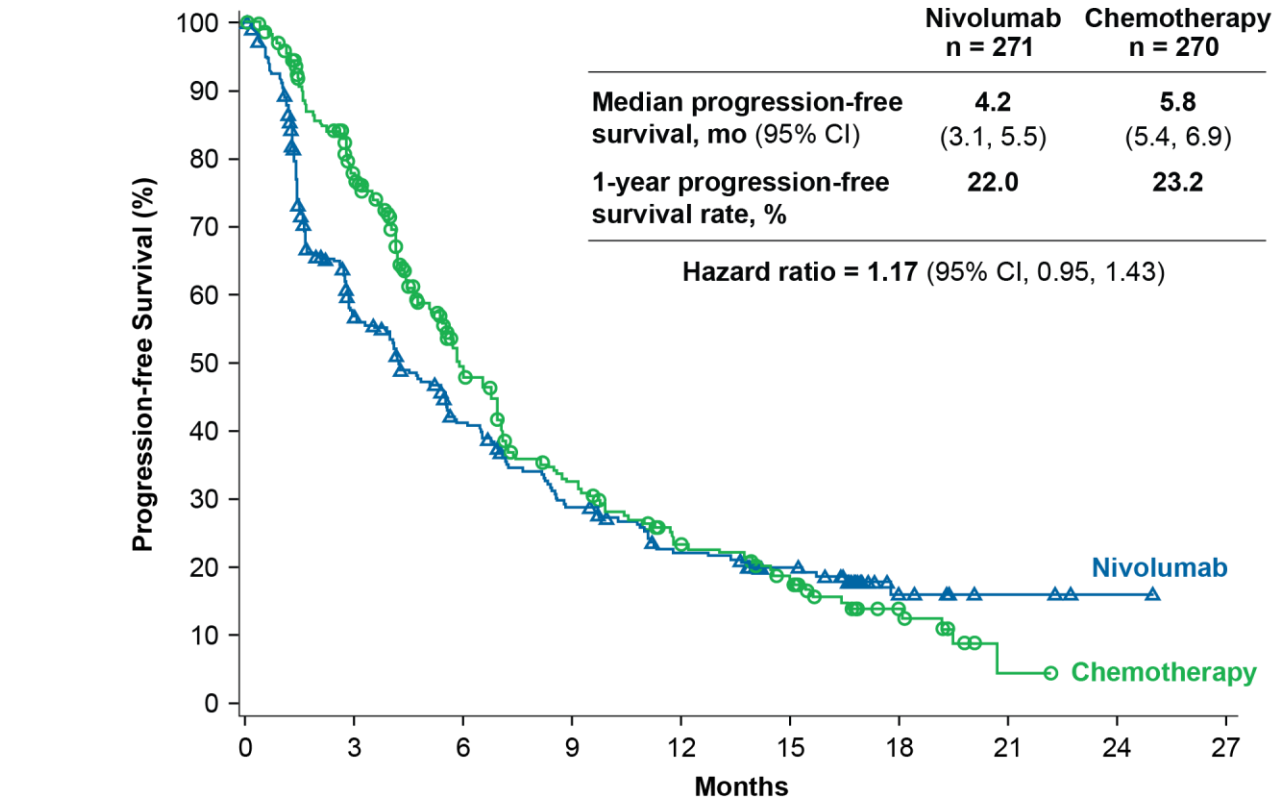


Figure S3. Kaplan–Meier Plot of Overall Survival in All Randomized Patients.

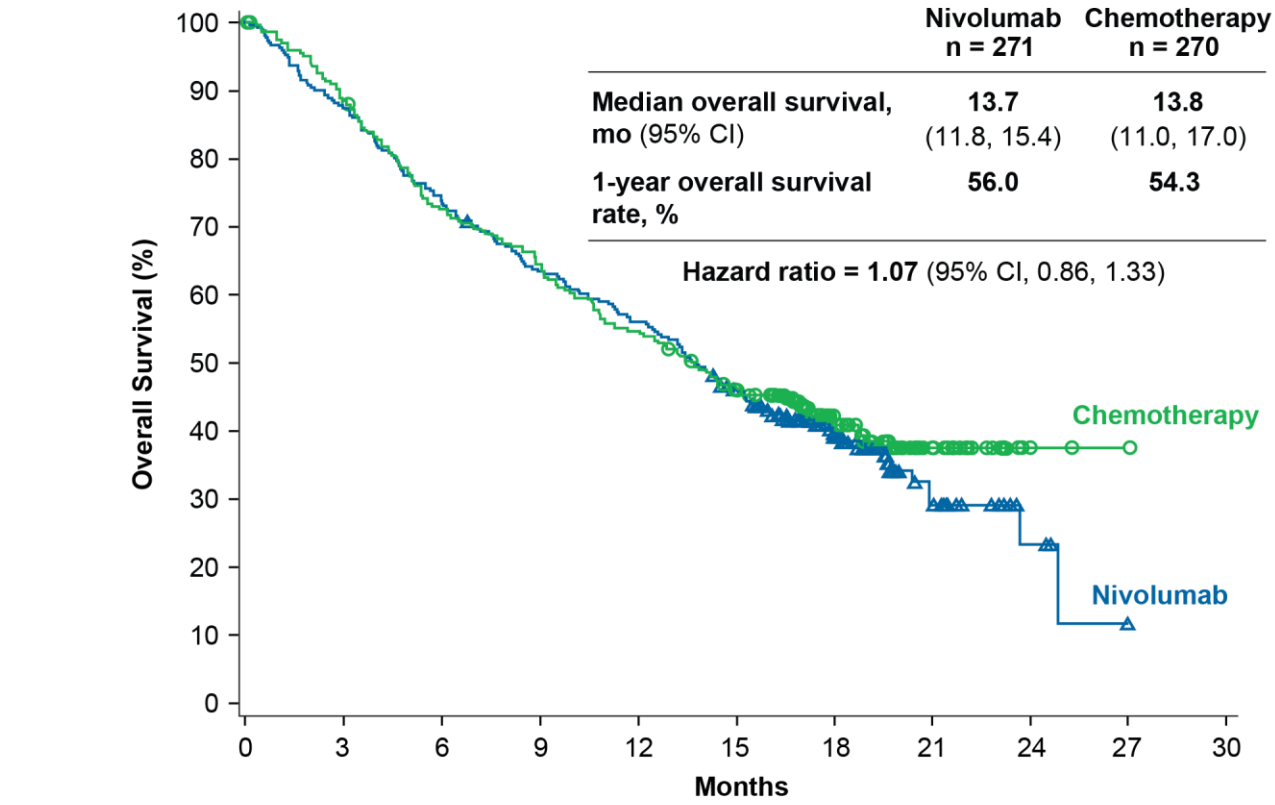


Figure S4A. Progression-free Survival in Subgroups of Patients with ≥5% PD-L1 Expression.

Subgroup	Nivolumab n	Nivolumab Median Progression-free Survival, mo	Chemotherapy n	Chemotherapy Median Progression-free Survival, mo	Unstratified Hazard Ratio (95% CI)
Overall	211	4.2	212	5.9	1.18 (0.94, 1.49)
≥65 yr	92	4.2	104	5.7	1.30 (0.93, 1.82)
<65 yr	119	5.4	108	6.5	1.11 (0.81, 1.54)
Male	143	4.2	118	5.8	1.14 (0.84, 1.53)
Female	68	4.1	94	6.0	1.20 (0.82, 1.74)
ECOG PS = 0	66	4.5	77	7.2	1.67 (1.12, 2.49)
ECOG PS ≥1	144	4.1	135	5.4	0.99 (0.75, 1.32)
Squamous	48	3.3	48	4.7	0.87 (0.53, 1.41)
Nonsquamous	163	4.2	164	6.8	1.24 (0.95, 1.62)
Never smoker	22	2.9	24	6.8	2.39 (1.16, 4.93)
Former smoker	145	4.2	145	5.7	1.11 (0.84, 1.47)
Current smoker	42	5.4	39	6.9	1.07 (0.63, 1.79)
≥50% PD-L1+	88	5.4	126	5.8	1.07 (0.77, 1.49)

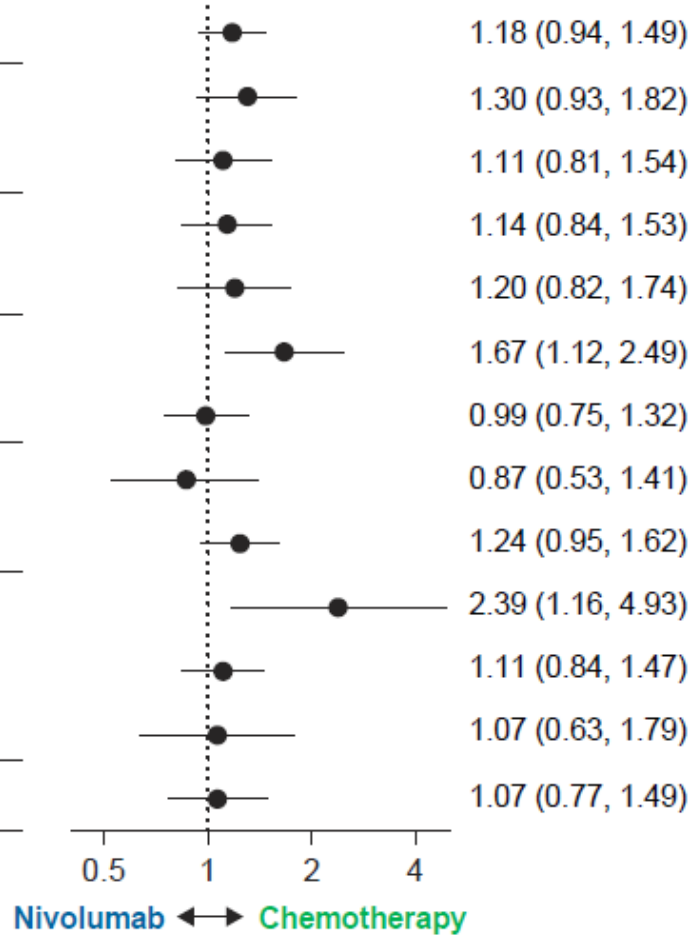


Figure S4B. Overall Survival in Subgroups of Patients with ≥5% PD-L1 Expression.

Subgroup	Nivolumab n	Nivolumab Median Overall Survival, mo	Chemotherapy n	Chemotherapy Median Overall Survival, mo	Unstratified Hazard Ratio (95% CI)
Overall	211	14.4	212	13.2	1.03 (0.81, 1.32)
≥65 yr	92	14.7	104	11.0	0.98 (0.69, 1.38)
<65 yr	119	14.4	108	16.7	1.10 (0.77, 1.56)
Male	143	13.3	118	10.7	0.98 (0.72, 1.33)
Female	68	18.0	94	16.7	1.00 (0.66, 1.53)
ECOG PS = 0	66	18.7	77	18.0	1.01 (0.63, 1.59)
ECOG PS ≥1	144	13.2	135	11.0	0.99 (0.74, 1.32)
Squamous	48	10.9	48	10.6	0.77 (0.48, 1.25)
Nonsquamous	163	14.5	164	16.5	1.13 (0.84, 1.50)
Never smoker	22	13.5	24	11.8	1.09 (0.53, 2.25)
Former smoker	145	15.2	145	12.9	1.04 (0.77, 1.40)
Current smoker	42	15.1	39	15.0	1.00 (0.56, 1.79)
≥50% PD-L1+	88	15.9	126	13.9	0.90 (0.63, 1.29)

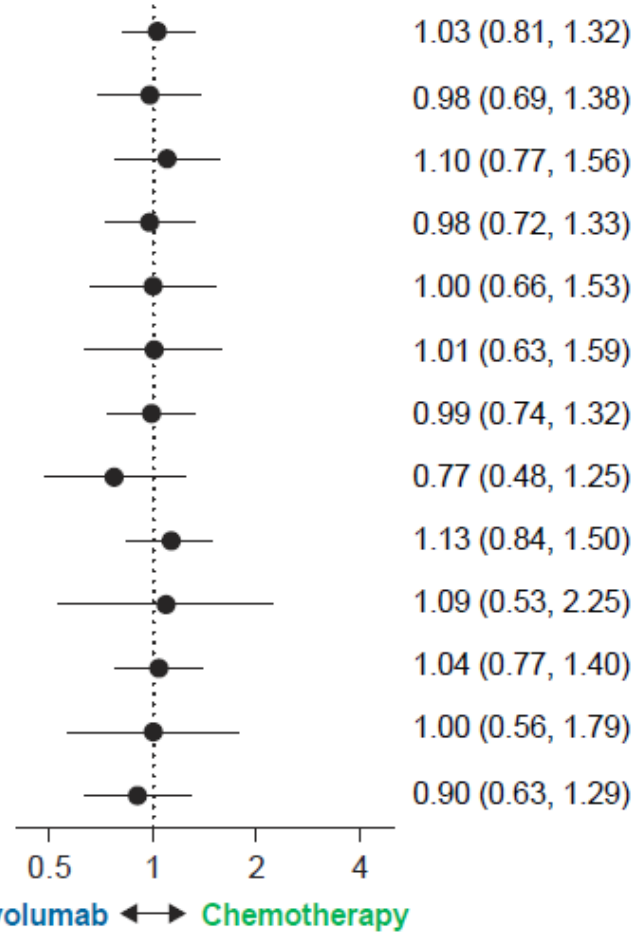
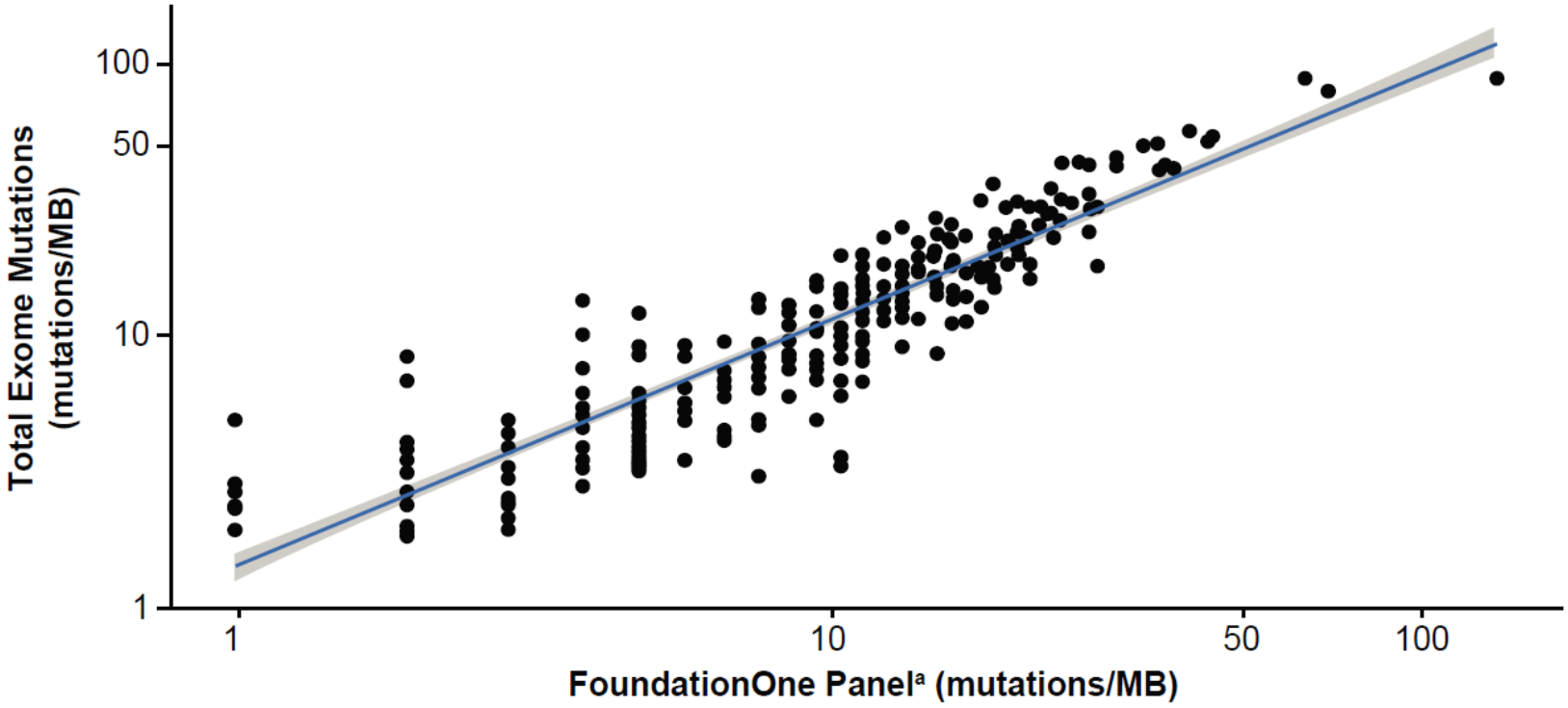


Figure S5. Total Exome Mutations Versus Genes in FoundationOne Panel[a]



[a]Based on in silico analysis filtering on 315 genes in FoundationOne comprehensive genomic profile (Foundation Medicine, Inc, Cambridge, MA, USA)[4]

Figure S6. Kaplan–Meier Plot of Progression-free Survival in Patients Evaluable for Tumor Mutation Burden.

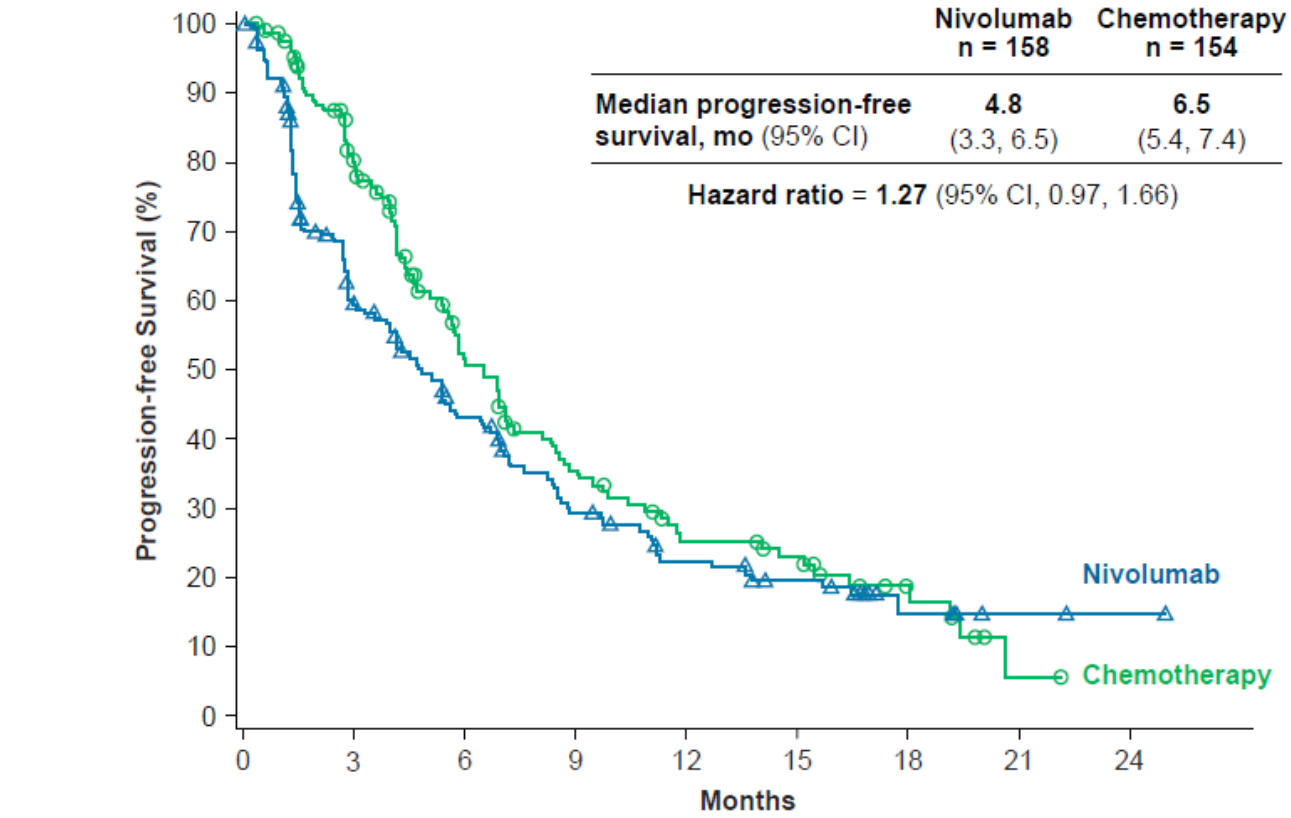


Figure S7. Kaplan–Meier Plot of Overall Survival in Patients Evaluable for Tumor Mutation Burden.

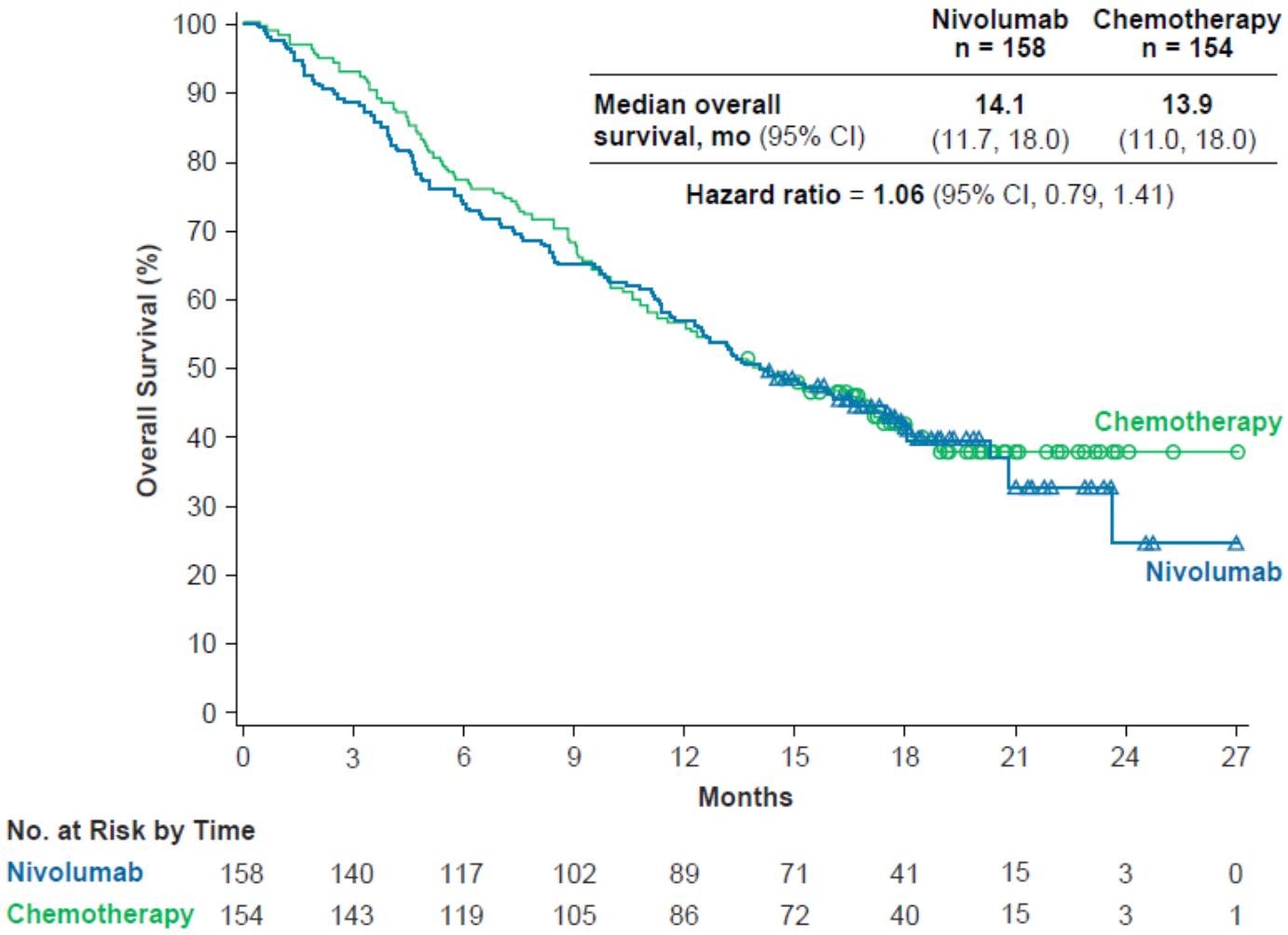


Figure S8. Kaplan–Meier Plot Overall Survival in Evaluable Patients with High Tumor Mutation Burden.

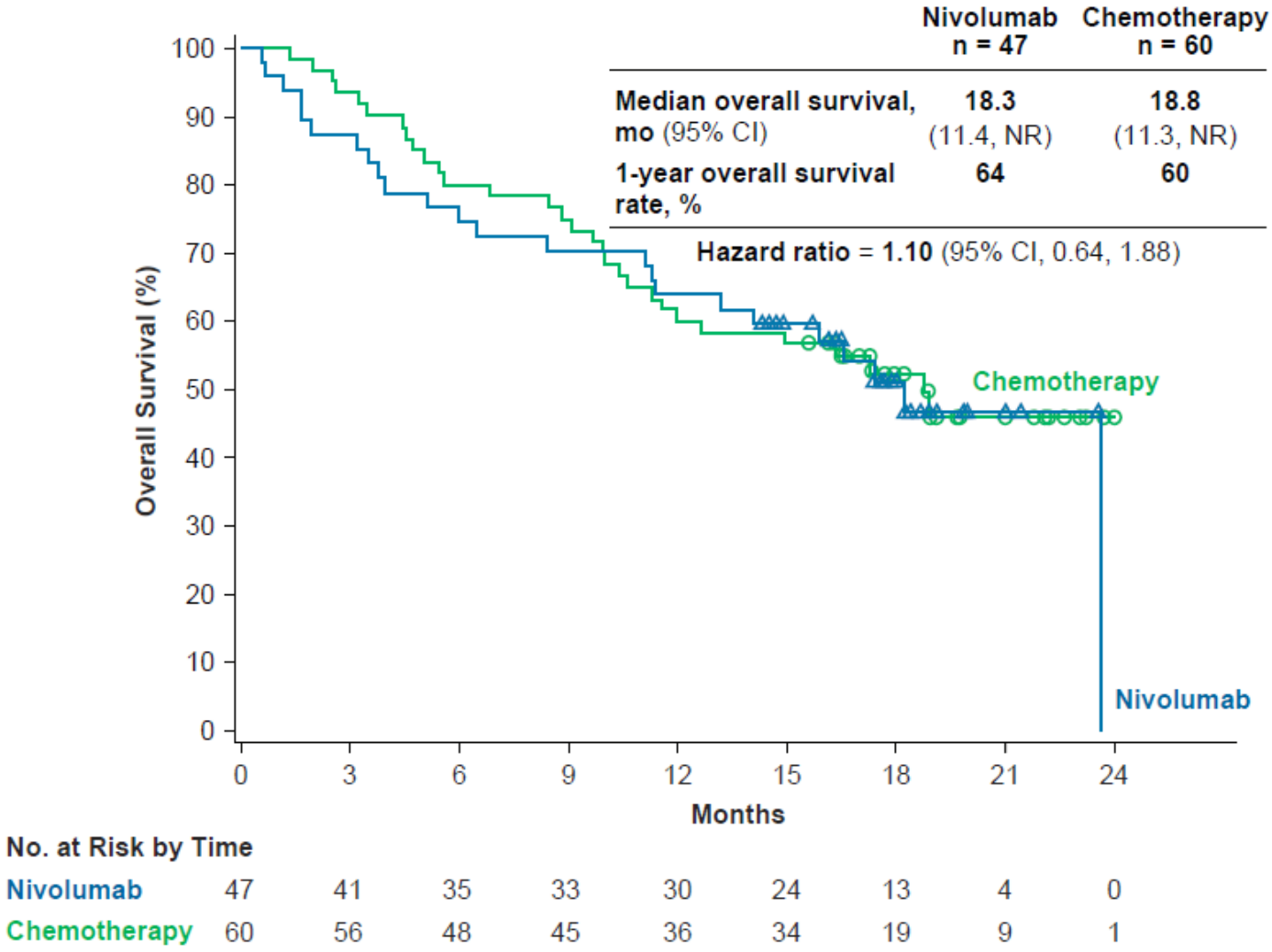


Figure S9. Kaplan–Meier Plot of Overall Survival in Evaluable Patients with Low or Medium Tumor Mutation Burden.

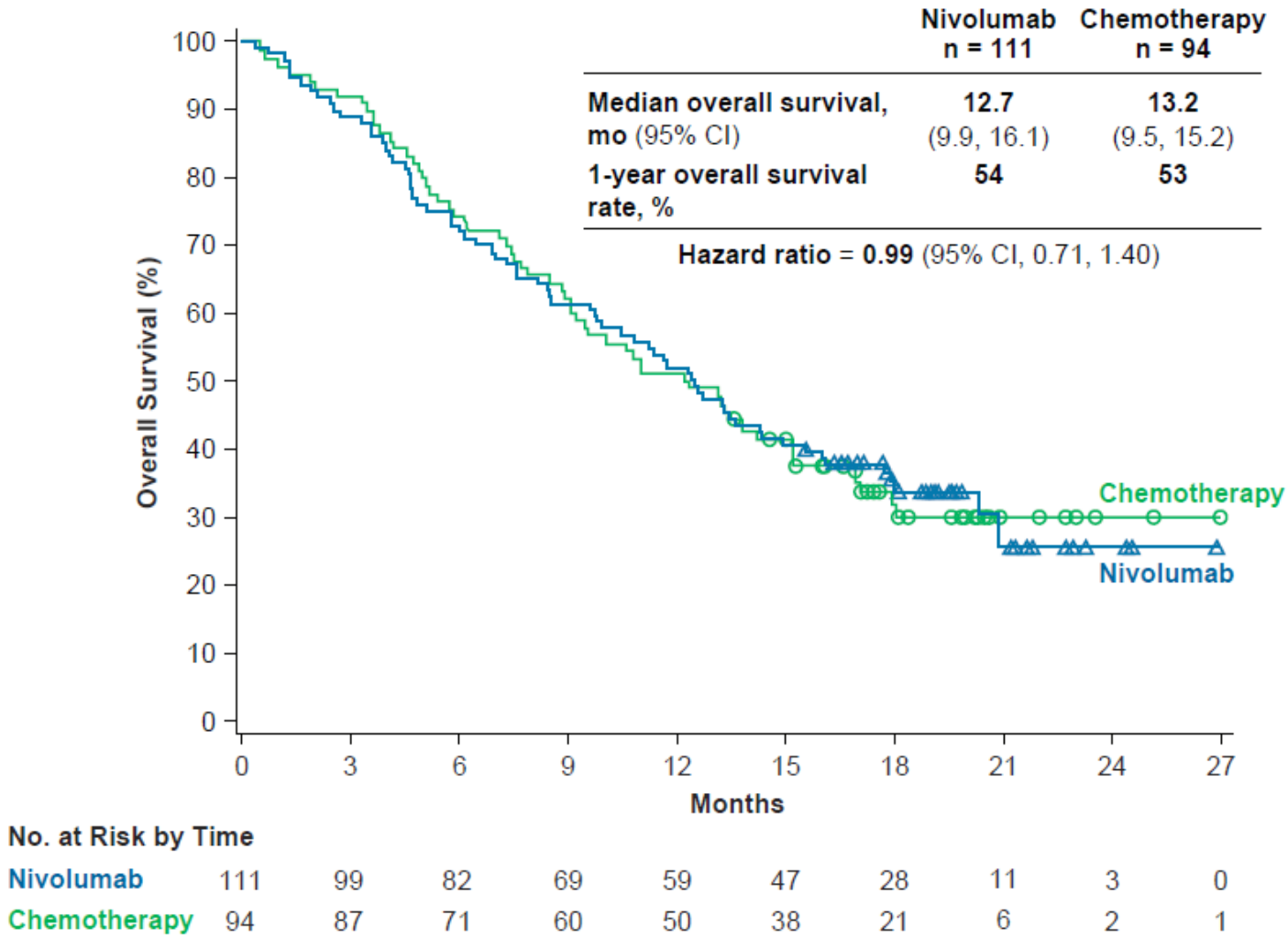
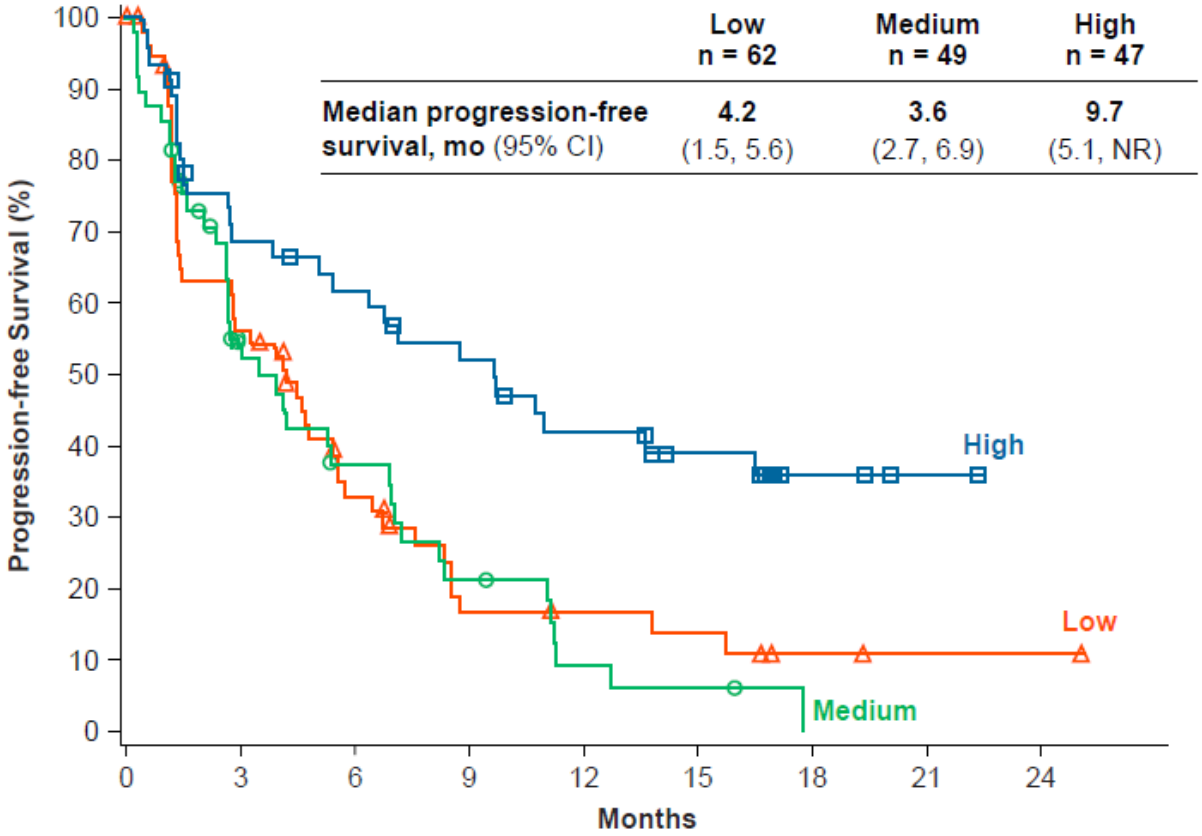
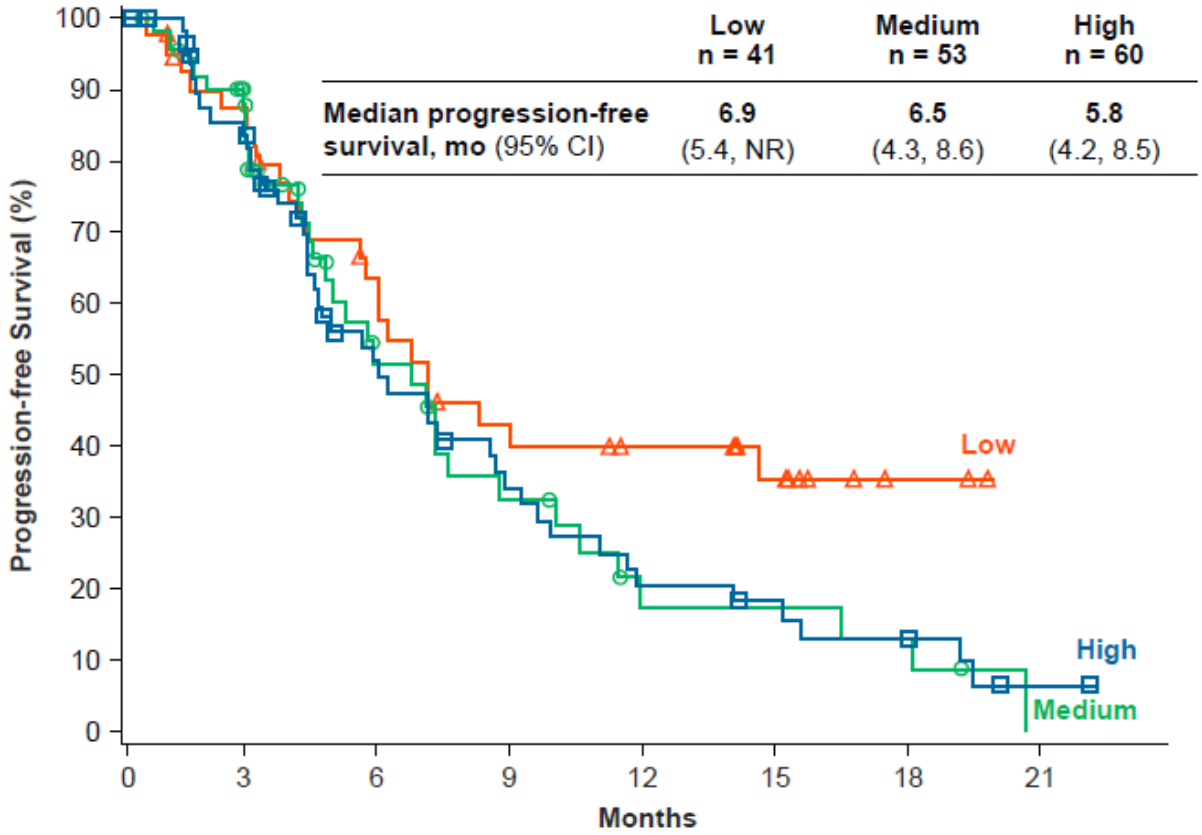


Figure S10. Kaplan–Meier Plot of Progression-free Survival by Tumor Mutation Burden (TMB) Tertile in the Nivolumab Arm.



TMB	No. at Risk by Time								
Low	62	32	16	7	6	5	2	1	1
Medium	49	22	14	8	3	2	0	0	0
High	47	30	26	21	16	12	4	1	0

Figure S11. Kaplan–Meier Plot of Progression-free Survival by Tumor Mutation Burden (TMB) Tertile in the Chemotherapy Arm.



TMB	No. at Risk by Time							
Low	41	31	20	13	11	8	2	0
Medium	53	34	17	10	4	4	3	0
High	60	42	22	15	9	7	4	1

Figure S12. Overall Response by Tumor Mutation Burden.

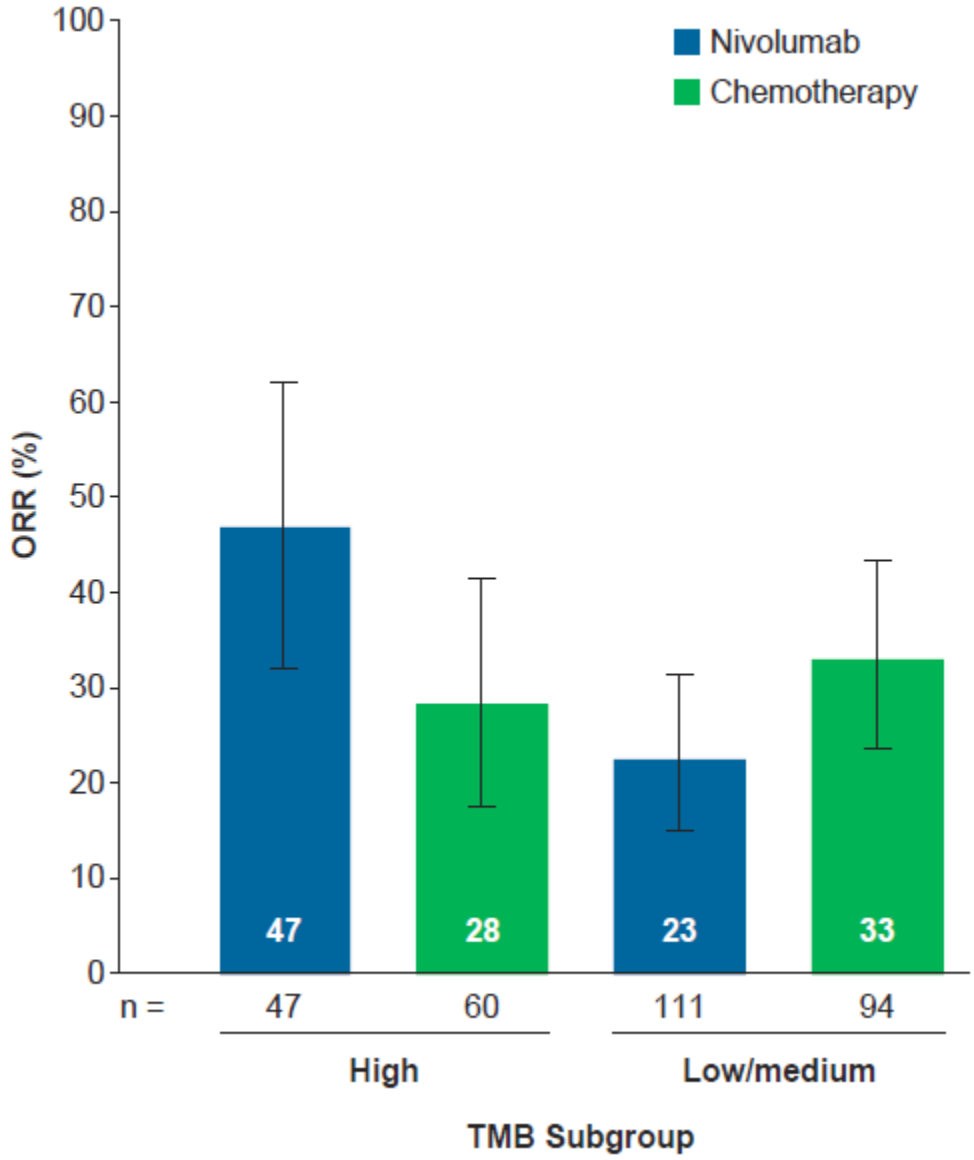
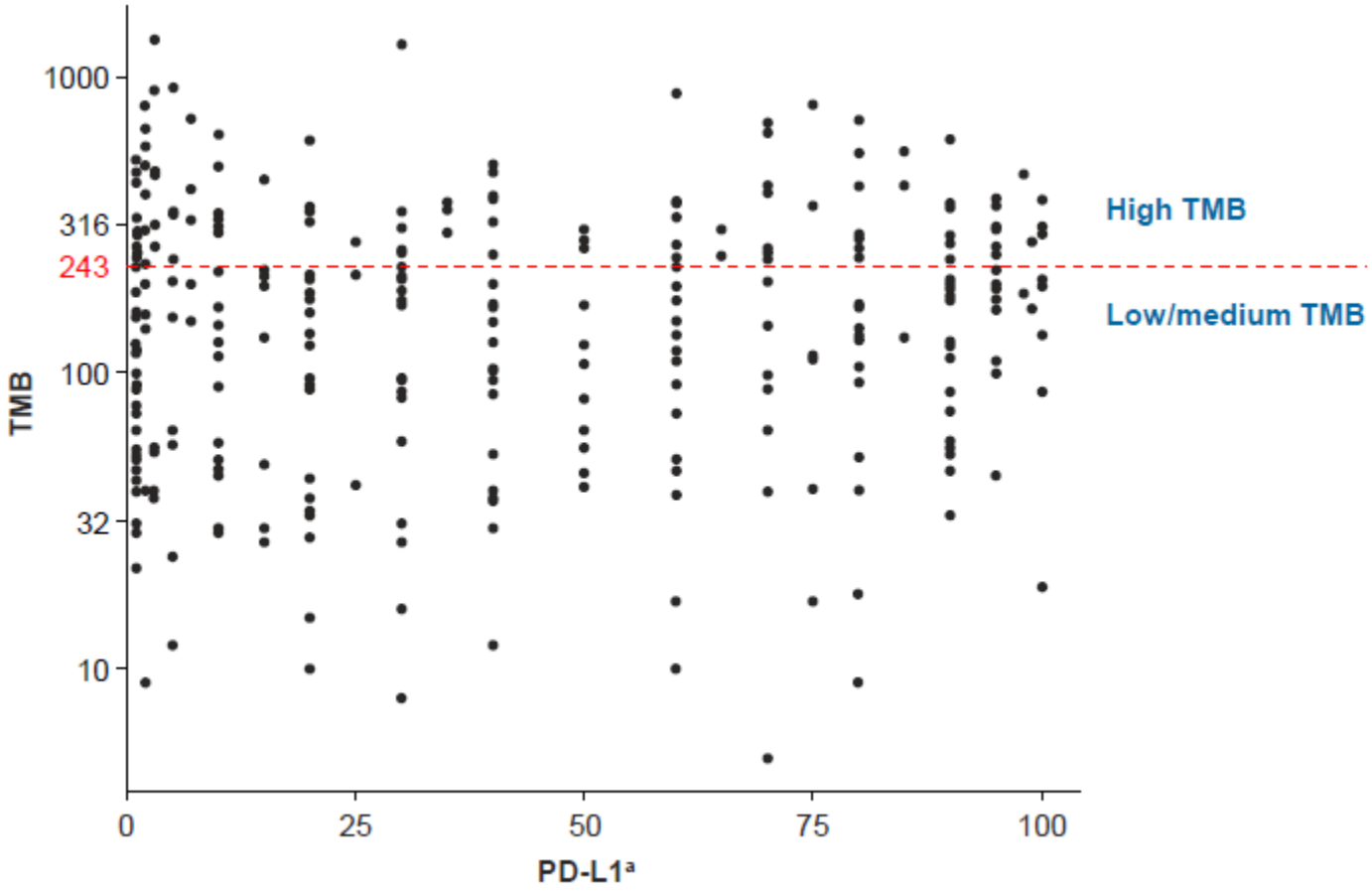


Figure S13. Analysis of the Association Between Tumor Mutation Burden and PD-L1 Expression[a] in Evaluable Patients.



Pearson's correlation coefficient = 0.059

[a]All patients in Checkmate 026 had ≥1% PD-L1 tumor expression

Figure S14. Overall Response by Tumor Mutation Burden and PD-L1 Expression.

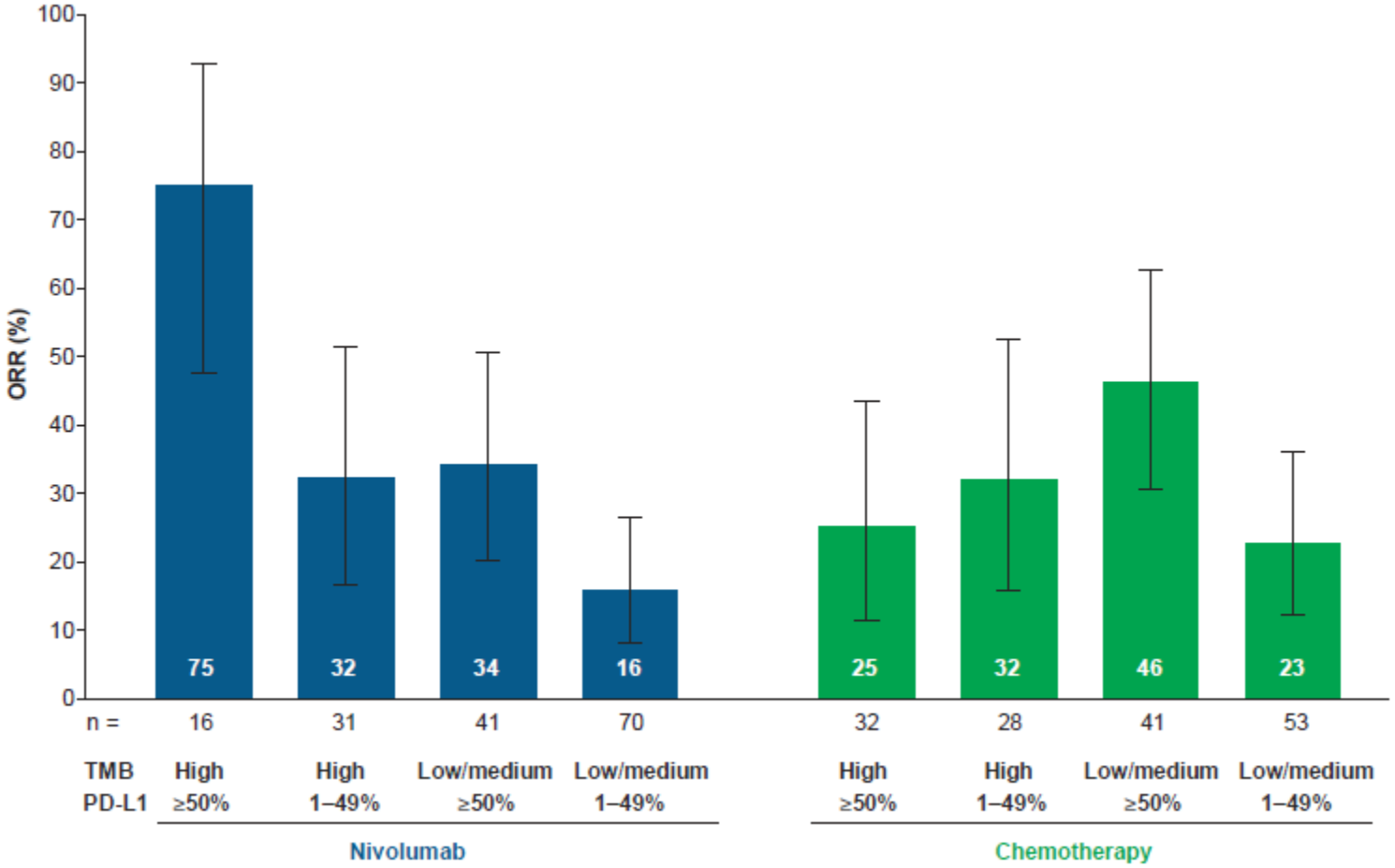


Table S1. End-of-Treatment Summary (All Treated Patients).

	Nivolumab n = 267	**Chemotherapy n = 263**
Patients continuing in the treatment period, n (%)	43 (16.1)	12 (4.6)
Patients not continuing in the treatment period, n (%)	224 (83.9)	251 (95.4)
Reason for not continuing in the treatment period, n (%)		
Disease progression	168 (62.9)	142 (54.0)
Study drug toxicity	27 (10.1)	30 (11.4)
Death	1 (0.4)	0
Adverse event unrelated to study drug	20 (7.5)	21 (8.0)
Patient request to discontinue study treatment	5 (1.9)	9 (3.4)
Patient withdrew consent	2 (0.7)	1 (0.4)
Maximum clinical benefit	0	18 (6.8)
Lack of compliance	1 (0.4)	0
Other	0	1 (0.4)
Completed required treatment cycles	0	29 (11.0)

Table S2. Baseline Characteristics of All Randomized Patients.

Characteristic	Nivolumab (n = 271)	Chemotherapy (n = 270)	Total (N = 541)
Age, year			
Median	63	65	64
Range	32–89	29–87	29–89
Age category, n (%)			
<65 years	148 (54.6)	133 (49.3)	281 (51.9)
≥65 to <75 years	93 (34.3)	105 (38.9)	198 (36.6)
≥75 years	30 (11.1)	32 (11.9)	62 (11.5)
Sex, n (%)			
Male	184 (67.9)	148 (54.8)	332 (61.4)
Female	87 (32.1)	122 (45.2)	209 (38.6)
Race, n (%)			
White	228 (84.1)	242 (89.6)	470 (86.9)
Black	6 (2.2)	10 (3.7)	16 (3.0)
Asian	30 (11.1)	17 (6.3)	47 (8.7)
American Indian or Alaska native	1 (0.4)	0	1 (0.2)
Other	6 (2.2)	1 (0.4)	7 (1.3)
Disease stage, n (%)			
Stage IV	255 (94.1)	244 (90.4)	499 (92.2)
Recurrent	16 (5.9)	25 (9.3)	41 (7.6)
Not reported	0	1 (0.4)	1 (0.2)
ECOG performance-status score, n (%)			
0	85 (31.4)	93 (34.4)	178 (32.9)
1	183 (67.5)	174 (64.4)	357 (66.0)
≥2	2 (0.7)	3 (1.1)	5 (0.9)
Not reported	1 (0.4)	0	1 (0.2)
Smoking status, n (%)			
Never smoker	30 (11.1)	29 (10.7)	59 (10.9)

Former smoker	186 (68.6)	182 (67.4)	368 (68.0)
Current smoker	52 (19.2)	55 (20.4)	107 (19.8)
Unknown	3 (1.1)	4 (1.5)	7 (1.3)
Prior systemic therapy, n (%)			
Adjuvant	22 (8.1)	25 (9.3)	47 (8.7)
Neoadjuvant	5 (1.8)	4 (1.5)	9 (1.7)
Prior radiotherapy, n (%)	102 (37.6)	107 (39.6)	209 (38.6)
Tumor histology, n (%)			
Squamous cell carcinoma	66 (24.4)	64 (23.7)	130 (24.0)
Nonsquamous cell carcinoma	205 (75.6)	206 (76.3)	411 (76.0)
Selected sites of metastatic lesions, n (%)			
Brain	33 (12.2)	36 (13.3)	69 (12.8)
Liver	54 (19.9)	36 (13.3)	90 (16.6)
Median sum of target lesion diameters, mm (range)	82.5 (14–218)	68.0 (15–272)	76.0 (14–272)
PD-L1 expression level, n (%)			
≥5%	208 (76.8)	210 (77.8)	418 (77.3)
≥25%	132 (48.7)	164 (60.7)	296 (54.7)
≥50%	88 (32.5)	126 (46.7)	214 (39.6)
≥75%	56 (20.7)	74 (27.4)	130 (24.0)

ECOG = Eastern Cooperative Oncology Group.

Table S3. Baseline Characteristics of Patients with ≥5% PD-L1 Expression.

Characteristic	Nivolumab (n = 211)	Chemotherapy (n = 212)	Total (N = 423)
Age, year			
Median	63	64	64
Range	32–89	29–87	29–89
Age category, n (%)			
<65 years	119 (56.4)	108 (50.9)	227 (53.7)
≥65 to <75 years	66 (31.3)	78 (36.8)	144 (34.0)
≥75 years	26 (12.3)	26 (12.3)	52 (12.3)
Sex, n (%)			
Male	143 (67.8)	118 (55.7)	261 (61.7)
Female	68 (32.2)	94 (44.3)	162 (38.3)
Race, n (%)			
White	177 (83.9)	186 (87.7)	363 (85.8)
Black	5 (2.4)	8 (3.8)	13 (3.1)
Asian	25 (11.8)	17 (8.0)	42 (9.9)
American Indian or Alaska native	1 (0.5)	0	1 (0.2)
Other	3 (1.4)	1 (0.5)	4 (0.9)
Disease stage, n (%)			
Stage IV	198 (93.8)	191 (90.1)	389 (92.0)
Recurrent	13 (6.2)	20 (9.4)	33 (7.8)
Not reported	0	1 (0.5)	1 (0.2)
ECOG performance-status score, n (%)			
0	66 (31.3)	77 (36.3)	143 (33.8)
1	142 (67.3)	132 (62.3)	274 (64.8)
≥2	2 (0.9)	3 (1.4)	5 (1.2)
Not reported	1 (0.5)	0	1 (0.2)
Smoking status, n (%)			
Never smoker	22 (10.4)	24 (11.3)	46 (10.9)

Former smoker	145 (68.7)	145 (68.4)	290 (68.6)
Current smoker	42 (19.9)	39 (18.4)	81 (19.1)
Unknown	2 (0.9)	4 (1.9)	6 (1.4)
Prior systemic therapy, n (%)			
Adjuvant	17 (8.1)	19 (9.0)	36 (8.5)
Neoadjuvant	2 (0.9)	3 (1.4)	5 (1.2)
Prior radiotherapy, n (%)	79 (37.4)	84 (39.6)	163 (38.5)
Tumor histology, n (%)			
Squamous cell carcinoma	48 (22.7)	48 (22.6)	96 (22.7)
Nonsquamous cell carcinoma	163 (77.3)	164 (77.4)	327 (77.3)
Selected sites of metastatic lesions, n (%)			
Brain	28 (13.3)	26 (12.3)	54 (12.8)
Liver	41(19.4)	26 (12.3)	67 (15.8)
Median sum of target lesion diameters, mm (range)	83.0 (14–215)	70.0 (15–272)	79.0 (14–272)
PD-L1 expression level, n (%)			
≥25%	132 (62.6)	164 (77.4)	296 (70.0)
≥50%	88 (41.7)	126 (59.4)	214 (50.6)
≥75%	56 (26.5)	74 (34.9)	130 (30.7)

Table S4. Chemotherapy Study Treatments (All Treated Patients).

Study treatments, n (%)	**Chemotherapy n = 263**
Pemetrexed/carboplatin	115 (43.7)
Pemetrexed/cisplatin	86 (32.7)
Gemcitabine/carboplatin	33 (12.5)
Gemcitabine/cisplatin	13 (4.9)
Paclitaxel/carboplatin	16 (6.1)
Maintenance pemetrexed, n (%)	100 (38.0)

Table S5. Subsequent Systemic Therapy in Patients with ≥5% PD-L1 Expression.

	Nivolumab n = 211	**Chemotherapy n = 212**
Subsequent systemic therapy[a], n (%)	92 (43.6)	136 (64.2)
Immunotherapy, n (%) Crossover nivolumab Post-study nivolumab Ipilimumab	3 (1.4) 0 2 (0.9) 1 (0.5)	128 (60.4) 122 (57.5) 7 (3.3) 0
ALK/EGFR tyrosine kinase inhibitors, n (%)	12 (5.7)	6 (2.8)
Experimental therapy, n (%)	2 (0.9)	2 (0.9)
Chemotherapy and other systemic anticancer agents, n (%)	88 (41.7)	30 (14.2)

ALK = anaplastic lymphoma kinase*; EGFR* = epidermal growth factor receptor*; PD-L1* = programmed death-1 ligand 1.

[a]Patients may have received more than one type of subsequent therapy

Table S6. Sample Attrition During Tumor Mutation Burden Determination.

Patients, n (%)	**Tumor DNA**	**Germline DNA[a]**
Randomized	541 (100)	541 (100)
Samples available for DNA extraction[b]	485 (90)	452 (84)
DNA available for sequencing	408 (75)	452 (84)
Successful preparation of next-generation sequencing library	402 (74)	452 (84)
Passed internal quality control[c]	320 (59)	432 (80)
Matched tumor-germline exome sequences for TMB analysis[d]	312 (58)	

[a]Matched germline DNA from whole blood was used to distinguish germline single-nucleotide polymorphisms from somatic missense mutations in the tumor DNA

[b]Samples were not available for various reasons, including but not limited to lack of patient pharmacogenetic consent, samples exhausted for PD-L1 testing, or poor tissue sampling

[c]Internal quality control included evaluation of factors including but not limited to discordance between tumor and germline DNA, too few sequence reads, and low or uneven target region coverage

[d]Eight patients with available tumor DNA sequences did not have matched germline DNA sequences

Table S7. Baseline Characteristics of All Randomized Patients and Patients with Evaluable Tumor Mutation Data.

Characteristic	All randomized patients (n = 541)	Patients with evaluable TMB data (n = 312)
Age, year		
Median	64	65
Range	29–89	32–89
Sex, n (%)		
Male	332 (61.4)	187 (59.9)
Female	209 (38.6)	125 (40.1)
Disease stage, n (%)		
Stage IV	499 (92.2)	291 (93.3)
Recurrent	41 (7.6)	20 (6.4)
Not reported	1 (0.2)	1 (0.3)
ECOG performance-status score, n (%)		
0	178 (32.9)	100 (32.1)
1	357 (66.0)	208 (66.7)
≥2	5 (0.9)	3 (1.0)
Not reported	1 (0.2)	1 (0.3)
Smoking status, n (%)		
Never smoker	59 (10.9)	29 (9.3)
Former smoker	368 (68.0)	223 (71.5)
Current smoker	107 (19.8)	56 (17.9)
Unknown	7 (1.3)	4 (1.3)
Tumor histology, n (%)		
Squamous cell carcinoma	130 (24.0)	71 (22.8)
Nonsquamous cell carcinoma	411 (76.0)	241 (77.2)
PD-L1 expression level, n (%)		

≥5%	418 (77.3)	252 (80.8)
≥25%	296 (54.7)	185 (59.3)
≥50%	214 (39.6)	130 (41.7)

ECOG = Eastern Cooperative Oncology Group; *PD-L1* = programmed death-1 ligand 1.

Table S8. Baseline Characteristics of Patients with Evaluable Tumor Mutation Data by Treatment Arm.

Characteristic	Nivolumab (n = 158)	Chemotherapy (n = 154)
Age, year		
Median	65	64
Range	32–89	34–87
Age category, n (%)		
<65 years	76 (48.1)	78 (50.6)
≥65 to <75 years	59 (37.3)	57 (37.0)
≥75 years	23 (14.6)	19 (12.3)
Sex, n (%)		
Male	105 (66.5)	82 (53.2)
Female	53 (33.5)	72 (46.8)
Race, n (%)		
White	126 (79.7)	135 (87.7)
Black	4 (2.5)	6 (3.9)
Asian	22 (13.9)	12 (7.8)
American Indian or Alaska native	1 (0.6)	0
Other	5 (3.2)	1 (0.6)
Disease stage, n (%)		
Stage IV	150 (94.9)	141 (91.6)
Recurrent	8 (5.1)	12 (7.8)
Not reported	0	1 (0.6)
ECOG performance-status score, n (%)		
0	46 (29.1)	54 (35.1)
1	110 (69.6)	98 (63.6)
≥2	1 (0.6)	2 (1.3)
Not reported	1 (0.6)	0
Smoking status, n (%)		

Never smoker	16 (10.1)	13 (8.4)
Former smoker	116 (73.4)	107 (69.5)
Current smoker	24 (15.2)	32 (20.8)
Unknown	2 (1.3)	2 (1.3)
Prior systemic therapy, n (%)		
Adjuvant	13 (8.2)	12 (7.8)
Neoadjuvant	2 (1.3)	2 (1.3)
Prior radiotherapy, n (%)	51 (32.3)	60 (39.0)
Tumor histology, n (%)		
Squamous cell carcinoma	36 (22.8)	35 (22.7)
Nonsquamous cell carcinoma	122 (77.2)	119 (77.3)
Selected sites of metastatic lesions, n (%)		
Brain	18 (11.4)	21 (13.6)
Liver	34 (21.5)	31 (20.1)
Median sum of target lesion diameters, mm (range)	79.5 (14−218)	70 (15−272)
PD-L1 expression level, n (%)		
≥5%	125 (79.1)	127 (82.5)
≥25%	86 (54.4)	99 (64.3)
≥50%	57 (36.1)	73 (47.4)
Tumor mutation burden, n (%)		
Low	62 (39.2)	41 (26.6)
Medium	49 (31.0)	53 (34.4)
High	47 (29.7)	60 (39.0)

ECOG = Eastern Cooperative Oncology Group.

Table S9. Treatment-Related Adverse Events in ≥5% of Patients Treated with Nivolumab or Chemotherapy.

Event, n (%)	Nivolumab n = 267		Chemotherapy n = 263	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any event	190 (71.2)	47 (17.6)	243 (92.4)	133 (50.6)
Fatigue	56 (21.0)	3 (1.1)	93 (35.4)	14 (5.3)
Diarrhea	37 (13.9)	3 (1.1)	34 (12.9)	5 (1.9)
Decreased appetite	32 (12.0)	1 (0.4)	73 (27.8)	4 (1.5)
Nausea	31 (11.6)	1 (0.4)	127 (48.3)	5 (1.9)
Rash	26 (9.7)	2 (0.7)	15 (5.7)	1 (0.4)
Aspartate aminotransferase increased	23 (8.6)	7 (2.6)	12 (4.6)	1 (0.4)
Pruritus	22 (8.2)	0	7 (2.7)	1 (0.4)
Alanine aminotransferase increased	19 (7.1)	7 (2.6)	14 (5.3)	2 (0.8)
Hypothyroidism	17 (6.4)	0	1 (0.4)	0
Vomiting	15 (5.6)	0	60 (22.8)	5 (1.9)
Pyrexia	14 (5.2)	0	13 (4.9)	1 (0.4)
Rash maculopapular	14 (5.2)	1 (0.4)	4 (1.5)	0
Constipation	9 (3.4)	0	29 (11.0)	0
Anemia	9 (3.4)	1 (0.4)	113 (43.0)	46 (17.5)
Asthenia	8 (3.0)	0	28 (10.6)	4 (1.5)
Dysgeusia	7 (2.6)	0	21 (8.0)	0
Peripheral edema	6 (2.2)	0	22 (8.4)	0
Blood creatinine increased	5 (1.9)	1 (0.4)	16 (6.1)	0
Stomatitis	5 (1.9)	0	15 (5.7)	1 (0.4)

Hypomagnesemia	4 (1.5)	0	25 (9.1)	2 (0.8)
Mucosal inflammation	4 (1.5)	0	20 (7.6)	0
Alopecia	3 (1.1)	0	23 (8.7)	0
Thrombocytopenia	2 (0.7)	1 (0.4)	38 (14.4)	22 (8.4)
Platelet count decreased	2 (0.7)	0	33 (12.5)	9 (3.4)
White blood cell count decreased	2 (0.7)	0	26 (9.9)	9 (3.4)
Neutrophil count decreased	1 (0.4)	1 (0.4)	36 (13.7)	20 (7.6)
Peripheral sensory neuropathy	1 (0.4)	0	15 (5.7)	0
Neutropenia	0	0	48 (18.3)	29 (11.0)
Leukopenia	0	0	16 (6.1)	9 (3.4)

Table S10. Treatment-Related Serious Adverse Events in ≥2% of Patients Treated with Nivolumab or Chemotherapy.

Event, n (%)	Nivolumab n = 267		Chemotherapy n = 263	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any event	46 (17.2)	35 (13.1)	48 (18.3)	41 (15.6)
Pneumonitis	7 (2.6)	4 (1.5)	0	0
Aspartate aminotransferase increased	6 (2.2)	6 (2.2)	0	0
Anemia	0	0	13 (4.9)	10 (3.8)
Febrile neutropenia	0	0	6 (2.3)	6 (2.3)
Thrombocytopenia	0	0	6 (2.3)	6 (2.3)

Table S11. Treatment-Related Adverse Events Leading to Discontinuation of Nivolumab.

Event, n (%)	Nivolumab n = 267	
	Any Grade	Grade 3–4
Any event	26 (9.7)	21 (7.9)
Aspartate aminotransferase increased	5 (1.9)	5 (1.9)
Alanine aminotransferase increased	5 (1.9)	5 (1.9)
Pneumonitis	3 (1.1)	3 (1.1)
Colitis	2 (0.7)	2 (0.7)
Transaminases increased	1 (0.4)	1 (0.4)
Interstitial lung disease	1 (0.4)	1 (0.4)
Autoimmune colitis	1 (0.4)	0
Diarrhea	1 (0.4)	0
Gastritis	1 (0.4)	0
Nausea	1 (0.4)	1 (0.4)
Rash	1 (0.4)	1 (0.4)
Rash maculopapular	1 (0.4)	1 (0.4)
Rash papular	1 (0.4)	1 (0.4)
Stevens-Johnson syndrome	1 (0.4)	1 (0.4)
Malaise	1 (0.4)	0
Multiple organ dysfunction	1 (0.4)	1 (0.4)
Adrenal insufficiency	1 (0.4)	1 (0.4)
Cholestasis	1 (0.4)	1 (0.4)
Hypersensitivity	1 (0.4)	1 (0.4)
Arthritis	1 (0.4)	0
Pericardial effusion malignant	1 (0.4)	1 (0.4)

Aphasia	1 (0.4)	1 (0.4)
Confused state	1 (0.4)	1 (0.4)

Table S12. Treatment-Related Adverse Events Leading to Discontinuation of Chemotherapy

Event, n (%)	Chemotherapy n = 263	
	Any Grade	Grade 3–4
Any event	35 (13.3)	17 (6.5)
Anemia	5 (1.9)	3 (1.1)
Blood creatinine increased	5 (1.9)	0
Febrile neutropenia	4 (1.5)	4 (1.5)
Neutropenia	3 (1.1)	1 (0.4)
Fatigue	3 (1.1)	2 (0.8)
General physical health deterioration	2 (0.8)	2 (0.8)
Decreased appetite	2 (0.8)	1 (0.4)
Asthenia	2 (0.8)	0
Chronic kidney disease	2 (0.8)	0
Renal infarction	1 (0.4)	1 (0.4)
Renal failure	1 (0.4)	0
Renal function test abnormal	1 (0.4)	0
Thrombocytopenia	1 (0.4)	1 (0.4)
Myocardial infarction	1 (0.4)	1 (0.4)
Pneumonia	1 (0.4)	1 (0.4)
Erysipelas	1 (0.4)	1 (0.4)
Sepsis	1 (0.4)	1 (0.4)
Bronchospasm	1 (0.4)	1 (0.4)
Pneumonitis	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	1 (0.4)

Nausea	1 (0.4)	0
Vomiting	1 (0.4)	0
Neurotoxicity	1 (0.4)	0
Peripheral sensory neuropathy	1 (0.4)	0
Tinnitus	1 (0.4)	0
Peripheral edema	1 (0.4)	0

Table S13. Treatment-Related Select Adverse Events[a] in Patients Treated with Nivolumab or Chemotherapy.

Select Adverse Event Category, n (%)	Nivolumab n = 267		Chemotherapy n = 263	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Skin	63 (23.6)	5 (1.9)	25 (9.5)	1 (0.4)
Gastrointestinal	39 (14.6)	6 (2.2)	34 (12.9)	5 (1.9)
Hepatic	33 (12.4)	9 (3.4)	26 (9.9)	2 (0.8)
Pulmonary	14 (5.2)	6 (2.2)	1 (0.4)	0
Hypersensitivity/infusion reaction	11 (4.1)	1 (0.4)	3 (1.1)	1 (0.4)
Renal	5 (1.9)	1 (0.4)	18 (6.8)	0

[a]Select adverse events are those with potential immunologic etiology that require frequent monitoring/intervention; includes events reported from the time of the first dose of study drug to 30 days after the last dose or to the time of the first dose of nivolumab crossover, whichever came first.

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