Supplementary Appendix

Nivolumab Plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer

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Supplemental Methods

Additional inclusion and exclusion criteria

Prior adjuvant or neoadjuvant chemotherapy or prior definitive chemoradiation for locally advanced disease was allowed up to 6 months before enrollment. Prior palliative radiotherapy to non–central nervous system lesions must have been completed ≥2 weeks before randomization. Patients with known *EGFR* mutations or *ALK* translocations sensitive to targeted therapy, an autoimmune disease, or untreated central nervous system metastases were excluded. Patient with central nervous system metastases were eligible if they were adequately treated and had neurologically returned to baseline for ≥2 weeks before randomization. Patients had to be off glucocorticoids or on stable or decreasing doses of ≤10 mg daily prednisone (or equivalent) for ≥2 weeks before randomization.

Treatment beyond progression and overall survival follow-up

Treatment continuation with nivolumab or nivolumab plus ipilimumab beyond progression was permitted if the patient had investigator-assessed clinical benefit and continued to tolerate treatment. Patients were followed for overall survival every 3 months via in-person or phone contact after discontinuation of study drug treatment.

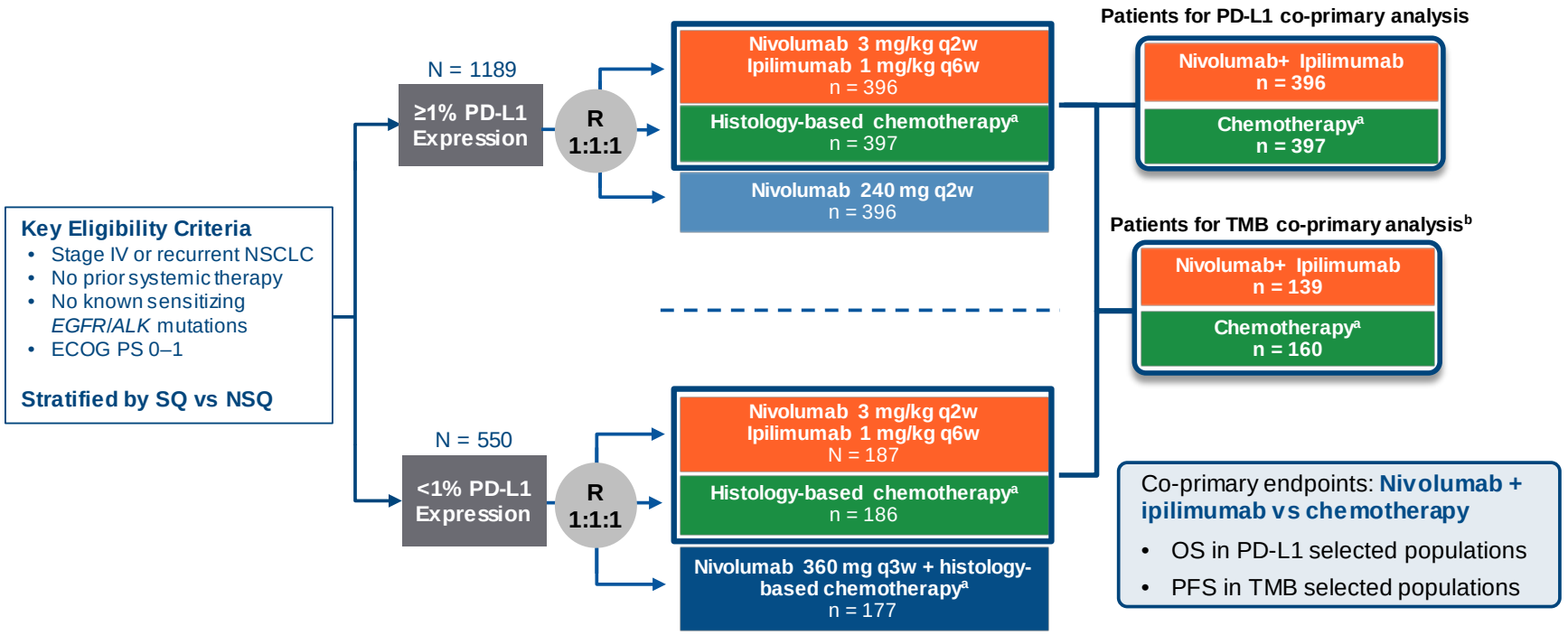
PD-L1 analysis for patient selection

Fresh or archival tumor-biopsy specimens obtained within 6 months before enrollment (and without the patient receiving any intervening systemic anti-cancer therapy) were tested for programmed death ligand 1 (PD-L1) by a centralized laboratory with the use of the anti–PD-L1 antibody (28-8 antibody).[1]

Tumor mutational burden analysis

Tumor mutational burden (TMB) was assessed in archival or fresh formalin-fixed, paraffin-embedded tumor samples using the validated assay FoundationOne CDx™, which employs next-generation sequencing to detect substitutions, insertions and deletion (indels), and copy number alterations in 324 genes and select gene rearrangements.[2] TMB was calculated according to previously defined methods.[3] Briefly, TMB was defined as the number of somatic, coding, base substitution, and short indels per megabase of genome examined. All base substitutions and indels in the coding region of targeted genes, including synonymous mutations, were filtered for both oncogenic driver events according to COSMIC and germline status according to dbSNP and ExAC databases, in addition to a private database of rare germline events compiled in the Foundation Medicine clinical cohort. Additional filtering based upon a computational assessment of germline status using the SGZ (somatic-germline-zygosity) tool was also performed.[4] The mutation count following application of these filters was divided by the region counted (0.8 Mb) to yield mutations/Mb.

Figure S1. Study Design



[a]Nonsquamous: pemetrexed (500 mg/m^2) + cisplatin (75 mg/m^2) or carboplatin (AUC 5 or 6), q3w for ≤4 cycles, with optional pemetrexed (500 mg/m^2) maintenance following chemotherapy or nivolumab (360 mg q3w) + pemetrexed (500 mg/m^2) maintenance following nivolumab + chemotherapy; squamous: gemcitabine (1000 or 1250 mg/m^2) + cisplatin (75 mg/m^2), or gemcitabine (1000 mg/m^2) + carboplatin (AUC 5), q3w for ≤4 cycles

[b]The TMB co-primary analysis was conducted in the subset of patients randomized to nivolumab + ipilimumab or chemotherapy who had evaluable TMB ≥10 mutations/Mb

ECOG PS = Eastern Cooperative Oncology Group performance status; *OS* = overall survival; *NCLSC* = non–small-cell lung cancer; *NSQ* = nonsquamous; *PD-L1* = programmed death ligand 1; *PFS* = progression-free survival; *q2w* = every 2 weeks; *q3w* = every 3 weeks; *q6w* = every 6 weeks; *SQ* = squamous; *TMB* = tumor mutational burden

Figure S2. Consolidated Standards of Reporting Trials (CONSORT) Diagram of Patient Disposition

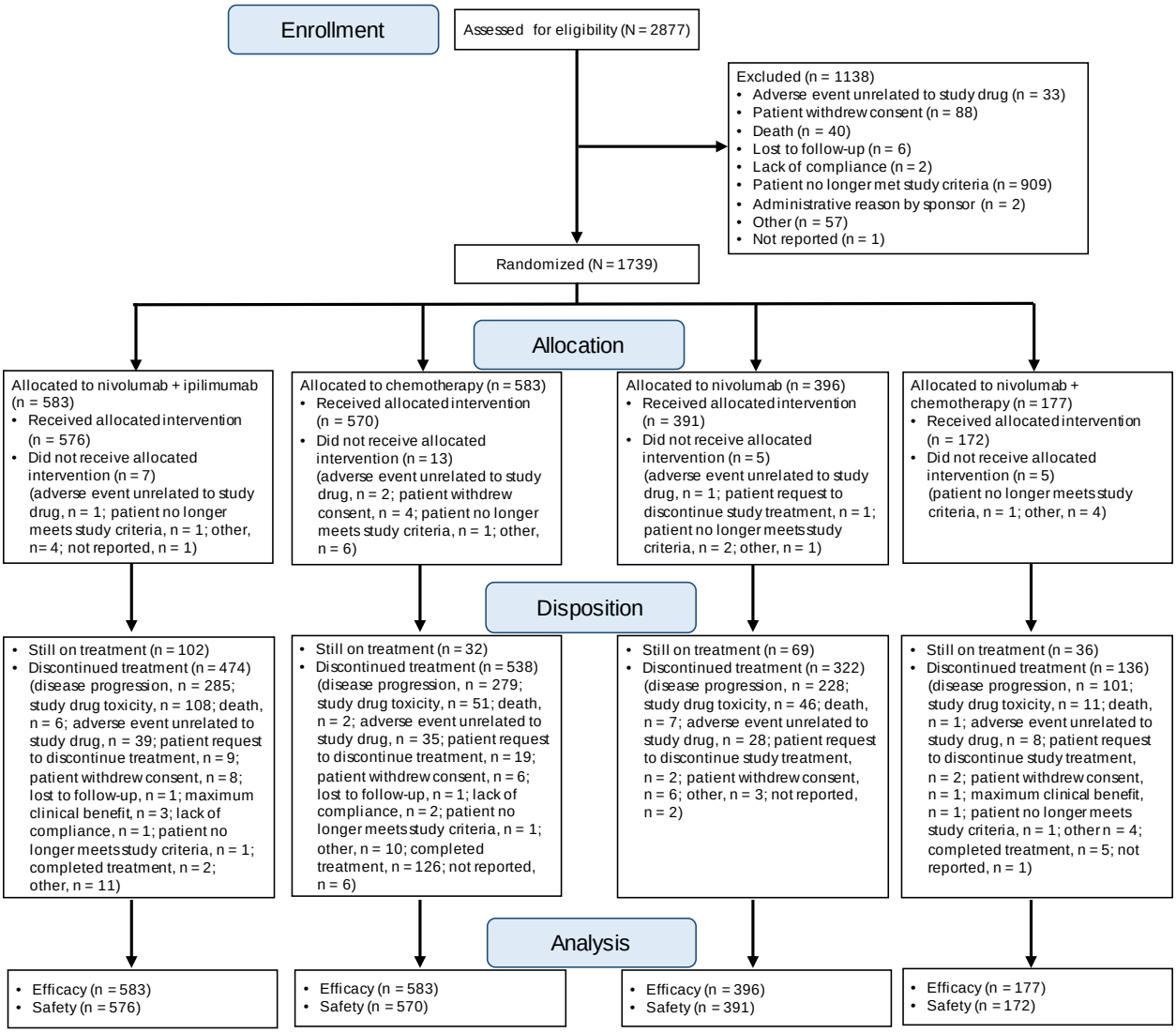
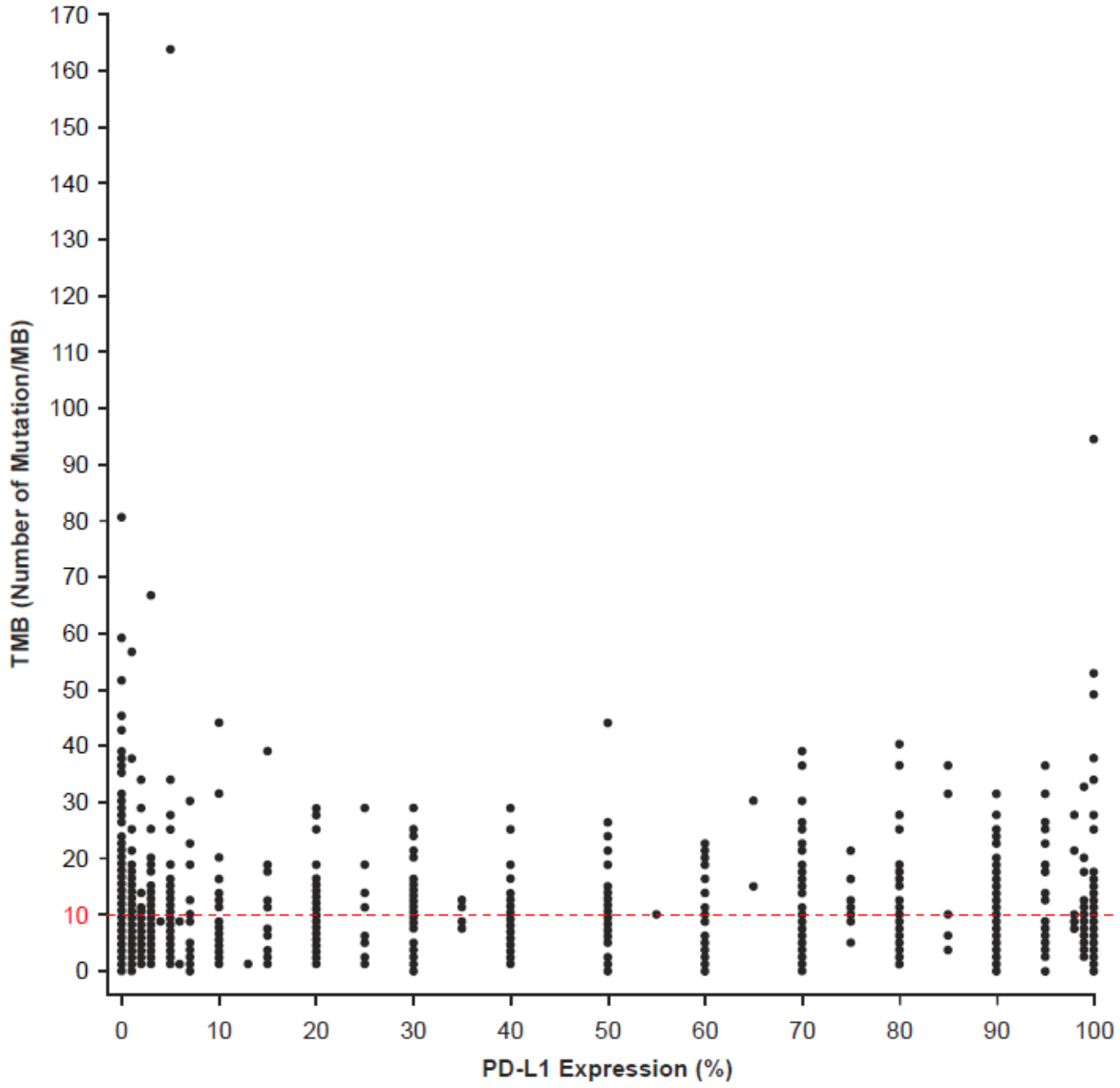
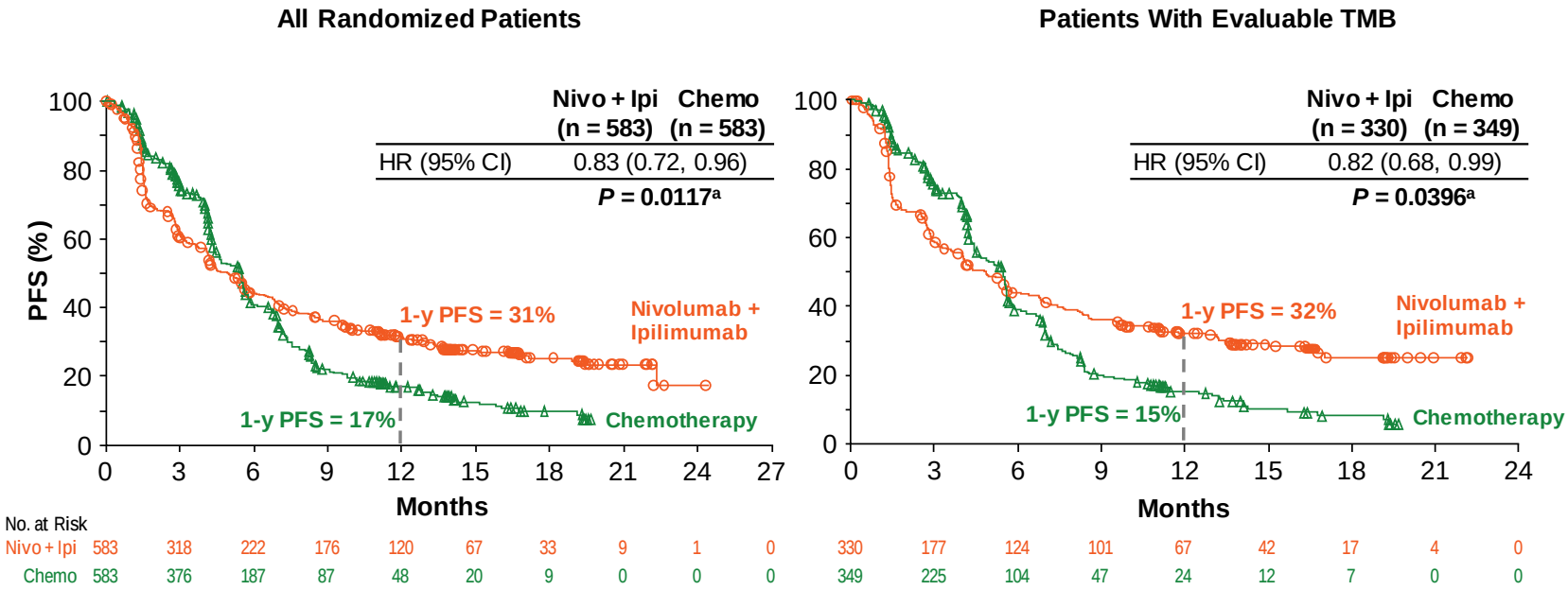


Figure S3. Scatterplot of TMB and PD-L1 Expression in All TMB-Evaluable Patients[a]



[a]Symbols (dots) in the scatterplot may represent multiple data points, especially for patients with <1% PD-L1 expression

Figure S4. Progression-free Survival With Nivolumab Plus Ipilimumab Versus Chemotherapy in All Randomized and TMB-Evaluable Patients



[a]*P* values are nominal and not adjusted for multiple comparisons

CI = confidence interval; *HR* = hazard ratio

Figure S5. Progression-free Survival With Nivolumab Plus Ipilimumab Versus Chemotherapy in Patients With TMB <10 Mutations/Mb

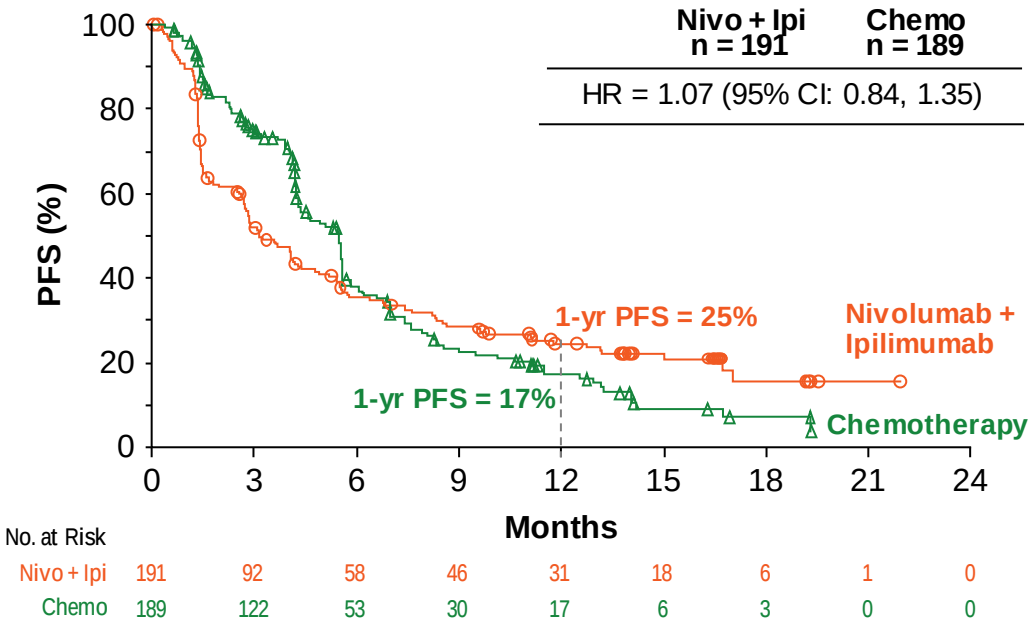
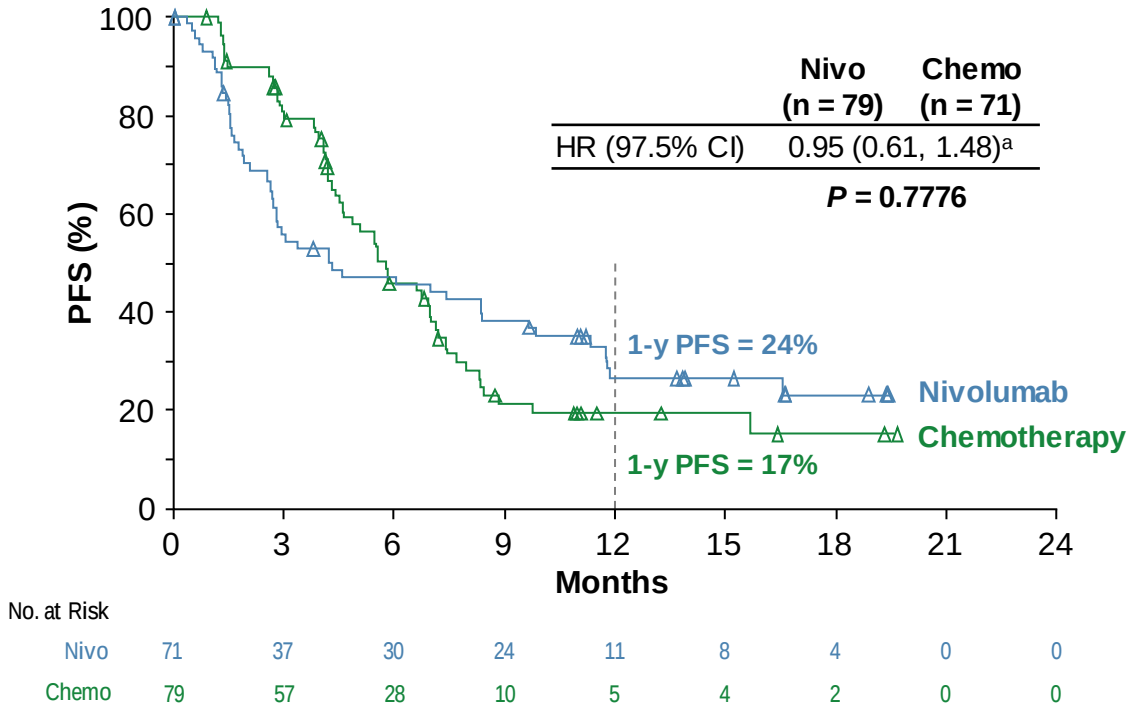
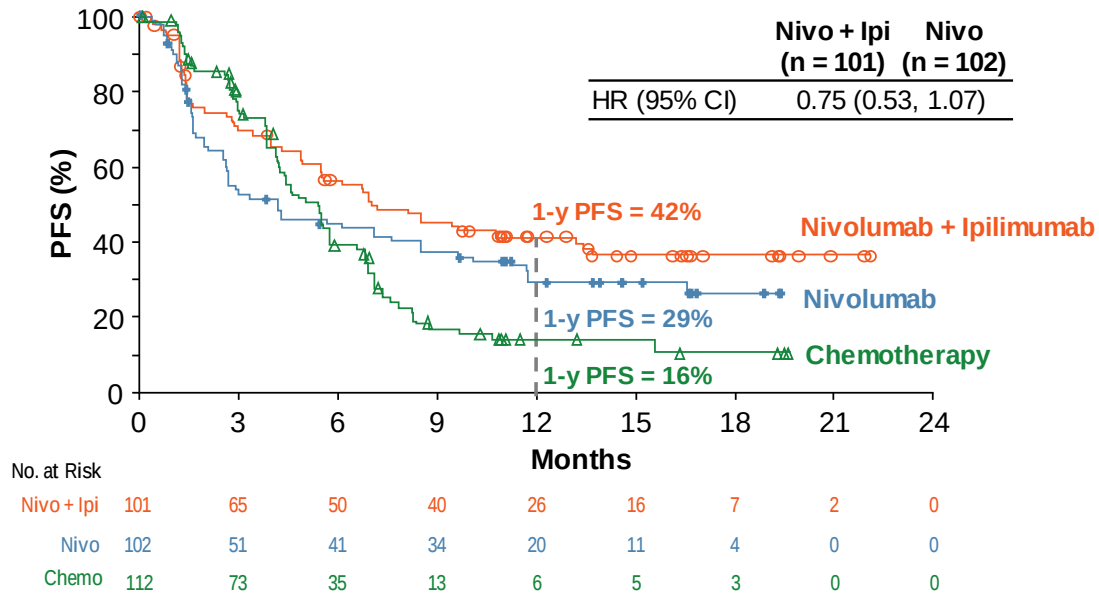


Figure S6. Progression-free Survival With Nivolumab Monotherapy Versus Chemotherapy in Patients With TMB ≥13 Mutations/Mb and ≥1% Tumor PD-L1 Expression



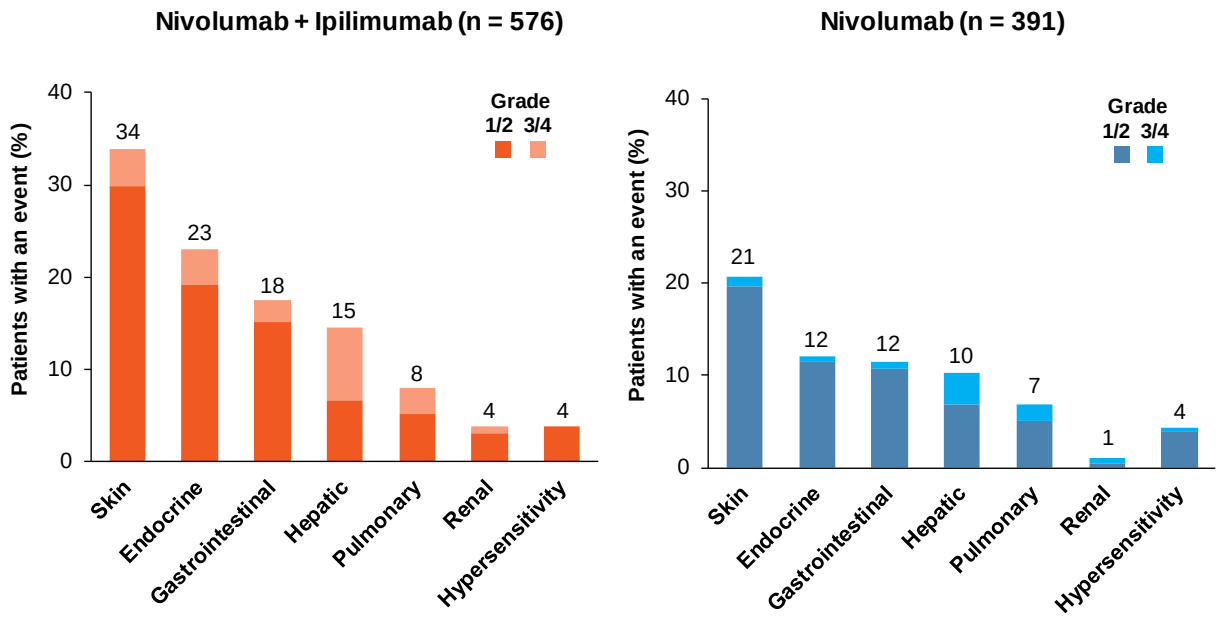
[a]HR (95% CI) = 0.95 (0.64, 1.40)

Figure S7. Progression-free Survival With Nivolumab Plus Ipilimumab Versus Nivolumab Monotherapy and Chemotherapy[a] in Patients With TMB ≥10 Mutations/Mb and ≥1% Tumor PD-L1 Expression



[a]HR (95% CI) = 0.62 (0.44, 0.88) for nivolumab + ipilimumab versus chemotherapy

Figure S8. Treatment-Related Select Adverse Events[a] by Category With Nivolumab Plus Ipilimumab



[a]Select adverse events are those with potential immunologic etiology that require frequent monitoring/intervention

Table S1. Sample Size Throughout TMB Determination

Patients, n (%)	
Randomized[a]	1739 (100)
Samples available	1649 (95)
TMB-evaluable samples[b]	1004 (58)

[a]Randomized patients include those from all treatment arms in part 1 (nivolumab + ipilimumab, nivolumab, chemotherapy, and nivolumab + chemotherapy arms)

[b]A pre-analytical quality control check was performed on all samples to flag inaccuracies comprised of but not limited to incorrect requisitions, receipt of insufficient sample, and duplicate samples. The FoundationOne CDx™ assay employs comprehensive quality control criteria, including the following critical characteristics: tumor purity, DNA sample size, tissue sample size, library construction size, and hybrid capture yields

Table S2. Baseline Characteristics of All Randomized and TMB-Evaluable Patients

	All Randomized Patients				TMB-Evaluable Patients			
	Nivolumab + Ipilimumab (n = 583)	**Nivolumab (n = 396)**	**Chemo-therapy (n = 583)**	**Total Study Population (N = 1739)[a]**	**Nivolumab + Ipilimumab (n = 330)**	**Nivolumab (n = 228)**	**Chemo-therapy (n = 349)**	**Total (N = 1004)**
Median age, years	64	64	64	64	64	64	64	64
Female, %	33	31	34	32	34	31	36	33
ECOG PS, %								
0	35	36	33	34	33	32	34	33
1	65	64	66	65	67	67	65	67
≥2	>1	0	1	<1	<1	0	1	<1
Not reported	0	<1	<1	<1	0	<1	<1	<1
Smoking status, %								
Current/former smoker	85	86	86	85	86	86	87	87
Never smoker	14	13	13	13	12	12	11	12
Unknown	1	1	1	1	2	1	1	1
Histology, %								
Squamous	28	30	28	28	28	29	32	29
Nonsquamous	72	70	72	72	72	71	68	71
PD-L1 expression, %								
<1%	32	0	32	32	27	0	31	29
≥1%	68	100	68	68	73	100	69	71

[a]Includes all treatments in part 1 of the study: nivolumab + ipilimumab, nivolumab, nivolumab + chemotherapy, and chemotherapy

Table S3. End-of-Treatment Summary

	All Treated Patients		TMB ≥10 Mutations/Mb	
	Nivolumab + Ipilimumab (n = 576)	**Chemo-therapy (n = 570)**	**Nivolumab + Ipilimumab (n = 135)**	**Chemo-therapy (n = 159)**
Patients continuing in the treatment period, n (%)	102 (17.7)	32 (5.6)	33 (24.2)	5 (3.1)
Patients not continuing in the treatment period, n (%)	474 (82.3)	538 (94.4)	102 (75.6)	154 (96.9)
Reason for not continuing in the treatment period, n (%)				
Disease progression	285 (49.5)	279 (48.9)	51 (37.8)	75 (47.2)
Study drug toxicity	108 (18.8)	51 (8.9)	35 (25.9)	14 (8.8)
Completed required treatment	2 (0.3)	126 (22.1)	0	42 (26.4)
Death	6 (1.0)	2 (0.4)	1 (0.7)	0
Adverse event unrelated to study drug	39 (6.8)	35 (6.1)	7 (5.2)	9 (5.7)
Patient request to discontinue	9 (1.6)	19 (3.3)	3 (2.2)	8 (5.0)
Patient withdrew consent	8 (1.4)	6 (1.1)	1 (0.7)	1 (0.6)
Lost to follow-up	1 (0.2)	1 (0.2)	0	0
Maximum clinical benefit	3 (0.5)	0	1 (0.7)	0
Lack of compliance	1 (0.2)	2 (0.4)	0	1 (0.6)
Patient no longer meets study criteria	1 (0.2)	1 (0.2)	0	0
Other	11 (1.9)	10 (1.8)	3 (2.2)	2 (1.3)
Not reported	0	6 (1.1)	0	2 (1.3)

Table S4. Subsequent Systemic Therapies in Patients With TMB ≥10 Mutations/Mb[a]

Patients, n (%)	Nivolumab + Ipilimumab (n = 139)	Chemotherapy (n = 160)
Any subsequent systemic therapy	23 (16.5)	69 (43.1)
Immunotherapy	3 (2.2)	45 (28.1)
Anti–PD-1 Nivolumab Pembrolizumab	3 (2.2) 3 (2.2) 0	42 (26.3) 36 (22.5) 6 (3.8)
Anti–PD-L1 (atezolizumab)	0	1 (0.6)
Anti–CTLA-4 (ipilimumab)	0	5 (3.1)[b]
Other immunotherapy	0	2 (1.3)
Targeted therapy	2 (1.4)	3 (1.9)
Chemotherapy	22 (15.8)	33 (20.6)

[a]At the time of database lock, 24% of patients treated with nivolumab + ipilimumab and 3% of those treated with chemotherapy were still on treatment

[b]All 5 patients received ipilimumab in combination with nivolumab

CTLA-4 = cytotoxic T lymphocyte antigen-4; *PD-1* = programmed death 1

Table S5. Treatment-Related Adverse Events Leading to Discontinuation of Nivolumab Plus Ipilimumab in ≥2 Patients

Event, n (%)[a]	Nivolumab + Ipilimumab (n = 576)	
	Any Grade	Grade 3–4
Any event	100 (17.4)	69 (12.0)
Pneumonitis	18 (3.1)	10 (1.7)
Diarrhea	11 (1.9)	8 (1.4)
Aspartate aminotransferase increased	7 (1.2)	6 (1.0)
Hepatitis	6 (1.0)	5 (0.9)
Interstitial lung disease	6 (1.0)	3 (0.5)
Alanine aminotransferase increased	5 (0.9)	4 (0.7)
Colitis	4 (0.7)	3 (0.5)
Adrenal insufficiency	4 (0.7)	1 (0.2)
Nausea	3 (0.5)	1 (0.2)
Autoimmune hepatitis	2 (0.3)	2 (0.3)
Gastritis	2 (0.3)	2 (0.3)
Hypopituitarism	2 (0.3)	2 (0.3)
Fatigue	2 (0.3)	1 (0.2)
Hypophysitis	2 (0.3)	1 (0.2)
Lipase increased	2 (0.3)	1 (0.2)
Infusion-related reaction	2 (0.3)	0

[a]Only includes adverse events leading to discontinuation of both nivolumab and ipilimumab

Table S6. Treatment-Related Adverse Events Leading to Discontinuation of Nivolumab Monotherapy in ≥2 Patients

Event, n (%)	Nivolumab (n = 391)	
	Any Grade	Grade 3–4
Any event	45 (11.5)	27 (6.9)
Pneumonitis	9 (2.3)	5 (1.3)
Diarrhea	4 (1.0)	1 (0.3)
Amylase increased	3 (0.8)	2 (0.5)
Alanine aminotransferase increased	2 (0.5)	2 (0.5)
Lipase increased	2 (0.5)	2 (0.5)

Table S7. Treatment-Related Adverse Events Leading to Discontinuation of Chemotherapy in ≥2 Patients

Event, n (%)	Chemotherapy (n = 570)	
	Any Grade	Grade 3–4
Any event	51 (8.9)	28 (4.9)
Anemia	5 (0.9)	2 (0.4)
Fatigue	5 (0.9)	2 (0.4)
Nausea	3 (0.5)	2 (0.4)
Blood creatinine increased	3 (0.5)	0
Neutrophil count decreased	2 (0.4)	2 (0.4)
Pancytopenia	2 (0.4)	2 (0.4)
Platelet count decreased	2 (0.4)	2 (0.4)
Sepsis	2 (0.4)	2 (0.4)
Acute kidney injury	2 (0.4)	1 (0.2)
Decreased appetite	2 (0.4)	1 (0.2)
Creatinine renal clearance	2 (0.4)	0

Table S8. Treatment-Related Serious Adverse Events in ≥2% of Patients

Event, n (%)	Nivolumab + Ipilimumab (n = 576)		Nivolumab (n = 391)		Chemotherapy (n = 570)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Any event	138 (24.0)	102 (17.7)	42 (10.7)	30 (7.7)	79 (13.9)	61 (10.7)
Pneumonitis	22 (3.8)	13 (2.3)	9 (2.3)	6 (1.5)	3 (0.5)	2 (0.4)
Adrenal insufficiency	12 (2.1)	9 (1.6)	1 (0.3)	1 (0.3)	0	0
Diarrhea	12 (2.1)	6 (1.0)	2 (0.5)	1 (0.3)	5 (0.9)	2 (0.4)
Anemia	3 (0.5)	1 (0.2)	1 (0.3)	1 (0.3)	14 (2.5)	11 (1.9)

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