Supplementary Appendix

First-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus chemotherapy alone (4 cycles) in advanced non-small cell lung cancer: CheckMate 9LA 2-year update

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Supplementary Methods

Additional eligibility criteria

Patients who had previous adjuvant or neoadjuvant chemotherapy for early-stage lung cancer and those with locally advanced non-small cell lung cancer (NSCLC) with recurrence after chemotherapy must have completed treatment at least 6 months before enrollment. Participants were required to have tumor tissue samples available at a central laboratory for programmed death ligand 1 (PD-L1) immunohistochemistry (IHC) testing during the screening period. Either a formalin-fixed, paraffin-embedded tissue block or 15 unstained tumor tissue sections, with an associated pathology report, was submitted for biomarker evaluation prior to treatment. Tumor tissue samples could be fresh or archival (archival tissue had to be obtained within 3 months prior to enrollment), with no systemic therapy (eg, adjuvant or neoadjuvant chemotherapy) given after the sample was obtained. Tissue had to be from a core needle biopsy, or an excisional or incisional biopsy. Fine needle biopsies or drainage of pleural effusions with cytospins were not considered adequate for biomarker review. Biopsies of bone lesions without a soft tissue component or decalcified bone tumor samples were not acceptable. Patients with autoimmune disease were not eligible for the study.

Histology-based chemotherapy

Intravenous chemotherapy for both treatment arms consisted of carboplatin (area under the concentration–time curve [AUC] 6) plus paclitaxel (200 mg/m^2) for patients with squamous tumor histology, and carboplatin (AUC 5 or 6) plus pemetrexed (500 mg/m^2) or cisplatin (75 mg/m^2); pemetrexed (500 mg/m^2) maintenance was permitted for patients with non-squamous tumor histology in the control arm only.

Treatment beyond progression

Patients could continue treatment with nivolumab plus ipilimumab beyond progression (for a maximum of 2 years from the start of study treatment) if they had investigator-assessed clinical benefit, no rapid disease progression, tolerance to study treatment, stable Eastern Cooperative Oncology Group performance status, and if continuing treatment did not delay any intervention to prevent serious complications of disease progression. If further progression (defined as an additional 10% increase in tumor burden with ≥5 mm absolute increase in the sum of diameters of all existing and new lesions from the time of initial progressive disease) was reported at subsequent tumor assessments, treatment was discontinued permanently.

Assessments

Brain tumors were assessed using magnetic resonance imaging or computed tomography scans at baseline and patients with a history of brain metastasis were assessed per standard of care (approximately every 12 weeks) using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1).

PD-L1 expression on viable tumor cells was assessed at a central laboratory using a validated approved immunohistochemical assay (PD-L1 IHC 28-8 pharmDx; Agilent Dako, Santa Clara, CA).

Efficacy outcomes

OS

Overall survival (OS) was defined as the time from randomization to the date of death from any cause. Survival time was censored at the last known alive date for those patients still alive, and at the date of randomization for patients who were randomized but had no follow-up.

PFS

Progression-free survival (PFS) was defined as the time from randomization to the date of first documented tumor progression, death from any cause, or censoring for subsequent therapy, whichever occurred first.

ORR

Objective response rate (ORR) was defined as the number of randomized patients who achieved a best response of confirmed complete response or confirmed partial response based on blinded independent central review assessments (using RECIST v1.1 criteria) divided by the number of all randomized patients.

Safety outcomes

Safety outcomes were reported between first dose and 30 days after last dose of study therapy, with the exception of immune-mediated adverse events (IMAEs), and graded per National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

Tables

Supplementary Table S1. Baseline characteristics

Characteristic	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 361)	Chemotherapy (*n* = 358)
Age, years		
Median (range)	65 (35–81)	65 (26–86)
<65, *n* (%)	176 (49)	178 (50)
≥65 to <75, *n* (%)	148 (41)	147 (41)
≥75, *n* (%)	37 (10)	33 (9)
Sex, *n* (%)		
Male	252 (70)	252 (70)
Female	109 (30)	106 (30)
Region, *n* (%)		
North America	36 (10)	28 (8)
Europe	212 (59)	213 (60)
Asia	28 (8)	30 (8)
Rest of the world	85 (24)	87 (24)
ECOG PS,[a] *n* (%)		
0	113 (31)	112 (31)
1	247 (68)	245 (68)
Smoking status, *n* (%)		
Never smoked	46 (13)	52 (14)
Current or former	315 (87)	306 (86)
Tumor histology, *n* (%)		
Squamous	115 (32)	112 (31)
Non-squamous	246 (68)	246 (69)
Metastasis, *n* (%)		
Liver	68 (19)	86 (24)
Bone	97 (27)	110 (31)
CNS	65 (18)	58 (16)
Tumor PD-L1 expression, *n* (%)		
Quantifiable	339 (94)	333 (93)
<1%	135 (40)	129 (39)
≥1%	204 (60)	204 (61)
1-49%	128 (38)	106 (32)
≥50%	76 (22)	98 (29)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1.

Percentages may not sum to 100% due to rounding.

Supplementary Table S2. Treatment and exposure summary characteristics

	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 358)	**Chemotherapy (*n* = 349)**
Duration of therapy, median (range), months	6.1 (0–24.4)	2.5 (0–34.5)
Number of doses, median (range)		
Nivolumab	9.0 (1–36)	Not applicable
Ipilimumab	4.0 (1–18)	
Cycles of chemotherapy received, *n* (%)		
1	25 (7)	23 (7)
2	333 (93)	49 (14)
3	Not applicable	16 (5)
4	Not applicable	261 (75)
Patients receiving pemetrexed maintenance therapy, *n* (%)	Not applicable	159[a] (46)

[a]67% of patients with non-squamous histology received optional pemetrexed maintenance.

Supplementary Table S3. Subsequent treatment for all randomized patients, patients with a PFS event per BICR, and patients with OS ≥ 2 years

	All randomized patients[a]		Patients with a PFS event[b]		Patients with OS ≥ 2 years[c]	
	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 361)	**Chemotherapy (*n* = 358)**	**Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 307)**	**Chemotherapy (*n* = 334)**	**Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 137)**	**Chemotherapy (*n* = 93)**
Any subsequent therapy, *n* (%)	141 (39)	181 (51)	141 (46)	175 (52)	48 (35)	51 (55)
Subsequent radiotherapy, *n* (%)	54 (15)	54 (15)	54 (18)	51 (15)	21 (15)	10 (11)
Subsequent systemic therapy, *n* (%)	122 (34)	163 (46)	122 (40)	158 (47)	40 (29)	49 (53)
Immunotherapy	26 (7)	127 (36)	26 (8)	125 (37)	17 (12)	47 (50)
Targeted therapy	23 (6)	28 (8)	23 (8)	28 (8)	10 (7)	11 (12)
Chemotherapy	114 (32)	85 (24)	114 (37)	81 (24)	35 (26)	20 (22)
Platinum-doublet chemotherapy	66 (18)	17 (5)	66 (22)	14 (4)	25 (18)	8 (9)

BICR, blinded independent central review; OS, overall survival; PFS, progression-free survival.

[a] All percentages for subsequent treatment types are calculated out of all randomized patients.

[b] Patients who had a PFS event per BICR (progression or death) or were censored for initiation of subsequent systemic therapy; all percentages for subsequent treatment types are calculated out of all patients who had a PFS event.

[c] All percentages for subsequent treatment types are calculated out of all patients with OS ≥ 2 years.

Supplementary Table S4. ORR and BOR in all randomized patients

	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 361)	**Chemotherapy (*n* = 358)**
ORR, *n* (%, [95% CI])	137 (38.0 [32.9–43.2])	91 (25.4 [21.0–30.3])
BOR, *n* (%)		
Complete response	12 (3.3)[a]	4 (1.1)
Partial response	125 (34.6)	87 (24.3)
Stable response	165 (45.7)	184 (51.4)
Progressive disease	33 (9.1)	44 (12.3)
Unable to determine	26 (7.2)	36 (10.1)
Not reported	0 (0)	3 (0.8)

BOR, best overall response; CI, confidence interval; DBL, database lock; ORR, objective response rate.

23.3 months minimum follow-up.

[a]4 patients who had a partial response as best response at a previous DBL (12.2 months minimum follow-up for response) improved to complete responses.

Supplementary Table S5. Response rates in patients with non-squamous and squamous histology

	Non-squamous		Squamous	
	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 246)	**Chemotherapy (*n* = 246)**	**Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 115)**	**Chemotherapy (*n* = 112)**
ORR, *n* (%)	81 (32.9)	56 (22.8)	56 (48.7)	35 (31.3)
95% CI	27.1–39.2	17.7–28.5	39.3–58.2	22.8–40.7
BOR, *n* (%)				
Complete response	5 (2.0)	3 (1.2)	7 (6.1)	1 (0.9)
Partial response	76 (30.9)	53 (21.5)	49 (42.6)	34 (30.4)
Stable response	125 (50.8)	134 (54.5)	40 (34.8)	50 (44.6)
Progressive disease	24 (9.8)	30 (12.2)	9 (7.8)	14 (12.5)
Unable to determine	16 (6.5)	23 (9.3)	10 (8.7)	13 (11.6)
Not reported	0 (0)	3 (1.2)	0 (0)	0 (0)

BOR, best overall response; CI, confidence interval; ORR, objective response rate.
23.3 months minimum follow-up.

Supplementary Table S6. Response rates in patients with tumor PD-L1 expression <1%, ≥1%, and ≥50%

	PD-L1 <1%		PD-L1 ≥1%		PD-L1 ≥50%	
	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 135)	**Chemotherapy (*n* = 129)**	**Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 204)**	**Chemotherapy (*n* = 204)**	**Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 76)**	**Chemotherapy (*n* = 98)**
ORR, *n* (%)	42 (31)	26 (20)	87 (43)	57 (28)	38 (50)	31 (32)
95% CI	23.4–39.6	13.6–28.1	35.8–49.7	21.9–34.6	38.3–61.7	22.6–41.8
BOR, *n* (%)						
Complete response	4 (3)	1 (1)	8 (4)	2 (1)	4 (5)	1 (1)
Partial response	38 (28)	25 (19)	79 (39)	55 (27)	34 (45)	30 (31)
Stable response	68 (50)	70 (54)	86 (42)	100 (49)	28 (37)	44 (45)
Progressive disease	12 (9)	17 (13)	18 (9)	25 (12)	5 (7)	14 (14)
Unable to determine	13 (10)	15 (12)	13 (6)	20 (10)	5 (7)	8 (8)
Not reported	0 (0)	1 (1)	0 (0)	2 (1)	0 (0)	1 (1)

BOR, best overall response; CI, confidence interval; ORR, objective response rate; PD-L1, programmed death ligand 1.
23.3 months minimum follow-up.

Supplementary Table S7. Safety summary

	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 358)		Chemotherapy (*n* = 349)	
TRAE,[a] *n* (%)	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any TRAE	328 (92)	173 (48)	306 (88)	132 (38)
Most frequent TRAEs in all randomized patients (≥10%)				
Nausea	97 (27)	5 (1)	125 (36)	3 (1)
Anemia	85 (24)	21 (6)	134 (38)	53 (15)
Pruritus	77 (22)	3 (1)	6 (2)	0 (0)
Diarrhea	76 (21)	15 (4)	42 (12)	2 (1)
Asthenia	74 (21)	4 (1)	63 (18)	8 (2)
Rash	71 (20)	6 (2)	11 (3)	0 (0)
Fatigue	62 (17)	9 (2)	38 (11)	1 (<1)
Decreased appetite	59 (16)	4 (1)	57 (16)	5 (1)
Hypothyroidism	57 (16)	1 (<1)	1 (<1)	0 (0)
Vomiting	48 (13)	6 (2)	52 (15)	5 (1)
Neutropenia	35 (10)	25 (7)	60 (17)	33 (9)
Constipation	31 (9)	0 (0)	40 (12)	0 (0)
TRAEs leading to discontinuation of any component of regimen	79 (22)	65 (18)	29 (8)	17 (5)
TRAEs leading to discontinuation of all components of regimen	61 (17)	49 (14)	21 (6)	12 (3)
Serious TRAEs	109 (30)	93 (26)	62 (18)	51 (15)
Treatment-related deaths[b]	8 (2)		6 (2)	

AE, adverse event; DBL, database lock; TRAE, treatment-related AE.

23.3 months minimum follow-up.

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

[b] AEs reported previously, treatment-related deaths in the nivolumab plus ipilimumab with chemotherapy arm (n = 8; 1 for each event) were due to acute renal failure due to chemotherapy only, thrombocytopenia due to chemotherapy only, pneumonitis, hepatic toxicity, hepatitis, sepsis with acute renal insufficiency; 2 events were due to diarrhea (1 of which was not reported as treatment-related at previous DBLs but updated by the investigator as treatment-related prior to this DBL); treatment-related deaths in the chemotherapy arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 serious AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).

Supplementary Table S8. Incidence, time to onset, and time to resolution of endocrine and non-endocrine IMAEs in the nivolumab plus ipilimumab with chemotherapy arm

IMAEs	Any grade				Grade 3/4			
	Incidence n (%)	Median time to onset (IQR), months	Median time to resolution (95% CI), months	Number resolved (%)	Incidence n (%)	Median time to onset (IQR), months	Median time to resolution (95% CI), months	Number resolved (%)
Endocrine								
Adrenal Insufficiency	13 (4)	5.1 (3.8–7.7)	NR (1.4–NR)	5 (38)	5 (1)	6.3 (5.1–8.8)	--	0
Hypothyroidism/thyroiditis	58 (16)	3.7 (2.8–4.8)	NR (NR–NR)	16 (28)	2 (1)	7.6 (3.8–11.4)	6.1 (1.2–11.1)	2 (100)
Diabetes mellitus	0	--	--	0	0	--	--	0
Hyperthyroidism	29 (8)	2.0 (1.4–2.7)	1.4 (1.2–1.7)	27 (93)	0	--	--	0
Hypophysitis	9 (2)	4.0 (3.5–5.4)	NR (0.1–NR)	4 (44)	6 (2)	3.9 (3.5–5.4)	NR (0.1–NR)	2 (33)
Non-endocrine								
Pneumonitis	21 (6)	5.1 (2.9–9.4)	3.4 (1.2–5.1)	15 (71)	10 (3)	6.0 (2.3–9.5)	1.8 (0.2–5.1)	7 (70)
Diarrhea/colitis	23 (6)	5.1 (1.2–7.0)	1.1 (0.7–2.6)	18 (78)	13 (4)	5.1 (1.2–10.3)	2.0 (0.4–3.5)	10 (71)
Hepatitis	20 (6)	3.6 (3.0–7.2)	1.8 (0.9–3.1)	15 (75)	16 (4)	3.6 (3.1–5.2)	1.8 (0.9–4.3)	12 (75)
Nephritis and renal dysfunction	5 (1)	3.5 (3.3–3.5)	1.2 (0.2–NR)	4 (80)	1 (<1)	3.3 (3.3–3.3)	0.2 (NR–NR)	1 (100)
Rash	61 (17)	0.8 (0.4–5.1)	2.1 (1.2–2.9)	51 (84)	14 (4)	0.8 (0.4–3.4)	1.0 (0.5–2.4)	13 (93)
Hypersensitivity	2 (1)	0.7 (0.7–0.7)	<1 (NR–NR)	2 (100)	0	--	--	0

AE, adverse event; CI, confidence interval; IMAE, immune-mediated AE; IQR, interquartile range; NR, not reached.
IMAEs includes AEs considered by investigator as potential immune-mediated events occurring within 100 days of last dose of study drug regardless of causality and treated with immune-modulating medication, with the exception of endocrine events (adrenal insufficiency, hypothyroidism/thyroiditis, hypothyroidism, thyroiditis, diabetes mellitus, hyperthyroidism, and hypophysitis), which were included in the analysis regardless of treatment since these events are often managed without immunosuppression.

Supplementary Table S9. Baseline characteristics of patients who discontinued all components of the nivolumab plus ipilimumab with chemotherapy treatment regimen due to TRAEs

Characteristic	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 61)
Age, years	
Median (range)	66 (44–78)
<65, *n* (%)	27 (44)
≥65 to <75, *n* (%)	25 (41)
≥75, *n* (%)	9 (15)
Sex, *n* (%)	
Male	39 (64)
Female	22 (36)
Region, *n* (%)	
North America	2 (3)
Europe	43 (70)
Asia	6 (10)
Rest of the world[a]	10 (16)
ECOG PS,[b] *n* (%)	
0	27 (44)
1	34 (56)
Smoking status, *n* (%)	
Never smoked	3 (5)
Current or former	58 (95)
Tumor histology, *n* (%)	
Squamous	13 (21)
Non-squamous	48 (79)
Metastasis, *n* (%)	
Liver	8 (13)
Bone	14 (23)
CNS	8 (13)
Tumor PD-L1 expression, *n* (%)	
Quantifiable	60 (98)
<1%	26 (43)
≥1%	34 (57)
1-49%	25 (42)
≥50%	9 (15)

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; TRAE, treatment-related adverse event.

[a] Argentina Australia, Brazil, and Chile.

[b] 67% of patients with non-squamous histology received optional pemetrexed maintenance.

Supplementary Table S10. PFS, ORR, DOR, and treatment-free interval in patients who discontinued treatment due to TRAEs

	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 61)
PFS	
Median, months (95% CI)	5.1 (2.6–14.5)
1-year rate (95% CI)	44.0 (28.9–58.1)
ORR, n/N (% [95% CI])	31/61 (51 [37.7–63.9])
Median DOR after discontinuation,[a] months (95% CI)	14.5 (2.9–NR)
Ongoing response for ≥1 year after discontinuation, % (95% CI)	56 (36–72)
Treatment-free interval[b]	
Median, months (95% CI)	11.9 (3.8–21.0)
1-year rate (95% CI)	48.4 (35.2–60.3)

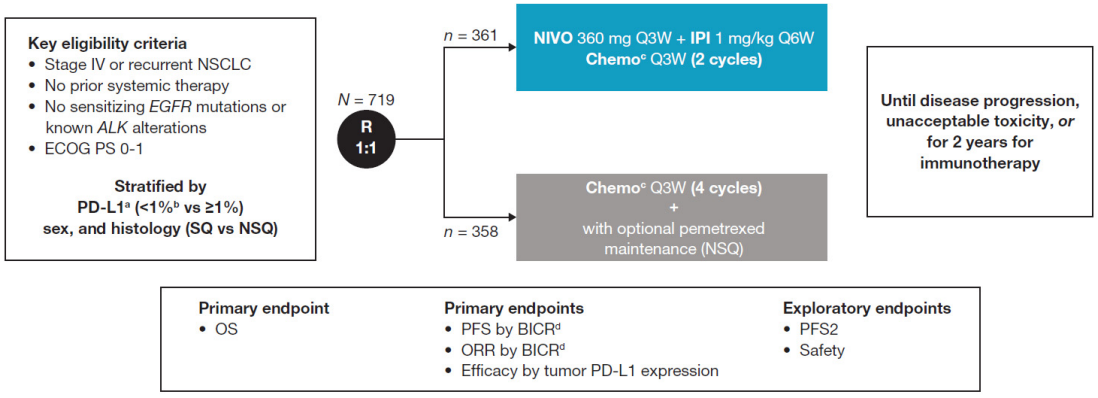
CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event.
23.3 months minimum follow-up; *post hoc* analysis includes patients with TRAEs (reported between first dose and 30 days after last dose of study treatment) that were considered leading to discontinuation of all components of study treatment.
[a] 2 responders (among patients who discontinued due to TRAEs) had their responses end before treatment end date and therefore were excluded from the analysis of DOR after discontinuation.
[b] Treatment-free interval is defined as time from last dose of study treatment to start of subsequent systemic treatment or death.

Supplementary Table S11. Subsequent treatment in patients who discontinued all components of the nivolumab plus ipilimumab with chemotherapy treatment due to TRAEs

	Patients who discontinued all components of regimen due to TRAEs[a,b]	
	Nivolumab plus ipilimumab with chemotherapy (2 cycles) (*n* = 61)	**Chemotherapy (*n* = 21)**
Any subsequent therapy, *n* (%)	19 (31)	11 (52)
Subsequent radiotherapy, *n* (%)	6 (10)	4 (19)
Subsequent systemic therapy, *n* (%)	14 (23)	10 (48)
Immunotherapy	4 (7)	8 (38)
Targeted therapy	3 (5)	2 (10)
Chemotherapy	13 (21)	8 (38)
Platinum-doublet chemotherapy	9 (15)	2 (10)

TRAE, treatment-related adverse event.
[a] All percentages for subsequent treatment types are calculated out of all patients who discontinued all components of the nivolumab plus nivolumab with chemotherapy treatment due to TRAEs.
[b] Patients with TRAEs reported between first dose and 30 days after last dose of study treatment that were considered leading to discontinuation of all components of regimen.

Supplementary Figure S1. Study design.



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ALK, anaplastic lymphoma kinase gene; BICR, blinded independent central review; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor gene; IHC, immunohistochemical; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PFS2, PFS after next line of treatment; Q3W, every 3 weeks; Q6W, every 6 weeks; SQ, squamous.

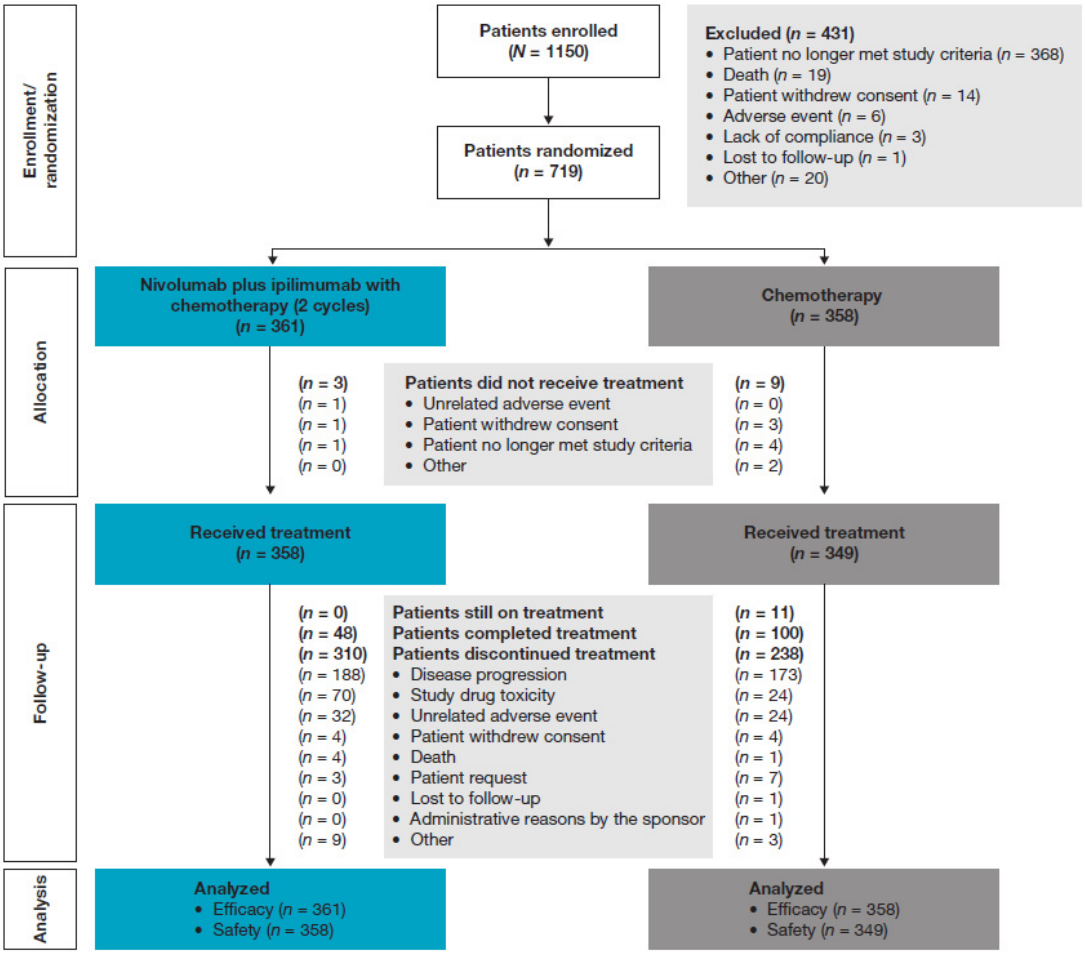
[a] Determined by the PD-L1 IHC 28-8 pharmDx assay (Agilent Dako).

[b] Patients unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients.

[c] NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin.

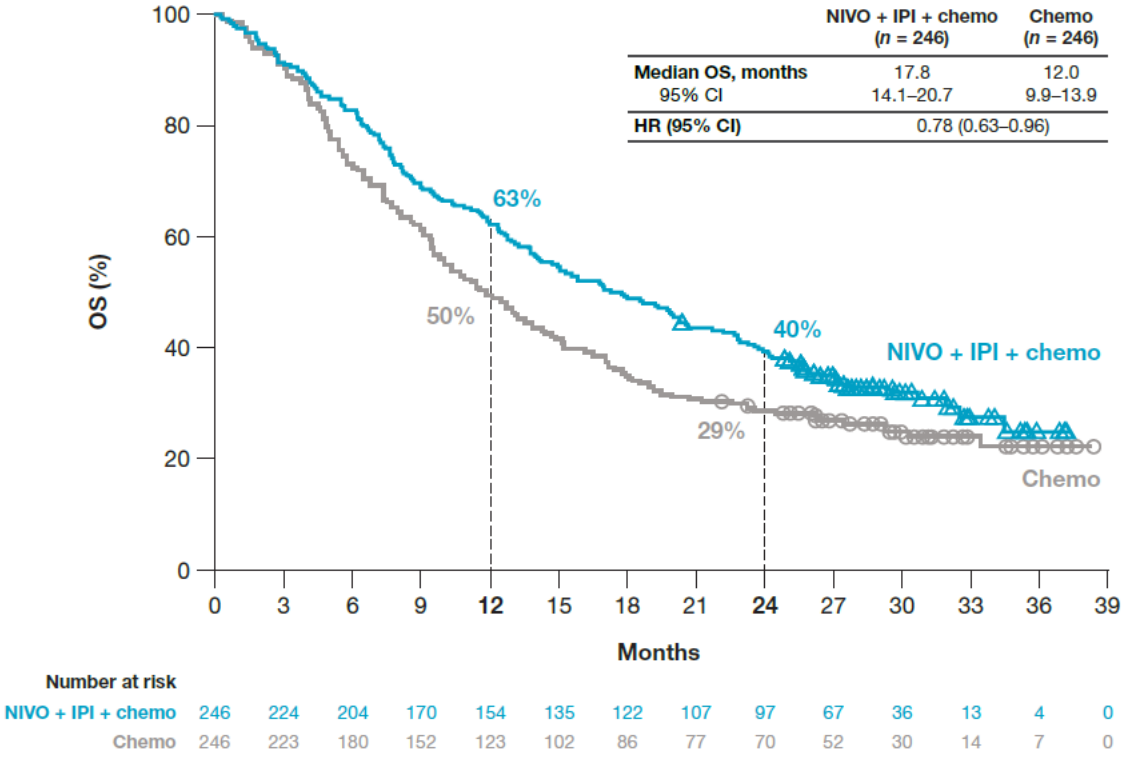
[d] Hierarchically statistically tested.

Supplementary Figure S2. CONSORT flow diagram.

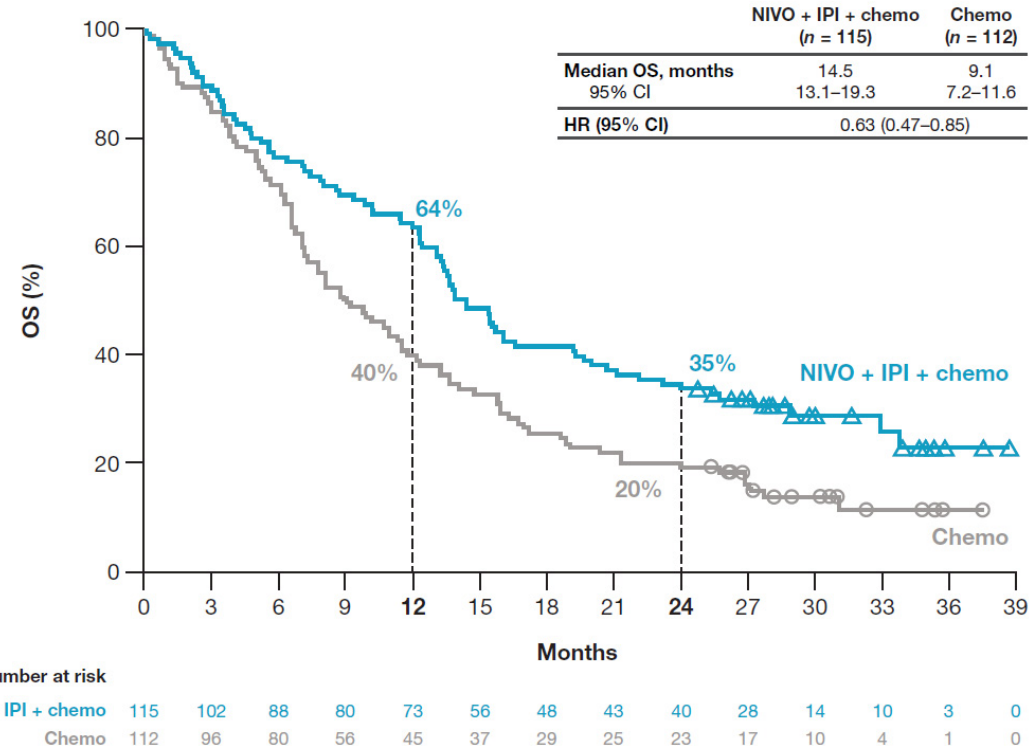


Supplementary Figure S3. OS in patients with non-squamous (A) and squamous (B) tumor histology.

A



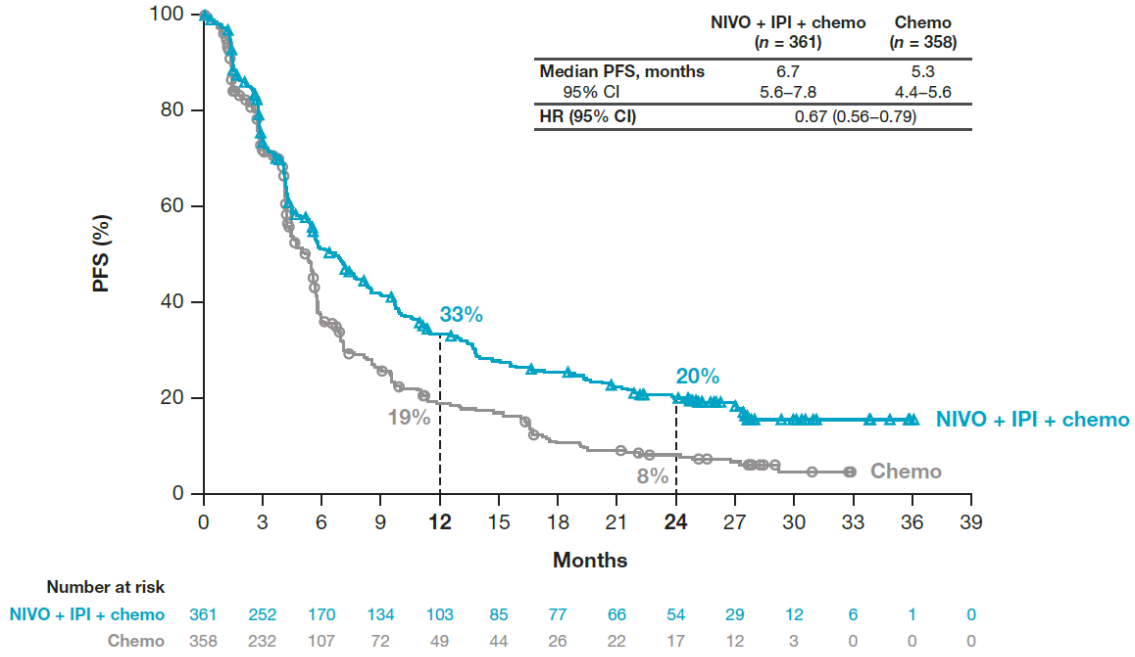
B



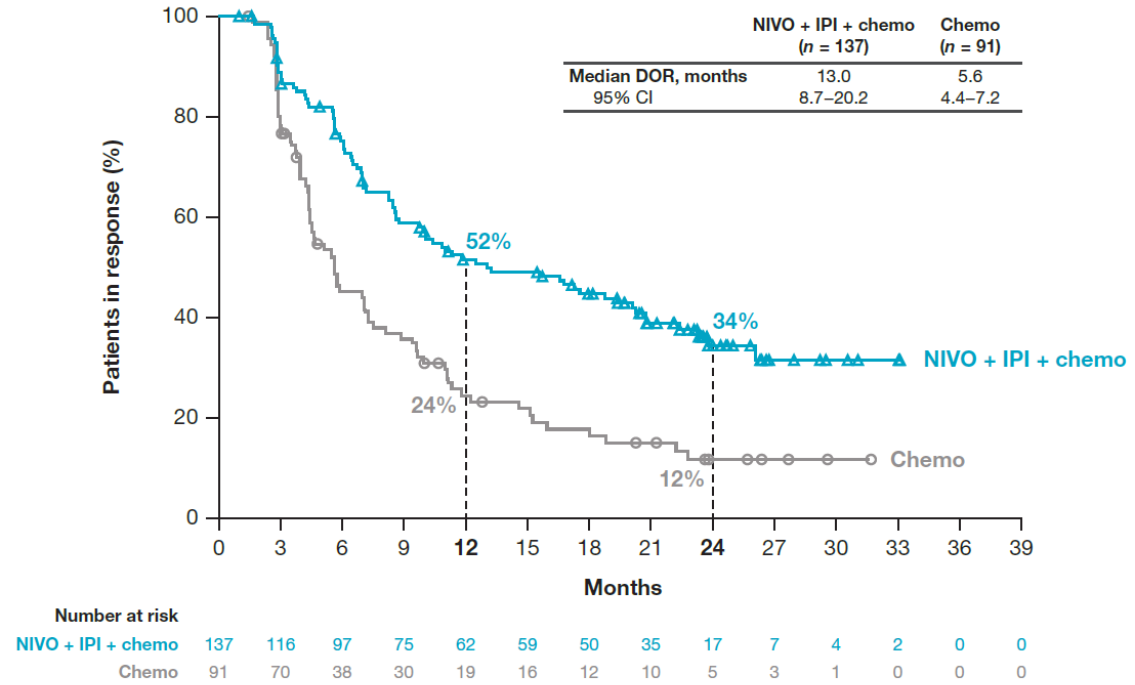
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.
24.4 months minimum follow-up.

Supplementary Figure S4. PFS (A) and DOR (B) in all randomized patients.

A



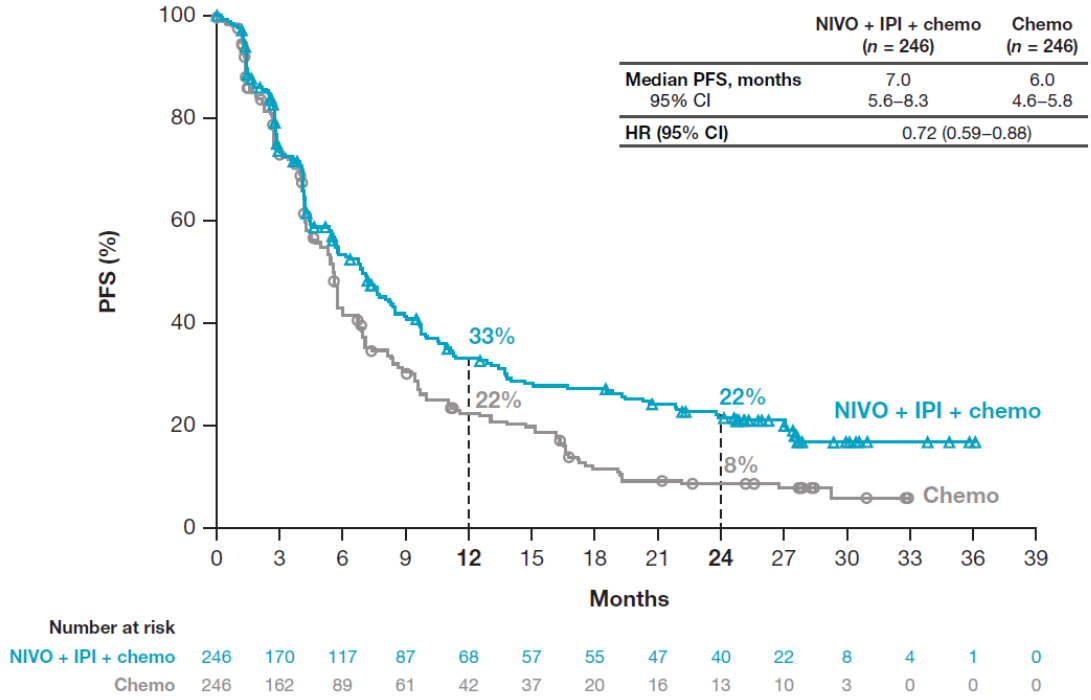
B



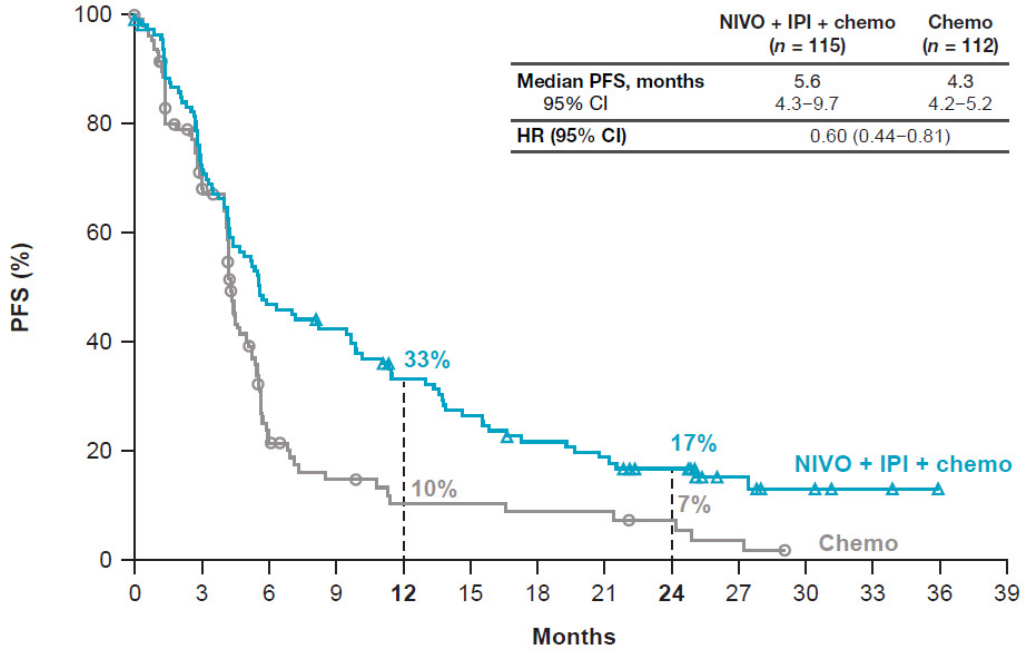
Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival.
23.3 months minimum follow-up.

Supplementary Figure S5. PFS by non-squamous (A) and squamous (B) tumor histology and by tumor PD-L1 expression <1% (C) and ≥1% (D).

A



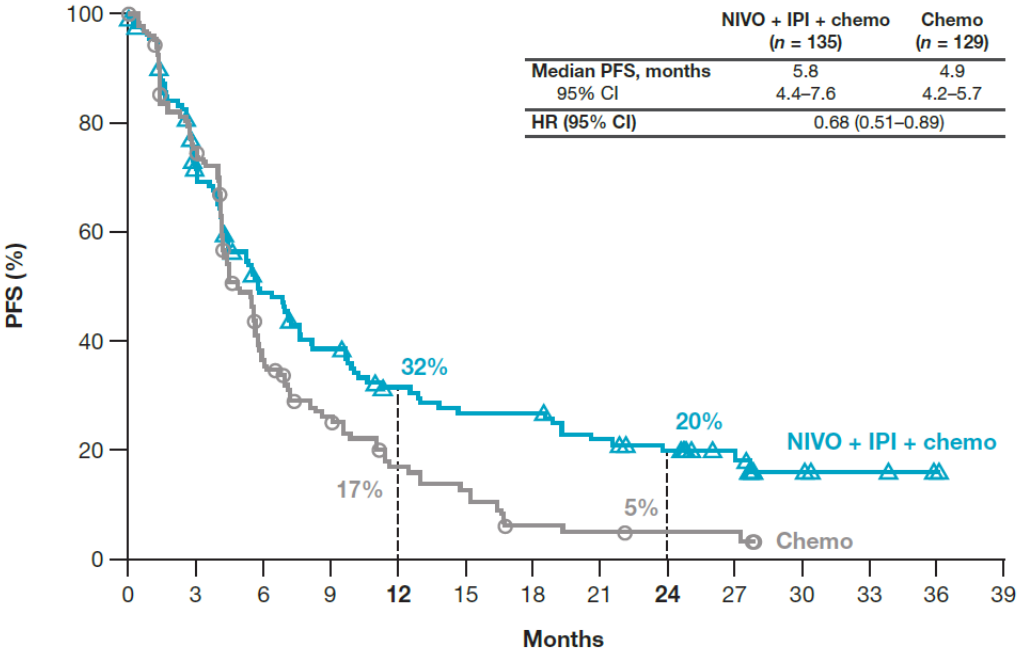
B



	NIVO + IPI + chemo (*n* = 115)	Chemo (*n* = 112)
Median PFS, months	5.6	4.3
95% CI	4.3–9.7	4.2–5.2
HR (95% CI)	0.60 (0.44–0.81)	

Number at risk														
NIVO + IPI + chemo	115	82	53	47	35	28	22	19	14	7	4	2	0	0
Chemo	112	70	18	11	7	7	6	6	4	2	0	0	0	0

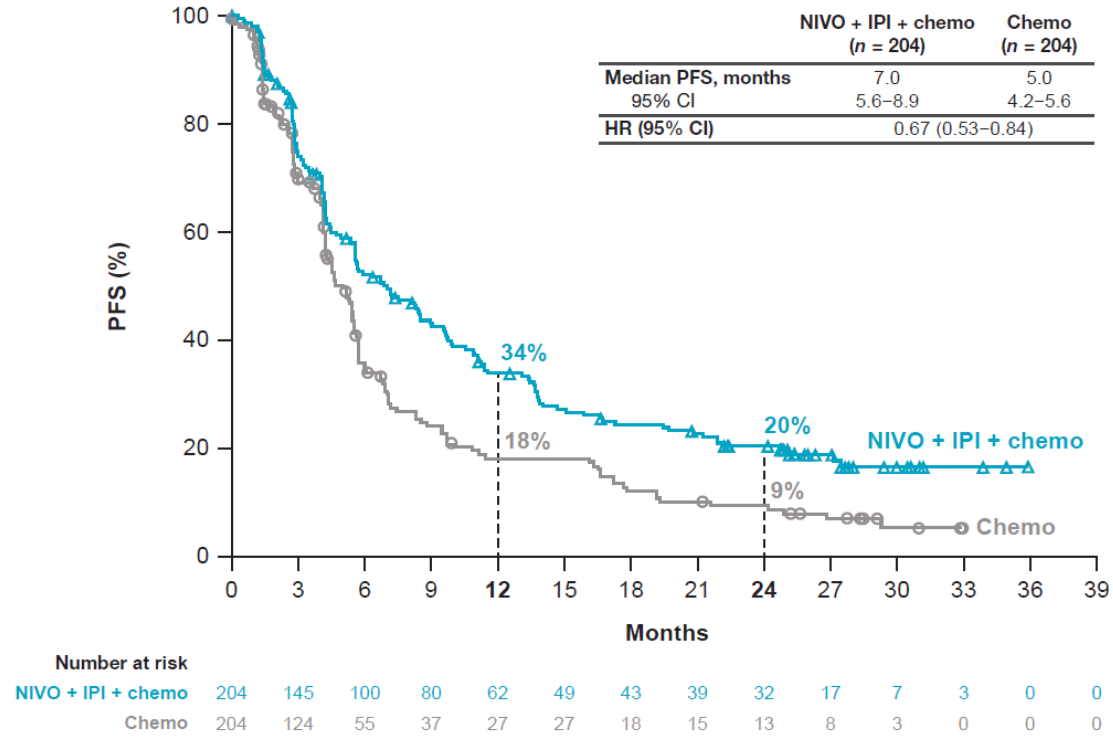
C



	NIVO + IPI + chemo (*n* = 135)	Chemo (*n* = 129)
Median PFS, months	5.8	4.9
95% CI	4.4–7.6	4.2–5.7
HR (95% CI)	0.68 (0.51–0.89)	

Number at risk														
NIVO + IPI + chemo	135	90	58	45	34	29	29	23	19	11	5	3	1	0
Chemo	129	91	41	27	16	12	5	4	3	3	0	0	0	0

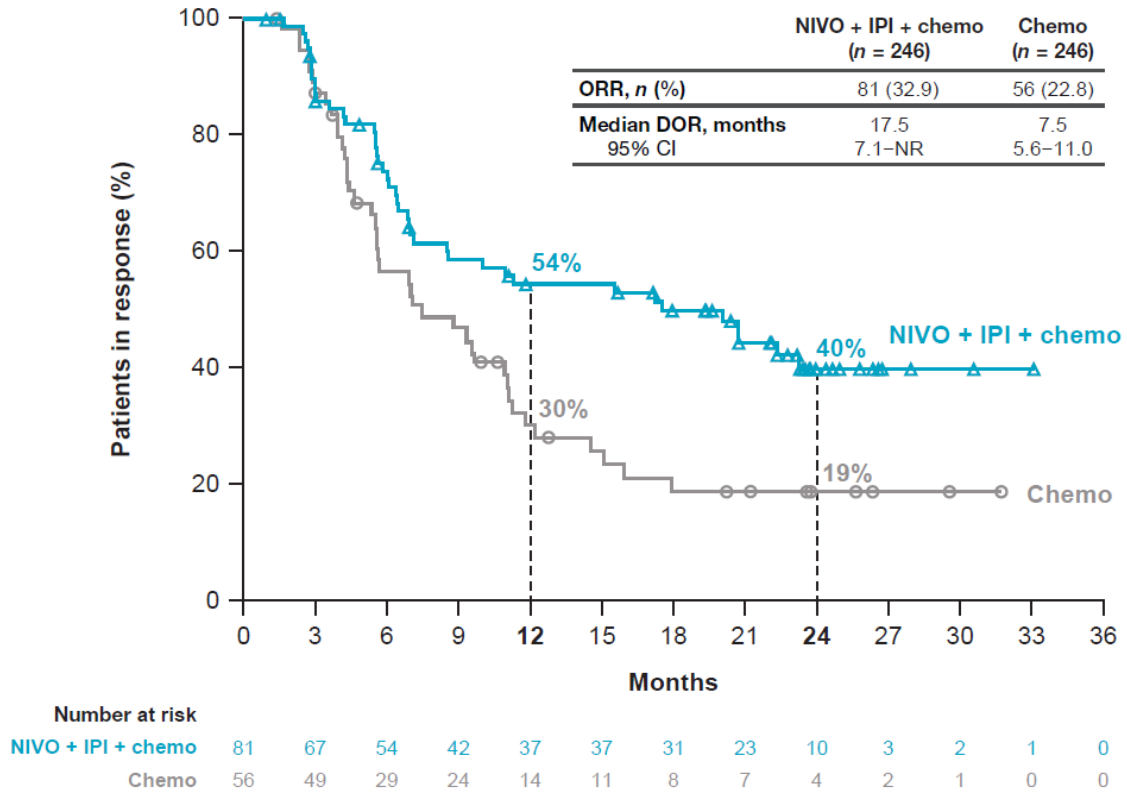
D



Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; PFS, progression-free survival.
23.3 months minimum follow-up.

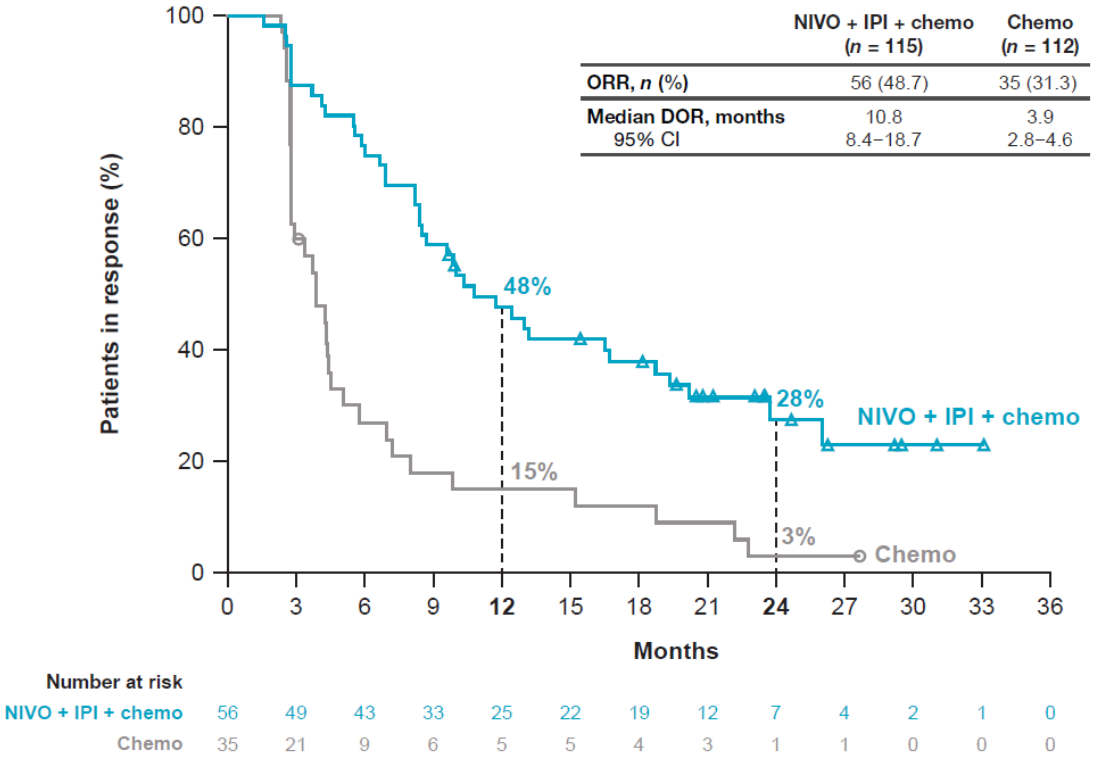
Supplementary Figure S6. DOR by non-squamous (A) and squamous (B) tumor histology, and by tumor PD-L1 expression <1% (C) and ≥1% (D).

A

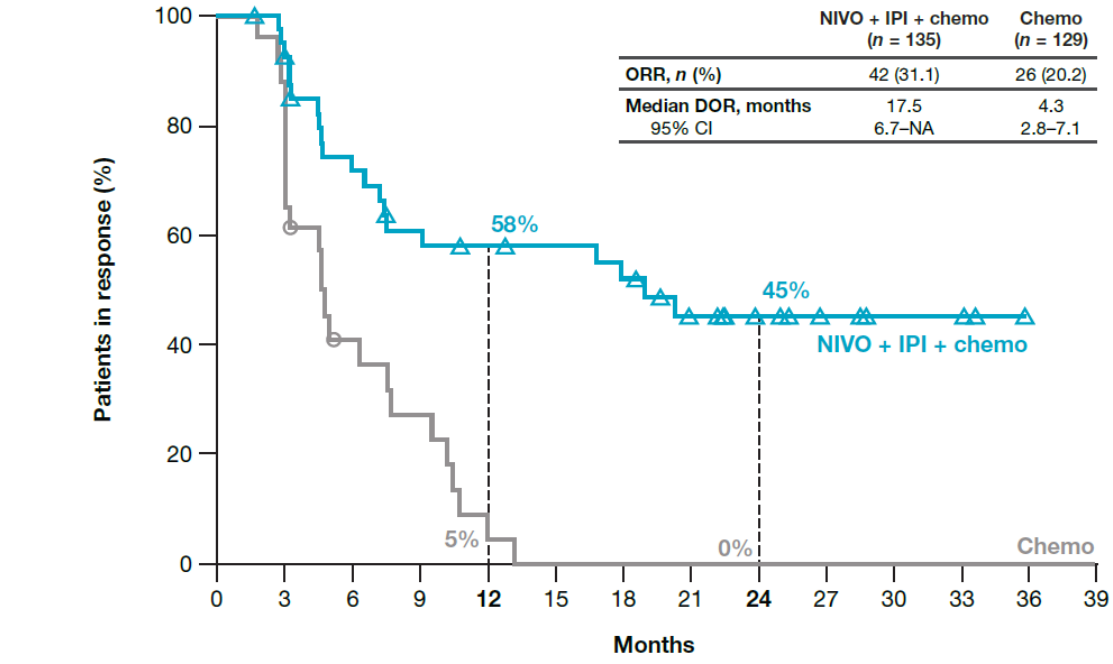


Number at risk													
NIVO + IPI + chemo	81	67	54	42	37	37	31	23	10	3	2	1	0
Chemo	56	49	29	24	14	11	8	7	4	2	1	0	0

B


NIVO + IPI + chemo (n = 115)
Chemo (n = 112)
ORR, n (%) 56 (48.7) 35 (31.3)
Median DOR, months 10.8 3.9
95% CI 8.4–18.7 2.8–4.6
Patients in response (%)
100
80
60
40
20
0
48%
28%
NIVO + IPI + chemo
15%
3%
Chemo
0 3 6 9 12 15 18 21 24 27 30 33 36
Months
Number at risk
NIVO + IPI + chemo 56 49 43 33 25 22 19 12 7 4 2 1 0
Chemo 35 21 9 6 5 5 4 3 1 1 0 0 0

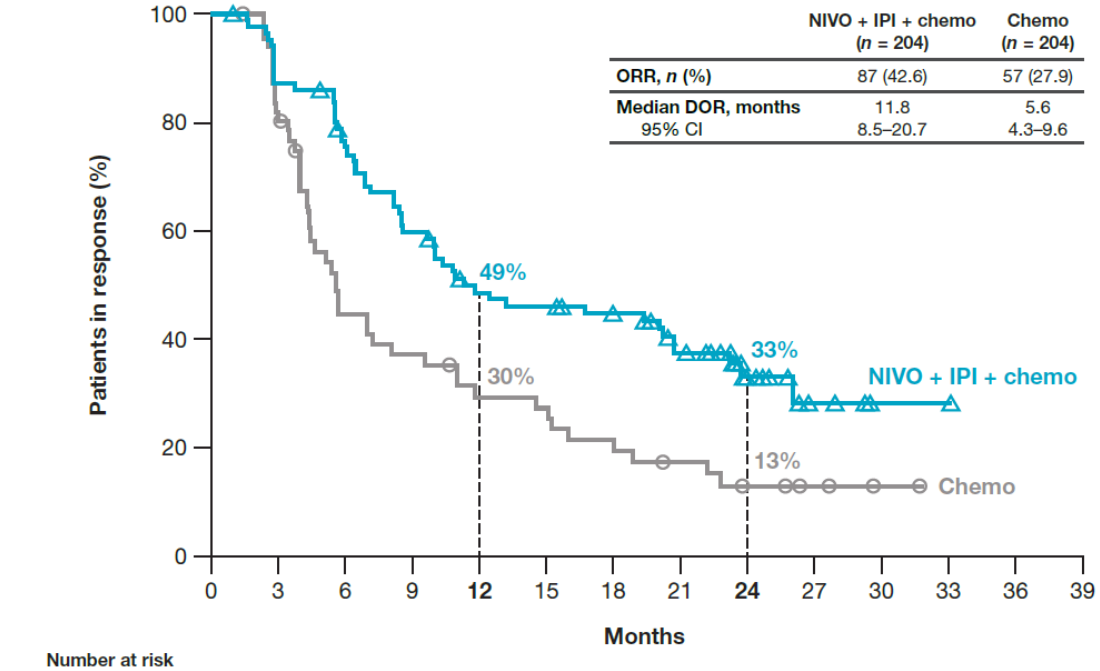
C



	NIVO + IPI + chemo (*n* = 135)	Chemo (*n* = 129)
ORR, *n* (%)	42 (31.1)	26 (20.2)
Median DOR, months	17.5	4.3
95% CI	6.7–NA	2.8–7.1

Number at risk														
NIVO + IPI + chemo	42	34	27	21	19	19	15	9	6	3	3	1	0	0
Chemo	26	17	8	5	1	0	0	0	0	0	0	0	0	0

D



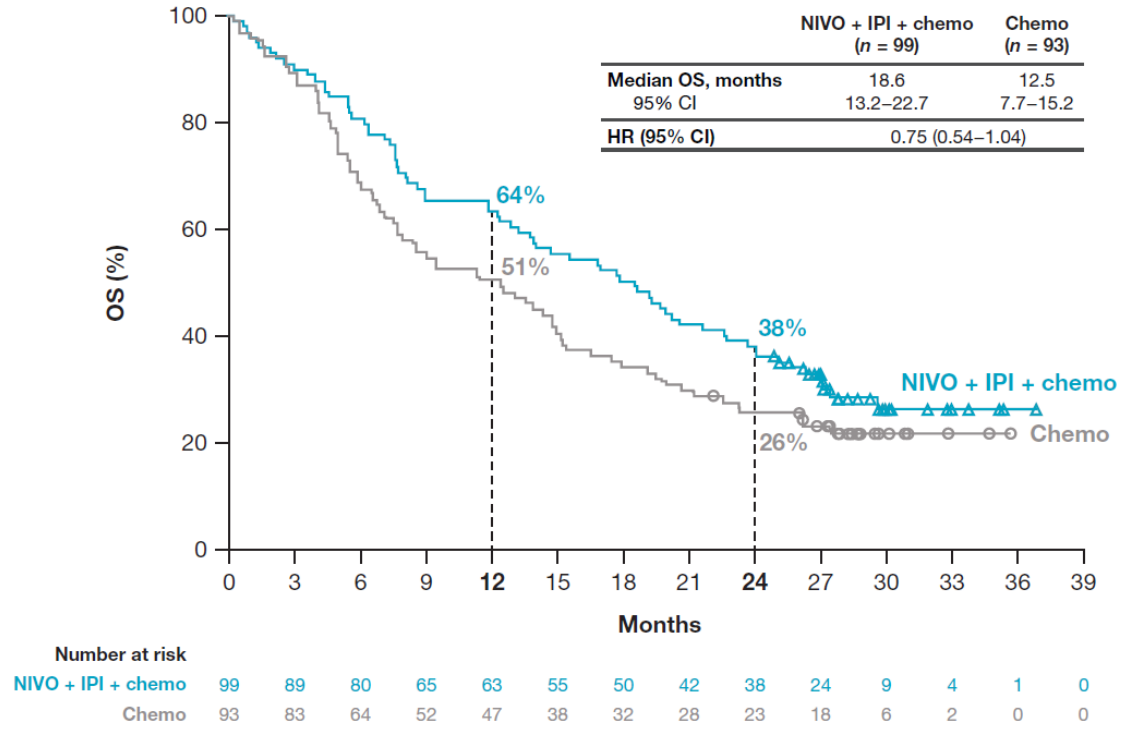
	NIVO + IPI + chemo (*n* = 204)	Chemo (*n* = 204)
ORR, *n* (%)	87 (42.6)	57 (27.9)
Median DOR, months	11.8	5.6
95% CI	8.5–20.7	4.3–9.6

Number at risk														
NIVO + IPI + chemo	87	75	64	50	39	37	33	25	11	4	1	1	0	0
Chemo	57	45	24	20	15	14	10	8	5	3	1	0	0	0

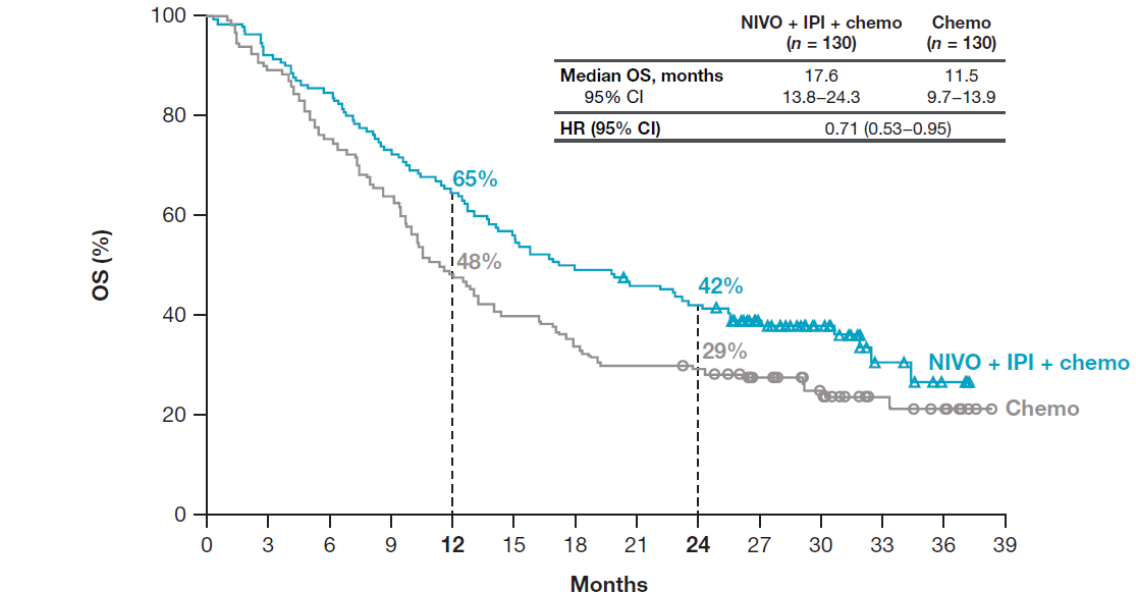
Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1.
23.3 months minimum follow-up.

Supplementary Figure S7. OS by combined histology and tumor PD-L1 expression level subgroups: patients with non-squamous histology and tumor PD-L1 expression level <1% (A), non-squamous histology and tumor PD-L1 expression level ≥1% (B), squamous histology and tumor PD-L1 expression level <1% (C), and squamous histology and tumor PD-L1 expression level ≥1% (D).

A



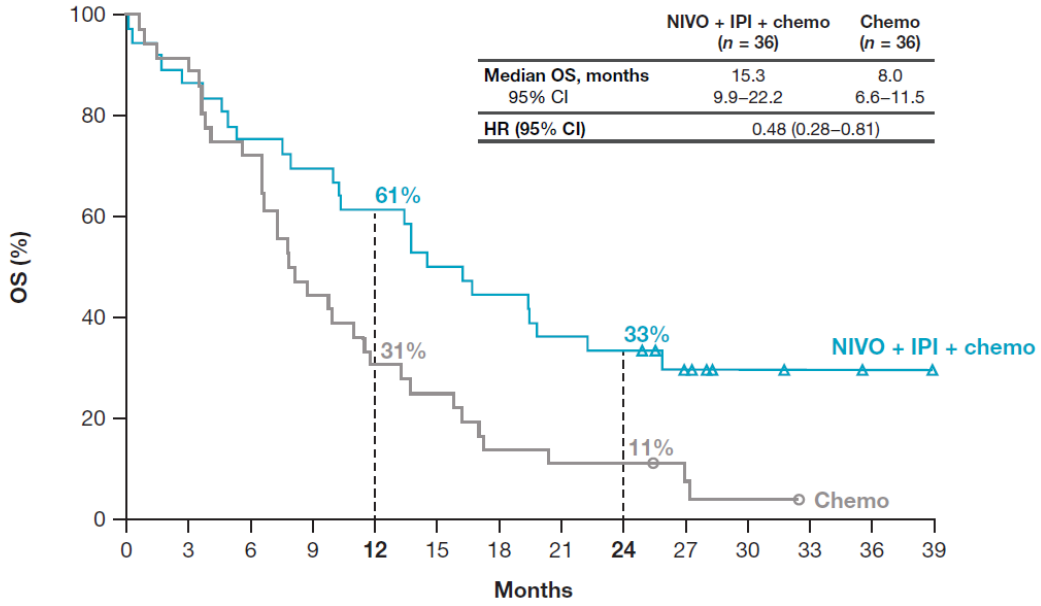
B



Number at risk

NIVO + IPI + chemo	130	120	110	95	84	73	65	59	54	39	25	9	3	0
Chemo	130	117	98	83	63	52	44	39	37	28	20	10	7	0

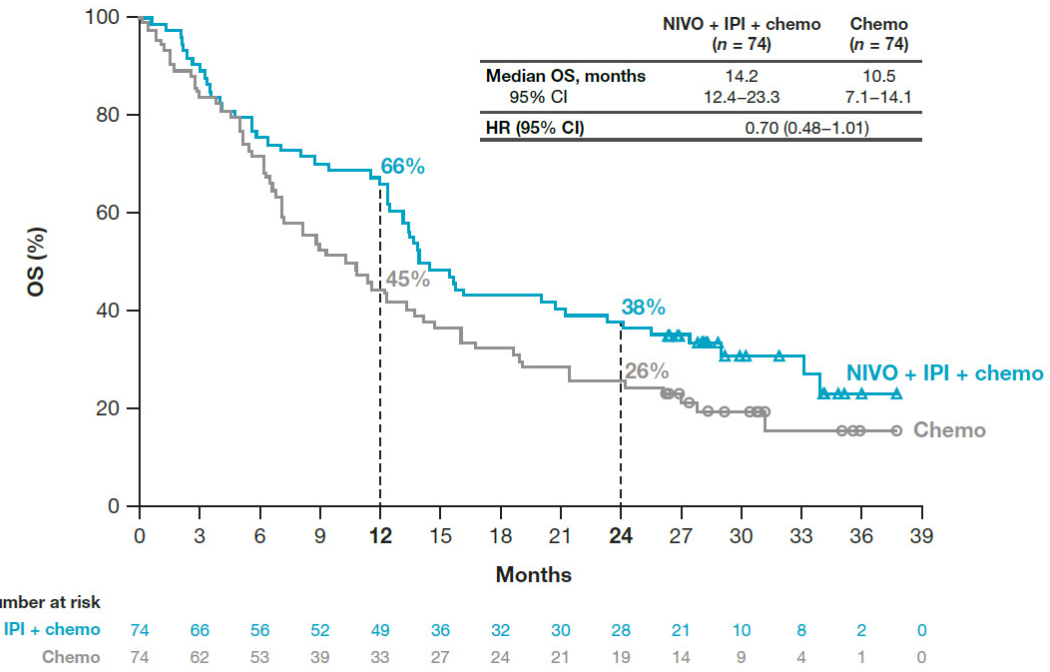
C



Number at risk

NIVO + IPI + chemo	36	31	27	25	22	18	16	13	12	7	4	2	1	0
Chemo	36	33	26	16	11	9	5	4	4	3	1	0	0	0

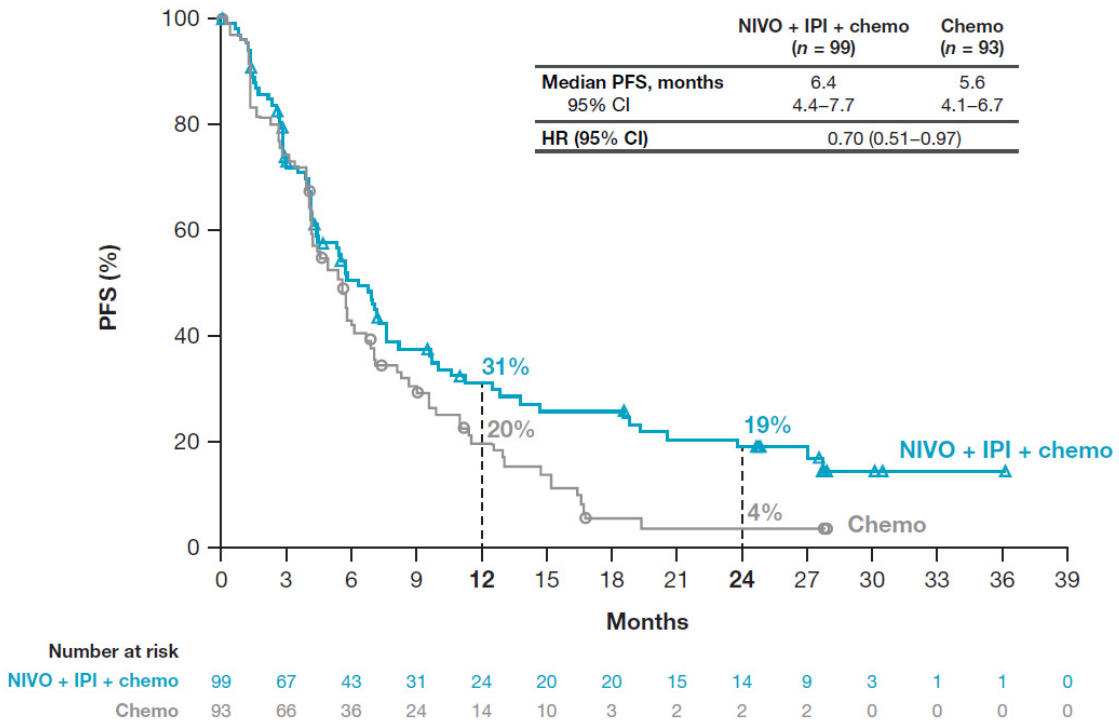
D



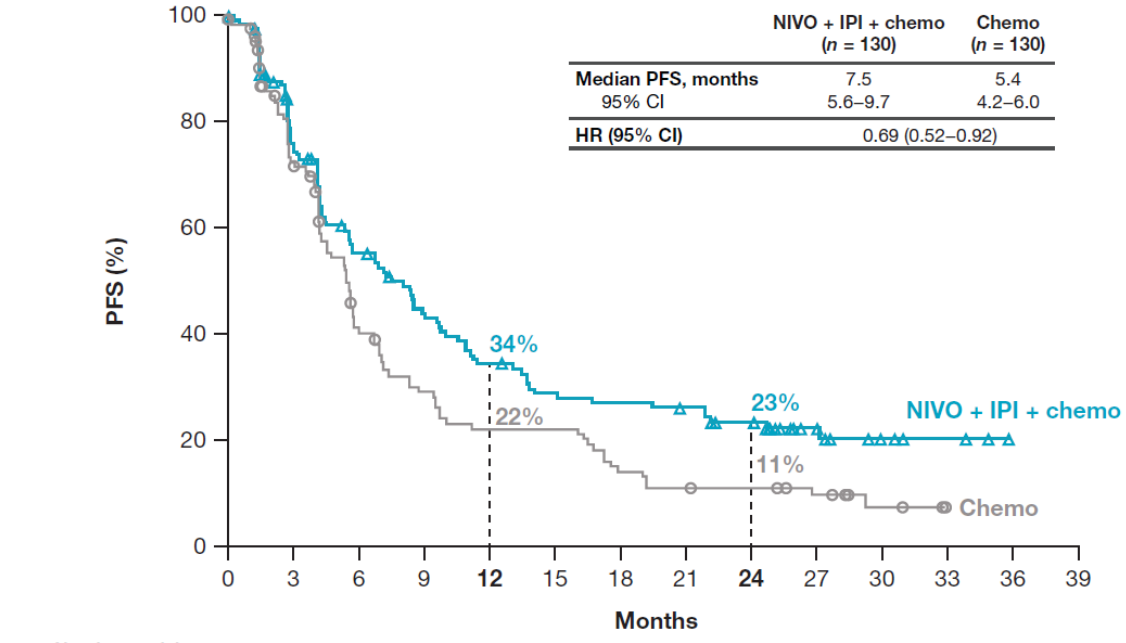
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.
24.4 months minimum follow-up.

Supplementary Figure S8. PFS by combined tumor histology and PD-L1 expression level subgroups: non-squamous histology and tumor PD-L1 expression level <1% (A), non-squamous histology and tumor PD-L1 expression level ≥1% (B), squamous histology and tumor PD-L1 expression level <1% (C), and squamous histology and tumor PD-L1 expression level ≥1% (D).

A



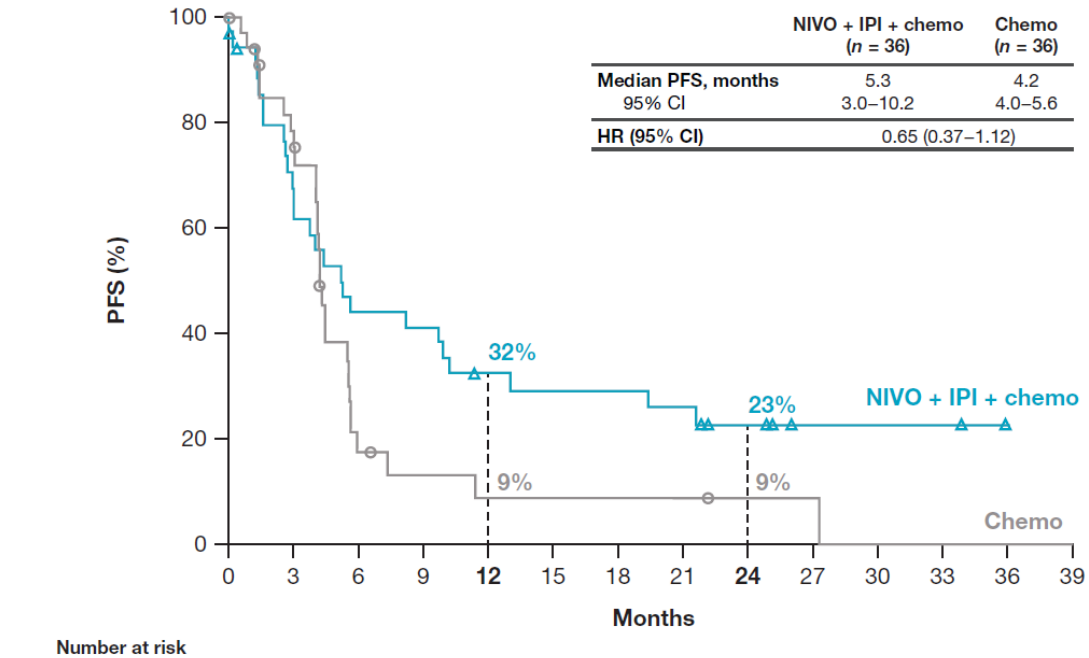
B



Number at risk

NIVO + IPI + chemo	130	91	65	50	39	32	30	28	23	12	5	3	0	0
Chemo	130	80	42	29	22	22	14	11	10	7	3	0	0	0

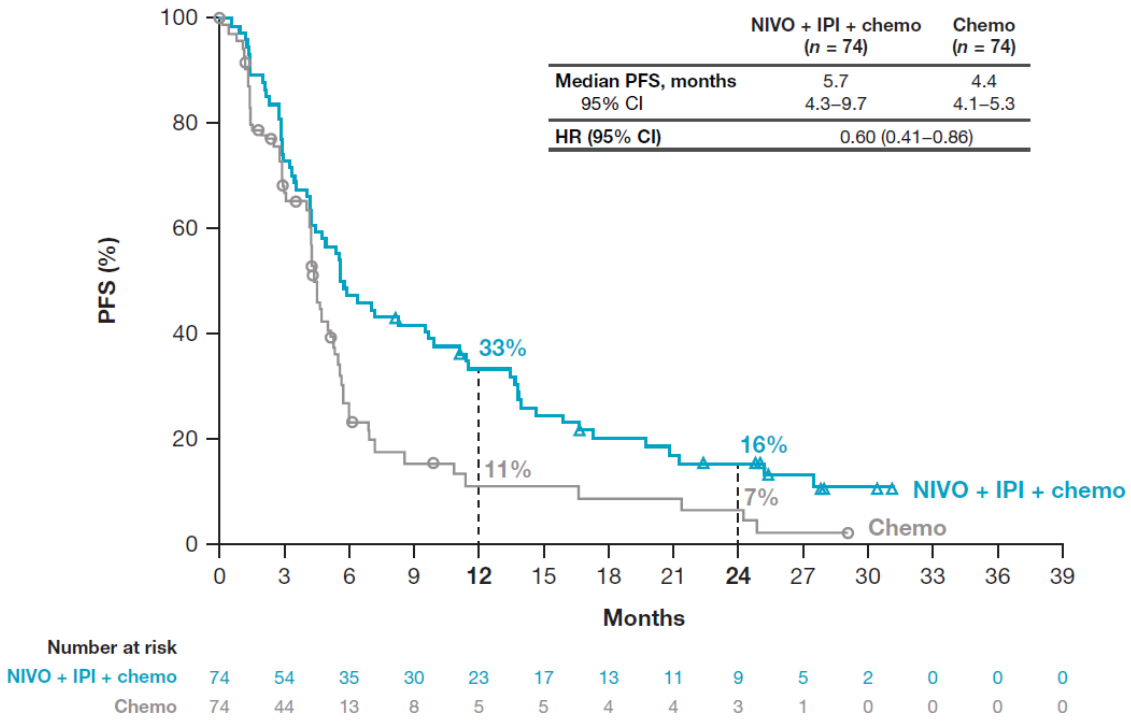
C



Number at risk

NIVO + IPI + chemo	36	23	15	14	10	9	9	8	5	2	2	2	0	0
Chemo	36	25	5	3	2	2	2	2	1	1	0	0	0	0

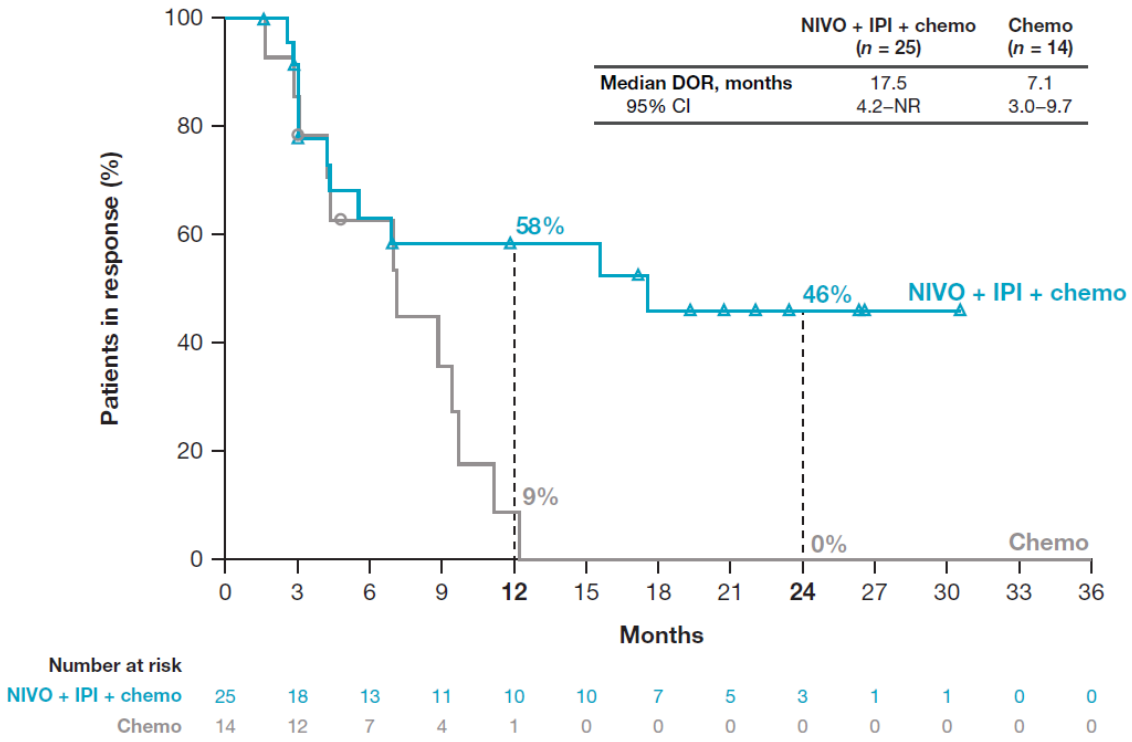
D



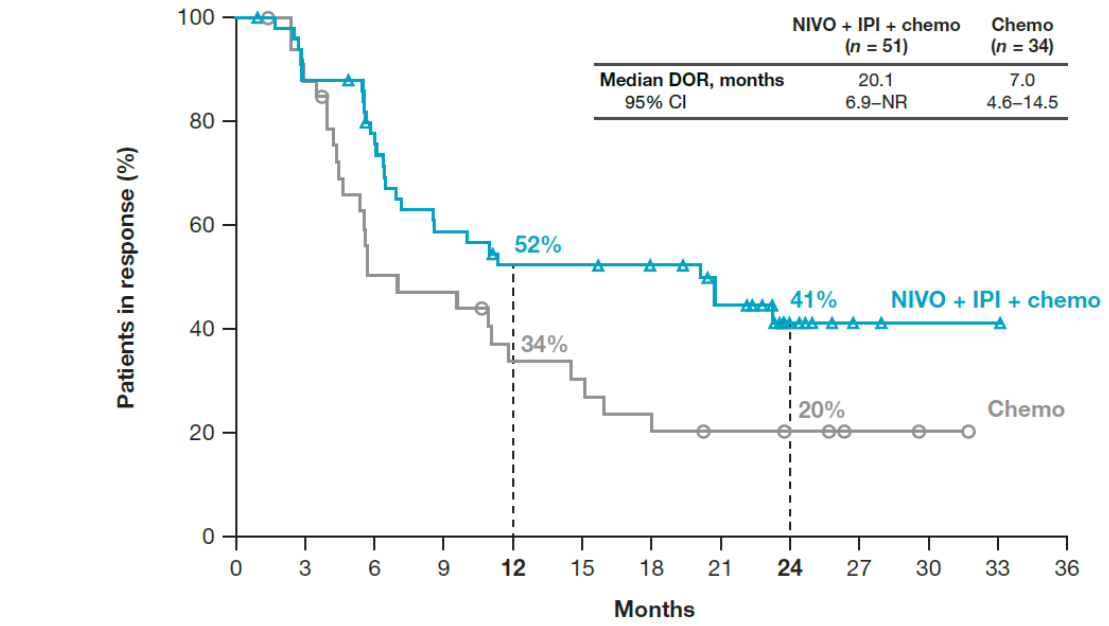
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; PFS, progression-free survival.
23.3 months minimum follow-up.

Supplementary Figure S9. DOR by combined histology and tumor PD-L1 expression level subgroups: non-squamous histology and tumor PD-L1 expression level <1% (A), non-squamous histology and tumor PD-L1 expression level ≥1% (B), squamous tumor PD-L1 expression level <1% (C), and squamous histology and tumor PD-L1 expression level ≥1% (D).

A



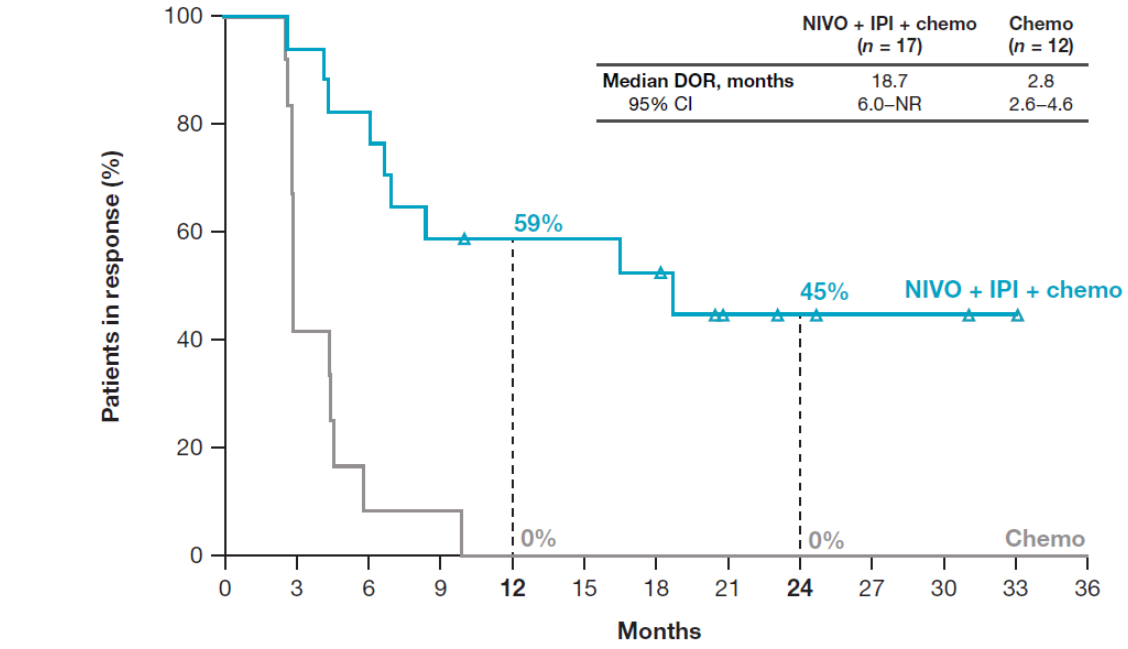
B



Number at risk

NIVO + IPI + chemo	51	44	37	28	24	24	22	17	7	2	1	1	0
Chemo	34	29	16	15	10	9	6	5	4	2	1	0	0

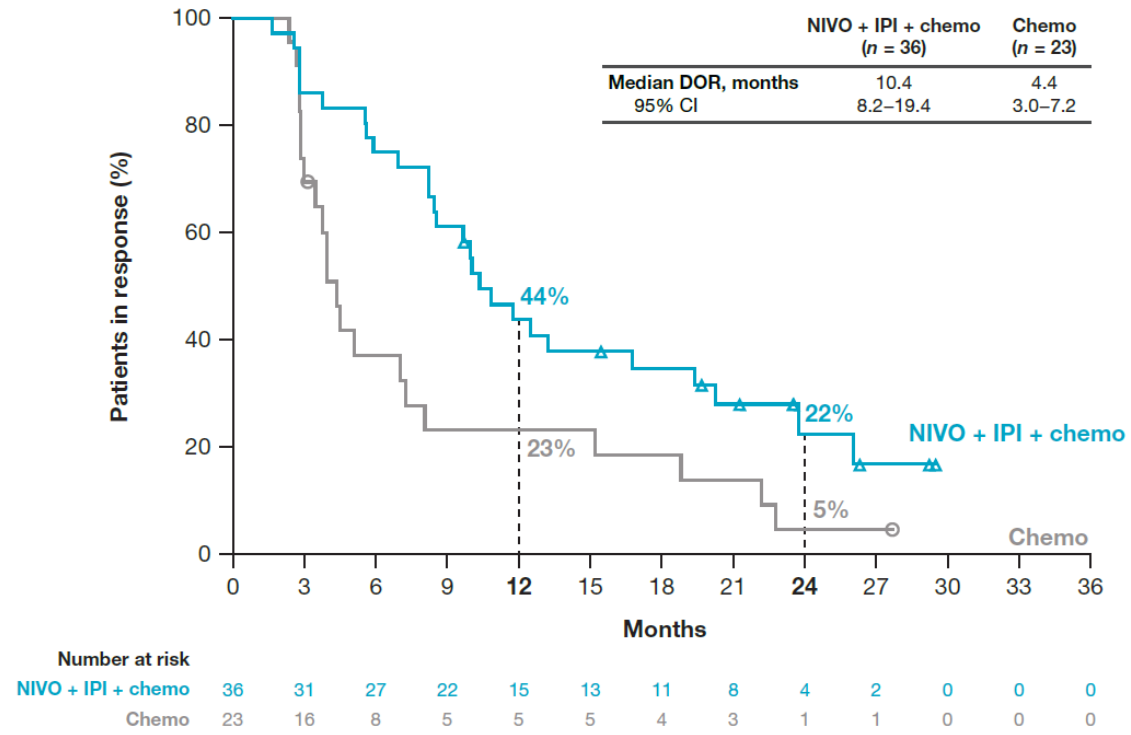
C



Number at risk

NIVO + IPI + chemo	17	16	14	10	9	9	8	4	3	2	2	1	0
Chemo	12	5	1	1	0	0	0	0	0	0	0	0	0

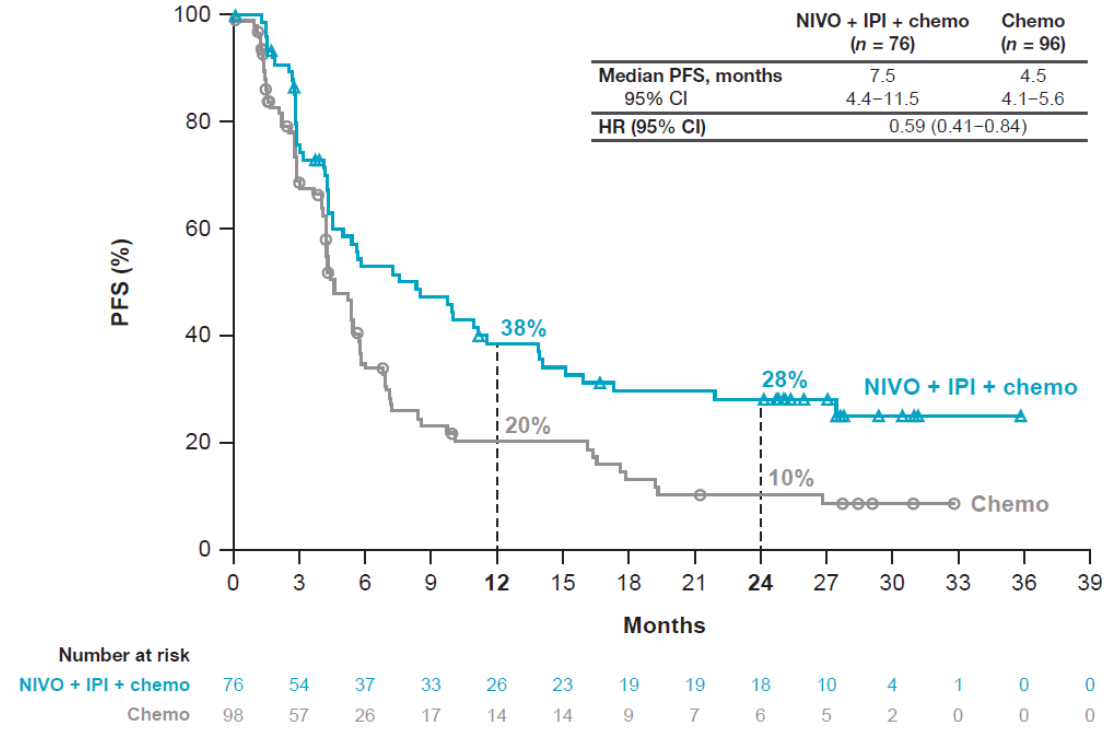
D



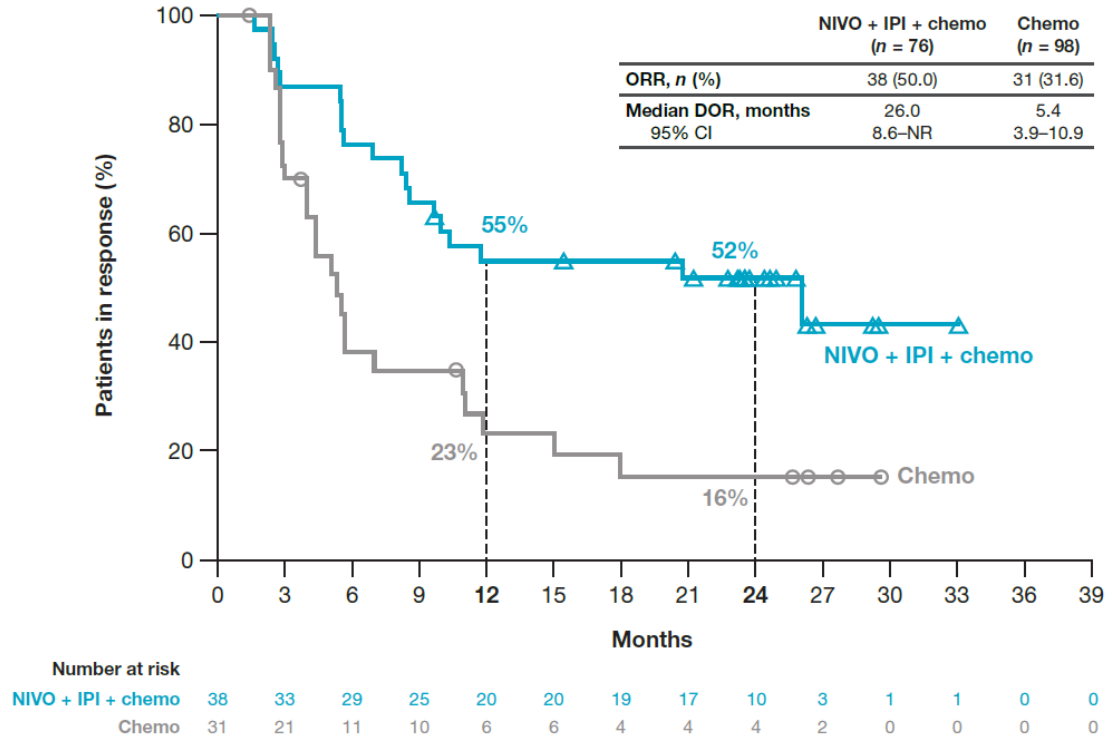
Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1.
23.3 months minimum follow-up.

Supplementary Figure S10. PFS (A) and DOR (B) in patients with tumor PD-L1 expression ≥50%.

A



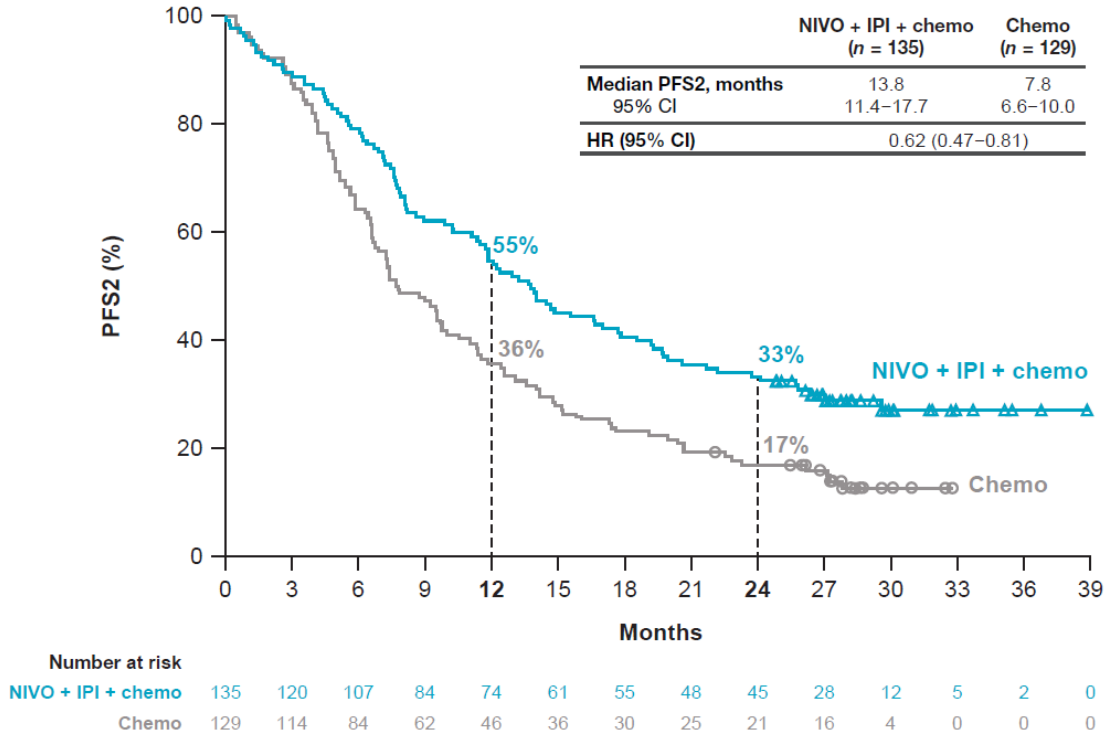
B



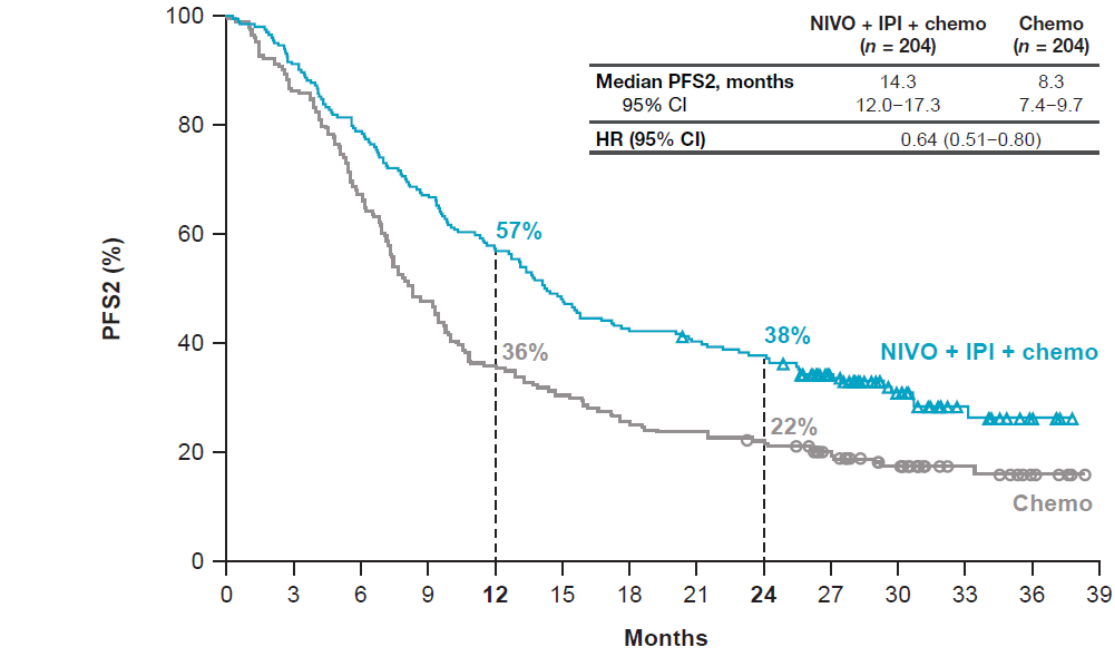
Chemo, chemotherapy; CI, confidence interval; DOR, duration of response; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1; PFS, progression-free survival.
23.3 months minimum follow-up.

Supplementary Figure S11. PFS2 by tumor PD-L1 expression <1% (A), ≥1% (B), and by non-squamous (C) and squamous (D) histology.

A

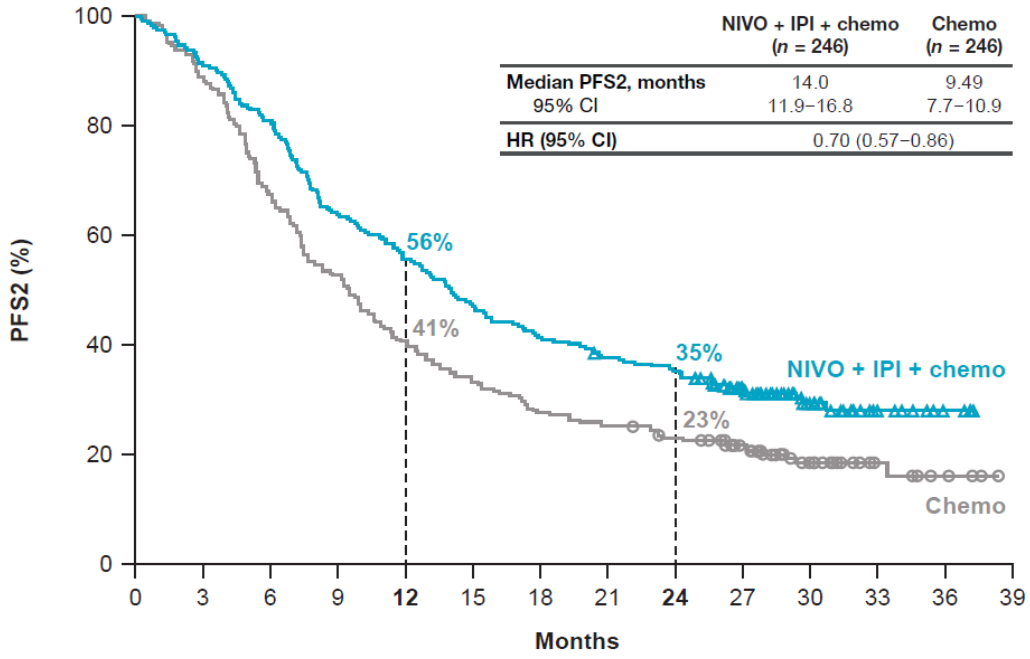


B



Number at risk														
NIVO + IPI + chemo	204	186	161	137	117	98	87	81	76	53	29	13	5	0
Chemo	204	176	138	97	73	62	51	48	44	34	23	11	5	0

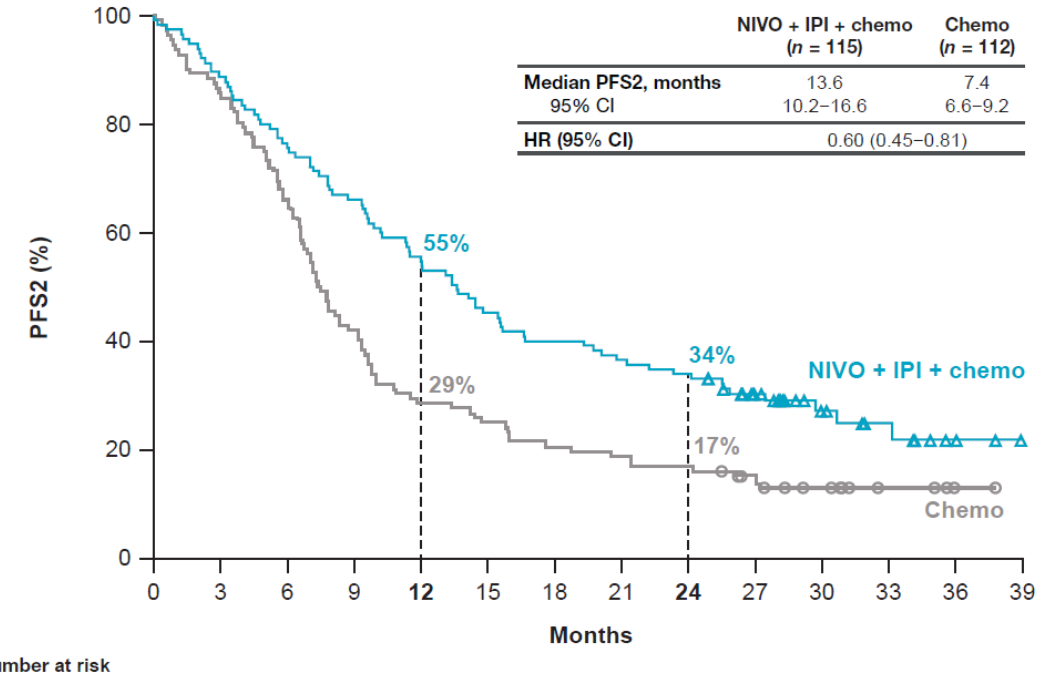
C



Number at risk

NIVO + IPI + chemo	246	224	199	157	137	116	102	92	86	59	30	10	4	0
Chemo	246	218	166	130	100	82	68	62	55	41	21	8	4	0

D

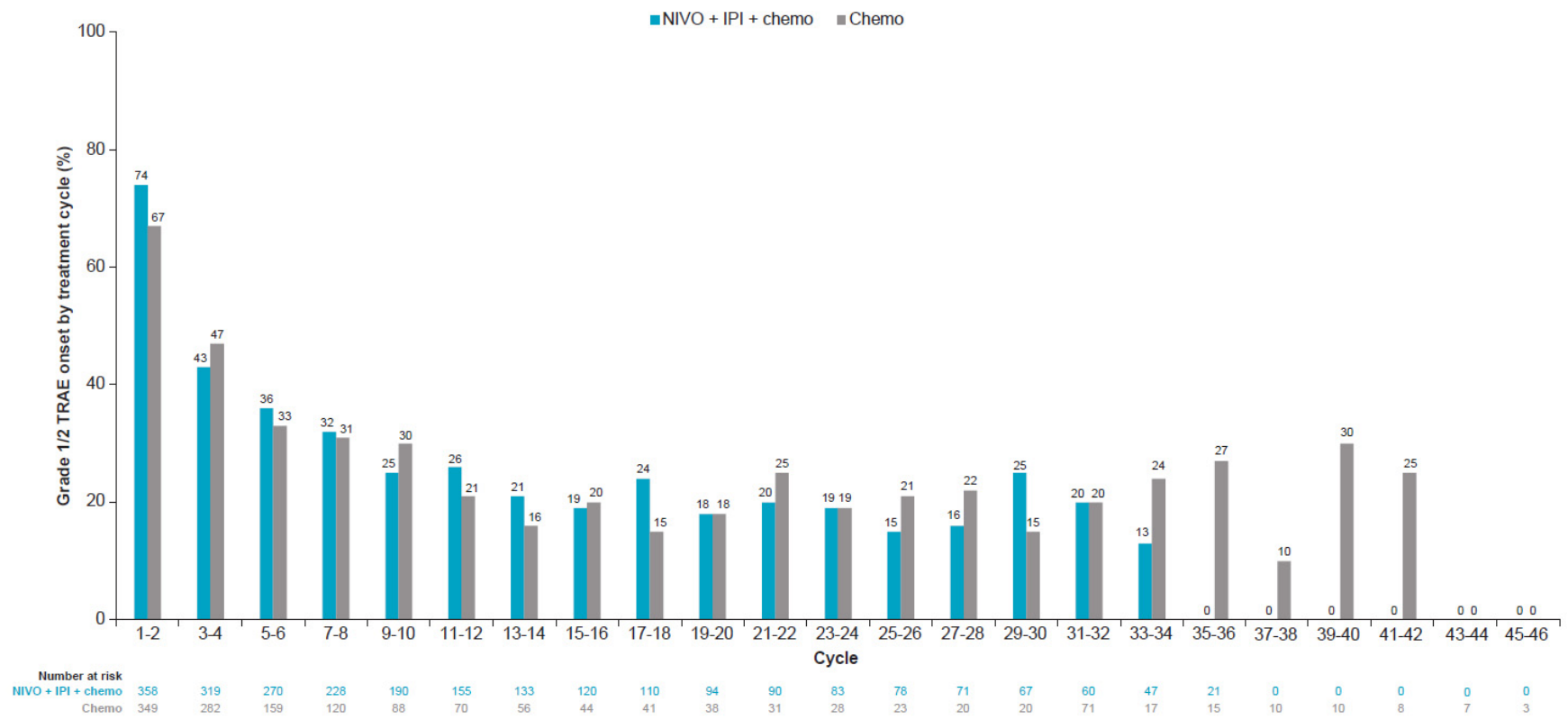


Number at risk

NIVO + IPI + chemo	115	102	88	76	63	52	46	42	39	26	13	8	3	0
Chemo	112	96	74	47	32	28	23	21	19	14	9	4	1	0

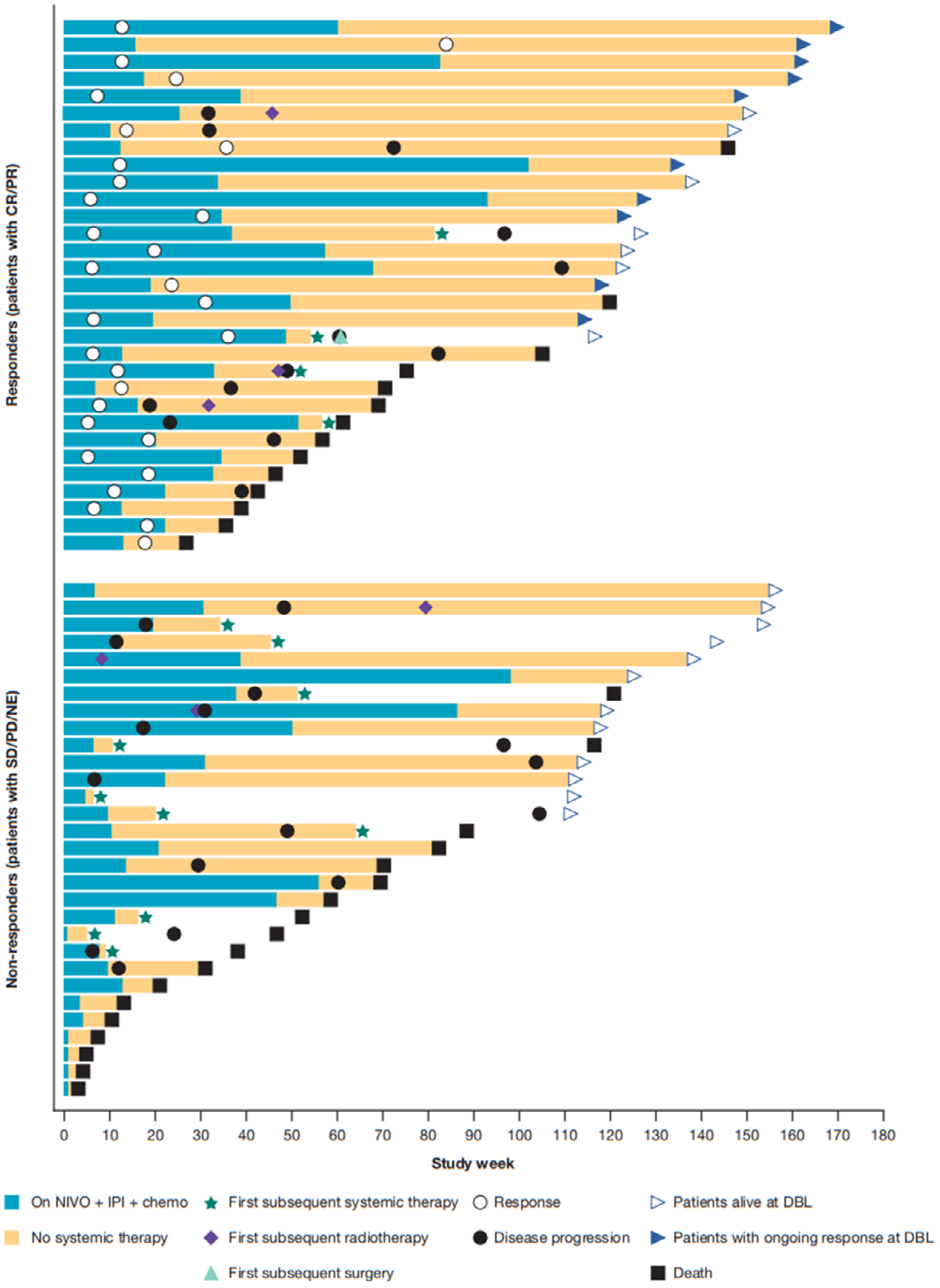
Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; PFS2, progression-free survival after next line of treatment. 23.3 months minimum follow-up.

Supplementary Figure S12. Grade 1/2 TRAE onset by treatment cycle.



Chemo, chemotherapy; IPI, ipilimumab; NIVO, nivolumab; TRAE, treatment-related adverse event.
Includes events reported between first dose and 30 days after last dose of study therapy. Overlapping TRAEs with same preferred term per patient were clustered and reported as unique TRAE. Patient is considered at risk in a pooled 2-cycle reporting interval if exposed to any study drug in that interval. Patient is counted once in each TRAE grade category for each pooled 2-cycle reporting interval with TRAE incidence.

Supplementary Figure S13. Treatment characteristics of patients who discontinued treatment with nivolumab plus ipilimumab due to TRAEs.



Chemo, chemotherapy; CR, complete response; DBL, database lock; IPI, ipilimumab; NE, not evaluable; NIVO, nivolumab; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event.