Supplemental Material

Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial

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Supplemental Methods

Statistical analysis

Inverse probability of censoring weighting (IPCW) involves censoring patients who switched from chemotherapy to immunotherapy at the point of switch and weighting remaining observations to eliminate censoring-related selection bias. Weights were calculated on the basis of baseline and time-varying characteristics (online supplemental table S1) to substitute data from patients censored at switch with data from patients with similar characteristics who did not switch. Logistic regression was used to calculate weights, and a weighted Cox proportional hazards model was used to estimate the HR and associated 95% CIs for nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone

Sensitivity analyses to test the robustness of the IPCW methodology were conducted using rank-preserving structural failure time (RPSFT), iterative parameter estimation (IPE), and two-stage estimation (TSE) methods. The RPSFT method estimated treatment effect by comparing counterfactual survival times (ie, assuming no switching from chemotherapy to any subsequent immunotherapy). Counterfactual survival times in the chemotherapy arm include time on chemotherapy plus time on immunotherapy multiplied by an acceleration factor determined by g-estimation.[1] The IPE method extended RPSFT by using parametric accelerated failure time distributions.[2] Both RPSFT and IPE assumed a common treatment effect for all participants, regardless of treatment timing, which may be problematic in later treatment lines. The TSE method also used a counterfactual framework.[3] In the first stage, a log-logistic parametric survival model estimated the effect of treatment switching (acceleration factor) in the chemotherapy arm to account for subsequent immunotherapy received by patients who switched. The first stage included patients with disease progression, defining a secondary baseline from that point. In the second stage, observed survival times in the nivolumab plus

ipilimumab with chemotherapy arm were compared with adjusted survival times in the chemotherapy arm using a Cox proportional hazards model. Bootstrapping was used to obtain 95% confidence intervals for hazard ratios in all three sensitivity analysis methods.

Supplemental Table S1. Summary of factors adjusted for each treatment-switching adjustment analysis methodology

Method	Covariates
All baseline covariates	Age, sex, smoking (current/former/never), EQ-5D, ECOG PS (0, ≥1), histology (squamous, nonsquamous), time since diagnosis
All time-varying covariates	Time since discontinuation, time since randomization, toxicity (adverse events ≥ grade 3), EQ-5D at visit, ECOG PS at visit
Significant covariates in the IPCW method	Age, smoking, histology, time since diagnosis, progression status
Significant covariates in the TSE method	EQ-5D at baseline, time since discontinuation, time since randomization, toxicity (adverse events ≥ grade 3)
Significant covariates in the RPSFT method	ECOG PS at baseline, EQ-5D at baseline
Significant covariates in the IPE method	ECOG PS at baseline, EQ-5D at baseline

ECOG PS, Eastern Cooperative Oncology Group performance status; EQ-5D, EuroQol-5 dimension; IPCW, inverse probability of censoring weighting; IPE, iterative parameter estimation; RPSFT, rank-preserving structural failure time; TSE, two-stage estimation.

Supplemental Table S2. Treatment and exposure summary

	Nivolumab plus ipilimumab with chemotherapy (n=358)	**Chemotherapy (n=349)**
Duration of therapy, months Median (range)	6.1 (0–24.4)	2.5 (0–58.2)
Median number of doses, (range)		
Nivolumab	9 (1–36)	NA
Ipilimumab	4 (1–18)	NA
Cycles of chemotherapy received, n (%)		
1	25 (7)	23 (7)
2	333 (93)	49 (14)
3	0	16 (5)
4	0	102 (29)
≥5	0	159 (46)
Patients receiving pemetrexed maintenance therapy,[a] n (%)	NA	159 (46[b])

[a]Pemetrexed maintenance therapy was optional for patients with nonsquamous tumor histology in the chemotherapy group. [b]Optional pemetrexed maintenance was received by 67% of patients with nonsquamous histology.

NA, not applicable.

Supplemental Table S3. PFS by tumor PD-L1 expression or histology

	Nivolumab plus ipilimumab with chemotherapy			Chemotherapy			
	n	Median PFS (95% CI), months	4-year PFS rate (95% CI), %	n	Median PFS (95% CI), months	4-year PFS rate (95% CI), %	HR (95% CI)
PD-L1 <1%	135	5.8 (4.4–7.7)	12 (7–19)	129	5.0 (4.2–5.8)	3 (<1–8)	0.70 (0.53–0.92)
PD-L1 ≥1%	204	6.9 (5.6–8.9)	12 (8–17)	204	4.7 (4.2–5.6)	6 (3–11)	0.70 (0.56–0.87)
PD-L1 1–49%	128	6.7 (4.5–8.5)	10 (5–16)	106	5.3 (4.2–5.7)	5 (1–11)	0.75 (0.56–1.00)
PD-L1 ≥50%	76	8.3 (4.4–12.5)	15 (8–25)	98	4.5 (4.1-5.6)	8 (3–16)	0.62 (0.44–0.88)
Squamous	115	5.6 (4.3–9.7)	8 (4–15)	112	4.3 (4.2–5.2)	4 (1–11)	0.64 (0.48–0.86)
Nonsquamous	246	6.9 (5.5–8.4)	13 (9–18)	246	5.6 (4.6–5.8)	5 (3–10)	0.75 (0.61–0.91)

PFS per blinded independent central review.

CI, confidence interval; HR, hazard ratio; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Supplemental Table S4. PFS and DOR in patients by tumor PD-L1 expression and histology

	PD-L1 <1%				PD-L1 ≥1%			
	Squamous		Nonsquamous		Squamous		Nonsquamous	
	Nivolumab plus ipilimumab with chemotherapy (n=36)	Chemotherapy (n=36)	Nivolumab plus ipilimumab with chemotherapy (n=99)	Chemotherapy (n=93)	Nivolumab plus ipilimumab with chemotherapy (n=74)	Chemotherapy (n=74)	Nivolumab plus ipilimumab with chemotherapy (n=130)	Chemotherapy (n=130)
4-y PFS rate, %	16	NA	10	2	5	4	16	7
ORR, n (%)	17 (47)	12 (33)	25 (25)	14 (15)	36 (49)	23 (31)	51 (39)	33 (25)
Median DOR, months (95% CI)	18.7 (6.0–NR)	2.8 (2.6–4.6)	17.5 (4.4–47.2)	7.1 (3.0–9.7)	10.4 (8.2–19.4)	4.4 (3.0–7.2)	20.1 (7.1–33.0)	5.7 (4.4–11.8)

PFS and DOR per blinded independent central review.

CI, confidence interval; DOR, duration of response; PD-L1, programmed death ligand 1; PFS, progression-free survival; ORR, objective response rate.

Supplemental Table S5. ORR and BOR in all randomized patients

	Nivolumab plus ipilimumab with chemotherapy (n=361)	**Chemotherapy (n=358)**
Complete response	15 (4)	5 (1)
Partial response	122 (34)	85 (24)
Stable disease	165 (46)	186 (52)
Progressive disease	33 (9)	43 (12)
Unable to determine	26 (7)	38 (11)
Not reported	0	1 (<1)
ORR, % (95% CI)	38 (33–43)	25 (21–30)
DCR, %	84	77
Median time to response, months (min, max)	2.5 (1.1–42.2)	1.6 (1.2–22.2)

Data are n (%) unless otherwise indicated.

BOR, best overall response; CI, confidence interval; DCR, disease control rate; max, maximum; min, minimum; ORR, objective response rate.

Supplemental Table S6. DOR by tumor PD-L1 expression

	PD-L1 1–49%		PD-L1 ≥50%	
	Nivolumab plus ipilimumab with chemotherapy (n=128)	**Chemotherapy (n=106)**	**Nivolumab plus ipilimumab with chemotherapy (n=76)**	**Chemotherapy (n=98)**
Median DOR, months (95% CI)	10.8 (6.9–19.4)	7.0 (3.9–14.5)	26.0 (8.6–33.3)	5.4 (3.9–10.9)
ORR, n (%) (95% CI)	49 (38) (30–47)	25 (24) (16–33)	38 (50) (38–62)	31 (32) (23–42)
Ongoing response at 4 years, % (95% CI)	21 (10–34)	NA	28 (14–43)	18 (6–33)

DOR per blinded independent central review.

CI, confidence interval; DOR, duration of response; NA, not applicable; ORR, objective response rate; PD-L1, programmed death ligand 1.

Supplemental Table S7. PFS and DOR in patients who discontinued NIVO + IPI with chemo due to TRAEs

	Nivolumab plus ipilimumab with chemotherapy (n=61)
PFS	
Median (95% CI), months	5.1 (2.6–14.5)
4-year rate (95% CI), %	17 (7–32)
DOR	
Median (95% CI), months	14.5 (2.9–35.3)
Ongoing response at 4 years (95% CI), %	23 (7–43)

CI, confidence interval; DOR, duration of response; PFS, progression-free survival; TRAE, treatment-related adverse event.

Supplemental Table S8. Baseline demographic and disease characteristics of patients who switched treatment from chemotherapy to immunotherapy

Characteristic	Patients who switched treatment (n=129)
Median age, years (range)	63.0 (26.0–79.0)
Sex	
Female	37 (29)
Male	92 (71)
Smoking status	
Current/former	117 (91)
Never smoked	12 (9)
ECOG PS	
0	48 (37)
1	81 (63)
Region	
Asia	21 (16)
Europe	89 (69)
North America	7 (5)
Rest of world	12 (9)
Tumor histology	
Squamous	41 (32)
Nonsquamous	88 (68)
Tumor PD-L1 expression	
<1% or non-quantifiable	53 (41)
≥1%	76 (59)
Metastasis	
CNS	14 (11)
Liver	30 (23)
Bone	44 (34)

Data are n (%) unless otherwise noted.

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

Supplemental Table S9. Summary of TRAEs in all treated patients

	Nivolumab plus ipilimumab with chemotherapy (n=358)		Chemotherapy (n=349)	
TRAE,[a]	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Any TRAE	328 (92)	172 (48)	306 (88)	133 (38)
Most frequent TRAEs in all treated patients (≥10%)				
Nausea	99 (28)	5 (1)	124 (36)	3 (1)
Anemia	85 (24)	21 (6)	135 (39)	54 (16)
Pruritus	77 (22)	3 (1)	6 (2)	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
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
Vomiting	50 (14)	6 (2)	52 (15)	5 (1)
Neutropenia	35 (10)	25 (7)	60 (17)	33 (10)
Constipation	32 (9)	0	40 (12)	0
TRAEs leading to discontinuation of any component of regimen	79 (22)	65 (18)	31 (9)	18 (5)
Serious TRAEs	109 (30)	93 (26)	63 (18)	52 (15)
Treatment-related deaths[b]	8 (2)[b]	–	6 (2)[b]	–

Minimum follow-up, 49.1 months. Data are n (%) unless otherwise noted.

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

[b]Treatment-related deaths of the last dose in the nivolumab plus ipilimumab with chemotherapy arm (n=8): acute renal failure, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, sepsis (n=1 each), and diarrhea (n=2); treatment-related deaths in the

chemotherapy arm (n=6; 1 for each event): sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia.

TRAE, treatment-related adverse event.

Supplemental Table S10. Incidence of endocrine and non-endocrine IMAEs in the nivolumab plus ipilimumab with chemotherapy arm (n = 358)

IMAE	Any grade incidence n (%)	Grade 3/4 incidence n (%)
Endocrine		
Adrenal insufficiency	14 (4)	5 (1)
Hypothyroidism/thyroiditis	58 (16)	2 (1)
Diabetes mellitus	0	0
Hyperthyroidism	29 (8)	0
Hypophysitis	9 (2)	6 (2)
Non-endocrine		
Pneumonitis	21 (6)	10 (3)
Diarrhea/colitis	22 (6)	13 (4)
Hepatitis	21 (6)	16 (4)
Nephritis and renal dysfunction	6 (2)	2 (1)
Rash	65 (18)	15 (4)
Hypersensitivity	3 (1)	1 (<1)

IMAEs include adverse events reported between first dose and 100 days after the last dose of study drug. Patients who experienced IMAEs without worsening from baseline grade were excluded from time-to-resolution analysis.

IMAE, immune-mediated adverse event.

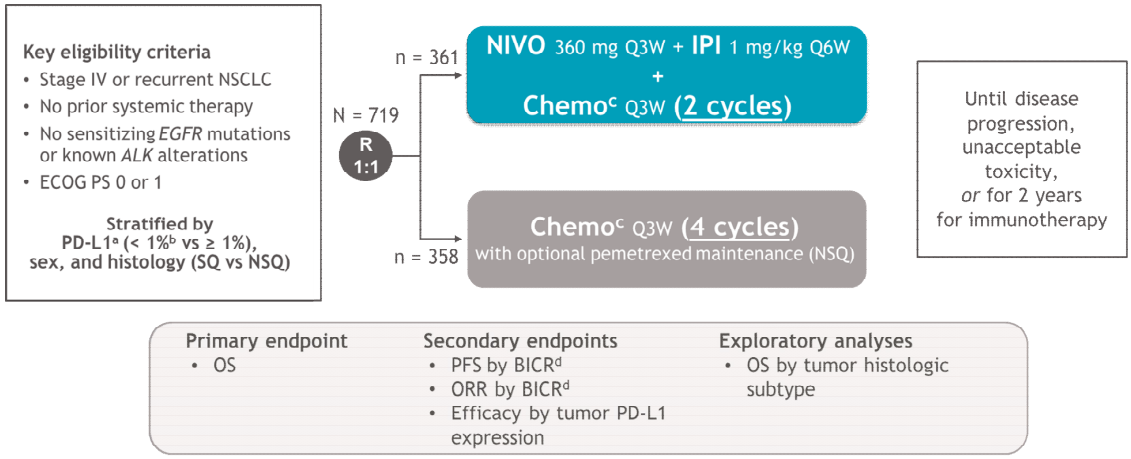
Supplemental Figure S1. Study design[4]

Database lock: February 13, 2023; minimum/median follow-up for overall survival (OS): 47.9/54.5 months.

[a]Determined by the programmed death ligand 1 (PD-L1) immunohistochemistry (IHC) 28-8 pharmDx assay (Dako). [b]Patients with tumors unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients. [c]Nonsquamous (NSQ): pemetrexed + cisplatin or carboplatin; squamous (SQ): paclitaxel + carboplatin. [d]Hierarchically statistically tested.

BICR, blinded independent central review; chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, ipilimumab; NIVO, nivolumab; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomized.

Figure reprinted from *Lancet Oncol* 22:198–211, Paz-Ares L, et al: First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial (2021), with permission from Elsevier.



Supplemental Figure S2. CONSORT flow chart[5]

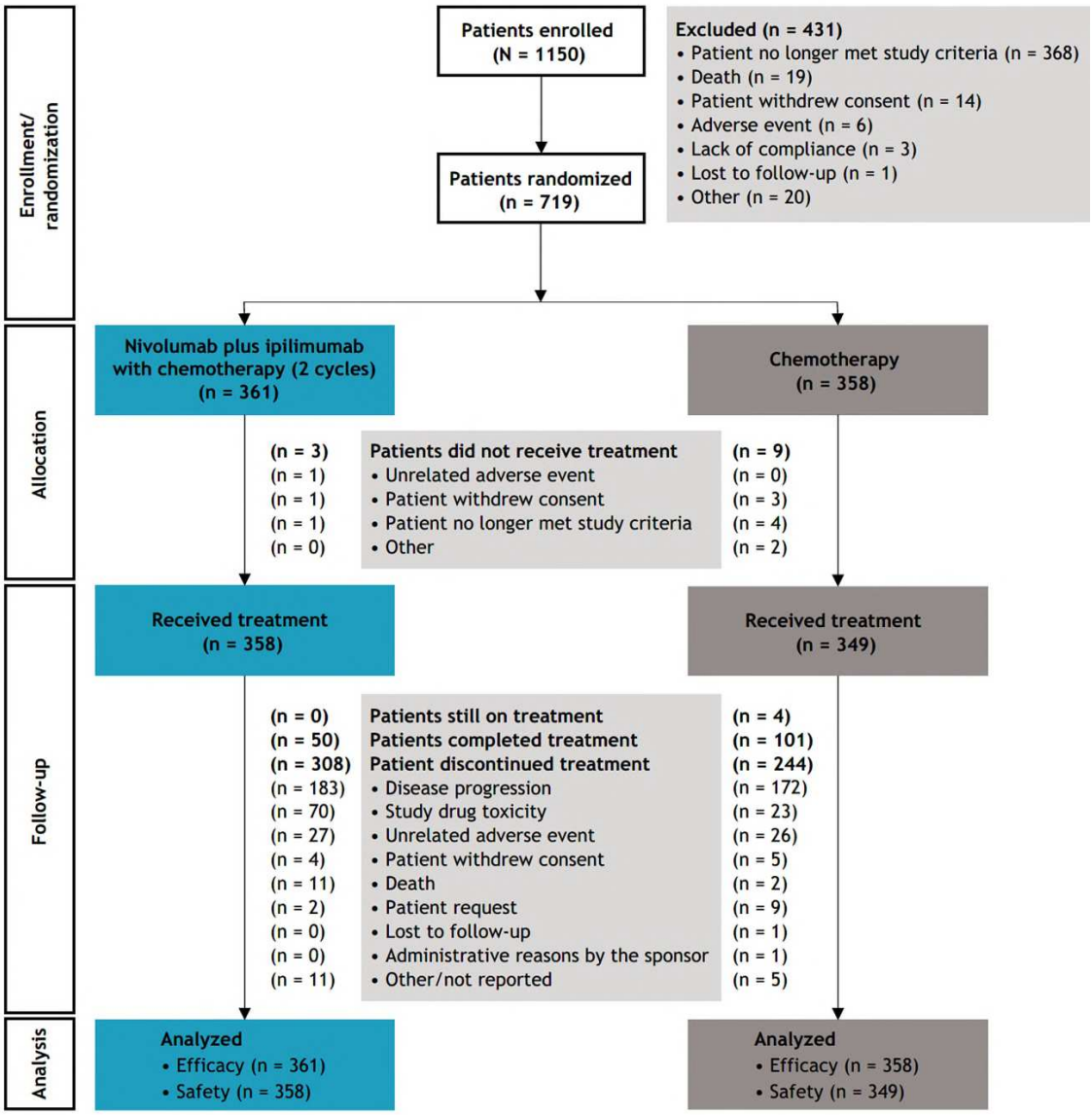


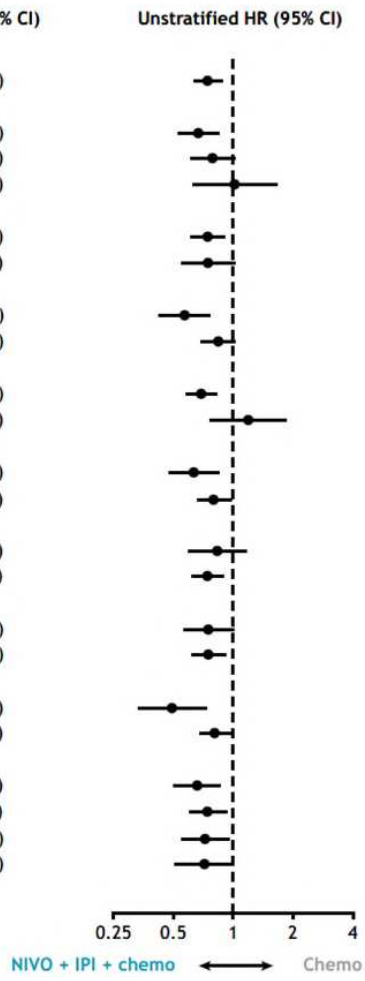
Figure reprinted with minor revisions from *ESMO Open* 6(5):100273, Reck M et al: First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update (2021), with permission from Elsevier. The follow-up data have been updated with data from the current database lock.

Supplemental Figure S3. OS by prespecified subgroups

Hazard ratio (HR) is not computed for subset (except age, race, region, and sex) category with fewer than 10 events per treatment group.

Chemo, chemotherapy; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1.

Subgroup	Median OS (95% CI) NIVO + IPI + chemo n=361	Median OS (95% CI) Chemo n=358	Unstratified HR (95% CI)
All randomized (N=719)	15.8 (13.9-19.7)	11.0 (9.5-12.7)	0.75 (0.63-0.88)
< 65 years (n=354)	15.9 (13.4-21.7)	10.7 (9.1-13.1)	0.67 (0.53-0.84)
≥ 65 to < 75 years (n=295)	19.0 (15.6-24.1)	11.9 (9.0-14.1)	0.79 (0.61-1.02)
> 75 years (n=70)	8.5 (5.6-13.5)	11.5 (5.8-15.2)	1.02 (0.63-1.65)
Male (n=504)	14.2 (12.9-16.9)	9.8 (8.2-11.5)	0.74 (0.61-0.90)
Female (n=215)	22.2 (15.8-27.4)	15.9 (11.0-18.4)	0.75 (0.55-1.02)
ECOG PS 0 (n=227)	27.3 (20.3-33.4)	13.9 (12.1-17.0)	0.57 (0.42-0.77)
ECOG PS ≥ 1 (n=490)	13.5 (11.9-15.3)	9.7 (8.2-11.4)	0.84 (0.70-1.02)
Smoker (n=621)	16.2 (14.0-20.0)	10.4 (9.0-12.2)	0.69 (0.58-0.82)
Never smoked (n=98)	14.1 (8.0-22.8)	14.4 (10.2-23.3)	1.19 (0.77-1.84)
Squamous (n=227)	14.5 (13.1-19.3)	9.1 (7.2-11.6)	0.64 (0.48-0.84)
Nonsquamous (n=492)	17.8 (14.1-20.7)	12.0 (9.9-13.9)	0.80 (0.66-0.97)
Liver metastases (n=154)	10.2 (7.4-12.4)	8.3 (6.7-10.0)	0.84 (0.60-1.17)
No liver metastases (n=565)	19.3 (15.5-22.7)	12.3 (10.4-14.4)	0.74 (0.62-0.89)
Bone metastases (n=208)	11.9 (8.6-15.0)	8.2 (6.6-9.8)	0.75 (0.56-1.00)
No bone metastases (n=511)	19.7 (15.6-23.3)	12.6 (10.7-15.2)	0.76 (0.62-0.92)
CNS metastases (n=123)	19.9 (12.4-25.6)	7.9 (5.0-10.7)	0.49 (0.33-0.73)
No CNS metastases (n=596)	15.6 (13.8-19.3)	11.8 (10.0-13.7)	0.81 (0.67-0.96)
PD-L1 < 1% (n=264)	17.7 (13.7-20.3)	9.8 (7.7-13.5)	0.66 (0.50-0.86)
PD-L1 ≥ 1% (n=408)	15.8 (13.8-22.2)	10.9 (9.5-13.2)	0.74 (0.60-0.92)
PD-L1 1-49% (n=234)	15.2 (12.6-21.2)	10.4 (8.7-12.4)	0.72 (0.55-0.96)
PD-L1 ≥ 50% (n=174)	18.9 (13.1-29.1)	12.9 (9.4-17.6)	0.72 (0.51-1.01)

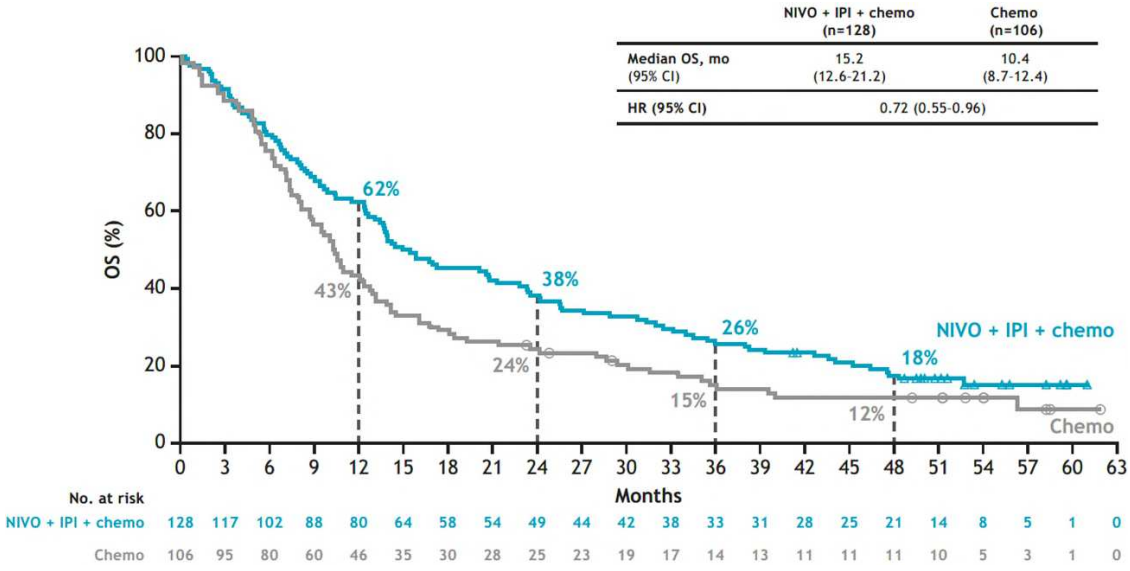


Supplemental Figure S4. OS in patients with tumor PD-L1 expression (A) 1–49% and (B) ≥50%

The 95% confidence intervals (CIs) for 4-year rates for nivolumab (NIVO) plus ipilimumab (IPI) with chemotherapy (Chemo) and chemotherapy alone, respectively, were: (A) 12–25 and 6–19; and (B) 17–36 and 13–29.

HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1.

A.



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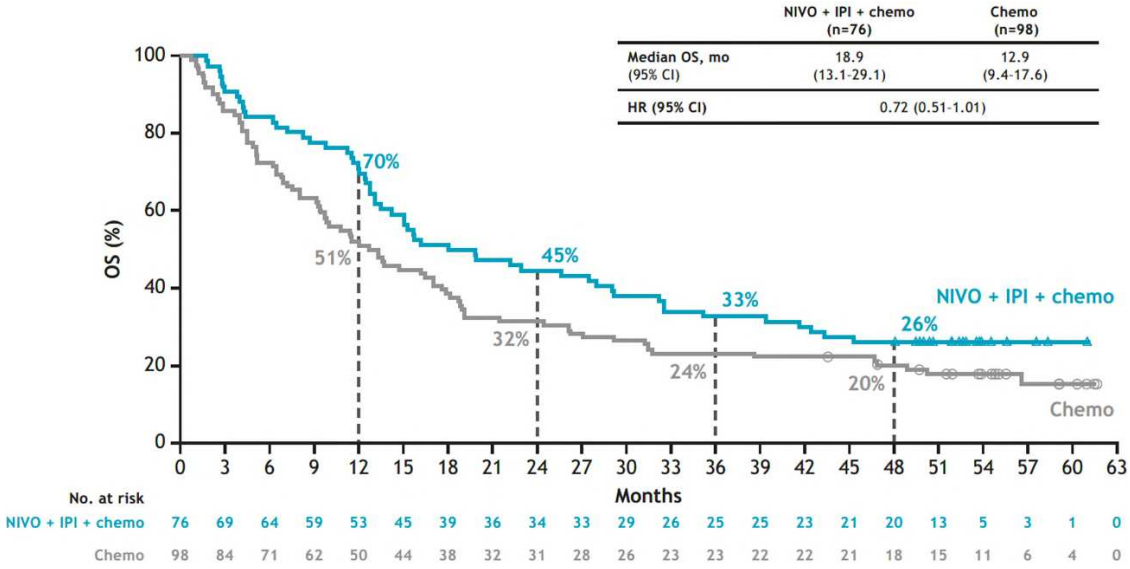
NIVO + IPI + chemo (n=76)
Chemo (n=98)
Median OS, mo (95% CI)
18.9 (13.1-29.1)
12.9 (9.4-17.6)
HR (95% CI)
0.72 (0.51-1.01)
OS (%)
100
80
60
40
20
0
70%
51%
45%
32%
33%
24%
26%
20%
NIVO + IPI + chemo
Chemo
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63
Months
No. at risk
NIVO + IPI + chemo 76 69 64 59 53 45 39 36 34 33 29 26 25 25 23 21 20 13 5 3 1 0
Chemo 98 84 71 62 50 44 38 32 31 28 26 23 23 22 22 21 18 15 11 6 4 0

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