Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Kato K, Doki Y, Chau I, et al. Nivolumab plus chemotherapy or ipilimumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma (CheckMate 648): 29-month follow-up from a randomized, open-label, phase III trial

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Table S1 Patient disposition

	All treated		
	Nivolumab plus chemotherapy (*n*=310)	**Nivolumab plus ipilimumab (*n*=322)**	**Chemotherapy (*n*=304)**
Discontinued treatment, *n* (%)	306 (99)	322 (100)	304 (100)
Reasons for treatment discontinuation, *n* (%)			
Disease progression	189 (61)	182 (57)	199 (65)
Adverse event related to treatment	36 (12)	59 (18)	38 (13)
Adverse event not related to treatment	26 (8)	19 (6)	11 (4)
Patient request	20 (6)	13 (4)	21 (7)
Completed treatment per protocol	14 (5)	28 (9)	0
Other†	35 (11)	49 (15)	35 (12)

†Other reasons for discontinuation included patient withdrawal of consent (nivolumab plus chemotherapy, *n*=4; nivolumab plus ipilimumab, *n*=3; chemotherapy, *n*=12), death (nivolumab plus chemotherapy, *n*=4; nivolumab plus ipilimumab, *n*=6; chemotherapy, *n*=4), maximum clinical benefit (nivolumab plus chemotherapy, *n*=3; nivolumab plus ipilimumab, *n*=1; chemotherapy, *n*=4), pregnancy (nivolumab plus ipilimumab, *n*=1), not reported (nivolumab plus chemotherapy, *n*=1), and additional reasons (nivolumab plus chemotherapy, *n*=9; nivolumab plus ipilimumab, *n*=10; chemotherapy, *n*=15).

Table S2 Efficacy outcomes in patients with tumor cell PD-L1 expression <1%

	Patients with tumor cell PD-L1 expression <1%		
	Nivolumab plus chemotherapy (*n*=163)	**Nivolumab plus ipilimumab (*n*=164)**	**Chemotherapy (*n*=166)**
Overall survival			
Median (95% CI), months	12.0 (9.8–15.2)	11.9 (10.1–16.0)	12.2 (10.7–14.0)
Hazard ratio (95% CI)	1.02 (0.80–1.30)	0.95 (0.74–1.22)	–
24-month overall survival estimate (95% CI), %	26 (19–33)	29 (22–37)	26 (19–33)
Progression-free survival per BICR			
Median (95% CI), months	5.6 (4.4–6.9)	2.8 (1.7–4.2)	5.7 (5.5–7.0)
Hazard ratio (95% CI)	0.95 (0.73–1.23)	1.44 (1.11–1.85)	–
24-month progression-free survival estimate (95% CI), %	11 (6–17)	9 (5–15)	6 (2–13)
Proportion of patients with objective response			
Responders, *n* (%)	69 (42)	33 (20)	55 (33)
95% CI	35–50	14–27	26–41
Best overall response, *n* (%)			
Complete response	20 (12)	10 (6)	12 (7)

	Patients with tumor cell PD-L1 expression <1%		
	Nivolumab plus chemotherapy (*n*=163)	**Nivolumab plus ipilimumab (*n*=164)**	**Chemotherapy (*n*=166)**
Partial response	49 (30)	23 (14)	43 (26)
Stable disease	62 (38)	60 (37)	75 (45)
Progressive disease	20 (12)	53 (32)	14 (8)
Not evaluable	12 (7)	18 (11)	22 (13)
Median time to response, months	1.5	1.5	1.5
IQR	1.4–1.7	1.4–2.8	1.5–1.7
Median duration of response per BICR (95% CI), months	7.1 (5.7–12.2)	11.1 (6.7–14.3)	7.2 (5.7–9.7)
Proportion of patients with duration of response ≥24 months, %	21	20	13
95% CI	11–32	7–36	4–29

BICR, blinded independent central review; PD-L1, programmed death ligand 1.

Table S3 Duration of treatment and dose modifications in all treated patients

Treatment	Median duration of treatment, months (range)	Dose reduction,†‡ *n* (%)	Dose delays,‡ *n* (%)
Nivolumab plus chemotherapy (*n*=310)			
Nivolumab	5.6 (0.0–24.8)	—	514/4640 (11)
Cisplatin	4.0 (0.0–24.0)	129/1293 (10)	285/1293 (22)
Fluorouracil	4.8 (0.1–42.0)	82/1857 (4)	406/1857 (22)
Nivolumab plus ipilimumab (*n*=322)			
Nivolumab	2.8 (0.0–24.1)	—	269/3641 (7)
Ipilimumab	2.8 (0.0–24.0)	—	176/1102 (16)
Chemotherapy (*n*=304)			
Cisplatin	2.9 (0.0–17.4)	89/1073 (8)	200/1073 (19)
Fluorouracil	3.4 (0.1–19.5)	40/1215 (3)	222/1215 (18)

†Dose reductions were not permitted for nivolumab or ipilimumab.

‡Dose modifications for chemotherapy were permitted per local standards to manage treatment-related toxicity.

Table S4 Treatment-related adverse events with potential immunologic cause

Organ categories†‡	Nivolumab plus chemotherapy (*n*=310)		Nivolumab plus ipilimumab (*n*=322)		Chemotherapy (*n*=304)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Endocrine	38 (12)	5 (2)	88 (27)	19 (6)	1 (<1)	0
Gastrointestinal	63 (20)	7 (2)	38 (12)	5 (2)	47 (15)	7 (2)
Hepatic	32 (10)	7 (2)	42 (13)	14 (4)	12 (4)	2 (<1)
Pulmonary	19 (6)	2 (<1)	28 (9)	10 (3)	1 (<1)	0
Renal	73 (24)	8 (3)	8 (2)	2 (<1)	57 (19)	5 (2)
Skin	55 (18)	1 (<1)	111 (34)	13 (4)	12 (4)	0

Data are No. (%).

†Treatment-related adverse events are those with potential immunologic cause that require frequent monitoring/intervention and were assessed during treatment and for up to 30 days after the last dose of trial treatment according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0.

‡Other Events of Special Interest occurring within 100 days of last dose included myositis/rhabdomyolysis (*n*=2, nivolumab plus chemotherapy, one event was grade 3–4; and *n*=2, nivolumab plus ipilimumab), myocarditis (*n*=2, nivolumab plus ipilimumab), pancreatitis (*n*=5, nivolumab plus ipilimumab, four events were grade 3–4), uveitis (*n*=2, nivolumab plus chemotherapy; and *n*=2, nivolumab plus ipilimumab, one event was grade 3–4), and encephalitis (*n*=3, nivolumab plus ipilimumab, all were grade 3–4), immune thrombocytopenia (*n*=1, nivolumab plus ipilimumab), immune-mediated arthritis (*n*=1, nivolumab plus ipilimumab).

Table S5 Summary of treatment-related adverse events by age ≥65 years and <65 years in all treated patients

Patients	Nivolumab plus chemotherapy		Nivolumab plus ipilimumab		Chemotherapy	
Age <65, *n*	**163**		**182**		**155**	
Age ≥65, *n*	**147**		**140**		**149**	
	Any grade†	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**
All events						
Age <65	155 (95)	74 (45)	145 (80)	54 (30)	141 (91)	44 (28)
Age ≥65	142 (97)	77 (52)	111 (79)	51 (36)	134 (90)	66 (44)
Serious events						
Age <65	36 (22)	25 (15)	56 (31)	41 (23)	23 (15)	16 (10)
Age ≥65	38 (26)	33 (22)	49 (35)	34 (24)	26 (17)	24 (16)
AEs leading to discontinuation‡						
Age <65	49 (30)	12 (7)	27 (15)	23 (13)	27 (17)	8 (5)
Age ≥65	58 (39)	18 (12)	33 (24)	21 (15)	36 (24)	10 (7)
Events leading to death§						
Age <65	2 (1)		3 (2)		3 (2)	
Age ≥65	3 (2)		3 (2)		2 (1)	
Adverse events reported in 10% or more of treated patients in any group						
Nausea						
Age <65	100 (61)	7 (4)	18 (10)	1 (<1)	84 (54)	4 (3)
Age ≥65	83 (57)	4 (3)	8 (6)	0	74 (50)	4 (3)
Decreased appetite						

Patients	**Nivolumab plus chemotherapy**		**Nivolumab plus ipilimumab**		**Chemotherapy**	
Age <65, *n*	**163**		**182**		**155**	
Age ≥65, *n*	**147**		**140**		**149**	
	Any grade†	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**
Age <65	67 (41)	6 (4)	7 (4)	1 (1)	60 (39)	3 (2)
Age ≥65	65 (44)	7 (5)	12 (9)	4 (3)	70 (47)	6 (4)
Stomatitis						
Age <65	39 (24)	14 (9)	7 (4)	0	27 (17)	2 (1)
Age ≥65	60 (41)	6 (4)	8 (6)	0	44 (30)	3 (2)
Anemia						
Age <65	48 (29)	13 (8)	5 (3)	1 (<1)	30 (19)	7 (5)
Age ≥65	45 (31)	17 (12)	8 (6)	1 (1)	37 (25)	10 (7)
Diarrhea						
Age <65	25 (15)	1 (1)	14 (8)	0	20 (13)	1 (1)
Age ≥65	34 (23)	2 (1)	18 (13)	2 (1)	26 (17)	5 (3)
Constipation						
Age <65	26 (16)	0	2 (1)	1 (<1)	23 (15)	0
Age ≥65	33 (22)	2 (1)	5 (4)	0	43 (29)	1 (1)
Neutrophil count decreased						
Age <65	33 (20)	12 (7)	2 (1)	0	16 (10)	6 (4)
Age ≥65	32 (22)	13 (9)	0	0	36 (24)	18 (12)
Fatigue						
Age <65	29 (18)	2 (1)	12 (7)	1 (<1)	30 (19)	7 (5)

Patients	**Nivolumab plus chemotherapy**		**Nivolumab plus ipilimumab**		**Chemotherapy**	
Age <65, *n*	**163**		**182**		**155**	
Age ≥65, *n*	**147**		**140**		**149**	
	Any grade†	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**
Age ≥65	32 (22)	5 (3)	17 (12)	3 (2)	20 (13)	4 (3)
Vomiting						
Age <65	34 (21)	3 (2)	12 (7)	4 (2)	28 (18)	8 (5)
Age ≥65	22 (15)	4 (3)	7 (5)	1 (1)	21 (14)	1 (1)
Malaise						
Age <65	21 (13)	0	6 (3)	0	18 (12)	0
Age ≥65	30 (20)	0	7 (5)	0	27 (18)	0
Hiccups						
Age <65	15 (9)	0	1 (<1)	0	29 (19)	0
Age ≥65	27 (18)	0	1 (1)	0	24 (16)	0
Platelet count decreased						
Age <65	13 (8)	3 (2)	3 (2)	0	14 (9)	3 (2)
Age ≥65	23 (16)	0	3 (2)	0	18 (12)	2 (1)
White blood cell count decreased						
Age <65	21 (13)	4 (3)	1 (<1)	0	9 (6)	1 (1)
Age ≥65	22 (15)	7 (5)	2 (1)	0	19 (13)	5 (3)
Blood creatinine increased						
Age <65	18 (11)	1 (1)	3 (2)	0	9 (6)	0
Age ≥65	20 (14)	0	2 (1)	0	23 (15)	1 (1)

Patients	**Nivolumab plus chemotherapy**		**Nivolumab plus ipilimumab**		**Chemotherapy**	
Age <65, *n*	**163**		**182**		**155**	
Age ≥65, *n*	**147**		**140**		**149**	
	Any grade†	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**
Mucosal inflammation						
Age <65	17 (10)	5 (3)	2 (1)	0	16 (10)	1 (1)
Age ≥65	17 (12)	3 (2)	1 (1)	0	10 (7)	3 (2)
Hyponatremia						
Age <65	12 (7)	8 (5)	5 (3)	5 (3)	9 (6)	2 (1)
Age ≥65	17 (12)	9 (6)	5 (4)	3 (2)	10 (7)	7 (5)
Creatinine renal clearance decreased						
Age <65	3 (2)	0	0	0	3 (2)	0
Age ≥65	16 (11)	0	0	0	6 (4)	1 (1)
Alopecia						
Age <65	17 (10)	0	2 (1)	0	13 (8)	0
Age ≥65	14 (10)	0	0	0	19 (13)	0
Neutropenia						
Age <65	16 (10)	6 (4)	0	0	15 (10)	6 (4)
Age ≥65	14 (10)	3 (2)	0	0	5 (3)	1 (1)
Rash						
Age <65	16 (10)	1 (1)	30 (17)	3 (2)	3 (2)	0
Age ≥65	8 (5)	0	26 (19)	4 (3)	2 (1)	0
Peripheral sensory neuropathy						

Patients	**Nivolumab plus chemotherapy**		**Nivolumab plus ipilimumab**		**Chemotherapy**	
Age <65, *n*	**163**		**182**		**155**	
Age ≥65, *n*	**147**		**140**		**149**	
	Any grade†	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**	**Any grade†**	**Grade 3–4†**
Age <65	11 (7)	1 (1)	0	0	7 (5)	1 (1)
Age ≥65	15 (10)	0	1 (1)	0	9 (6)	0
Pruritus						
Age <65	15 (9)	0	19 (10)	0	2 (1)	0
Age ≥65	8 (5)	0	24 (17)	3 (2)	1 (1)	0
Hypothyroidism						
Age <65	14 (9)	0	23 (13)	0	0	0
Age ≥65	6 (4)	0	20 (14)	0	0	0
Aspartate aminotransferase increased						
Age <65	9 (6)	0	18 (10)	2 (1)	4 (3)	1 (1)
Age ≥65	7 (5)	2 (1)	12 (9)	2 (1)	2 (1)	0

Data are *n* (%). Ages are in years.

†Patients who received at least one dose of the assigned treatment. Includes events reported between first dose and 30 days after last dose of trial therapy. Treatment-relatedness in the nivolumab plus chemotherapy group was attributed to either nivolumab or any of the chemotherapies or both. Treatment-relatedness in the nivolumab plus ipilimumab group was attributed to either nivolumab or ipilimumab or both. Adverse events were graded according to the Common Terminology Criteria for Adverse Events V.4.0 and *Medical Dictionary for Regulatory Activities* V.23.0.

‡Refers to adverse events leading to discontinuation of any drug in the regimen.

§Treatment-related adverse events leading to death were reported regardless of time frame.

Table S6 Subsequent therapies

	Patients with tumor cell PD-L1 expression ≥1%			Overall population		
	Nivolumab plus chemotherapy (*n*=158)†	Nivolumab plus ipilimumab (*n*=158)†	Chemotherapy (*n*=157)†	Nivolumab plus chemotherapy (*n*=321)†	Nivolumab plus ipilimumab (*n*=325)†	Chemotherapy (*n*=324)†
Any subsequent therapy‡	94 (59)	90 (57)	104 (66)	180 (56)	183 (56)	205 (63)
Subsequent radiotherapy	39 (25)	39 (25)	52 (33)	76 (24)	83 (26)	94 (29)
Curative	6 (4)	5 (3)	3 (2)	11 (3)	7 (2)	9 (3)
Palliative	35 (22)	33 (21)	49 (31)	67 (21)	75 (23)	85 (26)
Other	0	1 (1)	0	0	1 (<1)	0
Subsequent surgery	5 (3)	4 (3)	2 (1)	10 (3)	4 (1)	9 (3)
Tumor resection, curative	2 (1)	1 (1)	0	2 (1)	1 (<1)	3 (1)
Tumor resection, palliative	3 (2)	3 (2)	2 (1)	8 (2)	3 (1)	5 (2)
Subsequent systemic therapy	89 (56)	84 (53)	89 (57)	166 (52)	166 (51)	183 (57)
Anti–PD-1/PD-L1	18 (11)	9 (6)	25 (16)	28 (9)	21 (7)	58 (18)

Nivolumab	15 (9)	9 (6)	18 (11)	23 (7)	19 (6)	45 (14)
Pembrolizumab	1 (1)	0	3 (2)	3 (1)	1 (<1)	7 (2)
Sintilimab	1 (1)	0	1 (1)	1 (<1)	0	2 (1)
Camrelizumab	1 (1)	0	2 (1)	1 (<1)	1 (<1)	2 (1)
Ezabenlimab	—	—	—	0	0	1 (<1)
Sugemalimab	0	0	1 (1)	0	0	1 (<1)
Tislelizumab	0	0	1 (1)	0	0	1 (<1)
Toripalimab	—	—	—	0	0	1 (<1)
Anti–CTLA-4	—	—	—	0	1 (<1)	0
Ipilimumab	—	—	—	0	1 (<1)	0
Other systemic anticancer treatments§	86 (54)	84 (53)	84 (54)	163 (51)	164 (50)	172 (53)
Paclitaxel	49 (31)	31 (20)	40 (25)	88 (27)	60 (18)	89 (27)
Fluorouracil	27 (17)	57 (36)	34 (22)	52 (16)	116 (36)	68 (21)
Docetaxel	24 (15)	15 (9)	20 (13)	46 (14)	32 (10)	42 (13)
Cisplatin	22 (14)	54 (34)	22 (14)	36 (11)	111 (34)	47 (15)
Nedaplatin	13 (8)	6 (4)	9 (6)	19 (6)	12 (4)	16 (5)
Gimeracil:oteracil potassium; tegafur	10 (6)	7 (4)	4 (3)	21 (7)	12 (4)	12 (4)
Oxaliplatin	9 (6)	12 (8)	5 (3)	17 (5)	20 (6)	14 (4)
Carboplatin	9 (6)	9 (6)	6 (4)	18 (6)	14 (4)	13 (4)
Irinotecan	3 (2)	5 (3)	5 (3)	5 (2)	10 (3)	9 (3)

Data are *n* (%).

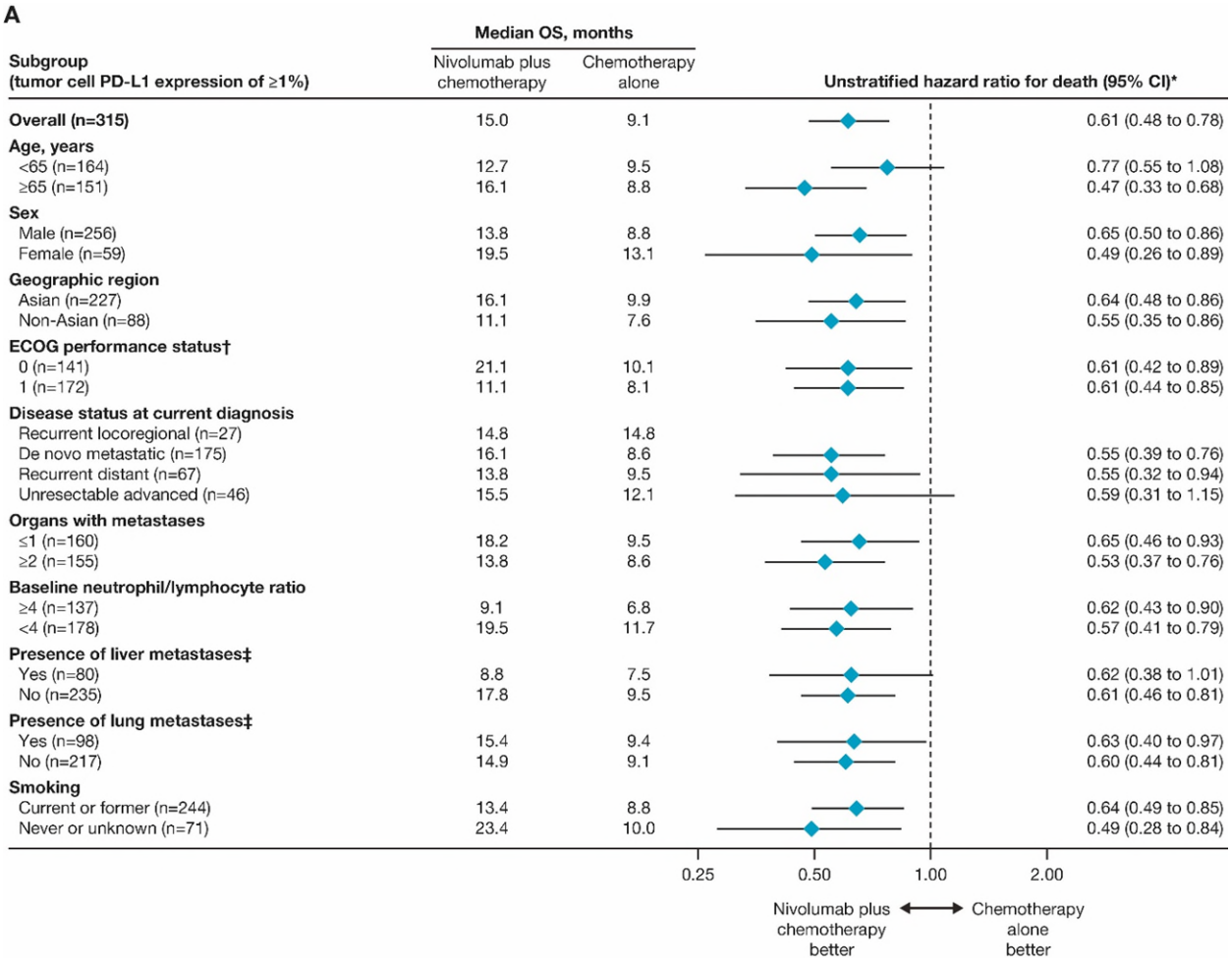
†Patients could have received more than one type of therapy.

‡Defined as therapy started on or after the first dosing date (randomization date if patient was never treated) for nivolumab plus chemotherapy, nivolumab plus ipilimumab, or chemotherapy.

§Treatment in ≥10 patients in any group.

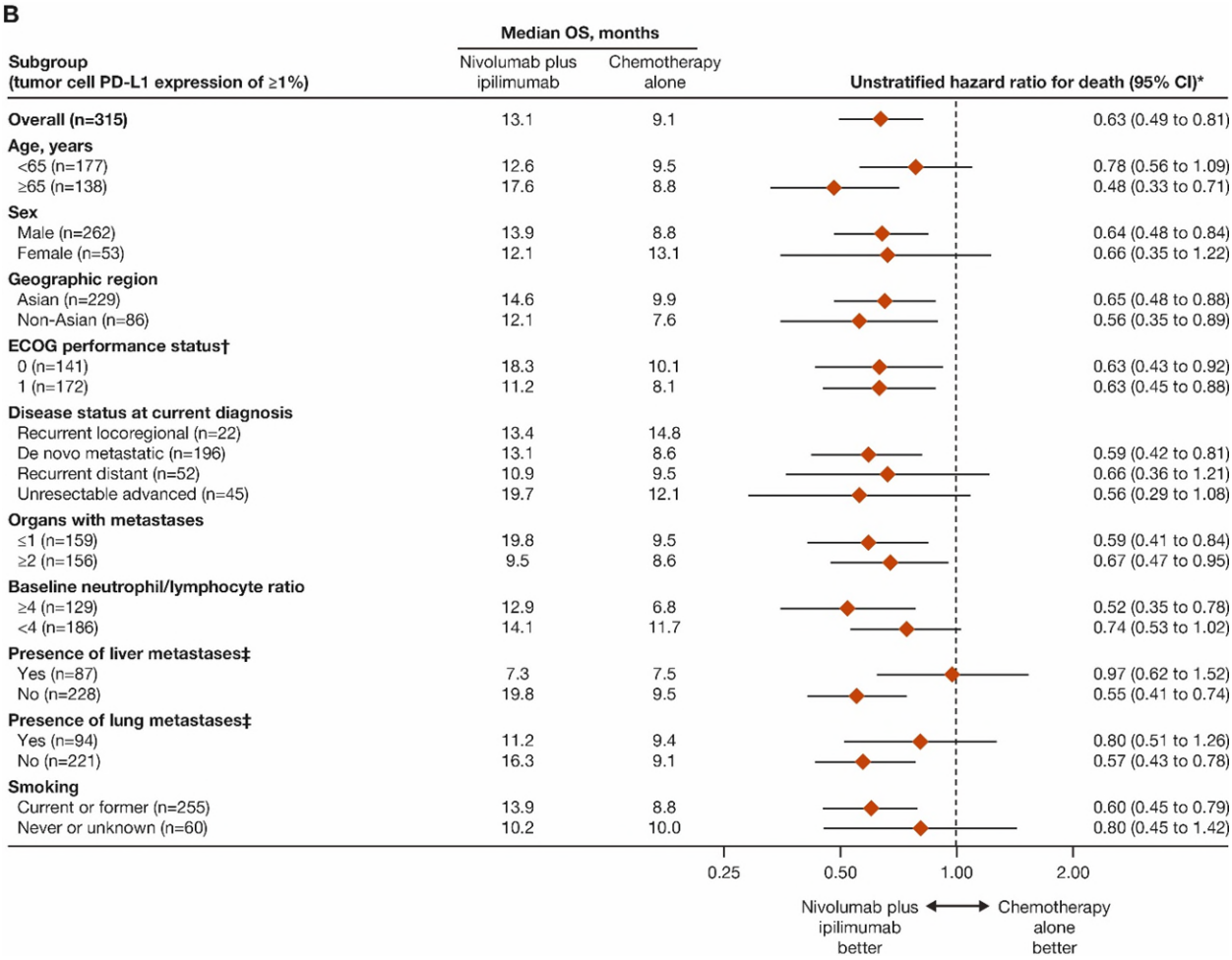
CTLA-4, cytotoxic T-lymphocyte-associated protein-4; PD-1, programmed death-1; PD-L1, programmed death ligand 1.

Figure S1 Forest plot of overall survival by prespecified subgroups (tumor cell PD-L1 expression ≥1%) with (A) nivolumab plus chemotherapy versus chemotherapy and (B) nivolumab plus ipilimumab versus chemotherapy



B

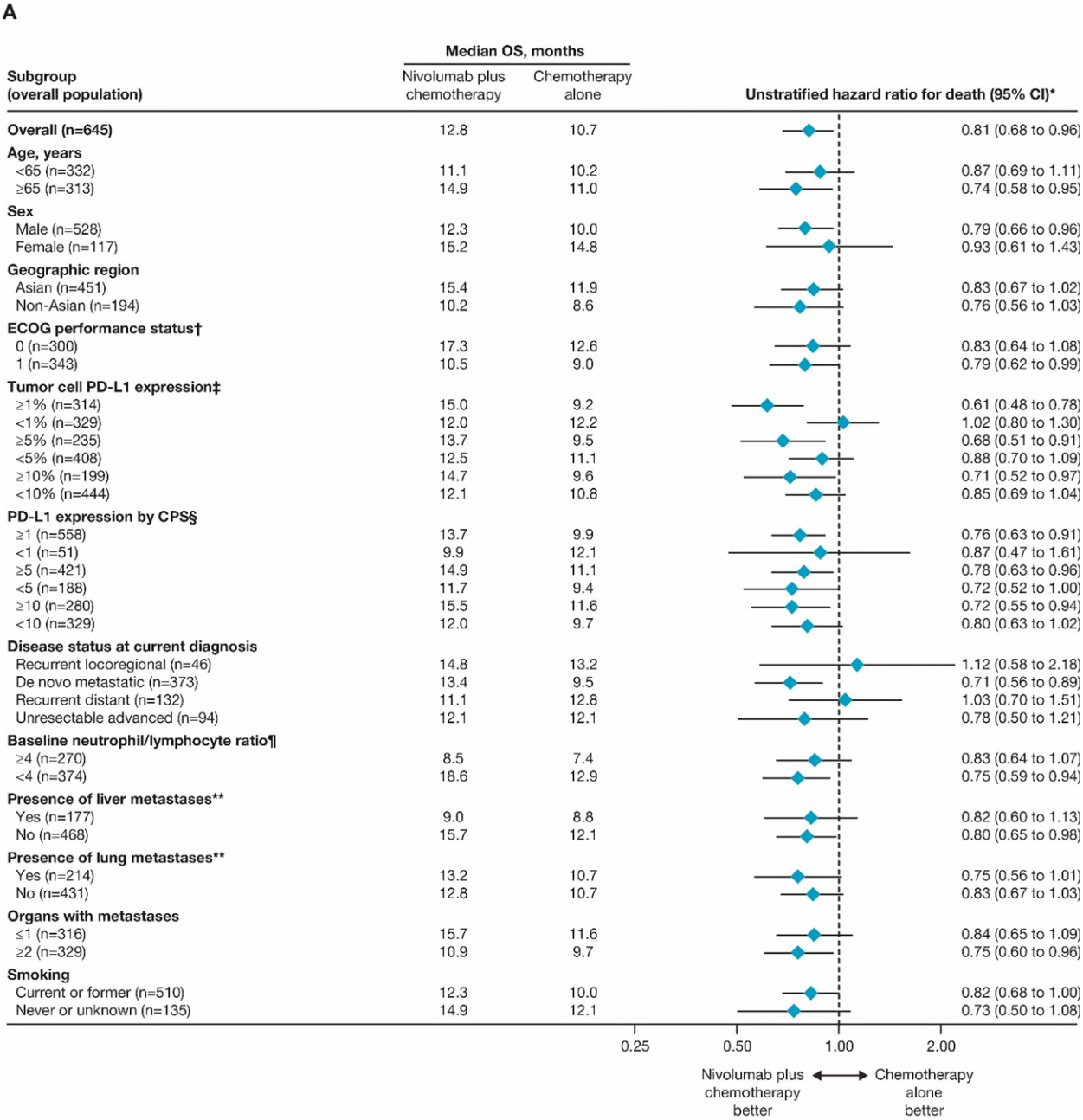
Subgroup (tumor cell PD-L1 expression of ≥1%)	Median OS, months: Nivolumab plus ipilimumab	Median OS, months: Chemotherapy alone	Unstratified hazard ratio for death (95% CI)*
Overall (n=315)	13.1	9.1	0.63 (0.49 to 0.81)
Age, years			
<65 (n=177)	12.6	9.5	0.78 (0.56 to 1.09)
≥65 (n=138)	17.6	8.8	0.48 (0.33 to 0.71)
Sex			
Male (n=262)	13.9	8.8	0.64 (0.48 to 0.84)
Female (n=53)	12.1	13.1	0.66 (0.35 to 1.22)
Geographic region			
Asian (n=229)	14.6	9.9	0.65 (0.48 to 0.88)
Non-Asian (n=86)	12.1	7.6	0.56 (0.35 to 0.89)
ECOG performance status†			
0 (n=141)	18.3	10.1	0.63 (0.43 to 0.92)
1 (n=172)	11.2	8.1	0.63 (0.45 to 0.88)
Disease status at current diagnosis			
Recurrent locoregional (n=22)	13.4	14.8	
De novo metastatic (n=196)	13.1	8.6	0.59 (0.42 to 0.81)
Recurrent distant (n=52)	10.9	9.5	0.66 (0.36 to 1.21)
Unresectable advanced (n=45)	19.7	12.1	0.56 (0.29 to 1.08)
Organs with metastases			
≤1 (n=159)	19.8	9.5	0.59 (0.41 to 0.84)
≥2 (n=156)	9.5	8.6	0.67 (0.47 to 0.95)
Baseline neutrophil/lymphocyte ratio			
≥4 (n=129)	12.9	6.8	0.52 (0.35 to 0.78)
<4 (n=186)	14.1	11.7	0.74 (0.53 to 1.02)
Presence of liver metastases‡			
Yes (n=87)	7.3	7.5	0.97 (0.62 to 1.52)
No (n=228)	19.8	9.5	0.55 (0.41 to 0.74)
Presence of lung metastases‡			
Yes (n=94)	11.2	9.4	0.80 (0.51 to 1.26)
No (n=221)	16.3	9.1	0.57 (0.43 to 0.78)
Smoking			
Current or former (n=255)	13.9	8.8	0.60 (0.45 to 0.79)
Never or unknown (n=60)	10.2	10.0	0.80 (0.45 to 1.42)



†Hazard ratio was not computed for subset category with less than ten events per treatment group. ‡ECOG performance status was not reported for two patients in the chemotherapy treatment group. §By investigator assessment. ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD-L1, programmed death ligand 1.

Figure S2 Forest plot of overall survival by prespecified subgroups (all randomized) with (A) nivolumab plus chemotherapy versus chemotherapy and (B) nivolumab plus ipilimumab versus chemotherapy

A



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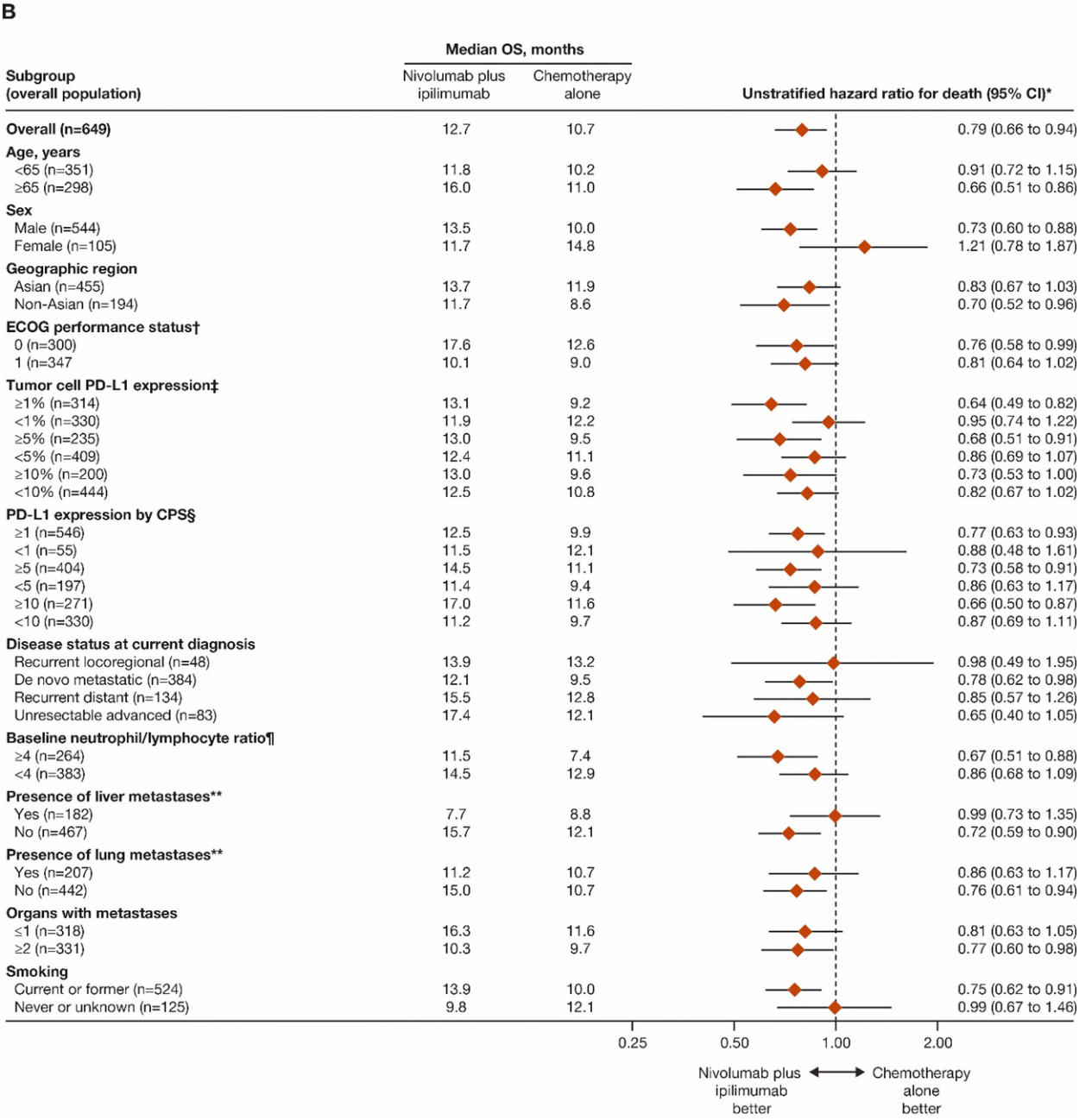
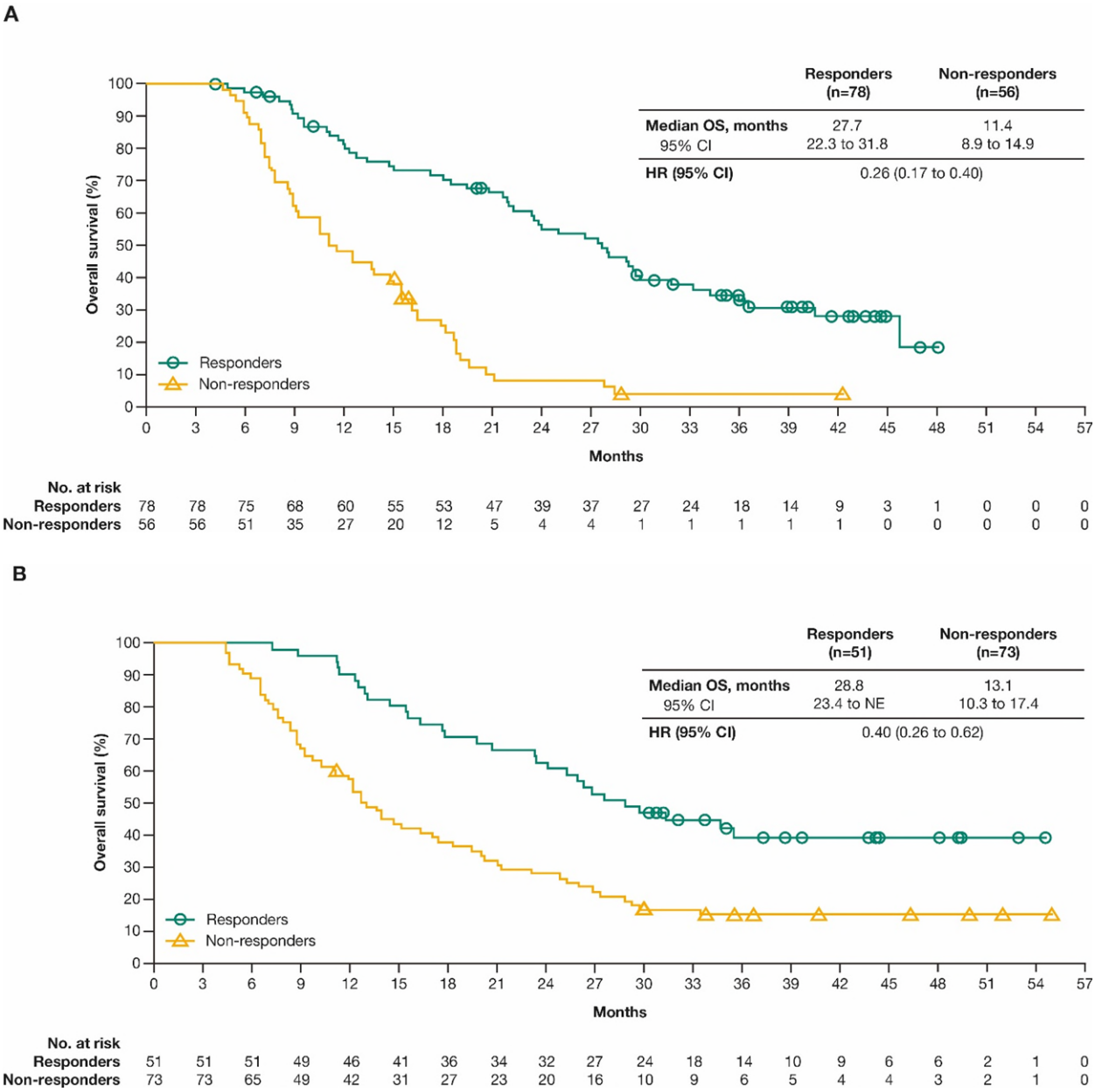
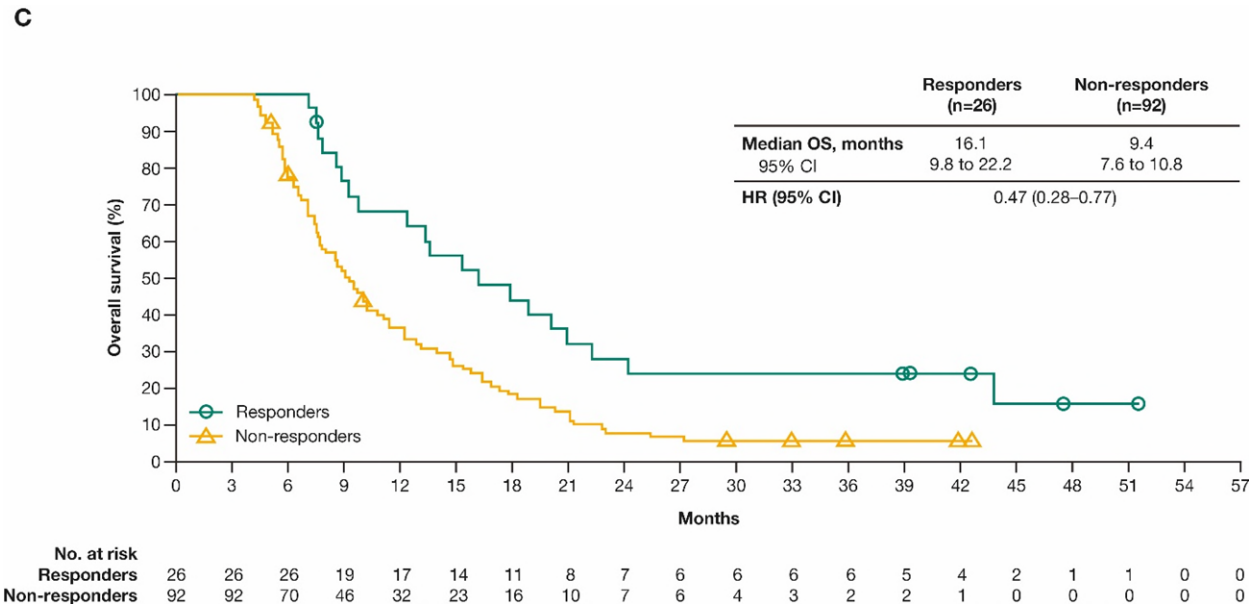


†Hazard ratio was not computed for subset category with less than ten events per treatment group. ‡ECOG performance status was not reported for two patients in the chemotherapy treatment group. §Tumor cell PD-L1 expression status was indeterminate, not evaluable, or missing for two patients who received nivolumab plus chemotherapy, five patients who received nivolumab plus ipilimumab, and one patient who received chemotherapy. ¶PD-L1 expression by CPS was indeterminate, not evaluable, or missing for 36 patients who received nivolumab plus chemotherapy, 48 patients who received nivolumab plus ipilimumab, and 13 patients who received chemotherapy. ††Overall baseline neutrophil/lymphocyte ratio was indeterminate, not evaluable, or missing for one patient in each of the nivolumab plus ipilimumab and chemotherapy treatment groups. ‡‡By investigator assessment. CPS, combined positive score;

ECOG, Eastern Cooperative Oncology Group; OS, overall survival; PD-L1, programmed death ligand 1.

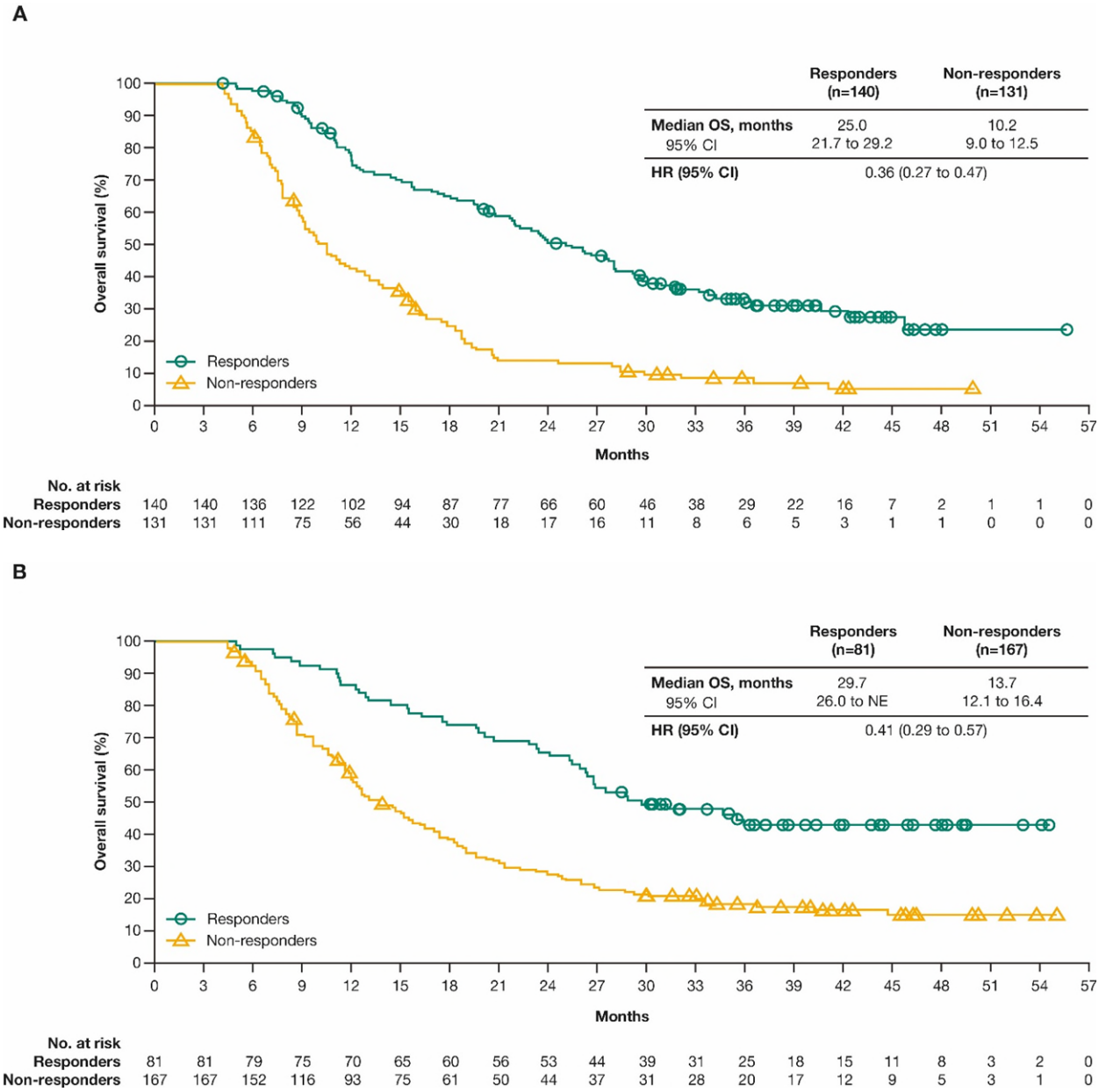
Figure S3 Landmark analysis of overall survival by response status per BICR at week 18 in patients with tumor cell PD-L1 expression ≥1% with (A) nivolumab plus chemotherapy, (B) nivolumab plus ipilimumab, and (C) chemotherapy

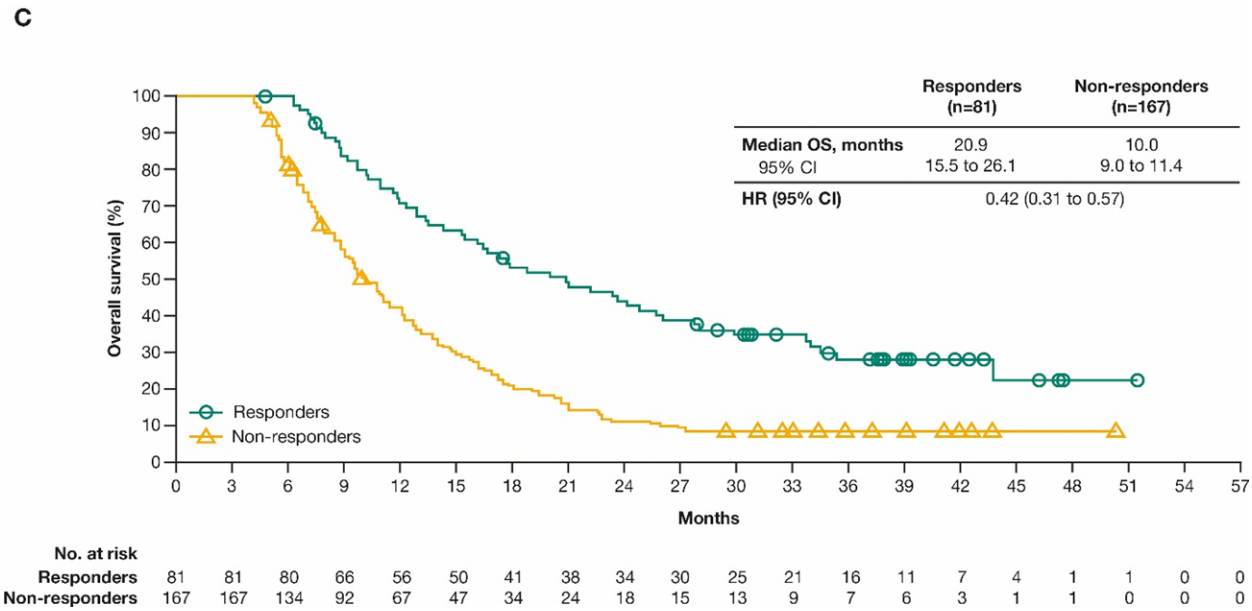




BICR, blinded independent central review; HR, hazard ratio; PD-L1, programmed death ligand 1.

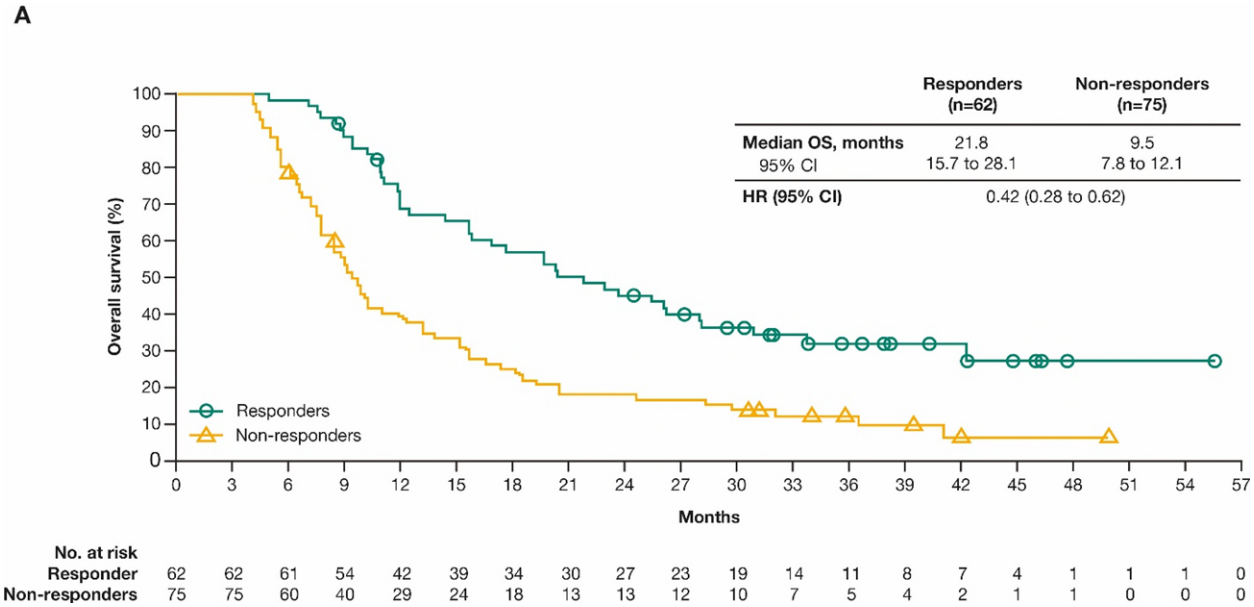
Figure S4 Landmark analysis of overall survival by response status per BICR at week 18 in the overall population with (A) nivolumab plus chemotherapy, (B) nivolumab plus ipilimumab, and (C) chemotherapy

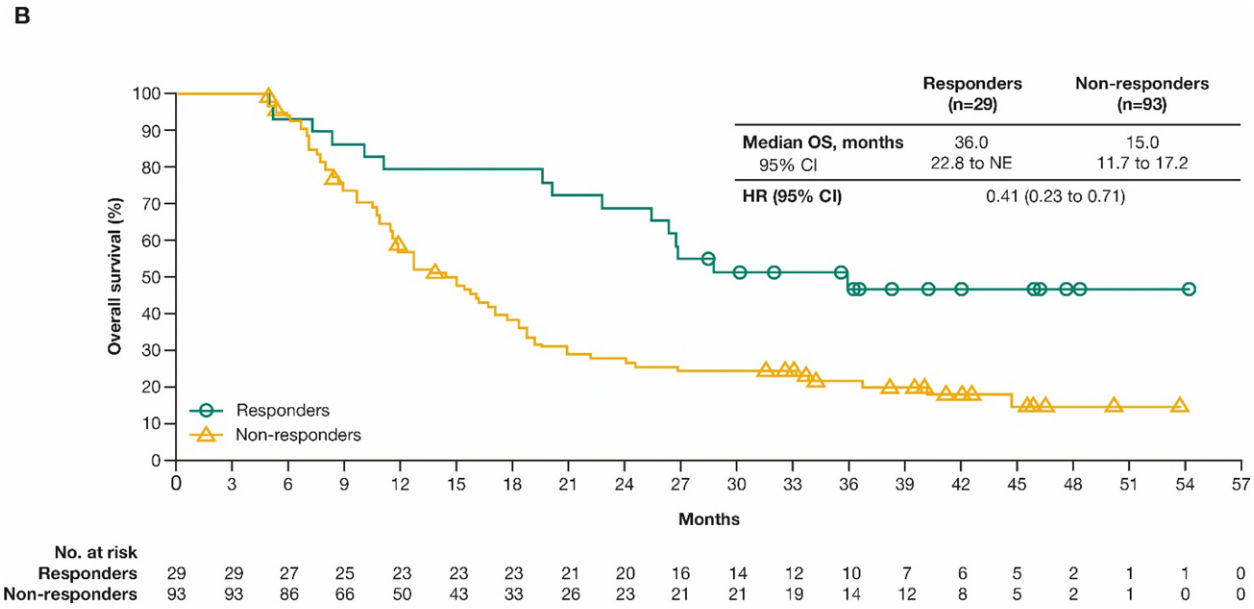


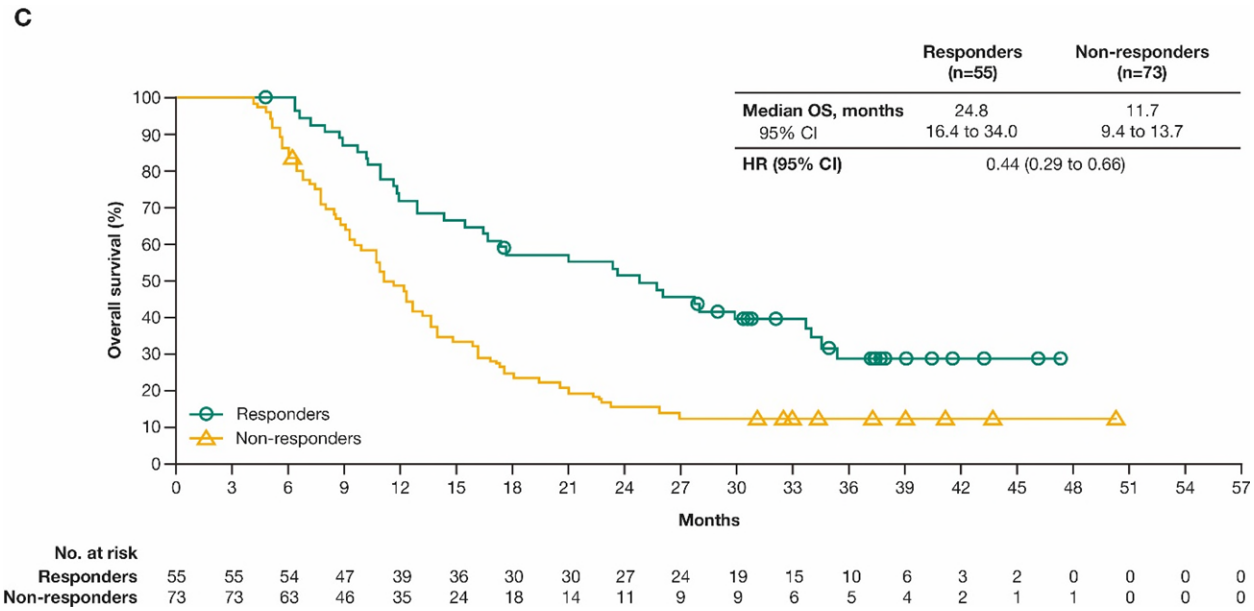


BICR, blinded independent central review; HR, hazard ratio.

Figure S5 Landmark analysis of overall survival by response status per BICR at week 18 in patients with tumor cell PD-L1 expression <1% with (A) nivolumab plus chemotherapy, (B) nivolumab plus ipilimumab, and (C) chemotherapy







BICR, blinded independent central review; HR, hazard ratio; PD-L1, programmed death ligand 1.