Case 2: 73-year-old man

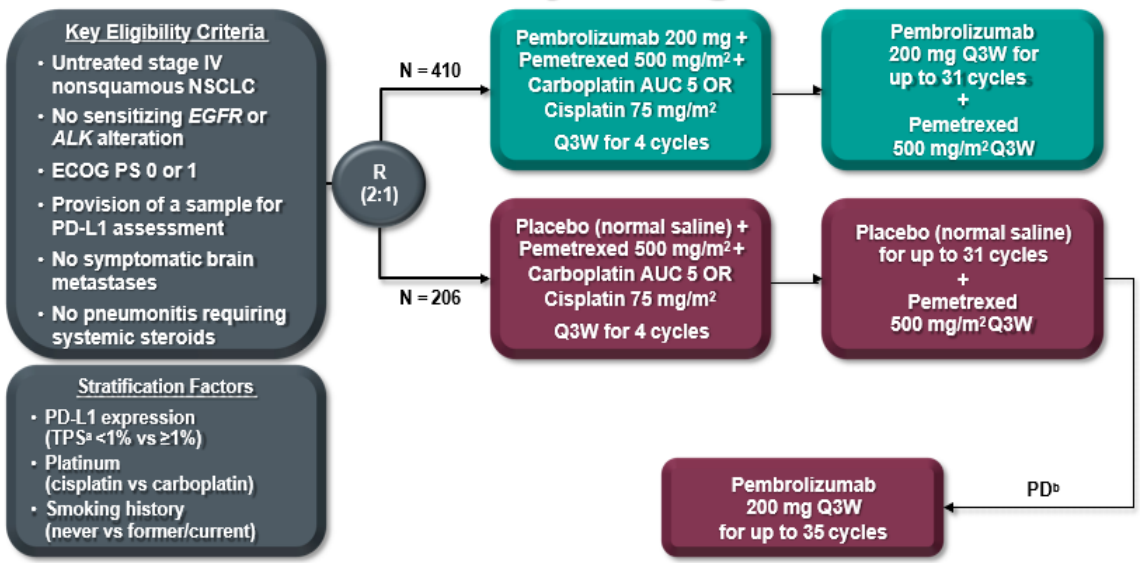
- Presented with shortness of breath on exertion and weight loss of 10 lbs
- Past medical, family, and social history
  - CABG 15 years ago, well controlled hypertension, dyslipidemia
  - COPD
  - Former smoker (30 pack years) and quit 15 years ago
- Physical examination
  - Current weight: 180 lbs
  - ECOG PS 1

Case 2 (Cont.)

- Diagnostic workup
  - CT of thorax discovered multiple bilateral lung masses measuring up to 2 cm, mediastinal adenopathy
  - CT of abdomen showed bilateral adrenal metastases
  - MRI of brain negative for brain metastases
- Final pathology: consistent with TTF1+ adenocarcinoma
  - Metastatic stage IV
- PD-L1 expression by IHC: 0%
- NGS: no actionable mutations

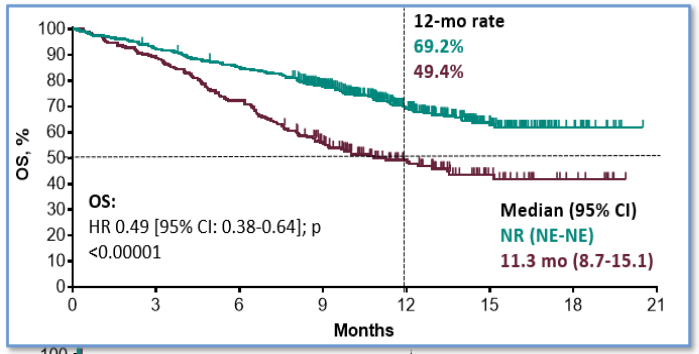
- **What treatment options should be considered?**

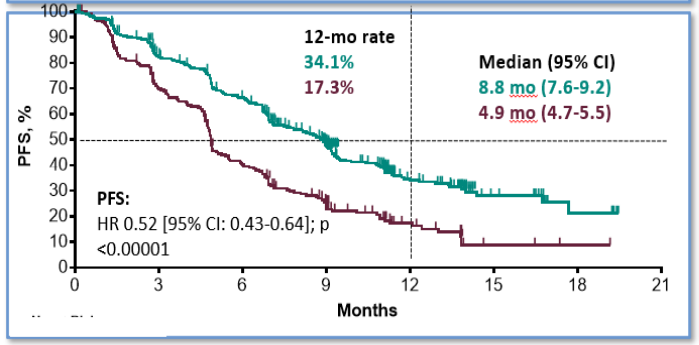
KEYNOTE-189: Study Design

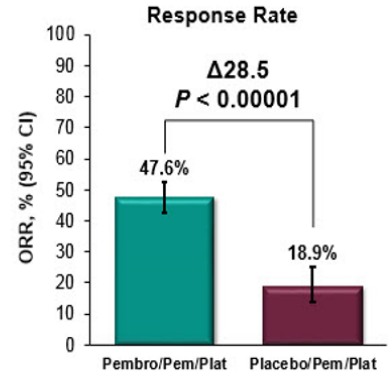


[a]Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 IHC 22C3 pharmDx assay. [b]Patients could crossover during the induction or maintenance phases. To be eligible for crossover, PD must have been verified by blinded, independent central radiologic review and all safety criteria had to be met.

Keynote 189: Met All Primary Endpoints





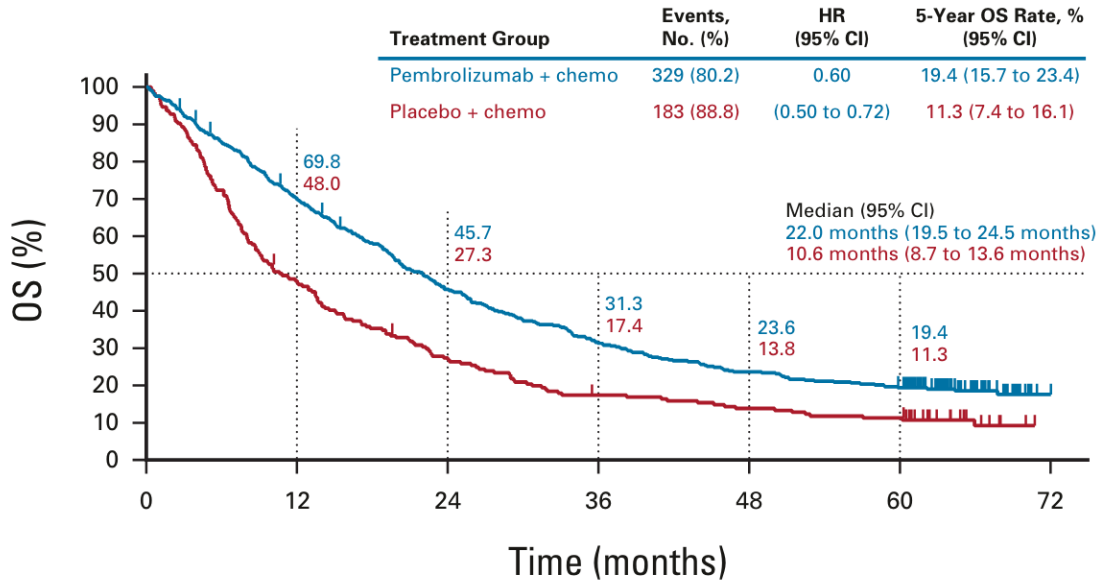


Subgroup Analyses
OS: Positive across all subgroups
PFS: Positive across all subgroups except for PD-L1 TPS <1%

Protocol for: Gandhi L, et al; KEYNOTE-189 Investigators. *N Engl J Med.* 2018;378(22):2078-2092.

KEYNOTE-189: 5-Year Outcomes

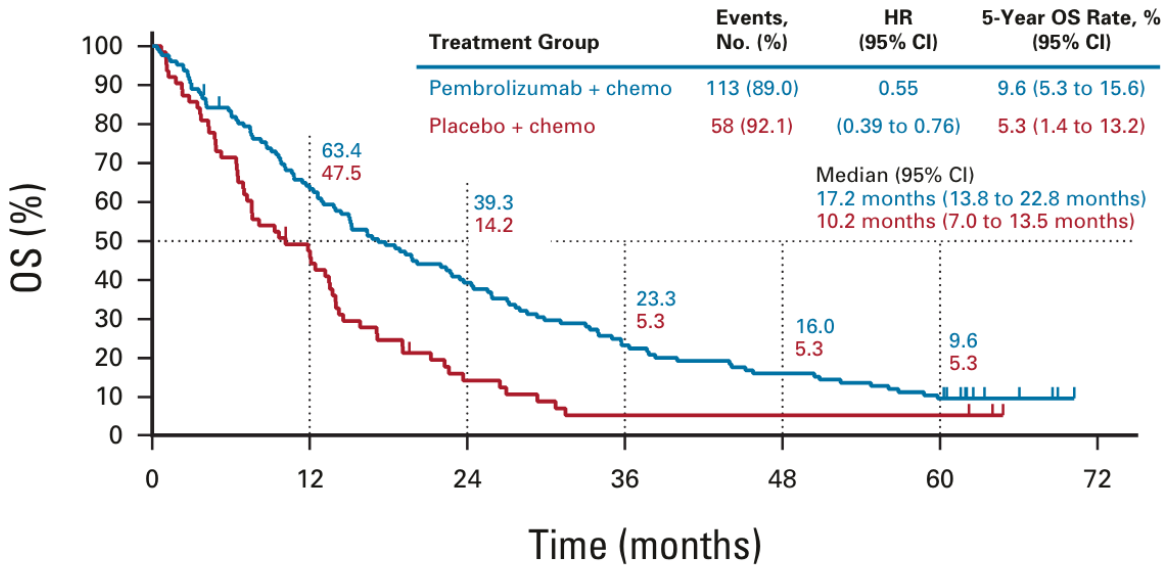
ITT



No. at risk:

Pembrolizumab + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

PD-L1 TPS <1%

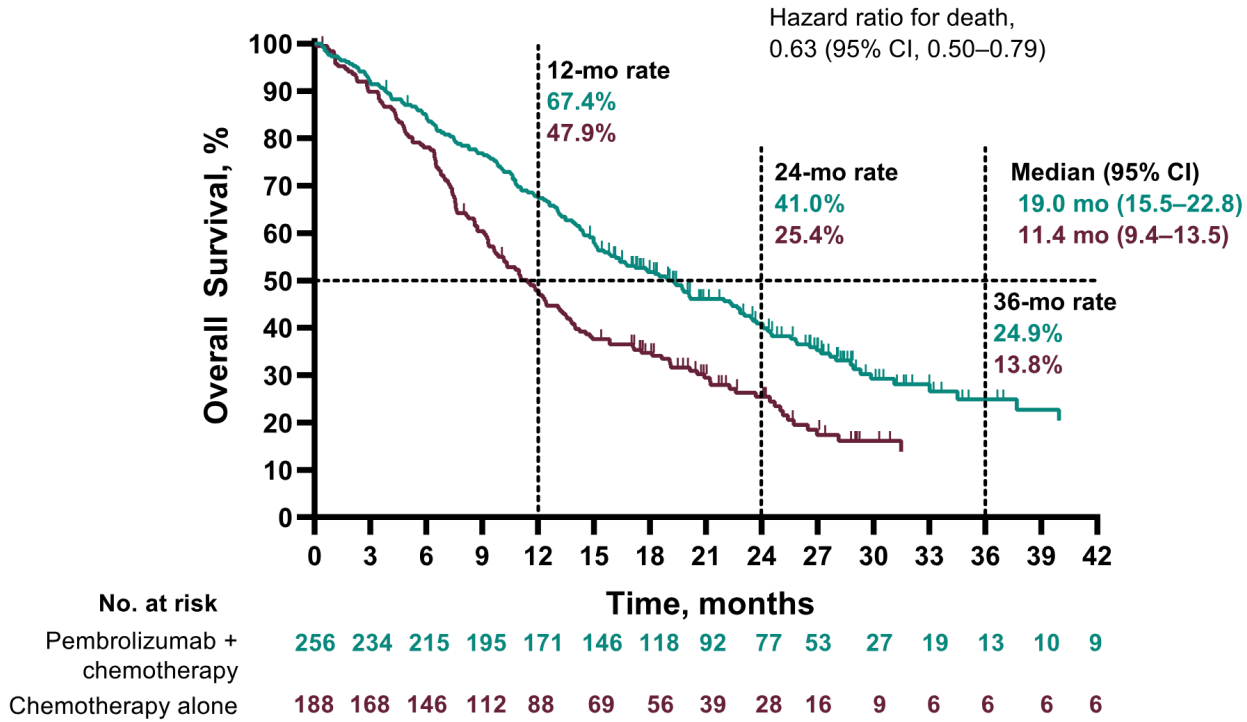


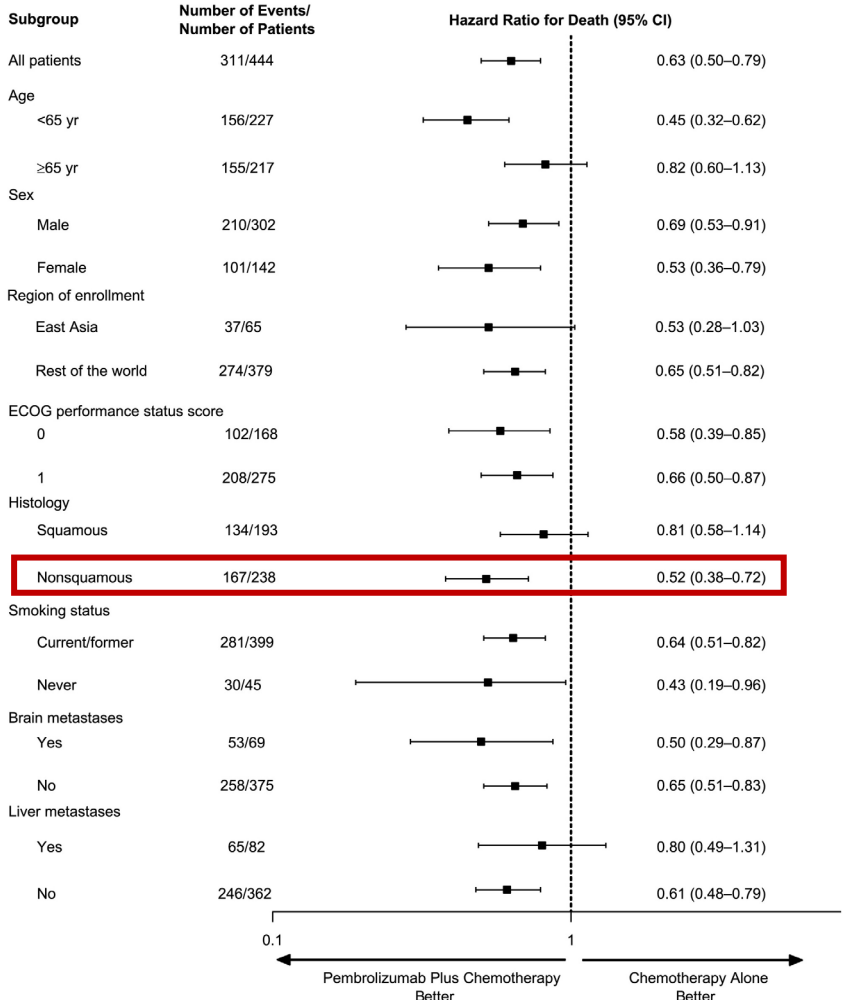
No. at risk:

Pembrolizumab + chemo	127	79	49	29	20	12	0
Placebo + chemo	63	29	8	3	3	3	0

Garassino MC, et al. *J Clin Oncol*. 2023;41:1992-1998.

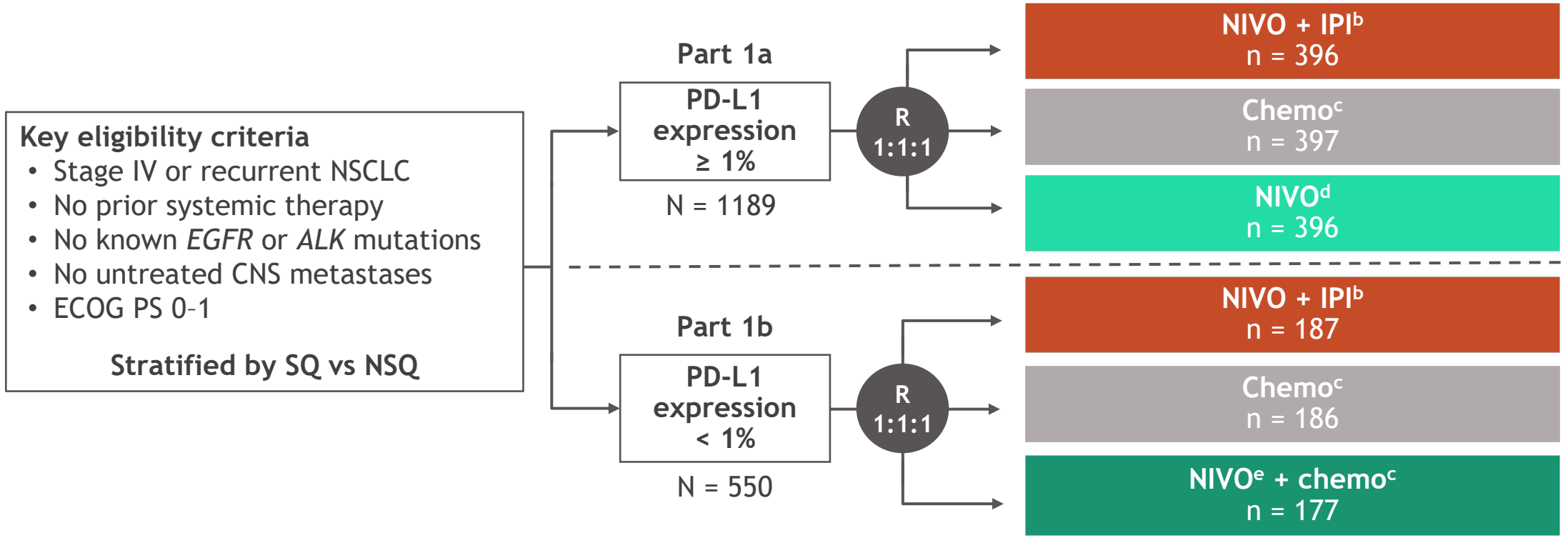
Pembrolizumab + Chemotherapy vs Chemotherapy in Patients With Advanced NSCLC Without Tumor PD-L1 Expression: A Pooled Analysis of 3 Randomized Controlled Trials





Borghaei H, et al. *Cancer.* 2020;126(22):4867-4877.

CheckMate 227 Part 1: Study Design



Independent primary endpoints (NIVO + IPI vs chemo)[f]
- PFS in patients with high TMB (≥ 10 mut/Mb)
- OS in patients with tumor PD-L1 ≥ 1%

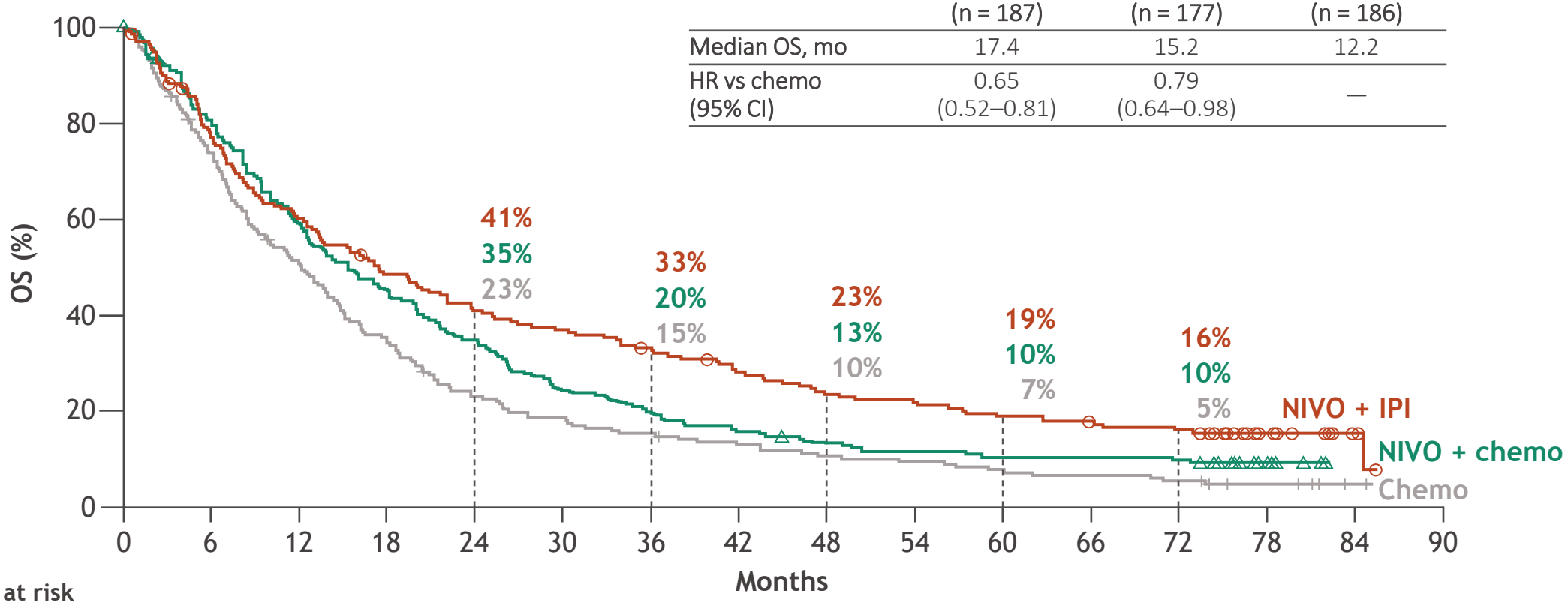
Exploratory analyses
- OS by response[g] and tumor burden reduction[h]
- OS by baseline HRQoL[i]

Database lock: February 21, 2023; minimum/median follow-up for OS: 73.5/78.8 months.

Ramalingam SS, et al. WCLC 2023. Abstract OA14.03.

CheckMate 227 Part 1: 6-Year OS in Patients With PD-L1 <1%

	NIVO + IPI (n = 187)	NIVO + chemo (n = 177)	Chemo (n = 186)
Median OS, mo	17.4	15.2	12.2
HR vs chemo (95% CI)	0.65 (0.52–0.81)	0.79 (0.64–0.98)	—



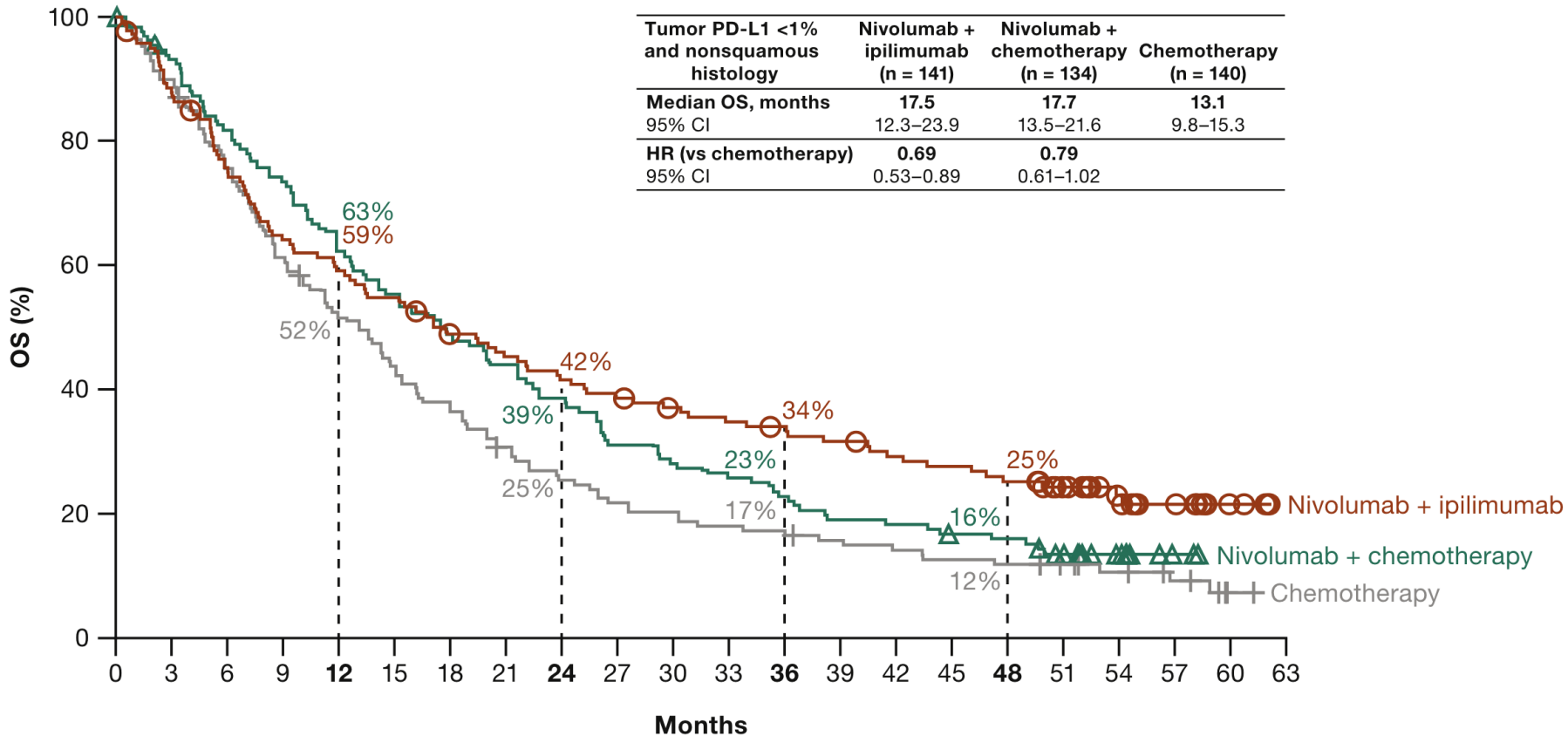
No. at risk																
NIVO + IPI	187	142	110	88	74	67	59	49	41	38	33	30	27	11	3	0
NIVO + chemo	177	139	102	78	60	42	34	27	22	19	17	17	16	5	0	0
Chemo	186	135	92	62	41	33	27	22	18	16	12	11	9	5	1	0

- In an exploratory analysis of OS by histology in patients with tumor PD-L1 < 1%, 6-year OS rates with NIVO + IPI vs chemo were **15% vs 6% (NSQ)** and 18% and 4% (SQ)

Ramalingam SS, et al. WCLC 2023. Abstract OA14.03.

CheckMate 227 Part 1: OS in Patients With PD-L1 <1% and Nonsquamous Histology

Tumor PD-L1 <1% and nonsquamous histology	Nivolumab + ipilimumab (n = 141)	Nivolumab + chemotherapy (n = 134)	Chemotherapy (n = 140)
Median OS, months	**17.5**	**17.7**	**13.1**
95% CI	12.3–23.9	13.5–21.6	9.8–15.3
HR (vs chemotherapy)	**0.69**	**0.79**	
95% CI	0.53–0.89	0.61–1.02	

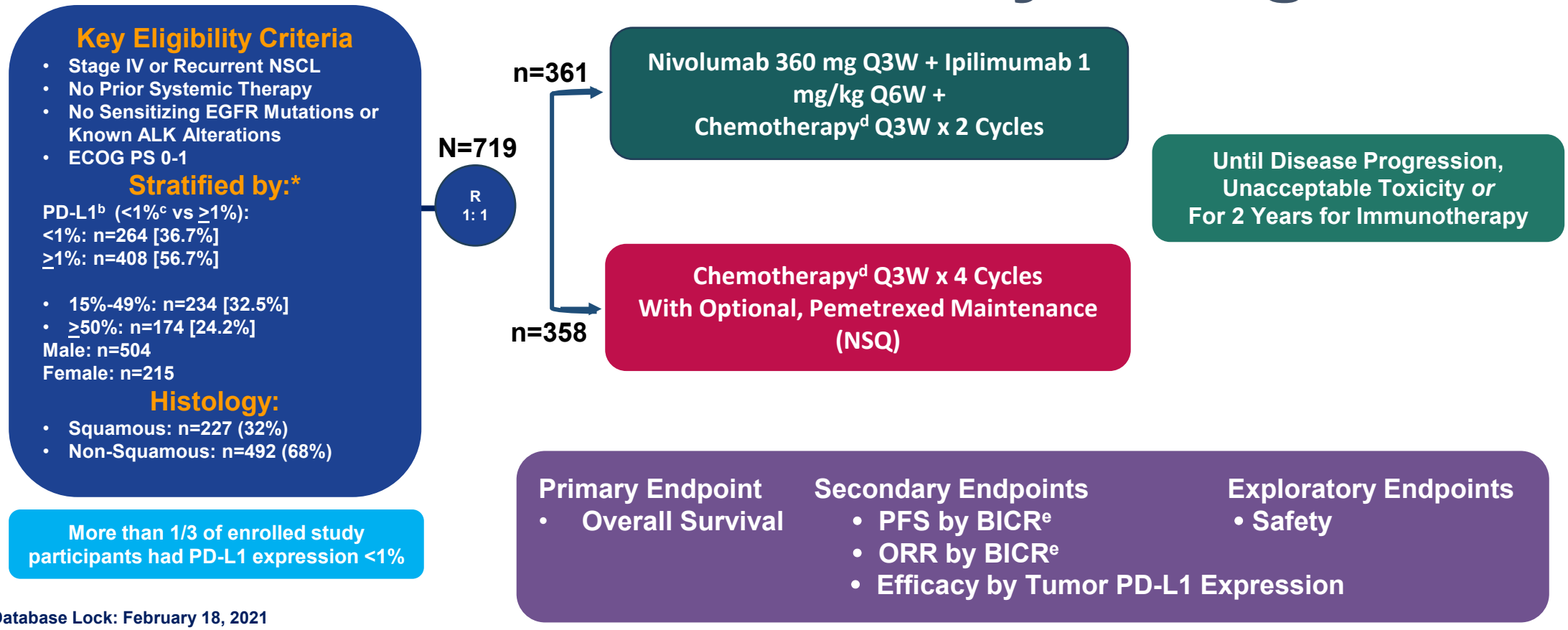


Number of patients at risk

Nivolumab + ipilimumab	141	122	104	89	82	76	66	61	56	52	48	45	43	40	36	34	31	24	16	11	4	0
Nivolumab + chemotherapy	134	123	108	97	83	73	65	58	51	41	37	34	30	25	24	21	20	15	9	2	0	0
Chemotherapy	140	126	105	85	71	59	50	41	34	29	27	24	23	20	18	16	15	12	9	6	1	0

Paz-Ares LG, et al. *J Thorac Oncol*. 2022;17(2):289-308.

CheckMate 9LA Trial: Study Design



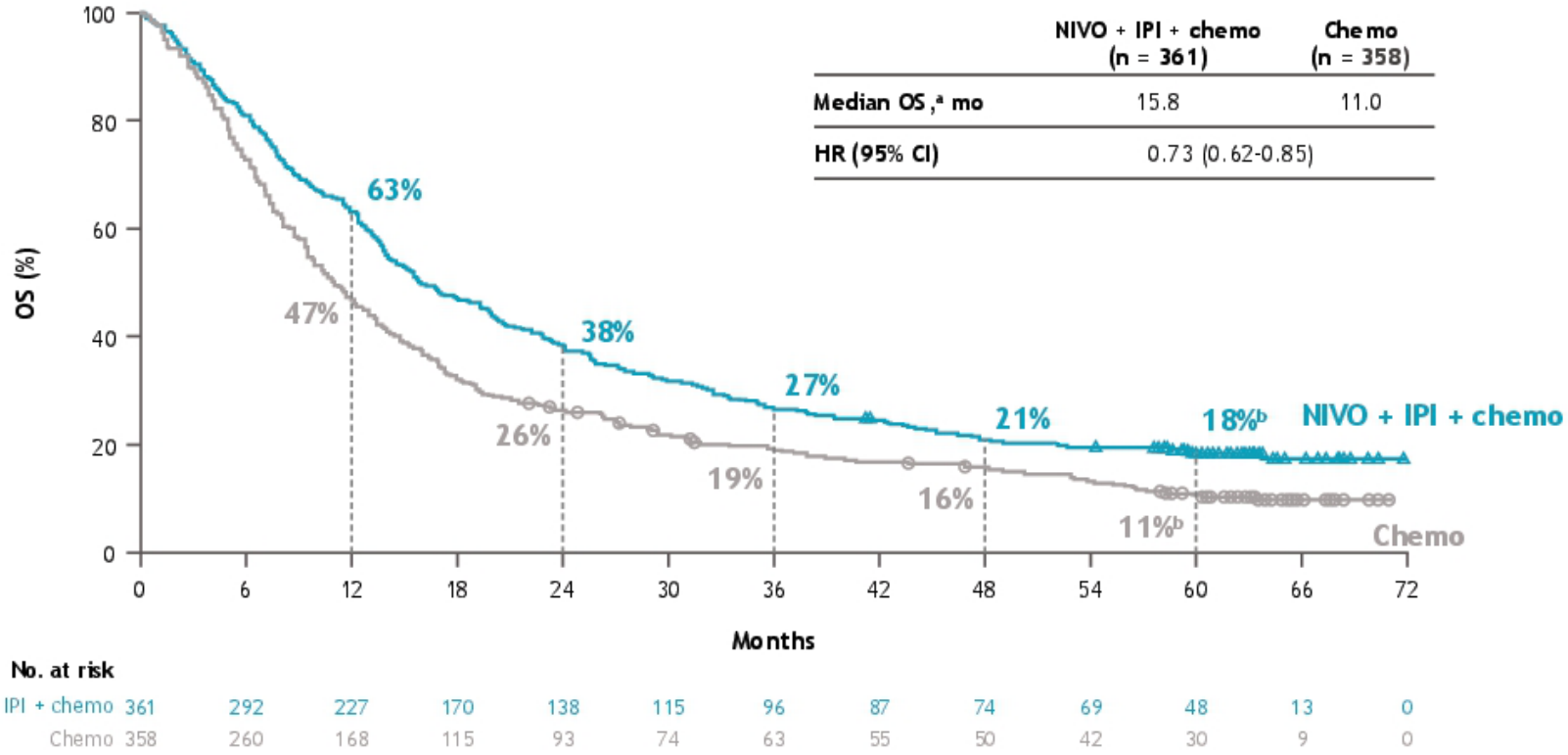
Database Lock: February 18, 2021
Minimum Follow-up for OS: 24.4 Months
Median Follow-up for OS: 30.7 Months

[a]NCT03215706
[b]Determined by the PD-L1 IHC 28.8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 <1% and capped to 10% of all randomized patients; [d]NSQ: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Reck M, et al. *J Clin Oncol.* 2021;39(15_suppl):9000.
Paz-Ares LG, et al. *Lancet Oncol.* 2021;22:198-211.

CheckMate 9LA: 5-Year OS

All Randomized

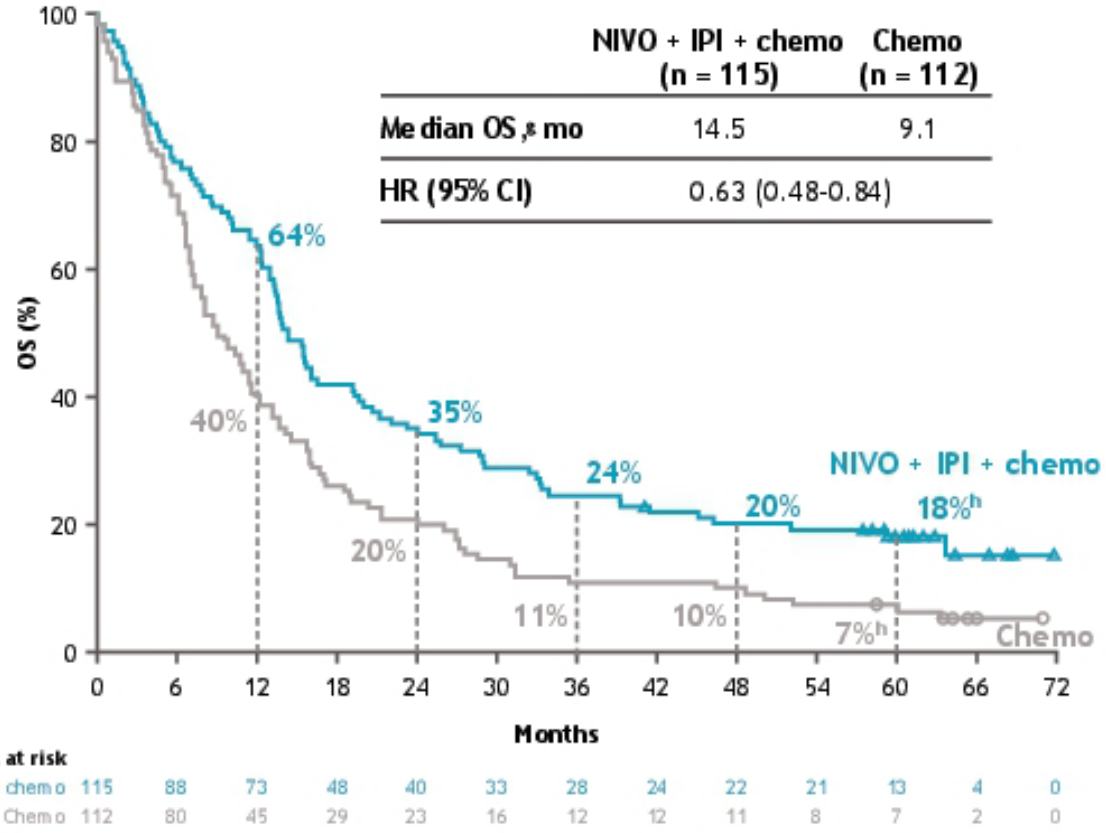


Database Lock: December 15, 2023
Minimum Follow-Up for OS: 57.3 Months
Maximum Follow-Up to OS: 64.5 Months

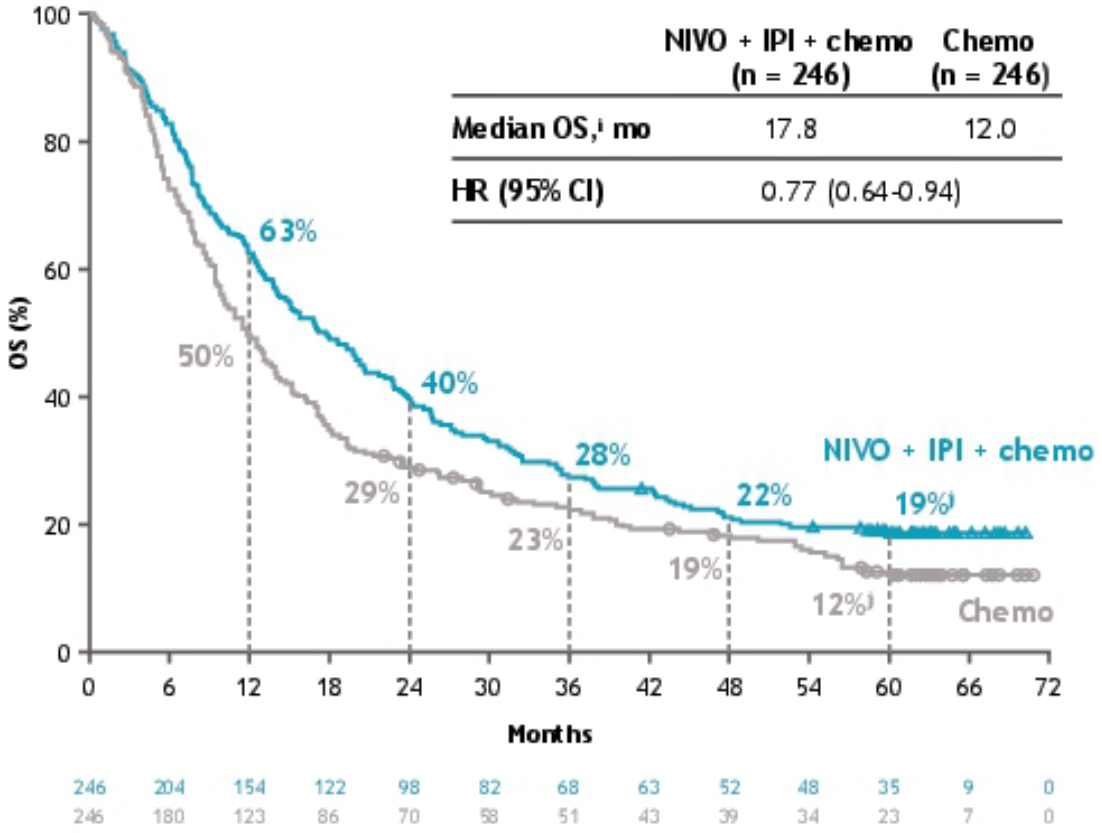
Reck M, et al. *J Clin Oncol.* 2024;42(16 suppl):8560.
Reck M, et al. ASCO 2024. Poster #424.

CheckMate 9LA: 5-Year OS by Histology

Squamous



Nonsquamous

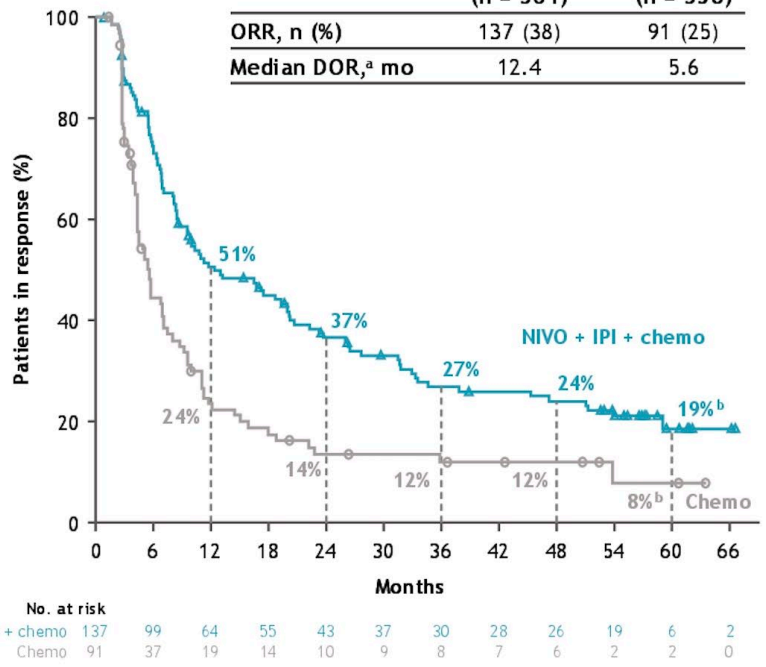


Reck M, et al. *J Clin Oncol.* 2024;42(16 suppl):8560.
Reck M, et al. ASCO 2024. Poster #424.

CheckMate 9LA: DoR by PD-L1 Expression

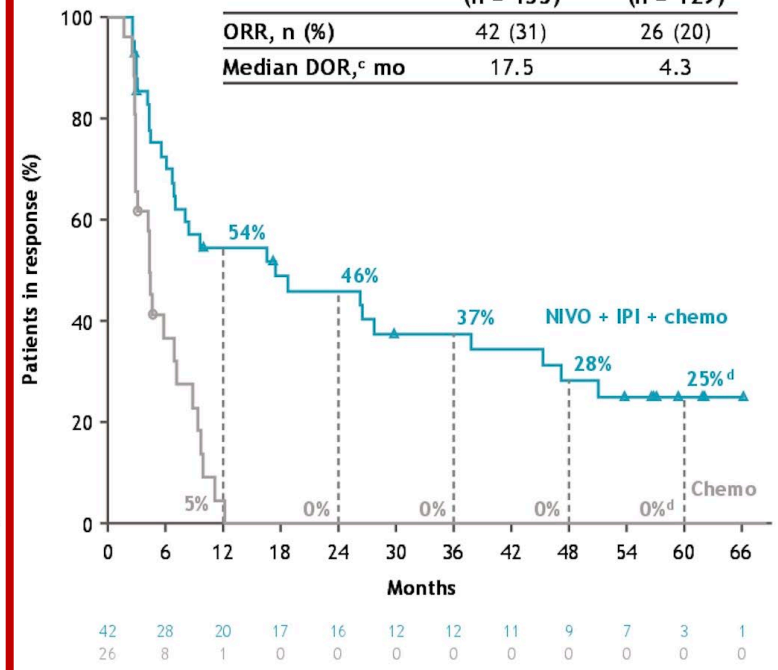
All Randomized

	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
ORR, n (%)	137 (38)	91 (25)
Median DOR,[a] mo	12.4	5.6



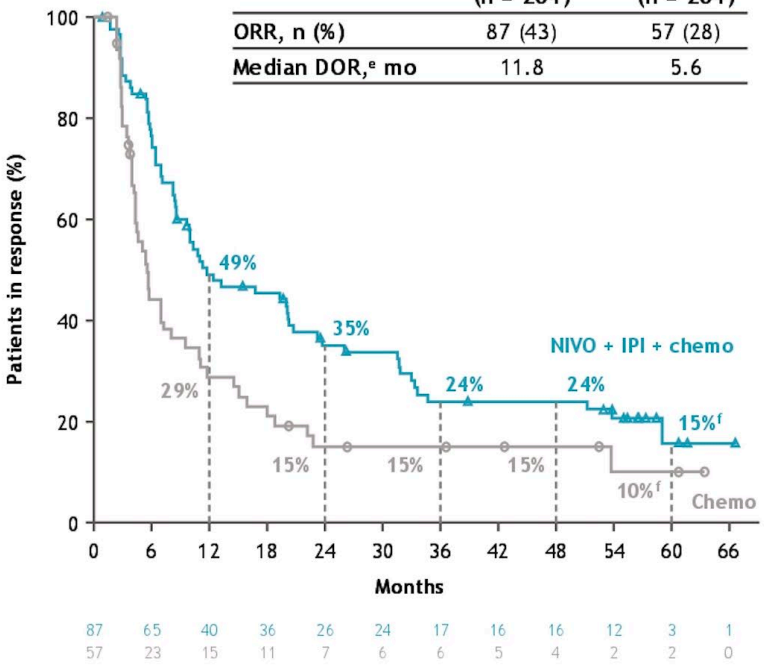
PD-L1 <1%

	NIVO + IPI + chemo (n = 135)	Chemo (n = 129)
ORR, n (%)	42 (31)	26 (20)
Median DOR,[c] mo	17.5	4.3



PD-L1 ≥1%

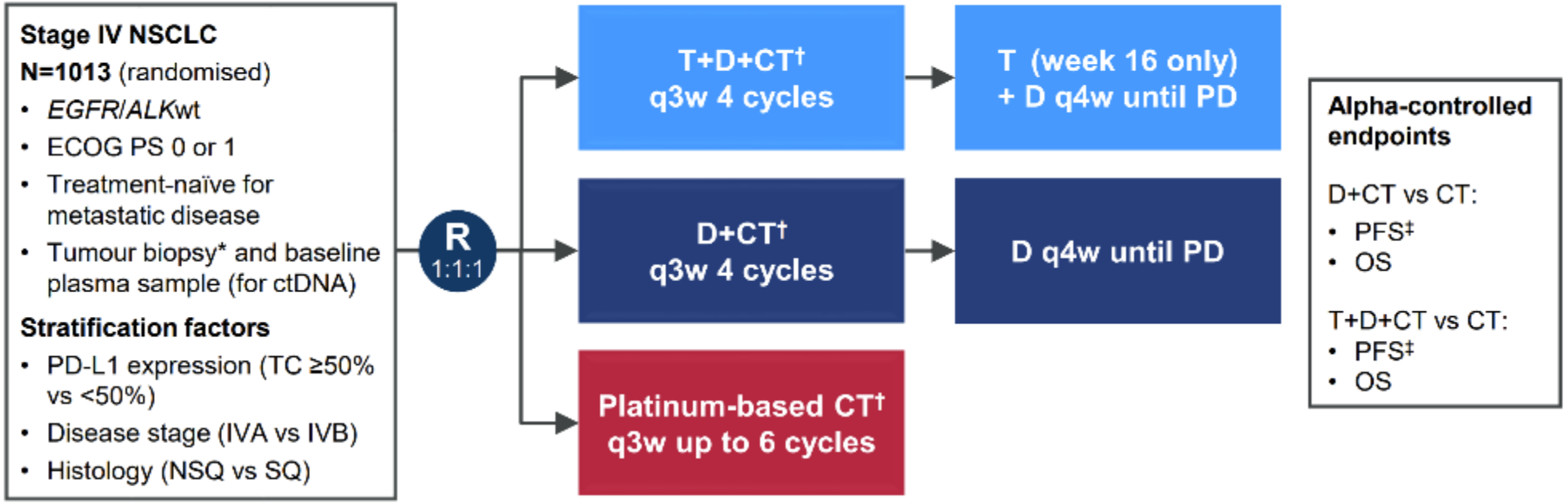
	NIVO + IPI + chemo (n = 204)	Chemo (n = 204)
ORR, n (%)	87 (43)	57 (28)
Median DOR,[e] mo	11.8	5.6



Reck M, et al. *J Clin Oncol.* 2024;42(16 suppl):8560.
Reck M, et al. ASCO 2024. Poster #424.

Phase III POSEIDON Clinical Trial: Study Design

Phase 3, global, randomised, open-label, multicentre study in 1L mNSCLC

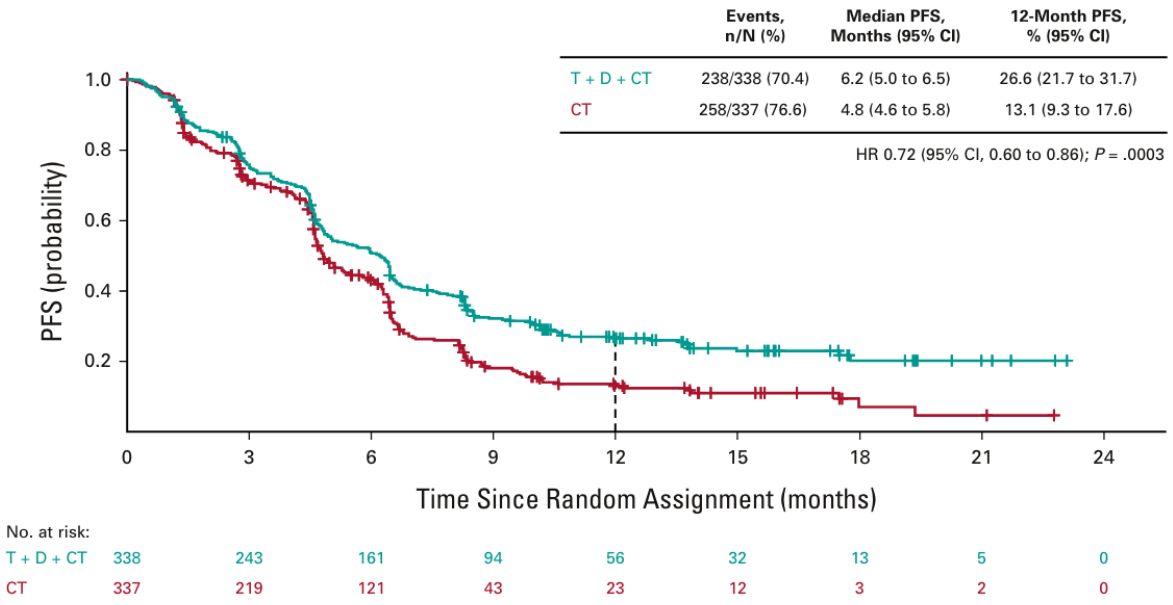


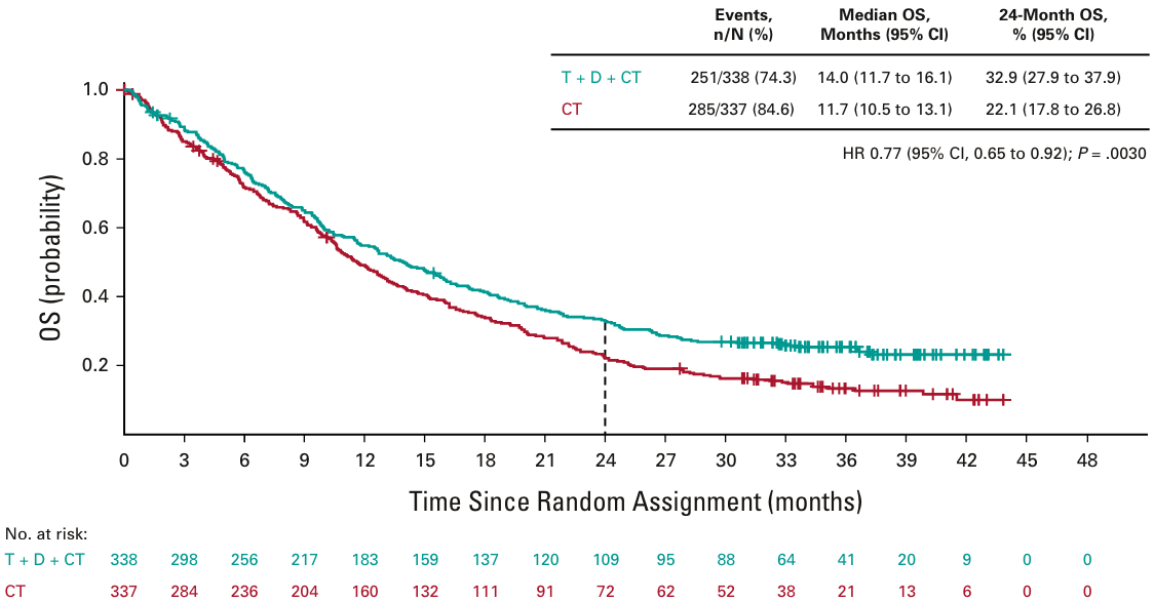
- **Durvalumab** 1500mg ± **limited-course tremelimumab** 75mg + **CT** q3w for **4 cycles**
  - One additional dose of tremelimumab post-CT (week 16; 5th dose)
- Followed by **durvalumab q4w maintenance** until PD, and optional pemetrexed q4w§

Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

ALKwt, anaplastic lymphoma kinase wild type; CT, platinum-based chemotherapy; ctDNA, circulating tumor DNA; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; NSG, non-squamous; OS, overall survival; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; q3w, every 3 weeks; SQ, squamous; T, tremelimumab; TC, tumor cellularity.

POSEIDON: 4-Year PFS and OS





Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

POSEIDON: OS in Patients With PD-L1 <1% or Squamous Histology

	Events/Patients, n/N		HR (95% CI)
	T + D + CT	CT	
All patients	251/338	285/337	0.77 (0.65 to 0.92)
Sex			
Male	202/269	220/248	0.70 (0.58 to 0.85)
Female	49/69	65/89	0.96 (0.66 to 1.38)
Age, years			
< 65	137/191	143/176	0.79 (0.62 to 1.00)
≥ 65	114/147	142/161	0.74 (0.58 to 0.94)
Tumor PD-L1 expression			
TC ≥ 50%	69/101	80/97	0.65 (0.47 to 0.89)
TC < 50%	182/237	205/240	0.82 (0.67 to 1.00)
TC ≥ 1%	151/213	170/207	0.76 (0.61 to 0.95)
TC < 1%	100/125	115/130	0.77 (0.58 to 1.00)
Histology			
Squamous	106/124	111/122	0.88 (0.68 to 1.16)
Nonsquamous	145/214	173/214	0.70 (0.56 to 0.87)
Planned chemotherapy			
Nab-paclitaxel doublet	16/23	17/19	0.55 (0.27 to 1.11)
Pemetrexed doublet	138/204	166/207	0.72 (0.57 to 0.90)
Gemcitabine doublet	97/111	102/111	0.90 (0.68 to 1.19)
Smoking history			
Current	59/84	56/66	0.54 (0.37 to 0.79)
Former	142/195	164/191	0.75 (0.60 to 0.94)
Never	50/59	64/79	1.15 (0.79 to 1.67)
Race			
Asian	72/99	103/128	0.97 (0.71 to 1.30)
Non-Asian	179/239	182/209	0.65 (0.53 to 0.80)
ECOG performance status			
0	73/110	93/119	0.80 (0.59 to 1.09)
1	178/228	192/218	0.72 (0.59 to 0.89)
AJCC disease stage at diagnosis			
IVA	121/171	138/166	0.72 (0.56 to 0.91)
IVB	130/165	146/170	0.84 (0.66 to 1.06)

Johnson ML, et al. *J Clin Oncol*. 2023;41(6):1213-1227.

EMPOWER-Lung 3 Trial: Study Design

Key Eligibility Criteria

- Treatment-naïve laNSCLC:
  - Non-squamous and squamous histology
- Any PD-L1 expression
- No EGFR, ALK, or ROS1 mutations
- ECOG PS 0 or 1
- Treated, clinically stable CNS metastases‡

Stratification Factors

- PD-L1 expression: <1% vs 1-49% vs ≥50%
  - <1%: n=95 (30.4%)
  - 1%-49%: n=114 (36.5%)
  - ≥50%: n=103 (33.0%)
- Histology:
  - Non-squamous: n=179 (57.4%)
  - Squamous: n=133 (42.6%)

Endpoints

- Primary: OS
- Key Secondary: PFS and ORR
- Additional Secondary: DOR, BOR, Safety, Tolerability, and PROs

R 2:1

Arm A

Cemiplimab 350 mg Q3W + Investigator's Choice Platinum-Doublet Chemotherapy Q3W x 4 Cycles

Arm B

Placebo Q3W + Investigator's Choice Platinum-Doublet Chemotherapy Q3W x 4 Cycles

Progression or 108 Weeks

Progression or 108 Weeks

Follow-Up

466 Patients in Full Analysis Population

69 Patients with laNSCLC Not Candidates for Definitive Interventions
Data Cutoff: June 14, 2022

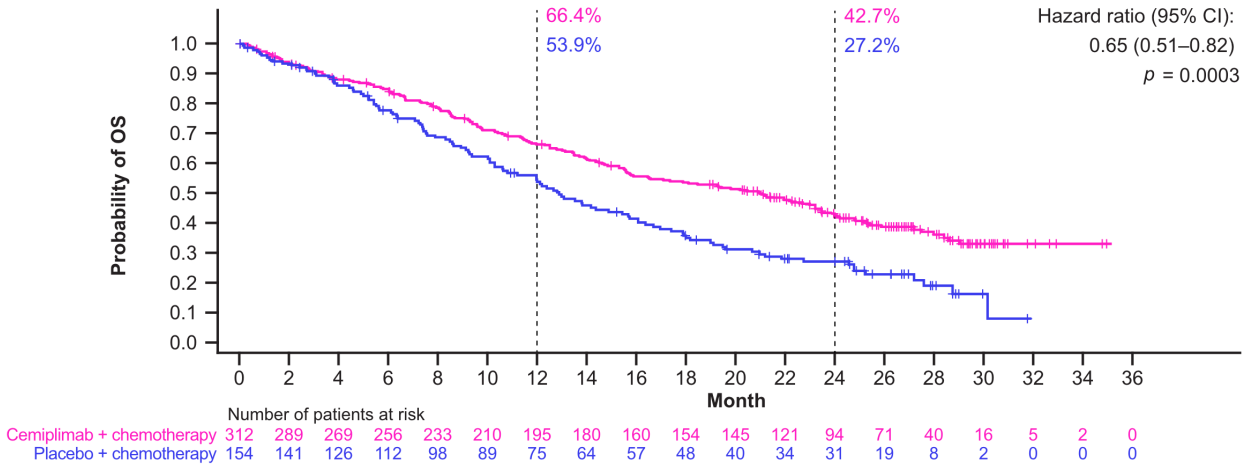
† Patient not a candidate for definitive chemoradiation.
- The indication to exclude concurrent radical chemo-radiation for stage IIIb/c patients was based on an individual decision by the principal investigator.

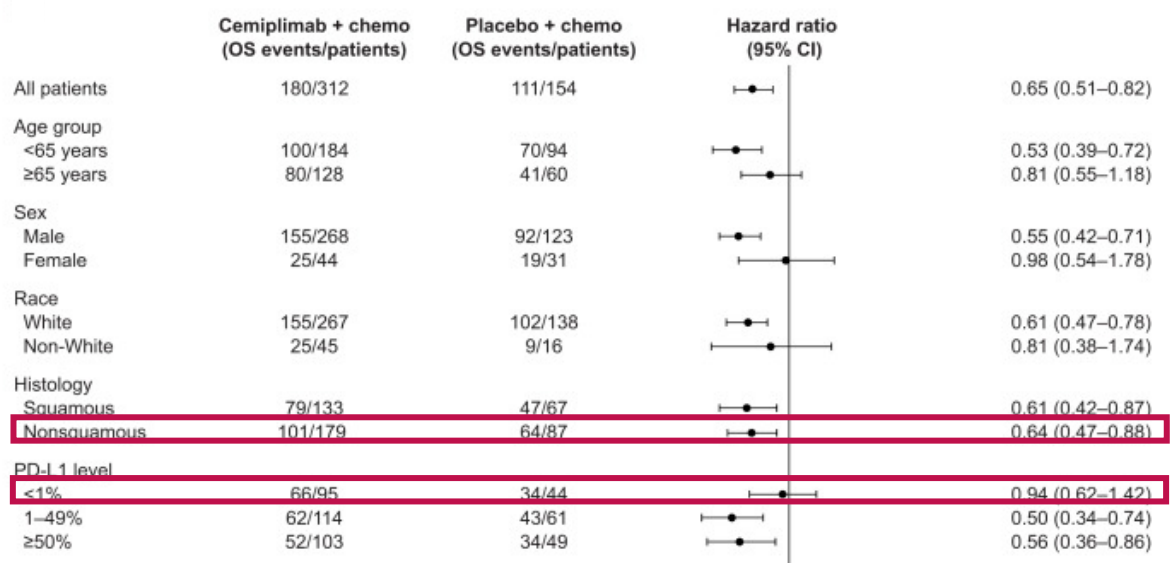
‡ Patient must have neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment).
§ For patients with non-squamous NSCLC, pemetrexed is mandatory as maintenance therapy for those patients initially assigned to receive a pemetrexed-containing regimen.

Gogishvili M, et al. *Nat Med.* 2022;28:2374-2380.

ALK, anaplastic lymphoma kinase gene; BOR, best overall response; CNS, central nervous system; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor gene; laNSCLC, locally advanced non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcomes; Q3W, every 3 weeks; R, randomized; ROS1, c-ros oncogene 1.

EMPOWER-Lung 3: 2-Year OS





Makharadze T, et al. *J Thorac Oncol.* 2023;18(6):755-768.

EMPOWER-Lung 3: OS and PFS by Histology

Subgroup	OS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy	Median OS (months)	OS HR (95% CI)	PFS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy	Median PFS (months)	PFS HR (95% CI)	ORR %
Squamous PD-L1: <1% (n=54)	23/38 vs 13/16	21.9 vs 16.7	0.60 (0.30-1.20)	31/38 vs 14/16	8.3 vs 6.1	0.70 (0.37-1.32)	50.0 vs 31.3
Squamous PD-L1: 1-49% (n=81)	31/53 vs 19/28	23.2 vs 8.6	0.52 (0.29-0.92)	45/53 vs 25/28	6.7 vs 4.2	0.55 (0.33-0.90)	43.4 vs 25.0
Squamous PD-L1: ≥50% (n=65)	25/42 vs 15/23	22.2 vs 15.1	0.77 (0.40-1.45)	33/42 vs 18/23	8.3 vs 5.5	0.51 (0.28-0.92)	47.6 vs 26.1
Non-Squamous PD-L1: <1% (n=85)	43/57 vs 21/28	9.6 vs 13.0	1.26 (0.74-2.12)	46/57 vs 25/28	5.2 vs 4.3	0.79 (0.49-1.30)	22.8 vs 14.3
Non-Squamous PD-L1: 1-49% (n=94)	31/61 vs 24/33	23.2 vs 12.0	0.48 (0.28-0.82)	42/61 vs 30/33	8.5 vs 6.2	0.42 (0.26-0.69)	42.6 vs 15.2
Non-Squamous PD-L1: ≥50% (n=87)	27/61 vs 19/26	24.8 vs 14.4	0.42 (0.23-0.76)	37/61 vs 21/26	12.5 vs 5.2	0.46 (0.27-0.80)	57.4 vs 26.9

Makharadze T, et al. *J Thorac Oncol.* 2023;18(6):755-768.