Case 3

- 58-year-old woman
- Presented with incidental finding of bilateral lung lesions when undergoing preoperative CT for hernia repair
  - Feels well without symptoms
- Past medical, family, and social history
  - Hypertension on a thiazide diuretic
  - Distant ex-smoker (10 pack years) and stopped smoking 25 years ago
- Physical examination
  - Current weight: 120 lbs
  - ECOG PS 1

Case 3 (Cont.)

- Diagnostic workup
  - CT of thorax discovered an R lower lobe mass
  - CT of abdomen showed an R adrenal metastasis and bone windows, suggesting bone metastases
  - MRI of brain negative for brain metastases
- Final pathology: consistent with adenocarcinoma, TTF1-, CDX2+, intestinal type
  - Metastatic stage IV
- PD-L1 expression by IHC: 40%
- NGS: no actionable mutations

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

Immunotherapy Options for Advanced NSCLC with PD-L1 Expression ≥1% or ≥1% to 49% (NCCN Cat 1)[9]

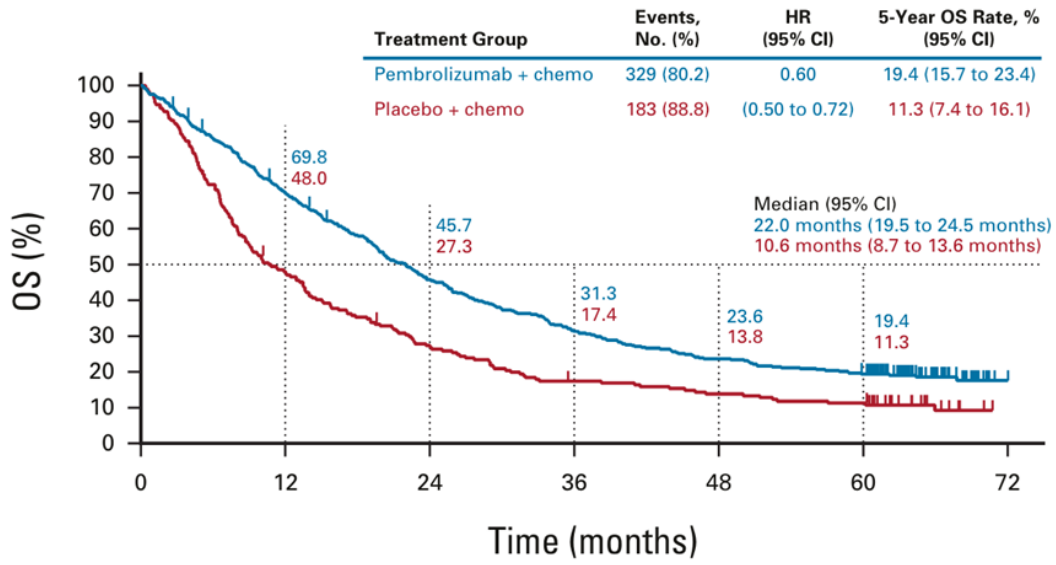
Regimen Trial NCCN status	IPI/NIVO CHECKMATE 227[1] n=396 NCCN Cat 1	IPI/NIVO+CT CHECKMATE 9LA[2] n=204 NCCN Cat 1	PEM+PC(AD) KEYNOTE-021[3] N=39 NCCN Cat 1 Preferred	PEM+PC(AD) KEYNOTE-189[4] n=128 NCCN Cat 1 Preferred	PEM+CP(SC) KEYNOTE-407[5] n=103 NCCN Cat 1 Preferred	ATEZO+BCP IMpower 150[6] n=359 NCCN Cat 1 AD only	CEM+CT EMPOWER-Lung 3[7] n-114 NCCN Cat 1	TREM/DURV+CT POSEIDON[8] n=338 NCCN Cat 1 AD only
PD-L1% parameter	TPS ≥ 1 % ‡	TPS ≥ 1 % ‡	TPS ≥ 1 % ᵠ	TPS ≥ 1 % - 49% ᵠ	TPS ≥ 1 % - 49% ᵠ	TC/IC 0-3 †ɣ	TPS ≥ 1 % - 49%ɣ	TC 1-2 ɣ
ORR,%	36%	87%	61%	50%	54.40%	55%*	43.0%	38.8%
Median DoR, mo	24.5	11.8	NR	13.6	11.1	10.8*	16.4*	9.5
Median OS, mo	17.1 (HR: 0.78)	15.8 (HR:0.73)	40.9 (HR:0.84)	21.8 (HR:0.65)	18.0 (HR 0.61)	19.2 (HR:0.78)* 18.9 (HR:0.69) PD-L1 TPS ≥ 1 %	23.2 (HR: 0.50)	14 (HR:0.77)

*Value represents all PD-L1 subtypes combined; ᵠBy PD-L1 22C3 assay; †By PD-L1 SP142 IHC assay; ‡By PD-L1 28-8 IHC assay; ɣ By PD-L1 SP263 IHC assay.
AD, adenocarcinoma; Atezo, atezolizumab; BCP, bevacizumab + carboplatin + paclitaxel; cat, category; CEM, cemiplimab; CP, paclitaxel/nab paclitaxel, carboplatin; CT, chemotherapy; DoR, duration of response; DURV, durvalumab; HR, hazard ratio; IC, immune cells; IPI, ipilimumab; mo, month; NCCN, National Comprehensive Cancer Network; NIVO, nivolumab; NR, not reported; OS, overall survival; ORR, objective response rate; PC, pemetrexed/carboplatin; PEM, pembrolizumab; PFS, progression-free survival; SC, squamous cell; TC, tumor cells; TPS, tumor proportion score; TREM, tremelimumab.

1. Ramalingam SS, et al. WCLC 2023. Abstract OA14.03. 2. Reck M, et al. ASCO 2024. Abstract 8560. 3. Awad MM, et al. *J Thorac Oncol*. 2021;16:162-168. 4. Garassino MC, et al. *J Clin Oncol*. 2023;41:1992-1998. 5. Novello S, et al. *J Clin Oncol*. 2023;41:1999-2006. 6. Socinski MA, et al. *J Thorac Oncol.* 2021;16:1909-1924. 7. Makharadze T, et al. *J Thorac Oncol*. 2023;18:755-768. 8. Johnson ML, et al. *J Clin Oncol*. 2023;41:1213-1227. 9. Riely GJ, et al. NCCN Guidelines. Non-Small Cell Lung Cancer (Version 3.2023). NCCN.org.

KEYNOTE-189: 5-Year Outcomes

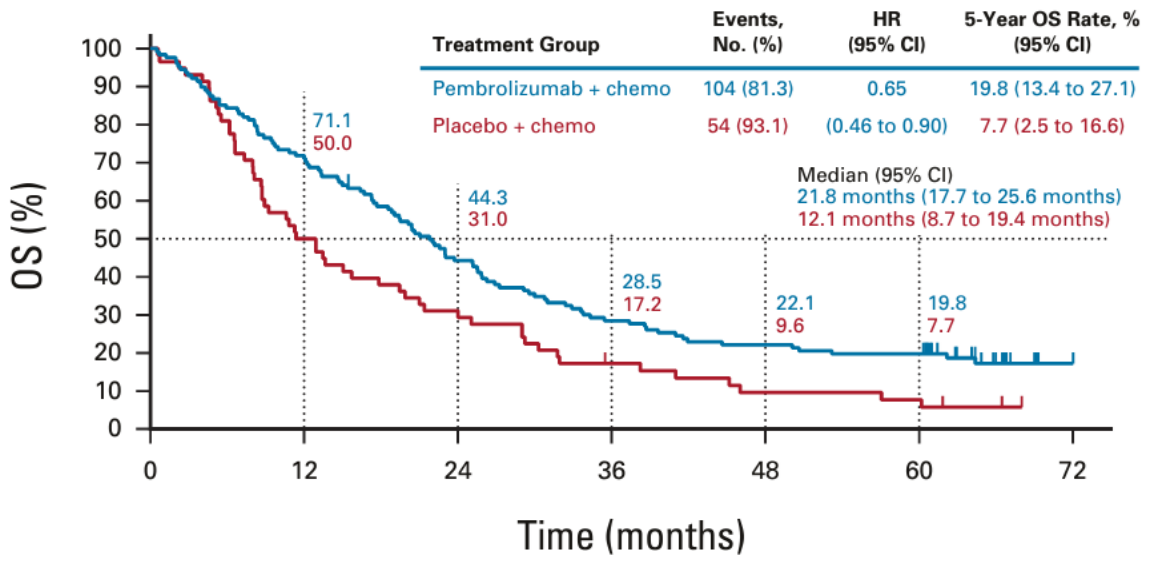
ITT



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%-49%

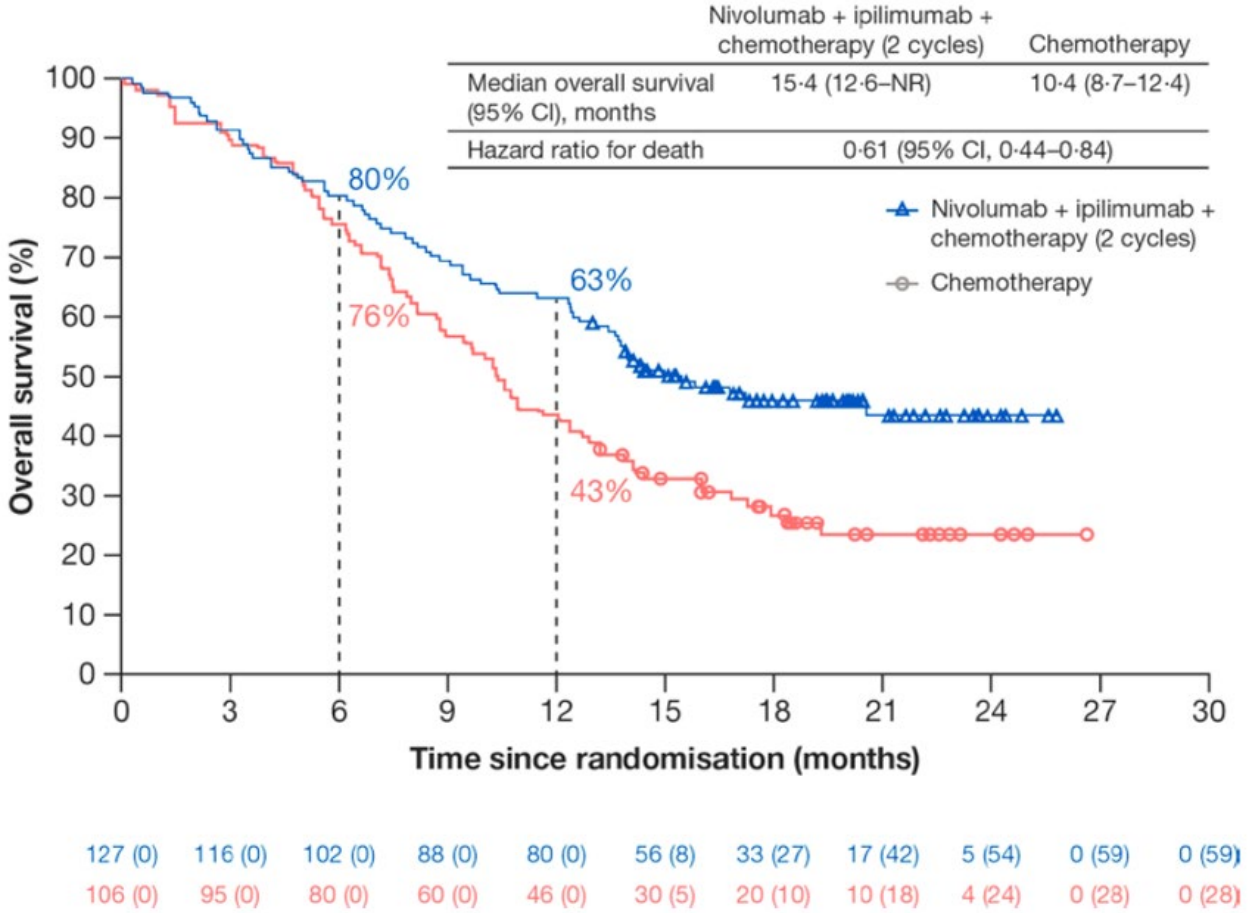


No. at risk:

Pembrolizumab + chemo	128	91	56	36	28	25	0
Placebo + chemo	58	29	18	9	5	4	0

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

First-Line Nivolumab/Ipilimumab + 2 Cycles of CT for Advanced NSCLC with PD-L1 1% to 49% (CheckMate 9LA)

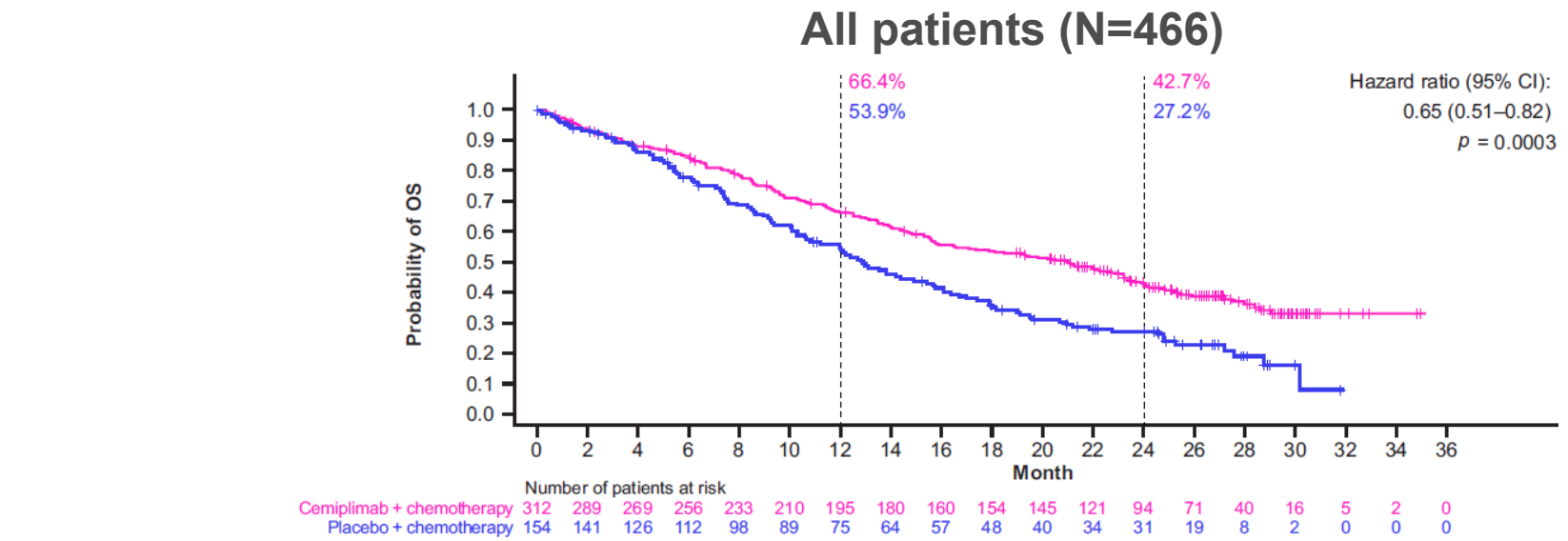


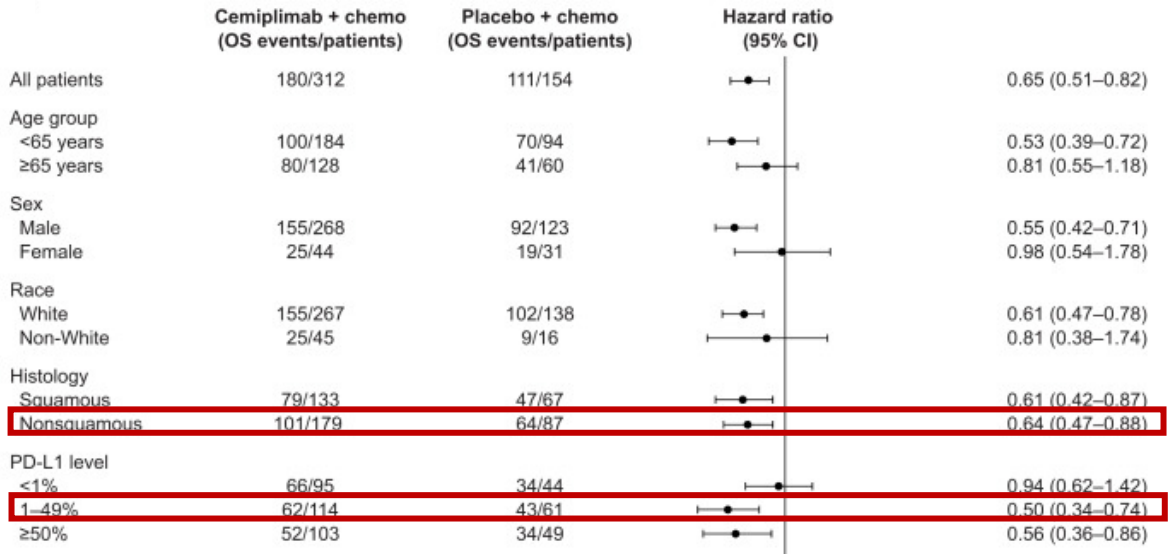
Outcomes: PD-L1≥1%-49%	Nivo/Ipi + CT (n=127)	CT (n=106)
ORR, % (n)	39.4	24.5
mDOR, mo (95% CI)	10.0 (6.5-13.2)	5.6 (3.9-15.2)

mDoR, median duration of response.

Paz-Ares L, et al. *Lancet Oncol.* 2021;22:198-211.

Cemiplimab ± Chemotherapy for NSCLC: EMPOWER-Lung 3





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

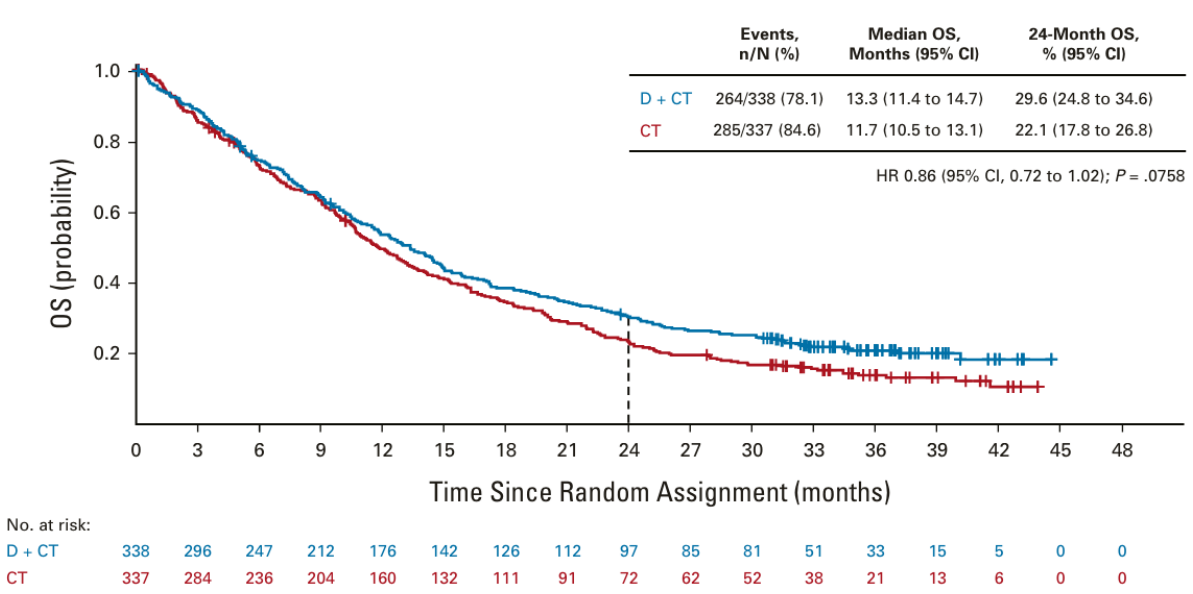
EMPOWER-Lung 3: OS and PFS by Histology

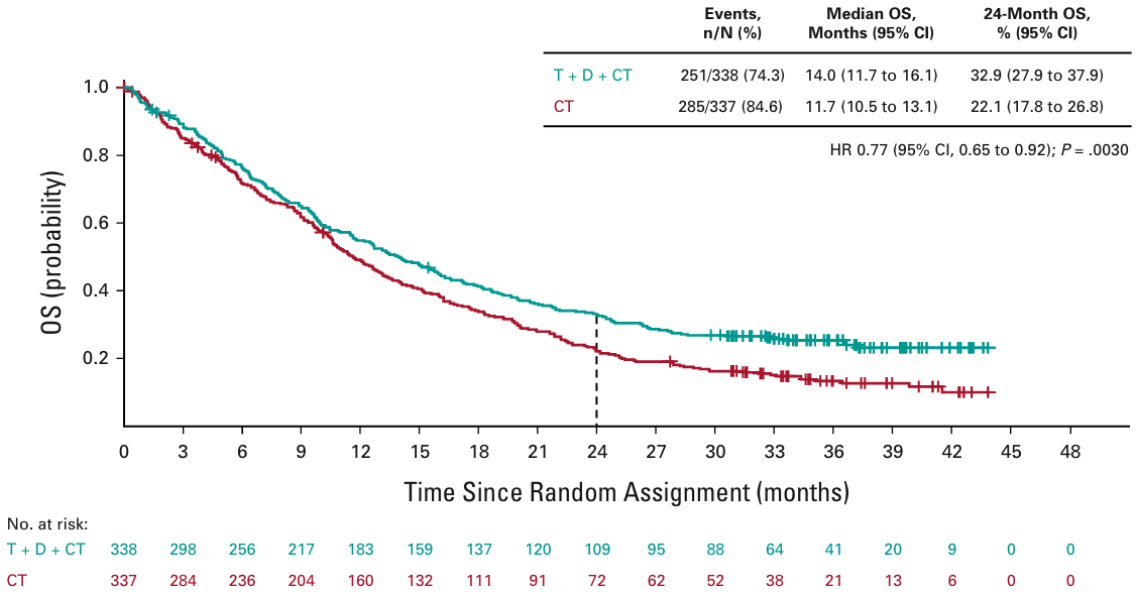
Subgroup	OS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy	Median OS (months)	OS HR (95% CI)	PFS Events Cemiplimab + Chemotherapy vs Placebo + Chemotherapy	Median PFS (months)	PFS HR (95% CI)	ORR %
Squamous PD-L1: <1% (n=54)	23/38 vs 13/16	21.9 vs 16.7	0.60 (0.30-1.20)	31/38 vs 14/16	8.3 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.

Durvalumab ± Tremelimumab in Combination with Chemotherapy (POSEIDON)

FDA approved November 10, 2022





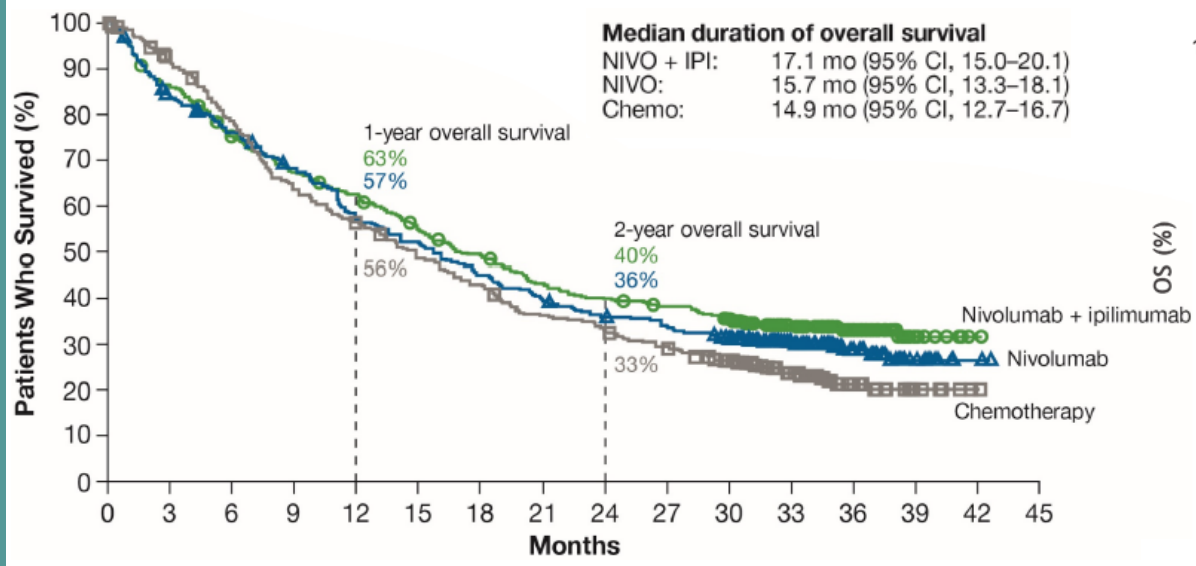
Johnson ML, et al. *J Clin Oncol*. 2023;41:1213-1227.

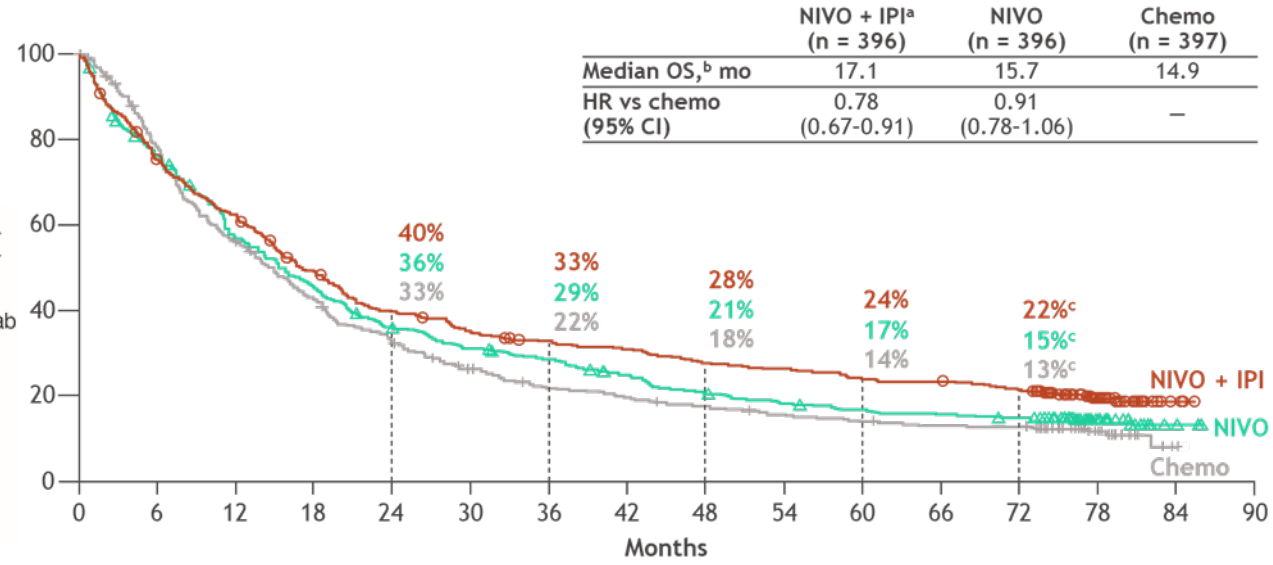
POSEIDON: OS in Patients With PD-L1 ≥1% or Nonsquamous Histology

	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.

First-Line Nivolumab+Ipilimumab Versus CT for Advanced or Metastatic NSCLC and PD-L1 ≥1% (CheckMate 227 Part 1)





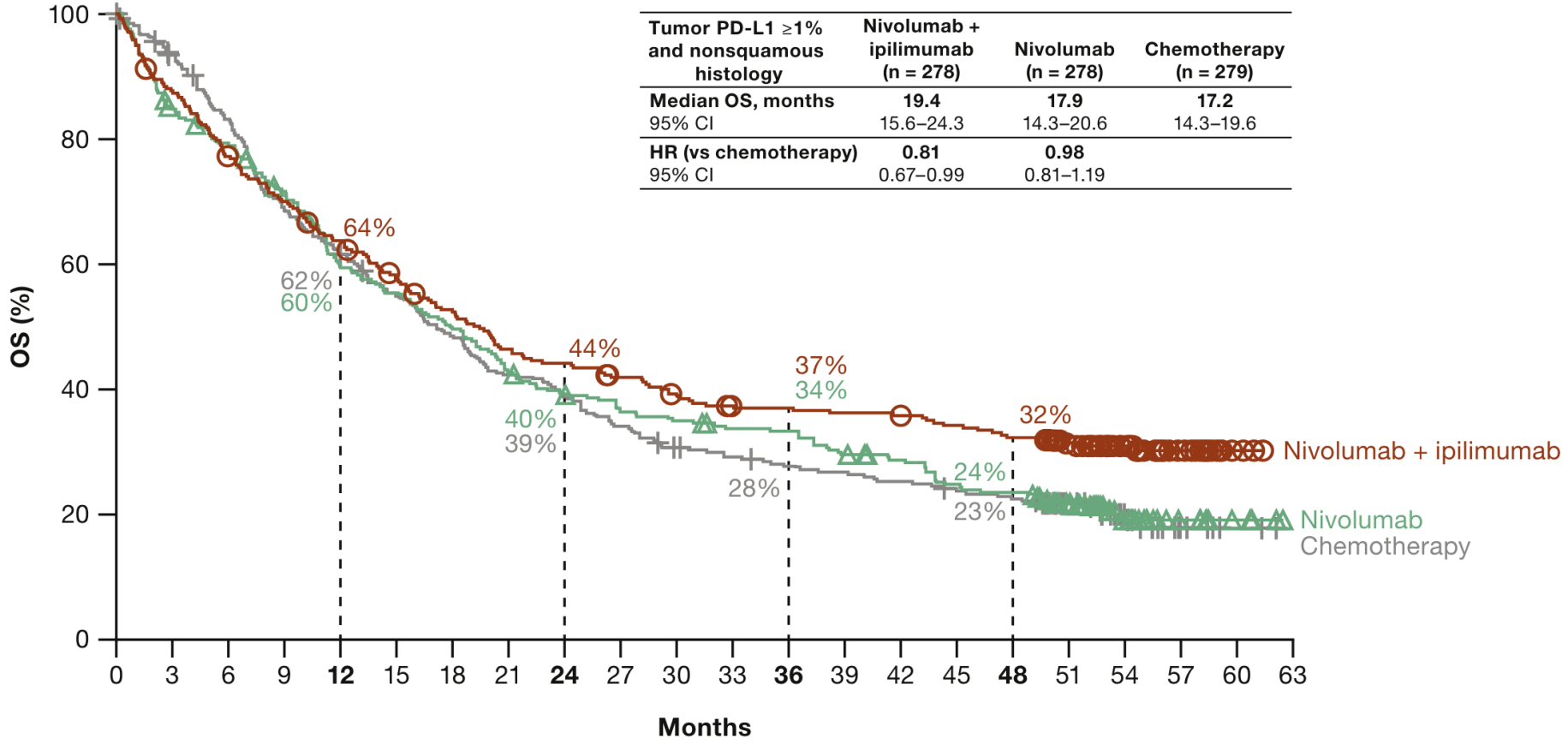
Outcomes	Nivolumab/Ipilimumab (n=396)	Nivolumab (n=396)	Chemotherapy (CT) (n=397)
ORR, % (95% CI)	35.9 (31.1-40.8)	27.5 (23.2-32.2)	30.0 (25.5-34.7)
mDOR, mo (95% CI)	23.2 (15.2-32.2)	15.5 (12.7-23.5)	6.2 (5.6-7.4)

Outcomes	Nivolumab/ Ipilimumab (n=396)	Nivolumab (n=396)	Chemotherapy (CT) (n=397)
ORR, % (n)	36 (144)	28 (109)	30 (118)
mDOR, mo (95% CI)	24.5 (15.5-34.5)	15.5 (12.7-20.8)	6.7 (5.6-7.6)

No data available for PD-L1 1%-49% group

Hellman MD, et al. *N Engl J Med.* 2019;381:2020-2031. Ramalingam SS, et al. WCLC 2023. Abstract OA14.03.

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



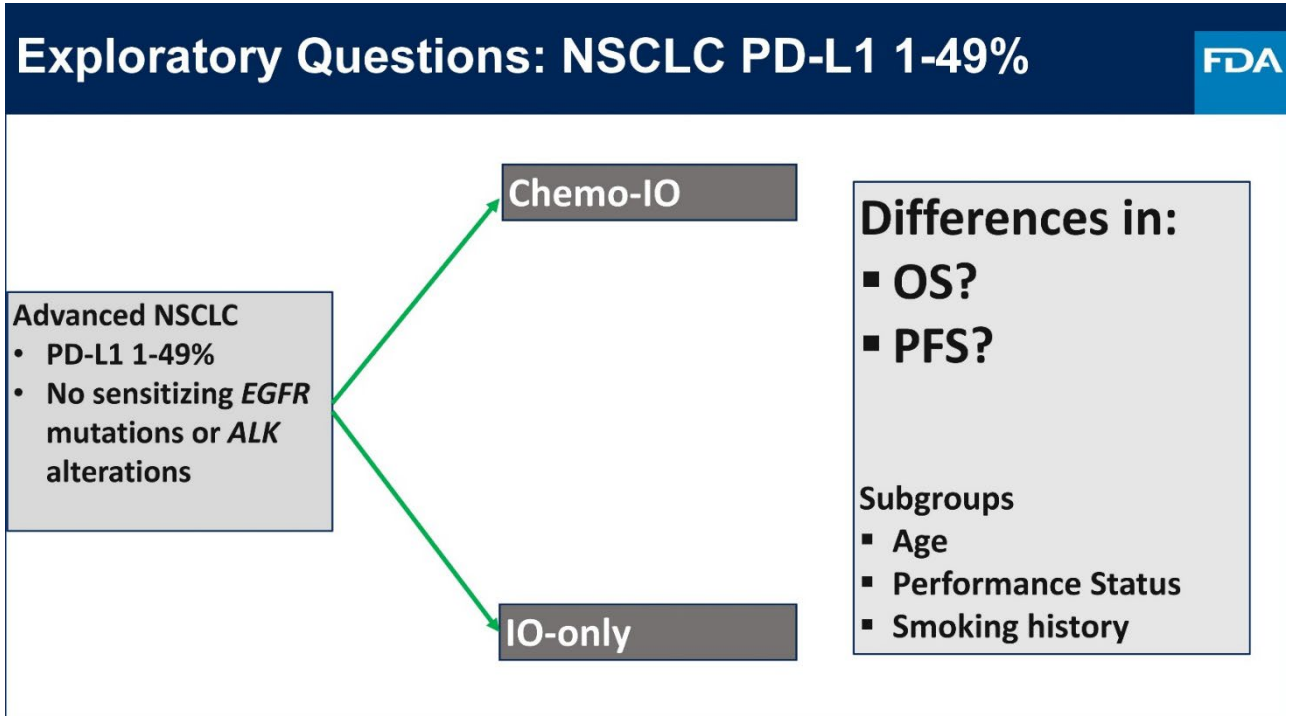
Tumor PD-L1 ≥1% and nonsquamous histology	Nivolumab + ipilimumab (n = 278)	Nivolumab (n = 278)	Chemotherapy (n = 279)
Median OS, months	**19.4**	**17.9**	**17.2**
95% CI	15.6–24.3	14.3–20.6	14.3–19.6
HR (vs chemotherapy)	**0.81**	**0.98**	
95% CI	0.67–0.99	0.81–1.19	

Number of patients at risk

Nivolumab + ipilimumab	278	243	213	193	175	156	142	125	119	111	102	96	95	93	91	87	82	67	46	17	3	0
Nivolumab	278	233	216	194	161	150	135	115	106	98	93	88	87	77	72	62	59	46	23	10	4	0
Chemotherapy	279	255	227	189	167	148	131	115	104	92	81	76	71	69	65	60	57	41	21	6	2	0

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

FDA Pooled Analysis

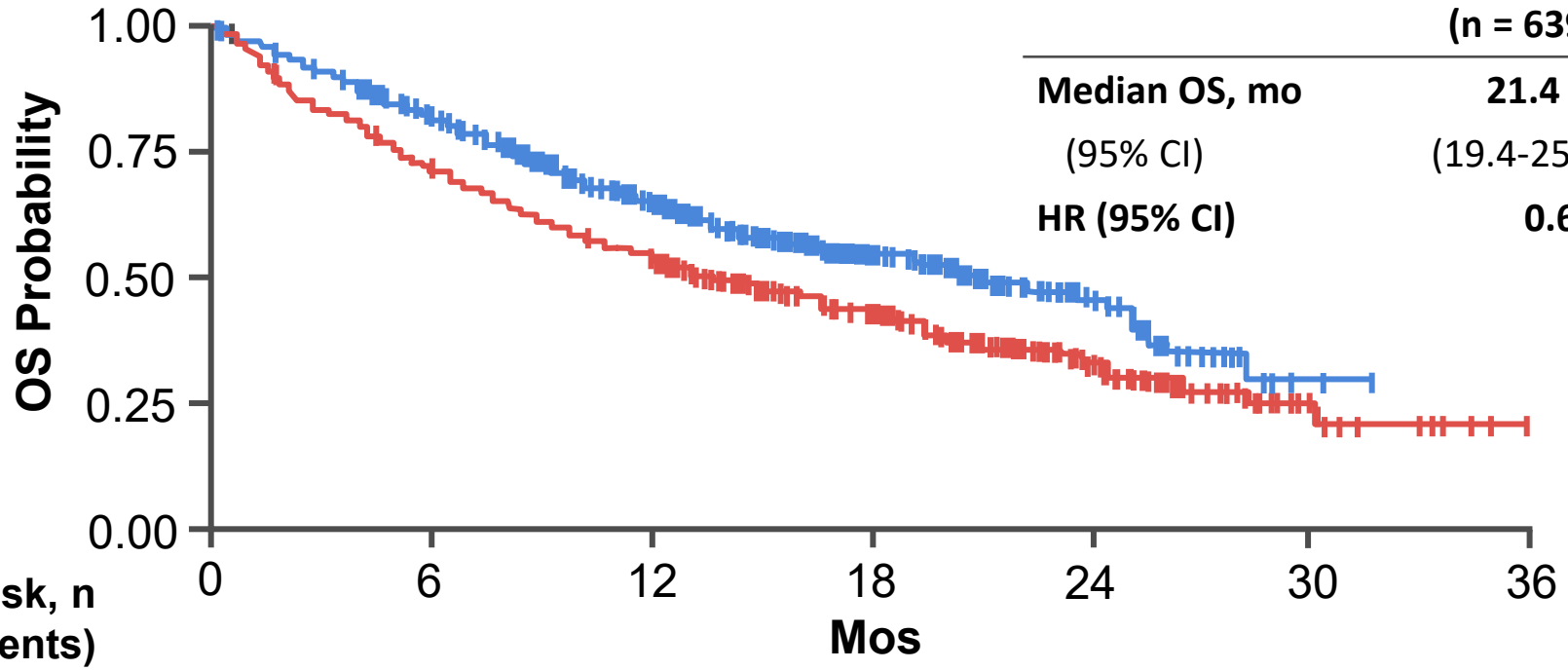


RCT Leading to Approval	Experimental Arm*†
IO alone	
▪ KEYNOTE-042	Pembro
▪ CheckMate 227	Nivo + ipi
Chemo-IO	
▪ KEYNOTE-189	Pembro + chemo
▪ KEYNOTE-407	Pembro + chemo
▪ KEYNOTE-021 (Cohort G)	Pembro + chemo
▪ IMpower150	Atezo + bev + chemo
▪ IMpower130	Atezo + chemo
▪ CheckMate 9LA	Nivo + ipi + chemo

*Chemo: platinum doublet; †Control arm in all trials was platinum-doublet chemo, except for IMpower150, which was bevacizumab + platinum-doublet chemo.
ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; IO, immuno-oncology; RCT, randomized controlled trial.

Akinboro O, et al, ASCO 2021. Abstract 9001.

FDA Pooled Analysis of First-Line Chemo-IO vs IO in Advanced NSCLC with PD-L1 1% to 49%: Exploratory OS



	Chemo-IO (n = 639)	IO Alone (n = 529)
Median OS, mo	**21.4**	**14.5**
(95% CI)	(19.4-25.2)	(12.2-16.9)
HR (95% CI)	**0.68 (0.52-0.90)**	

Patients at Risk, n (number of events)							
Chemo-IO	639 (0)	502 (108)	332 (203)	151 (246)	45 (261)	2 (270)	0 (270)
IO alone	529 (0)	378 (147)	283 (239)	183 (286)	77 (323)	14 (334)	0 (336)

Akinboro O, et al, ASCO 2021. Abstract 9001.

Summary

- No clear role for single agent immunotherapy
- Immunotherapy + chemotherapy or quadruplet regimens may be used