CHEMOTHERAPY + PD(L)1 FOR NSCLC: DATA + HOW I USE IT

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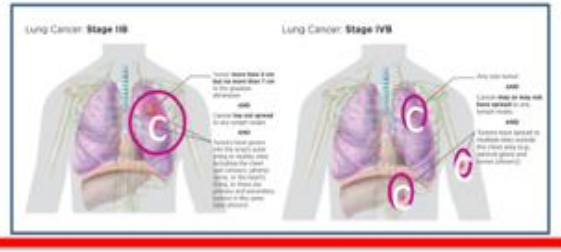
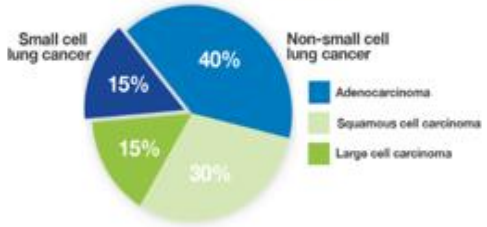
Introduction: Selection of optimal treatment

- ✓ Symptom burden
- ✓ Extent of disease
- ✓ Histology
- ✓ PS
- ✓ Comorbidities
- ✓ History of autoimmune
- ✓ disease or transplant
- ✓ Patient wishes
- ✓ Biomarker testing

Stage



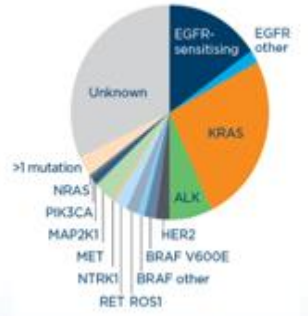
Histology



How much PD-L1 protein is present

This tumor has a high PD-L1 expression (more than 50% cancer cells produce PD-L1)

Whether tumor has a targetable mutation



Adapted from LUNGevity, 2021; LUNGevity, 2021b; URMC, 2022; NCCN, 2024

PD-L1 expression is the most commonly used predictive biomarker

- Tumor PD-L1 expression is quantified in a variety of ways, often reporting the fraction of positive tumor cells (TC), but sometimes also the fraction of positive immune cells (IC)

- Differential cutoffs are used for different antibodies in different studies

- About one third of patients with advanced NSCLC have tumors whose PD-L1 TPS is <1% (negative), 28-31% of patients have tumors with low levels of expression (TPS ≥1-49%), and 10-32% of patients have high levels of expression (TPS ≥50%)

Advanced NSCLC: PD-L1 <1%, ≥1%-49%

First-line Treatment in Patients Without Molecularly-driven Tumors

ADENOCARCINOMA

Preferred

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]
- Cemiplimab-rwlc/pemetrexed/(carboplatin or cisplatin) (category 1)[7,e]

Other Recommended

- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1) [6,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1)
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/pemetrexed[8,e] (category 1)

SQUAMOUS CARCINOMA

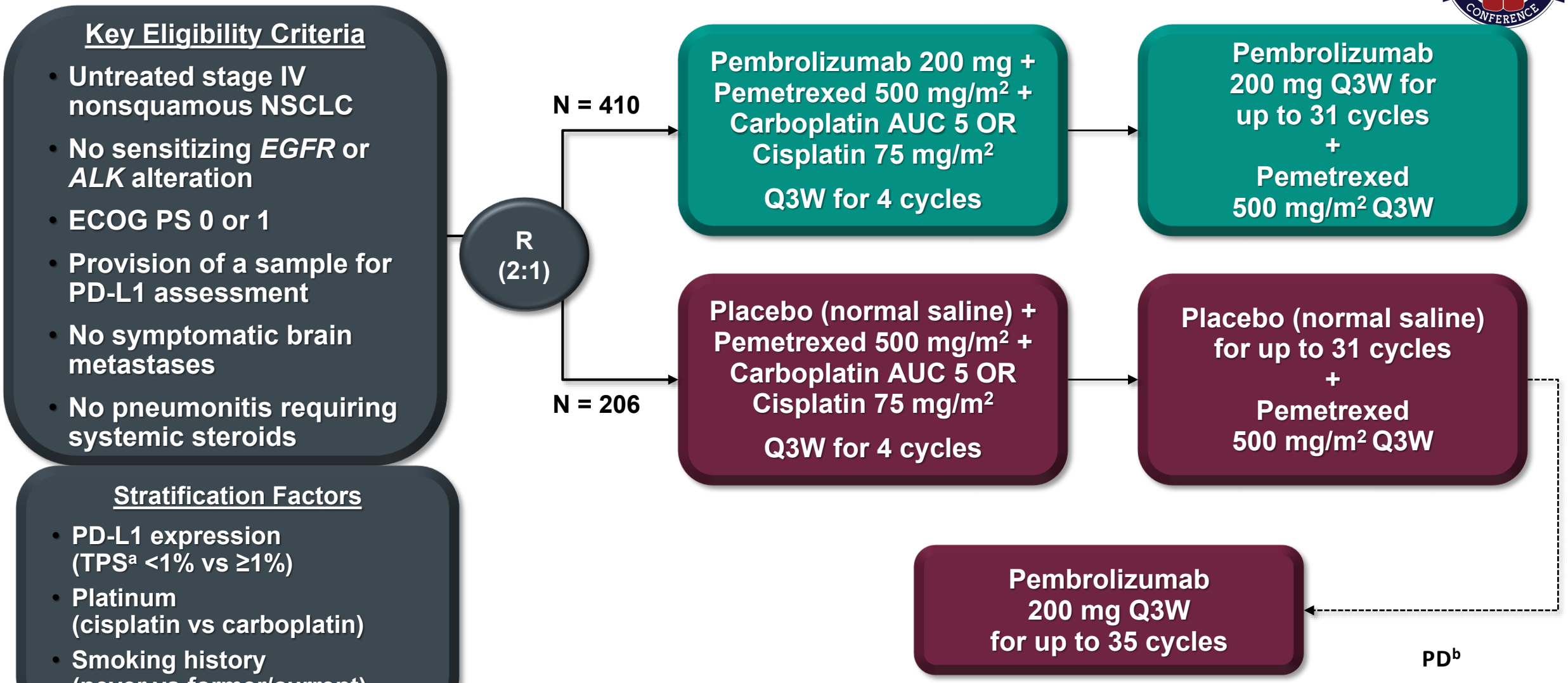
Preferred

- Pembrolizumab/carboplatin/paclitaxel (category 1)[36,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[36,e]
- Cemiplimab-rwlc/paclitaxel/(carboplatin or cisplatin) (category 1)[7,e]

Other Recommended

- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]
- Tremelimumab-actl/durvalumab/carboplatin/albumin-bound paclitaxel[8,e] (category 1)
- Tremelimumab-actl/durvalumab/(carboplatin or cisplatin)/gemcitabine[8,e] (category 1)

KEYNOTE 189 Study Design



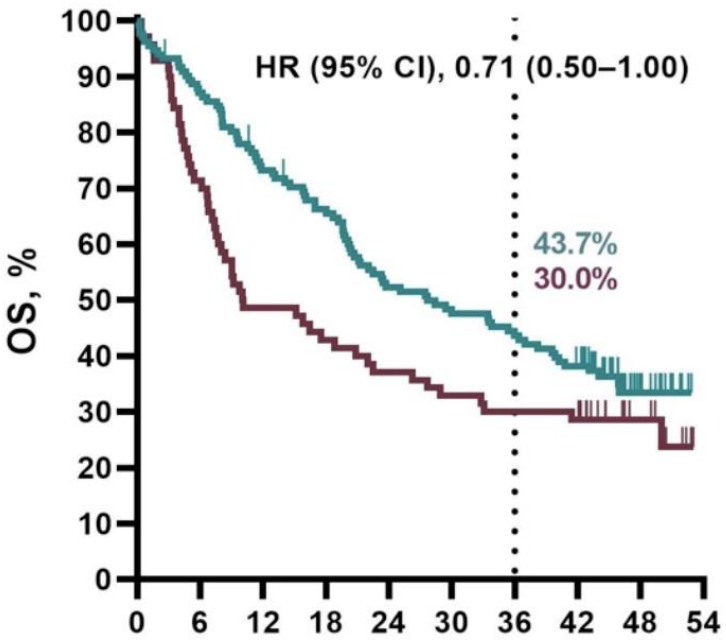
Gandhi et al. NEJM 2018; Gray et al. WCLC 2020

KEYNOTE 189: Pembrolizumab + chemo

3-year OS With Pembro + chemo versus chemo

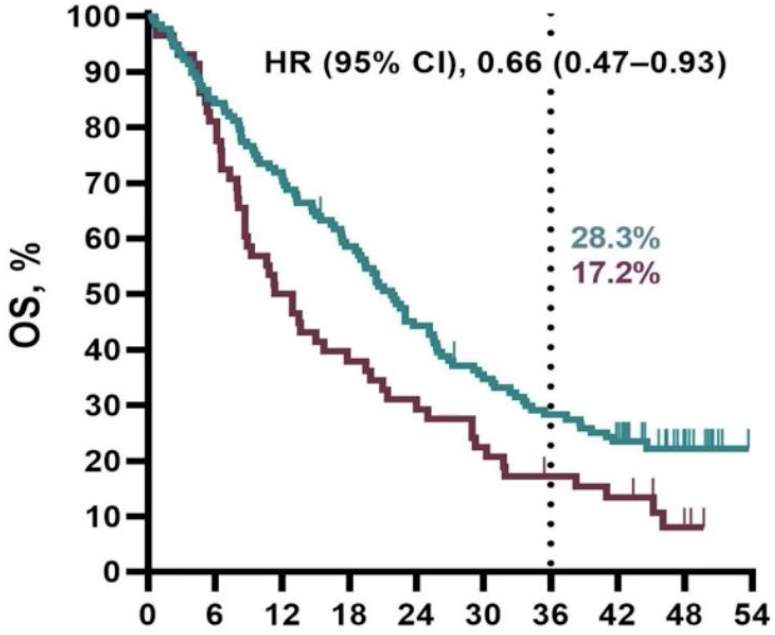
PD-L1 TPS ≥50%

	Events, %	Median, mo (95% CI)
Pembro + chemo	63.6	27.7 (20.4–38.2)
Placebo + chemo	72.9	10.1 (7.5–22.0)



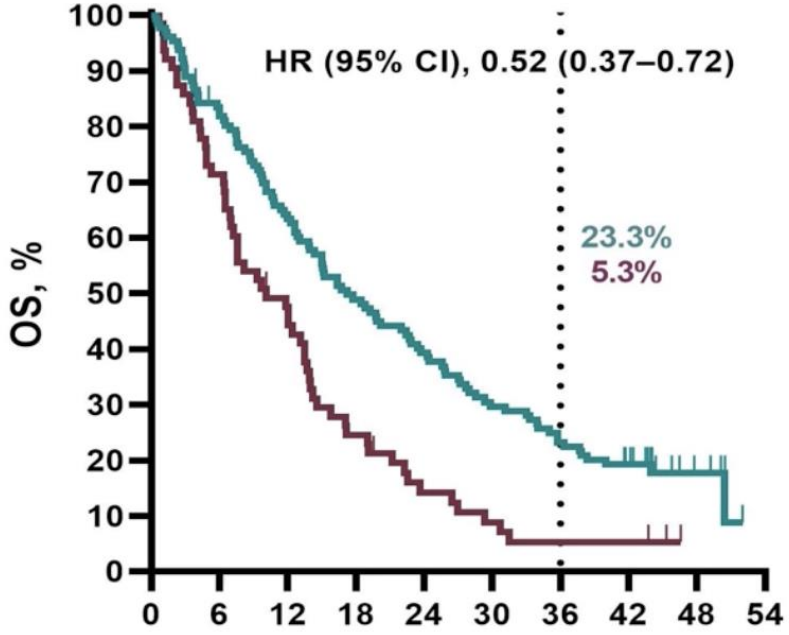
PD-L1 TPS 1–49%

	Events, %	Median, mo (95% CI)
Pembro + chemo	76.6	21.8 (17.7–25.6)
Placebo + chemo	89.7	12.1 (8.7–19.4)



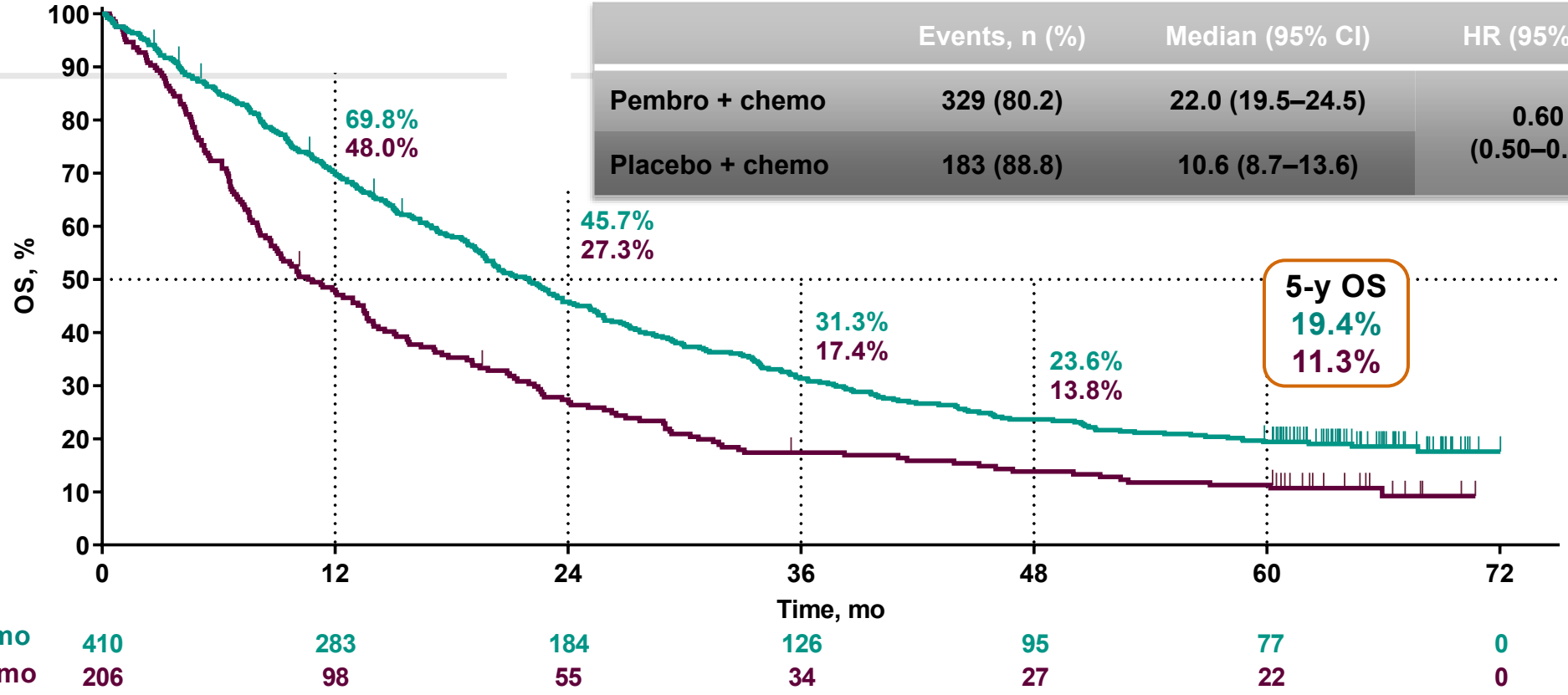
PD-L1 TPS <1%

	Events, %	Median, mo (95% CI)
Pembro + chemo	81.1	17.2 (13.8–22.8)
Placebo + chemo	92.1	10.2 (7.0–13.5)



Gray et al. WCLC 2020

KEYNOTE-189: 5-year OS



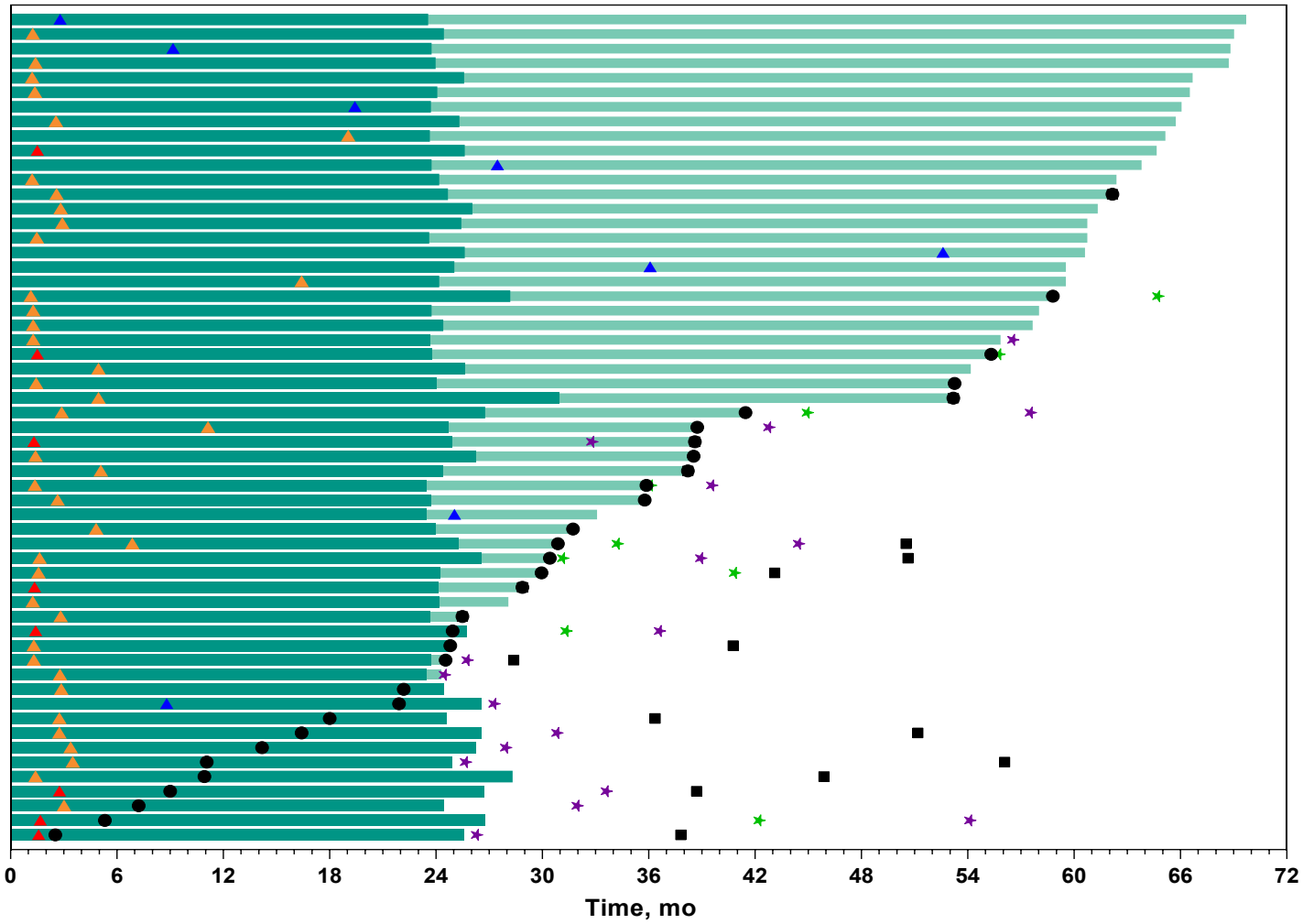
	Events, n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	329 (80.2)	22.0 (19.5–24.5)	0.60 (0.50–0.72)
Placebo + chemo	183 (88.8)	10.6 (8.7–13.6)	

No. at risk							
Pembro + chemo	410	283	184	126	95	77	0
Placebo + chemo	206	98	55	34	27	22	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 132)	Placebo + chemo (n = 70)	Pembro + chemo (n = 128)	Placebo + chemo (n = 58)	Pembro + chemo (n = 127)	Placebo + chemo (n = 63)
OS HR (95% CI)	0.68 (0.49–0.96)		0.65 (0.46–0.90)		0.55 (0.39–0.76)	
5-y OS rate,[a] %	29.6	21.4	19.8	7.7	9.6	5.3

Garassino et al. JCO 2023

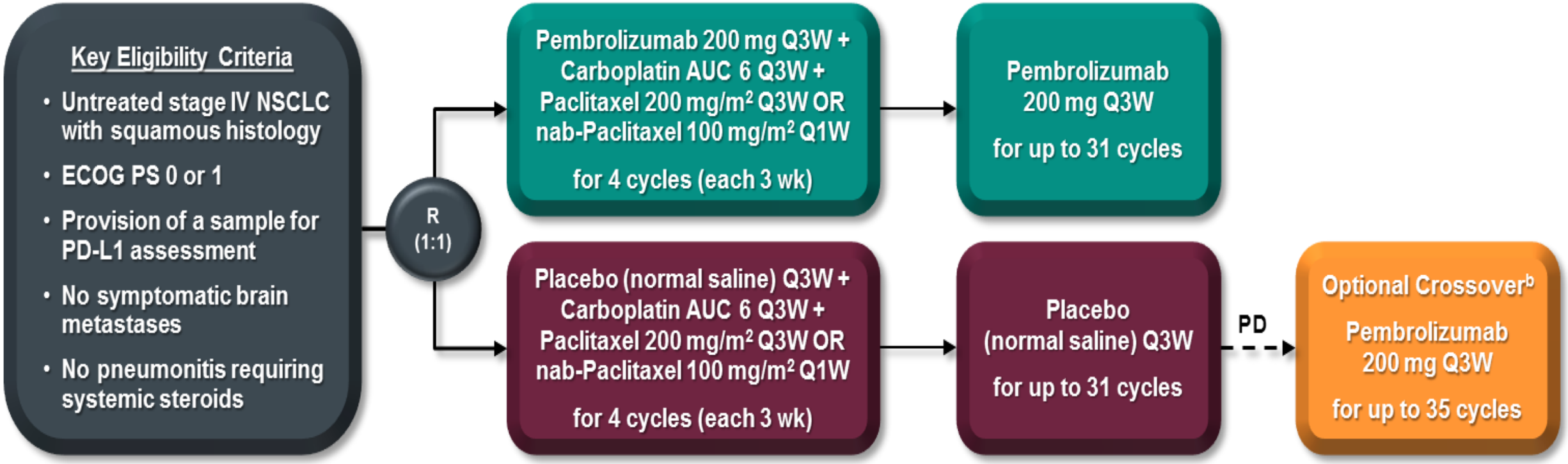
Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



	n = 57
ORR (95% CI),[a] %	86.0 (74.2–93.7)
Best overall response, n (%)	
CR	8 (14.0)
PR	41 (71.9)
Median DOR (range),[b] mo	57.7 (4.2 to 68.3+)
3-y OS rate after completing 35 cycles[c]	71.9%
Alive without PD or subsequent therapy, n (%)	23 (40.4)

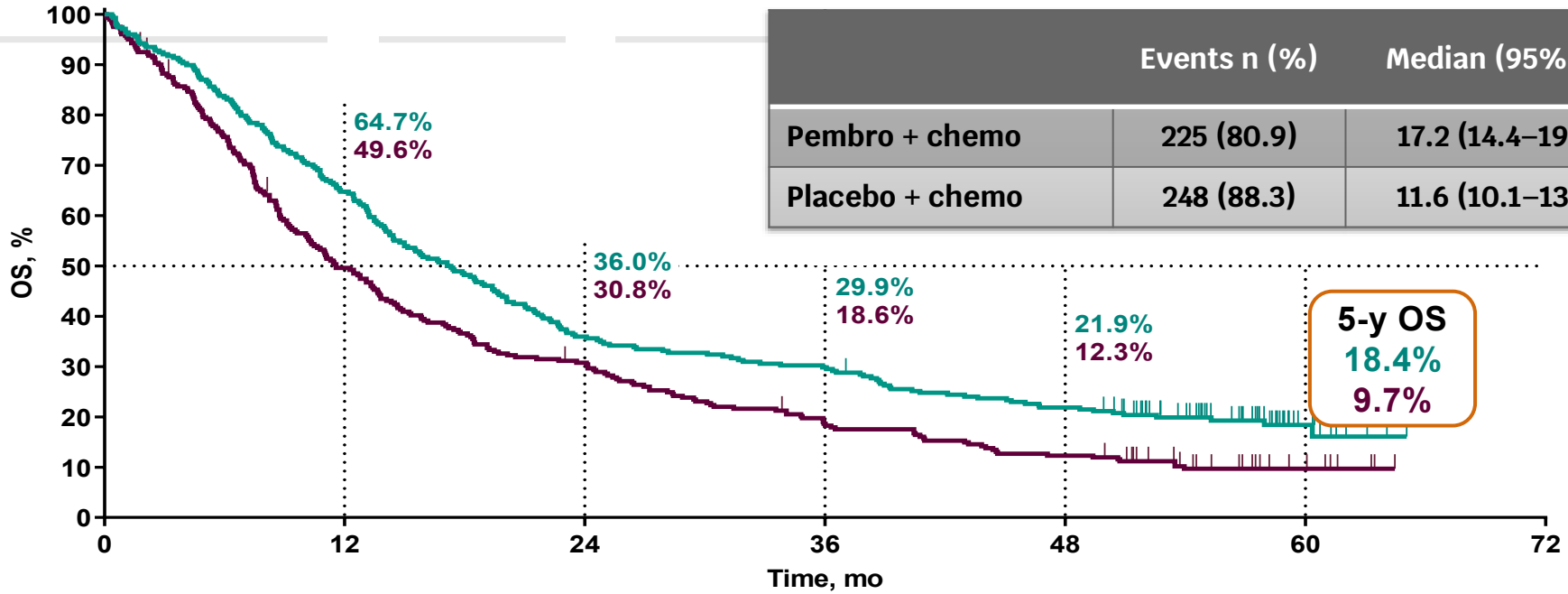
Garassino et al. JCO 2023

KEYNOTE-407 Study Design



Paz-Ares L et al. NEJM, 2018; Novello et al. JCO 2023

KEYNOTE-407: 5-year OS



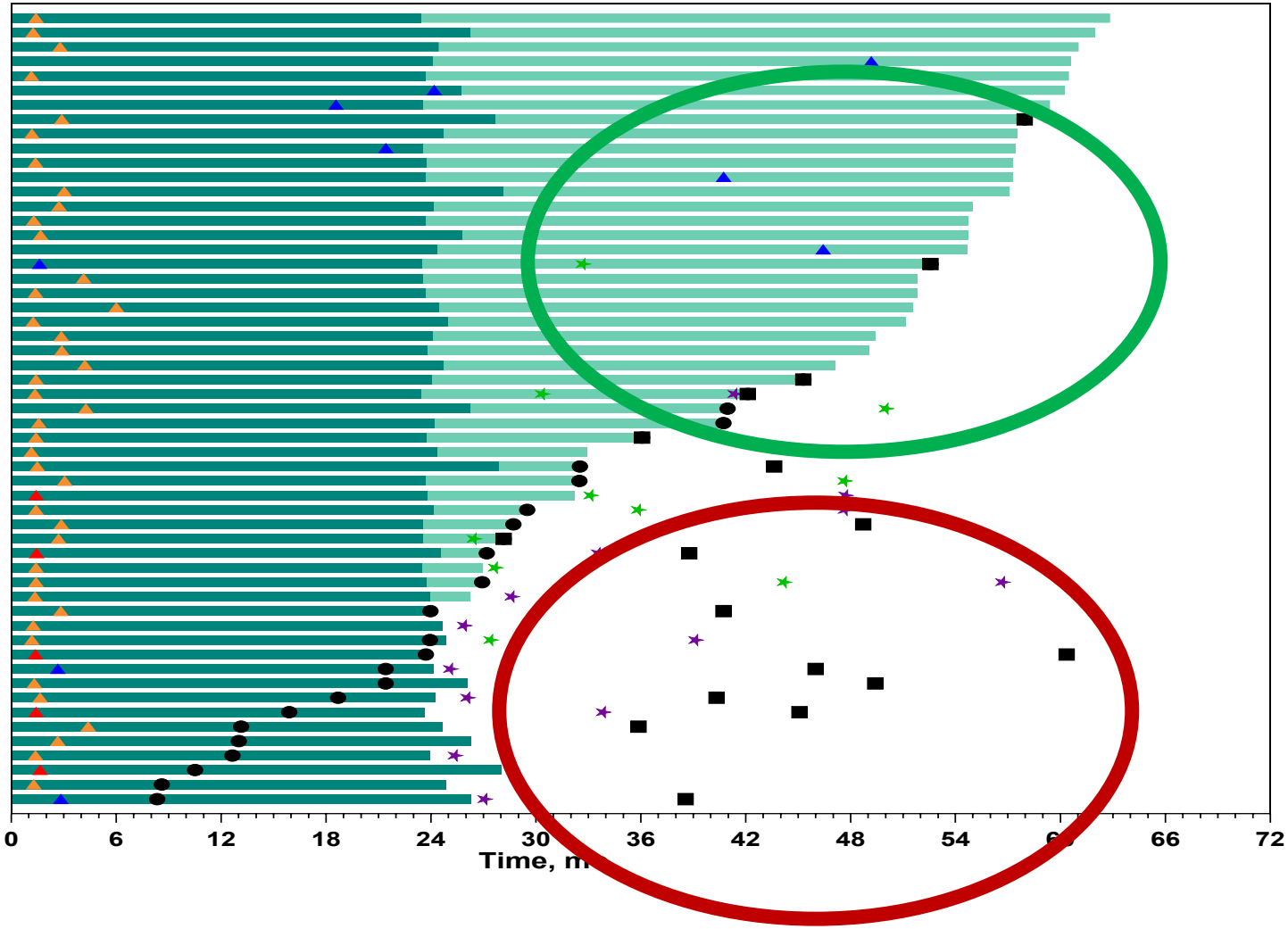
	Events n (%)	Median (95% CI)	HR (95% CI)
Pembro + chemo	225 (80.9)	17.2 (14.4–19.7)	0.71 (0.59–0.85)
Placebo + chemo	248 (88.3)	11.6 (10.1–13.7)	

No. at risk							
Pembro + chemo	278	180	100	83	60	10	0
Placebo + chemo	281	137	84	50	33	7	0

	PD-L1 TPS ≥50%		PD-L1 TPS 1%–49%		PD-L1 TPS <1%	
	Pembro + chemo (n = 73)	Placebo + chemo (n = 73)	Pembro + chemo (n = 103)	Placebo + chemo (n = 104)	Pembro + chemo (n = 95)	Placebo + chemo (n = 99)
OS HR (95% CI)	0.68 (0.47–0.97)		0.61 (0.45–0.83)		0.83 (0.61–1.13)	
5-y OS rate,[a] %	23.3	8.3	20.6	7.6	10.7	13.1

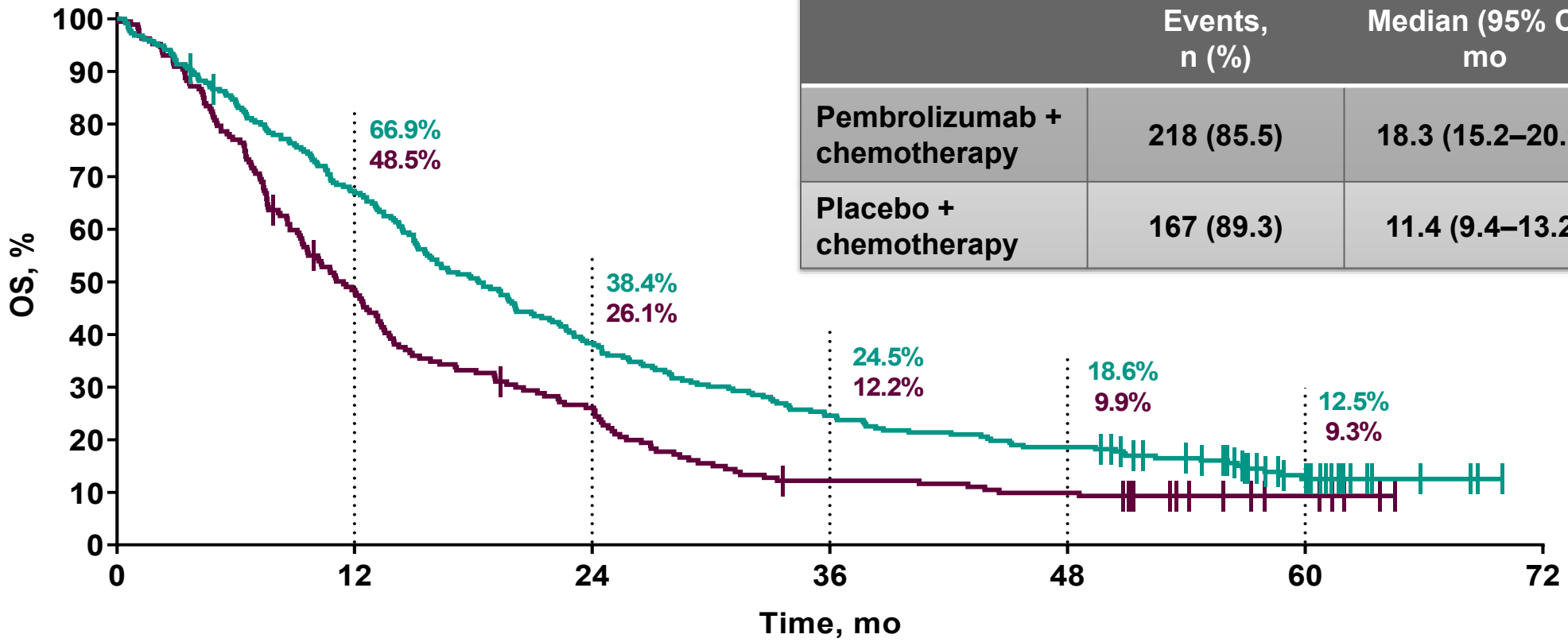
Novello et al. JCO 2023

KEYNOTE-407: Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab



	n = 55
ORR (95% CI),[a] %	90.9 (80.0–97.0)
Best overall response, n (%)	
CR	9 (16.4)
PR	41 (74.5)
Median DOR (range),[b] mo	NR (7.1 to 61.5+)
3-y OS rate after completing 35 cycles[c]	69.5%
Alive without PD or subsequent therapy, n (%)	24 (43.6)

Pooled analysis 5-Year OS of Pembrolizumab Plus Chemotherapy for Metastatic NSCLC With PD-L1 Tumor Proportion Score <1%

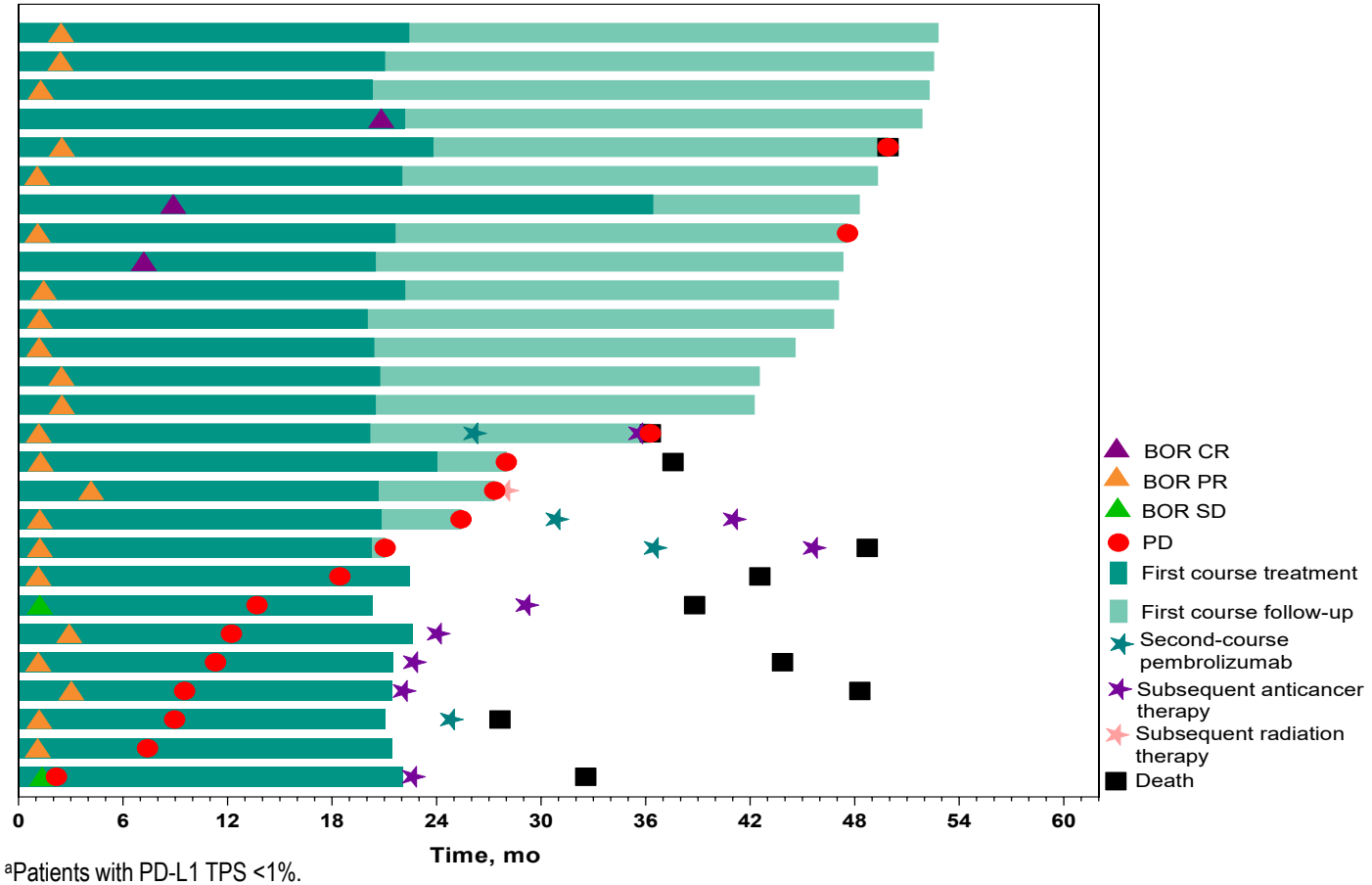


	Events, n (%)	Median (95% CI), mo	HR (95% CI)
Pembrolizumab + chemotherapy	218 (85.5)	18.3 (15.2–20.9)	0.64 (0.51–0.79)
Placebo + chemotherapy	167 (89.3)	11.4 (9.4–13.2)	

No. at risk							
	255	169	97	62	47	18	0
	187	89	47	21	17	6	0

Gadgeel et al. WCLC 2023

Pooled Analysis Outcomes in Patients Who Completed 35 Cycles of Pembrolizumab[a]



Outcome	Patients who completed 35 cycles[a] n = 27
ORR[b] (95% CI), %	92.6 (75.7–99.1)
Best overall response, n (%)	
Complete response	3 (11.1)
Partial response	22 (81.5)
Stable disease[c]	2 (7.4)
Median DOR (range), mo	55.1 (7.4 to 59.3+)
3-year OS rate after completing 35 cycles, %	56.7
Alive without subsequent therapy or PD, n (%)	12 (44.4)

[a]Patients with PD-L1 TPS <1%.
[b]Response assessed per RECIST v1.1 per blinded independent central review.
[c]Includes SD and non-CR/non-PD.
Data cutoff dates: KN189 Global, March 8, 2022; KN189 Japan Extension, February 7, 2023; KN407 Global, February 23, 2022; KN407 China Extension, February 10, 2023.

EMPOWER LUNG-3

Background: Cemiplimab (a high-affinity, fully human anti–PD-1) is approved as first-line monotherapy for advanced NSCLC with PD-L1 ≥50% (EMPOWER-Lung 1 Study[1])

Key eligibility criteria
- Treatment-naive advanced NSCLC (non-squamous and squamous histology; Stage IIIb/c†, IV)
- 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%
- Histology: non-squamous vs squamous

Endpoints
- Primary: OS
- Key secondary: PFS and ORR
- Additional secondary: DOR, BOR, safety, and PRO

R 2:1

Arm A
Cemiplimab 350 mg Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles§

Arm B
Placebo Q3W + investigator's choice platinum-doublet chemo Q3W for 4 cycles §

PD or 108 weeks

PD or 108 weeks

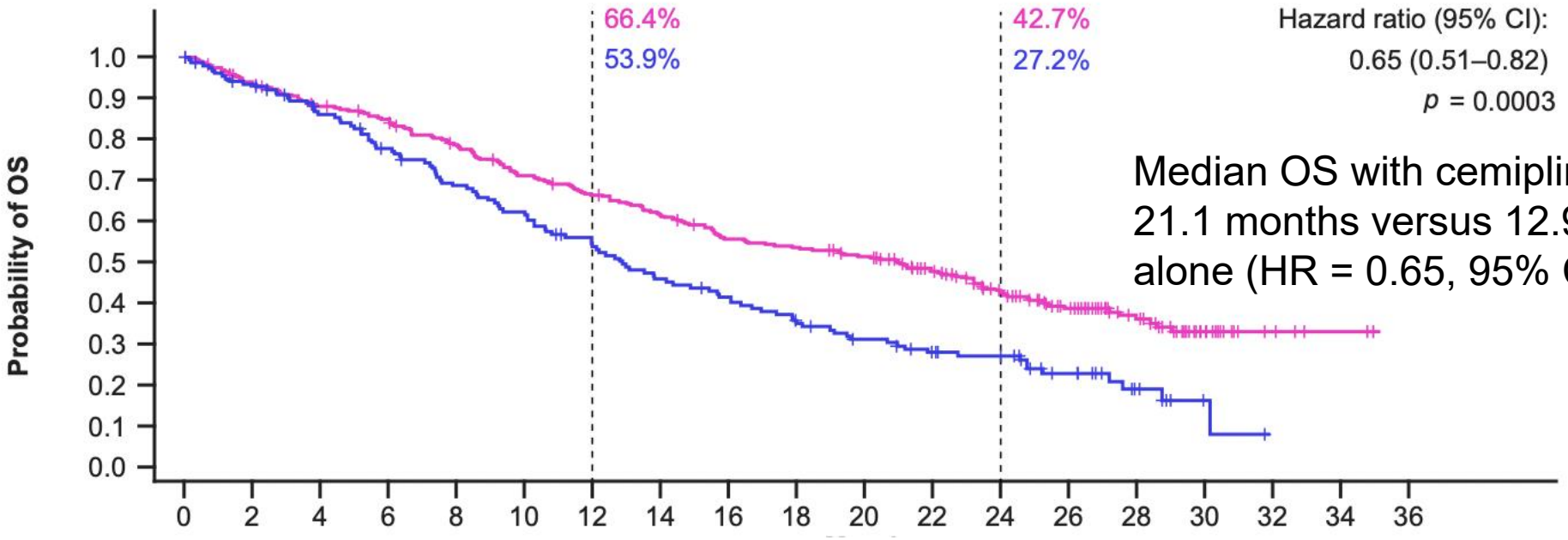
Follow-up

N=466

Two interim analyses were prespecified per protocol
Second interim analysis (14 June 2021) presented here

Makharadze T et al. ELCC 2023

EMPOWER LUNG-3: 2-year OS



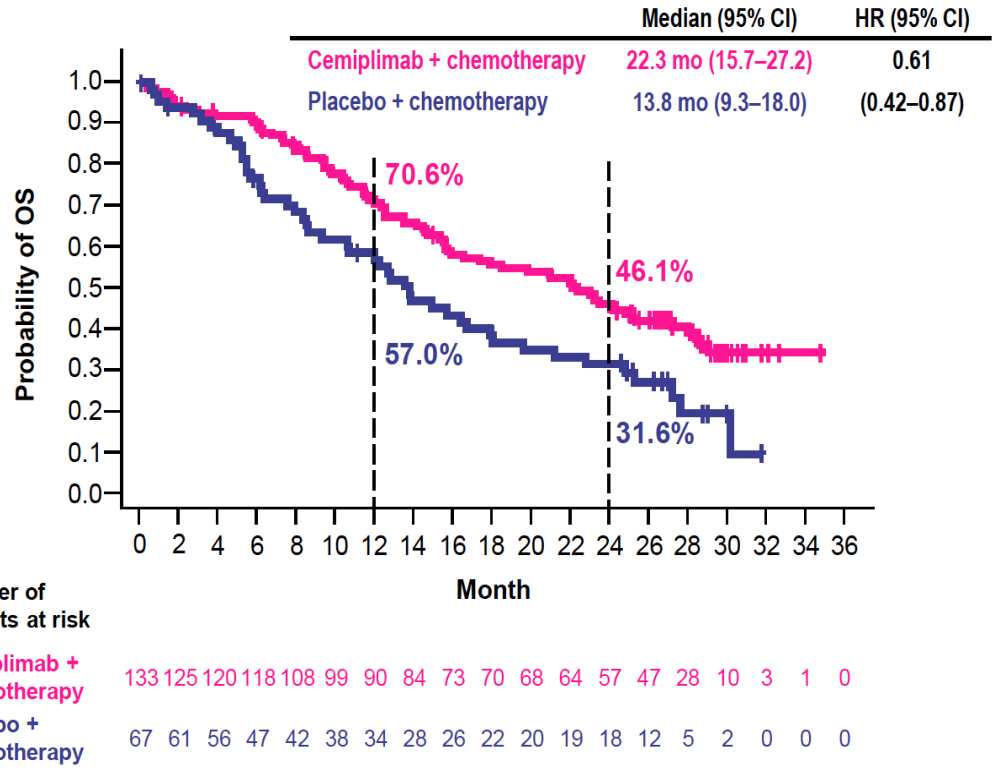
Median OS with cemiplimab plus chemotherapy was 21.1 months versus 12.9 months with chemotherapy alone (HR = 0.65, 95% CI: 0.51–0.82, p = 0.0003)

Median follow-up 28.4 mo

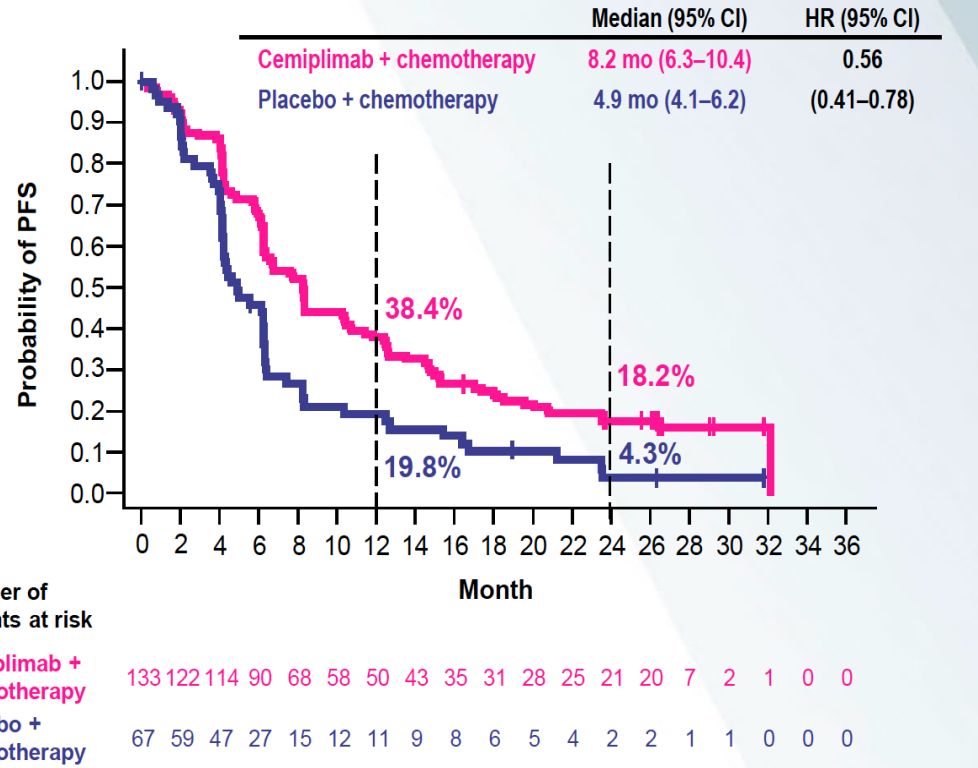
Makharadze et al. JTO 2023

EMPOWER LUNG-3: Outcomes in patients with squamous histology

Overall survival



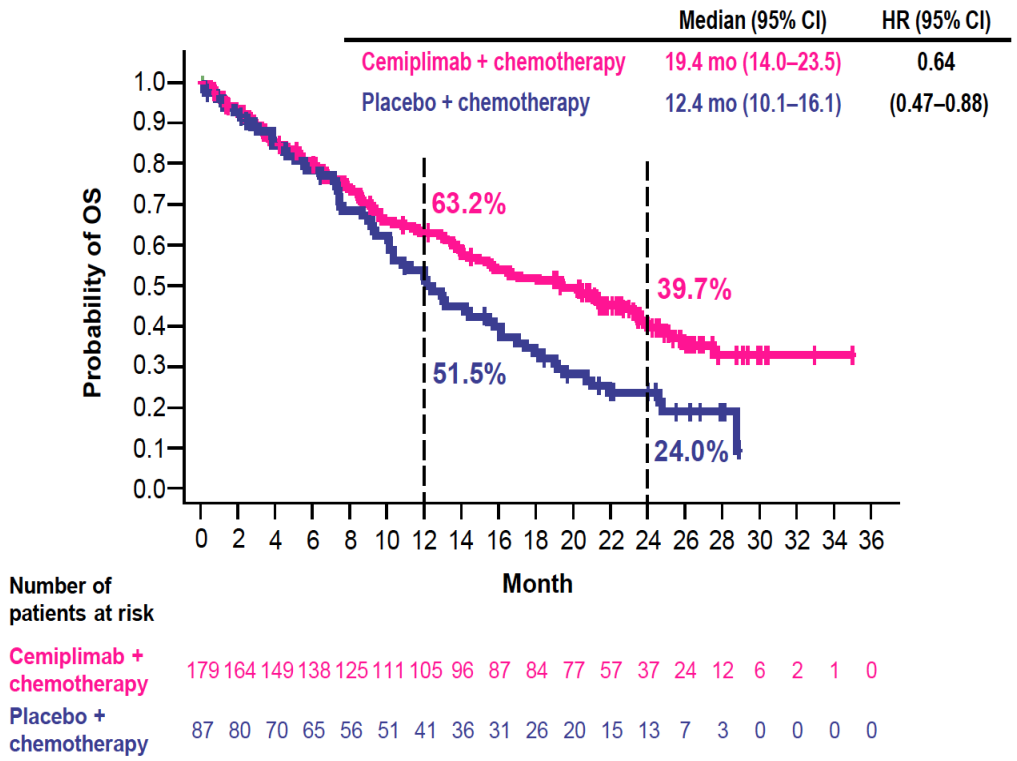
Progression-free survival



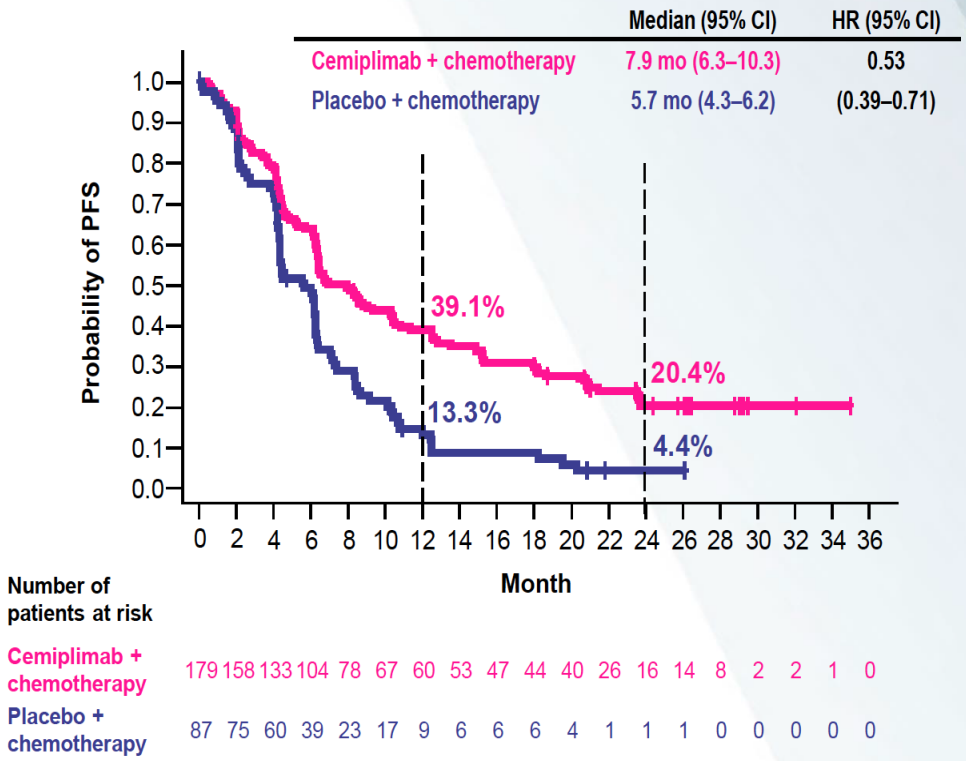
Makharadze T et al. ELCC 2023

EMPOWER LUNG-3: Outcomes in patients with nonsquamous histology

Overall survival

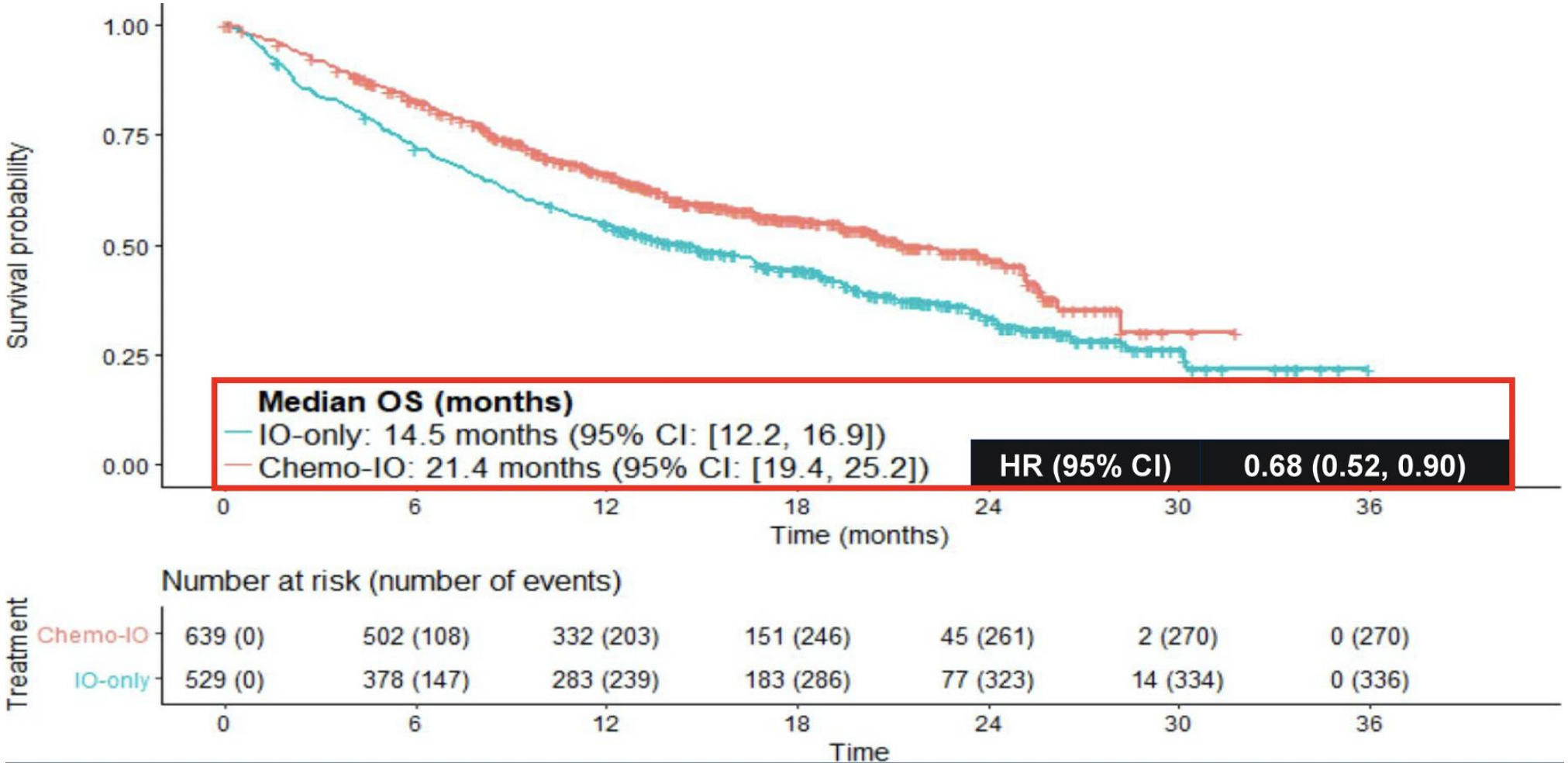


Progression-free survival



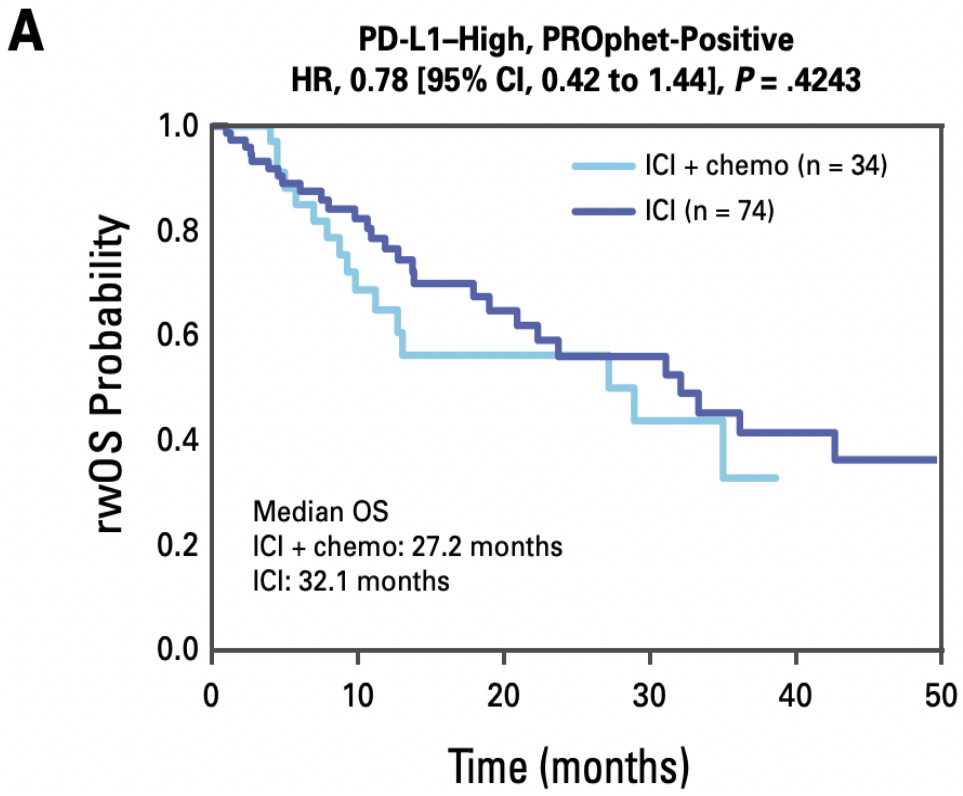
Makharadze T et al. ELCC 2023

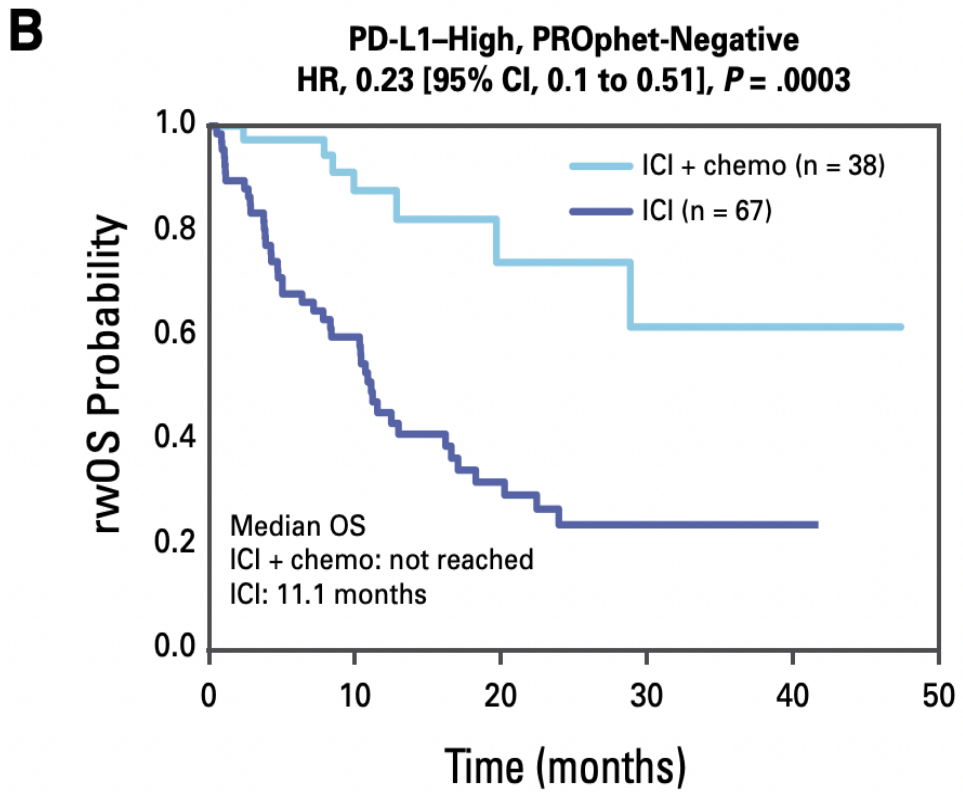
FDA Pooled Analysis in NSCLC with PD-L1 1-49%



Akinboro et al. JCO 2022

Clinical utility of PROphet in predicting differential OS outcomes within PD-L1–high expression level subgroups





Naidoo et al. AACR 2024; Christopoulos et. JCO Precis Oncol 2024

Conclusions

- PD-L1 expression is an established biomarker for assessing the likelihood of benefit from PD-1/L1 therapies
    - Tumor PD-L1 predicts ORR, PFS and OS

- PD-L1–high disease, single-agent PD-1 or PD-L1 is still the mainstay of treatment

- For PD-L1–low or –negative disease, chemo-IO combination is the preferred approach
- Composite biomarkers are of increasing interest in improving approaches to individualizing therapy.