PD1(PD-L1) Immunotherapy in Advanced NSCLC: Update from WCLC 2024

David R. Gandara, MD
University of California Davis Comprehensive Cancer Center

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Abstracts

- **EMPOWER Lung 1:** Cemiplimab monotherapy for 1st line advanced NSCLC patients with PD-L1 expression ≥50%: 5-year outcomes (Klickap et al)
- **HARMONi-2:** Phase III trial of Ivonescimab (AK112) vs Pembrolizumab as 1st Line Treatment for PD-L1+ advanced NSCLC (Caicun Zhou, et al)
- **Meta-Analysis:** Survival outcomes in single versus double immune checkpoint inhibitor in advanced non-small cell lung cancer (Ponvilawan, et al)
- **KEYLYNX-006:** Phase III trial of PARPi Olaparib maintenance therapy in advanced NSCLC (J. Gray et al)

Immunotherapy therapeutic landscape in advanced NSCLC: Phase III Trials in 1st Line Therapy

Study	Drug (vs CT)	PD-L1 selection	Control	Primary endpoint	HR primary endpoint	Result	Publication
KN-024	Pembro	≥50%	Platinum CT	PFS	0.50	Positive	Reck et al. *NEJM* 2016
CM026	Nivo	≥5%	Platinum CT	PFS	1.15	Negative	Carbone et al. *NEJM* 2017
KN-042	Pembro	≥1%	Platinum CT	OS	0.81 0.69 (50%)	Positive	Mok et al. *Lancet* 2019
IMpower110	Atezo	≥1%	Platinum CT	OS in TC3/IC3	0.59	Positive	Herbst et al. *NEJM* 2020
EMPOWER-Lung 1	Cemi	≥50%	Platinum CT	PFS, OS	0.54 (PFS) 0.57 (OS)	Positive	Sezer et al. *Lancet* 2021
MYSTIC	Durva or Durva/Tremi	≥25%	Platinum CT	PFS, OS	0.87 (PFS) durva 0.76 (OS) durva	Negative	Rizvi et al. *JAMA Oncol* 2020
CM227	Nivo or Nivo-Ipi	<1%/≥1% & TMB ≥10	Platinum CT	PFS, OS	0.58 (PFS) in TMB-H 0.62 (OS) in <1% 0.79 (OS) in ≥1%	Positive	Hellmann et al. *NEJM* 2018 Hellman et al. *NEJM* 2019
CM9LA	Nivo-Ipi-CT	≥1%	Platinum CT	OS	0.66	Positive	Paz Ares et al. *Lancet Oncol* 2021
KN-189 (NSQ)	Pembro-CT	≥1%	Platinum CT	PFS	0.52	Positive	Ghandi et al. *NEJM* 2018
KN-407 (SQ)	Pembro-CT	None	Platinum-Nab Pac	PFS, OS	0.56 (PFS) 0.64 (OS)	Positive	Paz Ares et al. *NEJM* 2018
IMpower150 (NSQ)	Atezo + Bev/Pac/Carbo	None	Bev/Pac/Carbo	PFS, OS	ACBP 0.71 (PFS) ACBP 0.78 (OS)	Positive	Socinski et al. *NEJM.* 2018
IMpower131 (SQ)	Atezo + nab Pac/Carbo	None	Pac/Carbo	PFS, OS	0.71 (PFS) 0.88 (OS)	Positive (PFS)	Jotte et al. *J Thorac Oncol* 2020
EMPOWER-Lung 3	Cemi-CT	None	Platinum CT	PFS, OS	0.56 (PFS) 0.71 (OS)	Positive	Gogishvili et al. Nat Med 2022
POSEIDON	Durva+Tremi-CT	None	Platinum CT	PFS, OS	0.77 (OS)	Positive	Johnson et al. JCO 2022

Parameters

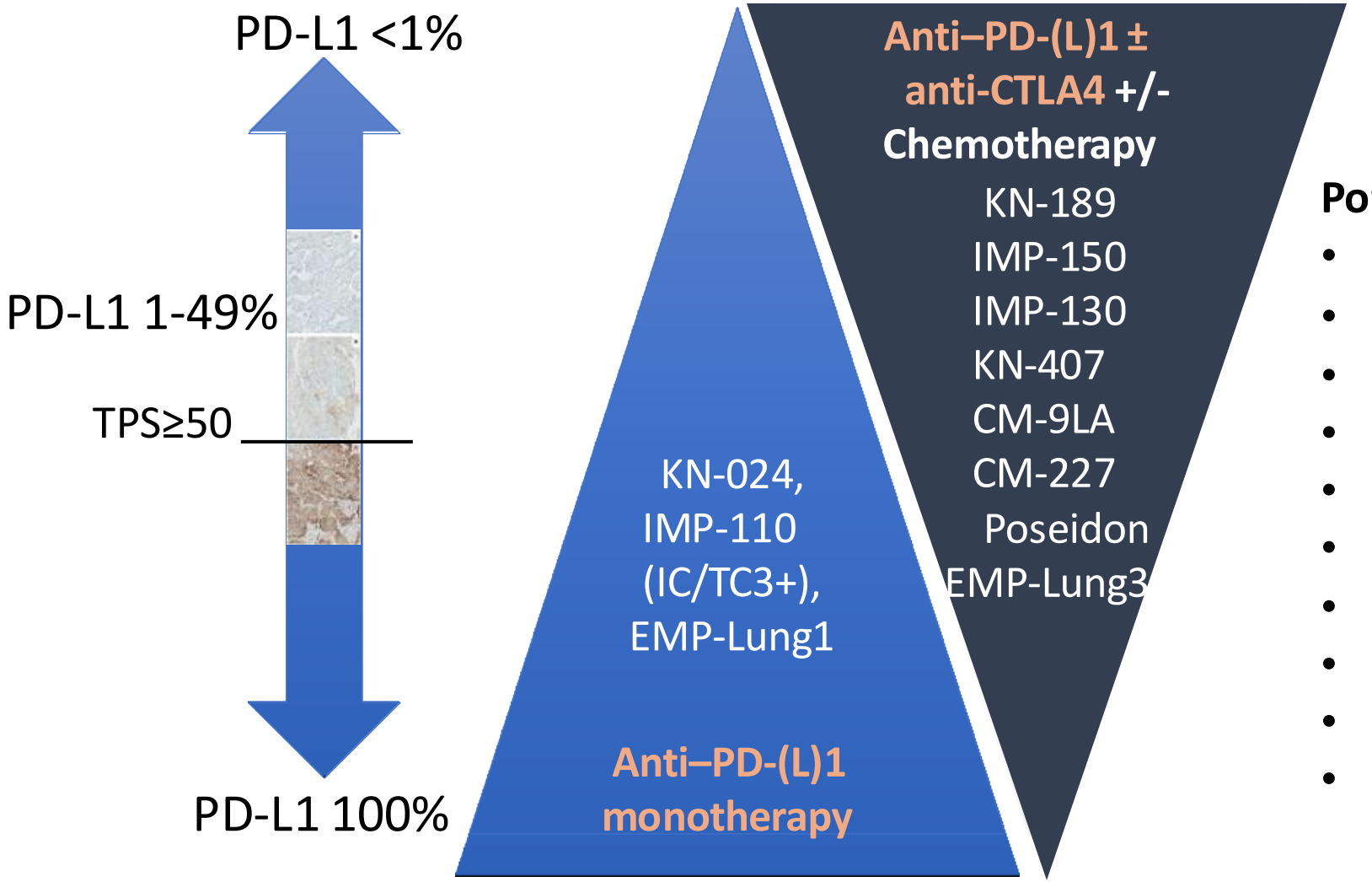
Test Regimen
ICI Monotherapy
ICI+CT
ICI+CT+Bev
ICI + CTLA-4

Biomarker
None
PD-L1
TMB

Histology
All
SQ
NSQ

Primary Endpoint
PFS
OS
Both

1st-line Immunotherapy Regimens in Advanced NSCLC based on PD-L1 score



Potential selection factors:

- Smoking status
- Disease burden
- Oncogenic drivers
- *STK11, KEAP1*
- *KRAS, TP53*
- TMB
- Histology—squamous/non
- CNS metastases
- Liver metastases
- Immune mediators

Garon EB, et al. *N Engl J Med*. 2015;372(21):2018-28. Reck M, et al. Presented at: ASCO;2021. Brahmer J, et al. ESMO;2020; Abstract LBA51. Gray JE, et al. WCLC;2020. Paz Arez L, et al. *J Thorac Oncol*. 2020;15(10):1657-1669. Herbst RS, et al. WCLC;2020. Reck M, et al. ASCO;2020.

EMPOWER-Lung 1: Cemiplimab vs Platinum Chemotherapy in 1st Line Therapy

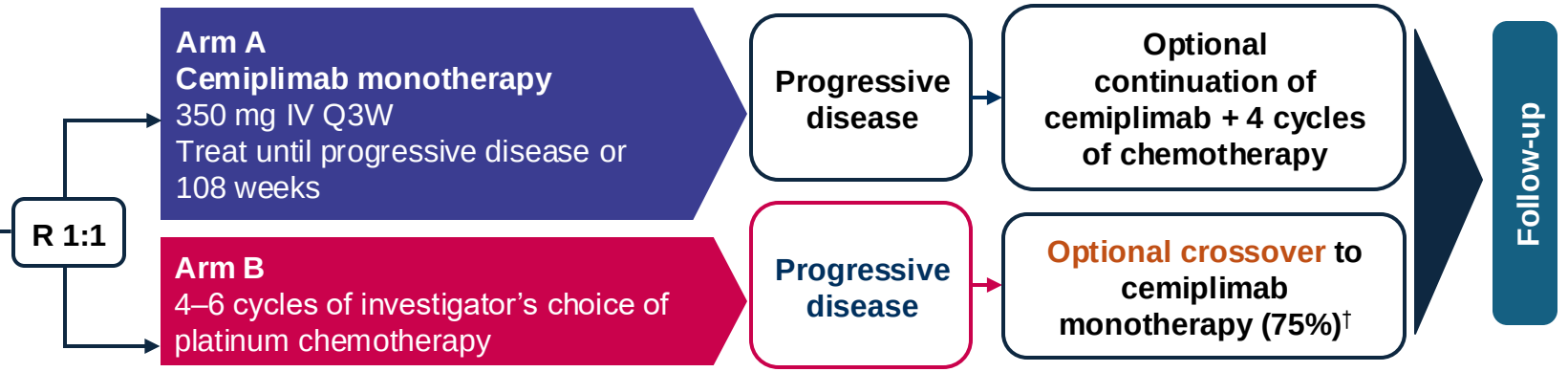
5 years

- Previous primary and 3-y update of EMPOWER-Lung 1 trial (NCT03088540) demonstrated survival benefits in patients with advanced NSCLC.[1-2]
- Here we report the protocol pre-specified final OS analysis with 5-year follow-up.

Key eligibility criteria
- Treatment-naive advanced NSCLC
- **PD-L1 ≥50%**
- No *EGFR*, *ALK,* or *ROS1* mutations
- ECOG performance status 0 or 1
- Treated, clinically stable CNS metastases and controlled hepatitis B or C or HIV were allowed

Stratification factors
- Histology (squamous vs non-squamous)
- Region (Europe, Asia, or ROW)

Endpoints
- Primary: OS and PFS



ITT (N=712)

PD-L1 ≥50% population (N=565)
PD-L1 testing by 22C3 assay performed per instructions for use

Protocol pre-specified final OS analysis (476/712 events)
Data cutoff at January 16, 2024
Median time from randomization to data cutoff: 59.6 months (range: 46.5–78.9)

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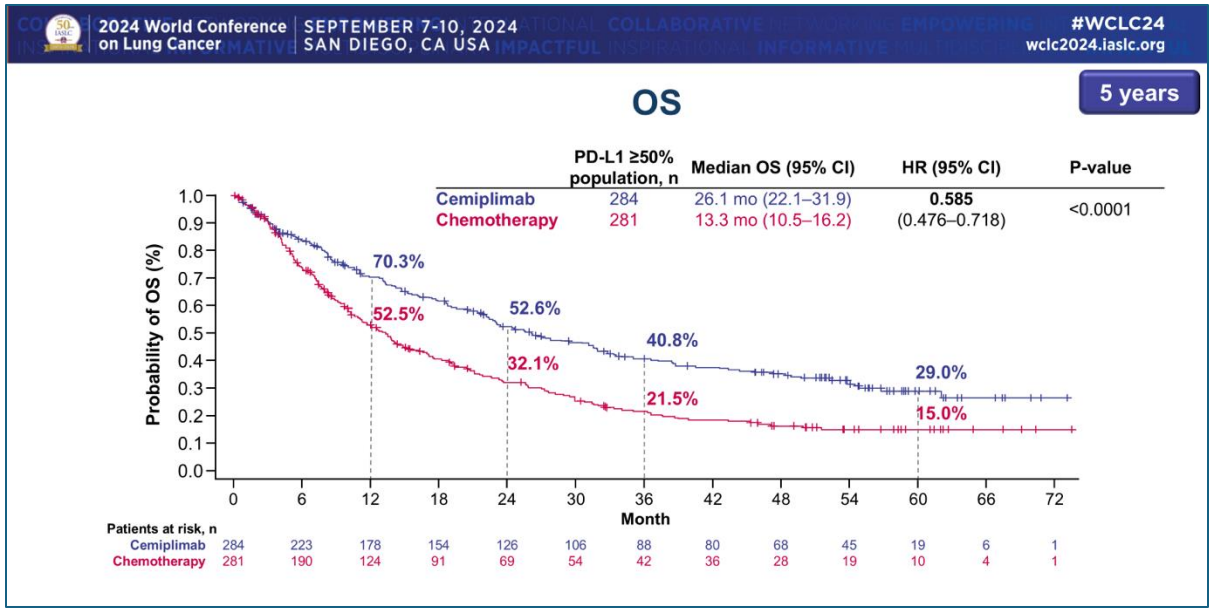
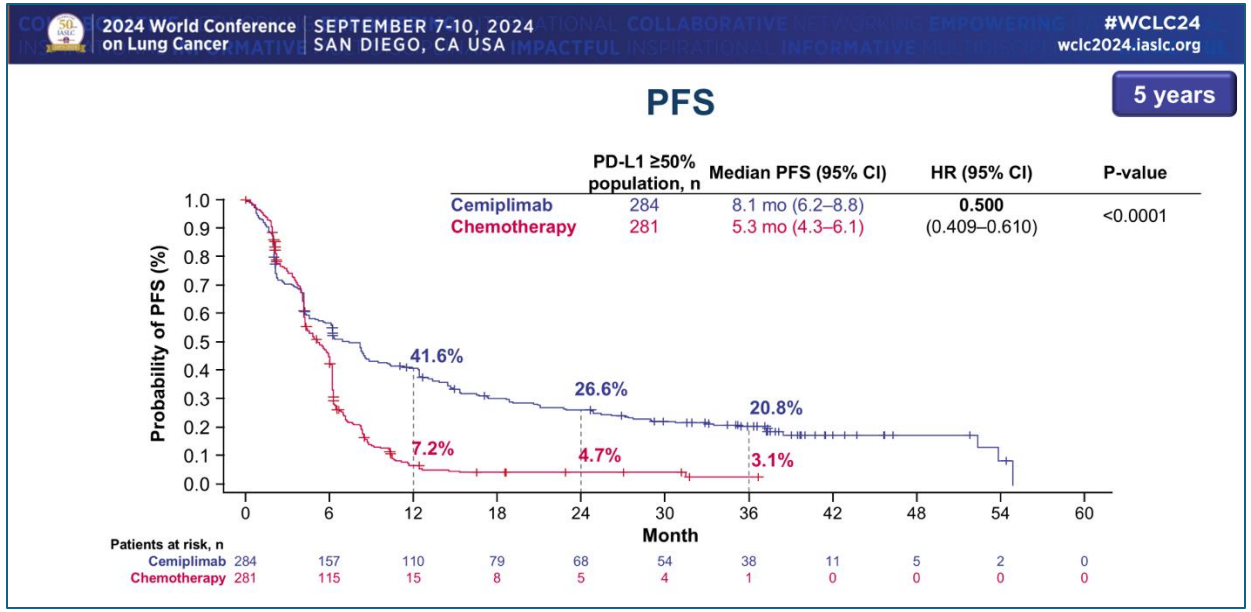
ALK, anaplastic lymphoma kinase; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HIV, human immunodeficiency virus; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomized; ROS1, c-ros oncogene 1; ROW, rest of the world.

1. Sezer A et al. *Lancet*. 2021;397:592–604 2. Ozguroglo M et al. *Lancet Oncol*. 2023;24: 989–1001.

EMPOWER-Lung 1: Cemiplimab vs Platinum Chemotherapy





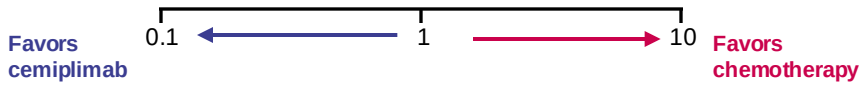
Effects of drug cross-over evident in the OS data of the Chemotherapy arm
(Cross-over from Chemotherapy to Cemiplimab in 75%)

EMPOWER-Lung 1: Cemiplimab vs Platinum Chemotherapy in 1st line therapy of adv NSCLC

5 years

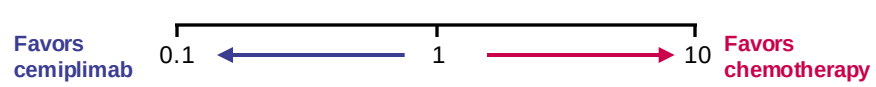
OS subgroup analysis

	Cemiplimab (events/total)	Chemotherapy (events/total)	HR (95% CI)
All patients	173/284	202/281	0.585 (0.476–0.718)
Age group, years			
<65	90/157	98/148	0.626 (0.468–0.836)
≥65	83/127	104/133	0.545 (0.407–0.731)
Sex			
Male	152/249	174/231	0.521 (0.417–0.650)
Female	21/35	28/50	0.918 (0.520–1.620)
Race			
White	152/244	173/241	0.612 (0.490–0.763)
Non-white	21/40	29/40	0.431 (0.242–0.767)
ECOG			
0	43/77	43/76	0.809 (0.529–1.236)
1	130/207	159/205	0.521 (0.411–0.660)
Histology			
Squamous	80/123	95/122	0.509 (0.376–0.689)
Non-squamous	93/161	107/159	0.664 (0.502–0.878)
Brain metastasis			
Yes	15/34	28/35	0.402 (0.209–0.772)
No	158/250	174/246	0.602 (0.483–0.750)
Cancer stage			
Locally advanced	27/45	28/42	0.683 (0.398–1.173)
Metastatic	146/239	174/239	0.564 (0.451–0.705)



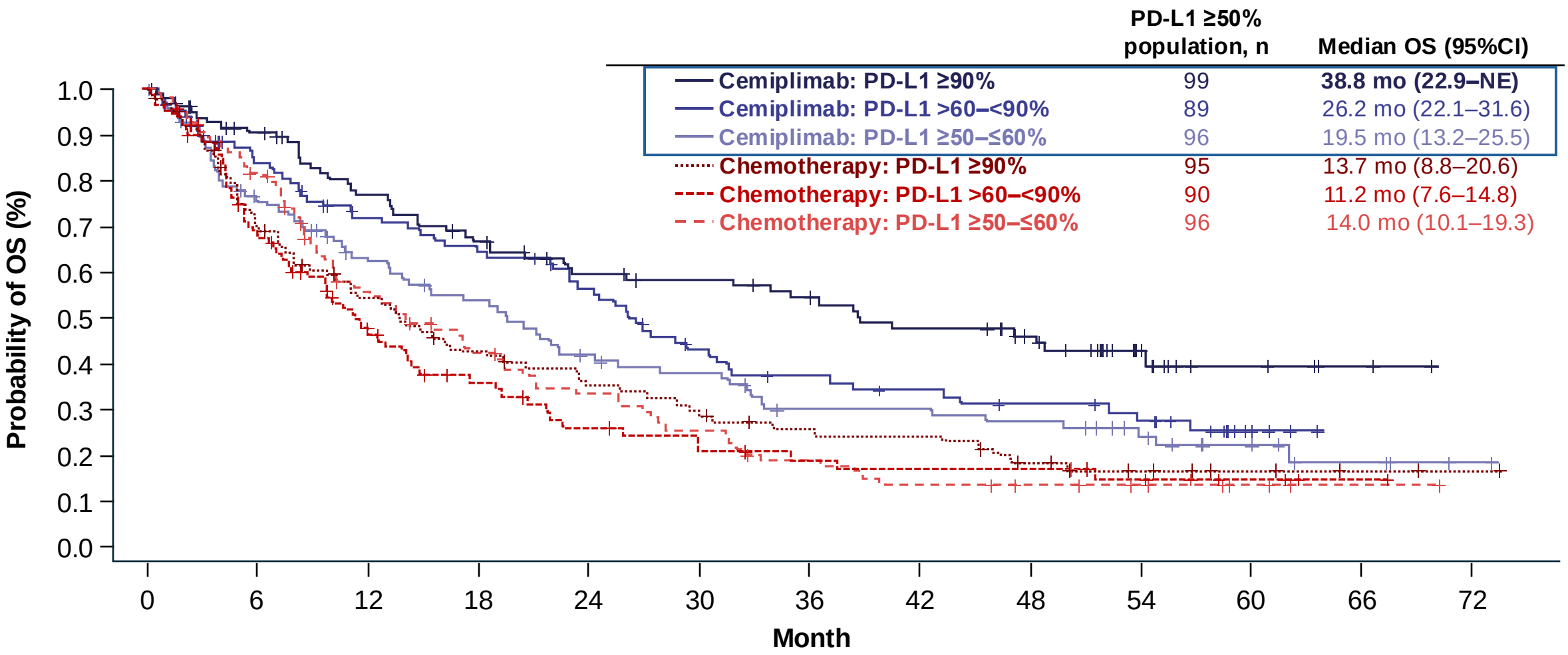
PFS subgroup analysis

	Cemiplimab (events/total)	Chemotherapy (events/total)	HR (95% CI)
	221/284	236/281	0.500 (0.409–0.610)
	119/157	123/148	0.488 (0.370–0.643)
	102/127	113/133	0.524 (0.393–0.700)
	191/249	203/231	0.447 (0.359–0.556)
	30/35	33/50	0.821 (0.483–1.397)
	193/244	203/241	0.504 (0.407–0.624)
	28/40	33/40	0.476 (0.277–0.818)
	63/77	58/76	0.633 (0.432–0.927)
	158/207	178/205	0.460 (0.364–0.582)
	100/123	104/122	0.439 (0.323–0.596)
	121/161	132/159	0.549 (0.422–0.715)
	23/34	32/35	0.339 (0.182–0.631)
	198/250	204/246	0.533 (0.431–0.658)
	36/45	33/42	0.564 (0.336–0.946)
	185/239	203/239	0.493 (0.397–0.612)



EMPOWER Lung 1: Cemiplimab OS benefit increases with higher PD-L1 expression

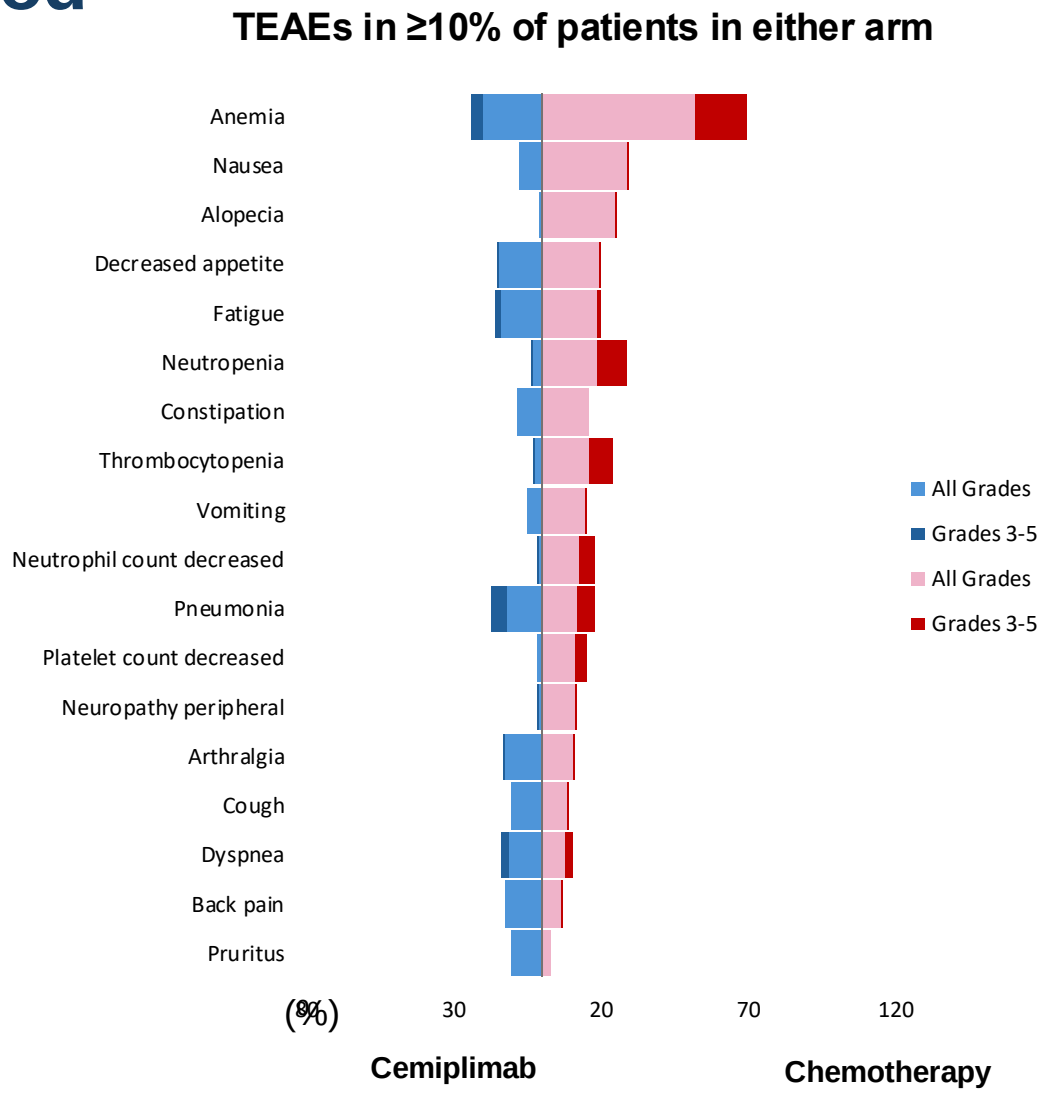
5 years



5 years

Cemiplimab safety profile remains good at 5 years

	Cemiplimab (n=356)		Chemotherapy (n=343)	
Duration of exposure, weeks, median (range)	36.0 (0.3–136.0)		18.0 (0.6–141.1)	
TEAEs, regardless of attribution, n (%)	Any grade	Grade 3–5	Any grade	Grade 3–5
Overall	330 (92.7)	163 (45.8)	329 (95.9)	177 (51.6)
Led to discontinuation	32 (9.0)	20 (5.6)	17 (5.0)	10 (2.9)
Led to death	36 (10.1)	36 (10.1)	33 (9.6)	33 (9.6)
Treatment-related TEAEs, n (%)				
Overall	224 (62.9)	65 (18.3)	310 (90.4)	137 (39.9)
Led to discontinuation	26 (7.3)	15 (4.2)	15 (4.4)	10 (2.9)
Led to death	10 (2.8)	10 (2.8)	7 (2.0)	7 (2.0)
Sponsor-identified immune-related TEAEs, n (%)				
Overall	83 (23.3)	17 (4.8)	12 (3.5)	2 (0.6)
Led to discontinuation	16 (4.5)	9 (2.5)	0	0
Led to death†	2 (0.6)	2 (0.6)	0	0



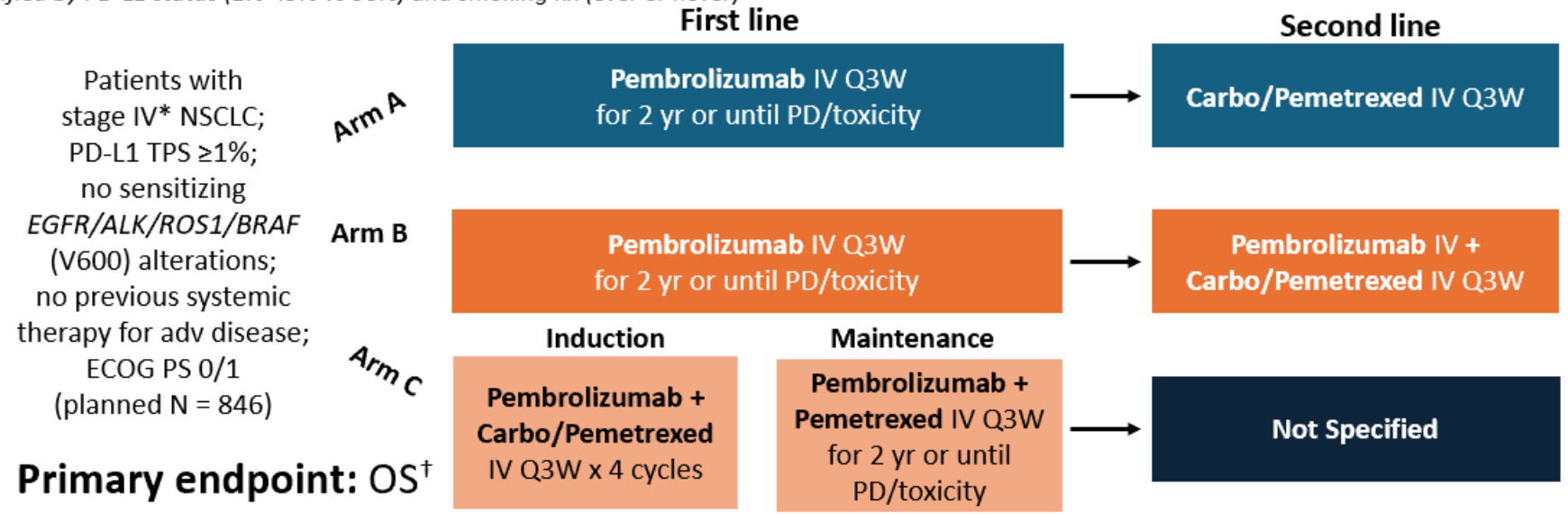
†Cause of death due to nephritis and myocarditis.
Adverse events are reported for all patients who received either intervention (safety analysis set). All events are listed as shown in the study safety report; hence, some events might reflect the same condition.
TEAEs, treatment-emergent adverse events.

What is optimal sequencing of ICI and Chemotherapy in Advanced NSCLC?

EA5163/S1709 INSIGNA

- Randomized phase III study

Stratified by PD-L1 status (1%-49% vs 50%) and smoking hx (ever or never)



Treatment beyond progression

- **Primary endpoint:** OS†
- **Secondary endpoints:** PFS,† ORR,† outcomes by PD-L1 TPS ≥50%, safety

NCT03793179.

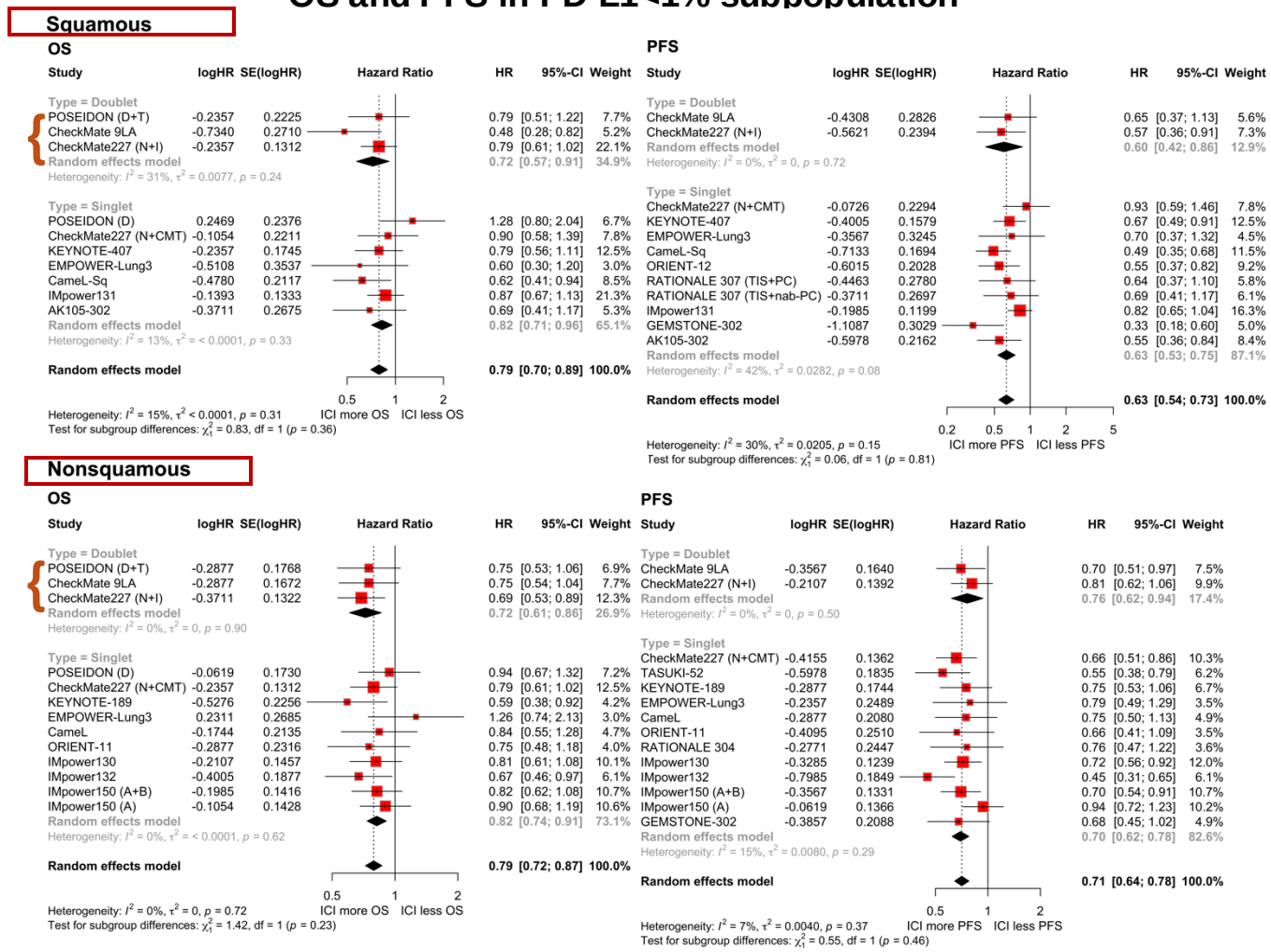
*Stage IIIB/C allowed if patient is not a candidate for cCRT. †Arm A vs arm C and arm B vs arm C.

Survival in Single vs Double immune checkpoint inhibitor (ICI) Regimens in advanced NSCLC: a Meta-Analysis

- **Question addressed:** When to use Double ICI: **Nivo-Ipi or Durva-Treme**
- Key subgroups of interest: **PD-L1<1%, STK11 & KEAP 1-mutated**
- 21 trials were included in the meta-analysis.

- **No** significant differences in OS or PFS benefits were noted in patients with PD-L<1% between **Single vs Double ICI** for both histological subtypes (Figure).
- **No** differential survival benefits were found in the positive PD-L1 subgroup as well

OS and PFS in PD-L1<1% subpopulation

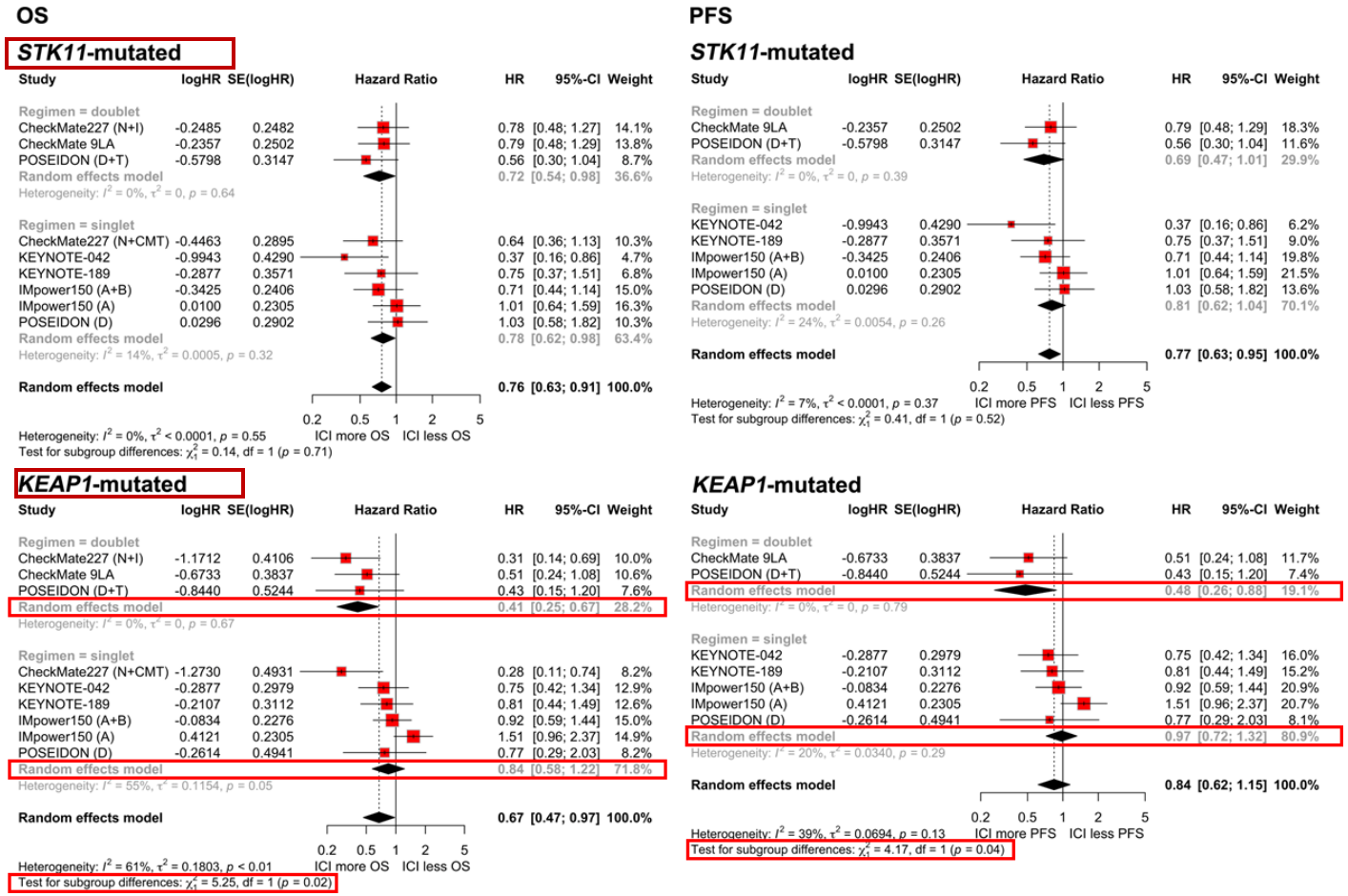


OS and PFS benefit for Double ICI in *KEAP1*-mutated, but not *KRAS*- or *STK11*-mutated subgroups

- Patients with ***KEAP1* mutation** had **improved** OS and PFS with Double ICI (HR 0.41; 95%CI 0.25-0.67 and PFS (0.48; 95%CI 0.26-0.88) but not single ICI.
- OS and PFS benefits did **not** differ based on any *KRAS*, *KRAS* G12C, or *STK11* mutations.

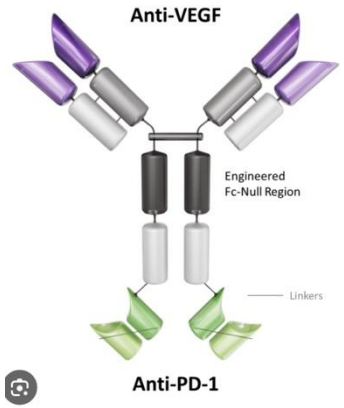
Conclusions:

- Consider Double ICI Regimens for patients with *KEAP1*-mutated NSCLC
- Clinical trials warranted



HARMONi-2 (Phase 3), primary analysis: Ivonescimab (AK112) vs Pembrolizumab as 1L treatment for PD-L1 ≥1% advanced NSCLC

Ivonescimab:
PD-1/VEGF-A targeted bispecific monoclonal antibody



HARMONi-2 (AK112-303) Study Design

A randomized, double-blind, phase 3 study[a]

Patient Population
- Stage IIIB-IV aNSCLC
- No prior systemic therapy
- No *EGFR* mutations or *ALK* rearrangements
- ECOG PS 0 or 1
- PD-L1 TPS ≥1%

R 1:1

N=398

Ivonescimab
20 mg/kg Q3W (N=198)

Pembrolizumab
200 mg Q3W (N=200)

Treatment until no clinical benefit, unacceptable toxicity or up to 24 months

Stratification
- Clinical stage (IIIB/C vs. IV)
- Histology (SQ vs. non-SQ)
- PD-L1 TPS (≥50% vs. 1-49%)

Chinese diagnostic antibody (E1L3N) for PD-L1 expression.

Endpoints

Primary: PFS by blind IRRC per RECIST v1.1
Secondary: OS, PFS assessed by INVs, ORR, DoR, TTR and safety
Exploratory: QoL

Baseline Characteristics

Characteristics, n (%)		Ivonescimab (n = 198)	Pembrolizumab (n = 200)	Total (n = 398)
Age (years)	<65	97 (49.0)	85 (42.5)	182 (45.7)
	≥65	101 (51.0)	115 (57.5)	216 (54.3)
Sex	Male	164 (82.8)	169 (84.5)	333 (83.7)
	Female	34 (17.2)	31 (15.5)	65 (16.3)
ECOG PS	0	25 (12.6)	26 (13.0)	51 (12.8)
	1	173 (87.4)	174 (87.0)	347 (87.2)
Smoker	Never	39 (19.7)	38 (19.0)	77 (19.3)
	Current	39 (19.7)	42 (21.0)	81 (20.4)
	Former	120 (60.6)	120 (60.0)	240 (60.3)
Clinical stage	IIIB/C	14 (7.1)	17 (8.5)	31 (7.8)
	IV	184 (92.9)	183 (91.5)	367 (92.2)
Pathology	SQ	90 (45.5)	91 (45.5)	181 (45.5)
	Non-SQ	108 (54.5)	109 (54.5)	217 (54.5)
PD-L1 TPS	≥50%	83 (41.9)	85 (42.5)	168 (42.2)
	1-49%	115 (58.1)	115 (57.5)	230 (57.8)
Liver metastases	Yes	25 (12.6)	28 (14.0)	53 (13.3)
	No	173 (87.4)	172 (86.0)	345 (86.7)
Brain metastases	Yes	33 (16.7)	39 (19.5)	72 (18.1)
	No	165 (83.3)	161 (80.5)	326 (81.9)

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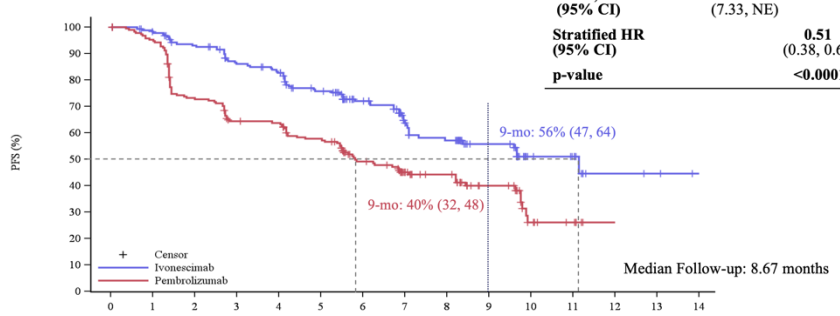
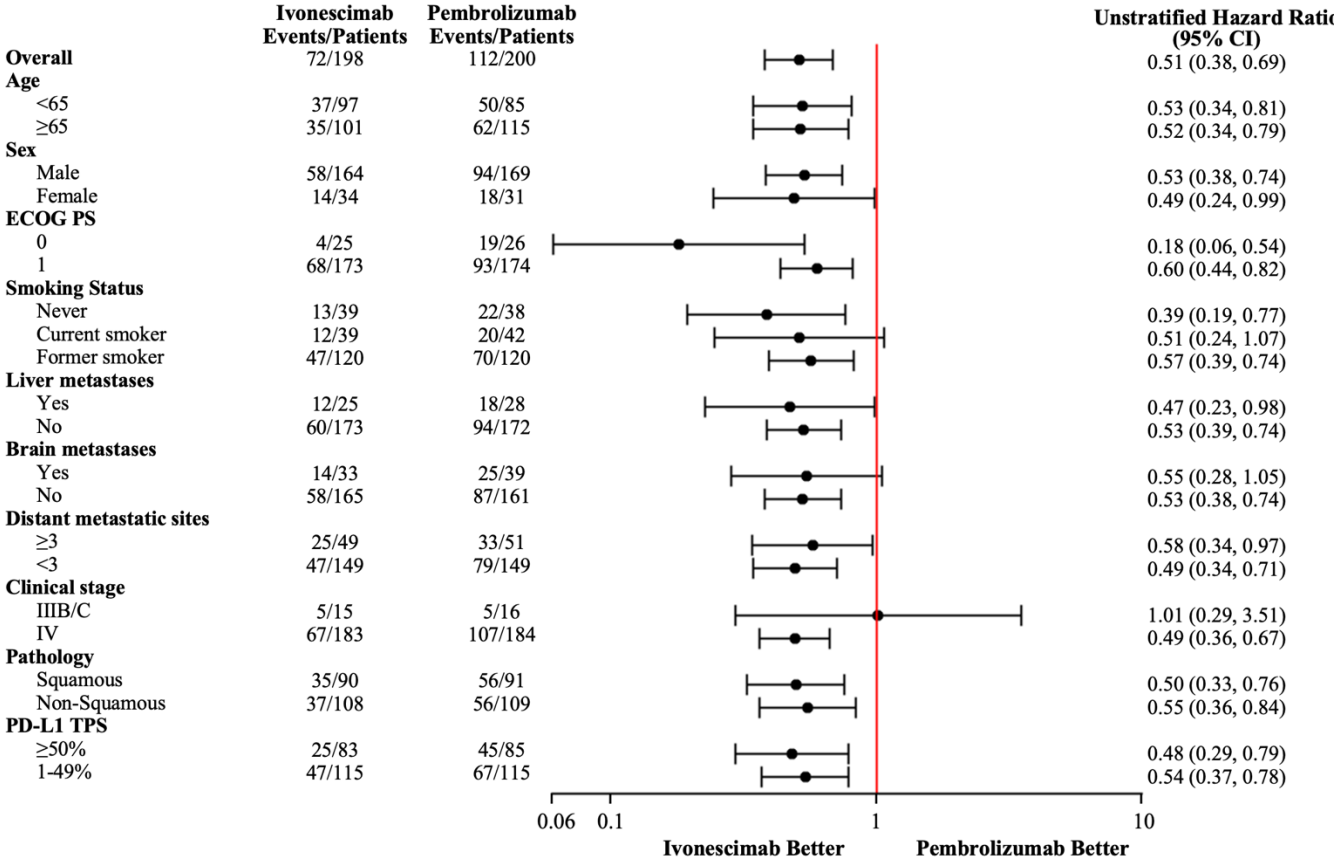
HARMONi-2 (Phase 3), primary analysis: Ivonescimab (AK112) vs pembrolizumab as 1L treatment for PD-L1+ advanced NSCLC

Primary endpoint: PFS per IRRC



	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	11.14 (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	0.51 (0.38, 0.69)	
p-value	<0.0001	

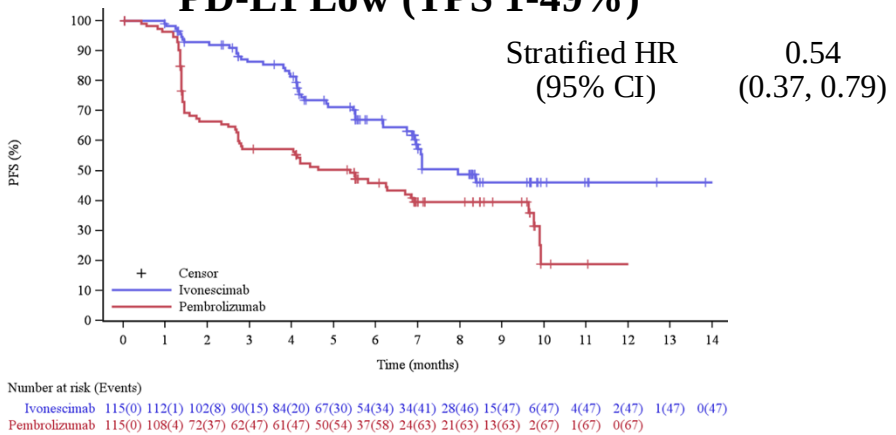
	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
ORR, % (95% CI)	**50.0** (42.8, 57.2)	38.5 (31.7, 45.6)



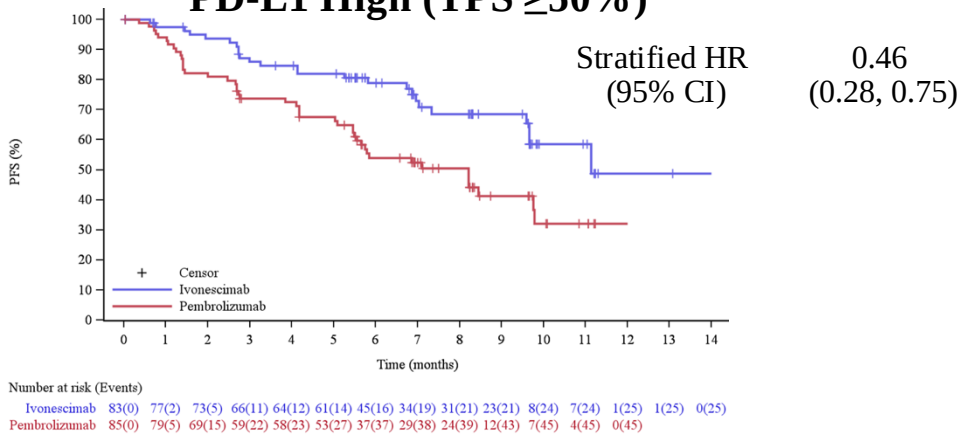
HARMONi-2: Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

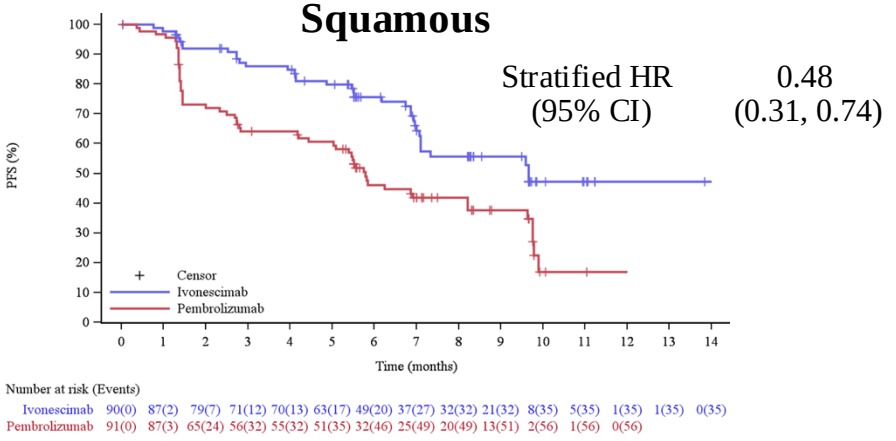


PD-L1 High (TPS ≥50%)

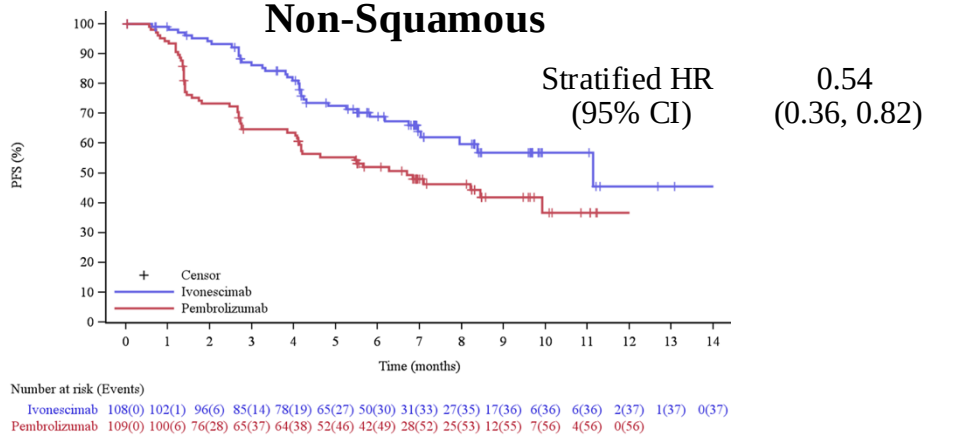


NSCLC Histology

Squamous



Non-Squamous



Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Abbreviations: PFS, progression-free survival; HR: hazard ratio; CI, confidence interval; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Safety Summary

TRAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

Ivonescimab showed manageable safety profile, which was consistent with previous studies.

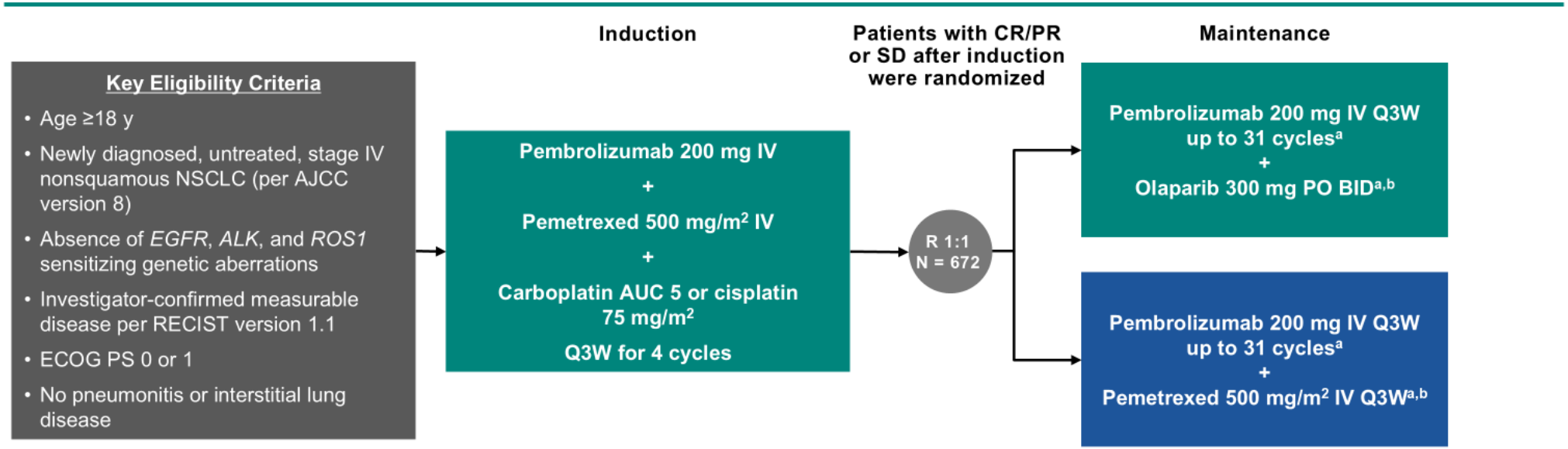
TRAEs in SQ Subgroup

Safety Summary, n (%)	Ivonescimab (n = 90[a])	Pembrolizumab (n = 91[a])
TRAEs (all grades)	77 (85.6)	73 (80.2)
Grade≥3	20 (22.2)	17 (18.7)
Serious TRAEs	17 (18.9)	17 (18.7)
Leading to discontinuation	2 (2.2)	3 (3.3)
Leading to death	0	1 (1.1)

Ivonescimab also demonstrated tolerable safety profile in SQ patients.

[a] Patients who received ≥1 dose of study treatment.
Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events; SQ, squamous cell carcinoma.

KEYLYNK-006: Maintenance PARPi Olaparib in Advanced NSCLC



Stratification Factors

- ECOG PS before randomization (0 vs 1)
- PD-L1 TPS[c] at randomization (<50% vs ≥50%)
- Response at randomization (CR/PR vs SD)

Dual Primary Endpoints (calculated from the time of randomization)

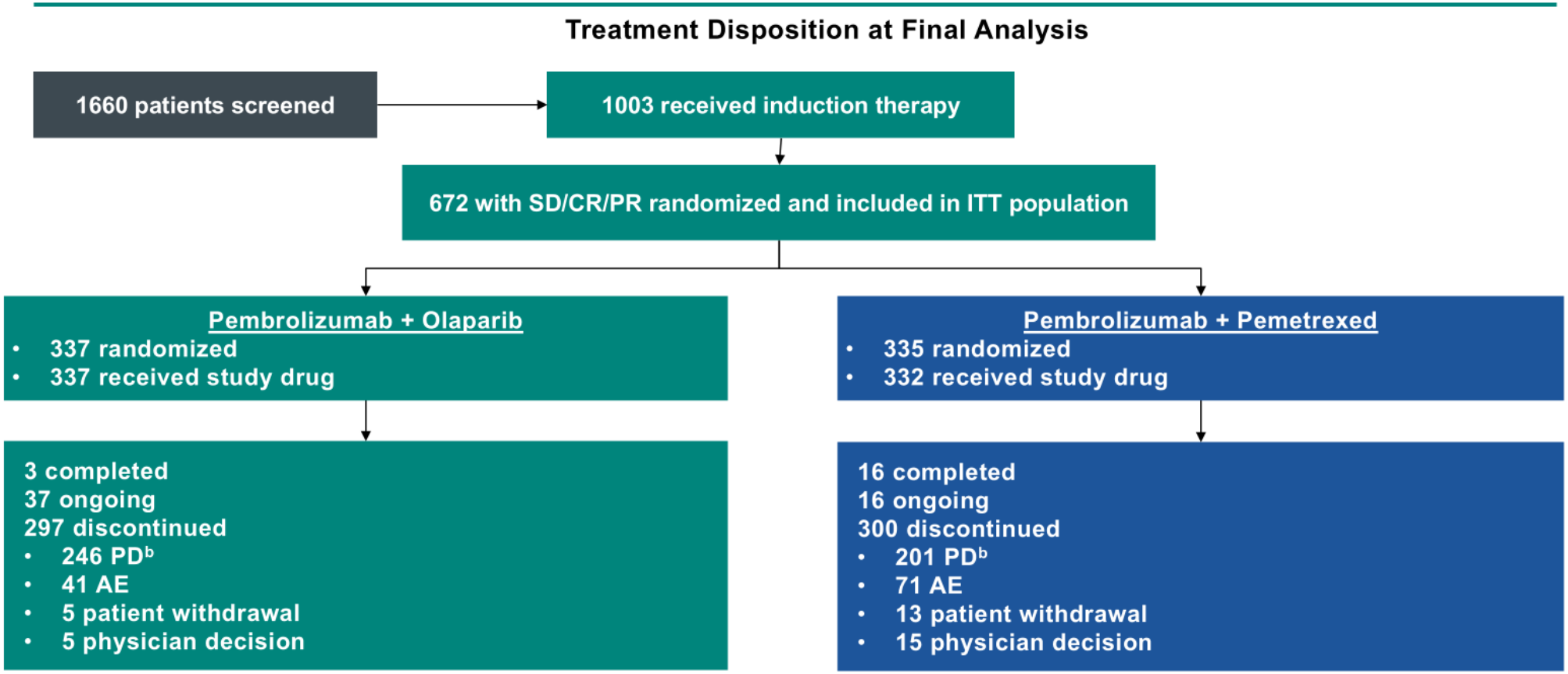
- PFS per RECIST version 1.1 by BICR
- OS

Statistical Analysis Plan

- Final PFS testing completed at interim analysis 2 (IA2); OS was evaluated at the final analysis (FA)

[a]Treatment continued until maximum treatment cycles or confirmed PD, unacceptable toxicity, intercurrent illness, or physician decision. [b]There was no maximum duration of exposure to olaparib or pemetrexed. [c]Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx (Agilent Technologies, Carpinteria, CA).

KEYLYNX-006: Phase III trial of the PARPi Olaparib maintenance therapy in advanced NSCLC



[a]ITT population includes patients who had CR, PR, or SD after induction and were randomized to receive either pembrolizumab plus olaparib or pembrolizumab plus pemetrexed. [b]Includes clinical progression and radiographic progressive disease.
Data cutoff date for FA: February 7, 2024.

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Baseline Characteristics	Pembro + Olaparib (n = 337)	Pembro + Pemetrexed (n = 335)
Age, median (range), y	63.0 (25–83)	62.0 (28–85)
Male	227 (67.4)	226 (67.5)
Race		
American Indian or Alaska Native	4 (1.2)	1 (0.3)
Asian	91 (27.0)	72 (21.5)
Black or African American	4 (1.2)	8 (2.4)
Native Hawaiian or other Pacific Islander	2 (0.6)	2 (0.6)
White	218 (64.7)	234 (69.9)
Other[b]	18 (5.3)	18 (5.4)
ECOG PS 1 at start of induction	199 (59.1)	219 (65.4)
ECOG PS 1 at randomization	195 (57.9)	200 (59.7)
Smoking status		
Former or current	280 (83.1)	284 (84.8)
Never	57 (16.9)	51 (15.2)

	Pembro + Olaparib (n = 337)	Pembro + Pemetrexed (n = 335)
PD-L1 TPS		
<50%	228 (67.7)	223 (66.6)
≥50%	109 (32.3)	110 (32.8)
Not evaluable/missing	0	2 (0.6)
Brain metastasis at screening	70 (20.8)	60 (17.9)
Liver metastasis at screening	43 (12.8)	41 (12.2)
Overall tumor stage		
III	0	2 (0.6)
IIIB	0	1 (0.3)
IVA	160 (47.5)	170 (50.7)
IVB	177 (52.5)	162 (48.4)
Tumor response at randomization per RECIST version 1.1 by BICR assessment		
CR or PR	189 (56.1)	192 (57.3)
SD	148 (43.9)	143 (42.7)

[a]ITT population includes patients who had CR, PR, or SD after induction and were randomized to receive either pembrolizumab plus olaparib or pembrolizumab plus pemetrexed. [b]Other includes: American Indian or Alaska Native and White (olaparib arm, n = 4; pemetrexed arm, n = 7); Black or African American and Native Hawaiian or other Pacific Islander (olaparib arm, n = 1); Black or African American and White (olaparib arm, n = 2; pemetrexed arm, n = 1); White and Asian (pemetrexed arm, n = 1); missing (olaparib arm, n = 11; pemetrexed arm, n = 9).
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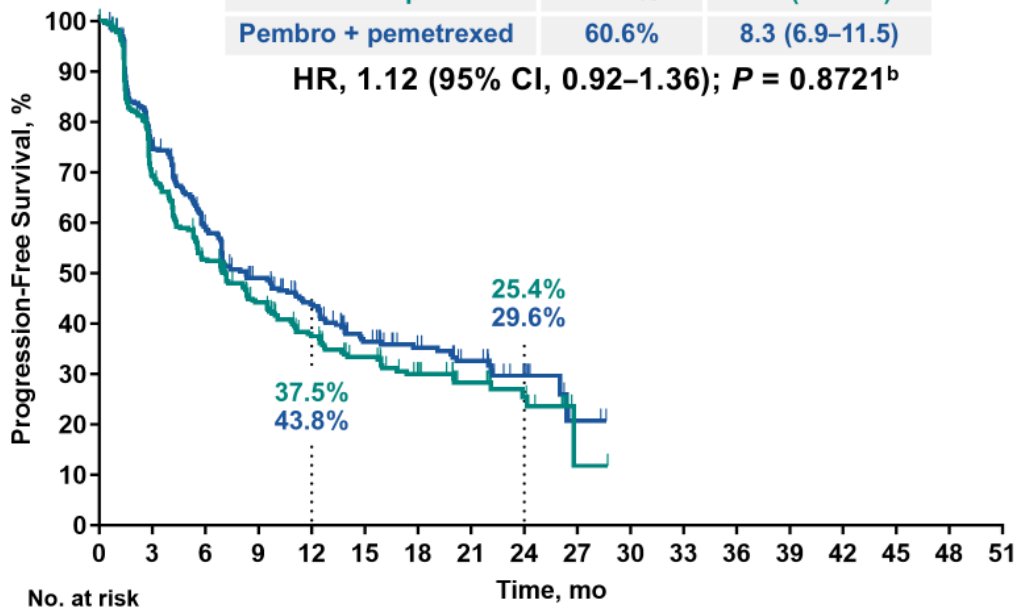
PFS (IA2)

	Pts w/ Event	Median, mo (95% CI)
Pembro + olaparib	64.1%	7.1 (5.6–8.7)
Pembro + pemetrexed	60.6%	8.3 (6.9–11.5)

HR, 1.12 (95% CI, 0.92–1.36); *P* = 0.8721[b]



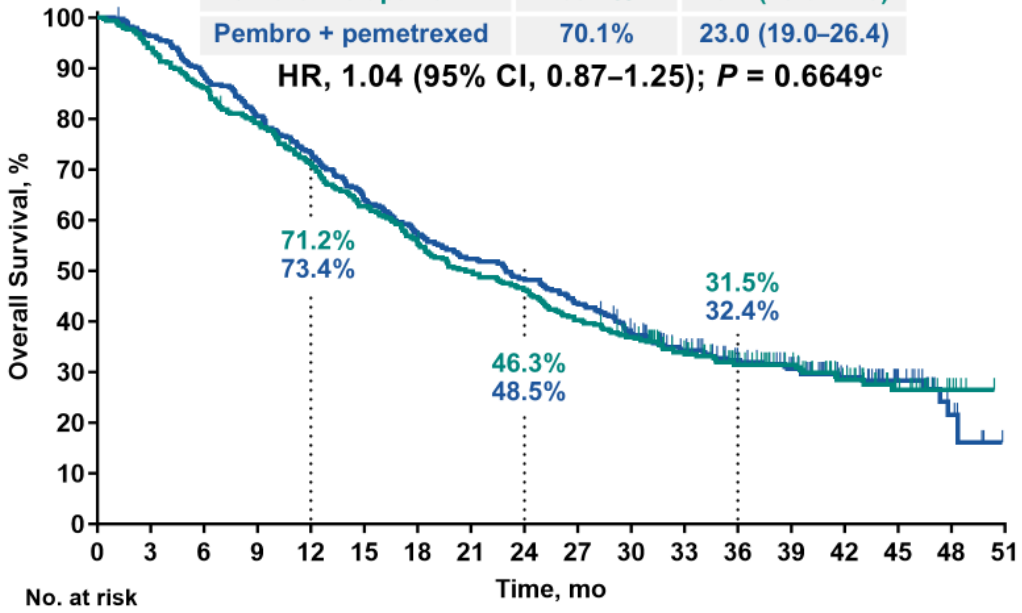
No. at risk

337	161	88	45	15	0	0	0	0
335	182	110	56	16	0	0	0	0

OS (FA)

	Pts w/ Event	Median, mo (95% CI)
Pembro + olaparib	69.1%	20.7 (18.0–24.8)
Pembro + pemetrexed	70.1%	23.0 (19.0–26.4)

HR, 1.04 (95% CI, 0.87–1.25); *P* = 0.6649[c]



No. at risk

337	290	238	187	154	116	72	39	7
335	296	245	192	162	120	79	43	8

[a]ITT population includes patients who had CR, PR, or SD after induction and were randomized to receive either pembrolizumab plus olaparib or pembrolizumab plus pemetrexed. [b]The boundary for statistical significance for PFS was 0.00485. [c]The boundary for statistical significance of OS was 0.014584.
Median time from randomization to IA2 data cutoff (May 18, 2022) was 19.2 (range, 7.4–30.8) months. Median time from randomization to FA data cutoff (February 7, 2024) was 39.9 (range, 28.1–51.5) months.
Data cutoff date: IA2, May 18, 2022; FA, February 7, 2024.

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Summary and Conclusions

- In patients with CR/PR or SD following induction with pembrolizumab plus pemetrexed and chemotherapy, pembrolizumab plus maintenance olaparib did not improve PFS or OS versus pembrolizumab plus maintenance pemetrexed in previously untreated metastatic nonsquamous NSCLC without targetable genetic alterations
- No new safety signals were identified in either treatment group
- Future biomarker analysis is needed to help identify subpopulations who may benefit from PARPi treatment for NSCLC
- Pembrolizumab plus chemotherapy continues to be a standard of care for patients with previously untreated metastatic nonsquamous NSCLC without targetable genetic alterations