Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: HARMONi-2

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Ivonescimab is an investigational therapy not approved by any regulatory authority other than China's National Medical Products Administration (NMPA)

Disclosures

- Honoraria as a speaker: Lilly China, Sanofi, BI, Roche, MSD, Qilu, Hengrui, Innovent Biologics, C-Stone, LUYE Pharma, TopAlliance Biosciences Inc, Amoy Diagnositics.
- Advisor: Innovent Biologics, Hengrui, Qilu, TopAlliance Biosciences Inc.

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Background

- Anti-PD-1/L1 monotherapy or in combination with chemotherapy has been the standard of care for the first-line treatment of PD-L1 positive aNSCLC without driver gene alterations.

- Monotherapy with an immune checkpoint inhibitor provides limited clinical benefit for PD-L1 positive aNSCLC[1-2].

- Ivonescimab (AK112) is a novel bispecific antibody against PD-1 and VEGF and has shown promising clinical efficacy and safety as front-line therapy for patients with PD-L1-positive aNSCLC in the phase 2 study (AK112-202)[3].

- HARMONi-2 (AK112-303, NCT05499390) is a randomized, double-blind, phase 3 study to compare the efficacy of ivonescimab with pembrolizumab as first-line treatment in patients with PD-L1-positive aNSCLC.

  - A sample size of approximately 388 patients and 264 PFS events would provide 90% power to detect a hazard ratio (HR) of 0.67.

  - An interim analysis of PFS was planned when 185 (70%) IRRC-assessed PFS events occurred.

1. Mok TSK, et al. Lancet. 2019;393(10183):1819-1830. 2. Yang JC, et al.J Thorac Oncol. 2024;19(6):941-953. 3.Wang L, et al. J Thorac Oncol. 2024;19(3):465-475.
Abbreviations: PD-1, programmed death receptor 1; PD-L1, programmed death ligand 1; aNSCLC, advanced non-small cell lung cancer; VEGF, vascular endothelial growth factor; PFS, progression-free survival; IRRC, independent radiology review committee.

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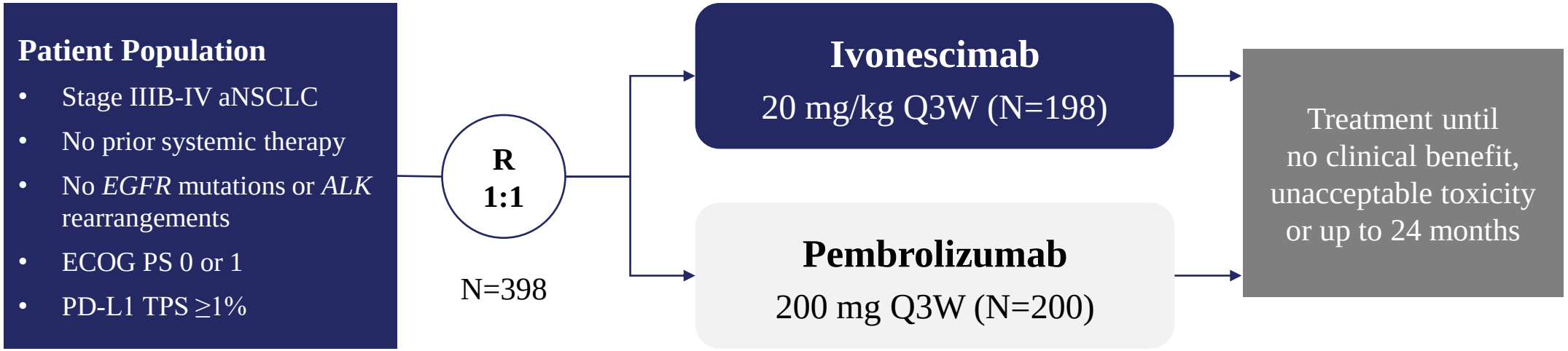
HARMONi-2 (AK112-303) Study Design

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



Stratification

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

Endpoints

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

[a] Patients were randomized from November 2022 to August 2023. Data cut off: January 29, 2024.

Abbreviations: aNSCLC, advanced non-small cell lung cancer; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; R, randomization; SQ, squamous cell carcinoma; Q3W, every three weeks; PFS, progression-free survival; IRRC, independent radiology review committee; OS, overall survival; INV, investigator; ORR, overall response rate; DoR, duration of response; TTR, time to response; QoL, quality of life.

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Baseline Characteristics

Characteristics, n (%)		Ivonescimab (n = 198[a])	Pembrolizumab (n = 200[a])	Total (n = 398[a])
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**	15 (7.6)	16 (8.0)	31 (7.8)
	IV	183 (92.4)	184 (92.0)	367 (92.2)
Pathology	**SQ**	90 (45.5)	91 (45.5)	181 (45.5)
	Tumor centrally located[b]	65 (72.2)	57 (62.6)	122 (67.4)
	Tumor with cavitation/necrosis[b]	9 (10.0)	7 (7.7)	16 (8.8)
	Tumor encasing large blood vessel[b]	6 (6.7)	1 (1.1)	7 (3.9)
	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)

[a] Patients who received randomization. [b] In 181 patients with SQ.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; SQ, squamous cell carcinoma.

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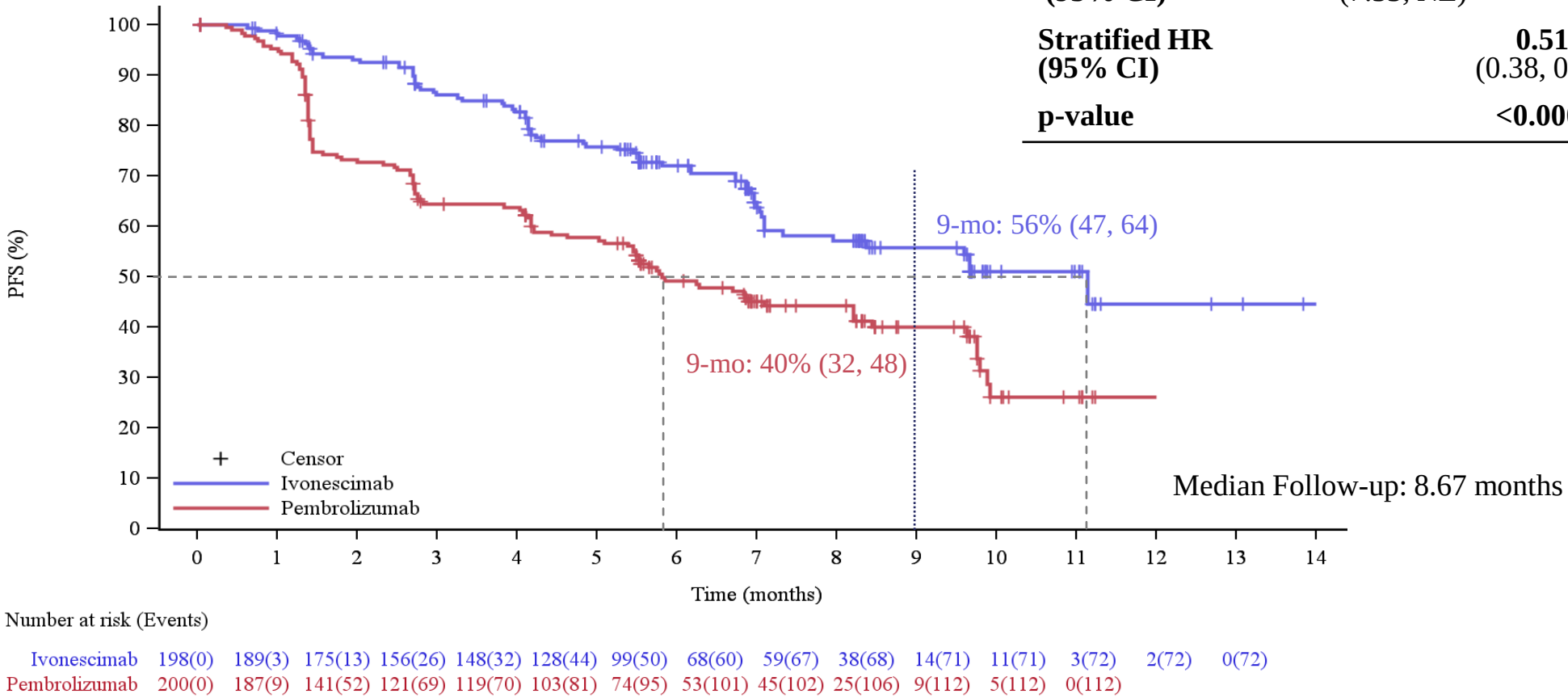
Primary endpoint: PFS per IRRC

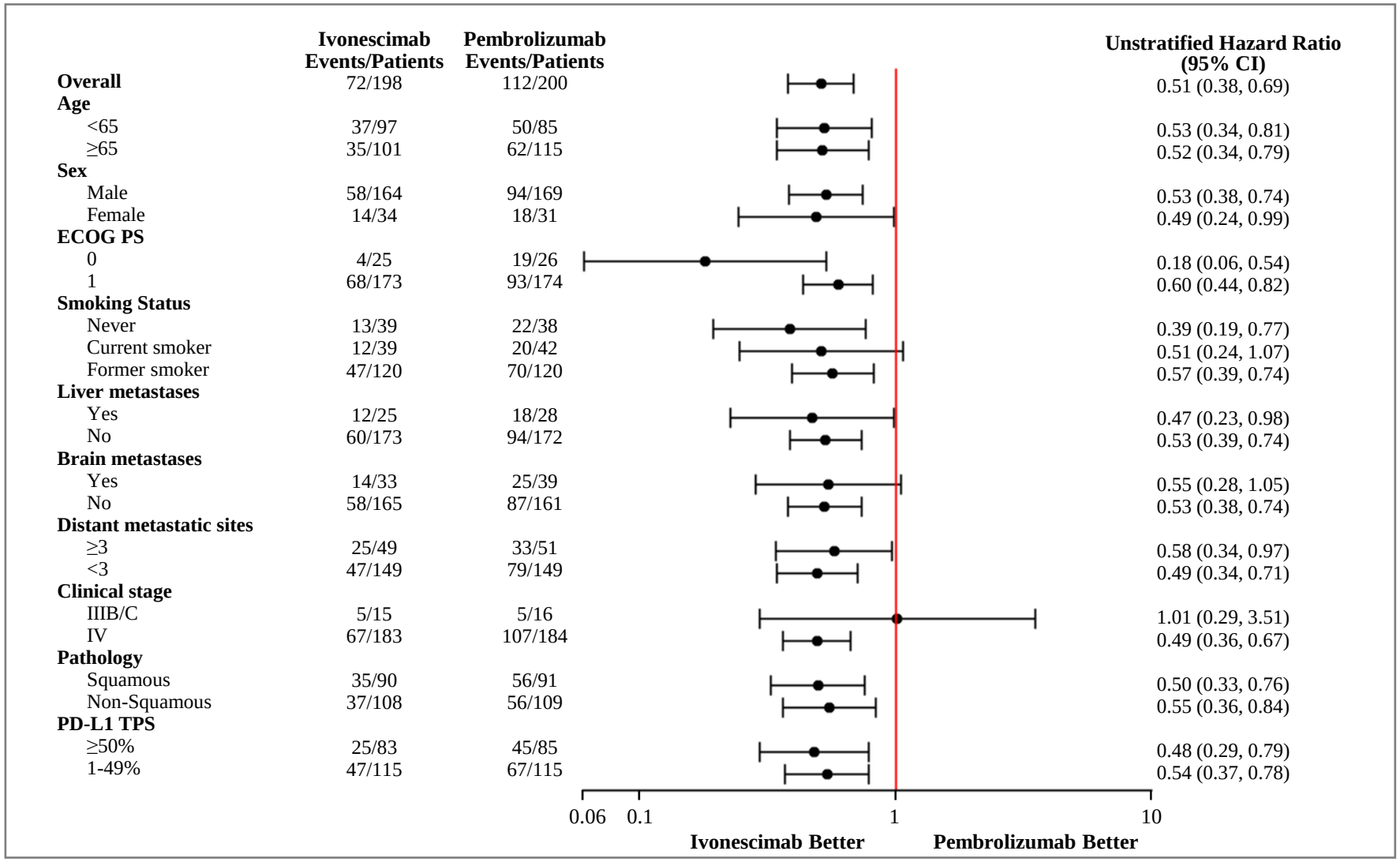
	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

Abbreviations: mPFS, median progression-free survival; IRRC, independent radiology review committee; mo, month; NE, not estimable; HR: hazard ratio; CI, confidence interval.

PFS Subgroup Analyses



Abbreviations: PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; SQ, squamous cell carcinoma; CI, confidence interval; aNSCLC, advanced non-small cell lung cancer.

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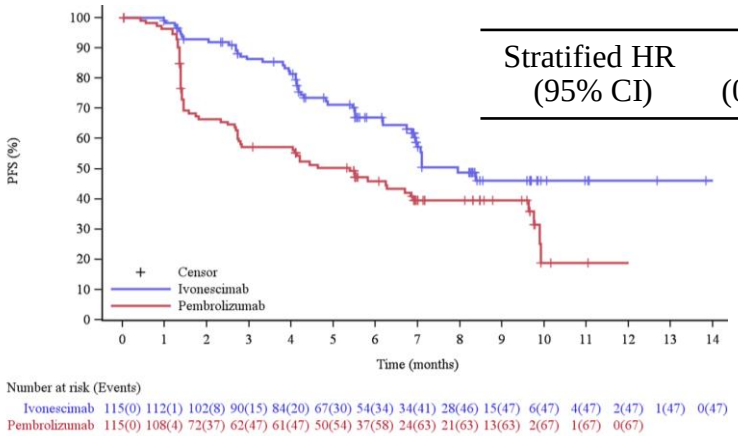
Key PFS Subgroup Analyses

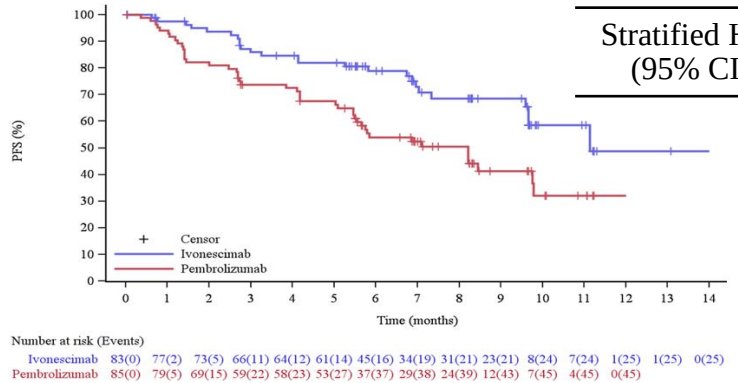
PD-L1 expression

PD-L1 Low (TPS 1-49%)



Stratified HR (95% CI)	0.54 (0.37, 0.79)

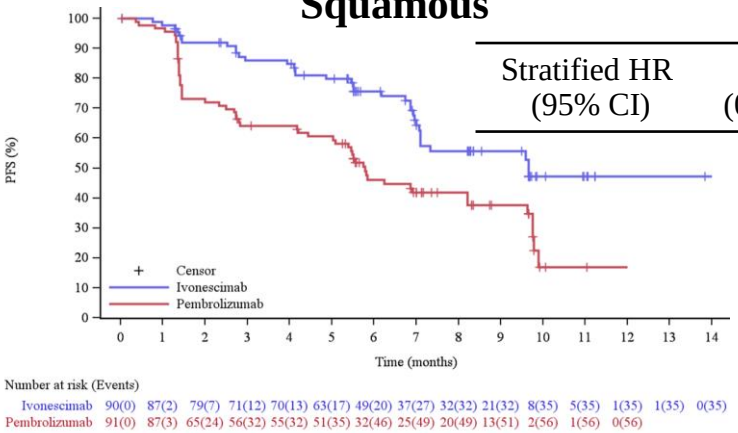
PD-L1 High (TPS ≥50%)



Stratified HR (95% CI)	0.46 (0.28, 0.75)

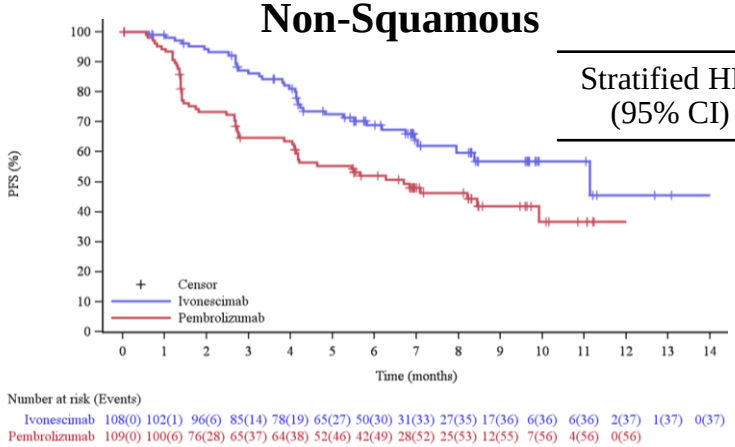
NSCLC Histology

Squamous



Stratified HR (95% CI)	0.48 (0.31, 0.74)

Non-Squamous

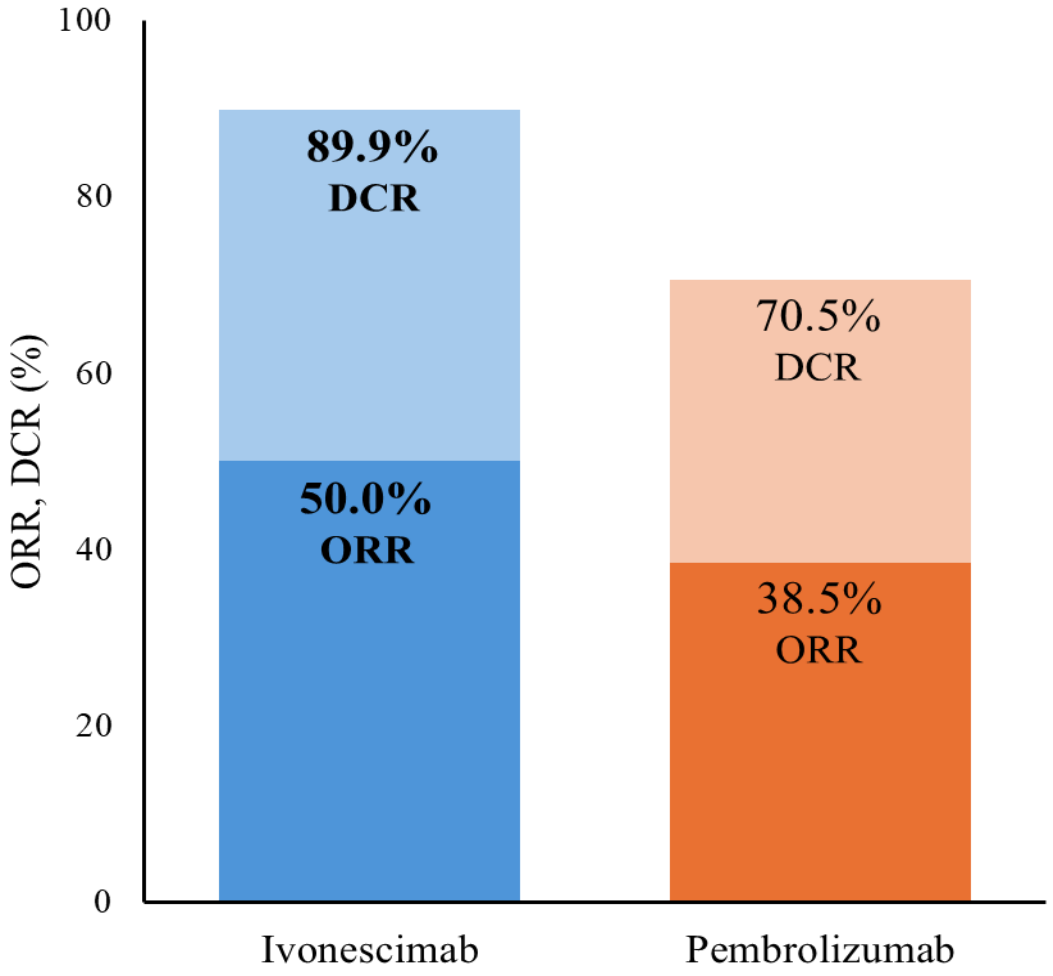


Stratified HR (95% CI)	0.54 (0.36, 0.82)

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; PD-L1, programmed death ligand 1; TPS, tumor proportion score; HR: hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer.

ORR, DCR and DoR per IRRC



	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
ORR, % (95% CI)	**50.0** (42.8, 57.2)	38.5 (31.7, 45.6)
DCR, % (95% CI)	**89.9** (84.8, 93.7)	70.5 (63.7, 76.7)
Median DoR, mos (95% CI)	**NR** (NE, NE)	NR (8.28, NE)

ORR and DCR were higher with ivonescimab vs. pembrolizumab.

Data cut off: January 29, 2024.
Abbreviations: ORR, overall response rate; DCR, disease control rate; DoR, duration of response; IRRC, independent radiology review committee; CI, confidence interval; mo, month; NR, not reached; NE, not estimable.

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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)

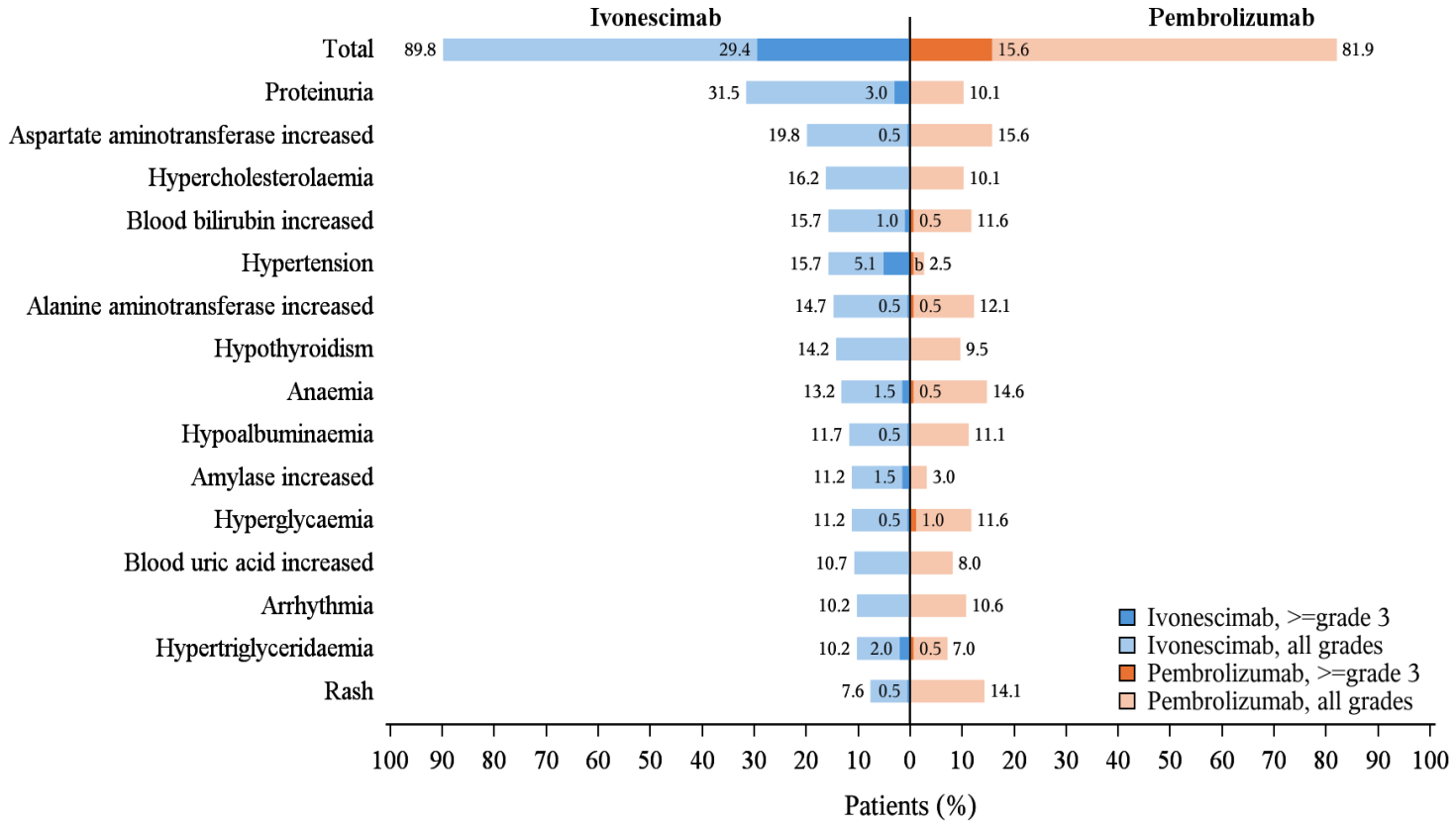
Ivonescimab showed a manageable safety profile, which was consistent with previous studies.

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 a tolerable safety profile in SQ patients.

The Most Common TRAEs (incidence ≥10%)



The differences in AEs were predominantly proteinuria, hypertension, and laboratory abnormalities.

[a] Patients who received ≥1 dose of study treatment. [b] The incidence of ≥grade 3 Hypertension was 0.5%.
Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events; SQ, squamous cell carcinoma.

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Immune-Related and Possible VEGF-Related AEs

irAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
irAEs (all grades)	59 (29.9)	56 (28.1)
Grade≥3	14 (7.1)	16 (8.0)
Serious irAEs	11 (5.6)	22 (11.1)
Leading to discontinuation	0	5 (2.5)
Leading to death	0	0

Ivonescimab exhibited similar irAEs to that of pembrolizumab.

Possible VEGF-Related AEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
Possible VEGF-Related AEs (all grades)	94 (47.7)	42 (21.1)
Grade≥3	20 (10.2)	2 (1.0)

Safety Summary by Classification, n (%)	Ivonescimab (n = 197[a])		Pembrolizumab (n = 199[a])	
	All Grade	Grade≥3	All Grade	Grade≥3
Proteinuria	62 (31.5)	6 (3.1)	20 (10.1)	0
Hypertension	31 (15.7)	10 (5.1)	5 (2.5)	1 (0.5)
Haemorrhage	29 (14.7)	2 (1.0)	22 (11.1)	1 (0.5)
Arterial thromboembolism	2 (1.0)	2 (1.0)	1 (0.5)	0
Venous thromboembolism	0	0	1 (0.5)	0

- All VEGF-related AEs were grades 1-3 in both arms.
- Grade 3 haemorrhage was observed in two patients with non-SQ and was not reported in SQ patients in the ivonescimab arm.

[a] Patients who received ≥1 dose of study treatment.
Abbreviations: VEGF, vascular endothelial growth factor; irAEs, immune-related AEs; AEs, adverse events; SQ, squamous cell carcinoma.

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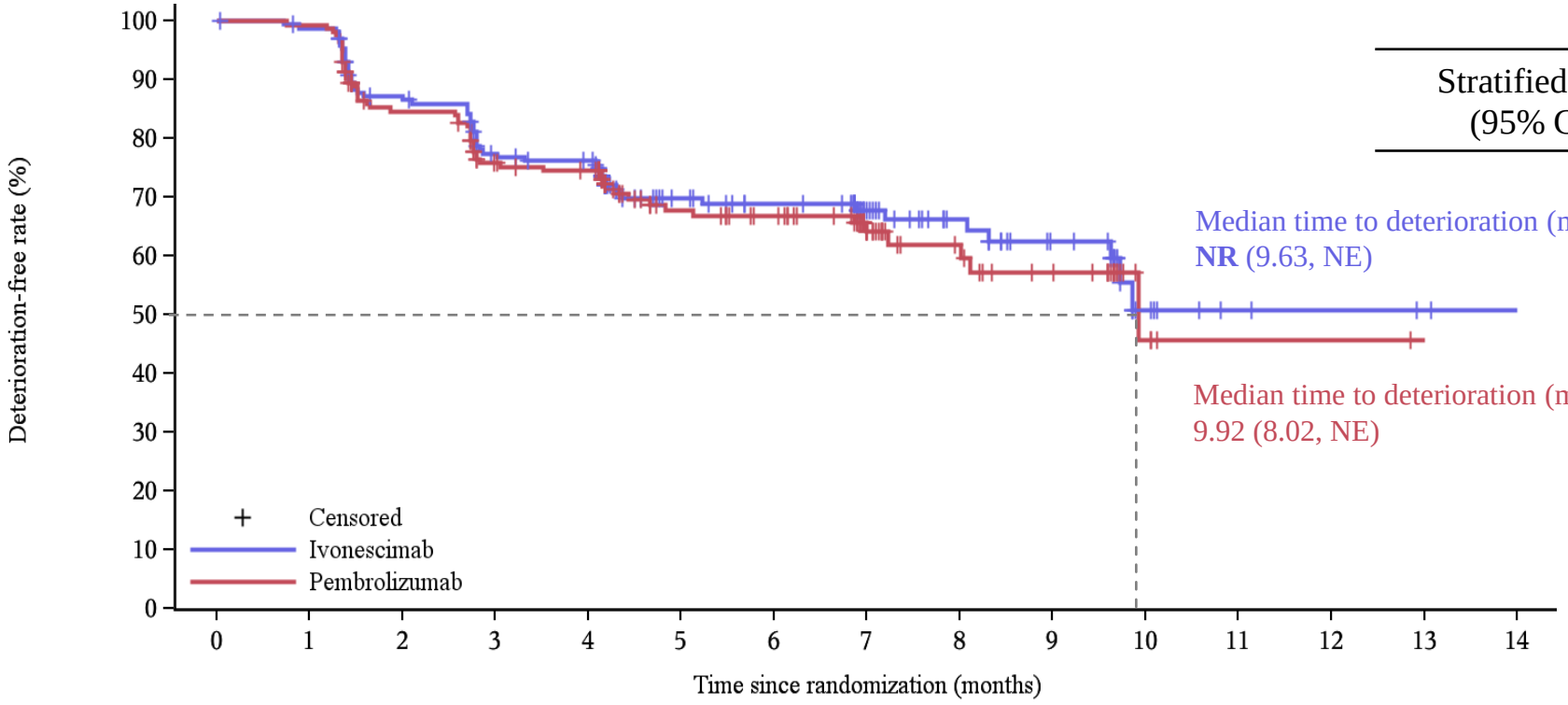
Global Health Status – EORTC QLQ-C30

Time to deterioration of global health status – EORTC QLQ-C30[a]



Stratified HR (95% CI)	0.92 (0.63, 1.33)

Number at risk (events)

Ivonescimab	177(0)[b]	173(2)	146(22)	125(38)	120(40)	80(49)	72(50)	48(51)	35(52)	25(54)	8(57)	3(57)	2(57)	1(57)	0(57)
Pembrolizumab	174(0)[b]	173(1)	137(26)	115(40)	110(42)	72(50)	65(51)	38(53)	26(54)	19(56)	4(57)	1(57)	1(57)	0(57)	

Ivonescimab was associated with comparable, numerically better time to deterioration of global health status.

[a] Deterioration of global health status/quality of life (QoL) refers to a decrease of 10 points or greater from the baseline in standardized score. Time to deterioration is defined as the time from the date of randomization to the date of first occurrence of deterioration. [b] Patients who completed EORTC QLQ-C30.
Abbreviations: mo, month; NR, not reached; NE, not estimated; HR: hazard ratio; CI, confidence interval.

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Conclusions

- First-line ivonescimab significantly improve IRRC-assessed PFS in patients with aNSCLC and PD-L1 TPS ≥1%, compared with pembrolizumab (**median PFS (mos), 11.14 vs. 5.82; HR, 0.51; *p*<0.0001**).
- PFS benefit with ivonescimab were consistent across major clinical subgroups:
  - TPS ≥50%, HR = 0.46 (0.28, 0.75); TPS 1-49%, HR = 0.54 (0.37, 0.79)
  - SQ, HR = 0.48 (0.31, 0.74); non-SQ, HR = 0.54 (0.36, 0.82)
- Higher ORR (50.0% vs. 38.5%) and DCR (89.9% vs. 70.5%) were observed with ivonescimab vs. pembrolizumab.
- OS was not matured at this time; the OS analysis is event-driven and will be reported in the future.
- The safety profile of ivonescimab was consistent with prior studies and well tolerated, including in patients with SQ-NSCLC.
- HRQoL with ivonescimab was comparable to pembrolizumab.

This is the first randomized phase 3 study to demonstrate a clinically significant improvement in efficacy with a novel drug compared to pembrolizumab in aNSCLC.

Ivonescimab is a novel 1st line treatment for patients with aNSCLC and positive PD-L1(TPS ≥1%).

Ivonescimab is an investigational therapy in this setting worldwide; ivonescimab is approved in 2L EGFRm NSCLC in China.
Abbreviations: IRRC, independent radiology review committee; PFS, progression-free survival; aNSCLC, advanced non-small cell lung cancer; PD-L1, programmed death ligand 1; TPS, tumor proportion score; mo, month; HR: hazard ratio; CI, confidence interval; SQ, squamous cell carcinoma; ORR, overall response rate; DCR, disease control rate; OS, overall survival.

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