Ivonescimab combined with chemotherapy in patients with EGFR-mutant non-squamous non-small cell lung cancer who progressed on EGFR-TKIs treatment: a randomized, double-blind, multi-center, phase 3 trial (HARMONi-A study)

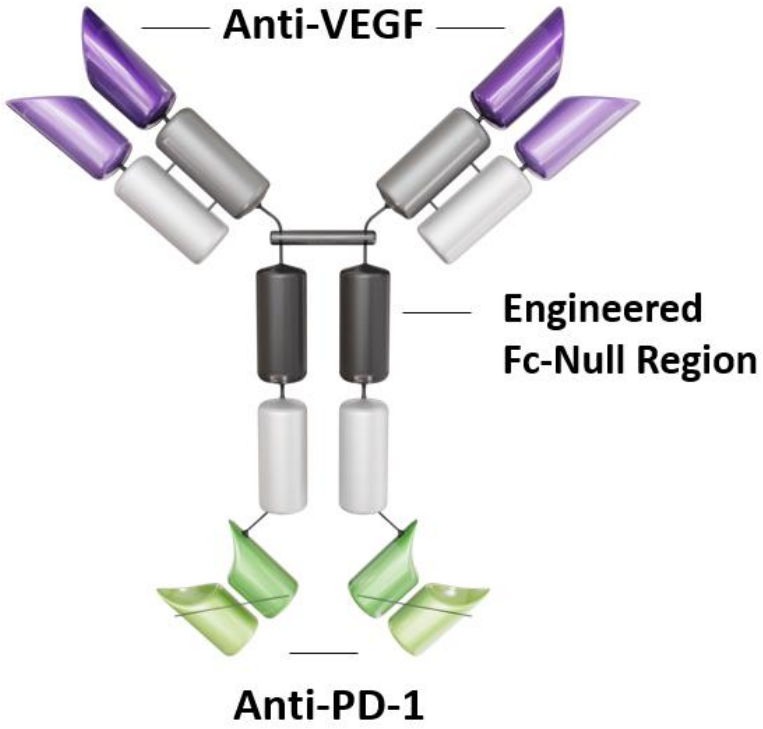
Li Zhang[1], Wenfeng Fang[1], Yuanyuan Zhao[1], Yongzhong Luo[2], Runxiang Yang[3], Yan Huang[1], Zhiyong He[4], Hui Zhao[5], Mingjun Li[6], Kai Li[7], Qibing Song[8], Xiaobo Du[9], Yulan Sun[10], Wei Li[11], Fei Xu[12], Zhiyu Wang[13], Kunning Yang[14], Yun Fan[15], Wenting Li[16], Michelle Xia[16]

[1]Sun Yat-sen University Cancer Center, Guangzhou, China; [2]Hunan Cancer Hospital, Changsha, China; [3]Yunnan Cancer Hospital, Kunming, China; [4]Fujian Provincial Tumor Hospital, Fuzhou, China; [5]The Second Hospital of Anhui Medical University, Hefei, China; [6]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [7]Tianjin Medical University Cancer Institute & Hospital. Tianjin, China; [8]Renmin Hospital of Wuhan University, Wuhan, China; [9]Mianyang Central Hospital, Mianyang, China; [10]Shandong Cancer Prevention and Treatment Institute, Jinan, China; [11]The First Affiliated Hospital of Bengbu Medical University, Bengbu, China; [12]The First Affiliated Hospital of Nanchang University, Nanchang, China; [13]The Fourth Hospital of Hebei Medical University, Shijiazhuang, China; [14]Weifang No.2 People's Hospital, Weifang, China; [15]Zhejiang Cancer Hospital, Hangzhou, China; [16]Akeso Biopharma, Inc., Zhongshan, China

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

Presented by Dr. Li Zhang, MD / ASCO 2024

Background



- For patients with EGFR-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard. However, drug resistance remains a challenge, and an effective therapy after progression is needed.
- Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.
- Phase II clinical studies have shown potential efficacy of Ivonescimab plus chemotherapy in NSCLC patients with EGFR mutations who progressed on prior EGFR-TKIs therapies[1-2].
- This phase 3 study aimed to evaluate and confirm the efficacy and safety of ivonescimab combined with chemotherapy compared to chemotherapy alone in this population (NCT05184712).

1. L Zhang et al: ASCO 2023; 2. YY Zhao et al: eClinicalMedicine 2023;62: 102106.

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

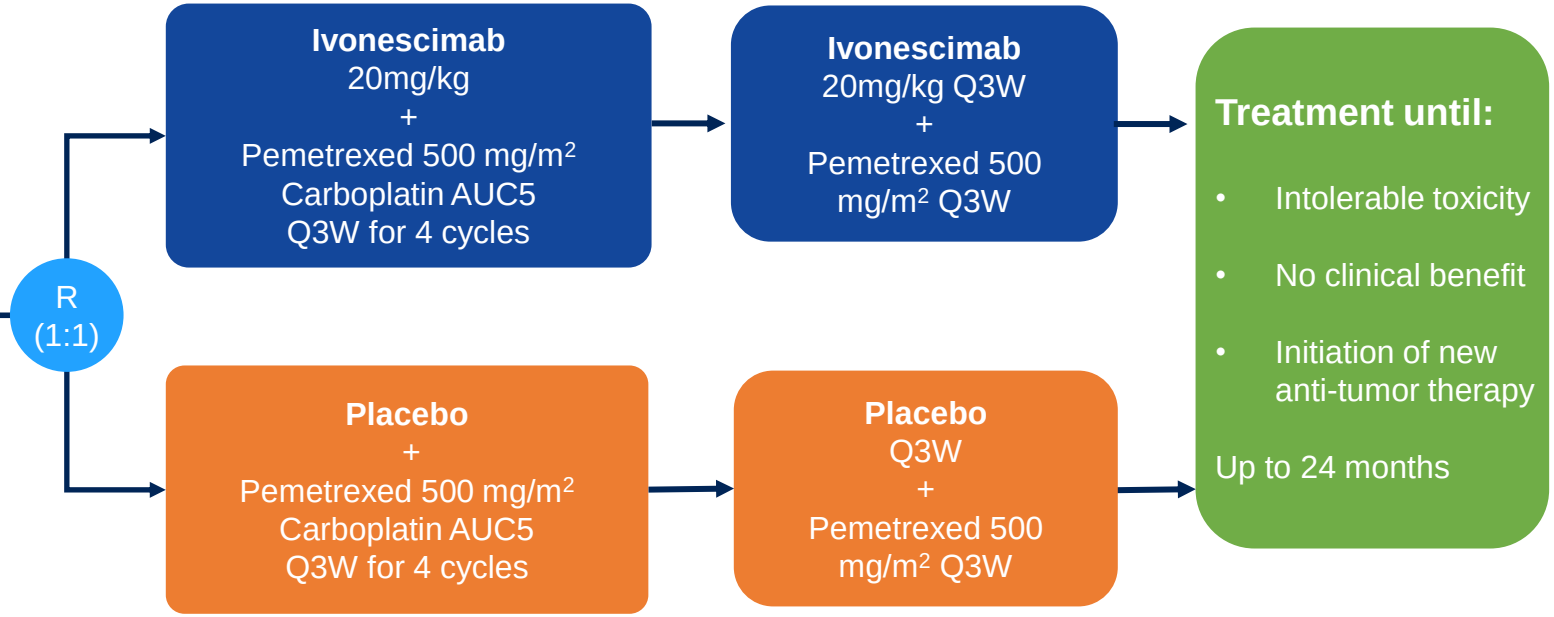
HARMONi-A Study Design

Key Eligibility Criteria

- nsq-NSCLC (Stage IIIB/C ineligible for surgery or local therapy and IV)
- EGFR sensitive mutation positive
- ECOG PS 0 or1
- Regardless PD-L1 expression

Stratification Factors:

- Exposure to 3rd EGFR-TKI before (yes vs. no)
- Brain metastases (yes vs. no)



Endpoints

- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

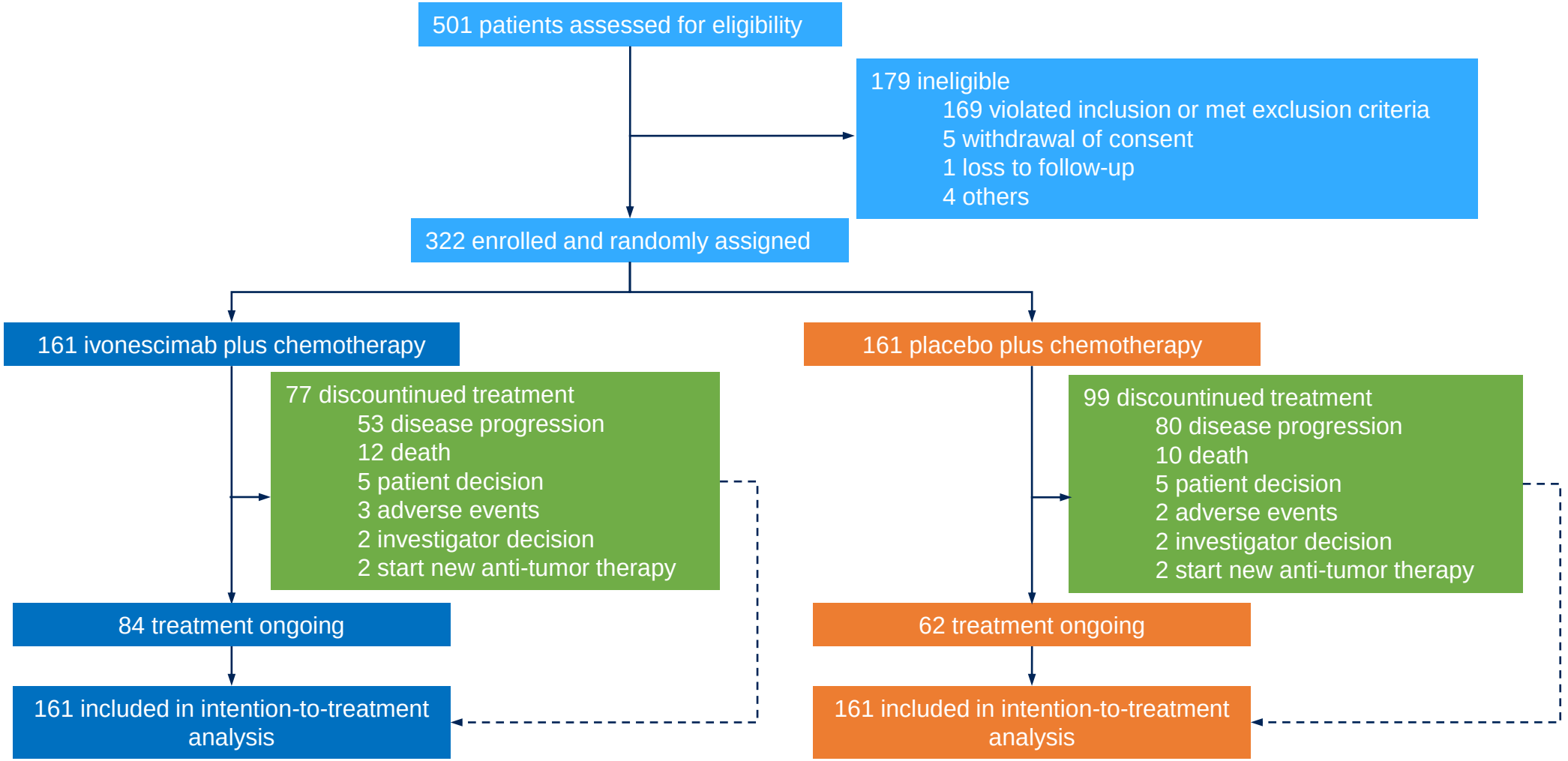
ClinicalTrials.gov, NCT05184712; NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor receptor; ECOG, eastern copperative oncology group; TKI, tyrosine-kinase inhibitor; Q3W, every 3 weeks.

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

Statistical Analyses

- **Estimated sample size:**
  - 320 patients (assuming HR=0.65, overall α=0.025 [one-side], power=89% for PFS)
- **Analysis methods:**
  - A stratified log-rank test was used to compare PFS between treatment groups
  - PFS was estimated using the Kaplan-Meier method and HR was through a stratified Cox regression model
- **All data (except OS) are based on the clinical data cutoff of March 2023, at which point the median follow-up duration was 7.89 months.**

Disposition of Study Treatment



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

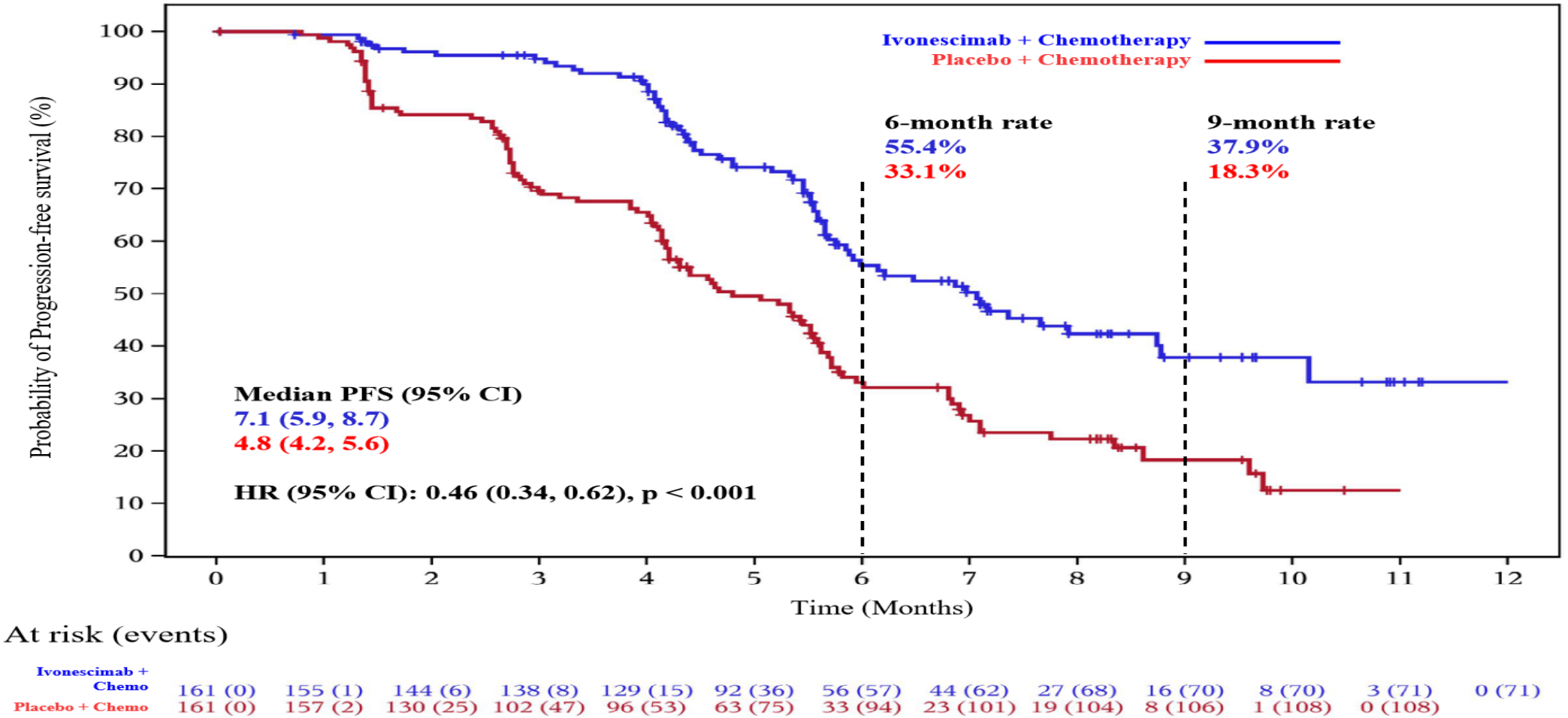
Baseline Characteristics

	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Age, n(%)		
Median (rang)，years	59.6 (32.3, 74.9)	59.4 (36.2, 74.2)
<65	111 (68.9)	110 (68.3)
≥65	50 (31.1)	51 (31.7)
Sex, n(%)		
Male	77 (47.8)	79 (49.1)
Female	84 (52.2)	82 (50.9)
ECOG, n(%)		
0	24 (14.9)	34 (21.1)
1	137 (85.1)	127 (78.9)
Smoking status, n(%)		
Never	112 (69.6)	115 (71.4)
Current or former	49 (30.4)	46 (28.6)
Stage, n(%)		
IIIB or IIIC	3 (1.9)	5 (3.1)
IV	158 (98.1)	156 (96.9)
Brain metastasis, n (%)	35 (21.7)	37 (23.0)
Liver metastasis, n (%)	21 (13.0)	17 (10.6)
Distant metastases≥3，n(%)	74 (46.0)	68 (42.2)
EGFR mutation, n (%)		
Exon 19 Del	92 (57.1)	78 (48.4)
Exon L858R	60 (37.3)	78 (48.4)
Other	35 (21.7)	25 (15.5)
T790M status, n (%)		
Negative	26 (16.1)	27 (16.8)
Positive	26 (16.1)	18 (11.2)
Unknown	109 (67.7)	116 (72.0)
Previous EGFR-TKI treatment, n (%)		
1st/2nd Gen TKI only	22 (13.7)	24 (14.9)
3rd Gen TKI only	49 (30.4)	58 (36.0)
1st/2nd Gen TKI, then 3rd Gen TKI	90 (55.9)	79 (49.1)

ECOG, eastern copperative oncology group; EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; Gen, generation.

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

Study Met Primary Endpoint of PFS per IRRC



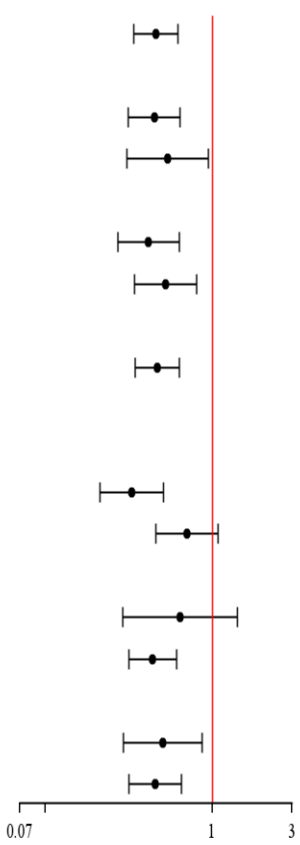
HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
HR, hazard ratio; CI, confidence interval; IRRC, independent radiology review committee.

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

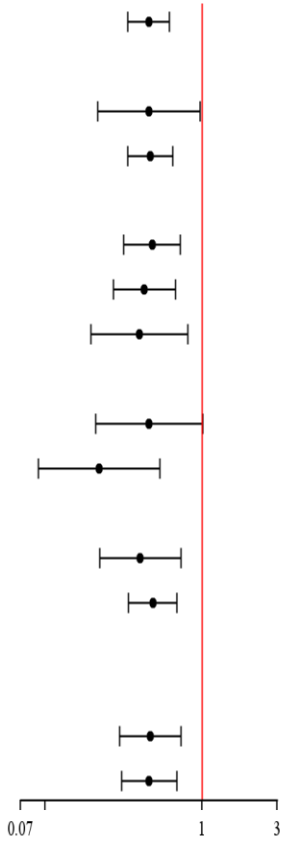
Presented by Dr. Li Zhang, MD / ASCO 2024

Subgroup Analysis of PFS per IRRC

	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Age			
<65 years	51/111	75/110	0.45 (0.31, 0.64)
>=65 years	20/50	33/51	0.54 (0.31, 0.95)
Sex			
Male	34/77	57/79	0.41 (0.27, 0.64)
Female	37/84	51/82	0.52 (0.34, 0.80)
Clinical Stage at Study Entry			
IV	69/158	105/156	0.47 (0.34, 0.63)
Number of Distant Metastasis Sites at Baseline			
<3	30/87	64/93	0.33 (0.21, 0.51)
>=3	41/74	44/68	0.70 (0.46, 1.08)
Liver Metastasis			
Presence	13/21	12/17	0.64 (0.29, 1.41)
Absence	58/140	96/144	0.44 (0.32, 0.61)
Smoking History			
Yes	23/49	31/46	0.50 (0.29, 0.87)
No	48/112	77/115	0.45 (0.32, 0.65)



	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Baseline ECOG Score			
0	10/24	22/34	0.46 (0.22, 0.97)
1	61/137	86/127	0.47 (0.33, 0.65)
Baseline EGFR Mutation			
19Del	39/92	53/78	0.48 (0.32, 0.73)
L858R	29/60	54/78	0.43 (0.27, 0.67)
Other	15/35	17/25	0.40 (0.20, 0.81)
T790M Mutation Status			
Negative	10/26	17/27	0.46 (0.21, 1.01)
Positive	12/26	13/18	0.22 (0.09, 0.54)
Baseline Brain Metastasis			
Presence	19/35	28/37	0.40 (0.22, 0.73)
Absence	52/126	80/124	0.48 (0.34, 0.69)
Previously Received EGFR-TKI Treatment			
One Line	30/71	52/82	0.47 (0.30, 0.73)
Two or More Lines	41/90	56/79	0.46 (0.31, 0.69)

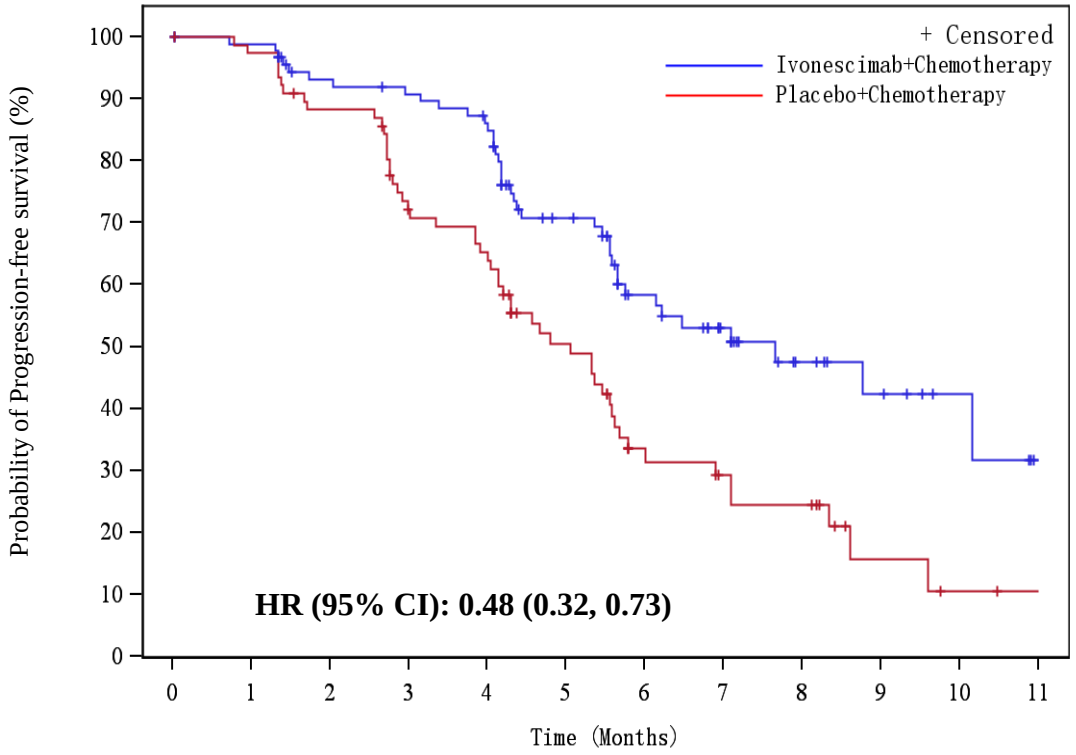


Ivonescimab is an investigational therapy not approved by any regulatory authority other than China's National Medical Products Administration (NMPA)

Presented by Dr. Li Zhang, MD / ASCO 2024

PFS of 19del and L858R

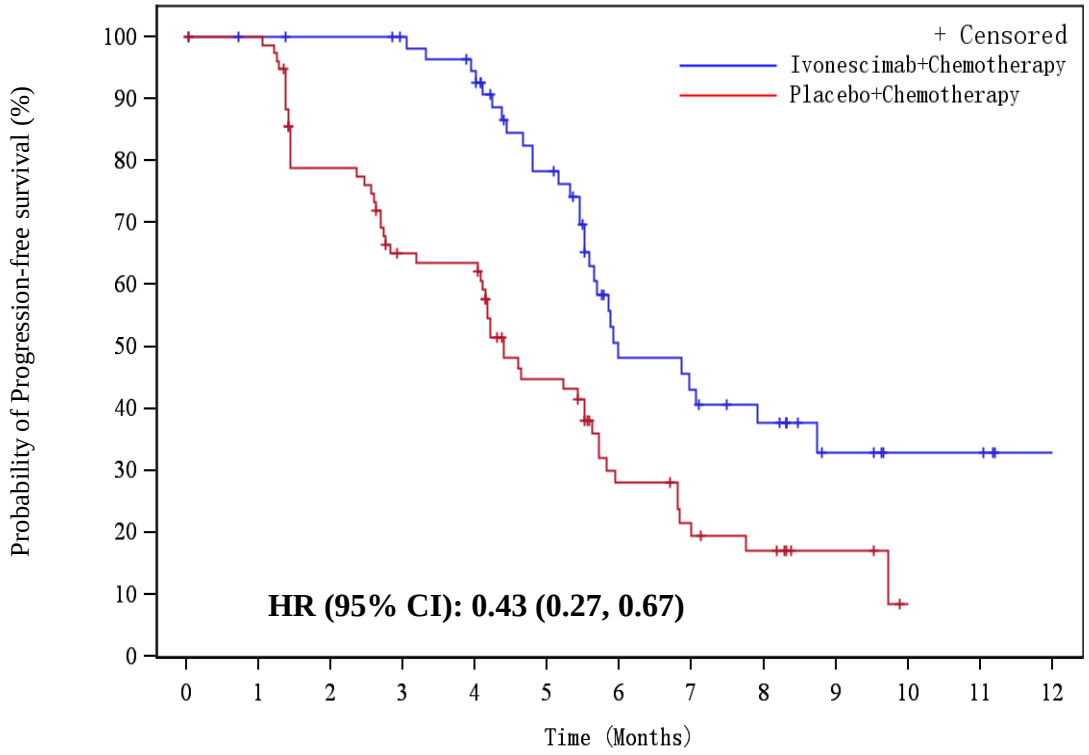
PFS Kaplan Meier Curve Evaluated by IRRC
with 19del



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	92 (0)	89 (1)	79 (6)	76 (8)	71 (12)	50 (24)	33 (32)	23 (35)	12 (37)	8 (38)	4 (38)	0 (39)
Placebo+Chemotherapy	78 (0)	75 (2)	67 (9)	52 (21)	47 (26)	31 (36)	16 (46)	12 (48)	10 (50)	3 (52)	1 (53)	0 (53)

PFS Kaplan Meier Curve Evaluated by IRRC
with L858R



Number of Subjects at Risk (Number of Events)

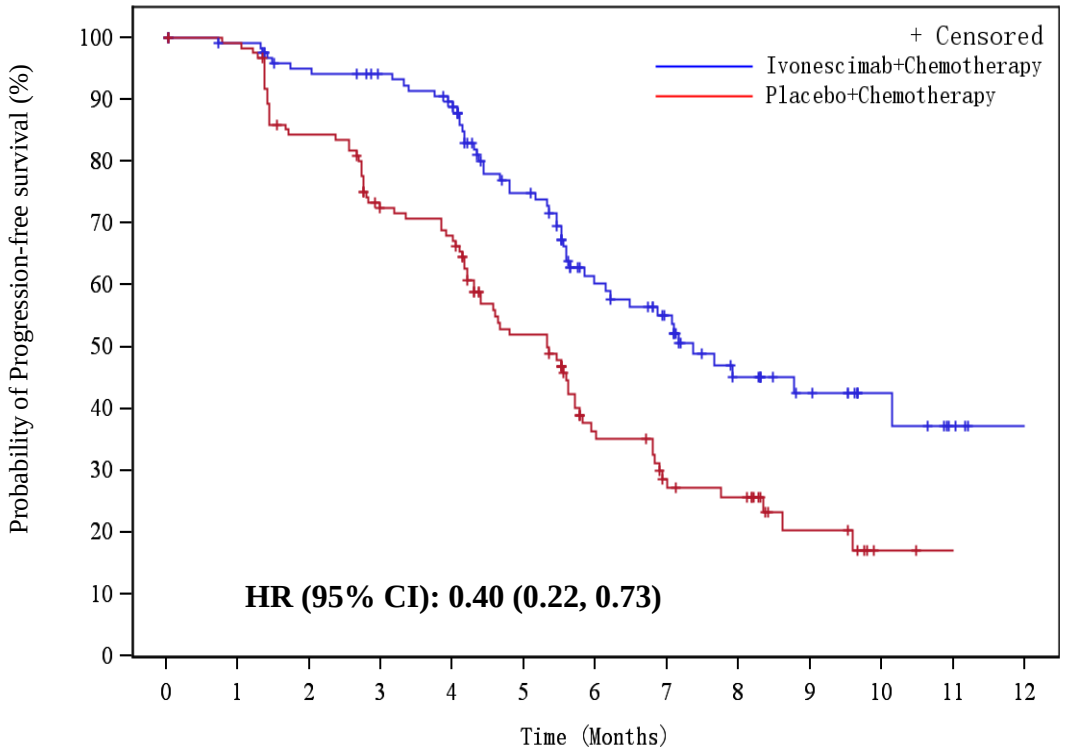
Ivonescimab+Chemotherapy	60 (0)	58 (0)	57 (0)	55 (0)	51 (3)	38 (11)	19 (24)	17 (26)	13 (28)	6 (29)	3 (29)	3 (29)	0 (29)
Placebo+Chemotherapy	78 (0)	77 (0)	58 (16)	45 (26)	44 (27)	27 (39)	14 (48)	9 (52)	7 (53)	3 (53)	0 (54)		

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

Presented by Dr. Li Zhang, MD / ASCO 2024

PFS by Presence of Brain Metastases

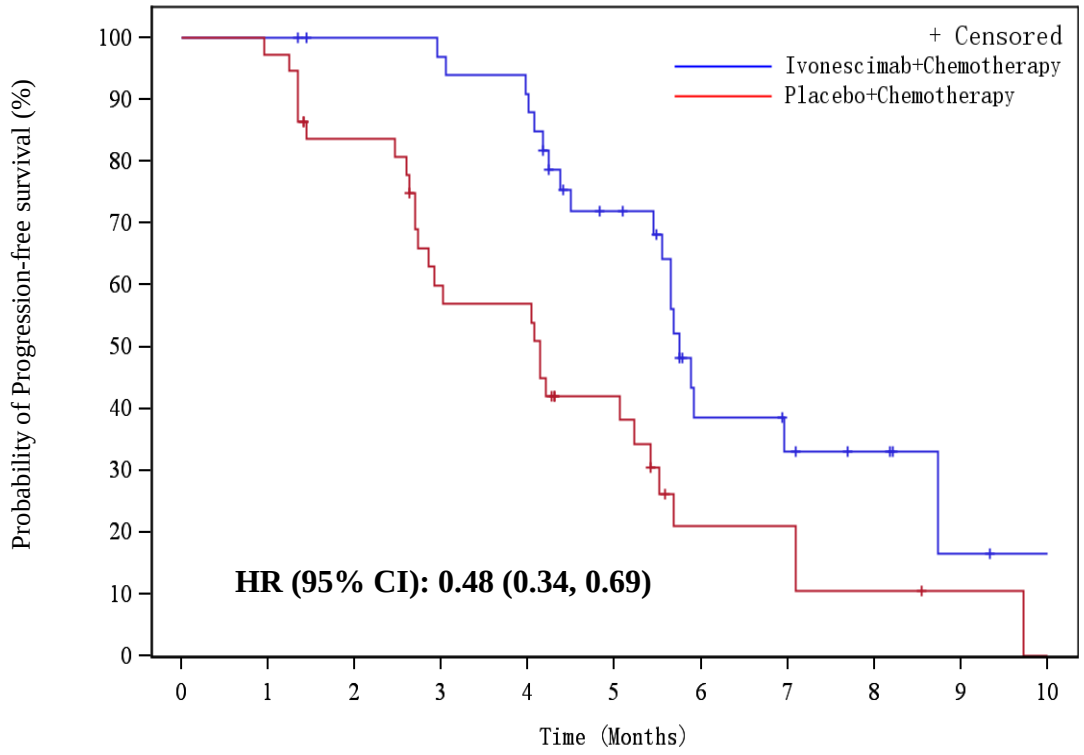
PFS Kaplan Meier Curve Evaluated by IRRC
without Brain Metastasis



Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	126 (0)	120 (1)	111 (6)	106 (7)	99 (12)	72 (27)	48 (40)	38 (44)	23 (50)	15 (51)	8 (51)	3 (52)	0 (52)
Placebo+Chemotherapy	124 (0)	121 (1)	101 (19)	82 (33)	77 (38)	52 (55)	29 (69)	19 (76)	17 (77)	7 (79)	1 (80)	0 (80)	

PFS Kaplan Meier Curve Evaluated by IRRC
with Brain Metastasis



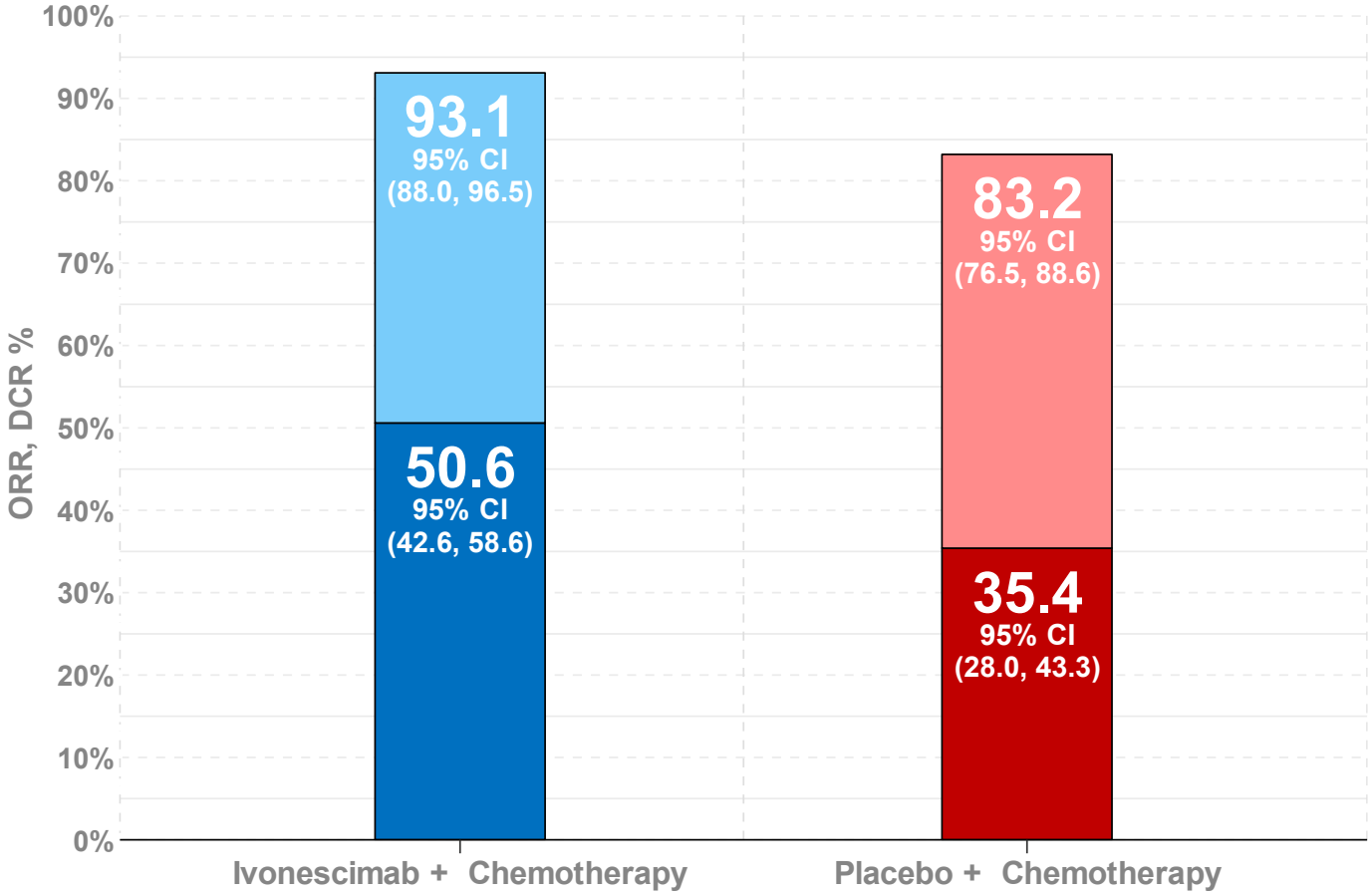
Number of Subjects at Risk (Number of Events)

Ivonescimab+Chemotherapy	35 (0)	35 (0)	33 (0)	32 (1)	30 (3)	20 (9)	8 (17)	6 (18)	4 (18)	1 (19)	0 (19)
Placebo+Chemotherapy	37 (0)	36 (1)	29 (6)	20 (14)	19 (15)	11 (20)	4 (25)	4 (25)	2 (27)	1 (27)	0 (28)

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

Presented by Dr. Li Zhang, MD / ASCO 2024

ORR, DCR and DoR per IRRC

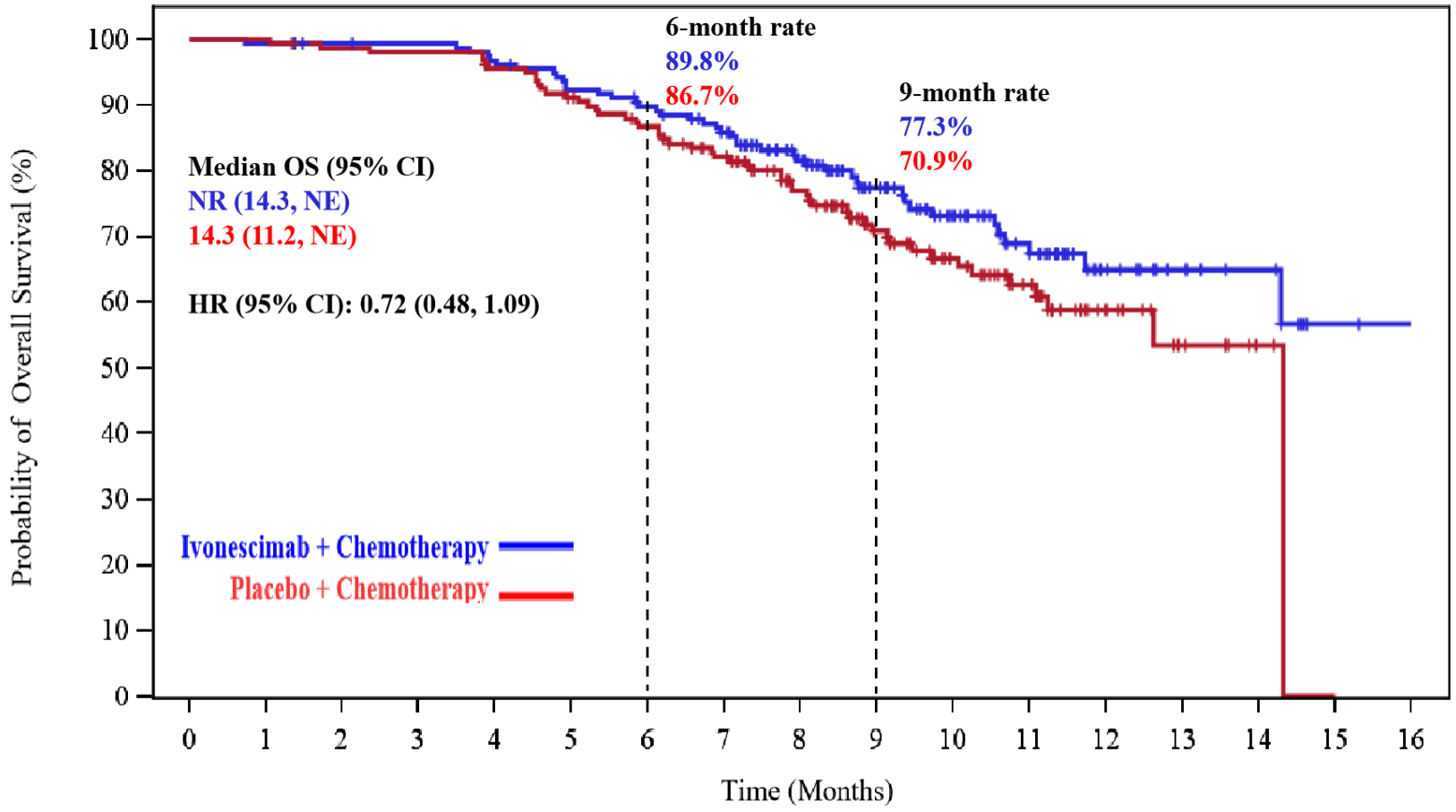


	Ivonescimab + Chemo	Placebo + Chemo
ORR, % (95% CI)	**50.6** (42.6, 58.6)	**35.4** (28.0, 43.3)
DCR, % (95% CI)	**93.1** (88.0, 96.5)	**83.2** (76.5, 88.6)
Median DoR, month (95% CI)	**6.6** (4.3, 7.6)	**4.2** (3.0, 4.7)

RD, rate difference; CI, confidence interval.
RD and CI were calculated using Miettinen-Nurminen method stratified by exposure to 3rd generation EGFR-TKI before (yes vs.no) and brain metastases (yes vs. no)

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

Overall Survival (at 30% of data maturity)



At risk (events)

Ivonescimab + Chemo	161(0)	160(1)	158(1)	157(1)	153(5)	145(12)	139(16)	129(22)	107(28)	82(33)	62(37)	46(40)	21(42)	13(42)	9(42)	1(43)	0(43)
Placebo + Chemo	161(0)	161(0)	158(2)	157(3)	152(7)	144(14)	135(21)	122(28)	99(35)	71(42)	54(46)	38(49)	16(51)	8(52)	2(52)	0(53)	

HR: 0.72 (0.48, 1.09) after 96 events, 30% data maturity

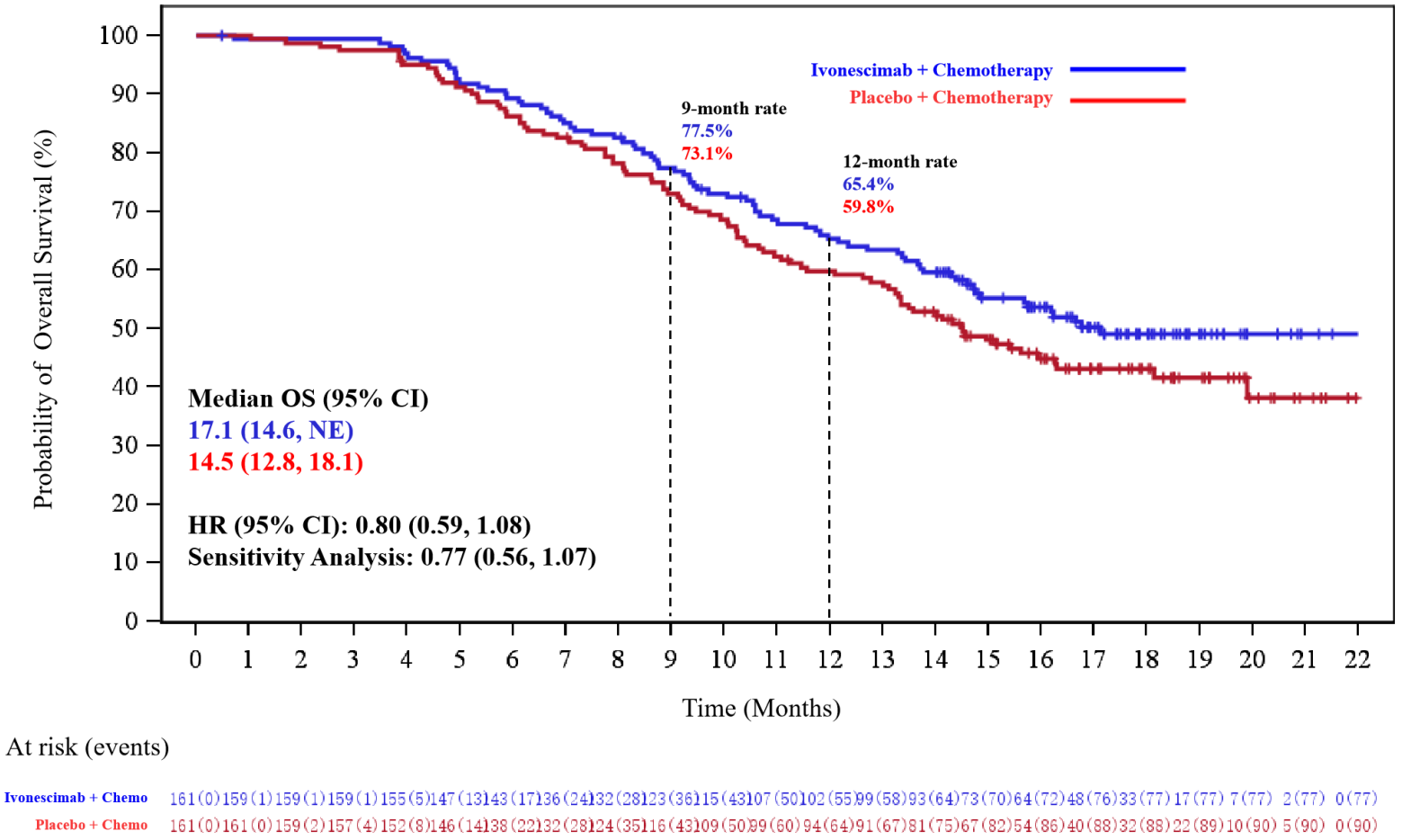
Two OS analyses were performed per request by Chinese Regulatory Authority (1st analysis at 30% and 2nd at 52% of data maturity)

Data cutoff date: June 25, 2023 (median follow-up of 10.2 months)

HR, hazard ratio; CI, confidence interval.

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

Overall Survival (at 52% of Data Maturity)



At risk (events)

Ivonescimab + Chemo	161(0)	159(1)	159(1)	159(1)	155(5)	147(13)	143(17)	136(24)	132(28)	123(36)	115(43)	107(50)	102(55)	99(58)	93(64)	73(70)	64(72)	48(76)	33(77)	17(77)	7(77)	2(77)	0(77)
Placebo + Chemo	161(0)	161(0)	159(2)	157(4)	152(8)	146(14)	138(22)	132(28)	124(35)	116(43)	109(50)	99(60)	94(64)	91(67)	81(75)	67(82)	54(86)	40(88)	32(88)	22(89)	10(90)	5(90)	0(90)

HR: 0.80 (0.59, 1.08) after 52% of data maturity

OS is consistent for both analysis

Data cutoff date: December 2023 (median follow-up of 17.6 months)

HR, hazard ratio; CI, confidence interval.

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

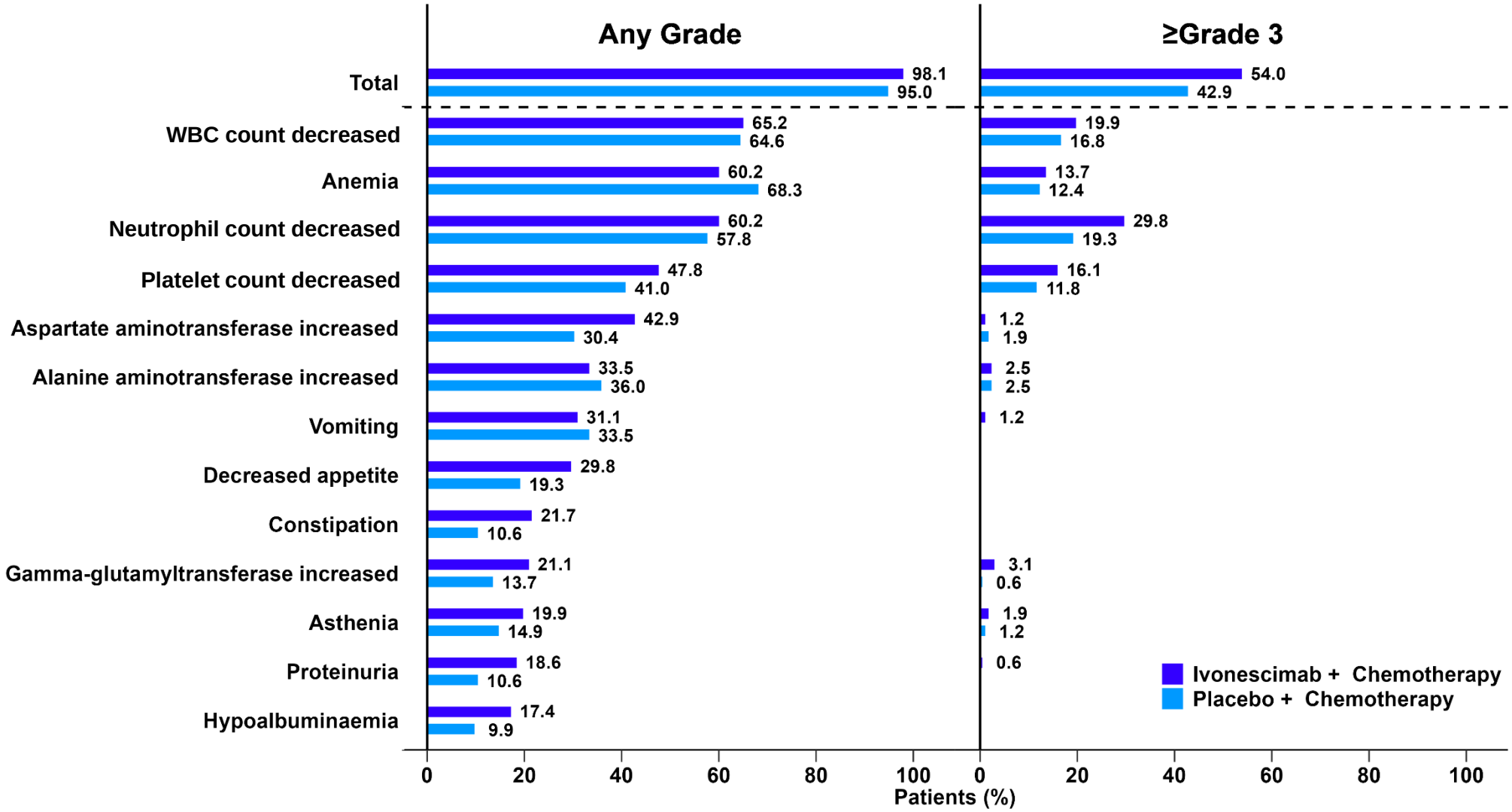
Safety Summary

TRAE, n(%)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Any grade	158 (98.1)	153 (95.0)
Grade≥3	87 (54.0)	69 (42.9)
Serious*	46 (28.6)	26 (16.1)
Led to discontinuation of ivonescimab/placebo	9 (5.6)	4 (2.5)
Led to death	0 (0.0)	0 (0.0)
Grade≥3 immune-related	10 (6.2)	4 (2.5)
Grade≥3 VEGF-related	5 (3.1)	4 (2.5)

* For any PT (excluding PD) in SAE, the PT with more than 2 cases in the experimental group compared to the control group were platelet count decreased (7.5% vs. 4.3%) and hepatic function abnormal (2.5% vs. 0%).
TRAE, treatment-related adverse event (related to any drug); PT, preferred term; PD, disease progression; SAE, serious adverse event.

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

The Most Common Adverse Events (incidence ≥ 15%)



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

Presented by Dr. Li Zhang, MD / ASCO 2024

Immune-related Adverse Events (irAE)

Categories	Ivonescimab + Chemotherapy (N=161)		Placebo + Chemotherapy (N=161)	
Preferred Term, n(%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
irAE	39 (24.2)	10 (6.2)	10 (6.2)	4 (2.5)
Hypothyroidism	17 (10.6)	1 (0.6)	0	0
Hyperthyroidism	9 (5.6)	0	0	0
Rash	6 (3.7)	4 (2.5)	2 (1.2)	1 (0.6)
Hyperglycaemia	4 (2.5)	0	3 (1.9)	0
Blood TSH increased	3 (1.9)	0	1 (0.6)	0
Interstitial lung disease	3 (1.9)	2 (1.2)	1 (0.6)	1 (0.6)
Pneumonitis	2 (1.2)	1 (0.6)	1 (0.6)	0
Dermatitis	2 (1.2)	2 (1.2)	1 (0.6)	0
Thyroid hormones increased	1 (0.6)	0	0	0
Cortisol abnormal	1 (0.6)	0	0	0
Pruritus	1 (0.6)	0	0	0
Hepatic function abnormal	1 (0.6)	1 (0.6)	0	0
Blood creatinine increased	1 (0.6)	0	0	0
Diarrhoea	0	0	1 (0.6)	1 (0.6)
Lipase increased	0	0	1 (0.6)	1 (0.6)

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

Adverse Events of Special Interest (AESI)

Categories	Ivonescimab + Chemotherapy (N=161)		Placebo + Chemotherapy (N=161)	
Preferred Term, n(%)	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
AESI	48 (29.8)	5 (3.1)	25 (15.5)	4 (2.5)
Proteinuria	28 (17.4)	1 (0.6)	13 (8.1)	0
Haemorrhage	11 (6.8)	0	8 (5.0)	0
Urinary occult blood positive	4 (2.5)	0	3 (1.9)	0
Haemoptysis	2 (1.2)	0	0	0
Epistaxis	3 (1.9)	0	1 (0.6)	0
Mouth haemorrhage	1 (0.6)	0	0	0
Gastrointestinal haemorrhage	0	0	1 (0.6)	0
Gingival bleeding	1 (0.6)	0	0	0
Eye haemorrhage	1 (0.6)	0	2 (1.2)	0
Vaginal haemorrhage	0	0	1 (0.6)	0
Occult blood positive	0	0	1 (0.6)	0
Hypertension	13 (8.1)	3 (1.9)	5 (3.1)	3 (1.9)
Arterial thromboembolism	1 (0.6)	0	1 (0.6)	1 (0.6)
Cardiac failure congestive	1 (0.6)	1 (0.6)	0	0

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

Presented by Dr. Li Zhang, MD / ASCO 2024

Conclusions

- Ivonescimab plus chemotherapy significantly improved PFS in patients who progressed on prior EGFR-TKIs treatments: **PFS HR 0.46 (95% CI: 0.34, 0.62), P<0.001**
- The prespecified subgroup analysis showed PFS benefit favoring patients receiving ivonescimab over those receiving the placebo across all subgroups.
- OS analyses show a favorable trend for prolonged OS for ivonescimab-chemotherapy
- The safety profile was generally manageable, without any unexpected adverse events and a low rate of treatment discontinuation.
- This study is being expanded globally, HARMONi (NCT06396065), to include patients from North America and Europe.

With the recent approval in China, ivonescimab plus chemotherapy is a new standard treatment option for NSCLC patients who progress after EGFR-TKI treatment

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

Acknowledgement

We thank all the patients and their families, investigators and all team members for supporting this trial.

The study was supported by Akeso Biopharma, Inc., Zhongshan, China.

JAMA

JAMA | Original Investigation

Ivonescimab Plus Chemotherapy in Non–Small Cell Lung Cancer With *EGFR* Variant
A Randomized Clinical Trial

HARMONi-A Study Investigators

IMPORTANCE For patients with non-small cell lung cancer whose disease progressed while receiving EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy, particularly third-generation TKIs, optimal treatment options remain limited.

OBJECTIVE To compare the efficacy of ivonescimab plus chemotherapy with chemotherapy alone for patients with relapsed advanced or metastatic non–small cell lung cancer with the epidermal growth factor receptor (*EGFR*) variant.

DESIGN, SETTING, AND PARTICIPANTS Double-blind, placebo-controlled, randomized, phase 3 trial at 55 sites in China enrolled participants from January 2022 to November 2022; a total of 322 eligible patients were enrolled.

INTERVENTIONS Participants received ivonescimab (n = 161) or placebo (n = 161) plus pemetrexed and carboplatin once every 3 weeks for 4 cycles, followed by maintenance therapy of ivonescimab plus pemetrexed or placebo plus pemetrexed.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intention-to-treat population assessed by an independent radiographic review committee (IRRC) per Response Evaluation Criteria in Solid Tumors version 1.1. The results of the first planned interim analysis are reported.

RESULTS Among 322 enrolled patients in the ivonescimab and placebo groups, the median age was 59.6 vs 59.4 years and 52.2% vs 50.9% of patients were female. As of March 10, 2023, median follow-up time was 7.89 months. Median progression-free survival was 7.1 (95% CI, 5.9-8.7) months in the ivonescimab group vs 4.8 (95% CI, 4.2-5.6) months for placebo (difference, 2.3 months; hazard ratio [HR], 0.46 [95% CI, 0.34-0.62]; $P < .001$). The prespecified subgroup analysis showed progression-free survival benefit favoring patients receiving ivonescimab over placebo across almost all subgroups, including patients whose disease progressed while receiving third-generation EGFR-TKI therapy (HR, 0.48 [95% CI 0.35-0.66]) and those with brain metastases (HR, 0.40 [95% CI, 0.22-0.73]). The objective response rate was 50.6% (95% CI, 42.6%-58.6%) with ivonescimab and 35.4% (95% CI, 28.0%-43.3%) with placebo (difference, 15.6% [95% CI, 5.3%-26.0%]; $P = .006$). The median overall survival data were not mature; at data cutoff, 69 patients (21.4%) had died. Grade 3 or higher treatment-emergent adverse events occurred in 99 patients (61.5%) in the ivonescimab group vs 79 patients (49.1%) in the placebo group, the most common of which were chemotherapy-related. Grade 3 or higher immune-related adverse events occurred in 10 patients (6.2%) in the ivonescimab group vs 4 (2.5%) in the placebo group. Grade 3 or higher vascular endothelial growth factor–related adverse events occurred in 5 patients (3.1%) in the ivonescimab group vs 4 (2.5%) in the placebo group.

CONCLUSIONS Ivonescimab plus chemotherapy significantly improved progression-free survival with tolerable safety profile in TKI-treated non–small cell lung cancer.

TRIAL REGISTRATION ClinicalTrials.gov identifier: NCT05184712

Visual Abstract

Supplemental content

JAMA. doi:10.1001/jama.2024.10613
Published online May 31, 2024.

Group Information: The HARMONi-A Study Investigators appear at the end of the article.

Corresponding Author: Li Zhang, MD, Sun Yat-sen University Cancer Center, Guangzhou, No. 651 Dong Feng Road E., Guangdong 510060, China (zhangli@sysucc.org.cn).

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

Presented by Dr. Li Zhang, MD / ASCO 2024