Final Overall Survival Analysis : HARMONi-A Study
Ivonescimab + chemotherapy versus Chemotherapy
In patients with *EGFR*-mutant NSCLC progressed on EGFR TKI

Presenter: **Xiuning Le**, MD PhD (MD Anderson Cancer Center)

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], Wenting Li[15], Baiyong Li[15], Michelle Xia[15]

[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]Akeso Biopharma, Inc., Zhongshan, China.

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Disclosure

Xiuning Le, MD, PhD

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Background

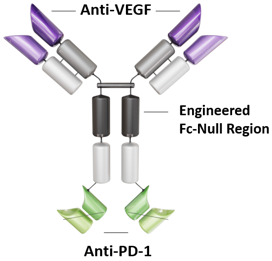
- *EGFR* mutations occur in non-small cell lung cancers (NSCLC) in 15-20% in Whites, and 40-50% in Asians. It is estimated to be 600,000 to 1 million new cases per year world-wide.
- The standard first-line therapy for advanced/metastatic *EGFR*-mutant NSCLC has been EGFR TKIs. However, acquired resistance to EGFR TKIs occur inevitably, and subsequent treatment options remain limited, with chemotherapy being the standard-of-care in the US and China.
- Adding anti-PD1/L1 checkpoints to chemotherapy have shown no added benefit in patients progressed on EGFR TKIs, as both KEYNOTE-789[1] and CHECKMATE-722[2] studies failed to show improved efficacy compared to chemotherapy.
- When an anti-angiogenic agent was added to anti-PD-1/L1 checkpoints plus chemotherapy, such as in IMPOWER-150[3] and ORIENT-31[4] studies, the combination have demonstrated that the addition of ant-angiogenic and anti-PD-1/L1 to chemotherapy significantly improved PFS in this population, but without the significant OS benefit.

[1]Yang JC, et al. J Clin Oncol. 2023;41(17); [2]Mok T, et al. J Clin Oncol. 2024;42(11):1252-1264; [3]Socinski MA, et al. N Engl J Med. 2018;378(24):2288-2301; [4]Lu S, et al. Lancet Oncol. 2022;23(9):1167-1179.

EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; ICI, immune checkpoint inhibitor; PD-1, programmed death-1; PD-L1, programmed death ligand 1; PFS, progression-free survival.

Background

- Ivonescimab is a first in class bispecific antibody that cooperatively targets both programmed cell death protein-1 (PD-1) and vascular endothelial growth factor (VEGF).
- Clinical trials (HARMONi series) evaluating ivonescimab in NSCLC have been comprehensively deployed across various treatment stages of lung cancer, and across Asian, North American and European countries .



Akesobio

China Phase 3

Conducted in China Fully Sponsored and Managed by Akeso

EGFR-TKI progressed NSCLC: Approvedby NMPA	HARMONi-A
1L PD-L1+ NSCLC: Approved by NMPA	HARMONi-2
1L squamous NSCLC: Submitted	HARMONi-6
IO-R NSCLC: Ongoing	HARMONi-8A

Summit therapeutics

Globla Phase 3

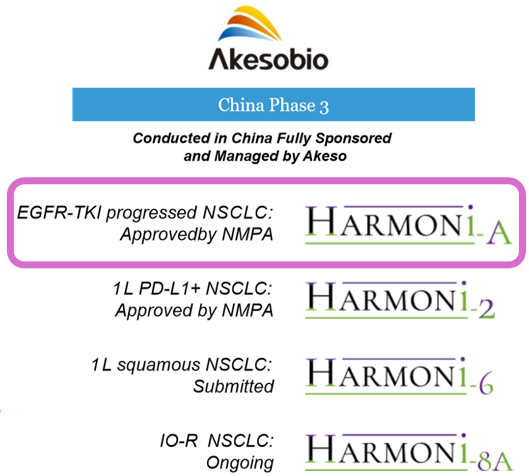
Planned and Ongoing Studies Sponsored by Summit Therapeutics

EGFR-TKI progressed NSCLC: plan to be submitted	HARMONi
1L PD-L1-high NSCLC: Ongoing	HARMONi-7
1L NSCLC all comers: Ongoing	HARMONi-3

NMPA: National Medical Products Administration.

Background

- In an earlier PFS interim analysis of HARMONi-A[1], ivonescimab plus chemotherapy significantly prolonged PFS compared with chemotherapy alone in patients with EGFR+ NSCLC progressed with EGFR-TKI treatment: **PFS HR 0.46 (95% CI: 0.34, 0.62), p<0.001**
- **Here, we report the overall survival (OS) results in the final and only formal OS analysis of this study.**



Clinical trial information: NCT05184712

[1]Fang W, Zhao Y, Luo Y, et al. Ivonescimab Plus Chemotherapy in Non-Small Cell Lung Cancer With EGFR Variant: A Randomized Clinical Trial (HARMONi-A). JAMA. 2024. doi:10.1001/jama.2024.10613.

Study design

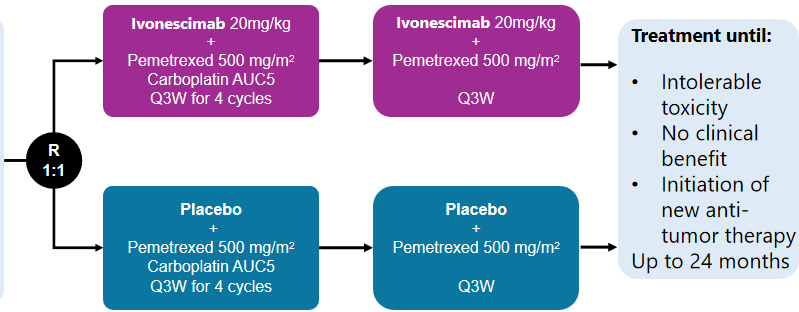
Enrollment：Jan 2022 - Nov 2022

Key Eligibility Criteria

- non-squamous 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)



Endpoint

- Primary endpoint: progression-free survival (PFS) by IRRC
- Key secondary endpoint: overall survival (OS)

EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; Q3W, every 3 weeks; IRRC, independent radiologic review committee.

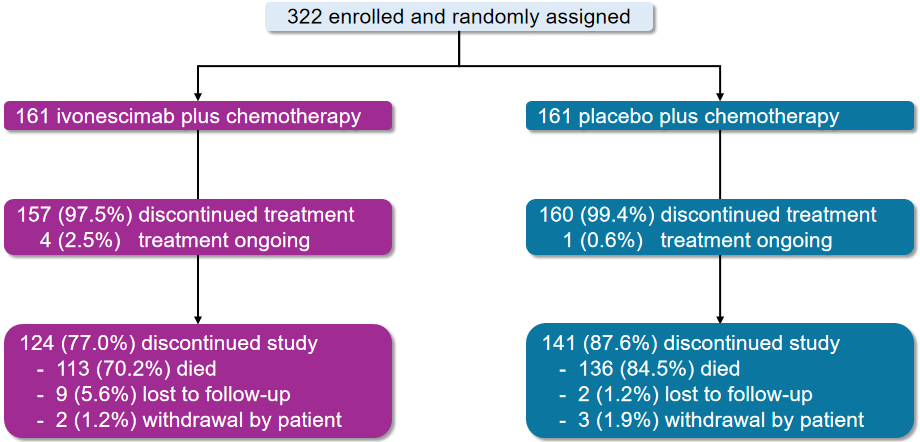
Statistical Analyses

- PFS was tested first at two-sided alpha level of 0.05, with OS tested at the same level only after PFS achieved statistical significance.
- PFS reached statistical significance at the interim analysis, and the closed sequential testing procedure was used in the final analysis of OS.
- The final analysis of OS for the study HARMONi-A will coincide with the global study HARMONi (NCT06396065) .

PFS, progression-free survival; OS, overall survival.

Patient disposition

Data cut-off date: April 2025 (median follow-up of 32.5 months)



Baseline characteristics

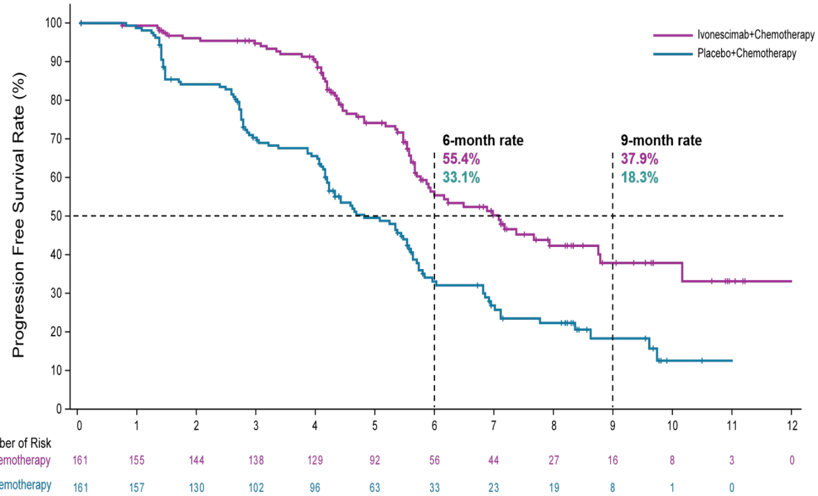
Characteristics		Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Age, n(%)	Median (rang), years	59.6 (32.3, 74.9)	59.4 (36.2, 74.2)
	<65	111 (68.9)	110 (68.3)
	≥65	50 (31.1)	51 (31.7)
Sex, n(%)	Male	77 (47.8)	79 (49.1)
	Female	84 (52.2)	82 (50.9)
ECOG, n(%)	0	24 (14.9)	34 (21.1)
	1	137 (85.1)	127 (78.9)
Smoking status, n(%)	Never	112 (69.6)	114 (70.8)
	Current or former	49 (30.4)	47 (29.2)
Stage, n(%)	IIIB or IIIC	3 (1.9)	5 (3.1)
	IV	158 (98.1)	156 (96.9)
Metastasis, n(%)	Brain metastasis	35 (21.7)	37 (23.0)
	Liver metastasis	21 (13.0)	17 (10.6)
	≥3 distant metastases	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 3rd Gen EGFR-TKI treatment, n(%)	Not received	22 (13.7)	24 (14.9)
	Received	139 (86.3)	137 (85.1)

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

Outcomes of interim analysis per IRRC

Data cut-off date: March 2023[1]
(median follow-up of 7.9 months)

	Ivonescimab + chemotherapy	Placebo + chemotherapy
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)
mPFS, months (95% CI)	**7.1** (5.9, 8.7)	**4.8** (4.2, 5.6)
HR (95% CI)	**0.46** (0.34, 0.62) **p<0.001**	



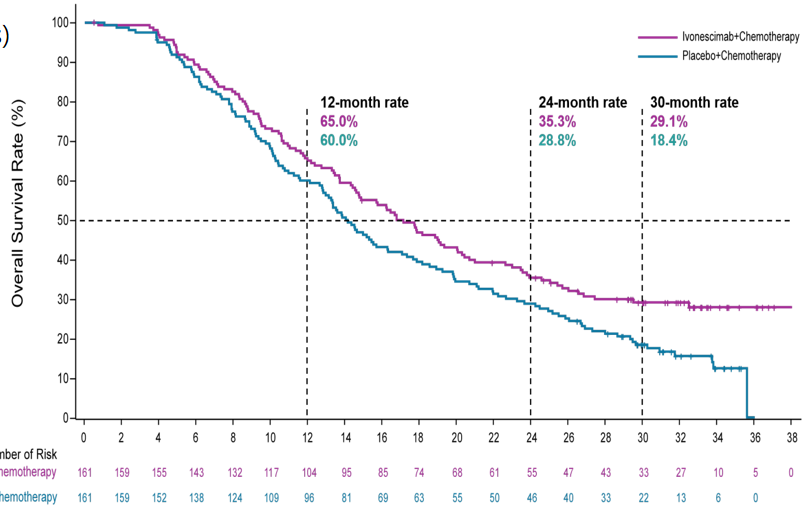
[1]Li Zhang, et al. ASCO 2024 Oral Abstract Session 8508.
IRRC, independent radiology review committee; ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval.

Final analysis of overall survival (OS)

Data cut-off date: April 2025
(median follow-up of 32.5 months)

	Ivonescimab + chemotherapy	Placebo + chemotherapy
ORR[1], % (95% CI)	**50.6** (42.6, 58.6)	**35.4** (28.0, 43.3)
DCR[1], % (95% CI)	**93.1** (88.0, 96.5)	**83.2** (76.5, 88.6)
mPFS[1], months (95% CI)	**7.1** (5.9, 8.7)	**4.8** (4.2, 5.6)
PFS HR[1] (95% CI)	**0.46** (0.34, 0.62) **p<0.001**	
mOS[2], months (95% CI)	**16.8** (14.5, 20.0)	**14.1** (12.8, 16.3)
OS HR[2] (95% CI)	**0.74** (0.58, 0.95) **p=0.019** (two-side)	

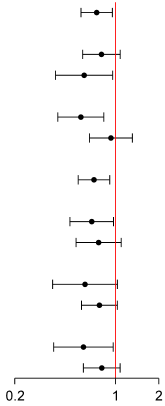
[1]Interim analysis
[2]Final analysis



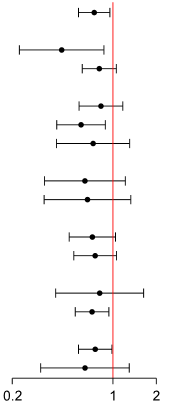
HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.05 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation; HR, hazard ratio; CI, confidence interval.

OS subgroup analysis

	Events/Number of patients		HR (95% CI)
	Ivonescimab +Chemo	Placebo +Chemo	
All Subjects	113/161	136/161	0.74 (0.58, 0.95)
Age			
<65 years	81/111	92/110	0.80 (0.59, 1.08)
>=65 years	32/50	44/51	0.61 (0.38, 0.96)
Sex			
Male	49/77	69/79	0.58 (0.40, 0.83)
Female	64/84	67/82	0.93 (0.66, 1.31)
Stage			
IV	111/158	134/156	0.71 (0.55, 0.91)
Metastasis Sites			
<3	56/87	74/93	0.68 (0.48, 0.97)
≥3	57/74	62/68	0.76 (0.53, 1.10)
Brain Metastasis			
Presence	25/35	35/37	0.61 (0.37, 1.03)
Absence	88/126	101/124	0.77 (0.58, 1.03)
Smoking			
Yes	30/49	40/47	0.60 (0.37, 0.96)
No	83/112	96/114	0.80 (0.60, 1.08)



	Events/Number of patients		HR (95% CI)
	Ivonescimab +Chemo	Placebo +Chemo	
All Subjects	113/161	136/161	0.74 (0.58, 0.95)
ECOG			
0	12/24	29/34	0.44 (0.22, 0.87)
1	101/137	107/127	0.80 (0.61, 1.06)
EGFR Mutation			
19Del	65/92	61/78	0.83 (0.58, 1.17)
L858R	41/60	72/78	0.60 (0.41, 0.89)
Other	26/35	20/25	0.73 (0.41, 1.31)
T790M Mutation			
Negative	16/26	22/27	0.64 (0.33, 1.22)
Positive	19/26	14/18	0.67 (0.33, 1.33)
Previously EGFR-TKI			
One-Line	48/71	68/82	0.72 (0.50, 1.04)
Two or More Lines	65/90	68/79	0.75 (0.54, 1.06)
Liver Metastasis			
Presence	17/21	15/17	0.81 (0.40, 1.63)
Absence	96/140	121/144	0.72 (0.55, 0.94)
Previous 3rd Gen EGFR-TKI			
Received	100/139	117/137	0.75 (0.58, 0.98)
Not Received	13/22	19/24	0.64 (0.32, 1.30)

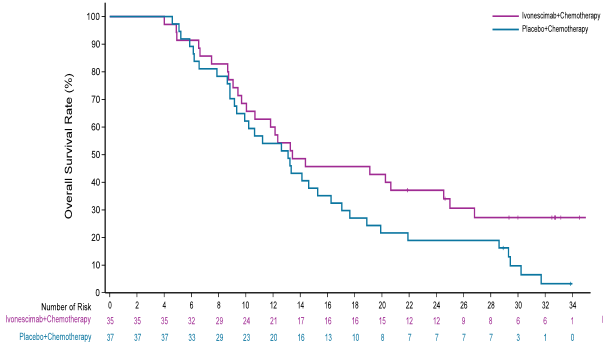


Data cut-off date: April 2025 (median follow-up of 32.5 months).

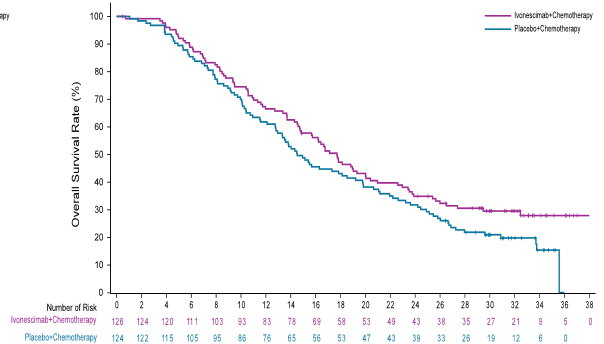
HR, hazard ratio; CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; Gen, generation.

OS benefit in patients *with* and *without* brain metastasis

With brain metastasis: HR 0.61 (0.37, 1.03)



Without brain metastasis: HR 0.77 (0.58, 1.03)

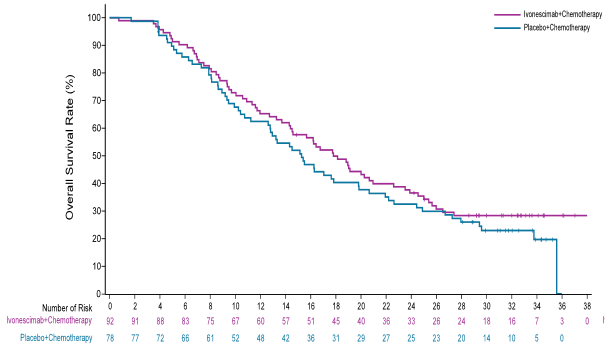


Data cut-off date: April 2025 (median follow-up of 32.5 months).

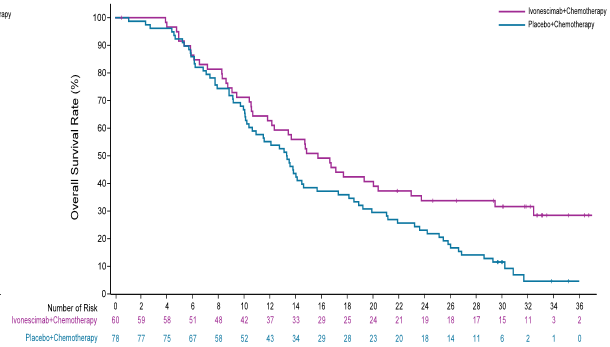
HR, hazard ratio.

OS benefit in EGFR *19Del* and *L858R* subgroups

EGFR 19Del: HR 0.83 (0.58, 1.17)



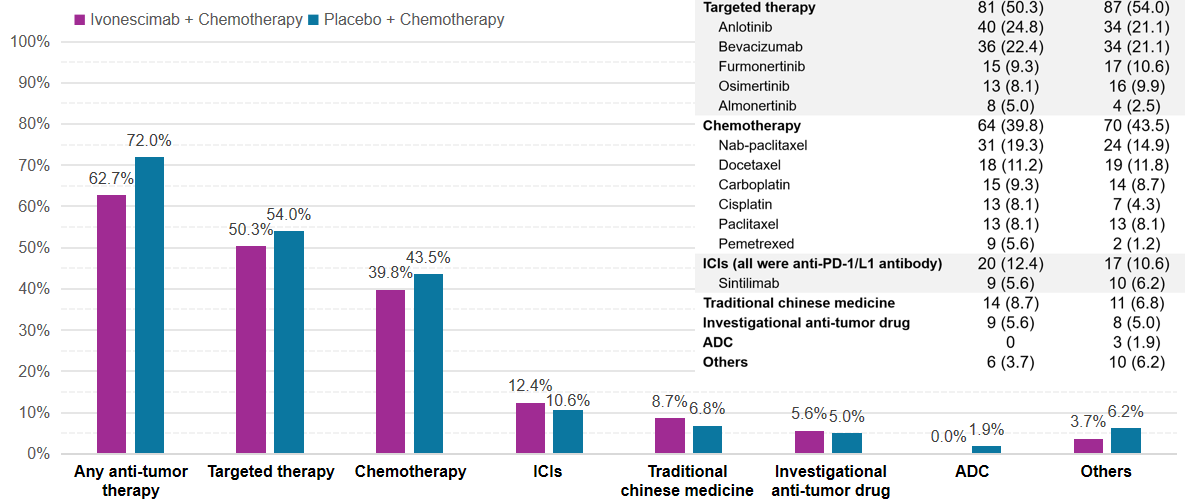
EGFR L858R: HR 0.60 (0.41, 0.89)



Data cut-off date: April 2025 (median follow-up of 32.5 months).

HR, hazard ratio.

Subsequent anti-tumor therapy



Category	Ivonescimab + Chemotherapy (N=161) n (%)	Placebo + Chemotherapy (N=161) n (%)
Any anti-tumor therapy	101 (62.7)	116 (72.0)
Targeted therapy	81 (50.3)	87 (54.0)
Anlotinib	40 (24.8)	34 (21.1)
Bevacizumab	36 (22.4)	34 (21.1)
Furmonertinib	15 (9.3)	17 (10.6)
Osimertinib	13 (8.1)	16 (9.9)
Almonertinib	8 (5.0)	4 (2.5)
Chemotherapy	64 (39.8)	70 (43.5)
Nab-paclitaxel	31 (19.3)	24 (14.9)
Docetaxel	18 (11.2)	19 (11.8)
Carboplatin	15 (9.3)	14 (8.7)
Cisplatin	13 (8.1)	7 (4.3)
Paclitaxel	13 (8.1)	13 (8.1)
Pemetrexed	9 (5.6)	2 (1.2)
ICIs (all were anti-PD-1/L1 antibody)	20 (12.4)	17 (10.6)
Sintilimab	9 (5.6)	10 (6.2)
Traditional chinese medicine	14 (8.7)	11 (6.8)
Investigational anti-tumor drug	9 (5.6)	8 (5.0)
ADC	0	3 (1.9)
Others	6 (3.7)	10 (6.2)

Data cut-off date: April 2025 (median follow-up of 32.5 months).

ICI, immune checkpoint inhibitor; ADC, antibody-drug conjugate.

Safety summary - TEAE

TEAE, n(%)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
	Data cut-off date: March 2023 (median follow-up of 7.9 months)		Data cut-off date: April 2025 (median follow-up of 32.5 months)	
Any grade	160 (99.4)	157 (97.5)	160 (99.4)	157 (97.5)
Grade≥3	99 (61.5)	79 (49.1)	108 (67.1)	88 (54.7)
SAE	66 (41.0)	41 (25.5)	78 (48.4)	52 (32.3)
Led to discontinuation of any drug	13 (8.1)	8 (5.0)	19 (11.8)	13 (8.1)
Led to death (excluding disease progression)	0	1 (0.6)	2 (1.2)	3 (1.9)

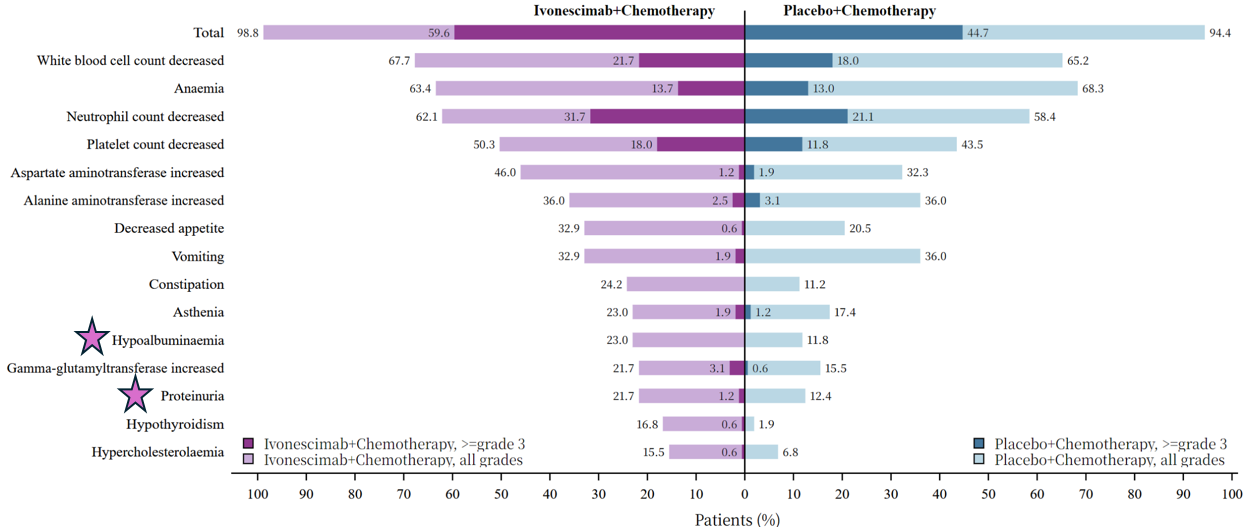
TEAE, treatment-emergent adverse event; SAE, serious adverse event.

Safety summary - TRAE

TRAE, n(%)	Data cut-off date: March 2023 (median follow-up of 7.9 months)		Data cut-off date: April 2025 (median follow-up of 32.5 months)	
	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)	Ivonescimab + Chemotherapy (N=161)	Placebo + Chemotherapy (N=161)
Any grade	158 (98.1)	153 (95.0)	159 (98.8)	152 (94.4)
Grade≥3	87 (54.0)	69 (42.9)	96 (59.6)	72 (44.7)
SAE	46 (28.6)	26 (16.1)	78 (32.3)	29 (18.0)
Led to discontinuation of any drug	11 (6.8)	7 (4.3)	18 (11.2)	10 (6.2)
Led to death (excluding disease progression)	0	0	0	1 (0.6)

TRAE, treatment-related adverse event (related to any drug as "related", "probably related", "possibly related", and missing relationship is considered as possibly related); SAE, serious adverse event.

The most common TRAEs (incidence≥15%)



Data cut-off date: April 2025 (median follow-up of 32.5 months).

The incidence rates of hypertension and epistaxis are 17 (10.6%) vs 6 (3.7%) and 3 (1.9%) vs 1 (0.6%) respectively, which are clinically controllable; TRAE, treatment-related adverse event (related to any drug as "related", "probably related", "possibly related", and missing relationship is considered as possibly related).

Conclusions

- Ivonescimab plus chemotherapy demonstrated a clinically meaningful and statistically significant OS benefit in patients with *EGFR*-mutant NSCLC post EGFR-TKI therapy while the combination therapy of anti-PD-1 and anti-VEGF failed the OS:

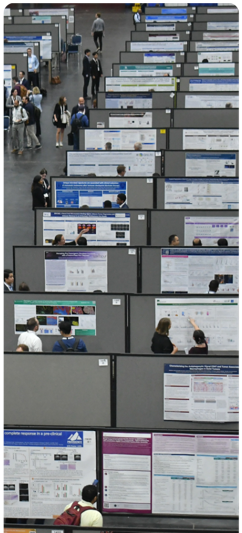
  OS HR 0.74 (95% CI : 0.58, 0.95), p=0.019 (key secondary endpoint)

  PFS HR 0.46 (95% CI: 0.34, 0.62), p<0.001 (primary endpoint)

- The safety remained favorable, with no new safety signals.
- With the approval by NMPA in China (May 2024), ivonescimab plus chemotherapy can provide a new standard of care for patients who progressed on prior EGFR TKIs.

The global study HARMONi (NCT06396065) will submit a New Drug Application (NDA) to the U.S. FDA this year for ivonescimab plus chemotherapy for the treatment of EGFR-mutant NSCLC progressed on 3rd generation EGFR-TKIs

EGFR, epidermal growth factor receptor; TKI, tyrosine-kinase inhibitor; NMPA: National Medical Products Administration; FDA: Food and Drug Administration.



Acknowledgement

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- We thank the investigators and their team members at each of the 55 study sites
- This study was sponsored by Akeso Biopharma, Inc.