2024 ASCO® ANNUAL MEETING

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)

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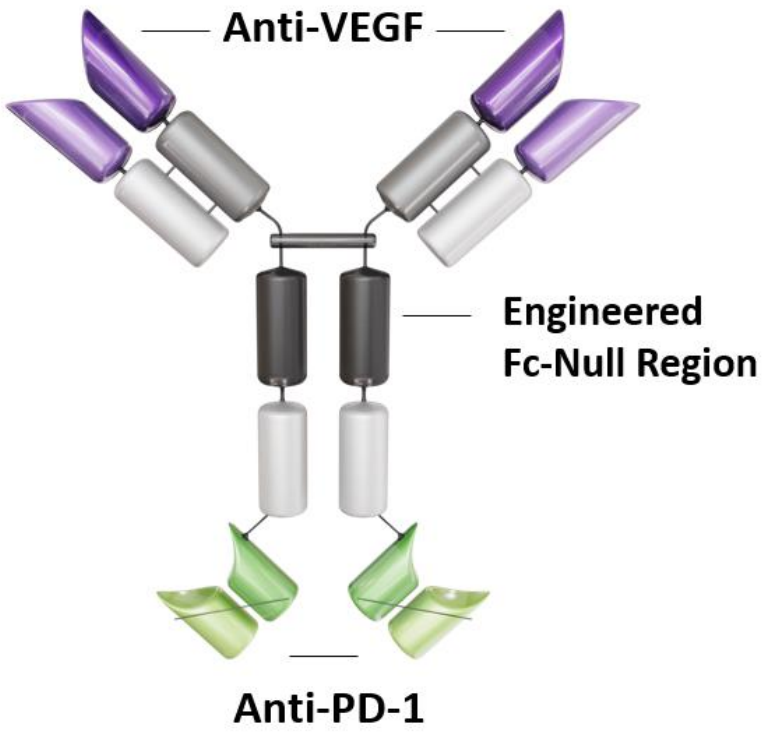
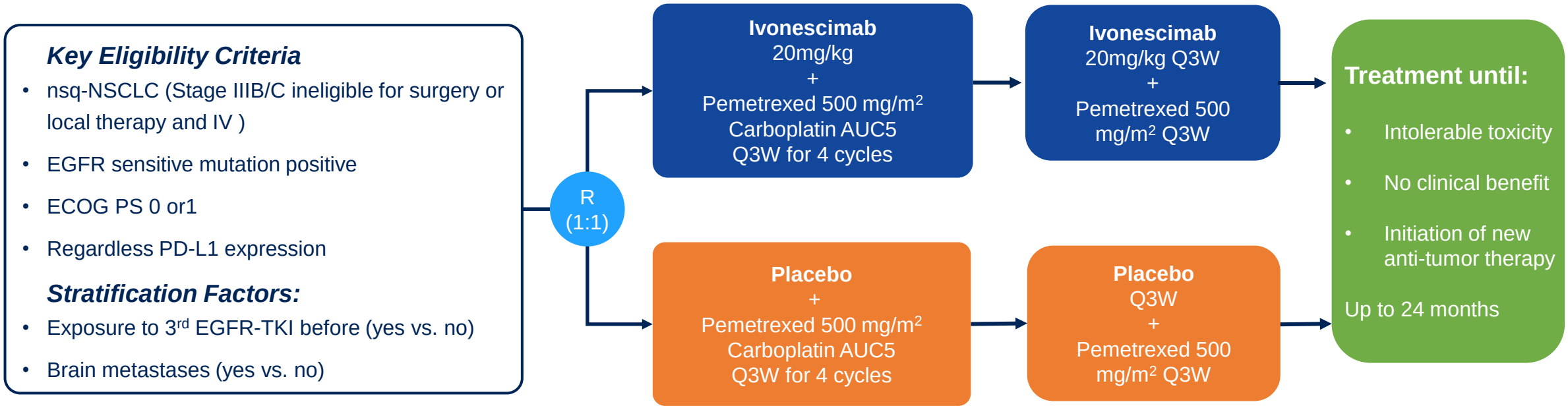
Background



- 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.

HARMONi-A Study Design



Endpoints

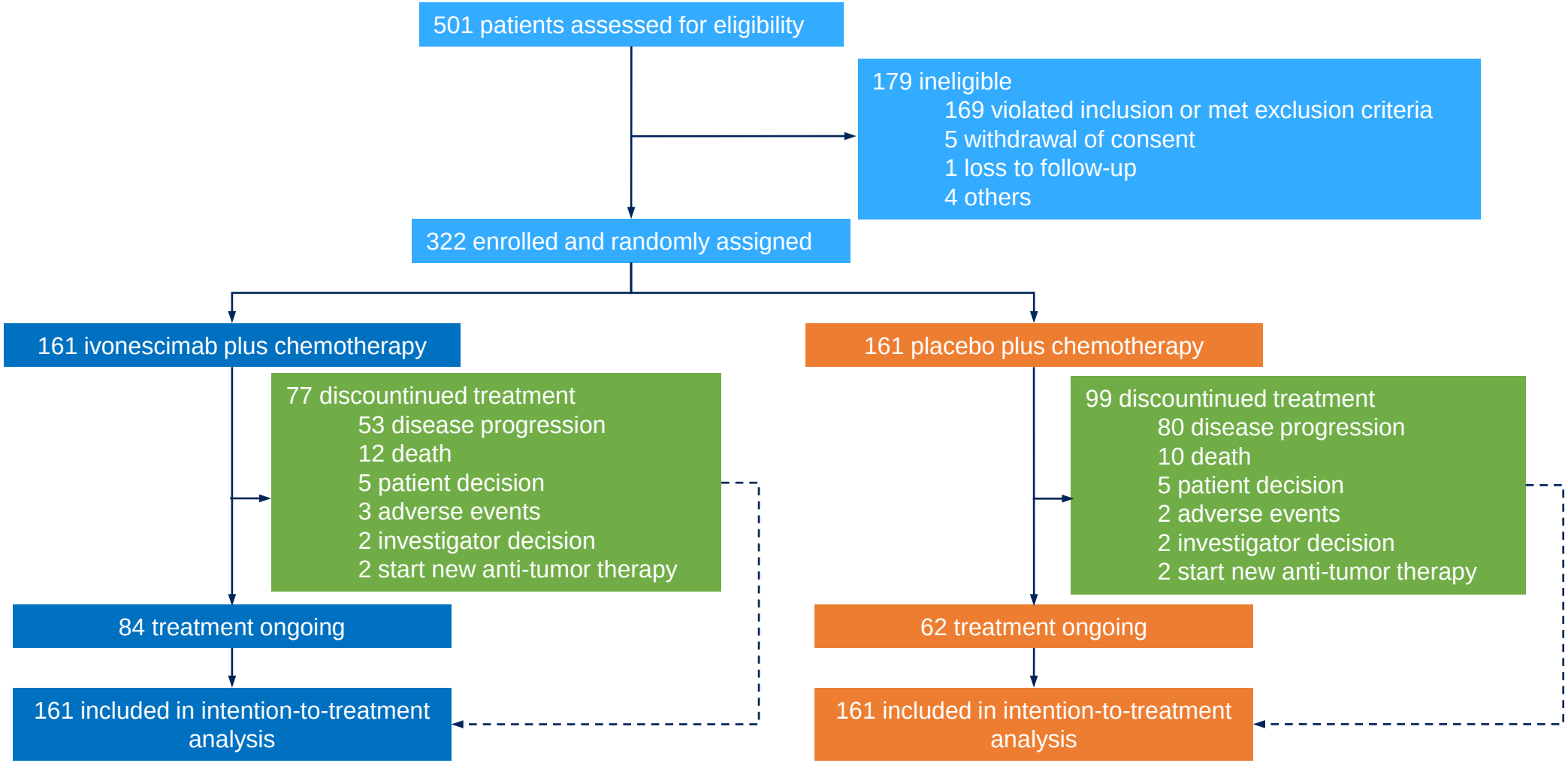
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

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.

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

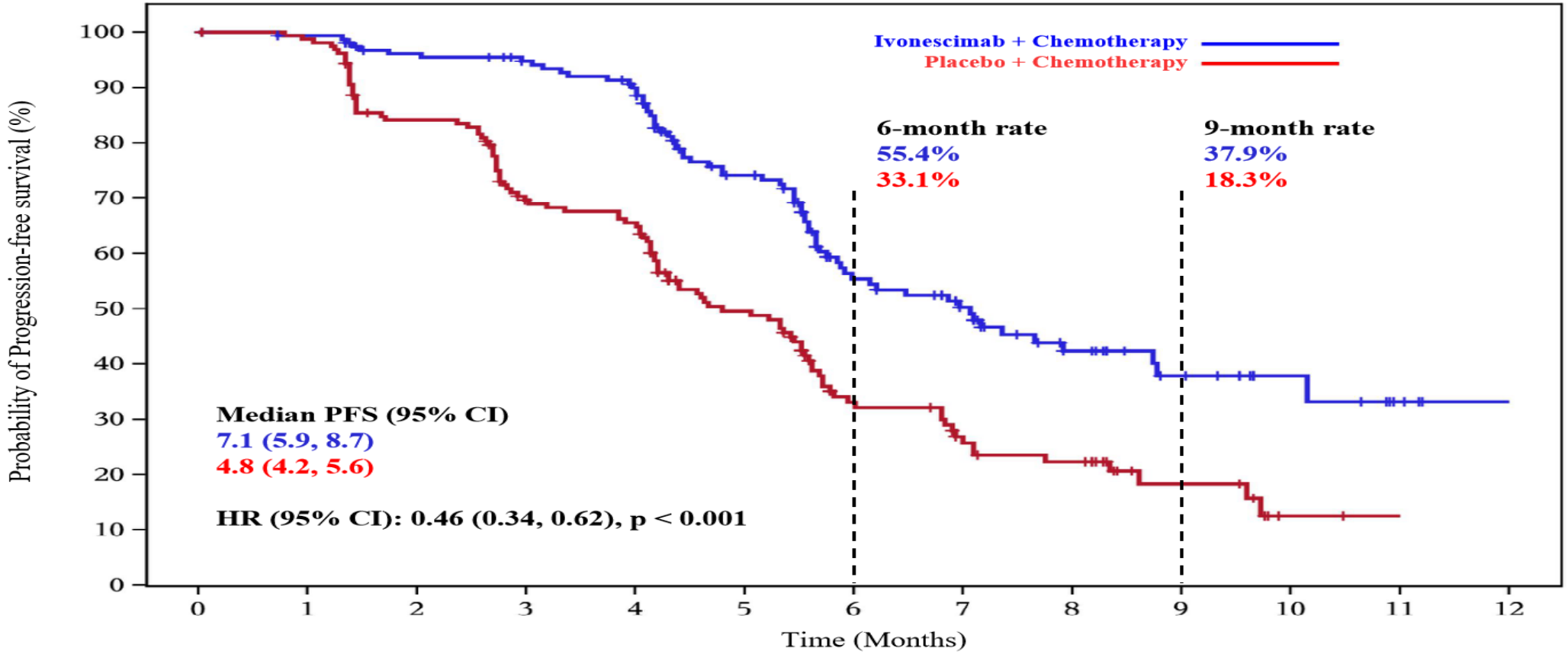


Baseline Characteristics

	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.

Study Met Primary Endpoint of PFS per IRRC



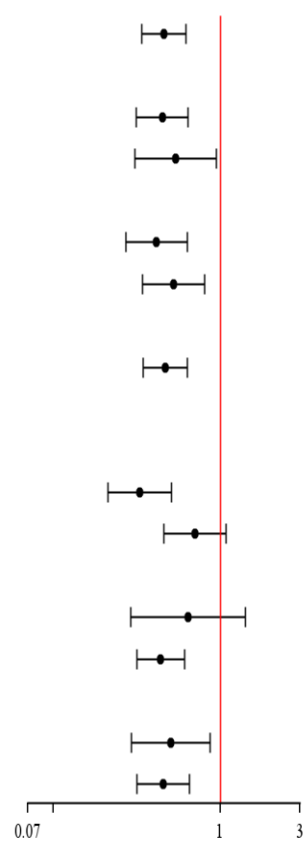
At risk (events)

Ivonescimab + Chemo	161 (0)	155 (1)	144 (6)	138 (8)	129 (15)	92 (36)	56 (57)	44 (62)	27 (68)	16 (70)	8 (70)	3 (71)	0 (71)
Placebo + Chemo	161 (0)	157 (2)	130 (25)	102 (47)	96 (53)	63 (75)	33 (94)	23 (101)	19 (104)	8 (106)	1 (108)	0 (108)	

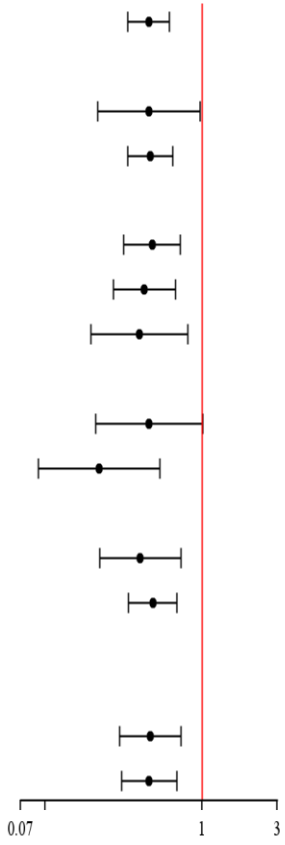
HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.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

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)

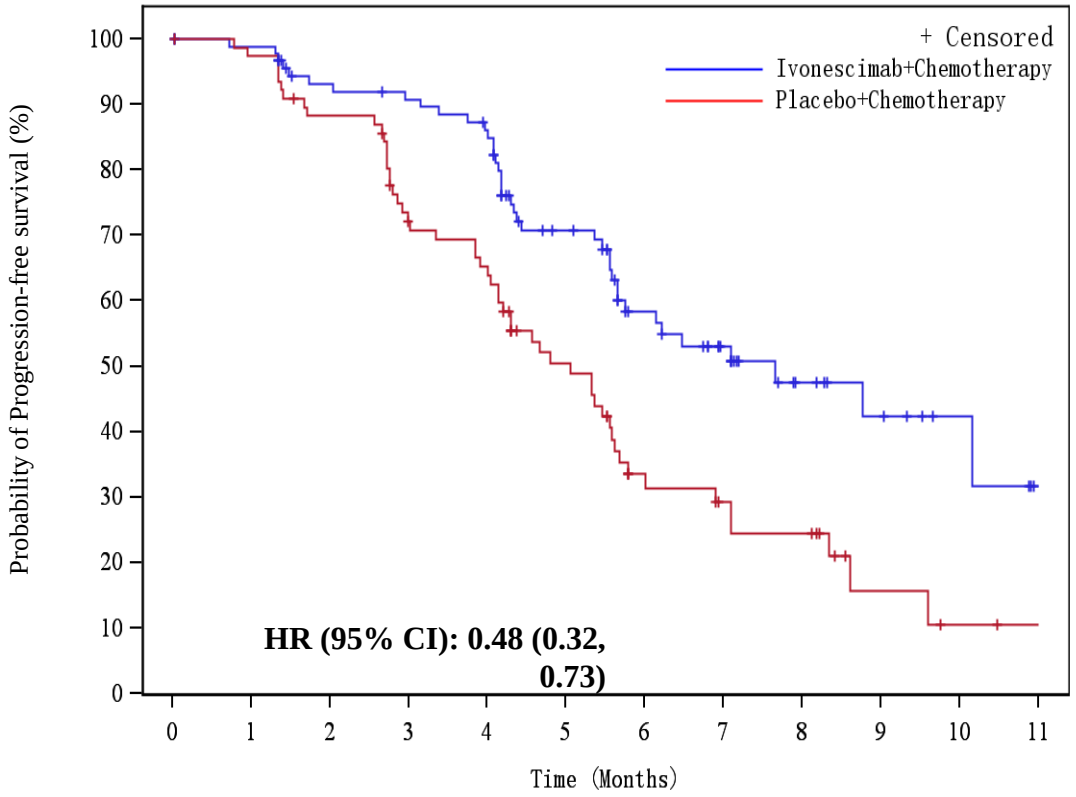


	No. of events/No. of patients		HR (95% CI)
	Ivonescimab + Chemo	Placebo + Chemo	
All Subjects	71/161	108/161	0.46 (0.34, 0.62)
Baseline ECOG Score			
0	10/24	22/34	0.46 (0.22, 0.97)
1	61/137	86/127	0.47 (0.33, 0.65)
Baseline EGFR Mutation			
19Del	39/92	53/78	0.48 (0.32, 0.73)
L858R	29/60	54/78	0.43 (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)



PFS of 19del and L858R

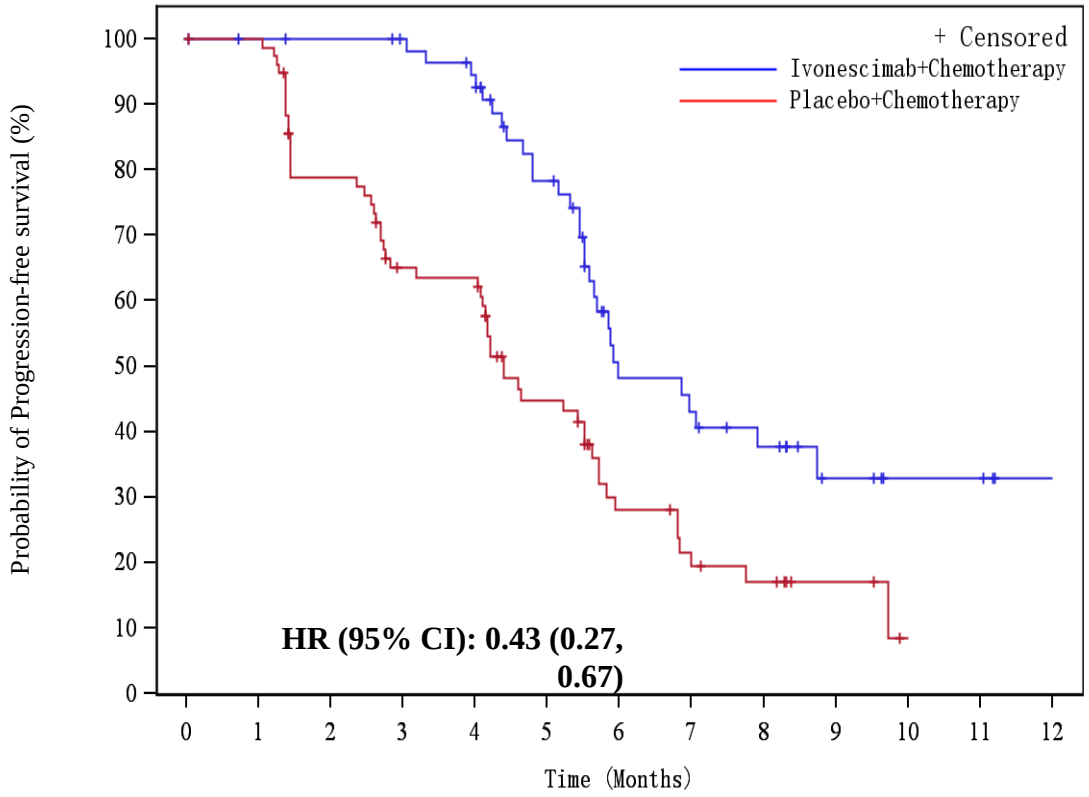
PFS Kaplan Meier Curve Evaluated by IRRC
with 19del



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

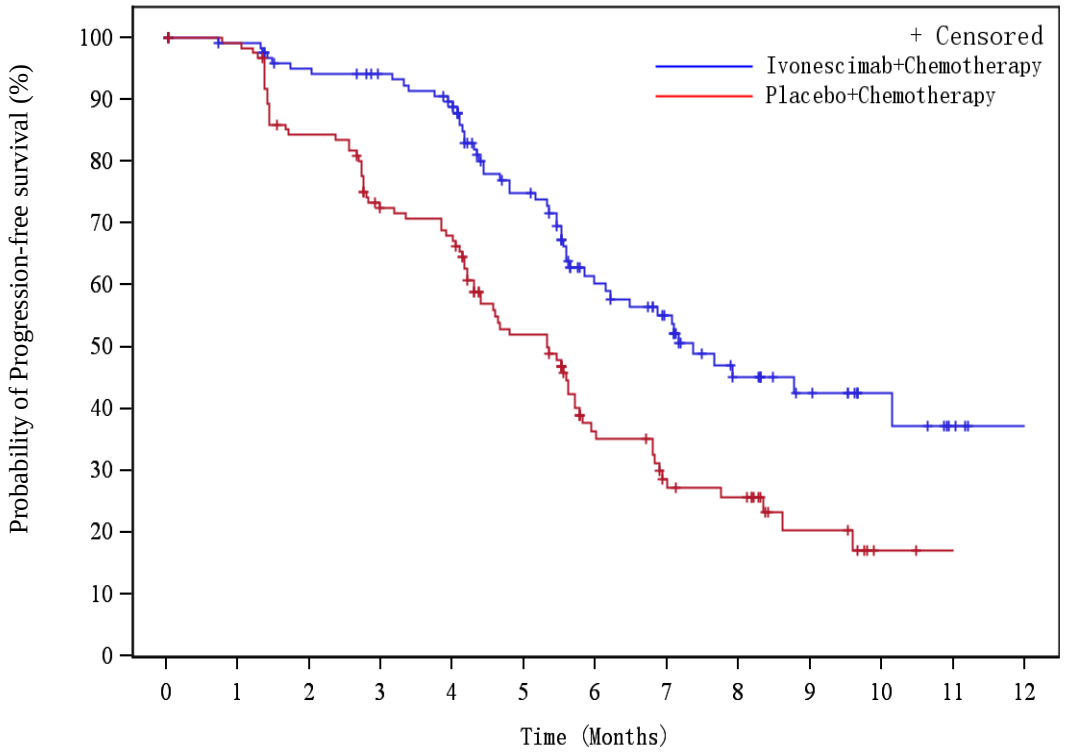


Number of Subjects at Risk (Number of Events)

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)		

PFS by Presence of Brain Metastases

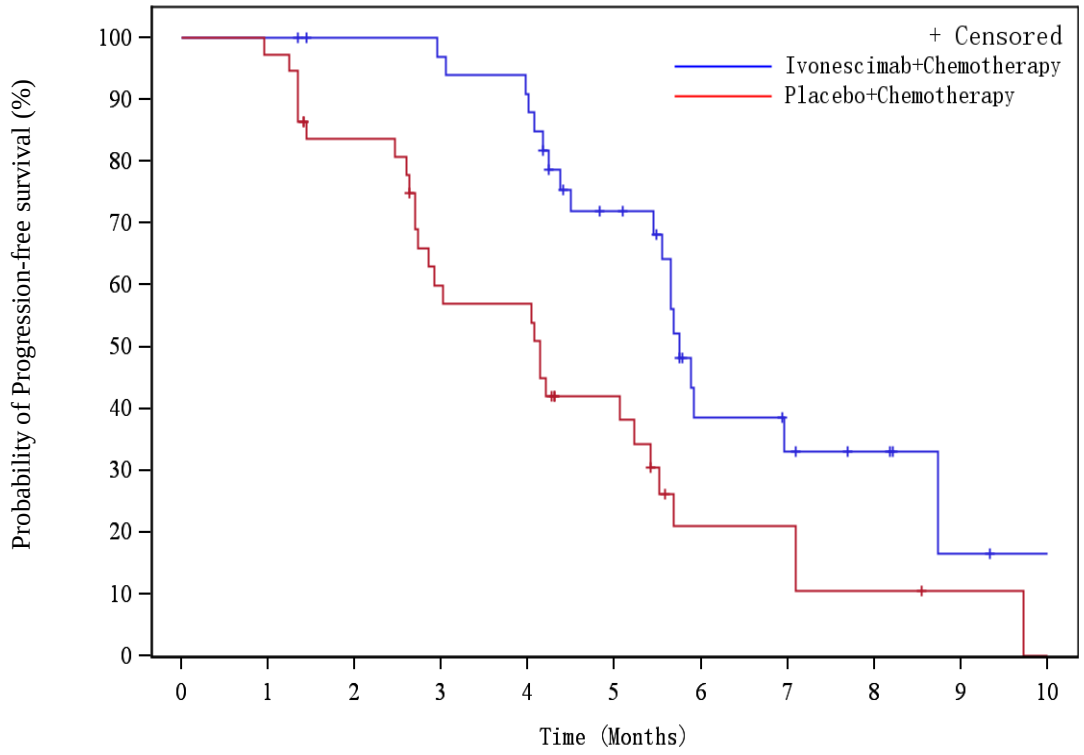
PFS Kaplan Meier Curve Evaluated by IRRC
without Brain Metastasis



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)	

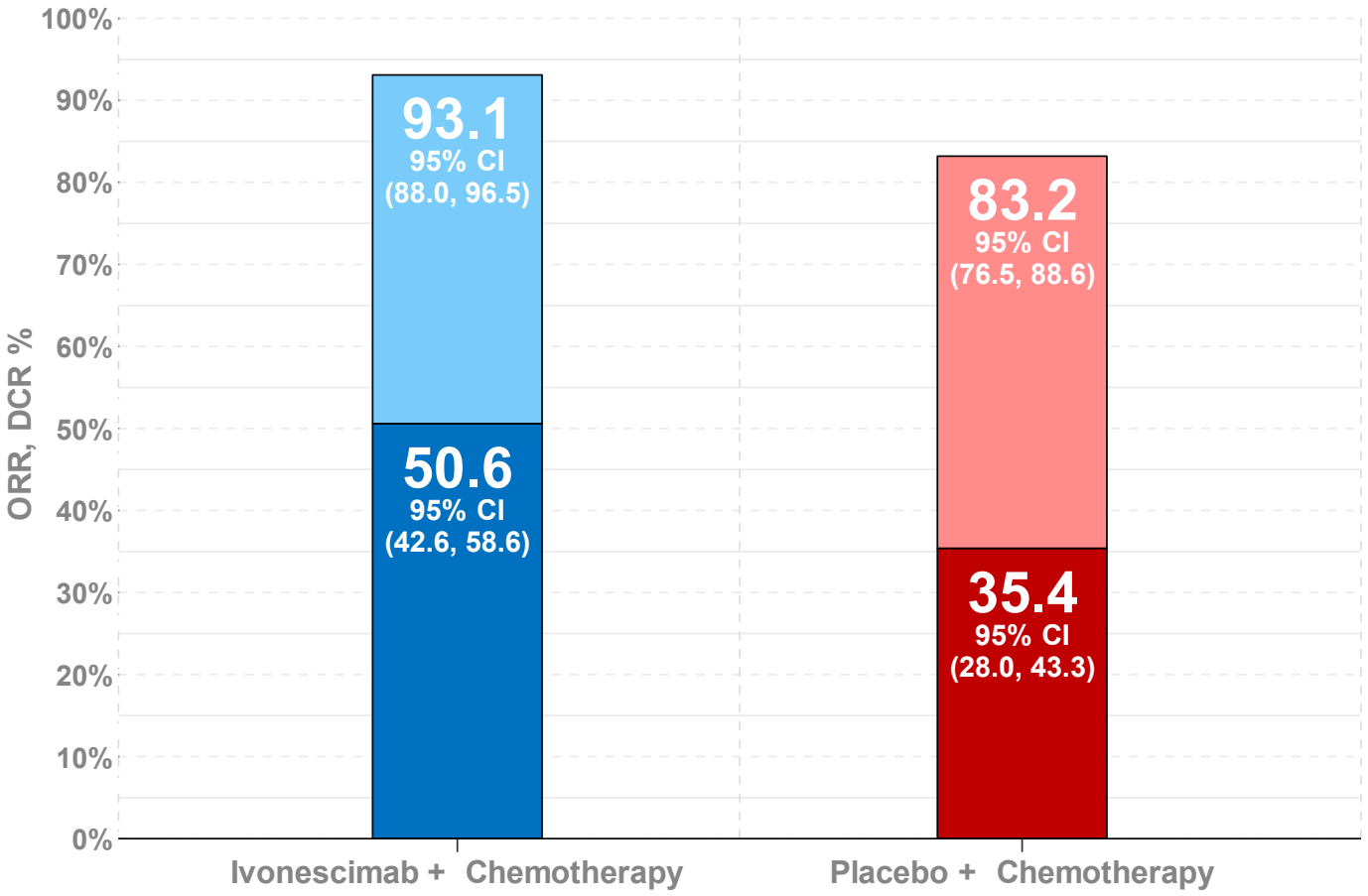
PFS Kaplan Meier Curve Evaluated by IRRC
with Brain Metastasis



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)

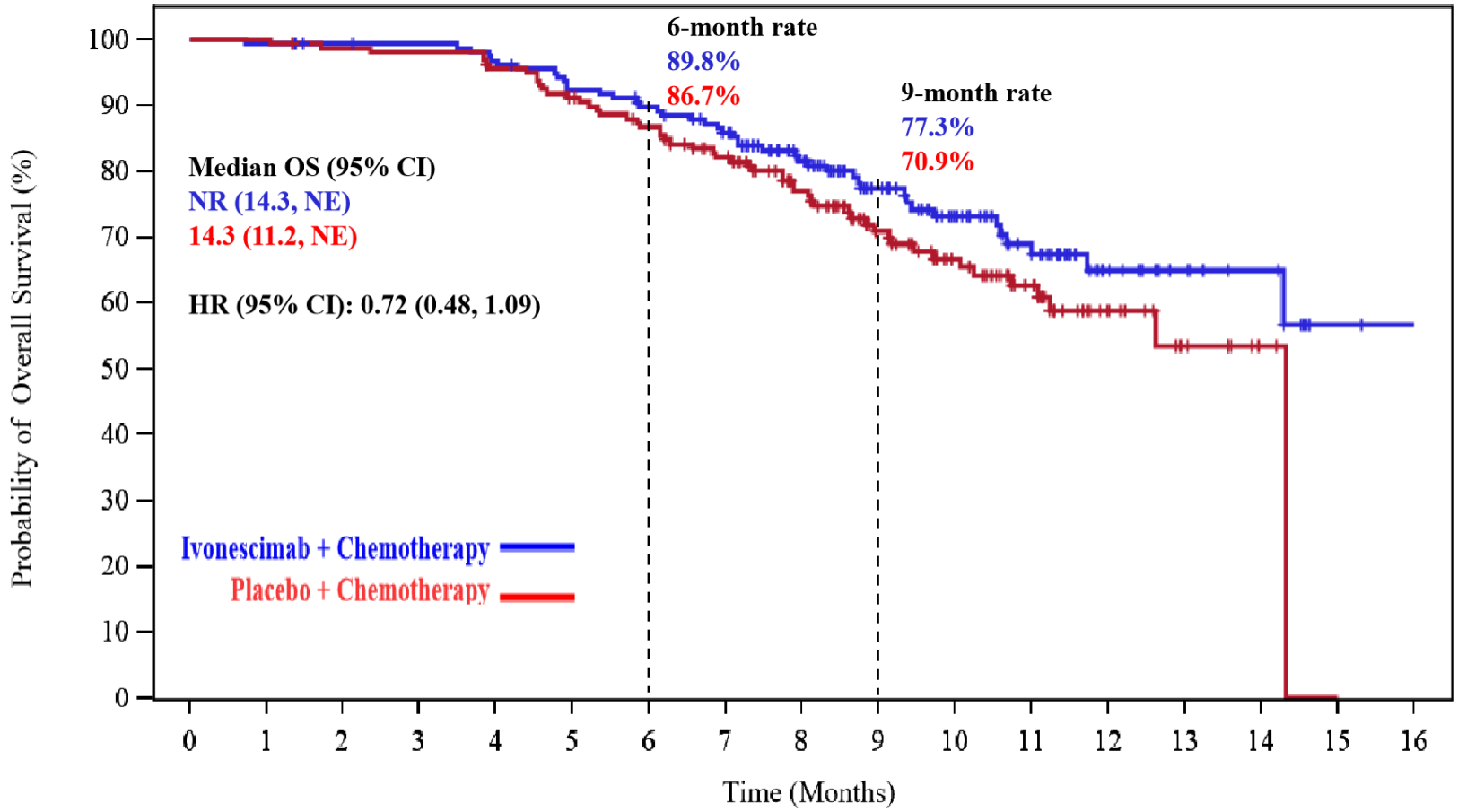
ORR, DCR and DoR per IRRC



	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)

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)	

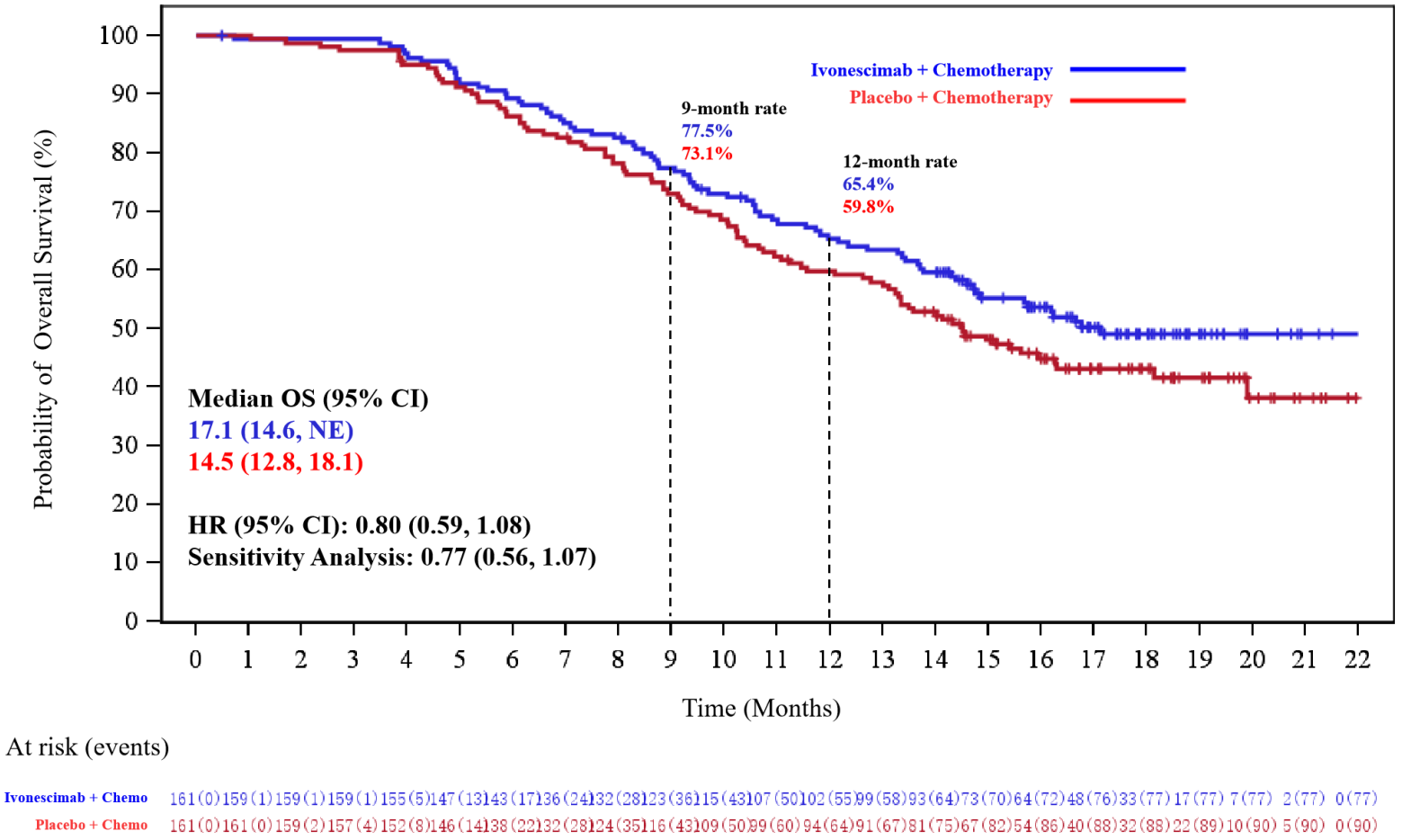
HR: 0.72 (0.48, 1.09) after 96 events, 30% data maturity

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.

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)

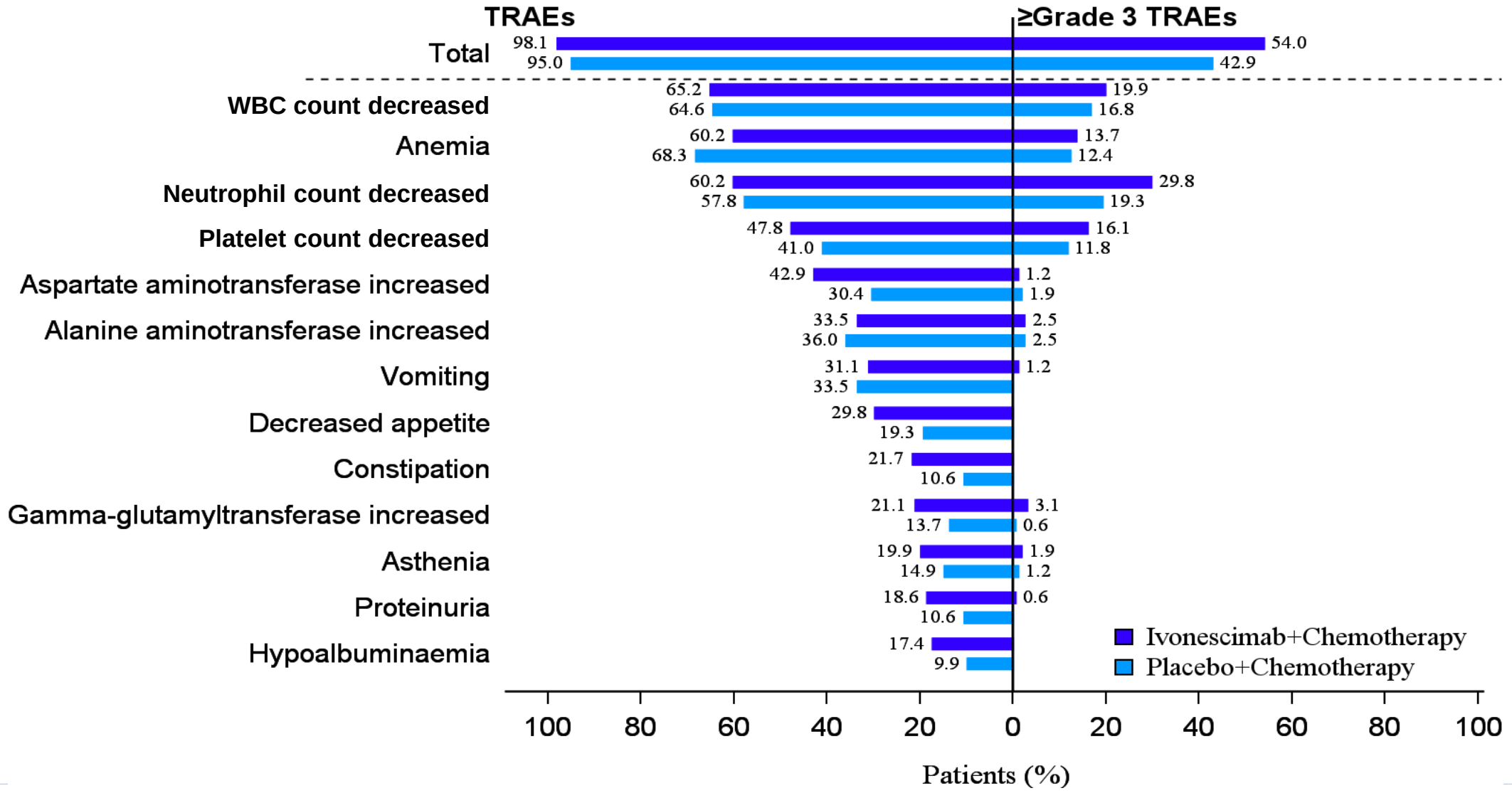
HR, hazard ratio; CI, confidence interval.

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.

The Most Common Adverse Events (incidence≥15%)



Immune-related Adverse Event (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)

Adverse Event 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

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)

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

Acknowledgement

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Research

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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.

Visual Abstract

Supplemental con

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