Lung Cancer UPDATES
ASCO HIGHLIGHTS
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Iniciativa científica de:
GECP
lung cancer research

Enfermedad metastásica con alteración molecular: EGFR y MET

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Enfermedad metastásica con alteración molecular: EGFR

Iniciativa científica de: GECP lung cancer research

Tratamiento 1L

- Abstract 8518
- Abstract 8504
- Abstract LBA8505

Tratamiento 2L

- Abstract 8508

Ex20ins

- Abstract 8513

Atípicas no-Ex20ins

- Abstract 8516

MET

- Abstract103

Enfermedad metastásica con alteración molecular: EGFR

Primera línea: Abstract 8518

Iniciativa científica de: GECP lung cancer research

Safety and efficacy of osimertinib plus consolidative stereotactic ablative radiation (SABR) in advanced *EGFR* mutant non-small cell lung cancer (NSCLC): results from a multi-center Phase II trial

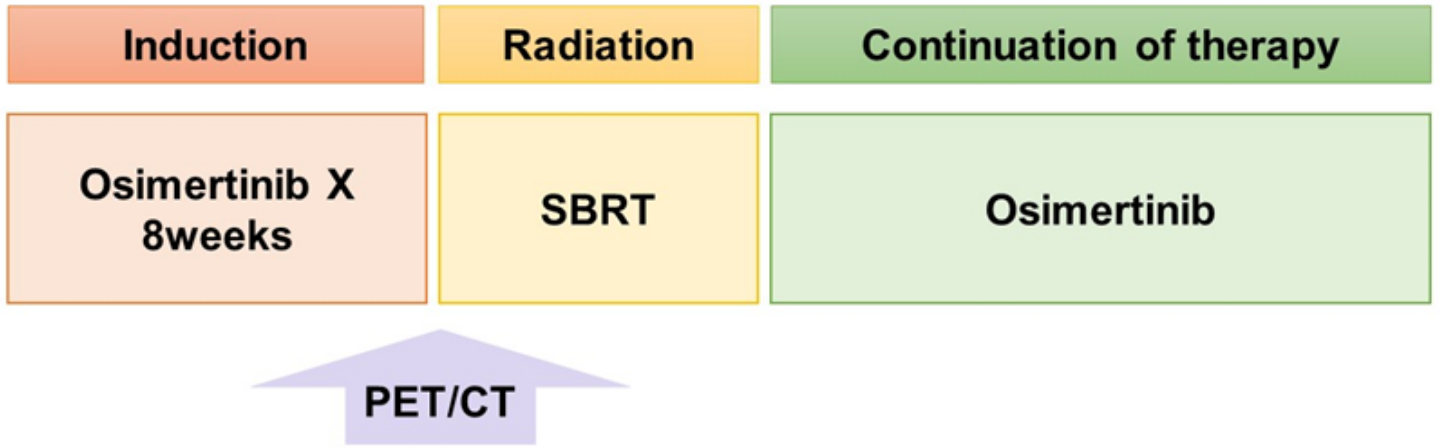
Sawsan Rashdan, Sagus Sampath, Puneeth Iyengar, Jonathan Dowell, Yuanyuan Zhang, Kenneth Westover, Suzanne Cole, Marianna Koczywas, Erminia Massarelli, Arya Amini, David Gerber.

Osimertinib until systemic progression or toxicity
Subsequent SABR was allowed for oligo-progressive disease.
We enrolled 43 patients. Primary objective: PFS
Secondary objectives: OS, duration on osimertinib, safety

Eligibility

- TKI Naïve, EGFR+ advanced NSCLC.
- Not restricted by number, site or size of metastases.
- No history of interstitial lung disease.
- ECOG ≤2

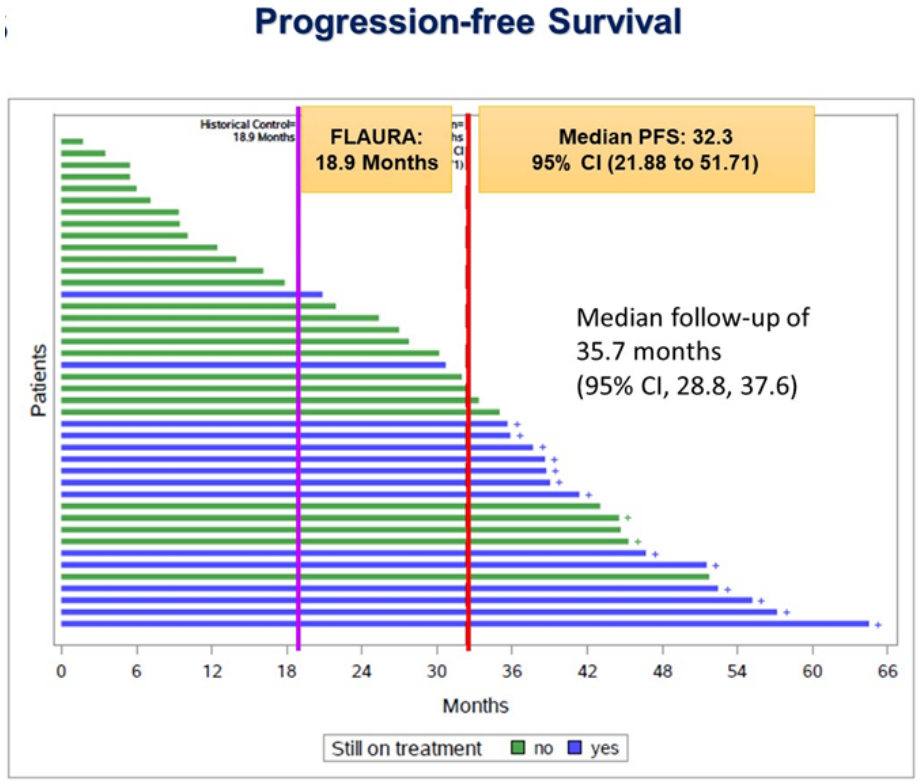
Multicenter, single arm phase 2 IIT

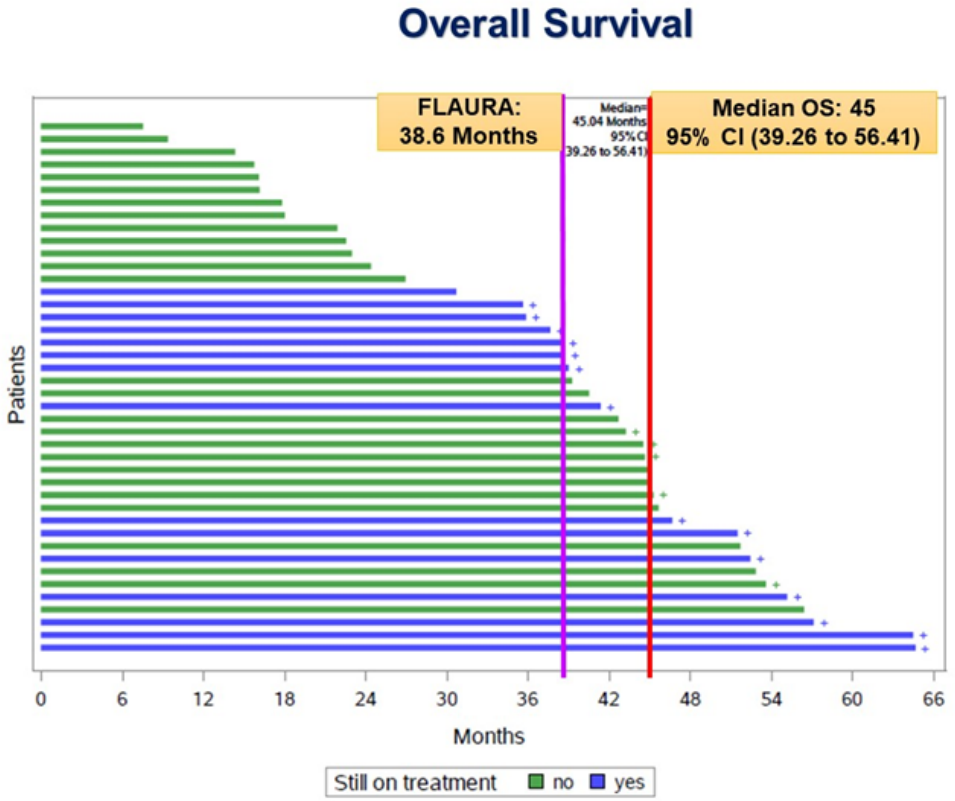


Enfermedad metastásica con alteración molecular: EGFR

Primera línea: Abstract 8518

Iniciativa científica de: GECP lung cancer research





Grade ≥3 adverse events	Number of patients
Pneumonitis	1 (2%)
Paronychia	1 (2%)
Liver enzyme elevation	1 (2%)
Hyponatremia	1 (2%)
Diarrhea	1 (2%)

Enfermedad metastásica con alteración molecular: EGFR

Primera línea: Abstract 8504

Iniciativa científica de: GECP lung cancer research

Amivantamab plus lazertinib vs osimertinib in first-line *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI[4,5]

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

2:2:1 randomization (N=1074)

Focus of this presentation

- **Amivantamab + Lazertinib** (n=429; open label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Primary endpoint of PFS[a] by BICR per RECIST v1.1:

- Amivantamab + Lazertinib vs Osimertinib

High-risk subgroups analyzed:

- Brain metastases
- Liver metastases
- *TP53* co-mutation
- Detectable *EGFR*m ctDNA at baseline
- Without *EGFR*m ctDNA clearance at Week 9 (C3D1)

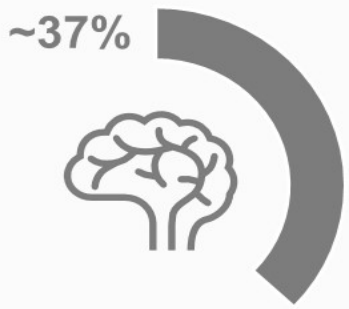
Diagnostic tests:

- ctDNA NGS[b]: baseline co-mutations
- ctDNA ddPCR[c]: detection and clearance of Ex19del and L858R

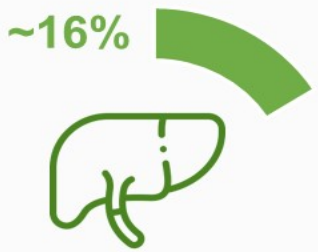
Multiple Features are Associated With Poor Outcomes in *EGFR*-mutant NSCLC

- High-risk features, such as brain or liver metastases, baseline *TP53* co-mutations, and ctDNA shedding are common in patients with *EGFR*m NSCLC[1-5]

Brain metastases[6,a]

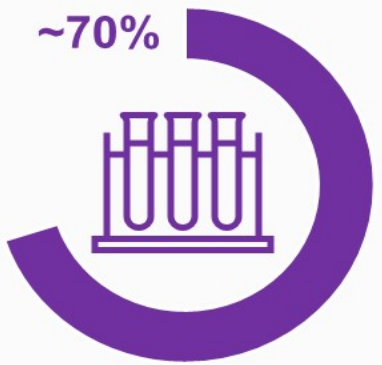


Liver metastases[7,a]



***TP53* co-mutations[8,a]**

Detectable ctDNA[9,a,b]



We assessed the efficacy of first-line amivantamab + lazertinib vs osimertinib among patients with these high-risk features included in the MARIPOSA trial

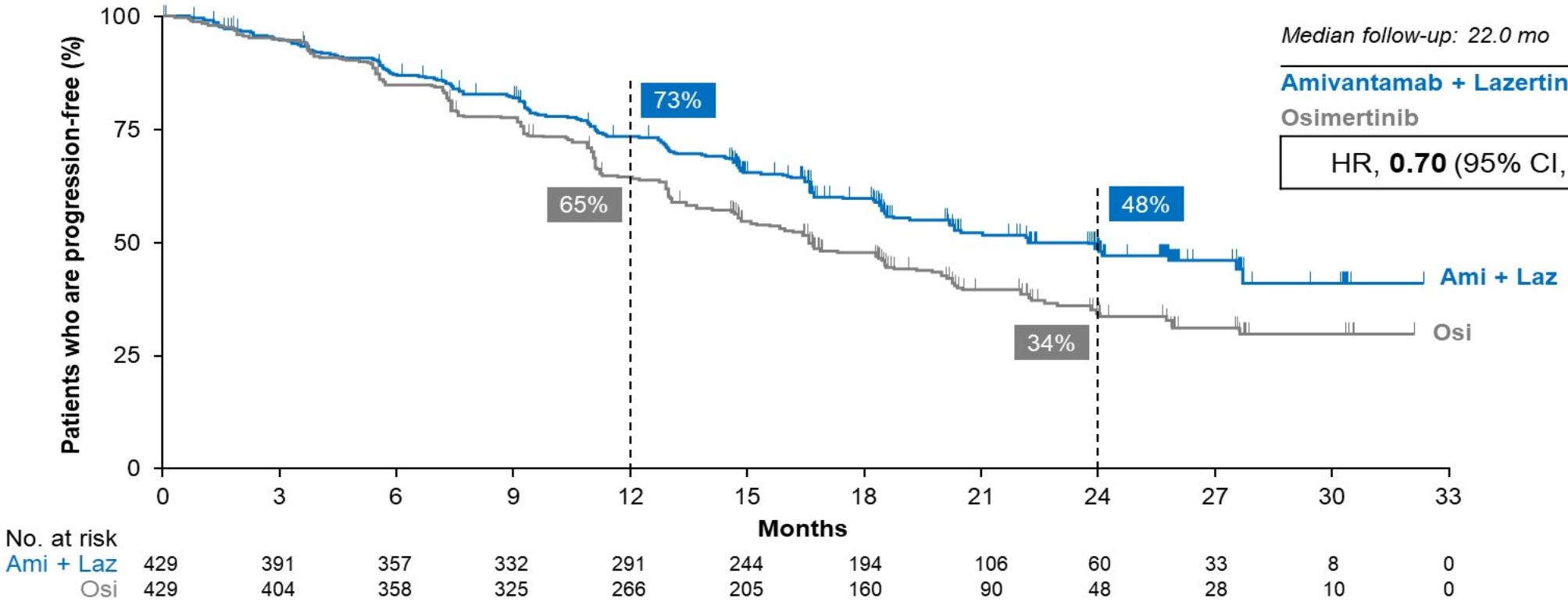
[a]At baseline. [b]*EGFR*m ctDNA detected by ddPCR.

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction.

1. Gray JE, et al. *Clin Cancer Res*. 2023;29(17):3340-3351. 2. Ma S, et al. *Transl Lung Cancer Res*. 2021;10(1):326-339. 3. Pérol M, et al. Presented at: the European Lung Cancer Congress (ELCC); March 20-23, 2024; Prague, Czech Republic. 26P. 4. Takeyasu Y, et al. *JTO Clin Res Rep*. 2024;5(2):100636. 5. Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125. 6. Taniguchi Y, et al. *Oncol Lett*. 2017;14(6):7589-7596. 7. Choi MG, et al. *Transl Lung Cancer Res*. 2021;10(6):2551-2561. 8. Jiang W, et al. *Cancer Med*. 2023;12(6):6649-6658. 9. Jänne PA, et al. Presented at: the American Association for Cancer Research (AACR) Annual Meeting; April 5-10, 2024; San Diego, CA, USA. CT017.

Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 mo	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

Amivantamab + lazertinib also meaningfully improved PFS2 and DoR vs osimertinib in MARIPOSA

Data cutoff: August 11, 2023.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

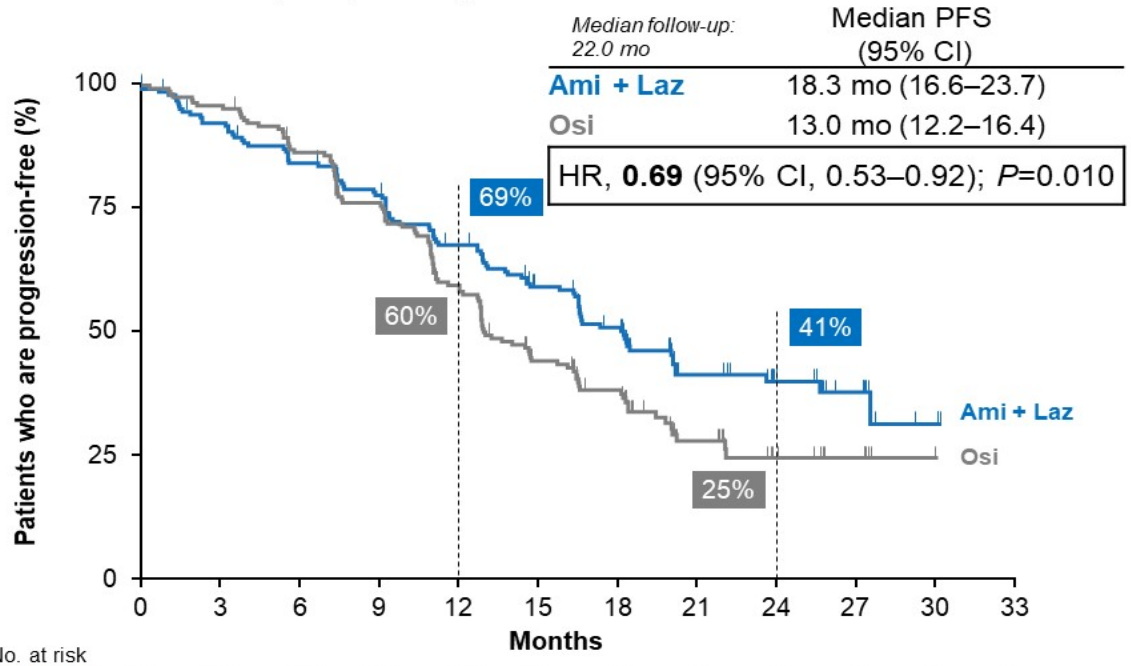
1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

MARIPOSA
Ami + Laz in
1L *EGFR*+ NSCLC

PFS by Baseline Brain Metastases

- In the amivantamab + lazertinib arm, 41% of patients had a history of brain metastases vs 40% in the osimertinib arm
- Osimertinib showed a median PFS of 13.0 mo in patients with a history of brain metastases
- Amivantamab + lazertinib reduced the risk of progression or death by 31% in this subgroup

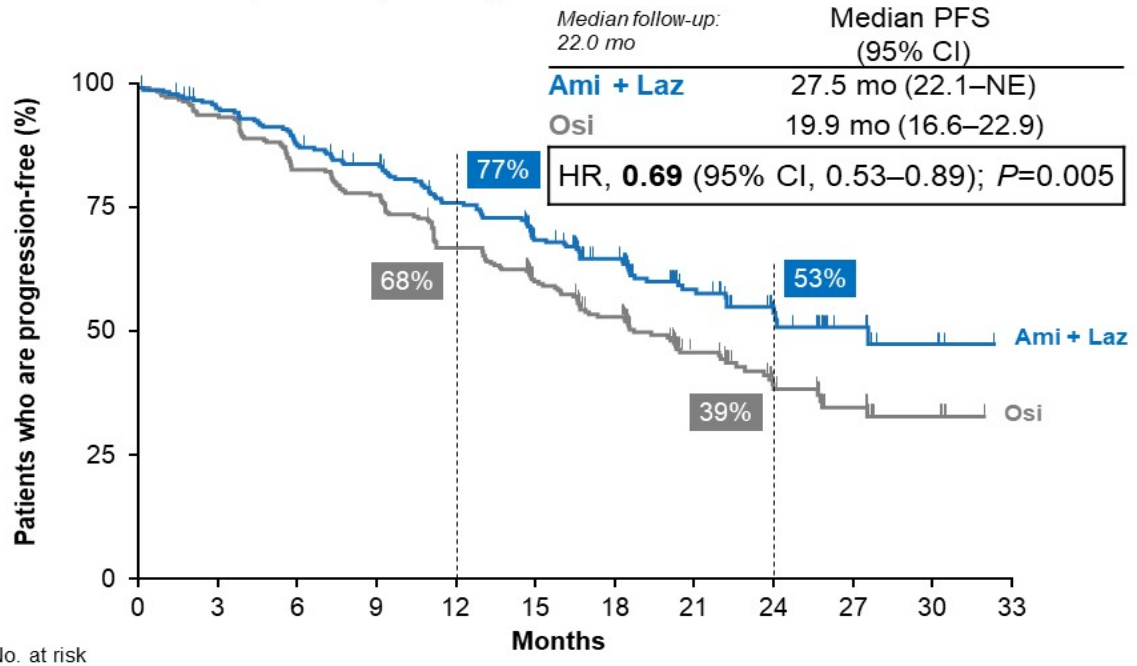
With History of Brain Metastases



No. at risk

Ami + Laz	178	162	146	134	115	92	71	34	24	12	3	0
Osi	172	164	146	126	95	64	47	21	11	6	1	0

Without History of Brain Metastases



No. at risk

Ami + Laz	251	229	211	198	176	152	123	72	36	21	5	0
Osi	257	240	212	199	171	141	113	69	37	22	9	0

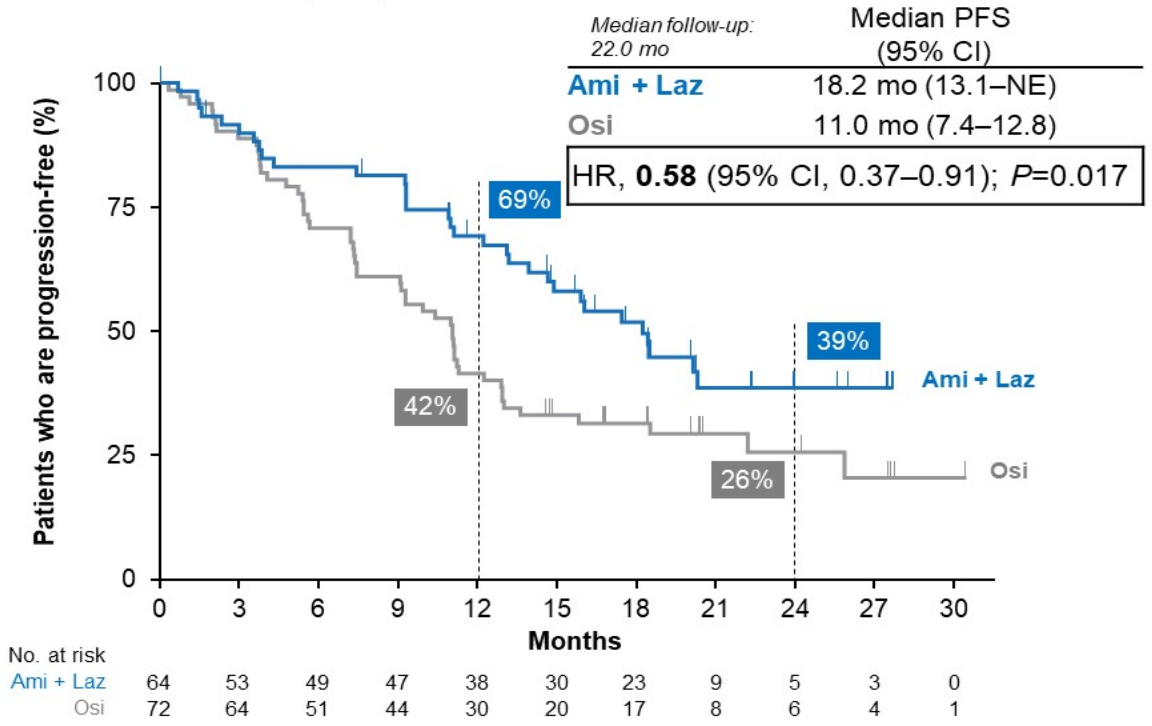
Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

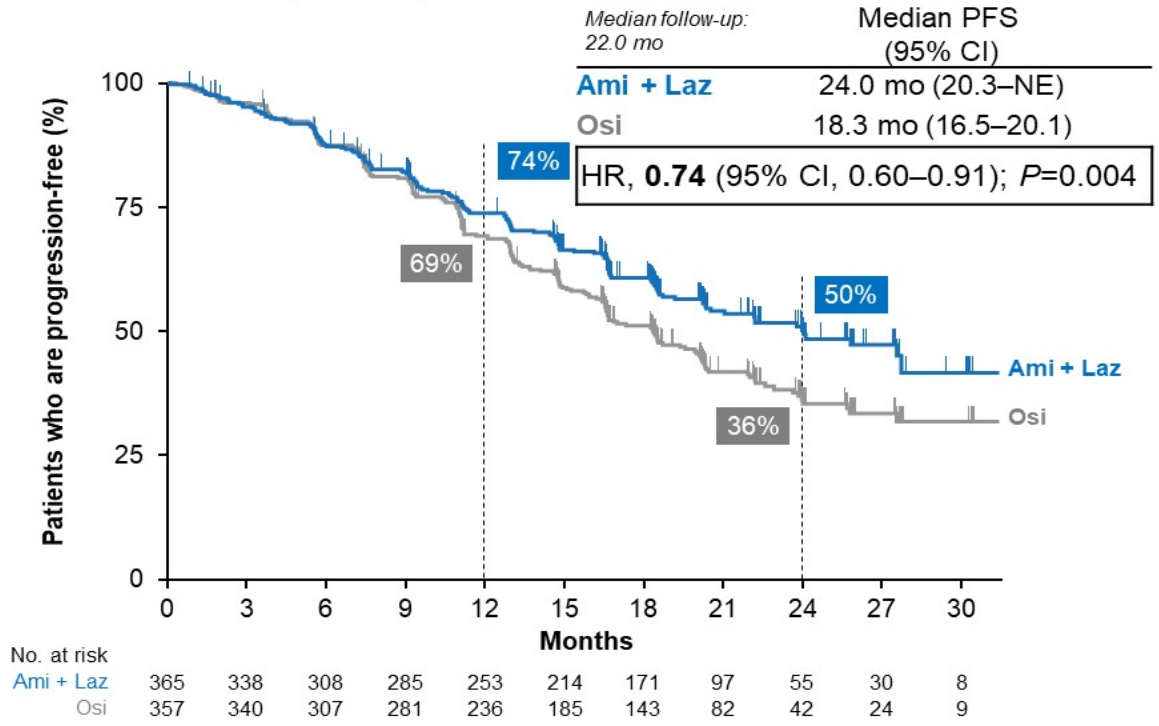
PFS by Baseline Liver Metastases

- In the amivantamab + lazertinib arm, 15% of patients had liver metastases at baseline vs 17% in the osimertinib arm
- Osimertinib showed a median PFS of 11.0 mo in patients with liver metastases at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 42% in this subgroup

With Baseline Liver Metastases



Without Baseline Liver Metastases



Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

Baseline Demographic and Clinical Characteristics by *TP53* Co-mutation Status

Baseline demographic characteristics were well-balanced between treatment arms

Characteristic, n (%)	*TP53* Co-mutation		Wild-type *TP53*	
	Amivantamab + Lazertinib (n=149)	Osimertinib (n=144)	Amivantamab + Lazertinib (n=117)	Osimertinib (n=130)
Median age, years (range)	64 (25–87)	63 (31–87)	65 (35–88)	63 (33–87)
Female	88 (59)	80 (56)	83 (71)	81 (62)
Race				
Asian	74 (50)	61 (42)	57 (49)	74 (57)
White	69 (46)	79 (55)	55 (47)	49 (38)
Other[a]	6 (4)	4 (3)	5 (4)	7 (5)
ECOG PS 1	99 (66)	99 (69)	68 (58)	84 (65)
History of smoking	50 (34)	51 (35)	38 (32)	34 (26)
History of brain metastases	80 (54)	72 (50)	40 (34)	43 (33)
Liver metastases at baseline	26 (17)	30 (21)	14 (12)	15 (12)
EGFR mutation type[b]				
Ex19del	93 (62)	81 (56)	70 (60)	87 (67)
L858R	56 (38)	63 (44)	47 (40)	43 (36)

Note: Pathogenic mutations were detected with the Guardant Health G360® panel.

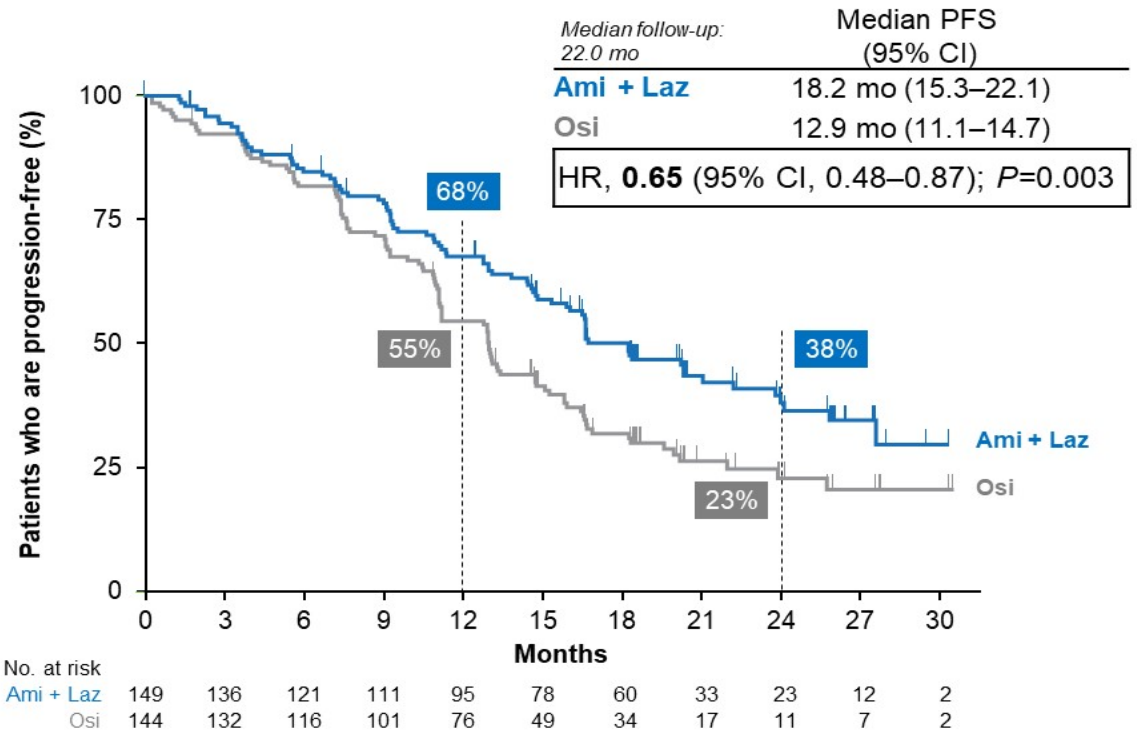
[a]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown. [b]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.

Ex19del, Exon 19 deletion.

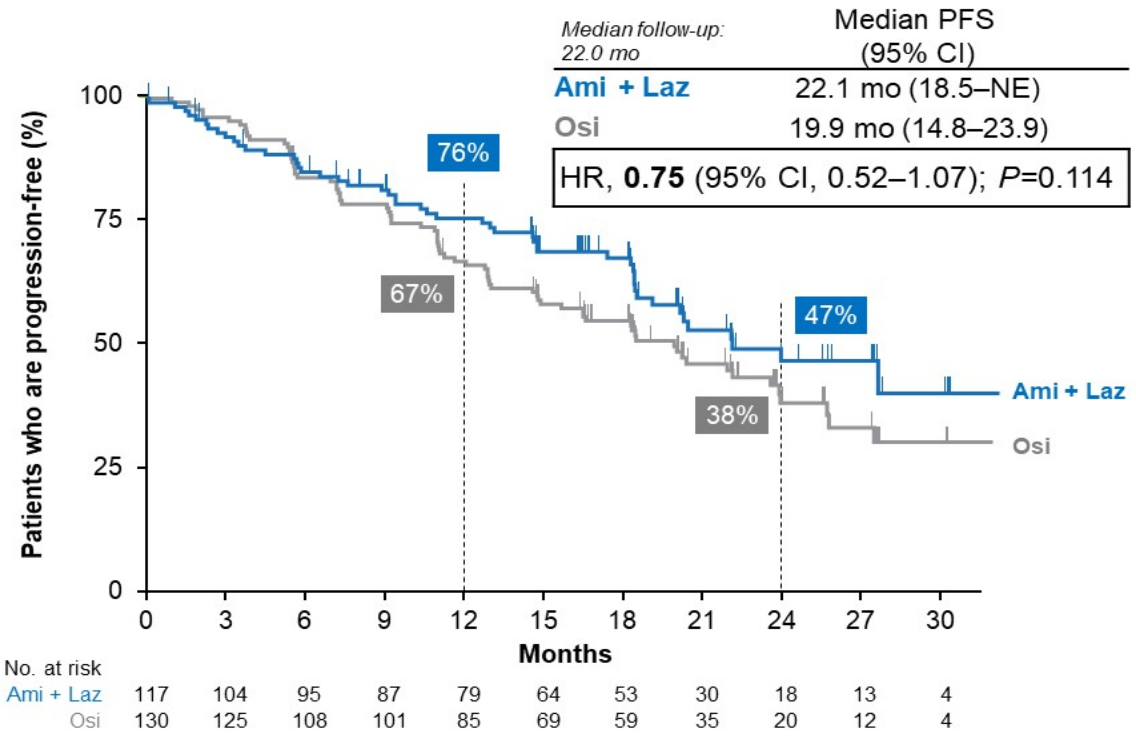
PFS by *TP53* Co-mutations and Wild-type *TP53*

- Osimertinib showed a median PFS of 12.9 mo in patients with *TP53* co-mutations at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 35% in this subgroup

TP53 Co-mutations



Wild-type TP53



Note: Pathogenic mutations were detected with the Guardant Health G360® panel.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

Baseline Demographic and Clinical Characteristics by ddPCR ctDNA Detection[a] Status

Baseline demographic characteristics were well-balanced between treatment arms

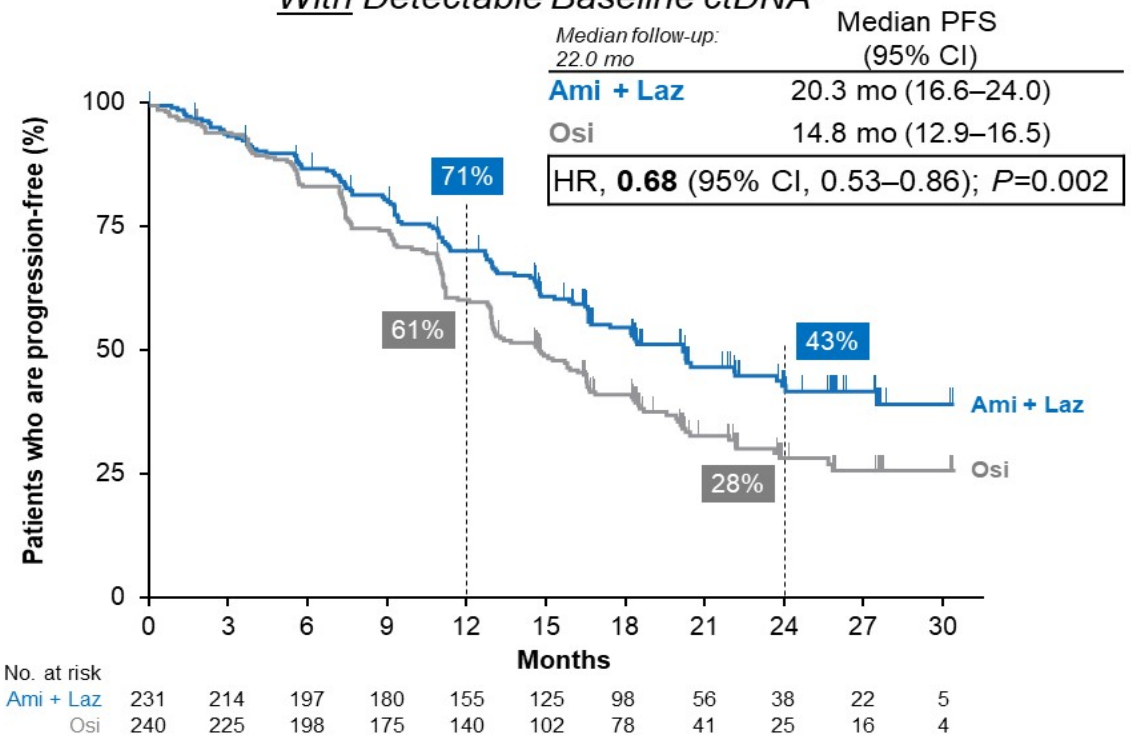
Characteristic, n (%)	With Detectable ctDNA[a] at Baseline		Without Detectable ctDNA[a] at Baseline	
	Amivantamab + Lazertinib (n=231)	Osimertinib (n=240)	Amivantamab + Lazertinib (n=105)	Osimertinib (n=96)
Median age, years (range)	63 (30–87)	63 (31–87)	67 (38–86)	66 (36–88)
Female	143 (62)	148 (64)	76 (72)	46 (48)
Race				
Asian	117 (51)	125 (52)	48 (46)	45 (47)
White	101 (44)	106 (44)	56 (53)	48 (50)
Other[b]	13 (6)	9 (4)	1 (1)	3 (3)
ECOG PS 1	155 (67)	162 (68)	50 (48)	53 (55)
History of smoking	76 (33)	72 (30)	31 (30)	34 (35)
History of brain metastases	109 (47)	110 (46)	29 (28)	24 (25)
Liver metastases at baseline	40 (17)	50 (21)	9 (9)	8 (8)
EGFR mutation type[c]				
Ex19del	143 (62)	145 (60)	66 (63)	63 (66)
L858R	88 (38)	95 (40)	38 (36)	33 (34)

[a]Ex19del or L858R by Biodesix ddPCR. [b]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown. [c]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.
ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion.

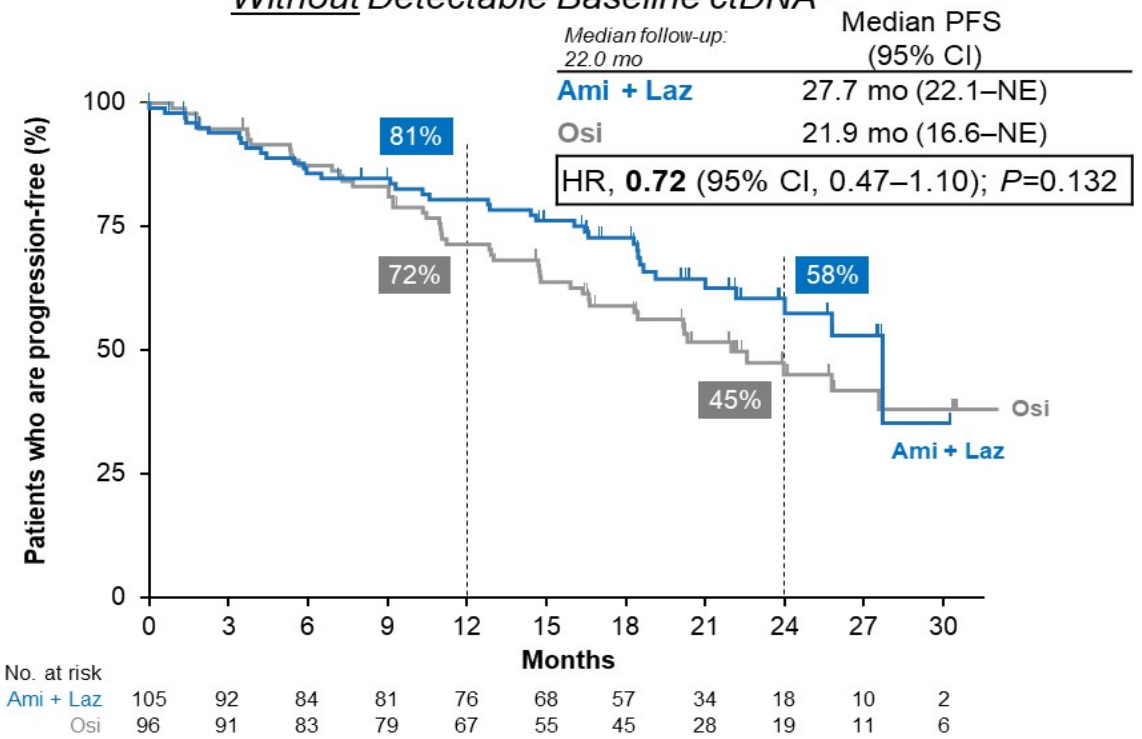
PFS by Detectable Baseline *EGFRm* ctDNA by ddPCR

- Osimertinib showed a median PFS of 14.8 mo in patients with detectable ctDNA[a] at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 32% in this subgroup
- Consistent results were seen in patients with detectable ctDNA using the NGS assay[b] (HR, 0.71 [95% CI, 0.57–0.89]; *P*=0.003)

With Detectable Baseline ctDNA[a]



Without Detectable Baseline ctDNA[a]



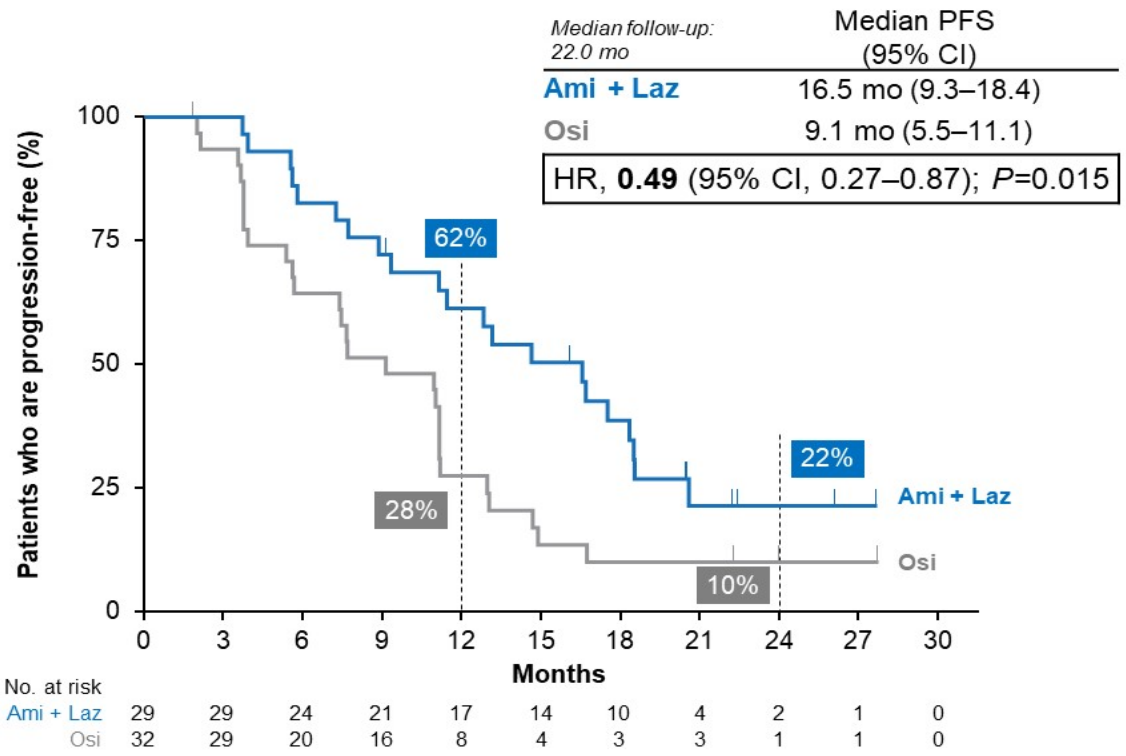
[a]Detection of Ex19del and L858R by Biodesix ddPCR. [b]Pathogenic mutations were detected with the Guardant Health G360® panel.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing; Osi, osimertinib.

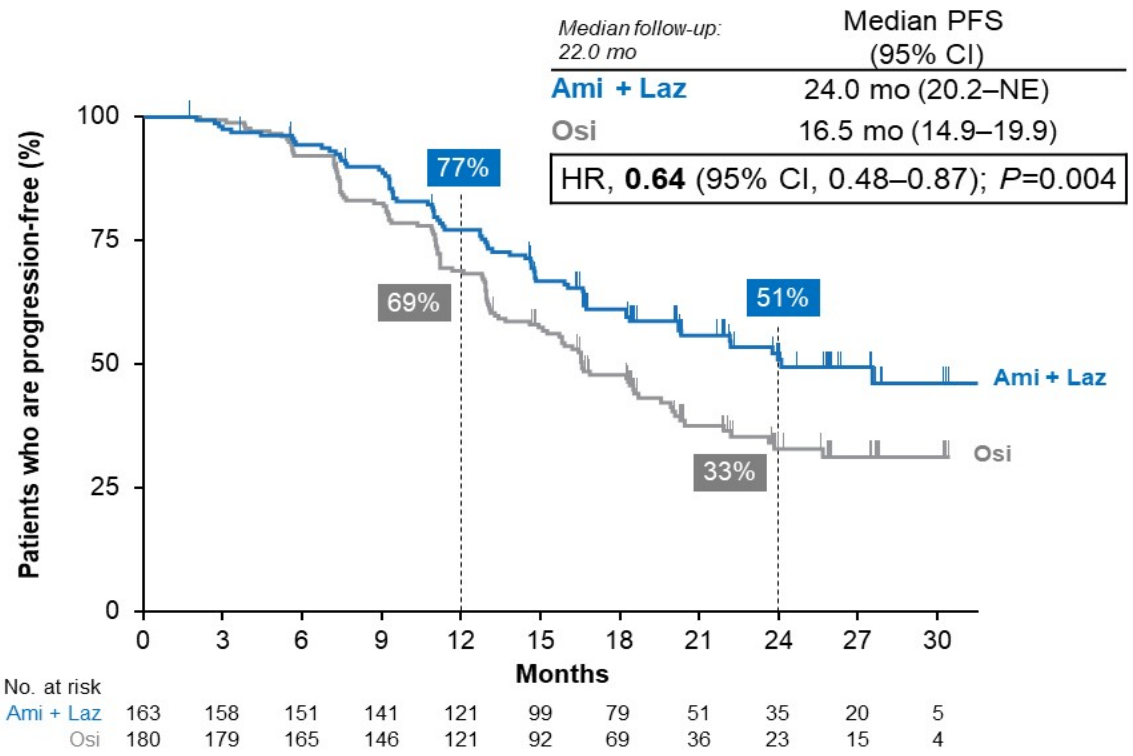
PFS Without and With Cleared *EGFR*m ctDNA[a] at Week 9 (C3D1)

- Osimertinib showed a median PFS of 9.1 mo in patients without cleared *EGFR*m ctDNA[a] at Week 9
- Amivantamab + lazertinib reduced the risk of progression or death by 51% in this subgroup

Without Cleared EGFRm ctDNA[a] at Week 9



With Cleared EGFRm ctDNA[a] at Week 9

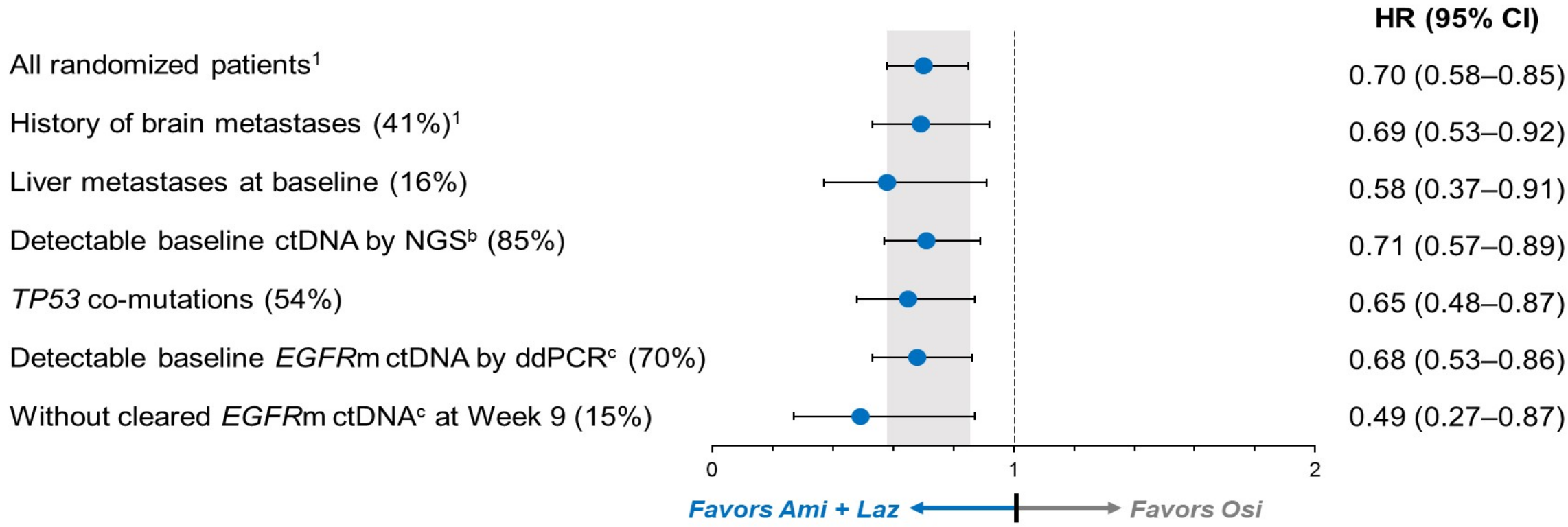


[a]Detection of Ex19del and L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; Osi, osimertinib.

PFS for Patients With High-risk Features

In the MARIPOSA study, 89% of patients had ≥1 high-risk feature detected at baseline[a]



[a]Patients with analyzable ctDNA by NGS at baseline were included in this pooled analysis. High-risk features included baseline detectable ctDNA by NGS or baseline metastases of the liver or brain. For patients with detectable ctDNA, it was assumed that *TP53* co-mutations would be identified if present. [b]Pathogenic mutations were detected with the Guardant Health G360® panel. [c]Ex19del and L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing.

1. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

Enfermedad metastásica con alteración molecular: EGFR

Líneas sucesivas: Abstract LBA8505

Iniciativa científica de: GECP lung cancer research

Subcutaneous amivantamab vs intravenous amivantamab, both in combination with lazertinib, in refractory *EGFR*-mutated, advanced non-small cell lung cancer

Primary results, including overall survival, from the global, phase 3, randomized controlled PALOMA-3 trial

Natasha B Leighl,[1] Hiroaki Akamatsu,[2] Sun Min Lim,[3] Ying Cheng,[4] Anna R Minchom,[5] Melina E Marmarelis,[6] Rachel E Sanborn,[7] James Chih-Hsin Yang,[8] Baogang Liu,[9] Thomas John,[10] Bartomeu Massutí,[11] Alexander I Spira,[12] John Xie,[13] Debopriya Ghosh,[13] Ali Alhadab,[14] Remy B Verheijen,[15] Mohamed Gamil,[16] Joshua M Bauml,[16] Mahadi Baig,[13] Antonio Passaro[17]

PALOMA-3: Phase 3 Study Design

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

SC Amivantamab + Lazertinib (n=206)

IV Amivantamab + Lazertinib (n=212)

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]**:**

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

- OS

PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

PRESENTED BY: Natasha B Leighl

Baseline Demographics

Demographics and baseline disease characteristics were well balanced between treatment groups

Characteristic, n (%)	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
Median age, years (range)	61 (35–82)	62 (29–81)
Male/female	68 (33) / 138 (67)	71 (33) / 141 (67)
Body weight: <80 kg/≥80 kg	184 (89) / 22 (11)	184 (87) / 28 (13)
Race		
Asian	126 (61)	129 (61)
White	78 (38)	77 (36)
Other[a]	2 (1)	6 (3)
Median prior lines of therapy (range)	**2 (1–5)**	**2 (1–4)**
ECOG PS		
0	58 (28)	61 (29)
1	148 (72)	151 (71)
EGFR mutation type at randomization		
Ex19del	135 (66)	138 (65)
L858R	71 (34)	74 (35)
History of brain metastases	**70 (34)**	**72 (34)**
History of smoking	65 (32)	67 (32)
Last therapy before randomization		
Osimertinib	91 (44)	96 (45)
Chemotherapy	115 (56)	116 (55)
Adenocarcinoma histology	204 (99)	207 (98)

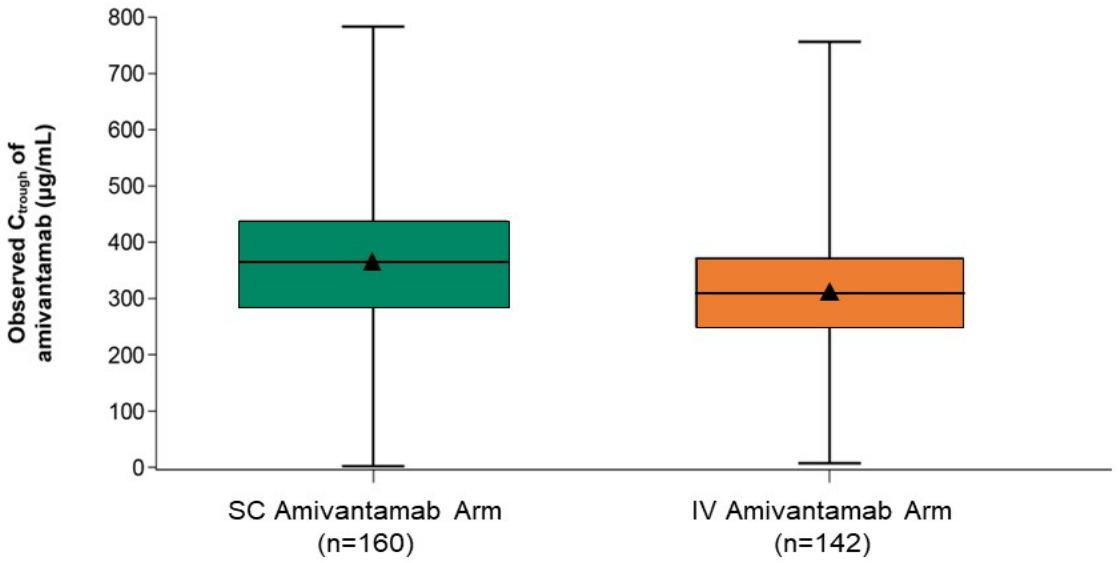
Note: Percentages may not sum to 100 due to rounding. [a]Other includes Black or African American, multiple, and unknown.

ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; SC, subcutaneous.

Co-primary PK Endpoints Met Noninferiority Criteria

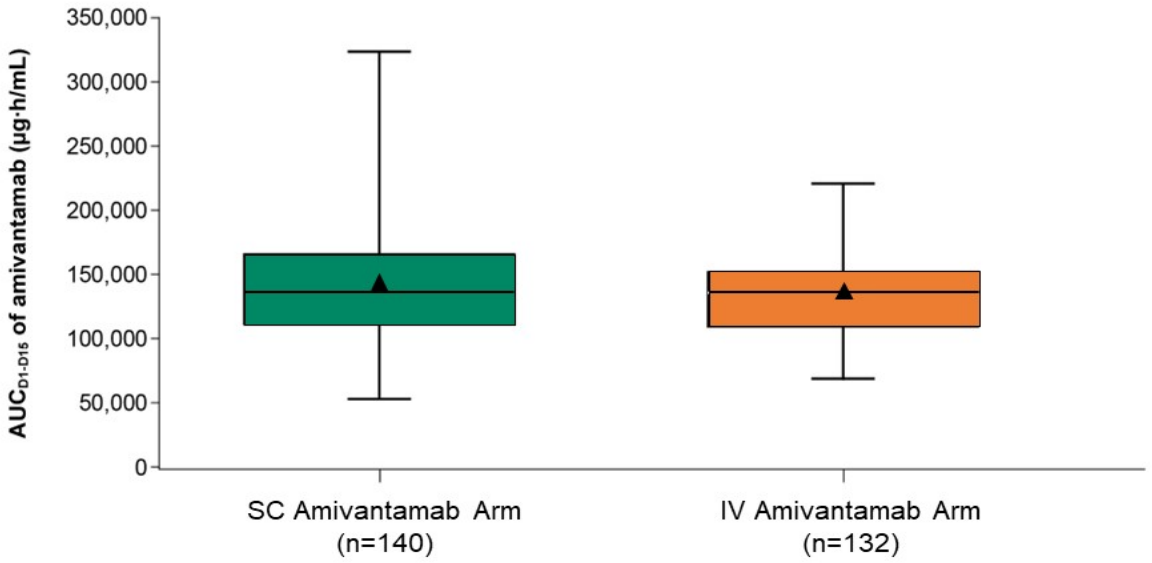
C_{trough} at C2D1

Geometric mean ratio=**1.15**
(90% CI, 1.04–1.26)



C2 $AUC_{D1\text{-}D15}$

Geometric mean ratio=**1.03**
(90% CI, 0.98–1.09)



- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)

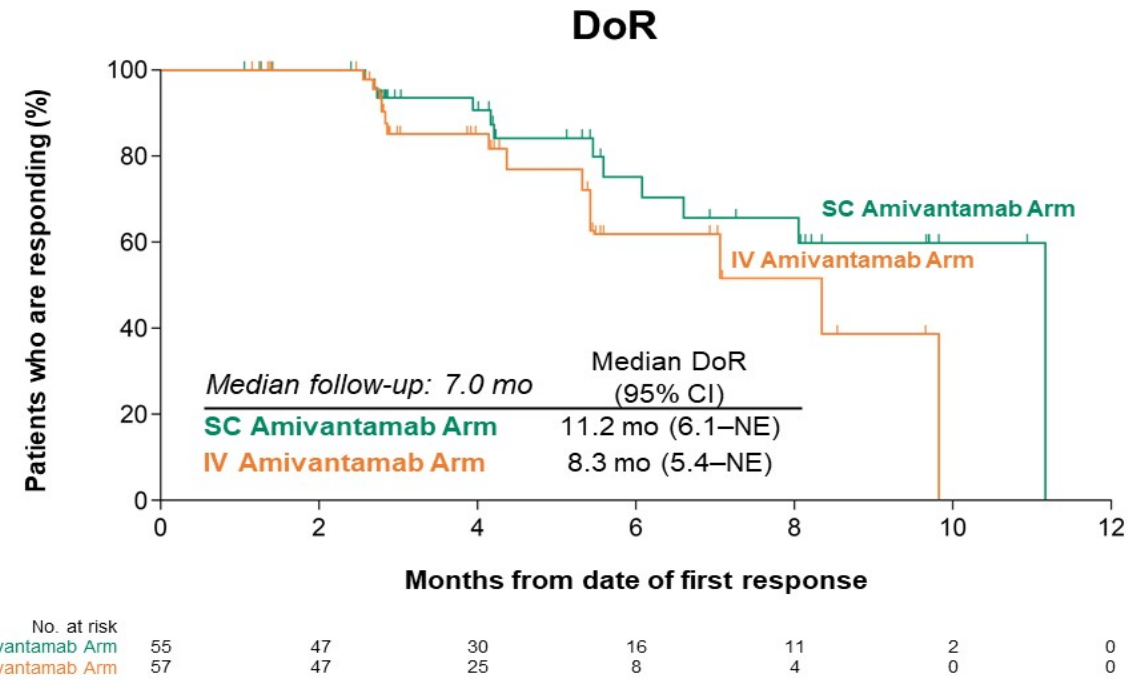
Note: The pharmacokinetic analysis for primary endpoints included all patients who received all doses without dose modification and provided the required PK samples through the final required PK sample relevant to the endpoint. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs.

AUC, area under the concentration-time curve; C, Cycle; CI, confidence interval; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous.

ORR and DoR

- ORR was noninferior between the SC and IV amivantamab arms
- DoR was 11.2 months in the SC arm vs 8.3 months in the IV arm, with twice as many patients, 29% in the SC arm vs 14% in the IV arm, having a response ≥6 months

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**

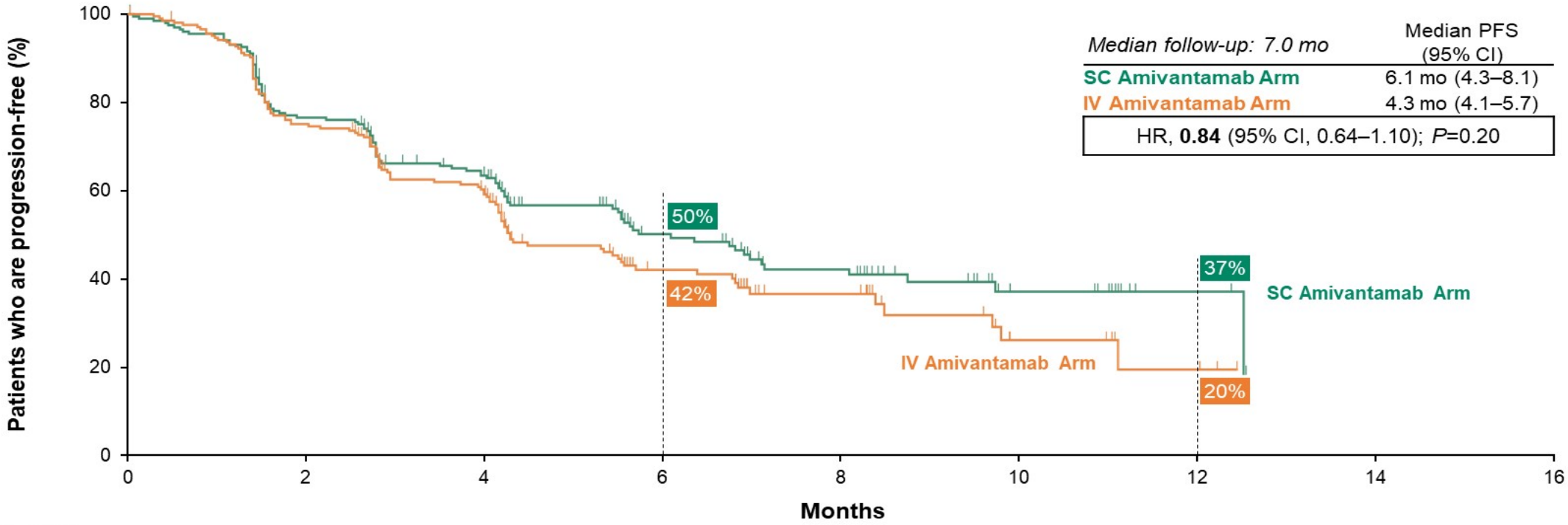


[a]The objective response (CR or PR) was assessed using RECIST v1.1 and analyzed using logistic regression. The lower bound of the 95% CI indicated ≥70% retention of ORR exceeding the predefined 60% retention assumed for determining noninferiority. [b]Not protocol specified.

CI, confidence interval; CR, complete response; DCR, disease control rate (CR+PR+SD); DoR, duration of response; IV, intravenous; mo, months; NE, not estimable; ORR, objective response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; SD, stable disease.

Progression-free Survival

PFS was numerically longer with SC vs IV amivantamab, with an HR of 0.84



Median follow-up: 7.0 mo	Median PFS (95% CI)
SC Amivantamab Arm	6.1 mo (4.3–8.1)
IV Amivantamab Arm	4.3 mo (4.1–5.7)

HR, **0.84** (95% CI, 0.64–1.10); *P*=0.20

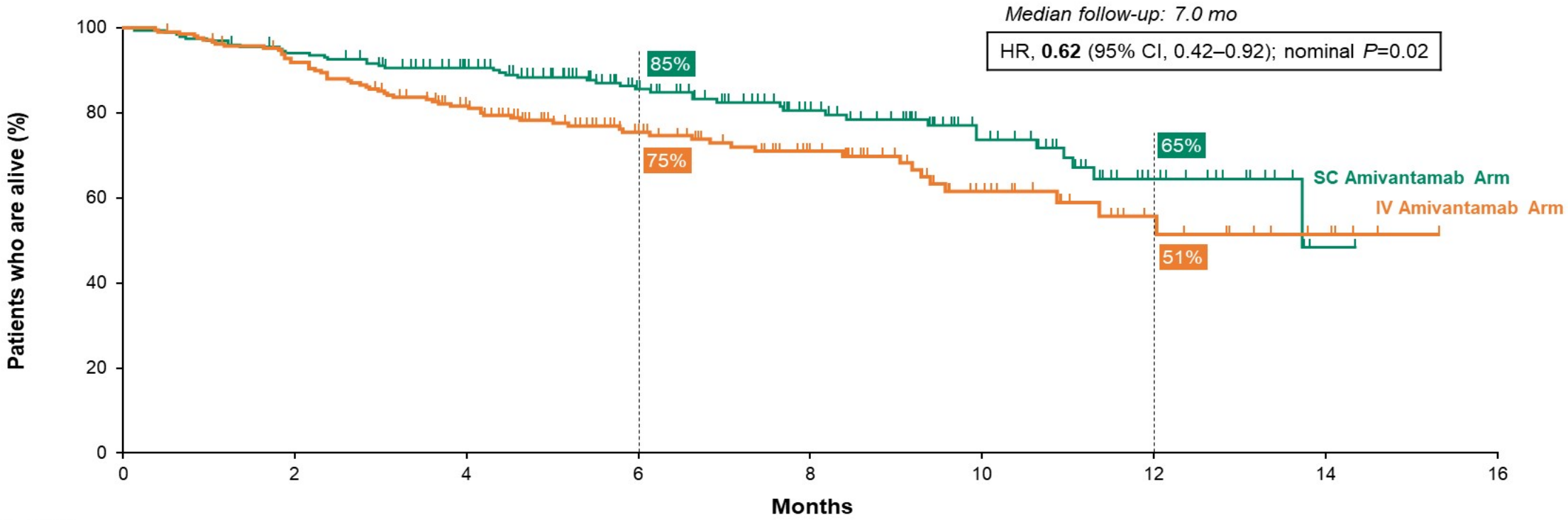
No. at risk									
SC Amivantamab Arm	206	153	116	57	37	14	3	0	0
IV Amivantamab Arm	212	154	109	43	23	7	3	0	0

Note: The efficacy population included all the patients who had undergone randomization. PFS was tested for superiority as part of the hierarchical testing strategy; *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy).

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; PFS, progression-free survival; SC, subcutaneous.

Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]



No. at risk									
SC Amivantamab Arm	206	192	163	109	71	36	10	0	0
IV Amivantamab Arm	212	191	144	92	51	24	10	1	0

Note: The efficacy population included all the patients who had undergone randomization. [a]There were 43 deaths in the SC amivantamab arm and 62 deaths in the IV amivantamab arm. Nominal *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy); the prespecified endpoint was exploratory and not part of hierarchical hypothesis testing.

CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; OS, overall survival; SC, subcutaneous.

Summary of AEs

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=210)
Median treatment duration, mo (range)	4.7 (0.1–13.2)	4.1 (0–13.2)
Treatment-emergent AEs, n (%)		
Any AEs	204 (99)	209 (99)
Grade ≥3 AEs	107 (52)	118 (56)
Serious AEs	59 (29)	64 (30)
Any AE leading to death	7 (3)	10 (5)
Any AE leading to treatment		
Interruptions of any agent	127 (62)	127 (60)
Reductions of any agent	63 (31)	52 (25)
Discontinuations of any agent	26 (13)	29 (14)

- Treatment-emergent AEs were consistent between arms
- AEs leading to death were uncommon and similar between arms
- Treatment-related discontinuations: 9% in SC arm and 12% in IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.
AE, adverse event; IV, intravenous; mo, months; SC, subcutaneous.

Safety Profile

Most common AEs were EGFR- and MET-related, majority grade 1-2, which is consistent with previous studies[1]

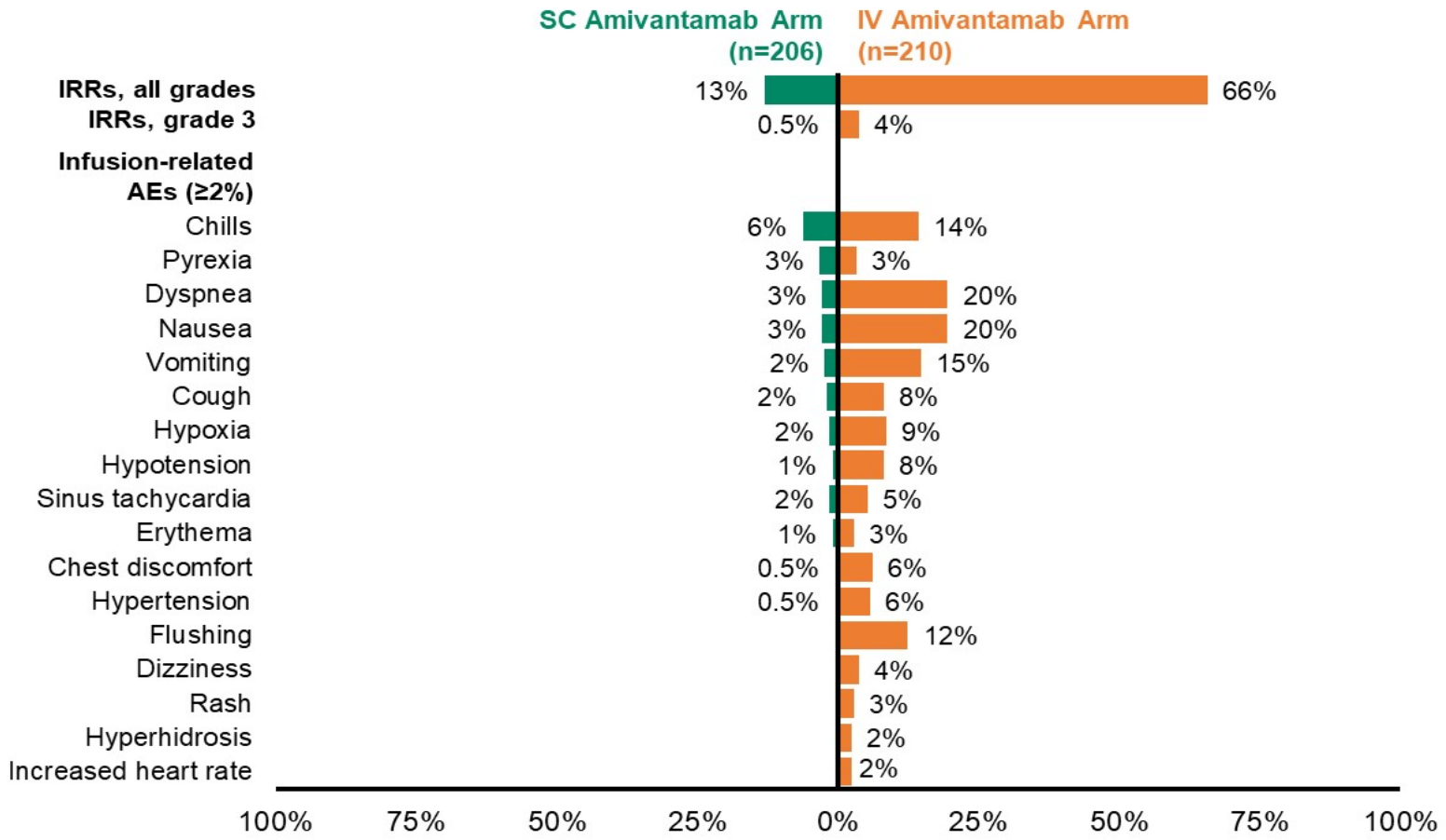
Most common AEs of any cause by preferred term (≥20%), n (%)	SC Amivantamab Arm (n=206)		IV Amivantamab Arm (n=210)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)
Other				
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Increased ALT	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (2)	43 (20)	5 (2)
Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Constipation	42 (20)	0	42 (20)	1 (0.5)
Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased AST	42 (20)	2 (1)	45 (21)	3 (1)
IRRs	27 (13)	1 (0.5)	138 (66)	8 (4)

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

1. Cho BC, et al. Presented at the European Society for Medical Oncology Annual Meeting; October 20-24, 2023; LBA14.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *EGFR*, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor receptor; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

Incidence of IRR-related Symptoms



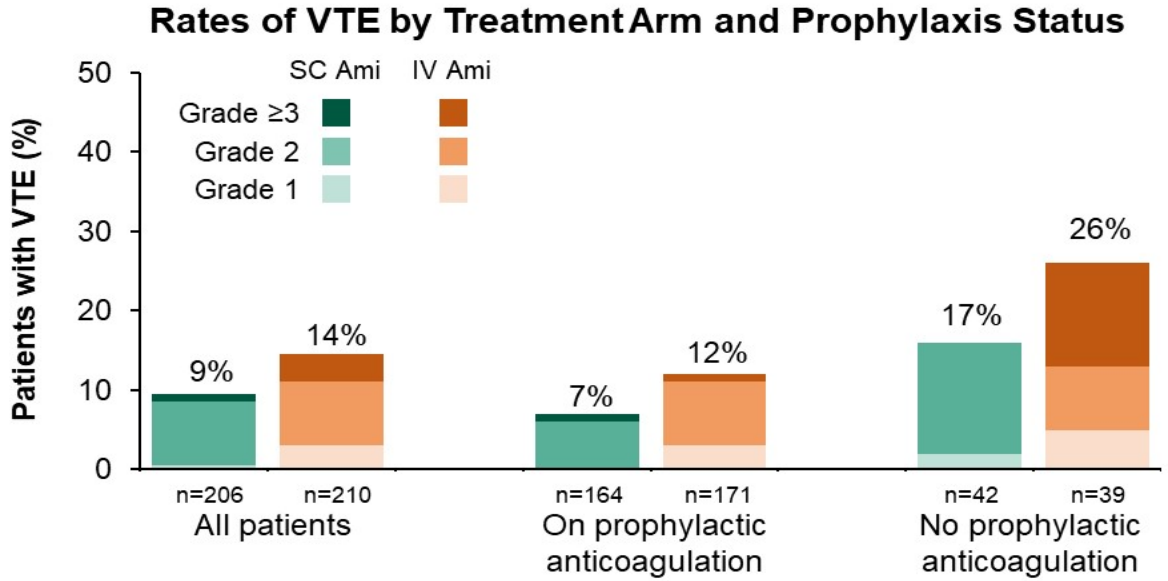
- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.

AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

Adverse Event of Special Interest: VTE[a]

- Prophylactic anticoagulation[b] was administered to 80% (164/206) of patients in the SC arm and 81% (171/210) for IV
- Among all patients in the study, VTE was reported in 10% (32/335) of those receiving prophylactic anticoagulation vs 21% (17/81) who did not
- Rates of grade ≥3 bleeding events were uncommon in the SC (2%) and IV (1%) arms for those receiving prophylactic anticoagulation



- Between study arms, incidence of VTE was less frequent in the SC amivantamab arm compared to the IV arm, regardless of prophylactic anticoagulation status

Note: The safety population included all the patients who had undergone randomization and received at least one dose of any trial treatment.

[a]Grouping includes pulmonary embolism, deep vein thrombosis, venous embolism, venous thrombosis limb, embolism, thrombosis, subclavian vein thrombosis, superficial vein thrombosis, pulmonary infarction, venous thrombosis. [b]VTE prophylaxis with apixaban, rivaroxaban, dalteparin, or enoxaparin was recommended by protocol (per the National Comprehensive Cancer Network guideline *Cancer-Associated Venous Thromboembolic Disease* v1.2022).

IV, intravenous; SC, subcutaneous; VTE, venous thromboembolism.

Conclusions

- SC amivantamab + lazertinib demonstrated PK and ORR noninferiority to IV amivantamab + lazertinib in patients with *EGFR*-mutated advanced NSCLC with disease progression on or after osimertinib and chemotherapy
- Compared to the IV arm, SC amivantamab also showed:
  - Numerically longer DoR (11.2 vs 8.3 months) and PFS (6.1 vs 4.3 months)
  - Significant improvement in OS (HR, 0.62; nominal *P*=0.02)
- Future studies are needed to evaluate whether SC absorption via the lymphatic system enhances amivantamab's immune-mediated activity
- The safety profile of SC amivantamab was consistent with IV, with fewer IRRs (13% vs 66%) and VTE (9% vs 14%)
- Administration time was substantially shorter for SC amivantamab (median <5 minutes) vs IV amivantamab (ranging from 2 to 5 hours), with significantly more patients reporting convenience (85% vs 35% at EOT)

SC amivantamab + lazertinib demonstrated noninferior efficacy, lower rates of IRRs and VTE, and is more convenient for patients and providers vs IV amivantamab + lazertinib

DoR, duration of response; EGFR, epidermal growth factor receptor; EOT, end of treatment; HR, hazard ratio; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; SC, subcutaneous; VTE, venous thromboembolism.

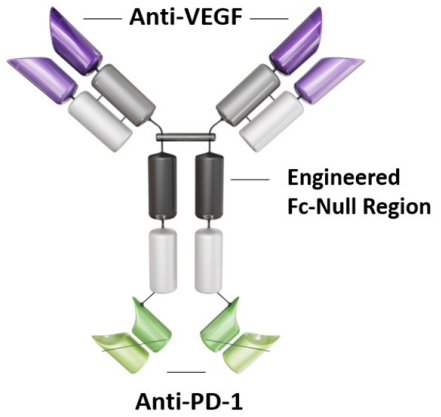
Enfermedad metastásica con alteración molecular: EGFR

Iniciativa científica de: GECP lung cancer research

Segunda línea: Abstract 8508

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]



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)

R (1:1)

Ivonescimab 20mg/kg + Pemetrexed 500 mg/m² Carboplatin AUC5 Q3W for 4 cycles → **Ivonescimab** 20mg/kg Q3W + Pemetrexed 500 mg/m² Q3W

Placebo + Pemetrexed 500 mg/m² Carboplatin AUC5 Q3W for 4 cycles → **Placebo** Q3W + Pemetrexed 500 mg/m² Q3W

Treatment until:

- Intolerable toxicity
- No clinical benefit
- Initiation of new anti-tumor therapy

Up to 24 months

Endpoints

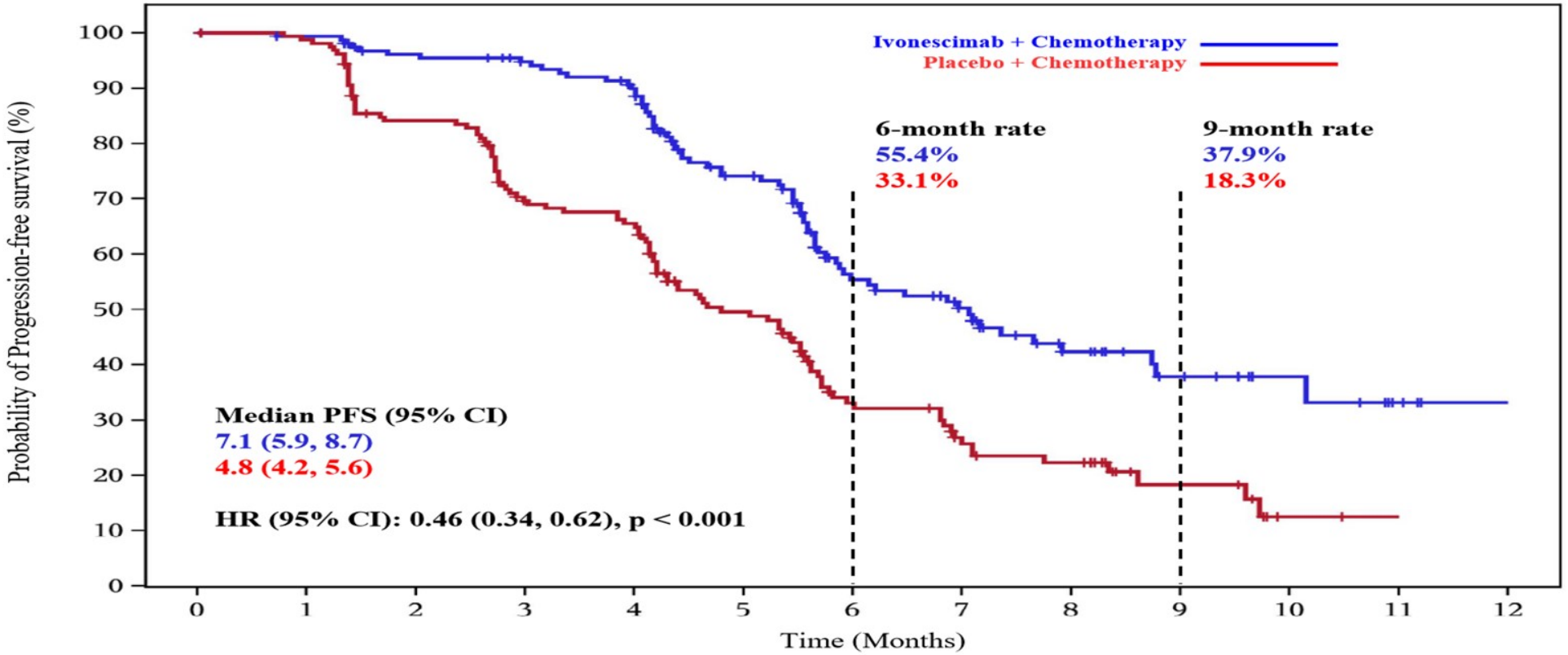
- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

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



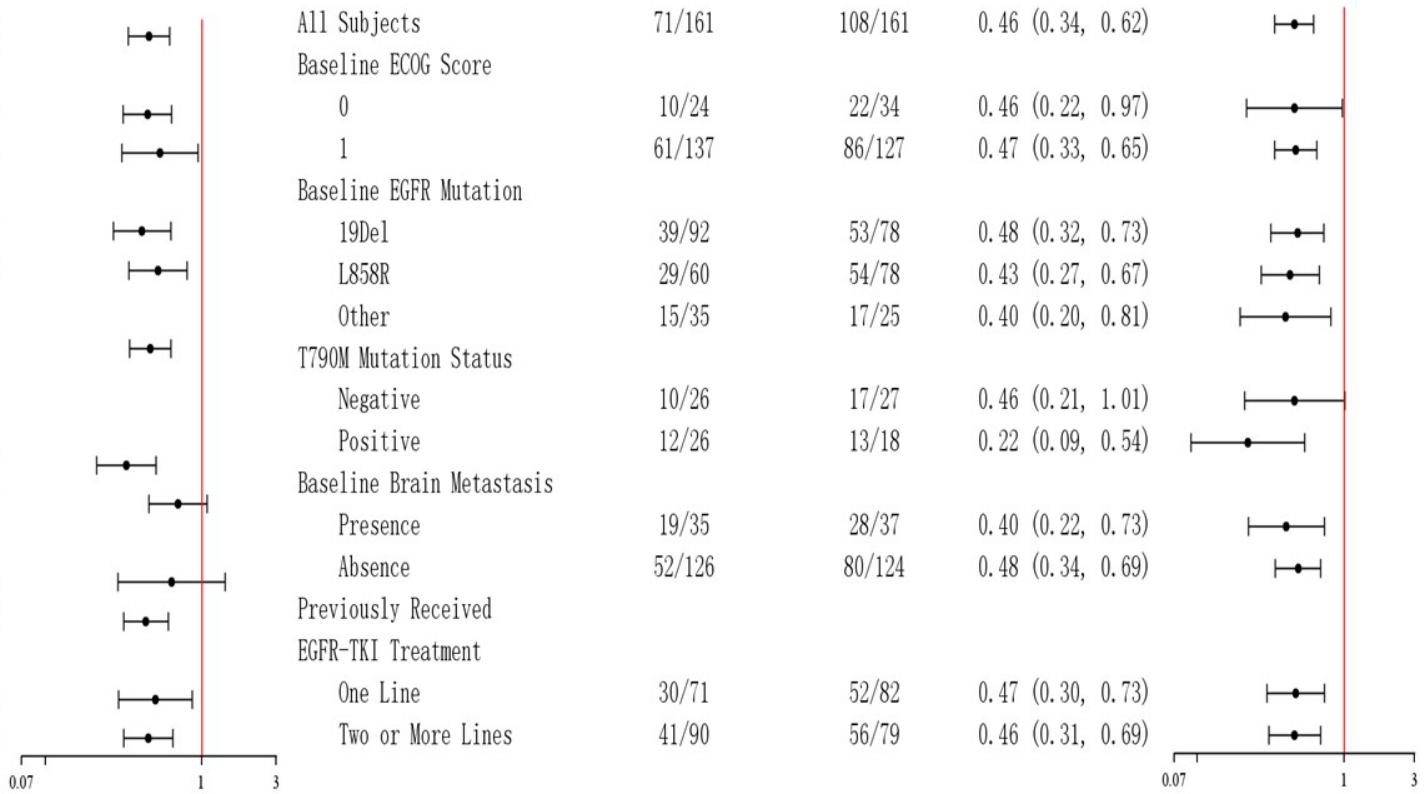
At risk (events)

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.

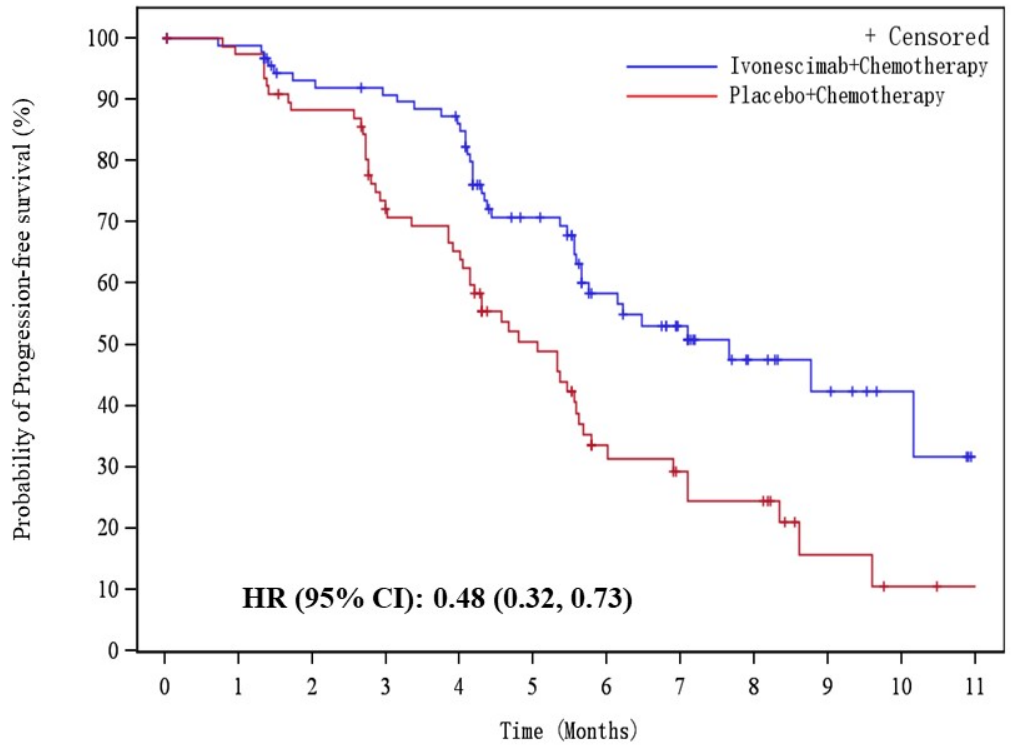
Subgroup Analysis of PFS per IRRC

	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)
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

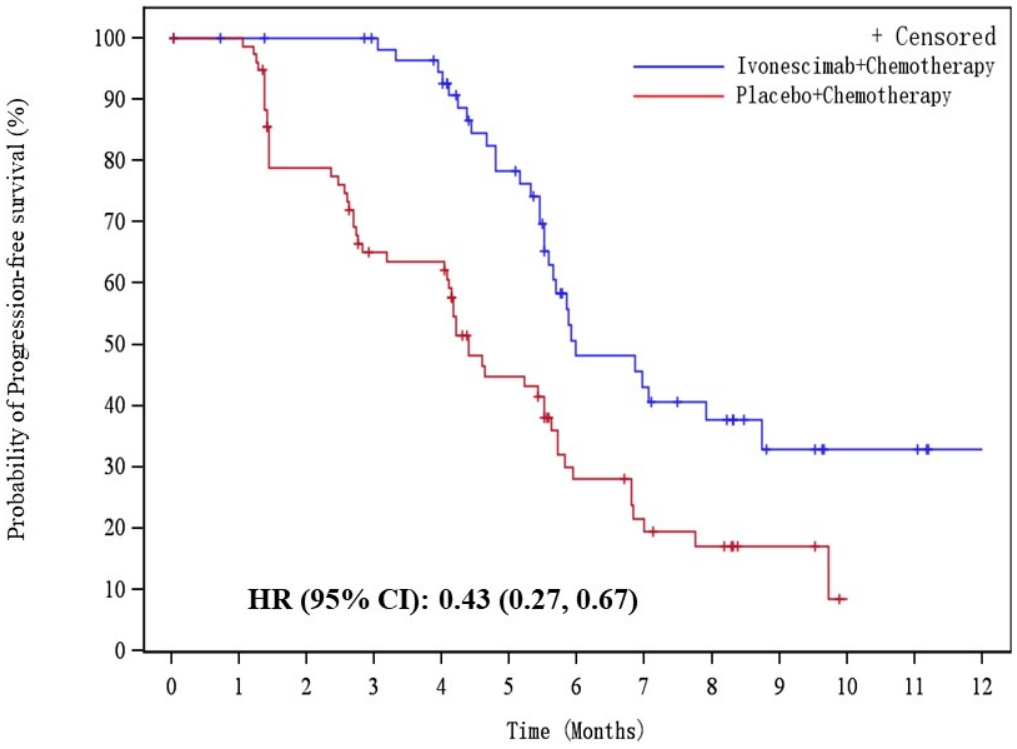
PFS Kaplan Meier Curve Evaluated by IRRC
with 19del



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

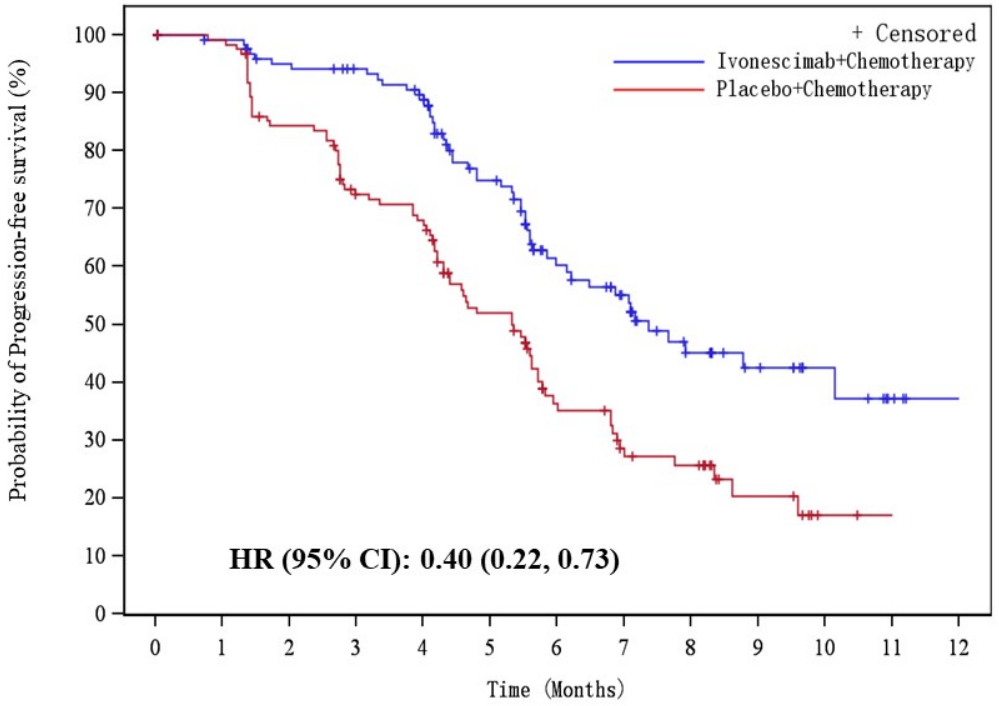


Number of Subjects at Risk (Number of Events)

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

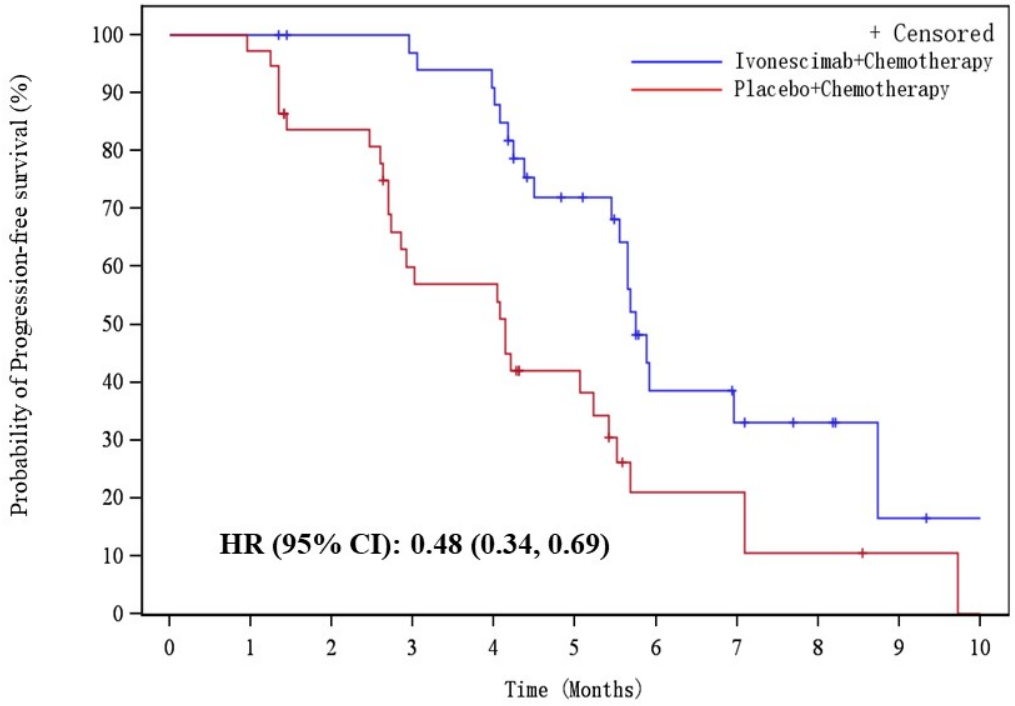
PFS Kaplan Meier Curve Evaluated by IRRC
without Brain Metastasis



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)	

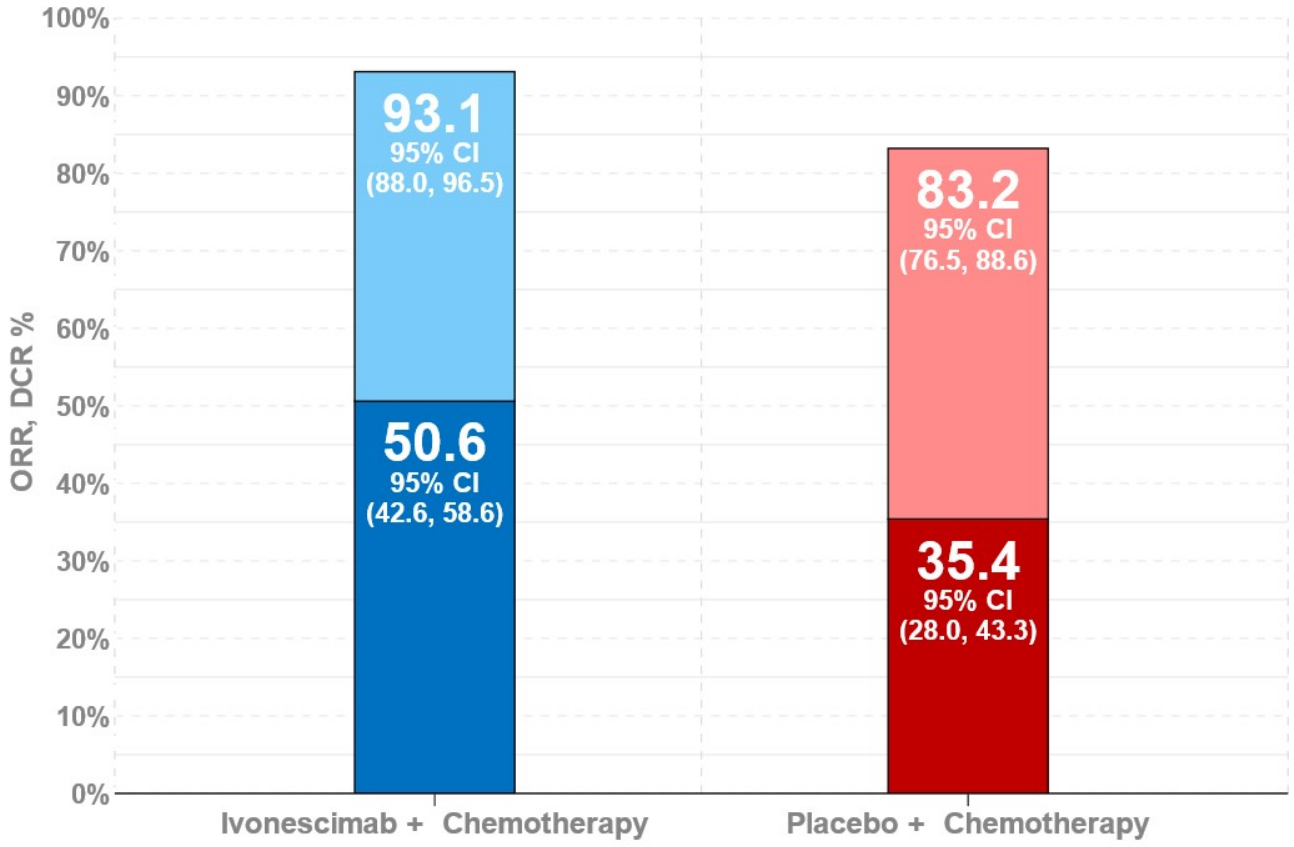
PFS Kaplan Meier Curve Evaluated by IRRC
with Brain Metastasis



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)

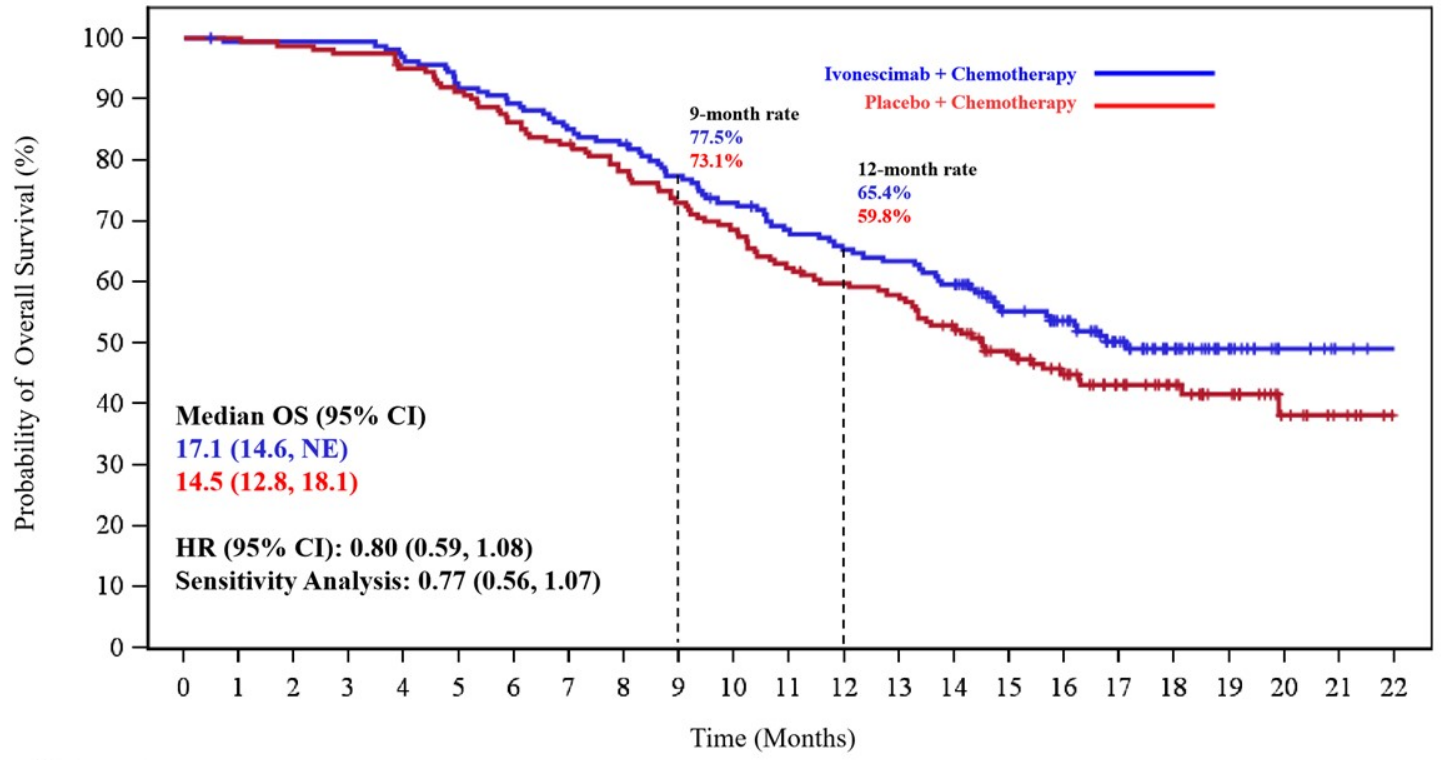
ORR, DCR and DoR per IRRC



	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 52% of Data Maturity)



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)

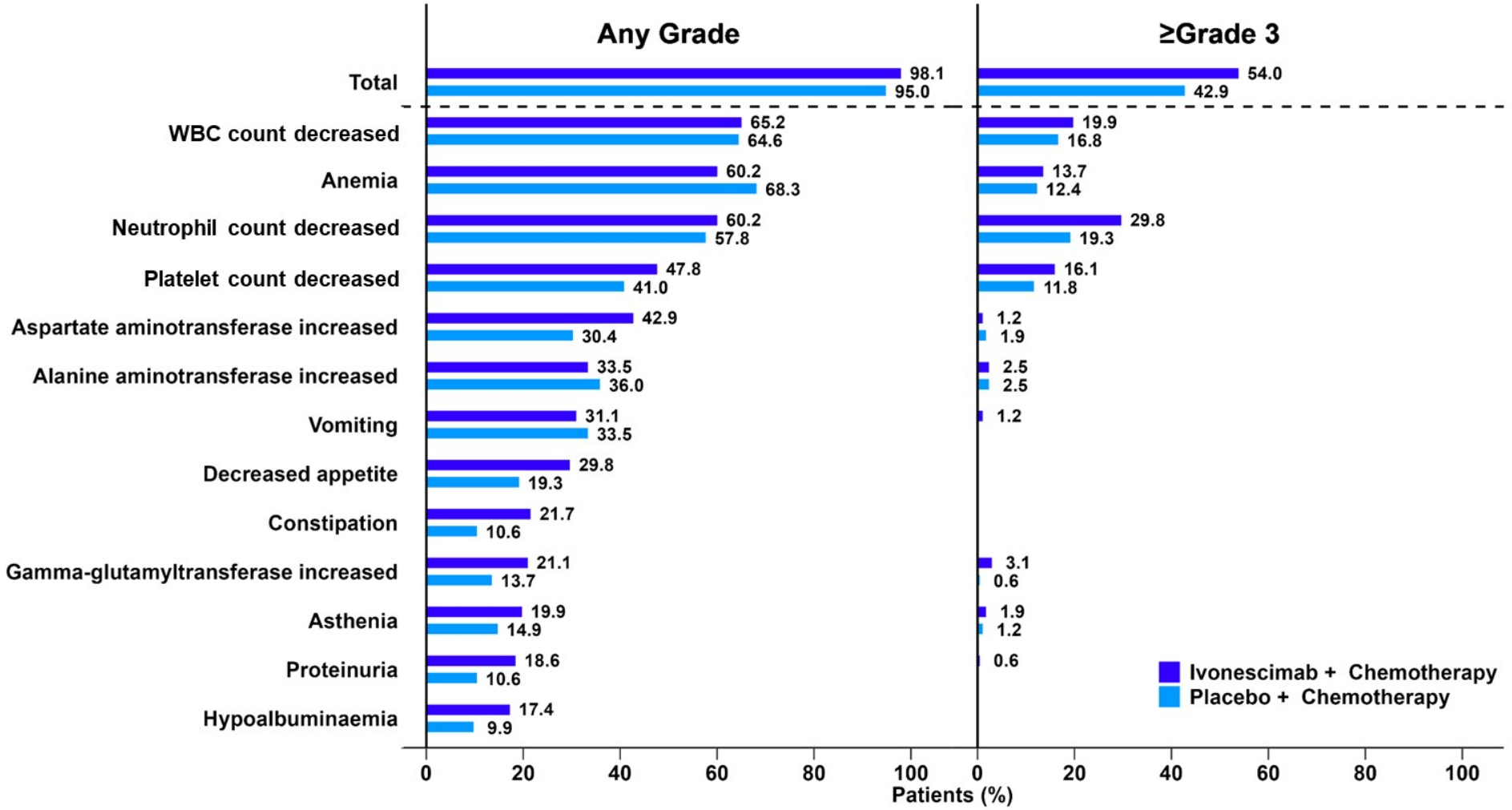
HR, hazard ratio; CI, confidence interval.

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 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)

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

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

Enfermedad metastásica con alteración molecular: EGFR

Ex20ins: Abstract 8513

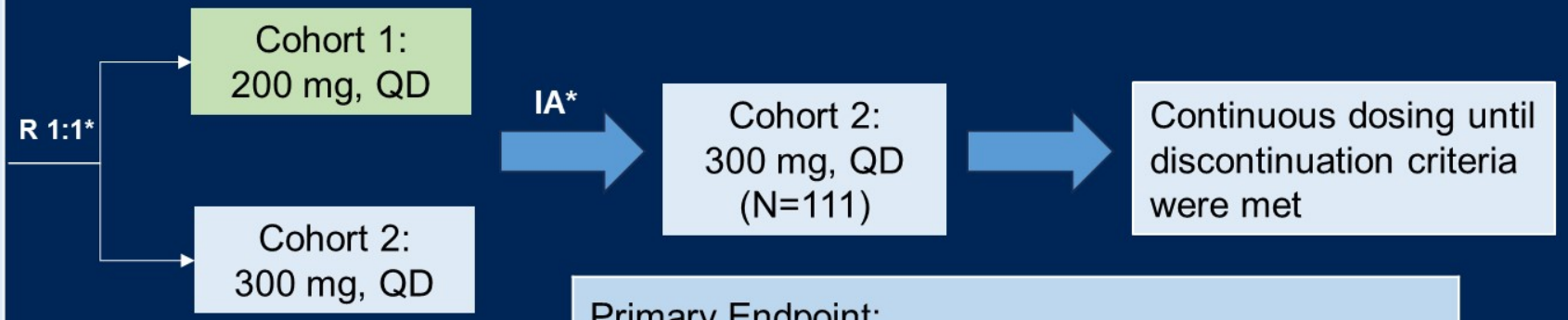
Iniciativa científica de: GECP lung cancer research

A Multinational Pivotal Study of Sunvozertinib in Platinum Pre-treated Non-Small Cell Lung Cancer with EGFR Exon 20 Insertion Mutations: Primary Analysis of WU-KONG1 Study

James Chih-Hsin Yang[1], Ludovic Doucet[2], Mengzhao Wang[3], Yun Fan[4], Meili Sun[5], Laurent Greillier[6], David Planchard[7], Julien Mazieres[8], Enriqueta Felip[9], Bruna Pellini[10], Joaquim Bosch-Barrera[11], Manuel Cobo-Dols[12], Alessandra Bearz[13], Luis G. Paz-Ares[14], Lyudmila Bazhenova[15], Elaine Shum[16], Marcello Tiseo[17], Hector Soto Parra[18], Li Zheng[19], Pasi A. Jänne[20]

WU-KONG1B Study Design

- Locally advanced or metastatic NSCLC
- Confirmed EGFR exon20ins in tumor tissues by local or sponsor designated laboratory testing
- ECOG PS of 0 or 1
- Prior treated with platinum-based chemotherapy



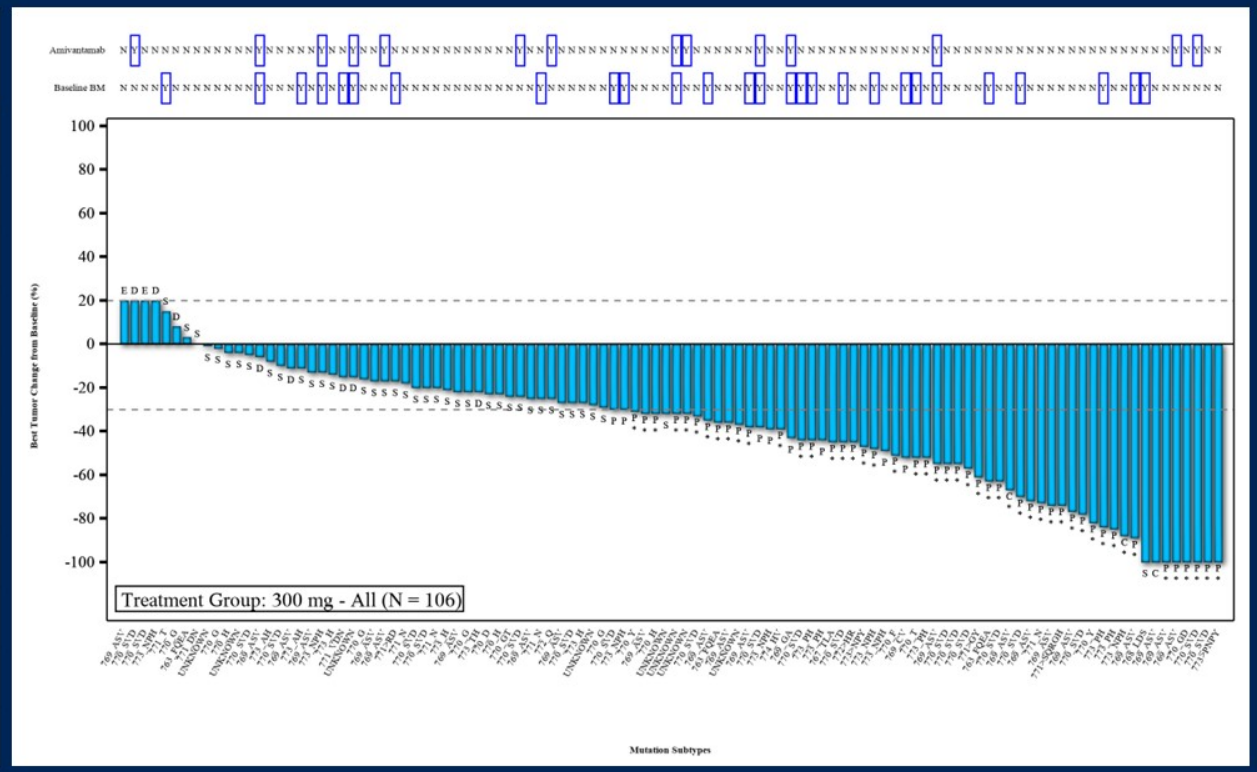
Primary Endpoint:
- ORR assessed by IRC#

Secondary Endpoints:
- DoR by IRC (key secondary endpoint), investigator assessed ORR and DoR, etc.

*Randomization ratio 1:1, and stratified by 1) brain metastasis; 2) number of prior treatment regimens.
**Interim analysis (IA) has been performed after 39 participants in each dose cohort completed at least 2 RECIST assessments.
#According to RECIST 1.1. Tumor assessment every 6 weeks from C1D1 until progression.
ORR: objective response rate; DoR: duration of response; IRC: independent review committee; INV: investigator; QD: once daily

Anti-tumor Efficacy

Tumor Response Per IRC	300 mg (N = 107)
Best ORR (%) with 97.5% CI	53.3 (42.0, 64.3)
Confirmed ORR (%) with 97.5% CI	44.9 (34.0, 56.1)
Best Response, n (%)	
Complete response	3 (2.8)
Complete response (confirmed)	2 (1.9)
Partial response	54 (50.5)
Partial response (confirmed)	46 (43.0)
Partial response (pending for confirmation)	4 (3.7)
Stable disease	39 (36.4)
Progressive disease	8 (7.5)
Not evaluable	3 (2.8)



- As of March 22, 2024, per IRC assessment, the best ORR was 53.3% (44.9% confirmed, and additional 3.7% pending confirmation). Two (1.9%) patients achieved complete response (both confirmed).
- The median DoR has not been reached, and the 9-month DoR rate was 57%.
- Anti-tumor efficacy was observed regardless of amivantamab treatment. The best ORRs in patients with or without prior amivantamab treatment were 50% and 53.8%, respectively.

Safety

Common (≥ 2%) ≥ grade 3 TRAE, n (n%)	300 mg (N = 111)
Diarrhea	19 (17.1)
Blood creatine phosphokinase increased	12 (10.8)
Anaemia	4 (3.6)
Rash	4 (3.6)
Lipase increased	4 (3.6)
Neutrophil count decreased	3 (2.7)
Hypokalaemia	3 (2.7)
Decreased appetite	3 (2.7)
Asthenia	3 (2.7)

CTCAE: Common Terminology Criteria for Adverse Events; TRAE: Treatment-related Adverse Event.
* 1.8% ≥ grade 3 ILD, no fatal case.

- Safety findings were similar to what has been previously reported in other sunvozertinib clinical studies
- TRAEs leading to drug dose reduction and treatment discontinuation were 36.0% and 6.3%, respectively
- At 300 mg, the most common TRAEs included diarrhea and CPK increased, etc.
- The majority of common TRAEs were of grade 1 or 2 and clinically manageable
- No TRAEs with fatal outcome

Summary

- WU-KONG1B study achieved its primary objective, with manageable safety profile in platinum-based chemotherapy pretreated NSCLC with EGFR exon20ins.
  - Efficacy:
    - The confirmed ORR was 44.9% with additional 3.7% pending confirmation per IRC assessment.
    - The efficacy was durable. The 9-month DoR rate was 57%.
    - Anti-tumor efficacy was observed regardless of prior amivantamab treatment.
  - Safety:
    - Similar AE profile to previously reported
- A phase III, multinational, randomized study (WU-KONG28, NCT05668988) is ongoing to assess sunvozertinib versus platinum-based chemotherapy in NSCLC patients with EGFR exon20ins NSCLC in the 1st line.

Enfermedad metastásica con alteración molecular: EGFR

Atípicas no Ex20ins: Abstract 8516

Iniciativa científica de: GECP lung cancer research

Amivantamab plus lazertinib in atypical *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2

Byoung Chul Cho[1], Yongsheng Wang[2], Enriqueta Felip[3], Jiuwei Cui[4], Alexander I Spira[5], Joel W Neal[6], Christina Baik[7], Melina E Marmarelis[8], Eiki Ichihara[9], Jong-Seok Lee[10], Se-Hoon Lee[11], James Chih-Hsin Yang[12], Sebastian Michels[13], Zacharias Anastasiou[14], Joshua C Curtin[15], Xuesong Lyu[16], Levon Demirdjian[17], Isabelle Leconte[18], Leonardo Trani[15], Mahadi Baig[19], Joshua M Bauml[15], Pascale Tomasini[20]

CHRYSALIS-2 Study Design

CHRYSALIS-2
Ami + Laz in
Atypical *EGFR*+
NSCLC

Dose escalation phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose expansion cohorts

- **Cohort A:** *EGFR* Ex19del or L858R[a] (post-osimertinib/post-platinum)
- **Cohort B:** *EGFR* Ex20ins[a] (post-SOC/post-platinum)
- **Cohort C: Atypical *EGFR* mutations (treatment naïve or post-TKI/chemo)**
- **Cohort D:** *EGFR* Ex19del or L858R[a] (post-osimertinib; biomarker validation)
- **Cohort E:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)
- **Cohort F[b]:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)

Primary endpoint:
- ORR by investigator per RECIST v1.1

Secondary endpoints:
- DoR
- CBR[c]
- PFS
- OS
- Safety (AEs)

Focus of this presentation

- Cohort C included patients with atypical *EGFR* mutations who were treatment naïve or had ≤2 prior lines (excluding 3rd-gen EGFR TKIs)
- Patients with **Ex20ins and Ex19del/L858R co-mutations were excluded**
- Baseline ctDNA NGS analyses were performed using Guardant Health G360[d]

CHRYSALIS-2 ClinicalTrials.gov Identifier: NCT04077463.
[a]Cohort A data were presented at ASCO 2022 (Shu et al. *J Clin* Oncol. 2022;40(16_suppl):abstract 9006); Cohort B data are pending; Cohort D data were presented at ASCO 2023 (Besse et al. *J Clin Oncol*. 2023;41(16_suppl):abstract 9013).
[b]Patients in Cohort F received amivantamab monotherapy.
[c]CBR is determined among patients with CR, PR, or SD (duration of ≥11 weeks).
[d]Patients from China were not analyzed for baseline ctDNA.

AE, adverse event; CBR, clinical benefit rate; chemo, chemotherapy; CR, complete response; ctDNA, circulating tumor DNA; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; Ex20ins, Exon 20 insertion; G360, Guardant360® panel (Redwood City, CA); gen, generation; IHC, immunohistochemistry; IV, intravenous; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2CD, recommended phase 2 combination dose; SD, stable disease; SOC, standard of care; TKI, tyrosine kinase inhibitor.

Demographic and Baseline Disease Characteristics

- As of January 12, 2024, 105 patients received amivantamab + lazertinib, with a median follow-up of 16.1 months (range, 0.1–31.5)

Characteristic, n (%)	Cohort C (n=105)
Median age, years (range)	64 (30–85)
Male / female	53 (50) / 52 (50)
Race	
White	31 (30)
Asian	71 (68)
Black or African American	1 (1)
Not reported	2 (2)
Brain metastases at baseline	33 (31)
Prior therapies in metastatic setting	
Treatment naïve	49 (47)
Prior afatinib	34 (32)
Prior 1st-/2nd-gen EGFR TKI (other than afatinib)[a]	9 (9)
Prior platinum chemotherapy	7 (7)
Prior afatinib + prior platinum chemotherapy	6 (6)

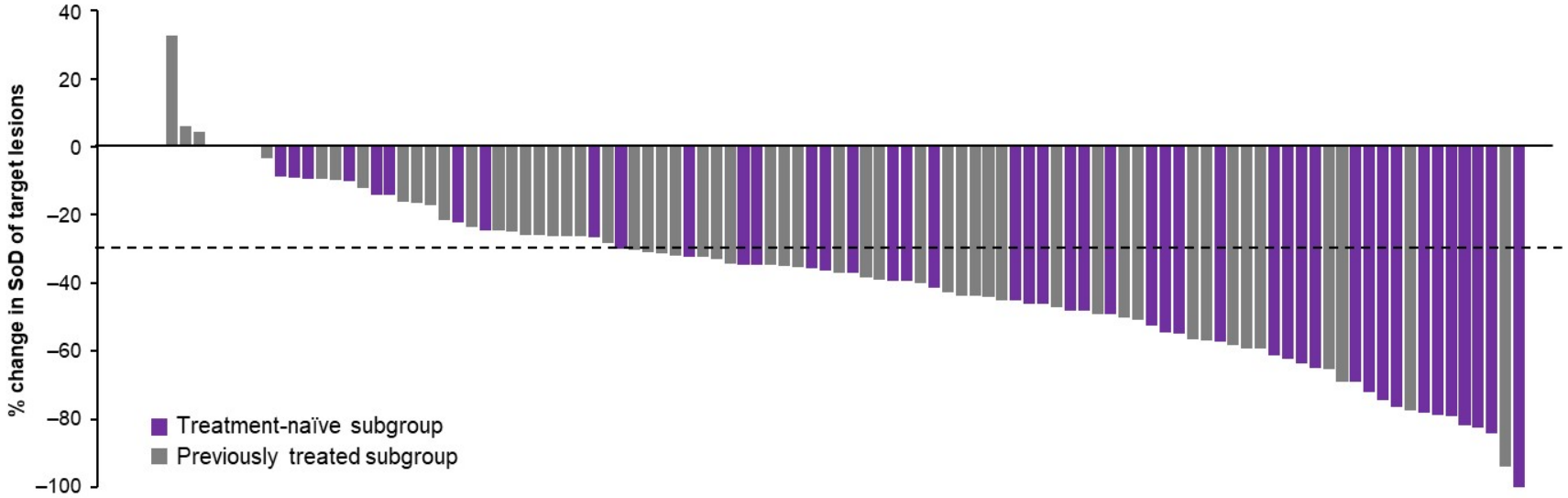
Characteristic, n (%)	Cohort C (n=105)
ECOG PS	
0	33 (31)
1	72 (69)
Type of *EGFR* mutation[b]	
Exon 18 G719X	60 (57)[c]
Exon 21 L861X	27 (26)[d]
Exon 20 S768X	25 (24)[e]
Exon 18 E709K	2 (2)
Exon 20 E709A	2 (2)
L833V	2 (2)
R776C	2 (2)
R776H	1 (1)
R831H	1 (1)
V744M	1 (1)
V769L	1 (1)
V774M	1 (1)
Other	10 (10)

[a]1st-/2nd-generation EGFR TKIs other than afatinib included gefitinib, dacomitinib, erlotinib, and icotinib. [b]Patients may be counted in ≥1 category. [c]G719X included G719A, G719S, and G719C. [d]L861X included L861Q, L861R, and L861G. [e]S768X included S768I and S768L.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

Efficacy Outcomes of Amivantamab + Lazertinib Among All Patients in Cohort C

CHRYSALIS-2
Ami + Laz in Atypical *EGFR*+ NSCLC

Investigator-assessed response (n=105)	
Median follow-up	16.1 mo (range, 0.1–31.5)
ORR	52% (95% CI, 42–62)
Median DoR	14.1 mo (95% CI, 9.5–26.2)
DoR ≥6 mo, n (%)[a]	38 (69)
Best response, n (%)	
CR	0
PR	55 (52)
SD	37 (35)
PD	8 (8)
Not evaluable/UNK	5 (5)
CBR[b]	79% (95% CI, 70–86)
Median PFS	11.1 mo (95% CI, 7.8–17.8)
Median OS	NE (95% CI, 22.8–NE)



- In a heterogeneous population, the **median PFS was 11.1 months** and **median OS was NE**

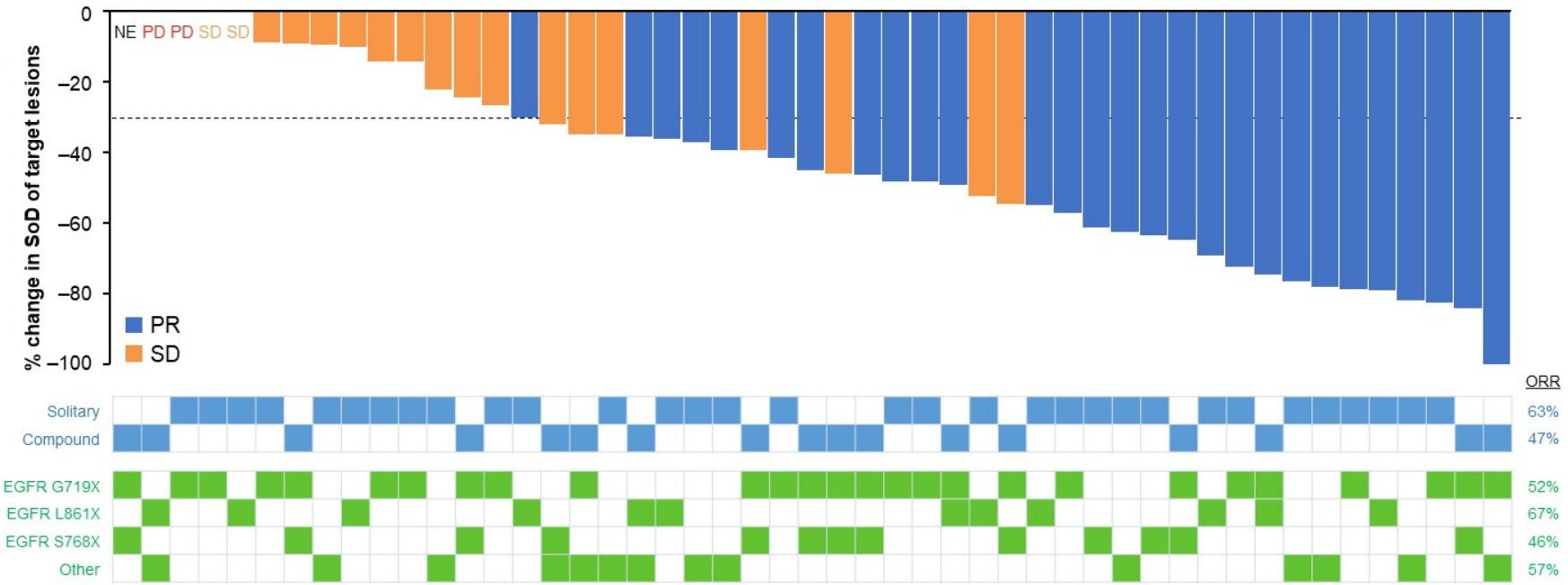
[a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters.

Efficacy Outcomes of First-line Amivantamab + Lazertinib

CHRYSALIS-2
Ami + Laz in Atypical *EGFR*+ NSCLC

Investigator-assessed response (n=49)	
Median follow-up	17.3 mo (range, 0.1–31.5)
ORR	57% (95% CI, 42–71)
Median DoR	20.7 mo (95% CI, 9.9–NE)
DoR ≥6 mo, n (%)[a]	21 (75)
CBR[b]	84% (95% CI, 70–93)
Median PFS	19.5 mo (95% CI, 11.2–NE)
Median OS	NE (95% CI, 26.3–NE)



- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 17.3 months, the **median PFS was 19.5 months** and **median OS was NE**

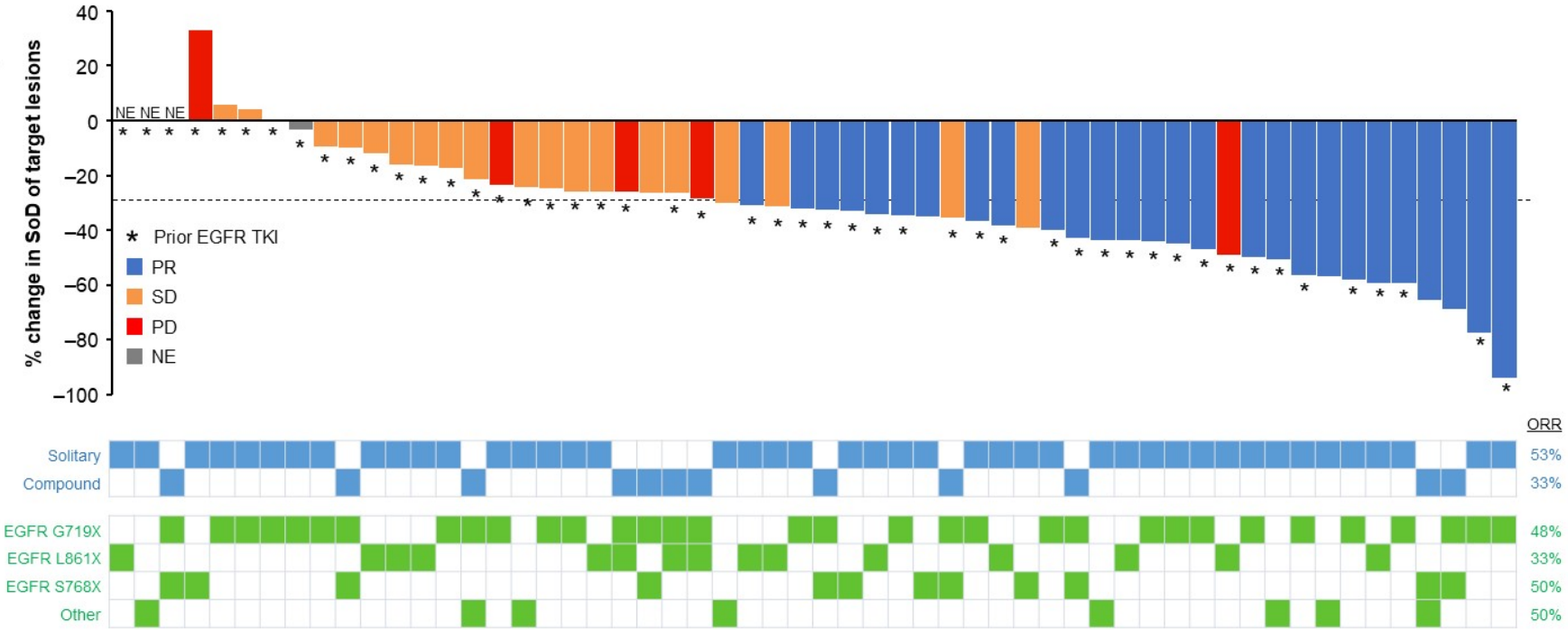
[a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; EGFR, epidermal growth factor receptor; mo, months; NE, not estimable/evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters.

Efficacy Outcomes of Second or Third-line Amivantamab + Lazertinib

CHRYSALIS-2
Ami + Laz in Atypical *EGFR*+ NSCLC

Investigator-assessed response (n=56)	
Median follow-up	15.4 mo (range, 0.3–30.8)
ORR	48% (95% CI, 35–62)
Median DoR	11.0 mo (95% CI, 4.5–NE)
DoR ≥6 mo, n (%)[a]	17 (63)
CBR[b]	75% (95% CI, 62–86)
Median PFS	7.8 mo (95% CI, 5.4–11.1)
Median OS	22.8 mo (95% CI, 16.9–NE)



- 88% of patients received a prior EGFR TKI
- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 15.4 months, the **median PFS was 7.8 months** and **median OS was 22.8 months**

*Patients who received prior EGFR TKI therapy. [a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; EGFR, epidermal growth factor receptor; mo, months; NE, not estimable/evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

Conclusions

- Amivantamab + lazertinib demonstrated durable antitumor activity in patients with atypical *EGFR*-mutated advanced NSCLC
  - In the treatment-naïve subgroup, the ORR was 57%, with a median PFS of **19.5 months**
    - Patients from CHRYSALIS-2 Cohort C had a numerically higher median TTD (14.0 vs 3.2 mo) and 24-month OS rate (79% vs 44%) than patients in a real-world database treated with available therapies
  - In the previously treated subgroup, the ORR was 48%, with a median PFS of 7.8 months
- The safety profile of amivantamab + lazertinib was consistent with prior reports, with no new signals
- Now, amivantamab-based combinations have demonstrated efficacy in patients with advanced NSCLC harboring common *EGFR* mutations,[1-2] *EGFR* Exon 20 insertions,[3] and atypical *EGFR* mutations

Amivantamab + lazertinib demonstrated clinically meaningful and durable antitumor activity in patients with atypical *EGFR*-mutated advanced NSCLC

EGFR, epidermal growth factor receptor; mo, months; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14. 2. Passaro A, et al. *Ann Oncol* 2024;35(1):77-90. 3. Zhou C, et al. *N Engl J Med*. 2023;389(22):2039-2051.

Enfermedad metastásica con alteración molecular: MET

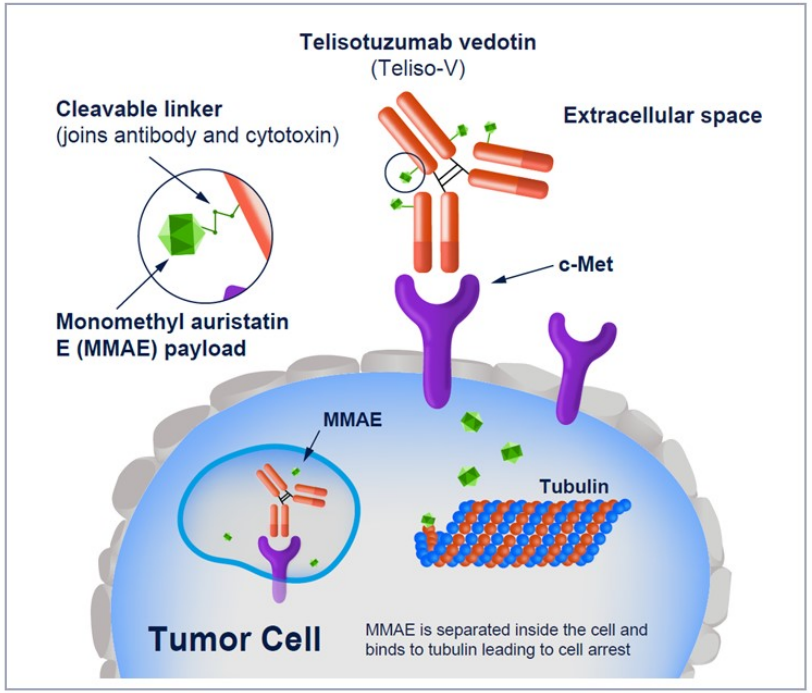
2L cMet Overexpressing nsq-NSCLC: Abstract 103

Iniciativa científica de: GECP lung cancer research

103

Telisotuzumab Vedotin Monotherapy in Patients With Previously Treated c-Met–Overexpressing Non-Squamous *EGFR* Wildtype Advanced NSCLC: Primary Analysis of the LUMINOSITY Trial

D. Ross Camidge, MD, PhD[1], Jair Bar, MD, PhD[2], Hidehito Horinouchi, MD, PhD[3], Jonathan Goldman, MD[4], Fedor Moiseenko, MD, PhD[5], Elena Filippova, MD[6], Irfan Cicin, MD[7], Tudor Ciuleanu, MD, PhD[8], Nathalie Daaboul, MD[9], Chunling Liu, MD[10], Penelope Bradbury, MB, BCh, FRACP, MD (UK)[11], Mor Moskovitz, MD[12], Nuran Katgi, MD[13], Pascale Tomasini, MD[14], Alona Zer, MD[15], Jim Looman, MD[16], Christine Ratajczak, PhD[16], Martha Li, PhD[16], Summer Xia, PhD[16], Shun Lu, MD, PhD[17]



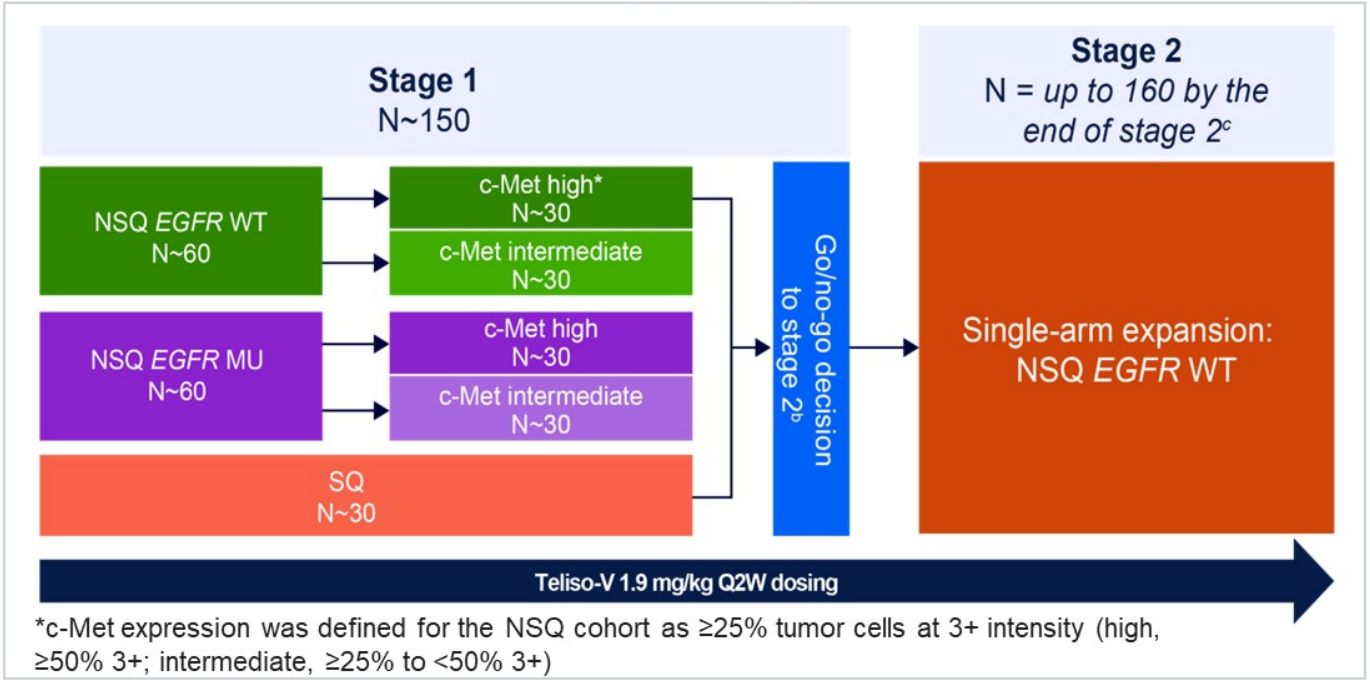
LUMINOSITY is a phase 2, multicenter, non-randomized, 2-stage study (NCT03539536)

Eligible Patients
- ≥18 years
- Advanced/metastatic NSCLC
- c-Met OE by IHC[a]
- Received ≤2 prior lines of systemic therapy in the advanced/metastatic setting, including cytotoxic CTx (≤1 line), immunotherapy (sequential or combined with CTx), and therapy targeting driver gene alterations (if eligible)

Primary Endpoint
- ORR assessed by ICR per RECIST v1.1

Secondary Endpoints
- DCR, DOR, PFS, and OS

Study Design



*c-Met expression was defined for the NSQ cohort as ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, ≥25% to <50% 3+)

- The SQ and *EGFR* MU NSQ cohorts met stopping criteria
- The *EGFR* WT NSQ cohort met criteria for expansion in stage 2

[a]IHC was undertaken using a clinical trial assay for MET (SP44) (Roche); [b]Go/no-go decision was based on the Bayesian posterior probability of success, defined as the posterior probability of the ORR exceeding 25%; if this fell below 0.10, the group was considered futile; if this went above 0.70, the group was expanded; [c]After completion of global Stage 2 enrollment, a China extension cohort of up to 12 patients dosing at 1.9 mg/kg was added. CTx, chemotherapy; DCR, disease control rate; DOR, duration of response; *EGFR*, epidermal growth factor receptor; ICR, independent central review; IHC, immunohistochemistry; MU, mutant; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OE, overexpression; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SQ, squamous; Teliso-V, telisotuzumab vedotin; WT, wildtype.

Baseline demographics and disease characteristics

- As of 28 September 2023 (data cutoff), 161 patients with c-Met–OE NSQ *EGFR* WT NSCLC were evaluable for efficacy[a]

Characteristic	c-Met OE Total[a] (N=161)
Median age, years (range)	64.0 (33–83)
Sex, n (%)	
Male	111 (68.9)
Female	50 (31.1)
Race, n (%)	
White	110 (68.3)
Black or African American	3 (1.9)
Asian	48 (29.8)
Tobacco use, n (%)	
Current	25 (15.5)
Former	101 (62.7)
Never	35 (21.7)
Brain metastasis,[b] n (%)	33 (20.5)

Characteristic	c-Met OE Total[a] (N=161)
ECOG performance status, n (%)	
0	47 (29.2)
1	113 (70.2)
2	1 (0.6)
Median no. of prior systemic cancer therapies (range)	1 (1–3)
Type of prior systemic cancer therapies, n (%)	
Platinum based	157 (97.5)
Immune checkpoint inhibitor based	132 (82.0)
Targeted therapy[c]	12 (7.5)

[a]Population comprised efficacy-evaluable patients who had c-Met OE, received ≥1 dose of Teliso-V, and received the first dose ≥7.5 months prior to the data cutoff date; [b]Patients with CNS metastasis were eligible if they had definitive therapy with no evidence of progression ≥2 weeks after definitive therapy and were asymptomatic and off systemic steroids and anticonvulsants for ≥2 weeks prior to first dose of Teliso-V; [c]Alterations in genes other than *EGFR* were allowed, although available site-reported data on other alterations were limited and indicated alterations in a minority of patients.ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NSQ, non-squamous; OE, overexpressing; Teliso-V, telisotuzumab vedotin; WT, wildtype.

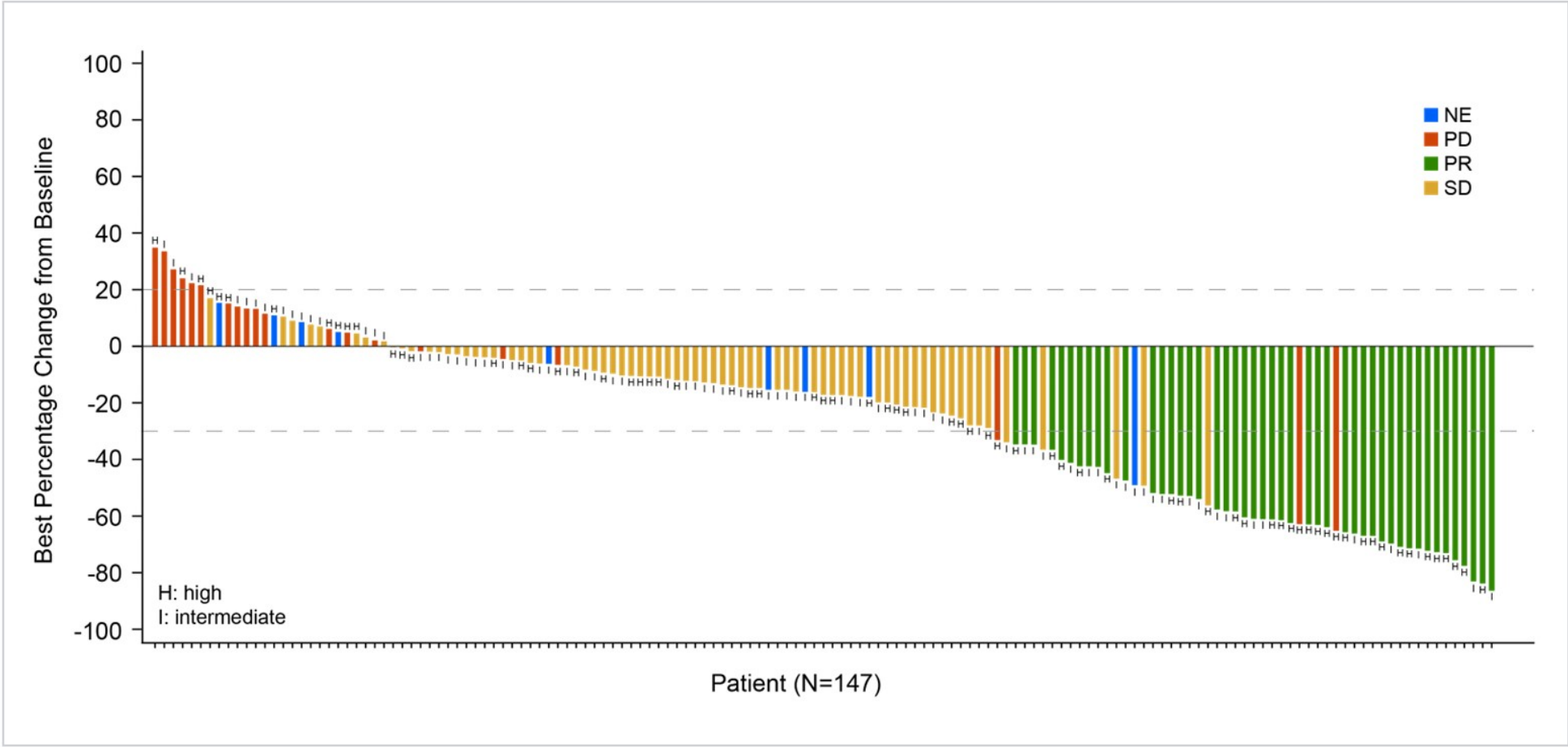
Patient disposition

Disposition, n (%)	c-Met OE Total (N=172)
Treatment duration	
Median, months	4.5
0–3 months	71 (47.3)
>3 to ≤6 months	37 (21.5)
>6 months to ≤9 months	27 (15.7)
>9 months	37 (21.5)
Discontinued study drug	159 (92.4)
Primary reasons for study drug discontinuation	
Progressive disease – RECIST v1.1	82 (47.7)
Adverse event	48 (27.9)
Withdrew consent	12 (7.0)
Progressive disease – clinical	10 (5.8)
Physician decision	5 (2.9)
Other	2 (1.2)
Discontinued study	116 (67.4)
Primary reasons for study discontinuation	
Death	105 (61.0)
Withdrew consent	7 (4.1)
Lost to follow-up	2 (1.2)
Other	2 (1.2)

Population comprised patients who have received ≥1 dose of Teliso-V.
OE, overexpressing; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Efficacy: Response and disease control

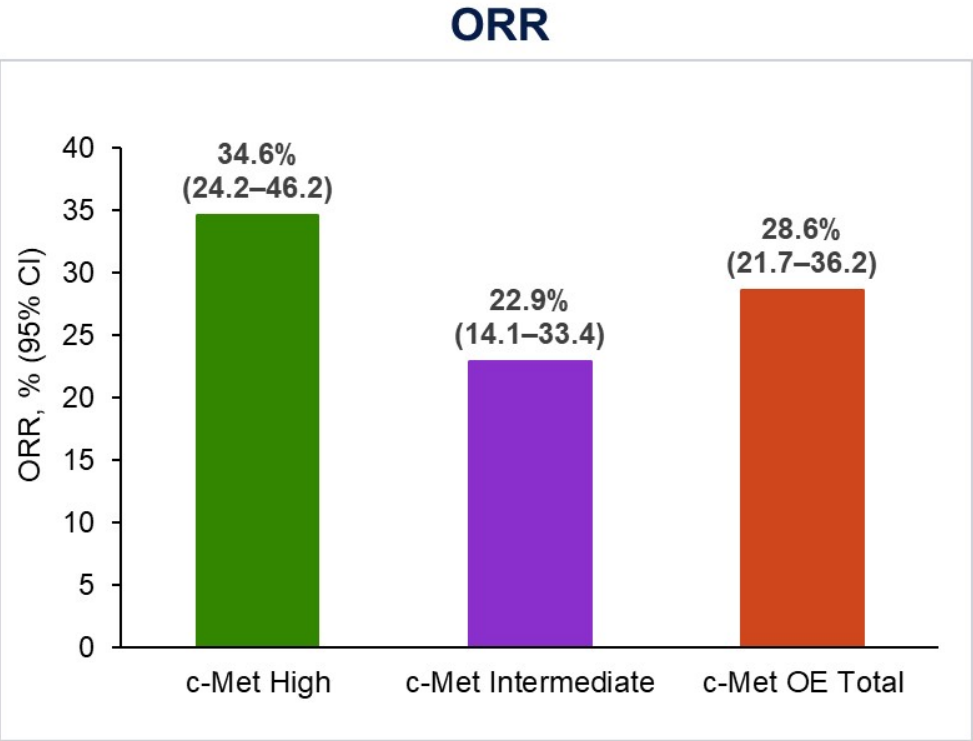
Best Reductions in Target Lesions[a] per ICR (n=147)



- DCR was 60.3% (c-Met high), 57.8% (c-Met intermediate), and 59.0% (c-Met OE total)

[a]Only patients who had measurable disease at baseline and who had at least 1 measurable post-baseline assessment were included in this analysis.
Efficacy-evaluable population comprised efficacy-evaluable patients who had c-Met OE, received ≥1 dose of Teliso-V, and received the first dose ≥7.5 months prior to the data cutoff date.
DCR, disease control rate; H, high; I, intermediate; ICR, independent central review; NE, not estimable; OE, overexpressing; PD, progressive disease; PR, partial response; SD, stable disease; Teliso-V, telisotuzumab vedotin.

Efficacy: ORR and DOR per ICR



	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Number of responders	27	19	46
Median DOR, months [95% CI]	9.0 [4.2, 13.0]	7.2 [5.3, 11.5]	8.3 [5.6, 11.3]
DOR ≥6 months, n (%)	17 (63.0)	9 (47.4)	26 (56.5)

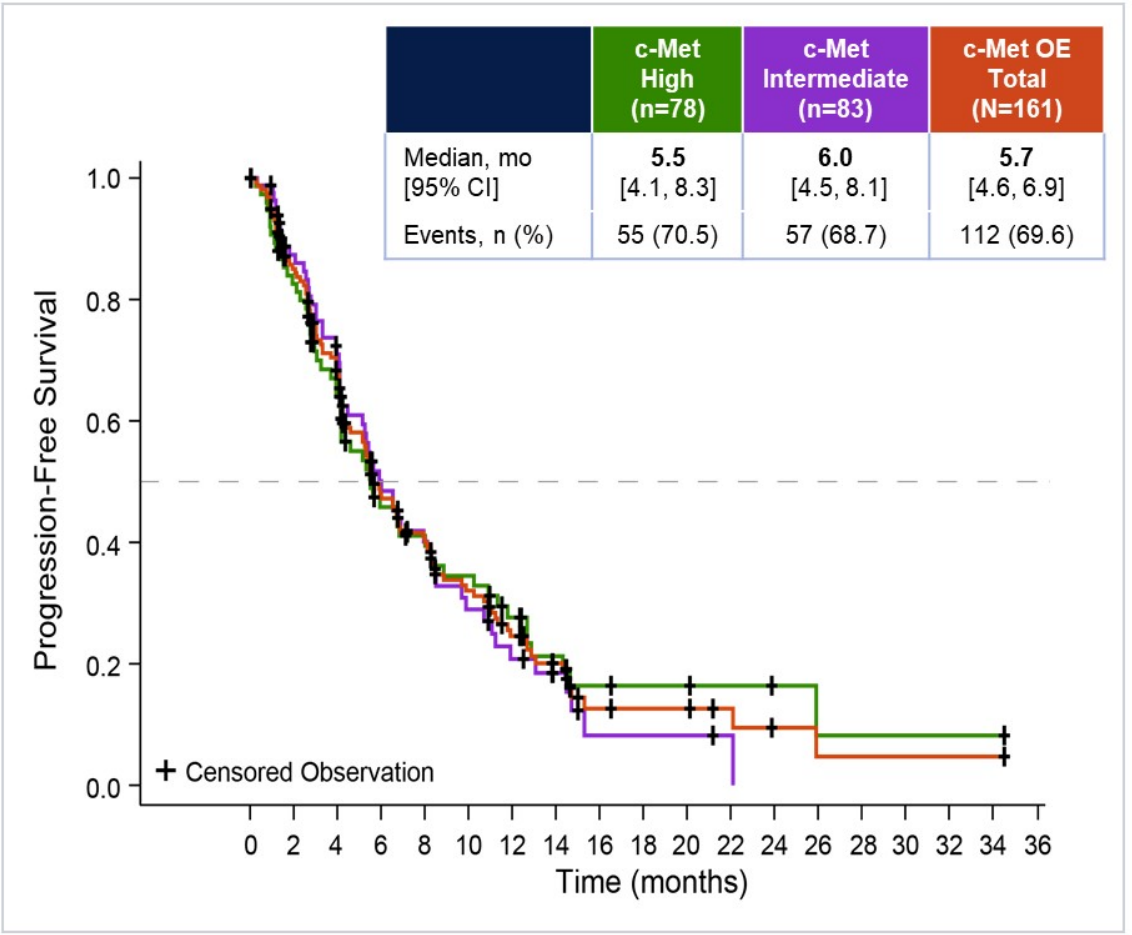
- Median time to onset of response per ICR was 1.41 months (range 1.0–7.4) for c-Met OE total

Efficacy-evaluable population comprised patients who had c-Met OE, received ≥1 dose of Teliso-V, and received the first dose ≥7.5 months prior to the data cutoff date.
CI, confidence interval; DOR, duration of response; ICR, independent central review; OE, overexpressing; ORR, overall response rate.

Efficacy: Progression-free per ICR and overall survival

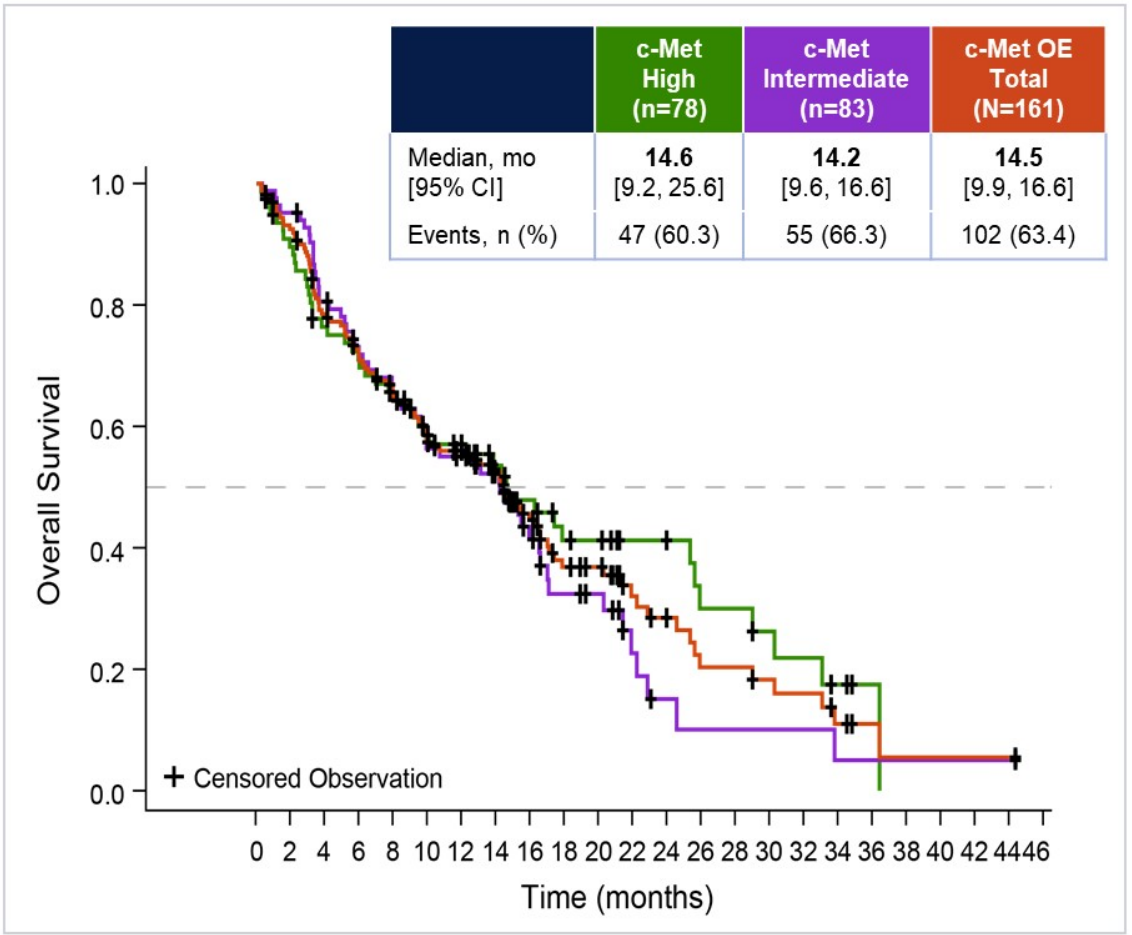
Progression-Free Survival

	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Median, mo [95% CI]	**5.5** [4.1, 8.3]	**6.0** [4.5, 8.1]	**5.7** [4.6, 6.9]
Events, n (%)	55 (70.5)	57 (68.7)	112 (69.6)



Overall Survival

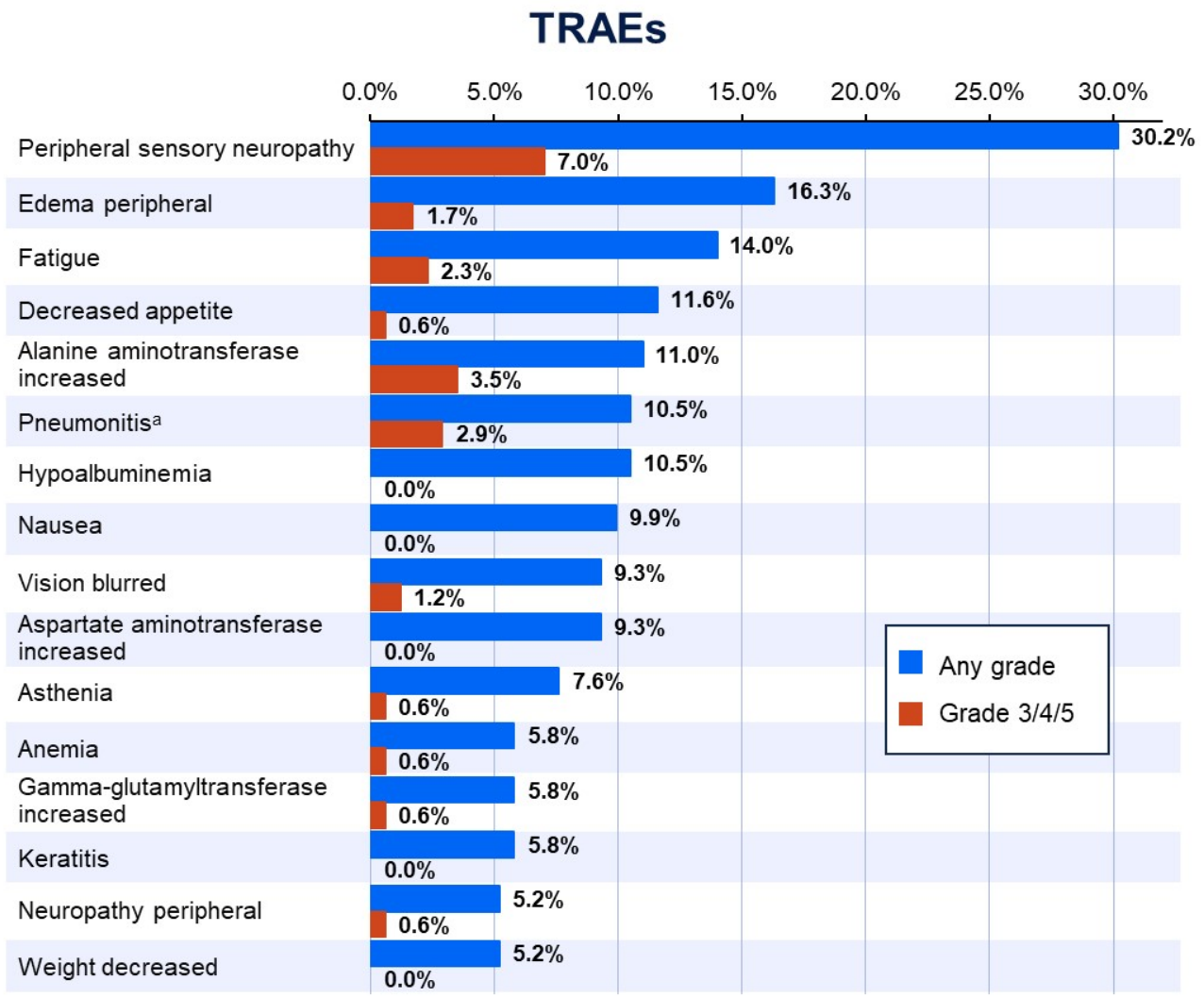
	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Median, mo [95% CI]	**14.6** [9.2, 25.6]	**14.2** [9.6, 16.6]	**14.5** [9.9, 16.6]
Events, n (%)	47 (60.3)	55 (66.3)	102 (63.4)



- 66 (41.0%) of patients received a subsequent systemic therapy after Teliso-V discontinuation

Efficacy-evaluable population comprised patients who had c-Met OE, received ≥1 dose of Teliso-V, and received the first dose ≥7.5 months prior to the data cutoff date. Median study follow up time was 19.3 months for c-Met OE total.
CI, confidence interval; ICR, independent central review; mo, months; OE, overexpressing; Teliso-V, telisotuzumab vedotin.

Safety: Treatment-related adverse events occurring in >5% of patients



Events (N=172)	TRAE[b]
Any grade	140 (81.4)
Grade ≥3	48 (27.9)
Serious	21 (12.2)
Leading to Teliso-V discontinuation	37 (21.5)
Leading to death	2 (1.2)

- No new safety signals were observed with Teliso-V
- TRAEs leading to death were ILD and respiratory failure in one patient each
- Possible pneumonitis/ILD cases were formally adjudicated retrospectively (see slide 11)

[a]Pneumonitis events shown are those with a MedDRA preferred term of "pneumonitis" according to the investigative site reporting. In addition, TRAEs with a preferred term of "ILD" according to investigative site reporting were noted in 4 (2.3%) patients; [b]Per investigator assessment. Safety population comprised patients who received ≥1 dose of Teliso-V.
ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; Teliso-V, telisotuzumab vedotin; TRAEs, treatment-related adverse events.

Conclusions

Teliso-V is the first-in-class c-Met–targeting ADC, and demonstrated durable responses in patients with c-Met protein–OE NSQ *EGFR* WT NSCLC

Biomarker enrichment was observed in patients with c-Met high OE tumors with an ORR of 34.6% vs. 22.9% among patients with c-Met intermediate OE tumors
- Analyses of overlap with genetic markers are ongoing

The most common TRAE was late-onset peripheral sensory neuropathy, consistent with observations for MMAE-based ADCs

Enrollment continues in the ongoing global, randomized phase 3 study TeliMET NSCLC-01 (NCT04928846) comparing Teliso-V vs. docetaxel in patients with previously treated locally advanced/metastatic, c-Met protein–OE NSQ *EGFR* WT NSCLC

Accepted manuscript is in production (*Journal of Clinical Oncology)*

Iniciativa científica de:

GECP lung cancer research

Gracias