15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

EGFR beyond Osimertinib

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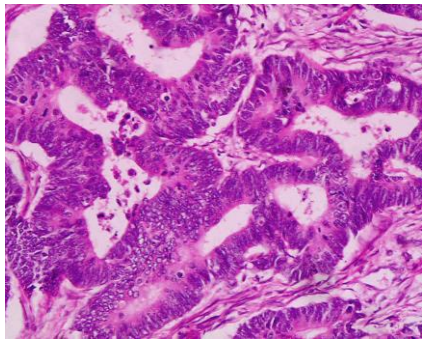
Disclosures

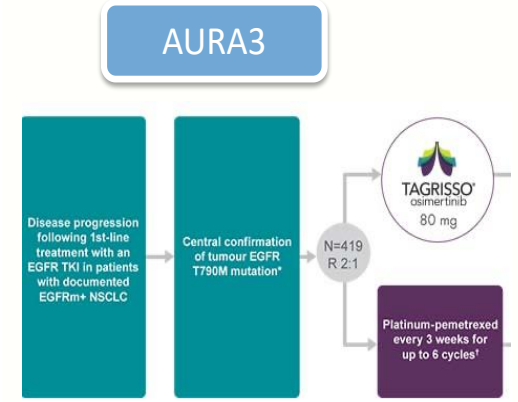
Advisory / Consultancy : AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Roche, Takeda

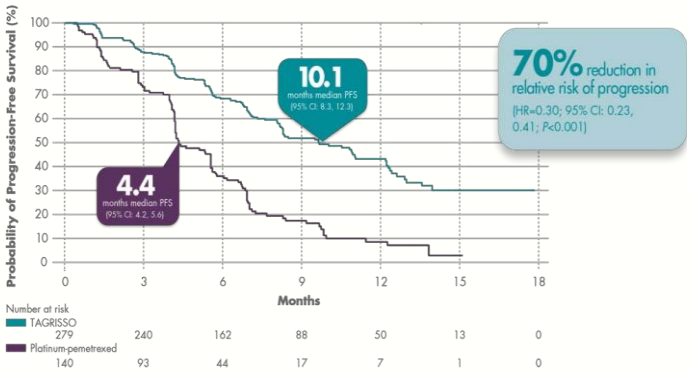
Speaker Bureau / Expert testimony: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche, Takeda

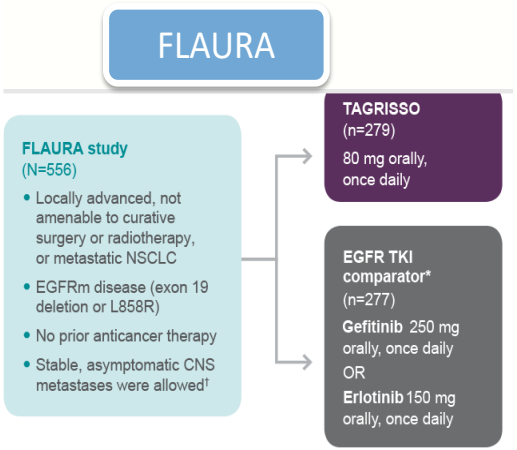
Travel / Accommodation / Expenses :Bristol-Myers Squibb, Pfizer, Roche, Takeda

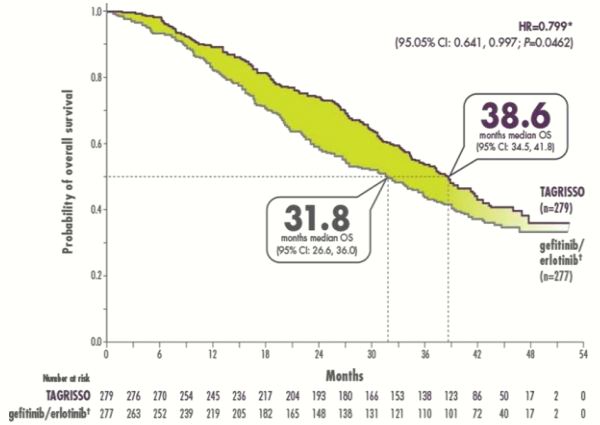
Introduction





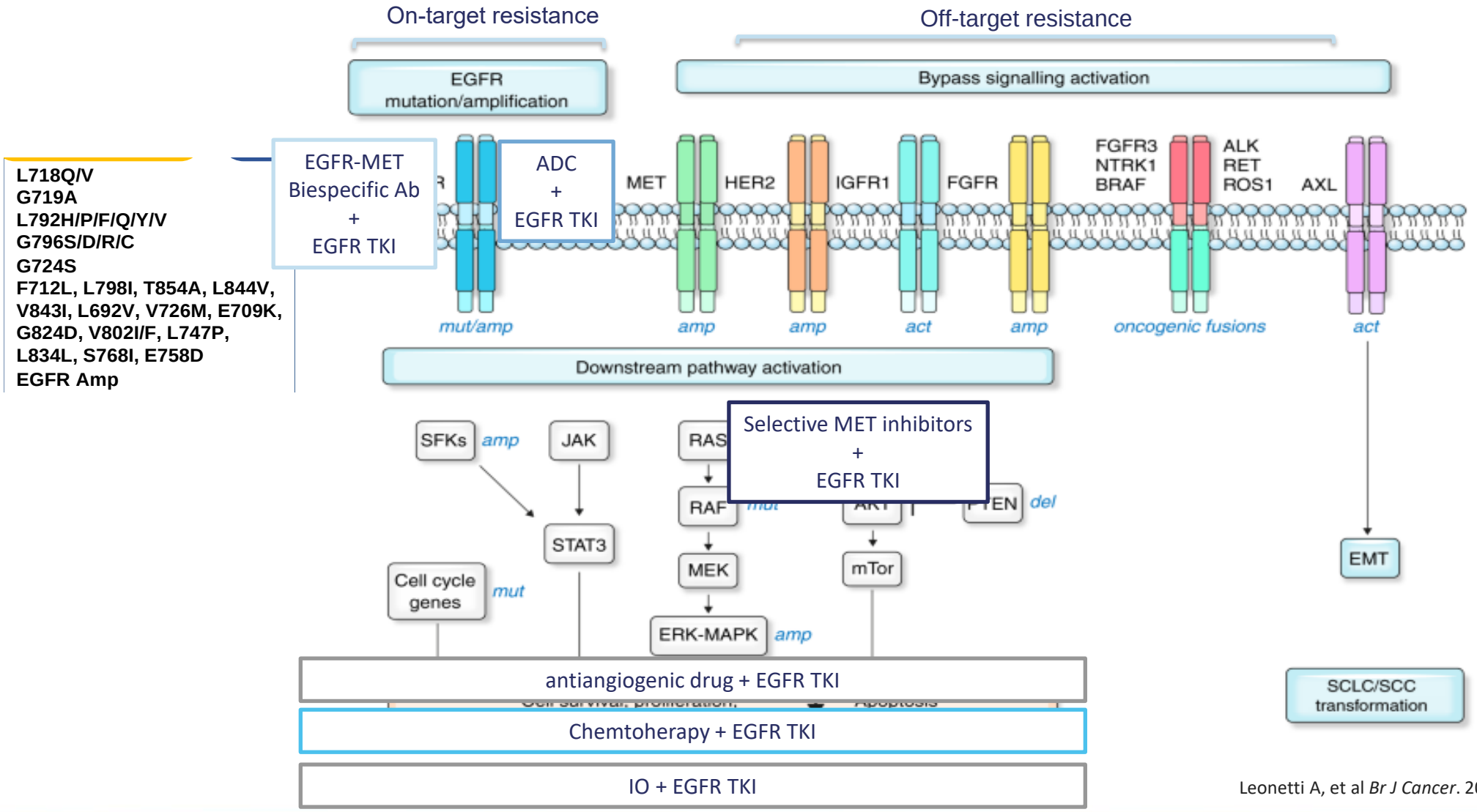






Mok TS, et al. N Engl J Med 2017;376(7):629-40.
Ramalingam SS, et al. N Engl J Med 2020;382(1):41-50.

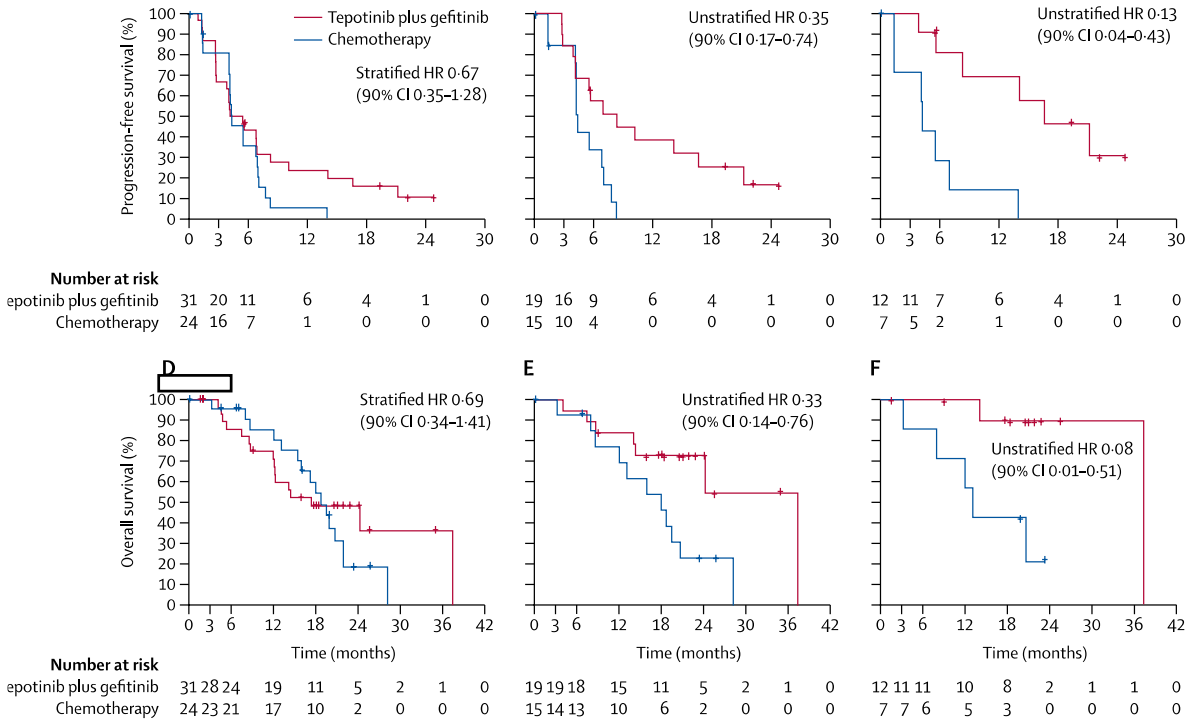
Treatment strategies based on the resistance mechanisms



Leonetti A, et al *Br J Cancer*. 2019;121(9):725-737.

Selective MET inh + EGFR TKI

INSIGHT: *Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial*



PFS and OS were longer with tepotinib plus gefitinib than with chemotherapy in patients with high (IHC3+) MET overexpression n=34

- median PFS **8·3 months** [4·1–16·6] *vs* **4·4 months** [4·1–6·8]; HR 0·35, 0·17–0·74
- median OS **37·3 months** [90% CI 24·2–37·3] *vs* **17·9 months** [12·0–20·7]; HR 0·33, 0·14–0·76

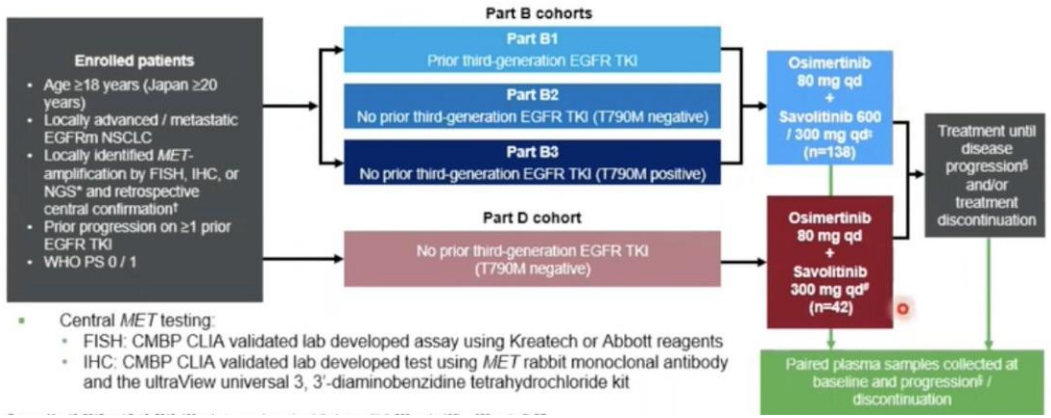
Or MET **amplification (mean gene copy number ≥5 or MET to centromere of chromosome 7 ratio ≥2)** n=19

- median PFS **16·6 months** [8·3–not estimable] *vs* **4·2 months** [1·4–7·0]; HR 0·13, 0·04–0·43
- median OS **37·3 months** [90% CI not estimable] *vs* **13·1 months** [3·25–not estimable]; HR 0·08, 0·01–0·51

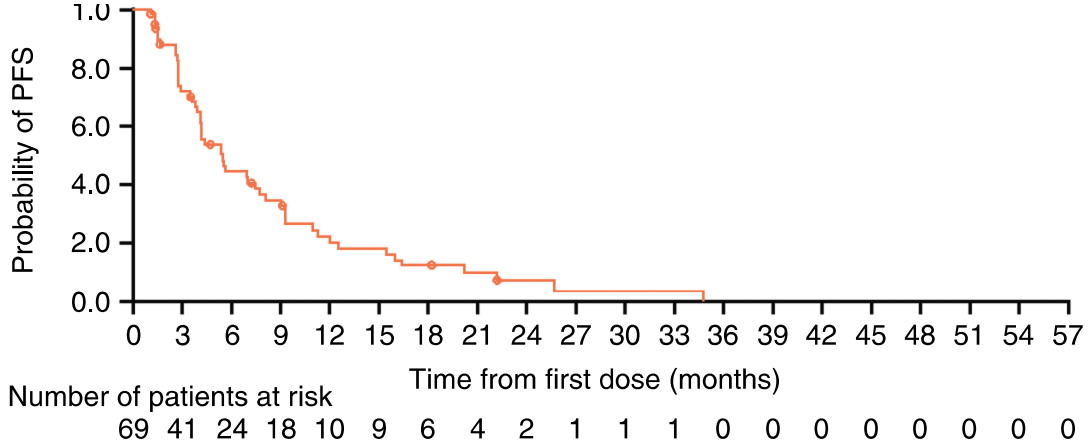
Wu YL, et al Lancet Respir Med. 2020;8(11):1132-1143.

Selective MET inh + EGFR TKI

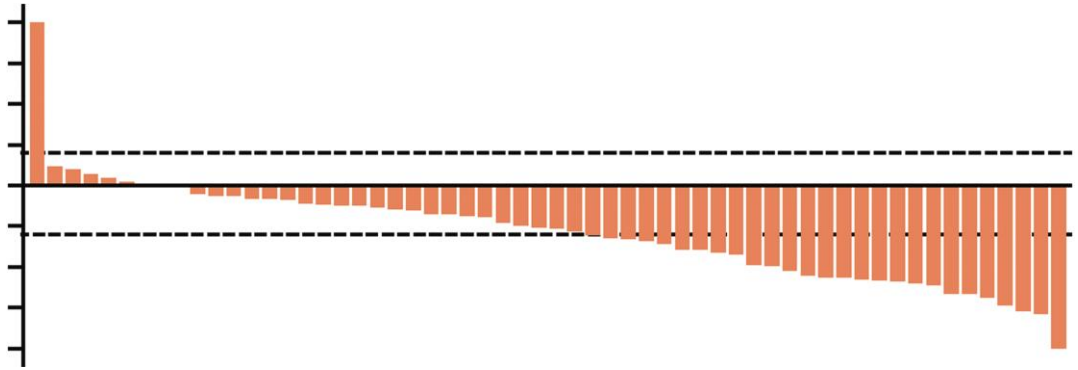
***TATTON TRIAL*: a multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer**



PFS



ORR



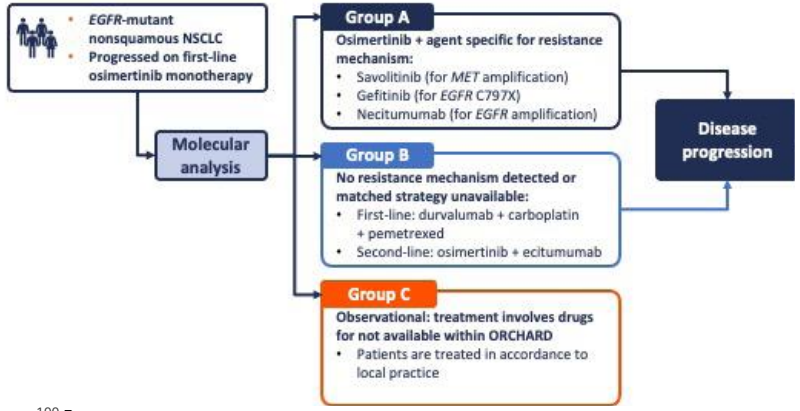
Efficacy endpoints

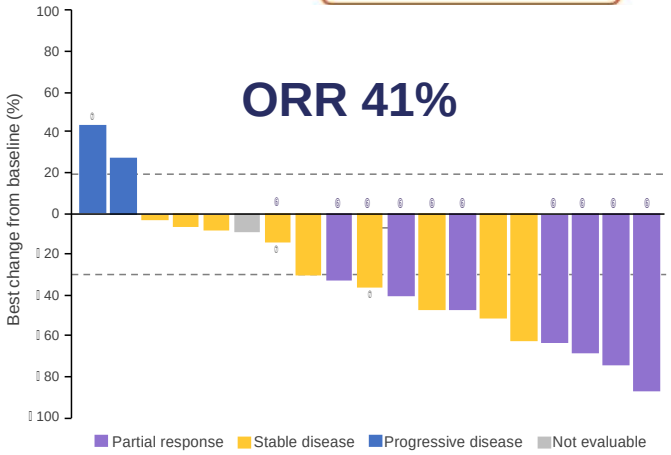
	Part B: osimertinib 80 mg + savolitinib 600/300[a] mg			Part D: osimertinib 80 mg + savolitinib 300 mg
	Previously treated with a 3G EGFR-TKI	No prior 3G EGFR-TKI, T790M-negative	No prior 3G EGFR-TKI, T790M-positive	No prior 3G EGFR-TKI, T790M-negative
Endpoint	*n* = 69	*n* = 51	*n* = 18	*n* = 42
ORR[b], *n* (%)	23 (33)	33 (65)	12 (67)	26 (62)
(95% CI)	(22–46)	(50–78)	(41–87)	(46–76)
Complete response	0	0	0	0
Partial response	23 (33)	33 (65)	12 (67)	26 (62)
Stable disease[c]	29 (42)	12 (24)	6 (33)	13 (31)
Progressive disease	8 (12)	3 (6)	0	1 (2)
Not evaluable	9 (13)	3 (6)	0	2 (5)
Median PFS, months (95% CI)	5.5 (4.1–7.7)	9.1 (5.5–12.8)	11.1 (4.1–22.1)	9.0 (5.6–12.7)
Total PFS events, *n* (%)	51 (74)	36 (71)	12 (67)	29 (69)
PFS rate at 6 months, % (95% CI)	45 (32–57)	58 (43–71)	77 (49–90)	63 (45–76)
PFS rate at 12 months, % (95% CI)	21 (11–33)	38 (24–52)	47 (23–68)	38 (23–53)
Median DoR, months (95% CI)	9.5 (4.2–14.7)	10.7 (6.1–14.8)	11.0 (2.8–NC)	9.7 (4.5–14.3)
Median OS,[d] months (95% CI)	30.3 (11.8–NC)	18.8 (15.1–NC)	NC (24.4–NC)	NC (13–NC)
OS rate at 6 months, % (95% CI)	86 (74–93)	90 (77–96)	94 (65–99)	93 (79–98)
OS rate at 12 months, % (95% CI)	62 (47–73)	69 (52–81)	94 (65–99)	78 (61–88)
OS rate at 18 months, % (95% CI)	53 (38–66)	52 (36–67)	87 (58–97)	66 (49–79)

Hartmaier RJ, et al Cancer Discov. 2023;13(1):98-113.

Selective MET inh + EGFR TKI

ORCHARD TRIAL Biomarker-Directed Phase II Platform Study in Patients With EGFR Sensitizing Mutation-Positive Advanced/Metastatic Non-Small Cell Lung Cancer Whose Disease Has Progressed on First-Line Osimertinib Therapy

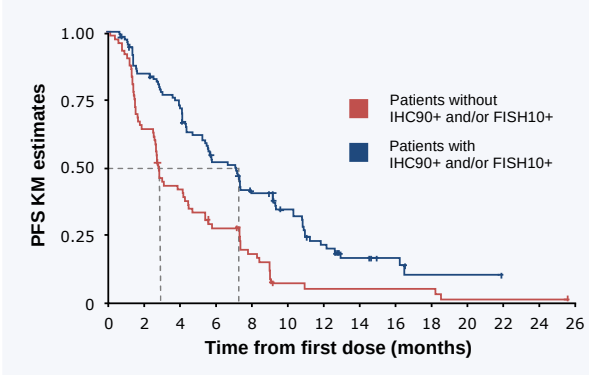




Yu AH et al. ESMO 2021. #3222.

SAVANNAH: Phase II Trial of Osimertinib + Savolitinib in EGFR-Mutant, MET-Driven Advanced NSCLC, Following Prior Osimertinib

- Osimertinib + Savolitinib
- Progressed on prior osimertinib - MET IHC3+ ≥50% and/or FISH GCN ≥5 or MET/CEP7 ratio ≥2



ORR 32%
mDOR 8.3 m
mPFS 5.3 m

Investigator assessment	With IHC90+ and/or FISH10+ status (N=108)		Without IHC90+ and/or FISH10+ status (N=77)	
	Total (N=108)	No prior CTx (n=87)	Total (N=77)	No prior CTx (n=63)
ORR (95% CI)	49% (39, 59)	52% (41, 63)	9% (4, 18)	10% (4, 20)
mDOR, months (95% CI)	9.3 (7.6, 10.6)	9.6 (7.6, 14.9)	6.9 (4.1, 16.9)	7.3 (4.1, NC)
mPFS, months (95% CI)	7.1 (5.3, 8.0)	7.2 (4.7, 9.2)	2.8 (2.6,4.3)	2.8 (1.8, 4.2)

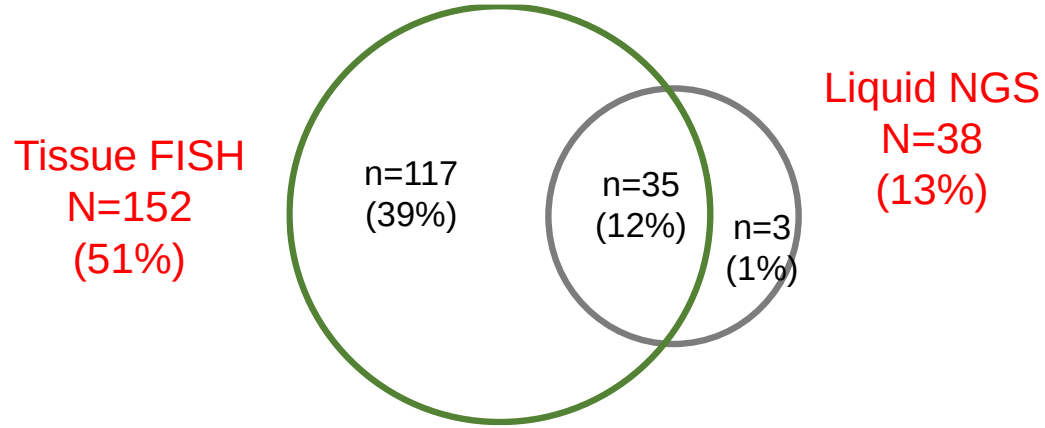
Ahn M-J et al. WCLC 2022. #EP08.02-140

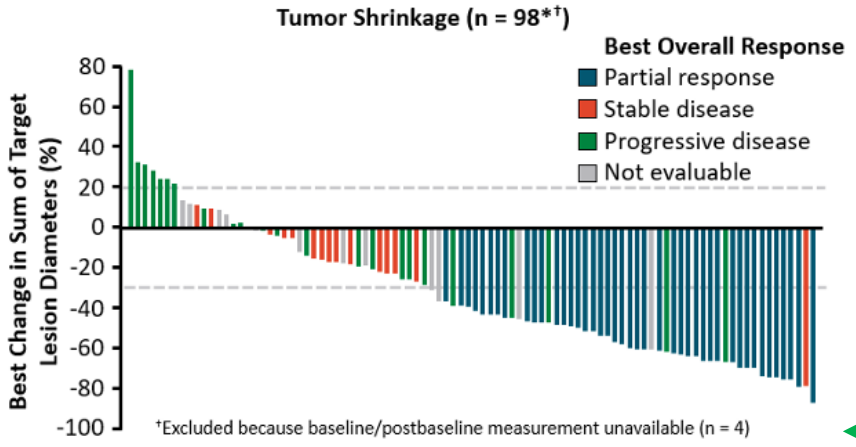
Selective MET inh + EGFR TKI

INSIGHT 2: a phase II study of tepotinib plus osimertinib in *MET*-amplified NSCLC and first-line osimertinib resistance *(n=122)*

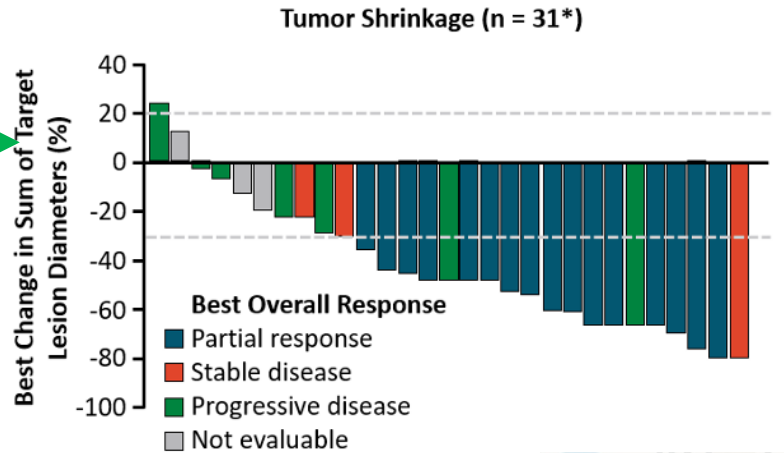
- Tepotinib 500mg po QD + Osimertinib 80mg
- Progressed on 1st line Osimertinib
- FISH (MET GCN ≥5 and/or MET/CEP7 ≥2) and/or liquid biopsy (MET plasma GCN ≥2.3)
- 175 out of 451 patients (38.8%) were MET (+)

FISH and/or liquid NGS (n=229)





	MET FISH (+)	Blood based NGS
	N=98	N=31
ORR	43.9%	51.6%
mDoR	9.7m	5.6m
mPFS	5.4m	4.6m
mOS	NE	NE



Tan et al ASCO 2023 Abstr 9021

ADC + EGFR TKI

Phase Ib Study of Telisotuzumab Vedotin in Combination With Erlotinib in Patients With c-Met Protein-Expressing Non-Small-Cell Lung Cancer

Teliso-V (2.7 mg/kg once every 21 days) plus erlotinib (150 mg once daily)

Phase I/Ib. n=42

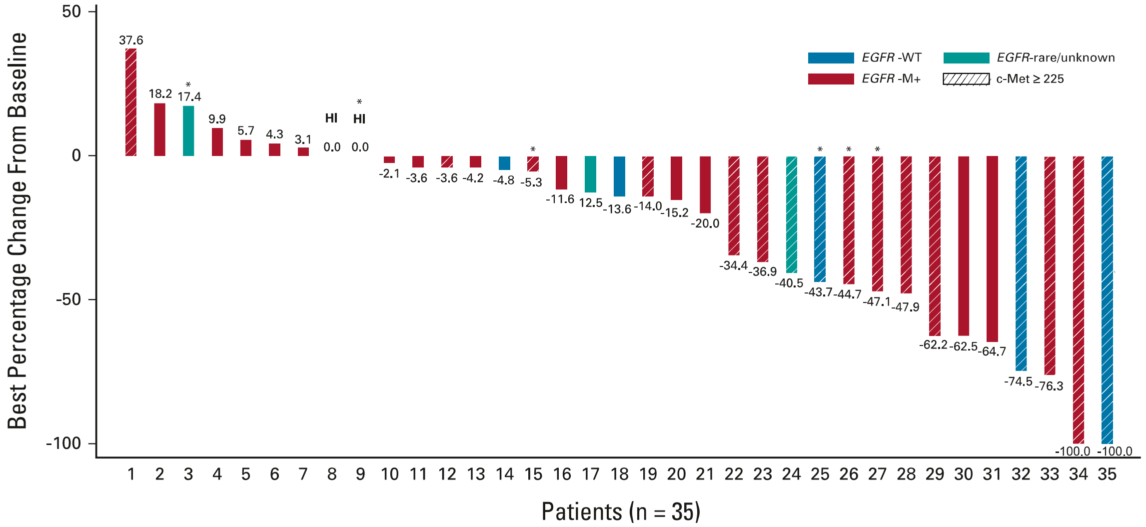
Patients with L858R or Del 19 EGFR mutation C-MET overexpressing

MET expression	N=25
Intermediate (25-49% cell MET IHC 3+)	11 (44%)
High ([illegible]	13 (52%)

Camidge DR et al Lung Cancer. *J Clin Oncol*. 2023;41(5):1105-1115.

Efficacy summary

Response	Teliso-V Plus Erlotinib: c-Met+ *EGFR*-M+ (n = 28), No./n (%)	c-Met+ *EGFR*-WT (n = 5), No./n (%)	c-Met+ *EGFR*-Rare/Unknown (n = 3), No./n (%)	Total (N = 36), No./N (%)
Best overall response[a]				
Complete response	1/28 (4)	0/5	0/3	1/36 (3)
Partial response	8/28 (29)	2/5 (40)	0/3	10/36 (28)
Stable disease	15/28 (54)	2/5 (40)	3/3 (100)	20/36 (56)
Progressive disease	4/28 (14)	1/5 (20)	0/3	5/36 (14)
Objective response rate[b] [95% CI]	9/28 (32.1) [15.9 to 52.4]	2/5 (40.0) [5.3 to 85.3]	0 [0.0 to 70.8]	11/36 (30.6) [16.3 to 48.1]
Disease control rate[c] [95% CI]	24/28 (85.7) [67.3 to 96.0]	4/5 (80.0) [28.4 to 99.5]	3/3 (100) [29.2 to 100]	31/36 (86.1) [70.5 to 95.3]
Progression-free survival				
Median, months [95% CI]	5.9 [2.8 to NR]	6.0 [1.2 to NR]	4.0 [1.6 to NR]	5.9 [2.8 to NR]



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
PFS	1.3	3.7	1.6	1.3	2.3	5.4	1.4	3.0	8.3	2.8	5.9	6.8	1.6	6.0	3.7	4.3	5.6	1.2	1.3	5.3	1.4	11.0	5.3	4.0	2.8	2.7	6.7	11.3	2.7	7.4	12.3	16.4	10.2	6.9	6.6
Response	PD	SD	SD	SD	SD	SD	PD	SD	SD	SD	SD	SD	SD	SD	SD	SD	SD	PD	SD	SD	PD	PR	PD	PD	PR	PR	PR	PR	PR	PR	PR	PR	PR	CR	PR

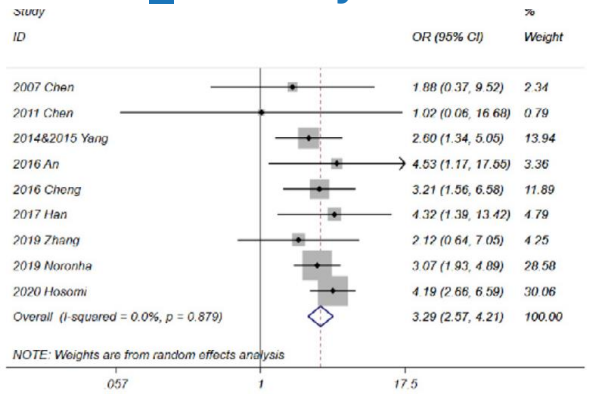
Chemotherapy + EGFR TKI

Comparison of gefitinib plus chemotherapy versus gefitinib alone: A meta analysis

Study ID	Study location	Rate of EGFR mutation	Type of tumor	Stage of cancer	Special type of population	Prospective and randomized	Combined treatment	Number of patients	Previous treatment
2007 Chen[16]	China	50%	Lung adenocarcinoma	IV	None	Yes	Vinorelbine	48	previous chemotherapy with > = 2 regimens
2011 Chen[17]	China	67%	Lung adenocarcinoma	IIIB/IV	None	Yes	Tegafur/Uracil	115	failed previous chemotherapy
2014 and 2015 Yang[19,24,a]	Asian multicentre	68%	NSCLC	IIIB/IV	Nonsmoker/Light former smoker	Yes	Pemetrexed + cisplatin	236	chemonaive
2016 An[20]	China	100%	NSCLC	IIIB/IV	None	Yes	Pemetrexed	90	N/A
2016 Cheng[21]	Asian multicentre	100%	Nonsquamous NSCLC	IV/Recurrent	None	Yes	Pemetrexed	191	no prior systemic chemotherapy, immunotherapy, or biologic therapy
2017 Han[22]	China	100%	Lung adenocarcinoma	IIIB/IV	None	Yes	Pemetrexed + Carboplatin	81	no prior systemic anticancer therapy for advanced disease
2019 Zhang[25]	China	100%	NSCLC	III/IV	None	No	Cisplatin	92	no prior surgery, chemotherapy, radio-therapy, or immunotherapy
2019 Noronha[26]	India	100%	NSCLC	IIIB/IV	None	Yes	Pemetrexed + Carboplatin	334	N/A
2020 Hosomi[18]	Japan	100%	Nonsquamous NSCLC	IIIB/IV/Recurrent	None	Yes	Pemetrexed + Carboplatin	341	no prior chemotherapy

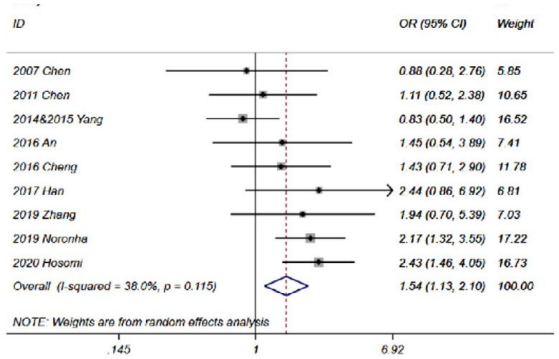
[a] The two studies by Yang et al. in 2014 and 2015 reported progression-free survival and overall survival of the same patient population, respectively. Thus, the two studies were considered as one in the present analysis.
EGFR, Epidermal Growth Factor Receptor; NSCLC, Non-Small Cell Lung Cancer; N/A, Not Available.

Grade ≥3 toxicity



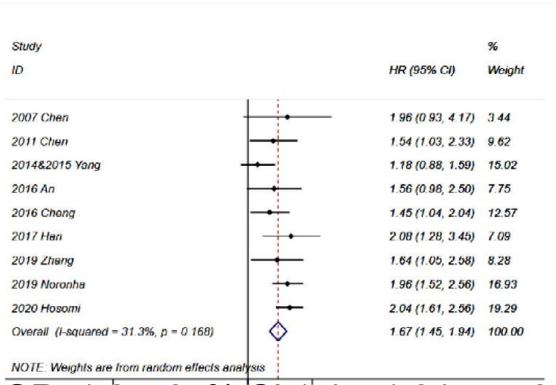
HR=3.29 (95% CI 2.57–4.21; p < 0.001)

ORR.



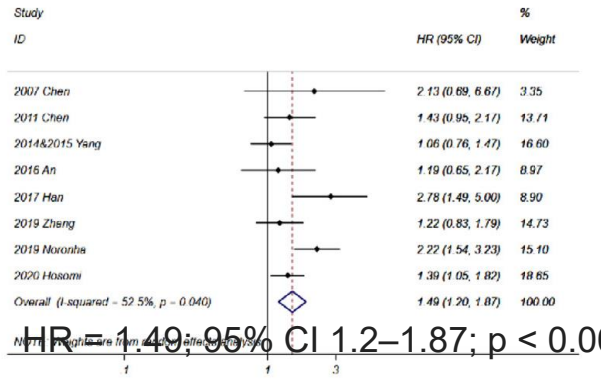
OR = 1.54; 95% CI, 1.13–2.1; p = 0.006

PFS



OR=1.67; 95% CI 1.45–1.94; p < 0.001

OS



HR = 1.49; 95% CI 1.2–1.87; p < 0.001

Yi M, He T et al *Clinics (Sao Paulo)*. 2023;78:100152.

Chemotherapy + EGFR TKI

FLAURA 2: Phase III trial osimertinib in combination with chemotherapy

Safety run-in period (N=30)
Published in ESMO Open, 2021†

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:
- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:
- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

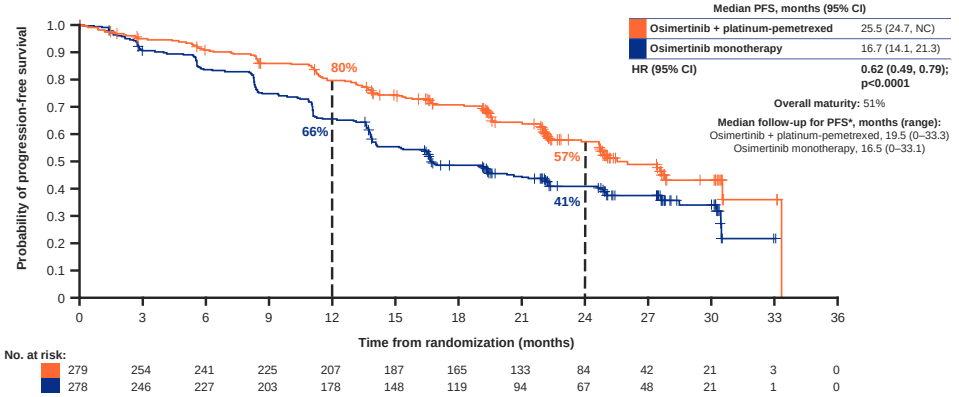
- Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments) → Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†
- Osimertinib 80 mg (QD)

Follow-up:
- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

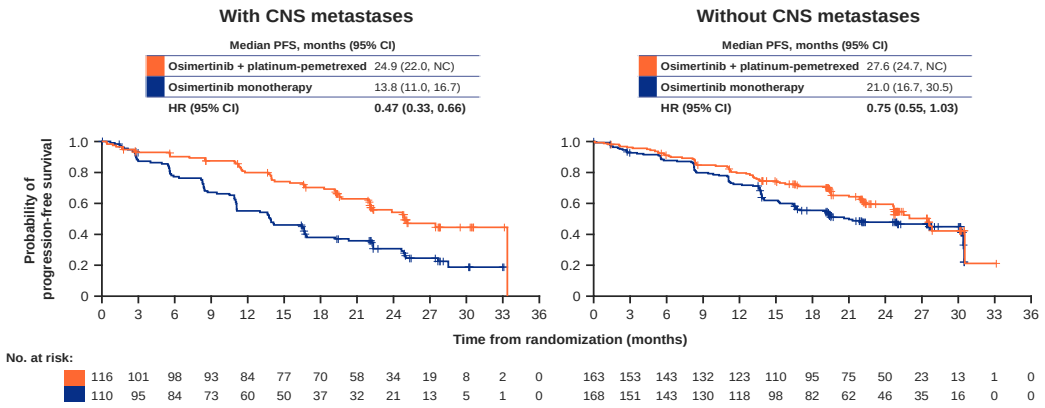
- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

Progression-free survival per investigator

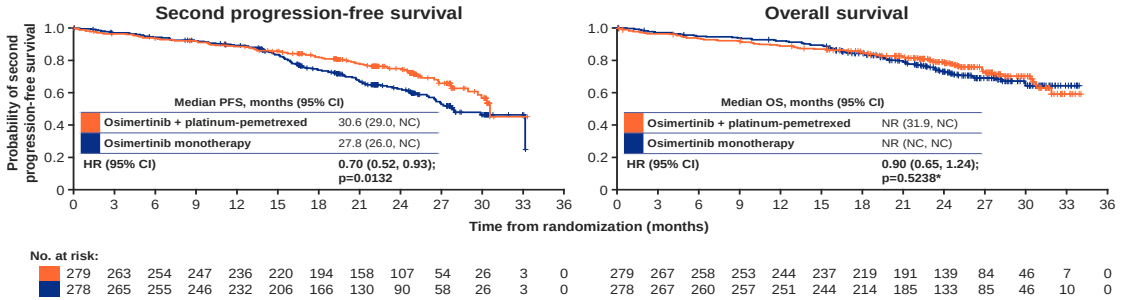
- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



PFS per investigator in patients with / without CNS metastases at baseline*



PFS2 and interim analysis of OS



- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

Pasi A. Jänne et al WCLC 2023

Chemotherapy + EGFR TKI

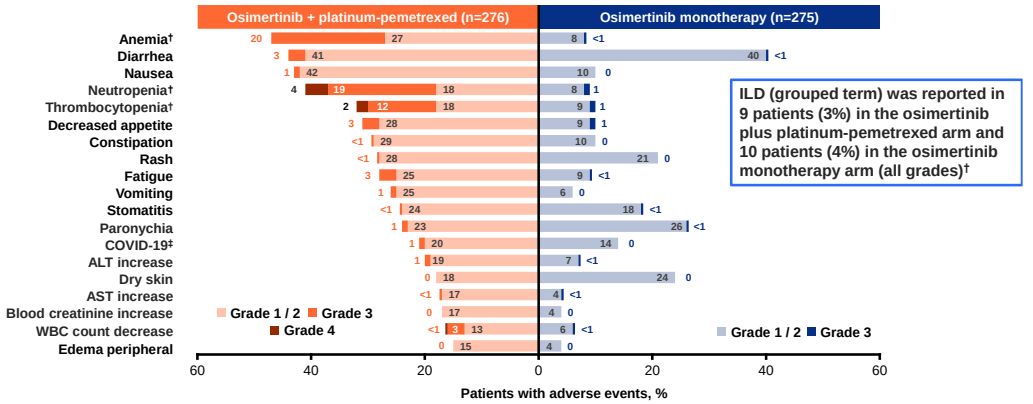
FLAURA 2: Phase III trial osimertinib in combination with chemotherapy

Safety summary

- Median total duration of osimertinib exposure was 22.3 months (range 0.1–33.8) in the osimertinib plus platinum-pemetrexed arm and 19.3 months (range 0.1–33.8) in the osimertinib monotherapy arm
- In the combination arm patients received a median of 12 cycles of pemetrexed (range 1–48) and 211 patients (76%) completed 4 cycles of platinum-based chemotherapy

Patients with AEs, n (%)*	Osimertinib + platinum-pemetrexed (n=276)	Osimertinib monotherapy (n=275)
AE any cause	**276 (100)**	**268 (97)**
Any AE	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any serious AE	104 (38)	53 (19)
Any AE leading to discontinuation	132 (48)	17 (6)
Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation	30 (11) / 46 (17) / 119 (43)	17 (6) / NA / NA
AE possibly causally related to treatment†	**269 (97)**	**241 (88)**
Any AE	146 (53)	29 (11)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	81 (29) / 104 (38) / 130 (47)	29 (11) / NA / NA
Any AE leading to death	5 (2)	1 (<1)
Causally related to osimertinib / carboplatin or cisplatin / pemetrexed	3 (1) / 2 (1) / 3 (1)	1 (<1) / NA / NA
Any serious AE	52 (19)	15 (5)

Common adverse events (



ILD (grouped term) was reported in 9 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†

- pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

- Osimertinib in combination with platinum-pemetrexed has demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy in patients with EGFRm advanced NSCLC (HR: 0.62)
  - **Investigator-assessed median PFS: 25.5 vs 16.7 months (improvement of ~8.8 months)**
  - **BICR-assessed median PFS: 29.4 vs 19.9 months (improvement of ~9.5 months)**
- PFS benefits were consistent across all pre-defined subgroups
- PFS2 and OS data were immature at this interim analysis
- The safety profiles were as expected for each treatment and were manageable with standard medical practice

Pasi A. Jänne et al WCLC 2023

Chemotherapy + EGFR-MET bispecific antibody

MARIPOSA-2, a Phase 3, Global, Randomized, Controlled Trial Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy in EGFR-mutated, Advanced NSCLC After Progression on Osimertinib

Study design

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Stratification Factors
- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

Serial brain MRIs were required for all patients[a]

- **Amivantamab-Lazertinib-Chemotherapy (n=263)**
- **Chemotherapy (n=263)**
- **Amivantamab-Chemotherapy (n=131)**

Dosing (in 21-day cycles)

Amivantamab: [illegible]

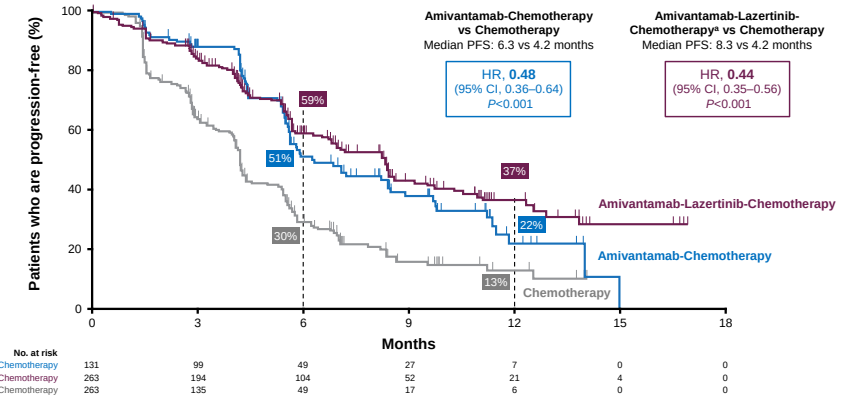
Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m^2 until disease progression

Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:
- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

Secondary endpoints:
- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

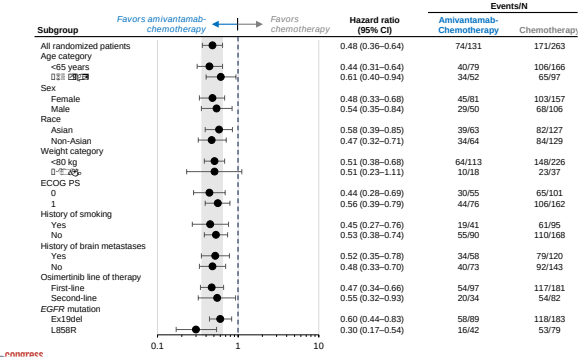
Primary Endpoint: Progression-free Survival by BICR



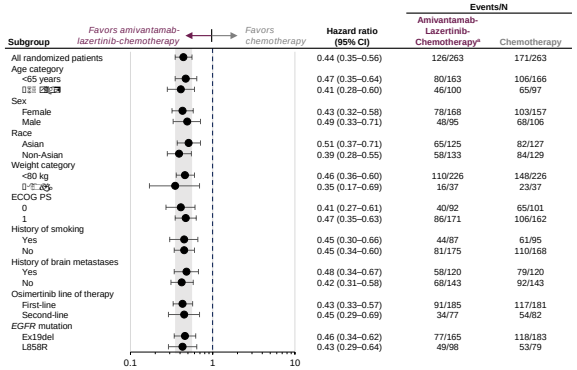
No. at risk							
Amivantamab-Chemotherapy	131	99	49	27	7	0	0
Amivantamab-Lazertinib-Chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001b) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001b)

PFS Benefit across subgroups



Subgroup	Hazard ratio (95% CI)	Events/N: Amivantamab-Chemotherapy	Events/N: Chemotherapy
All randomized patients	0.48 (0.36–0.64)	74/131	171/263
Age category			
<65 years	0.44 (0.31–0.64)	40/79	106/166
[illegible]	0.61 (0.40–0.94)	34/52	65/97
Sex			
Female	0.48 (0.33–0.68)	45/81	103/157
Male	0.54 (0.35–0.84)	29/50	68/106
Race			
Asian	0.58 (0.39–0.85)	39/63	82/127
Non-Asian	0.47 (0.32–0.71)	34/64	84/129
Weight category			
<80 kg	0.51 (0.38–0.68)	64/113	148/226
[illegible]	0.51 (0.23–1.11)	10/18	23/37
ECOG PS			
0	0.44 (0.28–0.69)	30/55	65/101
1	0.56 (0.39–0.79)	44/76	106/162
History of smoking			
Yes	0.45 (0.27–0.76)	19/41	61/95
No	0.53 (0.38–0.74)	55/90	110/168
History of brain metastases			
Yes	0.52 (0.35–0.78)	34/58	79/120
No	0.48 (0.33–0.70)	40/73	92/143
Osimertinib line of therapy			
First-line	0.47 (0.34–0.66)	54/97	117/181
Second-line	0.55 (0.32–0.93)	20/34	54/82
EGFR mutation			
Ex19del	0.60 (0.44–0.83)	58/89	118/183
L858R	0.30 (0.17–0.54)	16/42	53/79



Subgroup	Hazard ratio (95% CI)	Events/N: Amivantamab-Lazertinib-Chemotherapy[a]	Events/N: Chemotherapy
All randomized patients	0.44 (0.35–0.56)	126/263	171/263
Age category			
<65 years	0.47 (0.35–0.64)	80/163	106/166
[illegible]	0.41 (0.28–0.60)	46/100	65/97
Sex			
Female	0.43 (0.32–0.58)	78/168	103/157
Male	0.49 (0.33–0.71)	48/95	68/106
Race			
Asian	0.51 (0.37–0.71)	65/125	82/127
Non-Asian	0.39 (0.28–0.55)	58/133	84/129
Weight category			
<80 kg	0.46 (0.36–0.60)	110/226	148/226
[illegible]	0.35 (0.17–0.69)	16/37	23/37
ECOG PS			
0	0.41 (0.27–0.61)	40/92	65/101
1	0.47 (0.35–0.63)	86/171	106/162
History of smoking			
Yes	0.45 (0.30–0.66)	44/87	61/95
No	0.45 (0.34–0.60)	81/175	110/168
History of brain metastases			
Yes	0.48 (0.34–0.67)	58/120	79/120
No	0.42 (0.31–0.58)	68/143	92/143
Osimertinib line of therapy			
First-line	0.43 (0.33–0.57)	91/185	117/181
Second-line	0.45 (0.29–0.69)	34/77	54/82
EGFR mutation			
Ex19del	0.46 (0.34–0.62)	77/165	118/183
L858R	0.43 (0.29–0.64)	49/98	53/79

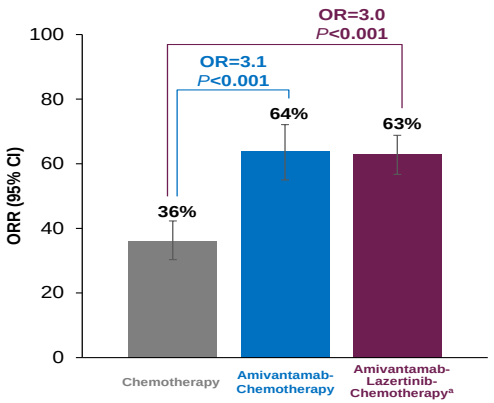
During the study, the IDMC identified increased hematologic toxicities in the amivantamab-lazertinib-chemotherapya arm
•The amivantamab-lazertinib-chemotherapy regimen was modified to start lazertinib after carboplatin completion

Passaro A et al ESMO 2023

Chemotherapy + EGFR-MET bispecific antibody

MARIPOSA-2, a Phase 3, Global, Randomized, Controlled Trial Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy in EGFR-mutated, Advanced NSCLC After Progression on Osimertinib

ORR ans DoR



BICR-assessed Response, n (%)[b]	Chemotherapy (n=263)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (36)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	10 (8)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[c]	5.6 mo (95% CI, 4.2–9.6)	6.9 mo (95% CI, 5.5–NE)	9.4 mo (95% CI, 6.9–NE)

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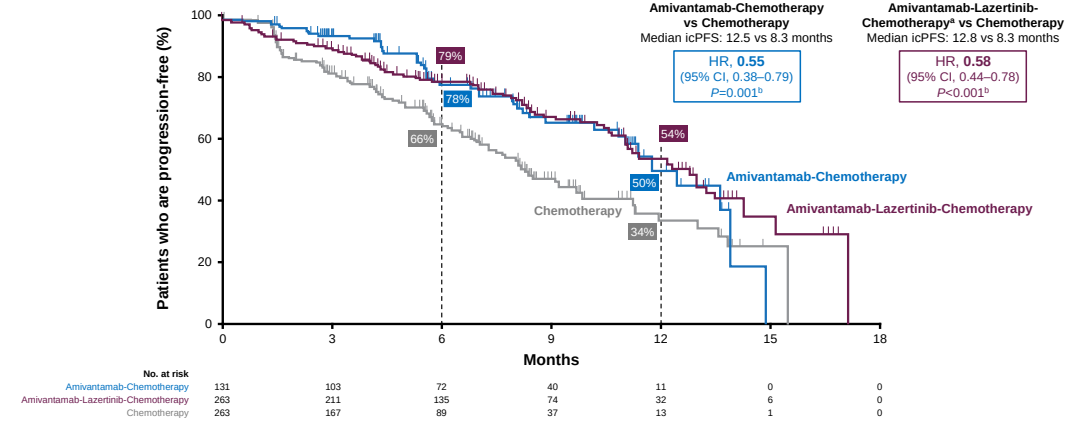
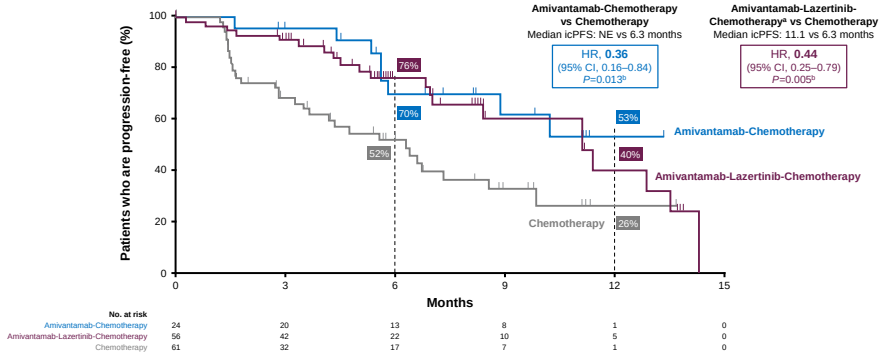
Intracranial Progression-free Survival by BICR



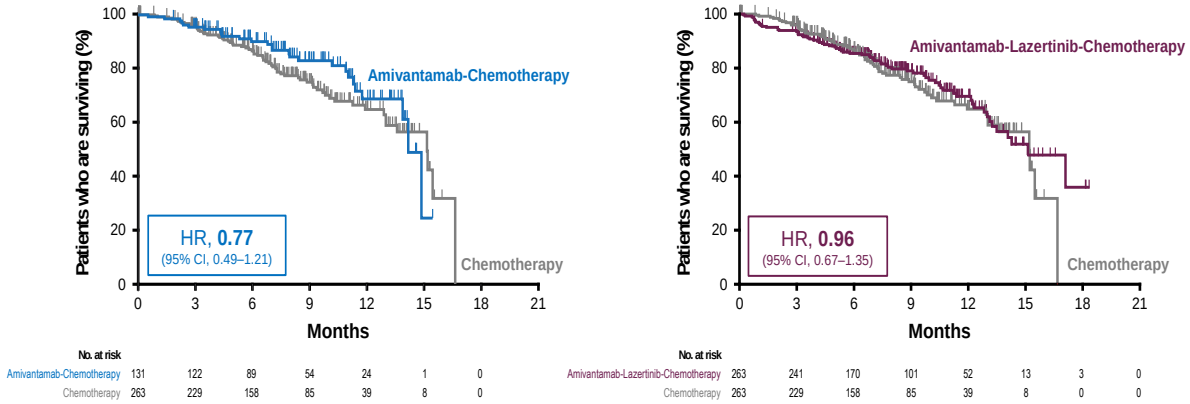
Intracranial Progression-free Survival by BICR Among Patients With a History of Brain Metastases and No Prior Brain Radiotherapy



Chemotherapy + EGFR-MET bispecific antibody

MARIPOSA-2, a Phase 3, Global, Randomized, Controlled Trial Amivantamab Plus Chemotherapy (With or Without Lazertinib) vs Chemotherapy in EGFR-mutated, Advanced NSCLC After Progression on Osimertinib

Early Interim Overall Survival



Includes all randomized patients regardless of dosing regimen received
- Median follow-up for the modified amivantamab-lazertinib-chemotherapy regimen was 5.4 months

At time of data cutoff, the median follow-up for the study was 8.7 months

Summary of Adverse Events (AEs)

	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=130)	Amivantamab-Lazertinib-Chemotherapy[a] (n=263)
Treatment duration, median (range)	3.7 months (0–15.9)	6.3 months (0–14.7)	5.7 months (0.1–18.6)
No. of chemotherapy cycles, median (range)			
Carboplatin	4 (1–5)	4 (1–4)	4 (1–4)
Pemetrexed	6 (1–23)	9 (1–22)	7 (1–25)

TEAE, n (%)	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=130)	Amivantamab-Lazertinib-Chemotherapy[a] (n=263)
Any AEs	227 (93)	130 (100)	263 (100)
[illegible]	117 (48)	94 (72)	242 (92)
Serious AEs	49 (20)	42 (32)	137 (52)
AEs leading to death	3 (1)	3 (2)	14 (5)
Any AE leading to treatment:			
Interruptions of any agent	81 (33)	84 (65)	202 (77)
Reductions of any agent	37 (15)	53 (41)	171 (65)
Discontinuations of any agent	9 (4)	24 (18)	90 (34)
Discontinuations of all agents due to AE	10 (4)	14 (11)	38 (14)

- Median treatment duration was longer for the amivantamab- containing arms vs chemotherapy
- Amivantamab-containing arms had higher rates of grade ≥3 AEs and dose modifications vs chemotherapy
- Aes leading to death were low
- Discontinuations of all agents due to treatment- related AEs was 2%, 8%, and 10%

Passaro A et al ESMO 2023

EGFR-MET bispecific antibody + EGFR TKI

CHRYSALIS-2: **Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy**

Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity

Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI with efficacy in activating *EGFR* mutations, T790M, and brain metastases

Study design

RYSALIS-2 (ClinicalTrails.gov Id
dy Design

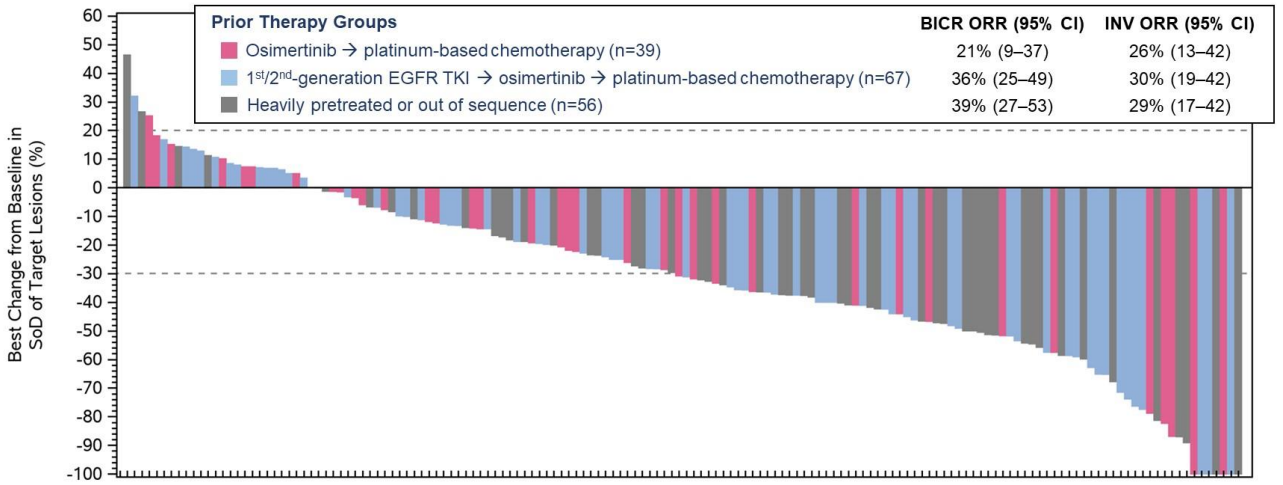
Dose Expansion Cohorts

RP2CD: Lazertinib 240 mg PO +
Amivantamab 1050 mg (1400 mg for ≥80 kg) IV

Cohort A: EGFR ex19del or L858R
Post-osimertinib and platinum-based chemotherapy (n=162)

Cohort B: EGFR ex20ins

Best antitumt response and ORR



CNS antitumor activity

ysis

Best CNS Lesion Assessment/evaluation	Untreated Brain Metastases (n=27)
Complete clearance (“absent”)	7 (26%)
Non-CR/non-PR (“present”)	20 (74%)
Progressive disease (“unequivocal progression”)	0

Shu C et al ASCO 2022

EGFR-MET bispecific antibody + EGFR TKI + chemotherapy

CHRYSALIS-2: **Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy**

Study design

S-2[a] Study Design

N=20

Dose Expansion Cohorts

- **Cohort A:** *EGFR* ex19del or L858R[b] — Post-osimertinib and platinum-based chemotherapy
- **Cohort B:** *EGFR* ex20ins[b] — Post-standard of care and platinum-based chemotherapy
- **Cohort C:** Uncommon *EGFR* mutations[b]

CHRYSALIS-2 (NCT04077463)

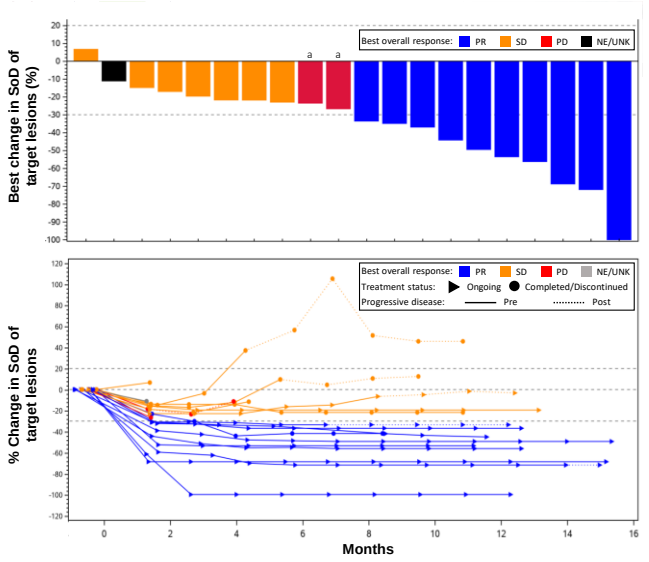
Eligibility
EGFR-mutated, advanced NSCLC post-TKI (max of 3 prior lines)

Dosing (21-day cycle)	
Lazertinib	240 mg daily
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1D8, C1D15, C2D1; 1750/2100[b] mg C3+ Q3W
Chemotherapy	Carboplatin (AUC5; stopped after 4 cycles)
	Pemetrexed (500 mg/m^2) until disease progression

Endpoints

- Adverse events (primary)
- Objective response rate
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival

Overall Response Rate



Investigator-assessed response (n=20)	
ORR	50% (95% CI, 27–73)
Median DOR	Not estimable
Ongoing response	8 of 10 responders
[illegible]	8 of 10 responders
CBR[b]	80% (95% CI, 56–94)

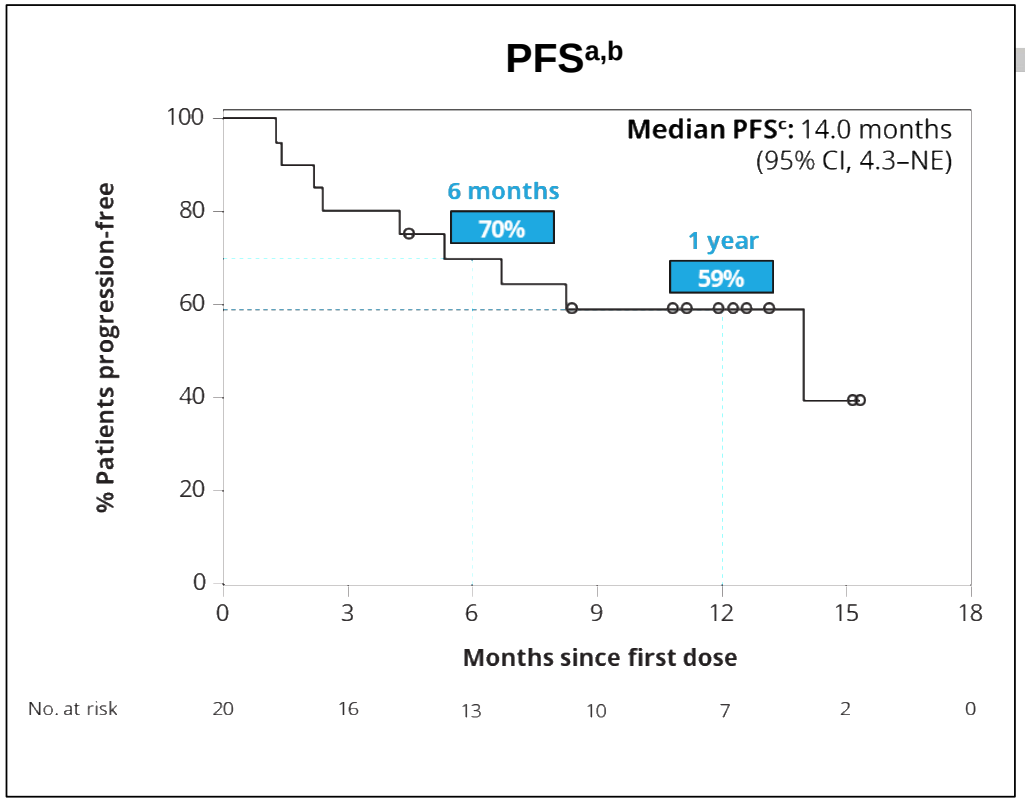
- At median follow-up of 13.1 months, 11 (55%) patients remain on treatment
- 3 of 7 patients with SD as best response had SD duration >6 m, 2 of which remain on treatment
- A total of 5 patients were treated beyond progression with increment median treatment duration after progression of 4.2 m

Se-Hoon Lee et al WCLC 2023

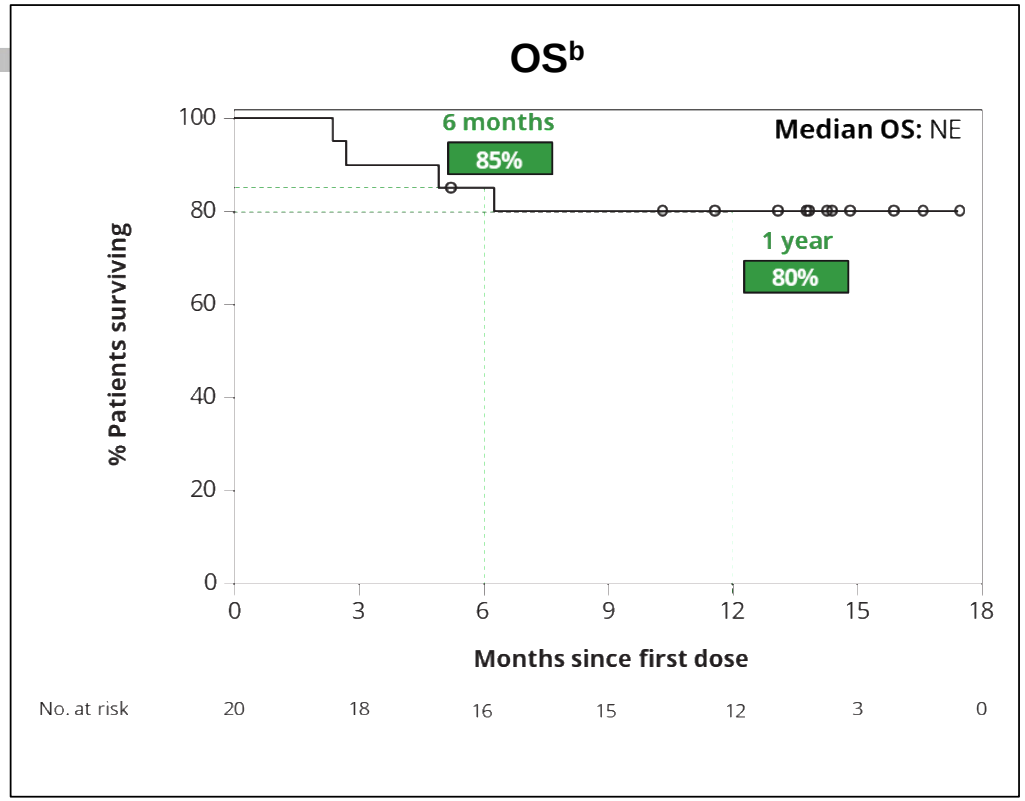
EGFR-MET bispecific antibody + EGFR TKI + chemotherapy

CHRYSALIS-2

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



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EGFR-MET bispecific antibody + EGFR TKI + chemotherapy

CHRYSALIS-2

SAFETY PROFILE

[illegible]	Total[a]	[illegible]
Associated with EGFR inhibition		
Rash	15 (75)	1 (5)
Paronychia	12 (60)	0
Stomatitis	12 (60)	0
Dermatitis acneiform	8 (40)	2 (10)
Diarrhea	6 (30)	1 (5)
Associated with MET inhibition		
Hypoalbuminemia	8 (40)	2 (10)
Other		
Neutropenia	18 (90)	14 (70)
IRR	13 (65)	0
Fatigue	10 (50)	5 (25)
Nausea	10 (50)	0
COVID-19	8 (40)	0
Thrombocytopenia	8 (40)	5 (25)
Constipation	7 (35)	0
Decreased appetite	7 (35)	1 (5)
Leukopenia	7 (35)	4 (20)
Alanine aminotransferase increased	6 (30)	0
Anemia	6 (30)	2 (10)
Pulmonary embolism	6 (30)	1 (5)
Aspartate aminotransferase increased	5 (25)	0
Back pain	5 (25)	0
Epistaxis	5 (25)	0
Hemorrhoids	5 (25)	0
Peripheral sensory neuropathy	5 (25)	0

- As of November 15, 2022, the median follow-up was 13.1 months
- Safety profile was consistent with that of individual components; no new safety signals, with most AEs at grade 1-2
- Median treatment cycles was 15.5 (range, 2–23)
- Median number of cycles of carboplatin and pemetrexed were 3.5 and 9.5, respectively

Efficacy according to MET expression

- ORR: 30%
- Median PFS: 5.7 months
- Median DoR: 10.8 months

	MET+ (n=28)	MET- (n=49)
ORR	61% (95% CI, 41–79)	14% (95% CI, 6–27)
Median DOR	10.8 months (95% CI, 2.9–NE)	6.8 months (95% CI, 1.9–NE)
CBR[a]	86% (95% CI, 67–96)	61% (95% CI, 46–75)
Median PFS	12.2 months (95% CI, 8.0–NE)	4.2 months (95% CI, 2.8–6.4)

MET 3+ staining on [illegible] tumor cells was identified as predictive of response
A total of 28 of 77 (36%) patients had MET 3+

Se-Hoon Lee et al WCLC 2023

Byyoung Chul Cho et al ESMO 2023

EGFR-MET bispecific antibody + EGFR TKI

MARIPOSA: Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in EGFR-mutated Advanced NSCLC

Study design

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors
- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

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

Dosing (in 28-day cycles)
Amivantamab: [redacted]
Lazertinib: 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:
- **Amivantamab + lazertinib** vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs osimertinib**:**
- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

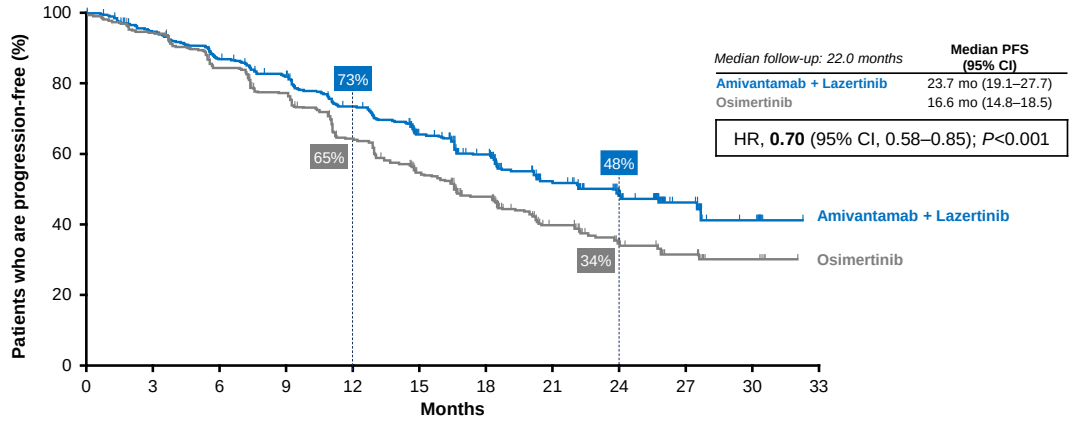
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]Brain MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.

[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.

[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

Primary Endpoint: Progression-free Survival by BICRa



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

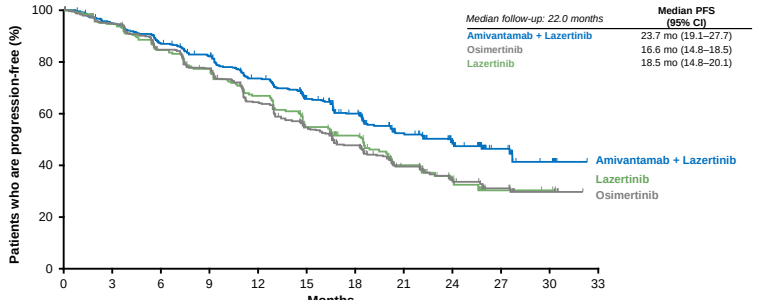
HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

No. at risk

Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

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

Lazertinib Monotherapy Demonstrates Meaningful Clinical Activity



Median follow-up: 22.0 months	Median PFS (95% CI)
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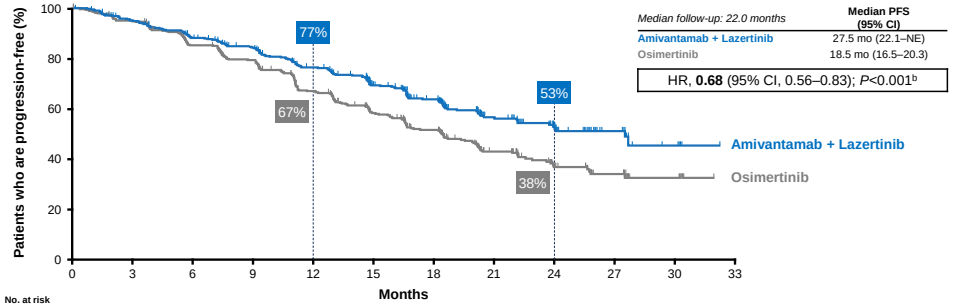
Osimertinib	16.6 mo (14.8–18.5)
Lazertinib	18.5 mo (14.8–20.1)

No. at risk

Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

Extracranial Progression-free Survival by BICRa



Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	18.5 mo (16.5–20.3)

HR, **0.68** (95% CI, 0.56–0.83); *P*<0.001[b]

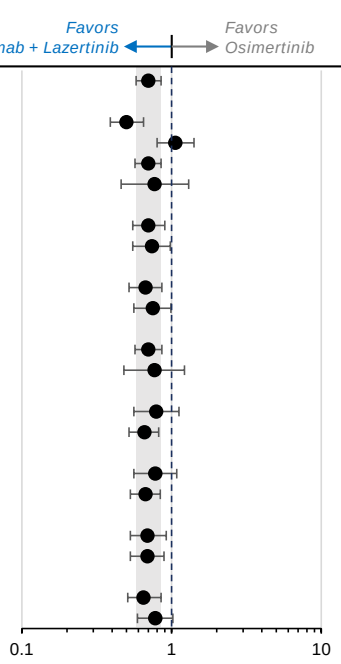
No. at risk

Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

EGFR-MET bispecific antibody + EGFR TKI

MARIPOSA: Amivantamab Plus Lazertinib Versus Osimertinib as First-line Treatment in EGFR-mutated Advanced NSCLC

PFS Benefit Seen Across Predefined Subgroups



Subgroup	HR (95% CI)	Events/N: Amivantamab + Lazertinib	Events/N: Osimertinib
All randomized patients	0.70 (0.58–0.85)	192/429	252/429
Age category			
<65 years	0.50 (0.39–0.65)	94/235	153/237
[illegible]	1.06 (0.80–1.41)	98/194	99/192
<75 years	0.70 (0.57–0.85)	165/378	220/376
[illegible]	0.77 (0.46–1.30)	27/51	32/53
Sex			
Female	0.70 (0.55–0.90)	112/275	140/251
Male	0.74 (0.55–0.98)	80/154	112/178
Race			
Asian	0.67 (0.52–0.86)	105/250	144/251
Non-Asian	0.75 (0.56–0.99)	85/117	108/177
Weight category			
<80 kg	0.70 (0.57–0.86)	161/376	209/368
[illegible]	0.77 (0.48–1.22)	31/53	43/61
ECOG PS			
0	0.79 (0.56–1.12)	56/141	76/149
1	0.66 (0.52–0.82)	136/288	176/280
History of smoking			
Yes	0.78 (0.56–1.08)	67/130	79/134
No	0.67 (0.53–0.84)	125/299	173/295
History of brain metastases			
Yes	0.69 (0.53–0.92)	94/178	111/172
No	0.69 (0.53–0.89)	98/251	141/257
EGFR mutation			
Ex19del	0.65 (0.51–0.85)	101/257	142/257
L858R	0.78 (0.59–1.02)	90/171	110/172

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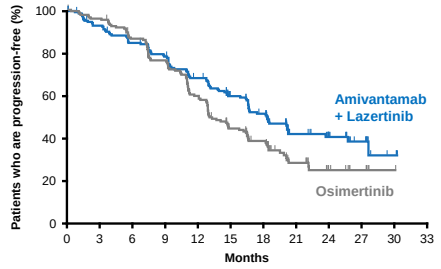
Consistent PFS (BICR) Benefit With or Without Brain Metastases

With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)

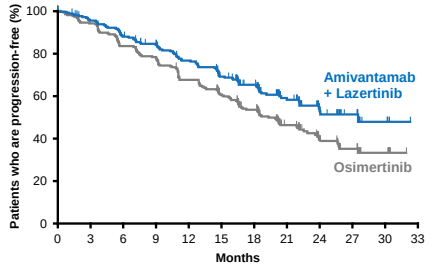


No. at risk

Amivantamab + Lazertinib	178	162	146	134	115	92	71	34	24	12	3	0
Osimertinib	172	164	146	126	95	64	47	21	11	6	1	0

Without History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	27.5 mo (22.1–NE)
Osimertinib	19.9 mo (16.6–22.9)

HR, **0.69** (95% CI, 0.53–0.89)

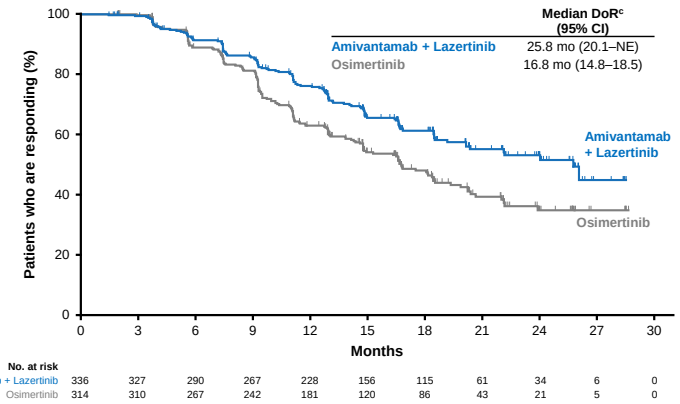


No. at risk

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

ORR and DoR by BICR

BICR-assessed response, n (%)[a]	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)
ORR		
All responders	86% (95% CI, 83–89)	85% (95% CI, 81–88)
Confirmed responders	80% (95% CI, 76–84)	76% (95% CI, 71–80)
Best response[b]		
CR	29 (7)	15 (4)
PR	334 (79)	335 (81)
SD	30 (7)	42 (10)
PD	7 (2)	11 (3)
NE/UNK	21 (5)	11 (3)
Ongoing responses	209 of 336 (62%)	151 of 314 (48%)



No. at risk

Amivantamab + Lazertinib	336	327	290	267	228	156	115	61	34	6	0	
Osimertinib	314	310	267	242	181	120	86	43	21	5	0	

Amivantamab + lazertinib improved median DoR by 9 months, suggesting longer time to resistance and progression

EGFR-MET bispecific antibody + EGFR TKI

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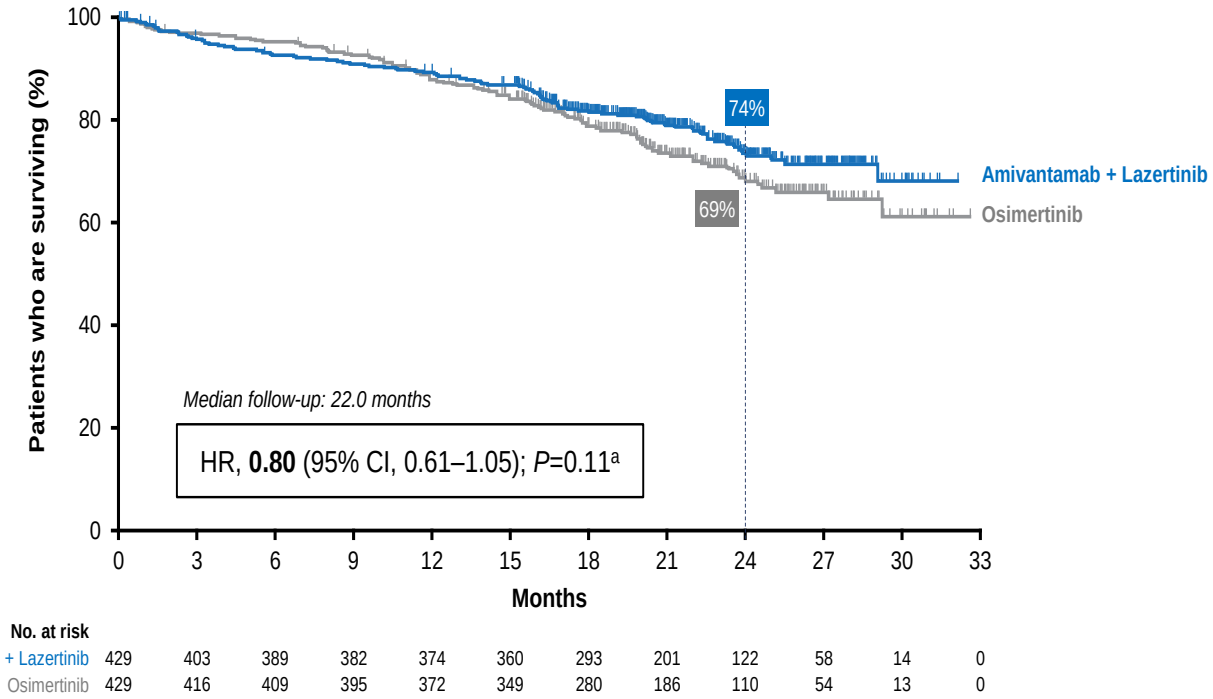
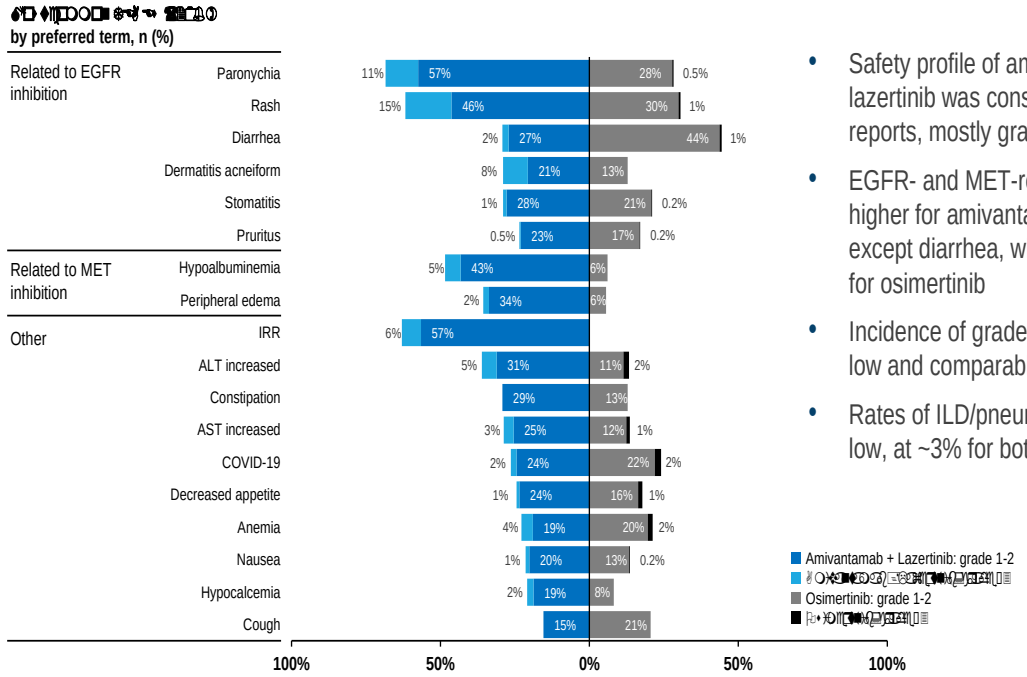
Interim Overall Survival



- VTE rates were higher for amivantamab + lazertinib
  - Most common preferred terms were pulmonary embolism and deep vein thrombosis
  - Most VTEs were grade 1-2
  - Incidence of grade 4-5 VTEs was low (<1%)
  - and comparable between arms

Safety Profile



- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

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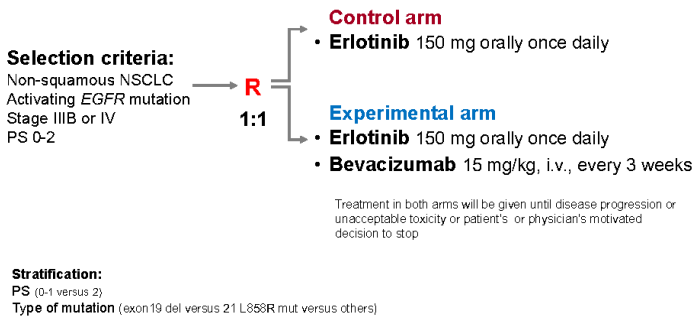
Antiangiogenic drugs + EGFR TKI

Fase 2 JO25567: Erlotinib + Bevacizumab *vs* Erlotinib	mPFS: 16 vs 9,7m; p=0,0015
Fase 2 : Erlotinib + Bevacizumab *vs* Erlotinib	mPFS: 17,9 vs 13,5m; p=0,33
F2 (T790M tras TKI): Osimertinib + Bevacizumab *vs* Osimertinib	mPFS: 9,4 vs 13,5m; p=0,20
F2: Osimertinib + Bevacizumab *vs* Osimertinib	mPFS: 20,2 vs 22,1m; p=0,213

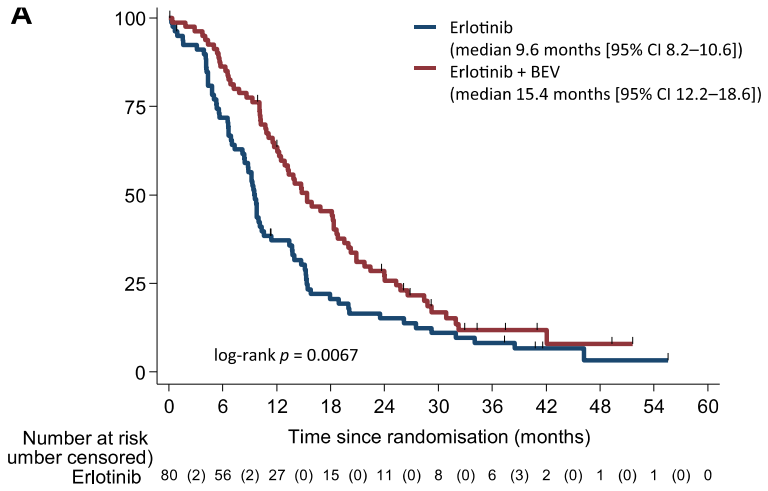
Maemondo M, et al. J Clin Oncol 2020;38:9506.
Akamatsu H, et al. Jama Oncol 2021;7:386.
Nakagawa K, et al. Lancet Oncol 2019;20:1655-69.
Piccirillo MC, et al. ESMO 2021 (Abstr 12070).

Beverly trial Addition of Bevacizumab to Erlotinib as First-Line Treatment of Patients With EGFR-Mutated Advanced Nonsquamous NSCLC

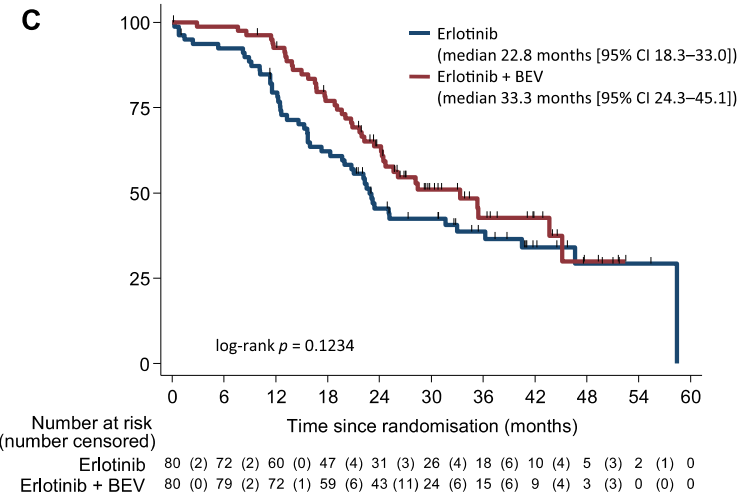


Seto T, et al. Lancet Oncol 2014;15:1236-44.
Stinchcombe TE, et al. Jama Oncol 2019;5:1448-55.
Saito H, et al. Lancet Oncol 2019;20:625-35.
Kenmotsu H, et al. ESMO 2021 (LBA44)

Progression Free Survival.



Overall Survival



Antiangiogenic drugs + EGFR TKI

RELAY: N=449

CYRAMZA + erlotinib vs placebo + erlotinib

- mNSCLC
- EGFR mut+ exon 21 (L858R) substitution or exon 19 deletion
- ECOG PS 0 or 1
- No CNS metastases
- No known EGFR T790M mutations at baseline

1:1 RANDOMIZATION*

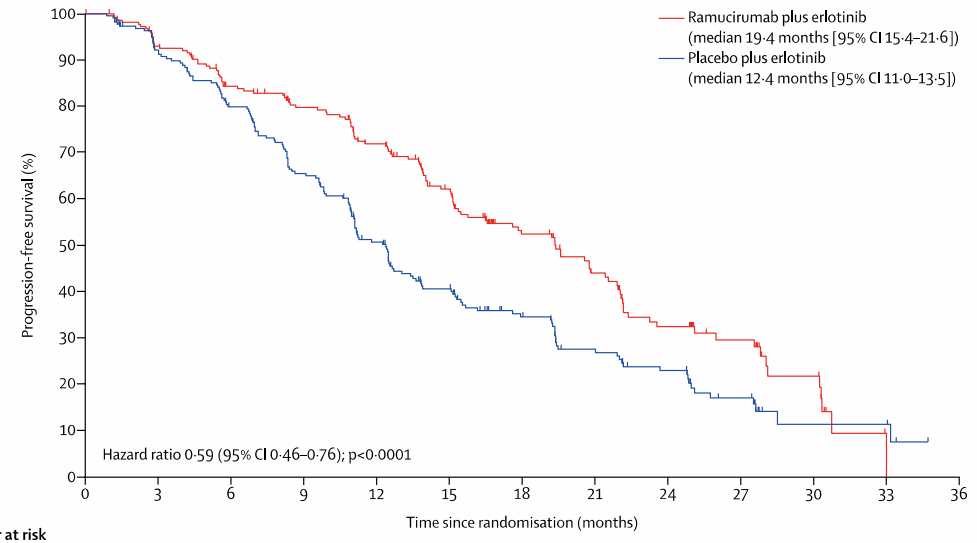
CYRAMZA 10 mg/kg Q2W via IV + **erlotinib** 150 mg/day orally (n=224)

Placebo Q2W + **erlotinib** 150 mg/day orally (n=225)

TREATMENT UNTIL DISEASE PROGRESSION OR UNACCEPTABLE TOXICITY

Major efficacy outcome measure
PFS
Supportive efficacy outcome measures
OS, ORR, DoR

Progression Free Survival



Number at risk (number censored)													
Ramucirumab plus erlotinib	224 (0)	196 (13)	170 (21)	154 (28)	133 (34)	103 (47)	69 (66)	49 (76)	32 (81)	20 (91)	10 (97)	1 (102)	0 (102)
Placebo plus erlotinib	225 (0)	196 (12)	167 (12)	136 (16)	99 (23)	72 (31)	52 (41)	37 (46)	27 (50)	15 (56)	4 (64)	4 (64)	0 (67)

Nakagawa K et al *Lancet Oncol*. 2019;20(12):1655-1669.

To wrap up…

- Chemotherapy combined with EGFR inhibition and EGFR-MET bispecific antibody + EGFR TKI, while awaiting overall survival data, represents a novel standard in first-line treatment.
- EGFR TKIs will remain the primary treatment for a significant proportion of patients with EGFR gene mutations.
- After first-line treatment of EGFR-mutated patients, exploring clinical trials for selective MET inhibitors or antibody-drug conjugates (ADCs) targeting the MET pathway in cases of MET overexpression could be considered. For patients previously treated with EGFR-MET bispecific antibody in the first line, uncertainties might arise regarding subsequent steps or treatments in their medical care pathway.
- Prioritizing research on anti-angiogenic drugs, especially in combination with emerging treatments, should continue in the management of EGFR gene mutation patients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“Algunas veces hay que decidirse entre una cosa a la que se está acostumbrado y otra que nos gustaría conocer.”
Paulo Coelho
Muchas Gracias