foro debate oncología

Zaragoza 26-29 septiembre 2023

Combos con EGFR-TKI

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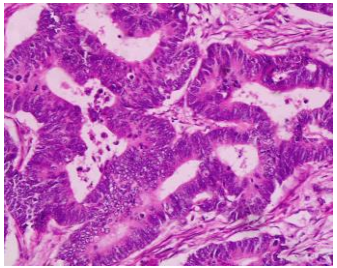
DISCLOSURES

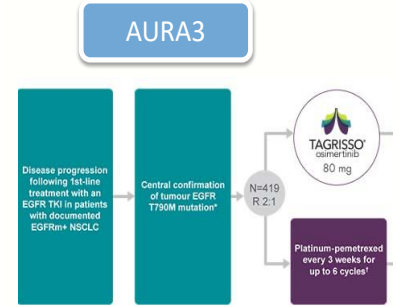
Advisory / Consultancy : AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Roche, Takeda

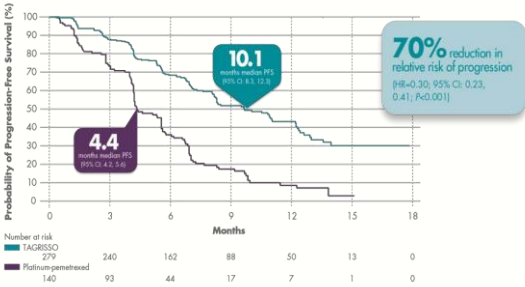
Speaker Bureau / Expert testimony: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Novartis, Pfizer, Roche, Takeda

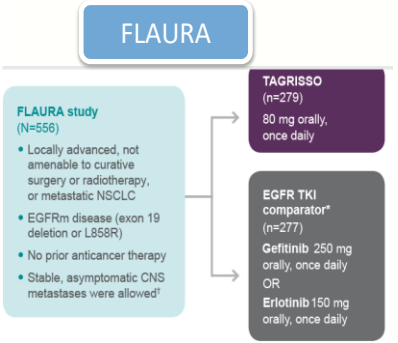
Travel / Accommodation / Expenses :Bristol-Myers Squibb, Pfizer, Roche, Takeda

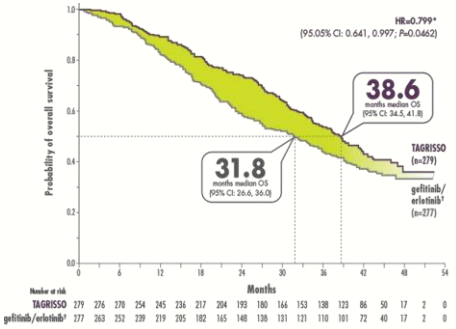
INTRODUCTION







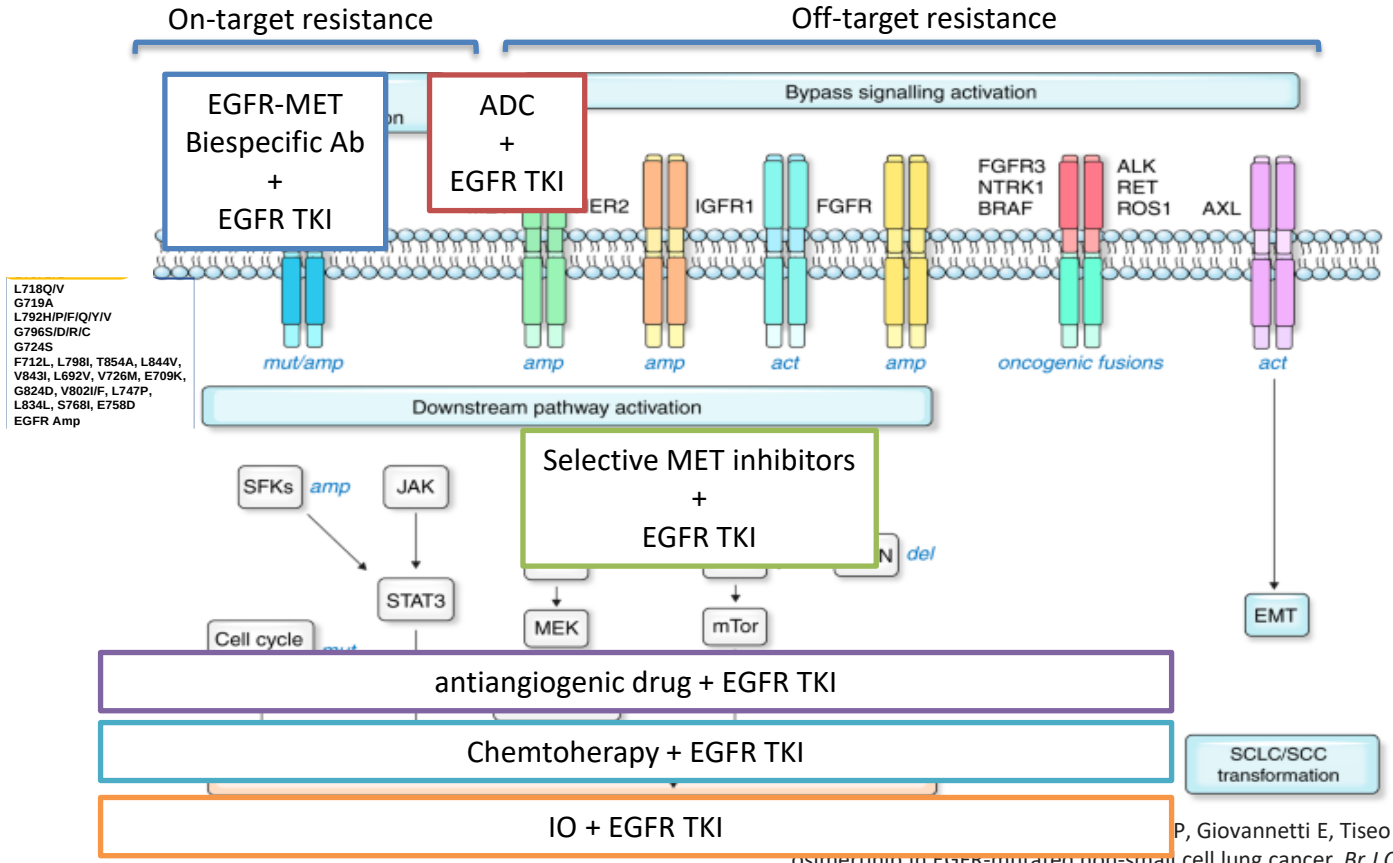




Mok TS, et al. N Engl J Med 2017;376(7):629-40.
Ramalingam SS, et al. N Engl J Med 2020;382(1):41-50.


Godelia
BIERZO

TREATMENT STRATEGIES BASED ON THE RESISTANCE MECHANISMS

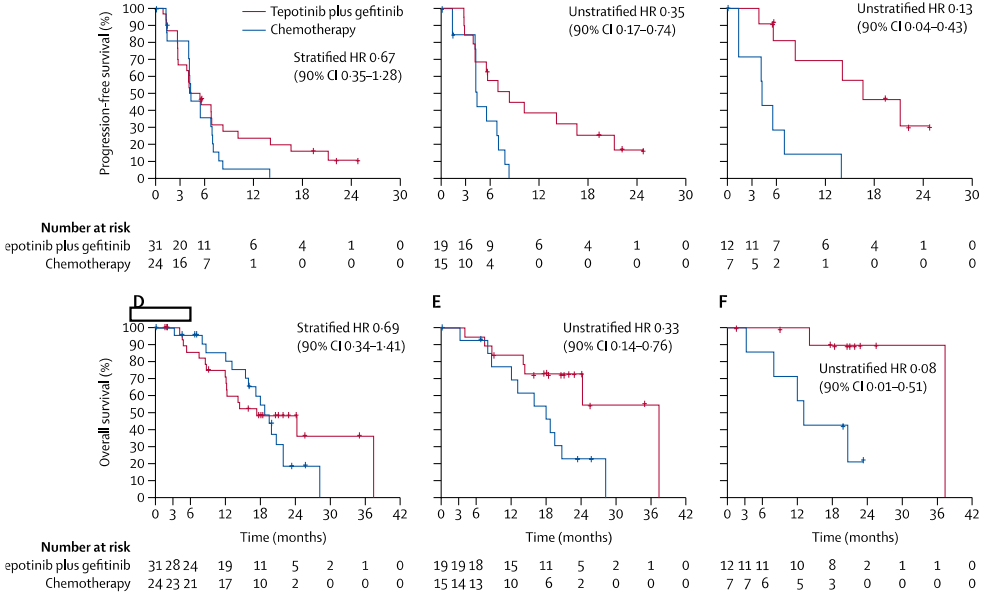


P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121(9):725-737.

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

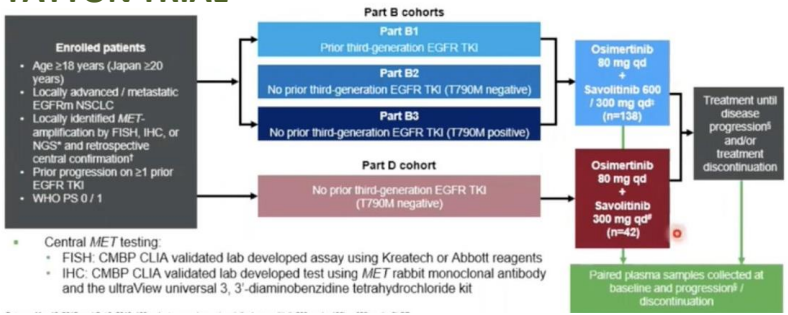
Or MET amplification n=19

- 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

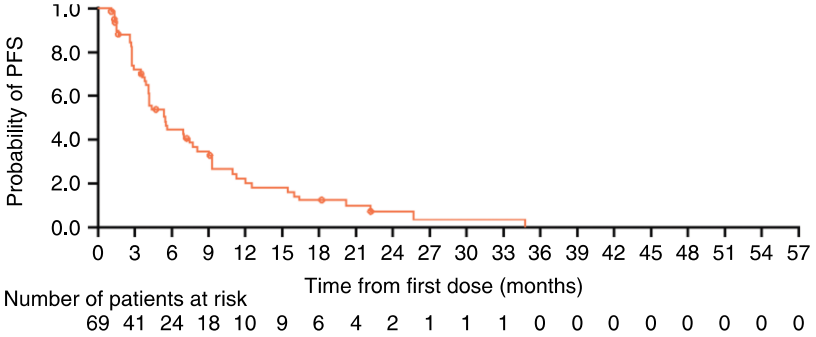
Wu YL, Cheng Y, Zhou J, et al. Tepotinib plus gefitinib in patients with EGFR-mutant non-small-cell lung cancer with MET overexpression or MET amplification and acquired resistance to previous EGFR inhibitor (INSIGHT study): an open-label, phase 1b/2, multicentre, randomised trial [published correction appears in Lancet Respir Med. 2020 Jul;8(7):e59]. *Lancet Respir Med*. 2020;8(11):1132-1143.

SELECTIVE MET INH + EGFR TKI

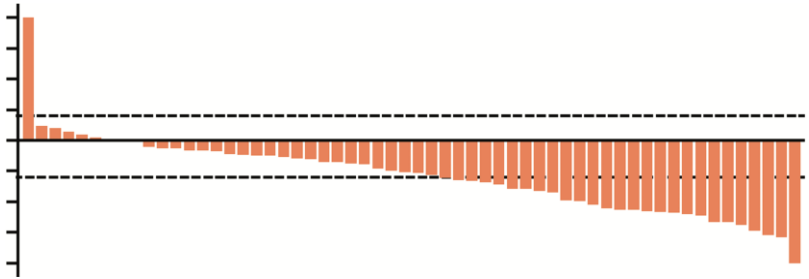
TATTON TRIAL



PFS



ORR



Efficacy endpoints

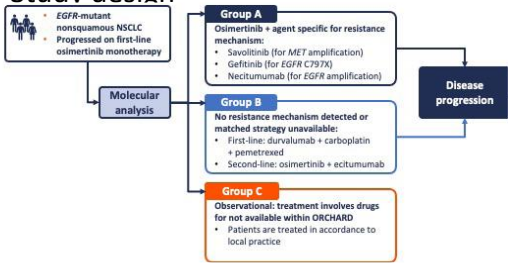
	Part B: osimertinib 80 mg + savolitinib 600/300* mg			Part D: osimertinib 80 mg + savolitinib 300 mg
Endpoint	Previously treated with a 3G EGFR-TKI n = 69	No prior 3G EGFR-TKI, T790M-negative n = 51	No prior 3G EGFR-TKI, T790M-positive n = 18	No prior 3G EGFR-TKI, T790M-negative n = 42
ORR[b], n (%)	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)

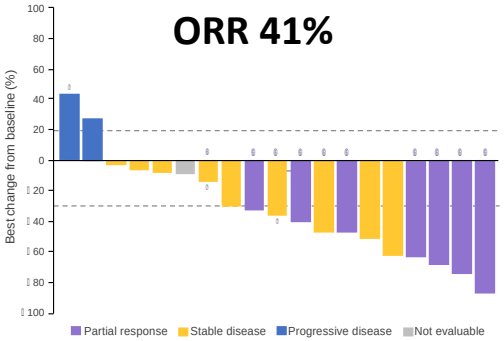
Hartmaier RJ, Markovets AA, Ahn MJ, et al. Osimertinib + Savolitinib to Overcome Acquired MET-Mediated Resistance in Epidermal Growth Factor Receptor-Mutated, MET-Amplified Non-Small Cell Lung Cancer: TATTON. *Cancer Discov.* 2023;13(1):98-113. doi:10.1158/2159-8290.CD-22-0586

SELECTIVE MET INH + EGFR TKI

ORCHARD TRIAL

Study design

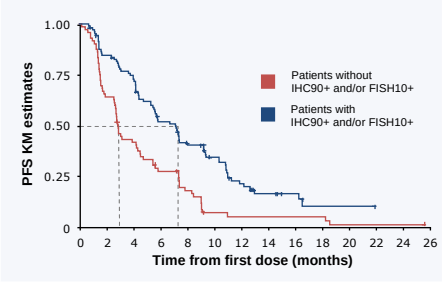




Yu AH et al. ESMO 2021. #3222.

SAVANNAH: A Phase II trial of osimertinib plus savolitinib

- 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

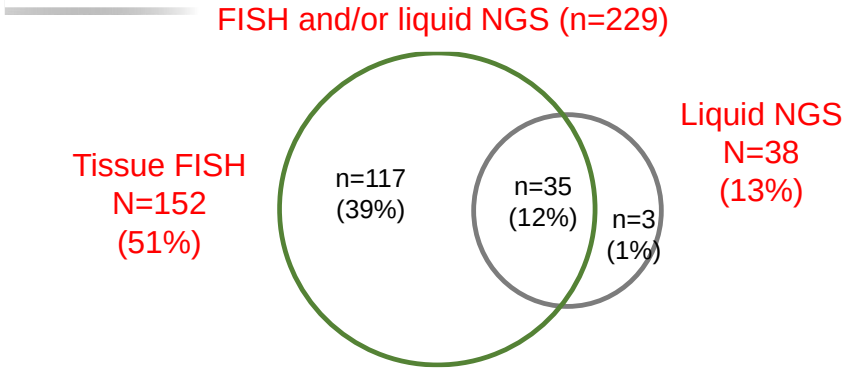
Investigator assessment	With IHC90+ and/or FISH10+ status (N=108)		Without IHC90+ and/or FISH10+ status (N=77)	
	Total (N=108)	No prior CTx (n=87)	Total (N=77)	No prior CTx (n=63)
ORR (95% CI)	49% (39, 59)	52% (41, 63)	9% (4, 18)	10% (4, 20)
mDOR, months (95% CI)	9.3 (7.6, 10.6)	9.6 (7.6, 14.9)	6.9 (4.1, 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)

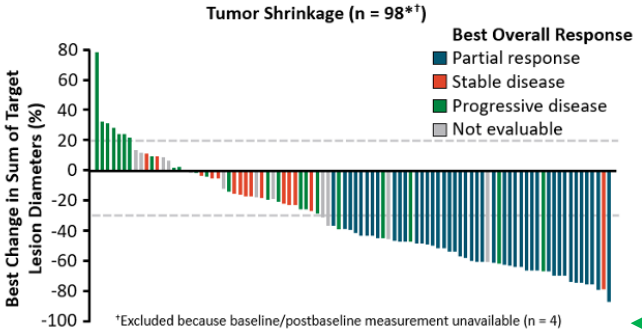
Ahn M-J et al. WCLC 2022. #EP08.02-140

SELECTIVE MET INH + EGFR TKI

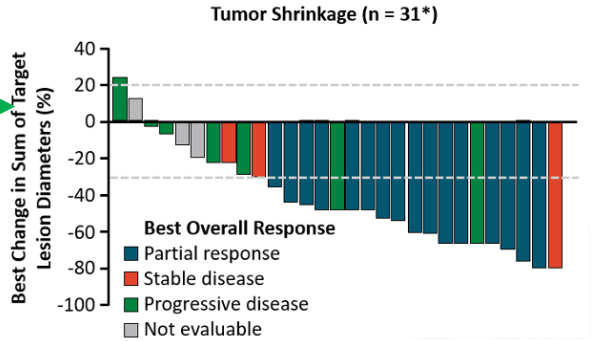
INSIGHT 2 (n=122)

- 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 (+)





	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

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

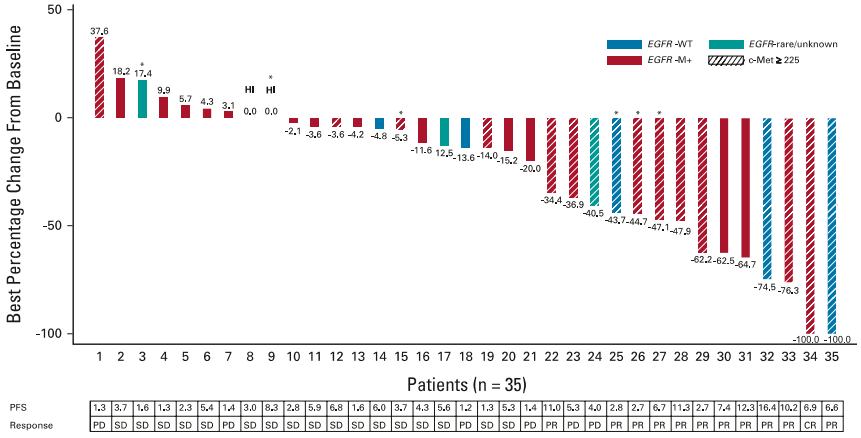
Phase I/Ib. n=42

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%)

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]



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

Camidge DR, Barlesi F, Goldman JW, et al. Phase Ib Study of Telisotuzumab Vedotin in Combination With Erlotinib in Patients With c-Met Protein-Expressing Non-Small-Cell Lung Cancer. *J Clin Oncol*. 2023;41(5):1105-1115.

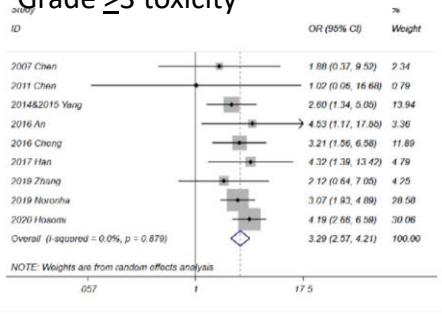
Chemotherapy + EGFR TKI

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, radiotherapy, 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

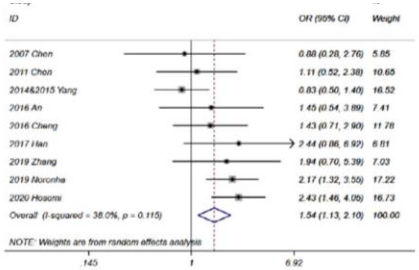
[a] The two studies by Yang et al. in 2014 and 2015 reported progression-free survival and overall survival of the same patient population, respectively. Thus, the two studies were considered as one in the present analysis.
EGFR, Epidermal Growth Factor Receptor; NSCLC, Non-Small Cell Lung Cancer; N/A,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

Grade ≥3 toxicity



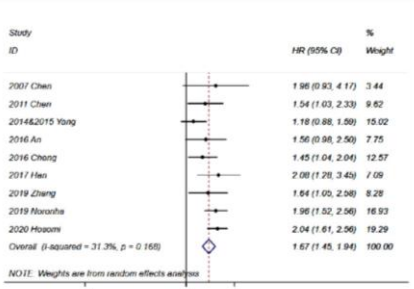
3.29 (95% CI 2.57–4.21; p < 0.001)

ORR



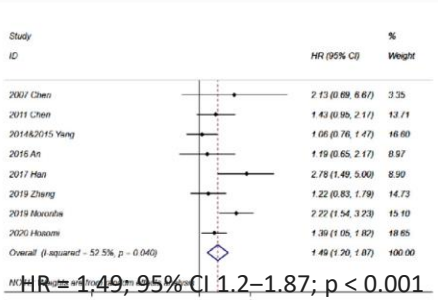
OR = 1.54; 95% CI, 1.13–2.1; p = 0.006

PFS



HR=1.67; 95% CI 1.45–1.94; p < 0.001

OS

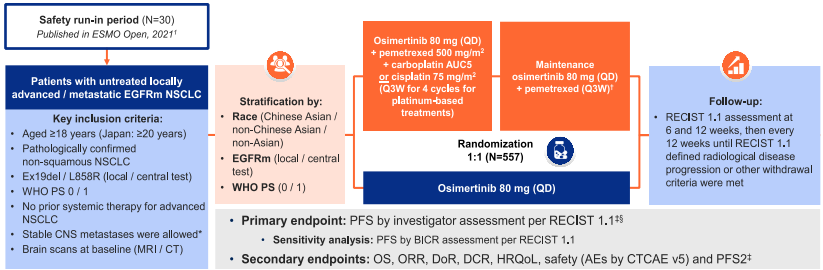


HR = 1.49; 95% CI 1.2–1.87; p < 0.001

Yi M, He T, Wang K, Wei Y. Comparison of gefitinib plus chemotherapy versus gefitinib alone for advanced non-small-cell lung cancer: A meta analysis. *Clinics (Sao Paulo)*. 2023;78:100152. Published 2023 Jan 19.

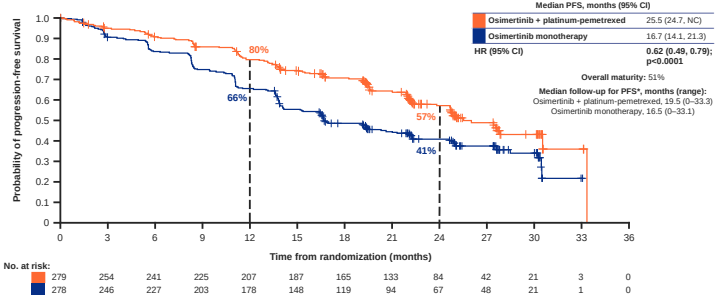
Chemotherapy + EGFR TKI

FLAURA 2

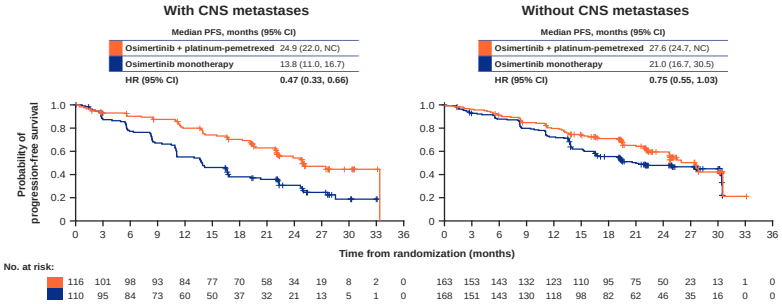


Progression-free survival per investigator

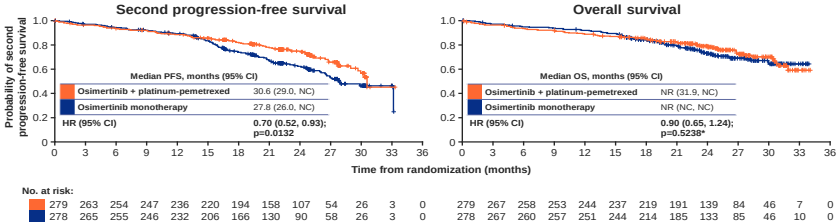
- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



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)†

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Chemotherapy + EGFR TKI

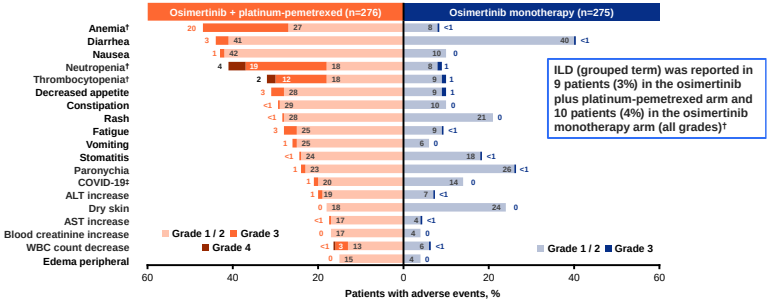
FLAURA 2

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 [illegible]	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 [illegible]	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 ([illegible])



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)†

[illegible] 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

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EGFR-MET bispecific antibody + EGFR TKI

CHRYSALIS-2

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

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/m²) until disease progression

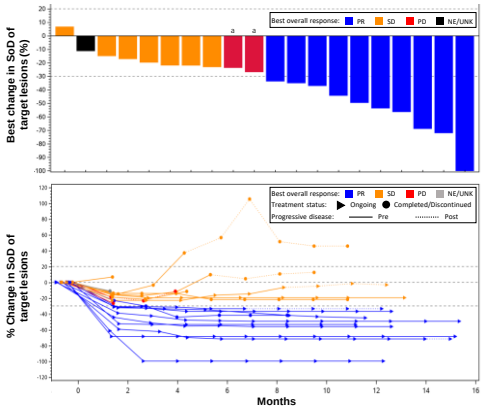
Endpoints
- Adverse events (primary)
- Duration of response
- Progression-free survival
- Objective response rate
- Clinical benefit rate[c]
- Overall survival

Clinical chacracteristics

Demographic and baseline disease characteristics, n (%)	n = 20
Median age, years (range)	61 (38–76)
Female / male	11 (55) / 9 (45)
Race	
Asian	11 (55)
White	8 (40)
Black	1 (5)
Exon 19 deletion / L858R	13 (65) / 7 (35)
ECOG PS 0 /1	4 (20) / 16 (80)
History of brain metastases	12 (60)
Median no. of prior lines[d] (range)	1 (1–3)
Prior therapy[d]	
1st/2nd-generation EGFR TKI	9 (45)
Osimertinib	14 (70)
Platinum-based chemotherapy[e]	5 (25)

- At a 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 months, 2 of which remain on treatment
- A total of 5 patients were treated beyond investigator-assessed progression,c with incremental median treatment duration after progression of 4.2 months

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)

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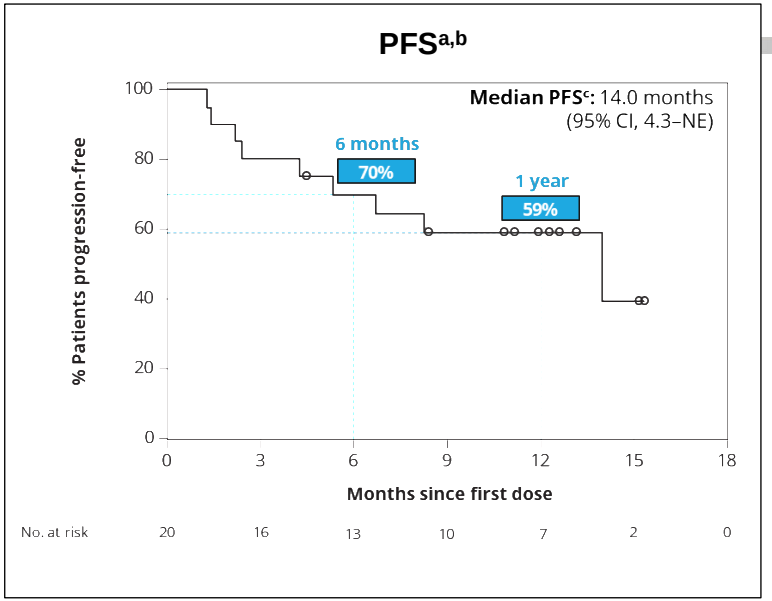
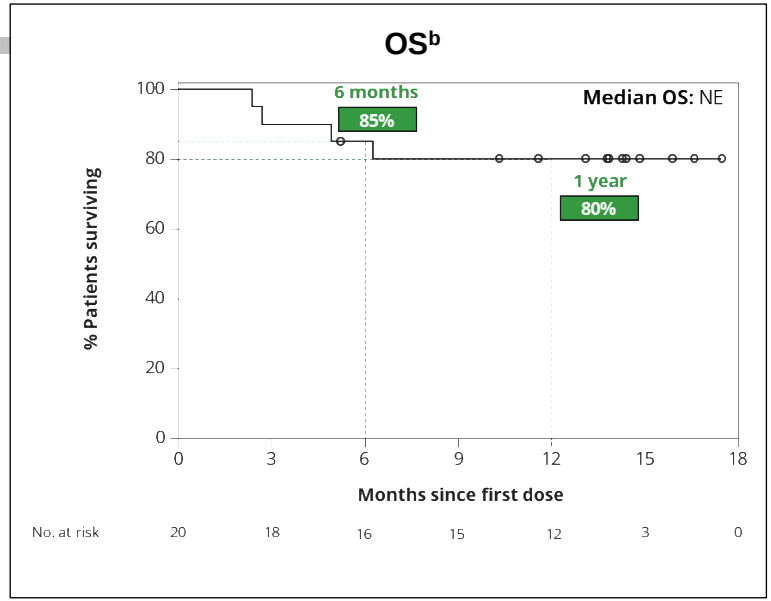
EGFR-MET bispecific antibody + EGFR TKI

CHRYSALIS-2

PROGRESSION FREE SURVIVAL



OVERALL SURVIVAL



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EGFR-MET bispecific antibody + EGFR TKI

CHRYSALIS-2

SAFETY PROFILE

	Total[a]	
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

Se-Hoon Lee et al WCLC 2023

- 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

- 18/20 (90%) patients developed neutropenia, of which 14 had grade ≥3 eventsb
  - – Highest incidences were in cycle 1 (when labs were measured weekly)
  - – After completion of carboplatin (cycle 5 onward), 1/17 (6%) patients experienced grade ≥3 neutropenia
  - – No patients developed neutropenic fever
- 8/20 (40%) patients developed thrombocytopenia, of which 5 were
- grade ≥3 events; most incidences occurred during cycle 1

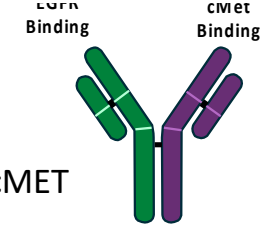
– After completion of carboplatin (cycle 5 onward), 1/17 (6%) patients experienced grade ≥3 thrombocytopenia

– 1 patient developed a grade 3 adrenal hemorrhage after thrombocytopenia

EGFR-MET bispecific antibody + EGFR TKI

CHRYSALIS-2 Cohort D

- Amivantamab:
  Fully humanized bispecific IgG1 Ab targeting EGFR and cMET



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[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]
  Treatment naïve or post-1st or 2nd generation EGFR TKI
- **Cohort D:** *EGFR* ex19del or L858R
  Post-osimertinib, chemotherapy naïve, biomarker validation

Endpoints

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

Focus of this presentation

- The **objective** of Cohort D was to prospectively validate potential biomarkers (IHC or ctDNA NGS[d])
- Response was assessed by the investigator per RECIST v1.1
- Plasma and tissue[e] were collected at baseline (after osimertinib and prior to treatment on trial)
- **Predefined Bayesian process allowed for biomarker retraining/validation**

(n=108, Osimertinib as 1st line: 70%, 2nd line: 30%)

- 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+

EGFR-MET bispecific antibody + EGFR TKI

Patients:

- ≥1 measurable lesion by RECIST v1.1 that has not been previously irradiated
- Locally advanced or metastatic EGFR Exon 19del or L858R mutation NSCLC
- Progressed on or after osimertinib

21-Day Cycles 1-4

Arm A
Amivantamab IV
Lazertinib PO
Pemetrexed IV
Carboplatin IV

21-Day Maintenance Cycles until PD

Arm A
Amivantamab IV
Lazertinib PO
Pemetrexed IV

Phase 3 MARIPOSA-2 Study Meets Dual Primary Endpoint Resulting in Statistically Significant and Clinically Meaningful Improvement in Progression-Free Survival for RYBREVANT® (amivantamab-vmjw) Plus Chemotherapy With and Without Lazertinib versus Chemotherapy Alone in Patients with EGFR-Mutated Non-Small Cell Lung Cancer after Disease Progression on Osimertinib

• PFS by BICR	• ORR • OS • DOR • TTST	• PFS2 • TTSP • Intracranial PFS • Safety	• PK • Immunogenicity • PROs

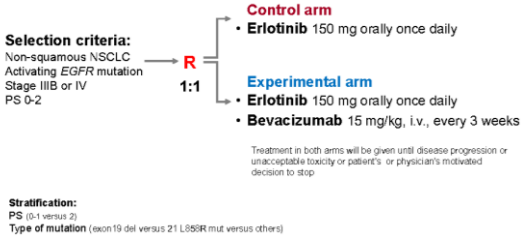
BICR, Blinded Independent Central Review; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression free survival; PFS2, progression free survival after first subsequent therapy; PD, disease progression; PRO, patient reported outcome; RECIST, Response Evaluation Criteria in Solid Tumors; TTSP, time to symptomatic progression; TTST, time to subsequent therapy; v, version; LDC, low dose corticosteroids.

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).

Antiangiogenic drugs + EGFR TKI

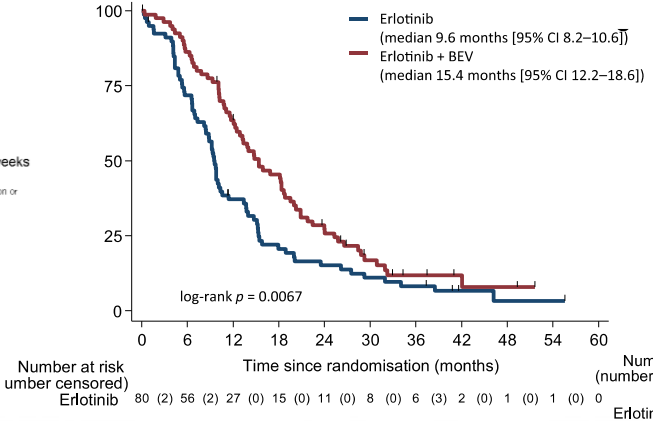
Fase 2 JO25567: Erlotinib + Bevacizumab *vs* Erlotinib	mPFS: 16 vs 9,7m; p=0,0015
Fase 2 : Erlotinib + Bevacizumab *vs* Erlotinib	mPFS: 17,9 vs 13,5m; p=0,33
F2 (T790M tras TKI): Osimertinib + Bevacizumab *vs* Osimertinib	mPFS: 9,4 vs 13,5m; p=0,20
F2: Osimertinib + Bevacizumab *vs* Osimertinib	mPFS: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

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

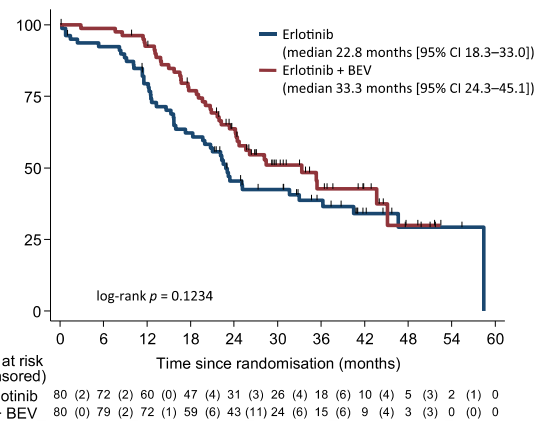


Seto T, et al. Lancet Oncol 2014;15:1236-44.
Stinchcombe TE, et al. Jama Oncol 2019;5:1448-55.
Saito H, et al. Lancet Oncol 2019;20:625-35.
Kenmotsu H, et al. ESMO 2021 (LBA44)

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*

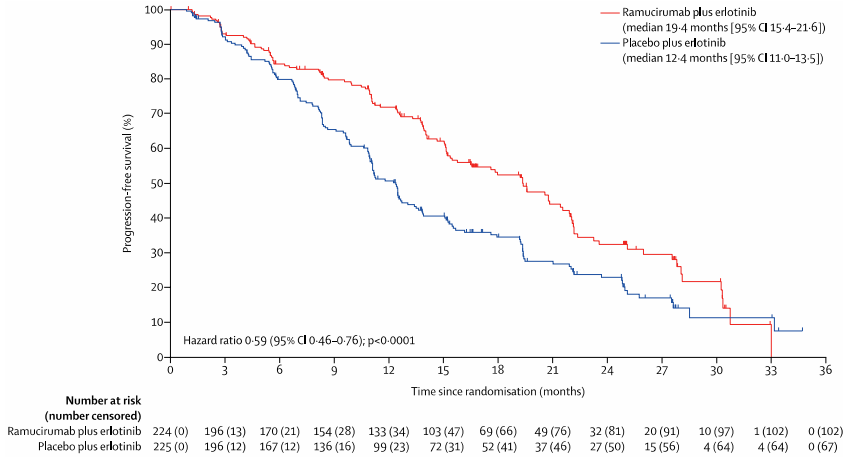
CYRAMZA 10 mg/kg Q2W via IV + **erlotinib** 150 mg/day orally (n=224)

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



Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(12):1655-1669.

CONCLUSIONES