ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

HOW DO I TREAT PATIENTS WITH EGFR MUTATIONS?

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DECLARATION OF INTERESTS

Personal financial interests

Consultancy/honoraria from AbbVie, Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi and Takeda.

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Non-financial interests

ESMO Council member as Women for Oncology Committee Chair.

ESMO Faculty for lung and other thoracic tumours.

IASLC Academy and Educational Committee member.

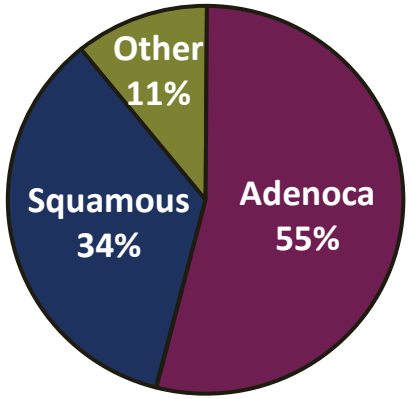
Former President of Spanish Medical Oncology Society (SEOM) and Spanish Federation of Medical Societies (FACME).

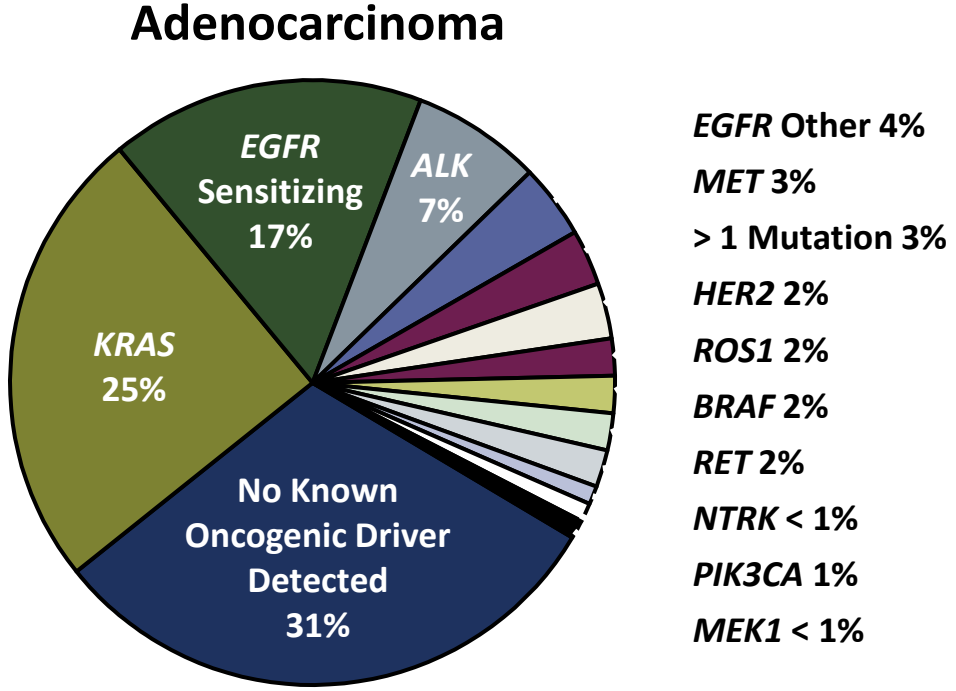
Member of the Spanish National Health Advisory Board.

President of the National Technical Committee and Executive Board member of the the Spanish Patients Against Cancer Association (AECC) and Member of the Scientific Committee of their Research Foundation.

Member of the Scientific Committee of the Spanish Lung Cancer Patient's Advocacy Association (AECAP)

LUNG CANCERs: MANY DISEASES!





Then — Histology-Based Subtyping — Now

Li. JCO. 2013;31:1039. Tsao. J Thorac Oncol. 2016;11:613.

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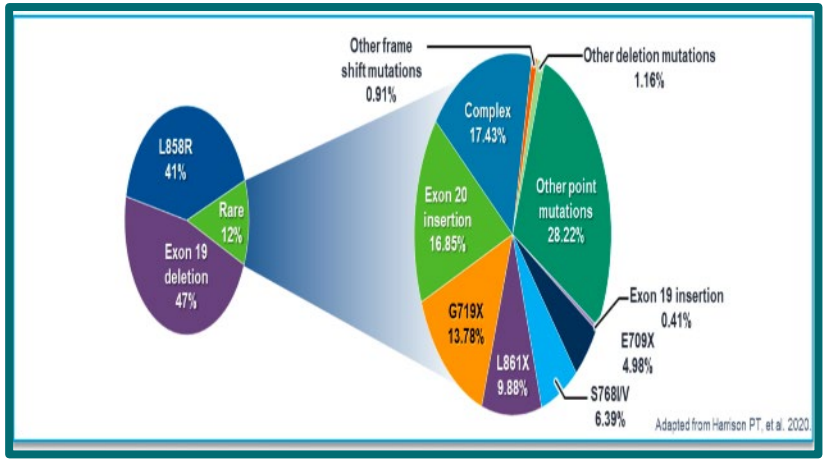
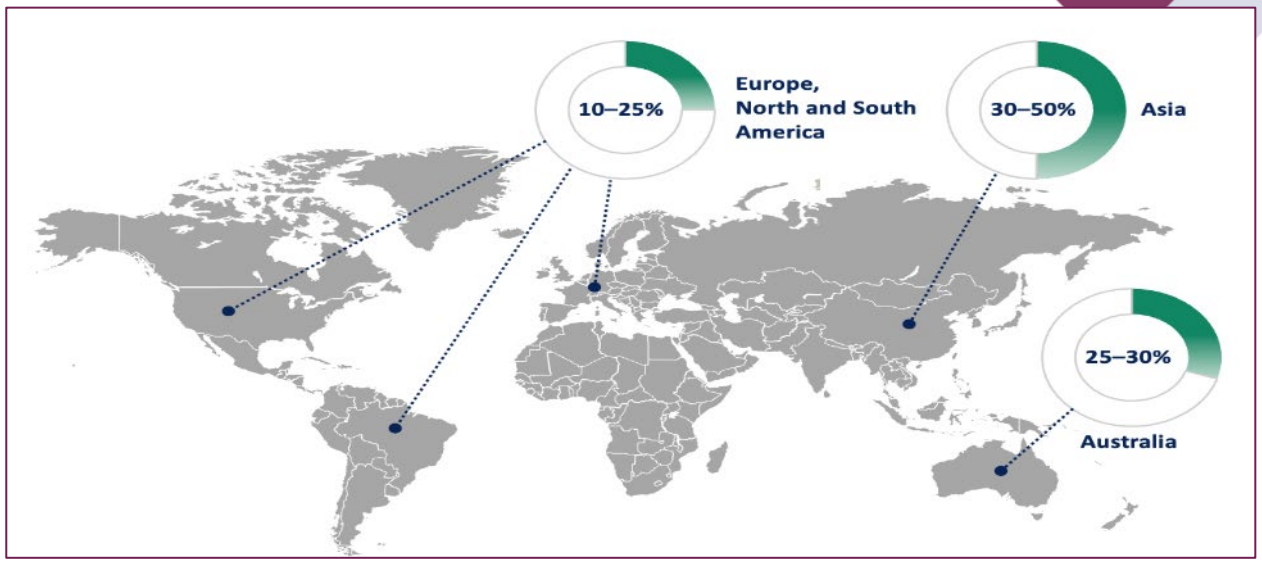
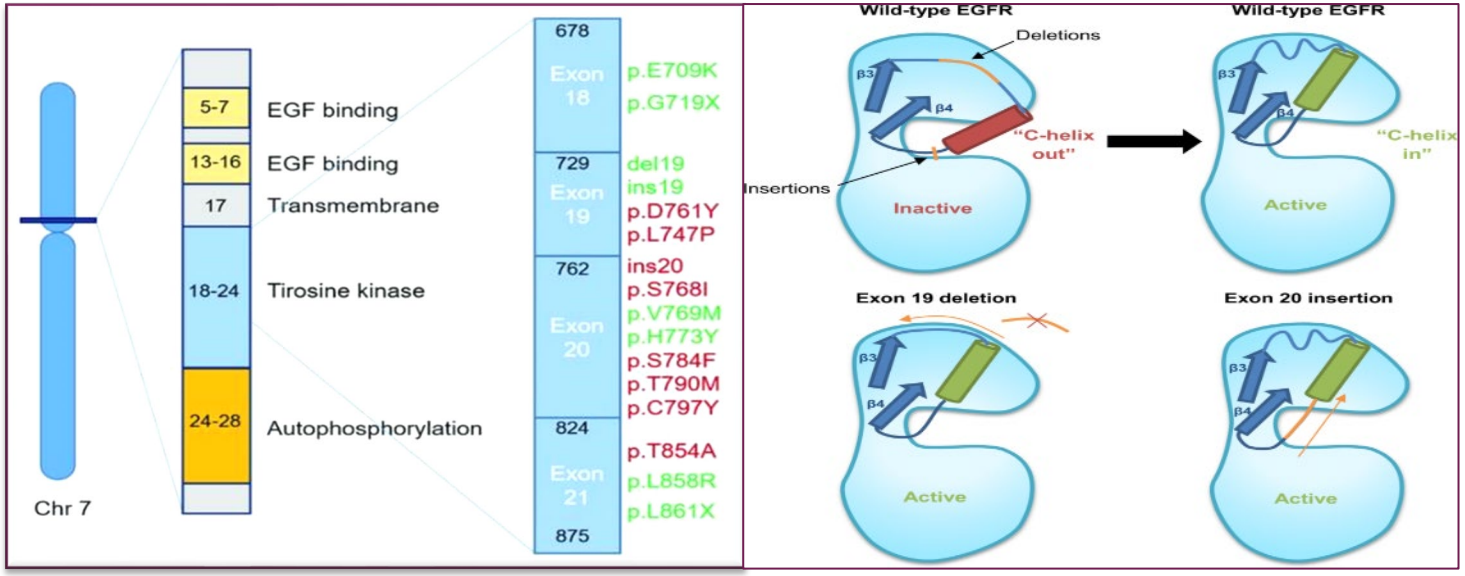
EGFR MUTATIONS

- 10- 14% NSCLC tumors in Western pop/30-50% Asian
- Clinical profile: non-smokers, female, CNS+, adenocarcinoma
- **Common EGFR mutations (85%)** : ex19del & ex21 (L858R) mut.
- **Exon 20 ins mut (4%)**: in-frame ins or dupl between amino acid positions 762 and 774 of the EGFR protein
- **Uncommon EGFR mutations**: ex18 & ex20, rarer ex19 & ex21 mut., i.e., L861Q (ex21)







Van Sanden, S., et al . Targ Oncol 2022, Vyse, S., et al. Sig Transduct Target Ther 2019, Ferreira D et al, Int. J. Mol. Sci. 2021

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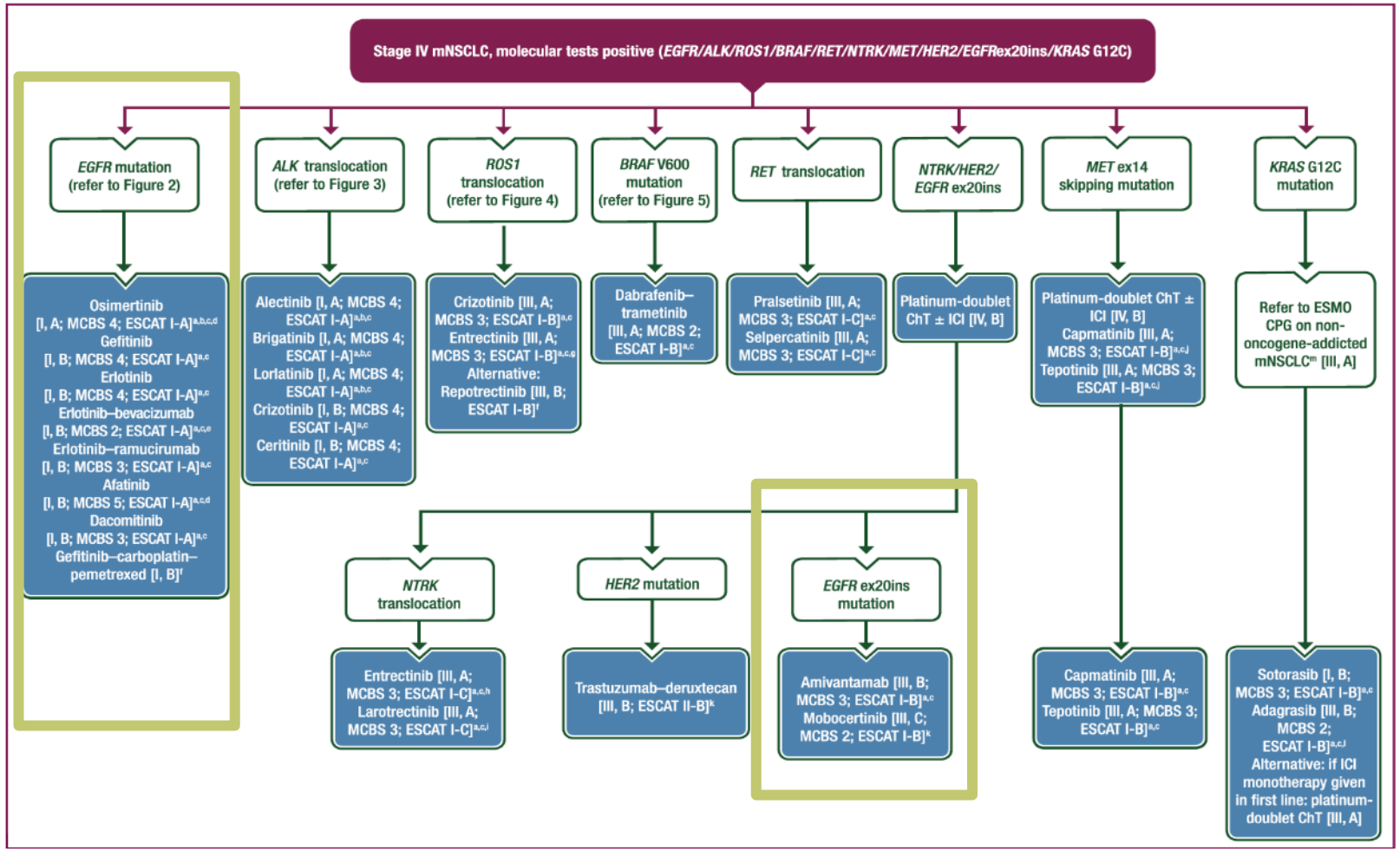
Courtesy Dr Mezquita

ESMO GUIDELINES

Different recommendations depending on the EGFR mutation



Hendriks L et al. Ann Oncol 2023

COMMON *EGFR* MUTATIONS

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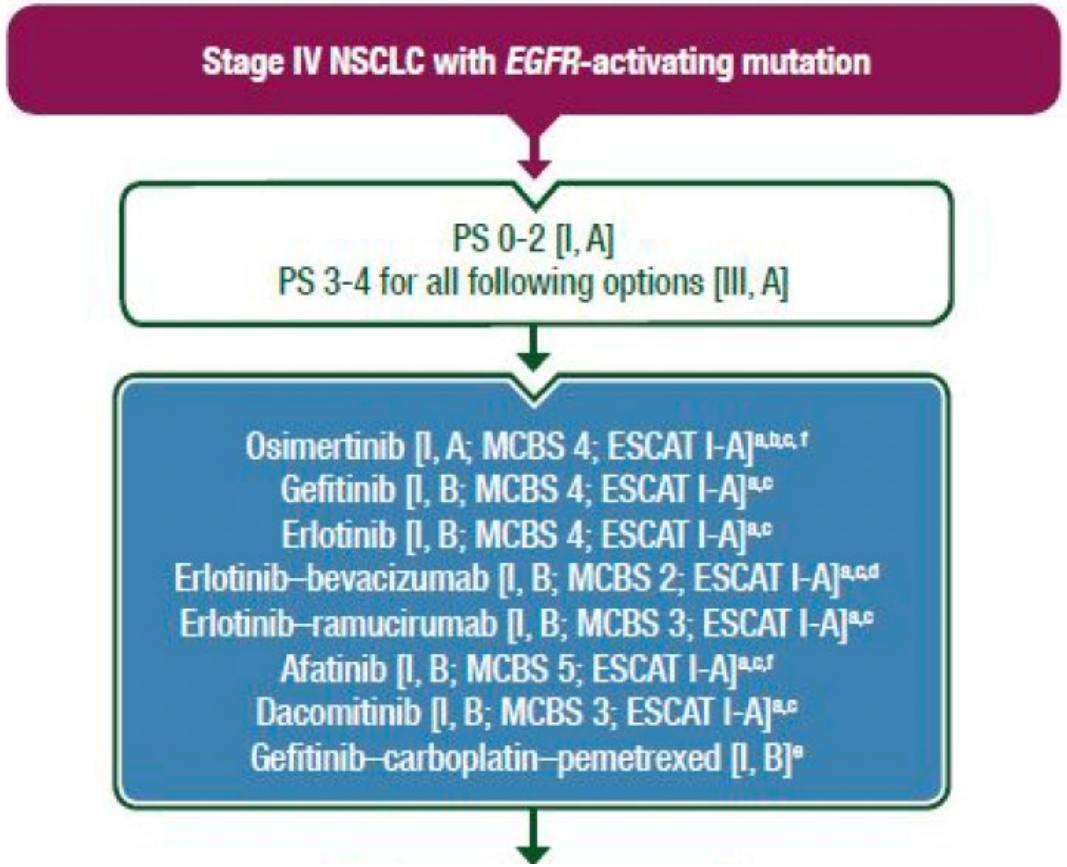
ESMO GUIDELINES

Classical sensitizing EGFR mutation, treatment naïve aNSCLC



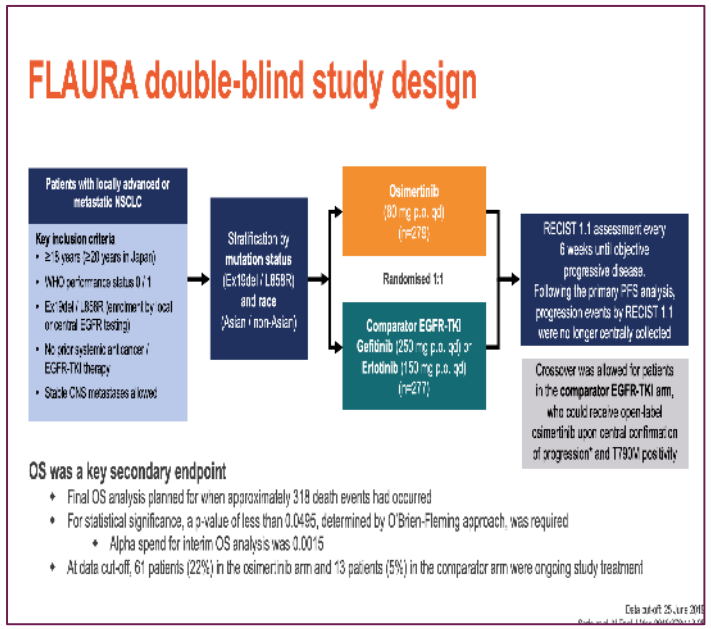
Hendriks L et al. Ann Oncol 2023;

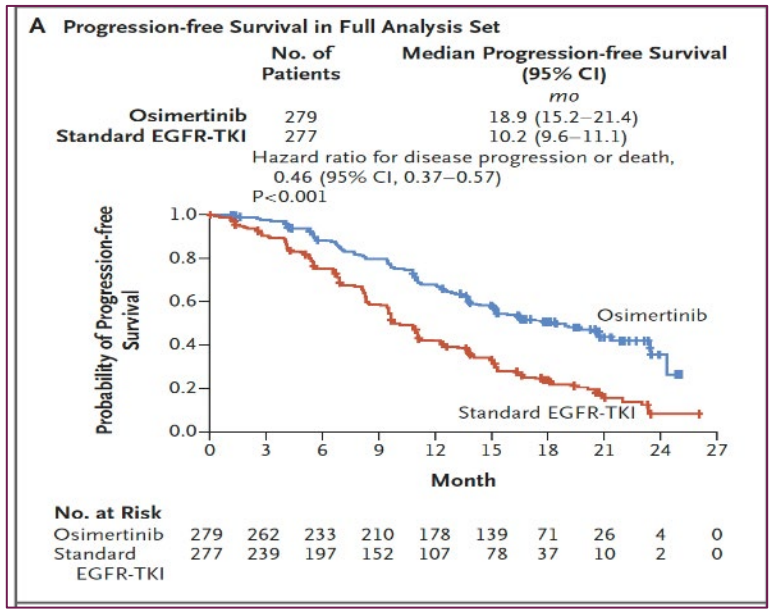
OSIMERTINIB: FIRST LINE GOLD STANDARD

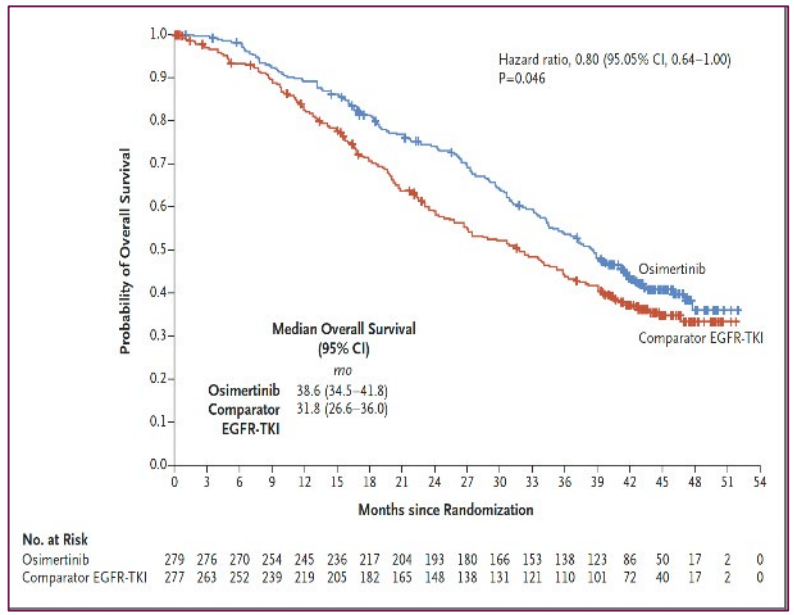
Osimertinib, a third-generation, CNS active EGFR-TKI, is the preferred first-line treatment for EGFRm advanced NSCLC based on superior PFS / OS benefit with osimertinib vs comparator EGFR-TKIs in the FLAURA study

Median PFS 18 months

Median OS 39 months







Soria JC, NEJM 2018; Ramalingan S, NEJM 2019

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3RD GENERATION EGFR TKIS BEYOND OSIMERTINIB

	Lazertinib [a]	Almonertinib [b]	Furmonertinib [c]	TY-9591	SH-1028	Limertinib [d]	Abivertinib [e]	Befotertinib [f]	Rezivertinib [g]
Structure Respect To Osi	pyrimidine and on phenyl rings	cyclopropyl group on the indole group	tphenyl ring and methyl group	Not released	indole ring	Indole and pyrimidine ring	pyrimidine and on phenyl rings	Not released	oxygen replacing on phenyl ring
IC_{50} nM (T790M+)	1.85	0.37	Not released	Not released	0.55	0.3	0.18	Not released	GI_{50} 22 nM
RP2D	240 mg	110 mg	80 mg	160 mg	200 mg	160 mg BID	300 mg BID	75–100 mg	180 mg
MTD	Not reached	Not reached	Not reached	unpublished	unpublished	unpublished	Not reached	Not reached	Not reached
Approved for T790M+	Korea 18 January 2021	China 18 March 2020	China 3 March 2021	-	-	-	-	-	-
Trial	Phase I/II Lee 2020 [84]	Apollo Lu 2020 [91]	Phase I/II Shi 2021 [92]	NCT04204473 Ongoing	Phase I/II Xiong 22 [93]	Phase IIb Li 2022 [94]	Phase I/II Zhou 2022 [95]	Phase I/II Lu 2022 [96]	Phase I Shi 2022 [97]
ORR (T790M+)	58%	69%	74%	-	60.4%	68.8%	56.5%	67.6%	60.5%
mPFS mos (T790M+)	11	12.3	9.6	-	12.6	11	8.5	16.6	9.7
Approved for	Korea 30 June	China 4 December	China 28 June	-	-	-	-	-	-

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"In the absence of any head-to-head comparison results, the real advantage taken from more similar drugs available in the market will be the potential improvement in the cost-effectiveness of these drugs"

Attili I. Cancers 2023

3RD GENERATION EGFR TKIs IN EGFRm NSCLC

Study	Region	N	3rd gen EGFR TKI	ORR	PFS (HR)	OS (HR)
FLAURA	Global	556	Osimertinib	80% v 76%	18.9m v 10.2m (0.46)	38.6 v 31.8 (0.8)
AENEAS	China	429	Aumolertinib	74% v 72%	19.2m v 9.9m (0.46)	Not reported
FURLONG	China	358	Furmonertinib	89% v 84%	20.8m v 11.1m (0.44)	Not reported
Shun Lu	China	362	Befotertinib	76% v 78%	22.1m v 13.8 (0.49)	Not reported
Cho et al	Global	393	Lazertinib	76% v 76%	20.6m v 9.7 (0.45)	Not reported

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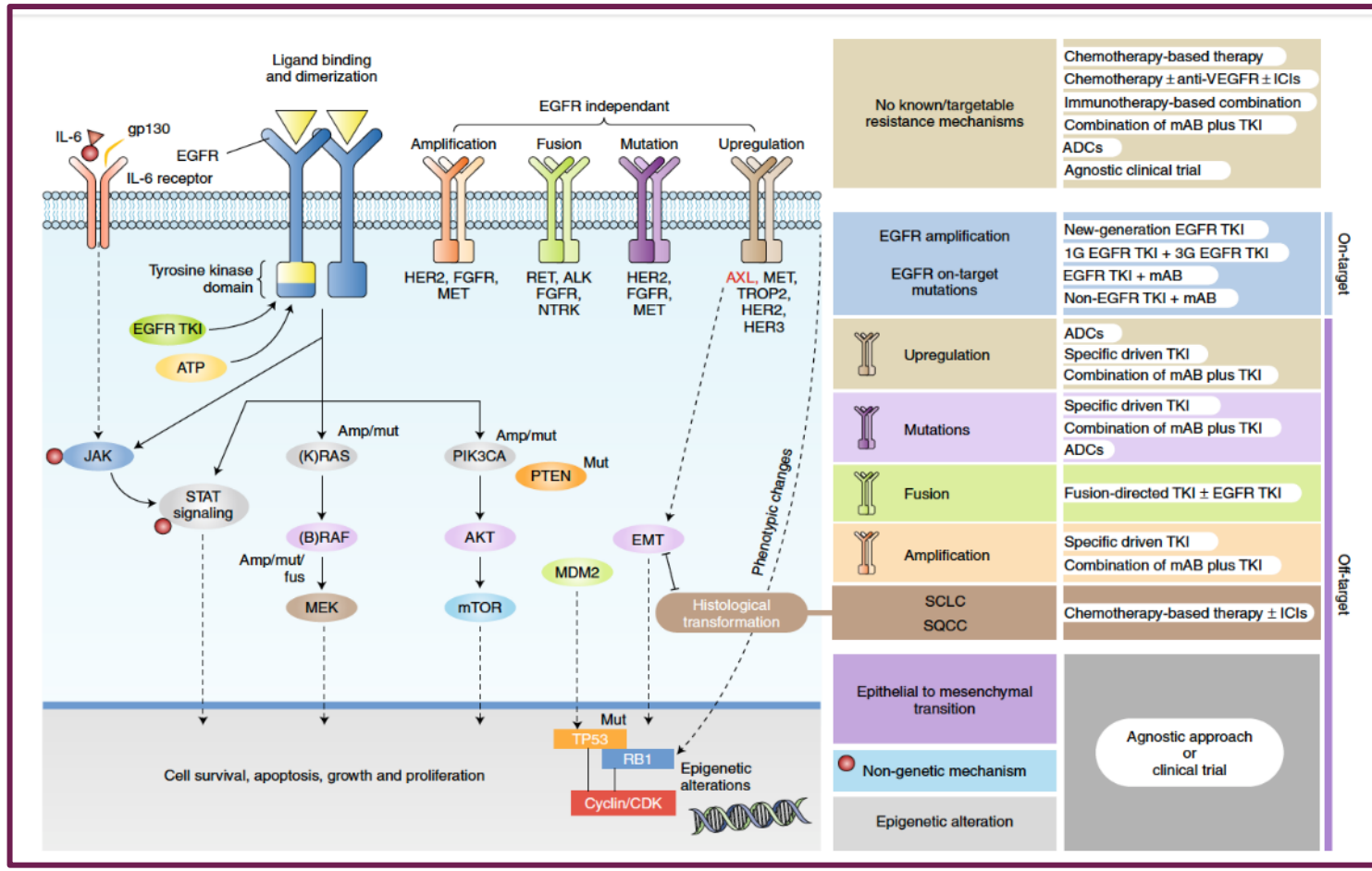
IMPROVING LONG-TERM RESULTS IS KEY

- **Treatment options *to prevent/delay* progression:**
  - CT+ EGFR TKIs
  - Amivantamb + EGFR TKI
  - VEGF inhibitors + EGFR TKIs
- Treatment options *after* disease progression:
  - Biomarker-driven approaches
  - Agnostic strategies



Passaro A, Peters S. Nature Cancer 2021

EGFR TKI + CT UPFRONT: AGAIN NEGATIVE TRIAL

JCOG1404/WJOG8214L study design (revised)

- NSqNSCLC
- Stage IIIB/IV or recurrence
- *EGFR* exon 19 DEL or L858R
- ECOG PS 0-1
- Age 20-74 years
- No prior systemic therapy
- Stable CNS metastases were allowed

Total: n = 500
(osimertinib: n =174)

Randomization 1:1

Adjusted by
- institution
- clinical stage IIIB/IV or recurrence
- sex
- mutation type exon 19DEL or L858R

Osimertinib 80 mg/day
day 1-PD
n = 87
(total: n = 250)

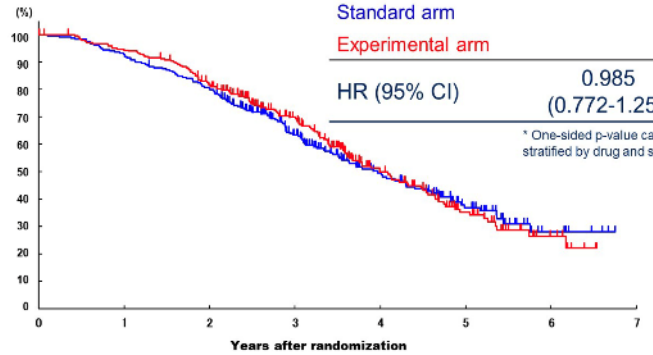
Osimertinib
day 1-56
n = 87
(total: n = 250)

Cisplatin 75 mg/m^2
Pemetrexed 500 mg/m^2
(q3w, 3 courses)
day 71, 92, 113

Osimertinib
day 134-PD

In October 2018, EGFR-TKI was changed from gefitinib to osimertinib considering the results of FLAURA study.

Primary endpoint: Overall survival (ITT)

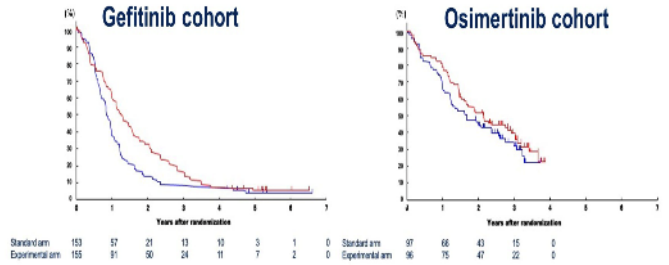


	Median OS (95% CI), months	
Standard arm	48.0	(40.8-55.2)
Experimental arm	48.0	(43.2-54.0)
HR (95% CI)	0.985 (0.772-1.257)	p=0.4496*

* One-sided p-value calculated from log-rank test stratified by drug and sex and *EGFR* mutation type.

Standard arm	250	232	200	124	70	36	7	0
Experimental arm	251	234	198	134	70	33	8	0

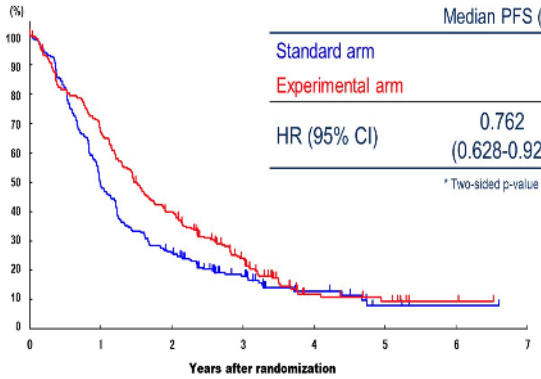
Progression-free survival by EGFR-TKI



Gefitinib cohort	Median PFS (95% CI), months		Osimertinib cohort	Median PFS (95% CI), months	
Standard arm	9.6	(9.6-12.0)	Standard arm	20.4	(14.4-28.8)
Experimental arm	14.4	(12.0-18.0)	Experimental arm	25.2	(18.0-34.8)
HR (95% CI)	0.687 (0.544-0.867)	p=0.0015*	HR (95% CI)	0.812 (0.572-1.155)	p=0.2475*

* Two-sided p-value calculated from log-rank test.

Progression-free survival (ITT)



	Median PFS (95% CI), months	
Standard arm	12.0	(10.8-14.4)
Experimental arm	18.0	(15.6-20.4)
HR (95% CI)	0.762 (0.628-0.925)	p=0.0058*

* Two-sided p-value calculated from log-rank test.

Standard arm	250	123	64	28	10	3	1	0
Experimental arm	251	166	97	46	11	7	2	0

Response rates and subsequent therapies

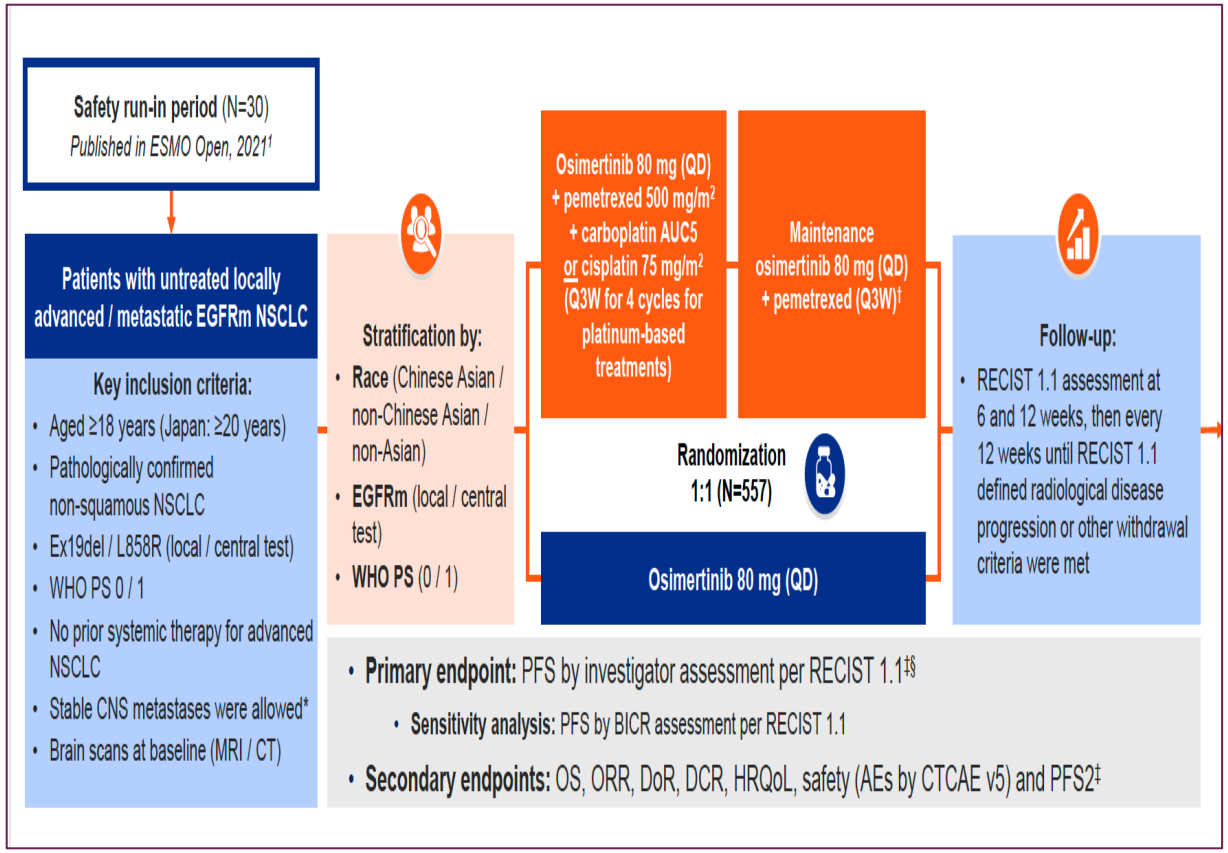
	Standard		Experimental	
Overall response rate (95% CI)	78.0% (72.0%-83.3%)		71.6% (65.3%-77.3%)	
n	Gefitinib 153	Osimertinib 97	Gefitinib 155	Osimertinib 96
Ongoing study treatment	5	31	5	27
Discontinued study treatment	148	66	150	69
1st subsequent therapy	139	61	139	65
3rd generation EGFR-TKI	29	32*	25	43*
The other EGFR-TKI	78*	7	97*	5
Platinum-based therapy	29	21	11	12
The other chemotherapy	3	1	6	5
2nd subsequent therapy	117	44	102	40
3rd generation EGFR-TKI	37	4	39	1
The other EGFR-TKI	8	6	18	4
Platinum-based therapy	60	24	22	22
The other chemotherapy	12	10	23	13

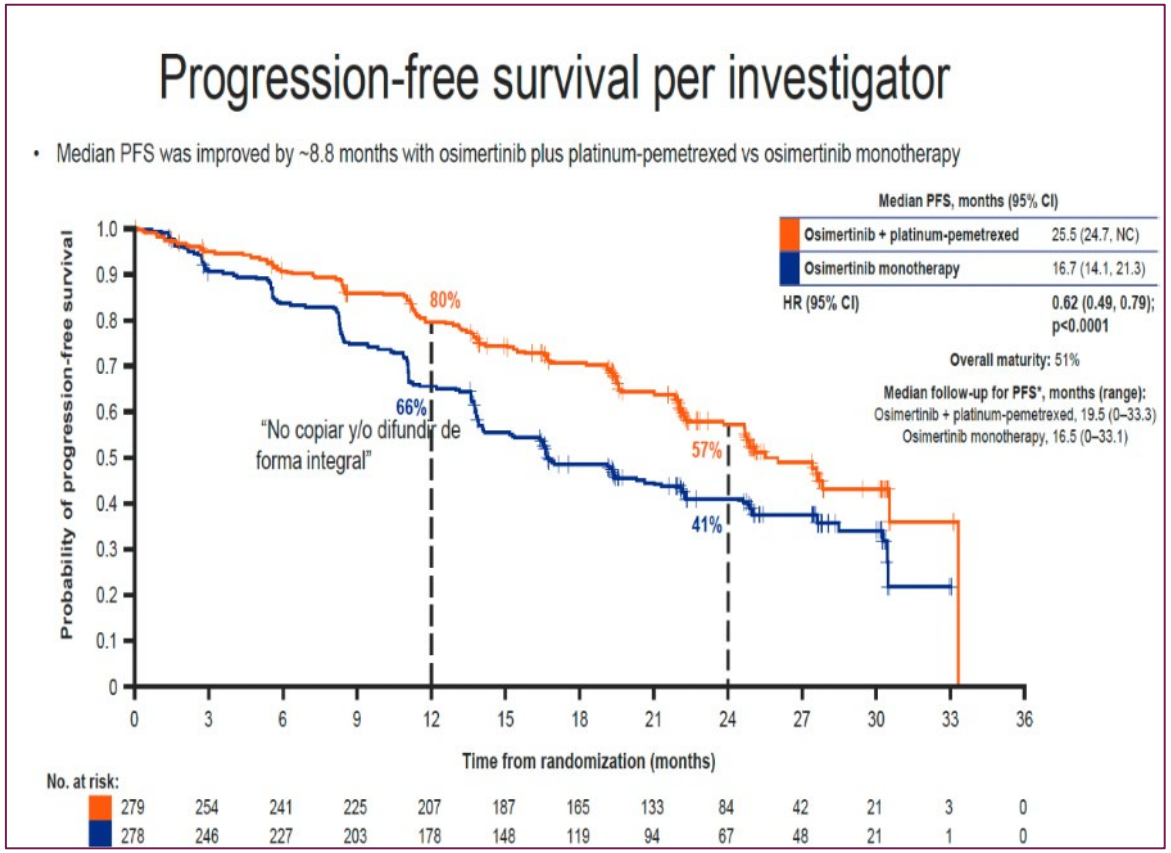
* Including gefitinib or osimertinib beyond PD

Kanda S. ASCO 2023

OSIMERTINIB WITH / WITHOUT PLATINUM-BASED CT (FLAURA 2)

9 months improvement in PFS !

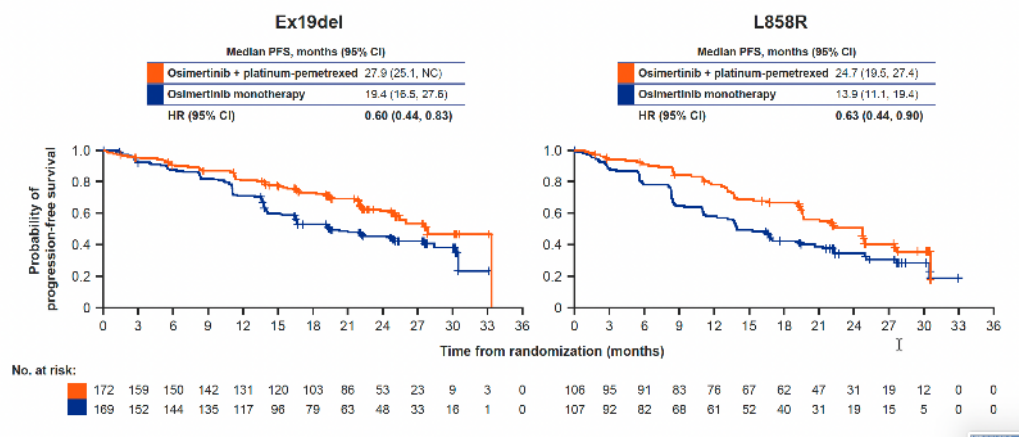




Janne P WCLC 2023; Planchard D, NEJM 2023

FLAURA 2 KEY FINDINGS

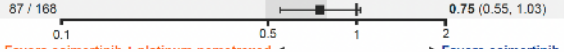
PFS per investigator by EGFR mutation type at baseline*



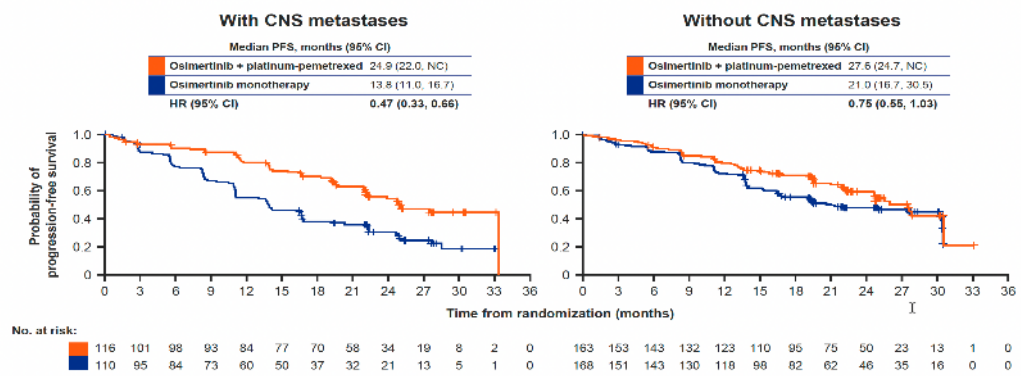
PFS per investigator across subgroups*

- PFS benefit was consistent across all pre-defined subgroups

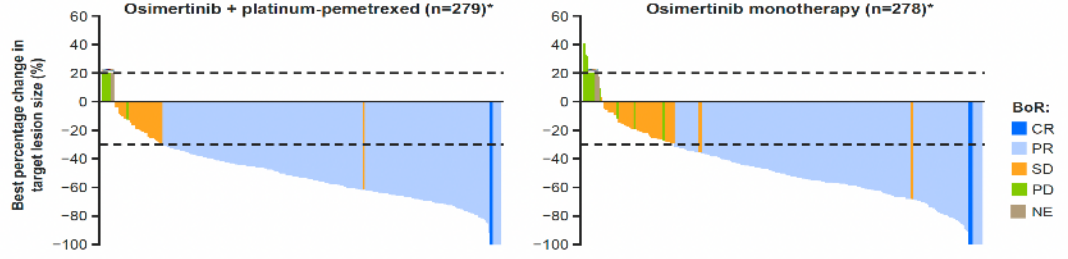
Subgroup		Osimertinib + platinum-pemetrexed (Events / patients)	Osimertinib monotherapy (Events / patients)	HR (95% CI)
All patients	Stratified log-rank	120 / 279	166 / 278	**0.62** (0.49, 0.79)
	Unadjusted Cox PH	120 / 279	166 / 278	**0.62** (0.49, 0.78)
Sex	Male	51 / 106	73 / 109	**0.54** (0.37, 0.77)
	Female	69 / 173	93 / 169	**0.67** (0.49, 0.92)
Race	Chinese Asian	26 / 71	43 / 69	**0.49** (0.30, 0.81)
	Non-Chinese Asian	54 / 107	65 / 107	**0.76** (0.53, 1.09)
	Non-Asian	40 / 101	58 / 102	**0.55** (0.37, 0.83)
EGFR mutation test method	Central	52 / 121	67 / 119	**0.73** (0.51, 1.05)
	Local	68 / 158	99 / 159	**0.55** (0.40, 0.74)
Age at screening	<65 years	73 / 174	97 / 166	**0.59** (0.44, 0.80)
	≥65 years	47 / 105	69 / 112	**0.68** (0.47, 0.98)
Smoking history	Yes	43 / 91	57 / 97	**0.63** (0.42, 0.94)
	No	77 / 188	109 / 181	**0.61** (0.46, 0.82)
EGFR mutation type†	Ex19del	65 / 172	94 / 169	**0.60** (0.44, 0.83)
	L858R	55 / 106	70 / 107	**0.63** (0.44, 0.90)
WHO PS	0	48 / 101	57 / 102	**0.79** (0.54, 1.16)
	1	72 / 178	109 / 176	**0.53** (0.39, 0.72)
CNS status at baseline	Yes	52 / 116	79 / 110	**0.47** (0.33, 0.66)
	No	68 / 163	87 / 168	**0.75** (0.55, 1.03)



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



Tumor response per investigator



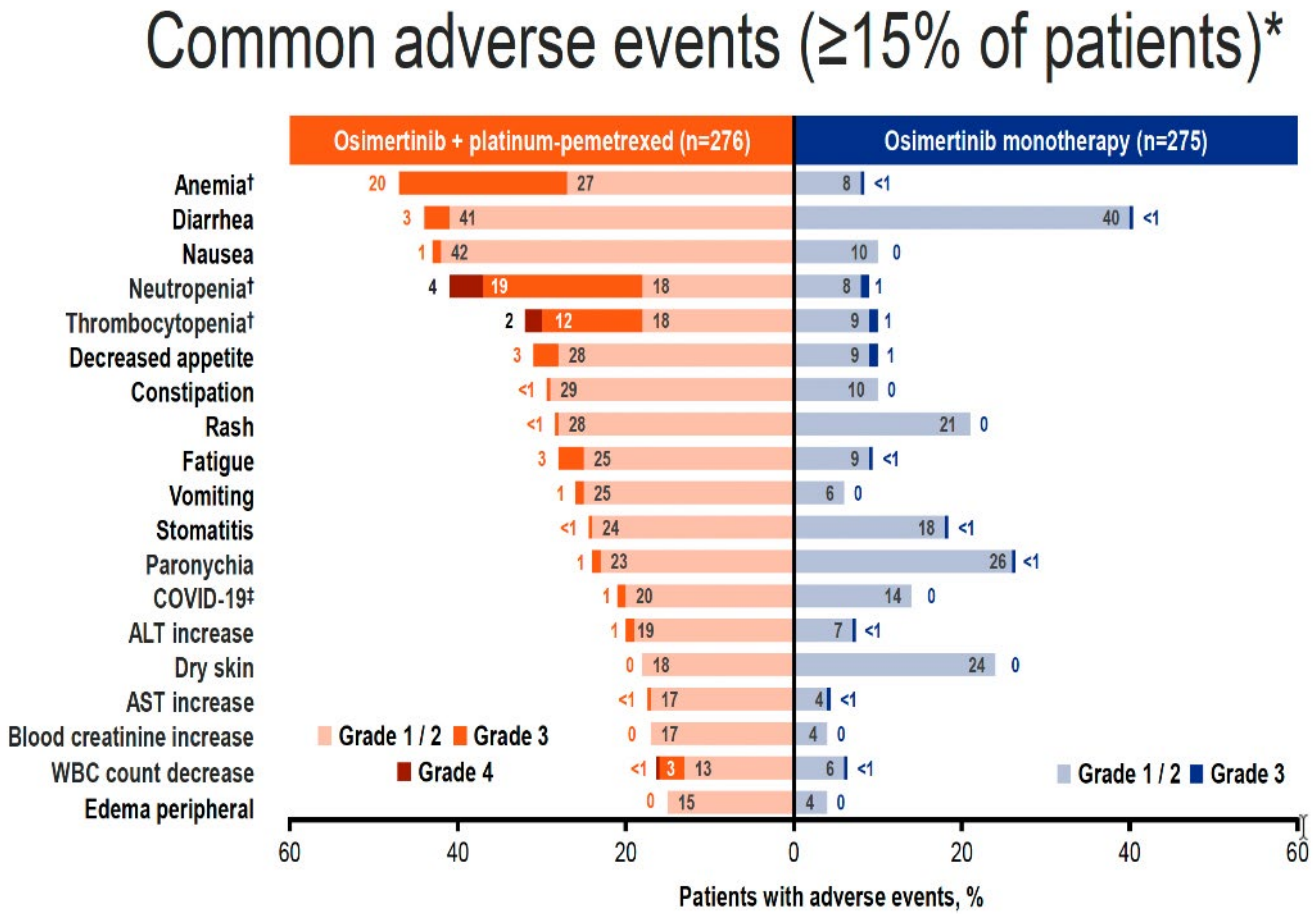
	Osimertinib + platinum-pemetrexed (n=279)	Osimertinib monotherapy (n=278)
Median best percentage change in target lesion size, % (range)	-52.6 (-100.0, 20.0)	-50.0 (-100.0, 40.4)
Objective response rate, % (95% CI)	83 (78, 87)	76 (70, 80)
Adjusted odds ratio (95% CI)†	1.61 (1.06, 2.44)	
Complete response, n (%)	1 (<1)	2 (1)
Partial response, n (%)	231 (83)	208 (75)
Stable disease ≥35 days, n (%)	34 (12)	51 (18)
Progression, n (%)‡	7 (3)	12 (4)
Median duration of response, months (95% CI)	24.0 (20.9, 27.8)	15.3 (12.7, 19.4)

Janne P WCLC 2023; Planchard D, NEJM 2023

FLAURA 2 LONGER PFS BENEFIT COMES AT THE COST WITH HIGHER TOXICITY

AEs (Combo vs Osi)

- Grade 3 : 64% vs 27%
  - Hematological 71% vs 24%
  - Pneumonitis 3% vs 4%
  - Cardiac Effects 9% vs 4%
  - Deaths 5 vs 1
- Leading to
  - Discontinuation 11% vs 6%
  - Interruption 43% vs 19%
  - Dose reduction 10% vs 3%



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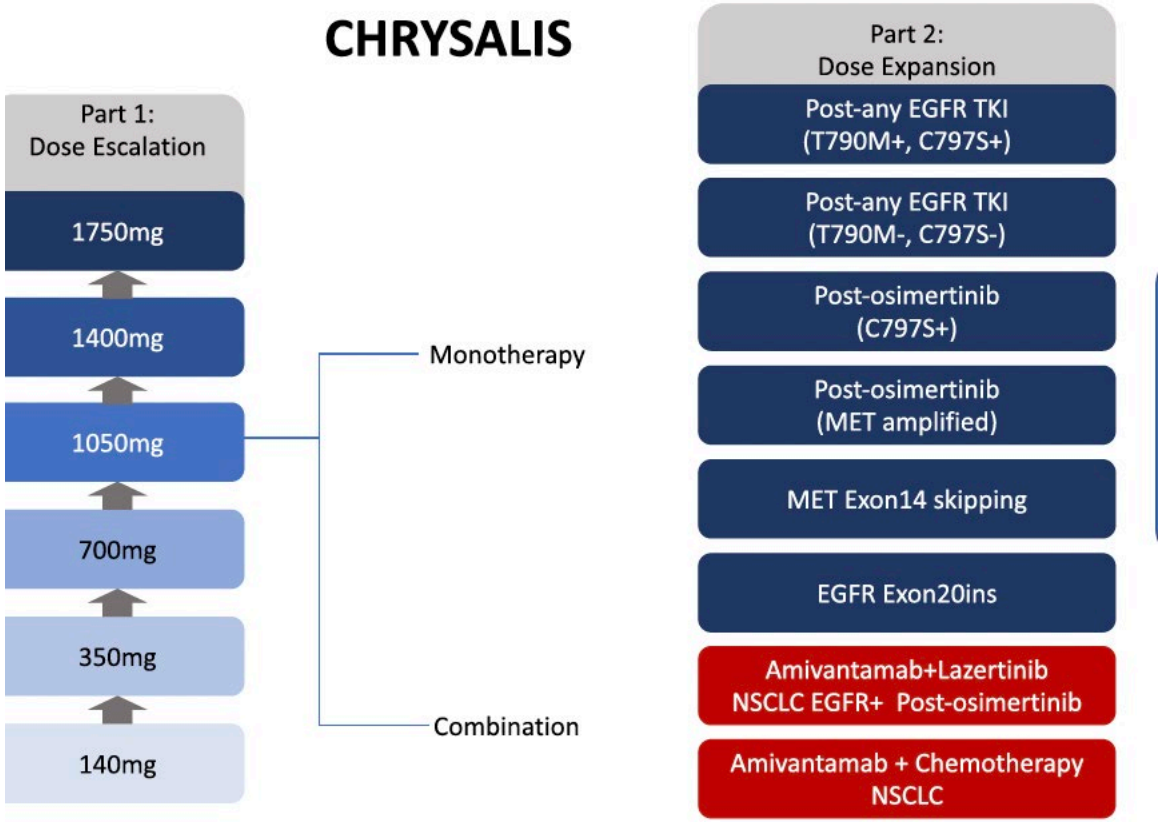
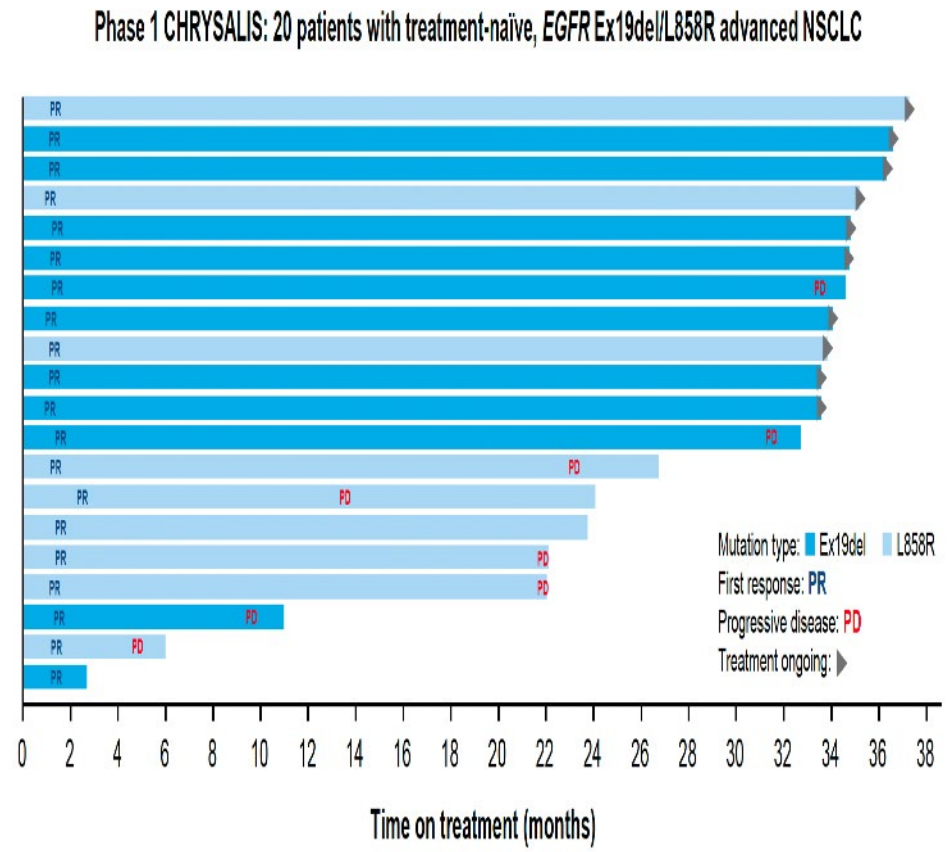
LAZERTINIB + AMIVANTAMAB: RATIONALE





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Cho BC, et al. J Thorac Oncol. 2022;17(9_suppl):S126. 2. Lee S-H, et al. J Clin Oncol. 2023;41(16_suppl):9134

MARIPOSA: PHASE 3

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: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
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:

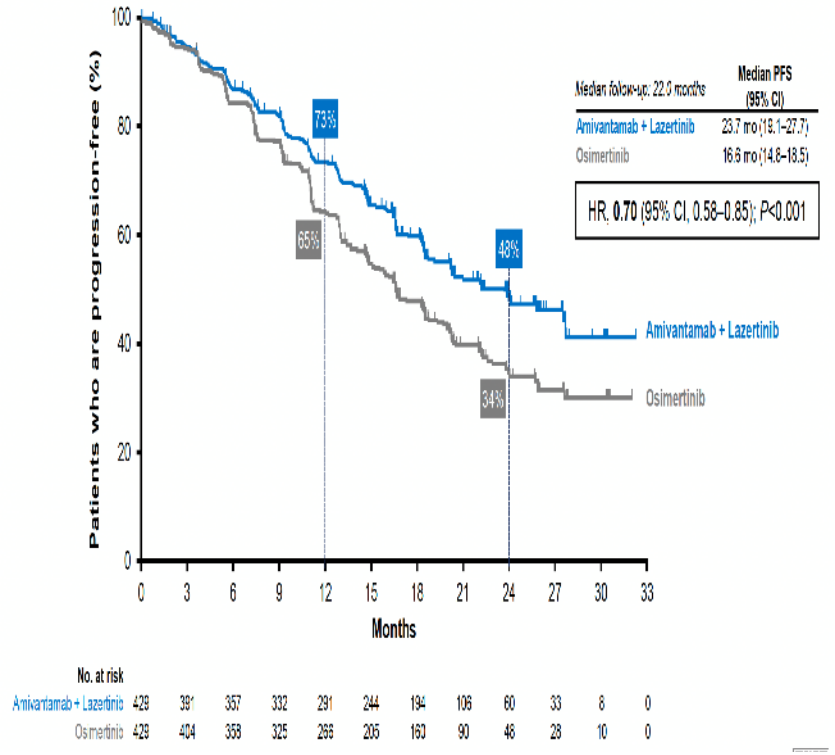
- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

7 months improvement in PFS !

Primary Endpoint: Progression-free Survival by BICR[a]

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

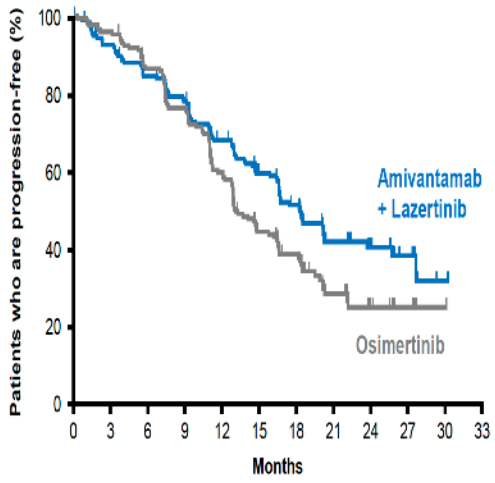


MARIPOSA: KEY RESULTS

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)

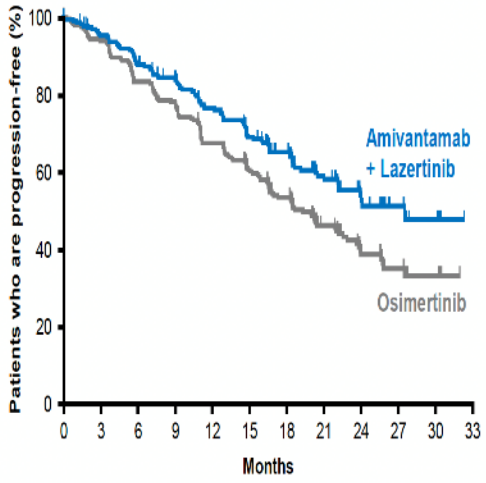


No. at risk

vantamab + 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)

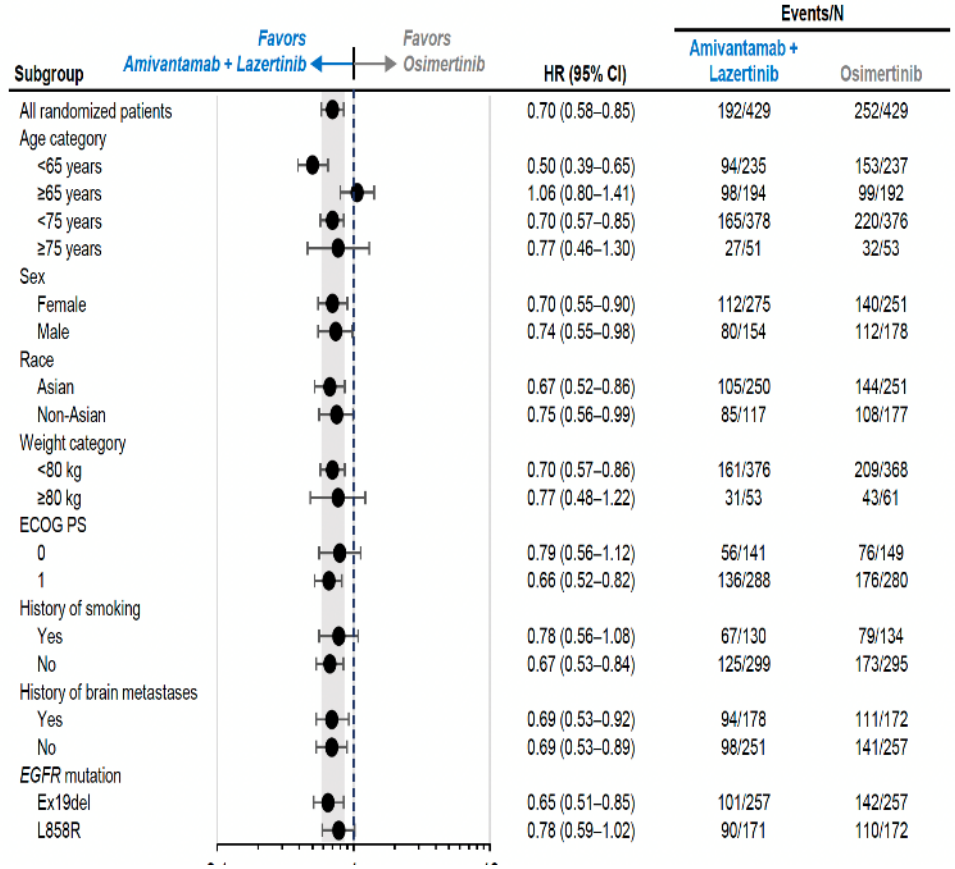
HR, **0.69** (95% CI, 0.53–0.89)



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

PFS Benefit Seen Across Predefined Subgroups



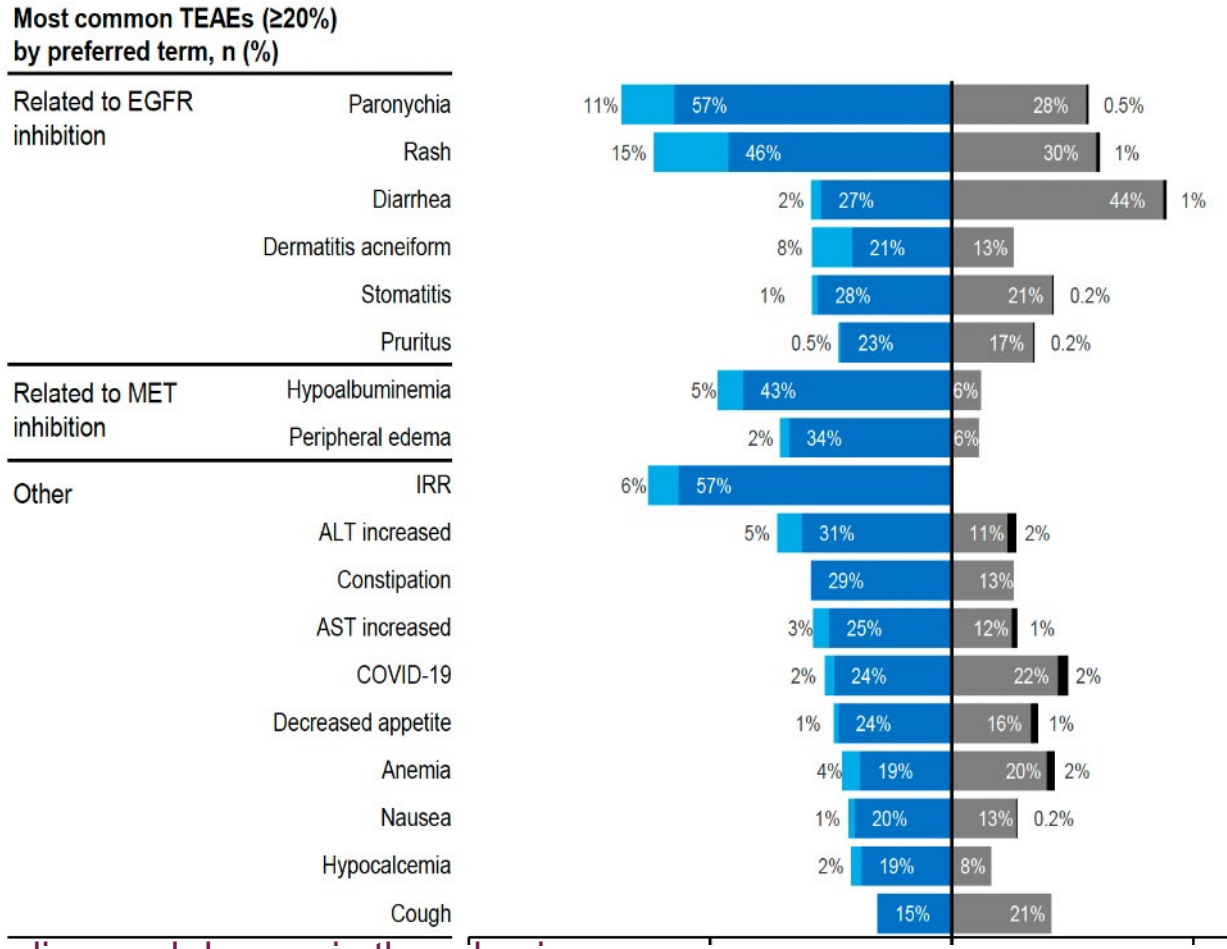
Subgroup	HR (95% CI)	Events/N: Amivantamab + Lazertinib	Events/N: Osimertinib
All randomized patients	0.70 (0.58–0.85)	192/429	252/429
Age category			
<65 years	0.50 (0.39–0.65)	94/235	153/237
≥65 years	1.06 (0.80–1.41)	98/194	99/192
<75 years	0.70 (0.57–0.85)	165/378	220/376
≥75 years	0.77 (0.46–1.30)	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
≥80 kg	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

MARIPOSA: LONGER PFS BENEFIT COMES AT THE COST WITH HIGHER TOXICITY

Median treatment duration was 18.5 mo for amivantamab + lazertinib and 18.0 mo for osimertinib

TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib



VTE rates were higher for amivantamab + lazertinib: Pulmonary embolism and deep vein thrombosis

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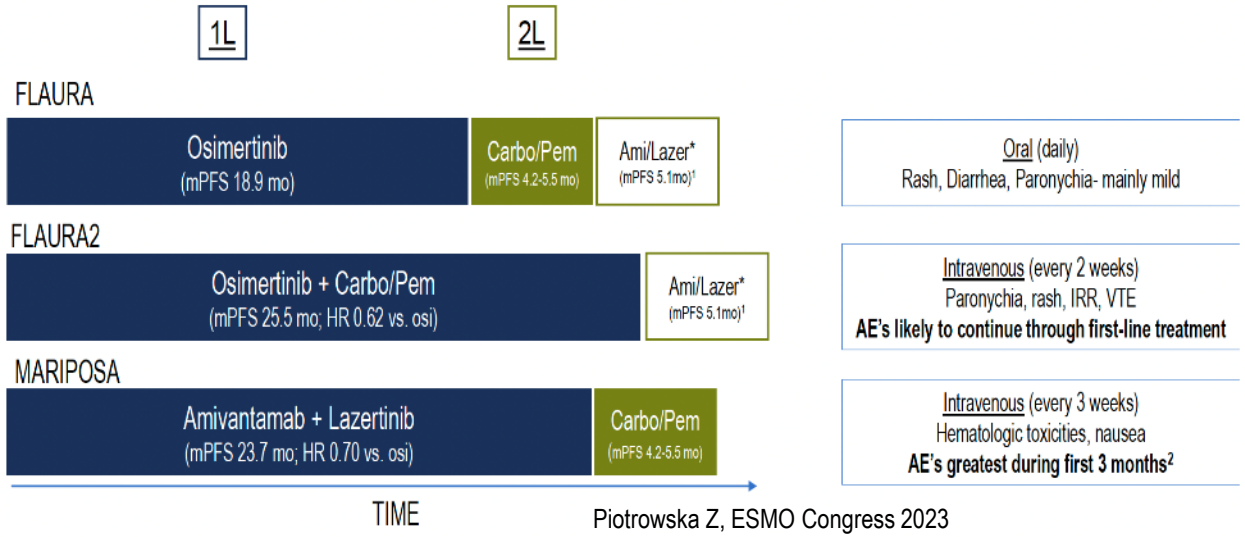
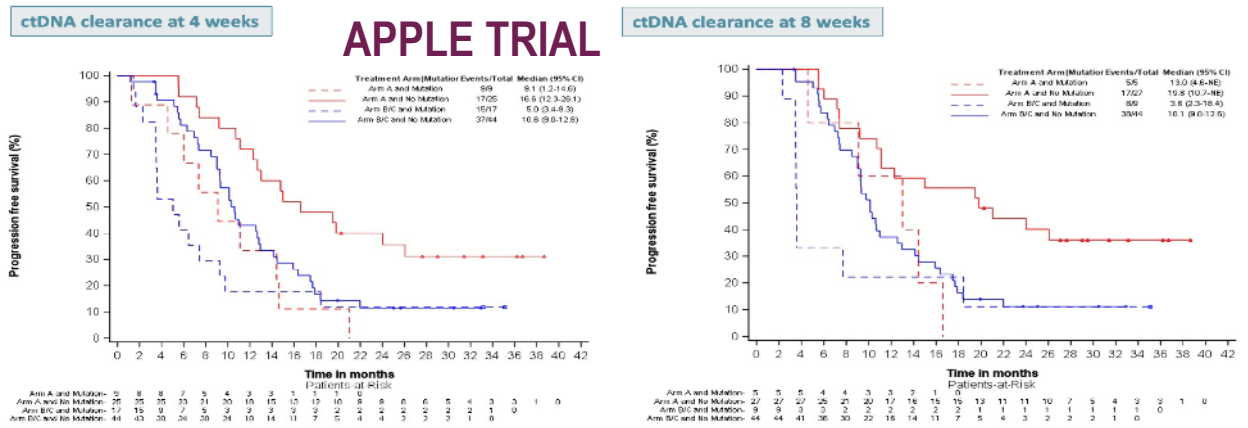
OPEN QUESTIONS IN THE FIRST LINE SETTING FOR EGFRm aNSCLC

- ✓ Key differences between FLAURA and MARIPOSA trial:
  - ✓ **Serial brain MRIs** required on MARIPOSA /FLAURA2
  - ✓ **PFS by** BICR (MARIPOSA) vs. Investigator (FLAURA2)
  - ✓ No **crossover** on MARIPOSA (vs. access to sequential chemo on FLAURA2) may impact final OS analysis.
- ✓ Toxicity impact: risk/benefit ratio
- ✓ PFS / OS
- ✓ Subsequent treatment options
- ✓ Selection of patients Which one?
  - ✓ ct DNA clearance?
    - ✓ FLAURA 24% persistent ctDNA at 3 wks (mPFS 11 mo) Gray J, et al. CCR 2023
  - ✓ Co-mutation status?
  - ✓ Clinical characteristics?



Piotrowska Z, ESMO Congress 2023

ctDNA clearance of *EGFR*m and PFS: exploratory analysis



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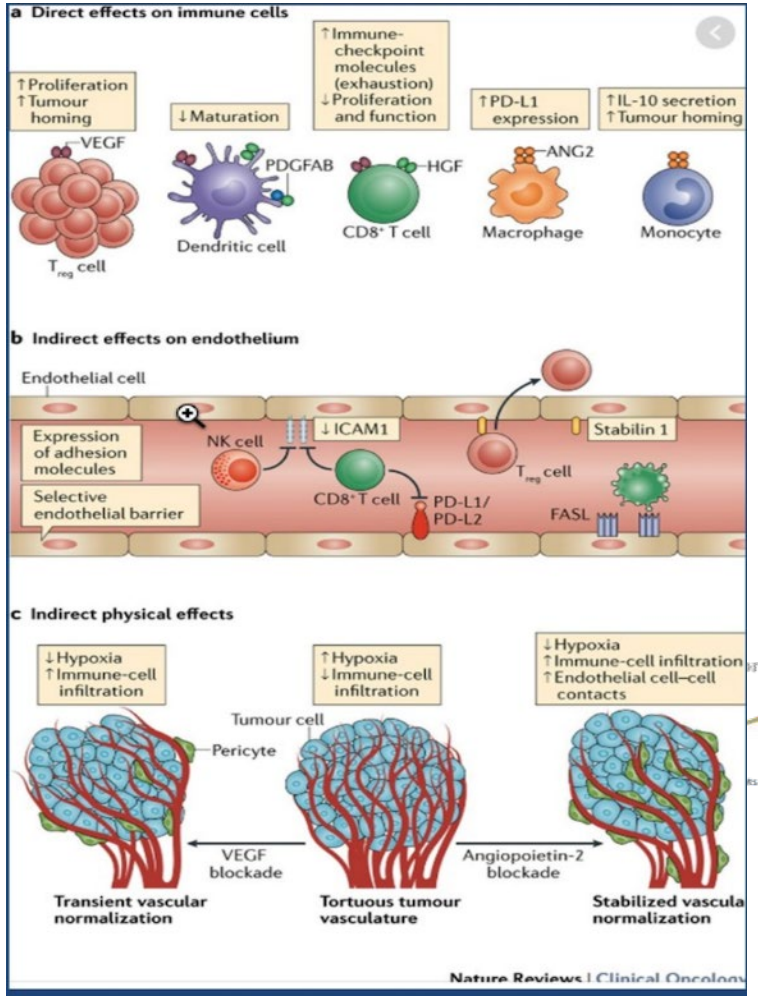
EGFT-TKI AND ANTI-VEGF: RATIONALE

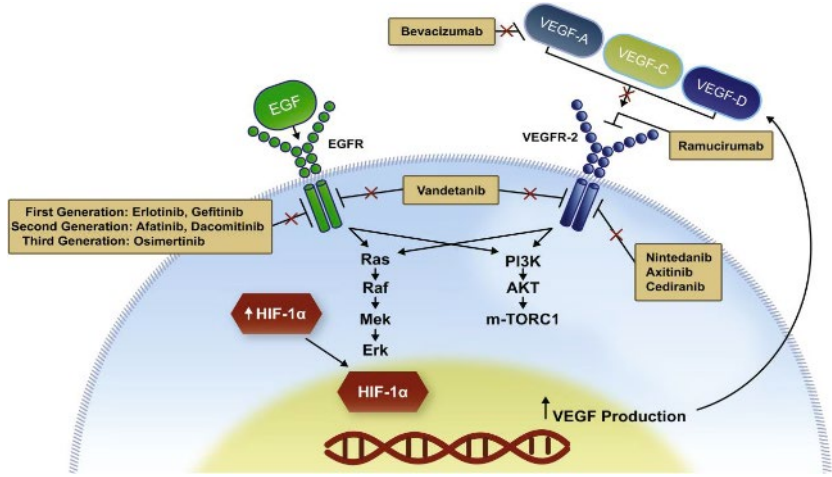
Synergistic preclinical activity

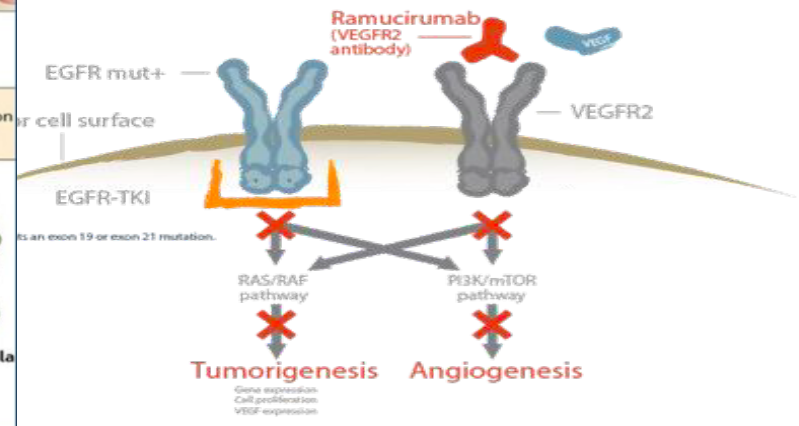
Resistance to EGFR inhibition associated with increased VEGF levels

EGFR signaling pathway can upregulate VEGF expression.

Alleviates immunosuppression and promotes efficient tumor infiltration by effector immune cells







Le X et al. J Thorac Oncol 2020; 16:205-215

CLINICAL VALUE OF DUAL INHIBITION VEGF/EGFR (ERLOTINIB)

STUDY	TREATEMENT	PHASE	N	mPFS	HR	RR	OS	HR
BELIEF	Erlotinib + Bev	II multinatio national	109	13	0.52 P:0.016	77	28.2	-
JO25567	Erlotinib ± Bev	RII Japan	154	16 vs 9,7	0.52 P: 0.0005	69 vs 64	47 vs 47,4	0.81 P:0.3
ALLIANCE	Erlotinib ± Bev	RII	88	17,9 vs 13,5	0.81 P:0.39	81 vs 83	32.4 vs 50,6	1.41 P:0.33
NEJ026	Erlotinib ± Bev	III Japan	228	16,9 vs 13,3	0.61 P: 0.016	72 vs 66	46,2 vs 50,7	1.01 P::0-97
ARTemis CTONG1509	Erlotinib ± Bev	III China	311	18 vs 11,3	0.55 P<0.001	86,3 vs 84,7	36.2 vs 31.6	0.92 P:0-58
RELAY	Erlotinib ± Ramucirumab	III Multi	449	19.4 vs 12.4	0.59 P<0.001	76 vs 75	NR	0.83 pNS
Beverly	Erlotinib ± Bev	III Italy		9.7 vs 15.4	0.60 P 0.0039		23 vs 28	0.7 P 0.12

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OSIMERTINIB + BEVACIZUMAB UPFRONT: NEGATIVE TRIAL

WJOG9717L: Study Design

KEY ELIGIBILITY CRITERIA
- Non-squamous NSCLC harboring *EGFR* activating mutations
- Clinical stage IIIB, IIIC, IV, or recurrence after surgical resection
- Previously untreated
- ECOG PS 0-1
- Age 20- years
- Absence of symptomatic brain metastases

N=122

RANDOMIZED

1:1

Osimertinib (80 mg, daily) + Bevacizumab (15 mg/kg, q3w)

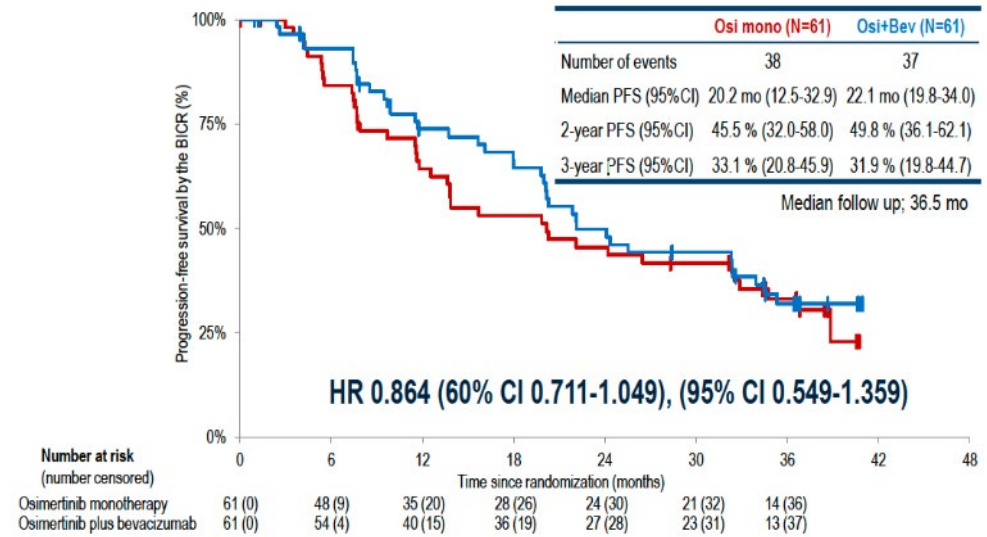
Osimertinib (80 mg , daily)

Stratification factors
Sex (female vs. male)
Clinical stage (IIIB-IV vs. recurrence)
EGFR mutation (Del19 deletion vs. L858R)

Primary endpoint: PFS by the BICRs
Secondary endpoints: PFS by investigators, Overall response rate
Overall survival, Adverse events

Clinical trial information: UMIN000030206

Primary Endpoint: PFS (ITT), assessed by BICRs



	Osi mono (N=61)	Osi+Bev (N=61)
Number of events	38	37
Median PFS (95%CI)	20.2 mo (12.5-32.9)	22.1 mo (19.8-34.0)
2-year PFS (95%CI)	45.5 % (32.0-58.0)	49.8 % (36.1-62.1)
3-year PFS (95%CI)	33.1 % (20.8-45.9)	31.9 % (19.8-44.7)

Safety summary

	Osimertinib monotherapy (n=60)		Osimertinib plus bevacizumab (n=61)	
Median duration of osimertinib (weeks)(range)	57.6	(1.4 – 157.9)	94.0	(1.6 – 158.0)
Median duration of bevacizumab (weeks)(range)	-		33.4	(0.1 – 133.9)
Grade 3-5 adverse events (AEs)	29	(48.3%)	34	(55.7%)
Serious adverse events (SAEs)	12	(20.0%)	20	(32.8%)
AEs leading to treatment discontinuation	16	(26.7%)	34	(55.7%)
SAEs leading to treatment discontinuation	3	(5.0%)	7	(11.5%)
AEs leading to dose modification	25	(41.7%)	39	(63.9%)
AEs leading to dose reduction	0	-	3	(4.9%)
AEs leading to treatment-related death	0	-	0	-

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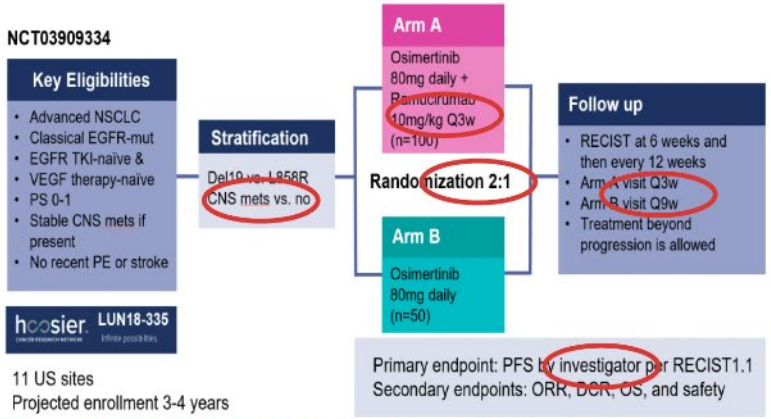
Kenmotsu H. J Thorac Oncol 2022

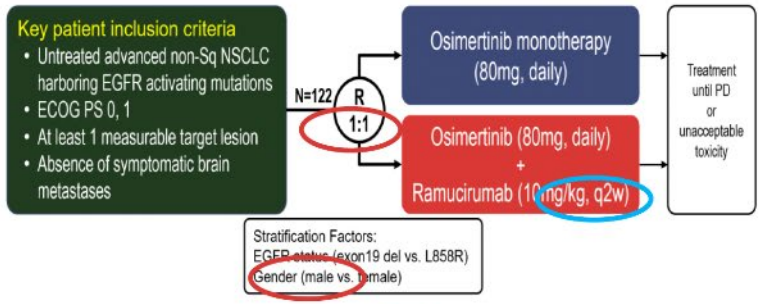
OSIMERTINIB + RAMUCIRUMAB

Different designs, different results

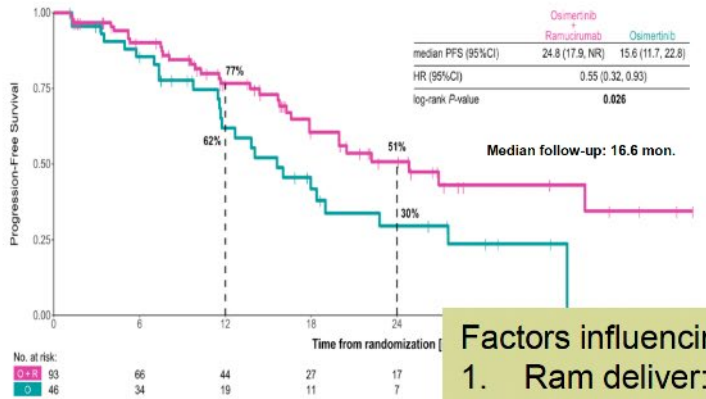
RAMOSE Phase 2 Study Design



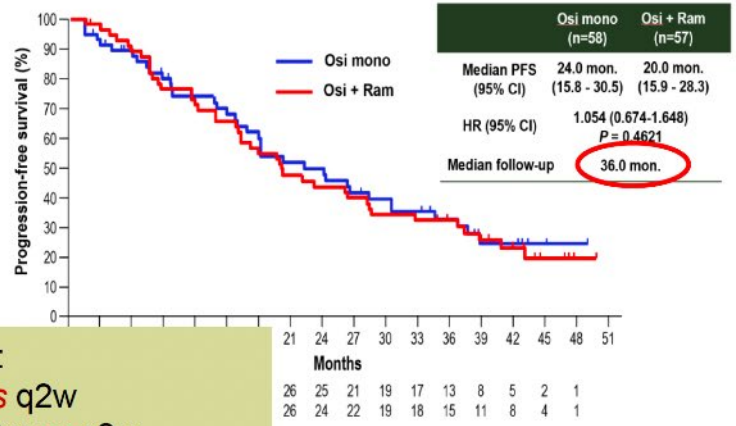
OSIRAM-1 (TORG1833) : Study Design



Progression-free survival by investigator (primary endpoint)



Progression-Free Survival, assessed by BICRs (Primary Endpoint)



Factors influencing PFS:

1. Ram deliver: q3w *vs* q2w
2. Follow-up visit: q3-9w *vs* q2w
3. PFS by Invest. *vs* PFS by BIRC
4. Exon19: 69% *vs* 61%

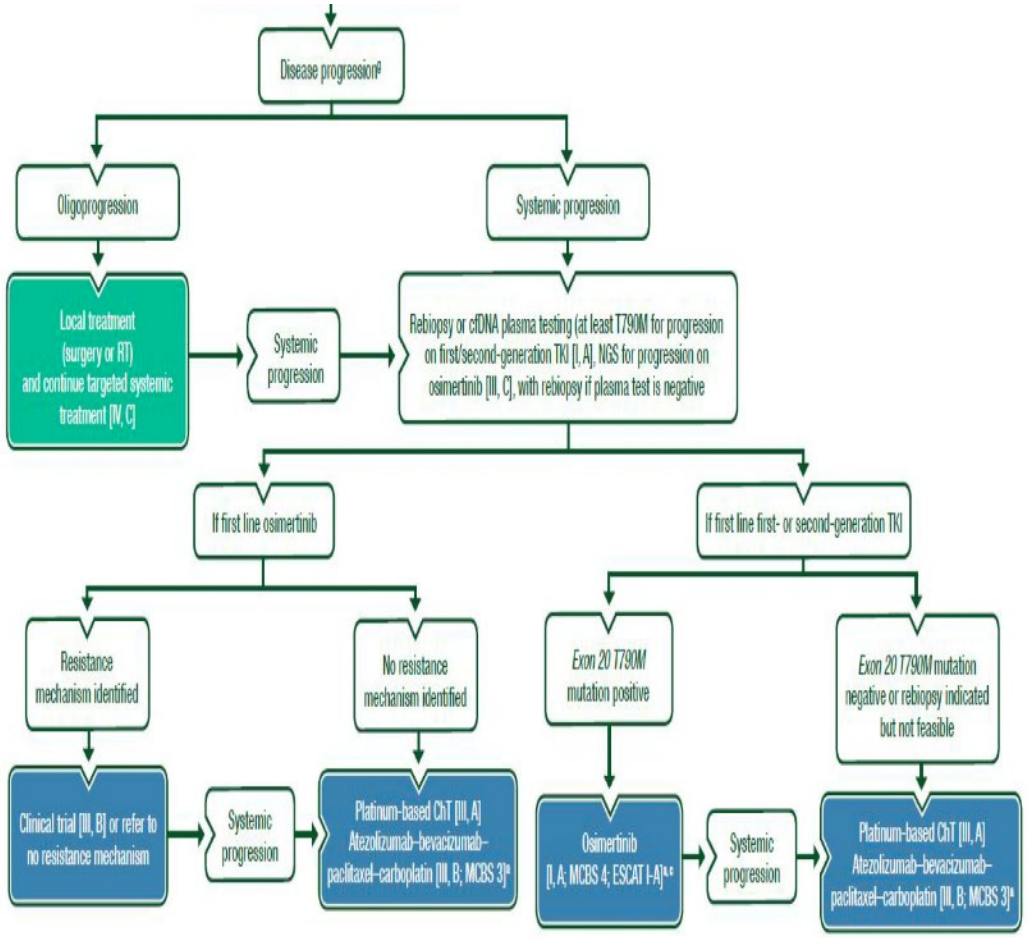
Pilar Garrido. Hospital

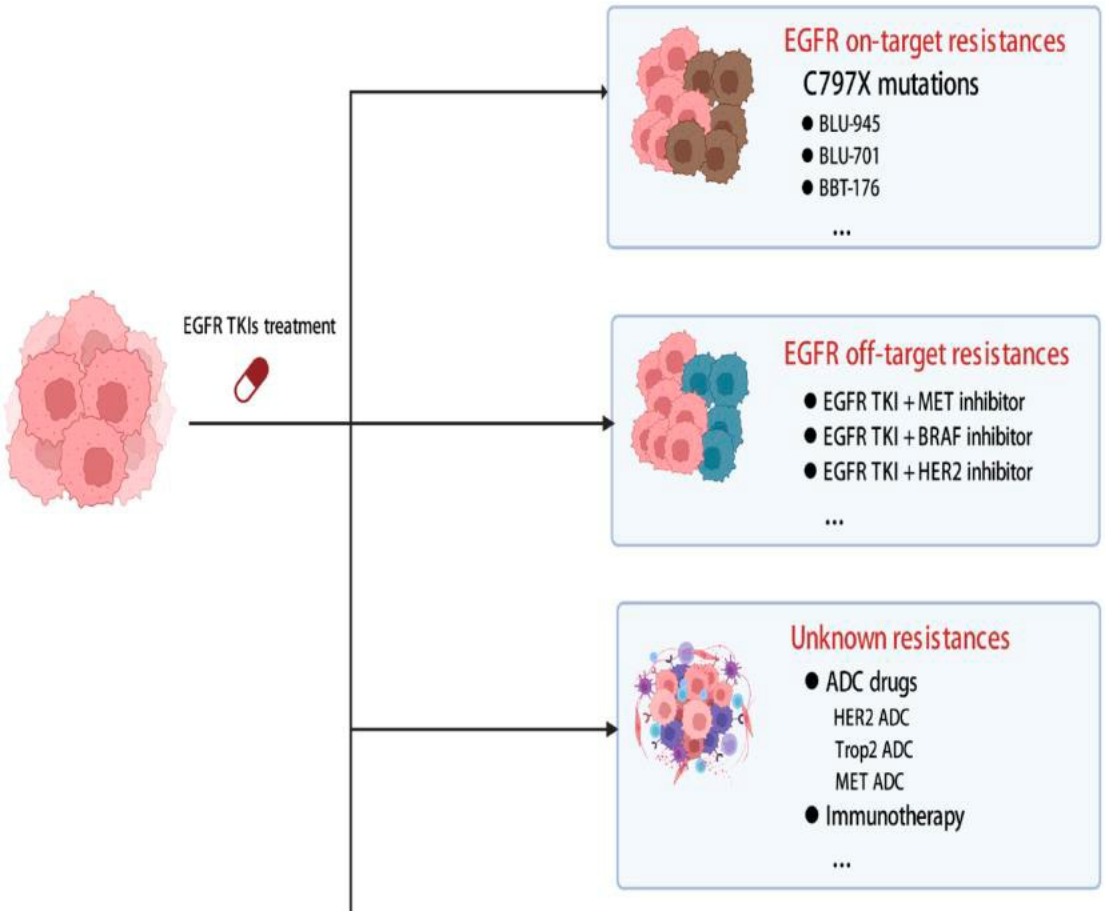
Le X, ESMO 2023

Nakahara Y. ESMO 2023

MANAGEMENT OF PRETREATED IV NSCLC EGFR+

ESMO GUIDELINES





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EXPLORING OPTIONS AT DISEASE PROGRESSION

	MET TKI + EGFR TKI			Bispecific Ab + EGFR TKI	ADC + EGFR TKI	ADC		CTx + IO	CTx + IO +antiangiogenic
STUDY NAME	**ORCHARD**	**SAVANNAH**	**INSIGHT2**	**CHRYSALIS-2 COHORT D**	**Teliso-V + Osimertinib**	**TROPION -PanTumor01 (AGA)**	**U31402-A-U102**	**CM722 /KN789**	**ORIENT-31 /IMpower150**
Drug	**Osimertinib +Savolitinib**	**Osimertinib +Savolitinib**	**Osimertinib +Tepotinib**	**Amivantamab + Lazertinib**	**Teliso-V + Osimertinib**	**Datopotomab deruxtecan**	**Patritumab deruxtecan**	**IO + CTx**	**IO + CTx +Anti-angiogenic**
n	N=20 (1L Osi)	N=193 (Prev Osi)	N=122 (1L Osi)	N=108 (Prev Osi)	N=25 (Prev Osi)	N=34	N=102 (Prev Osi)	N=294/492	N=158/59
Target	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	EGFR/MET	TROP2	HER3	-	-
Biomarker	NGS	MET IHC 3+ FGCN≥5 MET/CEP7≥2	GCN≥5 Liquid NGS MET/CEP7≥2	-	MET IHC	-	-	-	-
ORR	41%	32%	44%	30%	58%	35%	40%	31%/ 29%	44%/70%
mPFS	-	5.3 (4.2-5.8)	5.4	5.7 (4.0-8.2)	-	-	6.4 (5.3-8.3)	5.6/ 5.6	6.9/ 10.2
mDOR	NR	8.3 (6.9-9.7)	9.7	10.8 (5.5-NR)	-	9.5 (3.3-NR)	7.0 (3.1-NR)	6.7/ 6.3	8.3/ 11.1
Grade ≥ 3 TRAE	30%	45%	28%	9%	44%	26% (@6mg/kg)	32%	45%/ 55.9%	51%/ 64%

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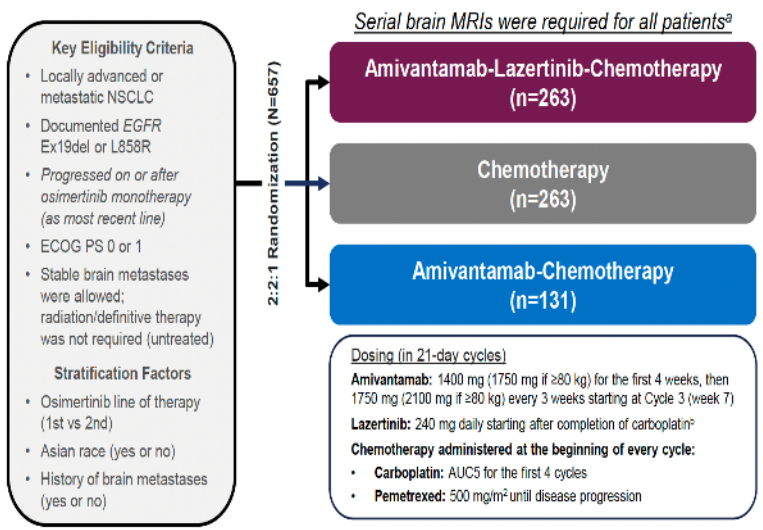
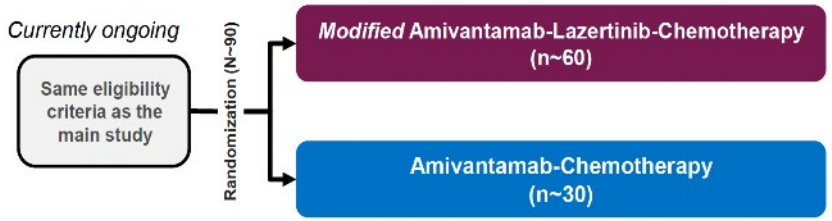
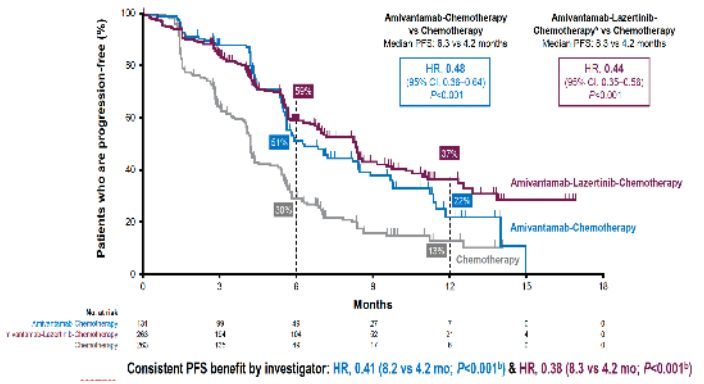
MARIPOSA 2: EGFR+ PROGRESSED ON OSIMERTINIB





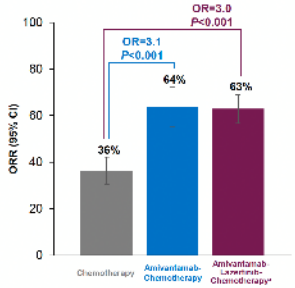
Primary Endpoint: Progression-free Survival by BICR

At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively



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

ORR and DoR by BICR



BICR-assessed Response, n (%)[a]	Chemotherapy (n=243)	Amivantamab-Chemotherapy (n=131)	Amivantamab-Lazertinib-Chemotherapy (n=263)
Best Response			
CR	1 (0.4)	2 (2)	6 (2)
PR	93 (38)	81 (62)	157 (61)
SD	82 (32)	30 (23)	61 (24)
PD	52 (20)	12 (9)	14 (5)
NE/UNK	32 (12)	7 (5)	21 (8)
Median DoR[b]	5.6 mo (95% CI, 4.2–8.6)	6.9 mo (95% CI, 5.6–NE)	9.4 mo (95% CI, 6.9–NE)

Most common TEAEs (≥25%) by preferred term, n (%)	Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy[a] (n=263)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition						
Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
Stomatitis	21 (9)	0	41 (32)	1 (1)	120 (46)	24 (9)
Diarrhea	18 (7)	1 (0.4)	18 (14)	1 (1)	68 (26)	10 (4)
Associated with MET inhibition						
Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Associated with Chemotherapy						
Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Anemia	97 (40)	23 (9)	51 (39)	15 (12)	141 (54)	48 (18)
Leukopenia	68 (28)	23 (9)	37 (28)	26 (20)	106 (40)	71 (27)
Other						
Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)
Nausea	90 (37)	2 (1)	58 (45)	1 (1)	131 (50)	16 (6)
Constipation	72 (30)	0	50 (38)	1 (1)	96 (37)	3 (1)
Decreased appetite	51 (21)	3 (1)	40 (31)	0	85 (32)	7 (3)
Vomiting	42 (17)	1 (0.4)	32 (25)	1 (1)	76 (29)	10 (4)
Fatigue	47 (19)	4 (2)	36 (28)	4 (3)	69 (26)	15 (6)
Asthenia	40 (16)	5 (2)	34 (26)	1 (1)	67 (25)	14 (5)
Alanine aminotransferase increased	67 (28)	10 (4)	26 (20)	7 (5)	55 (21)	14 (5)
AESIs by grouped term, n (%)						
Rash[b]	30 (12)	0	92 (71)	13 (10)	197 (75)	40 (15)
VTE[c]	11 (5)	7 (3)	13 (10)	3 (2)	58 (22)	17 (6)
ILD	0	0	2 (2)	1 (1)	7 (3)	5 (2)
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)	

IDMC identified increased hematologic toxicities in the amivantamab-lazertinib-chemotherapy arm

- The amivantamab-lazertinib-chemotherapy regimen was modified to start lazertinib after carboplatin completion
- An extension cohort was started, enrolling new patients, to evaluate the safety/efficacy of the modified regimen

Passaro A. ESMO congress 2023; Ann Oncol 2023

Pilar Garrido. Hospital Universitario Ramón y Cajal, Madrid, Spain

TROPION LUNG 05

Screening

Key inclusion criteria

- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

Dato-DXd
6 mg/kg
Q3W

Endpoints[a]

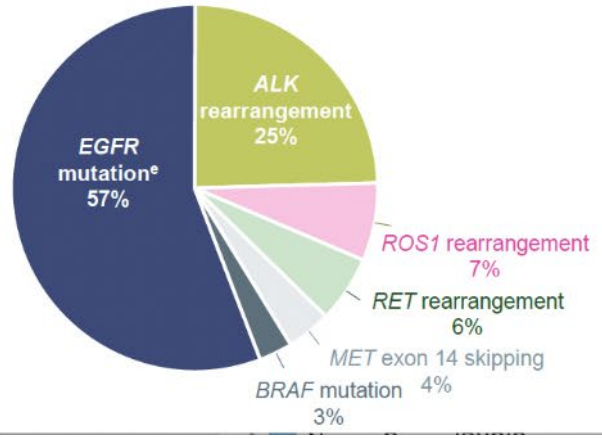
Primary: ORR by BICR

Secondary:

- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

≥3 prior lines of therapy for adv/met disease	98 (72)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)

Relative Frequency of Genomic Alterations[b-d]

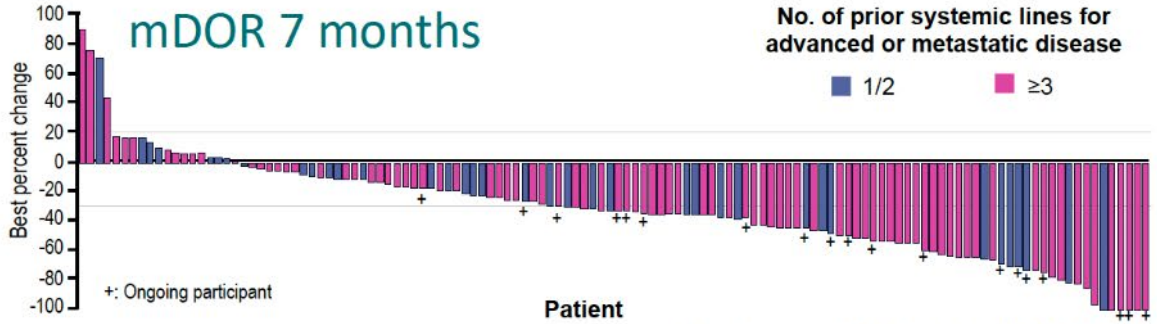


EGFRm+:

ORR 43.5% (49% in pretreated with osi)

DCR 82.1%

mDOR 7 months



Paz-Ares L, MO 1314 ESMO 2023

EARLY STAGE SETTING

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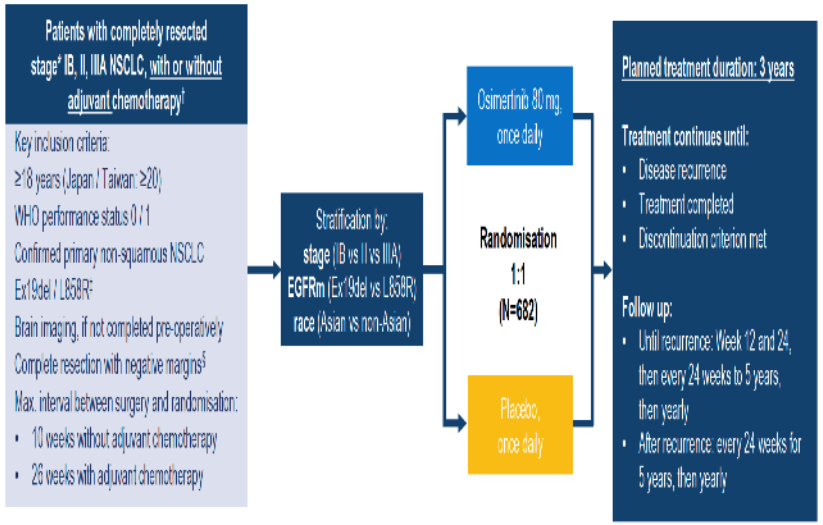
WE ALSO NEED TESTING IN EARLY STAGES!!

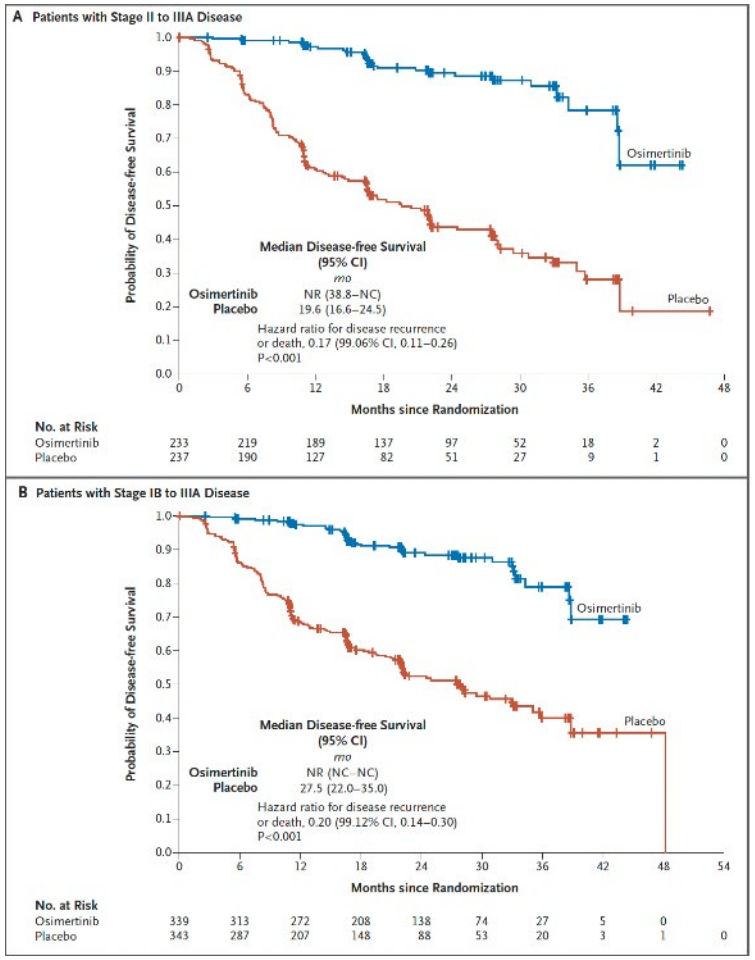
PHASE III ADAURA STUDY DESIGN



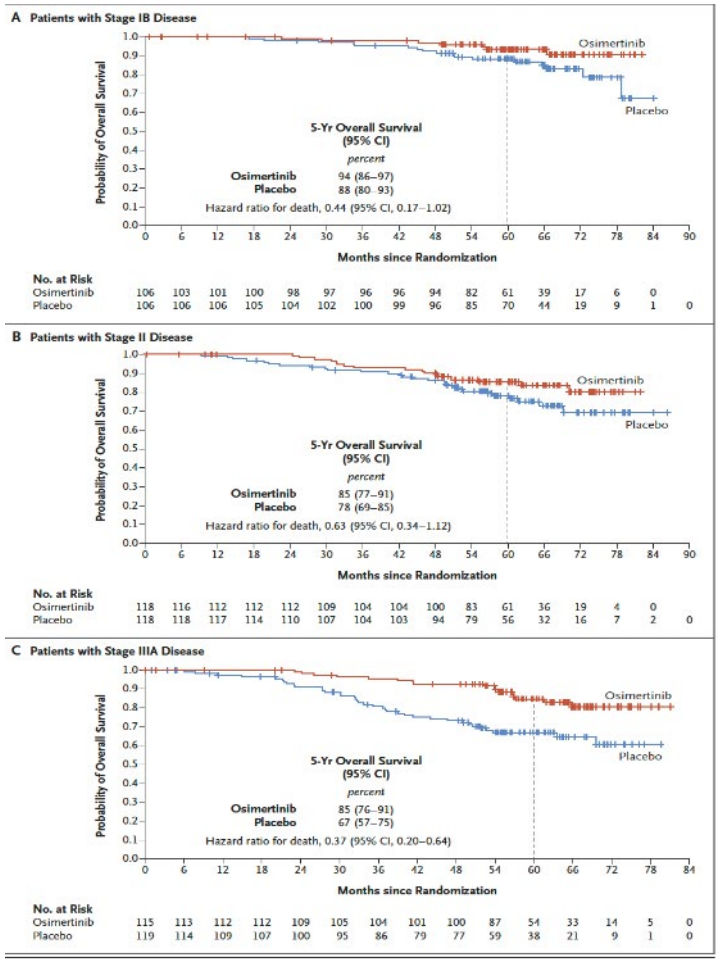
Endpoints

- **Primary endpoint:** DFS by investigator assessment in stage II / IIIA patients, designed for superiority under the assumed DFS HR of 0.70
- **Key secondary endpoints:** DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life
- **Pre-specified exploratory endpoints:** Patterns of recurrence, time to CNS disease recurrence or death (CNS DFS)

SIGNIFICANT BENEFIT OVER PLACEBO IN DFS AND OS



Wu, YL, NEJM 2020



Tsuboi M, NEJM 2023

NEOADJUVANT SCENARIO FOR EGFR +

Study	Phase	Stage	N	Therapy	Primary endpoint
NeoADAURA (NCT04351555)	III	II-IIIB (N2)	328	neoadjuvant chemo + placebo vs chemo + osimertinib vs osimertinib 9 wks → sx → investigator choice (osimertinib x 3yrs)	MPR
ANSWER (NCT04455594)	II	IIIA N2	168	neoadjuvant almonertinib vs investigator choice (erlotinib or chemo)	ORR
NCT04201756	II	III	47	neoadjuvant afatinib x 16wks → sx → afatinib x 1 yr	ORR
Neolpower (NCT05104788)	II	II-IIIB	27	neoadjuvant icotinib + chemo x 2 cycles → sx	MPR
NCT03749213	II	IIIA N2	36	neoadjuvant icotinib x 8wks → sx → icotinib x 2 yrs	ORR

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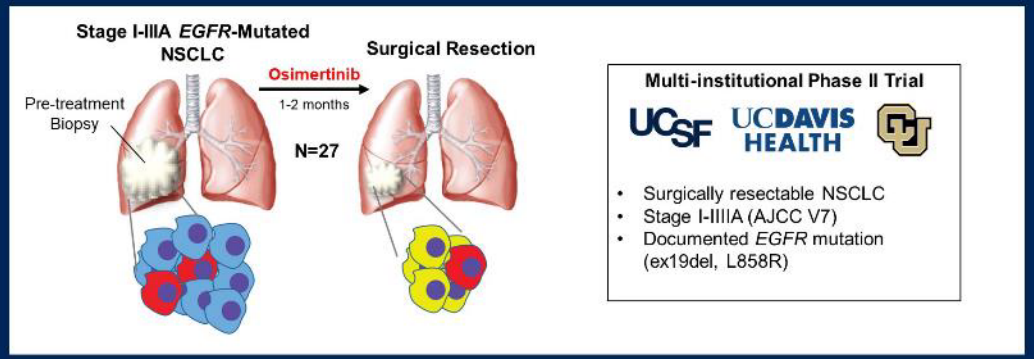
Neoadjuvant Osimertinib

Neoadjuvant Osimertinib for Stage I-IIIA *EGFR*-Mutated NSCLC (PI: Collin Blakely, UCSF)

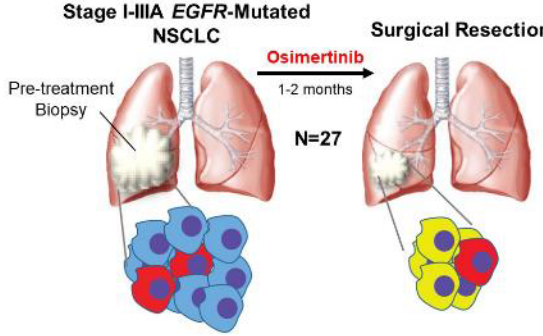


Multi-institutional Phase II Trial

UCSF UCDAVIS HEALTH

- Surgically resectable NSCLC
- Stage I-IIIIA (AJCC V7)
- Documented *EGFR* mutation (ex19del, L858R)

Primary Endpoint: Major Pathological Response Rate



Primary Endpoint:
Major Pathological Response (MPR) Rate
(Powered to detect MPR ~ 50%)

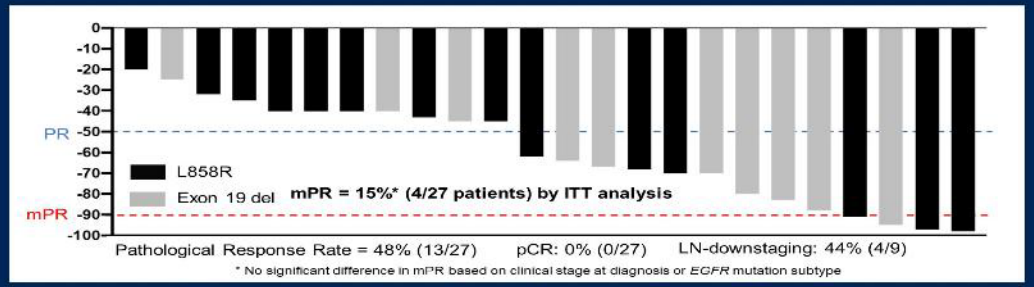
Secondary Endpoints:

Safety:
Surgical Complications
Unresectability Rate

Efficacy:
Lymph Node Downstaging
Pathological Response Rate
pCR Rate
5-year DFS/OS

Exploratory Endpoint:
Identify mechanisms underlying disease persistence

Primary Endpoint: Major Pathologic Response Rate = 15%



Median duration of neoadjuvant osimertinib: 56 days (IQR 41-62)

Safety

Surgical Resectability

- **24 of 27** patients **(89%)** completed R0 surgical resection
- **3 of 27 (11%)** were converted to definitive concurrent chemoradiotherapy, **1 (3.7%)** due to disease progression

Adverse Events

SAEs: 3 patients (11%) Pulmonary Embolism, Atrial Fibrillation, Dyspnea

Perioperative complications:
9 patients (38%) total, all grade 1-2
6 patients (25%) with grade 2 post-op atrial fibrillation, unrelated to osimertinib

Surgical complications:
None

TAKE- HOME MESSAGES

- There are new first-line treatment options for patients with aNSCLC EGFR mut tumors (FLAURA2, MARIPOSA) with better outcomes (PFS) but also higher toxicity.

- Additional data (biomarkers, PRO, PRE) and OS will help us to prioritize

- In the second line scenario we still need better options to improve long term survival

- In early stages, neoadjuvant trials largely awaited

- ***In all cases, treatment decisions should always be individualized to meet the specific needs and goals of each patient***.

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GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE

Thanks!!!!!

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