CÁNCER DE PULMÓN CON DRIVERS

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DISCLOSURES

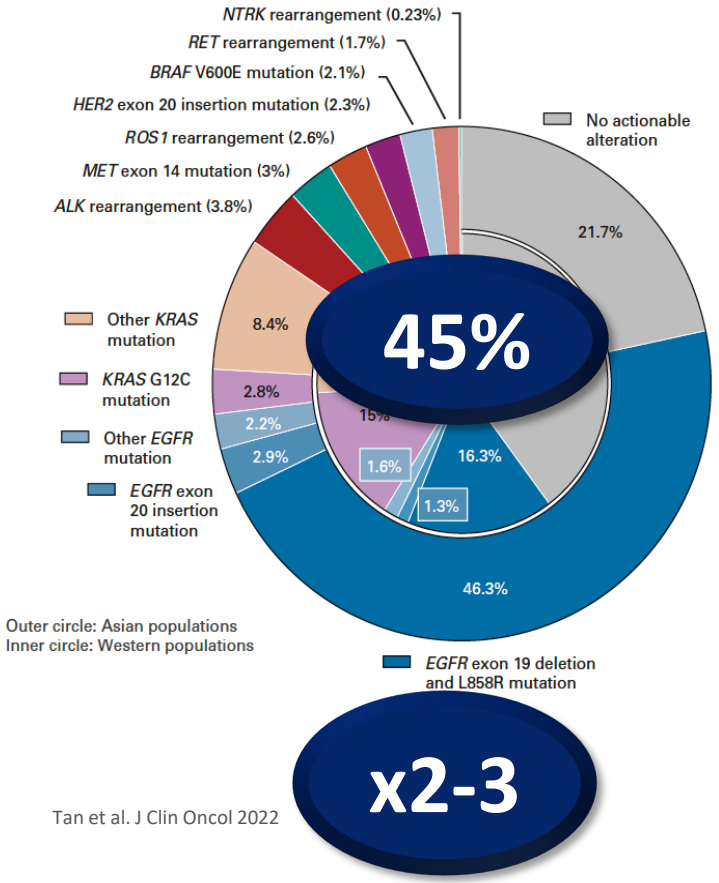
Personal financial interests

- **Consulation Honoraria**: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, Lilly, MSD, Pfizer, Sanofi, Takeda, Pfizer
- **Speaker Honoraria**: Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, F. Hoffmann-La Roche, Janssen, MSD, Novartis, Pfizer, Takeda, Merck, Amgen, Pfizer

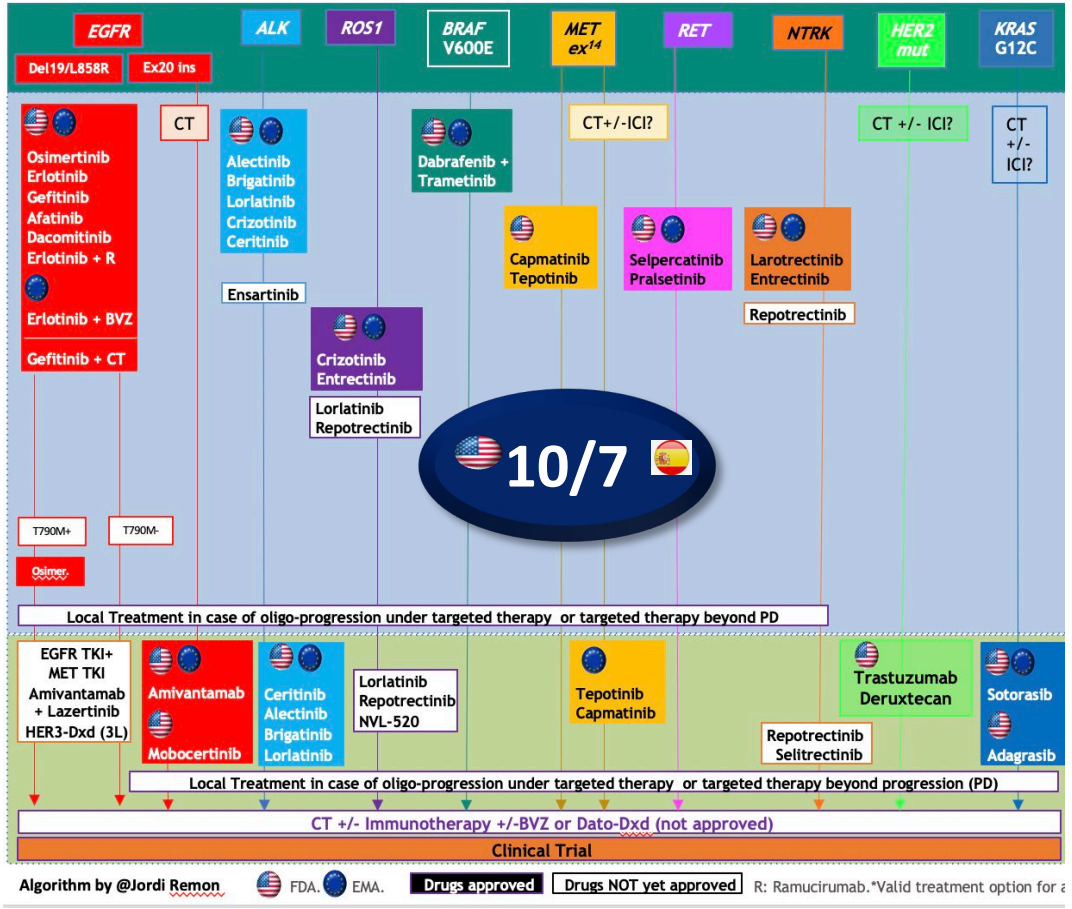
Institutional financial interests

- **Clinical Trials:** Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, DaiichiSankyo, F. Hoffmann-La Roche, GSK, Janssen, Lilly, Merck, Mirati Therapeutics, MSD, Novartis, Amgen, Pfizer
- **Research Grant**: BMS, F. Merck, Pfizer

New treatment paradigm in NSCLC 2024

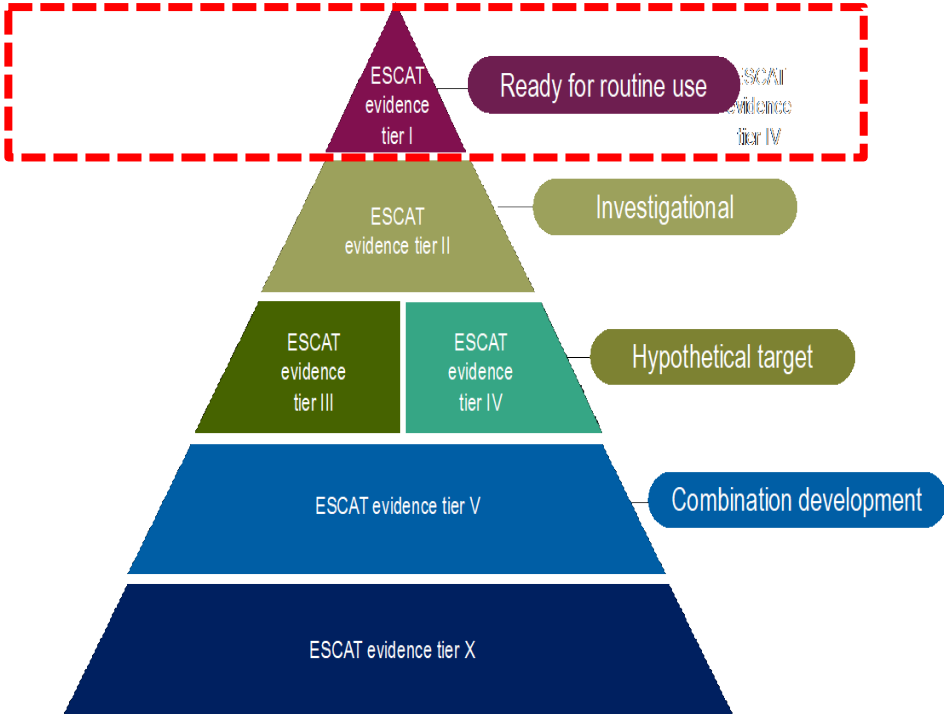


Tan et al. J Clin Oncol 2022



ESMO Scale of Clinical Actionability for molecular Targets (ESCAT)

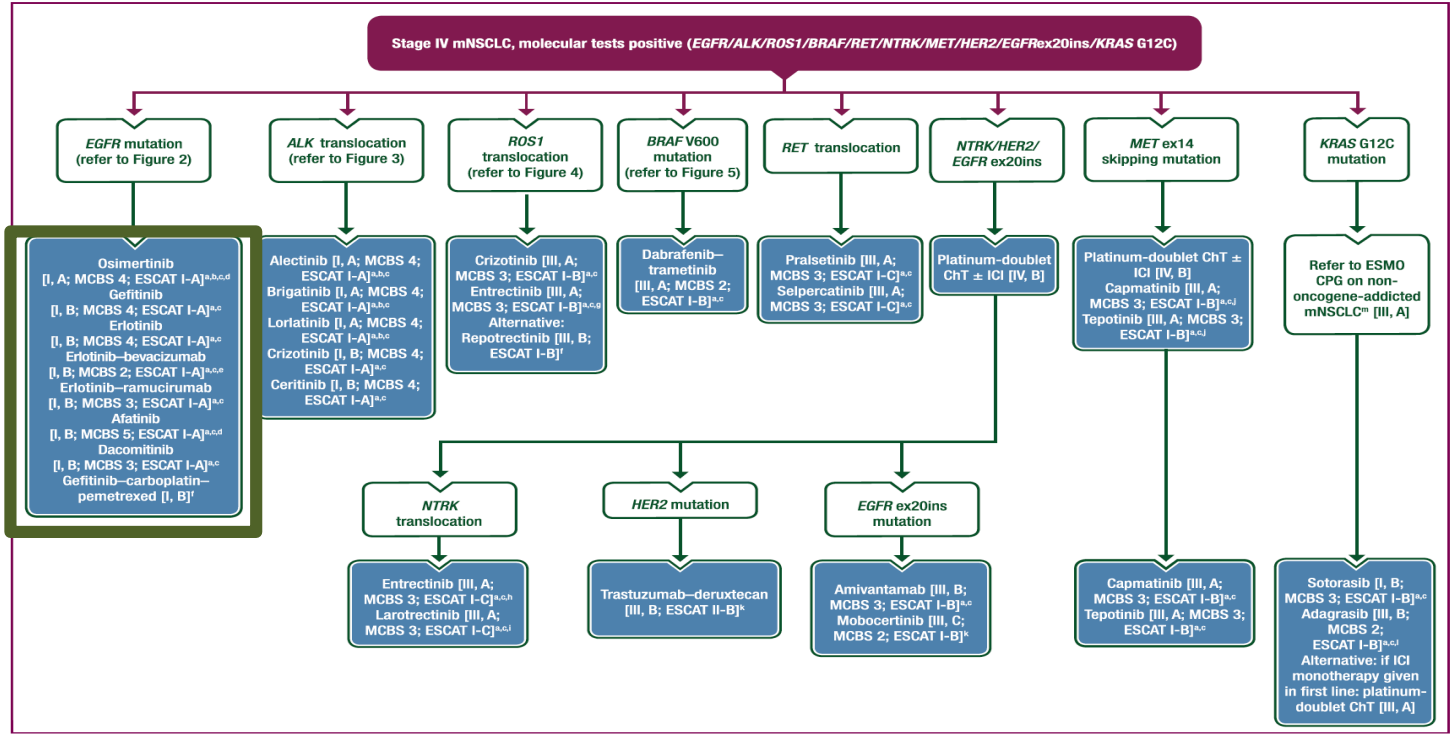
The ESMO Precision Medicine Working Group[1]



Gene	Alteration	ESCAT
	ESCAT TIER EVIDENCE I	
EGFR	Common mutations (Del19, L858R)	IA
	Acquired T790M exon 20	IA
	Uncommon (G719X exon 18, L861Q exon 21, S768I exon 20)	IB
ALK	Fusions (mutations as mechanism of resistance)	IA
MET	Mutations ex 14 skipping	IB
BRAF^{V600}	Mutations	IB
ROS1	Fusions (mutations as mechanism of resistance)	IB
NTRK	Fusions	IC
RET	Fusions	IC
	ESCAT TIER EVIDENCE II-III	
KRAS^{G12C}	Mutations	IIB
EGFR	Exon 20 insertion	IIB
ERBB2	Hotspot mutations and Amplifications	IIB
MET	Focal amplifications (acquired resistance on EGFR TKI)	IIB
BRCA 1/2	Mutations	IIIA
PIK3CA	Hotspot mutations	IIIA
NRG1	Fusions	IIIB

Mosele F., et al. Ann Oncol. 2020

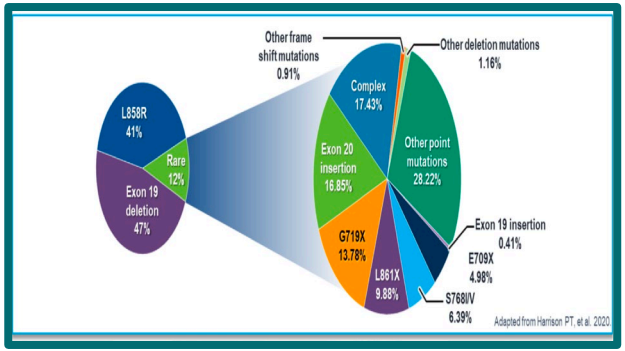
ESMO Guidelines

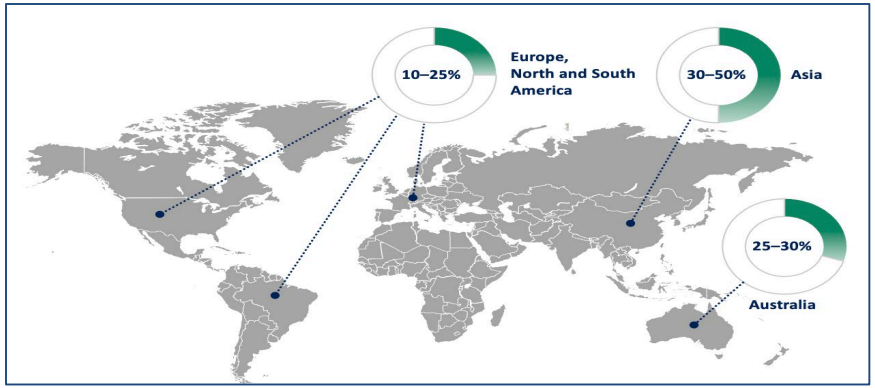


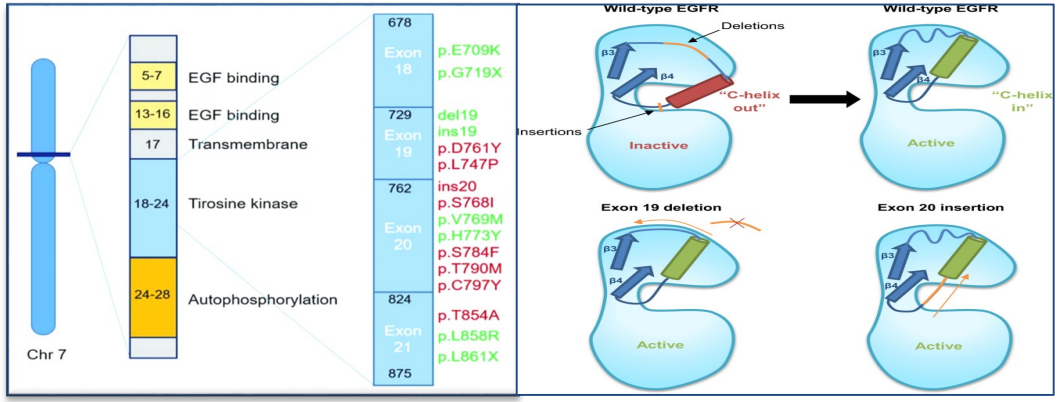
Hendriks L et al. Ann Oncol 2023

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

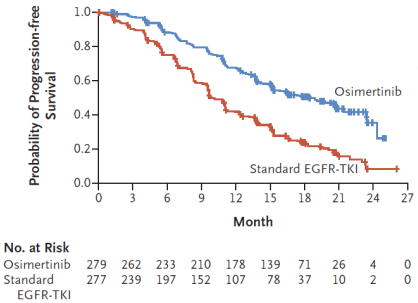
Courtesy Dr Mezquita

Have we reached a plateau in EGFR+ NSCLC?

FLAURA Trial

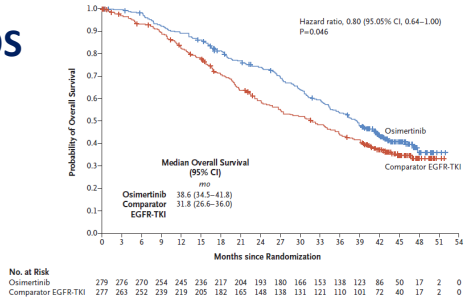
Osimertinib *vs.* Gefitinib/Erlotinib

PFS



18.9 vs **10.2** mo
HR 0.46
(95% CI 0.37-0.57)

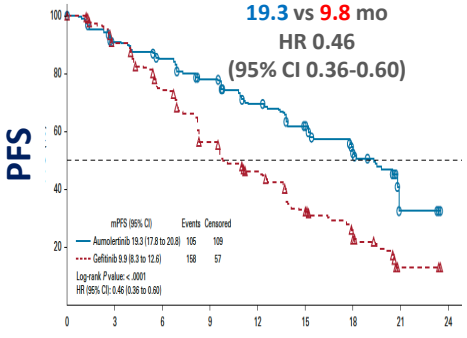
OS



38.6 vs **31.8** mo
HR 0.80
(95% CI 0.64-1.00)

AENEAS Trial

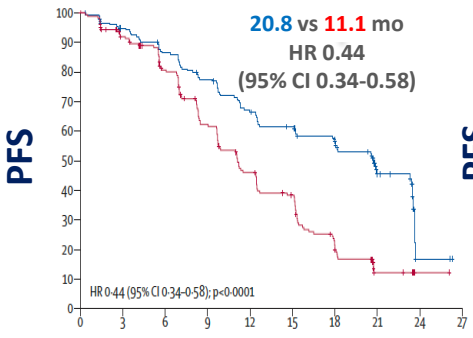
Almolertinib *vs.* Gefitinib



19.3 vs **9.8** mo
HR 0.46
(95% CI 0.36-0.60)

FURLONG Trial

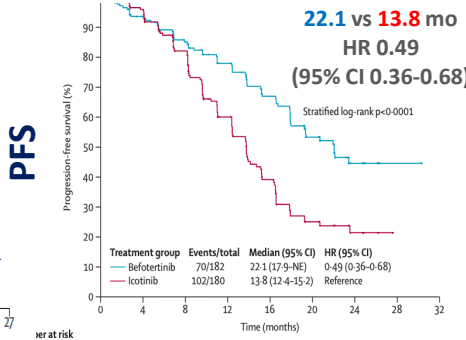
Furmonertinib *vs.* Gefitinib



20.8 vs **11.1** mo
HR 0.44
(95% CI 0.34-0.58)

NCT04206072

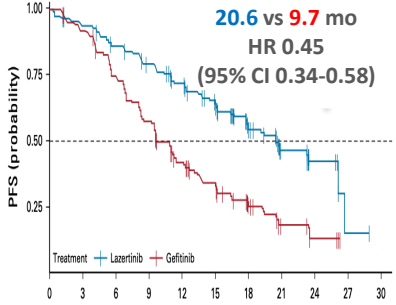
Befotertinib *vs.* Icotinib



22.1 vs **13.8** mo
HR 0.49
(95% CI 0.36-0.68)

LASER 301

Lazertinib *vs.* Gefitinib



20.6 vs **9.7** mo
HR 0.45
(95% CI 0.34-0.58)

Soria NEJM 2018 et al. Ramalingam et al. NEJM 2019; Lu et al. J Clin Oncol 2022; Shi et al. Lancet Resp Med 2022; Lu et a al Lancet Resp Med 2023; Cho et al. J Clin Oncol 2023

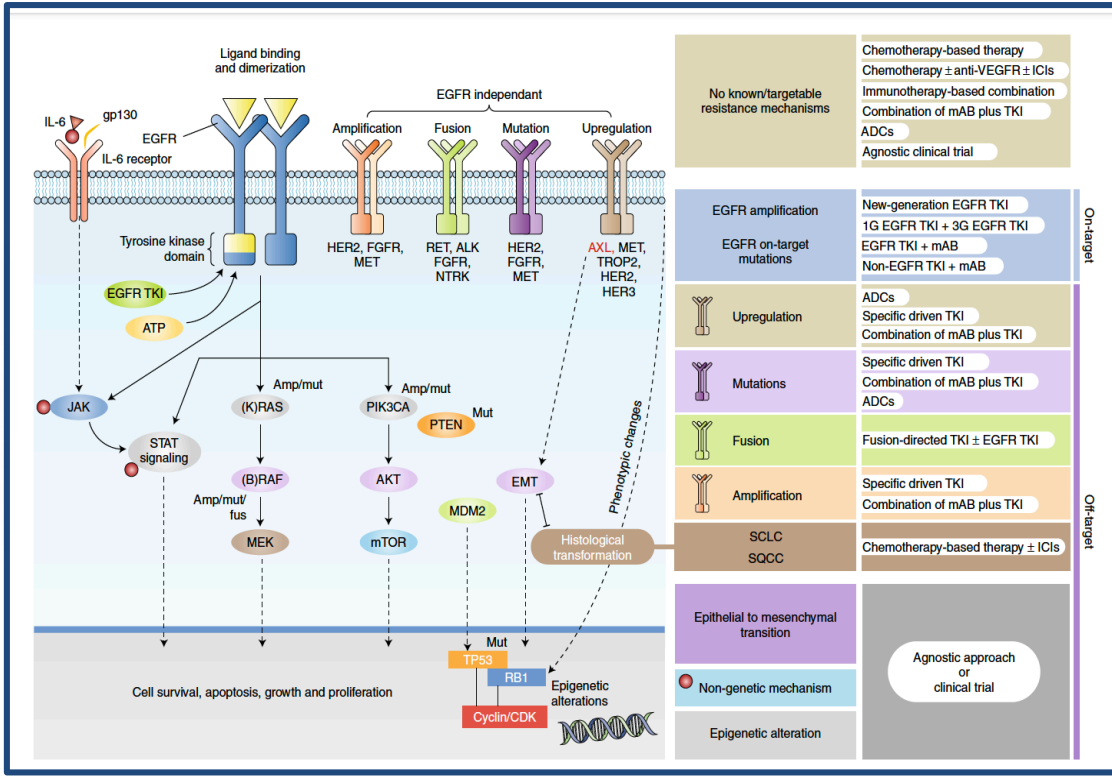
Improving long-term results is key

Treatment options *to prevent/delay* progression:

- CT+ EGFR TKIs
- Amivantamab + EGFR TKI
- VEGF inhibitors + EGFR TKIs

Treatment options *after* disease progression:

- Biomarker-driven approaches
- Agnostic strategies



Passaro A, Peters S. Nature Cancer 2021

What about combination approaches? VEFGi+EGFR TKIs

Trial	TKI	Comparing TKI	ORR (%)	PFS (months)	HR	OS (months)	HR
FLAURA*	Osimertinib	Gefitinib/ Erlotinib	80 v 76	18.9 v 10.2	0.46 (0.37-0.57)	38.6 v 31.8	0.80 (0.64-1.00)
NEJ 026	Erlotinib / BVZ.	Erlotinib	72 v 67	16.9 v 13.3	0.61 (0.42-0.88)	50.7 v 46.2	1.007 (0.68-1.49)
ARTEMIS	Erlotinib / BVZ.	Erlotinib	87 v 85	18.0 v 11.2	0.55 (0.41-0.73)	36 v 32 (NM)	0.92 (0.69-1.23)
RELAY*	Erlotinib / Ramuc.	Erlotinib	76 v 77	19.4 v 12.4	0.59 (0.46-0.76)	NE v NE (NM)	0.83 (0.53-1.30)
ACTIVE	Gefitinib / Apatinib	Gefitinib	77 v 74	13.7 v 10.2	0.71 (0.54-0.95)	NE v NE (NM)	1.10 (0.72-1.67)
BEVERLY	Erlotinib / BVZ.	Erlotinib	70 v 50	15.4 v 9.6	0.66 (0.47-0.92)	33.3 v 22.8	0.72 (0.47-1-10)
WJOG9717L	Osimertinib / BVZ	Osimertinib	82 v 86	22.1 v 20.2	0.86 (0.7-1.06)	NE v NE	0.97 (0.5-1.87)
RAMOSE Phase 2	Osimertinib/ Ramuc	Osimertinib	71 vs 37	24.8 vs 15.6	0.55 (0.32-0.93)	NR	NR
OSIRAM 1 Phase 2	Osimertinib/ Ramuc	Osimertinib	NR	20 vs 24	1.054 (0.67-1.6)	NR	NR

Soria NEJM 2018; Ramalingam NEJM 2019 ; Kawashima Lancet Oncol 2021; Zhou Cancer Cell 2021; Piccirillo ; JTO 2022; Nakagawa Lancet Oncol 2019; Nakagawa CCR 2021; Zhong JTO 2021 ; Kenmotsu JTO 2022; Hosomi CO 2019 ; Mirauchi JCO 2022; Noronha – JCO 201 ; Le et al. ESMO 2023; Nakahara ESMO 2023;

FLAURA 2

The global, open-label, randomised FLAURA2 study assessed the efficacy and safety of **osimertinib + platinum-pemetrexed vs osimertinib monotherapy** as **1L** treatment for *EGFR*m advanced NSCLC*[1]

Safety run-in period (N=30)[2]

Patients with untreated locally advanced/metastatic *EGFR*m NSCLC

Key inclusion criteria:
- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- *EGFR* exon19del/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)
- ***EGFR*m** (local/central test)
- **WHO PS** (0/1)

Randomisation 1:1 (N=557)

Osimertinib 80 mg (OD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments

Maintenance osimertinib 80 mg (OD) + pemetrexed (Q3W)‡

Osimertinib 80 mg (OD)

Follow-up:
- RECIST v1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST v1.1 defined radiological PD or other withdrawal criteria were met

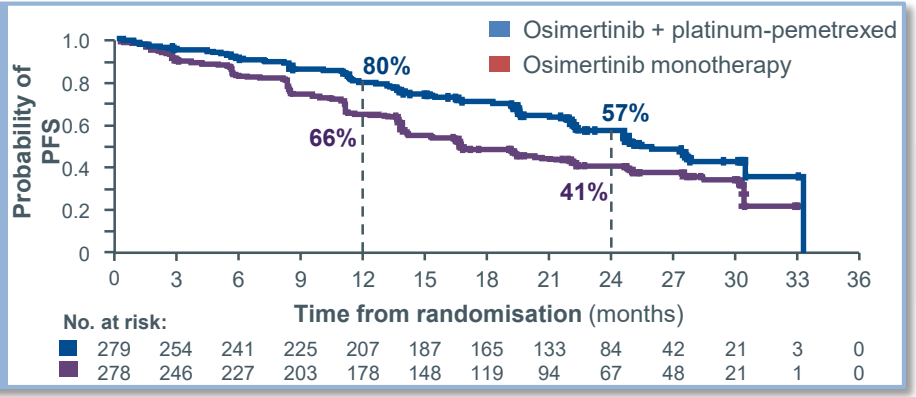
- **Primary endpoint:** PFS by INV assessment per RECIST v1.1§‖
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST v1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5), and PFS2§

Adapted from Jänne PA, et al. 2023.[1]

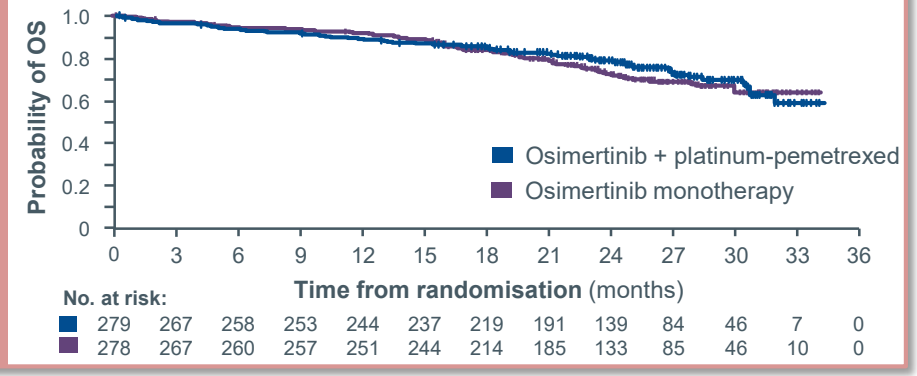
1. Jänne PA, et al. WCLC 2023: PL03.13; 2. Planchard D, et al. *ESMO Open*.

Results: PFS and OS

PFS per INV*



OS interim analysis



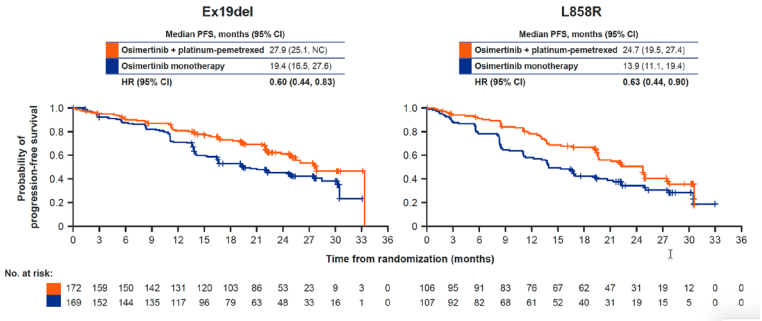
Endpoint	Osimertinib + platinum-pemetrexed (n=279)	Osimertinib monotherapy (n=278)
mPFS per INV, months (95% CI)		
Overall population	**25.5** (24.7–NC)	**16.7** (14.1–21.3)
	HR 0.62 (95% CI, 0.49–0.79); p<0.0001	
With CNS metastases†	**24.9** (22.0–NC)	**13.8** (11.0–16.7)
	HR 0.47 (95% CI, 0.33–0.66)	
Without CNS metastases†	**27.6** (24.7–NC)	**21.0** (16.7–30.5)
	HR 0.75 (95% CI, 0.55–1.03)	
mOS, months (95% CI)		
Overall population	**NR** (31.9–NC)	**NR** (NC–NC)
	HR 0.90 (95% CI, 0.65–1.24); p=0.5238‡	

Osimertinib + platinum-pemetrexed demonstrated a statistically significant and clinically meaningful improvement in PFS over osimertinib monotherapy

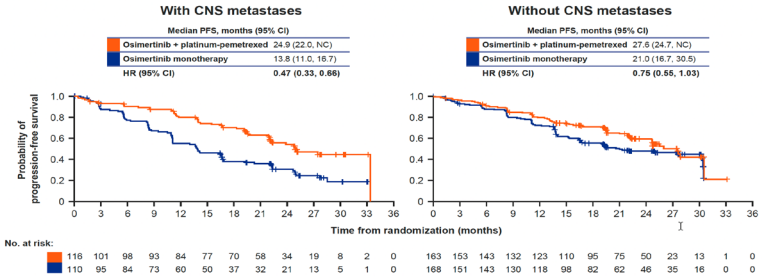
Janne P WCLC 2023; Planchard D, NEJM 2023

FLAURA 2: key findings

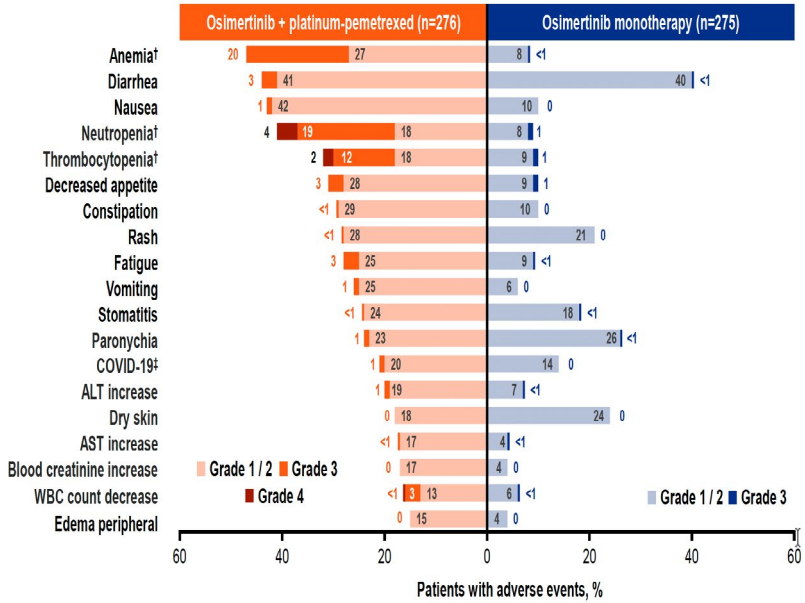
PFS per investigator by EGFR mutation type at baseline*



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



Common adverse events (≥15% of patients)*



- Discontinuation 11% vs 6%
- Interruption 43% vs 19%
- Dose reduction 10% vs 3%

Janne P WCLC 2023; Planchard D, NEJM 2023

MARIPOSA

A Phase 3, global, randomised, controlled trial investigating the efficacy and safety of **amivantamab + lazertinib vs osimertinib** as **1L** treatment in ***EGFR*-mutated advanced NSCLC***

Key eligibility criteria:

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* exon19del or L858R
- ECOG PS 0 or 1

Stratification factors:

- *EGFR* mutation type (exon19del or L858R)
- Asian race (yes or no)
- History of brain metastases† (yes or no)

Serial brain MRIs were required for all patients†

2:2:1 Randomisation (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 OD
Osimertinib: 80 mg OD

Median follow-up of 22.0 months

Primary endpoint of amivantamab + lazertinib vs osimertinib:

- PFS‡ by BICR per RECIST v1.1

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

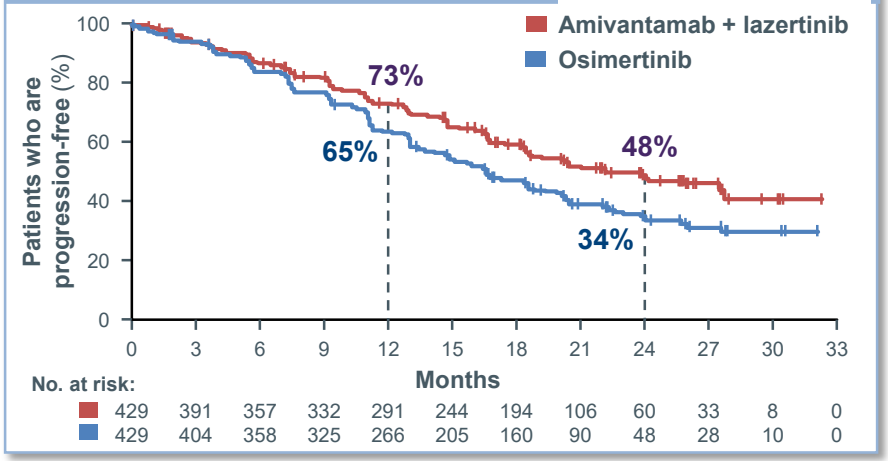
- OS‡
- ORR
- DoR
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS§
- Intracranial PFS§
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

Cho BC, et al. ESMO 2023

Results: PFS and extracranial PFS by BICR

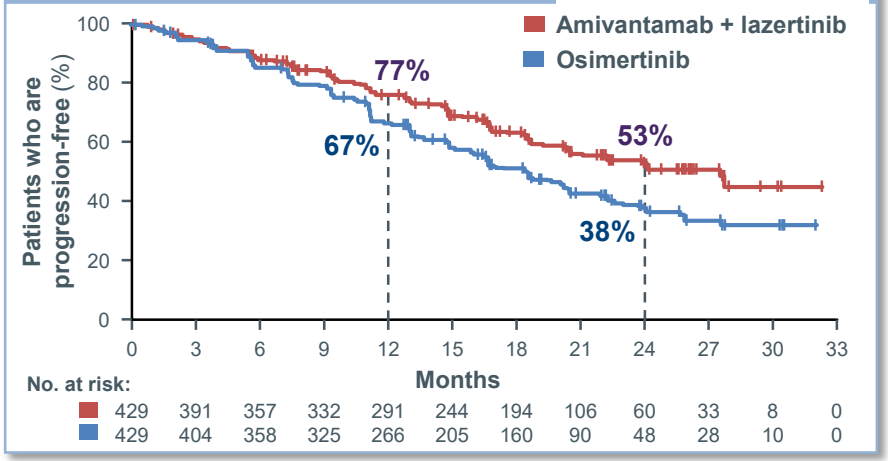
PFS*



Endpoint	Amivantamab + lazertinib	Osimertinib
mPFS, months (95% CI)	**23.7** (19.1–27.7)	**16.6** (14.8–18.5)
HR (95% CI)	**0.70** (0.58–0.85); p<0.001	

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

Extracranial PFS†‡



Endpoint	Amivantamab + lazertinib	Osimertinib
mPFS, months (95% CI)	**27.5** (22.1–NE)	**18.5** (16.5–20.3)
HR (95% CI)	**0.68** (0.56–0.83); p<0.001§	

Amivantamab + lazertinib reduced the risk of extracranial progression or death by 32% and improved mPFS by 9 months

Lazertinib monotherapy demonstrated meaningful clinical activity

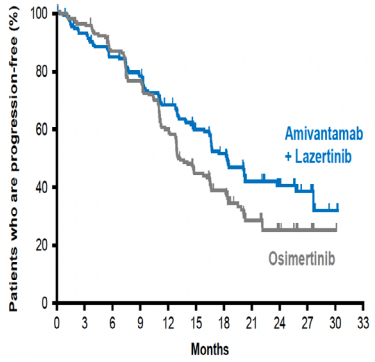
Cho BC, et al. ESMO 2023

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)

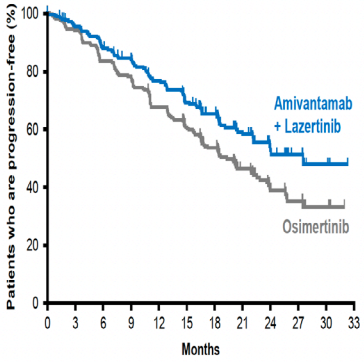


No. at risk

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)

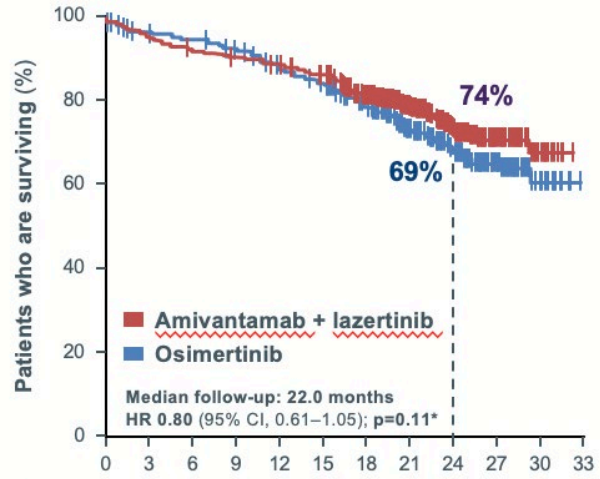
HR, **0.69** (95% CI, 0.53–0.89)



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

Interim OS



No. at risk

Amivantamab + lazertinib	429	403	389	382	374	360	293	201	122	58	14	0
Osimertinib	429	416	409	395	372	349	280	186	110	54	13	0

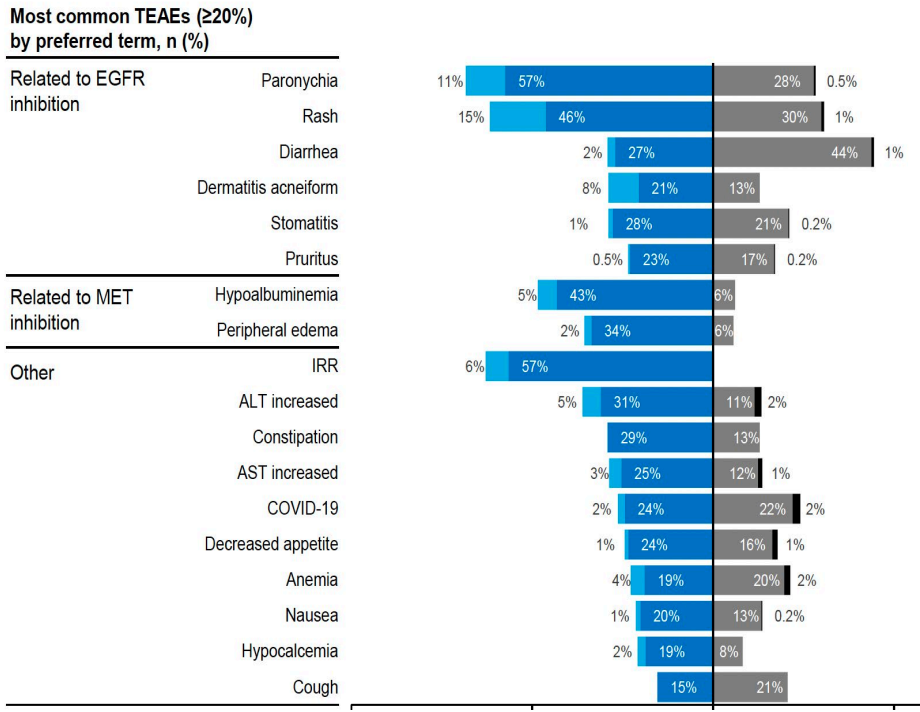
Cho BC, et al. Presented at ESMO 2023: LBA14.

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)

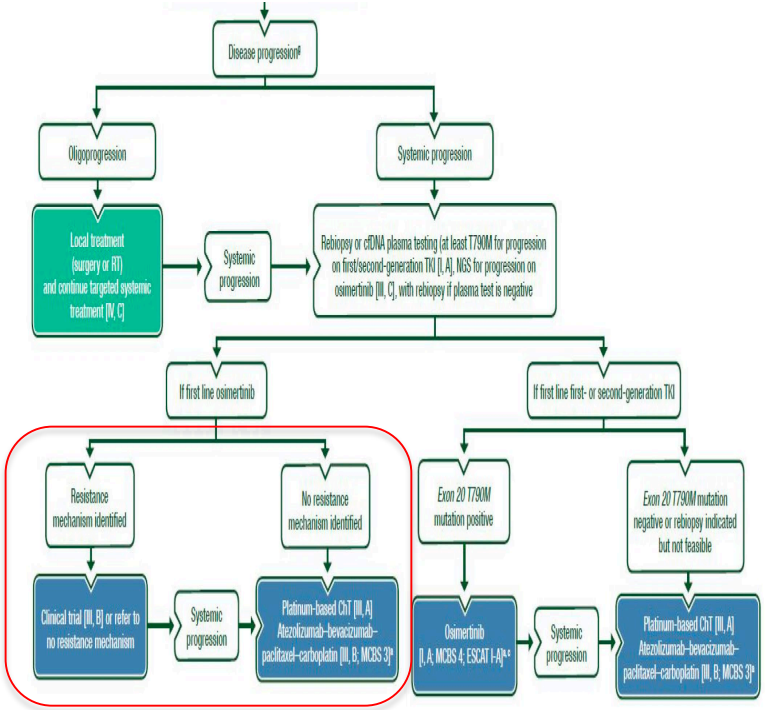
Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

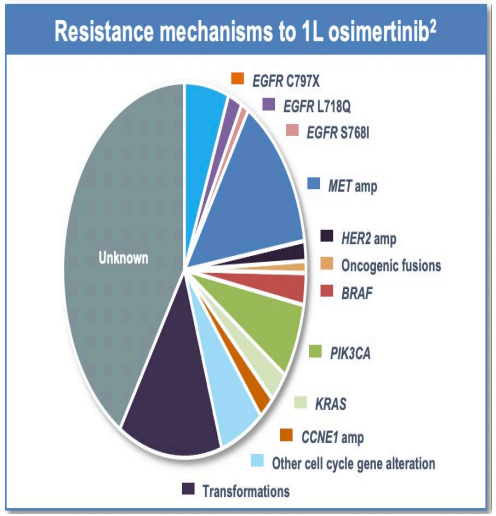


VTE rates were higher for amivantamab + lazertinib: Pulmonary embolism and deep vein thrombosis

MANAGEMENT OF PRETREATED IV NSCLC EGFRm

ESMO GUIDELINES





ACQUIRED RESISTANCE MECHANISMS

Functional groups	Acquired gene alteration, n (%)	FLAURA osimertinib monotherapy (n=109)[1]	FLAURA2 osimertinib monotherapy (n=73)	FLAURA2 osimertinib + platinum-pemetrexed (n=53)[a]
EGFR mutations	C797S	7 (6)	9 (12)	2 (4)
	Other Uncommon	5 (5)	3 (4)	ND
RTK amplifications	MET amplification	17 (16)	10 (14)	5 (9)
	ERBB2 amplification	2 (2)	1 (1)	3 (6)
MAPK / PI3K mutations	BRAF V600E	3 (3)	4 (5)	ND
	KRAS mutation	3 (3)	6 (8)	3 (6)
	PIK3CA mutation	6 (6)	6 (8)	2 (4)
	ERBB2 mutation	ND	1 (1)	ND
Cell cycle gene amplifications	CCND1 / E1 amplification	7 (6)	1 (1)	3 (6)
	CDK4 / 6 amplification	7 (6)	4 (5)	3 (6)
Fusions	RET	ND	3 (4)	1 (2)
	BRAF	ND	3 (4)	1 (2)
	ALK	1 (1)	2 (3)	ND
	Other	NR	5 (7)	2 (4)
RB1 loss (with *TP53*)		NR	4 (5)	ND
No known resistance alteration detected		NR	36 (49)	40 (75)

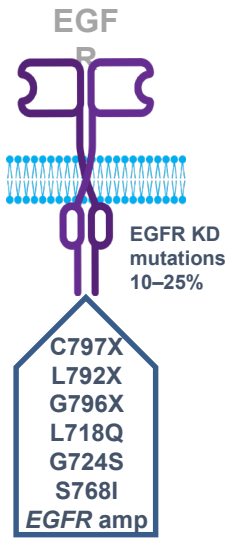
Acquired resistance mechanisms were broadly similar across treatment arms

Similar resistance mechanisms after Osi or Osi+CT

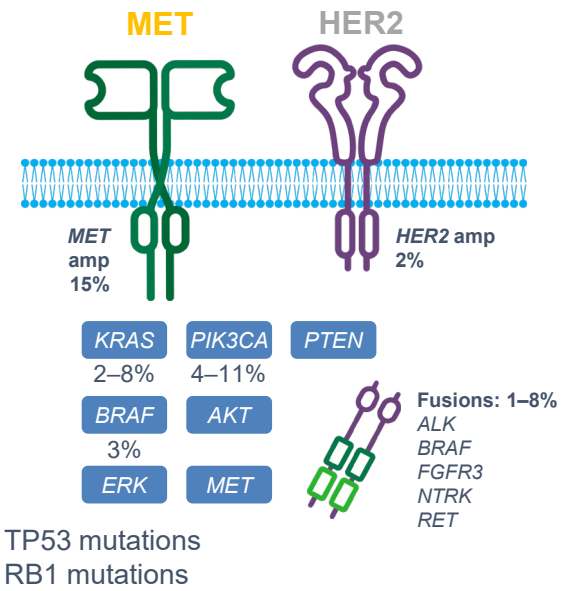
.Hendkriks L, et al Ann Oncol 2023; Ramalingam SS, et al. WCLC 2022; Lee et al. ESMO ASIA 2023

THE CHALLENGES IN OVERCOMING OSIMERTINIB RESISTANCE IN *EGFR*-MUTANT LUNG CANCER

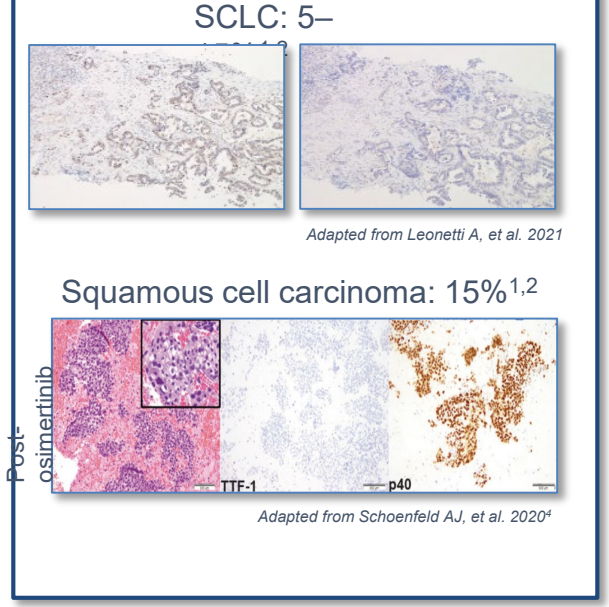
On-target resistance[1,2]



Bypass resistance[1,2]



Histologic transformation



4th generation EGFR TKI

EGFR-MET Biespecific AB+ EGFR TKI

EGFR TKI+ADCs

ADCs

EGFR TKI+MET TKI

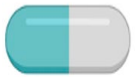
CT+IO+/Antiangiogenics

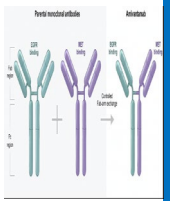
Figure courtesy of Gonzalo Recondo. ASCO 2022. (Modified).

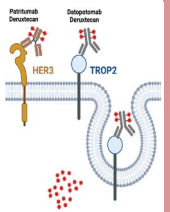
- 1. Passaro A, et al. *Nat Cancer.* 2021;2:377–91; 2. Leonetti A, et al. *Br J Cancer.* 2019;121:725–37; 3. Leonetti A, et al. *Front Oncol.* 2021;11:642190; 4. Schoenfeld AJ, et al. *Clin Cancer Res.* 2020;26:2654–63.

Overcoming after Osimertinib 1st line treatment

Selective MET TKI



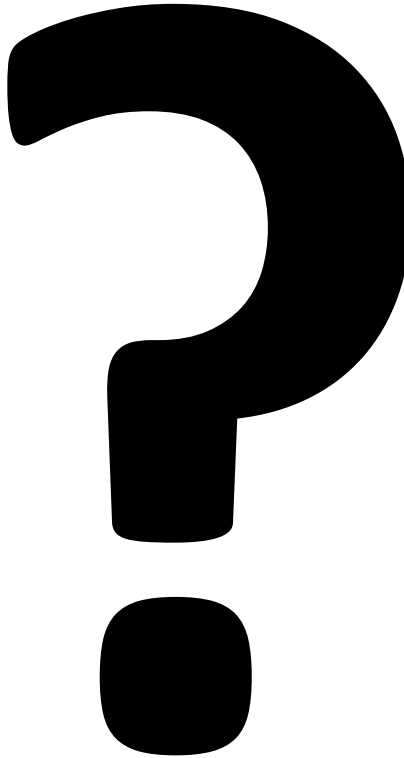




	Trial	Drug	N	RR (%)	DoR (mo.)	PFS (mo.)	OS (mo)
MET Ampl/ IHC Selective MET TKI+ Osimertinib	TATTON (Part B)	Osimertinib + Savolitinib	69	33	9.5	5.5	NR
	ORCHARD	Osimertinib + Savolitinib	17	41	NR	NR	NR
	SAVANNAH (MET IHC/ MET amp)	Osimertinib+Savolitinib	193	32-49	8.3-9.3	5.3-7.1	NR
	INSIGHT2 (MET ampl)	Osimertinib + Tepotinib	128	50	8.5	5.6	17.8
		Tepotinib	12	8.3	NR	NR	NR
Blinded Bispecific AB+EGFR TKI	CHRYSALIS	Lazertinib + Amivantamab	45	30	9.6	4.9	NR
	CHRYSALIS-2	Lazertinib + Amivantamab, post TKI, post CT	162	33	8.4	5.1	14.8
	CHRYSALIS-2	Lazertinib + Amivantamab + CT	20	50	NE	14	NE
	MARIPOSA 2	Lazertinib+Amivantamab+CT	263	63	9.4	8.3	HR 0.96
		Amivantamab+ CT	131	64	6.9	6.3	HR 0.77
ADCs+/-EGFR TKI Blinded	TELISO-V (MET IHC)	Osimertinib + Teliso V (MET IHC+)	19	58	NE	NE	NR
	TROPION PAN TUMOR 01	Datopotamab Deruxtecan	34	35	9.5	NE	NR
	TROPION LUNG 05	Dapototamab Deruxtecan	137 (57% EGFRmut)	49.1 (post Osi)	7	5.8	NR
	HERTHENA LUNG 1	Patritumab Deruxtecan	209 (prev Osi)	29.2	6.4	5.5	11.9

Hatmaier et al. Cancer Discov 2023; Yu et al, ESMO 2021; Ahn et al, WCLC 2022; Kim et al WCLC 2023 ; Cho et al, Nat Med 2023; Shu et al. ASCO 2022; Lee et al. WCLC 2023.
Goldman et al. ASCO 2022; Garón et al. ESMO 2021; Paz Ares et al. ESMO 2023; Yu H, et al. WCLC 2023

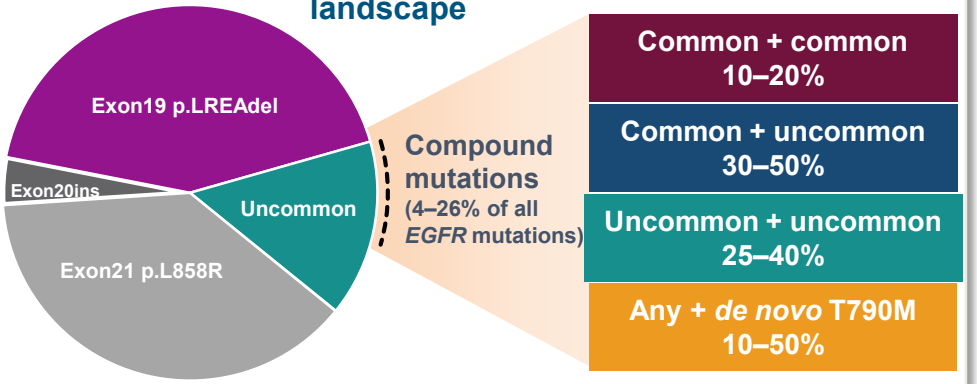
FLAURA	• MARIPOSA 2 (phase III) • ADC • OSI+MET INHIB • PLATINUM DOUBLET
FLAURA 2	• ADC • OSI+MET INH • RETREATMENT PLATINUM-DOUBLET
MARIPOSA	• PLATINUM-DOUBLET • ADC



Uncommon *EGFR* mutations in NSCLC

***EGFR* exon20ins are the third most common *EGFR* mutation in patients with NSCLC**
(up to 12% of all *EGFR* mutations; up to 4% of all NSCLC)

EGFR mutation landscape

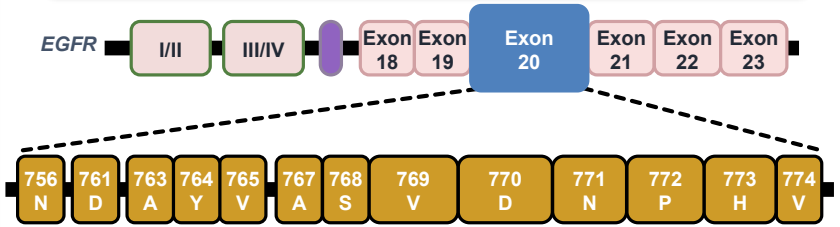


Heterogeneityof EGFR exon20ins

In majority, resistance to existing EGFR TKIs
(erlotinib, gefitinib, afatinib, osimertinib, etc.)

No significant ethnic differences in incidence of *EGFR* exon20ins, in contrast to ethnicity impact on incidence for common *EGFR* mutations

Low immunogenicity
Variable effect on PD-L1 expression



- **~90% of *EGFR* exon20ins** are detected within amino acids 767 and 775 and are all strongly resistant to existing TKIs, but sensitive to new drugs in development
- **~10% of *EGFR* exon20ins** are detected within amino acids 761 and 766 and some could display sensitivity to TKIs and to new drugs in development

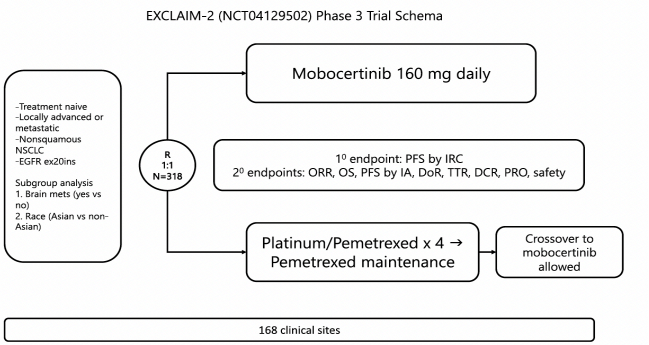
Clinical trials on emerging treatment options for *EGFR* exon 20 insertion+ NSCLC

	AMIVANTAMAB	MOBOCERTINIB	OSIMERTINIB 160 mg/day	OSIMERTINIB 160 mg/day			LUMINESPIB
Setting	After platinum chemo	After platinum chemo	1 prior line median, 2	43% naive	Previously treated	Previously treated	Previously treated
No. patients	114	114 (PPP) 96 (EXCLAIM)	21	25	115	50	29
ORR	37%	28% (PPP) 25% (EXCLAIM)	24%	28%	15%	31%	17%
mDoR, m	12.5	17.5 (PPP) NE (5.6 to NE) (EXCLAIM)	5.7	5.3	4.2	8.6	NR
mPFS, m	6.9	7.3 (PPP)	9.6	6.8	7.4	5.5	2.9
mOS, m	23	24.0 (PPP)	NR	15.2	NA	19.2	13

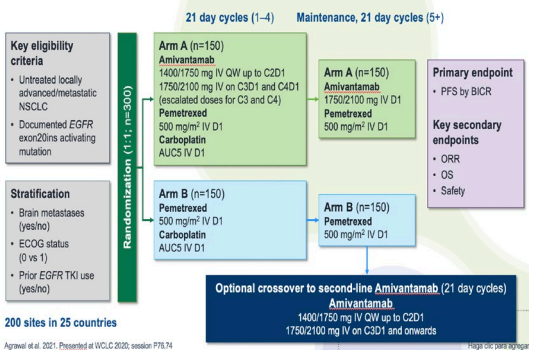
Garrido P, et al. ELCC 2023; Zhou et al. JAMA Oncol 2021; Park et al JCO 2021; Zhou et al. JAMA Oncol 2022; Piotrowska e t al; ASCO 2020; Zwierenga et al, Lung Cancer 2022; Elamin et al M. Cancer Cell 2022; Cornelissen et al WCLC 2020; Piotrowska et al. JTO 2017; Abs OA12.02

PHASE III TRIALS IN FIRST LINE SETTING

EXCLAIM-2 (NCT04129502)



PAPILLON (NCT04538664)



PAPILLON

A randomised, Phase 3, global study investigating **amivantamab + ChT vs ChT** as 1L treatment in **NSCLC** patients with ***EGFR* exon20ins mutations***

Eligibility criteria:
- Treatment-naïve,† locally advanced or metastatic NSCLC
- Documented *EGFR* exon20ins mutation
- ECOG PS 0 or 1

Stratification factors:
- ECOG PS
- History of brain metastases‡
- Prior EGFR TKI use†

1:1 R — N=308

- **Amivantamab + ChT** (n=153)
- **ChT** (n=155)

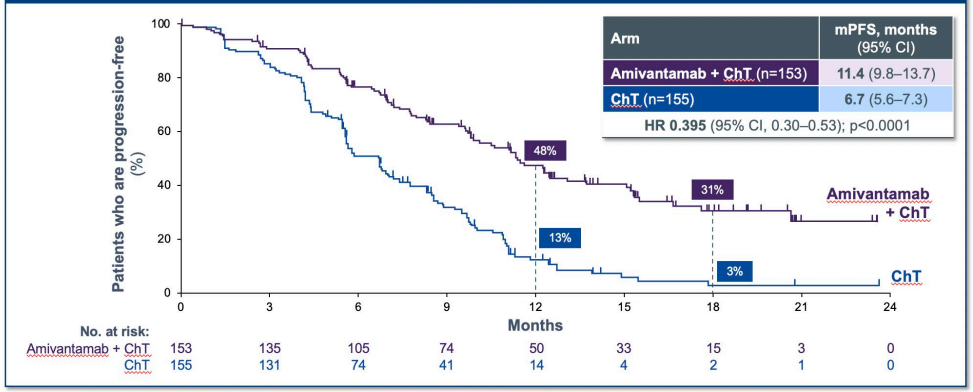
Dosing (in 21-day cycles):
Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Week 7 (first day of Cycle 3)
ChT on the first day of each cycle:
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Primary endpoint:
- PFS by BICR (RECIST v1.1) §

Secondary endpoints:
- ORR §
- DoR
- OS §
- PFS2
- Symptomatic PFS‖
- Time to subsequent therapy‖
- Safety

Optional crossover to 2L amivantamab monotherapy after BICR confirmation of PD¶

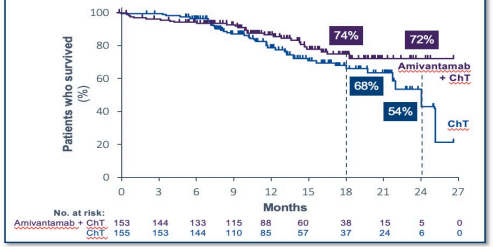
PFS by BICR*



Arm	mPFS, months (95% CI)
Amivantamab + ChT (n=153)	11.4 (9.8–13.7)
ChT (n=155)	6.7 (5.6–7.3)

HR 0.395 (95% CI, 0.30–0.53); p<0.0001

Interim OS‡§



Arm	mOS, months (95% CI)
Amivantamab + ChT (n=153)	NE (NE–NE)
ChT‖ (n=155)	24.4 (22.1–NE)

HR 0.675 (95% CI, 0.42–1.09); p=0.106

Amivantamab + ChT shows trend in reducing risk of death by over 30%

Girard N, et al. ESMO 2023

EXCLAIM-2

Key Eligibility Criteria
- Locally advanced or metastatic NSCLC
- *EGFR* ex20ins by local testing
- ≥1 measurable lesion per RECIST v1.1
- ECOG PS of 0 or 1
- No prior systemic anticancer treatment

N=354

Randomized 1:1

Mobocertinib 160 mg orally qd with or without food (Arm A)

Randomization was stratified by:
- CNS metastases at baseline (y/n)
- Race (Asian/non-Asian)

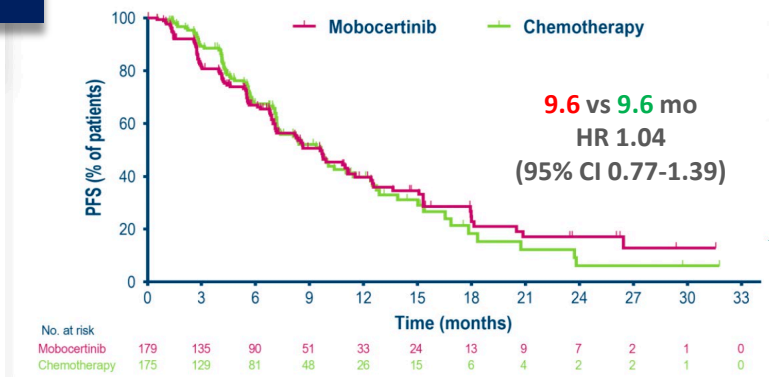
Pemetrexed 500 mg/m² + cisplatin 75 mg/m² IV or Pemetrexed 500 mg/m² + carboplatin AUC 5 IV (Arm B)

Disease assessed by CT and MRI at screening and at 6-week intervals through Cycle 18 and every 12 weeks thereafter; brain MRI at baseline

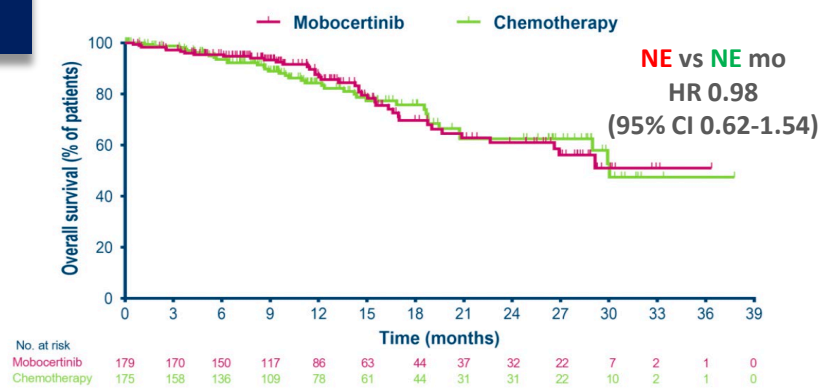
Continue until:
- IRC-assessed PD
- Intolerable toxicity
- Other discontinuation criteria

Patients in Arm B could cross over to mobocertinib after BICR-assessed PD

PFS



OS



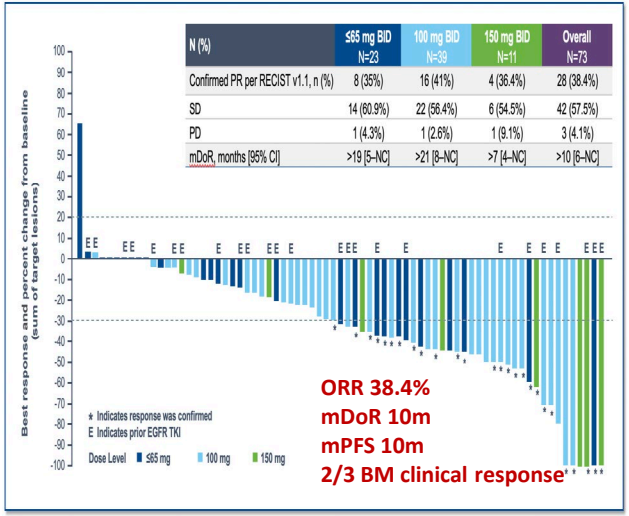
Janne P, et al. ESMO Asia 2023

THE NEW PLAYERS…

ZIPALERTINIB (CLN-081)

73p, 66% with >2 prior lines, 36% prior TKI (3p prior pozio and/or mobo), 38% BM

N (%)	≤65 mg BID N=23	100 mg BID N=39	150 mg BID N=11	Overall N=73
Confirmed PR per RECIST v1.1, n (%)	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDoR, months [95% CI]	>19 [5–NC]	>21 [8–NC]	>7 [4–NC]	>10 [6–NC]

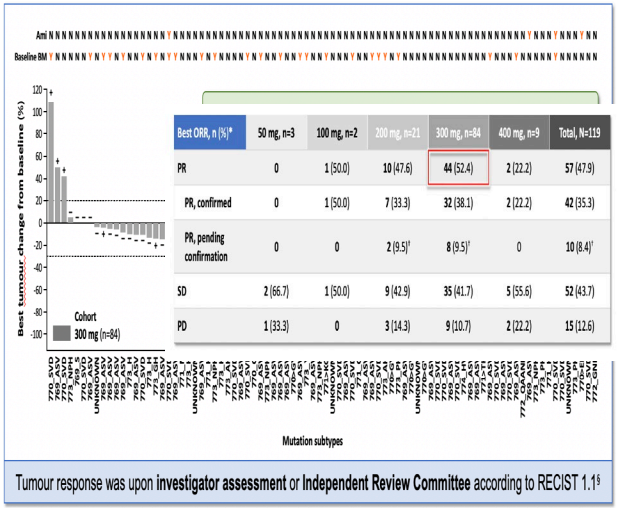


ORR 38.4%
mDoR 10m
mPFS 10m
2/3 BM clinical response[1]

REZILINET-3:
Zipalertinib+ CT vs CT

SUNVOZERTINIB

119 p; median prior lines 2, 31% BM



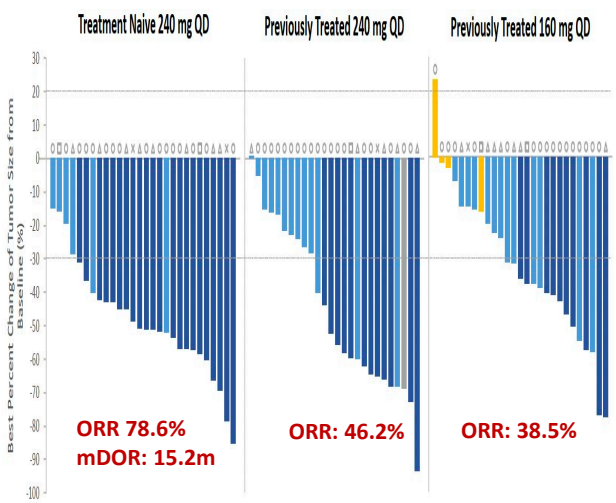
Best ORR, n (%)*	50 mg, n=3	100 mg, n=2	200 mg, n=21	300 mg, n=84	400 mg, n=9	Total, N=119
PR	0	1 (50.0)	10 (47.6)	44 (52.4)	2 (22.2)	57 (47.9)
PR, confirmed	0	1 (50.0)	7 (33.3)	32 (38.1)	2 (22.2)	42 (35.3)
PR, pending confirmation	0	0	2 (9.5)†	8 (9.5)†	0	10 (8.4)†
SD	2 (66.7)	1 (50.0)	9 (42.9)	35 (41.7)	5 (55.6)	52 (43.7)
PD	1 (33.3)	0	3 (14.3)	9 (10.7)	2 (22.2)	15 (12.6)

Tumour response was upon **investigator assessment** or **Independent Review Committee** according to RECIST 1.1§

NCT05607550
Sunvocertinib vs CT

Furmonertinib FAVOUR TRIAL

30 TxNaive p (12% BM)
56 previously treated (29-39% BM)



ORR 78.6%
mDOR: 15.2m

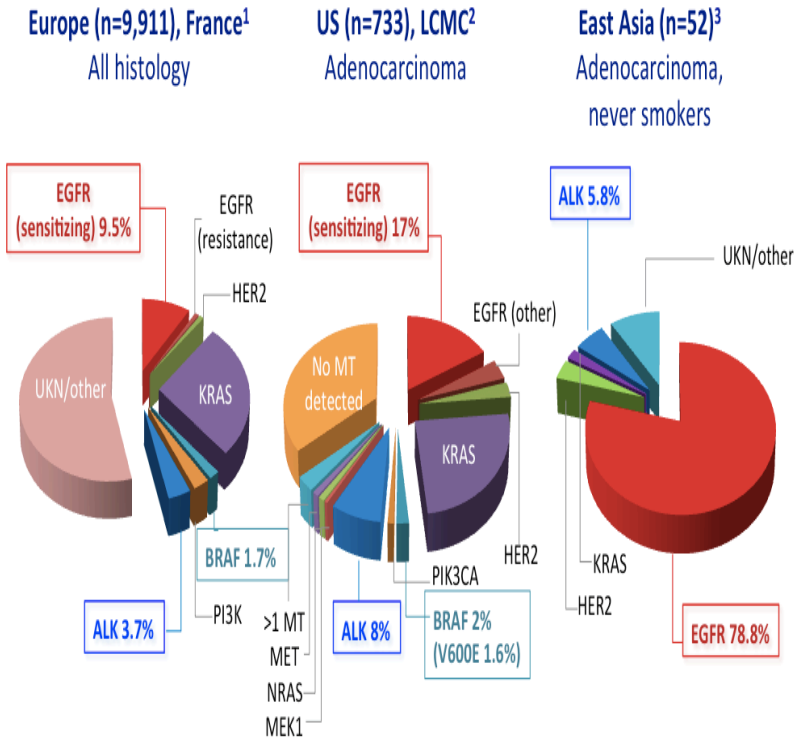
ORR: 46.2%

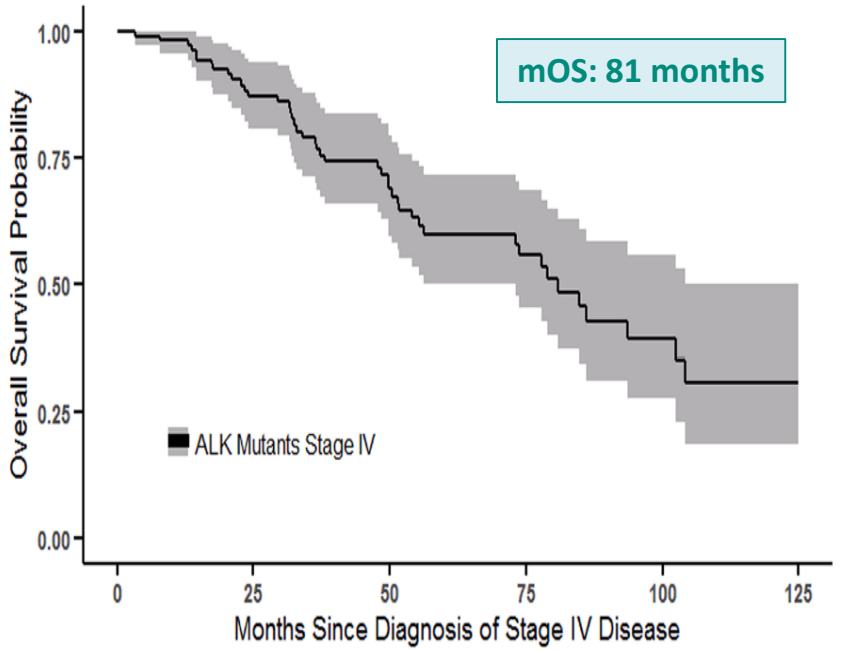
ORR: 38.5%

FURVENT/FURMO-004
Furmonertinib vs CT

Yu HA, et al. ASCO 2022; Yang et al. WCLC 2022, Hang WCLC 2023

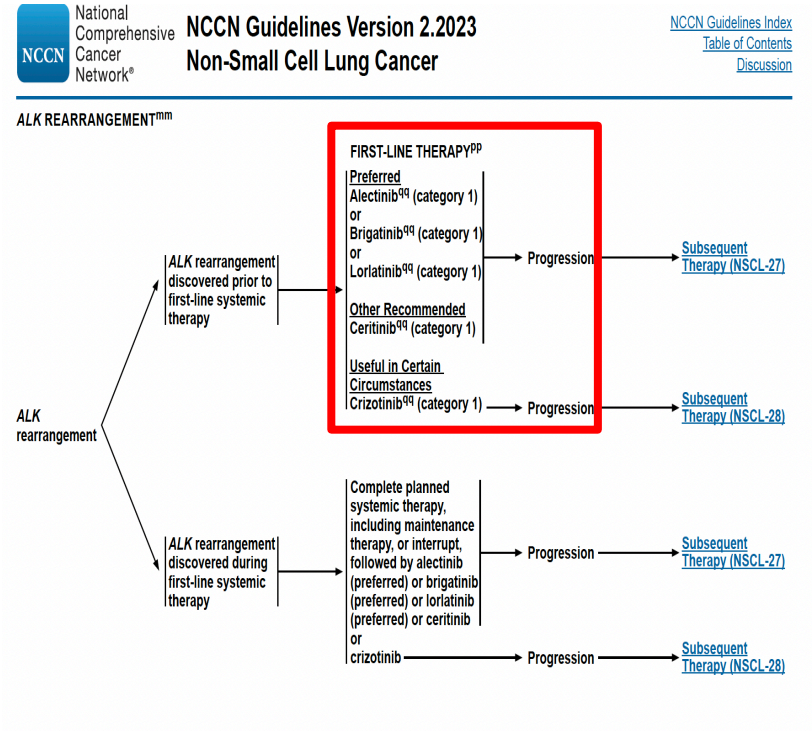
ALK prevalence in NSCLC

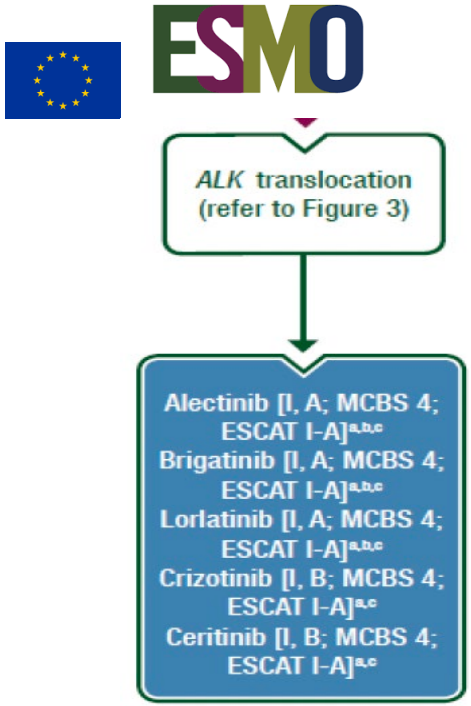




Barlesi – ASCO 2013 * Johnson ASCO 2013 * Sun JCO 2010 * Pacheco – JTO 2018

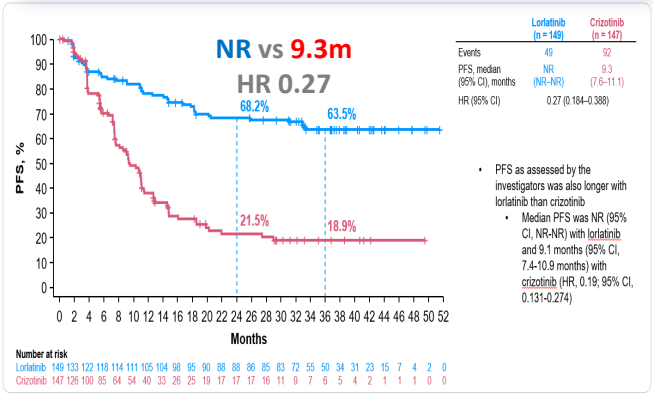
Guidelines (NCCN/ESMO)



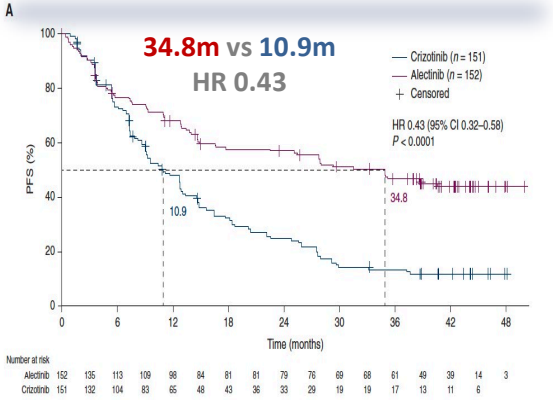


NCCN v 2.2023; Hendricks L, et al Ann Oncol 2023

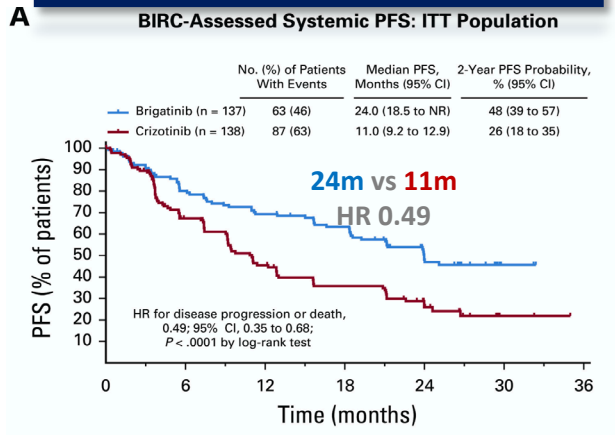
CROWN: Lorlatinib *vs.* crizotinib

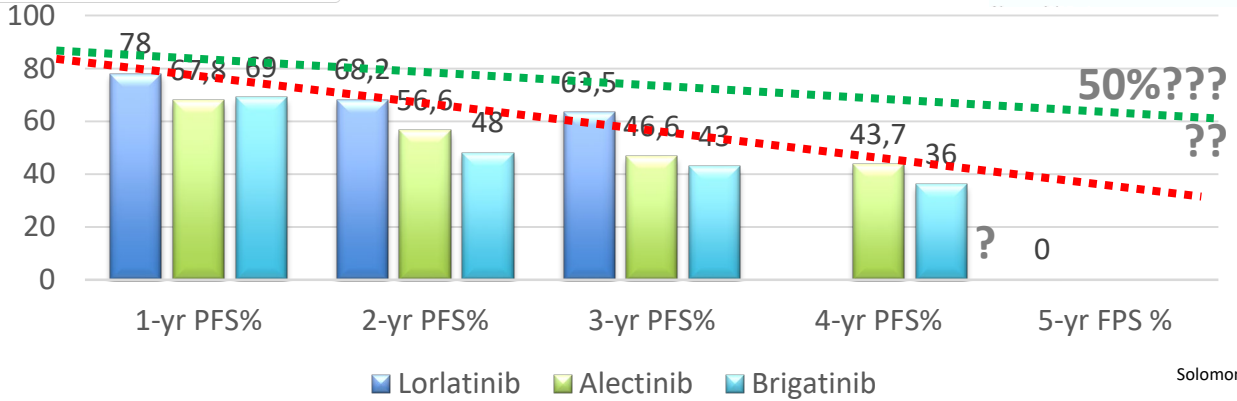


ALEX: Alectinib *vs.* Crizotinib



ALTA 1L: Brigatinib *vs.* Crizotinib





Solomon B, AACR 2022; Mok Ann Oncol 2020; Camidge J Clin Oncol 2022

Brain Efficacy Data: Phase III Trials

Intracranial Efficacy	ALTA-1L		ALEX		eXalt3		CROWN	
	Brigatinib	Crizotinib	Alectinib	Crizotinib	Ensartinib	Crizotinib	Lorlatinib	Crizotinib
Measurable brain metastases (N)	18	23	21	22	**11**	**19**	**18**	**13**
CNS ORR, % confirmed (95% CI)	78 (52-94)	26 (10-48)	NA	NA	64	21	83	23
CR, %	27.8	0	38.1	4.5	27	10	72.2	8
CNS DOR Median (95% CI)	27.9 (5.7-NR)	9.2 (3.9-9.2)	17.3 (14.8-NE)	5.5 (2.1-17.3)	Not reported	Not reported	NR	10.2 (9.4-11.1)
HR (95%CI) for PFS with any BM	0.24 (0.12-0.45)		0.37 (0.23-0.58)		**NR**		**0.20 (0.10-0.43)**	

Camidge DR, et al. ESMO Asia 2029. Abstract LBA1; Peters S, et al. *N Engl J Med*. 2017;377:829-838; Gadgeel S, et al. *Ann Oncol*. 2018;29:2214-2222; 3. Mok TSK, et al. ESMO 2019. Abstract 1484PD; Horn L, et al. WCLC 2020; Solomon B, et al. AACR 2022

Efficacy of ROS1-Directed TKI in TKI-naïve patients

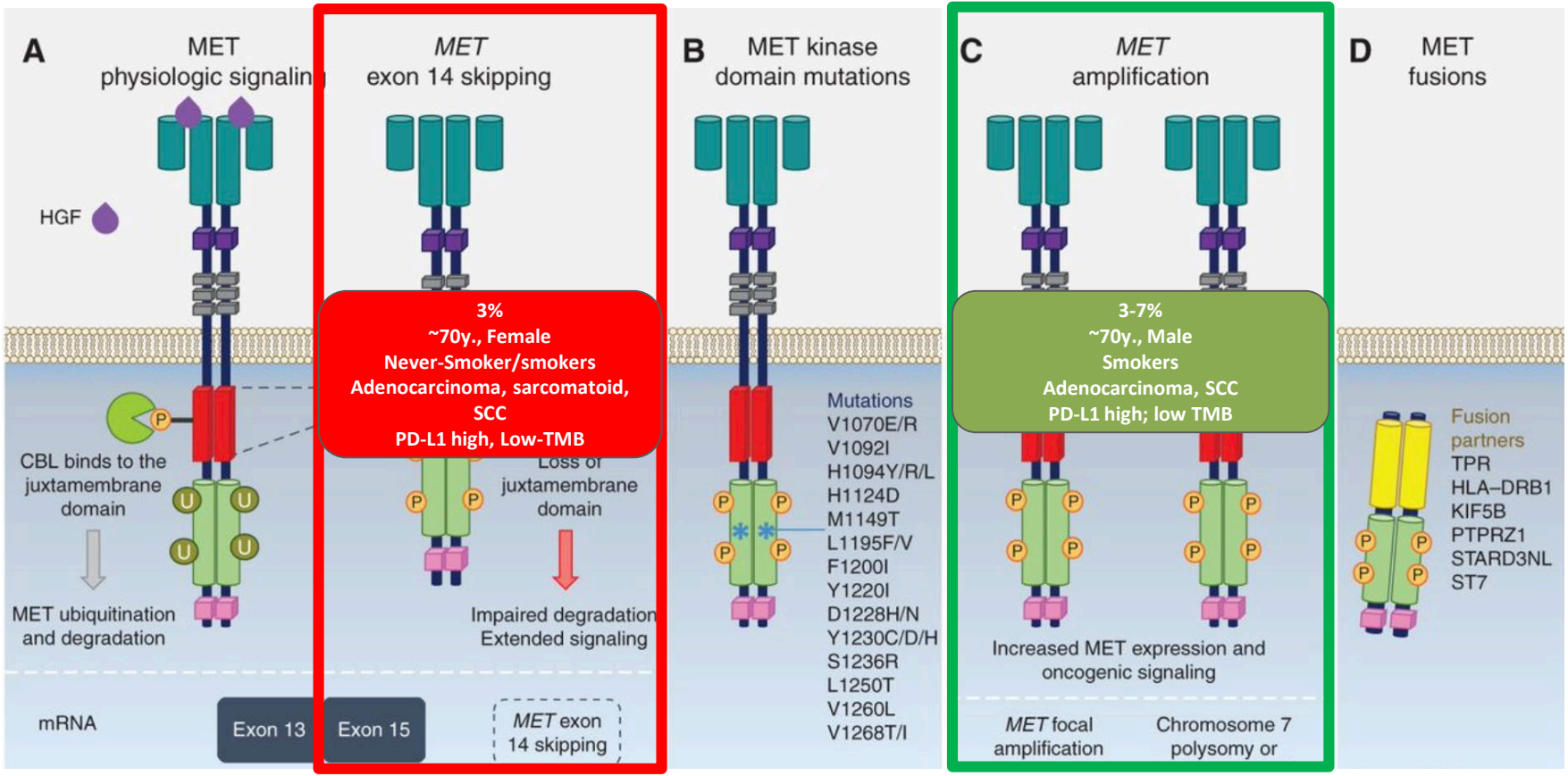
ROS-1 TKI	TRIAL	TKI-naïve (N)	ORR	mPFS mo	CNS RR
Crizotinib[1]	PROFILE 1001 Phase II (RP2D)	53	72%	19·3m	NA
Entrectinib[2]	ALKA-372-001 STARTRK-1/2 Phase I/II	168	68%	15.7m	52% patients with measurable and nonmesurable intracranial disease
Lorlatinib[3]	Global Phase I/II (EXP6)	21	62%	21m	64% patients with measurable and nonmesurable intracranial disease
Taletrectinib[4]	TRUST Chinese Phase II	67	93%	33.2	91.7% patients with baseline measurable CNS metastasis
Repotrectinib[5]	TRIDENT-1 Phase 1/2	71	79%	35.7	89% patients with measurable intracranial disease

1.-Alice T. Shaw et al. Annals of Oncol 2019; 2.--Drillon A. et al. CCR 2022;
3.- Shaw AT, et al. JCO 2021. 4- Li et al. ELCC 2023; 5- Cho et al. WCLC 2023

ROS1: Advances in Addressing Resistance with Next-Generation TKIs

	Lorlatinib (Phase 1/2)	Repotrectinib (TRIDENT-1 Phase 1/2)	Taletrectinib (TRUST China Phase 2)	NVL-520 (ARROS-1 Phase 1)
Patients	N=40	N=56	N=38	N=21
ORR	**35%** **(prior crizotinib)**	**38%** **(only 1 prior ROS1 TKI and no prior chemo)*** *FDA breakthrough therapy designation	**50%** **(prior crizotinib)*** *FDA breakthrough therapy designation	**48%** • **53% (9/17) with ≥2 prior ROS1 TKI, ≥1 chemo** • **50% (9/18) with prior lorlatinib or repotrectinib**
Median PFS	**8.5 months**	**9.0 months**	**9.8 months**	**Not reported**
CNS activity	12/24 (50%) with measurable or nonmeasurable CNS disease	5/13 (38%) with measurable CNS metastases	11/12 (92%) with measurable CNS metastases (TKI-naïve & crizotinib-pretreated)	CNS responses reported
Clinical ROS1 G2032R activity	Response in 0/6 **(0%)** patients with a baseline ROS1 G2032R in plasma	Responses in 10/17 (**59%**) patients with a baseline ROS1 G2032R	Responses in 4/5 (**80%**) patients with a baseline ROS1 G2032R	Responses in 7/9 (**78%**) patients with a baseline ROS1 G2032R
Most common TRAEs or TEAEs (all grades)	Hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy, cognitive/mood effects, weight increased	Dizziness, dysgeusia, constipation, paresthesia, dyspnea, anemia, fatigue, nausea, muscular weakness, ataxia	Diarrhea, nausea, vomiting, ALT increase, AST increase, anemia, neutrophil count decrease	No DLTs or treatment-related SAEs or dizziness reported
Reference	Shaw AT et al., Lancet Oncol 2019	Cho BC et al., WCLC 2023	Li W et al., ELCC 2023	Drilon A et al., EORTC-NCI-AACR 2022

MET aberrations in NSCLC



Recondo G, et al. Cancer Discovery 2020

TIMELINE FOR MET TARGETED DRUGS REGULATORY APPROVALS FOR ADVANCED NSCLC HARBORING METex14 MUTATIONS

2018

CRIZOTINIB

May 2018

2020

CAPMATINIB

May 2020

2021

TEPOTINIB

Feb 2021

SAVOLITINIB

June 2021

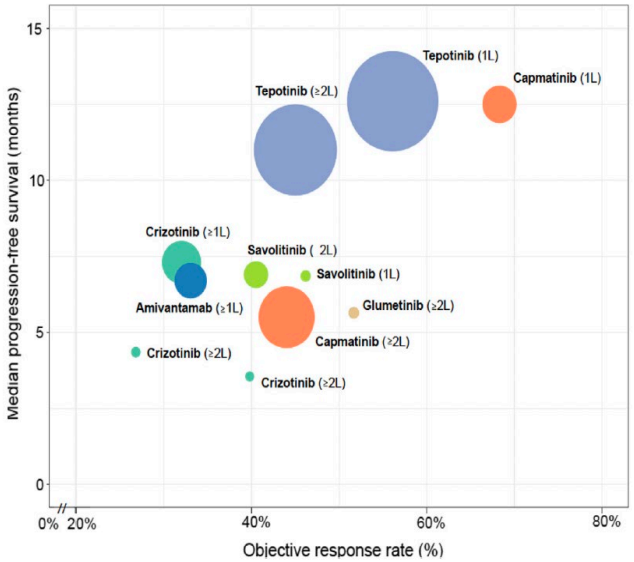
2022

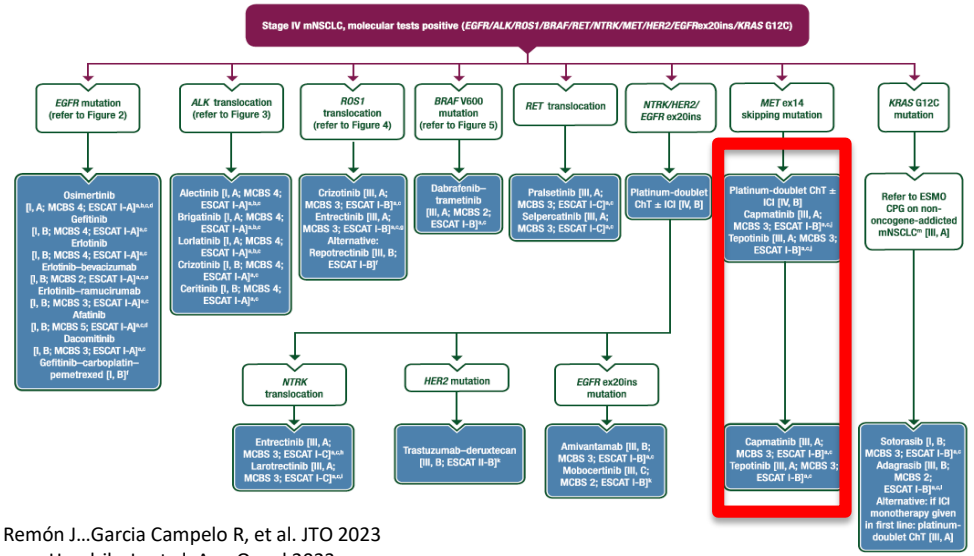
TEPOTINIB

Feb 2022

CAPMATINIB

April 2022





Remón J...Garcia Campelo R, et al. JTO 2023
Hendriks L, et al. Ann Oncol 2023

MET tyrosine kinase inhibitors

	Non-Selective		Selective TKI							
	CRIZOTINIB PROFILE 1001	ENSARTINIB	CAPMATINIB GEOMETRY Mono-1		TEPOTINIB VISION (A+C) (TBx)		SAVOLITINIB		GLUMETINIB GLORY	
IC_{50} (nM)	26,5	7.9	0.6		3.0		2.1		0.42	
Dose	250 mg BID	225 mg QD	400 mg BID		500 mg QD		400-600 mg QD		300 mg QD	
Line	≥1	1	1	≥2	1	≥2	1	≥2	1	≥2
N	69	29	60	100	111	97	28	42	46	38
RR (%)	32	67	68.3	44	56.8	49.5	46.4	40.5	71	60
DoR (mo.)	9.1	6.8	16.6	9.7	46.4	10.2	5.6	9.7	15.0	8.2
PFS (mo.)	7.3	6.1	12.5	5.5	15.3	11.5	6.9	6.9	11.7	7.6
OS (mo.)	20.5	NR	25.5	13.6	25.9	20.4	10.9	19.4	NE	16.2
Comments	Shorter PFS in ctDNA positive at baseline	Better intracranial activity than crizotinib	Higher activity in 1st *vs.* ≥2nd line		The RR regardless Age, line & type of previous therapy		Sarcom. *vs.* others RR: 40% *vs.* 44% PFS: 5.5 *vs.* 6.9		Higher activity in 1st *vs.* ≥2nd line	

2022 2022 (2nd) 2021 2021 (2nd) 2021

Drilon –Nature Med 2020 * Xia – Cancer Letter 2023 * Wolf –ELCC 2022 * Wolf – ASCO 2021 * Thomas – WCLC 2022 * Lu – Lancet Resp Med 2021 * Lu – ELCC 2022 * Yu– eClinicalMedicine 2023

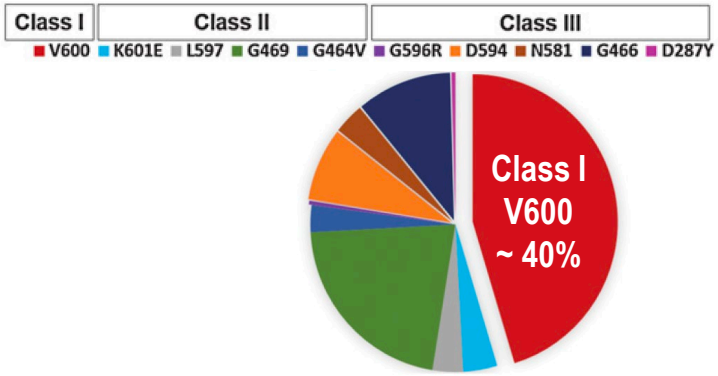
Slide Courtesy J. Remón

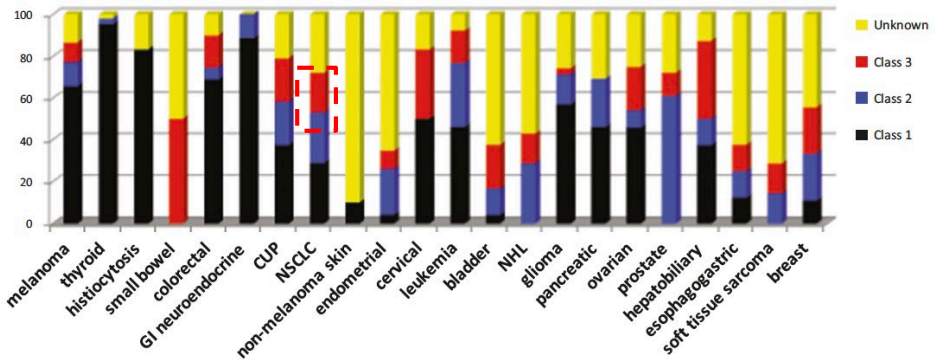
BRAF
Epidemiology & Clinical Profile

- BRAF mutations are found in **~ 4%** of NSCLC
- BRAF Class I (V600) comprise **~2%** NSCLC

BRAF V600 mutations are reported in about 2% of patients with advanced NSCLCs

AGE				
~60-70 years	Equal gender distribution	Smokers and non-smokers (never 20-30%)	More frequent in adenocarcinoma (less frequent squamous and large cell carcinoma)	High PD-L1 Low-intermediate TMB





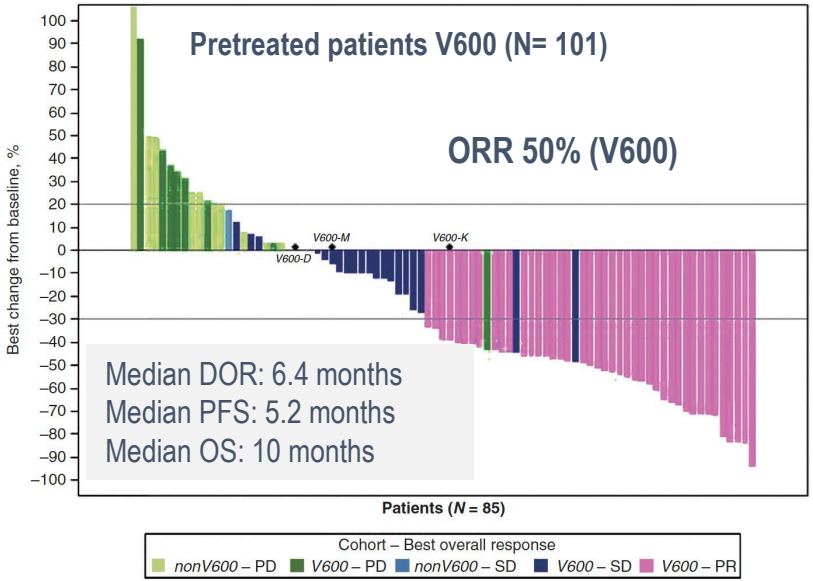
1.- Chevallier M, et al. World J Clin Oncol. 2021; 2.-Dagogo-Jack I., et al. Clin Cancer Res 2019; 3.- Dankner M ., et al. Oncogene 2018

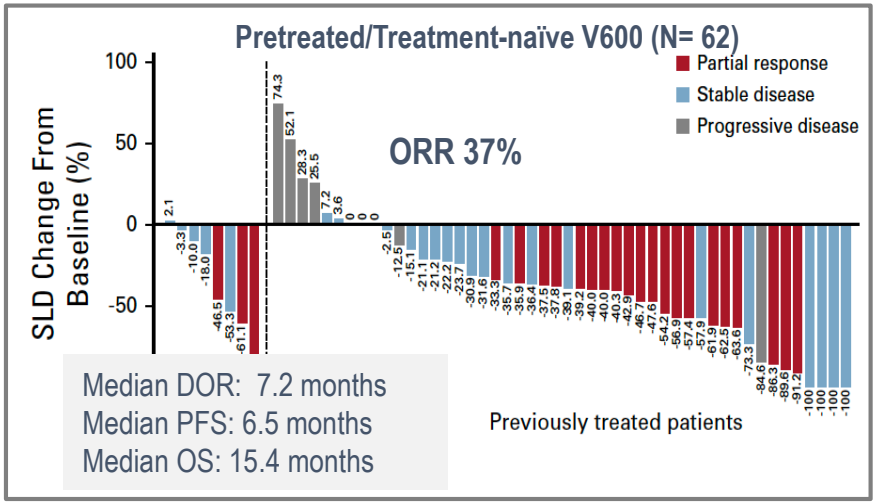
THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

AcSé

VE-BASKET

- **Strategy 1: BRAF "monomer" inhibitor — Vemurafenib (AcSé ,VE-BASKET)**





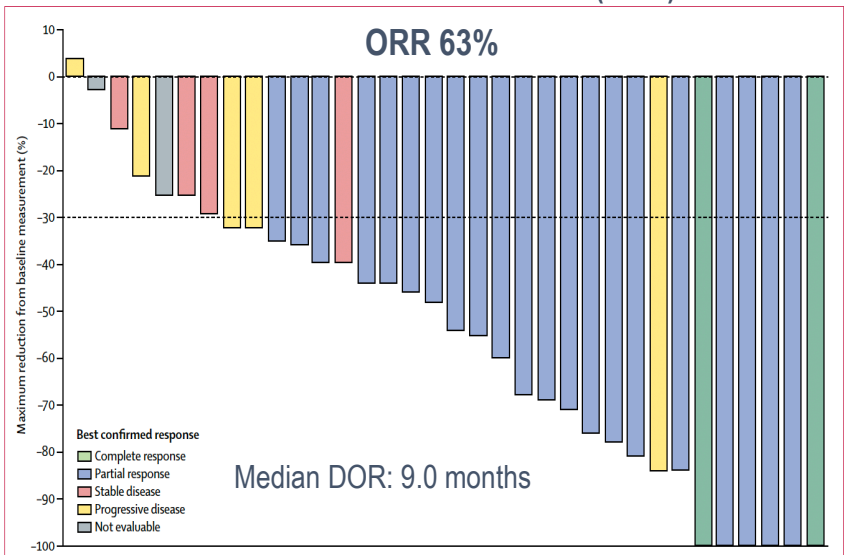
Mazieres J. et. al., Annals of Oncology 2020; Subbiah V et al., JCOPO 2019

THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

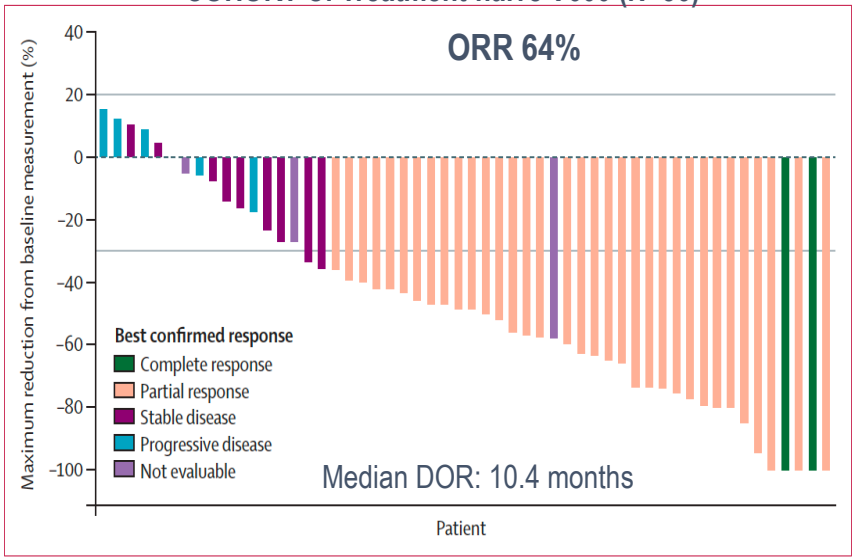
Strategy 2: Double BRAF/MEK Blockade — Dabrafenib + Trametinib (BRF 113928, Phase 2 Trial)

Dabrafenib 150 mg BID + Trametinib 2 mg QD

COHORT B: Pretreated V600 (N=57)



COHORT C: Treatment-naïve V600 (N=36)



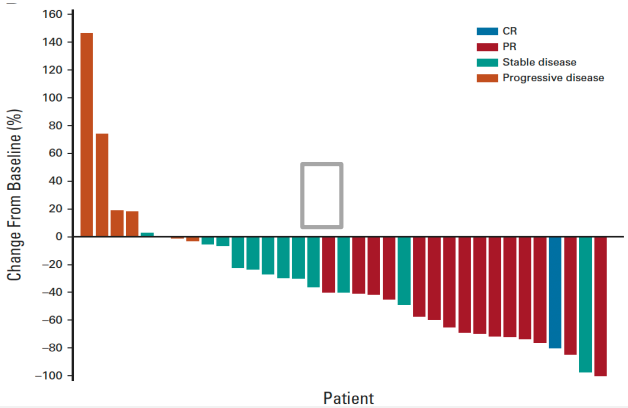
Planchard D., et al, Lancet Oncol 2016; Planchard D., et al, Lancet Oncol 2017

THERAPEUTIC TARGETING OF CLASS I BRAF MUTATIONS (V600E)

NEW COMBOS — Encorafenib + Binimetinib (PHAROS Trial)

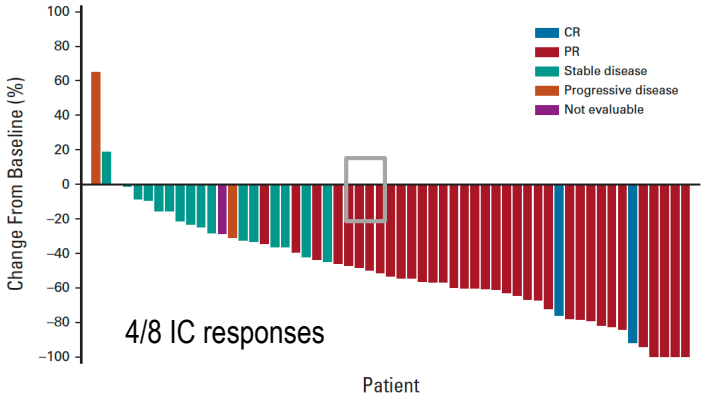
Encorafenib 450 mg QD + Binimetinib 45 mg BID

Pretreated V600 (N=39)



ORR 46%
Median DOR: 9.0 months
Median PFS: 9.3 months
Median OS: NE

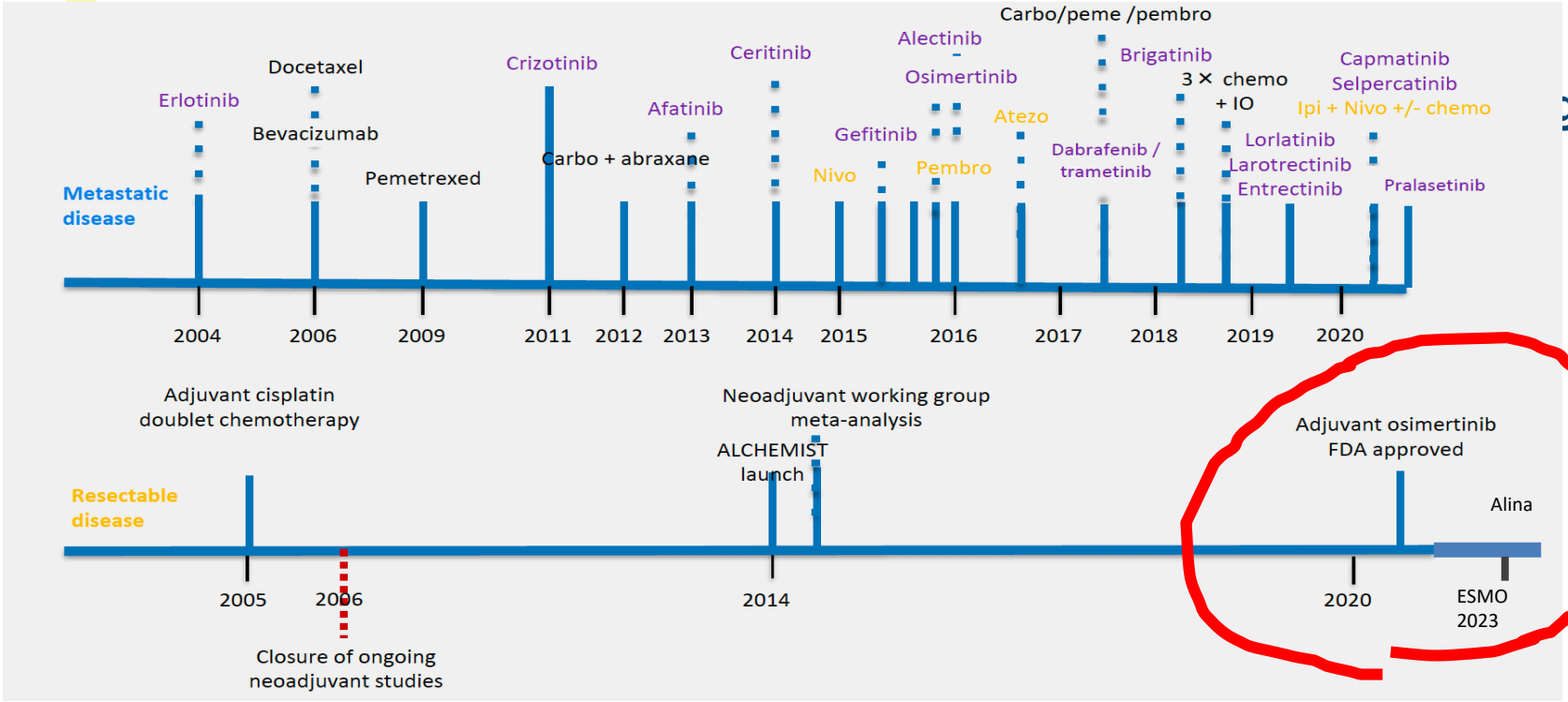
Treatment-naïve V600 (N=59)



ORR 75%
Median DOR: 10.4 months
Median PFS: NE
Median OS: NE

Riely GJ et al ASCO 2023; Riely GJ et al JCO 2023

ges…


Metastatic disease
Erlotinib
Docetaxel
Bevacizumab
Pemetrexed
Crizotinib
Carbo + abraxane
Afatinib
Ceritinib
Nivo
Gefitinib
Alectinib
Osimertinib
Pembro
Atezo
Carbo/peme /pembro
Dabrafenib / trametinib
Brigatinib
3 × chemo + IO
Lorlatinib
Larotrectinib
Entrectinib
Capmatinib
Selpercatinib
Ipi + Nivo +/- chemo
Pralasetinib
2004
2006
2009
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Resectable disease
Adjuvant cisplatin doublet chemotherapy
Neoadjuvant working group meta-analysis
ALCHEMIST launch
Adjuvant osimertinib FDA approved
Alina
2005
2006
2014
2020
ESMO 2023
Closure of ongoing neoadjuvant studies

ADAURA

18 Dec 2020 26 Apr 2021 1 Dec 2022

Objectives

Updated results of the Phase 3 ADAURA trial, exploring adjuvant osimertinib therapy vs placebo. Reported here are updated exploratory analyses of DFS, recurrence patterns, and safety after 2 years added follow-up.

ADAURA study design

Key eligibility criteria

- Patients with completely* resected stage IB – IIIA *EGFR*-mutant (exon19del/L858R[†]) NS-NSCLC
- With or without adjuvant chemotherapy[‡]
- WHO performance status 0/1
- 10 (adjuvant chemotherapy) and 26 (no adjuvant chemo) weeks maximum interval between surgery and randomisation

Osimertinib 18 mg OD

Randomisation 1:1 (N=682)

Placebo OD

Primary endpoint: DFS by investigator assessment in stage II/IIIA patients

Secondary endpoints: DFS in overall population[§], DFS at 2, 3, 4, and 5 years, OS, safety, health-related QoL

Pre-specified exploratory endpoints: Patterns of recurrence, CNS DFS

Baseline characteristics

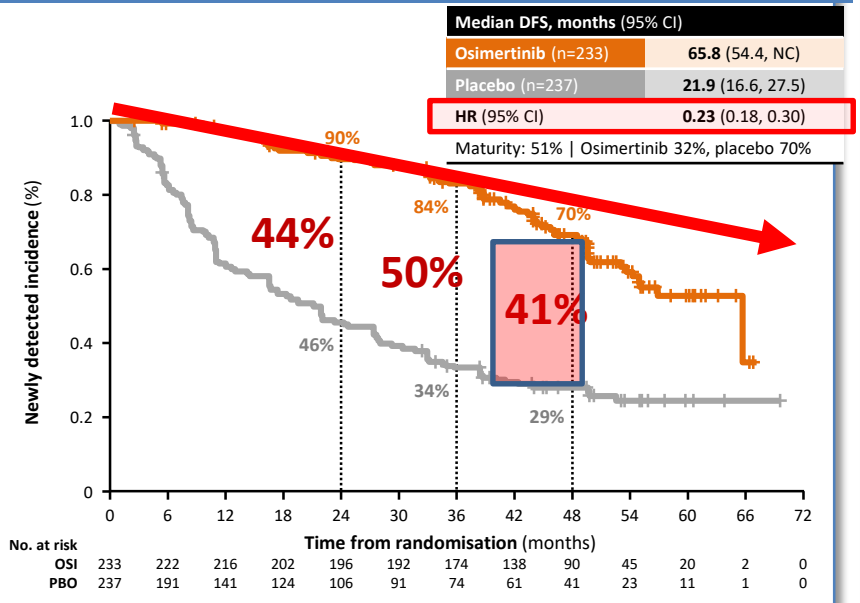
	Osi (n=339) (%)	Placebo (n=343) (%)
Sex: male / female	32 / 68	28 / 72
Age: median (range), **years**	64 (30–86)	62 (31–82)
Smoking history: yes[||] / no	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	63 / 37	64 / 36
AJCC/UICC staging at diagnosis (7th edition): **IA / IB / II / IIIA / IIIB**	1 / 32 / 33 / 35 / 0	0 / 31 / 34 / 35 / 0
Histology: Adenocarcinoma/other	96 / 4	97 / 3
***EGFR* mutation at randomisation: exon19del / L859R**	55 / 45	55 / 45
Adjuvant chemo: yes / no	60 / 40	60 / 40

At baseline 50% had brain MRI, 50% had brain CT but the % of PET is unknown

Tsuboi M, et al. ESMO 2022

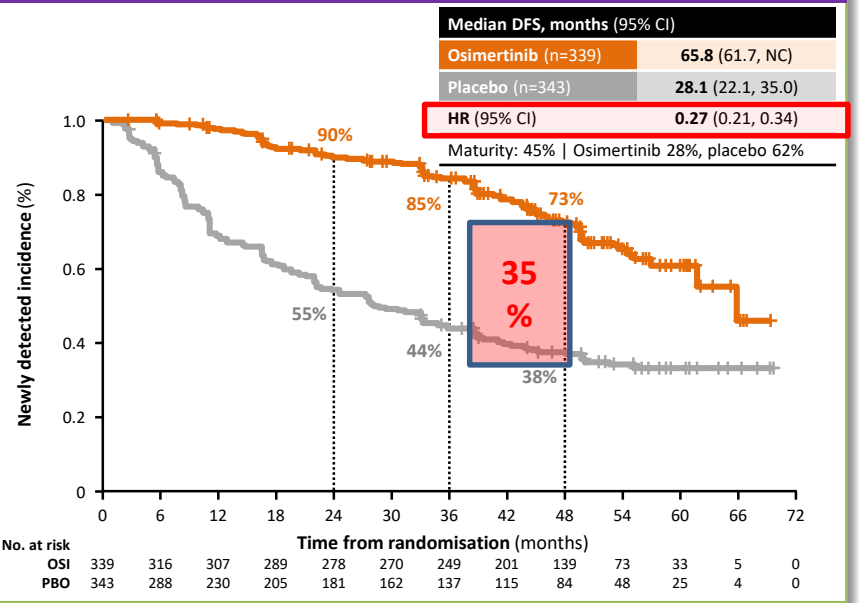
Updated DFS in stage II / IIIA population and overall population

Updated DFS in stage II / IIIA disease*† (primary endpoint)



77% reduction in risk of **disease recurrence** or **death** in **stage II / IIIA** population

Updated DFS in stage IB / II / IIIA disease*§ (overall population)

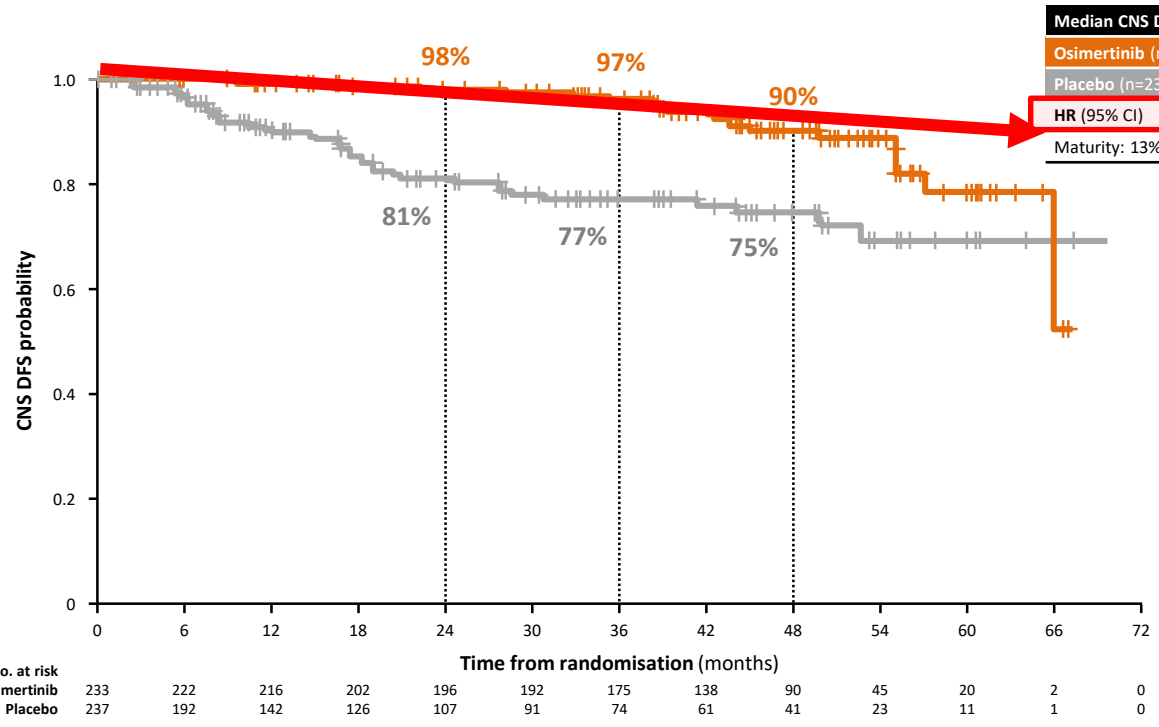


73% reduction in risk of **disease recurrence** or **death** in **overall population**

Tsuboi M, et al. ESMO 2022

Updated CNS DFS

Updated CNS DFS in stage II / IIIA disease†



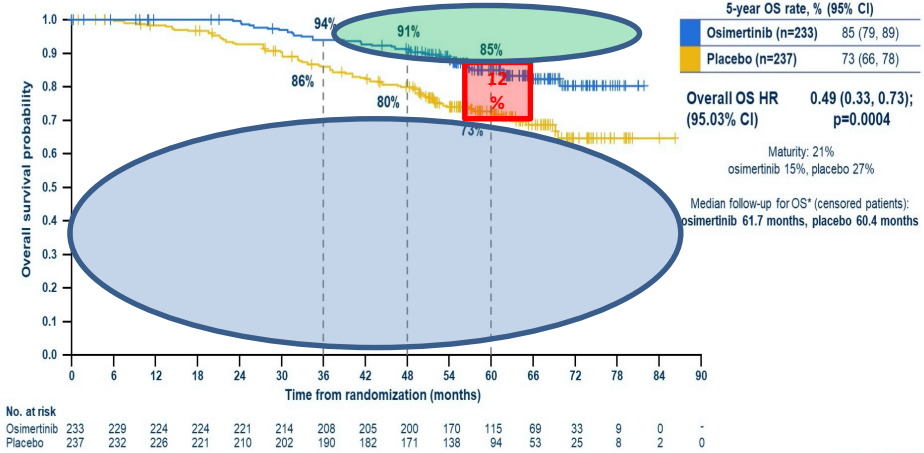
- Overall, 63 patients had CNS DFS events:
  - Osimertinib n=22
  - Placebo n=41
- Adjuvant osimertinib therapy demonstrated a **76% reduction** in risk of **CNS recurrence** or **death** vs placebo in patients with **stage II / IIIA** disease

Tsuboi M, et al. ESMO 2022

ADAURA…FINALLY WE HAVE OS DATA

Overall survival: patients with stage II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)
Overall OS HR (95.03% CI)	0.49 (0.33, 0.73); p=0.0004

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

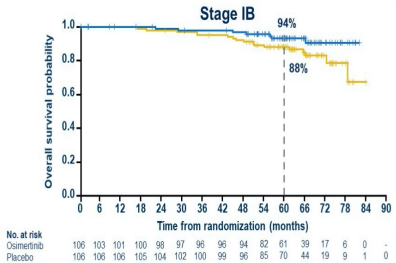
Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.

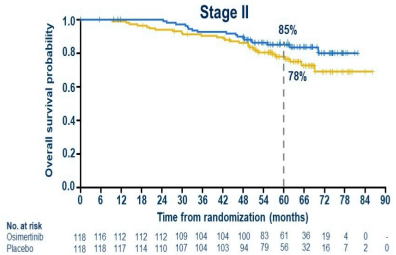
CI, confidence interval; HR, hazard ratio; OS, overall survival

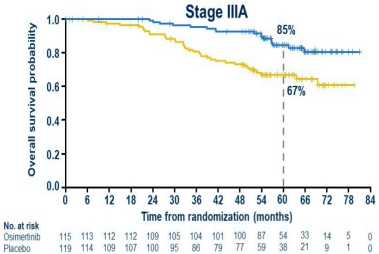
2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Roy S. Herbst

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Overall survival by disease stage







5 year OS rate, % (95% CI)	Stage IB	Stage II	Stage IIIA
Osimertinib	94 (86, 97)	85 (77, 91)	85 (76, 91)
Placebo	88 (80, 93)	78 (69, 85)	67 (57, 75)
Overall HR (95% CI)	0.44 (0.17, 1.02)	0.63 (0.34, 1.12)	0.37 (0.20, 0.64)

Data cut-off: January 27, 2023. Tick marks indicate censored data.
CI, confidence interval; HR, hazard ratio; OS, overall survival

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Roy S. Herbst

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Only 38.5% in placebo arm received Osi at progresssion

Herbst R, et al. ASCO 2023

ALINA

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → Recurrence

Platinum-based chemotherapy† Q3W; 4 cycles → Recurrence

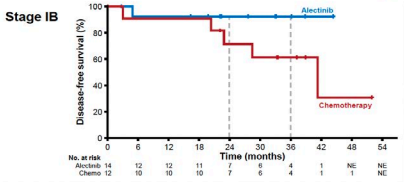
Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

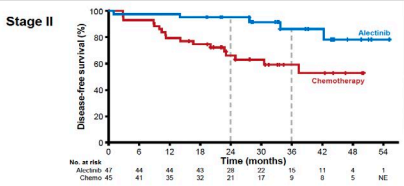
Other endpoints
- CNS disease-free survival
- OS
- Safety

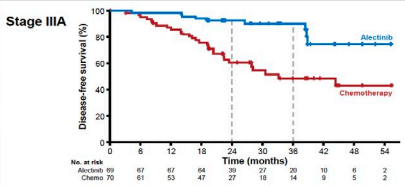
Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Disease-free survival by stage*

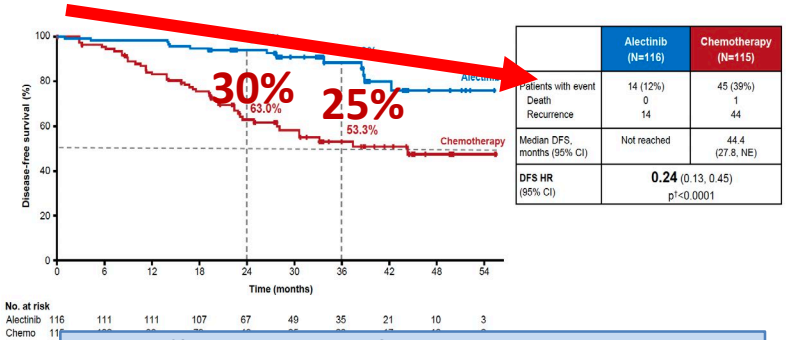


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)





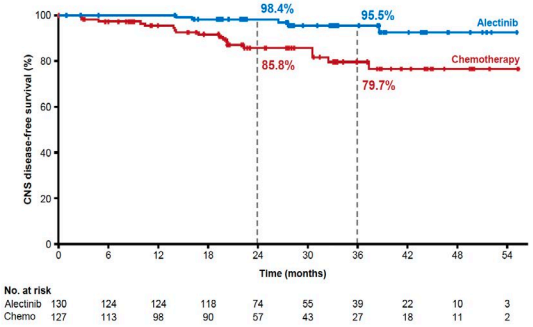
Disease-free survival: stage II–IIIA*



	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	0.24 (0.13, 0.45) p†<0.0001	

76% reduction in risk of **disease recurrence** or **death** in **stage II / IIIA** population

CNS disease-free survival in the ITT population



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Brain recurrence	5 1 4	18 4 14
CNS-DFS HR* (95% CI)	0.22 (0.08, 0.58)	

Solomon B, et al ESMO 2023

IN SUMMARY…

- New and more potents TKI and new drugs with new MoA: we are increasing the “arsenal”, but still far from curing…
- The major limitation: tumor/ plasma genotyping, drug access…
- Personalized medicine has arrived to early stages: ADAURA and ALINA
- Personalized treatment in oncogenic addicted NSCLC at baseline and at PD… how to build the sequencing approach