Targeted Therapy in NSCLC

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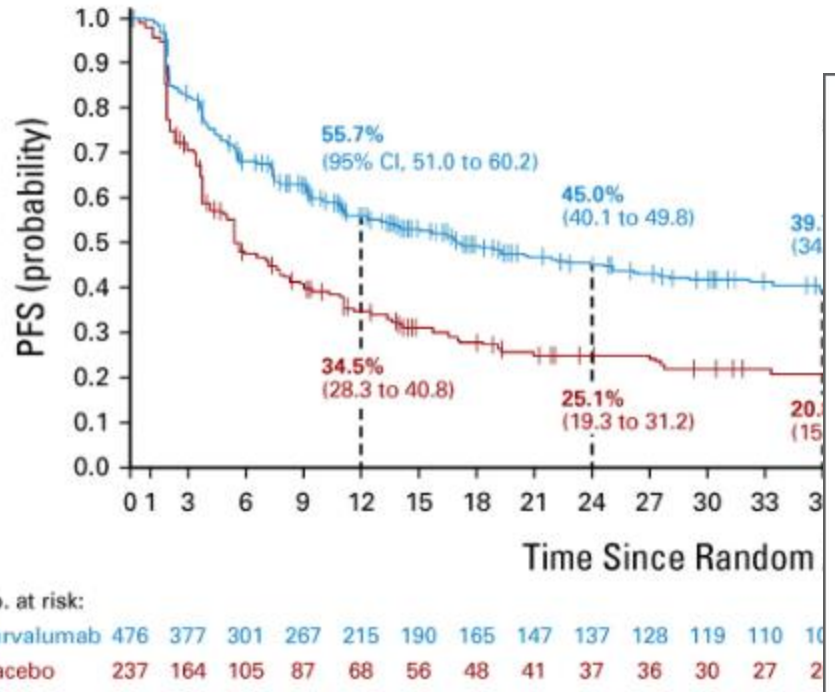
Outline

- EGFR common mutations
  - Stage III & IV: 1st line treatment options
  - 2nd line treatment options
- EGFR exon 20 insertions: 1st and 2nd line treatments
- ALK fusions: 1st line treatment
- ROS1 fusions: 2nd line treatment
- HER2 overexpression: 2nd line treatment

Unresectable stage III NSCLC with *EGFR* mut
until June/2024



Arm	No. of Events/ Total No. of Patients (%)	Median PFS (95% CI), Months
Durvalumab	268/476 (56.3)	16.9 (13.0 to 23.9)
Placebo	175/237 (73.8)	5.6 (4.8 to 7.7)

Subgroup	Durvalumab	Placebo	Unstratified Hazard Ratio for Disease Progression or Death (95% CI)
	no. of patients		
All patients	476	237	0.55 (0.45–0.68)
Sex			
Male	334	166	0.56 (0.44–0.71)
Female	142	71	0.54 (0.37–0.79)
Age at randomization			
<65 yr	261	130	0.43 (0.32–0.57)
≥65 yr	215	107	0.74 (0.54–1.01)
Smoking status			
Smoker	433	216	0.59 (0.47–0.73)
Nonsmoker	43	21	0.29 (0.15–0.57)
NSCLC disease stage			
IIIA	252	125	0.53 (0.40–0.71)
IIIB	212	107	0.59 (0.44–0.80)
Tumor histologic type			
Squamous	224	102	0.68 (0.50–0.92)
Nonsquamous	252	135	0.45 (0.33–0.59)
Best response			
Complete response	9	7	—
Partial response	232	111	0.55 (0.41–0.75)
Stable disease	222	114	0.55 (0.41–0.74)
PD-L1 status			
≥25%	115	44	0.41 (0.26–0.65)
<25%	187	105	0.59 (0.43–0.82)
Unknown	174	88	0.59 (0.42–0.83)
EGFR mutation			
Positive	29	14	0.76 (0.35–1.64)
Negative	315	165	0.47 (0.36–0.60)
Unknown	132	58	0.79 (0.52–1.20)

https://ascopubs.org/doi/full/10.1200/JCO.21.01308
https://www.nejm.org/doi/full/10.1056/NEJMoa1709937

What is new?
ASCO 2024

LAURA

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

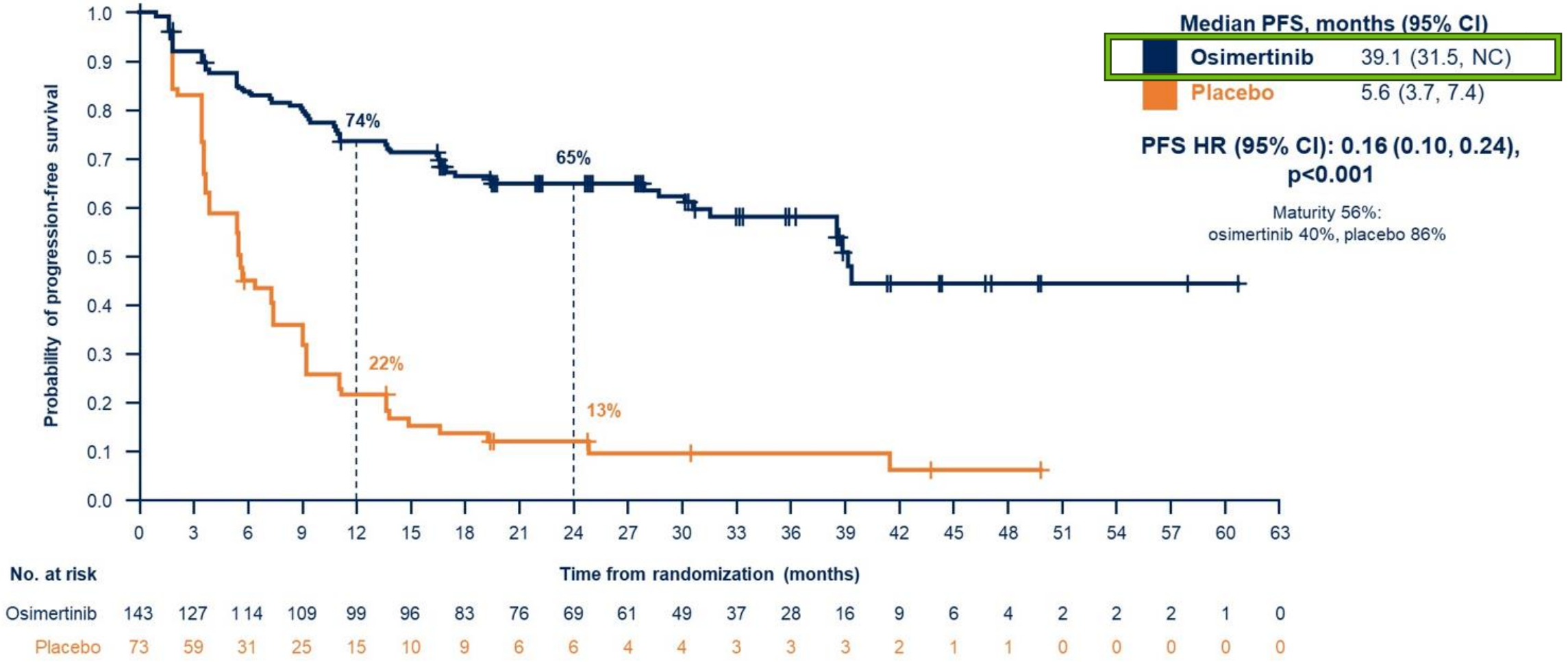
Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Endpoints
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

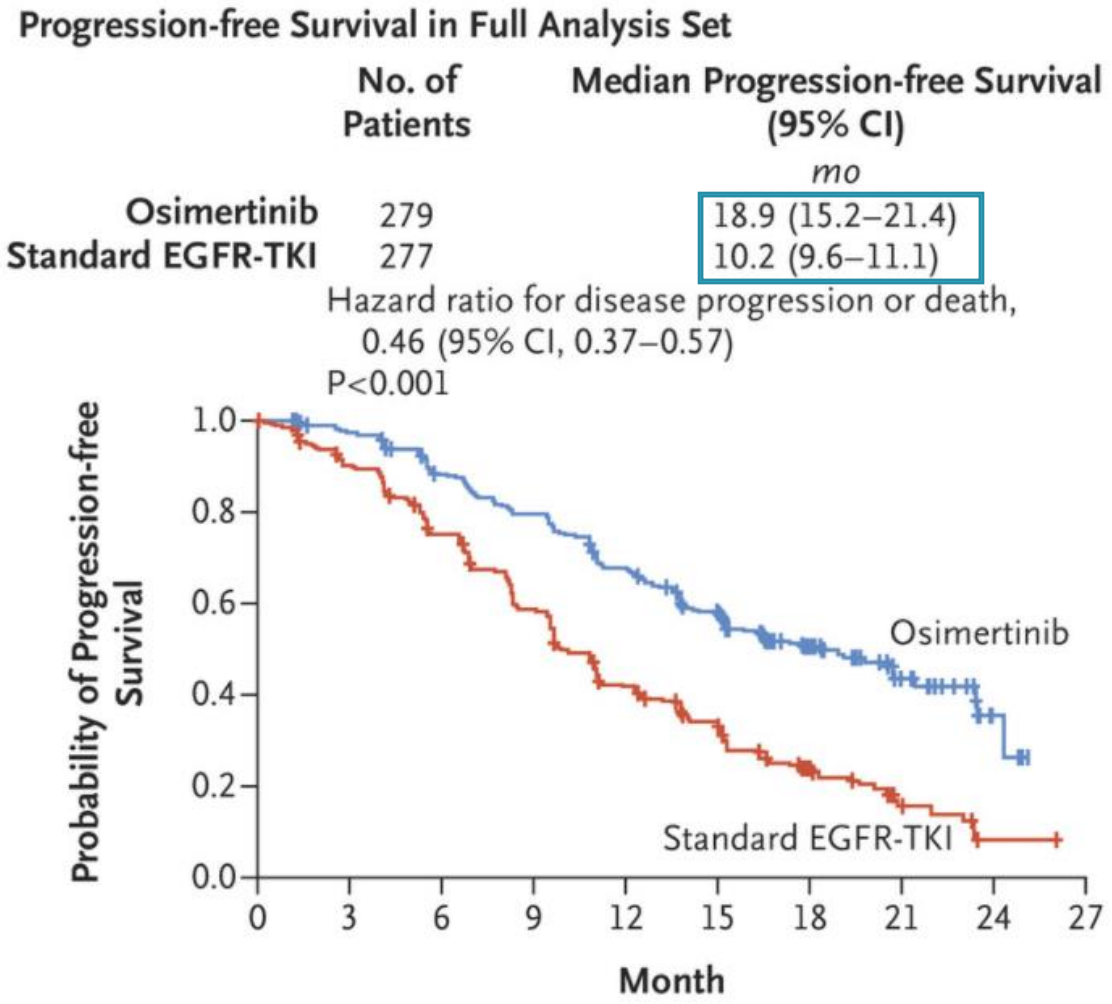
Presented by Ramalingam S et al, ASCO 2024

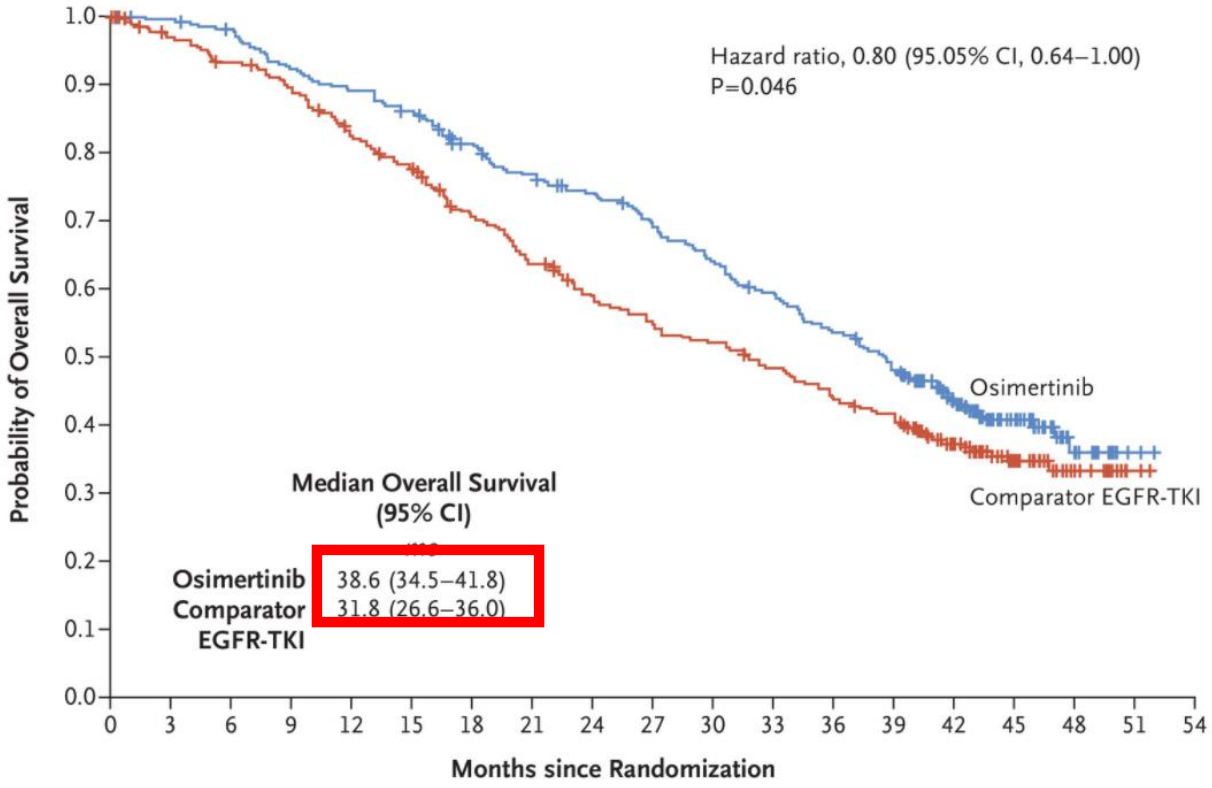
What is new?
ASCO 2024



Presented by Ramalingam S et al, ASCO 2024

EGFR typical mutations (FLAURA)
until~September/2023

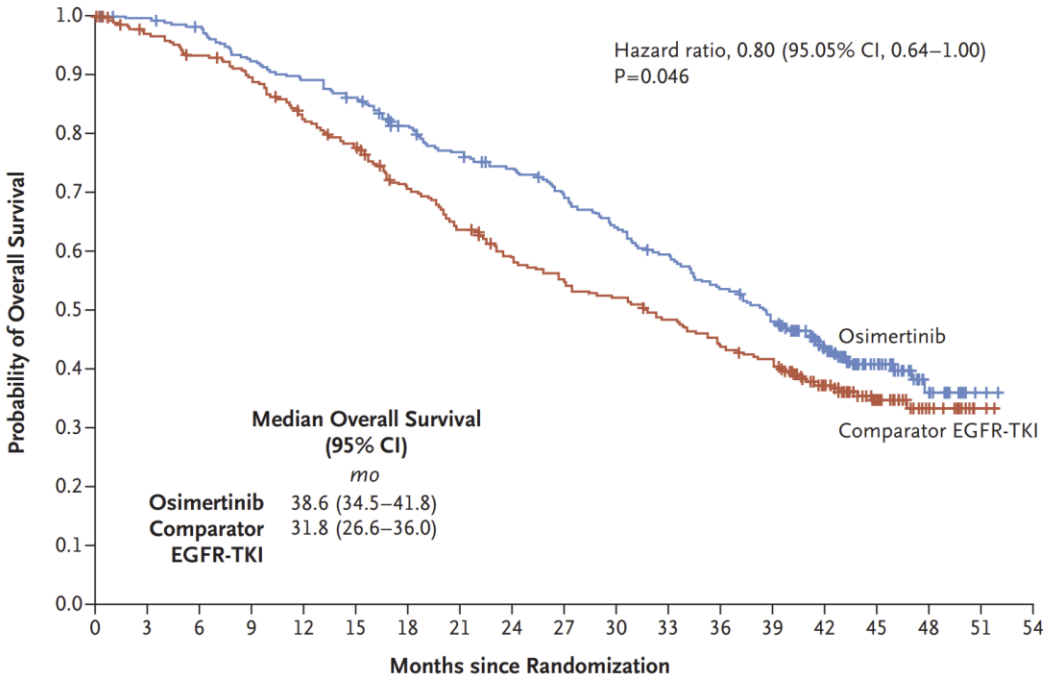




Soria JC. N Engl J Med. 2018
Ramalingam SS,. N Engl J Med. 2020
Piotrowska Z. JAMA Oncol. 2016

ESMO 2023

FLAURA: Osimertinib > 1st Gen TKI



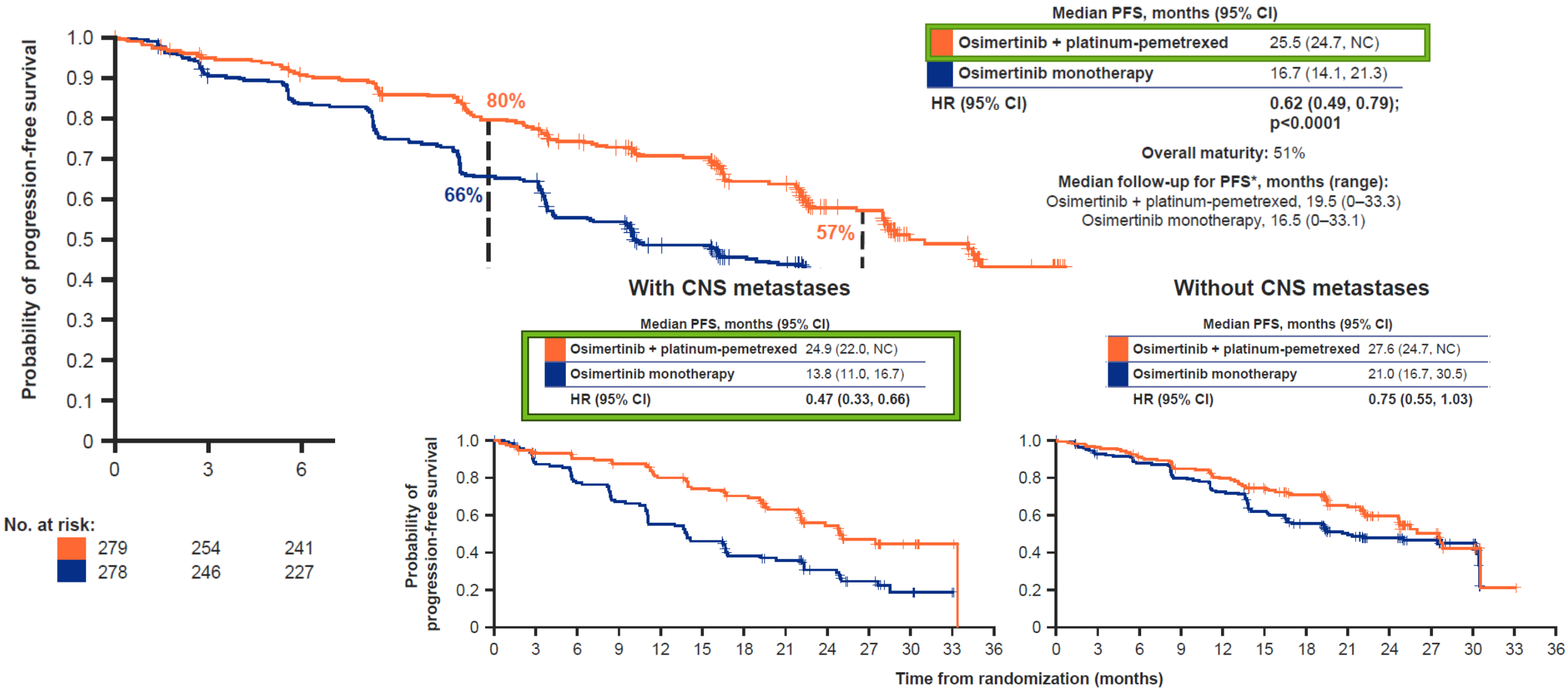
Soria et al NEJM 2018

1L Treatment of EGFRm NSCLC ~November 2023

+Chemo	**FLAURA2:** Osimertinib + Chemotherapy > Osimertinib
+EGFR/MET mAb	**MARIPOSA:** Amivantamab + Lazertinib > Osimertinib or Lazertinib
+VEGF	**RAMOSE:** Osimertinib + anti-VEGFR

Slide courtesy from Dr. Julia Rotow. NY Lung 2023.

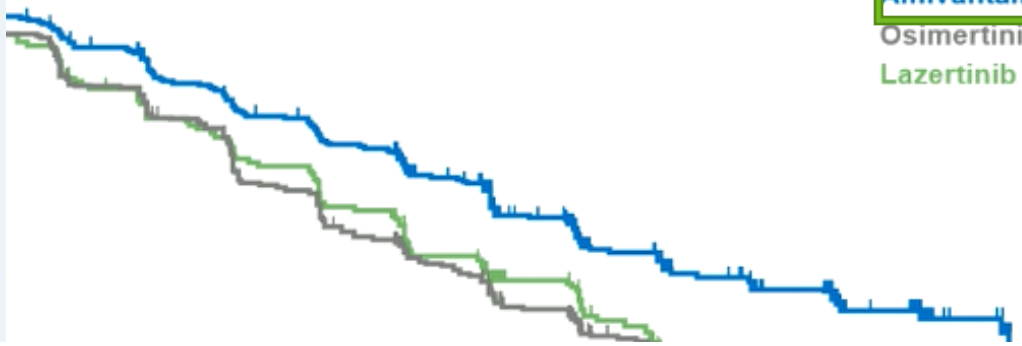
FLAURA2: PFS per Investigator



Slide courtesy from Dr. J

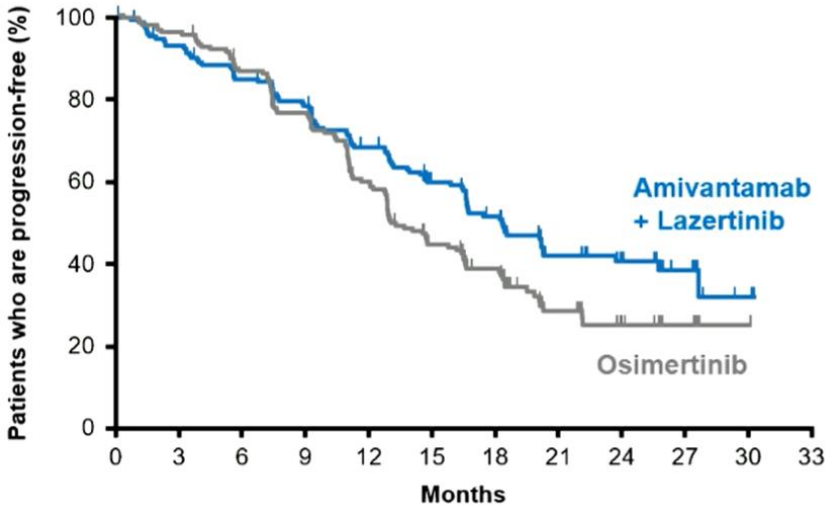
MARIPOSA: PFS by BICR

Median follow-up: 22.0 months	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)
Lazertinib	18.5 mo (14.8–20.1)



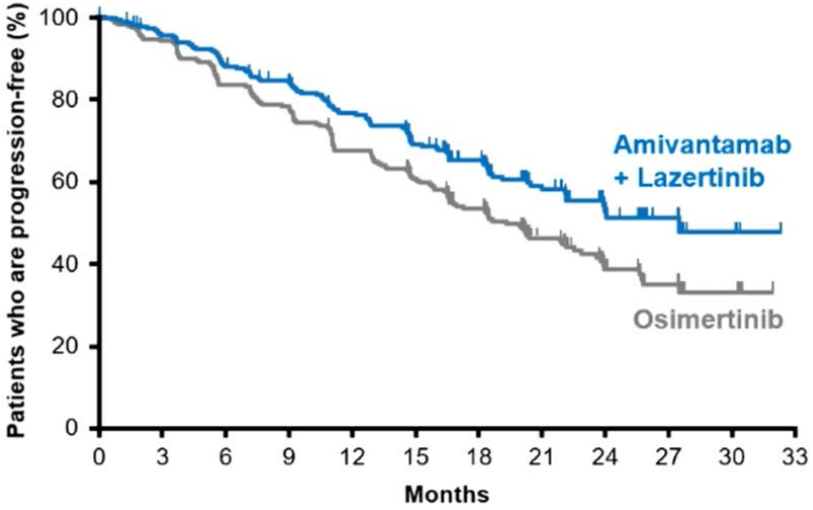
With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



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)

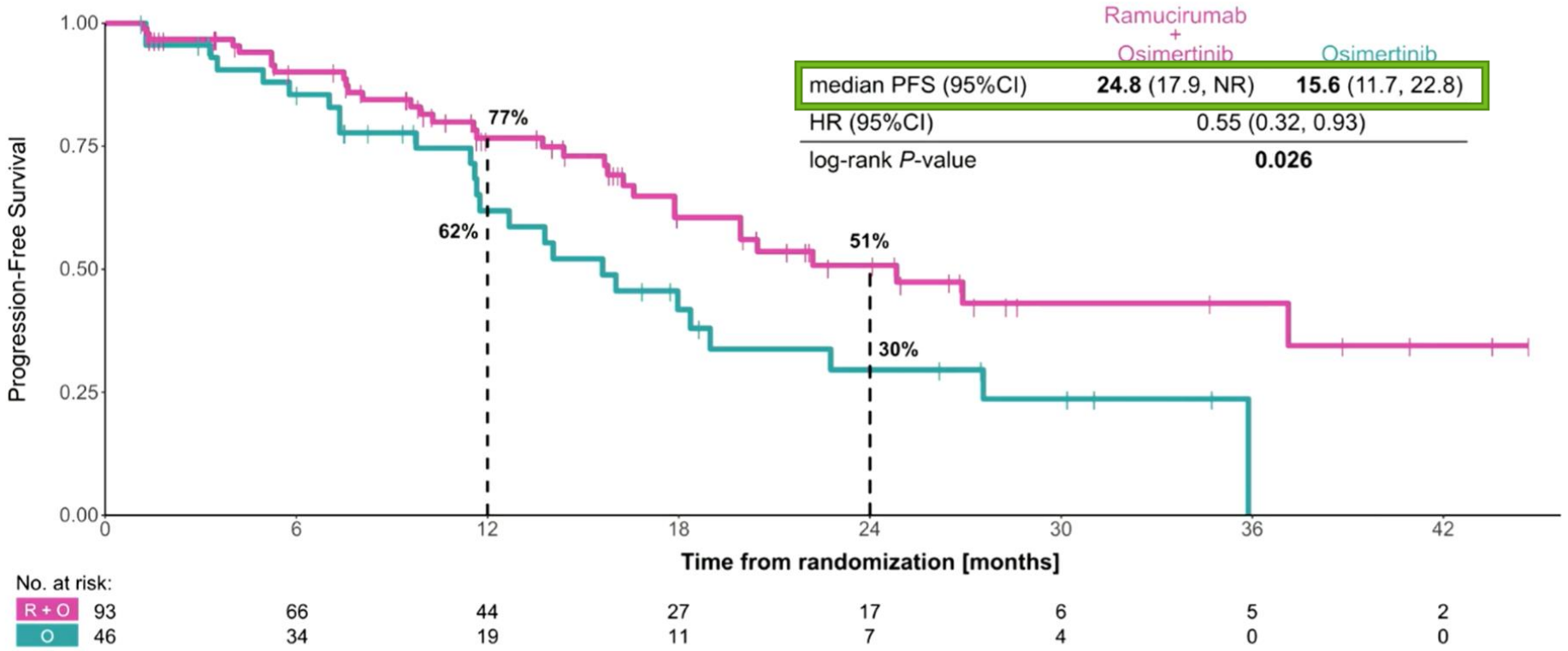


No. at risk			
ıantamab + Lazertinib	429	391	3
Osimertinib	429	404	3
Lazertinib	216	200	1

Slide courtesy from Dr. Ju

RAMOSE: Osimertinib +/- Ramucirumab

Progression-free survival by investigator (primary endpoint)

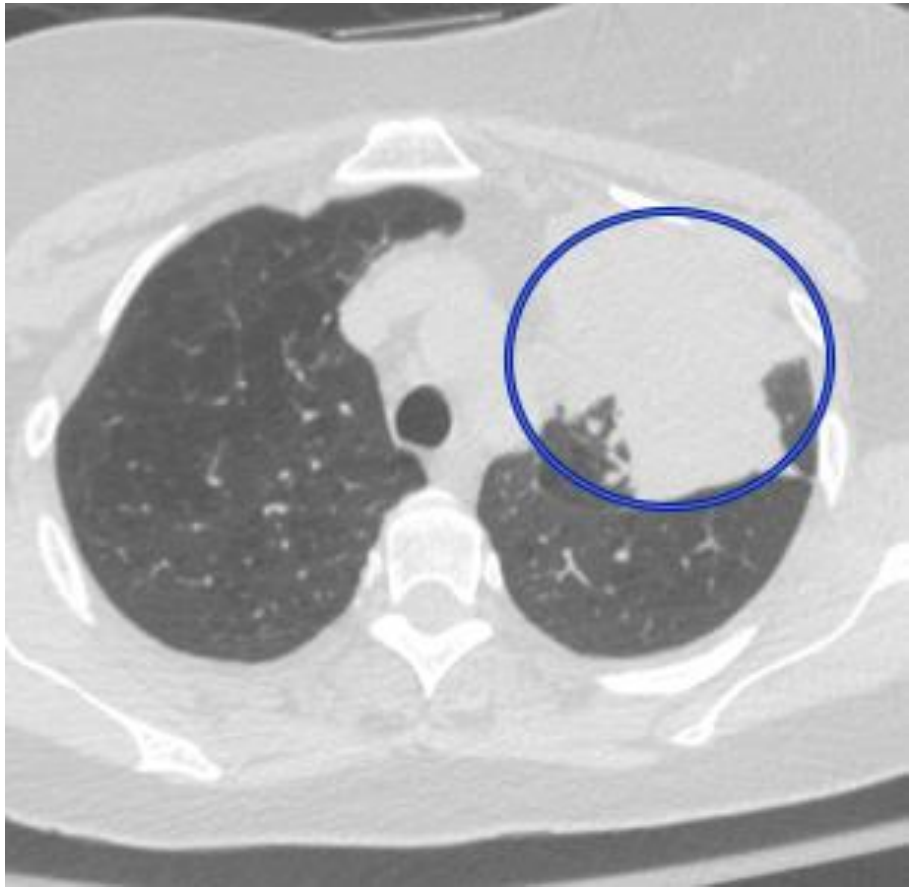


- Median follow up: 16.6 months
- Median duration of ramucirumab treatment (Arm A): 14.2 months
- Dose intensity ramucirumab 86.6%

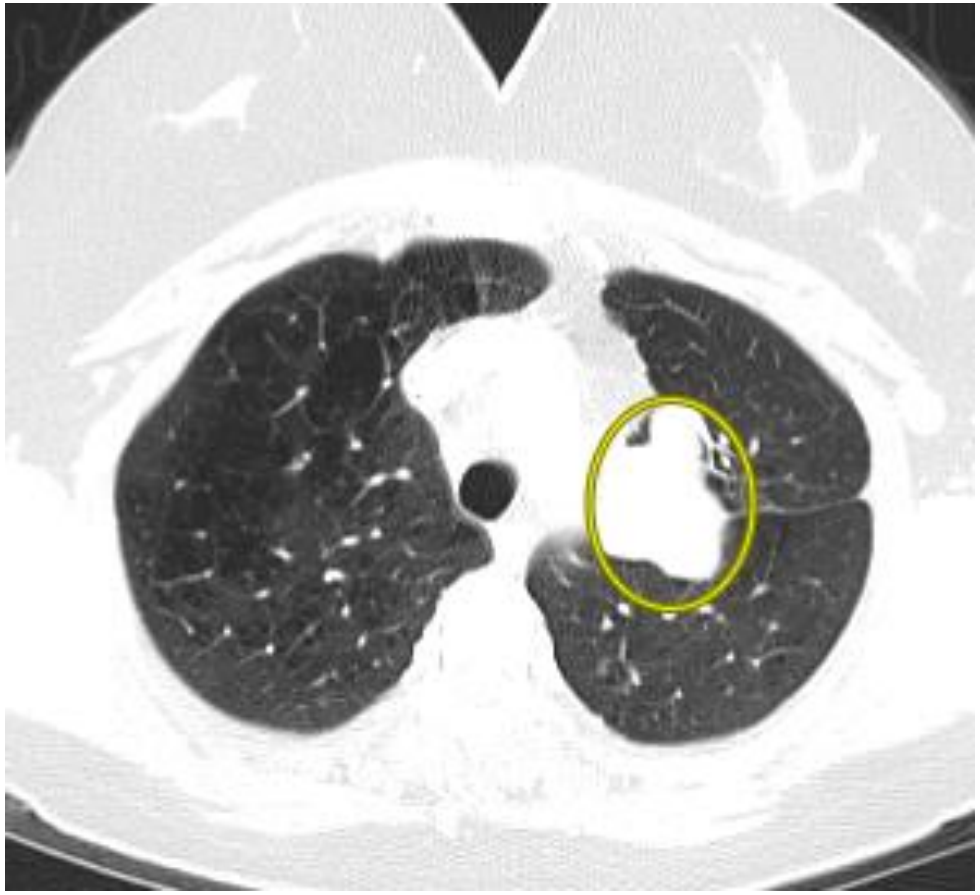
Le et al. ESMO 2023.

Slide courtesy from Dr. Julia Rotow. NY Lung 2023

EGFR exon 19 del (RAMOSE trial patient)



Pre-Treatment
(RAMOSE trial)



3 months post-Osimertinib +
Ramucirumab

*TKI=tyrosine kinase inhibitor

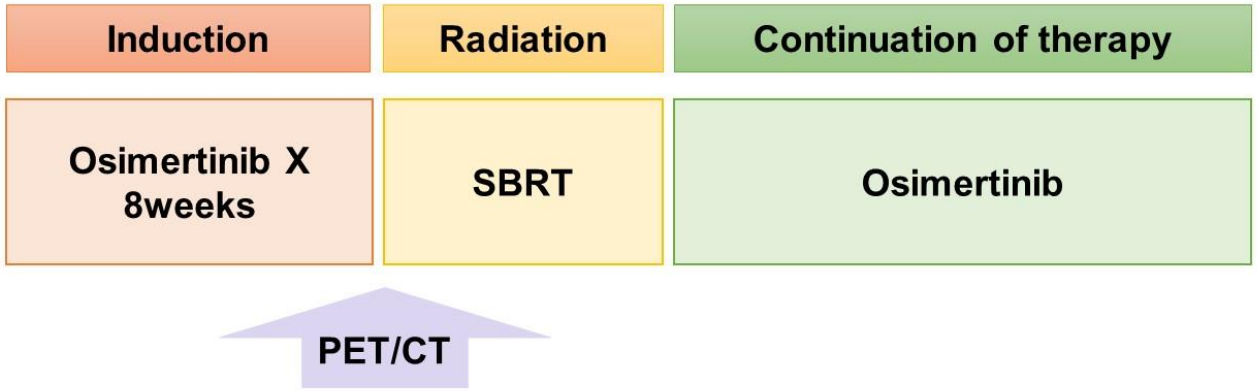
What is new?
ASCO 2024

Methods

Eligibility

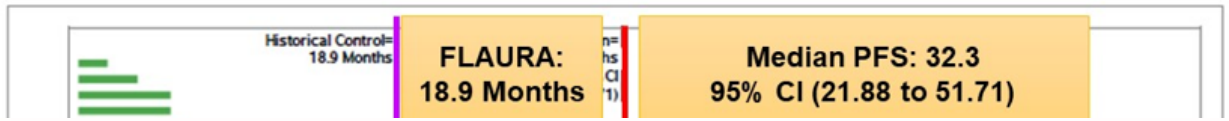
- TKI Naïve, EGFR+ advanced NSCLC.
- Not restricted by number, site or size of metastases.
- No history of interstitial lung disease.
- ECOG ≤2

Multicenter, single arm phase 2 IIT

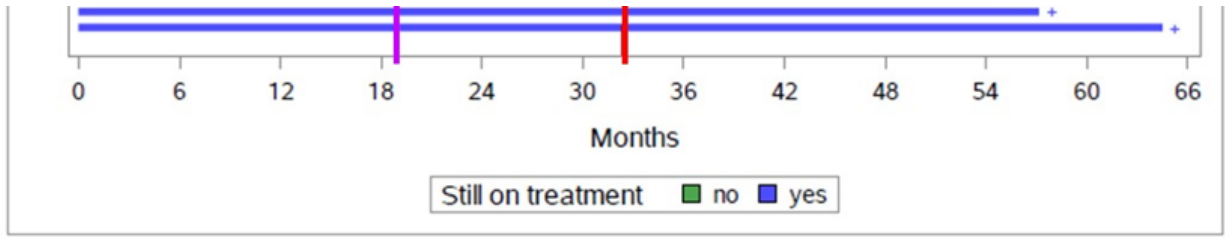


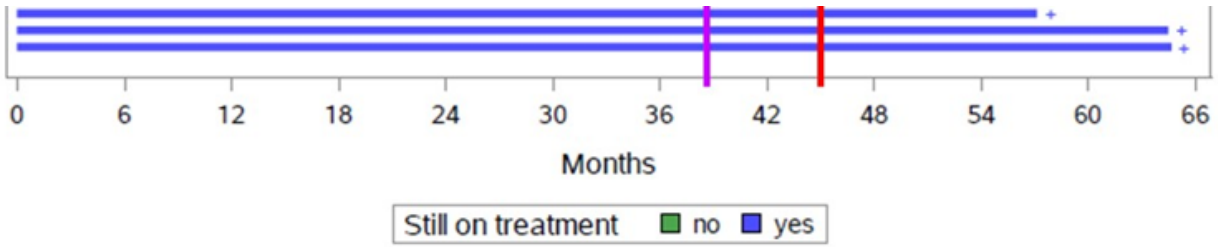
- Osimertinib until systemic progression or toxicity
- Subsequent SABR was allowed for oligo-progressive disease.
- We enrolled 43 patients. Primary objective: PFS
- Secondary objectives: OS, duration on osimertinib, safety

What is new?
ASCO 2024



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





Presented by Rashdan S et al, ASCO 2024

What is new?

EGFR mutations 2nd line

Key eligibility criteria:

- Locally advanced or metastatic NSCLC
- Documented EGFR Ex19del or L858R
- Progressed on or after osimertinib monotherapy
- ECOG PS 0 or 1
- Stable brain metastasis (untreated allowed)
- Stratification factors:

1. Osimertinib 1st vs. 2nd line
2. Asian race
3. History of brain metastasis

MARIPOSA-2

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=657)

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

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 Cycle 3 (week 7)

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

Chemotherapy administered at the beginning of every cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:

- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

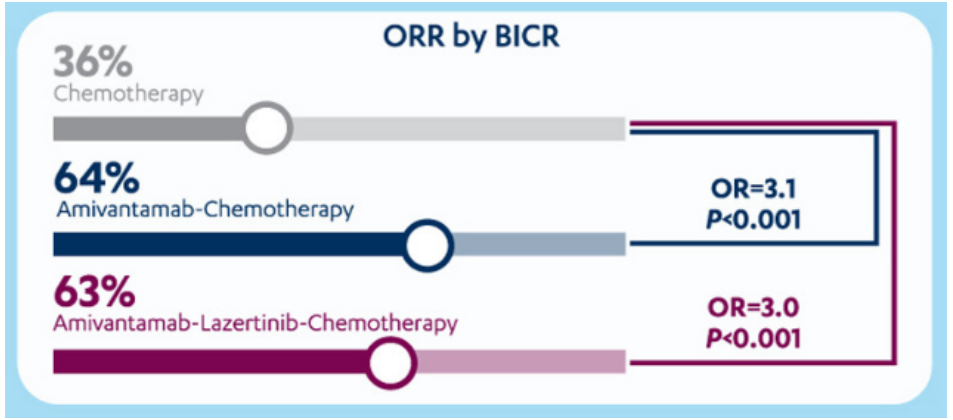
Secondary endpoints:

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

Presented by Passaro A et al, ESMO 2023

MARIPOSA-2

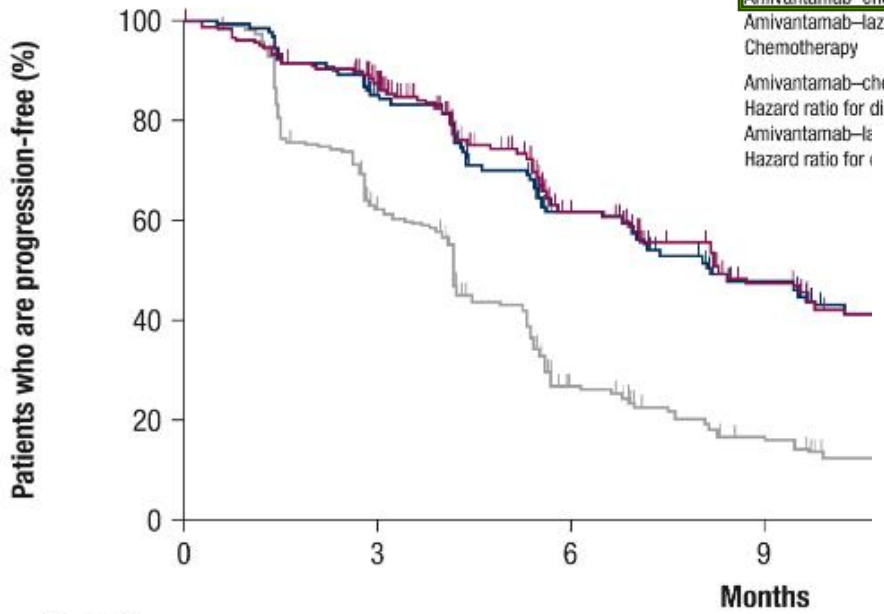
EGFR common mutations (2nd line)



B

	n	Median progression-free survival, months (95% CI)
Amivantamab–chemotherapy	131	8.2 (6.8-10.9)
Amivantamab–lazertinib–chemotherapy	263	8.3 (7.1-9.9)
Chemotherapy	263	4.2 (4.0-4.5)

Amivantamab–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.41** (95% CI 0.30-0.54)
Amivantamab–la
Hazard ratio for

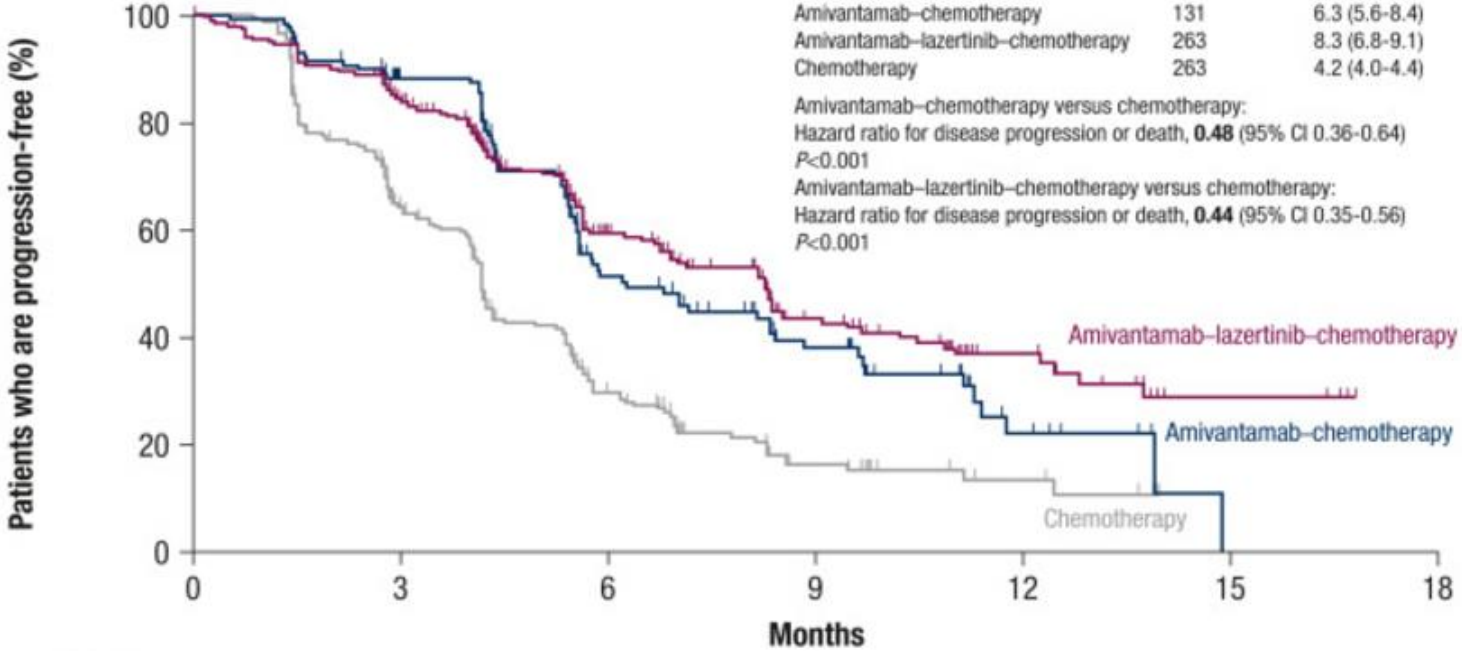


No. at risk				
Amivantamab–chemotherapy	131	99	61	33
Amivantamab–lazertinib–chemotherapy	263	201	110	57
Chemotherapy	263	139	48	19

Independent central review

	n	Median progression-free survival, months (95% CI)
Amivantamab–chemotherapy	131	6.3 (5.6-8.4)
Amivantamab–lazertinib–chemotherapy	263	8.3 (6.8-9.1)
Chemotherapy	263	4.2 (4.0-4.4)

Amivantamab–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.48** (95% CI 0.36-0.64)
P<0.001
Amivantamab–lazertinib–chemotherapy versus chemotherapy:
Hazard ratio for disease progression or death, **0.44** (95% CI 0.35-0.56)
P<0.001



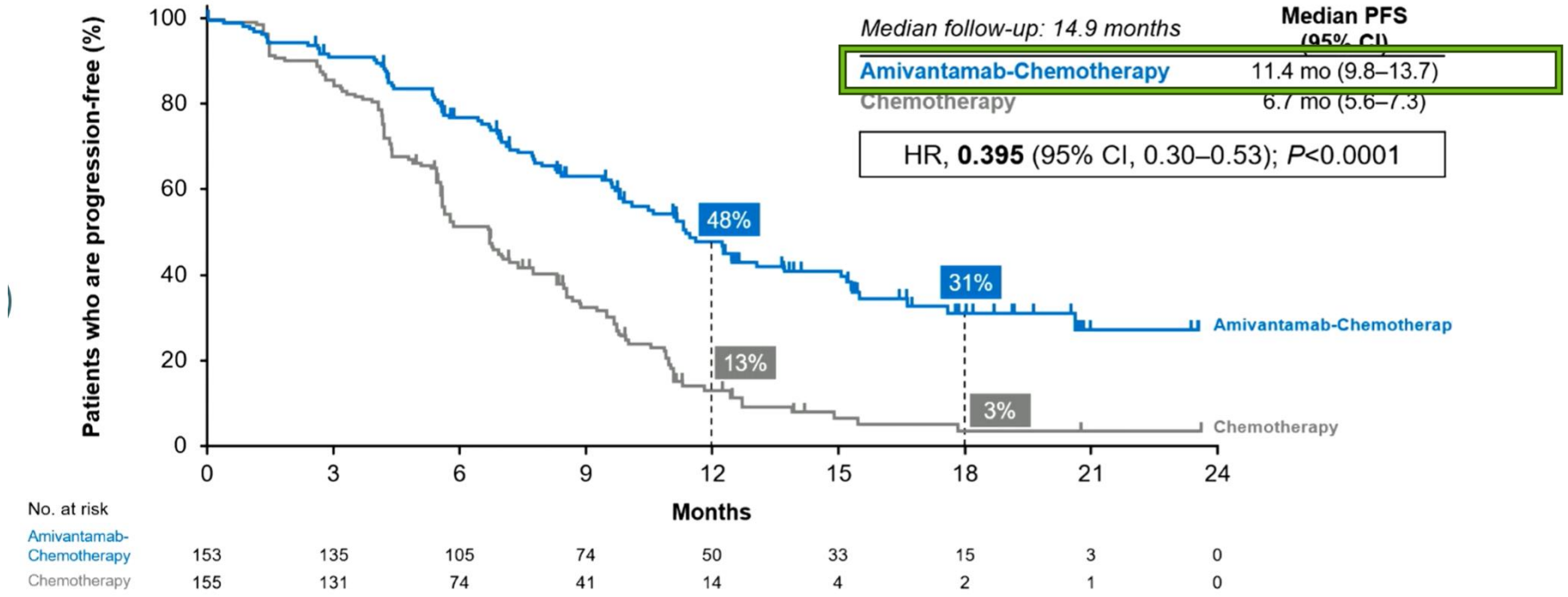
EGFR exon 20 insertions

1st line

PAPILLION

Primary Endpoint: Progression-free Survival by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%



MADRID 2023 ESMO congress

Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

G3+ TEAE
75% vs 54%

Amivantamab discontinuation rate
7%

Presented by Girard et al, ESMO 2023 Abstract LBA5

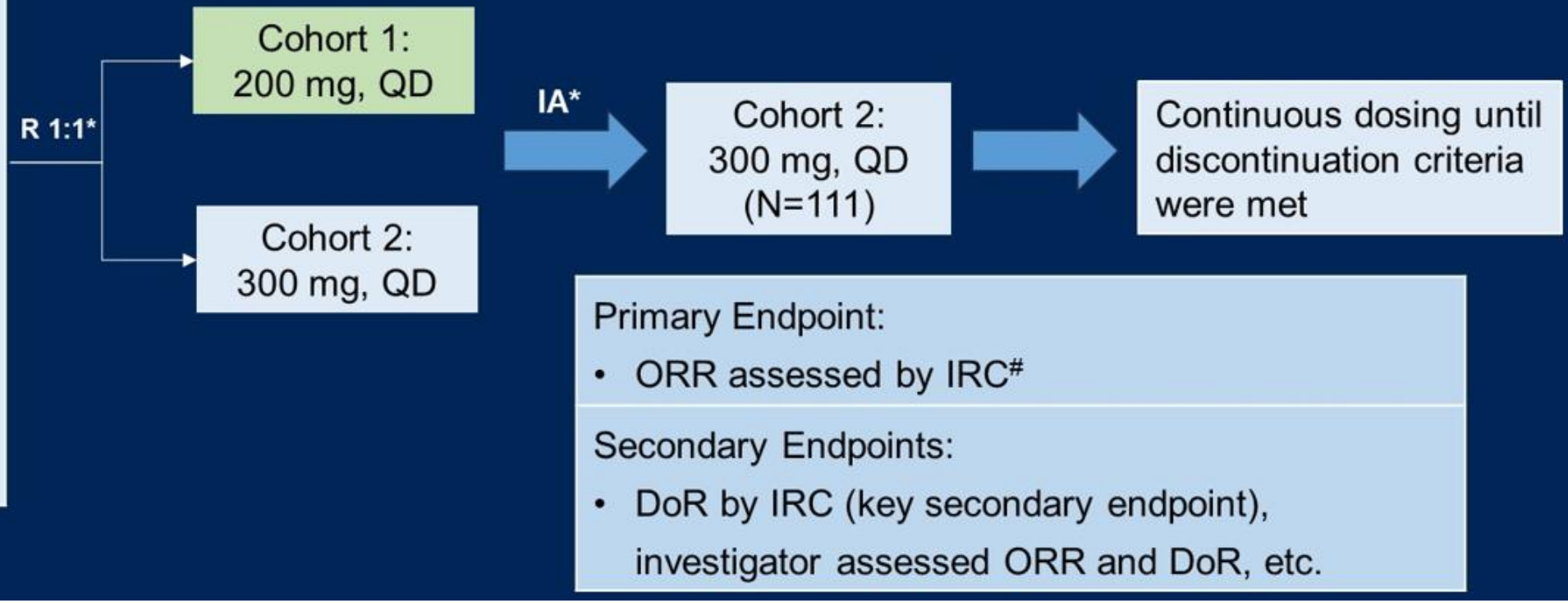
What is new?

ASCO 2024

EGFR exon20ins 2nd line

WU-KONG1B

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



Primary Endpoint:

- ORR assessed by IRC#

Secondary Endpoints:

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

Presented by Yang et al, ASCO 2024

What is new?

ASCO 2024

WU-KONG1B
(Sunvozertinib)

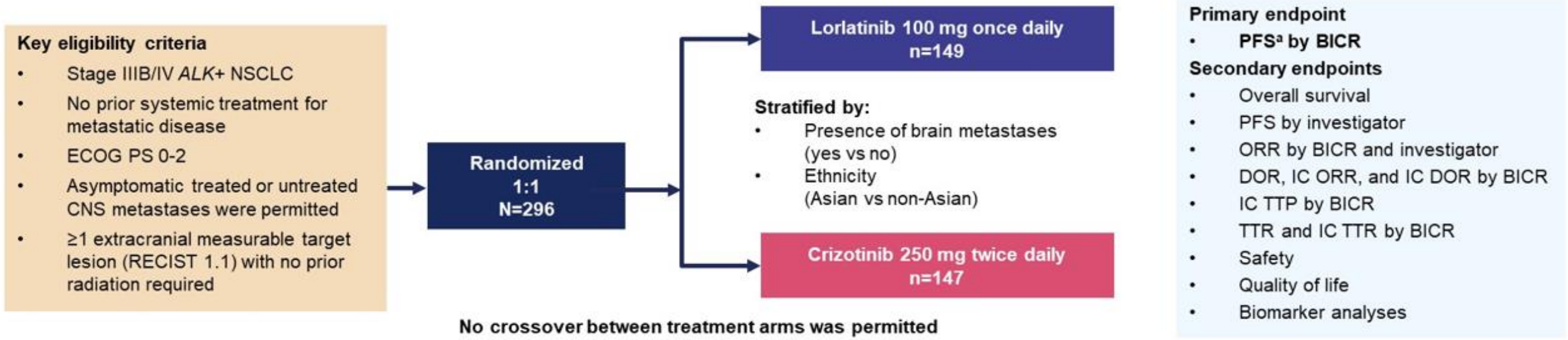
Tumor Response Per IRC	300 mg (N = 107)
Best ORR (%) with 97.5% CI	53.3 (42.0, 64.3)
Confirmed ORR (%) with 97.5% CI	44.9 (34.0, 56.1)
Best Response, n (%)	
Complete response	3 (2.8)
Complete response (confirmed)	2 (1.9)
Partial response	54 (50.5)
Partial response (confirmed)	46 (43.0)
Partial response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

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

What is new? ALK fusions
ASCO 2024

CROWN: A Randomized Global Phase 3 Study

- Lorlatinib is a brain-penetrant, third-generation ALK TKI that has broader coverage of *ALK* resistance mutations than second-generation ALK TKIs[1,2]

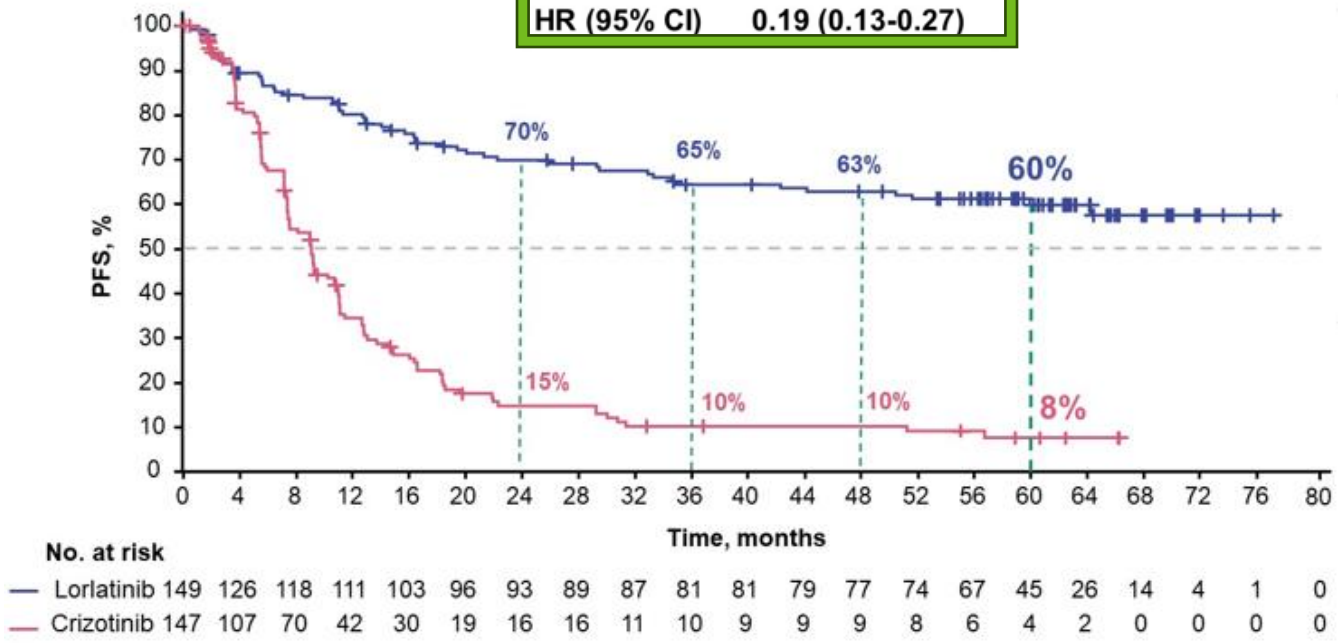


Presented by Solomon B et al, ASCO 2024

CROWN study (Phase III)

Lorlatinib

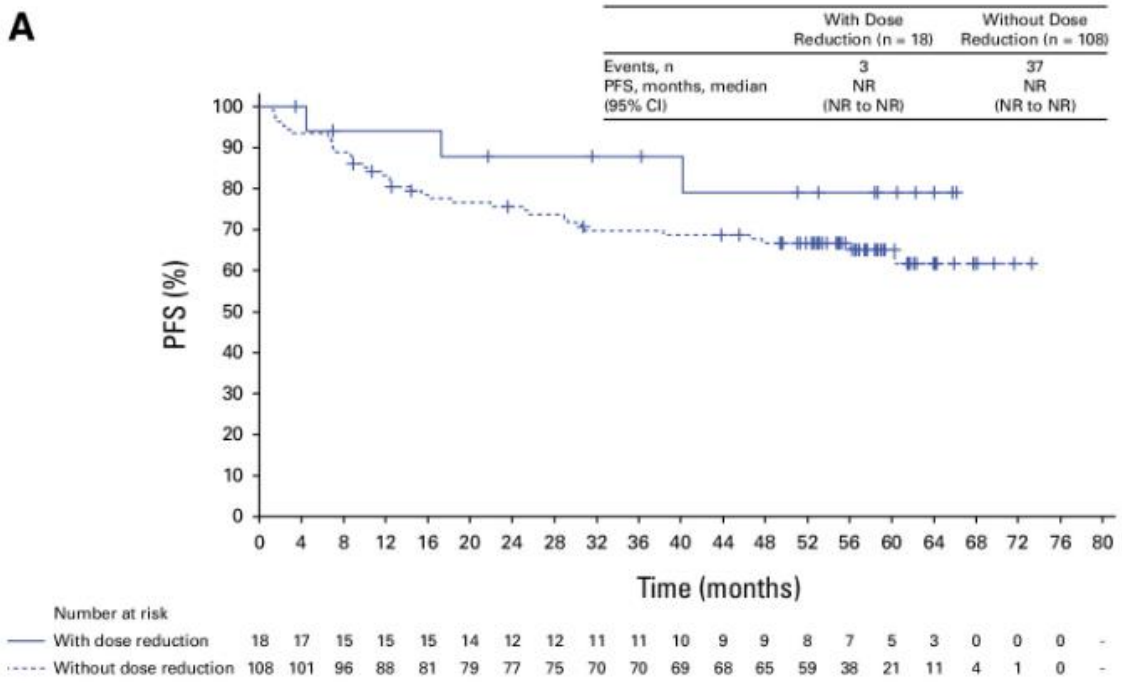
	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	



Grade 3/4 AE 66%

39% temporary dose discontinuation

21% dose reduction



Solomon B et al. 2024 ASCO Annual Meeting

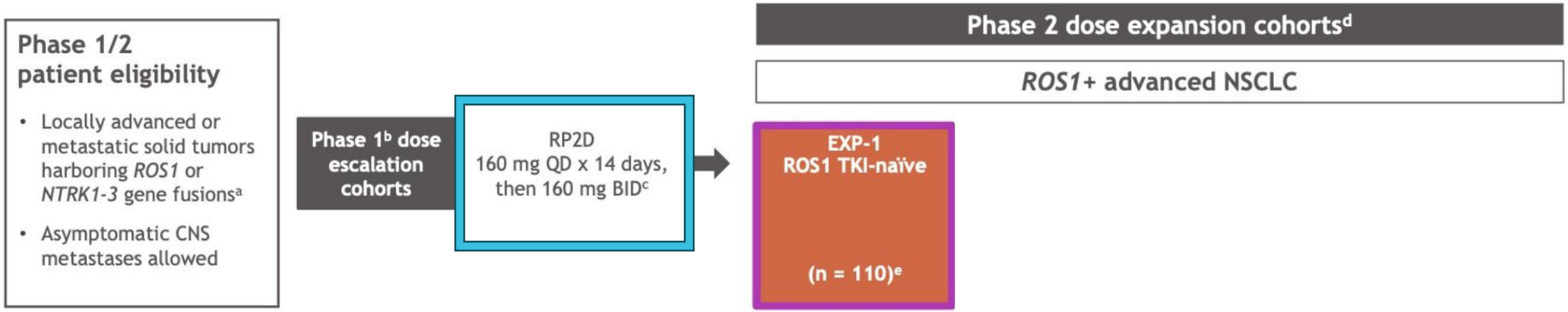
https://doi.org/10.1200/JCO.24.00581

What is new? ROS1 fusions

WCLC23

TRIDENT-1: overview of phase 1/2 trial design

Repotrectinib



Phase 2 (*ROS1*+ advanced NSCLC cohorts)

Primary endpoint	Key secondary endpoints
cORR by BICR using RECIST v1.1	• DOR,[f] CBR,[f] TTR[f] • cORR[e] in TKI-pretreated patients harboring *ROS1* G2032R • PFS,[f] OS • icORR by mRECIST v1.1 in patients with measurable brain metastases • Safety, patient-reported outcomes

- Primary efficacy population includes patients pooled from phase 1[g] and 2 who began repotrectinib treatment approximately 14 months prior to data cutoff date of December 19, 2022

Presented by Cho BC et al, WCLC 2023

What is new? ASCO 2024

Repotrectinib

Table 2. Efficacy summary

	ROS1 TKI-naïve (n = 71)
cORR,[a] % (95% CI)	79 (68–88)
With prior chemo (n = 20)	70 (46–88)
Without prior chemo (n = 51)	82 (69–92)
BOR,[a] n (%)	
CR	
PR	
PD	
SD	
CBR,[a,b] % (95% CI)	
Median time to response, months (range)	
Median PFS,[c] months (95% CI)	
With prior chemo	
Without prior chemo	
Median DOR,[d] months (95% CI)	
With prior chemo	
Without prior chemo	
icORR, % (95% CI) [n/N]	

Table 4. Safety summary in all treated patients[a]

AEs, n (%)	All patients treated with ≥ 1 dose of repotrectinib (n = 565)		All patients with *ROS1+* locally advanced or metastatic NSCLC treated with ≥ 1 dose of repotrectinib (n = 367)	
	TEAEs	TRAEs	TEAEs	TRAEs
All patients with AEs	562 (99)	535 (95)	365 (99)	350 (95)
Leading to dose reduction	216 (38)	195 (34)	141 (38)	123 (34)
Leading to drug interruption	291 (52)	197 (35)	200 (54)	128 (35)
Leading to treatment discontinuation	61 (11)	23 (4)	39 (11)	17 (5)
Serious AEs	230 (41)	48 (8)	153 (42)	29 (8)
Grade ≥ 3 AEs	323 (57)	162 (29)	213 (58)	107 (29)
Fatal AEs	35 (6)	2 (< 1)	25 (7)	1 (< 1)

Presented by Drilon A et al, ASCO 2024

What's new? HER-2 overexpression
2nd line setting

DESTINY-Lung01 trial

Key eligibility criteria

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed from or is refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS of 0 or 1
- Locally reported *HER2* mutation (for Cohort 2)[b]

→

Cohort 1: HER2-overexpressing[c] (IHC 3+ or IHC 2+) T-DXd 6.4 mg/kg q3w N = 49	Cohort 1a: HER2-overexpressing[c] (IHC 3+ or IHC 2+) T-DXd 5.4 mg/kg q3w N = 41

Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

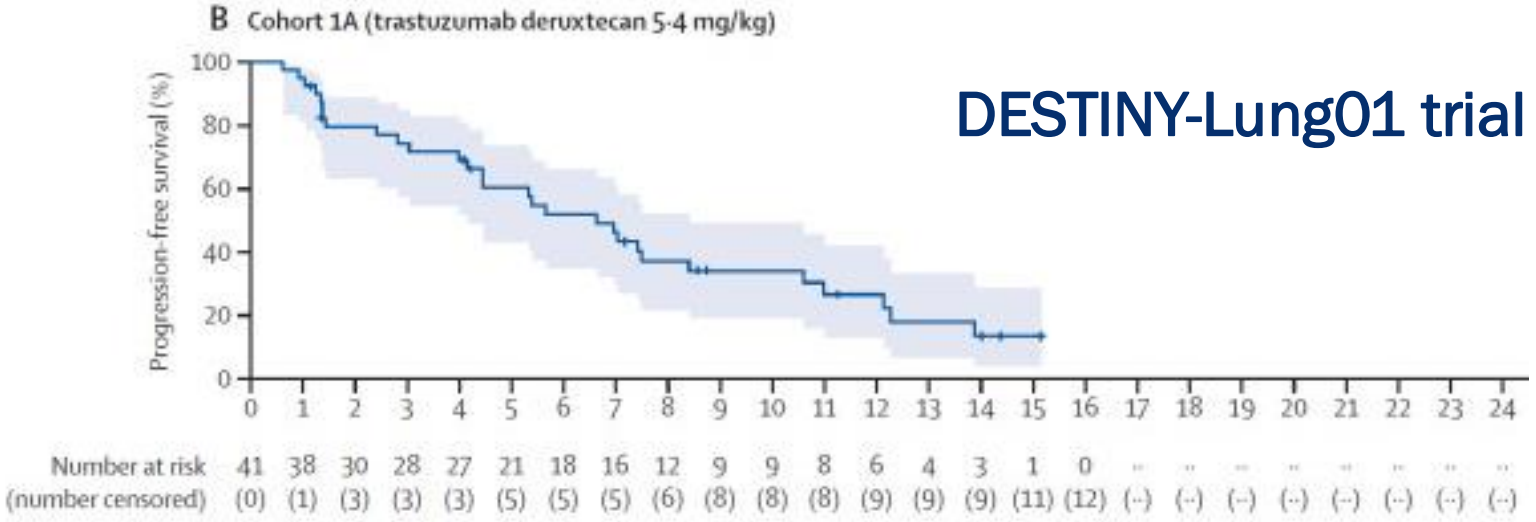
- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

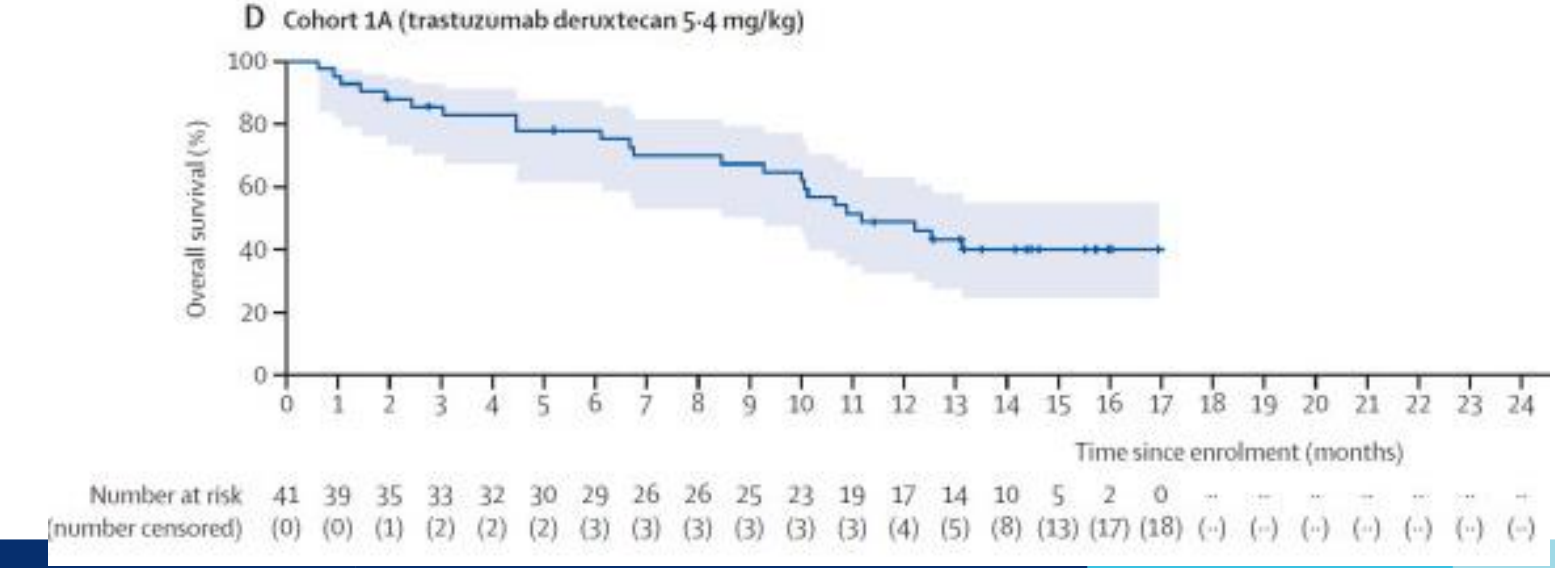
Smit EFS et al. Lancet Oncol.2024

What's new? HER-2 overexpression
2nd line setting



DESTINY-Lung01 trial

Key Findings (N=49)	
ORR	34%
mPFS	6.7 months
mOS	11.2 months



FDA approval is for HER-2 IHC 3+ *only* (gastric scoring)

Smit EFS et al. Lancet Oncol.2024

Take home points

- Maintenance osimertinib after CCRT is the new standard of care for patients with unresectable stage III NSCLC with a common EGFR mutation
- There are multiple options for 1st line treatment for stage IV NSCLC with common EGFR mutations. Choice should be individualized based on clinical characteristics and drug toxicity profile and schedule.
- Sunvozertinib should become available soon for the treatment of EGFR exon 20 insertion + NSCLC previously treated with a platinum-doublet
- Lorlatinib 100 mg daily is an excellent choice for 1st line treatment of ALK + NSCLC
- Repotrectinib is an excellent choice for 1st or 2nd line treatment for ROS1 + NSCLC
- T-DXd is approved for HER2 3+ NSCLC in the 2nd line setting

Questions?

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