Updates in First Line NSCLC Targeted Therapy

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UCDAVIS COMPREHENSIVE CANCER CENTER

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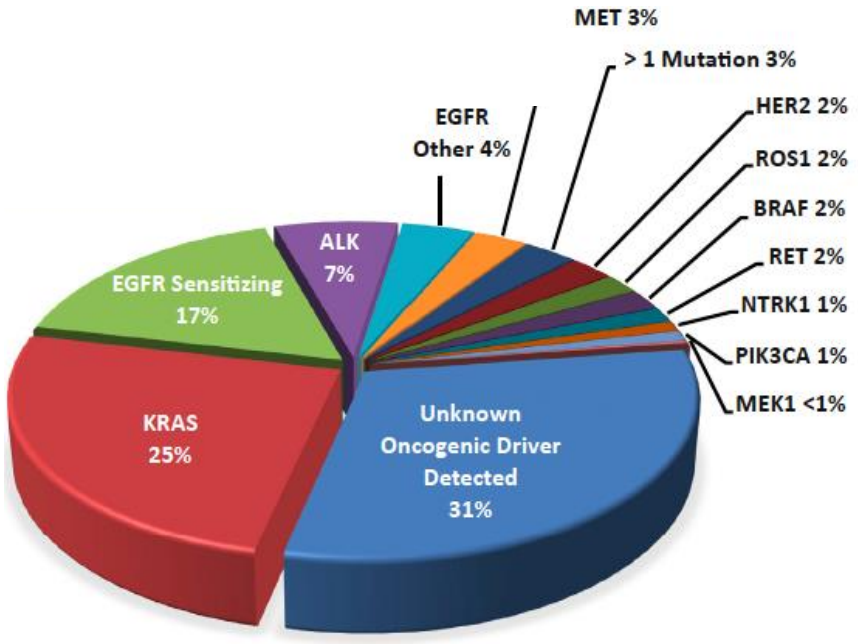
Progress in Targeted Therapy for NSCLC-Adenocarcinoma



KRAS G12C
adagrasib, sotorasib

EGFR exon 20 insertions
mobocertinib, poziotinib, amivantamab

EGFR:
gefitinib, afatinib, erlotinib, osimertinib+/-
platinum/pemetrexed,, dacomitinib, amivantamab+lazertinib

ALK:
Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib,
entrectinib, NVL655

ROS1:
Crizotinib, cabozatinib, ceritinib, brigatinib, lorlatinib,
entrectinib, repotrectinib, NVL550, taletrectinib

BRAF:
Dabrafenib/trametinib, vemurafenib, dabrafenib,
encorafenib+binemetinib

MET:
Crizotinib, cabozatinib, capmatinib, tepotinib, savolitinib,
merestinib, glesatinib

HER2:
Trastuzumab emtansine, afatinib, dacomitinib, poziotinib,
neratinib-temsirolimus, XMT-1522, TAK-788, Trastuzumab
deruxtecan

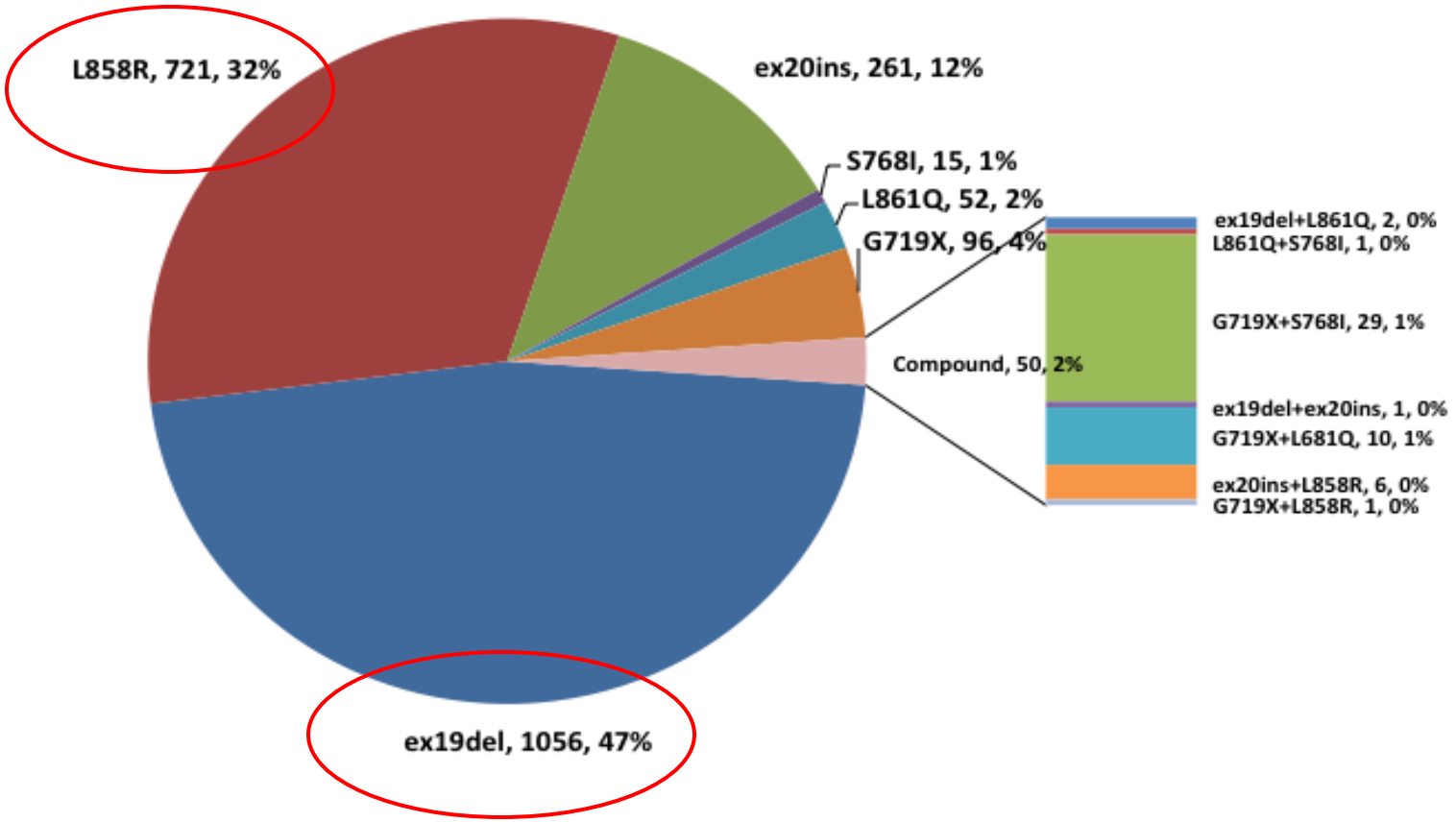
RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib,
lenvatinib, apatinib, selpercatinib,pralsetinib, RXDX-105

NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.

Frequency and Distribution of 2,251 *EGFR* mutations in NSCLC Detected by Broad Genomic Profiling.



JW Riess et al. Journal of Thoracic Oncology 2018.

FLAURA: Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years old
- WHO performance status 0/1
- Exon 19 deletion/L858R (enrollment by local or central *EGFR* testing)
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable CNS metastases were allowed

Stratification by **mutation status** (exon 19 deletion/ L858R) and **race** (Asian/non-Asian)

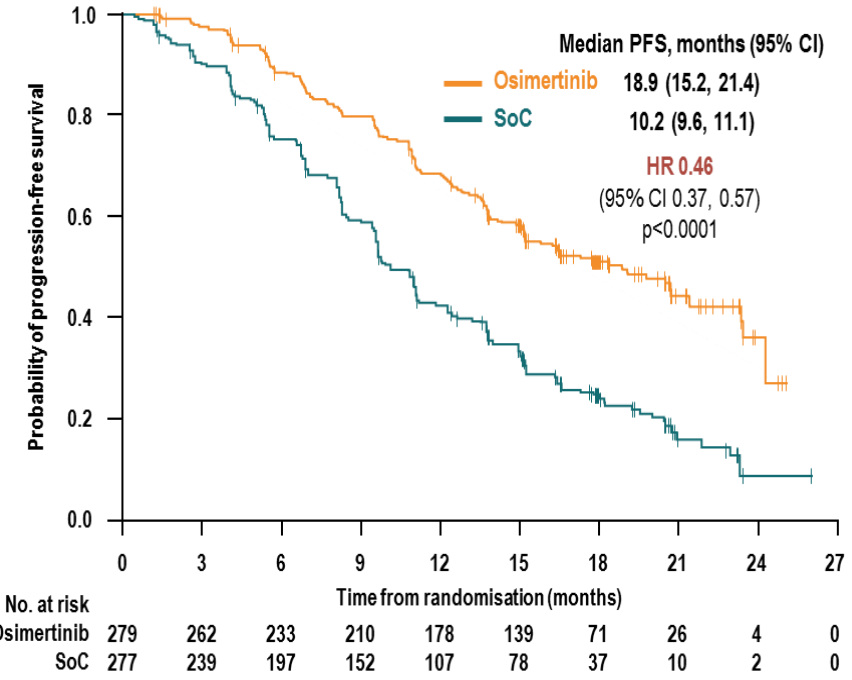
R 1:1

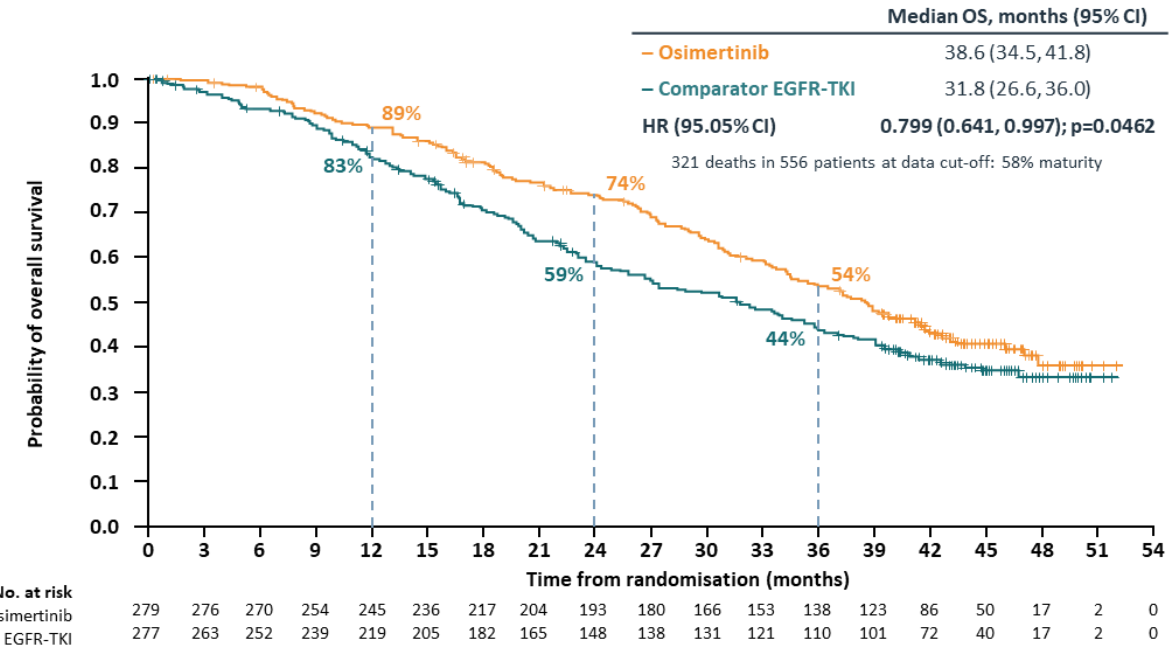
Osimertinib (80 mg po qd) (n=279)

Comparator EGFR-TKI; **Gefitinib** (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity





Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

First-line intensification strategies

Standard-of-care for mEGFR-mut NSCLC

Osimertinib PFS 18.9 months

FLAURA2

Randomized phase III
EGFR mutation NSCLC
Stage IIIb/IV
Primary endpoint: PFS

R

- Osimertinib + carboplatin + pemetrexed x 4 cycles
- Osimertinib + pemetrexed
- Osimertinib

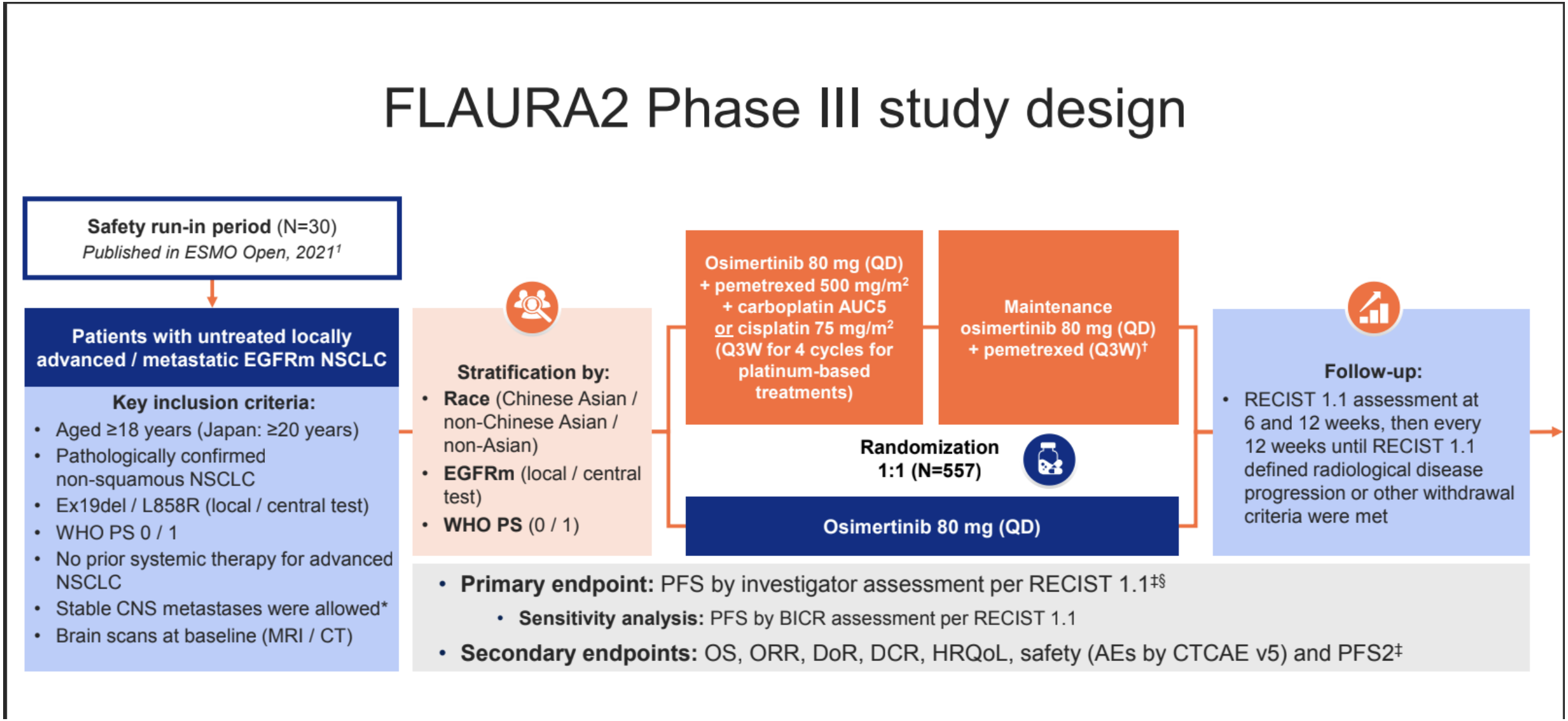
MARIPOSA

Randomized phase III
EGFR mutation NSCLC
Stage IIIb/IV
Primary endpoint: PFS

R

- Lazertinib + amivantamab
- Lazertinib
- Osimertinib

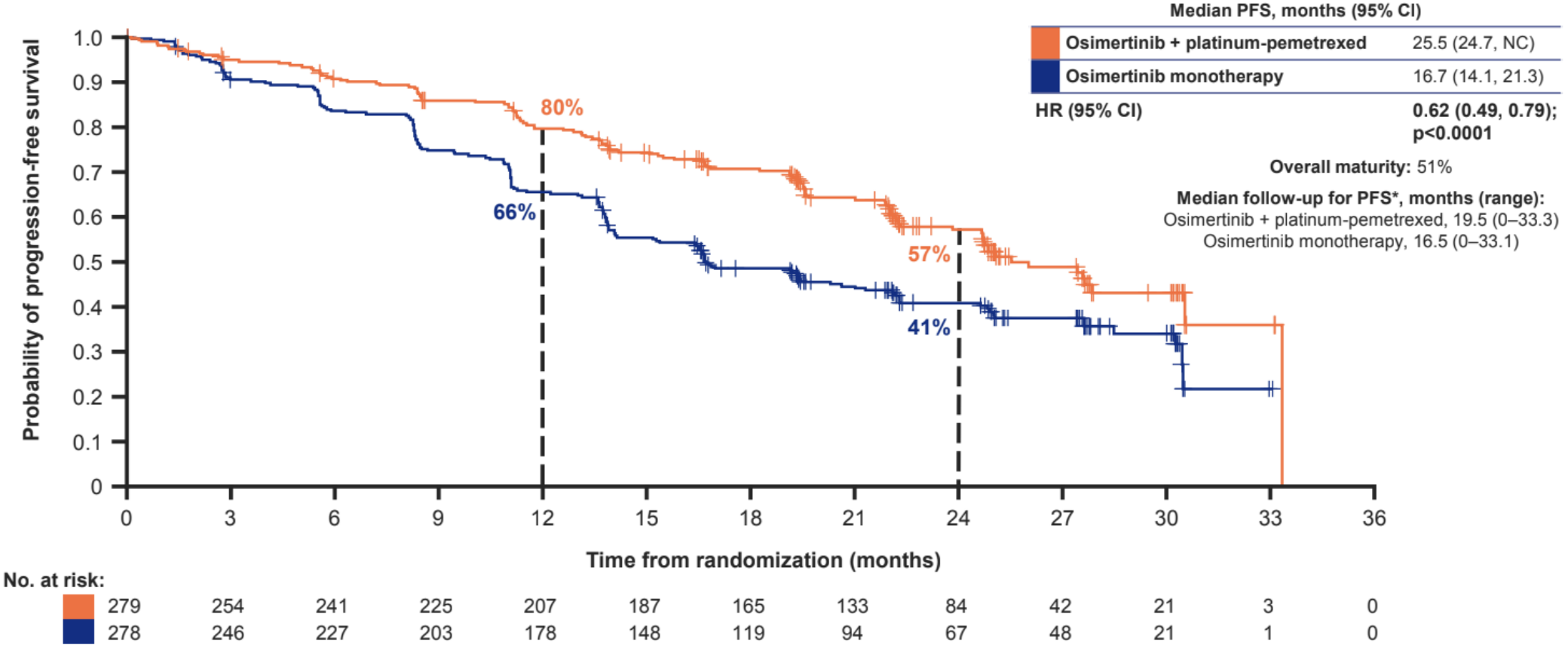
FLAURA 2: Osimertinib + Chemotherapy in the Front-Line Setting



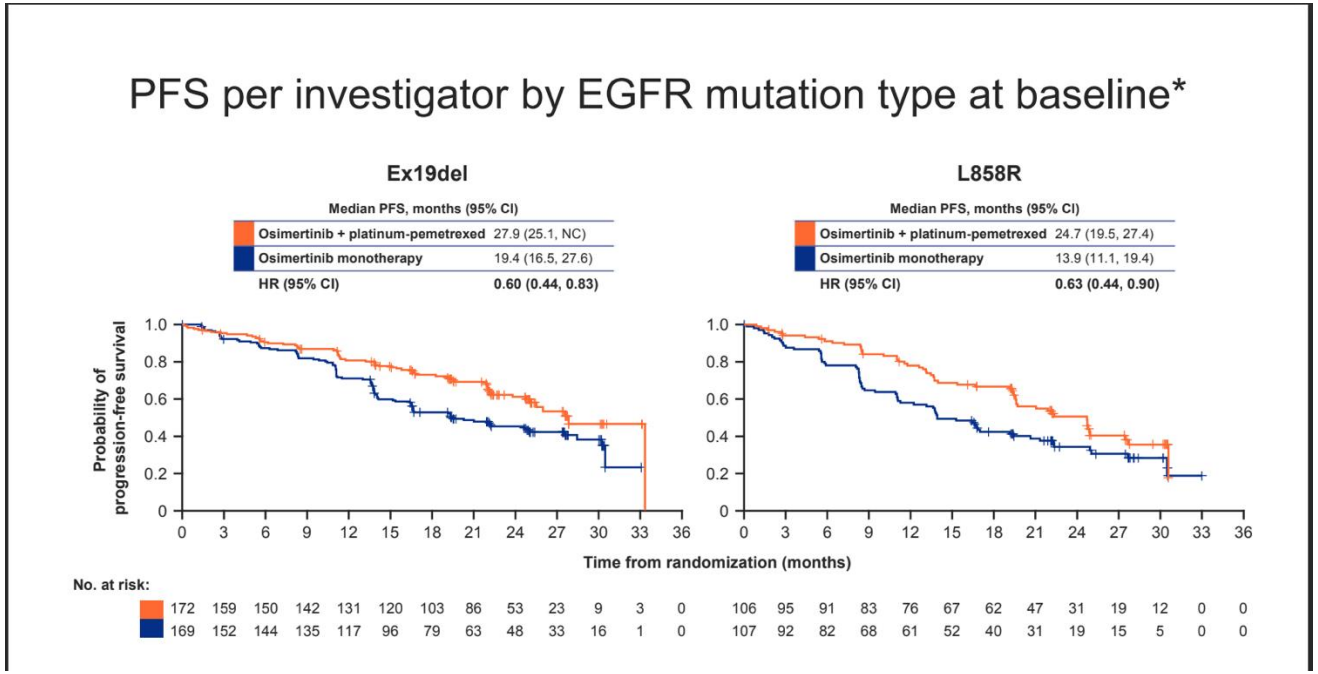
FLAURA 2

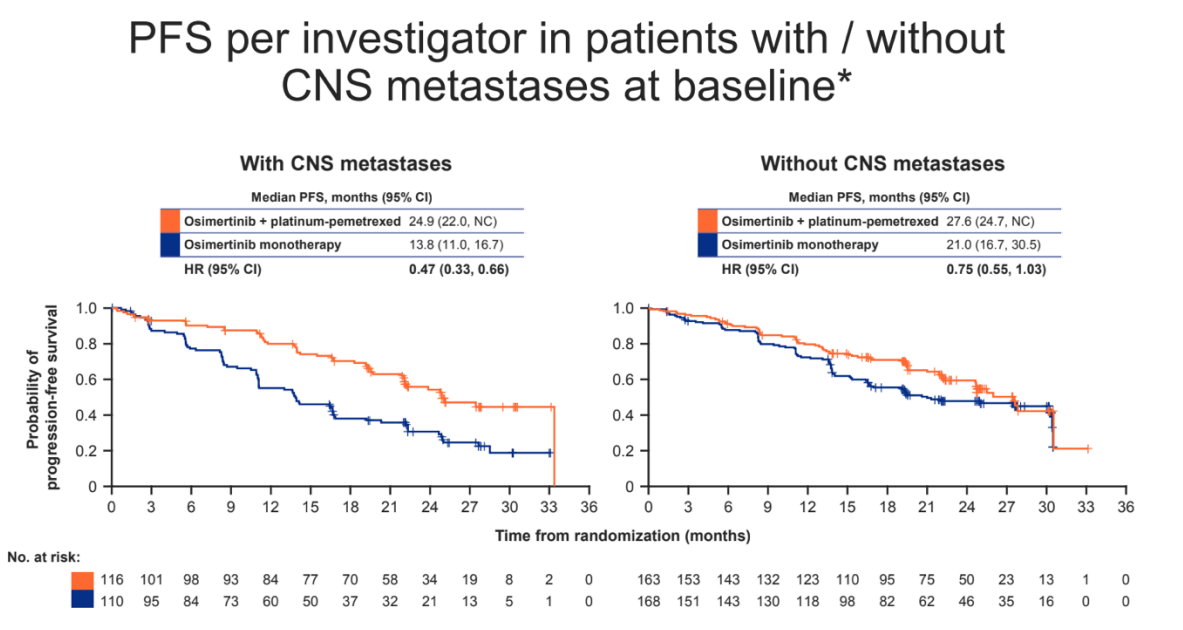
Progression-free survival per investigator

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

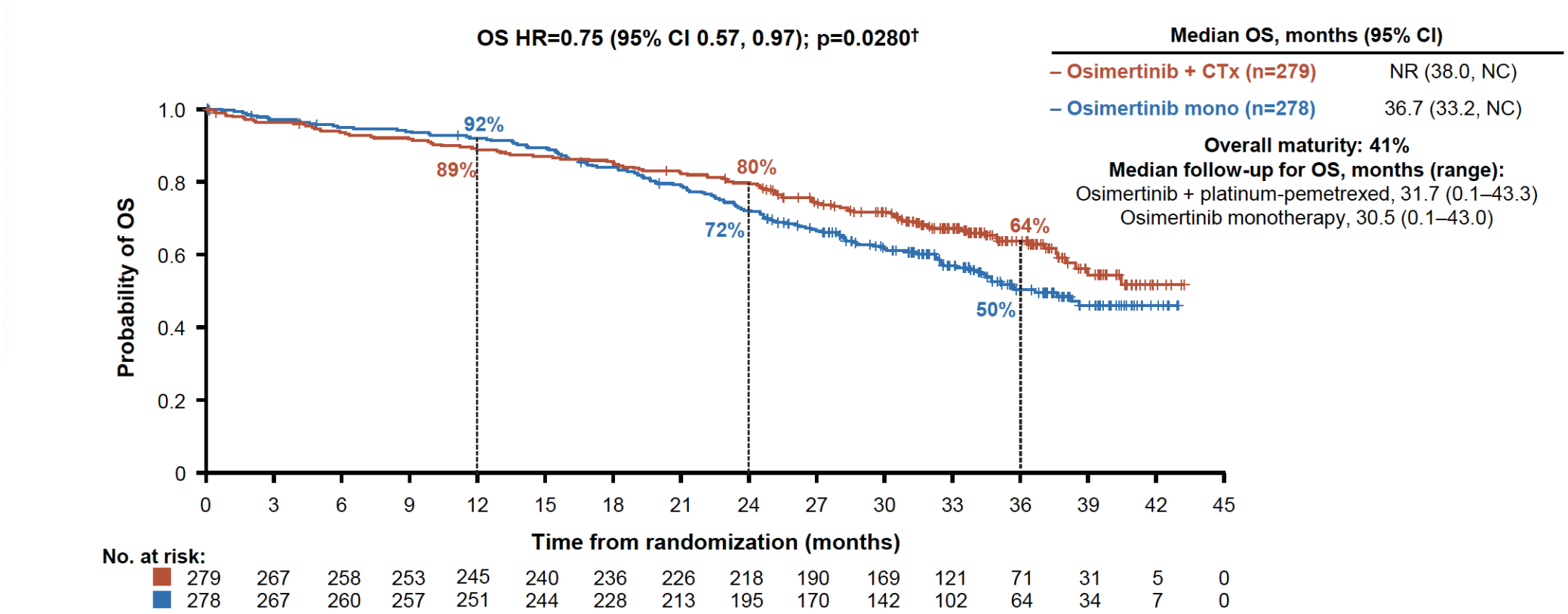


FLAURA 2: Patient Characteristics of Interest





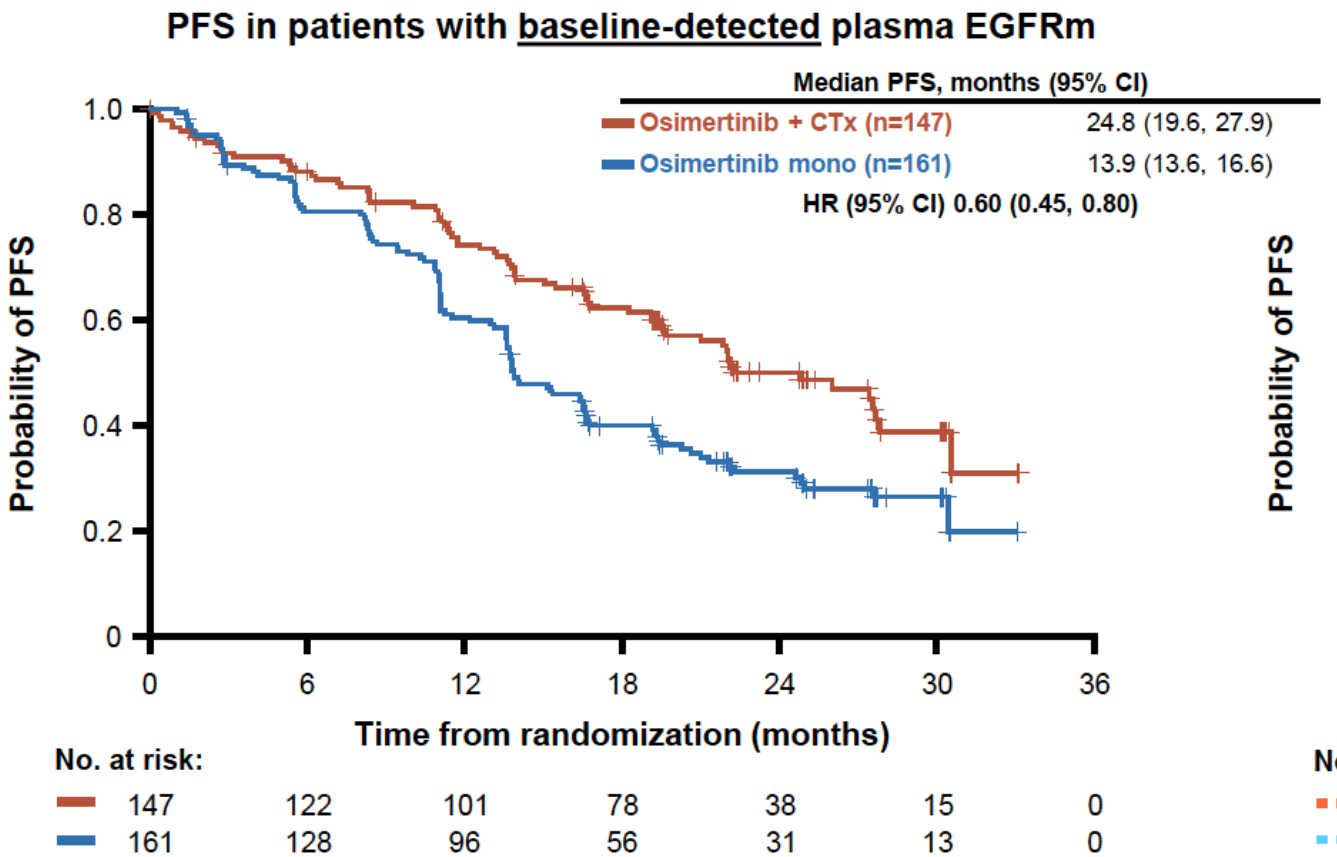
Second Interim OS Analysis

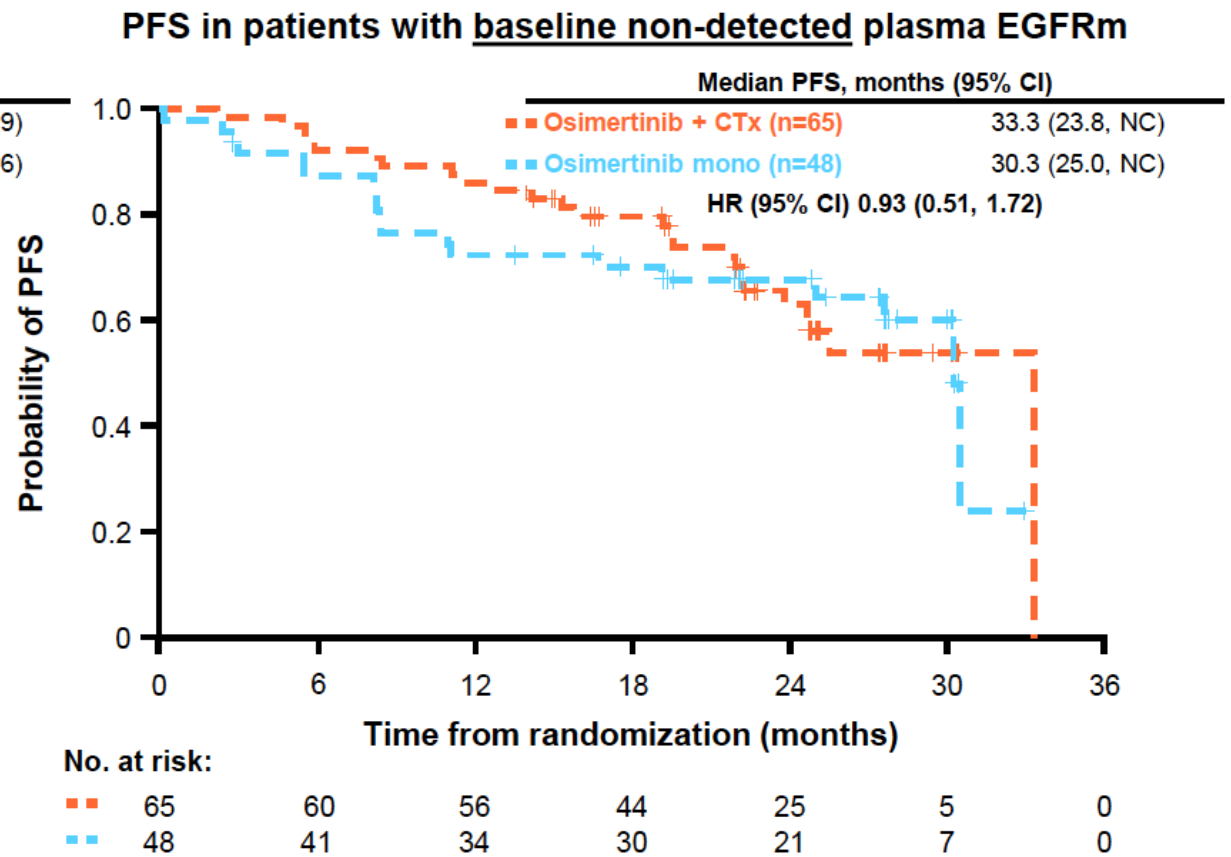


Data cut-off: 08 January 2024. HR was calculated by a stratified log-rank test. Figure from Valdiviezo N, et al. Presented at: ELCC 2024 (4O)
†A p-value of ≤0.000001 was required for statistical significance at this second interim analysis
Valdiviezo N, et al. ESMO Open 2024;9:102583
CI, confidence interval; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; NC, not calculable; NR, not reached; OS, overall survival

Valdiviezo. NA et al. ELCC 2024: Abstract 4O.

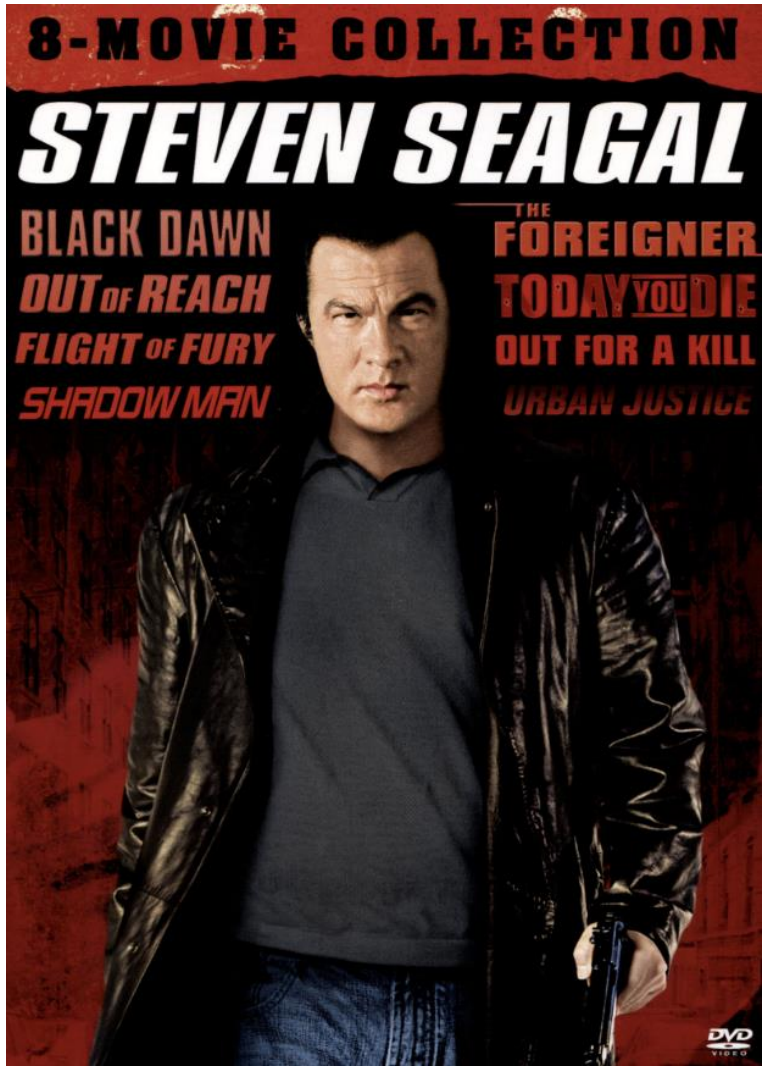
PFS improved with osimertinib plus chemotherapy in patients with baseline-detected plasma EGFRm versus osimertinib alone





P. Janne AACR 2024

Guide for Treatment Intensification: Who are the bad actors?



- ctDNA positive at baseline
- Co-mutations p53, RBM10, NRF2 genotypes
- CNS metastases, Liver metastases
- Tumor volume/disease burden?

MARIPOSA Phase 3 study design

Key Eligibility Criteria

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

Stratification Factors

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

Serial brain MRIs were required for all patients[a]

2:2:1 Randomization (N=1074)

Amivantamab + Lazertinib
(n=429; open-label)

Osimertinib
(n=429; blinded)

Lazertinib
(n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 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

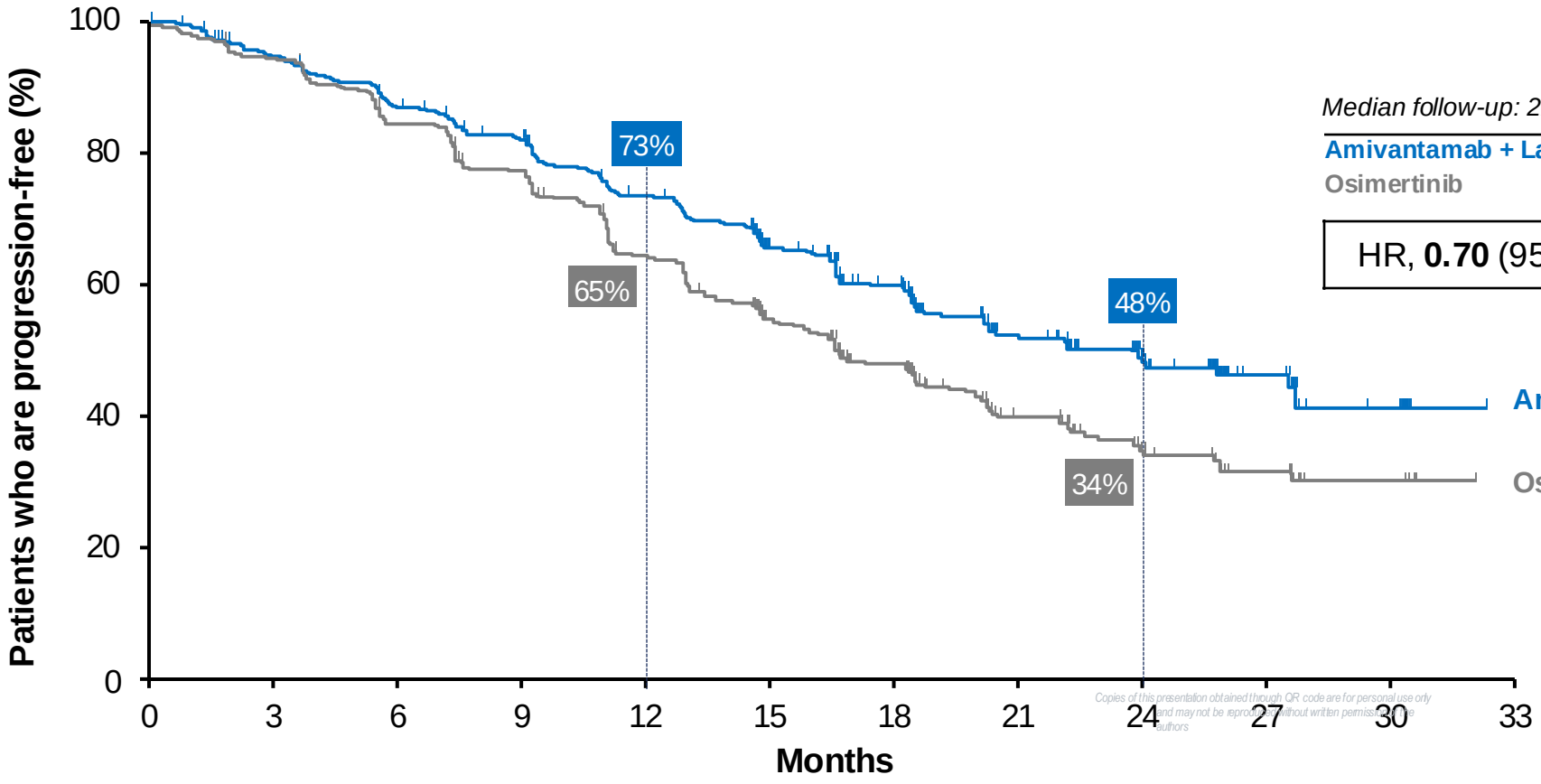
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.
[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.
[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio;

Cho B, et al., *ESMO Congress*, 2023

Progression-free survival between Ami-lazertinib vs. osimertinib



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

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

No. at risk												
Amivantamab + Lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

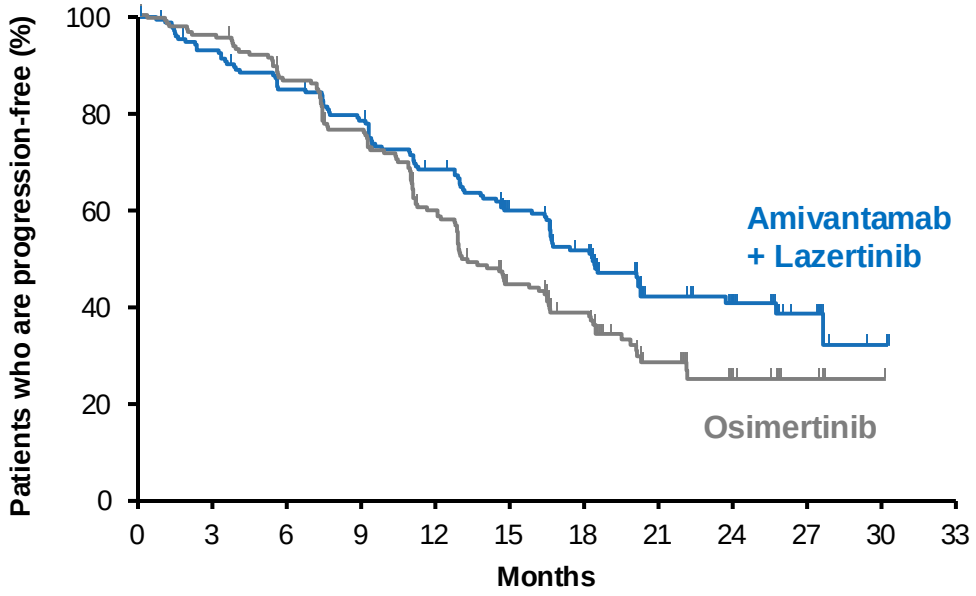
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

Cho B, et al., *ESMO Congress*, 2023

Consistent PFS (BICR) Benefit With or Without Brain Metastases

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

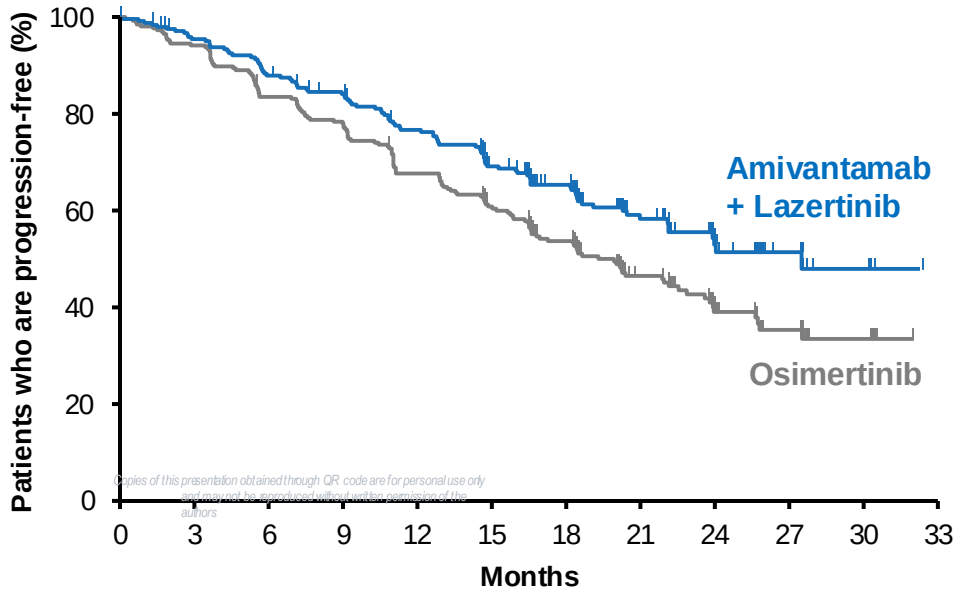
HR, **0.69** (95% CI, 0.53–0.92)



No. at risk												
Amivantamab + Lazertinib	178	162	146	134	115	92	71	34	24	12	3	0
Osimertinib	172	164	146	126	95	64	47	21	11	6	1	0

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

HR, **0.69** (95% CI, 0.53–0.89)



No. at risk												
Amivantamab + Lazertinib	251	229	211	198	176	152	123	72	36	21	5	0
Osimertinib	257	240	212	199	171	141	113	69	37	22	9	0

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

Cho B, et al., *ESMO Congress*, 2023

Safety summary

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

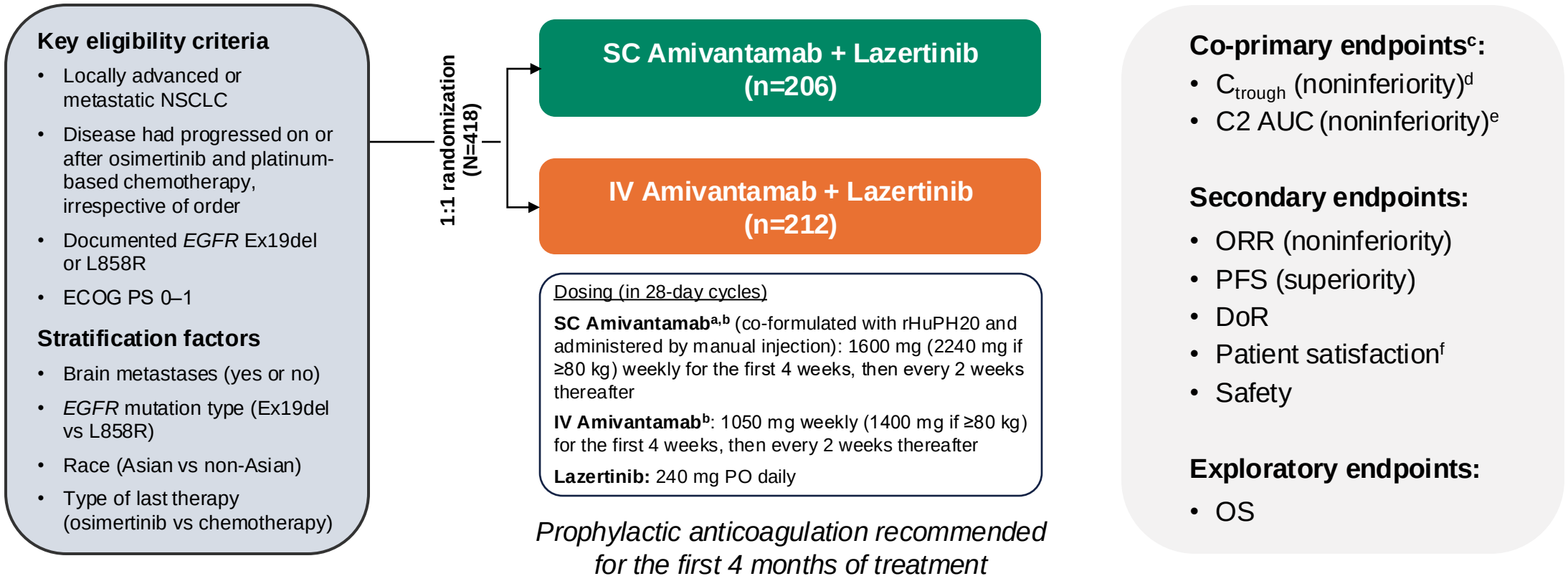
TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)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

AE, adverse event; mo, months; TEAE, treatment-emergent AE.

Cho B, et al., *ESMO Congress*, 2023

PALOMA-3: Phase 3 Study Design



PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

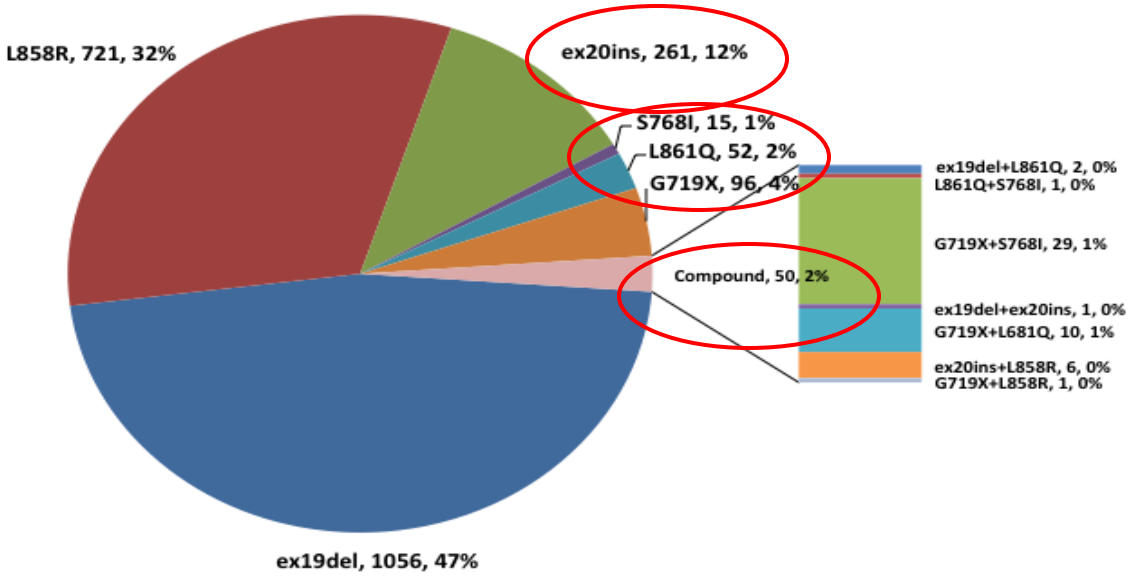
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

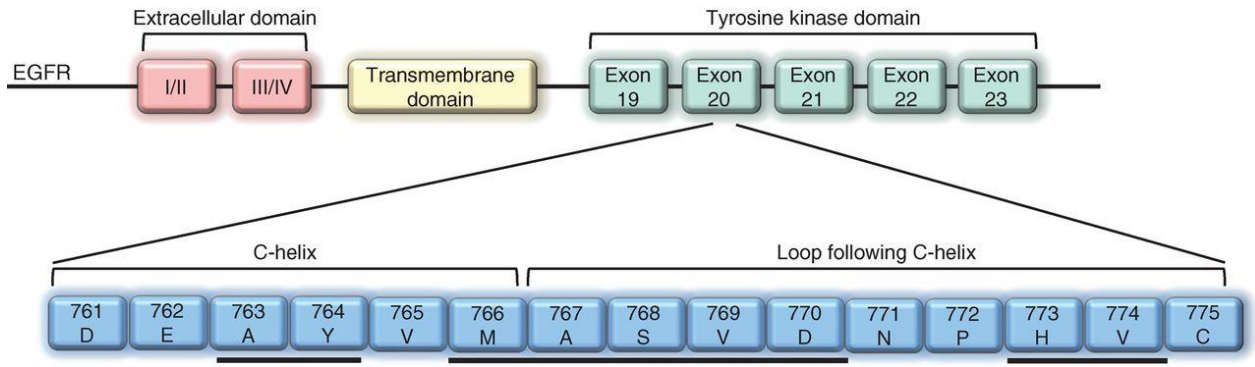
AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

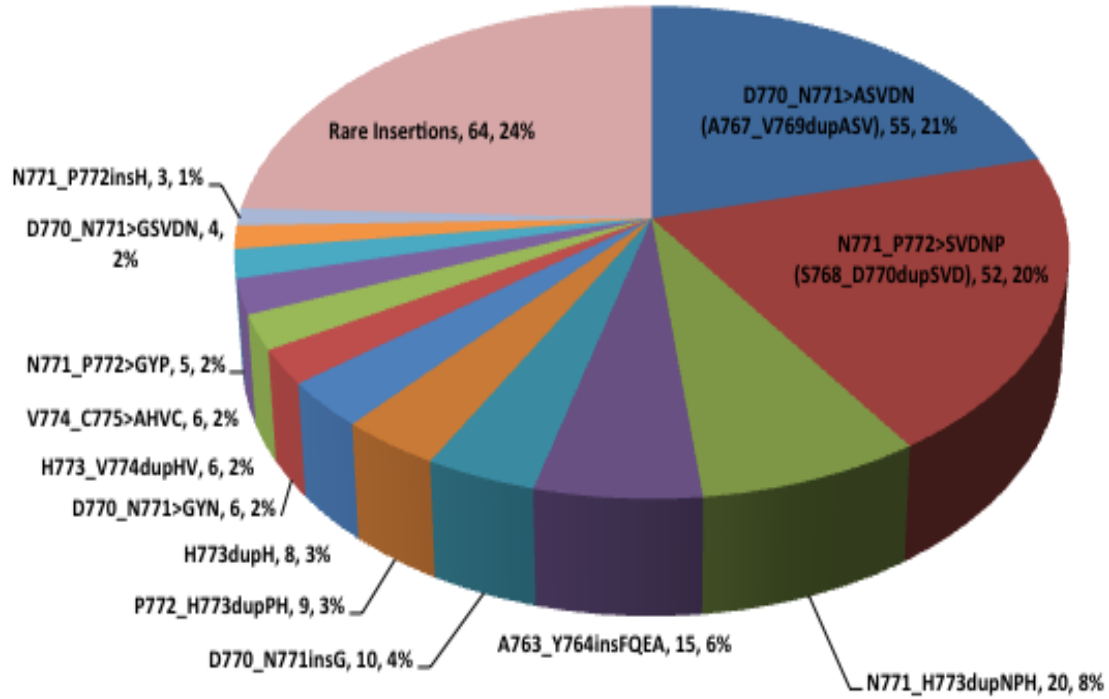
Trial	Treatment	PFS (Months)	OS	Adverse Events of Interest
FLAURA	Osimertinib vs. gefitinib/erlotinib	18.9 vs. 10.2, P<0.001	38.6 vs. 30.8 months, p=0.046	
FLAURA2	Carbo/Pem/Osi vs. Osi	25.5 vs. 16.8, P<0.001	HR=0.75 (p=0.028)	Chemo side effects
MARIPOSA	lazertinib/amivantamab vs. osi vs lazertinib	23.7 vs. 17, p<0.001 (lazertinib 18.5)	Immature HR, 0.80 (95% CI, 0.61 1.05); P =0.11	infusion reaction, VTE (37% vs. 9%), rash

Soria et al NEJM 2018, Ramalingam et al NEJM 2020, Janne et al. WCLC 2023, AACR 2024, Cho et al. ESMO 2023

EGFR mutations are heterogeneous

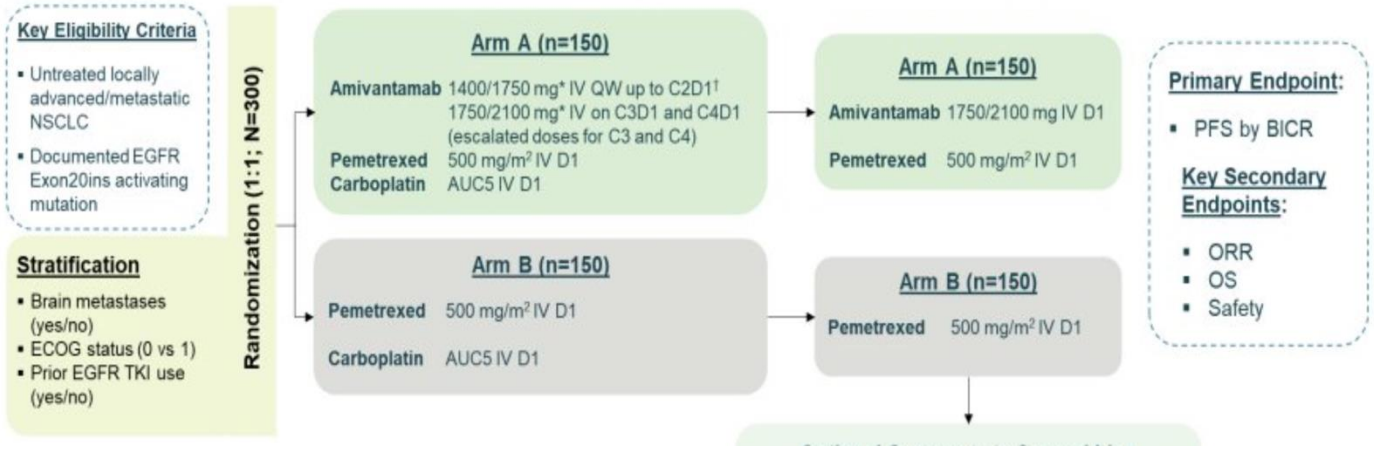


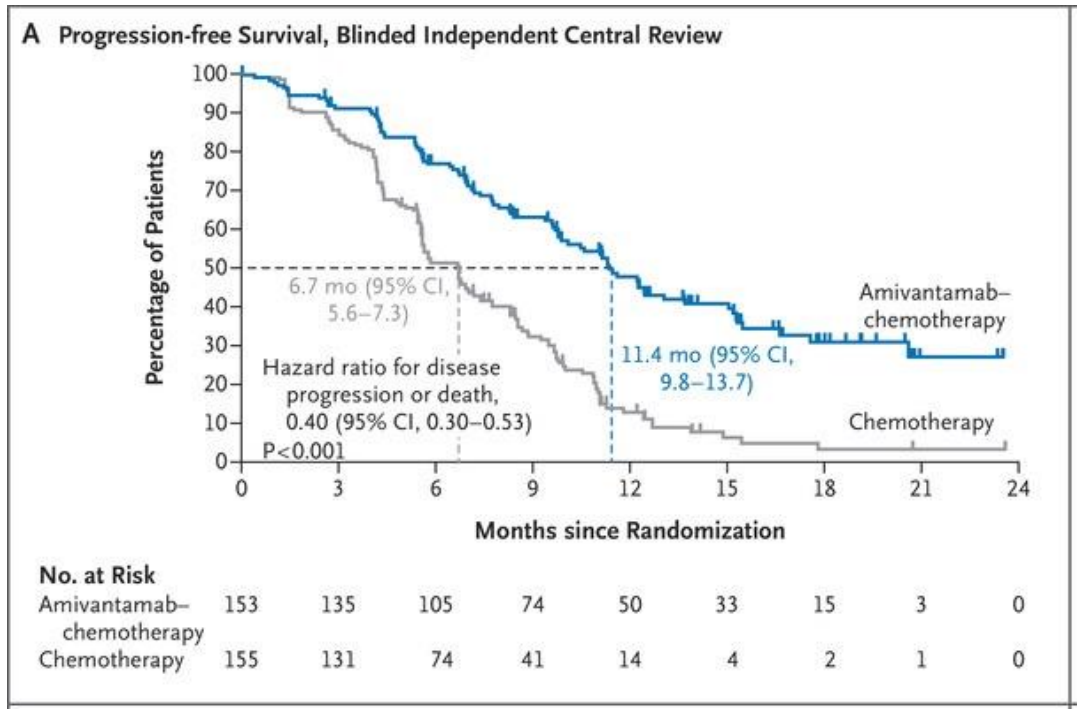


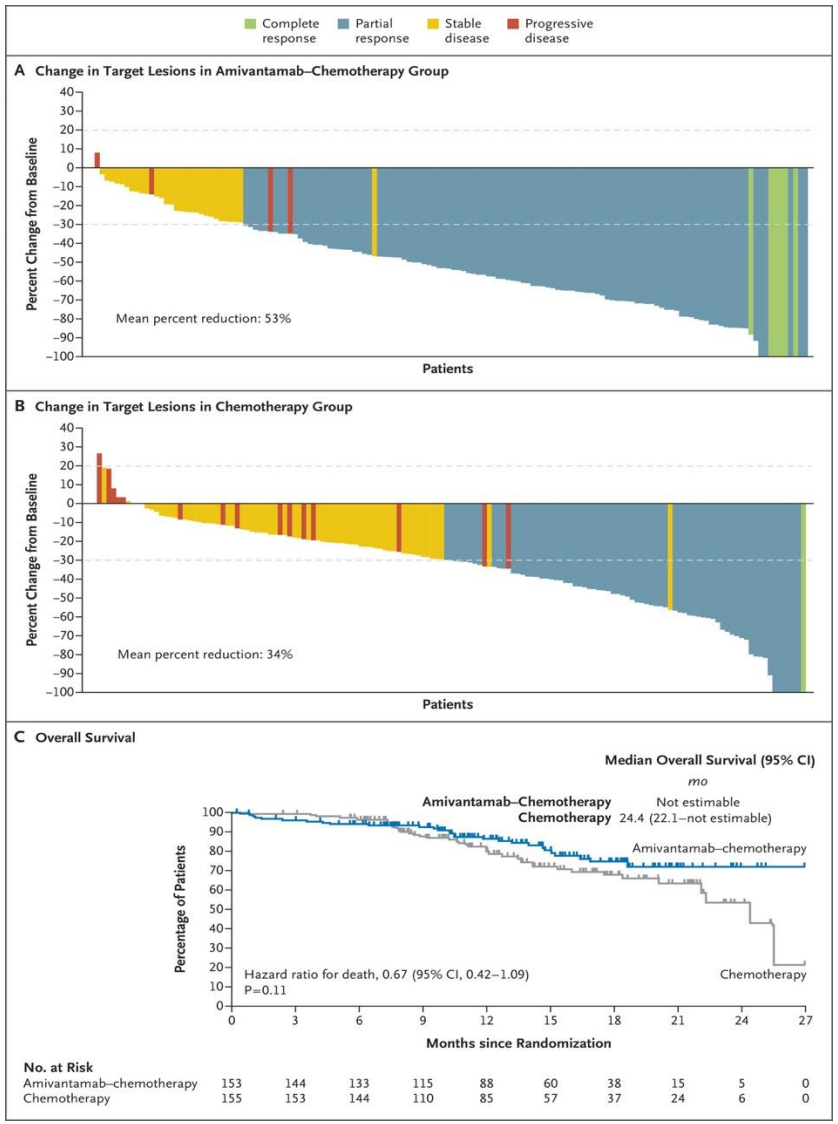


Meador, L. Sequist, Z. Piotrowska. Cancer Discov. 2021, 2021 Sep;11(9):2145-2157. Y. Elamin et al Cancer Cell 2022 40: 754-67. JW Riess et al JTO 2018. 13:10. P1560-1568,

Chemo-Amivantamab in 1L EGFR Exon 20 ins NSCLC (Papillon)







C. Zhou et al NEJM 2023

Key Takeaways – EGFR 1L

- Treatment Intensification with Chemotherapy+Osimertinib or Amivantamab+Lazertinib improves PFS
- No free lunch. Toxicity limitations that are distinct. Need for IV administration
- SC Amivantamab may alter the risk-benefit calculation for expanded treatment intensification.
- Await more mature OS data
- Need to identify patients by clinical and molecular characteristics where treatment intensification will be most helpful (or not)
- Amivantamab + Platinum-Pemetrexed new First Line Option in EGFR Exon 20 ins NSCLC

2024 ASCO® ANNUAL MEETING

Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

Benjamin J. Solomon,[1] Geoffrey Liu,[2] Enriqueta Felip,[3] Tony S. K. Mok,[4] Ross A. Soo,[5] Julien Mazieres,[6] Alice T. Shaw,[7] Filippo de Marinis,[8] Yasushi Goto,[9] Yi-Long Wu,[10] Dong-Wan Kim,[11] Jean-François Martini,[12] Rossella Messina,[13] Jolanda Paolini,[13] Anna Polli,[13] Despina Thomaidou,[14] Francesca Toffalorio,[13] Todd M. Bauer[15]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]Princess Margaret Cancer Centre, Toronto, ON, Canada; [3]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [4]State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong; [5]National University Cancer Institute, Singapore; [6]Toulouse University Hospital and Centre de Recherche Cancérologie Toulouse CRCT, INSERM, France; [7]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [8]European Institute of Oncology, IRCCS, Milan, Italy; [9]National Cancer Center Hospital, Tokyo, Japan; [10]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangdong, China; [11]Seoul National University College of Medicine and Seoul National University Hospital, Seoul, South Korea; [12]Pfizer, La Jolla, CA, USA; [13]Pfizer, Milan, Italy; [14]Pfizer, Athens, Greece; [15]Greco-Hainsworth Centers for Research/Tennessee Oncology, Nashville, TN, USA

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Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Crizotinib 250 mg twice daily n=147

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

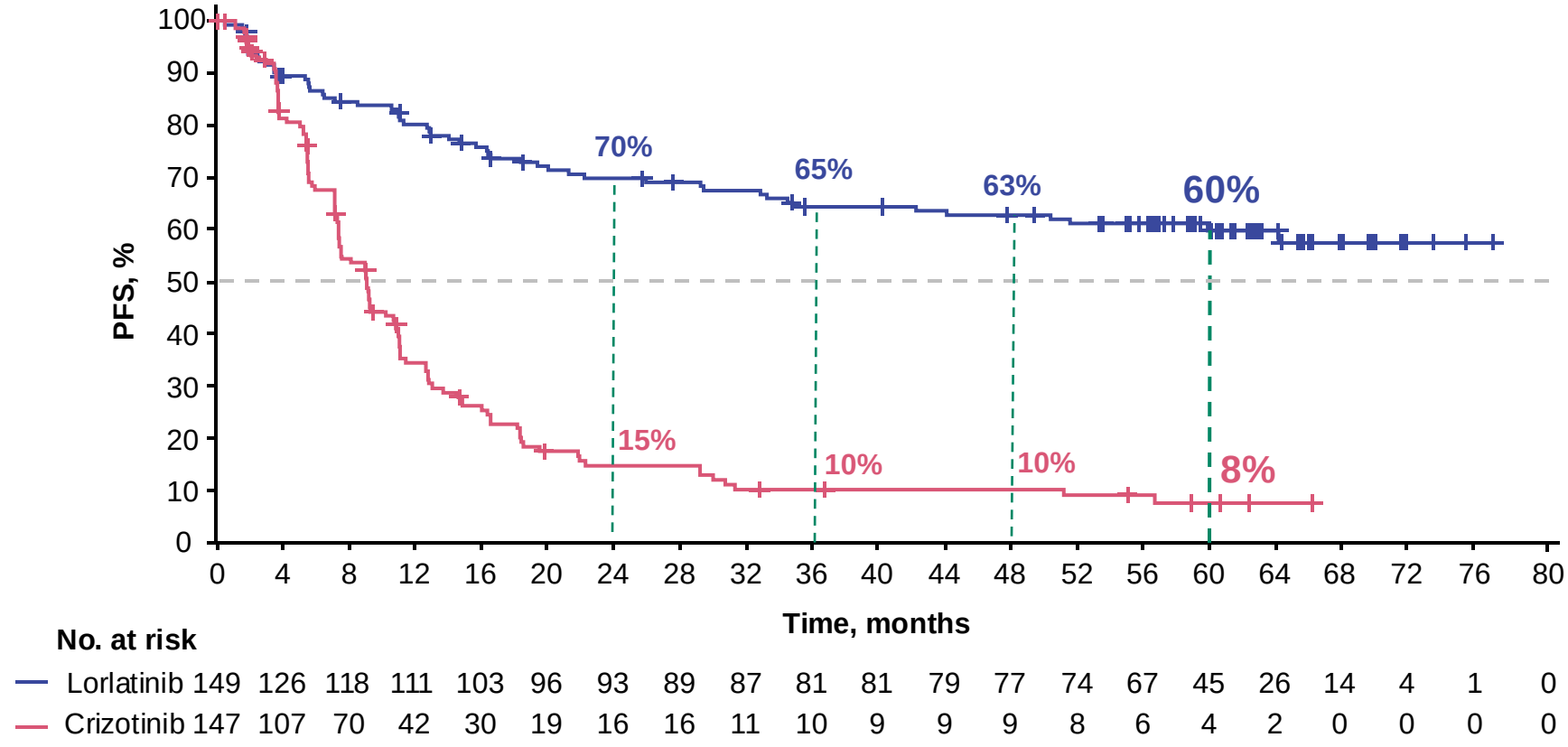
- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

Benjamin J. Solomon (Ben.Solomon@petermac.org)

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With 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)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

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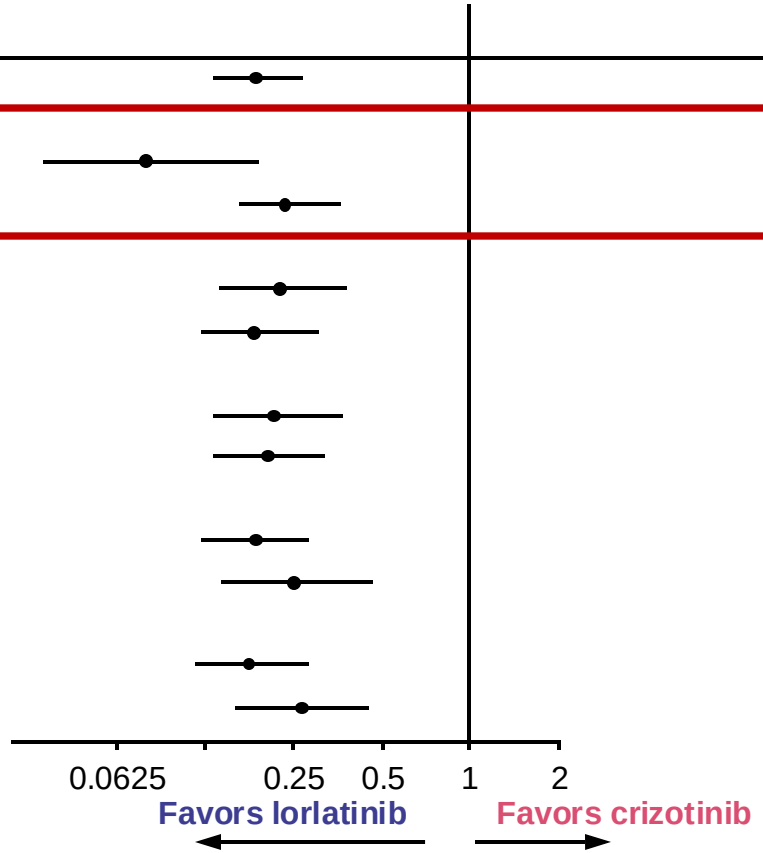
PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



PFS, progression-free survival.

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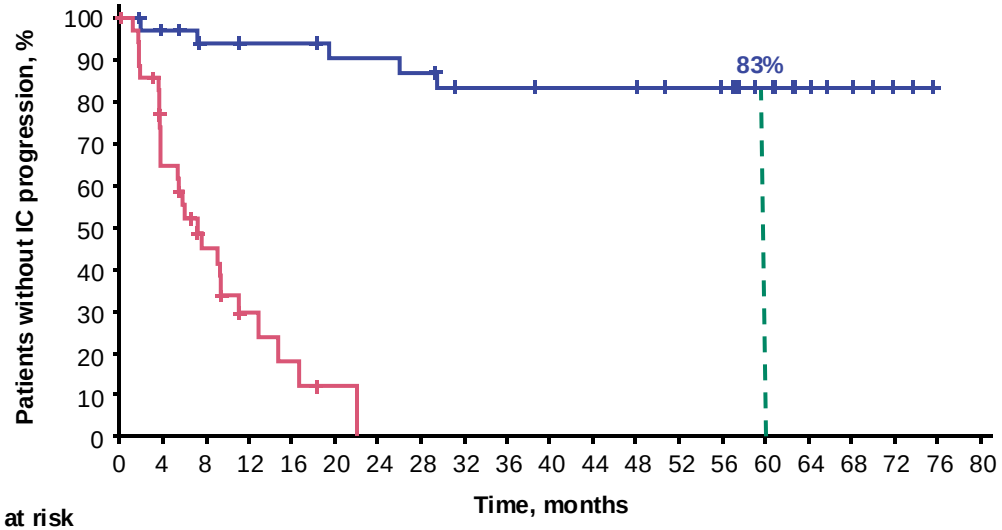
Time to IC Progression Was Longer With Lorlatinib in Presence or Absence of Baseline Brain Metastases

With Baseline Brain Metastases

	Lorlatinib (n=35)	Crizotinib (n=38)
Events, n	5	26
Time to IC progression, median (95% CI), months	NR (NR-NR)	7.2 (3.7-11.0)
HR (95% CI)	**0.03 (0.01-0.13)**	

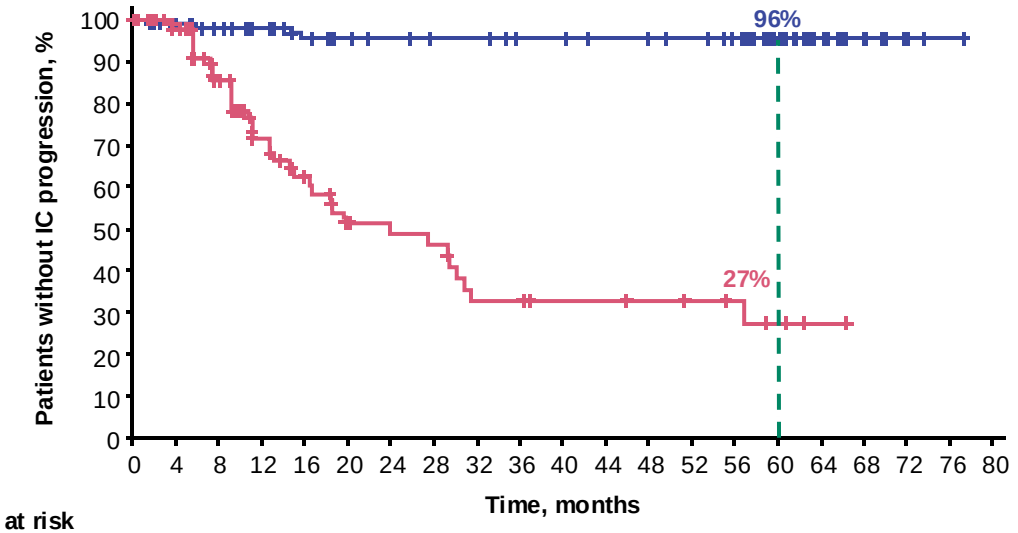


No. at risk

Lorlatinib	35	32	29	28	28	26	26	25	22	22	20	20	19	18	17	12	7	5	2	0	-
Crizotinib	38	21	12	5	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-

Without Baseline Brain Metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	39
Time to IC progression, median (95% CI), months	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.05 (0.02-0.13)**	



No. at risk

Lorlatinib	114	96	90	84	77	72	70	67	67	64	64	61	60	59	55	38	22	9	3	1	0
Crizotinib	109	86	63	41	31	21	19	18	12	12	10	10	9	8	6	4	2	0	0	0	0

HR, hazard ratio; IC, intracranial; NR, not reached.

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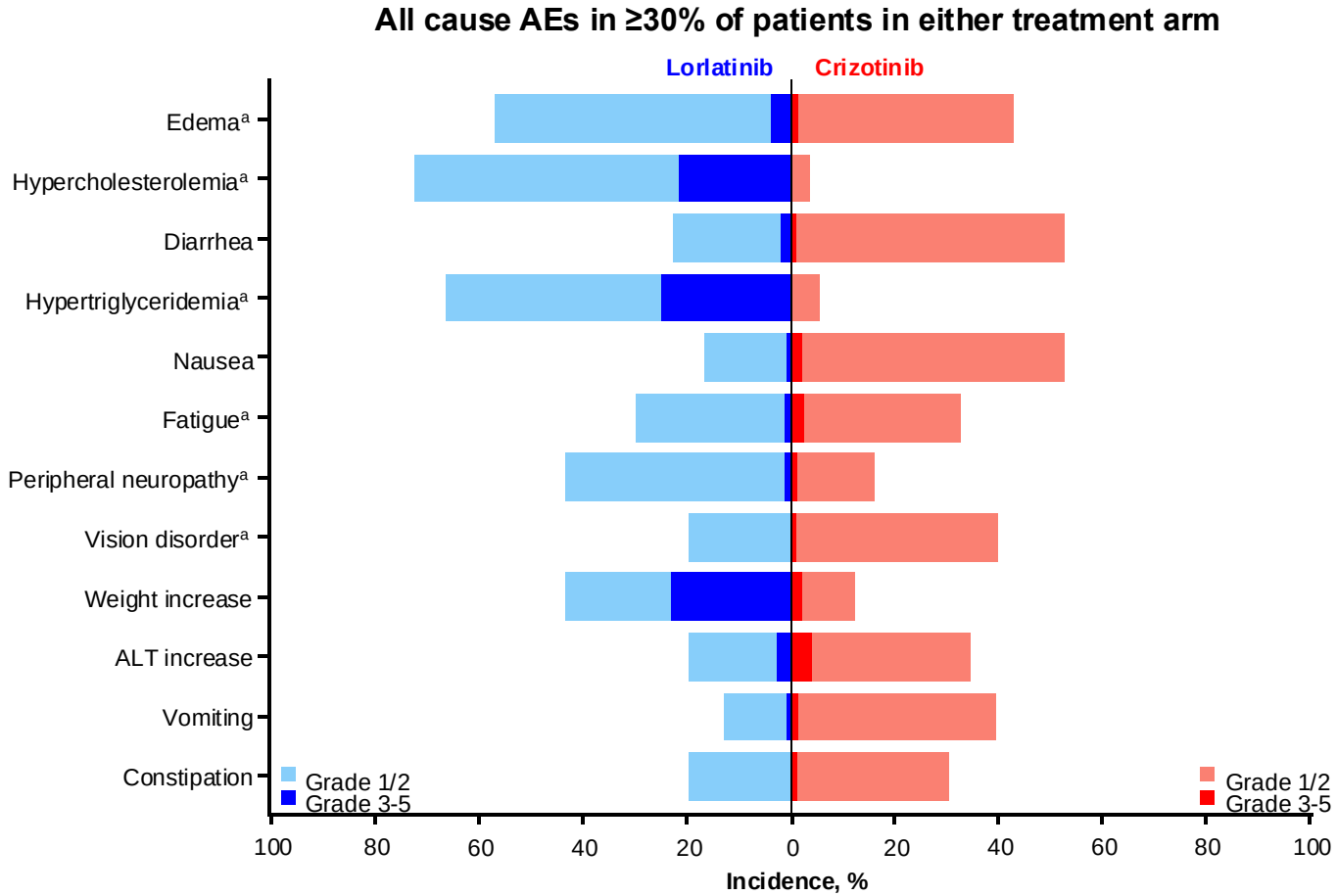
Safety Profile of Lorlatinib Was Consistent With That Observed in Prior Analyses

All-causality AEs observed in the lorlatinib arm:

- AEs of any-grade, grade 3/4, and serious occurred in 100%, 77%, and 44% of patients
- The higher incidence of grade 3/4 AEs was largely due to hypertriglyceridemia (25%), weight increase (23%), hypercholesterolemia (21%), and hypertension (12%)
- CNS AEs[b] occurred in 42% of patients in the lorlatinib arm, 86% of which were grade 1/2
- AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%; of which 5% were due to treatment-related AEs, all reported during the first 26 months



AE, adverse event; CNS, central nervous system.

[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

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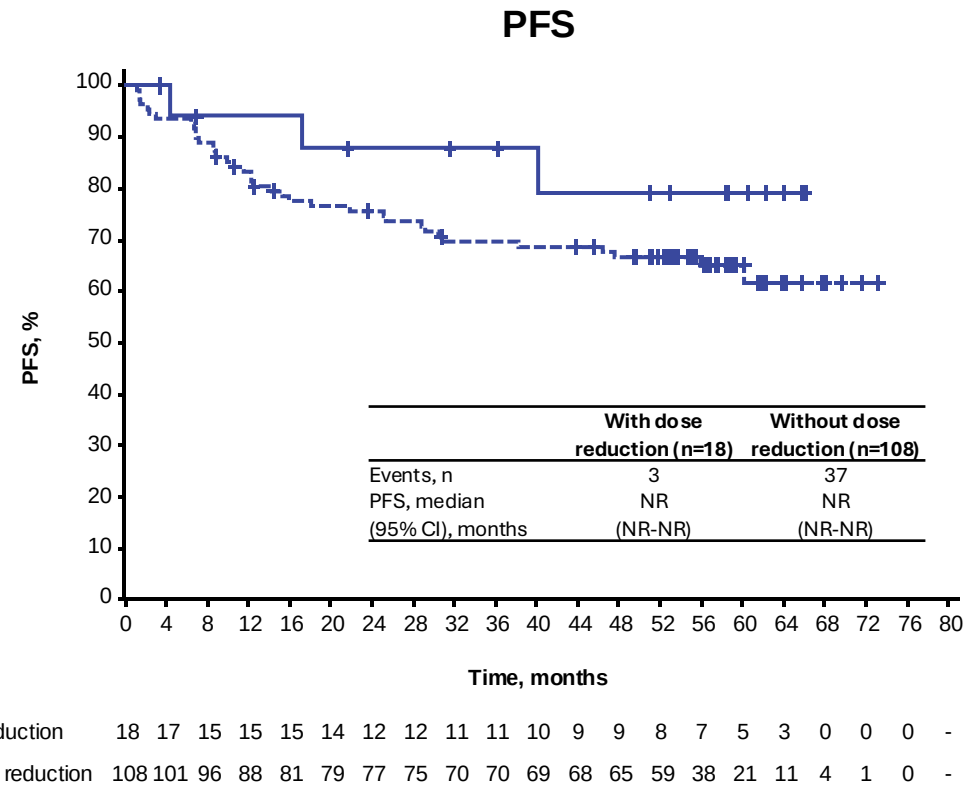
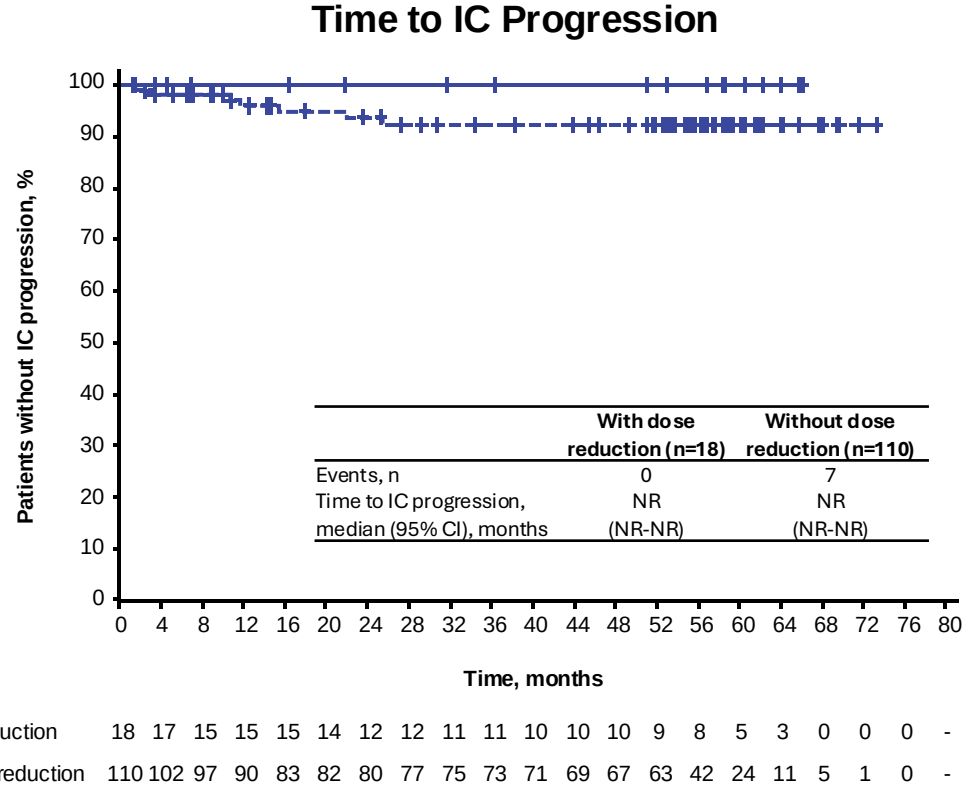
Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks





IC, intracranial; NR, not reached; PFS, progression-free survival.

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Emerging New *ALK* Mutations Were Not Detected in ctDNA Collected at the End of Lorlatinib Treatment

	Lorlatinib (n=31) n (%)	**Crizotinib (n=89)** n (%)
Resistance mechanisms		
New single ALK mutation	0	8 (9)
ALK compound mutation	0	2 (2)
Bypass mechanism	9 (29)	10 (11)
MAPK pathway aberration	3 (10)	1 (1)
PI3K/MTOR/PTEN pathway aberration	2 (6)	0
RTK pathway aberration	4 (13)	5 (6)
Cell cycle pathway aberration	2 (6)	5 (6)
Other gene aberration	11 (35)	19 (21)
Unknown	13 (42)	56 (63)

ctDNA from plasma collected at screening was analyzed with a validated, commercially available, 74-gene ctDNA next-generation sequencing assay (Guardant360 panel version 2.11; bioinformatics pipeline version 3.5.3; Guardant Health, Inc., Redwood City, CA).
ctDNA, circulating tumor DNA.

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Key Takeaways

- Exceptional clinical activity of 1L Lorlatinib.
- After 5 years of follow-up in the CROWN study, with lorlatinib treatment: Median PFS has still not been reached and PFS was 60%.
- Superb intracranial activity. The probability of being free of intracranial progression was 92%.
- Activity in ALK subsets considered a poorer prognosis.

- **1L, first-line**

How to Choose? FDA Approved Next Generation ALK inhibitors for 1L Therapy: Efficacy and Toxicity

	Alectinib	Brigatinib	Lorlatinib
ORR	79%	71%	76%
Med PFS by ICR	25.7 mo	24 mo	NR (3yr follow-up)
Med PFS by IR	34.8	30.8	NR (5-yr PFS=60%)
Med OS	>5 yr	NR	NR
Toxicity	Fatigue, constipation, myalgia (CPK), edema, transaminitis (moderate) Weight gain	Nausea, diarrhea, fatigue, HA, HTN, pulmonary tox, transaminitis	Edema, neuropathy, cognitive changes (mood), lipids, weight gain

- **1L, first-line**

The Oncologist®

Lung Cancer

Clinical Management of Adverse Events Associated with Lorlatinib

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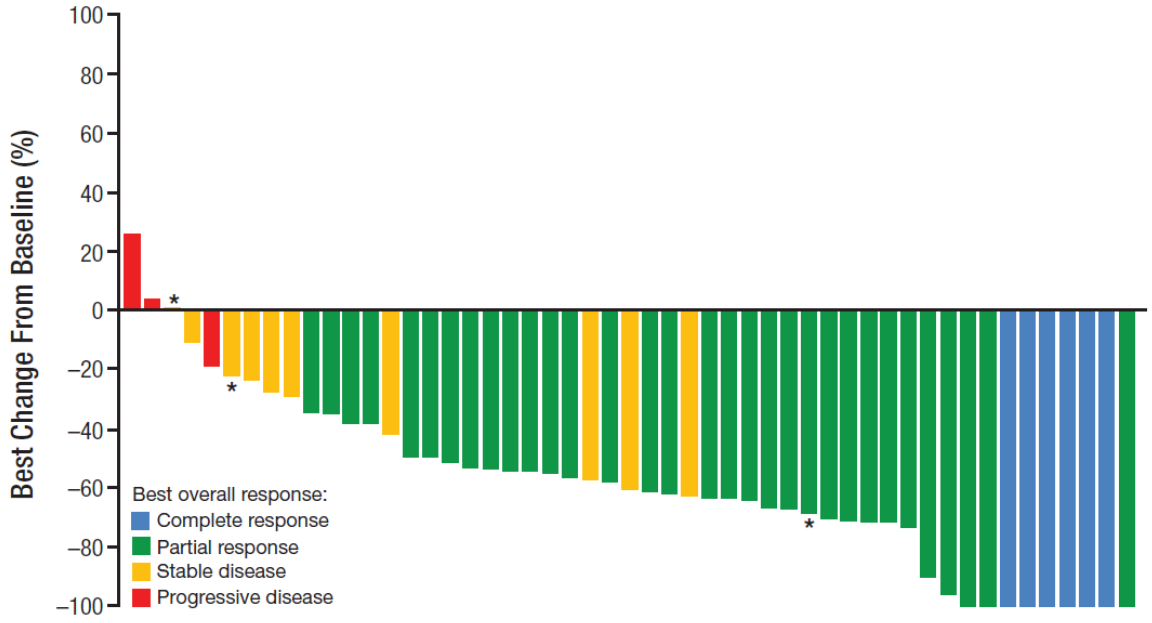
Disclosures of potential conflicts of interest may be found at the end of this article.

T. Bauer et al. Oncologist. 2019 Aug; 24(8): 1103–1110.

Phase 1 PROFILE 1001 Study: Crizotinib in *ROS1*-Rearranged NSCLC—Updated Analysis

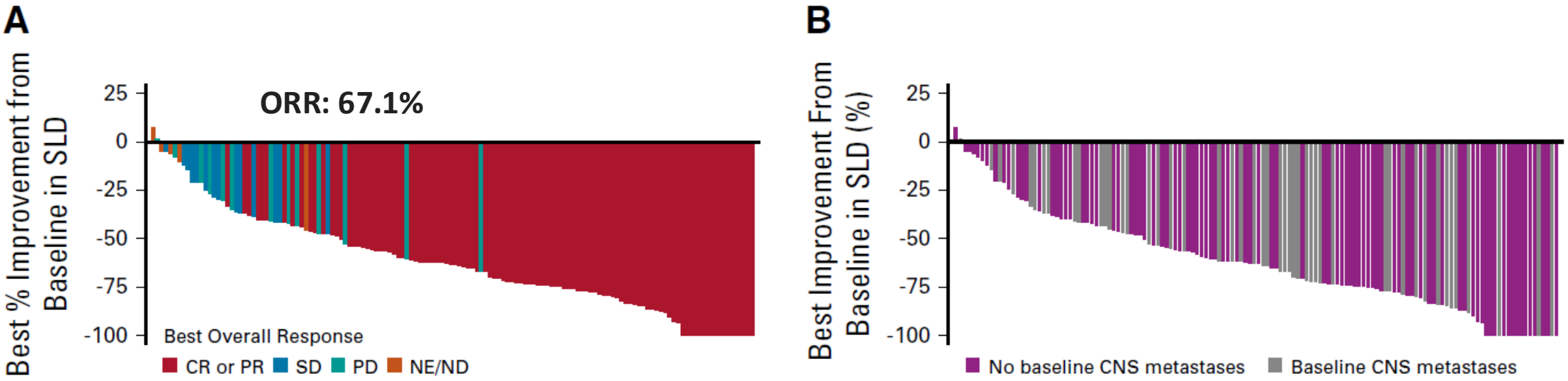
- ROS1 NSCLC ~ 1.5% NSCLC
- 53 patients received crizotinib; median duration of treatment: 22.4 mo
- ROS1 status determined by FISH or RT-PCR; all patients received crizotinib 250 mg BID starting dose
- Median follow up: 62.6 mo
- ORR- 72% (58-83)
- mPFS- 19.3 (15.2-39.1)



Shaw AT, et al. *Ann Oncol*. 2019; 30(7):1121–1126.

Entrectinib in *ROS1*-Fusion-Positive NSCLC: Updated Analysis

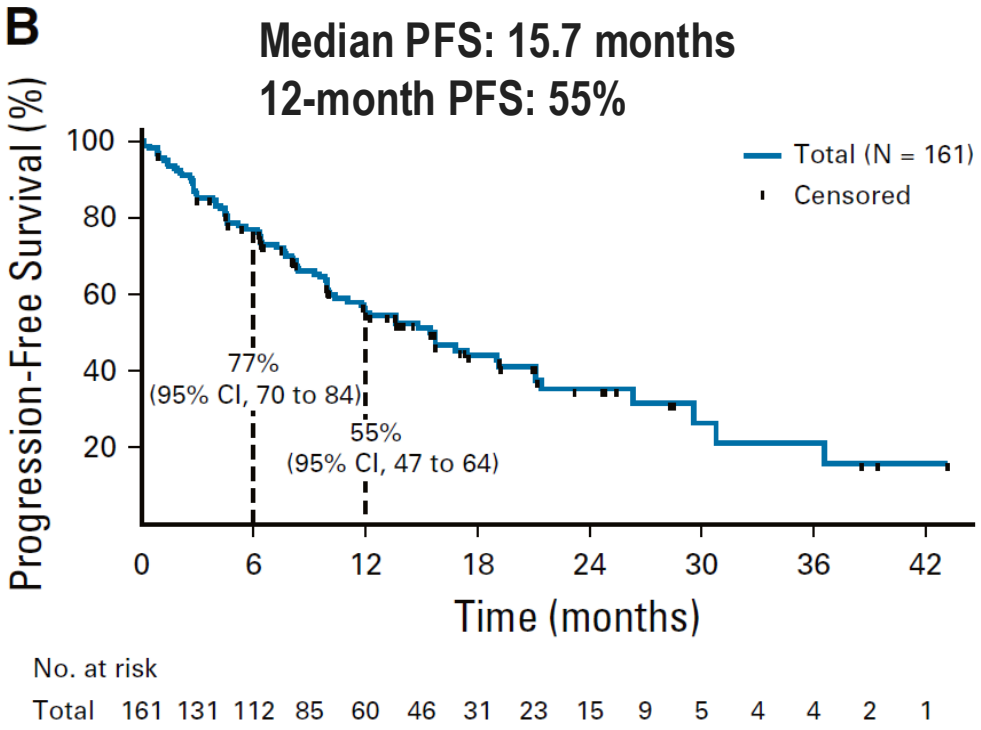
- Updated integrated analysis of 3 phase I/II clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) of entrectinib, in *ROS1* fusion-positive NSCLC
- 161 patients with a follow-up of ≥ 6 months were evaluable
- Median duration of follow-up, 15.8 months
- Median treatment duration was 10.7 months

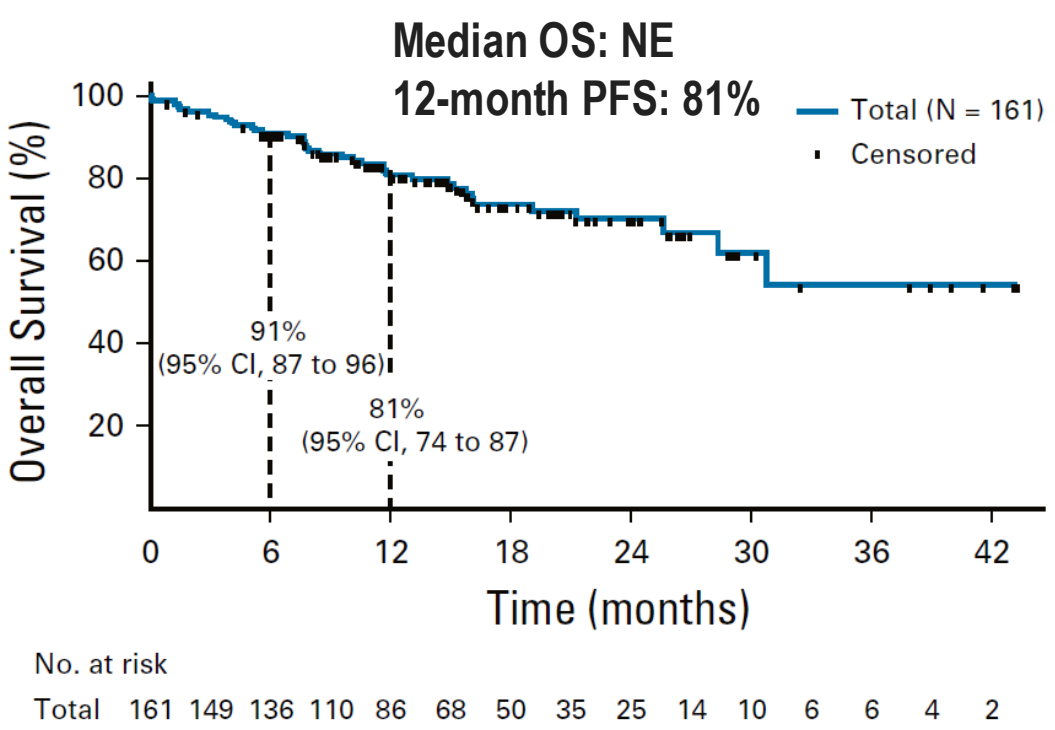


Intracranial ORR: 79.2% (n = 19/24)[b]; median intracranial DoR: 12.9 months (12-mo rate, 55%)

Dziadziuszko R, et al. *J Clin Oncol*. 2021;39(11):1253-1263.

Entrectinib in *ROS1*-Fusion-Positive NSCLC: PFS and OS—Updated Analysis



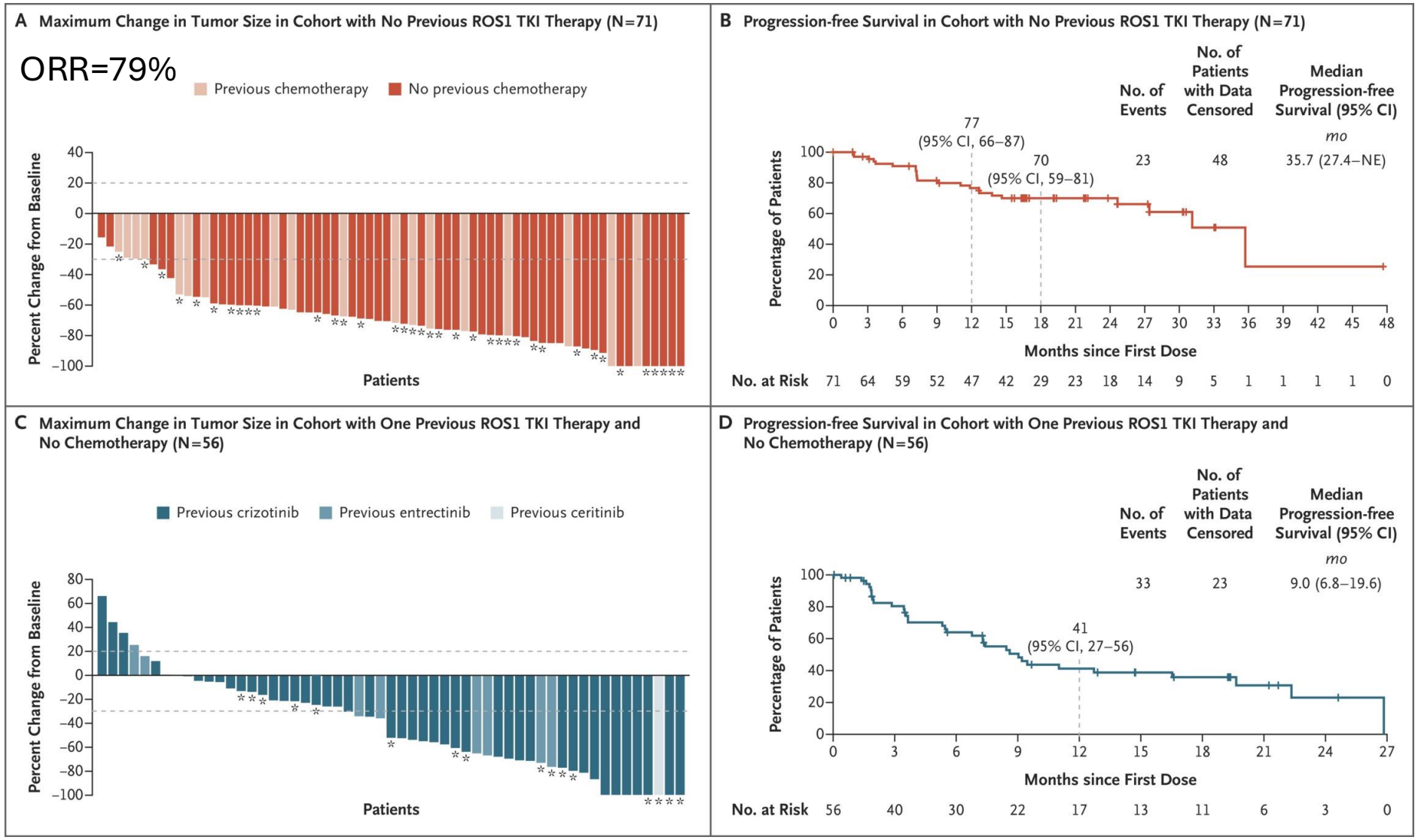


Side effects: hyperuricemia, weight gain, dizziness/CNS taste changes, edema, GI side effects, AST/ALT elevation

Median duration of follow-up, 15.8 months

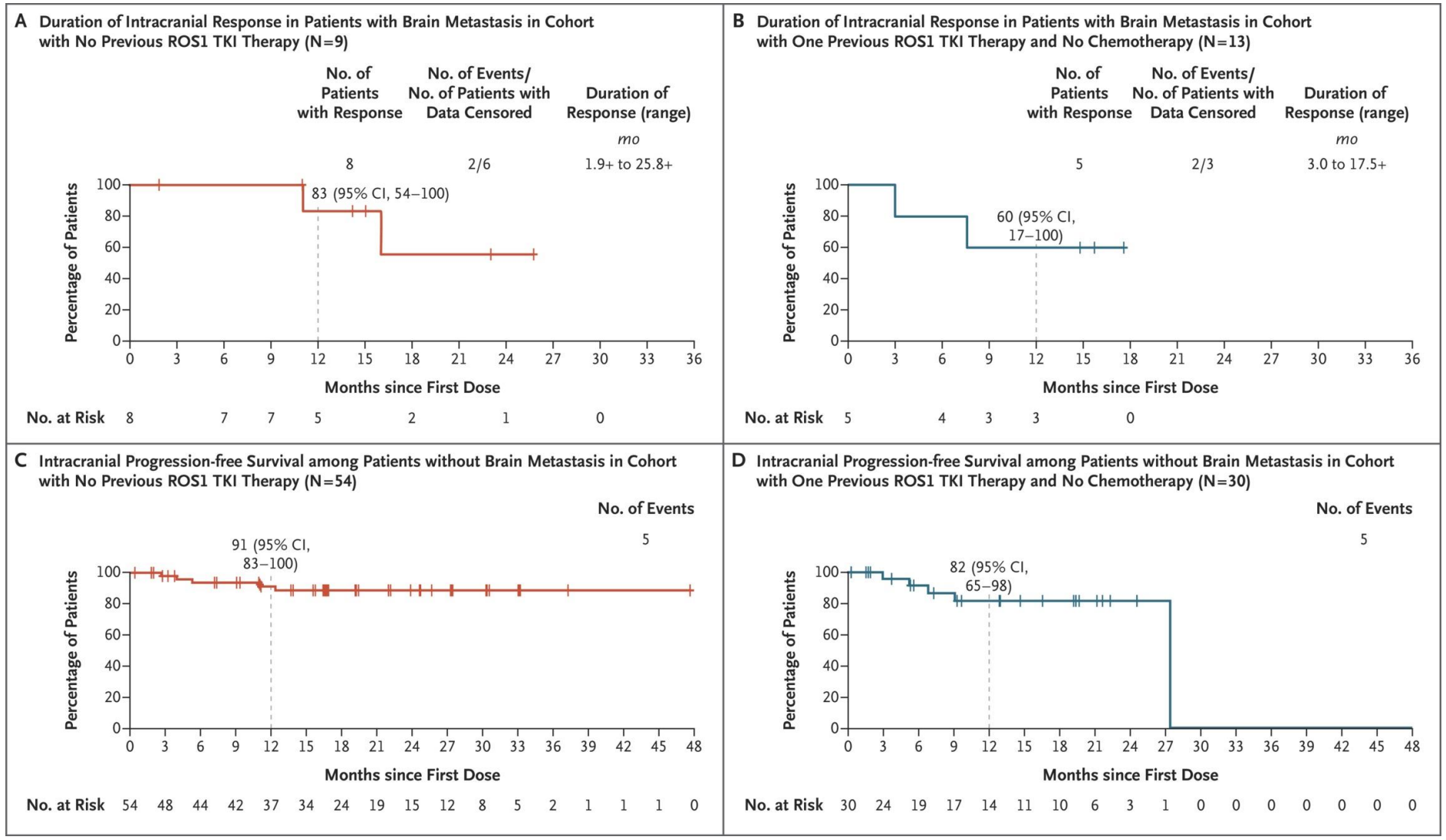
Dsziadziuszko R, et al. *J Clin Oncol*. 2021;39(11):1253-1263.

Repotrectinib: Efficacy in the Primary Efficacy Population



Drilon A et al. N Engl J Med2024;390:118-131

Intracranial Activity of Repotrectinib



Drilon A et al. N Engl J Med2024;390:118-131

Summary of ROS1 TKIs in TKI-Naïve ROS1+ NSCLC

	Crizotinib* (PROFILE 1001)	Entrectinib* (ALKA-372-001, STARTRK-1, STARTRK-2)	Ceritinib (Korean Phase 2)	Taletrectinib (Chinese Phase 2)	Lorlatinib (Phase 1/2)	Repotrectinib# (TRIDENT-1 Phase 1/2)
N	53	161	20	106	21	71
ORR	72%	67% (n=108)	67%	90.6%	62%	79%
Median PFS	19.3 months	15.7 months	19.3 months	NR (30.4-NR)	21.0 months	35.7
CNS activity	N/A	19/24 (79%) patients with measurable intracranial disease	2/5 (40%) patients with measurable or non-measurable intracranial disease	88%	7/11 (64%) patients with measurable or non-measurable intracranial disease	8/9 (89%) patients with measurable intracranial disease
Reference	Shaw et al. Ann Oncol 2019	Dziadziuszko et al. JCO 2021	Lim et al. JCO 2017	Li et al., ASCO 2024	Shaw et al. Lancet Oncol 2019	Drilon et al. NEJM 2024


YOU MUST CHOOSE...
BUT CHOOSE WISELY