Dr. Dieter Stevens
Department of Respiratory Diseases
Thoracic Oncology Cluster
UZ Gent
www.uzgent.be/thoracale-oncologie

POST ASCO 2026: UPDATE IN ONCOGENE DRIVEN NSCLC

TOGA meeting 17/06/2026

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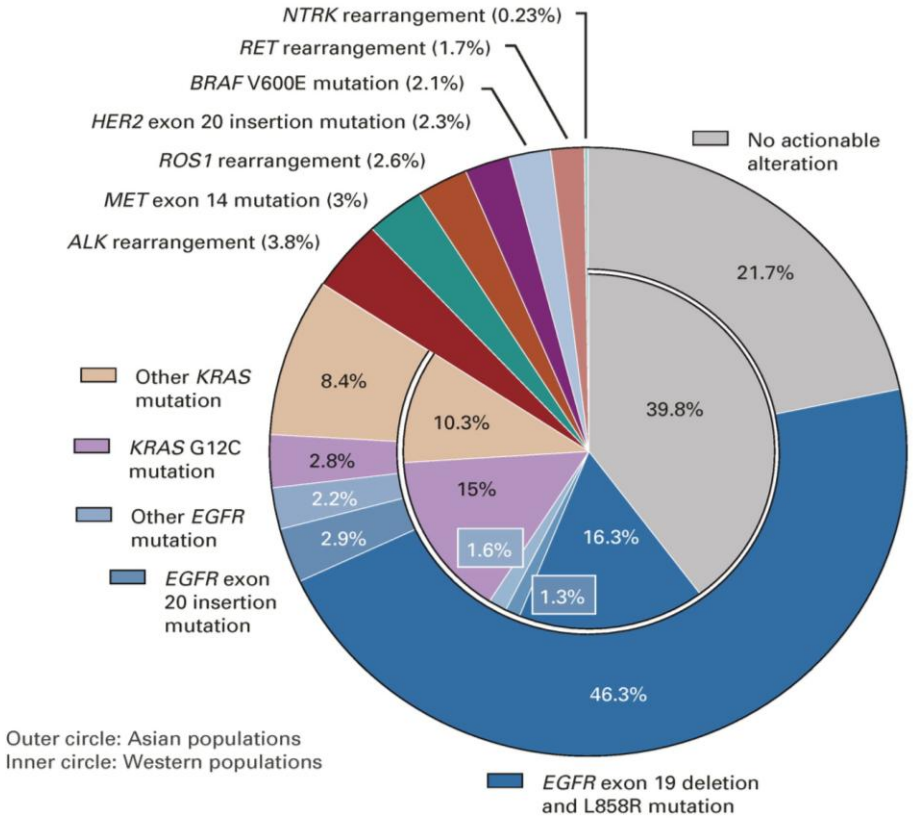
2026 ASCO ANNUAL MEETING

~ 40-60% of NSCLC is oncogene driven



CLINICAL PRACTICE GUIDELINES

An ESMO Product

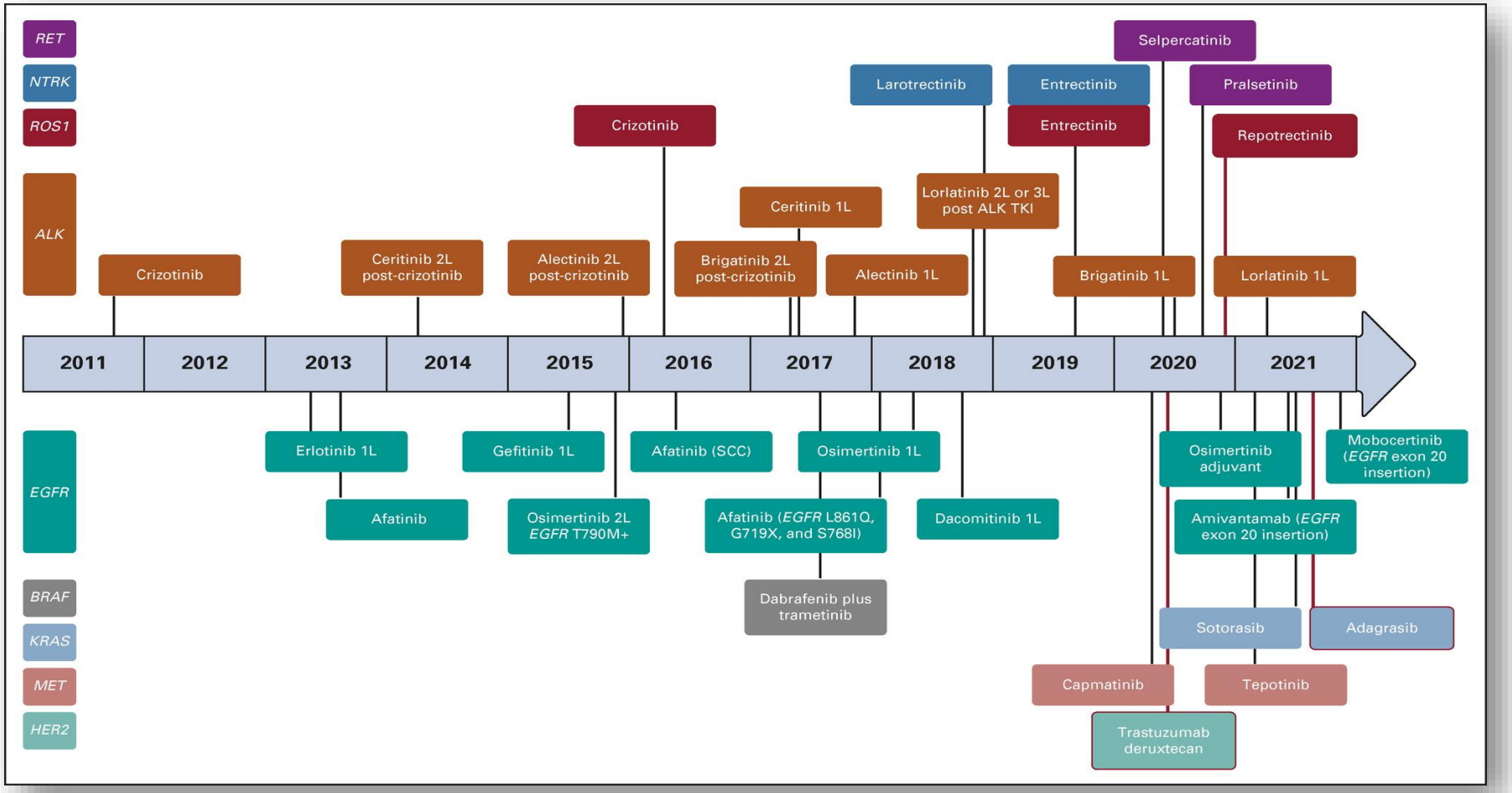
Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer

ESMO Living Guideline, v1.3 February 2026

L Hendriks, F Cortiula, E Mariamidze, D Martins-Branco, G Pentheroudakis, M Reck

Tan AC and Tan DSW. J Clin Oncol. 2022;40(6):611-625.

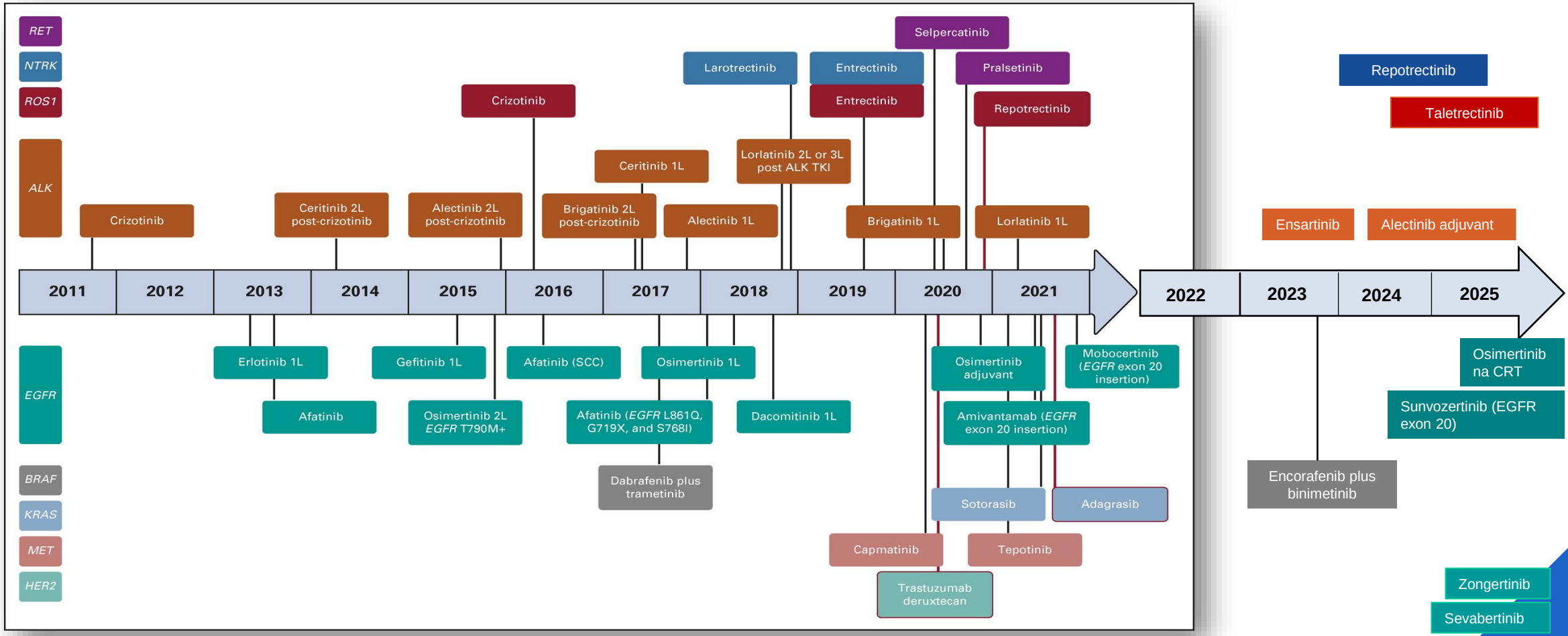
Timeline of FDA-approved targeted therapies for oncogene-driven NSCLC



Tan AC and Tan DSW. J Clin Oncol. 2022;40(6):611-625.

* FDA approvals

Timeline of FDA-approved targeted therapies for oncogene-driven NSCLC



Tan AC and Tan DSW. J Clin Oncol. 2022;40(6):611-625.

* FDA approvals

EGFR

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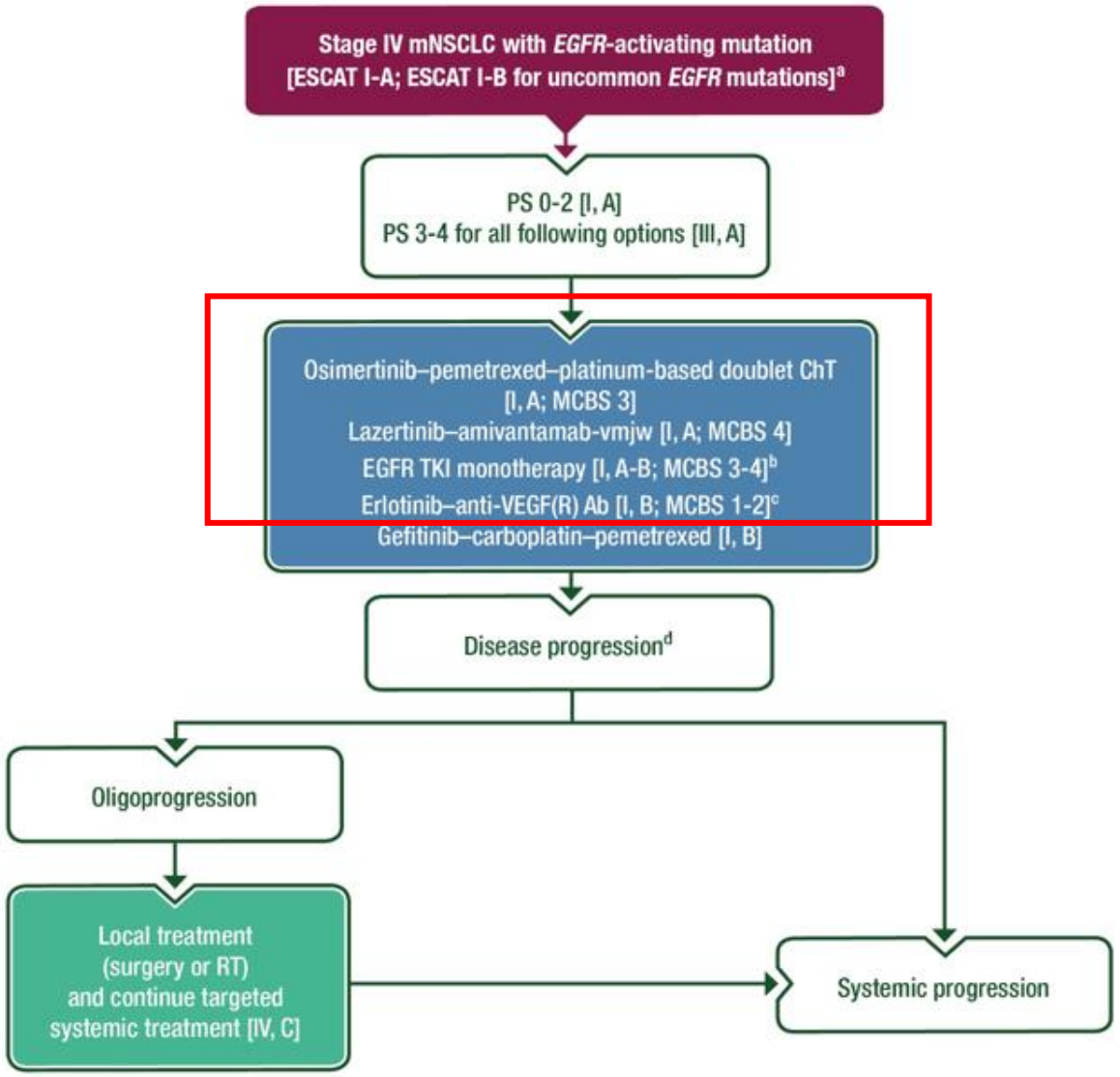
Common EGFR

CLINICAL PRACTICE GUIDELINES

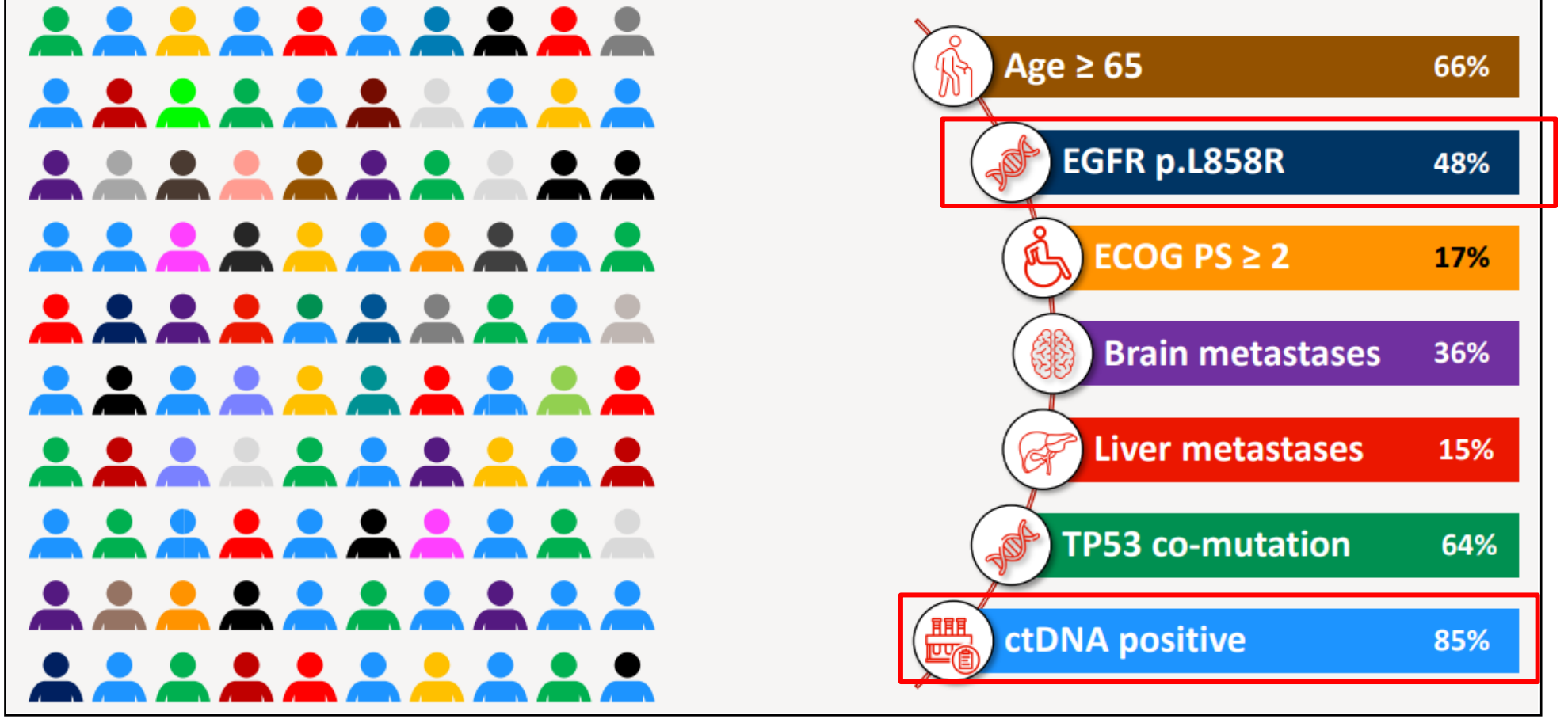
ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

v1.3 February 2026



Risk-factors associated with poorer overall survival on EGFR TKI monotherapy

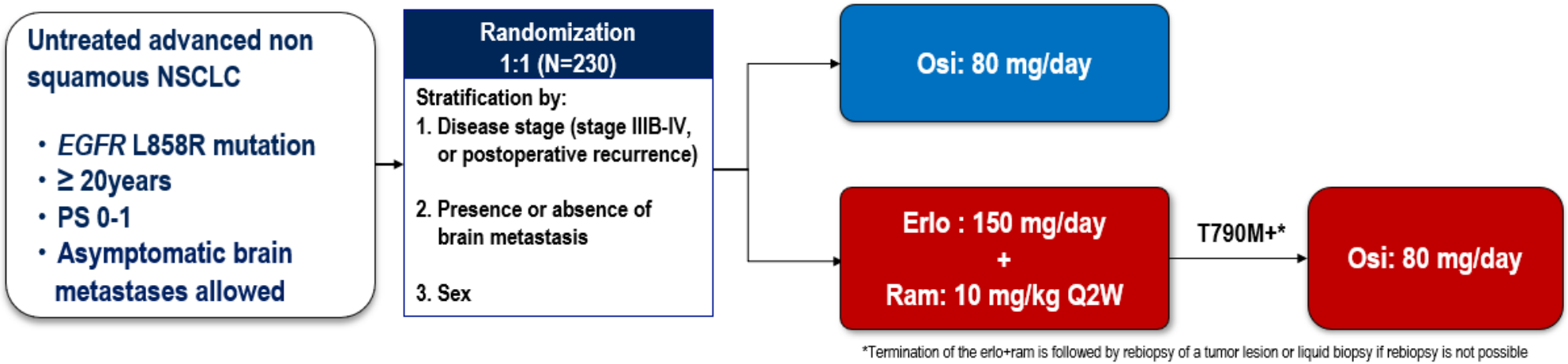
95% of EGFRm NSCLC patients in the real-world have ≥ 1 high-risk feature[1]



[1] Sabari JK, et al. J Thorac Oncol 2025; Passaro A. ELCC 2025

REVOL858R trial

Design



Primary endpoint: **Time to failure of strategy (TFS)***

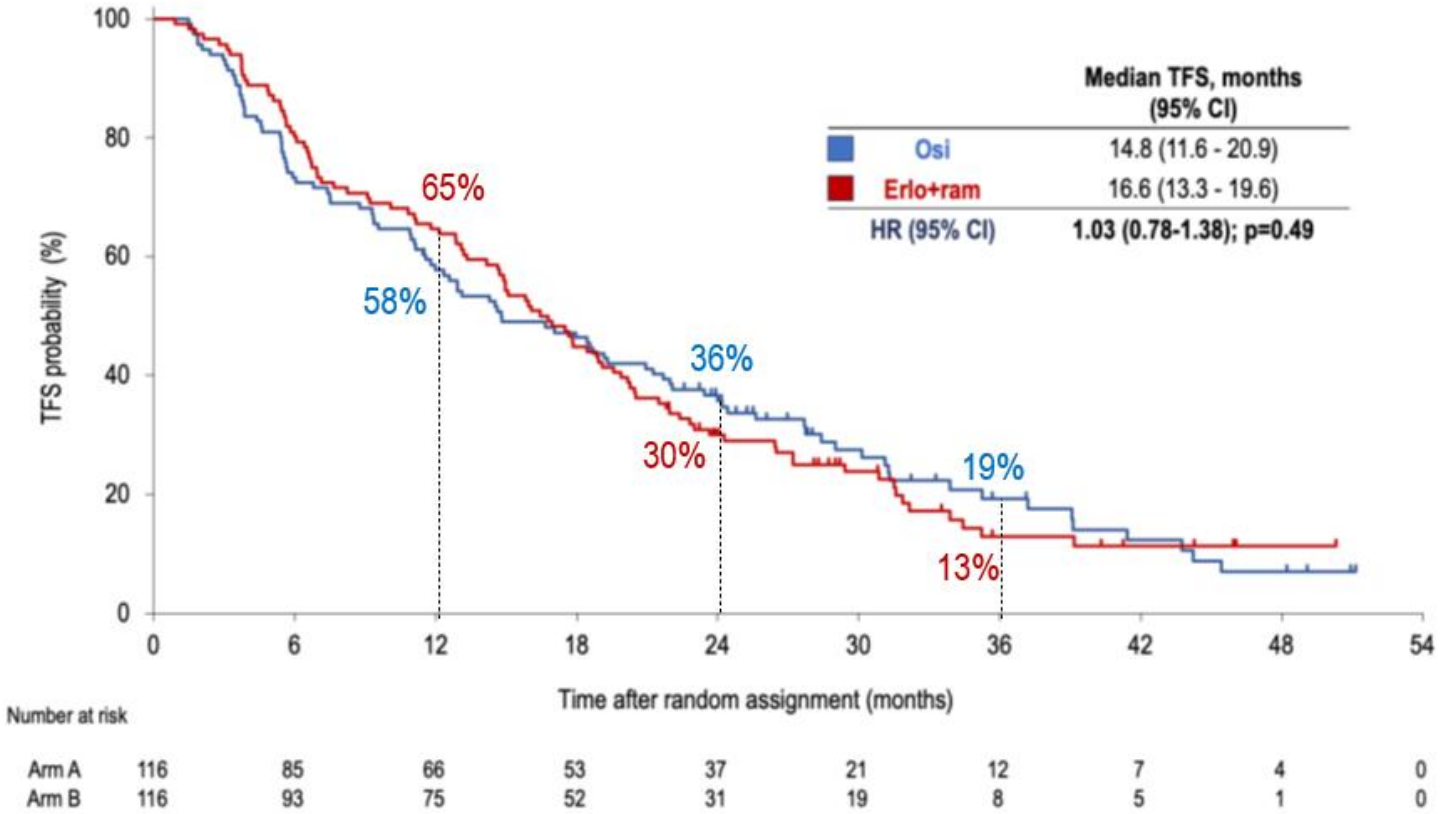
Secondary endpoint : **OS (Key secondary endpoint)** , PFS, PFS2, ORR, TTF, TD-TKI, and safety

Study objective: To determine whether sequential erlo + ram followed by osi improves TFS versus upfront osi in untreated advanced *EGFR* L858R-mutated NSCLC.

Haratake N, et al. ASCO 2026

REVOL858R trial

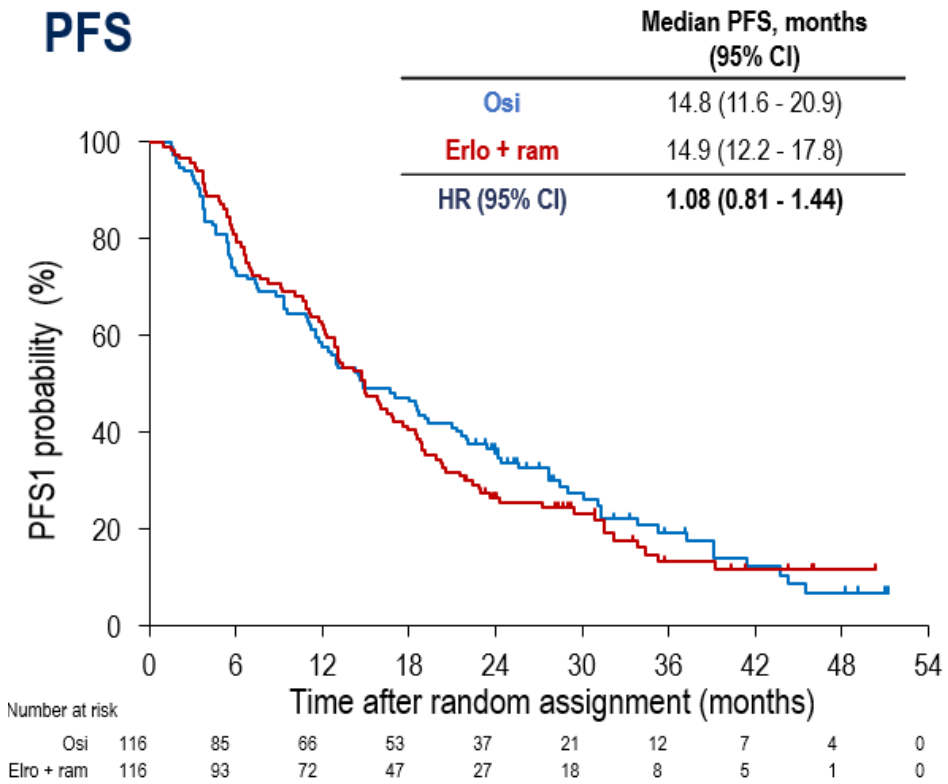
TFS

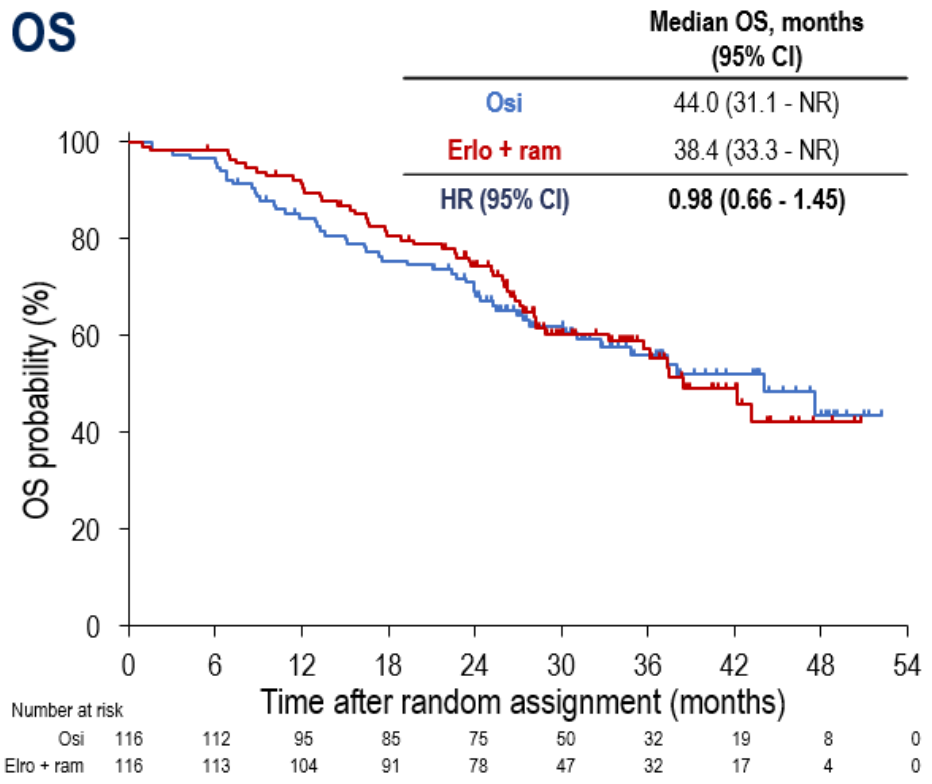


Haratake N, et al. ASCO 2026

REVOL858R trial

PFS and OS

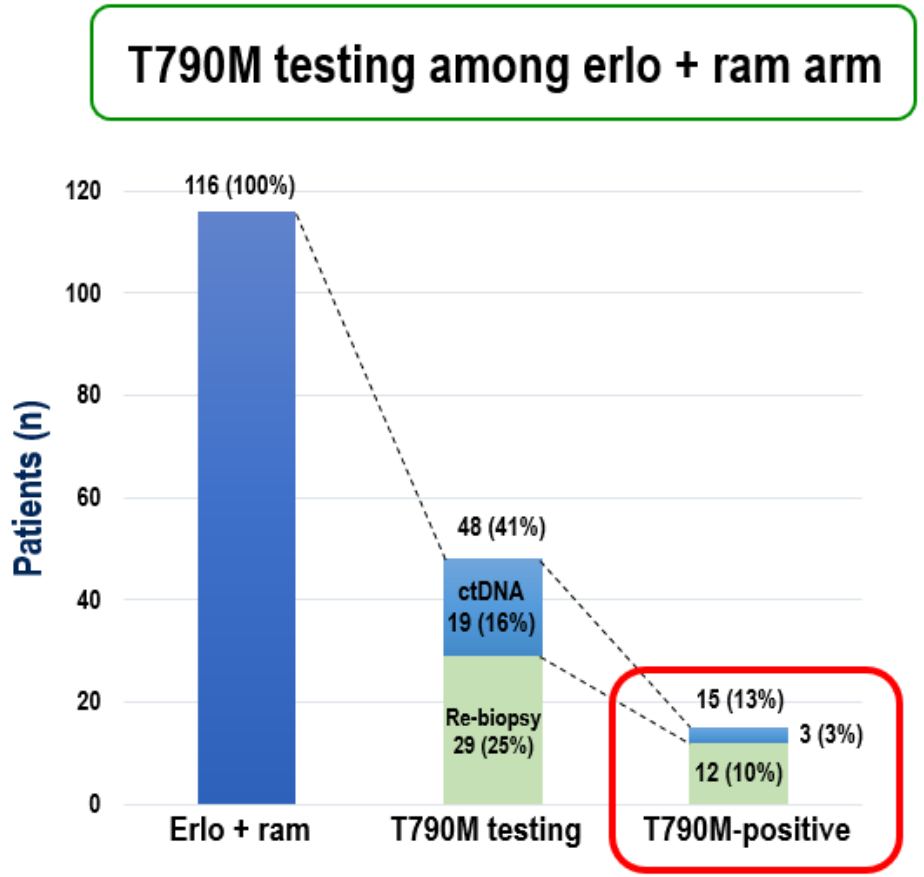




Haratake N, et al. ASCO 2026

REVOL858R trial

T790M testing



First subsequent treatment, n (%)	Osi (n=116)	Erlo + ram (n=116)
Osi	23 (20%)	16 (14%)
1st or 2nd generation EGFR-TKIs*	7 (6%)	28 (24%)
Platinum-based cytotoxic chemotherapy	34 (29%)	28 (24%)
Nonplatinum cytotoxic chemotherapy	1 (1%)	3 (3%)
Other	3 (3%)	0 (0%)
No subsequent treatment	48 (41%)	41 (35%)

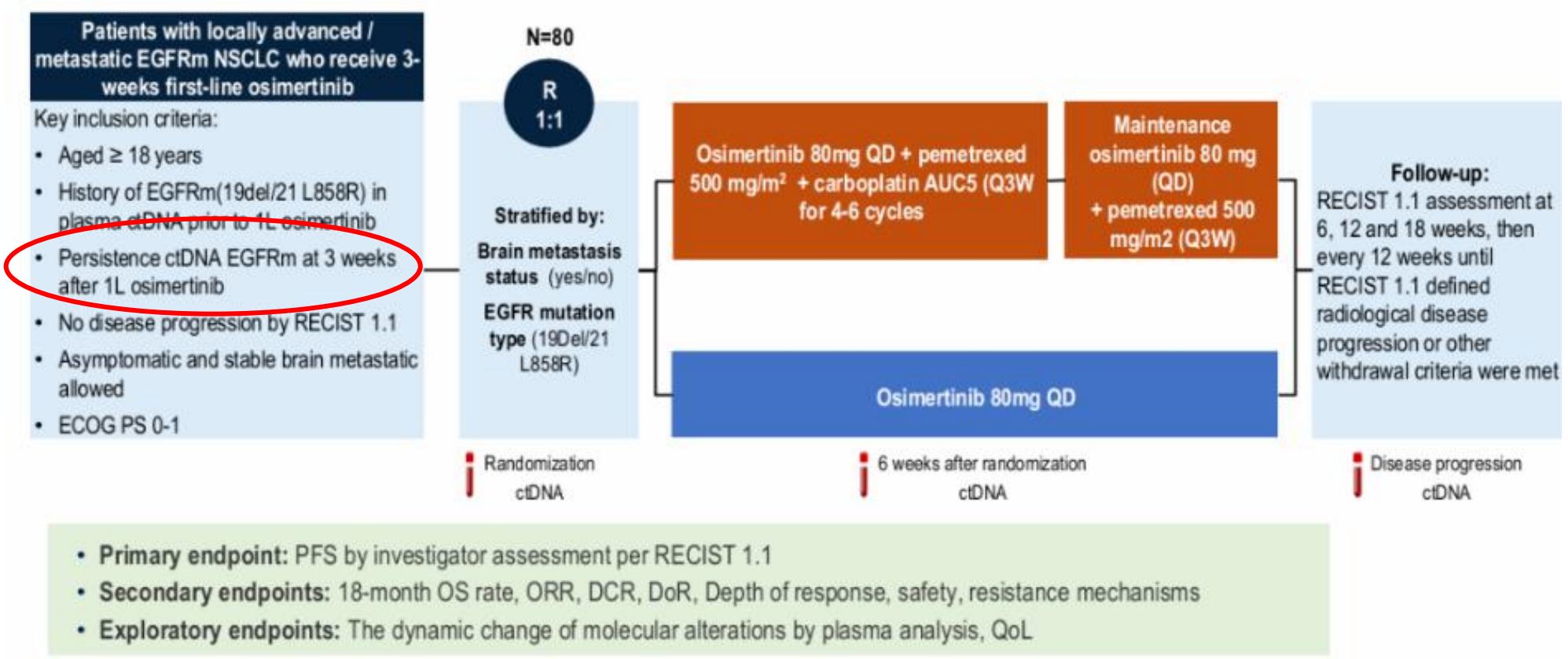
*Including antiangiogenic combination therapy

Haratake N, et al. ASCO 2026

PFS by baseline prognostic factors

	FLAURA 2		MARIPOSA	
	Osimertinib + CT	Osimertinib	Amivantamab + Lazertinib	Osimertinib
CNS metastases at baseline	N = 116 **24.9** (22.0-NE)	N = 110 13.8 (11.0-16.7))	N = 178 **18.3** (16.6-23.7)	N = 172 13.0 (12.2-16.4)
	0.47 (0.33-0.66)		**0.69** (0.53-0.92)	
L858R EGFR mutation	N = 106 **24.7** (19.5-27.4)	N = 107 13.9 (11.1-19.4)	N = 171 **18.4** (16.6-21.0)	N = 172 14.8 (12.9-16.6)
	0.63 (0.44-0.90)		**0.78** (0.59-1.02)	
Liver metastases at baseline	N = 43 **19.5** (11.5-24.9)	N = 66 11.1 (8.3-16.8)	N = 64 **18.2** (13.1-NE)	N = 72 11.0 (7.4-12.8)
	0.66 (0.41-1.07)		**0.58** (0.37-0.91)	
TP53 mutation	N = 41 **27.6** (24.7-27.6)	N = 38 27.6 (13.9-30.3)	N = 149 **18.2** (15.3-22.1)	N = 144 12.9 (11.1-14.7)
	0.57 (0.43-0.77)		**0.65** (0.48-0.87)	
ctDNA positive at baseline	N = 148 **24.8** (19.6-27.9)	N = 161 13.9 (13.6-16.6)	N = 266 **20.3** (18.2-23.9)	N = 274 14.8 (12.9-14.7)
	0.60 (0.45-0.80)		**0.71** (0.57-0.89)	

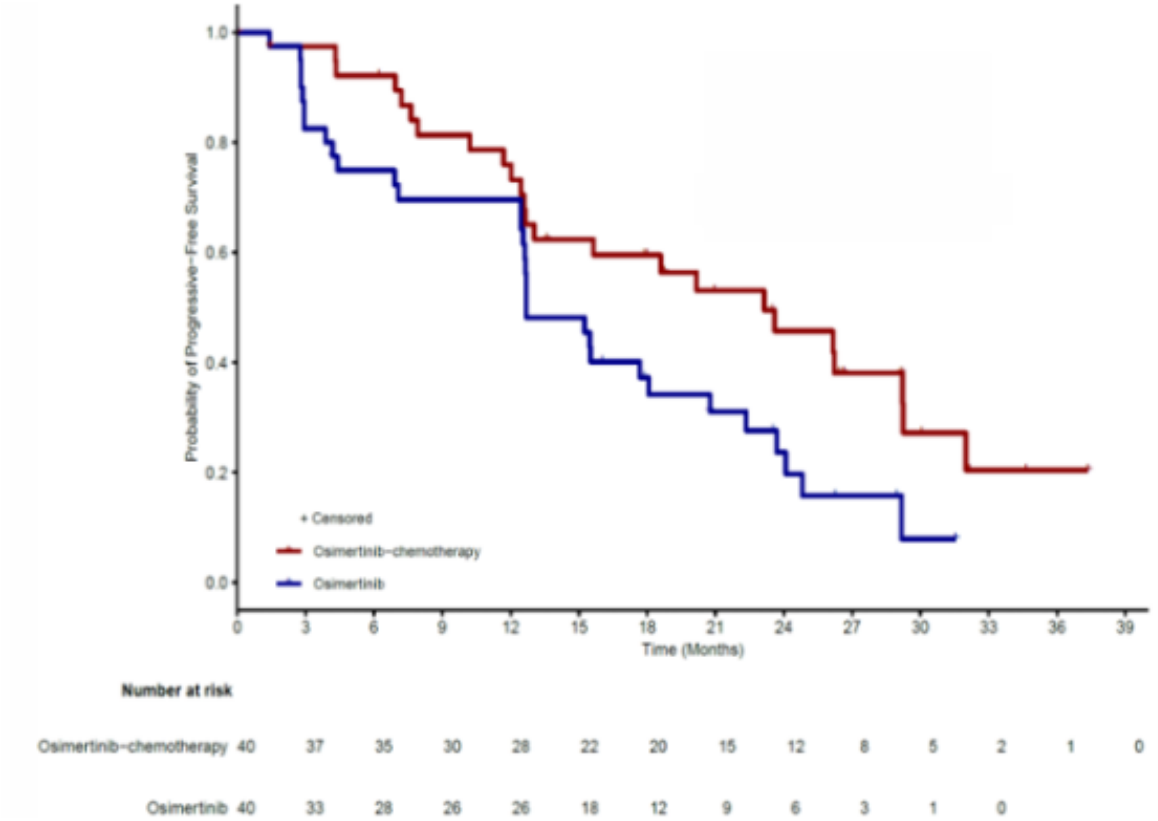
FLAME
Design



- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1
- **Secondary endpoints:** 18-month OS rate, ORR, DCR, DoR, Depth of response, safety, resistance mechanisms
- **Exploratory endpoints:** The dynamic change of molecular alterations by plasma analysis, QoL

Wang Z, et al. ASCO 2026

FLAME
PFS



	Osimertinib–chemotherapy (N=40)	Osimertinib (N=40)
Number of Events	24	31
Median PFS, mo (95% CI)	23.1 (12.65-29.24)	12.7 (12.45-18.07)
HR (90% CI)	**0.54** (0.34, 0.86); ***P=0.028***	

Overall maturity: 68.8%

Median follow-up for PFS*, months (95%CI):
Osimertinib-chemotherapy, 17.9(12.5~23.1)
Osimertinib monotherapy, 12.7(7.1~16.0)

Wang Z, et al. ASCO 2026

PFS by baseline prognostic factors

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ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

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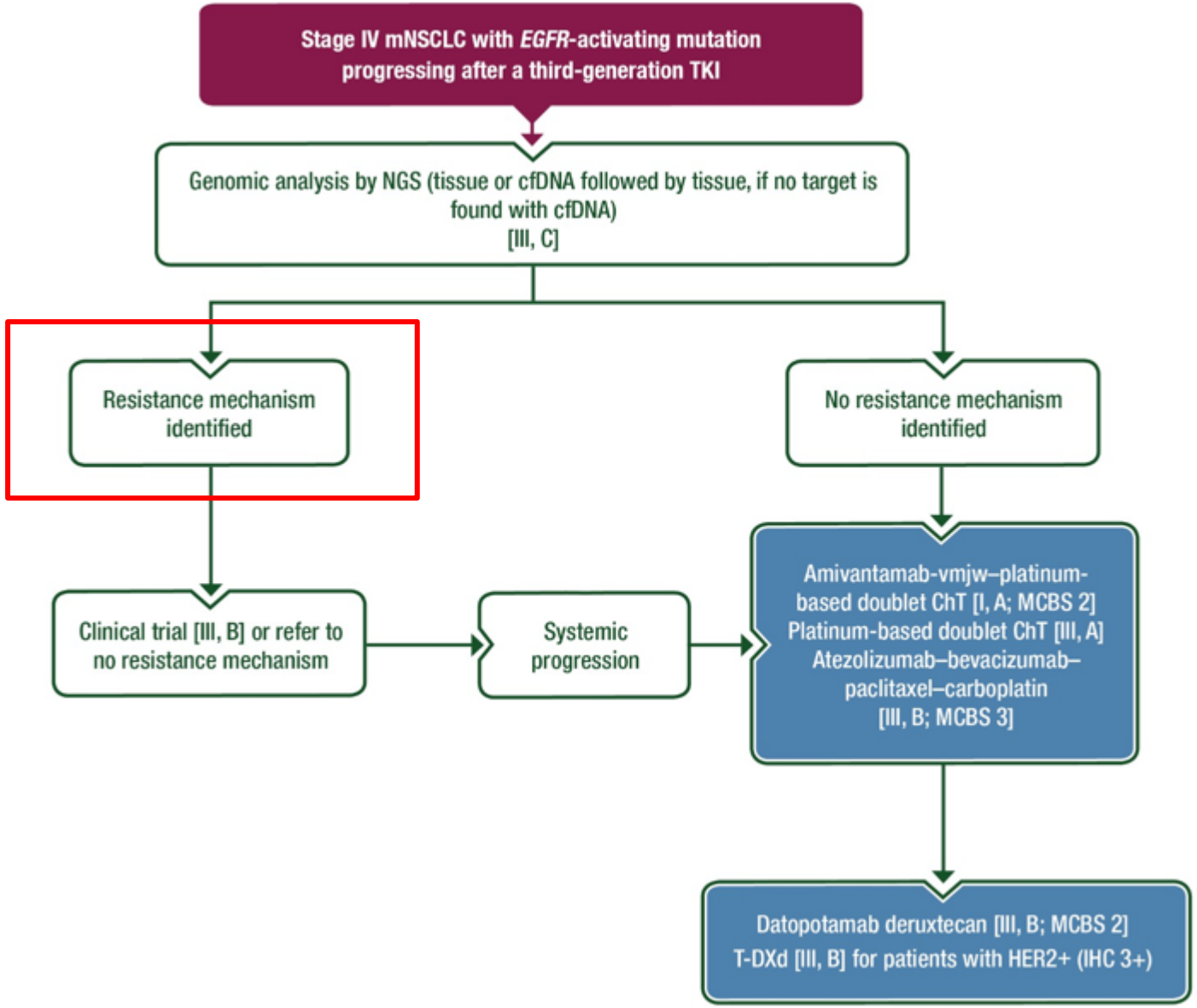
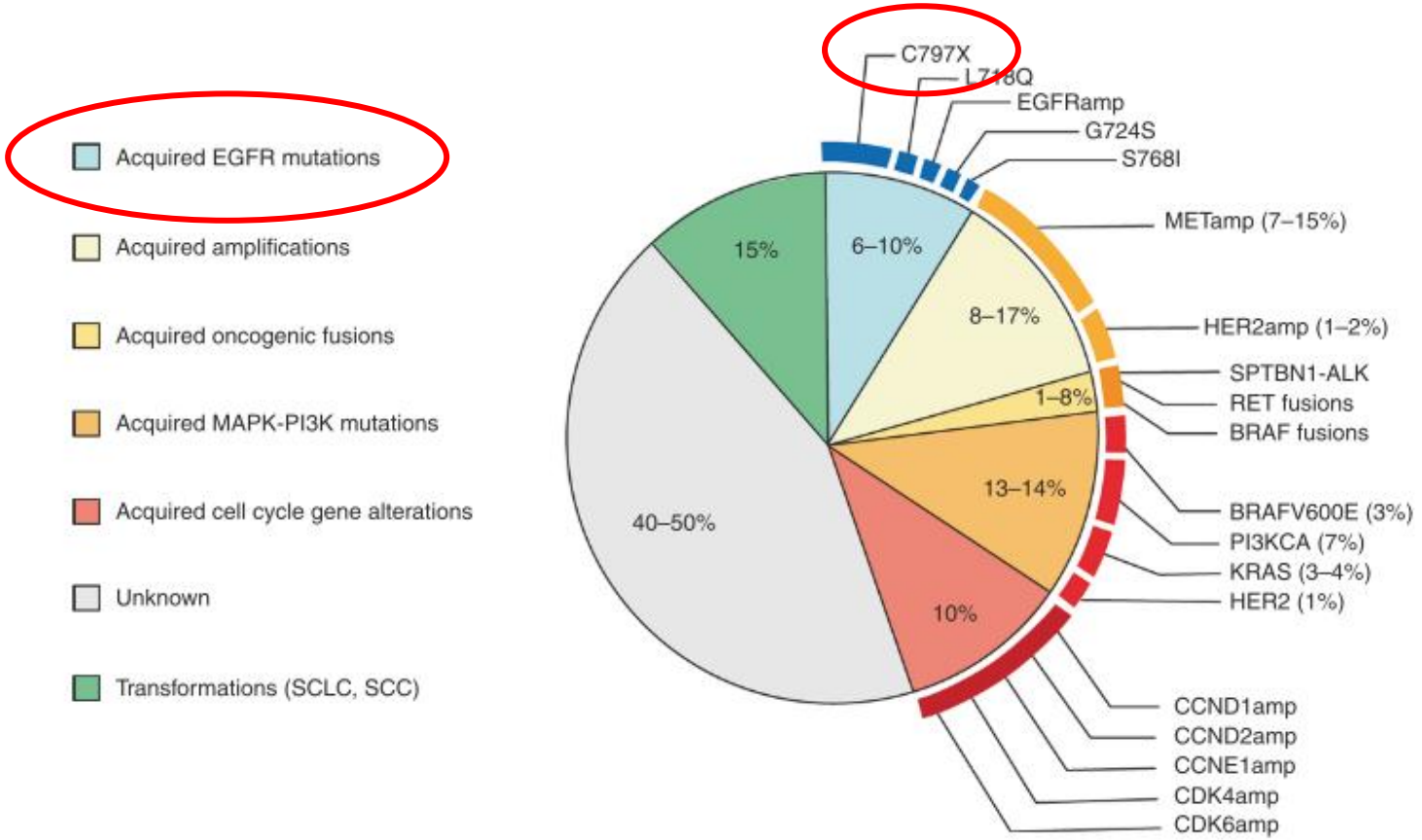


Resistance mechanisms post-osimertinib

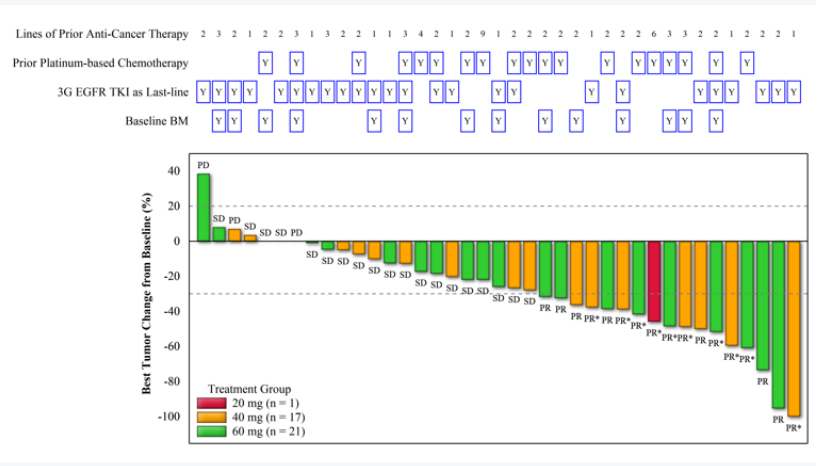


Leonetti A, et al. British Journal of Cancer 2019;121:725-737

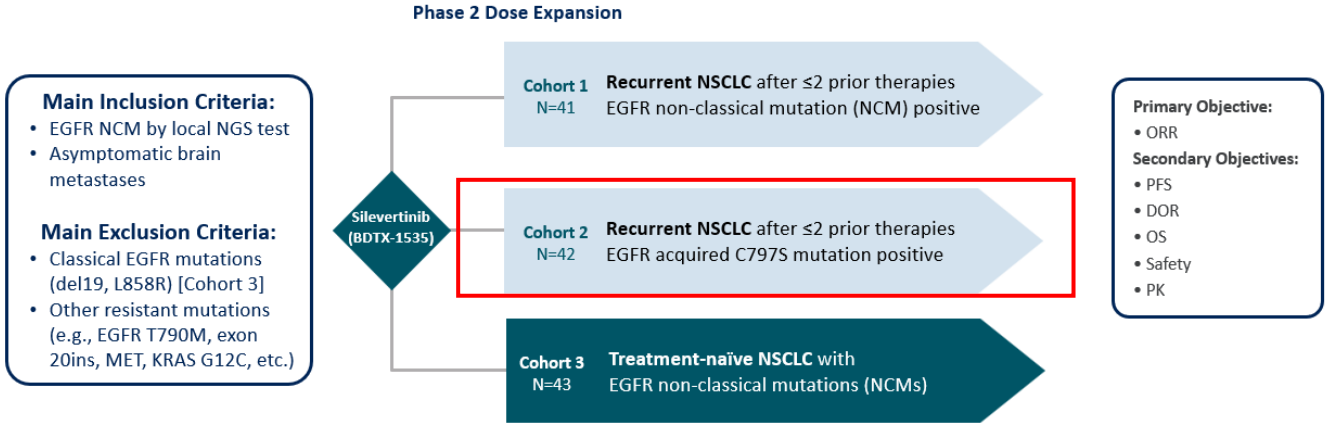
Fourth-generation EGFR-TKIs in pretreated NSCLC-patients with EGFR C797S

- **DZD6008**
  - TIAN-SHAN phase 1/2 trial
  - Progression after 3th generation EGFR-TKI

	40 mg QD (n = 17)	60 mg QD (n = 21)
ORR, n (%) [95% CI]	7 (41.2) (18.4, 67.1)	9 (42.9) (21.8, 66.0)
DCR, n (%) [95% CI]	16 (94.1) (71.3, 99.9)	19 (90.5) (69.6, 98.8)
BOR, n (%)		
PR	7 (41.2)	9 (42.9)
SD	9 (52.9)	10 (47.6)
PD	1 (5.9)	2 (9.5)
PFS rate at 6 mo, % (95% CI)	70.6 (38.9, 88.0)	61.8 (35.8, 79.8)
Median follow-up, mo	6.1	5.7



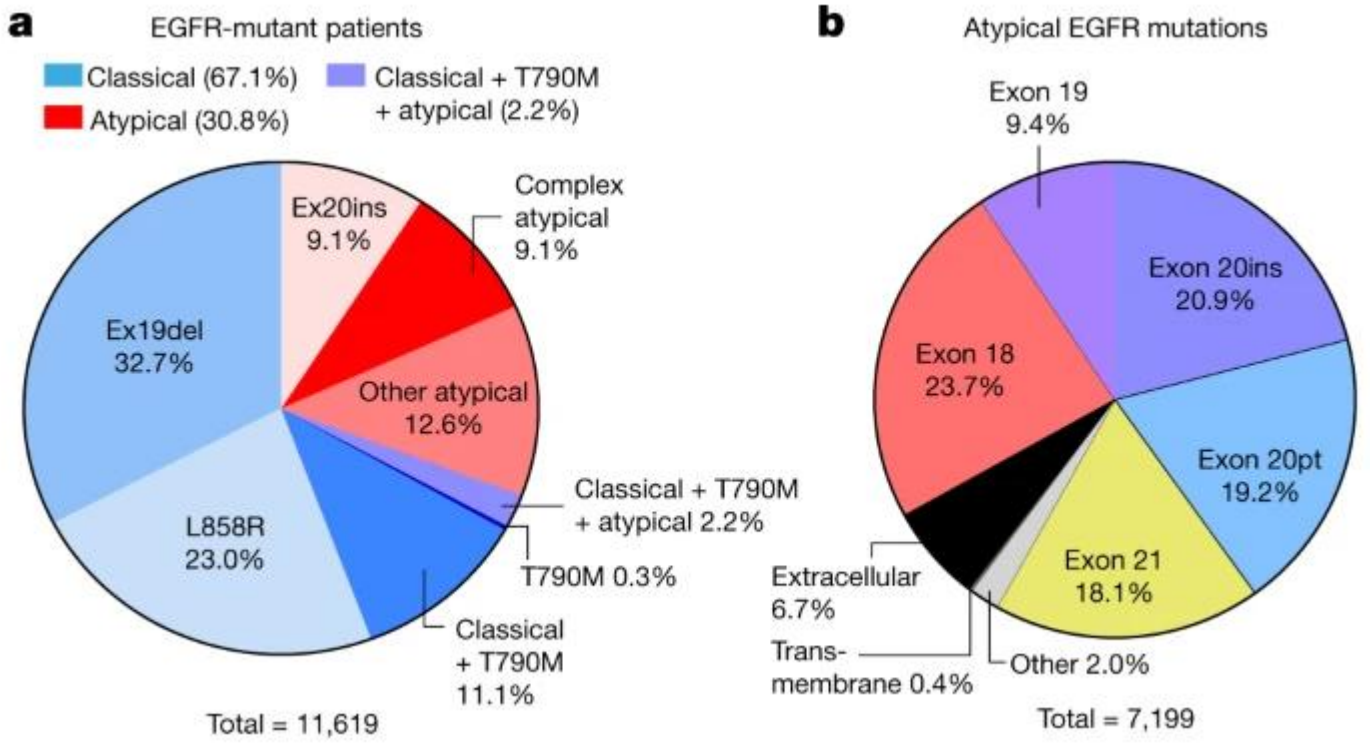
- **Silevertinib**
  - Phase 2 trial
  - ORR (C797S cohort) = 36,4%



Wang M, et al. ASCO 2026 ; Alexandra H, et al. ASCO 2026

Uncommon EGFR

Atypical EGFR mutations



- Atypical EGFR-mutations (including PACC mutations) are identified in ~ 30% of newly diagnosed EGFRm-patients.
- Patients with atypical EGFR-mutations have worse outcomes compared to patients with classical EGFR-mutations (exon19del, L858R).

Robichaux J, et al. Nature 2021

CLINICAL PRACTICE GUIDELINES

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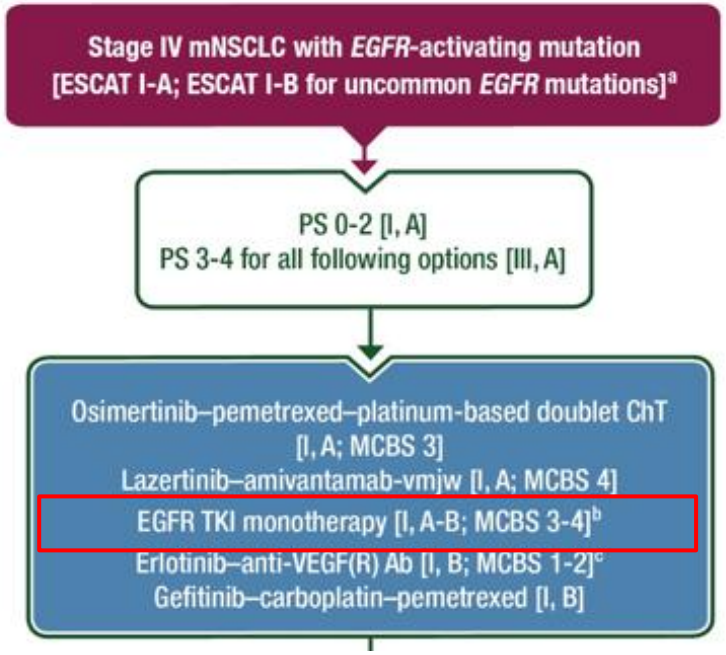
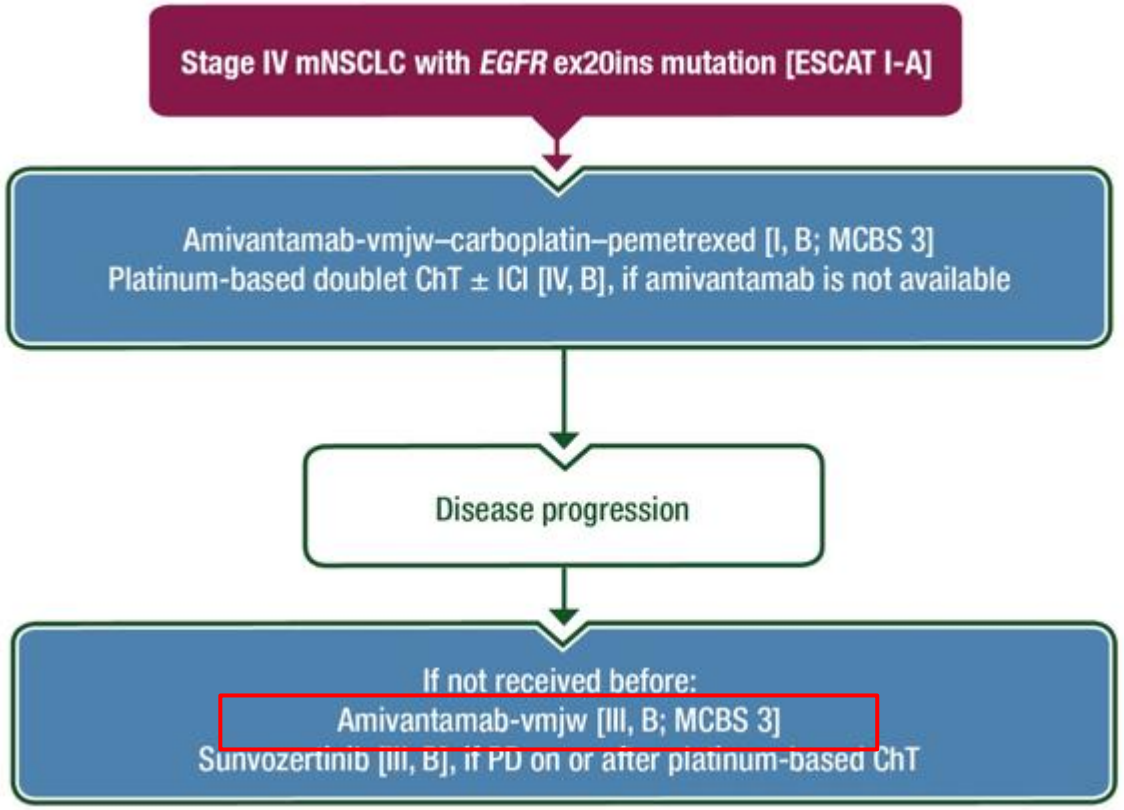
Uncommon EGFR mutation

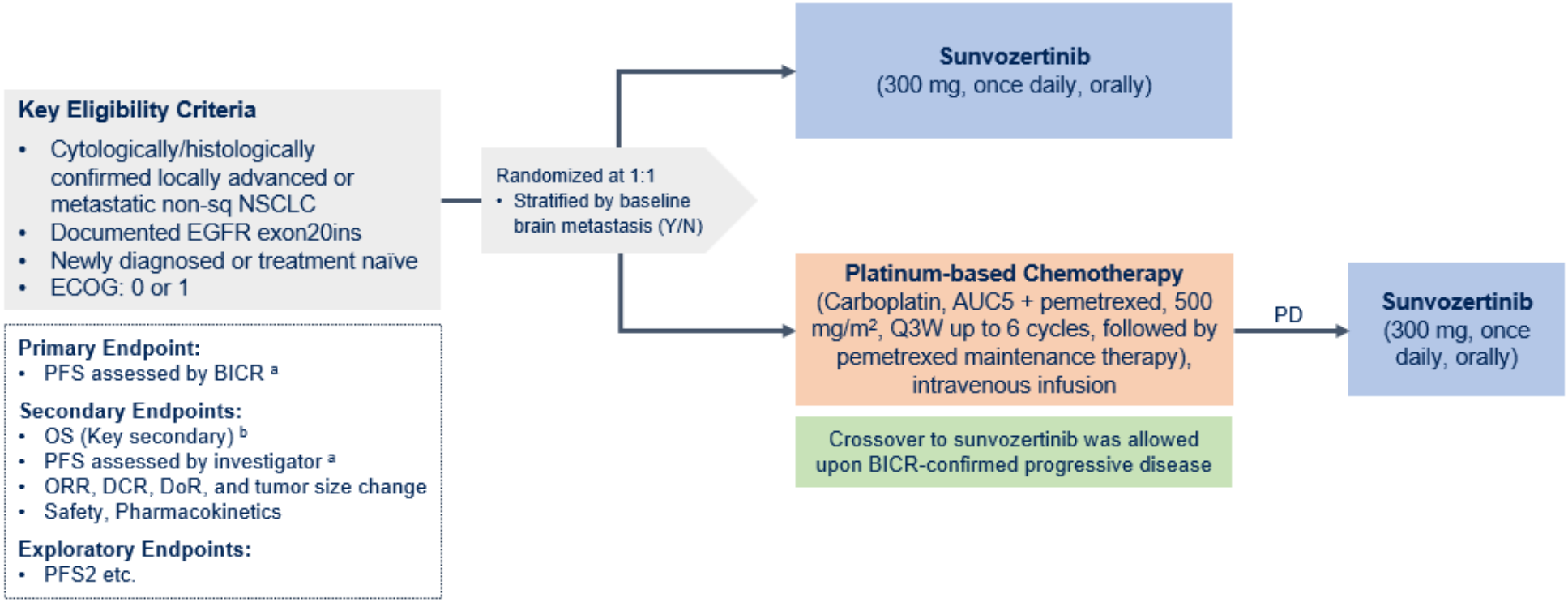


Afatinib [I, B; **ESMO-MCBS v2.0 score: 4**] or osimertinib [III, B] is recommended for patients with a major uncommon, non-exon 20 insertion, sensitising *EGFR* mutation.

EGFR exon20ins



WU-KONG28
Design



Heymach J, et al. ASCO 2026

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Baseline Characteristics

Baseline Characteristics	Sunvozertinib (N=163)	Chemotherapy (N=161)
Median age, years (range)	62.0 (27, 87)	62.0 (28, 85)
Female, n (%)	87 (53.4)	105 (65.2)
Never smoker, n (%)	101 (62.0)	107 (66.5)
Race, Asian/non-Asian, n (%)	102 (62.6)/61 (37.4)	102 (63.4)/59 (36.6)
ECOG score, 0/≥1[a], n (%)	46 (28.2)/117 (71.8)	43 (26.7)/118 (73.3)
Baseline brain metastasis, yes/no, n (%)	21 (12.9)/142 (87.1)	20 (12.4)/141 (87.6)
Extent of disease, locally advanced/metastatic, n (%)	4 (2.5)/159 (97.5)	4 (2.5)/157 (97.5)
Number of organ/site involvement, 1-3/>3 , n (%)	92 (56.4)/71 (43.6)	106 (65.8)/55 (34.2)
EGFR exon20ins subtype, n (%) [b]		
769_ASV	51 (31.3)	52 (32.3)
770_SVD	21 (12.9)	32 (19.9)
Others and Unknown	91 (55.8)	77 (47.8)

[a] The latest assessment result relative to first dosing was selected as the baseline value. Two patients had an ECOG score of 1 at screening, which turned into 2 after randomization. [b] At least 54 EGFR exon20ins mutation subtypes were enrolled in this study.

Heymach J, et al. ASCO 2026

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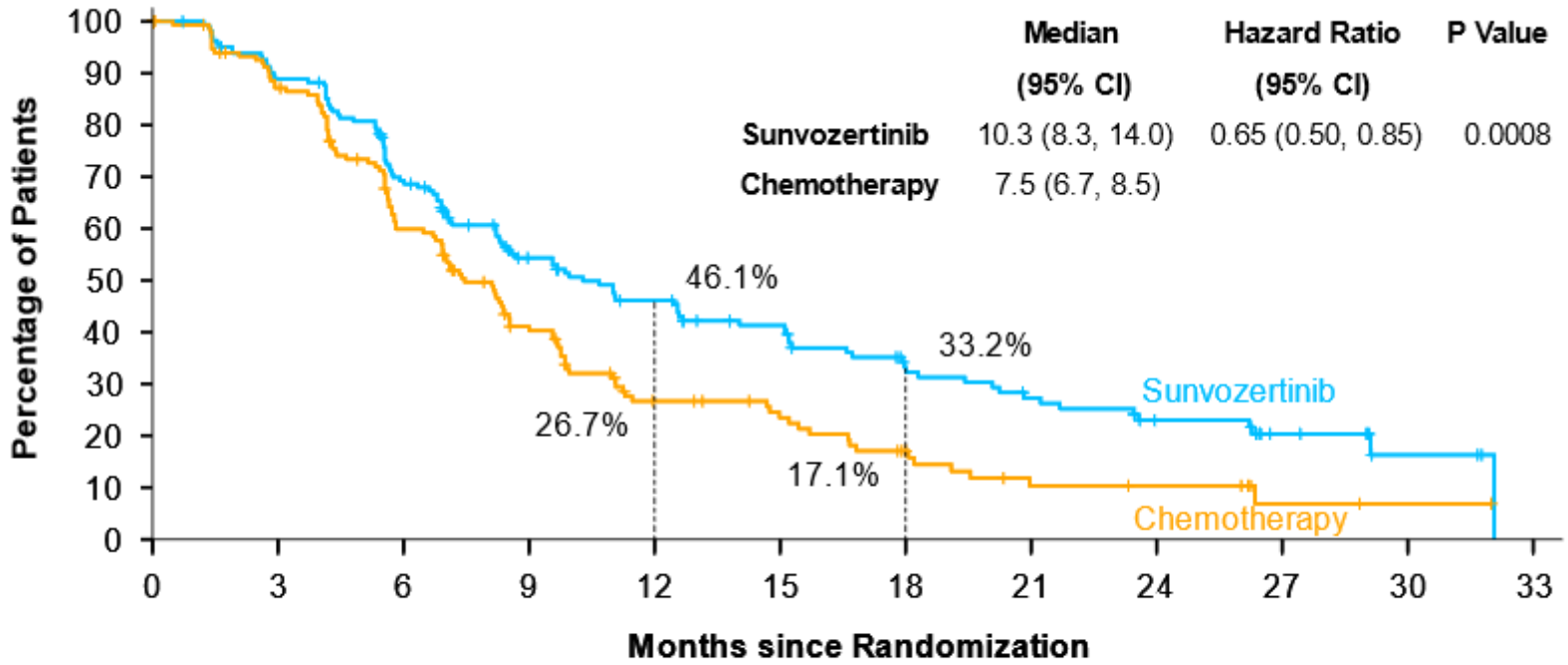
PFS



Number At Risk:

Sunvozertinib	163	143	108	74	60	48	34	26	18	9	3	0
Chemotherapy	161	128	84	51	28	22	14	7	6	2	1	0

Heymach J, et al. ASCO 2026

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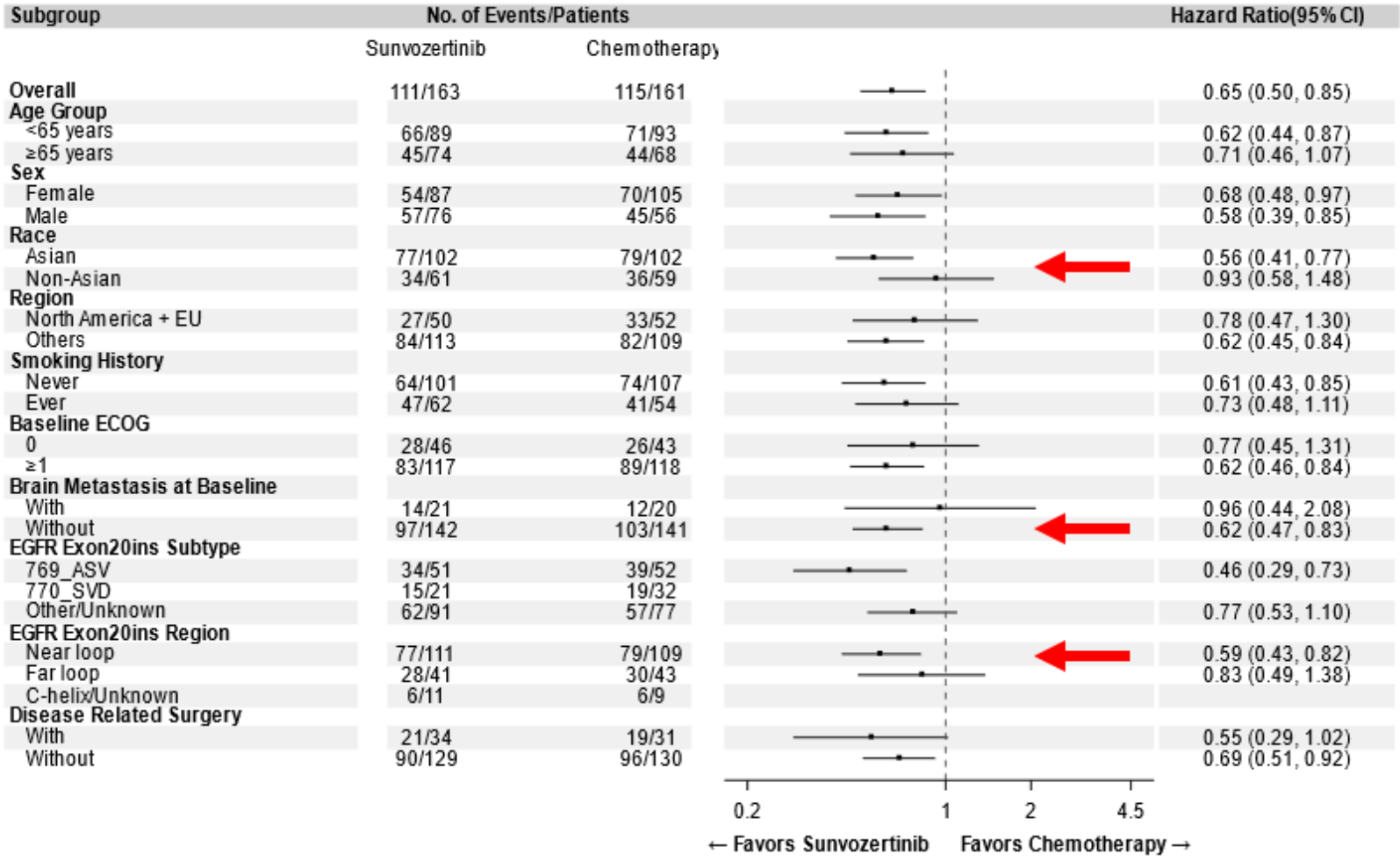
PFS by subgroups



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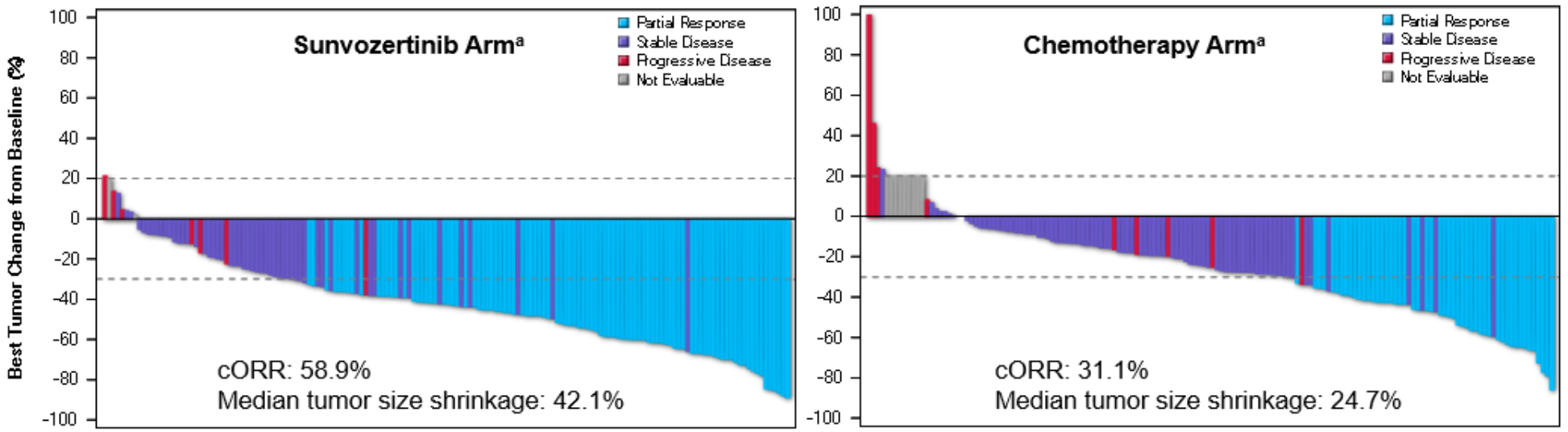
Tumor response



	Sunvozertinib (N=163)	Chemotherapy (N=161)
Best Objective Response Rate, % (95% CI)	68.1 (60.4, 75.2)	35.4 (28.0, 43.3)
Confirmed Objective Response Rate, % (95% CI)	58.9 (50.9, 66.5)	31.1 (24.0, 38.8)
Odds Ratio (95% CI); P value	3.2 (2.0, 5.0); P<0.0001	
Disease Control Rate, % (95% CI)	94.5 (89.8, 97.4)	85.7 (79.3, 90.7)

[a] Calculated in patients with measurable target lesions at baseline assessed by BICR, including 158 patients in the sunvozertinib arm and 154 patients in the chemotherapy arm.

Heymach J, et al. ASCO 2026

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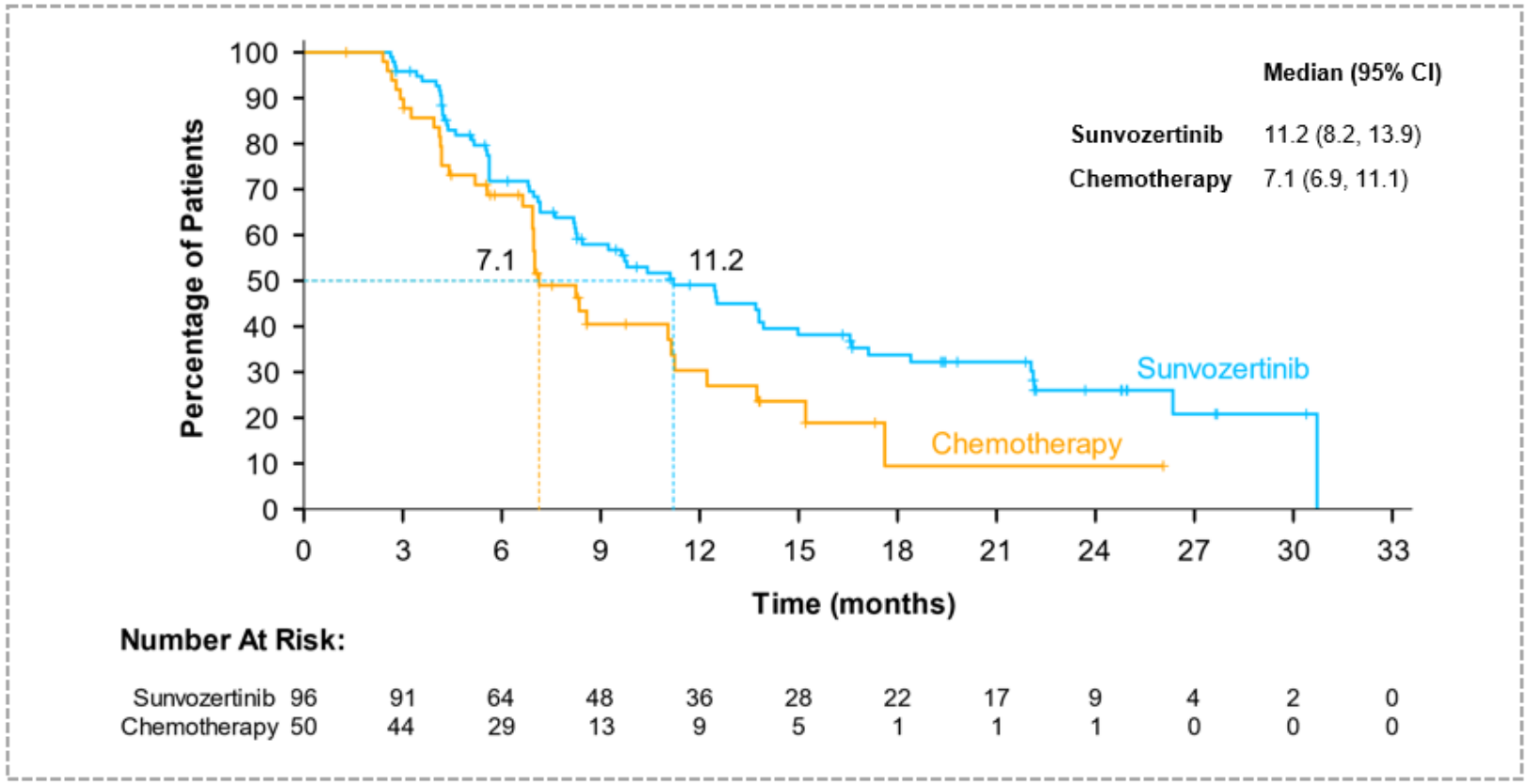
Duration of response



Median follow-up time: 22.1 months in the sunvozertinib arm and 13.8 months in the chemotherapy arm.

Heymach J, et al. ASCO 2026

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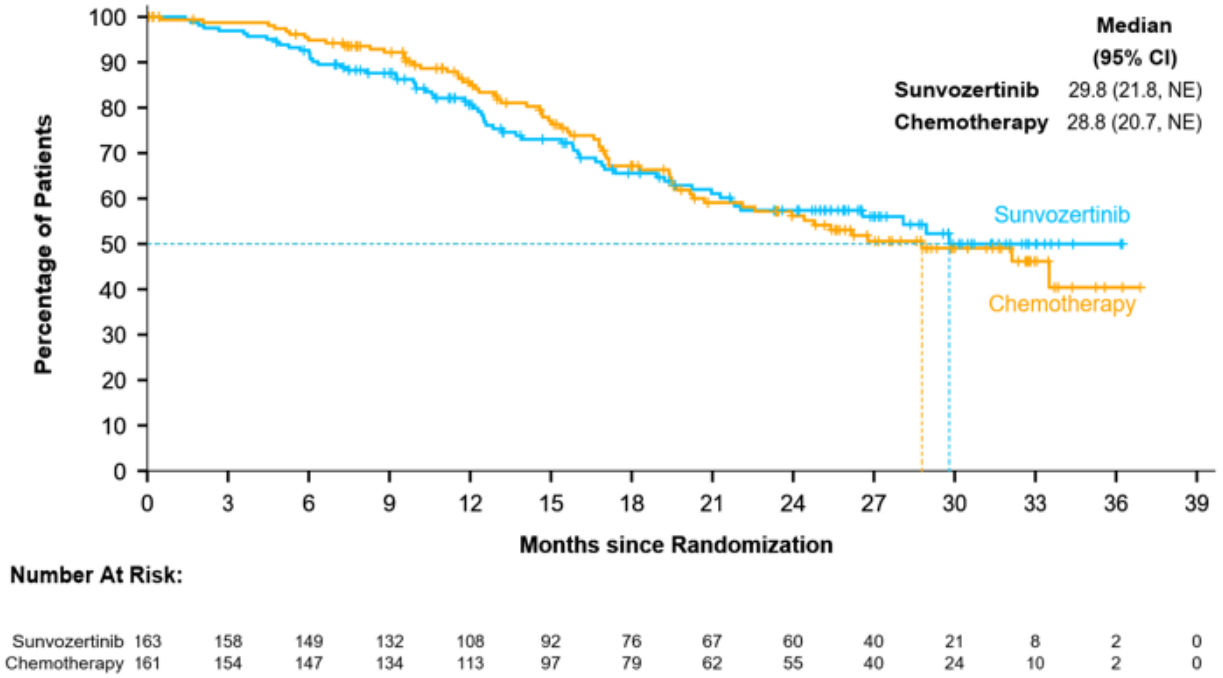
OS



OS data maturity

- 38.9% (126/324)
  - ✓ 38.0% (62/163) in the sunvozertinib arm
  - ✓ 39.8% (64/161) in the chemotherapy arm

In-study crossover

- ✓ 90.2% (101/112) patients with BICR-confirmed progressive disease crossed over to receive sunvozertinib treatment

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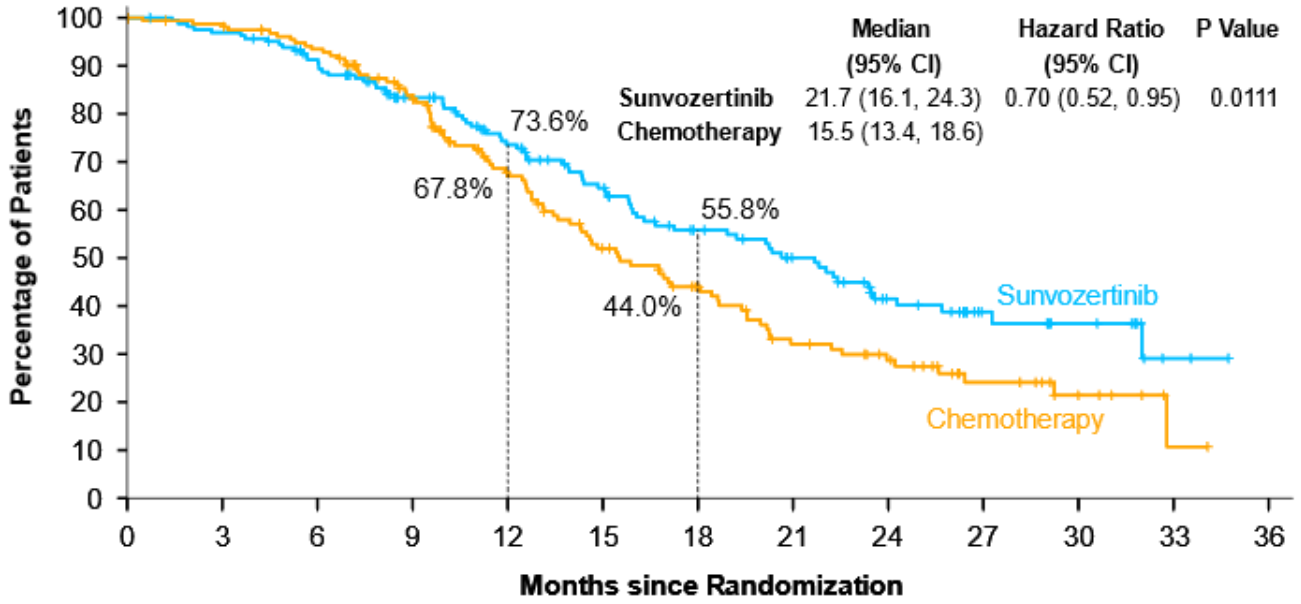
PFS2



First subsequent systemic therapy

Sunvozertinib arm

- 46.6% (76/163) started subsequent therapy
  - ✓ 72.4% (55/76) received chemotherapy

Chemotherapy arm

- 72.0% (116/161) started subsequent therapy
  - ✓ 91.4% (106[a]/116) received sunvozertinib (90.2% through in-study crossover)

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Safety

	Sunvozertinib (N=163)[a]	Chemotherapy (N=150)[a]
Participants with Any TRAE	163 (100.0)	146 (97.3)
Any TRAE with Grade ≥3	100 (61.3)	74 (49.3)
Any Treatment-related SAE	30 (18.4)	19 (12.7)
Any TRAE Leading to Dose Interruption	74 (45.4)	41 (27.3)
Any TRAE Leading to Dose Reduction	66 (40.5)	36 (24.0)
Any TRAE Leading to Treatment Discontinuation	12 (7.4)	17 (11.3)
Any TRAE with Fatal Outcome	0 (0.0)	1 (0.7)[b]

- In the sunvozertinib arm, the top TRAEs leading to dose interruption and reduction included blood CPK increased and diarrhea, which did not lead to treatment discontinuation.

Heymach J, et al. ASCO 2026

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Safety

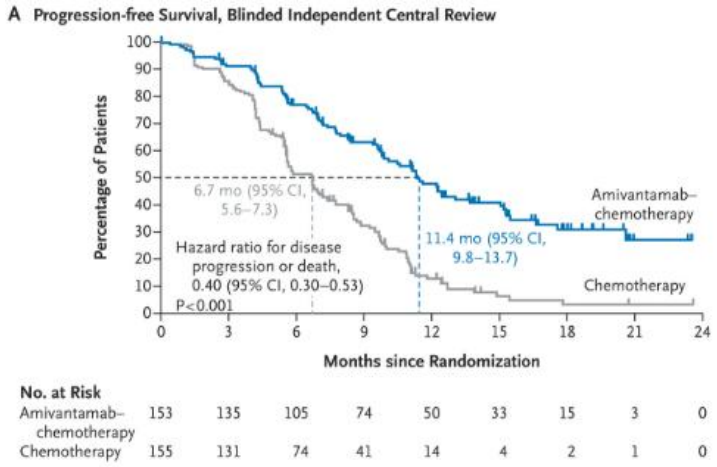
	Sunvozertinib (N=163)		Chemotherapy (N=150)	
	All Grade	≥ Grade 3	All Grade	≥ Grade 3
Participants with Any TRAE	163 (100.0)	100 (61.3)	146 (97.3)	74 (49.3)
Diarrhea	137 (84.0)	22 (13.5)	15 (10.0)	0 (0.0)
Blood creatine phosphokinase increased	90 (55.2)	33 (20.2)	5 (3.3)	1 (0.7)
Rash	84 (51.5)	1 (0.6)	8 (5.3)	0 (0.0)
Paronychia	79 (48.5)	6 (3.7)	0 (0.0)	0 (0.0)
Anemia	75 (46.0)	10 (6.1)	91 (60.7)	15 (10.0)
Weight decreased	56 (34.4)	5 (3.1)	15 (10.0)	1 (0.7)
Decreased appetite	52 (31.9)	1 (0.6)	39 (26.0)	2 (1.3)
Blood creatinine increased	50 (30.7)	1 (0.6)	12 (8.0)	0 (0.0)
Vomiting	40 (24.5)	3 (1.8)	32 (21.3)	3 (2.0)
Nausea	38 (23.3)	3 (1.8)	66 (44.0)	2 (1.3)
Aspartate aminotransferase increased	35 (21.5)	3 (1.8)	52 (34.7)	1 (0.7)
Lipase increased	35 (21.5)	9 (5.5)	8 (5.3)	1 (0.7)
Amylase increased	34 (20.9)	2 (1.2)	11 (7.3)	0 (0.0)
Alanine aminotransferase increased	25 (15.3)	2 (1.2)	50 (33.3)	2 (1.3)
Neutrophil count decreased	22 (13.5)	4 (2.5)	68 (45.3)	28 (18.7)
White blood cell count decreased	20 (12.3)	1 (0.6)	58 (38.7)	10 (6.7)
Platelet count decreased	11 (6.7)	2 (1.2)	32 (21.3)	10 (6.7)
Constipation	4 (2.5)	0 (0.0)	30 (20.0)	0 (0.0)

Heymach J, et al. ASCO 2026

Sunvozertinib in EGFR exon20ins NSCLC: new SOC?

- Sunvozertinib is the first oral targeted therapy to demonstrate superior efficacy over platinum-based chemotherapy in treatment-naïve EGFR exon 20 insertion NSCLC.
- The magnitude of PFS benefit is clinically meaningful but remains modest compared with the benefits observed with osimertinib in classical EGFR-mutated NSCLC.
- The control arm may no longer reflect the evolving standard of care. The relative efficacy of sunvozertinib versus amivantamab-based regimens remains unknown.
- Intracranial efficacy remains insufficiently characterized, and more mature CNS-specific data are needed to define its role in patients with brain metastases.

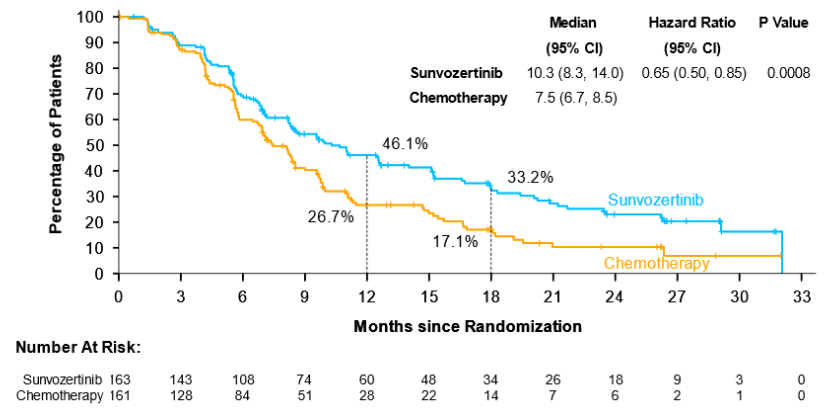
PAPILLON
1L chemo + amivantamab



mPFS = 11,4 m
ORR = 73%
Grade ≥3 AE = 75%

Zhou C, et al. NEJM 2023

WU-KONG28
1L sunvozertinib



mPFS = 10,3 m
ORR = 59%
Grade ≥3 AE = 61%

Heymach J, et al. ASCO 2026

CHRYSALIS-2
Design

Dose escalation phase

RP2CD was identified:
IV amivantamab 1050 mg
(1400 mg if ≥80 kg)[a]

plus

Lazertinib 240 mg orally

Dose expansion cohorts

- **Cohort A:** *EGFR* Ex19del or L858R
  Post-osimertinib and platinum-based chemotherapy
- **Cohort B:** *EGFR* Ex20ins
  Post–standard of care and platinum-based chemotherapy
- **Cohort C:** Atypical *EGFR* mutations
  Treatment naïve or post–EGFR TKI/chemotherapy[b]
- **Cohort D:** *EGFR* Ex19del or L858R
  Post-osimertinib, biomarker validation
- **Cohort E:** *EGFR* Ex19del or L858R
  Post-osimertinib, MET IHC+ analysis (amivantamab + lazertinib)
- **Cohort F:** *EGFR* Ex19del or L858R
  Post-osimertinib, MET IHC+ analysis (amivantamab monotherapy)

Previously reported[1]

Primary endpoint:
- ORR by investigator per RECIST v1.1

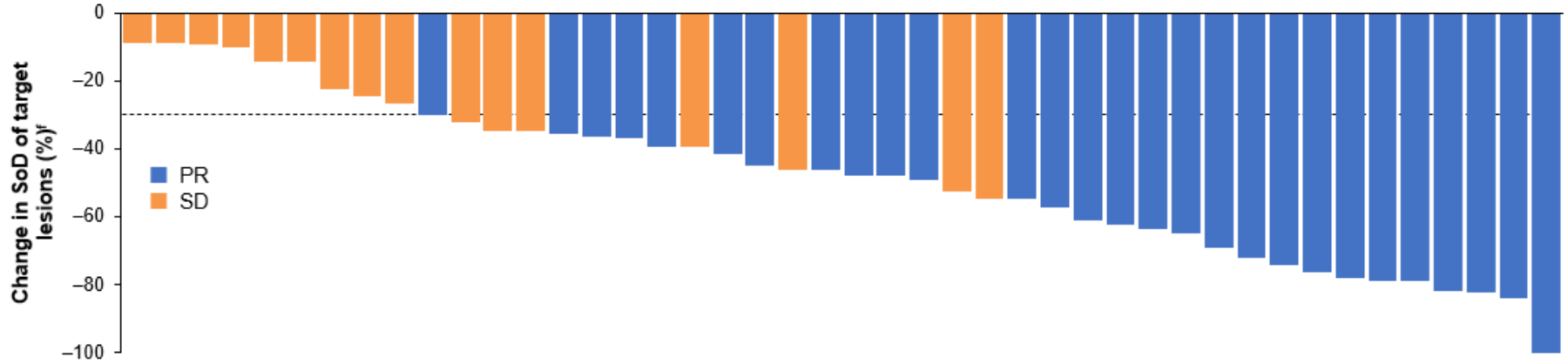
Secondary endpoints:
- DoR
- CBR[c]
- PFS
- OS
- Safety (AEs)

- **Participants with Ex20ins and Ex19del/L858R co-mutations were excluded**
- CHRYSALIS-2 enrolled prior to COCOON[2], SKIPPirr[3], and PALOMA-3[4]
  - Therefore, participants did not receive the enhanced prophylaxis for dermatologic AEs and IRRs, and subcutaneous amivantamab was not available

Neal J, et al. ASCO 2026

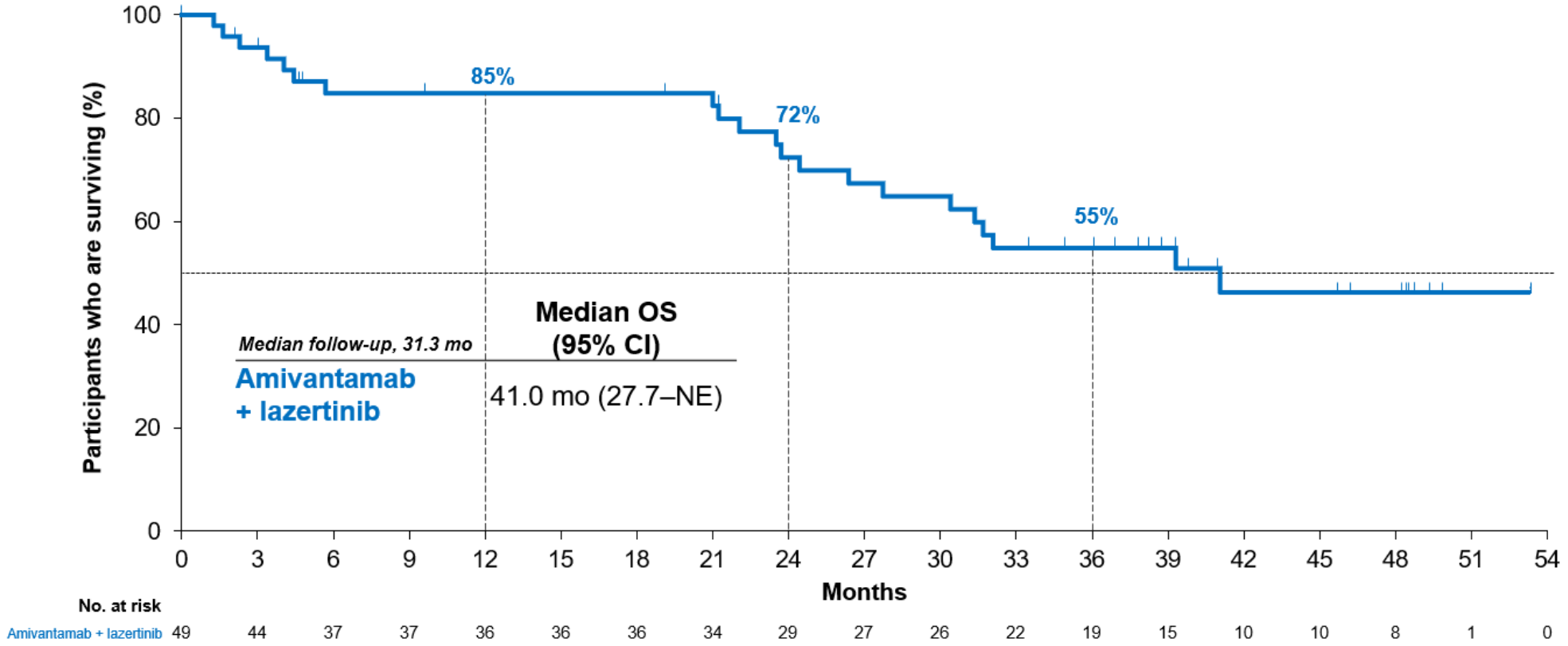
CHRYSALIS-2
Tumor response

- In CHRYSALIS-2 Cohort C, a total of 49 treatment-naïve participants with atypical *EGFR*-mutated NSCLC were enrolled globally to receive 1L amivantamab + lazertinib
  - Median age was 60 years, 45% were female, and 57% were Asian
  - Most frequent *EGFR* mutations[a] included G719X[b] (55%), S768X[c] (27%), and L861X[d] (24%)
  - Compound mutations were observed in 35% of tumors
- At a median follow-up of 16.1 months, **ORR was 57%**
  - CBR[e] was 84%, and all evaluable patients with ≥1 post-baseline assessment achieved PR or SD
  - Median DoR was 20.7 months and **median PFS was 19.5 months (95% CI, 11.2–NE)**



Neal J, et al. ASCO 2026

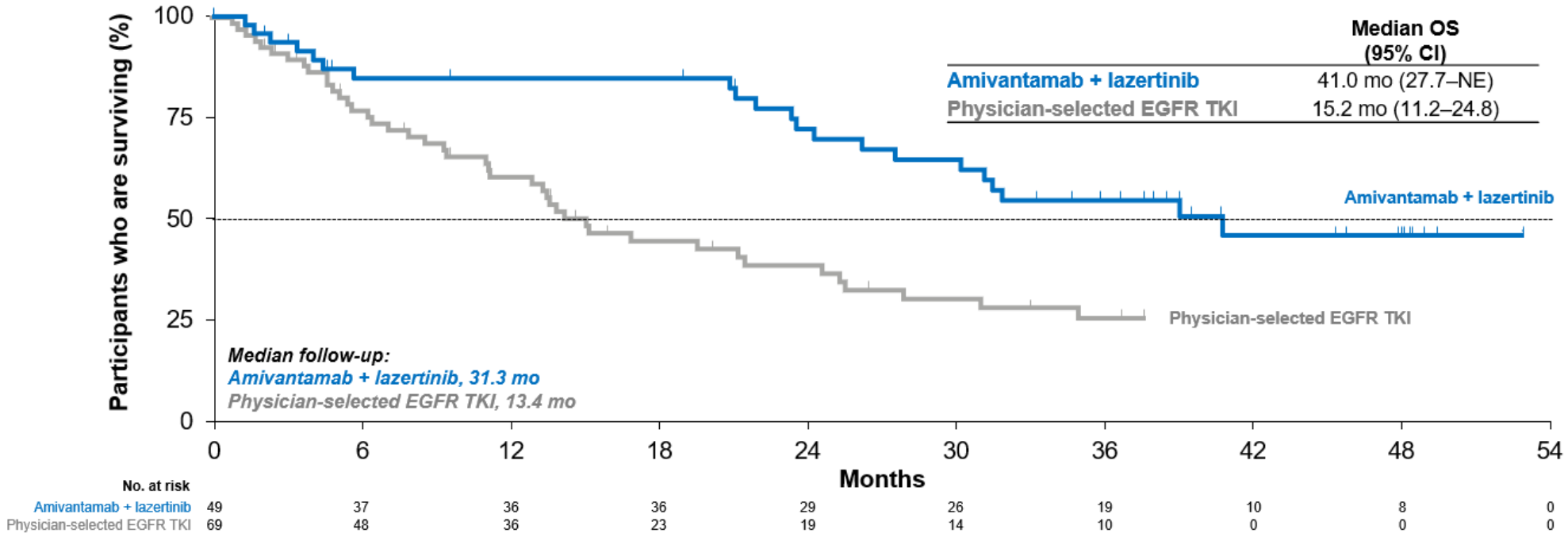
CHRYSALIS-2
OS



Neal J, et al. ASCO 2026

CHRYSALIS-2
OS

- A descriptive, retrospective, observational analysis[a] was conducted to evaluate OS of a real-world atypical *EGFR*-mutated NSCLC cohort from the FH/FMI CGDB that received a physician-selected 1L EGFR TKI[b], and provide context for the single-arm CHRYSALIS-2 Cohort C



Neal J, et al. ASCO 2026

CHRYSALIS-2
Safety

- The safety profile was manageable and consistent with prior reports of IV amivantamab + lazertinib[1,2], with no additional safety signals identified
  - Most AEs were grade 1 or 2
- CHRYSALIS-2 was conducted prior to SC amivantamab approval[3] as well as COCOON[4] and SKIPPirr[5]; therefore, participants received IV amivantamab and did not receive enhanced prophylaxis for dermatologic AEs and IRRs

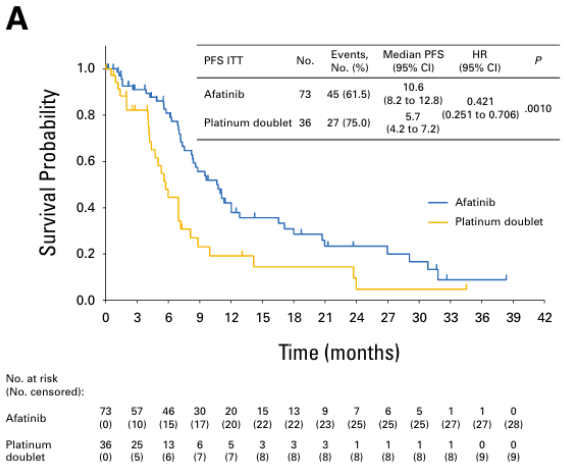
Treatment-emergent AEs (≥30%) by preferred term, n (%)	n=49	
	All grades	Grade ≥3
Related to EGFR inhibition		
Paronychia	38 (78)	4 (8)
Rash	32 (65)	7 (14)
Diarrhea	17 (35)	0
Stomatitis	17 (35)	0
Pruritus	15 (31)	0
Related to MET inhibition		
Hypoalbuminemia	30 (61)	3 (6)
Peripheral edema	20 (41)	1 (2)
Other		
Infusion-related reaction	30 (61)	3 (6)
ALT increased	26 (53)	2 (4)
AST increased	24 (49)	1 (2)
Hypocalcemia	23 (47)	0
COVID-19	20 (41)	1 (2)
Nausea	15 (31)	1 (2)
Constipation	15 (31)	0

Neal J, et al. ASCO 2026

Amivantamab-lazertinib in atypical EGFR: new SOC?

- CHRYSALIS-2 demonstrates clinical activity of amivantamab + lazertinib in atypical EGFR-mutated NSCLC, but interpretation is limited by the absence of a randomized comparator.
- Survival outcomes appear encouraging compared with historical real-world data, although cross-trial and external comparisons remain inherently limited by the heterogeneity of the population.
- Toxicity remains clinically relevant and may impact long-term tolerability.

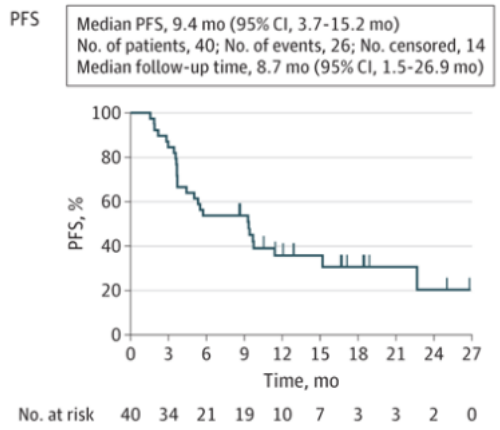
ACHILLES/TORG1834
1L afatinib



mPFS = 10,6 m
mOS = NR
ORR = 61%
Grade ≥3 AE = 44%

Miura S, et al. JCO 2025

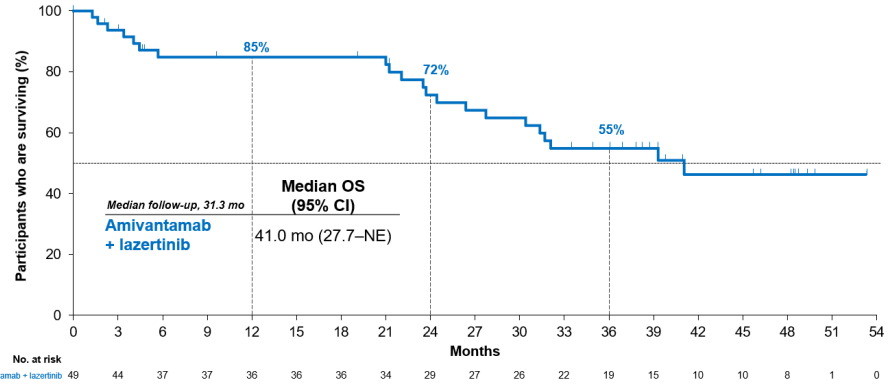
UNICORN
1L osimertinib



mPFS = 9,4 m
mOS = NR
ORR = 55%
Grade ≥3 AE = 27,5%

OkumaY, et al. JAMA 2024

CHRYSALIS-2
1L amivantamab-lazertinib



mPFS = 19,5 m
mOS = 41 m
ORR = 57%
Grade ≥3 AE = 70%

Neal J, et al. ASCO 2026

ALK

UZ GENT

UNIVERSITEIT GENT

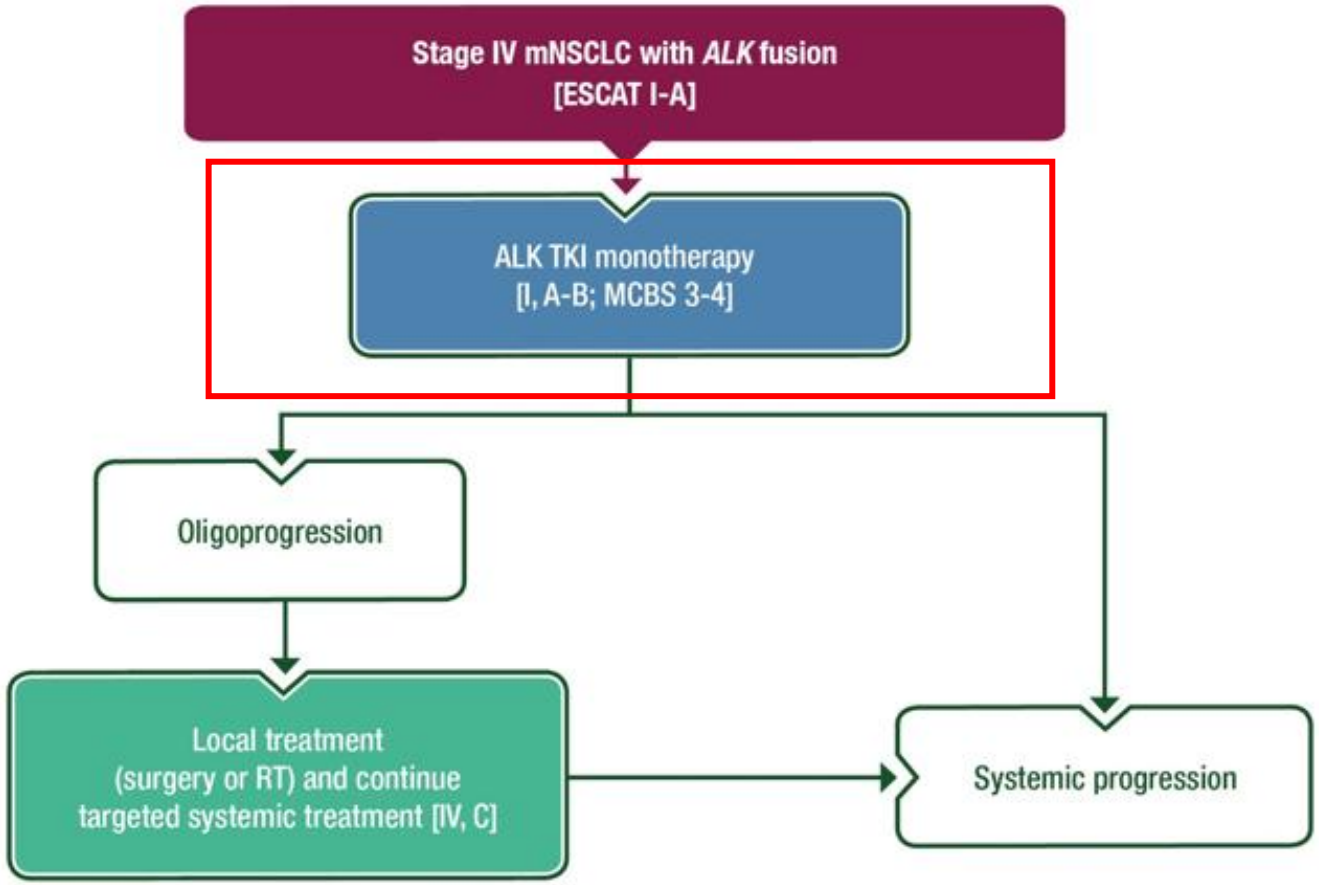
ALK

Metastatic

CLINICAL PRACTICE GUIDELINES

ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

v1.3 February 2026

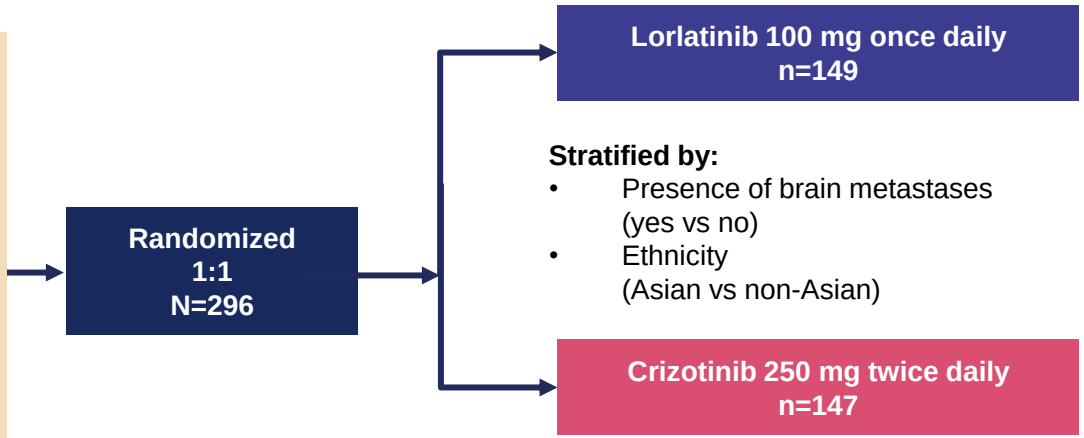


CROWN: 7-year update

Design

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



Stratified by:

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

No crossover between treatment arms was permitted

Primary endpoint

- **PFS[a] by BICR**

Key secondary endpoint

- **OS**

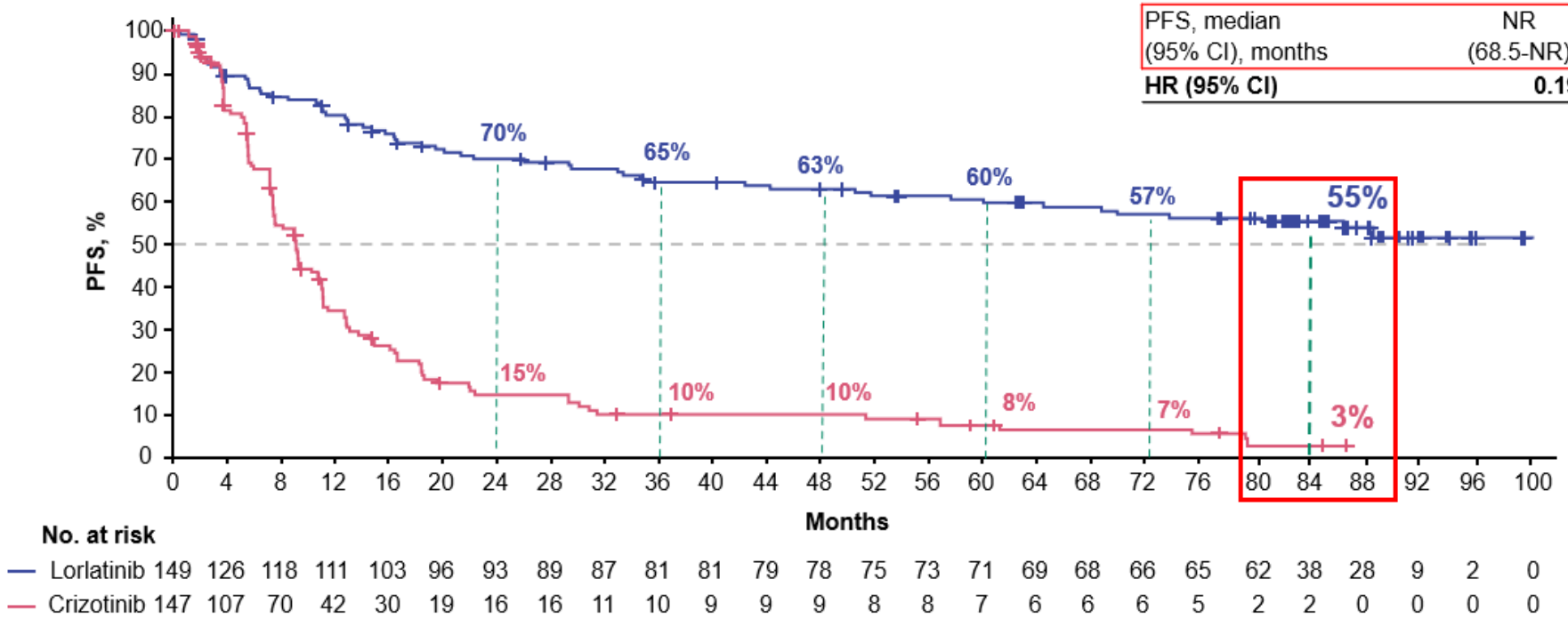
Other secondary endpoints

- PFS by investigator
- ORR by BICR and investigator
- IC ORR, IC TTP, DOR, IC DOR, TTR and IC TTR by BICR and investigator
- Safety
- Quality of life
- Biomarker analyses

CROWN: 7-year update

PFS in the ITT population

	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	62	119
PFS, median (95% CI), months	NR (68.5-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.26)**	



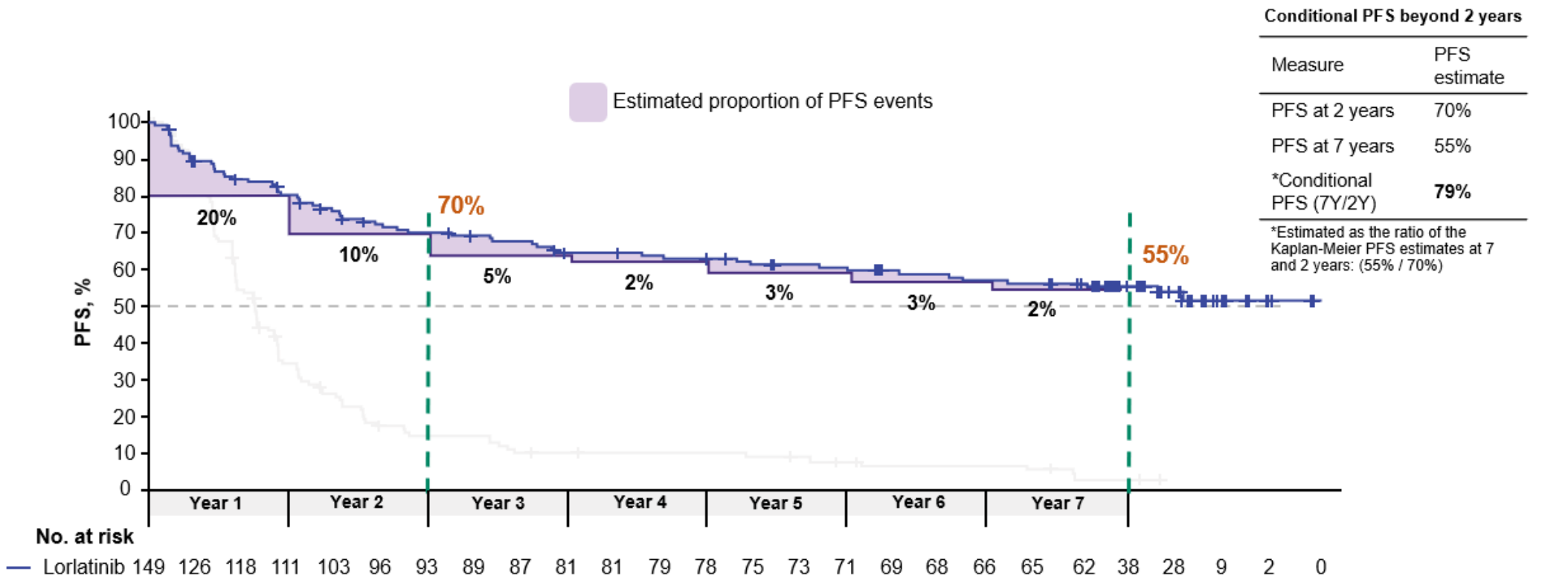
7 new PFS events occurred between 5 and 7 years with lorlatinib: 4 progression events and 3 deaths (not treatment related)

At the time of this analysis, median PFS by investigator was still not reached with lorlatinib

Mok T, et al. ASCO 2026

CROWN: 7-year update

Conditional PFS



Conditional PFS beyond 2 years

Measure	PFS estimate
PFS at 2 years	70%
PFS at 7 years	55%
*Conditional PFS (7Y/2Y)	**79%**

*Estimated as the ratio of the Kaplan-Meier PFS estimates at 7 and 2 years: (55% / 70%)

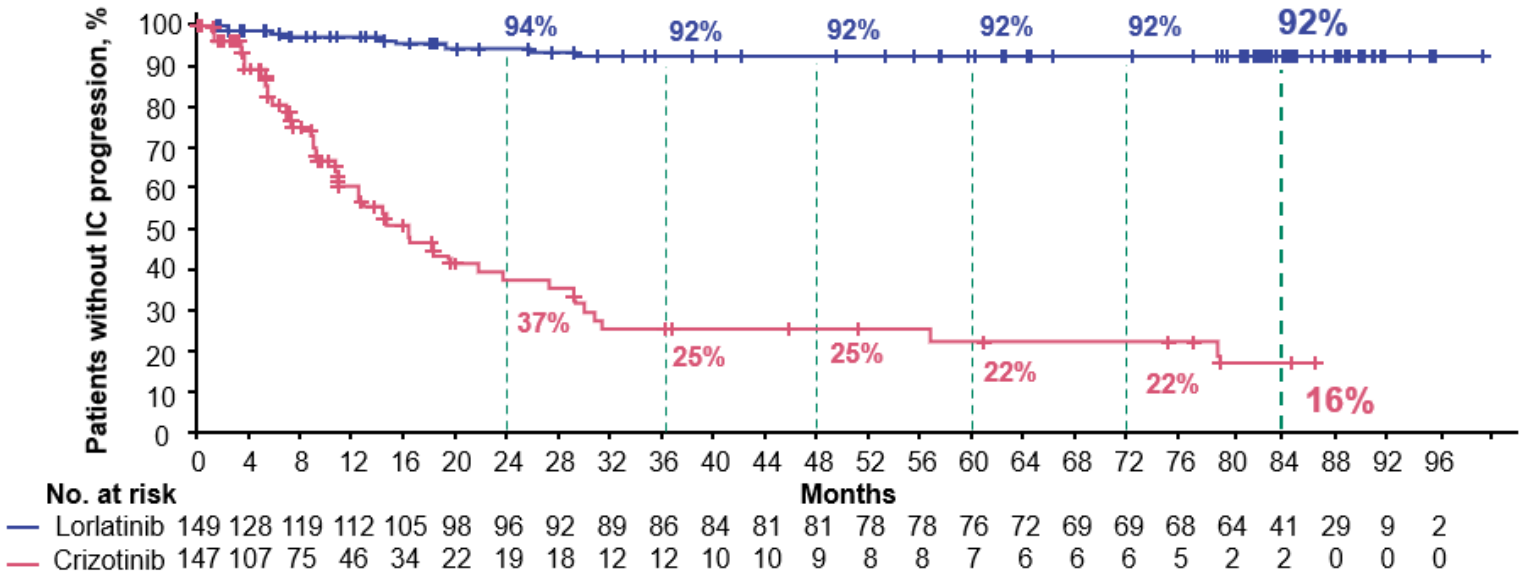
Patients without a PFS event in the first 24 months on lorlatinib have a 79%* probability of remaining alive and progression-free at 7 years

PFS, progression-free survival.

Mok T, et al. ASCO 2026

CROWN: 7-year update

Time to IC progression



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	66
Time to IC progression, months, median (95% CI)	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

Tumor assessments, including brain MRI, have been performed every 8 weeks up to 5 years and every 16 weeks afterwards in all patients throughout the study

No new IC progression events occurred after the first 30 months on lorlatinib

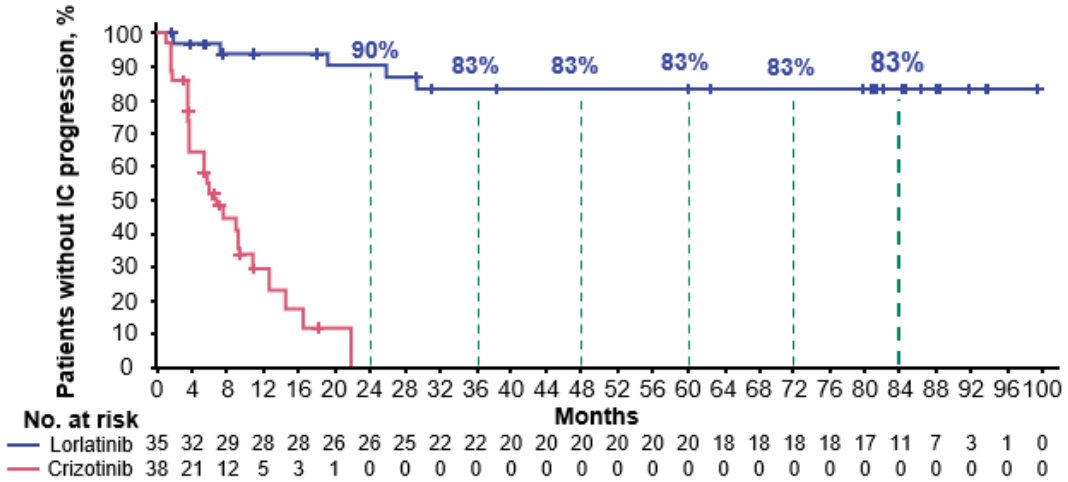
Mok T, et al. ASCO 2026

CROWN: 7-year update

Time to IC progression by brain metastases

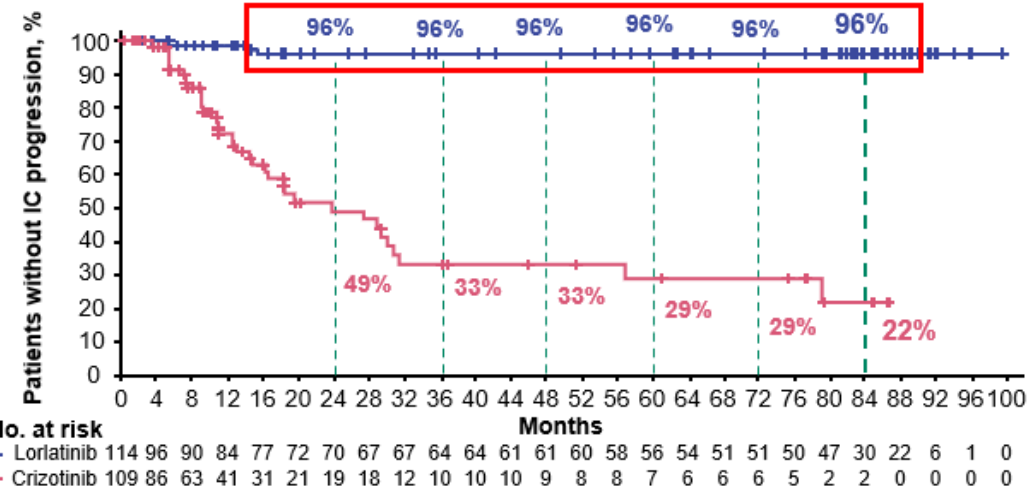
With baseline brain metastases

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



Without baseline brain metastases

	Lorlatinib (n=114)	Crizotinib (n=109)
Events, n	4	40
Time to IC progression, months, median (95% CI)	NR (NR-NR)	23.9 (16.4-30.8)
HR (95% CI)	**0.04 (0.02-0.12)**	



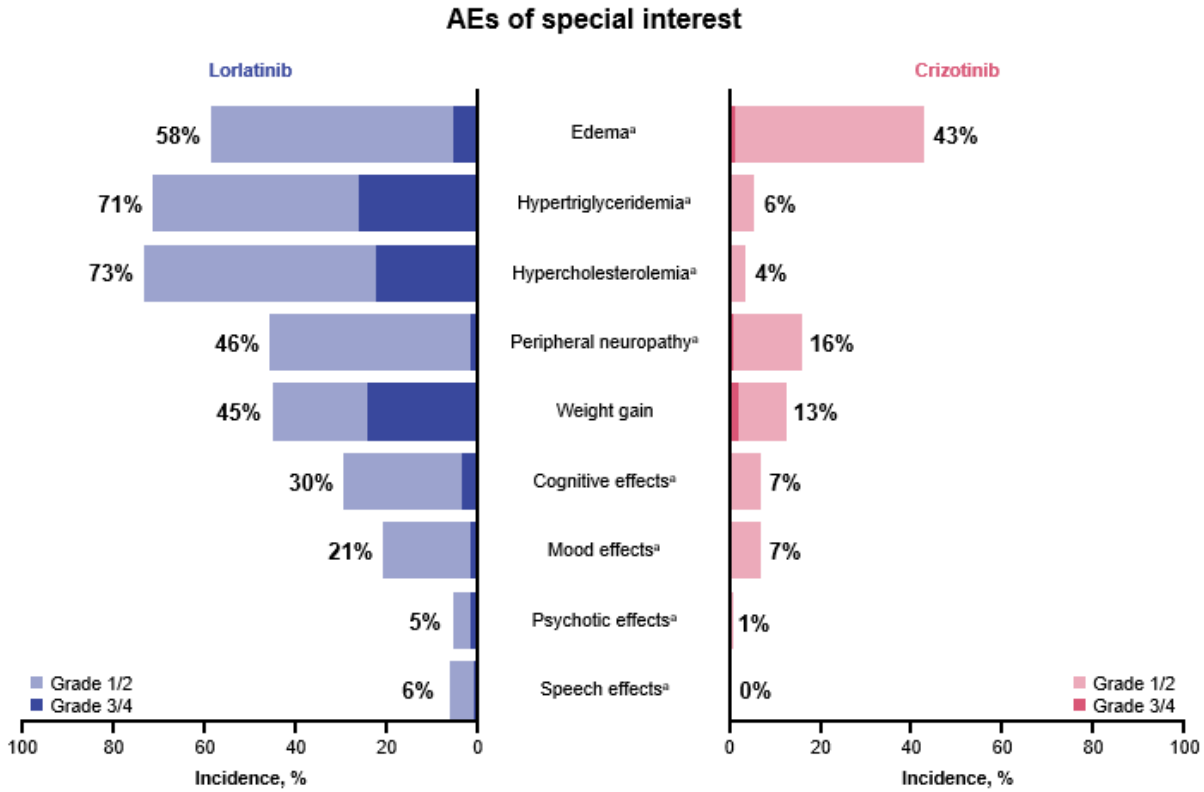
Sustained plateau in time to IC progression indicates a prolonged protective effect against the development of new brain metastases and a sustained control of the existing ones

Mok T, et al. ASCO 2026

CROWN: 7-year update

Adverse events

- No increase in frequency of grade 3 or 4 AEs since the 5-year analysis (77%)
  - Majority were due to an increase in lipid values
- Despite higher rates of hyperlipidemia with lorlatinib, no increase in cardiovascular AEs was observed compared with crizotinib
- Frequency of CNS AEs was consistent with longer follow-up; most were grade 1 or 2
- Dose reductions were reported in 34% of patients in the lorlatinib group; median time to dose reduction was 25 weeks
- All treatment-related discontinuations (5%) occurred within the first 26 months



Safety profile of lorlatinib was consistent with prior analyses with no new safety signals with longer follow-up

AE, adverse event; CNS, central nervous system.
[a]Comprised a cluster of AEs that may represent similar clinical symptoms or syndromes.

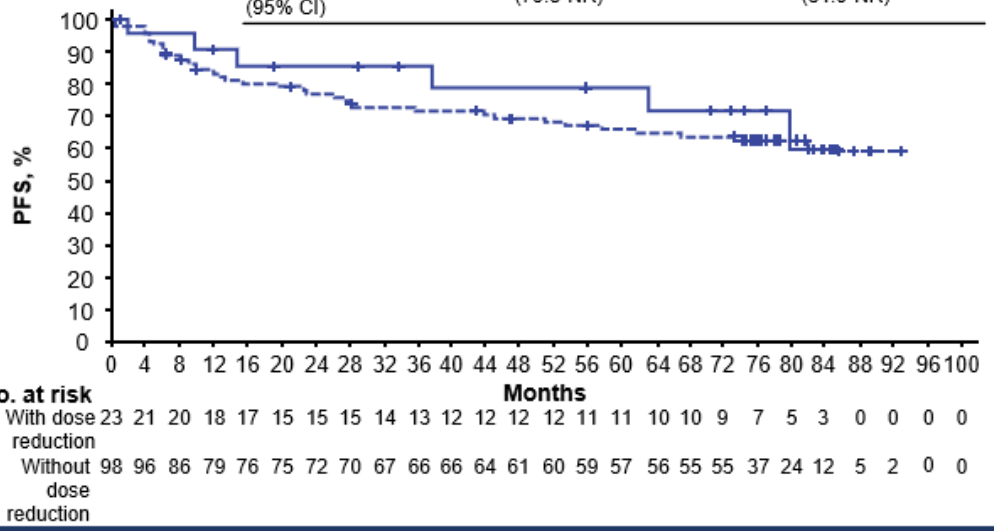
Mok T, et al. ASCO 2026

CROWN: 7-year update

Impact of dose reduction

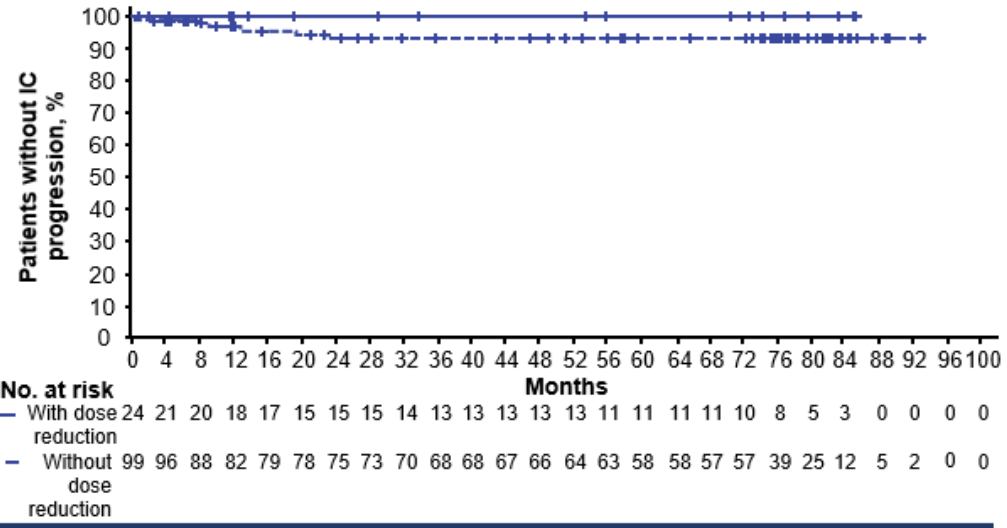
PFS

	With dose reduction (n=23)	Without dose reduction (n=98)
Events, n	6	36
PFS, months, median (95% CI)	NR (79.8-NR)	NR (81.9-NR)



Time to IC progression

	With dose reduction (n=24)	Without dose reduction (n=99)
Events, n	0	6
Time to IC progression, months, median (95% CI)	NR (NR-NR)	NR (NR-NR)

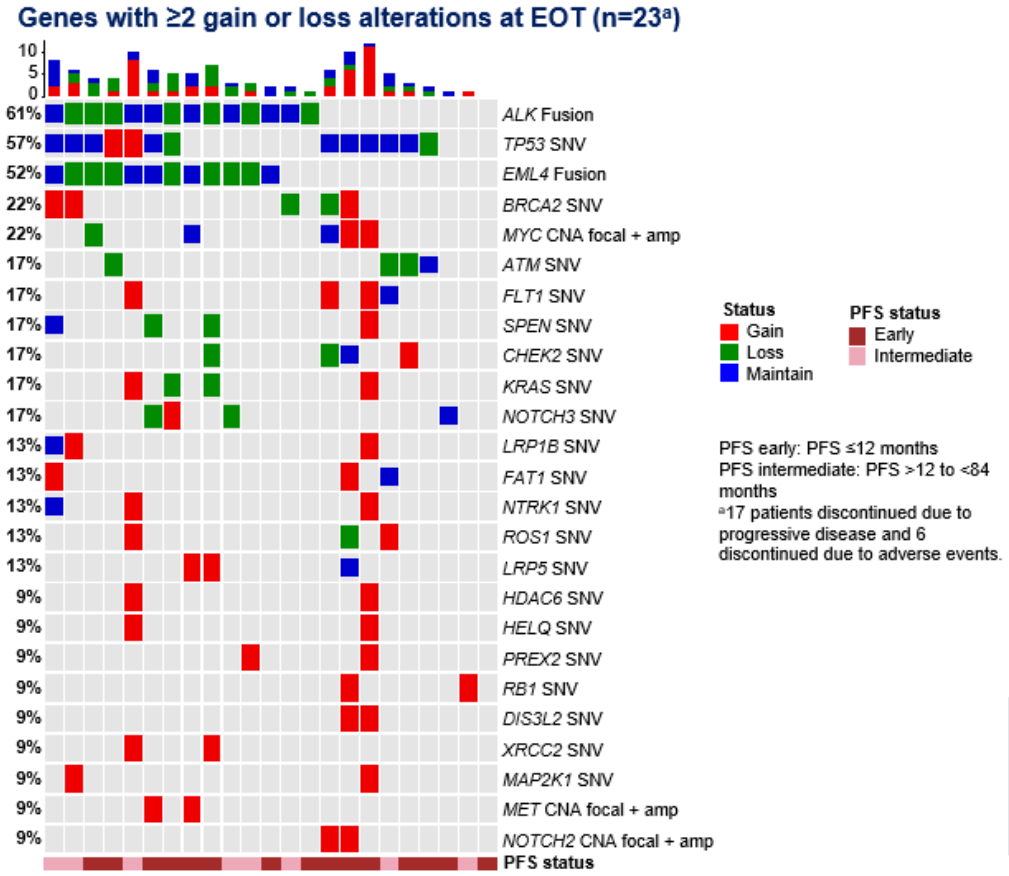


Long-term efficacy with lorlatinib was similar between patients with and without dose reduction within 26 weeks. PFS and IC TTP were also consistent across lorlatinib dose levels (100, 75, or 50 mg)

Mok T, et al. ASCO 2026

CROWN: 7-year update

Resistance mechanisms



amp, amplification; CNA, copy number alteration; ctDNA, circulating tumor DNA; EOT, end of treatment; PFS, progression-free survival; SNV, single-nucleotide variation.

Previously identified resistance mechanisms

- *RTK/RAS/MAPK* pathways: *MAP2K1*, *MET*, *KRAS, and NTRK1*
- Tumor suppressors: *RB1*, *LRP5*, and *FAT1*
- Amplified oncogenes (copy number ≥2.1): *MYC*, *MET*, and *NOTCH2*

Off-target

New putative resistance mechanisms

- Angiogenesis pathway: *FLT1/VEGFR1*
- DNA damage repair: *XRCC2*
- Epigenetic regulation pathway: *HDAC6*

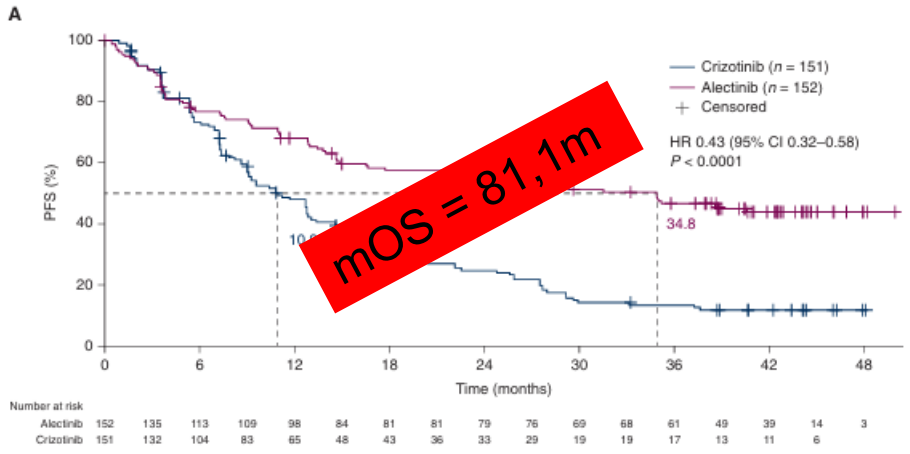
No emerging new *ALK* resistance mutations were detected in the ctDNA samples collected at end of lorlatinib treatment

Mok T, et al. ASCO 2026

Transforming ALK-positive NSCLC into a chronic disease

- Lorlatinib has demonstrated the longest PFS ever reported in advanced (ALK+) NSCLC
- Lorlatinib is able to persistently control the disease, both systemically and intracranially
- Most PFS events occur within the first two years: Primary resistance? Co-mutations (TP53)? More agressive tumor biology?
- The challenge is not late resistance, but identifying the patients who (will) progress early

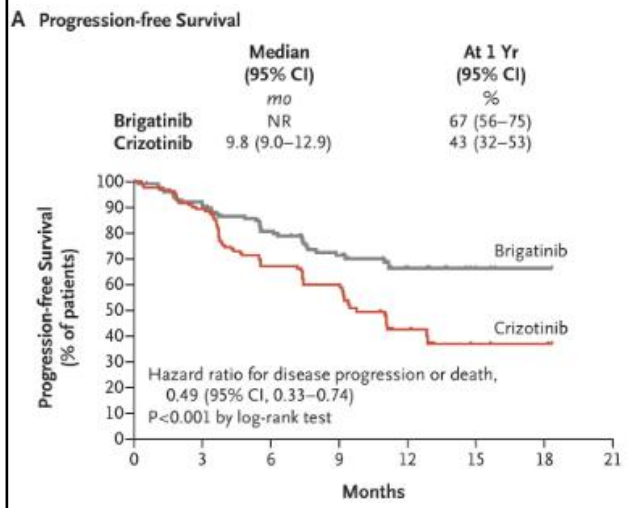
ALEX: alectinib



mPFS = 34,8 m
ORR = 83%
Grade ≥3 AE = 41%

Mok T, et al. Ann Oncol 2020; Peters S, et al. Ann Oncol 2026

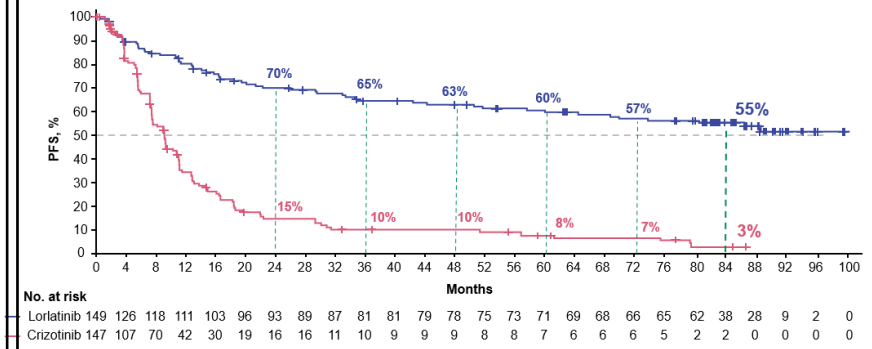
ALTA: brigatinib



mPFS = 29,3m
ORR = 79%
Grade ≥3 AE = 74%

Camidge R, et al. NEJM 2018; Camidge R, et al. Lung Cancer 2025

CROWN: lorlatinib



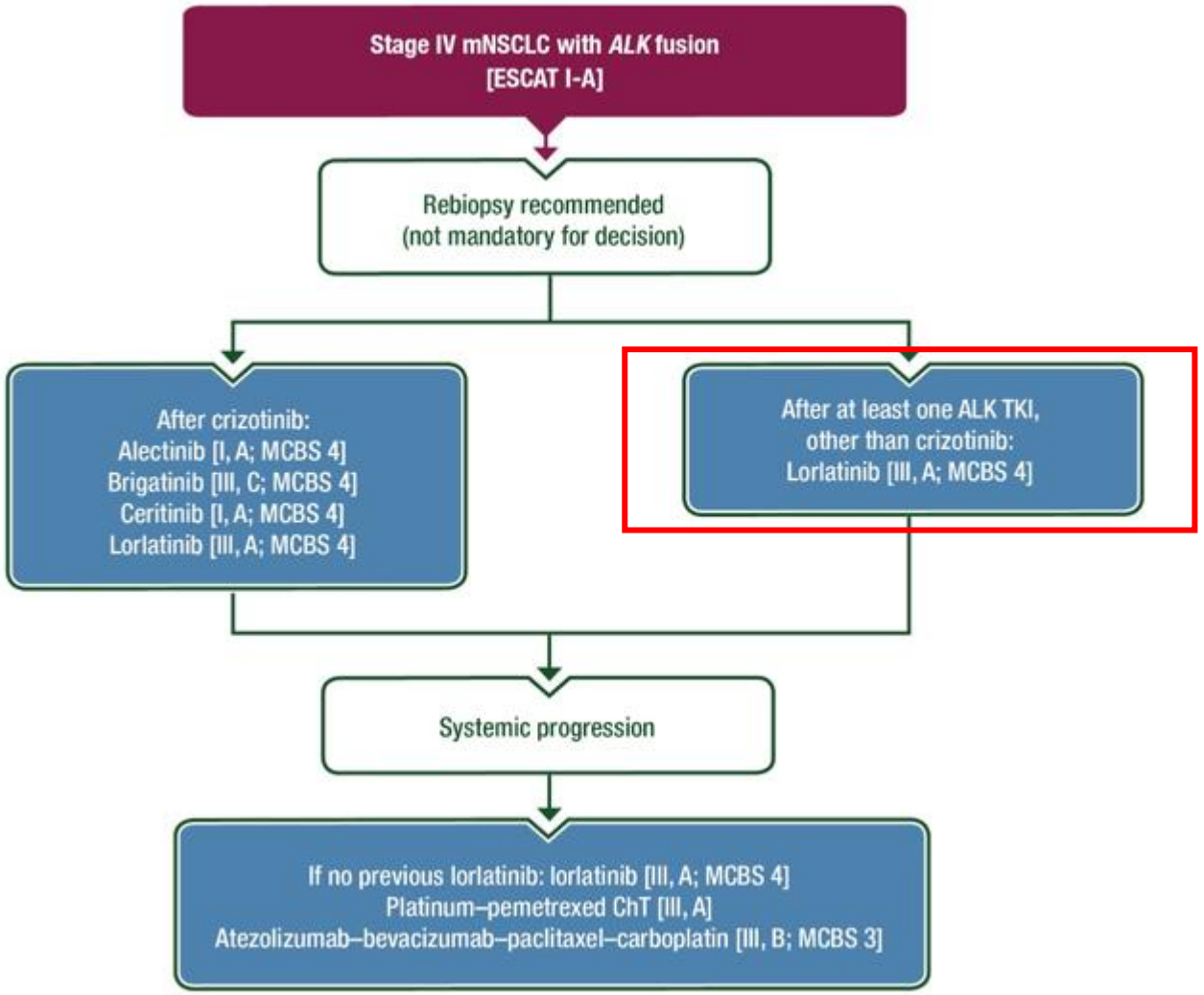
mPFS = NR
ORR = 76%
Grade ≥3 AE = 77%

Mok T, et al. ASCO 2026

CLINICAL PRACTICE GUIDELINES

ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

v1.3 February 2026



ALKOVE-1: neladalkib

Design

PHASE 1

Neladalkib dose escalation (15 – 200 mg QD) in patients with advanced *ALK*+ solid tumors

PHASE 2: Neladalkib 150 mg QD (RP2D)

PATIENT POPULATION	PRIOR ALK TKI	PRIOR LINES CHEMO/I-O	PHASE 2 ENDPOINTS
***ALK*+ NSCLC**	**1 prior 2G** *(ceritinib, alectinib, or brigatinib)*	0-2	• **Primary:** ORR by BICR • **Secondary:** Additional efficacy measures (DOR, TTR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile
	2-3 prior, any generation *(crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib [a])*	0-2	
	1 prior 3G *(lorlatinib)*	≤ 1	
	None (TKI-naïve)	≤ 1	
	Any *(not eligible for other cohorts)*	Any	
Other *ALK*+ Solid Tumors	**≥ 1 prior ALK TKI or systemic therapy** (or for whom no satisfactory standard therapy exists)	Any	

Lin J, et al. ASCO 2026

ALKOVE-1: neladalkib

Baseline characteristics

Patient Characteristic	ALK TKI-Pretreated [a] Efficacy Population N = 253
Age, median (range)	56 (24 – 83)
Female	145 (57%)
No history of smoking	167 (66%)
Geographic region	
Asia Pacific	50 (20%)
Europe	101 (40%)
North America	102 (40%)
ECOG PS	
0	90 (36%)
1	163 (64%)
Baseline CNS metastases [b]	101 (40%)
Secondary *ALK* mutation [c]	91 (36%)
G1202R mutation [d]	47 (19%)
≥2 *ALK* mutations [e]	43 (17%)

Treatment History		ALK TKI-Pretreated [a] Efficacy Population N = 253
Prior anticancer therapy, median (range)		3 (1 – 11)
Chemotherapy		128 (51%)
Prior ALK TKIs [f]		
1G	crizotinib	67 (26%)
2G	any 2G	240 (95%)
	alectinib	220 (87%)
	brigatinib	55 (22%)
	ceritinib	27 (11%)
	ensartinib	3 (1%)
3G	lorlatinib	190 (75%)
Lorlatinib-naïve [g, h]		**63 (25%)**
	≥1 prior 2G	**63/63 (100%)**
	1 ALK TKI (alectinib)	**44/63 (70%)**
	≥ 2 ALK TKIs	**17/63 (27%)**
Lorlatinib-experienced		**190 (75%)**
	≥2 ALK TKIs, including 2G and lorlatinib	**177/190 (93%)**
	≥3 ALK TKIs, including 2G and lorlatinib	**69/190 (36%)**

CNS, central nervous system; G, generation; PS, performance score; TKI, tyrosine kinase inhibitor.
[a] Includes 25 patients with other oncogenic driver(s) in addition to ALK. [b] Includes patients with treated or untreated, measurable or non-measurable CNS lesions by BICR. [c] *ALK* mutations as per local or central testing of blood (ctDNA) or tissue. [d] Patients may have had other mutations in addition to *ALK* G1202R. [e] Includes 15 patients with confirmed compound mutations (cis-allelic configuration). [f] One patient received an investigational TKI. [g] No patients received crizotinib as the only prior ALK TKI. [h] 46 patients received 1 prior ALK TKI only (alectinib, n = 44; brigatinib, n = 2).

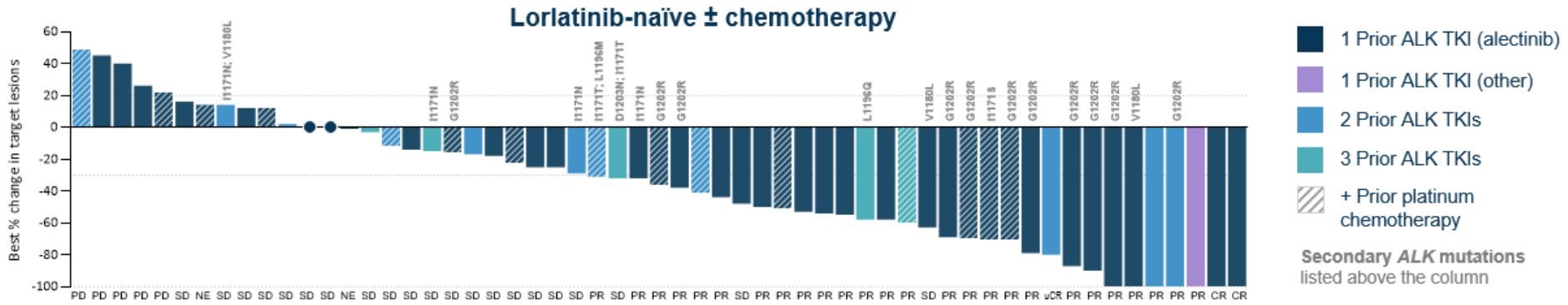
ALKOVE-1: neladalkib

ORR in ALK TKI pretreated patients

Advanced *ALK*+ NSCLC RECIST v1.1 by BICR	Any prior ALK TKI [a] (1–5 prior ALK TKIs ± chemotherapy) **N = 253**	Lorlatinib-naive (1–3 prior ALK TKIs ± chemotherapy) **N = 63**	Lorlatinib-experienced (1–5 prior ALK TKIs ± chemotherapy) **N = 190**
ORR, % (n/N) [95% CI]	**31%** (79/253) [b] [26, 37]	**46%** (29/63) [33, 59]	**26%** (50/190) [b] [20, 33]
CR, % (n/N)	2% (6/253) [c]	5% (3/63) [d]	2% (3/190) [d]

[a] Median duration of follow-up of 11.3 months. [b] Includes 2 single-timepoint PR pending confirmation for ongoing patients. [c] Includes 2 single-timepoint CR pending confirmation in ongoing patients with prior confirmed PR. [d] Includes 1 single-timepoint CR pending confirmation in ongoing patient with prior confirmed PR.

- **Prior alectinib only ± chemotherapy:** ORR = **48%** (21/44, 5% CR)
- **≥ 2 prior ALK TKIs ± chemotherapy:** ORR = **28%** (56/198) [b]



BICR, blinded independent central review; CI, confidence interval; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

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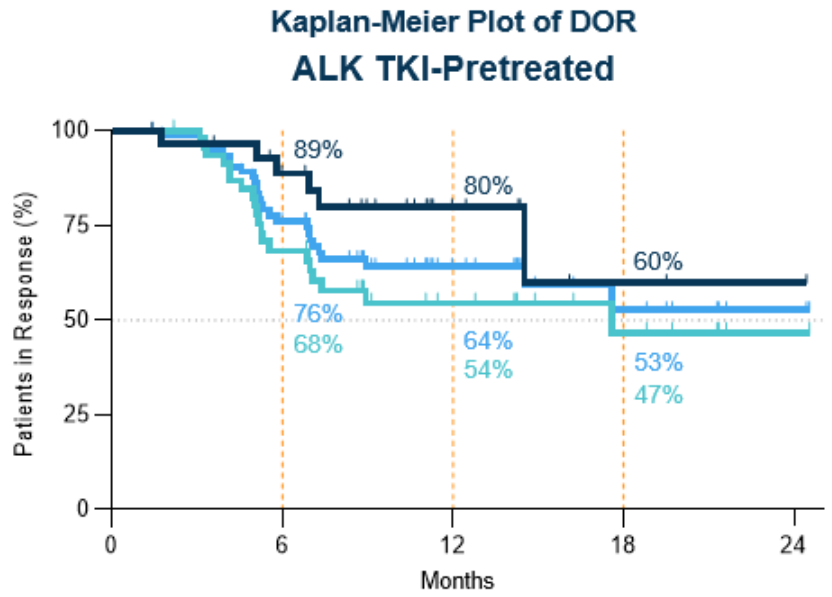
ALKOVE-1: neladalkib

DOR

TKI-Pretreated Advanced *ALK*+ NSCLC Kaplan-Meier Estimate	Any prior ALK TKI (1–5 prior ALK TKI ± chemotherapy) N = 77	Lorlatinib-naive (1–3 prior ALK TKI ± chemotherapy) N = 29	Lorlatinib-experienced (1–5 prior ALK TKI ± chemotherapy) N = 48
DOR ≥ 6 months [95% CI]	**76%** [64, 84]	**89%** [69, 96]	**68%** [52, 80]
DOR ≥ 12 months [95% CI]	**64%** [51, 75]	**80%** [58, 91]	**54%** [38, 68]
DOR ≥ 18 months [95% CI]	**53%** [34, 68]	**60%** [19, 85]	**47%** [27, 64]
Median DOR [95% CI]	**NR** [14.5, NE]	**NR** [14.5, NE]	**17.6** [6.9, NE] [a]

[a] Emerging median continues to mature.

- **Prior alectinib only ± chemotherapy:** median DOR = NR (95% CI: NE, NE).
- **≥ 2 prior ALK TKIs ± chemotherapy**: Emerging median DOR of 17.6 months (95% CI: 7.1, NE) continues to mature.



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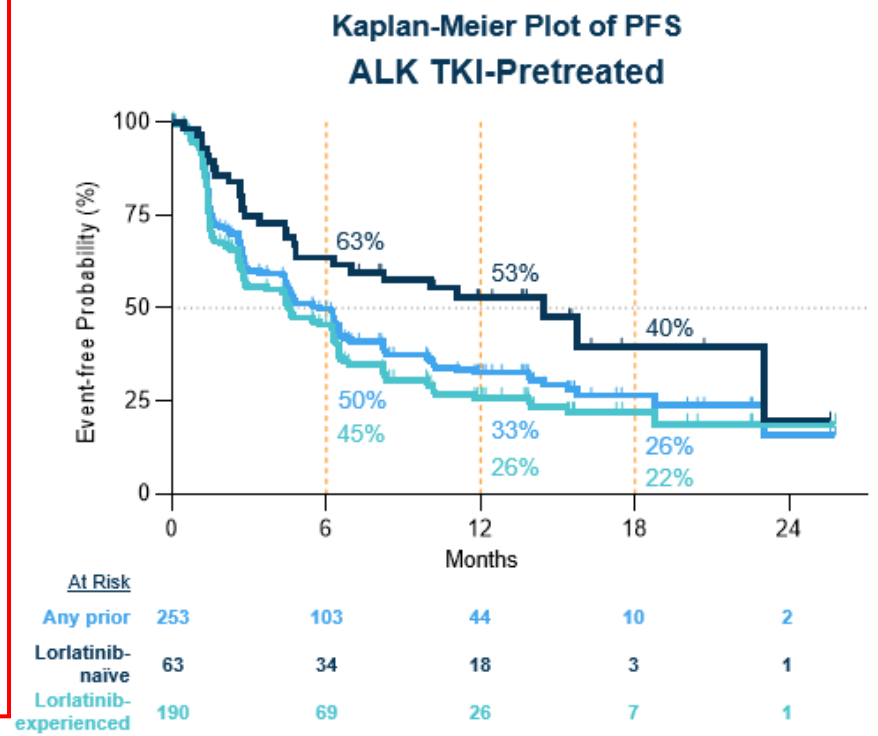
ALKOVE-1: neladalkib

PFS

TKI-Pretreated Advanced *ALK*+ NSCLC Kaplan-Meier Estimate	Any prior ALK TKI (1–5 prior ALK TKI ± chemotherapy) N = 253	Lorlatinib-naive (1–3 prior ALK TKI ± chemotherapy) N = 63	Lorlatinib-experienced (1–5 prior ALK TKI ± chemotherapy) N = 190
PFS ≥ 6 months [95% CI]	**50%** [43, 56]	**63%** [49, 75]	**45%** [38, 53]
PFS ≥ 12 months [95% CI]	**33%** [26, 39]	**53%** [38, 65]	**26%** [19, 33]
PFS ≥ 18 months [95% CI]	**26%** [20, 34]	**40%** [21, 58]	**22%** [15, 30]
Median PFS [95% CI]	**5.7** [4.4. 6.5]	**14.5** [4.8, NE] [a]	**4.6** [2.8, 6.2]

[a] Emerging median continues to mature.



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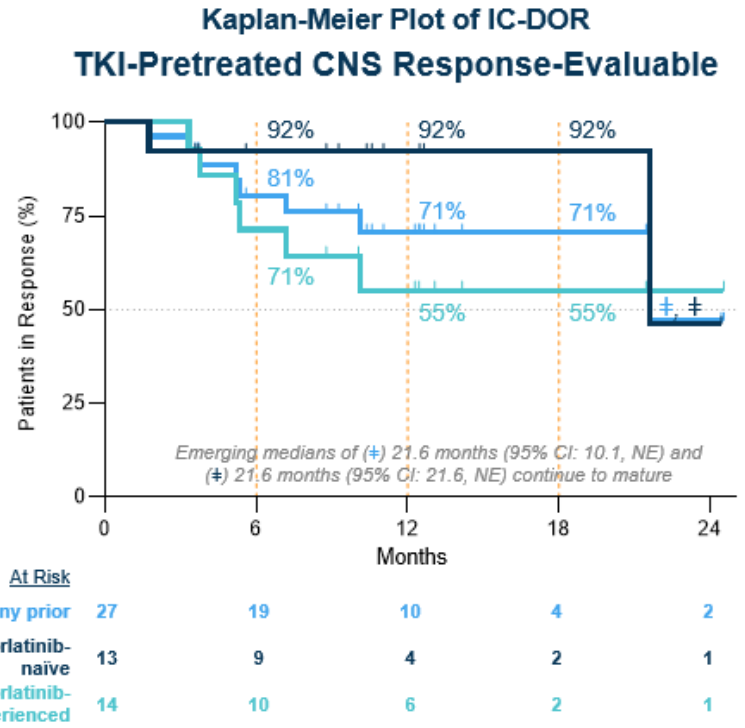
ALKOVE-1: neladalkib

CNS activity

TKI-Pretreated CNS Response-Evaluable [a] RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy N = 92	Lorlatinib-naive ± chemotherapy N = 24	Lorlatinib-experienced ± chemotherapy N = 68
IC-ORR, % (n/N)	**32%** (29/92) [b] [22, 42]	**63%** (15/24) [b] [41, 81]	**21%** (14/68) [12, 32]
IC-CR, % (n/N)	13% (12/92) [c]	21% (5/24) [c]	10% (7/68)
IC-DOR ≥ 6 months [d]	**81%** [59, 91]	**92%** [57, 99]	**71%** [41, 88]
IC-DOR ≥ 12 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]
IC-DOR ≥ 18 months [d]	**71%** [48, 85]	**92%** [57, 99]	**55%** [26, 77]

[a] Includes patients with measurable (≥5mm) CNS lesions by BICR at baseline and no brain radiation within 2 months before first dose of neladalkib. [b] Includes 2 single-timepoint IC-PR pending confirmation in ongoing patients. [c] Includes 1 single-timepoint IC-CR pending confirmation in ongoing patient with prior confirmed IC-PR. [d] Analyses of DOR based on Kaplan-Meier estimates.

- **CNS response-evaluable after prior alectinib only ± chemotherapy:** IC-ORR = **60%** (9/15; 1 IC-uPR); no intracranial progressors among confirmed intracranial responders.
- **CNS response-evaluable after ≥ 2 prior ALK TKIs ± chemotherapy:** IC-ORR = **25%** (19/75; 1 IC-uPR); IC-DOR at 6 months = **78%** (95% CI: 51, 91) and at 12 and 18 months = **66%** (95% CI: 39, 83).



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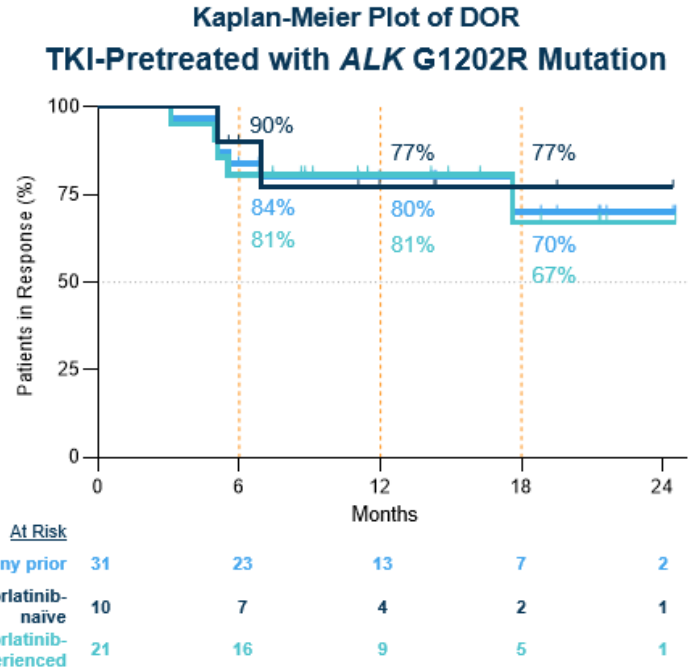
ALKOVE-1: neladalkib

Activity in secondary ALK-mutations

TKI-Pretreated with *ALK* G1202R mutation RECIST 1.1, BICR [95% CI]	Any prior ALK TKI ± chemotherapy [a] N = 47	Lorlatinib-naive ± chemotherapy N = 12	Lorlatinib-experienced ± chemotherapy N = 35
ORR, % (n/N)	**68%** (32/47) [b] [53, 81]	**83%** (10/12) [52, 98]	**63%** (22/35) [b] [45, 79]
DOR ≥ 6 months [c]	**84%** [65, 93]	**90%** [47, 99]	**81%** [56, 92]
DOR ≥ 12 months [c]	**80%** [61, 91]	**77%** [34, 94]	**81%** [56, 92]
DOR ≥ 18 months [c]	**70%** [42, 86]	**77%** [34, 94]	**67%** [32, 87]

[a] Patients may have had other mutations in addition to *ALK* G1202R. [b] Includes 1 single-timepoint PR pending confirmation for ongoing patient. [c] Analysis of DOR based on Kaplan-Meier estimates.

- ***ALK* G1202R after prior alectinib only ± chemotherapy**: ORR = **82%** (9/11); DOR at 12 and 18 months = **74%** (95% CI: 29, 93).
- ***ALK* G1202R after ≥ 2 prior ALK TKIs ± chemotherapy**: ORR = **64%** (23/36, 1 uPR); DOR at 12 months = **82%** (95% CI: 58, 93) and DOR at 18 months = **70%** (95% CI: 37, 88).



Responses also observed in patients with:

- **≥2 *ALK* mutations after ≥2 prior ALK TKIs ± chemotherapy**: ORR = **58%** (25*/43; includes 1 uPR), mDOR = NR (range, 2.2+ to 24.5+ months), DOR at 12 months = **69%** (95% CI: 45, 84)
- ***ALK* mutations other than G1202R**, including C1156Y, I1171N, I1171T, F1174C, F1174L, V1180L, L1196M, L1198F, D1203N, E1210K, and G1269A

* Among the 25 patients with response, 9 had confirmed compound mutations (cis-allelic configuration).

BICR, blinded independent central review; **CI**, confidence interval; **DOR**, duration of response; **NE**, not estimable; **NR**, not reached; **ORR**, objective response rate; **TKI**, tyrosine kinase inhibitor; **uPR**, unconfirmed partial response.

ALKOVE-1: neladalkib

Safety

Dose reduction due to TEAE: 17%

- Most common (≥1% of patients):
  ALT increased (10%), AST increased (8%) [a]

Discontinuation due to TEAE: 5%

- Most common (≥1% of patients):
  ALT increased (2%), AST increased (1%)

Most common TEAE were transaminase elevations

- Most were asymptomatic lab abnormalities, and observed to be low-grade, transient, and reversible with dose interruptions or reductions
- Preliminary data suggest increased incidence in less heavily pre-treated patients
- Enhanced monitoring and prompt dose interventions implemented in the protocol for the Phase 3 ALKAZAR trial

Overall safety profile consistent with avoiding TRK-related neurotoxicities

All Treatment-Emergent Adverse Events (TEAEs) in ≥ 15% of TKI-Naïve or TKI-Pretreated Patients with Advanced *ALK*+ NSCLC Receiving Neladalkib 150 mg QD (N = 656)

Preferred Term	Any Grade	Grade ≥3
ALT increased	47%	20%
AST increased	44%	16%
Constipation	28%	0.2%
Dysgeusia	23%	0
Peripheral edema	18%	0.3%
Cough	16%	0.5%
Nausea	16%	0.8%

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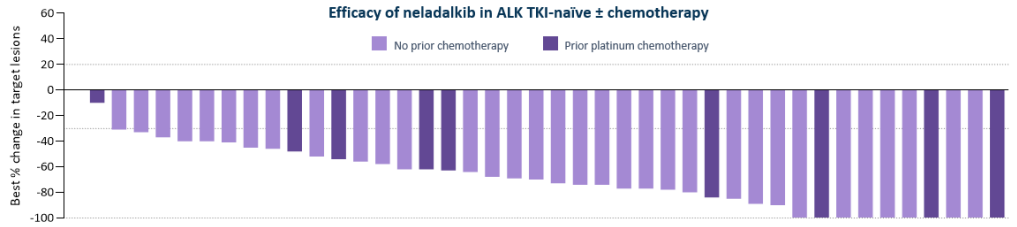
Neladalkib: treatment option post-lorlatinib?

- Clinical activity appears modest, with an ORR of 26% and median PFS of 4.6 months post-lorlatinib.
  - However, responses are durable once achieved (mDOR 17.6 months).
- The intracranial activity is encouraging, but the value must be interpreted in the context of the excellent CNS control already achieved with frontline lorlatinib.
- Activity was observed across both single and compound ALK resistance mutations, addressing an important unmet need after lorlatinib.
  - However, no single or compound ALK mutations were identified in CROWN. How large is the population that will eventually need 4th-generation ALK-inhibitors?
- Whether this agent has a future in the frontline setting remains to be determined.
  - High activity has been reported in ALK-TKI naïve disease (ORR 86%), but the bar set by lorlatinib is exceptionally high.
  - Phase-3 ALKAZAR trial is ongoing: niladalkib versus alectinib



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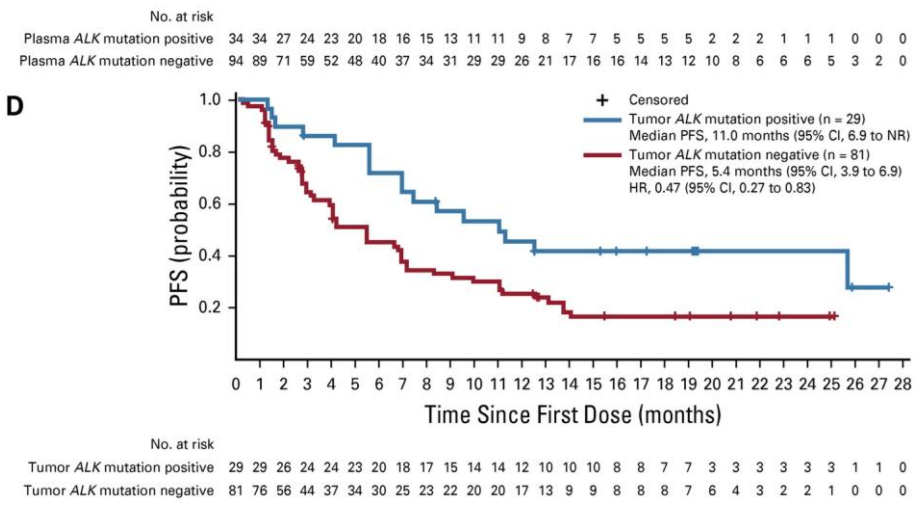
Where could neladalkib fit?

- Based on the current evidence, neladalkib appears better positioned as a mutation-directed therapy
  - Secondary ALK mutations are frequent after second-generation ALK-TKI's (ALK G1203R and others)
  - Compound ALK-mutations are frequent after sequential ALK-TKI therapy (including lorlatinib)

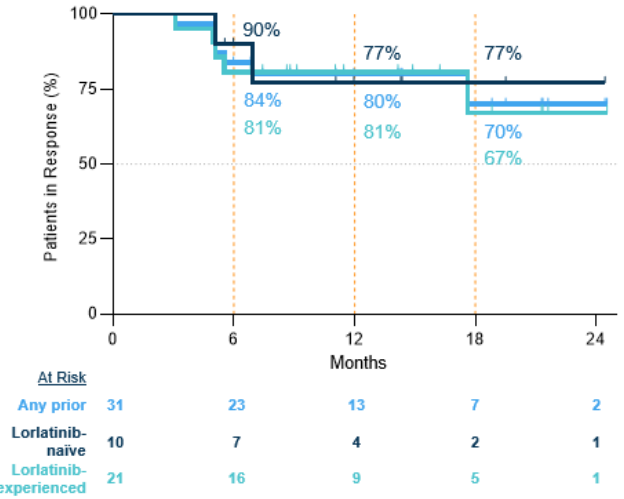
Lorlatinib in TKI pretreated



ORR = 69%
mPFS = 11m

Shaw AT, et al. J Clin Oncol 2019

Neladalkib in TKI pretreated



Lorlatinib naïve: ORR = 83% ; DOR ≥ 12 months = 77%
Lorlatinib experienced: ORR = 63% ; DOR ≥ 12 months = 81%

ARCHER

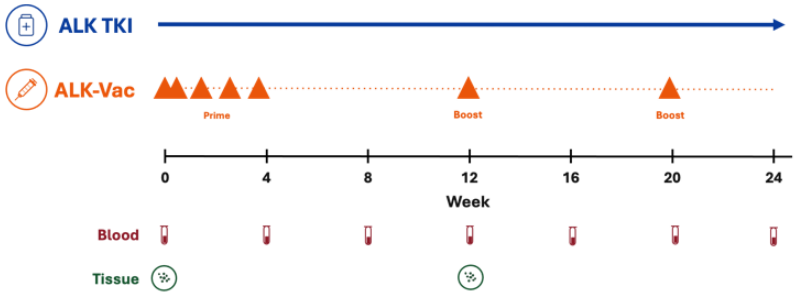
Profylactic peptide vaccine targeting resistance mutations in advanced ALK+ NSCLC

- ALK-Vac is a synthetic peptide vaccine targeting 7 common ALK resistance mutations

Key Inclusion

- Advanced or unresectable ALK+ NSCLC
- Without known resistance alterations targeted by the peptide vaccine
- Disease control for ≥ 4 months on standard of care TKI

Design



Endpoints

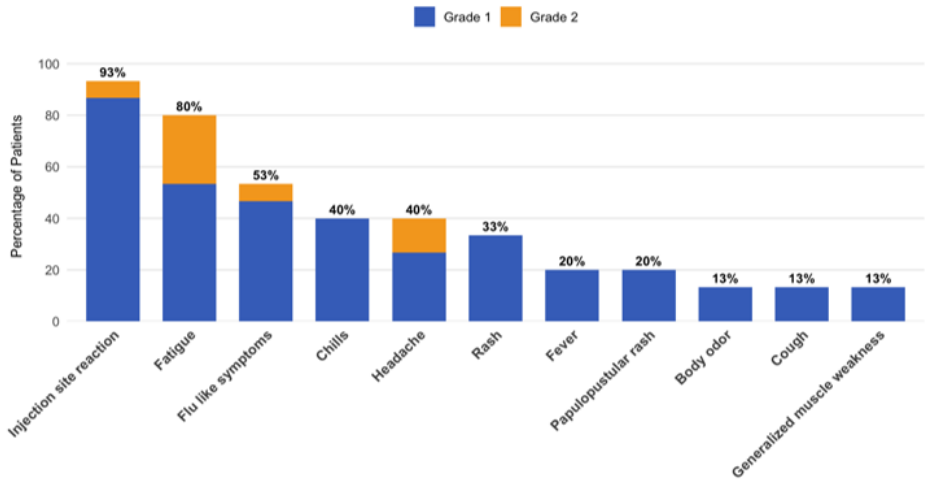
Co-primary
- Safety
- Vaccine induced immune response

Secondary
- Post-progression genomic alterations
- PFS
- OS

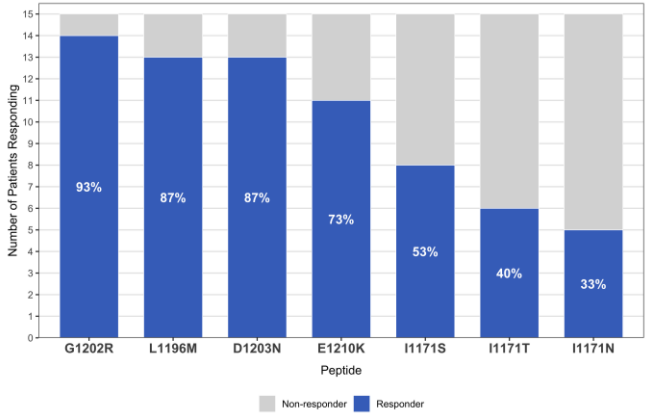
Patient characteristics

Characteristic	Overall (n = 15)
Age, years — median (range)	49 (40–82)
Sex: Female / Male — n (%)	10 (66.7) / 5 (33.3)
Race: White / Asian — n (%)	12 (80.0) / 3 (20.0)
Histology: Adenocarcinoma — n (%)	15 (100.0)
TKI at enrollment — n (%)	
Alectinib	7 (46.7)
Lorlatinib	5 (33.3)
Brigatinib	3 (20.0)
TKI line — n (%)	
First line	13 (86.7)
Second line	2 (13.3)
Time on TKI, months — median (range)	43.9 (4.6–74.2)
ALK fusion: EML4-ALK v1 / v3 / v5 / other / unknown — n (%)	8 (53.3) / 3 (20.0) / 1 (6.7) / 1 (6.7) / 2 (13.3)
Measurable disease — n (%)	5 (33.3)

Safety



Immunogenicity

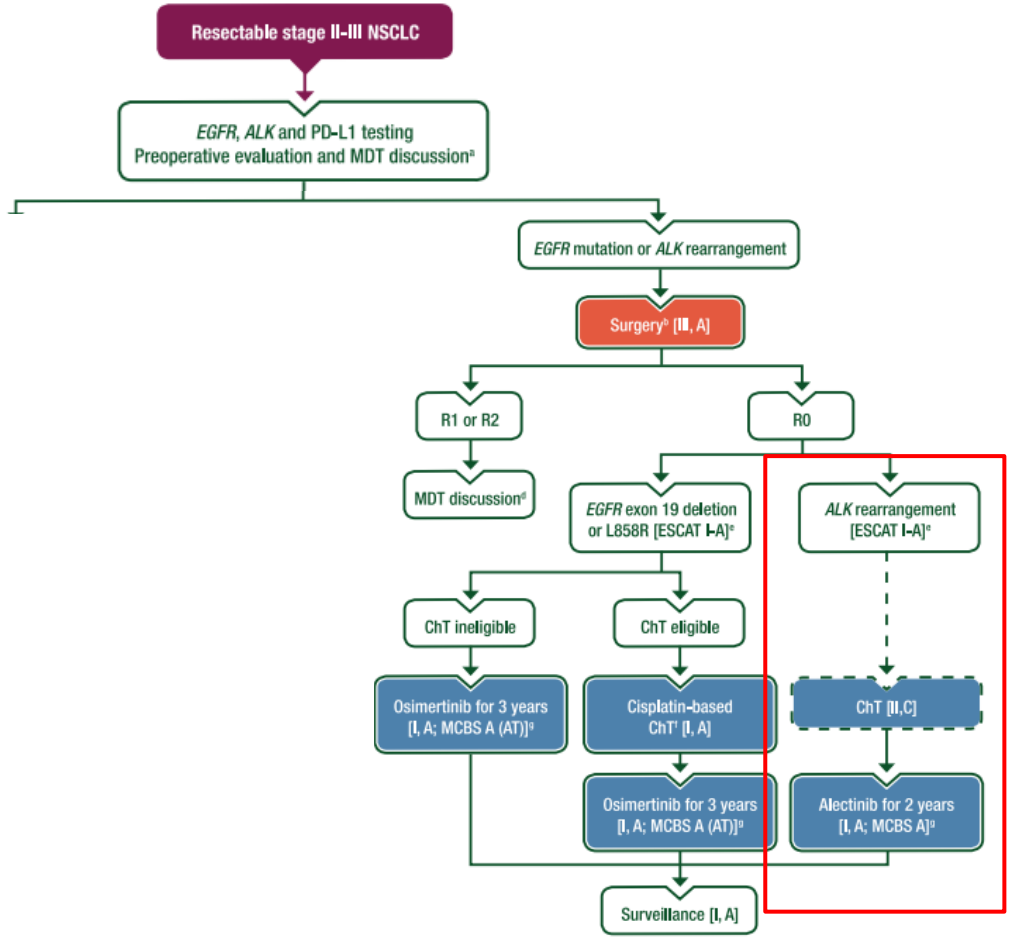


Lam V, et al. ASCO 2026

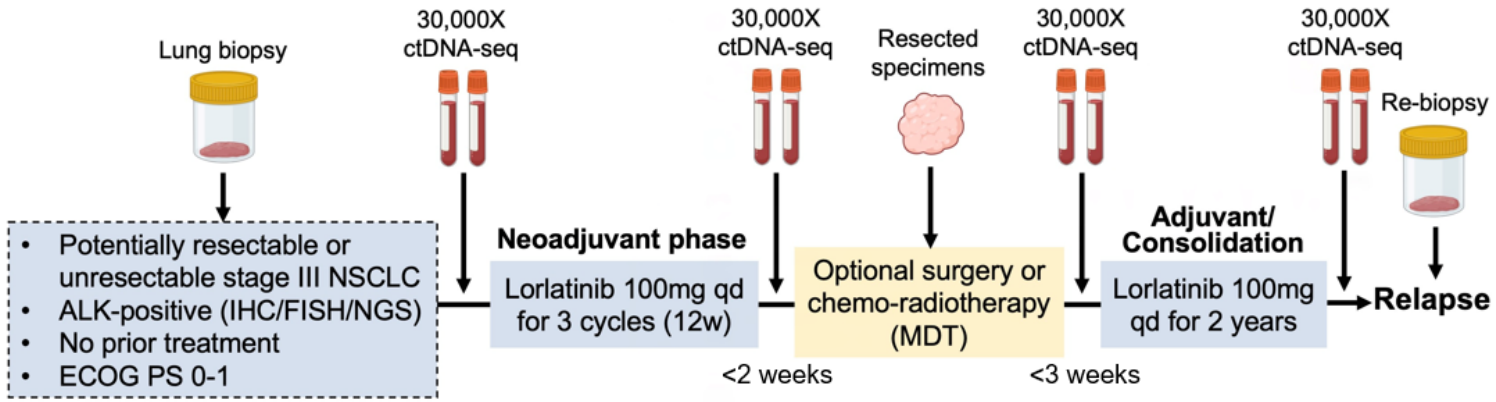
ALK

Non metastatic

Early-stage resectable ALK-fusion positive NSCLC



LORIN
Design



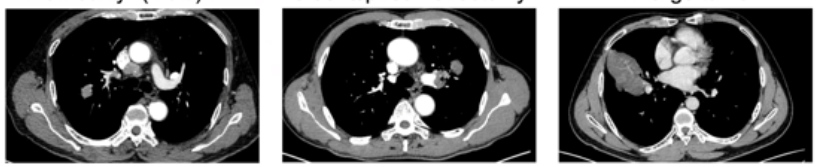
Primary endpoint: pCR (IASLC criteria)
Secondary endpoints: MPR (IASLC criteria), ORR, EFS, OS, AEs

Exploratory analysis: (Spatial transcriptomics & proteomics) Characterization of DTPCs after lorlatinib and the correlation between dynamic changes in the tissue immune microenvironment and pathological response

Definition of resectability in this study

Potentially resectable

Non-bulky[a] (multi) N2 | Sleeve/pneumonectomy | T4 large tumor



[a]Bulky N2: lymph nodes with a short-axis diameter >2.5–3 cm

Unresectable

Supraclavicular N3 | Contralateral N3

For patients with initially unresectable disease, contralateral lymph node sampling or neck dissection was conducted in most cases prior to treatment. After neoadjuvant therapy, pathological assessment included EBUS-TBNA, intraoperative contralateral lymph node dissection, or neck dissection was performed as needed.

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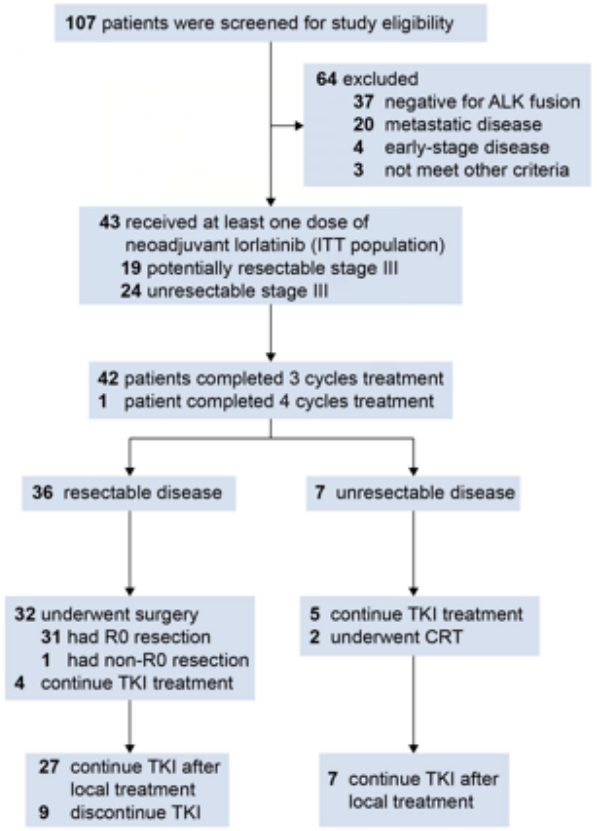
LORIN

Patient demographics



Characteristic	N=43
Age, median (IQR)	52 (41.5, 62)
Gender, n (%)	
Male	12 (27.9%)
Female	31 (72.1%)
Smoking status, n (%)	
Ever-smoker	7 (16.3%)
Non-smoker	36 (83.7%)
cN status, n (%)	
N0	1 (2.3%)
N1	2 (4.7%)
N2	16 (37.2%)
N3	24 (55.8%)
cTNM, n (%)[a]	
IIIA	16 (37.2%)
IIIB	22 (51.2%)
IIIC	5 (11.6%)

Characteristic	N=43
Resectability, n (%)	
Unresectable	24 (55.8%)
Resectable	19 (44.2%)
Histology, n (%)	
Adeno	42 (97.7%)
Squamous	1 (2.3%)
ALK status, n (%)	
NGS	40 (93%)
IHC/FISH only	3 (7%)
PD-L1, n (%) (n=39)	
Negative	9 (23.1%)
Low exp.	17 (43.6%)
High exp.	13 (33.3%)

[a]All patients underwent PET/enhanced CT plus brain MRI for staging except for one patient only underwent PET/CT

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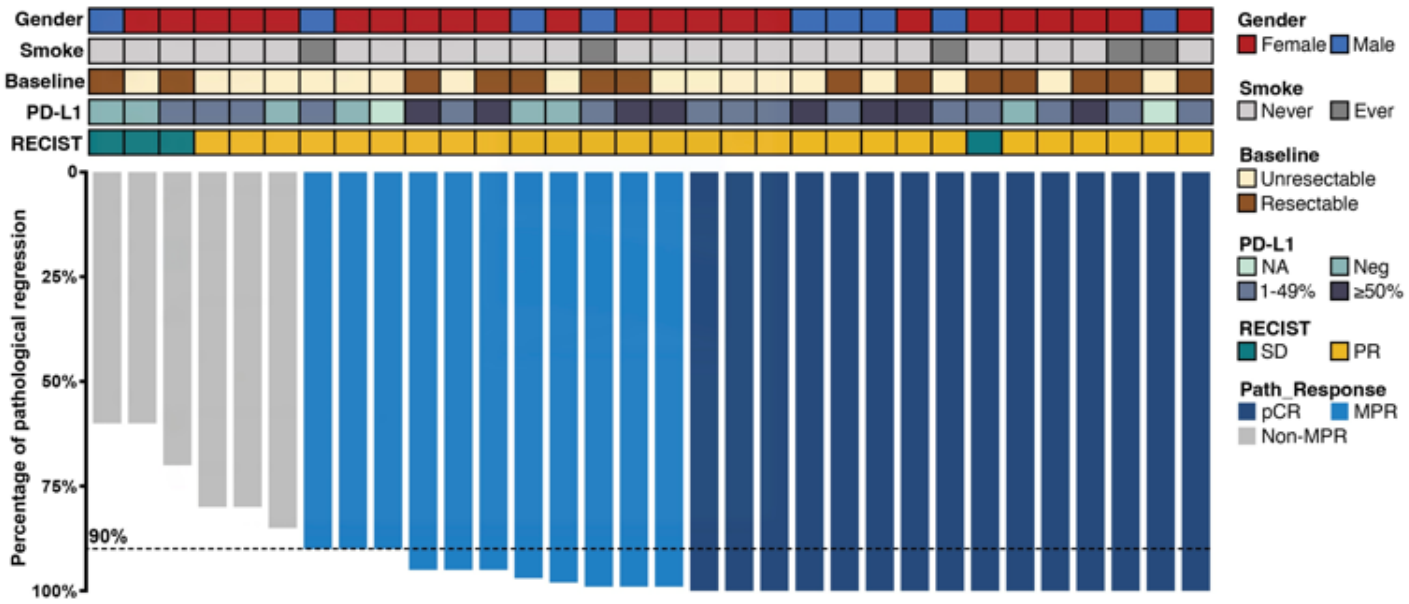
LORIN

Pathologic response



Overall	N=32 (n, %)
pCR	**15 (47)**
MPR	26 (81)
Median/Mean RVT	**1%/7%**

Resectability	pCR/MPR
Resectable	50%/86%
Unresectable	44%/78%

	Median PD-L1 exp.
MPR/pCR	25%
Non-MPR	1%
p value <0.01	

Among patients who underwent surgery, the pCR and MPR rates were **46.9% (15/32) (95%CI, 29.1%-65.2%) [34.9% for ITT]** and **81.3% (26/32) [60.5% for ITT]**, respectively, reaching the primary endpoint.

PR, partial response; SD, stable disease; pCR, pathological complete response; MPR, major pathological response; NA, not assessed; Neg, negative; RVT, residual viable tumor

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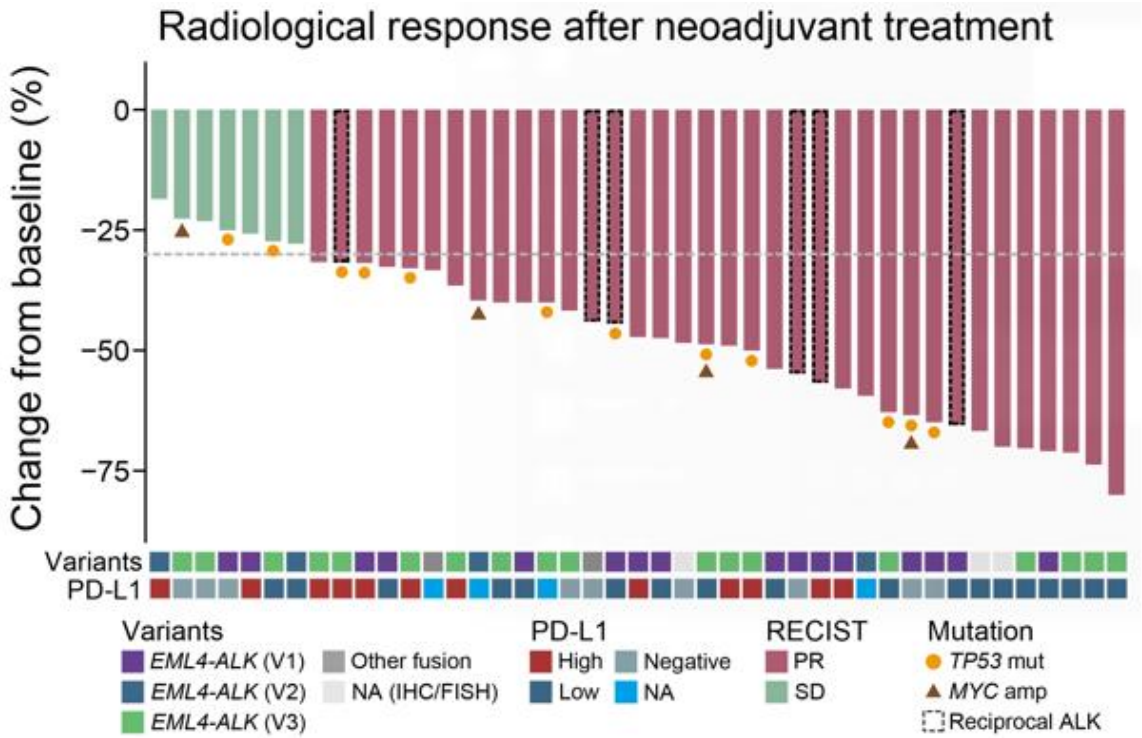
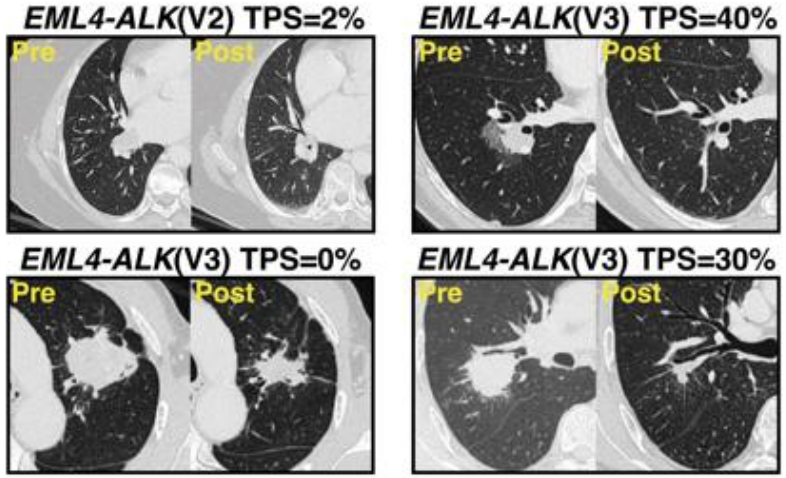
ORR and survival



Objective response	N=43
CR, n (%)	0 (0)
PR, n (%)	36 (84)
SD, n (%)	7 (16)
PD, n (%)	0 (0)
ORR, n (%)	**36 (84)**



After a median follow-up of 13 months (range 2.6-34.1months), 3 patients experienced local disease relapse without distant metastasis. The 1-year EFS rate was 97.1% (95% CI, 91.5-100). Median EFS and OS were not reached.

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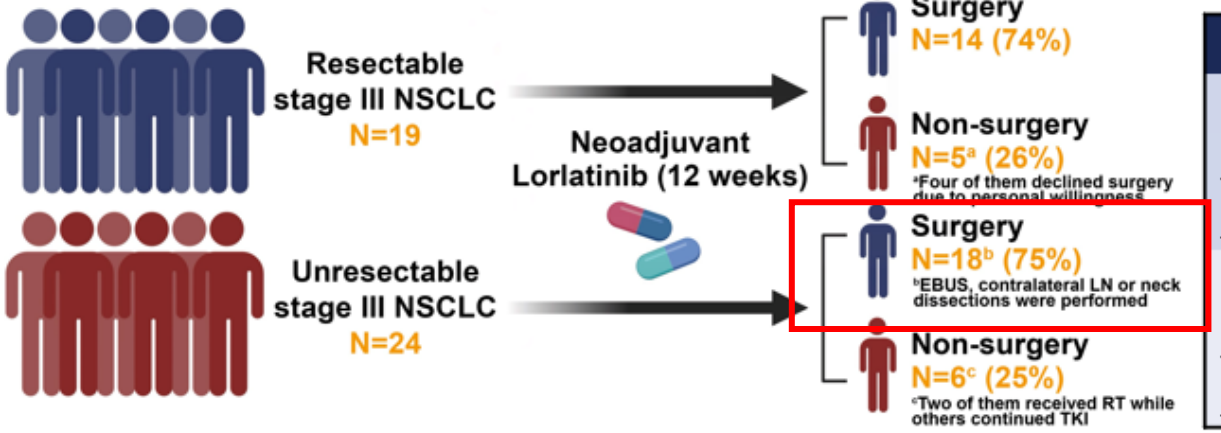
Surgical outcomes



Overall pN downstaging **90%**

cN-pN shift	Num. (%)
cN3(n=18)→pN3	1 (6)
cN3(n=18)→pN1/N2	**4 (22)**
cN3(n=18)→pN0	**13 (72)**
cN2(n=12)→pN2	1 (8)
cN2(n=12)→pN1	**0 (0)**
cN2(n=12)→pN0	**11 (92)**

Operation	N=32
R0 resection, n (%)	31 (97)*
Types of surgery, n (%)	
VATS#/RATS/Open surgery	27(84) /2(7) /3(9)
Conversion to open surgery	3 (9)

Operation details	N=32
Median surgical duration	180mins (90-315)
Median harvested LNs	12 (7-31)
Median estimated blood loss	50ml (30-800)
Clavien-Dindo (grade II)	5 (16%)

*One patient had pathologically confirmed N3 positive after lorlatinib and surgery; #All patients underwent lobectomy with 3 underwent bilobectomy

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LORIN
Safety

Neoadjuvant phase	N=43
Any TRAEs, n (%)	43 (100)
Grade 3-4, n (%)	10 (23)
TRAE lead to dose reduction, n (%)	7 (16)
TRAE lead to discontinuation, n (%)	1 (2)[a]

Adjuvant/consolidation phase	N=34
Any TRAEs, n (%)	32 (94)
Grade 3-4, n (%)	7 (21)
TRAE lead to dose reduction[b], n (%)	8 (24)
TRAE lead to treatment switch[c], n (%)	4 (12)

TRAEs	Neoadjuvant		CROWN	
	Any	G3-G4[d]	Any	G3-G4
Hypertriglyceridemia	33 (77)	6 (14)	99 (66)	37 (25)
Hypercholesterolemia	30 (70)	5 (12)	108 (72)	32 (21)
Edema	21 (49)	3 (7)	85 (57)	6 (4)
Increased weight	20 (46)	4 (9)	65 (44)	34 (23)
Peripheral neuropathy	12 (28)	1 (2)	65 (44)	2 (1)
Constipation	9 (21)	/	29 (19)	/
Nausea	8 (19)	/	25 (17)	1 (1)
Cognitive effect	8 (19)	/	41 (28)	5 (3)
ALT increased	6 (14)	/	29 (19)	4 (3)
Rash	5 (12)	/	18 (12)	/
Anemia	4 (9)	/	37 (25)	6 (4)

[a]This patient discontinued lorlatinib due to grade 3 ILD; [b]Only dose reduction during adjuvant/consolidation phase was counted; [c]All patients switched to alectinib; [d]All grade 4 AEs were dyslipidemia

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Neo-adjuvant ALK-TKI in (un)resectable disease?

- LORIN demonstrated high rates of pCR and MPR
  - ALK+ tumors show strong oncogene addiction with high MPR rates across perioperative trials (<-> EGFR MPR ~ 25% in NeoADAURA).
- LORIN demonstrated a high conversion-to-surgery rate.
  - Should we redefine unresectable disease?
- The correlation between pCR/MPR and EFS is not yet fully established.
  - Yet, early EFS signals are encouraging.
- The incremental benefit over the ALINA regimen in resectable disease is not yet clear
  - LORIN suggests that perioperative lorlatinib may represent a potential next step in ALK-positive stage III NSCLC, however ALINA remains the current standard of care.

ALNEO Phase 2

- Resectable stage III ALK-positive NSCLC
- Alectinib (8 weeks) → surgery → alectinib (96 weeks)
- MPR 46%
- pCR 12%
- ORR 67%

Leonetti A, et al. ASCO 2025

NAUTIKA1 Phase 2 (umbrella)

- Resectable stage IB-IIIA ALK-positive NSCLC
- Alectinib (8 weeks) → surgery → chemotherapy (4 cycles) → alectinib (2 years)
- MPR 61%
- pCR 25%
- ORR 63%

Lee JM, et al. WCLC 2025

RET

UZ GENT

UNIVERSITEIT GENT

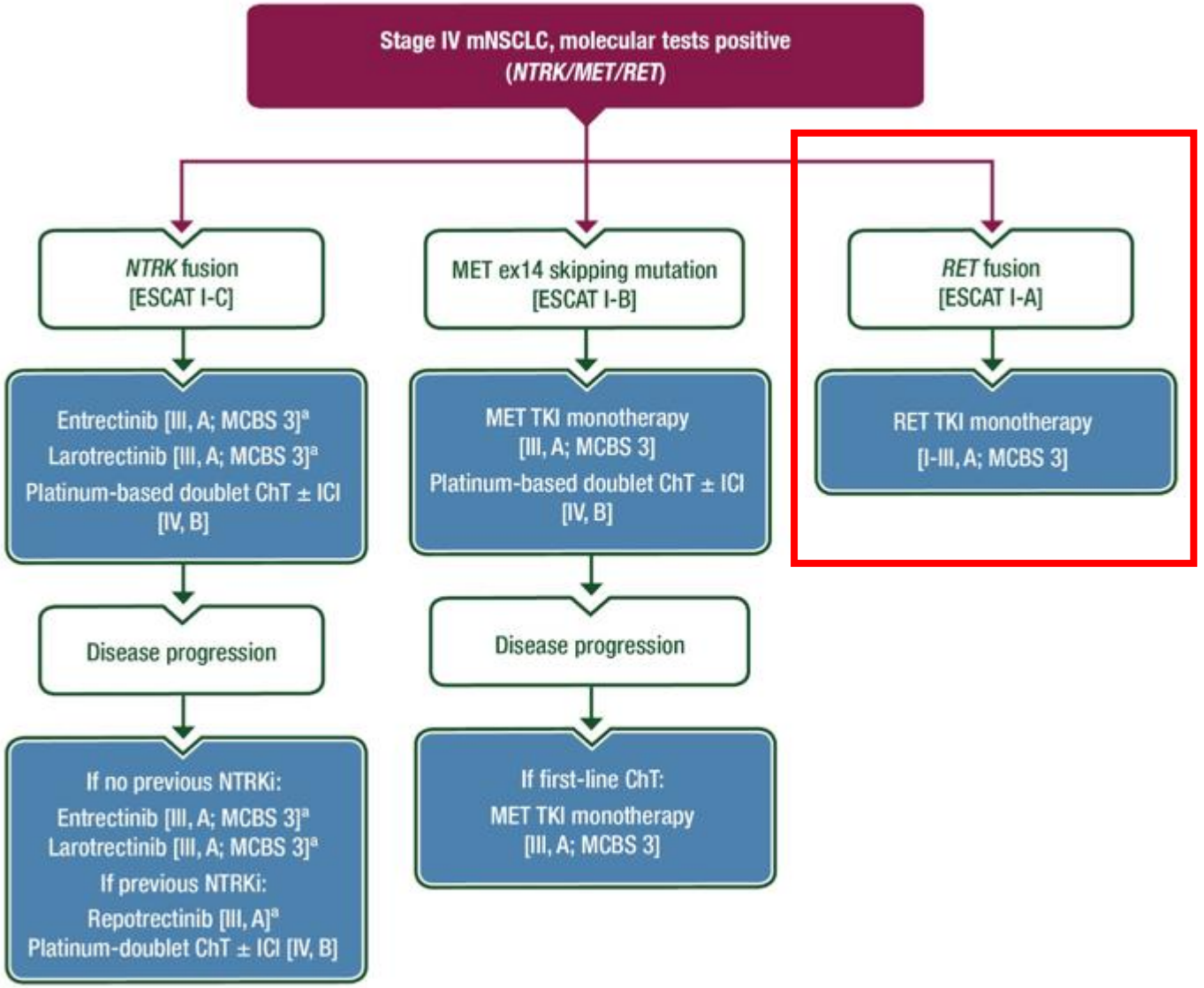
RET

Metastatic

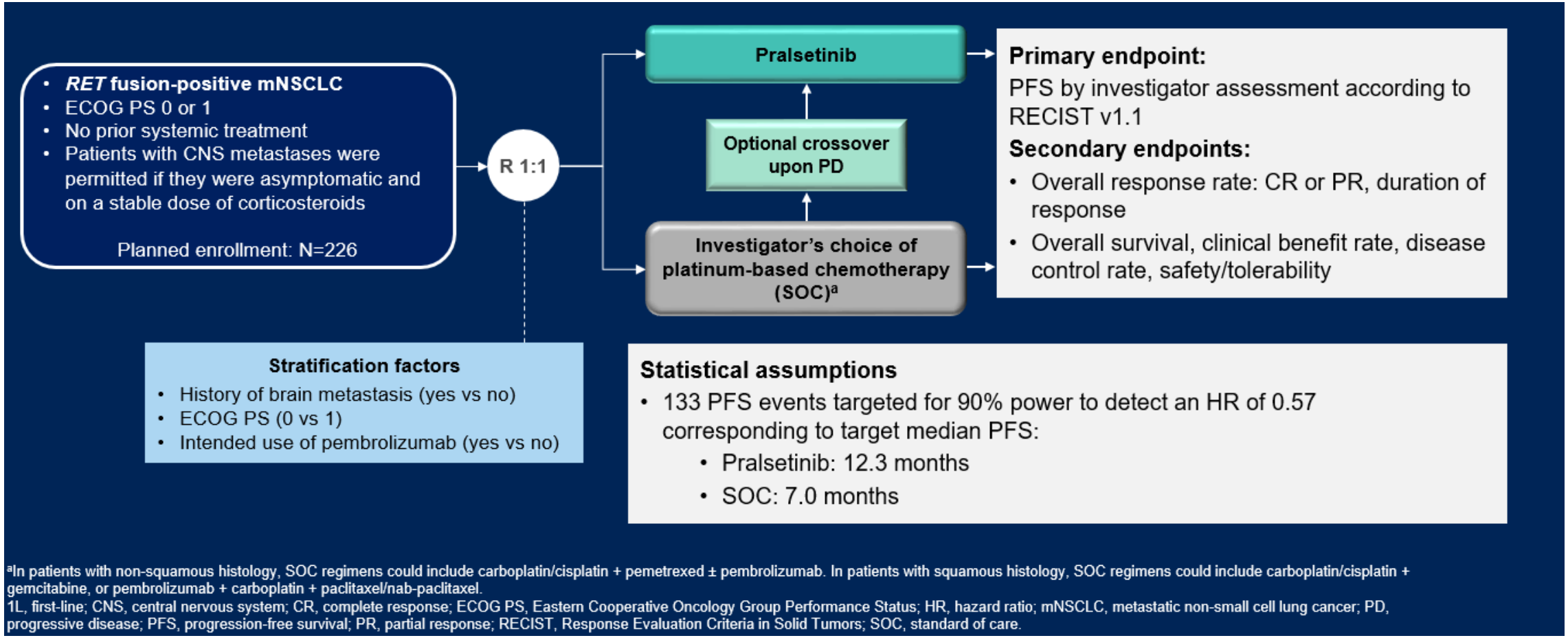
CLINICAL PRACTICE GUIDELINES

ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

v1.3 February 2026



AcceleRET-Lung
Design



[a]In patients with non-squamous histology, SOC regimens could include carboplatin/cisplatin + pemetrexed ± pembrolizumab. In patients with squamous histology, SOC regimens could include carboplatin/cisplatin + gemcitabine, or pembrolizumab + carboplatin + paclitaxel/nab-paclitaxel.
1L, first-line; CNS, central nervous system; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; mNSCLC, metastatic non-small cell lung cancer; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care.

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AcceleRET-Lung

Baseline characteristics

Patient characteristics, n (%)[a]		Pralsetinib n=110	SOC n=113
Age, years	Median (range)	62.0 (25-82)	63.0 (25-88)
Age group	<65 years	66 (60)	63 (56)
	≥65 years	44 (40)	50 (44)
Sex	Male	57 (52)	49 (43)
	Female	53 (48)	64 (57)
Race	White	68 (62)	65 (58)
	Asian	21 (19)	22 (20)
	American Indian/Alaska Native	9 (8)	7 (6)
	Black/African American	2 (2)	2 (2)
	Other	1 (1)	3 (3)
	Not reported or unknown	9 (8)	14 (12)
Region	Asia	17 (16)	19 (17)
	Australia	2 (2)	2 (2)
	Central/South America	13 (12)	11 (10)
	Europe	78 (71)	81 (72)
	North America	0 (0)	0 (0)

Patient characteristics, n (%)		Pralsetinib n=110	SOC n=113
ECOG PS[b]	0	42 (38)	43 (38)
	1	68 (62)	68 (60)
Smoking status[c]	Never smoked	65 (59)	67 (59)
	Former smoker	33 (30)	39 (35)
	Current smoker	9 (8)	5 (4)
NSCLC histology	Adenocarcinoma	109 (99)	109 (97)
Disease stage[d]	IIIB or IIIC	4 (4)	3 (3)
	IV	31 (28)	49 (43)
	IVA	29 (26)	26 (23)
	IVB	45 (41)	33 (29)
History of metastases	CNS	30 (27)	33 (29)
Intended use of pembrolizumab if randomized to SOC	Yes	73 (66)	74 (66)

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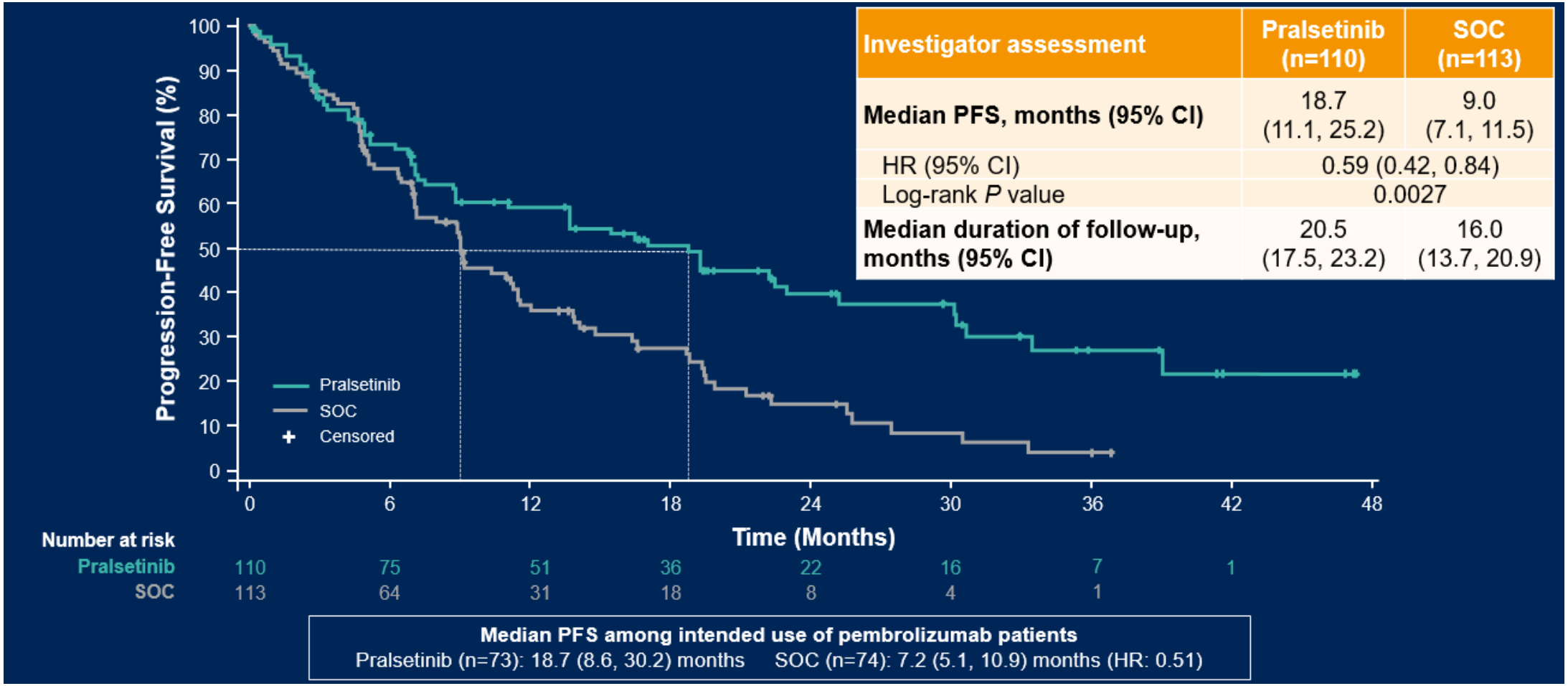
AcceleRET-Lung

PFS



Investigator assessment	Pralsetinib (n=110)	SOC (n=113)
Median PFS, months (95% CI)	18.7 (11.1, 25.2)	9.0 (7.1, 11.5)
HR (95% CI)	0.59 (0.42, 0.84)	
Log-rank *P* value	0.0027	
Median duration of follow-up, months (95% CI)	20.5 (17.5, 23.2)	16.0 (13.7, 20.9)

Median PFS among intended use of pembrolizumab patients

Pralsetinib (n=73): 18.7 (8.6, 30.2) months SOC (n=74): 7.2 (5.1, 10.9) months (HR: 0.51)

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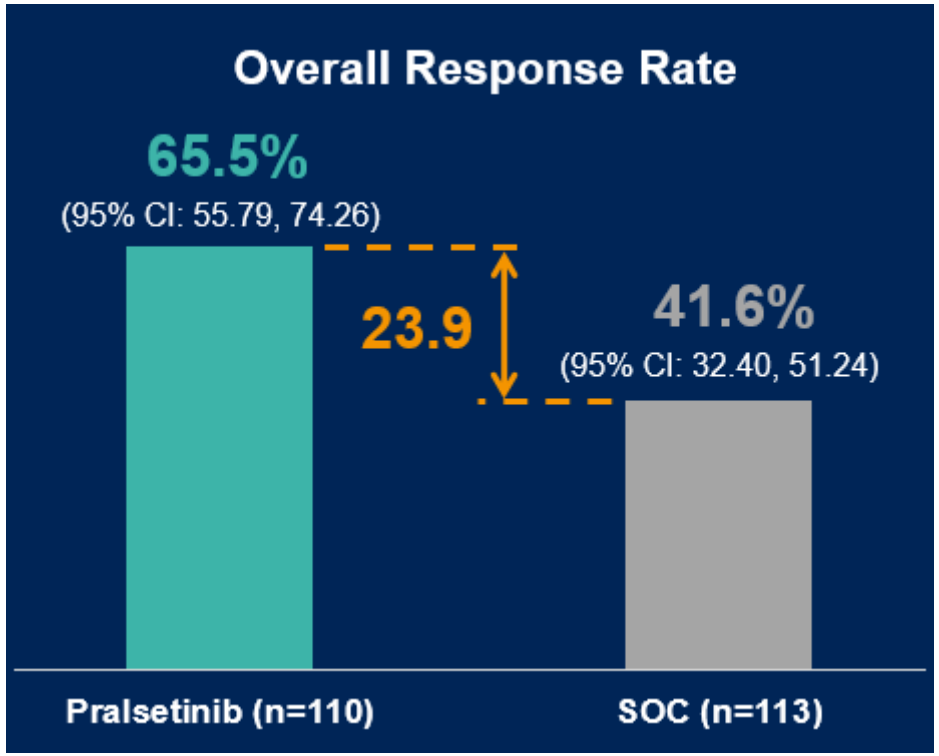
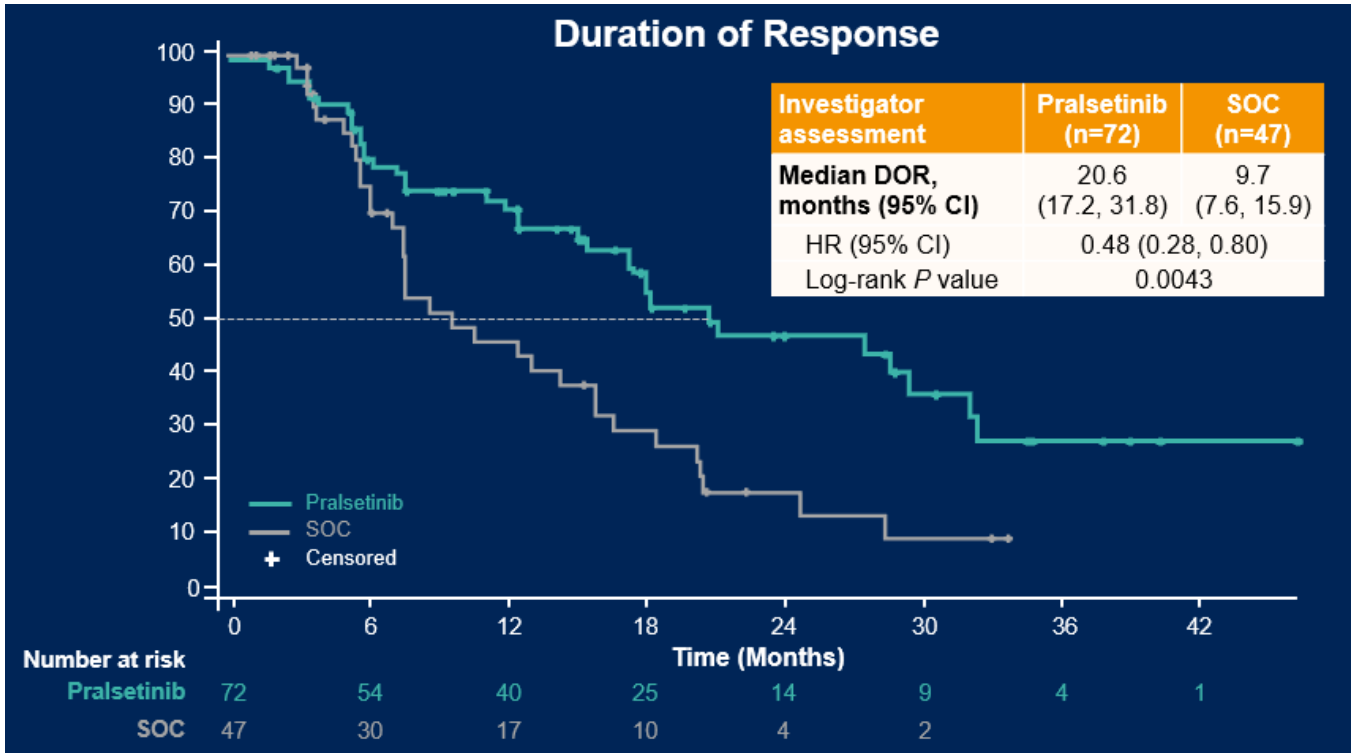
AcceleRET-Lung

ORR and DOR





Investigator assessment	Pralsetinib (n=72)	SOC (n=47)
Median DOR, months (95% CI)	20.6 (17.2, 31.8)	9.7 (7.6, 15.9)
HR (95% CI)	0.48 (0.28, 0.80)	
Log-rank *P* value	0.0043	

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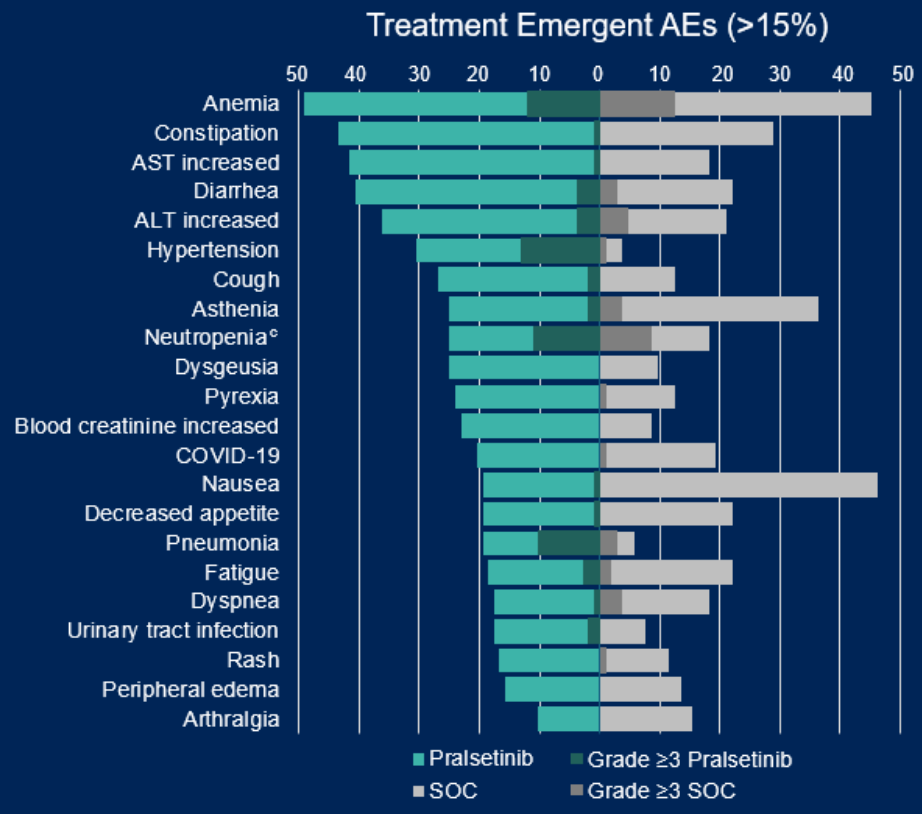
AcceleRET-Lung

Safety

Treatment exposure	Pralsetinib (n=108)	SOC	
		Chemotherapy[a] (n=35)	Chemotherapy + Pembrolizumab (n=69)
Median duration, months (range)	12.9 (0-50)	6.9 (0-25)	8.8 (0-25)

- Time on treatment was 87% longer for pralsetinib vs chemotherapy alone and 47% longer for pralsetinib vs chemotherapy + pembrolizumab

Adverse events (main treatment period)	Pralsetinib (n=108)	SOC (n=104)
Patients with ≥1 AE	108 (100)	104 (100)
Related AEs	101 (93.5)	96 (92.3)
Serious AEs	67 (62.0)	38 (36.5)
Related serious AEs	23 (21.3)	9 (8.7)
Grade 3-5 AEs	84 (77.8)	60 (57.7)
Deaths due to AEs[b]	16 (14.8)	5 (4.8)
Deaths due to infections[b]	8 (7.4)	0
Grade ≥3 QT prolongation	3 (2.8)	0
AEs leading to withdrawal from treatment	18 (16.7)	25 (24.0)
AEs leading to dose modification/interruption	80 (74.1)	57 (54.8)



[a]Chemotherapy includes carboplatin, cisplatin, and pemetrexed. [b]Patients who crossed over from SOC to pralsetinib are excluded. [c]Decreased neutrophil counts were also observed in patients in the pralsetinib arm (any grade, 11.1%; grade ≥3, 7.4%) and SOC arm (any grade, 5.8%; grade ≥3, 4.8%).
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SOC, standard of care.

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AcceleRET-Lung

Safety

Infection-related AEs	Pralsetinib (n=108)	SOC (n=104)
Any grade infection AEs, n (%)	77 (71.3)	54 (51.9)
Grade ≥3 infection AEs, n (%)	31 (28.7)	10 (9.6)
Mean (SD) months to first severe infection	6.2 (8.0)	5.1 (5.8)
Fatal infection events, n (%)	8 (7.4)[a]	0
Any grade opportunistic infections, n (%)	10 (9.3)	1 (1.0)
Grade ≥3 opportunistic infections, n (%)[b]	7 (6.5)	0

Protocol amendment in October 2024 updated recommendations on monitoring for infection and pralsetinib dose interruption, reduction, or permanent discontinuation, depending on AE severity

Off-target JAK/STAT-inhibition

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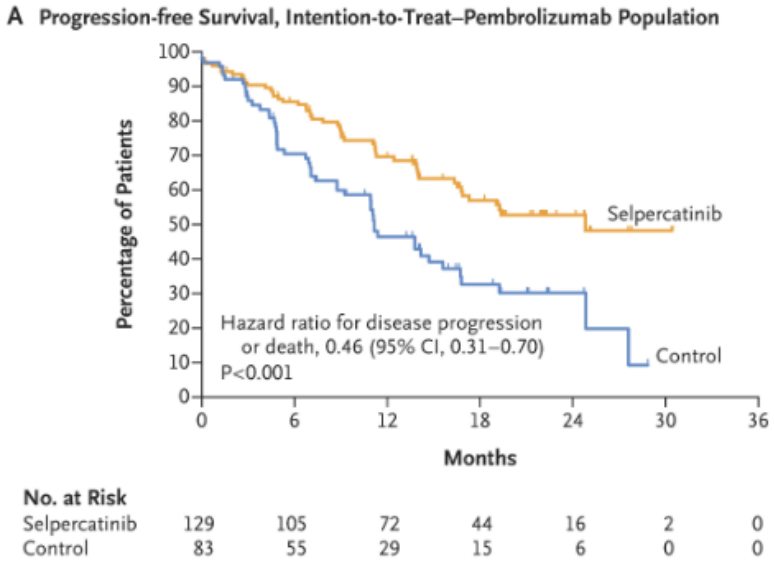
Advanced/metastatic RET-fusion positive NSCLC

- The AcceleRET-Lung data reinforce the role of selective RET-TKIs in the first-line treatment of RET fusion-positive NSCLC.

Libretto-431
1L selpercatinib



mPFS = 24,8 m
ORR = 84%
Grade ≥3 AE = 70%

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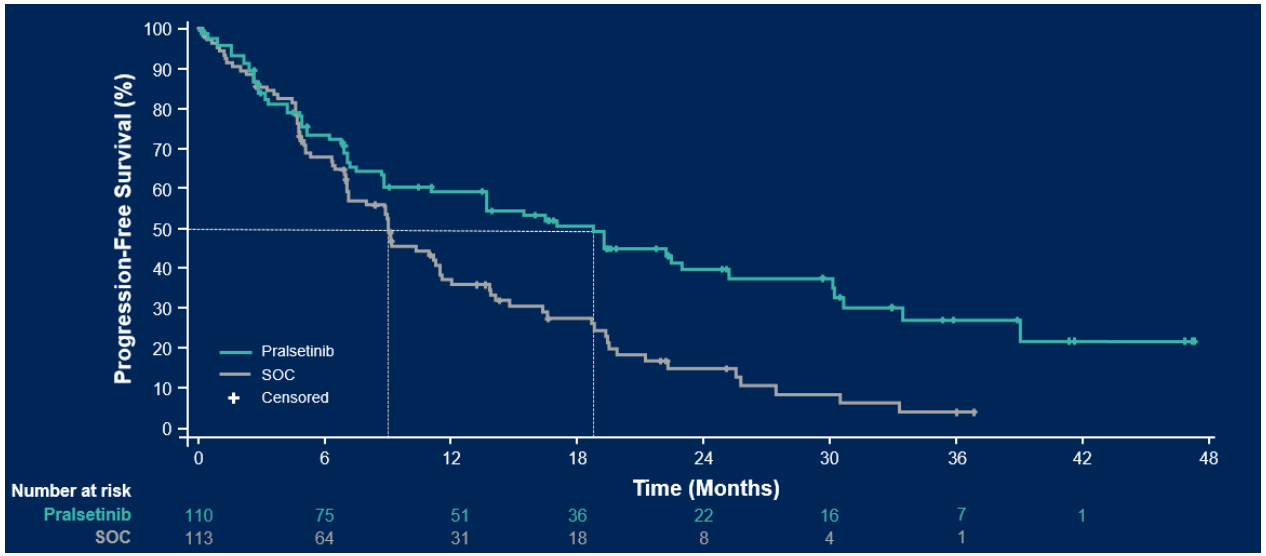
AcceleRET-Lung
1L pralsetinib



mPFS = 18,7 m
ORR = 66%
Grade ≥3 AE = 78%

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Lunbotinib = next-generation RET-TKI

Phase 2

Cohort 1: Prior Treatment
Prior platinum-based chemotherapy and immunotherapy[a] (N = 71)

Cohort 2: Treatment-Naïve
No prior systemic therapy (N=92)

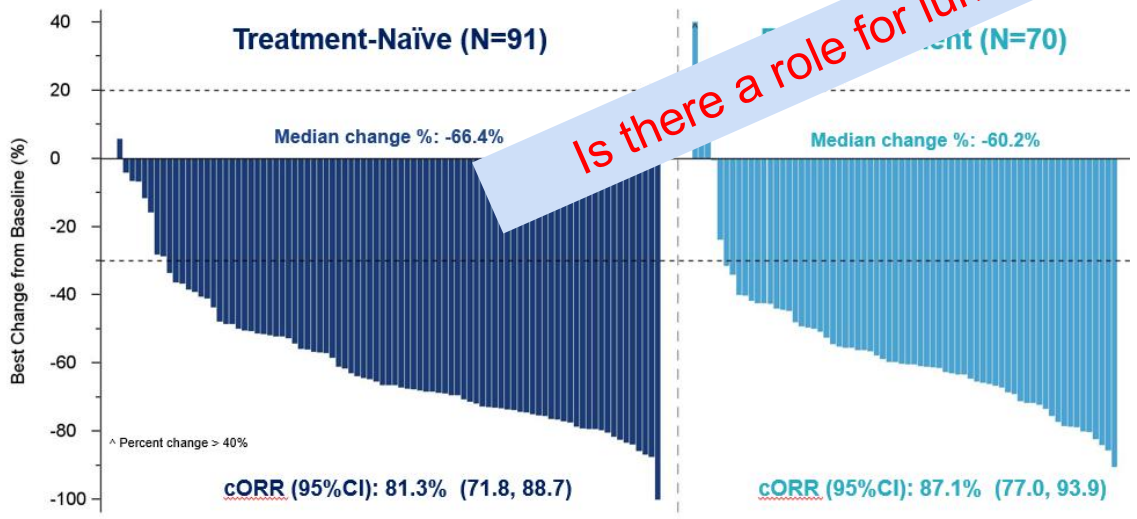
Key eligibility criteria
- LA/M RET fusion-positive NSCLC
- ECOG PS 0–1
- At least one measurable lesion per RECIST v1.1

Lunbotinib dosing
90 mg QD

Endpoints
Primary endpoint
- ORR by IRC

Secondary endpoints
- ORR by investigator, PFS, DOR, TTR, DCR
- OS
- CNS ORR/DOR[b]
- Safety

- Tumor assessment: every 8 weeks for the first 48 weeks and every 12 weeks afterwa

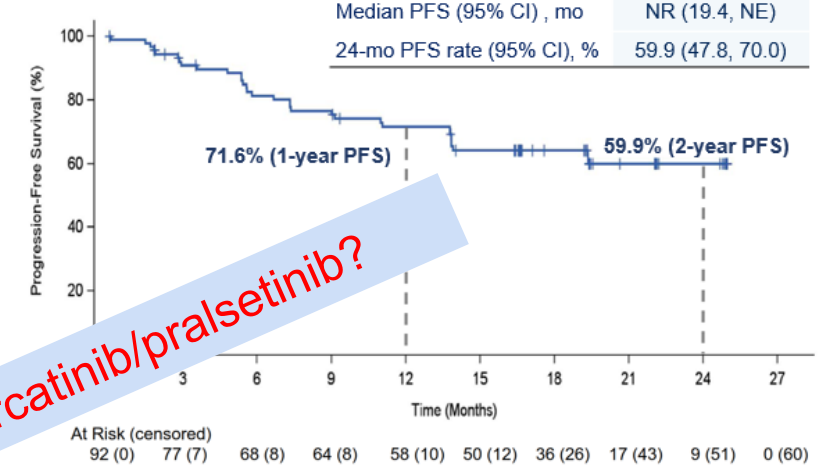


Is there a role for lunbotinib post selpercatinib/pralsetinib?

Treatment naive

PFS (ITT)

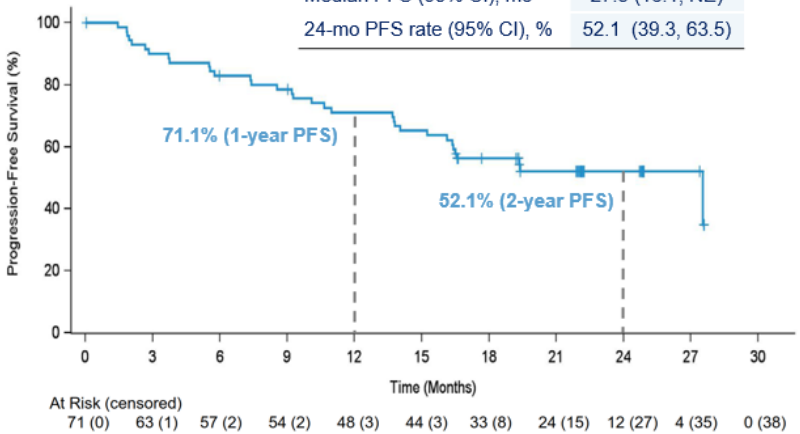
	Treatment-Naïve (N=92)
PFS events, n (%)	32 (34.8)
Median PFS (95% CI) , mo	NR (19.4, NE)
24-mo PFS rate (95% CI), %	59.9 (47.8, 70.0)



Prior therapy (no RET-TKI)

PFS (ITT)

	Prior Treatment (N=71)
PFS events, n (%)	33 (46.5)
Median PFS (95% CI), mo	27.5 (16.1, NE)
24-mo PFS rate (95% CI), %	52.1 (39.3, 63.5)



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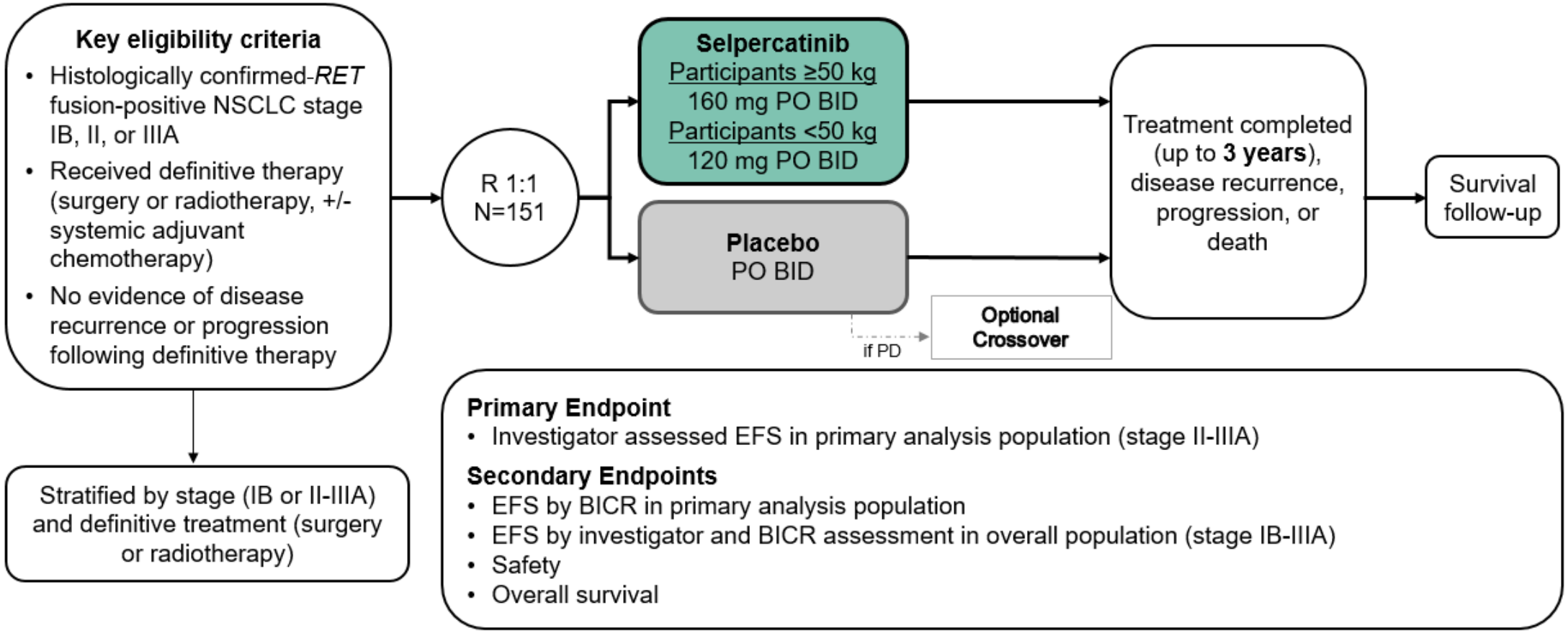
RET

Non metastatic

LIBRETTO-432
Design



Abbreviations: PO, by mouth; BID, twice daily; EFS, event-free survival; BICR, blinded independent central review; PD, progressive disease

NCT04819100

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Baseline characteristics in primary analysis population

		Selpercatinib N=54	Placebo N=55
Age, years	Median (range)	59.5 (41.0-84.0)	61.0 (26.0-78.0)
Sex, n (%)	Female	34 (63.0)	30 (54.5)
	Male	20 (37.0)	25 (45.5)
Race, n (%)[a]	Asian	33 (61.1)	32 (58.2)
	White	21 (38.9)	21 (38.2)
Geographic Region, n (%)	East Asia	31 (57.4)	31 (56.4)
	Europe/North America	18 (33.3)	21 (38.2)
	Other	5 (9.3)	3 (5.5)
Smoking Status, n (%)	Never	37 (68.5)	38 (69.1)
	Former / Current	17 (31.5)	17 (30.9)
ECOG PS, n (%)[b]	0	30 (55.6)	36 (65.5)
	1	24 (44.4)	18 (32.7)
RET fusion, n (%)	KIF5B:: RET	33 (61.1)	34 (61.8)
	CCDC6:: RET	14 (25.9)	11 (20.0)
	Other	7 (13.0)	10 (18.2)
PD-L1, n (%)[c]	Negative	11 (20.4)	16 (29.1)
	Positive	25 (46.3)	28 (50.9)
	Unknown	17 (31.5)	11 (20.0)
Prior anti-cancer therapy, n (%)	Surgery	54 (100.0)	54 (98.2)
	Radiotherapy	2 (3.7)	6 (10.9)
	Systemic therapy	50 (92.6)	50 (90.9)

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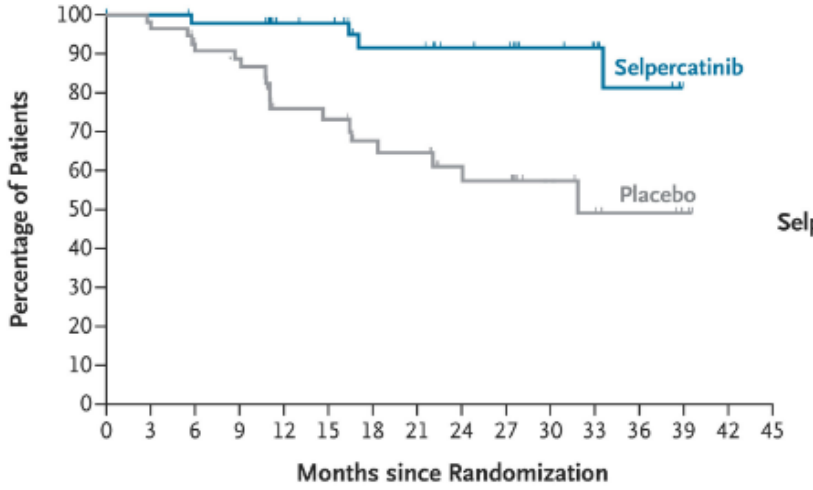
LIBRETTO-432
EFS

A Event-free Survival in the Primary Analysis Population

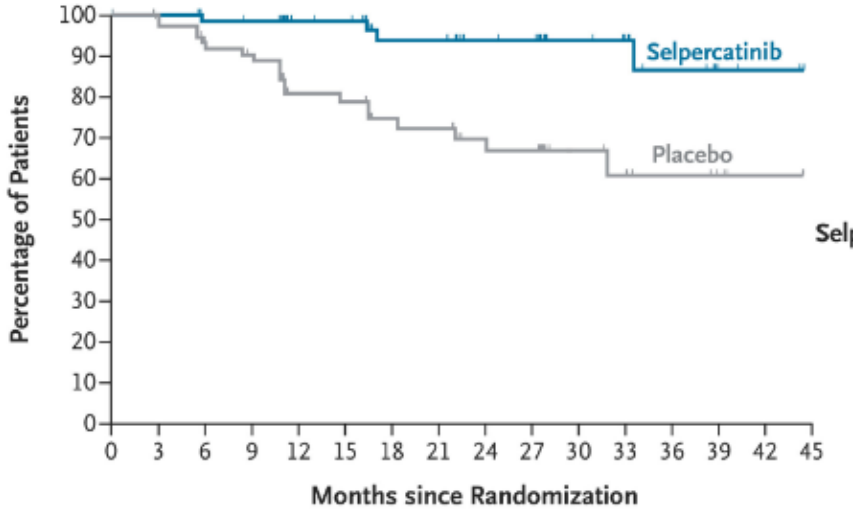


	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Selpercatinib	54	4	NE (33.5 to NE)
Placebo	55	19	31.8 (18.4 to NE)

Hazard ratio for disease recurrence, progression, or death, 0.17 (95% CI, 0.06–0.51)
P<0.001

No. at Risk															
Selpercatinib	54	49	45	45	37	36	27	27	22	21	15	12	7	0	0
Placebo	55	54	47	44	28	27	22	21	16	15	8	6	4	2	0

B Event-free Survival in the Overall Population



	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Selpercatinib	75	4	NE
Placebo	76	20	NE (31.8 to NE)

Hazard ratio for disease recurrence, progression, or death, 0.16 (95% CI, 0.06–0.48)
P<0.001

No. at Risk															
Selpercatinib	75	68	63	62	51	50	37	37	30	29	20	17	10	3	2	0
Placebo	76	73	64	61	40	39	31	30	25	24	12	10	6	4	2	0

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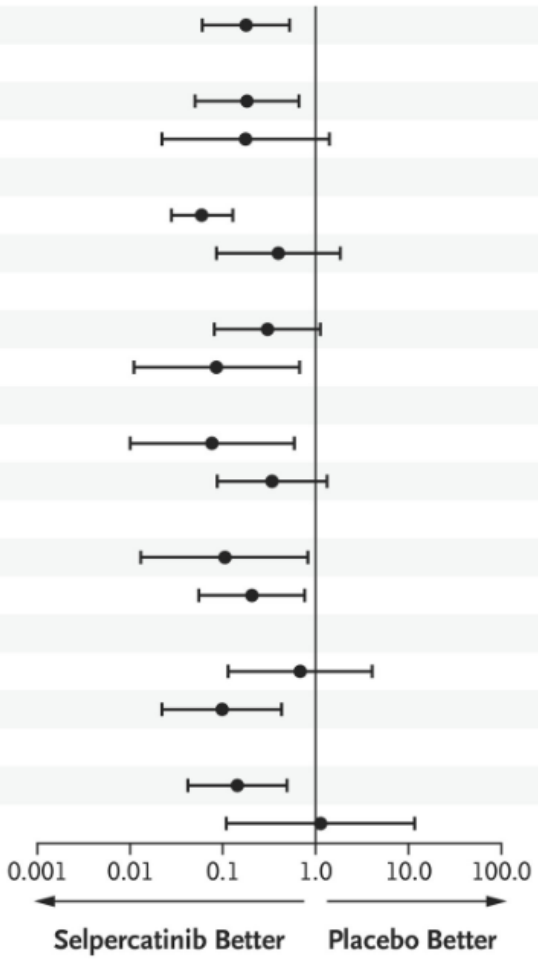
EFS by subgroups

Subgroup	Total No. of Patients	Selpercatinib (no. of patients with event)	Placebo (no. of patients with event)	Hazard Ratio for Disease Recurrence, Progression, or Death (95% CI)
Overall	109	4	19	0.18 (0.06–0.52)
Sex				
Female	64	3	11	0.18 (0.05–0.66)
Male	45	1	8	0.18 (0.02–1.41)
Age				
≤65 yr	78	2	10	0.13 (0.03–0.59)
>65 yr	31	2	9	0.40 (0.08–1.84)
Geographic region				
North America or Europe	39	3	9	0.30 (0.08–1.12)
Other	70	1	10	0.08 (0.01–0.67)
Smoking status				
Never	75	1	12	0.08 (0.01–0.59)
Former or current	34	3	7	0.34 (0.09–1.32)
ECOG performance-status score				
0	66	1	10	0.10 (0.01–0.82)
>0	42	3	9	0.20 (0.06–0.76)
Disease stage				
Stage II	47	2	3	0.68 (0.11–4.08)
Stage IIIA	62	2	16	0.10 (0.02–0.43)
Previous chemotherapy				
Yes	100	3	17	0.14 (0.04–0.49)
No	9	1	2	1.13 (0.11–11.70)



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	Selpercatinib N=54	Placebo N=55
Median follow-up, months (IQR)	25 (13.9, 33.2)	27 (15.8, 34.1)
On treatment, n (%)	30 (55.6)	24 (43.6)
Off treatment, n (%)	24 (44.4)	31 (56.4)
Death, n	0	3

16 stage II-IIIA patients crossed over to selpercatinib following disease recurrence

- 12 of these patients remain on selpercatinib at data cutoff
- 3 deaths occurred in patients who crossed over*

No deaths occurred in the selpercatinib arm

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Safety

Events, n (%)	Selpercatinib N=75	Placebo N=76
Any TEAE	75 (100)	74 (97.4)
Grade ≥3 TEAEs	50 (66.7)	18 (23.7)
Serious TEAEs ≥1	17 (22.7)	10 (13.2)
Discontinued study treatment due to TEAEs*	13 (17.3)	1 (1.3)
Discontinued due to SAE	2 (2.7)	1 (1.3)
Dose modifications	66 (88.0)	35 (46.1)
Dose interruptions due to TEAEs	58 (77.3)	20 (26.3)
Dose reductions due to TEAEs	41 (54.7)	6 (7.9)
TEAEs leading to death, on study treatment	0	0

Grade ≥3 TEAEs were manageable with dose modifications

Discontinuations were mostly due to low grade events in the selpercatinib arm

*Most common reasons for selpercatinib discontinuation were ALT increase n=4; AST increase n=2; interstitial lung disease n=2

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LIBRETTO-432
Safety

	Selpercatinib N=75		Placebo N=76	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with ≥1 TEAE (≥ 20%), no. (%)	75 (100.0)	50 (66.7)	74 (97.4)	18 (23.7)
ALT increase	47 (62.7)	13 (17.3)	14 (18.4)	1 (1.3)
AST increase	45 (60.0)	14 (18.7)	12 (15.8)	2 (2.6)
Diarrhea	29 (38.7)	3 (4.0)	13 (17.1)	0
Dry mouth	30 (40.0)	0	12 (15.8)	0
Cough	20 (26.7)	0	18 (23.7)	0
Bilirubin increase	20 (26.7)	1 (1.3)	11 (14.5)	0
Hypertension	23 (30.7)	8 (10.7)	8 (10.5)	2 (2.6)
Constipation	17 (22.7)	0	10 (13.2)	0
Hyperuricemia	15 (20.0)	0	8 (10.5)	0
Other AEs of special Interest				
Hypersensitivity	5 (6.7)	0	0	0
ECG QT prolongation	7 (9.3)	1 (1.3)	1 (1.3)	1 (1.3)

AEs were generally consistent with the known safety profile of selpercatinib

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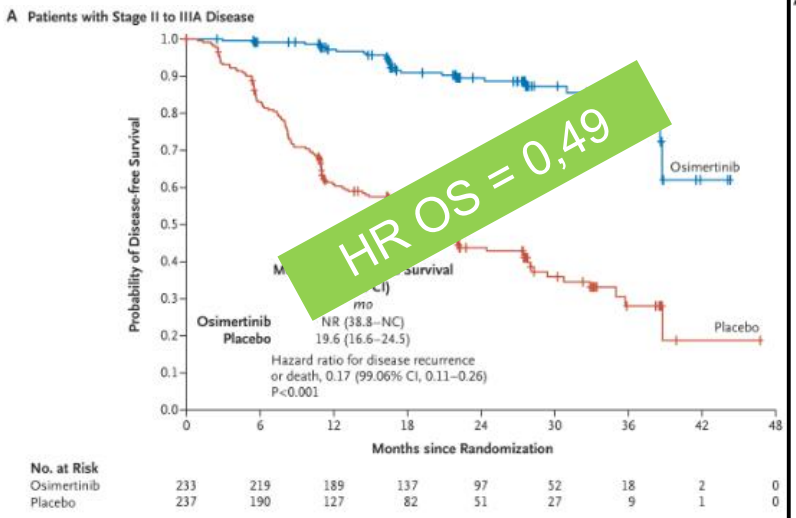
Adjuvant selpercatinib as a new SOC in early stage RET-fusion positive NSCLC

- Targeted therapy is moving upstream: from metastatic disease to curative-intent treatment.
- Molecular testing should be performed at diagnosis, regardless of stage.
- Important questions remain: optimal duration? Is adjuvant chemotherapy necessary? OS?

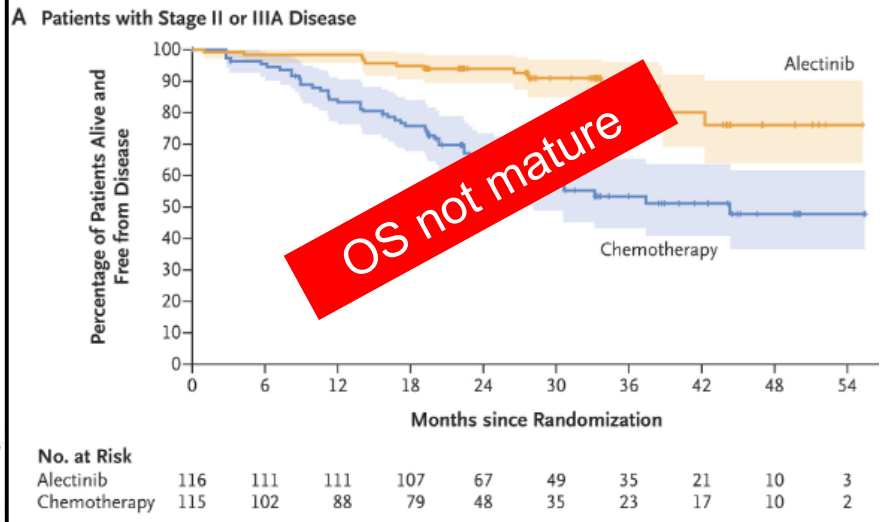
ADAURA: *EGFR*
Adjuvant **osimertinib** 3y



HR DFS = 0,17

Tsuboi M, et al. NEJM 2023

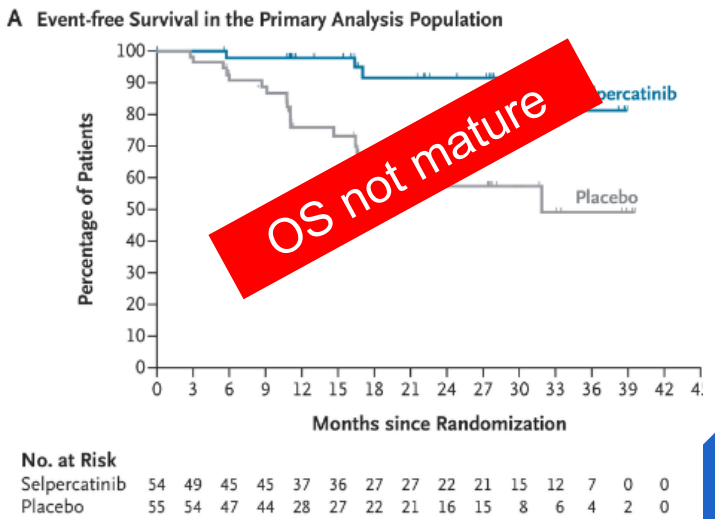
ALINA: *ALK*
Adjuvant **alectinib** 2y



HR DFS = 0,24

Wu YL, et al. NEJM 2024

LIBRETTO-432: *RET*
Adjuvant **selpercatinib** 3y



HR EFS = 0,17

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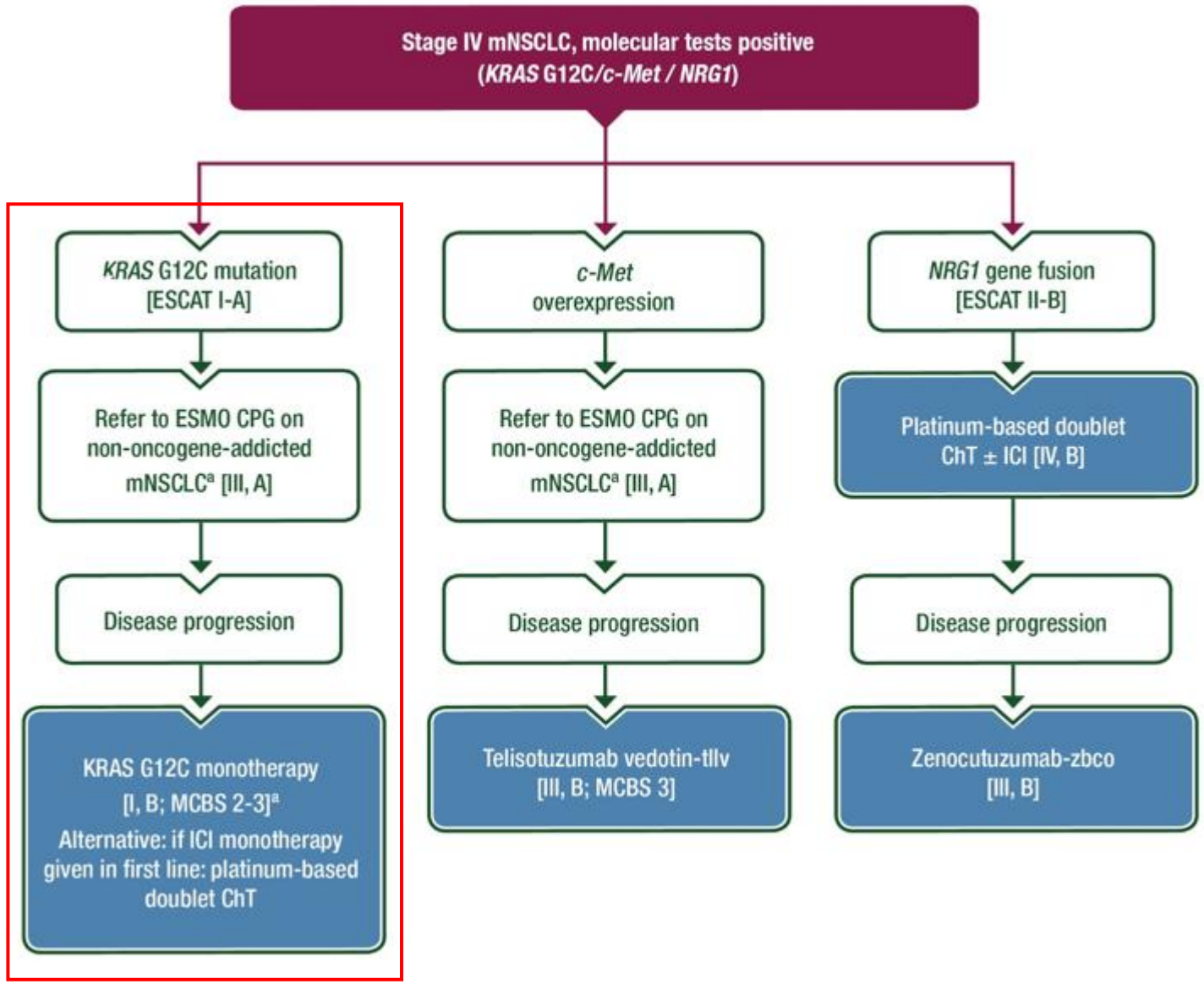
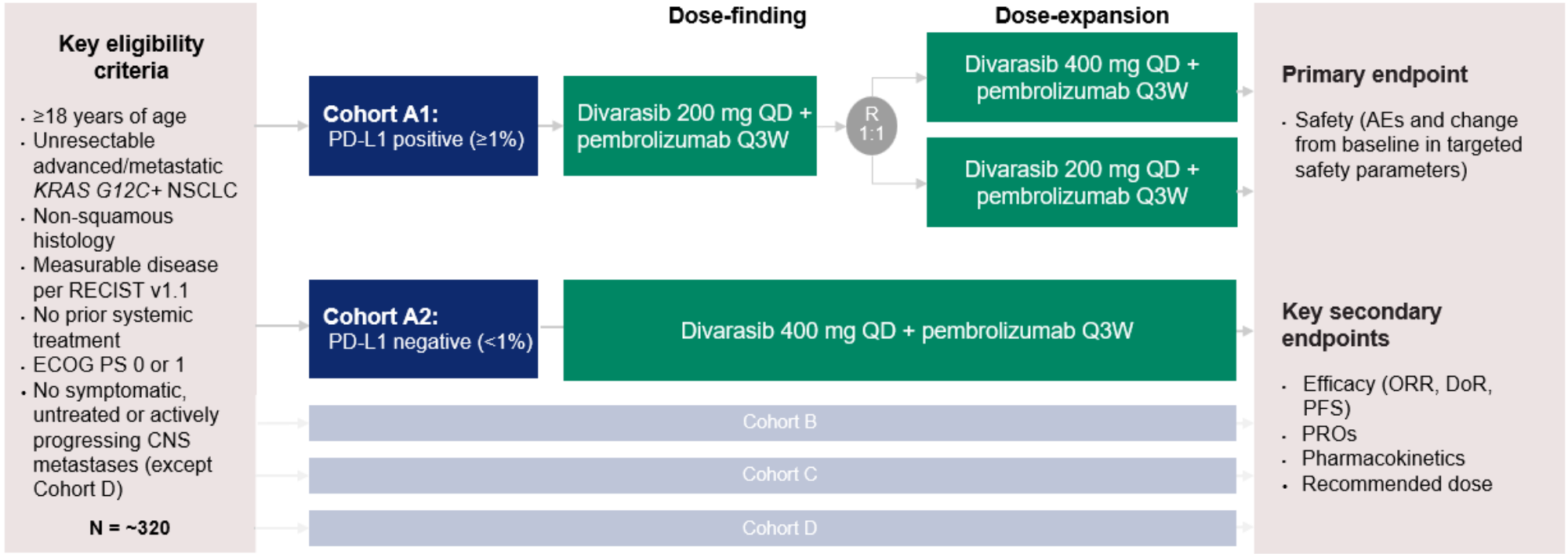
CLINICAL PRACTICE GUIDELINES

ESMO Oncogene-addicted Metastatic Non-small-cell Lung Cancer Living Guideline

v1.3 February 2026



KRASCENDO 170
Design



We report the primary analysis for divarasib 400 mg plus pembrolizumab in the PD-L1 positive cohort (≥1%; Cohort A1) and key preliminary data for the PD-L1 negative cohort (<1%; Cohort A2)

Skoulidis F, et al. ASCO 2026

KRASCENDO 170

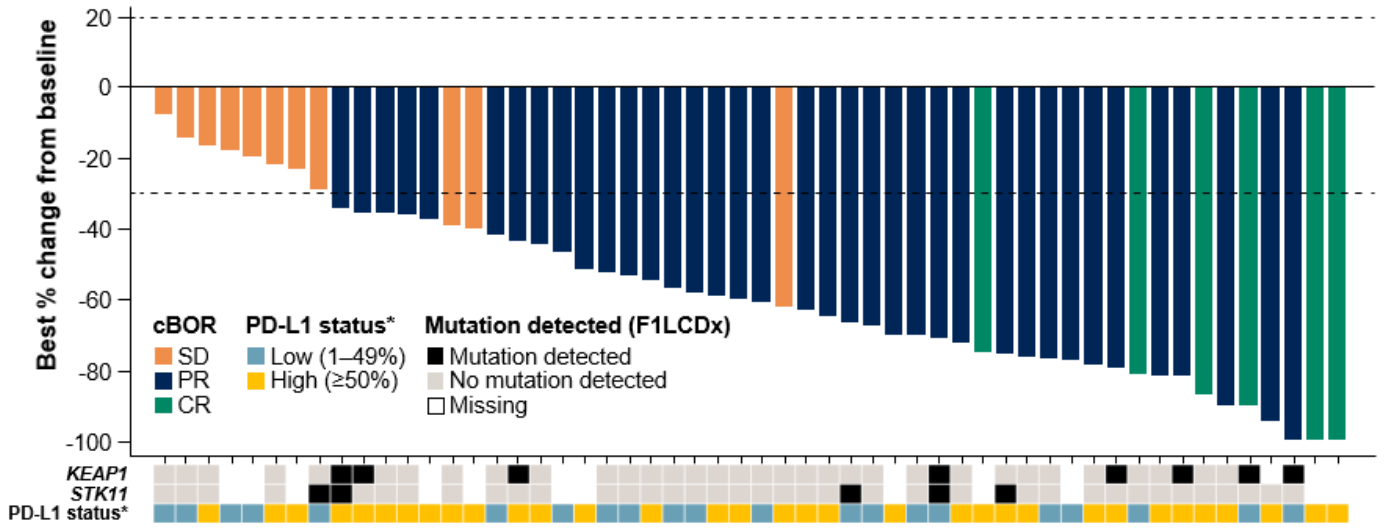
Baseline characteristics cohort A1

Characteristic, n (%) unless specified	Divarasib + pembrolizumab (N=59)
Median age, years (range)	67.0 (46–83)
Age: <65 / ≥65	19 (32.2) / 40 (67.8)
Sex: male / female	37 (62.7) / 22 (37.3)
Race: White Asian Black or African American Not reported	 40 (67.8) 13 (22.0) 2 (3.4) 4 (6.8)
ECOG PS: 0 / 1	16 (27.1) / 43 (72.9)
PD-L1 status:* Low (1–49%) High (≥50%)	*n=58*† 22 (37.3) 36 (61.0)
Smoking history: current / former / never	13 (22.0) / 45 (76.3) / 1 (1.7)
CNS metastases‡	12 (20.3)
Liver metastases	5 (8.5)

Median follow-up was 12.2 months

KRASCENDO 170

Tumor response cohort A1



n (%) unless specified	Divarasib + pembrolizumab (N=59)†
Confirmed ORR [95% CI]	43 (72.9) [59.7–83.6]
CR	6 (10.2)
PR	37 (62.7)
SD	11 (18.6)
PD	0
Not evaluable/missing	5 (8.5)
Median time to first response, days (range)	43 (36–164)
Median DoR, months (95% CI)	NE (14.5–NE)

- Among all enrolled patients, confirmed ORR was 72.9%
  - Confirmed ORR was 76.8% in the 56 patients who received any study treatment
  - Responses were observed regardless of PD-L1, *KEAP1*, and *STK11* status
- All patients with a post-baseline assessment had a reduction in tumor size
- Median DoR has not yet been reached and data are immature

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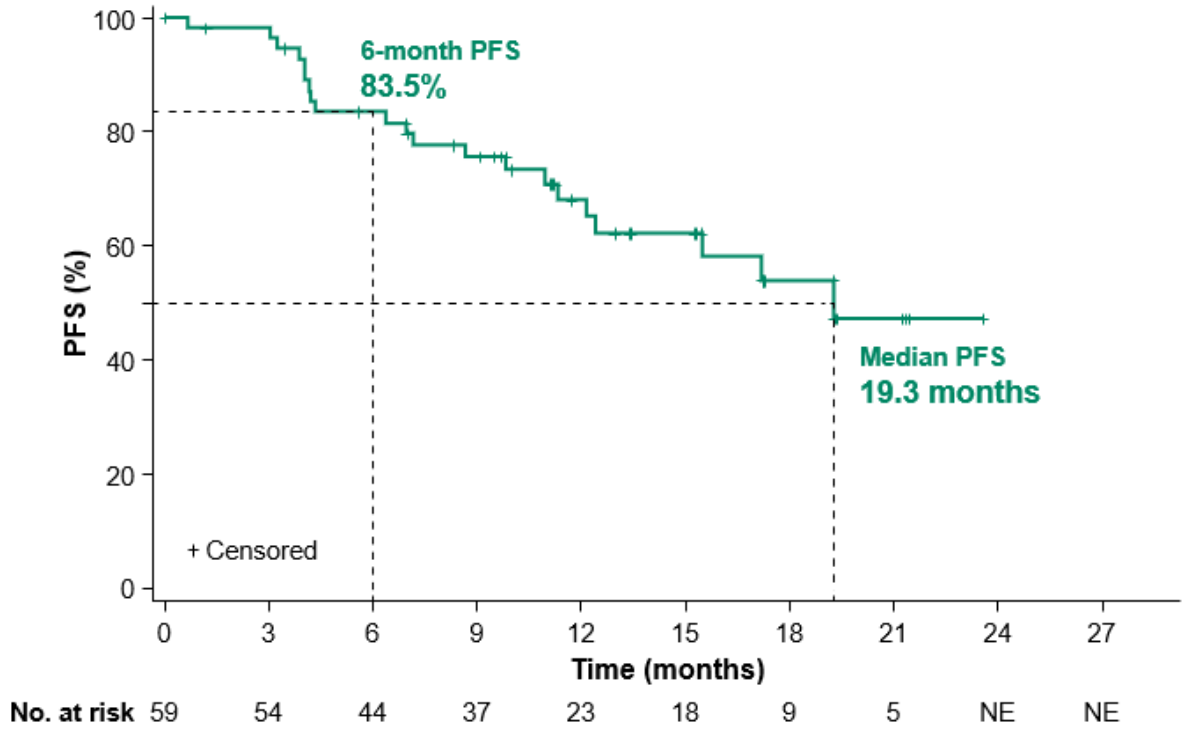
KRASCENDO 170

Tumor response cohort A1



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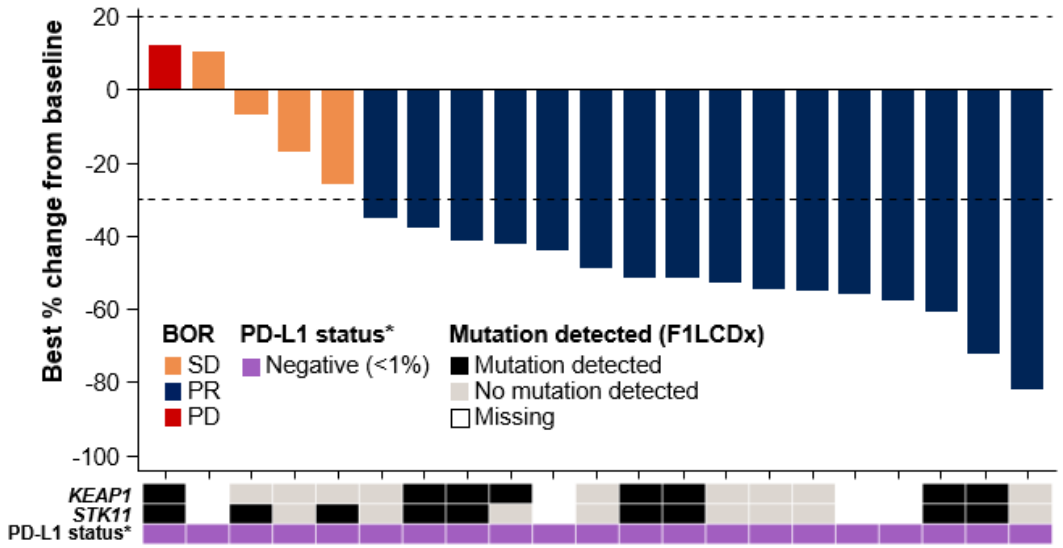
Baseline characteristics cohort A2

Characteristic, n (%) unless specified	Divarasib + pembrolizumab (N=23)
Median age, years (range)	72.0 (52–86)
Age: <65 / ≥65	4 (17.4) / 19 (82.6)
Sex: male / female	16 (69.6) / 7 (30.4)
Race: White Asian Not reported	 16 (69.6) 5 (21.7) 2 (8.7)
ECOG PS: 0 / 1	6 (26.1) / 17 (73.9)
PD-L1 status:* Negative (<1%)	 23 (100)
Smoking history: current / former / never	3 (13.0) / 19 (82.6) / 1 (4.3)
CNS metastases†	3 (13.0)
Liver metastases	3 (13.0)

Median follow-up was 3.4 months

KRASCENDO 170

Tumor response cohort A2



n (%) unless specified	Divarasib + pembrolizumab (N=23)
Unconfirmed† ORR [95% CI]	16 (69.6) [47.1–86.8]
CR	0
PR	16 (69.6)
SD	4 (17.4)
PD	1 (4.3)
Not evaluable/missing	2 (8.7)
Median time to first response, days (range)	40.5 (36–120)

- Unconfirmed ORR was 69.6%
  - Most patients with a post-baseline assessment had a reduction in tumor size
  - Responses were observed regardless of *KEAP1* and *STK11* status
- PFS was immature

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KRASCENDO 170

Safety

Event, n (%)	Divarasib + pembrolizumab (n=78)*
Any grade AE	78 (100)
Grade ≥3	60 (76.9)†
Serious	39 (50.0)
Any grade TRAE	77 (98.7)
Grade 3–4	51 (65.4)
Grade 5	0
Serious	22 (28.2)
TRAE leading to divarasib dose reduction	41 (52.6)
TRAE leading to dose interruption	54 (69.2)
TRAE leading to study treatment discontinuation	10 (12.8)

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KRASCENDO 170

Safety

Event, n (%)	Divarasib + pembrolizumab (n=78)*	
	Any grade	Grade 3–4
Diarrhea	58 (74.4)	14 (17.9)
Nausea	50 (64.1)	1 (1.3)
Vomiting	36 (46.2)	1 (1.3)
Alanine aminotransferase increase	41 (52.6)	18 (23.1)
Aspartate aminotransferase increase	38 (48.7)	14 (17.9)
Lipase increase	23 (29.5)	7 (9.0)
Decreased appetite	24 (30.8)	0
Amylase increase	16 (20.5)	3 (3.8)

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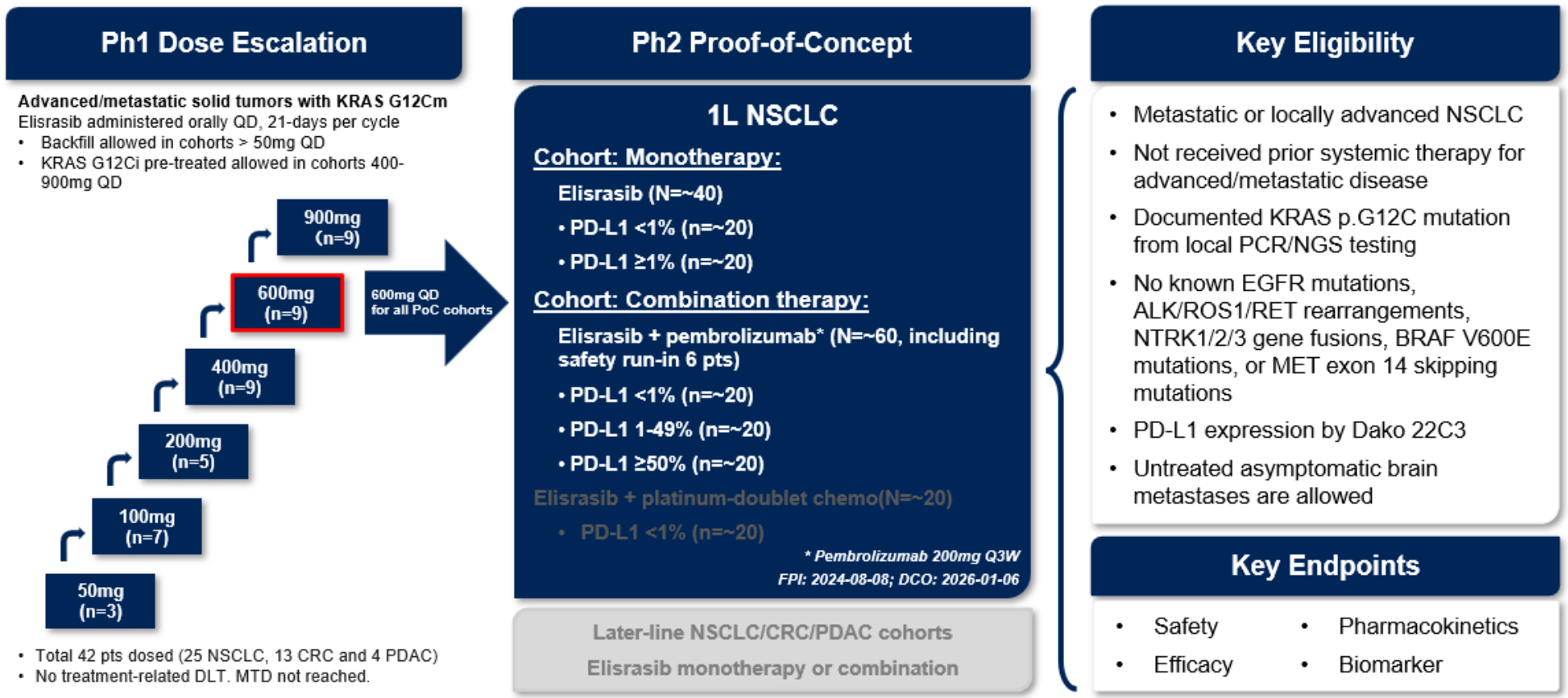
ELISRASIB
Design

Study Design



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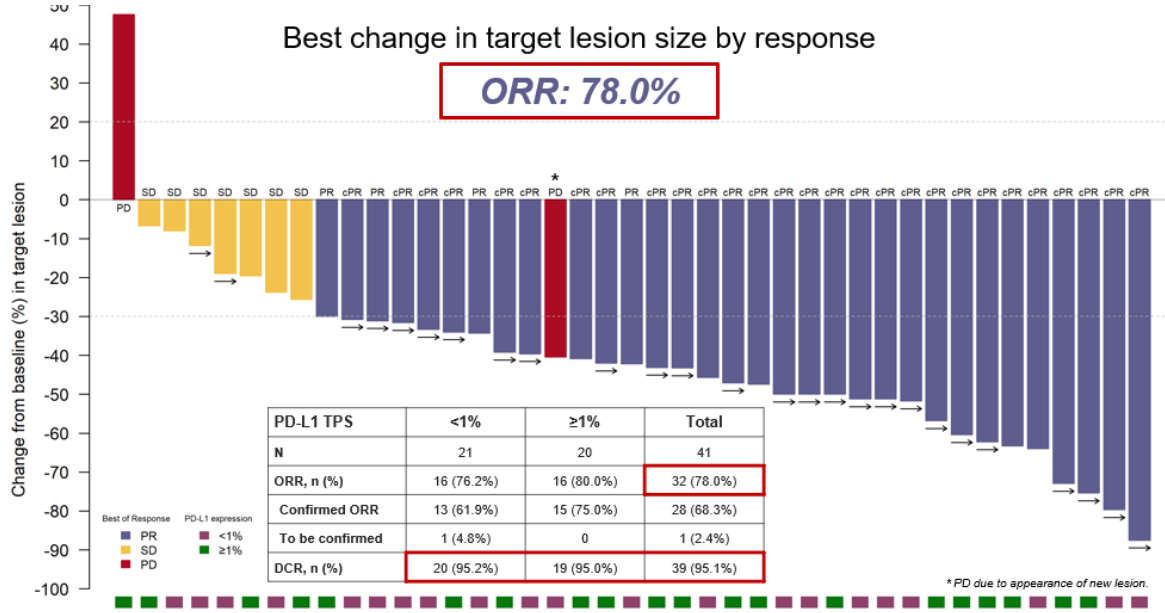
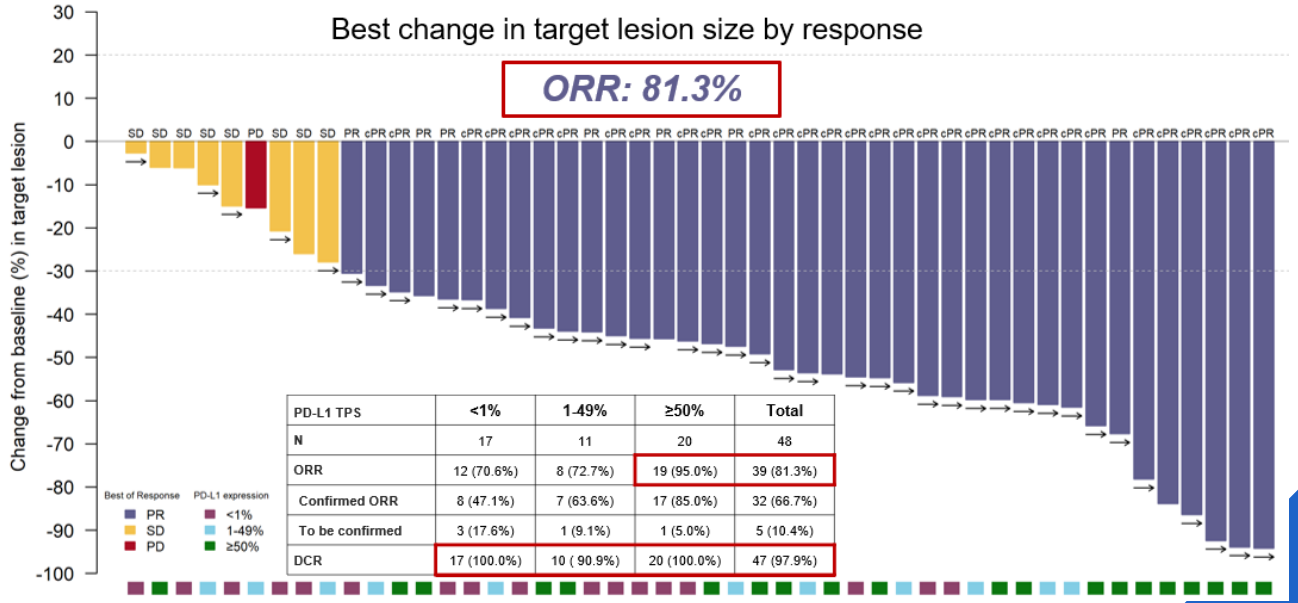
ELISRASIB
ORR

Elisrasib



PD-L1 TPS	<1%	≥1%	Total
N	21	20	41
ORR, n (%)	16 (76.2%)	16 (80.0%)	32 (78.0%)
Confirmed ORR	13 (61.9%)	15 (75.0%)	28 (68.3%)
To be confirmed	1 (4.8%)	0	1 (2.4%)
DCR, n (%)	20 (95.2%)	19 (95.0%)	39 (95.1%)

Elisrasib + pembrolizumab



PD-L1 TPS	<1%	1-49%	≥50%	Total
N	17	11	20	48
ORR	12 (70.6%)	8 (72.7%)	19 (95.0%)	39 (81.3%)
Confirmed ORR	8 (47.1%)	7 (63.6%)	17 (85.0%)	32 (66.7%)
To be confirmed	3 (17.6%)	1 (9.1%)	1 (5.0%)	5 (10.4%)
DCR	17 (100.0%)	10 (90.9%)	20 (100.0%)	47 (97.9%)

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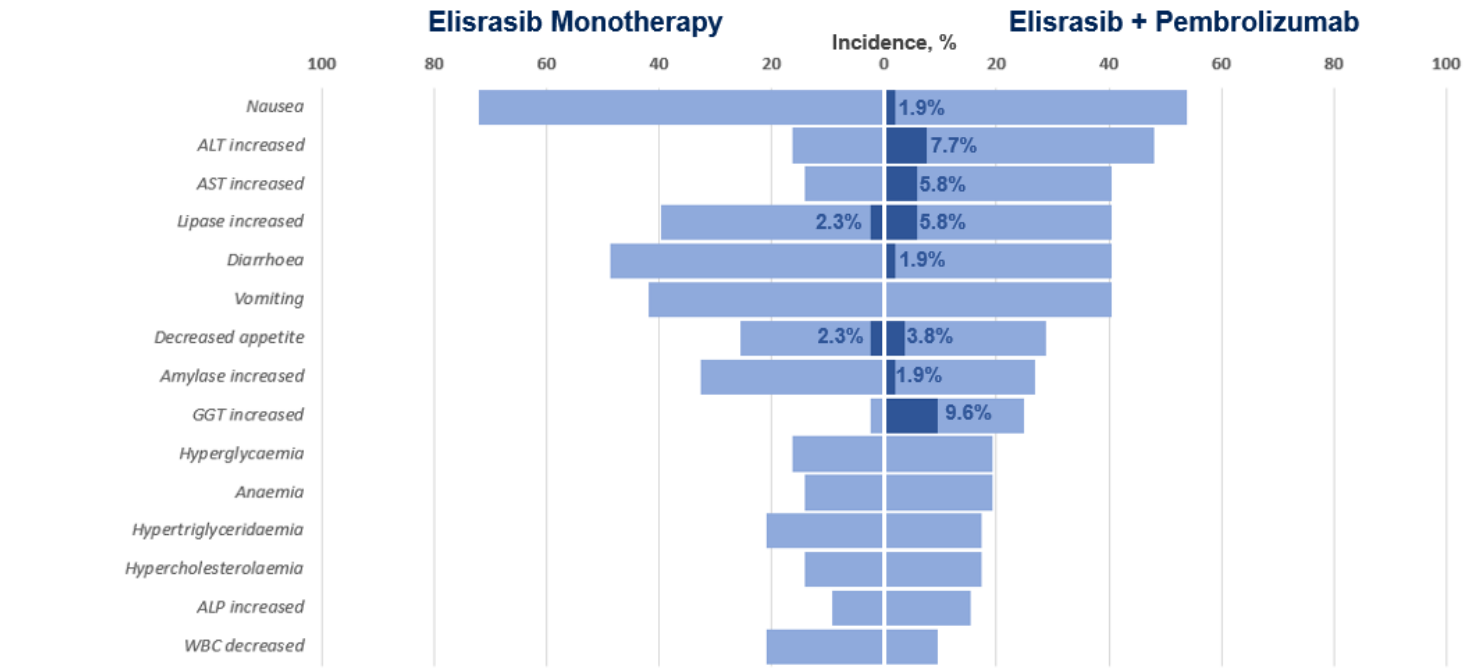
ELISRASIB
Safety

Treatment-related* adverse events (TRAEs) – n (%)	Elisrasib Monotherapy (N=43)	Elisrasib + Pembrolizumab (N=52)
Any TRAE	41 (95.3%)	48 (92.3%)
Any Grade 3 or higher TRAE**	3 (7.0%)	17 (32.7%)
Any Serious TRAE	1 (2.3%)	9 (17.3%)
Any TRAE leading to discontinuation of Elisrasib***	0	1 (1.9%)
Any TRAE leading to discontinuation of Pembrolizumab****	-	5 (9.6%)
Any TRAE leading to dose reduced of Elisrasib	0	12 (23.1%)
Any TRAE leading to dose interrupted of Elisrasib	4 (9.3%)	26 (50.0%)
Any TRAE leading to dose delayed of Pembrolizumab	-	22 (42.3%)



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KRAS G12C inhibitors move to the front-line setting

Trial	Phase	Experimental drug	Comparator	PD-L1 IHC	N	ORR (%)	mPFS	Grade ≥ TRAEs (%)
KRYSTAL-7	1/2	Adagrasib + pembrolizumab		All ≥ 50%	149 54	36 59	11,0 27,7	68,4
SUNRAY-01	1/2	Olomorasib + pembrolizumab		All ≥ 50%	46 20	74 90	NA NA	33,4 39,6
KRASCENDO-170	1/2	Divarasib + pembrolizumab		> 1% < 1%	59 23	77 70	19,3 NA	65,4
D3S-001	1	Elisrasib + pembrolizumab		All	52	81	NR	32,7
KRASCENDO-2	3	Divarasib + pembrolizumab	Carboplatin-pemetrexed-pembrolizumab	All				
Krystal-7	3	Adagrasib + pembrolizumab	Pembrolizumab	≥ 50%				
Krystal-4	3	Adagrasib + pembrolizumab + carboplatin-pemetrexed	Carboplatin-pemetrexed-pembrolizumab	All				
SUNRAY-01	3	Olomorasib + pembrolizumab Olomorasib + pembrolizumab + carboplatine-pemetrexed	Pembrolizumab Carboplatin-pemetrexed-pembrolizumab	≥ 50% All				
CodeBreaK-202	3	Sotorasib + carboplatin-pemetrexed	Carboplatin-pemetrexed-pembrolizumab	< 1%				
Kandelit-004	3	Calderasib + pembrolizumab	Pembrolizumab	≥ 50%				
Kandelit-007	3	Calderasib + pembrolizumab (SC)	Carboplatin-pemetrexed-pembrolizumab (SC)	All				

Jänne P, et al. ASCO 2025 ; Burns TF, et al. JTO 2026, Skoulidis F, et al. ASCO 2026, Lu S, et al. ASCO 2026

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Krystal-4	3	Adagrasib + pembrolizumab + carboplatin-pemetrexed	Carboplatin-pemetrexed-pembrolizumab	All				
SUNRAY-01	3	Olomorasib + pembrolizumab Olomorasib + pembrolizumab + carboplatine-pemetrexed	Pembrolizumab Carboplatin-pemetrexed-pembrolizumab	≥ 50% All				
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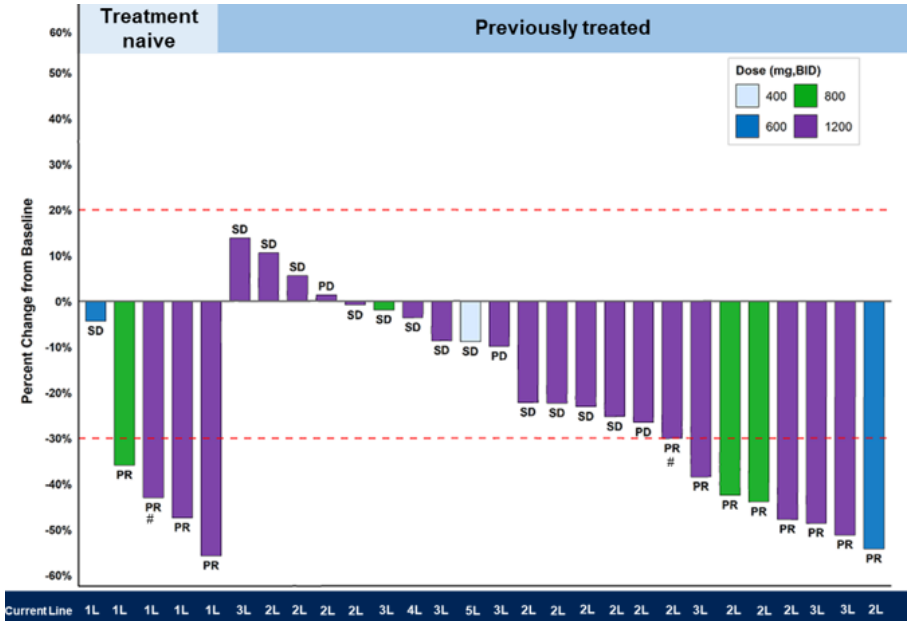
KRAS G12D inhibitors in development

TSN1611

- Phase 1/2 trial
- Locally advanced or metastatic solid tumors with KRAS G12D mutation
- 42 pt with NSCLC
- Grade 3 TRAEs 21,4%
- ORR 44,4% (80% in treatment-naïve)
- DCR 88,9% (100% in treatment-naïve)



RNK08954

- Phase 1 FIH trial
- Locally advanced or metastatic solid tumors with KRAS G12D mutation who progressed following SOC therapy
- 47 pt with NSCLC
- Grade 3 TRAEs 23,4%
- ORR 38,5%
- DCR 94,9%

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CONCLUSIONS

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Take home messages

- **RET**
  - RET-targeted therapy (selpercatinib) joins EGFR and ALK in the adjuvant setting, reinforcing the role of early molecular profiling
  - Pralsetinib confirms selective RET inhibition as a first-line standard in RET fusion-positive NSCLC
- **EGFR**
  - The EGFR space is broadening beyond classical mutations, with increasing relevance of uncommon alterations.
  - Sunvozertinib (EGFR exon 20 insertion mutations) and amivantamab-lazertinib (uncommon EGFR mutations) emerge as promising first-line options.
- **ALK**
  - CROWN sets a new benchmark for PFS, supporting ALK-positive NSCLC as a long-term controlled disease.
  - Perioperative ALK inhibition is emerging, while next-generation TKIs (neladalkib) continue to evolve.
- **KRAS G12C**
  - KRAS G12C is moving into first-line therapy, increasingly in combination approaches
  - Early efficacy signals are strong, with phase III data expected to redefine future standards of care.

Thank you for your attention!

Universitair Ziekenhuis Gent
C. Heymanslaan 10 | B 9000 Gent
T +32 (0)9 332 21 11
E info@uzgent.be

www.uzgent.be

Volg ons op

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