Where Science Becomes Hope

UPDATES IN MUTATION-DRIVEN NSCLC

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DISCLOSURES

Honoraria: None

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TOP 5 THINGS TO DO IN SEA ISLAND WHILE ATTENDING A CONFERENCE

1. Attend the conference
2. Play a round of golf at Seaside course
3. Walk the beach at sunrise or sunset
4. Take a marsh or dolphin cruise
5. Have dinner and drinks at The Cloister

OUTLINE

- EGFR common mutations
- EGFR Exon 20 insertion
- HER-2 mutation
- ALK fusion
- ROS1 fusion
- KRAS mutation
- Adjuvant therapy for RET fusion

TREATMENT OF COMMON EGFR MUTATIONS (EXON 19 & 21)

First line therapy

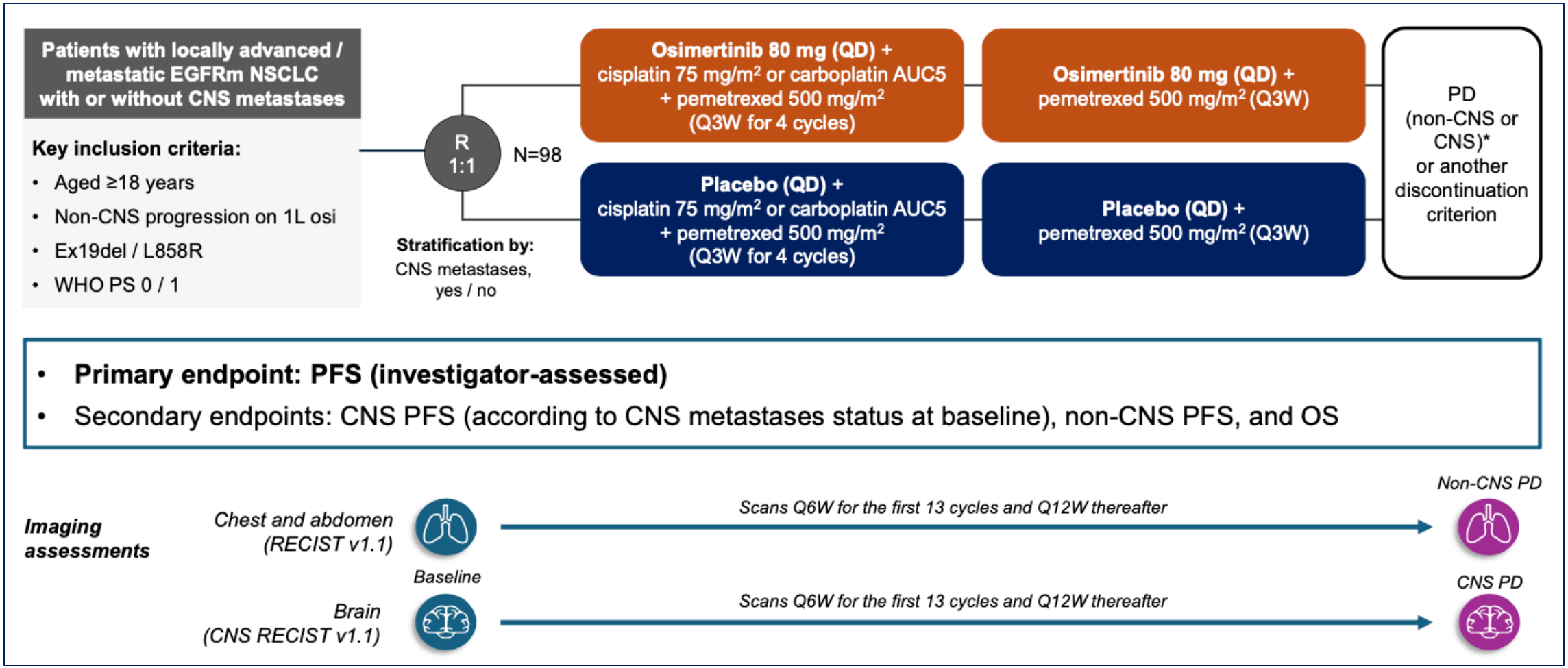
- Osimertinib
- Chemo + Osimertinib
- Amivantamab + Lazertinib

Second line therapy

- Chemotherapy + Amivantamab
- Chemotherapy
- Datopotamab deruxtecan
- Clinical trials

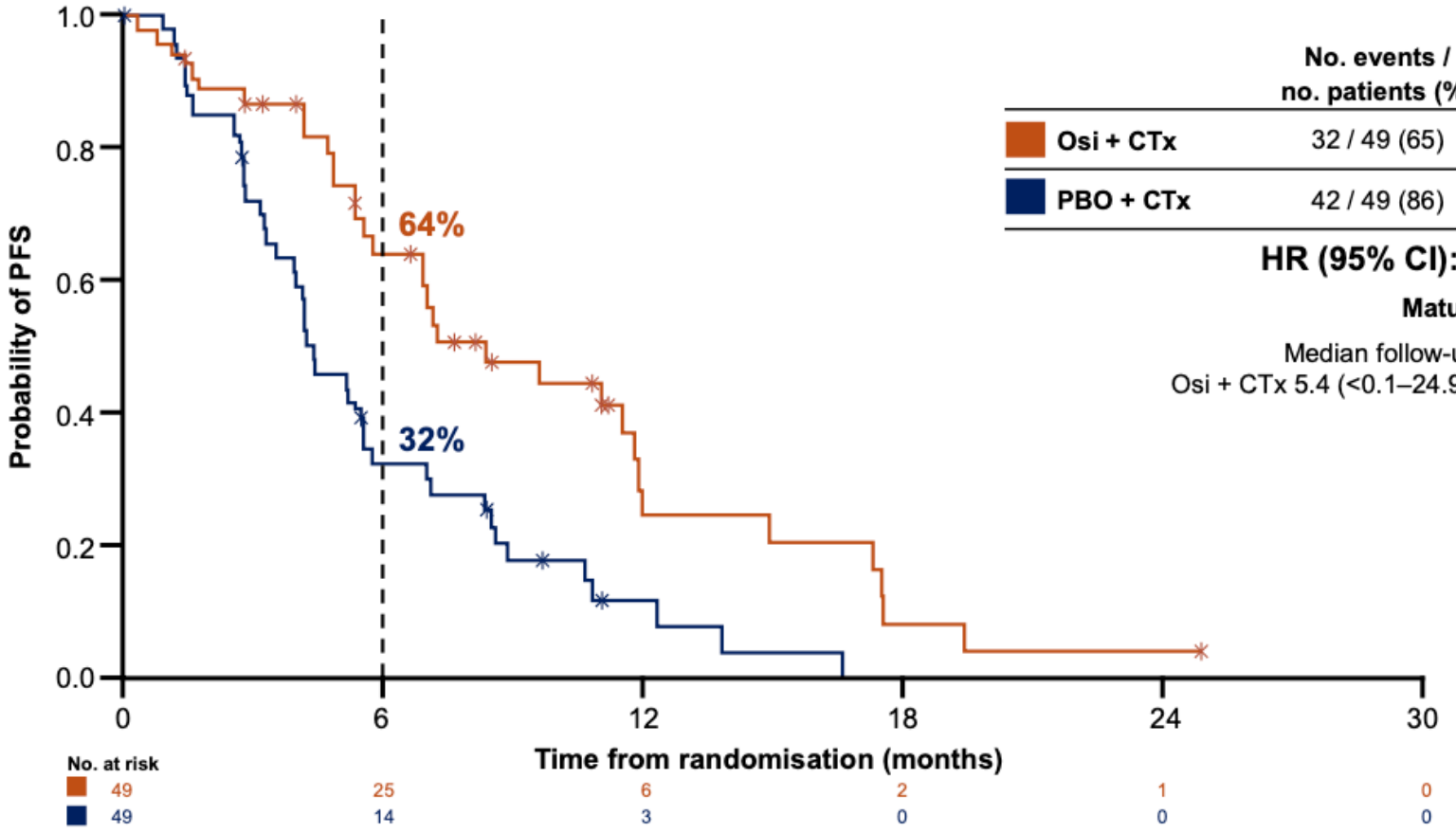
Consider conversion to small cell histology in appropriate clinical context

COMPEL STUDY: CONTINUATION OF OSIMERTINIB WITH CHEMOTHERAPY



Pasello G et al, WCLC 2025.

COMPEL: PROGRESSION-FREE SURVIVAL



	No. events / no. patients (%)	Median PFS, months (95% CI)
Osi + CTx	32 / 49 (65)	8.4 (5.7, 11.8)
PBO + CTx	42 / 49 (86)	4.4 (3.5, 5.6)

HR (95% CI): 0.43 (0.27, 0.70)

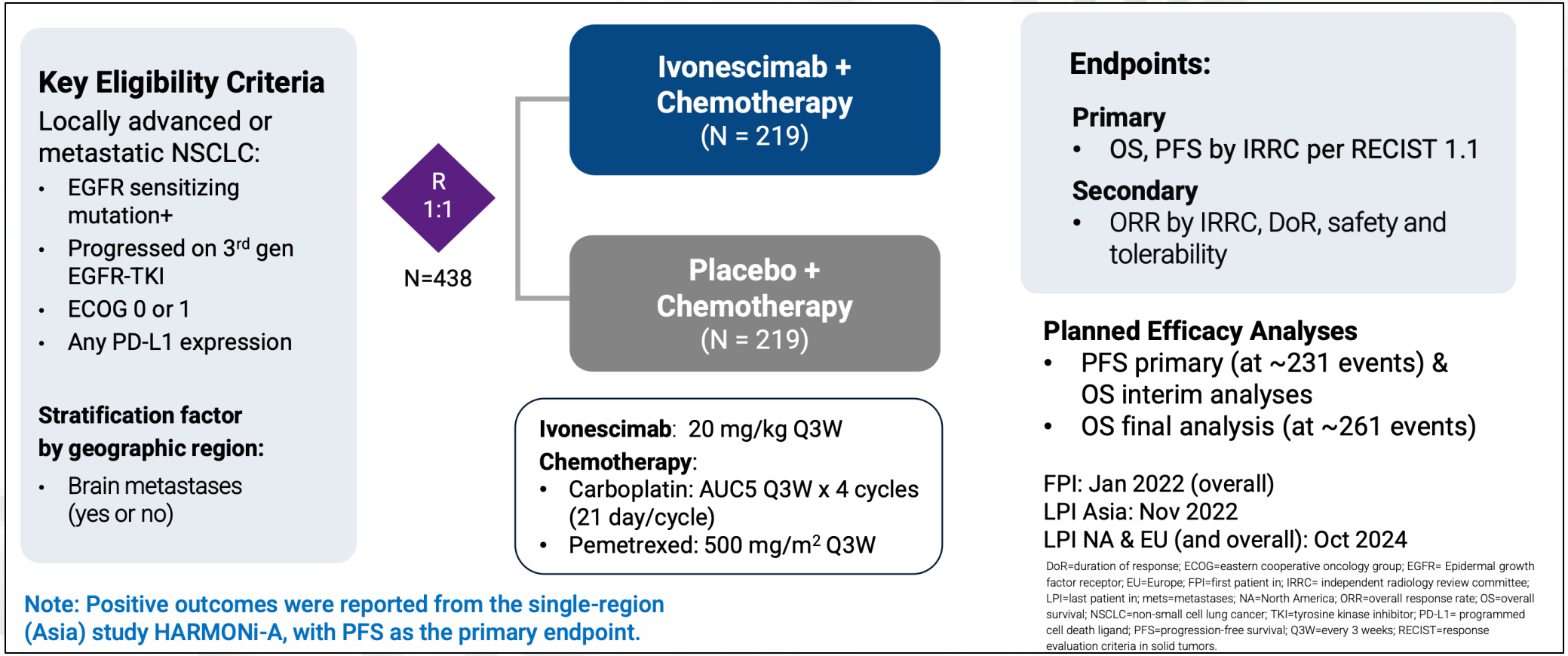
Maturity: 76%

Median follow-up,† months (range):
Osi + CTx 5.4 (<0.1–24.9); PBO + CTx 5.5 (<0.1–11.1)

Osi + CTx was associated with improved PFS versus PBO + CTx

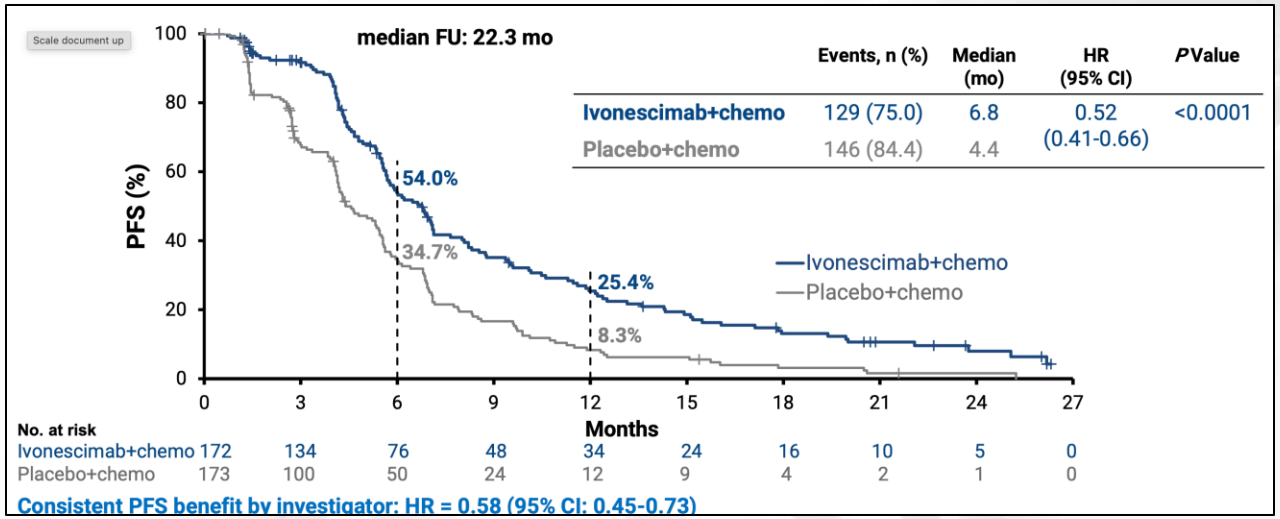
Pasello G et al, WCLC 2025.

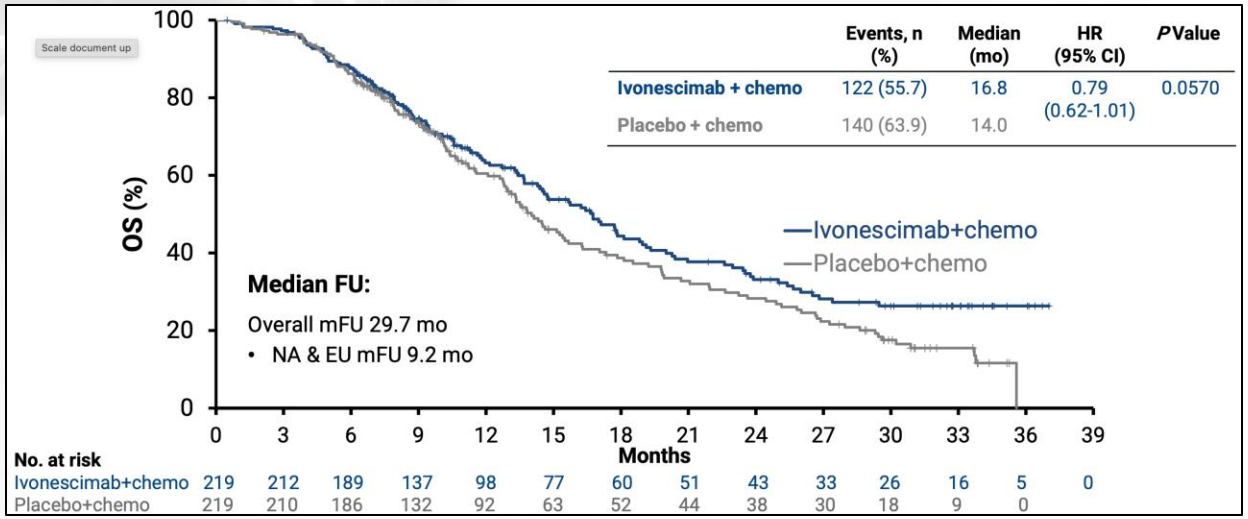
HARMONI PHASE 3 TRIAL



Goldman J et al, WCLC 2025.

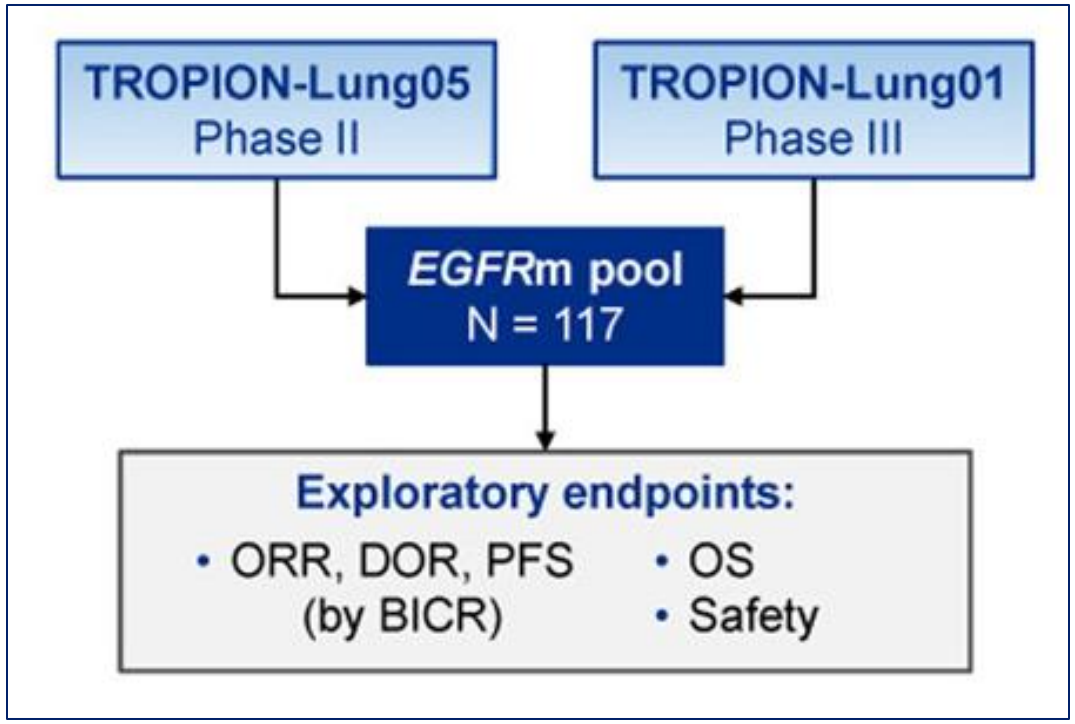
HARMONI: PFS & OS

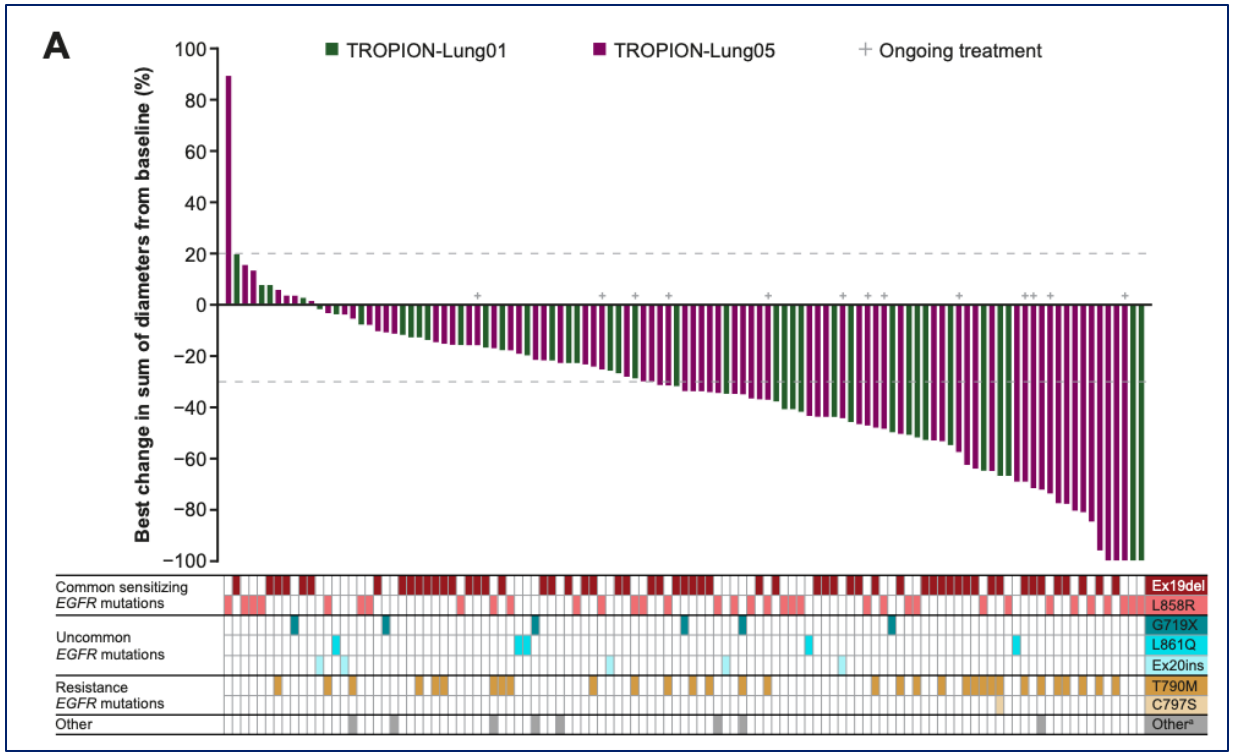




Goldman J et al, WCLC 2025.

DATOPOTAMAB IN EGFR^{MT} NSCLC





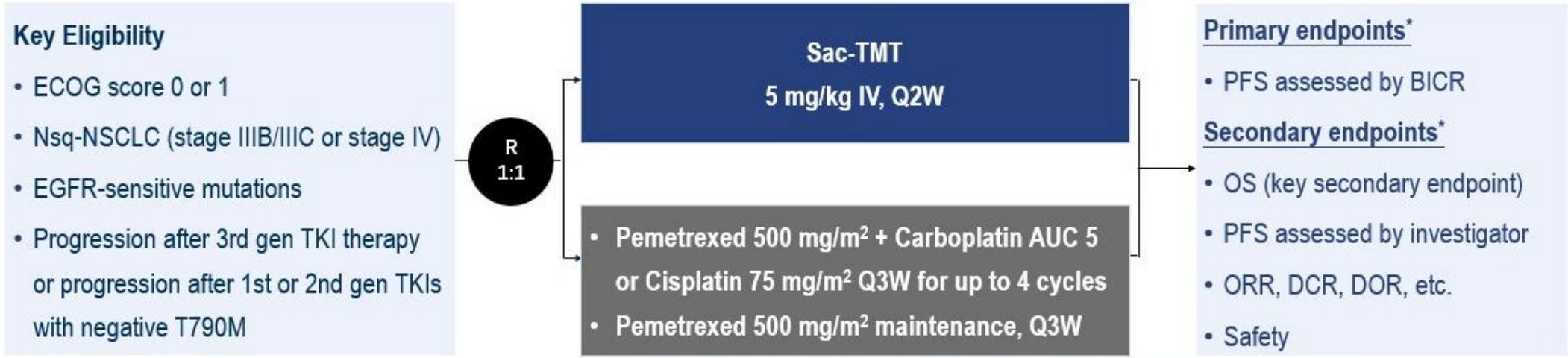
RR: 43% mPFS: 5.8m; mOS: 15.6m

AE: Stomatitis 69% (Gr 1 36%; Gr 2 24%; Gr 3 9%)

Ahn M et al, JTO 2025.

OptiTROP-Lung04 Study Design

Randomized, multicenter, open-label, phase 3 trial (NCT05870319)



Stratification factors:

1. Prior EGFR-TKI therapy
   (**3rd gen TKI in 1st line** *vs* **in 2nd line** *vs* **no 3rd gen TKI**)
2. Brain metastases (**yes** *vs* **no**)

Statistical considerations:

- Hierarchical testing was conducted for PFS by BICR and OS.
- Pre-specified interim analysis for OS:
  at approximately 50% maturity,
  or 24 months after the first patient randomized.

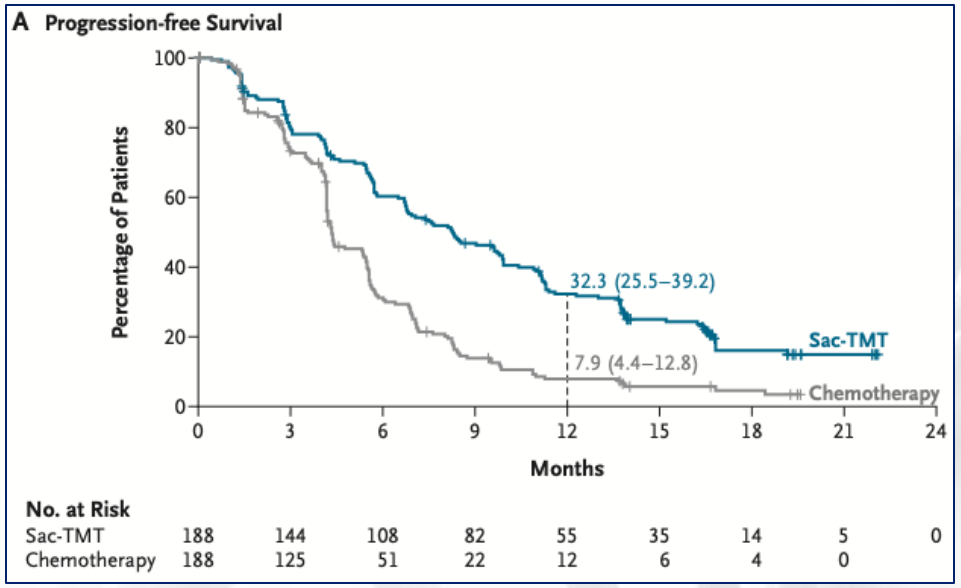
*Tumor response was assessed using RECIST version 1.1.

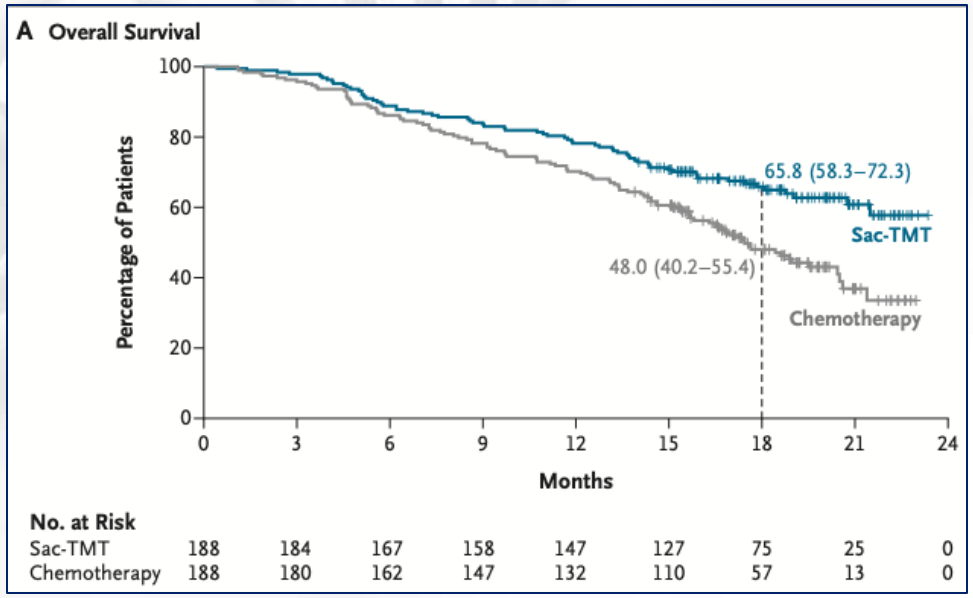
BICR, blinded independent central review; OS, overall survival; ORR, objective response rate; DOR, duration of response; DCR, disease control rate; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; IA, interim analysis; ECOG, Eastern Cooperative Oncology Group.

Limited to patients of age < 75 yrs

Fang W et al, NEJM, 2025.

OPTITROP-LUNG04 TRIAL





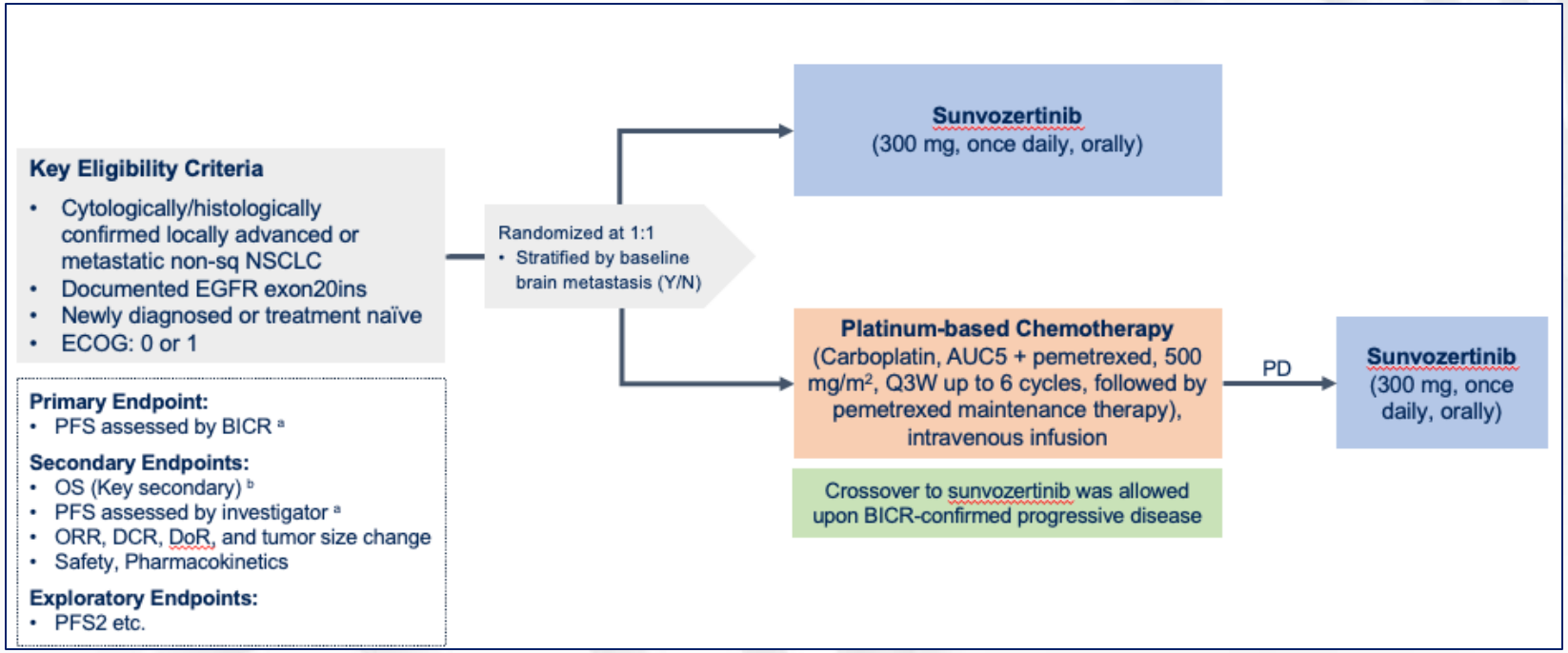
HR: 0.49; 8.3m vs. 4.3m

HR: 0.6; NE vs 17.4m

Salient AE with Sac-TMT:
Stomatitis; 64% (Gr 1 22%, Gr 2 37% & Gr 3 5%)

Fang W et al, NEJM, 2025.

FIRST-LINE THERAPY FOR EGFR EXON 20 MUTATION: WU-KONG 28 STUDY



- N=324 patients
- Median PFS: 10.3m vs. 7.5 m (HR 0.65)
- Response rate: 59% vs. 31%

Salient AEs:

- Diarrhea- 84% (14%)
- CPK elevation- 55% (20%)
- Rash- 52% (<1%)
- Paronychia- 49% (4%)

Heymach J et al, ASCO 2026.

TREATMENT OPTIONS FOR EXON 20 INSERTION

1st line

- Chemotherapy + Amivantamab
- Sunvozertinib

2nd line therapy

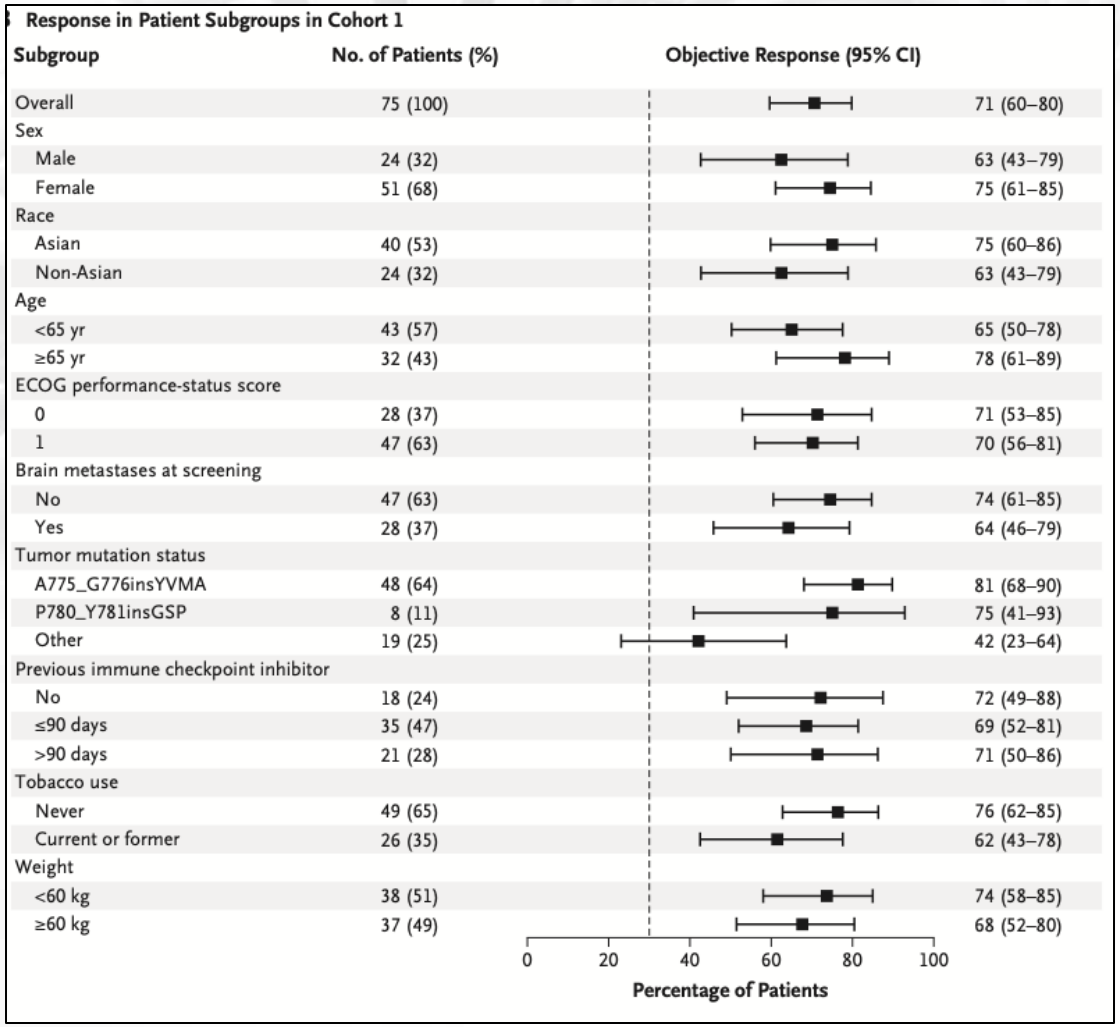
- Sunvozertinib
- Zipalertinib

No evidence that immunotherapy is effacious in this patient population

ZONGERTINIB: EFFICACY IN PREVIOUSLY TREATED NSCLC (HER-2 ^{MT})

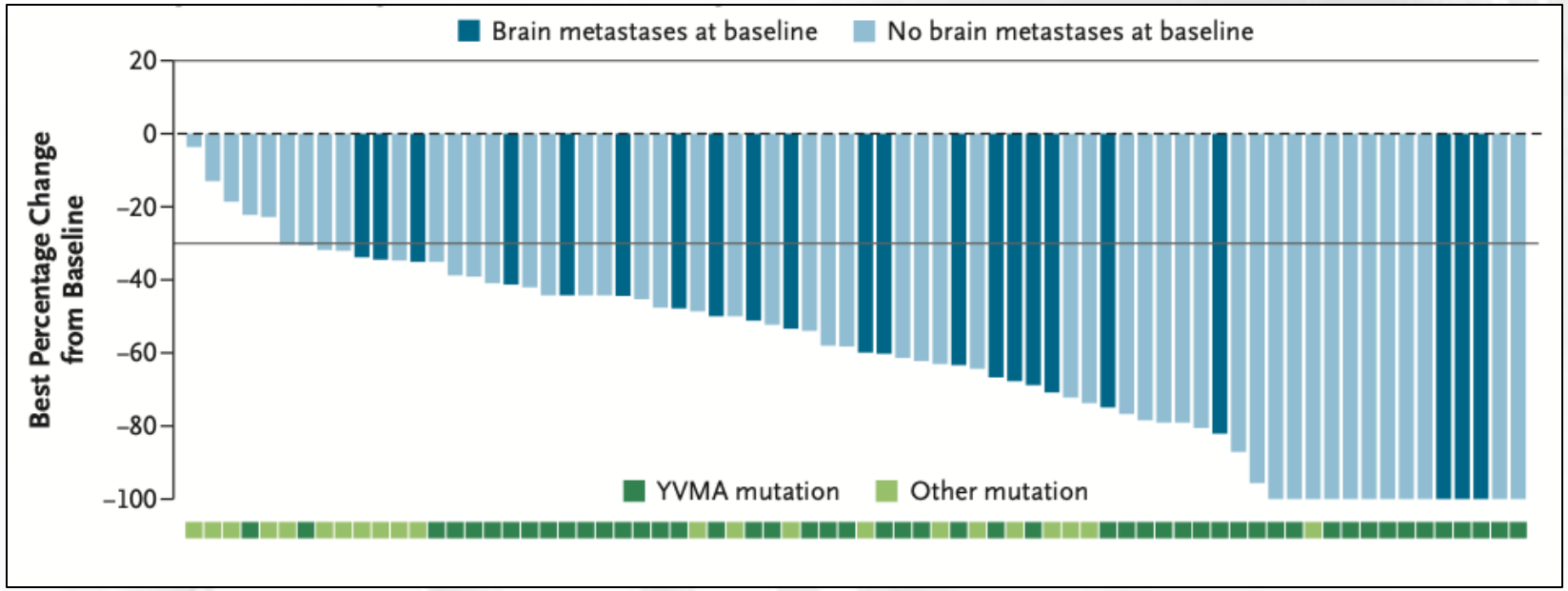
Response	Cohort 1 (N=75)
Objective response	
Total no. of patients	53
Percent (95% CI)	71 (60–80)
P value	<0.001
Complete response — no. (%)	5 (7)
Partial response — no. (%)	48 (64)

Median duration of response: 14.1m
Median PFS: 12.4m
Intra-cranial response rate: 41%



Heymach J et al, N Engl J Med, 2025.

ZONGERTINIB: FIRST-LINE THERAPY (HER2 ^{MT})



N=74 patients
Previously untreated
Dose: 120 mg/d
Response rate: 76%
Median duration of response: 15.2m
Median PFS: 14.4 m
intra-cranial response rate: 47%

Heymach J et al, N Engl J Med, 2026.

SEVABERTINIB: EFFICACY IN HER2^{MT} NSCLC

Cohort	No prior HER-2 targeted therapy (N=81 pts)	Prior HER-2 targeted therapy (ADC) (N=55 pts)	No prior therapy (N=73 pts)
Response rate	64%	38%	71%
Median duration of response	9.2m	8.5m	11 m
Median PFS	8.3m	5.5m	Immature

Le X et al, N Engl J Med, 2025.

SEVABERTINIB: SAFETY (COHORT D)

	All Grade	G3/4
Diarrhea	86%	23%
Rash	51%	1%
Paronychia	27%	0
Stomatitis	19%	1%
AST/ALT elevation	17%	0

Recommended dose: 20 mg twice daily
AE leading to dose reduction: 26%
AE leading to dose interruption: 31%
AE leading to dose discontinuation: 5%

Le X et al, N Engl J Med, 2025.

TREATMENT OF HER2^{MT} NSCLC

1st line

- Zongertinib/Sevabertinib

2nd line

- Platinum-based chemotherapy

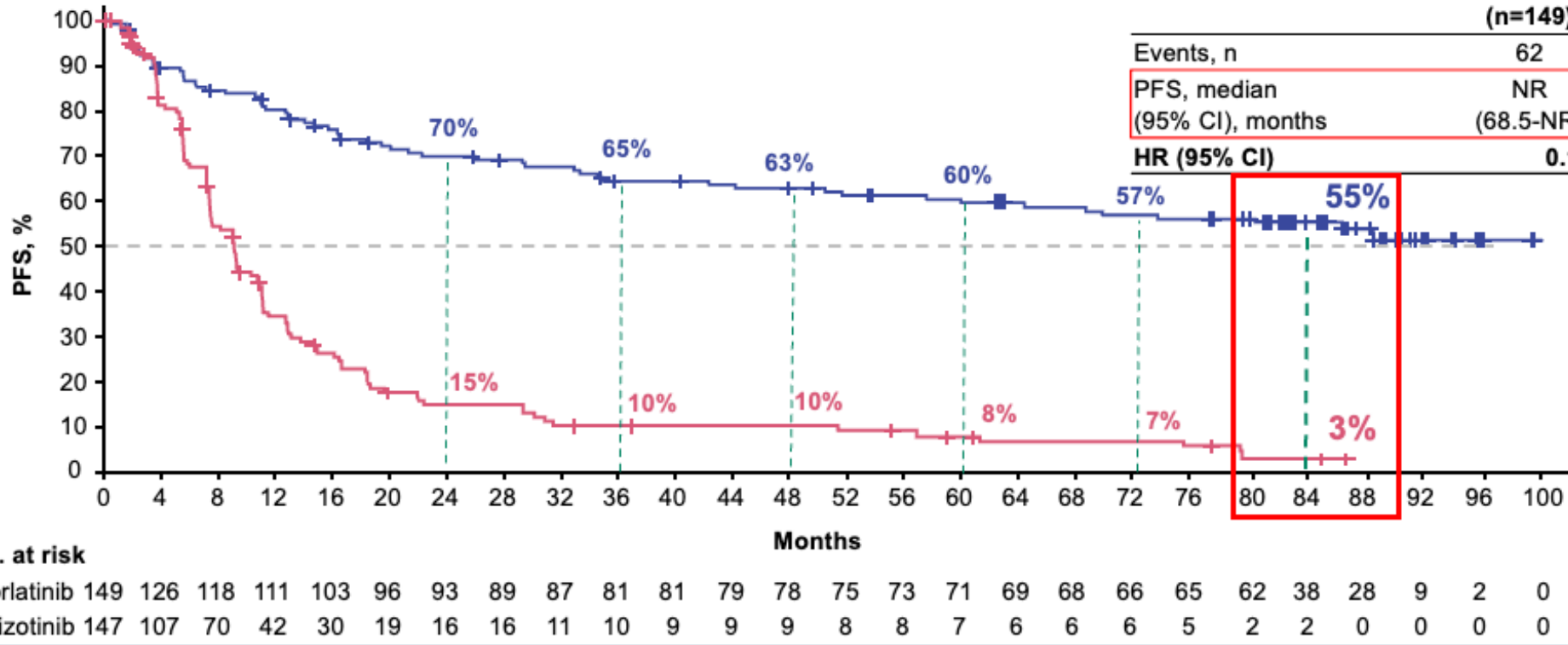
Role of trastuzumab deruxtecan

- Efficacy data post-TKI are awaited

CROWN: LORLATINIB VS. CRIZOTINIB IN ADVANCED NSCLC (ALK+)

- The median duration of follow-up for PFS was **83.0 months** (95% CI, 81.2-86.3) in the lorlatinib arm and **77.2 months** (95% CI, 36.8-not evaluable) in the crizotinib arm

	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)**	

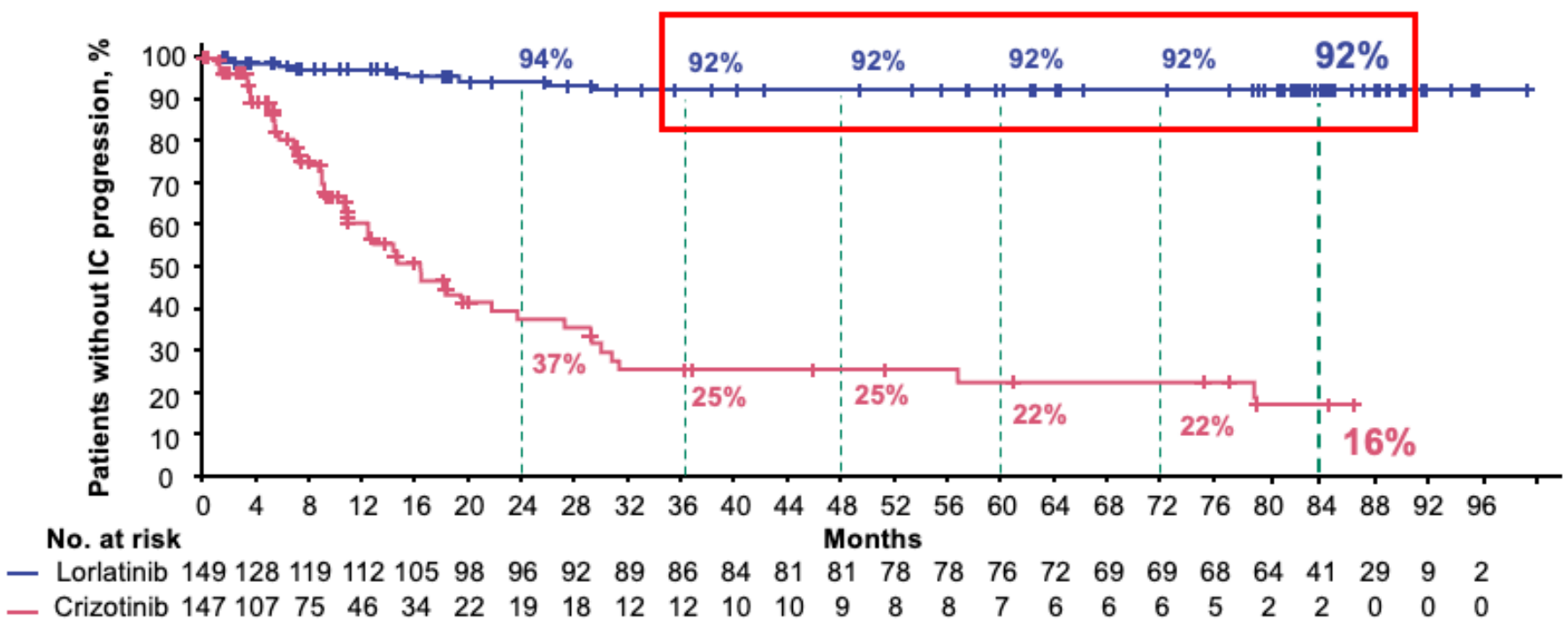


7 new PFS events occurred between 5 and 7 years with lorlatinib: 4 progression events and 3 deaths (not treatment related)

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

Mok T et al, ASCO 2026.

CROWN: TIME TO INTRACRANIAL PROGRESSION

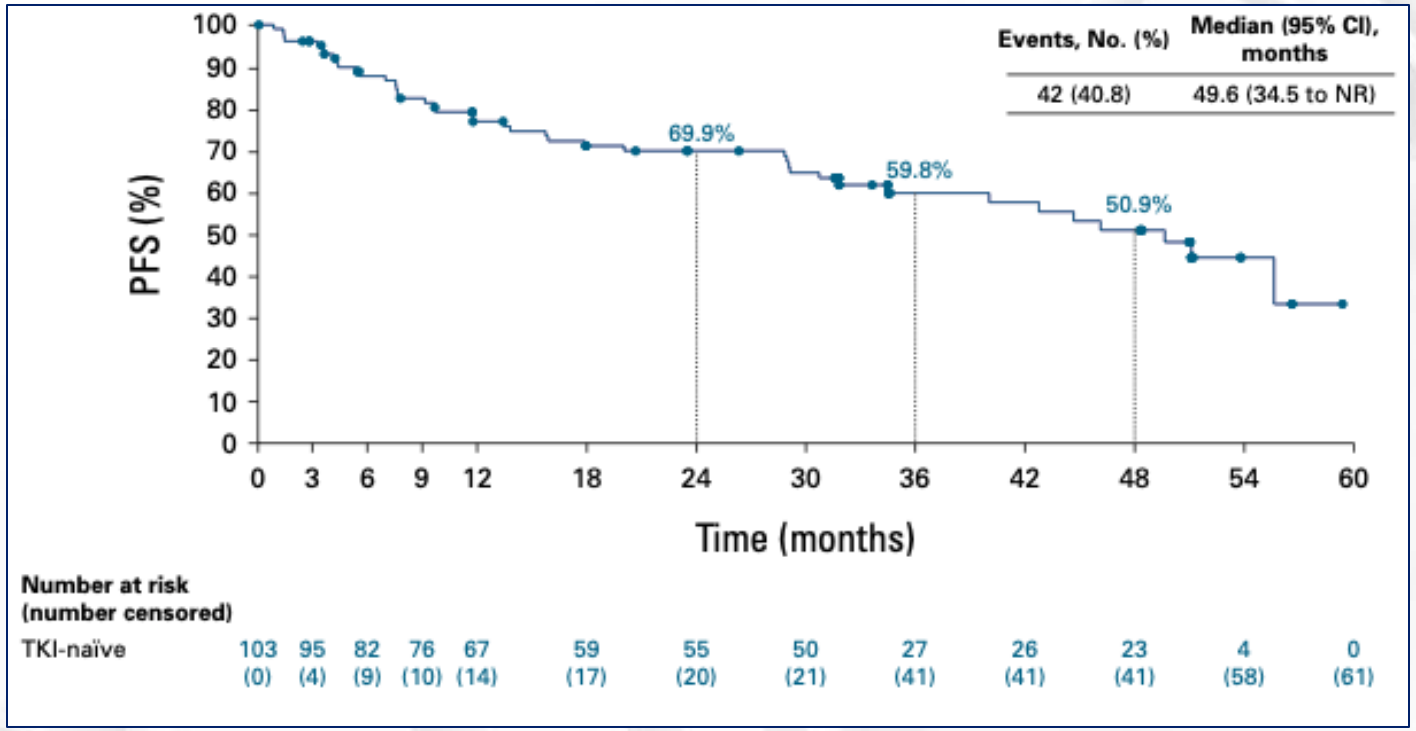


	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	66
Time to IC progression, months, median (95% CI)	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

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

Mok T et al, ASCO 2026.

ROS1+ NSCLC: ROLE OF TALETRECTINIB



Salient AEs:

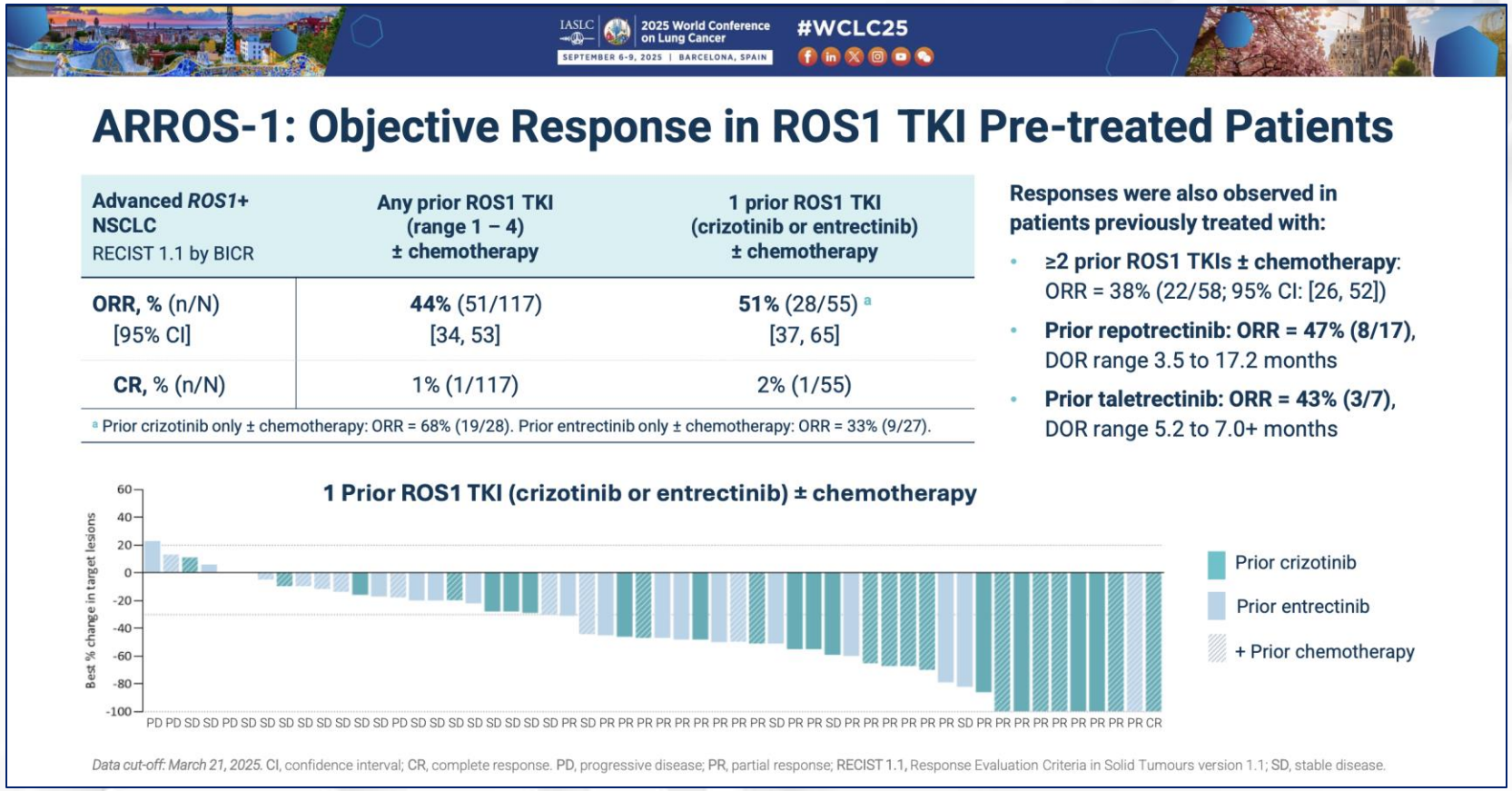
AST/ALT elevation: ~70% (5-10%)

Diarrhea: 70% (4%)

Anemia: 55% (4%)

Li W et al, J Clin Oncol, 2026.

ZIDESAMTINIB: FDA-APPROVED FOR ROS1+ NSCLC



Dose
100 mg/day

Salient AEs:

Edema
Constipation
CPK elevation

Drilon A et al, WCLC 2025.

TREATMENT OF KRAS G12C^{MT} NSCLC

Drug	Mech of Action	Response Rate	mPFS
Sotorasib	Ras off inhibitor	28%	5.6 m
Adagrasib	Ras off inhibitor	32%	5.5 m
Divarasib	2nd gen Ras off inhibitor	53%	13.1 m
Eisrasib	2nd gen Ras off inhibitor	60%	12.2 m
Elironrasib	RAS on inhibitor	56%	10.3 m
BBO-8520	Off and On inhibitor	65%	Not reported
Daroxonrasib	Pan- KRAS inhibitor	38%	9.8m

Wednesday, Jul 1, 2026

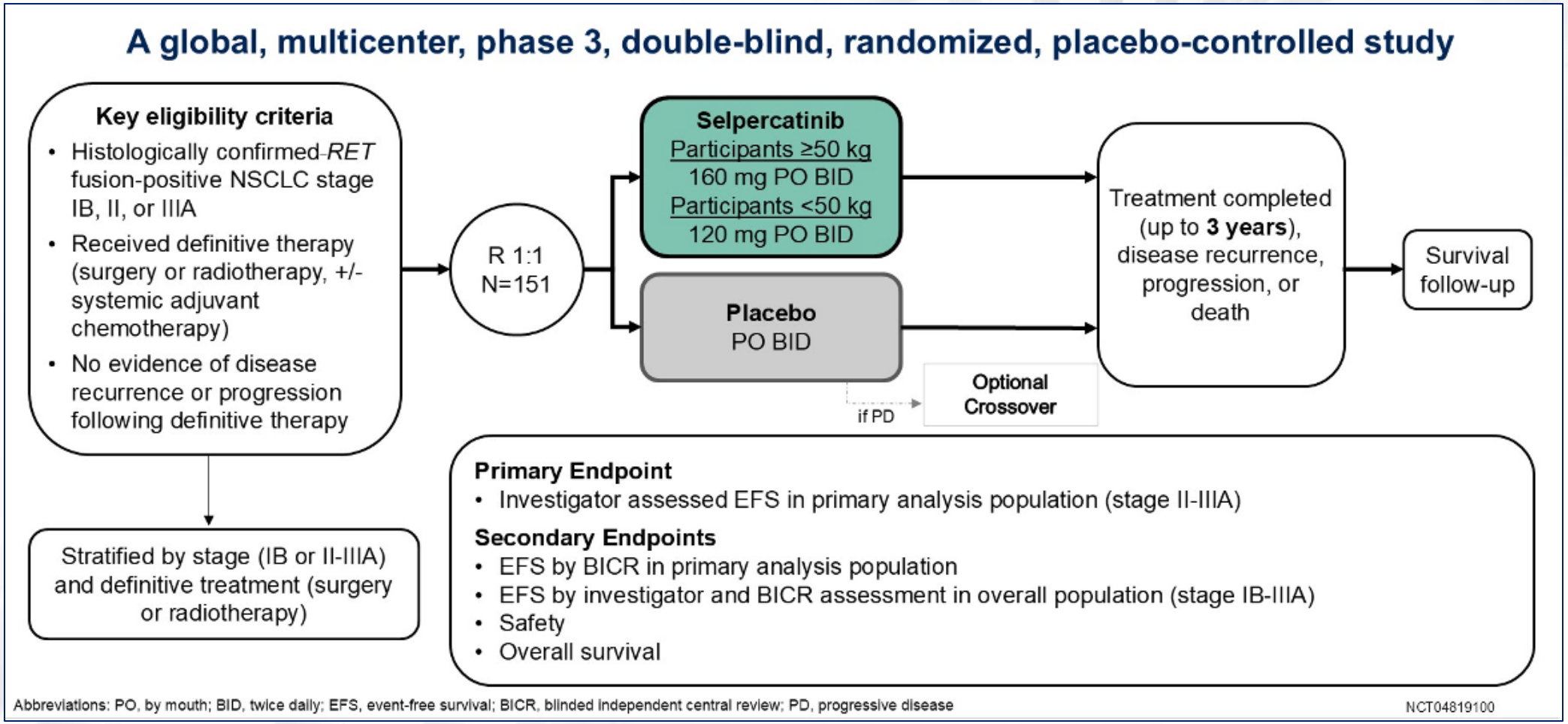
Divarasib Shows Superiority in Head-to-Head Phase III Trial Against Approved KRAS G12C Inhibitors in Non-Small Cell Lung Cancer

- Phase III (Krascendo 1) demonstrates best-in-class potential for patients with previously treated advanced KRAS G12C non-small cell lung cancer
- Divarasib showed clinically meaningful improvements in progression-free survival compared to approved KRAS G12C inhibitors; no new safety signals were observed
- Statistical significance for overall survival was achieved at the interim analysis in this poor-prognosis patient population
- Data will be submitted to health authorities and presented at an upcoming medical meeting

KRAS ^{MT} NSCLC

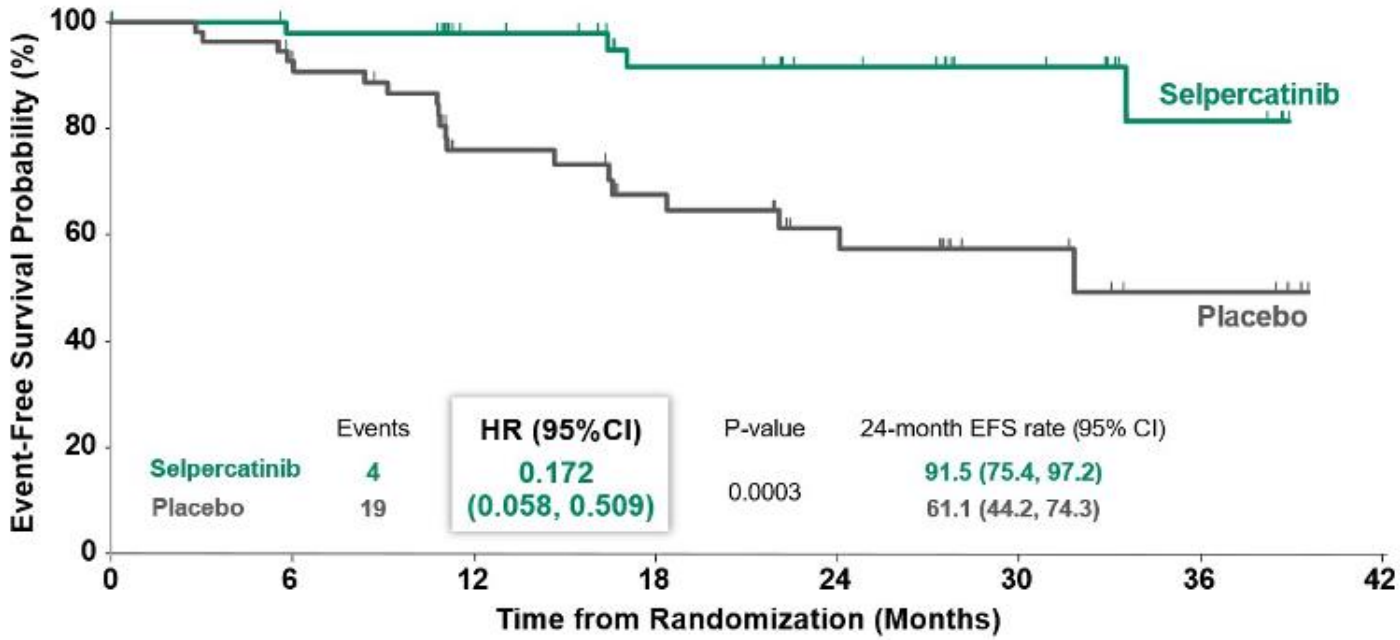
- Rapidly evolving space
- Current treatment strategies are limited to 2nd line and beyond in metastatic NSCLC
- Combination approaches are being explored
  - Combinability with IO still under investigation
- Role of co-mutations (KEAP1)
- Toxicity management
- Dose optimization

ADJUVANT THERAPY FOR RET+ NSCLC: LIBRETTO-432 TRIAL



Goldman J et al, ASCO 2026.

EFS IN STAGE II-IIIA NSCLC: INVESTIGATOR ASSESSMENT



The primary endpoint was met, as selpercatinib demonstrated a statistically significant improvement in EFS

Reduction in progression in local, locoregional and distant sites with selpercatinib

Goldman J et al, ASCO 2026.

LIBRETTO-432 TRIAL: SAFETY RESULTS

	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)

Goldman J et al, ASCO 2026.

CONCLUSIONS

- New treatment options continue to improve outcomes for patients with driver mutations
- Options for KRAS mutated NSCLC expanding quickly
- NGS testing at diagnosis for all patients with NSCLC is critical regardless of stage
- Adjuvant therapy for RET positive NSCLC improves EFS