Where Science Becomes Hope

TARGETING EGFR: WHAT IS NEW?

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DISCLOSURES

Honoraria: None

Research support (to institution): Amgen, Astra Zeneca, BMS, Merck, Pfizer

OUTLINE

- 1st line therapy
- Management of acquired resistance
- Early Stage NSCLC
- Exon 20 mutation
- Her-2 mutation

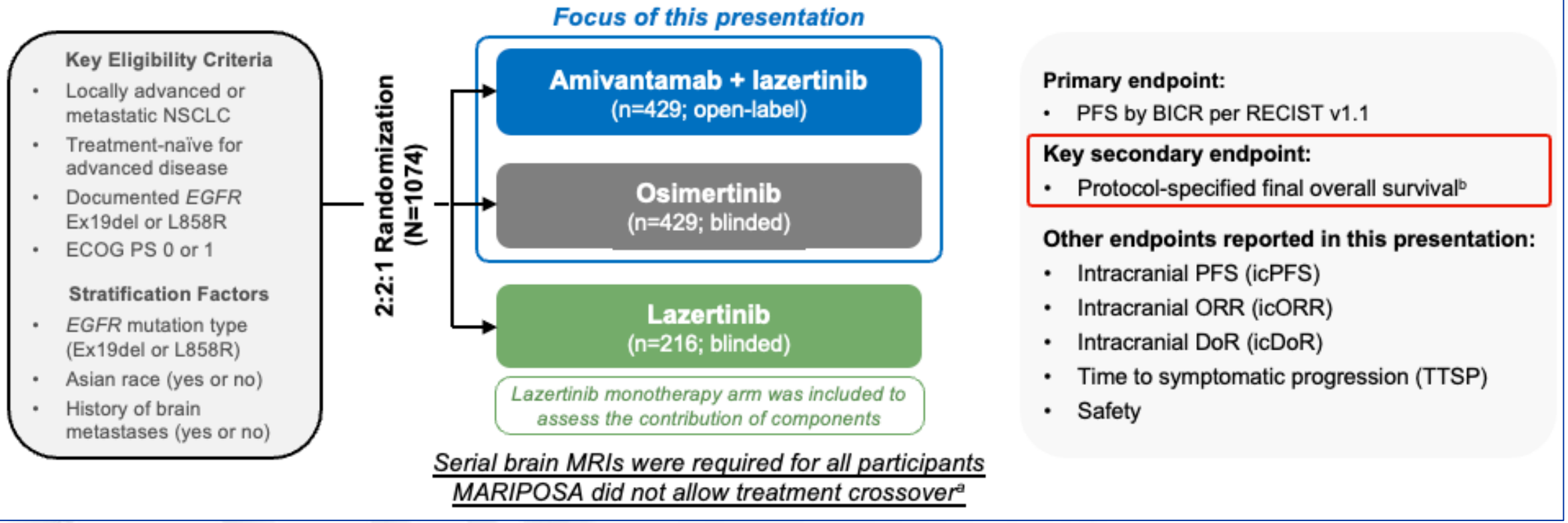
elcc European Lung Cancer Congress 2025

Amivantamab Plus Lazertinib vs Osimertinib in First-line *EGFR*-mutant Advanced NSCLC

Final Overall Survival from the Phase 3 MARIPOSA Study

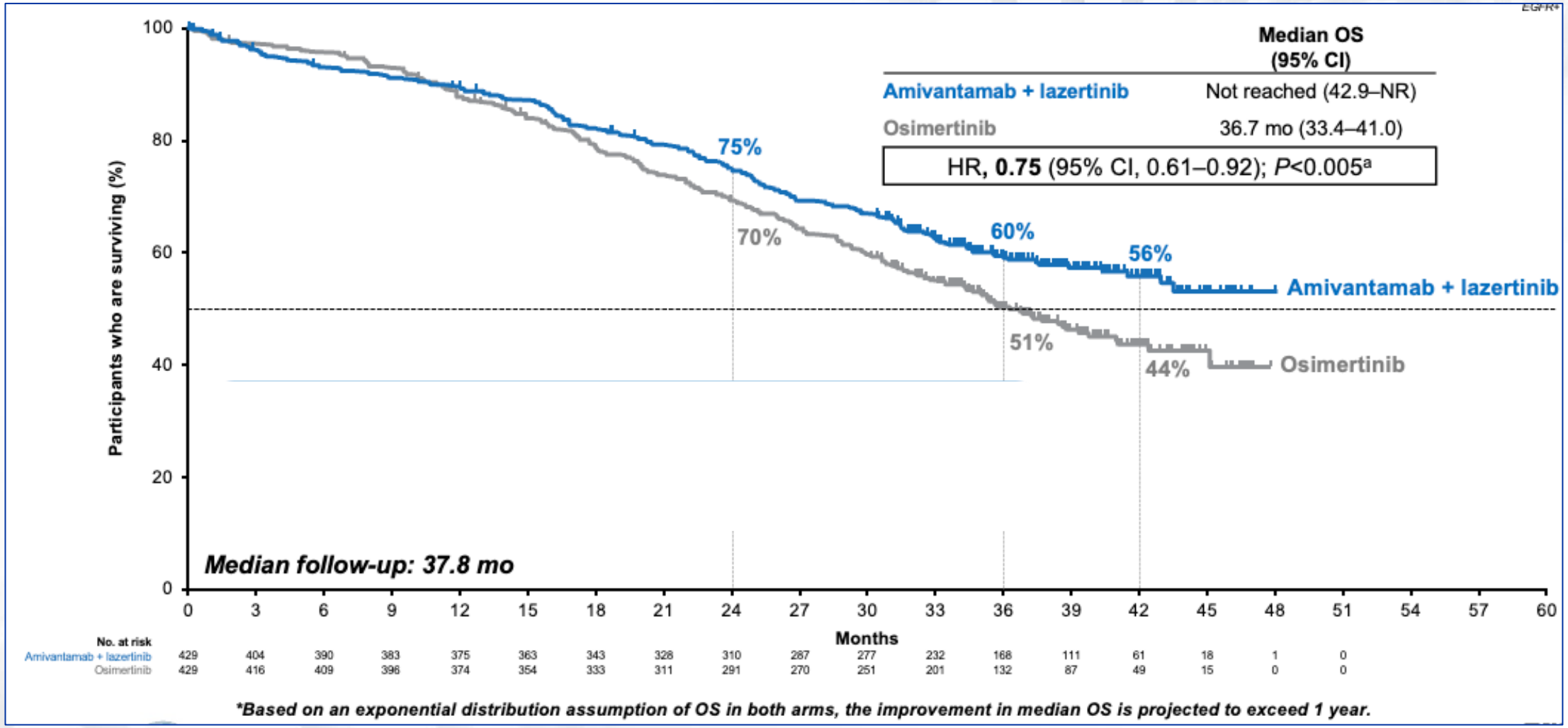
James Chih-Hsin Yang[1], Yu Jung Kim[2], Se-Hoon Lee[3], Baogang Liu[4], Yurii Ostapenko[5], Shun Lu[6], Adlinda Alip[7], Ernesto Korbenfeld[8], Josiane Mourão Dias[9], Pongwut Danchaivijitr[10], Nicolas Girard[11], Enriqueta Felip[12], Hidetoshi Hayashi[13], Alexander I Spira[14], Benjamin Besse[15], Tao Sun[16], Mariah Ennis[17], Seema Sethi[17], Joshua M Bauml[17], Byoung Chul Cho[18]

MARIPOSA: STUDY DESIGN



Yang J et al, ELCC 2025.

MARIPOSA: OVERALL SURVIVAL



*Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is projected to exceed 1 year.

Yang J et al, ELCC 2025.

MARIPOSA: ADVERSE EVENTS

AEs by preferred term (≥20% of participants in either group)	Amivantamab + lazertinib (n=421)		Osimertinib (n=428)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Related to EGFR inhibition				
Paronychia	291 (69)	49 (12)	127 (30)	2 (<1)
Rash	271 (64)	73 (17)	136 (32)	3 (<1)
Diarrhea	133 (32)	9 (2)	200 (47)	4 (<1)
Dermatitis acneiform	127 (30)	37 (9)	55 (13)	0
Stomatitis	126 (30)	5 (1)	92 (21)	1 (<1)
Pruritus	107 (25)	2 (<1)	75 (18)	1 (<1)
Related to MET inhibition				
Hypoalbuminemia	216 (51)	26 (6)	29 (7)	0
Peripheral edema	162 (38)	8 (2)	29 (7)	1 (<1)
Other				
Infusion-related reaction	275 (65)	27 (6)	0	0
ALT increased	170 (40)	28 (7)	66 (15)	8 (2)
AST increased	139 (33)	15 (4)	68 (16)	6 (1)
Constipation	130 (31)	0	70 (16)	0
COVID-19	125 (30)	8 (2)	112 (26)	9 (2)
Anemia	114 (27)	20 (5)	112 (26)	10 (2)
Decreased appetite	114 (27)	4 (1)	84 (20)	7 (2)
Nausea	99 (24)	5 (1)	65 (15)	1 (<1)
Hypocalcemia	96 (23)	11 (3)	37 (9)	0
Asthenia	84 (20)	13 (3)	54 (13)	7 (2)
Muscle spasms	84 (20)	3 (<1)	36 (8)	0
Thrombocytopenia	74 (18)	4 (1)	92 (21)	6 (1)

Yang J et al, ELCC 2025.

Osimertinib plus chemotherapy demonstrated statistically significant and clinically meaningful improvement in overall survival in EGFR-mutated advanced lung cancer

PUBLISHED
21 July 2025

Longer-term follow up in the FLAURA2 Phase III trial confirms the favourable benefit-risk profile of this combination

Overall survival results reinforce osimertinib as the backbone therapy in EGFRm lung cancer across stages

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SECOND LINE THERAPY

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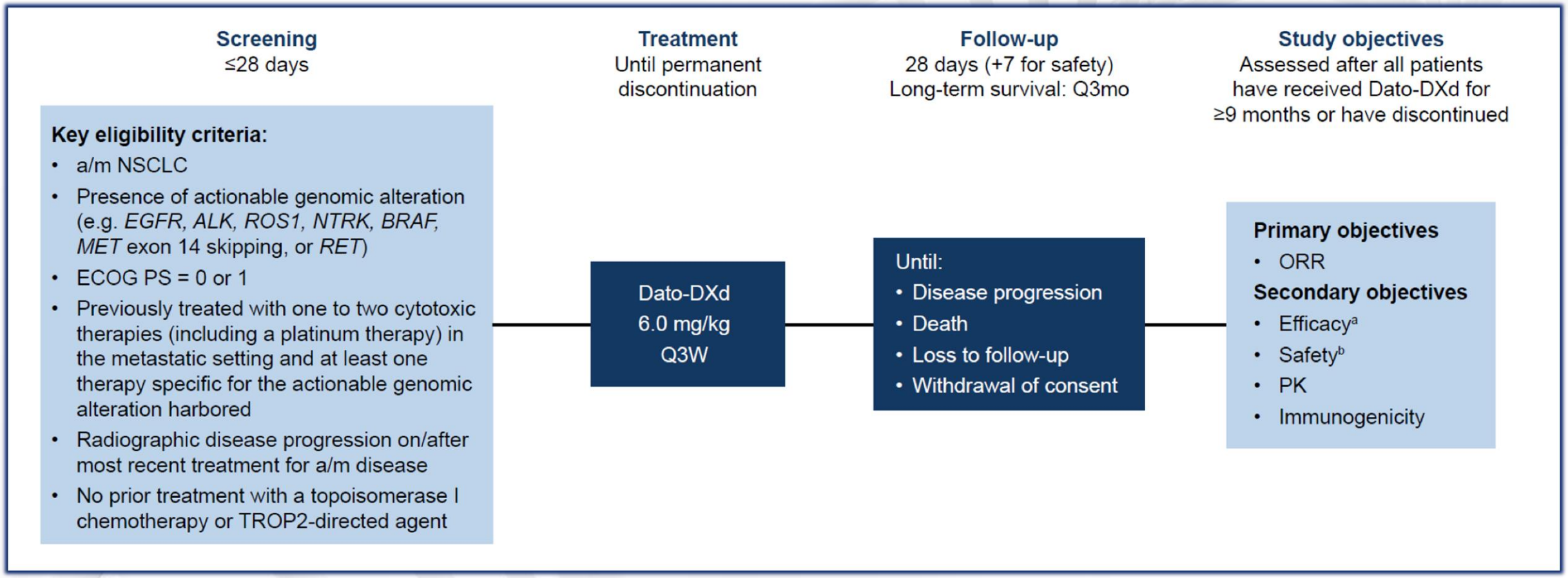
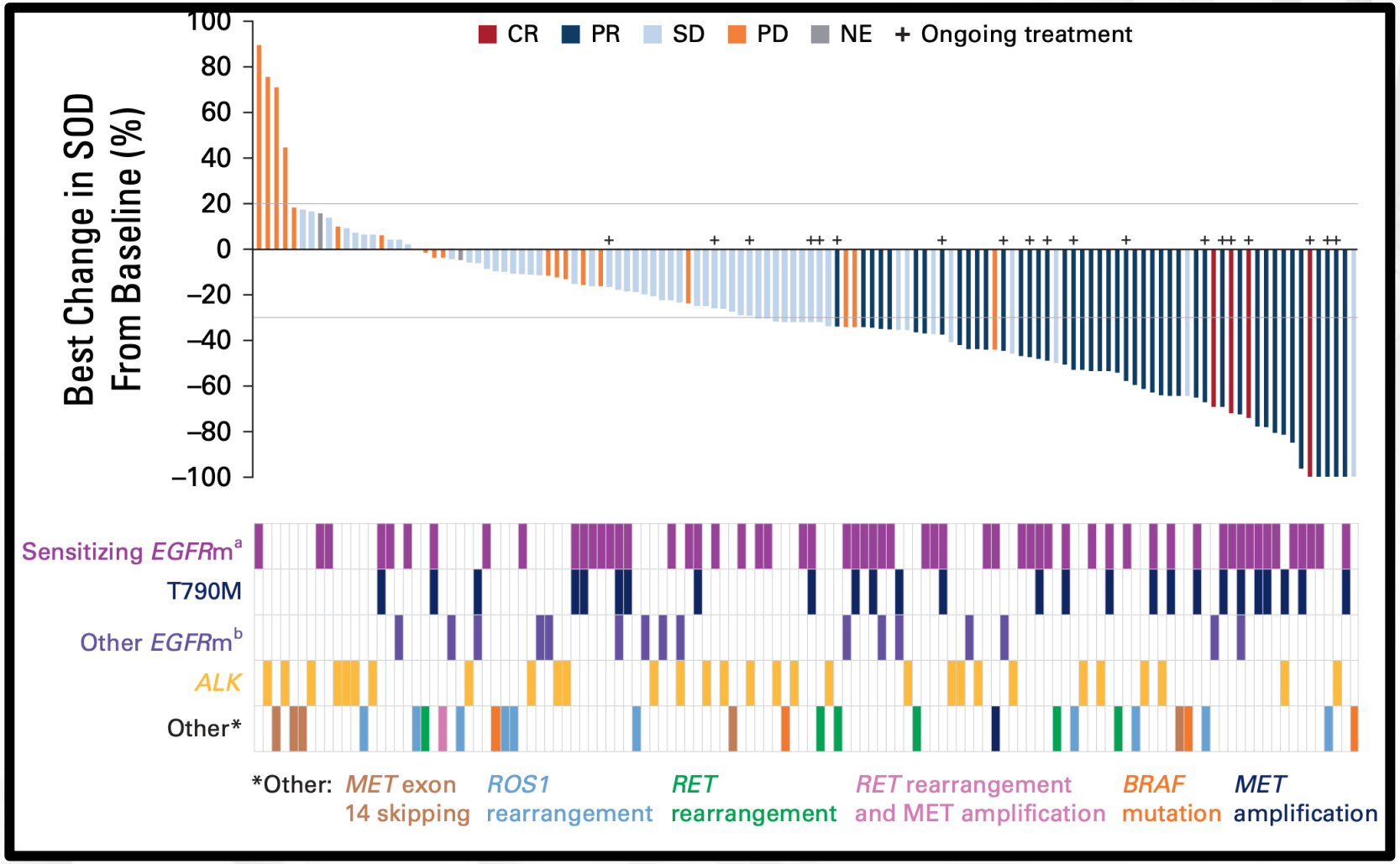
TROPION LUNG 05 STUDY



Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: EFFICACY



EGFR^{MT} NSCLC Cohort

N=78 pts

RR=44%

mDOR: 7.0m

mPFS: 5.8m

Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: TOXICITY

AESI	Any grade	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (65.7)	45 (32.8)	30 (21.9)	15 (10.9)
Treatment discontinuation	1 (0.7)	1 (0.7)[a]	0	0
Patients with reported events (PTs)				
Stomatitis	80 (58.4)	39 (28.5)	28 (20.4)	13 (9.5)
Oropharyngeal pain	8 (5.8)	6 (4.4)	2 (1.5)	0
Dysphagia	7 (5.1)	5 (3.6)	0	2 (1.5)
Aphthous ulcer	4 (2.9)	4 (2.9)	0	0
Pharyngeal inflammation	2 (1.5)	1 (0.7)	0	1 (0.7)

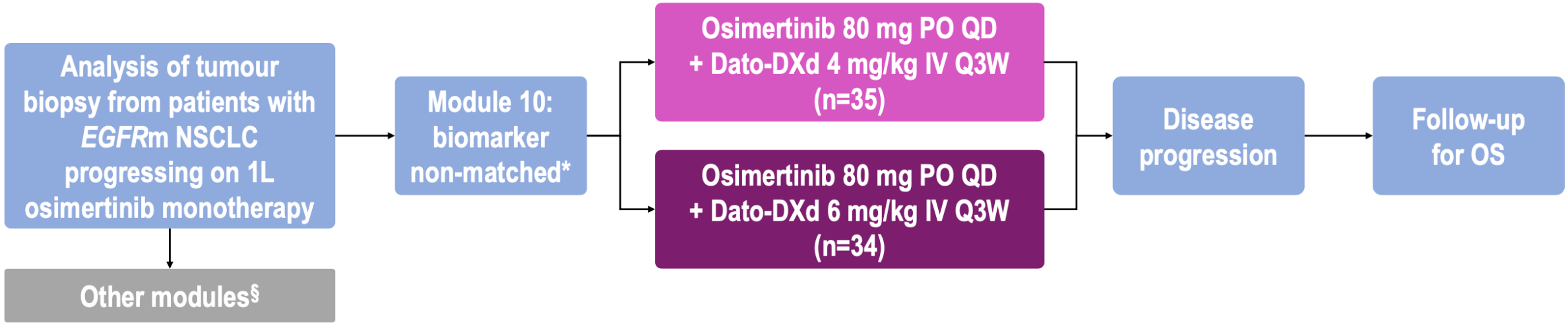
Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: TOXICITY

Ocular surface events	36 (26.3)	26 (19.0)	7 (5.1)	3 (2.2)
Treatment discontinuation	0	0	0	0
Patients with reported events (PTs)				
Dry eye	15 (10.9)	13 (9.5)	2 (1.5)	0
Vision blurred	12 (8.8)	10 (7.3)	2 (1.5)	0
Keratitis	7 (5.1)	5 (3.6)	2 (1.5)	0
Corneal disorder	2 (1.5)	0	1 (0.7)	1 (0.7)
Cornea verticillate	1 (0.7)	0	0	1 (0.7)
Punctate keratitis	1 (0.7)	0	0	1 (0.7)

Sands J et al, J Clin Oncol, 2025.

ORCHARD module 10 study design



- **Primary endpoint:** ORR based on RECIST v1.1 by investigator assessment
- **Key secondary endpoints:** PFS‡, DoR‡, OS, AEs, SAEs

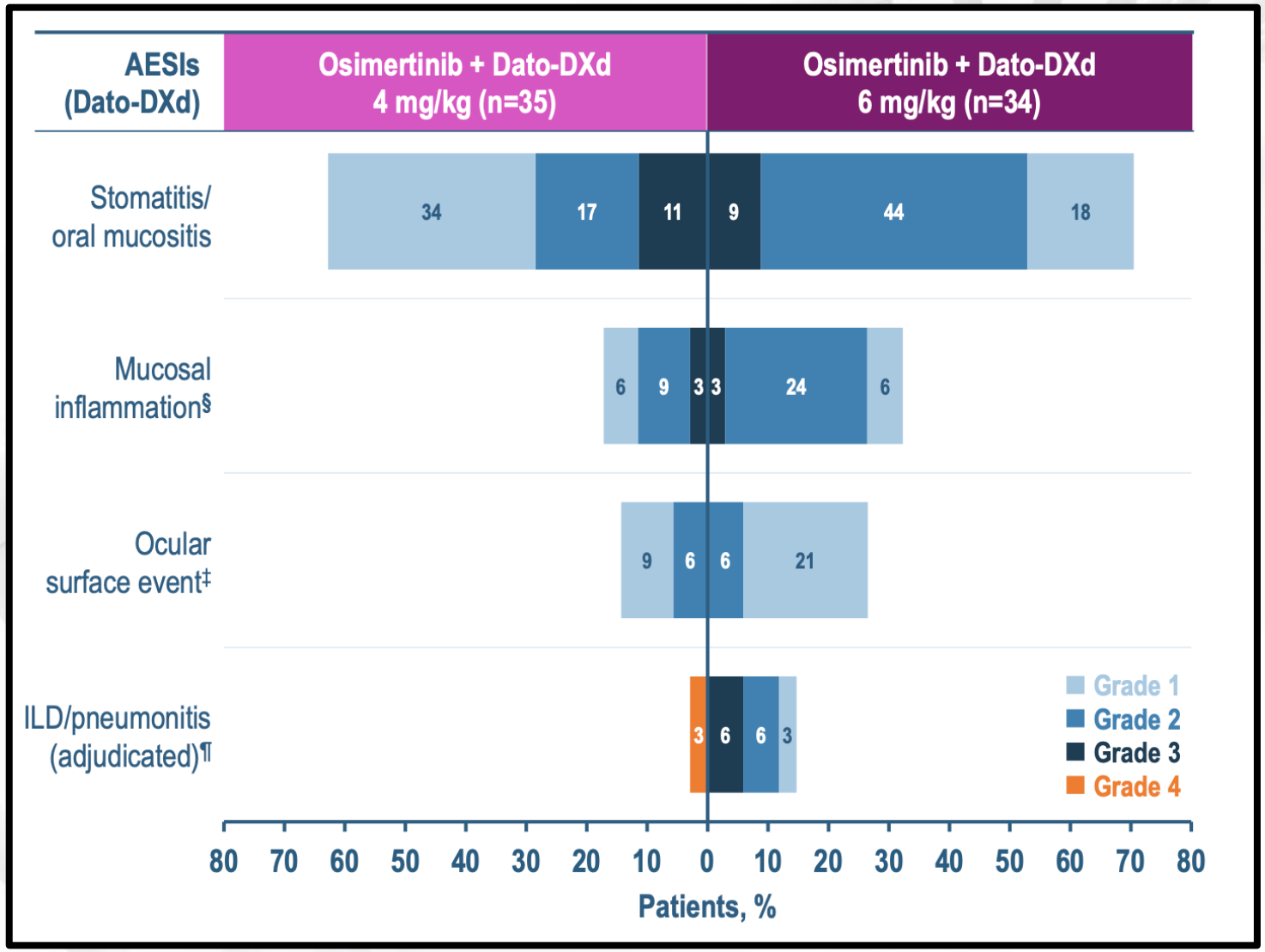
Le X et al, ELCC 2025.

ORCHARD MODULE 10: EFFICACY

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
PFS		
mPFS, months (95% CI)	**9.5 (7.2, 9.8)**	**11.7 (8.3, NC)**
6-month rate, % (95% CI)	74 (56, 85)	80 (61, 91)
9-month rate, % (95% CI)	50 (33, 65)	70 (49, 83)
12-month rate, % (95% CI)	21 (9, 35)	39 (21, 57)
ORR, % (80% CI)	**43 (31, 55)**	**36 (25, 49)**
DoR		
mDoR, months (95% CI)*	**6.3 (3.8, 8.2)**	**20.5 (6.2, NC)**
6-month rate, % (95% CI)	60 (32, 80)	92 (54, 99)
9-month rate, % (95% CI)	15 (2, 38)	64 (30, 85)
Median time to onset of response, months (Q1, Q3)	**2.7 (1.5, 4.1)**	**1.4 (1.2, 2.1)**
Median duration of follow-up, months	13.4	13.8
OS events, n (%)	16 (46)	9 (27)

Le X et al, ELCC 2025.

ORCHARD MODULE 10: SALIENT TOXICITY



Sands J et al, J Clin Oncol, 2025.

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EARLY STAGE NSCLC

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NeoADAURA

Patients with completely resectable EGFRm stage II–IIIB NSCLC*

Key inclusion criteria:

- Aged ≥18 years
- Histologically / cytologically confirmed non-squamous NSCLC
- Ex19del / L858R†
- WHO PS 0 / 1

N=358

R 1:1:1

Stratification by:
Stage II / III
Chinese‡ / other Asian / non-Asian
Ex19del / L858R

- Osi 80 mg QD (≥9 weeks)§¶ + carboplatin AUC5 or cisplatin 75 mg/m² + pemetrexed 500 mg/m² (Q3W for 3 cycles)
- Osi mono 80 mg QD (≥9 weeks)¶#
- PBO QD (≥9 weeks)§¶ + carboplatin AUC5 or cisplatin 75 mg/m² + pemetrexed 500 mg/m² (Q3W for 3 cycles)

Surgery

Investigator choice of adjuvant treatment

Post-surgery follow-up visits**

Sponsor-supplied adjuvant osi was available for eligible patients who completed surgery in all arms††

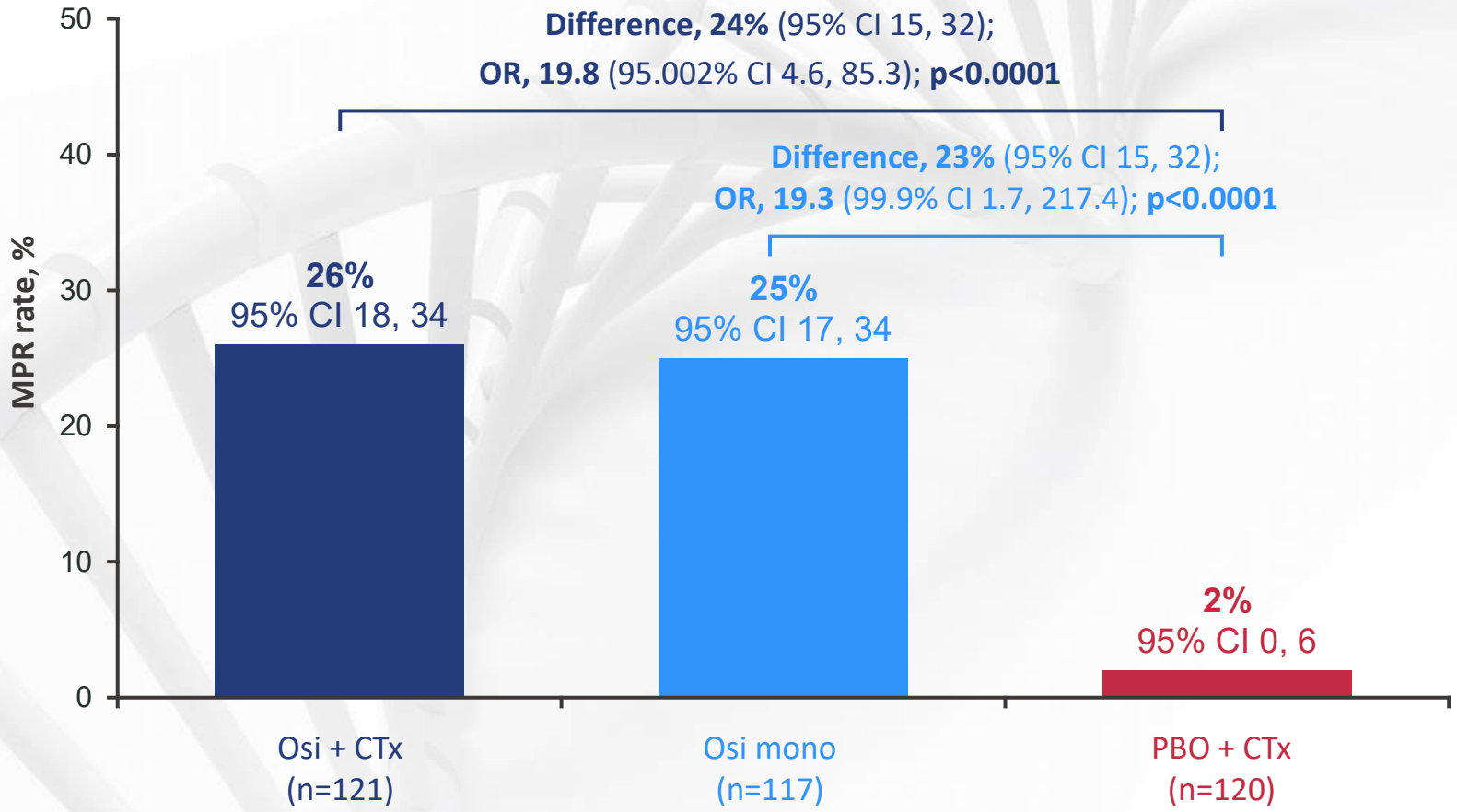
Endpoints:

- **Primary: major pathological response (MPR; by blinded central pathology review)**
- Secondary: event-free survival, pathological complete response, nodal downstaging and safety

Chaft J et al, ASCO 2025.

MPR

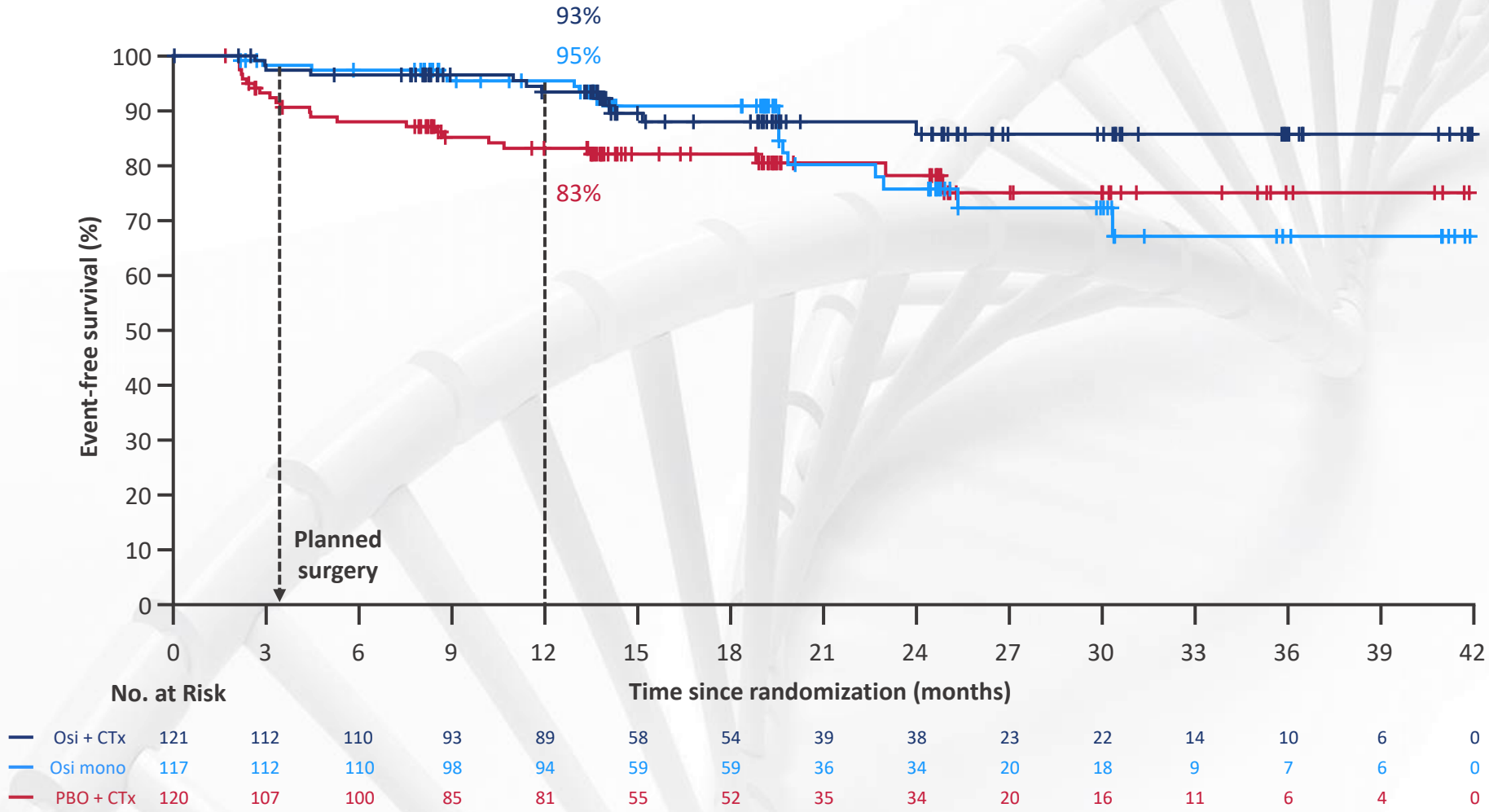
The MPR rate was statistically significantly higher with both osi-containing regimens



Chaft J et al, ASCO 2025.

CI, confidence interval; CTx, chemotherapy; EGFR, epidermal growth factor receptor; ES-SCLC, Extensive-stage SCLC; IASLC, International Association for the Study of Lung Cancer; mono, monotherapy; MPR, major pathological response; OR, odds ratio; osi, osimertinib; PBO, placebo; SCLC, small cell lung cancer.

Interim EFS analysis (15% maturity)



EFS HR vs PBO + CTx

Osi + CTx: 0.50
(99.8% CI 0.17, 1.41); p=0.0382†

Osi mono: 0.73
(95% CI 0.40, 1.35)†

Median follow-up, months‡
osi + CTx 14.3, osi mono 18.3,
PBO + CTx 14.3

Chaft J et al, ASCO 2025.

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LOCALLY ADVANCED NSCLC

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Osimertinib after definitive chemoradiotherapy in patients with unresectable stage III EGFRm NSCLC: Updated overall survival analysis from the LAURA study

Suresh S. Ramalingam,[1] Mustafa Özgüroğlu,[2] Myung-Ju Ahn,[3] Xiaorong Dong,[4] James Chih-Hsin Yang,[5] Satoshi Oizumi,[6] Koichi Goto,[7] Manuel Cobo,[8] Sang-We Kim,[9] Te-Chun Hsia,[10] Jarin Chindaprasirt,[11] Fernanda Fujiki,[12] Natalia Valdiviezo,[13] Ignacio Casarini,[14] Terufumi Kato,[15] Xiangning Huang,[16] Azura Evans,[17] Ana Bolanos,[18] Shun Lu[19]

LAURA STUDY DESIGN[1]

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

R
2:1

N=216

Osimertinib 80 mg, once daily

Placebo, once daily

Endpoints

- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Key secondary endpoints:** OS, CNS PFS
- **Secondary post-progression endpoints:** TFST, PFS2, TSST

Key inclusion criteria:

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

Treatment continued until BICR-assessed progression (per RECIST 1.1), toxicity, or other discontinuation criteria met

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

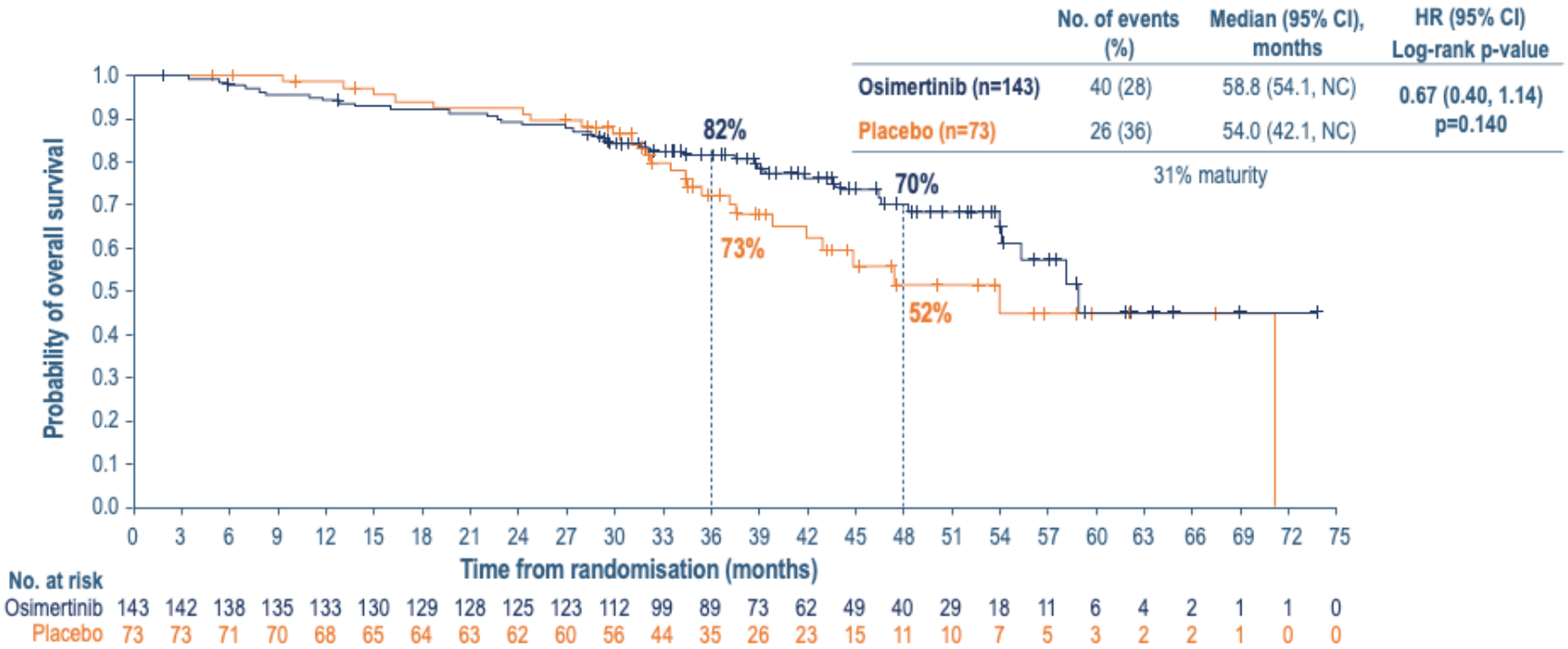
Tumour assessments:

- Chest CT / MRI and brain MRI
  - At baseline, every 8 weeks to Week 48, then every 12 weeks until progression
  - After progression, PFS2 and OS were assessed by the investigator every 12 weeks and defined by local practice

Ramalingam S et al, ELCC 2025.

Updated DCO

IMPROVED TREND TOWARDS OS BENEFIT SEEN WITH OSIMERTINIB AT UPDATED ANALYSIS



	No. of events (%)	Median (95% CI), months	HR (95% CI) Log-rank p-value
Osimertinib (n=143)	40 (28)	58.8 (54.1, NC)	0.67 (0.40, 1.14) p=0.140
Placebo (n=73)	26 (36)	54.0 (42.1, NC)	

- 55/69 (80%) patients who discontinued study treatment in the placebo group received subsequent treatment with a 3rd-gen EGFR-TKI*

Ramalingam S et al, ELCC 2025.

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EGFR EXON 20 INSERTION

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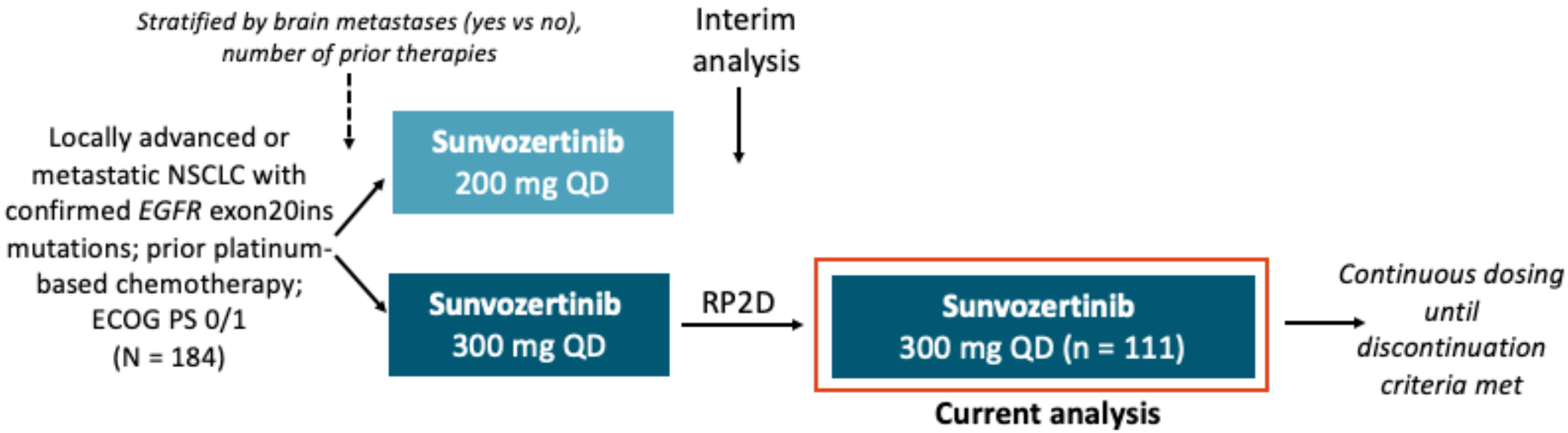
WU-KONG1: Study Design

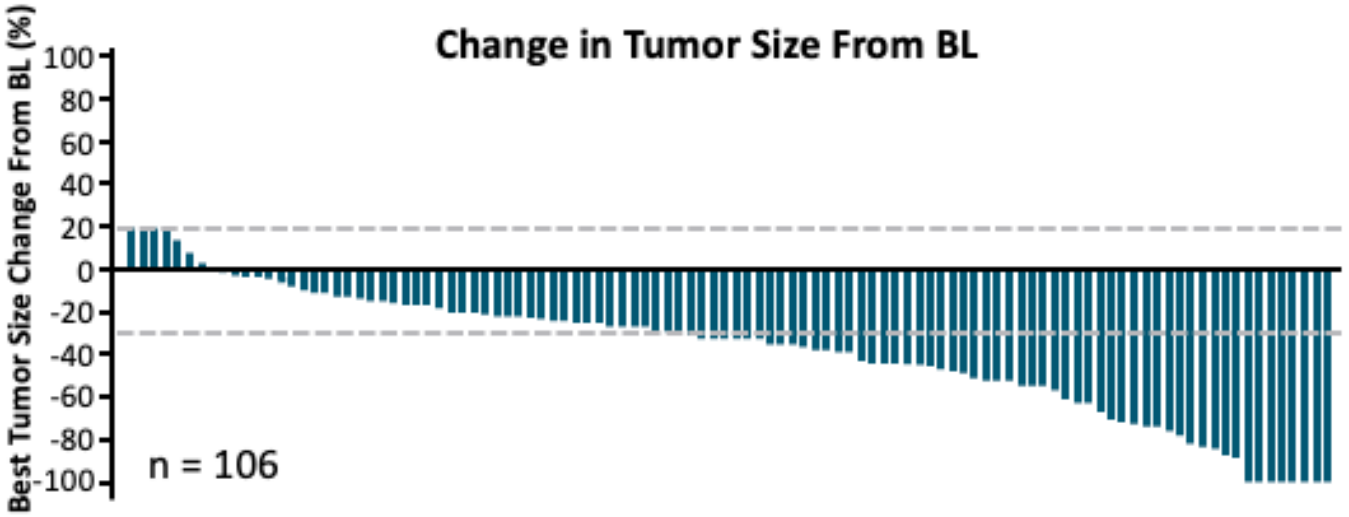
- Multinational phase II study with a randomized, dose-finding phase followed by a single-arm phase after interim analysis identified RP2D



- **Primary endpoint:** ORR assessed by IRC
- **Secondary endpoints**: DoR by IRC, investigator-assessed ORR, DoR

Yang. ASCO 2024. Abstr 8513.

WU-KONG1: Antitumor Activity



Tumor Response per IRC	All Patients (n = 107)	
	Overall	Confirmed
ORR, % (97.5% CI)	53.3 (42.0-64.3)	44.9 (34.0-56.1)
CR, n (%)	3 (2.8)	2 (1.9)
PR, n (%)	54 (50.5)	46 (43.0)
SD, n (%)	44 (41.1)	--
PD, n (%)	8 (7.5)	--
Not evaluable, n (%)	3 (2.8)	--

- Median DoR not reached
- 9-month DoR rate: 57%
- Sunvozertinib activity noted regardless of previous amivantamab therapy
  - ORR in patients with prior amivantamab: 50%
  - ORR in patients without prior amivantamab: 53.8%

Yang. ASCO 2024. Abstr 8513. Reproduced with permission.

WU-KONG1: Safety

Grade ≥3 TRAEs in ≥2%, n (%)	Sunvozertinib 300 mg (n = 111)
Diarrhea	19 (17.1)
Blood creatinine phosphokinase increased	12 (10.8)
Anemia	4 (3.6)
Rash	4 (3.6)
Lipase increased	4 (3.6)
Neutrophil count decreased	3 (2.7)
Hypokalemia	3 (2.7)
Decreased appetite	3 (2.7)
Asthenia	3 (2.7)

- TRAEs leading to dose reduction: 36.0%
- TRAEs leading to treatment discontinuation: 6.3%
- Most common TRAEs were grade 1-2 and manageable
- No fatal TRAEs occurred

Yang. ASCO 2024. Abstr 8513.

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HER-2 MUTATION

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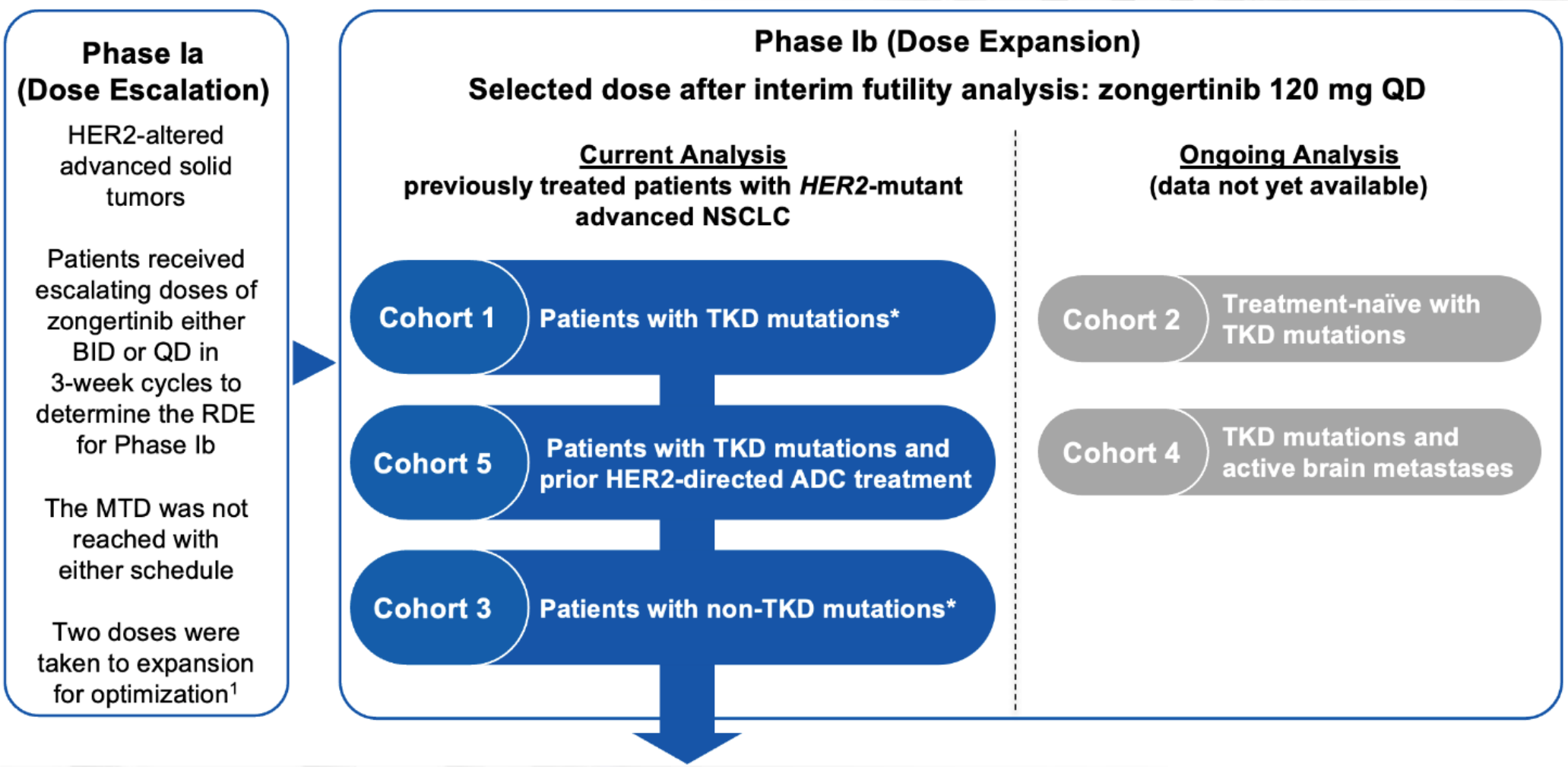
ZONGERTINIB (BI 1810631): BEAMION LUNG 01

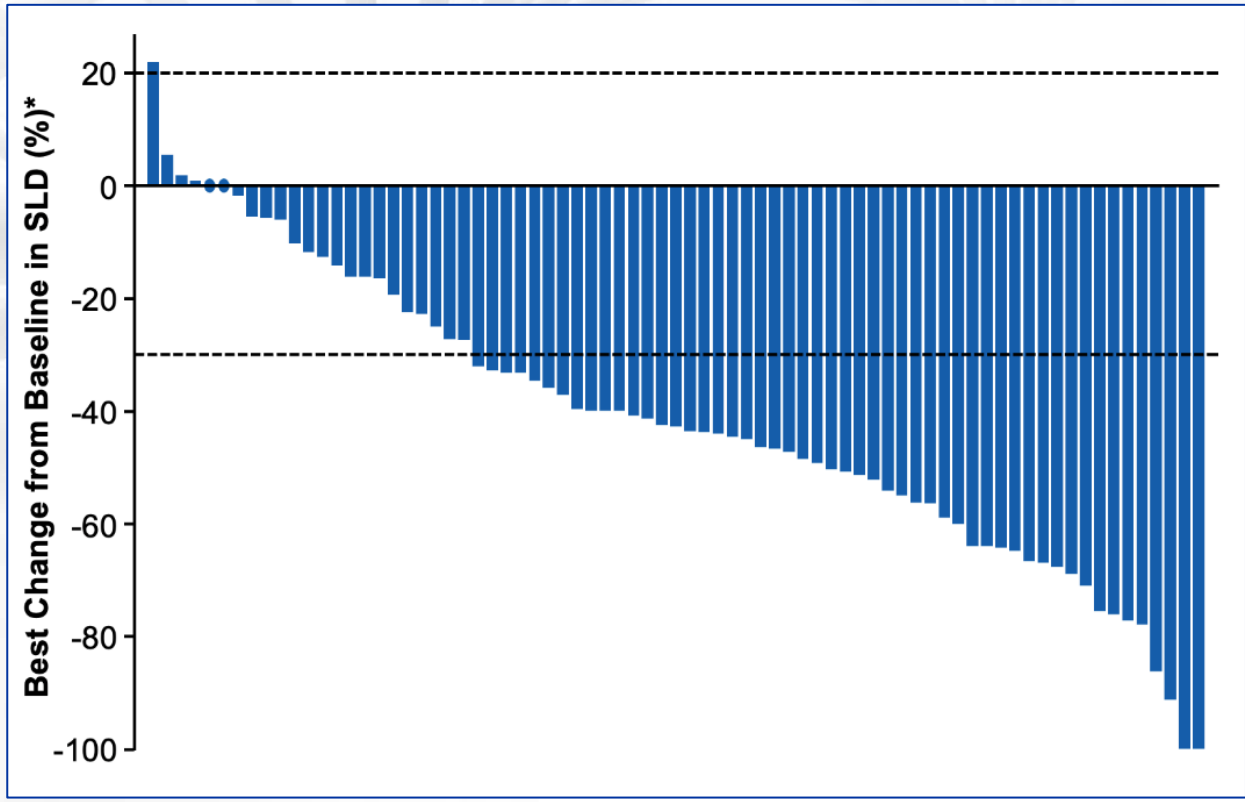


Heymach, AACR 2025; Heymach, NEJM 2025

ZONGERTINIB IN HER2 MUTATED NSCLC

Dose: 120 mg QD PO

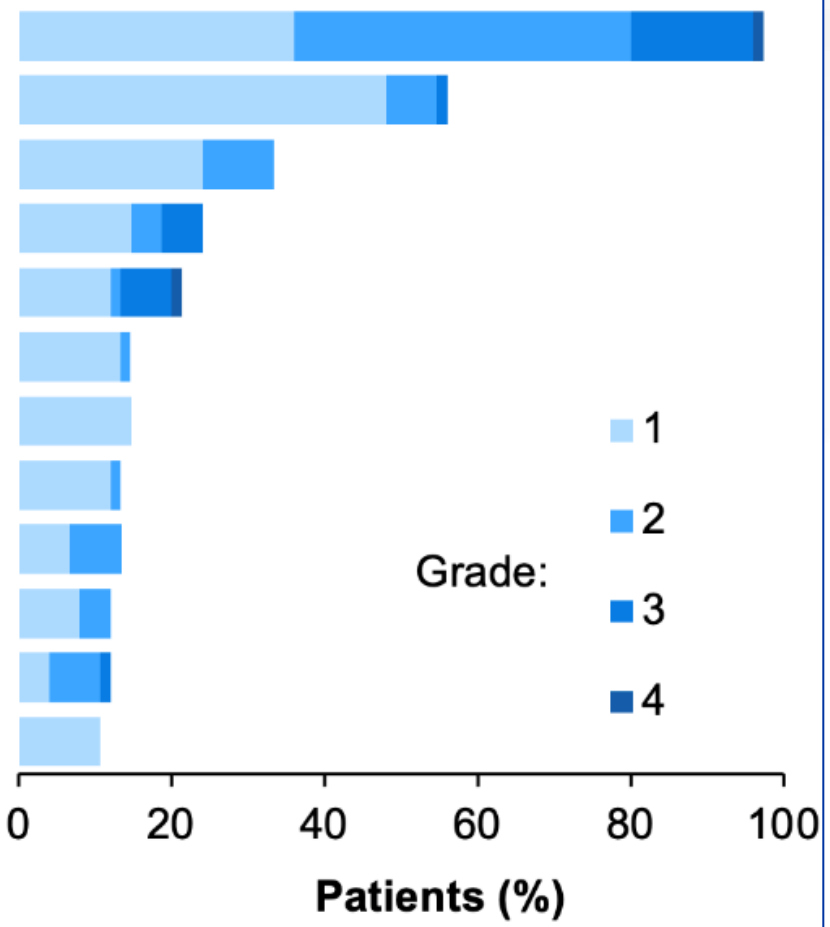
- Previously treated
- RR 71%
- DCR 96%
- mDOR 14.1m
- mPFS 12.4m



Heymach, AACR 2025; Heymach, NEJM 2025

ZONGERTINIB (BI 1810631): ADVERSE EVENTS

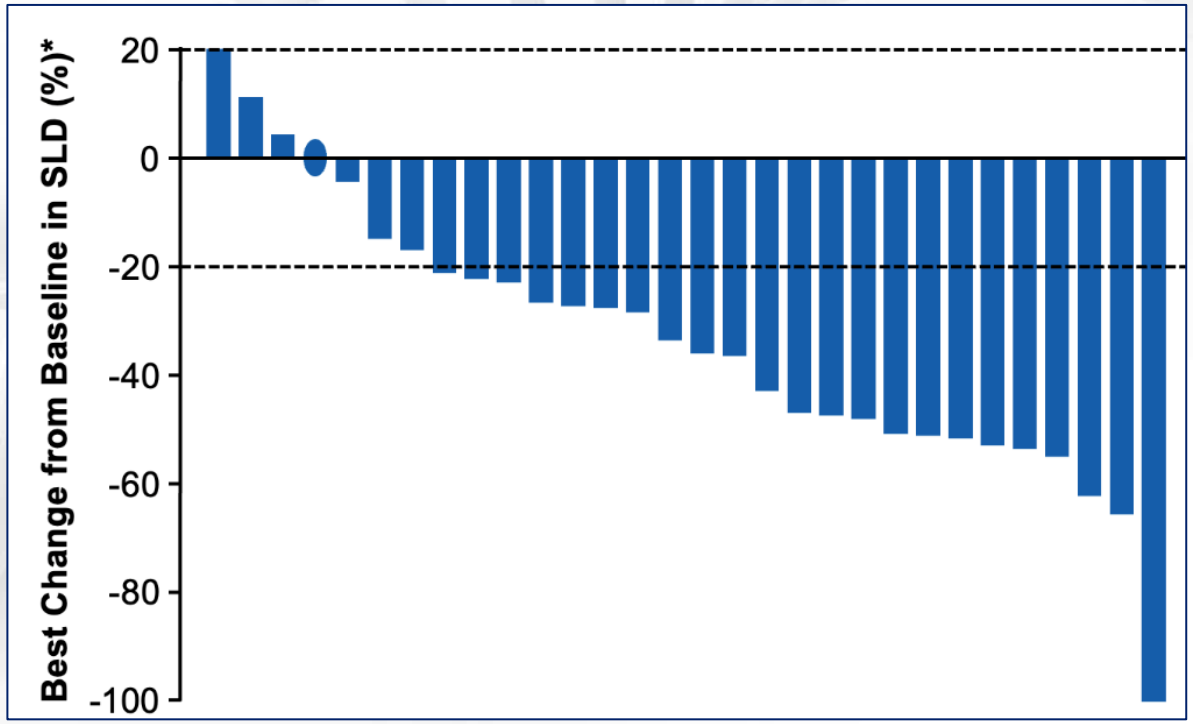
Drug-related AEs‡, n (%)	Cohort 1 All	Cohort 1 G≥3
Any	73 (97)	13 (17)
Diarrhea§	42 (56)	1 (1)
Rash§	25 (33)	0
AST increased	18 (24)	4 (5)
ALT increased	16 (21)	6 (8)
Nausea	11 (15)	0
Dry skin	11 (15)	0
Pruritus	10 (13)	0
WBC count decreased	10 (13)	0
Anemia	9 (12)	0
Neutrophil count decreased	9 (12)	1 (1)
Nail disorder	8 (11)	0



Heymach, AACR 2025; Heymach, NEJM 2025

ZONGERTINIB IN PATIENTS PREVIOUSLY TREATED WITH A HER2 TARGETED AGENT

- Previously treated
  - Prior HER2 ADC
- RR 48%
- DCR 97%
- Prior T-DXd
  - RR 41%



Heymach, AACR 2025; Heymach, NEJM 2025

CONCLUSIONS

- Combination therapy is an option for 1st line treatment of EGFR mt NSCLC
- Individualize based on brain metastasis, patient preference and co-mutation status
- Datopotamab is a new option for patients with acquired resistance
- Sunvozertinib is approved for EGFR exon 20 insertion mutation
- Zongertinib is effective for HER2 mutated NSCLC