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LUNG CONNECT MICRO LEARNING

THE EVOLVING TREATMENT LANDSCAPE IN *HER2*-MUTANT NSCLC

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THIS PROGRAMME HAS BEEN DEVELOPED BY A GROUP OF EXPERTS

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EDUCATIONAL OBJECTIVES

1. Understand the latest **clinical trial data and emerging profiles** of therapies for the treatment of *HER2*-mutant NSCLC

2. Know the **potential toxicities** of treatments for *HER2*-mutant NSCLC and how to manage for optimal outcomes

3. Recognise the **appropriate placement of therapies** for the treatment of *HER2*-mutant NSCLC across the patient journey

NSCLC, non-small cell lung cancer

CLINICAL TAKEAWAYS

- **Test early and accurately:** Next generation sequencing (NGS) is required to identify *HER2* mutations and guide therapy
- **Targeted therapies improve outcomes:** Antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan and next-generation tyrosine kinase inhibitors (TKIs) (zongertinib, sevabertinib) show high response rates, durable responses, and activity in patients with brain metastases
- **Manage toxicities proactively:** ADCs carry interstitial lung disease risk; TKIs mainly cause low-grade diarrhea and rash, manageable with supportive care and dose adjustments
- **Thoughtful sequencing of HER2-targeted therapies:** may help optimise outcomes, particularly when used earlier in the treatment pathway, considering central nervous system involvement, efficacy, safety, and patient factors

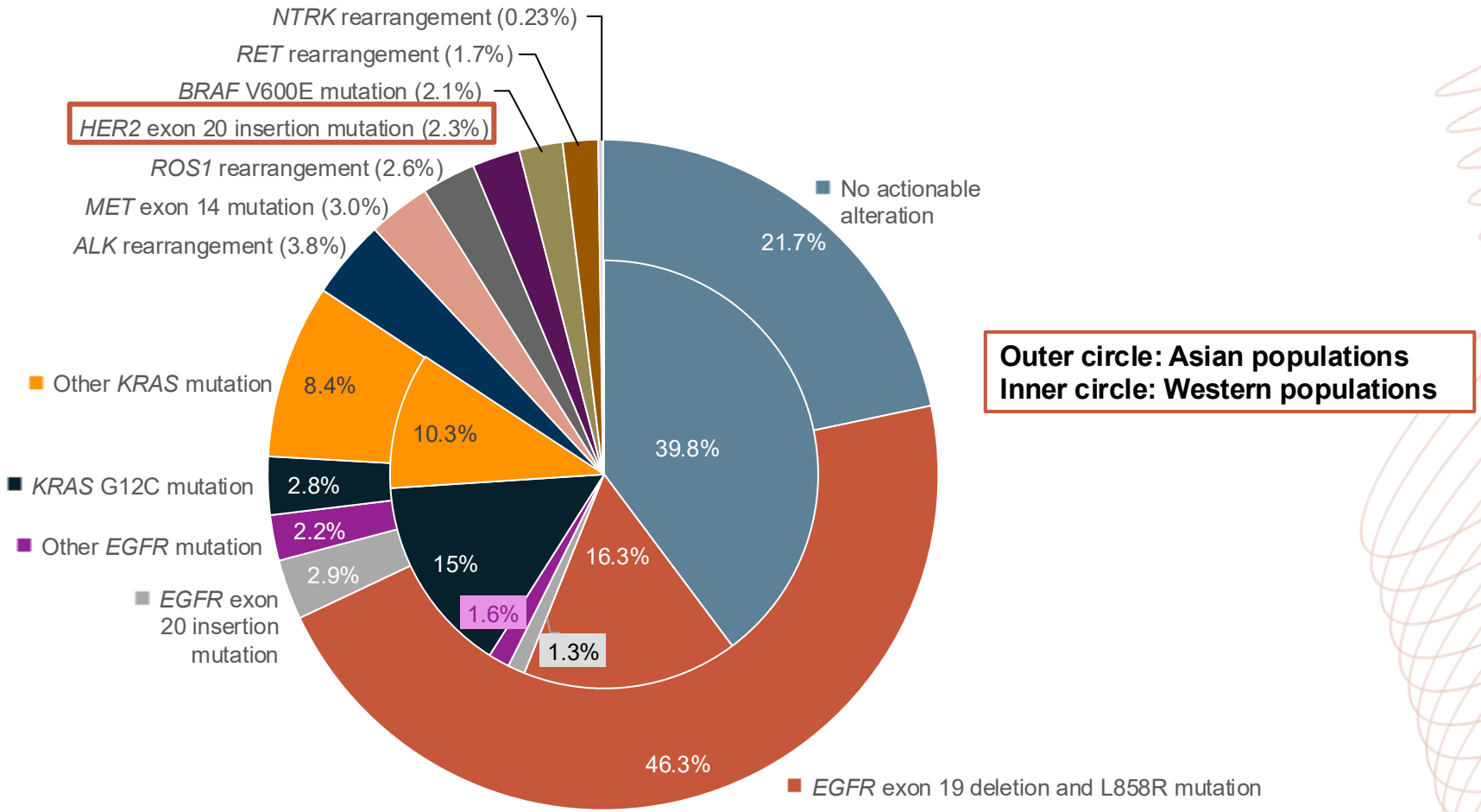
NSCLC, non-small cell lung cancer

HER2 MUTATIONS IN NSCLC

NSCLC, non-small cell lung cancer

ONCOGENIC DRIVERS IN NSCLC

HER2 (*ERBB2*) MUTATIONS ARE REPORTED IN 2-4% OF NSCLC



BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten ras oncogene; MET, MET proto-oncogene; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, RET proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase

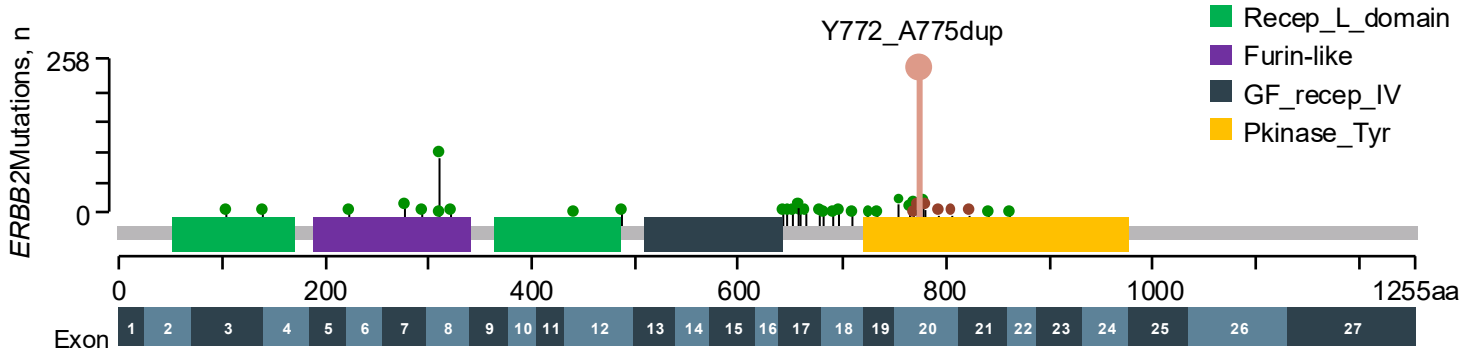
Tan AC and Tan DSW. J Clin Oncol. 2022;40:611-625

HER2 MUTATIONS IN LUNG CANCER

AROUND 74% OF TARGETABLE *HER2* MUTATIONS OCCUR IN THE TYROSINE KINASE DOMAIN (TKD) OF *HER2 (ERBB2)*[1]

- TKD drives intracellular signalling for tumour growth and survival[1,2]
- *HER2* mutations in TKD are mostly ex20 insertions (~90%)[1]
- The most frequent *HER2* ex20ins is A775_G776insYVMA (alternatively known as p.772_A775dup)[1]

***HER2 (ERBB2)* mutational profile in newly diagnosed NSCLC patients**



ERBB2 oncogenic mutations and proportion reported by OncoKB and COSMIC in Guardant360

aa, amino acids

1. Trillo Aliaga P, et al. Molecules 2025;30:2645; 2. Hong L, et al. NPJ Precis Oncol. 2024;8,217

CLINICAL SIGNIFICANCE OF *HER2* ALTERATIONS IN NSCLC

More common in **females, younger patients, non-smokers**, and in **adenocarcinoma**[1,2] and are considered **markers of poor prognosis**[3]

HER2 **mutations and amplification** are 2 of the **mechanisms of acquired resistance** to EGFR TKIs in NSCLC patients[3]

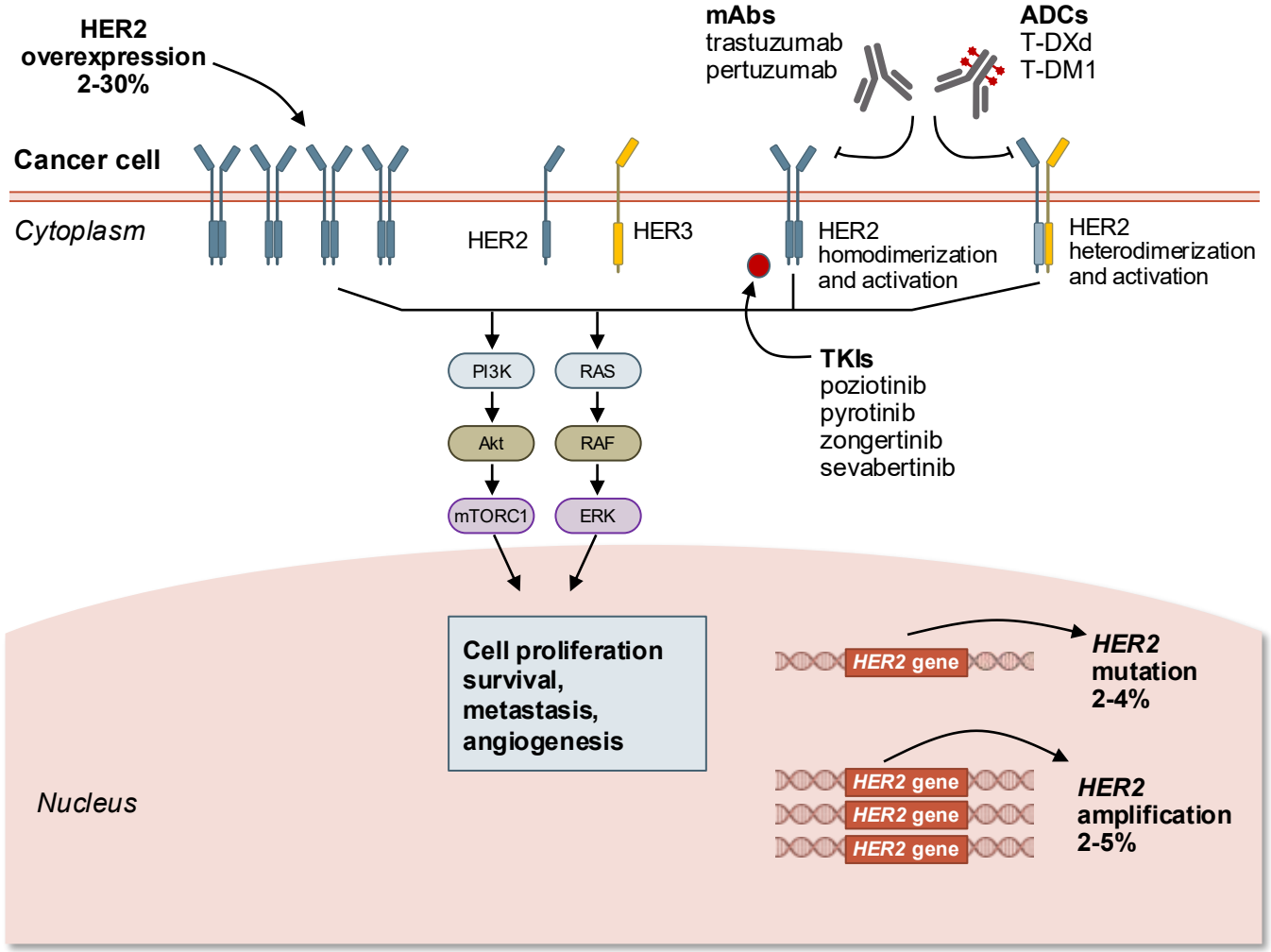
Patients with *HER2* mutations were found to be **more likely to experience brain metastases** during treatment in comparison with *KRAS*-mutant and *EGFR*-mutant diseases (28% *HER2* vs 8% *KRAS* vs 16% *EGFR*)[2,3]

Lung adenocarcinomas with *HER2* mutations **exhibit a more aggressive behaviour** on enhanced CT compared with *KRAS*- and *EGFR*-mutant controls, and show a more frequent nodal metastatic spread compared with *KRAS*-mutant controls[3]

CT, computed tomography; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

1. Lee Y, et al. Mod Pathol. 2024;37:100490; 2. Ismail A, et al. Front Oncol. 2025;15:1624124; 3. Ren S, et al. ESMO Open. 2022;7(1):100395

TARGETING *HER2* IN LUNG CANCERS: EVOLVING TREATMENT LANDSCAPE AND DRUG DEVELOPMENT STRATEGIES

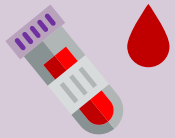


Adapted from Reinhorn et al. *2025*

ADC, antibody-drug conjugate; mAb, monoclonal antibody; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

Reinhorn D, et al. Cancer. 2025:131 Suppl 1:e35780; Das D and Newsom-Davis T, personal communication

CLINICAL TESTING OPTIONS FOR ACTIVATING *HER2* MUTATIONS IN NSCLC

Next-generation sequencing (NGS)[1-5] *Recommended Method*	PCR/Sanger sequencing[1-5]	Liquid biopsy (ctDNA)[1]
		
• Captures all actionable alterations (including exon 20 insertions & point mutations)	• Detects known hotspot mutations	• Non-invasive, plasma-based
• **Tissue (preferred)** • Can be based on either the analysis of DNA or RNA • Broad panel profiling allows simultaneous multiple-gene assays to detect actionable alterations • Turnaround time can vary if samples have to be sent to an external lab	• **Tissue (preferred)** • Can miss rare exon 20 insertions • Single-gene testing or targeted hotspot panels • Generally, a faster turnaround time than NGS	• **Blood/plasma sample** • Useful when tissue not available or sample insufficient • Sensitivity is dependent on disease load • Negative results should be confirmed using tissue

HER2 mutation detected

Eligible for Targeted Therapy[6]:

Trastuzumab deruxtecan (ADC)

or

HER2-selective TKIs

sevabertinib, zongertinib

ADC, antibody drug conjugate; ctDNA, circulating tumour DNA; NSCLC, non-small cell lung cancer; PCR, polymerase chain reaction; TKI, tyrosine kinase inhibitor

1. Rolfo C, et al. J Thorac Oncol. 2021;16:1647-62; 2. Riudavets M, et al. ESMO Open. 2021;6 (5):100260; 3. Ren S, et al. ESMO Open 2022; 7 (1):100395; 4. Dorta-Suarez M, et al. Cancer Treatment Reviews 2024; 124: 102671; 5. Bastvina CM, et al. JMCP 2024; 30(12): 1467-1478; 6. NCCN. Non-small cell lung cancer (v5.2026). Available here (accessed March 17, 2026)

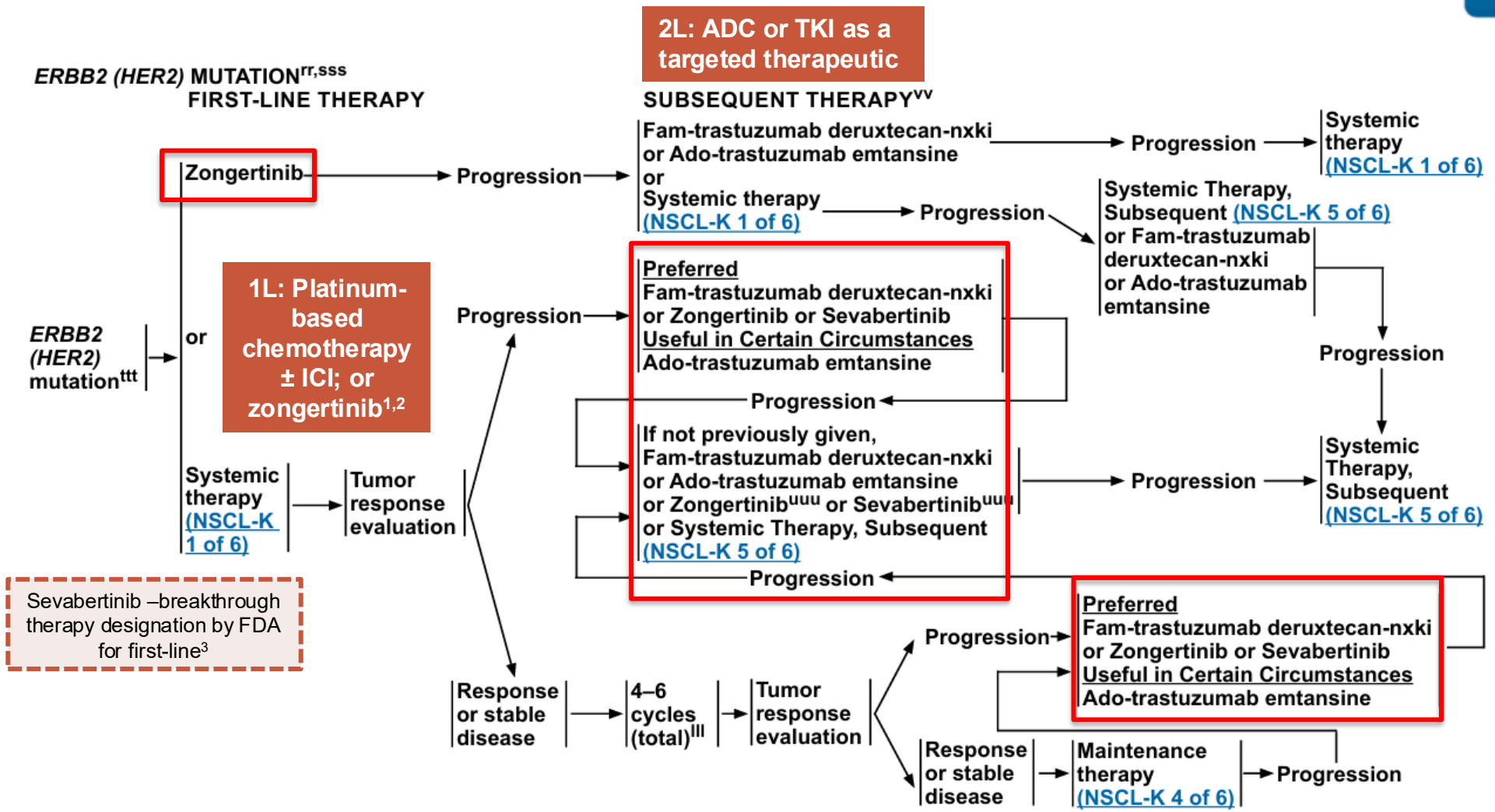
GUIDELINE RECOMMENDATIONS FOR TREATING *HER2*-MUTANT NSCLC

NSCLC, non-small cell lung cancer

CURRENT STANDARD OF CARE GUIDELINES (US)[1]

National Comprehensive Cancer Network®

v5.2026



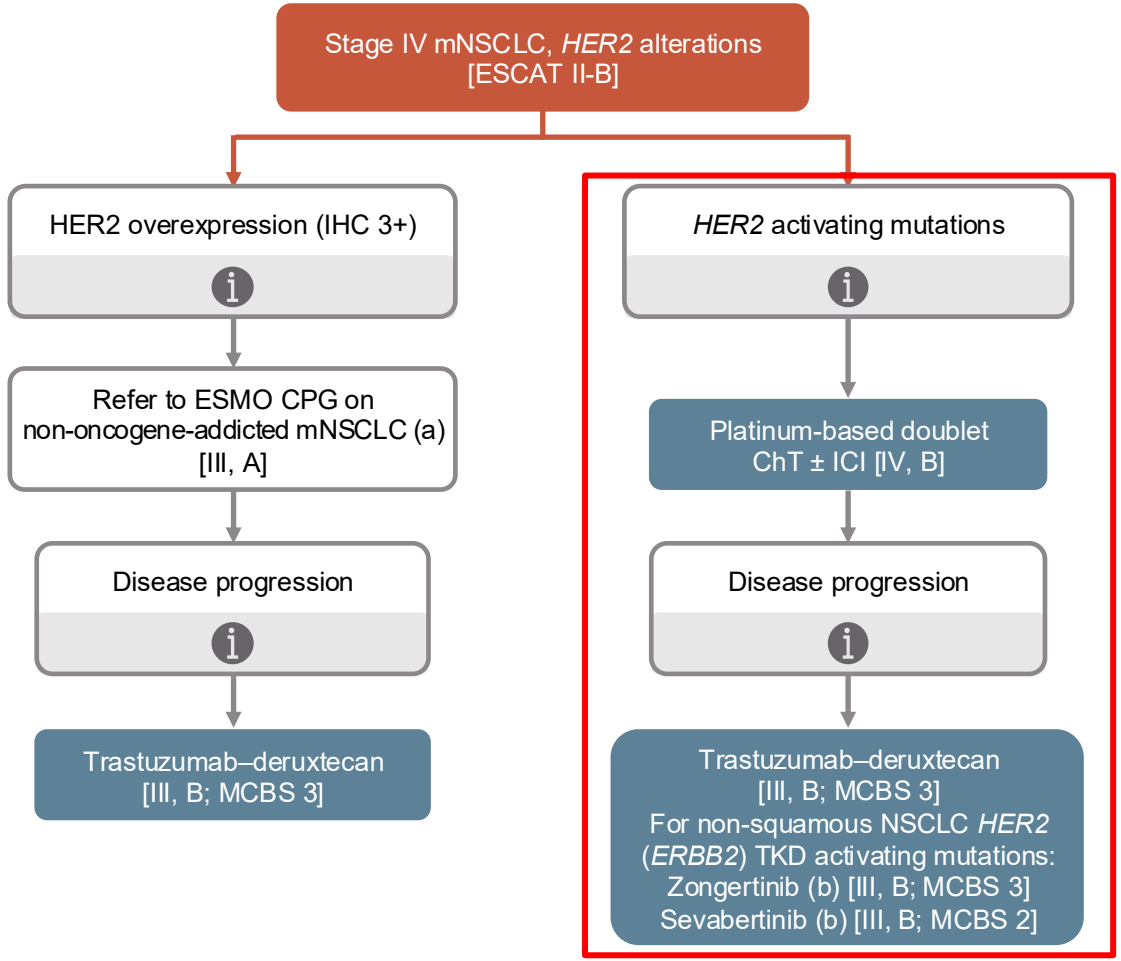
1/2L, first/second-line; ADC, antibody-drug conjugate; FDA, US Food and Drug Administration, ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; US, United States

1. NCCN. Non-small cell lung cancer (v5.2026). Available here (accessed March 17, 2026); 2. Aliaga PT, et al. Molecules 2025; 30: 2645; 3. Bayer Global. Bayer receives Breakthrough Therapy Designation in the U.S. and China for sevabertinib as a first-line treatment for patients with HER2-mutant non-small cell lung cancer. Available here (accessed March 20, 2026)

CURRENT STANDARD OF CARE GUIDELINES (EU)

STAGE IV mNSCLC, MOLECULAR TESTS POSITIVE FOR HER2

V1.3
Feb 2026



ChT, chemotherapy; ChT, chemotherapy; CPG, Clinical Practice Guideline; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; EU, European Union; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MCBS, ESMO-Magnitude of Clinical Benefit Scale; (m)NSCLC, (metastatic) non-small-cell lung cancer; TKD, tyrosine kinase domain

Hendricks LE, et al. Ann Oncol. 2023;34(4):339-357; ESMO Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guideline, v1.3 - February 2026. Available here (accessed March 20, 2026)

PATIENT FACTORS TO CONSIDER WHEN SELECTING THERAPY FOR *HER2*-MUTANT NSCLC

Performance Status & Comorbidities	Prior Therapies & Line of Treatment	PD-L1 Expression & Immunotherapy Suitability	Organ Function & Safety Monitoring	Patient Preference & Logistics
• ECOG PS 0–2 patients tolerate platinum-based chemotherapy ± immunotherapy better[1] • Comorbidities may influence chemotherapy or targeted therapy choice	• First-line: platinum-based chemo ± immunotherapy or zongertinib[a] [*Sevabertinib also encouraging data 1st line*][2-5] • Second-line: ADCs (trastuzumab deruxtecan) or HER2-selective TKIs (sevabertinib, zongertinib)[3]	• Low or negative PD-L1 often predicts limited benefit from ICI monotherapy; supports chemo-ICI combinations[2,3]	• Lung disease: risk of ILD with trastuzumab deruxtecan[6] • Renal/hepatic impairment: may require dose adjustments for TKIs or chemo[7]	• Oral TKIs (sevabertinib, zongertinib) vs IV ADCs (trastuzumab deruxtecan) • Frequency of clinic visits, infusion schedules, monitoring requirements

[a] Based on FDA approval and NCCN treatment guidelines v5.2026[2,4]

ADC, antibody drug conjugate; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; IV, intravenous; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor

1. Kataoka S, et al. Annals of Oncology 2024; 34_suppl 4: S1646-S1647; 2. Trillo Aliaga P, et al. Molecules 2025;30:2645; 3. NCCN. Non-small cell lung cancer (v5.2026). Available here (accessed March 17, 2026); 4. Bayer Global. Bayer receives Breakthrough Therapy Designation in the U.S. and China for sevabertinib as a first-line treatment for patients with HER2-mutant non-small cell lung cancer. Available here (accessed March 20, 2026); 5. Boehringer Ingelheim. FDA approves HERNEXEOS®, the first targeted therapy for adults with HER2-mutant advanced NSCLC as an initial treatment option. Available here (accessed March 20, 2026); 6. Sharma P et al. J Natl Compre Canc Netw. 2025;23(3.5):CLO25-067; 7. Zhao D, et al. Oncol Rep. 2021;45:413-426

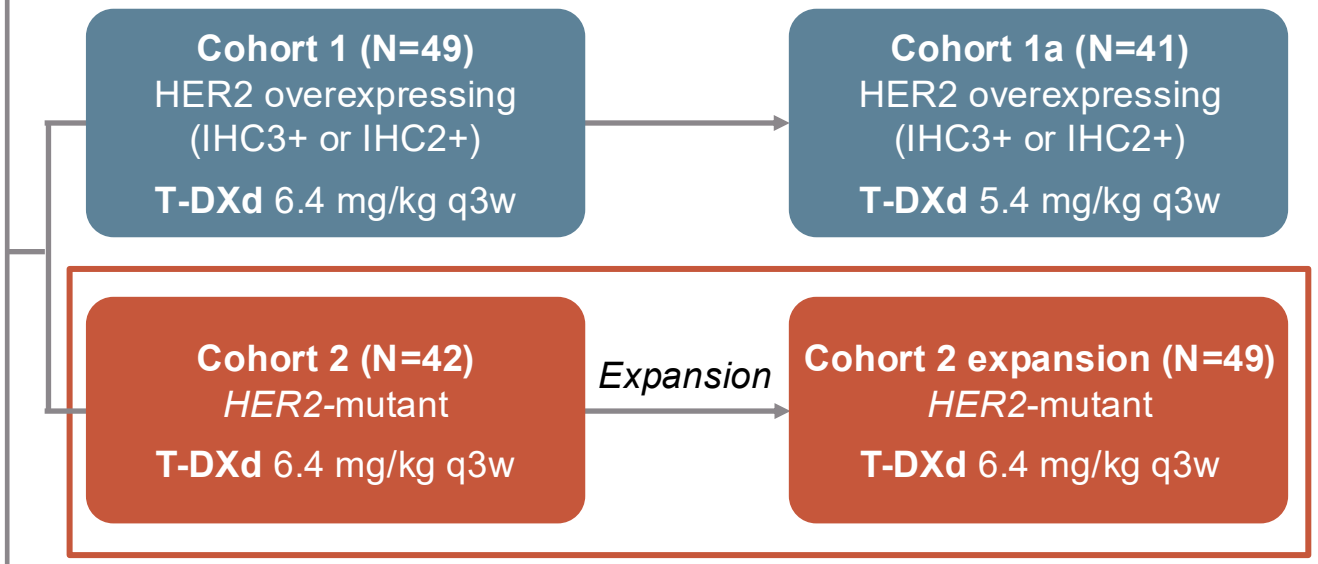
KEY CLINICAL DATA
ANTIBODY-DRUG CONJUGATES

DESTINY-LUNG01: STUDY DESIGN

PREVIOUSLY TREATED *HER2*-MUTANT NSCLC

Key Eligibility Criteria

- Unresectable/metastatic non-squamous NSCLC
- Relapsed from or is refractory to standard treatment
- HER2-expressing or *HER2*-activating mutation
- No prior HER2-targeted therapy, except pan-HER2 TKIs
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline
- ECOG PS of 0 or 1



Primary Endpoints:

- Confirmed ORR by independent review

Secondary Endpoints:

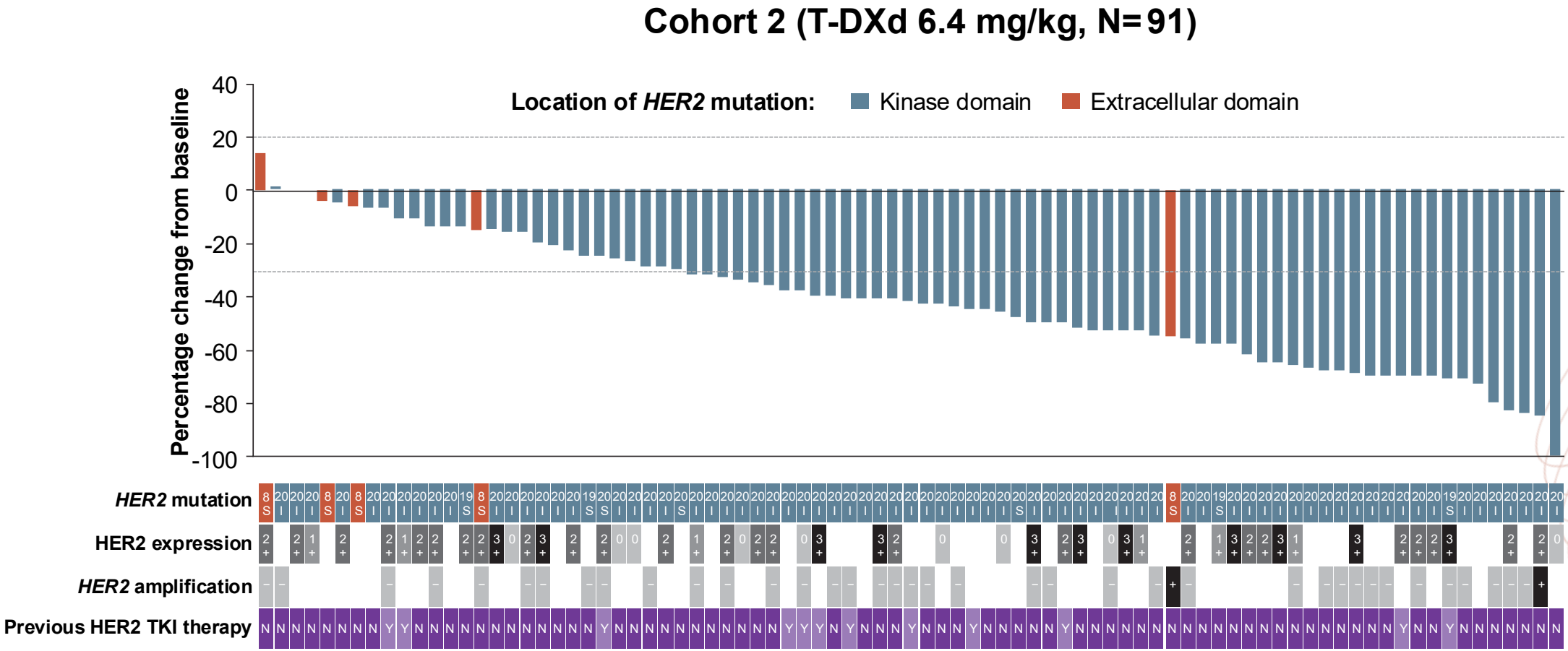
- ORR (INV assessment)
- DoR
- PFS
- OS
- DCR

CNS, central nervous system; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; INV, investigator; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

ClinicalTrials.gov identifier. NCT03505710; Li BT. N Engl J Med. 2022;386(3):241-51; Smit EF, et al. Abstract 975P, ESMO 2022 (poster session)

DESTINY-LUNG01: *HER2*-MUTANT NSCLC (COHORT 2)

ANTI-TUMOUR ACTIVITY[a]



[a] Best percentage change in sum of largest tumour diameters

NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y/N, yes/no

Li BT. N Engl J Med. 2022;386(3):241-51

DESTINY-LUNG01: *HER2*-MUTANT NSCLC (COHORT 2)

EFFICACY OUTCOMES

Response to Trastuzumab Deruxtecan as Assessed by Independent Central Review

Response assessment	Patients (N=91)
Confirmed objective response, n (%) [95% CI]	50 (55) [44-65]
Best response, n (%)	
Complete response	1 (1)
Partial response	49 (54)
Stable disease	34 (37)
Progressive disease	3 (3)
Response could not be evaluated	4 (4)
DCR, n (%) [95% CI]l	84 (92) (85-97)
Median time to response (range), months	1.5 (1.2-9.3)
Median duration of response (95% CI), months	9.3 (5.7-14.7)

HER2-mutant subgroup:
- ORR: 55%
- DCR: 92%

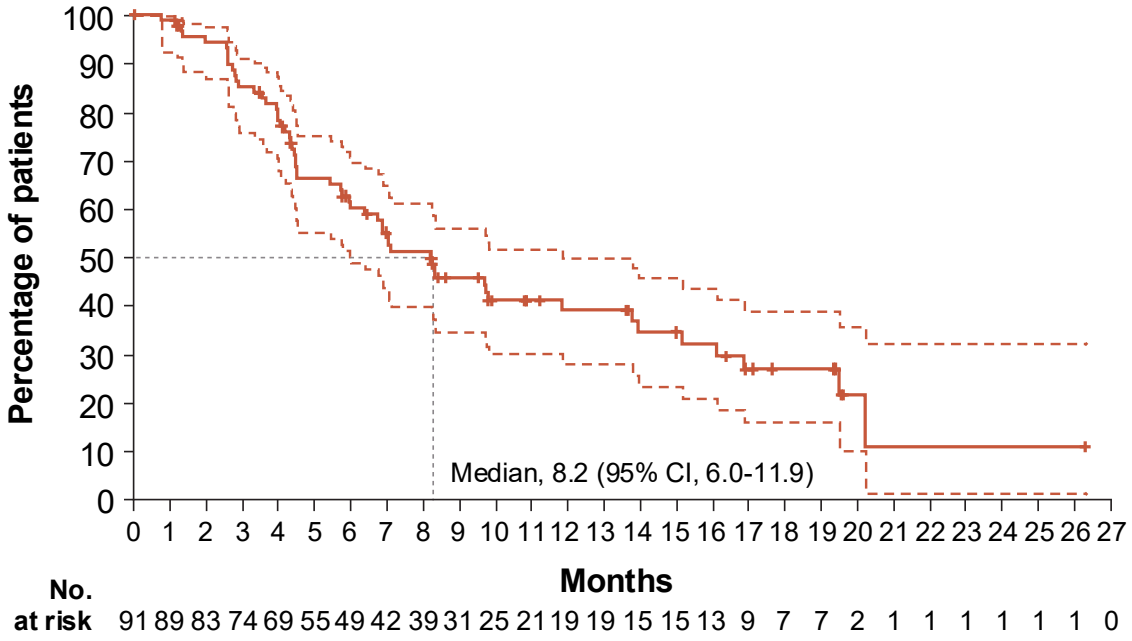
CI, confidence interval; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, objective response rate

Li BT, et al. N Engl J Med. 2022;386:241-51

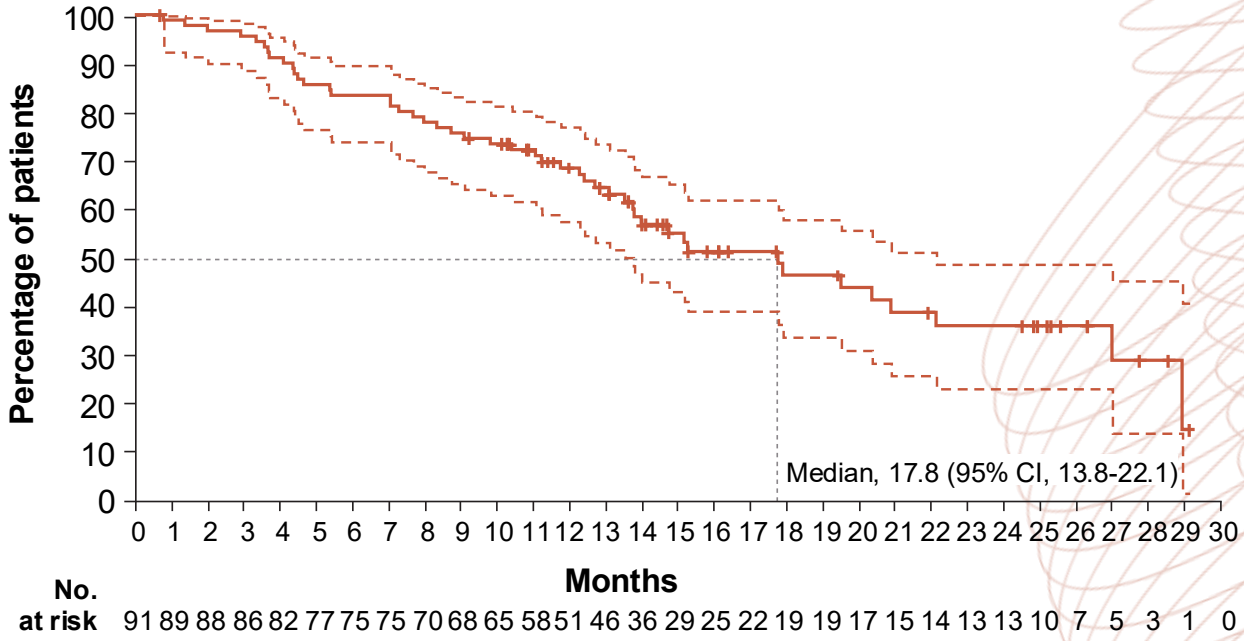
DESTINY-LUNG01: *HER2*-MUTANT NSCLC (COHORT 2)

HER2-MUTANT SUBGROUP: MEDIAN PFS: 8.2 mo, MEDIAN OS: 17.8 mo

Progression-free survival



Overall survival



CI, confidence interval; mo, months; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

Li BT, et al. N Engl J Med. 2022;386:241-51

DESTINY-LUNG01: *HER2*-MUTANT NSCLC (COHORT 2)

SAFETY

- 97% incidence of TRAEs, 46% grade ≥3
- 34% required dose reduction
- 25% discontinued treatment
- Main adverse effect: interstitial lung disease (26% incidence, 2 deaths)

Most common investigator-reported drug-related adverse events in the study population

Event	Grade 1-2	Grade 3	Grade 4	Grade 5	Overall
	Patients, n (%) (N=91)				
Drug-related adverse event	46 (51)	37 (41)	4 (4)	1 (1)[a]	88 (97)
Drug-related adverse events with ≥20% incidence					
Nausea	58 (64)	8 (9)	0	0	66 (73)
Fatigue	42 (46)	6 (7)	0	0	48 (53)
Alopecia	42 (46)	0	0	0	42 (46)
Vomiting	33 (36)	3 (3)	0	0	36 (40)
Neutropenia	15 (16)	14 (15)	3 (3)	0	32 (35)
Anemia	21 (23)	9 (10)	0	0	30 (33)
Diarrhea	26 (29)	2 (2)	1 (1)	0	29 (32)
Decreased appetite	27 (30)	0	0	0	27 (30)
Leukopenia	17 (19)	4 (4)	0	0	21 (23)
Constipation	20 (22)	0	0	0	20 (22)

[a] One patient had grade 5 (i.e., fatal) pneumonitis that was assessed as drug-related by the investigator (subsequently adjudicated as interstitial lung disease). Another patient had grade 3 interstitial lung disease, as reported by the investigator, and died; the reported interstitial lung disease was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee

NSCLC, non-small cell lung cancer; TRAE, treatment-related adverse event

Li BT, et al. N Engl J Med. 2022;386:241-51

DESTINY-LUNG01: DRUG-RELATED INTERSTITIAL LUNG DISEASE

RISK OF DEVELOPING ILD OR PNEUMONITIS WAS 26.4%

HER2-Mutant NSCLC Receiving T-DXd 6.4 mg/kg q3w (N=91)						
Patients, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Incidence of ILD	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)	24 (26.4)

- The median time to onset of first reported drug-related ILD was 141 days (range, 14-462 days), with a median duration of 43 days (95% CI, 24-94)
- 75% of adjudicated drug-related ILD/pneumonitis cases were of low grade (grade 1 or 2)
- 21 of 24 patients with adjudicated drug-related ILD/pneumonitis received ≥1 dose of glucocorticoids. However, not all glucocorticoid treatment was administered per the ILD management guidelines

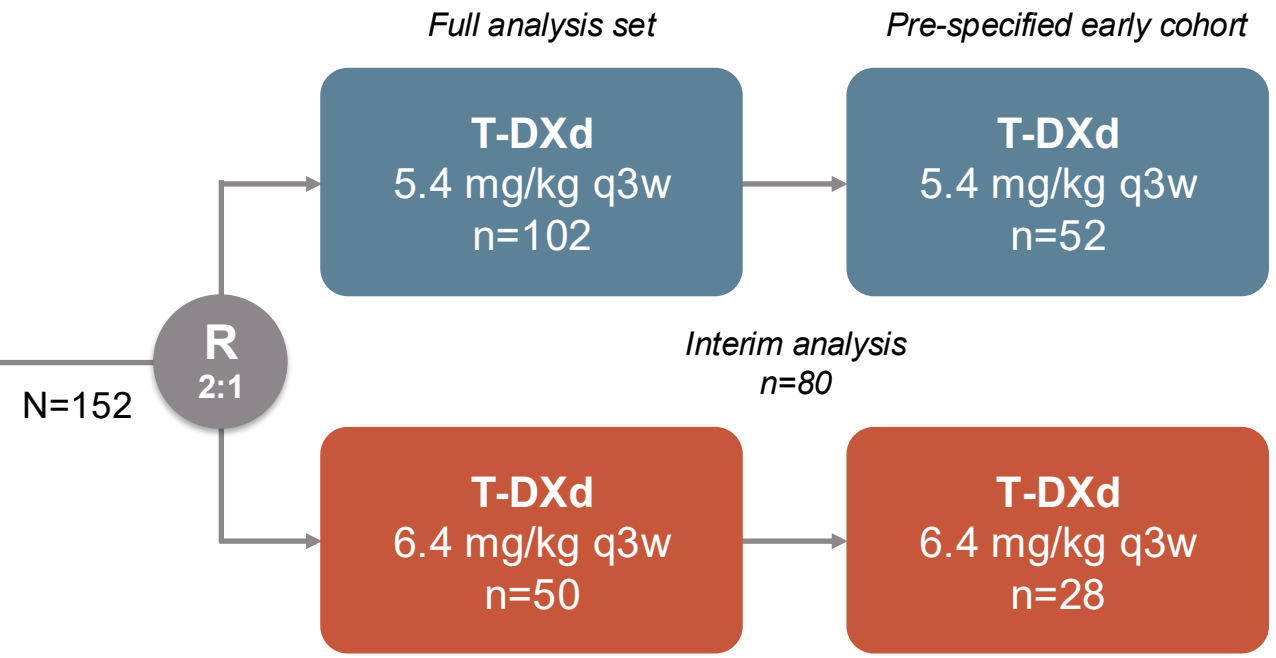
CI, confidence interval; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; q3w, every 3 weeks; T-DXd, trastuzumab deruxtecan

Li BT, et al. N Engl J Med. 2022;386:241-251 (Supplementary Appendix)

DESTINY-LUNG02: STUDY DESIGN[1,2]

Patient Population

- Pathologically confirmed mNSCLC with an activating *HER2* mutation
- Prior Tx on a platinum-based therapy in the metastatic or locally advanced setting with progression during or after Tx, or discontinuation due to toxicities
- At least 1 measurable lesion, able to provide solid tissue sample
- ECOG PS = 0-1



FDA approved (5.4 mg/kg q3w) August 11, 2022 for patients with previously treated *HER2*-mutant NSCLC[3]; first-line use under investigation[4]

Primary Endpoint:

- ORR per RECIST v1.1 by BICR

Secondary Endpoints:

- ORR per RECIST v1.1 by investigator assessment
- DoR, DCR, PFS by BICR and INV
- OS
- Safety

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDA, US Food and Drug Administration; INV, investigator-assessed; mNSCLC, (metastatic) non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; Tx, treatment

1. ClinicalTrials,gov identifier: NCT04644237; 2. Goto K. Ann Oncol. 2022;33 (suppl_7):S808-S869 (ESMO 2022, oral presentation); 3. Mehta GU, et al. The Oncologist 2024; 29: 667-671; 4. ClinicalTrials.gov identifier: NCT05048797

DESTINY-LUNG02: EFFICACY AND SAFETY

EFFICACY

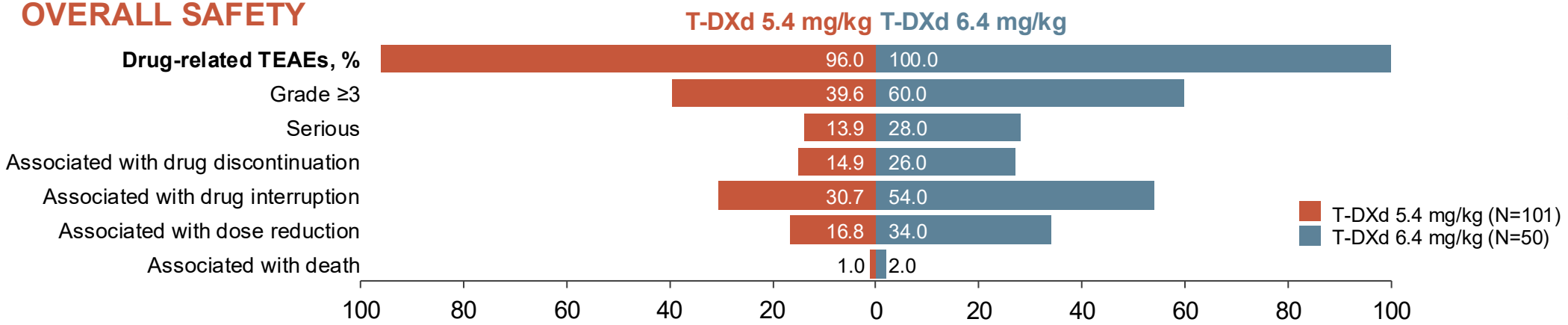
Efficacy summary (BICR)	T-DXd 5.4 mg/kg n=102	T-DXd 6.4 mg/kg n=50
cORR, n (%) [95% CI] CR | PR, n (%) SD | PD, n (%) Non-evaluable, n (%)	51 (50.0) [39.9–60.1] 3 (2.9) | 48 (47.1) 44 (43.1) | 4 (3.9) 3 (2.9)	28 (56.0) [41.3-70.0] 4 (8.0) | 24 (48.0) 18 (36.0) | 2 (4.0) 2 (4.0)
DCR, n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0 [80.8-97.8]
Median DoR (95% CI), months	12.6 (6.4-NE)	12.2 (7.0-NE)
Median PFS (95% CI), months	10.0 (7.7-15.2)	12.9 (7.2-16.7)
Median OS (95% CI), months	19.0 (14.7-NE)	17.3 (13.8-NE)

Median follow-up of 15.8 months (T-DXd 5.4 mg/kg) and 16.5 months (T-DXd 6.4 mg/kg)

SAFETY

Adjudicated as drug-related ILD, n (%)	T-DXd 5.4 mg/kg N=101	T-DXd 6.4 mg/kg N=50
Total	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)
Time since prior anti-PD-(L)1 therapy, n/N (%)		
>3 months	5/44 (11.4)	10/28 (35.7)
≤3 months	6/30 (20.0)	3/11 (27.3)
No prior therapy	4/27 (14.8)	3/11 (27.3)

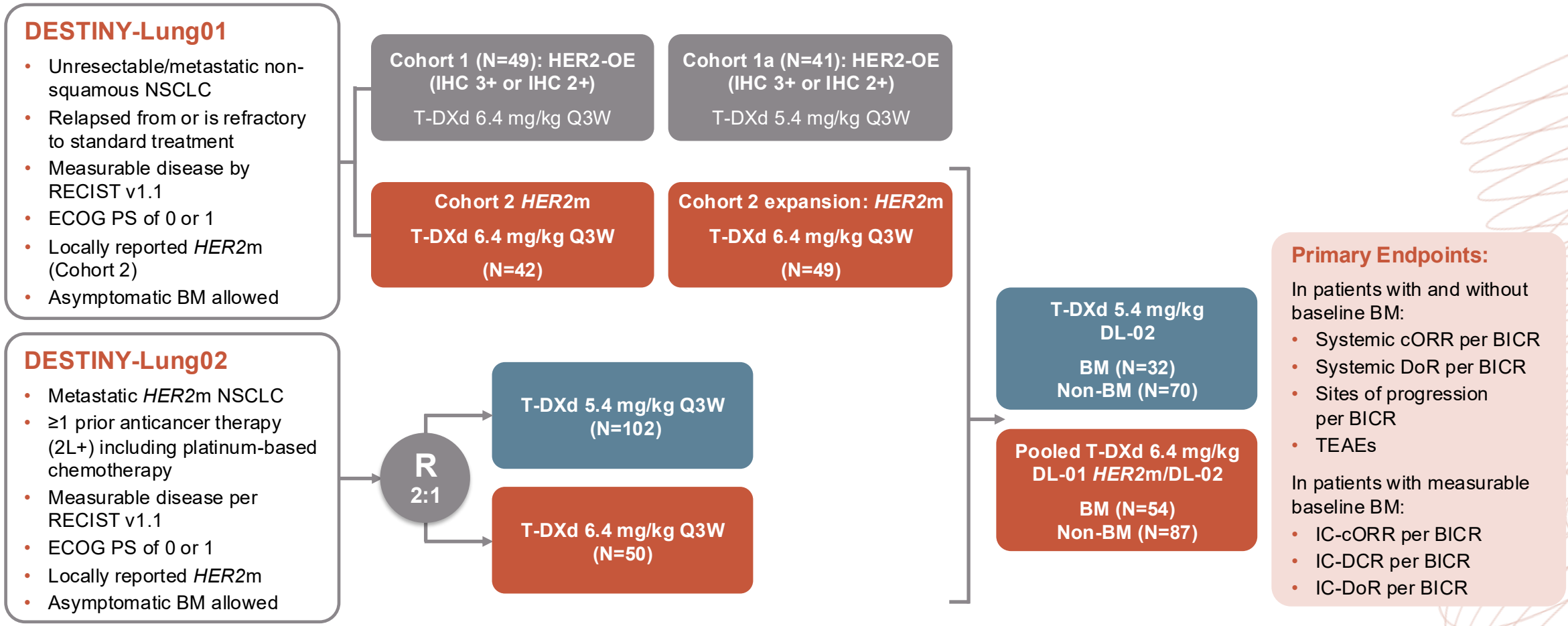
OVERALL SAFETY



BICR, blinded independent central review; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; ILD, interstitial lung disease; NE, not estimable; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death-(ligand) 1; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment emergent adverse event

Jänne PA, et al. J Thorac Oncol. 2025; 20(12):1814-1828 (including supplementary material)

DESTINY-LUNG01 AND DESTINY-LUNG02: BRAIN METASTASIS EXPLORATORY POOLED ANALYSIS



2L, second-line; BICR, blinded independent central review; BM, brain metastases; cORR, confirmed objective response rate; DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group performance status; HER2m, HER2 mutant; IC, intracranial; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; OE, overexpression; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.

Li B, et al. Ann Oncol. 2023;34:s762-S763. Oral presentation (1321MO) presented at ESMO 2023

DESTINY-LUNG01 AND -LUNG02: SYSTEMIC OBJECTIVE RESPONSE RATE (BICR) WITH OR WITHOUT BMs

T-DXd showed antitumour activity in patients with previously treated *HER2*-mutant metastatic NSCLC +/- BMs

Baseline BM status	T-DXd 5.4 mg/kg DL-02 (n=102)				Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 (n=141)			
	With measurable BMs n=14	With non-measurable BMs n=18	Overall n=32	Without BM n=70	With measurable BMs n=30	With non-measurable BMs n=24	Overall n=54	Without BM n=87
ORR, n (%) [95% CI]	9 (64) [35-87]	6 (33) [13-59]	15 (47) [29-65]	35 (50) [38-62]	13 (43) [26-63]	14 (58) [37-78]	27 (50) [36-64]	51 (59) [48-69]
CR, n (%)	0	0	0	1 (1)	0	0	0	3 (3)
PR, n (%)	9 (64)	6 (33)	15 (47)	34 (49)	13 (43)	14 (58)	27 (50)	48 (55)
SD, n (%)	5 (36)	9 (50)	14 (44)	31 (44)	14 (47)	9 (38)	23 (43)	29 (33)
PD, n (%)	0	2 (11)	2 (6)	2 (3)	1 (3)	1 (4)	2 (4)	3 (3)
NE, n (%)	0	1 (6)	1 (3)	2 (3)	2 (7)	0	2 (4)	4 (5)
Missing, n (%)	0	0	0	2 (3)	0	0	0	4 (5)
DCR, n (%) [95% CI]	14 (100) [77-100]	15 (83) [59-96]	29 (91) [75-98]	66 (94) [86-98]	27 (90) [74-98]	23 (96) [79-100]	50 (93) [82-98]	80 (92) [84-97]
Median DoR [95% CI], months	5.0 [3.6-NE]	4.6 [2.8-NE]	4.6 [4.2-9.5]	16.8 [8.7-NE]	5.8 [4.6-NE]	NE [2.9-NE]	7.2 [5.3-NE]	14.1 [9.3-NE]
Median PFS [95% CI], months	7.1 [5.4-NE]	6.9 [5.5-9.7]	7.1 [5.5-9.7]	18.0 [8.5-NE]	6.4 [4.0-7.1]	8.5 [4.3-NE]	7.1 [4.5-9.6]	11.9 [7.2-16.1]
Median OS [95% CI], months	13.6 [5.4-NE]	NE [6.2-NE]	13.6 [9.4-NE]	19.5 [14.9-NE]	11.2 [7.1-14.8]	21.1 [13.8-NE]	13.8 [11.1-19.5]	27.9 [17.8-NE]

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; CR, complete response; DCR, disease control rate; DL- 01/02, DESTINY-LUNG01/02; DoR, duration of response; HER2m, HER2 mutant; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan

Jänne PA, et al. JAMA Network Open. 2025;8(11):e2543107. doi:10.1001/jamanetworkopen.2025.43107

DESTINY-LUNG01 AND-LUNG02: INTRACRANIAL RESPONSE (BICR) WITH OR WITHOUT PRIOR THERAPY

IC RESPONSES WERE SIMILAR IN PATIENTS WITH OR WITHOUT PRIOR BM TREATMENT AMONG PATIENTS WITH BM AT BASELINE

Baseline BM status	T-DXd 5.4 mg/kg DL-02 (n=102)			Pooled T-DXd 6.4 mg/kg DL-01 *HER2*m/DL-02 (n=141)		
	With measurable BMs n=14	With prior treatment n=8	Without prior treatment n=6	With measurable BMs n=30	With prior treatment n=14	Without prior treatment n=16
IC-ORR, n (%) [95% CI]	7 (50) [23-77]	4 (50) [16-84]	3 (50) [12-88]	9 (30) [15-49]	3 (21) [5-51]	6 (38) [15-65]
CR, n (%)	3 (21)	0	3 (50)	0	0	0
PR, n (%)	4 (29)	4 (50)	0	9 (30)	3 (21)	6 (38)
SD, n (%)	6 (43)	3 (38)	3 (50)	13 (43)	7 (50)	6 (38)
PD, n (%)	1 (7)	1 (13)	0	4 (13)	3 (21)	1 (6)
NE, n (%)	0	0	0	2 (7)	0	2 (13)
Missing, n (%)	0	0	0	2 (7)	1 (7)	1 (6)
IC-DCR, n (%) [95% CI]	13 (93) [66-100]	7 (88) [47-100]	6 (100) [54-100]	22 (73) [54-88]	10 (71) [42-92]	12 (75) [48-93]
Median IC-DoR [95% CI], months	9.5 [3.6-NE]	7.1 [3.6-NE]	9.5 [NE-NE]	4.4 (2.9-10.2)	4.4 [2.9-NE]	5.6 [2.9-NE]
Median time to IC progression [range], months	NA	2.8 [1.3-10.9]	NE [NE-NE]	NA	2.6 [1.2-6.9]	5.6 [0.6-14.0]

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; DoR, duration of response; HER2m, HER2 mutant; IC, intracranial; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan

Jänne PA, et al. JAMA Network Open. 2025;8(11):e2543107. doi:10.1001/jamanetworkopen.2025.43107

DESTINY-LUNG04: STUDY DESIGN

FIRST-LINE *HER2*-MUTANT NSCLC

Patient Population

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic non-squamous NSCLC with *HER2* exon 19 or 20 mutations
- Naïve to systemic therapy
- No known other targetable oncogenic mutations/alterations

N=454

R
1:1

Arm 1: T-DXd

Arm 2: Standard of care
Platinum (cisplatin or carboplatin) + pemetrexed + pembrolizumab

Primary Endpoints:
- PFS, BICR

Secondary Endpoints:
- OS
- PFS (INV)
- ORR, DoR
- CNS-PFS
- Safety

BICR, blinded independent central review; CNS, central nervous system; DoR, duration of response; INV, investigator-assessed; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every 3 weeks; R, randomisation; T-DXd, trastuzumab deruxtecan

Li BT, et al. J Clin Oncol. 2022;40 (No 16_suppl): TPS9137 (ASCO 2022, poster presentation); ClinicalTrials.gov identifier. NCT05048797

ANTIBODY DRUG CONJUGATES IN DEVELOPMENT FOR *HER2*-MUTANT NSCLC (ONGOING TRIALS)[1]

Trial	Stage	NSCLC population	Treatment line	Therapeutic regimen	Primary Endpoint
DESTINY-Lung04 (NCT05048797)[2]	Phase 3	*HER2* (ex19 or ex20) mutations	first-line	Experimental group: T-DXd Control group: platinum + pemetrexed + T-DXd	PFS
ELPIS (NCT06250777)	phase 2	*HER2* mutations (asymptomatic brain metastases)	≥ first-line	T-DXd	Intracranial PFS
HUDSON (NCT03334617)	Phase 2	Umbrella trial: PD on ICI and CT (includes pts with HER2 overexpressing or *HER2* mutant tumours)[3]	≥ second-line	Durvalumab + T-DXd (among other combinations)	ORR
NCT05482568	Phase 1/2	*HER2* alterations (overexpression, amplification, or mutation)	≥ second-line	Group 1: Trastuzumab rezetecan + pyrotinib Group 2: Trastuzumab rezetecan + adebrelimab	DLT; ORR (efficacy expansion stage)
NCT04042701	Phase 1	HER2 protein overexpression; *HER2* gene mutations	≥ second-line	T-DXd + pembrolizumab	DLT; ORR
NCT04311034	Phase 1b	HER2 protein overexpression; *HER2* mutations	≥ second-line	Disitamab vedotin	ORR, DCR, PFS, DoR, OS
NCT05141786	phase 2	*HER2* mutations	≥ second-line	MRG002	ORR
NCT05745740	Phase 1/2b	*HER2* mutations	≥ second-line	Disitamab vedotin + pyrotinib	MTD
NCT05650879	Phase 1	*HER2* mutations	≥ second-line	Group 1: ELVN-002 (TKI) Group 2:T-DXd + ELVN-002 (TKI)	DLT, safety

Data derived from ClinicalTrials.gov (March 08, 2026) and Liu et al. 2025

CT, chemotherapy; DCR, disease control rate; DLT, dose-limiting toxicities; DoR, duration of response; ex, exon; ICI, immune checkpoint inhibitor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

1. Liu J, et al. J Transl Med. 2025;23:600; 2. Li BT, et al. J Clin Oncol. 2022;40 (No 16_suppl): TPS9137 (ASCO 2022, poster presentation); 3. Cheema P, et al. J Immunother Cancer 2023;11(Suppl 1):A1–A1731. Available here (accessed March 20, 2026)

KEY CLINICAL DATA
TYROSINE KINASE INHIBITORS

TYROSINE KINASE INHIBITORS FOR *HER2*-MUTANT NSCLC

NEWER TKIs ARE DESIGNED TO BE MORE SELECTIVE FOR *HER2* MUTATIONS WHILE MINIMISING WILD-TYPE EGFR INHIBITION, IMPROVING TOLERABILITY AND CNS PENETRATION

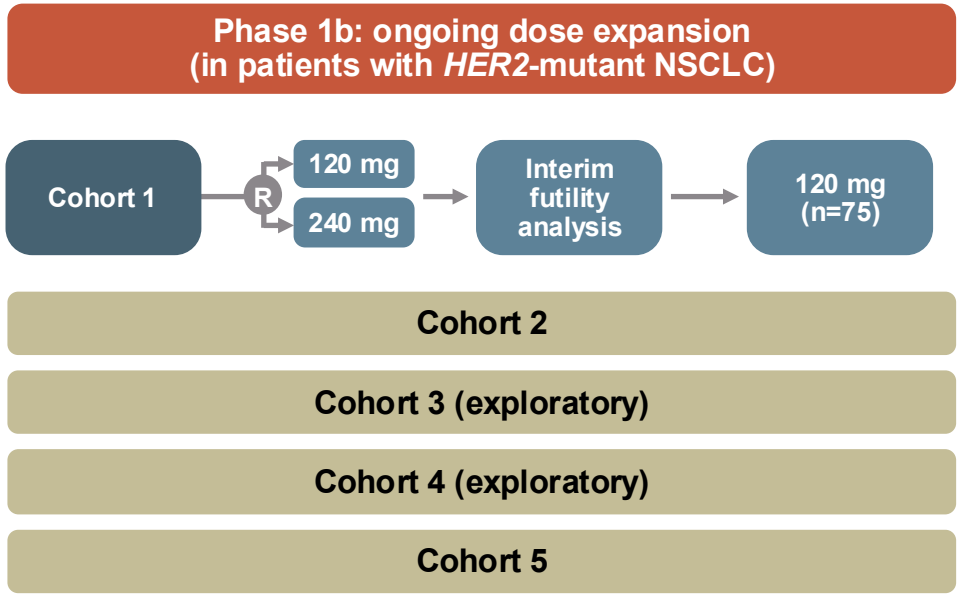
Pan-HER (non-selective) TKIs
Pyrotinib
Next-generation *HER2*-mutant TKIs
***HER2*-selective (EGFR sparing):** Zongertinib ELVN-002
***HER2*-focused (dual EGFR/HER2):** Sevabertinib NVL-330
Emerging: IAM1363

- **Targeted Approach:**
  - **Next generation *HER2*-mutant TKIs** may offer a better therapeutic index vs. early **pan-HER TKIs** like pyrotinib, which is limited by severe toxicities (rash, diarrhea)
- **Recent Developments:**
  - **Zongertinib**
  - **Sevabertinib**

CNS, central nervous system; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

BEAMION LUNG-1: STUDY DESIGN

- **Zongertinib, a novel HER2-specific TKI**, binds selectively and covalently to the HER2 tyrosine kinase domain while sparing wild-type EGFR and limiting EGFR-related adverse events
- **Beamion LUNG-1** is a Phase 1a/1b, open-label trial, is evaluating the safety and efficacy of zongertinib in patients with *HER2* aberration-positive solid tumours (Phase 1a) and *HER2* mutation-positive NSCLC (Phase 1b)



NCT04886804

Cohort 1: Pre-treated NSCLC[a,b] with a *HER2* TKD mutation

Cohort 2: Treatment-naïve NSCLC with *HER2* TKD mutation

Cohort 3: NSCLC with a non-TKD *HER2* mutation or *HER2* TKD mutation-positive squamous NSCLC, pre-treated[a]

Cohort 4: NSCLC with active brain metastases with *HER2* TKD mutation

Cohort 5: Pre-treated[a] NSCLC with a *HER2* TKD mutation and prior treatment with HER2 directed ADCs

Phase 1b primary endpoint

- ORR by RECIST

Key inclusion criteria

- Patients with *HER2* mutation-positive NSCLC
- Received ≥1 line of platinum-based combination chemotherapy (Cohorts 1,3,5)

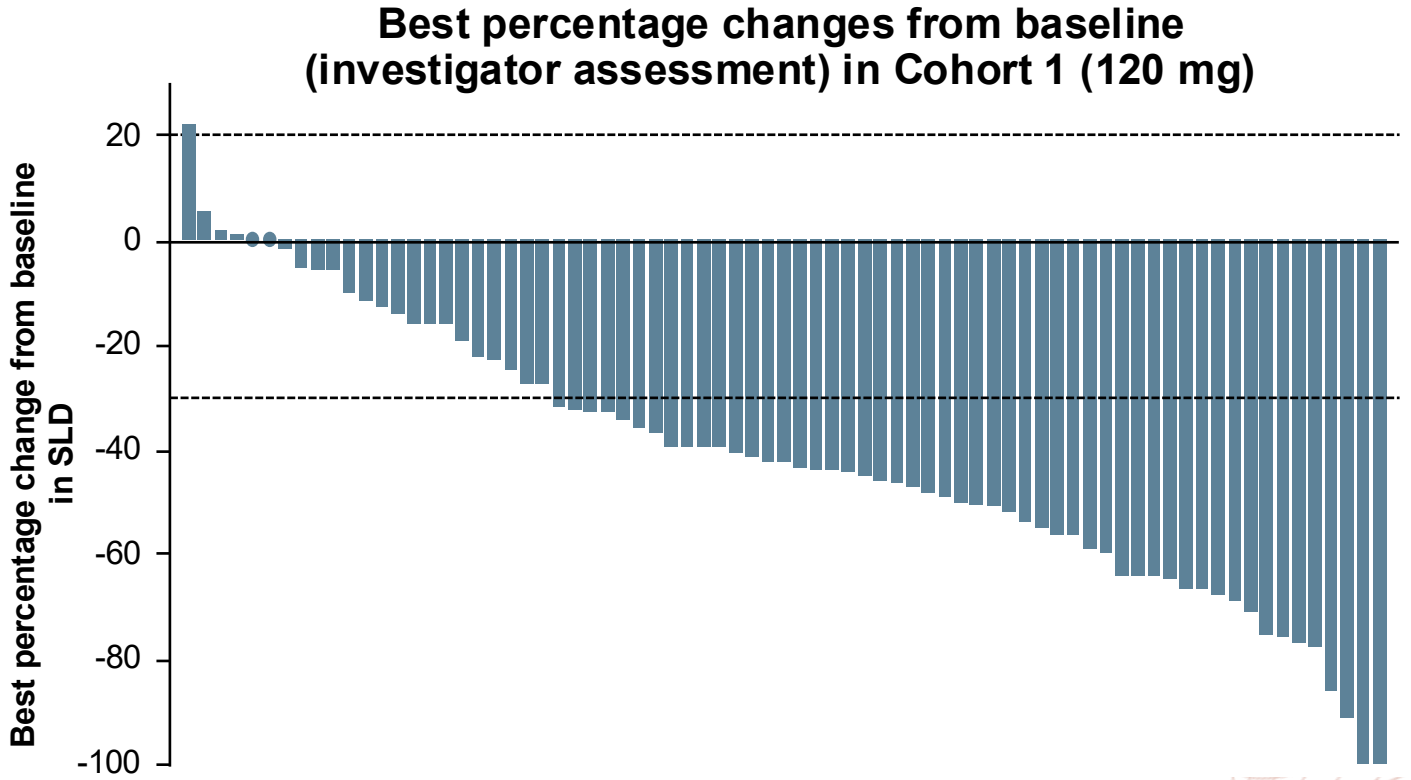
[a] Received ≥1 line of platinum-based combination chemotherapy; [b] excluding patients treated with ADCs

ADC, antibody-drug conjugate; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

Ruiter G, et al. Abstract PL04.04, WCLC 2024 (oral presentation); Heymach JV, et al. N Engl J Med. 2025; 392:2321-33

BEAMION LUNG-1: ZONGERTINIB IN PRE-TREATED PATIENTS: TUMOUR RESPONSE (COHORT 1)

Tumour response[a] by RECIST, v1.1 and clinical outcomes, n (%)[b]	120 mg N=75
ORR [95% CI]	53 (71) [60-80]
CR	5 (7)
PR	48 (64)
DCR [95% CI]	72 (96) [89-99]
SD,	19 (25)
PD	3 (4)
Median DoR (95% CI), mos [n=53]	14.1 (6.9-NE)
Median PFS (95% CI), mos	12.4 (8.2-NE)



[a] Confirmed Best Overall Response by BICR

[b] Unless stated otherwise

Data cut-off: Nov 29, 2024

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; mos, months; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SLD, sum of target lesion diameter

Heymach JV, et al. N Engl J Med. 2025;392:2321-33 (including Supplementary Appendix)

BEAMION LUNG-1: ZONGERTINIB IN PRE-TREATED *HER2*-MUTANT NSCLC WITH BRAIN METASTASES AT BASELINE (COHORT 1)[a]

RESPONSE IN PATIENTS WITH BRAIN METASTASES AT BASELINE

Response assessment (BICR) by RECIST	N=28
Objective response, n (%) [95% CI]	18 (64) [46-79]
CR, n (%)	1 (4)
PR, n (%)	17 (61)

INTRACRANIAL RESPONSE IN PATIENTS WITH BRAIN METASTASES AT BASELINE

IC response assessment (BICR) RANO-BM	Cohort 1 120 mg (N=27)[b]
Objective response, n (%) [95% CI]	11 (41) [25-59]
CR, n (%)	4 (15)
PR, n (%)	7 (26)
DCR, n (%) [95% CI]	22 (81) [63-92]
SD, n (%)	11 (41)
PD, n (%)	2 (7)
NE, n (%)	3 (11)

[a] In previously treated patients with a *HER2* TKD mutation

[b] In patients eligible for RANO-BM assessment only patients where any target or non-target lesion was entered for RANO-BM assessment at baseline

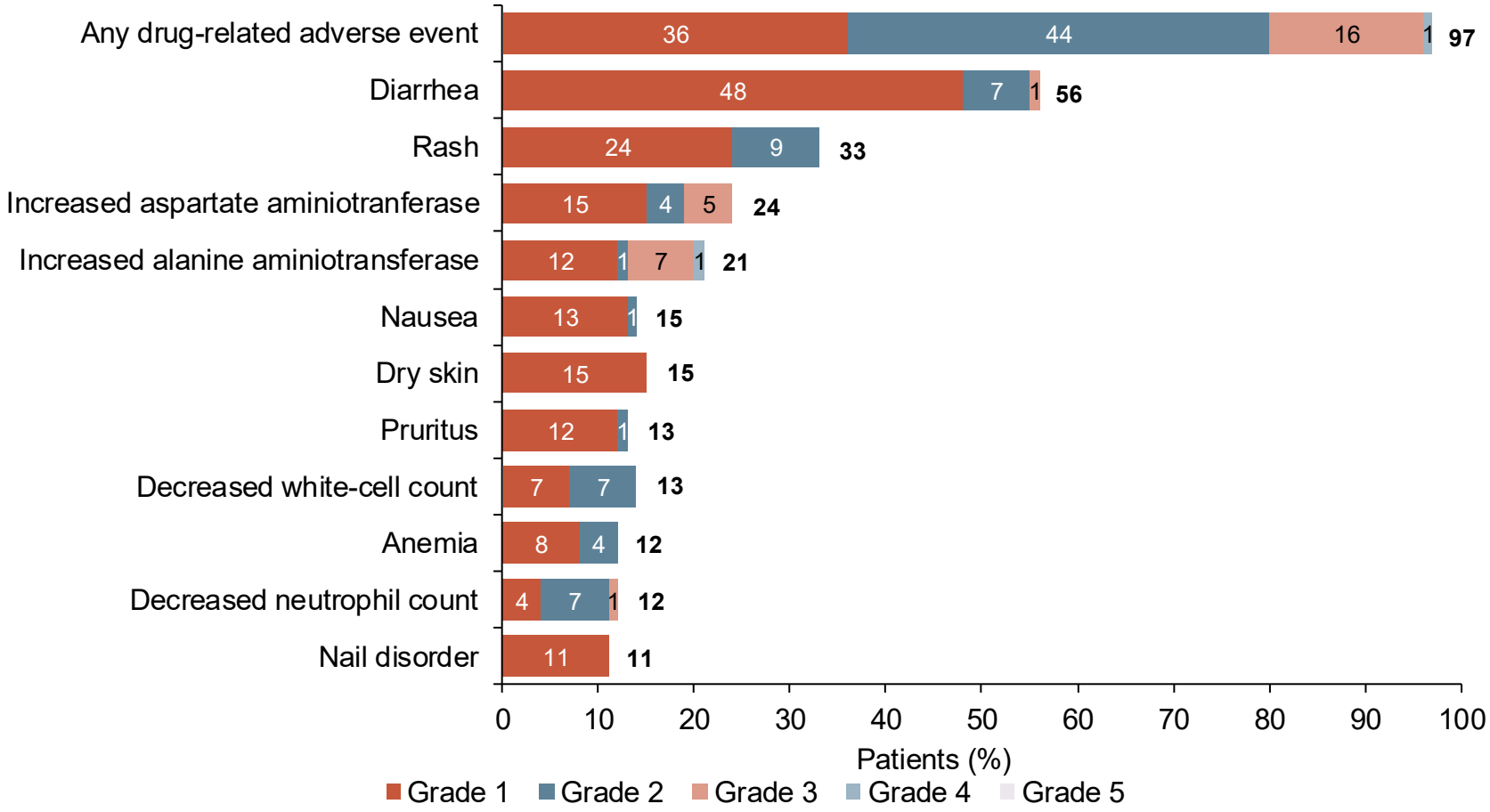
Data cut-off: November 29, 2024

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; IC, intracranial; NE, not evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; TKD, tyrosine kinase domain

Heymach JV, et al. N Engl J Med. 2025;392:2321-33 (including Supplementary Appendix)

BEAMION LUNG-1: ZONGERTINIB SAFETY RESULTS (COHORT 1)

MOST COMMON TRAEs[a] AMONG PRE-TREATED PATIENTS RECEIVING 120 mg (N=75)



[a] TRAEs were assessed by the investigator; those reported in more than 10% of patients are included. Percentages may not sum to totals due to rounding

TRAE, treatment-relate adverse event

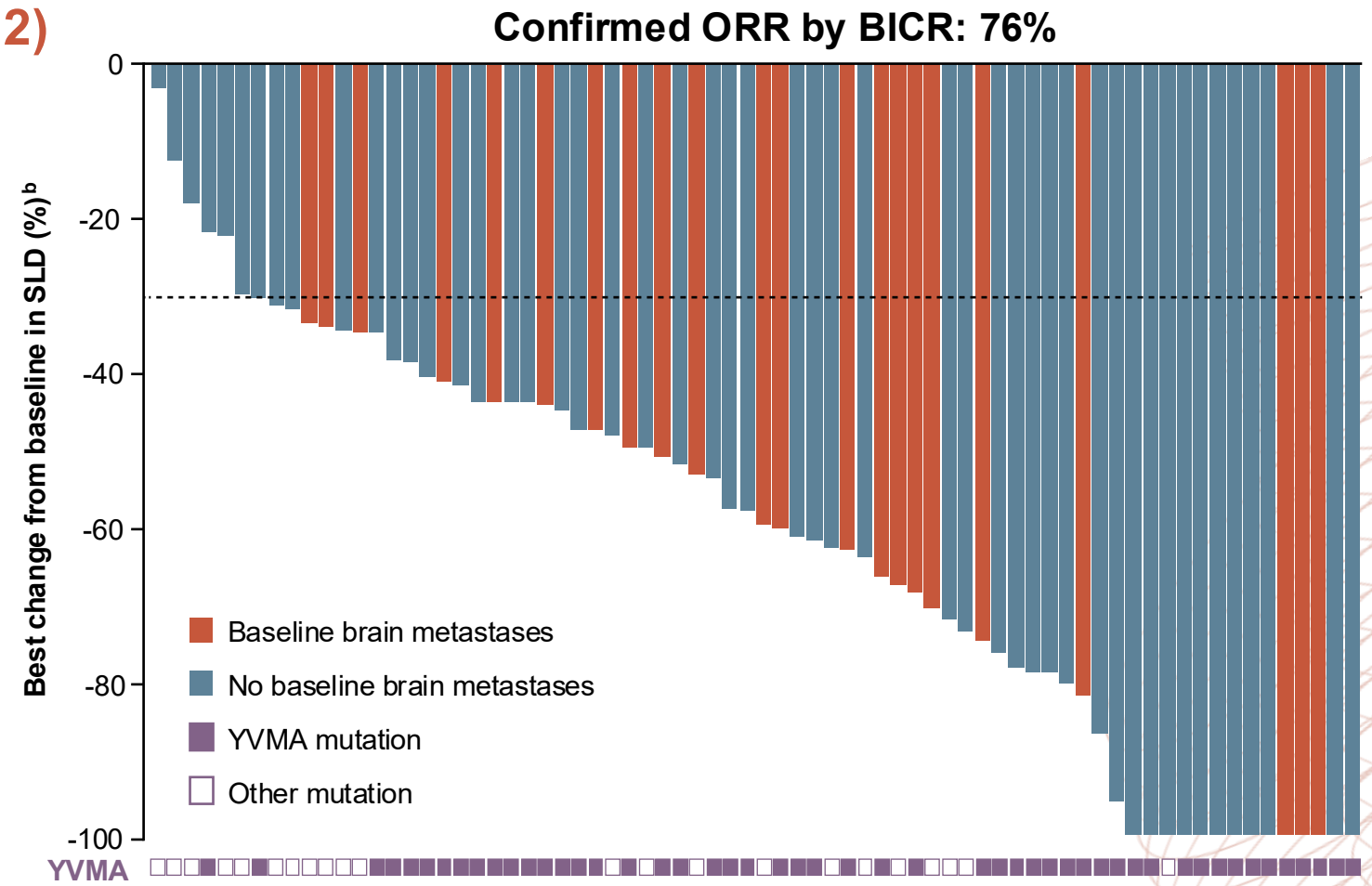
Heymach JV, et al. N Engl J Med. 2025;392:2321-33

BEAMION-LUNG-1: ZONGERTINIB IN 1L TREATMENT-NAÏVE PATIENTS

TUMOUR RESPONSE (COHORT 2)

Confirmed response by BICR (RECIST v1.1)	Cohort 2: Treatment-naïve patients N=74
ORR	76%
CR, n (%)	8 (11)
PR, n (%)	48 (65)
DCR	96%
SD, n (%)	15 (20)
PD, n (%)	1 (1)[a]
Median DoR (95% CI), mos	15.2 (9.8-NE)
Median PFS (95% CI), mos	14.4 (11.1-NE)

- Median time to objective response was 1.4 months (95% CI, 1.1 to 6.9)



1L zongertinib demonstrated clinical benefit in all patients, irrespective of *HER2* mutation type

[a] PD due to non-target lesion progression; [b] two patients were not evaluable for response (images were not available)

Median follow-up for DoR: 13.8 months (95% CI, 12.4–15.3). Median best percentage change in SLD was -59% (range, -4% to -100%)

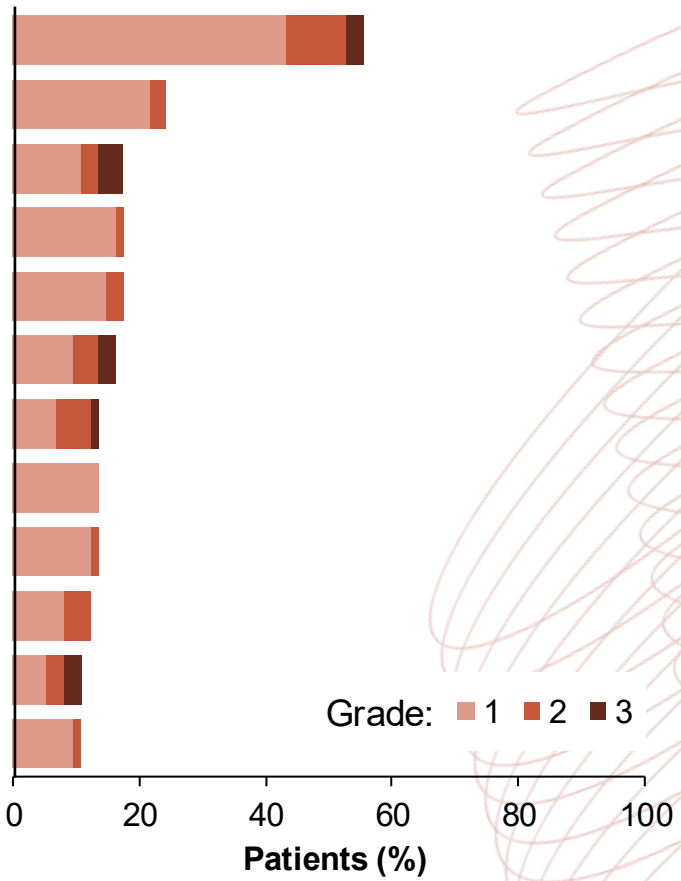
1L, first-line; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease; SLD, sum of lesion diameter

Heymach J, et al. Abstract 6MO, ELCC 2026 (oral presentation)

BEAMION-LUNG-1: ZONGERTINIB IN 1L TREATMENT-NAÏVE PATIENTS: SAFETY PROFILE (COHORT 2)

- Zongertinib had a manageable safety profile in treatment-naïve patients (Cohort 2):
  TRAEs were reported in 67 (91%) patients, with grade ≥3 TRAEs in 14 (19%) patients
  - Most common grade ≥3 TRAE was increased ALT
  - Low rates of grade ≥3 diarrhea and rash
  - AEs leading to dose reduction occurred in 12 (16%) patients
  - AEs leading to discontinuation occurred in 7 (9%) patients

TRAEs, n (%)[a]	All	Grade 3
Diarrhea	41 (55)	2 (3)
Rash[b]	18 (24)	0
Increased ALT	13 (18)	3 (4)
Dysgeusia	13 (18)	0
Nausea	13 (18)	0
Increased AST	12 (16)	2 (3)
Paronychia	10 (14)	1 (1)
Dry skin	10 (14)	0
Pruritus	10 (14)	0
Fatigue	9 (12)	0
Anemia	8 (11)	2 (3)
Stomatitis	8 (11)	0



[a] TRAEs as assessed by the investigator that occurred in ≥10% of patients are shown; [b] grouped term

Median duration of treatment: 14.0 months (range, 0–21.0); two cases (3%) of ILD/pneumonitis were reported (both grade 2); there was one grade 4 TRAE (decreased neutrophil count) and no grade 5 TRAEs

1L, first-line; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TRAE, treatment-related adverse event

Heymach J, et al. Abstract 6MO, ELCC 2026 (oral presentation)

BEAMION LUNG-1: ZONGERTINIB TUMOUR RESPONSE (COHORT 3 & 5)

Response assessment by RECIST, v1.1, n (%)	Prior systemic treatment, non–TKD mutation Cohort 3 (INV); 120 mg N=20	Prior HER2-targeted ADC Cohort 5 (BICR); 120 mg N=31
ORR	6 (30) [95% CI: 15-52]	15 (48) [95% CI: 32-65]
CR	0	1 (3)
PR	6 (30)	14 (45)
DCR	13 (65) [95% CI: 43-82]	30 (97) [95% CI: 84-99]
SD	7 (35)	15 (48)
PD	6 (30)	0
NE	1 (5)	1 (3)

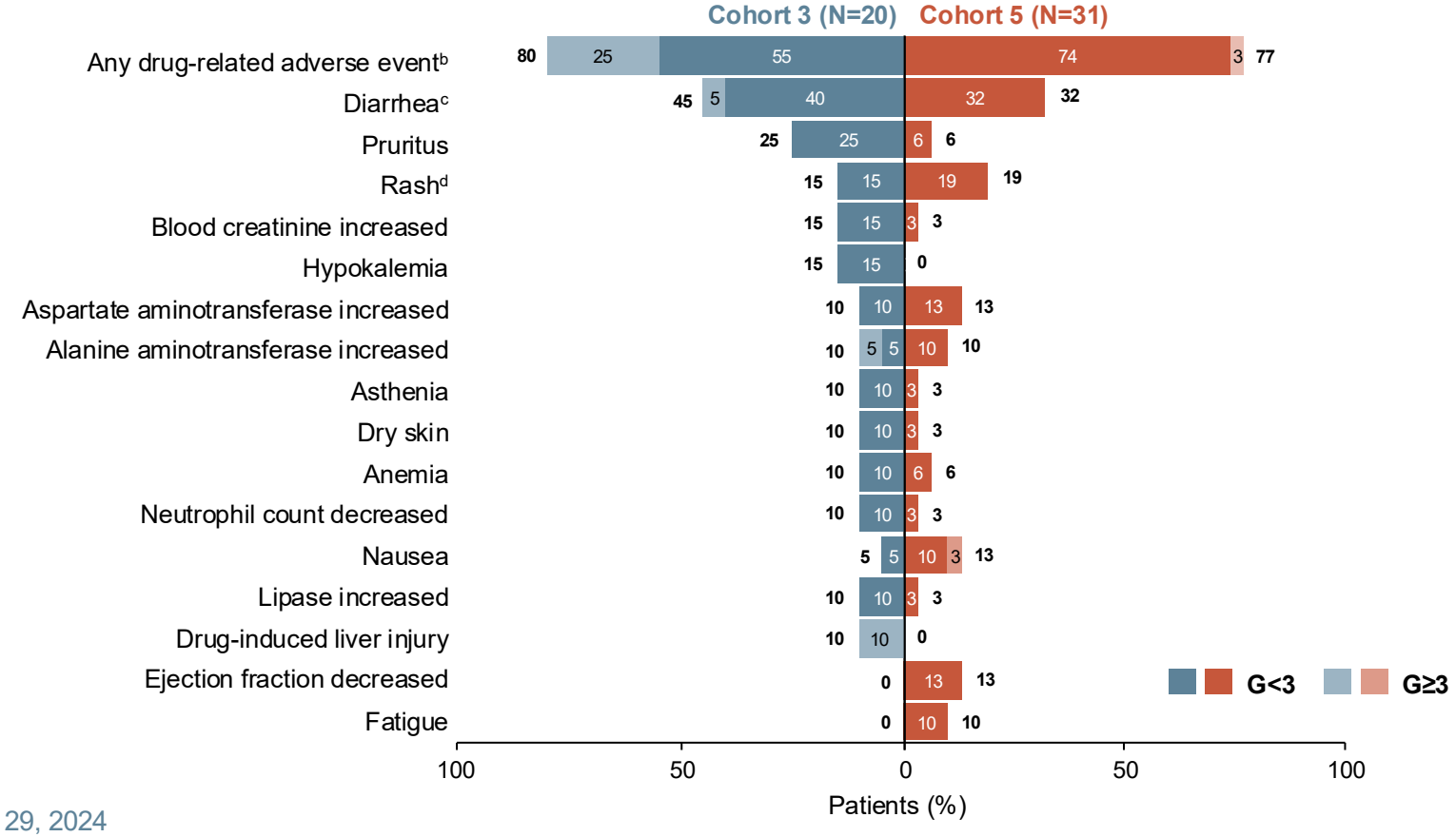
Data cut-off: Nov 29, 2024

ADC, antibody drug conjugate; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; INV, investigator; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease

Heymach JV, et al. N Engl J Med. 2025;392:2321-33 (including Supplementary Appendix)

BEAMION LUNG-1: ZONGERTINIB SAFETY RESULTS (COHORT 3 & 5)

MOST COMMON TRAEs[a] AMONG PATIENTS RECEIVING 120 mg



Data cut-off: Nov 29, 2024

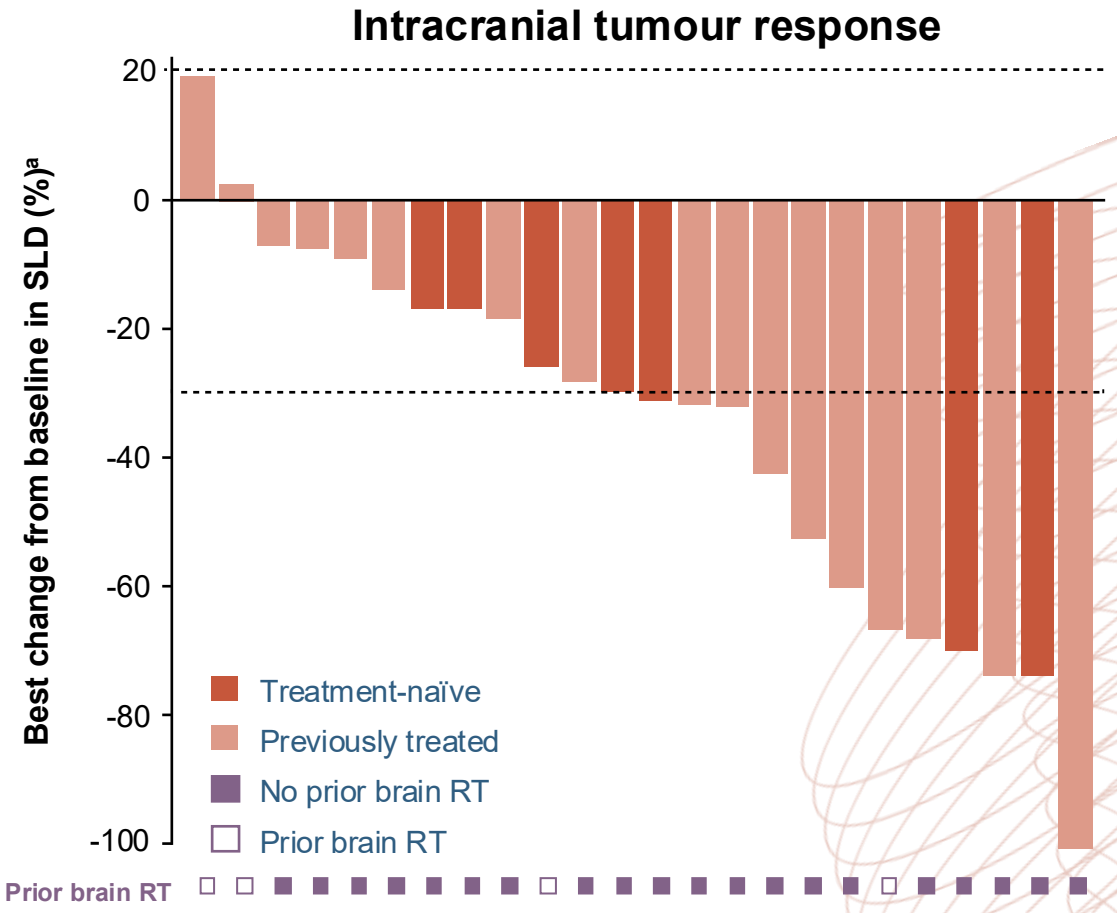
[a] TRAEs reported at least 10% of patients are included. [b] As assessed by the investigator; those reported in ≥10% of patients in any cohort are shown; [c] Grouped term including preferred terms diarrhea only (Cohort 3) and diarrhea, gastroenteritis, and enteritis (Cohort 5); [d] Grouped term including preferred terms rash, dermatitis and rash maculo-papular (Cohort 3), and dermatitis acneiform, post procedural erythema and rash (Cohort 5). Percentages may not sum to totals due to rounding

G, grade; TRAE, treatment-related adverse events

Heymach JV, et al. N Engl J Med. 2025;392:2321-33 (including Supplementary Appendix)

BEAMION-LUNG-1: ZONGERTINIB IN PATIENTS WITH ACTIVE BRAIN METASTASES (COHORT 4)

	Cohort 4: Active brain metastases	
Confirmed intracranial response by BICR (RANO-BM)	**N=30**	**No prior brain RT and confirmed measurable intracranial disease N=17**
ORR	47%	59%
CR, n (%)	2 (7)	1 (6)
PR, n (%)	12 (40)	9 (53)
DCR	87%	94%
SD, n (%)	12 (40)	6 (35)
NE, n (%)	4 (13)	1 (6)
Median DoR, months 95% CI	6.9 2.9-NE	6.2 2.7-NE
Median PFS, months 95% CI	8.2 4.1-11.3	NE NE



Zongertinib showed intracranial activity in patients with active, untreated brain metastases

[a] Patients who had a baseline assessment and at least one post-baseline assessment (from at least one central reader)

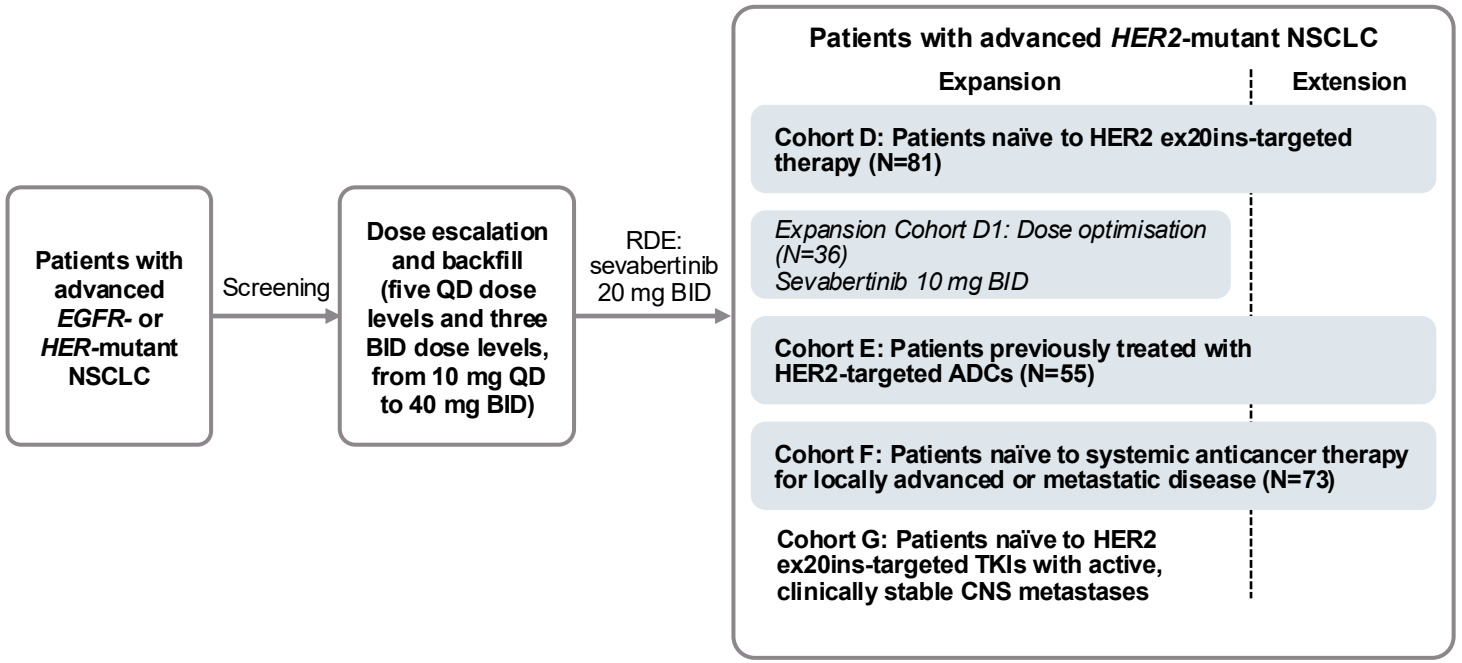
For Cohort 4 (N = 30): median follow-up for DoR: 11.8 months (95% CI, 4.2–NE) and median follow-up for PFS: 9.6 months (95% CI, 6.9–NE)

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RT, radiotherapy; SD, stable disease; SLD, sum of lesion diameter

Heymach J, et al. Abstract 6MO, ELCC 2026 (oral presentation)

SOHO-01: STUDY DESIGN

- **Sevabertinib** is an oral, reversible **tyrosine kinase inhibitor (TKI) that potently inhibits HER2 and mutant EGFR** in preclinical models and has shown anti-tumour activity in patients with advanced NSCLC harbouring *HER2* mutations
- The **SOHO-01 study** an open-label, multicenter, multicohort, phase 1–2 study evaluating sevabertinib at a twice-daily dose of 20 mg in patients with locally advanced or metastatic *HER2*-mutant NSCLC



Dose Escalation/Expansion

Primary end points:
- Safety and tolerability
- Pharmacokinetics

Secondary end points:
- ORR per RECIST v1.1 by INV
- OS

Extension

Primary end point:
- ORR per RECIST v1.1 by BICR

Secondary end points:
- DoR, PFS [RECIST v1.1 (BICR/INV)]
- Safety and tolerability

Patients with *EGFR*-mutant NSCLC
Expansion
Cohort A: *EGFR* ex20ins mutations and naïve to EGFR ex20ins-targeted therapy
Cohort B1: *EGFR* ex20ins mutations and previously treated with EGFR ex20ins-targeted bispecific antibodies
Cohort B2: *EGFR* ex20ins mutations and previously treated with one EGFR ex20ins-targeted TKI
Cohort C: *EGFR* C797X mutation and naïve to EGFR C797X-TKIs

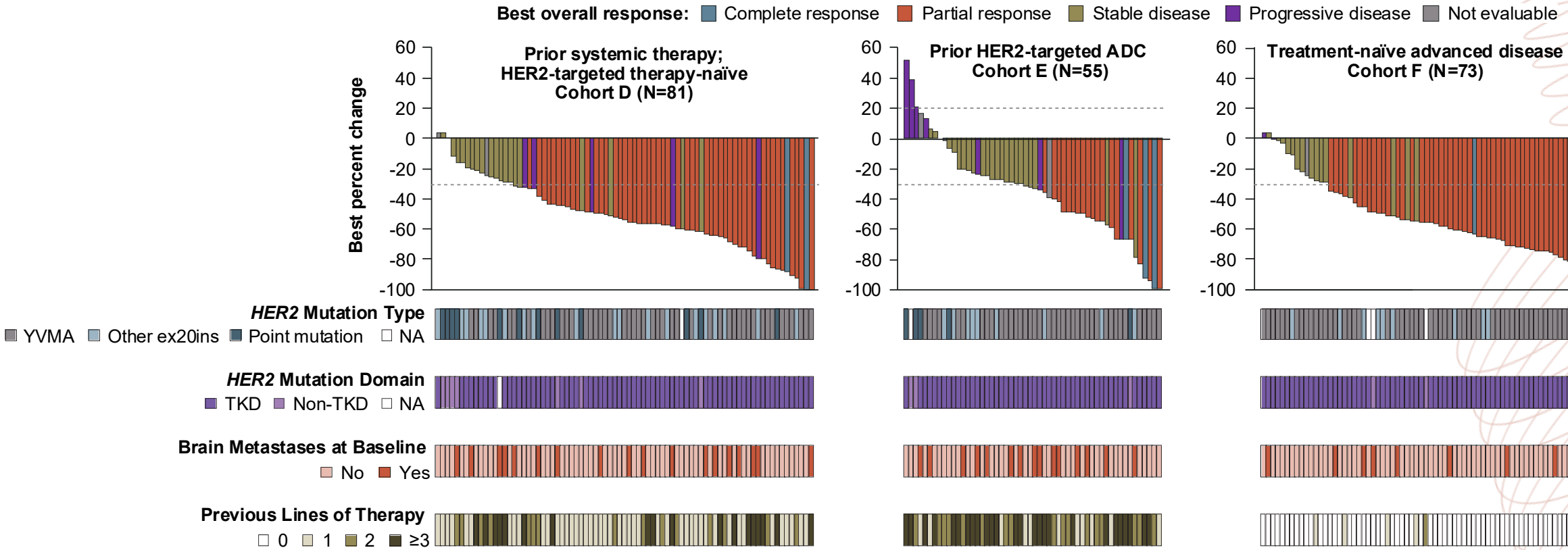
Data cut off June 27, 2025

ADC, antibody-drug conjugate; BID, twice daily; CNS, central nervous system; DoR, duration of response; ex20ins, exon 20 insertion; INV, investigator-assessed; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RDE, recommended dose for expansion

Le X, et al. N Engl J Med. 2025;393:1819-32 (including Supplementary Appendix)

SOHO-01: TUMOUR RESPONSE AND CLINICAL FEATURES

BEST PERCENT CHANGE IN THE SLD OF TARGET LESIONS



ADC, antibody drug conjugate; ex20ins, exon 20 insertion; NA, not applicable; SLD, sum of largest diameter; TKD, tyrosine kinase inhibitor

Le X, et al. N Engl J Med. 2025;393:1819-32 (including Supplementary Appendix)

SOHO-01: PHASE 1/2 STUDY ON SEVABERTINIB IN LOCALLY ADVANCED OR METASTATIC *HER2*-MUTANT NSCLC[1,2]

Response (BICR) in patients treated with sevabertinib (all-treated)	Cohort D[1,a] Prior systemic therapy; HER2-targeted therapy-naïve (n=81)	Cohort E[2, b] Prior HER2-targeted ADC (n=55)	Cohort F[1, a] Treatment-naïve advanced disease (n=73)
ORR, % [95% CI]	67 [55-77]	38 [25-52]	75 [64-85]
DCR, % [95% CI]	81 [71-89]	71 [57-82]	89 [80-95]
Median DoR, mos (95% CI)	9.5 [6.3-13.5]	8.5 [5.6-16.4]	12.2 [8.8-NE]
Median PFS, mos (95% CI)	8.3 [6.9-12.3]	5.5 [4.3-8.3]	13.5 [10.0-NE]

mDoR/ mPFS longer in treatment-naïve **(cohort F)** than in pts previously treated **(cohort D)**, including those with N-sq histology and *HER2* TKD/YVMA mutations[1,c]

[a] Data cut-off November 17, 2025; [b] Data cut-off June 27, 2025; [c] Data shown only for all-treated

Results derived from different data cut-offs and should not be compared directly across datasets

ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; DCR, disease control rate; (m)DoR, (median) duration of response; mos, months; NE, not estimable; NSCLC, non-small cell lung cancer; N-sq, non-squamous; ORR, objective response rate; (m)PFS, (median) progression-free survival; TKD, tyrosine kinase domain

1. Loong H, et al. J Clin Oncol. 2026;44(suppl 16). Abstr 8622 (ASCO 2026, Poster presentation); 2. Le X, et al. N Engl J Med. 2025;393:1819-32

SOHO-01: SEVABERTINIB IN *HER2*-MUTANT NSCLC WITH AND WITHOUT BRAIN METASTASES AT BASELINE

OBJECTIVE RESPONSE RATE IN PATIENTS WITH AND WITHOUT BRAIN METASTASES AT BASELINE

Patients, n/N (%)	Cohort D Prior systemic therapy; HER2-targeted therapy-naïve	Cohort E Prior HER2-targeted ADC	Cohort F Treatment-naïve advanced disease	Cohorts D, E, F
Brain metastases at baseline				
Yes	18/81 (22)	15/55 (27)	9/73 (12)	42/209 (20)
No	63/81 (78)	40/55 (73)	64/73 (88)	167/209 (80)
Objective response rate				
All patients	52/81 (64)	21/55 (38)	52/73 (71)	125/209 (60)
Brain metastases	11/18 (61)	4/15 (27)	7/9 (78)	22/42 (52)
No brain metastases	41/63 (65)	17/40 (43)	45/64 (70)	103/167 (62)

Analysis cut-off date: June 27, 2025

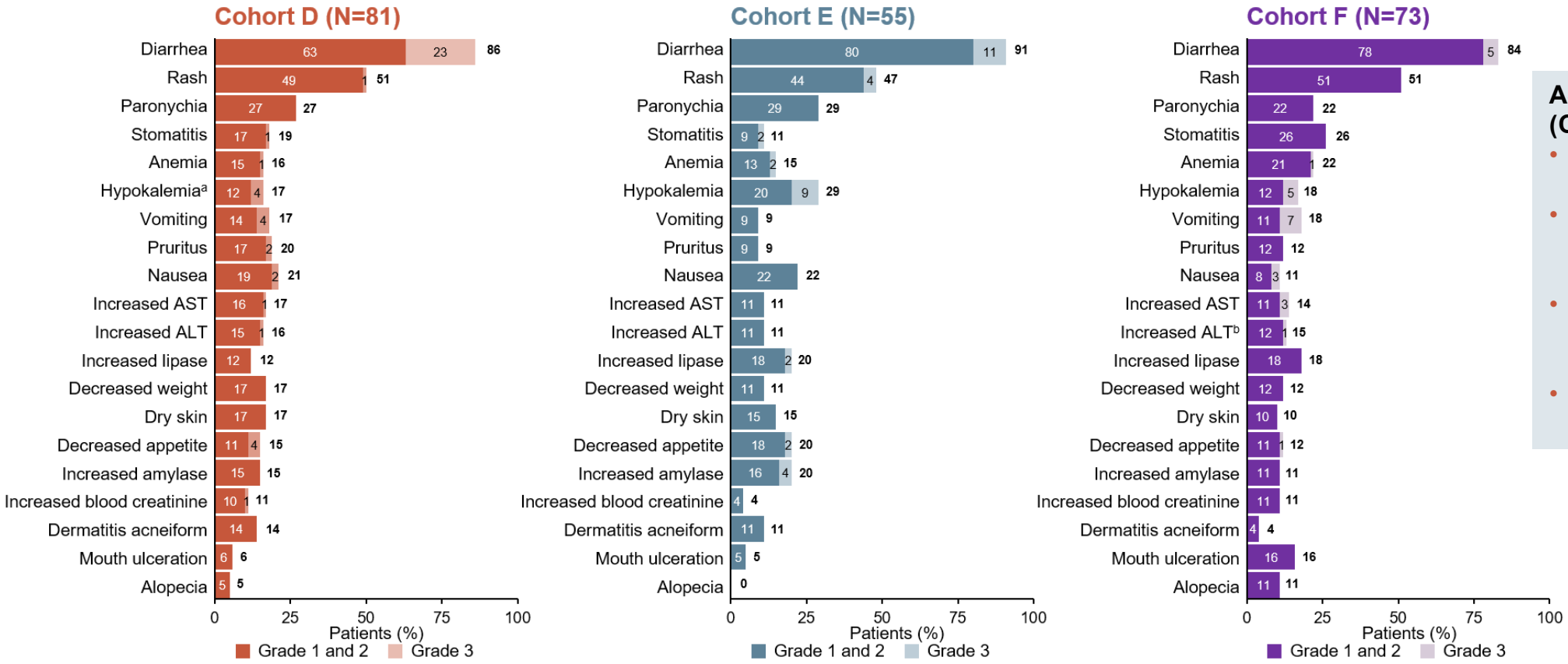
Response assessed by blinded independent central review

NSCLC, non-small cell lung cancer

Le X, et al. N Engl J Med. 2025;393:1819-1832 (including Supplementary Appendix)

SOHO-01: SEVABERTINIB SAFETY RESULTS

Most common TRAEs in >10% of patients treated with sevabertinib 20 mg BID[1,c]



ASCO 2026 safety update[2] (Cohorts D and F only)[d]:

- No new safety signals identified
- Discontinuations due to TEAEs remained low (5% Cohort D; 3% Cohort F)
- No ILD, grade 4 diarrhea, or diarrhea-related discontinuations
- Dose modifications in ~50% of patients

[a] One grade 4 adverse event was reported in Cohort D; [b] One grade 4 adverse event was reported in Cohort F; [c] Data cut-off June 27, 2025. [d] Data cut-off for ASCO 2026 update was Nov 17, 2025 - Cohort E was not included in the updated safety analysis presented by Loong et al. (ASCO 2026).

TRAEs categorised according to MedDRA v28.0, graded using CTCAE v5.0. Percentages may not sum to totals due to rounding

ALT alanine aminotransferase, AST aspartate aminotransferase; BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

1. Le X, et al. N Engl J Med. 2025;393:1819-32 (including Supplementary Appendix); 2. Loong H, et al. J Clin Oncol. 2026;44 (suppl 16). Abstr 8622 (ASCO 2026, Poster presentation)

SOHO-01: EXPLORATORY ANALYSIS RESULTS

CHARACTERISATION AND MANAGEMENT OF TREATMENT-EMERGENT DIARRHEA

	Cohort D (N=81)	Cohort F (N=73)
No diarrhea, n (%)	11 (14)	9 (12)
Treatment-emergent diarrhea (worst toxicity grade), n (%)	70 (86)	64 (88)
Grade 1	21 (26)	36 (49)
Grade 2	30 (37)	24 (33)
Grade 3	19 (23)	4 (5)
Grade 4	0	0
Onset at grade 3, n (%)	2 (2)	0
Action taken due to diarrhea, n (%)	70 (86)	64 (88)
Dose not changed	69 (85)	60 (82)
Dose interruptions or delays	12 (15)	3 (4)
Dose reductions[a]	10 (12)	6 (8)
Discontinuation	0	0
Loperamide use, n (%)	56 (69)	39 (53)
Loperamide started ≤24 hours after first diarrhea event of any grade	30 (37)	13 (18)
Characteristics of grade 3 diarrhea events		
Patients with >1 episode, n (%)	3 (4)	0
Median episodes per patient (IQR)	1 (1-1)	1 (1-1)
Median duration of episodes (IQR), days	4 (2-11)	2 (2-2)
Median time to first episode (IQR), days	39 (15-123)	29 (14-50)
Median cumulative duration (IQR), days	6 (3-14)	2 (2-2)

- Patients with grade 3 diarrhea had a median of 1 episode with a median duration of 2-4 days
- Loperamide use was not mandated and was reported in 69% (Cohort D) and 53% (Cohort F) of patients

[a] Dose was not re-escalated after reduction for toxicity

IQR, interquartile range

Girard N, et al. Abstract 18P, ELCC 2026 (poster presentation)

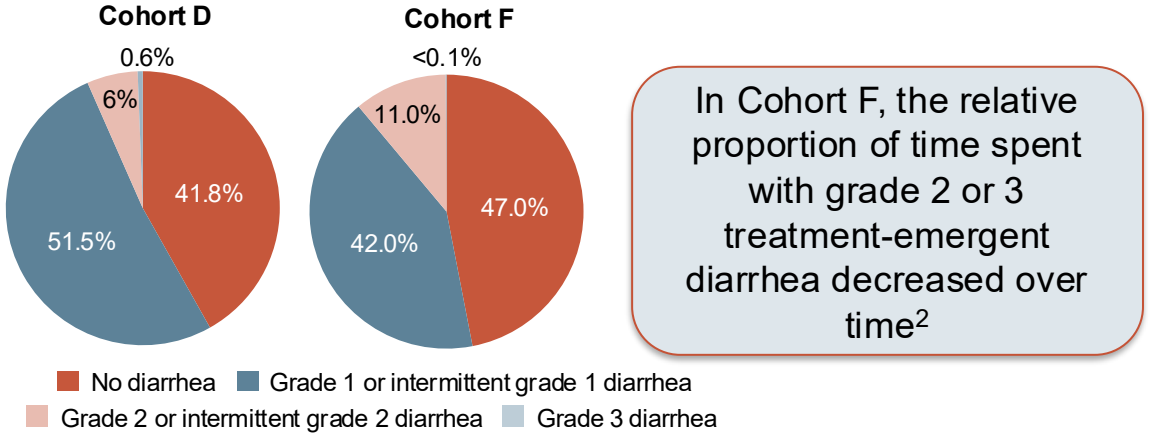
SOHO-01 EXPLORATORY ANALYSIS RESULTS

RESPONSE PER BICR (RECIST V1.1) BY PRESENCE OF GRADE ≥2 DIARRHEA[1]

- In Cohorts D and F, efficacy was generally similar among patients who did or did not experience grade ≥2 diarrhea

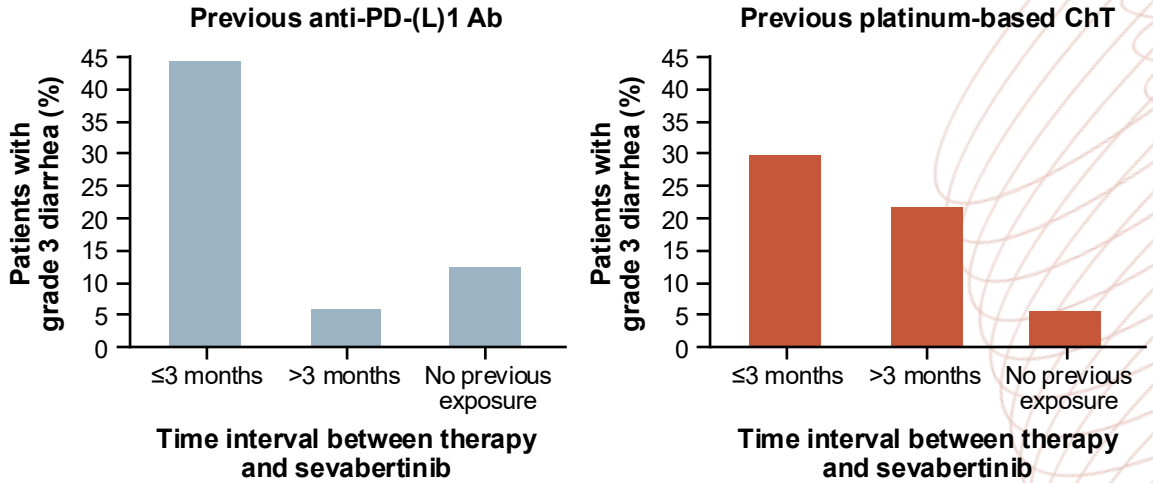
	Cohort D (N=81)		Cohort F (N=73)	
	Grade ≥2 diarrhea (N=49)	No grade ≥2 diarrhea (N=32)	Grade ≥2 diarrhea (N=28)	No grade ≥2 diarrhea (N=45)
ORR, n (%)	34 (69)	20 (63)	20 (71)	33 (73)
Median DoR (min, max), months[a]	7 (2, 30)	6 (1, 15)	9 (2, 13)	7 (1, 13)
Median PFS (min, max), months	8 (1, 31)	5 (0, 16)	9 (0, 15)	8 (0, 15)

PROPORTION OF PATIENT-DAYS WITH DIARRHEA[1]



In Cohort F, the relative proportion of time spent with grade 2 or 3 treatment-emergent diarrhea decreased over time[2]

DIARRHEA FREQUENCY BY TIMING OF PRIOR THERAPY[1,b]



[a] Based on patients with an objective response; [b] In cohorts D, E, F and D1

Ab, antibody; BICR, blinded independent central review; ChT, chemotherapy; DoR, duration of response; max, maximum; min, minimum; ORR, objective response rate; PD-(L)1: programmed cell death-1/programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

1. Girard N, et al. Abstract 18P, ELCC 2026 (poster presentation); 2. Loong H, et al. J Clin Oncol. 2026;44 (suppl 16). Abstr 8622 (ASCO 2026, Poster presentation)

ONGOING TRIALS OF TKIs IN *HER2*-MUTANT NSCLC

Trial	Phase	Setting	Therapy	Primary EP
PYRAMID-1 NCT04447118	3	Advanced NSCLC with *HER2* exon 20 mutation who progressed on plat-based therapy	Pyrotinib vs docetaxel	PFS
Beamion LUNG-2 NCT06151574	3	1L advanced NSCLC with *HER2* TKD mutations	Zongertinib vs pembro + platinum-pemetrexed chemotherapy	PFS
Beamion LUNG-3 NCT07195695	3	Early-stage NSCLC after surgery and standard perioperative treatment	Zongertinib vs observation or immunotherapy	DFS
SOHO-02 NCT06452277	3	1L advanced NSCLC with *HER2* activating mutations	Sevabertinib vs pembro + platinum-pemetrexed chemotherapy	PFS
ELVN-002 NCT05650879	1a/1b	*HER2*-mutated advanced NSCLC	ELVN-002 monotherapy ELVN-002 + T-DXd ELVN-002 + T-DM1	Safety
IAM1363 NCT06253871	1/1b	*HER2*-altered advanced cancers	IAM1363	Safety, DLT, PK, ORR
HEROEX-1 NCT06521554	1a/1b	Advanced *HER2*-altered NSCLC	NVL-330	Safety, MTD, RP2D

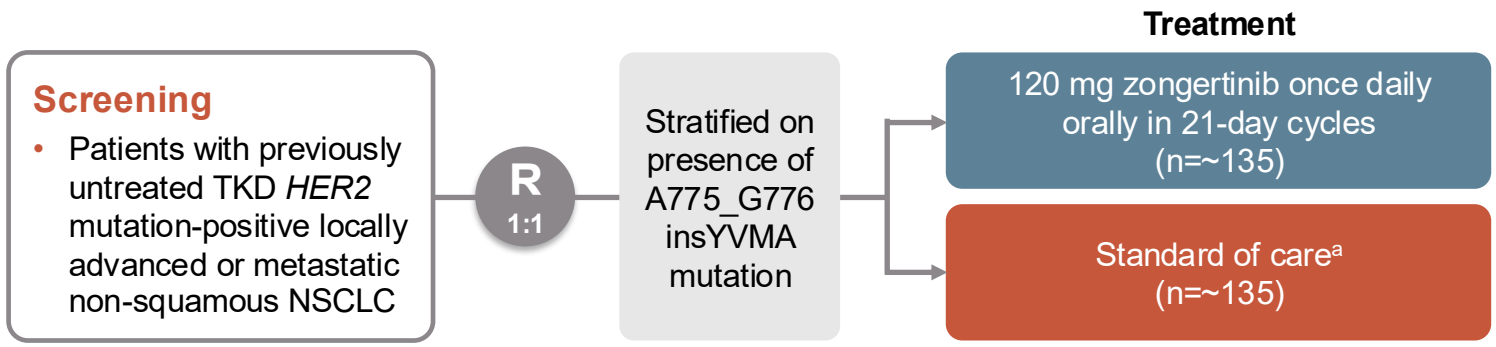
Data derived from ClinicalTrials.gov (June 24, 2026)

1L, first-line; DFS, disease-free survival; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; pembro, pembrolizumab; PFS, progression-free survival; PK, pharmacokinetic; RP2D, recommended phase 2 dose; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

BEAMION LUNG-2: STUDY DESIGN

ZONGERTINIB IN 1ST LINE

- Beamion LUNG-2 (NCT06151574) is a Phase 3 trial which will assess the efficacy and safety of first-line zongertinib compared with standard of care in patients with locally advanced or metastatic *HER2*-mutation-positive NSCLC



Endpoints

Primary:

- Progression-free survival (RECIST v1.1)[b]

Secondary:

- OR (RECIST v1.1;[b] best overall response of complete or partial response)
- Overall survival
- Duration of response[b]
- Patient-reported outcomes from baseline to Week 25, including NSCLC-SAQ total, pain, dyspnea, cough, appetite, and fatigue scores, and EORTC-QLQ-C30 scores
- Adverse events and serious adverse events during the on-treatment period (CTCAE v5)

[a] Intravenous 500 mg/m^2 pemetrexed chemotherapy plus 200 mg intravenous pembrolizumab followed by either 75 mg/m^2 cisplatin or carboplatin Area Under the Curve 5 on Day 1 (determined by investigator prior to randomisation), every three weeks, for four 21-day treatment cycles, followed by maintenance therapy with 200 mg pembrolizumab plus pemetrexed 500 mg/m^2 every three weeks for up to 35 cycles

[b] Determined by blinded central independent review

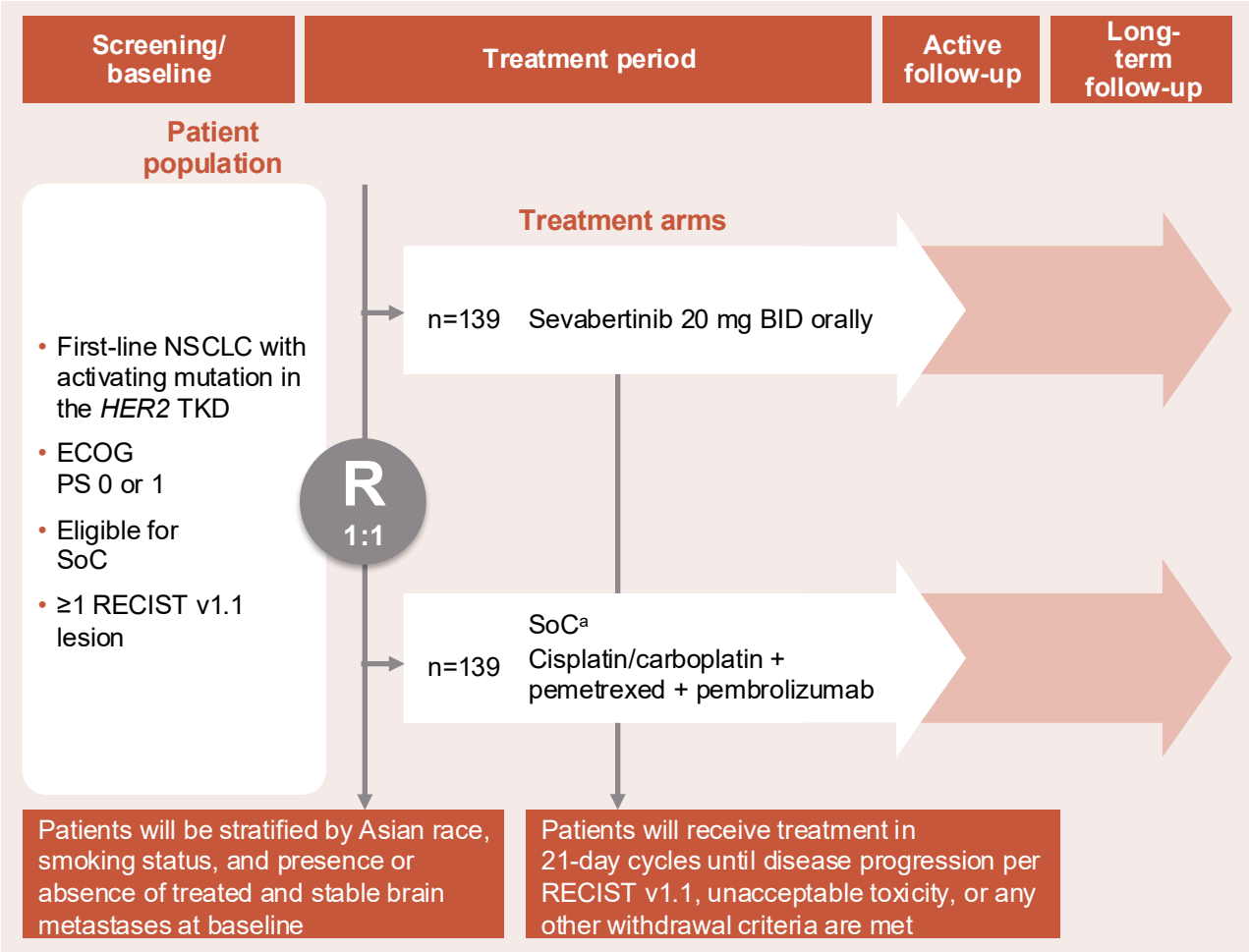
CTCAE, common terminology criteria for adverse events; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; NSCLC(-SAQ), non-small cell lung cancer (-Symptom Assessment Questionnaire); OR, objective response; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TKD, tyrosine kinase domain

Johnson ML, et al. J Clin Oncol. 2024:42 (16_suppl): TPS8654 (poster presentation)

SOHO-02: STUDY DESIGN

SEVABERTINIB IN 1ST LINE

- The SOHO-02, phase 3 trial is evaluating the efficacy and safety of sevabertinib as 1st line therapy in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations[1]



Key study endpoints:

Primary
- PFS per RECIST v1.1 by BICR

Secondary
- Overall survival
- ORR per RECIST v1.1 by BICR
- Safety and tolerability
- PFS per RECIST v1.1 by investigator
- ORR by investigator
- Disease control rate per RECIST v1.1 by BICR and investigator
- Duration of response by BICR and investigator
- Patient-reported outcomes

NCT06452277

[a] SoC treatment based on NCCN/ESMO treatment guidelines and dosing based on approved labels

BICR, blinded independent central review; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; Q3W, every 3 weeks; Q6W, every 6 weeks; R, randomisation; RECIST v1.1, Response Evaluation Criteria in Solid Tumours 1.1; SoC, standard of care; TKD, tyrosine kinase domain

1. Le X, et al. J Clin Oncol 2025;43(suppl 16). Abstr TPS8648 (ASCO 2025, poster presentation)

SUMMARY

- *HER2* mutations are an actionable target of NSCLC and should be identified early through broad next-generation sequencing (NGS) in patients with advanced or metastatic disease
- Treatment strategies are evolving, platinum–pemetrexed chemotherapy ± immunotherapy has historically been first-line therapy for *HER2*-mutant NSCLC
- Next-generation HER2 TKIs are reshaping the treatment landscape: zongertinib is now approved for first-line treatment, while sevabertinib has received priority review status by the FDA, and both have demonstrated activity in patients with previously treated disease
- The HER2 antibody-drug conjugate (ADC) trastuzumab deruxtecan is approved after disease progression and has demonstrated substantial response rates in previously treated *HER2*-mutant NSCLC
- Toxicity management is critical: ADCs carry a risk of interstitial lung disease/pneumonitis, while HER2 TKIs commonly cause diarrhea and rash; both require early recognition and proactive management

FDA, Dood and Drug Administration; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

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