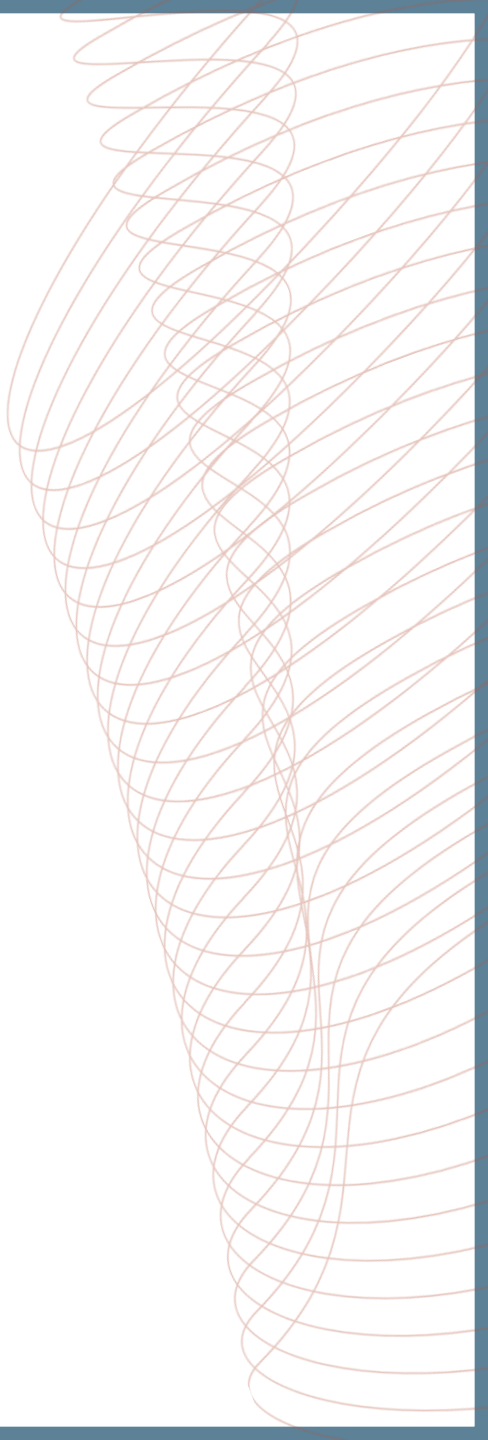




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LUNG CONNECT

HER2-MUTATED NSCLC HIGHLIGHTS FROM WCLC 2026

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DEVELOPED BY LUNG CONNECT

This programme is developed by LUNG CONNECT, an international group of experts in the field of thoracic oncology and brought to you alongside PRECISION ONCOLOGY CONNECT, an international group of experts in the field of detection and treatment of targetable genetic/genomic alterations in various cancers



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- This educational programme is intended for healthcare professionals only
- The views expressed within this programme are the personal opinions of the experts. They do not necessarily represent the views of the experts' institutions, or the rest of the LUNG CONNECT group.

Expert disclosures:

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CLINICAL TAKEAWAYS

- **DESTINY-Lung04:** First-line trastuzumab deruxtecan significantly improved PFS versus standard chemo-immunotherapy in advanced *HER2*-mutant NSCLC, supporting a potential shift towards *HER2*-directed treatment in the first-line setting
- **SOHO-01:** Exploratory biomarker analysis provides early insights into potential mechanisms of acquired resistance to sevabertinib, identifying secondary *HER2* T862A as the most frequent putative genomic resistance alteration
- **Beamion Lung-1:** Exploratory biomarker analysis suggests resistance to zongertinib is molecularly heterogeneous, with diverse genomic alterations converging on common biological pathways

EDUCATIONAL OBJECTIVES

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

FIRST-LINE TRASTUZUMAB DERUXTECAN (T-DXd) IN PATIENTS WITH METASTATIC *HER2*-MUTANT NSCLC: DESTINY-LUNG04 PRIMARY RESULTS

Rotow J, et al. Abstract PL03.08, WCLC 2026

DESTINY-LUNG04: BACKGROUND AND STUDY DESIGN

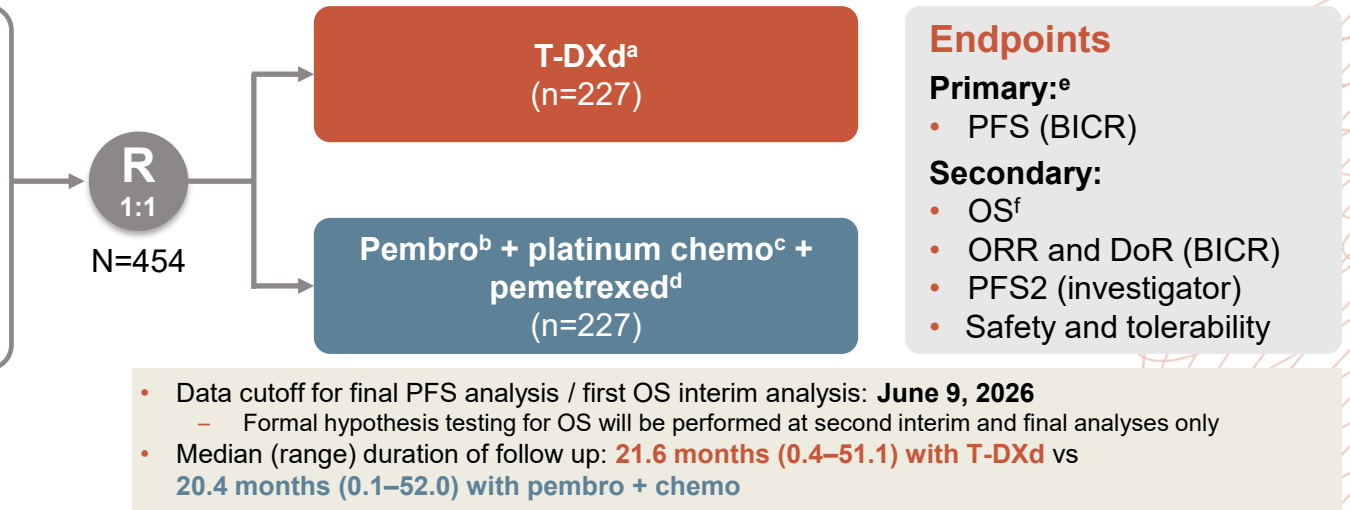
- **HER2-mutant NSCLC** is an aggressive disease characterised by **poor prognosis**
- **Many patients do not respond to first-line SOC** immunotherapy + chemotherapy, underscoring the need for HER2-directed treatment options in this population
- **DESTINY-Lung04** (NCT05048797) evaluated first-line T-DXd (a HER2-directed ADC) versus pembrolizumab + chemotherapy in advanced/metastatic **HER2-mutant NSCLC**

Patients

- Unresectable locally advanced or metastatic non-squamous NSCLC
- Treatment naïve for advanced disease
- **HER2** exon 19 or 20 mutation by central/local test
- ECOG PS 0 or 1
- Asymptomatic/stable/treated brain metastases permitted
- ≥1 measurable lesion per RECIST 1.1

Stratification factor

- Presence/history of brain metastases (yes vs no)
- Smoking history status (ever vs never)



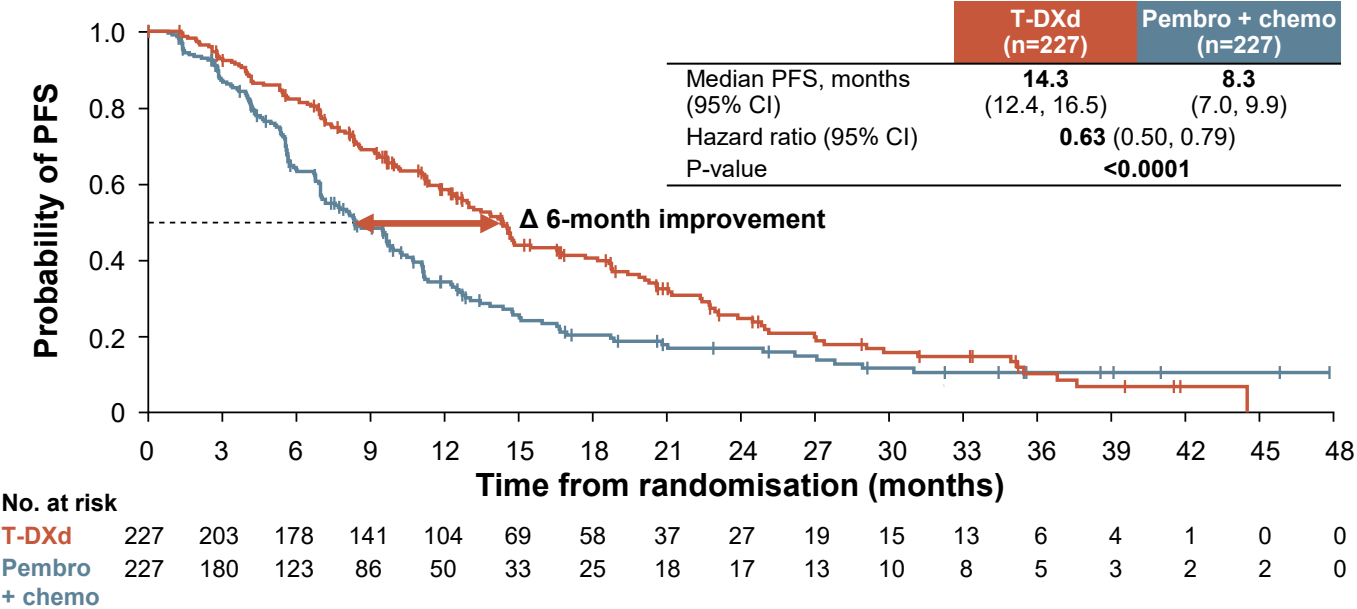
PFS, ORR, and DoR all per RECIST 1.1. Participants with objective radiological CNS disease progression per RECIST 1.1 could continue with their assigned trial treatment if, in the investigator's opinion, they continued to receive clinical benefit and were without any discontinuation criteria. Treatment crossover was not permitted

^a 5.4 mg/kg IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; ^b 200 mg IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; ^c Investigator choice of cisplatin (75 mg/m²) or carboplatin (AUC 5) IV Q3W for up to four cycles; ^d 500 mg/m² IV Q3W until disease progression, unacceptable toxicity, or other discontinuation criteria; ^e For the final PFS analysis, ~306 events provided 90% power to detect a hazard ratio of 0.69 with a two-sided significance level of 5%; ^f The first OS interim analysis was conducted at the time of final PFS analysis; no formal hypothesis testing was planned

ADC, antibody-drug conjugate; AUC, area-under-curve; BICR, blinded independent central review; chemo, chemotherapy; CNS, central nervous system; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS(2), progression-free survival (2); Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care; T-DXd, trastuzumab deruxtecan

DESTINY-LUNG04: EFFICACY RESULTS

PROGRESSION-FREE SURVIVAL (BICR) – PRIMARY ENDPOINT



T-DXd monotherapy demonstrated a statistically significant and clinically meaningful PFS improvement vs standard-of-care pembro + doublet chemo

- PFS effects were consistent across subgroups studied
- No OS benefit observed with T-DXd; imbalance in subsequent treatments may have impacted results

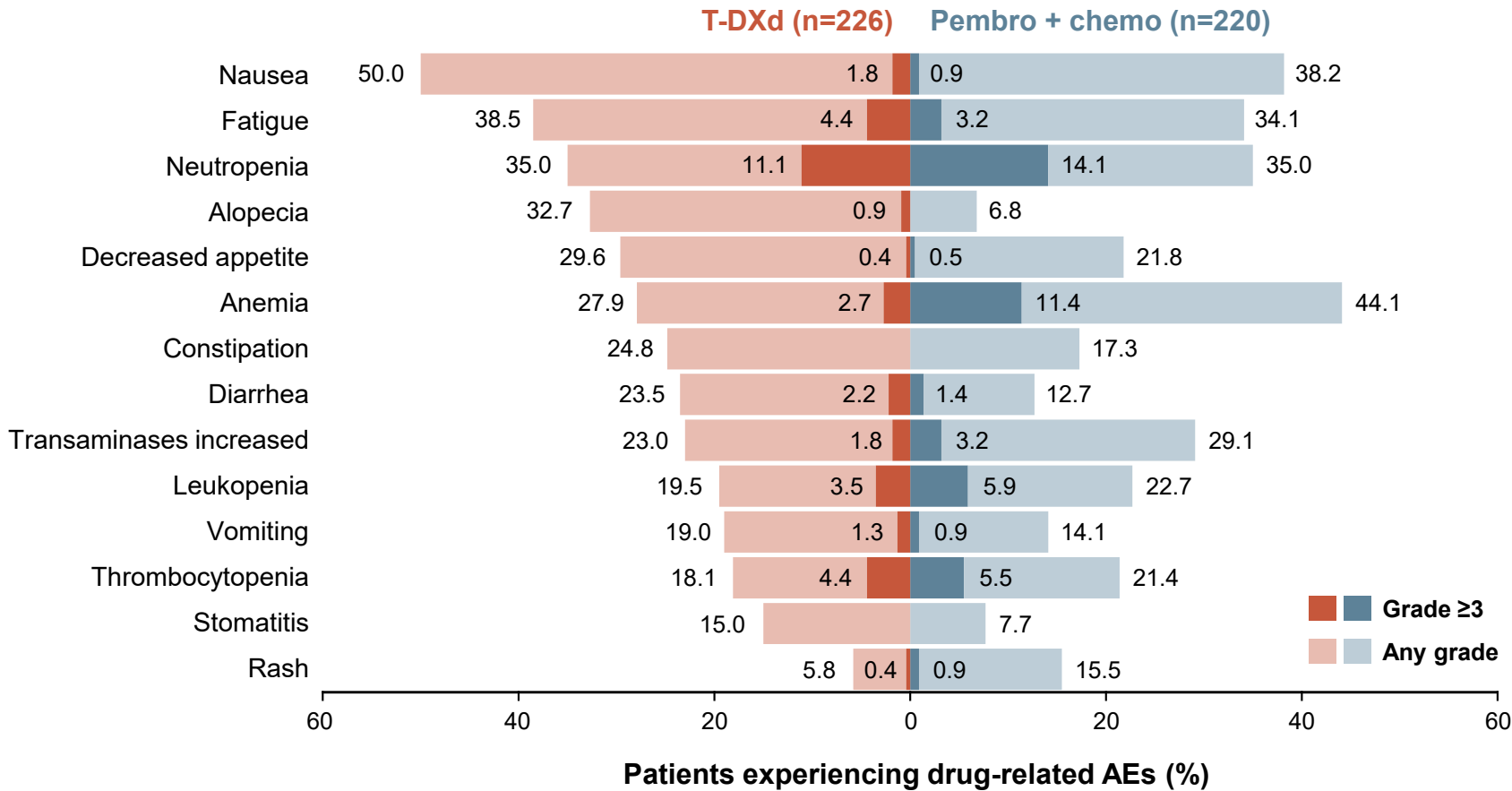
Median (range) duration of follow up was 21.6 months (0.4-51.1) with T-DXd and 20.4 months (0.1-52.0) with pembro+chemo
BICR, blinded independent central review; chemo, chemotherapy; CI, confidence interval; DoR, duration of response; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan
Rotow J, et al. Abstract PL03.08, WCLC 2026 (oral presentation)

SECONDARY EFFICACY ENDPOINTS

	T-DXd (n=227)	Pembro + chemo (n=227)
ORR, % (95% CI)	70 (63.6, 75.9)	44.5 (37.9, 51.2)
Median DoR, months (95% CI)	13.4 (10.4, 17.2)	9.7 (7.0, 11.1)
Median OS, months (95% CI)	29.3 (26.2, 33.4)	33.1 (27.7, 40.7)
HR (95% CI)	1.15 (0.88, 1.52)	

DESTINY-LUNG04: SAFETY RESULTS

MOST COMMON (≥15%) DRUG-RELATED AEs (INV ASSESSED)



INTERSTITIAL LUNG DISEASE (ILD)

- Adjudicated drug-related ILD/pneumonitis occurred in 47 patients (20.8%; most were Grade 1/2 [78.7%]) treated with T-DXd and 5 patients (2.3%; all Grade 1/2) treated with pembro + chemo
- Grade 5 drug-related ILD/pneumonitis occurred in 4 patients (1.8%) treated with T-DXd
- ILD remains an important risk of T-DXd and should be monitored/managed appropriately

DESTINY-LUNG04: SUMMARY

- This is the first global Phase 3 trial to demonstrate a statistically significant and clinically meaningful improvement in PFS with first-line T-DXd versus SOC pembro + chemo in patients with advanced/metastatic HER2-mutant NSCLC
- T-DXd treatment improved response rates and durability compared with pembro + chemo
- Imbalance in subsequent therapies confound the interpretability of the OS results
- Safety was generally consistent with the known profile of T-DXd

Clinical perspective

- T-DXd moves from a predominantly post-platinum setting towards a potential first-line strategy
- The optimal sequencing of T-DXd with emerging HER2-targeted TKIs and the role of subsequent therapies still needs to be established

chemo, chemotherapy; NSCLC, non-small cell lung cancer; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; SOC, standard of care; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor

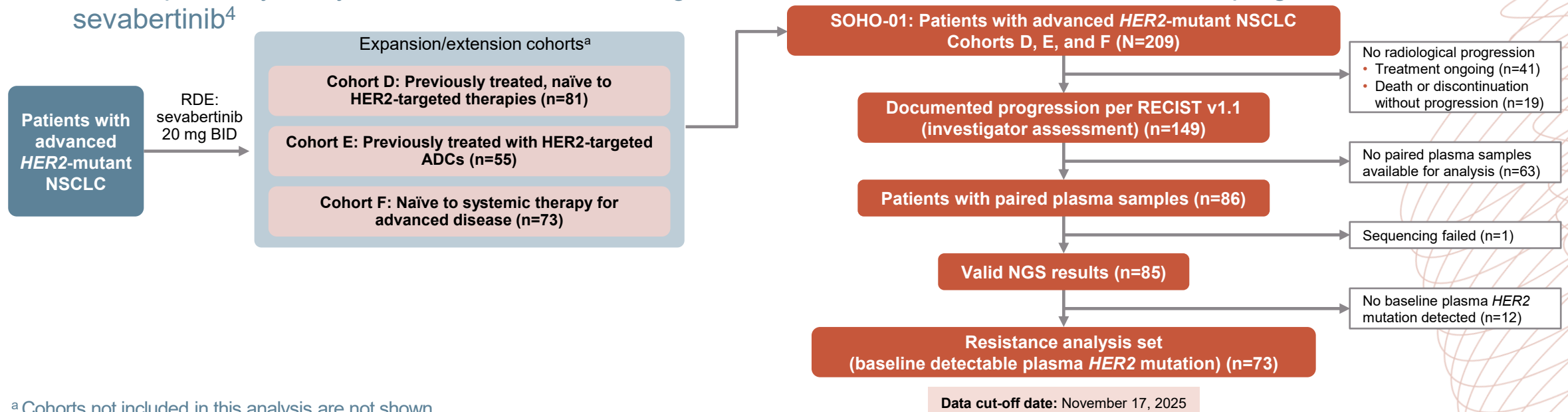
Rotow J, et al. Abstract PL03.08, WCLC 2026

MOLECULAR LANDSCAPE OF ACQUIRED RESISTANCE TO SEVABERTINIB IN *HER2*-MUTANT NSCLC: EXPLORATORY BIOMARKER ANALYSIS OF SOHO-01

Le X, et al. Abstract MO12.04, WCLC 2026

SOHO-01 BIOMARKER ANALYSIS: BACKGROUND AND STUDY DESIGN

- **Sevabertinib** is an oral, **reversible tyrosine kinase inhibitor** that **potently inhibits HER2 and EGFR** in preclinical models^{1,2}
- Sevabertinib demonstrated significant antitumor activity and manageable safety in patients with *HER2*-mutant NSCLC who were **previously treated (Cohorts D & E)** or were **treatment-naïve (Cohort F)** in the **Phase 1/2 SOHO-01 trial** (NCT05099172)³
- This exploratory analysis aimed to characterise genomic alterations associated with disease progression on sevabertinib⁴



^a Cohorts not included in this analysis are not shown

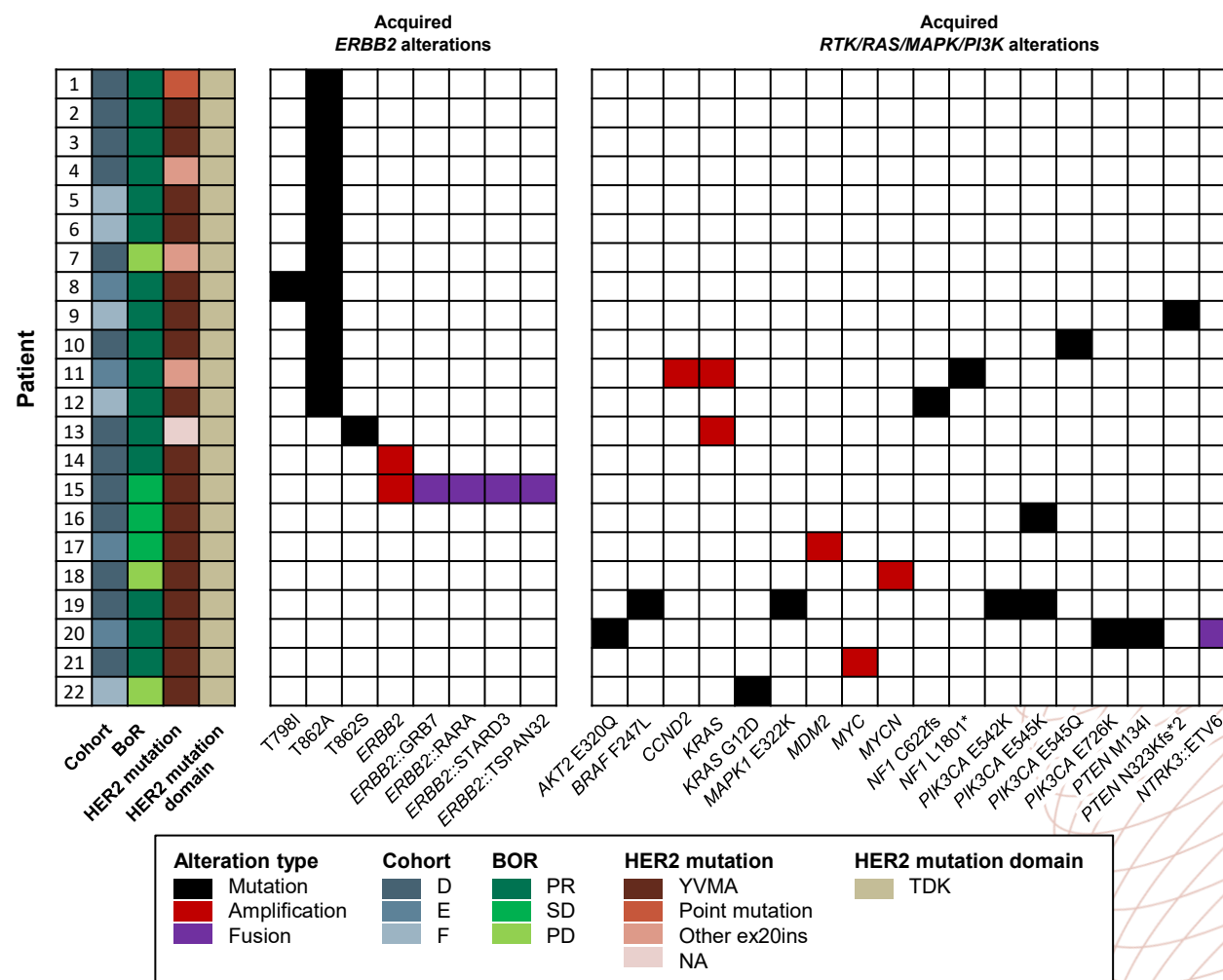
ADC, antibody drug conjugate; BID, twice daily; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumours

1. Girard N, et al. J Clin Oncol. 2024;42(suppl 17). Abstr LBA8598; 2. Loong HHF, et al. Ann Oncol. 2023;34(Supplement 2):S761-S762; 3. Le X, et al. N Engl J Med. 2025;393:1819-1832; 4. Le X, et al. Abstract MO12.04, WCLC 2026 (oral presentation)

SOHO-01: PUTATIVE MECHANISMS OF ACQUIRED RESISTANCE

EXPLORATORY BIOMARKER ANALYSIS

- Putative resistance-associated genomic events were identified in 30% of pts
- HER2 T862A substitutions were the most common secondary *HER2* alterations (16%)
- HER2 amplifications were found in 3% of pts
- No C805S or S783C mutations were detected in PD plasma samples
- Bypass/downstream alterations were less frequent and predominantly involved emergent alterations in PI3K/PTEN and *MAPK*-pathway genes (12%)
- Multiple alterations can coexist in the same patient



BoR, best overall response; NA, not applicable; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease; TKD, tyrosine kinase domain

Le X, et al. Abstract MO12.04, WCLC 2026 (Oral presentation)

SOHO-01: RESPONSE AND PFS IN ACQUIRED T862A CASES

EXPLORATORY BIOMARKER ANALYSIS

- Patients who acquired T862A at PD had an ORR of 92% (11/12)
- Patients who acquired T862A at PD had comparable DoR and PFS compared with those without
- One patient had T862A detected at baseline, whose tumour had primary resistance to sevabertinib (Cohort E, post-HER2-targeted-ADC)

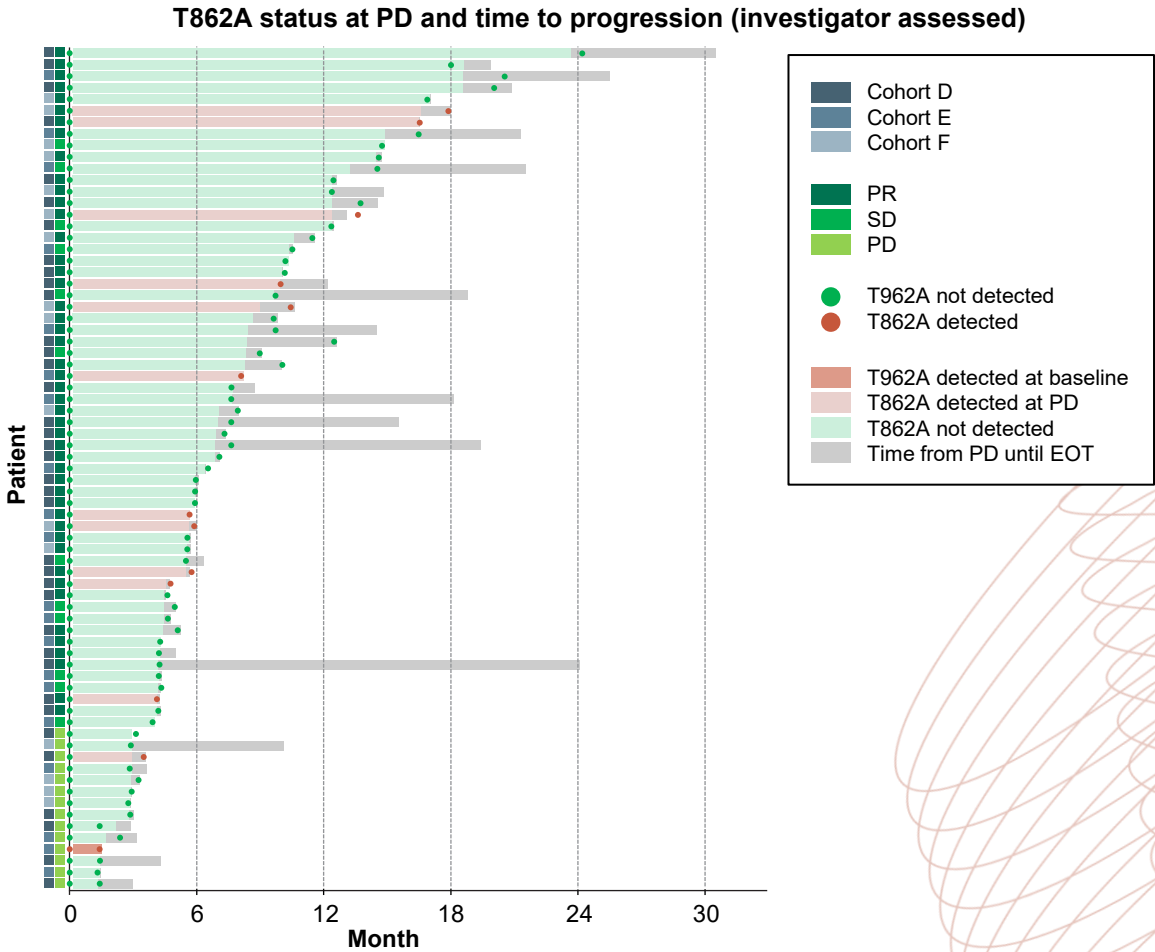
Summary of PFS by investigator by T862A detection status at progression (Cohorts D, E and F)		
New T862A mutation at progression	N	PFS range (months)
No	60	1.1-23.5
Yes	12	2.8-16.4

One patient who had a T862A mutation at baseline was excluded

Data cut-off: November 17, 2025. Progression samples were taken within 4 weeks before or at any time after radiographic PD (RECIST 1.1). Included are patients from Cohorts D, E, and F (20 mg BID) who had successful NGS results, who had paired baseline and progression timepoint data (investigator confirmed clinical progression), and whose locally reported HER2-activating mutation was detected in the baseline plasma sample

ADC, antibody-drug conjugate; BID, twice daily; DoR, duration of response; EOT, end of treatment; NGS, next-generation sequencing; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease;

Le X, et al. Abstract MO12.04, WCLC 2026 (Oral presentation)



SOHO-01 BIOMARKER ANALYSIS: SUMMARY

- Secondary HER2 T862A appears to be the predominant putative mechanism of acquired resistance to sevabertinib, while bypass/downstream pathway alterations were less common
- Most patients with disease progression lacked identifiable genomic resistance drivers, suggesting important roles for non-genetic or adaptive mechanisms
- Clinically, patients harbouring secondary HER2 T862A mutations exhibited comparable duration of response and time to progression compared with those without
- Preclinical and structural modelling studies are underway to elucidate the biological impact of the HER2 T862A alterations on sevabertinib binding and activity

Clinical perspective

- The SOHO-01 exploratory biomarker analysis provides early insight into the molecular mechanisms underlying acquired resistance to sevabertinib, identifying secondary HER2 T862A as a potential resistance alteration
- However, the clinical implications for subsequent HER2-directed treatment and sequencing remain to be established

ACQUIRED RESISTANCE TO ZONGERTINIB TREATMENT IN PATIENTS WITH *HER2*- MUTANT NSCLC: PHASE 1B BEAMION LUNG-1 STUDY

Planchard D, et al. Abstract MO12.05, WCLC 2026

BEAMION LUNG-1 BIOMARKER ANALYSIS: BACKGROUND AND STUDY DESIGN

- **Zongertinib, a novel HER2-specific TKI**, binds selectively and covalently to the HER2 tyrosine kinase domain while sparing wild-type EGFR¹ and limiting EGFR-related adverse events²
- **Beamion LUNG-1** is a phase 1b, ongoing dose-expansion study of zongertinib as monotherapy in patients with advanced/metastatic *HER2*-mutant NSCLC with or without prior treatment.³ Potential acquired resistance mechanisms to zongertinib were evaluated and reported.⁴

Beamion LUNG-1 Phase Ib (dose expansion): patients with advanced *HER2*-mutant NSCLC

Cohort 1	Previously treated* patients with TKD mutations (n=75)
Cohort 2	Treatment-naïve patients with TKD mutations (n=74)
Cohort 3	Previously treated ^a patients with non-TKD mutations (n=20)
Cohort 4	Treatment-naïve or previously treated patients with TKD mutations and active brain metastases (n=30)
Cohort 5	Patients previously treated with HER2-directed ADC and with TKD mutations (n=31)

Here, we analysed paired tumour tissue and plasma samples collected before treatment and at disease progression to explore acquired resistance mechanisms to zongertinib

Genomics

Acquired oncogenic driver alterations

Tumour DNA analysis:
TruSight™ Oncology 500

Plasma ctDNA analysis:
NGS AVENIO assay

Transcriptomics

Differential gene expression and pathway activation downstream of, or independent of, HER2

Roche KAPA Total RNAseq

^a Excluding those previously treated with a HER2-directed ADC

ADC, antibody–drug conjugate; ctDNA, circulating tumour DNA; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RNAseq, ribonucleic acid sequencing; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor

1. Heymach JV, et al. Clin Lung Cancer. 2023;24:e65-e68; 2. Wilding B, et al. Cancer Discov. 2024;15:119-138; 3. Heymach JV, et al. N Engl J Med. 2025;392:2321-33;

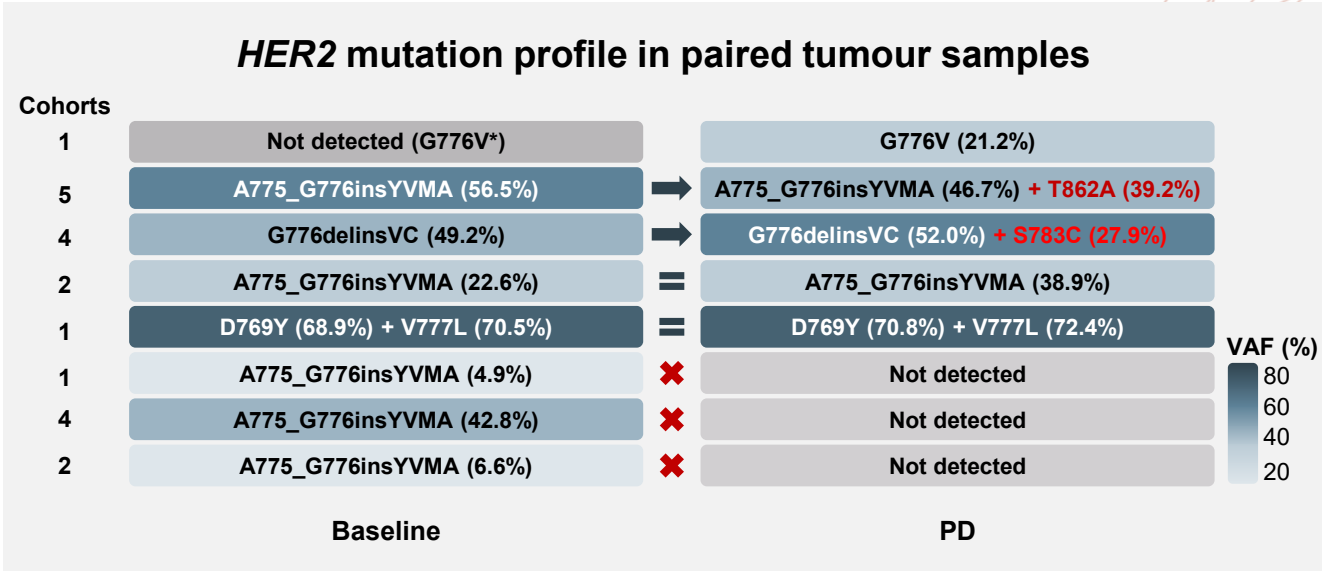
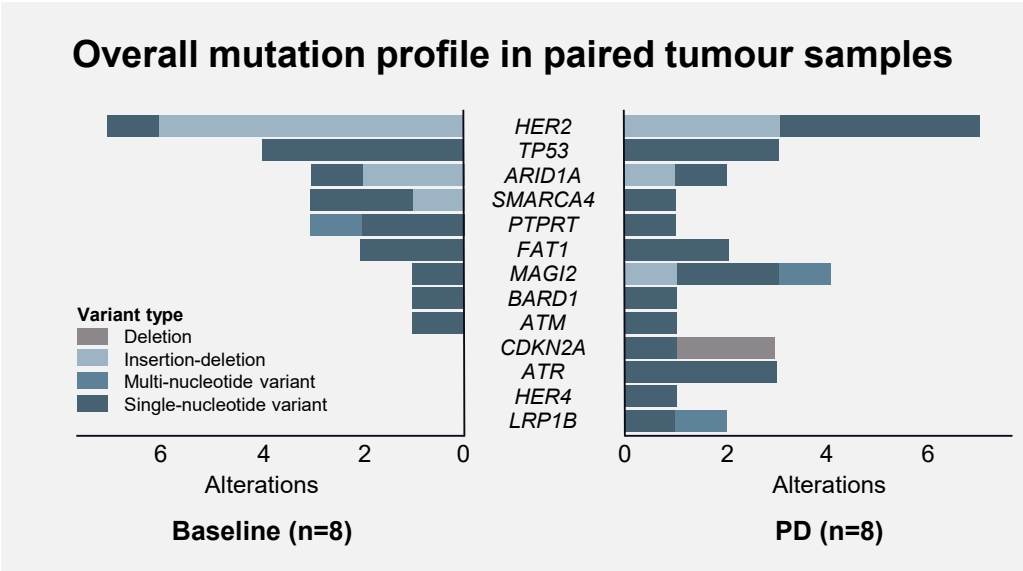
4. Planchard D, et al. Abstract MO12.05, WCLC 2026 (oral presentation)

BEAMION LUNG-1: A HETEROGENOUS RESISTANCE LANDSCAPE AT DISEASE PROGRESSION

EXPLORATORY ANALYSIS

Tumour tissue DNA analysis revealed:

- Emergent mutations identified at PD, but not at baseline, included *HER2*, *CDKN2A*, *ATR*, *HER4*, and *LRP1B*
- Acquired *HER2* mutations, **S783C** and **T862A**, were detected at PD, which may potentially disrupt key hydrogen bond interactions between zongertinib and *HER2*
- No acquired *HER2* T798I (gatekeeper) or C805S (binding site for zongertinib) mutations were detected at PD



BEAMION LUNG-1: EXPLORATORY BIOMARKER ANALYSIS

PLASMA ctDNA ANALYSES SUPPORTED KEY GENOMIC FINDINGS AT DISEASE PROGRESSION

- Plasma ctDNA analyses showed broad concordance with tumour DNA analyses, however:
 - The acquired **T862A** mutation was not detected in plasma ctDNA, and corresponding plasma data were not available for **S783C**

TUMOUR TISSUE RNA ANALYSES REVEALED SHARED PATHWAYS AT DISEASE PROGRESSION

- Transcriptomic analyses of predefined signalling pathways (HALLMARK) identified changes consistent with:
 - Increased proliferative signalling
 - Increased metabolic reprogramming
 - Reduced tumour immunogenicity
- No significant changes in specific bypass pathways, such as HER2 feedback loop, suggest that progression is driven by broader biological adaptation rather than recurrent activation of a single mechanism

BEAMION LUNG-1 BIOMARKER ANALYSIS: SUMMARY

- This analysis of tumour samples from patients with *HER2*-mutant advanced/metastatic NSCLC identified a heterogeneous resistance landscape to zongertinib, no predominant resistance mutation was identified
- Acquired genomic alterations were diverse, but RNA analyses identified convergent biological pathways, characterised by enhanced proliferation, metabolic reprogramming and potential reductions in tumour immunogenicity
- Overall, these findings highlight the necessity of molecularly guided, patient-specific therapeutic strategies at disease progression

Clinical perspective

- Resistance to zongertinib appears molecularly heterogeneous, with diverse genomic alterations converging on pathways associated with proliferation, metabolism and reduced immunogenicity
- The clinical implications for treatment sequencing remain to be established



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