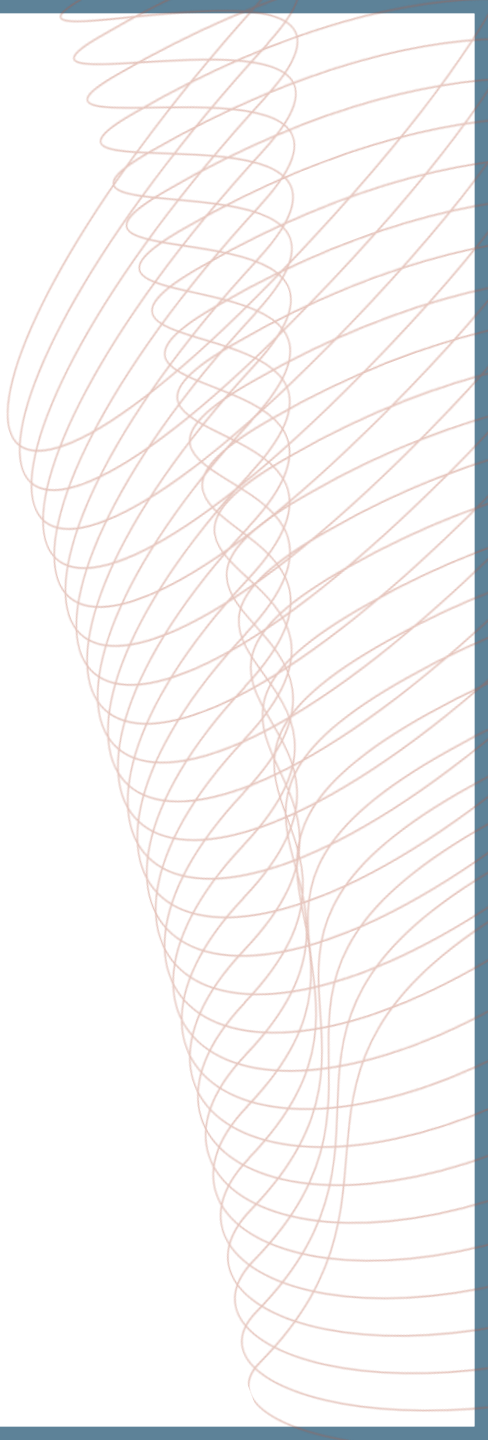




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LUNG CONNECT

HER2-MUTATED NSCLC HIGHLIGHTS FROM ESMO 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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Expert disclosures:

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CLINICAL TAKEAWAYS

- **DESTINY-Lung04:** First-line trastuzumab deruxtecan showed favourable patient-reported pulmonary symptom outcomes versus pembrolizumab plus chemotherapy, with generally comparable treatment tolerability
- **GENIE Registry:** Poor prognosis in *HER2*-mutant NSCLC highlights the unmet need, with median overall survival of 18 months from diagnosis, decreasing to 13 months from second-line and 6 months from third-line treatment
- **SOHO-01:** Sevabertinib continued to demonstrate durable responses across treatment-naïve and previously treated patients with *HER2*-mutant NSCLC, including intracranial activity in heavily pretreated patients with active brain metastases

EDUCATIONAL OBJECTIVES

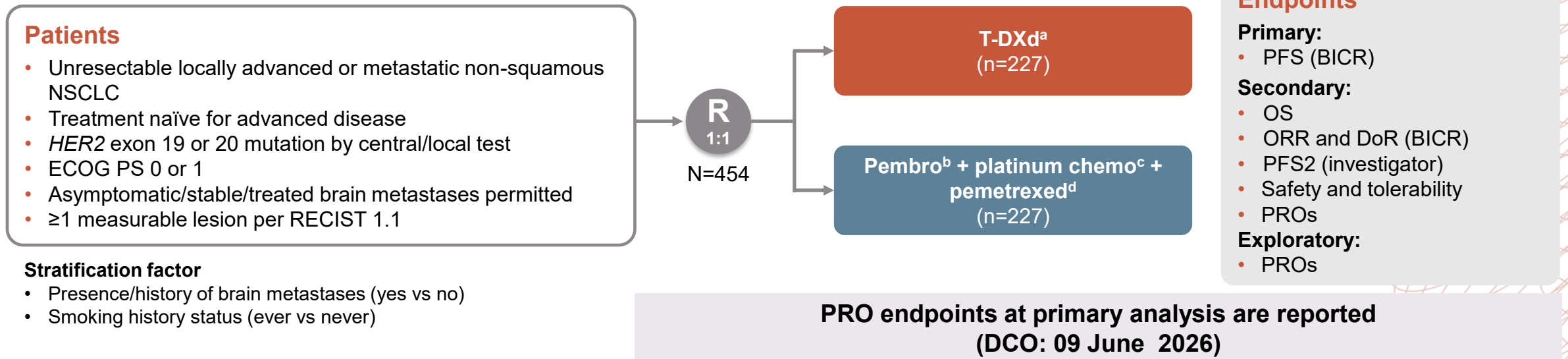
- Understand the latest **clinical trial data and emerging profiles** of therapies for the treatment of *HER2*-mutant NSCLC

DESTINY-Lung04: PATIENT-REPORTED OUTCOMES OF FIRST-LINE TRASTUZUMAB DERUXTECAN IN PATIENTS WITH *HER2*-MUTANT NSCLC

Novello S, et al. Abstract LBA74, ESMO 2026

DESTINY-LUNG04: BACKGROUND AND STUDY DESIGN

- **DESTINY-Lung04** (NCT05048797) evaluated first-line T-DXd (a HER2-directed ADC) versus pembrolizumab + chemotherapy in advanced/metastatic *HER2*-mutant NSCLC and demonstrated a statistically significant and clinically meaningful improvement in PFS with first-line T-DXd versus SOC pembro + chemo¹
- Pre-specified patient reported outcomes (PRO) were reported at ESMO 2026²



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

ADC, antibody-drug conjugate; AUC, area-under-curve; BICR, blinded independent central review; chemo, chemotherapy; CNS, central nervous system; DCO, data cut-off; 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; pembro, pembrolizumab; PFS(2), progression-free survival (2); PRO, patient reported outcomes; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; SOC, standard of care; T-DXd, trastuzumab deruxtecan

1. Rotow J, et al. Abstract PL03.08, WCLC 2026; 2. Novello S, et al. Abstract LBA74, ESMO 2026 (oral presentation)

DESTINY-LUNG04: EFFICACY RESULTS

TIME TO DETERIORATION IN PATIENT-REPORTED PULMONARY SYMPTOMS (NSCLC-SAQ)

Symptom	T-DXd N=227	Pembro + chemo N=227	HR (95% CI)
	Median TTD (95% CI), months		
Cough	26.2 (17.1, NC)	11.0 (7.4, NC)	0.66 (0.44–0.99)
Dyspnea	10.1 (6.5, NC)	5.1 (3.2, 11.0)	0.77 (0.54–1.09)
Chest pain	NC (11.5, NC)	14.3 (8.3, NC)	0.80 (0.54–1.18)

T-DXd monotherapy delayed time to, and reduced risk of, deterioration in cough versus pembro + chemo.
Favourable numerical trends for dyspnea and chest pain

chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; NC, not calculable; pembro, pembrolizumab; NSCLC-SAQ, Non-Small Cell Lung Cancer – Symptom Assessment Questionnaire; T-DXd, trastuzumab deruxtecan; TTD, time to deterioration
Novello S, et al. Abstract LBA74, ESMO 2026 (oral presentation)

DESTINY-LUNG04: SAFETY RESULTS

PHYSICAL FUNCTIONING (PF) (EORTC QLQ-C30)

The proportion of pts with maintained/improved PF was similar across arms until Week 18 and generally higher with T-DXd from Week 20, including at end of treatment (EOT, 66.7% T-DXd vs 57.7% pembro + chemo)

OVERALL TREATMENT TOLERABILITY (PGI-TT)

Overall side-effect bother was similar across arms for most timepoints. The proportion of patient-weeks with high side-effect bother was 13.4% in each arm^a

SYMPTOMS RELATED TO AEs (EORTC QLQ-C30/EORTC IL/PRO-CTCAE)

T-DXd vs pembro + chemo (measured across the duration of treatment):

8/15
symptoms

Generally better with T-DXd

Cough, dyspnea, general pain, chest pain, watery eyes, headache, arm/leg swelling and rash

2/15
symptoms

Similar between arms

Fatigue and constipation

5/15
symptoms

Generally worse with T-DXd

Hair loss, appetite loss, nausea, diarrhea and vomiting

^aRestricted to first 12 weeks of treatment

AE, adverse event; chemo, chemotherapy; EORTC, European Organisation for Research and Treatment of cancer; IL, item library; pembro, pembrolizumab; PF, physical functioning; PGI-TT, Patients Global Impression of Treatment Tolerability; PRO-CTCAE, Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events; QLQ-C30, Quality of Life Questionnaire Core 30; T-DXd, trastuzumab deruxtecan
Novello S, et al. Abstract LBA74, ESMO 2026 (oral presentation)

DESTINY-LUNG04: SUMMARY

- Time to deterioration in patient-reported pulmonary symptoms (cough, chest pain, dyspnea) favoured T-DXd vs pembro + chemo
- Patient-reported treatment tolerability (physical functioning and overall/high side-effect bother) was generally comparable between treatment arms, with physical functioning generally higher with T-DXd from Week 20 and at EOT

Clinical perspective

- DESTINY-Lung04 PRO data, alongside efficacy and safety results from the primary analysis, support T-DXd as a new 1st line treatment option for patients with *HER2*-mutant NSCLC

chemo, chemotherapy; EOT, end of treatment; NSCLC, non-small cell lung cancer; pembro, pembrolizumab; PRO, patient reported outcomes; T-DXd, trastuzumab deruxtecan

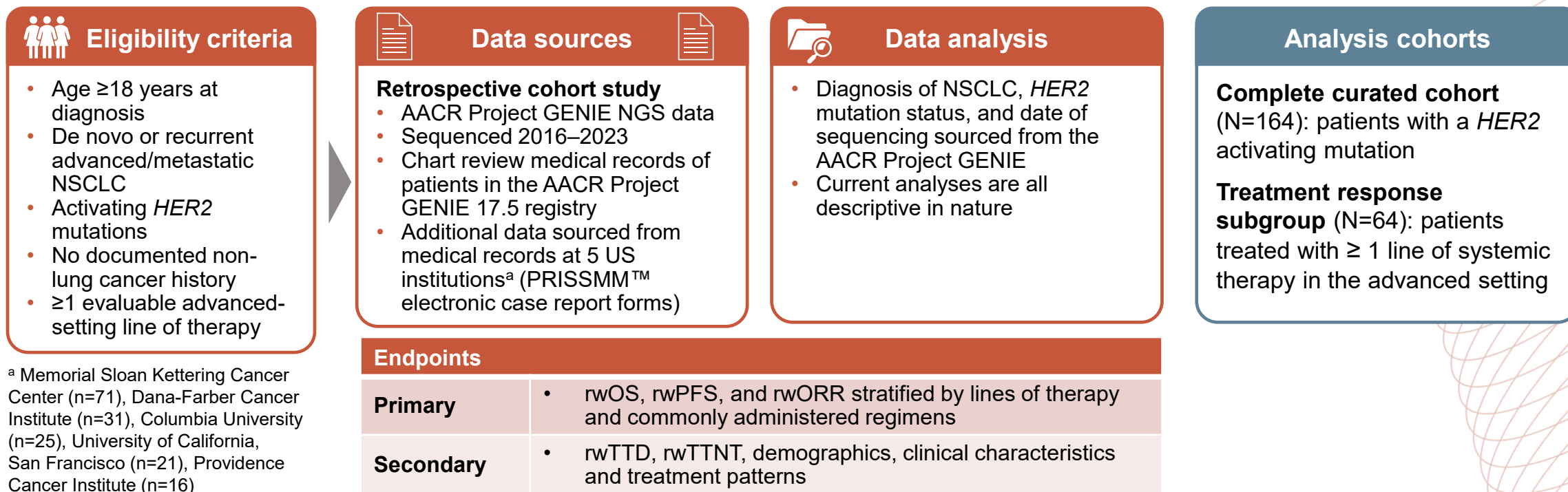
Novello S, et al. Abstract LBA74, ESMO 2026 (oral presentation)

GENIE REGISTRY: MOLECULAR PROFILE, TREATMENT PATTERNS, AND REAL-WORLD OUTCOMES IN *HER2*-MUTANT NSCLC

Kehl K, et al. Abstract 2696P, ESMO 2026

GENIE REGISTRY: BACKGROUND AND STUDY DESIGN

- *HER2* mutations occur in 2-5% of patients with NSCLC and are associated with a poor prognosis¹⁻³
- The AACR GENIE registry study was designed to evaluate real world outcomes of patients with pre-treated advanced/metastatic *HER2*-mutant NSCLC⁴



AACR, American Association for Cancer Research; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; rWORR, real-world overall response rate; rWOS, real-world overall survival; rWPFS, real-world progression-free survival; rWTTD, real-world time to deterioration; rWTTNT, real-world time to next treatment; US, United States

1. Pillai RB, et al. Cancer. 2017;123 (21):4099-105; 2. Uy NF, et al. Cancers (Basel). 2022;14(7):4155; 3. Wei XW, et al. Thorac Cancer. 2020;11(6):1512-21; 4. Kehl K, et al. Abstract 2696P, ESMO 2026 (poster presentation)

GENIE REGISTRY: EFFICACY RESULTS

PATIENTS AND TREATMENT PATTERNS

In the complete cohort (n=164):

- median age 66 years
- 68% were females
- 50% were never smokers
- 87% had adenocarcinoma
- 45% had stage 4 disease at diagnosis
- The most frequent *HER2* variant was p.Y772_A775dup (52%)
- Non-HER2 sequence-level co-occurring alterations were detected in 82%, most commonly TP53

REAL-WORLD OUTCOMES BY LINE OF THERAPY

Median (95% CI), months	1 st line (n=60)	2 nd line (n=43)	3 rd line (n=28)
rwOS	17.6 (11.2-29.1)	12.8 (6.4-22.0)	6.2 (4.3-15.5)
rwPFS ^a	6.3 (4.2-10.5)	5.2 (2.7-8.9)	2.2 (1.2-8.3)
rwTTNT	8.0 (6.0-10.8)	8.2 (4.6-12.9)	4.1 (3.0-10.4)

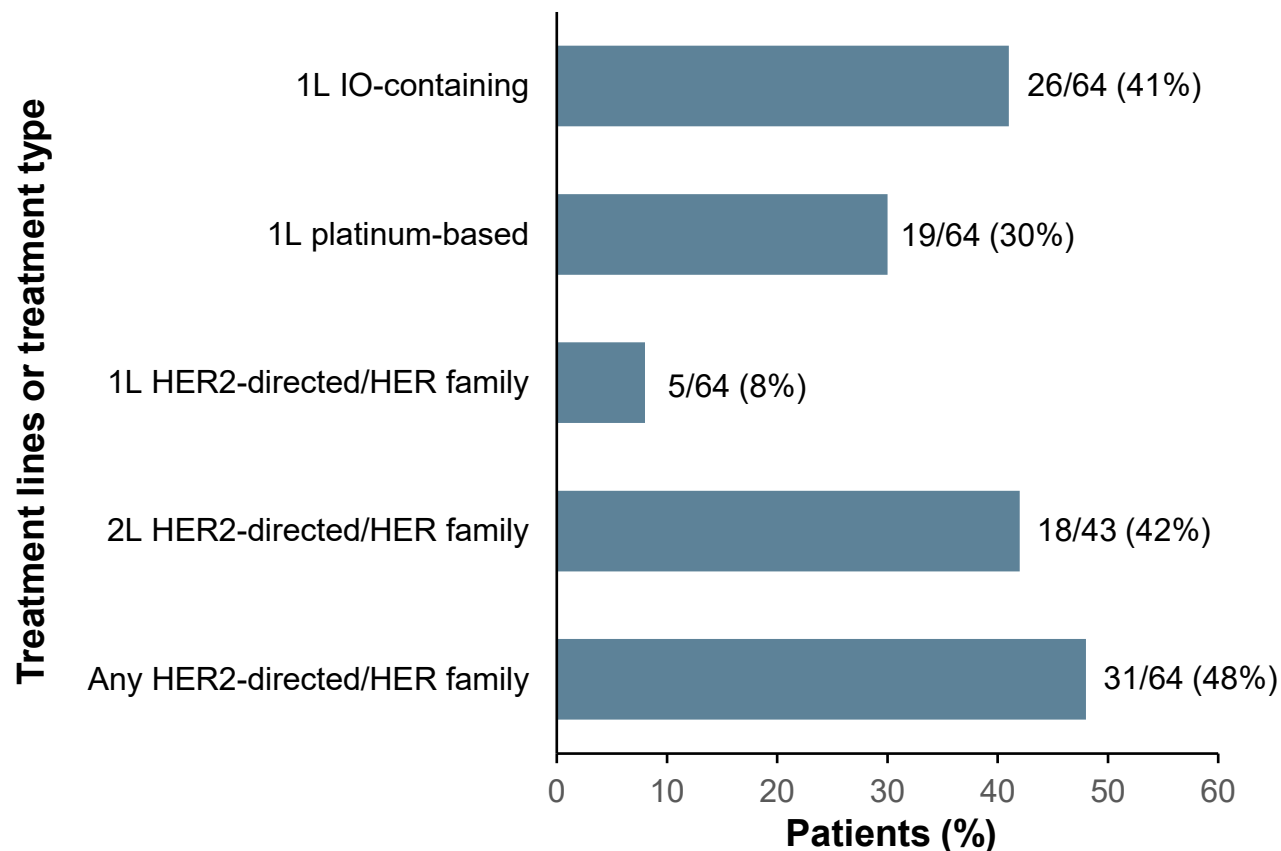
^a For rwPFS: 1st line (n=57), 2nd line (n=36), 3rd line (n=23)

CI, confidence interval; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTNT, real-world time to next treatment

Kehl K, et al. Abstract 2696P, ESMO 2026 (poster presentation)

GENIE REGISTRY: RESULTS

TREATMENT PATTERNS OF PATIENTS (N=64)^a



In the treatment response subgroup (n=64):

- Most common 1st line treatments were immunotherapy-containing regimens and platinum-based chemotherapy
- 44% received T-DXd, most often in 2nd line
- Prior therapy:
 - 33% had one line of therapy
 - 67% had 2+ lines of prior therapy
 - 44% had 3+ lines of prior therapy

^a N=64 patients were line of treatment-evaluable overall; n=43 were evaluable in 2L. *HER2*-directed therapy included T-DXd, T-DM1, or another *HER2/HER*-family directed agent (including afatinib, trastuzumab, tucatinib).

Line-specific *HER2*-directed counts are mutually exclusive within each line; any-line counts are not mutually exclusive (1 patient received T-DXd in multiple lines)

1L, first-line; 2L, second-line; IO, immuno-oncology; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

Kehl K, et al. Abstract 2696P, ESMO 2026 (poster presentation)

GENIE REGISTRY: SUMMARY

- This real-world cohort demonstrates molecular heterogeneity, treatment patterns, and line of treatment outcomes in *HER2*-mutant NSCLC
- *HER2* directed/*HER*-family therapy, particularly T-DXd, was used primarily after 1st line
- These data provide benchmarks for treatment sequencing in this actionable NSCLC population

Clinical perspective

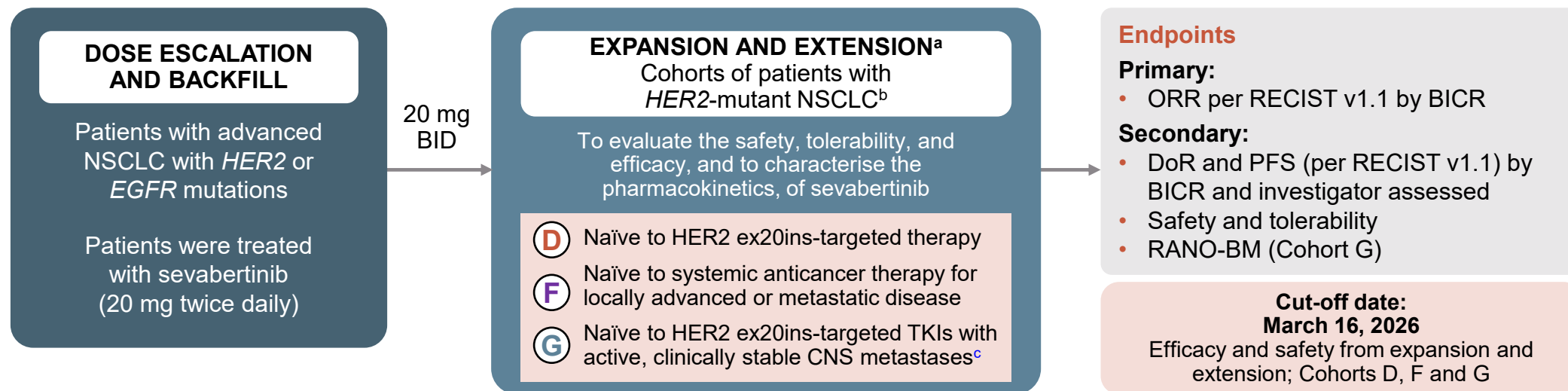
- These data provide important real-world context for treatment considerations in patients with *HER2*-mutant NSCLC

SOHO-01: UPDATED EFFICACY AND SAFETY OF SEVABERTINIB IN ADVANCED *HER2*-MUTANT NSCLC, INCLUDING 1ST LINE PATIENTS AND THOSE WITH ACTIVE BRAIN METASTASES

Le X, et al. Abstract 2712P, ESMO 2026

SOHO-01: BACKGROUND AND STUDY DESIGN

- **Sevabertinib** is an oral, **reversible tyrosine kinase inhibitor that potently inhibits HER2 and EGFR** in preclinical models¹
- Sevabertinib demonstrated 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)²
- Updated results from Cohorts D and F with longer follow-up are reported together with Cohort G³



^a Cohorts whose data are not presented in this poster are not included herein, including the *EGFR*-mutant NSCLC cohort; ^b Patients from dose escalation and expansion who were treated at the same dose level and who met the same eligibility criteria for an extension group were combined for the respective statistical analysis; ^c New or progressing brain metastases that do not require immediate CNS-directed treatment as per the investigator's judgement

BID, twice daily; CNS, central nervous system; DoR, duration of response; ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor

1. Girard N, et al. J Clin Oncol. 2024;42(suppl 17). Abstr LBA8598; 2. Le X, et al. N Engl J Med. 2025;393:1819-1832; 3. Le X, et al. Abstract 2712P, ESMO 2026 (poster presentation)

SOHO-01: UPDATED EFFICACY RESULTS

SUBGROUP ANALYSIS – TUMOUR RESPONSE

	Cohort D		Cohort F		Cohort G (RANO-BM by BICR)		
	All treated patients (n=81)	Treated patients with non-squamous histology + <i>HER2</i> TKD mutation (n=70)	All treated patients (n=73)	Treated patients with non-squamous histology + <i>HER2</i> TKD mutation (n=69)	All patients (n=31) ^a	Measurable intracranial target lesions (n=16)	Non-measurable intracranial target lesions (n=15)
Median follow-up (range), months	22.8 (0.9-41.4)	23.0 (0.9-41.4)	17.4 (0.2-24.0)	17.9 (0.2-24.0)	13.2 (NR, NR)	NR	NR
ORR, % (95% CI)	67 (55, 77)	73 (61, 83)	75 (64, 85)	75 (64, 85)	26 (12, 45)	13 (2, 38)	40 (16, 68)
DCR, % (95% CI)	81 (71, 89)	84 (74, 92)	89 (80, 95)	90 (80, 96)	45 (27, 64)	31 (11, 59)	60 (32, 84)
Median DoR (95% CI), months	9.5 (6.3, 13.5)	9.5 (6.3, 13.5)	15.1 (9.1, NE)	15.1 (9.1, NE)	6.9 (2.9, 10.4)	5.1 (2.9, NE)	6.9 (4.2, NE)
Median PFS (95% CI), months	8.3 (6.9, 12.3)	9.6 (6.9, 14.5)	13.5 (10.0, NE)	16.4 (10.0, NE)	4.0 (2.7, 5.6)	2.8 (2.0, 4.0)	8.1 (2.7, 14.4)

^a 94% of patients received prior systemic anticancer therapy

CI, confidence interval; DCR, disease control rate; DoR, duration of response; NE, not estimable; NR, not reported; ORR, objective response rate;

PFS, progression-free survival; TKD, tyrosine kinase domain

Le X, et al. Abstract 2712P, ESMO 2026 (poster presentation)

SOHO-01: UPDATED SAFETY RESULTS

SAFETY SUMMARY

- The safety profile of sevabertinib was manageable and consistent with previous reports
- Majority of drug-related TEAEs were below grade 3 in cohorts D, F and G
- Most common drug-related TEAE was diarrhea across cohorts
 - Grade 3 drug-related diarrhea occurred in 25% of patients in Cohort D, 5% in Cohort F and 26% in Cohort G
 - No treatment discontinuations due to diarrhea

INCIDENCE AND SEVERITY OF DRUG-RELATED TEAEs

n (%)	Cohort D (N=81)	Cohort F (N=73)	Cohort G (N=31)
Any	78 (96)	71 (97)	30 (97)
Grade 1-2	45 (56)	49 (67)	16 (52)
Grade ≥3	33 (41)	22 (30) ^a	14 (45)
Serious	12 (15)	8 (11)	5 (16)
Leading to dose reduction	20 (25)	23 (32)	8 (26)
Leading to dose interruption or delay	26 (32)	24 (33)	8 (26)
Leading to permanent treatment discontinuation	4 (5)	2 (3)	1 (3)
Most common drug-related TEAEs (>20% of patients)			
Diarrhea	70 (86)	62 (85)	27 (87)
Rash	42 (52)	42 (58)	11 (35)
Paronychia	23 (28)	20 (27)	6 (19)
Anemia	15 (19)	20 (27)	2 (6)
Stomatitis	15 (19)	20 (27)	7 (23)
Increased ALT	14 (17)	17 (23) ^b	6 (19)
Hypokalemia	15 (19) ^c	16 (22)	6 (19) ^d

AEs were graded by the investigator based on CTCAE v5.0

^a Cardiorespiratory arrest (n=1) occurred in a 69-year-old patient with emphysema, coronary-artery calcification, sinus tachycardia, and left anterior fascicular block and was deemed by the investigator as possibly related to the study drug;

^b One patient had a grade 4 drug-related increased ALT; ^c One patient had a grade 4 treatment-emergent hypokalemia, which was deemed by the investigator to be drug-related;

^d Two patients had grade 4 treatment-emergent hypokalemia and in one patient it was considered related to the drug

AE, adverse event; ALT, alanine transferase; CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event

Le X, et al. Abstract 2712P, ESMO 2026 (poster presentation)

SOHO-01: SUMMARY

- Sevabertinib demonstrated meaningful and durable responses in treatment-naïve (Cohort F) and previously treated patients (Cohort D) with *HER2*-mutant NSCLC, including intracranial activity in heavily pretreated patients with active brain metastases (Cohort G)
- The safety profile was manageable and consistent with previous reports

Clinical perspective

- Updated SOHO-01 results support the continued clinical activity of sevabertinib in *HER2*-mutant NSCLC, including intracranial responses in heavily pretreated patients with active brain metastases, an important consideration in this patient population



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