COR2ED

THE HEART OF MEDICAL EDUCATION

LUNG CONNECT

ONCOGENE-ADDICTED NSCLC HIGHLIGHTS FROM WCLC 2025

Dr Devika Das, MD
University of Mississippi, Mississippi, USA

SEPTEMBER 2025

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

LUNG connect® POWERED BY COR2ED

PRECISION ONCOLOGY connect® POWERED BY COR2ED

Acknowledgement and disclosures

This LUNG CONNECT programme is supported through an independent educational grant from Bayer. The programme is therefore independent, the content is not influenced by the supporter and is under the sole responsibility of the experts.

Please note:

- 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:

- **Dr Devika Das** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: Boehringer Ingelheim

CLINICAL TAKEAWAYS

- **Global TRUST-II:** taletrectinib demonstrated high and durable response rates, strong intracranial activity, and a favourable safety profile in both TKI-naive and TKI-pretreated *ROS1*+ NSCLC patients, reinforcing its potential as a next-generation ROS1 inhibitor
- **SHERLOCK:** first-line treatment with sotorasib plus bevacizumab and chemotherapy achieved high response rates and promising progression-free survival in *KRAS* G12C–mutant NSCLC across all PD-L1 groups and molecular subgroups
- **REZILIENT1:** zipalertinib showed meaningful efficacy and a manageable safety profile in *EGFR* exon 20 insertion–positive NSCLC patients who had previously received chemotherapy and amivantamab, addressing an important unmet need where no approved options currently exist
- **SOHO-01:** In *HER2*-mutant NSCLC, sevabertinib demonstrated greater efficacy in patients who had received fewer prior lines of therapy and in those with the *HER2* YVMA variant, highlighting the importance of integrating clinical and molecular features to guide treatment selection
- **Beamion LUNG-1:** zongertinib showed both systemic and intracranial activity with durable responses in *HER2*-mutant NSCLC patients with brain metastases, supporting its potential as a targeted therapy for this high-risk population

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

EDUCATIONAL OBJECTIVES

- Understand the **clinical trial data and emerging profiles** of therapies for the treatment of molecularly driven lung cancer, including treatments for HER2-directed NSCLC

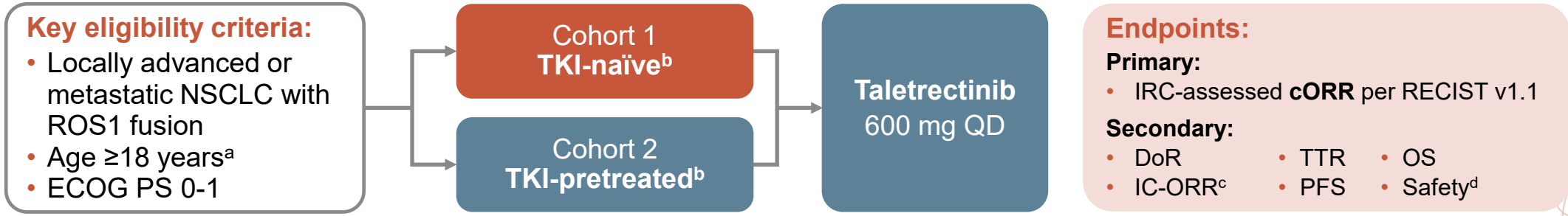
UPDATED EFFICACY AND SAFETY OF TALETRECTINIB IN PATIENTS WITH *ROS1*+ NSCLC: THE GLOBAL TRUST-II STUDY

Liu G, et al. Abstract MA02.02, WCLC 2025

NSCLC, non-small cell lung cancer

GLOBAL TRUST-II: BACKGROUND AND STUDY DESIGN

- **Taletrectinib**, an oral, potent, central nervous system-active, **selective next-generation ROS1 inhibitor**, **demonstrated high and durable responses**, robust intracranial activity, prolonged progression-free survival (PFS), favourable tolerability, and low rates of neurologic adverse events in a pooled analysis from the **regional TRUST-I** (NCT04395677) and **global TRUST-II** (NCT04919811) trials[1,2]
- **Updated efficacy and safety** in tyrosine kinase inhibitor (TKI)-naive and TKI-pretreated patients **from the registrational arms of the phase 2, TRUST-II trial** evaluating the efficacy and safety of taletrectinib in patients with advanced ROS1+ NSCLC **are reported here[3]**



Data cutoff: October 28, 2024

[a] Or ≥20 years, as required by local regulations; [b] Registrational cohorts are shown; [c] Assessed by IRC per mRECIST v1.1; [d] Safety population includes all patients who received ≥1 dose of taletrectinib 600 mg

DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; QD, once daily; (m)RECIST v1.1, (modified) Response Evaluation Criteria In Solid Tumours version 1.1; TKI, tyrosine kinase inhibitor; TTR, time to response

1. Pérol M, et al. J Clin Oncol. 2025:;43:1920-1929; 2. Liu G, et al. J Thorac Oncol. 2024;19:S72-S73; 3. Liu G, et al. Abstract MA02.02, WCLC 2025. Oral presentation

GLOBAL TRUST-II: DEMOGRAPHY AND EFFICACY RESULTS

- As of October 28, 2024, 105 patients were enrolled in TRUST-II registrational cohorts (median age: 57 years; 55% female; 55% never smoked); 47% were from North America/Europe. Among TKI-naive and TKI-pretreated patients, 34.5% and 56% had measurable baseline brain metastases, respectively

Efficacy	TKI-naïve (n=54)[a]	TKI pretreated (n=47)[a]
cORR (95% CI), %	85.2 (72.9-93.4)	61.7 (46.4-75.5)
cORR: prior chemotherapy		
Yes, n/N (%)	9/10 (90.0)	15/19 (78.9)
No, n/N (%)	37/44 (84.1)	14/28 (50.0)
Median DoR (95% CI),[b] months	NR (20.6-NR)	19.4 (10.7-NR)
Median PFS (95% CI), months	NR (15.9-NR)	11.8 (7.7-20.6)
Median TTR (95% CI),[b] months	1.4 (1.3-1.4)	1.4 (1.4-1.6)
IC efficacy	**TKI-naïve (n=9)[c]**	**TKI pretreated (n=16)[c]**
IC-ORR (95% CI), %	66.7 (29.9-92.5)	56.3 (29.9-80.3)

Data cutoff: October 28, 2024

[a] Response evaluable population includes patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib
[b] TTR and DoR reported in responders only; [c] Patients with ≥1 measurable brain metastasis at baseline

CI, confidence interval; DoR, duration of response; IC, intracranial; NR, not reached; (c)ORR, (confirmed) objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTR, time to response

Liu G, et al. Abstract MA02.02, WCLC 2025. Oral presentation

GLOBAL TRUST-II: SAFETY RESULTS

TEAEs IN ≥15% OF PATIENTS (N=171)[a]

Patients, n (%)	Any grade	Grade ≥3
Any TEAEs	**169 (98.8)**	**90 (52.6)**
Most frequent TEAEs (≥15% of patients)		
Increased ALT	115 (67.3)	26 (15.2)
Increased AST	112 (65.5)	12 (7.0)
Diarrhoea	99 (57.9)	1 (0.6)
Nausea	89 (52.0)	3 (1.8)
Vomiting	59 (34.5)	2 (1.2)
Constipation	41 (24.0)	0
Anaemia	34 (19.9)	7 (4.1)
Increased blood CPK	34 (19.9)	6 (3.5)
Dysgeusia	33 (19.3)	0
Dizziness	30 (17.5)	0
Electrocardiogram QT prolonged	28 (16.4)	6 (3.5)
Decreased appetite	26 (15.2)	1 (0.6)

- Most common treatment-emergent adverse events (TEAEs) among patients receiving taletrectinib 600 mg were increased ALT (67%), increased AST (65%), and diarrhoea (58%)
- Rates of neurologic TEAEs were low and limited to grade 1 or 2. (dysgeusia 19%; dizziness 18%)
- 2.3% of patients discontinued treatment due to treatment-related AEs

Data cutoff: October 28, 2024

[a] Safety population includes all patients who received ≥1 dose of taletrectinib 600 mg. Median exposure to taletrectinib was 9.7 months (range: 0.2-31.8)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; TEAE, treatment-emergent adverse event

1. Liu G, et al. J Thorac Oncol. 2024;19:S72-S73; 2. Liu G, et al. Abstract MA02.02, WCLC 2025. Oral presentation

GLOBAL TRUST-II: SUMMARY

- With longer follow-up in a geographically diverse population, taletrectinib continues demonstrating high and durable objective responses and a favourable safety profile in both TKI-naïve and TKI-pretreated patients with advanced *ROS1*+ NSCLC
- Efficacy and safety of taletrectinib will be directly compared with crizotinib in an ongoing randomised, phase 3 trial in TKI-naive patients with locally advanced or metastatic ROS1+ NSCLC (NCT06564324)

Clinical perspective

- The efficacy outcomes for taletrectinib are impressive
- Unlike the two prior drugs, entrectinib and repotrectinib, that are approved in the US, taletrectinib has significantly fewer side effects
- Most side effects are related to the GI system, and include nausea, vomiting, and diarrheal and are extremely transient
- Need to see the TRUST-II data mature to confirm that results do not change with longer follow up

GI, gastrointestinal; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; US, United States

Liu G, et al. Abstract MA02.02, WCLC 2025. Oral presentation

PRIMARY ENDPOINT RESULTS FROM SHERLOCK: A PHASE 2 TRIAL OF SOTORASIB, BEVACIZUMAB AND CHEMOTHERAPY IN ADVANCED *KRAS* G12C NSCLC

Lee CK, et al. Abstract OA08.04, WCLC 2025

NSCLC, non-small cell lung cancer

SHERLOCK: BACKGROUND AND STUDY DESIGN

- Sotorasib, a KRAS G12C inhibitor, is FDA approved for use in previously treated patients with advanced NSCLC[1]
- The combination of sotorasib plus carboplatin/pemetrexed has been shown to be effective in the front-line setting.[2,3] These findings support upfront combination treatment strategies that may enhance anti-tumour efficacy and delay treatment resistance in patients with NSCLC harbouring *KRAS* G12C mutations
- SHERLOCK is an investigator-initiated, multicentre, open-label, phase 2 trial investigated whether adding bevacizumab to sotorasib plus carboplatin/pemetrexed as a novel 1st-line regimen could improve outcome for patients with advanced *KRAS* G12C NSCLC[4]

Key eligibility:
- Newly diagnosed metastatic NSCLC or recurrent NSCLC
- *KRAS* G12C mutation
- Treatment naïve advanced disease
- PS 0-1
- No untreated symptomatic brain metastases (untreated asymptomatic brain metastases allowed)

N=52 patients

Induction:
Sotorasib 960 mg daily + Carboplatin AUC 5 + Pemetrexed 500 mg/m^2 + Bevacizumab-biosimilar 15 mg/kg Q3W

× 4 cycles

Maintenance:
Sotorasib 960 mg daily + Pemetrexed 500 mg/m^2 + Bevacizumab-biosimilar 15 mg/kg Q3W

Until intolerance or disease progression

Endpoints:

Primary endpoint:
- ORR by RECIST v1.1

Secondary endpoints:
- PFS
- Duration of response
- Depth of response
- OS
- Adverse events
- PRO-CTCAE

Correlative analyses

AUC, area under the curve; FDA, Food and Drug Administrartion; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PRO-CTCAE, Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events; PS, performance status; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1

1. Sotorasib is First KRAS Inhibitor Approved by FDA – NCI; 2. Akamatsu H, et al. J Thorac Oncol. 2025;20:775-785; 3. Li BT, et al, J Clin Oncol. 2024; 42, abstract 8515; 4. Lee CK, et al. Abstract OA08.04, WCLC 2025. Oral presentation

SHERLOCK: DEMOGRAPHY AND EFFICACY RESULTS

- Between August 2022 and June 2025, a total of 52 participants were enrolled
- Baseline characteristics: median age of 67 years, 62% female; 40% with ECOG PS 0; 96% former or current smokers; and 38% had brain metastases
- Baseline tumour characteristics showed PD-L1 expression ≥50% in 23% (12/52). In ctDNA evaluable participants, baseline *TP53* co-mutation occurred in 50% (19/38), *STK11* in 32% (12/38), and *KEAP1* in 18% (8/38)

EFFICACY RESULTS

Efficacy	Evaluable patients (N=47)
cORR (95% CI), %	64 (46-72)
Unconfirmed ORR (95% CI),[a] %	69 (55-80)
Median PFS (95% CI), months	9.1 (7.9-15.0)
Median OS (95% CI), months	25.0 (14.0-NR)

[a]Three patients did not undergo response evaluation beyond baseline, and two recently enrolled patients are yet to be evaluated, resulting in the total 49 potentially evaluable patients

TREATMENT RESPONSES ACROSS PD-L1 AND CO-MUTATIONAL STATUS

	Confirmed ORR
PD-L1 ≥50%, % (n/N)	80 (8/10)
PD-L1 1-49%, % (n/N)	67 (8/12)
PD-L1 <1%, % (n/N)	57 (13/23)

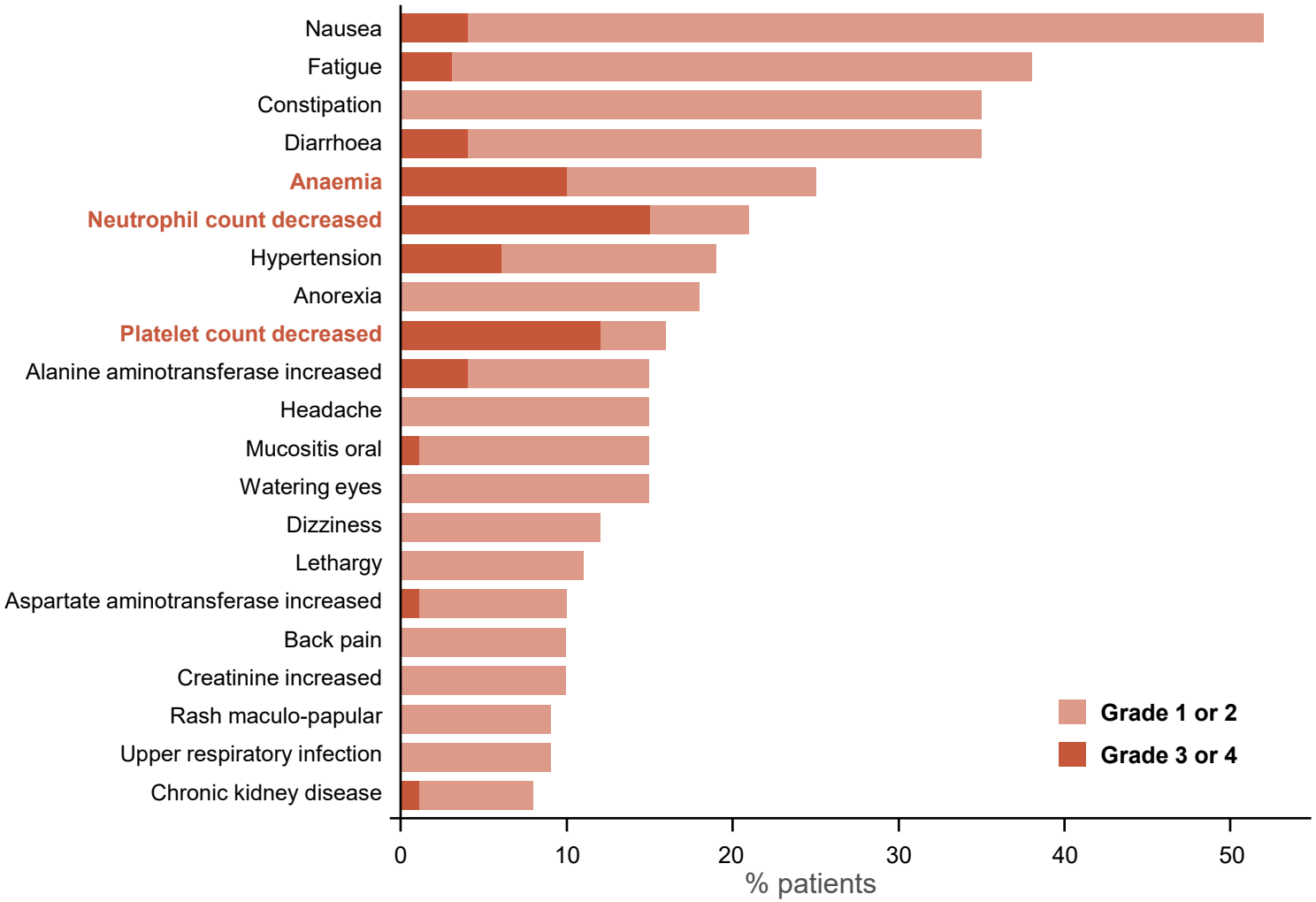
	Median PFS
No co-mutations	8.3 (6.4-NR)
1 co-mutation	9.6 (8.0-NR)
2 or 3 co-mutations	11.0 (5.8-NR)

CI, confidence interval; (c)ORR, (confirmed) objective response rate; ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; (c)ORR, (confirmed) objective response rate; OS, overall; survival; PFS, progression-free survival

Lee CK, et al. Abstract OA08.04, WCLC 2025. Oral presentation

SHERLOCK: SAFETY RESULTS

COMMON TREATMENT RELATED ADVERSE EVENTS



- **Treatment discontinuation:**[a]
  - Sotorasib – 12 (23%)
  - Carboplatin – 2 (4%)
  - Pemetrexed – 4 (8%)
  - Bevacizumab – 7 (13%)
- **Sotorasib dose reduction:**
  - 480 mg – 8 (15%)
  - 240 mg – 2 (4%)
- **Grade 5 events of any cause:** 5 (10%)
  - Bronchopulmonary haemorrhage (n=1), stroke (n=1), sepsis (n=1), febrile neutropenia (n=1), cardiac arrest (n=1)

[a] Some patients discontinued more than one agent

Lee CK, et al. Abstract OA08.04, WCLC 2025. Oral presentation

SHERLOCK: SUMMARY

- Sotorasib, in combination with bevacizumab and chemotherapy, demonstrated promising anti-tumour activity as a 1st-line treatment for advanced NSCLC with *KRAS* G12C mutation
- High ORR were observed across all PD-L1 expression levels and molecular subgroups, including those with TP53, STK11, or KEAP1 co-mutations
- The combination treatment demonstrates a manageable safety profile consistent with the known adverse effects of chemotherapy

Clinical perspective

- These findings warrant further evaluation in a randomised phase 3 trial and further investigations into other RAS inhibitor-based combination strategies

NSCLC, non-small lung cancer; ORR, objective response rate;
Lee CK, et al. Abstract OA08.04, WCLC 2025. Oral presentation

ZIPALERTINIB IN NSCLC PATIENTS WITH *EGFR* EXON 20 INSERTION MUTATIONS WHO RECEIVED PRIOR AMIVANTAMAB (REZILIENT1)

Piotrowska Z, et al. Abstract MA08.02, WCLC 2025

NSCLC, non-small cell lung cancer

REZILIENT1: BACKGROUND AND STUDY DESIGN

- While amivantamab is approved for the first and second-line treatment of *EGFR* ex20ins + NSCLC,[1] an unmet need remains for patients intolerant to or progressing on or after amivantamab
- Zipalertinib is a novel, irreversible and selective EGFR ex20ins TKI with promising clinical activity and manageable safety as reported previously[2]
- Updated data from the phase 2b REZILIENT1 study (NCT04036682) is presented with a focus on patients with *EGFR* ex20ins mutant NSCLC previously treated with amivantamab[3]

Key eligibility criteria:

- Locally advanced or metastatic NSCLC
- Documented *EGFR* ex20ins
- ***Progressed on or after amivantamab***
- ECOG PS 0 or 1
- Stable/asymptomatic brain metastases allowed

→

Zipalertinib
100 mg BID oral

Primary endpoint:

- ORR and DoR per RECIST v1.1

Secondary endpoints:

- Safety
- PFS
- DCR

Data cut-off: June 13, 2025

BID, twice daily; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ex20ins; exon 20 insertion; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKI, tyrosine kinase inhibitor

1. FDA approves amivantamab-vmjw for EGFR exon 20 insertion-mutated non-small cell lung cancer indications | FDA; 2. Piotrowska Z, et al. J Clin Oncol. 2023;41:4218-4225; 3. Piotrowska Z, et al. Abstract MA08.02, WCLC 2025. Oral presentation

REZILIENT1: EFFICACY RESULTS

As of the 13 Jun 2025 data cut-off (DCO), 84 patients with prior amivantamab were enrolled. Patients had a median age of 62 years (31-85) and had received a median of 3 (1-7) prior treatment lines, including chemotherapy in 80 (95.2%) patients, anti-PD-(L)1 in 38 (45.2%), other ex20ins-specific TKIs in 30 (36.0%)

Efficacy per BICR Outcome, n (%) [95% CI]	Prior amivantamab only (n=54)	Prior amivantamab + other ex20ins-targeted therapy (n=30)	Total (N=84)
Confirmed best overall response			
CR	0	0	0
PR	17 (31.5) [19.5-45.6]	6 (20.0) [7.7-38.6]	23 (27.4) [18.2-38.2]
Unconfirmed PR	2 (3.7) [0.5-12.7]	1 (3.3) [0.1-17.2]	3 (3.6) [0.7-10.1]
SD	28 (51.9) [37.8-65.7]	17 (56.7) [37.4-74.5]	45 (53.6) (42.4-64.5]
PD	1 (1.9) [0.0-9.9]	3 (10.0) [2.1-26.5]	4 (4.8) [1.3-11.7]
NA	6 (11.1) [4.2-22.6]	3 (10.0) [2.1-26.5]	9 (10.7) [5.0-19.4]
Confirmed ORR (CR+PR)	**17 (31.5) [19.5-45.6]**	**6 (20.0) [7.7-38.6]**	**23 (27.4) [18.2-38.2]**
DCR (CR+PR+SD)	47 (87.0) [75.1-94.6]	24 (80.0) [61.4-92.3]	71 (84.5) [75.0-91.5]
CBR (CR+PR+SD ≥24 weeks)	30 (55.6) [41.4-69.1]	13 (43.3) [25.5-62.6]	43 (51.2) [40.0-62.3]
Median DoR, months (95% CI)	9.5 (6.2-NE)	8.3 (3.9-NE)	8.5 (6.2-14.8)
Median PFS, months (95% CI)	**7.4 (5.4-9.7)**	**5.2 (3.4-11.5)**	**6.5 (5.4-8.9)**

BICR, blinded independent central review; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; ex20ins, exon 20 insertion; NA, not available; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor

Piotrowska Z, et al. Abstract MA08.02, WCLC 2025. Oral presentation

REZILIENT1: SAFETY RESULTS

MOST COMMON TEAEs

TEAE (all grade) ≥10%, n (%)	Prior amivantamab only (n=54)	Prior amivantamab + other ex20ins-targeted therapy (n=30)	Total (N=84)	
			All grade	Grade ≥3
Preferred term				
Paronychia	22 (40.7)	13 (43.3)	35 (41.7)	0
Anaemia	19 (35.2)	13 (43.3)	32 (38.1)	13 (15.5)
Rash	20 (37.0)	9 (30.0)	29 (34.5)	3 (3.6)
Nausea	13 (24.1)	11 (36.7)	24 (28.6)	1 (1.2)
Diarrhoea	11 (20.4)	8 (26.7)	19 (22.6)	2 (2.4)
Dry skin	13 (24.1)	5 (16.7)	18 (21.4)	0
Dermatitis acneiform	11 (20.4)	7 (23.3)	18 (21.4)	1 (1.2)
Dyspnoea	12 (22.2)	5 (16.7)	17 (20.2)	5 (6.0)
Constipation	8 (14.8)	7 (23.3)	15 (17.9)	0
Pruritus	11 (20.4)	4 (13.3)	15 (17.9)	0
Cough	11 (20.4)	2 (6.7)	13 (15.5)	1 (1.2)
Vomiting	7 (13.0)	6 (20.0)	13 (15.5)	1 (1.2)
Stomatitis	6 (11.1)	6 (20.0)	12 (14.3)	2 (2.4)
Fatigue	7 (13.0)	4 (13.3)	11 (13.1)	0
Pneumonia	4 (7.4)	7 (23.3)	11 (13.1)	9 (10.7)
Rash maculopapular	6 (11.1)	4 (13.3)	10 (11.9)	1 (1.2)

ex20ins, exon 20 insertion; TEAE, treatment emergent adverse event

Piotrowska Z, et al. Abstract MA08.02, WCLC 2025. Oral presentation

REZILIENT1: SUMMARY

- Zipalertinib demonstrated promising efficacy in patients who progressed on or after prior chemotherapy and amivantamab without other EGFR ex20ins targeted therapy
- Zipalertinib was well tolerated and demonstrated a manageable safety profile in patients who progressed on prior chemotherapy and amivantamab with or without other ex20ins-targeted therapy. No new safety signals have been identified

Clinical perspective

- Zipalertinib demonstrated clinically meaningful efficacy with a manageable safety profile in patients with ex20ins NSCLC who have received prior chemotherapy and prior amivantamab, reflecting a clinically-relevant patient population for which there are currently no approved therapies

ex20ins, exon 20 insertion; NSCLC, non-small cell lung cancer

Piotrowska Z, et al. Abstract MA08.02, WCLC 2025. Oral presentation

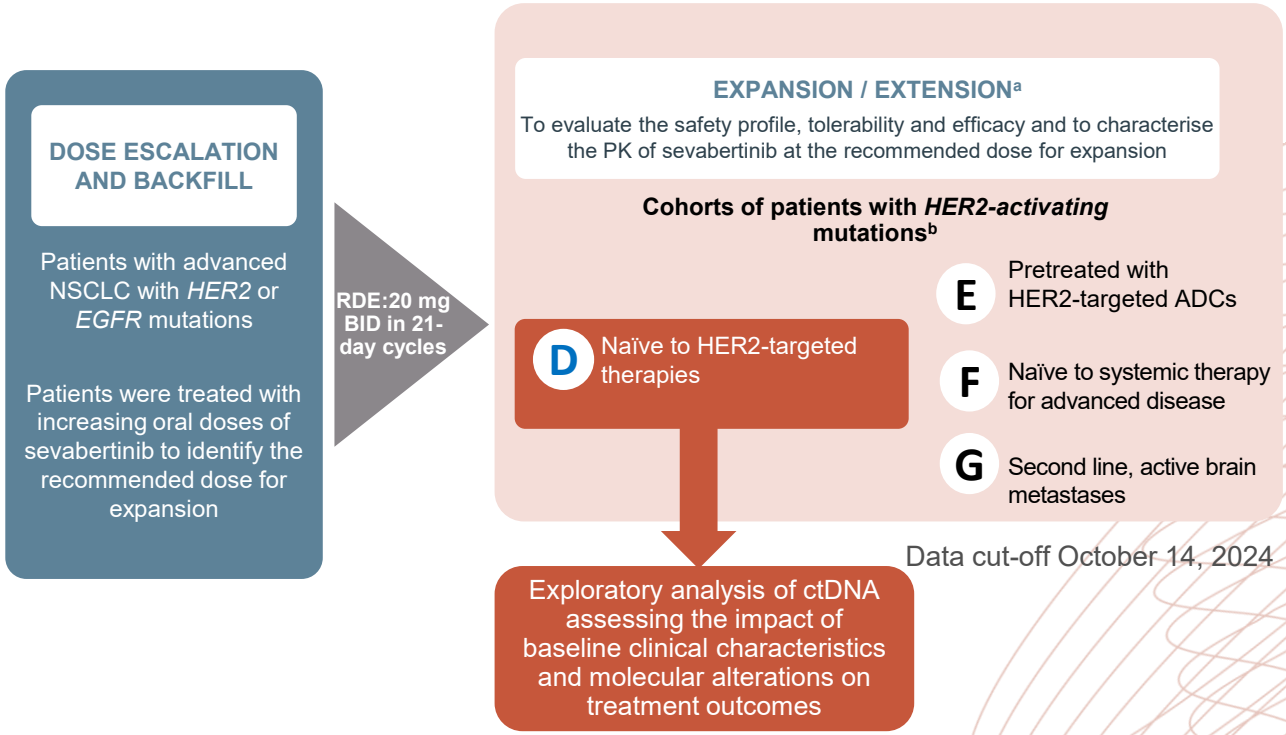
SOHO-01: FACTORS ASSOCIATED WITH CLINICAL OUTCOMES IN PATIENTS WITH *HER2*-MUTANT NSCLC TREATED WITH SEVABERTINIB (BAY 2927088)

Le X, et al. Abstract P3.12.41, WCLC 2025

NSCLC, non-small cell lung cancer

SOHO-01: BACKGROUND AND STUDY DESIGN

- *HER2*-activating mutations have been reported in approximately 2-4% of patients with NSCLC and are associated with poor prognosis[1-3]
- Sevabertinib is a potent, oral, reversible *HER2* tyrosine kinase inhibitor that has demonstrated durable responses and a manageable safety profile in patients with advanced NSCLC and *HER2* mutations[3,4,5]
- This exploratory analysis[6] assessed the impact of baseline clinical characteristics and molecular alterations on treatment outcomes in patients from expansion Cohort D of the SOHO-01 study (NCT05099172)
  - Patients had advanced NSCLC with a HER2-activating mutation and experienced disease progression after ≥1 systemic therapy, but were naïve to HER2-targeted therapy, and received treatment with sevabertinib 20 mg twice daily



Data cut-off October 14, 2024

Primary endpoints
- Safety and tolerability
- PK

Secondary endpoints (investigator assessed and BICR):
- ORR (investigator-assessed)
- DoR, DCR and PFS

Figure adapted from Loong HH, et al. Abstract 8504, ASCO 2025, oral presentation

[a] Patients from dose escalation/backfill treated with 20 mg BID and who met the same eligibility criteria were combined for statistical analysis
[b] Cohorts of patients with *EGFR* mutations are not shown

ADC, antibody-drug conjugate; BICR, blinded independent central review; BID, twice daily; ctDNA, circulating tumour DNA; DCR, disease control rate; DoR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; RDE, recommended dose for expansion

1. Riudavets M, et al. ESMO Open. 2021;6:100260; 2. Remon J, et al. Cancer Treat Rev. 2020;90:102105; 3. Girard N, et al. J Clin Oncol. 2024;42(suppl 17). Abstr LBA8598;
4. Loong HHF, et al. Ann Oncol. 2023;34(Supplement 2):S761-S762 (Abstract 1320MO); 5. Girard N, et al. J Thorac Oncol. 2025;20 (1 Suppl):S5-S6. ELCC 2025 (oral presentation, Abstract 3O);
6. Le X, et al. Abstract P3.12.41, WCLC 2025. Poster presentation

SOHO-01: DEMOGRAPHY & EFFICACY RESULTS

BASELINE CHARACTERISTICS

- Of the 44 patients treated in expansion Cohort D, 43 patients who had a post-baseline tumour assessment were included
- At baseline, median age was 62.0 years, 65.1% were female, 72.1% had never smoked, and 46.5% had received <2 prior lines of therapy. *TP53* mutations were the most frequently observed co-alterations, found in 13 out of 37 patients (35.1%) with detectable *HER2* ctDNA

EFFICACY RESULTS

	Previous lines of therapy [a]		Baseline ECOG PS		YVMA variant [b]		*TP53* co-alteration [c]	
	<2 lines (n=20)	≥2 lines (n=23)	PS 0 (n=19)	PS 1 (n=24)	Present (n=30)	Other (n=13)	Not detected (n=24)	Detected (n=13)
ORR, n (%) (95% CI)	15 (75.0) (50.9-91.3)	16 (69.6) (47.1-86.8)	12 (63.2) (38.4-83.7)	19 (79.2) (57.8-92.9)	26 (86.7) (69.3-96.2)	4 (30.8) (9.1-61.4)	19 (79.2) (57.8-92.9)	9 (69.2) (38.6-90.9)
mDoR, months (95% CI)	NR (6.8-NR)	5.2 (2.8-12.2)	7.7 (4.5-12.2)	NR (2.8-NR)	9.7 (5.3-NR)	2.8 (2.7-NR)	NR (3.1-NR)	5.3 (2.8-6.8)
mPFS, months (95% CI)	NR (4.3-NR)	6.7 (4.1-8.1)	7.5 (5.3-9.9)	9.6 (4.1-NR)	9.9 (6.7-NR)	3.9 (2.0-5.3)	10.6 (4.2-NR)	6.7 (2.7-8.1)

mDoR data from a subset of patients with confirmed partial response or complete response: [a] <2 lines, n=15; ≥2 lines, n=16; PS 0, n=12; PS 1, n=19); [b] YVMA variant present, n=26; other, n=4; [c] *TP53* co-alteration not detected, n=19; detected, n=9

- Multivariate analysis showed that YVMA and *TP53* status were both significantly associated with PFS when adjusted for previous treatment lines and ECOG PS

CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; mDoR, median duration of response; (m)PFS, (median) progression-free survival; NR, not reached; ORR, objective response rate

Le X, et al. Abstract P3.12.41, WCLC 2025. Poster presentation

SOHO-01: SUMMARY

- This exploratory analysis of clinical and molecular factors in patients with *HER2*-mutant NSCLC indicates treatment with sevabertinib results in favourable DoR and PFS among those who had received only one prior line of therapy or who had specific molecular characteristics
  - Treatment with <2 previous lines of therapy was associated with improved treatment efficacy compared with patients who had received ≥ 2 previous lines
  - Presence of the YVMA variant was associated with enhanced treatment efficacy compared with other *HER2* alterations, whereas *TP53* co-alterations were linked to reduced treatment efficacy
- Multivariate analysis indicated that both *TP53* and *HER2* YVMA provide independent prognostic information when adjusted for clinical factors

Clinical perspective

- The findings underscore the importance of integrating clinical and molecular features to identify potential prognostic or predictive markers
- As these results are limited to a single expansion cohort in an ongoing trial, further validation in larger studies is required to confirm these insights and further explore therapeutic strategies for patients with *HER2*-altered cancers

DoR, duration of response; PFS, progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate

Le X, et al. Abstract P3.12.41, WCLC 2025. Poster presentation

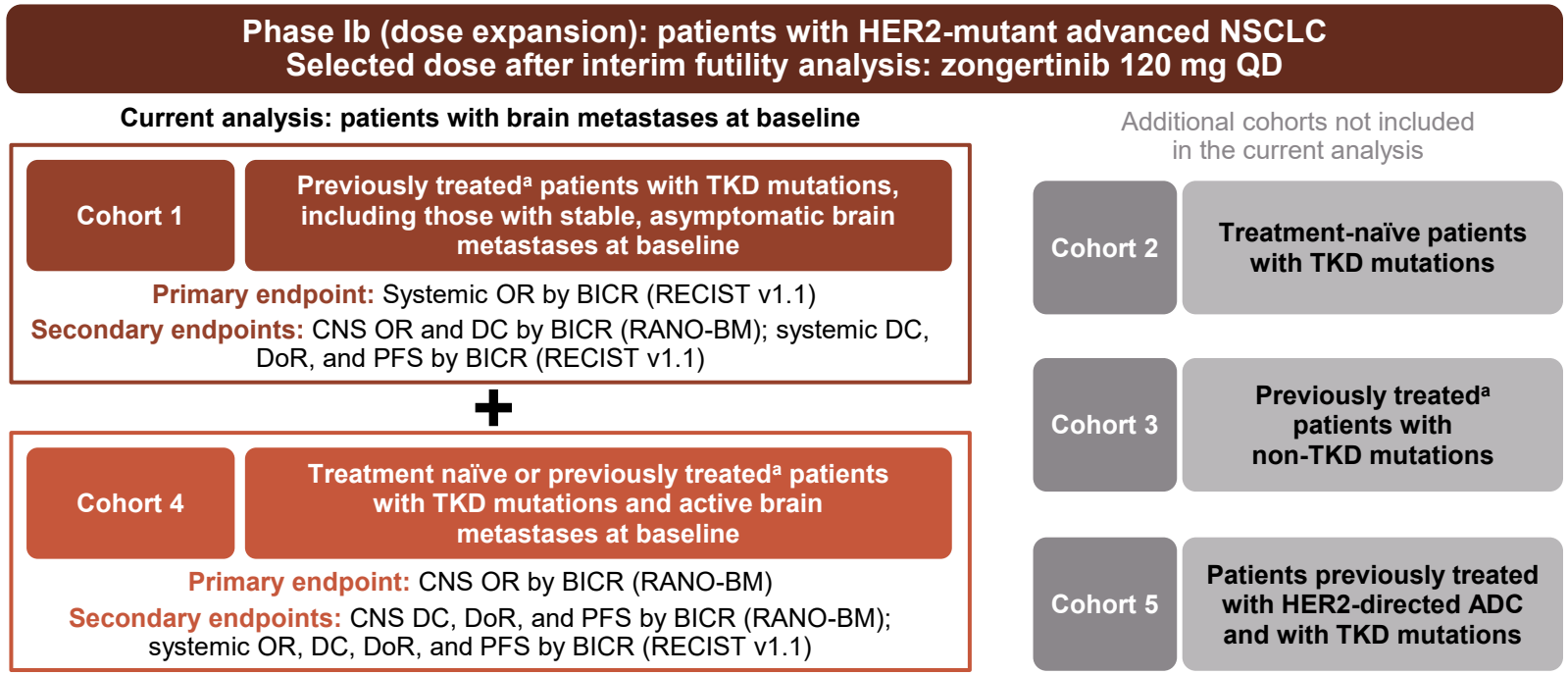
ZONGERTINIB IN PATIENTS WITH PREVIOUSLY TREATED *HER2*-MUTANT NSCLC AND BRAIN METASTASES AT BASELINE: BEAMION LUNG-1 STUDY

Ruiter G, et al. Abstract PT2.12.03, WCLC 2025

NSCLC, non-small cell lung cancer

BEAMION LUNG-1: BACKGROUND AND STUDY DESIGN

- Patients with *HER2*-mutant NSCLC have a high incidence of brain metastases (BMs).[1] Therefore, it is important to consider the intracranial activity of emerging HER2-targeting therapies
- Phase Ib of Beamion LUNG-1 (NCT04886804) is evaluating the tyrosine kinase inhibitor, zongertinib, in patients with *HER2*-mutant advanced/metastatic NSCLC, including those with BMs at baseline.[2] Data from previously treated patients with active BMs (Cohort 4) or stable/asymptomatic BMs (Cohort 1) at baseline are reported[3]



[a]Excluding those previously treated with a HER2-directed ADC

ADC, antibody drug conjugate; BICR, blinded independent central review; BM, brain metastasis; CNS, central nervous system; DC, disease control; DoR, duration of response; NSCLC, non-small cell lung cancer; OR, objective response; PFS, progression-free survival; QD, once daily; RANO-BM, Response Assessment in Neuro-Oncology - Brain Metastases; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TKD, tyrosine kinase domain

1. Zhang Q, et al. Lung Cancer 2025; 205: 108616; 2. www.clinicaltrials.gov/study/NCT04886804; 3. Ruiter G, et al. Abstract PT2.12.03, WCLC 2025. Poster presentation

BEAMION LUNG-1: DEMOGRAPHY DATA

	Cohort 1: no brain metastases n=47	Cohort 1: stable, asymptomatic brain metastases n=28	Cohort 4: active brain metastases N=30
Median age, years (range)	60 (30-80)	63 (32-80)	59 (38-77)
Female, n (%)	32 (68)	19 (68)	19 (63)
Race, n (%)[a]			
Asian	26 (55)	14 (50)	15 (50)
Non-Asian	20 (43)	9 (32)	10 (33)
Lines of prior systemic anticancer treatment, n (%)			
0	2 (4)[b]	1 (4)[b]	10 (33)
1	32 (68)	11 (39)	13 (43)
≥2	13 (28)	16 (57)	7 (23)
No prior brain radiotherapy, n (%)	–	17 (60)	24 (80)
ECOG PS, n (%)			
0	16 (34)	12 (43)	13 (43)
1	31 (66)	16 (57)	17 (57)

Data but-off: March 26, 2025

[a] Not reported: n=1 in Cohort 1 no brain metastases group and n=5 in both Cohort 1 and 4 brain metastases groups; [b] Patients had received previous treatment in an adjuvant context only; prior treatment was allowed in the adjuvant setting, these patients were therefore considered as previously treated in the advanced/metastatic setting per protocol

ECOG PS, Eastern Cooperative Oncology Group performance status

Ruiter G, et al. Abstract PT2.12.03, WCLC 2025. Poster presentation

BEAMION LUNG-1: EFFICACY RESULTS

CONFIRMED INTRACRANIAL RESPONSE BY RECIST v1.1

Efficacy	Patients with stable, asymptomatic brain metastases Cohort 1 (n=8)[a]
Confirmed Intercranial response by RECIST v1.1	
ORR, %	50
DCR, %	100
Median DoR (95% CI),[b] months	12.5 (11.1-NC)

CONFIRMED INTRACRANIAL RESPONSE BY RANO-BM

Pooled analysis of patients with stable, asymptomatic (cohort 1) or active brain metastases (cohort 4)	Including patients with prior brain radiotherapy Cohorts 1 & 4 (n=58)	No prior brain radiotherapy Cohorts 1 & 4 (n=41)
CR, %	9	7
PR, %	33	37
SD, %	41	39
PD, %	7	5
NE, %	10	12
ORR, %	41	44
DCR, %	83	83
mPFS (95% CI), months	8.2 (4.5-12.3)	8.1 (4.1-12.3)

[a] Patients with RECIST v1.1 measurable CNS lesions; [b] Median follow-up for DoR: 16.6 months (95% CI: 11.0-16.6)

CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; mPFS, median progression-free survival; NC, not calculable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease

Ruiter G, et al. Abstract PT2.12.03, WCLC 2025. Poster presentation

BEAMION LUNG-1: SUMMARY

- Zongertinib demonstrated encouraging intracranial efficacy by RANO-BM in patients with advanced/metastatic *HER2*-mutant NSCLC and stable, asymptomatic or active brain metastases at baseline
- This effect was observed in patients with and without prior brain radiotherapy

Clinical perspective

- These findings underscore a clinically meaningful advancement in managing patients with brain metastases who have limited therapeutic options

NSCLC, non-small cell lung cancer; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases

Ruiter G, et al. Abstract PT2.12.03, WCLC 2025. Poster presentation

COR2ED
THE HEART OF MEDICAL EDUCATION

For more information visit

LUNG connect®
POWERED BY COR2ED

Connect on
LinkedIn @LUNG CONNECT

Watch on
YouTube @COR2ED

Email
info@cor2ed.com

Visit us at
https://cor2ed.com/

Follow us on
X @LungConnect

Heading to the heart of Independent Medical Education since 2012