COR2ED

THE HEART OF MEDICAL EDUCATION

LUNG CONNECT

ONCOGENE-ADDICTED NSCLC HIGHLIGHTS FROM ASCO 2025

Prof. Mark A Socinski, MD
AdventHealth Cancer Institute, Florida, USA

JUNE 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:

- **Prof. Mark A. Socinski** has received financial support/sponsorship for research support, consultation, or speaker fees from the following companies: AstraZeneca, Beigene, BMS, Cullinan, Eli Lilly, Genentech, GI Therapeutics, Guardant, Janssen, Jazz, Merck, Novartis, OncoC4, Regeneron, Spectrum, Summit

CLINICAL TAKEAWAYS

- **SOHO-01/SOHO-02:** Sevabertinib (BAY 2927088) produced meaningful and durable response rates in patients with advanced *HER2*-mutant NSCLC. The ongoing phase 3 trial, SOHO-02, will provide further data on the efficacy and safety of sevabertinib as 1st line therapy in patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations
- **SACHI:** The combination of savolitinib plus osimertinib demonstrated statistically significant and clinically meaningful improvement in PFS in *MET*-amplified NSCLC post first-line EGFR-TKI. This represents a significant therapeutic advancement for these patients and based on these results the combination therapy has been granted priority review by the China NMPA
- **OptiTROP-Lung03:** Sac-TMT improved PFS and OS compared to docetaxel in relapsed *EGFR*-mutant NSCLC post TKI and platinum-based chemotherapy, with a manageable safety profile. Sac-TMT has recently been approved by the China NMPA based on these results
- **HERTHENA-Lung02:** HER3-DXd more effective than platinum-based chemotherapy for PFS in relapsed *EGFR*-mutant NSCLC post 3rd generation TKI but no benefit in overall survival was observed. Patritumab deruxtecan biologics license application has been voluntarily withdrawn

HER3-Dxd, patritumab deruxtecan; NMPA, National Medical Products Administration; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; sac-TMT, sacituzumab tirumotecan; 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

NSCLC, non-small cell lung cancer

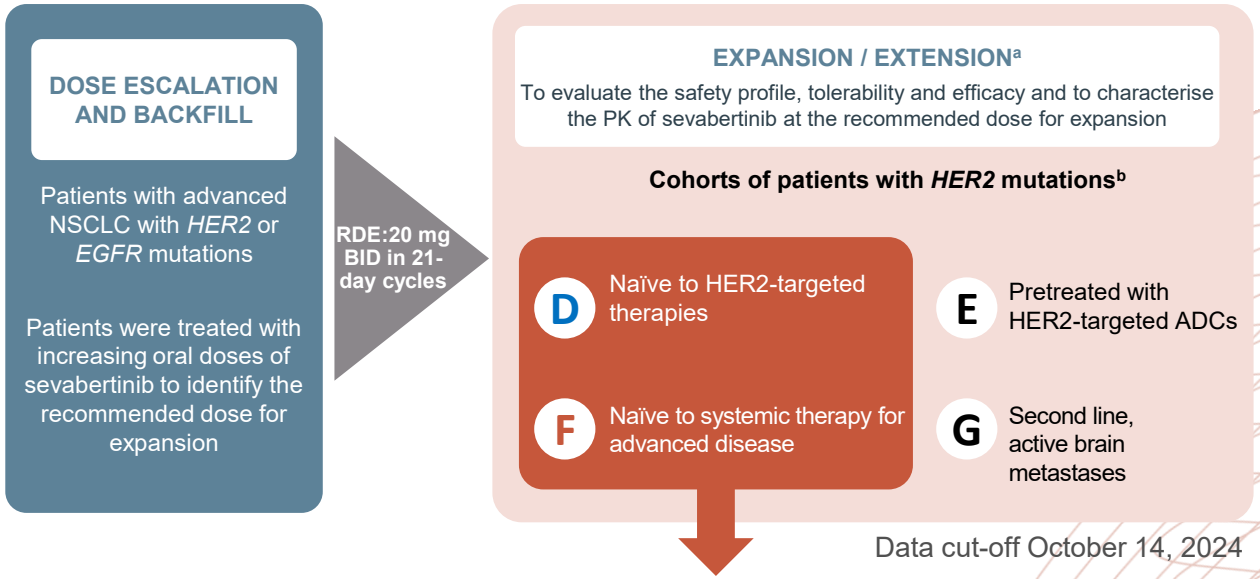
SOHO-01: SAFETY AND EFFICACY OF SEVABERTINIB IN PATIENTS WITH ADVANCED *HER2*-MUTANT NSCLC WHO WERE PRETREATED BUT NAÏVE TO HER2-TARGETED THERAPY OR HAD NOT RECEIVED ANY TREATMENT FOR ADVANCED DISEASE

Loong H, et al. Abstract 8504, ASCO 2025

NSCLC, non-small cell lung cancer

SOHO-01: BACKGROUND[1-5] AND STUDY DESIGN[6]

- *HER2*-activating mutations have been reported in approximately 2-4% of patients with NSCLC and are associated with poor prognosis[1-3]
- Sevabertinib (BAY 2927088) is an oral, reversible tyrosine kinase inhibitor that potently inhibits *HER2*-activating mutations[3,4]
- Encouraging anti-tumour activity and manageable safety were observed in patients with NSCLC harbouring a *HER2*-activating mutation treated with sevabertinib[3,4]
- The FDA has granted Breakthrough Therapy designation for BAY 2927088 for previously-treated patients with advanced NSCLC and activating *HER2* mutations[3,5]
- Here we report results from cohorts of the ongoing, open-label, multicentre Phase 1/2 SOHO-01 (NCT05099172)[6]



Primary endpoints
- Safety and tolerability
- PK

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

[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; DCR, disease control rate; DoR, duration of response; FDA, Food and Drug Administration; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics; RDE, recommended daily exposure

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; 5. Bayer receives U.S. FDA Breakthrough Therapy designation for BAY 2927088 for non-small cell lung cancer harboring HER2 activating mutations. Available here (accessed June 2025); 6. Loong H, et al. J Clin Oncol 2025;43(suppl 16). Abstr 8504 (ASCO 2025; oral presentation)

SOHO-01: EFFICACY RESULTS

BASELINE CHARACTERISTICS

- As of October 14, 2024, 81 (cohort D) and 39 (cohort F) patients were treated. Median age was 60 years (D) and 65 years (F), 61.7% (D) and 64.1% (F) were female, 61.7% (D) and 79.5% (F) had never smoked, and 43.2% (D) had received ≥2 systemic therapies

EFFICACY RESULTS

	Cohort D (N=81)		Cohort F (N=39)
N (%)	**INV**	**BICR**	**INV**
CR	1 (1.2)	1 (1.2)	0
PR	47 (58.0)	48 (59.3)	23 (59.0)
SD	22 (27.2)	22 (27.2)	12 (30.8)
PD	10 (12.3)	7 (8.6)	3 (7.7)
Not evaluable[a,b]	2 (1.2)	3 (3.7)	1 (2.6)
ORR[c] [95% CI]	**48 (59.3)** [47.8, 70.1]	**49 (60.5)** [49.0, 71.2]	**23 (59.0)** [42.1, 74.4]
DCR[d] [95% CI]	**68 (84.0)** [74.1, 91.2)	**68 (81.5)** [71.3, 89.2]	**33 (84.6)** [69.5, 94.1]

Median follow up[e]:

- 7.3 months for cohort D
- 5.6 months for cohort F

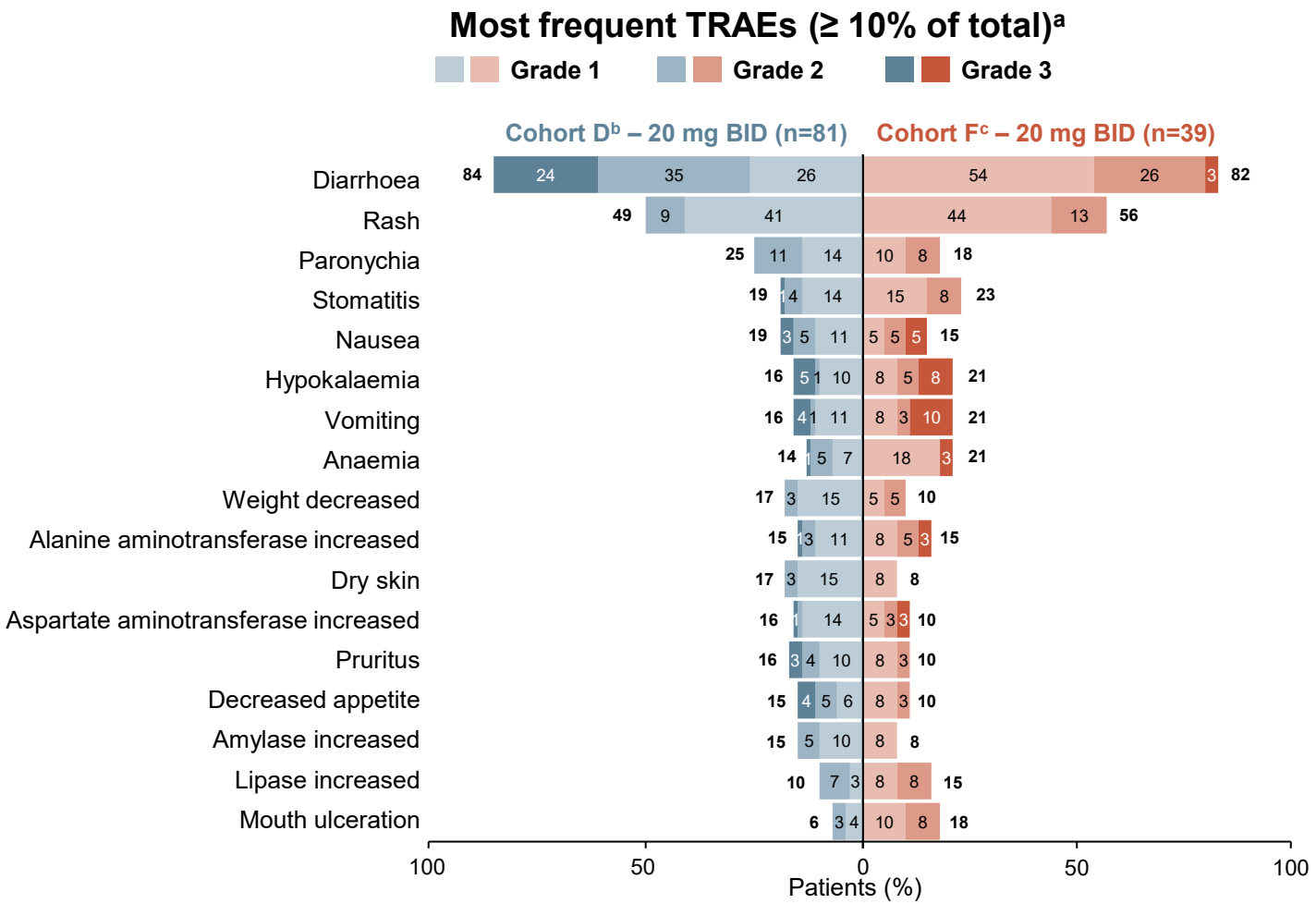
- Cohort D (n=81): ORR is consistent across all subgroups including number of prior systemic treatments and patients with brain metastases at baseline. Patients with *HER2* TKD mutations at baseline had an ORR of 65.3% (95% CI 53.1, 76.1)
- In Expansion cohort D (n=44)[d]: median DoR (95% CI) was 9.2 months (5.2, NE) and 12-month DoR was 49.3% (48% of patients were censored)

[a] Requirement for CR/PR/SD or PD was not met for cohort D; [b]cohort F-not available: post-baseline tumour assessment but discontinued due to drug-related toxicity, death, or progression by clinical judgement before disease was re-evaluated; [c] Confirmed CR or PR; [d] Confirmed CR/PR or SD for ≥12 weeks;
[e] Data for Extension Cohorts D and F are immature at DCO

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; INV, investigator assessed; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKD, tyrosine kinase domain

Loong H, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8504 (ASCO 2025; oral presentation)

SOHO-01: SAFETY RESULTS



- **In pretreated patients (Cohort D), the safety profile was consistent with previous reports**
  - Grade 3 treatment-related diarrhoea occurred in 24% of patients
  - Exploratory analysis showed a median of 1 episode (IQR 1, 1) and a median time to onset of 1.3 months (IQR 0.5, 3.6)
- **In first-line patients (Cohort F), treatment-related grade 3 diarrhoea was reported in only 1 patients (3%)**
- **Overall, there were no cases of grade 4 diarrhoea**
- **There were no reported cases of interstitial lung disease or pneumonitis**
- **4 patients (4.9%) in Cohort D and 1 patient (2.6%) in Cohort F had TRAEs leading to treatment discontinuation[d]**

[a] MedDRA v27.1, CTCAE v5.0; [b] Patients naïve to HER2-targeted therapies; [c] Patients naïve to systemic therapy for advanced disease; [d] Abnormal hepatic function (D: n=1), corneal epithelial microcysts and reduced visual acuity (D: n=1), dyspnoea (D: n=1), electrocardiogram QT prolonged (D: n=1), and renal failure (F: n=1)

BID, twice daily; CTCAE v5.0, Common Terminology for Adverse Events version 5.0; IQR, interquartile range; MEDRA v27.1, Medical Dictionary for Regulatory Activities version 27.1; TRAE, treatment-related adverse event

Loong H, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8504 (ASCO 2025; oral presentation)

SOHO-01: SUMMARY

- Sevabertinib demonstrated manageable safety in both cohorts, consistent with previous reports
  - Diarrhoea was the most common TRAE with grade 3 diarrhoea occurring in 24% of patients in cohort D and 3% of patients in cohort F
  - There were no cases of pneumonitis or interstitial lung disease
- Similar response rates were observed in patients with advanced *HER2*-mutant NSCLC who were pretreated but naïve to HER2-targeted therapy and in those treated in the first-line setting
- ORR were consistent across all key subgroups, including patients with brain metastases at baseline

Clinical perspective

- Response rates observed in SOHO-01 are promising but it is too early to look at duration of response and PFS as the median follow-up is under a year
- The ongoing phase 3 trial, SOHO-02, will provide further data on the efficacy and safety of sevabertinib in patients with *HER2*-mutant NSCLC

NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; TRAE, treatment-related adverse event

Loong H, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8504 (ASCO 2025; oral presentation)

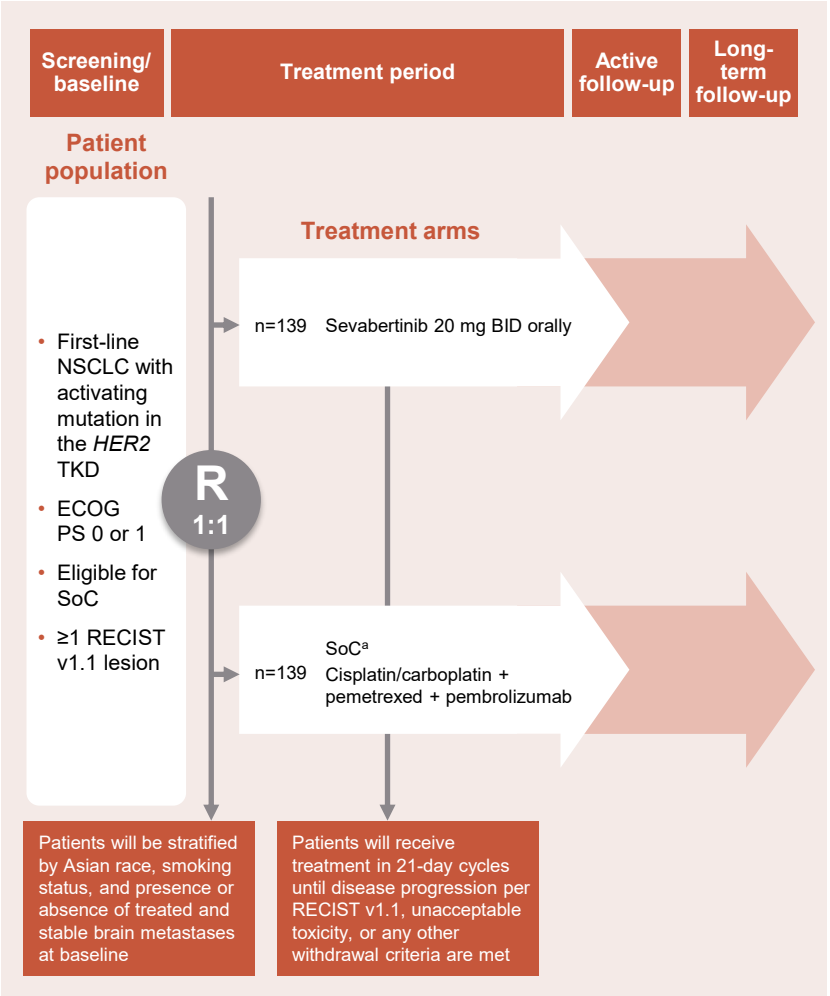
SOHO-02: PHASE 3 TRIAL OF BAY 2927088 IN PATIENTS WITH LOCALLY ADVANCED OR METASTATIC NSCLC WITH *HER2*-ACTIVATING MUTATIONS

Le X, et al. Abstract TPS8648, ASCO 2025

NSCLC, non-small cell lung cancer

SOHO-02: BACKGROUND AND STUDY DESIGN

- Approximately 2-4% of NSCLC harbour activating *HER2* mutations, the majority of which are exon 20 insertions[1,2]
- No 1st line HER2-targeted therapies are currently approved for patients with locally advanced or metastatic NSCLC with *HER2*-activating mutations[3]
- Sevabertinib (BAY 2927088) is an oral, reversible tyrosine kinase inhibitor that potently targets HER2 and mutant EGFR receptor[4]
- Preliminary evidence from the Phase 1/2 SOHO-01 trial has demonstrated anti-tumour activity and a manageable safety profile in previously treated patients with NSCLC with *HER2*-activating mutations[5]
- 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[3]



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

[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. Remon J, et al. Cancer Treat Rev 2020;90:102105; 2. Tan AC, et al. JCO Precis Oncol 2022;6:e2200278; 3. Le X, et al. J Clin Oncol 2025;43(suppl 16). Abstr TPS8648 (ASCO 2025, poster presentation); 4. Siegel F, et al. Cancer Res 2023;83(7 Suppl). Abstr 4035; 5. Girard N, et al. J Clin Oncol. 2024;42(suppl 17). Abstr LBA8598

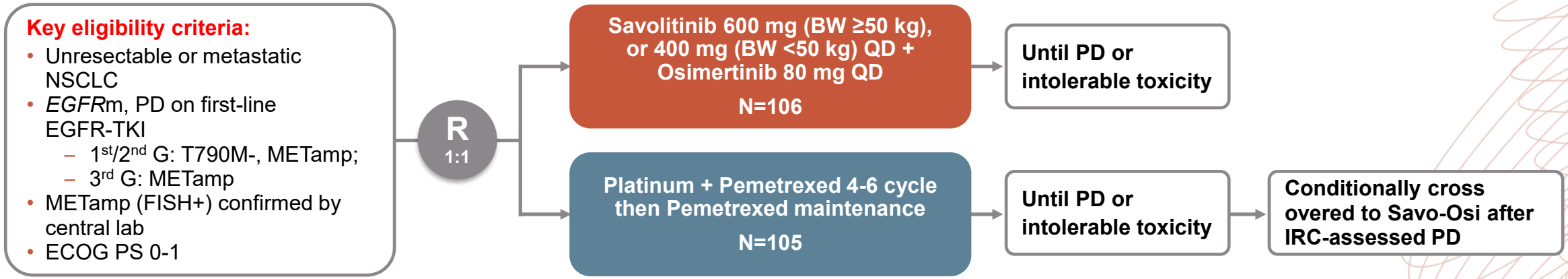
SAVOLITINIB COMBINED WITH OSIMERTINIB VERSUS CHEMOTHERAPY IN *EGFR*-MUTANT AND *MET*-AMPLIFICATION ADVANCED NSCLC AFTER DISEASE PROGRESSION ON EGFR TKI: RESULTS FROM A RANDOMISED PHASE 3 SACHI STUDY

Lu S, et al. Abstract LBA8505, ASCO 2025

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

SACHI: BACKGROUND AND STUDY DESIGN

- *MET* amplification is a known resistance mechanism in up to 22% of pre-treated *EGFR*-mutant NSCLC[1,2], and is also associated with early progression and poor prognosis[3]
- Savolitinib, a highly selective *MET*-TKI, combined with osimertinib, may overcome acquired *MET*-driven resistance in *EGFR*m advanced NSCLC after PD on EGFR-TKIs[4]
- Primary results of the prespecified interim analysis of the SACHI study, comparing efficacy and safety of savolitinib plus osimertinib with chemotherapy in this disease setting are presented[5]



METamp:
- **Post 1st/2nd G**: MET copy number ≥5 or MET/CEP7 ≥2
- **Post 3rd G**: MET copy number ≥10

Stratification factors:
- **Brain metastasis**: (yes or no)
- **Prior 3rd G EGFR-TKI**: (yes or no)
- *EGFR* mutation: (ex19del vs L858R vs others)

Primary endpoint: PFS by investigator
Secondary endpoints: PFS by IRC, ORR, DCR, DoR, TTR, OS, safety

1st/2nd/3rd G, first or second or third generation; BW, body weight; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRm, EGFR mutation; FISH, fluorescence in situ hybridisation; IRC, independent review committee; METamp, MET amplification; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, once daily; R, randomisation; Savo-Osi, savolitinib-osimertinib; TKI, tyrosine kinase inhibitor; TTR, time to response

1. Matikas A, et al. Clin Lung Cancer 2015;16:252-61; 2. Leonetti A, et al. Br J Cancer 2019;121:725-37; 3. Ahn BC, et al. Cancers (Basel) 2021;13:3096; 4. Ahn M-J, et al. J Thorac Oncol 2025;20(3):S4-5; 5. Lu S, et al. J Clin Oncol 2025;43(suppl 17). Abstr LBA8505 (ASCO 2025, oral presentation)

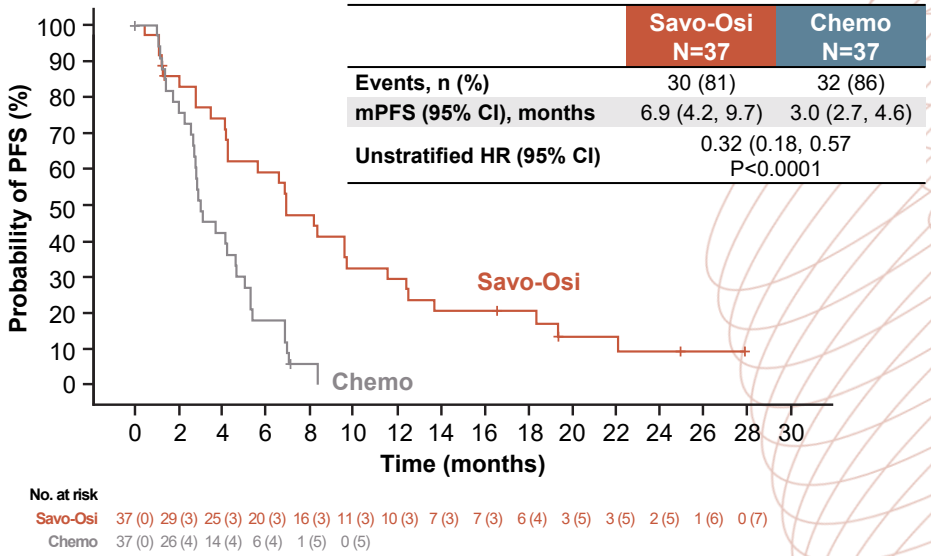
SACHI: EFFICACY RESULTS

- At the time of DCO (30 Aug 2024), 211 pts were randomised to receive savolitinib plus osimertinib or chemotherapy (n=106 vs 105). Baseline characteristics were well balanced
- mPFS by INV was significantly longer with savolitinib plus osimertinib vs chemotherapy in both 3rd generation EGFR-TKI treatment-naïve set and ITT set
- In 3rd generation EGFR-TKI treated patients, mPFS was also significantly prolonged with savolitinib plus osimertinib
- IRC-assessed PFS benefits were consistent. OS was immature at this DCO

ITT set	Savo + osi N=106	Chemo N=105	Hazard ratio/ odds ratio	Two sided-p value
mPFS (95% CI) (INV), m	8.2 (6.9, 11.2)	4.5 (3.0, 5.4)	0.34	<0.0001
mPFS (95% CI) (IRC), m	7.2 (5.7, 11.1)	4.2 (4.0, 5.7)	0.40	<0.0001
mOS (95% CI), m[a]	22.9 (16.8, NE)	17.7 (14.9, 26.3)	0.84	0.4191
ORR, % (95% CI)	58 (49-68)	34 (25-44)	2.74 (1.50-4.98)	0.0004
DCR, % (95% CI)	89 (81-94)	67 (57-76)	3.98 (1.81-8.82)	0.0001
Median DoR, m (95% CI)	8.4 (5.9-11.1)	3.2 (2.8-4.2)	–	NA

[a] 52.4% of pts in chemo group were crossover to receive savo + osi or other MET inhibitors

PFS BY PRIOR 3RD GEN EGFR-TKI TREATED SUBGROUP (INV)



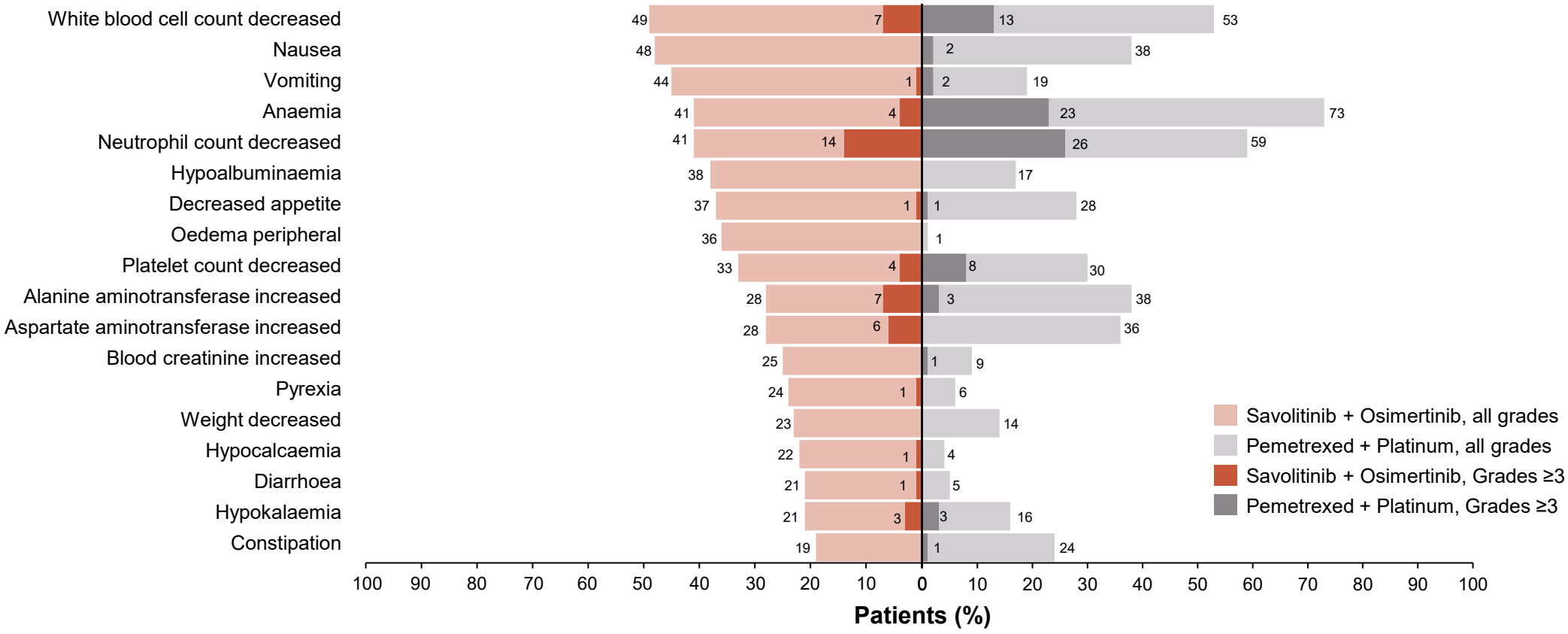
CI, confidence interval; chemo, chemotherapy; DCO, data cut-off; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; INV, investigator-assessed; IRC, independent review committee; ITT, intention-to-treat; m, months; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; ORR, objective response rate; osi, osimertinib; pts, patients; savo, savolitinib; TKI, tyrosine kinase inhibitor

Lu S, et al. J Clin Oncol 2025;43(suppl 17). Abstr LBA8505 (ASCO 2025, oral presentation)

SACHI: SAFETY RESULTS

- Grade ≥3 TEAE occurred in 56.6% vs 57.3% of pts with savolitinib plus osimertinib vs chemotherapy; savolitinib plus osimertinib had lower rates of hematologic events than chemotherapy

ADVERSE EVENTS IN ≥20% OF PATIENTS IN EITHER GROUP



pts, patients; TEAE, treatment-emergent adverse event

Lu S, et al. J Clin Oncol 2025;43(suppl 17). Abstr LBA8505 (ASCO 2025, oral presentation)

SACHI: SUMMARY

- Savolitinib in combination with osimertinib demonstrated statistically significant and clinically meaningful improvements in mPFS, ORR and DoR versus chemotherapy in *MET*-amplified NSCLC post first-line EGFR-TKI
- The safety profile of savolitinib in combination with osimertinib was favourable with no new safety signals or unexpected toxicities
- Savolitinib plus osimertinib could be a new chemo-free treatment option for *MET*-amplified NSCLC patients post first-line EGFR-TKI

Clinical perspective

- The combination of savolitinib plus osimertinib represents a significant therapeutic advancement for patients with *EGFR*-mutant NSCLC who develop *MET* amplification after EGFR inhibitor treatment
- Based on the results from this Chinese study, the combination therapy has been granted priority review by China's NMPA

DoR, duration of response; mPFS, median progression-free survival; NMPA, National Medical Products Administration; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor

Lu S, et al. J Clin Oncol 2025;43(suppl 17). Abstr LBA8505 (ASCO 2025, oral presentation)

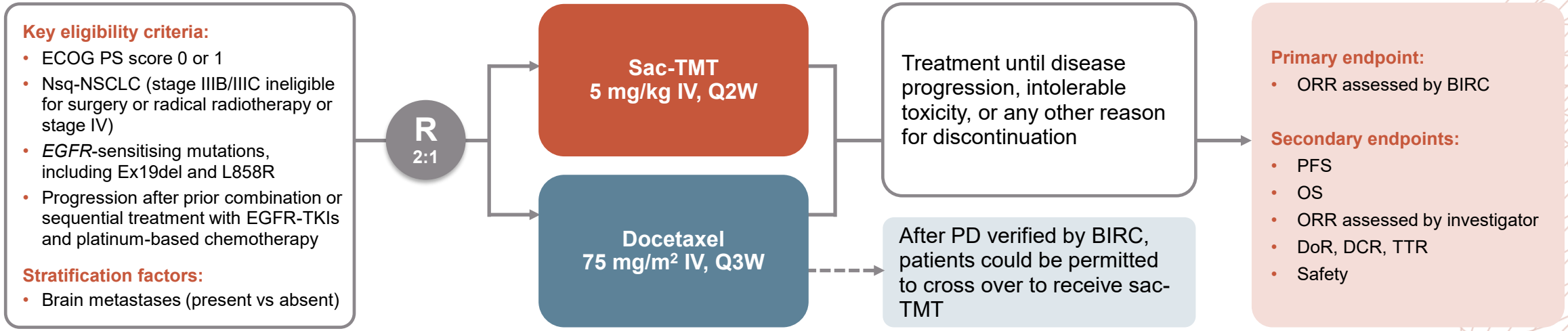
SACITUZUMAB TIRUMOTECAN IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED *EGFR*-MUTATED NSCLC: RESULTS FROM THE RANDOMISED OptiTROP-Lung03 STUDY

Zhang L, et al. Abstract 8507, ASCO 2025

NSCLC, non-small cell lung cancer

OptiTROP-Lung03: BACKGROUND AND STUDY DESIGN

- *EGFR* mutations are present in ~10-15% of NSCLC patients in the Western population and ~40-50% in the Asian population[1,2]
- Single-agent chemotherapy is standard of care for patients with *EGFR*-mutant NSCLC who have progressed on EGFR-TKIs and platinum-based chemotherapy[3]
- Sac-TMT is a TROP2 ADC developed with a novel linker conjugated to a novel topoisomerase I inhibitor which has shown encouraging antitumor activity in *EGFR*-mutant NSCLC pts in phase 1/2 trials[3,4]
- Results from OptiTROP-Lung03, a multicentre, randomised, controlled study comparing sac-TMT with docetaxel in previously treated *EGFR*-mutant NSCLC pts are reported (NCT05631262)[3]



ADC, antibody-drug conjugate; BIRC, blinded independent review committee; DCR, disease control rate; DoR, duration of response; ECOG PS, European Cooperative Oncology Group performance status; Ex19del, exon 19 deletion; IV, intravenous; (Nsq-)NSCLC, non-squamous non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; pts, patients; Q2/3W, every 2 or 3 weeks; R, randomisation; sac-TMT, sacituzumab tirumotecan; TKI, tyrosine kinase inhibitor; TTR, time to response

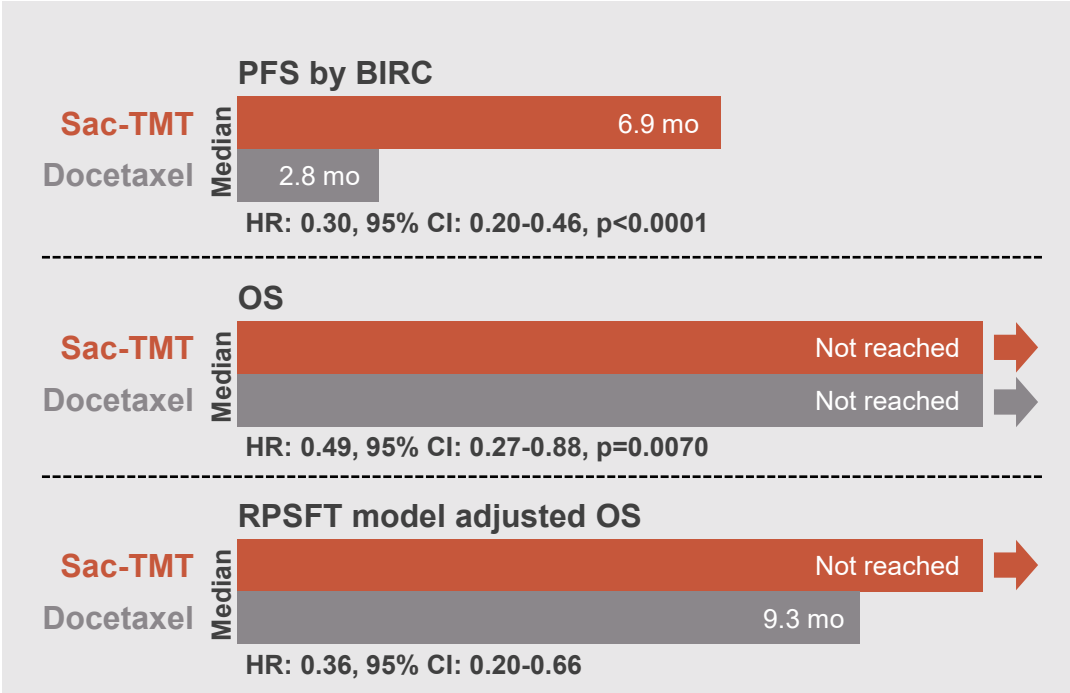
1. Melosky B, et al. Mol Diagn Ther 2022;26(1):7-18; 2. Tan AC and Tan DSW. J Clin Oncol 2022;40:611-25; 3. Zhang L, et al. J Clin Oncol 2025;43(suppl 16). Abstr 8507 (ASCO 2025, oral presentation); 4. Zhao S, et al. Nat Med 2025. doi: 10.1038/s41591-025-03638-2. Online ahead of print

OptiTROP-Lung03: EFFICACY RESULTS

TUMOUR RESPONSE BY BIRC PRIMARY ENDPOINT

	Sac-TMT (N=91)	Docetaxel (N=45)
cORR, n (%) (95% CI)	41 **(45.1)** (34.6, 55.8)	7 **(15.6)** (6.5, 29.5)
Difference (95% CI)	**28.9 (14.5, 43.2)**	
One-sided P-value	0.0004	
DCR, n (%) (95% CI)	75 (82.4) (73.0, 89.6)	27 (60.0) (44.3, 74.3)
Difference (95% CI)	22.3 (6.0, 38.7)	
DoR, n (%)	26 (63.4)	6 (85.7)
Median DoR, months (95% CI)	**7.0** (5.4, 9.1)	**5.1** (3.1, NE)

SECONDARY ENDPOINTS



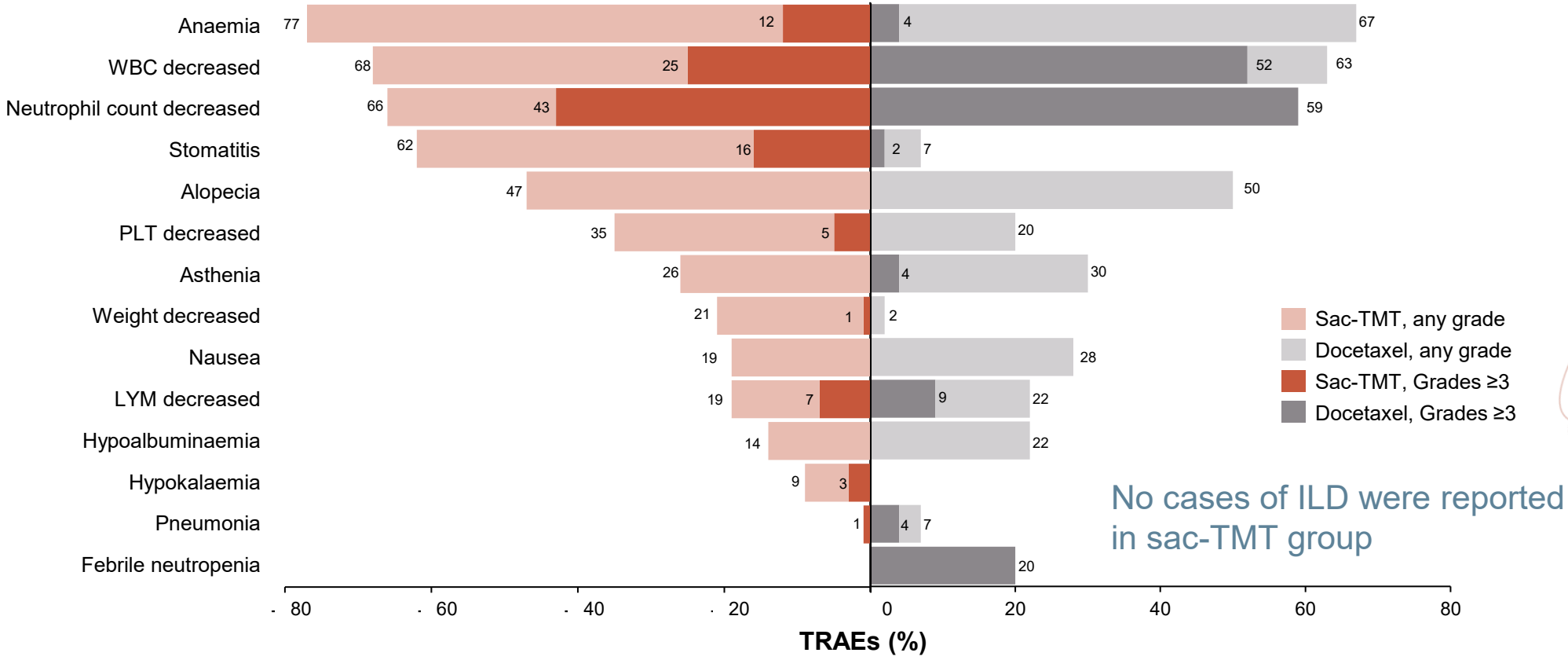
BIRC, blinded independent review committee; CI, confidence interval; (c)ORR, (confirmed) ORR; DCR, disease control rate; DoR, duration of response; HR, hazard ratio; NE, not evaluable; OS, overall survival; PFS, progression-free survival; RPSFT, rank-preserve structural failure time model; sac-TMT, sacituzumab tirumotecan

Zhang L, et al. J Clin Oncol 2025;43(suppl 16). Abstr 8507 (ASCO 2025, oral presentation)

OptiTROP-Lung03: SAFETY RESULTS

- Grade ≥3 TRAEs occurred in 56.0% of pts in sac-TMT group vs 71.7% in docetaxel group, and treatment-related SAEs were 16.5% vs 41.3%

COMMON TRAEs[a]



No cases of ILD were reported in sac-TMT group

ILD, interstitial lung disease; LYM, lymphocytes; PLT, platelets; pts, patients; sac-TMT, sacituzumab tirumotecan; SAE, serious adverse event; TRAE, treatment-related adverse event; WBC, white blood cell

Zhang L, et al. J Clin Oncol 2025;43(suppl 16). Abstr 8507 (ASCO 2025, oral presentation)

OptiTROP-Lung03: SUMMARY

- Sac-TMT demonstrated statistically significant and clinically meaningful improvements in ORR, PFS and OS compared to docetaxel, in pts with previously treated advanced *EGFR*-mutant NSCLC
- Sac-TMT had a manageable safety profile with no unexpected safety signals identified
- These results highlight significant survival benefits and suggest that sac-TMT could emerge as a new standard of care for this population

Clinical perspective

- Sac-TMT improved PFS and OS compared to docetaxel in relapsed *EGFR*-mutant NSCLC post TKI and platinum-based chemotherapy
- Sac-TMT has recently been approved by the China NMPA based on these results

NMPA, National Medical Products Administration; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pts, patients; sac-TMT, sacituzumab tirumotecan; TKI, tyrosine kinase inhibitor

Zhang L, et al. J Clin Oncol 2025;43(suppl 16). Abstr 8507 (ASCO 2025, oral presentation)

PATRITUMAB DERUXTECAN IN RESISTANT *EGFR*-MUTATED ADVANCED NSCLC AFTER A THIRD-GENERATION EGFR TKI: THE PHASE 3 HERTHENA-Lung02 STUDY

Mok T, et al. Abstract 8506, ASCO 2025

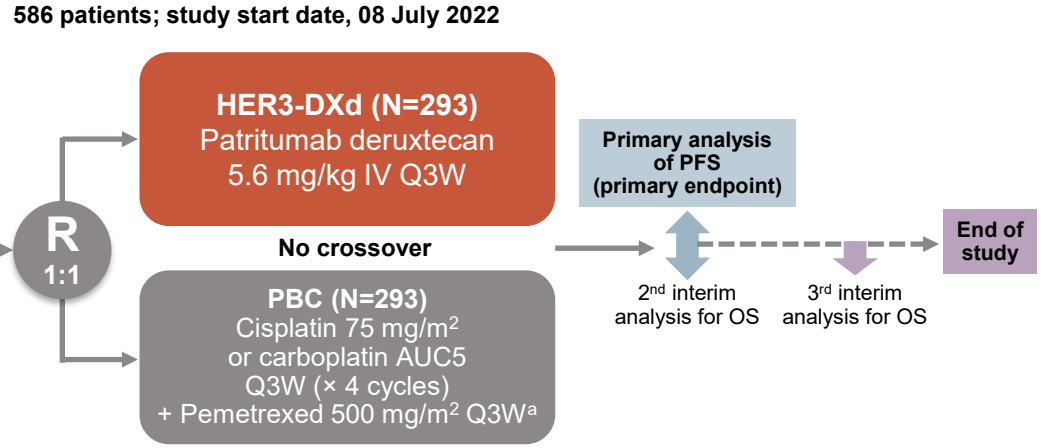
NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor

HERTHENA-Lung02: BACKGROUND AND STUDY DESIGN

- After disease progression on a 3rd-generation (3G) EGFR-TKI for advanced *EGFR*m NSCLC, available therapies provide limited efficacy[1]
- HER3-DXd, an ADC consisting of a fully human mAb to HER3 attached to a topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker, showed promising efficacy in HERTHENA-Lung01[2]
- HERTHENA-Lung02 (NCT05338970) is a phase 3, randomised, open-label study of HER3-DXd vs platinum-based chemotherapy (PBC) in patients with advanced *EGFR*m (Ex19del or L858R) NSCLC following disease progression on a 3G EGFR-TKI[1]

Select eligibility criteria:

- Advanced non-squamous NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- 1 or 2 prior line(s) of an approved EGFR-TKI (must include a third-generation EGFR-TKI)
  - Non-osimertinib third-generation TKIs ≤20% in each arm
- Disease progression while or after receiving a third-generation EGFR-TKI
- Stable brain metastases (asymptomatic and not requiring corticosteroids or anticonvulsants) were permitted



Primary endpoint:

- PFS (by BICR per RECIST v1.1)

Secondary endpoints:

- Key secondary: OS
- Other secondary:
  - Safety
  - Intracranial PFS in patients with baseline brain metastases (by CNS BICR per CNS RECIST)[b]
  - HER3 protein expression and its relationship with efficacy

Stratification factors:

- Third generation EGFR-TKI (osimertinib, other)
- Line of third generation EGFR-TKI (first, second)
- Region (Asia, Non-Asia)
- Presence of stable brain metastases (yes, no)

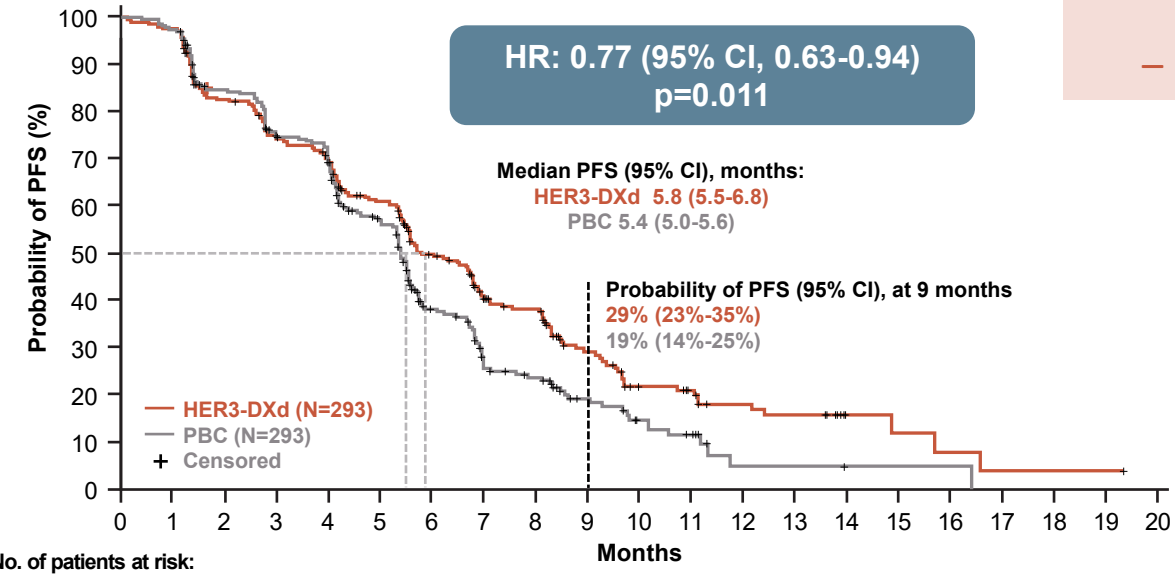
[a] No limit to the number of cycles of pemetrexed (maintenance as per label); [b] Brain imaging assessed by BICR according to CNS RECIST criteria

ADC, antibody-drug conjugate; AUC5, area under the curve of 5 mg/mL·min; BICR, blinded independent central review; CNS, central nervous system; EGFRm, EGFR mutation; Ex19del, exon 19 deletion; HER3-DXd, patritumab deruxtecan; IV, intravenous; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; Q3W, every 3 weeks; R, randomisation; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor

1. Mok T, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8506 (ASCO 2025, oral presentation); 2. Yu HA, et al. J Clin Oncol 2023;41:5363-75

HERTHENA-Lung02: EFFICACY RESULTS

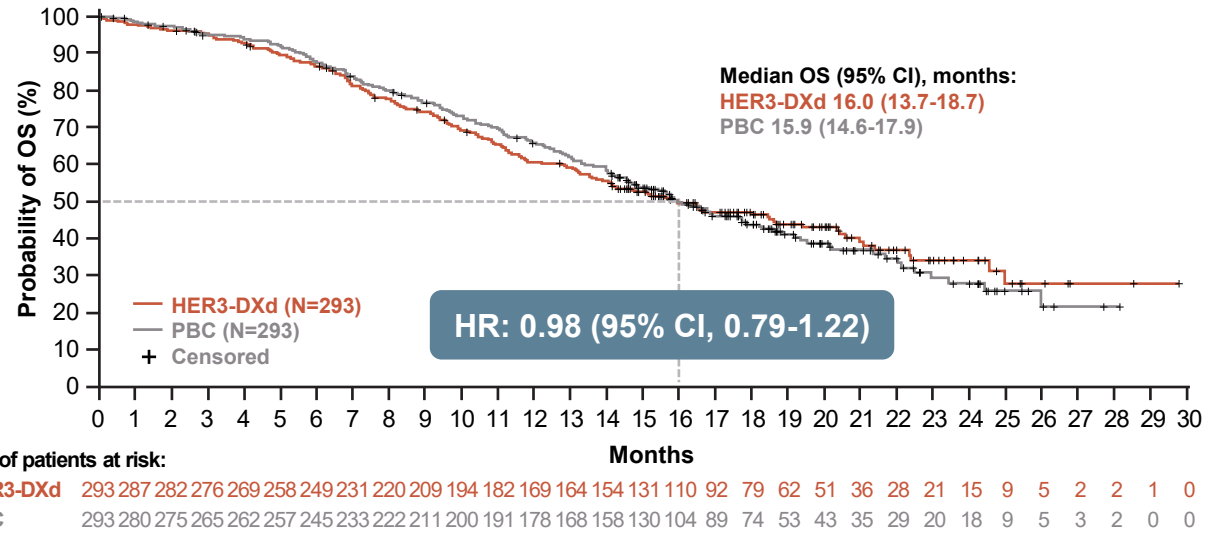
PROGRESSION-FREE SURVIVAL (Primary Analysis)



DCO: May 31 2024
Median follow-up: HER3-DXd 8.5 mo (95% CI 8.2-10.9), PBC 8.3 mo (95% CI 6.9-8.8 mo)

- **Responses by BICR per RECIST (HER3-DXd vs PBC):**
  - ORR (95% CI): 35.2% (29.7%-40.9%) vs 25.3% (20.4%-30.6%)
  - Median DoR (95% CI): 5.7 (5.1-7.3) mo vs 5.4 (4.1-5.6) mo

OVERALL SURVIVAL (3rd Interim Analysis)



DCO: Feb 28 2025
Median follow-up: HER3-DXd 18.7 mo (95% CI 17.9-19.9), PBC 18.6 mo (95% CI 17.9-19.6 mo)

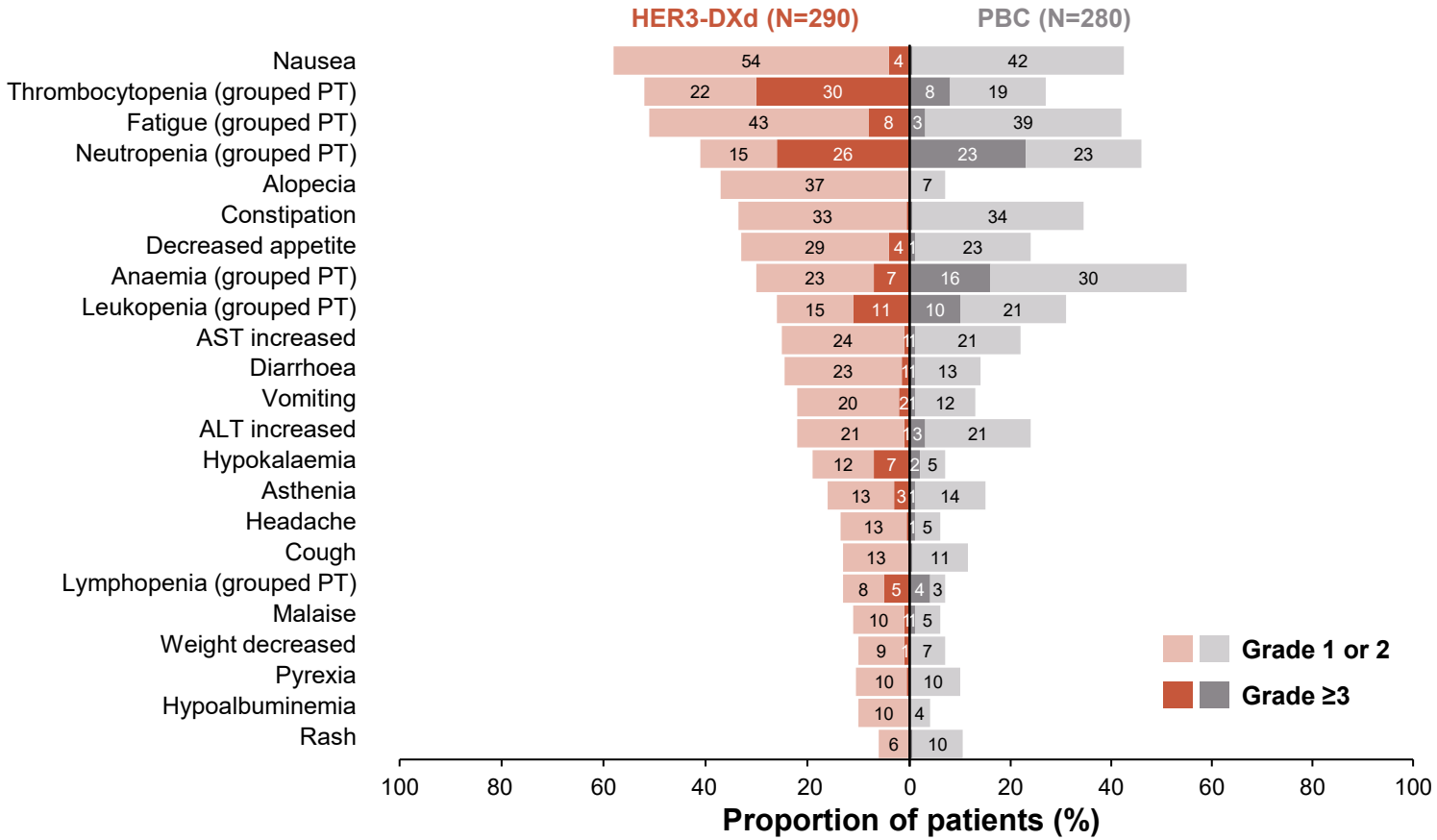
BICR, blinded independent central review; CI, confidence interval; DCO, data cut-off; DoR, duration of response; HER3-DXd, patritumab deruxtecan; HR, hazard ratio; mo, months; ORR, overall response rate; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours

Mok T, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8506 (ASCO 2025, oral presentation)

HERTHENA-Lung02: SAFETY RESULTS

TEAEs OCCURRING IN ≥10% OF PATIENTS

- TEAEs occurred in 100% of pts in the HER3-DXd arm and 99% in the PBC arm. TEAEs were associated with treatment discontinuation in 33 pts (11%) in the HER3-DXd arm and 27 (10%) in the PBC arm



- Hematologic toxicities occurred in cycle 1 or 2 and were transient and not associated with clinical sequelae
- Each arm had 1 G≥3 bleeding event associated with G≥3 platelet count decreased
- Adjudicated drug-related ILD occurred in 14 pts (5%; 11 G1/2, 1 G3, 2 G5) in the HER3-DXd arm

ALT, alanine aminotransferase; AST, aspartate aminotransferase; G, grade; HER3-DXd, patritumab deruxtecan; ILD, interstitial lung disease; PBC, platinum-based chemotherapy; PT, preferred term; pts, patients; TEAE, treatment emergent adverse event

Mok T, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8506 (ASCO 2025, oral presentation)

HERTHENA-Lung02: SUMMARY[1]

- HER3-DXd demonstrated statistically significant improvement in PFS vs PBC in pts with *EGFR*m NSCLC post EGFR-TKI therapy
- Data from the 3rd interim analysis demonstrated no improvement in OS for patients treated with HER3-DXd compared to PBC
- The safety profile was manageable, consistent with prior reports. Most common TEAEs were hematologic and gastrointestinal
- Follow-up is ongoing, along with further exploration of secondary/exploratory/biomarker endpoints from this data cut

Clinical perspective

- HER3-DXd more effective than platinum-based chemotherapy for PFS in relapsed *EGFR*-mutant NSCLC post 3rd generation TKI but no benefit in overall survival was observed
- Patritumab deruxtecan biologics license application for patients with previously treated locally advanced or metastatic *EGFR*-mutated NSCLC voluntarily withdrawn[2]

BLA, biologics license application; EGFRm, EGFR mutation; HER3-DXd, patritumab deruxtecan; NSCLC, non-small cell lung cancer; OS, overall survival; PBC, platinum-based chemotherapy; PFS, progression-free survival; TEAE, treatment emergent adverse event; TKI, tyrosine kinase inhibitor

Mok T, et al. J Clin Oncol. 2025;43(suppl 16). Abstr 8506 (ASCO 2025, oral presentation); OncLive. BLA Is Withdrawn for Patritumab Deruxtecan in EGFR-Mutated NSCLC. Available here (accessed June 2025)

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