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LUNG CONNECT

ONCOGENE-ADDICTED NSCLC
HIGHLIGHTS FROM WCLC AND ESMO 2024

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CLINICAL TAKEAWAYS

ROS1:

- **TRUST-II:** Taletrectinib demonstrated high and durable overall responses, robust IC activity in TKI-naïve and TKI-pretreated patients with *ROS1+* NSCLC, and is a potential new therapy for this patient population. Data from TRUST-II supports the efficacy and safety of taletrectinib across regions and ethnicities

KRAS:

- **LOXO-RAS-20001:** demonstrates the feasibility of combining *KRAS* G12C inhibitors with chemotherapy and immunotherapy. Preliminary efficacy was demonstrated with an ORR of 50% in a higher risk (PD-L1 low/negative) population. Olomorasib combined with chemo-immunotherapy demonstrated a manageable safety profile

***HER2* mutations:**

- **SOHO-01:** Treatment with BAY 2927088 led to rapid, substantial, and durable responses in patients with heavily pretreated *HER2*-mutant NSCLC. The safety profile of BAY 2927088 was manageable and consistent with previous reports
- **Beamion LUNG-1:** Zongertinib demonstrated significant and clinically meaningful activity in patients with pre-treated NSCLC with a *HER2* TKD mutation, including in those with brain metastases and was well tolerated

***HER2* Over expression:**

- **DESTINY-Lung03:** T-DXd monotherapy demonstrated encouraging antitumor activity in patients with pretreated advanced or metastatic HER2-OE NSCLC, and had an acceptable safety profile, consistent with the known profile of T-DXd

ALK:

- **ALKOVE-1:** NVL-655 was well-tolerated and the emerging safety profile was consistent with ALK-selective, TRK-sparing design. Durable responses were observed in a heavily pre-treated population and across patient subgroups

EGFR:

- **MARIPOSA:** Amivantamab plus lazertinib had significantly reduced the incidence of *MET* amplifications and *EGFR* resistance alterations versus osimertinib

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; T-DXd, trastuzumab deruxtecan

EDUCATIONAL OBJECTIVES

- Understand the clinical trial data and emerging profile of targeted therapies for the treatment of molecularly driven lung cancer from WCLC and ESMO 2024

WCLC 2024

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

Liu G, et al. WCLC 2024. Abstract #MA06.03

NSCLC, non-small cell lung cancer; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase

TRUST-II: BACKGROUND AND STUDY DESIGN

- **Taletrectinib**, a highly potent, next-generation, CNS-active, **selective ROS1 tyrosine kinase inhibitor** (TKI), demonstrated high overall and intracranial response rates, prolonged progression-free survival, and activity against the *ROS1* G2032R acquired resistance mutation with favourable tolerability in the Chinese TRUST-I (NCT04395677) study[1]
- Updated results in TKI-naive and TKI-pretreated patients from the global phase 2 trial, **TRUST-II** (NCT04919811), evaluating the **efficacy and safety of taletrectinib in patients with advanced ROS1+ non-small cell lung cancer** are reported[2]

Key eligibility criteria

Inclusion criteria:

- Locally advanced or metastatic NSCLC[a]
- Age ≥18 years[b]
- ECOG PS 0-1
- Evidence of *ROS1* fusion
- Stable brain mets allowed

Cohort 1: ROS1 TKI naïve
Taletrectinib 600 mg QD

Cohort 2: 1 Prior ROS1 TKI
Taletrectinib 600 mg QD

Endpoints

Primary:

- **IRC-assessed cORR per RECIST v1.1**

Secondary:

- DoR
- DCR
- Safety[c]
- IC-ORR
- TRR
- BoR
- PFS

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

BoR, best overall response; CNS, central nervous system; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; IRC, independent review committee; mets, metastases; NSCLC, non–small cell lung cancer; (c)ORR, (confirmed) objective response rate; PFS, progression-free survival; QD, every day; RECIST, Response Evaluation Criteria in Solid Tumours; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TKI, tyrosine kinase inhibitor; TTR, time to response

1. Li W, et al. J Clin Oncol. 2024;42(22):2660-70; 2. Liu G, et al. Abstract MA06.03, WCLC 2024 (oral presentation)

TRUST-II: EFFICACY RESULTS

DEMOGRAPHY

Category[a]	TKI Naïve (n=55)	TKI pretreated (n=50)	Overall (N=159)
Median age, years (range)	57.0 (27-82)	55.0 (27-79)	57.0 (27-83)
Female	31 (56.4)	27 (54.0)	89 (56.0)
Never smoker	28 (50.9)	30 (60.0)	90 (56.6)
Region, Asia/ non-Asia	34 (61.8)/ 21 (38.2)	22 (44.0)/ 28 (56.0)	74 (46.5)/ 85 (53.5)
ECOG PS 0/1	22 (40.0)/ 33 (60.0)	24 (48.0)/ 26 (52.0)	66 (41.5)/ 93 (58.5)
Stage IV disease	49 (89.1)	49 (98.0)	151 (95.0)
Prior anticancer chemotherapy	11 (20.0)	19 (38.0)	64 (40.3)
Brain metastasis	19 (34.5)	28 (56.0)	72 (45.3)
Prior crizotinib/ entrectinib	–	40 (80.0)/ 10 (20.0)	82 (51.6)/ 27 (17.0)

[a] n (%), except where indicated

TALOTRECTINIB RESPONSES

	TKI-naïve	TKI-pre-treated
Response rate (cORR)		
N	54	47
cORR, % (95% CI)	85.2 (72.88-93.38)	61.7 (46.38, 75.49)
Asia		
n	33	21
cORR, % (95% CI)	87.9 (71.80, 96.60)	57.1 (34.02, 78.18)
Non-Asia		
n	21	26
cORR, % (95% CI)	(81.0; 58.09, 94.55)	65.4 (44.33, 82.79)
IC-ORR (pts with measurable brain metastases at baseline)		
N	9	16
IC-ORR, % (95% CI)	66.7 (29.93, 92.51)	56.3 (29.88, 80.25)
CR, n (%)	2 (22.2)	1 (6.3)
PR, n (%)	4 (44.4)	8 (50.0)

Median follow-up: TKI-naïve patients: 15.8 mo (range: 3.6-29.8); TKI-pretreated: 15.7 mo (range: 3.9-29.8)

CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, intracranial; mo, months; (c)ORR, (confirmed) objective response rate; PR, partial response; TKI, tyrosine kinase inhibitor

Liu G, et al. Abstract MA06.03, WCLC 2024 (oral presentation)

TRUST-II: SAFETY RESULTS

TEAEs IN ≥15% OF PATIENTS (N=159)

Category, n (%)	Any grade	Grade ≥3
Increased ALT	108 (67.9)	24 (15.1)
Increased AST	107 (67.3)	11 (6.9)
Diarrhoea	90 (56.6)	1 (0.6)
Nausea	82 (51.6)	3 (1.9)
Vomiting	53 (33.3)	2 (1.3)
Constipation	40 (25.2)	0 (0)
Anaemia	32 (20.1)	7 (4.4)
Dysgeusia	31 (19.5)	0 (0)
Increased blood CPK	29 (18.2)	6 (3.8)
Dizziness	27 (17.0)	0 (0)
Prolonged QT	24 (15.1)	5 (3.1)

Data cut-off: 7th June 2024

- Median exposure of taletrectinib was 8.4 months (range: 0.1-28.9)
- **37.1%** of patients had a TEAE leading to a dose reduction
  - The most common events leading to dose reduction were **elevated liver enzymes (16.4%)**
- 7.5% of patients had a TEAE leading to treatment discontinuation; **1.3% were treatment-related**
- Rates of neurologic TEAEs were low (dysgeusia: 19.5%; dizziness: 17.0%); none were grade ≥3
- No treatment-related AE led to death

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

Liu G, et al. Abstract MA06.03, WCLC 2024 (oral presentation)

TRUST-II: SUMMARY

- **Taletrectinib** continues to demonstrate **high and durable overall responses**, robust IC activity **in TKI-naïve and TKI-pretreated patients with *ROS1*+ NSCLC**
- Efficacy was comparable between patients in Asia and non-Asia
- **Taletrectinib had a favourable safety profile:**
  - Low rate of treatment discontinuations due to TEAEs
  - Low rate of neurological TEAEs
  - No treatment related deaths
- The efficacy and safety of taletrectinib in TRUST-II remains highly consistent with TRUST-I

Clinical Perspective

- Taletrectinib demonstrated activity in *ROS1*-rearranged NSCLC, and is a potential new therapy for this patient population
- Data from TRUST-II supports the efficacy and safety of taletrectinib across regions and ethnicities

IC, intracranial; NSCLC, non–small cell lung cancer; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; TEAE, treatment-emergent adverse event; TKI, tyrosine kinase inhibitor

Liu G, et al. Abstract MA06.03, WCLC 2024 (oral presentation)

EFFICACY AND SAFETY OF OLOMORASIB WITH PEMBROLIZUMAB + CHEMOTHERAPY AS FIRST-LINE TREATMENT IN PATIENTS WITH *KRAS* G12C-MUTANT ADVANCED NSCLC (LOXO-RAS-20001)

Fujiwara Y, et al. WCLC 2024. Abstract #OA14.04

KRAS, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer

LOXO-RAS-20001: BACKGROUND AND STUDY DESIGN

- The combination of targeted therapy plus chemo-immunotherapy represents an opportunity to improve upon first-line outcomes in patients with *KRAS* G12C-mutant non-small cell lung cancer (NSCLC)
- **Olomorasib** is a potent, selective **second-generation *KRAS* G12C inhibitor** which has demonstrated **promising activity** with favourable tolerability **in *KRAS* G12C-mutant NSCLC** as monotherapy and combined with pembrolizumab
- LOXO-RAS-20001 (NCT04956640): a phase 1a dose escalation and phase 1b dose expansion study of olomorasib
  - Patients with advanced *KRAS* G12C-mutant NSCLC were enrolled into multiple cohorts and two doses of olomorasib (50 mg and 100 mg, orally twice daily) were investigated combined with standard chemotherapy platinum/pemetrexed and pembrolizumab (all at labelled doses)
- The first clinical data describing olomorasib combined with chemo-immunotherapy in the *KRAS* G12C-mutant NSCLC population are reported

Cohort B9: NSCLC

Olomorasib[a] + pembrolizumab[b] + pemetrexed[c] + platinum[d] (N=21)[e]

Cohort B9 Eligibility

- Treatment naïve for advanced or metastatic NSCLC
- PD-L1 expression 0-100% and *KRAS* G12C mutation based on local testing
- **Allowance of up to one 21-day cycle of any combination of pembrolizumab, pemetrexed, and carboplatin or cisplatin**
- Prior adjuvant or neoadjuvant therapy allowed, provided last dose was completed at least 6 months prior to enrolment

Part G: NSCLC

G
Olomorasib + pembrolizumab[c]

Part G was simultaneously enrolled regardless of PD-L1 expression and enrolment into Cohort B9 or Part G was at the investigator discretion

[a] Two doses of olomorasib (50 mg and 100 mg BID) were studied, not randomised; [b] Pembrolizumab 200 mg IV, Q3W; [c] Pemetrexed 500 mg/m^2 IV, Q3W; [d] Cisplatin 75 mg/m^2 IV, Q3W, or carboplatin AUC 5 mg/mL/min IV, Q3W; [e] Final cohort size will not exceed ~40 patients

AUC, area under the curve; BID, twice daily; IV, intravenous; KRAS, Kirsten rat sarcoma viral oncogene homologue; PD-L1, programmed death ligand 1; Q3W, once every 3 weeks

Fujiwara Y, et al. Abstract OA14.04. WCLC 2024 (oral presentation)

LOXO-RAS-20001: RESULTS

- As of 05-Jul-2024, 89 patients received olomorasib+pembrolizumab. The WCLC 2024 presentation reported on the subset of 21 (50 mg, n=10; 100 mg, n=11) who also received chemotherapy in that regimen
- Median age was 67 years (range, 56-81); 19 (90%) were PD-L1 low or negative, 1 (5%) was PD-L1-high and 1 (5%) was unknown; 9 (43%) patients received one cycle of SoC therapy prior to enrolment
- Median duration of therapy was 4.5 months, and 76% patients remained on study at time of data cut-off

SAFETY

	All doses and patients (50 + 100 mg BID, N=21)			
	Treatment-emergent AEs (≥15%)[a], n (%)		Treatment-related AEs[b], n (%)	
Adverse event	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE	21 (100)	14 (67)	19 (91)	9 (43)
Anaemia	10 (48)	5 (24)	9 (43)	4 (19)
Nausea	9 (43)	–	8 (38)	–
AST increased[c]	8 (38)	1 (5)	5 (24)	–
ALT increased	7 (33)	2 (10)	6 (29)	1 (5)
Decreased appetite	7 (33)	1 (5)	5 (24)	1 (5)
Dyspnoea	6 (29)	2 (10)	2 (10)	1 (5)
Fatigue	6 (29)	–	6 (29)	–
Constipation	6 (29)	–	2 (10)	–
Neutrophil count decreased	6 (29)	6 (29)	5 (24)	5 (24)
Platelet count decreased	5 (24)	4 (19)	4 (19)	3 (14)
Diarrhoea	4 (19)	2 (10)	4 (19)	2 (10)
Vomiting	4 (19)	1 (5)	3 (14)	–
Blood creatinine increased	4 (19)	–	4 (19)	–
Hypomagnesemia	4 (19)	–	1 (5)	–

EFFICACY

Objective Response Rate, % (n/N)	**50** (10/20)
Disease Control Rate, % (n/N)	**85** (17/20)

[a] The following TEAEs (≥10%), were observed in 3 patients (14%): blood alkaline phosphatase, hypotension, rash and rash maculopapular
[b] TRAEs are AEs related to any treatment. Total % may be different from the individual components due to rounding
[c] No grade 4 AST/ALT elevations observed

AE, adverse event; ALT alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; PD-L1, programmed death ligand 1; SoC, standard of care; TEAE, treatment-emergent AE; TRAE, treatment-related AE

Fujiwara Y, et al. Abstract OA14.04.

WCLC 2024 (oral presentation)

LOXO-RAS-20001: SUMMARY

- Olomorasib combined with chemo-immunotherapy demonstrated a manageable safety profile, consistent with the safety profiles observed with other combinations of chemotherapy and targeted therapy
- The results of LOXO-RAS-20001, demonstrate the feasibility of combining *KRAS* G12C inhibitors with chemotherapy and immunotherapy
- Preliminary efficacy was demonstrated with an ORR of 50% in a higher risk (PD-L1 low/negative) population
- A global, registrational study investigating this combination in first-line advanced *KRAS* G12C-mutated NSCLC is currently ongoing (SUNRAY-01, NCT06119581)

Clinical Perspective

- The LOXO-RAS-20001 study highlights the potential of combining targeted therapy with immunotherapy to improve outcomes for patients with *KRAS* G12C–mutant cancers

KRAS, Kirsten rat sarcoma viral oncogene homologue; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death ligand 1

Fujiwara Y, et al. Abstract OA14.04. WCLC 2024 (oral presentation)

HER2 MUTATIONS

HER2, human epidermal growth factor receptor 2

SAFETY AND EFFICACY OF BAY 2927088 IN PATIENTS WITH *HER2*-MUTANT NSCLC: EXPANSION COHORT FROM THE PHASE 1/2 SOHO-01 STUDY

Le X, et al. WCLC 2024. Abstract #PL04.03

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer

SOHO-01: BACKGROUND AND STUDY DESIGN

- ***HER2* mutations** have been reported in approximately 2-4% of patients with NSCLC,[1] and are **associated with poor prognosis[2]**
- **BAY 2927088** is an oral, reversible **tyrosine kinase inhibitor that potently inhibits *HER2* and mutant *EGFR*** in preclinical models and has shown preliminary anti-tumour activity in patients with advanced NSCLC harbouring *HER2* mutations [1]
- The FDA has granted Breakthrough Therapy designation for BAY 2927088 for previously-treated patients with advanced NSCLC and activating *HER2* mutations.[1] Updated results from the **SOHO-01 study** are reported from an expansion cohort of patients with ***HER2*-mutant NSCLC naïve to HER2-targeted therapy (Cohort D)**

Dose escalation & backfill

- Advanced NSCLC patients *HER2* or *EGFR* mutations
- Patients were treated with increasing oral doses of BAY 2927088 to identify the recommended doses for expansion

Recommended dose (or doses) for expansion

20 mg BID

Expansion / extension[a]

To evaluate the safety profile, tolerability, and efficacy, and characterise the PK of BAY 2927088 at the recommended dose or doses for expansion

Expansion cohorts of patients with either *HER2* or *EGFR* mutations[b]

D. *HER2* activating muts
HER2 ex20ins
Targeted Tx naïve
(Data presented here[c])

E. HER2 activating muts
Prior HER2-ADC

F. 1L naïve to any prior systemic Tx

G. 2L + active brain metastases

NCT05099172

Endpoints

Primary:

- Safety and tolerability
- Pharmacokinetics

Secondary:

- ORR (investigator assessed)
- PFS, DoR and DCR

[a] Extension phase ongoing in selected cohorts; [b] EGFR cohorts not presented here; [c] July 1, 2024 data cut-off. Dose optimisation cohort (D1) ongoing; not shown.

1L, first-line; 2L, second-line; ADC, antibody-drug conjugate; BID, twice daily; DCR, disease control rate; DoR, duration of response; EGFR, epidermal growth factor receptor; ex20ins, exon 20 insertion mutations; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; muts, mutations; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetics; Tx, treatment

1. Girard N, et al. J Clin Oncol. 2024; 42(suppl 17; abstr LBA8598); 2. Le X, et al. Abstract PL04.03, WCLC 2024 (oral presentation)

SOHO-01: EFFICACY RESULTS (COHORT D)

- Forty-four patients were treated, with a median follow-up of 10.9 months. Median age was 62 years, 63.6% were female, 70.5% had never smoked, and 54.5% had received ≥2 lines of therapy

ORR PER INVESTIGATOR (RECIST V1.1)

n (%)	Patients[a] (N=43)
ORR[b]	31 (72.1)
95% CI	56.3, 84.7
CR	1 (2.3)
PR	30 (69.8)
SD[c]	7 (16.3)
PD	5 (11.6)

- **Median DoR (N=31):** 8.7 months (95% CI 4.5, NE)
- **DCR[c]:** 83.7%
- **Median PFS (N=43):** 7.5 months (95% CI: 4.4, 12.2)

SUBGROUP ANALYSES

Subgroup		Patients,[a] n	ORR, n (%; 95% CI)
All evaluable patients in cohort D		43	31 (72.1; 56.3, 84.7)
HER2 YVMA insertion	Yes	30	27 (90.0; 73.5, 97.9)
	No	13	4 (30.8; 9.1, 61.4)
Brain metastases at baseline	Yes	8	5 (62.5; 24.5, 91.5)
	No	35	26 (74.3; 56.7, 87.5)
Previous therapy	Previous platinum, no previous immunotherapy	17	12 (70.6; 44.0, 89.7)
	Previous platinum, and immunotherapy	25	18 (72.0; 50.6, 87.9)

In patients with YVMA insertion (n=30)

- **Median DoR:** 9.7 months (95% CI: 5.5, NE)
- **DCR[c]:** 96.7%
- **Median PFS:** 9.9 months (95% CI: 6.9, NE)

[a] All evaluable patients; [b] Patients with confirmed CR or PR; [c] Patients with confirmed CR or confirmed PR or SD for ≥12 weeks

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not estimable; ORR, objective 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 PL04.03, WCLC 2024 (oral presentation)

SOHO-01: SAFETY RESULTS (COHORT D)

n (%)	All grades (N=44)	Grade ≥3 (N=44)
Any TRAE	42 (95.5)	19 (43.2)
Most common TRAEs occurring in ≥10% of patients		
Diarrhoea	38 (86.4)	11 (25.0)
Rash	19 (43.2)	0
Paronychia	11 (25.0)	0
Nausea	11 (25.0)	1 (2.3)
Vomiting	9 (20.5)	2 (4.5)
Dermatitis acneiform	8 (18.2)	0
Stomatitis	8 (18.2)	1 (2.3)
Dry skin	7 (15.9)	0
Increased aspartate aminotransferase	6 (13.6)	1 (2.3)
Decreased appetite	6 (13.6)	2 (4.5)
Increased amylase	5 (11.4)	0
Anaemia	5 (11.4)	0
Increased lipase	5 (11.4)	0
Decreased weight	5 (11.4)	0
Pruritis	5 (11.4)	1 (2.3)

- TRAEs were reported in 95.5% of patients, with grade 3 TRAEs reported in 43.2%
- There were no grade 4 TRAEs and one grade 5 event (dyspnoea); no reports of ILD/pneumonitis
- Diarrhoea was the most common TRAE (86.4%; 25.0% grade 3)
- Three patients (6.8%) discontinued due to TRAEs
- 5 patients (11.4%) had serious TRAEs

ALT alanine aminotransferase; ILD, interstitial lung disease; TRAE, treatment-related adverse event

Le X, et al. Abstract PL04.03, WCLC 2024 (oral presentation)

SOHO-01: SUMMARY

- Treatment with BAY 2927088 led to rapid, substantial, and durable responses in patients with heavily pretreated *HER2*-mutant NSCLC
- The safety profile of BAY 2927088 was manageable and consistent with previous reports
- These data support the ongoing investigation of BAY 2927088 in patients with advanced NSCLC harbouring *HER2* mutations

Clinical Perspective

- These results from the expansion phase of the SOHO-01 trial demonstrate the potential of this targeted therapy to improve outcomes for patients with *HER2*-mutant NSCLC, which has limited treatment options and a poor prognosis

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer

Le X, et al. Abstract PL04.03, WCLC 2024 (oral presentation)

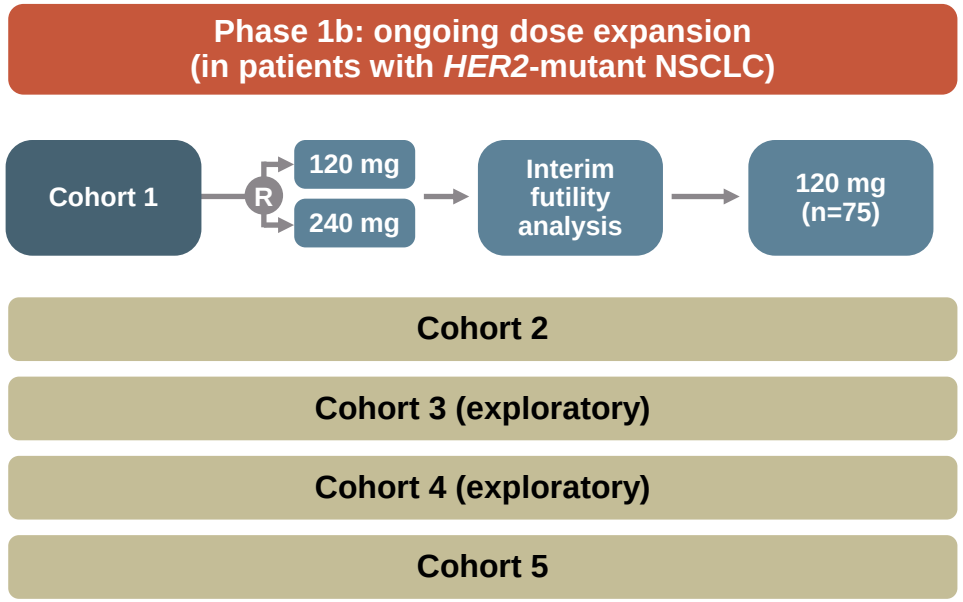
PRIMARY PHASE 1B ANALYSIS OF Beamion LUNG-1: ZONGERTINIB IN PATIENTS WITH *HER2* MUTATION-POSITIVE NSCLC

Ruiter G, et al. WCLC 2024. Abstract #PL04.04

HER2, human epidermal growth factor receptor 2; NSCLC, non-small cell lung cancer

BEAMION LUNG-1: BACKGROUND AND STUDY DESIGN

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



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

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

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

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

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

Phase 1b primary endpoint

- ORR

Key inclusion criteria

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

NCT04886804

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

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

Ruiter G, et al. Abstract PL04.04, WCLC 2024 (oral presentation)

BEAMION LUNG-1: EFFICACY RESULTS

DEMOGRAPHY

- As of May 2024, 132 patients have been treated in Phase 1b Cohort 1 and have received zongertinib at 120 mg/240 mg QD (n=75 / n=57)
- 57.6% were female and median age at baseline was 62 years (range: 30-82). Median follow-up for efficacy was approximately 13 weeks; treatment was ongoing in two-thirds of patients at cut-off

TUMOUR RESPONSE ALL TREATED PATIENTS

- The **primary endpoint, confirmed response by BICR, was met** for all treated patients at 120 mg (n=75) in Phase 1b Cohort 1
  - ORR by central review: 66.7% (97.5% CI: 53.8-77.5), p<0.0001
- **Tumour shrinkage** of any magnitude was **observed in 94% of patients** (124/132), per investigator assessment
- **DoR and PFS data are currently immature**, two-thirds of patients remained on treatment at data cut-off

TUMOUR RESPONSE WITH 1:1 RANDOMISATION[a]

Confirmed Best Overall Response by Central Review, n (%)	120 mg N=58	240 mg N=55
ORR	42 (72.4)	43 (78.2)
CR	1 (1.7)	2 (3.6)
PR	41 (70.7)	41 (74.5)
DCR	55 (94.8)	55 (100.0)
SD	13 (22.4)	12 (21.8)
PD	3 (5.2)	0
NE	0	0

[a] 1:1 randomisation for both doses allows a proper comparison

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease

Ruiter G, et al. Abstract PL04.04, WCLC 2024 (oral presentation)

Beamion LUNG-1: SAFETY RESULTS

TRAEs, n (%)	120 mg N=75		240 mg N=57	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any AE[a]	69 (92)	13 (17)	57 (100)	11 (19)
Diarrhoea	36 (48)	1 (1)	37 (65)	1 (2)
Rash[b]	18 (24)	0	17 (30)	0
AST increased	14 (19)	6 (8)	16 (28)	6 (11)
AST increased	16 (21)	4 (5)	14 (25)	4 (7)
Anaemia	8 (11)	0	10 (18)	0
Nausea	10 (13)	0	4 (7)	0
Neutrophil count decreased	7 (9)	1 (1)	7 (12)	3 (5)
Pruritus	6 (8)	0	8 (14)	0
Serious TRAE	3 (4)	3 (4)	7 (12)	5 (9)

[a] TRAEs as assessed by the investigator, that occurred in ≥10% of all patients
[b] Combined term, includes rash, rash maculo-papular and dermatitis acneiform

- Majority of TRAEs were mild and manageable
- Most cases of diarrhoea and rash were mild
- Diarrhoea: 43% grade 1, 11% grade 2
- Rash: 19% grade 1, 8% grade 2
- No fatal TRAEs occurred
- AEs leading to **dose reduction** occurred in 14 (11%) patients
- Only 4 patients (3%) had AEs leading to **treatment discontinuation**

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TRAE, treatment-related adverse event

Ruiter G, et al. Abstract PL04.04, WCLC 2024 (oral presentation)

BEAMION LUNG-1: SUMMARY

- Zongertinib demonstrated significant and clinically meaningful activity in patients with pre-treated NSCLC with a *HER2* TKD mutation, including in those with brain metastases
- Zongertinib was very well tolerated, with no deaths attributed to treatment and a low incidence of dose reductions and treatment discontinuations
- Beamion LUNG-2, a Phase 3 randomised study of zongertinib compared to SoC as first-line treatment for patients with advanced NSCLC with *HER2* mutations is currently enrolling (NCT06151574)

Clinical Perspective

- The BEAMION LUNG-1 study highlights zongertinib as a promising treatment for *HER2*-mutated NSCLC, offering significant tumour reduction, disease control, and manageable safety. This could potentially improve outcomes for patients with this challenging form of lung cancer.

HER2, human epidermal growth receptor 2; NSCLC, non-small cell lung cancer; SoC, standard of care; TKD, tyrosine kinase domain

Ruiter G, et al. Abstract PL04.04, WCLC 2024 (oral presentation)

HER2 OVEREXPRESSION

HER2, human epidermal growth factor receptor 2

TRASTUZUMAB DERUXTECAN MONOTHERAPY IN PRE-TREATED HER2-OVEREXPRESSING NONSQUAMOUS NSCLC: DESTINY-Lung03 PART 1

Planchard D, et al. WCLC 2024. Abstract #OA16.05

HER2, human epidermal growth factor receptor 2, NSCLC, non-small cell lung cancer

DESTINY-Lung03: BACKGROUND AND STUDY DESIGN

- **HER2 overexpression in NSCLC** is associated with limited treatment response and a **poor prognosis**[1]
- **Trastuzumab deruxtecan** (T-DXd) is **approved** in several regions, including the US and EU, for patients with **unresectable or metastatic *HER2* mutant NSCLC** who have received prior systemic therapy[2,3]
  - In **DESTINY-Lung01**, T-DXd monotherapy demonstrated encouraging anti-tumour activity in extensively pretreated patients with unresectable and/or metastatic HER2-overexpressing (HER2-OE) NSCLC[1]
  - **DESTINY-Lung03** is an open-label, multicentre, Phase 1b, multipart study evaluating T-DXd-based treatments in patients with HER2-OE NSCLC. Part 1 monotherapy is reported[1]

Patient population

- Aged ≥18 years
- Centrally assessed HER2-OE (IHC 3+/2+)[a] unresectable, locally advanced or metastatic nonsquamous NSCLC
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0-1
- Patients in Part 1 had one or two prior lines of therapy; those with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation[b] (enrolment complete)
Arm 1A: T-DXd + durvalumab + cisplatin
Arm 1B: T-DXd + durvalumab + carboplatin

Part 1: T-DXd monotherapy (enrolment complete)
Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)
T-DXd + volrustomig ± carboplatin

Part 4: safety run-in and expansion (currently recruiting)
T-DXd + rilvegostomig ± carboplatin

Key endpoints: T-DXd monotherapy (arm 1D)

Secondary:

- ORR
- DoR
- DCR
- PFS

(Investigator assessed)

- OS
- Safety and tolerability

Exploratory:

- Efficacy outcomes by:
  - HER2 IHC status
  - Prior EGFR TKI exposure[c]

[a] HER2 overexpression was defined as ≥25% of tumour cells with IHC 3+ or 2+ by central testing using the Dako HER2-low IHC assay;
[b] arm 1C: T-DXd + durvalumab + pemetrexed treatment was planned but not initiated;
[c] patients had HER2-OE (IHC 3+/2+) NSCLC

NCT04686305

DCR, disease control rate; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EU, European Union; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, once every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; US, United States; WHO, World Health Organization

1. Planchard D, et al. Abstract OA16.05, WCLC 2024 (oral presentation); 2. Trastuzumab deruxtecan SmPC: https://www.ema.europa.eu/en/documents/product-information/enhertu-epar-product-information_en.pdf (last accessed: September 2024); 3. Trastuzumab deruxtecan USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761139s028lbl.pdf (last accessed: September 2024)

DESTINY-Lung03: EFFICACY RESULTS (PART 1 MONOTHERAPY)

DEMOGRAPHY

- At data cut-off (April 1, 2024), 36 patients with HER2-OE NSCLC had received T-DXd 5.4 mg/kg
  - median duration of T-DXd total treatment was 7.2 months (range: 0.7-23.3)
  - median duration of follow up was 14.9 months (range: 0.7-25.3)
- Patients were predominantly female (61.1%) and from Asia (88.9%)
- Median age was 66.5 years (range: 47-80)
- Targeted therapy was the most common prior treatment modality (58.3%)

RESPONSE AND SURVIVAL OUTCOMES

Part 1: T-DXd monotherapy (arm 1D)	N=36
Confirmed ORR, (n) %[a] 95% CI	16 (44.4) 27.9, 61.9
Best objective response, n (%)[a] Complete response Partial response Stable disease ≥5 weeks Disease progression[b] Not evaluable	 0 16 (44.4) 15 (41.7) 4 (11.1) 1 (2.8)
DCR at 12 weeks, % (95% CI)[a]	77.8 (60.9, 89.9)
Median DoR, months (95% CI)[a]	11.0 (5.5, 16.7)
Median PFS, months (95% CI)	8.2 (6.7, 11.1)
Median OS, months (95% CI)	17.1 (11.6, 23.8)

[a] Investigator assessed per RECIST v1.1;
[b] including RECIST-defined disease progression or death

CI, confidence interval; DCR, disease control rate; DoR, duration of response; HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; T-DXd, trastuzumab deruxtecan

Planchard D, et al. Abstract OA16.05, WCLC 2024 (oral presentation)

DESTINY-Lung03: SAFETY RESULTS (PART 1 MONOTHERAPY)

Part 1: T-DXd monotherapy (arm 1D) n (%) of patients		N=36
Drug-related AEs		34 (94.4)
Drug-related Grade ≥3 AEs		15 (41.7)
Drug-related serious AEs		6 (16.7)
Drug-related AEs leading to discontinuations		3 (8.3)
Drug-related AEs leading to dose reductions		7 (19.4)
Drug-related AEs leading to dose interruptions		5 (13.9)
Drug-related AEs with outcome of death		1 (2.8)[a]
Adjudicated drug-related ILD/pneumonitis[b]	Any grade	2 (5.6)
	Grade 2	2 (5.6)
Drug-related left ventricular dysfunction	Any grade	1 (2.8)[c]
	Grade 2	1(2.8)[c]

Most common (>10%) any-grade drug-related AEs,[d,e] n(%)	Any grade	Grade ≥3
Nausea	52.8	2.8
Vomiting	30.6	0
Fatigue	30.6	8.3
Anaemia	25.0	11.1
Decreased appetite	19.4	0
Alopecia	13.9	0
Dyspepsia	13.9	0
Thrombocytopenia	11.1	0
Neutrophil count decreased	11.1	2.8

Assessed by investigator (unless specified otherwise) in patients who received ≥1 dose of T-DXd

[a] Neutropenic colitis; [b] assessed by the ILD adjudication committee; [c] ejection fraction decreased; [d] graded according to CTCAE version 5; [e] individual preferred terms; patients with multiple events in the same preferred term are counted only once in that preferred term and patients with events in more than one preferred term are counted once in each of those preferred terms

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan

Planchard D, et al. Abstract OA16.05, WCLC 2024 (oral presentation)

DESTINY-Lung03: SUMMARY

- T-DXd monotherapy (5.4 mg/kg) demonstrated encouraging antitumor activity in patients with pretreated advanced or metastatic HER2-OE NSCLC, consistent with results from DESTINY-Lung01
- The safety profile was acceptable and generally manageable, consistent with the known profile of T-DXd

Clinical Perspective

- DESTINY-Lung03 study highlights the potential of combining targeted therapies with immunotherapy and chemotherapy to improve treatment outcomes for patients with *HER2*-positive NSCLC

HER2, human epidermal growth factor receptor 2; HER2-OE, HER2-overexpressing; NSCLC, non-small cell lung cancer; T-DXd, trastuzumab deruxtecan

Planchard D, et al. Abstract OA16.05, WCLC 2024 (oral presentation)

ESMO 2024

PHASE 1/2 ALKOVE-1 STUDY OF NVL-655 IN *ALK*-POSITIVE SOLID TUMOURS

Drilon A, et al. ESMO 2024. Abstract #1253O

ALK, anaplastic lymphoma kinase

ALKOVE-1: BACKGROUND AND STUDY DESIGN

- NVL-655 is a potent, brain-penetrant, **ALK-selective tyrosine kinase inhibitor** (TKI) designed to address key limitations of prior generation ALK TKIs
  - it demonstrates **preclinical activity against diverse *ALK* fusions and resistance mutations**, including lorlatinib refractory compound mutations
  - **It avoids TRK inhibition** (TRK-sparing), which is associated with neurologic toxicities
- ALKOVE-1 is a global, first-in-human, phase 1/2 trial of NVL-655 in advanced *ALK*-positive NSCLC and other solid tumours (NCT05384626)

Patient population

- Advanced solid tumours harbouring an *ALK* fusion or activating mutation (by local testing)
- Patients with NSCLC: ≥1 prior 2G or 3G ALK TKI
- ≤2 prior chemotherapies /immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., *EGFR/ROS1/MET/RET/BRAF* alterations)
- Evaluable but non-measurable disease allowed

Phase 1 dose-escalation completed, follow-up continues

Enrolment June 2022 to February 2024 (data cut-off: 15 June 2024)

NVL-655 Phase 1	All doses	15 mg QD	25 mg QD	50 mg QD	100 mg QD	150 mg QD (RP2D)	200 mg QD
All treated population, n	N=133	3	12	12	32	52	22
NSCLC response evaluable population, n	N=103	3	7	10	27	39	17

Phase 1 objectives

- Primary: selection of RP2D and, if applicable, MTD
- Overall safety and tolerability
- PK characterisation
- Preliminary antitumour activity
- Intracranial activity

2G, second generation; 3G, third generation; ALK, anaplastic lymphoma kinase; BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; QD, once daily; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; RP2D, recommended phase 2 dose; TRK, tyrosine receptor kinase

Drilon A, et al. Ann Oncol. 2024;35 (suppl_2):S802-S877 (ESMO 2024 oral presentation, Abstract #1253O)

ALKOVE-1: RESULTS

DEMOGRAPHY

- 133 patients with solid tumours (131 NSCLC) received NVL-655 (15-200 mg orally once daily) in phase 1
- Patients previously received a median of 3 (range: 1-9) prior anticancer therapies, including any 2G ALK TKI or lorlatinib (100%), ≥2 ALK TKI & lorlatinib (79%), ≥3 ALK TKIs (46%), and chemotherapy (56%); 56% had a history of treated/untreated CNS metastases

EFFICACY

Activity of NVL-655 at RP2D (RECIST 1.1)	ORR, %	Median DoR, mo	DoR ≥ 6 mo (%)
All prior ALK + NSCLC response evaluable (1-5 prior ALK TKIs ± prior chemotherapy)	38%	Not reached	100
Prior lorlatinib (≥2 prior ALK TKIs ± prior chemotherapy)	35%	Not reached	100
With compound *ALK* resistance mutations	64%	Not reached	100
Lorlatinib-naïve (≥1 prior 2G ± 1G ALK TKI ± prior chemotherapy)	57%	Not reached	100
With *ALK* resistance mutation(s)	80%	Not reached	100

RP2D was 150 mg once daily

SAFETY

Treatment-related adverse events (TRAEs) in ≥10% of patients all treated (N=133)

Preferred term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade
ALT increased	21 (16%)	6 (5%)	17 (13/%)	1 (1%)	45 (34%)
AST increased	21 (16%)	7 (5%)	12 (9%)	–	40 (30%)
Constipation	15 (11%)	6 (5%)	–	–	21 (16%)
Dysgeusia	15 (11%)	2 (2%)	–	–	17 (13%)
Nausea	15 (11%)	1 (1%)	–	–	16 (12%)

- Discontinuation due to TRAE: 2% (3/133)
- Dose reduction due to TRAE: 15% (20/133)

1G, first generation; 2G, second generation; ALK, anaplastic lymphoma kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNS, central nervous system; DoR, duration of response; mo, months; NSCLC, non-small cell lung cancer; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumours; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event; TKI, tyrosine kinase inhibitor

Drilon A, et al. Ann Oncol. 2024;35 (suppl_2):S802-S877 (ESMO 2024 oral presentation, Abstract #1253O)

ALKOVE-1: SUMMARY

- In ALKOVE-1, NVL-655 was well-tolerated and the emerging safety profile was consistent with ALK-selective, TRK-sparing design
- Durable responses were observed in a heavily pre-treated population and across patient subgroups
- Durable intracranial responses were also observed

Clinical Perspective

- The ALKOVE-1 trial highlights NVL-655 as a potent and selective ALK inhibitor with significant potential to improve treatment outcomes for patients with *ALK*-positive NSCLC, particularly those with brain metastases and resistance mutations

ALK, anaplastic lymphoma kinase; TRK, tyrosine receptor kinase

Drilon A, et al. Ann Oncol. 2024;35 (suppl_2):S802-S877 (ESMO 2024 oral presentation, Abstract #1253O)

MECHANISMS OF ACQUIRED RESISTANCE TO FIRST-LINE AMIVANTAMAB PLUS LAZERTINIB VERSUS OSIMERTINIB IN PATIENTS WITH *EGFR*-MUTANT ADVANCED NSCLC: AN EARLY ANALYSIS FROM THE PHASE 3 MARIPOSA STUDY

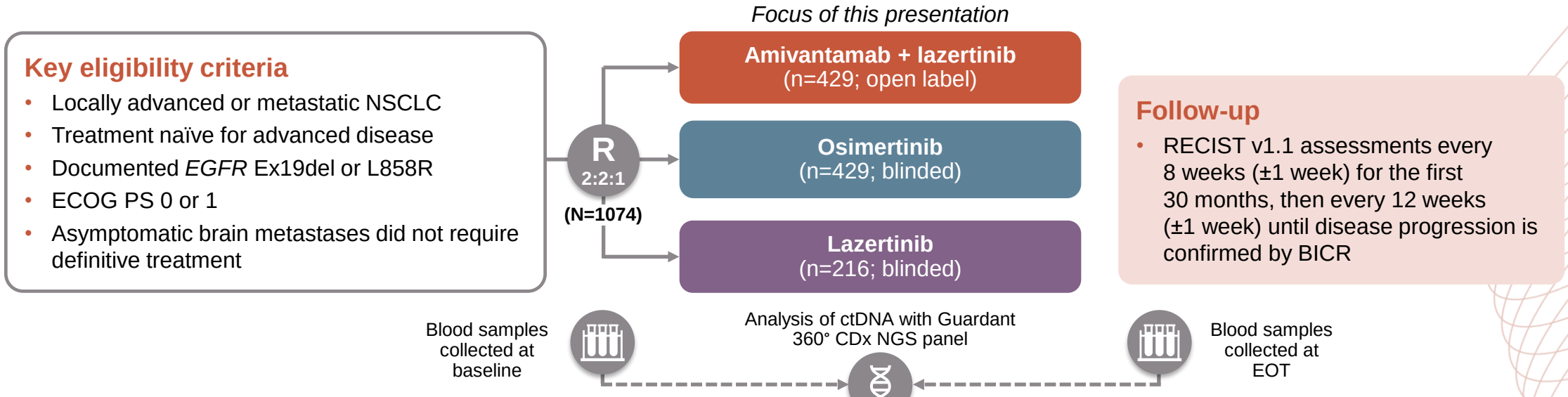
Besse B, et al. ESMO 2024. Abstract #LBA55

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer

MARIPOSA: BACKGROUND AND STUDY DESIGN

- In the phase 3 MARIPOSA study (NCT04487080), first-line amivantamab plus lazertinib significantly improved progression-free survival vs osimertinib in patients with *EGFR*-mutant advanced non-small cell lung cancer (HR: 0.70; p<0.001) and is now approved in the US for the first-line treatment of *EGFR*-mutant NSCLC[1]
- Acquired resistance mechanisms for patients who progressed on first-line amivantamab plus lazertinib in the MARIPOSA trial are reported here

Paired blood samples were collected at baseline and EOT for analysis of detectable ctDNA by NGS

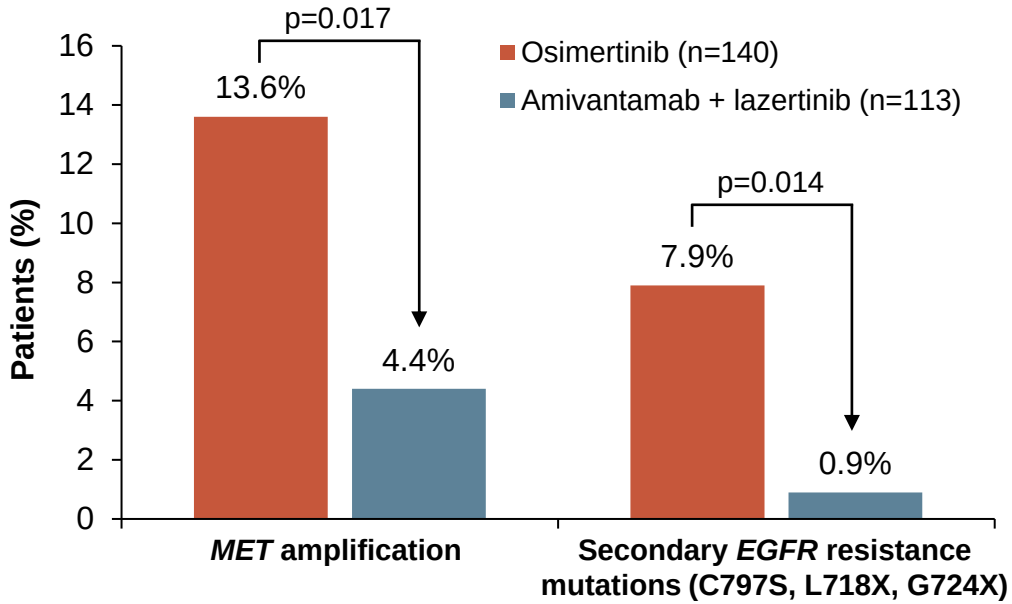


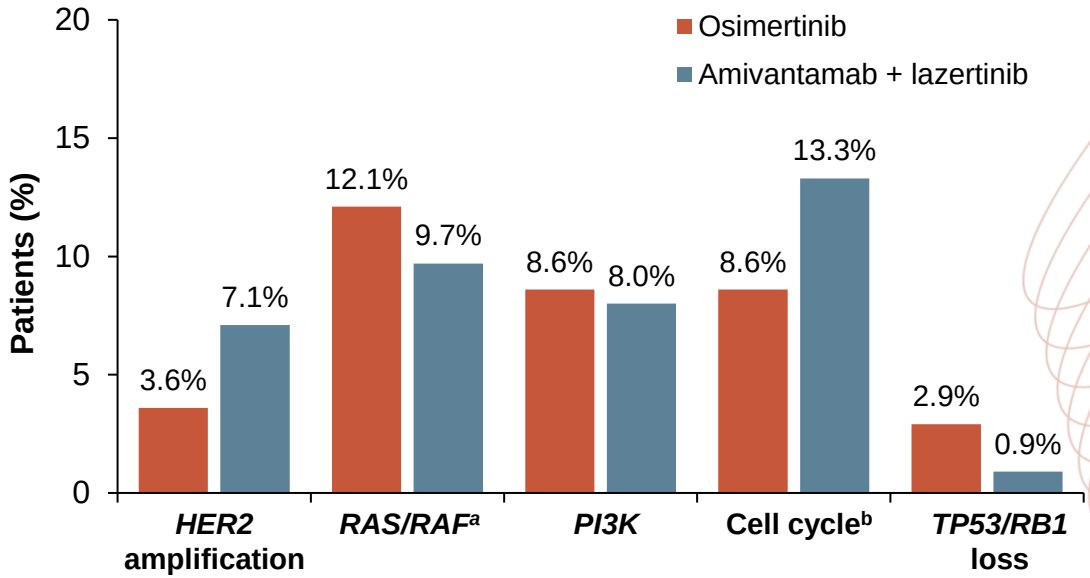
BICR, blinded-independent central review; CDx, companion diagnostics; ctDNA, circulating tumour DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EOT, end of trial; Ex19del, exon 19 deletion; HR, hazard ratio; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours; US, United States

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761210s005lbl.pdf (last accessed: September 2024); 2. Besse B, et al. Ann Oncol. 2024;35 (suppl_2):1-72 (ESMO 2024 oral presentation, Abstract #LBA55)

MARIPOSA: ACQUIRED RESISTANCE RESULTS

- Among patients who discontinued treatment, 113/215 (53%) for amivantamab + lazertinib and 140/252 (56%) for osimertinib had matched baseline and EOT ctDNA data.
- Acquired *MET* amplifications were ~ 3-fold lower and *EGFR* resistance mutations were ~8 fold lower for amivantamab + lazertinib vs osimertinib
- No statistically significant difference were seen between arms for other resistance mechanisms





[a]Includes BRAF and KRAS; [b]Includes CCNE1, CDKN2A, CDK4, CDK6 and CCND2

ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; EOT, end of trial; HER2, human epidermal growth factor receptor; MET, mesenchymal epithelial transition factor; PI3K, phosphatidylinositol-3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; RB1, retinoblastoma 1; TP53, tumour protein p53

Besse B, et al. Ann Oncol. 2024;35 (suppl_2):1-72 (ESMO 2024 oral presentation, Abstract #LBA55)

MARIPOSA: SUMMARY

- Amivantamab plus lazertinib had significantly reduced the incidence of *MET* amplifications and *EGFR* resistance alterations versus osimertinib
- Trends for lower rates of *TP53* resistance mutations and *RB1* loss were observed with the combination treatment compared with osimertinib
- These initial findings suggest that first-line amivantamab plus lazertinib is changing the biology of acquired resistance and demonstrate clear proof of mechanism with potent inhibition of resistance via the EGFR and MET pathways

Clinical Perspective

- The multi-targeted EGFR/MET approach of amivantamab plus lazertinib narrowed the spectrum and reduced the complexity of acquired resistance versus osimertinib

EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor; RB1, retinoblastoma 1; TP53, tumour protein p53

Besse B, et al. Ann Oncol. 2024;35 (suppl_2):1-72 (ESMO 2024 oral presentation, Abstract #LBA55)

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