Perspectives on *EGFR*-mutant and wildtype NSCLC: Tailoring treatment advances in late-stage disease

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EGFR-mutant NSCLC: Navigating the horizon in *EGFR*-mutant NSCLC

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Overview of course content

Current module

1

***EGFR*-mutant NSCLC**

- Unmet needs
- Latest advances
- Practical insights

2

***EGFR*-wildtype NSCLC**

- Unmet needs
- Latest advances
- Practical insights

3

Bringing it together for optimal care

- Patient management
- Biomarker landscape
- Key learnings

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

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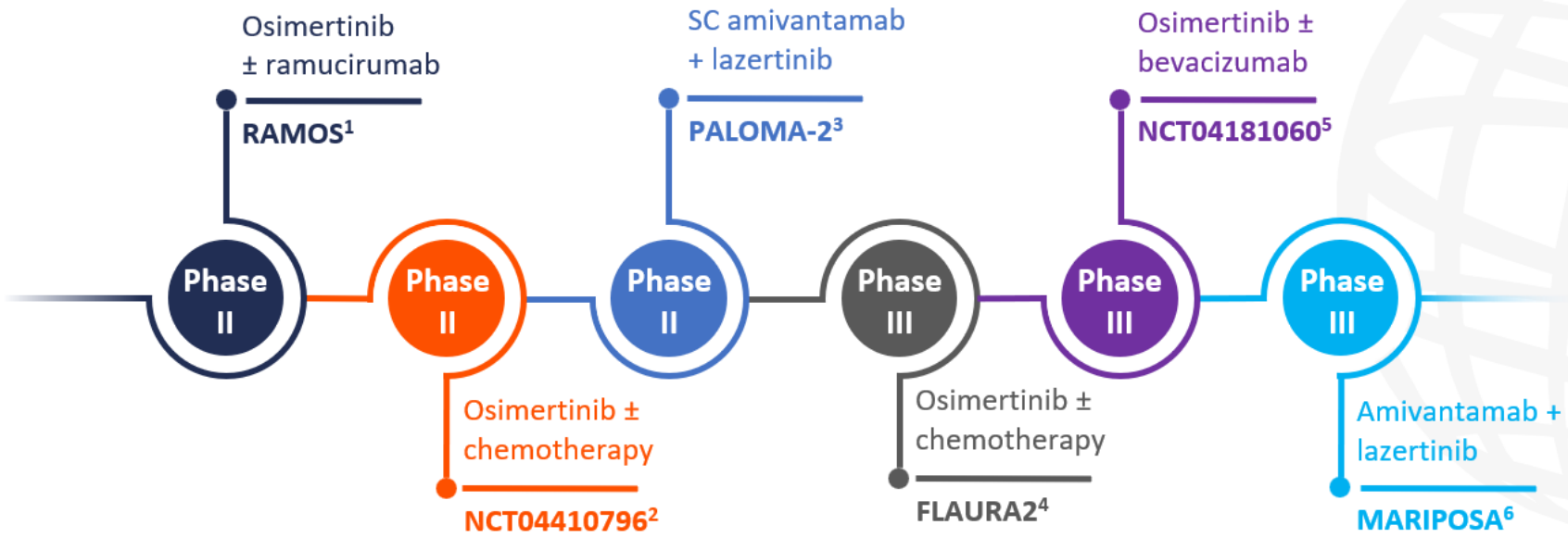
Key clinical trials in *EGFR*-mutant NSCLC in the first-line



EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SC, subcutaneous.
1. NCT03909334; 2. NCT04410796; 3. NCT05498428; 4. NCT04035486; 5. NCT04181060; 6. NCT04487080.
All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ (accessed 19 July 2024).

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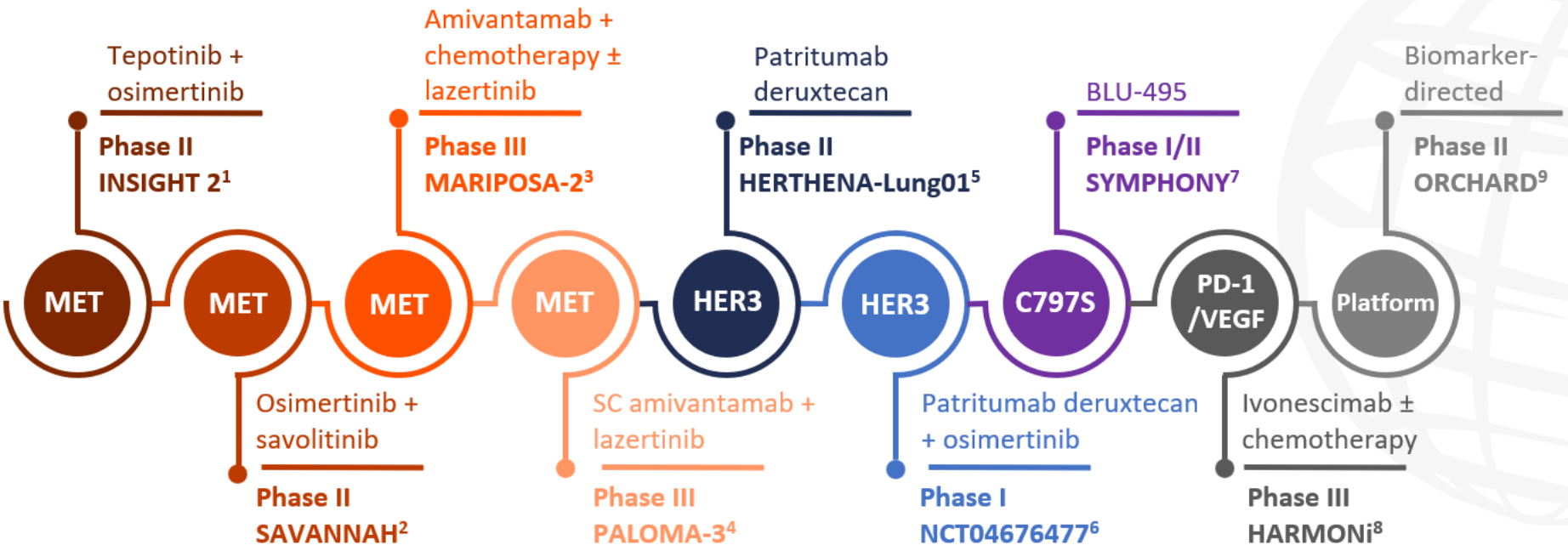
Key clinical trials in *EGFR*-mutant NSCLC in the second-line



EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; MET, mesenchymal epithelial transition factor receptor; NSCLC, non-small cell lung cancer; PD-1, programmed cell death protein 1; SC, subcutaneous; VEGF, vascular endothelial growth factor.

1. NCT03940703; 2. NCT03778229; 3. NCT04988295; 4. NCT05388669; 5. NCT04619004; 6. NCT04676477; 7. NCT04862780; 8. NCT06396065; 9. NCT03944772.

All clinical trials searchable by NCT number. Available at: https://clinicaltrials.gov/ (accessed 19 July 2024).

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EGFR-mutant NSCLC: Evaluating the latest advances in therapeutic strategies

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FLAURA2: Results at 24 months[1,2]

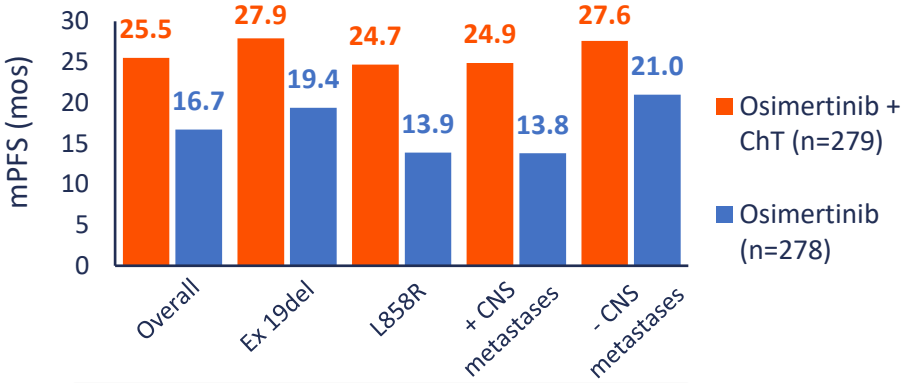
Phase III international trial of osimertinib ± Pt-ChT vs osimertinib* in *EGFR*-mutant advanced NSCLC

Trial population

- Ia/mNSCLC
- No prior systemic treatment
- *EGFR* Exon 19 deletion or L858R either alone or in combination with other *EGFR* mutations e.g. T790M
- Stable CNS disease

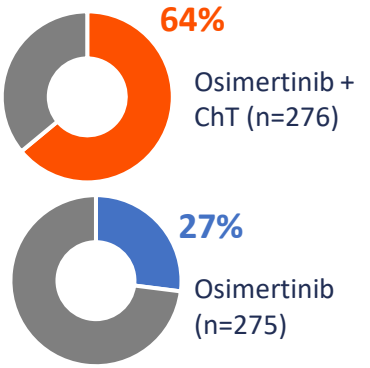
Primary efficacy outcomes across subgroups

Investigator-assessed PFS per RECIST v1.1



HR for disease progression or death:
No CNS metastases = 0.75 (95% CI, 0.55–1.03)

Safety: Grade ≥3 AEs



Haematologic toxic effects:
Osimertinib + ChT: 71%
Osimertinib: 24%

*Osimertinib (80 mg once daily) + IV pemetrexed (500 mg/m²) + either cisplatin (75 mg/m²) or carboplatin (pharmacologically guided dose) on day 1 of 21-day cycles for four cycles followed by osimertinib (80 mg once daily) + pemetrexed maintenance (500 mg/m²) every 3 weeks vs osimertinib (80 mg once daily). AE, adverse event; CNS, central nervous system; ChT, chemotherapy; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; IV, intravenous; Ia/mNSCLC, locally advanced/metastatic non-small cell lung cancer; m, median; mos, months; PFS, progression-free survival; Pt-ChT, platinum-based ChT; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1. 1. Planchard D, et al. *N Engl J Med*. 2023;389:1935–48; 2. NCT04035486. Available at: https://clinicaltrials.gov/study/NCT04035486?term=NCT04035486&rank=1 (accessed 16 July 2024).

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MARIPOSA: Median follow-up 22 months[1–3]

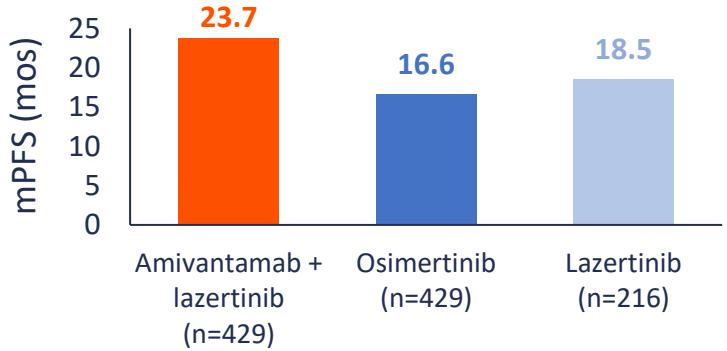
Phase III trial of amivantamab + lazertinib vs osimertinib* in *EGFR*-mutant advanced NSCLC

Trial population

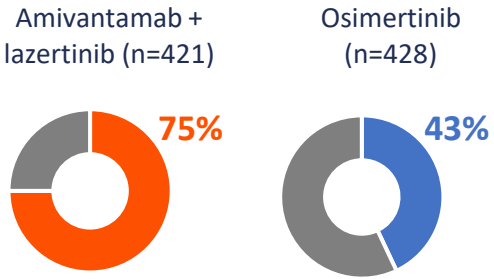
- la/mNSCLC
- No prior systemic therapy
- *EGFR* exon 19 deletion or L858R
- Asymptomatic or stable CNS disease
- No prior ILD

Primary efficacy outcomes

PFS by BICR per RECIST v1.1



Safety: Grade ≥3 AEs



VTEs: Increased rates for amivantamab + lazertinib (mostly grade 1 or 2)

Reduced risk of disease progression or death by 30% (95% CI 0.58–0.85, p<0.001). PFS benefit seen across all subgroups including age, gender, race, smoking history, classic *EGFR* mutations and BMs (18.3 vs 13.0 mos)

*Patients were randomized 2:2:1 in the following cohorts: Arm A – combination therapy with amivantamab 1,050 mg IV (or 1,400 mg if >80 kg) weekly for 4 weeks then every 2 weeks plus lazertinib 240 mg daily; Arm B – osimertinib 80 mg daily; Arm C – lazertinib 240 mg daily.

AE, adverse event; BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IV, intravenous; la/mNSCLC, locally advanced/metastatic non-small cell lung cancer; m, median; mos, months; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; VTE, venous thromboembolism.

1. Cho BC, et al. Presented at: 2023 ESMO Congress, Madrid, Spain. 20–25 October 2023. Abstr. LBA14; 2. Brazel D, Nagasaka M. *Lung Cancer (Auckl)*. 2024;15:41–7; 3. NCT04487080. Available at: https://www.clinicaltrials.gov/study/NCT04487080 (accessed 16 July 2024).

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MARIPOSA: Analysis of high-risk subgroups[1,2]

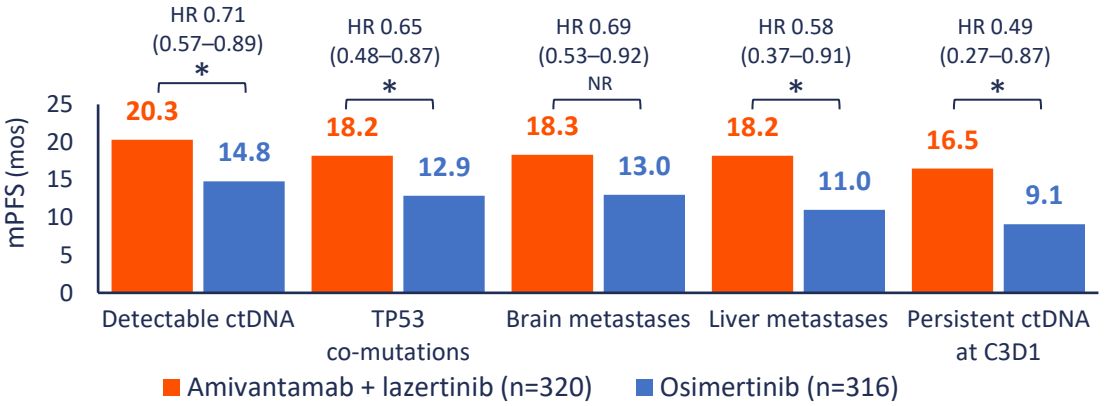
Secondary analysis exploring efficacy outcomes with amivantamab + lazertinib vs osimertinib in patients with high-risk disease

Subgroup analysis population

At baseline, 89% (n=636) of patients with *EGFR*-mutant NSCLC had ≥1 high-risk feature

- **Detectable ctDNA by NGS:** 85%
- ***TP53* co-mutations:** 54%
- **Brain metastases:** 41%
- **Liver metastases:** 16%
- **Persistent ctDNA at C3D1:** 15%

Efficacy outcomes: mPFS by per RECIST v1.1



PFS outcomes were better among high-risk patients who received amivantamab + lazertinib vs osimertinib

Ranges after HRs denote 95% confidence intervals. *Nominal p<0.05.
C3D1, cycle 3 day 1; ctDNA, circulating tumour DNA; EGFR, epidermal growth factor receptor; HR, hazard ratio; mos, months; m, median; NGS, next-generation sequencing; NR, not reported; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TP53, tumour protein p53.

1. Felip E, et al. *Ann Oncol*. 2024. doi: 10.1016/j.annonc.2024.05.541 [Epub ahead of print]; 2. Cho BC, et al. *N Engl J Med*. 2024 (supplementary appendix). doi: 10.1056/NEJMoa2403614 [Epub ahead of print].

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HERTHENA-Lung01: Primary analysis[1,2]

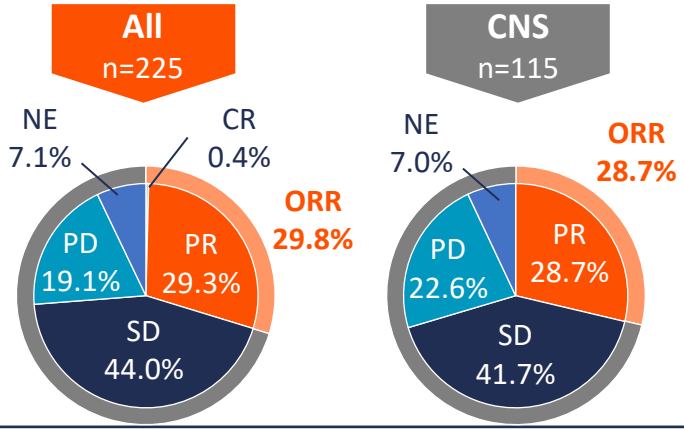
Phase II trial of patritumab deruxtecan (HER3-Dxd)* in *EGFR*-mutant advanced NSCLC

Trial population

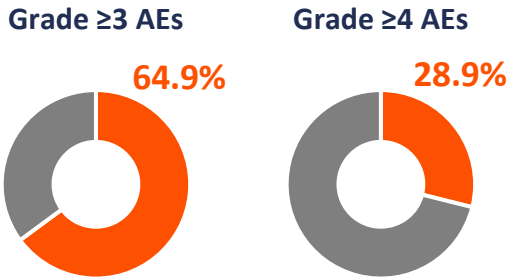
- Tumour progression with ≥1 EGFR-TKI (osimertinib) + ≥1 Pt-ChT
- *EGFR* exon 19del or L858R activating mutations
- Clinically inactive/treated brain metastases
- No previous or current evidence of ILD
- ECOG PS 0 or 1

Primary efficacy outcomes

Confirmed ORR by BICR per RECIST v1.1



Safety (n=225)



- Most common grade ≥3 AEs were haematological toxicities
- ILD: 5.3% (mainly grade 1 or 2)

*One of two dose schedules HER3-Dxd administered intravenously once every 3 weeks. Patients in arm 1 received a fixed-dose regimen of 5.6 mg/kg. Patients in arm 2 received an uptitration regimen: cycle 1 day 1, 3.2 mg/kg; cycle 2 day 1, 4.8 mg/kg; cycle 3 day 1 and subsequent cycles, 6.4 mg/kg. **Results reported are for arm 1.**

AE, adverse event; BICR, blinded independent central review; CNS, central nervous system; CR, complete response; ECOG PS, European Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; ILD, interstitial lung disease; NE, not evaluable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; Pt-ChT, platinum-based chemotherapy; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TKI, tyrosine kinase inhibitor.

1. Yu HA, et al. *J Clin Oncol*. 2023;41:5363–75; 2. NCT05338970. Available at: https://www.clinicaltrials.gov/study/NCT05338970 (accessed 16 July 2024).

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MARIPOSA-2: Primary results[1,2]

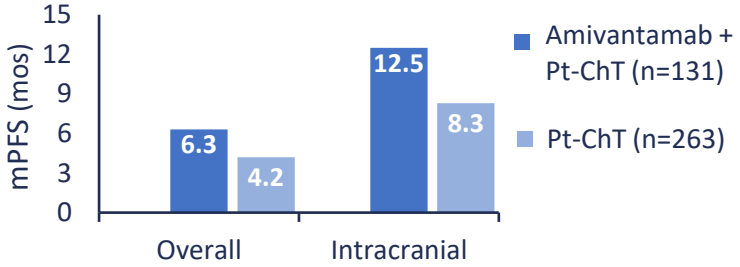
Phase III trial of IV amivantamab + Pt-ChT ± lazertinib vs Pt-ChT* in *EGFR*-mutant advanced NSCLC following EGFR-TKI failure

Trial population

- Ia/mNSCLC
- *EGFR* exon 19 deletion or exon 21 L858R
- Tumour progression on or immediately after osimertinib
- Clinically stable or asymptomatic CNS disease

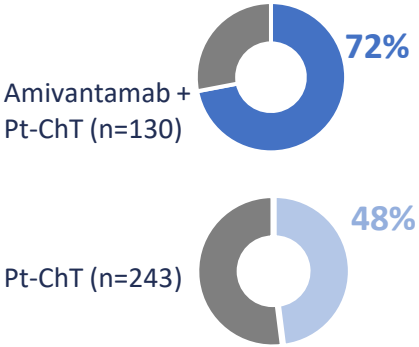
Primary efficacy outcomes

PFS of doublet regimen vs Pt-ChT by BICR per RECIST v1.1



Doublet: HR for disease progression or death (0.48, 95% CI 0.36–0.64, p< 0.001)

Safety: Grade ≥3 AEs



*IV amivantamab 1,400 mg (1,750 mg for body weight ≥80 kg) weekly for the first 4 weeks, and then 1,750 mg (2,100 mg for body weight ≥80 kg) every 3 weeks starting at cycle 3 (week 7). Oral lazertinib 240 mg daily. IV chemotherapy at the beginning of every cycle, with pemetrexed at 500 mg/m^2 administered every cycle and carboplatin at AUC 5 for the first four cycles. AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; IV, intravenous; Ia/mNSCLC, locally advanced/metastatic non-small cell lung cancer; m, median; PFS, progression-free survival; Pt-ChT, platinum-based chemotherapy; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor.

1. Passaro A, et al. *Ann Oncol*. 2024;35:77–90; 2. NCT04988295. Available at: https://clinicaltrials.gov/study/NCT04988295?term=NCT04988295&rank=1 (accessed 16 July 2024).

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PALOMA-3: Primary results

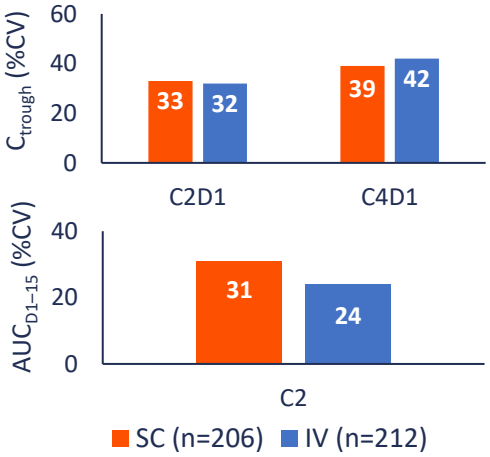
Phase III global trial of SC vs IV amivantamab + lazertinib* in advanced *EGFR*-mutant NSCLC after disease progression on osimertinib and Pt-ChT

Trial population

- a/mNSCLC
- *EGFR* exon 19del or exon 21 L858R mutations
- Progression on/after treatment with osimertinib (or other third-generation TKI) and Pt-ChT

Co-primary PK outcomes

Change in C_{trough} and $AUC_{D1–15}$



Safety

Any AE — **99% across groups**

IRR — 13% — 66%

0.5% (n=1) of patients in the SC group and 4% (n=8) in the IV group had a grade 3 event

VTE — 9% — 14%

Most events occurred within the first 4 months

schedule with first infusion split across 2 days (350 mg on C1D1, remainder on C1D2); both regimens provided alongside oral lazertinib (240 mg) daily.

AE, adverse event; a/mNSCLC, advanced/metastatic non-small cell lung cancer; AUC_{D1-D15}, area under the curve from cycle 2, days 1–15; C2, cycle 2; C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; C_{trough}, observed serum concentration of amivantamab at steady state; CV, coefficient of variation; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous; Pt-Cht, platinum-based chemotherapy; TKI, tyrosine kinase inhibitor; VTE, venous thromboembolism.

Leighl NB, et al. *J Clin Oncol*. 2024. doi: 10.1200/JCO.24.01001 [Epub ahead of print].

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HARMONi-A: First planned interim analysis[1,2]

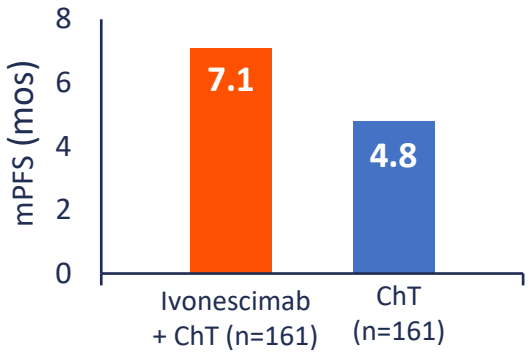
Phase III trial of ivonescimab + ChT vs ChT* in *EGFR*-mutant NSCLC following prior EGFR-TKI therapy

Trial population

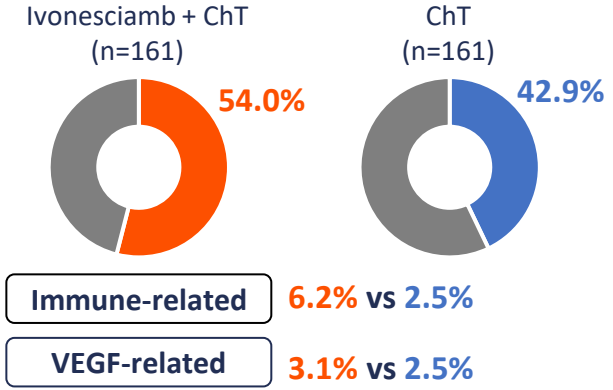
- Ia/mNSCLC
- *EGFR* mutation
- Tumour progression on prior EGFR-TKI
- No other prior systemic therapy
- Stable CNS disease

Primary efficacy outcomes

PFS in ITT by IRRC per RECIST v1.1



Safety: Grade ≥3 AEs



PFS benefit seen in patients who progressed on third-generation EGFR-TKIs **(HR 0.48, 95% CI 0.35–0.66)**; brain metastases **(HR 0.40, 95% CI 0.22–0.73)**; *EGFR* deletion 19 **(HR 0.48, 95% CI 0.32–0.73)**; and T790M mutation positive **(HR 0.22, 95% CI 0.09–0.54)**

*Ivonescimab (20 mg/kg) plus pemetrexed (500 mg/m^2) and carboplatin (AUC 5) or placebo plus chemotherapy once every 3 weeks for four cycles.

AE, adverse event; AUC, area under curve; ChT, chemotherapy; CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; IRRC, independent radiographic review committee; ITT, intention-to-treat; Ia/mNSCLC, locally advanced or metastatic non-small cell lung cancer; m, median; mos, months; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TKI, tyrosine kinase inhibitor; VEGF, vascular epidermal growth factor.

1. Zhang L, et al. Presented at: 2024 ASCO Annual Meeting, Chicago, IL, USA. 31 May–4 June 2024. Abstr.8508;
2. NCT06396065. Available at: https://www.clinicaltrials.gov/study/NCT05184712 (accessed 16 July 2024).

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EGFR-mutant NSCLC: Practical insights and implications for NSCLC practice

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Patient case: Initial presentation

Patient demographics

Age: 55 years

Sex: Female

Ethnicity: Hispanic

Occupation: Teacher

Medical history

Never-smoker

Stage IV *EGFR* exon 19del

Previously untreated for NSCLC

Metastases to pleura, bone and lymph node

Symptomatic with shortness of breath due to pleural effusion

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

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Guideline recommendations: First-line therapy

ESMO 2023[1]

First-line for stage IV mNSCLC with *EGFR*-activating mutation

Performance status 0–4

- Osimertinib (**preferred**)
- Gefitinib
- Erlotinib
- Erlotinib + bevacizumab
- Erlotinib + ramucirumab
- Afatinib
- Dacomitinib
- Gefitinib + carboplatin + pemetrexed

NCCN 2024[2]

First-line for *EGFR* exon 19 deletion or exon 21 L858R mutations

- Osimertinib (**preferred**)
- Osimertinib + pemetrexed + (cisplatin or carboplatin) (nonsquamous) OR
- Erlotinib
- Afatinib
- Gefitinib
- Dacomitinib
- Erlotinib + ramucirumab
- Erlotinib + bevacizumab

EGFR, epidermal growth factor receptor; ESMO, European Society for Medical Oncology; mNSCLC, metastatic non-small cell lung cancer; NCCN, National Comprehensive Cancer Network.

1. Hendriks LE, et al. *Ann Oncol.* 2023;34:339–57; 2. NCCN Guidelines. Non-small cell lung cancer. Version 7.2024. Available at: www.nccn.org (accessed 26 July 2024).

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Patient case: First-line treatment

Patient demographics

Age: 55 years

Sex: Female

Ethnicity: Hispanic

Occupation: Teacher

Medical history

Never-smoker

Stage IV *EGFR* exon 19del

Metastases to pleura, bone and lymph node

Treatment initiated

Osimertinib 80 mg QD

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; QD, once daily.

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Patient case: Disease progression

Patient demographics

Age: 55 years

Sex: Female

Ethnicity: Hispanic

Occupation: Teacher

Medical history

Never-smoker

Stage IV *EGFR* exon 19del

Metastases to pleura, bone and lymph node

Treatment history

Osimertinib 80 mg QD

Progression with brain metastases at 18 months

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; QD, once daily.

Guideline recommendations: Second-line therapy

ESMO 2023[1]

Progression with osimertinib

Resistance mechanism

- Clinical trial
- Or refer to *no resistance mechanism*

Systemic progression

No resistance mechanism

- Pt-ChT
- Atezolizumab + bevacizumab + paclitaxel + carboplatin

NCCN 2024[2]

Progression with osimertinib

Symptomatic

Systemic

- Consider definitive local therapy for limited lesions (e.g. SRS)
- Continue osimertinib OR if multiple lesions
- Amivantamab + carboplatin + pemetrexed (**preferred**)

CNS, central nervous system; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; Pt-ChT, platinum-based chemotherapy; SRS, stereotactic radiosurgery.

1. Hendriks LE, et al. *Ann Oncol.* 2023;34:339–57. 2. NCCN Guidelines. Non-small cell lung cancer. Version 7.2024. Available at: www.nccn.org (accessed 26 July 2024).

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