# Les Transversales
# « By IFODS »

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*En partenariat avec les Cours St-Paul*

Données hors AMM

# POST-ESMO 2023
# EGFR

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# DISCLOSURE

**- Clinical research:**
- Amgen
- Astra-Zeneca
- Abbvie
- Beigene
- BMS
- Boehringer-Ingelheim
- Daiichi-Sankyo
- Gilead
- Hoffmann-La Roche
- Janssen
- LeoPharma
- Lilly
- Merck
- MSD
- Novartis
- Sivan

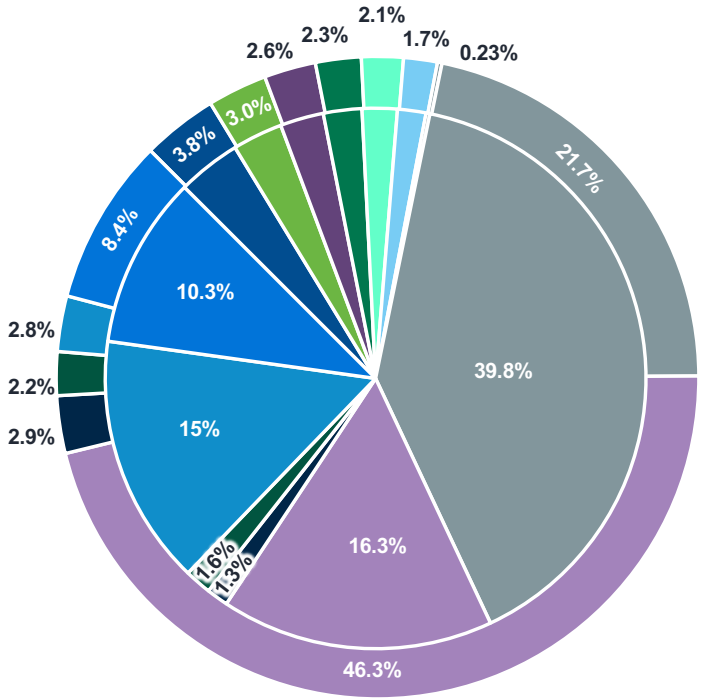
**- Symposia:**
- Abbvie
- Amgen
- Astra-Zeneca
- BMS
- Daiichi-Sankyo
- Janssen
- Medtronic
- Mirati
- MSD
- Pfizer
- Sanofi

**- Hospitality:**
- Hoffman-La Roche
- Janssen

**- Consultancy:**
- Abbvie
- Amgen
- Astra-Zeneca
- Beigene
- BMS
- Daiichi-Sankyo
- Gilead
- Ipsen
- Janssen
- Hoffman-La Roche
- LeoPharma
- Lilly
- Novartis
- Medtronic
- MSD
- Pfizer
- Pierre-Fabre
- Sanofi
- Takeda

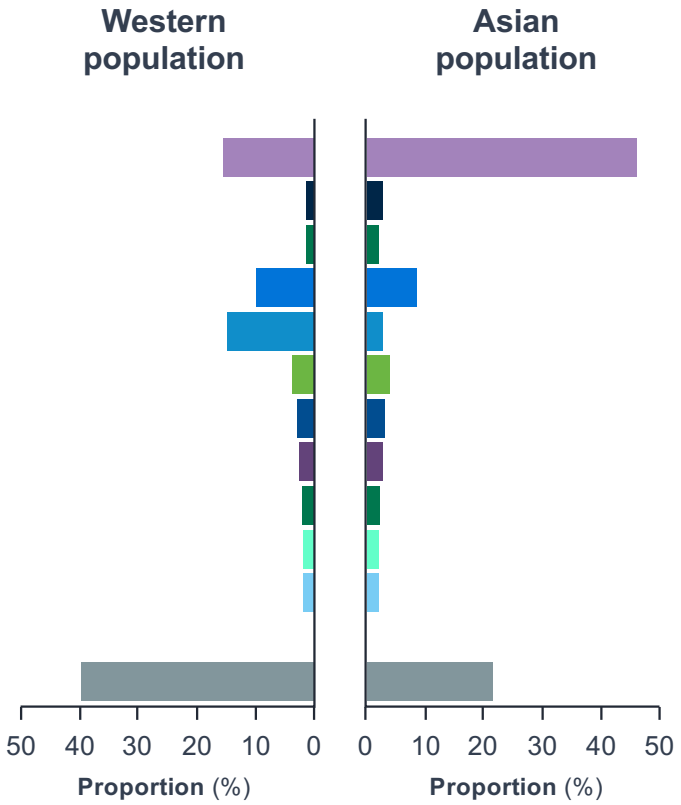
**Public declaration of interest**
https://dpi.sante.gouv.fr/dpi-public-webapp/app/recherche/declarant

# NSCLC is associated with several oncogenic driver alterations[1]




**Outer circle**: Asian populations
**Inner circle**: Western populations

- No actionable alteration
- *EGFR* exon 19 deletion and L858R mutation
- *EGFR* exon 20 insertion mutation
- Other *EGFR* mutation
- *KRAS* G12C mutation
- Other *KRAS* mutation
- *ALK* rearrangement
- *MET* exon 14 mutation
- *ROS1* rearrangement
- *HER2* exon 20 insertion mutation
- *BRAF* V600E mutation
- *RET* rearrangement
- *NTRK* rearrangement




*Adapted from Tan AC and Tan DSW. 2022.*[2]

ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection.

1. Kerr KM, et al. *Lung Cancer*. 2021;154:161–75; 2.Tan AC and Tan DSW. *J Clin Oncol*. 2022;40:611−25.

# *EGFR* mutation testing in NSCLC is critical for the application of targeted therapies[1]

## ESMO 2023 GUIDELINES[2]

**Complete sequencing of *EGFR* exon 18–21 by NGS is strongly recommended** [III, A]

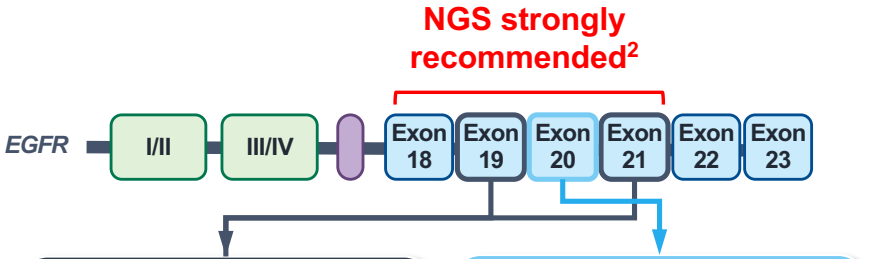
**Some allele-specific *EGFR* sequencing solutions do not provide complete coverage**

- EGFR FISH or IHC have no clinical utility and should not be tested

**At a minimum, when resources/materials are limited, the most common activating mutations should be determined**

- *EGFR* exon19del and exon 21 L858R [I, A]

## *EGFR* TESTING




***EGFR* exon19del and exon 21 L858R**

The most common alterations conferring sensitivity to 1–3G EGFR TKIs[2]

***EGFR* exon20ins**

The third most frequent subtype of *EGFR* mutations[3]

*Adapted from Malapelle U, et al. 2022.[4]*

1. Shah P, et al. *Lung Cancer*. 2021;160:118–26; 2. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57; 3. Riess JW, et al. *J Thorac Oncol*. 2018;13:1560–8;
4. Malapelle U, et al. *Crit Rev Oncol Hematol*. 2022;169:103536.

1–3G, first- to third-generation; ESMO, European Society for Medical Oncology; exon19del, exon 19 deletion; exon20ins, exon 20 insertion; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing.

# ESMO 2023 clinical practice guidelines recommend osimertinib as the preferred 1L option for c*EGFR*-mutant NSCLC

**Stage IV mNSCLC with *EGFR*-activating mutation**

PS 0–2 [I, A]
PS 3–4 for all following options [III, A]

- **Osimertinib [I, A; MCBS 4; ESCAT I–A]*†‡§**
- Gefitinib [I, B; MCBS 4; ESCAT I–A]*‡
- Erlotinib [I, B; MCBS 4; ESCAT I–A]*‡
- Erlotinib + bevacizumab [I, B; MCBS 2; ESCAT I–A]*‡‖
- Erlotinib + ramucirumab [I, B; MCBS 3; ESCAT I–A]*‡
- Afatinib [I, B; MCBS 5; ESCAT I–A]*‡§
- Dacomitinib [I, B; MCBS 3; ESCAT I–A]*‡
- Gefitinib + carboplatin + pemetrexed [I, B]¶

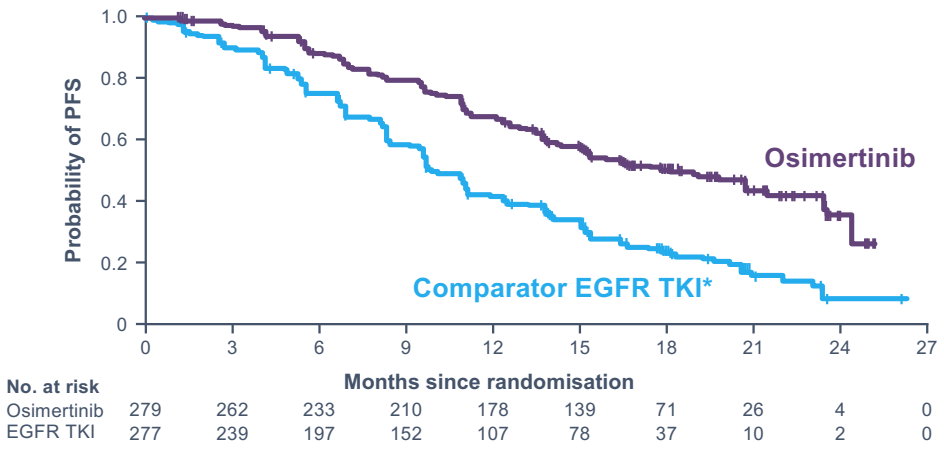
*ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. These scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee; †Preferred option; ‡ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group; §Recommended treatment option for patients with a major uncommon, non-exon20ins, sensitising EGFR mutation [III, B; ESMO-MCBS v1.1 score: 4 for afatinib; ESCAT: I–B]; ‖ESMO-MCBS v1.1 score for the combination of bevacizumab with gefitinib or erlotinib; ¶Not EMA approved.
1L, first-line; cEGFR, common EGFR; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Medical Oncology; exon20ins, exon 20 insertion; FDA, Food and Drug Administration; MCBS, ESMO-Magnitude of Clinical Benefit Scale; mNSCLC, metastatic NSCLC; PS, performance status.

Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57.

# Osimertinib is the preferred 1L EGFR TKI for c*EGFR* mutations[1]

## FLAURA: Osimertinib vs a comparator EGFR TKI* in common *EGFR*-mutant NSCLC†[2,3]

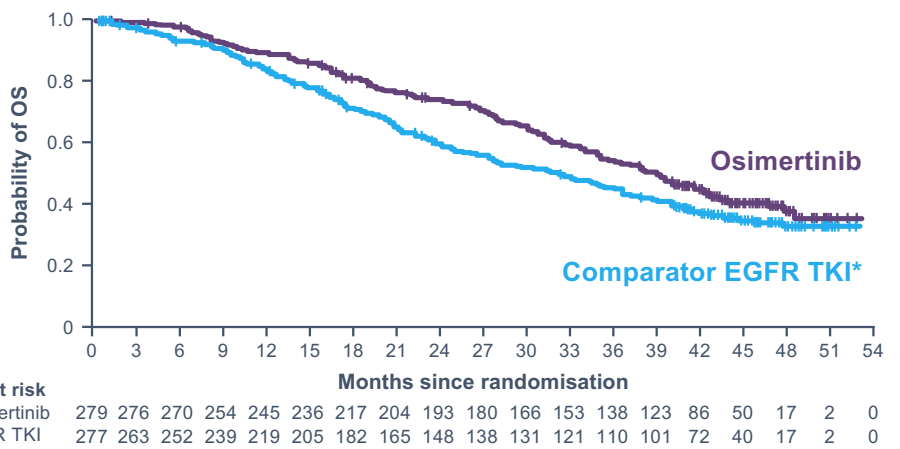
### PFS[2]




| | mPFS, mo (95% CI) | HR (95% CI) | p value |
|---|---|---|---|
| **Osimertinib** (n=279) | **18.9** (15.2–21.4) | **0.46** (0.37–0.57) | **<0.001** |
| **EGFR TKI*** (n=277) | **10.2** (9.6–11.1) | | |

*Adapted from Soria J-C, et al. 2018.[2]*

### OS[3]



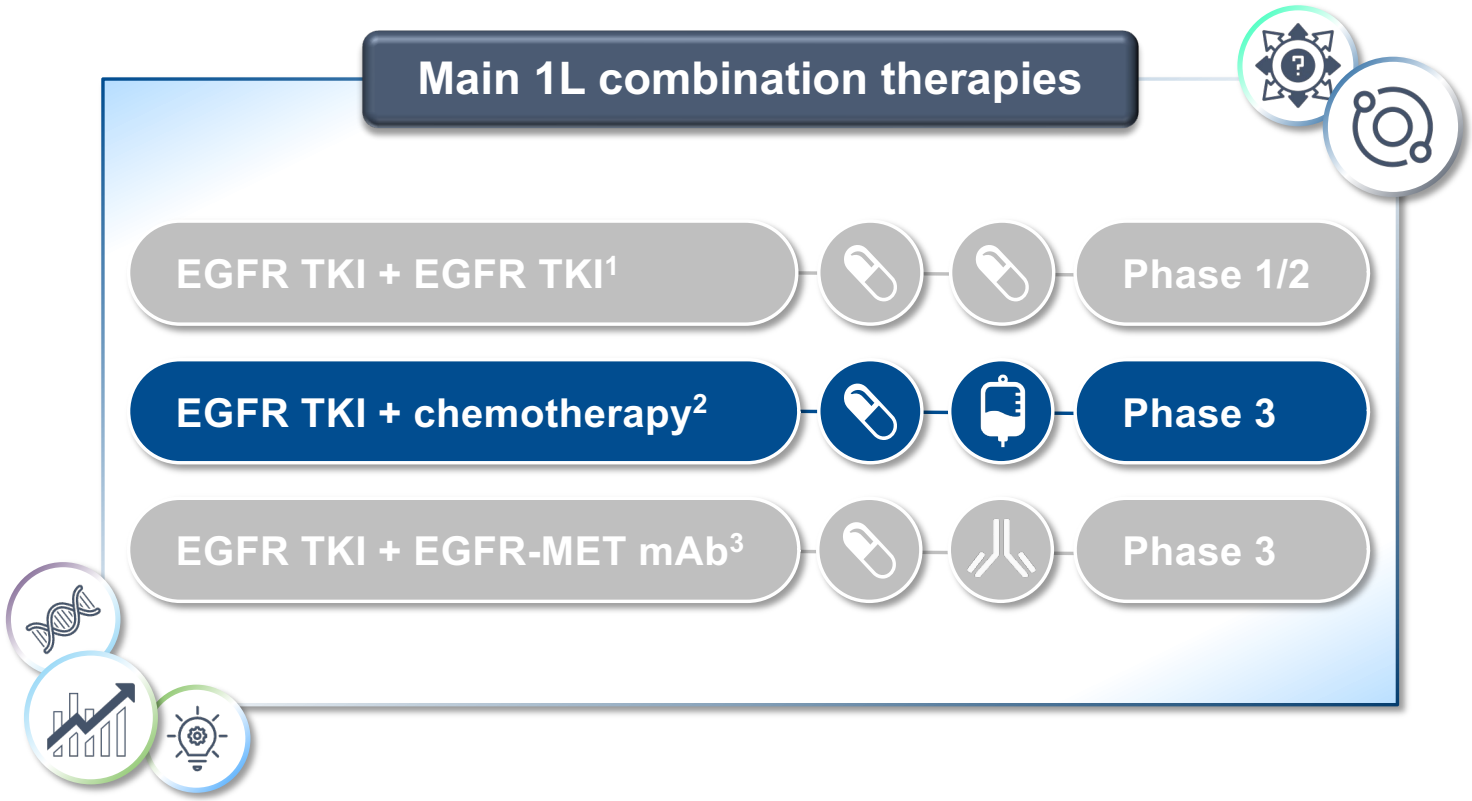

| | mOS, mo (95% CI) | HR (95% CI) | p value |
|---|---|---|---|
| **Osimertinib** (n=279) | **38.6** (34.5–41.8) | **0.80** (0.64–1.00) | **0.046** |
| **EGFR TKI*** (n=277) | **31.8** (26.6–36.0) | | |

*Adapted from Ramalingam SS, et al. 2020.[3]*


1. Hendriks LE, et al. *Ann Oncol*. 2023;S0923–7534:04781–0; 2. Soria J-C, et al. *N Engl J Med*. 2018;378:113–25; 3. Ramalingam SS, et al. *N Engl J Med*. 2020;382:41–50.


*Comparator EGFR TKI was erlotinib or gefitinib. †Exon 19 deletion or exon 21 L858R.
1L, first-line; cEGFR, common-EGFR; CI, confidence interval; HR, hazard ratio; mo, months; mOS, median OS; mPFS, median PFS; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

# 1L combination treatment strategies in c*EGFR*-mutant NSCLC




**FLAURA-2**

**WCLC 2023**
**ESMO 2023**

1. Huang M, et al. Presented at WCLC 2023: MA13.05; 2. Jänne PA, et al. Presented at WCLC 2023: PL03.13; 3. NCT04487080. Available at: https://clinicaltrials.gov/ct2/show/NCT04487080. Accessed October 2023; 4. Bertoli E, et al. *Int J Mol Sci*. 2022;23:6936.

**This schematic provides an overview and is not comprehensive.**
1L, first-line; cEGFR, common EGFR; mAb, monoclonal antibody; MET, mesenchymal-epithelial transition.

# FLAURA2: Study design

**Safety run-in period** (N=30)
*Published in ESMO Open, 2021*[1]

**Patients with untreated locally advanced / metastatic EGFRm NSCLC**

**Key inclusion criteria:**

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

**Stratification by:**

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

**Randomization 1:1 (N=557)**

**Osimertinib 80 mg (QD) + pemetrexed 500 mg/m$^2$ + carboplatin AUC5 or cisplatin 75 mg/m$^2$ (Q3W for 4 cycles for platinum-based treatments)**

**Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†**

**Osimertinib 80 mg (QD)**

**Follow-up:**

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

1. Planchard et al. ESMO Open 2021;6:100271

*Not requiring steroids for at least two weeks; †Pemetrexed maintenance continued until a discontinuation criterion was met; ‡Efficacy analyses in the full analysis set, defined as all patients randomized to study treatment regardless of the treatment actually received, and safety analyses in the safety analysis set, defined as all randomized patients who received ≥1 dose of study treatment – one patient who was randomized to osimertinib plus platinum-pemetrexed received only osimertinib and was therefore included in the osimertinib monotherapy safety analysis set; §The study provided 90% power to demonstrate a statistically significant difference in PFS assuming HR=0.68 at 5% two-sided significance level

AE, adverse event; AUC, area under curve; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; EGFRm, epidermal growth factor receptor-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; Ex19del, exon 19 deletion; HR, hazard ratio; HRQoL, health-related quality of life; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival; QD, once-daily; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; WHO PS, World Health Organization performance status

# FLAURA2: baseline characteristics

- Patient demographics / clinical characteristics were balanced between arms, and almost half of patients had CNS metastases at baseline

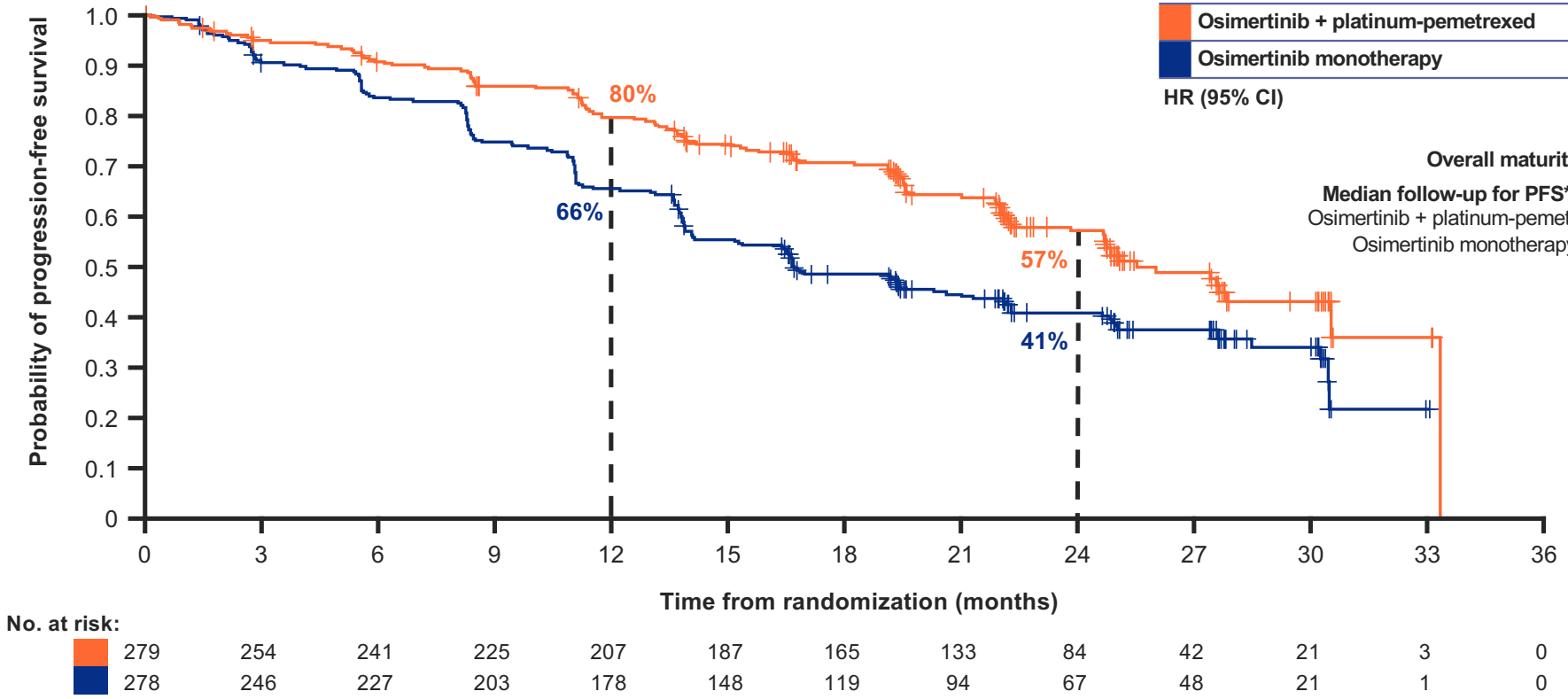
| Characteristics, %* | Osimertinib + platinum-pemetrexed (n=279)† | Osimertinib monotherapy (n=278)† |
|---|---|---|
| Sex: male / female | 38 / 62 | 39 / 61 |
| Age: median (range), years | 61 (26–83) | 62 (30–85) |
| Race: Chinese Asian / non-Chinese Asian / non-Asian / missing | 25 / 39 / 35 / <1 | 25 / 38 / 36 / 1 |
| WHO PS: 0 / 1‡ | 37 / 62 | 37 / 63 |
| Smoking status: never / current / former | 67 / 1 / 31 | 65 / 1 / 33 |
| Histology: adenocarcinoma / adenosquamous / other | 99 / 1 / 1 | 99 / 0 / 1 |
| EGFR mutation at randomization§: Ex19del / L858R | 61 / 38 | 60 / 38 |
| Locally advanced / metastatic | 5 / 95 | 3 / 97 |
| Extra-thoracic metastases‖ | 53 | 54 |
| CNS metastases | 42 | 40 |
| Baseline tumor size, mean (SD) / median (range), mm | 65 (42) / 57 (10–284) | 64 (39) / 57 (11–221) |

Data cut-off: 03 April 2023

*Percentages calculated and rounded to nearest whole number; †Three patients in each arm were randomized to either treatment arm, but received no study treatment; ‡One patient had a WHO PS of 2; §Central and local EGFR mutation test; three patients in the osimertinib + platinum-pemetrexed arm and one patient in the monotherapy arm had both Ex19del and L858R mutation – one patient in the osimertinib + platinum-pemetrexed arm and two patients in the monotherapy arm had unknown / not detected EGFR mutations; ‖Extra-thoracic visceral metastases included CNS metastases; CNS, central nervous system; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; SD, standard deviation; WHO PS, World Health Organization performance status

# FLAURA2: PFS by investigator

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy




| Median PFS, months (95% CI) | |
|---|---|
| Osimertinib + platinum-pemetrexed | 25.5 (24.7, NC) |
| Osimertinib monotherapy | 16.7 (14.1, 21.3) |
| **HR (95% CI)** | **0.62 (0.49, 0.79); p<0.0001** |

**Overall maturity:** 51%

**Median follow-up for PFS*, months (range):**
Osimertinib + platinum-pemetrexed, 19.5 (0–33.3)
Osimertinib monotherapy, 16.5 (0–33.1)

Data cut-off: 03 April 2023
*In all patients
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

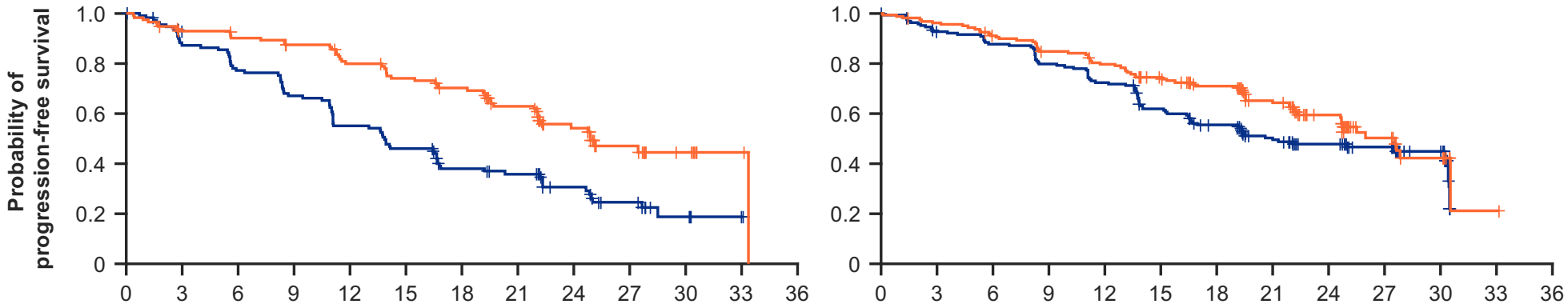
# FLAURA2: PFS by investigator

## With CNS metastases

| Median PFS, months (95% CI) | |
|---|---|
| Osimertinib + platinum-pemetrexed | 24.9 (22.0, NC) |
| Osimertinib monotherapy | 13.8 (11.0, 16.7) |
| **HR (95% CI)** | **0.47 (0.33, 0.66)** |

## Without CNS metastases

| Median PFS, months (95% CI) | |
|---|---|
| Osimertinib + platinum-pemetrexed | 27.6 (24.7, NC) |
| Osimertinib monotherapy | 21.0 (16.7, 30.5) |
| **HR (95% CI)** | **0.75 (0.55, 1.03)** |



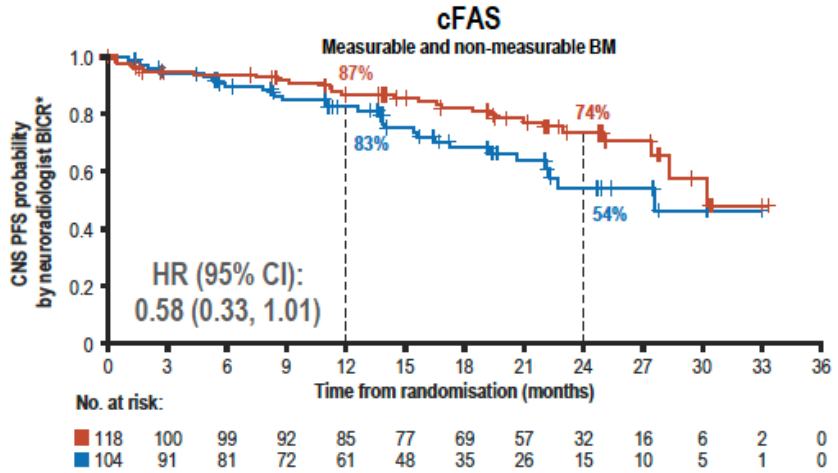

**No. at risk:**

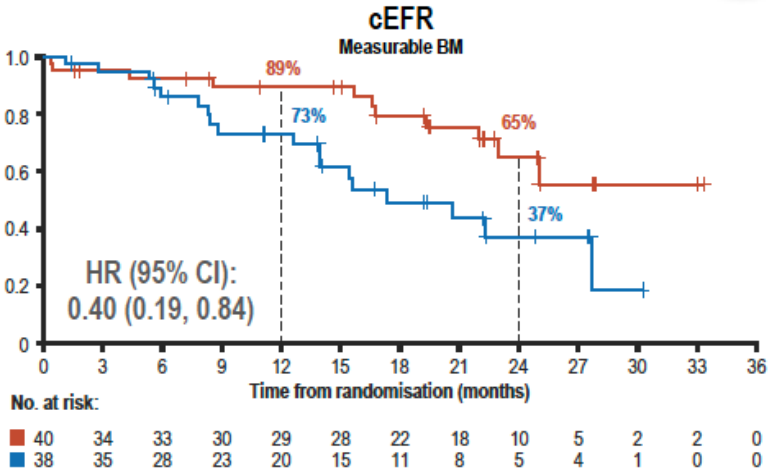
| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 116 | 101 | 98 | 93 | 84 | 77 | 70 | 58 | 34 | 19 | 8 | 2 | 0 | | 163 | 153 | 143 | 132 | 123 | 110 | 95 | 75 | 50 | 23 | 13 | 1 | 0 |
| | 110 | 95 | 84 | 73 | 60 | 50 | 37 | 32 | 21 | 13 | 5 | 1 | 0 | | 168 | 151 | 143 | 130 | 118 | 98 | 82 | 62 | 46 | 35 | 16 | 0 | 0 |

Data cut-off: 03 April 2023
*CNS metastases determined by the investigator and recorded in the eCRF
CI, confidence interval; CNS, central nervous system; eCRF, electronic case report form; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

# FLAURA2: CNS enpoints

## OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED IMPROVED CNS PFS VS OSIMERTINIB BY CNS BICR



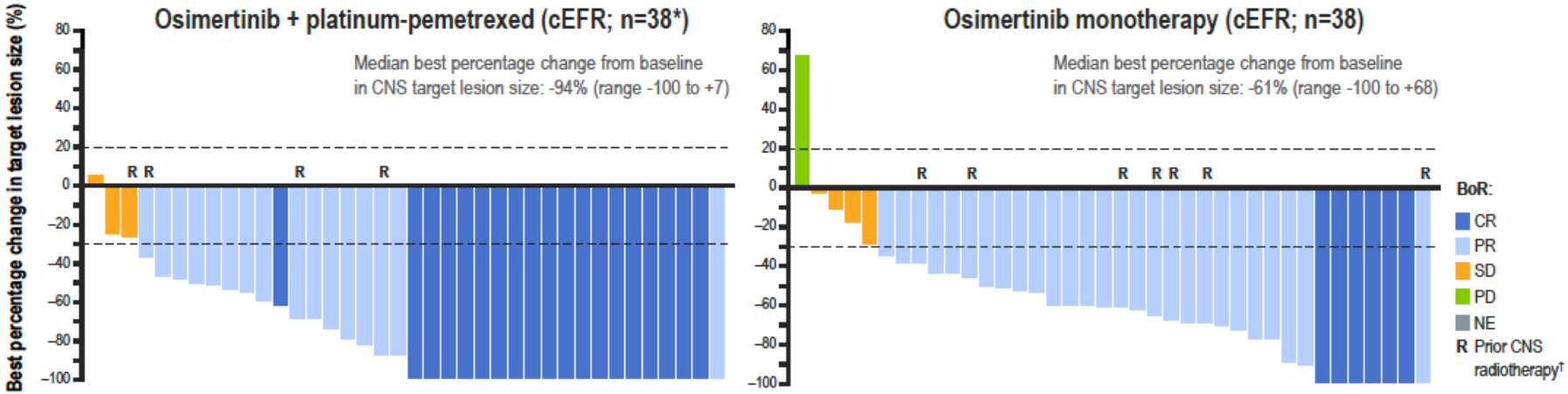

| | cFAS (n=222) Measurable + non-measurable BM | | cEFR (n=78) Measurable BM | |
|---|---|---|---|---|
| n (%)† | Osi + CTx (n=118) | Osi mono (n=104) | Osi + CTx (n=40) | Osi mono (n=38) |
| Any CNS RECIST progression‡ | 11 (9) | 20 (19) | 5 (13) | 13 (34) |
| Progression in CNS target lesions | 2 (2) | 7 (7) | 2 (5) | 7 (18) |
| Progression in non-target CNS lesions | 0 | 4 (4) | 0 | 3 (8) |
| Progression due to new CNS lesions | 9 (8) | 12 (12) | 3 (8) | 6 (16) |
| Death without CNS progression | 17 (14) | 11 (11) | 6 (15) | 5 (13) |

*Median follow-up for CNS PFS in the cFAS was 20.1 months (range 0-33.3) in the osimertinib + platinum-pemetrexed arm and 13.9 months (0-33.1) in the osimertinib monotherapy arm. CNS PFS data maturity was 27% (59/222 events across both arms); †Only includes CNS progression events that occurred within two consecutive scheduled visits (plus visit window) of the last CNS assessment or randomisation; ‡Target lesions, non-target lesions, and new lesions were not necessarily mutually exclusive.

BICR, blinded independent central review; BM, brain metastases; CI, confidence interval; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CNS, central nervous system; CTx, chemotherapy; HR, hazard ratio; mono, monotherapy; osi, osimertinib; PFS, progression-free survival; pts, patients; RECIST, Response Evaluation Criteria in Solid Tumours
Data cut-off: 03 April 2023.

# FLAURA2: CNS enpoints

## OSIMERTINIB WITH THE ADDITION OF CTx DEMONSTRATED A HIGH PROPORTION OF COMPLETE RESPONSES IN THE CNS BY CNS BICR




| | cFAS (n=222) Measurable + non-measurable BM | | cEFR (n=78) Measurable BM | |
|---|---|---|---|---|
| CNS response‡ | Osi + CTx (n=118) | Osi mono (n=104) | Osi + CTx (n=40) | Osi mono (n=38) |
| CNS ORR, % (95% CI) | 73 (64 to 81) | 69 (59 to 78) | 88 (73 to 96) | 87 (72 to 96) |
| Complete response, n (%) | 70 (59) | 45 (43) | 19 (48) | 6 (16) |
| Partial response, n (%) | 16 (14) | 27 (26) | 16 (40) | 27 (71) |
| CNS DCR, % (95% CI) | 91 (84 to 95) | 93 (87 to 97) | 95 (83 to 99) | 97 (86 to 100) |
| Median DoR, months (95% CI)§ | NR (23.8, NC) | 26.2 (19.4, NC) | NR (21.6, NC) | 20.9 (12.6, NC) |

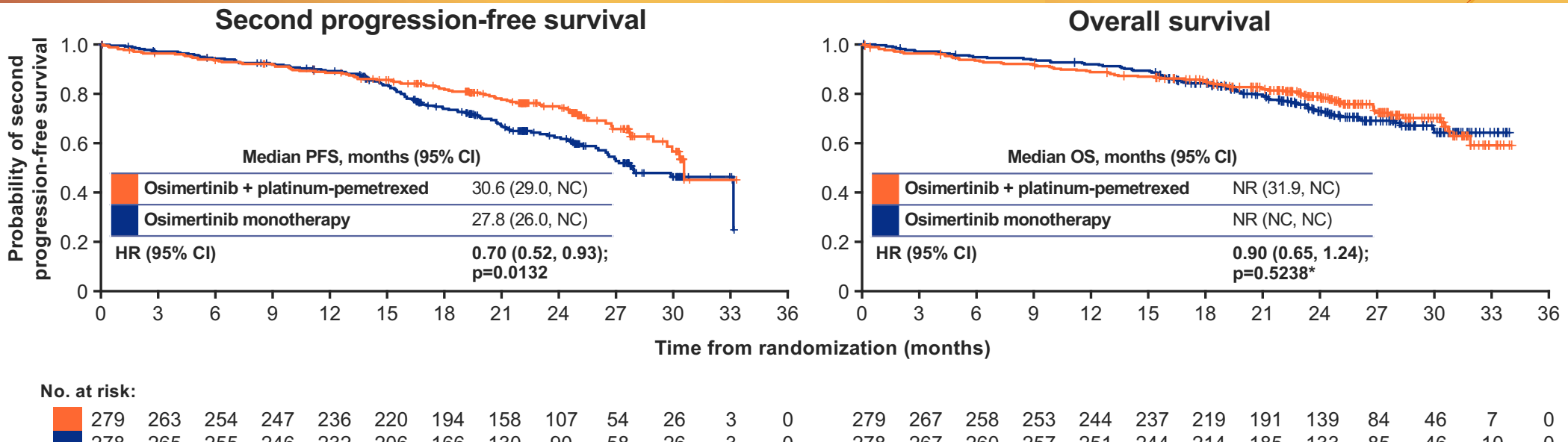
*Two pts had ≥1 measurable CNS lesion at baseline by CNS BICR but died before the follow-up CNS BICR scan; †In the cEFR, 4/40 pts (10%) in the osimertinib + platinum-pemetrexed arm and 7/38 pts (18%) in the osimertinib arm had received prior CNS radiotherapy; stable neurological status for ≥2 weeks after completion of definitive treatment and steroids was required before study entry, if received; ‡Responses did not require confirmation, per RECIST guidance on randomized studies; §Kaplan–Meier estimates.

BICR, blinded independent central review; BM, brain metastases; BoR, best overall response; cEFR, CNS evaluable-for-response set; cFAS, CNS full analysis set; CI, confidence interval; CNS, central nervous system; CR, complete response; CTx, chemotherapy; DCR, disease control rate; DoR, duration of response; mono, monotherapy; NC, not calculable; NE, not evaluable; NR, not reached; ORR, objective response rate; osi, osimertinib; PD, progressive disease; PR, partial response; pts, patients; SD, stable disease

Data cut-off: 03 April 2023.

MADRID 2023 ESMO congress

# FLAURA2: PFS2 and interim OS




**No. at risk:**

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 279 | 263 | 254 | 247 | 236 | 220 | 194 | 158 | 107 | 54 | 26 | 3 | 0 | 279 | 267 | 258 | 253 | 244 | 237 | 219 | 191 | 139 | 84 | 46 | 7 | 0 |
| | 278 | 265 | 255 | 246 | 232 | 206 | 166 | 130 | 90 | 58 | 26 | 3 | 0 | 278 | 267 | 260 | 257 | 251 | 244 | 214 | 185 | 133 | 85 | 46 | 10 | 0 |

- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

Data cut-off: 03 April 2023
*Significance level is p-value <0.00158 at this interim for OS; †Subsequent anti-cancer treatments included those with a start date after the date of the last dose of study treatment; patients could have received more than one subsequent anti-cancer treatment, and percentages of patients by treatment type are calculated from the number of patients who discontinued randomized study treatment
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

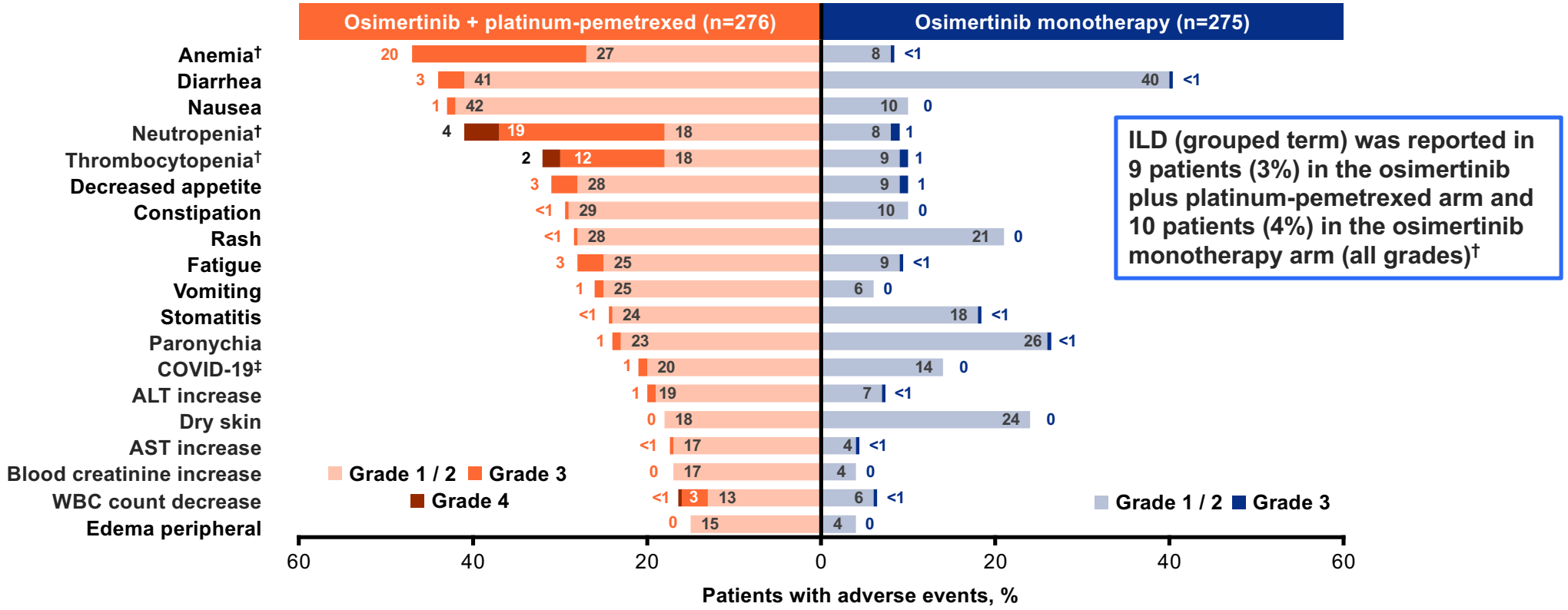
# FLAURA2: Safety summary

- Median total duration of osimertinib exposure was 22.3 months (range 0.1–33.8) in the osimertinib plus platinum-pemetrexed arm and 19.3 months (range 0.1–33.8) in the osimertinib monotherapy arm
- In the combination arm patients received a median of 12 cycles of pemetrexed (range 1–48) and 211 patients (76%) completed 4 cycles of platinum-based chemotherapy

| Patients with AEs, n (%)* | Osimertinib + platinum-pemetrexed (n=276) | Osimertinib monotherapy (n=275) |
|---|---|---|
| **AE any cause** | **276 (100)** | **268 (97)** |
| Any AE Grade ≥3 | 176 (64) | 75 (27) |
| Any AE leading to death | 18 (7) | 8 (3) |
| Any serious AE | 104 (38) | 53 (19) |
| Any AE leading to discontinuation | 132 (48) | 17 (6) |
| Osimertinib / carboplatin or cisplatin / pemetrexed discontinuation | 30 (11) / 46 (17) / 119 (43) | 17 (6) / NA / NA |
| **AE possibly causally related to treatment†** | **269 (97)** | **241 (88)** |
| Any AE Grade ≥3 | 146 (53) | 29 (11) |
| Causally related to osimertinib / carboplatin or cisplatin / pemetrexed | 81 (29) / 104 (38) / 130 (47) | 29 (11) / NA / NA |
| Any AE leading to death | 5 (2) | 1 (<1) |
| Causally related to osimertinib / carboplatin or cisplatin / pemetrexed | 3 (1) / 2 (1) / 3 (1) | 1 (<1) / NA / NA |
| Any serious AE | 52 (19) | 15 (5) |

Data cut-off: 03 April 2023
*Percentages calculated and rounded to nearest whole number; †Per investigator assessment
AE, adverse event; NA, not applicable

# FLAURA2: Safety profile




**ILD (grouped term) was reported in 9 patients (3%) in the osimertinib plus platinum-pemetrexed arm and 10 patients (4%) in the osimertinib monotherapy arm (all grades)†**

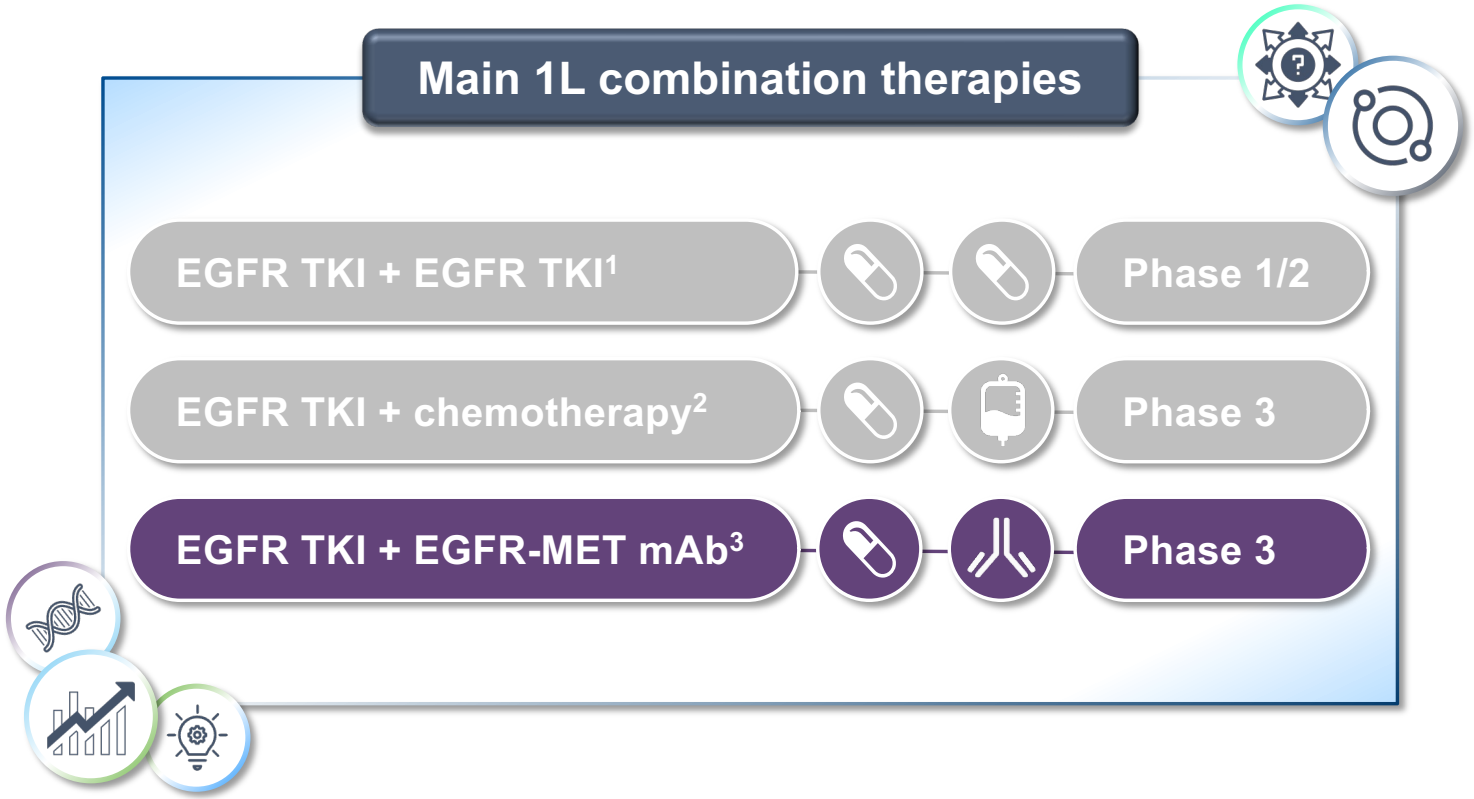
- Of most common AEs (occurring in ≥15% of patients in either arm), all Grade 4 AEs in the osimertinib plus platinum-pemetrexed arm were hematological toxicities, known to be associated with chemotherapy; there were no common Grade 4 AEs in the monotherapy arm

Data cut-off: 03 April 2023

*In commonly reported AEs, defined as occurring in >15% of patients in either treatment arm, by MedDRA preferred terms (unless stated as a grouped term of the same medical concepts); †Grouped term: anemia / hemoglobin decreased, thrombocytopenia / platelet count decreased, neutropenia / neutrophil count decreased, and interstitial lung disease / pneumonitis / organizing pneumonitis (by preferred terms); ‡Of common AEs (≥15% of patients), one Grade 5 AE of COVID-19 was reported in the osimertinib plus platinum-pemetrexed arm

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID, coronavirus disease; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; WBC, white blood cell

# 1L combination treatment strategies in c*EGFR*-mutant NSCLC




**MARIPOSA**

**ESMO 2023**

1. Huang M, et al. Presented at WCLC 2023: MA13.05; 2. Jänne PA, et al. Presented at WCLC 2023: PL03.13; 3. NCT04487080. Available at: https://clinicaltrials.gov/ct2/show/NCT04487080. Accessed October 2023; 4. Bertoli E, et al. *Int J Mol Sci*. 2022;23:6936.

**This schematic provides an overview and is not comprehensive.**
1L, first-line; cEGFR, common EGFR; mAb, monoclonal antibody; MET, mesenchymal-epithelial transition.

# MARIPOSA: Phase 3 Study Design

MARIPOSA

**Key Eligibility Criteria**

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

**Stratification Factors**

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases[a] (yes or no)

*Serial brain MRIs were required for all patients*[a]

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Dosing (in 28-day cycles)

**Amivantamab:** 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks
**Lazertinib:** 240 mg daily
**Osimertinib:** 80 mg daily

**Primary endpoint of progression-free survival (PFS)[b] by BICR per RECIST v1.1:**

- **Amivantamab + lazertinib** vs **osimertinib**

**Secondary endpoints of amivantamab + lazertinib vs osimertinib:**

- Overall survival (OS)[b]
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[c]
- Intracranial PFS[c]
- Safety

***Lazertinib monotherapy arm was included to assess the contribution of components***

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; data cut-off: 11-Aug-2023.

[a]Baseline brain MRI was required for all patients and performed ≤28 days prior to randomization; patients who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months and then every 12 weeks thereafter for patients with a history of brain metastasis and every 24 weeks for patients with no history of brain metastasis. Extracranial tumor assessments were conducted every 8 weeks for the first 30 months and then every 12 weeks until disease progression is confirmed by BICR.
[b]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS.
[c]These secondary endpoints (symptomatic and intracranial PFS) will be presented at a future congress.

BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

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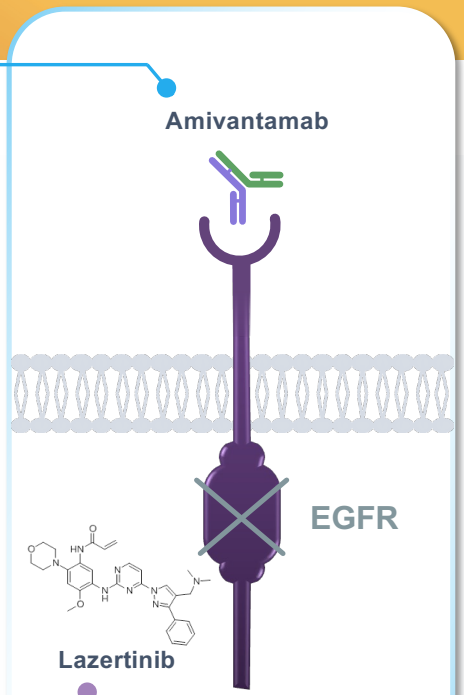
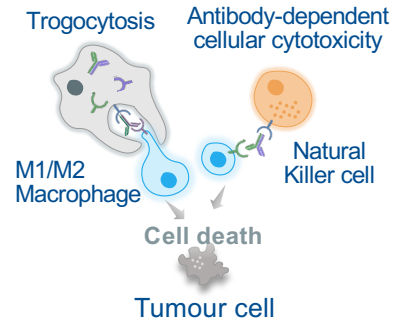
# Mechanism of action: Amivantamab, lazertinib, and chemotherapy

- A low-fucose, fully-human, IgG1-based, **EGFR-MET bispecific antibody**[1]
- Demonstrates **three** distinct **MoAs**, including **immune cell-directing activity**[1–3]
- Binds to the **extracellular** domains of **EGFR** and **MET**[1]

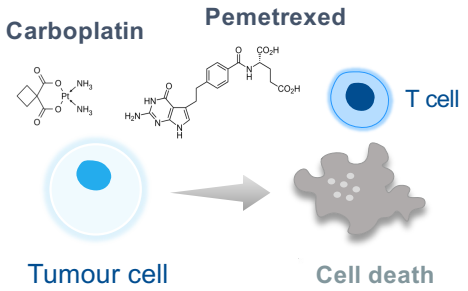
- An oral, potent, irreversible, **brain-penetrant,** 3G EGFR TKI[4,5]
- Targets the **intracellular active site** of **EGFR**, thus **blocking** the activation of intracellular signalling[5]
- **Mutant-selective** (T790M, exon19del, and L858R), while **sparing WT EGFR**[4]




**Amivantamab + lazertinib EGFR binding**[5]




**Amivantamab immune cell-directing activity**[3]



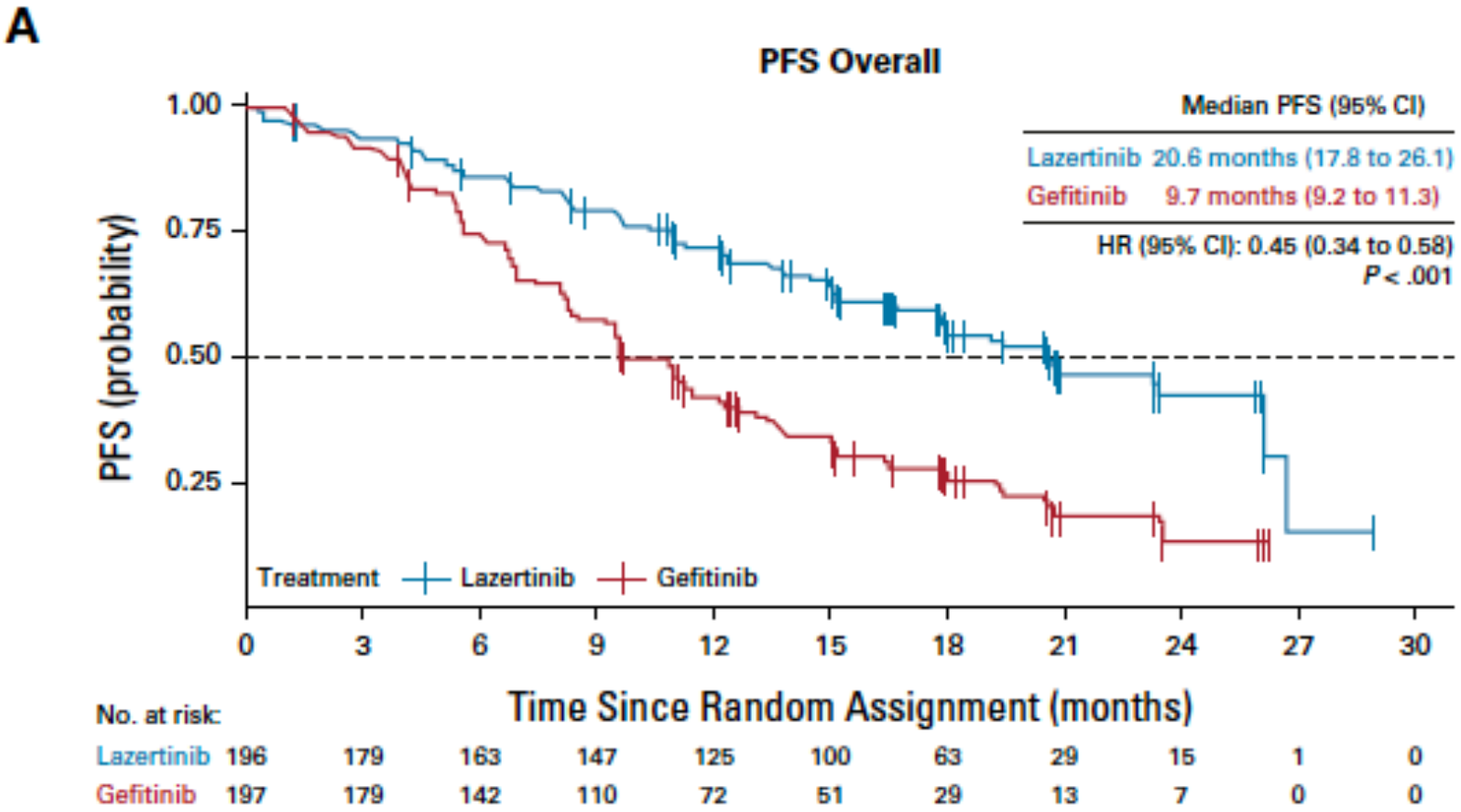

**Chemotherapy-mediated cell death**[6]

- **The synergistic MoA of amivantamab** (extracellular binding)**, combined with lazertinib** (intracellular binding)**,** may lead to a **more potent inhibition** of the **EGFR pathway**[5]
- The addition of **amivantamab** and **lazertinib** to **chemotherapy** could **address resistance** to **osimertinib**[7,8]

1. EMA. Rybrevant Summary of Product Characteristics. January 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf. Accessed October 2023; 2. Moores SL, et al. *Cancer Res*. 2016;76:3942–53; 3. Guo MZ, et al. *TouchREVIEWS in Oncol & Hematol*. 2021;17:42–7; 4. Dhillon S. *Drugs*. 2021;81:1107–13; 5. Shu CA, et al. Presented at ASCO 2021: TPS9132; 6. Wang Y-J, et al. *Genes Dis*. 2018;5:194–203; 7. Nagasaka M, et al. Presented at WCLC 2023: P50.04; 8. Lee S-H, et al. Presented at WCLC 2023: MA13.06.

3G, third-generation; exon19del, exon 19 deletion; IgG1, immunoglobulin G1; MET, mesenchymal-epithelial transition; MoA, mechanism of action; WT, wild-type.

# LAZERTINIB: Third generation TKI that showed similar efficacy than Osimertinib as first-line therapy




Cho et al. J Clin Oncol 2023;41:4308

# MARIPOSA: Phase 3 Study Design

MARIPOSA

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BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumors.

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# MARIPOSA: Baseline characteristics

MARIPOSA

| Characteristic, n (%) | Amivantamab + Lazertinib (n=429) | Osimertinib (n=429) | Lazertinib (n=216) |
|---|---|---|---|
| Median age, years (range) | 64 (25-88) | 63 (28-88) | 63 (31-87) |
| Female | 275 (64) | 251 (59) | 136 (63) |
| Race | | | |
| Asian | 250 (58) | 251 (59) | 128 (59) |
| White | 164 (38) | 165 (38) | 79 (37) |
| Other[a] | 15 (3) | 13 (3) | 9 (4) |
| ECOG PS 1 | 288 (67) | 280 (65) | 140 (65) |
| History of smoking | 130 (30) | 134 (31) | 73 (34) |
| History of brain metastases | 178 (41) | 172 (40) | 86 (40) |
| *EGFR* mutation type[b] | | | |
| Ex19del | 258 (60) | 257 (60) | 131 (61) |
| L858R | 172 (40) | 172 (40) | 85 (39) |
| Adenocarcinoma subtype | 417 (97) | 415 (97) | 212 (98) |

**Note**: percentages may not sum to 100 due to rounding.

[a]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown.
[b]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions.

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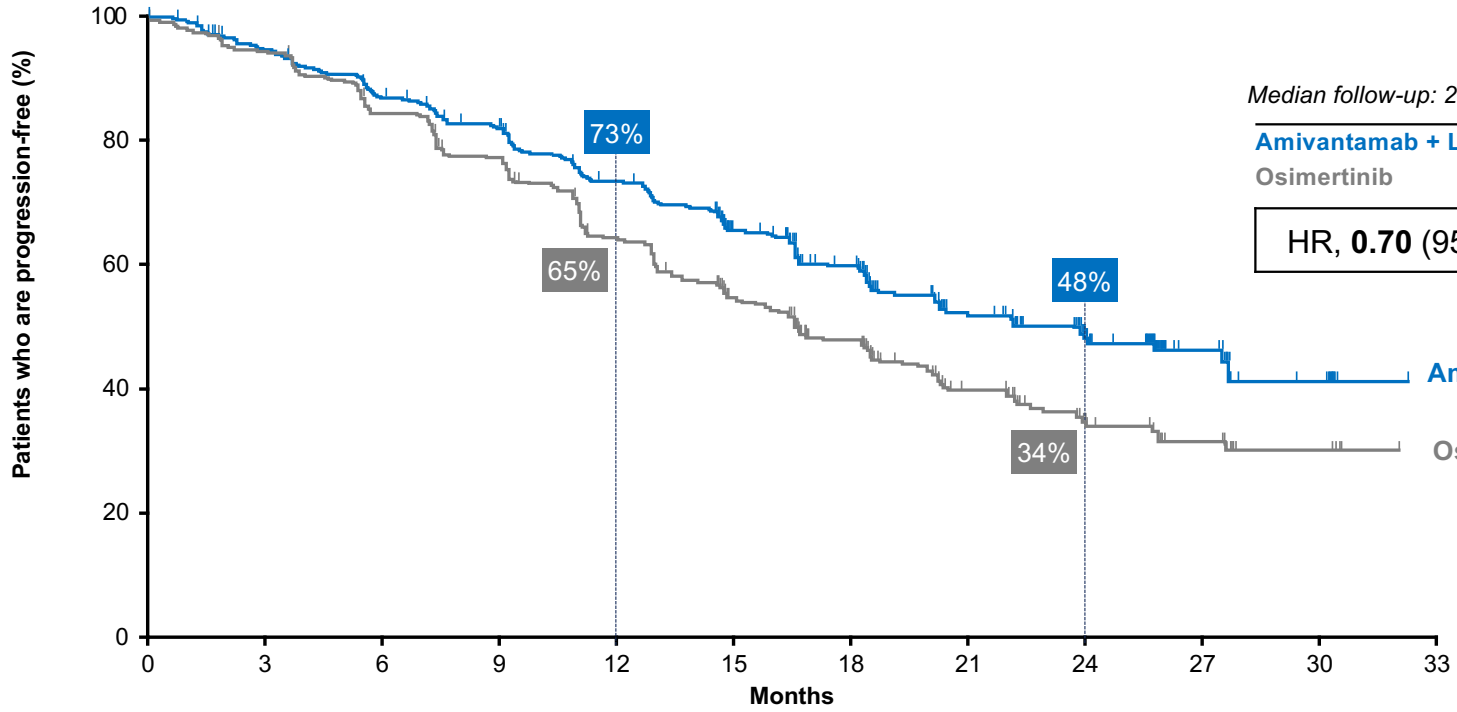
# MARIPOSA: Progression-free Survival by BICR[a]

*Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months*




| *Median follow-up: 22.0 months* | **Median PFS (95% CI)** |
|---|---|
| **Amivantamab + Lazertinib** | 23.7 mo (19.1–27.7) |
| Osimertinib | 16.6 mo (14.8–18.5) |

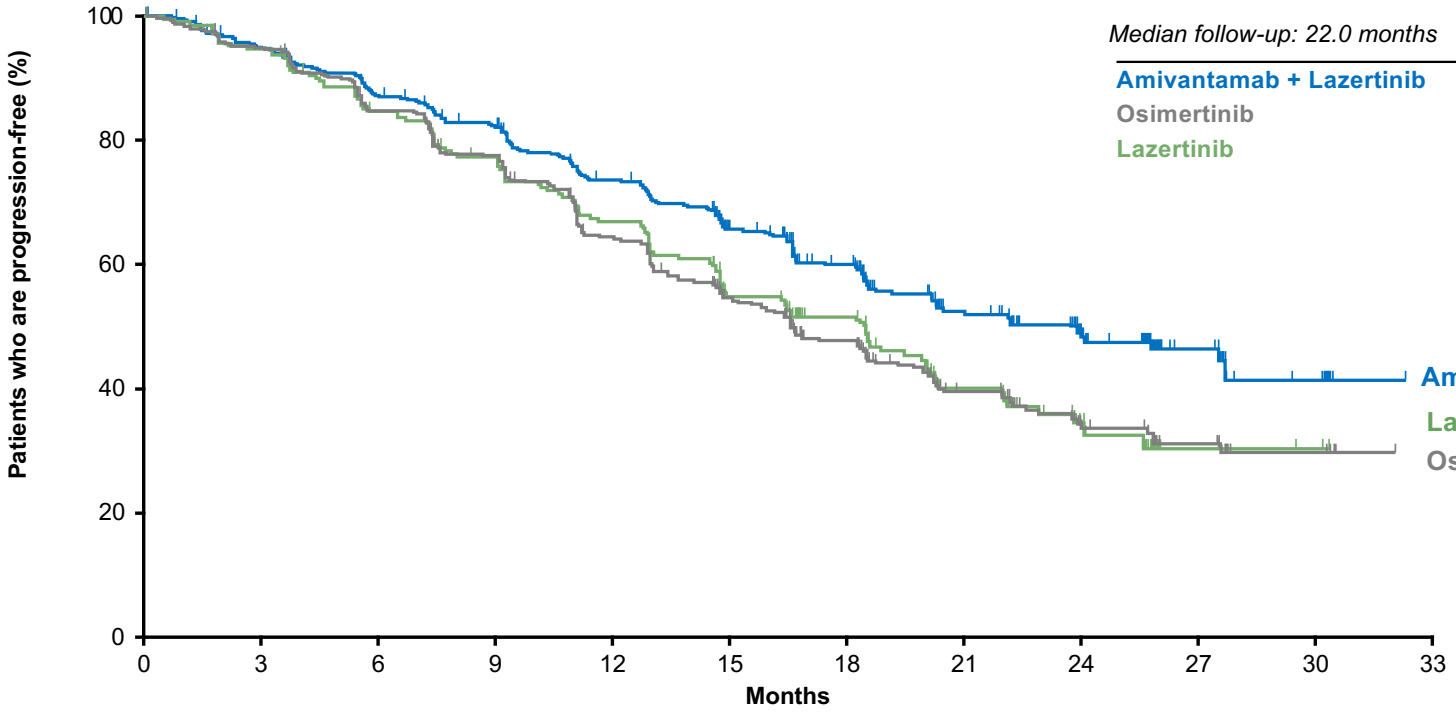
HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

| **No. at risk** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 429 | 391 | 357 | 332 | 291 | 244 | 194 | 106 | 60 | 33 | 8 | 0 |
| Osimertinib | 429 | 404 | 358 | 325 | 266 | 205 | 160 | 90 | 48 | 28 | 10 | 0 |

[a]At time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

# MARIPOSA: Progression-free Survival by BICR[a]




*Median follow-up: 22.0 months*

| | Median PFS (95% CI) |
|---|---|
| Amivantamab + Lazertinib | 23.7 mo (19.1–27.7) |
| Osimertinib | 16.6 mo (14.8–18.5) |
| Lazertinib | 18.5 mo (14.8–20.1) |

| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 429 | 391 | 357 | 332 | 291 | 244 | 194 | 106 | 60 | 33 | 8 | 0 |
| Osimertinib | 429 | 404 | 358 | 325 | 266 | 205 | 160 | 90 | 48 | 28 | 10 | 0 |
| Lazertinib | 216 | 200 | 174 | 157 | 134 | 103 | 83 | 41 | 19 | 6 | 2 | 0 |

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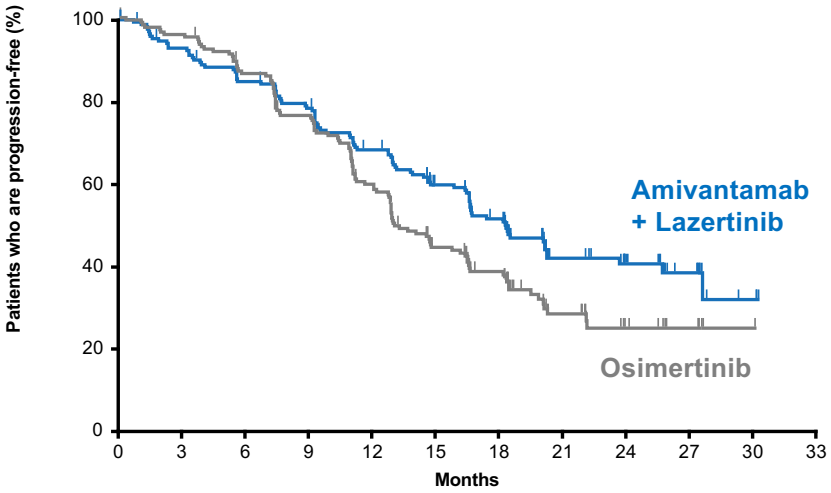
CI, confidence interval; mo, months; PFS, progression-free survival.

# MARIPOSA: Progression-free Survival by BICR[a]

MARIPOSA MARIPOSA

| With History of Brain Metastases | Median PFS (95% CI) |
|---|---|
| Amivantamab + Lazertinib | 18.3 mo (16.6–23.7) |
| Osimertinib | 13.0 mo (12.2–16.4) |

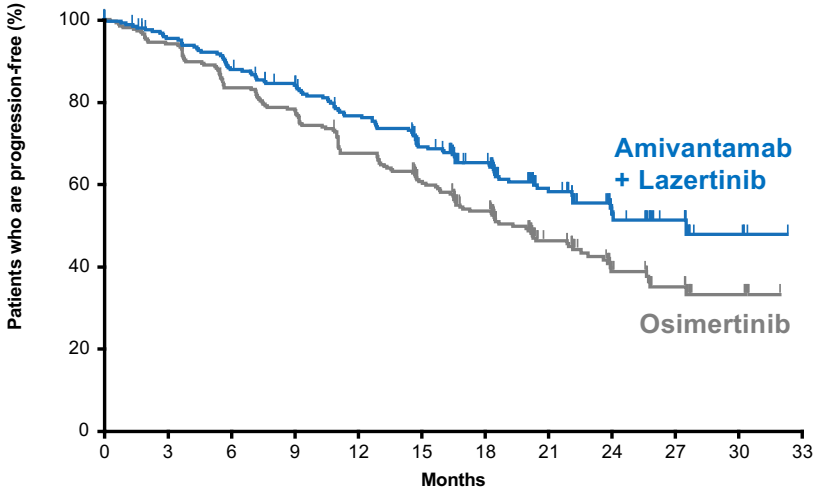
HR, **0.69** (95% CI, 0.53–0.92)




| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 178 | 162 | 146 | 134 | 115 | 92 | 71 | 34 | 24 | 12 | 3 | 0 |
| Osimertinib | 172 | 164 | 146 | 126 | 95 | 64 | 47 | 21 | 11 | 6 | 1 | 0 |

| Without History of Brain Metastases | Median PFS (95% CI) |
|---|---|
| Amivantamab + Lazertinib | 27.5 mo (22.1–NE) |
| Osimertinib | 19.9 mo (16.6–22.9) |

HR, **0.69** (95% CI, 0.53–0.89)




| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 251 | 229 | 211 | 198 | 176 | 152 | 123 | 72 | 36 | 21 | 5 | 0 |
| Osimertinib | 257 | 240 | 212 | 199 | 171 | 141 | 113 | 69 | 37 | 22 | 9 | 0 |

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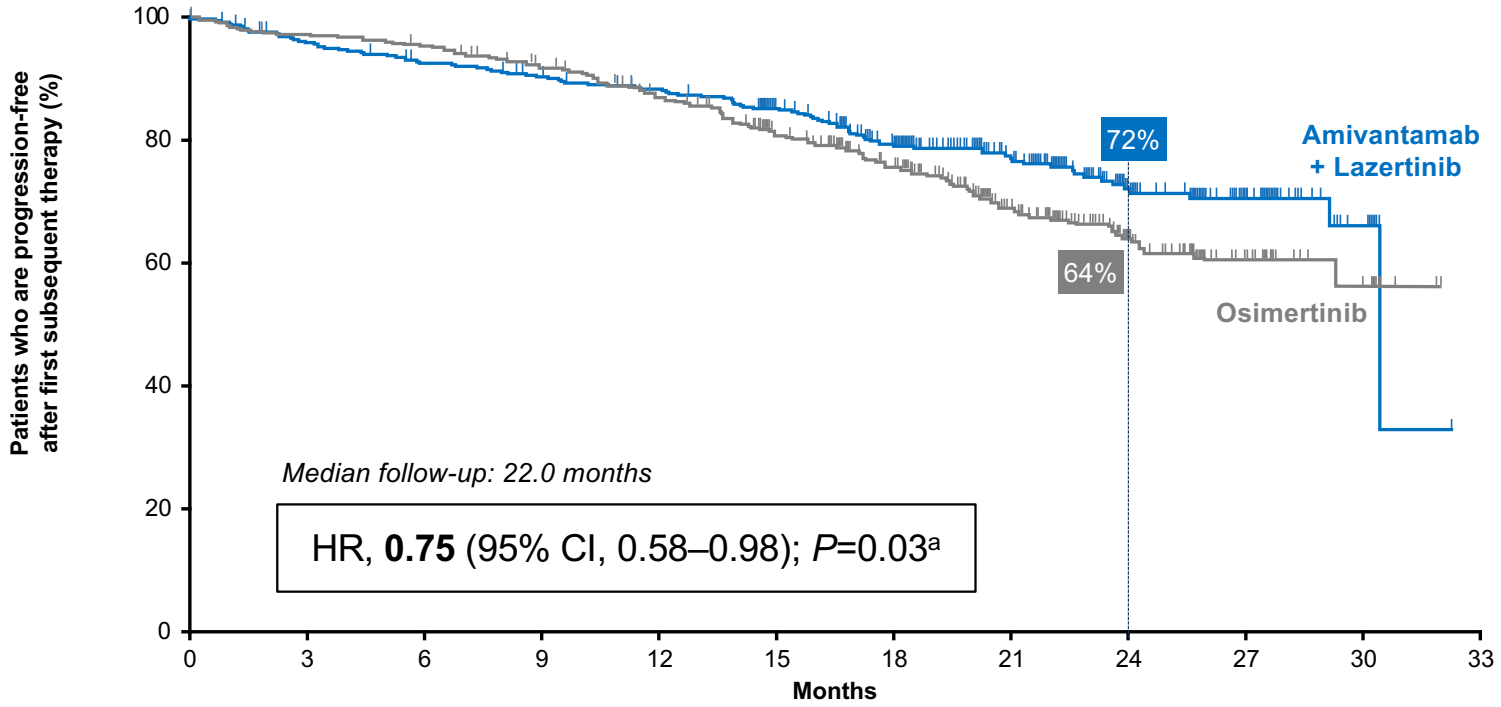
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival.

# MARIPOSA: Progression-free Survival2

*Amivantamab + lazertinib reduced the risk of 2nd disease progression or death by 25%*




**Most Common First Subsequent Therapy**

| | |
|---|---|
| Amivantamab + Lazertinib | |
| 98 started subsequent therapy | |
| EGFR TKI monotherapy: 48 (49%) | |
| Chemotherapy alone: 32 (33%) | |
| Osimertinib | |
| 137 started subsequent therapy | |
| Chemotherapy alone: 53 (39%) | |
| EGFR TKI monotherapy: 37 (27%) | |

**No. at risk**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 429 | 400 | 383 | 370 | 357 | 325 | 268 | 175 | 97 | 47 | 11 | 0 |
| Osimertinib | 429 | 415 | 406 | 387 | 358 | 303 | 249 | 153 | 87 | 42 | 12 | 0 |

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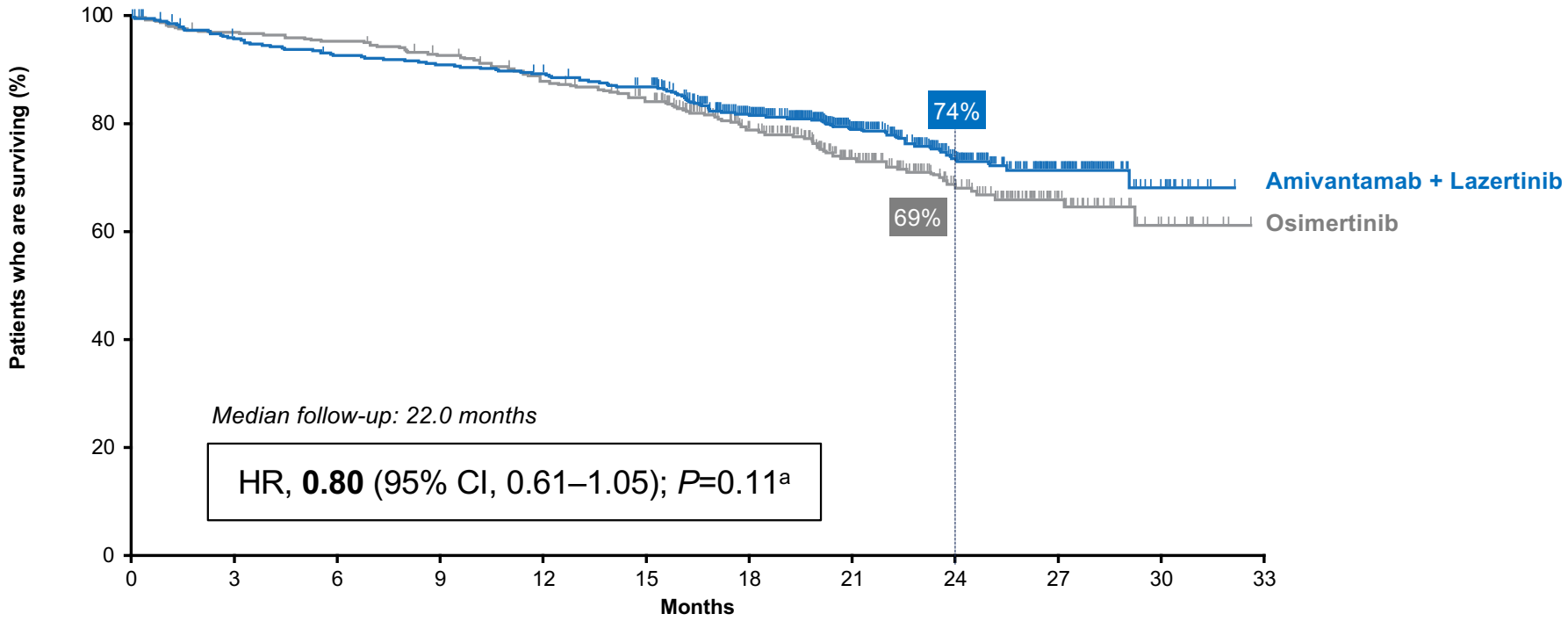
[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. Median estimates, at this time, are unreliable.

CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

# MARIPOSA: Interim Overall Survival

*Early survival data show a trend favoring amivantamab + lazertinib vs osimertinib*




| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab + Lazertinib | 429 | 403 | 389 | 382 | 374 | 360 | 293 | 201 | 122 | 58 | 14 | 0 |
| Osimertinib | 429 | 416 | 409 | 395 | 372 | 349 | 280 | 186 | 110 | 54 | 13 | 0 |

[a]There were a total of 214 deaths in the amivantamab + lazertinib and osimertinib arms at time of the prespecified interim OS analysis, which represents 25% of all randomized patients and 55% of the ~390 projected deaths for the final OS analysis. Medians at this time are not estimable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

# MARIPOSA: Summary of Adverse Events (AEs)

MARIPOSA

- Median treatment duration was 18.5 mo for amivantamab + lazertinib and 18.0 mo for osimertinib

| TEAE, n (%) | Amivantamab + Lazertinib (n=421) | Osimertinib (n=428) |
|---|---|---|
| Any AE | 421 (100) | 425 (99) |
| Grade ≥3 AEs | 316 (75) | 183 (43) |
| Serious AEs | 205 (49) | 143 (33) |
| AEs leading to death | 34 (8) | 31 (7) |
| Any AE leading to treatment: | | |
| Interruptions of any agent | 350 (83) | 165 (39) |
| Reductions of any agent | 249 (59) | 23 (5) |
| Discontinuations of any agent | 147 (35) | 58 (14) |

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

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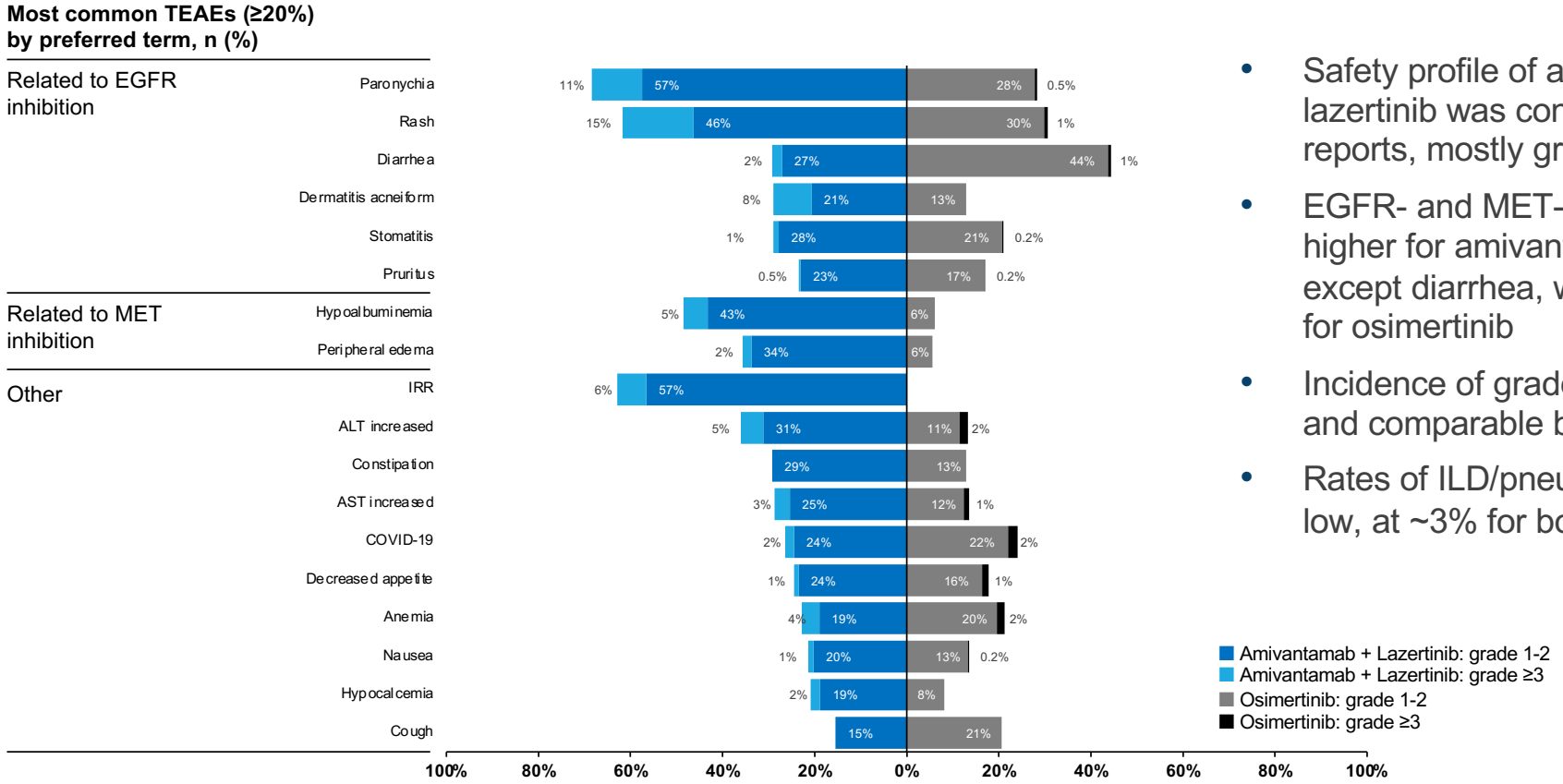
AE, adverse event; mo, months; TEAE, treatment-emergent AE.

# MARIPOSA: Safety Profile

MARIPOSA




- Safety profile of amivantamab + lazertinib was consistent with prior reports, mostly grades 1-2
- EGFR- and MET-related AEs were higher for amivantamab + lazertinib except diarrhea, which was higher for osimertinib
- Incidence of grade 4-5 AEs was low and comparable between arms
- Rates of ILD/pneumonitis remained low, at ~3% for both arms

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AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease (includes pneumonitis); IRR, infusion-related reaction; TEAE, treatment-emergent AE.

# 2L treatment strategies under investigation post-osimertinib

| Resistance mechanism | Clinical trial | Intervention(s) | Phase |
|---|---|---|---|
| **EGFR C797S** | ORCHARD[1] | Osimertinib + gefitinib | 2 |
| | SYMPHONY[2] | BLU-945 | 1/2 |
| | HARMONY[3] | BLU-701 | 1/2 |
| | NCT04820023[4] | BBT-176 | 1/2 |
| | NCT05256290[5] | BDTX-1535 | 1 |
| | NCT05394831[6] | JIN-A02 | 1/2 |
| **MET amplification** | SAFFRON[7] | Osimertinib + savolitinib vs ChT | 3 |
| | SAVANNAH[8] | Savolitinib +/- osimertinib | 2 |
| | INSIGHT 2[9] | Tepotinib +/- osimertinib | 2 |
| **ALK fusion** | ORCHARD[1] | Osimertinib + alectinib | 2 |
| **RET fusion** | ORCHARD[1] | Osimertinib + selpercatinib | 2 |
| **BRAF fusions, BRAF mutations** | ORCHARD[1] | Osimertinib + selumetinib | 2 |
| **SCLC transformation** | ORCHARD[1] | Carboplatin + pemetrexed + durvalumab | 2 |
| **No resistance mechanism identified/agnostic strategies** | ORCHARD[1,10] | Pemetrexed + carboplatin + durvalumab, or osimertinib + necitumumab, or future treatments | 2 |
| | COMPEL[11] | ChT +/- osimertinib | 3 |
| | NCT04676477[12] | Patritumab deruxtecan +/- osimertinib | 1 |
| | PALOMA-3[13] | Amivantamab + lazertinib | 3 |
| | CHRYSALIS-2[14] | Amivantamab +/- lazertinib | 1 |
| | MARIPOSA-2[15] | ChT +/- amivantamab + lazertinib | 3 |

1. NCT03944772. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03944772. Accessed March 2023; 2. NCT04862780. Available at: https://clinicaltrials.gov/ct2/show/NCT04862780. Accessed March 2023; 3. NCT05153408. Available at: https://www.clinicaltrials.gov/ct2/show/NCT05153408. Accessed March 2023; 4. NCT04820023. Available at: https://clinicaltrials.gov/ct2/show/NCT04820023. Accessed March 2023; 5. NCT05256290. Available at: https://clinicaltrials.gov/ct2/show/NCT05256290. Accessed March 2023; 6. NCT05394831. Available at: https://clinicaltrials.gov/ct2/show/NCT05394831. Accessed March 2023; 7. NCT05261399. Available at: https://clinicaltrials.gov/ct2/show/NCT05261399. Accessed March 2023; 8. NCT03778229. Available at: https://clinicaltrials.gov/ct2/show/NCT03778229. Accessed March 2023; 9. NCT03940703. Available at: https://clinicaltrials.gov/ct2/show/NCT03940703. Accessed March 2023; 10. Yu HA, et al. Presented at ESMO 2021; 11. NCT04765059. Available at: https://clinicaltrials.gov/ct2/show/NCT04765059. Accessed March 2023; 12. NCT04676477. Available at: https://clinicaltrials.gov/ct2/show/NCT04676477. Accessed March 2023; 13. NCT05388669. Available at: https://clinicaltrials.gov/ct2/show/NCT05388669. Accessed March 2023; 14. NCT04077463. Available at: https://clinicaltrials.gov/ct2/show/NCT04077463. Accessed March 2023; 15. NCT04988295. Available at: https://clinicaltrials.gov/ct2/show/NCT04988295. Accessed March 2023.

**This list provides an overview and is not comprehensive or comparative.**

2L, second-line; ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homologue B1; ChT, chemotherapy; MET, mesenchymal-epithelial transition; RET, rearranged during transfection; SCLC, small cell lung cancer.

# MARIPOSA-2: Phase 3 Study Design



MARIPOSA-2

**Key Eligibility Criteria**

- Locally advanced or metastatic NSCLC
- Documented *EGFR* Ex19del or L858R
- *Progressed on or after osimertinib monotherapy (as most recent line)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

**Stratification Factors**

- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

*Serial brain MRIs were required for all patients[a]*

**Amivantamab-Lazertinib-Chemotherapy (n=263)**

**Chemotherapy (n=263)**

**Amivantamab-Chemotherapy (n=131)**

Dosing (in 21-day cycles)

**Amivantamab:** 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at Cycle 3 (week 7)

**Lazertinib:** 240 mg daily starting after completion of carboplatin[b]

**Chemotherapy administered at the beginning of every cycle:**

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m$^2$ until disease progression

**Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:**

- **Amivantamab-Lazertinib-Chemotherapy** vs **Chemotherapy**
- **Amivantamab-Chemotherapy** vs **Chemotherapy**

**Secondary endpoints:**

- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- Intracranial PFS
- Time to subsequent therapy[d]
- PFS after first subsequent therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10-Jul-2023

[a]Patients who could not have MRI were allowed to have CT scans.

[b]All patients randomized before 7Nov2022 initiated lazertinib on the first day of Cycle 1 (see next slide).

[c]Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy, respectively, vs chemotherapy to detect a HR of 0.65 using a log-rank test, with an overall two-sided alpha of 0.05 (median PFS of 8.5 months for amivantamab-containing arms vs 5.5 for chemotherapy). Statistical hypothesis testing included PFS, ORR, and then OS.

[d]These secondary endpoints (time to subsequent therapy, PFS2, and symptomatic PFS) will be presented at a future congress.

AUC, area under the curve; BICR, blinded independent central review; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; HR, hazard ratio; IDMC, independent data monitoring committee; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

# MARIPOSA-2: Baseline Disease Characteristics



MARIPOSA-2

| Characteristic, n (%) | Chemotherapy (n=263) | Amivantamab-Chemotherapy (n=131) | Amivantamab-Lazertinib-Chemotherapy (n=263) |
|---|---|---|---|
| Median age, years (range) | 62 (31–85) | 62 (36–84) | 61 (23–83) |
| Female | 157 (60) | 81 (62) | 168 (64) |
| Race | | | |
| Asian | 127 (48) | 63 (48) | 125 (48) |
| White | 123 (47) | 60 (46) | 129 (49) |
| Other[a] | 13 (5) | 8 (6) | 9 (3) |
| ECOG PS 1 | 162 (62) | 76 (58) | 171 (65) |
| History of smoking | 95 (36) | 41 (31) | 87 (33) |
| History of brain metastases | 120 (46) | 58 (44) | 120 (46) |
| No prior brain radiation | 61 of 120 (51) | 24 of 58 (41) | 56 of 120 (47) |
| Osimertinib line of therapy[b] | | | |
| First | 181 (69) | 97 (74) | 185 (70) |
| Second | 82 (31) | 34 (26) | 77 (29) |
| *EGFR* mutation type | | | |
| Ex19del | 183 (70) | 89 (68) | 165 (63) |
| L858R | 79 (30) | 42 (32) | 98 (37) |

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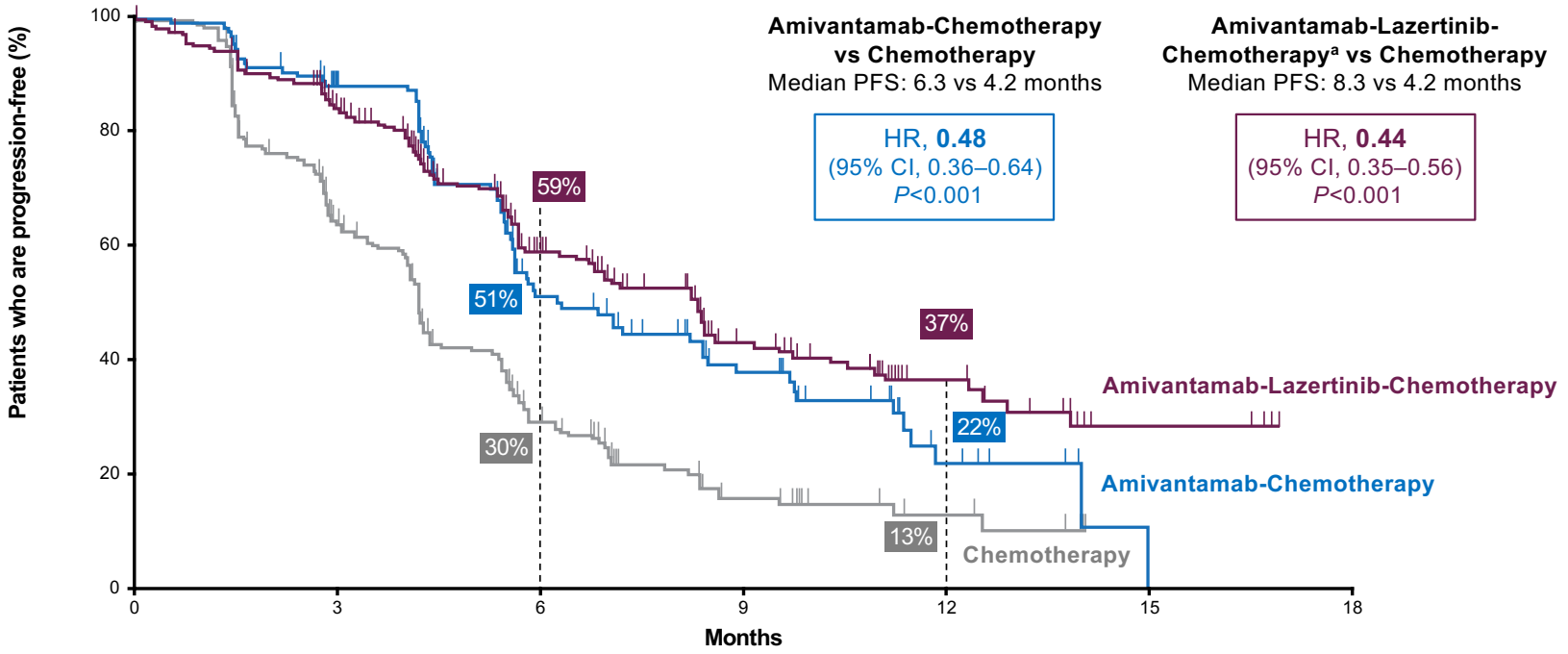
**Note**: percentages may not sum to 100 due to rounding.

[a]Other includes American Indian or Alaska Native, Black or African American, multiple, and unknown.
[b]One patient in the amivantamab-lazertinib-chemotherapy arm received osimertinib later than second-line and is not included in the table.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions.

# MARIPOSA-2: Progression-free Survival by BICR

*At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively*



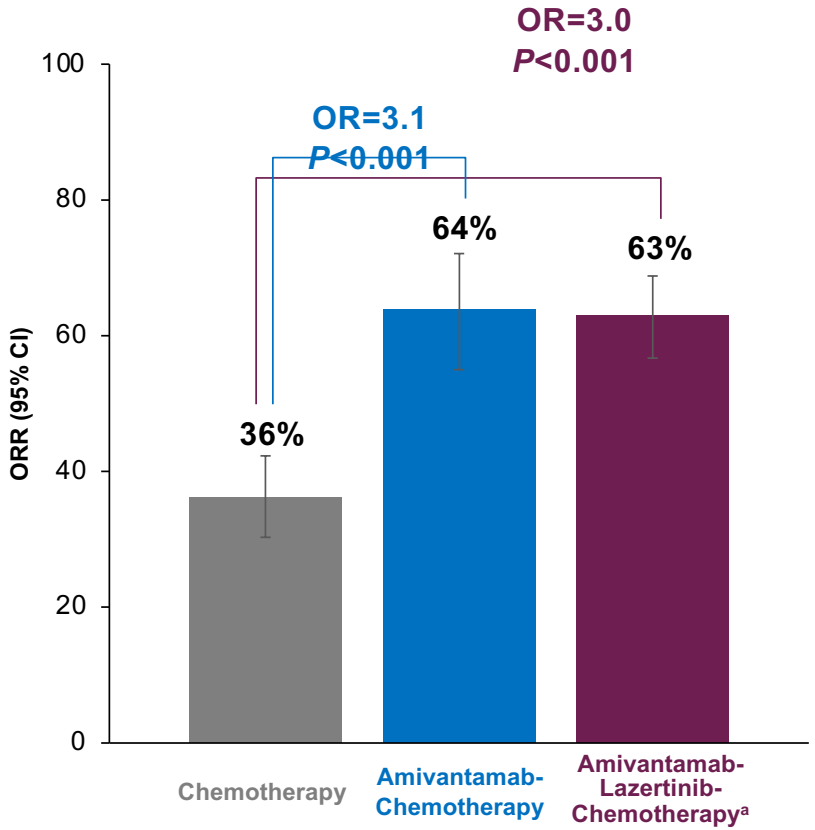

| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Amivantamab-Chemotherapy | 131 | 99 | 49 | 27 | 7 | 0 | 0 |
| Amivantamab-Lazertinib-Chemotherapy | 263 | 194 | 104 | 52 | 21 | 4 | 0 |
| Chemotherapy | 263 | 135 | 49 | 17 | 6 | 0 | 0 |

**Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; *P*<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; *P*<0.001[b])**

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

# MARIPOSA-2: ORR and DoR by BICR




| BICR-assessed Response, n (%)[b] | Chemotherapy (n=263) | Amivantamab-Chemotherapy (n=131) | Amivantamab-Lazertinib-Chemotherapy (n=263) |
|---|---|---|---|
| Best Response | | | |
| CR | 1 (0.4) | 2 (2) | 6 (2) |
| PR | 93 (36) | 81 (62) | 157 (61) |
| SD | 82 (32) | 30 (23) | 61 (24) |
| PD | 52 (20) | 10 (8) | 14 (5) |
| NE/UNK | 32 (12) | 7 (5) | 21 (8) |
| Median DoR[c] | 5.6 mo (95% CI, 4.2–9.6) | 6.9 mo (95% CI, 5.5–NE) | 9.4 mo (95% CI, 6.9–NE) |

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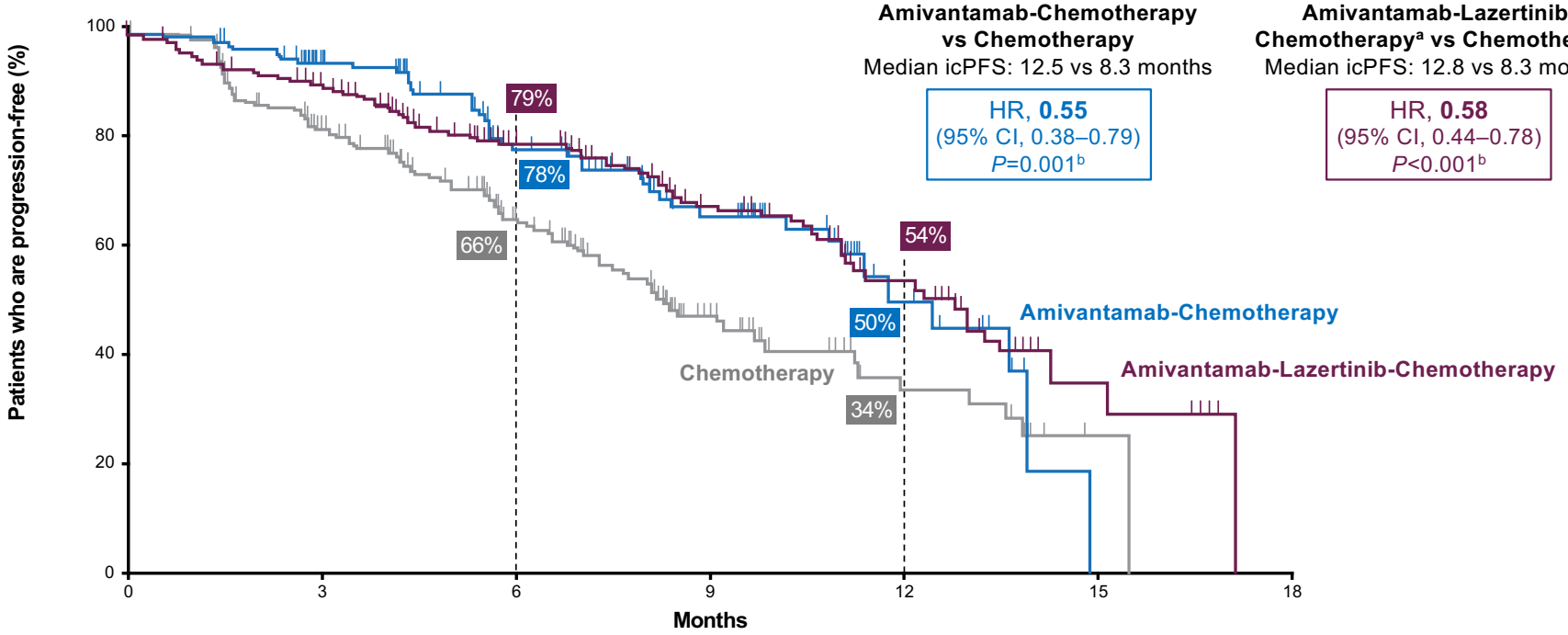
[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]No. of patients with measurable disease at baseline by BICR was 260 for chemotherapy, 130 for amivantamab-chemotherapy, and 259 for amivantamab-lazertinib-chemotherapy. [c]Among confirmed responders.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; NE, not estimable; NE/UNK, not evaluable/unknown; OR, odds ratio; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

# MARIPOSA-2: Intracranial Progression-free Survival

*Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial by 45% and 42%, respectively*




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Amivantamab-Chemotherapy | 131 | 103 | 72 | 40 | 11 | 0 | 0 |
| Amivantamab-Lazertinib-Chemotherapy | 263 | 211 | 135 | 74 | 32 | 6 | 0 |
| Chemotherapy | 263 | 167 | 89 | 37 | 13 | 1 | 0 |

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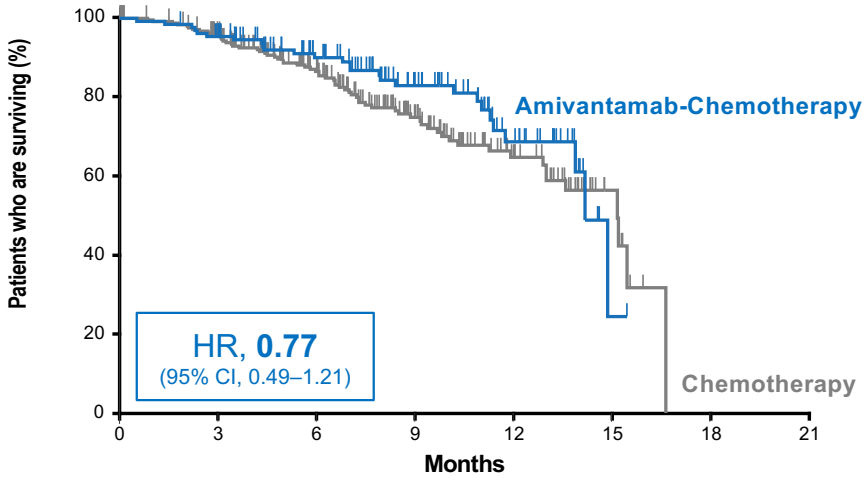
[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

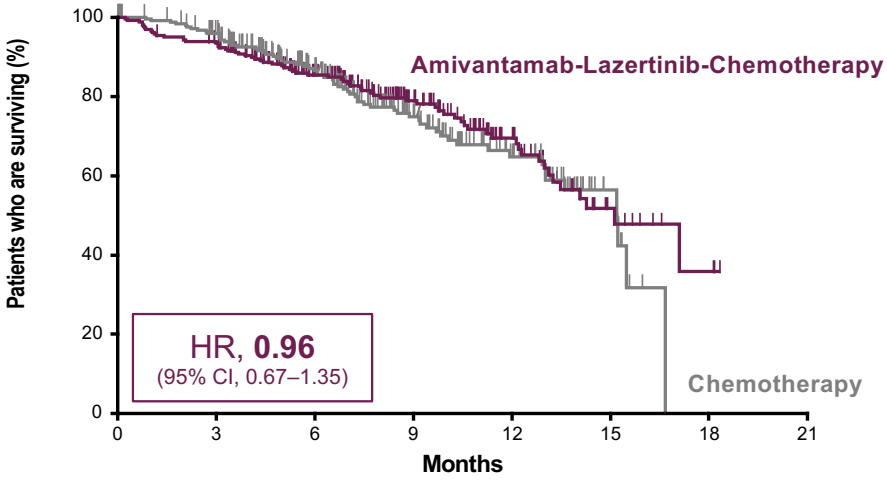
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival.

# MARIPOSA-2: Early Interim Overall Survival[a]

At time of data cutoff, the median follow-up for the study was 8.7 months




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| Amivantamab-Chemotherapy | 131 | 122 | 89 | 54 | 24 | 1 | 0 |
| Chemotherapy | 263 | 229 | 158 | 85 | 39 | 8 | 0 |




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Amivantamab-Lazertinib-Chemotherapy | 263 | 241 | 170 | 101 | 52 | 13 | 3 | 0 |
| Chemotherapy | 263 | 229 | 158 | 85 | 39 | 8 | 0 | 0 |

Includes all randomized patients regardless of dosing regimen received
- Median follow-up for the modified amivantamab-lazertinib-chemotherapy regimen was 5.4 months

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[a]There were 161 deaths in the study at the time of the prespecified interim OS analysis (representing 25% of all randomized patients and 40% of the 400 projected deaths for the final OS analysis). Median estimates at this time (median follow-up of 8.7 months) are not reliable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

# MARIPOSA-2: Summary of Adverse Events (AEs)

| | Chemotherapy (n=243) | Amivantamab-Chemotherapy (n=130) | Amivantamab-Lazertinib-Chemotherapy[a] (n=263) |
|---|---|---|---|
| Treatment duration, median (range) | 3.7 months (0–15.9) | 6.3 months (0–14.7) | 5.7 months (0.1–18.6) |
| No. of chemotherapy cycles, median (range) | | | |
| Carboplatin | 4 (1–5) | 4 (1–4) | 4 (1–4) |
| Pemetrexed | 6 (1–23) | 9 (1–22) | 7 (1–25) |

| **TEAE, n (%)** | Chemotherapy (n=243) | Amivantamab-Chemotherapy (n=130) | Amivantamab-Lazertinib-Chemotherapy[a] (n=263) |
|---|---|---|---|
| Any AEs | 227 (93) | 130 (100) | 263 (100) |
| Grade ≥3 AEs | 117 (48) | 94 (72) | 242 (92) |
| Serious AEs | 49 (20) | 42 (32) | 137 (52) |
| AEs leading to death | 3 (1) | 3 (2) | 14 (5) |
| Any AE leading to treatment: | | | |
| Interruptions of any agent | 81 (33) | 84 (65) | 202 (77) |
| Reductions of any agent | 37 (15) | 53 (41) | 171 (65) |
| Discontinuations of any agent | 9 (4) | 24 (18) | 90 (34) |
| Discontinuations of all agents due to AE | 10 (4) | 14 (11) | 38 (14) |

- Median treatment duration was longer for the amivantamab-containing arms vs chemotherapy
- Amivantamab-containing arms had higher rates of grade ≥3 AEs and dose modifications vs chemotherapy
  - Highest in the amivantamab-lazertinib-chemotherapy arm
- AEs leading to death were low
- Discontinuations of all agents due to treatment-related AEs was 2%, 8%, and 10%

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received.

TEAE, treatment-emergent adverse event.

# MARIPOSA-2: Safety Profile

| Most common TEAEs (≥25%) by preferred term, n (%) | Chemotherapy (n=243) | | Amivantamab-Chemotherapy (n=130) | | Amivantamab-Lazertinib-Chemotherapy[a] (n=263) | |
|---|---|---|---|---|---|---|
| | All grades | Grade ≥3 | All grades | Grade ≥3 | All grades | Grade ≥3 |
| **Associated with EGFR inhibition** | | | | | | |
| Paronychia | 1 (0.4) | 0 | 48 (37) | 3 (2) | 133 (51) | 11 (4) |
| Rash | 12 (5) | 0 | 56 (43) | 8 (6) | 126 (48) | 17 (6) |
| Stomatitis | 21 (9) | 0 | 41 (32) | 1 (1) | 120 (46) | 24 (9) |
| Diarrhea | 16 (7) | 1 (0.4) | 18 (14) | 1 (1) | 68 (26) | 10 (4) |
| **Associated with MET inhibition** | | | | | | |
| Hypoalbuminemia | 21 (9) | 1 (0.4) | 29 (22) | 3 (2) | 104 (40) | 12 (5) |
| Peripheral edema | 15 (6) | 0 | 42 (32) | 2 (2) | 85 (32) | 1 (0.4) |
| **Associated with Chemotherapy** | | | | | | |
| Neutropenia | 101 (42) | 52 (21) | 74 (57) | 59 (45) | 181 (69) | 144 (55) |
| Thrombocytopenia | 72 (30) | 22 (9) | 57 (44) | 19 (15) | 158 (60) | 96 (37) |
| Anemia | 97 (40) | 23 (9) | 51 (39) | 15 (12) | 141 (54) | 48 (18) |
| Leukopenia | 68 (28) | 23 (9) | 37 (28) | 26 (20) | 106 (40) | 71 (27) |
| **Other** | | | | | | |
| Infusion-related reaction | 1 (0.4) | 0 | 76 (58) | 7 (5) | 148 (56) | 9 (3) |
| Nausea | 90 (37) | 2 (1) | 58 (45) | 1 (1) | 131 (50) | 16 (6) |
| Constipation | 72 (30) | 0 | 50 (38) | 1 (1) | 96 (37) | 3 (1) |
| Decreased appetite | 51 (21) | 3 (1) | 40 (31) | 0 | 85 (32) | 7 (3) |
| Vomiting | 42 (17) | 1 (0.4) | 32 (25) | 1 (1) | 76 (29) | 10 (4) |
| Fatigue | 47 (19) | 4 (2) | 36 (28) | 4 (3) | 69 (26) | 15 (6) |
| Asthenia | 40 (16) | 5 (2) | 34 (26) | 1 (1) | 67 (25) | 14 (5) |
| Alanine aminotransferase increased | 67 (28) | 10 (4) | 26 (20) | 7 (5) | 55 (21) | 14 (5) |
| **AESIs by grouped term, n (%)** | | | | | | |
| Rash[b] | 30 (12) | 0 | 92 (71) | 13 (10) | 197 (75) | 40 (15) |
| VTE[c] | 11 (5) | 7 (3) | 13 (10) | 3 (2) | 58 (22) | 17 (6) |
| ILD | 0 | 0 | 2 (2) | 1 (1) | 7 (3) | 5 (2) |

- Amivantamab-containing arms had higher rates of EGFR- and MET-related AEs
- Neutropenia and thrombocytopenia:
  - Mostly occurred during cycle 1
  - Low rates of febrile neutropenia (2%, 2%, and 8%)
  - Low rates of grade 3-4 bleeding[d] (0%, 1%, and 3%)
- VTE highest in amivantamab-lazertinib-chemotherapy arm
  - No grade 5 events
  - Rates of discontinuation due to VTE were low (0%, 1%, and 0.4%)
- Incidence of ILD was low in all arms (<3%)

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[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Grouping includes the following preferred terms: rash, dermatitis acneiform, rash maculo-papular, erythema, acne, rash pruritic, rash erythematous, rash macular, drug eruption, folliculitis, dermatitis, skin lesion, rash pustular, papule, rash follicular, exfoliative rash, pustule, rash papular, skin exfoliation. [c]Grouping includes the following preferred terms: pulmonary embolism, deep vein thrombosis, embolism, renal vein thrombosis, venous thrombosis limb, venous thrombosis, embolism venous, jugular vein thrombosis, superficial vein thrombosis, thrombophlebitis, thrombosis. [d]Identified by the standardized MedDRA query for "Haemorrhage Terms (Excl Laboratory Terms)".

AE, adverse event; AESI, AE of special interest; EGFR, epidermal growth factor receptor; ILD, interstitial lung disease (includes pneumonitis); TEAE, treatment-emergent AE; VTE, venous thromboembolism.

# Back to multiple sequencing options

**Enrichment** of 1L standards: **EGFR TKI** as single agent, combined with **ChT**, combined with **amivantamab**[1]

**1L treatment choice** impacts **subsequent therapies** and defines the treatment strategy[1]

- How to sequence ChT?
- How to sequence novel options such as amivantamab + lazertinib?
  - Salvage vs upfront?

**Current sequence**[1]

**Osimertinib → doublet ChT → ?**

**Emerging sequences**[1]

**Osimertinib → amivantamab + ChT → ?**

**Osimertinib + doublet ChT → single-agent ChT → ?**

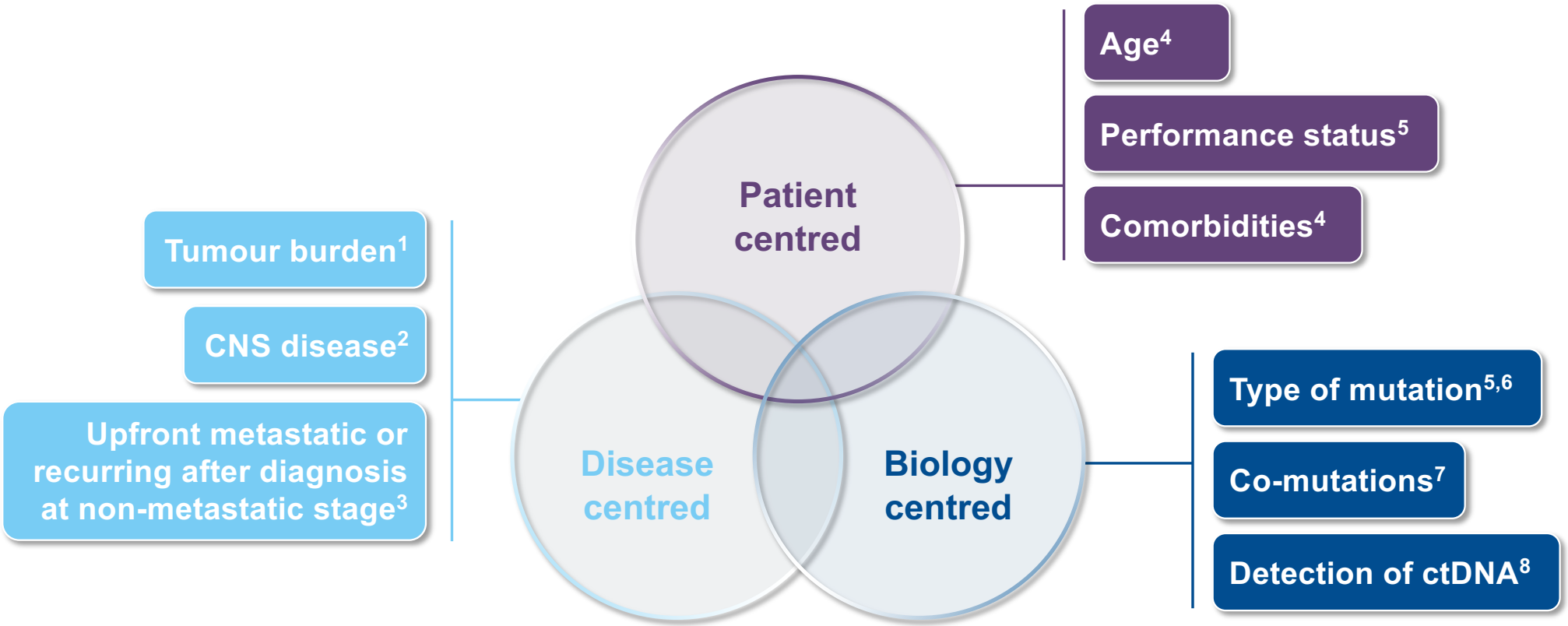
**Amivantamab + lazertinib → doublet ChT → ?**

**~25% of patients with *EGFR*m NSCLC receiving 1L osimertinib die prior to receiving 2L therapy**[2]

1. Speaker's opinion; 2. Girard N, et al. Presented at ELCC 2023: 19P.

1/2L, first/second-line; ChT, chemotherapy; EGFRm, EGFR-mutant.

# Stratification of patients to define optimal treatment approaches

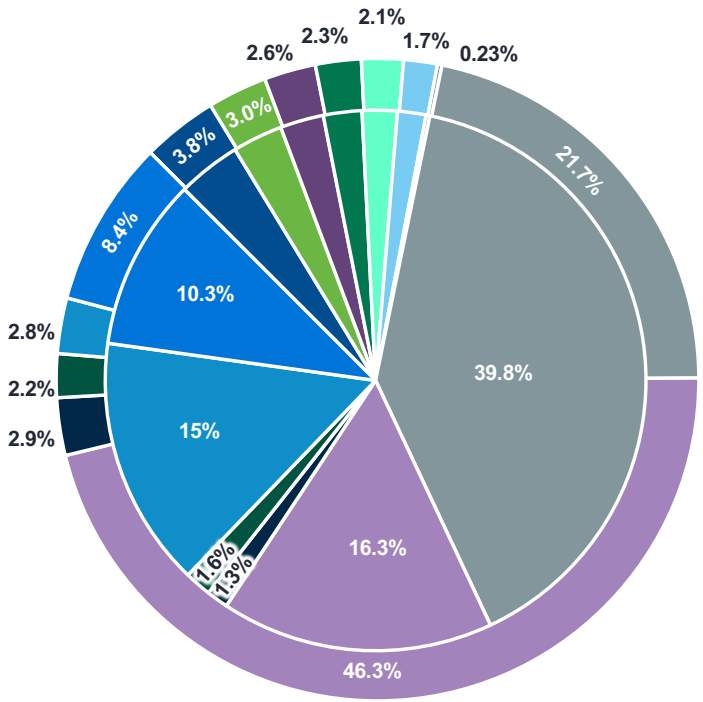



1. Gómez OH, et al. *Cancer Manag Res*. 2021;13:4665–70; 2. Christopoulos P, et al. *Lung Cancer*. 2020;148:105–12; 3. Speaker's opinion; 4. Bergqvist M, et al. *Int J Cancer*. 2020;146:2510–7; 5. Wu A-G, et al. *ERJ Open Res*. 2017;3:00092–2016; 6. Oxnard GR, et al. *J Thoracic Oncol*. 2013;8:179−84; 7. Zhang Y, et al. *J Thorac Dis*. 2022;14:185–93; 8. Guo K, et al. *Transl Lung Cancer R*es. 2021;10:3213–25.

**This schematic provides an overview and is not comprehensive.**

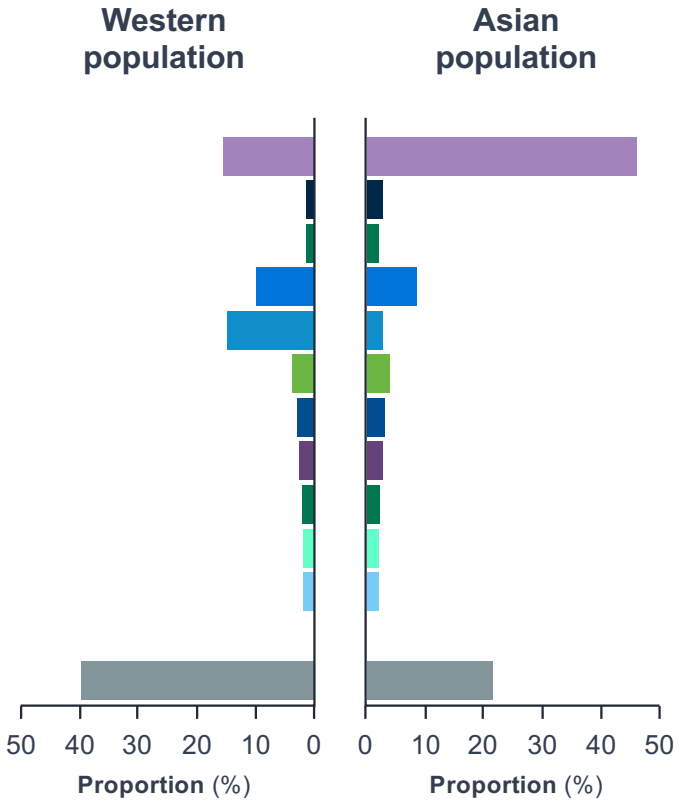
CNS, central nervous system; ctDNA, circulating tumour DNA.

# NSCLC is associated with several oncogenic driver alterations1




**Outer circle**: Asian populations
**Inner circle**: Western populations

- No actionable alteration
- *EGFR* exon 19 deletion and L858R mutation
- *EGFR* exon 20 insertion mutation
- Other *EGFR* mutation
- *KRAS* G12C mutation
- Other *KRAS* mutation
- *ALK* rearrangement
- *MET* exon 14 mutation
- *ROS1* rearrangement
- *HER2* exon 20 insertion mutation
- *BRAF* V600E mutation
- *RET* rearrangement
- *NTRK* rearrangement

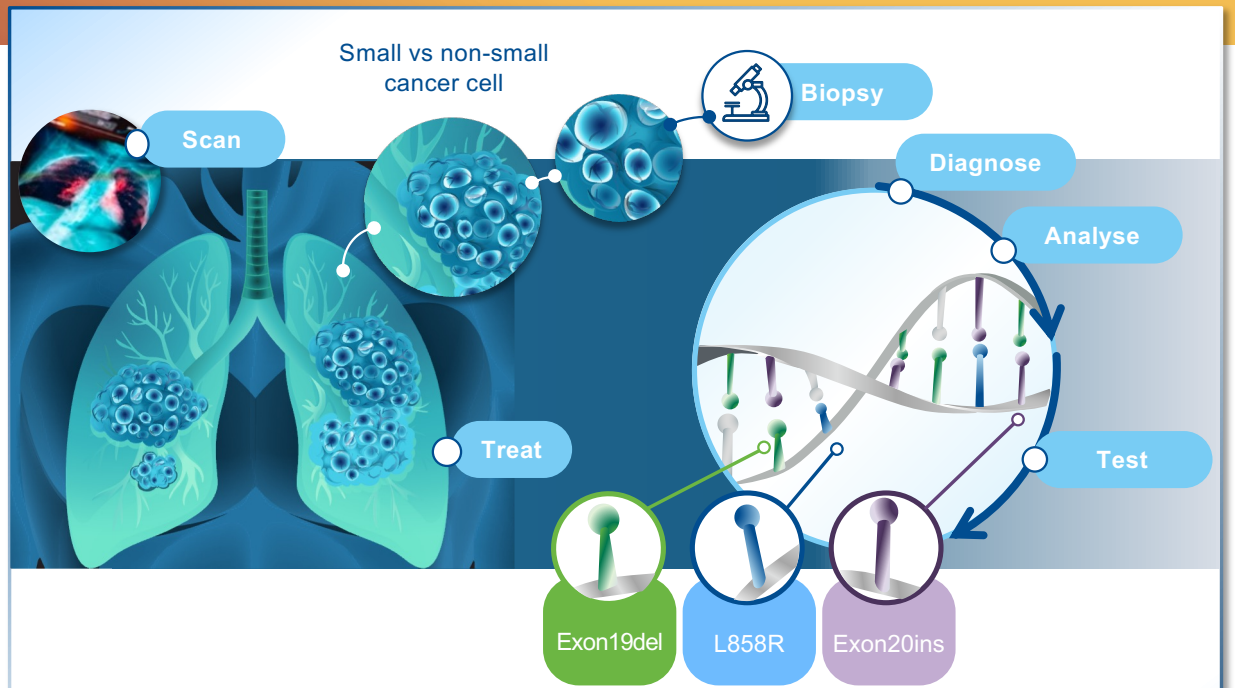



*Adapted from Tan AC and Tan DSW. 2022.*[2]

ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma virus; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection.

1. Kerr KM, et al. *Lung Cancer*. 2021;154:161–75; 2.Tan AC and Tan DSW. *J Clin Oncol*. 2022;40:611–25.

# EGFR exon20ins vs c*EGFR* mutations in NSCLC




| | Exon19del | Exon20ins | |
|---|---|---|---|
| Prevalence[1] | 79 | 12 | % |
| Median rwOS to EGFR TKI[2] | 25.5 | 16.2 | months |
| Median rwPFS to EGFR TKI[2] | 10.5 | 2.9 | months |

**169% increased** risk of progression or death on TKI treatment with *EGFR* exon20ins vs c*EGFR*[2]

TKIs are generally associated with **worse outcomes** in *EGFR* exon20ins vs other mutations across treatment lines[3]

*Adapted from O'Sullivan DE, et al. 2022.[4]*

*Image sourced from AdobeStock, 91894693.*

1. Riess JW, et al. *J Thorac Oncol*. 2018;13:1560–8; 2. Bazhenova L, et al. *Lung Cancer*. 2021;162:154–61;
3. Burnett H, et al. *PLoS One*. 2021;16:e024762; 4. O'Sullivan DE, et al. *Curr Oncol*. 2022;29:7198–208.

cEGFR, common EGFR; exon19del, exon 19 deletion; exon20ins, exon 20 insertion; rw, real-world.

# Unmet needs for patients with *EGFR* exon20ins mutations in NSCLC

**Testing**
PCR misses 51.4% of all *EGFR* exon20ins detected by NGS[1]

**Poor prognosis**
Confer limited sensitivity to standard EGFR TKIs due to steric hinderance[2,3]

**1L therapies**
PBC is the SoC, with no targeted therapies approved in this setting[2]

**Treatment options with improved tolerability**
GI toxicities, skin toxicities, and IRRs are difficult to manage[4]

**CNS metastases**
Common in NSCLC patients with *EGFR* exon20ins mutations[5]

**Acquired resistance**
Remains an unknown for current and emerging agents and will be important to evaluate in the future[4]

1. Viteri S, et al. *Mol Oncol*. 2023;17:230–7; 2. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57; 3. Meador CB, et al. *Cancer Discov*. 2021;11:2145–57; 4. Speaker's opinion; 5. Mountzios G, et al. *JTO Clin Res Rep*. 2022;4:100433.

1L, first-line; CNS, central nervous system; exon20ins, exon 20 insertion; GI, gastrointestinal; IRR, infusion-related reaction; NGS, next-generation sequencing; PBC, platinum-based chemotherapy; PCR, polymerase chain reaction; SoC, standard of care.

# ESMO 2023 clinical practice guidelines: Management of *EGFR* exon20ins mutations in NSCLC[1]

**Recommend sanger sequencing or NGS for the detection of *EGFR* exon20ins** [ESCAT, I–B]*[2]

**The preferred 1L treatment option is platinum-doublet ChT ± ICI** [IV, B]

**Historically used option[3]**

**Disease progression**

**2L treatment options**

**Ongoing global withdrawal[4]**

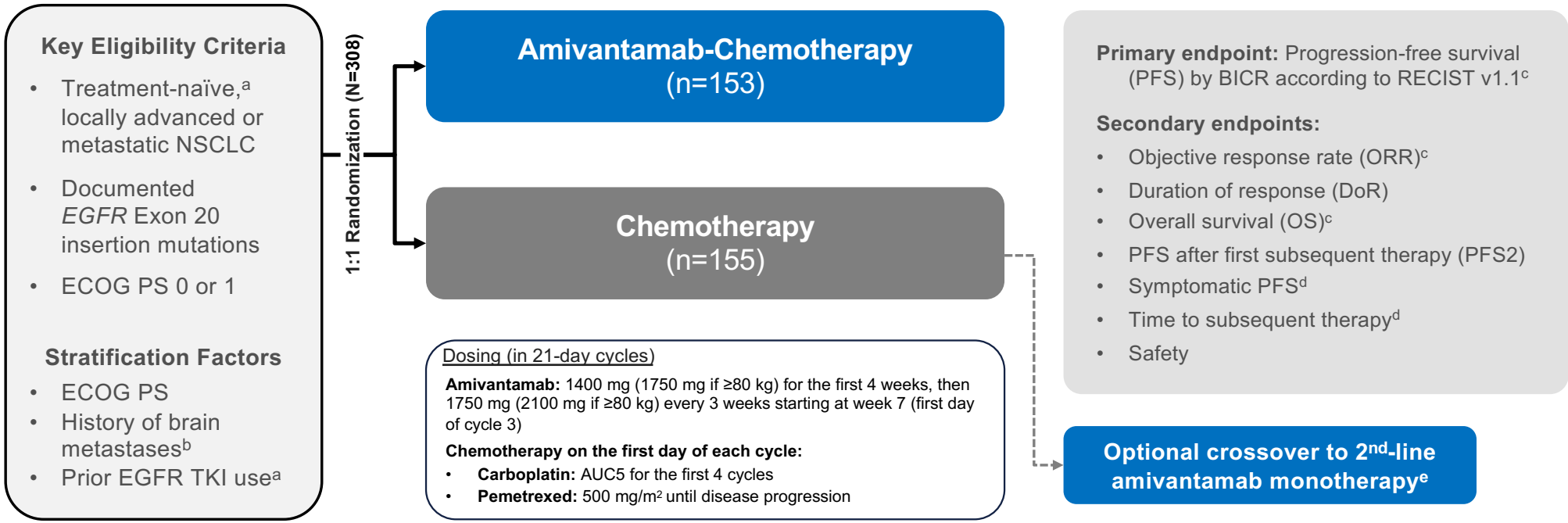
**Amivantamab**
- FDA and EMA approved
- [III, B; MCBS 3; ESCAT I–B]*,†

**Mobocertinib**
- FDA approved
- [III, C; ESCAT I–B]*,†,‡

1. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57; 2. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57 (Supplementary appendix); 3. Speaker's opinion; 4. Takeda Provides Update on EXKIVITY® (mobocertinib). Available at: https://www.takeda.com/newsroom/newsreleases/2023/Takeda-Provides-Update-on-EXKIVITY-mobocertinib/. Accessed October 2023.

*ESMO-MCBS v1.1 score for new therapy/indication approved by the EMA or FDA. These scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee; †ESCAT scores apply to genomic alterations only. These scores have been defined by the guideline authors and validated by the ESMO Translational Research and Precision Medicine Working Group; ‡Not EMA-approved.
1/2L, first/second-line; ChT, chemotherapy; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; ICI, immune checkpoint inhibitor; MCBS, ESMO-Magnitude of Clinical Benefit Scale; NGS, next-generation sequencing.

# PAPILLON: Phase 3 Study Design




PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

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# PAPILLON: Demographic and Baseline Characteristics

| Characteristic, n (%) | Amivantamab-Chemotherapy (n=153) | Chemotherapy (n=155) |
|---|---|---|
| Median age, years (range) | 61 (27–86) | 62 (30–92) |
| Female / male | 85 (56) / 68 (44) | 93 (60) / 62 (40) |
| Race[a] | | |
| Asian | 97 (64) | 89 (59) |
| White | 49 (32) | 60 (39) |
| Other[b] | 5 (3) | 3 (2) |
| ECOG PS 0 / 1 | 54 (35) / 99 (65) | 55 (35) / 100 (65) |
| History of smoking: yes / no | 65 (42) / 88 (58) | 64 (41) / 91 (59) |
| History of brain metastases: yes / no | 35 (23) / 118 (77) | 36 (23) / 119 (77) |
| Prior EGFR TKI use: yes[c] / no | 1 (1) / 152 (99) | 3 (2) / 152 (98) |
| Histology: adenocarcinoma subtype / other[d] | 151 (99) / 2 (1) | 153 (99) / 2 (1) |

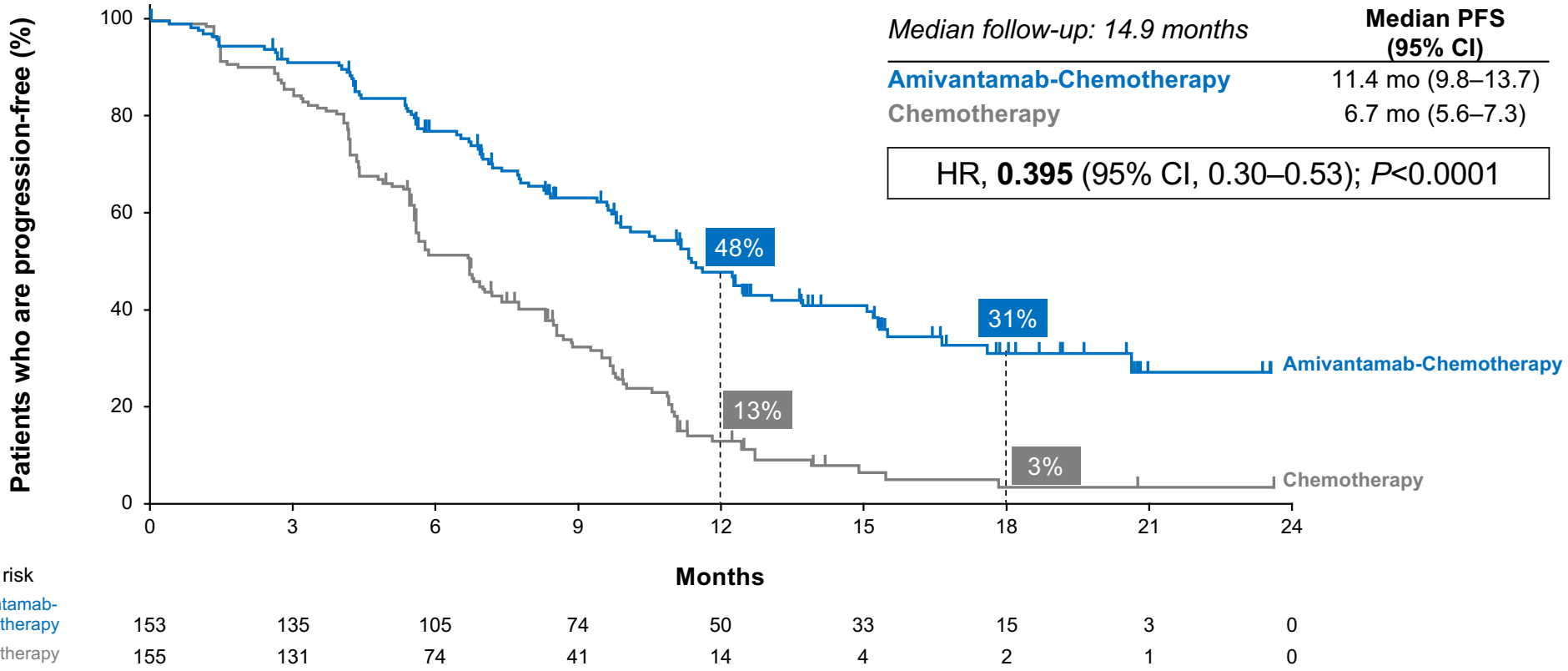
**Note**: percentages may not sum to 100 due to rounding.

[a]In some regions, the reporting of race was not required (amivantamab-chemotherapy, n=151; chemotherapy alone, n=152).
[b]Other includes American Indian or Alaska Native, Black or African American, multiple, and unknown.
[c]Transient monotherapy with common EGFR TKIs was allowed if lack of response was documented.
[d]Other includes large cell carcinoma, squamous cell carcinoma, and other.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

# PAPILLON: Primary Endpoint: Progression-free Survival by BICR

*Amivantamab-chemotherapy reduced risk of progression or death by 60%*



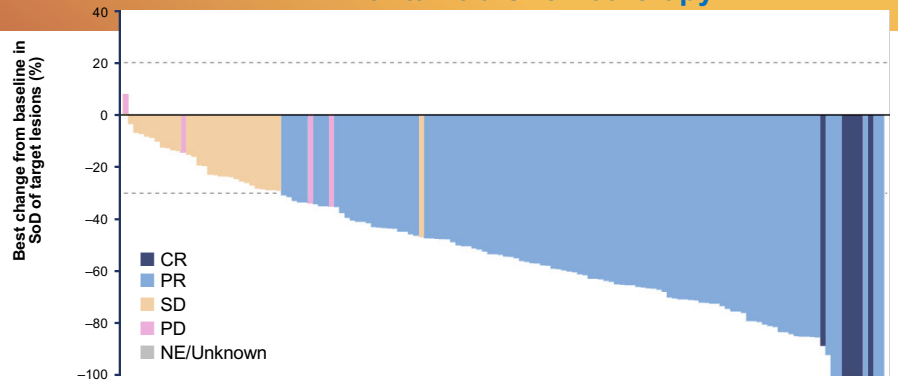

**Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])**

[a]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing. BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival.

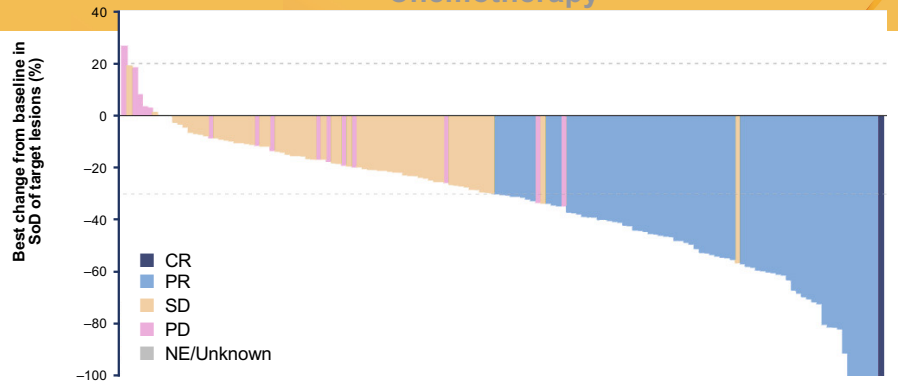
# PAPILLON: Best Response and ORR by BICR

PAPILLON

**Amivantamab-Chemotherapy[a]**




**Chemotherapy[a]**




| BICR-assessed response[b] | Amivantamab-Chemotherapy (n=153) | Chemotherapy (n=155) |
|---|---|---|
| Mean percent change of SoD | -53%[c] | -34% |
| ORR | 73% (95% CI, 65–80) | 47% (95% CI, 39–56) |
| Odds ratio | 3.0 (95% CI, 1.8–4.8); *P*<0.0001 | |
| Best response, n (%) | | |
| Complete response | 6 (4) | 1 (1) |
| Partial response | 105 (69) | 71 (47) |
| Stable disease | 29 (19) | 62 (41) |
| Progressive disease | 4 (3) | 16 (11) |
| NE/Unknown | 8 (5) | 2 (1) |
| Median time to response | 6.7 wk (range, 5.1–72.5) | 11.4 wk (range, 5.1–60.2) |

## Consistent results with investigator assessment: ORR of 66% vs 43% (OR, 2.6; *P*<0.0001)

[a]Patients without postbaseline tumor assessment were not included in this plot. [b]No. of patients with measurable disease at baseline by BICR was 152 in both arms; response data presented among all responders. [c]Nominal *P*<0.001; endpoint not part of hierarchical testing.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; mo, month; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; wk, weeks.

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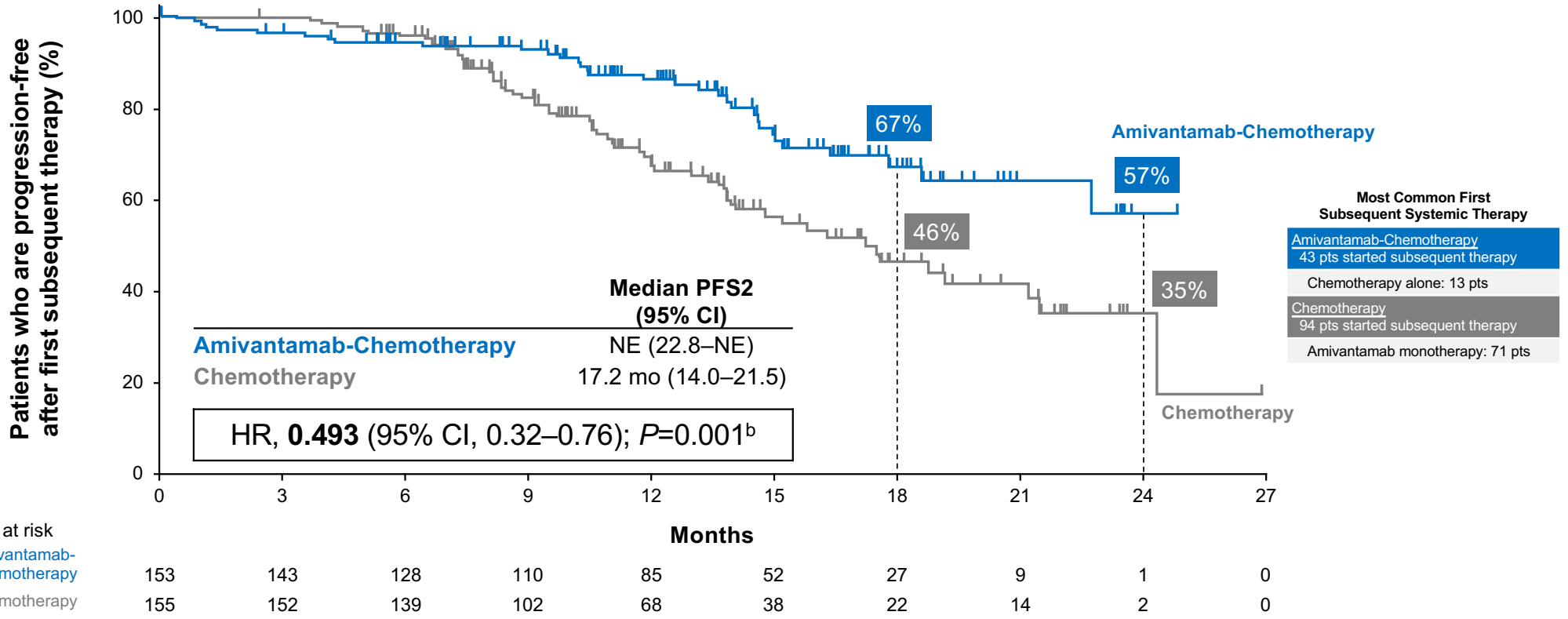
# PAPILLON: PFS2: PFS After First Subsequent Therapy[a]

*Amivantamab-chemotherapy reduced risk of 2nd progression or death by over 50%*




No. at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Amivantamab-Chemotherapy | 153 | 143 | 128 | 110 | 85 | 52 | 27 | 9 | 1 | 0 |
| Chemotherapy | 155 | 152 | 139 | 102 | 68 | 38 | 22 | 14 | 2 | 0 |

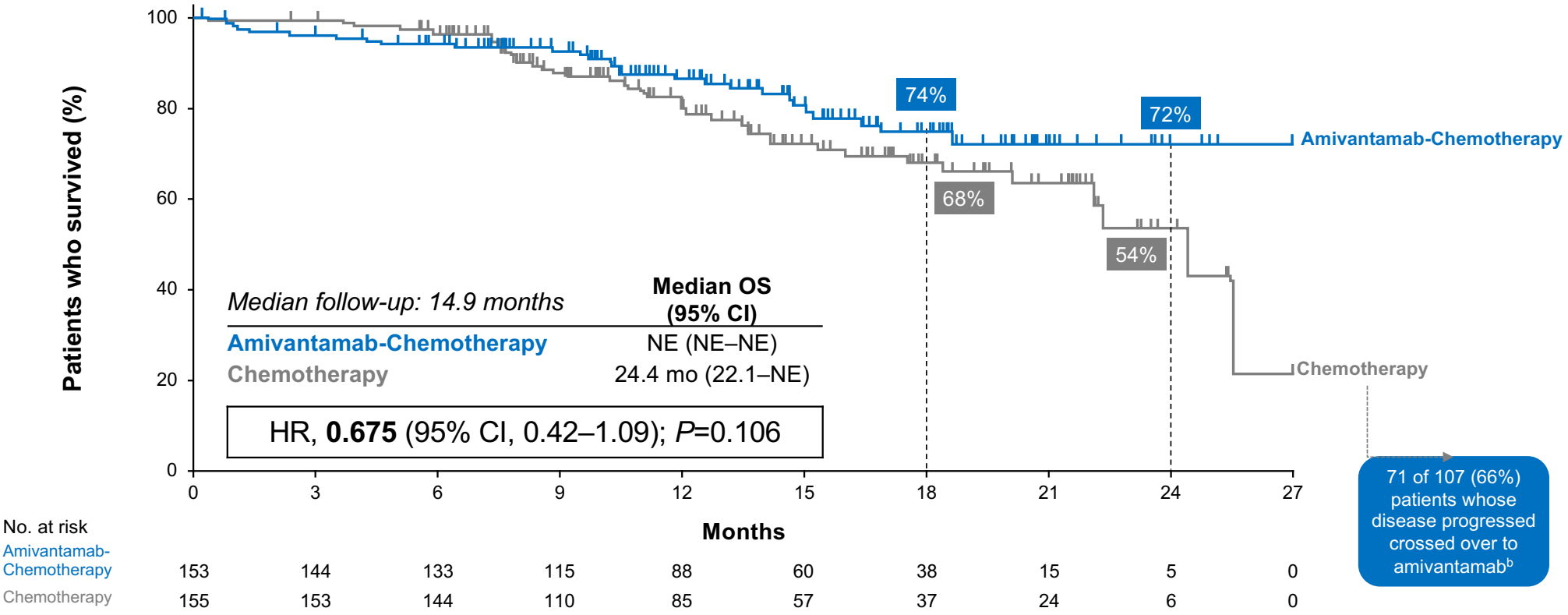
[a]PFS2 is defined from the time of randomization until the time of second objective disease progression (based on investigator assessment) or death, whichever comes first, after the initiation of first subsequent anticancer therapy.

[b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; PFS, progression-free survival; pt, patient.

# PAPILLON: Interim Overall Survival[a]

*Amivantamab-chemotherapy shows trend in reducing risk of death by over 30%*




[a]There were 70 deaths in the study at the time of the prespecified interim OS analysis, which represents 23% of all randomized patients and 33% of the ~210 projected deaths for the final OS analysis. [b]A total of 71 patients (65 patients as part of the crossover arm plus an additional 6 patients off-protocol) received second-line amivantamab monotherapy out of 107 chemotherapy-randomized patients with disease progression.

CI, confidence interval; HR, hazard ratio; mo, months; NE, not estimable; OS, overall survival.

# PAPILLON: Summary of Adverse Events (AEs)

| | Amivantamab-Chemotherapy (n=151) | Chemotherapy (n=155) |
|---|---|---|
| Median treatment duration, months (range) | 9.7 (0.1–26.9) | 6.7 (0–25.3) |
| No. of chemotherapy cycles, median (range) | | |
| Carboplatin | 4 (1–4) | 4 (1–5) |
| Pemetrexed | 13 (1–34) | 10 (1–37) |

| **Treatment-emergent AEs, n (%)** | Amivantamab-Chemotherapy (n=151) | Chemotherapy (n=155) |
|---|---|---|
| Any AEs | 151 (100) | 152 (98) |
| Grade ≥3 AEs | 114 (75) | 83 (54) |
| Serious AEs | 56 (37) | 48 (31) |
| AEs leading to death | 7 (5) | 4 (3) |
| Any AE leading to treatment: | | |
| Interruptions of any agent | 104 (69) | 56 (36) |
| Related interruptions of amivantamab | 63 (42) | – |
| Reductions of any agent | 73 (48) | 35 (23) |
| Related reductions of amivantamab | 54 (36) | – |
| Discontinuations of any agent | 36 (24) | 16 (10) |
| Related discontinuations of amivantamab | 10 (7) | – |
| Discontinuations of all study agents due to AEs | 12 (8) | 12 (8) |

- Amivantamab-chemotherapy had a longer median treatment duration than chemotherapy (9.7 vs 6.7 months, respectively)
- Serious AEs and AEs leading to death were comparable between arms
- Similar rates of discontinuation of all study agents due to AEs across arms
- Treatment-related discontinuations of amivantamab were low (7%)

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# PAPILLON: Safety Profile

| Most common AEs of any cause by preferred term (≥20%), n (%) | Amivantamab-Chemotherapy (n=151) | | Chemotherapy (n=155) | |
|---|---|---|---|---|
| | All grades | Grade ≥3 | All grades | Grade ≥3 |
| **Associated with EGFR inhibition** | | | | |
| Paronychia | 85 (56) | 10 (7) | 0 | 0 |
| Rash | 81 (54) | 17 (11) | 12 (8) | 0 |
| Dermatitis acneiform | 47 (31) | 6 (4) | 5 (3) | 0 |
| Stomatitis | 38 (25) | 2 (1) | 9 (6) | 0 |
| Diarrhea | 31 (21) | 5 (3) | 20 (13) | 2 (1) |
| **Associated with MET inhibition** | | | | |
| Hypoalbuminemia | 62 (41) | 6 (4) | 15 (10) | 0 |
| Peripheral edema | 45 (30) | 2 (1) | 16 (10) | 0 |
| **Other** | | | | |
| Neutropenia | 89 (59) | 50 (33) | 70 (45) | 35 (23) |
| Anemia | 76 (50) | 16 (11) | 85 (55) | 19 (12) |
| Infusion-related reaction | 63 (42) | 2 (1) | 2 (1) | 0 |
| Constipation | 60 (40) | 0 | 47 (30) | 1 (1) |
| Leukopenia | 57 (38) | 17 (11) | 50 (32) | 5 (3) |
| Nausea | 55 (36) | 1 (1) | 65 (42) | 0 |
| Thrombocytopenia | 55 (36) | 15 (10) | 46 (30) | 16 (10) |
| Decreased appetite | 54 (36) | 4 (3) | 43 (28) | 2 (1) |
| Alanine aminotransferase increased | 50 (33) | 6 (4) | 56 (36) | 2 (1) |
| Aspartate aminotransferase increased | 47 (31) | 1 (1) | 51 (33) | 1 (1) |
| COVID-19 | 36 (24) | 3 (2) | 21 (14) | 1 (1) |
| Hypokalemia | 32 (21) | 13 (9) | 13 (8) | 2 (1) |
| Vomiting | 32 (21) | 5 (3) | 29 (19) | 1 (1) |

- EGFR- and MET-related AEs were increased with amivantamab-chemotherapy, primarily grade 1-2
- Chemotherapy-associated hematologic and GI toxicities were comparable except for neutropenia
- Neutropenia was transient; majority of events were not serious, with low rates of discontinuations
- Pneumonitis was reported in 4 (3%) patients in the amivantamab-chemotherapy arm

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AE, adverse event; EGFR, epidermal growth factor receptor; GI, gastrointestinal.

# PAPILLON: Conclusions

PAPILLON PAPILLON

## *EGFR* exon20ins

Associated with primary resistance to standard EGFR TKIs and confer poor prognosis[1]

## 1L therapeutic landscape

ESMO 2023 guidelines recommend PBC ± ICI.[2] Targeted treatment options are currently under investigation[3–5]

## 1L amivantamab + ChT

Demonstrated improved PFS vs ChT in the PAPILLON study.[3] Safety profile was consistent with that of each individual agent[3]

## 2L therapeutic landscape

Amivantamab is approved in 2L.[2] Novel EGFR TKIs are currently under investigation[6]

## CNS metastases

Constitutes a major clinical issue, highlighting the need for more CNS penetrant options in the future[7]

1. Wang F, et al. *Transl Cancer Res*. 2020;9:2982–91; 2. Hendriks LE, et al. *Ann Oncol*. 2023;34:339–57; 3. Girard N, et al. Presented at ESMO 2023: LBA5. Abstract; 4. Han B, et al. Presented at WCLC 2023: OA03.04; 5. Yang J C-H, et al. Presented at ESMO 2023: 1325P; 6. Low JL, et al. *Ther Adv Med Oncol*. 2023;15:1–19; 7. Meador CB, et al. *Cancer Discov*. 2021;11:2145–57.

1/2L, first/second-line; ChT, chemotherapy; CNS, central nervous system; ESMO, European Society for Medical Oncology; exon20ins, exon 20 insertion; ICI, immune checkpoint inhibitor; PBC, platinum-based chemotherapy.