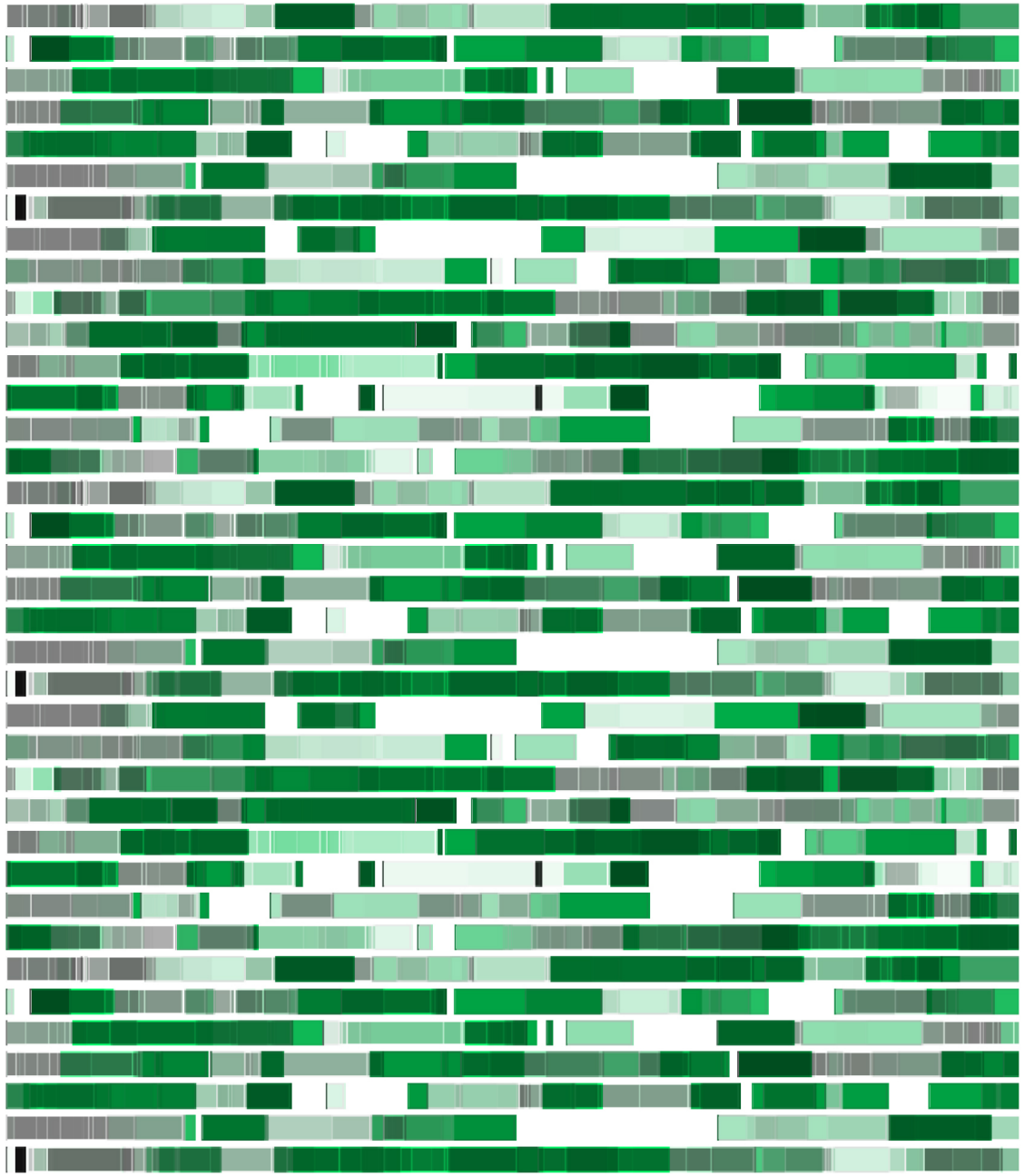
# III JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN:

A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 12 Y 13 DE FEBRERO DE 2026



## Nuevas estrategias para la enfermedad EGFR

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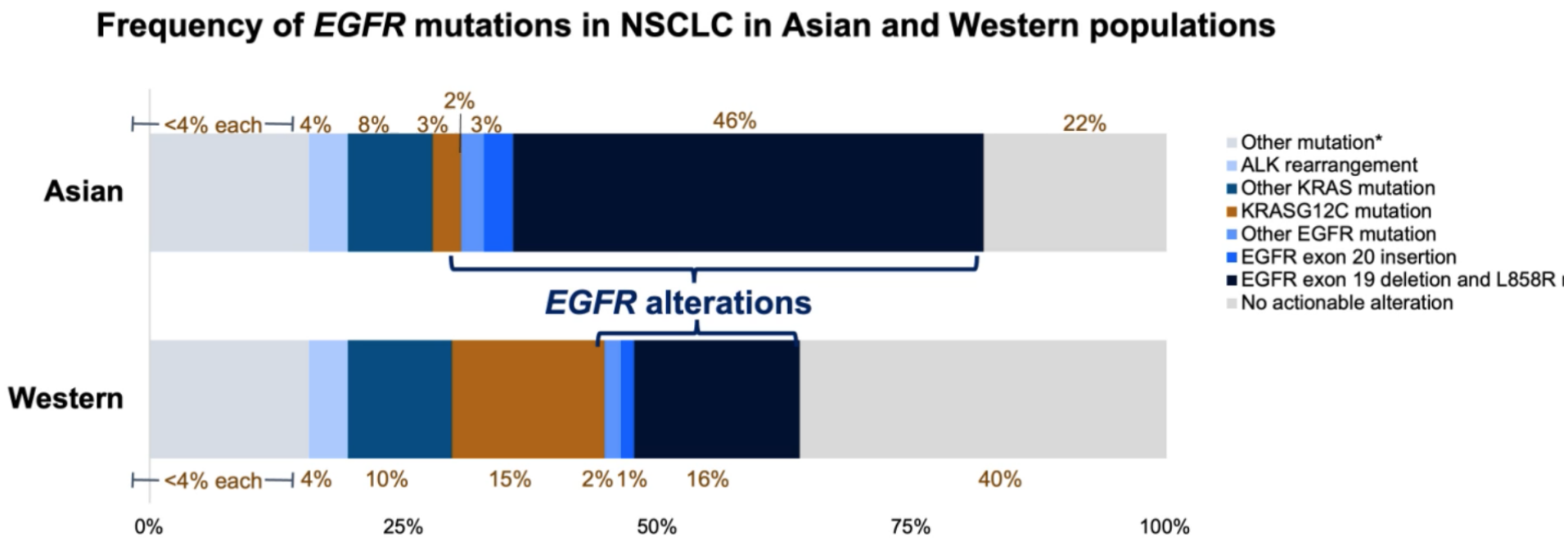
Organizador por:

HENDERE HEALTHCARE

# Conflictos de interés

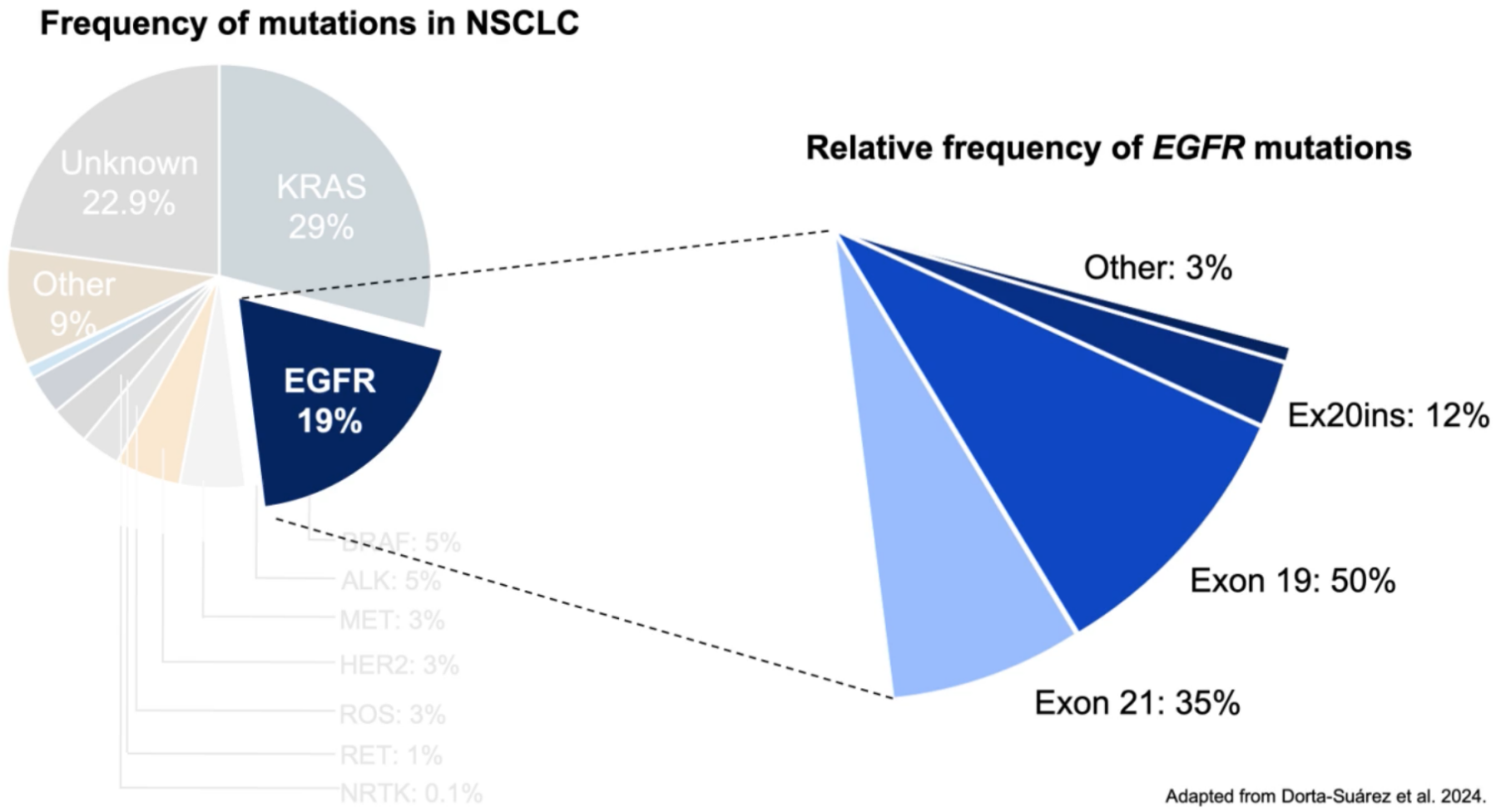
- Advisory role: Boehringer, MSD, BMS, Takeda, Merck, GSK
- Speaker: AstraZeneca, BMS, Boehringer, Merck, Bayer, Eisai, Regeneron
- Travel grant: MSD, AstraZeneca, BMS

# *EGFR* mutations in NSCLC are heterogeneous




*Other includes NTRK rearrangement, RET rearrangement, BRAFV600E mutation, HER2 exon 20 insertion mutation, ROS1 rearrangement, MET exon 14 mutation, ALK rearrangement.
NSCLC, non-small cell lung cancer.
Tan & Tan. J Clin Oncol. 2022;40(6):611-625.

# *EGFR* mutations in NSCLC are heterogeneous

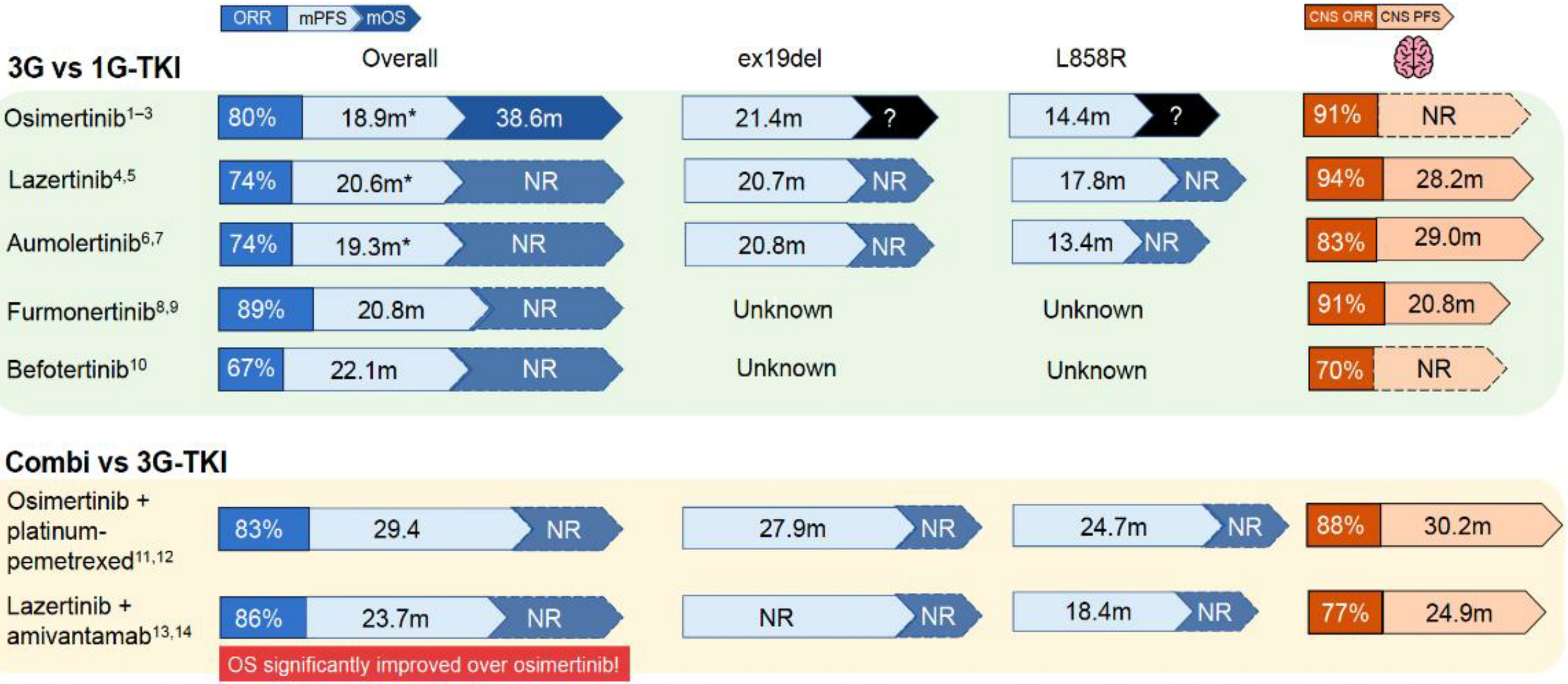



Adapted from Dorta-Suárez et al. 2024.

Dorta-Suárez M, et al. Cancer Treat Rev. 2024;124:102671.

# First-line treatment for *EGFR*-mutated advanced NSCLC

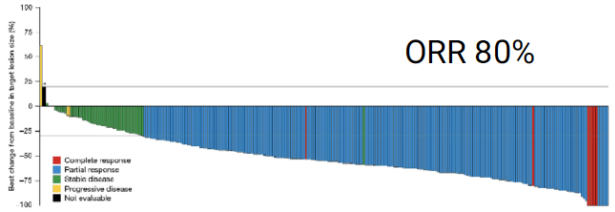
# Efficacy of first-line treatment options in advanced *EGFR*-mutated NSCLC

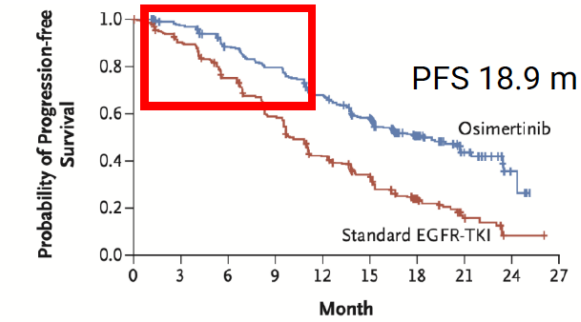



Published in: Stephanie P.L. Saw; Xiuning Le; Lizza E.L. Hendriks; Jordi Remon Am Soc Clin Oncol Educ Book 2024 04-1

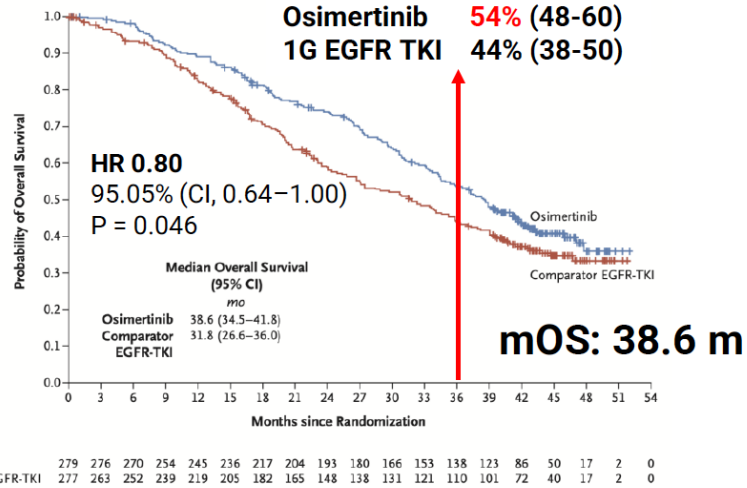
# Frontline strategies for *EGFR*-mutated NSCLC

## Early progressors




## Current SoC: Osimertinib



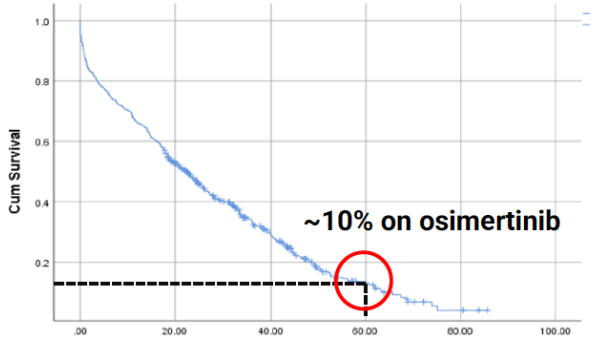

**Patient's continuing to receive 1L drug (%)**

| | Osimertinib | 1G TKI |
|---|---|---|
| 12 m | 70% | 47% |
| 24 m | 42% | 16% |
| 36 m | 28% | 9% |

## Few long term responders

**FLAURA**
12.9% remain on osi > 4.5 yrs

**NCCS data**
n=506, Stage IV, 2018-2023

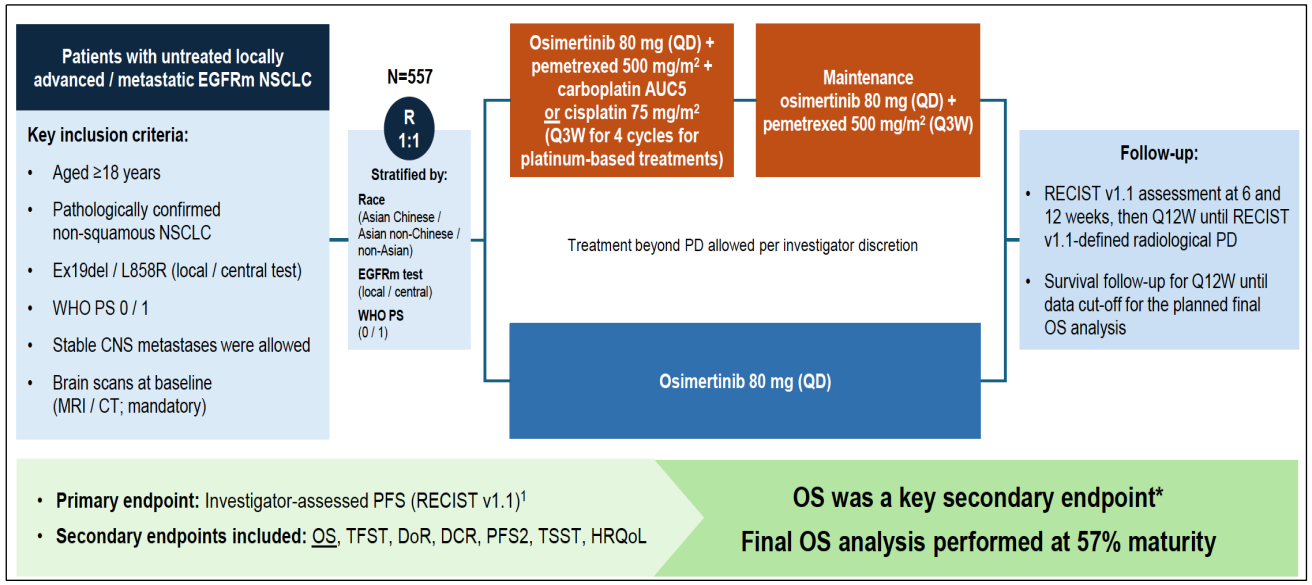



*Dr Tan Wei Chong , NCCS Data Science Core*

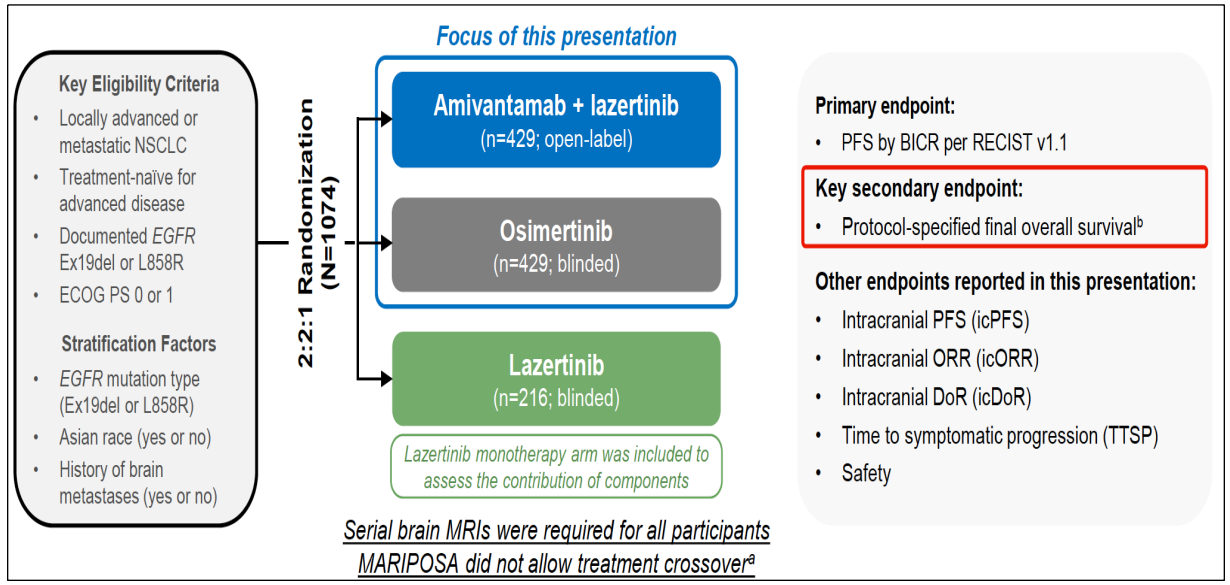
Soria et al. NEJM 2018; Ramalingam et al. NEJM 2020; Garassino et al. Lung Cancer 2025

# Advanced *EGFR*-mutated NSCLC: New first-line current options

## FLAURA 2




## MARIPOSA

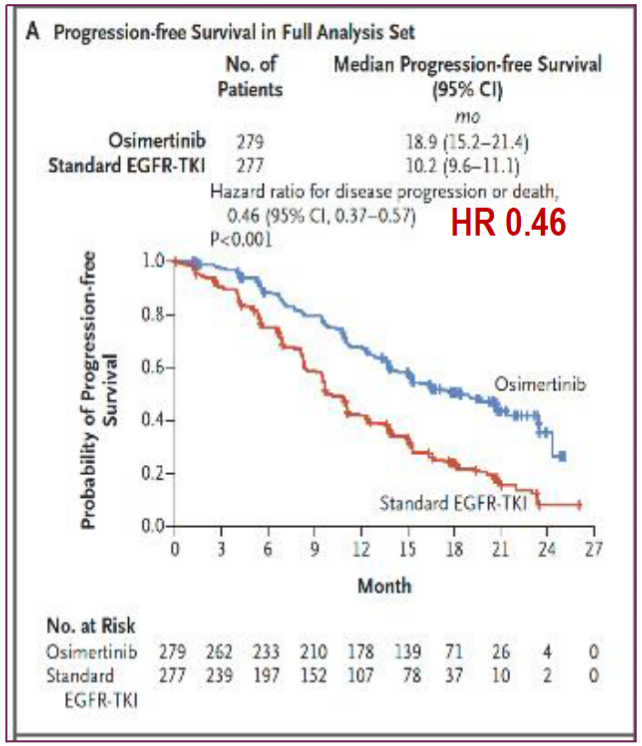



Planchard D et al, NEJM 2023, Jänne PA et al. NEJM 2026;
Cho BC et al, NEJM 2024; Yang JCH et al, NEJM 2025

# Combinations are superior in PFS (primary endpoint)

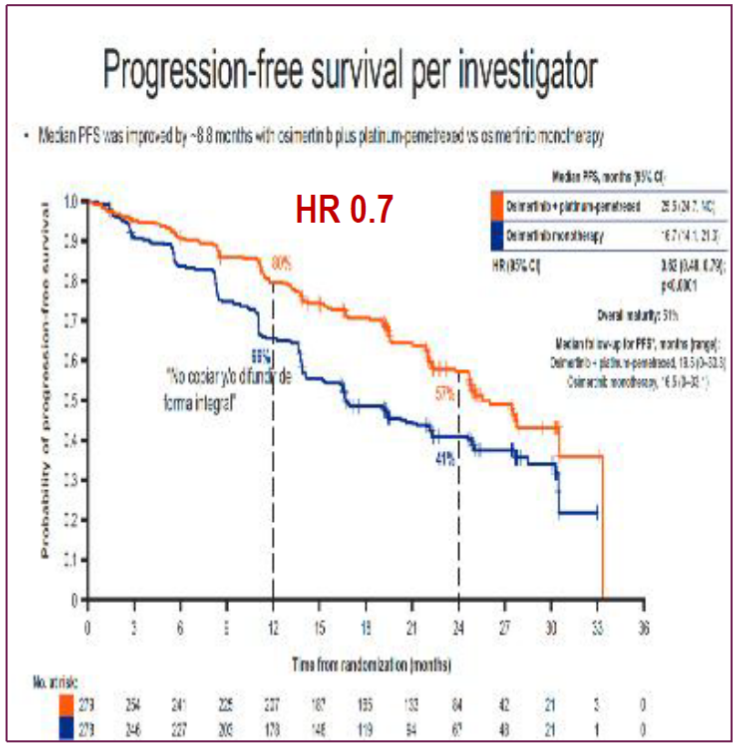
**FLAURA: mPFS 18.9 mo**

Osimertinib vs 1G TKI



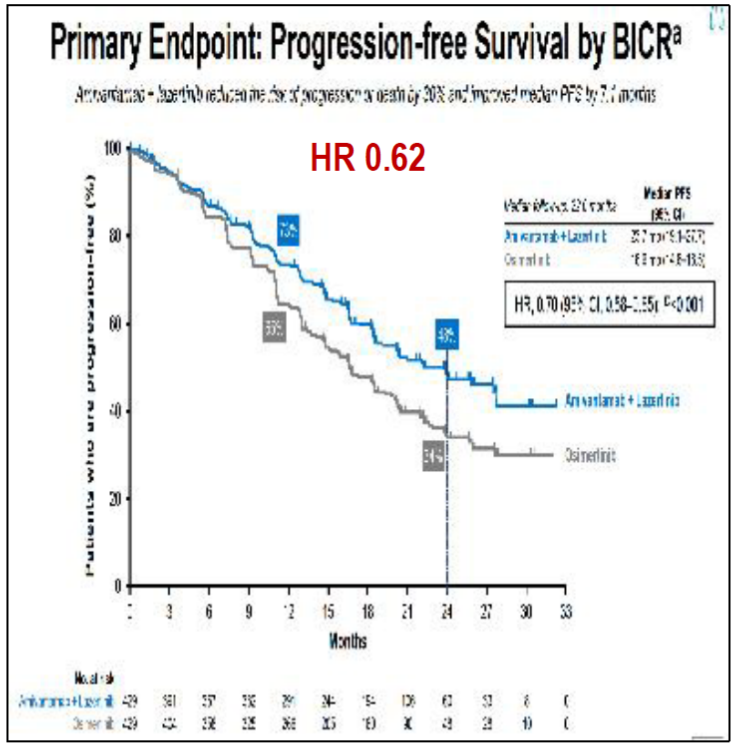

**FLAURA 2: mPFS 25.5 mo**

Osimertinb + PB CT vs Osimertinib




**MARIPOSA: mPFS 23.7 mo**

Amivantamab + Lazertinb vs Osimertinib

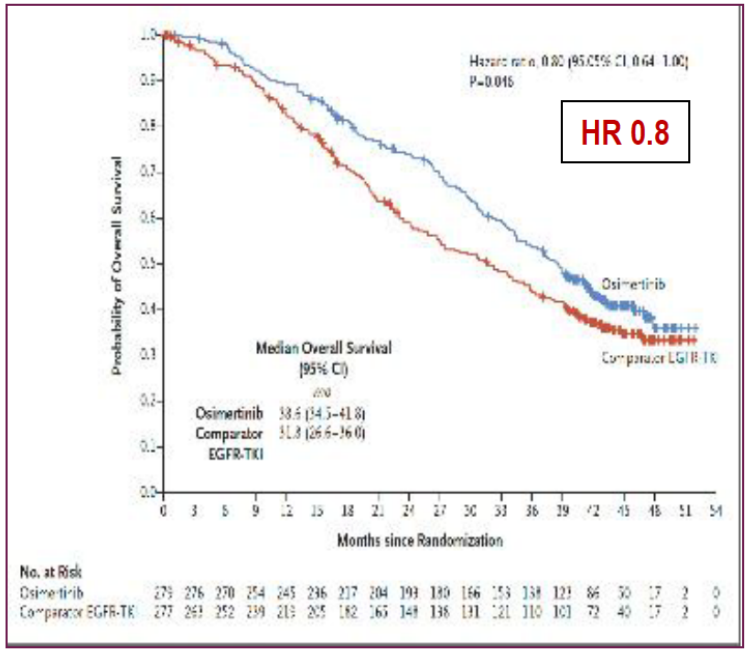



Soria JC et al, NEJM 2018; Ramalingam SS et al, NEJM 2019; Planchard D et al, NEJM 2023, Jänne PA et al, NEJM 2026; Cho BC et al, NEJM 2024; Yang JCH et al, NEJM 2025

# PFS benefit translated into OS advantage

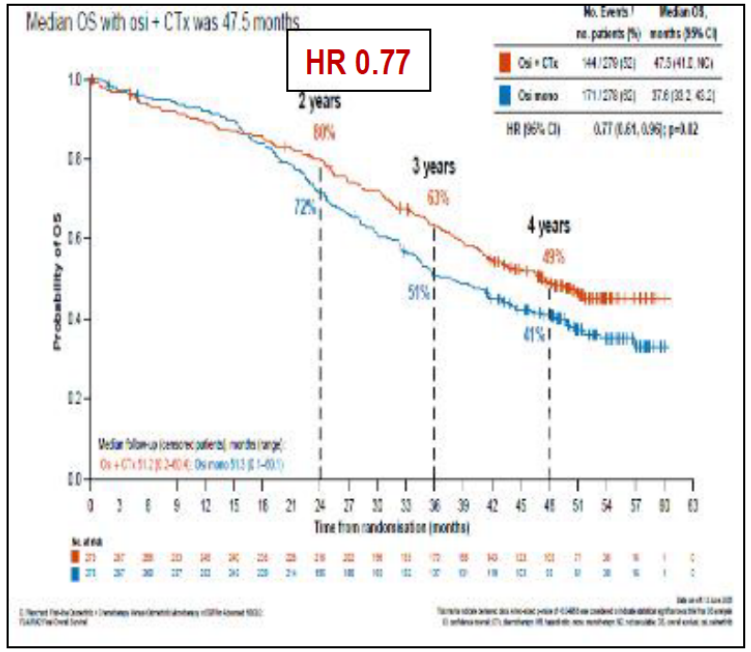
**FLAURA: mOS 39 mo**

Osimertinib vs 1G TKI



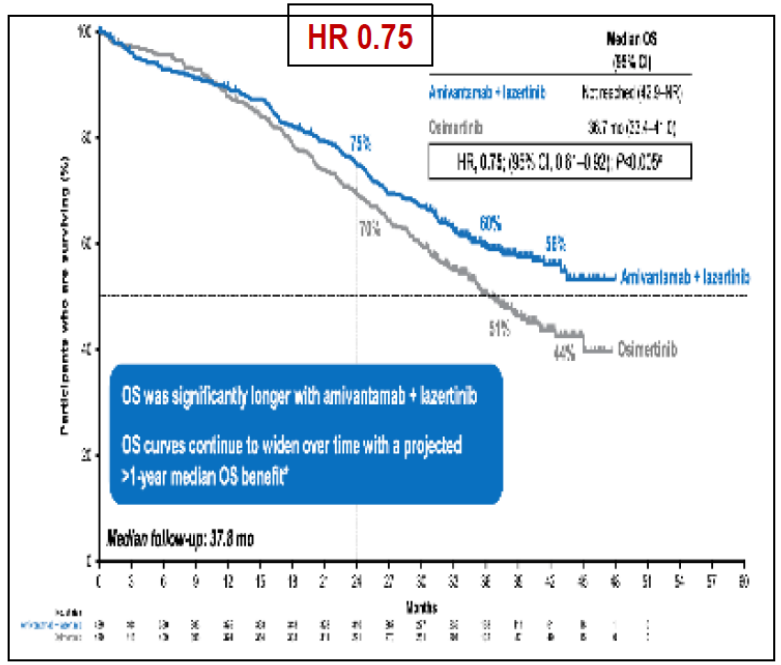

**FLAURA 2: mOS 47.5 mo**

Osimertinb + PB CT vs Osimertinib




**MARIPOSA: mOS NR**

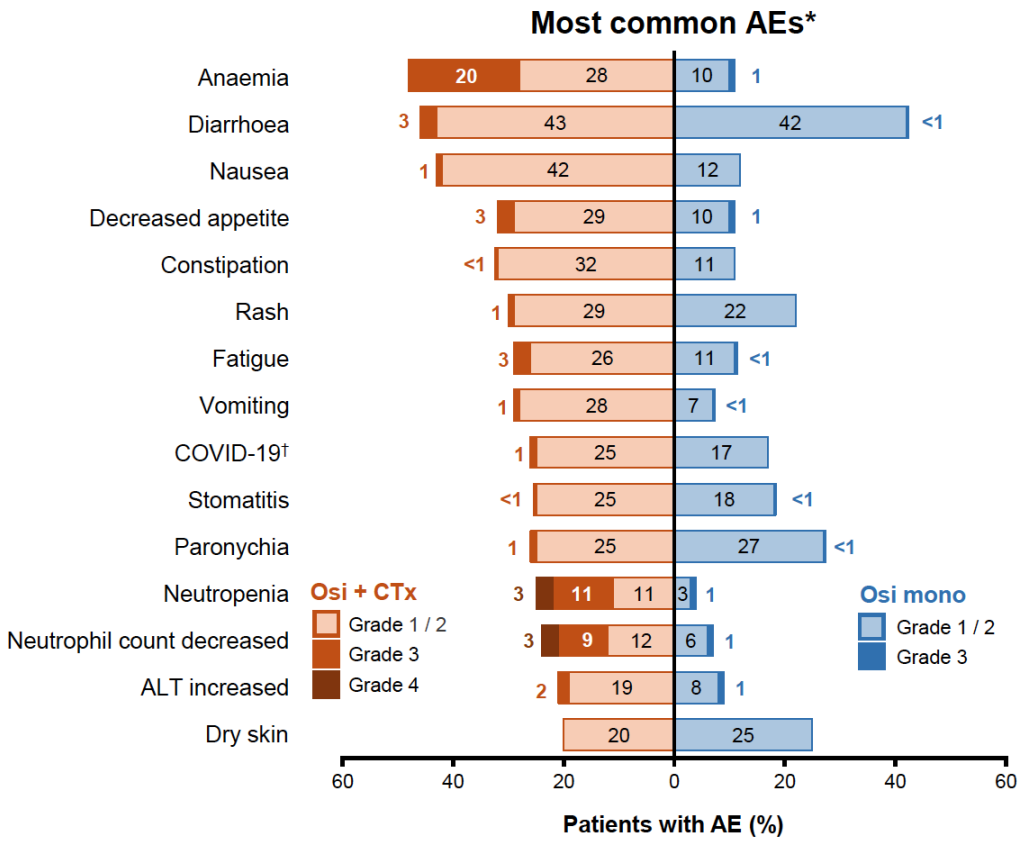
Amivantamab + Lazertinb vs Osimertinib




Soria JC et al, NEJM 2018; Ramalingam SS et al, NEJM 2019;
Planchard D et al, NEJM 2023, Jänne PA et al, NEJM 2026;
Cho BC et al, NEJM 2024; Yang JCH et al, NEJM 2025

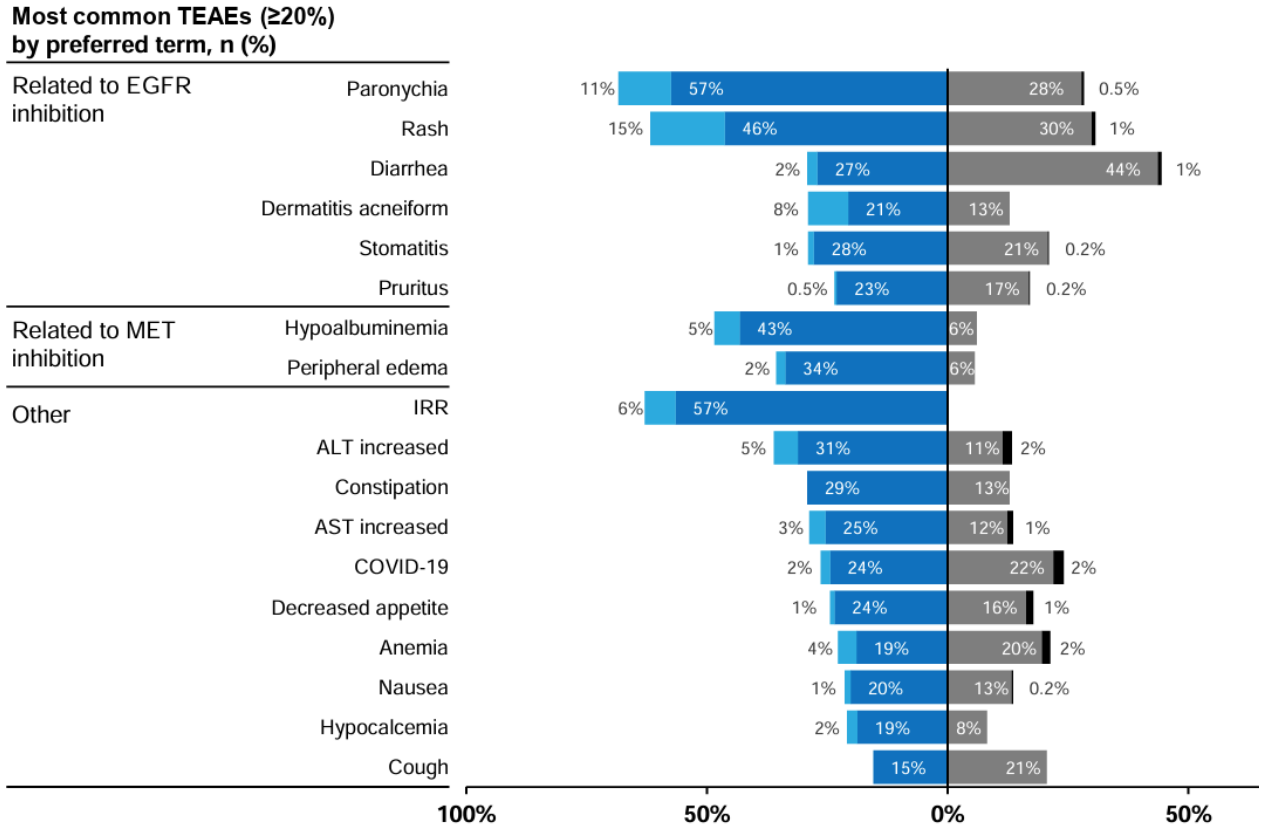
# Benefit with combos, at the cost of higher toxicity

## FLAURA 2 study




Jänne P et al. WCLC 2023, Planchard D. NEJM 2024

## MARIPOSA study




Passaro A et al. Ann Oncol 2023

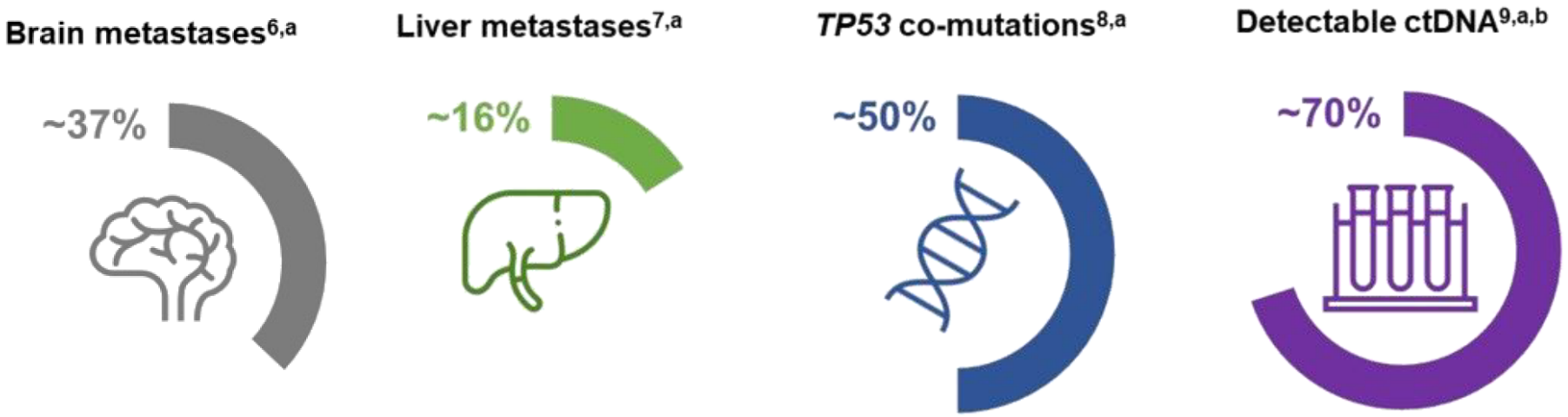
# Combinations have increased toxicities

| | AE of interest | Osimertinib + Pemetrexed + Platinum | Amivantamab + Lazertinib | |
|---|---|---|---|---|
| Chemo-related | Anaemia (≥G3) | 46% (20%) | 23% (4%) | |
| | Neutropenia (≥G3) | 25% (14%) | Not reported | |
| | Thrombocytopenia (≥G3) | 18% (7%) | Not reported | |
| | Nausea (≥G3) | 43% (1%) | 21% (1%) | |
| EGFR-inhibition | Diarrhoea (≥G3) | 43% (3%) | 29% (2%) | EGFR-inhibition |
| | Rash | 28% (<1%) | 61% (15%) | |
| | Paronychia | 24% (1%) | 68% (11%) | |
| | Peripheral edema | 0 | 36% (2%) | MET-inhibition |
| | Infusion-related reaction (≥G3) | 0 | 63% (6%) | Role of SC formulation? |
| | Venous thromboembolism (≥G3) | 0 | 37% (11%) | Anticoagulation prophylaxis for first 4m |

Jänne P et al. WCLC 2023, Planchard D. NEJM 2024

Passaro A et al. Ann Oncol 2023

# High risk features in metastatic EGFR-mutant NSCLC

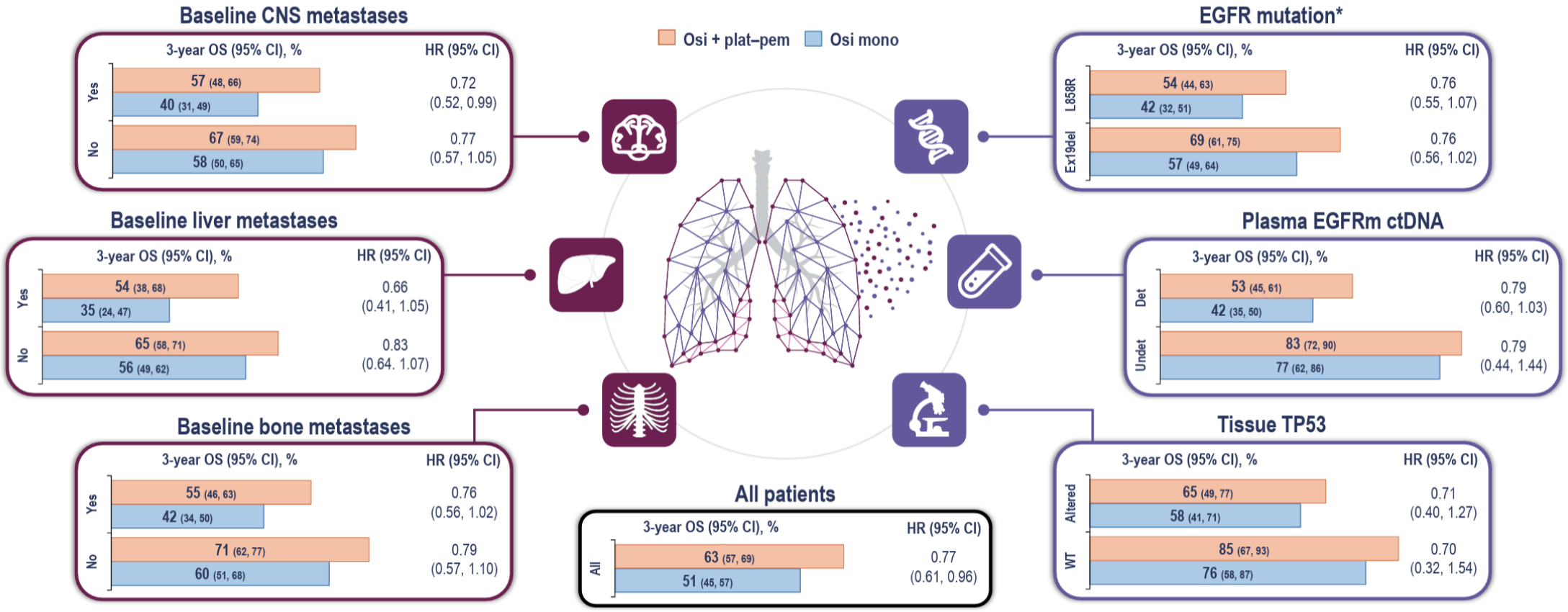



- Any single high-risk feature requires the discussion of combination treatment
- Only about 10-15% patients have no high-risk features.

**Patients with risk factors treated with current therapies continue to have poor survival and would benefit from upfront treatment with more effective therapies.**

Chua KP et al. CCR 2022; Sabari JK et al. JTO 2025; Janne P et al. AACR 2024

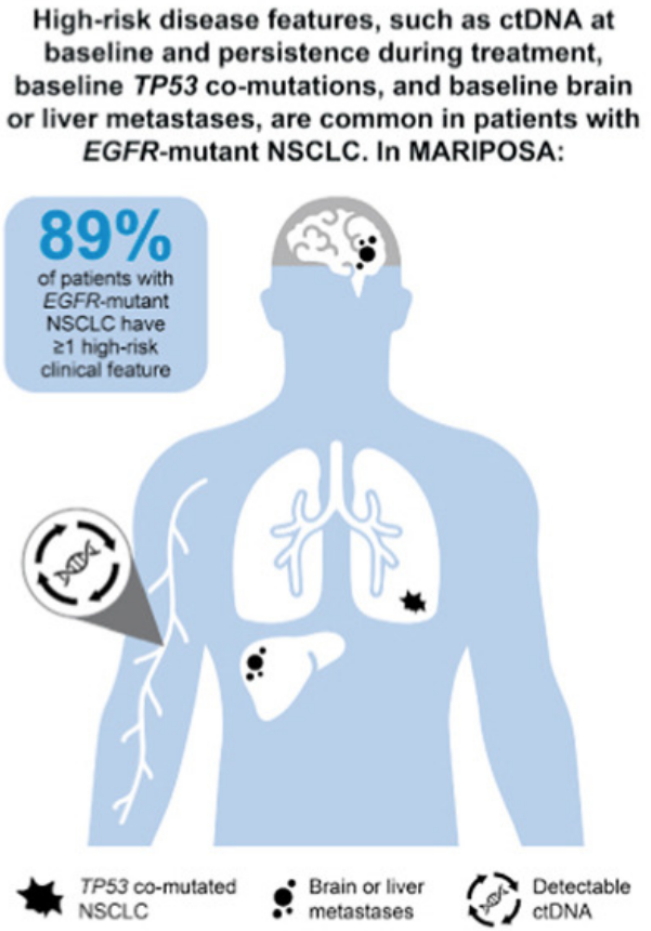
# FLAURA 2: OS by baseline prognostic factors

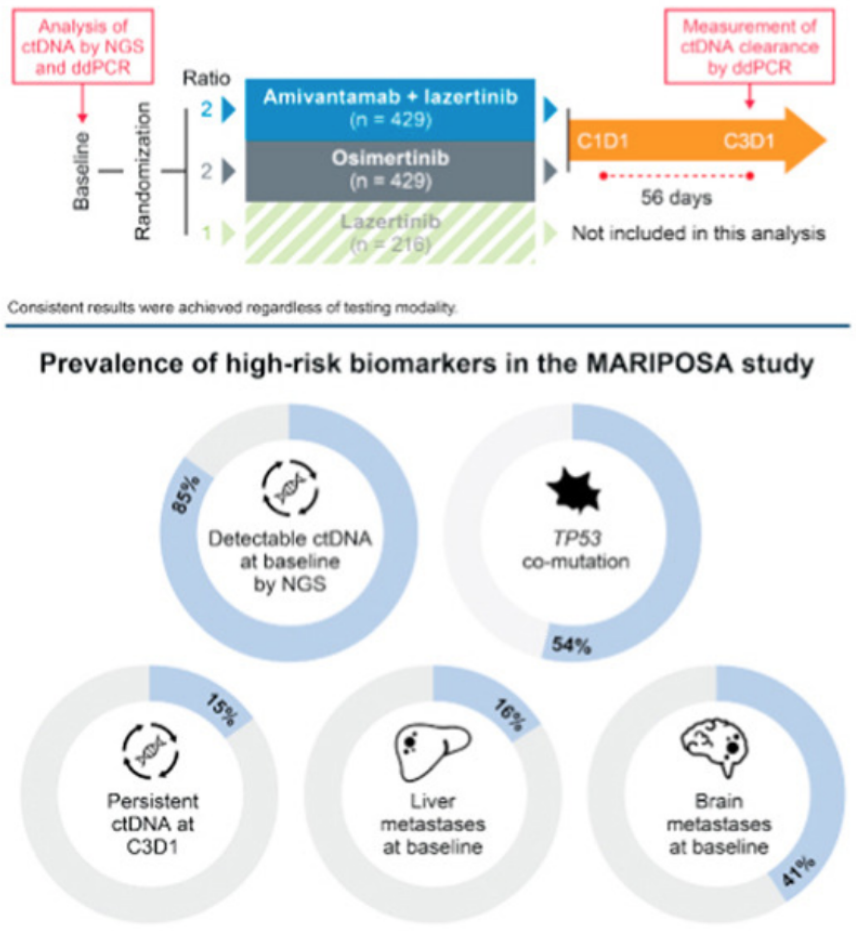


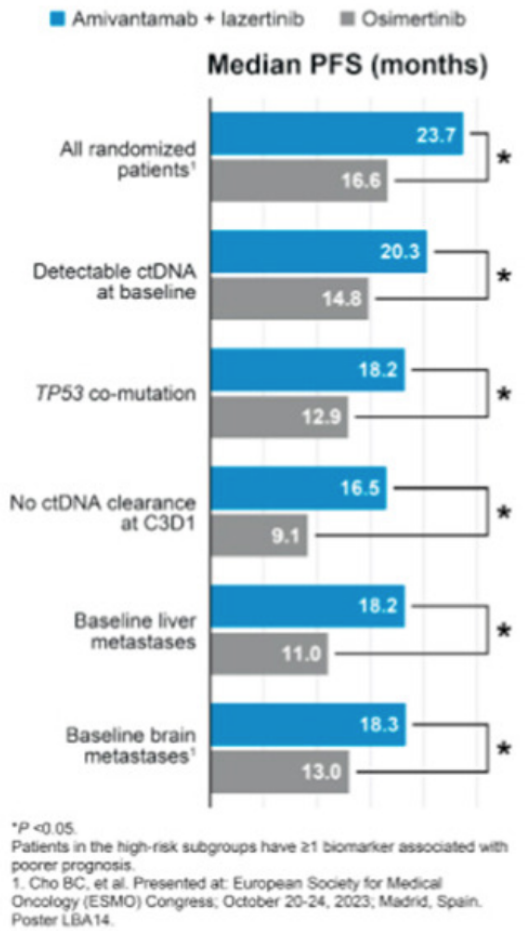

**An OS benefit with osimertinib plus platinum-pemetrexed versus osimertinib monotherapy was consistently observed regardless of baseline prognostic factors**

Jänne P et al. WCLC 2025

# Amivantamab plus lazertinib vs osimertinib in EGFR-mutant advanced NSCLC



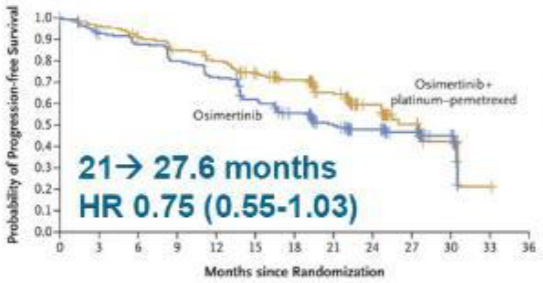




Felip E et al. Ann Oncol 2024

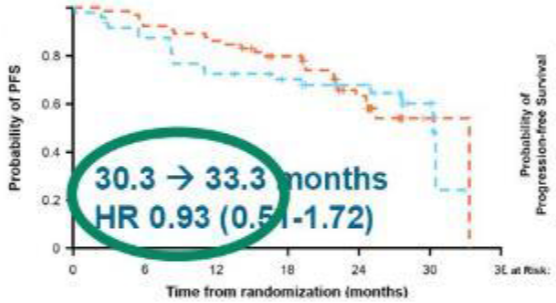
# MARIPOSA and FLAURA 2 outcomes in lower risk populations

## FLAURA2

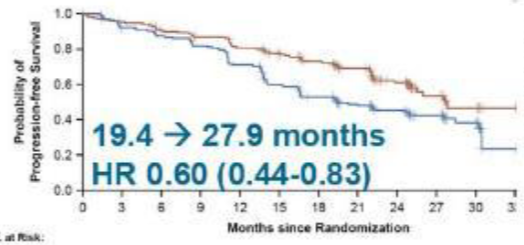
### Without Brain Metastases



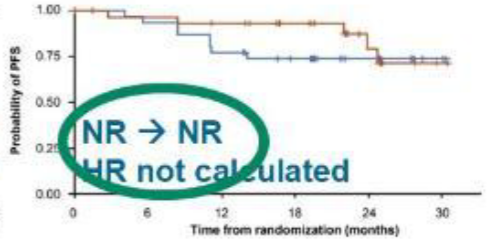

### Plasma EGFR Undetectable




### EGFR Exon 19 Deletions

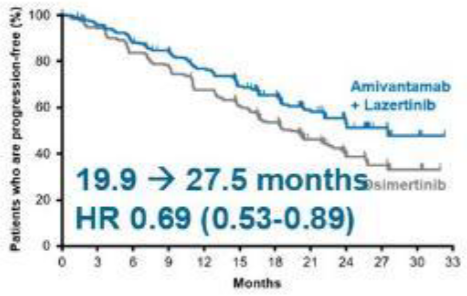



### TP53 Wild Type



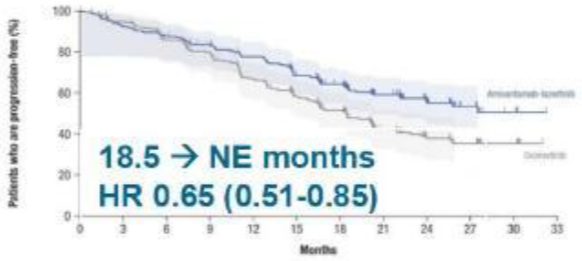

## MARIPOSA

### Without Brain Metastases




### Plasma EGFR Undetectable

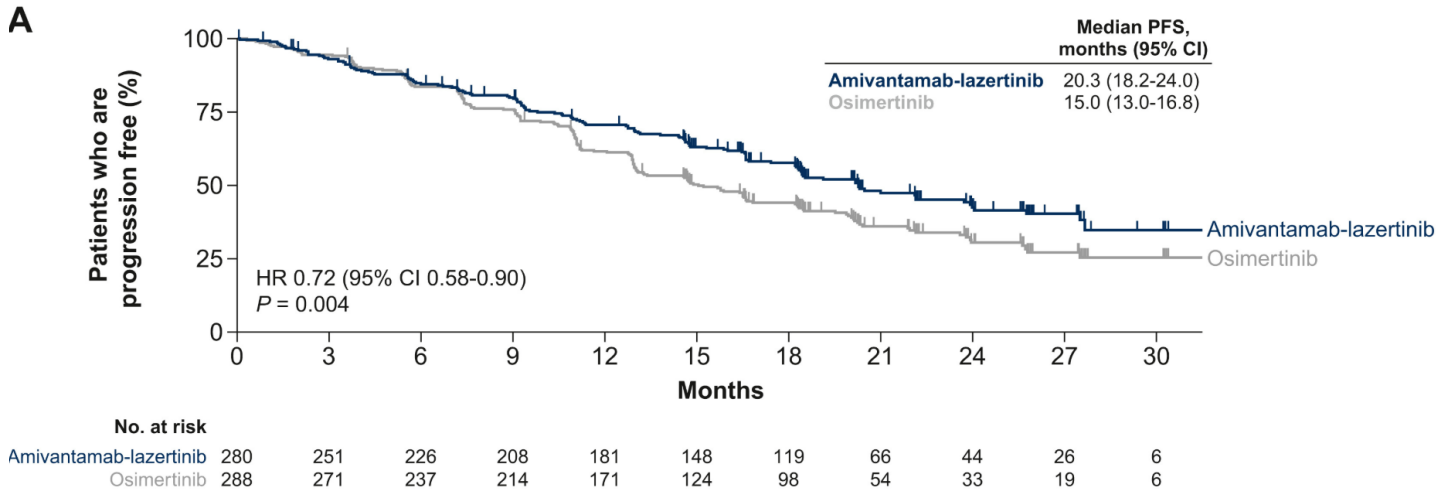

### EGFR Exon 19 Deletions



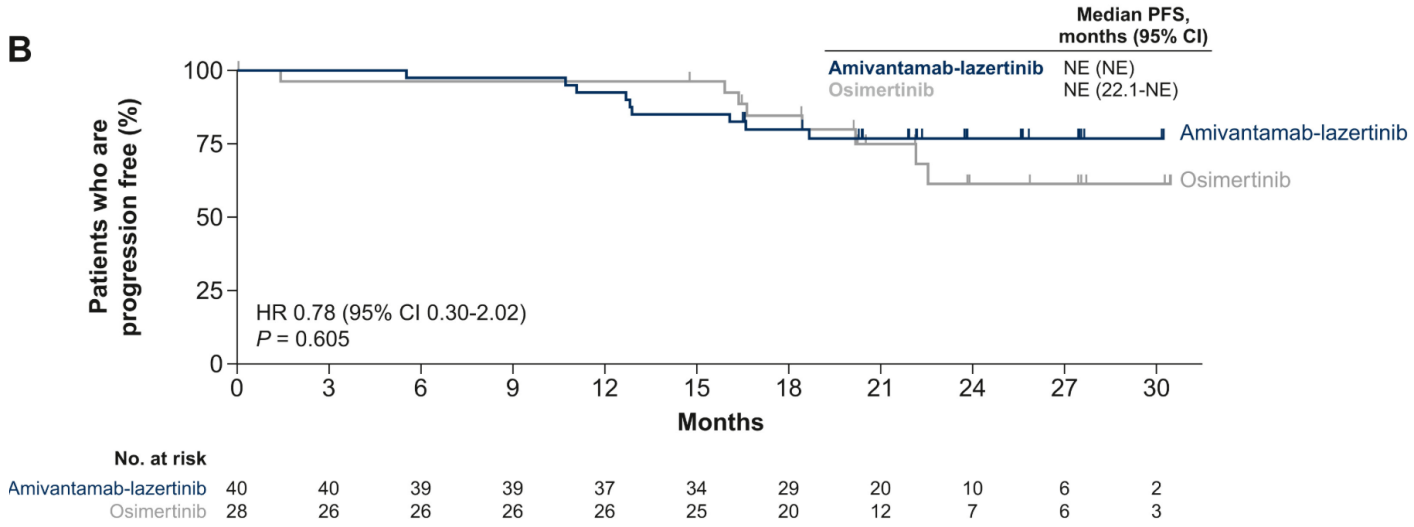

### TP53 Wild Type


Planchard D et al. NEJM 2023; Janne P et al. AACR 2024; Cho BC et al. ESMO 2023 LBA14; Felip E et al. ASCO 2024; Cho BC et al. NEJM 2024

# MARIPOSA: PFS for patients with and without high-risk features



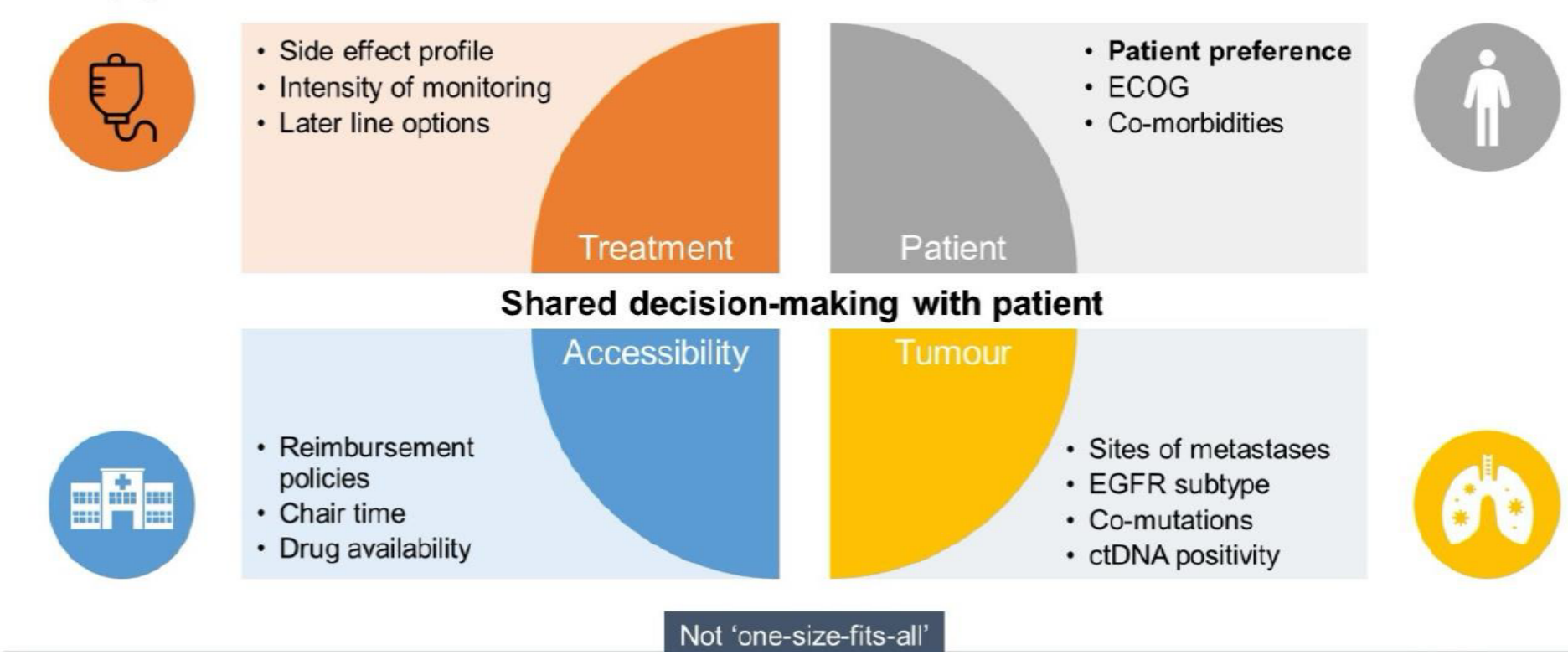

**With high risk features**




**Without high risk features**

Felip E et al. Ann Oncol 2024

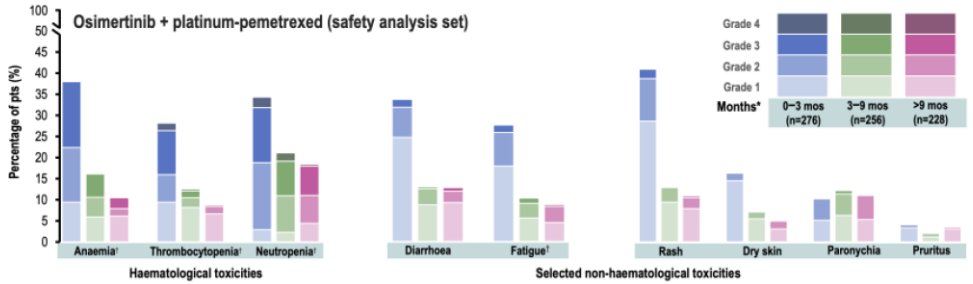
# Key considerations in choosing the treatment approach in metastatic setting



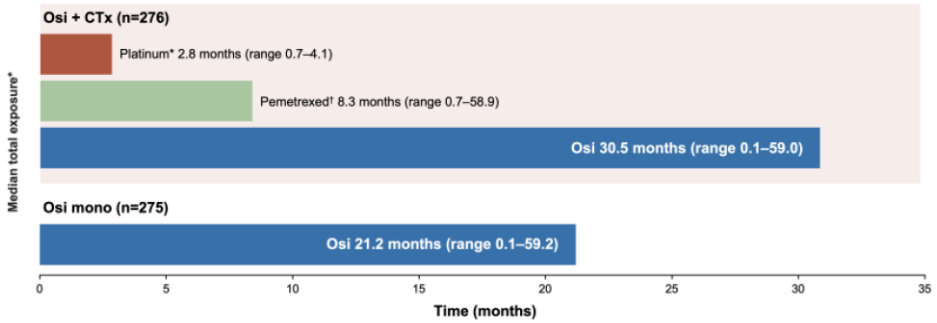

Stephanie P.L. Saw; Xiuning Le; Lizza E.L. Hendriks; Jordi Remon Am Soc Clin Oncol Educ Book 2024 04-1

# Ongoing supportive care with combination therapy

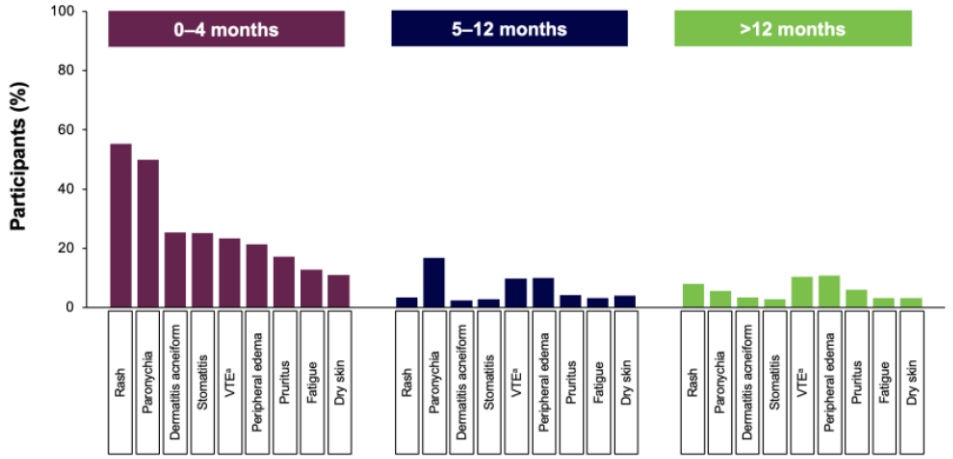
## Osimertinib-platinum pemetrexed



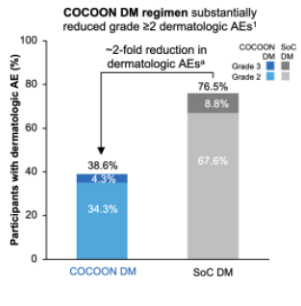

1. **Toxicities typically worse in initial 4 months**
2. **Initial chemotherapy can forestall resistance**
   - Pemetrexed-platinum: 2.8 m (0.7 – 4.1)
   - Maintenance pemetrexed: 8.3 m (range 0.7 – 58.9)



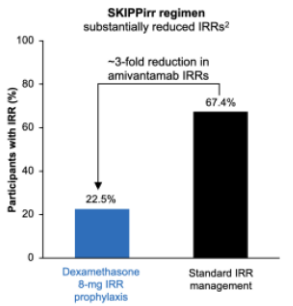

## Amivantamab-lazertinib



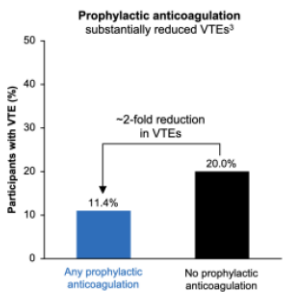

### COCOON




### SKIPPirr




### VTE prophylaxis




Planchard et al. WCLC 2025; Yang et al. ELCC 2025

# Criterios para la selección de la primera línea de tratamiento

| | MARIPOSA | FLAURA 2 |
|---|---|---|
| *EGFRL858R* | HR 0.78 | HR 0.63 |
| *EGFRDel19* | HR 0.65 | HR 0.60 |
| M1 SNC | HR 0.69 | HR 0.47 |
| Sin M1 SNC | HR 0.69 | HR 0.66 |
| M1 hepáticas | HR 0.58 | HR 0.63 |
| Sin M1 hepáticas | HR 0.74 | HR 0.66 |
| co-mutación TP53 | HR 0.65 | HR 0.57 |
| Sin co-mutación TP53 | HR 0.75 | No calculable |
| ctDNA basal positivo | HR 0.68 | HR 0.60 |
| ctDNA basal negativo | HR 0.72 | HR 0.93 |
| No aclaramiento del ctDNA | HR 0.64 | HR 0.62 |
| Aclaramiento del ctDNA | HR 0.49 | HR 0.51 |

*Cortesía Dr Remon. Planchard NEJM 2023; Jänne JCO 2023; Jänne AACR 2024; Cho NEJM 2024; Felip ASCO 2024; Felip AoO2024; Yang WCLC 2024; Valdiviezo WCLC 2024*

## Combinaciones FLAURA 2/ MARIPOSA

- Buen PS
- Sin comorbilidades que limitan el uso de combinaciones
- M1 en SNC u otros factores clínicos de riesgo
- Presencia de TP53
- ctDNA positivo basal

## Osimertinib monoterapia

- Bajo PS
- Comorbilidades que limitan el uso de combinaciones
- No M1 en SNC u otros factores clínicos de riesgo
- Ausencia de TP53
- ctDNA negativo basal

Morán T. SEOM 2025

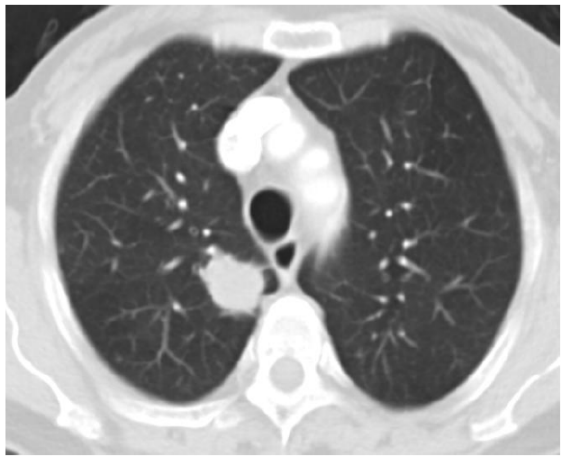
# Selected first-line *EGFR*-mutated NSCLC trials

| | n | Phase | Selection | Intervention | Target/ payload | Primary Endpoint |
|---|---|---|---|---|---|---|
| **All comers** | | | | | | |
| TROPION-Lung14 [NCT06350097] | 582 | Phase III | EGFR mutated | Osimertinib ± Datopotamab deruxtecan | Trop2-Topo-1 | PFS |
| Temab-A + Osimertinib [NCT07005102] | 694 | Phase II/III | EGFR mutated | Osimertinib ± Telisotuzumab adizutecan | cMET-Topo-1 | PFS |
| BL-B01D1 [NCT06838273] | 696 | Phase III | EGFR mutated | Osimertinib ± BL-B01D1 | EGFR-HER3 Ed-04 Topo-1 | PFS |
| OSTARA [NCT05801029] | 80 | Phase II | EGFR mutated | Osimertinib + amivantamab | | ORR, PFS |
| **Selected molecular subsets** | | | | | | |
| TOP [NCT04695925] | 291 | Phase III | Concurrent EGFR and TP53 mutation | Osimertinib ± Pemetrexed-carboplatin | | PFS |
| ACROSS1 [NCT04500704] | 166 | Phase III | EGFR mutation with concomitant co-drivers | Aumolertinib ± chemotherapy | | PFS |
| ACROSS2 [NCT04500717] | 126 | Phase III | EGFR mutation with tumour suppressor gene mutation | Aumolertinib ± chemotherapy | | PFS |
| SHEDDER (Risk adapted) [NCT04410796] | 571 | Phase II | ctDNA detected after 3 cycles of osimertinib | Osimertinib ± chemotherapy | | PFS |

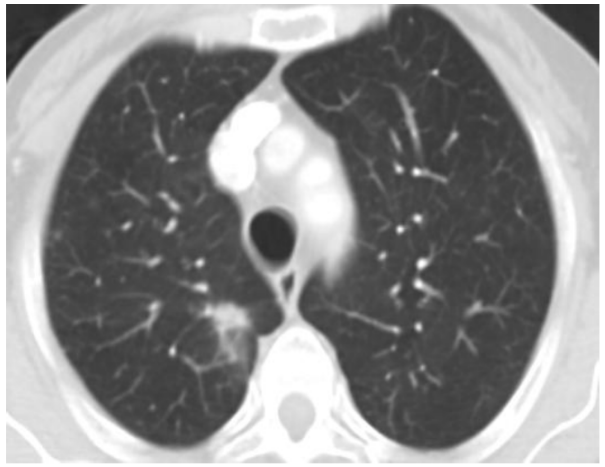
*Slide courtesy of Dr Stephanie Saw*

# Managing progression in *EGFR*-mutant NSCLC

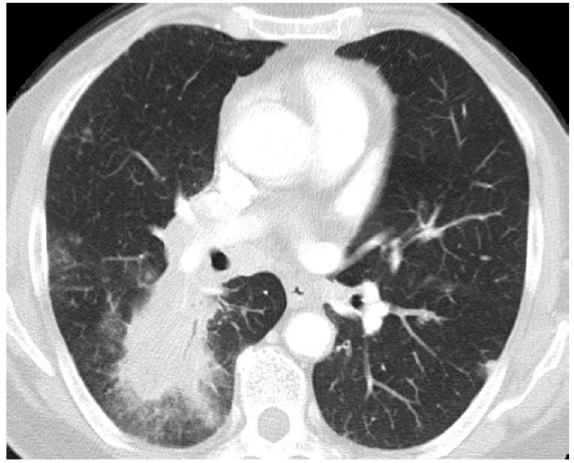
# Sensitivity and resistance to EGFR TKIs in lung cancer



Diagnosis



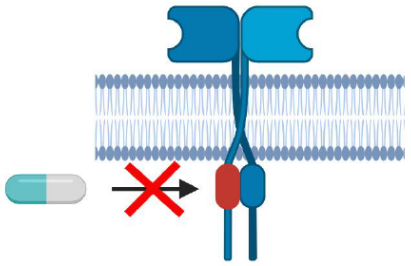
Maximal Response



Acquired Drug Resistance

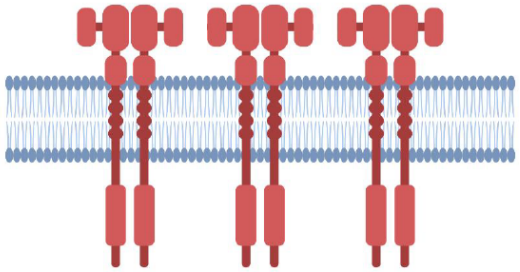
# Mechanisms of acquired resistance to TKI in lung cancer

Mutations in the drug target



Impact drug binding

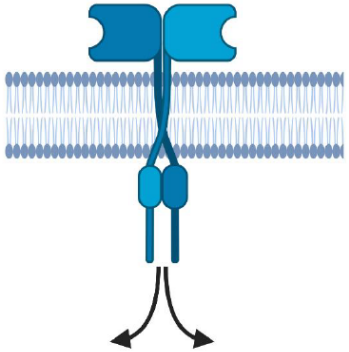
Bypass Signaling

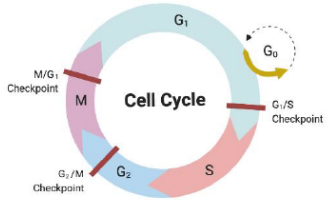


Oncogene Amplification

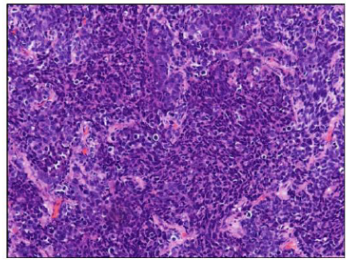
Oncogene Rearrangement

Mutations in Downstream Effectors



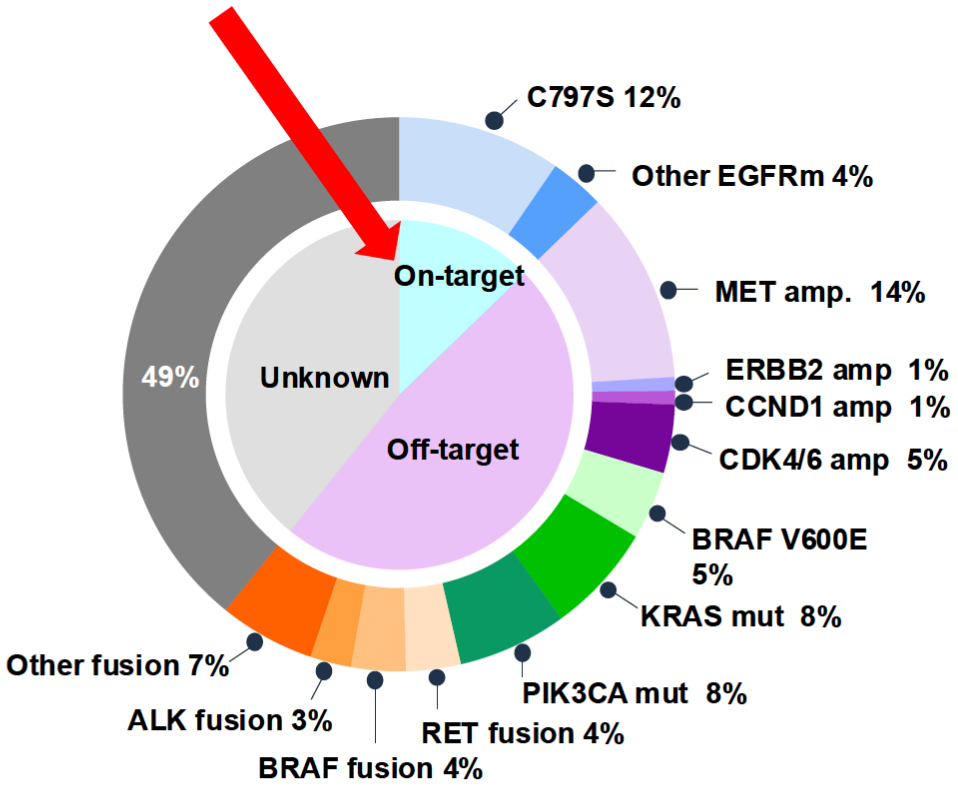

State Transformation



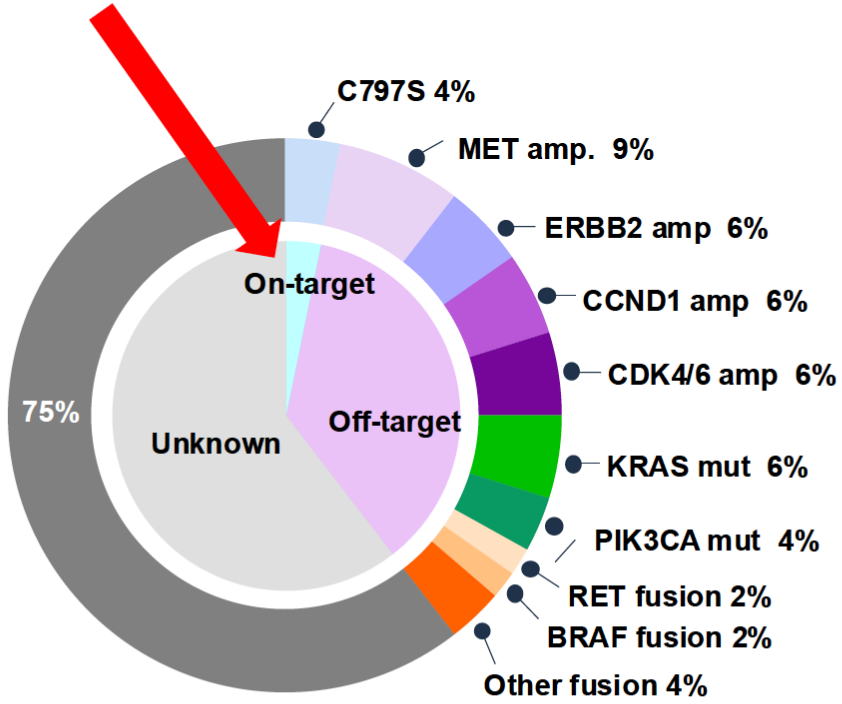
Small Cell Lung cancer
Squamous Cell lung cancer

# FLAURA 2: acquired resistance mutational landscape

## Osimertinib

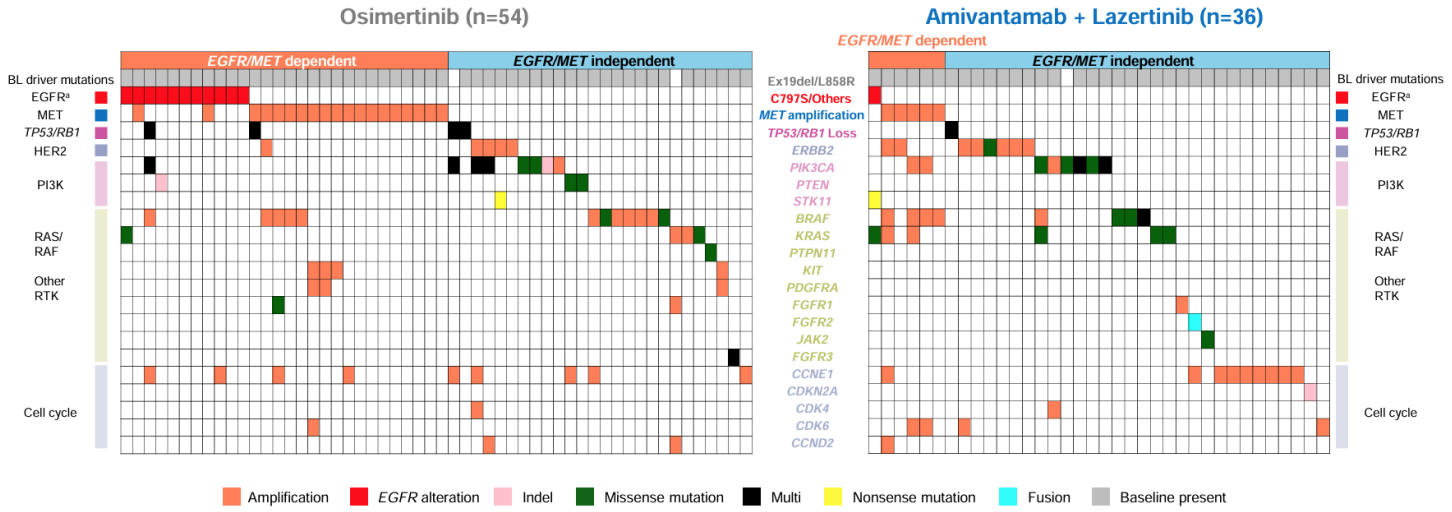


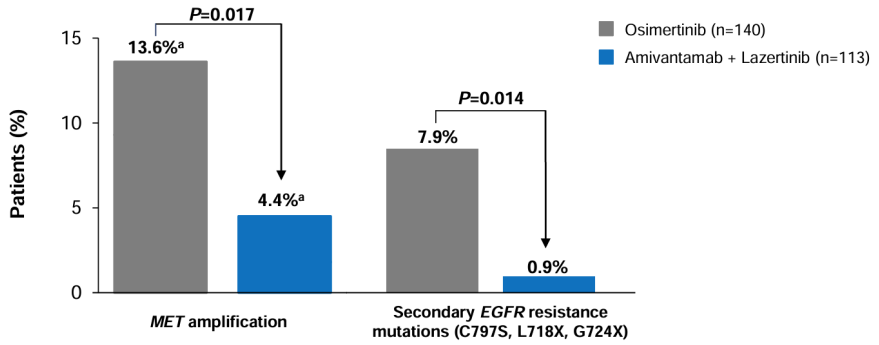

## Osimertinib + Chemotherapy




Yang JCH et al. ESMO 2024

# MARIPOSA: acquired resistance mutational landscape



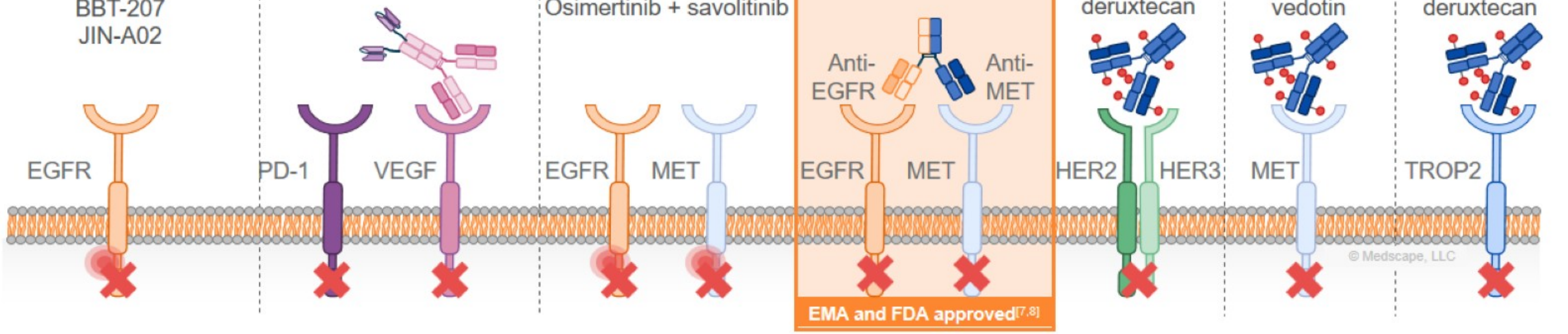

**Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib**

Besse B, Cho BC et al. ESMO 2024

# Treatment landscape for EGFR-mutated advanced NSCLC beyond the frontline

**For patients with an *EGFR* mutation who have disease progression on an EGFR TKI, chemotherapy remains the most often used 2L option, but several alternative treatments have sought to challenge this standard**

| On-Target Inhibition | Off-Target Inhibition | Combined On- And Off-Target Inhibition | | Targeting Tumor-Associated Antigens | | |
|---|---|---|---|---|---|---|
| 4G EGFR TKI[1-3] | VEGF-PD-1 mAb + chemo[4] | 3G EGFR TKI + MET TKI[1,5] | EGFR-MET mAb + chemo[6] | HER3 ADC[1] | MET ADC[9] | TROP2 ADC[10] |
| BBT-176<br>BBT-207<br>JIN-A02 | Ivonescimab + chemo | Osimertinib + tepotinib<br>Osimertinib + savolitinib | Amivantamab + chemo | Patritumab deruxtecan | Telisotuzumab vedotin | Datopotamab deruxtecan |




2l, second-line; ADC, antibody drug conjugate; ASCO, American Society of Clinical Oncology; EMA, European Medicines Agency; FDA, US Food and Drug Administration; HER3, human epidermal growth factor receptor 3; PD1, programmed cell death protein 1; Trop, tropion; VGEF, vascular endothelial growth factor.

1. Lim SM, et al. Cancer Discov. 2022;12:16-19; 2. ClinicalTrials.gov. NCT05920135. Accessed May 1, 2025; 3. Lim SM, et al. ASCO 2024. Presentation TPS8658; 4. Zhang L, et al. J Clin Oncol. 2024;42(suppl 16): Abstract 8508; 5. Kim TM, et al. WCLC 2023. Presentation OA21.05; 6. Passaro A, et al; MARIPOSA-2 Investigators. Ann Oncol. 2024:35;77-90; 7. Amivantamab [PI]. Approved 2021. Revised March 2024; 8. Amivantamab [PI]. EMA. Published December 9, 2021. Updated September 11, 2023; 9. Goldman JW, et al. J Clin Oncol. 2022;40: Abstract 9013; 10. Paz-Ares L, et al. ESMO 2023. Presentation 1314MO.

# Amivantamab in pretreated EGFR-mutant NSCLC: MARIPOSA 2 study

## MARIPOSA-2 Study Design

**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

2:2:1 Randomization[a] (N=657)

- Amivantamab-Lazertinib-Chemotherapy[b] (n=263)
- Chemotherapy (n=263)
- Amivantamab-Chemotherapy (n=131)

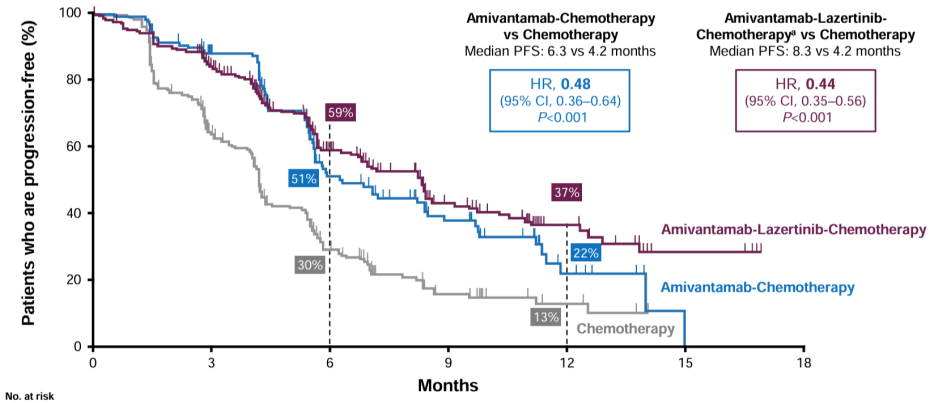
*Focus of this presentation*

**Secondary/Exploratory Efficacy Endpoints Reported:**

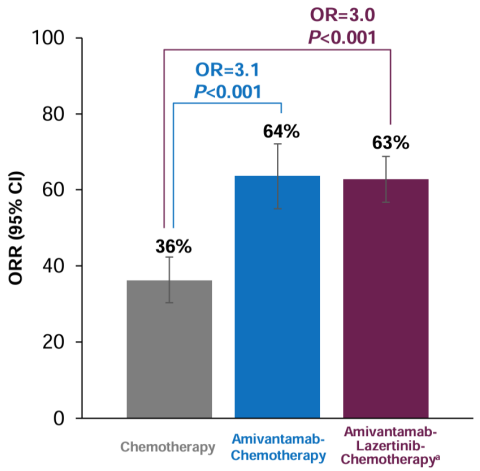
- Overall survival (OS)
- Time to symptomatic progression (TTSP)
- Time to treatment discontinuation (TTD)
- Time to subsequent therapy (TTST)
- PFS after first subsequent therapy (PFS2)

## Primary Endpoint: 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*



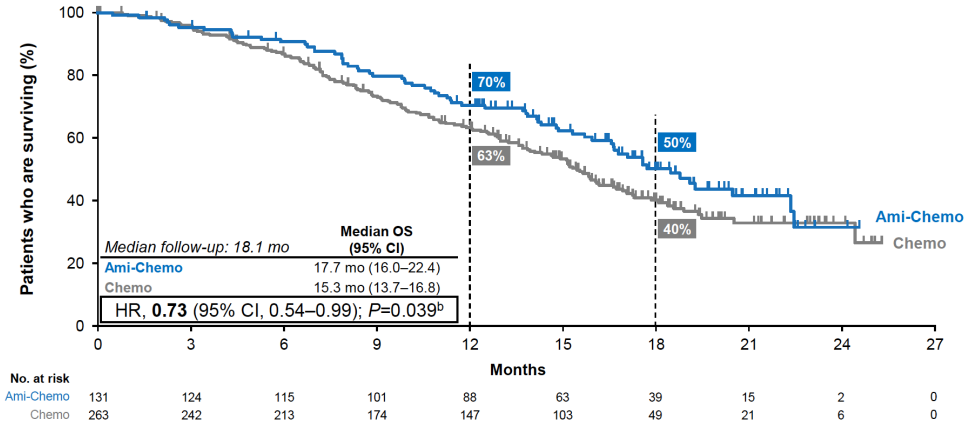

## ORR and DoR by BICR




| 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) |

## Overall Survival

*Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend vs chemotherapy[a]*

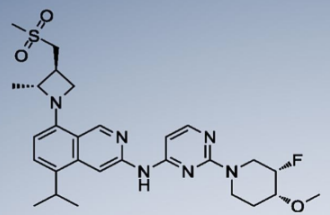



Passaro A et al. ESMO 2023, Popat S et al. ESMO 2024

# Fourth-generation EGFR TKIs

**FOURTH-GENERATION EGFR TKIs**

**THIAZOLE AMID-BASED**



**BLU-945**
**TRX-221**
**BDTX-1535**
**BAY 2927088**
**H002**
**JIN-A02***

**REVERSIBLE ALLOSTERIC INHIBITION**

- ***EGFR* Ex19Del/L858R** ●
- ***EGFR* wild type** ×
- ***EGFR* uncommon** ▲
- ***ERBB2/ERBB4*** ×
- ***EGFR* T790M** ●
- ***cEGFR*/T790M/C797S** ●
- ***cEGFR*/C797S** ●
- **CNS** ●

| Drug | Sponsor | Activating Mutations (preclinical) | Resistance Mutations (preclinical) | Clinical trial | Phase | Enrollment | Study intervention | Recruitment status |
|---|---|---|---|---|---|---|---|---|
| **BLU-701** | Blueprint Medicines | *cEGFR** | *cEGFR*/C797S *cEGFR*/T790M/C797S | NCT05153408 (HARMONY) | I/II | 20 | BLU-701 BLU-701 + osimertinib BLU-701 + PBC | Terminated by the Sponsor |
| **BBT-176** | Bridge Biotherapeutics | *cEGFR* | *EGFR* ex19del/T790M *cEGFR*/C797S *cEGFR*/T790M/C797S | NCT04820023 | I/II | 45 | BBT-176 | Terminated by the Sponsor |
| **BLU-945 (tigozertinib)** | Blueprint Medicines | EGFR L858R | *cEGFR*/T790M EGFRL858R/C797S *cEGFR*/T790M/C797S | NCT04862780 (SYMPHONY) | I/II | 190 | BLU-945 BLU-945 + osimertinib | Terminated by the Sponsor |
| **TRX-221** | Therapex Co., Ltd | *cEGFR* | *cEGFR*/C797S *cEGFR*/T790M/C797S | NCT06186076 | I/II | 115 | TRX-221 | Not yet recruiting |
| **BPI-361175** | Xcovery Holdings, Inc. | *cEGFR* | *cEGFR*/C797S EGFR ex19del/T790M/C797S | NCT05393466 | I/II | 30 | BPI-361175 | Recruiting |
| **BDTX-1535** | Black Diamond Therapeutics | *cEGFR* | *cEGFR*/C797S *cEGFR* /T790M/C797S | NCT05256290 | I/II | 200 | BDTX-1535 | Recruiting |
| **JIN-A02** | J Ints Bio | *cEGFR* | *cEGFR* /T790M EGFR ex19del/C797S *cEGFR* /T790M/C797S | NCT05394831 | I/II | 150 | JIN-A02 | Recruiting |
| **BAY 2927088** | Bayer | *cEGFR* | *cEGFR*/C797S | NCT05099172 | I | 460 | BAY 2927088 | Recruiting |
| **H002** | R&G Pharma Studies Co.,Ltd. | *cEGFR* | *cEGFR*/T790M; *cEGFR*/C797S; *cEGFR*/T790M/C797S | NCT05552781 | I/II | 76 | H002 | Recruiting |

cEGFR: common EGFR activating mutations (exon 19 deletions, exon 21 L858R point mutations); EGFR: epidermal growth-factor receptor.

▲ Retrospective and/or preclinical data
× No data available
■ Prospective data and phase 3 clinical trials
● Phase 1 and 2 clinical trials

*Corvaja Cancer Treat Rev 2024*

# SACHI-Trial: Osimertimib + Savolitinib vs chemotherapy in MET amplified EGFR+ NSCLC after PD

- Unresectable or metastatic NSCLC
- EGFRm, PD on first-line EGFR-TKI
  - ➢ 1st /2nd G: T790M-, METamp;
  - ➢ 3rd G: METamp
- METamp (FISH+) confirmed by central lab
- ECOG PS 0-1

1:1

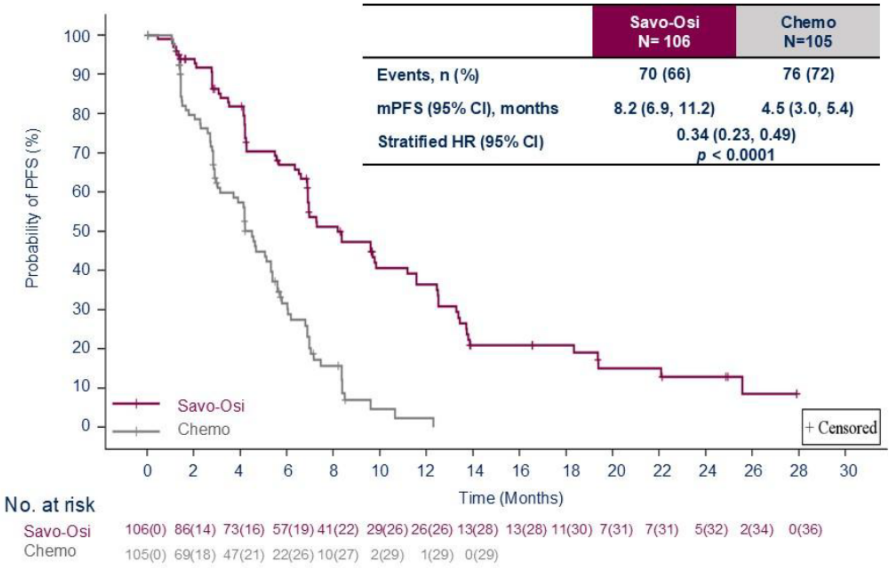
Savolitinib 600mg (BW≥50kg), or 400mg (BW<50kg) QD + Osimertinib 80mg QD
N = 106

→ Until PD or intolerable toxicity

Platinum +Pemetrexed 4~6 cycle then Pemetrexed maintenance
N = 105

→ Until PD or intolerable toxicity → Conditionally crossovered to Savo-Osi after IRC-assessed PD

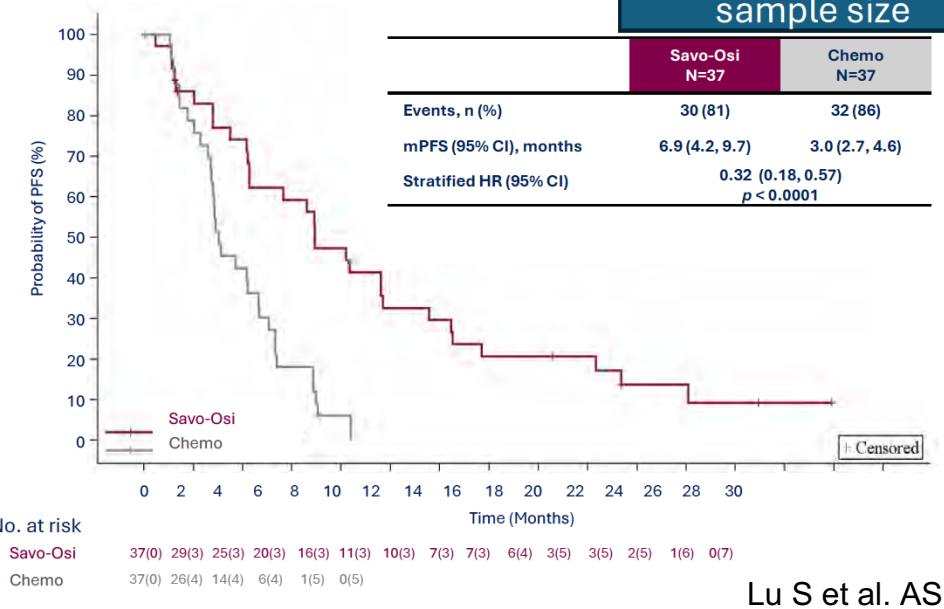
## ITT population




| | Savo-Osi N= 106 | Chemo N=105 |
|---|---|---|
| Events, n (%) | 70 (66) | 76 (72) |
| mPFS (95% CI), months | 8.2 (6.9, 11.2) | 4.5 (3.0, 5.4) |
| Stratified HR (95% CI) | 0.34 (0.23, 0.49) $p < 0.0001$ | |

## Investigator

Relative small sample size

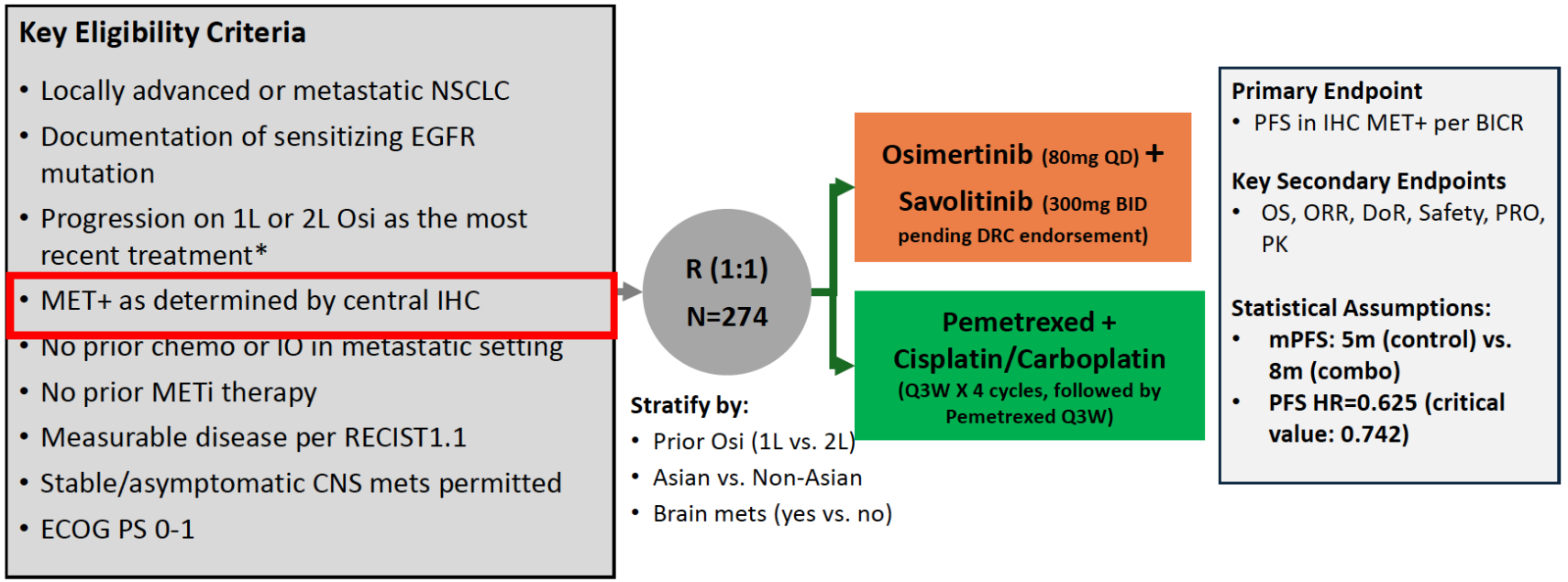



| | Savo-Osi N=37 | Chemo N=37 |
|---|---|---|
| Events, n (%) | 30 (81) | 32 (86) |
| mPFS (95% CI), months | 6.9 (4.2, 9.7) | 3.0 (2.7, 4.6) |
| Stratified HR (95% CI) | 0.32 (0.18, 0.57) $p < 0.0001$ | |

Lu S et al. ASCO 2025

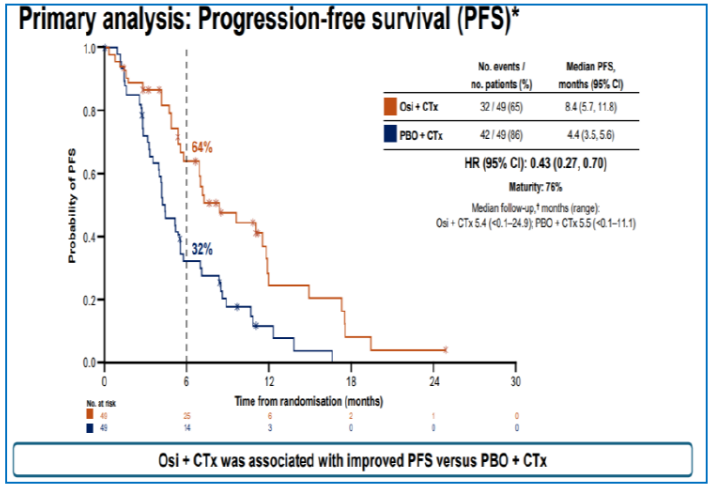
# SAFFRON: Phase III Savolitinib + Osimertinib vs Platinum-based doublet

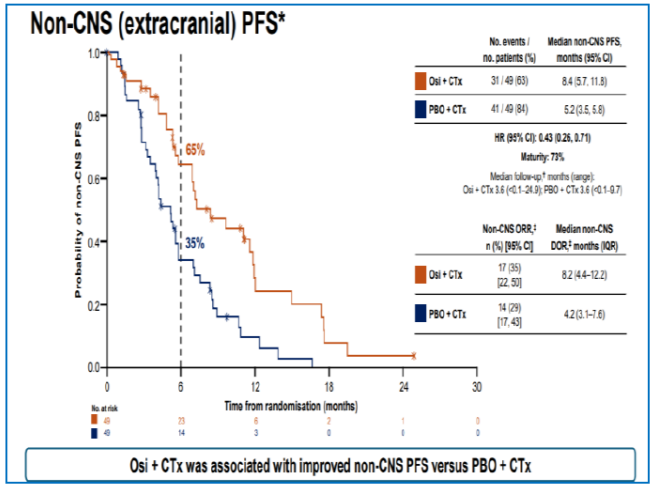
Phase III, Randomized, Open-Label Trial of Savolitinib in Combination with Osimertinib vs Platinum-Based Doublet Chemotherapy in Patients with EGFR mutated, MET+, Locally Advanced or Metastatic Non-Small Cell Lung Cancer who have Progressed Following Treatment with Osimertinib

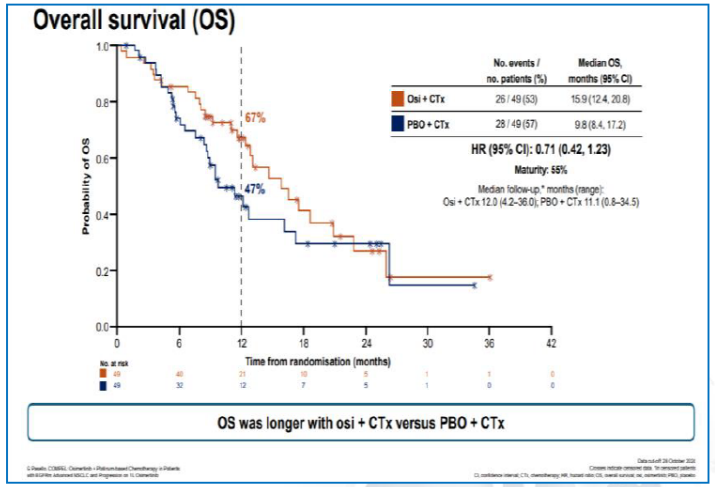



https://clinicaltrials.gov/study/NCT05261399

# COMPEL: Osimertinib + Platinum Based Chemotherapy in Patients with EGFRm Advanced NSCLC and Progression on 1L Osimertinib

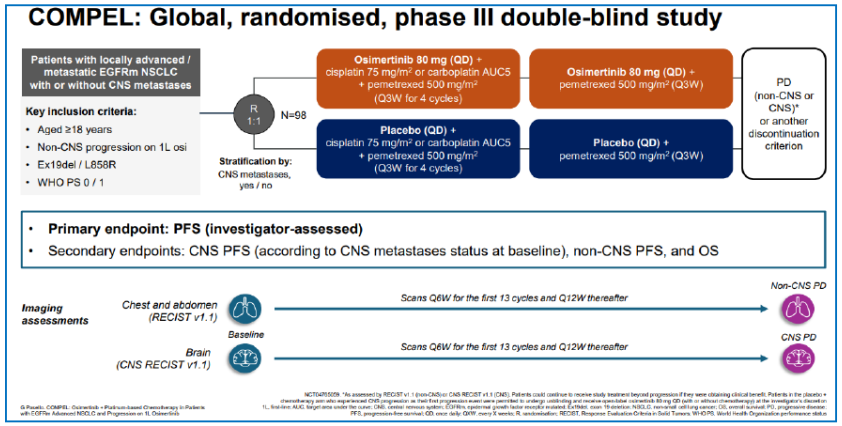



HR 0.43

HR 0.71




Pasello G et al. WCLC 2025

# Harmoni A: Ivonescimab vs placebo + chemotherapy

## Phase 3 Study Design

HARMONi

**Key Eligibility Criteria**
Locally advanced or metastatic NSCLC:
- EGFR sensitizing mutation+
- Progressed on 3rd gen EGFR-TKI
- ECOG 0 or 1
- Any PD-L1 expression

**Stratification factor by geographic region:**
- Brain metastases (yes or no)

R 1:1
N=438

- **Ivonescimab + Chemotherapy** (N = 219)
- **Placebo + Chemotherapy** (N = 219)

**Ivonescimab**: 20 mg/kg Q3W
**Chemotherapy**:
- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m² Q3W

Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

**Endpoints:**

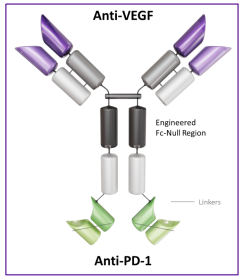
**Primary**
- OS, PFS by IRRC per RECIST 1.1

**Secondary**
- ORR by IRRC, DoR, safety and tolerability

**Planned Efficacy Analyses**
- PFS primary (at ~231 events) & OS interim analyses
- OS final analysis (at ~261 events)

FPI: Jan 2022 (overall)
LPI Asia: Nov 2022
LPI NA & EU (and overall): Oct 2024

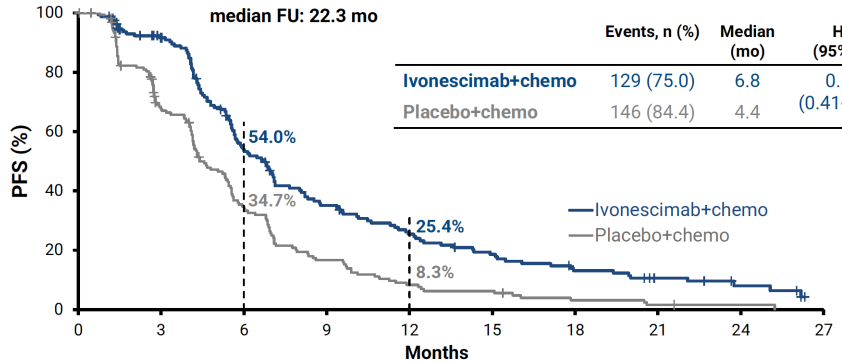
DoR=duration of response; ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; EU=Europe; FPI=first patient in; IRRC= independent radiology review committee; LPI=last patient in; mets=metastases; NA=North America; ORR=overall response rate; OS=overall survival; NSCLC=non-small cell lung cancer; TKI=tyrosine-kinase inhibitor; PD-L1= programmed cell death ligand; PFS=progression-free survival; Q3W=every 3 weeks; RECIST=response evaluation criteria in solid tumors.




## Primary Endpoint: PFS by IRRC

HARMONi

**Statistically significant and clinically meaningful benefit with ivonescimab**




| | Events, n (%) | Median (mo) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Ivonescimab+chemo | 129 (75.0) | 6.8 | 0.52 (0.41-0.66) | <0.0001 |
| Placebo+chemo | 146 (84.4) | 4.4 | | |

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab+chemo | 172 | 134 | 76 | 48 | 34 | 24 | 16 | 10 | 5 | 0 |
| Placebo+chemo | 173 | 100 | 50 | 24 | 12 | 9 | 4 | 2 | 1 | 0 |

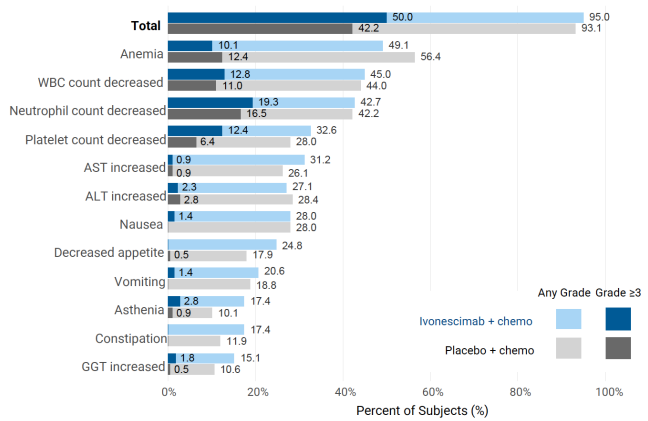
## Treatment-Related Adverse Events (TRAEs)

HARMONi

**Most common were lab abnormalities, nausea, decreased appetite**

| TRAE, n(%) | Ivonescimab + chemo (N=218) | Placebo + chemo (N=218) |
|---|---|---|
| Any Grade | 207 (95.0) | 203 (93.1) |
| Grade ≥3 | 109 (50.0) | 92 (42.2) |
| Serious | 61 (28.0) | 33 (15.1) |
| Led to d/c of ivonescimab/placebo | 16 (7.3) | 11 (5.0) |
| Led to death | 4 (1.8) | 5 (2.3) |
| Grade ≥3 irAE | 21 (9.6) | 13 (6.0) |
| Grade ≥3 VEGF-related | 16 (7.3) | 7 (3.2) |

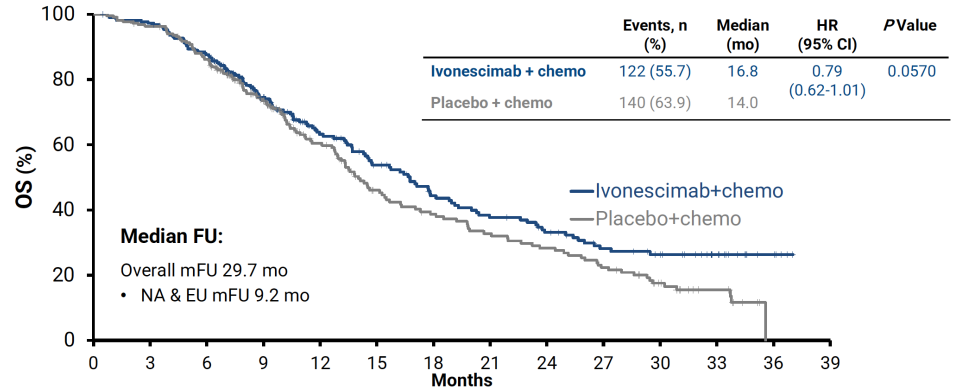
One patient in each treatment arm did not receive study drug




## Primary Endpoint: Overall Survival

HARMONi

**Favorable Trend Observed; NA & EU Follow-up Not Yet Mature**

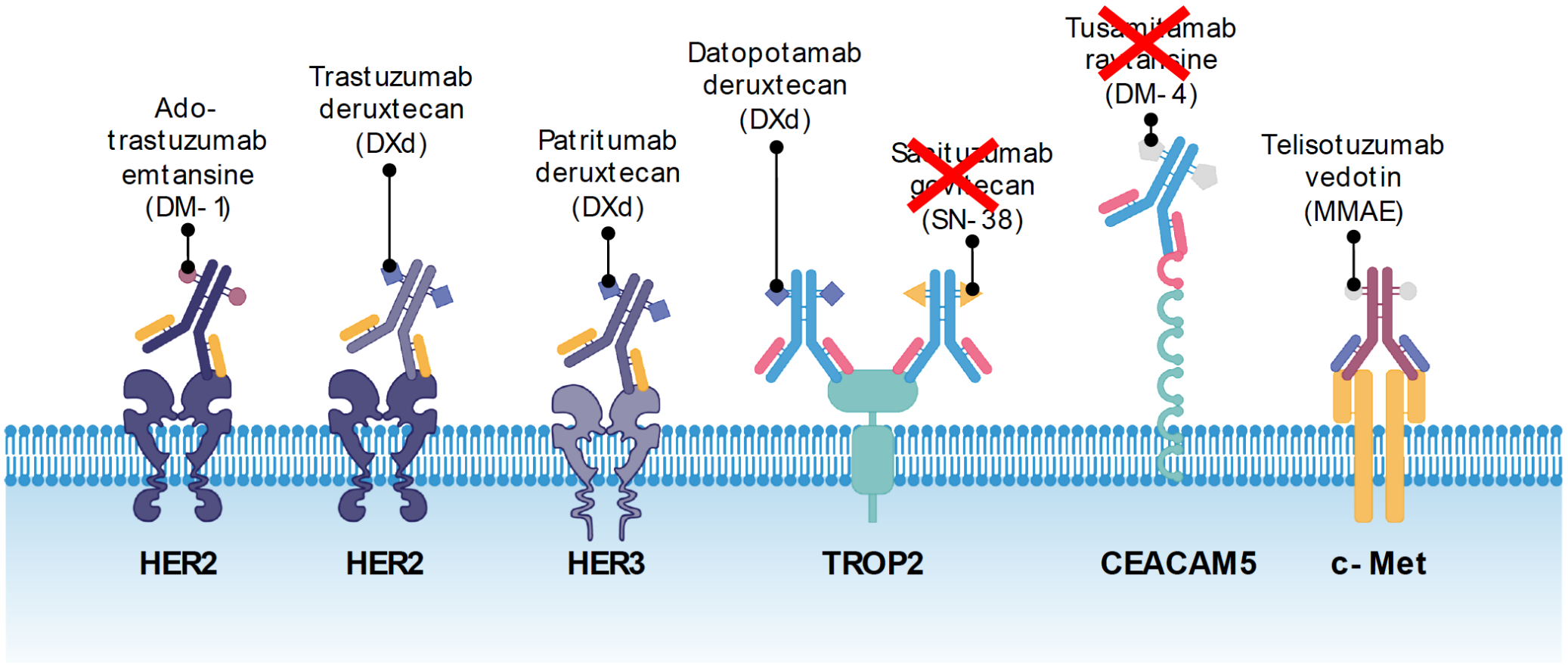



| | Events, n (%) | Median (mo) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Ivonescimab + chemo | 122 (55.7) | 16.8 | 0.79 (0.62-1.01) | 0.0570 |
| Placebo + chemo | 140 (63.9) | 14.0 | | |

| No. at risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ivonescimab+chemo | 219 | 212 | 189 | 137 | 98 | 77 | 60 | 51 | 43 | 33 | 26 | 16 | 5 | 0 |
| Placebo+chemo | 219 | 210 | 186 | 132 | 92 | 63 | 52 | 44 | 38 | 30 | 18 | 9 | 0 | |

Godman JW et al. WCLC 2025

# Emerging targets antibody drug conjugate targets in NSCLC




Desai A et al. Lung Cancer 2022

# HERTHENA-Lung02: Patritumab deruxtecan vs platinum-based chemotherapy

## Study design

HERTHENA-Lung02: A phase 3, global, multi-center, randomized, open-label study[1]

**Select Eligibility Criteria**

- Advanced nonsquamous NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- 1 or 2 prior line(s) of an approved EGFR TKI (must include a third-generation EGFR TKI)
  - Non-osimertinib third-generation TKIs ≤20% in each arm
- Disease progression while receiving or after a third-generation EGFR TKI
- No other prior systemic therapies for advanced disease
- Pretreatment tumor biopsy or archived tumor tissue since progression was required
- Stable brain metastases (asymptomatic and not requiring corticosteroids or anticonvulsants) were permitted

**586 patients; study start date, 08 July 2022**

Randomized 1:1

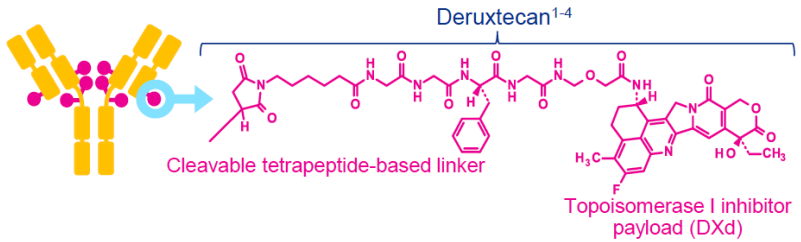
**HER3-DXd (N=293)**
Patritumab deruxtecan 5.6 mg/kg IV Q3W

No crossover

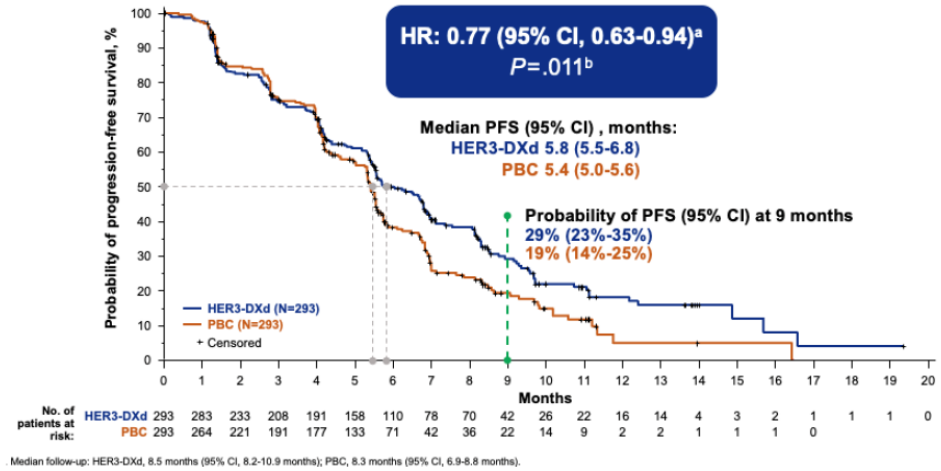
**PBC (N=293)**
Cisplatin 75 mg/m$^2$ *or* carboplatin AUC5 Q3W (× 4 cycles) + Pemetrexed 500 mg/m$^2$ Q3W[a]

**HER3-DXd is an ADC composed of 3 parts[1-4]:**

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

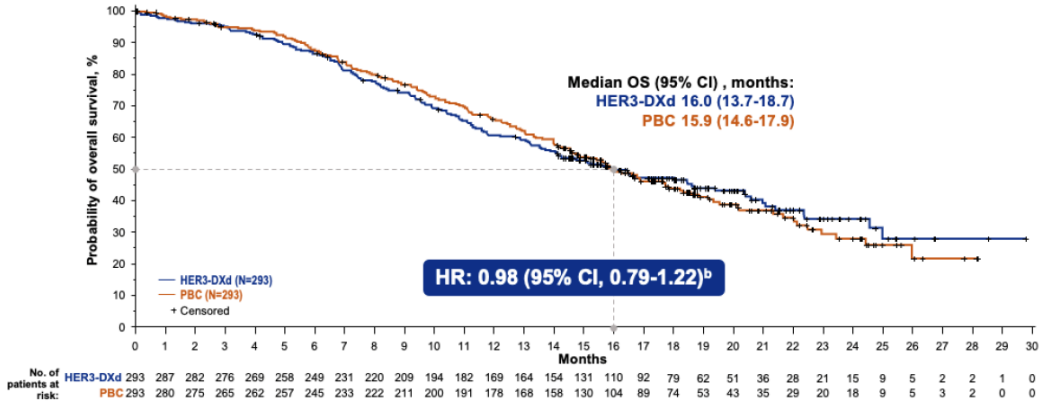



## PFS




Median follow-up: HER3-DXd, 8.5 months (95% CI, 8.2-10.9 months); PBC, 8.3 months (95% CI, 6.9-8.8 months).

## OS




Mok T et al. ASCO 2025

# OptiTROP-Lung04: Sacituzumab tirumotecan vs chemotherapy in *EGFR*m NSCLC post EGFR TKI

## OptiTROP-Lung04 Study Design

**Randomized, multicenter, open-label, phase 3 trial (NCT05870319)**

**Key Eligibility**
- ECOG score 0 or 1
- Nsq-NSCLC (stage IIIB/IIIC or stage IV)
- EGFR-sensitive mutations
- Progression after 3rd gen TKI therapy or progression after 1st or 2nd gen TKIs with negative T790M

R 1:1

- **Sac-TMT** 5 mg/kg IV, Q2W
- Pemetrexed 500 mg/m² + Carboplatin AUC 5 or Cisplatin 75 mg/m² Q3W for up to 4 cycles
- Pemetrexed 500 mg/m² maintenance, Q3W

Treatment until disease progression, intolerable toxicity, or patient request to discontinue treatment.

**Primary endpoints***
- PFS assessed by BICR

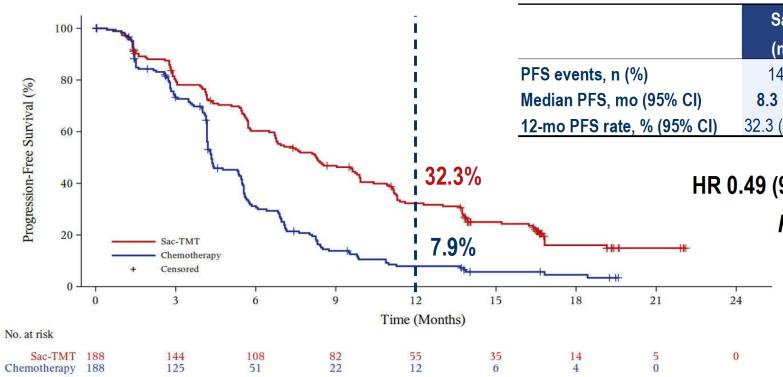
**Secondary endpoints***
- OS (key secondary endpoint)
- PFS assessed by investigator
- ORR, DCR, DOR, etc.
- Safety

**Stratification factors:**
1. Prior EGFR-TKI therapy (**3rd gen TKI in 1st line** *vs* **in 2nd line** *vs* **no 3rd gen TKI**)
2. Brain metastases (**yes** *vs* **no**)

**Statistical considerations:**
- Hierarchical testing was conducted for PFS by BICR and OS.
- Pre-specified interim analysis for OS: at approximately 50% maturity, or 24 months after the first patient randomized.

## Progression-Free Survival by BICR

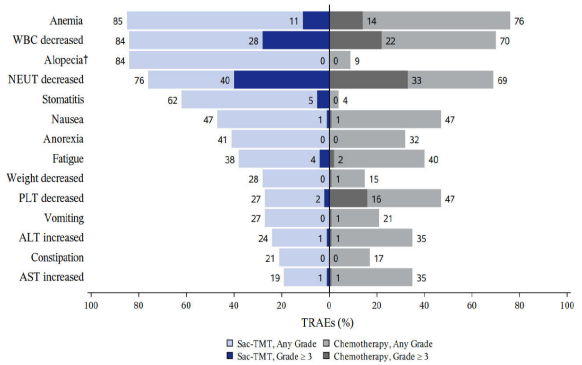
**Sac-TMT significantly improved PFS over chemotherapy with 51% lower risk of disease progression or death.**




| | Sac-TMT (n = 188) | Chemotherapy (n = 188) |
|---|---|---|
| PFS events, n (%) | 144 (76.6) | 159 (84.6) |
| Median PFS, mo (95% CI) | **8.3** (6.7 - 9.9) | **4.3** (4.2 - 5.5) |
| 12-mo PFS rate, % (95% CI) | 32.3 (25.5 - 39.2) | 7.9 (4.4 - 12.8) |

**HR 0.49 (95% CI: 0.39 - 0.62)**
***P* < 0.0001**

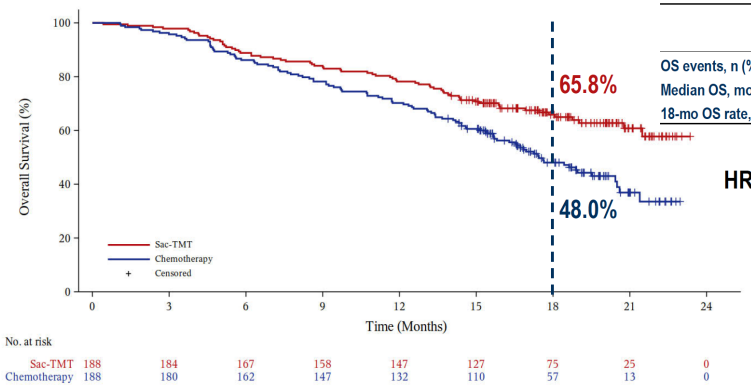
## Common TRAEs*




- The most common TRAEs for both sac-TMT and chemotherapy were hematologic toxicities.
- Sac-TMT was associated with a higher incidence of stomatitis; most cases were grade 1 - 2 and manageable.
- Ocular surface toxicity: occurred in 9.6% of patients in the sac-TMT group, all of which were grade 1 - 2.
- No cases of ILD/pneumonitis were reported in the sac-TMT group.

## Overall Survival

**At the interim analysis, sac-TMT significantly improved OS over chemotherapy with 40% lower risk of death.**




| | Sac-TMT (n = 188) | Chemotherapy (n = 188) |
|---|---|---|
| OS events, n (%) | 67 (35.6) | 101 (53.7) |
| Median OS, mo (95% CI) | **NR** (21.5 - NE) | **17.4** (15.7 - 20.4) |
| 18-mo OS rate, % (95% CI) | 65.8 (58.3 – 72.3) | 48.0 (40.2 - 55.4) |

**HR 0.60 (95% CI: 0.44 - 0.82)**
**two-sided *P* = 0.001***

Zhang L et al. ESMO 2025; Fang W et al. NEJM 2025

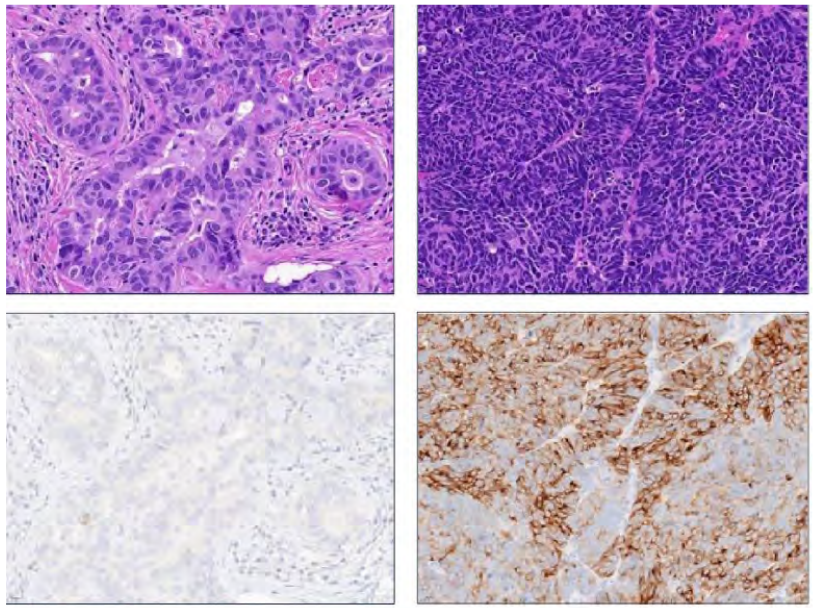
# High DLL3 expression after SCLC transformation

**Table 2**
Therapies in 2nd and later lines after SCT.

| Regimen | Number of patients | Objective Response | Time on Treatment, Median (95 % CI) |
|---|---|---|---|
| Topotecan / Irinotecan | 10/31 (32 %) | 0/10 | 1 months (0.1 −2.0) |
| EGFR inhibitor | 8/31 (26 %) | 1/8 | 2 months (1.1 −2.9) |
| Platinum doublet + /- ICI | 8/31 (26 %) | 3/10 | 2 months (NE) |
| ICI monotherapy | 5/31 (16 %) | 0/5 | 1 months (0.0 −3.1) |
| Paclitaxel/Docetaxel-based | 6/31 (19 %) | 0/5 | 2 months (NE) |
| ACO / VAC | 4/31 (13 %) | 1/5 | 3 months (NE) |
| Clinical Trial, other chemotherapy, unknown | 4/31 (13 %) | NA | NA |
| EGFR inhibitor + chemotherapy | 2/31 (6 %) | 1/2 | 2 months (NE) |

ACO / VAC: Adriamycin / doxorubicin, cyclophosphamide, vincristine

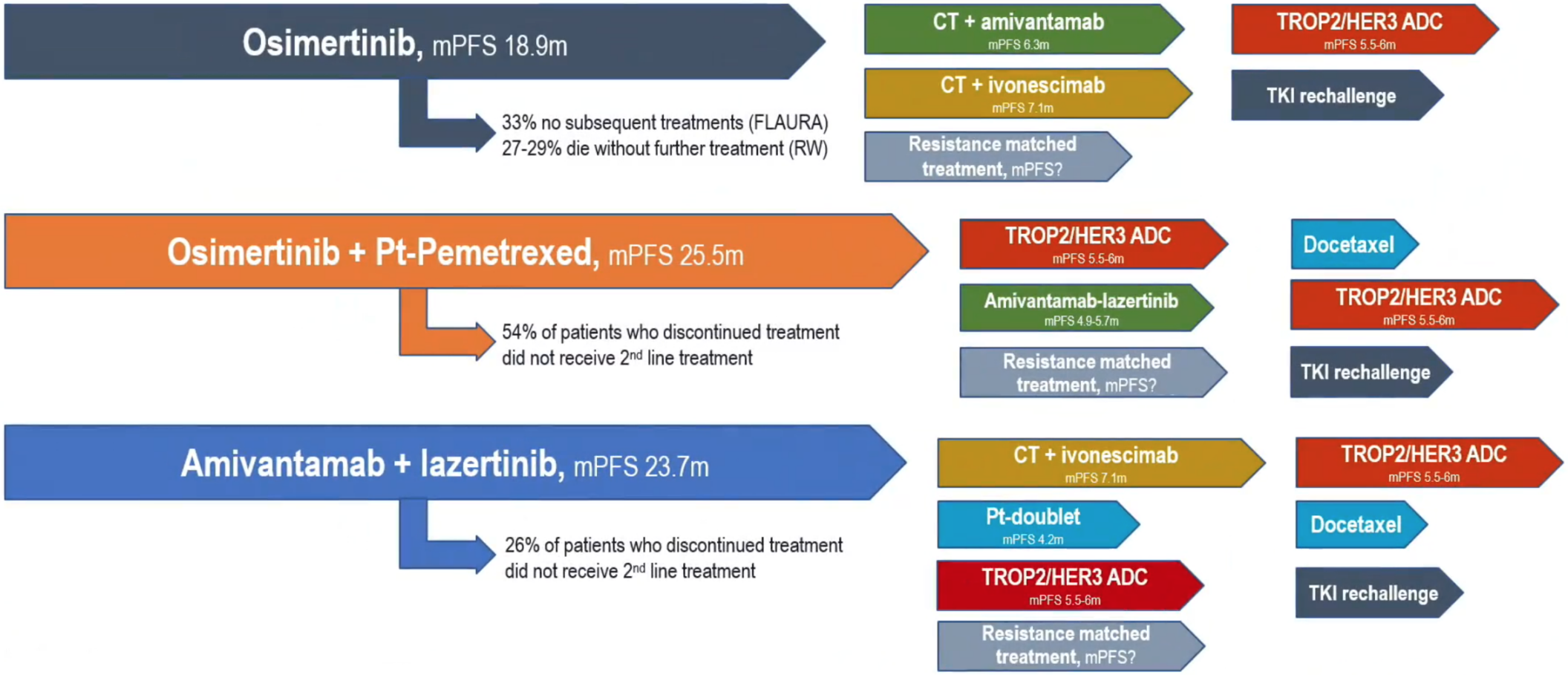
**Tarlatamab?**



| | | Median H-Score (IQR) | DLL3 positivity % (n/N) |
|---|---|---|---|
| Before SCT | Cytoplasmatic | 0 (0-0) | 0% (0/16) |
| | Membranous | 0 (0-0) | |
| After SCT | Cytoplasmatic | 105 (80-165) | 93% (14/15) |
| | Membranous | 15 (10-112.5) | |

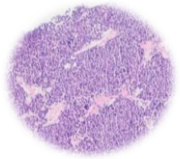
Saalfeld et al. EJC 2024

# Upfront treatment will determine the entire treatment sequence with a major impact on OS




Pero M. ESMO 2024

# Posible algoritmo de secuenciación de tratamiento



Transformación histológica

QT+/-aPDL1 para CPCP o CPCNP sq

Osimertinib

Osimertinib

Osimertinib+ QT

Osimertinib+ QT

Lazertinib+ amivantanab

Lazertinib+ amivantanab

LAT

*On-target*

ITQ 4G

*Off-target*

MET

Otros

ITQ-MET

Combinaciones ITQ

Tepotinib+osimertinib — *INSIGHT*

savolitinib+osimertinib — *TATTON SAVANNAH SAFFRON*

Otros aMET

IHQ+3

Lazertinib+amivantanab — *MARIPOSA-2*

QT+amivantanab — *MARIPOSA-2*

*Tratamiento agnóstico*

**QT**

QT+aVEGF

QT+aVEGF+ aPDL1 — *IMPOWER 150*

QT+Osimertinib — *COMPEL*

**ADC**

AntiHER3 — *HERTENA 02*

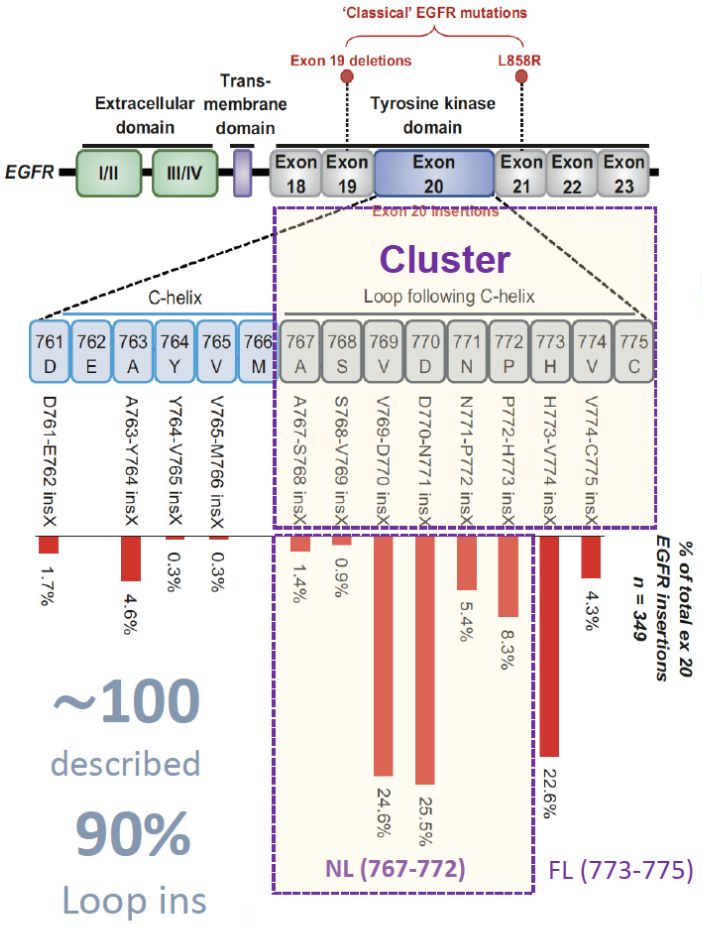
AntiTROP-2 — *OPTITROP TROPION LUNG*

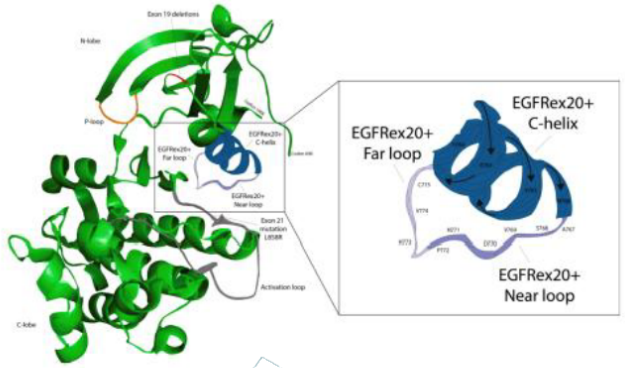
**BisAB**

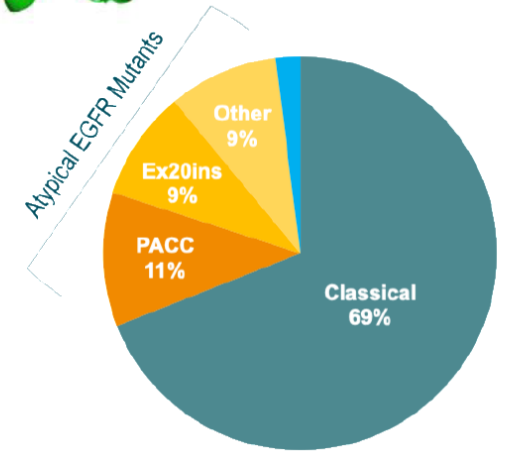
aVEGF+ aPDL1 — *HARMONI*

# New treatments in the setting of *EGFR* Ex20ins mutated NSCLC

# Exon20ins: A rare but distinct subtype of EGFRm




**Incidence:** rare ~ 1–2% of NSCLC (among most common atypical EGFR mutation, ~9–12%)[1-2]

**Molecular Diversity**[3-4]**:**

- Heterogeneity, ~100 variants described
- Location: c-Helix or Loop following C-helix

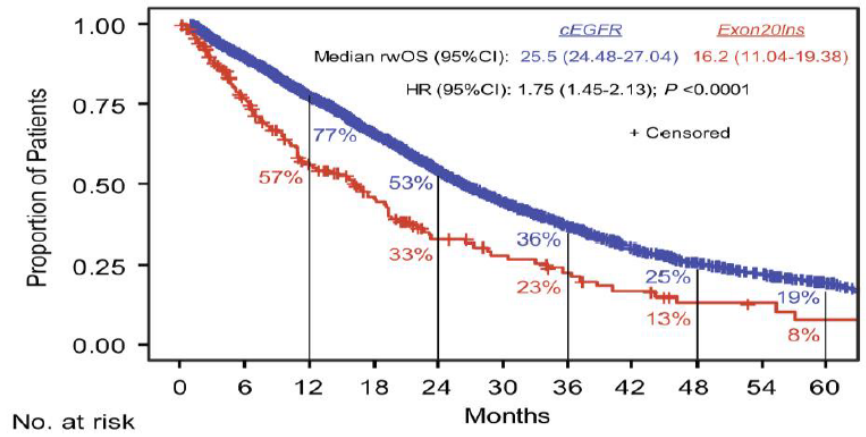
**Mutually exclusivity** with other AGAs

**Clinical Features:** enriched in non-smokers, adenocarcinoma histology and Asian populations

1.- Vyse S et al. Signal TransTarget Ther 2019; 2.- Low JL et al. Ther Adv Med Oncol 2023; 3.-Yasuda H et al. Lancet Oncol 2012; 4.- Friedlaender A et al. Nature Reviews 2021; 5.- Wang F et al. Transl Cancer Res. 2020; 6.- Meng Hu et al. Frontiers 2024; pie from

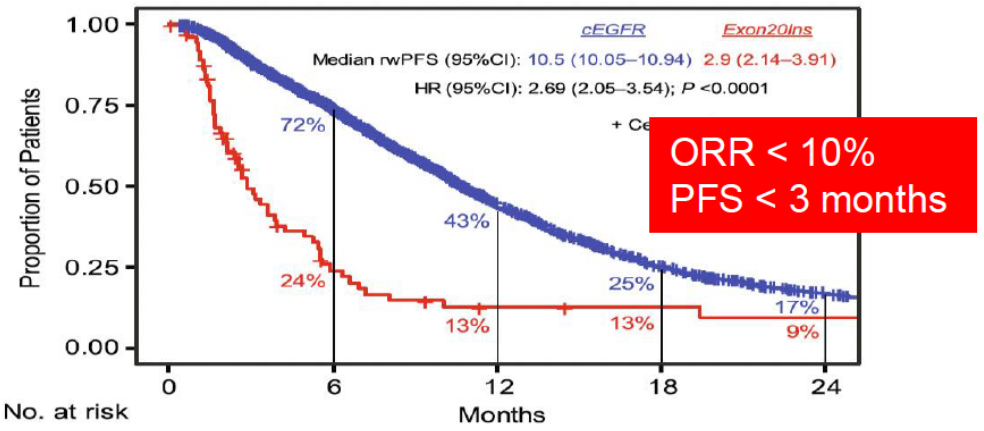
# Historically poor outcomes vs classical *EGFR* mutations

## RW Prognosis of Ex20ins




**Worst Prognosis**
compared to classical EGFRm

## RW Predictive Value of Ex20ins to 1L Early-G TKIs




ORR < 10%
PFS < 3 months

**Minimal Benefit from Early-G TKIs**
compared to classical EGFRm

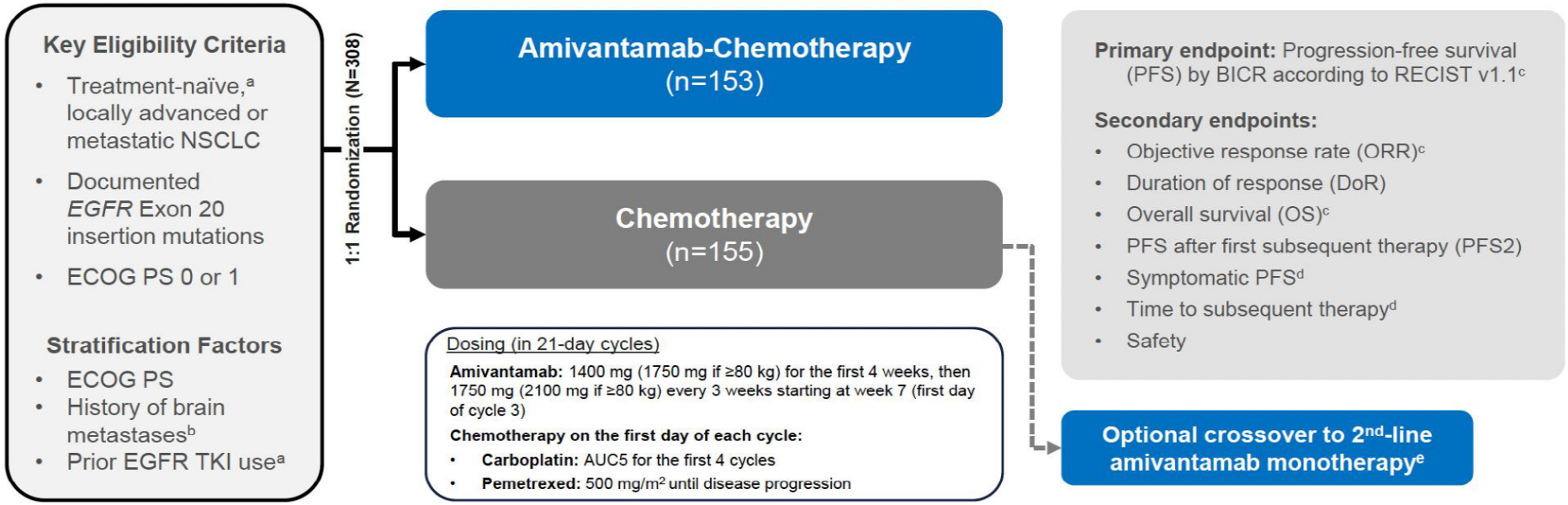
Flatiron Health database

**EGFR ex20ins: poor outcomes and limited benefit from early-generation TKIs**

Bazhenova L et al. Lung Cancer 2021

# First-line: PAPILLON trial

## PAPILLON TRIAL
### Ami + Chemo in Frontline EGFR Ex20ins

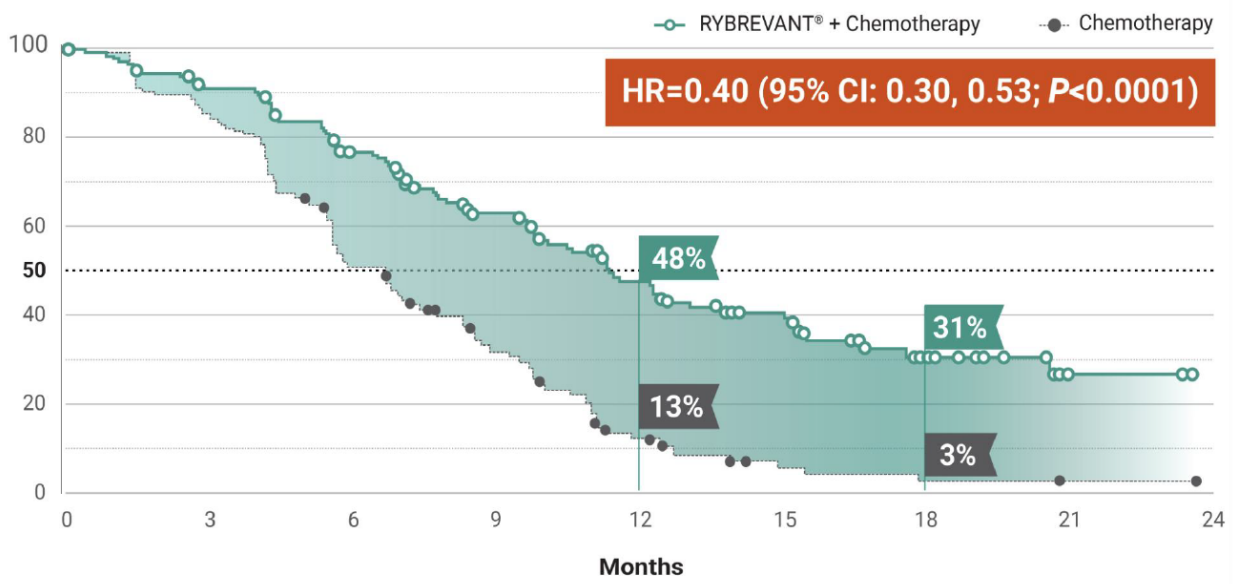



Girard N et al. ESMO 2023; Zhou C et al. NEJM 2023

# PAPILLON trial: Primary endpoint

## Ami + Chemo in Frontline EGFR Ex20ins

**PFS by BIRC (Primary Endpoint)[1]**




| | | |
|---|---|---|
| **Ami + ChT** | **11.4** (9.8–13.7) | HR 0.40 (95% CI 0.30–0.53) |
| **ChT** | **6.7** (5.6–7.3) | |

Girard N et al. ESMO 2023; Zhou C et al. NEJM 2023

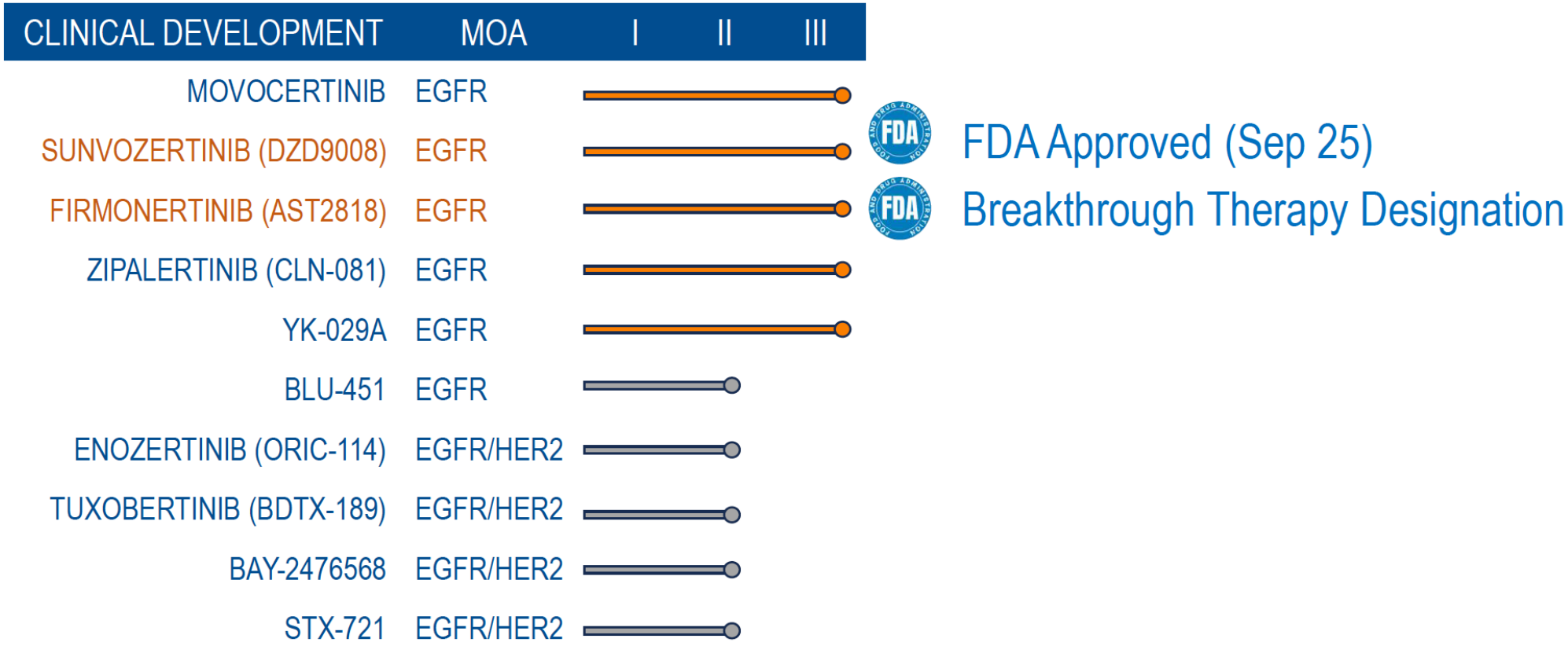
# Early data TKIs in EGFRex20ins (naïve and pretreated)

| AGENT | PHASE | N | SETTING | ORR | mDoR (mo) | AEs Gr≥3 | Diarrhea (all Gr) |
|---|---|---|---|---|---|---|---|
| **ZIPALERTINIB[1] 100 mg BID** | I/II (REZILIENT1) | 176 | Pretreated | 35% | 8.8 | 56% | 22% |
| | | 30 | - Prior ami only | 30% | 14.7 | | |
| **SUNVOZERTINIB[2-3] 200 mg QD** | II (WU-KONG1B) | 107 | Pretreated | 46% | 11 | 59% | 68% |
| | | 12 | - Prior ami only | 42% | - | | |
| **FIRMONERTINIB[4] 240 mg QD** | I (FAVOUR) | 26 | Pretreated | 46% | 13.1 | 13-29% | 73-86% |
| | | 28 | Naïve | 79% | 15.2 | | |
| **YK-029A[5] 200 mg QD** | I | 26 | Naïve | 73% | 7.5 | 38% | 49% |

**Diarrhea is a class-typical AE among EGFRex20 TKIs (zipalertinib appears to be an exception)**
**Most patients not exposed to AMI or PAPILLON regimen**

1. Piotrowska et al. JCO 2025; 2.- Yang J et al. JCO 2025; 3.- Doucet et al, ESMO 2024; 4.- Han et al, WCLC 2023; 5.- Duan et al JTO 2024

# New oral TKIs under investigation for EGFRex20ins




Sunvozertinib 200 mgQD is the only FDA-approved EGFR-TKI (Sept 2025): Firmonertinib has received for breakthrough therapy designation.

Meng Hu et al. Frontiers 2024

# Furmonertinib (FURMO-002)

## Brain activity in naïve EGFR PACC NSCLC

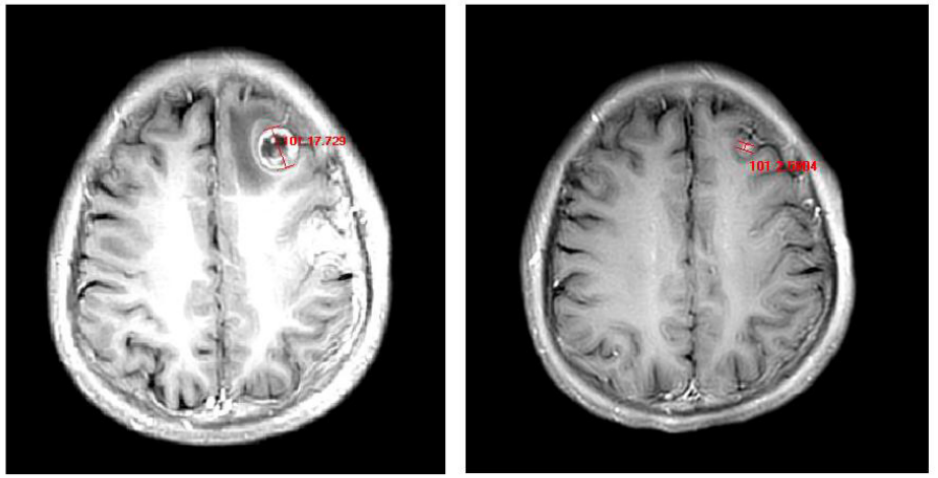
### Confirmed CNS ORR in Response Evaluable CNS Population

| | 160 mg N=9* | 240 mg N=7* | 1L Only (N=13) |
|---|---|---|---|
| **Confirmed ORR, % (95% CI)** | **55.6 (21.2 - 86.3)** | **42.9 (9.9 - 81.6)** | **46.2 (19.2 – 74.9)** |
| **Best Overall Response, n (%)** | | | |
| **Complete response (CR)** | 4 (44.4) | 3 (42.9) | 5 (38.5) |
| **Partial response (PR)** | 1 (11.1) | 0 | 1 (7.7) |
| **Stable disease (SD)** | 1 (11.1) | 0 | 1 (7.7) |
| **Non-CR/Non-PD**** | 2 (22.2) | 3 (42.9) | 4 (30.8) |
| **Progressive disease (PD)** | 1 (11.1) | 1 (14.3) | 2 (15.4) |
| **DCR (CR+PR+SD) % (95% CI)** | **88.9 (51.8 - 99.7)** | **85.7 (42.1 - 99.6)** | **84.6 (54.6 – 98.1)** |

Data as of June 20, 2024

Response Evaluable CNS Population: Received ≥ 1 dose; at least 2 post-baseline CNS tumor assessment by BICR (modified RECIST) or had PD or discontinued from the study.
* Combined 1L and 2L+ PACC patients
** PD utilized for non-measurable CNS patients.

1L patient with no prior CNS radiotherapy
Treated with firmonertinib 160 mg QD



Screening MRI
CNS target lesion 17.7mm

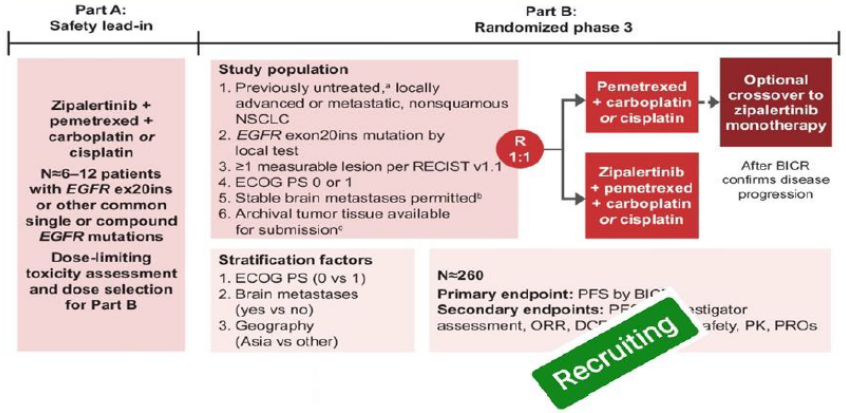
Week 24 MRI
CNS target lesion 3.1mm
(-82.5% change in size)

**CNS tumor shrinkage with firmonertinib**

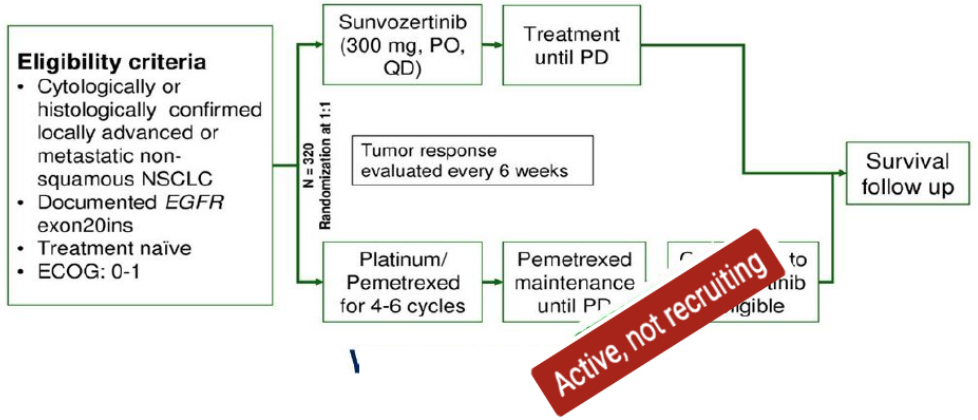
Planchard D et al. WCLC 2024

# Pivotal front-line phase III trials with TKIs

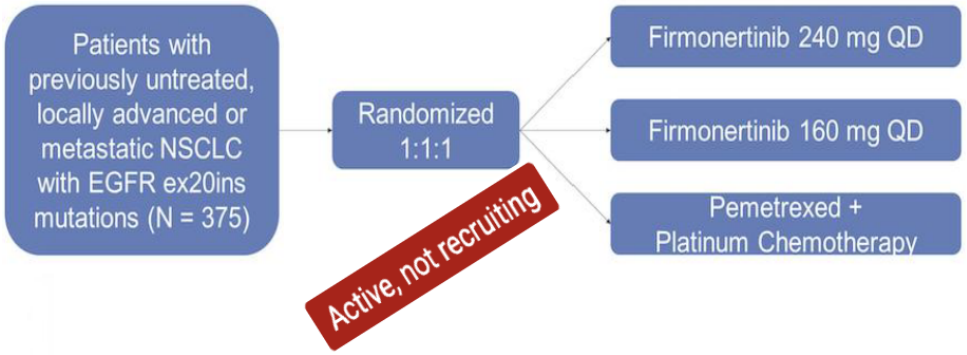
## REZILIENT3 (NCT05973773)



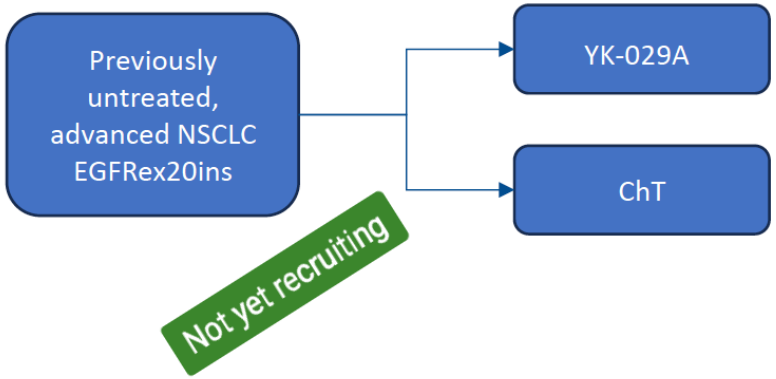

## WU-KONG28 (NCT05668988)




## FURVENT/FURMO-004 (NCT05607550)




## YK-029A (NCT05767892)



# Conclusions

- Based on recent results of FLAURA 2 and MARIPOSA trials, combination therapy should be considered for most patients with a NSCLC classical EGFR sensitizing mutations
- Important to priorize the combination strategies in patients who are fit, or present with poor prognostic features
- It is critical to understand the patients who may not benefit from combination strategies
- Resistancce to EGFR inhibitors (and combinations) is inevitable and heterogeneous
- Multiple options of novel second/third line therapeutic options are available
- Exon 20 insertions are the third most frequent EGFR mutation
- Maximizing survival benefits require identifying patients with different risks and tailoring treatment strategies

# GRacias!

II JORNADA TRASLACIONAL DE ONCOLOGÍA DE PRECISIÓN: A TRAVÉS DE LAS VÍAS DE SEÑALIZACIÓN

SEVILLA, 6 Y 7 DE FEBRERO DE 2025