Penn Medicine

The Evolving Approach to Management of Stage IV EGFRm NSCLC

Patient VV

- 64 yo female who with a 6-8 week h/o dry hacking cough despite antibiotic course
- **CT chest** with new 2 cm cavitary RUL nodule, multiple pulmonary nodules, mediastinal adenopathy and left adrenal mass concerning for metastatic carcinoma. New pericardial effusion and left diaphragmatic elevation. Confirmed on **PET**.
- **MRI Brain** with 3 metastases, all <1 cm, minimal mass effect
- Bronchoscopy with EBUS, NSCLC, adenocarcinoma.
- **Plasma NGS**: EGFR L858R (VAF 4.3%), TP53 P250_I251 Del (VAF 4.9%)
- Performance Status, ECOG: Grade 0

FLAURA2: Osimertinib ± Platinum-Based CT as 1L Treatment

Study Design

Pts 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

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles), followed by maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)*
n=279

Randomisation 1:1 (N=557)

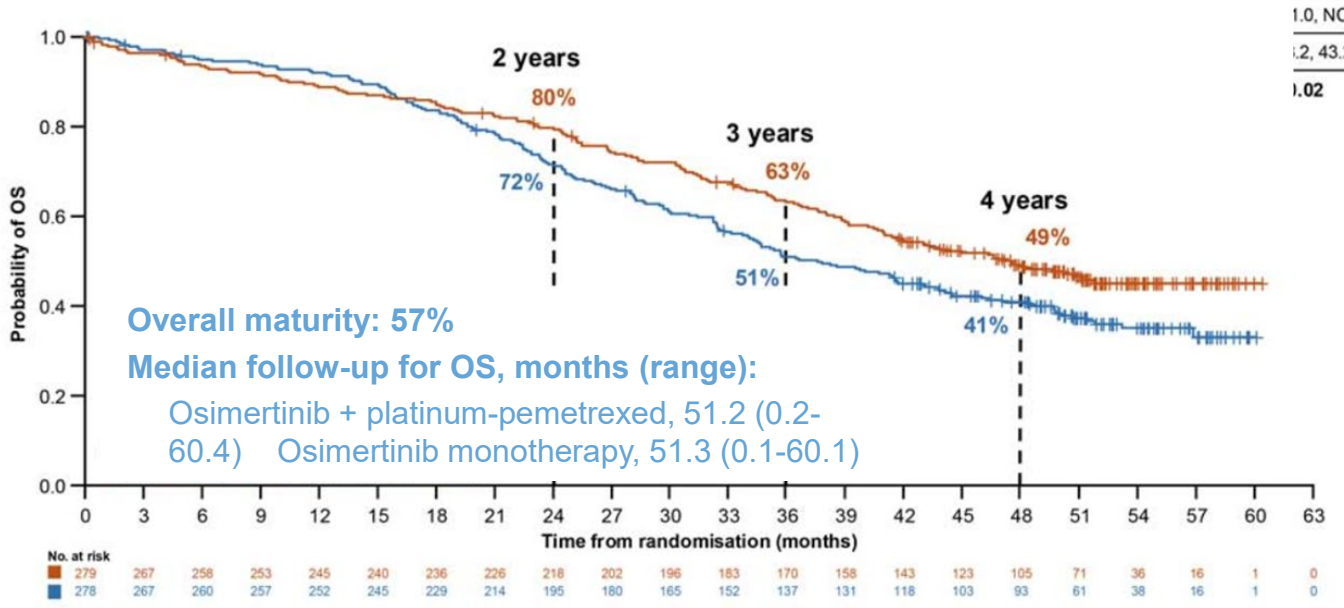
Osimertinib 80 mg (QD)
n=278

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

Final Overall Survival Analysis[1]

Median OS, months (95% CI)	
Osimertinib + platinum-pemetrexed	47.5 (41.0-NC)
Osimertinib monotherapy	37.6 (33.2-43.2)

HR=0.77 (95% CI, 0.61-0.96); *P*=0.0202[a]



Overall maturity: 57%

Median follow-up for OS, months (range):

Osimertinib + platinum-pemetrexed, 51.2 (0.2-60.4) Osimertinib monotherapy, 51.3 (0.1-60.1)

Data cutoff: June 12, 2025.

[a] For statistical significance, a 2-sided *p*-value of less than 0.04953, as determined by the O'Brien and Fleming spending rule, was required.

1. Planchard D, et al. WCLC 2025. Abstract PL02.04. **2**. Valdiviezo N, et al. ELCC 2024. Abstract 4O.

MARIPOSA: 1L Amivantamab + Lazertinib vs Osimertinib

Study Design

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 (yes or no)

2:2:1 Randomization (N=1074)

Serial brain MRIs were required for all patients

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

Focus of this presentation

- **Lazertinib** (n=216; blinded)

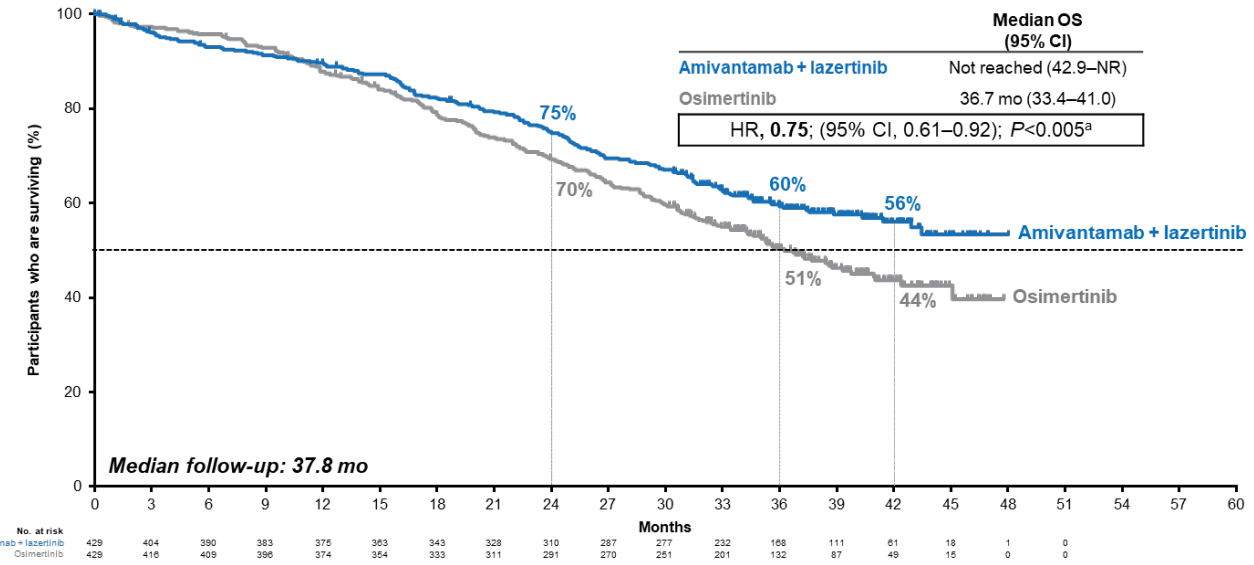
Lazertinib monotherapy arm was included to assess the contribution of components

Primary endpoint of progression-free survival (PFS) by BICR per RECIST v1.1:
- Amivantamab + lazertinib vs osimertinib

Endpoints reported in this presentation[a]:
- Intracranial PFS (icPFS)
- Intracranial DoR (icDoR)
- Intracranial ORR (icORR)
- Time to treatment discontinuation (TTD)
- Time to subsequent therapy (TTST)
- PFS after first subsequent therapy (PFS2)
- Overall survival

[a]Endpoints not part of formal statistical testing; all *P*-values in this presentation are nominal

Final OS Analysis[1]



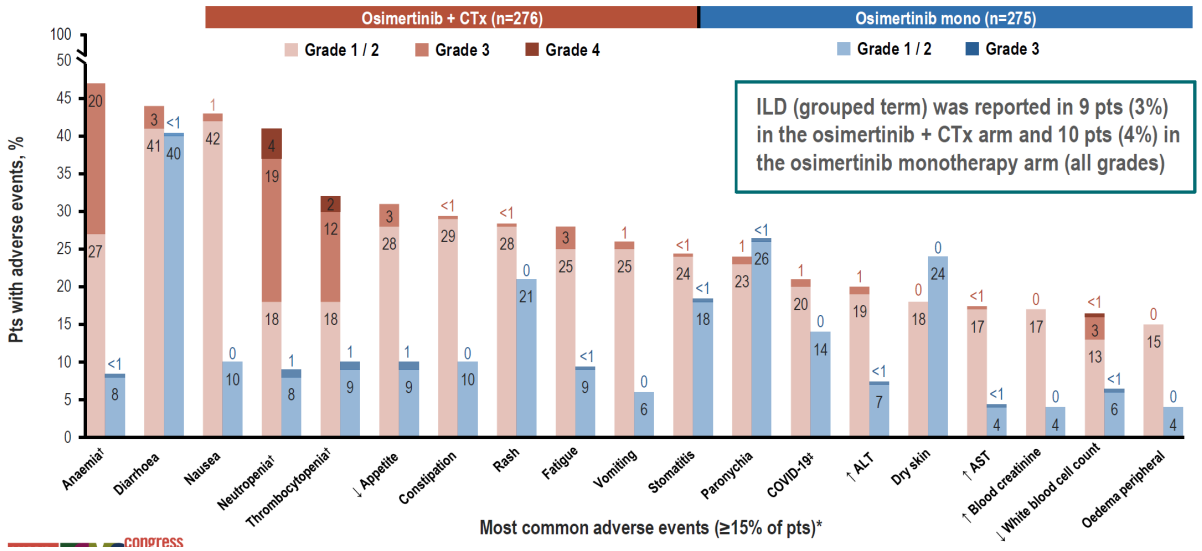
[a] P-value was calculated from a log-rank test stratified by mutation type (ex19del or exon 21 L858R), race (Asian or Non-Asian), and history of brain metastases (present or absent). Hazard ratio was calculated from a stratified pr
subsequent treatment (1 as a monotherapy and 1 in combination with lazertinib). [d] Includes 1 patient who received herbal + doublet CT.
[e] Other category included herbals, ADCs, ALK TKIs, C-MET TKIs, amivantamab, and investigational agents.

1. Yang JC-H, et al. ELCC 2025. Abstract 40. **2**. Gadgeel S, et al. WCLC 2024. Abstract OA02.03.

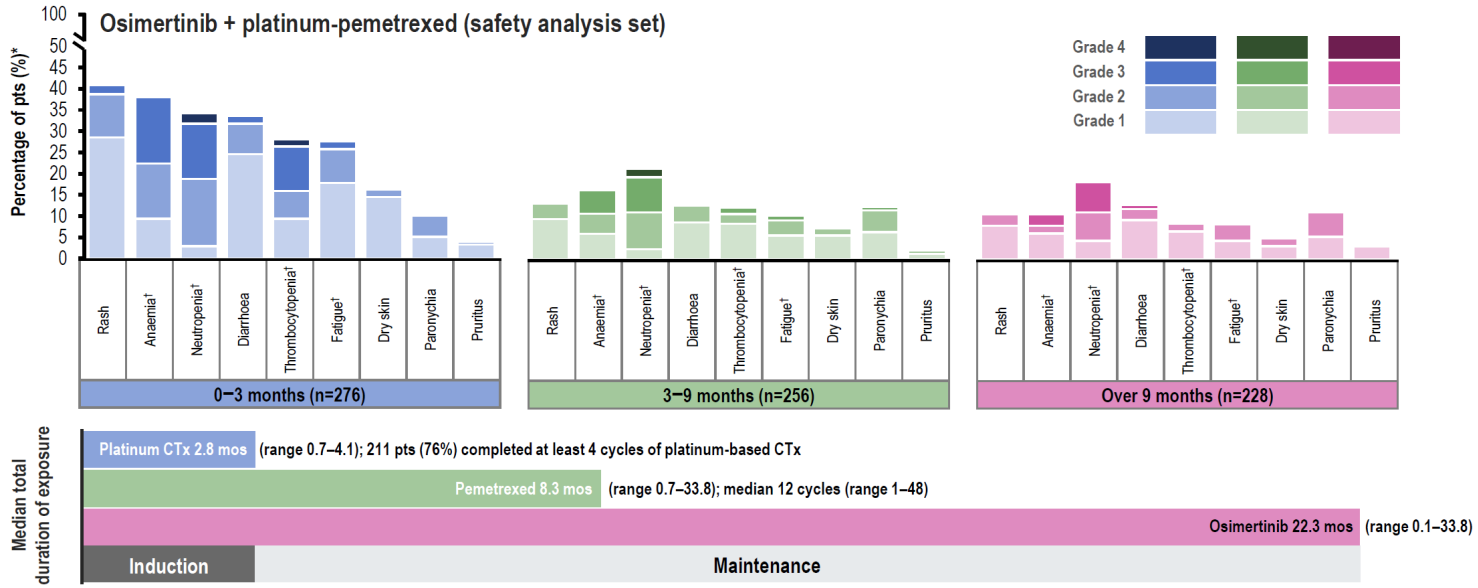
Subset Analyses from Trials

	MARIPOSA	FLAURA2
CNS Metastases +	0.69 (0.53-0.92)	0.47 (0.33-0.66)
CNS Metastases -		0.75 (0.55-1.03)
Exon 19	0.65 (0.51-0.85)	0.6 (0.44-0.83)
Exon 21	0.78 (0.59-1.02)	0.63 (0.44-0.9)
ctDNA +	0.68 (0.53-0.86)	0.6 (0.45-0.8)
ctDNA -	0.72 (0.47-1.1)	0.95 (0.5-1.72)
TP53 MT	0.65 (0.48-0.87)	0.57 (0.29-1.12)
TP53 WT	0.75 (0.52-1.07)	NC
Liver Mets +	0.58 (0.37-0.91)	0.66 (0.41-1.07)
Liver Mets -	0.74 (0.6-0.91)	0.63 (0.48-0.83)

FLAURA2 Trial: Adverse Events



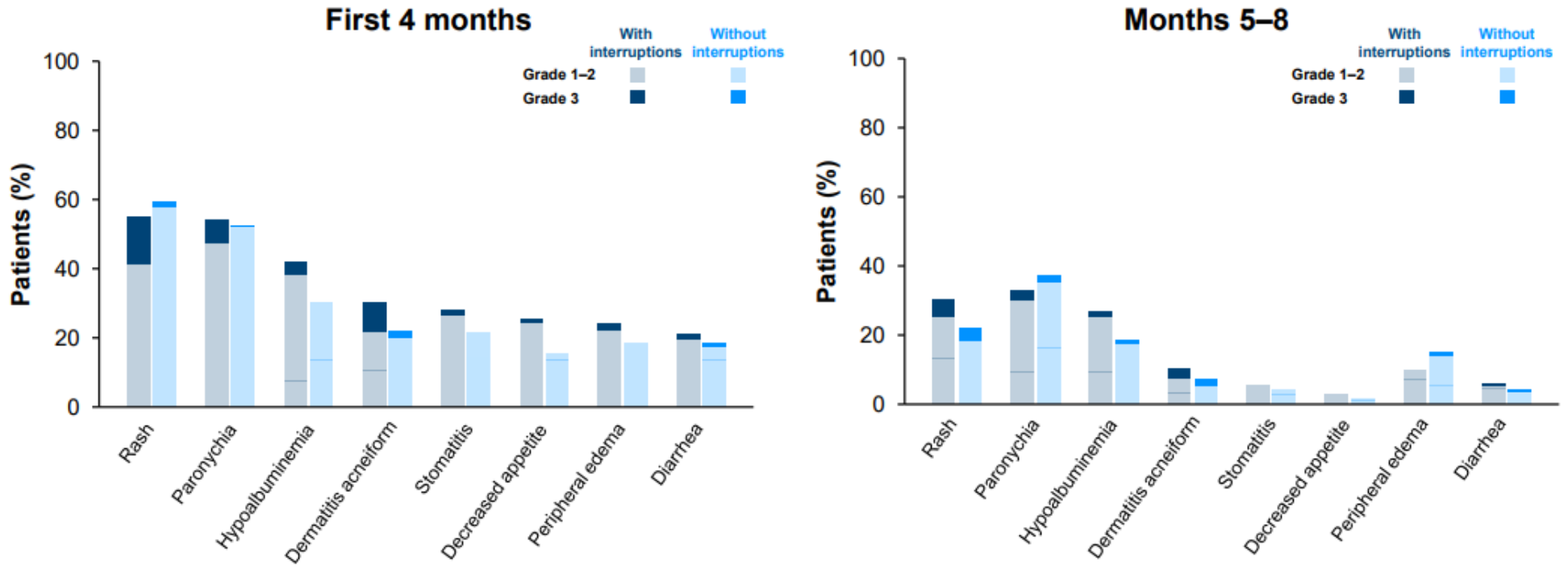
- In the osi + CTx arm, the onset of ≥Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)



Planchard D, et al. ESMO 2023. LBA68; Planchard D, et al. *N Engl J Mec*

MARIPOSA: Prevalence of Key AEs Over Time

- Key AEs occurred most frequently during the first 4 months and declined over the next 4 months[a]
  - Notably, rash decreased by ~50%, paronychia by ~30%, and diarrhea by ~70%
- No grade 4 or 5 AEs were reported



Campelo, et al. ELCC 2024. Abstract 5MO

MARIPOSA: Adverse Events of Special Interest

AESI, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any Venous Thromboembolism, n (%)* • Grade 1 • Grade 2 • Grade 3 • Grade 4 • Grade 5	157 (37) 5 (1) 105 (25) 43 (10) 2 (0.5) 2 (0.5)	39 (9) 0 24 (6) 12 (3) 1 (0.2) 2 (0.5)
Any VTE Leading to Death, n (%)	2 (0.5)	2 (0.5)
Any VTE Leading to Any Discontinuation, n(%)	12 (3)	2 (0.5)
Anticoagulant Use at Time of First VTE, n (%) • On Anticoagulants • Not on Anticoagulants	 5 (1) 152 (36)	 0 39 (9)
Median Onset to First VTE, days Within First 4 Months, n (%)	84 97 of 157 (62)	194 13 of 39 (33)

*Most common preferred terms were pulmonary embolism and deep vein thrombosis
AESI, adverse event of special interest; VTE, venous thromboembolism

Most VTEs were Grade 1-2

Incidence of Grade 4-5 VTEs was <1% and comparable between arms

At the Time of First VTE:

- **Most patients were not on anticoagulants**
- **Majority in the amivantamab plus lazertinib arm occurred within the first 4 months**

Prophylactic dose anticoagulation is now recommended for the initial 4 months of treatment in ongoing trials of amivantamab + lazertinib

Cho BC. ESMO Congress 2023. October 20-24; Madrid, Spain: LBA14.

How to measure the cost of more intensive 1L therapy?

- **Rates of high-grade adverse events?**
- **Adverse events impacting QoL or compromising continuation of treatment?**
- **Time toxicity – how much time will a patient spend interacting with the healthcare system**
- **Cost to the healthcare system – of treatment and of toxicity management**

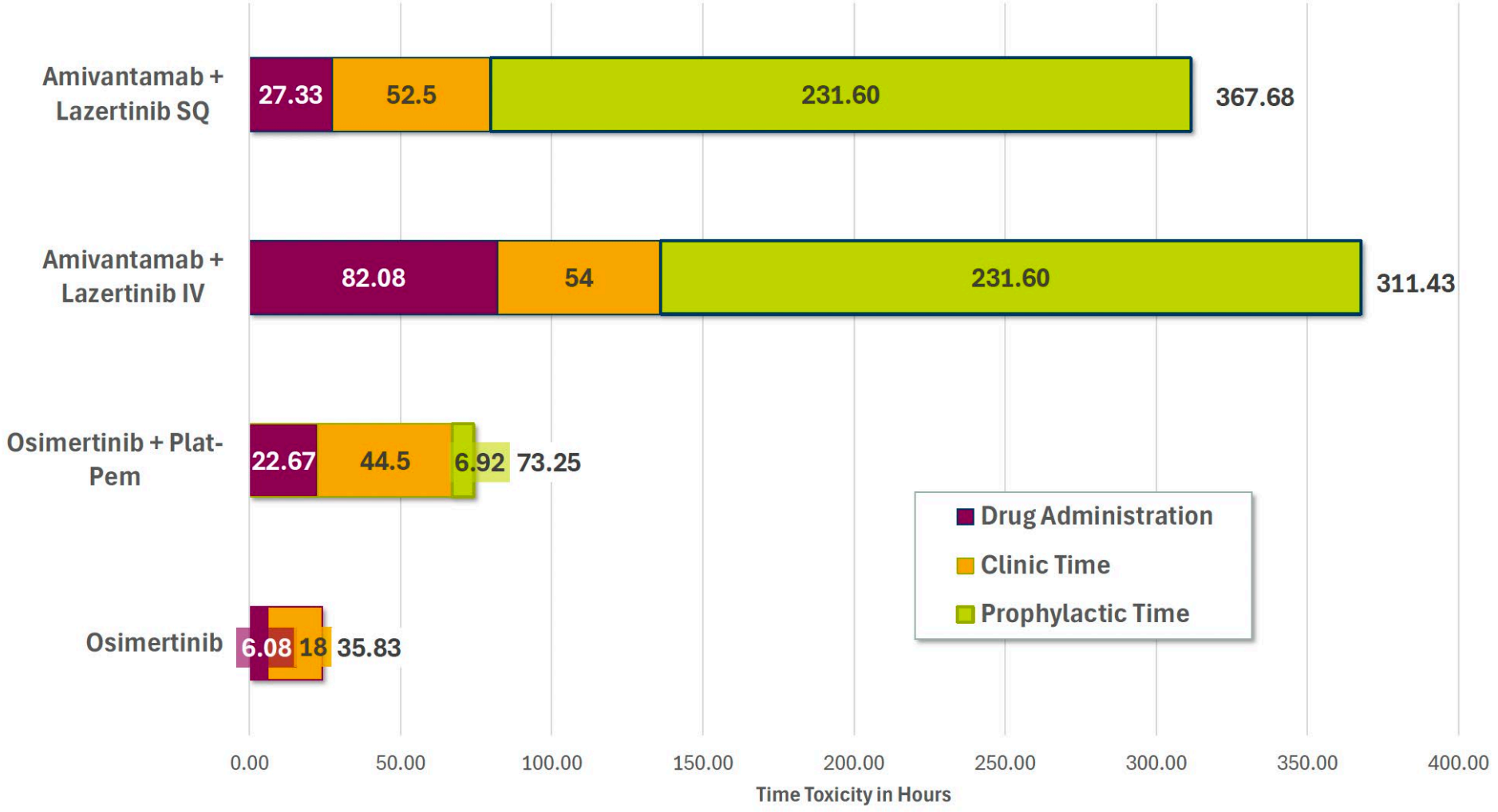
Estimated Number of Clinic Visits in the First Year of Tx

Assuming no extra encounters for AE management

Assuming no treatment discontinuations

FLAURA ~7 Visits	FLAURA2 ~19 Visits	MARIPOSA ~30 Visits
Daily Oral Therapy	Daily Oral Therapy	Daily Oral Therapy
	~40 min Infusions	~4-6 Hr → 2 Hr Infusions
Moisturizer	Moisturizer	Moisturizer
PRN	PRN	PRN
Antidiarrheal	Antidiarrheal	Antidiarrheal
	Folic Acid	Oral antibiotics
	Dexamethasone	Topical Steroids
	PRN Antiemetics	Topical Rx to Nails
		Anticoagulant

Figure 2. Visual Comparison of Time Toxicity by Regimen



What should I offer to my patient

- Who is a candidate for Osi alone?
  - Patients with limited burden of disease (e.g. intrathoracic disease only), oligometastatic disease
  - Patients who are frail/ poor PS
  - ctDNA non shedder
  - If toxicity is a concern (e.g. young working mother)

- When do I think of choosing combination tx:
  - ctDNA+
  - Co-mutations
  - Brain Mets
  - L858R mutation

- Pros and Cons to discuss with patients
  - AE profile: Rash/Paronychia/IRRs/VTEs vs. Cytopenia/Fatigue
  - Infusion Schedule: D1/D2, then Qw (first 4 w)→Q2 vs. Q3w

Patient VV

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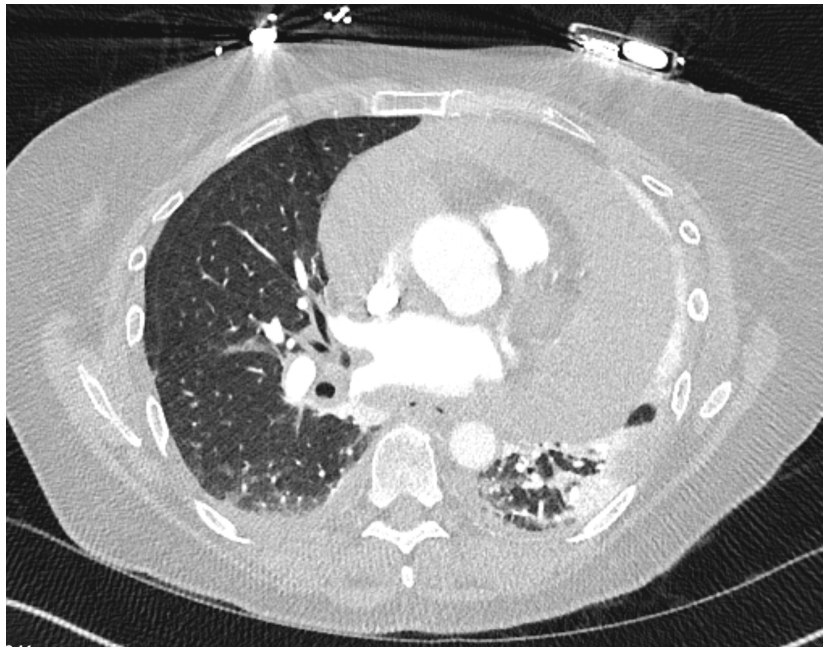
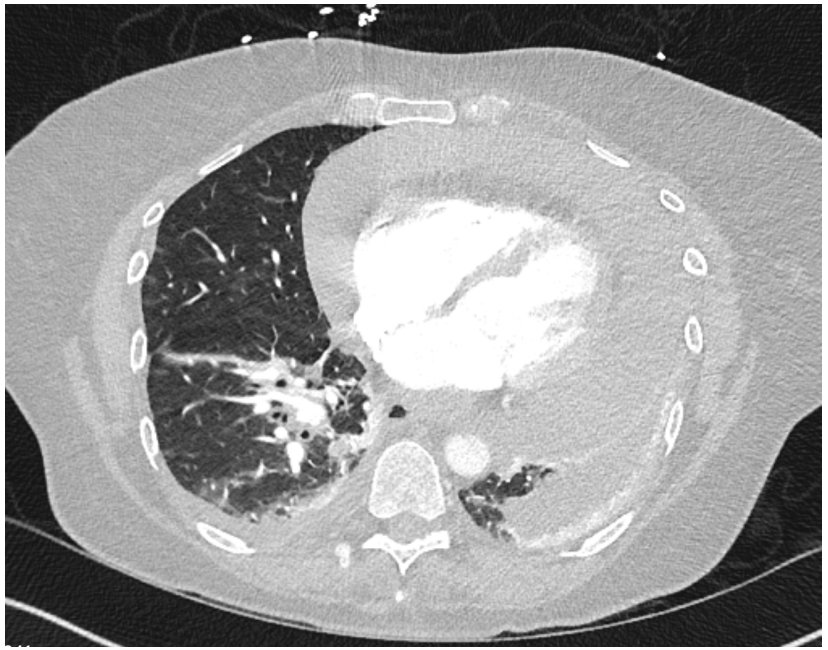
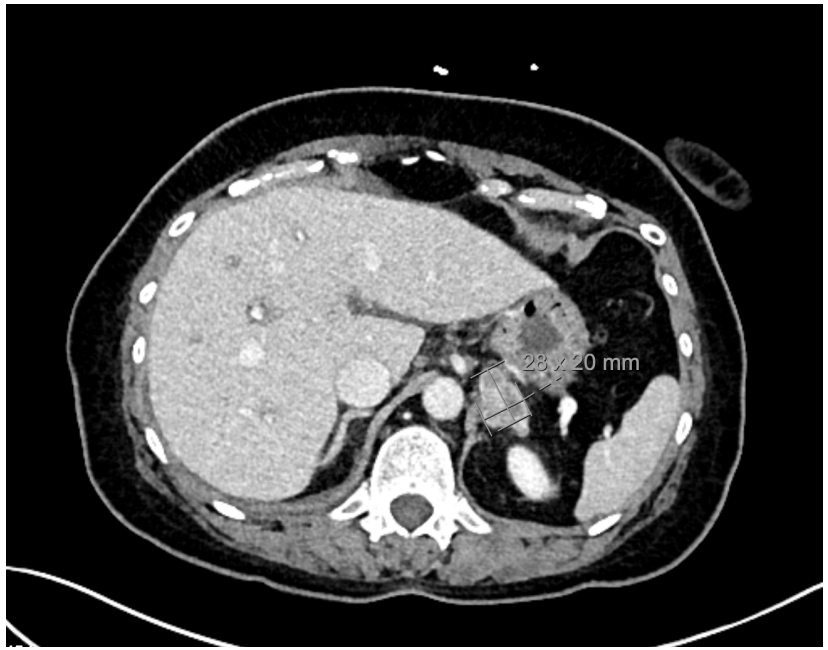
- **CT chest** with new 2 cm cavitary RUL nodule, multiple pulmonary nodules, mediastinal adenopathy and left adrenal mass concerning for metastatic carcinoma. New pericardial effusion and left diaphragmatic elevation. Confirmed on **PET**.
- **MRI Brain** with 3 metastases, all <1 cm, minimal mass effect
- Bronchoscopy with EBUS, NSCLC, adenocarcinoma.
- **Plasma NGS**: EGFR L858R (VAF 4.3%), TP53 P250_I251 Del (VAF 4.9%)
- Performance Status, ECOG: Grade 0

Patient VV

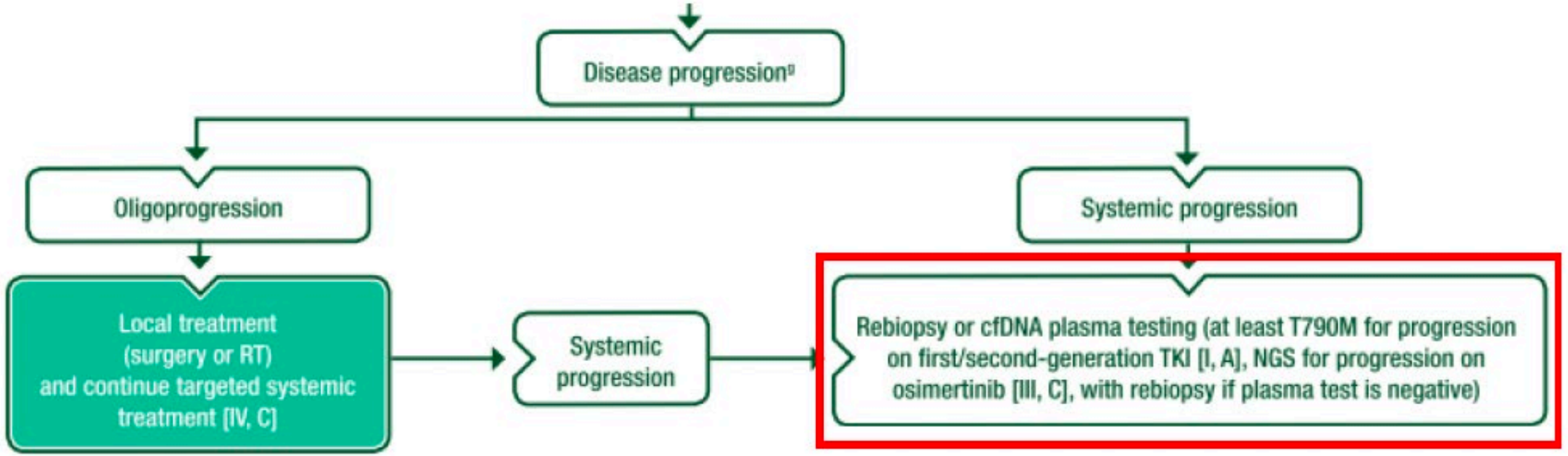
- She was treated with carboplatin, pemetrexed and osimertinib
- Had a very short duration of response and presented with shortness of breath, fatigue, and low blood pressure
- She was found to have enlarging mediastinal LAD, Pericardial Effusion and Tamponade physiology







What to do in case of Progressive Disease: ESMO Guidelines

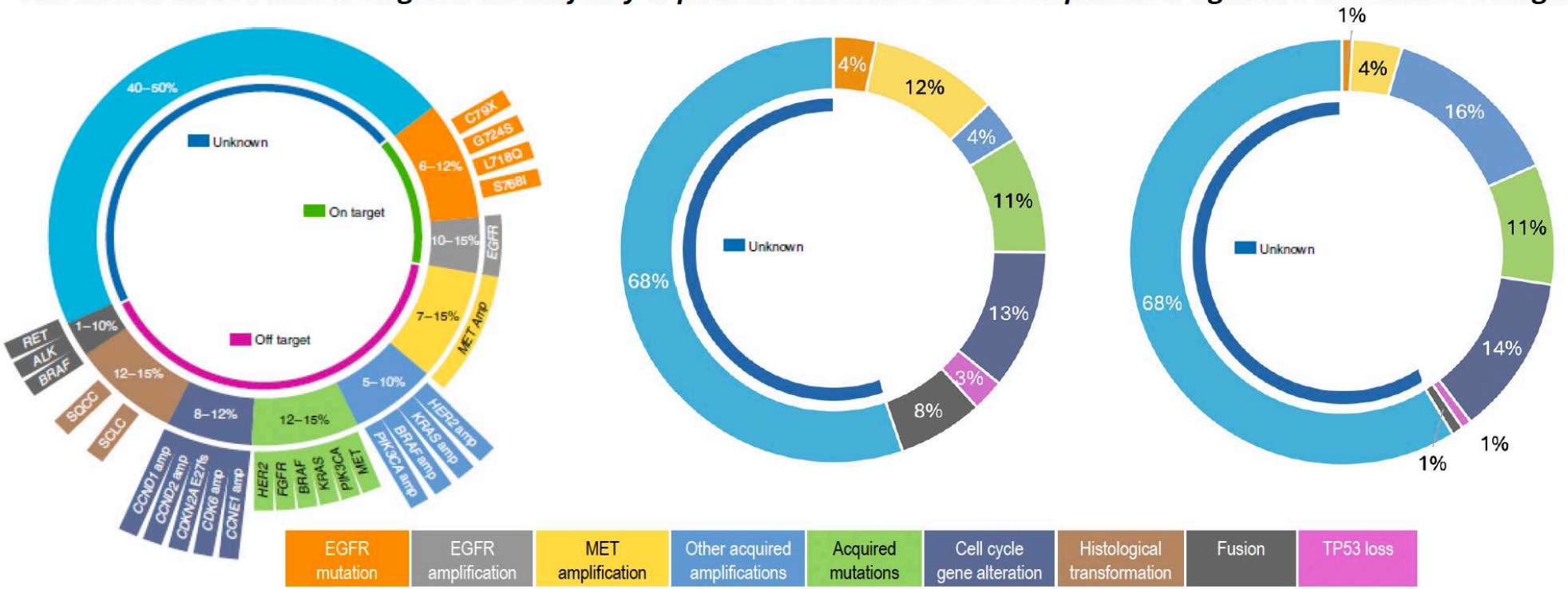


First Line Therapy Shapes Resistance

Osimertinib | Osimertinib + chemotherapy | Amivantamab + Lazertinib

New tumor sample or ct DNA at PD

The lack of an actionable target in the majority of patients validates the development of agnostic treatment strategies

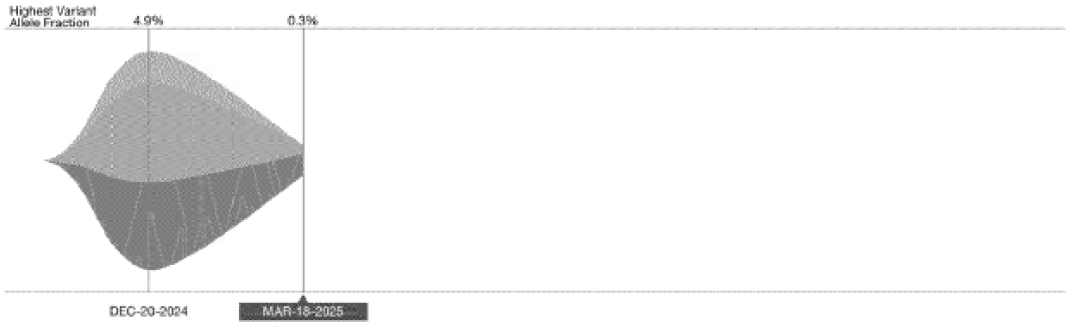


Adapted from Passaro A, Nature Cancer 2021; Yang J, Presented at WCLC 2024; Besse B, Presented at ESMO 2024

Patient VV – Testing

Guardant360 Tumor Response Map

The Guardant360 laboratory developed test (LDT) Tumor Response Map illustrates the variant allele fraction (% cfDNA) of observed somatic variants at each sample submission. Amplifications are not plotted, and only the first and last five test dates are plotted. Please see the Physician Portal (portal.guardanthealth.com) for the Tumor Response Map with all test dates.



Detected Alteration(s) / Biomarker(s)	% cfDNA or Amp	Alteration Trend	
EGFR L858R	0.3%	4.3% → 0.3%	
TP53 P250_I251del	0.1%	4.9% → 0.1%	
MET I1129I	ND	1.3% → ND	
EGFR L788F	0.9%	0.6% → 0.8%	Variants of Uncertain Clinical Significance §
RB1 M904I	ND	4.7% → ND	Variants of Uncertain Clinical Significance §

The table above annotates the variant allele fraction (% cfDNA) detected in this sample, listed in descending order.
§ See definitions section for more detail

- Tissue Biopsy: Adenocarcinoma
- Tissue NGS: EGFR, TP53
- MET (FISH 7q31)/7cen (XL MET amp)
  Number of Cells Analyzed: 100
  ABNORMAL RESULT: POSITIVE FOR MET AMPLIFICATION
- Her 2 IHC, cMET IHC: Negative

What should be our next step?

MARIPOSA 2/ PALOMA 3

Phase III MARIPOSA 2: Study Design

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
- 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/m² until disease progression

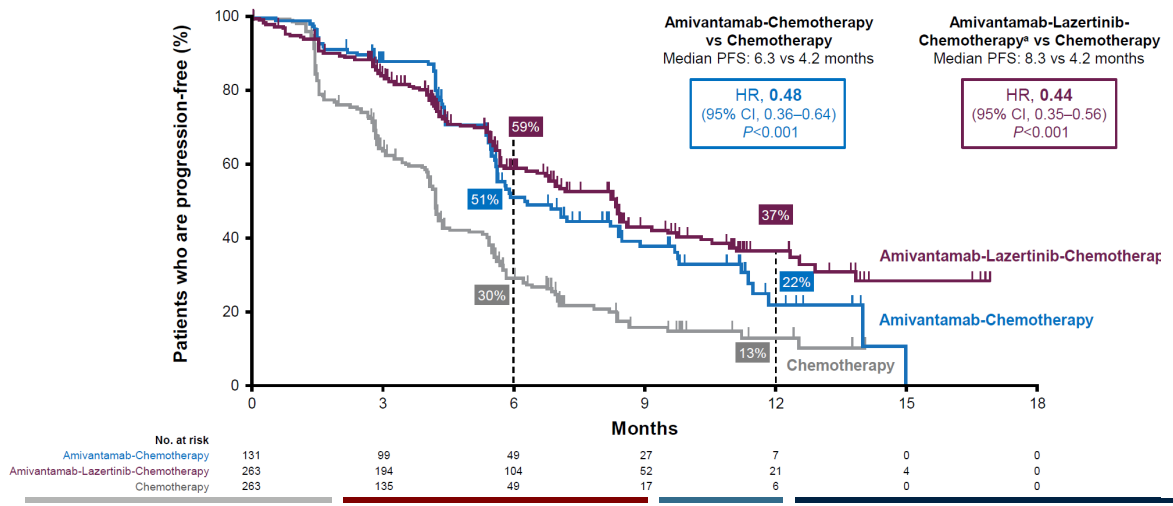
Dual primary endpoint of PFS[c] by BICR per RECIST v1.1:
- Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy
- Amivantamab-Chemotherapy vs Chemotherapy

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

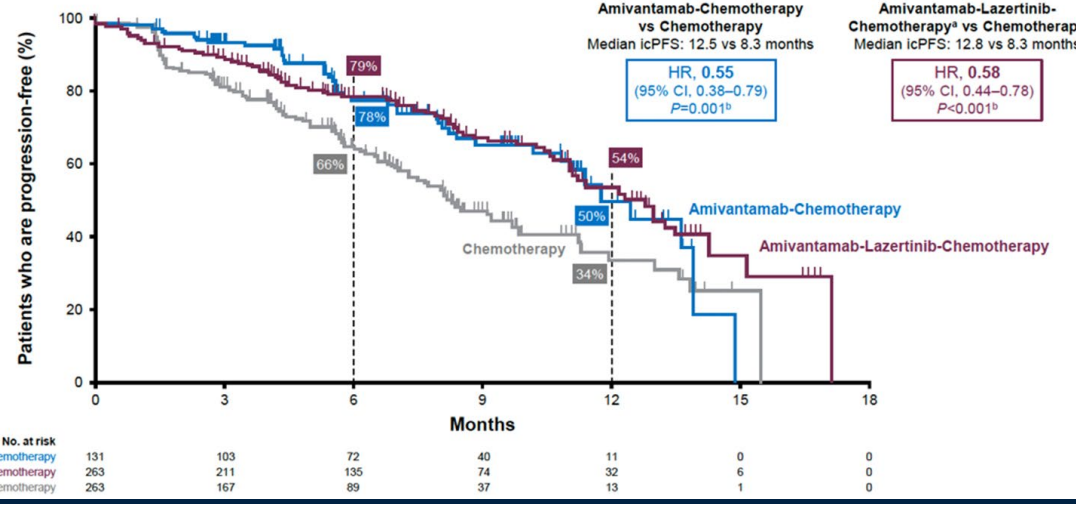
Response

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)

PFS by BICR

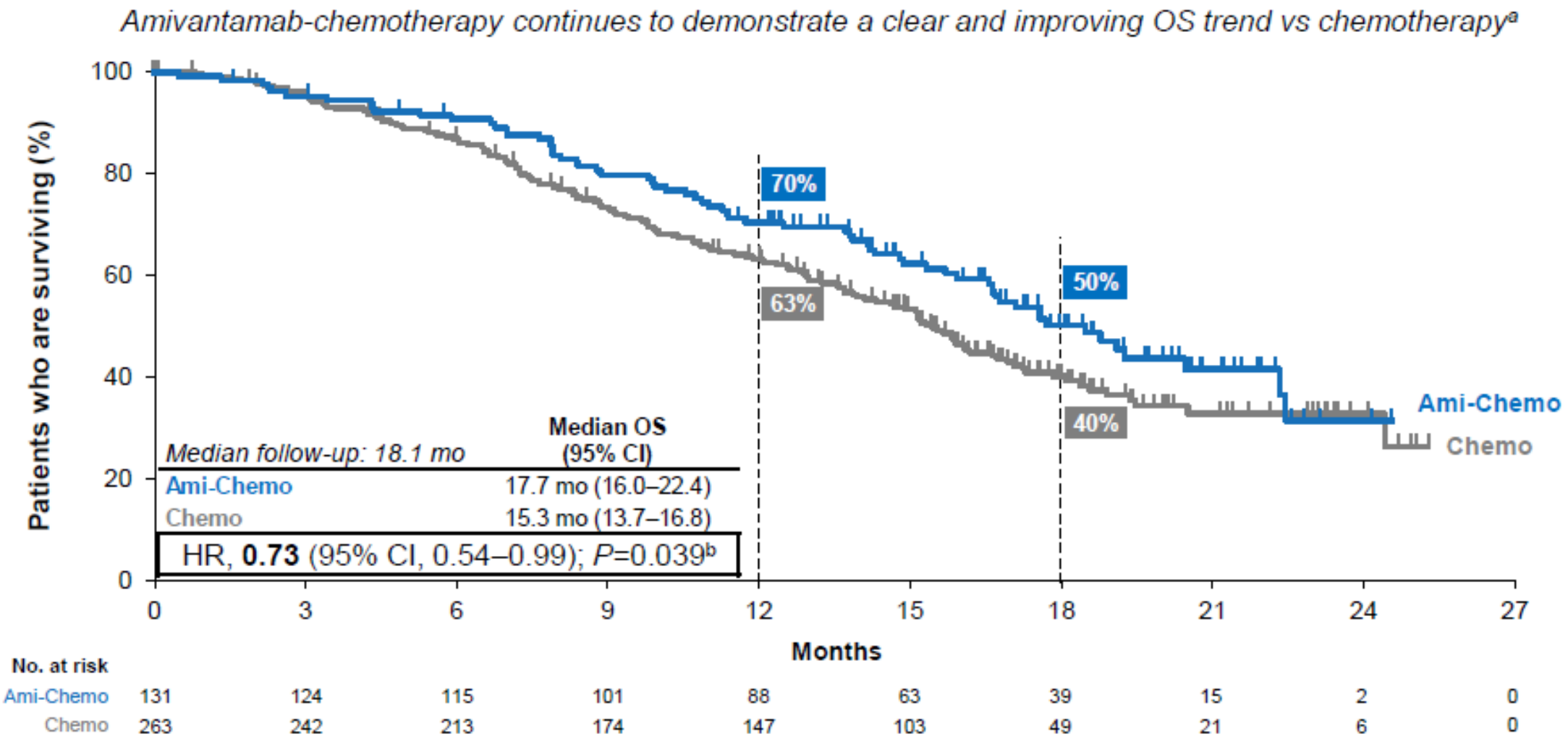


Intracranial PFS



Passaro A, et al. ESMO Congress 2023. Abs LBA15

MARIPOSA 2: 2nd Interim Overall Survival



Popat S, et al. ESMO 2024. Abs LBA54.

MARIPOSA 2: Summary of Adverse Events

	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)

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

Amivantamab-containing arms had higher rates of Grade ≥3 AEs and dose modifications compared with chemotherapy

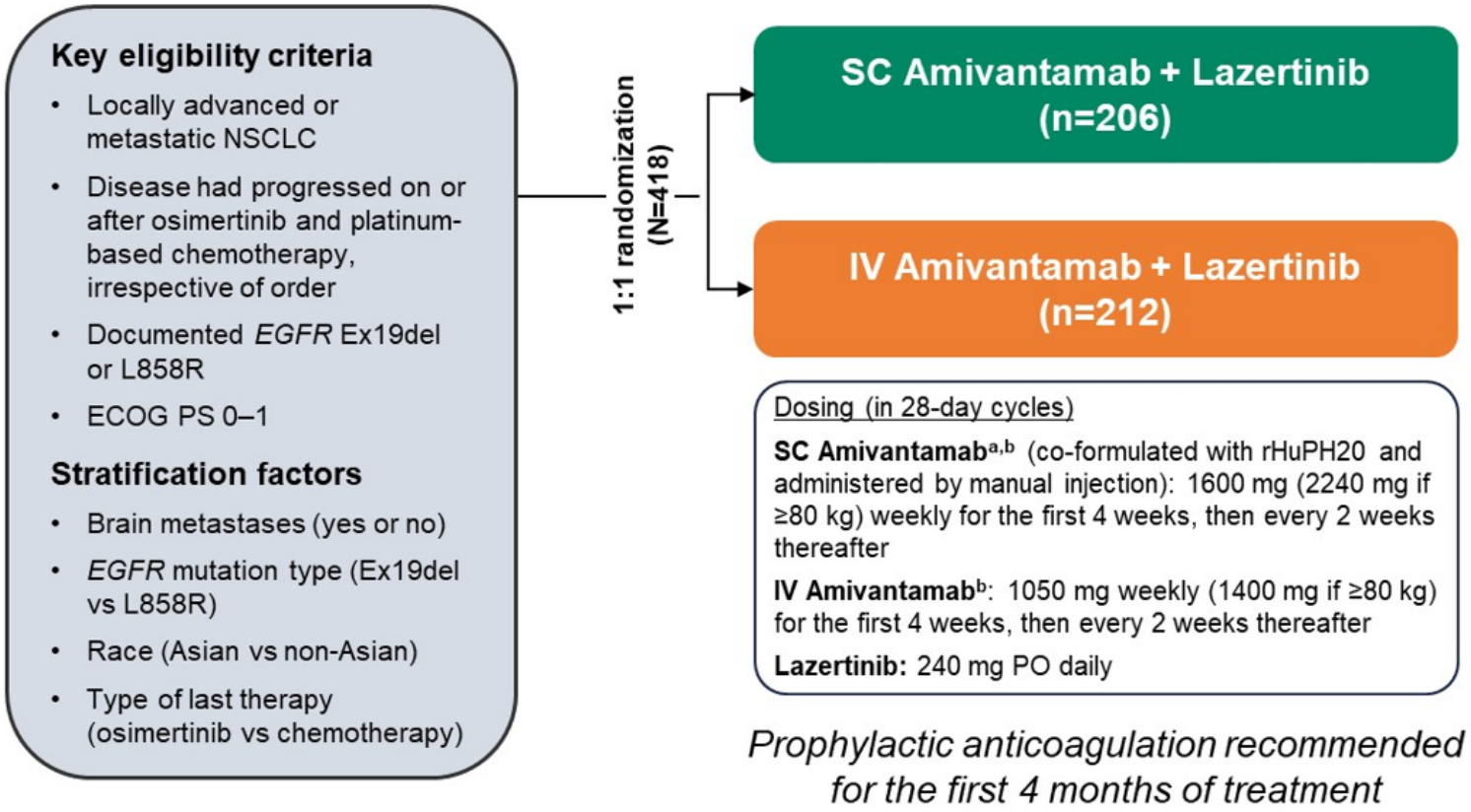
- Highest reported in the amivantamab-lazertinib-chemotherapy arm

Discontinuations of all agents due to TEAEs were:

- Chemotherapy: 2%
- Amivantamab-Chemotherapy: 8%
- Amivantamab-Lazertinib-Chemotherapy:10%

Passaro A, et al. ESMO Congress 2023. Abs LBA15.

PALOMA-3: Subcutaneous (SC) Amivantimab + Lazertinib in 2L Treatment of *EGFR*-Mutant NSCLC



Co-primary endpoints[c]:
- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:
- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:
- OS

Leighl NB, et al. ASCO 2024. Abs LBA8505.

PALOMA-3: Efficacy Outcomes

Pharmacokinetics

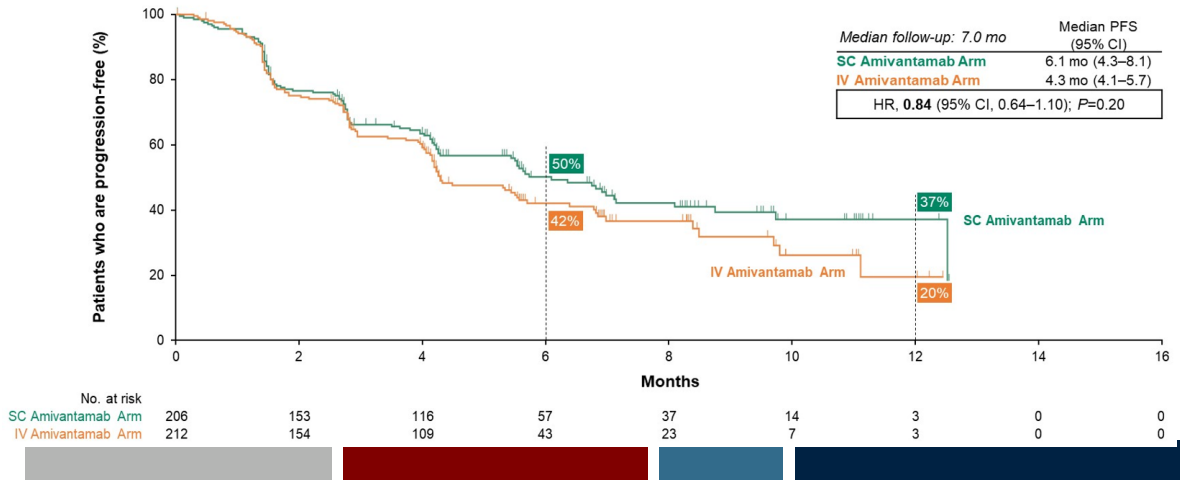
PK Parameter	Geometric Mean Ratio
C_{trough}	
C2D1, (90% CI)	1.15 (1.04–1.26)
C4D1, (90% CI)	1.43 (1.27–1.61)
C2 $AUC_{D1\text{-}D15}$	1.03 (0.98–1.09)

$AUC_{D1\text{-}D15}$, C2 area under the curve; C2D1, cycle 2 day 1; C4D1, cycle 4 day 1; C_{Trough}, trough concentration

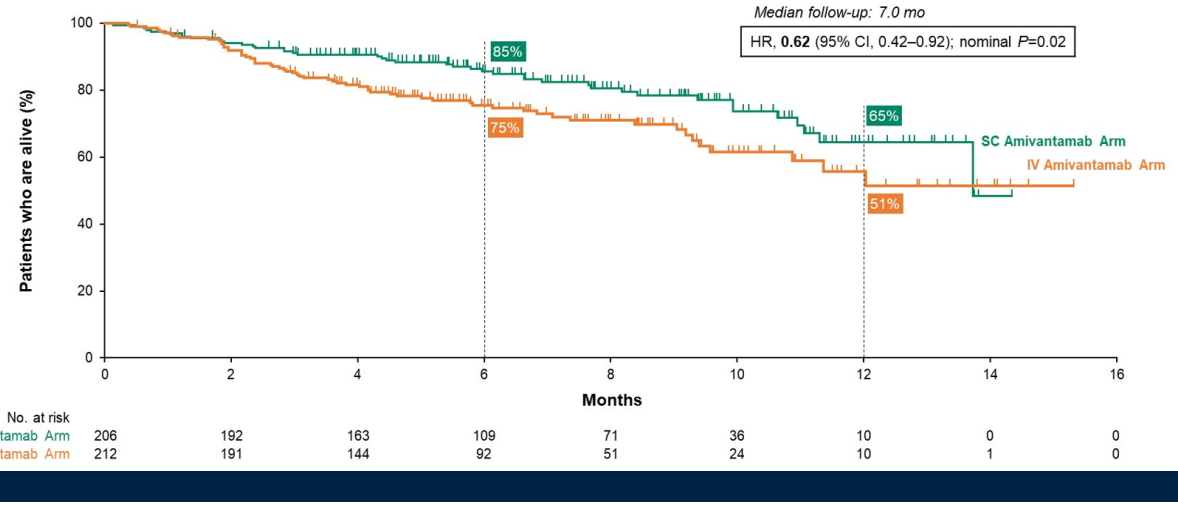
Response

	SC Amivantamab Arm (n=206)	IV Amivantamab Arm (n=212)
ORR, % (95% CI)[a]		
All responders	**30 (24–37)**	**33 (26–39)**
	Relative risk, 0.92 (95% CI, 0.70–1.23); *P*=0.001	
Confirmed responders	**27 (21–33)**	**27 (21–33)**
	Relative risk, 0.99 (95% CI, 0.72–1.36); *P*<0.001	
Best response, n (%)		
CR	1 (0.5)	1 (0.5)
PR	61 (30)	68 (32)
SD	93 (45)	81 (38)
PD	37 (18)	42 (20)
Not evaluable	14 (7)	20 (9)
DCR, % (95% CI)[b]	**75 (69–81)**	**71 (64–77)**
Median time to response (range), mo	**1.5 (1.2–6.9)**	**1.5 (1.2–9.9)**

PFS

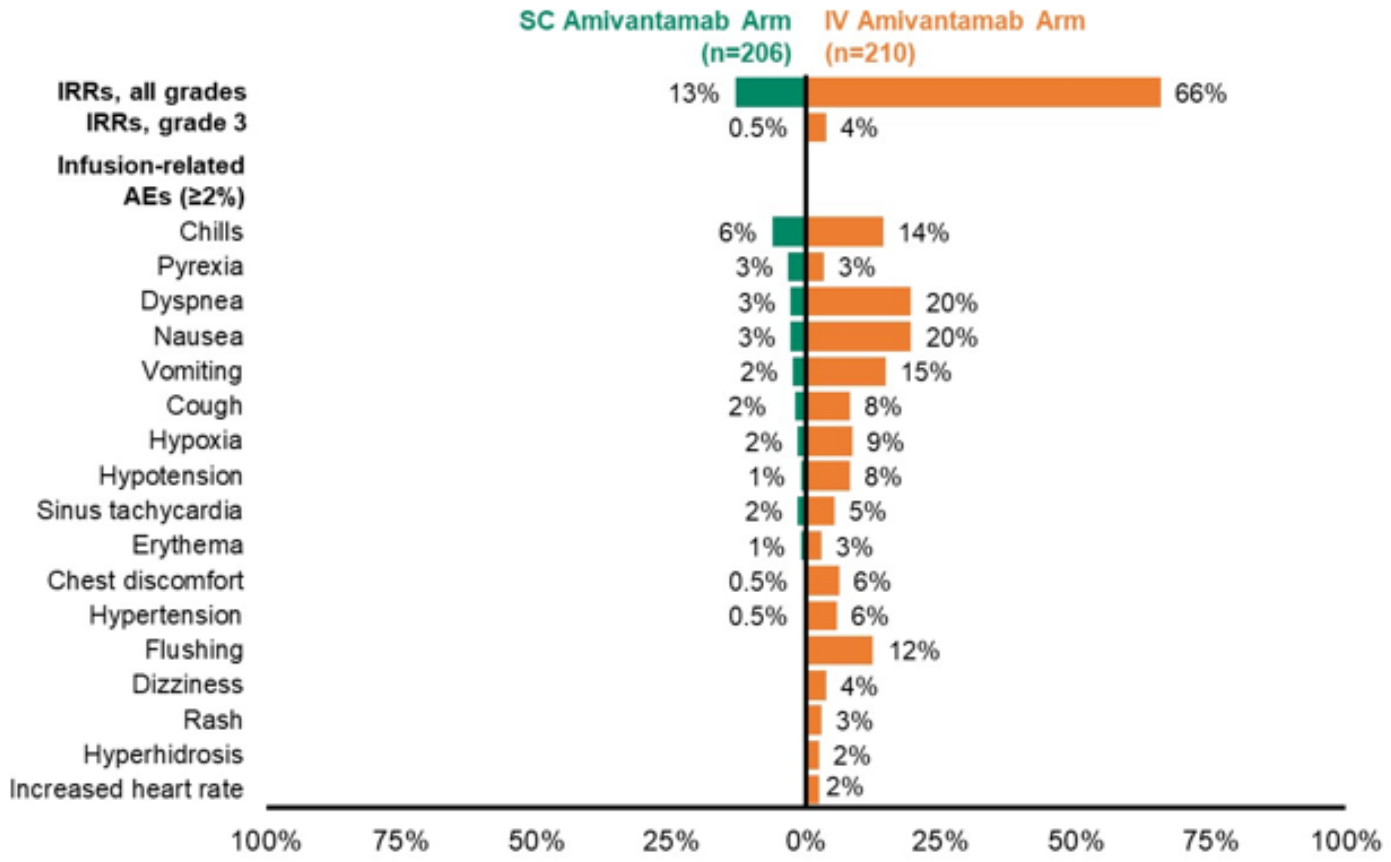


Overall Survival



Leighl NB, et al. ASCO 2024. Abs LBA8505.

PALOMA-3: Incidence of IRR-related Symptoms



- IRRs were observed in 13% of patients in the SC arm vs 66% in the IV arm, representing a 5-fold reduction
  - There were no grade 4 or 5 IRRs
  - Most IRRs occurred during Cycle 1
- IRRs leading to hospitalization were not observed in the SC arm vs 2 events in the IV arm
- No IRR-related discontinuations occurred in the SC arm vs 4 events in the IV arm

Will SubQ Ami be the s

- PALOMA 3 evaluated subQ IV Ami/Laz in 2L+ Setting
- In short, IRRs are less, othe the same

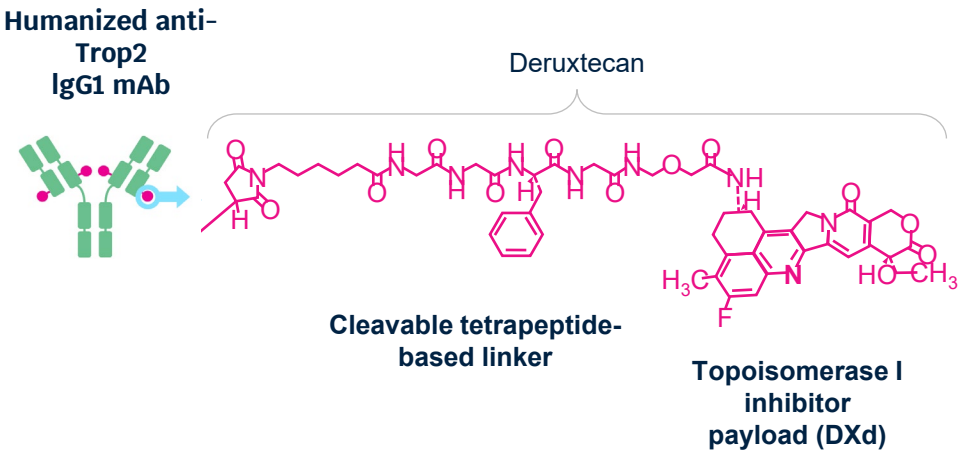
TABLE 3. Overview of AEs

AE[a]	Subcutaneous Group (n = 206), No. (%)		Intravenous Group (n = 210), No. (%)	
Any event	204 (99)		209 (99)	
Grade ≥3	107 (52)		118 (56)	
Any serious event	59 (29)		64 (30)	
Any event resulting in death	7 (3)		10 (5)	
Any event leading to:				
Interruption of any study agent[b]	127 (62)		127 (60)	
Reduction of any study agent	63 (31)		52 (25)	
Discontinuation of any study agent	26 (13)		29 (14)	
AEs reported in ≥15% of patients in either group[c]	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Nausea	60 (29)	1 (0.5)	52 (25)	3 (1)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)
Increased alanine aminotransferase	46 (22)	6 (3)	56 (27)	8 (4)
Decreased appetite	45 (22)	1 (0.5)	52 (25)	3 (1)
Fatigue	44 (21)	3 (1)	43 (20)	5 (2)
Vomiting	44 (21)	2 (1)	41 (20)	1 (0.5)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Constipation	42 (20)	0	42 (20)	1 (0.5)
Headache	42 (20)	1 (0.5)	36 (17)	1 (0.5)
Increased aspartate aminotransferase	42 (20)	2 (1)	45 (21)	3 (1)
Anemia	39 (19)	4 (2)	40 (19)	5 (2)
Pruritus	33 (16)	0	25 (12)	0
Hypocalcemia	33 (16)	0	27 (13)	0
Myalgia	32 (16)	0	13 (6)	0
Asthenia	31 (15)	4 (2)	23 (11)	2 (1)
Thrombocytopenia	29 (14)	4 (2)	33 (16)	2 (1)
IRR	27 (13)	1 (0.5)	138 (66)	8 (4)

TROPION Lung 05/01

Datopotamab deruxtecan (Dato-DXd)

June 23, 2025: FDA granted accelerated approval of datopotamab deruxtecan-dlnk for the treatment of adults with locally advanced or metastatic *EGFR*-mutated NSCLC who have previously received EGFR-directed therapy and platinum-based chemotherapy.



7 key attributes of Dato-DXd
Payload mechanism of action: Topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ~ 4
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Bystander antitumor effect

Steuer. ASCO 2022.

TROPION-Lung05: Efficacy With Dato-DXd in NSCLC With Actionable Genomic Alterations

TROPION-Lung05 (Phase II study)

- **Presence of ≥1 actionable genomic alteration** *(EGFR, ALK, ROS1, NTRK, BRAF, MET* exon 14 skipping, or *RET)*
  - ≥1 line of targeted therapy
  - 1–2 prior cytotoxic agent–containing therapies including Pt-CT in the metastatic setting
  - Radiographic disease progression after most recent therapy

→ **Dato-DXd**
6 mg/kg Q3W[a]
(N=137)

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months[b]	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

Paz-Ares L et al. ESMO 2023. Abstract 1314MO; Garassino et al. WCLC 2024 PL.02.11

Pooled Analysis: TROPION-Lung05 and Lung01

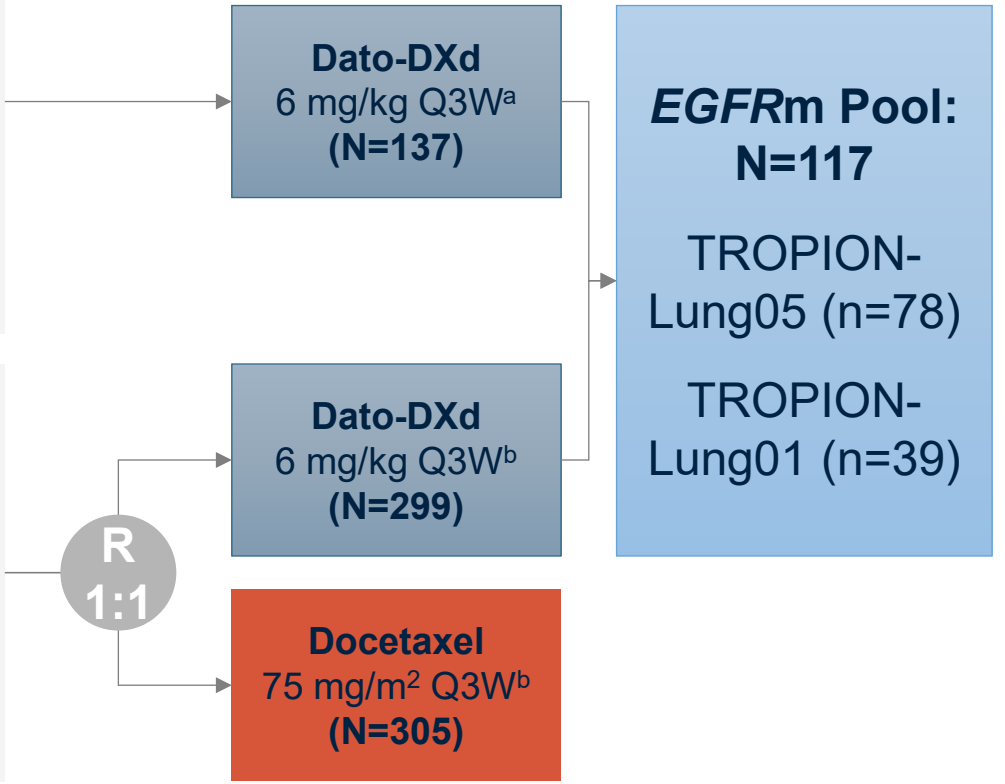
Patients with *EGFR*m NSCLC who received Dato-DXd 6 mg/kg Q3W were included in the pool

TROPION-Lung05 (Phase II study)

- **Presence of ≥1 actionable genomic alteration** *(EGFR, ALK, ROS1, NTRK, BRAF, MET* exon 14 skipping, or *RET)*
  - ≥1 line of targeted therapy
  - 1–2 prior cytotoxic agent–containing therapies including Pt-CT in the metastatic setting
  - Radiographic disease progression after most recent therapy

TROPION-Lung01 (Phase III study)

- **In those with actionable genomic alterations** *(EGFR, ALK, ROS1, NTRK, BRAF, MET* exon 14 skipping, or *RET)*
  - 1–2 prior approved targeted therapies + Pt-CT, and ≤1 anti–PD-(L)1 mAb
  - No prior docetaxel



Endpoints:

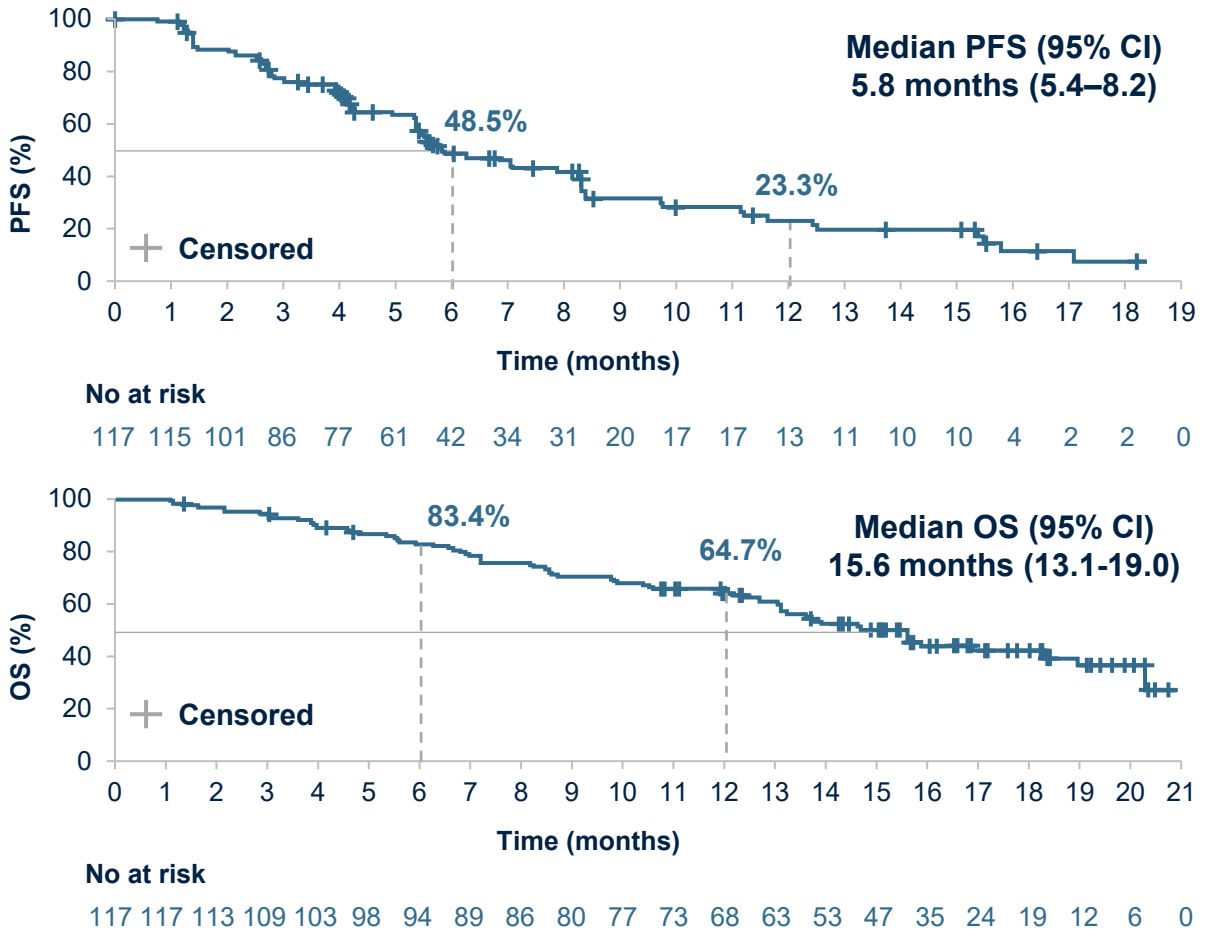
- ORR per BICR
- BOR per BICR
- DCR per BICR
- DOR per BICR
- PFS per BICR
- OS
- Safety

Ahn et al. ESMO Asia 2024.

Pooled Analysis: Efficacy

Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%)	50 (**42.7**)	43 (**44.8**)
[95% CI]	[33.6–52.2]	[34.6–55.3]
BOR, n (%)		
CR	5 (**4.3**)	4 (**4.2**)
PR	45 (**38.5**)	39 (**40.6**)
SD	48 (41.0)	37 (38.5)
Non-CR/Non-PD	3 (2.6)	2 (2.1)
PD	12 (10.3)	10 (10.4)
NE	4 (3.4)	4 (4.2)
Median DOR, months (95% CI)	**7.0** (4.2–9.8)	**6.9** (4.2–9.8)
DCR,[b] n (%)	101 (**86.3**)	82 (**85.4**)
[95% CI]	[78.7–92.0]	[76.7–91.8]
Median PFS, months (95% CI)	**5.8** (5.4–8.2)	**5.7** (5.4–7.9)
Median OS, months (95% CI)	**15.6** (13.1–19.0)	**14.7** (13.0–18.3)

PFS and OS in the *EGFR*m Pool (N=117)

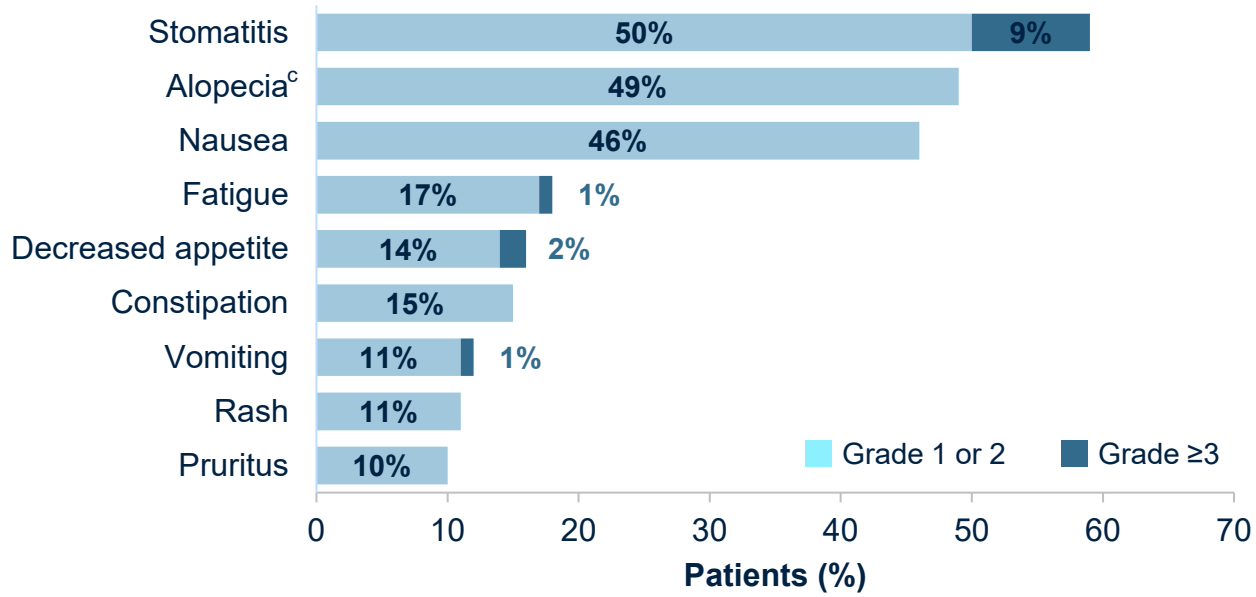


Ahn et al. ESMO Asia 2024.

Pooled Analysis: Safety

	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs[a], n (%)	
Stomatitis/oral mucositis	81 (69)
Grade 3[b]	11 (9)
Ocular surface events	38 (32)
Grade 3[b]	3 (3)
Adjudicated drug-related ILD	5 (4)
Grade 3[b]	1 (1)

TRAEs Occurring in ≥10% of *EGFR*m Pool (N=117)



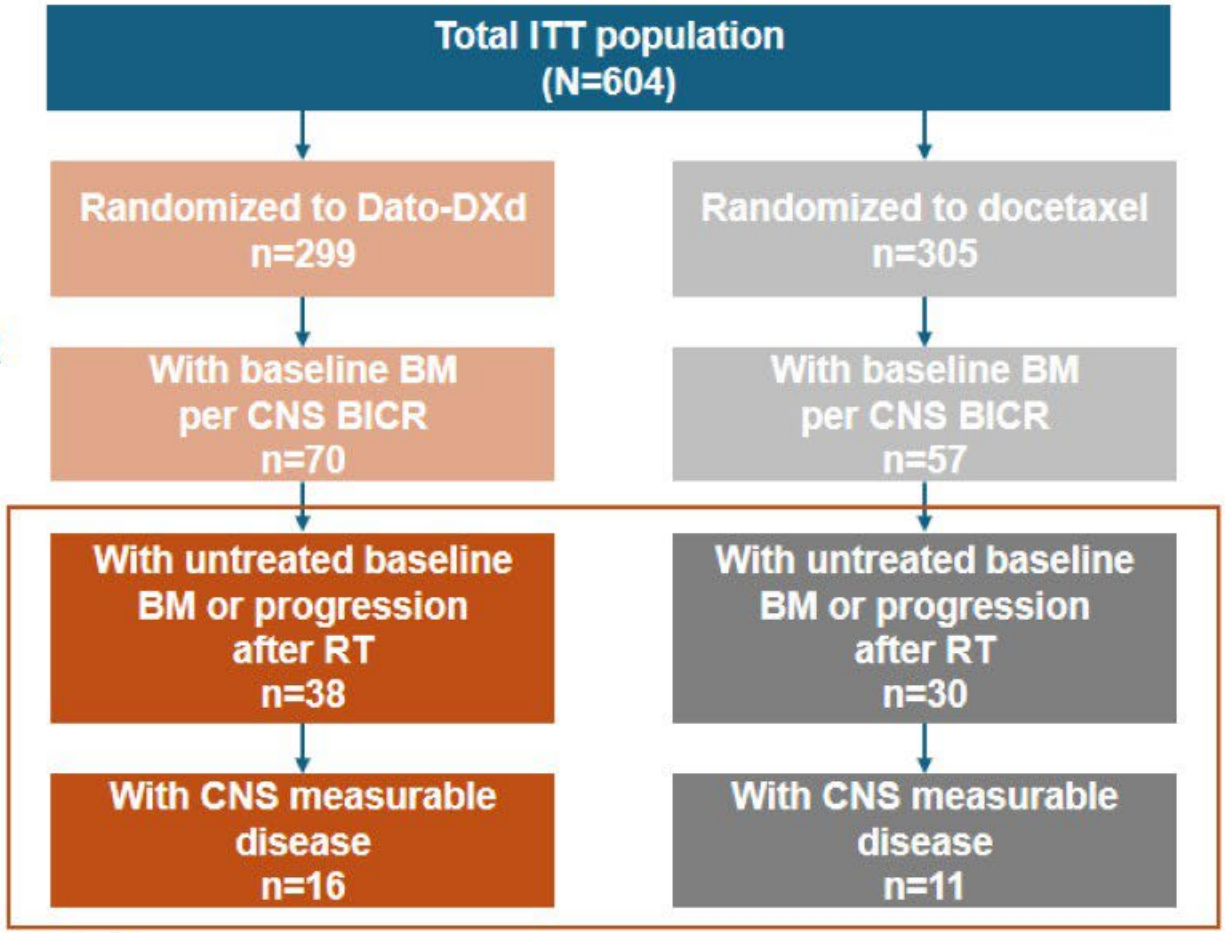
- Median Dato-DXd treatment duration: **6.1 months**

- Overall safety profile consistent with TROPION-Lung01 and 05
- No grade 4 or 5 adjudicated drug-related ILD
- Ocular surface events[a] were primarily dry eye (12%), vision blurred and keratitis (each 7%)
- No TRAEs associated with death

Ahn et al. ESMO Asia 2024.

Methods and Patient Population

- Brain imaging (MRI or CT) was performed prior to enrollment for all patients, and every 6 weeks thereafter for those with investigator-identified BM at baseline[a]
- Patients with baseline BM identified by CNS BICR (neuroradiologist-reviewed brain imaging) per CNS RECIST were analyzed



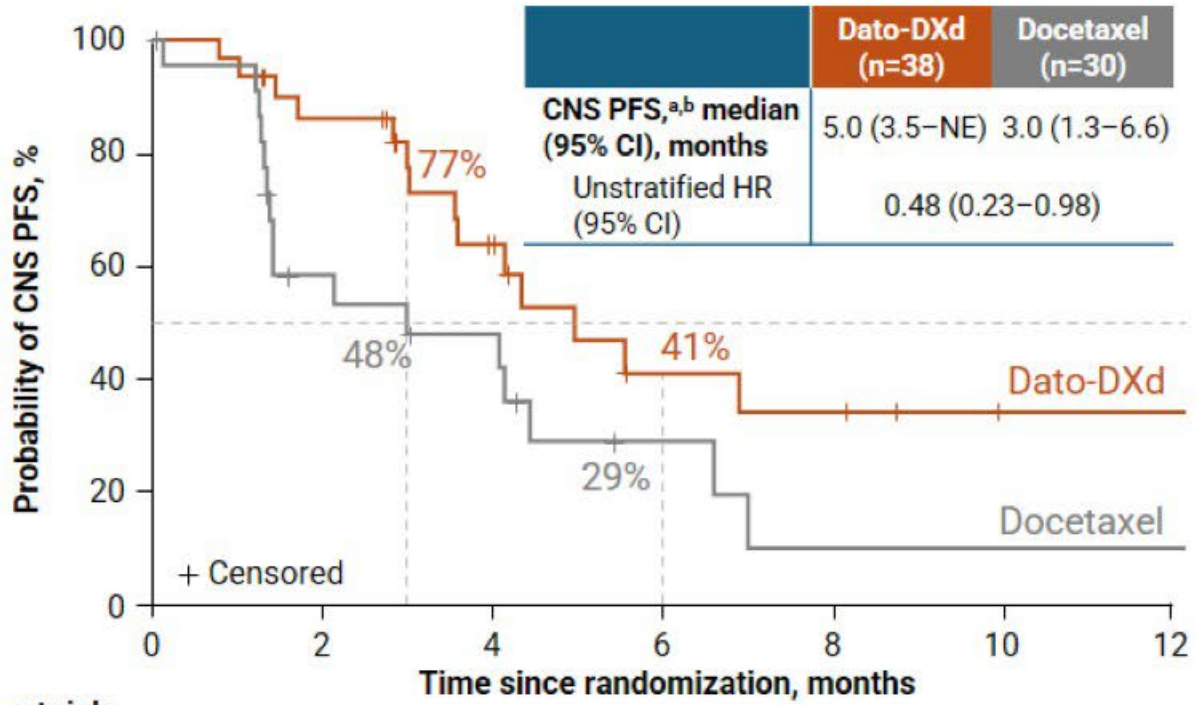
Data cutoff: August 30, 2024.

[a]For assessment of CNS response, on-treatment imaging must have been performed using the same modality as at baseline.

BM, brain metastases; CT, computed tomography; ITT, intent-to-treat; MRI, magnetic resonance imaging; RT, radiotherapy.

CNS PFS

All Patients With Untreated BM or Progression After RT

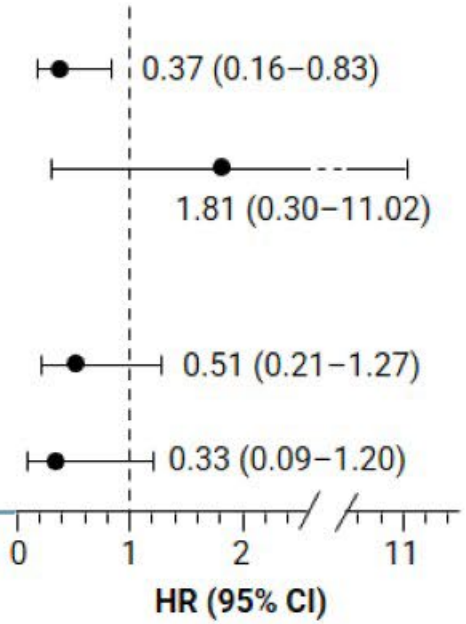


	Dato-DXd (n=38)	Docetaxel (n=30)
CNS PFS,[a,b] median (95% CI), months	5.0 (3.5–NE)	3.0 (1.3–6.6)
Unstratified HR (95% CI)	0.48 (0.23–0.98)	

No. at risk

Dato-DXd	38	23	13	6	5	2	2
Docetaxel	30	11	8	3	1	1	1

Subgroup	Events, n / N: Dato-DXd (n=38)	Events, n / N: Docetaxel (n=30)	HR (95% CI)
Histology			
Nonsquamous (n=56)	11 / 31	13 / 25	0.37 (0.16–0.83)
Squamous (n=12)	3 / 7	3 / 5	1.81 (0.30–11.02)
***EGFR*m**			
Absent (n=46)	9 / 27	10 / 19	0.51 (0.21–1.27)
Present (n=22)	5 / 11	6 / 11	0.33 (0.09–1.20)

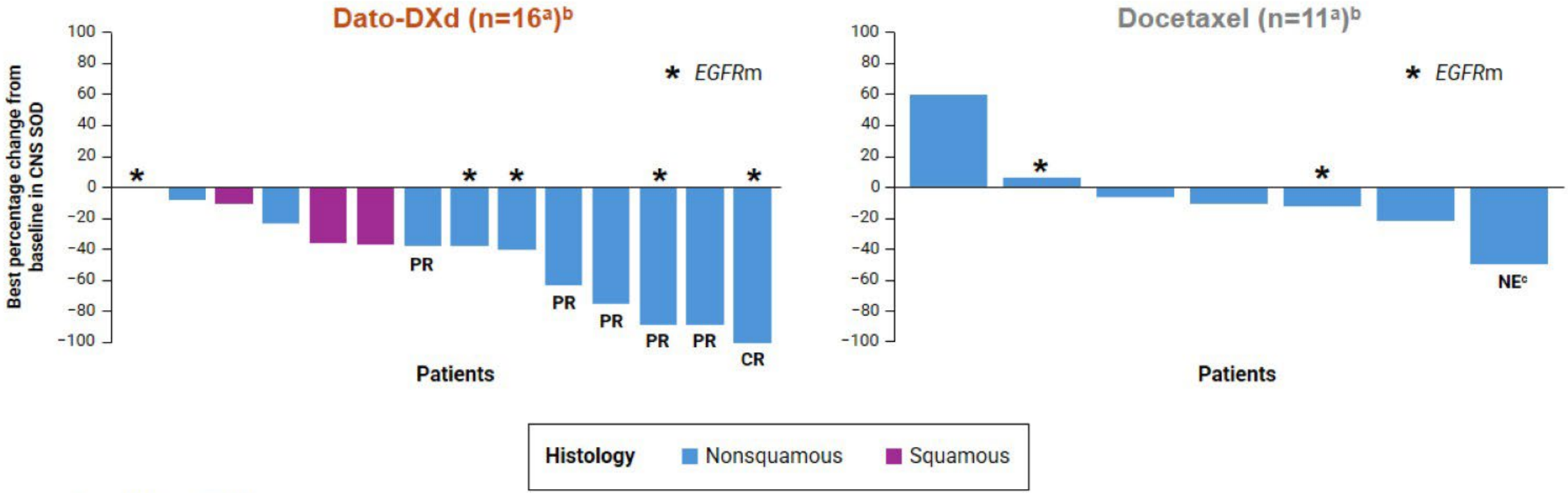


Data cutoff: August 30, 2024.

[a]In the Dato-DXd and docetaxel arms, 24 (63.2%) and 14 (46.7%) patients, respectively, were censored. PFS was defined as the time (in months) from randomization to first documentation of PD or death due to any cause, whichever occurred first. In estimations of CNS PFS, patients without PD were not censored or considered to have PD at the start of a subsequent anticancer therapy. [b]Assessed by CNS BICR per CNS RECIST.
CI, confidence interval; HR, hazard ratio; NE, not estimable; PD, progressive disease.

Intracranial Activity

Patients With Untreated BM or Progression After RT, and CNS Measurable Disease



Data cutoff: August 30, 2024.

[a]Two patients in the Dato-DXd arm and 4 patients in the docetaxel arm did not have adequate post-baseline tumor assessments and were excluded from the waterfall plots. [b]CNS BOR assessed by CNS BICR per CNS RECIST is presented underneath bars for patients with CNS BOR of PR, CR, or NE. [c]This patient had an initial CNS assessment that was <5 weeks after randomization and a subsequent assessment of PD due to new brain lesions, resulting in a CNS BOR of NE.

NE, not evaluable.

Management of Stomatitis

Toxicity management recommendations

- **Daily use of prophylactic steroid-containing mouthwash highly recommended** (4 times daily, swish for 1–2 minutes)
  - If steroid-containing mouthwash is not available, substitute with non-alcoholic and/or bicarbonate-containing mouthwash (4 to 6 times per day)
- **Good oral hygiene and education** (gentle teeth brushing after meals/bedtime with bland, fluoride toothpaste; daily flossing; hygiene/hydration education)
- **Cryotherapy** (iced chips or iced water held in mouth throughout infusion)

Ocular toxicity with Dato-DXd

TIMING OF OCULAR TOXICITY

Median time to onset: **65 days**

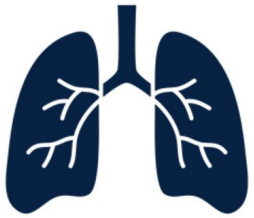
Median time to resolution‡: **67 days**

Management:

- **Ophthalmic exam** at treatment initiation, annually while on treatment, at end of treatment, and as clinically indicated.
- Advise patients to **avoid contact lenses**
- **Lubricant eye drops** several times daily (e.g. x4) for prophylaxis

Proactive Management of ILD With ADCs – The 5 S Rules

1



Screen

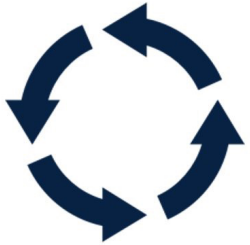
- Careful patient selection is warranted before initiating T-DXd to optimize the monitoring strategies based on the baseline risk
- Screening continues during treatment, with regular clinical assessments to exclude signs/symptoms of ILD

2

Scan

- The fundamental diagnostic tools for ILD remain radiological scans, with preference for high-resolution CT scans of the chest
- A baseline scan is recommended, with repeat scans to be performed every 6-12 weeks

3



Synergy

- Minimizing the risk of ILD involves teamwork, which includes educating patients and all the care team, as well as multidisciplinary management once ILD is suspected

4

Suspend Treatment

- T-DXd should always be interrupted if ILD is suspected; it can only be restarted in the case of asymptomatic ILD that fully resolves

5

Steroids

- The mainstay for treating T-DXd–induced ILD remains corticosteroids, with the dose to be adapted to the toxicity grade

MET Targeted Therapy

SACHI Phase 3 Study Design

Randomized, open-label, multi-center phase 3 study conducted across 68 centers in China.

- 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

→ **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**

METamp:

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

Stratification factors:

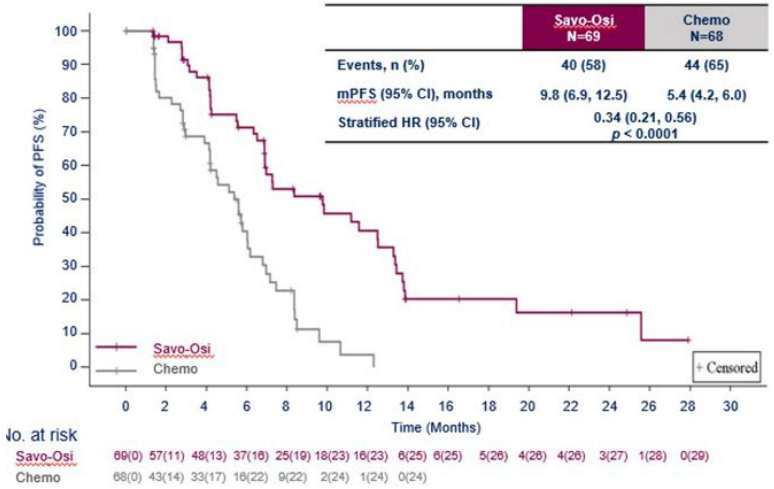
- **Brain metastasis**: (yes or no)
- **Prior 3rd G EGFR-TKI**: (yes or no)
- **EGFR mutation**: (ex19del vs L858R vs others)

Primary endpoint: PFS by investigator

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

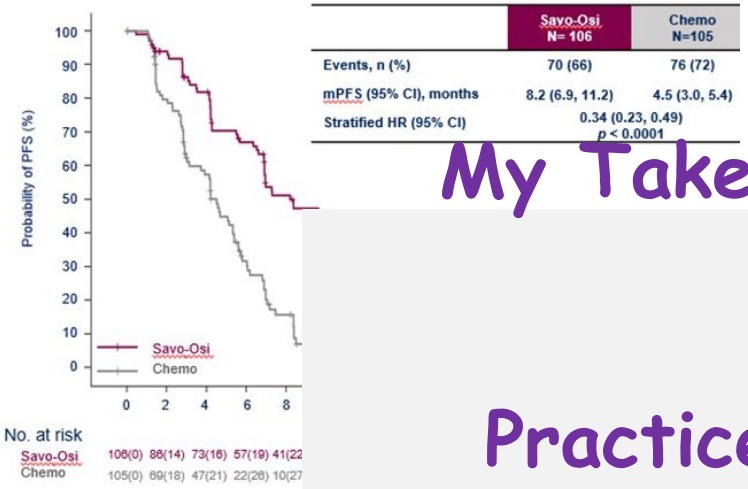
Lu S et al, ASCO Annual Meeting 2025

Prior 1st /2nd G EGFR-TKI-treated population



	Savo-Osi N=69	Chemo N=68
Events, n (%)	40 (58)	44 (65)
mPFS (95% CI), months	9.8 (6.9, 12.5)	5.4 (4.2, 6.0)
Stratified HR (95% CI)	0.34 (0.21, 0.56) $p < 0.0001$	

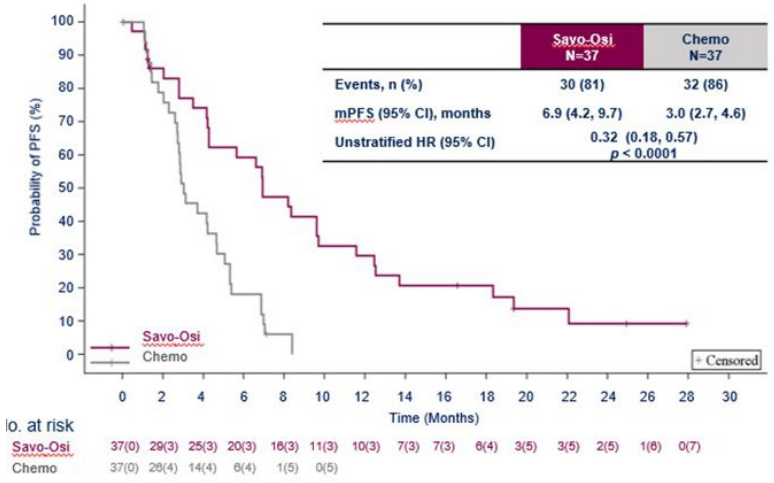
ITT population



	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) $p < 0.0001$	

- Prior 3rd G EGFR-TKI treated subgroup

Investigator



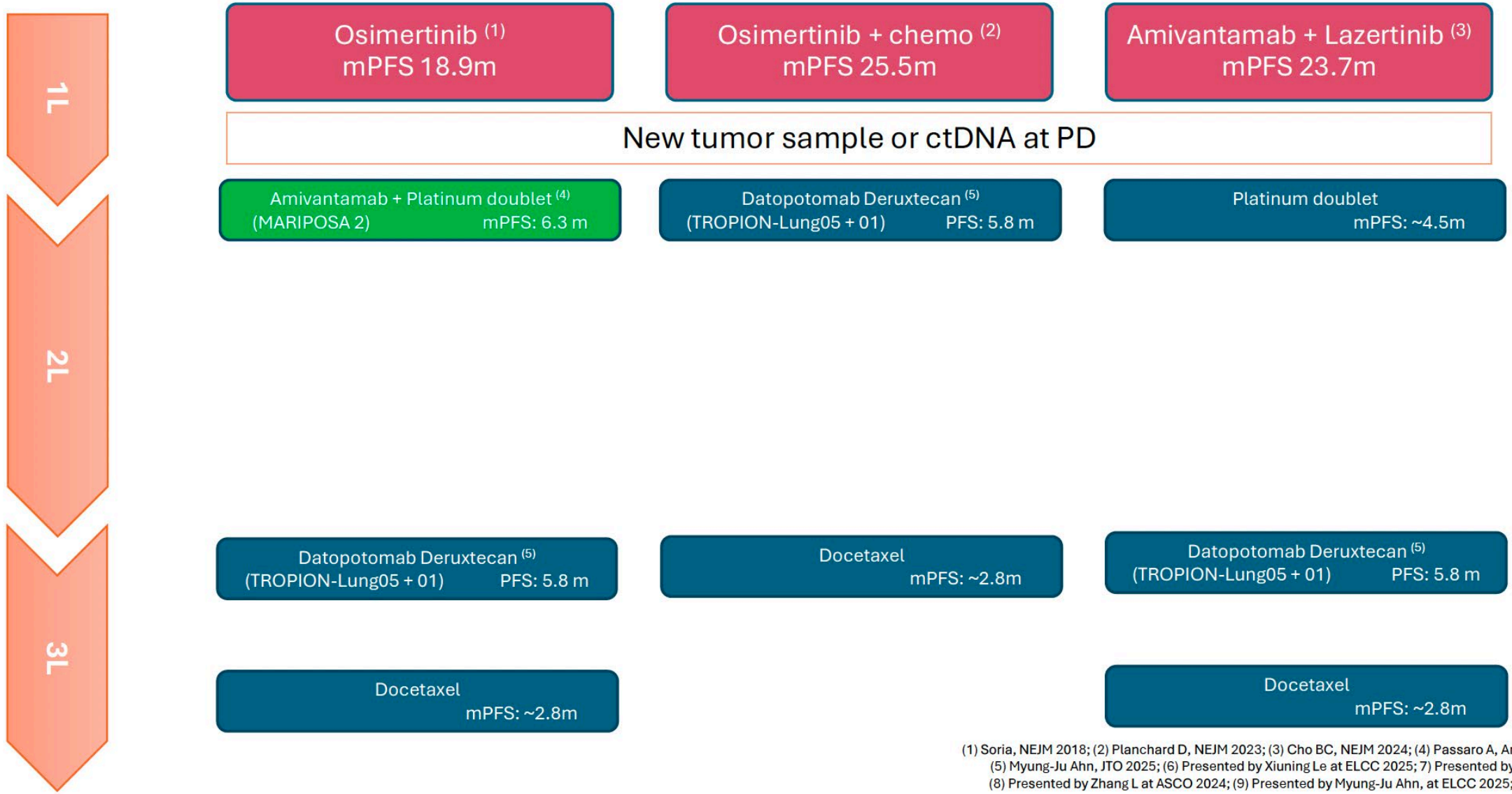
	Savo-Osi N=37	Chemo N=37
Events, n (%)	30 (81)	32 (86)
mPFS (95% CI), months	6.9 (4.2, 9.7)	3.0 (2.7, 4.6)
Unstratified HR (95% CI)	0.32 (0.18, 0.57) $p < 0.0001$	

My Takeaways – EGFR MT NSCLC

Practice Affirming Data

- Check for MET FISH upon PD
- Use of Capmatinib upon PD
- More Options = Better for Pts!

Lu S et al, ASCO Annual Meeting 2025



(1) Soria, NEJM 2018; (2) Planchard D, NEJM 2023; (3) Cho BC, NEJM 2024; (4) Passaro A, Annals of Oncology 2023; (5) Myung-Ju Ahn, JTO 2025; (6) Presented by Xiuning Le at ELCC 2025; 7) Presented by Zhang L at ASCO 2025; (8) Presented by Zhang L at ASCO 2024; (9) Presented by Myung-Ju Ahn, at ELCC 2025; (10) Besse B, JTO 2025

Cases

57 year old male with Oligometastatic lung cancer presenting with a left upper lobe of lung mass and lytic lesion in the left humeral head and sternum, diagnosed 11/2024. Guardant liquid biopsy and CARIS NGS with EGFR Exon 21 mutation.

a. Status post surgical stabilization of the left humerus
b. Started carboplatin, pemetrexed, and Tagrisso based on an eGFR mutation 12/03/2024, along with Zometa.
c. Transitioned to pemetrexed and Tagrisso maintenance, starting 03/14/2025.
d. Oligoprogression in the left upper lobe noted on PET 08/07/2025.
e. Status post SBRT to the area of oligometastatic progression in the left upper lobe.

Continue Tagrisso and pemetrexed → Tagrisso monotherapy.

Clinical stage IIIA (cT1c pN2 cM0) pulmonary adenocarcinoma of the RUL with ipsilateral mediastinal/hilar involvement

- Small burden N2 disease only pathologically detected on EBUS-guided sampling but was not measurable imaging
- Instead of concurrent cCRT, neoadjuvant systemic therapy followed by surgery being planned
- NGS showed **EGFR exon 19 deletion**, PD-L1 CPS 60%
- Pre-treatment ctDNA positive 0.024 %
- Neoadjuvant Osimertinib offered per recent NeoADAURA study - MPR were significantly higher for osimertinib given with (26%) and without (25%) chemotherapy versus placebo plus chemotherapy (2%); however role of added chemotherapy to osimertinib is unknown
- If the patient is chemotherapy eligible and willing, would you still advocate adding chemo to osimertinib or defer chemo?

Extra Slides

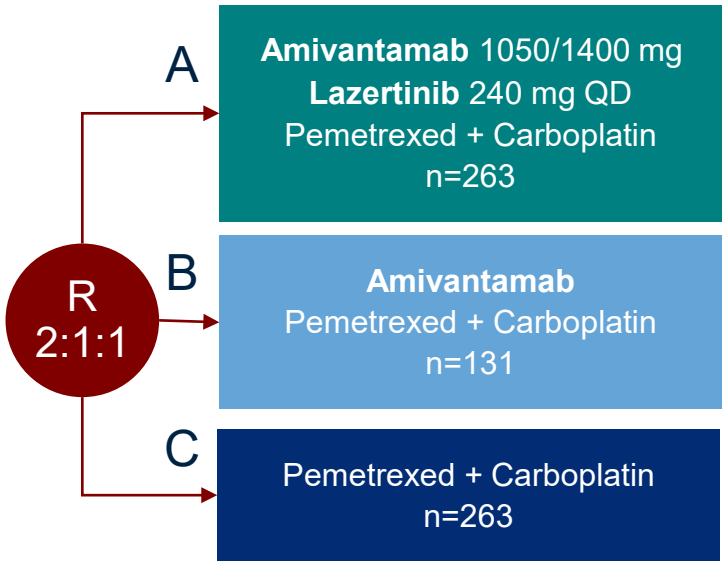
MARIPOSA-2: Amivantamab + Lazertinib + CT vs CT in *EGFR*m mNSCLC After Osimertinib Failure

Study population (N=657)

- Locally advanced or metastatic NSCLC
- After PD to osimertinib
- *EGFR* Exon19del or L858R mutation

Randomization stratified by:

- *EGFR* mutation (Exon19del/L858R)
- Asian race (yes/no)
- Brain metastases (yes/no)



Primary:

- PFS by BICR

Key secondary:

- OS
- ORR
- DOR
- PFS2
- Intracranial PFS
- Safety

- 44%-46% of pts had a history of CNS metastases

Efficacy, n (%)	**Ami + Laz + CT** (n=263)	**Ami + + CT** (n=131)	**CT** (n=263)
mPFS, mo	8.3	6.3	4.2
HR vs CT (95% CI) *P* value	0.44 (0.35-0.56) <0.001	0.48 (0.36-0.64) <0.001	-
ORR, % *P* value	63 <0.001	64 <0.001	36 -
Interim OS HR (95% CI)	0.96 (0.67-1.35)	0.77 (0.49-1.21)	-
Intracranial PFS, mo	12.8	12.5	8.3
HR vs CT *P* value	0.58 <0.001	0.55 <0.001	-

Safety Summary

- Predominant AEs in the Ami-containing arms were hematologic-, EGFR-, and MET-related. Ami + CT had lower rates of hematologic AEs than Ami + Laz + CT

Median follow-up of 8.7 mo.

1. ClinicalTrials.gov. NCT04988295. October 11, 2023. http//clinicaltrials.gov/ct2/show/NCT04988295 2. Passaro A, et al. ESMO 2023. Abstract LBA15.