Cases from the Community: Investigators Discuss the Optimal Management of EGFR-Mutated Non-Small Cell Lung Cancer

Friday, May 29, 2026
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Sarah B Goldberg, MD, MPH
Jonathan Goldman, MD
Joel W Neal, MD, PhD
Antonio Passaro, MD, PhD

Moderator

Jacob Sands, MD

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Clinicians in the Meeting Room

Networked iPads are available.

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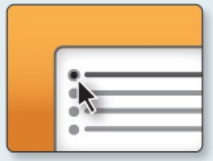

Answer Survey Questions: Complete the pre- and postmeeting surveys. Survey questions will be discussed throughout the meeting.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

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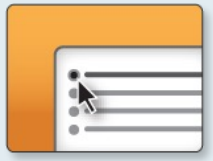

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About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based program. An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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Friday May 29	**Gastroesophageal Cancers** 11:30 AM – 1:00 PM CT (12:30 PM – 2:00 PM ET)
	Non-Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Chronic Lymphocytic Leukemia 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	Colorectal Cancer 6:30 PM – 8:00 PM CT (7:30 PM – 9:00 PM ET)
Saturday May 30	**Ovarian Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Prostate Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Small Cell Lung Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Sunday May 31	**Oral SERDs and Agents Targeting the PI3K/AKT/mTOR Pathway for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Endometrial Cancer 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	CAR T-Cell Therapy and Bispecific Antibodies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 1	**ADCs for Breast Cancer** 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Novel Therapies for Non-Hodgkin Lymphoma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
	Relapsed/Refractory Multiple Myeloma 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 2	**Myelofibrosis (Webinar)**

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Moderator

Jacob Sands, MD

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Cases from the Community

Susmitha Apuri, MD
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& Research Institute
Inverness and Lecanto, Florida

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Northside Hospital Cancer Institute
Athens, Georgia

Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

Neil Love, MD
Research To Practice
Miami, Florida

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Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

Module 2: EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC — Dr Neal

Module 3: Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC — Dr Sands

Module 4: Emerging Role of Bispecific Antibody-Based Approaches for EGFR-Mutated NSCLC — Dr Goldman

Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

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Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

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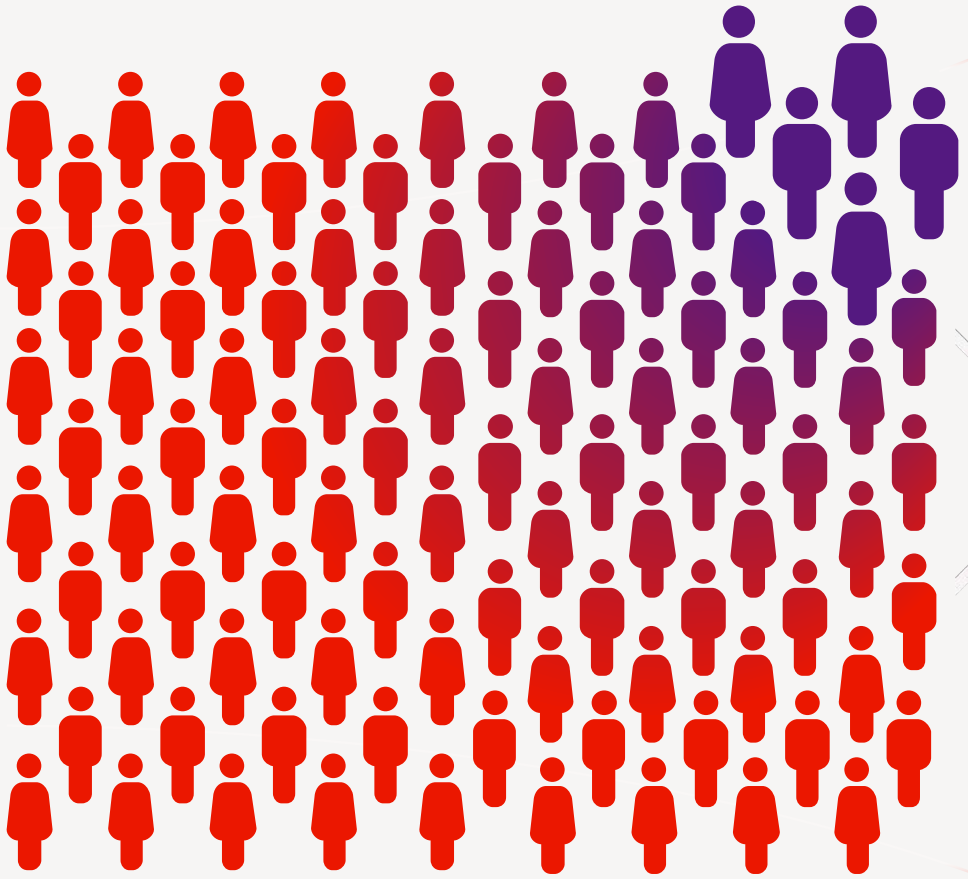
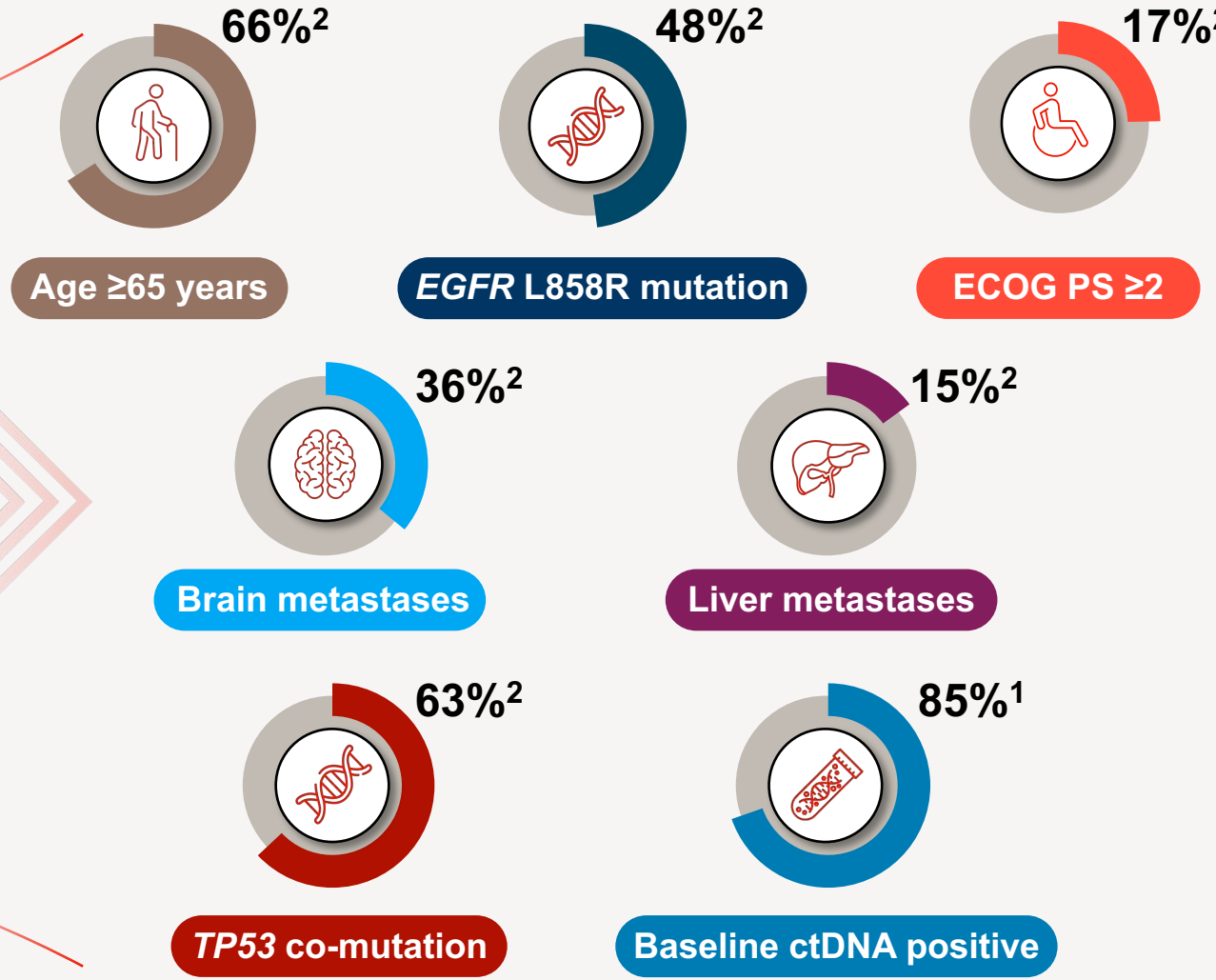
Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC)

Antonio Passaro, MD PhD
Division of Thoracic Oncology
European Institute of Oncology – IEO, Milan, Italy
Email: antonio.passaro@ieo.it **X**: @APassaroMD

~89–95% of *EGFR*-mutant NSCLC patients in the real-world have ≥1 high-risk feature[1,2]



Adapted from Passaro A. ELCC 2025.

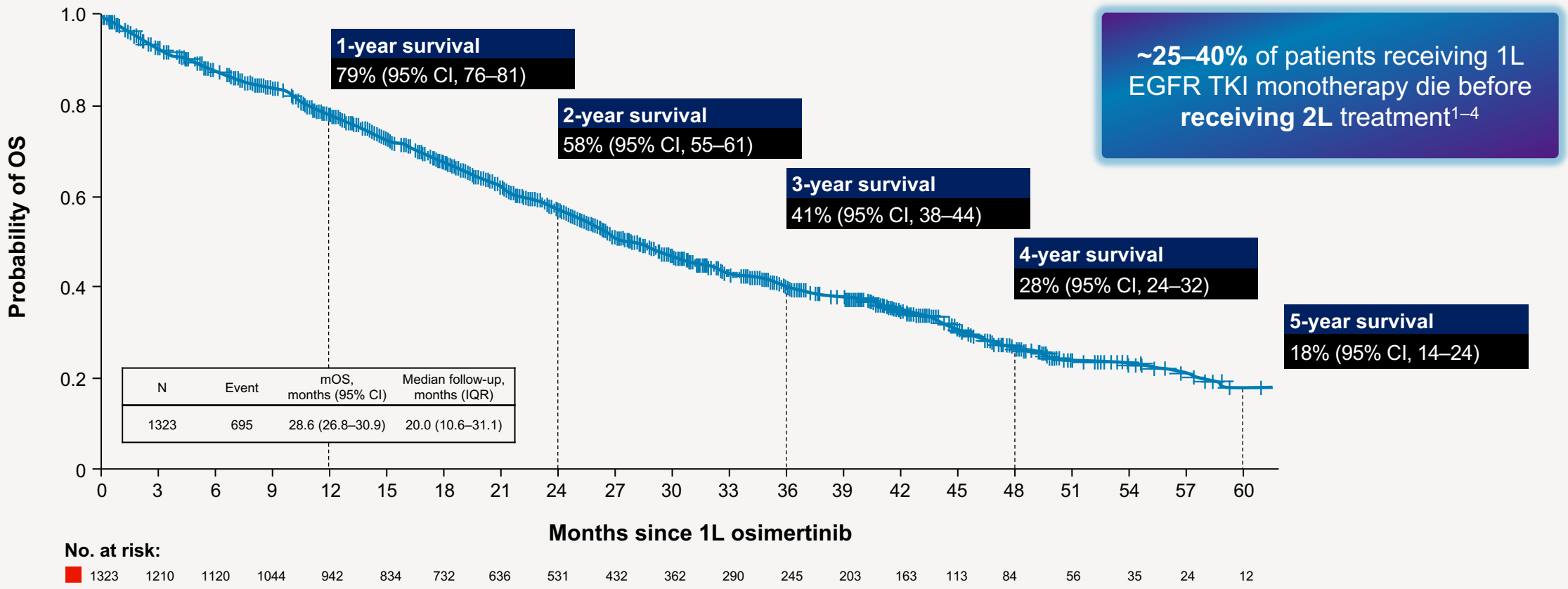


1. Felip E, et al. *Ann Oncol*. 2024;35:805–16; 2. Sabari JK, et al. *J Thorac Oncol*. 2025;20:1268–78.

ECOG PS, Eastern Cooperative Oncology Group performance status; ctDNA, circulating tumour DNA; TP53, tumour protein 53.

Despite advances in EGFR TKI monotherapy, long-term survival of patients remains poor

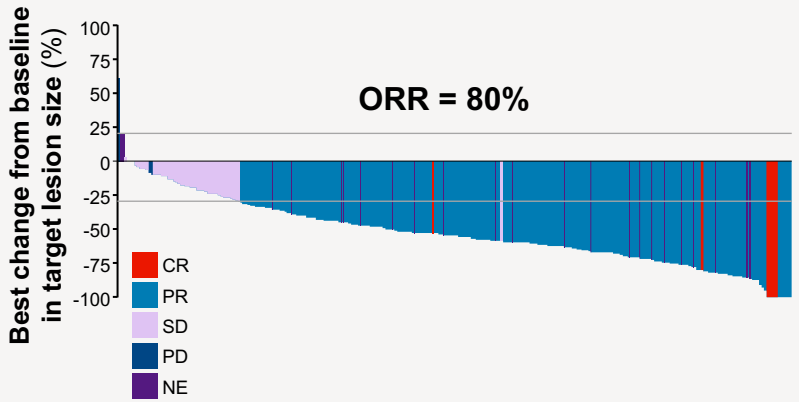
Real-world OS in patients with *EGFR*-mutant NSCLC treated with 1L osimertinib monotherapy

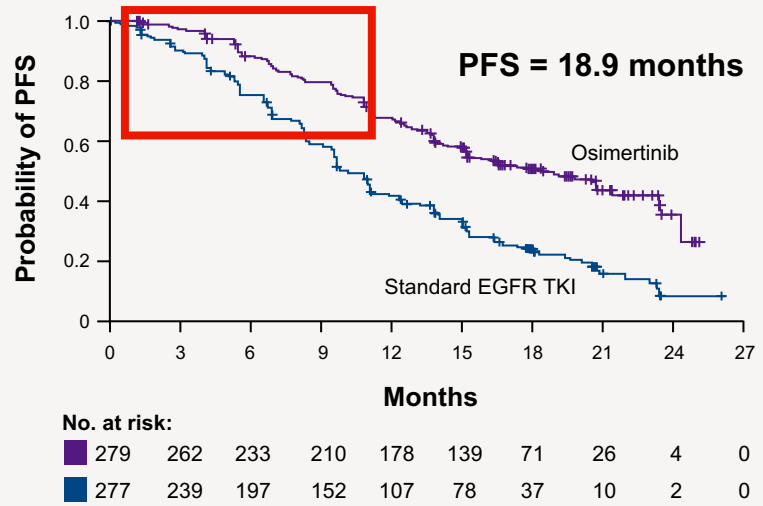


1. Sabari JK, et al. *J Thorac Oncol*. 2025;20:1268–78; 2. Girard N, et al. Presented at ELCC 2023: 19P;
3. Nieva J, et al. Presented at ESMO 2023: 1344P; 4. Lee JY, et al. *J Thorac Oncol*. 2022;17:S440.

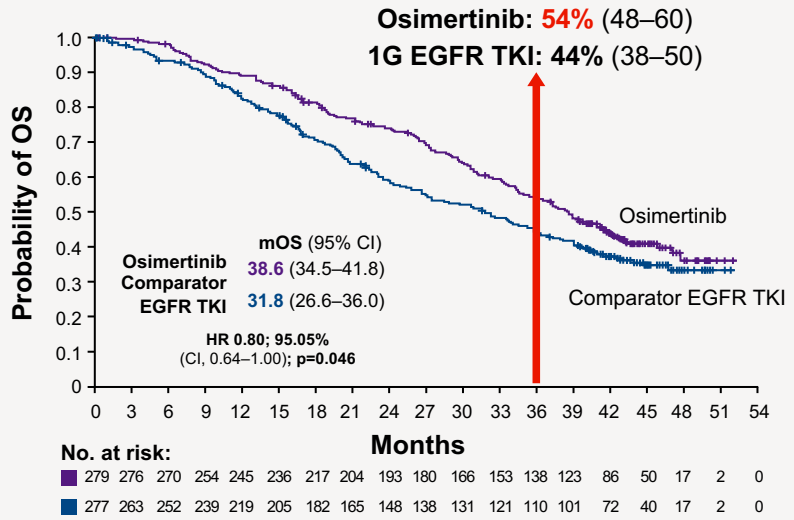
Why the need for upfront combinations?[1]

Early progressors[2,3]





OS[4]



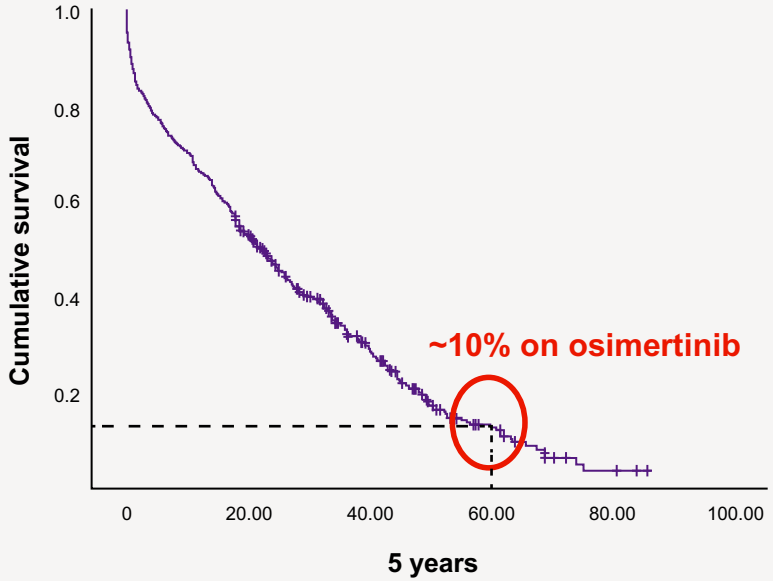
Patients continuing to receive 1L drug

Months	Osimertinib (%)	1G EGFR TKI (%)
12	70	47
24	42	16
36	28	9

Few long-term responders[1]

FLAURA
12.9% remain on osimertinib for >4.5 years

NCCS data
N=506, stage IV, 2018–2023

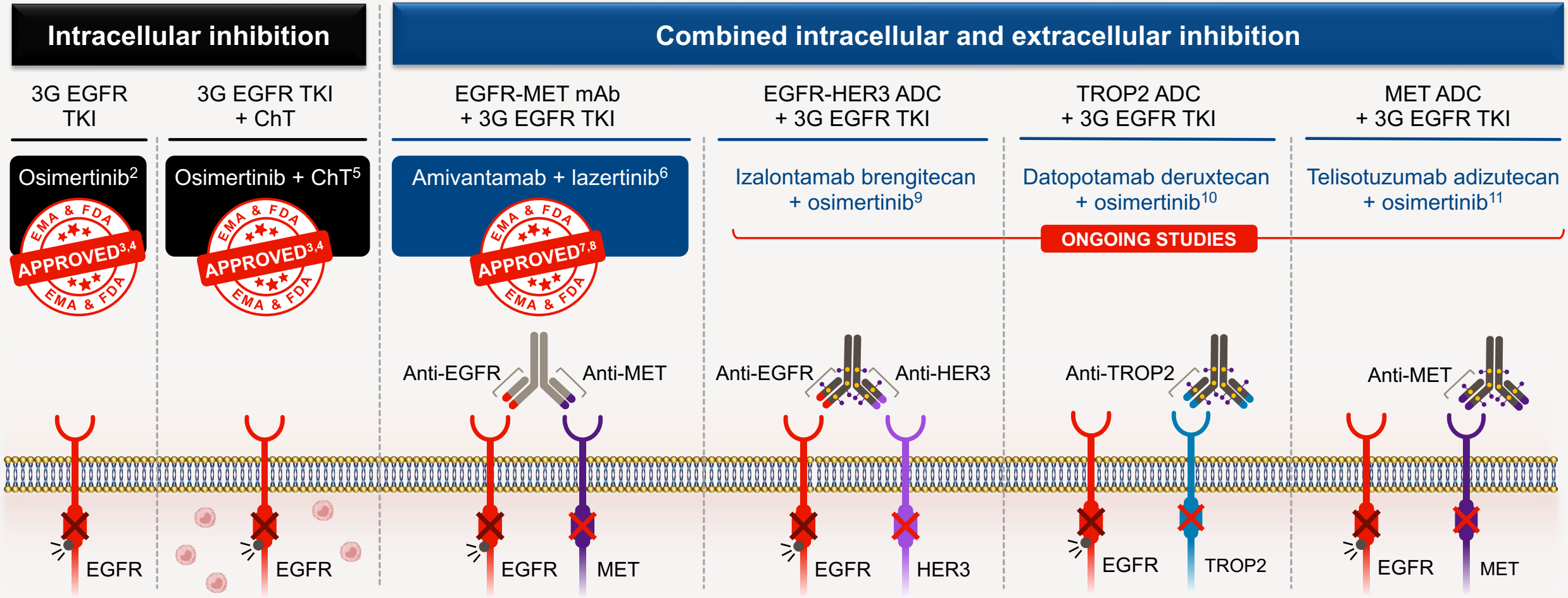


Adapted from Tan DSW. WCLC 2025.[1]

1. Tan DSW. Presented at WCLC 2025: PL02.04 (Discussant); 2. Soria JC, et al. *N Engl J Med*. 2018;378:113–25 (Supplementary appendix); 3. Soria JC, et al. *N Engl J Med*. 2018;378:113–25; 4. Ramalingam SS, et al. *N Engl J Med*. 2020;382:41–50.

1G, first-generation; 1L, first-line; CR, complete response; HR, hazard ratio; mOS, median OS; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Studies are evaluating EGFR TKIs in various combination regimens to improve 1L treatment outcomes[1]



1. Bertoli E, et al. *Int J Mol Sci*. 2022;23:6936; 2. Soria JC, et al. *N Engl J Med*. 2018;378:113–25; 3. EMA. TAGRISSO (osimertinib) Summary of Product Characteristics. January 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/tagrisso-epar-product-information_en.pdf. Accessed October 2025; 4. FDA. TAGRISSO (osimertinib) Prescribing Information. September 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/208065s033lbl.pdf. Accessed October 2025; 5. Planchard D, et al. *N Engl J Med*. 2023;389:1935–48; 6. Cho BC, et al. *N Engl J Med*. 2024;391:1486–98; 7. EMA. RYBREVANT (amivantamab) Summary of Product Characteristics. July 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/rybrevant-epar-product-information_en.pdf. Accessed October 2025; 8. FDA. RYBREVANT (amivantamab) Prescribing Information. September 2024. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761210s004lbl.pdf. Accessed October 2025; 9. Zhou F, et al. Presented at WCLC 2025: OA10.04; 10. Lu S, et al. Presented at ASCO 2025: TPS8647; 11. NCT07005102. Available at: https://www.clinicaltrials.gov/study/NCT07005102. Accessed October 2025.

Disclaimer: This schematic provides an overview and is not comprehensive.

1L, first-line; 3G, third-generation; ADC, antibody–drug conjugate; ChT, chemotherapy; EMA, European Medicines Agency; FDA, Food and Drug Administration; HER3, human epidermal growth factor receptor 3; mAb, monoclonal antibody; TROP2, trophoblast 2.

Osimertinib + ChT: PFS by INV

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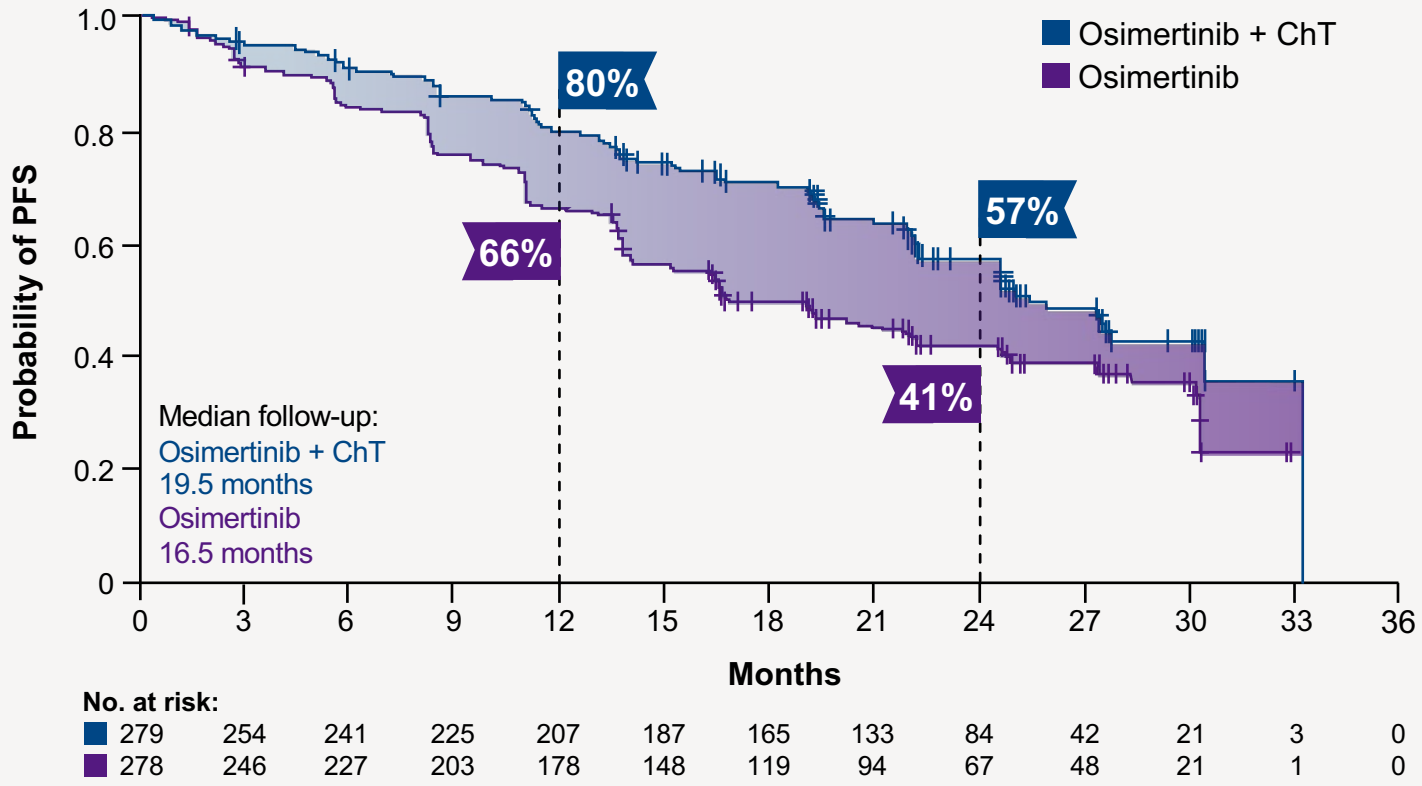
PFS[1,2]



mPFS, months (95% CI)		
Osimertinib + ChT	**25.5** (24.7–NC)	**HR, 0.62** (95% CI, 0.49–0.79); **p<0.001**
Osimertinib	**16.7** (14.1–21.3)	

1L osimertinib + ChT demonstrated a statistically significant improvement in PFS vs osimertinib monotherapy[1,2]

1. Planchard D, et al. *N Engl J Med.* 2023;389:1935–48; 2. Jänne PA, et al. Presented at WCLC 2023: PL03.13.

1L, first-line; ChT, chemotherapy; HR, hazard ratio; INV, investigator; mPFS, median PFS; NC, not calculable.

Osimertinib + ChT: PFS across subgroups

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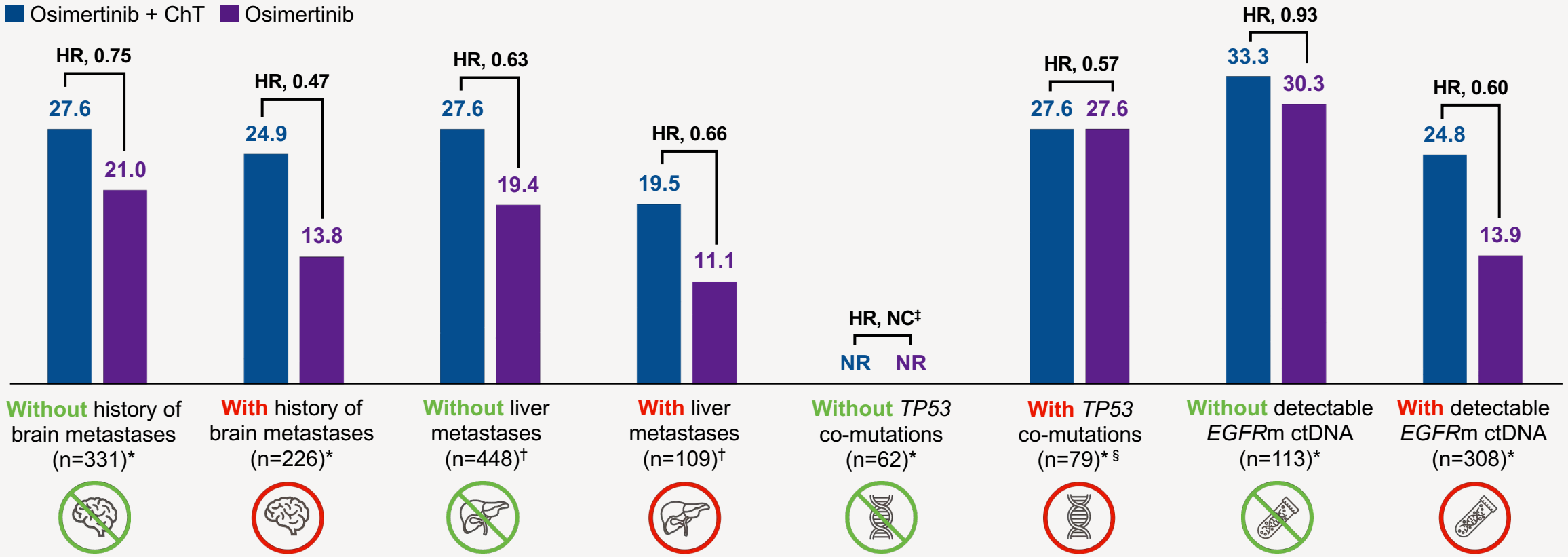
mPFS (months) across subgroups at baseline[1–4]



1L osimertinib + ChT demonstrated improved mPFS across most subgroups vs osimertinib monotherapy[1–4]

1. Planchard D, et al. *N Engl J Med*. 2023;389:1935–48; 2. Valdiviezo N, et al. Presented at WCLC 2024: MA12.04; 3. Yang JCH, et al. Presented at WCLC 2024: MA12.03; 4. Jänne PA, et al. Presented at AACR 2024: CT017.

*Exploratory analysis; †Post-hoc analysis; ‡HR not calculated where there were <20 events across both treatment arms; §TP53 alterations excluded variants with unknown oncogenic significance.
1L, first-line; ChT, chemotherapy; ctDNA, circulating tumour DNA; EGFRm, EGFR-mutant; HR, hazard ratio; mPFS, median PFS; NC, not calculable; NR, not reached; TP53, tumour protein 53.

Osimertinib + ChT: Final OS[1,2]

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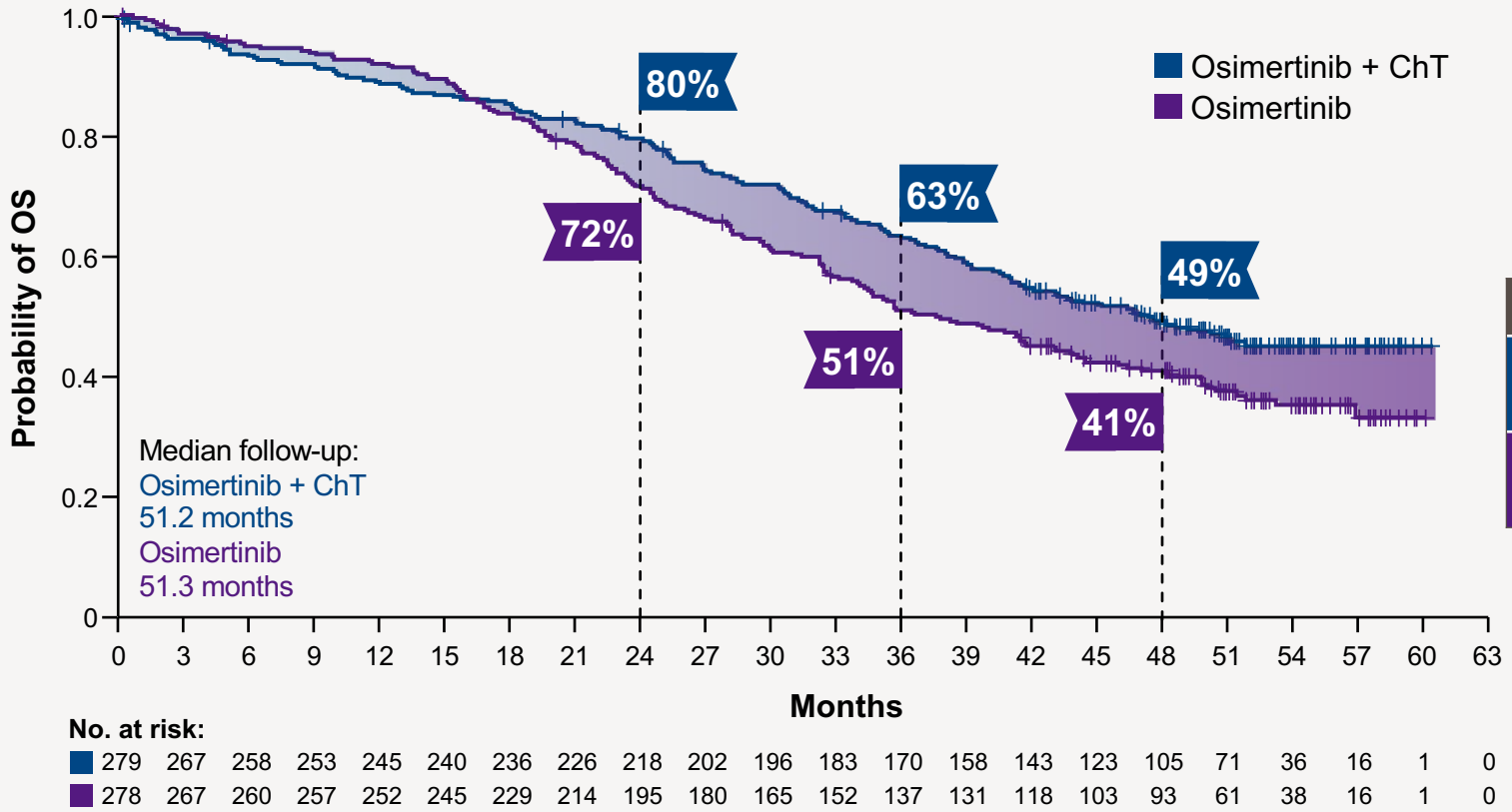
Final OS*



mOS, months (95% CI)		
Osimertinib + ChT	**47.5** (41.0–NC)	**HR, 0.77** (95% CI, 0.61–0.96); **p=0.02**
Osimertinib	**37.6** (33.2–43.2)	

1L osimertinib + ChT demonstrated a statistically significant improvement in OS vs osimertinib monotherapy

1. Planchard D, et al. Presented at WCLC 2025: PL02.06;
2. Jänne PA, et al. *N Engl J Med*. 2025 (Epub ahead of print).

*Tick marks indicate censored data. A 2-sided p-value of <0.04953 was considered to indicate statistical significance at this final OS analysis.
1L, first-line; ChT, chemotherapy; HR, hazard ratio; mOS, median OS; NC, not calculable.

Osimertinib + ChT: CNS PFS by BICR

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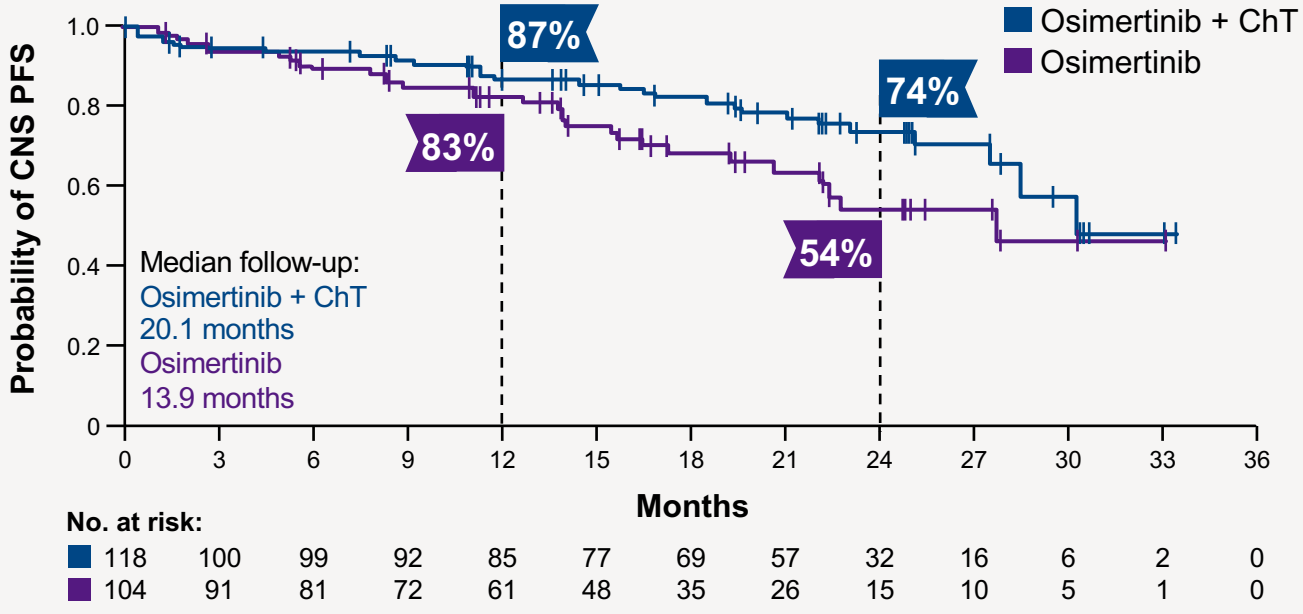
CNS PFS in the CNS full analysis set[1]



Median CNS PFS, months (95% CI)		
Osimertinib + ChT	**30.2** (28.4–NC)	**HR, 0.58** (95% CI, 0.33–1.01); **p=0.0548**
Osimertinib	**27.6** (22.1–NC)	

Among patients with brain metastases or a history of brain metastases at baseline:[2]

- Brain MRI/CT at baseline and at 6 and 12 weeks, then every 12 weeks until RECIST v1.1 defined PD

Among patients without brain metastases or a history of brain metastases at baseline:[2]

- Brain MRI/CT at baseline and then only performed when there is a suspected CNS progression and at the point of RECIST v1.1 defined extracranial progression

1L osimertinib + ChT demonstrated improved CNS efficacy vs osimertinib monotherapy[1]

1. Jänne PA, et al. *J Clin Oncol*. 2024;42:808–20; 2. Planchard D, et al. *N Engl J Med*. 2023;389:1935–48 (Study protocol).

1L, first-line; BICR, blinded independent central review; ChT, chemotherapy; CNS, central nervous system; CT, computed tomography; HR, hazard ratio; MRI, magnetic resonance imaging; NC, not calculable; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours.

Osimertinib + ChT: Resistance mechanisms (plasma)

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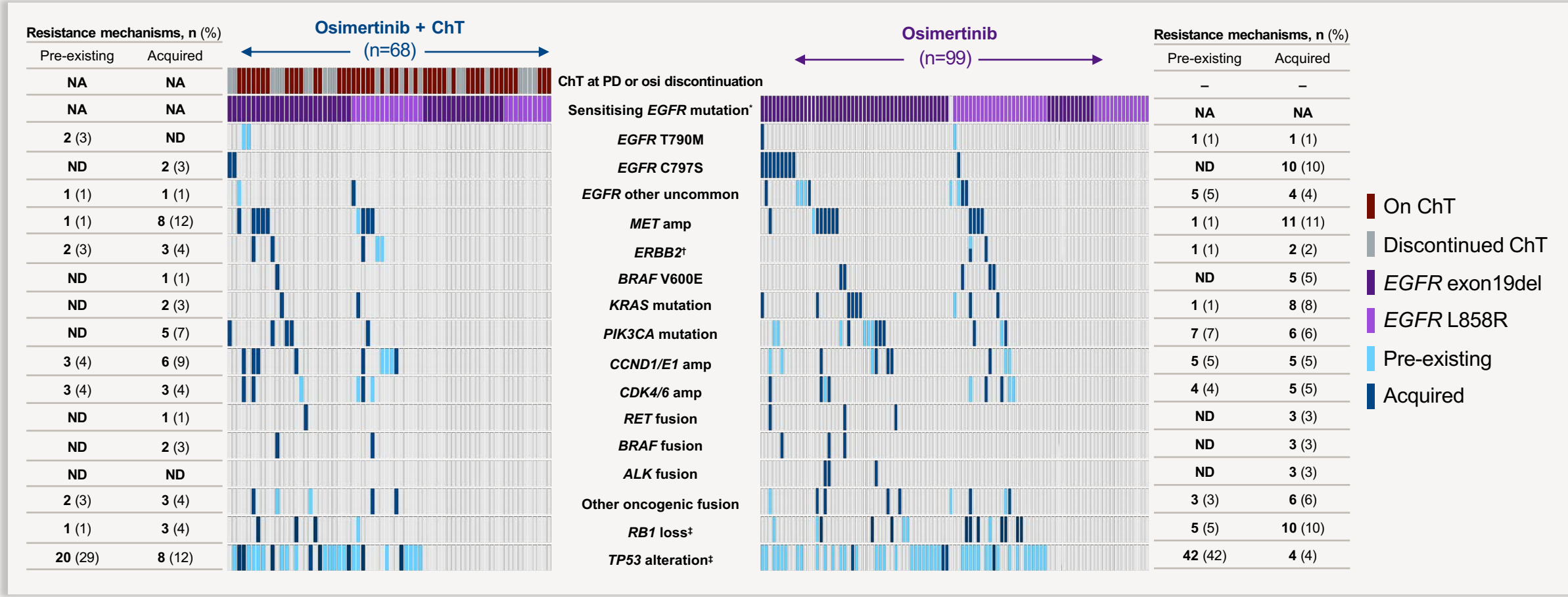


Acquired resistance mechanisms were broadly similar with both osimertinib + ChT and osimertinib monotherapy, including secondary *EGFR* mutations and *MET* amp

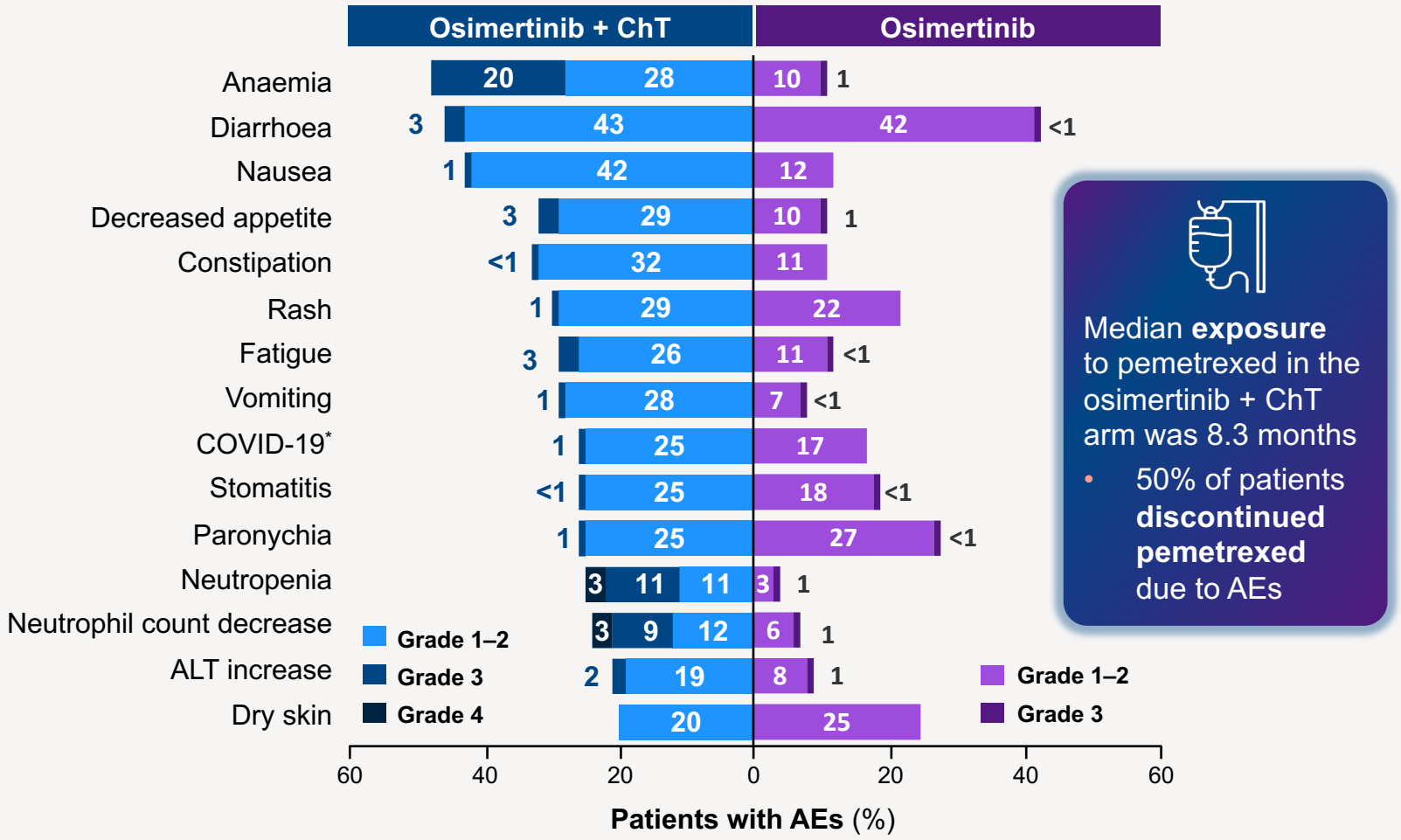
*At baseline; †Osimertinib monotherapy arm: 1 patient had pre-existing ERBB2 amp and an acquired ERBB2 mutation and 1 patient had acquired ERBB2 amp, osimertinib + ChT arm: 1 patient had pre-existing ERBB2 amp, 1 patient had pre-existing ERBB2 mutation, and 3 patients had acquired ERBB2 amp; ‡TP53 alteration + RB1 loss had to be co-occurring to count as putative resistance. ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homologue B1; CCND2/CCNE1, G1/S-specific cyclin-D2/-E1; CDK4/6, cyclin-dependent kinase-4/-6; ChT, chemotherapy; ERBB2, Erb-B2 receptor tyrosine kinase 2; exon19del, exon 19 deletion; KRAS, Kirsten rat sarcoma viral oncogene homologue; NA, not applicable; ND, not detected; osi, osimertinib; PD, progressive disease; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RB1, retinoblastoma 1; RET, rearranged during transfection; TP53, tumour protein 53.

Yang JCH, et al. Presented at WCLC 2024: MA12.03.

Osimertinib + ChT: Safety profile

FLAURA2

Most common AEs (≥20%)[1]



Median **exposure** to pemetrexed in the osimertinib + ChT arm was 8.3 months

- 50% of patients **discontinued pemetrexed** due to AEs

- Since the primary analysis (>2 years additional follow-up):[1,2]
  - No new safety signals were observed
  - AEs leading to discontinuation of osimertinib remained low
  - No new treatment-related deaths were observed with osimertinib + ChT (vs 1 with osimertinib monotherapy)
- Grade ≥3 AEs were reported in 70% of patients in the osimertinib + ChT group vs 34% in the osimertinib group[1]
- Haematological AEs† were reported in 71% of patients in the osimertinib + ChT group vs 24% in the osimertinib group[2]

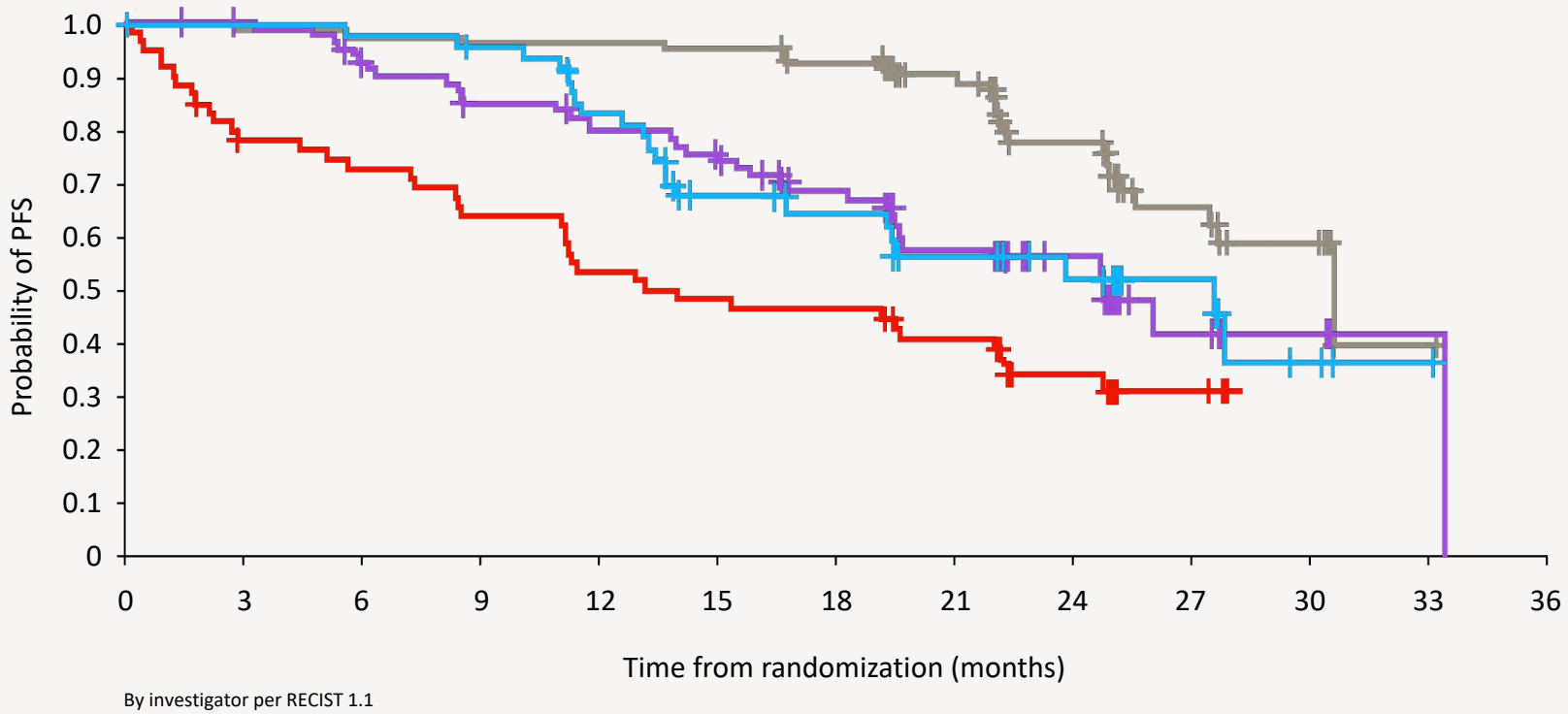
*1 patient reported a Grade 5 AE of COVID-19 in the osimertinib + ChT arm;
†Grouped term: Anaemia/haemoglobin decrease, thrombocytopenia/platelet count decrease, neutropenia/neutrophil count decrease, and ILD/pneumonitis/organising pneumonitis (by preferred terms).
AE, adverse event; ALT, alanine aminotransferase; ChT, chemotherapy; COVID-19, coronavirus 2019; ILD, interstitial lung disease.

1. Planchard D, et al. Presented at WCLC 2025: PL02.06; 2. Planchard D, et al. *N Engl J Med*. 2023;389:1935–48.

The Role of ChT in the FLAURA2 regimen

FLAURA2

FLAURA2 post-hoc analysis



By investigator per RECIST 1.1

Sustained exposure to pemetrexed is associated with improved efficacy demonstrated in the FLAURA2 study

Almost a quarter (23%) of patients in the FLAURA2 trial received <3 cycles of pemetrexed

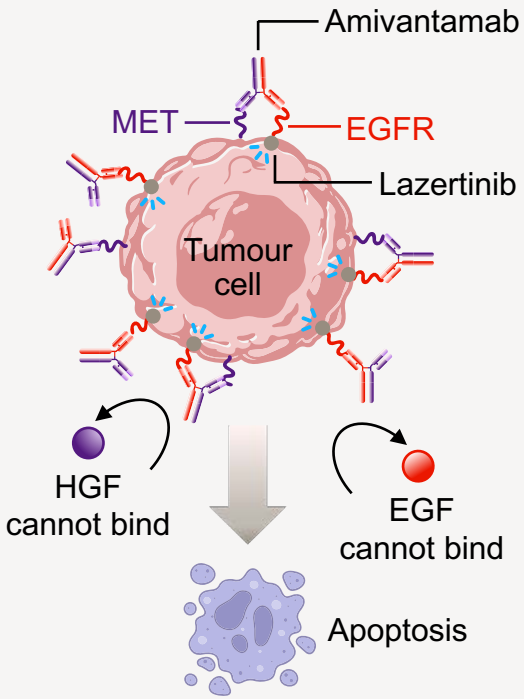
Median PFS, months (95% CI)	
0–<3 months (n=63)	13.1 (8.4–22.2)
3–<9 months (n=84)	24.7 (19.6–NC)
9–<18 months (n=49)	27.6 (16.7–NC)
≥18 months (n=83)	30.6 (27.4–NC)

CI, confidence interval; NC, not calculable, PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Planchard D, et al. Presented at ELCC 2025. Poster 53P.

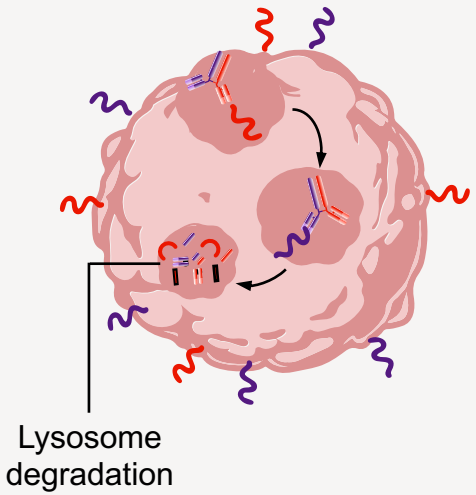
Amivantamab + lazertinib: Disease-modifying, ChT-free, triple MoA[1–3]

Inhibition of ligand binding via amivantamab + lazertinib[2,3]



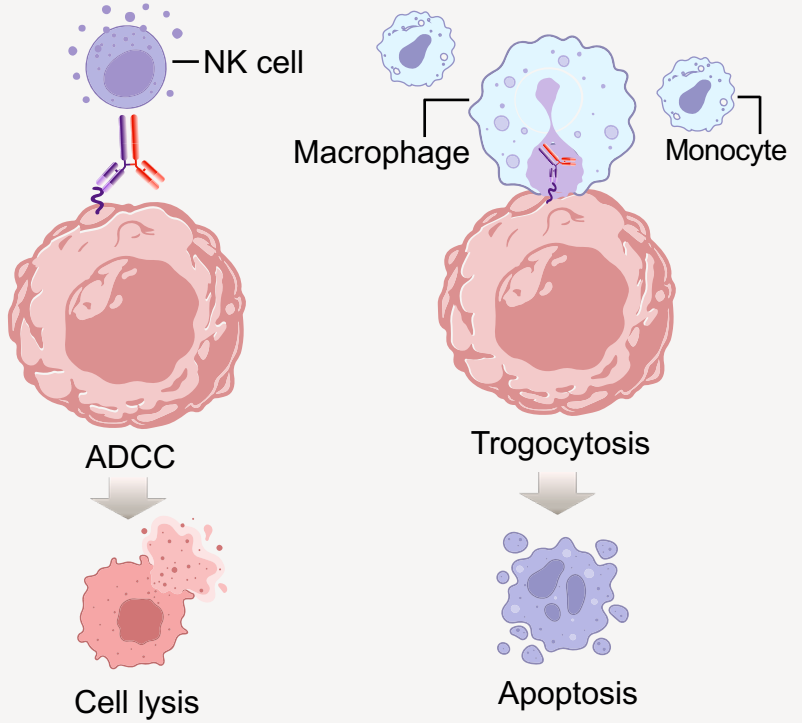
Synergistic extra- and intracellular binding to EGFR by amivantamab and lazertinib, respectively;[2,3] and extracellular binding to MET by amivantamab[2]

Receptor degradation via amivantamab[2]



Amivantamab binding triggers EGFR and MET receptor degradation by the tumour cell, leading to receptor inactivation[2]

Immune-mediated activity via amivantamab[2]



Amivantamab binds to the Fc gamma receptors-IIIa/CD16a on effector cells, with its immune-mediated activity leading to improved destruction of tumour cells[2]

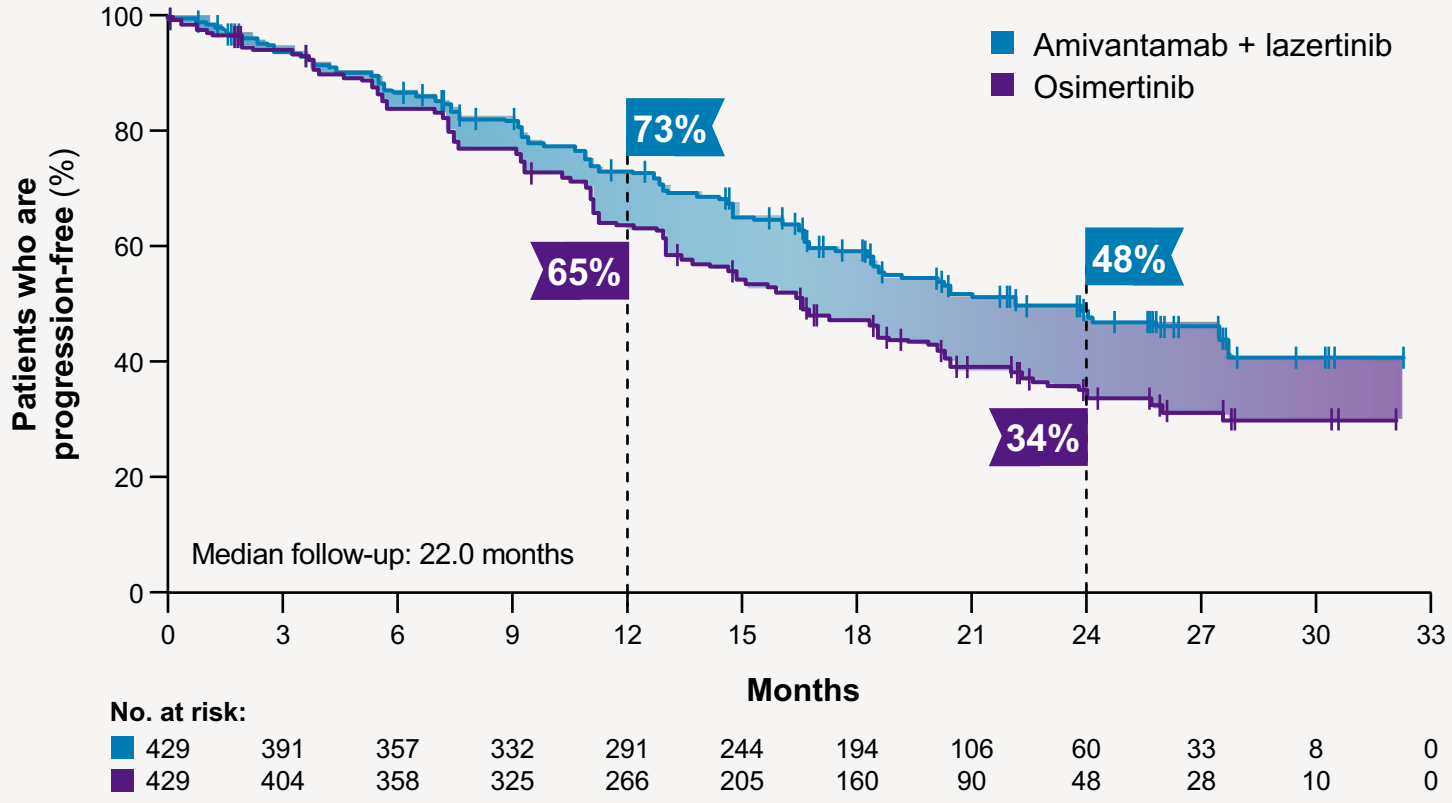
1. Hayashi H, et al. Presented at WCLC 2025: PT1.03.06; 2. Cho BC, et al. *Clin Lung Cancer*. 2023;24:89–97; 3. Shu CA, et al. Presented at ASCO 2021: TPS9132.

ADCC, antibody-dependent cellular cytotoxicity; ChT, chemotherapy; EGF, epidermal growth factor; HGF, hepatocyte growth factor; MoA, mechanism of action; NK, natural killer.

Amivantamab + lazertinib: PFS by BICR

MARIPOSA

PFS*[1,2]



mPFS, months (95% CI)		
Amivantamab + lazertinib	**23.7** (19.1–27.7)	**HR, 0.70** (95% CI, 0.58–0.85); **p<0.001**
Osimertinib	**16.6** (14.8–18.5)	

1L amivantamab + lazertinib reduced the risk of progression or death by 30% vs osimertinib[1,2]

1. Cho BC, et al. *N Engl J Med*. 2024;391:1486–98;
2. Cho BC, et al. Presented at ESMO 2023: LBA14.

*At the time of the prespecified final PFS analysis, there were a total of 444 PFS events in the amivantamab + lazertinib and osimertinib arms combined.
1L, first-line; BICR, blinded independent central review; HR, hazard ratio; mPFS, median PFS.

Amivantamab + lazertinib: PFS across subgroups[1,2]

MARIPOSA

mPFS (months) across subgroups at baseline (secondary analysis)

1L amivantamab + lazertinib showed a numerical PFS benefit vs osimertinib in low-risk subgroups, and significantly improved mPFS in high-risk subgroups

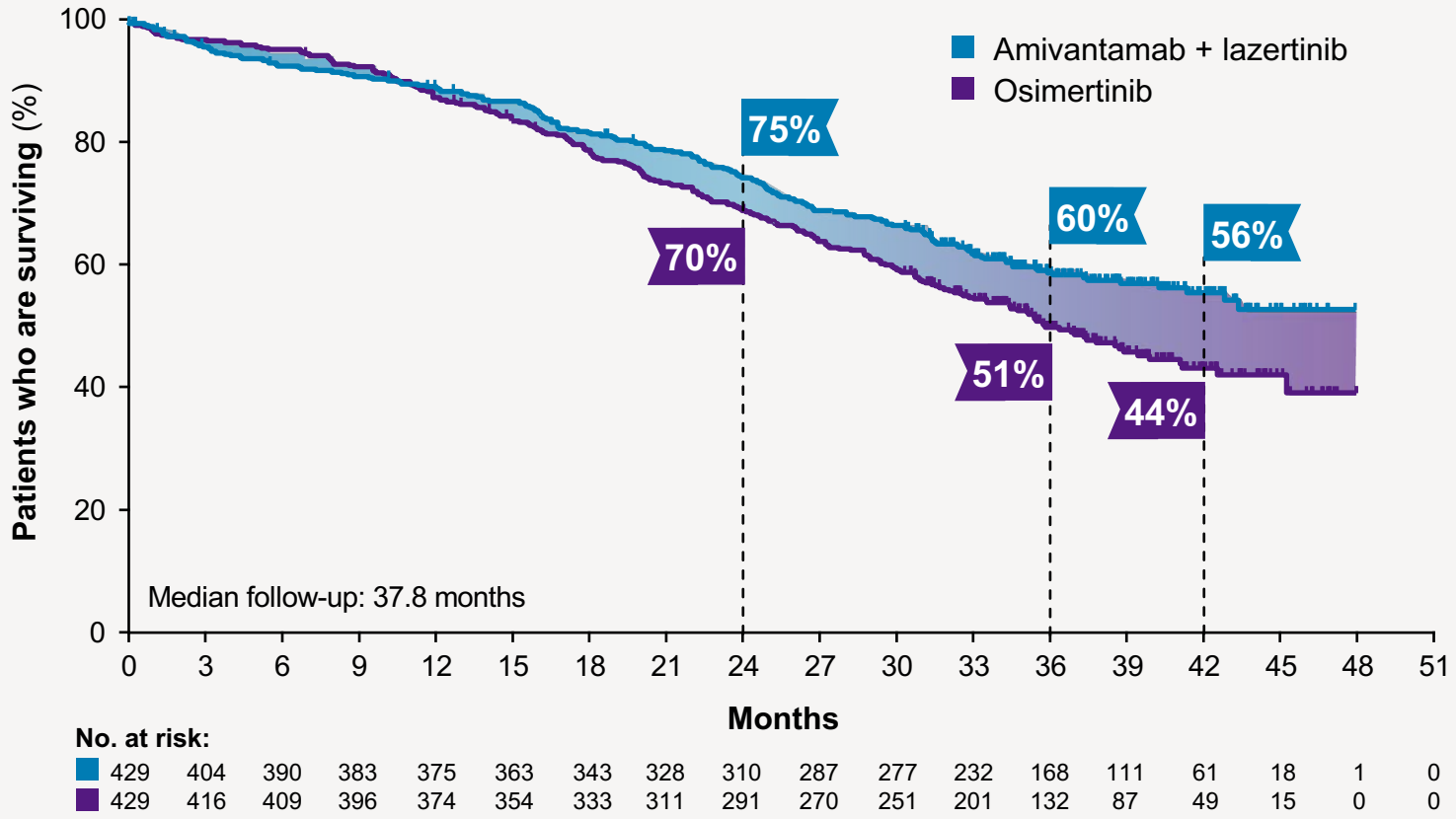
1. Felip E, et al. Presented at ASCO 2024: 8504;
2. Felip E, et al. *Ann Oncol*. 2024;35:805–16.

*Nominal p-values; †Pathogenic mutations were detected with the Guardant Health G360® panel; ‡Detection of EGFR exon19del and L858R by Biodesix ddPCR.
1L, first-line; ctDNA, circulating tumour DNA; ddPCR, droplet digital polymerase chain reaction; EGFRm, EGFR-mutant; exon19del, exon 19 deletion; HR, hazard ratio; mPFS, median PFS; TP53, tumour protein 53.

Amivantamab + lazertinib: Overall survival[1,2]

MARIPOSA

Protocol-specified final OS*



mOS, months (95% CI)		
Amivantamab + lazertinib	NE (42.9–NE)	**HR, 0.75** (95% CI, 0.61–0.92); **p=0.005**†
Osimertinib	**36.7** (33.4–41.0)	

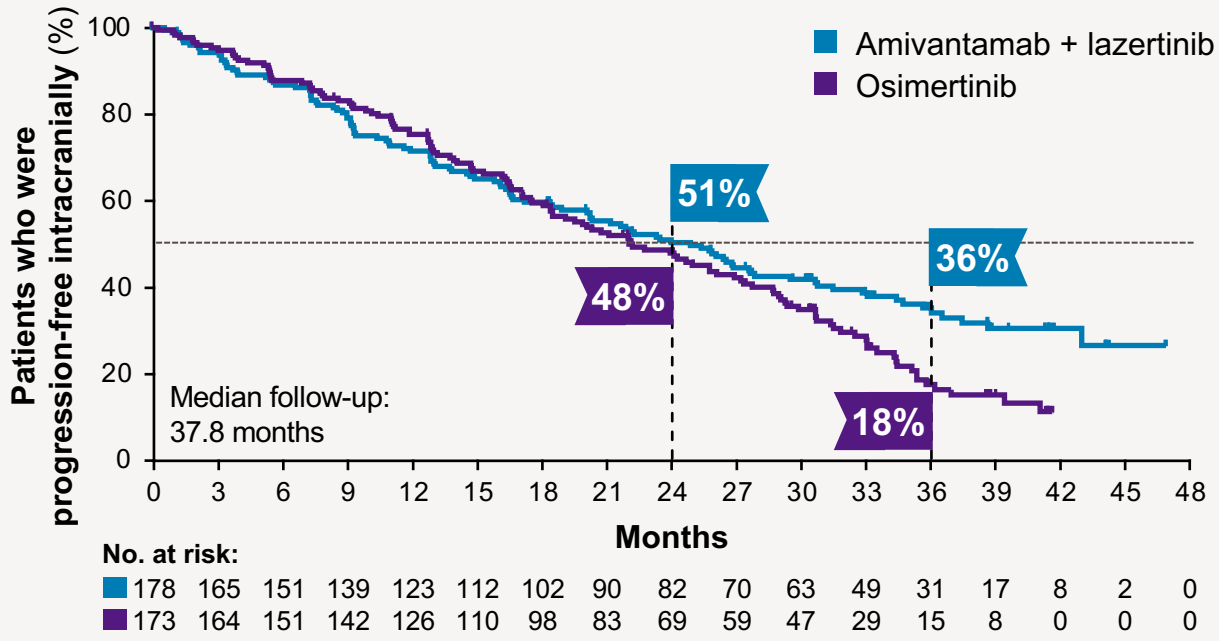
OS was significantly longer with 1L amivantamab + lazertinib vs osimertinib, and the curves continue to widen over time

1. Yang JCH, et al. Presented at ELCC 2025: 4O;
2. Yang JCH, et al. *N Engl J Med*. 2025 (Epub ahead of print).

Amivantamab + lazertinib: icPFS by BICR

MARIPOSA

icPFS in patients with baseline CNS metastases*[1]



Median icPFS, months (95% CI)		
Amivantamab + lazertinib	**25.4** (20.1–29.5)	**HR, 0.79** (95% CI, 0.61–1.02); **p=0.07**†
Osimertinib	**22.2** (18.4–26.9)	

Among patients with a history of brain metastases at screening:[2,3]

- Brain MRI (or CT if MRI contraindicated) at baseline and every 8 weeks (±1 week) for the first 30 months, then every 12 weeks (±1 week) until PD by BICR
- 16 scheduled scans in the first 120 weeks

Among patients without a history of brain metastases at screening:[2,3]

- Brain MRI (or CT if MRI contraindicated) at baseline and every 24 weeks (±1 week) until PD by BICR
- 6 scheduled scans in the first 120 weeks

MARIPOSA conducted serial brain MRIs on all patients, with 1L amivantamab + lazertinib demonstrating improved icPFS vs osimertinib[1–3]

*icPFS was defined as time from randomisation until the date of intracranial disease progression (progression of brain metastases or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among participants with a history of brain metastases; †P-value was calculated from a log-rank test stratified by mutation type (exon19del or L858R) and race (Asian or non-Asian). HR was calculated from a stratified Cox regression model.

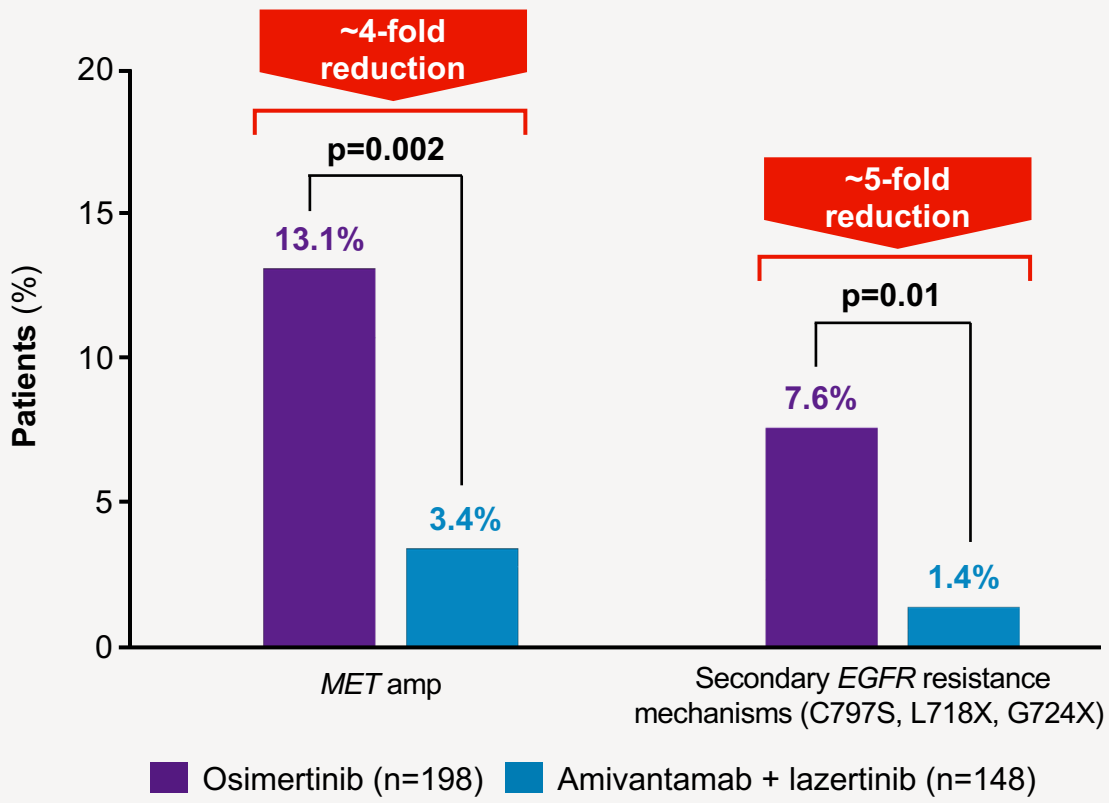
1L, first-line; BICR, blinded independent central review; CNS, central nervous system; CT, computed tomography; exon19del, exon 19 deletion; HR, hazard ratio; icPFS, intracranial PFS; MRI, magnetic resonance imaging; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours.

1. Yang JCH, et al. Presented at ELCC 2025: 4O; 2. Cho BC, et al. *N Engl J Med*. 2024;391:1486–98; 3. Cho BC, et al. Presented at ESMO 2023: LBA14.

Amivantamab + lazertinib: Resistance mechanisms (plasma)

MARIPOSA

MET- and *EGFR*-dependent resistance



Amivantamab + lazertinib significantly reduced the incidence of **acquired *MET* amp** and ***EGFR* resistance mutations** vs osimertinib, highlighting that the combination therapy may change the underlying biology of *EGFR*-mutant NSCLC

No meaningful increases in **other molecular escape pathways** were observed with amivantamab + lazertinib*

Resistance complexity (≥2 pathogenic alterations) **was significantly lower following 1L amivantamab + lazertinib vs osimertinib treatment** (p=0.02)

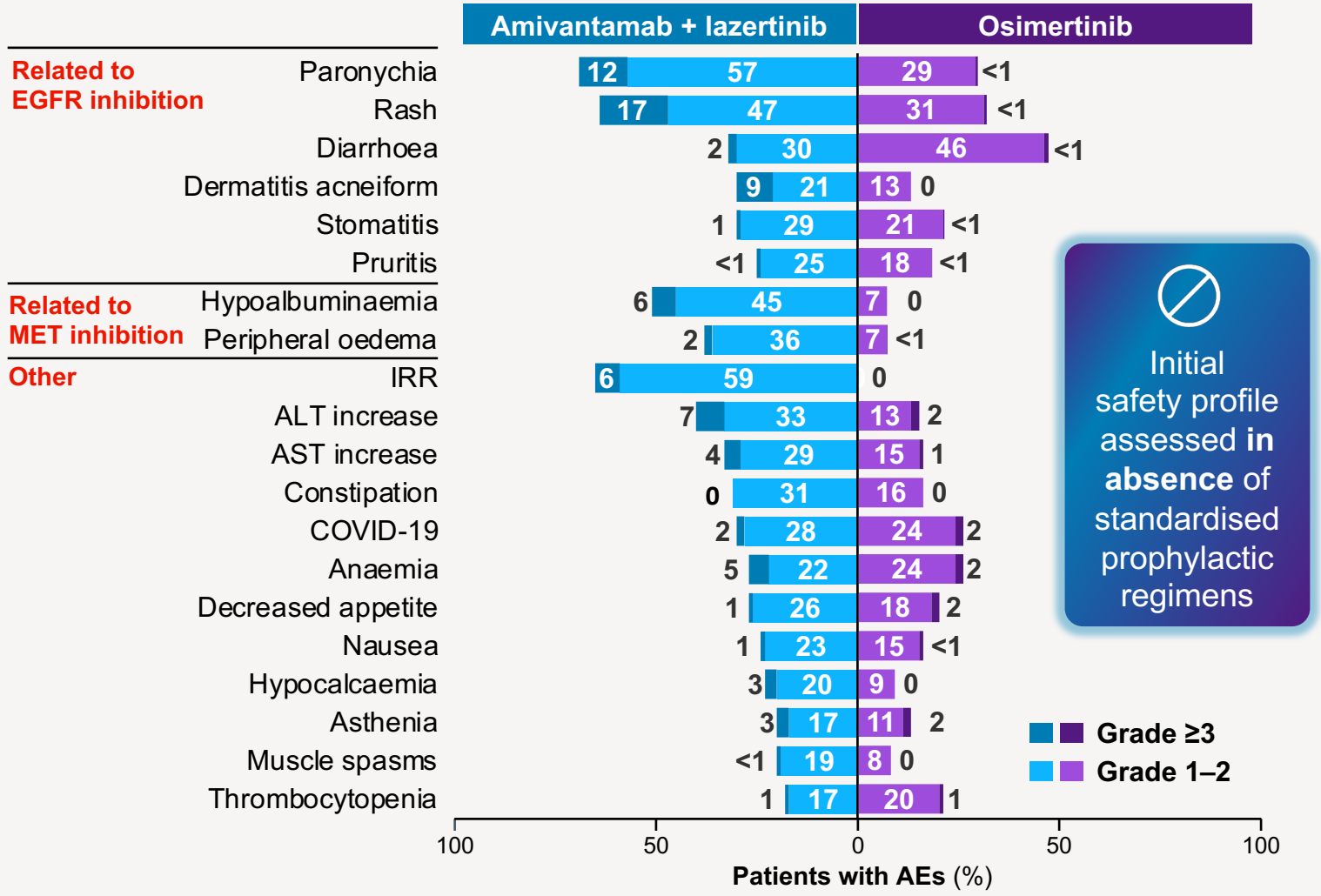
Hayashi H, et al. Presented at WCLC 2025: PT1.03.06.

*Differences between other pathways were not statistically significant.
1L, first-line; amp, amplification.

Amivantamab + lazertinib: Safety profile

MARIPOSA

Most common TEAEs (≥20%) by preferred term[1]



- Safety profile was consistent with the primary analysis[1,2]
  - AEs were mostly EGFR- and MET-related and Grades 1–2
- Few were on anticoagulation (5%) at baseline, with VTE (grouped term)* occurring in 40% in the amivantamab + lazertinib arm and 11% in the osimertinib arm[1]
- Subsequent studies including SKIPPirr, COCOON, and PALOMA-2/3 have demonstrated reduced incidence of IRRs, dermatologic AEs, and VTEs with use of prophylactic regimens[3–6]

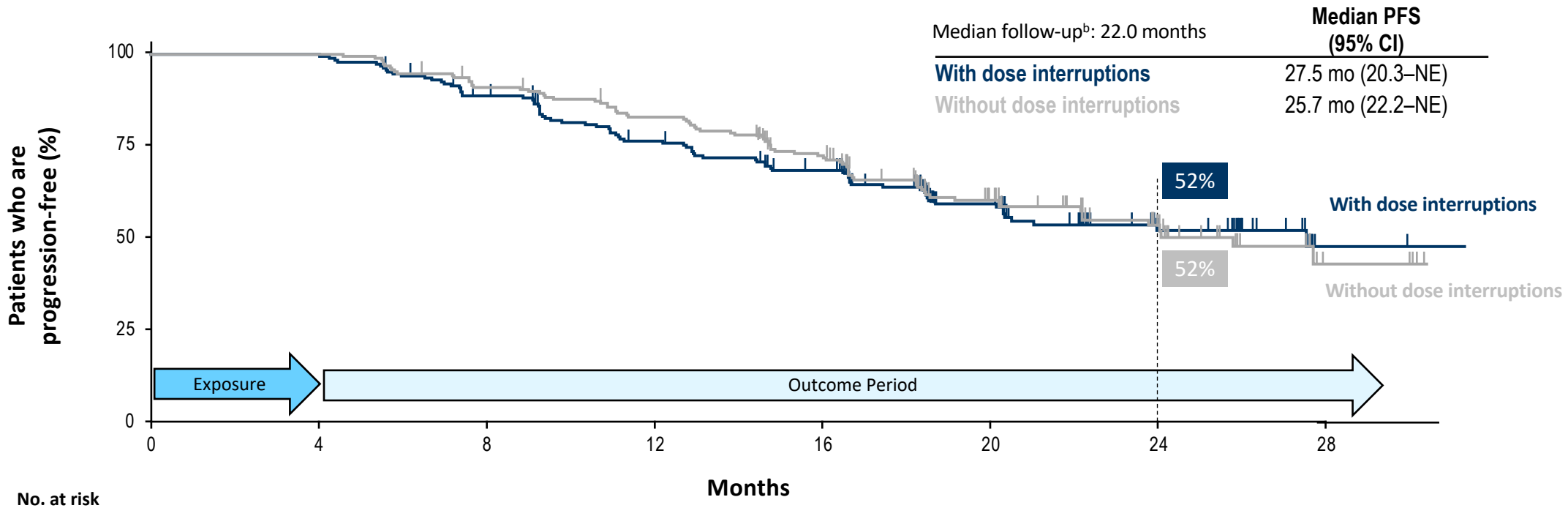
1. Yang JCH, et al. Presented at ELCC 2025: 4O; 2. Cho BC, et al. *N Engl J Med.* 2024;391:1486–98;
3. Spira AI, et al. *J Thorac Oncol.* 2025;20:809–16; 4. Cho BC, et al. *J Thorac Oncol.* 2025;20:1517–30;
5. Lim SM, et al. Presented at ASCO 2024: LBA8612; 6. Leighl NB, et al. *J Clin Oncol.* 2024;42:3593–605.

*VTE is a grouped term, which included pulmonary embolism, deep vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular vein thrombosis, sigmoid sinus thrombosis, axillary vein thrombosis, pulmonary infarction, vena cava thrombosis, central venous catheterisation, portal vein thrombosis, post thrombotic syndrome, pulmonary thrombosis, superior sagittal sinus thrombosis, transverse sinus thrombosis, pelvic venous thrombosis, and superior vena cava syndrome.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus 2019; IRR, infusion-related reaction; TEAE, treatment-emergent AE; VTE, venous thromboembolism.

Association of dose interruptions with progression-free survival

- Median PFS after 4 months was similar between patients with and without dose interruptions
- The PFS HR by multivariable analysis[a] adjusting for age, ECOG PS, *EGFR* mutation type, Asian race, and history of brain metastases was **1.06** (95% CI, 0.73–1.44), indicating no significant association of dose interruption with PFS after the 4-month exposure period

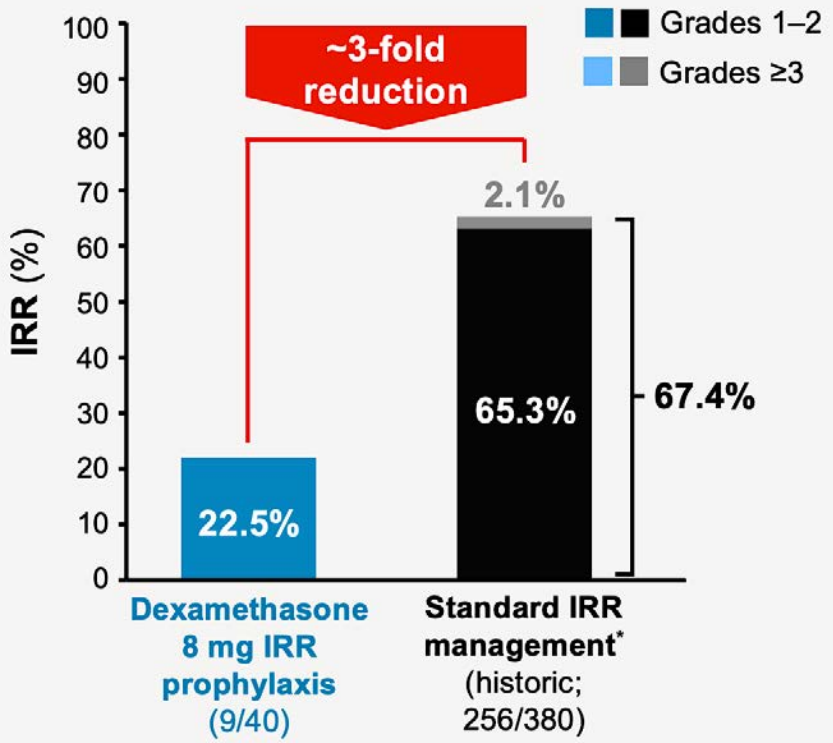


[a]Via multivariate Cox proportional hazards model, only including patients still at risk of PFS at 4 months. [b]Median follow-up of the MARIPOSA study, as of the clinical cutoff of 11 August 2023, was 22.0 months.
CI, confidence interval; EGFR, epidermal growth factor receptor; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; NE, not estimable; PFS, progression-free survival.

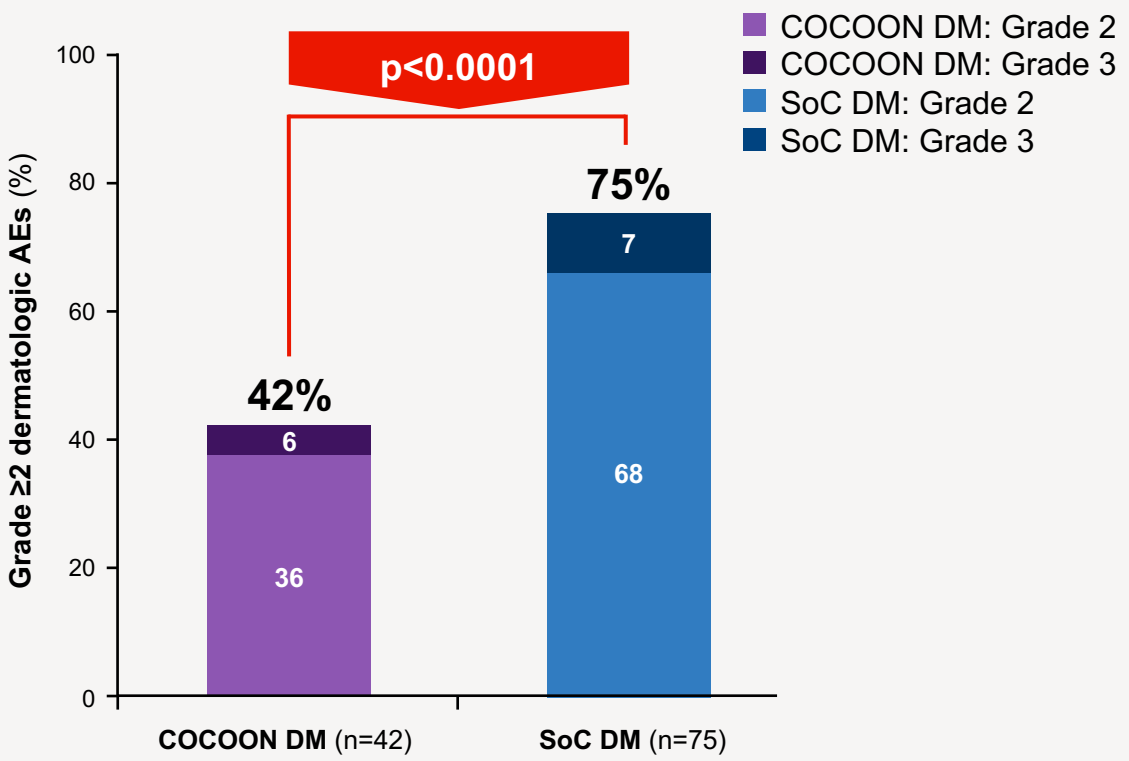
Presented by M Campelo at the European Lung Cancer Congress; March 20–23 2024; Prague, Czech Republic

Prophylactic management for MARIPOSA combo

SKIPPirr prophylactic

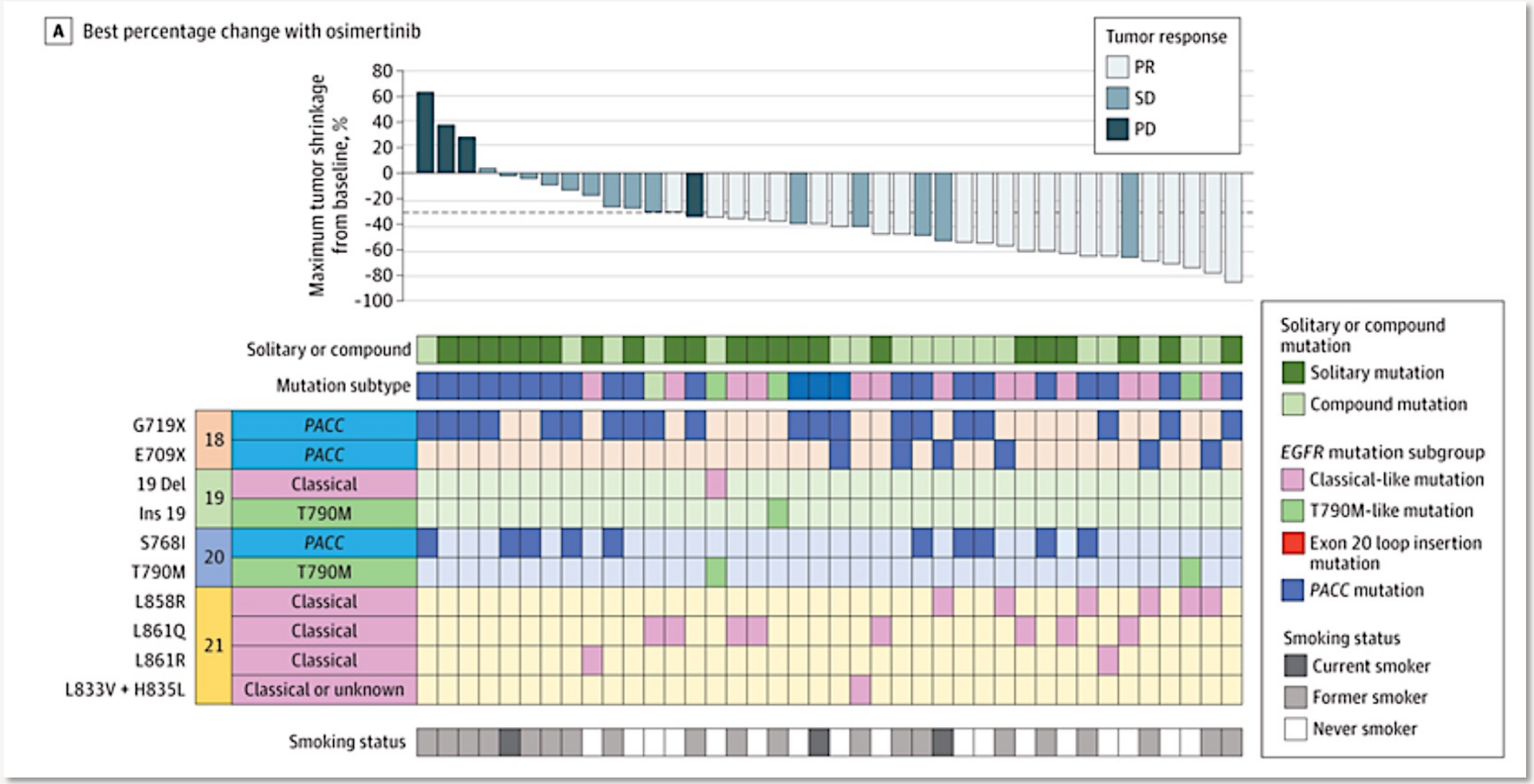


COCOON prophylactic



Cho BC et al. J Thorac Oncol. 2025;20(10):1517-1530. Spira AI et al. J Thorac Oncol. 2025;20(6):809-816.

Osimertinib in atypical EGFR mutations: Phase II UNICORN study



Okuma Y et al. JAMA Oncol. 2024;10(1):43-51.

Osimertinib in atypical EGFR mutations: Phase II UNICORN study

Table 2. Treatment Response to Osimertinib Among Patients Harboring Uncommon *EGFR* Mutations

Characteristic	Value
Overall (full analysis set [N = 40])	
Complete response, No. (%)	0
Partial response, No. (%)	22 (55.0)
Stable disease, No. (%)	14 (35.0)
Progressive disease, No. (%)	4 (10.0)
Not evaluable, No. (%)	0
Overall response rate, % (90% CI)	55.0 (40.9-68.5)
Overall response rate, % (95% CI)	55.0 (38.5-70.7)
Disease control rate, % (95% CI)	90.0 (76.3-97.2)
Progression-free survival, median (95% CI), mo	9.4 (3.7-15.2)
Overall survival, median (95% CI), mo	NR (19.3-NR)
Time to treatment failure, median (95% CI), mo	9.5 (5.6-30.3)
Duration of response, median (95% CI), mo	22.7 (9.5-NR)

Okuma Y et al. JAMA Oncol. 2024;10(1):43-51.

Amivantamab/lazertinib in atypical EGFR mutations: CHRYSALIS-2 study

Characteristic, n (%)	Cohort C (n=105)
ECOG PS	
0	33 (31)
1	72 (69)
Type of *EGFR* mutation[b]	
Exon 18 G719X	60 (57)[c]
Exon 21 L861X	27 (26)[d]
Exon 20 S768X	25 (24)[e]
Exon 18 E709K	2 (2)
Exon 20 E709A	2 (2)
L833V	2 (2)
R776C	2 (2)
R776H	1 (1)
R831H	1 (1)
V744M	1 (1)
V769L	1 (1)
V774M	1 (1)
Other	10 (10)

Investigator-assessed response (n=105)	
Median follow-up	16.1 mo (range, 0.1–31.5)
ORR	52% (95% CI, 42–62)
Median DoR	14.1 mo (95% CI, 9.5–26.2)
DoR ≥6 mo, n (%)[a]	38 (69)
Best response, n (%)	
CR	0
PR	55 (52)
SD	37 (35)
PD	8 (8)
Not evaluable/UNK	5 (5)
CBR[b]	79% (95% CI, 70–86)
Median PFS	11.1 mo (95% CI, 7.8–17.8)
Median OS	NE (95% CI, 22.8–NE)

Cho ASCO 2024; Abstract 8516.

Amivantamab/lazertinib in atypical EGFR mutations: CHRYSALIS-2 study

Abstract #: 8501 Oral Abstract Session

Overall survival of first-line amivantamab plus lazertinib in atypical *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): Updated results from the CHRYSALIS-2 study.

Authors: Joel W. Neal, Byoung Chul Cho, Yongsheng Wang, Lin Wu, Enriqueta Felip, Jiuwei Cui, Alexander I. Spira, Melina E. Marmarelis, Eiki Ichihara, Se-Hoon Lee, James Chih Hsin Yang, Sebastian Y. Michels, Joshua C. Curtin, Xuesong Lu, Zacharias Anastasiou, Isabelle Leconte, Leonardo Trani, Sujay Shah, Pascale Tomasini

As of Oct 31, 2025, the median follow-up was 31.3 months (range, 0.1–53.2). The median OS was 41.0 months (95% CI, 27.7–not estimable), with 55% alive at 3 years and 46% alive at 4 years.

As of data cutoff, 20% (10/49; 6 were confirmed responders and 4 had stable disease) of pts were still ongoing 1L treatment (range, 2.5–4.4 years), with 7 pts receiving ami treatment for >3 years. Safety profile was consistent with prior reports; no additional safety signals were identified with longer-term follow-up.

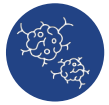
Neal JW et al. ASCO 2026; Abstract 8501.

Key takeaways

3rd gen EGFR TKI monotherapy
Effective, CNS-active but **biologically incomplete** → early residual disease & adaptive resistance

Combinations strategy (FLAURA2 and MARIPOSA trial)
Deeper upfront suppression of tumor heterogeneity
Delay emergence of resistant clones
↑ toxicity / ↑ complexity but to be considered in a **dynamic optimization way**

Clinical positioning
Low-risk / "indolent" biology → monotherapy …..Yet poorly defined at baseline
High-risk / high burden / TP53 / ctDNA+ → combo strategy → **Likely majority rather than exception**



Not regimen selection but disease biology-driven strategy
→ **Risk-adapted upfront intensification as default paradigm**

Cases from the Community

Stephen “Fred” Divers, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

How do you approach initial therapy for patients with metastatic NSCLC who need to start treatment before biomarker results can be obtained?

What would you most likely have recommended in this patient's case? Would you have started with chemotherapy alone while awaiting NGS results?

What differentiating factors would prompt you to recommend first-line osimertinib monotherapy versus osimertinib/chemotherapy versus amivantamab/lazertinib for your patients with EGFR-mutated NSCLC? What do you see as the major advantages and disadvantages of each?

Do you typically approach first-line treatment for patients with uncommon EGFR mutations in the same way you do for those with exon 19 deletions or L858R mutations?

Cases from the Community

Susmitha Apuri, MD

Neil Love, MD

RTP RESEARCH TO PRACTICE

Discussion Questions

What has been your experience with the toxicities of amivantamab/lazertinib, and what prophylactic approaches do you recommend to prevent them?

How do you approach dose reductions for patients who are experiencing tolerability issues while receiving amivantamab/lazertinib?

Are you at all surprised that subcutaneous administration of amivantamab prolonged overall survival in the PALOMA-3 study? Why do you think this is? Have you switched to subcutaneous administration of amivantamab for all or most of your patients receiving that agent? What dosing schedule do you prefer?

Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

Module 2: EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC — Dr Neal

Module 3: Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC — Dr Sands

Module 4: Emerging Role of Bispecific Antibody-Based Approaches for EGFR-Mutated NSCLC — Dr Goldman

Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

RTP RESEARCH TO PRACTICE

EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC

Joel W. Neal, MD, PhD
Professor of Medicine (Oncology)
May 29, 2026

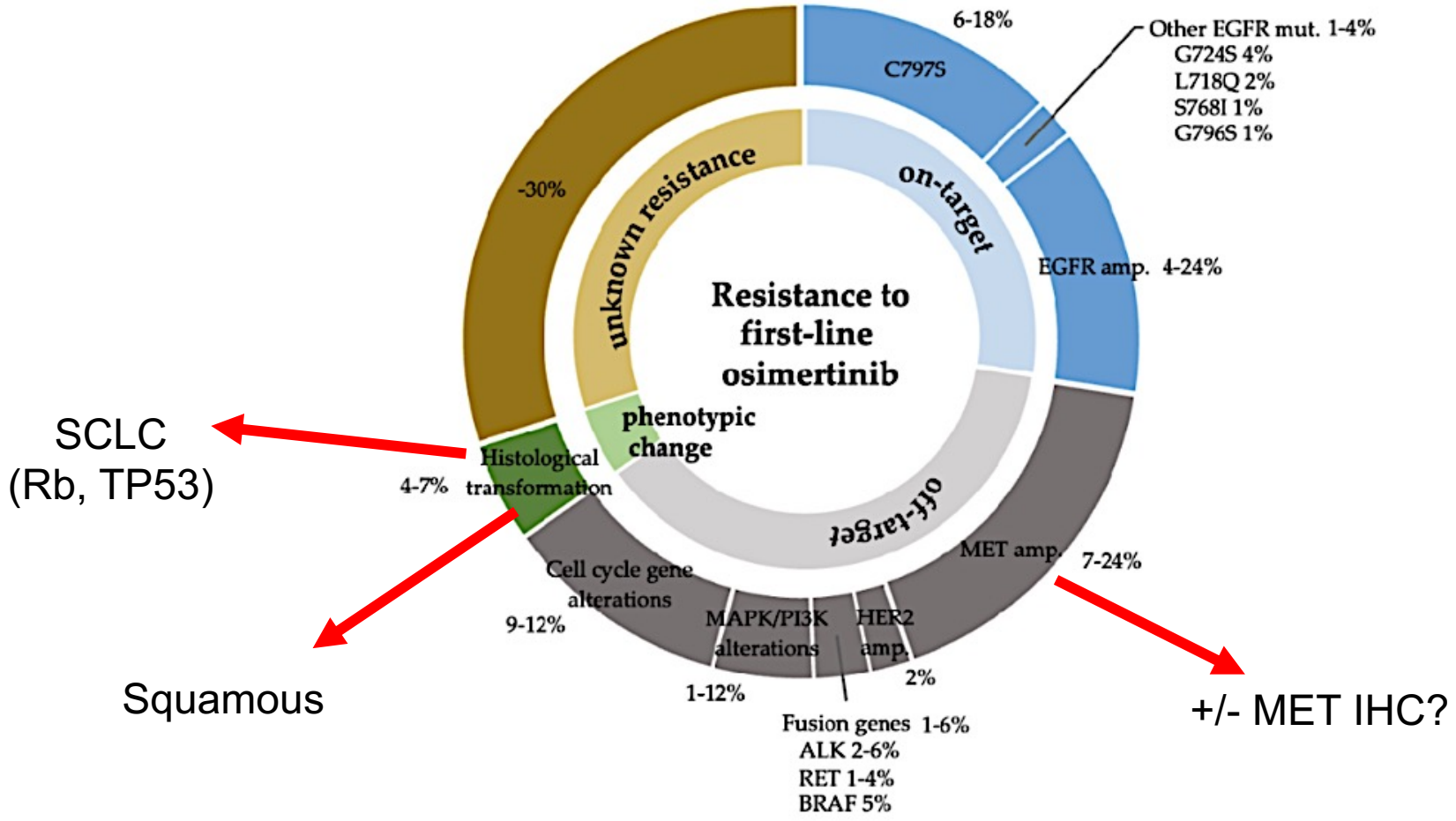
STANFORD
CANCER INSTITUTE
Stanford University Medical Center
A NATIONAL CANCER INSTITUTE-DESIGNATED CANCER CENTER

Agenda

EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC

- Key data from the Phase III MARIPOSA-2 study of amivantamab in combination with platinum-based chemotherapy for patients with progressive EGFR mutation-positive advanced NSCLC
- Efficacy and safety outcomes documented with a subcutaneous formulation of amivantamab in combination with lazertinib in refractory and treatment-naïve EGFR-mutated advanced NSCLC
- Available findings from the COMPEL trial comparing platinum-based chemotherapy with and without osimertinib in patients with EGFR-mutated advanced NSCLC and non-CNS progression on first-line osimertinib
- Early data with and ongoing studies combining osimertinib with other systemic therapies in order to overcome common mechanisms of resistance

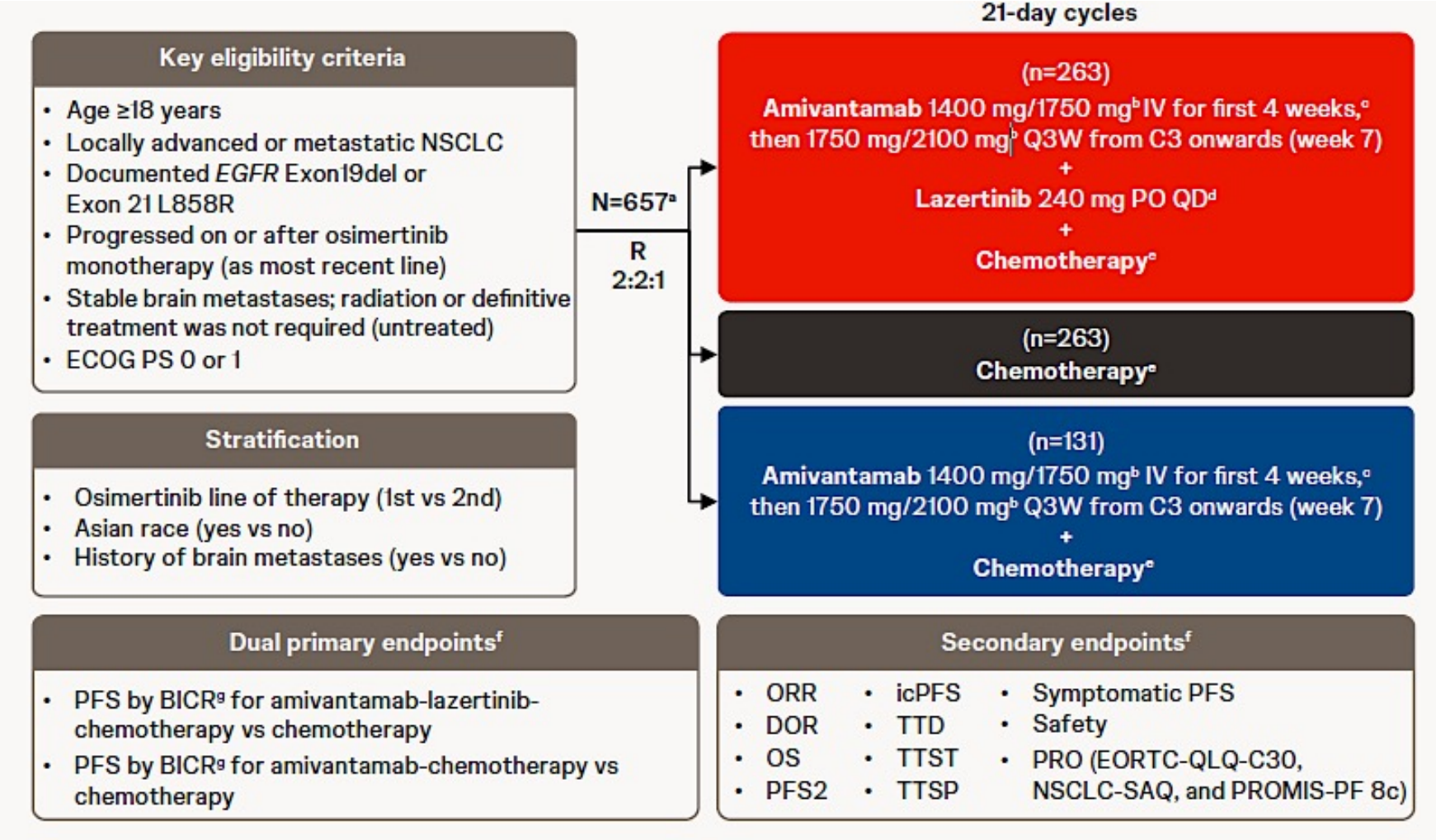
Acquired resistance after third generation EGFR TKIs



Summarized from 10x 1L trials of Osi. Adapted from Fukuda S et al Biomedicines 2024

Amivantamab and chemotherapy after 1L TKI

MARIPOSA-2 study

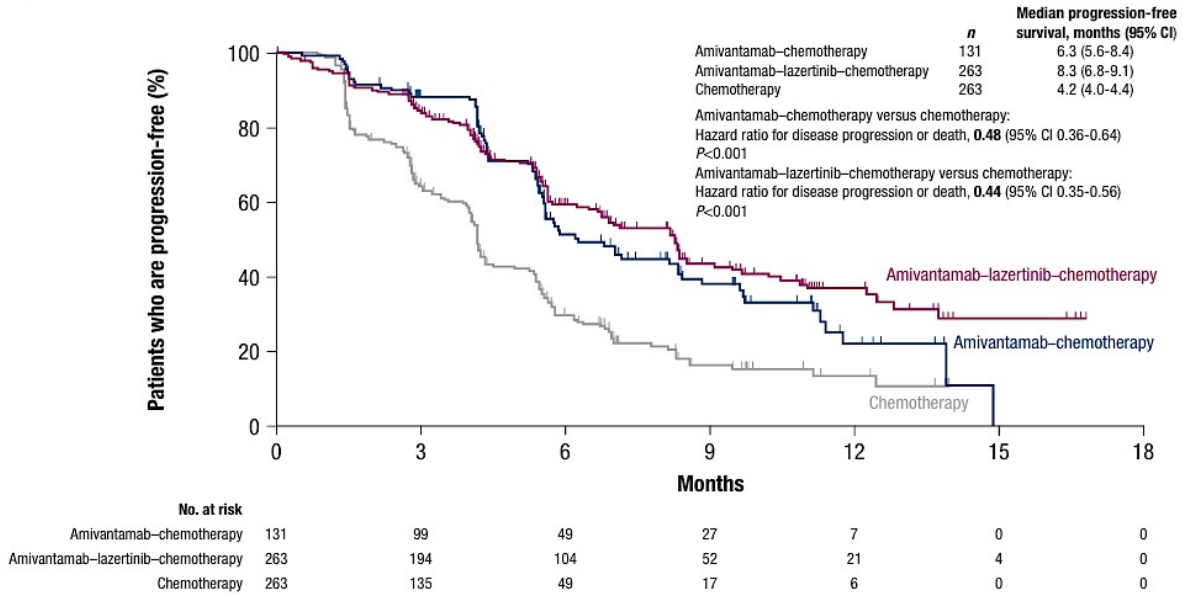


Passaro et al Ann Oncol 2024

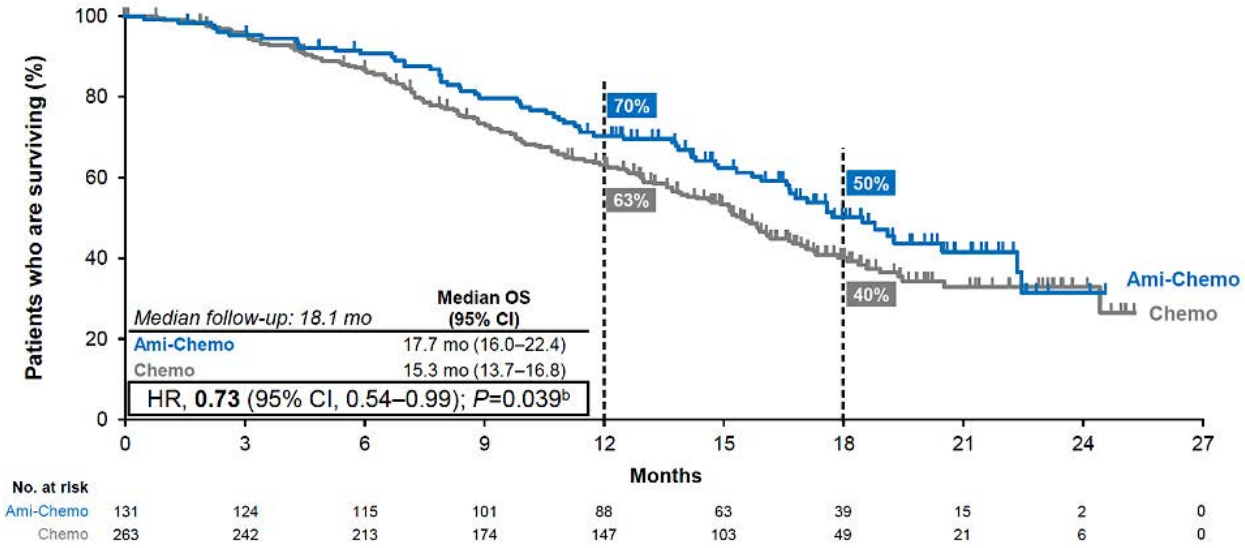
Amivantamab and chemotherapy after 1L TKI

ORR 52% (INV) 64% BICR

PFS 6.3m (vs 4.2m)



OS 17.7 months (vs 15.3)

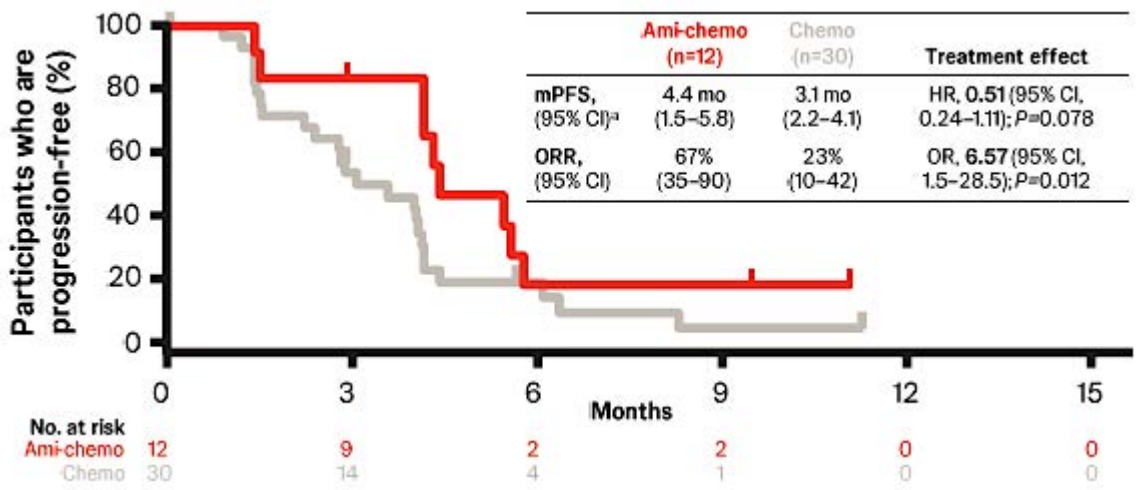


Passaro et al Ann Oncol 2024

Amivantamab and chemotherapy after 1L TKI

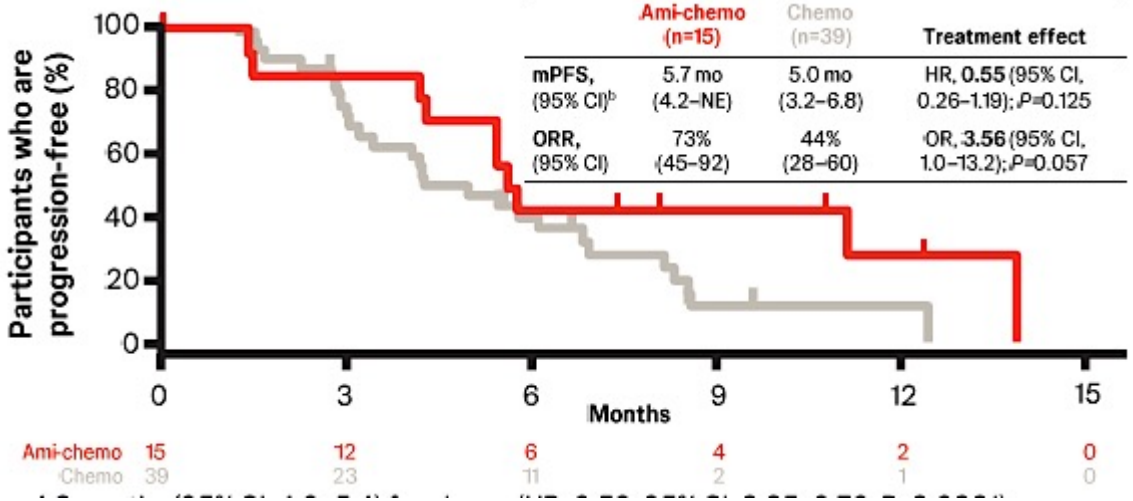
MARIPOSA-2 study: Amivantamab + chemotherapy

MET amp



	Ami-chemo (n=12)	Chemo (n=30)	Treatment effect
mPFS, (95% CI)[a]	4.4 mo (1.5–5.8)	3.1 mo (2.2–4.1)	HR, **0.51** (95% CI, 0.24–1.11); *P*=0.078
ORR, (95% CI)	67% (35–90)	23% (10–42)	OR, **6.57** (95% CI, 1.5–28.5); *P*=0.012

EGFR secondary mutations



	Ami-chemo (n=15)	Chemo (n=39)	Treatment effect
mPFS, (95% CI)[b]	5.7 mo (4.2–NE)	5.0 mo (3.2–6.8)	HR, **0.55** (95% CI, 0.26–1.19); *P*=0.125
ORR, (95% CI)	73% (45–92)	44% (28–60)	OR, **3.56** (95% CI, 1.0–13.2); *P*=0.057

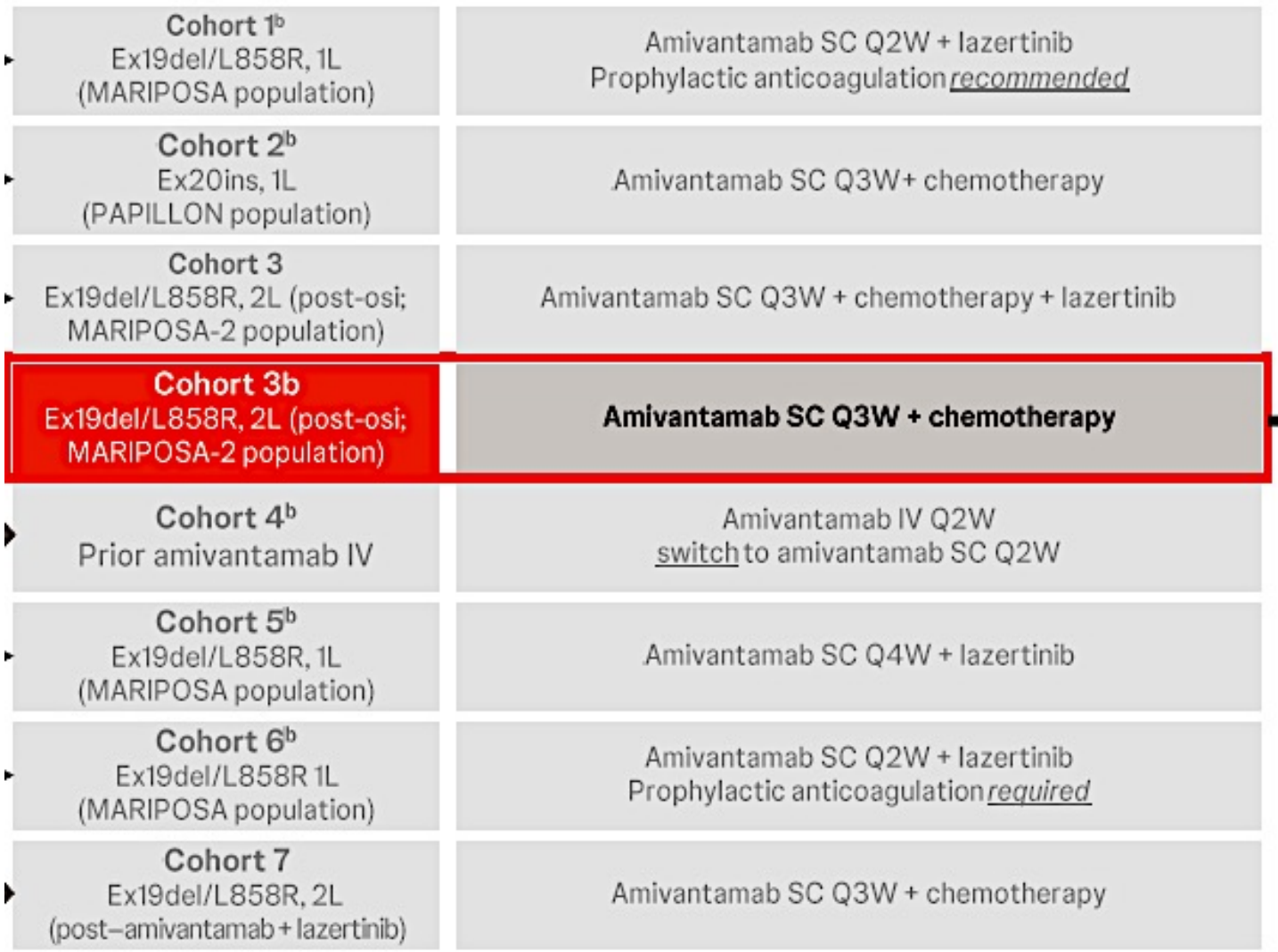
Califano et al ASCO 2025

Amivantamab and chemotherapy after 1L TKI

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)

Passaro et al Ann Oncol 2024

Subcutaneous amivantamab with chemotherapy (PALOMA-2)



Cohort 3b

Primary endpoint:

- ORR by INV[c]

Secondary endpoints:

- ORR by ICR
- DoR by INV
- TTR by INV
- CBR by INV[d]
- PFS
- OS
- Safety
- PK

Dosing (in 21-day cycles)

Amivantamab SC Q3W[e]:
SC abdominal injection at 1600 mg (2240 mg if ≥80 kg) on C1D1, then 2400 mg (3360 mg if ≥80 kg) on Days 8 and 15 of C1, and Q3W thereafter

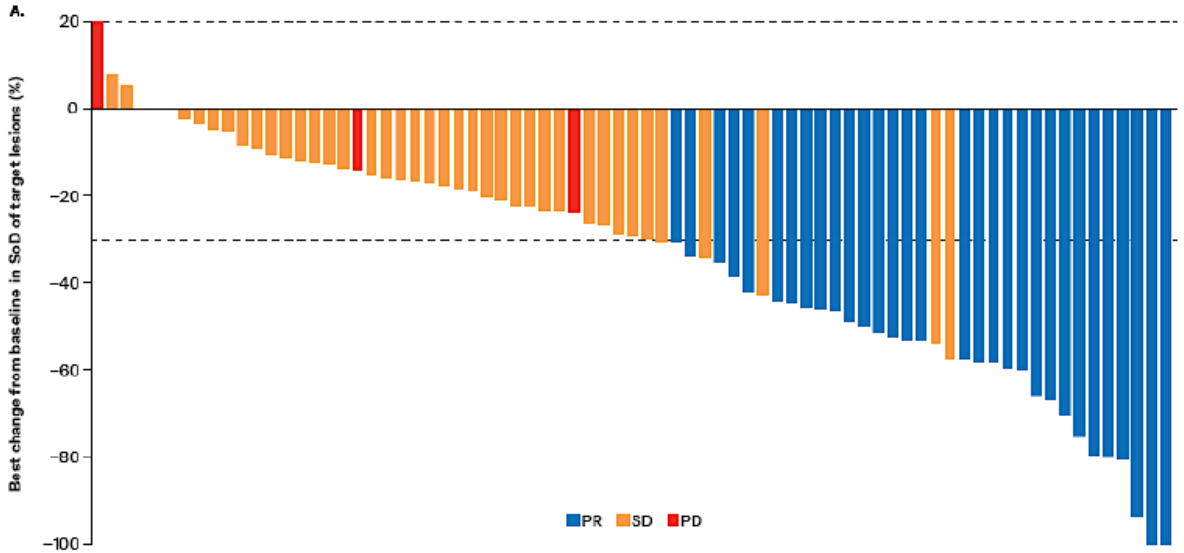
Chemotherapy on the first day of each cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² until disease progression

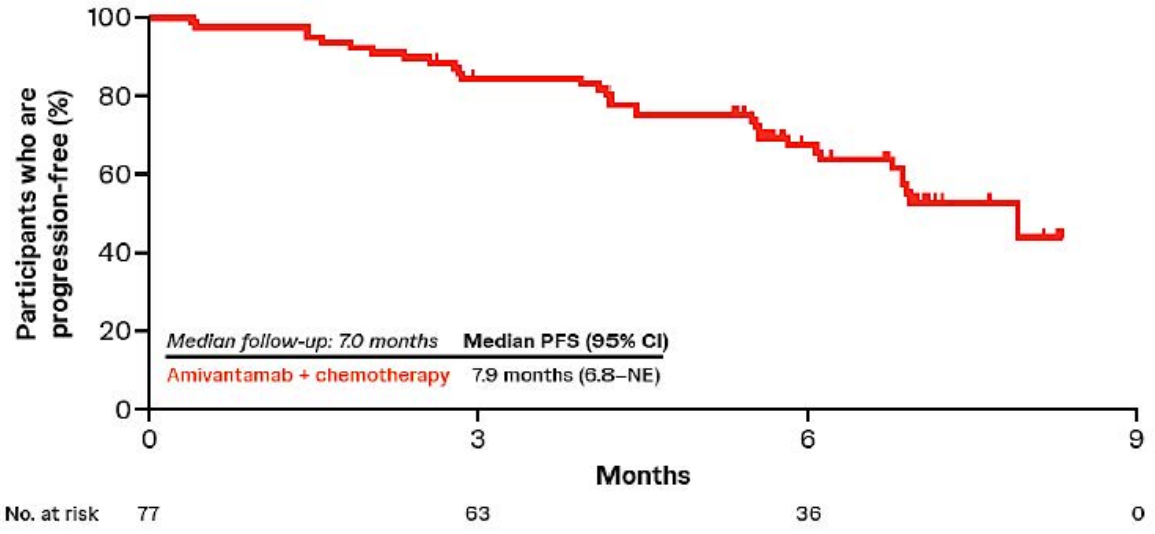
Lim et al ELCC 2025

Subcutaneous amivantamab with chemotherapy (PALOMA-2)

ORR 47% (INV) 53% BICR



PFS 7.9 m (INV)



Nadal et al ESMO 2025

Subcutaneous amivantamab with chemotherapy (PALOMA-2)

5% discontinued treatment

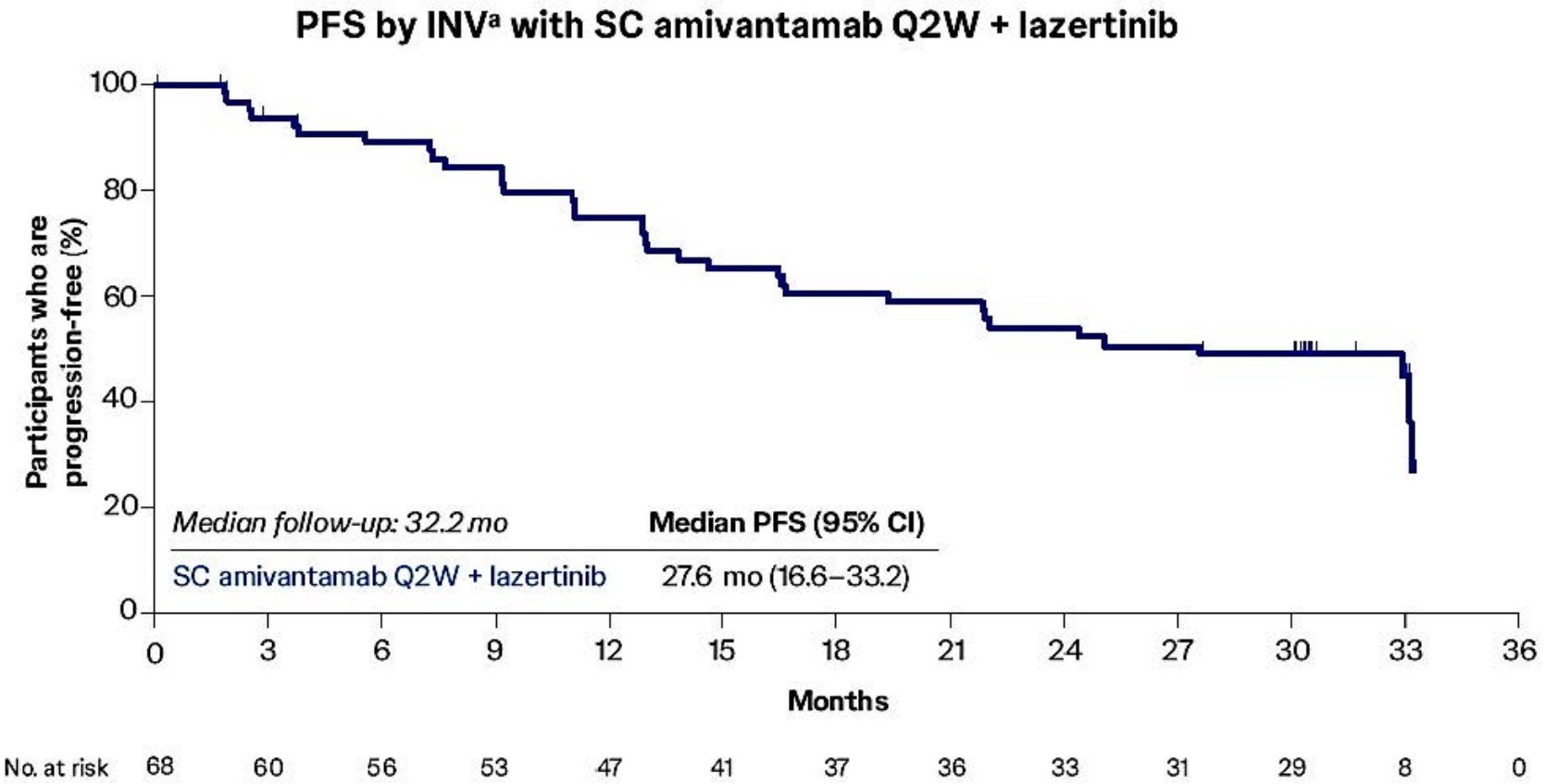
ARR in 8%, none grade 3

TEAEs (≥20%) by preferred term, n (%)	Cohort 3b (N=77)	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Paronychia	42 (55)	2 (3)
Rash	39 (51)	3 (4)
Stomatitis	27 (35)	3 (4)
Dermatitis acneiform	16 (21)	2 (3)
Associated with MET inhibition		
Hypoalbuminemia	27 (35)	5 (6)
Peripheral edema	19 (25)	0
Other		
Neutropenia[a]	43 (56)	26 (34)
Nausea	35 (45)	2 (3)
Constipation	32 (42)	0
Thrombocytopenia[a]	31 (40)	10 (13)
Anemia	27 (35)	5 (6)
ALT increased	25 (33)	4 (5)
Decreased appetite	25 (33)	1 (1)
Leukopenia	24 (31)	12 (16)
Fatigue	22 (29)	4 (5)
Vomiting	20 (26)	6 (8)
AST increased	20 (26)	3 (4)
Asthenia	16 (21)	2 (3)

Nadal et al ESMO 2025

1L Q2W SQ Amivantamab (PALOMA-2)

ORR 85%
(ICR, including unconfirmed)

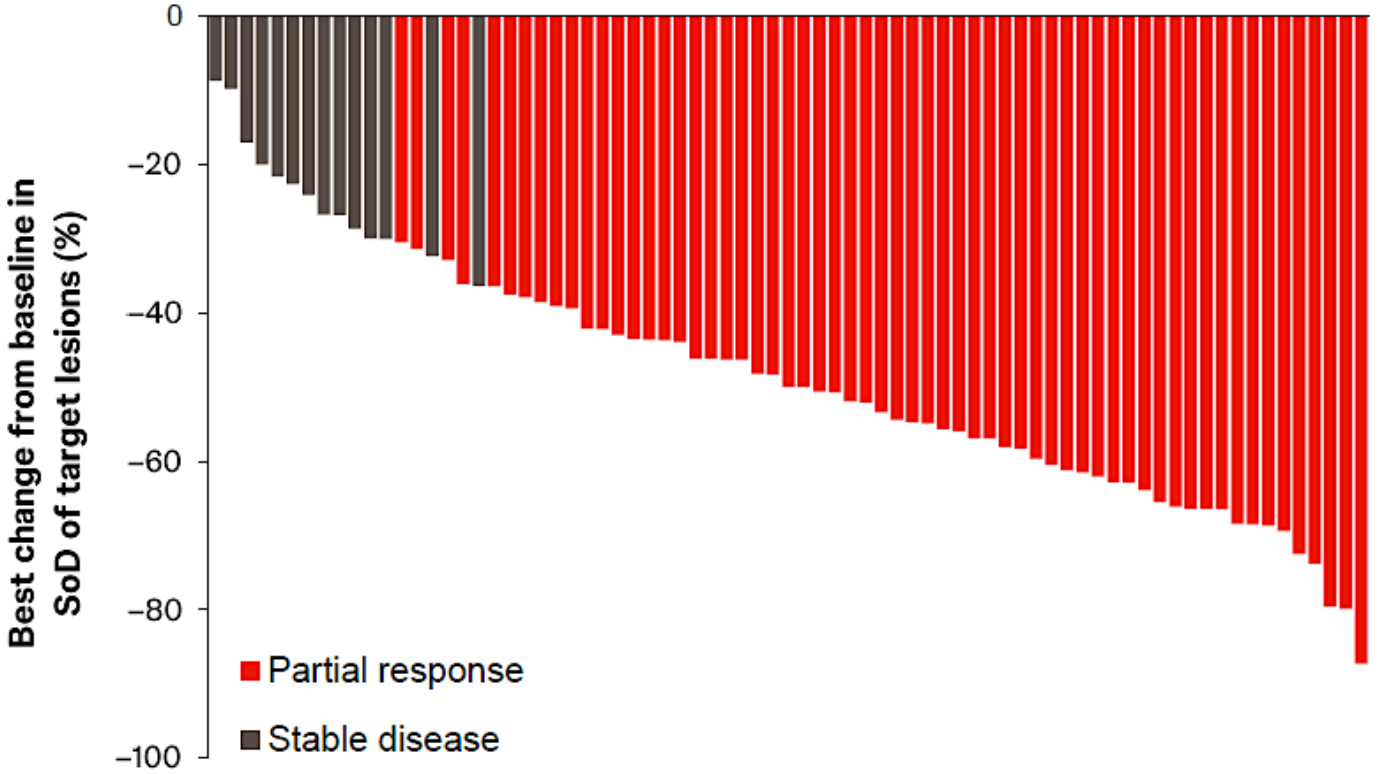


Girard et al ELCC 2026;Abstract 13P

1L Q4W SQ Amivantamab (PALOMA-2)

Cohort 5[b] Ex19del/L858R, 1L (MARIPOSA population)	Amivantamab SC Q4W + lazertinib

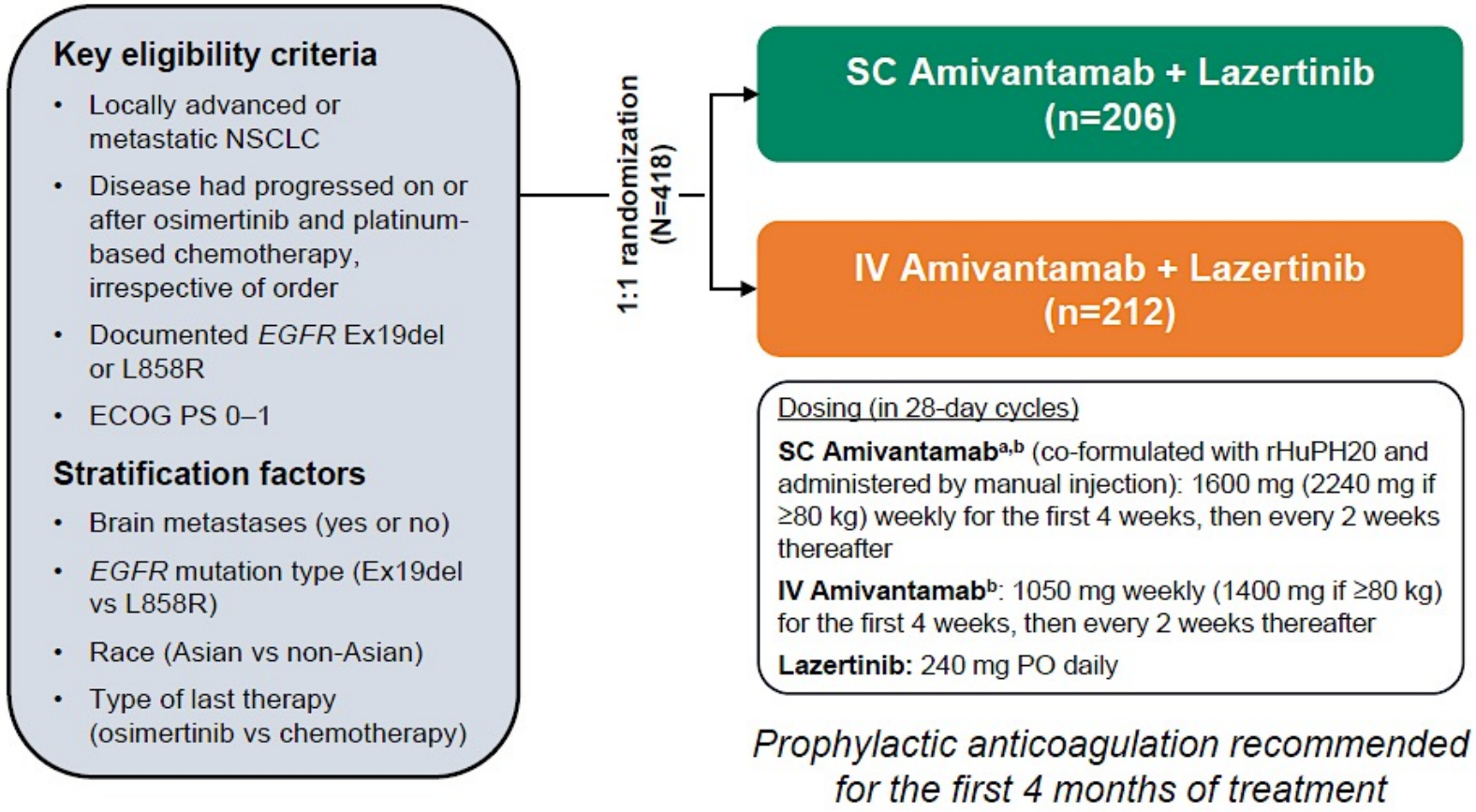
Confirmed ORR 79%



PFS, OS, DOR not reached--

Scott et al WCLC 2025

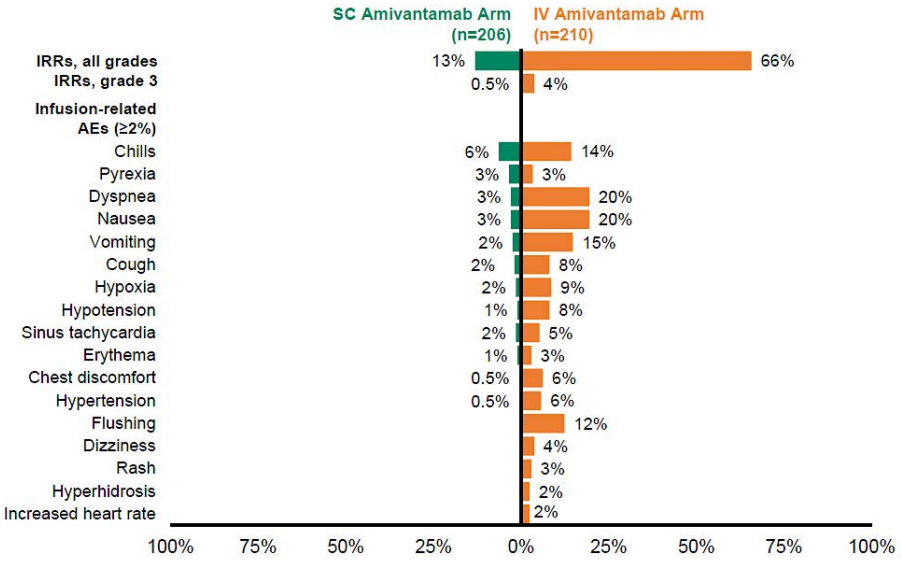
IV vs SQ Amivantamab (PALOMA-3)



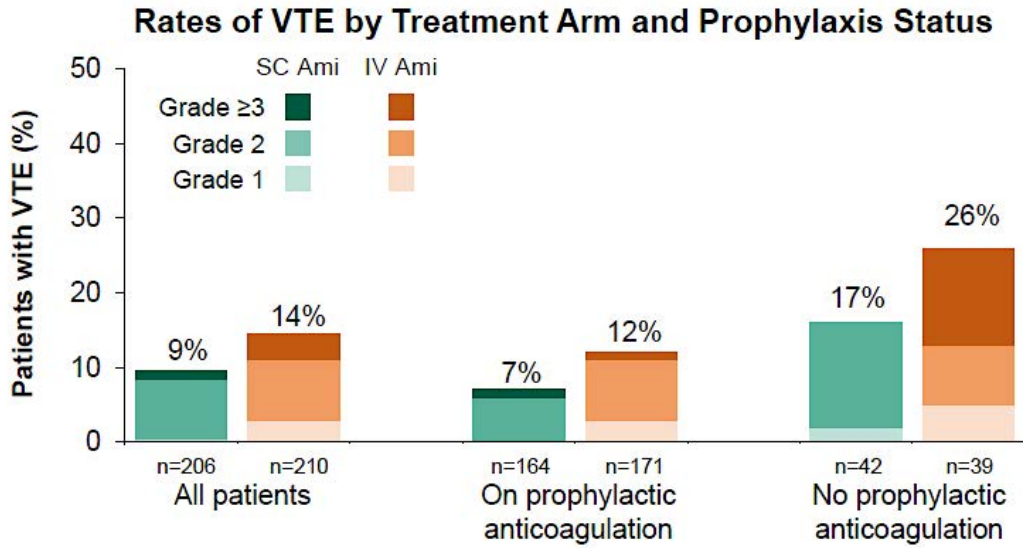
ORR: 30% vs 33%
PFS: 6.1m vs 4.3 mo
OS: NR (HR 0.62, p=0.02)

Leighl et al ASCO 2024

IV vs SQ Amivantamab (PALOMA-3)



Administration-related reactions



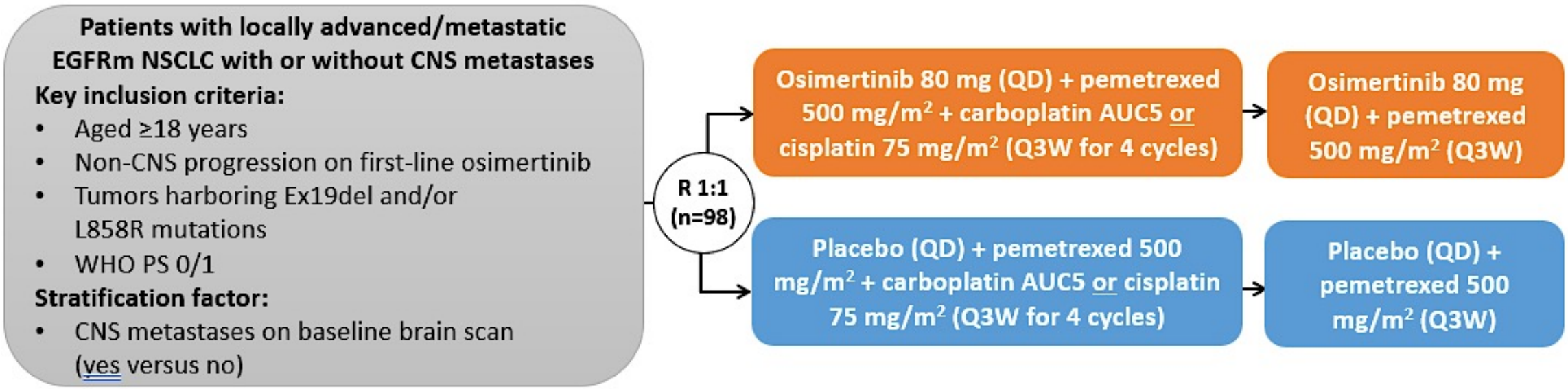
VTE rates

Most common AEs of any cause by preferred term (≥20%), n (%)	SC Amivantamab Arm (n=206)		IV Amivantamab Arm (n=210)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	111 (54)	8 (4)	108 (51)	3 (1)
Rash	95 (46)	8 (4)	91 (43)	8 (4)
Dermatitis acneiform	64 (31)	18 (9)	69 (33)	12 (6)
Stomatitis	57 (28)	1 (0.5)	69 (33)	5 (2)
Diarrhea	43 (21)	3 (1)	39 (19)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	96 (47)	9 (4)	77 (37)	8 (4)
Peripheral edema	52 (25)	6 (3)	58 (28)	1 (0.5)

EGFR and MET side effects

Leighl et al ASCO 2024

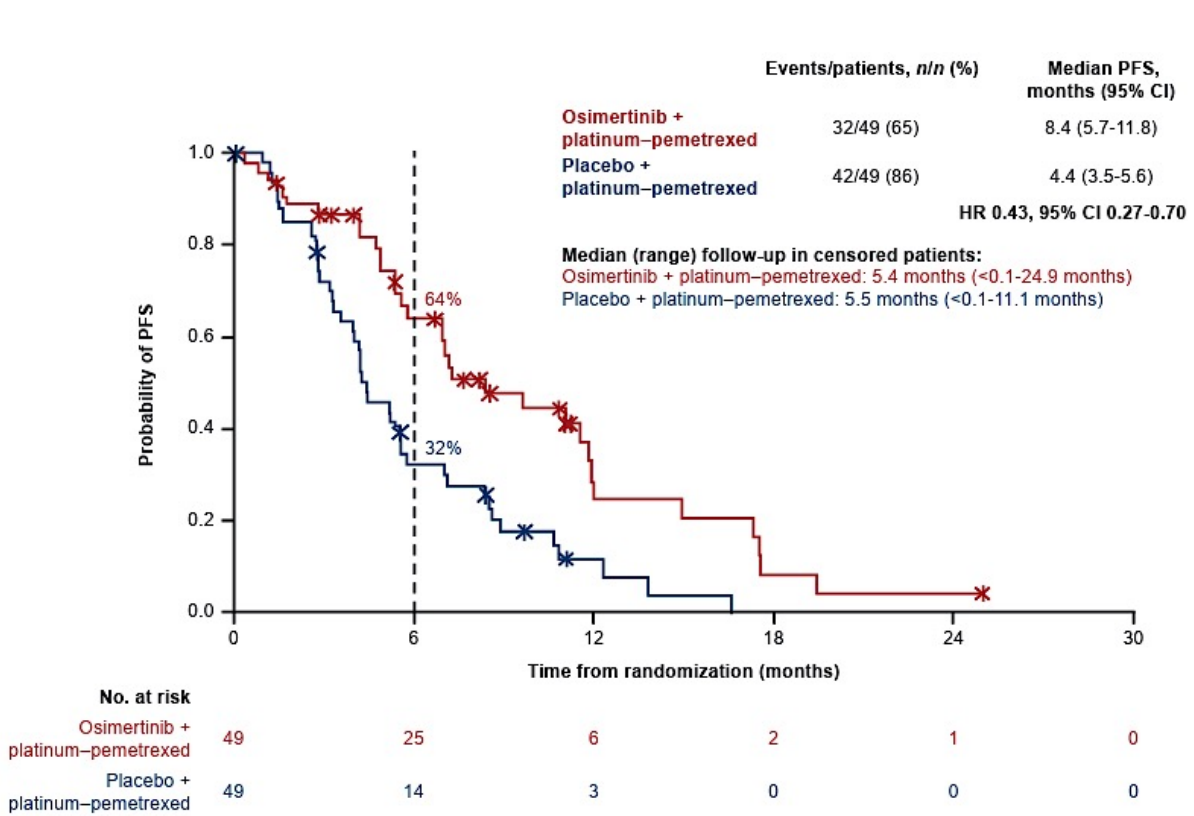
Continuation osimertinib with chemotherapy after 1L TKI
(COMPEL study)



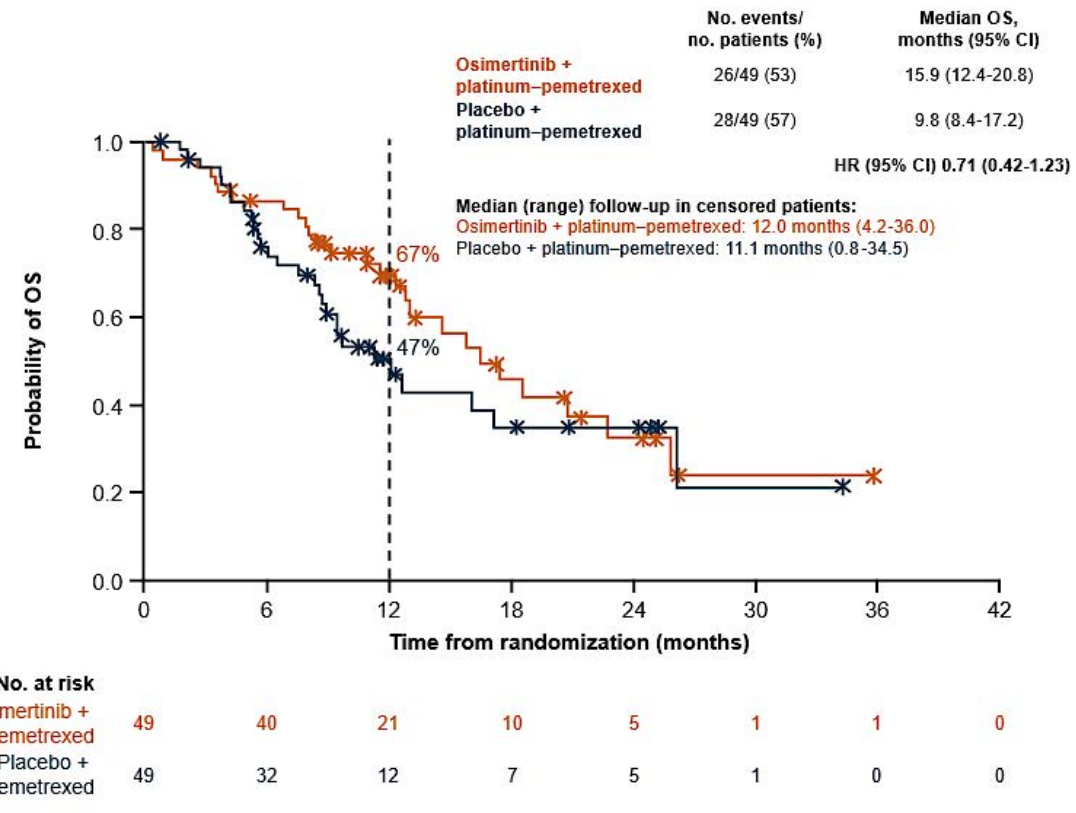
Peled N, et al. *ESMO Open*. 2025

Continuation osimertinib with chemotherapy after 1L TKI
(COMPEL study)

PFS 8.4 mo (vs 4.4m)



OS 15.9m (vs 9.8m)

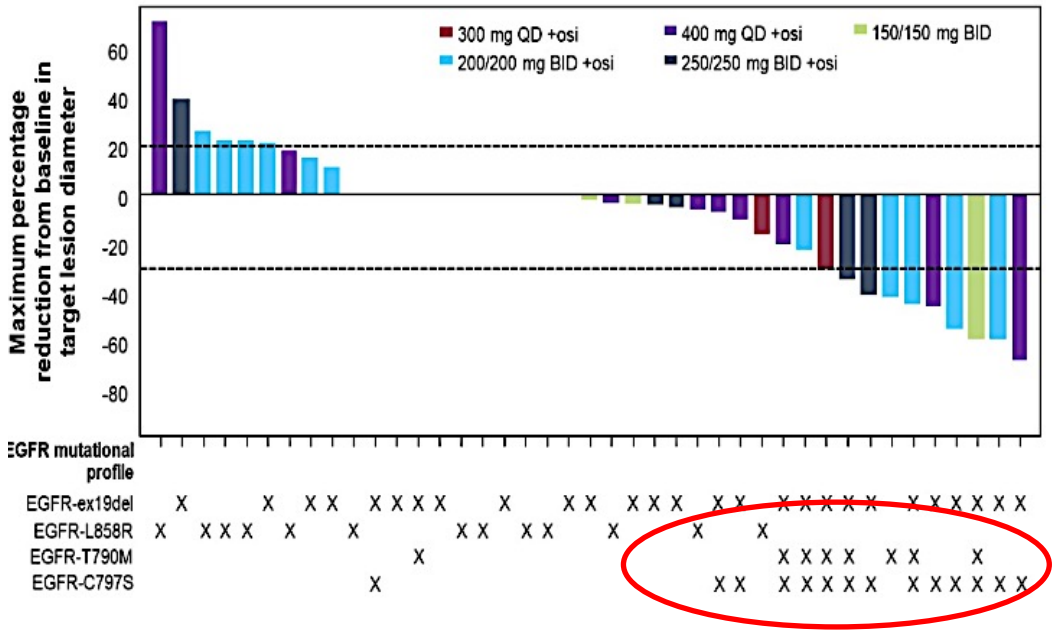


Peled N, et al. *ESMO Open*. 2025

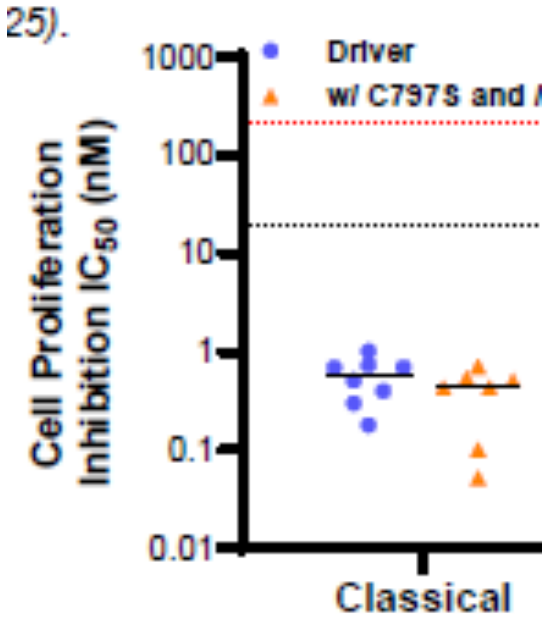
EGFR C797S acquired mutations

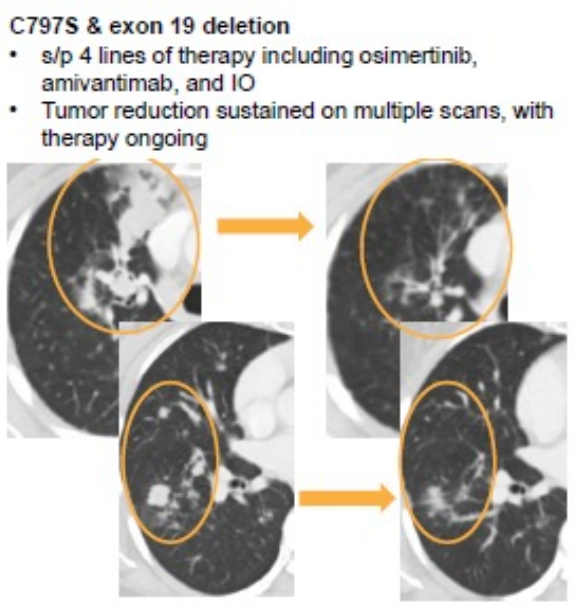
BLU-945 +/- Osi

4 PR's, mostly in E19 del
Drug no longer being pursued



BH-30643





Elamin et al ASCO 2023; Spira A, AACR 2025

Small cell transformation

Carbo/etoposide active, anti PD-(L)1 not so much.

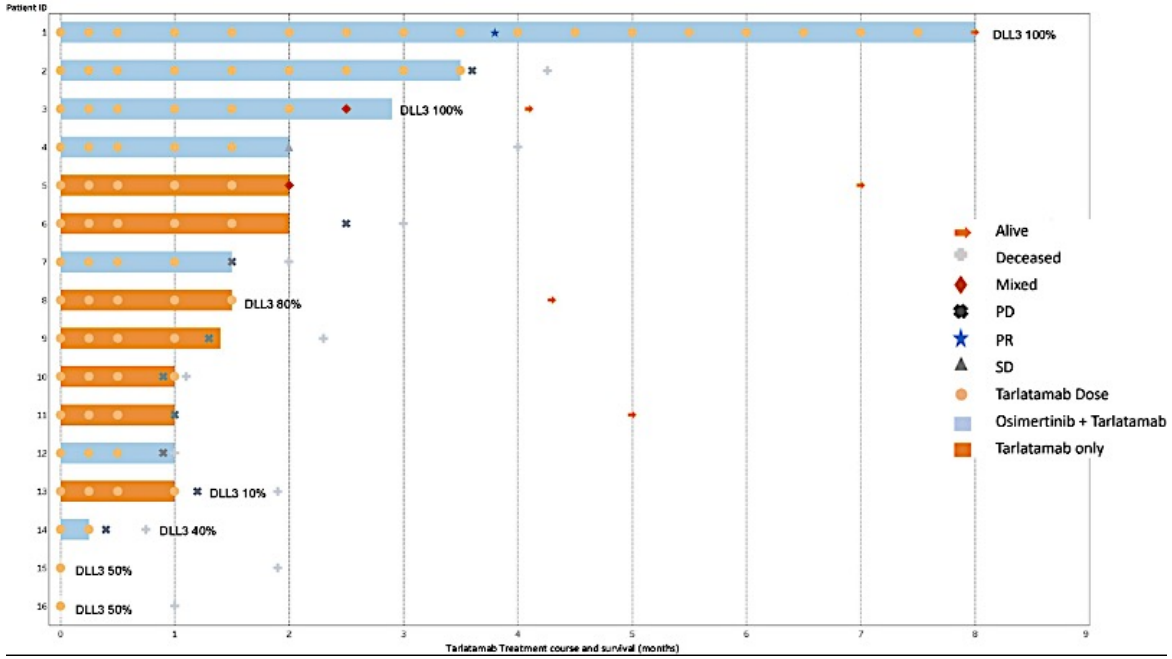
Tarlatamab?

- DLL3 positive in 11/15
- 2 pts treated with DLL3 100%
- 1 patient progressed
- 1 patient responded then progressed, then responded briefly with addition of osimertinib

Aredo, J JTO CCR 2025

"Of the 3 EGFR transformed cases that had a repeat imaging on treatment, 2 had tumor growth and 1 had a mixed response".

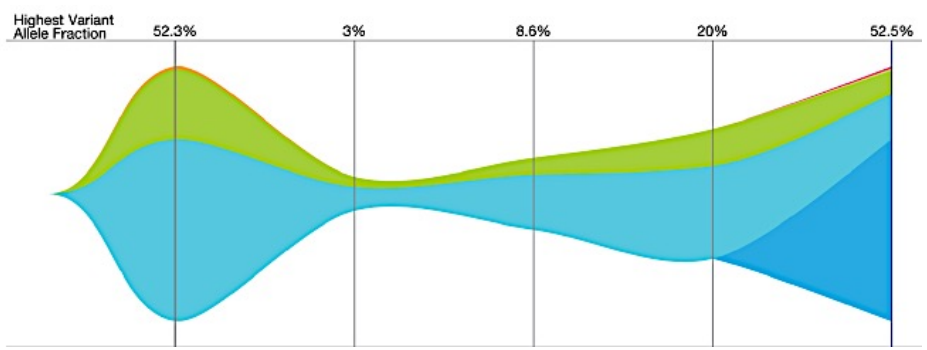
Parma M, ASCO 2025 poster

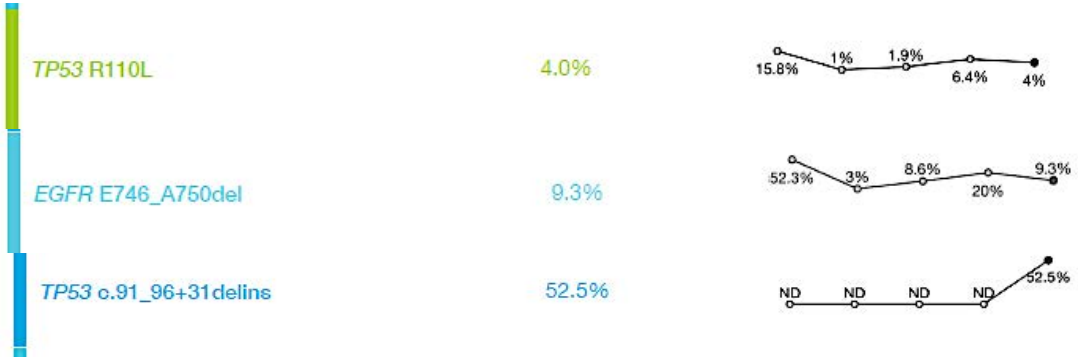


Cooper A, JCO Precision Oncol 2025

Complex resistance may emerge

EGFR E746_A750del (Exon 19 deletion)	✓ Afatinib, Amivantamab, Amivantamab+lazertinib, Dacomitinib, Datopotamab deruxtecan, Erlotinib, Erlotinib+ramucirumab, Gefitinib, Osimertinib	Yes	9.3%
ZFP64-BRAF Fusion	~ Tovorafenib	Yes	0.2%
TP53 R110L	None	Yes	4.0%
HRAS P34T	None	Yes	0.2%
TP53 c.91_96+31delins (Splice Site Indel)	None	Yes	52.5%





Other noteworthy strategies for EGFR refractory NSCLC

- **TROP2 ADC**
- **PD-(L)1/VEGF bispecific antibodies**
- Subsequent lines of chemo (ie docetaxel +/- ramucirumab)
- BRAF/KRAS/ALK etc: KI/TKI combos - I haven't had much success
- ERBB2/HER2 IHC 3+: trastuzumab deruxtecan - pan-tumor approved
- **HER3 ADC** (patritumab deruxtecan withdrawn)
- **EGFR ADC**
- **MET ADC**
- **Bispecifics (+/- ADC),** trispecifics, novel immunotherapy targets?
- Molecular glues/degraders? Vaccines? Cell therapy?

EGFR TKI and/or Amivantamab with any of these strategies?

Conclusions

- Acquired resistant EGFR mutant lung cancer is a complex, heterogeneous disease

- EGFR TKI, chemotherapy, and amivantamab are important initial tools in therapy

- Repeat biopsy may identify specific subsequent targets

- Many current options, and many more in the future!

Cases from the Community

Priya Rudolph, MD, PhD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

How often do you monitor brain MRI for patients with EGFR-mutated NSCLC and brain metastases? How do you approach CNS imaging for patients without a history of brain metastases?

Given the intracranial efficacy documented with osimertinib with and without chemotherapy and amivantamab/lazertinib, do you generally start your patients with EGFR-mutated NSCLC and brain metastases on systemic therapy and hold off on local interventions such as stereotactic body radiation therapy (SBRT)/resection and whole-brain radiation therapy? When do you still incorporate local therapy into initial management?

For patients with an oligometastatic CNS lesion, how do you choose between SBRT and resection?

Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

Module 2: EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC — Dr Neal

Module 3: Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC — Dr Sands

Module 4: Emerging Role of Bispecific Antibody-Based Approaches for EGFR-Mutated NSCLC — Dr Goldman

Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

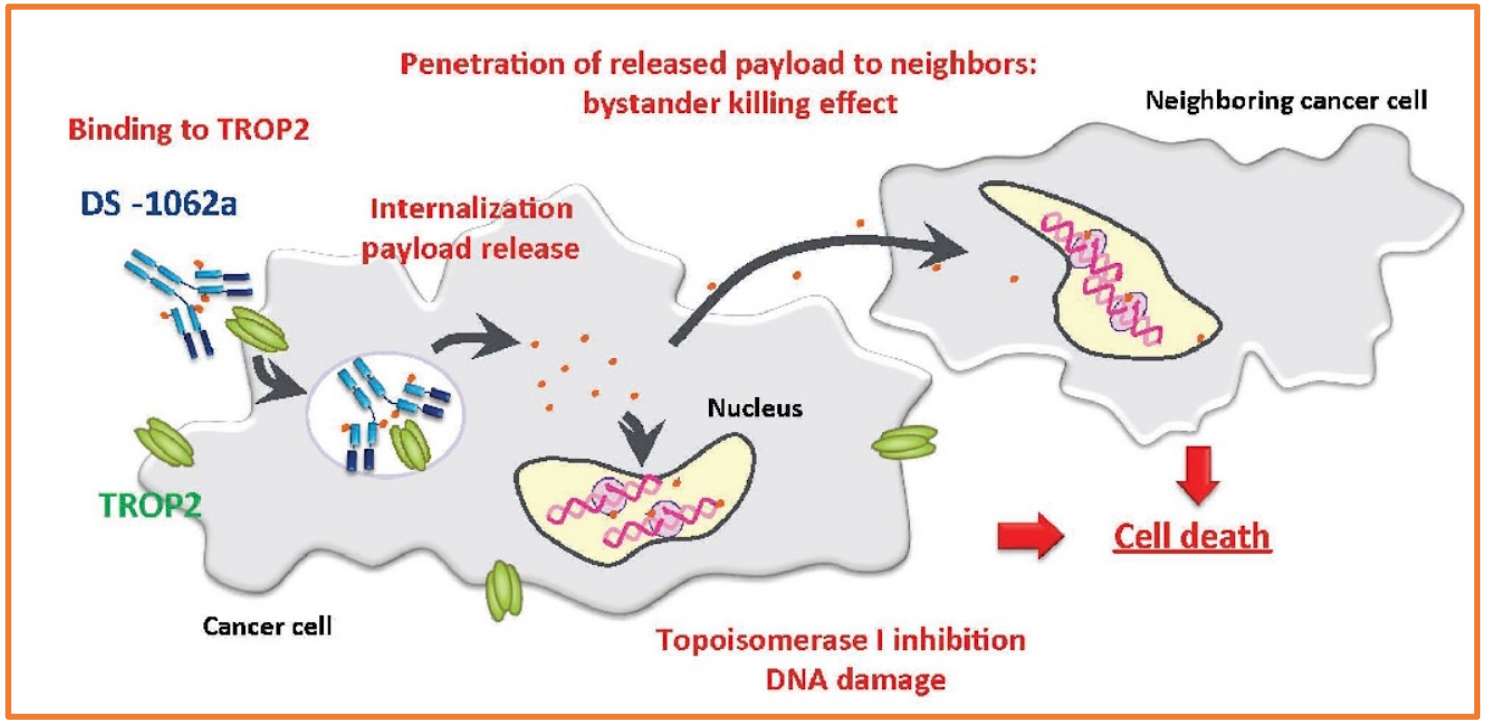
RTP RESEARCH TO PRACTICE

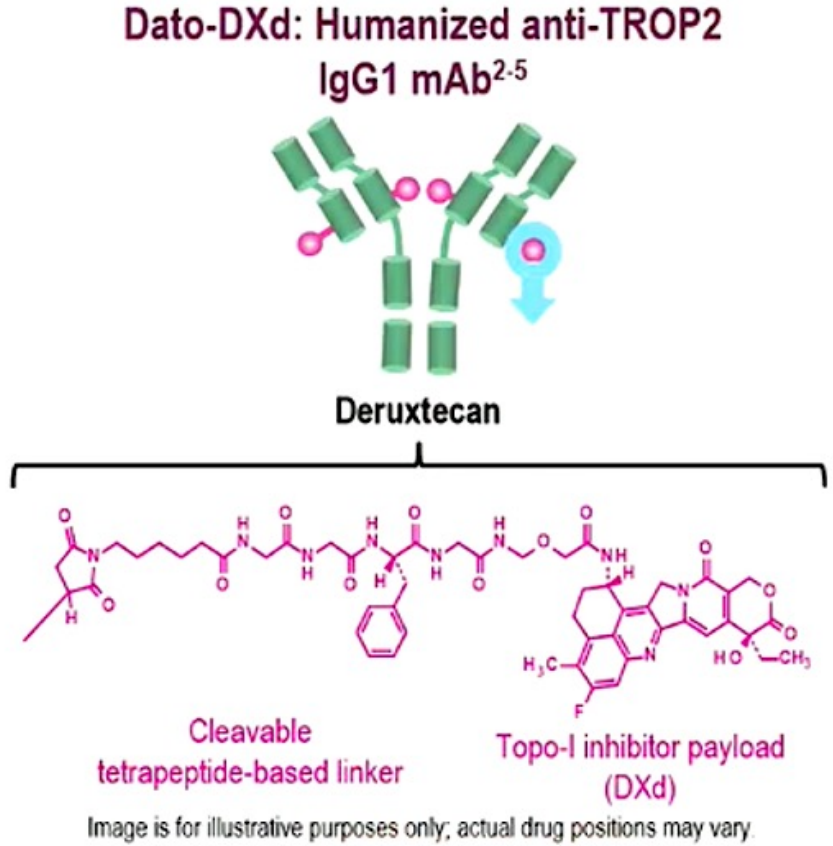
Dana-Farber
Cancer Institute

Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC

Jacob Sands, MD

Datopotamab Deruxtecan





Lisberg et al. ASCO 2020; Spira et al. WCLC 2020

Datopotamab deruxtecan (Dato-DXd)

- TROPION Lung-01 and TROPION Lung-05 Combined Cohort

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

R 1:1

Dato-DXd
6 mg/kg Q3W[a]
(N=137)

Dato-DXd
6 mg/kg Q3W[b]
(N=299)

Docetaxel
75 mg/m^2 Q3W[b]
(N=305)

***EGFR*m Pool: N=117**

TROPION-Lung05
(n=78)
TROPION-Lung01
(n=39)

Endpoints:

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

Dana-Farber Cancer Institute

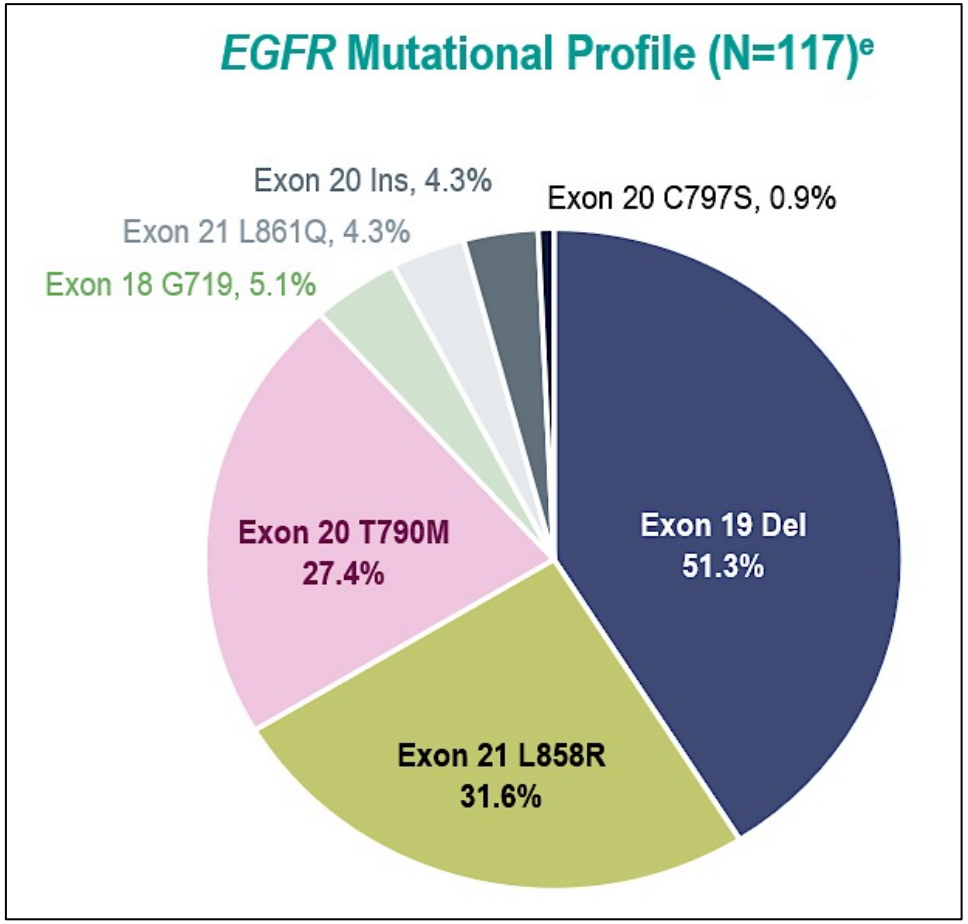
Ahn et al. ESMO Asia 2024; Ahn et al. J Thorac Oncol 2025

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Datopotamab deruxtecan (Dato-DXd)

- TROPION Lung-01 and TROPION Lung-05 Combined Cohort

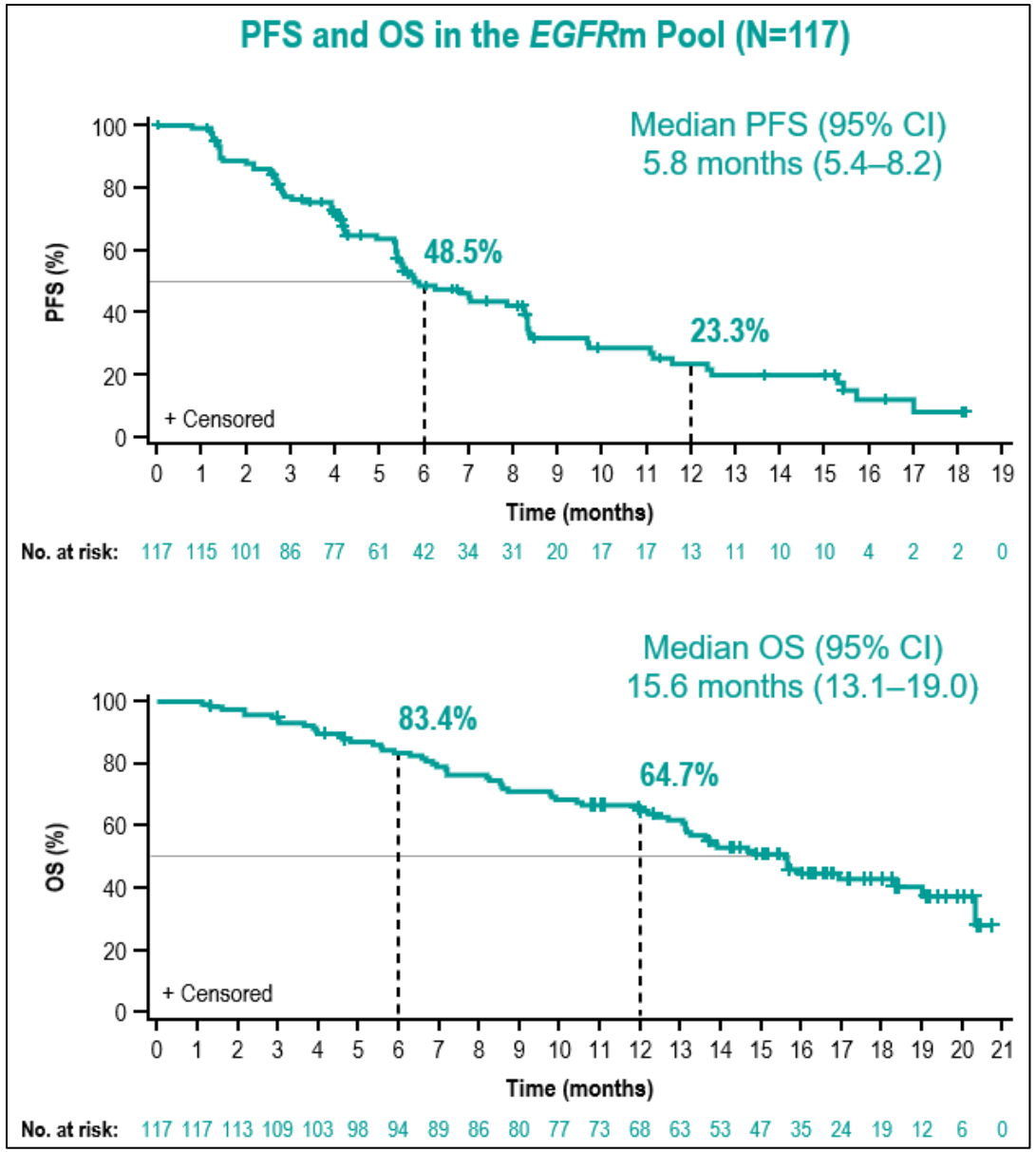
Characteristic, n (%)	*EGFR*m Pool (N=117)	TROPION-Lung05 (N=78)	TROPION-Lung01 (N=39)
Median age (range), years	63 (36–81)	63 (36–77)	62 (39–81)
Sex, female	73 (62.4)	52 (66.7)	21 (53.8)
Race			
Asian	81 (69.2)	55 (70.5)	26 (66.7)
White	27 (23.1)	20 (25.6)	7 (17.9)
Black or African American	1 (0.9)	0	1 (2.6)
Other/missing	8 (6.8)	3 (3.8)	5 (12.8)
ECOG PS			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a]	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b]	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry	36 (30.8)	21 (26.9)	15 (38.5)
Median lines systemic therapy (range)[c]	3 (1–5)	3 (1–5)	2 (1–5)
Prior osimertinib[d]	96 (82.1)	61 (78.2)	35 (89.7)
First line	47 (40.2)	27 (34.6)	20 (51.3)
Second line	34 (29.1)	20 (25.6)	14 (35.9)



Ahn et al. ESMO Asia 2024; Ahn et al. J Thorac Oncol 2025

Datopotamab deruxtecan (Dato-DXd)

Response	*EGFR*m Pool (N=117)	Prior Osimertinib (N=96)
Confirmed ORR,[a] n (%) [95% CI]	50 (**42.7**) [33.6–52.2]	43 (**44.8**) [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 (%) [95% CI]	101 (**86.3**) [78.7–92.0]	82 (**85.4**) [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)



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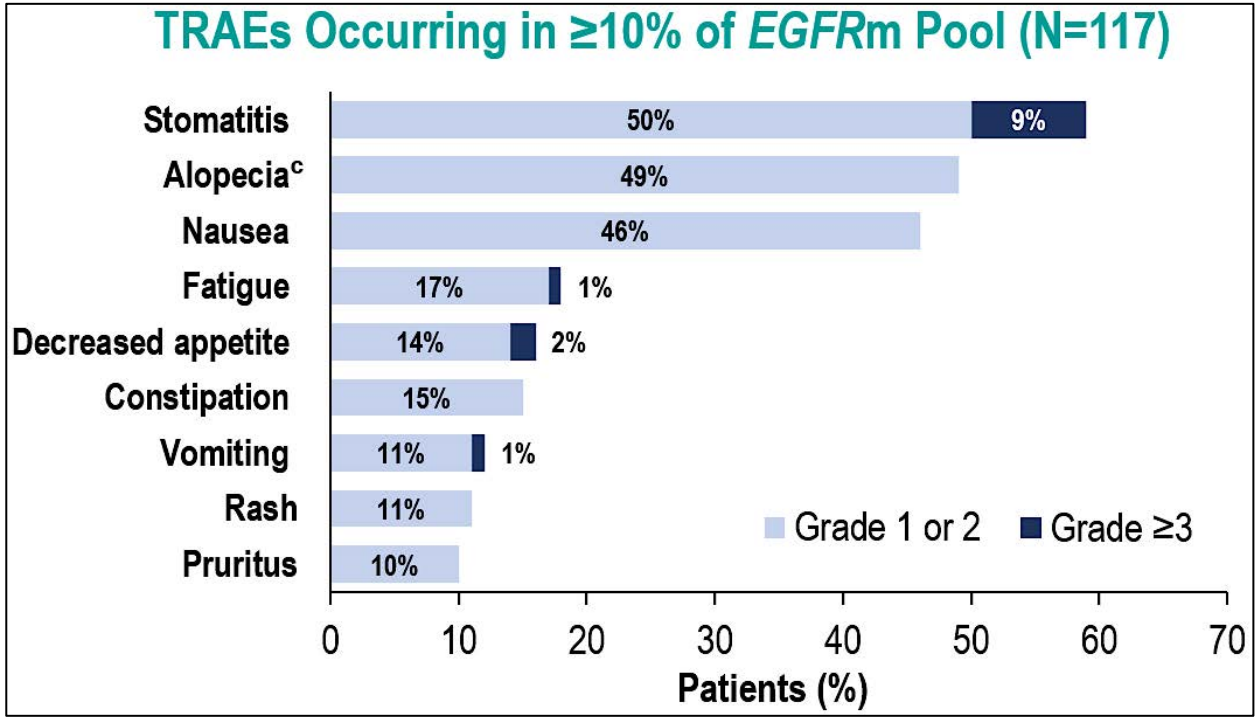
Ahn et al. ESMO Asia 2024; Ahn et al. J Thorac Oncol 2025

Datopotamab deruxtecan (Dato-DXd)

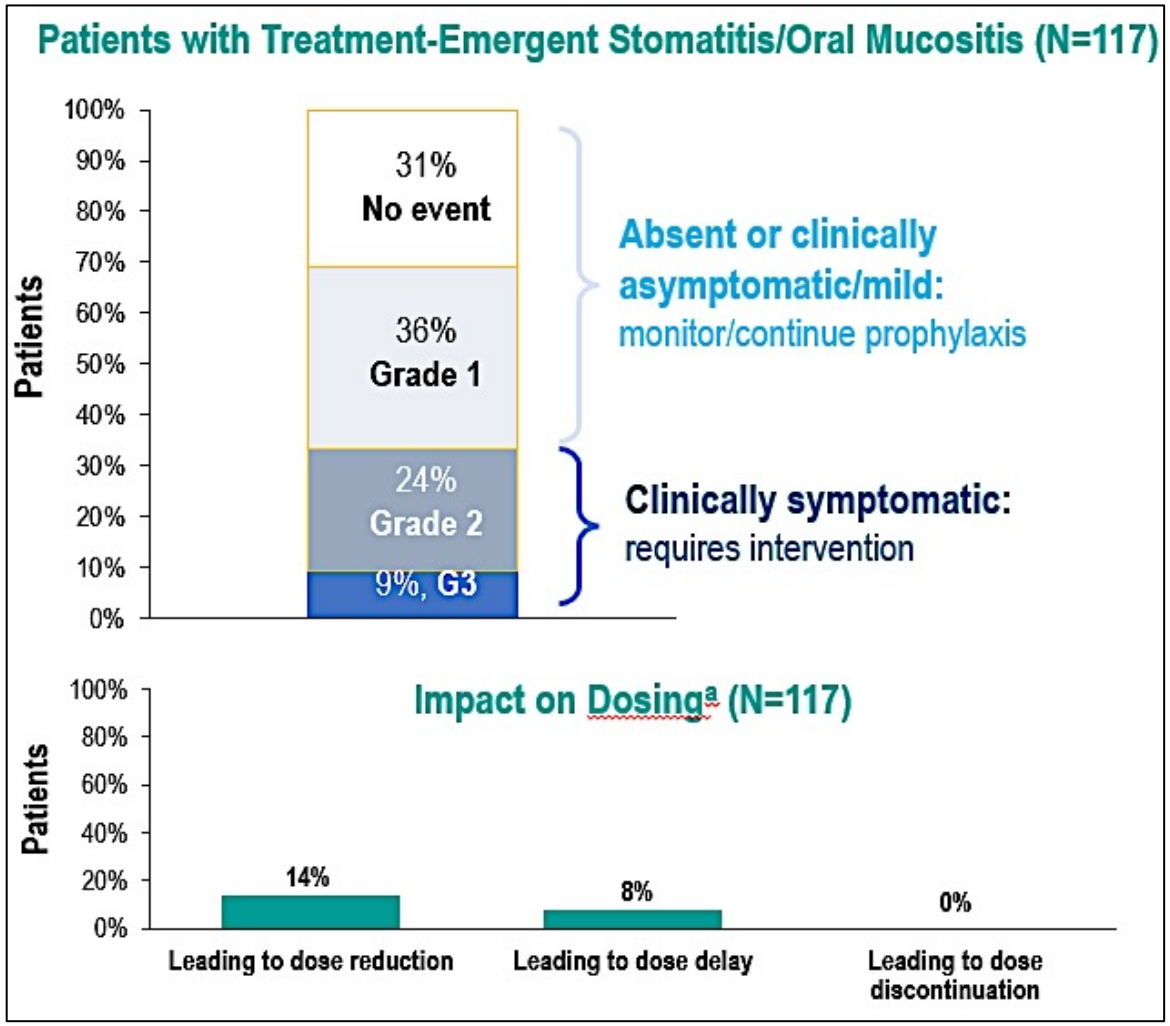
	*EGFR*m Pool (N=117)
TRAEs, n (%)	111 (95)
Grade ≥3	27 (23)
Associated with dose reduction	26 (22)
Associated with dose delay	27 (23)
Associated with treatment discontinuation	6 (5)
Associated with death	0 (0)
Serious TRAEs	9 (8)
AESIs, n (%)	
Stomatitis/oral mucositis[a]	81 (69)
Grade 3[b]	11 (9)
Ocular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



Ahn et al. ESMO Asia 2024;
Ahn et al. J Thorac Oncol 2025

[b]No grade 4 or 5 events occurred

Datopotamab deruxtecan (Dato-DXd)



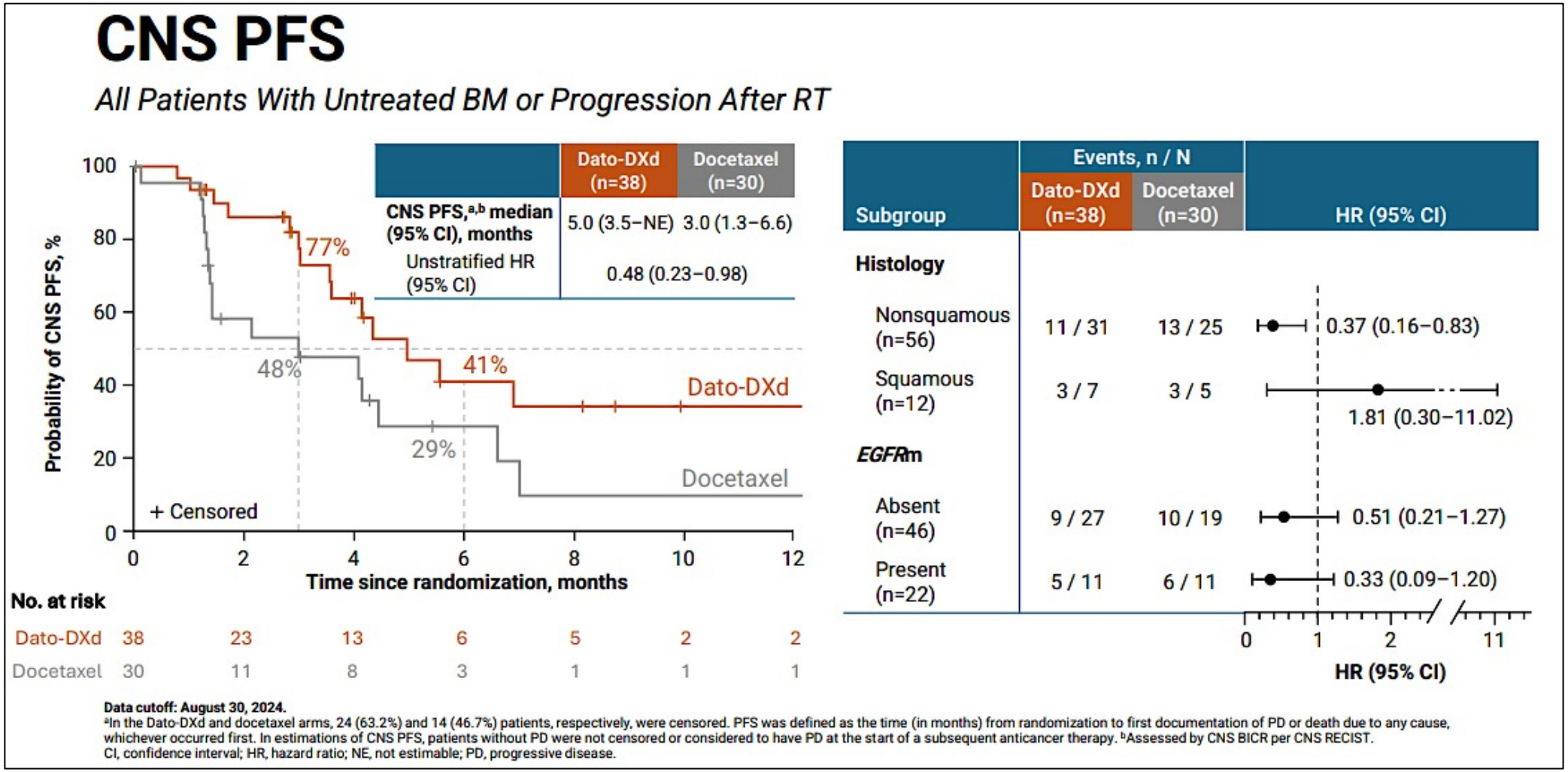
Median time to onset[b]: **29 days**

Median time to asymptomatic resolution[c]: **50 days**

Toxicity management recommendations[1]

- **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)

Intracranial efficacy Dato-DXd from TROPION-Lung01



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.

Pons-Tostivint et al. WCLC 2025

Intracranial Response by CNS BICR

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

	Dato-DXd (n=16)	Docetaxel (n=11)
CNS confirmed ORR,[a] % (95% CI)	38 (15–65)	0 (0–29)
CNS confirmed BOR,[a] n (%)		
CR	1 (6)	0
PR	5 (31)	0
SD	8 (50)	4 (36)
PD	0	2 (18)
NE	2 (13)	5 (46)
CNS confirmed DCR,[a] % (95% CI)	88 (62–98)	36 (11–69)

Data cutoff: August 30, 2024.
CNS cORR in all patients with untreated BM or progression after RT, including those with non-measurable disease: Dato-DXd (n=38), 16% (95% CI, 6–31); docetaxel (n=30), 0% (95% CI, 0–12).
All lesions were identified by BICR but not necessarily by the investigator. As such, follow-up scans for the majority of non-measurable lesions were not available. These are deemed non-evaluable for intracranial efficacy and limit clinical interpretation of intracranial efficacy.
[a]Assessed by CNS BICR per CNS RECIST.
BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease.

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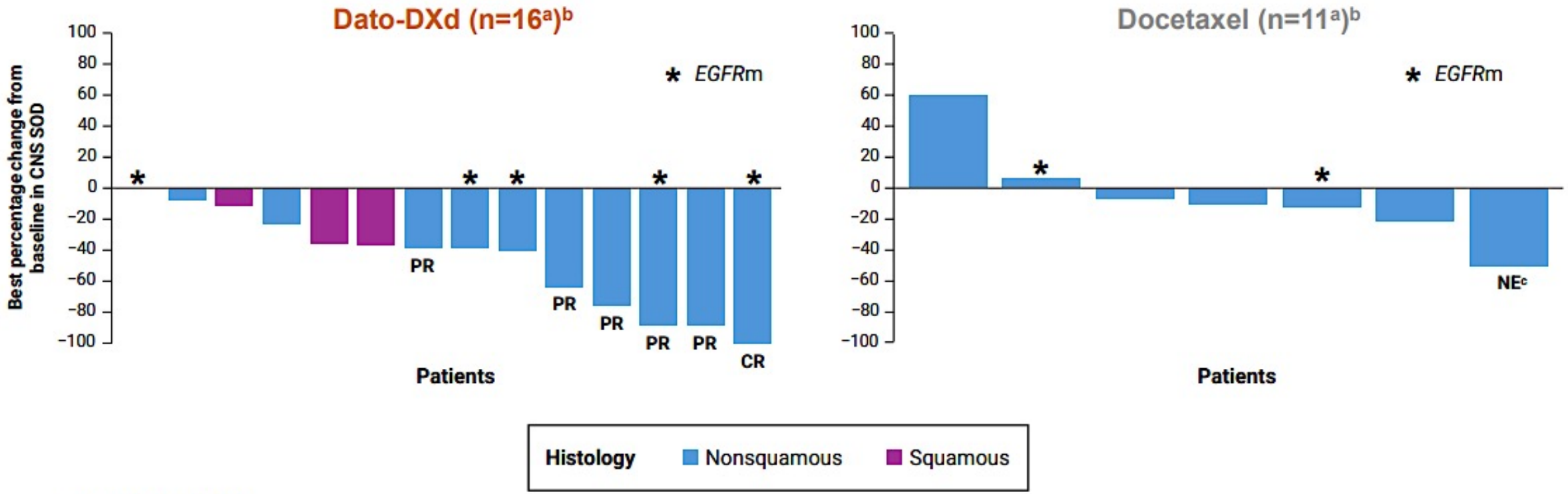
Intracranial Activity

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



Data cutoff: August 30, 2024.

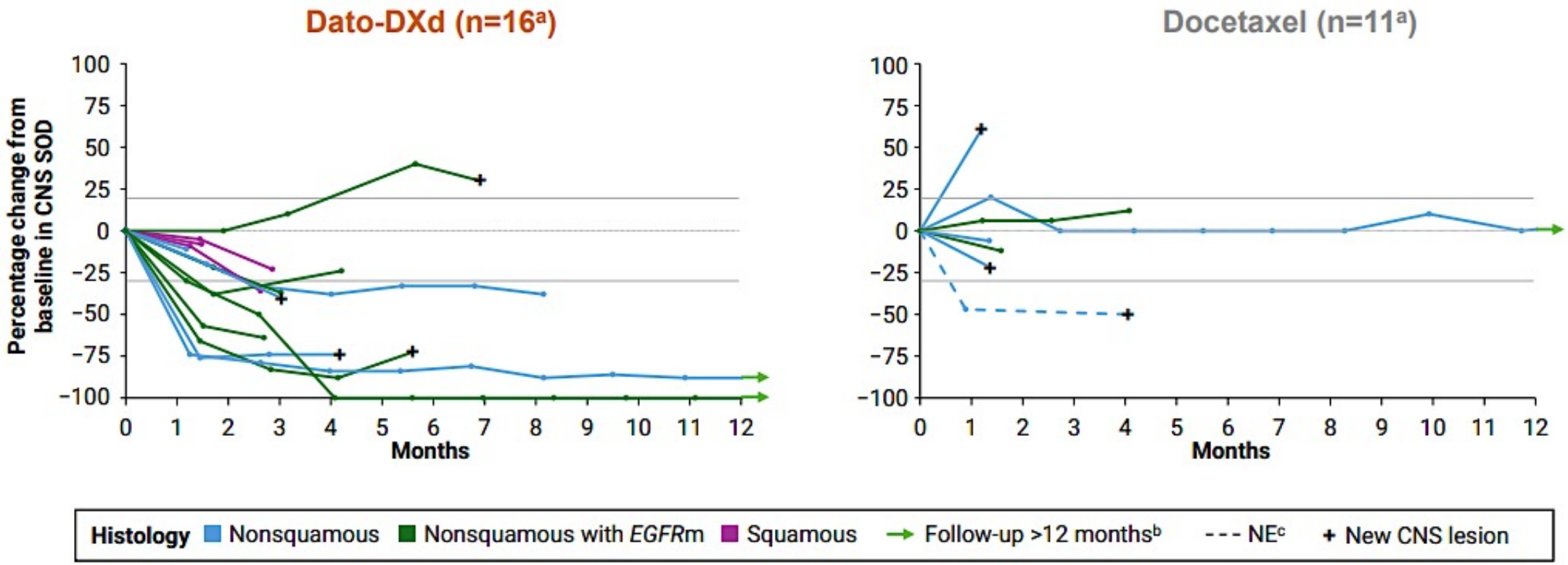
[a]Two patients in the Dato-DXd arm and 4 patients in the docetaxel arm did not have adequate post-baseline tumor assessments and were excluded from the waterfall plots. [b]CNS BOR assessed by CNS BICR per CNS RECIST is presented underneath bars for patients with CNS BOR of PR, CR, or NE. [c]This patient 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.

Pons-Tostivint et al. WCLC 2025

Intracranial Activity Over Time

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 spider plots. [b]Dato-DXd: One patient with a CNS CR up to ~19.5 months (systemic BOR: SD) and 1 patient with a CNS PR up to ~27.5 months (systemic BOR: PR); docetaxel: CNS SD up to ~27.0 months (systemic BOR: PR). [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.

Pons-Tostivint et al. WCLC 2025

Dato-DXd is granted accelerated approval by the FDA in EGFR-mutated NSCLC

Press Release: June 23, 2025

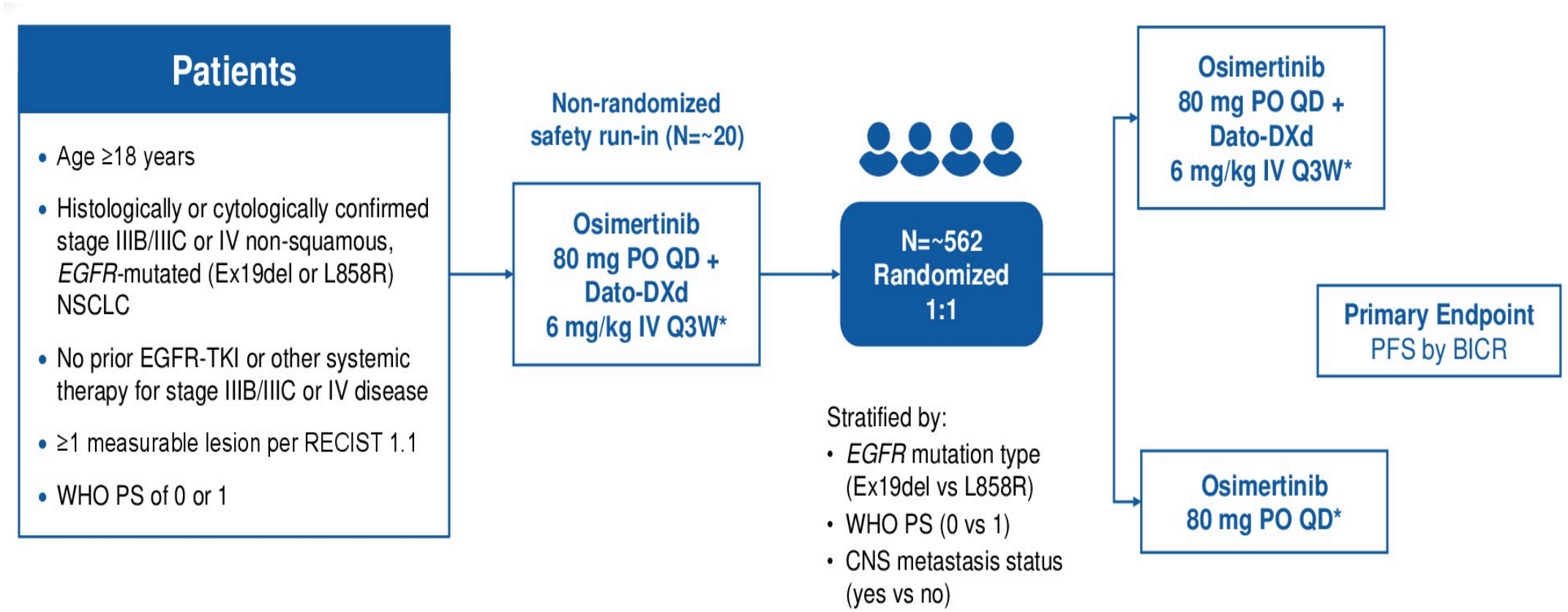
“On June 23, 2025, the Food and Drug Administration granted accelerated approval to datopotamab deruxtecan-dlnk for adults with locally advanced or metastatic epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer (NSCLC) who have received prior EGFR-directed therapy and platinum-based chemotherapy.

Efficacy was evaluated in a pooled subgroup of 114 patients with locally advanced or metastatic EGFR-mutated NSCLC who had received prior treatment with an EGFR-directed therapy and platinum-based chemotherapy and received datopotamab deruxtecan-dlnk at the recommended dose across two clinical trials: TROPION-Lung05 and TROPION-Lung01. TROPION-Lung05 (NCT04484142) was a multicenter, single-arm trial, while TROPION-Lung01 (NCT04656652) was a multicenter, open-label, randomized controlled trial.

The major efficacy outcome measures were confirmed overall response rate (ORR) and duration of response (DOR) determined by blinded independent central review per RECIST v1.1. ORR was 45% (95% CI: 35, 54) and median DOR was 6.5 months (95% CI: 4.2, 8.4).

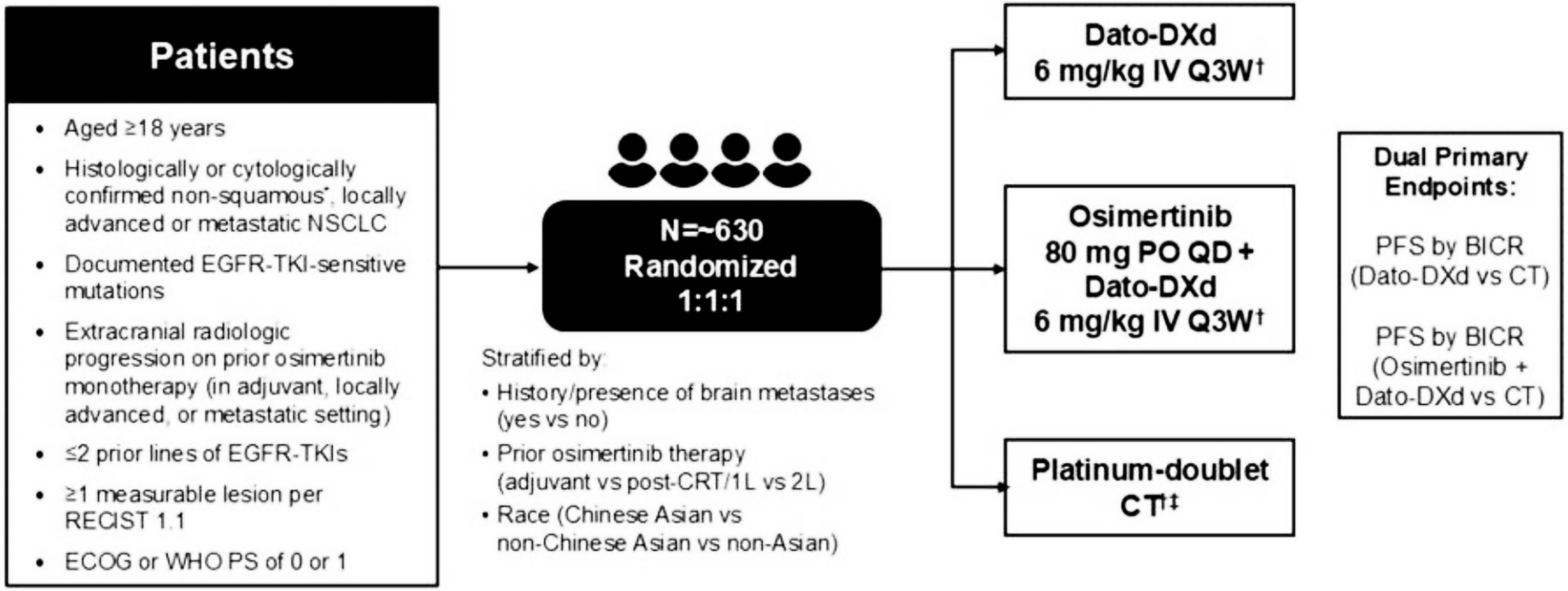
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-datopotamab-deruxtecan-dlnk-egfr-mutated-non-small-cell-lung-cancer

TROPION-Lung14: A Phase 3 study of osimertinib ± Dato-DXd as 1L therapy



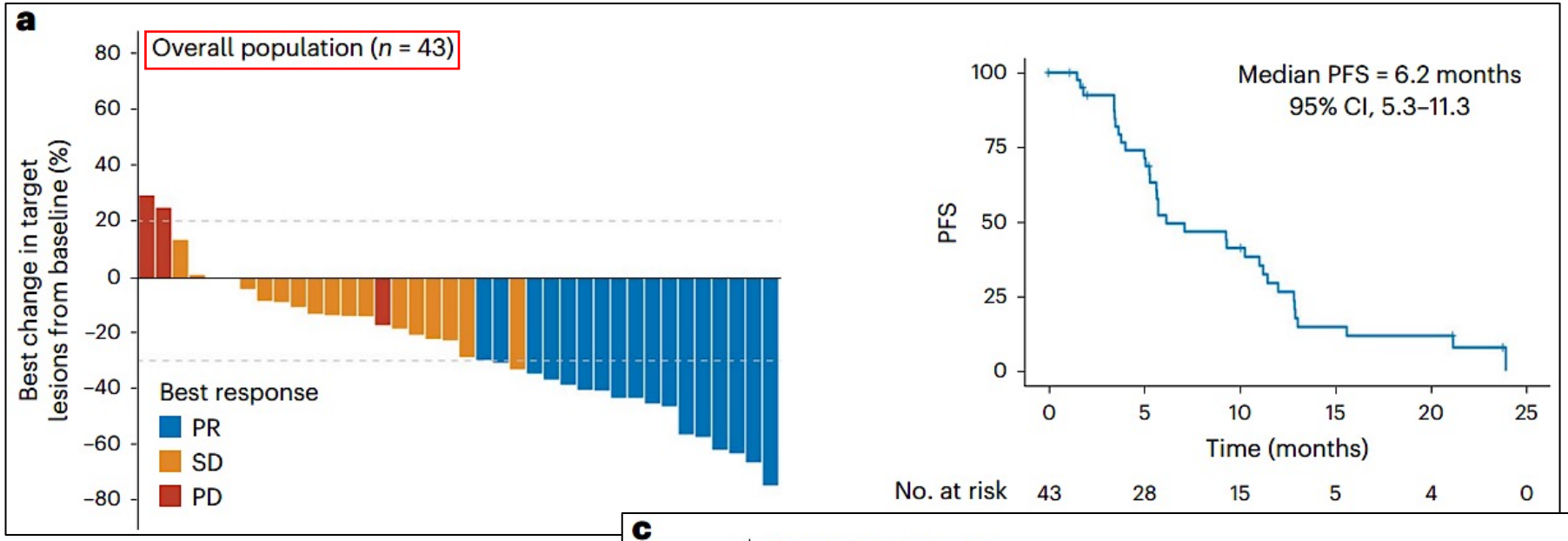
Lu et al. ASCO 2025

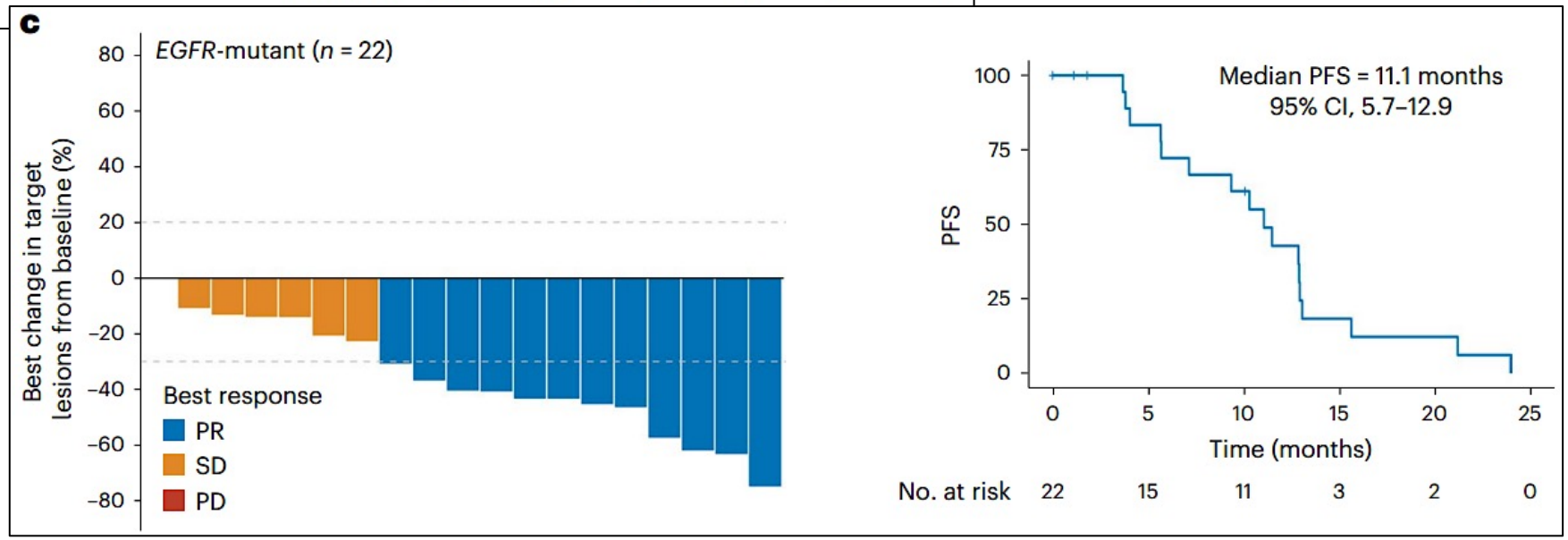
TROPION-Lung15: A Phase 3 study of Dato-DXd ± osimertinib in EGFRm NSCLC that has progressed on prior osimertinib



Tan DS et al. Ther Adv Med Oncol. 2025;17:17588359251385410.

Sacituzumab tirumotecan (Sac-TMT)





Zhao et al. Nature Medicine 2025

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2026 VOL. 394 NO. 1

Sacituzumab Tirumotecan in EGFR-TKI–Resistant, *EGFR*-Mutated Advanced NSCLC

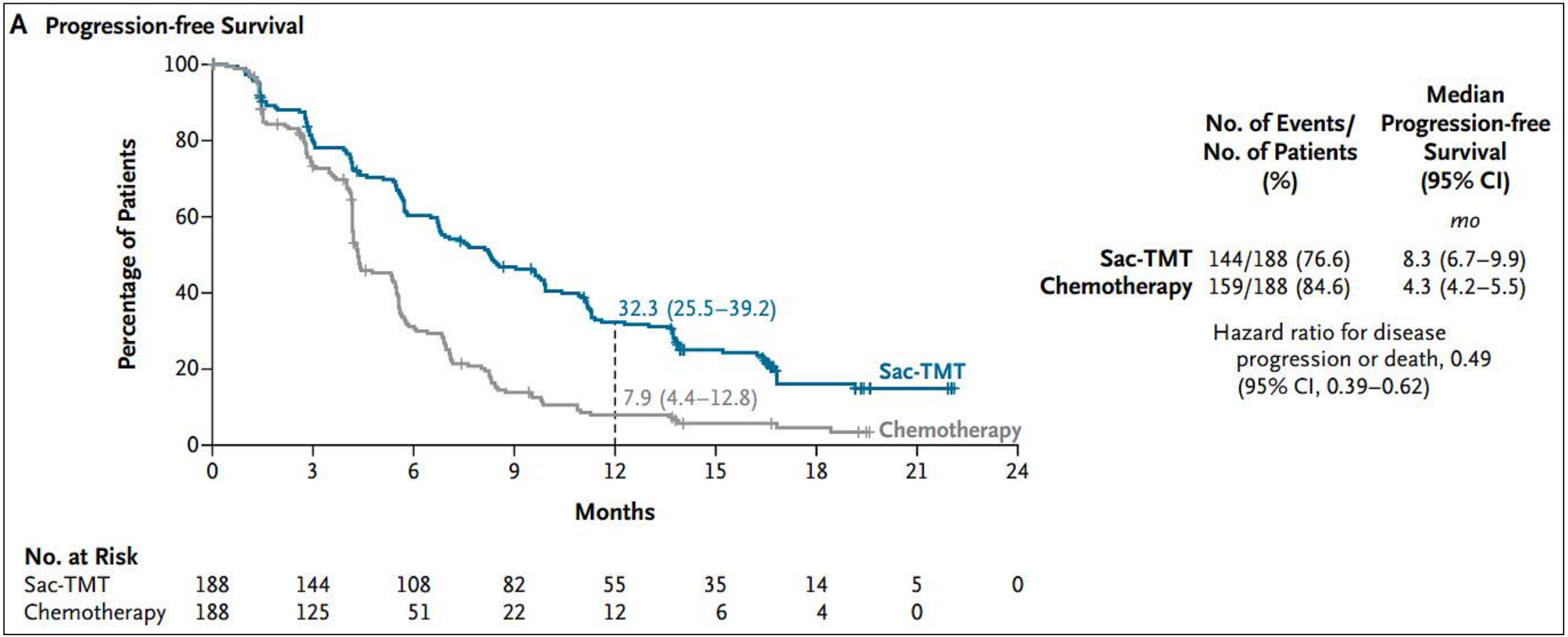
W. Fang,[1] L. Wu,[2] X. Meng,[3] Y. Yao,[4] W. Zuo,[5] W. Yao,[6] Y. Xie,[7] Yu Zhang,[8] J. Cui,[9] Yongchang Zhang,[10] X. Li,[11] W. Zhuang,[12] J. Fang,[13] Q. Wang,[14] W. Jiang,[15] K. Li,[16] Y. Bai,[17] Y. Luo,[18] F. Ma,[19] Y. Yu,[20] W. Zheng,[21] Z. Liu,[22] B. Yang,[23] R. Ma,[24] Y. Fang,[25] R. Yang,[26] L. Jiang,[27] J. Hu,[28] J. Yang,[29] Y. Diao,[29] X. Jin,[29] J. Ge,[30] Y. Yang,[1] and L. Zhang[1]

Sac-TMT vs Chemo Baseline Characteristics

Table 1. Baseline Characteristics of the Patients (intention-to-Treat Population).*

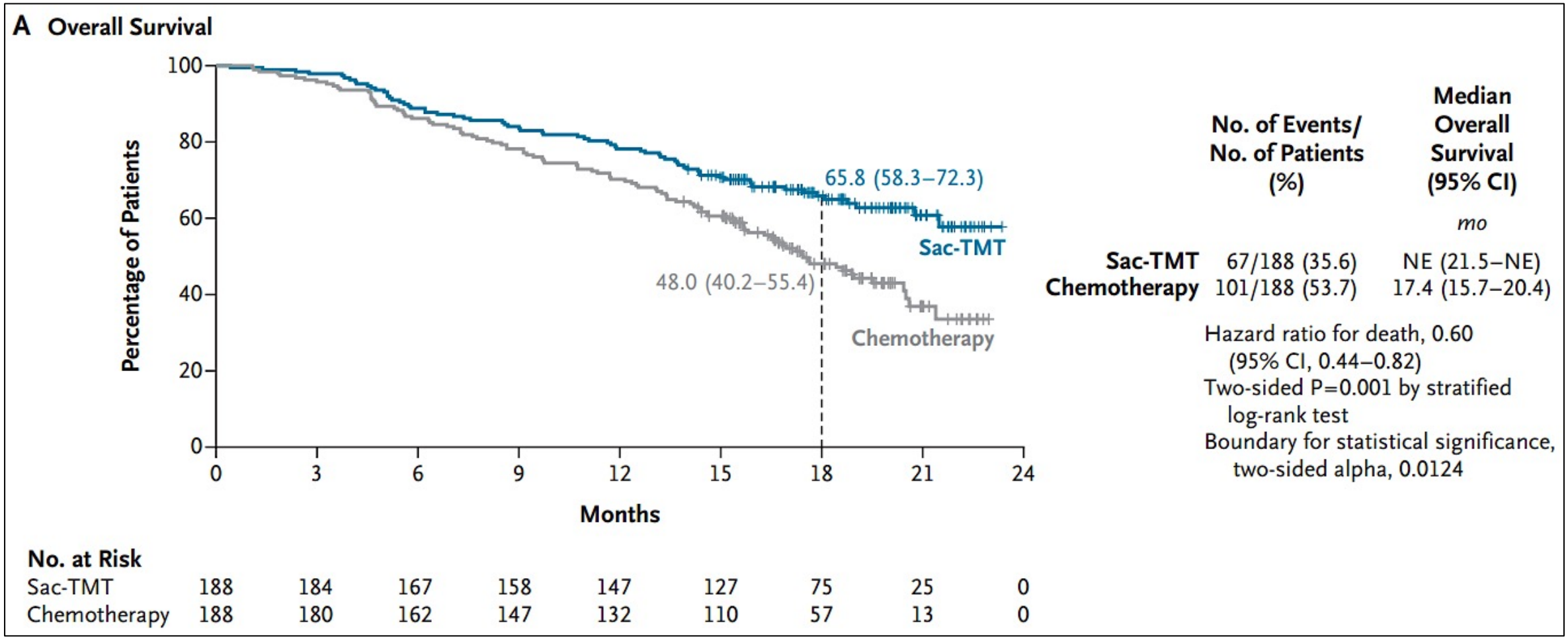
Characteristic	Sacituzumab Tirumotecan (N=188)	Chemotherapy (N=188)
Age		
Median (range) — yr	60 (31–75)	59 (33–75)
≥65 yr — no. (%)	58 (30.9)	51 (27.1)
Male sex — no. (%)	66 (35.1)	83 (44.1)
Asian race — no. (%)	188 (100.0)	188 (100.0)
Smoking history — no. (%)		
Current or former smoker	43 (22.9)	53 (28.2)
Never smoked	145 (77.1)	135 (71.8)
EGFR mutation subtype — no. (%)§		
Exon 21 L858R substitution	84 (44.7)	71 (37.8)
Exon 19 deletion	106 (56.4)	118 (62.8)
Other	8 (4.3)	7 (3.7)
T790M mutation status — no. (%)¶		
Negative	48 (25.5)	40 (21.3)
Positive	29 (15.4)	36 (19.1)
Unknown	111 (59.0)	112 (59.6)
Previous third-generation EGFR-TKI — no.(%)‖	178 (94.7)	178 (94.7)
First-line therapy	118 (62.8)	117 (62.2)
Second-line therapy	60 (31.9)	60 (31.9)

Fang et al. NEJM 2026



Fang et al. NEJM 2026

Fang et al. NEJM 2026



Fang et al. NEJM 2026

Table 3. Treatment-Related Adverse Events (Safety Population).*

Event	Sacituzumab Tirumotecan (N=188)		Chemotherapy (N=182)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	number of patients (percent)			
Any treatment-related adverse event	188 (100.0)	109 (58.0)	179 (98.4)	98 (53.8)
Leading to dose reduction	57 (30.3)	—	41 (22.5)	—
Leading to dose interruption	69 (36.7)	—	60 (33.0)	—
Leading to treatment discontinuation	0	—	1 (0.5)	—
Leading to death†	0	—	1 (0.5)	—
Any treatment-related serious adverse event	17 (9.0)	—	32 (17.6)	—
Treatment-related adverse event with an incidence of ≥10% in either group				
Anemia	159 (84.6)	21 (11.2)	139 (76.4)	26 (14.3)
White-cell decreased	157 (83.5)	52 (27.7)	127 (69.8)	40 (22.0)
Alopecia	157 (83.5)	0	17 (9.3)	0
Neutrophil count decreased	142 (75.5)	75 (39.9)	126 (69.2)	60 (33.0)
Stomatitis‡	121 (64.4)	9 (4.8)	9 (4.9)	0
Nausea	89 (47.3)	1 (0.5)	86 (47.3)	2 (1.1)
Anorexia	78 (41.5)	0	58 (31.9)	0
Fatigue	72 (38.3)	7 (3.7)	73 (40.1)	4 (2.2)
Weight loss	52 (27.7)	0	28 (15.4)	1 (0.5)
Thrombocytopenia	51 (27.1)	4 (2.1)	85 (46.7)	30 (16.5)
Vomiting	50 (26.6)	0	39 (21.4)	1 (0.5)

Fang et al. NEJM 2026

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Stomatitis‡	121 (64.4)	9 (4.8)	9 (4.9)	0
Nausea	89 (47.3)	1 (0.5)	86 (47.3)	2 (1.1)
Anorexia	78 (41.5)	0	58 (31.9)	0
Fatigue	72 (38.3)	7 (3.7)	73 (40.1)	4 (2.2)
Weight loss	52 (27.7)	0	28 (15.4)	1 (0.5)
Thrombocytopenia	51 (27.1)	4 (2.1)	85 (46.7)	30 (16.5)
Vomiting	50 (26.6)	0	39 (21.4)	1 (0.5)

Ocular surface events in 9.6%
No ILD or pneumonitis

Fang et al. NEJM 2026

Cases from the Community

Stephen “Fred” Divers, MD

Susmitha Apuri, MD

Neil Love, MD

RTP RESEARCH TO PRACTICE

Discussion Questions

In the modern era, how do you broadly think through therapeutic sequencing for patients with metastatic EGFR-mutated NSCLC? What do you generally recommend next for patients who experience disease progression on first-line osimertinib monotherapy? What about osimertinib/chemotherapy? What about amivantamab/lazertinib? How does the duration of response to up-front therapy affect your decision-making?

Where in the treatment sequence are you most likely to employ Dato-DXd for patients with EGFR-mutated NSCLC? Are you comfortable using it for patients with uncommon EGFR mutations?

In your experience, how does the global tolerability of Dato-DXd compare to that of traditional chemotherapy? Is it better tolerated or about the same?

Discussion Questions

Would you consider starting Dato-DXd at a lower dose for a patient who is particularly concerned about potential side effects? Is this feasible without compromising efficacy? Have you observed durable responses among your patients with EGFR-mutated NSCLC receiving reduced-dose Dato-DXd?

What prophylactic measures do you recommend for your patients who are about to start treatment with Dato-DXd to reduce the risk of side effects?

Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

Module 2: EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC — Dr Neal

Module 3: Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC — Dr Sands

Module 4: Emerging Role of Bispecific Antibody-Based Approaches for EGFR-Mutated NSCLC — Dr Goldman

Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

RTP RESEARCH TO PRACTICE

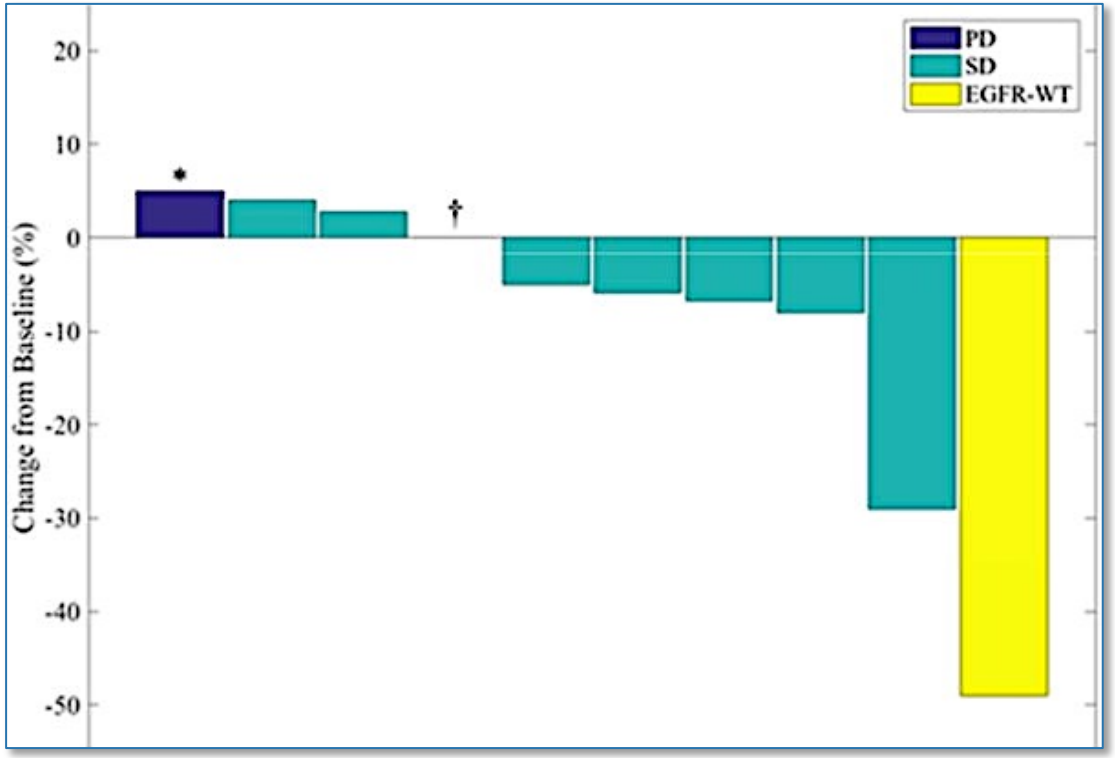
Immunotherapy & Bispecifics for EGFR-mutated NSCLC

Jonathan Goldman, MD
Professor, UCLA

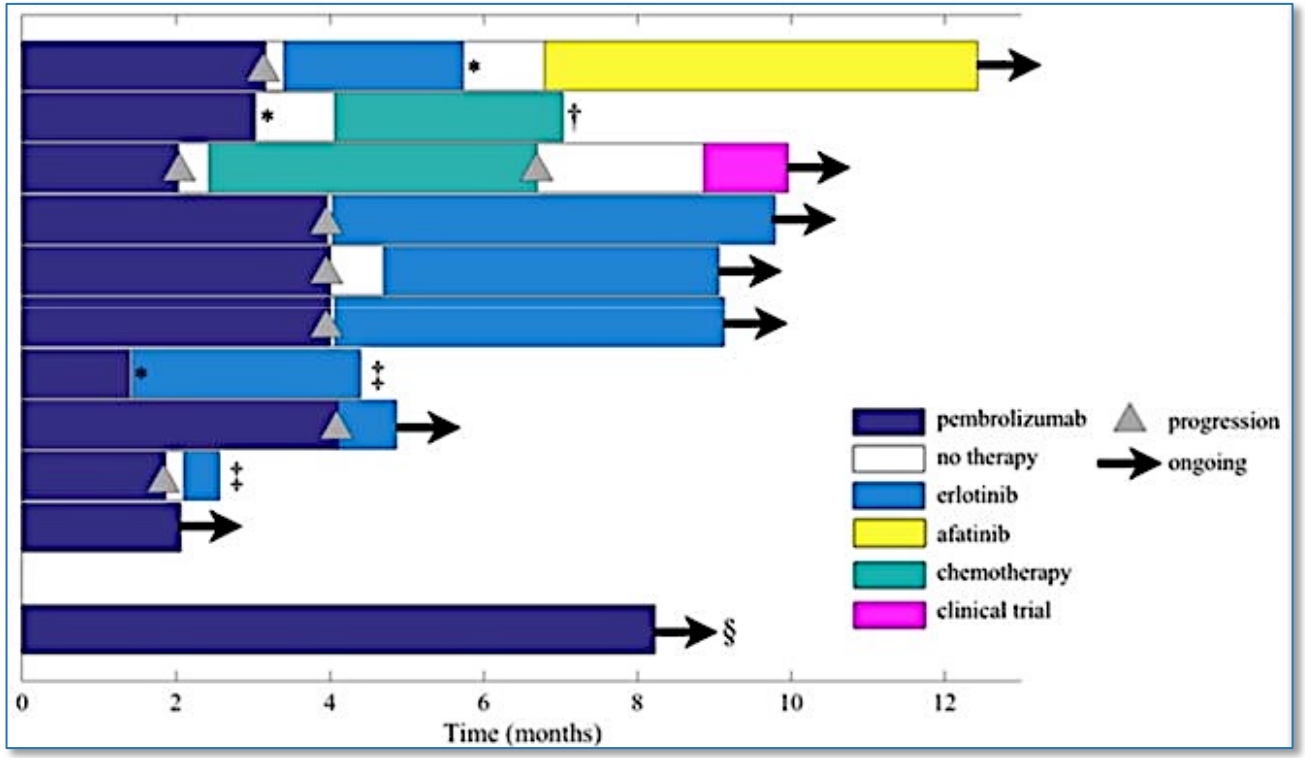
Overview

1. Challenges for Immune Checkpoint Inhibitors in EGFRm NSCLC
2. Mechanism of Ivonescimab
3. Phase III HARMONi results and implications
4. Mechanism of Izalontamab brengitecan (Iza-bren)
5. Current data with Iza-bren

First Line PD-1 Checkpoint Inhibition in EGFRm NSCLC



Waterfall Plot

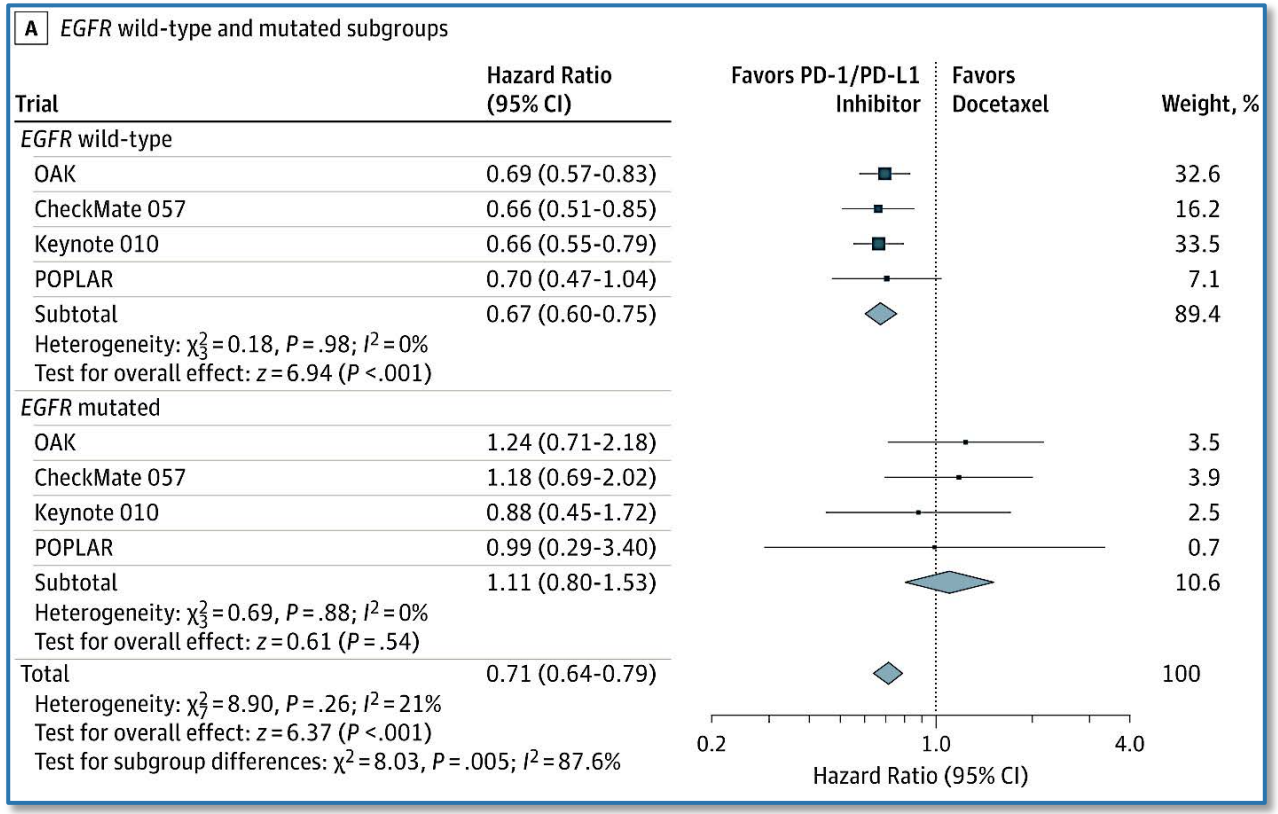


Swimmers Plot

Lisberg, et al. J Thorac Oncol, 2018.

Poor Immunotherapy Response in EGFRm

OVERALL SURVIVAL HAZARD RATIOS



KEY CHEMO-IO TRIALS POST-TKI

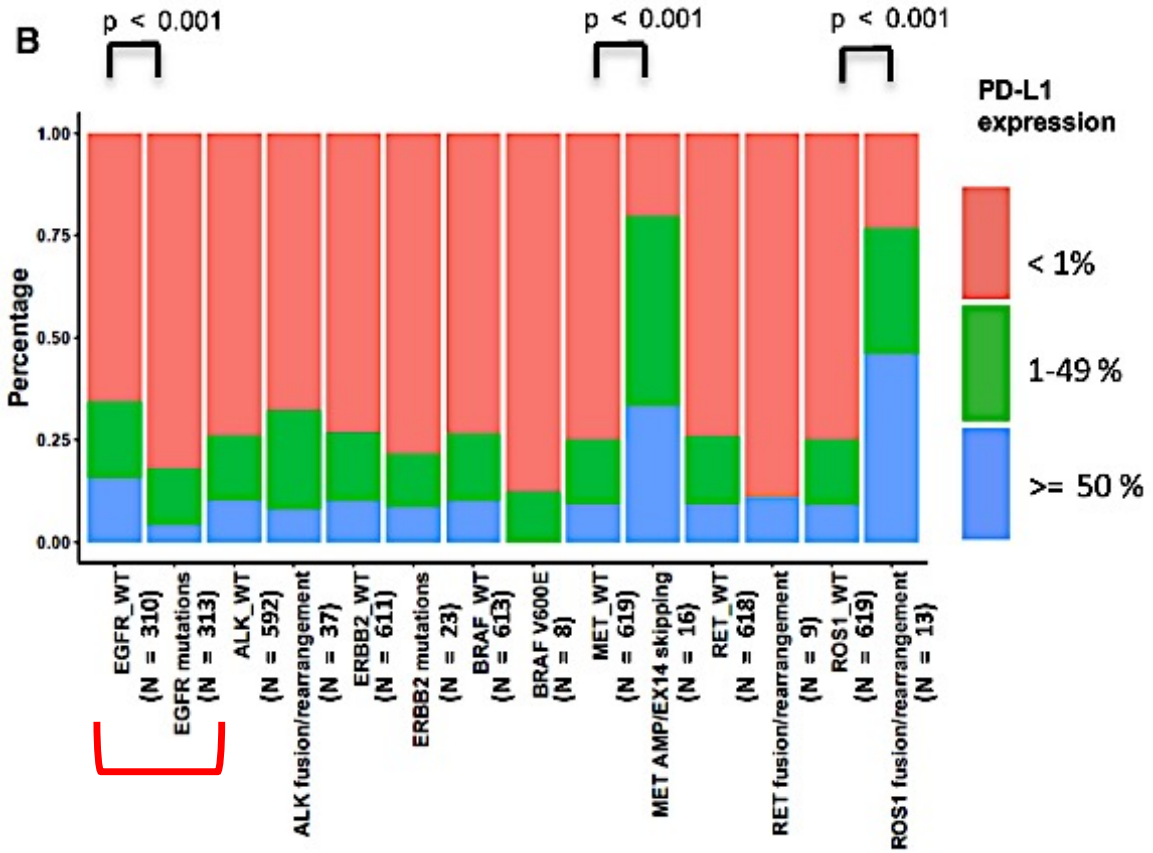
- Meta-Analysis JAMA Oncology 2018
- KEYNOTE-789: pembrolizumab + chemo
- CheckMate-722: nivolumab + chemo
- ORIENT-31: sintilimab + chemo

1. Lee, et al. JAMA Oncology, 2018.
2. Yang, et al. J Clin Oncol, 2024.
3. Mok, et al. J Clin Oncol, 2024.
4. Lu, et al. Lancet Oncol, 2022 and Lancet Respir Med, 2023.

Poor Immunotherapy Response in EGFRm

MECHANISMS

- Low tumor mutational burden
- Immunosuppressive TME
- Disrupted helper T cell signaling
- EGFR-mediated suppression of IFN-γ
- TGF-β upregulation



Shi, et al. Cancer Medicine, 2021.

Poor Immunotherapy Response in EGFRm

MECHANISMS

- Low tumor mutational burden
- Immunosuppressive TME
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- EGFR-mediated suppression of IFN-γ
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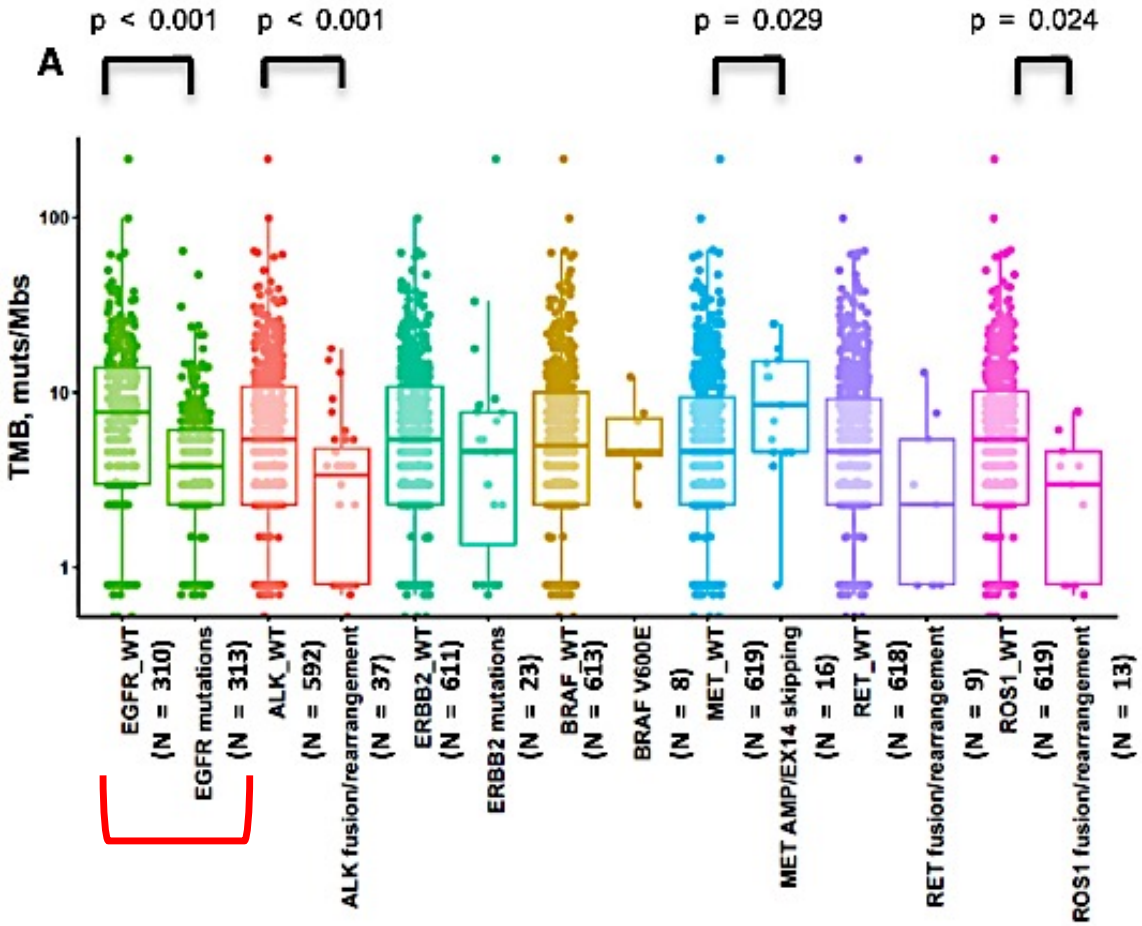
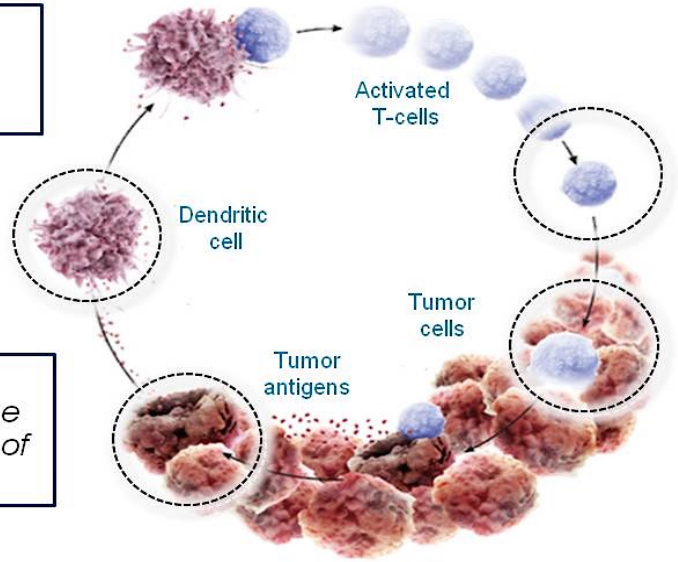


Shi, et al. Cancer Medicine, 2021.

Rationale for the Combination of Atezolizumab + Bevacizumab + Chemotherapy

- In addition to its known anti-angiogenic effects[1], bevacizumab's inhibition of VEGF has immune modulatory effects[2]

Inhibition of VEGF can promote T-cell priming and activation via dendritic cell maturation[2-4]



Normalization of the tumor vasculature through VEGF inhibition increases T-cell tumor infiltration[2,5-8]

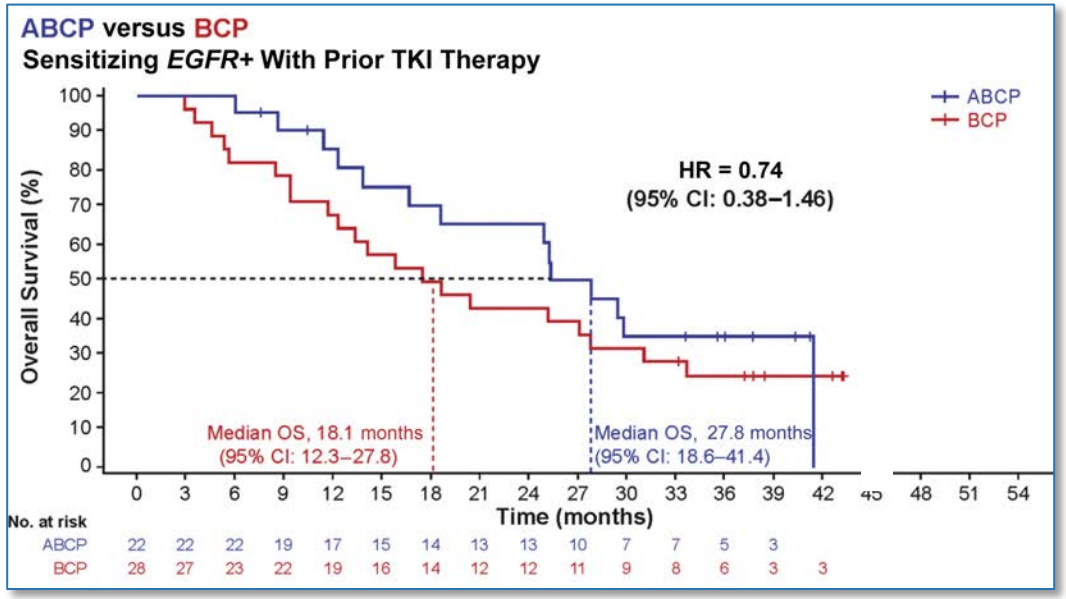
Tumor cell killing by chemotherapy may expose the immune system to high levels of cancer cell antigens[9]

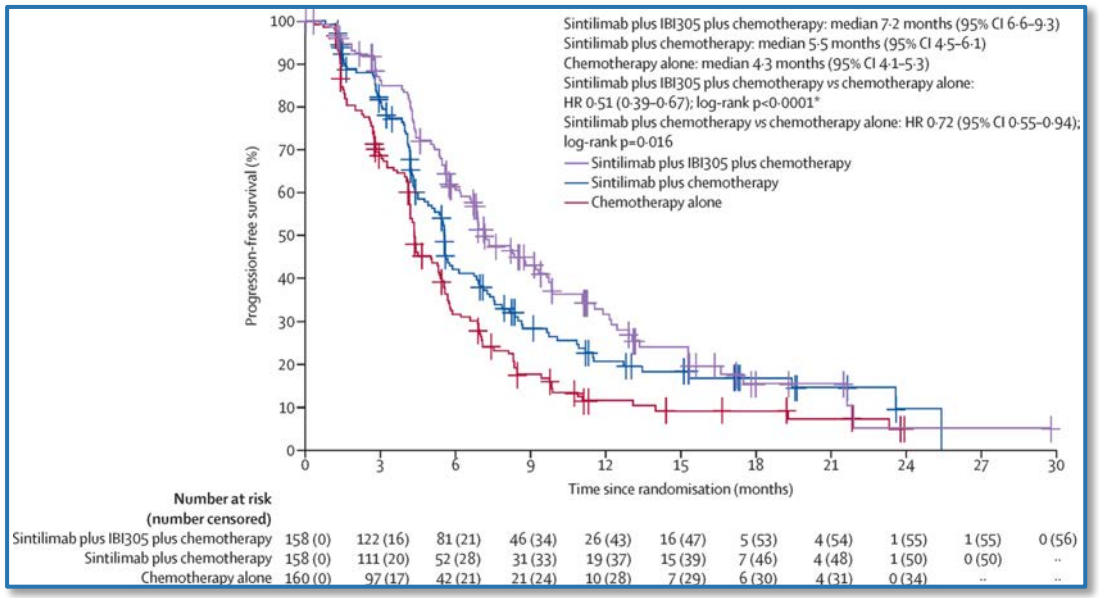
VEGF blockade can establish an immune-permissive tumor microenvironment by decreasing myeloid-derived suppressor cell and regulatory T cell populations[2,8,10-13]

- Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression

1. Ferrara N, et al. *Nat Rev Drug Discov*, 2004. 2. Hegde PS, et al. *Semin Cancer Biol*. 2017 . 3. Gabrilovich DI, et al. *Nat Med*, 1996. 4. Oyama T, et al. *J Immunol*, 1998. 5. Goel S, et al. *Physiol Rev*, 2011. 6. Motz GT, et al. *Nat Med*, 2014. 7. Hodi FS, et al. *Cancer Immunol Res*, 2014. 8. Wallin JJ, et al. *Nat Commun*, 2016. 9. Zitvogel L, et al. *Immunity*, 2013. 10. Gabrilovich DI, Nagaraj S. *Nat Rev Immunol*, 2009. 11. Roland CL, et al. *PLoS One*, 2009. 12. Facciabene A, et al. *Nature*, 2011. 13. Voron T, et al. *J Exp Med*, 2015. Figure adapted from Chen DS, Mellman I. *Immunity*, 2013.

Combination chemotherapy with VEGFi and IO





IMpower150: chemo+VEGF vs chemo+VEGF+IO

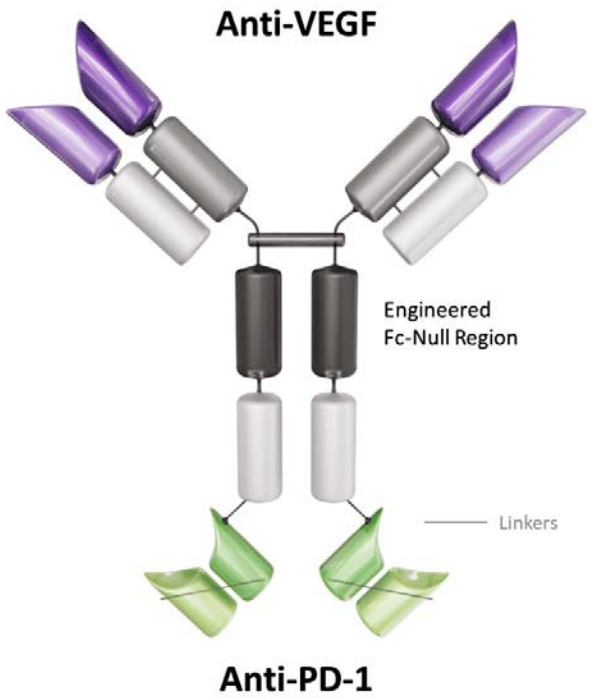
- Exploratory analysis in 123 patients with EGFRm.
  For all pt, OS HR 0.60.
  For those treated with previous TKI, HR 0.74.

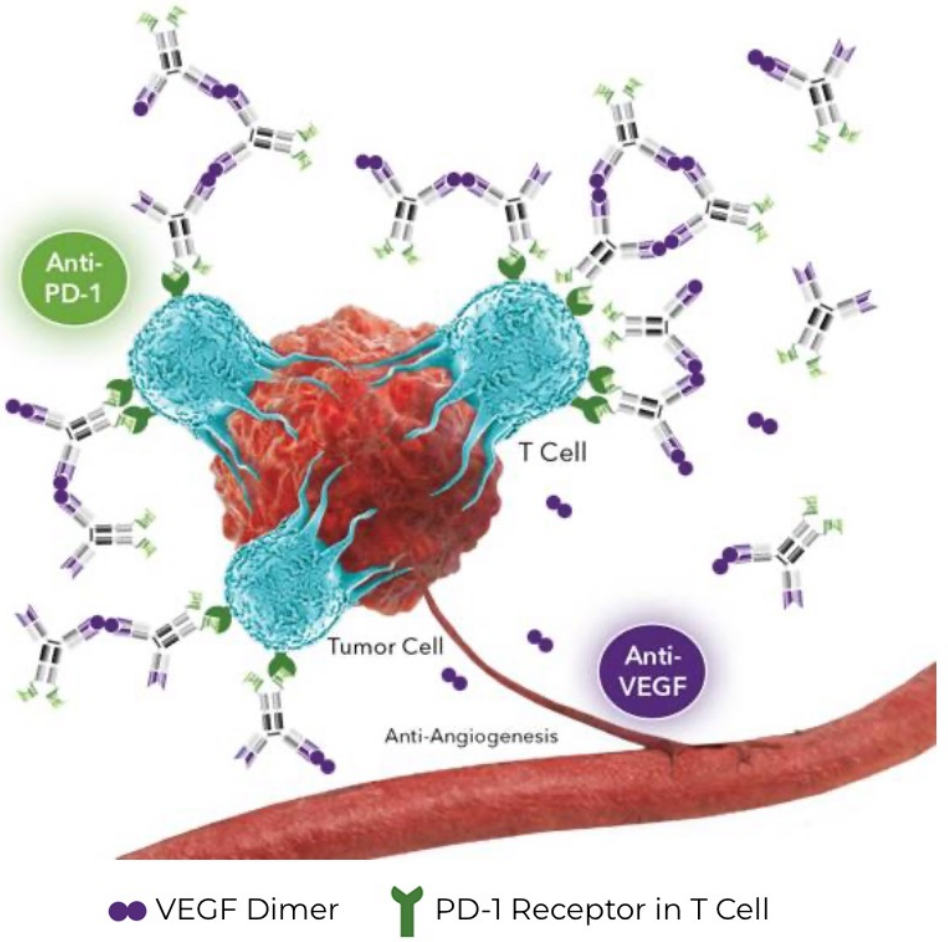
ORIENT-31: chemo vs chemo+IO vs chemo+VEGF+IO

- PFS 4.3 vs 5.5 vs 7.2 months.
- OS curves are overlapping

1. Socinski, et al. New Eng J Med, 2018.
2. Reck, et al. Lancet Respir Med, 2019, and Nogami, et al. J Thor Oncol, 2022.
3. Lu, et al. Lancet Respir Med, 2023.

Ivonescimab: A PD-1/VEGF Bispecific Antibody





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/m^2 Q3W

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

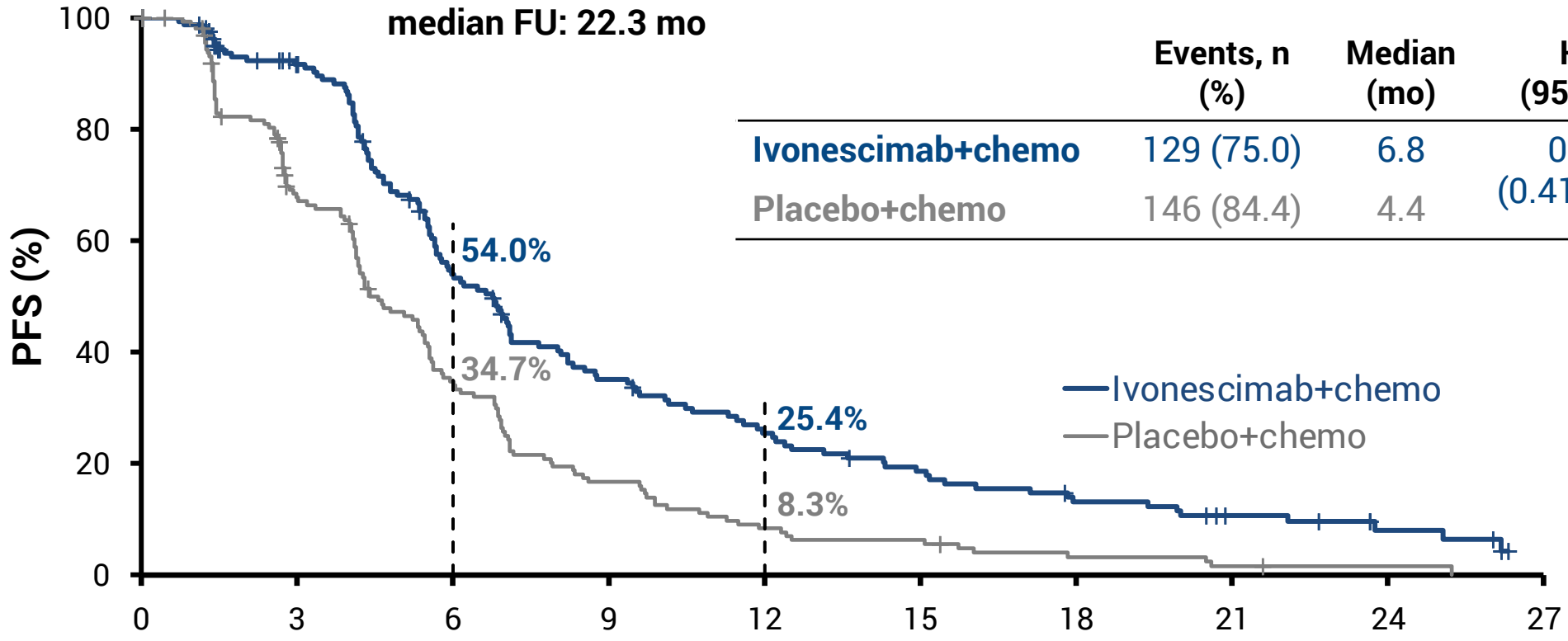
Note: Positive outcomes were reported from the single-region (Asia) study HARMONi-A, with PFS as the primary endpoint.

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

Consistent PFS benefit by investigator: HR = 0.58 (95% CI: 0.45-0.73)

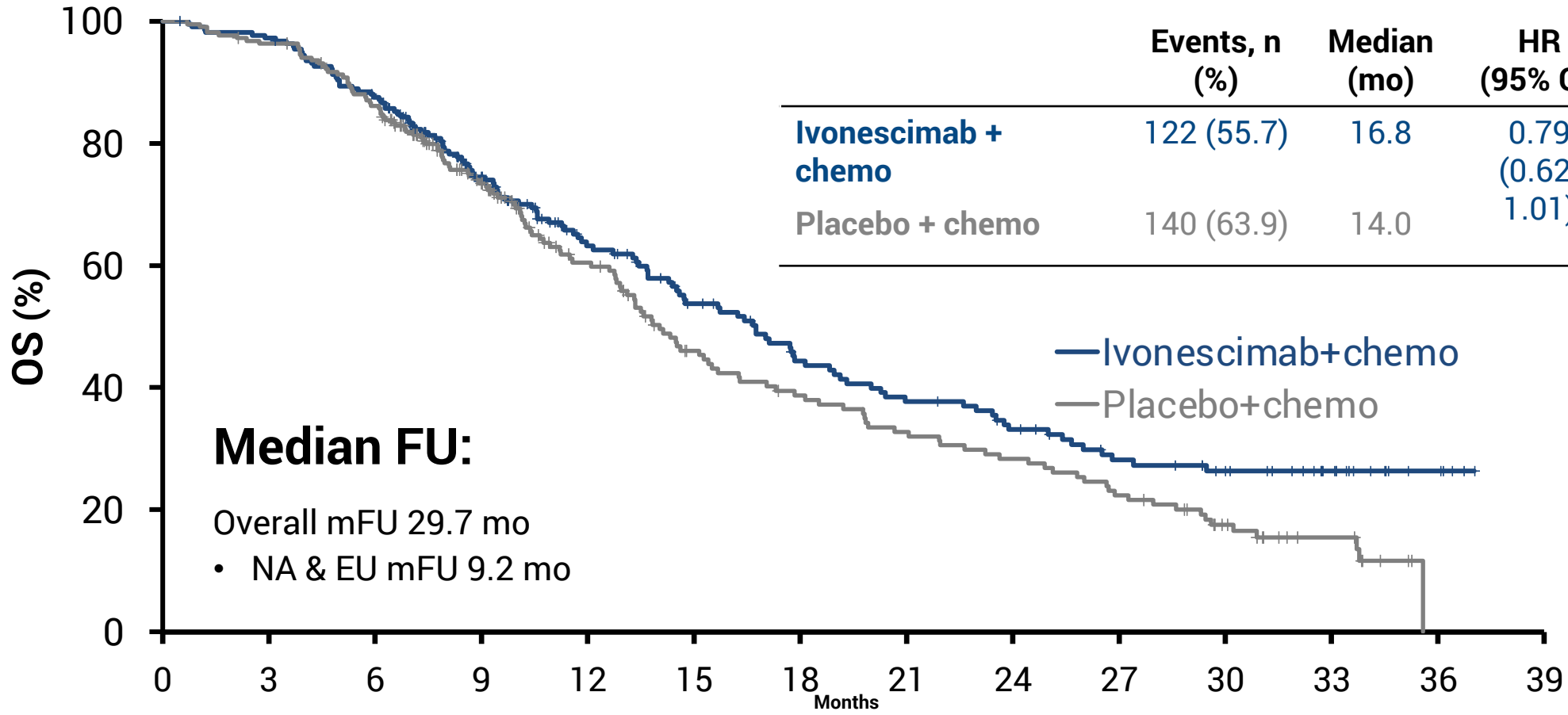
CI=confidence interval; FU=follow-up; HR=hazard ratio; IRRC= independent radiology review committee; PFS=progression-free

Primary Endpoint: Overall Survival

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

HARMONi

	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	

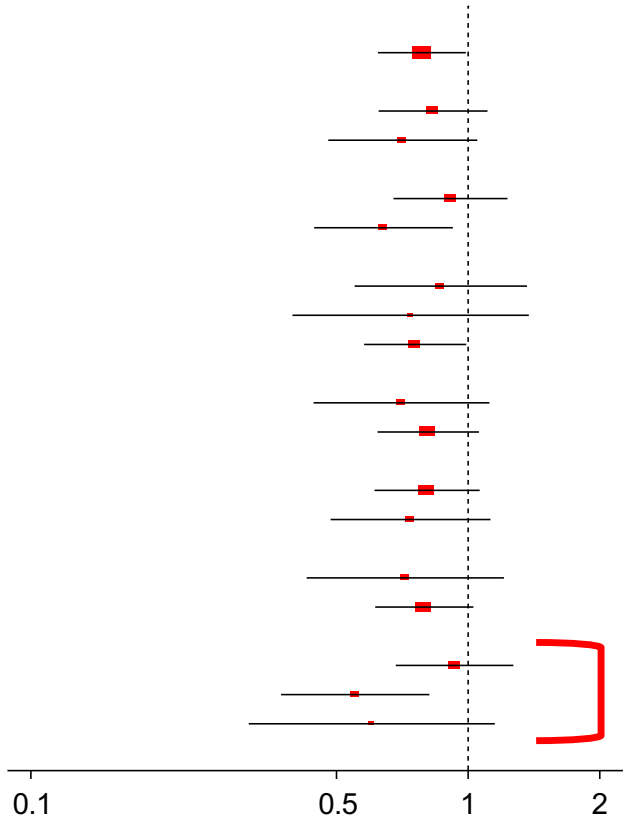
CI=confidence interval; EU=Europe; FU=follow-up; HR=hazard ratio; NA=North America; OS=overall survival.

Overall Survival Subgroup Analysis – Longer Term FU

Consistent across pre-defined subgroups

HARMONi

	Ivonescimab + chemo (Events/N)	Placebo + chemo (Events/N)	Hazard Ratio (95% CI)
Overall population	134/219	156/219	0.78 (0.62-0.99)
Age			
<65 years	90/136	98/131	0.83 (0.62-1.11)
>=65 years	44/83	58/88	0.71 (0.48-1.05)
Sex			
Female	84/130	87/127	0.91 (0.67-1.23)
Male	50/89	69/92	0.64 (0.44-0.92)
Geographic region			
NA & EU	36/83	39/82	0.87 (0.55-1.36)
NA	17/43	24/50	0.74 (0.40-1.38)
Asia	98/136	117/137	0.76 (0.58-0.99)
Brain metastases prior to study entry			
Present	33/54	40/54	0.70 (0.44-1.12)
Absent	101/165	116/165	0.81 (0.62-1.06)
Smoking history			
Never	92/143	111/155	0.81 (0.61-1.06)
Former/Current	42/76	45/64	0.74 (0.48-1.13)
Baseline ECOG performance status			
0	24/57	35/62	0.72 (0.43-1.21)
1	110/162	121/157	0.79 (0.61-1.03)
Baseline EGFR mutation			
19Del	84/131	77/118	0.93 (0.68-1.27)
L858R	39/74	73/90	0.55 (0.37-0.82)
T790M	19/29	18/25	0.60 (0.31-1.15)



ECOG=eastern cooperative oncology group; EGFR= Epidermal growth factor receptor; NA = North America, EU = Europe, PS=performance status; TKI=tyrosine kinase inhibitor.

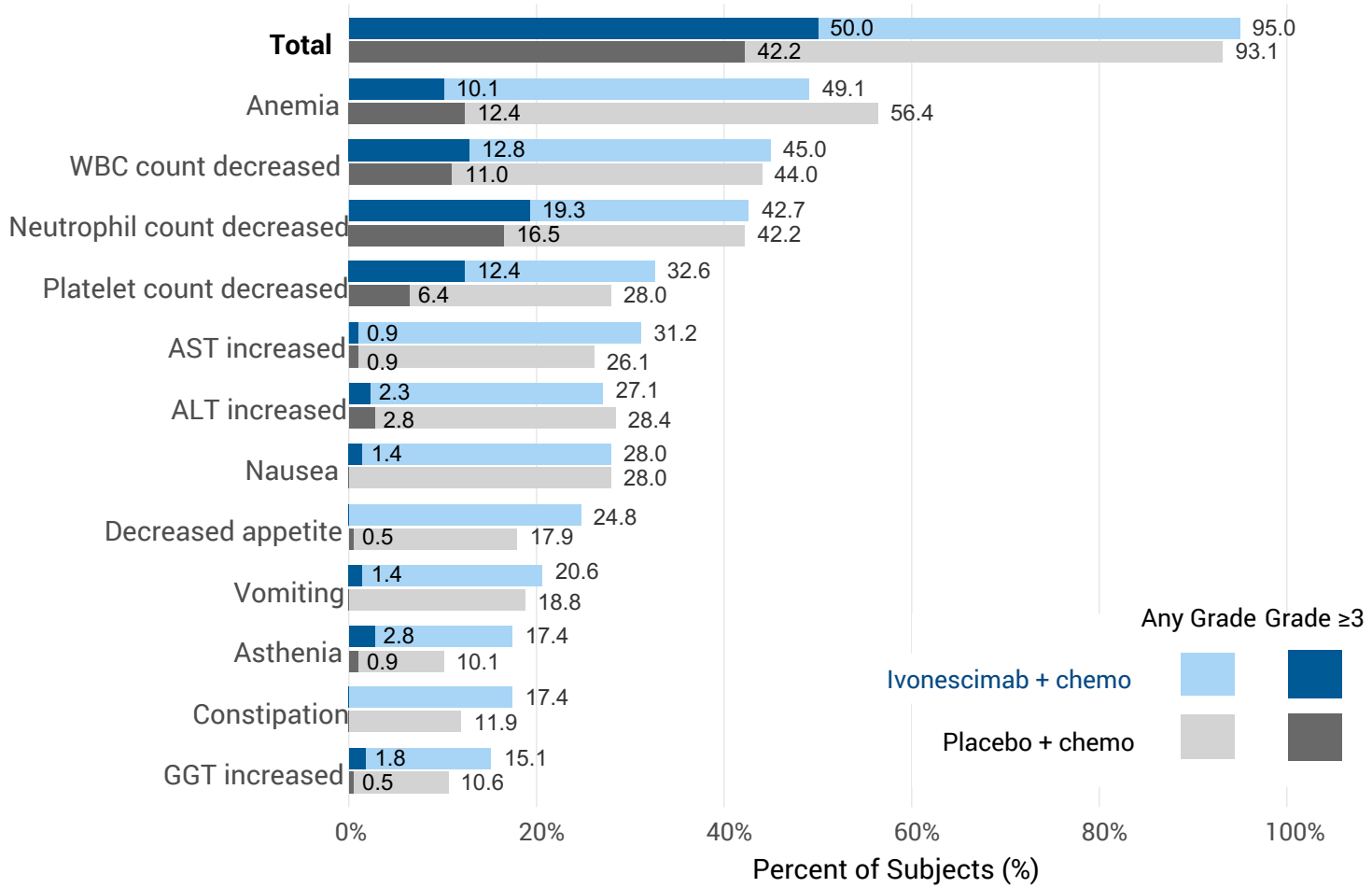
Treatment-Related Adverse Events (TRAEs)

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



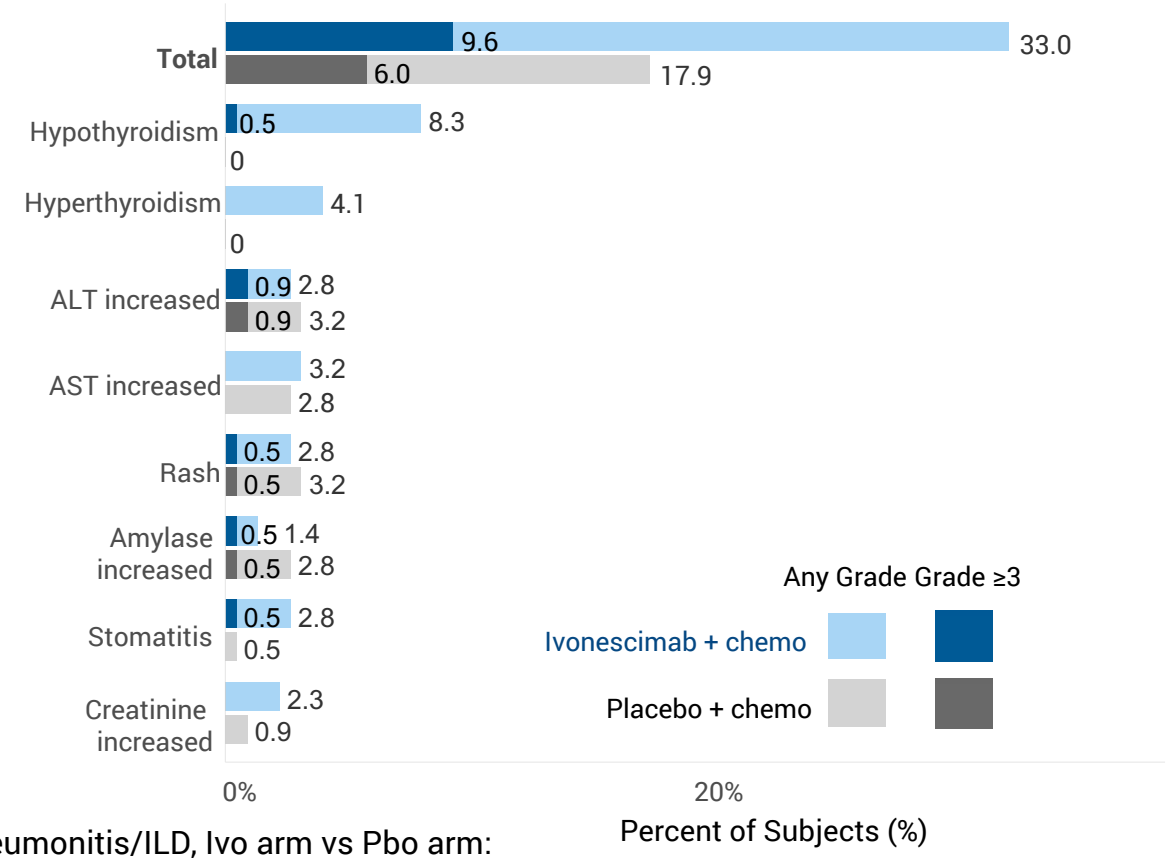
d/c=discontinuation; irAE=immune-related adverse events; VEGF= vascular endothelial growth factor.

Immune-related and VEGF-related TRAEs

HARMONi

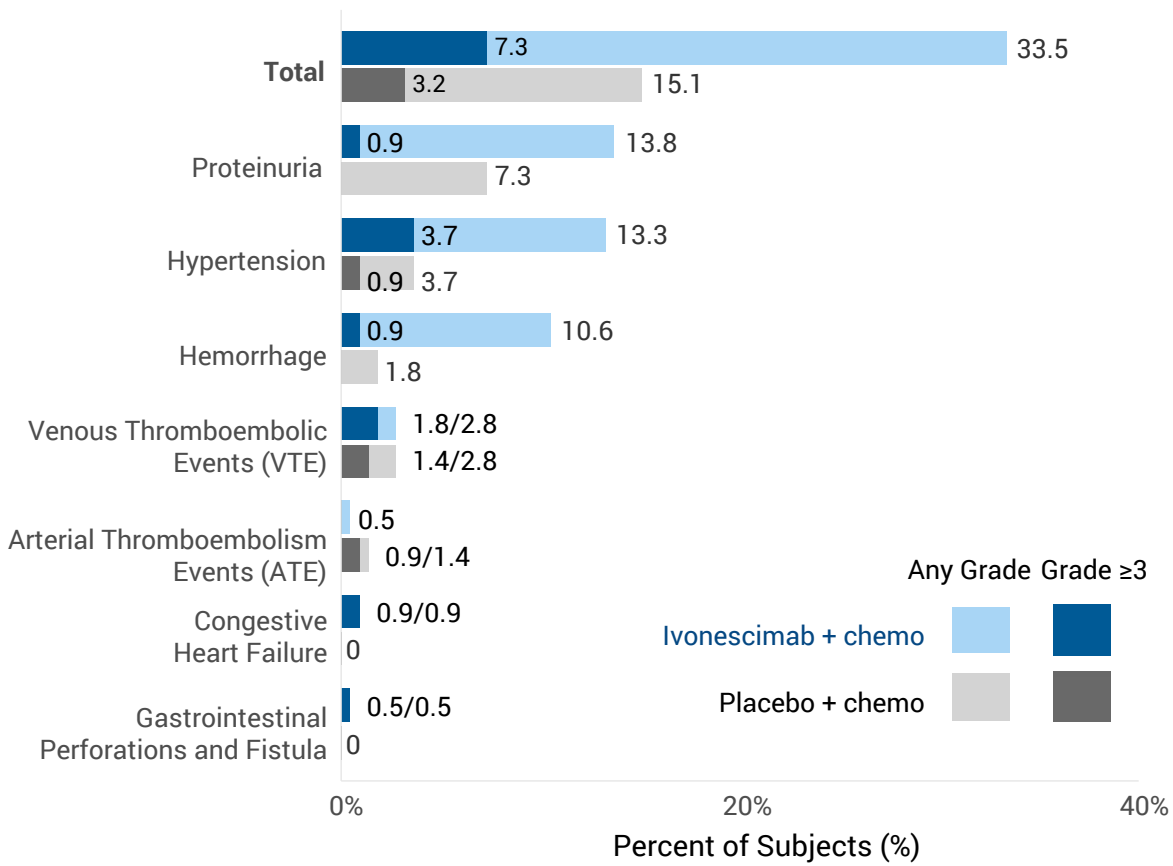
Most common irAEs: hypo/hyperthyroidism, transaminase elevation, rash; mostly low grade
Most common VEGF-related TRAEs: proteinuria, hypertension, hemorrhage; mostly low grade

irAE



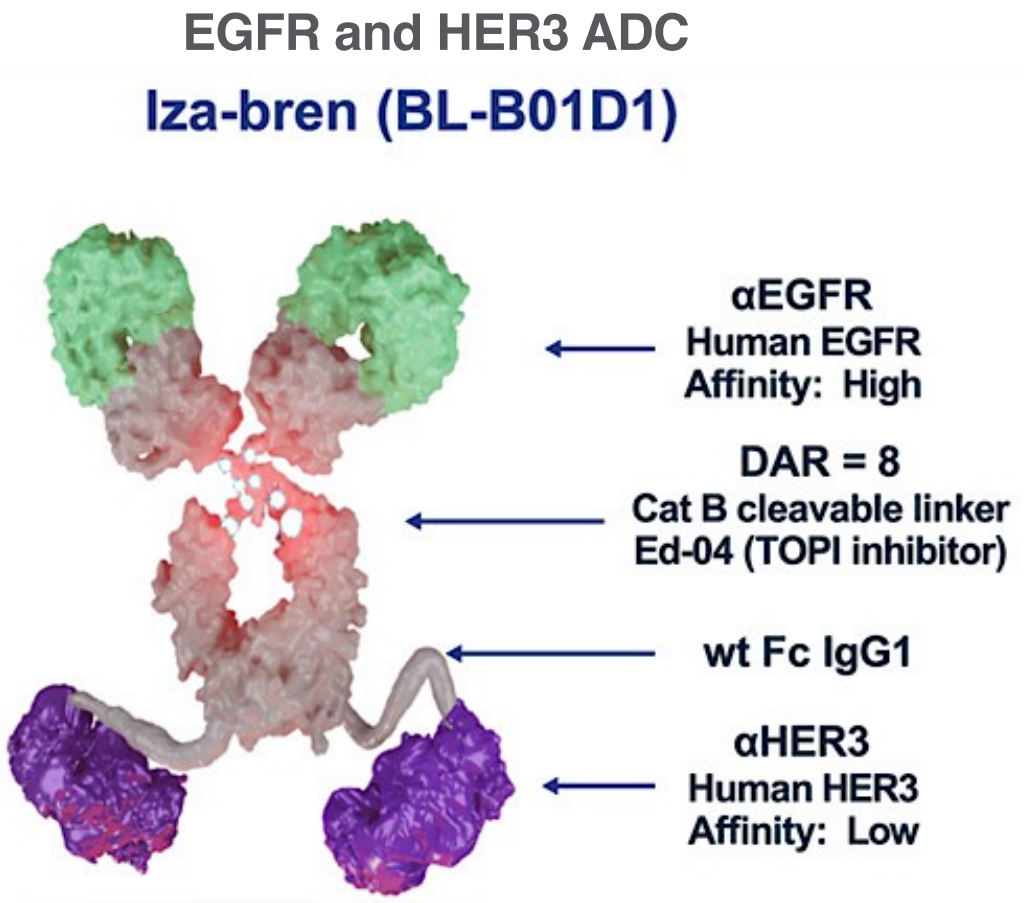
Pneumonitis/ILD, Ivo arm vs Pbo arm:
2.8% (1.4% Grade ≥3) vs **1.8%** (1.4% Grade ≥3)

VEGF-related



d/c=discontinuation; ILD=interstitial lung disease; irAE=immune-related adverse events; ivo=ivonescimab; pbo=pembrolizumab; TRAE=treatment-related adverse events; VEGF= vascular endothelial growth factor.

Izalontamab brengitecan (Iza-bren)



NEW GENERATION OF ADC

Novel ADCs targeting two antigens

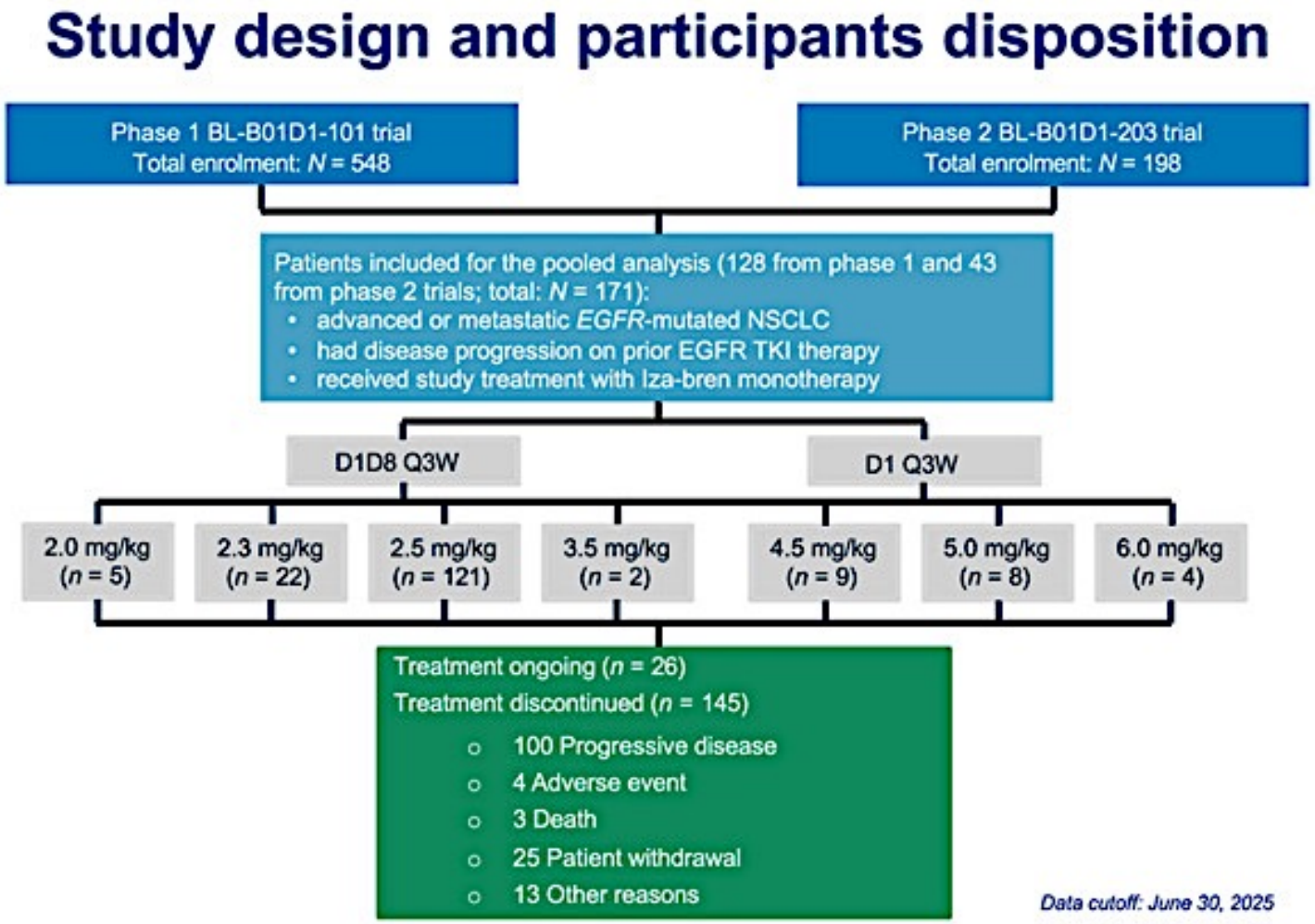
- Improved anticancer activity due to cross-linking and improved internalization
- Decreased toxicity by decreasing off-tumor binding

Tumor types of interest include

- Nasopharyngeal carcinoma (ORR 54.6% vs 27.9% inv choice)
- Castration-resistant prostate cancer
- Triple negative breast cancer
- NSCLC with EGFR and other mutations

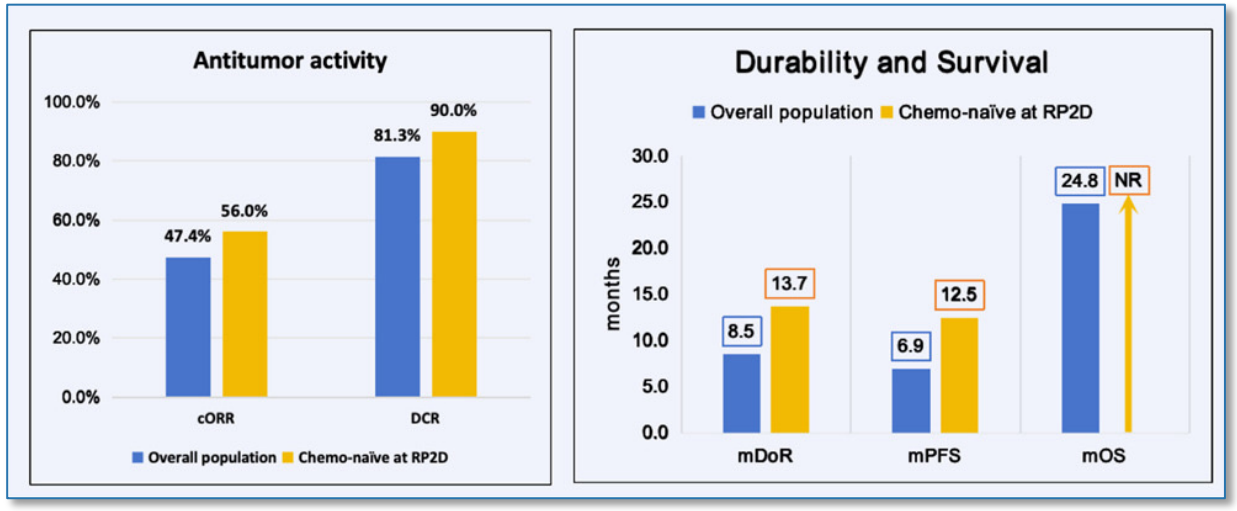
S.-D. Hong, et al. Annals of Oncology, 2026.

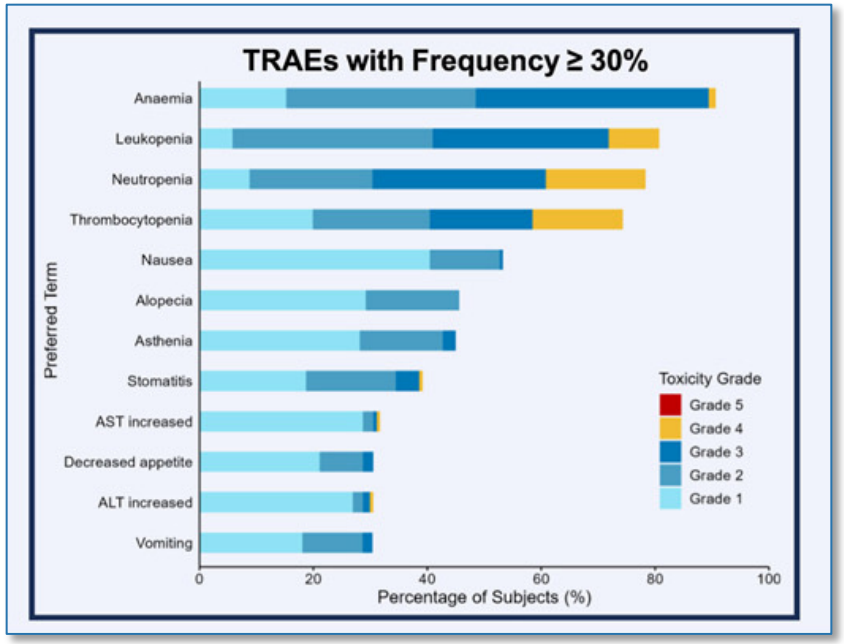
Pooled analysis of Phase I and II trials

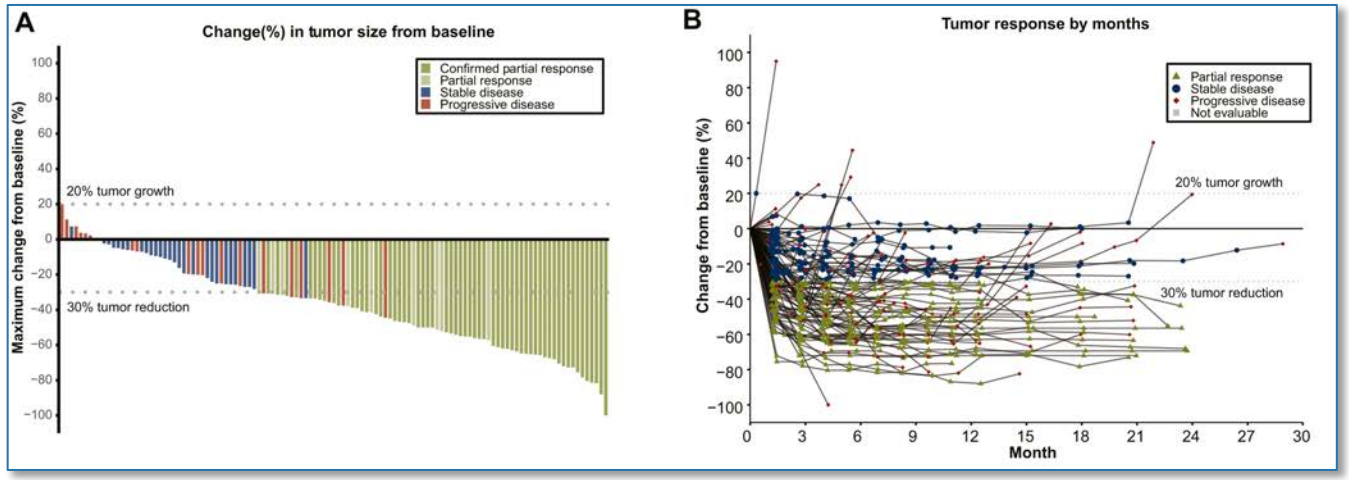


S.-D. Hong, et al. Annals of Oncology, 2026.

Activity and Tolerability of Iza-bren







Goldman
RTP ASCO 2026

S.-D. Hong, et al. Annals of Oncology, 2026.

Conclusions

1. EGFRm NSCLC has an immunosuppressive phenotype
2. Combination chemotherapy and VEGF and CPI may overcome this
   - Bispecific Antibody Ivonescimab with chemotherapy
3. Bispecific ADCs may improve efficacy and tolerability
   - Izalontamab brengitecan (Iza-bren)

Cases from the Community

Stephen “Fred” Divers, MD

Neil Love, MD

RTP
RESEARCH
TO PRACTICE

Discussion Questions

With the use of contemporary therapies, what do you expect in terms of overall survival and duration of disease control for patients with EGFR-mutated metastatic NSCLC? If a patient with newly diagnosed disease were to ask you how long they would be alive with a reasonably good quality of life, how would you respond?

Would you offer this patient adjuvant chemotherapy for her colon cancer?

What other novel agents or strategies currently under investigation for EGFR-mutated metastatic NSCLC are you particularly excited about?

Agenda

Module 1: Evolving First-Line Treatment for Metastatic EGFR-Mutated Non-Small Cell Lung Cancer (NSCLC) — Prof Passaro

Module 2: EGFR-Targeted Therapeutic Strategies for Relapsed EGFR-Mutant NSCLC — Dr Neal

Module 3: Utility of TROP2-Targeted Antibody-Drug Conjugates in the Management of EGFR-Mutant NSCLC — Dr Sands

Module 4: Emerging Role of Bispecific Antibody-Based Approaches for EGFR-Mutated NSCLC — Dr Goldman

Module 5: Tolerability Considerations with the Use of Available and Emerging Therapies for EGFR-Mutated NSCLC — Dr Goldberg

RTP RESEARCH TO PRACTICE

Tolerability considerations with the use of available and emerging therapies for EGFR mutation-positive NSCLC

Research To Practice Symposium
May 29, 2026

Sarah Goldberg, MD, MPH

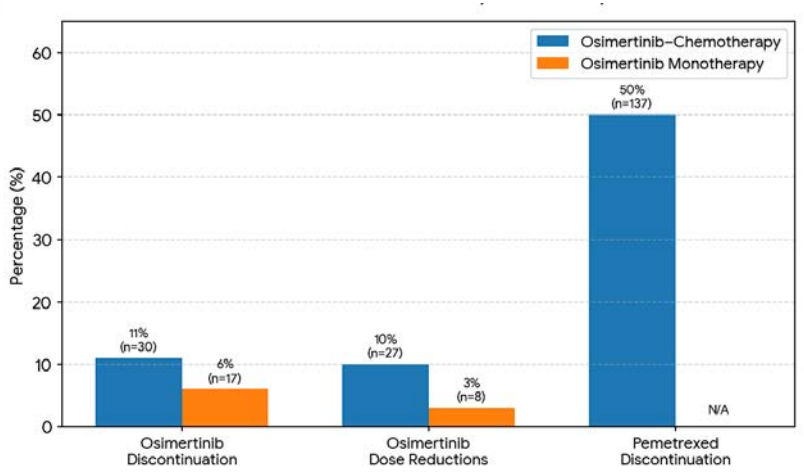
Professor of Medicine (Medical Oncology)
Division Chief, Thoracic Oncology
Co-Director, Center for Thoracic Cancers
Yale School of Medicine and Yale Cancer Center

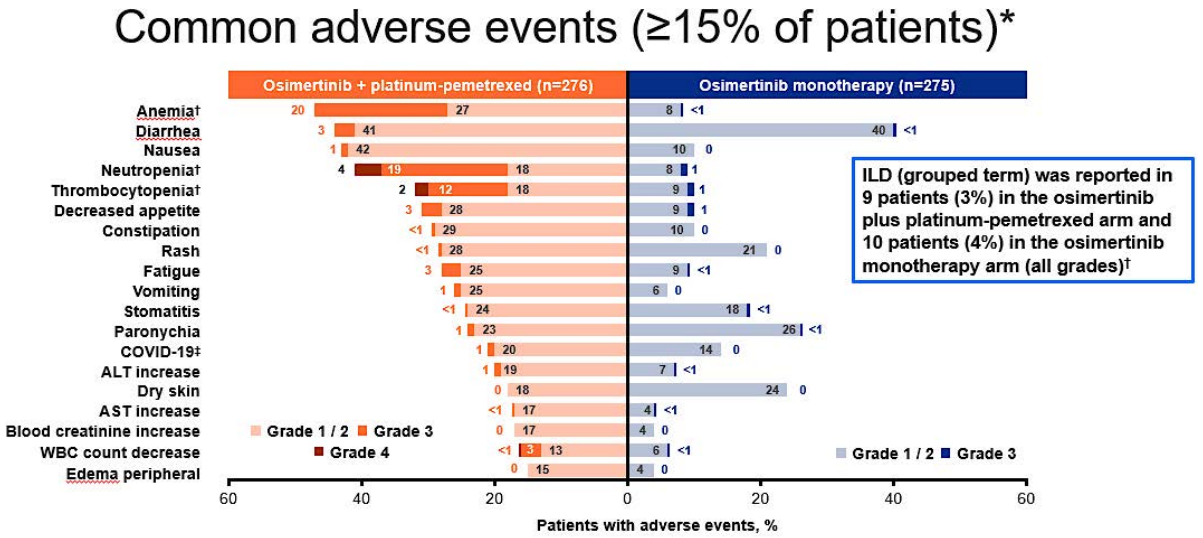
Outline

- Compare tolerability profiles of osimertinib/chemotherapy and amivantamab/lazertinib
- Reducing toxicity from amivantamab
- Monitoring for, mitigating and managing AEs from dato-DXd
- Toxicities associated with ivonescimab

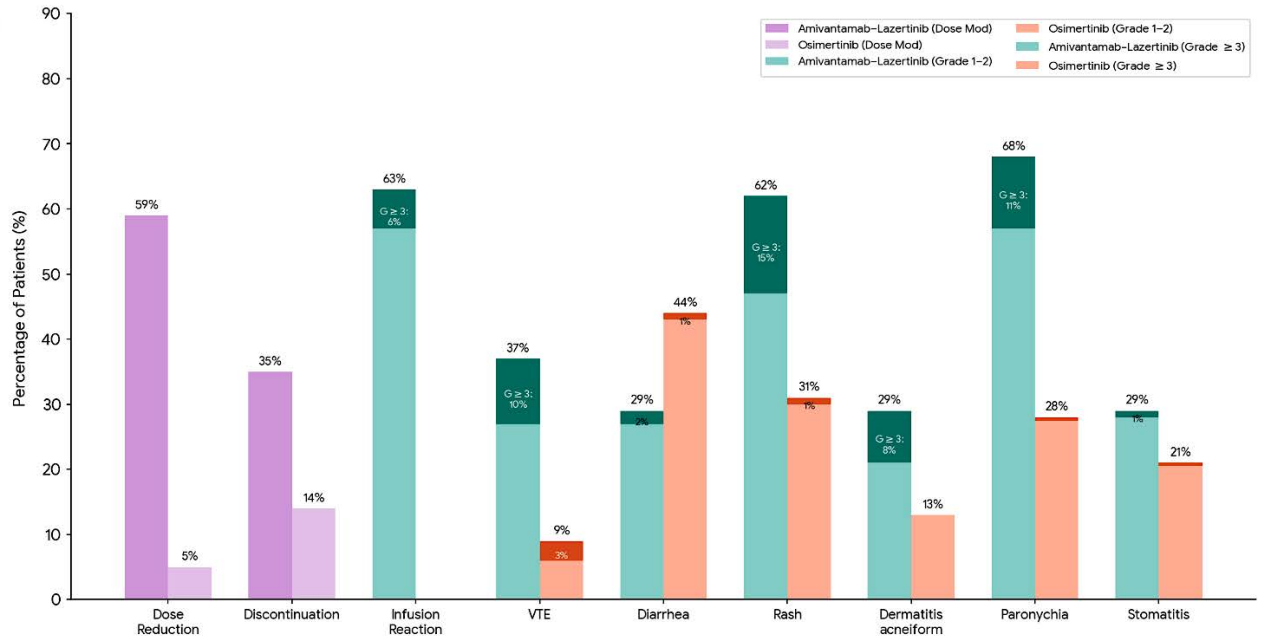
Toxicity of first-line options for EGFR-mutant NSCLC

FLAURA2





MARIPOSA

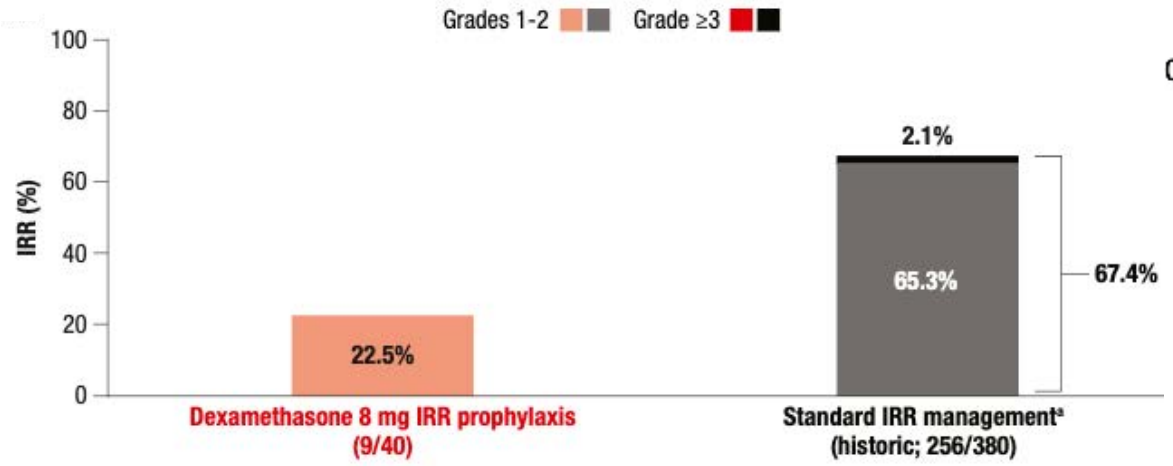


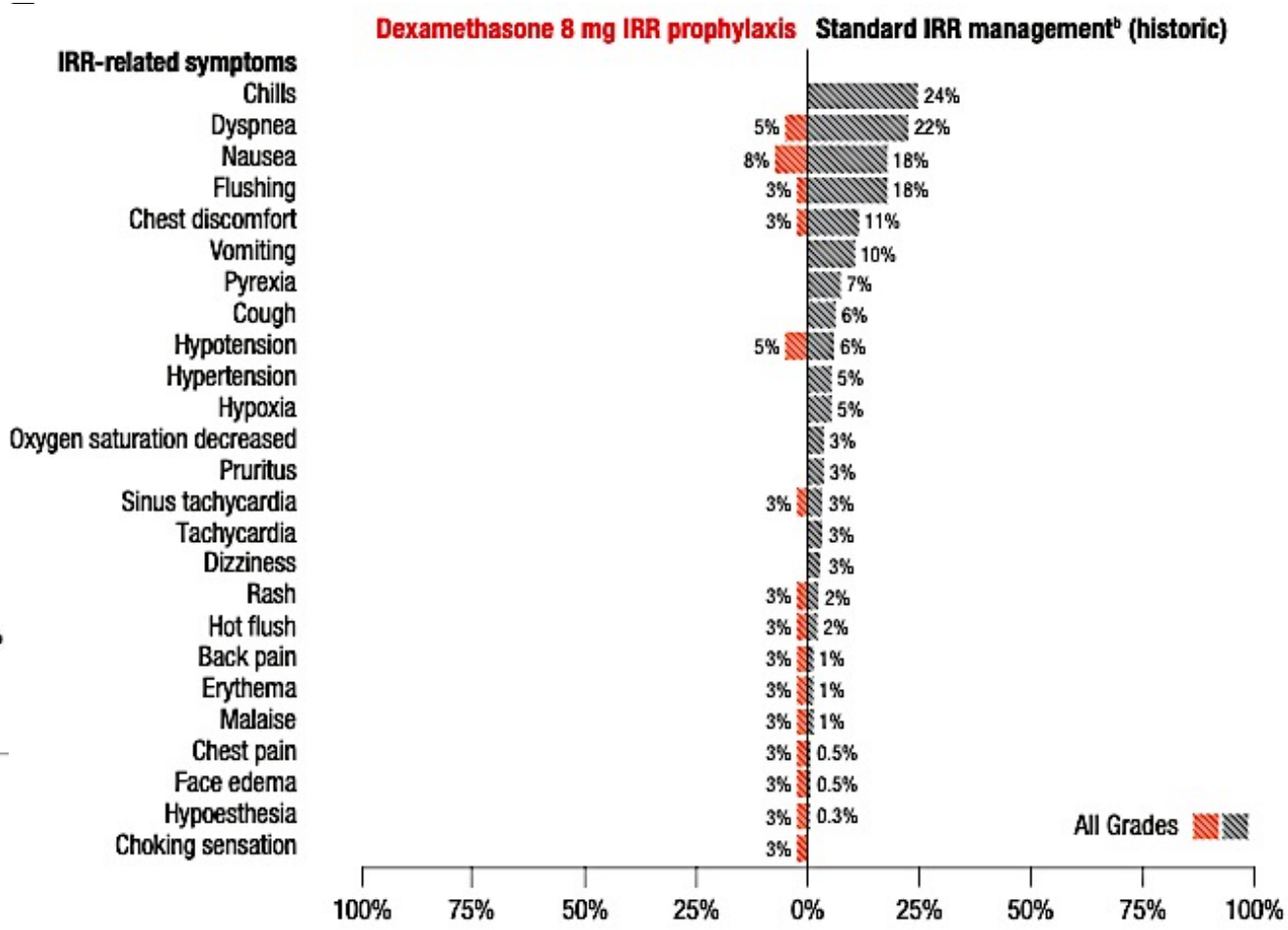
Janne PA, et al. NEJM 2026
Cho BC, et al. NEJM 2024

SKIPPirr: Preventing infusion-related reactions with intravenous amivantamab

4 independent prophylactic approaches were evaluated using Simon's two-stage design with an expansion stage if a cohort passed both stages.

Oral dexamethasone 8 mg cohort passed both stages (8 mg twice daily given on C1D-2, C1D-1, and the morning of C1D1 [5 doses])





Spira AI et al. JTO 2025.

PALOMA-3: Subcutaneous vs intravenous amivantamab plus lazertinib

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Disease had progressed on or after osimertinib and platinum-based chemotherapy, irrespective of order
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0–1

Stratification factors

- Brain metastases (yes or no)
- *EGFR* mutation type (Ex19del vs L858R)
- Race (Asian vs non-Asian)
- Type of last therapy (osimertinib vs chemotherapy)

1:1 randomization (N=418)

- **SC Amivantamab + Lazertinib (n=206)**
- **IV Amivantamab + Lazertinib (n=212)**

Dosing (in 28-day cycles)

SC Amivantamab[a,b] (co-formulated with rHuPH20 and administered by manual injection): 1600 mg (2240 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks thereafter

IV Amivantamab[b]: 1050 mg weekly (1400 mg if ≥80 kg) for the first 4 weeks, then every 2 weeks thereafter

Lazertinib: 240 mg PO daily

Prophylactic anticoagulation recommended for the first 4 months of treatment

Co-primary endpoints[c]:

- C_{trough} (noninferiority)[d]
- C2 AUC (noninferiority)[e]

Secondary endpoints:

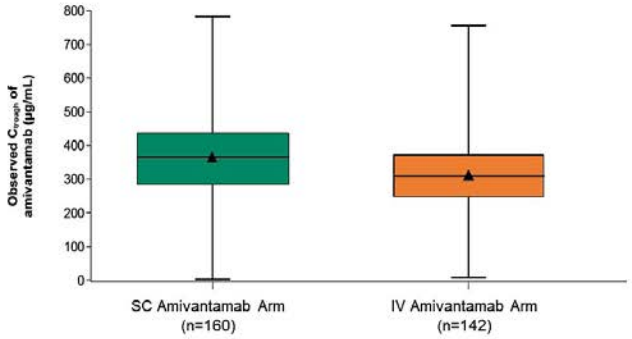
- ORR (noninferiority)
- PFS (superiority)
- DoR
- Patient satisfaction[f]
- Safety

Exploratory endpoints:

- OS

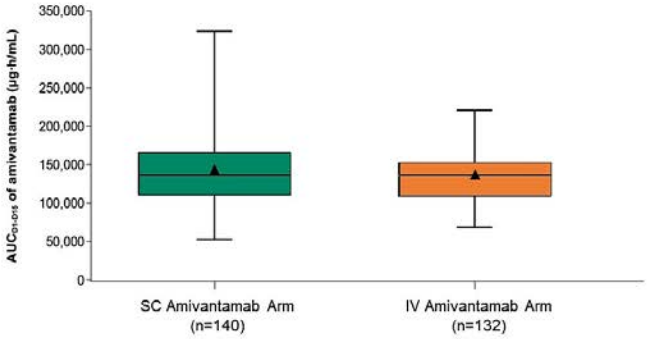
C_{trough} at C2D1

Geometric mean ratio=**1.15**
(90% CI, 1.04–1.26)

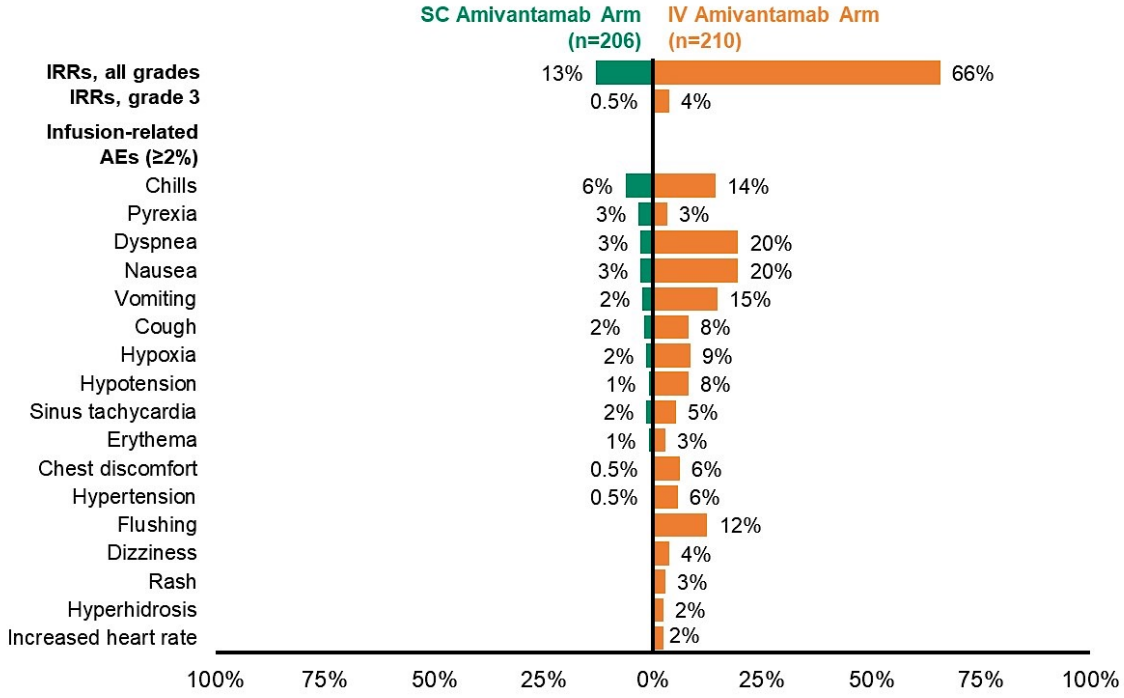


C2 AUC_{D1-D15}

Geometric mean ratio=**1.03**
(90% CI, 0.98–1.09)

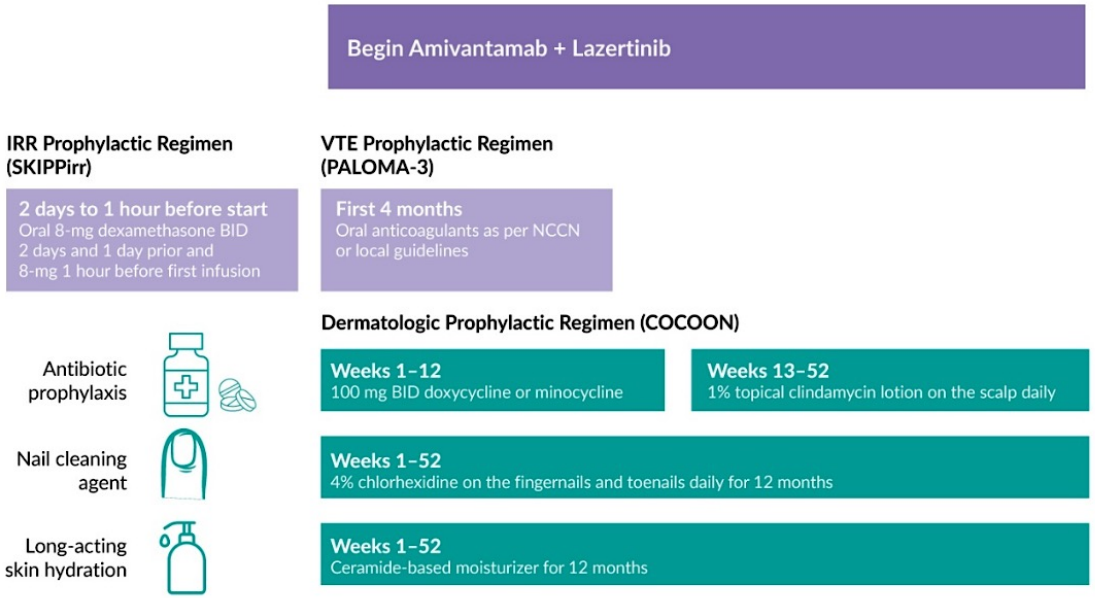


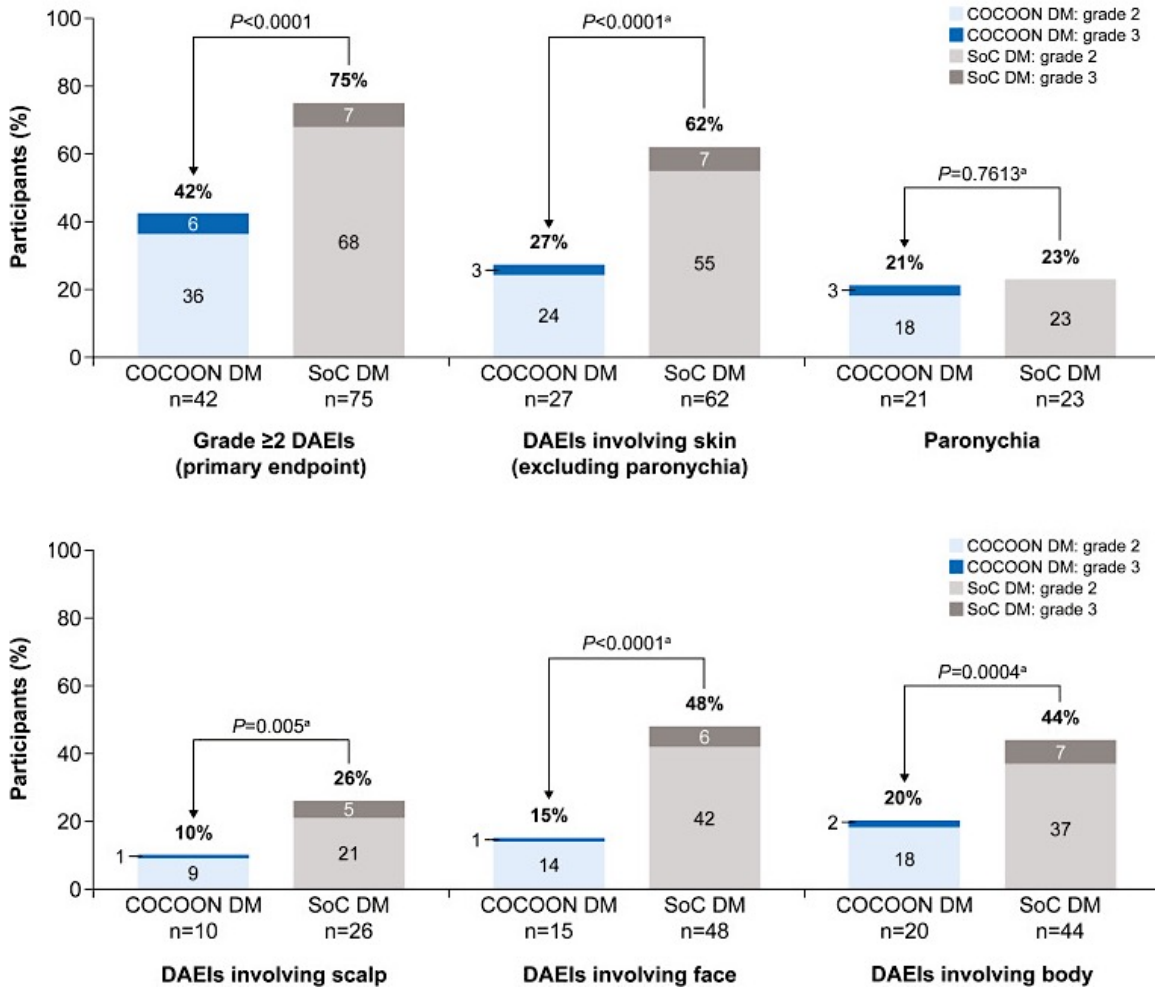
- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)



Leighl NB, ASCO 2024; J Clin Oncol 2024

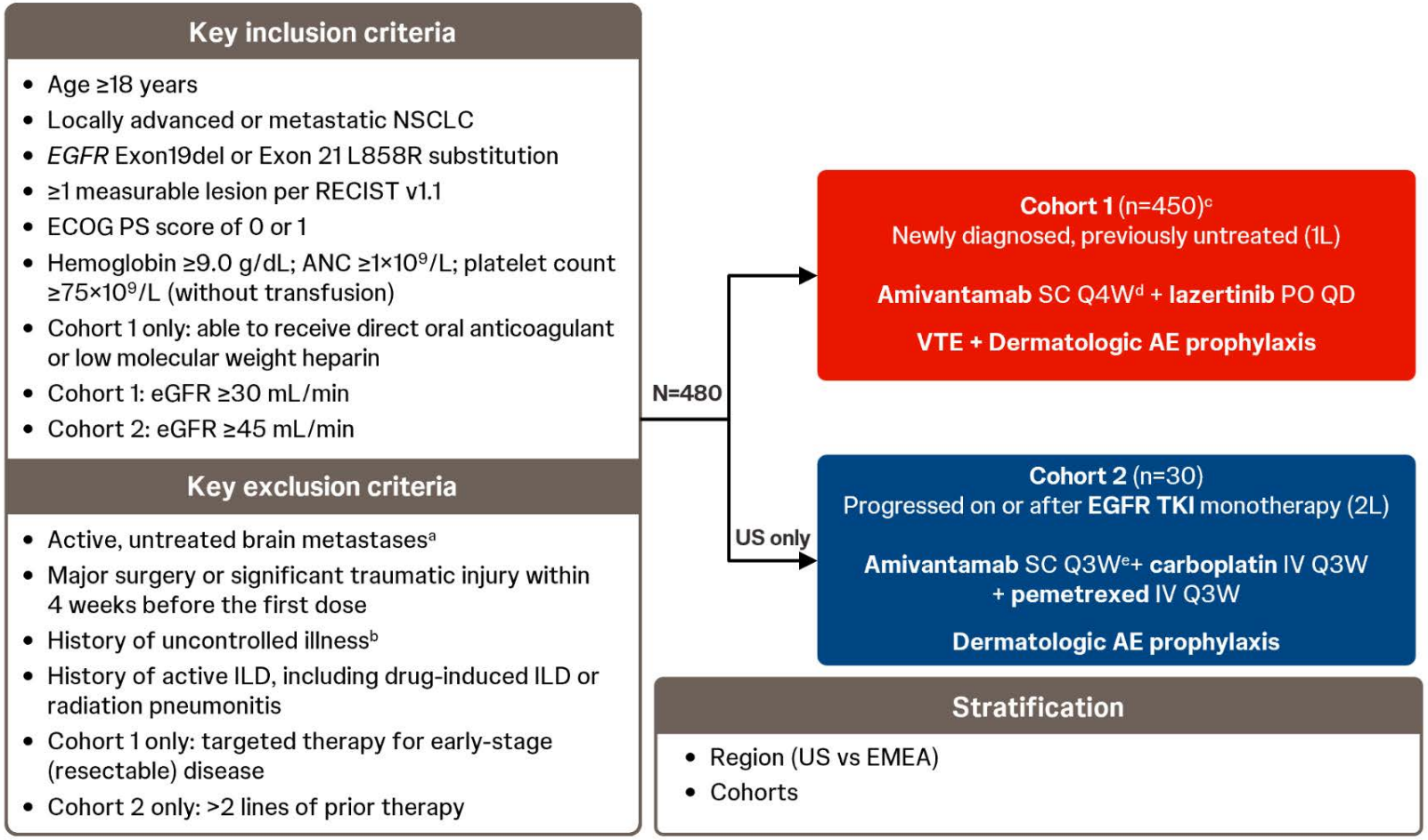
COCOON: Amivantamab/lazertinib with enhanced dermatologic prophylaxis





Borgeaud M, et al. healthbook TIMES Onco Hema 2025
Cho BC, et al. JTO 2025.

COPERNICUS Study Design



Goldberg SB, et al. ASCO 2026; Abstract 8613.

COPERNICUS: SC amivantamab plus lazertinib with dermatologic and VTE prophylaxis (Cohort 1)

- First-line SC amivantamab q4w plus lazertinib
- Includes dermatologic prophylaxis with the COCOON regimen and VTE prophylaxis
- 190 patients enrolled in the US

	MARIPOSA	COPERNICUS
Therapy Discontinuation due to AEs	34%	5%
Infusion/Administration-Related Reactions (ARRs/IRRs)	63%	9%
Rash	62%	22%
Paronychia	68%	26%
Venous Thromboembolism (VTE)	36%	7%

Goldberg SB, et al. ASCO 2026; Abstract 8613.

COPERNICUS: SC amivantamab plus chemotherapy with dermatologic prophylaxis (Cohort 2)

As of data cutoff (02 Jan 2026), 29 pts had enrolled in Cohort 2 (target enrollment, 30; median [range] follow-up: 7.6 [0.5+–10.2] mo); 76% were still ongoing in the study. Median age was 62 y, with 45% of pts ≥65 y and 21% ≥75 y; 38% were Asian and 7% African American.

Median PFS was 7.4 mo (95% CI, 4.8–NE; Table). AEs were mostly grade 1–2, with no new safety signals; 31% of pts interrupted ami due to AEs. With dermatologic prophylaxis, paronychia and rash occurred in 24% and 14% of pts, respectively, showing numerical reductions vs MARIPOSA-2. ARRs (grouped term) were also numerically lower at 21%.

Median PFS, mo (95% CI)	7.4 (4.8–NE)
ORR (95% CI)	24.1% (10.3–43.5)
Partial response	7 (24.1%)
Stable disease	15 (51.7%)
Progressive disease	2 (6.9%)

Leal T, et al. ASCO 2026; Abstract 8614.

Dato-DXd (TROPION-Lung01)

TRAEs ≥15% and Adjudicated Drug-Related ILD

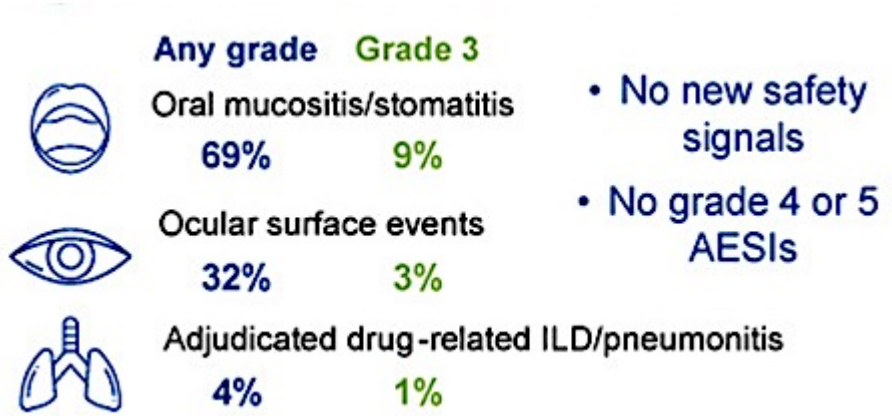
TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

- Stomatitis and nausea were the most frequent TRAEs seen with Dato-DXd and were predominantly grade 1 or 2
- 20% of patients on Dato-DXd required a dose reduction
- 8% discontinued treatment due to toxicity

Sands J et al. WCLC 2024. Abstract OA08.03.

Dato-DXd in patients with EGFR-mutant NSCLC

Dato-DXd (pooled analysis from TROPION-Lung 05 and Lung01)



Dato-DXd plus osimertinib (ORCHARD)

Category, *n* (%)	Osimertinib plus Dato-DXd 4 mg/kg (*N* = 35)	Osimertinib plus Dato-DXd 6 mg/kg (*N* = 34)
Stomatitis/oral mucositis		
All grade	24 (69)	29 (85)
Grade ≥3	5 (14)	4 (12)
ILD/pneumonitis (adjudicated)		
All grade	1 (3)	5 (15)
Grade 1	0	1 (3)
Grade 2	0	2 (6)
Grade 3	0	2 (6)
Grade 4	1 (3)	0
Grade 5	0	0

Ahn MJ, et al. JTO 2025
Riess JW, et al. Ann Oncol 2026

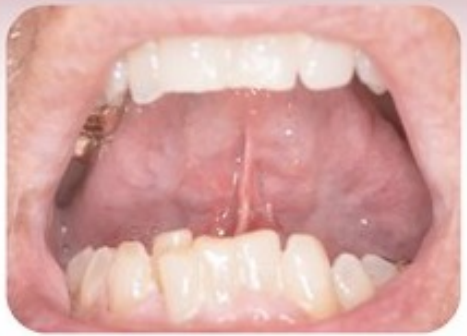
Monitoring for, mitigating, and managing oral mucositis/stomatitis associated with Dato-DXd

STEP 1: Prophylaxis

Initiate daily oral care plan prior to administration of first Dato-DXd dose

- **Gently brushing** teeth after meals and at bedtime using a soft toothbrush and a **bland fluoride-containing toothpaste**
- **Daily flossing**, unless it causes pain or bleeding
- Daily use of a **steroid-containing mouthwash**[a,b]
- **Cryotherapy** should be considered
- **Education** on the importance of oral hygiene, hydration, and lubrication of the oral mucosa and **adherence to oral care plan**

STEP 2: Monitor



STEP 3: Manage

Supportive care

- Increase frequency of bland mouthwashes to up to every hour, if necessary
- As soon as oral pain, inflammation, and/or ulceration develops, strongly consider using a steroid-containing mouthwash[a]
- Provide pain management
- Consider referral to a dentist, oral surgeon, oral medicine expert, or dermatologist for severe or persistent events

Grading and dose modifications

Grade 1
- Maintain dose

Grade 2
- Consider a dose delay or reduction if clinically indicated

Grade 3
- If prophylactic/supportive medications have not yet been optimized, delay dose until event has been resolved to ≤ grade 1 or baseline, optimize medications, then maintain dose
- If prophylactic/supportive medications have already been optimized, delay dose until resolved to ≤ grade 1 or baseline, and then reduce dose by 1 level

Grade 4
- Discontinue Dato-DXd

Meric-Bernstam F, et al. Oncologist 2025

Monitoring for, mitigating, and managing ILD associated with Dato-DXd

STEP 1: Monitor

Suspected ILD/pneumonitis

⇩

Hold Dato-DXd

Rule out ILD/pneumonitis if a patient develops radiographic changes potentially consistent with ILD/pneumonitis or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever

STEP 2: Confirm

All ILD/pneumonitis events, regardless of severity or seriousness, must be followed until resolution, including after discontinuation of Dato-DXd

Evaluations should include:

- High-resolution computed tomography
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture and complete blood count, and other blood tests as needed
- Bronchoscopy and bronchoalveolar lavage, if clinically indicated and feasible
- Pulmonary function tests
- Pulse oximetry (SpO_2)
- Arterial blood gases, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible

STEP 3: Manage

Hold Dato-DXd for any ILD/pneumonitis events, regardless of grade

Grade 1

- Monitor symptoms and closely follow-up in 2–7 days for onset of clinical symptoms and SpO_2
- Consider follow-up imaging in 1–2 weeks (or as clinically indicated)
- Consider starting systemic steroids[a]
- Hold Dato-DXd until fully resolved,[b] then
  - If resolved in ≤28 days from onset date, maintain dose
  - If resolved in >28 days from onset date, reduce dose 1 level
  - If the grade 1 ILD/pneumonitis event does not resolve within 84 days from the last infusion, permanently discontinue Dato-DXd

Grade 2

- Permanently discontinue Dato-DXd
- Monitor symptoms closely and re-image as clinically indicated
- Promptly start treatment with systemic steroids[c]
- If worsening or no improvement is observed in ≤5 days, then
  - Consider increasing the dose of steroids[d]
  - Re-consider work-up for alternative etiologies (return to Step 2)
  - Escalate care as clinically indicated

Grade 3–4

- Permanently discontinue Dato-DXd
- Hospitalization required
- Promptly initiate high-dose systemic steroids[c]
- Re-image as clinically indicated
- If no improvement within 3–5 days, then
  - Re-consider work-up for alternative etiologies (return to Step 2)
  - Consider other immunosuppressants and/or treat per local practice

Sands J et al. ASCO 2024;Abstract 8263.

Ivonescimab for EGFR-mutant lung cancer

Immune-related toxicity

	Ivonescimab plus chemotherapy (n=161) n (%)		Placebo plus chemotherapy (n=161) n (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any irAE	39 (24.2)	10 (6.2)	10 (6.2)	4 (2.5)
Hypothyroidism	17 (10.6)	1(0.6)	0	0
TSH increased	3 (1.9)	0	1 (0.6)	0
Hyperthyroidism	9 (5.6)	0	0	0
Thyroid hormones increased	1 (0.6)	0	0	0
Blood glucose increased	4 (2.5)	0	3 (1.9)	0
Abnormal corticotrophin	1 (0.6)	0	0	0
Rash	6 (3.7)	4(2.5)	2 (1.2)	1(0.6)
Dermatitis	2 (1.2)	2(1.2)	1 (0.6)	0
Pruritus	1 (0.6)	0	0	0
Interstitial lung disease	3 (1.9)	2	1 (0.6)	1
Pneumonitis	2 (1.2)	1	1 (0.6)	0
Abnormal liver function	1 (0.6)	1	0	0
Serum creatinine increased	1 (0.6)	0	0	0
Diarrhea	0	0	1 (0.6)	1
Lipase increased	0	0	1 (0.6)	1

VEGF blockade-related toxicity

	Ivonescimab plus chemotherapy (n = 161) n (%)		Placebo plus chemotherapy (n = 161) n (%)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Any AESI	48 (29.8)	5 (3.1)	25 (15.5)	4 (2.5)
Proteinuria	28 (17.4)	1 (0.6)	13 (8.1)	0
Haematuria	4 (2.5)	0	3 (1.9)	0
Hemoptysis	2 (1.2)	0	0	0
Epistaxis	3 (1.9)	0	1 (0.6)	0
Oral hemorrhage	1 (0.6)	0	0	0
Gastrointestinal hemorrhage	0	0	1 (0.6)	0
Gingival bleeding	1 (0.6)	0	0	0
Ophthalmorrhagia	1 (0.6)	0	2 (1.2)	0
Vaginal bleeding	0	0	1 (0.6)	0
Occult blood	0	0	1 (0.6)	0
Elevation of blood pressure	13 (8.1)	3 (1.9)	5 (3.1)	3 (1.9)
Artery embolism	1 (0.6)	0	1 (0.6)	1 (0.6)
Congestive heart failure	1 (0.6)	1 (0.6)	0	0

- Potentially the biggest risk with ivonescimab in EGFR-mutant lung cancer is stopping the EGFR TKI

HARMONi-A Study Investigators, JAMA. 2024

Summary

- Therapeutics for EGFR-mutant lung cancer have distinct toxicity profiles which must be considered when selecting treatment for patients
- Prophylaxis can be useful for some agents such as amivantamab and Dato-DXd
- Early identification and management of toxicity is critical in the care of patients with EGFR-mutant lung cancer, including treatment holds, dose reduction, and supportive measures

Cases from the Community

Stephen “Fred” Divers, MD

Neil Love, MD

RTP
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TO PRACTICE

Discussion Questions

What would you recommend for a patient with significant diarrhea on osimertinib?

Are you comfortable reducing osimertinib dosing to 40 mg daily if patients are unable to tolerate the recommended dose? Can this be done without compromising efficacy?

Has the introduction of subcutaneous administration and various practical approaches to toxicity prophylaxis changed your impression of the tolerability of amivantamab in any way?

Cases from the Community

Susmitha Apuri, MD
Florida Cancer Specialists
& Research Institute
Inverness and Lecanto, Florida

Priya Rudolph, MD, PhD
Georgia Cancer Specialists
Northside Hospital Cancer Institute
Athens, Georgia

Stephen "Fred" Divers, MD
Chief Medical Officer
American Oncology Network
Hot Springs, Arkansas

Neil Love, MD
Research To Practice
Miami, Florida

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Consensus or Controversy? Documenting and Discussing Investigators' Approaches to the Management of Ovarian Cancer

Saturday, May 30, 2026
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Ramez N Eskander, MD
Ursula Matulonis, MD
Alexander B Olawaiye, MD
David M O'Malley, MD

Moderator

Kathleen N Moore, MD, MS

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TO PRACTICE

What Clinicians Want to Know: Addressing Community Oncologists' Questions About the Care of Patients with Prostate Cancer

Saturday, May 30, 2026

7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Wassim Abida, MD, PhD

Rahul Aggarwal, MD

Emmanuel S Antonarakis, MD

Karim Fizazi, MD, PhD

Moderator

Rana R McKay, MD, FASCO

RTP RESEARCH TO PRACTICE

Second Opinion: Investigators Provide Perspectives on the Current and Future Management of Small Cell Lung Cancer

Saturday, May 30, 2026
7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)

Faculty

Anne Chiang, MD, PhD
Apar Kishor Ganti, MD, MS
Luis Paz-Ares, MD, PhD

Moderator

Misty Dawn Shields, MD, PhD

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