Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer

Friday, May 30, 2025
6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)

Faculty

Nicolas Girard, MD, PhD
Jonathan Goldman, MD
Pasi A Jänne, MD, PhD, FASCO
Suresh S Ramalingam, MD
Joshua K Sabari, MD

Moderator

Helena Yu, MD

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Friday May 30	**Immunotherapy and Antibody–Drug Conjugates in Lung Cancer** 11:15 AM – 12:45 PM CT (12:15 PM – 1:45 PM ET)
	Colorectal Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
	EGFR Mutation–Positive Non–Small Cell Lung Cancer 6:30 PM – 8:30 PM CT (7:30 PM – 9:30 PM ET)
Saturday May 31	**Urothelial Bladder Cancer** 6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)
	Non–Hodgkin Lymphoma 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)
Sunday June 1	**Chronic Lymphocytic Leukemia (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	HER2–Positive Gastrointestinal Cancers 7:00 PM – 8:30 PM CT (8:00 PM – 9:30 PM ET)
	Ovarian and Endometrial Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Monday June 2	**Renal Cell Carcinoma (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)
	Multiple Myeloma (Webinar) 6:00 PM – 7:00 PM CT (7:00 PM – 8:00 PM ET)
	Metastatic Breast Cancer 7:00 PM – 9:00 PM CT (8:00 PM – 10:00 PM ET)
Tuesday June 3	**Soft Tissue Sarcoma and Other Connective Tissue Neoplasms (Webinar)** 7:00 AM – 8:00 AM CT (8:00 AM – 9:00 AM ET)

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Clinicians in the Meeting Room

Networked iPads are available.

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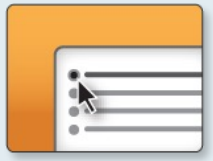

Answer Survey Questions: Complete the pre- and postmeeting surveys.

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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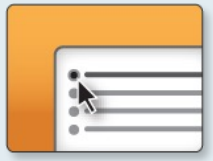

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About the Enduring Program

- 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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Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer

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Suresh S Ramalingam, MD
Joshua K Sabari, MD

Moderator

Helena Yu, MD

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Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

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MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

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Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Lung Cancers

Risk stratification and patient preference

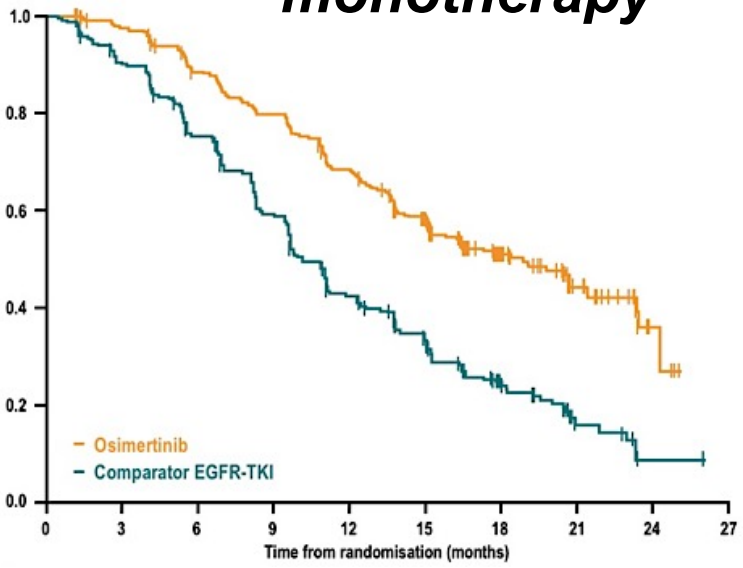
Memorial Sloan Kettering Cancer Center

Helena Yu
Associate Attending
Thoracic Oncology Service
May 2025

Current options for 1L treatment for EGFR+ lung cancers

FLAURA

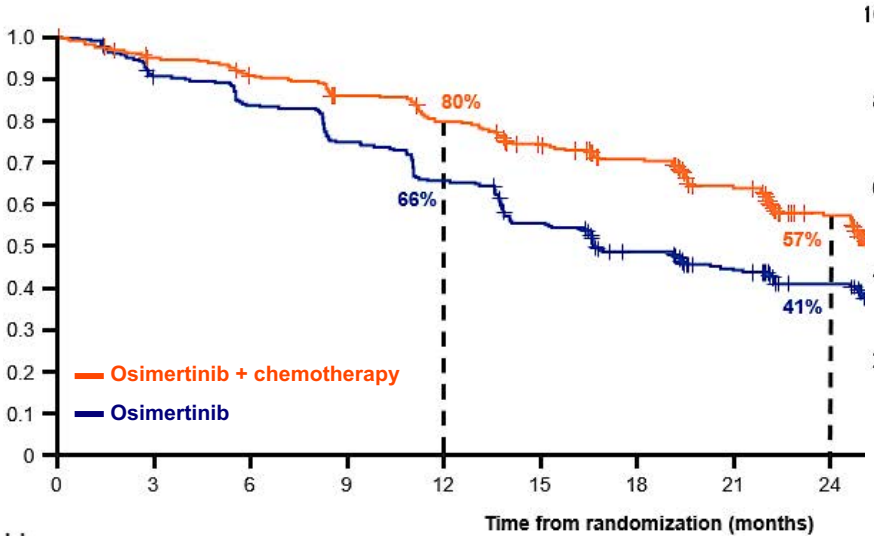
Osimertinib monotherapy



Progression-free survival
Osimertinib 18.9 mo
1st gen TKI 10.2 mo

FLAURA 2

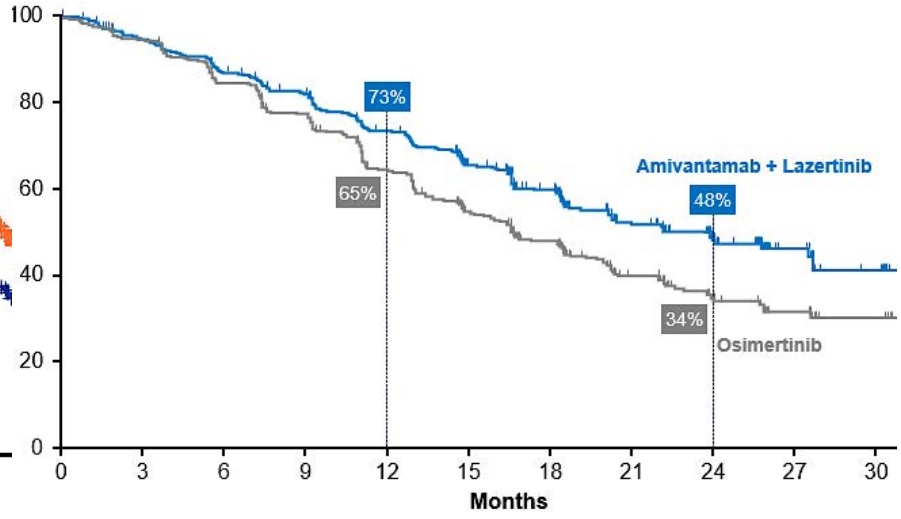
Osimertinib + chemotherapy



Progression-free survival
Osi+chemo 25.5 mo
Osimertinib 16.7 mo

MARIPOSA

Amivantamab + Lazertinib



Progression-free survival
Ami+Laz 23.7 mo
Osimertinib 16.6 mo

Soria NEJM 2018, Planchard NEJM 2023, Cho NEJM 2024

Considerations for 1L treatment

Quality of life

Side effects

Time and effort

Financial cost

Patient preference

Efficacy

Progression-free survival

Overall survival

Ability to sequence treatments

CNS outcomes

LOWER-RISK

No brain metastases

No liver metastases

No TP53 co-mutation

ctDNA clearance

No baseline ctDNA

HIGH-RISK

Brain metastases

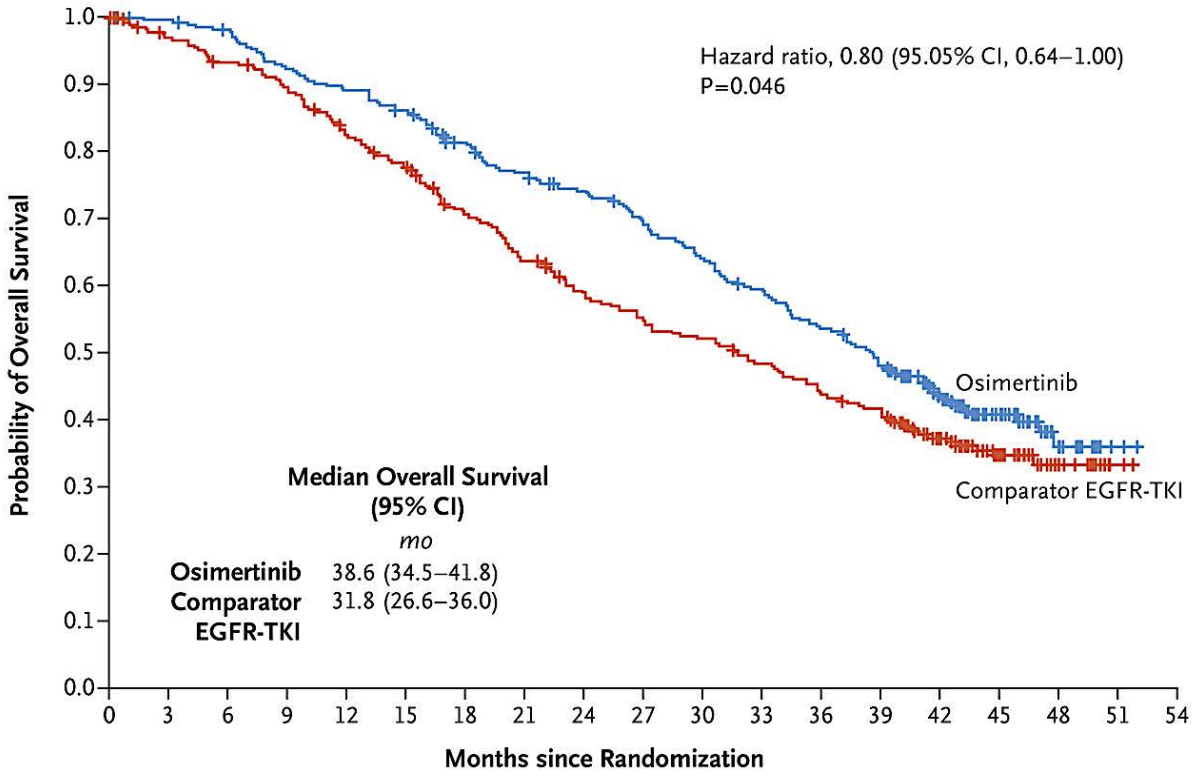
Liver metastases

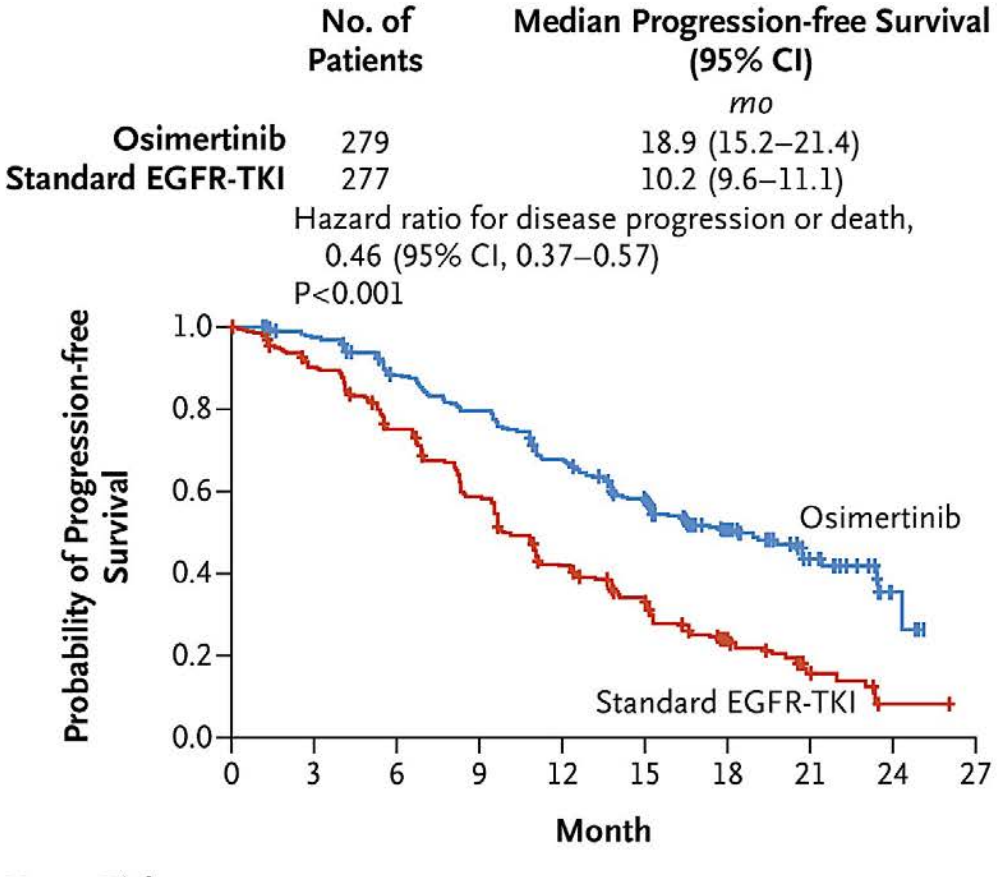
TP53 co-mutation

ctDNA persistence

Baseline ctDNA

Osimertinib monotherapy

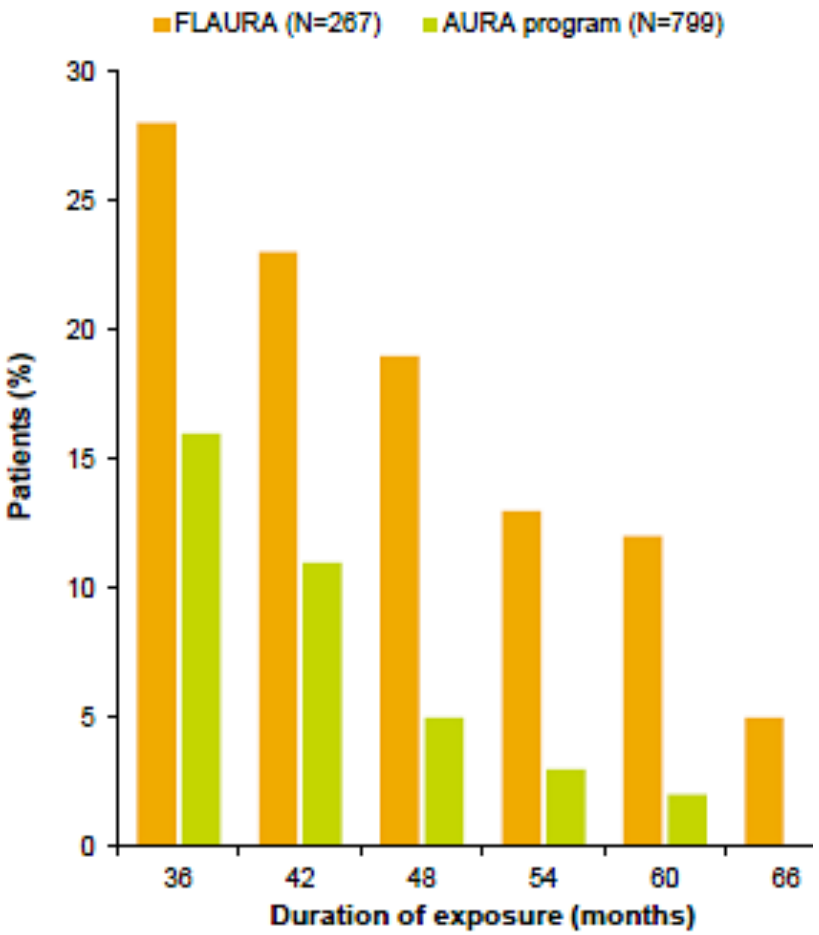




- well-tolerated standard of care with clear improvement in PFS and OS over earlier-generation EGFR TKIs
- oral therapy with typical MD visit schedule of every 3 months
- toxicity profile is manageable, low rate of treatment discontinuation
- real-world studies have shown similar efficacy and safety in the larger patient population

Ramalingam SS NEJM 2020,
Watanabe JTO CRR 2024

Osimertinib long term safety



In FLAURA, 28% and 13% received osi for >3 yrs or 4.5 yrs

On study data for pts with exposure > 36mo

Adverse event, n (%)	FLAURA (n=76)	AURA program (n=124)
Any AE	73 (96)	123 (99)
Any treatment-related* AE	68 (89)	113 (91)
Any AE ≥Grade 3	27 (36)	48 (39)
Any treatment-related* AE ≥Grade 3	8 (11)	16 (13)
Any AE resulting in death (including TRAEs)*	0	1 (1)
Any SAE (including outcome of death)	13 (17)	44 (35)
Any treatment-related* SAE (including outcome of death)	2 (3)	6 (5)
Any SAE leading to interruption of treatment	8 (11)	19 (15)
Any SAE leading to discontinuation of treatment	0	2 (2)

Garassino WCLC 2022

FLAURA2: Osimertinib + chemotherapy

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

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

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles)

Maintenance osimertinib 80 mg (QD) + pemetrexed 500 mg/m² (Q3W)†

Follow-up: RECIST v1.1 assessment at 6 and 12 weeks, then Q12W until RECIST v1.1 defined radiological disease progression or other withdrawal criteria were met

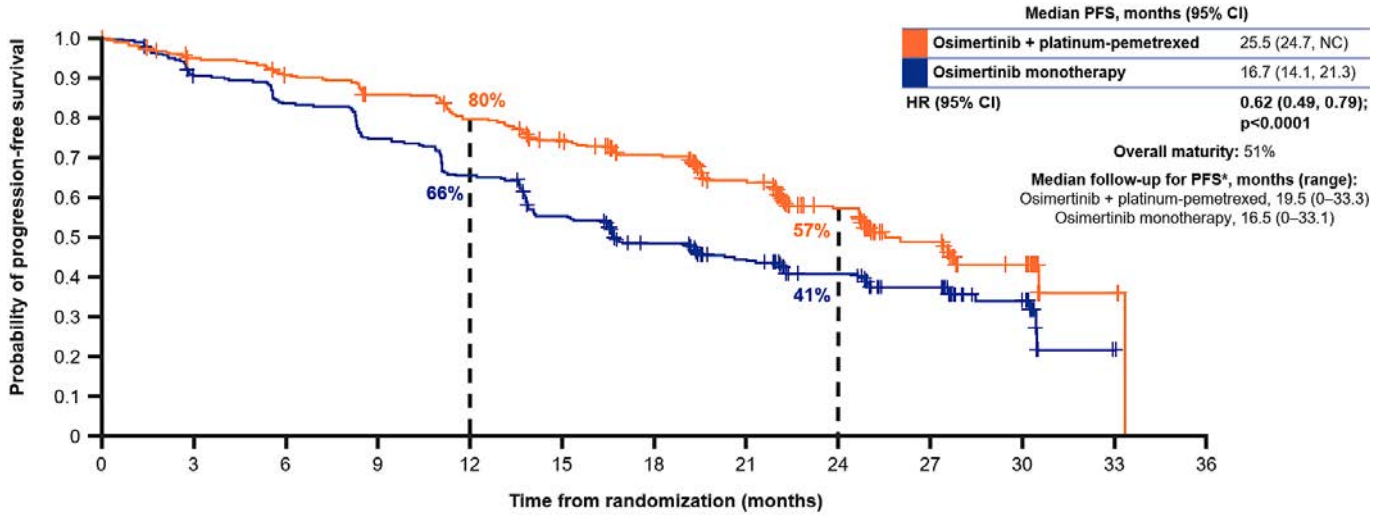
Randomization 1:1 (N=557)
Stratification by: race (Chinese Asian / non-Chinese Asian / non-Asian); **EGFR test** (local / central); **WHO PS** (0 / 1)

Osimertinib 80 mg (QD)

- **Primary endpoint:** PFS by investigator assessment per RECIST v1.1‡§
- **Secondary endpoints include:** OS, ORR, DoR, DCR, HRQoL and safety (AEs by CTCAE v5) and PFS2‡

Progression-free survival per investigator

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

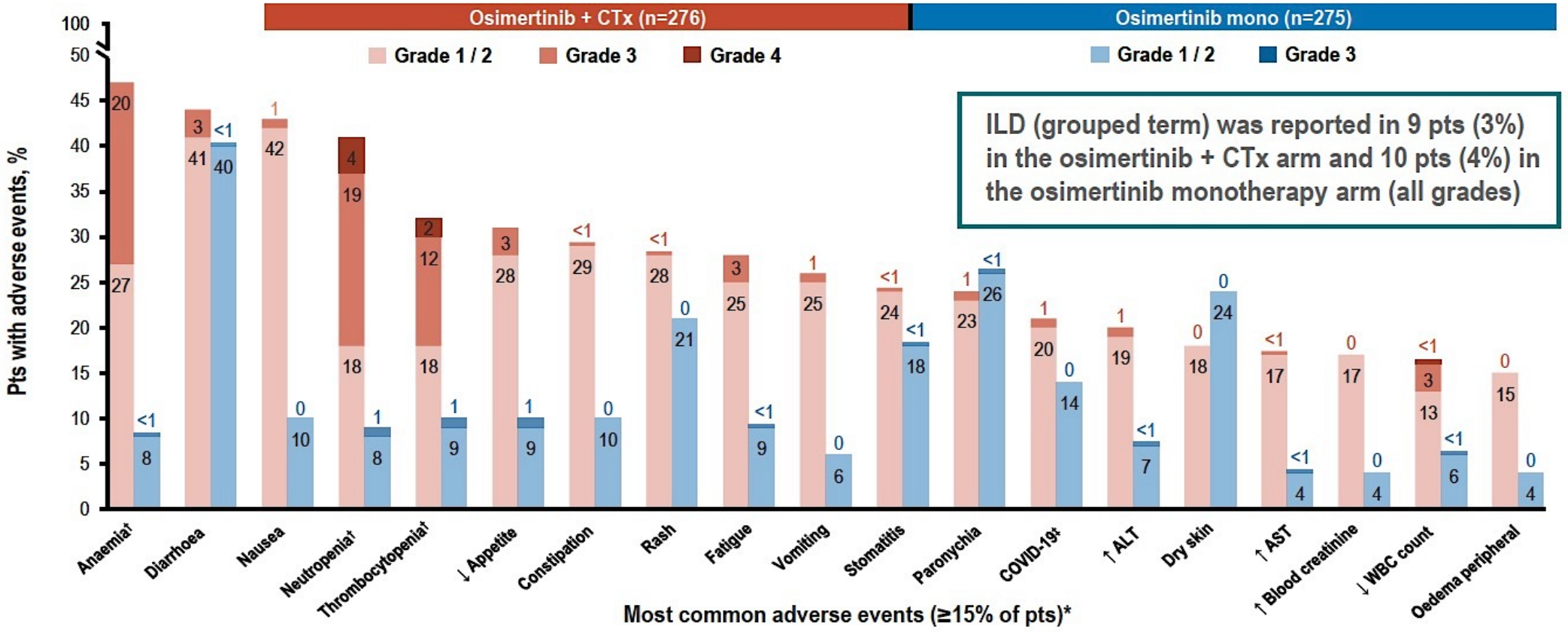


Clear PFS benefit ~ 9mo

HR 0.62 (CI 0.49-0.79)

Planchard ESMO 2023

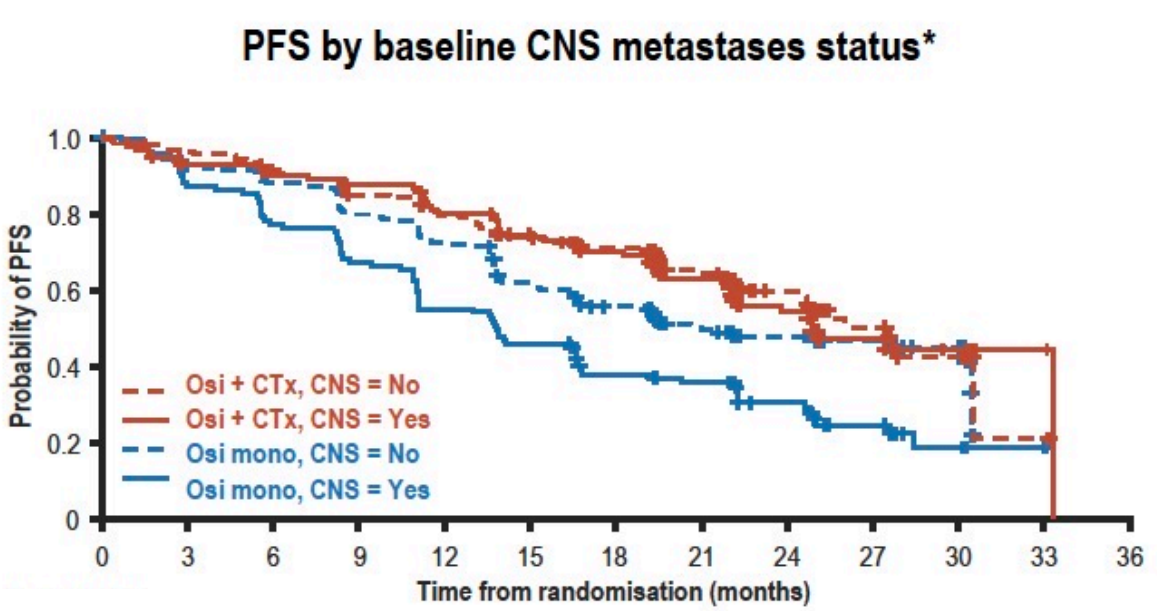
Osimertinib + chemotherapy – Safety

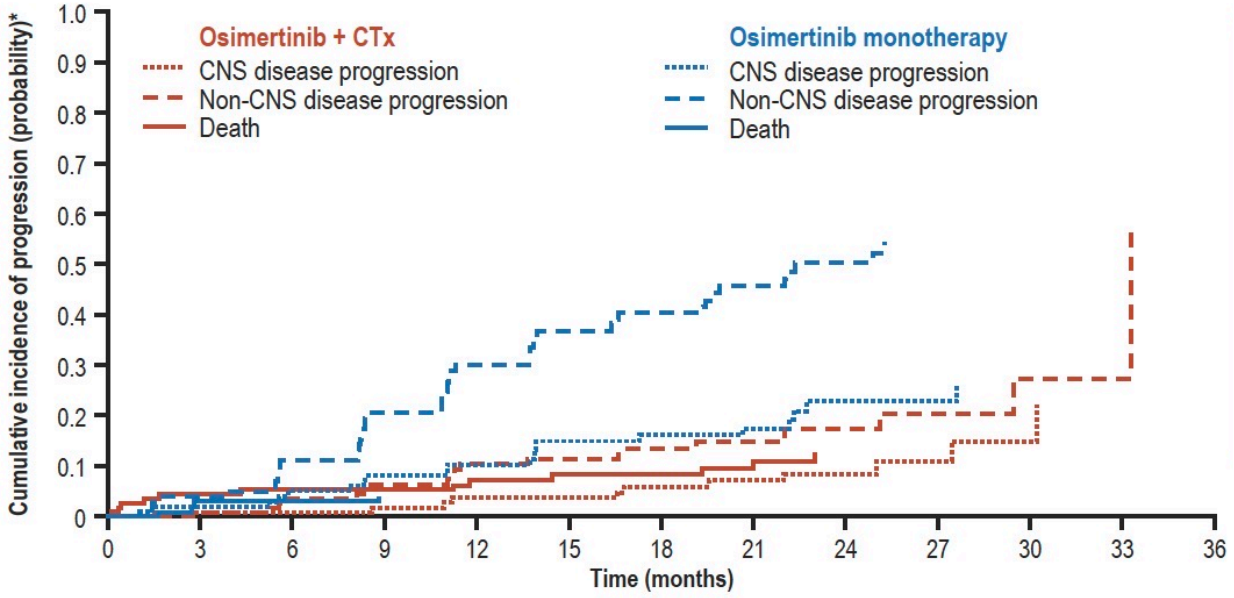


- More toxicity than osimertinib monotherapy and for a longer duration
- Chemotherapy toxicities include cytopenia, renal insufficiency, edema
- QOL and financial cost of frequent infusions and clinic visits
- Using two lines of effective therapy in one line.

Planchard ESMO 2023

Osimertinib + chemotherapy – CNS efficacy





PFS w/ CNS mets

HR 0.47 (25 vs 14mo)

PFS w/o CNS mets

HR 0.75 (28 vs 21mo)

Not just prognostic but predictive – added benefit of chemo in pts with CNS metastases

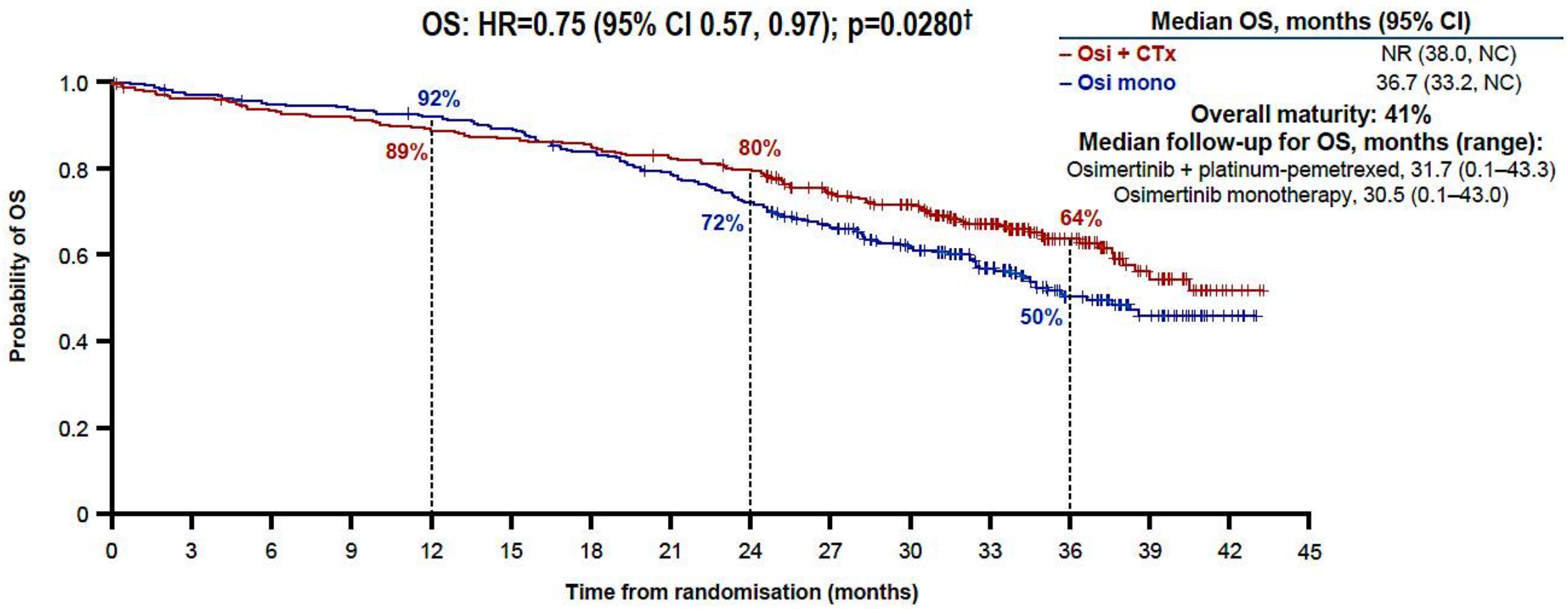
CNS

In pts with CNS metastases at baseline (by CNS BICR), the addition of CTx to osimertinib:

- Reduced the risk of CNS progression or death
  - cFAS: CNS PFS HR 0.58 (95% CI 0.33, 1.01)
  - cEFR: CNS PFS HR 0.40 (95% CI 0.19, 0.84)
- Increased CNS ORR, and the proportion of pts achieving CNS complete response
  - cFAS: complete responses 59% vs 43%
  - cEFR: complete responses 48% vs 16%
- Improved durability of CNS responses
  - cFAS: mDoR NR (95% CI 23.8, NC) vs 26.2 months (95% CI 19.4, NC)
  - cEFR: mDoR NR (95% CI 21.6, NC) vs 20.9 months (95% CI 12.6, NC)

Planchard ESMO 2023

Osimertinib + chemotherapy – Overall survival (immature)

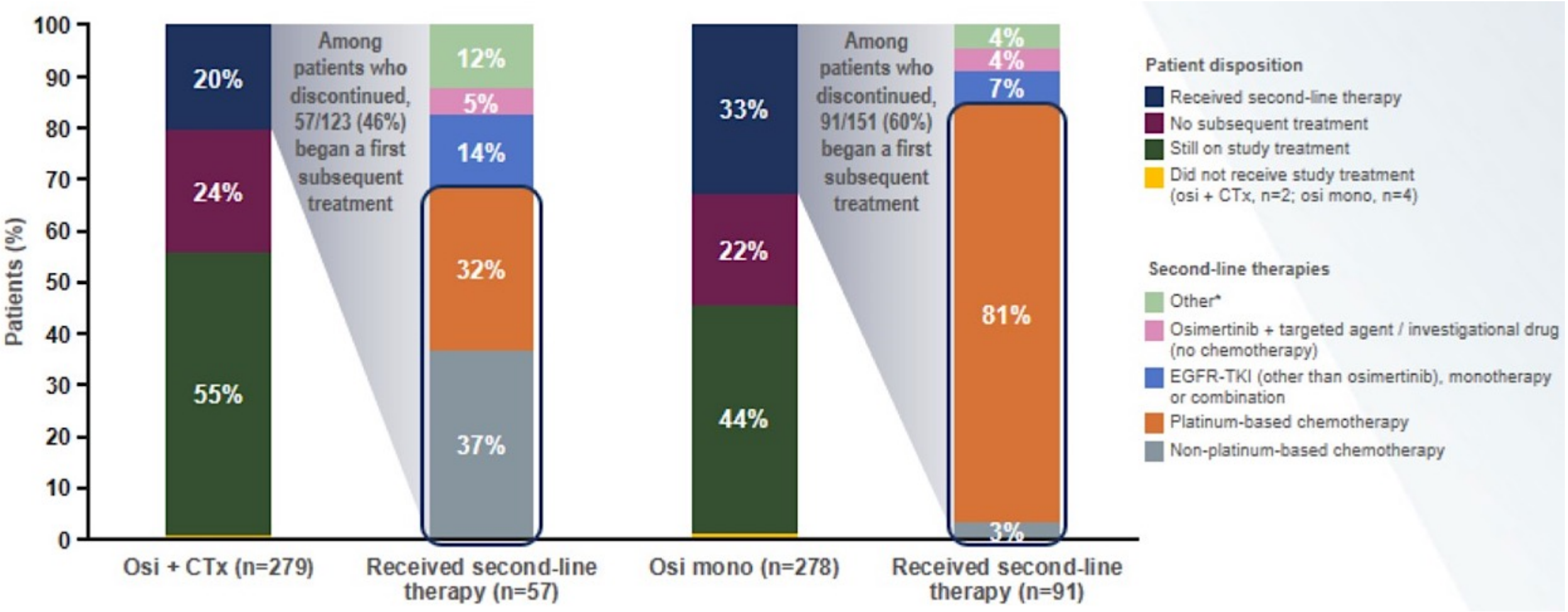


Immature OS data (41% maturity)

Trend towards OS benefit, HR 0.75

Valdiviezo ELCC 2024

Osimertinib + chemotherapy



- Vast majority (81%) of pts on osimertinib received 2L platinum-based chemotherapy
- 22% of patients on osimertinib monotherapy did not receive subsequent 2L therapy

Use your best therapy first! Don't always get a second chance

Valdiviezo ELCC 2024

Amivantamab + Lazertinib

Key Eligibility Criteria

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

Stratification Factors

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

2:2:1 Randomization (N=1074)

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

Lazertinib monotherapy arm was included to assess the contribution of components

Primary endpoint:

- PFS by BICR per RECIST v1.1

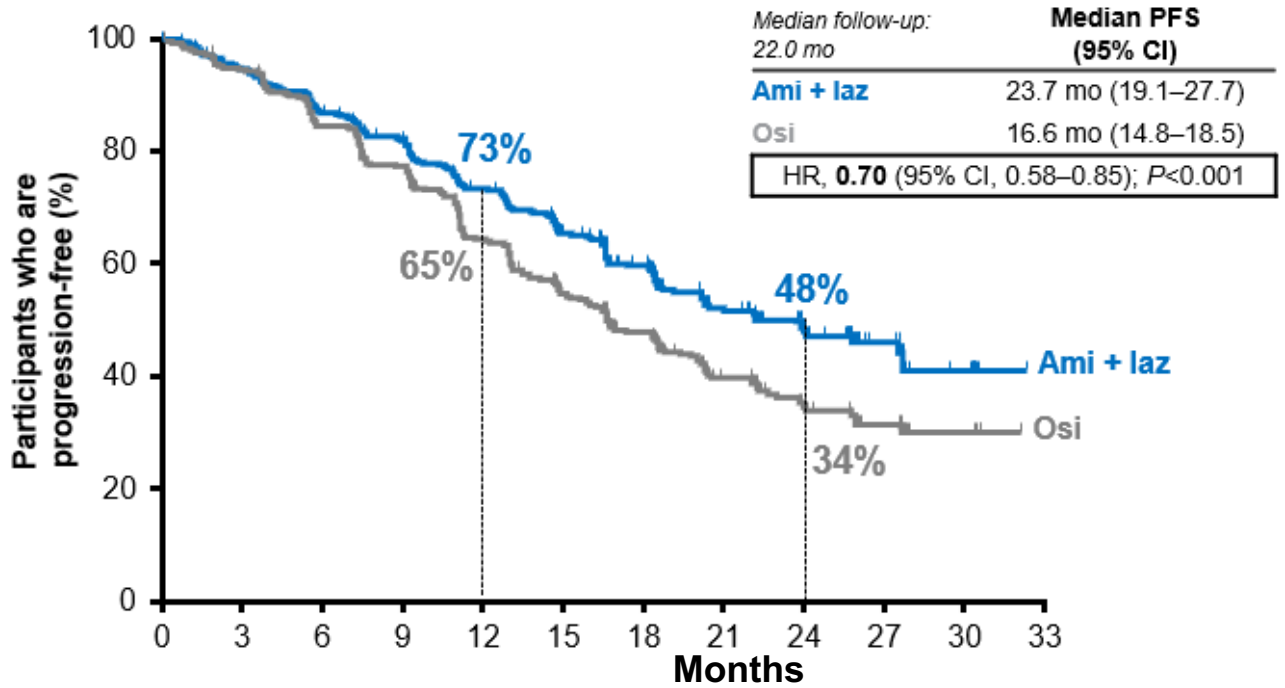
Key secondary endpoint:

- Protocol-specified final overall survival[b]

Other endpoints reported in this presentation:

- Intracranial PFS (icPFS)
- Intracranial ORR (icORR)
- Intracranial DoR (icDoR)
- Time to symptomatic progression (TTSP)
- Safety

PFS



Clear PFS benefit ~ 7mo

HR 0.70 (CI 0.58-0.85)

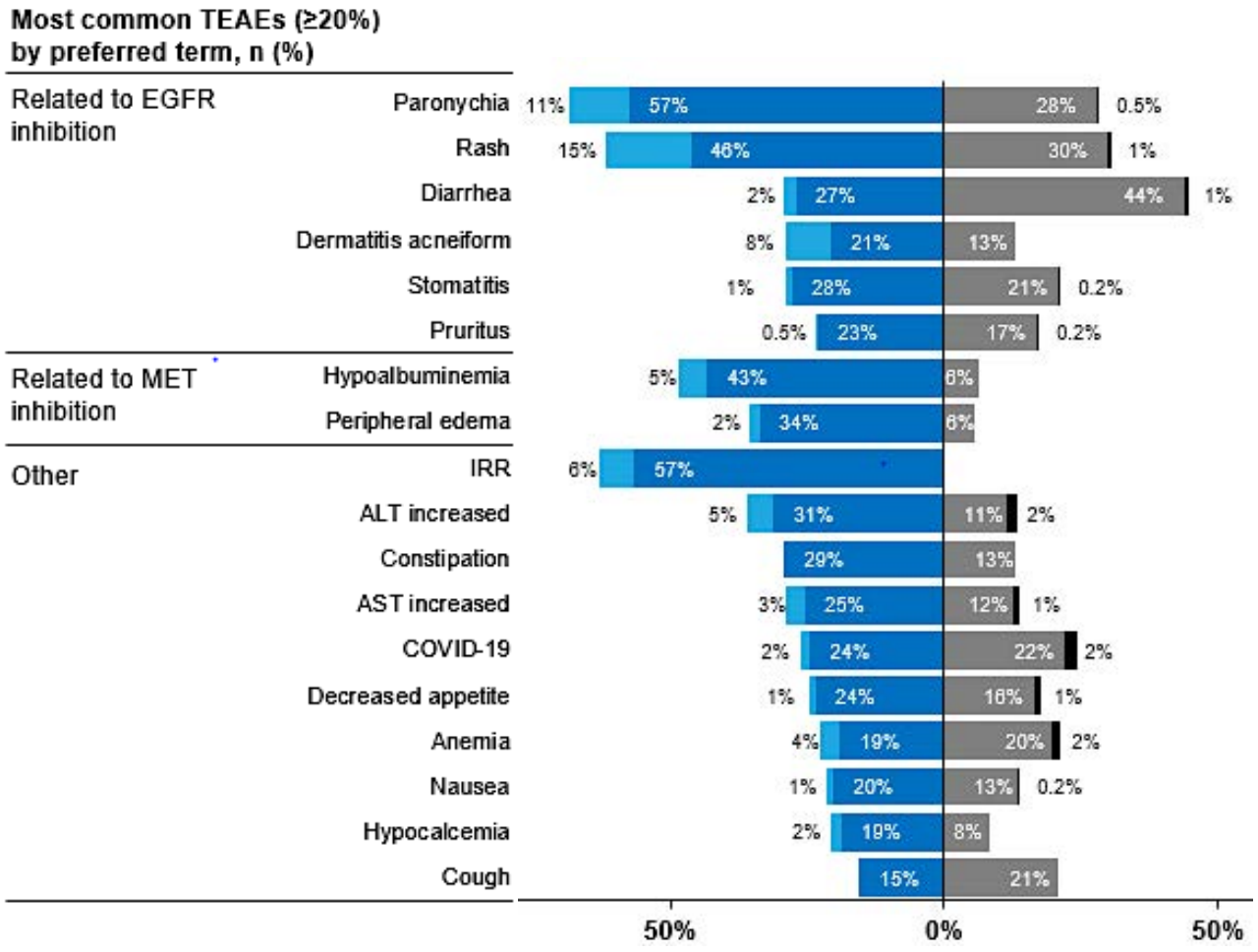
Cho NEJM 2024

Amivantamab + Lazertinib – Safety

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

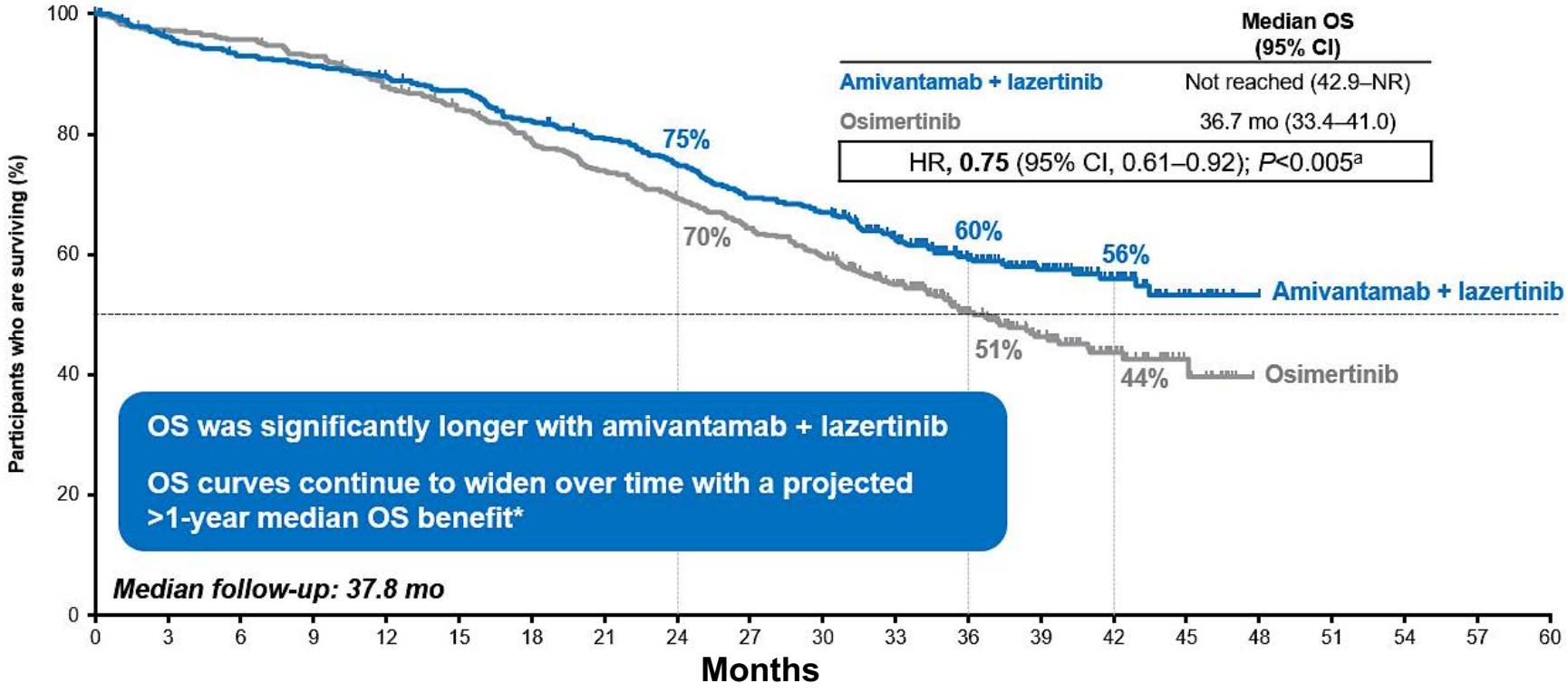
	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)

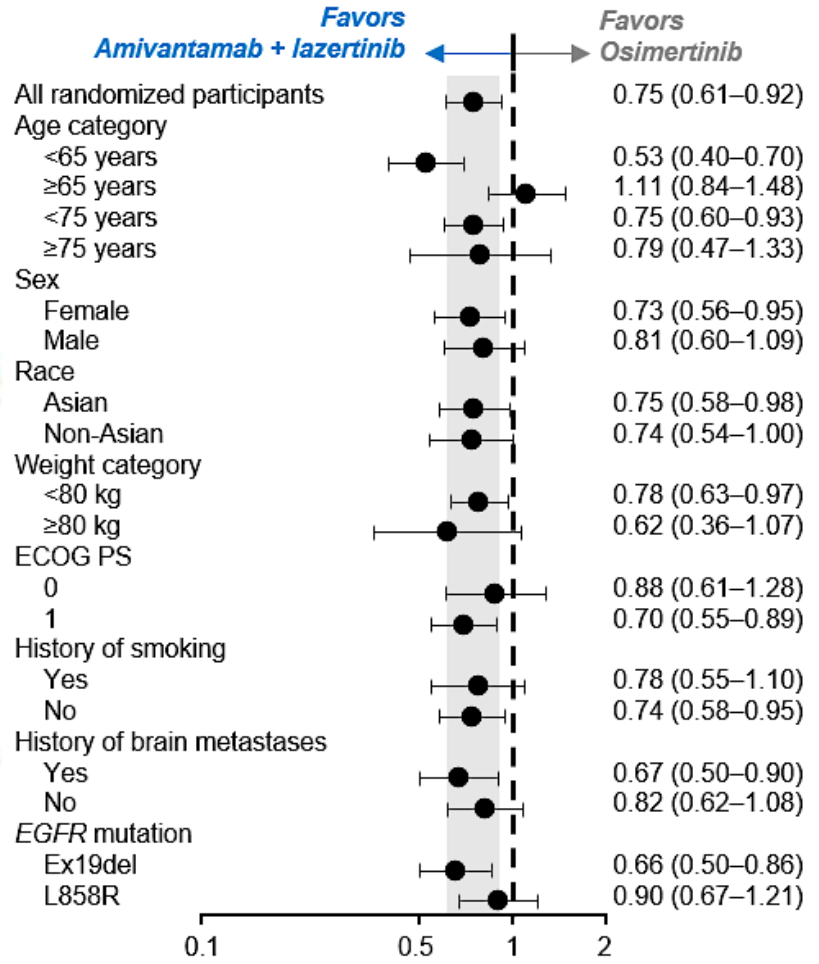
- More toxicity than osimertinib monotherapy and for a longer duration
- Wild type EFR toxicity (paronychia, acneiform rash), MET toxicity (swelling) and VTE (37%).
- QOL and financial cost of frequent infusions and clinic visits



- Rash, paronychia, stomatitis, VTE all front-loaded in first 4 mo
- COCOON trial, SKIPPirr and anticoagulation all significantly decrease rash, IRR and VTE events

Amivantamab + Lazertinib – Overall Survival

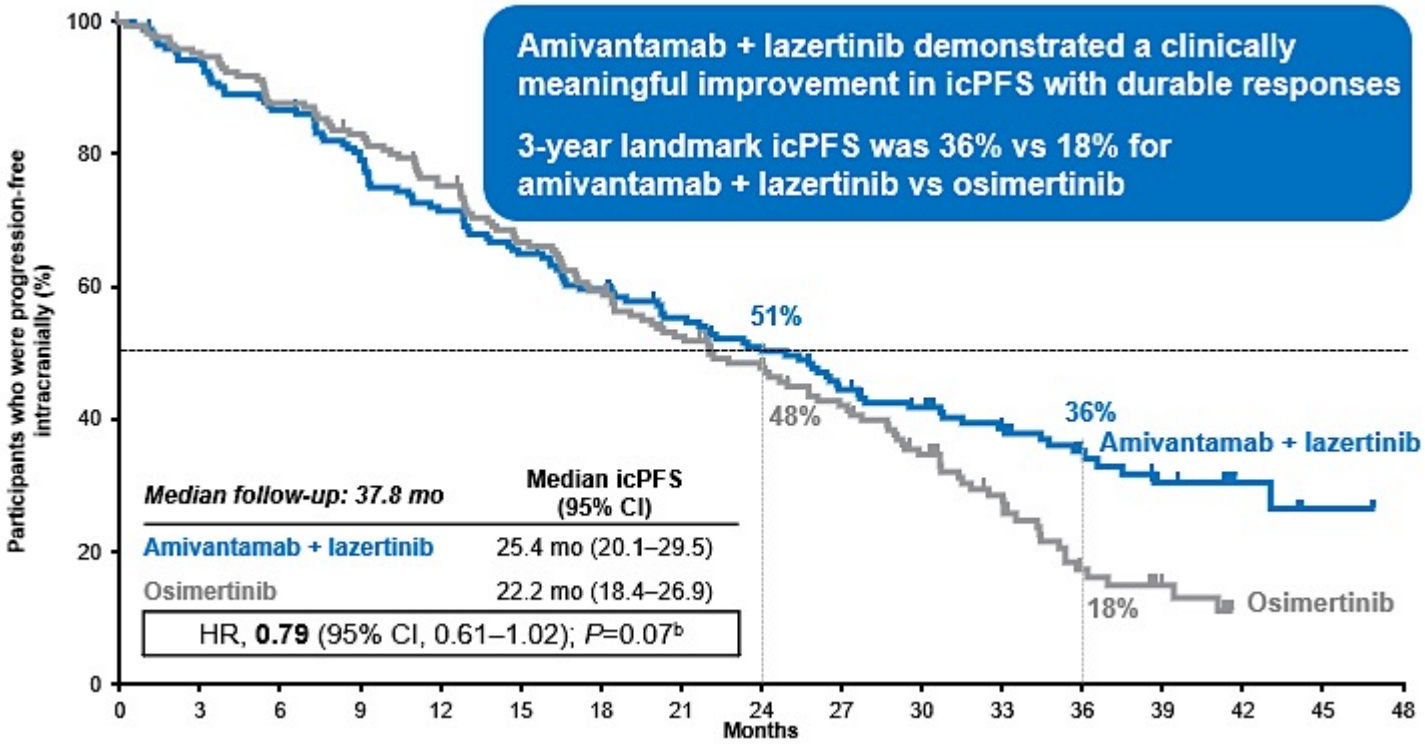


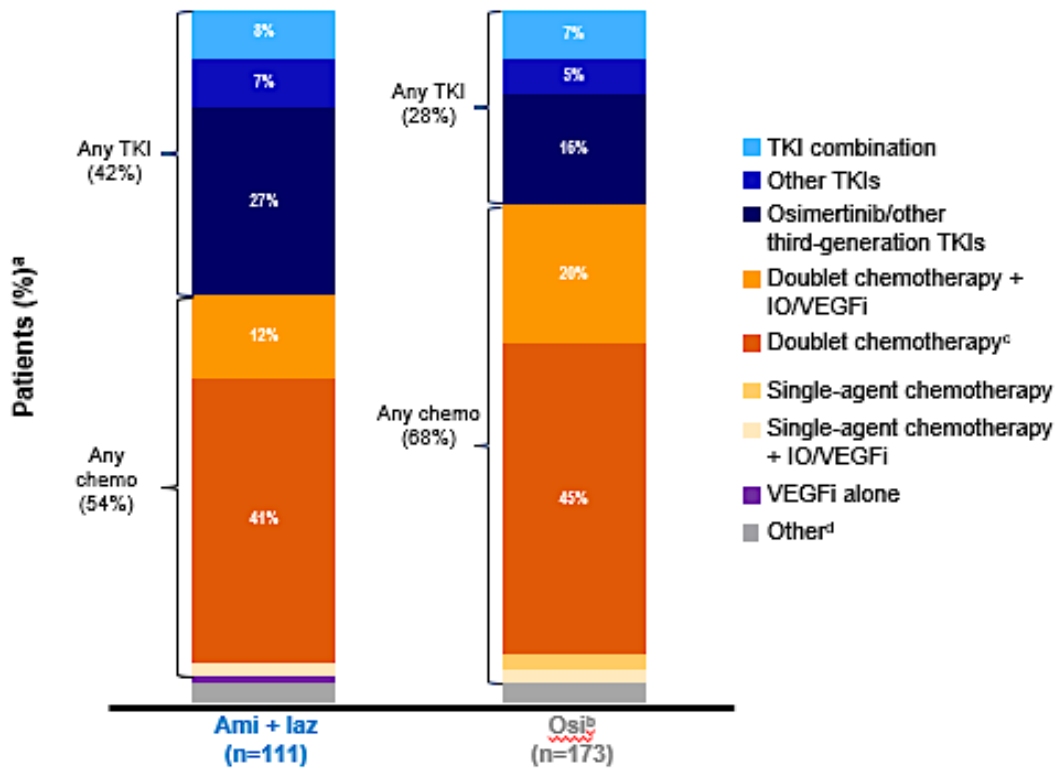


Only first-line therapy currently with a statistically-significant overall survival benefit over 1L osimertinib monotherapy

Yang ELCC 2025

Amivantamab + Lazertinib – CNS Efficacy





Improved CNS control with Amivantamab and lazertinib

3 yr landmark icPFS 36 vs 18%

How to interpret OS in the setting of no crossover?

3/173 (1%) pts in osimertinib arm received Amivantamab

We have access to these drugs in the second-line setting.

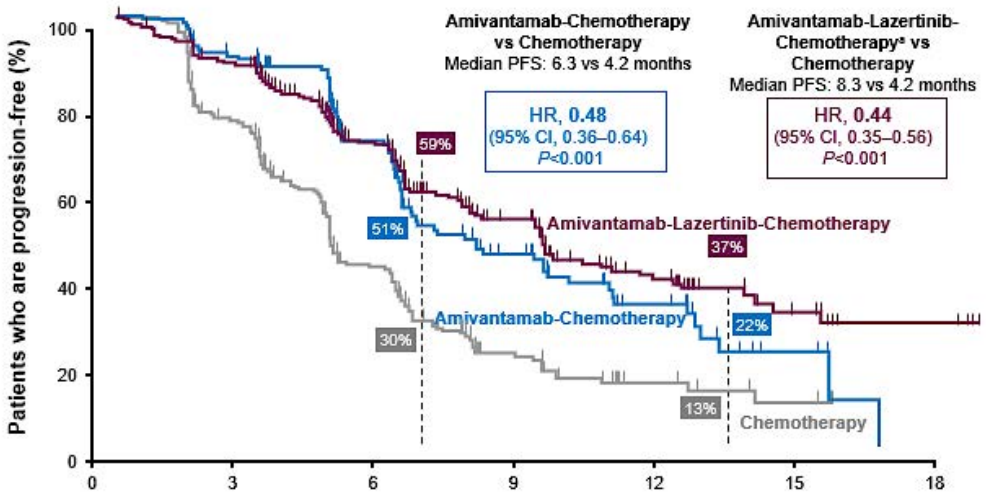
How do we best sequence when we balance efficacy and toxicity?

Yang ELCC 2025

Amivantamab – use in 1L vs second-line

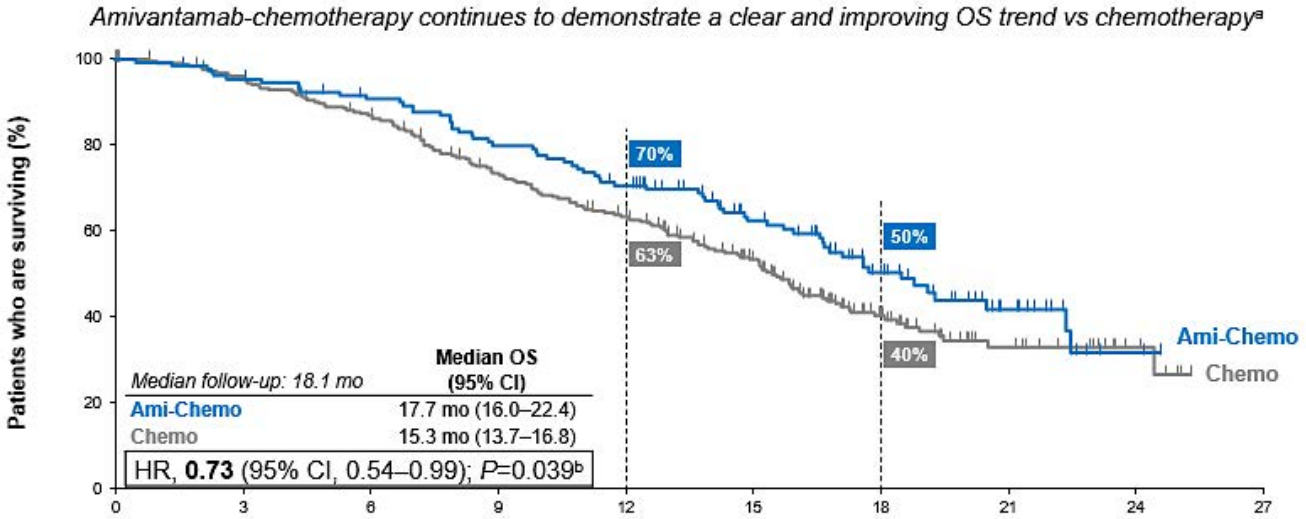
PFS: MARIPOSA 2

Primary Endpoint: Progression-free Survival by BICR



OS: MARIPOSA 2

Overall Survival



Chemotherapy with Amivantamab approved as a 2L therapy after osimertinib

MARIPOSA OS benefit – does it demonstrate survival benefit of amivantamab anytime vs no amivantamab?

MARIPOSA2 chemotherapy arm with n=3 (2%) with amivantamab in subsequent line of therapy – OS HR 0.73 (NS)

Perhaps better to reserve efficacious, but more toxic therapy for later-line, when other options are limited

Popat ESMO 2024
Passaro ESMO 2023

What do patients want?

Patient Perspective: Patients With EGFR+ NSCLC May Still Opt for Quality Over Quantity After FLAURA2

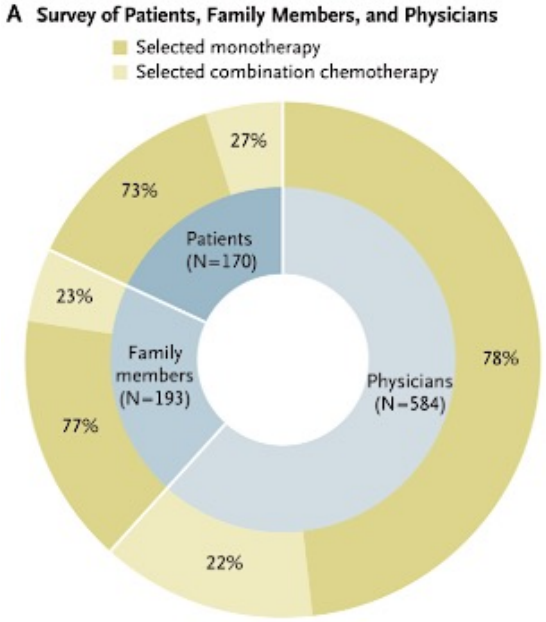
By: Ivy Elkins, MBA

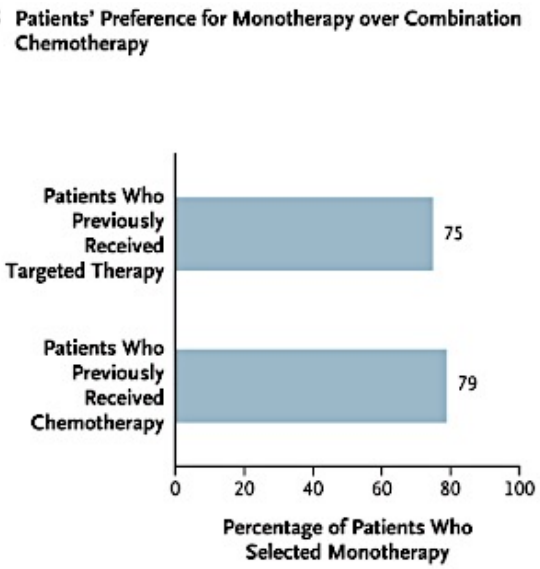
How will my husband keep working if he has to take care of me?
What will my quality of life on treatment be like?
Will I still be able to be an active participant in my family's lives?
How will this impact us financially?

I obviously wanted to extend my life as long as possible, but I also had concerns about what that life would be like. I think this is the true crux of the issue regarding combining chemotherapy and osimertinib upfront.
Patients want improved efficacy, but not necessarily at the expense of their quality of life. Combination treatment comes with increased toxicities, which make maintaining a normal life more difficult. Even grade 1 side effects such as diarrhea or nausea can make it difficult to hold a job or enjoy activities. Increased side effects also come with more doctor's appointments and additional medications to treat these issues. Many of these medications are not covered

Because of my ability to take an EGFR targeted therapy, I was able to actively raise my children, get involved in advocacy work for lung cancer research, and travel for both advocacy and personal reasons. I was able to limit my scans and visits to my oncologist to every 3 months as long as I was doing well on a treatment. And I was able to live my life fairly normally the rest of the time. I wasn't tied to an every-three-week chemotherapy cycle. I could "forget" (even though I never really forgot) that I had advanced lung cancer for more extended periods of time.

A possible additional 9 months of PFS would not have been enough for me to choose to start treatment with a combination of chemotherapy and osimertinib.





- Chinese Thoracic Oncology Group Survey – 170 pts, 193 family members, 584 MDs
- Told that combination therapy would delay recurrence by 9 months

FINANCIAL COST

Estimated monthly OOP costs $316-741

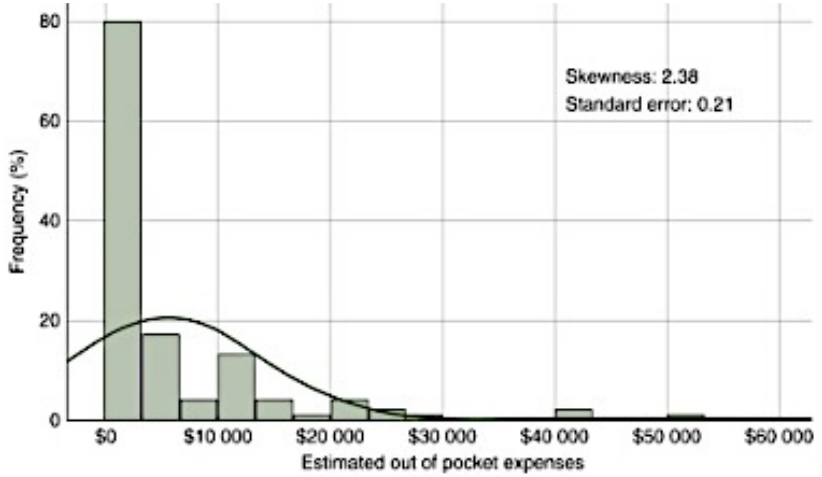
Only 54% of NCI-designated cancer centers have free parking

Lung cancer specifically:

At 6 mo follow up, 28% made sacrifices to pay for care (savings, borrowing)

18% could not afford basic necessities (gas, food, bills)

Estimated out of pocket costs for next 6 mo. for pts with lung cancer



Hazell Ann Onc 2020, Friedes JCO OP 2021, Wu NEJM 2023

Risk-adaptive treatment strategies

Should we treat these patients the same? Right now, we do.

What factors can we use to risk-adapt treatment?

76 yo, EGFR ex19 deletion only
Asymptomatic
Oligometastatic disease
Thoracic only disease
Slow growing
ctDNA neg
On osimertinib x 4 years

Median PFS on 1L osimertinib

↓

19 months

52yo, EGFR G719A, TP53, RB1
High symptom burden
Diffuse mets including brain, liver, bone
Large tumor burden
ctDNA pos at 3 weeks
Progression within 4 mo on osimertinib

How do we escalate treatment?

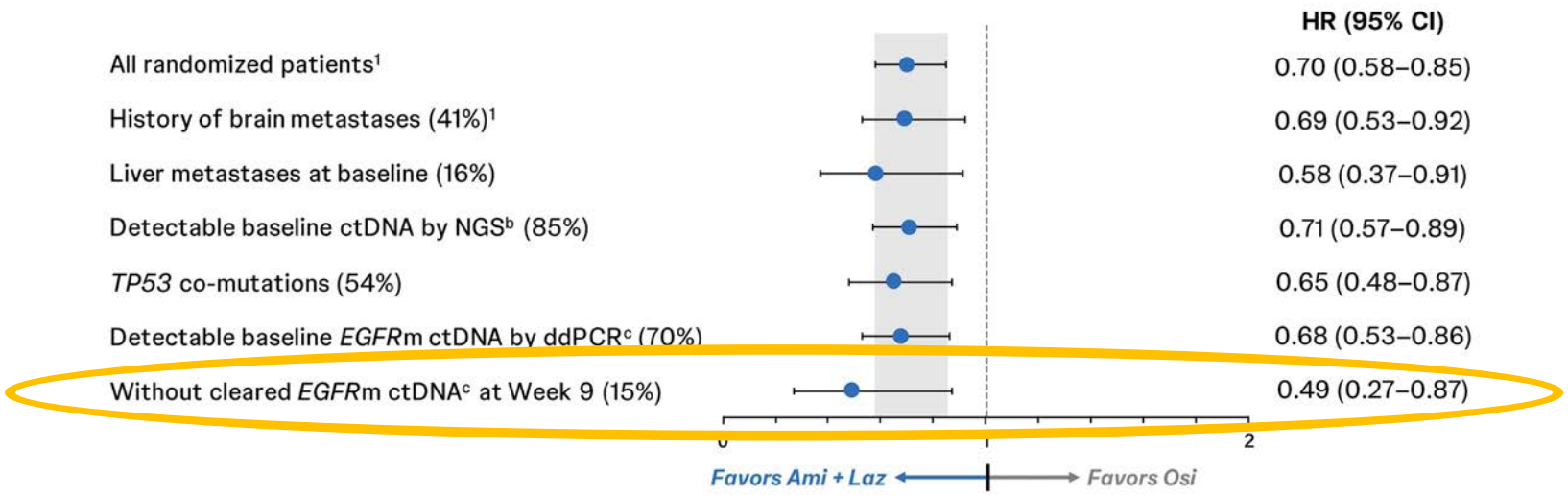
Who do we escalate?

At what timepoint should we escalate?

Risk-adaptive treatment strategies

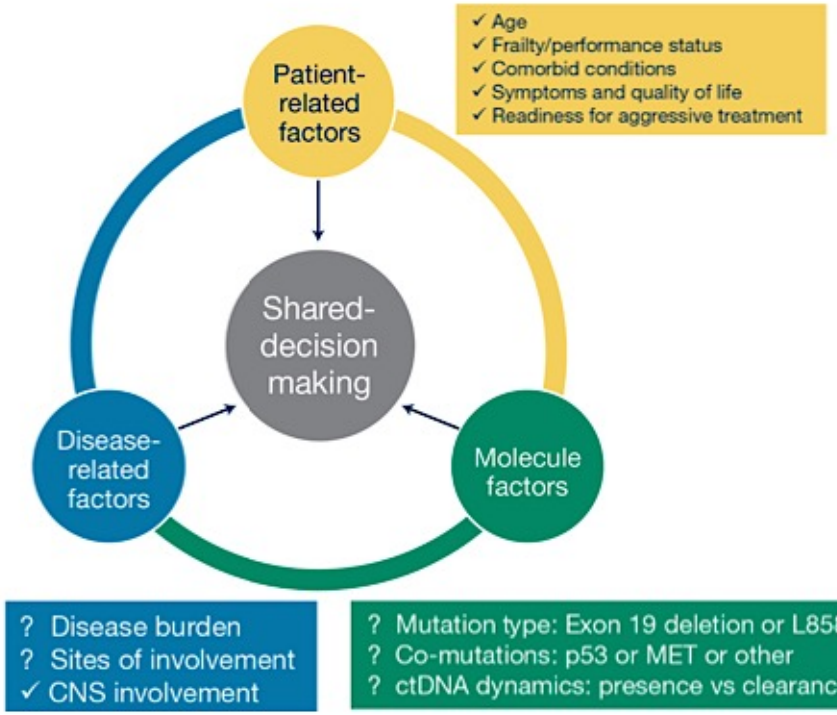
OS across subgroups		Osi + CTx (Events / patients)	Osi mono (Events / patients)	HR	95% CI
All patients	Stratified log-rank	100 / 279	126 / 278	0.75	0.57, 0.97
	Unadjusted Cox PH	100 / 279	126 / 278	0.75	0.58, 0.97
Sex	Male	45 / 106	55 / 109	0.76	0.51, 1.12
	Female	55 / 173	71 / 169	0.74	0.52, 1.05
Race	Chinese Asian	16 / 71	29 / 69	0.49	0.27, 0.91
	Non-Chinese Asian	50 / 107	48 / 107	1.04	0.70, 1.54
	Non-Asian	34 / 101	49 / 102	0.64	0.41, 0.99
EGFR mutation test method	Central	44 / 121	53 / 119	0.81	0.54, 1.20
	Local	56 / 158	73 / 159	0.71	0.50, 1.00
Age at screening	<65 years	52 / 174	73 / 166	0.63	0.44, 0.90
	≥65 years	48 / 105	53 / 112	0.97	0.65, 1.43
Smoking history	Yes	33 / 91	43 / 97	0.72	0.46, 1.13
	No	67 / 188	83 / 181	0.76	0.55, 1.05
EGFR mutation†	Ex19del	52 / 172	69 / 169	0.74	0.52, 1.06
	L858R	48 / 106	57 / 107	0.72	0.49, 1.06
WHO PS	0	30 / 101	36 / 102	0.82	0.51, 1.33
	1	70 / 178	90 / 176	0.71	0.52, 0.98
CNS status at baseline	Yes	44 / 116	62 / 110	0.59	0.40, 0.87
	No	56 / 163	64 / 168	0.89	0.62, 1.28

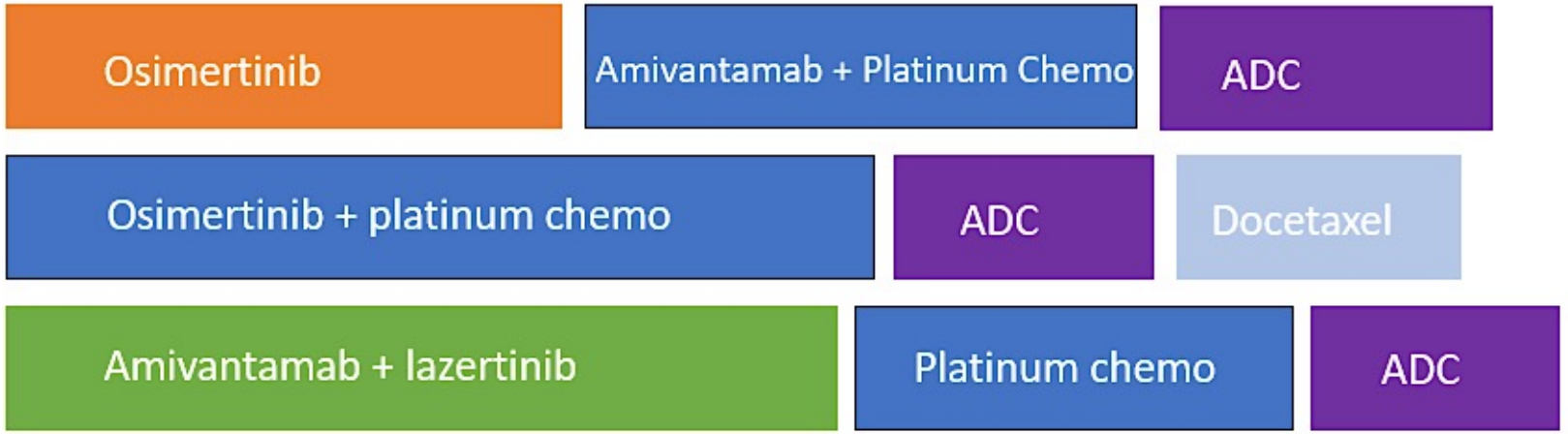
Propose that CNS mets and lack of ctDNA clearance may be reasonable risk-stratification biomarkers



Felip ASCO 2024, Janne WCLC 2023

No size fits all: shared decision making + risk stratification





Risk stratification will select pts who need the most aggressive treatment upfront.

For low-risk patients, optimizing QOL and sequencing therapies considering toxicity makes sense.

With clear OS benefit with combination therapy, can opt out of combination therapy for treatment de-escalation.

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for an otherwise healthy 65-year-old patient with nonsquamous mNSCLC with minimal disease burden and symptoms and an EGFR exon 19 deletion, and a PD-L1 tumor proportion score (TPS) of 0?

 Prof Girard	Amivantamab/lazertinib
 Dr Goldman	Osimertinib + chemotherapy
 Dr Jänne	Osimertinib
 Dr Ramalingam	Osimertinib
 Dr Sabari	Amivantamab/lazertinib
 Dr Yu	Osimertinib
 Dr Gadgeel	Osimertinib
 Dr Spira	Osimertinib

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for an otherwise healthy 65-year-old patient with symptomatic nonsquamous mNSCLC with significant tumor bulk and disease burden (excluding the brain) and an EGFR exon 19 deletion, and a PD-L1 tumor proportion score (TPS) of 0?

 Prof Girard	Amivantamab/lazertinib
 Dr Goldman	Amivantamab/lazertinib
 Dr Jänne	Osimertinib + chemotherapy
 Dr Ramalingam	Osimertinib + chemotherapy
 Dr Sabari	Amivantamab/lazertinib
 Dr Yu	Osimertinib + chemotherapy
 Dr Gadgeel	Amivantamab/lazertinib
 Dr Spira	Amivantamab/lazertinib

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for an otherwise healthy 85-year-old patient with symptomatic nonsquamous mNSCLC with significant tumor bulk and disease burden (excluding the brain) and an EGFR exon 19 deletion, and a PD-L1 tumor proportion score (TPS) of 0?

 Prof Girard	Osimertinib
 Dr Goldman	Osimertinib
 Dr Jänne	Osimertinib
 Dr Ramalingam	Osimertinib
 Dr Sabari	Osimertinib
 Dr Yu	Osimertinib
 Dr Gadgeel	Osimertinib
 Dr Spira	Osimertinib

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for an otherwise healthy 65-year-old patient with nonsquamous mNSCLC with several symptomatic small brain metastases and an EGFR exon 19 deletion, and a PD-L1 tumor proportion score (TPS) of 0?

 Prof Girard	Amivantamab/lazertinib
 Dr Goldman	Amivantamab/lazertinib
 Dr Jänne	Osimertinib + chemotherapy
 Dr Ramalingam	Osimertinib + chemotherapy
 Dr Sabari	Amivantamab/lazertinib
 Dr Yu	Osimertinib + chemotherapy
 Dr Gadgeel	Amivantamab/lazertinib
 Dr Spira	Osimertinib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for a 65-year-old patient with nonsquamous mNSCLC with an EGFR exon 19 deletion, loss of TP53 and RB1, and a PD-L1 TPS of 0?

 Prof Girard	Amivantamab/lazertinib
 Dr Goldman	Amivantamab/lazertinib
 Dr Jänne	Osimertinib + chemotherapy
 Dr Ramalingam	Osimertinib + chemotherapy
 Dr Sabari	Amivantamab/lazertinib
 Dr Yu	Osimertinib + chemotherapy
 Dr Gadgeel	Amivantamab/lazertinib
 Dr Spira	Amivantamab/lazertinib

RTP RESEARCH TO PRACTICE

Regulatory and reimbursement issues aside, what treatment would you recommend for a patient with locally advanced unresectable nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 0 who received chemoradiation therapy followed by 2 years of osimertinib and experienced disease progression as described?

	9 months	2.5 years
 Prof Girard	Amivantamab + chemotherapy or ivonescimab	Amivantamab/lazertinib
 Dr Goldman	Amivantamab/lazertinib	Amivantamab/lazertinib
 Dr Jänne	Osimertinib	Osimertinib
 Dr Ramalingam	Osimertinib	Osimertinib
 Dr Sabari	Amivantamab/lazertinib	Amivantamab/lazertinib
 Dr Yu	Amivantamab/lazertinib	Osimertinib + chemotherapy
 Dr Gadgeel	Amivantamab/lazertinib	Amivantamab/lazertinib
 Dr Spira	Amivantamab/lazertinib	Amivantamab/lazertinib

Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

RTP RESEARCH TO PRACTICE

EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC: Strategies to Facilitate Delivery of Recently Approved Agents

Joshua Sabari, MD
NYU Langone Health
New York, NY

Acquired Resistance

EGFR mutant NSCLC

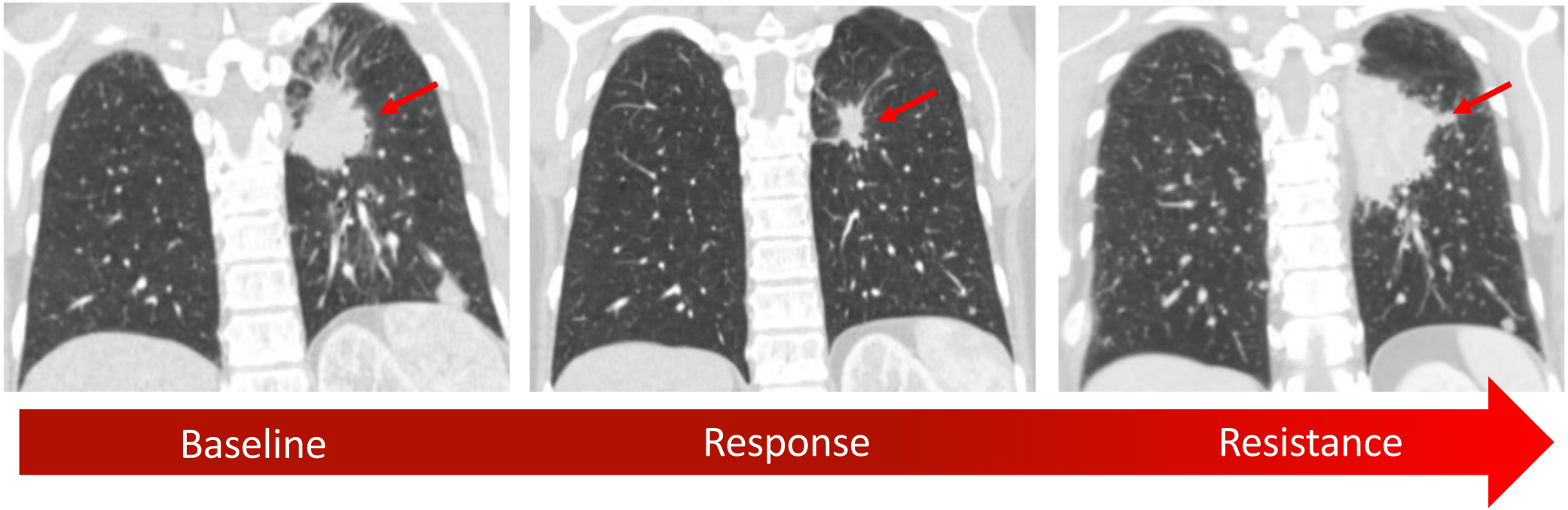
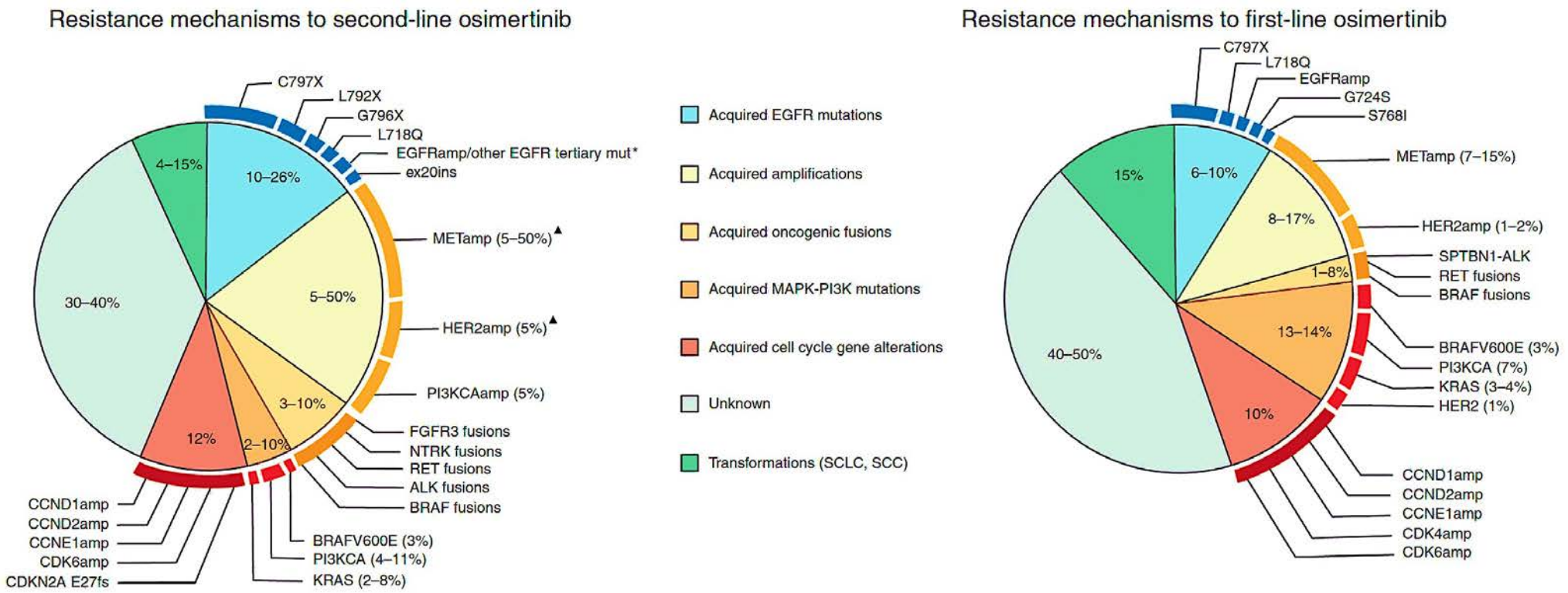


Image Courtesy of Dr. Joshua Sabari, NYU, New York, NY

Resistance Mechanisms to EGFR TKI

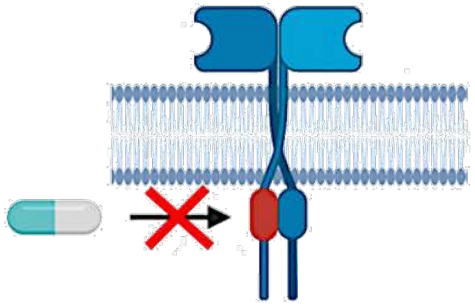


- ***EGFR* T790M is** the predominant mechanism with 1st and 2nd generation TKIs
- Acquired *EGFR* or *HER2* mutations, and *EGFR, HER2*, or *MET* amplification are common with first-line osimertinib
  - ✓ Other mechanisms include acquired cell cycle gene alterations, MAPK-PIK3CA alterations (*BRAF V600E, KRAS*), and acquired oncogenic fusions (*ALK, RET*)

Westover D, et al. *Ann Oncol*. 2018;29(Supp 1):i10–i19; Leonetti A, et al. *Br J Cancer*. 2019;121:725–737.

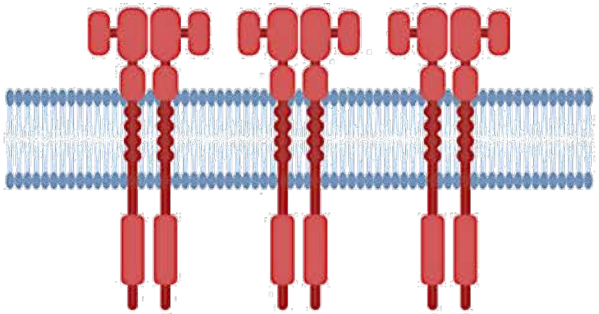
Mechanisms of Resistance to TKI

Mutations in the Drug Target



Impact drug binding

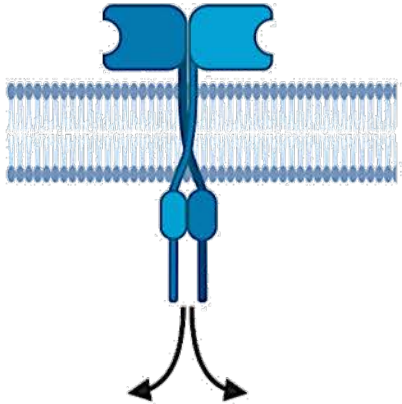
Bypass Signaling

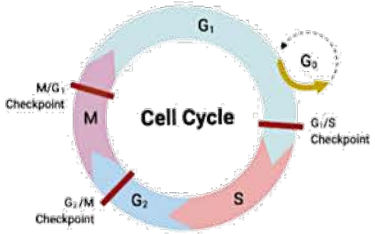


Oncogene Amplification

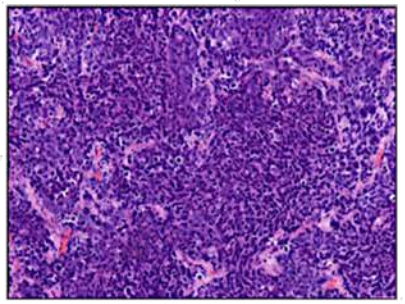
Oncogene Rearrangement

Mutations in Downstream Effectors





State Transformation

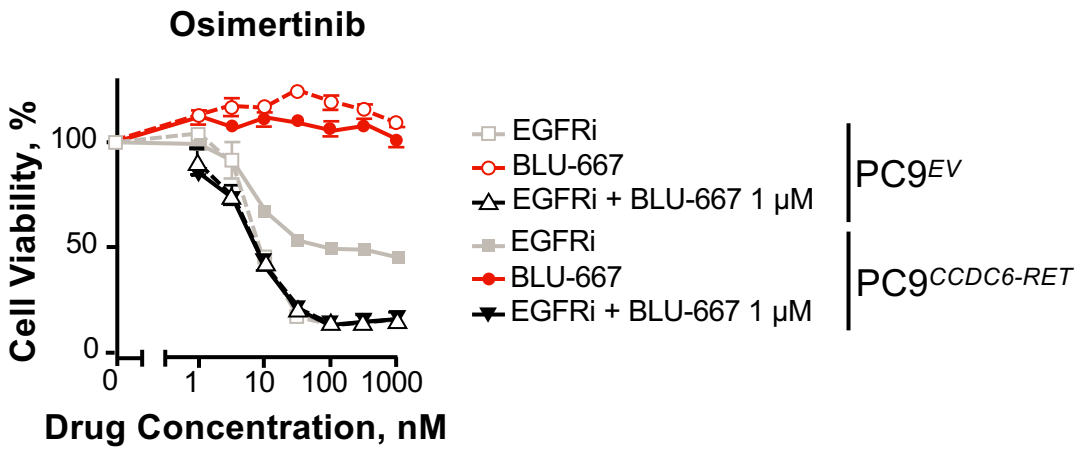


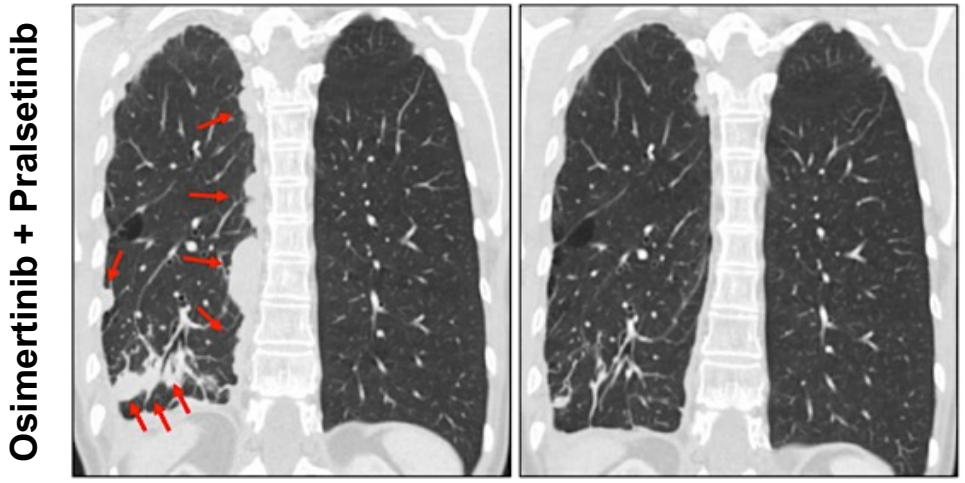
Small cell lung cancer
Squamous cell lung cancer

Westover D, et al. *Ann Oncol*. 2018;29(Supp 1):i10–i19; Leonetti A, et al. *Br J Cancer*. 2019;121:725–737.

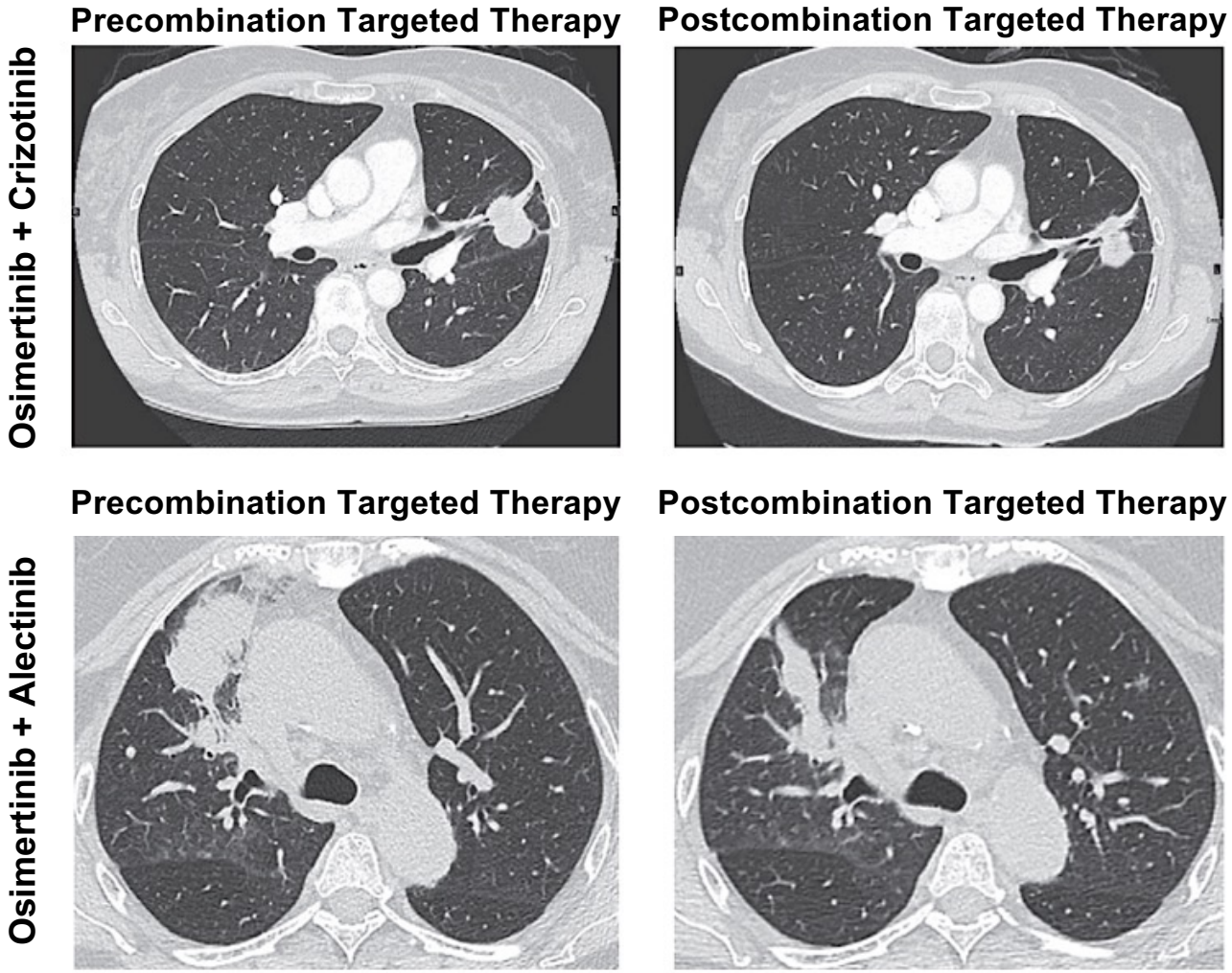
Targeting Acquired *RET*, *ALK*, and Other Fusions

Acquired *RET* Fusions





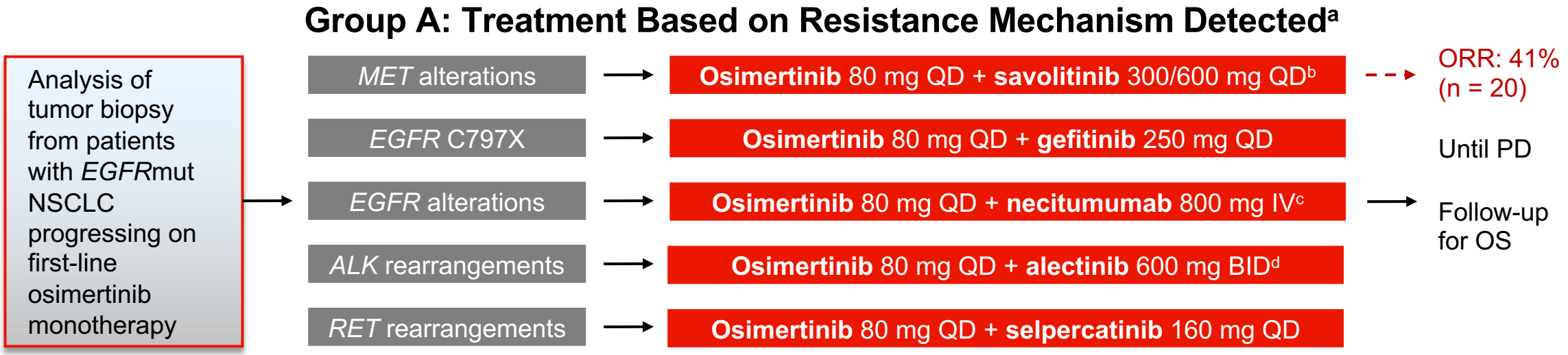
Acquired *ALK* Fusions



1. Piotrowska Z et al. *Cancer Discov*. 2018;8:1529-1539. 2. Offin M et al. *JCO Precis Oncol*. 2018;2:PO.18.00126.

ORCHARD: Biomarker-Directed Study in Advanced *EGFR*mut NSCLC Progressing on 1L Osimertinib

- Open-label, multicenter, multidrug, biomarker-directed phase 2 platform trial



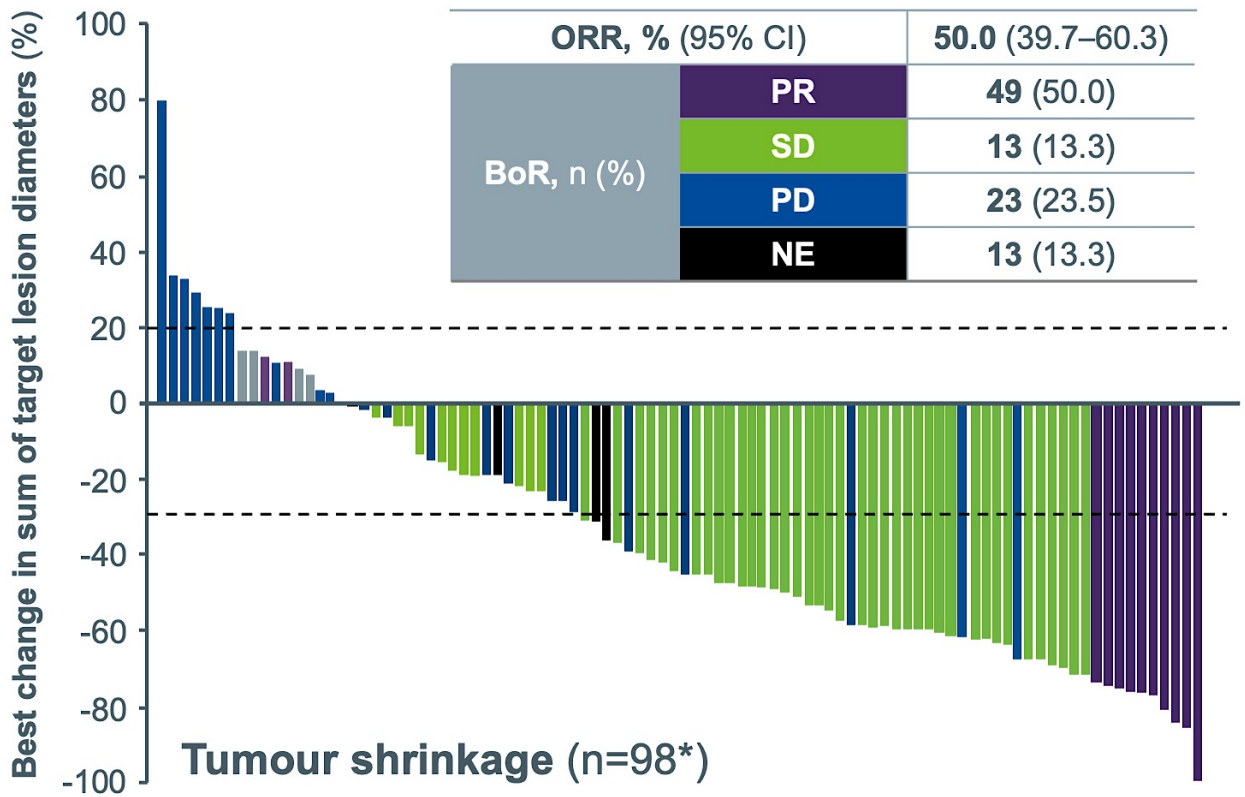
- **Group B**: Nonmatched arm for patients without a detectable resistance mechanism will sequentially be assigned to durvalumab + chemotherapy > osimertinib + necitumumab > others
- **Group C**: Observational arm for patients whose optimal treatment falls outside of group A or B (eg, transformation to SCLC)
- Patients with failed baseline NGS results go directly to follow-up

[a] Future arms may be added. [b] Savolitinib dose 300 mg QD for all new patients. [c] Day 1 and 8 of 3 week cycle. [d] 300 mg BID in Japan.

1. Cho BC et al. *J Thorac Oncol*. 2021;16:S598. 2. Yu H et al. *Clin Lung Cancer*. 2021;22:601. 3. Yu H et al. ESMO 2021. Abstract 1239P.

INSIGHT 2: Tepotinib + osimertinib *MET*amp post-osimertinib

ORR by IRC in patients with TBx FISH *MET*amp (n=98)



ORR, % (95% CI)		50.0 (39.7–60.3)
BoR, n (%)	PR	49 (50.0)
	SD	13 (13.3)
	PD	23 (23.5)
	NE	13 (13.3)

Patients with TBx FISH *MET*amp (n=98)	
ORR, % (95% CI)	**50.0** (39.7–60.3)
mDoR, months (95% CI)	**8.5** (6.1–NE)
mPFS, months (95% CI)	**5.6** (4.2–8.1)
mOS, months (95% CI)	**17.8** (11.1–NE)
Patients with LBx NGS *MET*amp† (n=31)	
ORR, % (95% CI)	**54.8** (36.0–72.7)
mDoR, months (95% CI)	**5.7** (2.9–15.4)
mPFS, months (95% CI)	**5.5** (2.7–7.2)
mOS, months (95% CI)	**13.7** (9.6–NE)

Better outcomes were observed when there were no co-occurring mechanisms of osimertinib resistance

Kim TM, et al. Presented at WCLC 2023: OA21.05.

1st Line MARIPOSA Study Design

Paired blood samples were collected at baseline and EOT[a] for analysis of detectable ctDNA by NGS[b]

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

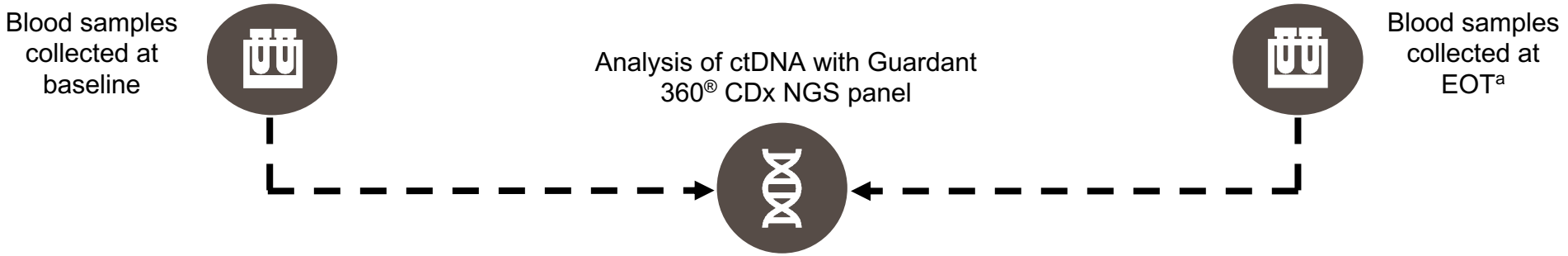
Focus of this presentation

2:2:1 Randomization (N=1074)[c]

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

Follow-up

RECIST v1.1 assessments every 8 weeks (±1 week) for the first 30 months, then every 12 weeks (±1 week) until disease progression is confirmed by BICR



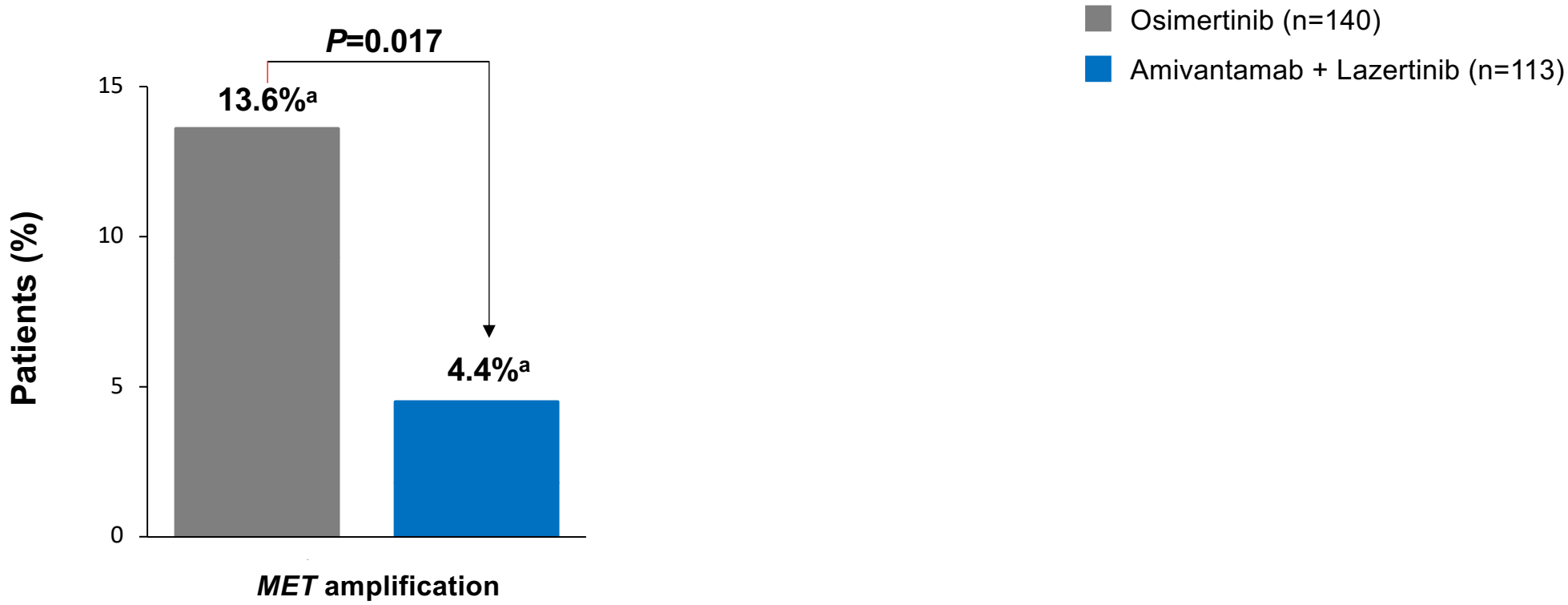
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022. Last EOT sample was collected Feb 2024.

[a]Defined as at disease progression/treatment discontinuation or within 90 days of discontinuation. [b]Using Guardant 360® companion diagnostics. [c]Stratification factors included *EGFR* mutation type (Ex19del or L858R), Asian race (yes or no), and history of brain metastases (yes or no). [d]Lazertinib monotherapy arm was included to assess the contribution of components.

ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion; NGS, next-generation sequencing.

MET and *EGFR*-based Resistance Mechanisms

Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib



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

[a]9.3% of patients in the osimertinib arm had focal *MET* amplifications vs 1.8% in the amivantamab + lazertinib arm.

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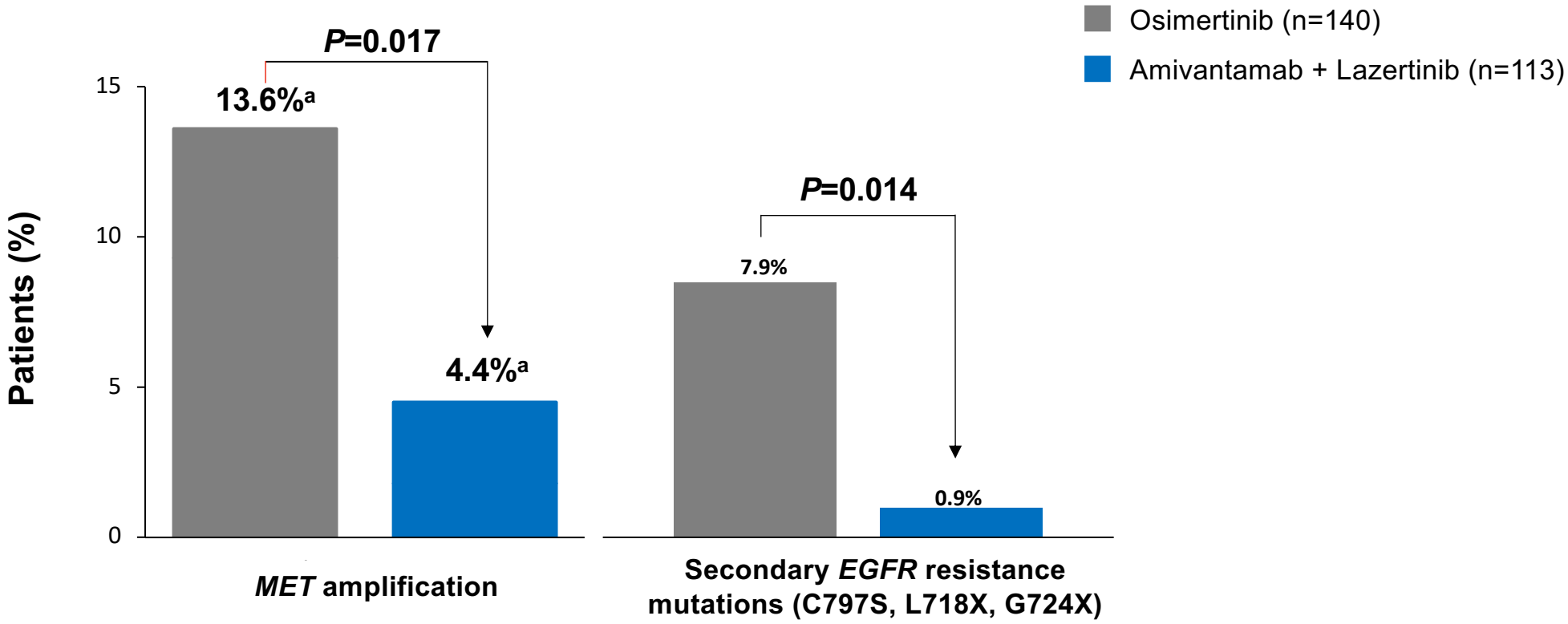

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Biomarker agnostic approaches

Phase III MARIPOSA 2: Study Design

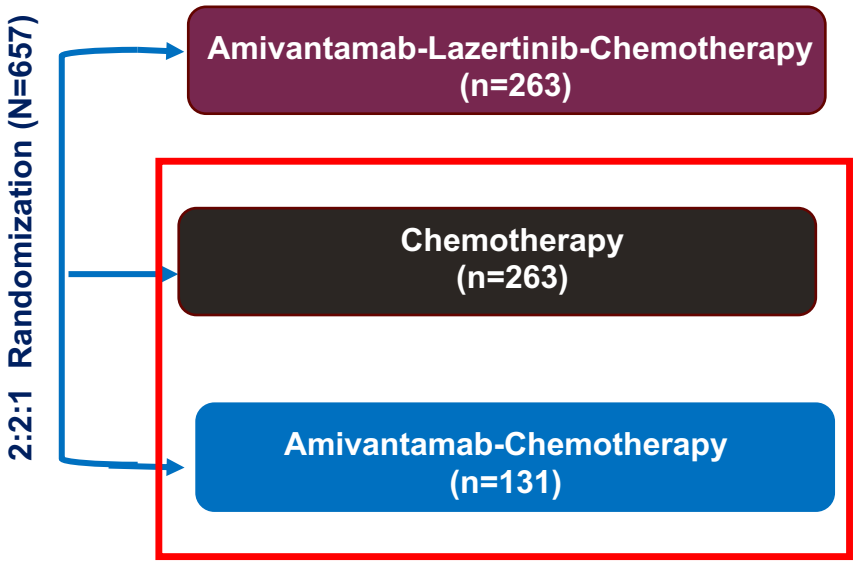
Serial Brain MRIs Were Required for all Patients[a]

Key Eligibility Criteria

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

Stratification Factors

- Osimertinib line of therapy (first vs second)
- Asian race (yes or no)
- History of brain metastases (yes or no)



Dosing (in 21 –Day Cycles)
Amivantamab: 1400 mg (1750 mg if ≥80 kg) x first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) Q3W starting at Cycle 3 (Week 7)
Lazertinib: 240 mg QD starting after completion of carboplatin[b]
Chemotherapy Administered at the Beginning of Every Cycle
- **Carboplatin: AUC5 for the First 4 Cycles**
- **Pemetrexed: 500 mg/m^2 Until Disease Progression**

Dual Primary Endpoint of PFS[c] by BICR per RECIST v1.1

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

Secondary Endpoints:

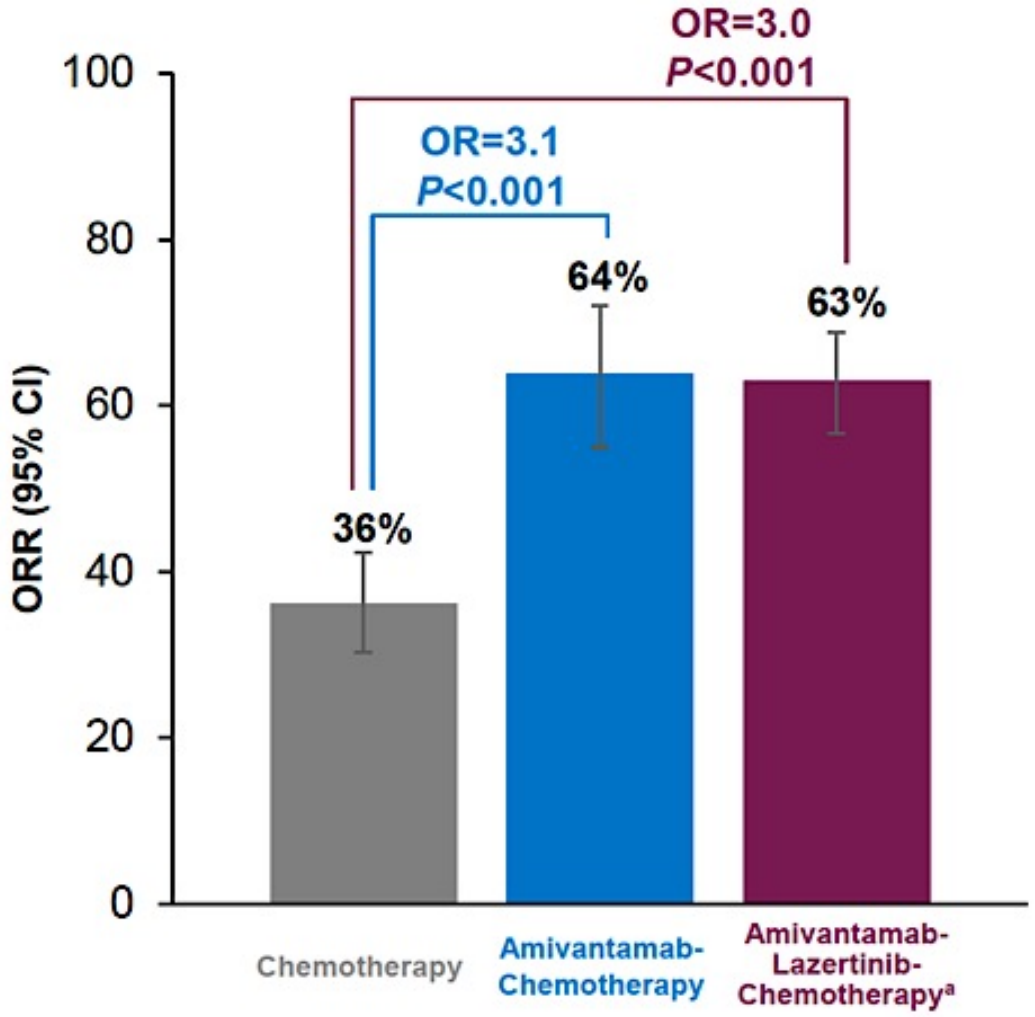
- Objective Response Rate (ORR)[c]
- Duration of Response (DoR)
- Overall Survival (OS)[c]
- Intracranial PFS
- Time to Subsequent Therapy[d]
- PFS After First Subsequent Therapy (PFS2)[d]
- Symptomatic PFS[d]
- Safety

[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before November 7, 2022, initiated lazertinib on the first day of Cycle 1
[c]Key statistical assumptions: 600 patients with 350 events across all 3 arms would provide approximately 83% and 93% power for amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy, respectively, vs chemotherapy to detect a HR of 0.65 using a log-rank test, with an overall two-sided alpha of 0.05

NCT: 04988295

Passaro A, et al. *Ann Oncol*. 2024;35(1):77-90.

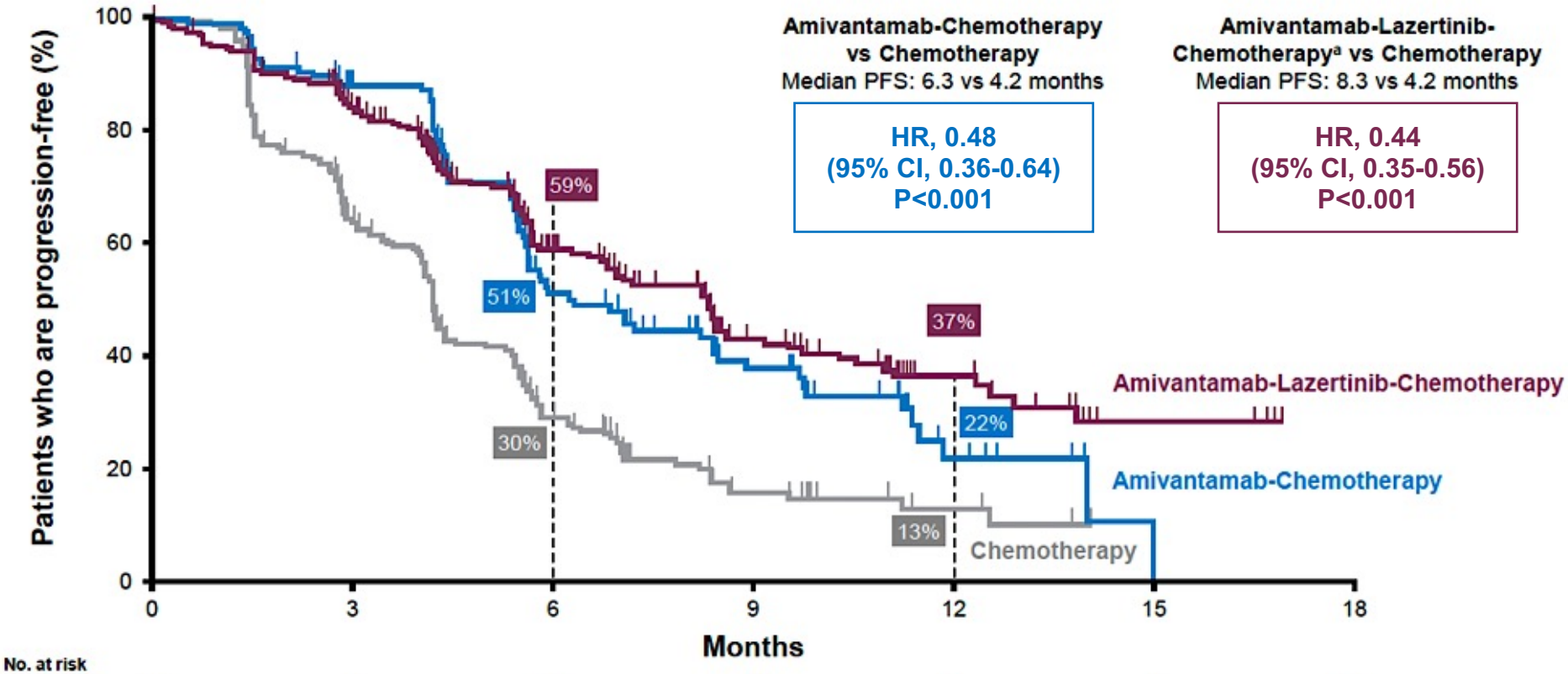
MARIPOSA 2: Objective Response Rate and Duration of Response by BICR



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

Passaro A, et al. *Ann Oncol*. 2024;35(1):77-90.

MARIPOSA 2: Progression-Free Survival by BICR



Amivantamab-Chemotherapy vs Chemotherapy
Median PFS: 6.3 vs 4.2 months

HR, 0.48
(95% CI, 0.36-0.64)
P<0.001

Amivantamab-Lazertinib-Chemotherapy[a] vs Chemotherapy
Median PFS: 8.3 vs 4.2 months

HR, 0.44
(95% CI, 0.35-0.56)
P<0.001

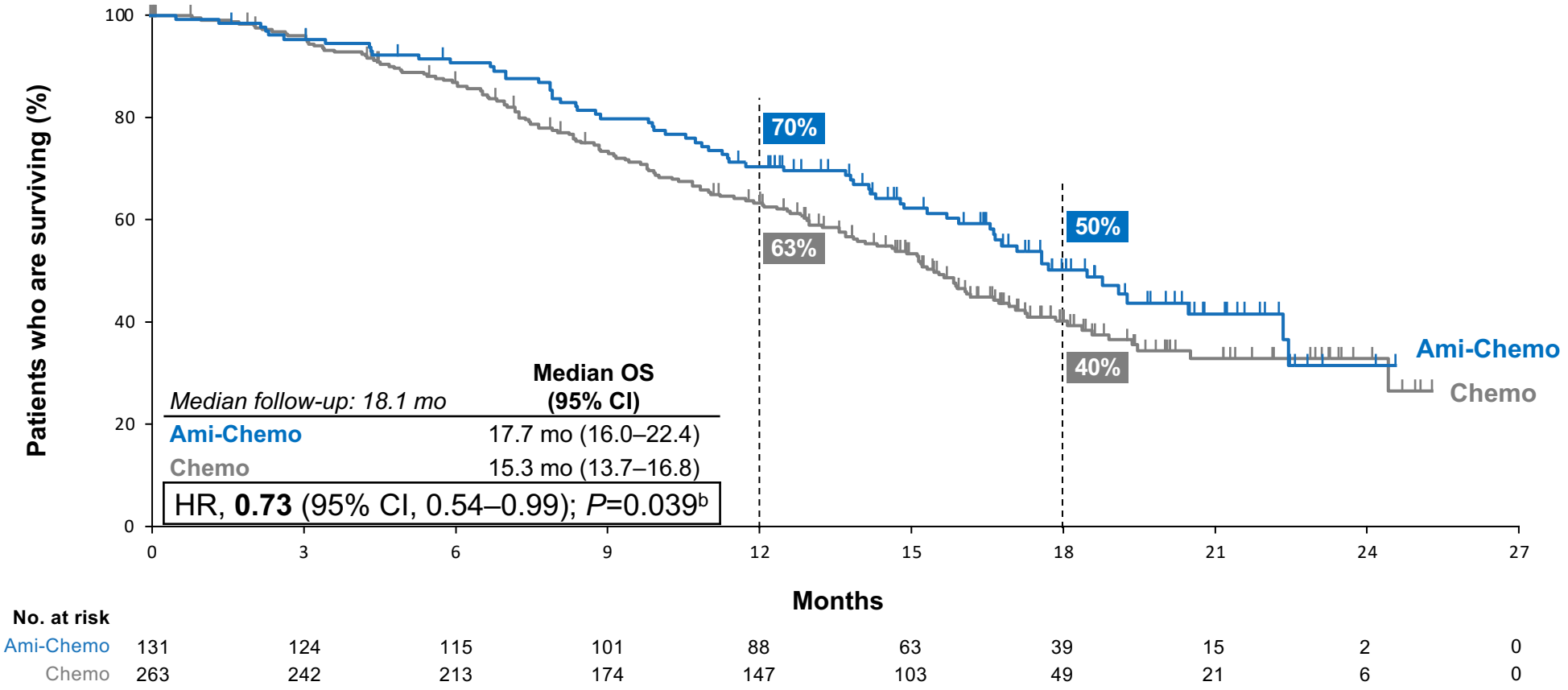
No. at risk							
Amivantamab-Chemotherapy	131	99	49	27	7	0	0
Amivantamab-Lazertinib-Chemotherapy	263	194	104	52	21	4	0
Chemotherapy	263	135	49	17	6	0	0

Consistent PFS Benefit by Investigator:
HR, 0.41 (8.2 vs 4.2 months; P<0.001[b])
HR, 0.38 (8.3 vs 4.2 months; P<0.001[b])

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received.
[b]Normal P-value: endpoint not part of hierarchal hypothesis testing.
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
Median follow-up: 8.7 months..
Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15

MARIPOSA 2: Overall Survival

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



No. at risk										
Ami-Chemo	131	124	115	101	88	63	39	15	2	0
Chemo	263	242	213	174	147	103	49	21	6	0

18-month landmark for OS was 50% for amivantamab-chemotherapy vs 40% for chemotherapy

[a]OS benefit of amivantamab-chemotherapy vs chemotherapy was generally consistent among pre-defined subgroups. [b]*P*-value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). OS was evaluated at a 2-sided alpha of 0.0142.

Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Popat.S, et al. Presented at the European Society for Medical Oncology 2024 Meeting.

MARIPOSA-2: Summary of Adverse Events

	Amivantamab + Chemotherapy (n=130)	Chemotherapy (n=243)
Treatment duration, median (range)	6.3 months (0-14.7)	3.7 months (0-15.9)
No. of chemotherapy cycles, median (range)		
Carboplatin	4 (1-4)	4 (1-5)
Pemetrexed	9 (1-22)	6 (1-23)

TEAE, n (%)	Amivantamab + Chemotherapy (n=130)	Chemotherapy (n=243)
Any AEs	130 (100)	227 (93)
Grade ≥3 AEs	94 (72)	117 (48)
Serious AEs	42 (32)	49 (20)
AEs leading to Death	3 (2)	3 (1)
Any AE leading to treatment:		
Interruption of any agent	84 (65)	81 (33)
Reductions of any agent	53 (41)	37 (15)
Discontinuations of any agent	24 (18)	9 (4)
Discontinuations of all agents due to AE	14 (11)	10 (4)

Passaro A, et al. Presented at the European Society for Medical Oncology 2023 Meeting. 20-24 October 2023. Madrid, Spain. Abstract LBA15.

PALOMA-3: Phase 3 Study Design

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

PALOMA-3 (ClinicalTrials.gov Identifier: NCT05388669) enrollment period: August 2022 to October 2023; data cutoff: 03-Jan-2024.

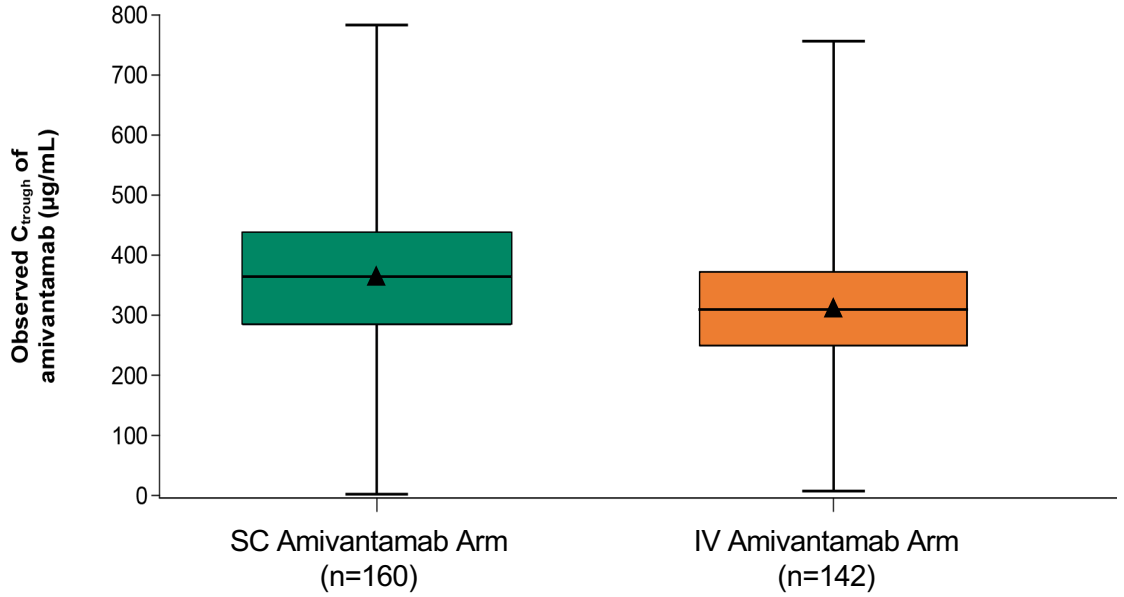
[a]SC amivantamab was co-formulated with rHuPH20 at a concentration of 160 mg/mL. [b]C1 for IV: Days 1 to 2 (Day 2 applies to IV split dose only [350 mg on Day 1 and the remainder on Day 2]), 8, 15, and 22; C1 for SC: Days 1, 8 , 15, and 22; after C1 for all: Days 1 and 15 (28-day cycles). [c]For calculating primary and key secondary outcomes, we estimated that a sample size of 400 patients would provide >95% power for a 1-sided alpha of 0.05 allocated to each of the co-primary endpoints and 80% power with a 1-sided alpha of 0.025 allocated to ORR. A hierarchical testing approach at a 2-sided alpha of 0.05 was used for the co-primary endpoints (noninferiority), followed by ORR (noninferiority) and PFS (superiority), with a combined 2-sided alpha of 0.05. [d]Two definitions of the same endpoint were used as per regional health authority guidance. [e]Measured between C2D1 and C2D15. [f]Assessed by modified TASQ.

AUC, area under the concentration-time curve; C, Cycle; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; rHuPH20, hyaluronidase; SC, subcutaneous; TASQ, Therapy Administration Satisfaction Questionnaire.

Co-primary PK Endpoints Met Noninferiority Criteria

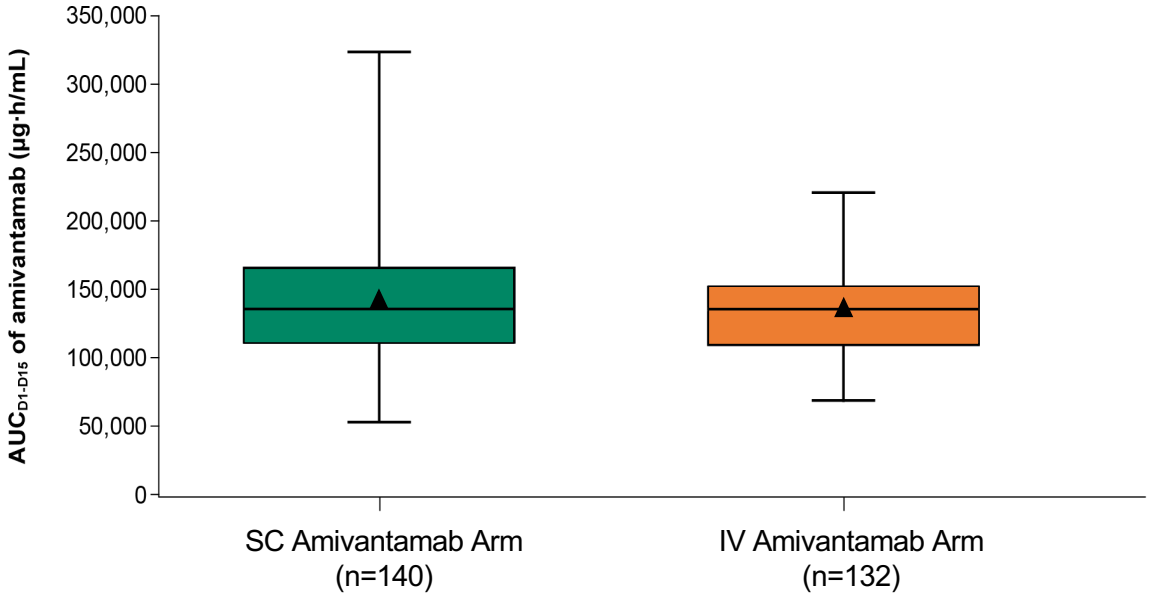
C_{trough} at C2D1

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



C2 $AUC_{D1\text{-}D15}$

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



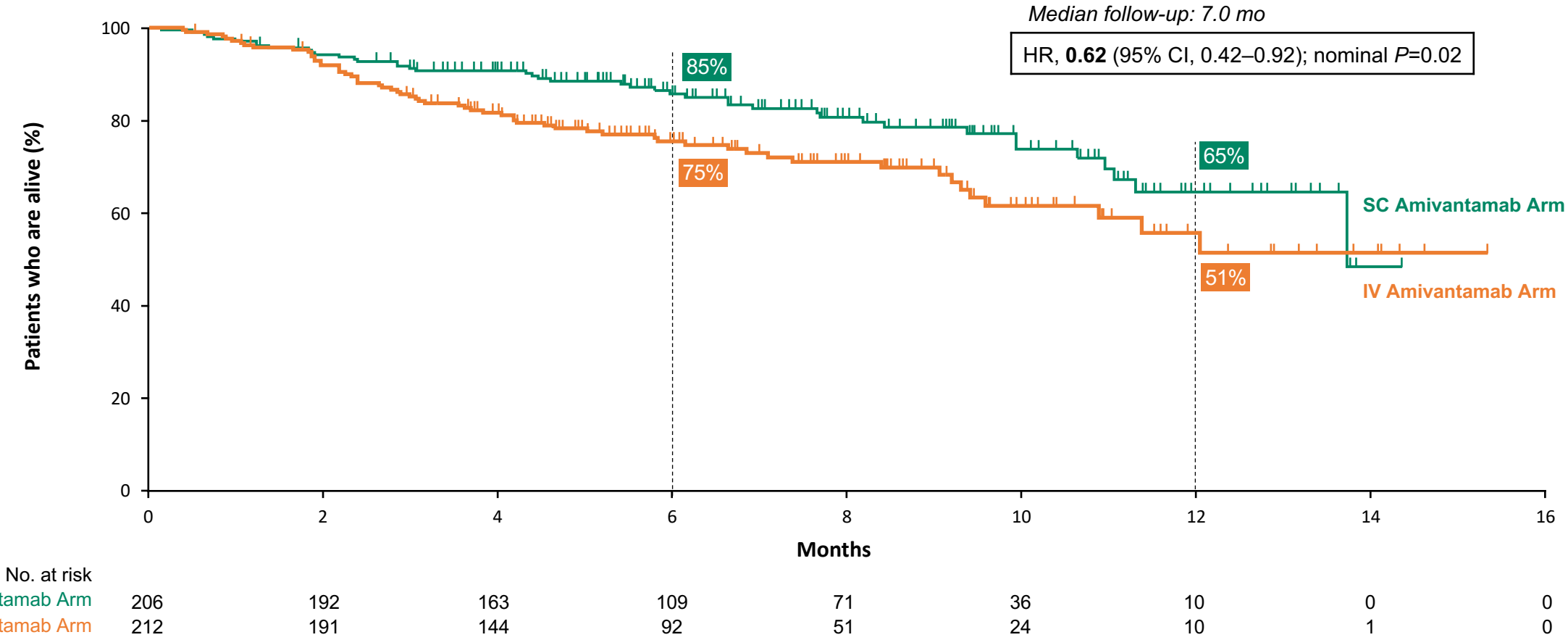
- Geometric mean ratio for C_{trough} at steady state (C4D1) was 1.43 (90% CI, 1.27–1.61)

Note: The pharmacokinetic analysis for primary endpoints included all patients who received all doses without dose modification and provided the required PK samples through the final required PK sample relevant to the endpoint. The upper and lower ends of the boxes indicate the 25th and 75th quartiles, the triangles indicate the means, the horizontal lines within the boxes indicate the medians, and the error bars indicate 95% CIs.
AUC, area under the concentration-time curve; C, Cycle; CI, confidence interval; C_{trough}, observed serum concentration of amivantamab at steady state; D, Day; GMR, geometric mean ratio; IV, intravenous; PK, pharmacokinetic; SC, subcutaneous.

NB Leighl J Clin Oncol 2024

Overall Survival

There was an OS benefit associated with SC amivantamab, with an HR of 0.62 compared to the IV amivantamab arm[a]



Note: The efficacy population included all the patients who had undergone randomization. [a]There were 43 deaths in the SC amivantamab arm and 62 deaths in the IV amivantamab arm. Nominal *P* value was calculated from a log-rank test stratified by history of brain metastases, Asian race, *EGFR* mutation type (Ex19del or L858R), and last line of therapy (osimertinib or platinum-based therapy); the prespecified endpoint was exploratory and not part of hierarchical hypothesis testing.
CI, confidence interval; *EGFR*, epidermal growth factor receptor; Ex19del, Exon 19 deletion; HR, hazard ratio; IV, intravenous; mo, months; OS, overall survival; SC, subcutaneous.

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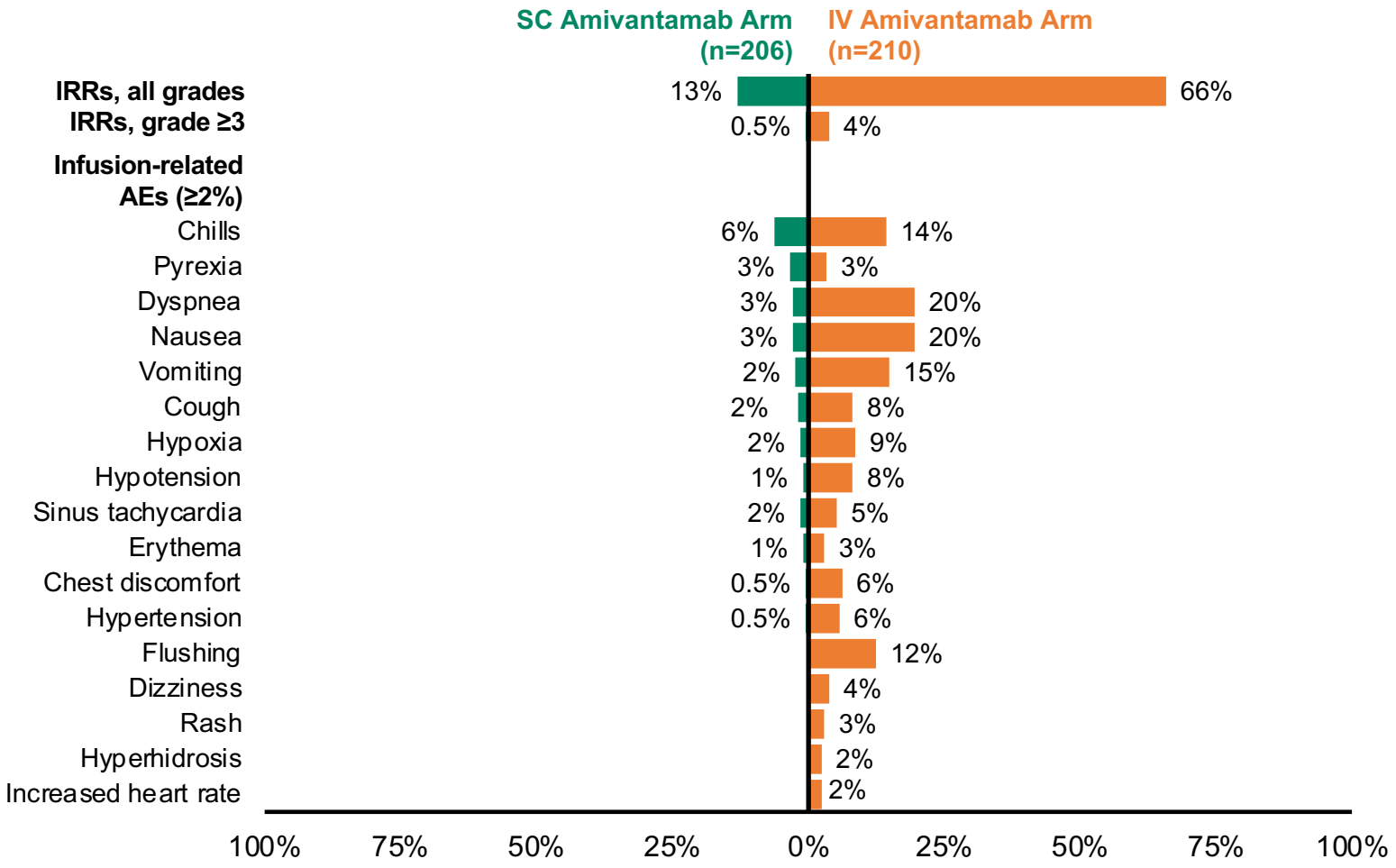
Incidence of IRR-related Symptoms



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

Note: The safety population included all the patients who had undergone randomization and received ≥1 dose of any trial treatment.
AE, adverse event; IRR, infusion-related reaction; IV, intravenous; SC, subcutaneous.

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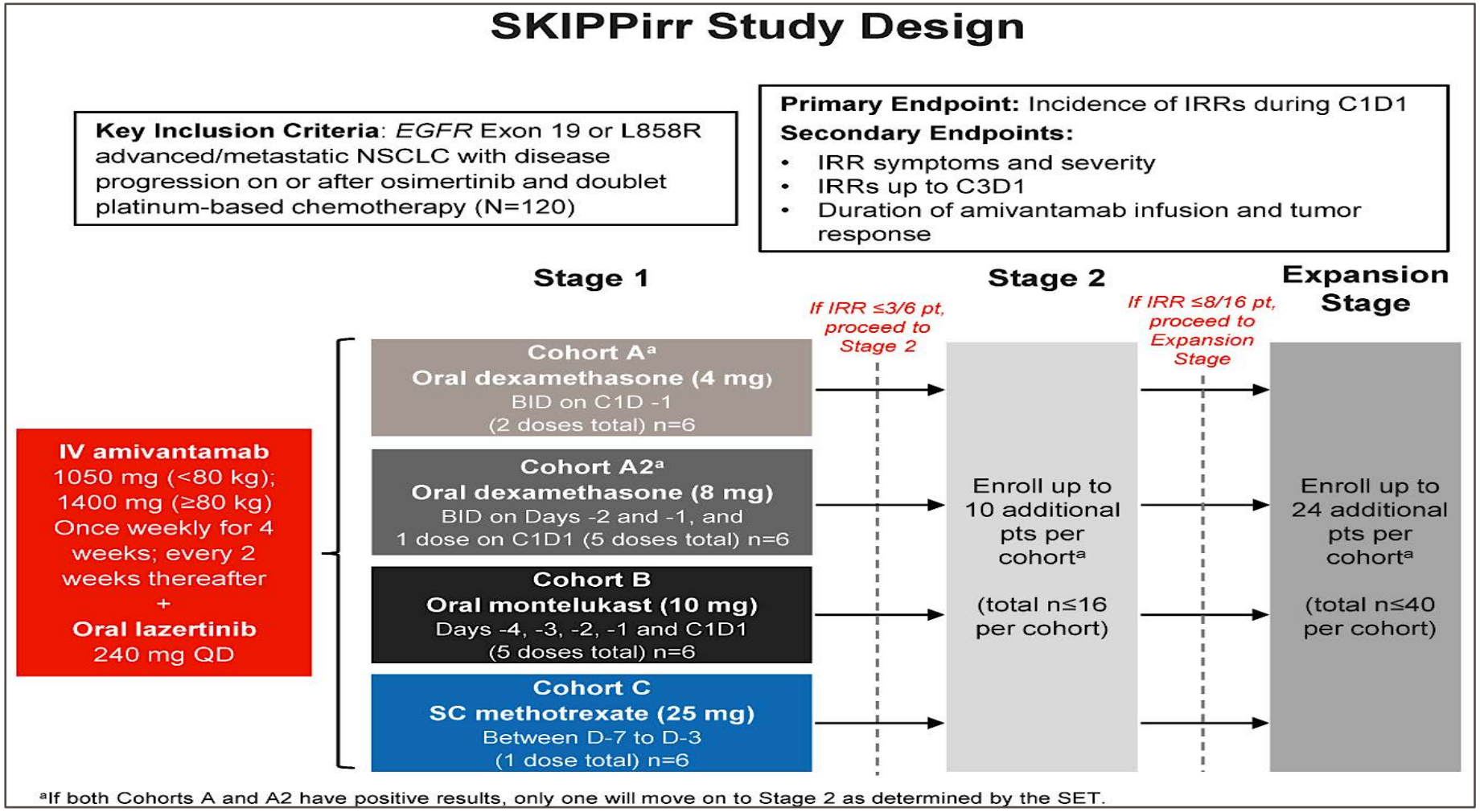
Can we prevent infusion related reactions? SKIPPirr

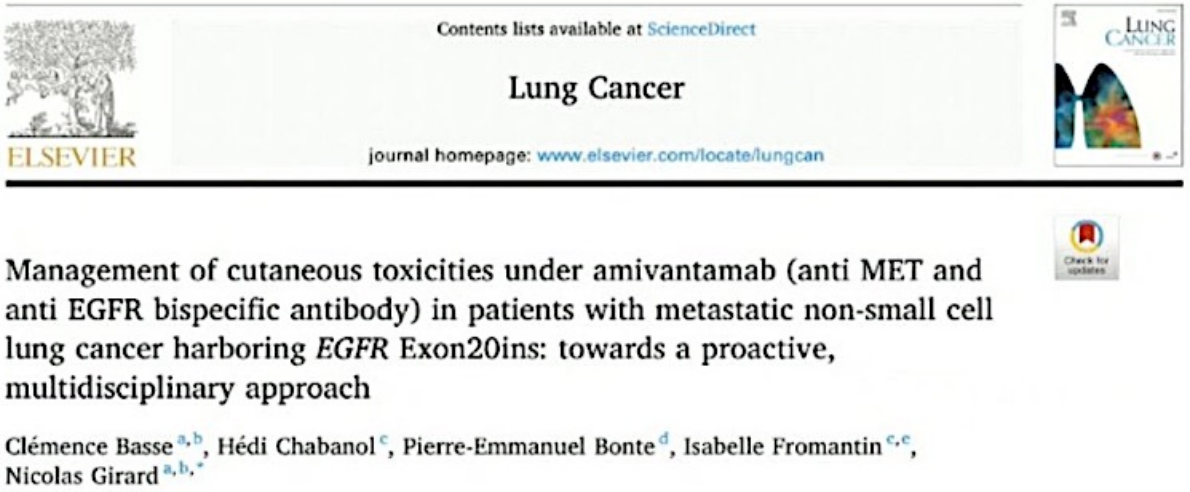


Prophylaxis with 8mg oral dexamethasone resulted in reduction in IRR compared to historical data

Lopes, G et al Abstract MA12.08 WCLC2024

Cocoon Trial

Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGFR)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib (COCOON)



Contents lists available at ScienceDirect

Lung Cancer

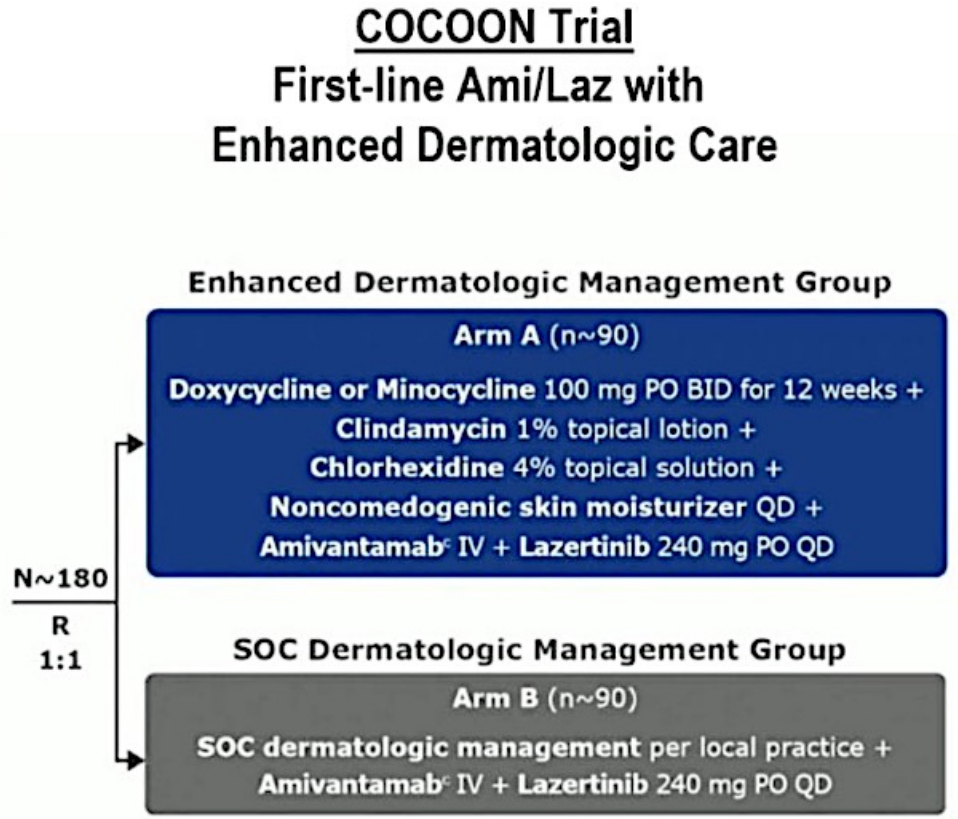
journal homepage: www.elsevier.com/locate/lungcan

Management of cutaneous toxicities under amivantamab (anti MET and anti EGFR bispecific antibody) in patients with metastatic non-small cell lung cancer harboring *EGFR* Exon20ins: towards a proactive, multidisciplinary approach

Clémence Basse[a,b], Hédi Chabanol[c], Pierre-Emmanuel Bonte[d], Isabelle Fromantin[c,e], Nicolas Girard[a,b,*]

Key Points:

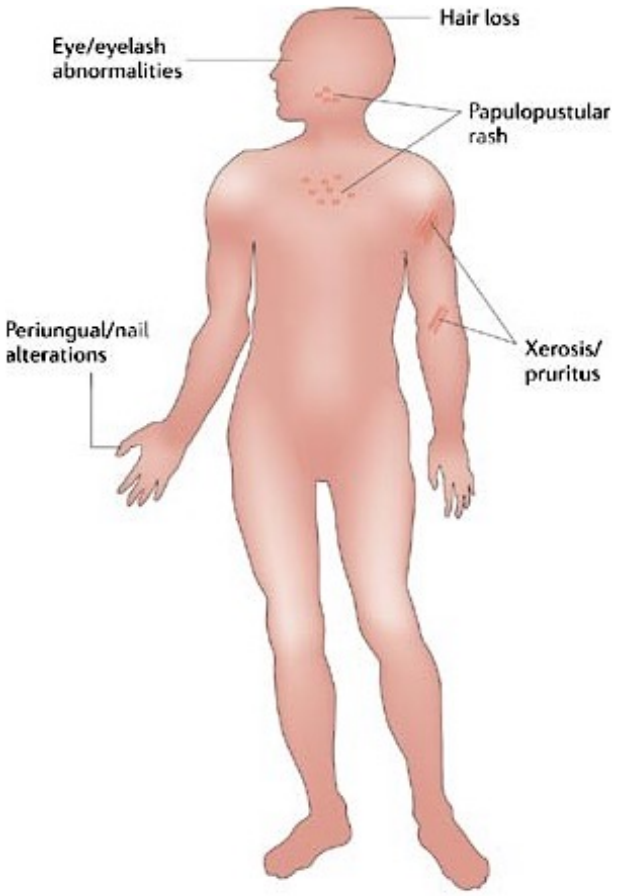
- Prophylactic tetracycline antibiotics at the start of treatment
- Early introduction of moisturizers and topical corticosteroids
- Consider treatment interruption if grade 2+
- Multi-disciplinary care with dermatology

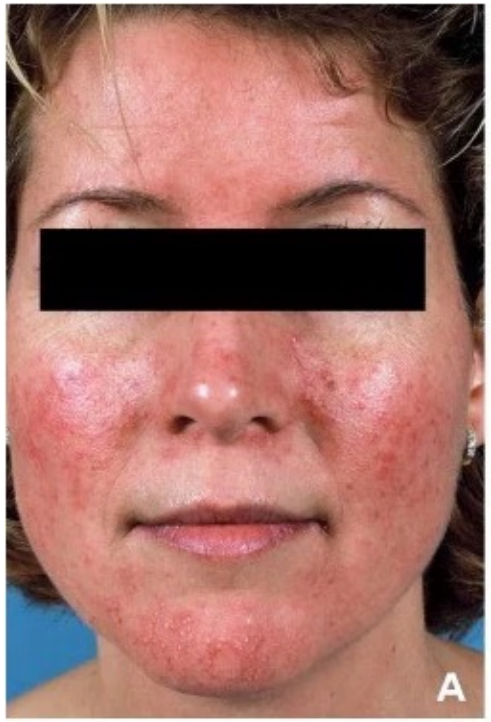


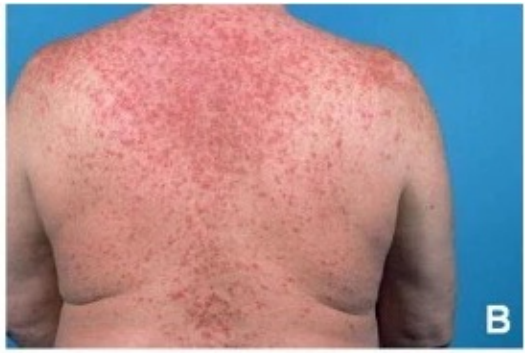
Piotrowska Z ELCC 2024; Basse C et al Lung Cancer 2022; Cocoon trial NCT06120140

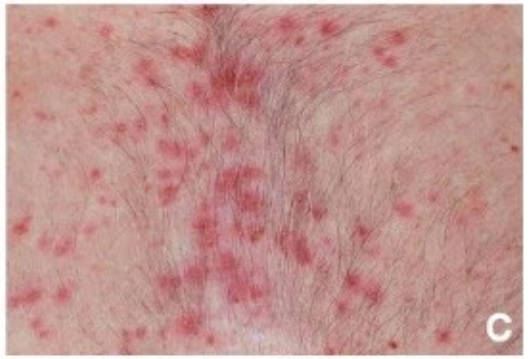
EGFR inhibition mediated cutaneous toxicities

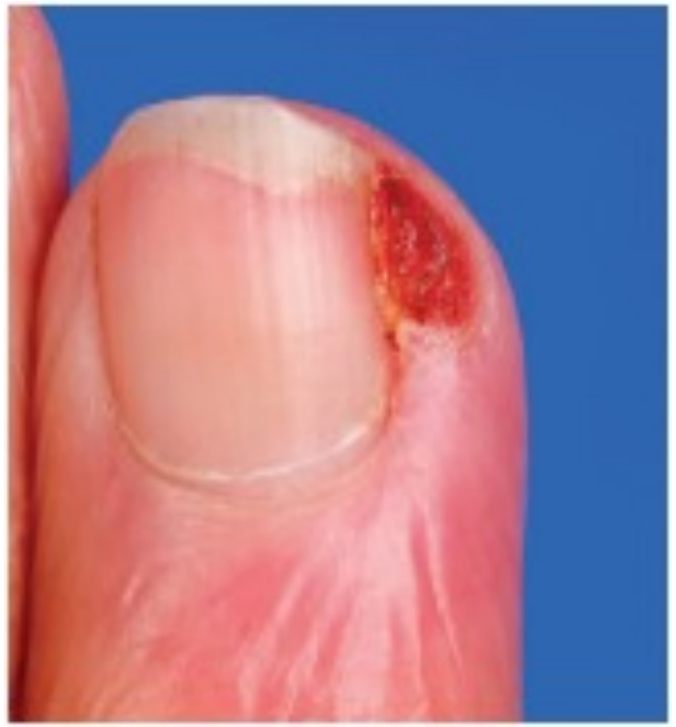
Cutaneous











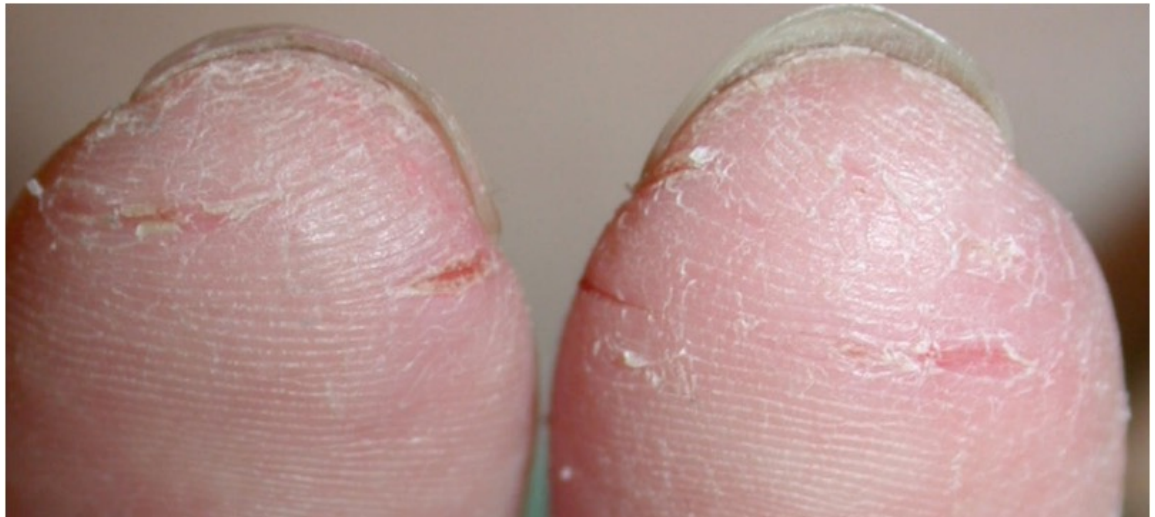
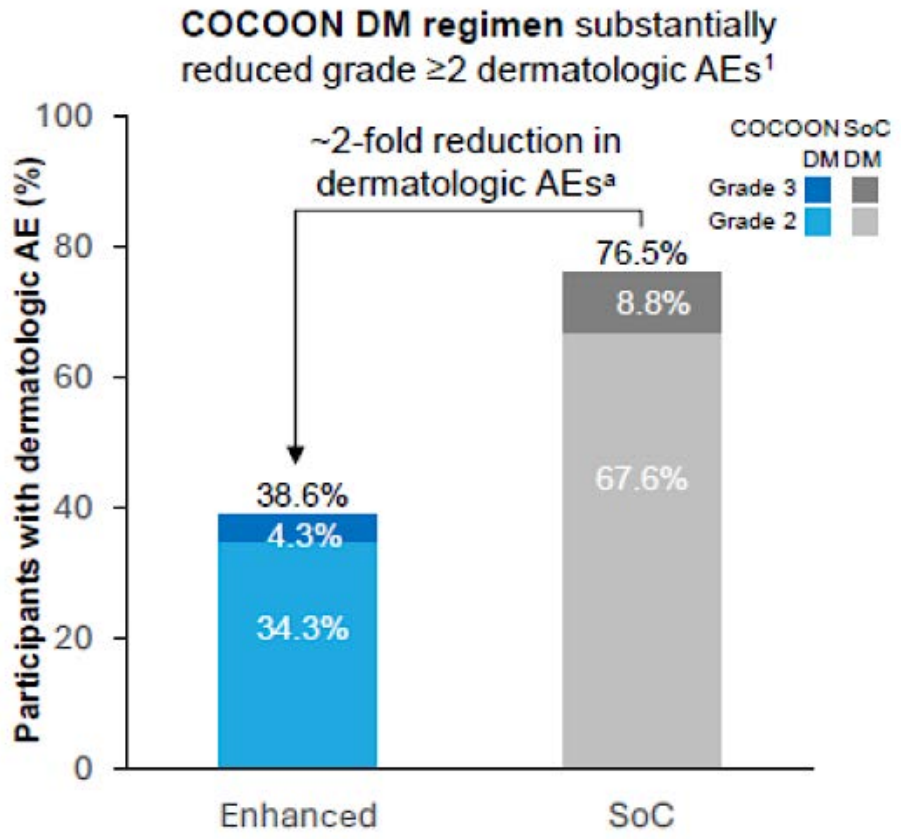


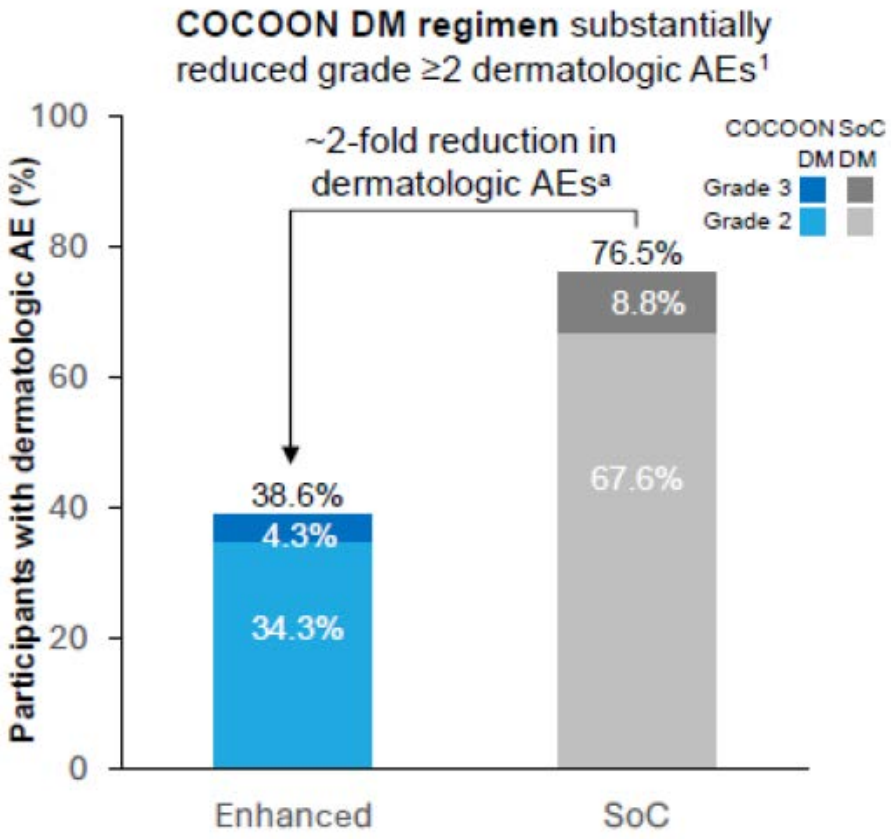
Image Courtesy of Dr. Joshua Sabari, NYU, New York, NY

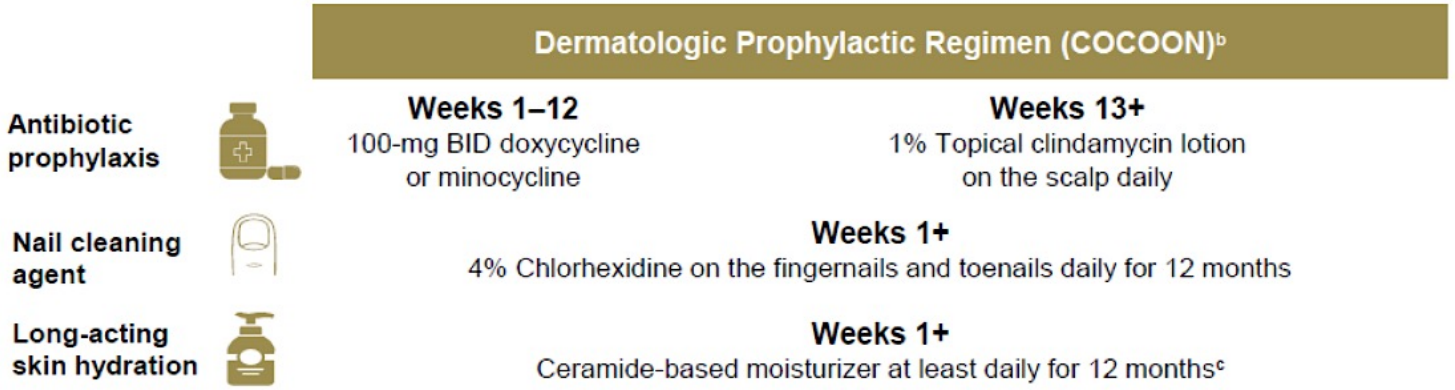
Early Onset Adverse Events can be Reduced with Prophylactic Approaches



Girard N et al ELCC 2025

Early Onset Adverse Events can be Reduced with Prophylactic Approaches





Girard N et al ELCC 2025

Conclusions

- Acquired Resistance (EGFR & non EGFR mediated) is inevitable!
  - EGFR C797S; MET AMP and others
- We need therapeutics with novel MOA targeting EGFR and non-EGFR mediated resistance
  - High risk features: brain metastases, EGFR L858R, co-mutation TP53, detectable ctDNA and lack of ctDNA clearance
  - Need better predictive biomarkers
- Due to heterogeneity of acquired resistance - targeting one resistance mechanism is often of limited benefit.
  - MARIPOSA 2: Ami + Chemo in 2L post Osimertinib – ORR 64%, mPFS 6.3m, intracranial mPFS 12.5m, OS immature
    - Most common TEAEs: neutropenia, thrombocytopenia, IRR, nausea and rash
    - Prophylaxis with SKIPPiRR, COCOON dermatologic regimen, and anticoagulation can reduce toxicity

Ivonescimab Plus Chemotherapy Demonstrates Statistically Significant and Clinically Meaningful Improvement in PFS in Patients with EGFR-Mutant NSCLC after EGFR TKI Therapy in Global Study

Press Release: May 30, 2025

[The manufacturer] today announced topline results from the Phase III clinical trial, HARMONi, the first global Phase III study evaluating ivonescimab, successfully met the progression-free survival (PFS) primary endpoint and showed a positive trend in the other primary endpoint, overall survival (OS).

HARMONi is a multiregional, double-blinded, placebo-controlled, Phase III study evaluating ivonescimab plus platinum-doublet chemotherapy compared to placebo plus platinum-doublet chemotherapy in patients with epidermal growth factor receptor (EGFR)-mutated, locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have progressed after treatment with a 3rd generation EGFR tyrosine kinase inhibitor (TKI).

At the prespecified primary data analysis, ivonescimab in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in progression-free survival, with a hazard ratio of 0.52 (95% CI: 0.41 – 0.66; $p<0.00001$).

Ivonescimab in combination with chemotherapy showed a positive trend in OS in the primary analysis without achieving a statistically significant benefit with a hazard ratio of 0.79 (95% CI: 0.62 – 1.01; $p=0.057$).

https://www.businesswire.com/news/home/20250530679531/en/Ivonescimab-Plus-Chemotherapy-Demonstrates-Statistically-Significant-and-Clinically-Meaningful-Improvement-in-Progression-Free-Survival-in-Patients-with-EGFR-Mutant-Non-Small-Cell-Lung-Cancer-after-EGFR-TKI-Therapy-in-Global-Study

In general, for a patient with metastatic nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 0 who receives first-line targeted treatment with response followed by disease progression, would you recommend repeat mutation testing?

 Prof Girard	Yes
 Dr Goldman	Yes, both tissue and liquid biopsy
 Dr Jänne	Yes, tissue biopsy
 Dr Ramalingam	Yes, liquid biopsy and then tissue if liquid is negative
 Dr Sabari	Yes, liquid biopsy and then tissue if liquid is negative
 Dr Yu	Yes, both tissue and liquid biopsy
 Dr Gadgeel	Yes, liquid biopsy and then tissue if liquid is negative
 Dr Spira	Yes, liquid biopsy

RTP
RESEARCH TO PRACTICE

A 65-year-old patient with nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 0 responds to first-line osimertinib and then experiences asymptomatic disease progression after 18 months. Regulatory and reimbursement issues aside, what would be your second-line treatment recommendation if the patient had acquired no further mutations?

 Prof Girard	Amivantamab + chemotherapy
 Dr Goldman	Amivantamab + chemotherapy
 Dr Jänne	Continue osimertinib and add chemotherapy
 Dr Ramalingam	Amivantamab + chemotherapy
 Dr Sabari	Amivantamab + chemotherapy
 Dr Yu	Amivantamab + chemotherapy
 Dr Gadgeel	Continue osimertinib and add chemotherapy
 Dr Spira	Amivantamab + chemotherapy

RTP RESEARCH TO PRACTICE

A 65-year-old patient with nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 0 responds to first-line osimertinib with chemotherapy and then experiences asymptomatic disease progression after 18 months. Regulatory and reimbursement issues aside, what would be your second-line treatment recommendation if the patient had acquired no further mutations?

 Prof Girard	Amivantamab + chemotherapy
 Dr Goldman	Patritumab deruxtecan
 Dr Jänne	Amivantamab + chemotherapy
 Dr Ramalingam	Amivantamab + chemotherapy
 Dr Sabari	Amivantamab + chemotherapy
 Dr Yu	Patritumab deruxtecan
 Dr Gadgeel	Patritumab deruxtecan
 Dr Spira	Amivantamab/lazertinib

RTP RESEARCH TO PRACTICE

A 65-year-old patient with nonsquamous NSCLC with an EGFR exon 19 deletion and a PD-L1 TPS of 0 responds to first-line amivantamab/lazertinib and then experiences asymptomatic disease progression after 18 months. Regulatory and reimbursement issues aside, what would be your second-line treatment recommendation if the patient had acquired no further mutations?

 Prof Girard	Chemotherapy + ivonescimab; HER3-DXd; Dato-DXd
 Dr Goldman	Chemotherapy +/- bevacizumab
 Dr Jänne	Osimertinib + chemotherapy
 Dr Ramalingam	Chemotherapy +/- bevacizumab
 Dr Sabari	Patritumab deruxtecan
 Dr Yu	Osimertinib + chemotherapy
 Dr Gadgeel	Patritumab deruxtecan
 Dr Spira	Chemotherapy +/- bevacizumab

Dato-DXd = datopotamab deruxtecan; HER3-DXd = patritumab deruxtcan

RTP RESEARCH TO PRACTICE

Do you generally use enhanced dermatologic management, as evaluated in the COCOON study, for your patients receiving first-line amivantamab/lazertinib?

	Enhanced dermatologic management	Effective
 Prof Girard	Yes	Yes
 Dr Goldman	Yes	Too early in treatment to tell
 Dr Jänne	Yes	Yes
 Dr Ramalingam	No	N/A
 Dr Sabari	Yes	Yes
 Dr Yu	Yes	Modest improvement only
 Dr Gadgeel	Yes	Too early in treatment to tell
 Dr Spira	Yes	Yes

Do you believe that subcutaneous amivantamab has better tolerability compared to intravenous amivantamab?

 Prof Girard	Yes, less IRR; possibly fewer cutaneous side effects
 Dr Goldman	Yes, somewhat better
 Dr Jänne	Yes, somewhat better
 Dr Ramalingam	Yes, somewhat better
 Dr Sabari	Yes, somewhat better
 Dr Yu	No
 Dr Gadgeel	Yes, significantly better
 Dr Spira	Yes, significantly better

IRR = infusion-related reaction

Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

RTP RESEARCH TO PRACTICE

TROP2 TARGETED THERAPY FOR EGFR-MUTATED NSCLC

Suresh S. Ramalingam, MD
Executive Director

Winship Cancer Institute
of Emory University

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

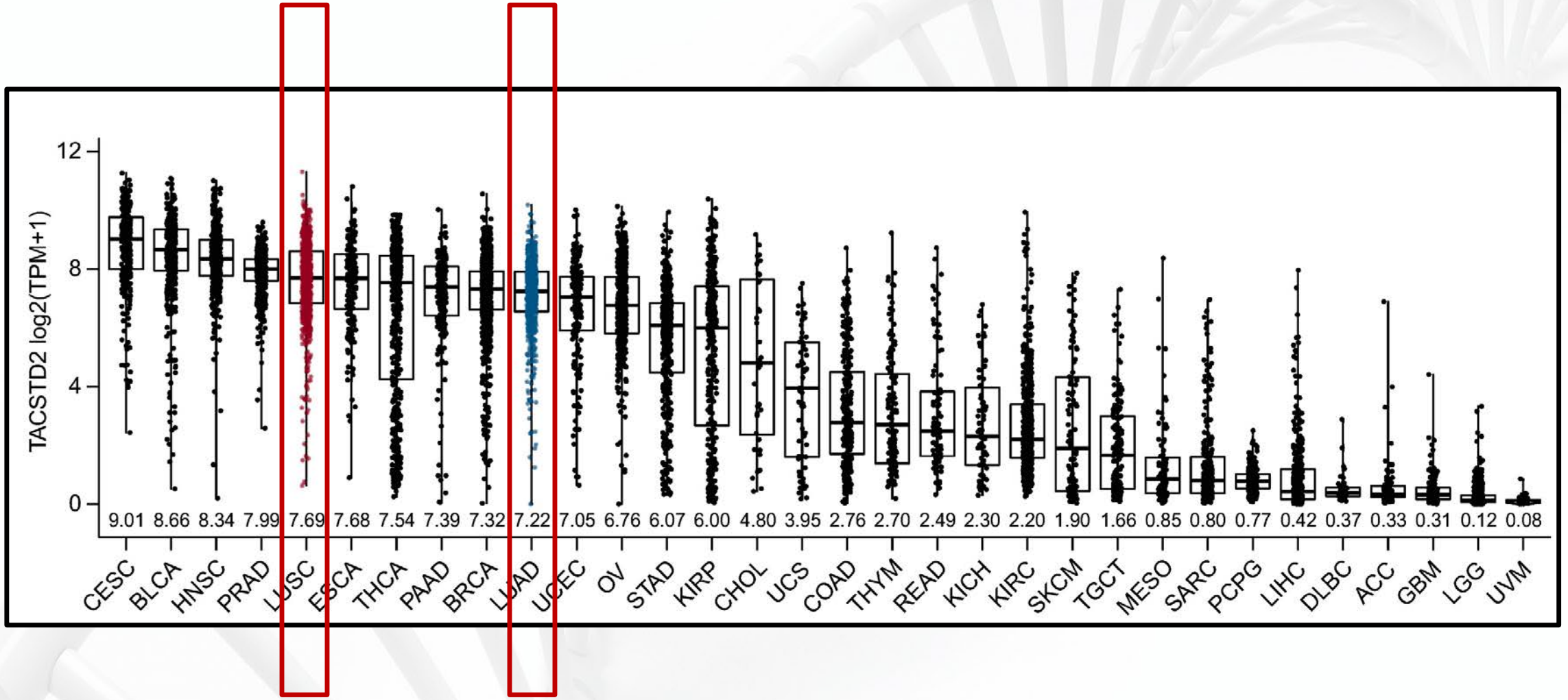
NCI Designated Comprehensive Cancer Center

Where Science Becomes Hope®

FDA BREAKTHROUGH THERAPY DESIGNATION IN EGFR^{MT} NSCLC

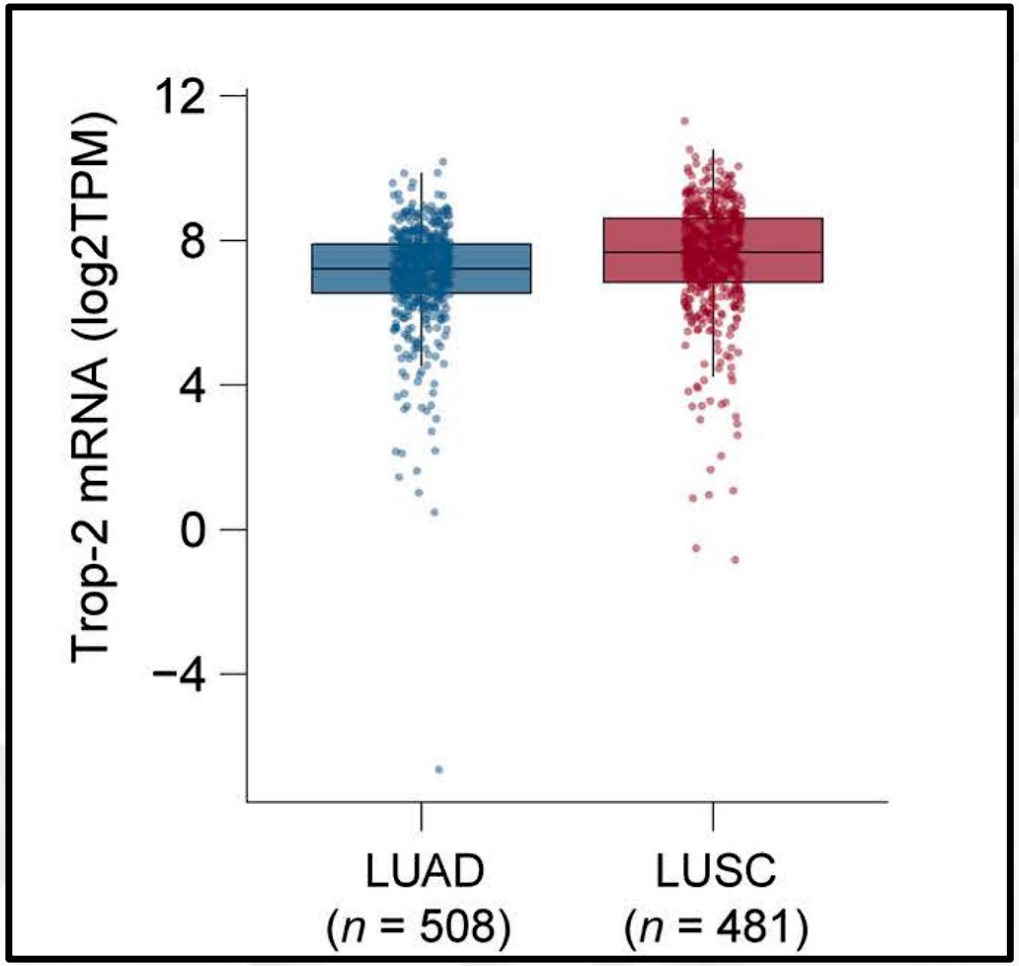
Drug	Mechanism of Action	Key Differentiators
Datopotamab Deruxtecan	TROP2-directed ADC delivering a topoisomerase I inhibitor (DXd) payload via a cleavable tetrapeptide linker.	Uses proprietary DXd payload and linker system for controlled release.
Sacituzumab Tirumotecan	TROP2-directed ADC delivering a SN-38 (irinotecan active metabolite) payload via a hydrolysable linker.	Utilizes a hydrolysable linker with a well-characterized SN-38 payload.

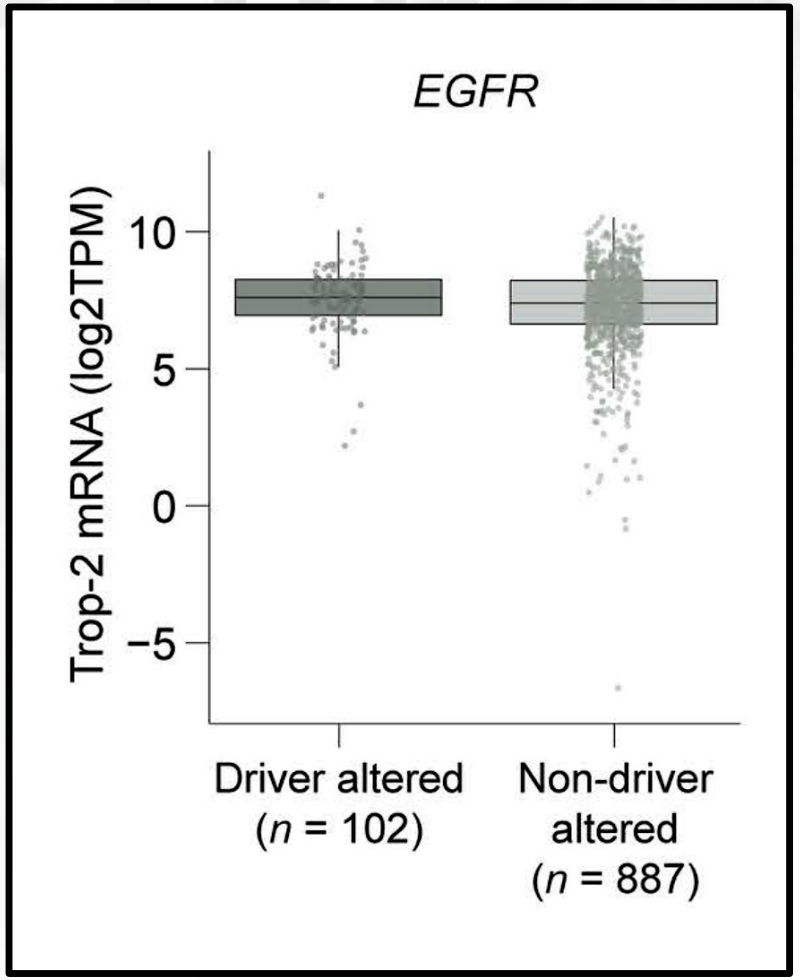
TROP2 EXPRESSION ACROSS SOLID ORGAN MALIGNANCIES: TCGA DATA



Kuo P et al, PLoS One, 2025.

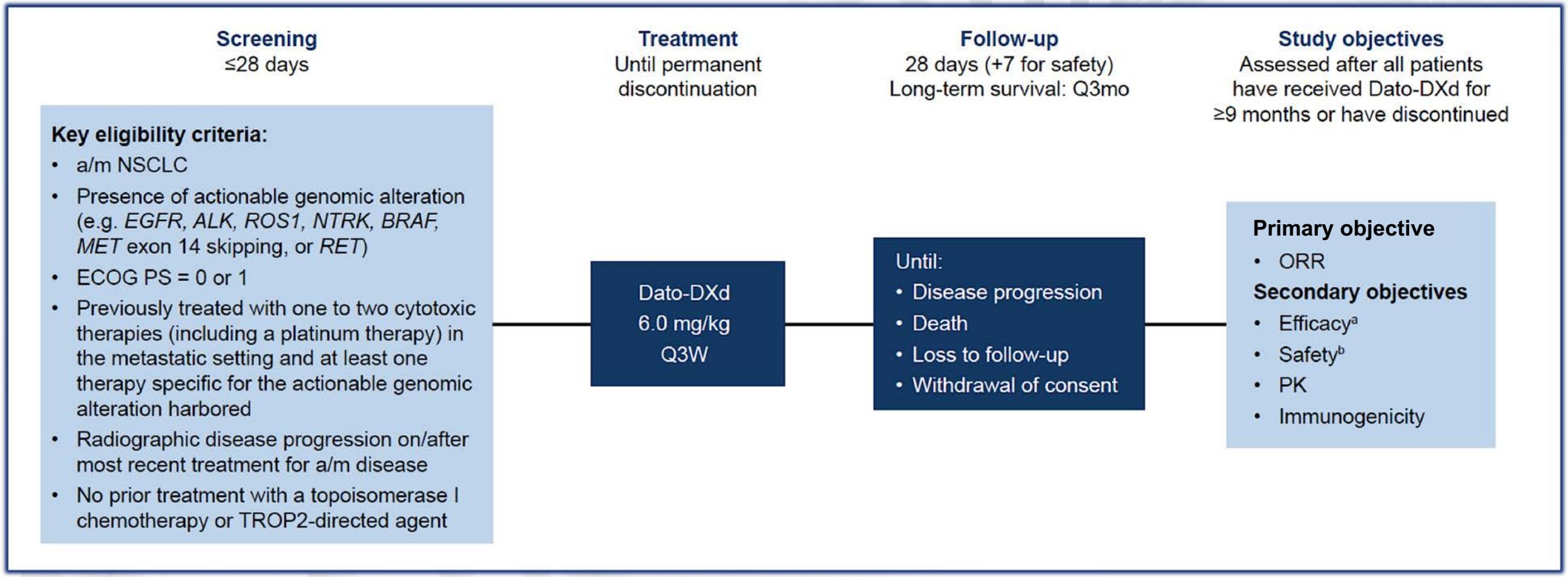
TROP-2 EXPRESSION IN NSCLC





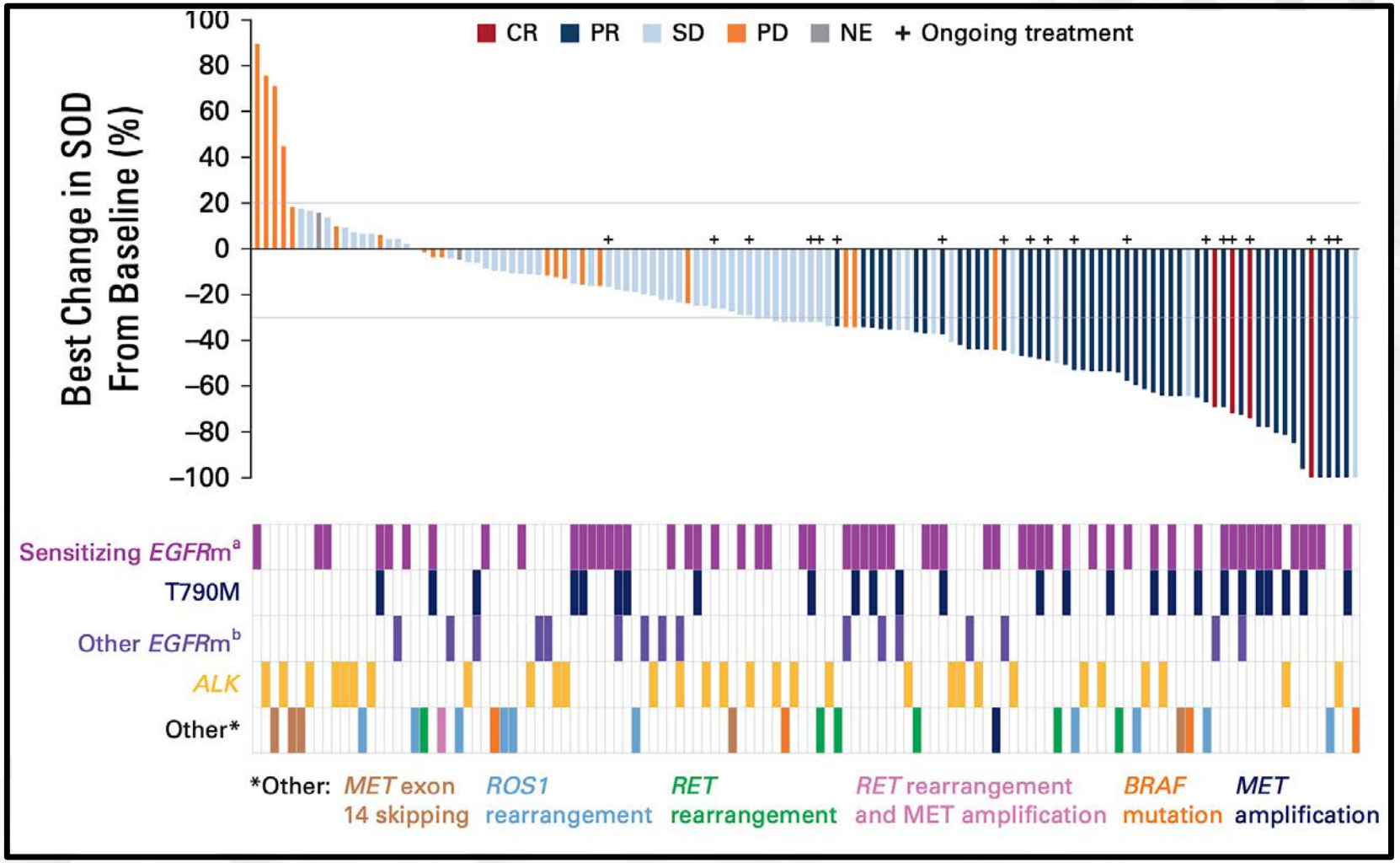
Kuo P et al, PLoS One, 2025.

TROPION LUNG 05 STUDY



Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: EFFICACY



EGFR^{MT} NSCLC Cohort

N=78 pts

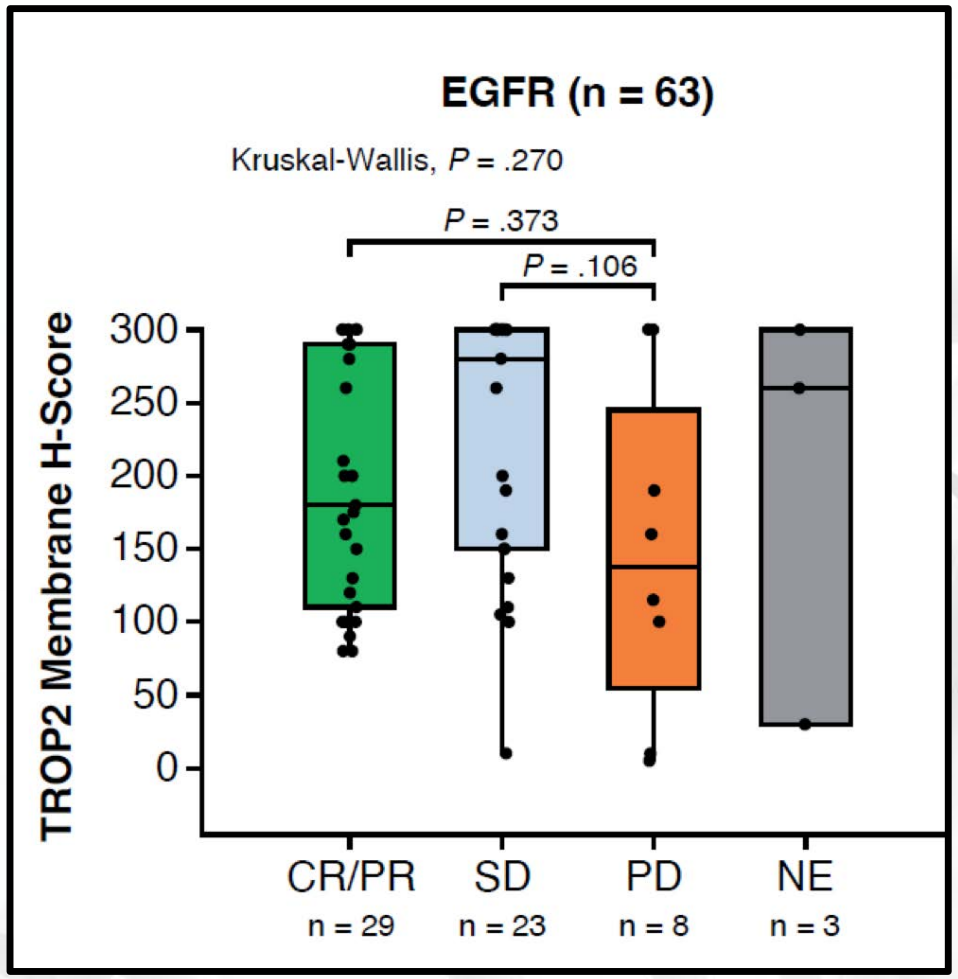
RR=44%

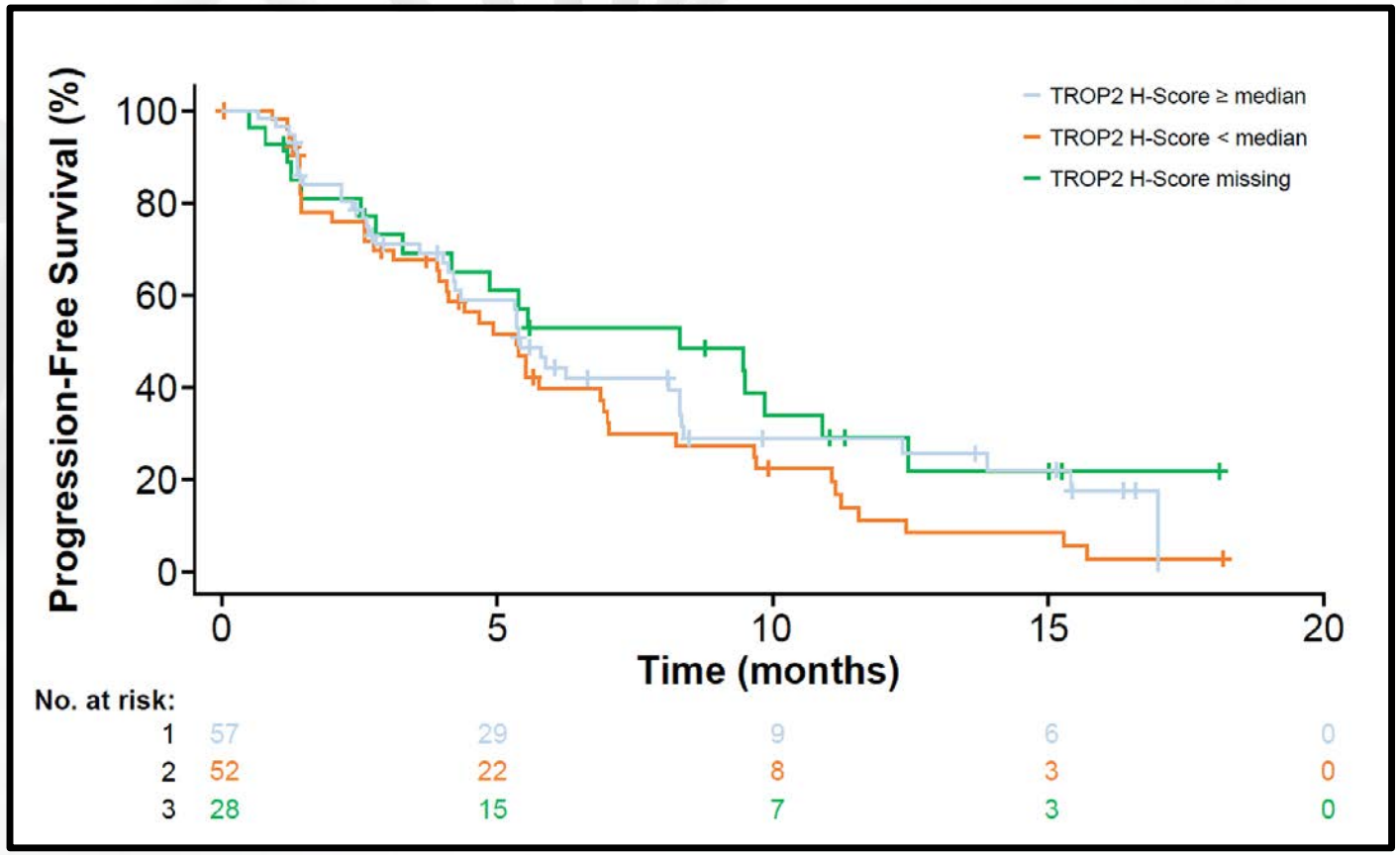
mDOR: 7.0m

mPFS: 5.8m

Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: EFFICACY BASED ON TROP-2 EXPRESSION LEVELS





Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: TOXICITY

AESI	Any grade	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (65.7)	45 (32.8)	30 (21.9)	15 (10.9)
Treatment discontinuation	1 (0.7)	1 (0.7)[a]	0	0
Patients with reported events (PTs)				
Stomatitis	80 (58.4)	39 (28.5)	28 (20.4)	13 (9.5)
Oropharyngeal pain	8 (5.8)	6 (4.4)	2 (1.5)	0
Dysphagia	7 (5.1)	5 (3.6)	0	2 (1.5)
Aphthous ulcer	4 (2.9)	4 (2.9)	0	0
Pharyngeal inflammation	2 (1.5)	1 (0.7)	0	1 (0.7)

Sands J et al, J Clin Oncol, 2025.

TROPION LUNG 05: TOXICITY

Ocular surface events	36 (26.3)	26 (19.0)	7 (5.1)	3 (2.2)
Treatment discontinuation	0	0	0	0
Patients with reported events (PTs)				
Dry eye	15 (10.9)	13 (9.5)	2 (1.5)	0
Vision blurred	12 (8.8)	10 (7.3)	2 (1.5)	0
Keratitis	7 (5.1)	5 (3.6)	2 (1.5)	0
Corneal disorder	2 (1.5)	0	1 (0.7)	1 (0.7)
Cornea verticillate	1 (0.7)	0	0	1 (0.7)
Punctate keratitis	1 (0.7)	0	0	1 (0.7)

Sands J et al, J Clin Oncol, 2025.

POOLED ANALYSIS OF TROPION-LUNG05 AND TROPION-LUNG01

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

TROPION-Lung05 (Phase II study)

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

TROPION-Lung01 (Phase III study)

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

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)

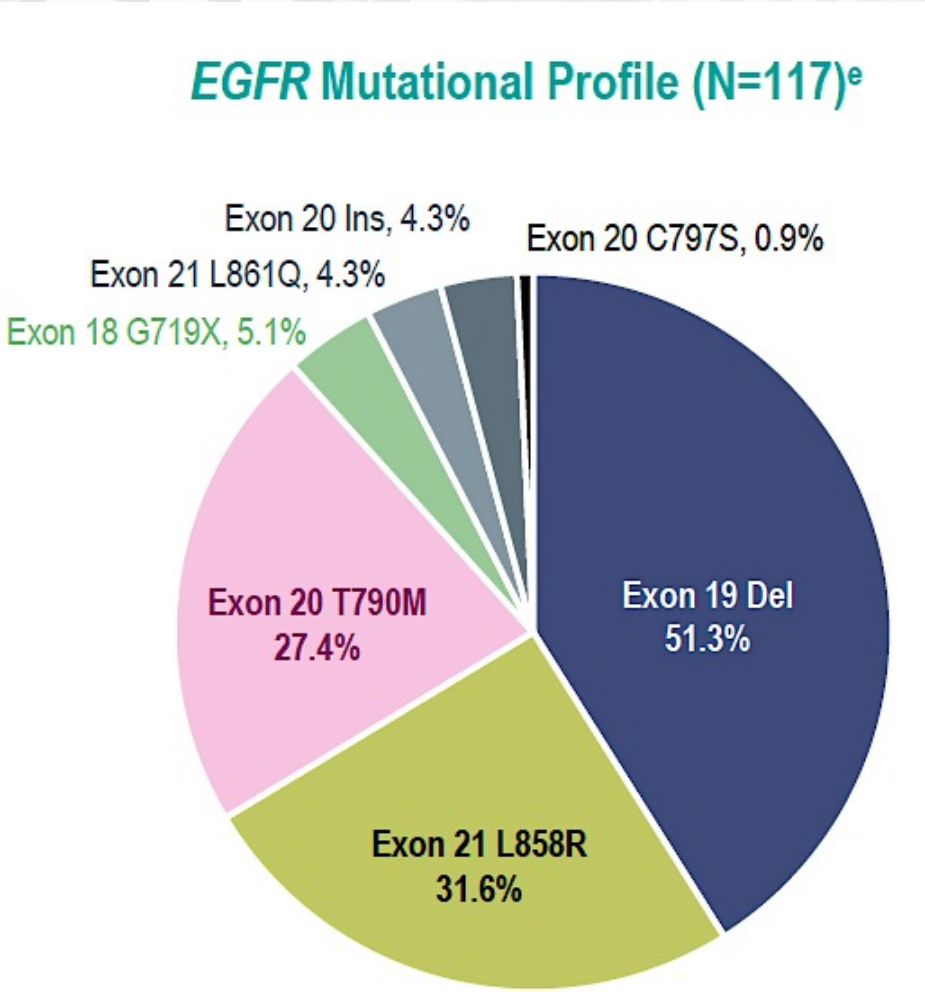
Endpoints:

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

Ahn M et al. ESMO 2024;Abstract LBA7.

POOLED ANALYSIS OF TROPION-LUNG05 AND TROPION-LUNG01

Characteristic	*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, n (%)	73 (62.4)	52 (66.7)	21 (53.8)
Race, n (%)			
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, n (%)			
0	39 (33.3)	24 (30.8)	15 (38.5)
1	78 (66.7)	54 (69.2)	24 (61.5)
Smoker[a], n (%)	55 (47.0)	34 (43.6)	21 (53.8)
Nonsquamous histology[b], n (%)	115 (98.3)	77 (98.7)	38 (97.4)
Brain metastasis at study entry, n (%)	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], n (%)	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)



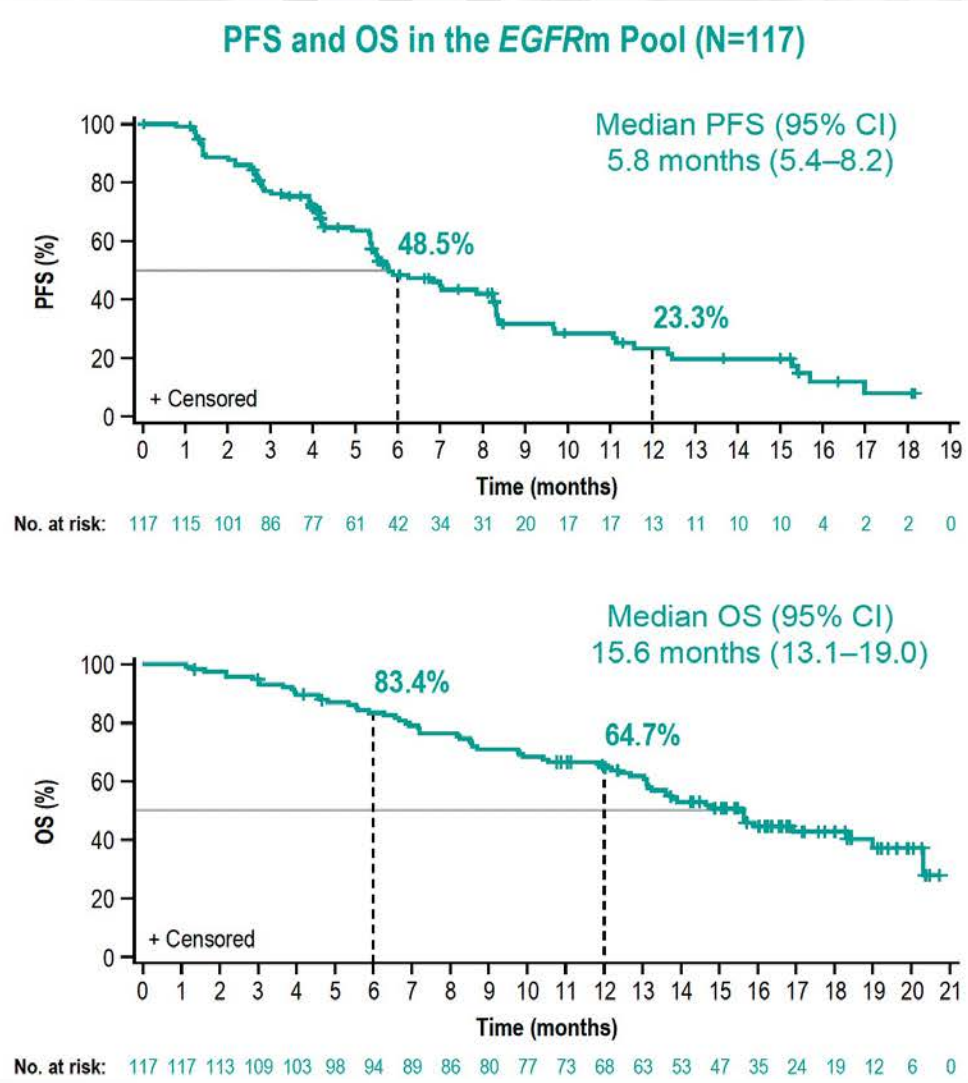
Ahn M et al. ESMO 2024;Abstract LBA7.

POOLED ANALYSIS OF TROPION-LUNG05 AND TROPION-LUNG01

Efficacy

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)

[a]CR+PR; [b]CR+PR+SD or non-CR/non-PD. BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; DOR, duration of response; *EGFR*m, *EGFR* mutated; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease.



Ahn M et al. ESMO 2024;Abstract LBA7.

Datopotamab Deruxtecan Granted Priority Review in the US for Patients with Previously Treated Advanced EGFR-Mutated NSCLC

Press Release: January 13, 2025

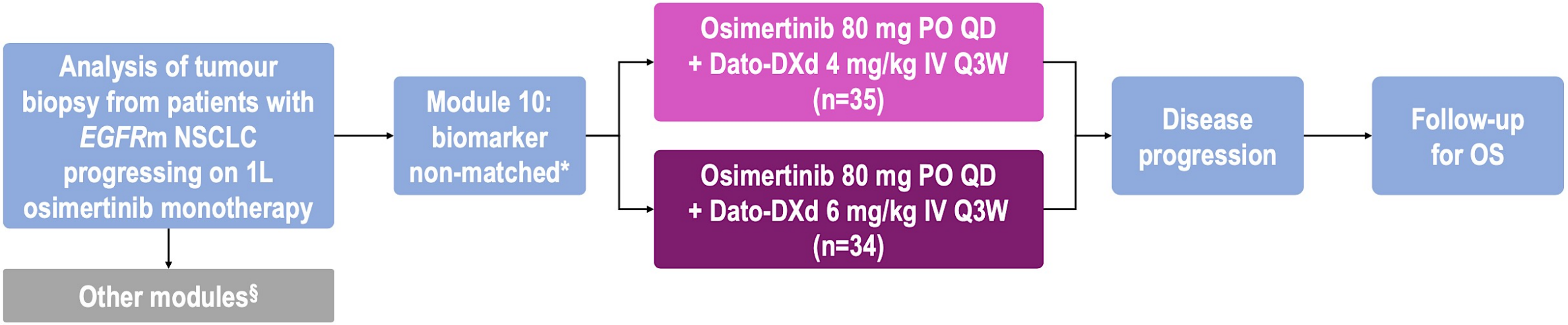
"[The] Biologics License Application (BLA) for datopotamab deruxtecan (Dato-DXd) has been accepted and granted Priority Review in the US for the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor-mutated (*EGFR*m) non-small cell lung cancer (NSCLC) who have received prior systemic therapies, including an *EGFR*-directed therapy.

In a pooled analysis of patients with previously treated advanced or metastatic *EGFR*m NSCLC in the TROPION-Lung05 and TROPION-Lung01 trials presented at the European Society for Medical Oncology (ESMO) Asia 2024 Congress, datopotamab deruxtecan demonstrated a confirmed objective response rate (ORR) of 42.7% (95% confidence interval [CI] 33.6-52.2) as assessed by blinded independent central review (BICR) and a median duration of response (DoR) of 7.0 months (95% CI 4.2-9.8). The safety profile of datopotamab deruxtecan was consistent with previous reports from the TROPION-Lung05 and TROPION-Lung01 trials, with no new safety concerns identified."

https://www.astrazeneca.com/media-centre/press-releases/2025/datopotamab-deruxtecan-granted-priority-review-in-the-us-for-patients-with-previously-treated-advanced-egfr-mutated-non-small-cell-lung-cancer.html#:~:text=AstraZeneca%20and%20Daiichi%20Sankyo's%20Biologics,small%20cell%20lung%20cancer%20(NSCLC)

RTP RESEARCH TO PRACTICE

ORCHARD module 10 study design



- **Primary endpoint:** ORR based on RECIST v1.1 by investigator assessment
- **Key secondary endpoints:** PFS‡, DoR‡, OS, AEs, SAEs

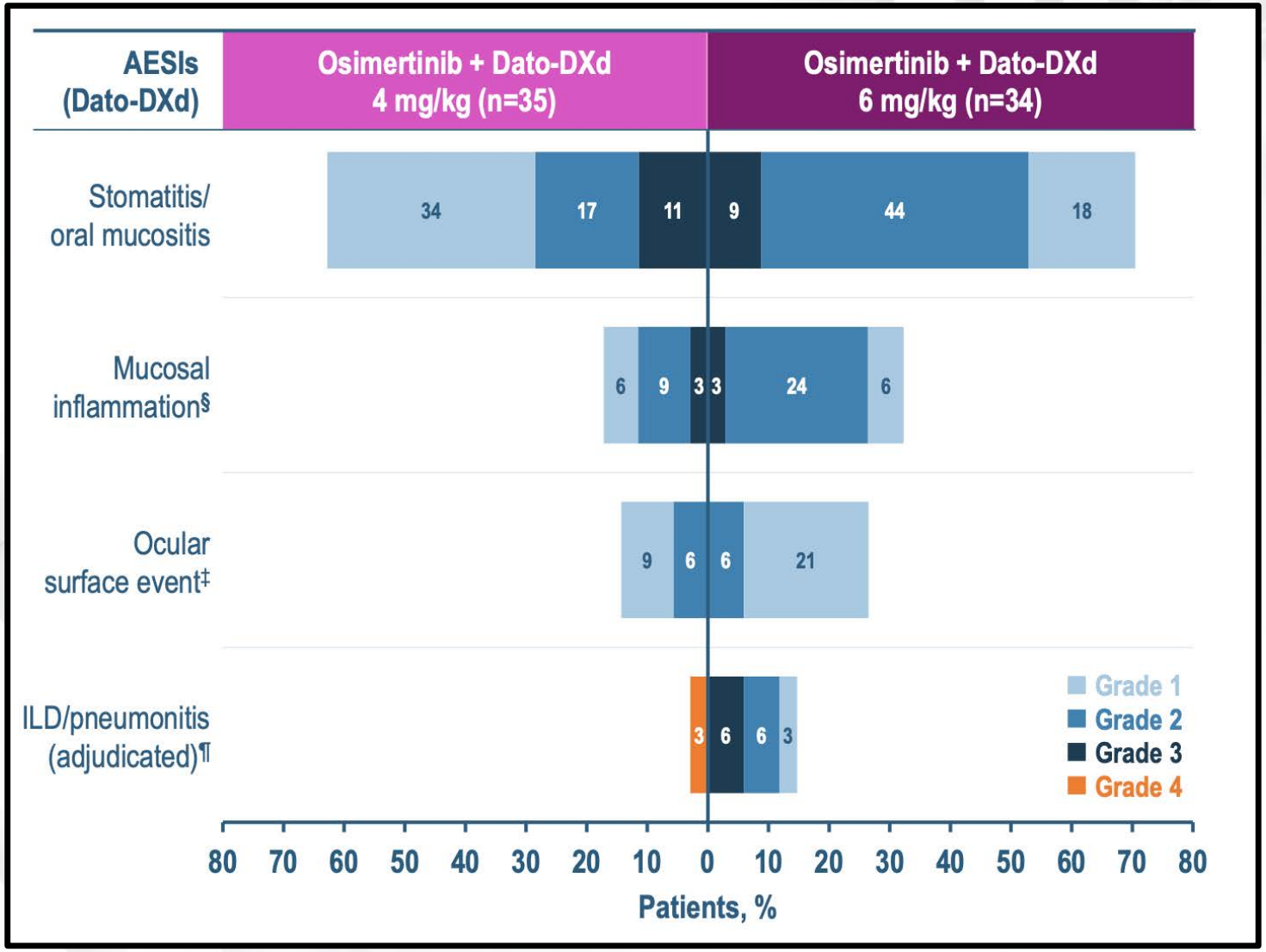
Le X et al, ELCC 2025.

ORCHARD MODULE 10: EFFICACY

	Osimertinib + Dato-DXd 4 mg/kg (n=35)	Osimertinib + Dato-DXd 6 mg/kg (n=33)
PFS		
mPFS, months (95% CI)	**9.5 (7.2, 9.8)**	**11.7 (8.3, NC)**
6-month rate, % (95% CI)	74 (56, 85)	80 (61, 91)
9-month rate, % (95% CI)	50 (33, 65)	70 (49, 83)
12-month rate, % (95% CI)	21 (9, 35)	39 (21, 57)
ORR, % (80% CI)	**43 (31, 55)**	**36 (25, 49)**
DoR		
mDoR, months (95% CI)*	**6.3 (3.8, 8.2)**	**20.5 (6.2, NC)**
6-month rate, % (95% CI)	60 (32, 80)	92 (54, 99)
9-month rate, % (95% CI)	15 (2, 38)	64 (30, 85)
Median time to onset of response, months (Q1, Q3)	**2.7 (1.5, 4.1)**	**1.4 (1.2, 2.1)**
Median duration of follow-up, months	13.4	13.8
OS events, n (%)	16 (46)	9 (27)

Sands J et al, J Clin Oncol, 2025.

ORCHARD MODULE 10: SALIENT TOXICITY



Sands J et al, J Clin Oncol, 2025.

ONGOING TRIAL

TROPION-Lung14

Phase III, randomized, open -label, multicenter, global study

Osimertinib (EGFR) | **Datopotamab deruxtecan** (TROP2/TOP1i)

- *EGFR*m (Ex19del and/or L858R) locally advanced, metastatic (Stage IIIB/C or IV), or recurrent nonsquamous NSCLC
- No prior EGFR-TKI therapy or prior treatment for advanced disease
- WHO PS 0 or 1
- Measurable disease per RECIST v1.1
- Stable CNS metastases are allowed

N≈582[a]

Safety run in (n=20)

Dato-DXd 6 mg/kg IV Q3W + Osimertinib 80 mg PO QD

Stratification Factors:
- Mutation type (Ex19Del vs L858R)
- WHO PS (0 vs 1)
- CNS metastasis (Yes vs No)

R 1:1

Randomized Phase 3 trial (N=562)

- Dato-DXd 6 mg/kg IV Q3W + Osimertinib 80 mg PO QD
- Osimertinib 80 mg PO QD

Primary Endpoint
- PFS by BICR

Secondary Endpoints
- OS
- CNS PFS[b]
- PFS[c]
- ORR (CR+PR)[d]
- DoR[d]
- Prevention of CNS metastases[e]
- PF2
- PK
- ADA for Dato-DXd
- Safety

MANAGEMENT OF STOMATITIS RELATED TO DATOPOTAMAB

Grade	Symptoms	Recommended Interventions	Dose Modifications
Grade 1	Minimal symptoms, no impact on daily activities	Maintain oral hygiene, use mouth rinses	No dose modification
Grade 2	Moderate pain, some impact on daily activities	Topical analgesics, increase oral hygiene measures	Consider dose reduction if persistent
Grade 3	Severe pain, significant impact on daily activities	Systemic analgesics, consider dose reduction	Dose reduction or interruption until improvement
Grade 4	Life-threatening, urgent intervention required	Hospitalization, intravenous analgesics, discontinue treatment	Discontinue treatment

- ❑ Use dexamethasone oral solution 0.1 mg/mL for prophylaxis 4 times daily
- ❑ Hold ice chips in mouth during infusion

DATOPOTAMAB DERUXTECAN: MANAGEMENT OF KEY TOXICITY

Keratitis[1]

Severity	Dose modification
Nonconfluent superficial keratitis	• Monitor
Confluent superficial keratitis, a cornea epithelial defect, or 3-line or more loss in best corrected visual acuity	• Withhold until improved or resolved, then maintain at same dose level or consider dose reduction
Corneal ulcer or stromal opacity or best corrected distance visual acuity 20/200 or worse	• Withhold until improved or resolved, then reduce by 1 dose level
Corneal perforation	• Permanently discontinue

ILD/pneumonitis[1]

Severity	Dose modification
Asymptomatic Grade 1	Withhold datopotamab deruxtecan until ILD/pneumonitis is completely resolved, then: • If resolved in ≤28 days, maintain dose • If resolved in >28 days, reduce by 1 dose level • Consider corticosteroid treatment (eg, ≥0.5 mg/kg/day prednisolone or equivalent)
Symptomatic Grade ≥2	• Permanently discontinue • Promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/day prednisolone or equivalent) and continue for ≥14 days followed by gradual taper for ≥4 weeks

- ❑ Preservative-free lubricant eye drops at least 4 times daily
- ❑ Baseline ophthalmology evaluation
- ❑ Avoid using contact lenses during infusion

ONGOING TRIAL

TROPION-Lung15

Phase III, randomized, open -label study [1-3]

Osimertinib (EGFR) | Datopotamab deruxtecan (TROP2/TOP1i)

- Patients with advanced/metastatic NSCLC
- EGFRm (Ex19del, L858R, G719X, S768I, or L861Q either alone or in combination with other EGFR mutations, which may include T790M)
- Locally advanced, metastatic (Stage IIIB/C or IV), or recurrent non-squamous NSCLC
- Progressed on ≤2 lines of EGFR TKIs[b]
- WHO PS 0 or 1
- Measurable disease per RECIST v1.1

N≈630[a]

R 1:1:1

- Dato-DXd 6 mg/kg IV Q3W + Osimertinib 80 mg PO QD
- Dato-DXd 6 mg/kg IV Q3W
- Pemetrexed 500 mg/m ^{2} + carboplatin AUC5 OR cisplatin 75 mg/m^2 IV Q3W (max. 4 cycles) Followed by Pemetrexed 500 mg/m ^{2} IV Q3W

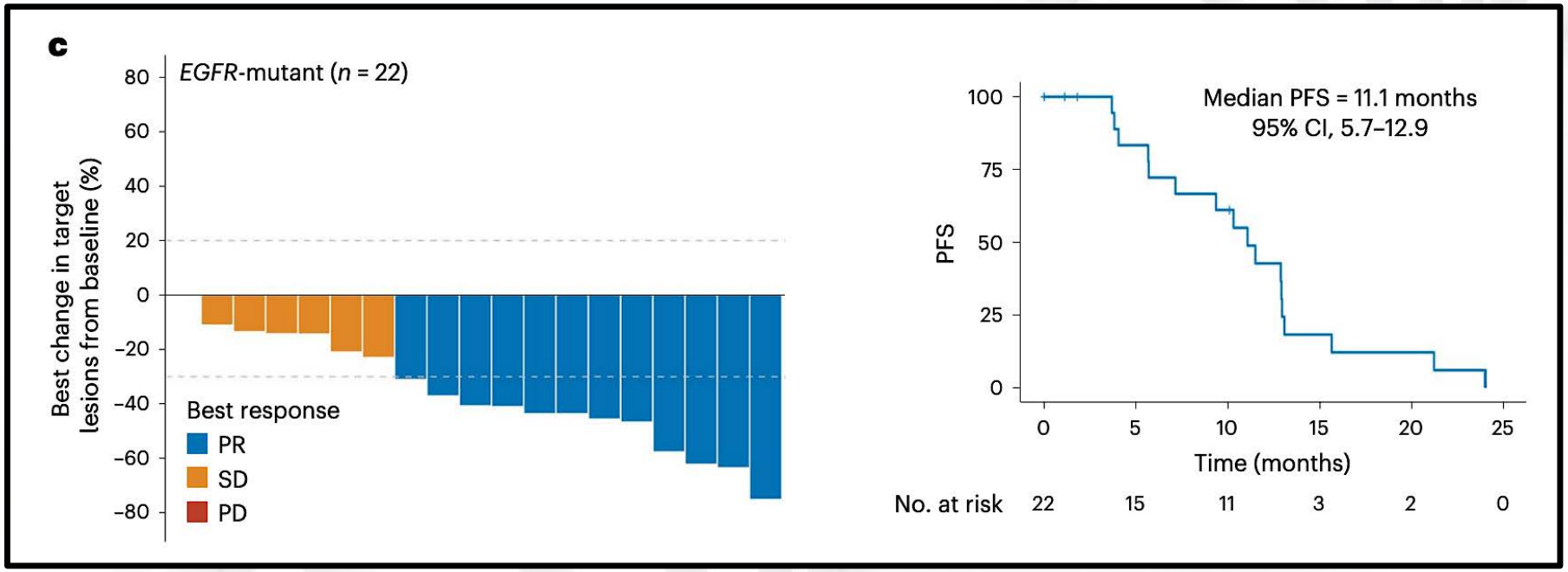
Dual Primary Endpoint

- PFS by BICR (monotherapy vs chemotherapy
- PFS by BICR (combination vs chemotherapy

Secondary Endpoints

- OS
- CNS PFS[c]
- ORR[d]
- DoR[e]
- PFS2
- ORR[f]
- DoR[f]
- TTD[g]
- PK
- ADA for Dato-DXd
- Safety

SACITUZUMAB TIRUMOTECAN IN EGFR^{MT} NSCLC



RR: 55%
mPFS 11.1m

Prior chemo cohort:
RR: 42%
mPFS: 7.2m

Chemo-naïve cohort:
RR: 70%
mPFS: 12.9m

Salient AE:
Neutropenia
Stomatitis

Zhao S et al, Nature Med, 2025.

KEY ASCO PRESENTATIONS

Oral Presentation

6/1/2025

8:00 AM-11:00 AM CDT

- Sacituzumab tirumotecan (sac-TMT) in patients (pts) with previously treated advanced EGFR-mutated non-small cell lung cancer (NSCLC): Results from the randomized OptiTROP-Lung03 study.
- ABSTRACT 8507

Poster

5/31/2025

1:30 PM-4:30 PM CDT

- Sacituzumab Tirumotecan (sac-TMT) in patients (pts) with previously treated locally advanced or metastatic (LA/M) non-small cell lung cancer (NSCLC) harboring uncommon EGFR mutations: Preliminary results from a phase 2 study.
- ABSTRACT 8615

Based on the published literature and/or your clinical experience, would you like to have access to datopotamab deruxtecan (Dato-DXd) right now for patients with nonsquamous mNSCLC with an EGFR mutation?

 Prof Girard	I'm not sure
 Dr Goldman	Yes
 Dr Jänne	Yes
 Dr Ramalingam	Yes
 Dr Sabari	I'm not sure
 Dr Yu	Yes
 Dr Gadgeel	I'm not sure
 Dr Spira	Yes

RTP RESEARCH TO PRACTICE

If Dato-DXd were to become available for the treatment of relapsed nonsquamous mNSCLC with an EGFR deletion mutation, when, if at all, would you integrate it into the treatment algorithm for patients who received first-line targeted therapy as described?

	Osimertinib	Osimertinib with chemotherapy	Amivantimab/ lazertinib
 Prof Girard	Third line after amivantamab + chemotherapy	Second line	Third line after chemotherapy + ivonescimab
 Dr Goldman	Third line after amivantamab + chemotherapy	Second line	Third line
 Dr Jänne	Second line	Second line	Second or third line
 Dr Ramalingam	Third line	Second line	Third line
 Dr Sabari	Third line	Second or third line	Third line
 Dr Yu	After amivantamab + chemotherapy	After amivantamab + chemotherapy	After osimertinib + chemotherapy
 Dr Gadgeel	After second line	Second or third line	Second or third line
 Dr Spira	After amivantamab + chemotherapy	After amivantamab + chemotherapy	—

Based on the published literature and/or your clinical experience, what is the primary toxicity patients experience during treatment with Dato-DXd that leads to withholding this regimen?

 Prof Girard	Stomatitis
 Dr Goldman	Mucositis
 Dr Jänne	Mucositis
 Dr Ramalingam	Stomatitis
 Dr Sabari	Stomatitis, ILD, hematologic toxicities
 Dr Yu	Mucositis; fatigue
 Dr Gadgeel	Fatigue
 Dr Spira	Mucositis

ILD = interstitial lung disease

RTP RESEARCH TO PRACTICE

Based on the published literature and/or your clinical experience, approximately what proportion of patients with EGFR mutation-positive nonsquamous mNSCLC receiving Dato-DXd experience mucositis? What preemptive strategies, if any, do you employ to prevent the development of mucositis associated with Dato-DXd?

	Chance of developing mucositis	Preemptive strategies
 Prof Girard	30%	Easy to manage
 Dr Goldman	65%	Oral dexamethasone rinse prophylaxis
 Dr Jänne	50%	Steroid mouthwash
 Dr Ramalingam	50%	Oral dexamethasone rinse prophylaxis
 Dr Sabari	40%	Oral dexamethasone; ice pops
 Dr Yu	60%	Oral dexamethasone rinse prophylaxis
 Dr Gadgeel	15%	Steroid mouthwash, ice chips
 Dr Spira	80%	Oral dexamethasone rinse prophylaxis

Based on the published literature and/or your clinical experience, approximately what proportion of patients with EGFR mutation-positive nonsquamous mNSCLC receiving Dato-DXd experience interstitial lung disease (ILD)? What is your approach to screening for ILD in patients with EGFR mutation-positive nonsquamous mNSCLC receiving Dato-DXd?

	Chance of developing ILD	ILD screening approach
 Prof Girard	3%	Imaging assessments of disease
 Dr Goldman	5%	Imaging every 6-9 weeks; clinical symptoms
 Dr Jänne	5%-10%	Surveillance imaging and symptom-guided management
 Dr Ramalingam	10%	Clinical monitoring and radiographic images
 Dr Sabari	15%	Close CT chest monitoring, holding therapy for GI toxicity
 Dr Yu	10%	Clinical symptoms and scan assessments of disease
 Dr Gadgeel	6%	Scans every 2 cycles for the first 4 cycles, then every 3 cycles for the first year
 Dr Spira	5%	Imaging assessments of disease

Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

RTP RESEARCH TO PRACTICE

UCLA Health | David Geffen School of Medicine

Optimal Care for Patients with Nonmetastatic EGFR-Mutant NSCLC

Jonathan Goldman, MD
Professor, UCLA Hematology & Oncology
Director of Clinical Trials in Thoracic Oncology
Associate Director of Drug Development

Three Approaches to Adjuvant Systemic Therapy for NSCLC

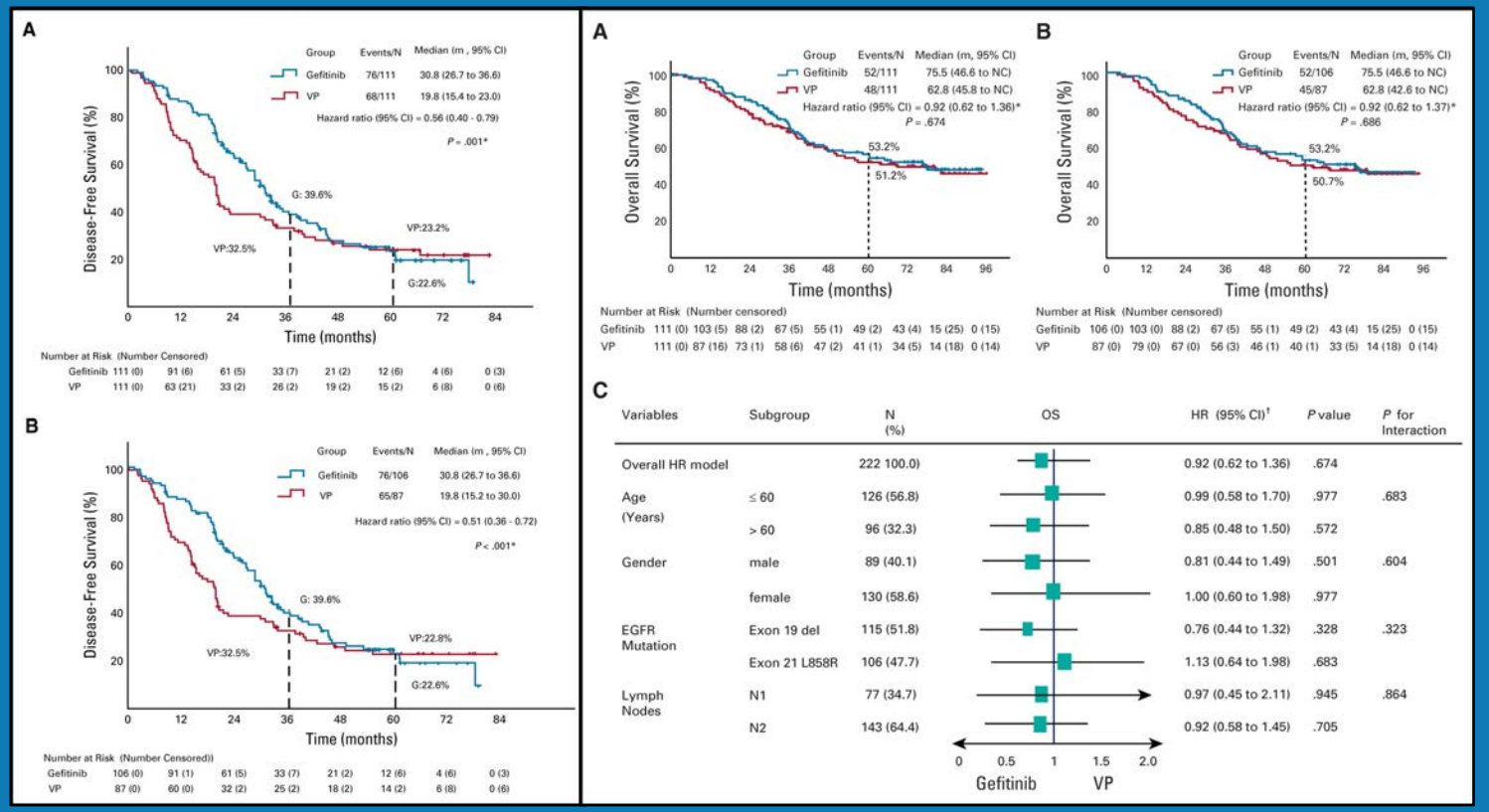
1. Chemotherapy carries high toxicity, with high number to treat to lead to 1 cure (10-20:1)

2. Immunotherapy can provide a significant DFS benefit, with promising durability, especially in higher stage, high PDL1 disease

3. Mutation-targeted TKI based treatment has a high response rate but the duration of response in the metastatic setting is typically 1.5 to 3 years, which may or may not be associated with a *cure* in the adjuvant setting

1st Gen EGFR TKI Trials

1. **RADIANT**: erlotinib v placebo
   - 973 subjects, EGFR+, IHC or FISH. Among EGFRm, DFS 46 v 29m, NS.
2. **SELECT**: erlotinib
   - 69% completed 2y course
   - 2 yr DFS 88%
3. **CTONG1104**: gefitinib v chemo
   - Improved DFS
   - OS 75 v 63 m, NS
4. **EVIDENCE**: icotinib v chemo
   - Improved DFS, similar OS (immature)



Kelly, JCO 2015. Pennell, JCO 2019. Zhong, JCO 2021. He, Lancet Respir Med, 2021.

Landmark Studies
Non-metastatic EGFR+ NSCLC

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Practice Changing:

1. ADAURA: adjuvant osimertinib vs placebo for 3 years for stage IB-IIIA
2. LAURA: adjuvant osimertinib vs placebo until disease progression for stage IIIA/B/C

Practice Informing:

1. NEOS trial (Lv, et al, Lung Cancer 2023)
2. Neoadjuvant osimertinib for stage I-IIIA (Blakely, et al, JCO 2024)

Underway:

1. NeoADAURA: neoadjuvant chemotherapy, osimertinib, or chemo-osi for stage II-IIIB N2, followed by adjuvant osimertinib, reporting at ASCO 2025.
2. ADAURA2: adjuvant osimertinib vs placebo for 3 years for stage IA2/3
3. TARGET: adjuvant osimertinib for 5 years for stage II-IIIB
4. PACIFIC-4 (EGFR subset): Osimertinib following SBRT in patients with stage I-II unresected EGFRm NSCLC

ADAURA

Osimertinib in resected EGFR-mutated NSCLC

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Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non squamous NSCLC
Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non Asian)

Osimertinib 80 mg, once daily

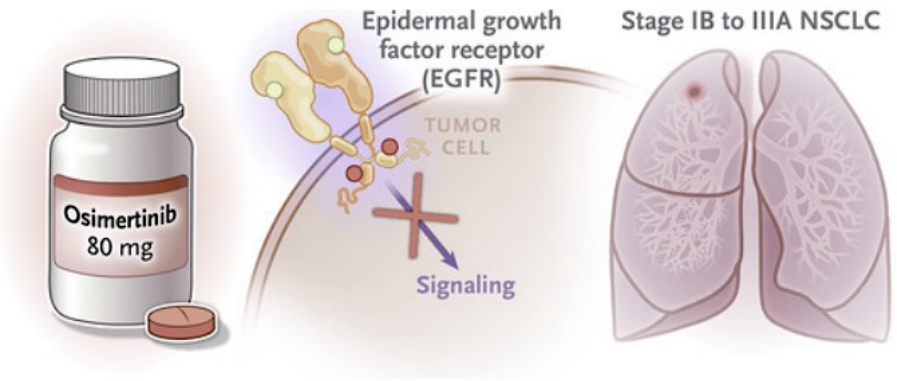
Randomization 1:1 (N=682)

Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly



Wu Y-L, Tsuboi M, He J, et al. NEJM 2020;383:1711-23

ADAURA: DFS & OS in Stage II-IIIA Disease

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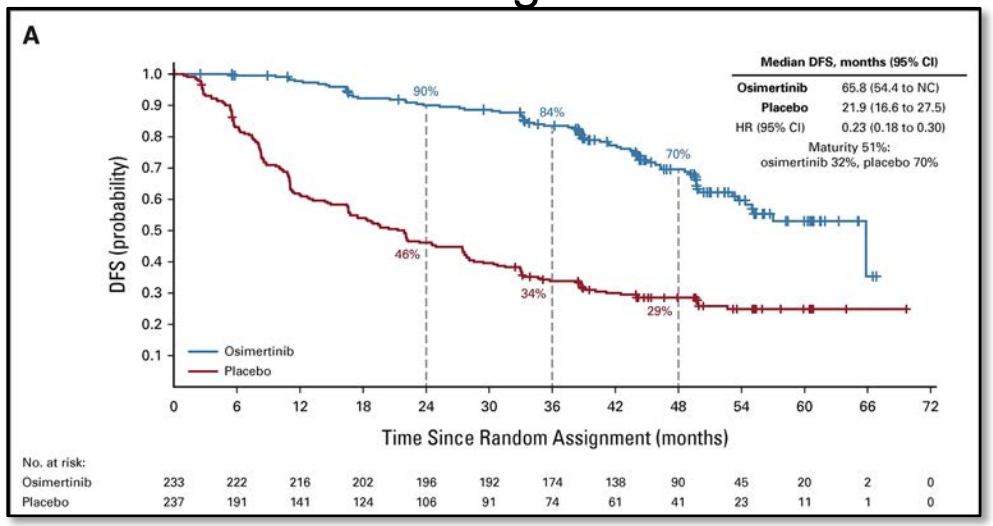
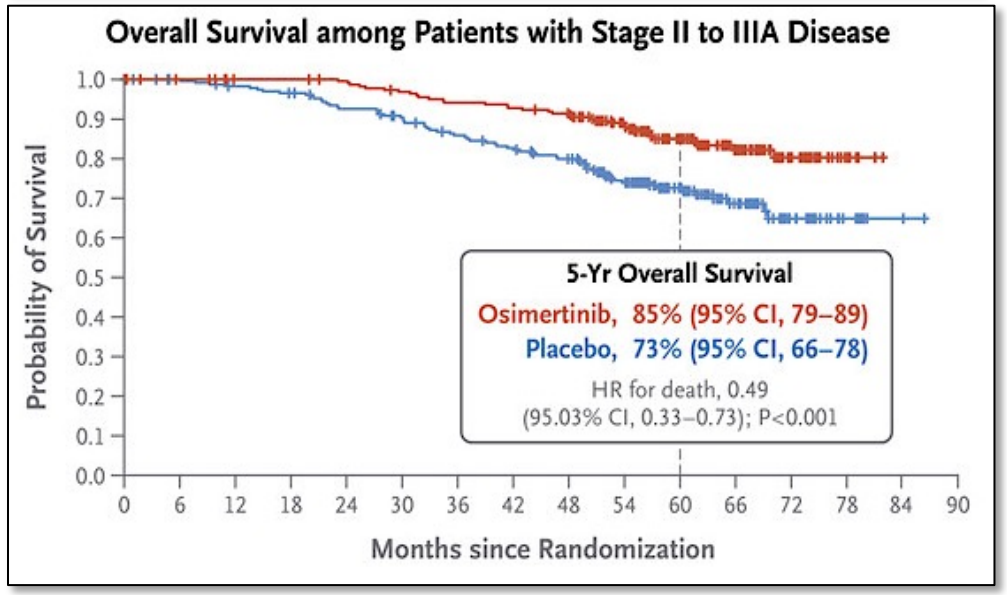
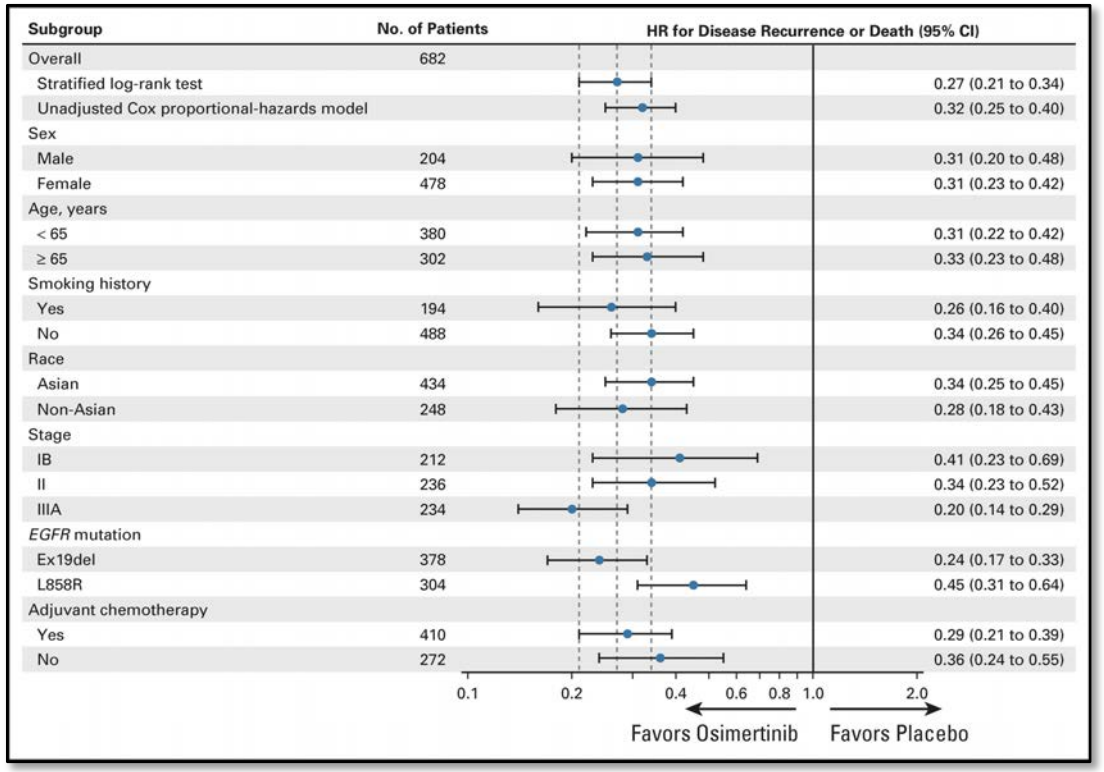
DFS in Stage II-IIIA





Forest Plot

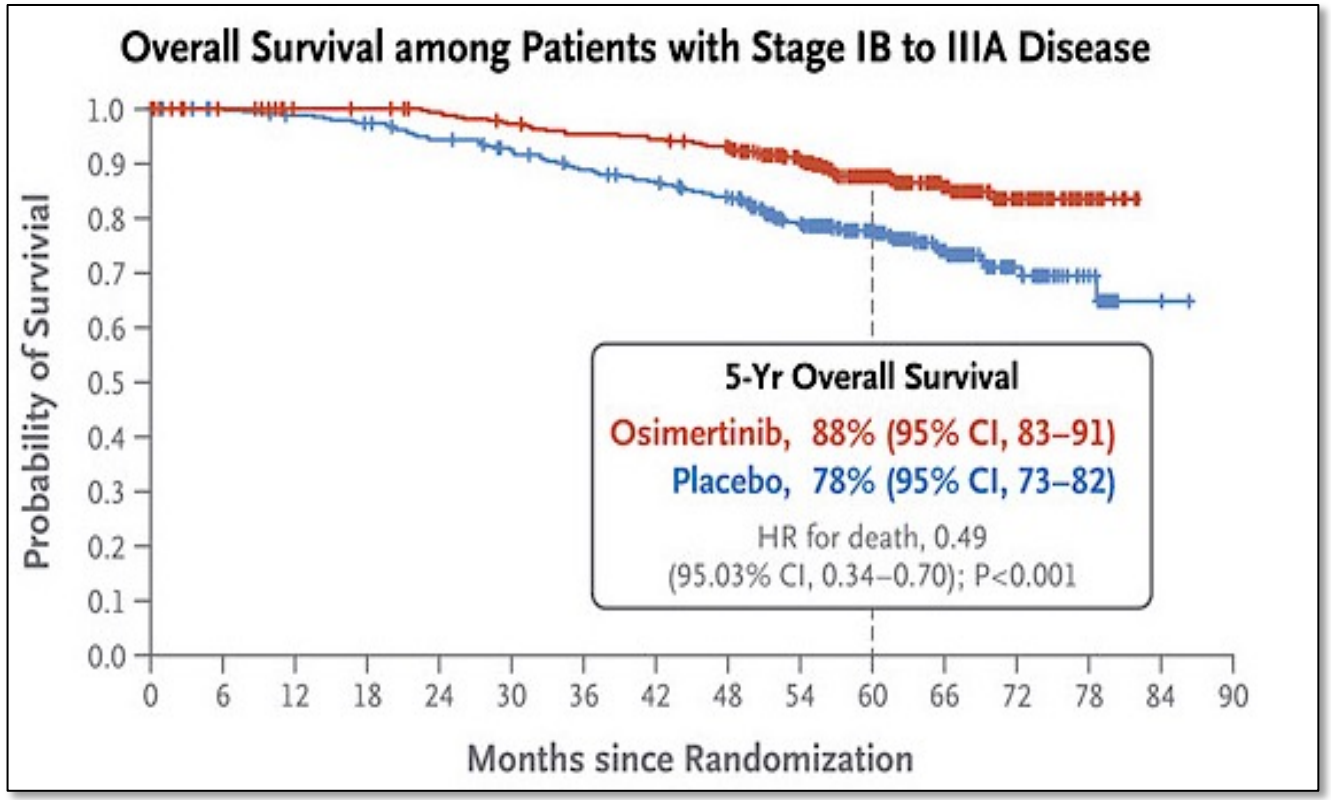


Subgroup	No. of Patients	HR for Disease Recurrence or Death (95% CI)
Overall	682	
Stratified log-rank test		0.27 (0.21 to 0.34)
Unadjusted Cox proportional-hazards model		0.32 (0.25 to 0.40)
Sex		
Male	204	0.31 (0.20 to 0.48)
Female	478	0.31 (0.23 to 0.42)
Age, years		
< 65	380	0.31 (0.22 to 0.42)
≥ 65	302	0.33 (0.23 to 0.48)
Smoking history		
Yes	194	0.26 (0.16 to 0.40)
No	488	0.34 (0.26 to 0.45)
Race		
Asian	434	0.34 (0.25 to 0.45)
Non-Asian	248	0.28 (0.18 to 0.43)
Stage		
IB	212	0.41 (0.23 to 0.69)
II	236	0.34 (0.23 to 0.52)
IIIA	234	0.20 (0.14 to 0.29)
EGFR mutation		
Ex19del	378	0.24 (0.17 to 0.33)
L858R	304	0.45 (0.31 to 0.64)
Adjuvant chemotherapy		
Yes	410	0.29 (0.21 to 0.39)
No	272	0.36 (0.24 to 0.55)

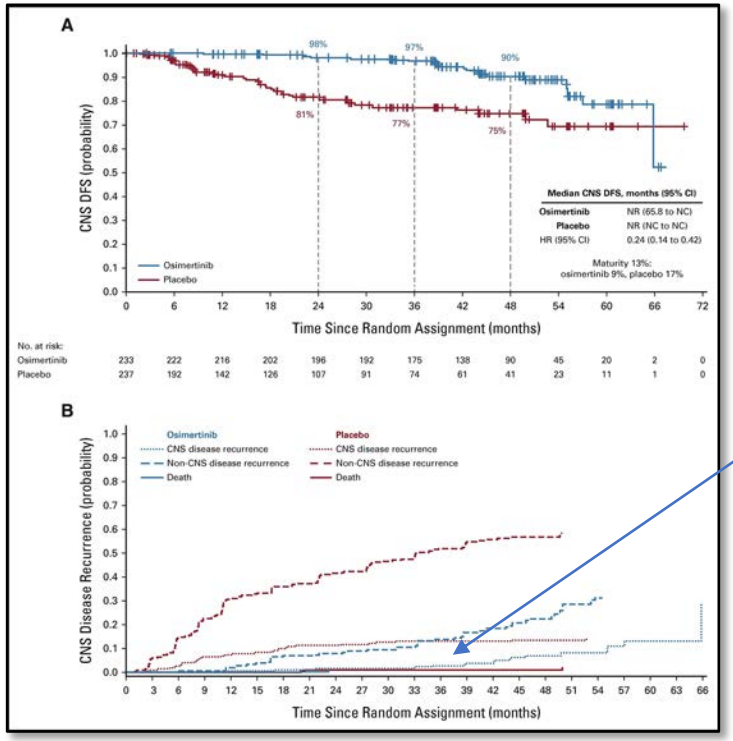
- 5-year OS with Osimertinib was 85%, vs placebo at 73%
- *Median follow up:* Greater than 5+ years for both arms
- mOS was not reached

Wu, NEJM 2020.
Tsuboi, NEJM 2023 and Herbst, JCO 2023.

ADAURA: OS in Overall Population



- 5-year OS with Osimertinib was 88%
- Placebo at 78%
- *Median follow up for OS*: 60.4 months with Osimertinib and 59.4 with placebo.



CNS Control

CNS events creep up at 36 m

Wu, NEJM 2020.
Tsuboi, NEJM 2023 and Herbst, JCO 2023.

NSCLC Biomarker Testing in the Operative Setting

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- EGFR mutation and ALK fusion are required based on FDA approvals
- PD-L1 testing may also be helpful to predict immunotherapy benefit for non-oncogene driven (non-AGA) pts

EGFR by PCR, ALK by IHC or FISH, and PD-L1 by IHC;
or, NGS (ideally from tissue) and PD-L1 by IHC;
or, a combination.
Sufficient tissue and rapid turn-around times are crucial.

- Future directions include testing for other optimally targeted oncogenes:
  - Yes: RET
  - No: KRAS G12C, BRAF
  - Maybe: ROS1, HER2, EGFR exon 20, MET, NTRK

Take home points:

- DFS and OS benefits for stage IB-IIIA strongly support adjuvant osimertinib for 3 years
- Necessary Triad for Potential Adjuvant TKI: high response rate (>50-60%), excellent tolerability for prolonged use, and good CNS penetration
- Adjuvant TKIs may or may not lead to “cures,” but a significant increase in DFS may lead to improved OS
- Future directions may include new targeted agents, longer durations of adjuvant therapy for higher stage and higher risk disease (possibly informed by an MRD analysis)

ADAURA-2: study design

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ADAURA2 (NCT05120349) is a Phase III, global, randomised, double-blind study of adjuvant osimertinib in **stage IA2–IA3** EGFRm (Ex19del or L858R) NSCLC following complete tumor resection

Adult participants with completely resected stage IA2 or IA3* EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years
- Confirmed primary non-squamous pathological stage IA2 or IA3* NSCLC
- EGFR mutation (Ex19del or L858R) either alone or in combination with other EGFR mutations
- Complete (R0) surgical resection of the primary tumour with negative margins (by lobectomy, segmentectomy or sleeve resection)
- Tumour sample submission for central pathology assessment of:
  - Invasive tumour size
  - Presence of lymphovascular invasion
  - Tumour histology
- WHO performance status 0 / 1
- No pre- / post-operative radiotherapy or systemic therapy
- Not eligible for any other local SOC treatment

Stratification by:

- **Risk** (high risk vs low risk†)
- **EGFR mutation type** (Ex19del vs L858R)
- **Race** (Chinese Asian vs non-Chinese Asian vs non-Asian)

Randomisation 1:1 (N=380)

Osimertinib 80 mg PO QD

Placebo PO QD

3-year treatment duration until treatment completion or discontinuation, or disease recurrence

*Based on the eighth edition UICC / AJCC TNM staging system. †High risk defined as presence of ≥1 of the following factors: largest diameter of invasive component of primary tumor>2 cm, lymphovascular invasion and / or high-grade histology (≥20% micropapillary, solid or complex gland adenocarcinoma). Low risk defined as absence of any high-risk factors.

Primary endpoint:
DFS per investigator assessment in high-risk† stratum

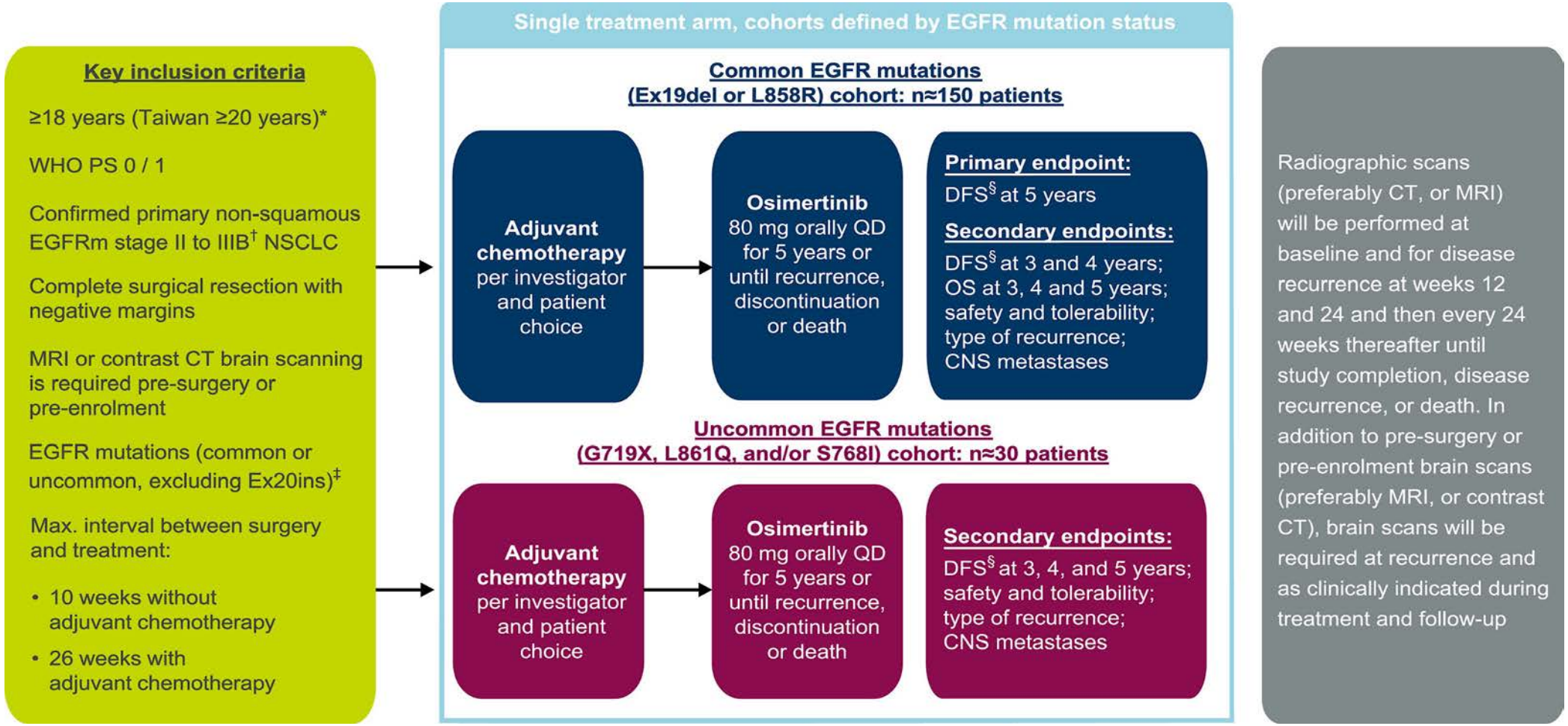
Secondary endpoints:

- DFS in overall population
- OS in high-risk† stratum
- OS in overall population
- HRQoL
- Safety / tolerability
- PK
- CNS DFS

Goldman, WCLC 2022

TARGET: study design

TARGET (NCT05526755) is a Phase II, multinational, open-label, single-arm study of adjuvant osimertinib **for 5 years** in stage II–IIIB EGFRm (common or **uncommon**) NSCLC following complete tumor resection



Soo, Clinical Lung Cancer 2024

Neoadjuvant osimertinib

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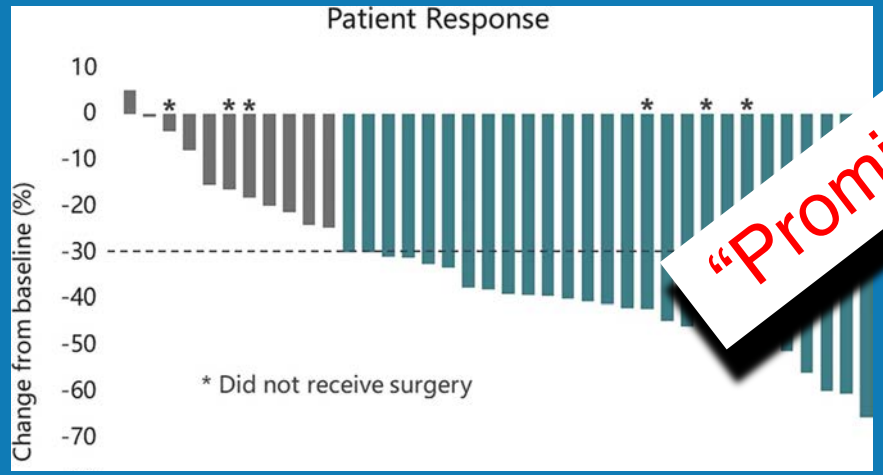
NEOS trial

Enrolled 40 subjects, stage II-IIIB.
2 withdrew consent prior to completing 6w osimertinib.

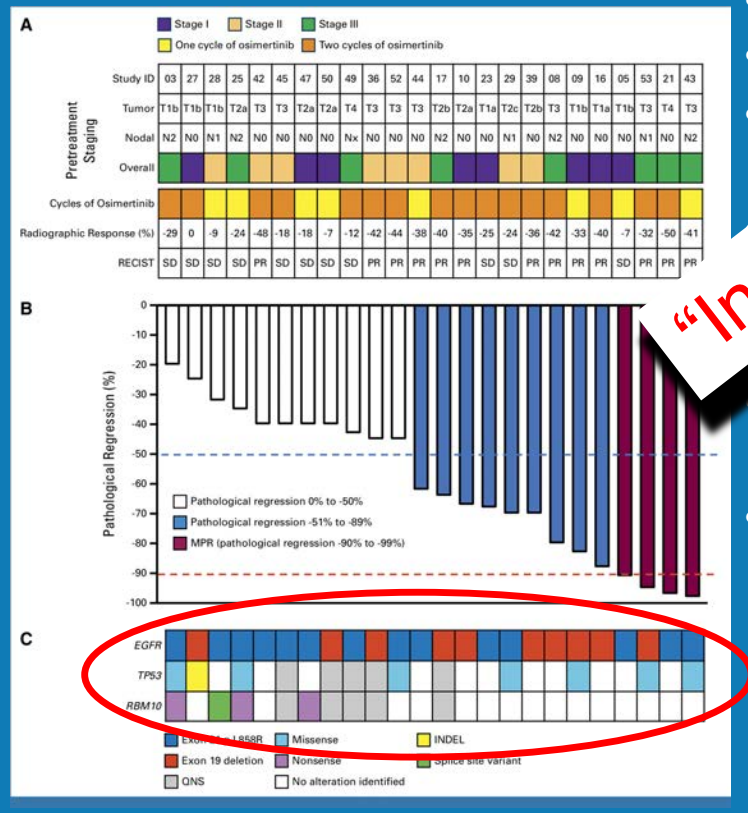


"Promising"

- ORR seen in 27/38 (71.1%)
- 30/32 (93.8%) R0 resections
- 3/28 (10.7%) major path response, incl 1 (3.6%) path CR
- Downstaging in 15/32 (46.9%)
  - 7/17 (41.2%) pts with N2 disease → N1 (2) or N0 (5)

Blakely trial

Enrolled 27 subjects, stage IA-IIIA, to receive 1-2 m osimertinib.

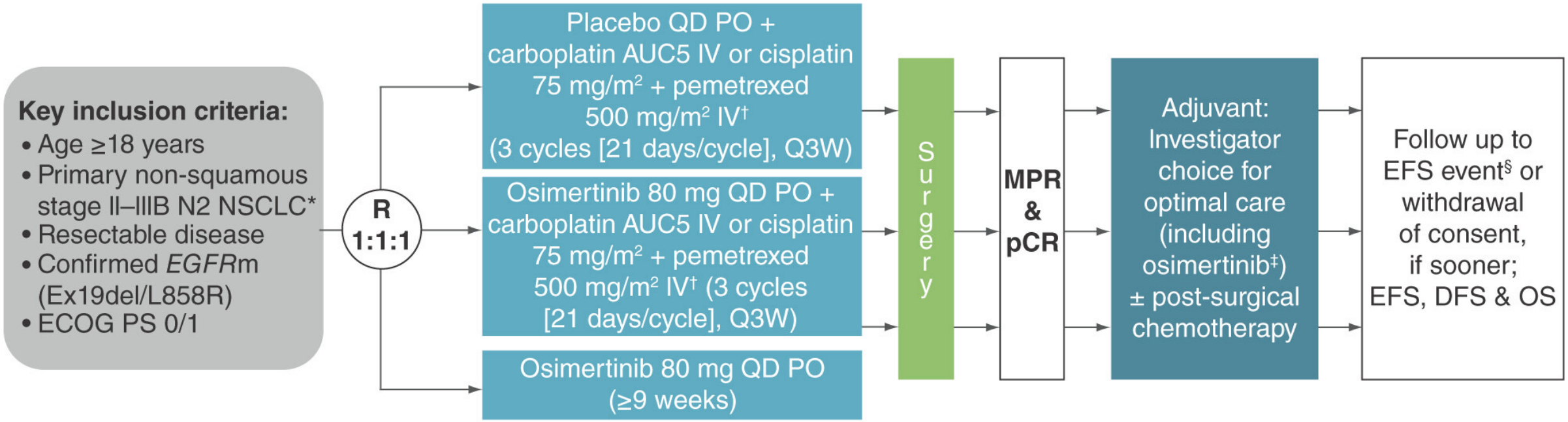


"Insufficient"

- ORR 51.9%
- 1/28 PD
- 23/2 R0 r
  .7%)
  or path resp,
  pCR
- Upstaging in 4 (12.5%)
- Downstaging in 13/24 (54.2%)
  - 3/5 (60%) pts with N2 disease → N1 (1) or N0 (2)
- mDFS 40.9 m

Lv, Lung Cancer, 2023. Blakely, JCO 2024.

NeoADAURA Trial



NeoADAURA (NCT04351555), is a phase III, randomized study that evaluates neoadjuvant osimertinib ± chemotherapy. Planned to enroll 351 patients with resectable stage II-IIIB (8th ed) EGFR-mutated NSCLC. The primary endpoint is major pathological response. Secondary end points include event-free survival, pathological complete response, nodal downstaging at the time of surgery, disease-free survival, overall survival and health-related quality of life.

Abstract 8001 oral session, ASCO 2025, Chaft, et al. Major path response rate 26% and 25% in osi-containing arms, and 2% in PBO-chemo arm. pCR rate 4% and 9% vs 0%.

Tsuboi, Future Oncol, 2021.

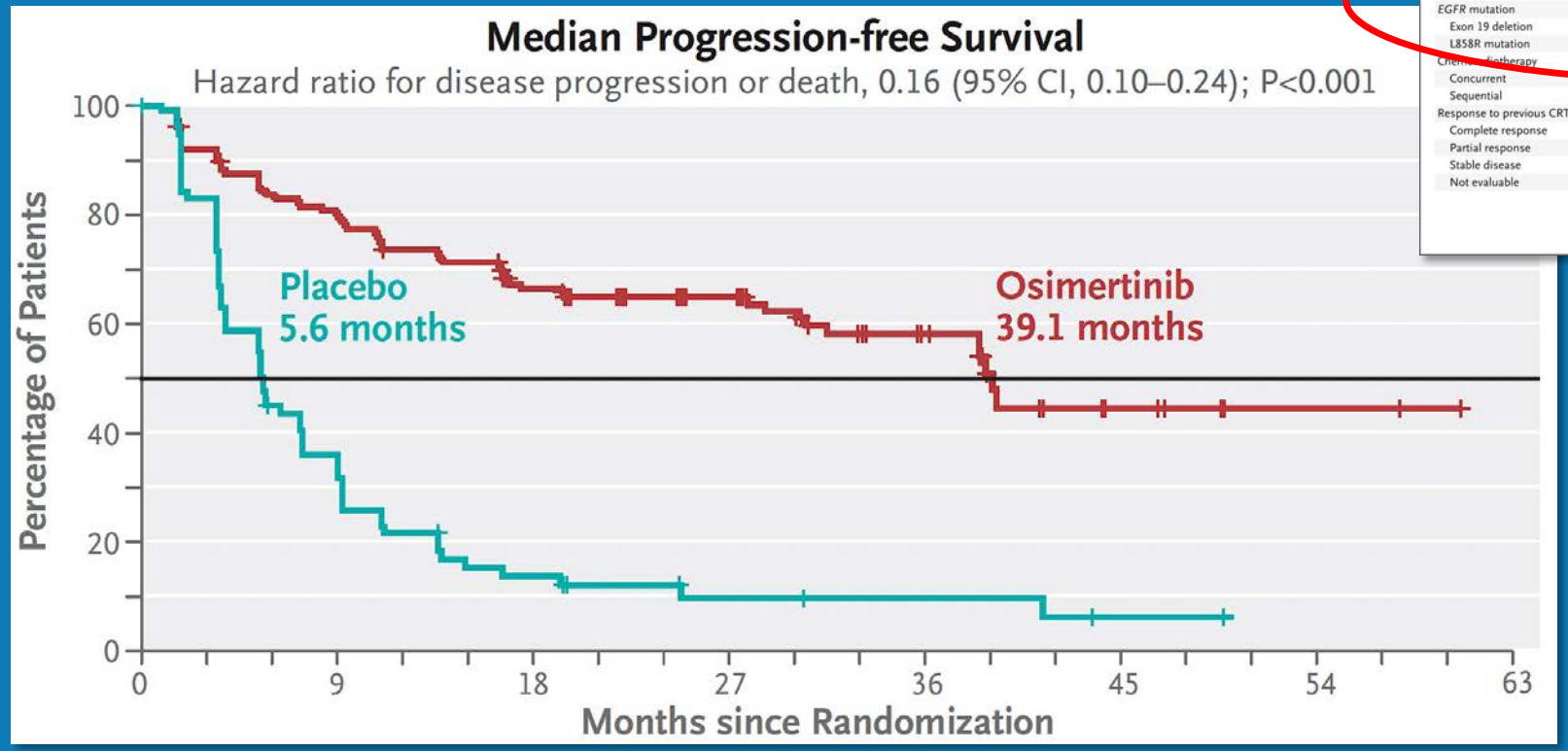
LAURA trial: consolidation osimertinib

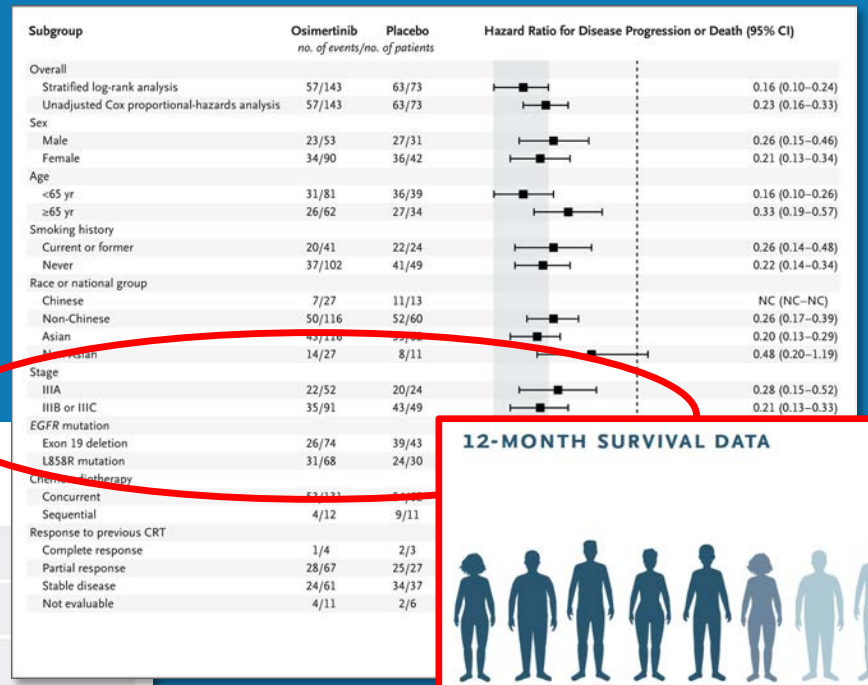
UCLA Health | David Geffen School of Medicine

Trial Design

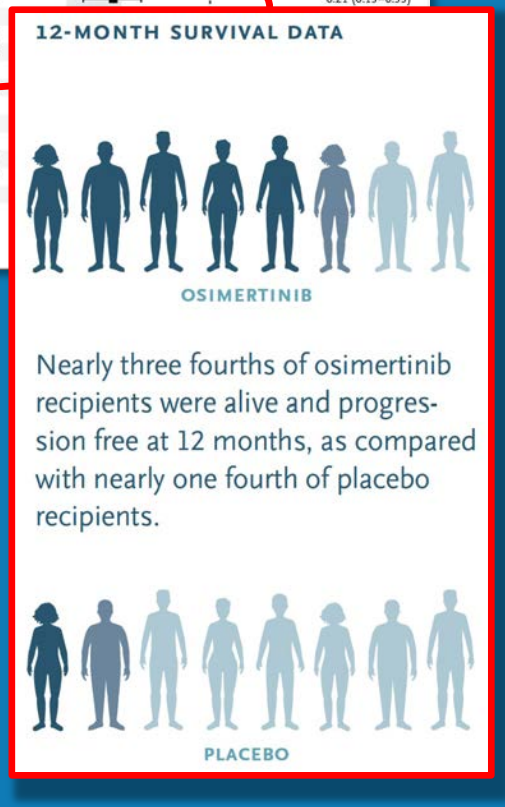
216 pts, following chemoradiation, randomized 2:1 to osimertinib vs placebo until progression per BICR

Primary Endpoint: PFS





Subgroup	Osimertinib	Placebo	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall			
Stratified log-rank analysis	57/143	63/73	0.16 (0.10–0.24)
Unadjusted Cox proportional-hazards analysis	57/143	63/73	0.23 (0.16–0.33)
Sex			
Male	23/53	27/31	0.26 (0.15–0.46)
Female	34/90	36/42	0.21 (0.13–0.34)
Age			
<65 yr	31/81	36/39	0.16 (0.10–0.26)
≥65 yr	26/62	27/34	0.33 (0.19–0.57)
Smoking history			
Current or former	20/41	22/24	0.26 (0.14–0.48)
Never	37/102	41/49	0.22 (0.14–0.34)
Race or national group			
Chinese	7/27	11/13	NC (NC–NC)
Non-Chinese	50/116	52/60	0.26 (0.17–0.39)
Asian			0.20 (0.13–0.29)
[illegible]	14/27	8/11	0.48 (0.20–1.19)
Stage			
IIIA	22/52	20/24	0.28 (0.15–0.52)
IIIB or IIIC	35/91	43/49	0.21 (0.13–0.33)
EGFR mutation			
Exon 19 deletion	26/74	39/43	
L858R mutation	31/68	24/30	
Chemoradiotherapy			
Concurrent			
Sequential	4/12	9/11	
Response to previous CRT			
Complete response	1/4	2/3	
Partial response	28/67	25/27	
Stable disease	24/61	34/37	
Not evaluable	4/11	2/6	

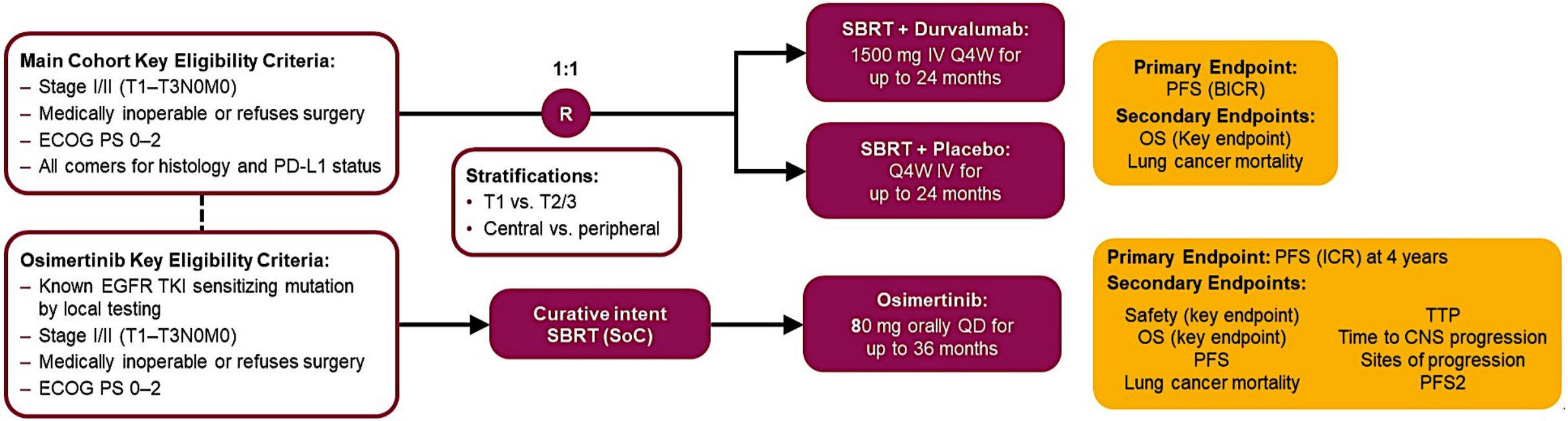


Lu, NEJM, 2024.

PACIFIC-4 Trial: consolidation after SBRT

UCLA Health | David Geffen School of Medicine

- In PACIFIC-4, a main cohort of ~630 patients will be randomized (1:1) in a double-blind manner, stratified by tumor size (T1 vs. T2/3) and location (central vs. peripheral), to receive concurrent SoC SBRT with either durvalumab (1500 mg IV) or placebo Q4W for up to 26 cycles.
- The original protocol was amended (at version 4) to:
  i. Exclude patients with an identified EGFR mutation by local testing from the main cohort, and
  ii. Add a separate cohort of ~60 patients with identified EGFR mutations (L858R or Ex19del) who will receive oral osimertinib 80 mg QD for up to 36 months, following SoC SBRT.
- This updated protocol is approved in all countries except France and the UK, where the osimertinib cohort is not available.



Robinson, ASCO, 2023.

Cure vs sustained DFS

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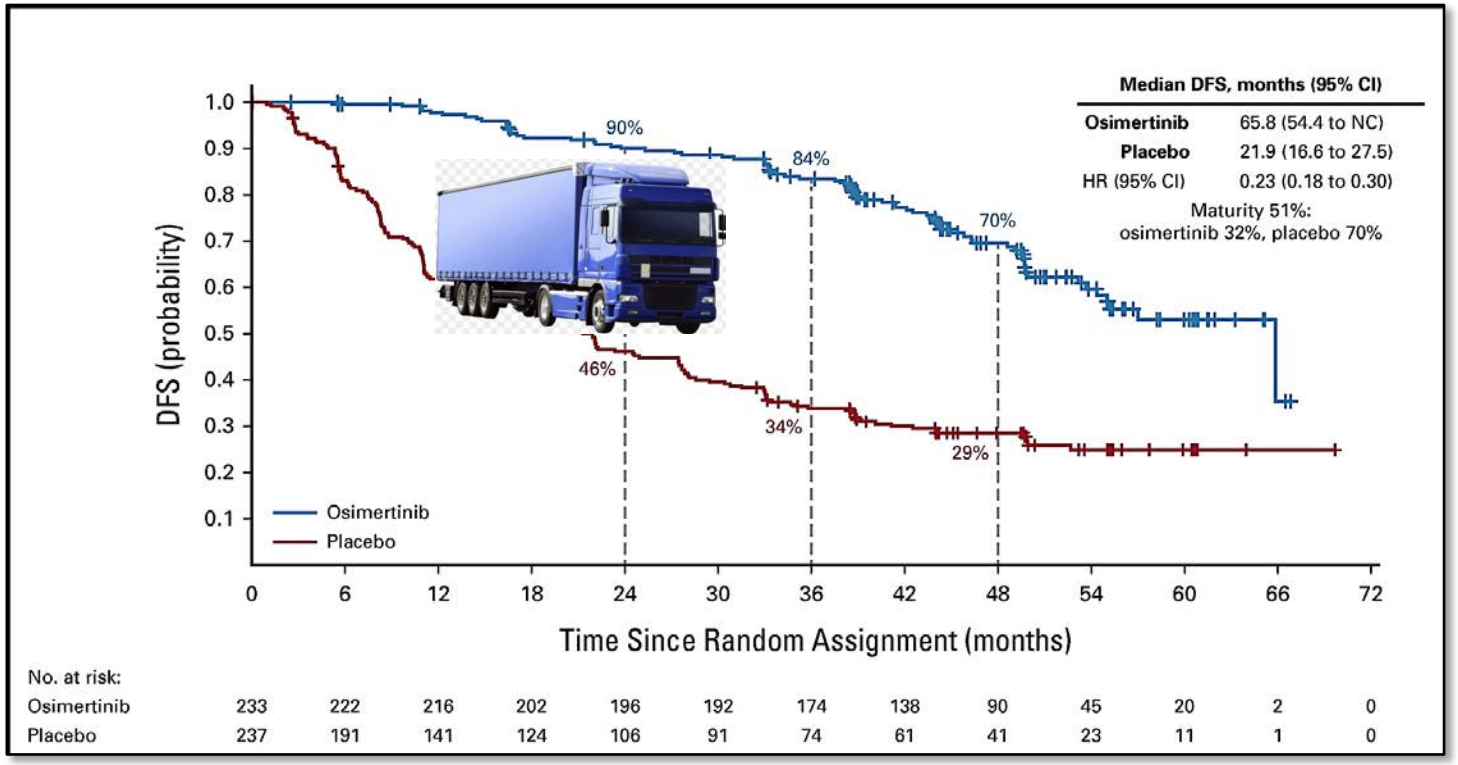
The Crucial Question

Will adjuvant TKI therapy improve the cure rate and OS?

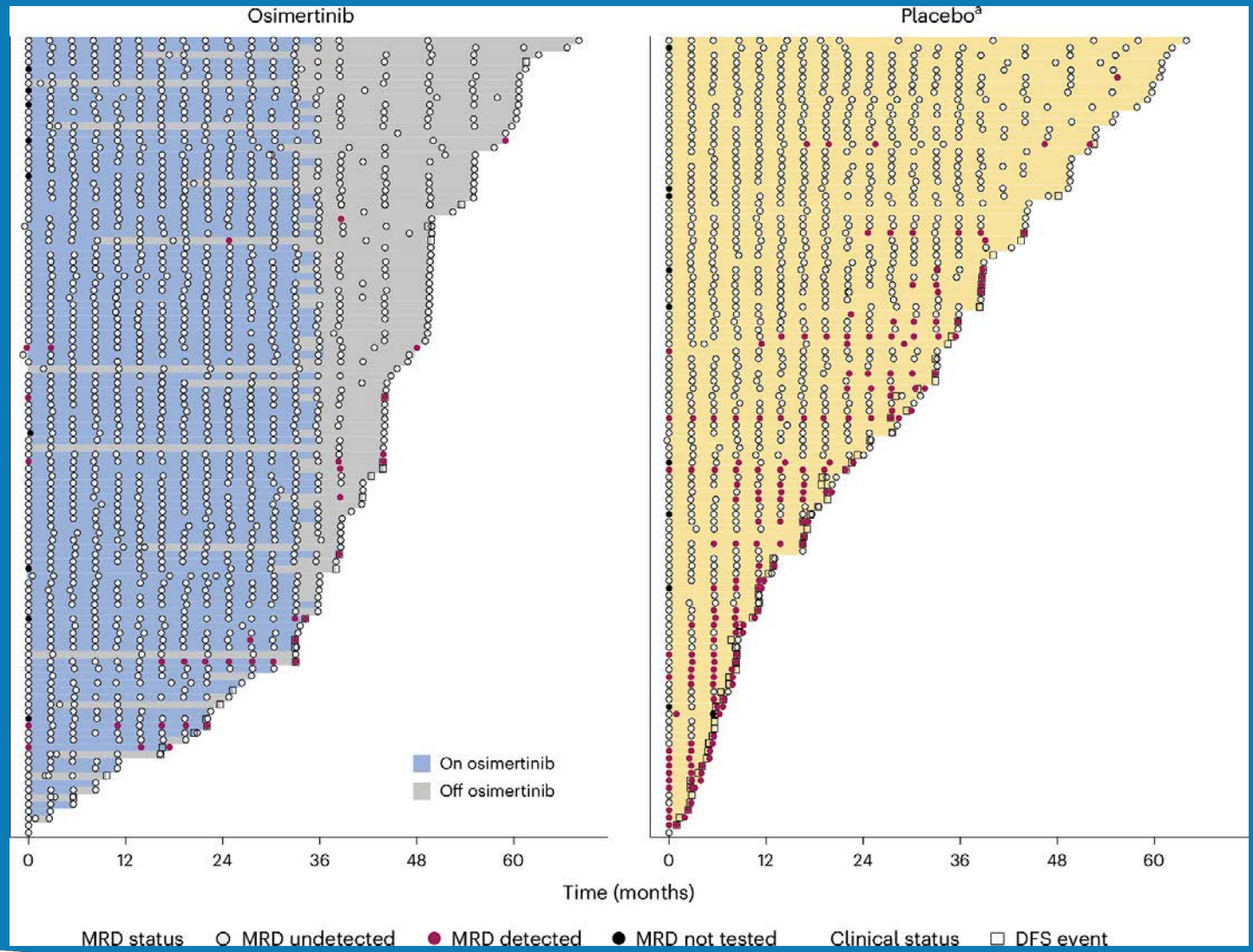


Herbst, JCO 2023.

- On placebo (natural history) median disease recurrence/death is at 21.9 m. If the average PFS of 1L osi at recurrence is 18.9 m, then at **40.8 m** the median patient will have recurred post chemo and progressed post TKI.
- On 3 yr adjuvant osi, median DFS **65.8 m**, to reach the same post-chemo & TKI point.
- The slope of the osimertinib line suggests that resistance develops more slowly in the adjuvant setting than in the metastatic one.

The Future?: MRD analysis

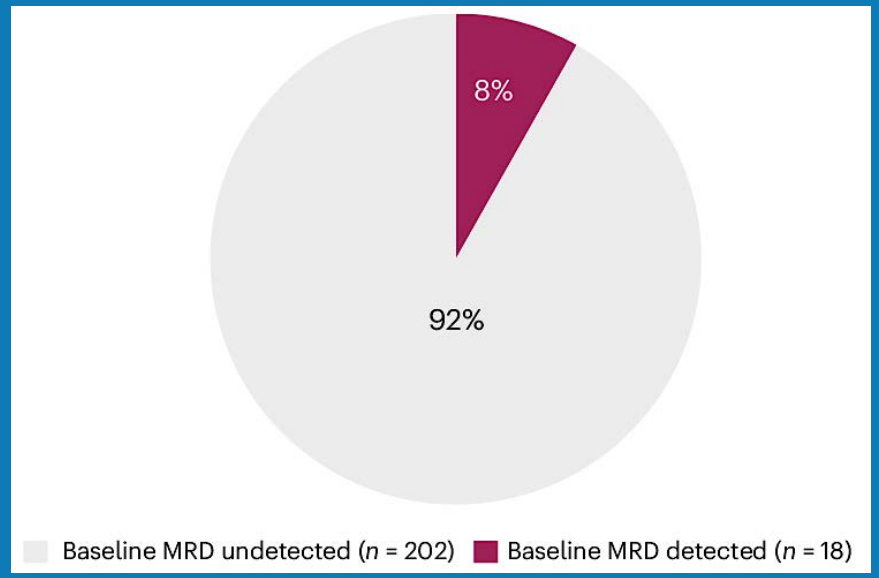
ADAURA post hoc analysis

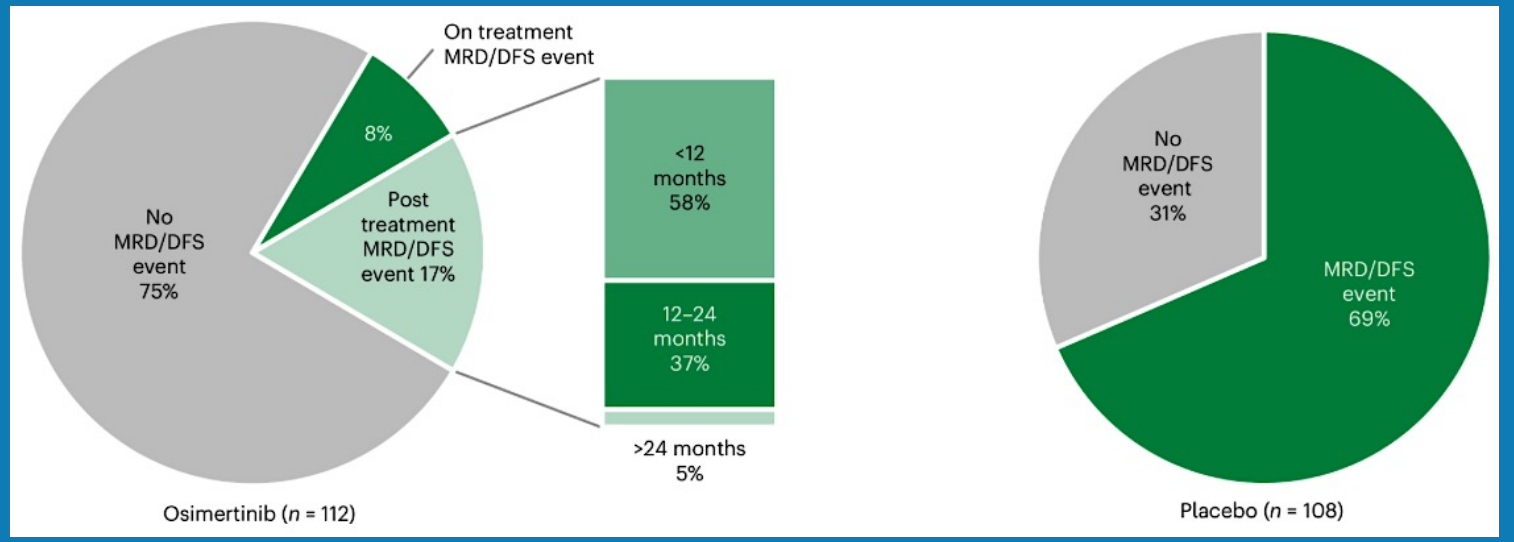


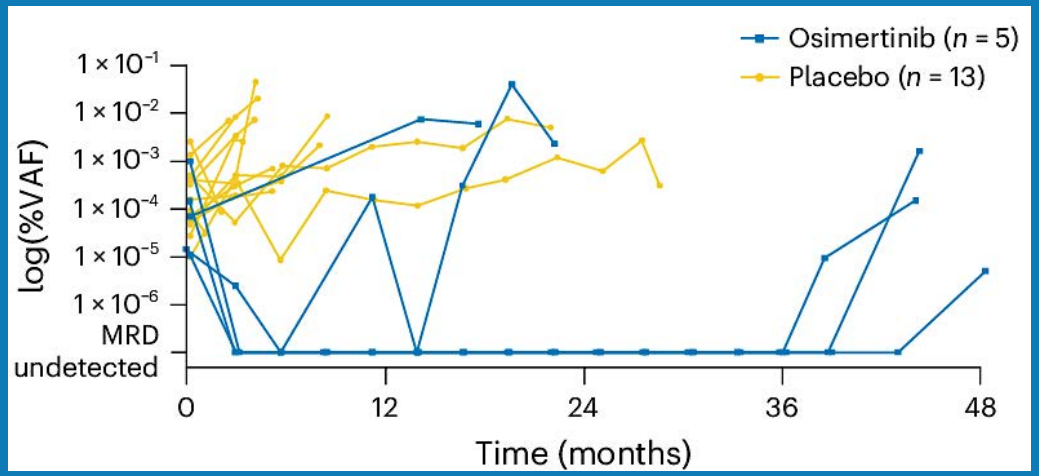
Herbst, Nat Med 2025

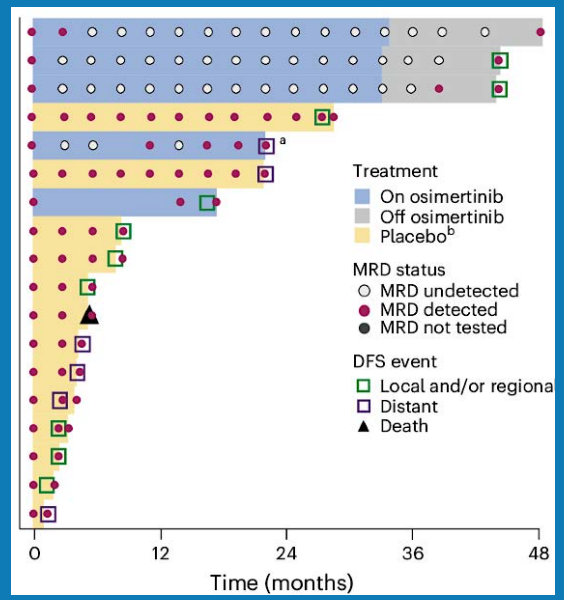
The Future?: MRD analysis

ADAURA post hoc analysis





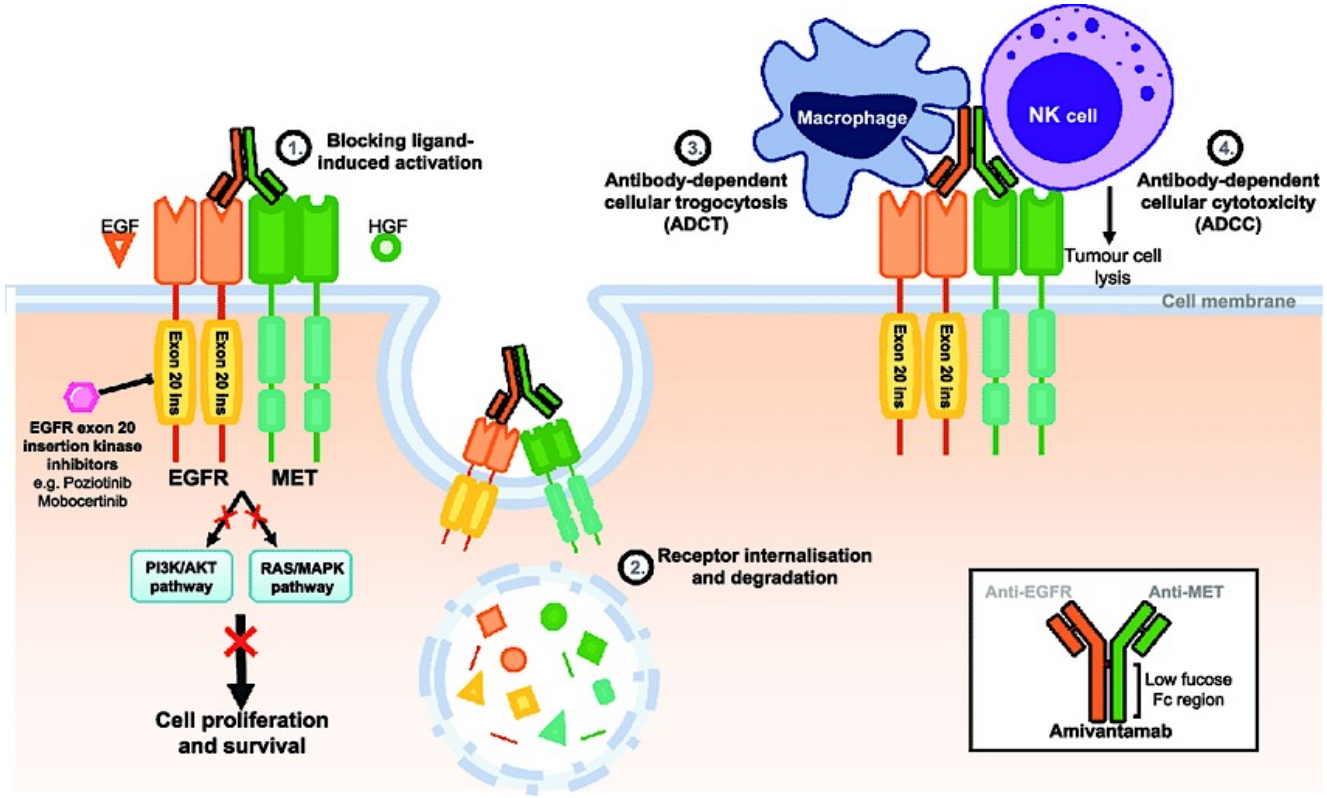




Herbst, Nat Med 2025

Novel agents?

1. Novel TKIs, eg for EGFR exon 20 insertion mutations
2. Cytotoxic combinations
3. Bispecific antibodies
4. Antibody drug conjugates



Vyse S. *Expert Rev Anticancer Ther*, 2022.

Conclusion

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- **Biomarker testing is crucial to identify patients for targeted therapy.**
- **Necessary Triad for Potential Adjuvant TKI**: high response rate (>50-60%), excellent tolerability for prolonged use, and good CNS penetration
- Adjuvant TKIs may or may not lead to “cures,” but a significant increase in DFS may lead to improved OS
- Future directions may include new targeted agents, longer durations of adjuvant therapy for higher stage and higher risk disease (possibly informed by an **MRD analysis**)

Practice Changing Trials:

1. **ADAURA**: adjuvant osimertinib vs placebo for 3 years for stage IB-IIIA
2. **LAURA**: adjuvant osimertinib vs placebo until disease progression for stage IIIA/B/C

New data: NeoADAURA: neoadjuvant chemotherapy, osimertinib, or chemo-osi for stage II-IIIB N2, followed by adjuvant osimertinib, reporting at ASCO 2025.

Ongoing trials: ADAURA2, TARGET, PACIFIC-4 (EGFR subset)

Regulatory and reimbursement issues aside, in general, which adjuvant treatment would you recommend for an otherwise healthy 65-year-old patient with localized nonsquamous NSCLC as described with an EGFR exon 19 deletion and a PD-L1 TPS of 0?

	Stage IB	Stage IIA	Stage IIIA
 Prof Girard	Osimertinib	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Goldman	Osimertinib	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Jänne	Osimertinib	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Ramalingam	None	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Sabari	Osimertinib	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Yu	Osimertinib	Chemotherapy → osimertinib	Chemotherapy → osimertinib
 Dr Gadgeel	None	Osimertinib + chemotherapy	Osimertinib + chemotherapy
 Dr Spira	None	Osimertinib	Osimertinib

Regulatory and reimbursement issues aside, how long would you continue adjuvant osimertinib for a patient with high-risk localized nonsquamous NSCLC with an EGFR exon 19 deletion who is tolerating therapy well?

 Prof Girard	Until progression
 Dr Goldman	36 months for Stage IB-II; indefinitely for Stage III
 Dr Jänne	36 months
 Dr Ramalingam	36 months
 Dr Sabari	Indefinitely
 Dr Yu	Indefinitely
 Dr Gadgeel	36 months (for Stage III may continue indefinitely)
 Dr Spira	36 months

Regulatory and reimbursement issues aside, what would you most likely recommend as consolidation treatment for a patient with unresectable locally advanced NSCLC who has completed chemoradiation therapy and is found to have an EGFR exon 19 deletion?

 Prof Girard	Osimertinib
 Dr Goldman	Osimerinib
 Dr Jänne	Osimertinib
 Dr Ramalingam	Osimertinib
 Dr Sabari	Osimertinib
 Dr Yu	Osimertinib
 Dr Gadgeel	Osimertinib
 Dr Spira	Osimertinib

RTP RESEARCH TO PRACTICE

To what degree do you believe adherence is an issue for patients receiving adjuvant osimertinib for localized NSCLC?

 Prof Girard	Moderate
 Dr Goldman	Not at all
 Dr Jänne	Somewhat
 Dr Ramalingam	Somewhat
 Dr Sabari	Moderate
 Dr Yu	Not at all
 Dr Gadgeel	Moderate
 Dr Spira	Moderate

RTP RESEARCH TO PRACTICE

Outside of a clinical trial setting, have you or would you employ neoadjuvant osimertinib for a patient with resectable NSCLC and a documented EGFR mutation?

 Prof Girard	Not at this time, awaiting data to be presented
 Dr Goldman	I have
 Dr Jänne	I have
 Dr Ramalingam	I have not but would for the right patient
 Dr Sabari	I have
 Dr Yu	I have
 Dr Gadgeel	I have
 Dr Spira	I have

RTP RESEARCH TO PRACTICE

Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

RTP RESEARCH TO PRACTICE

EGFR exon20 ins

Pr. Nicolas Girard

Institut Curie,
INSERM U932,
Université Paris-Saclay

New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

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

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

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

1L therapies
Oncologists may not be aware of practice-changing data

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

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

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

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

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

New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

Amivantamab as first-line therapy
PAPILLON as current standard-of-care

PAPILLON: Global, randomized, phase 3 trial in treatment-naïve, NSCLC with *EGFR* Exon20ins mutation

Eligibility criteria

- Treatment-naïve,* locally advanced or metastatic NSCLC
- Documented *EGFR* exon20ins mutation
- ECOG PS 0 or 1

Stratification factors

- ECOG PS
- History of brain metastases†
- Prior EGFR TKI use*

1:1 R — **N=308**

- **Amivantamab + ChT** (n=153)
- **ChT** (n=155)

Dosing (in 21-day cycles):

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

ChT on the first day of each cycle:

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

Primary endpoint

- PFS by BICR (RECIST v1.1)‡

Secondary endpoints

- ORR‡
- DoR
- OS‡
- PFS2
- Symptomatic PFS§
- Time to subsequent therapy§
- Safety

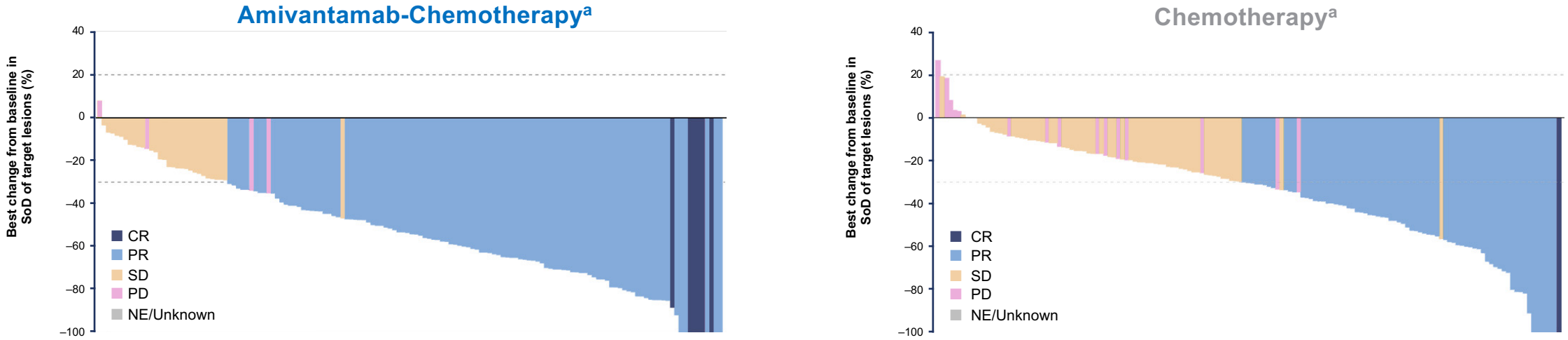
Optional crossover to 2L amivantamab monotherapy‖

Data cut-off: 3 May 2023.

*Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented);
†Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomisation;
‡Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing;
§These secondary endpoints (time to subsequent therapy and symptomatic PFS) will be presented at a future congress; ‖Crossover was only allowed after BICR confirmation of disease progression, amivantamab monotherapy on Q3W dosing per main study.
1/2L, first/second-line; AUC, area under the curve; BICR, blinded independent central review; ChT, chemotherapy; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; exon20ins, exon 20 insertion; HR, hazard ratio; ORR, overall response rate; PFS2, second PFS; Q3W, every 3 weeks; R, randomised; RECIST, Response Evaluation Criteria in Solid Tumours.

Girard, et al. ESMO 2023

PAPILLON: Secondary endpoint Objective Response



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

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

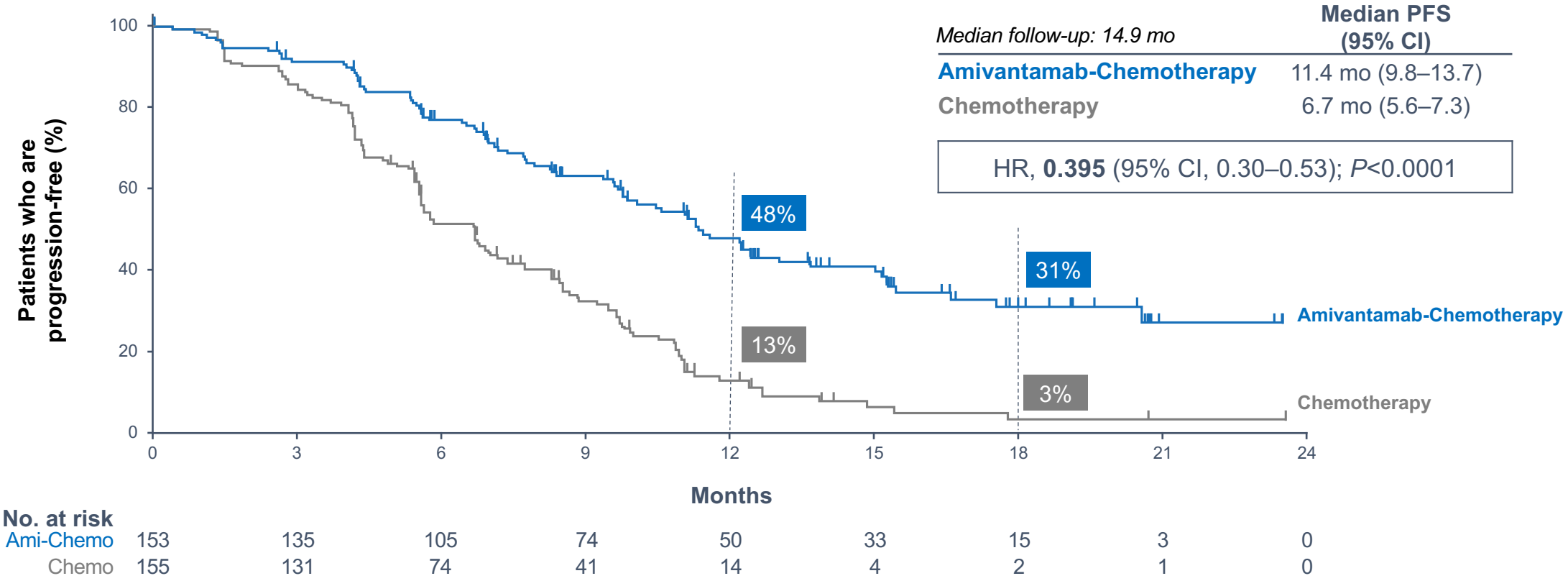
[a]Patients without postbaseline tumor assessment were not included in this plot. [b]No. of patients with measurable disease at baseline by BICR was 152 in both arms; response data presented among all responders. [c]Nominal *P*<0.001; endpoint not part of hierarchical testing.

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

MADRID 2023 ESMO congress

Girard, et al. ESMO 2023

PAPILLON: Primary endpoint
Progression-Free Survival

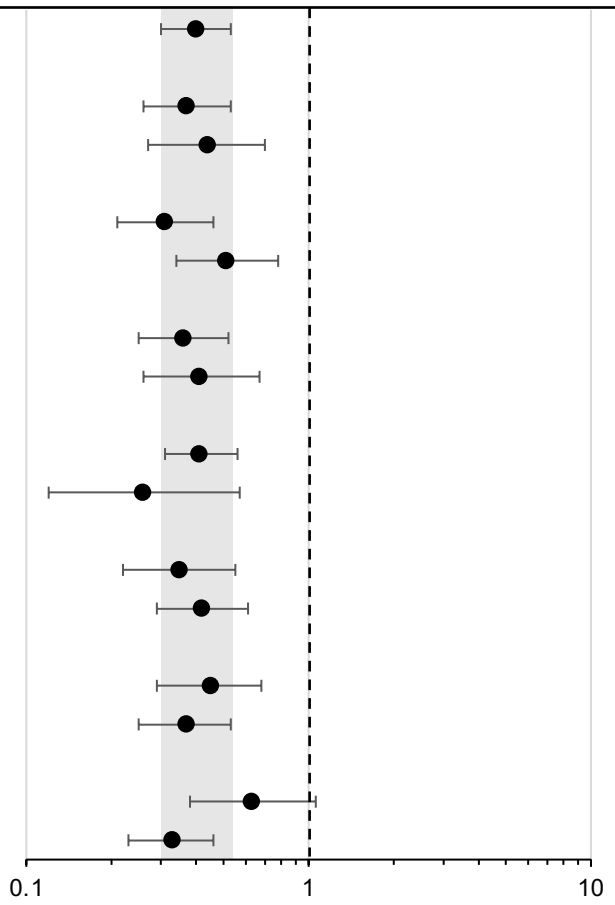


- **Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001)**

Ami-Chemo, Amivantamab-Chemotherapy; BICR, blinded independent central review; Chemo, Chemotherapy; CI, confidence interval; EGFR, epidermal growth factor receptor; Ex20ins, Exon 20 insertions; HR, hazard ratio; mo, months; NSCLC, non-small cell lung cancer; PFS, progression-free survival; US, United States.

1. Zhou C, et al. *N Engl J Med*. 2023;389(22):2039–2051. 2. Girard N, et al. Presented at:: European Society for Medical Oncology (ESMO) 20-24 October 2023; Madrid, Spain. 3. U.S. Food & Drug Administration. *FDA*. Published online March 1, 2024. Accessed March 7, 2024. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-amivantamab-vmjw-egfr-exon-20-insertion-mutated-non-small-cell-lung-cancer-indications.

PAPILLON: Primary endpoint Progression-Free Survival



Subgroup	HR (95% CI)	Events/N: Amivantamab-Chemotherapy	Events/N: Chemotherapy
All randomized patients	0.40 (0.30–0.53)	84/153	132/155
Age category			
<65 years	0.37 (0.26–0.53)	56/97	77/92
≥65 years	0.44 (0.27–0.70)	28/56	55/63
Sex			
Female	0.31 (0.21–0.46)	41/85	81/93
Male	0.51 (0.34–0.78)	43/68	51/62
Race			
Asian	0.36 (0.25–0.52)	55/97	77/89
Non-Asian	0.41 (0.26–0.67)	27/53	51/62
Weight category			
<80 kg	0.41 (0.31–0.56)	74/132	108/128
≥80 kg	0.26 (0.12–0.57)	10/21	24/27
ECOG PS			
0	0.35 (0.22–0.55)	31/59	51/58
1	0.42 (0.29–0.61)	53/94	81/97
History of smoking			
Yes	0.45 (0.29–0.68)	37/65	57/64
No	0.37 (0.25–0.53)	47/88	75/91
History of brain metastases			
Yes	0.63 (0.38–1.06)	28/36	34/38
No	0.33 (0.23–0.46)	56/117	98/117

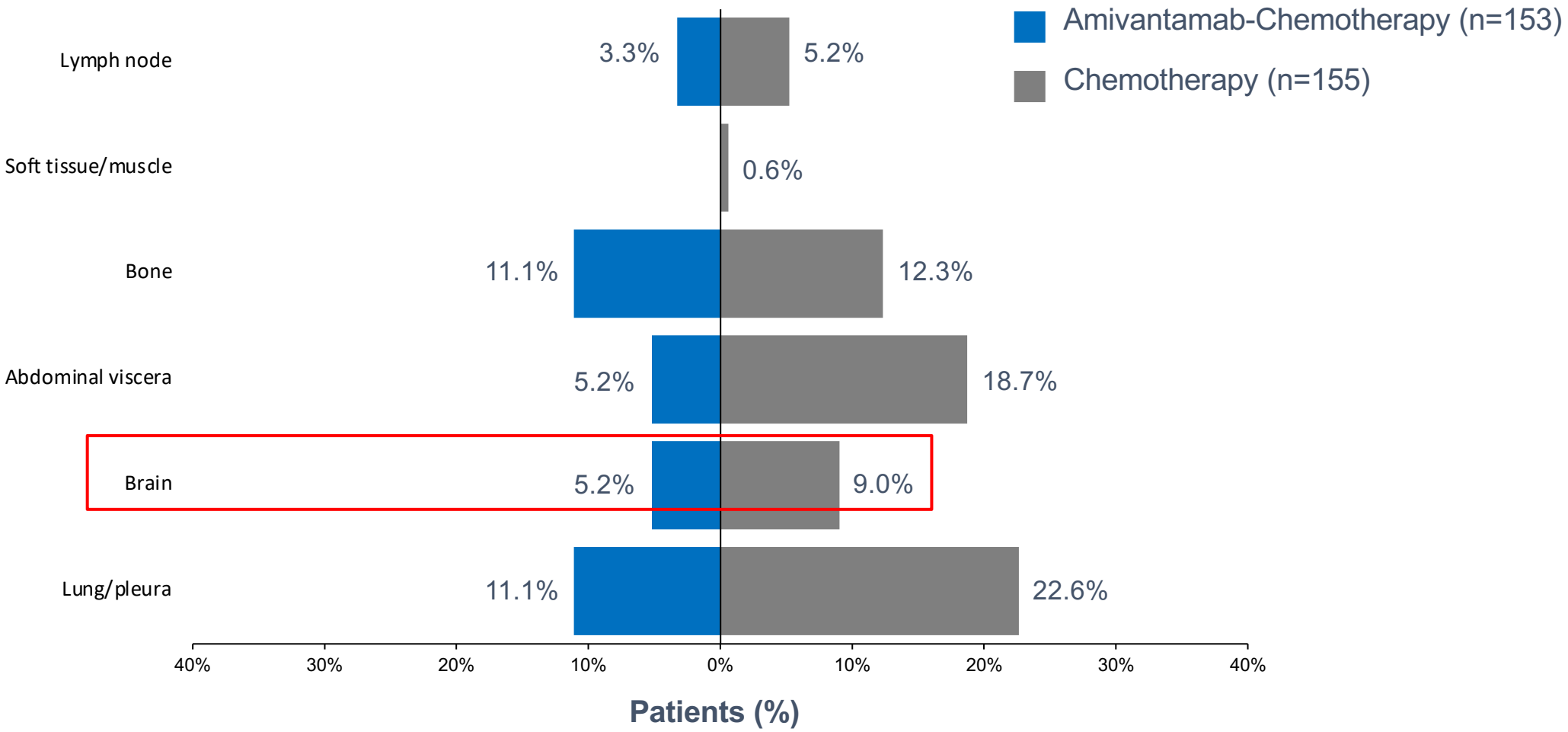
Note: Gray box indicates 95% CI of HR for all randomized patients.

BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; PFS, progression-free survival.

Girard, et al. ESMO 2023

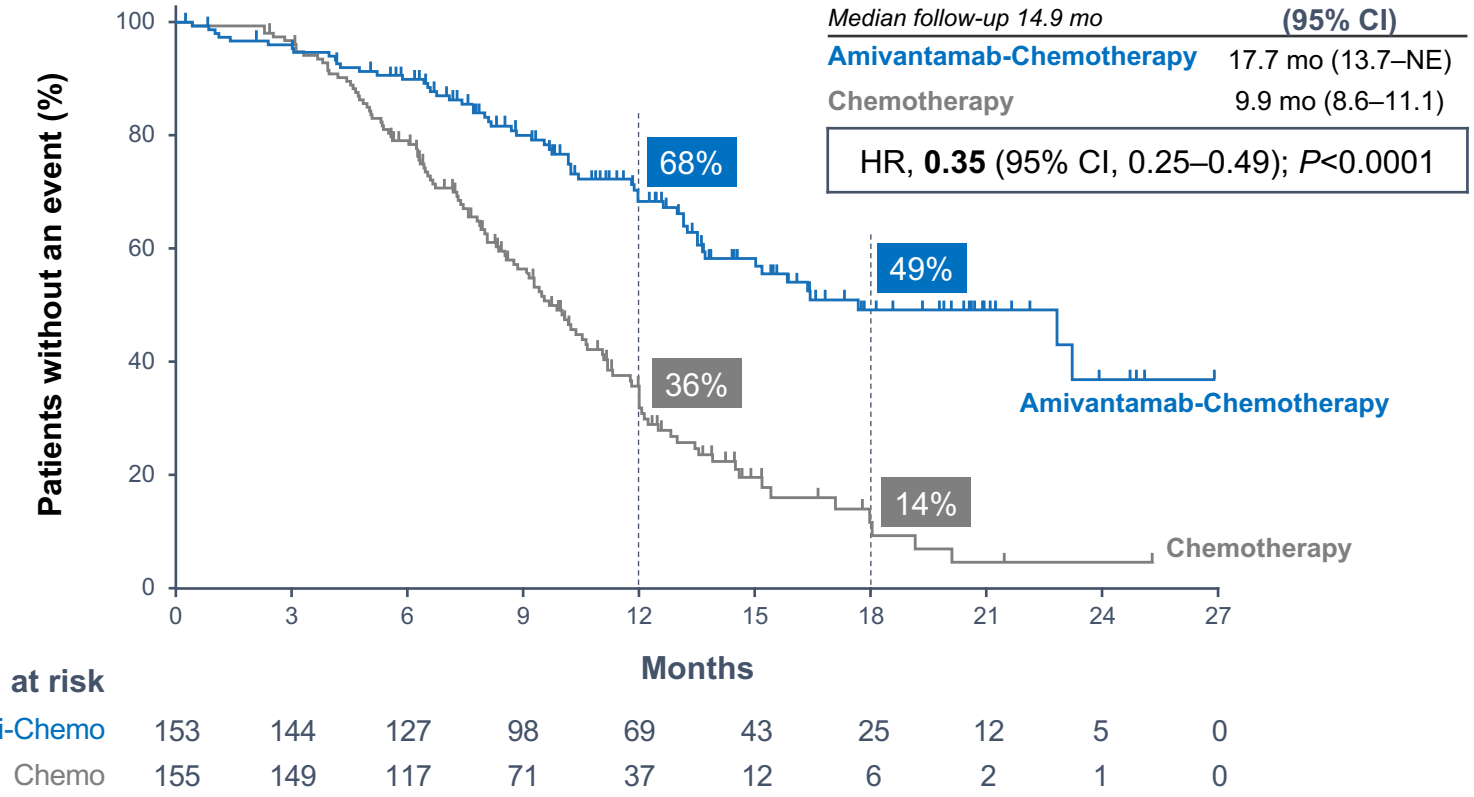
PAPILLON: sites of first progression

Rates of first progression at all sites were lower with amivantamab-chemotherapy compared to chemotherapy



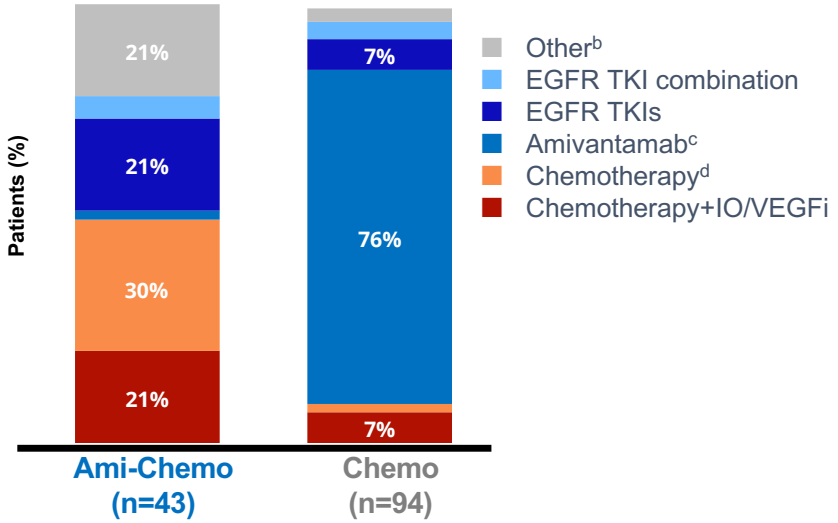
Note: Each patient can have multiple sites of progression at first disease progression.

PAPILLON: Secondary endpoint Time-To-Subsequent Therapy



Most Common First Subsequent Therapy Classes

- In the amivantamab-chemotherapy arm, **43 patients** went on to receive subsequent therapy during the study versus **94 patients** in the chemotherapy arm

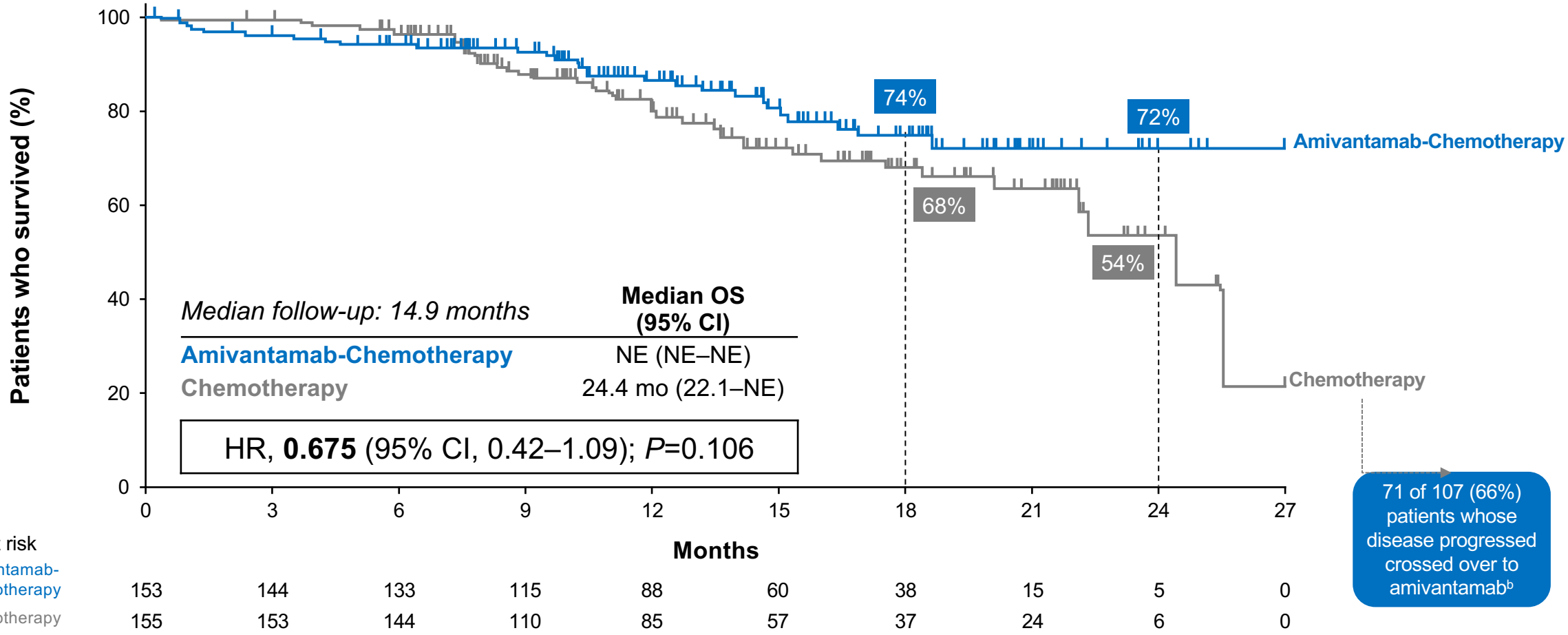


[a]TTST was defined as the time from the date of randomization to the start date of the first subsequent anticancer therapy following study treatment discontinuation or death, whichever occurred first. [b]Other category included IO alone and investigational agents. [c]Six patients received amivantamab monotherapy off-protocol. [d]In the amivantamab-chemotherapy and chemotherapy arms, 23% and 1% of patients received single-agent chemotherapy, respectively, and 7% and 1% of patients received doublet chemotherapy, respectively.

Ami-Chemo, Amivantamab-Chemotherapy; Chemo, Chemotherapy; CI, confidence interval; EGFR, epithelial growth factor receptor; HR, hazard ratio; IO, immuno-oncology; mo, months; NE, not estimable; TKI, tyrosine kinase inhibitor; TTST, time to subsequent therapy; VEGFi, vascular endothelial growth factor inhibitor.

Felip, et al. ELCC 2024

PAPILLON: Secondary endpoint
Overall survival (interim)



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

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

MADRID 2023 ESMO congress

Girard, et al. ESMO 2023

PAPILLON: Summary of adverse events

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

SAEs and AEs leading to death were comparable between arms

Similar rates of discontinuation of all study agents due to AEs was observed across arms

Treatment-related discontinuations of amivantamab were low (7%)

Girard, N, et al. ESMO 2023

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ChT, chemotherapy; IRR, infusion-related reaction; MET, mesenchymal-epithelial transition; SAE, serious AE.

EGFR Ex20ins mutated NSCLC
NCCN Guidelines 2025

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2025
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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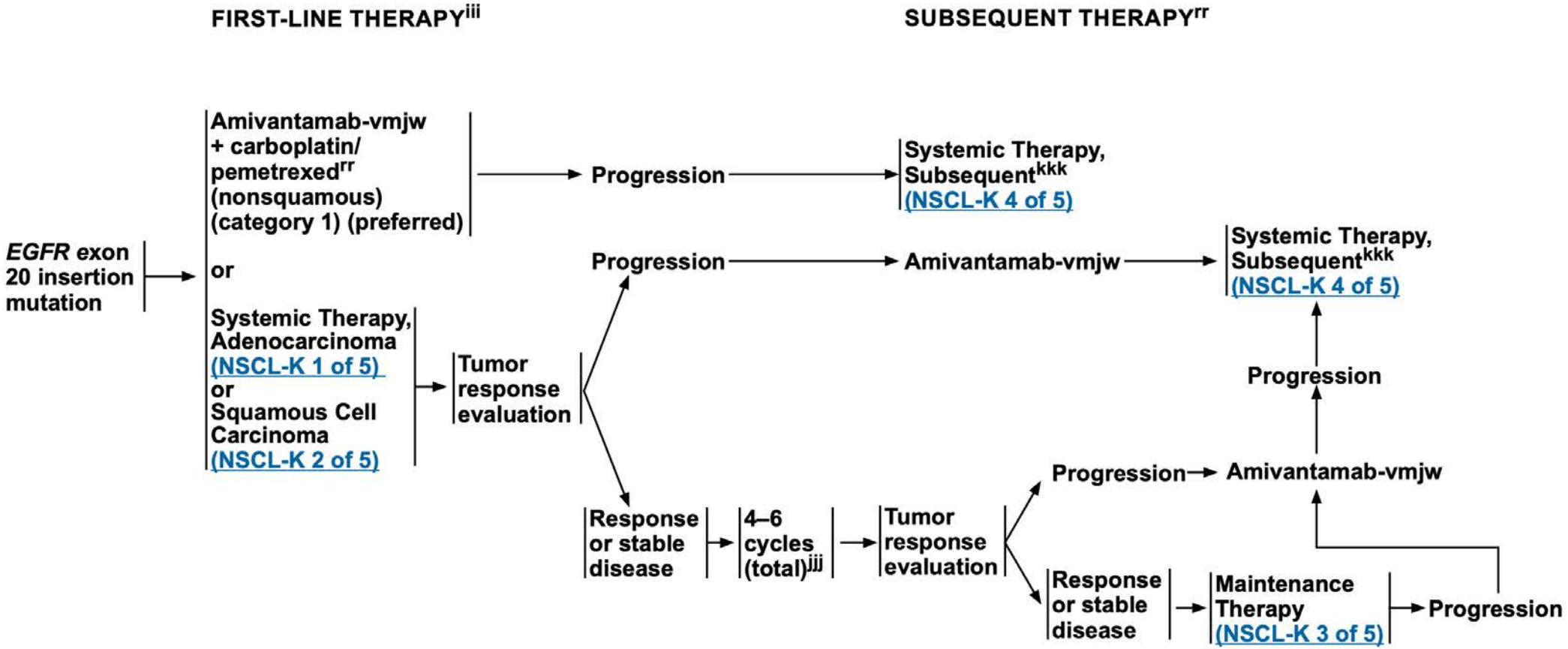
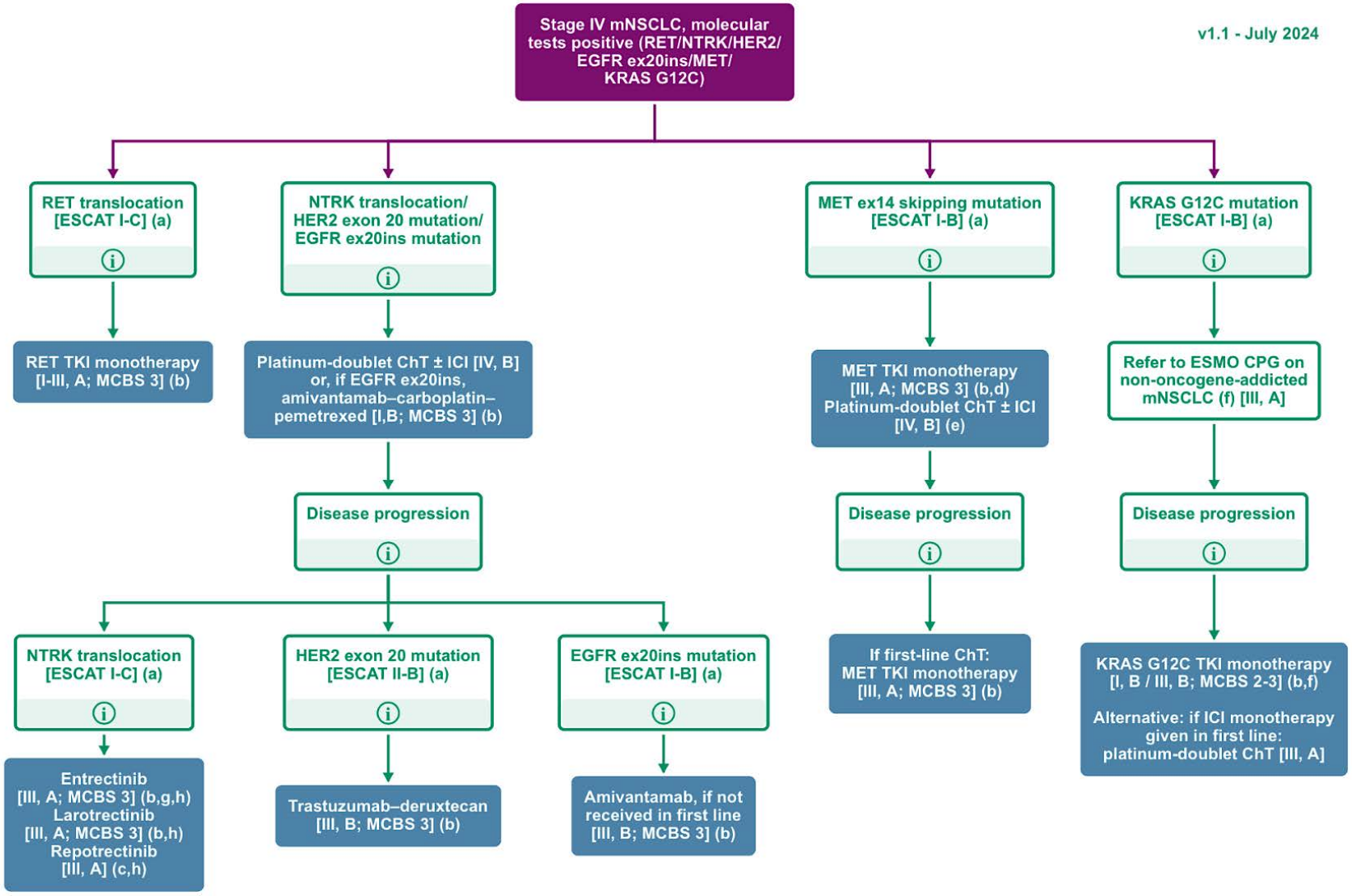
Discussion

***EGFR* EXON 20 INSERTION MUTATION[nn]**



EGFR Ex20ins mutated NSCLC
ESMO CPG 2025



New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

Amivantamab as first-line therapy
PAPILLON as current standard-of-care

Amivantamab in pre-treated patients

CHRYSALIS: Amivantamab in post-platinum *EGFR* Exon20ins mutations in NSCLC

Key objectives

Part 1: Establish RP2D

Part 2: Safety and efficacy at RP2D

Key eligibility criteria

- Metastatic or unresectable NSCLC
- Failed or ineligible for SoC therapy
- Advanced NSCLC (part 1)
- Measurable disease (part 2)
- Activating or resistance *EGFR* or *MET* mutations or amplifications (part 2)

Part 1: Dose escalation

1750 mg

1400 mg

1050 mg

700 mg

350 mg

140 mg

RP2D
1050 mg amivantamab (<80 kg)
1400 mg amivantamab (≥80 kg)

Intravenous dosing

C1 weekly and C2+ biweekly

Part 2: Dose expansion

Cohort A
EGFR-dependent resistance

Cohort B
EGFR-independent resistance

Cohort C
Post-EGFR 3G TKI and C797S+

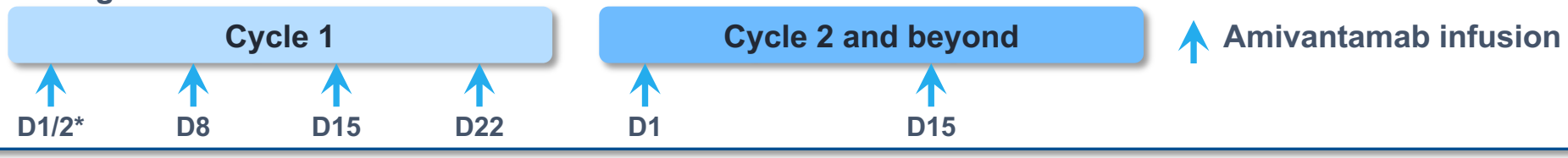
Cohort D
EGFR exon20ins

Cohort MET-1
*MET*amp and post-EGFR TKI

Cohort MET-2
MET exon 14 skipping

Adapted from Park K, et al. 2021.

Dosing schedule



*Split first dose.

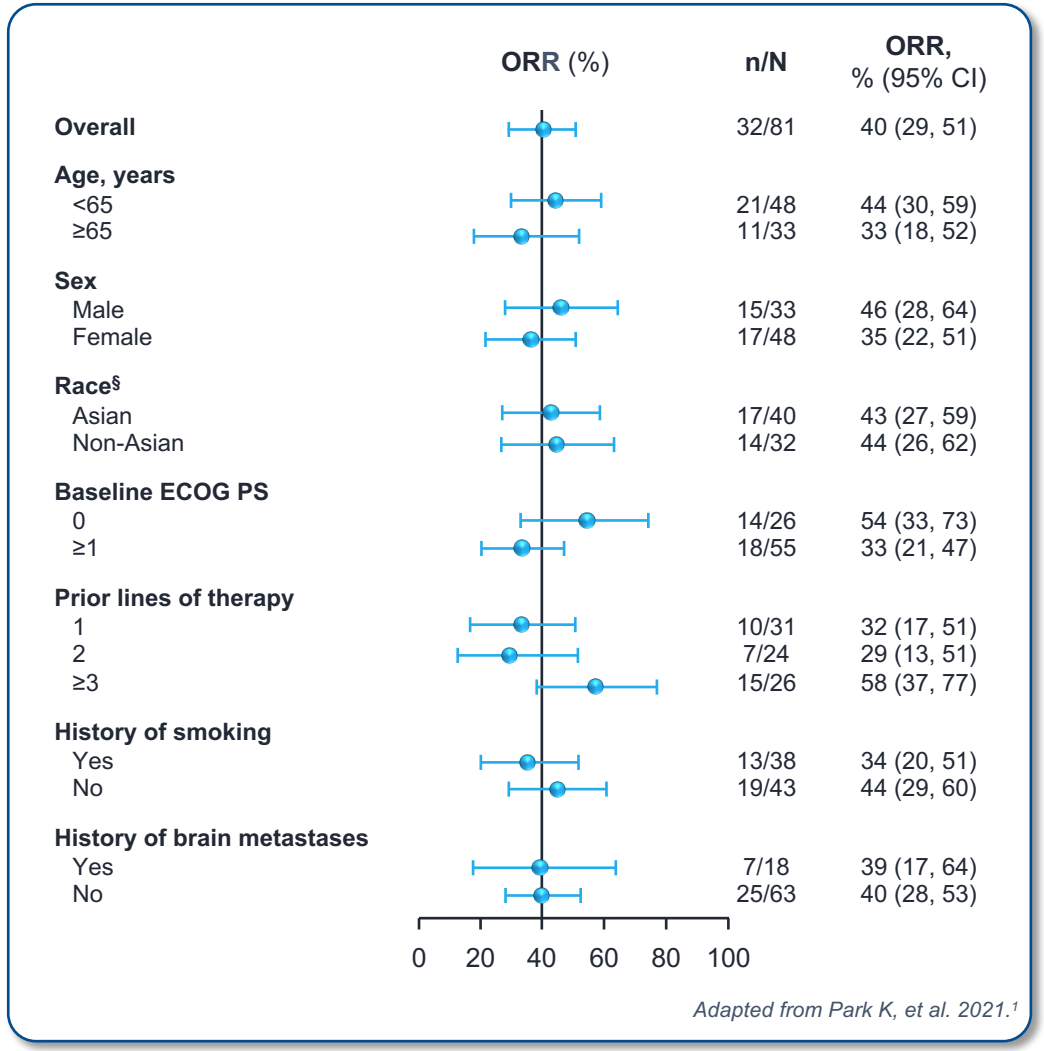
3G, third generation; C, Cycle; D, Day; exon20ins, exon 20 insertion; MET, mesenchymal-epithelial transition; RP2D, recommended Phase 2 dose; SoC, standard of care.

Park K, et al. *J Clin Oncol*. 2021;39:3391−402.

CHRYSALIS: Amivantamab in post-platinum *EGFR* Exon20ins mutations in NSCLC

CHRYSALIS: Efficacy data

Response	Efficacy population[1] (n=81)	SmPC efficacy population (n=114)[2]
ORR, **%** (95% CI)	**40** (29–51)*†	**43** (34–53)†
mDoR, **mo** (95% CI)	**11.1** (6.9–NR)	**10.8** (6.9–15.0)†
mPFS, **mo** (95% CI)	**8.3** (6.5–10.9)†	–
mOS, **mo** (95% CI)	**22.8** (14.6–NR)	–
CBR, **%** (95% CI)	**74** (63–83)†‡	–



Adapted from Park K, et al. 2021.[1]

*Proportion of total patients in the efficacy population who had partial and complete response; †Response as assessed by BICR. ‡Proportion of total patients in the efficacy population who had partial and complete response or stable disease for at least 11 weeks (corresponding to two disease assessments). §Does not include nine patients with race not reported and multiple race.

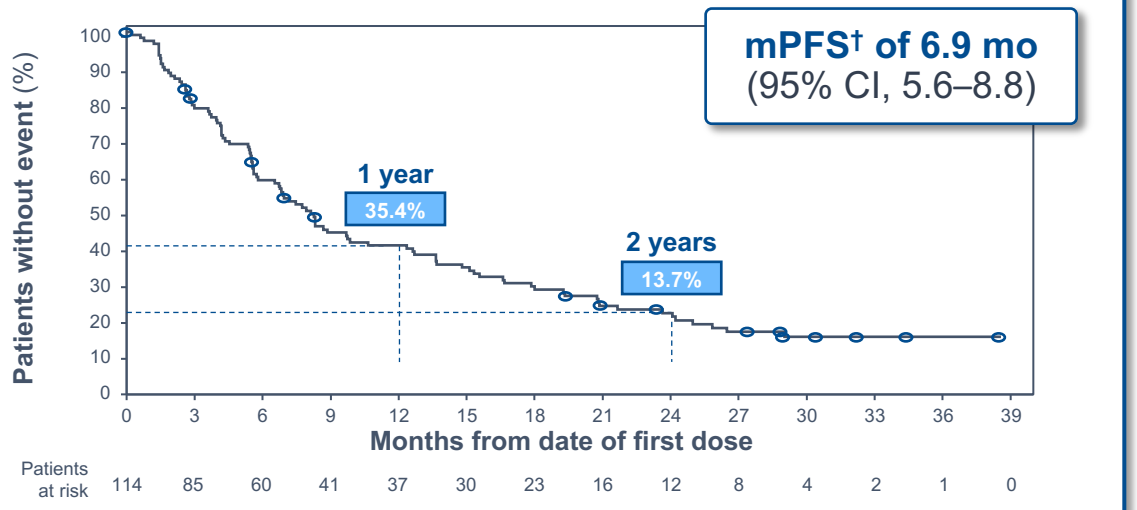
BICR, blinded independent central review; CBR, clinical benefit rate; ECOG PS, Eastern Cooperative Oncology Group performance status; mDoR, median duration of response; MET, mesenchymal-epithelial transition; mOS, median overall survival; mPFS, median PFS; NR, not reached; ORR, overall response rate; SmPC, Summary of Product Characteristics.

1. Park K, et al. *J Clin Oncol*. 2021;39:3391–402

CHRYSALIS: Long-term efficacy with amivantamab

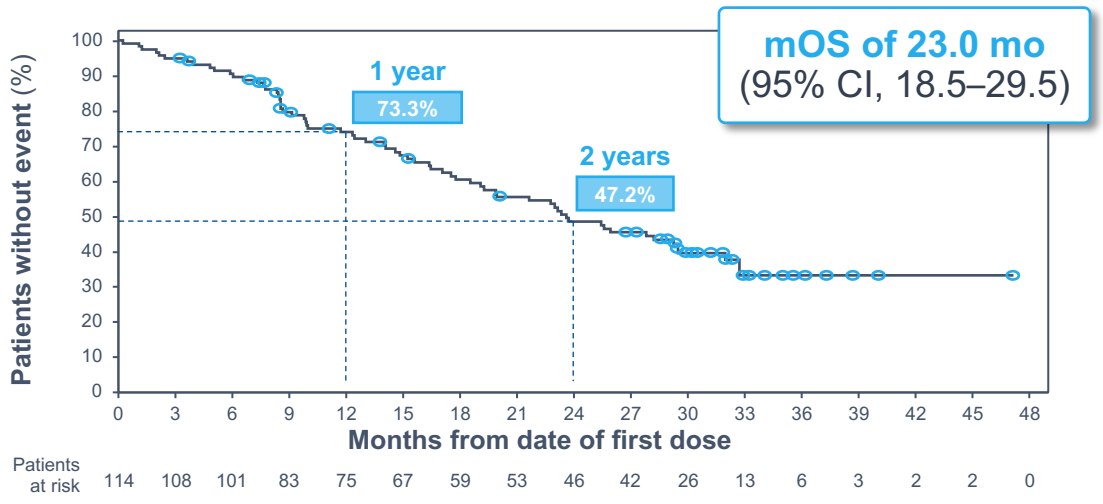
Long-term efficacy and safety results of amivantamab in *EGFR* exon20ins mutations in aNSCLC, post-PBC*

PFS (n=114)



Adapted from Garrido P, et al. 2023.

OS (n=114)



Adapted from Garrido P, et al. 2023.

- Median follow-up = **19.2 months**
- Amivantamab demonstrated **consistent efficacy** regardless of **prior therapies** or **response to prior PBC**
- **42%** (n=48) of patients had a **sustained clinical benefit** (on amivantamab for ≥12 cycles‡)
- **13%** (n=15) of patients **remain on amivantamab** for a median **treatment duration** of **2.6 years**

Garrido P, et al. Presented at ELCC 2023: 3O.

*Data cut-off: 12 September 2022. †As assessed by the investigator. ‡Cycle duration was 28 days.
aNSCLC, advanced NSCLC; exon20ins, exon 20 insertion; mo, months; mOS, median OS; mPFS, median PFS; PBC, platinum-based chemotherapy.

CHRYSALIS: Long-term safety profile with amivantamab

AEs (≥15%) by preferred term, n (%)	Exon20ins post-PBC (n=114)		RP2D (n=474)	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Paronychia	**66** (58)	**4** (4)	**204** (43)	**9** (2)
Dermatitis acneiform	**54** (47)	**1** (1)	**165** (35)	**5** (1)
Rash	**49** (43)	**2** (2)	**167** (35)	**8** (2)
Stomatitis	**29** (25)	**1** (1)	**97** (20)	**2** (0.4)
Pruritus	**23** (20)	**0**	**84** (18)	**0**
Diarrhoea	**21** (18)	**4** (4)	**53** (11)	**6** (1)
MET-related				
Hypoalbuminemia	**45** (39)	**5** (4)	**153** (32)	**11** (2)
Peripheral oedema	**31** (27)	**1** (1)	**119** (25)	**5** (1)
Other				
IRR	**76** (67)	**3** (3)	**319** (67)	**14** (3)
Nausea	**32** (28)	**1** (1)	**111** (23)	**3** (1)
Constipation	**30** (26)	**0**	**115** (24)	**1** (0.2)
Fatigue	**30** (26)	**4** (4)	**100** (21)	**9** (2)
Dyspnoea	**29** (25)	**6** (5)	**101** (21)	**24** (5)
Cough	**24** (21)	**0**	**87** (18)	**0**
Arthralgia	**24** (21)	**0**	**53** (11)	**1** (0.2)

AEs (≥15%) by preferred term, n (%)	Exon20ins post-PBC (n=114)		RP2D (n=474)	
	Total	Grade ≥3	Total	Grade ≥3
Other continued				
Back pain	**23** (20)	**1** (1)	**66** (14)	**4** (1)
Decreased appetite	**23** (20)	**1** (1)	**83** (18)	**2** (0.4)
ALT increased	**20** (18)	**4** (4)	**80** (17)	**10** (2)
Dry skin	**19** (17)	**0**	**59** (12)	**0**
Vomiting	**19** (17)	**1** (1)	**59** (12)	**2** (0.4)
AEs of special interest by grouped term				
Rash*	**102** (89)	**5** (4)	**349** (74)	**17** (4)
ILD†	**8** (7)	**0**	**16** (3)	**4** (1)
VTE‡	**13** (11)	**7** (6)	**50** (11)	**25** (5)

- **No new safety signals** were detected
- Treatment-related dose **interruptions** = **29%** (n=33)
- Treatment-related **reductions** = **18%** (n=20)
- Treatment-related **discontinuations** = **7%** (n=8)
- Cumulative grouped **rash*** and **IRRs** = **most frequent AEs**

*Grouping includes the following related preferred terms: Rash, dermatitis acneiform, rash maculo-papular, folliculitis, erythema, rash pustular, acne, palmar-plantar erythrodysaesthesia syndrome, rash erythematous, rash papular, skin lesion, rash pruritic, dermatitis, skin exfoliation, dermatitis exfoliative generalized, macule, pustule, blister, dermatitis atopic, dermatitis bullous, dermatitis infected, eczema asteatotic, erythema multiforme, hand dermatitis, perineal rash, perioral dermatitis, rash macular, rash vesicular, and toxic epidermal necrolysis. †Includes ILD and pneumonitis. ‡Includes pulmonary embolism, deep vein thrombosis, embolism, thrombophlebitis superficial, venous thrombosis limb, pulmonary thrombosis, and thrombosis.
AE, adverse event; ALT, alanine aminotransferase; exon20ins, exon 20 insertion; ILD, interstitial lung disease; IRR, infusion-related reaction; MET, mesenchymal-epithelial transition; PBC, platinum-based chemotherapy; RP2D, recommended phase 2 dose; VTE, venous thromboembolism.

Garrido P, et al. Presented at ELCC 2023: 3O.

New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

Amivantamab as first-line therapy
PAPILLON as current standard-of-care

Amivantamab in pre-treated patients

New agents

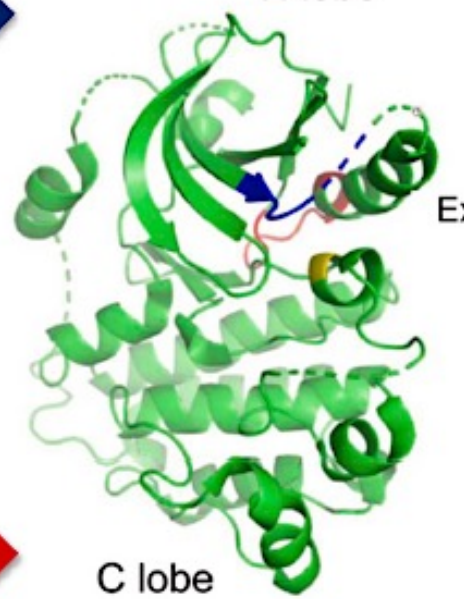
TKIs overview

Exon20ins evolving landscape beyond Amivantamab

Tuxobertinib (BDTX-189)
EGFR/HER2 Exon20ins irreversible ATP-competitive inhibitor.

BAY-2476568
Selective & reversible EGFR exon20 ins inhibitor

STX-721
irreversible highly selective EGFR and ERBB2 ex20ins TKIS



YK-029A
3rd generation EGFR TKI

ORIC-114
EGFR/HER2 Exon20ins TKI

Ph3 TKI vs chemo

Sunvozertinib
irreversible & selective EGFR exon20ins TKI
Ph3 Sunvozertinib vs chemo

Zipalertinib
Pan-EGFR mutation TKI
Ph3 Zipalertinib plus Chemo vs Chemo

Furmonertinib
3rd gen EGFR/HER2 Exon20ins TKI
Ph3 Furmonertinib vs chemo

Phase 3 ongoing

Passaro. ELCC 2024

Furmonertinib: Efficacy

FAVOUR

Efficacy by IRC*†	Treatment-naïve 240 mg (n=28)§	Previously treated 240 mg (n=26)‖	Previously treated 160 mg (n=26)‖
cORR, % (95% CI)	**78.6** (59.05–91.70)	**46.2** (26.59–66.63)	**38.5** (20.23–59.43)
Best response, n (%)			
PR	**22** (78.6)	**12** (46.2)	**10** (38.5)
SD	**6** (21.4)	**12** (46.2)	**12** (46.2)
PD	**0**	**0**	**4** (15.4)
NE/ND	**0/0**	**1** (3.8)/**1** (3.8)	**0/0**
mDoR, months (95% CI)	**15.2** (8.74–24.84)	**13.1** (5.62–13.80)	**9.7** (5.59–NA)
DCR, % (95% CI)‡	**100** (87.66–100.00)	**92.3** (74.87–99.05)	**84.6** (65.13–95.64)

Furmonertinib showed promising efficacy in previously treated patients with advanced NSCLC and *EGFR* exon20ins mutations (cORR of 46.2% [240 mg] and 38.5% [160mg])

*Analysis is based on patients with EGFR exon20ins mutations who had measurable disease at baseline by IRC, had ≥2 tumour assessments, had PD/death, or discontinued from treatment; †Patients received follow-up until disease progression every 6 weeks, and after disease progression or initiation of new therapy every 12 weeks; ‡DCR defined as CR + PR + SD; §2 patients: 1 patient had no measurable target lesion at baseline by IRC, another patient did not have an EGFR exon20ins mutation; ‖26 of the 28 patients in 240 mg and 160 mg cohorts, respectively, had at least 2 tumour assessments by 15 June 2023.
cORR, confirmed overall response rate; CR, complete response; DCR, disease control rate; exon20ins, exon 20 insertion; IRC, Independent Review Committee; mDoR, median duration of response; NA, not available; ND, not done; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Han B, et al. Presented at WCLC 2023: OA03.04.

Furmonertinib: Safety profile

FAVOUR

Most common TRAEs (≥20%) by preferred term, n (%)[1]	Treatment-naïve 240 mg (n=30)		Previously treated 240 mg (n=28)		Previously treated 160 mg (n=28)	
	Total	Grade ≥3	Total	Grade ≥3	Total	Grade ≥3
Diarrhoea	22 (73)	0	24 (86)	0	9 (32)	2 (7)
Anaemia	13 (43)	0	7 (25)	1 (4)	4 (14)	1 (4)
AST increase	8 (27)	0	7 (25)	0	10 (36)	0
ALT increase	7 (23)	0	7 (25)	1 (4)	8 (29)	0
Blood creatinine	6 (20)	0	8 (29)	0	7 (25)	0
Mouth ulceration	9 (30)	1 (3)	4 (14)	0	5 (18)	0
Rash	7 (23)	0	6 (21)	0	4 (14)	0
ECG QT prolongation	8 (27)	1 (3)	4 (14)	2 (7)	2 (7)	0
WBC count decrease	6 (20)	1 (3)	5 (18)	0	6 (21)	0
Decreased appetite	3 (10)	0	8 (29)	0	0	0
Weight loss	3 (10)	0	7 (25)	1 (4)	3 (11)	0
Skin fissures	6 (20)	0	3 (11)	0	0	0
Paronychia	6 (20)	0	2 (7)	0	1 (4)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; TRAE, treatment-related adverse event; WBC, white blood cell.

Han B, et al. Presented at WCLC 2023: OA03.04.

Sunvozertinib: Efficacy and safety profile

WU-KONG1B

Best response, n (%)*	Prior amivantamab treatment		Prior IO treatment	
	With (n=14)	Without (n=93)	With (n=52)	Without (n=55)
CR	0	3 (3.2)	2 (3.8)	1 (1.8)
PR	7 (50.0)	47 (50.5)	26 (50.0)	28 (50.9)
PR, confirmed	5 (35.7)	41 (44.1)	23 (44.2)	23 (41.8)
PR, pending confirmation	1 (7.1)	3 (3.2)	2 (3.8)	2 (3.6)
SD	4 (28.6)	35 (37.6)	21 (40.4)	18 (32.7)
PD	3 (21.4)	5 (5.4)	1 (1.9)	7 (12.7)
NE	0	3 (3.2)	2 (3.8)	1 (1.8)

- The most common TRAEs included diarrhoea, blood creatinine phosphokinase increase, and rash
- 36.0% of patients had dose reduction
- 6.3% of patients had dose discontinuation
- No patients had fatal TRAEs
- Safety profiles were comparable across different demographics and baseline disease characteristics

Sunvozertinib demonstrated promising efficacy in patients with advanced NSCLC harbouring *EGFR* exon20ins mutations, regardless of prior amivantamab or IO status

*IRC-assessed.
CR, complete response; exon20ins, exon 20 insertion; IO, immunotherapy; IRC, Independent Review Committee; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TRAE, treatment-related adverse event.

Doucet L, et al. Presented at ESMO 2024: 1260P.

New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

Amivantamab as first-line therapy
PAPILLON as current standard-of-care

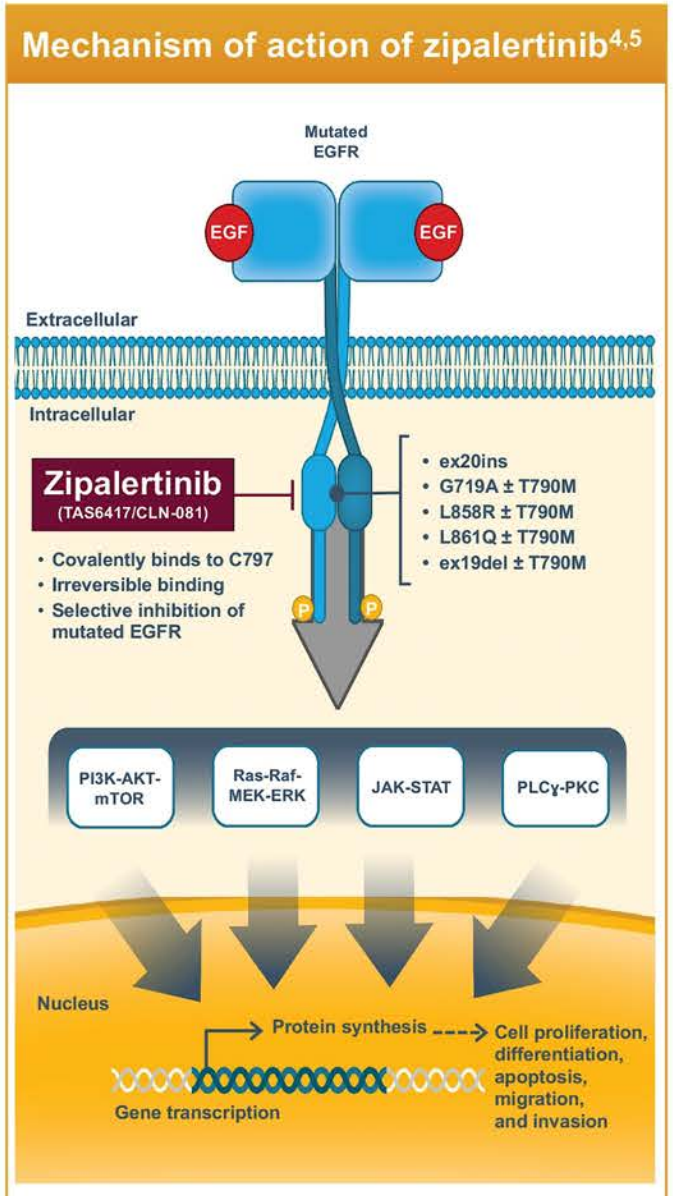
Amivantamab in pre-treated patients

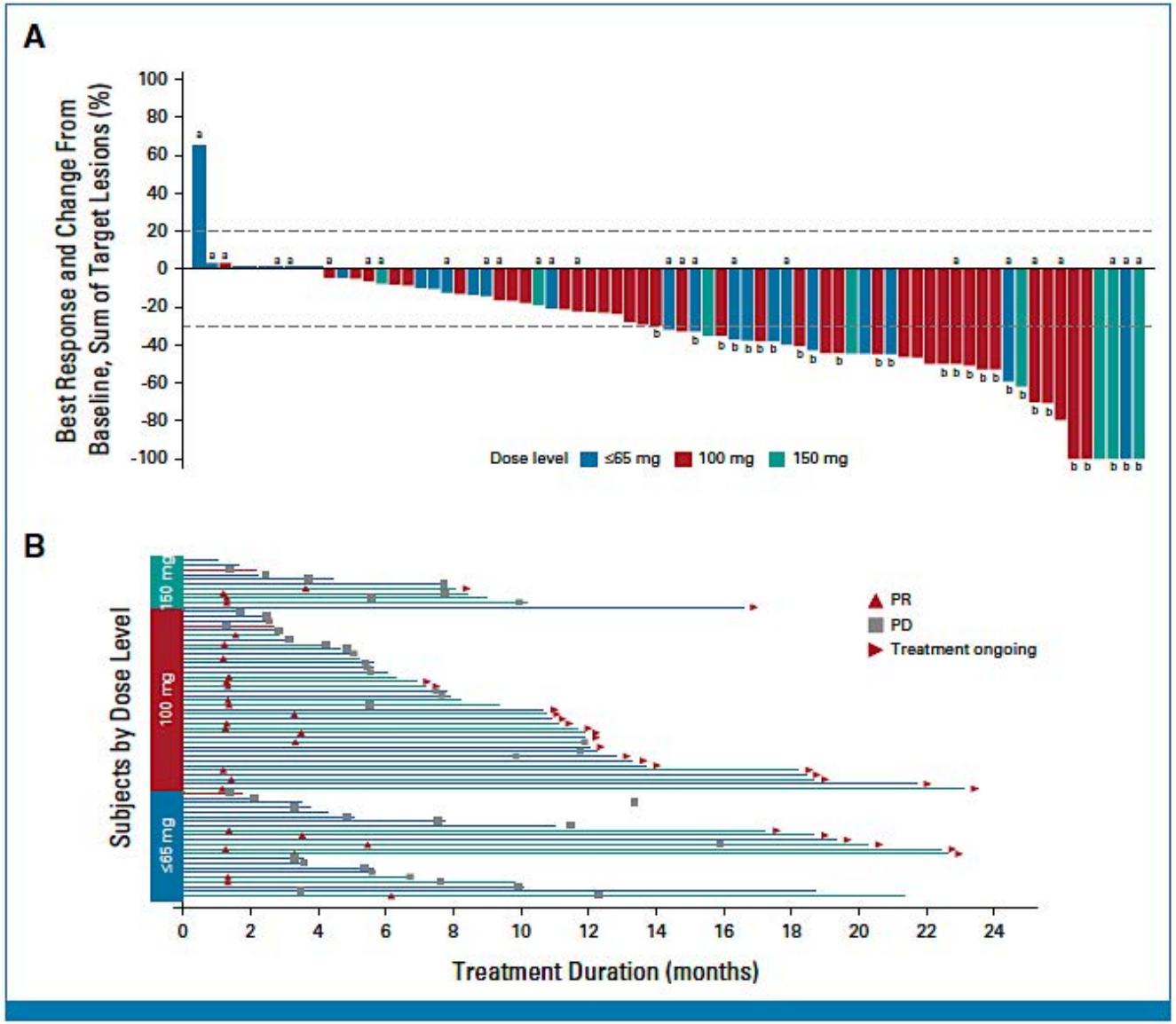
New agents

TKIs overview

Zipalertinib

Zipalertinib: REZILIENT1, EGFR exon20 post-platinum





ORR 38%

mDoR 10 months
mPFS 10 months

Piotrowska et al. J Clin Oncol 2024;41:4218

Zipalertinib: REZILIENT1, EGFR exon20 post-platinum

TABLE 2. Treatment-Related AEs Observed in ≥10% of Subjects Overall

	≤65 mg Twice a Day (N = 23)		100 mg Twice a Day (N = 39)		150 mg Twice a Day (N = 11)		Overall (N = 73)	
AE[a]	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17.4)	5 (13)	1 (2.6)	2 (18)	2 (18.2)	14 (19)	7 (9.6)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4.3)	3 (8)	1 (2.6)	2 (18)	1 (9.1)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0

Abbreviations: AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events.
[a]CTCAE v5.0.

Piotrowska et al. J Clin Oncol 2024;41:4218

REZILIENT1: Zipalertinib post-amivantamab

REZILIENT1 Phase 2b Module C: Study Rationale and Design

- Zipalertinib, a novel irreversible and selective EGFR ex20ins TKI, has been granted Breakthrough Therapy Designation by the US FDA after demonstrating promising efficacy and favorable safety profile in a Phase 1/2a study (*JCO* 2023)
- Module C of this Phase 2b study investigates the efficacy and safety of zipalertinib in patients who progressed on or after amivantamab, a significant emerging unmet medical need (NCT04036682)

Key eligibility criteria
- Locally advanced or metastatic NSCLC
- Documented *EGFR* exon 20 insertion
- *Progressed on or after amivantamab*
- ECOG PS 0 or 1
- Stable/asymptomatic brain metastases allowed

→ **Zipalertinib**
100 mg BID oral[a]

[a]Zipalertinib may be taken with or without food

Primary endpoint:
- ORR and DOR per RECIST v1.1

Secondary endpoints:
- Safety
- PFS
- DCR

- At data cutoff on March 29, 2024, 45 patients were enrolled
- 30 patients were response evaluable (≥2 on-treatment tumor assessments or had disease progression/death)

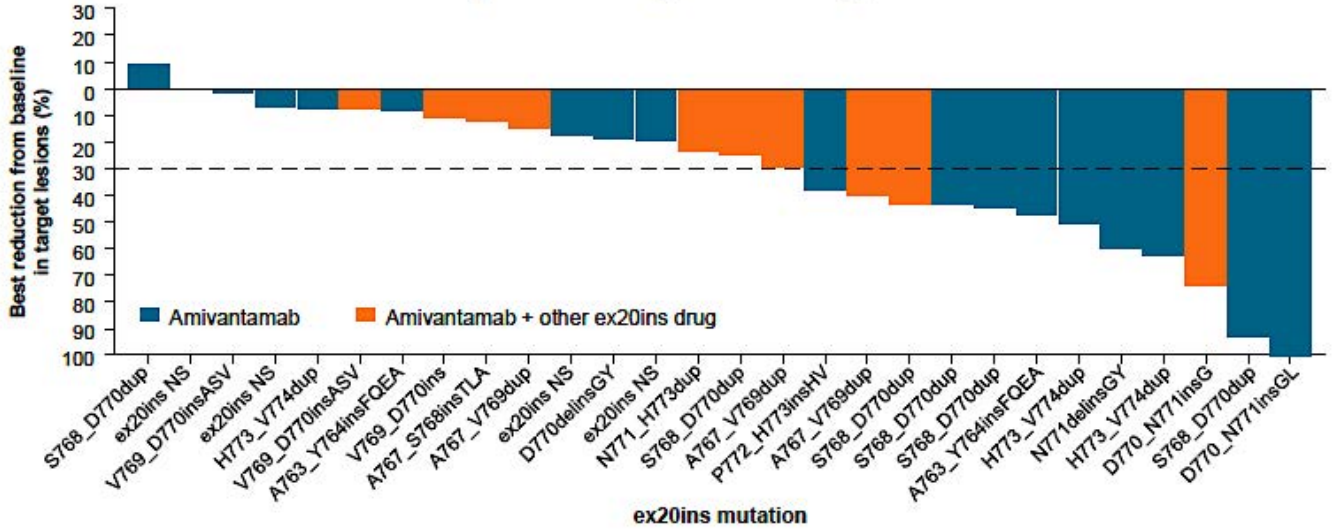
Summary of Treatment-Related Adverse Events

TRAE ≥10%, n (%)	Ami only (n=28)	Ami + other ex20ins (n=17)	Total (N=45)
Rash	12 (43)	5 (29)	17 (38)
Paronychia	11 (39)	5 (29)	16 (36)
Anemia	6 (21)	5 (29)	11 (24)
Dry skin	5 (18)	4 (24)	9 (20)
Dermatitis acneiform	3 (11)	4 (24)	7 (16)
Nausea	4 (14)	3 (18)	7 (16)
Stomatitis	2 (7)	3 (18)	5 (11)

TRAE Grade ≥3 (≥2 patients), n (%)	Ami only (n=28)	Ami + other ex20ins (n=17)	Total (N=45)
Anemia	2 (7)	2 (12)	4 (9)
Rash	2 (7)	1 (6)	3 (7)
Pneumonitis/ILD	3 (11)	0	3 (7)
Dose reduction[a]	2 (7)	1 (6)	3 (7)
Dose discontinuation[b]	3 (11)	0	3 (7)

[a]Platelet count decrease, anemia, anemia/rash. [b]Pneumonitis/ILD.
ILD: interstitial lung disease; TRAE: treatment-related adverse event.

Best Percentage Change From Baseline in Target Lesions and Confirmed Response by Investigators

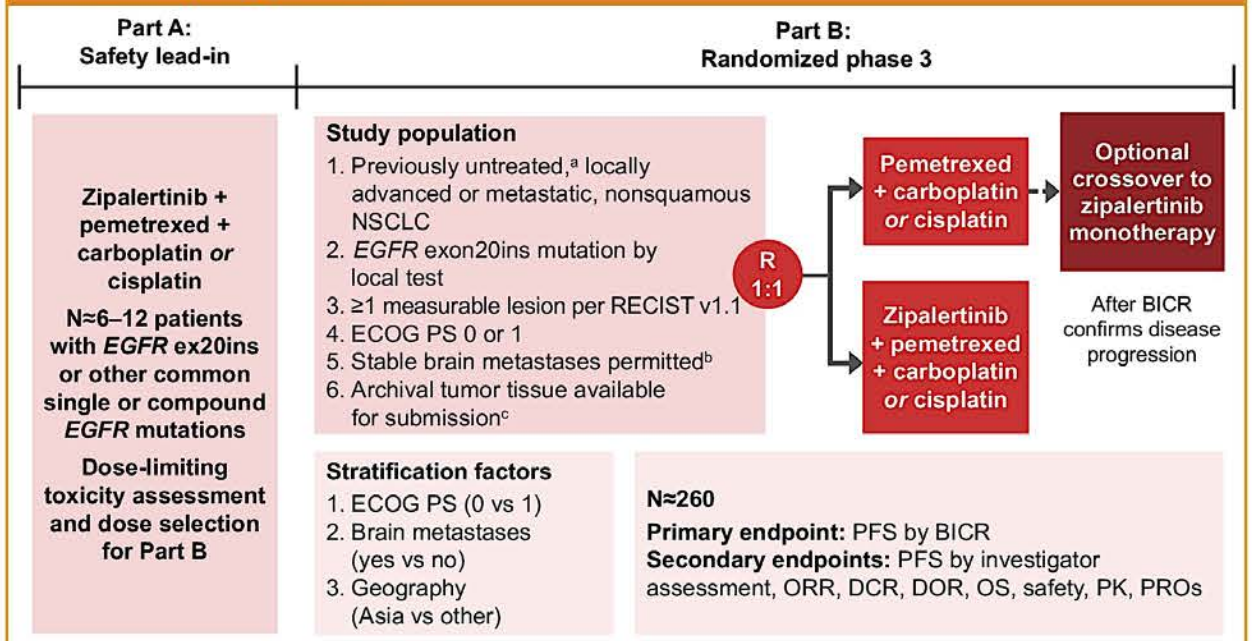


ASCO 2025: Abstract 8503
Efficacy of zipalertinib in NSCLC patients with EGFR exon 20 insertion mutations who received prior platinum-based chemotherapy with or without amivantamab.
June 1, 2025 – 9:00 AM CDT
Arie Crown Theater

Passaro et al. ESMO 2024

REZILIENT3: Zipalertinib + CT as First Line in Patients With *EGFR* Exon20ins NSCLC

Pemetrexed until disease progression
Carboplatin *or* cisplatin × 4 cycles and zipalertinib until disease progression



[a]Prior EGFR TKI monotherapy (not targeting ex20ins mutations) lasting <8 weeks, with documented lack of response and resolved associated toxicities, and >2 weeks/4 half-lives before randomization is allowed; alternatively, an approved prior adjuvant/ neoadjuvant treatment >6 months before the first dose of study treatment is allowed for early-stage NSCLC. [b]Patients with previously treated brain metastases and stable central nervous system disease (defined as being neurologically stable and off corticosteroids for ≥2 weeks before enrollment) are eligible. Asymptomatic brain metastases ≤2 cm in size can be eligible for inclusion if, in the opinion of the investigator, immediate definitive treatment is not indicated. [c]Patients with insufficient tissue may be eligible following discussion with the sponsor. BICR, blinded independent central review; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epidermal growth factor receptor; ex20ins, exon 20 insertions; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TKI, tyrosine kinase inhibitor.

Endpoints

- The primary endpoint in Part A is the incidence of dose-limiting toxicities (per CTCAE v5.0) during Cycle 1

Part B endpoints			
Primary	• PFS per RECIST v1.1 by BICR		
Secondary	• Investigator-assessed PFS, ORR, DCR, and DOR per RECIST v1.1 • ORR, DOR, and DCR per RECIST v1.1 by BICR	• Intracranial ORR, DCR, and DOR • Adverse events per CTCAE v5.0	• OS • PK profile • PROs

BICR, blinded independent central review; CTCAE v5.0, Common Terminology Criteria for Adverse Events, version 5.0; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.

Yu et al. ASCO 2024

New clinical strategies for EGFR Ex20ins mutated NSCLC

EGFR Ex20ins mutated NSCLC

Amivantamab in pre-treated patients

Amivantamab as first-line therapy
PAPILLON as new standard-of-care

New agents

TKIs overview

Zipalertinib

Regulatory and reimbursement issues aside, which first-line systemic therapy would you recommend for an otherwise healthy 65-year-old patient with nonsquamous mNSCLC with an EGFR exon 20 insertion mutation and a PD-L1 TPS of 0 and the disease characteristics as described?

	Minimal disease burden and symptoms	Symptomatic, with significant tumor bulk and disease burden (excluding the brain)
 Prof Girard	Amivantamab + chemotherapy	Amivantamab + chemotherapy
 Dr Goldman	Amivantamab + chemotherapy	Amivantamab + chemotherapy
 Dr Jänne	Amivantamab + chemotherapy	Amivantamab + chemotherapy
 Dr Ramalingam	Amivantamab + chemotherapy	Amivantamab + chemotherapy
 Dr Sabari	Amivantamab + chemotherapy	Symptomatic, with significant tumor bulk and disease burden (excluding the brain)
 Dr Yu	Zipalertinib	Amivantamab + chemotherapy
 Dr Gadgeel	Amivantamab + chemotherapy	Amivantamab + chemotherapy
 Dr Spira	Amivantamab + chemotherapy	Amivantamab + chemotherapy

A 65-year-old patient with nonsquamous mNSCLC with an EGFR exon 20 insertion mutation and a PD-L1 TPS of 0 responds to first-line amivantamab/chemotherapy and then experiences asymptomatic disease progression after 12 months. Regulatory and reimbursement issues aside, what would be your second-line treatment recommendation if the patient had acquired no further actionable mutations?

 Prof Girard	Zipalertinib; sunvozertinib
 Dr Goldman	Zipalertinib
 Dr Jänne	Sunvozertinib
 Dr Ramalingam	Chemotherapy +/- bevacizumab
 Dr Sabari	Zipalertinib
 Dr Yu	Zipalertinib
 Dr Gadgeel	Zipalertinib
 Dr Spira	Zipalertinib

RTP RESEARCH TO PRACTICE

Based on the published literature and/or your clinical experience, how would you indirectly compare the global efficacy and tolerability of zipalertinib to that of amivantamab for patients with NSCLC and EGFR exon 20 insertion mutations?

	Efficacy	Tolerability
 Prof Girard	Amivantamab is more efficacious	Zipalertinib is more tolerable
 Dr Goldman	I'm not sure	Zipalertinib is more tolerable
 Dr Jänne	Efficacy is similar with each agent	Zipalertinib is more tolerable
 Dr Ramalingam	Efficacy is similar with each agent	Zipalertinib is more tolerable
 Dr Sabari	Zipalertinib is more efficacious	Zipalertinib is more tolerable
 Dr Yu	Efficacy is similar with each agent	Zipalertinib is more tolerable
 Dr Gadgeel	Efficacy is similar with each agent	Zipalertinib is more tolerable
 Dr Spira	I'm not sure	Zipalertinib is more tolerable

Based on the published literature and/or your clinical experience, what are the main side effects associated with zipalertinib?

 Prof Girard	Diarrhea, rash
 Dr Goldman	GI, rash, LFT elevation
 Dr Jänne	GI, rash
 Dr Ramalingam	Rash, paronychia, anemia
 Dr Sabari	Rash, GI toxicity (well tolerated)
 Dr Yu	Leg cramps, mild fatigue
 Dr Gadgeel	Diarrhea
 Dr Spira	Mild rash

Agenda

MODULE 1: Evolving First-Line Treatment for Metastatic EGFR Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) — Dr Yu

MODULE 2: EGFR-Targeted Approaches for Relapsed EGFR-Mutant NSCLC; Strategies to Facilitate Delivery of Recently Approved Agents — Dr Sabari

MODULE 3: Potential Utility of TROP2-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Ramalingam

MODULE 4: Contemporary Care for Patients with Nonmetastatic EGFR-Mutant NSCLC — Dr Goldman

MODULE 5: Current and Future Management of EGFR Exon 20 Mutation-Positive NSCLC — Prof Girard

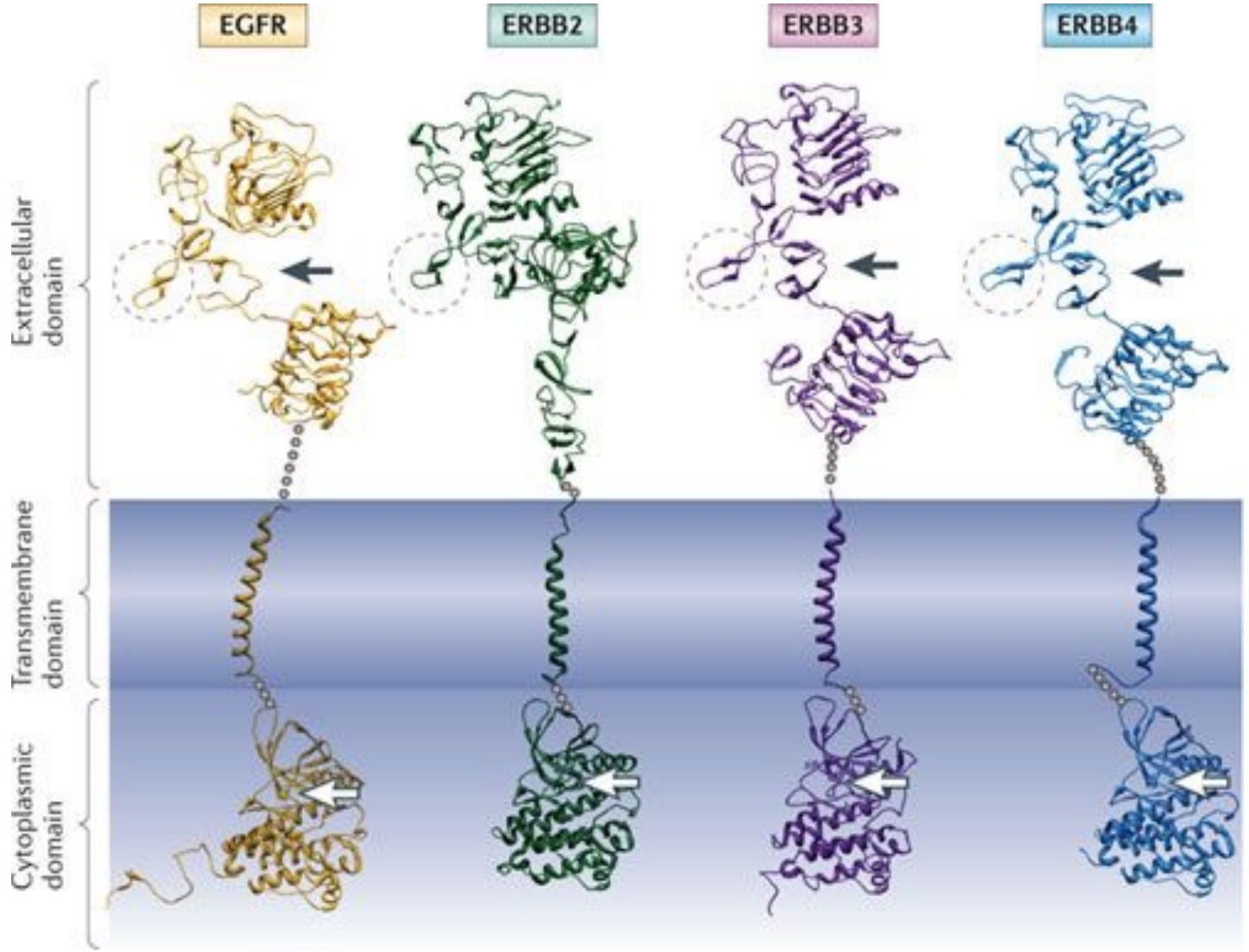
MODULE 6: Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC — Dr Jänne

Emerging Role of HER3-Targeted Therapy in the Management of EGFR-Mutant NSCLC

Pasi A. Jänne MD, PhD

Dana-Farber Cancer Institute | Lowe Center for Thoracic Oncology

EGFR mutant cancers often co-express other ERBB family members

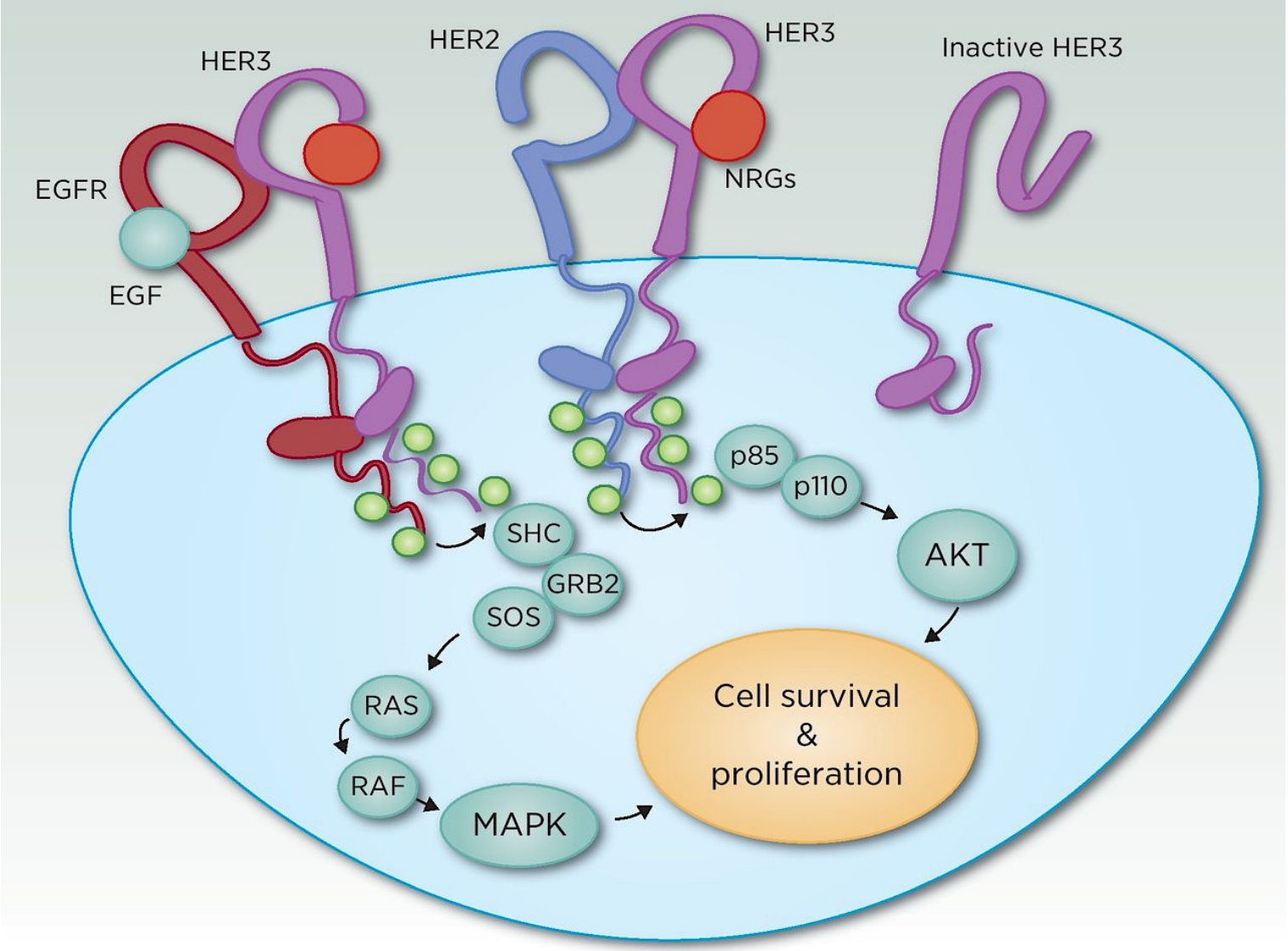


HER2
- Amplification a known resistance mechanism

HER3
-Used to activate PI3K signaling
-Not a known resistance mechanism to EGFR TKIs
Expressed in the majority of EGFR mutant NSCLCs

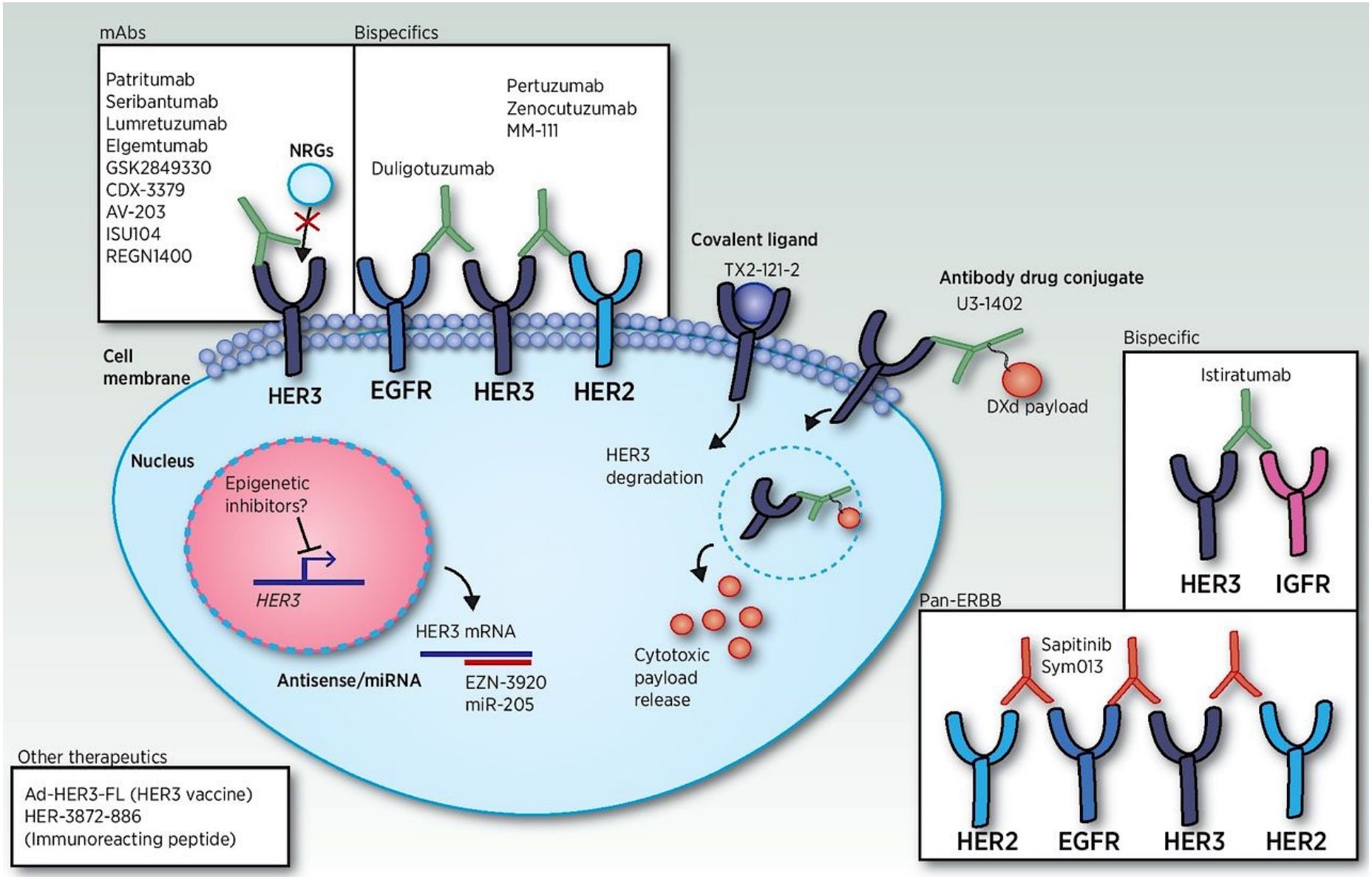
Yarden Y, Pines G. *Nat Rev Cancer*. 2012;12:553-563.

HER3 forms heterodimers upon ligand activation



Haikala et al. CCR 2021

Therapeutic strategies to inhibit HER3



Haikala et al. CCR 2021

Cancer Therapy: Clinical

Clinical Cancer Research

Phase I Study of U3-1287, a Fully Human Anti-HER3 Monoclonal Antibody, in Patients with Advanced Solid Tumors

Patricia LoRusso[1], Pasi A. Jänne[2], Moacyr Oliveira[3], Naiyer Rizvi[5], Lisa Malburg[1], Vicki Keedy[6], Lorrin Yee[4], Catherine Copigneaux[7], Thore Hettmann[8], Chi-Yuan Wu[9], Agnes Ang[9], Abdel-Baset Halim[7], Robert A. Beckman[7], Darrin Beaupre[9], and Jordan Berlin[6]

57 patients; 20 NSCLC patients; most prior EGFR TKI therapy.

No PRs; SD ~ 50% of patients

Well tolerated

Phase I study of the HER3-targeted antibody patritumab (U3-1287) combined with erlotinib in Japanese patients with non-small cell lung cancer☆

Makoto Nishio[a,*], Atsushi Horiike[a], Haruyasu Murakami[b], Nobuyuki Yamamoto[b], Hiroyasu Kaneda[c], Kazuhiko Nakagawa[c], Hidehito Horinouchi[d], Masaki Nagashima[e], Masaru Sekiguchi[e], Tomohide Tamura[d]

24 patients; 54% EGFR mutant; TKI naïve and prior TKI treated.

1 PR; 14 SD

PFS longer in EGFR mutant patients

Circulating heregulin level is associated with the efficacy of patritumab combined with erlotinib in patients with non-small cell lung cancer

Kimio Yonesaka[a,*], Kenji Hirotani[b], Joachim von Pawel[c], Mircea Dediu[d], Shuquan Chen[e], Catherine Copigneaux[e], Kazuhiko Nakagawa[a]

Randomized phase II trial; patritumab/erlotinib vs. erlotinib; no improvement in PFS

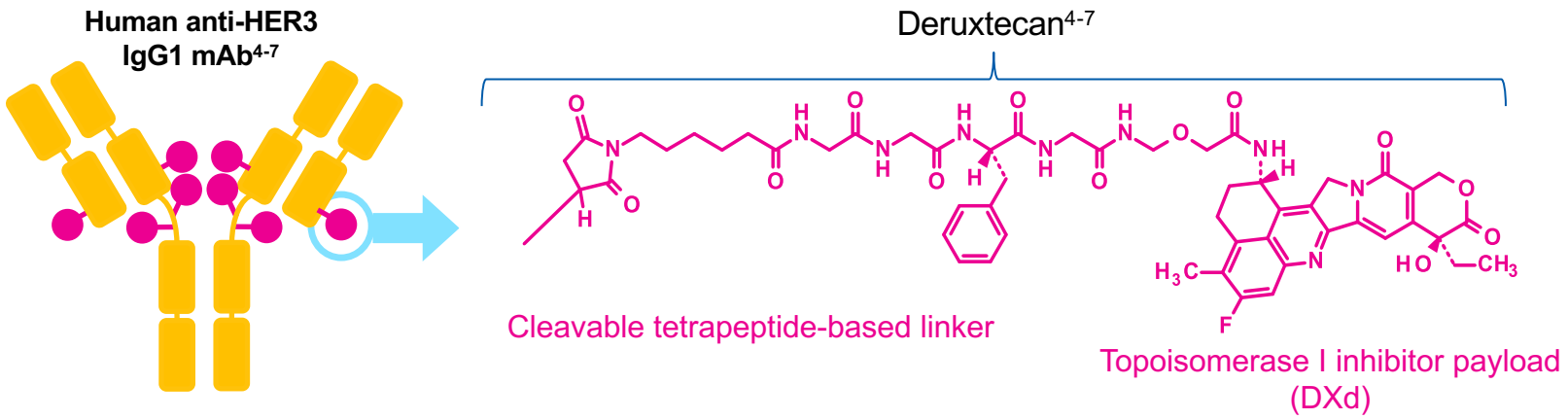
Patients with high soluble serum heregulin had prolonged PFS

LoRusso et al. CCR 2013; Nishio et al. Lung Cancer 2015; Yonesaka et al. Lung Cancer 2017

Patritumab deruxtecan (HER3-DXd) Structure and Attributes

HER3-DXd is an antibody drug conjugate with 3 components[4-7]

- A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



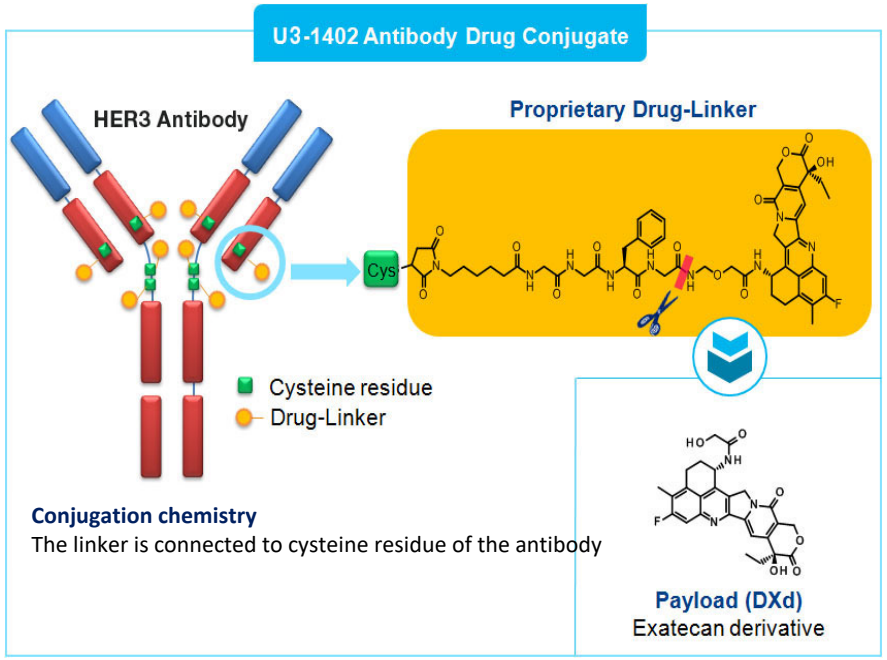
The 7 Key Attributes of HER3-DXd

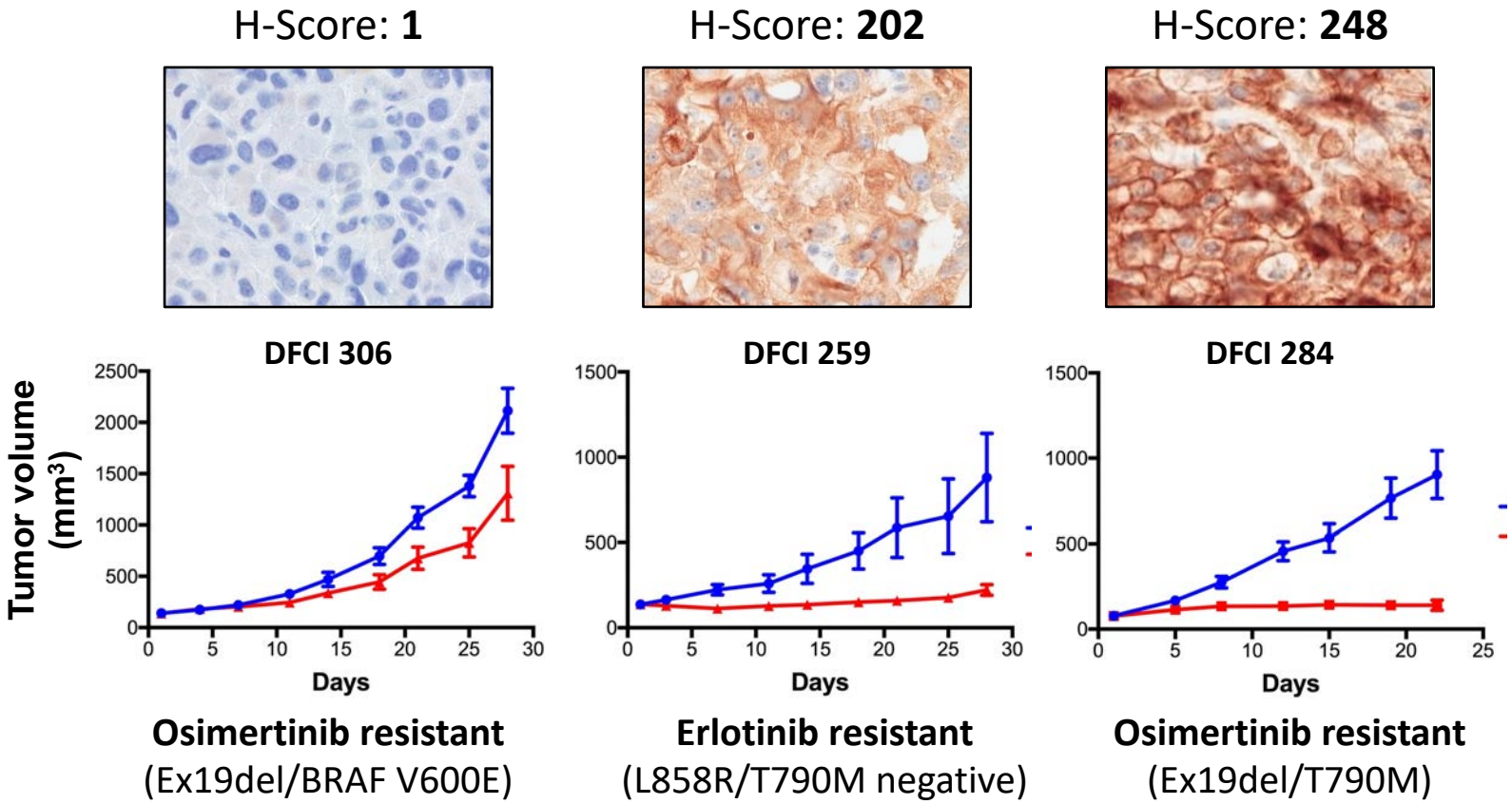
- Payload mechanism of action: topoisomerase I inhibitor[4-7,a]
- High potency of payload[4-7,a]
- High drug-to-antibody ratio ≈8[4,5,a]
- Payload with short systemic half-life[5,6,a,b]
- Stable linker-payload[5-7,a]
- Tumor-selective cleavable linker[4-8,a]
- Bystander antitumor effect[5,9,a]

[a] The clinical relevance of these features is under investigation.
[b] Based on animal data.

IgG1, immunoglobulin G1; mAb, monoclonal antibody.

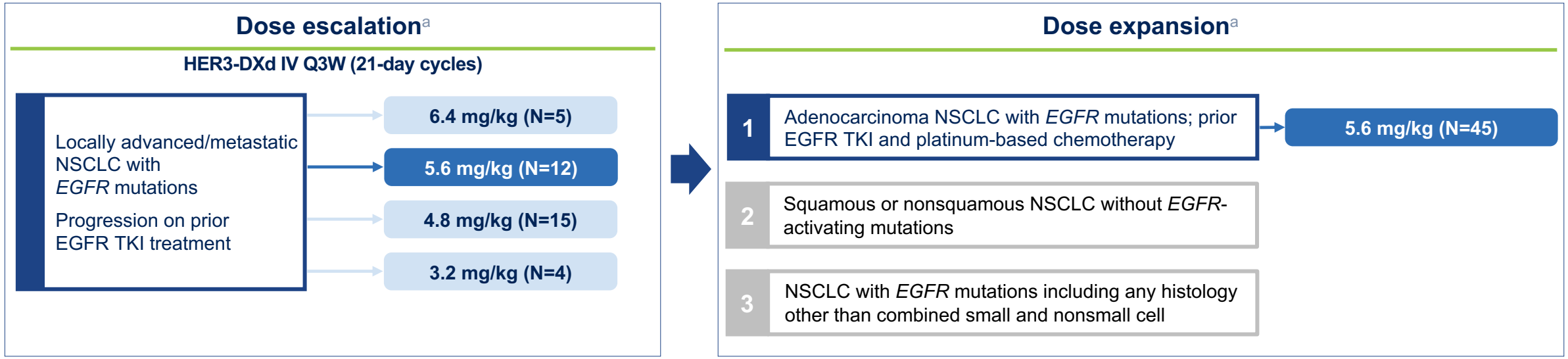
Patritumab deruxtecan is effective in EGFR inhibitor resistant PDX models





Haikala et al. Cancer Research 2021

Phase 1 Dose Escalation and Dose Expansion Study of HER3-DXd in Patients With NSCLC



Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Data cutoff: September 24, 2020

57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

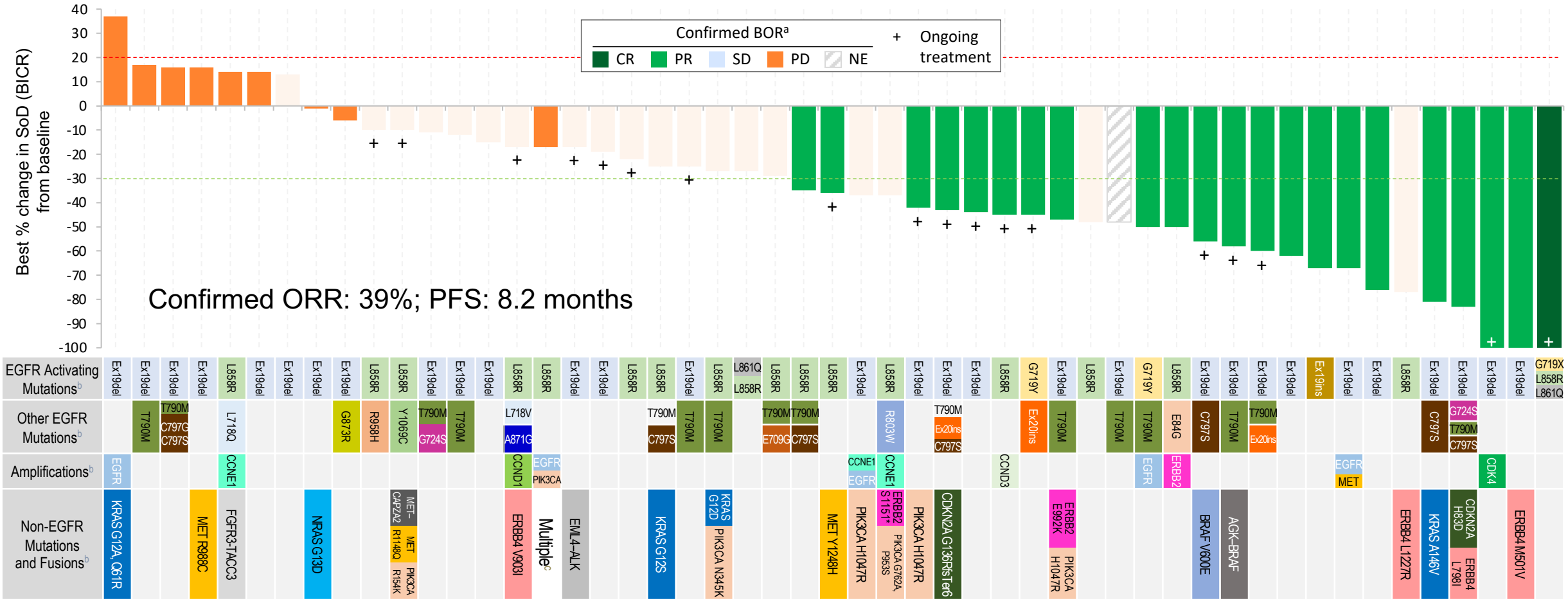
- Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.
- [a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

HER3-DXd Demonstrated Durable Antitumor Activity After Failure of EGFR TKI and Platinum-based Chemotherapy (PBC)

Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	HER3-DXd 5.6 mg/kg Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

Jänne et al. Cancer Discovery 2022

HER3-DXd Demonstrated Activity in Patients With Diverse Mechanisms of EGFR TKI Resistance



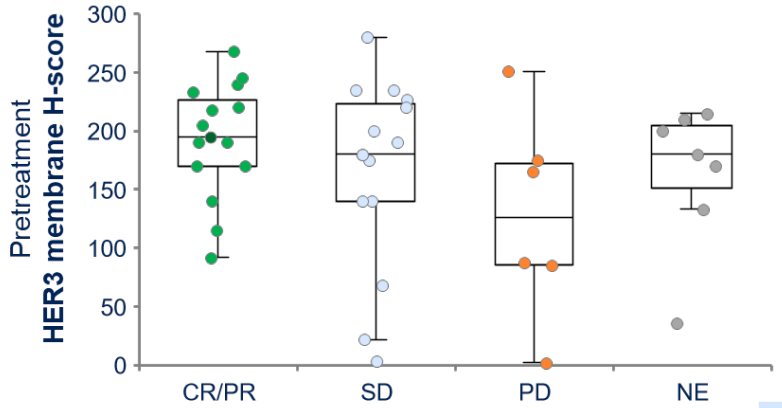
- BICR, blinded independent central review; BOR, best overall response; CR/PR, complete response/partial response; NE, not evaluable; PD, progressive disease; SD stable disease; SoD, sum of diameters.
- Data cutoff: September 24, 2020.
- [a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*.

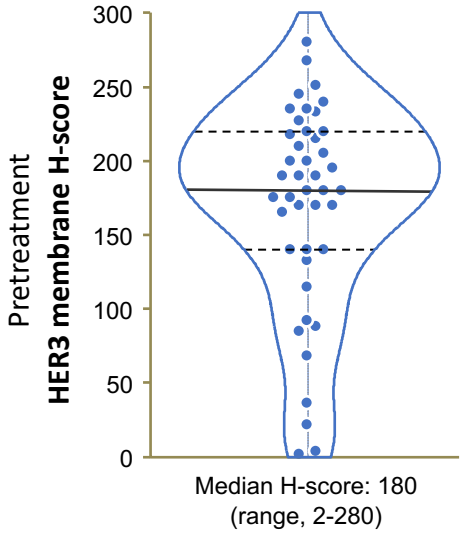
Jänne et al. Cancer Discovery 2022

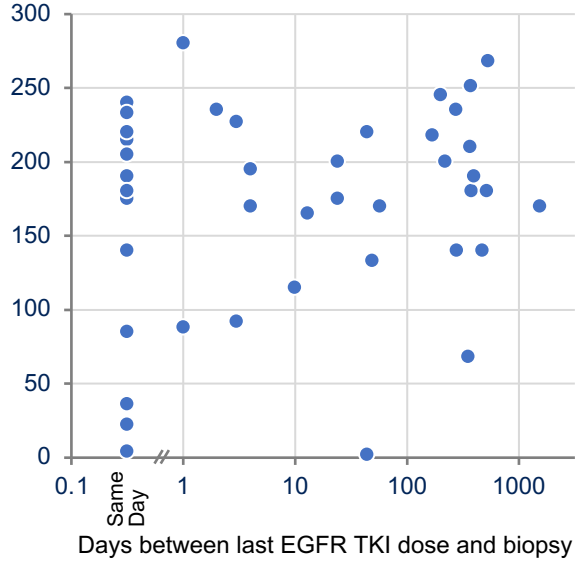
Clinical Responses Were Observed Across the Spectrum of Baseline HER3 Expression

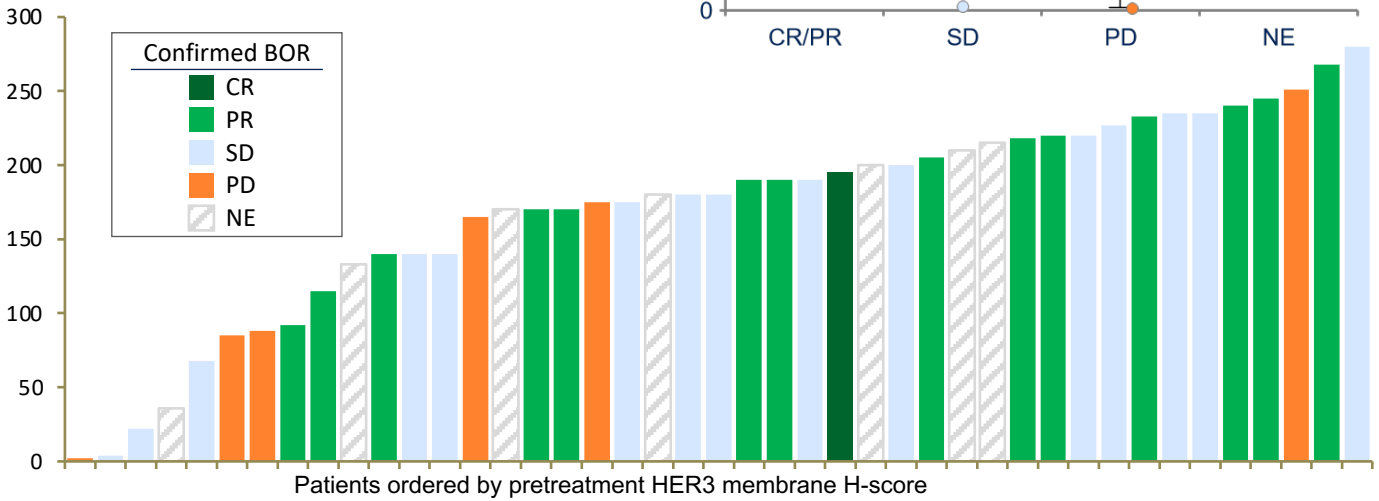
- HER3 was expressed in all evaluable patients' (43/57) tumors[a]
- HER3 expression was not correlated with time since last EGFR TKI dose

Responses were observed in patients with a wide range of baseline HER3 membrane H-scores









- BOR, best overall response; CR/PR, complete response/partial response; NE, not evaluable; PD, progressive disease; SD stable disease.
- Data cutoff: September 24, 2020; BOR by blinded independent central review.
- [a] Immunohistochemistry analysis of membrane HER3 in pre-treatment biopsy tissue from patients subsequently receiving HER3-DXd 5.6 mg/kg (N=43; taken since progression on last treatment and within the 6 months prior to enrollment).

Jänne et al. Cancer Discovery 2022

HERTHENA-Lung01: Phase 2 Study Design

This is a randomized, multicenter, open-label, phase 2 study of patritumab deruxtecan (HER3-DXd) in patients with locally advanced/metastatic NSCLC with an *EGFR*-activating mutation

Select Eligibility Criteria

- **Metastatic/unresectable NSCLC with an *EGFR*-activating mutation** (exon 19 deletion or L858R)
- **≥1 prior platinum-based chemotherapy regimen and prior treatment with osimertinib**
- **Progression during/after most recent systemic therapy**
- **Pretreatment tumor biopsy or archived tumor tissue since progression is required**

(N≈260)

Patritumab deruxtecan IV Q3W (21-day cycles)

R 1:1

5.6 mg/kg — **N≈210**

Uptitration — **N≈50**
- C1D1: **3.2 mg/kg**
- C2D1: **4.8 mg/kg**
- C3D1 and subsequent cycles: **6.4 mg/kg**

Data from U31402-A-U102 phase 1 supported the choice of 5.6mg/kg fixed dosing[a]

Objectives

Primary

- ORR by BICR per RECIST v1.1

Secondary

- DOR[b]
- PFS[b]
- ORR by investigator
- DCR, TTR, best percent change in SoD[b]
- Safety and tolerability
- HER3 as a biomarker
- Immunogenicity of patritumab deruxtecan
- OS

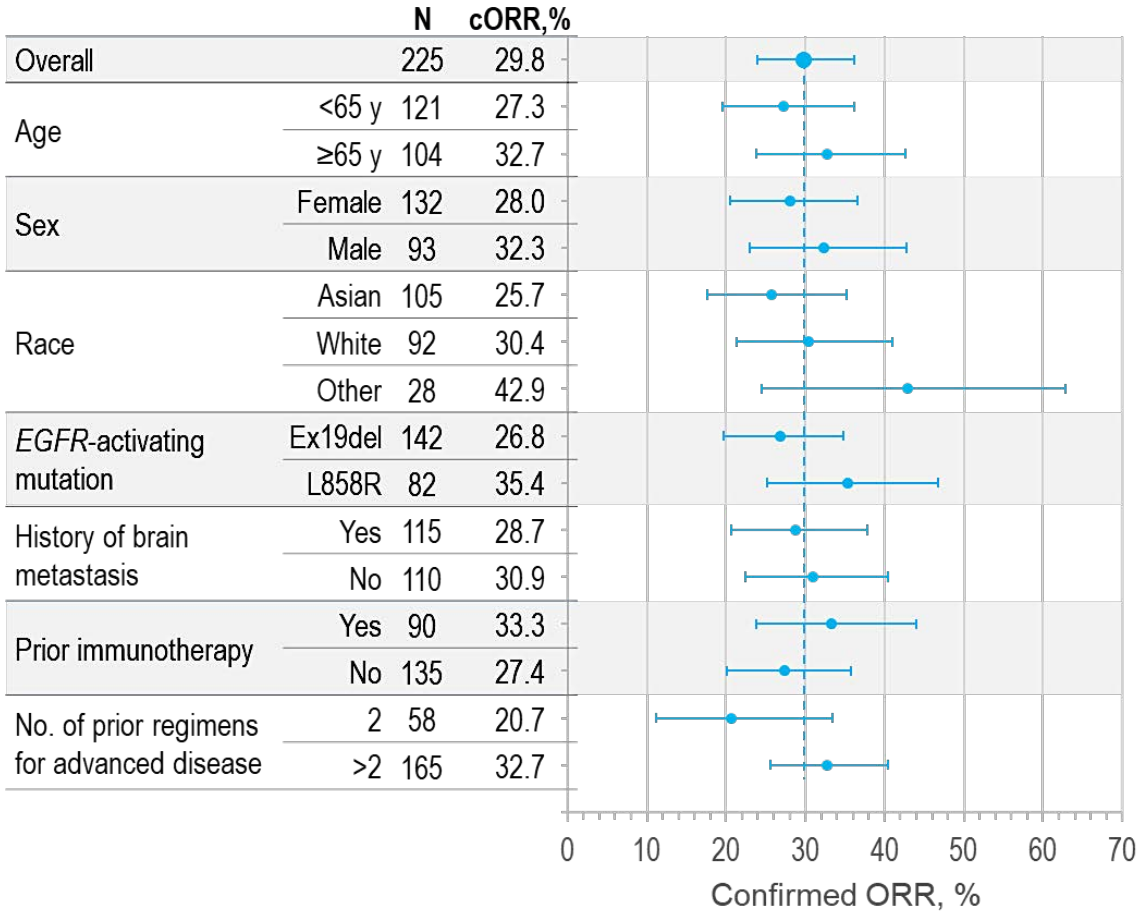
NCT04619004

HERTHENA-Lung01 Efficacy

Confirmed responses and survival		Prior EGFR TKI (any) and PBC (N=225)	Subset with prior 3G EGFR TKI and PBC (n=209)
cORR (95% CI), %		**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

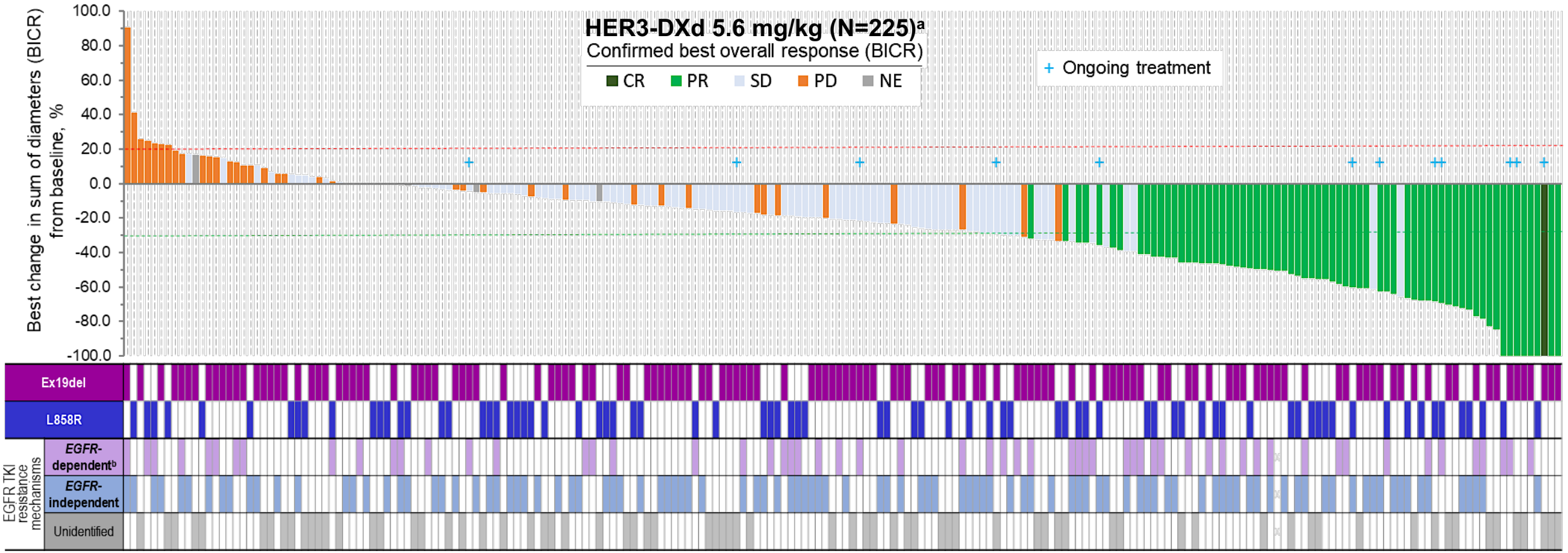
cORR by Patient and Disease Characteristics at Study Entry



3G, third generation; BICR, blinded independent central review; cORR, confirmed objective response rate (CR or PR confirmed ≥4 weeks after initial response [RECIST v1.1]); CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n=12); SD too early (SD <5 weeks after start of study treatment [n=4]).

Presented by: Helena A. Yu, Memorial Sloan Kettering Cancer Center, USA

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

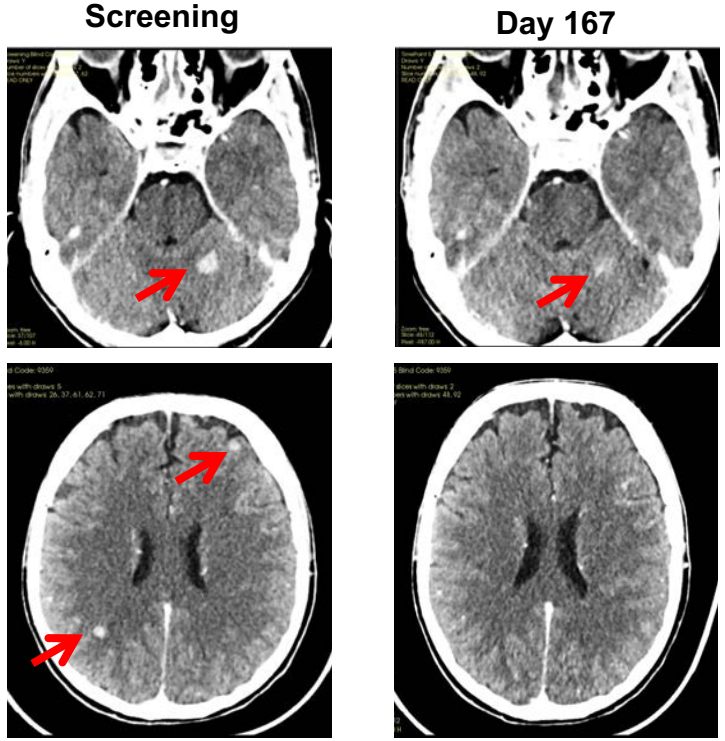
BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included. [b] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance.

Intracranial Responses (by CNS BICR) Observed With HER3-DXd

Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases at Baseline

Intracranial response by CNS BICR per CNS RECIST	Patients with brain metastasis at baseline and no prior radiotherapy (N=30)[a]
Confirmed ORR (95% CI), %	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
NE, n (%)	3 (10.0)
DCR (95% CI), %	76.7 (57.7-90.1)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion



BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] 7 patients had measurable target lesions; 23 patients had only nontarget lesions. [b] 8 patients had only nontarget lesions. [c] Includes non-CR/non-PD.

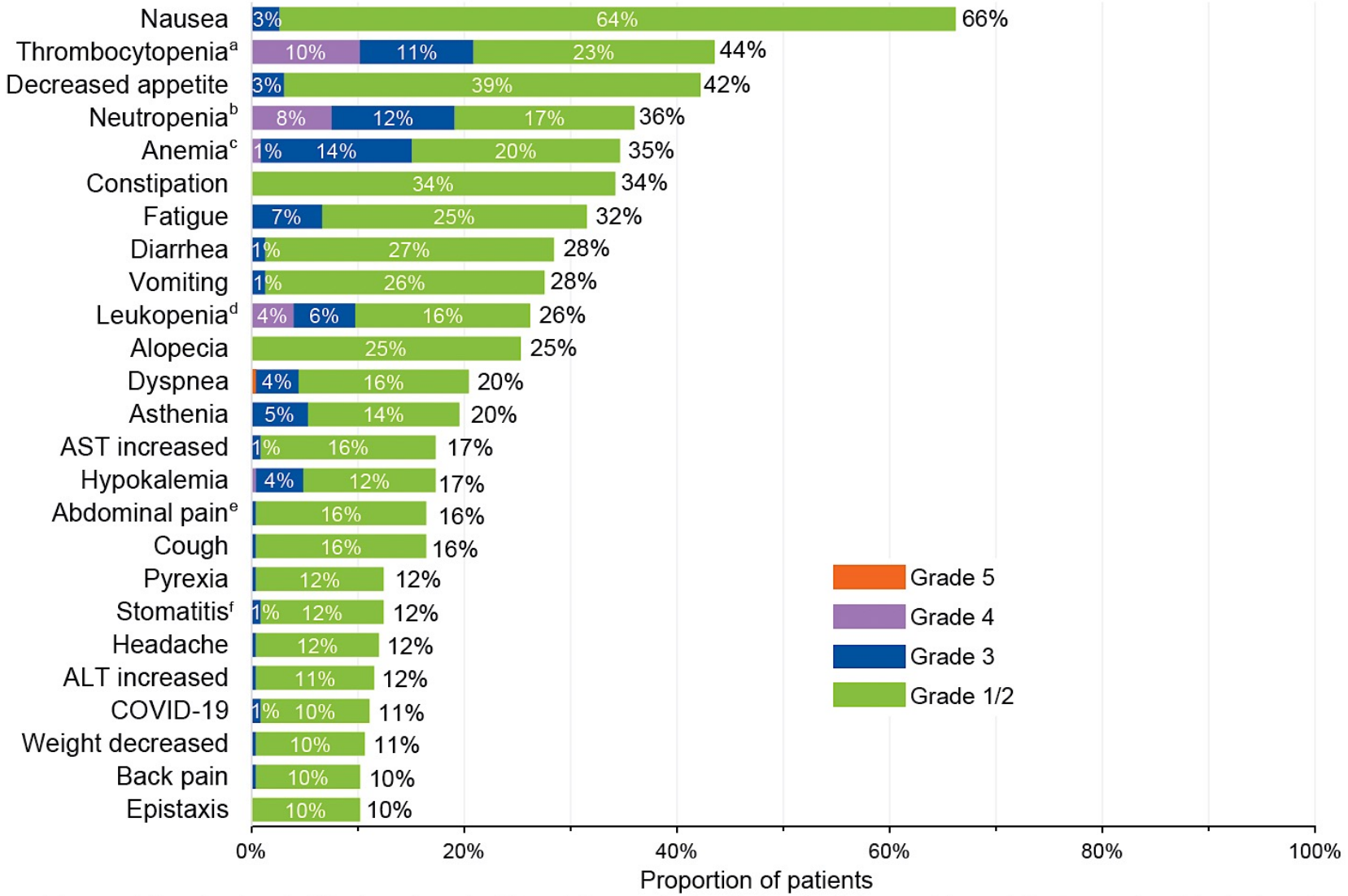
HERTHENA-Lung01 Overall Safety

Safety summary	HER3-DXd 5.6 mg/kg (N=225)
Study drug exposure	
Treatment duration, median (range), months	5.5 (0.7-23.7)
Dose intensity, median (range), mg/kg/cycle	5.45 (3.2-6.0)
Relative dose intensity, median (range), %	97.4 (57.1-107.8)
TEAEs	
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation	19 (8.4)
Associated with treatment dose reduction	50 (22.2)
Associated with treatment dose interruption	93 (41.3)
Grade ≥3 TEAE, n (%)	147 (65.3)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[a]	4 (1.8)
Grade ≥3	104 (46.2)
Serious TEAE	36 (16.0)

[a] Pneumonitis, GI perforation, pneumonia, respiratory failure (n=1 each)

Hayashi H et al. ELCC 2024;Abstract 11P.

HERTHENA-Lung01 Most Common TEAEs



[a] Platelet count decreased, thrombocytopenia. [b] Neutropenia, neutrophil count decreased. [c] Anemia, hematocrit decreased, hemoglobin decreased, red blood cell count decreased. [d] Leukopenia, white blood cell count decreased. [e] Abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper. [f] Aphthous ulcer, mouth ulceration, oral mucosa erosion, oral mucosal blistering, stomatitis.

Hayashi H et al. ELCC 2024;Abstract 11P.

HERTHENA-Lung02: Phase 3 Study Design

This is a randomized, open-label, phase 3 study of patritumab deruxtecan (HER3-DXd) vs platinum-based

by

Press Release (9/17/24):
Patritumab Deruxtecan Demonstrated Statistically Significant Improvement in Progression-Free Survival Versus Doublet Chemotherapy in Patients with Locally Advanced or Metastatic EGFR-Mutated Non-Small Cell Lung Cancer in HERTHENA-Lung02 Phase 3 Trial

Mok et al. Lung Cancer Oral session. June 1st 10:00 – 10:12 am; Arie Crown Theater

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End of Study

Objectives	Primary	Secondary		
	• Progression-free survival (BICR)	• Overall survival (**key secondary**) • Progression-free survival (Investigator) • ORR	• DOR • Safety and TEAEs • DCR • CBR	• Immunogenicity • Correlation of efficacy and HER3 expression • TTR • PRO of disease-related symptoms

NCT05338970

Patritumab Deruxtecan Biologics License Application for Patients with Previously Treated Locally Advanced or Metastatic EGFR-Mutated NSCLC Voluntarily Withdrawn

Press Release: May 29, 2025

"The Biologics License Application (BLA) seeking accelerated approval in the US for patritumab deruxtecan (HER3-DXd), based on the HERTHENA-Lung01 Phase 2 trial for the treatment of adult patients with locally advanced or metastatic EGFR-mutated non-small cell lung cancer (NSCLC) previously treated with two or more systemic therapies, has been voluntarily withdrawn.

The decision to withdraw the BLA is based on topline overall survival (OS) results from the confirmatory HERTHENA-Lung02 Phase 3 trial where OS did not meet statistical significance, as well as discussions with the US Food and Drug Administration. The decision is unrelated to the Complete Response Letter that was received in June 2024 and outlined findings pertaining to an inspection of a third-party manufacturing facility.

Results from the HERTHENA-Lung02 Phase 3 trial, including previously reported statistically significant progression-free survival (PFS) along with topline OS results, will be presented during an oral presentation (#8506) at the 2025 American Society of Clinical Oncology Annual Meeting on Sunday, June 1, 2025."

https://www.merck.com/news/patritumab-deruxtecan-biologics-license-application-for-patients-with-previously-treated-locally-advanced-or-metastatic-egfr-mutated-non-small-cell-lung-cancer-voluntarily-withdrawn/

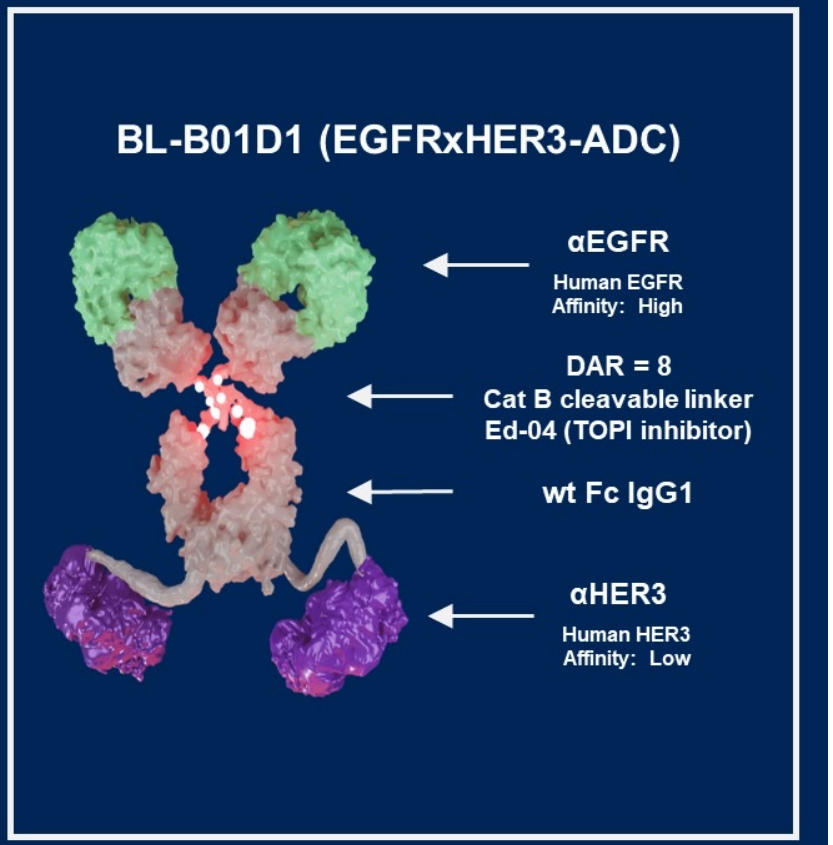
Other HER3 ADCs

- DB-1310
  - Developmental Therapeutics Molecularly Targeted Agents and Tumor Biology; Friday May 30th; 2:45 pm CDT; Hall D1
    - 35.7% RR; PFS 7.0 months in previously treated EGFR mutant NSCLC

Lisberg et al. ASCO 2025

Background

- EGFR and HER3 are highly expressed in various epithelial tumors. Targeting these receptors could provide a broad-spectrum and pan-tumor killing therapy.
- Antibody-drug conjugates have emerged as a powerful strategy in cancer therapy.
- BL-B01D1 is a first-in-class (FIC) ADC consisting of an EGFRxHER3 bispecific antibody bounded to a novel topoisomerase I inhibitor payload via a cleavable linker.
- We assessed its safety, tolerability, and preliminary efficacy in patients with solid tumors in a first-in-human (FIH) trial (BL-B01D1-101).

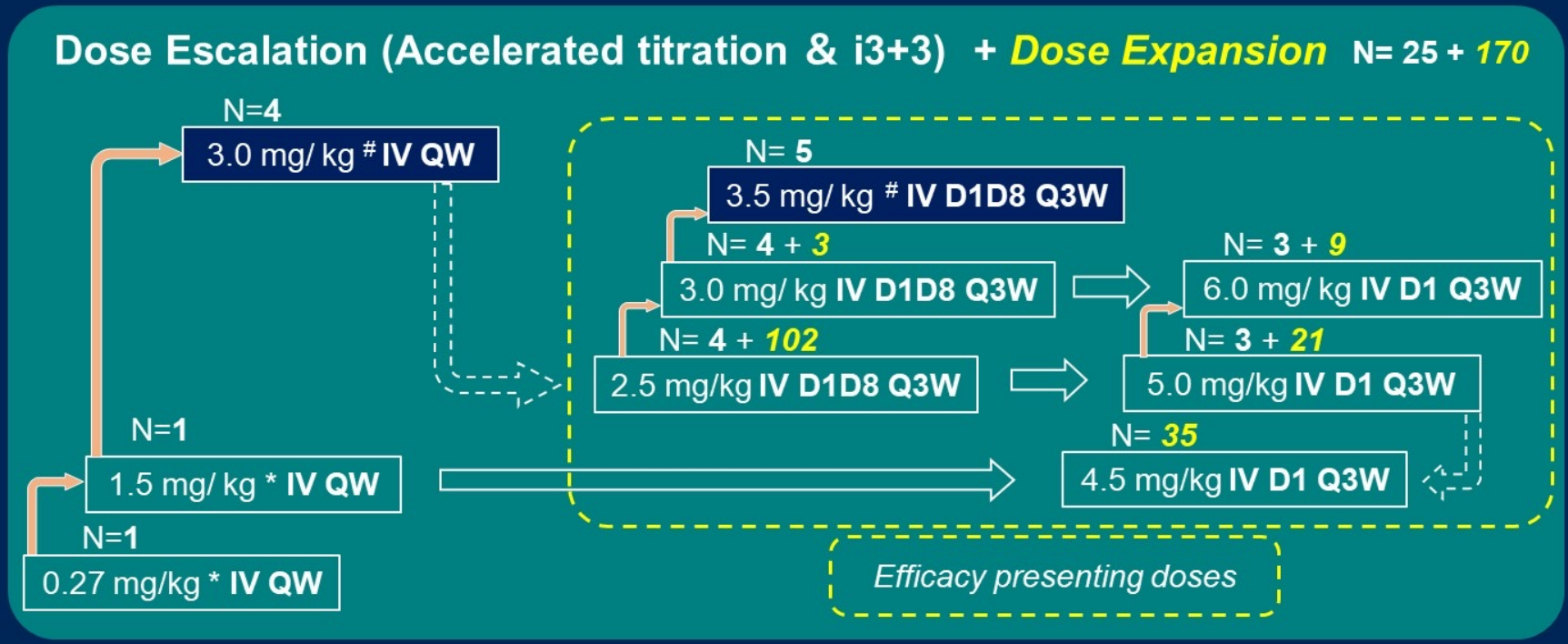


Zhang L et al. ASCO 2023;Abstract 3001.

BL-B01D1-101 Study design and results overview

Key Inclusion Criteria:

- Locally advanced or metastatic NSCLC or other solid tumors
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Failed standard therapy or without feasible treatment



Primary Endpoint:
DLT, MTD (or MAD), RP2D

Secondary Endpoint:
PK, ADA, ORR, DCR, DOR

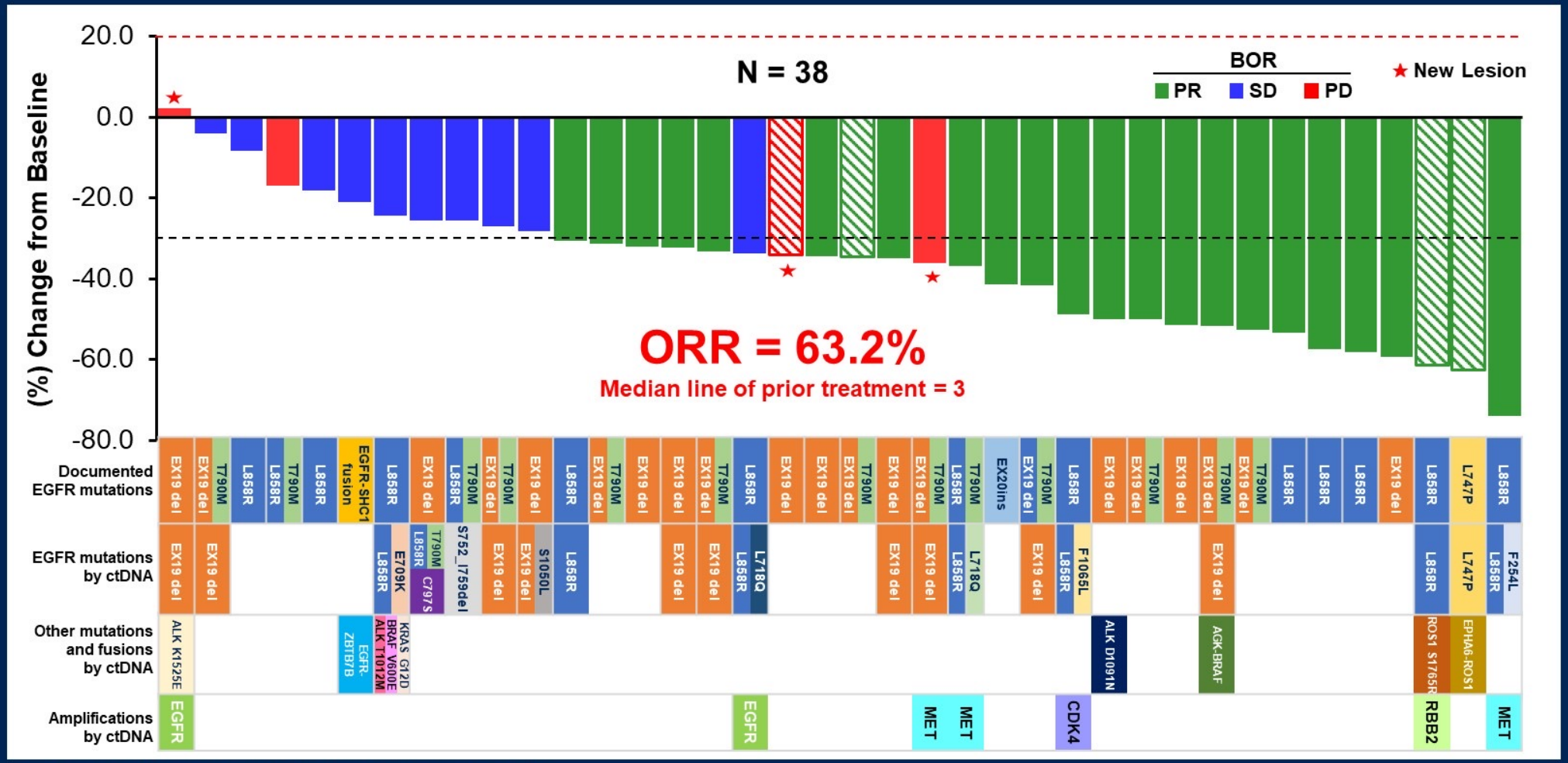
Exploratory Endpoint:
PFS, OS, Biomarker, Nab

* Accelerated titration; # 2 DLTs in each dose.

Data cutoff: March 13, 2023

Zhang L et al. ASCO 2023;Abstract 3001.

Antitumor Response in EGFRmut NSCLC Patients



Zhang L et al. ASCO 2023;Abstract 3001.

Safety of BL-B01D1-101 Study

Overall Safety Summary	ALL Patients (n=195)
Median Follow-up (months)	4.1
Treatment Related AE (TRAE)	180(92%)
Treatment discontinuation	5(3%)
Dose reduction	48(25%)
Associated with death	2(1%)[#]
Grade ≥3 TRAE	111(57%)
Treatment Related-SAE	56(29%)

[#] Two drug related deaths were because of pulmonary infection, myelosuppression.

TRAE in ≥10% patients, n (%)	BL-B01D1-101 (N=195)	
	All Grade	≥G3
Leukopenia	119 (61%)	59 (30%)
Anemia	114 (58%)	49 (25%)
Neutropenia	104 (53%)	67 (34%)
Thrombocytopenia	98 (50%)	46 (24%)
Nausea	65 (33%)	1 (<1%)
Vomiting	58 (30%)	2 (1%)
Alopecia	56 (29%)	NA
Asthenia	43 (22%)	2 (1%)
Decreased appetite	43 (22%)	1 (<1%)
Mouth ulceration	34 (17%)	3 (2%)
Diarrhea	34 (17%)	1 (<1%)
Hypophagia	32 (16%)	0
Rash	25 (13%)	0
Hypokalemia	22 (11%)	5 (3%)

No Interstitial lung disease (ILD) was observed.

Data cutoff: March 13, 2023

Zhang L et al. ASCO 2023;Abstract 3001.

Based on the published literature and/or your clinical experience, would you like to have access to patritumab deruxtecan (HER3-DXd) for patients with nonsquamous mNSCLC with an EGFR mutation?

 Prof Girard	Yes
 Dr Goldman	Yes
 Dr Jänne	Yes
 Dr Ramalingam	Yes
 Dr Sabari	Yes
 Dr Yu	Yes
 Dr Gadgeel	Yes
 Dr Spira	I'm not sure

RTP RESEARCH TO PRACTICE

Based on the published literature and/or your clinical experience, what have you observed in terms of the tolerability of HER3-DXd for patients with nonsquamous mNSCLC with an EGFR mutation?

 Prof Girard	Thrombocytopenia
 Dr Goldman	HER3-DXd generally well tolerated. Less mucositis and less fatigue
 Dr Jänne	Similar to chemotherapy (nausea/vomiting, hematologic toxicity)
 Dr Ramalingam	Nausea, emesis, fatigue
 Dr Sabari	Similar toxicities to other deruxtecan-containing agents — ILD, stomatitis, hematologic toxicities, etc
 Dr Yu	Tolerable
 Dr Gadgeel	As tolerable as T-DXd, may have more GI symptoms
 Dr Spira	Typical ADC side effects

ADC = antibody-drug conjugate

Consensus or Controversy? Clinical Investigators Provide Perspectives on the Current and Future Clinical Care of Patients with Urothelial Bladder Cancer

A CME Symposium Held in Conjunction with the 2025 ASCO® Annual Meeting

Saturday, May 31, 2025
6:45 AM – 7:45 AM CT (7:45 AM – 8:45 AM ET)

Faculty

Andrea Necchi, MD
Thomas Powles, MBBS, MRCP, MD

Moderator

Matthew D Galsky, MD

RTP RESEARCH TO PRACTICE

Thank you for joining us!
Your feedback is very important to us.

Please complete the survey currently up on the iPads for attendees in the room and on Zoom for those attending virtually. The survey will remain open up to 5 minutes after the meeting ends.

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Online/Zoom attendees: The CME credit link is posted in the chat room.

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