2026

DEBATES AND DIDACTICS in Hematology and Oncology

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

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DEBATE:
Treatment of acquired resistance in 2nd line EGFR mutant NSCLC should ***NOT*** be mechanism based

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When would mechanism-based salvage therapy make sense?

- A highly prevalent resistance mutation (Gatekeeper?)

- Availability of a potent, mutant selective, targeted therapy with a tolerable side effect profile

Precision medicine isn't about ordering every possible test. It's about ordering the right test for the right patient at the right time…
And impact management

There was a time when acquired resistance in EGFRm NSCLC was mechanism based IN 2015!

University of Miami Medical School 2015

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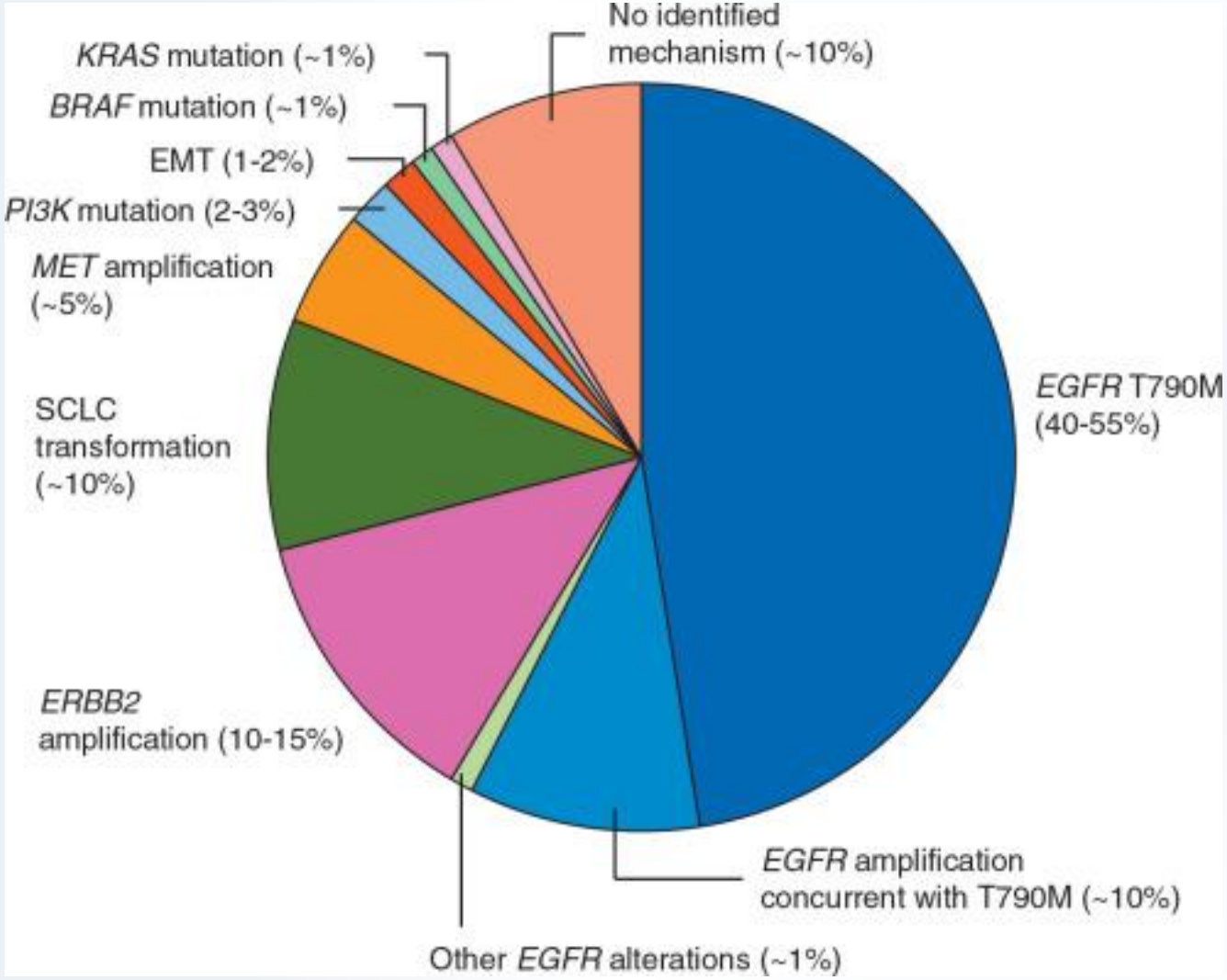


University of Miami Medical School 2015

D. Westover et al. Annals of Oncology, 29(1), 2018

There was a time when acquired resistance in EGFRm NSCLC was mechanism based IN 2015!

AURA trial P2 extension: Osimertinib

327 patients' samples were eligible for T790M testing.

207 (64%) had positive test results for T790M.

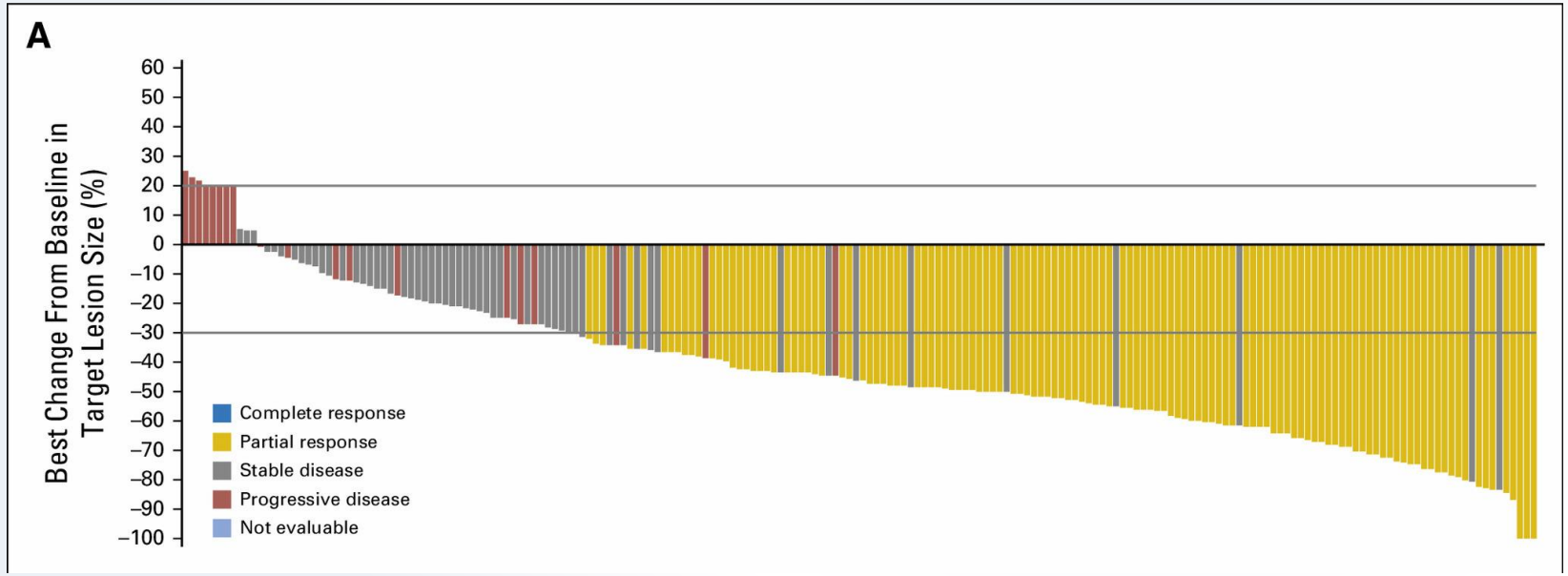
201 received osimertinib treatment (61 as 2nd line and 140 as 3rd + line

ORR was 62% (95% CI, 54%-68%)

Disease control rate was 90% (95% CI, 85-94).

Median DOR in 122 responding patients was 15.2 months (95% CI, 11.3-NC)

Median PFS was 12.3 months (95% CI, 9.5 to 13.8)



University of Miami Medical School 2015

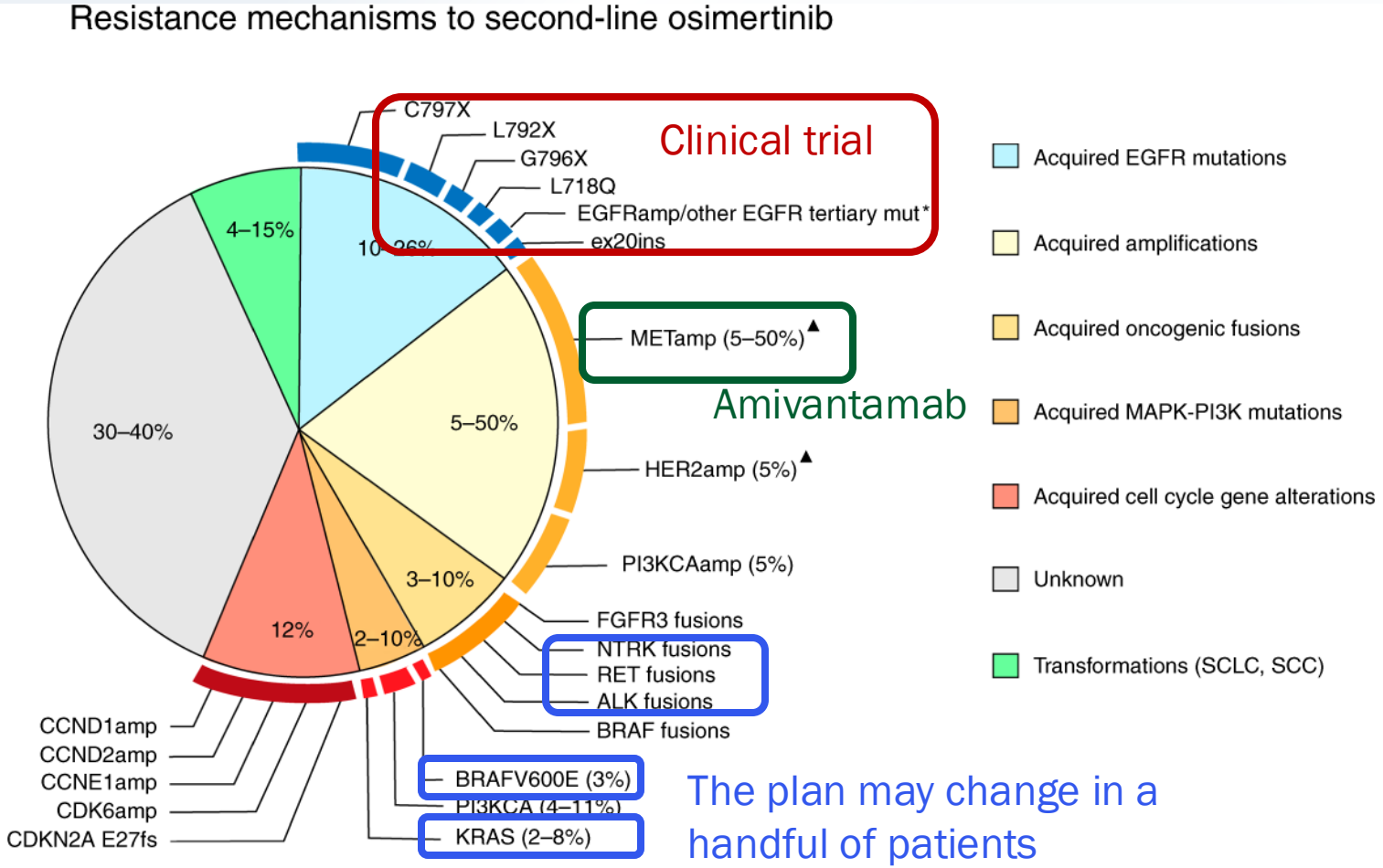
James Chih-Hsin Yang et al. *J Clin Oncol* **35**, 1288-1296 (2017)

Why we need to invest in mechanism agnostic approaches:

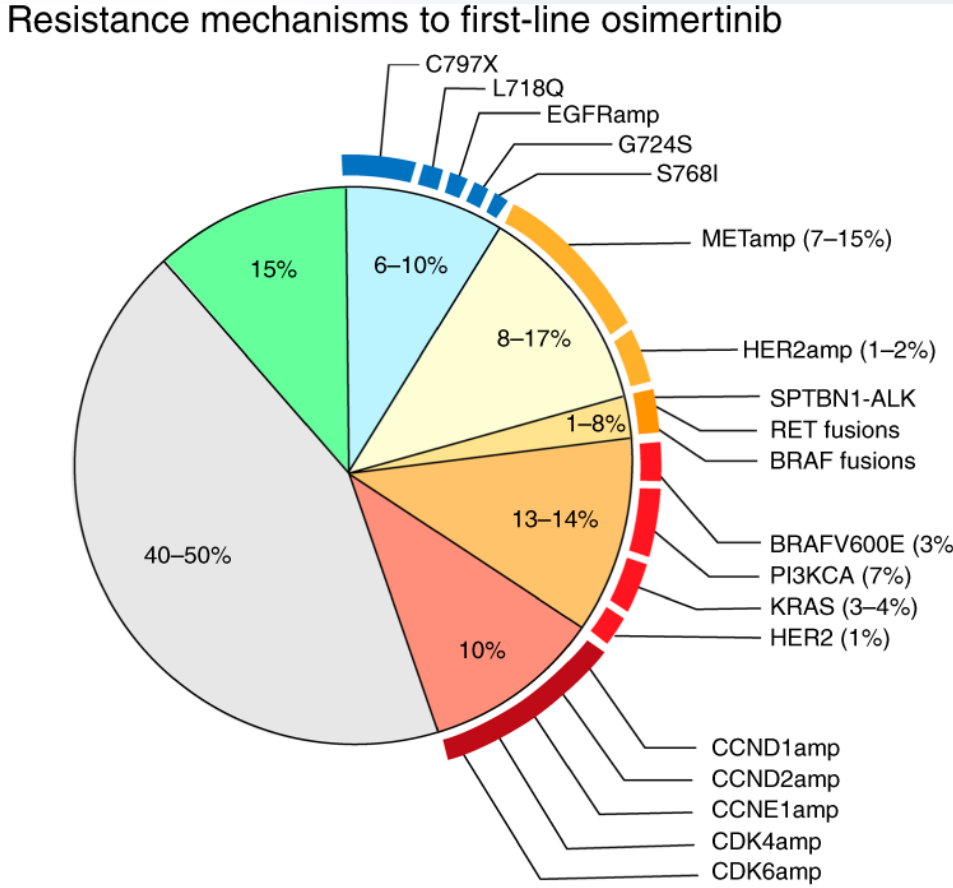
* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

Leonetti, A., Sharma, S., Minari, R. *et al.* Resistance mechanisms to osimertinib in *EGFR*-mutated non-small cell lung cancer. *Br J Cancer* **121**, 725–737 (2019).

Why we need to invest in mechanism agnostic approaches:



The plan may change in a handful of patients



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Why we need to invest in mechanism agnostic approaches:

1. Chemo works!

2. Amivantamab works!

3. ADCs work!

Clinical trial approaches targeting mechanisms of resistance have an important role in a subset of patients:

- who want to undergo repeat testing, and sometimes invasive biopsies
- have the performance status
- measurable disease
- creatinine clearance (often > 60!)
- lack of active brain metastases
- and have the family and logistic support for travel, frequent appointments

Many patients still start with osimertinib first:

COMPEL: osimertinib plus platinum-based chemotherapy in patients with EGFR-mutated advanced NSCLC and progression on first-line osimertinib

Background

- Some tumor cells may retain sensitivity to EGFR-TKIs following progression on first-line osimertinib (osi), particularly in the central nervous system (CNS)

- EGFR-TKI sensitive cells
- EGFR-TKI resistant cells

- COMPEL compared osi + chemotherapy (CTx) versus placebo (PBO) + CTx in patients with EGFR-mutated advanced NSCLC and non-CNS progression on first-line osi

Patients

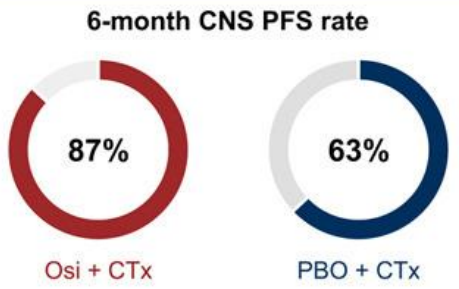
Randomized 1:1 (n = 98)

Osi + CTx		PBO + CTx
63 years	Median age	61 years
61%	Female	80%
22%	CNS metastases	24%

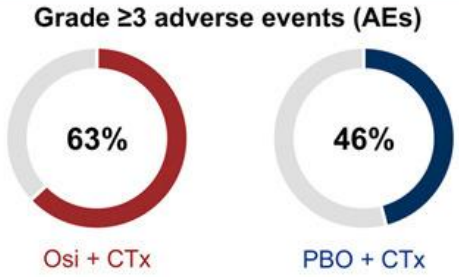
Results

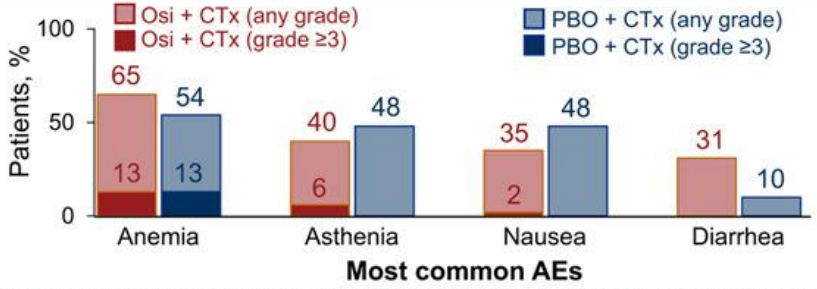
Osi + CTx was associated with improved progression-free survival (PFS) and longer overall survival (OS) versus PBO + CTx (n = 98)

CNS PFS was also longer with osi + CTx versus PBO + CTx in patients without baseline CNS metastases (n = 75)



Safety findings were consistent with the known safety profiles of each drug (n = 96)

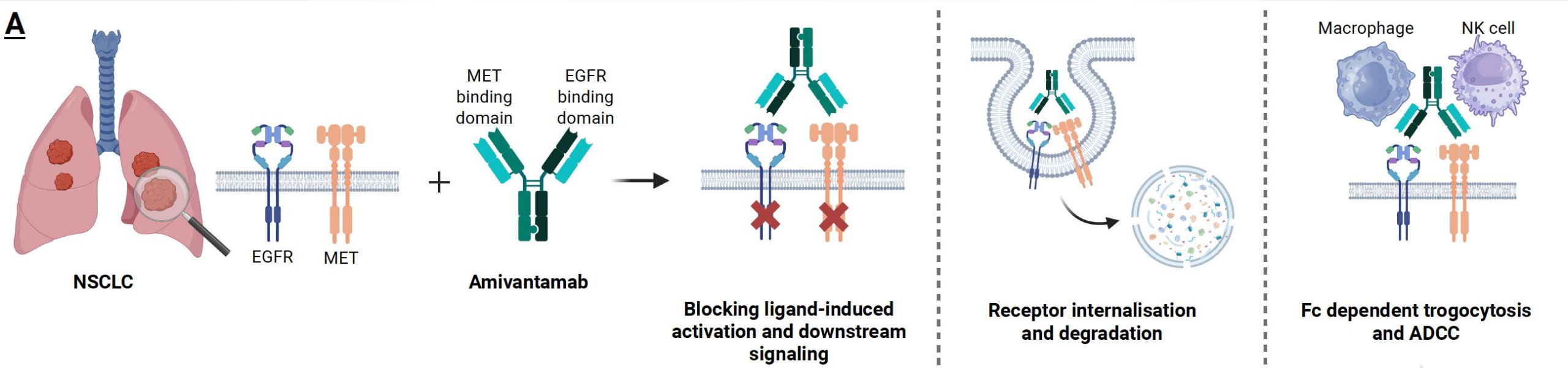




CONCLUSION: Osi + CTx was associated with improved PFS and longer OS compared with PBO + CTx in patients with non-CNS progression on first-line osi. These findings support osi as a backbone treatment for EGFR-mutated advanced NSCLC through lines of therapy.

Peled, N et al. ESMO Open (2025)

Amivantamab



Carlisle et al., ASCO Education Book, 2025

MARIPOSA-2 (NCT04988295) demonstrated improved PFS versus chemotherapy after disease progression on osimertinib in patients with *EGFR*-mutated advanced NSCLC

MARIPOSA-2 is a randomized,[a] open-label, Phase 3 study

evaluating the efficacy and safety of 2 regimens of amivantamab (with and without lazertinib) and chemotherapy

1. Amivantamab-Chemotherapy (n=131)
2. Amivantamab-Lazertinib-Chemotherapy (n=263)
3. Chemotherapy (n=263)

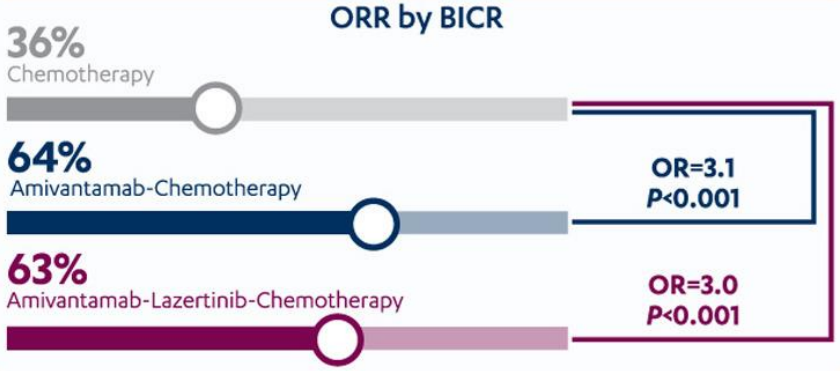
There are currently no targeted therapies approved for patients who progress on osimertinib

[a]Patients were randomized 1:2:2 to Amivantamab-Chemotherapy, Amivantamab-Lazertinib-Chemotherapy, and Chemotherapy, respectively.

Amivantamab + Lazertinib + Chemotherapy and Amivantamab + Chemotherapy improved PFS, intracranial PFS, ORR, and other key endpoints versus Chemotherapy alone

Amivantamab-Chemotherapy vs Chemotherapy	Amivantamab-Lazertinib-Chemotherapy vs Chemotherapy
HR for disease progression or death, **0.48** (95% CI, 0.36–0.64); *P*<0.001	HR for disease progression or death, **0.44** (95% CI, 0.35–0.56); *P*<0.001

ORR by BICR



BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; OR, odds ratio; ORR, objective response rate; PFS, progression-free survival.

Predominant AEs in the amivantamab-containing arms were hematologic and EGFR-and MET-related

Most hematologic AEs were transient, with majority occurring in Cycle 1

The safety profile of amivantamab-chemotherapy is consistent with that of its individual components

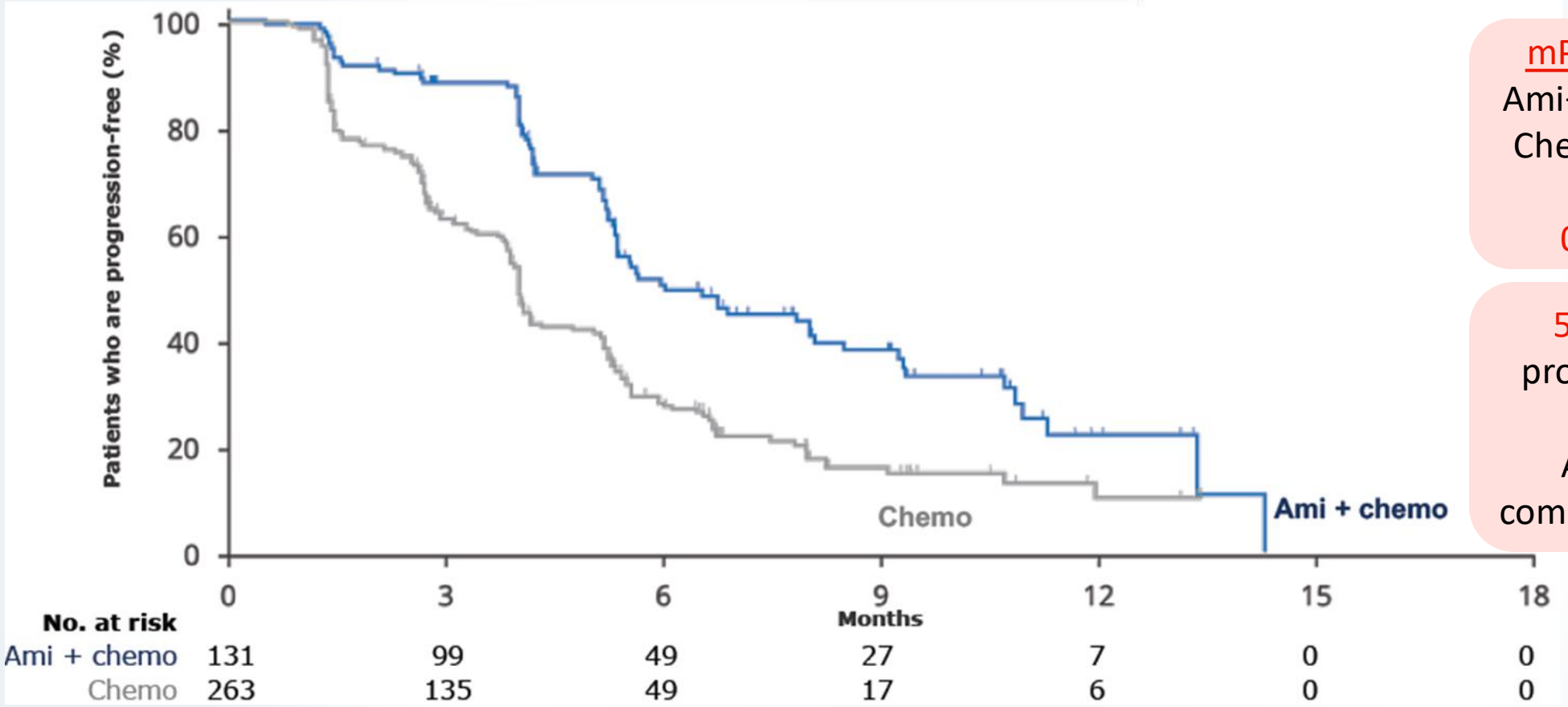
Most common EGFR-, MET-, and chemotherapy-associated AEs, n (%)		Chemotherapy (n=243)		Amivantamab-Chemotherapy (n=130)		Amivantamab-Lazertinib-Chemotherapy (n=263)	
		All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
	Any AEs	227 (93)	117 (48)	130 (100)	94 (72)	263 (100)	242 (92)
EGFR	Paronychia	1 (0.4)	0	48 (37)	3 (2)	133 (51)	11 (4)
	Rash	12 (5)	0	56 (43)	8 (6)	126 (48)	17 (6)
MET	Hypoalbuminemia	21 (9)	1 (0.4)	29 (22)	3 (2)	104 (40)	12 (5)
	Peripheral edema	15 (6)	0	42 (32)	2 (2)	85 (32)	1 (0.4)
Chemotherapy	Neutropenia	101 (42)	52 (21)	74 (57)	59 (45)	181 (69)	144 (55)
	Thrombocytopenia	72 (30)	22 (9)	57 (44)	19 (15)	158 (60)	96 (37)
Other	Infusion-related reaction	1 (0.4)	0	76 (58)	7 (5)	148 (56)	9 (3)

AE, adverse event; EGFR, epidermal growth factor receptor; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Passaro A et al. Annals of Oncology, 2023; 35, 77-90

MARIPOSA-2 (post osimertinib)

Primary endpoint PFS by BICR



mPFS, months (95% CI)
Ami+Chemo: 6.3 (5.6–8.4)
Chemo: 4.2 mo (4.0–4.4)
HR: 0.48 (95% CI, 0.3–0.64); P<0.001

52% reduced risk of progression or death in patients in the Ami+Chemo group compared to Chemo alone

Passaro A et al. Annals of Oncology, 2023; 35, 77-90

A pooled analysis of datopotamab deruxtecan in patients with *EGFR*–mutated NSCLC

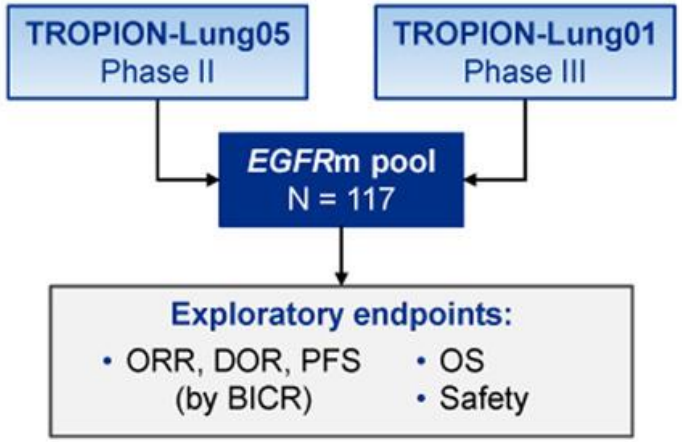
Journal of Thoracic Oncology

Background

A critical unmet need exists for effective later-line treatment options for patients with *EGFR*m advanced NSCLC

Methods

Pooled analysis from two trials assessing the TROP2-directed ADC Dato-DXd in pretreated patients with *EGFR*m NSCLC



Results

Pooled study population (N = 117)

- 63 years MEDIAN AGE
- 62% FEMALE
- 69% ASIAN
- 23% WHITE

Median 3 prior lines of therapy (EGFR-directed and platinum chemotherapy)

Prior osimertinib 82%

Most common *EGFR* mutations

- Patients may have had tumors with >1 *EGFR*m

*Occurring as co-mutations.

Dato-DXd elicited robust and durable clinical efficacy

Safety profile consistent with the individual studies

	Any grade	Grade 3
Oral mucositis/stomatitis	69%	9%
Ocular surface events	32%	3%
Adjudicated drug-related ILD/pneumonitis	4%	1%

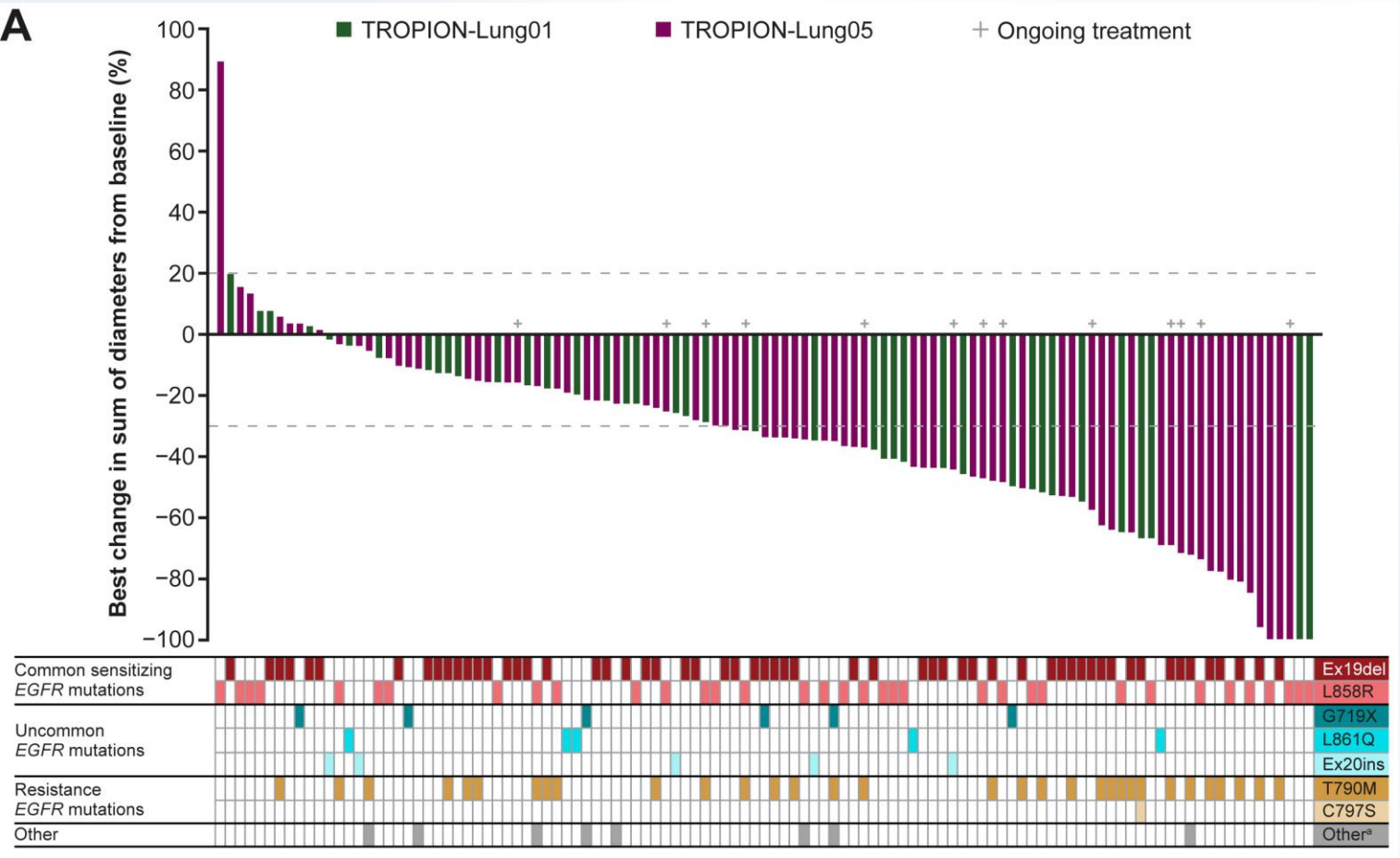
- No new safety signals
- No grade 4 or 5 AESIs

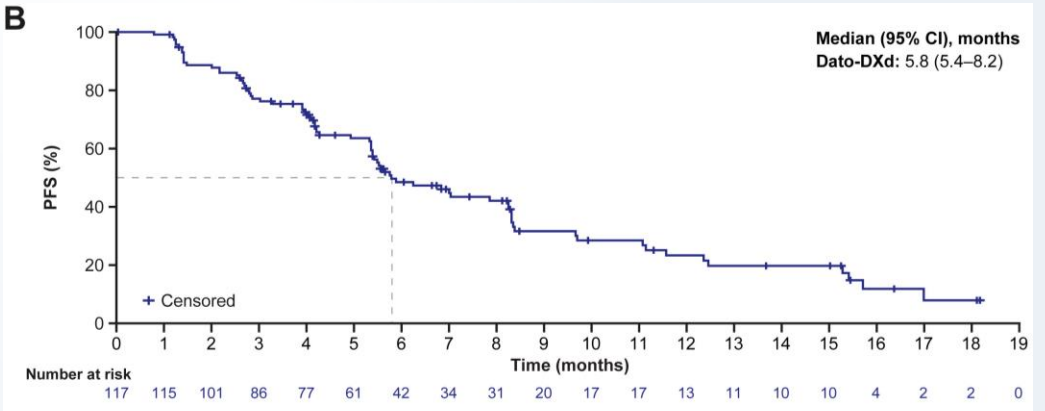
CONCLUSION: Dato-DXd demonstrated clinically meaningful activity and had a manageable safety profile in previously treated patients with advanced *EGFR*m NSCLC

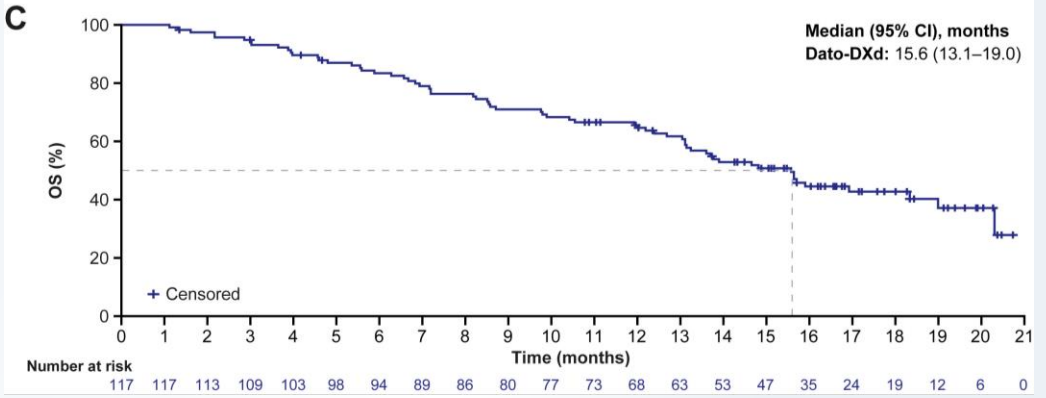
ORR to docetaxel (n=45) 9%

Ahn M-J et al. J Thor Onc (2025)

Datopotamab deruxtecan (TROP-2 ADC with topo-1 payload)







Ahn M-J et al. J Thor Onc (2025)

Conclusions:

Molecular testing at progression can certainly be useful for some patients.

- Liquid biopsies are convenient, patient friendly
- Tissue needed to r/o transformation to SCLC, SCC

<u>But the majority of patients do not have a target!</u>

Clinical trial data support mechanism agnostic approaches in relapsed classical EGFR mutant NSCLC

- FDA approved amivantamab with carboplatin and pemetrexed - Sept 2024
- FDA accelerated approval of Dato-DXD – June 2025

We can collect information on mutations

but we should also ask ourselves, will it change the plan?

Q&A