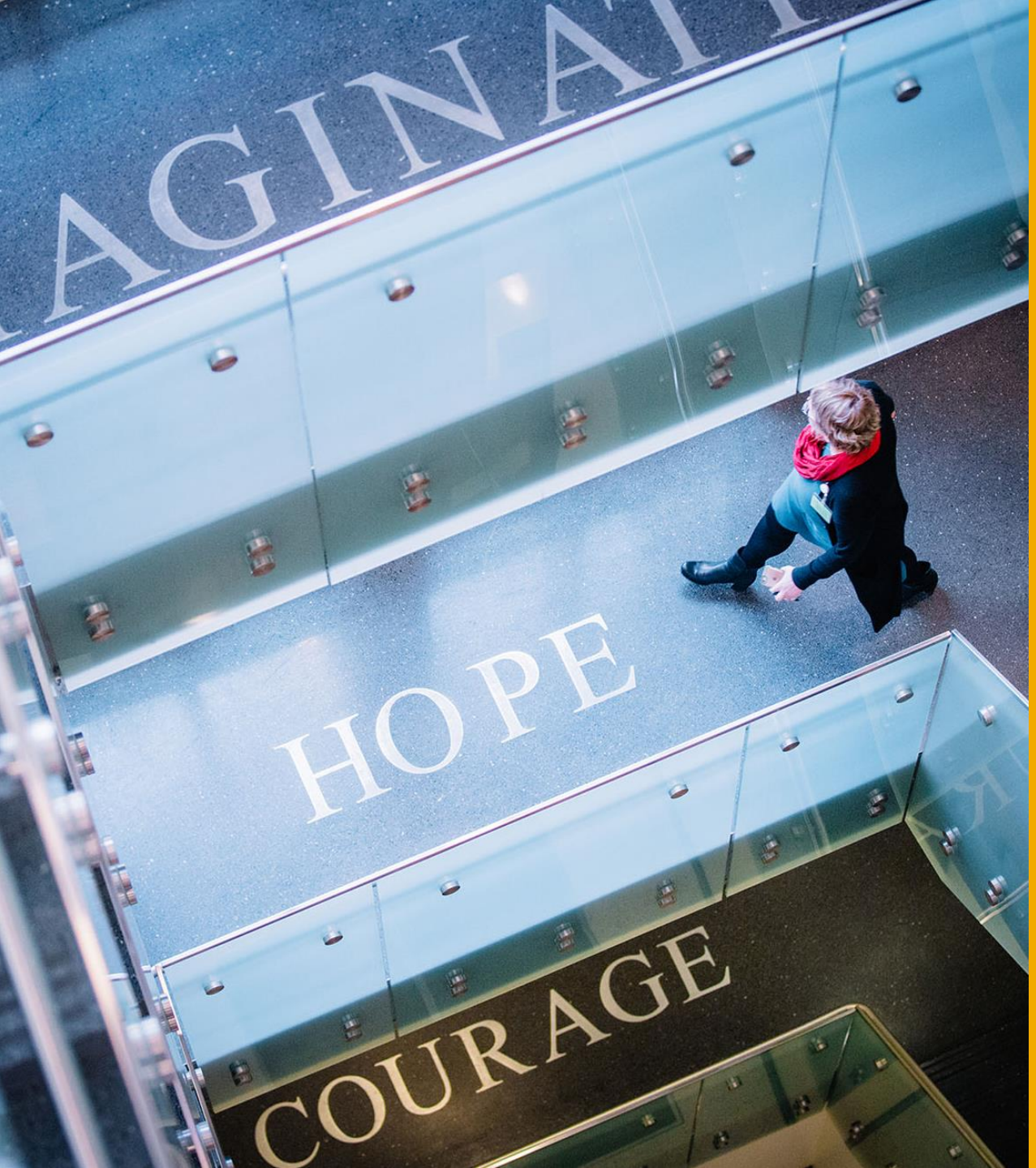


TREATMENT OF ACQUIRED RESISTANCE IN 2L EGFR-MUTANT NSCLC SHOULD BE MECHANISM BASED

Kelsey Pan, MD, MPH

Assistant Professor
Winship Cancer Institute of Emory University
Emory University School of Medicine

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

NCI Designated Comprehensive Cancer Center

Disclosures – 24 months

Advisory Board: Johnson & Johnson, Avyxos, Astrazeneca

Consulting/Honorarium: MJH Life Sciences, Ultimate Opinions in Medicine, Medical Logix

Opponent: Dr. Jenny Carlisle

- World-class clinician
- Exemplary researcher/ investigator
- Eloquent speaker
- Fierce debater
- Strong mentorship track record
- Loving mother of adorable twins
- One of my personal mentors

Patient walks into Dr. Carlisle's clinic…

- 58F with metastatic lung adenocarcinoma with EGFR L858R mutation
- Asymptomatic adrenal mets, no brain mets
- Dr. Carlisle starts frontline Osimertinib
- Pt has treatment response

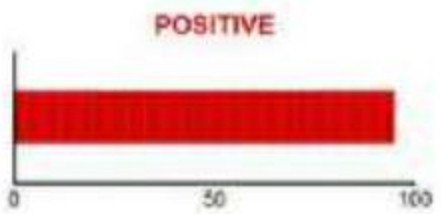
18 months later….

- Pt has enlarging hepatic metastases and mediastinal LAD
- Liquid NGS is repeated

Patient walks into Dr. Carlisle's clinic…

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
EGFR	Seq	DNA-Tumor	Pathogenic Variant Exon 21 | p.L858R	BENEFIT	afatinib, dacomitinib, erlotinib, erlotinib + ramucirumab, gefitinib, lazertinib + amivantamab, osimertinib	Level 2
					datopotamab deruxtecan	Level 2
MET	Seq	RNA-Tumor	Exon 14 Skipping Detected	BENEFIT	capmatinib, tepotinib	Level 2
	CNA-Seq	DNA-Tumor	Amplified		crizotinib	Level 2

c-MET CDx for NSCLC:
POSITIVE
Percentage of Cells with 3+ Membrane and/or Cytoplasmic Staining:
95%



Reference Ranges	
Positive	>/=50% of 3+ Membrane and/or Cytoplasmic Staining
Negative	<50% of 3+ Membrane and/or Cytoplasmic Staining

Patient walks into Dr. Carlisle's clinic…

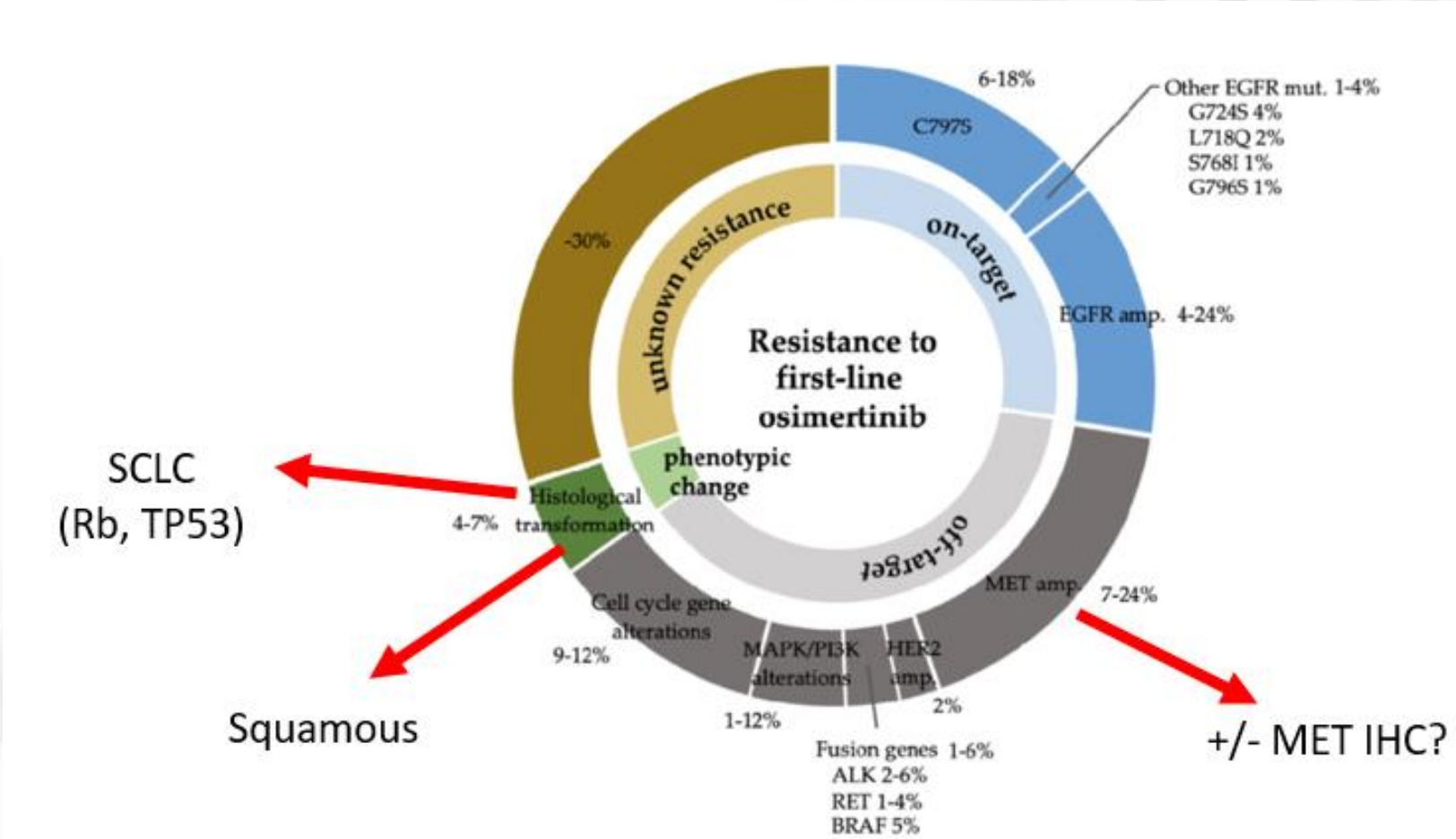
Patient walks into Dr. Carlisle's clinic…

- Patient was started on platinum-based chemotherapy + osimertinib per COMPEL

AI Overview

Dr. Jennifer Carlisle (Emory University/Winship Cancer Institute) specializes in thoracic oncology, focusing on mechanism-directed therapies and precision immuno-oncology for lung cancer. Her work targets how molecular alterations dictate therapeutic resistance. OncLive · OncLive +4

Acquired resistance after 3G EGFR TKIs



Adapted from Fukada et al., Biomedicines 2024

EGFR + MET amplification

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
EGFR	Seq	DNA-Tumor	Pathogenic Variant Exon 21 | p.L858R	BENEFIT	afatinib, dacomitinib, erlotinib, erlotinib + ramucirumab, gefitinib, lazertinib + amivantamab, osimertinib	Level 2
					datopotamab deruxtecan	Level 2
MET	Seq	RNA-Tumor	Exon 14 Skipping Detected		capmatinib, tepotinib	Level 2
	CNA-Seq	DNA-Tumor	Amplified	BENEFIT	crizotinib	Level 2

- MET amplification: most common EGFR-independent resistance mechanism (~15–25%)

POSITIVE
Percentage of Cells with 3+ Membrane and/or Cytoplasmic Staining:
95%

Positive	>/=50% of 3+ Membrane and/or Cytoplasmic Staining
Negative	<50% of 3+ Membrane and/or Cytoplasmic Staining

Phase 3 SACHI Trial: Savolitinib/ Osimertinib vs. Chemo in EGFRm and MET-amp NSCLC after EGFR TKI

SACHI Phase 3 Study Design

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

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

1:1

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

→ Until PD or intolerable toxicity

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

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

METamp:

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

Stratification factors:

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

Primary endpoint: PFS by investigator

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

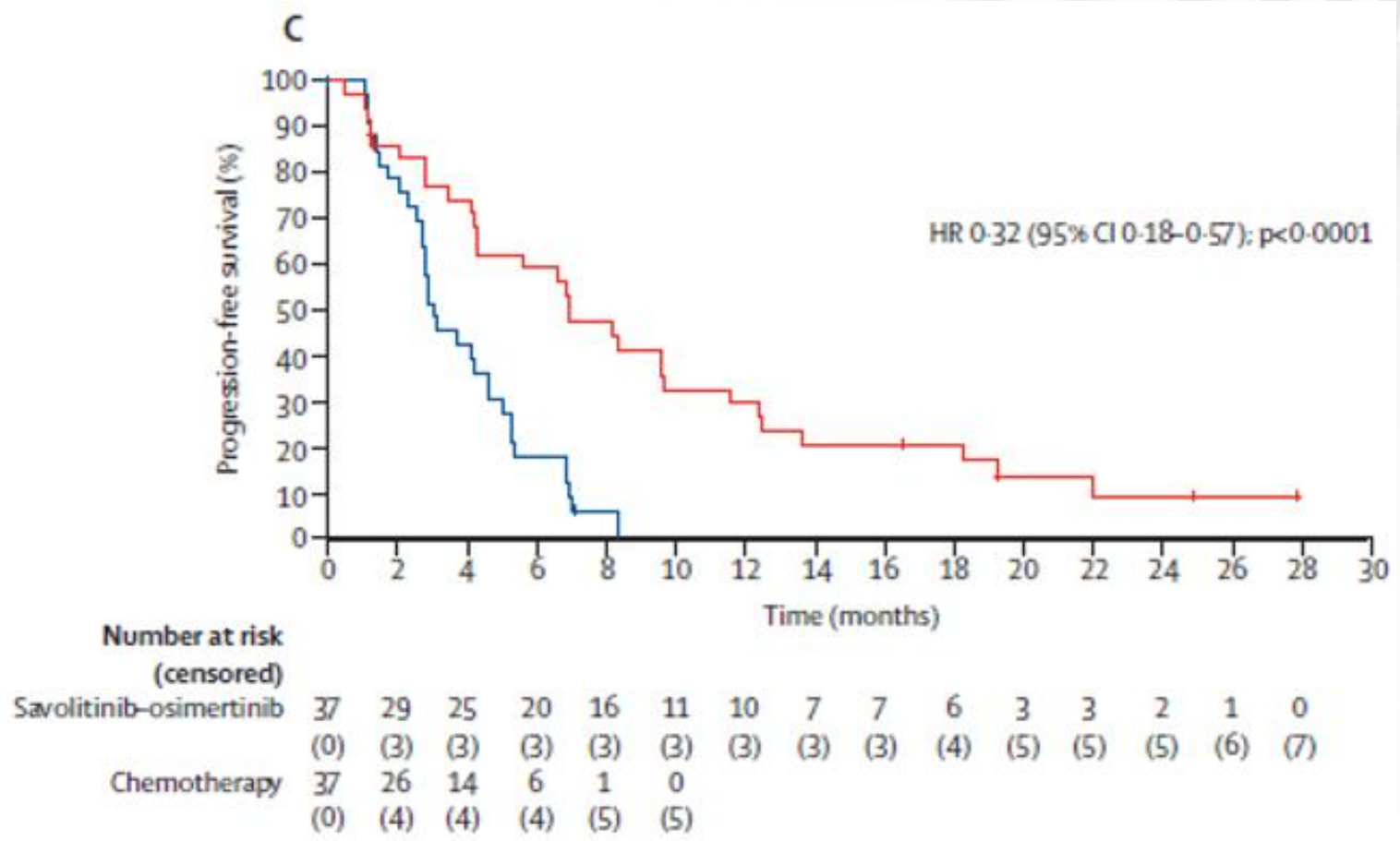
2025 ASCO ANNUAL MEETING #ASCO25

PRESENTED BY: Shun Lu, MD, PhD

1st /2nd G: first or second generation; 3rd G: third generation; BW: body weight; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; EGFRm, EGFR mutant; FISH, fluorescence in situ hybridization; IRC, independent review committee; METamp, MET amplification; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; QD, once daily; Savo-Osi, Savolitinib-Osimertinib; TKI, tyrosine kinase inhibitor; TTR, time to response.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Phase 3 SACHI Trial: Savolitinib/ Osimertinib vs. Chemo in EGFRm and MET-amp NSCLC after EGFR TKI



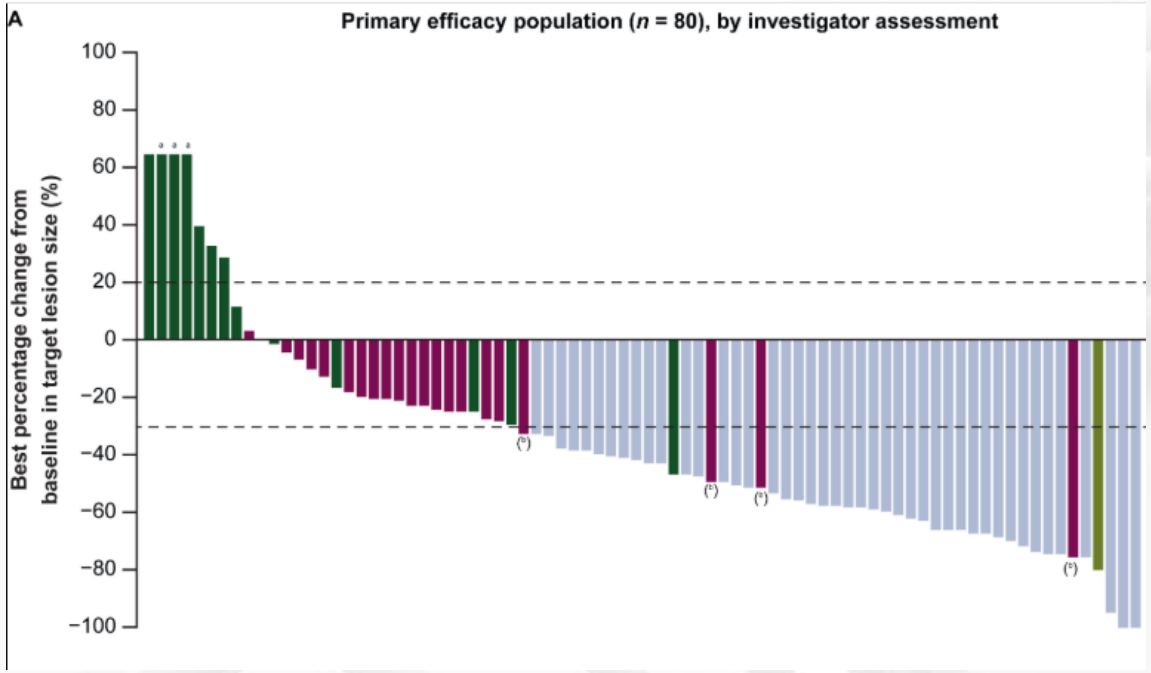
Prior 3G TKI subset:

ORR: 62% vs. 27%

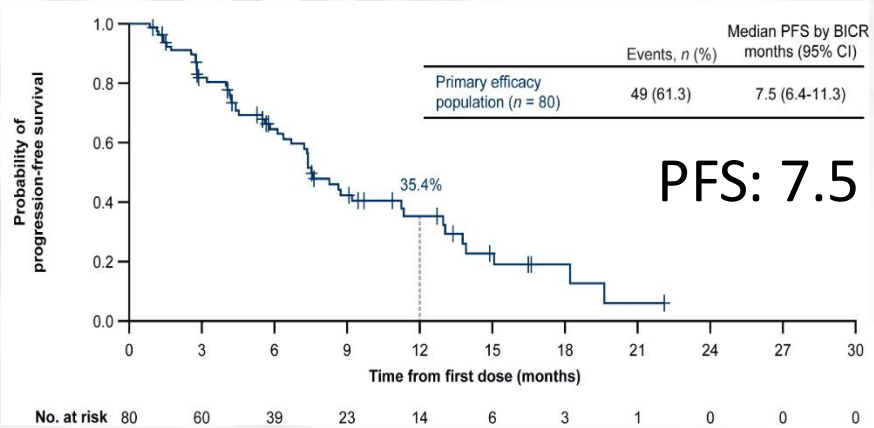
PFS: 6.9 vs. 3.0 mo (HR 0.32)

Lu et al., Lancet 2026

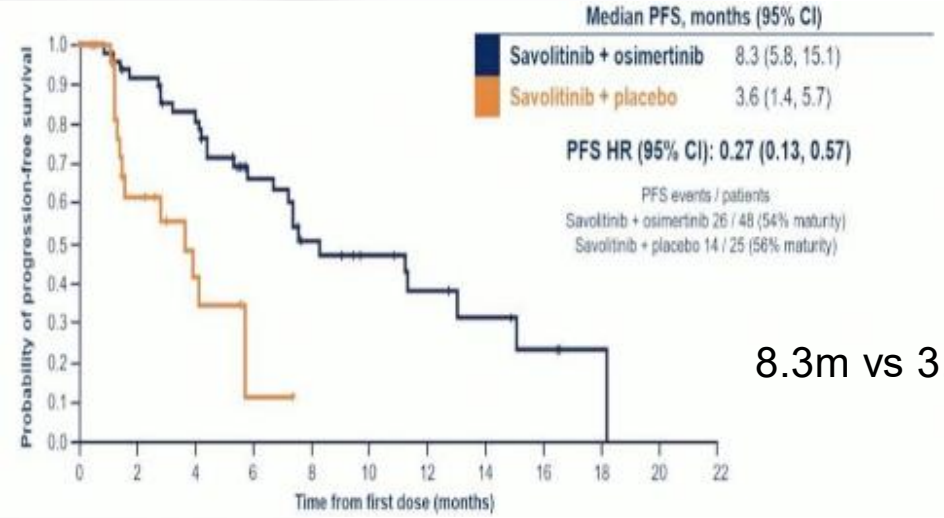
Phase 2 SAVANNAH: Savolitinib/ Osimertinib in EGFRm NSCLC with MET overexpression and/or amplification



ORR: 56%



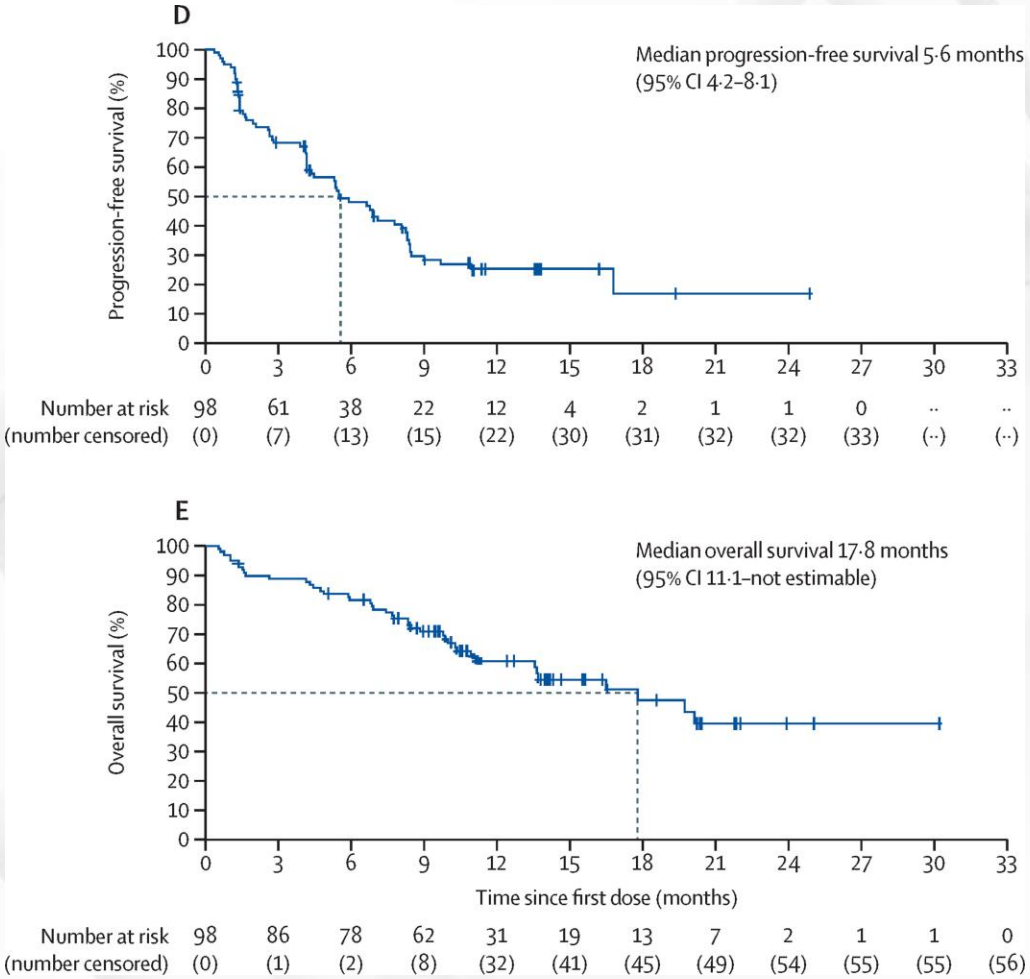
PFS: 7.5 mo



8.3m vs 3.6m PFS

Marinis et al., Ann Oncol 2025

Phase 2 INSIGHT2: Tepotinib/ Osimertinib in EGFRm NSCLC with MET amp after frontline osimertinib



ORR: 50%

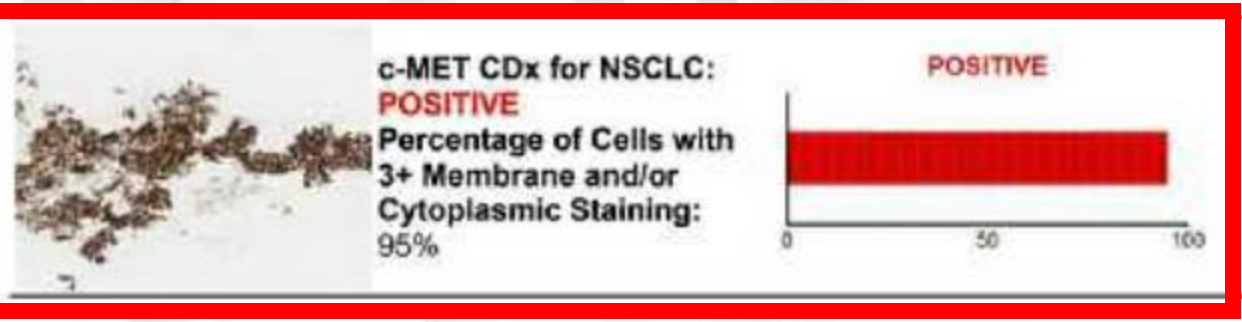
mPFS: 5.6 mo

mOS: 17.8 mo

Wu et al., Lancet 2024

EGFR + MET IHC

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
EGFR	Seq	DNA-Tumor	Pathogenic Variant Exon 21 | p.L858R	BENEFIT	afatinib, dacomitinib, erlotinib, erlotinib + ramucirumab, gefitinib, lazertinib + amivantamab, osimertinib	Level 2
					datopotamab deruxtecan	Level 2
MET	Seq	RNA-Tumor	Exon 14 Skipping Detected	BENEFIT	capmatinib, tepotinib	Level 2
	CNA-Seq	DNA-Tumor	Amplified		crizotinib	Level 2



Reference Ranges	
Positive	>/=50% of 3+ Membrane and/or Cytoplasmic Staining
Negative	<50% of 3+ Membrane and/or Cytoplasmic Staining

Phase Ib Telisotuzumab Vedotin/ Osimertinib in c-MET overexpressing EGFRm NSCLC after osimertinib progression

Arm E: Phase 1/1b Multicenter, Open-Label Study Design (NCT02099058)

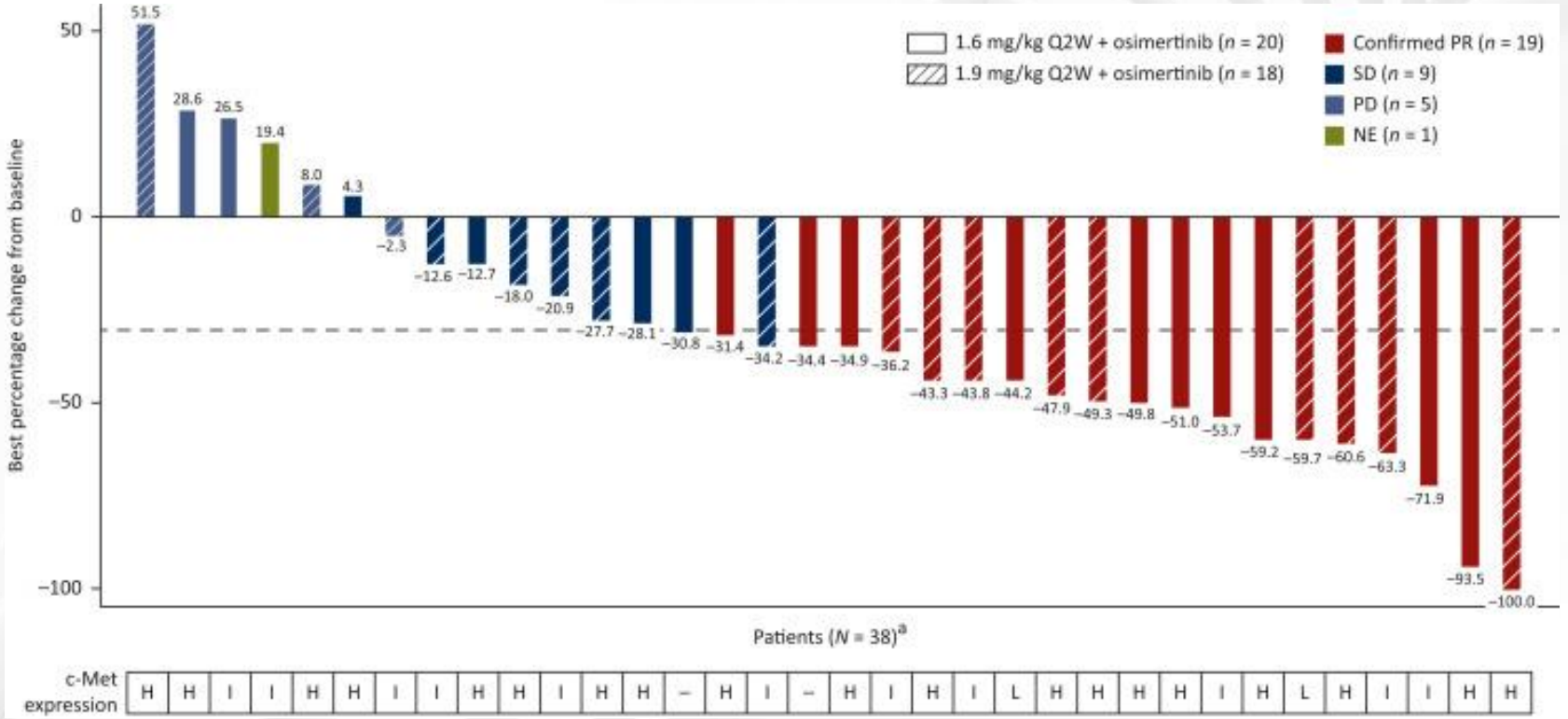
- Patients (≥18 years of age) with metastatic nSQ NSCLC who had progressed on prior Osi
- Documented L858R or del19 *EGFR* mutation(s)
- c-Met overexpressing (by central IHC)
  - c-Met overexpression: ≥25% tumor cells at 3+ intensity (high, ≥50% 3+; intermediate, 25 to 49% 3+)

- Tumor assessments were performed Q8W according to RECIST v1.1
- Efficacy analyses included all evaluable dosed patients
- Safety analyses included all patients who received ≥1 dose of Teliso-V (AE severity by NCI CTCAE v4.03)
- PK were assessed throughout the study
- Patients received study treatment until disease progression, unacceptable toxicity, or for up to 24 months

*Two or fewer prior lines of systemic therapy; 1 must have contained Osi, and no more than 1 may have contained chemotherapy (ie, second- and third-line patients).
AE, adverse event; EGFR, epidermal growth factor receptor; IHC immunohistochemistry; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; nSQ, non-squamous; Osi, osimertinib; PK, pharmacokinetics; Q2W, every 2 weeks; Q8W, every 8 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; Teliso-V, telisotuzumab vedotin; v, version.

Horinouchi et al., Ann Oncol 2025

Phase Ib Telisotuzumab Vedotin/ Osimertinib in c-MET overexpressing EGFRm NSCLC after Osimertinib progression



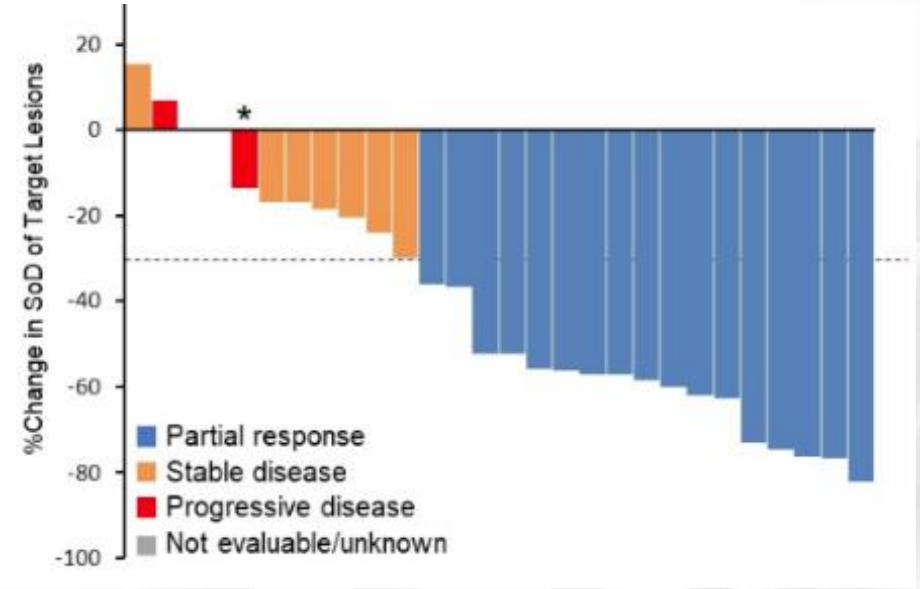
ORR: 50%

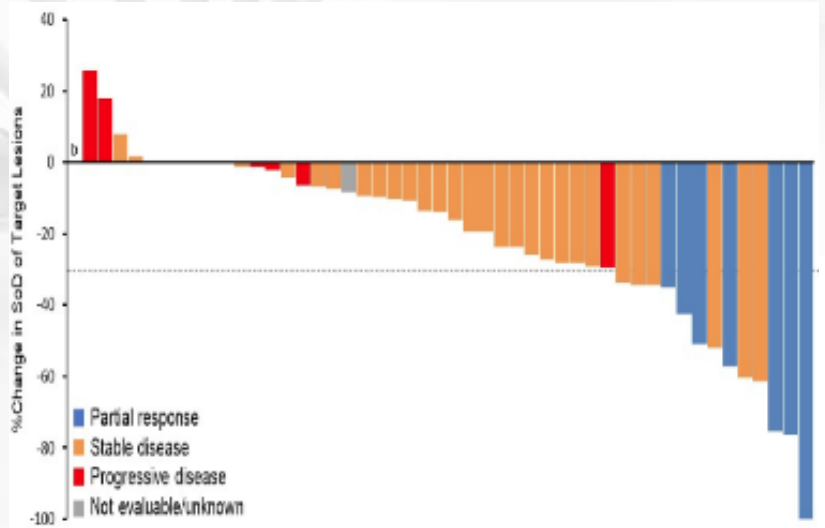
mPFS: 7.4 mo

DoR: NR

Horinouchi et al., Ann Oncol 2025

Phase Ib CHRYSALIS-2: Amivantamab/ Lazertinib in EGFRm NSCLC after osimertinib progression (Cohort D)





MET IHC+: ORR 61%

mPFS: NR (4.3-NE)

MET IHC-: ORR 14%

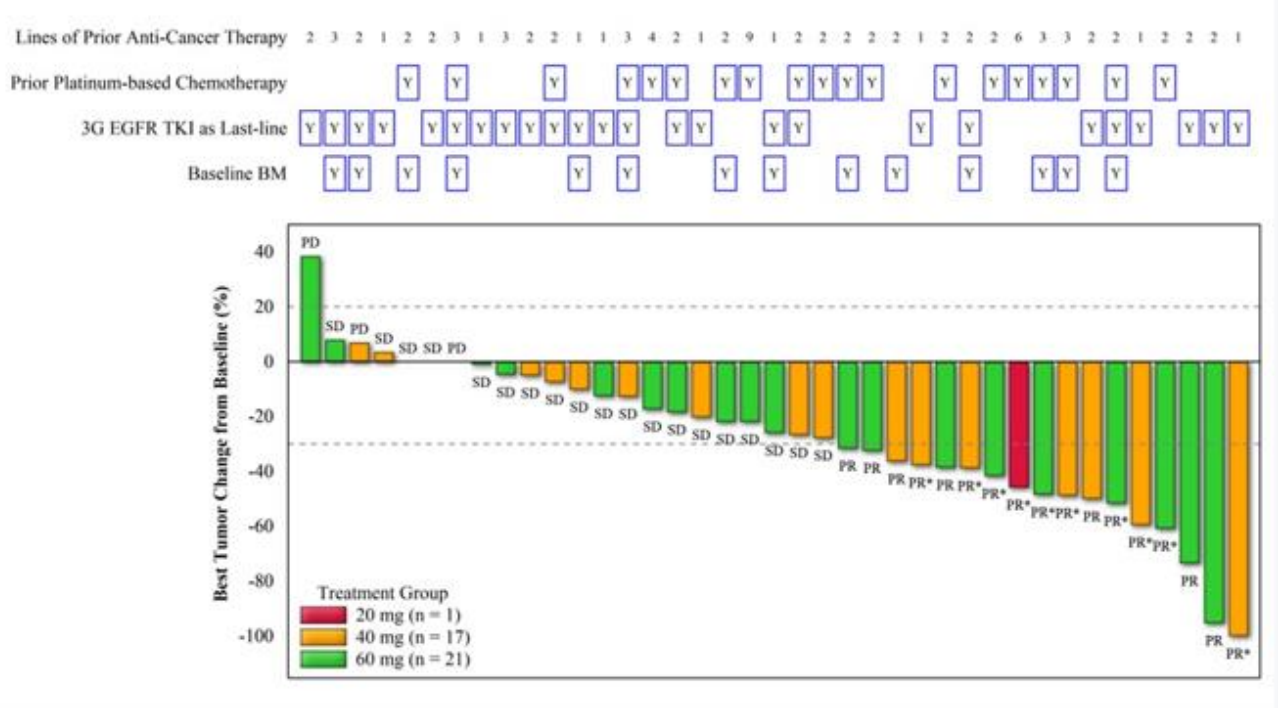
mPFS: 4.1 mo (2.8-5.7)

MET IHC (+) in 36% of cases!

Besse et al, WCLC 2025; Besse ASCO 2023

EGFR + on-target EGFR C797X

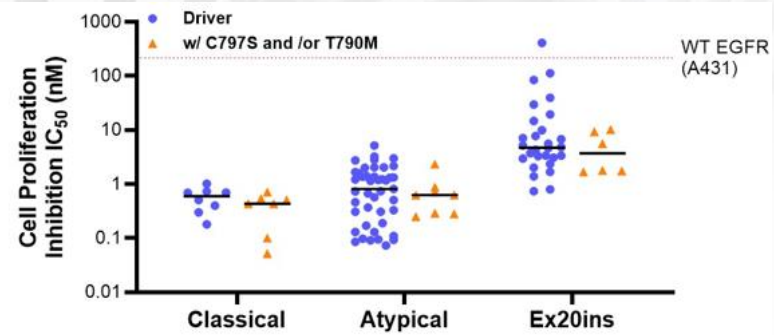
DZD6008

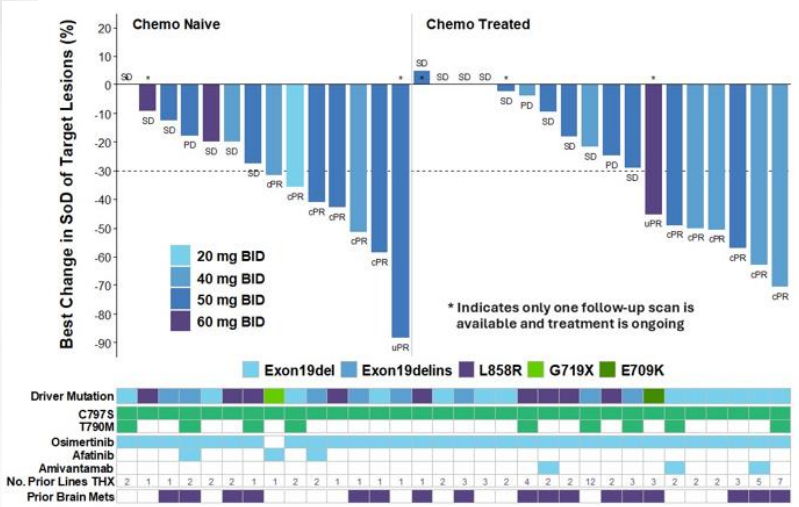


ORR: 41-43%

6-mo PFS: 62-71%

BH-30643

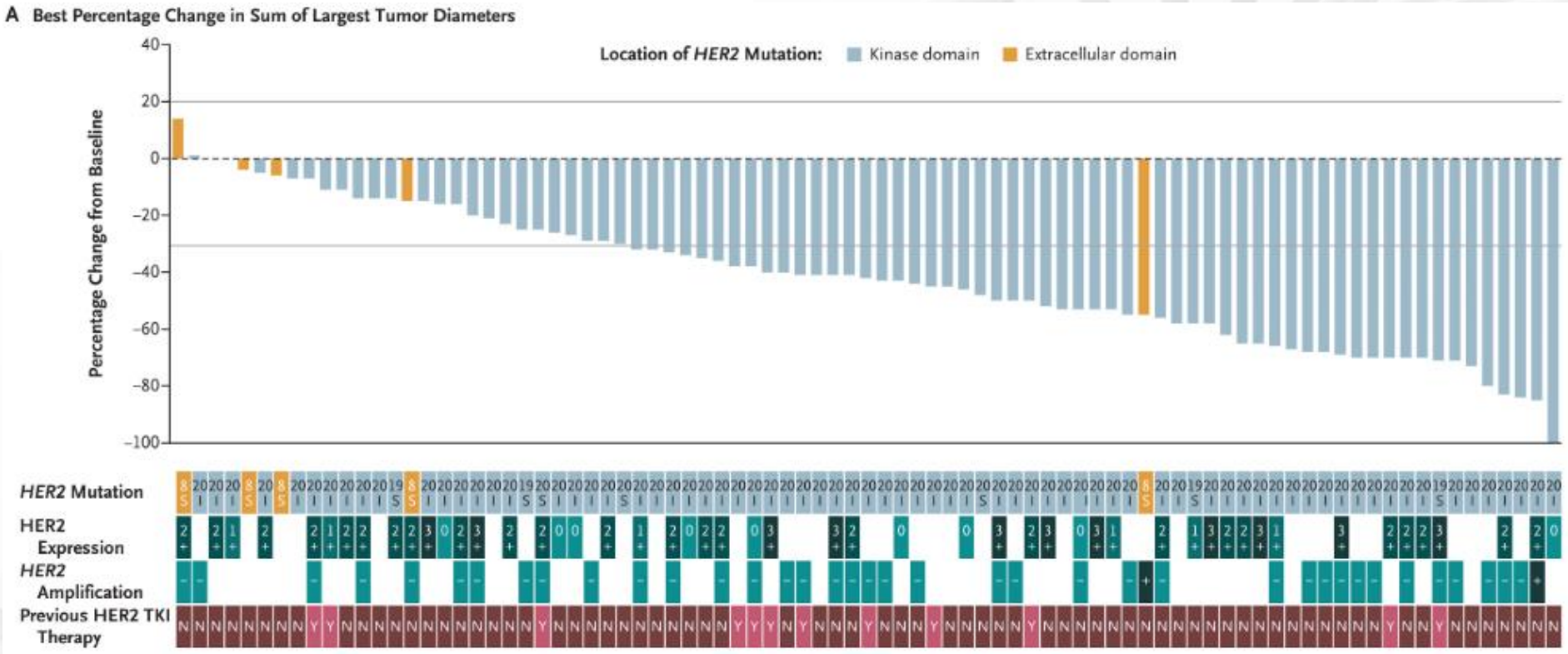




C797S ORR: 50% (chemo naïve)
39% (chemo pretreated)

Wang et al., ASCO 2026; Le et al., ASCO 2026

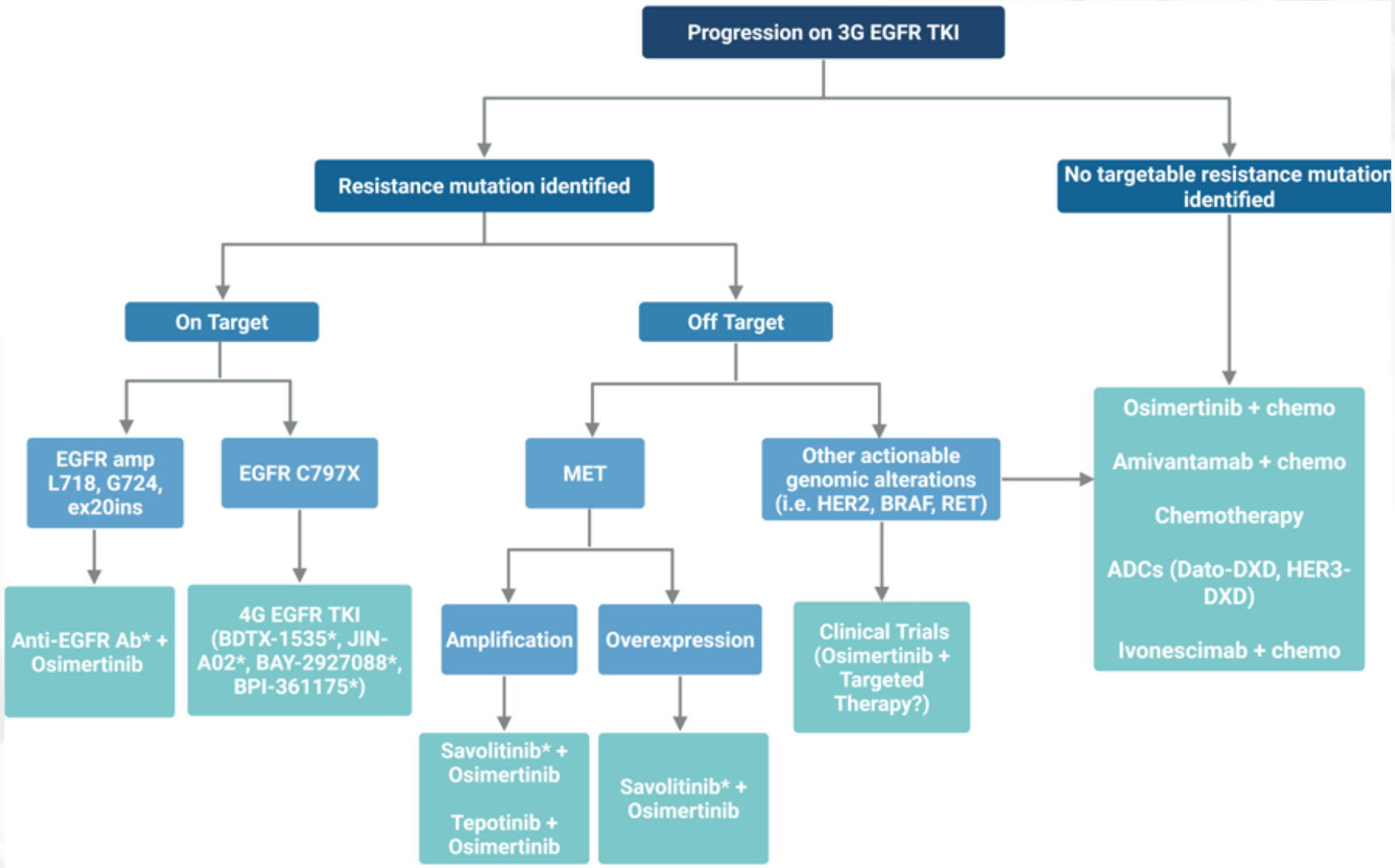
EGFR + HER2 amp/mutation



Trastuzumab Deruxtecan: pan-tumor approval for HER2 3+ IHC

Zongertinib + Osi?

Li et al., NEJM 2022


Progression on 3G EGFR TKI
Resistance mutation identified
No targetable resistance mutation identified
On Target
Off Target
EGFR amp L718, G724, ex20ins
EGFR C797X
MET
Other actionable genomic alterations (i.e. HER2, BRAF, RET)
Osimertinib + chemo
Amivantamab + chemo
Chemotherapy
ADCs (Dato-DXD, HER3-DXD)
Ivonescimab + chemo
Anti-EGFR Ab* + Osimertinib
4G EGFR TKI (BDTX-1535*, JIN-A02*, BAY-2927088*, BPI-361175*)
Amplification
Overexpression
Clinical Trials (Osimertinib + Targeted Therapy?)
Savolitinib* + Osimertinib
Tepotinib + Osimertinib
Savolitinib* + Osimertinib
*indicates investigational agent

Summary:

- Acquired resistance in EGFRm NSCLC is heterogenous and complex, with MET amp and EGFR amp/ C797X being most commonly identified
- Repeat NGS +- biopsy recommended to identify subsequent targets
- Mechanism-based approaches add an additional line of therapy!
- Precision medicine is only getting more precise, and several emerging mechanism-directed trials are ongoing
- Mechanism-agnostic approaches (amivantamab, chemo, ADC) are always available as next-line tx

Thank you to our clinical team:

Medical oncologists:
Suresh Ramalingam
Ticiana Leal
Conor Steuer
Jennifer Carlisle
Shirish Gadgeel
Laercio DaSilva

Thoracic surgeons:
Seth Force
Felix Fernandez
Onkar Khullar
Alicia Bonanno
Tommy O'Malley

Interventional Pulmonologists:
David Berkowitz
Matt Schimmel
Abesh Niroula
Wissam Jaber

Radiation Oncologists:
Sibo Tian
Aparna Kesarwala
Natalie Ridge
William Stokes

APPs:
Lindsey Allen
Courtney Oshiro
Tyronda Gray

Pharmacist:
Katie O'Reilly

Nurses:
Sheona Wilson
Katelyn Celestina
Paula Barber
Alexis Wilborn
Josie Lamana
Caroline Smith

Clinical Trial Team:
Led by:
Ryan Hanula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