Targeted Treatment of Metastatic Lung Cancer

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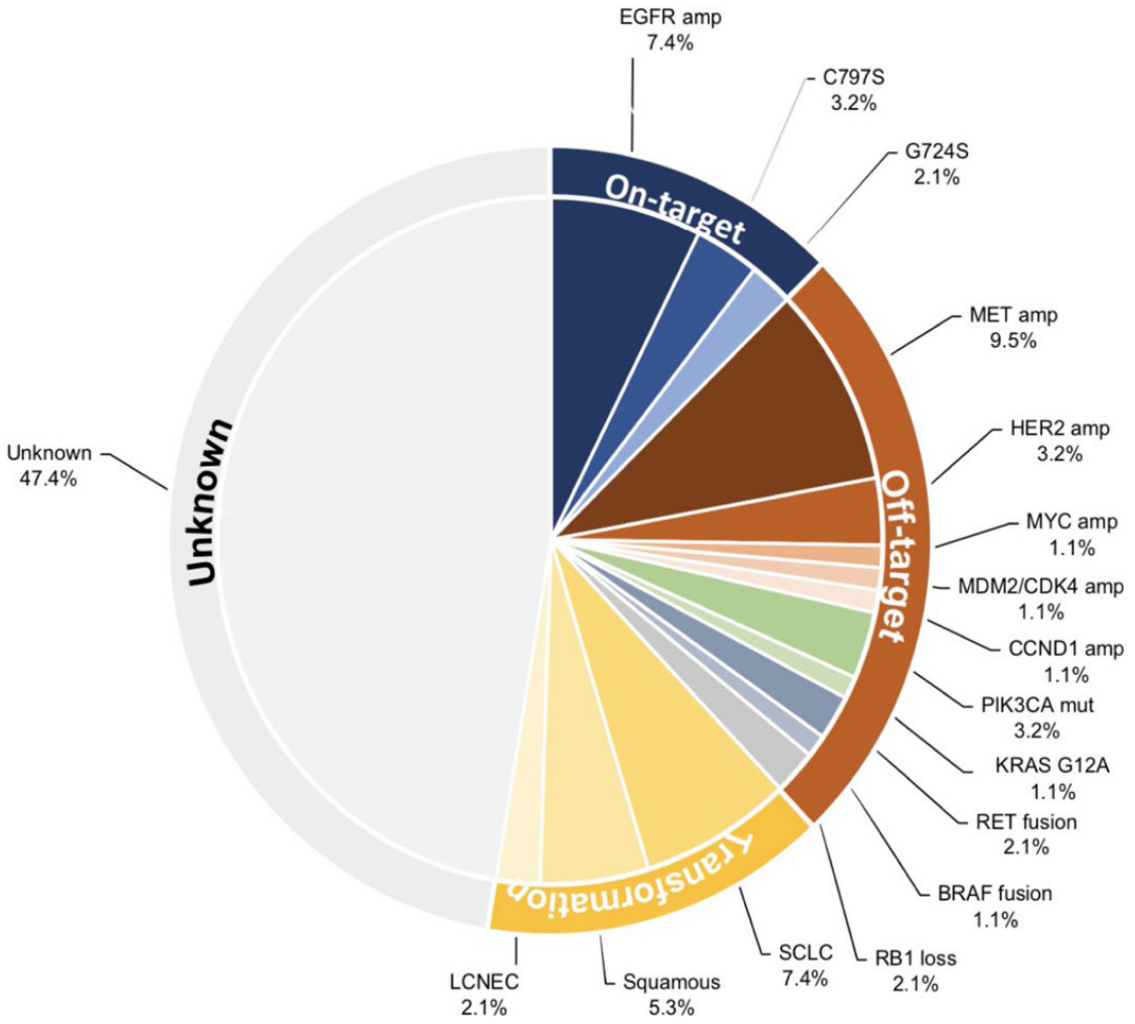
Discussion Question

How do you generally approach therapeutic selection for patients with metastatic non-small cell lung cancer (NSCLC) and EGFR mutations who experience disease progression on front-line osimertinib? Do you believe patritumab deruxtecan and/or amivantamab/lazertinib will play a role in this setting in the near future?

RTP
RESEARCH
TO PRACTICE

Approach to EGFR+ NSCLC After Progression on 1st Line Osimertinib

- **What is the extent of progression?**
  - Consider local therapy and continuing osimertinib beyond progression
  - Progressing brain metastases?
- **What is the molecular basis of progression?**
  - Repeat biopsy (tissue vs plasma)
- **How aggressive is the progression?**
  - Could this be SCLC?
  - Symptomatic?
- **Next Line Treatment Options?**
  - Chemo +/- Osimertinib vs Clinical Trial vs Off-Label Combination



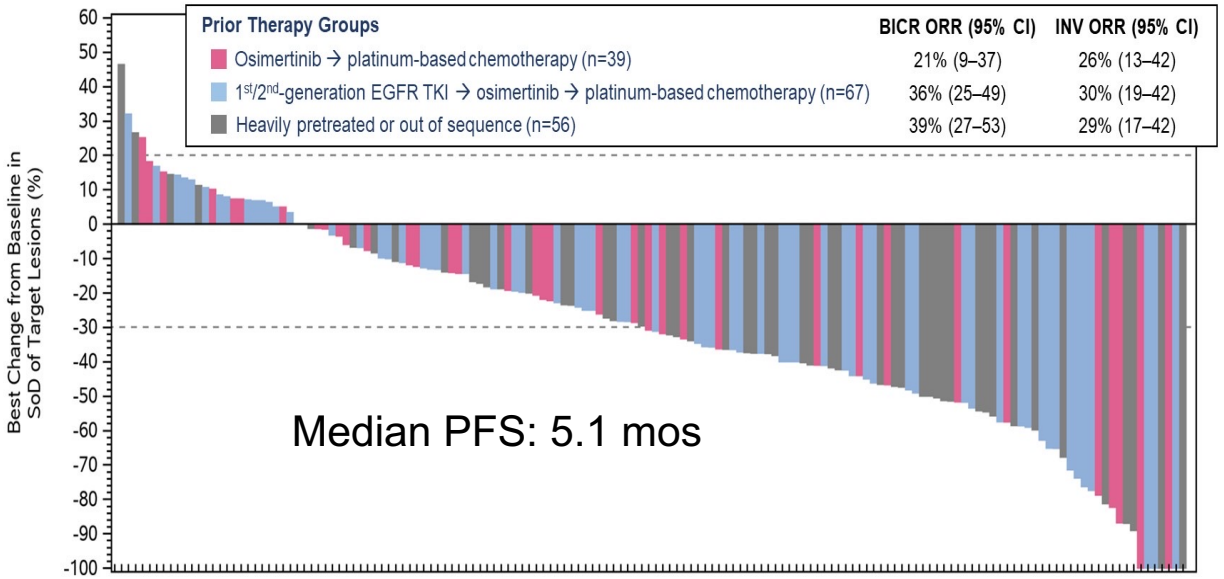
Choudhury JTO 2022

Chalk Talk — Ibiayi Dagogo-Jack, MD

Antibody-Based Therapies for EGFR+ NSCLC Post-Osimertinb: Patritumab Deruxtecan & Amivantamab

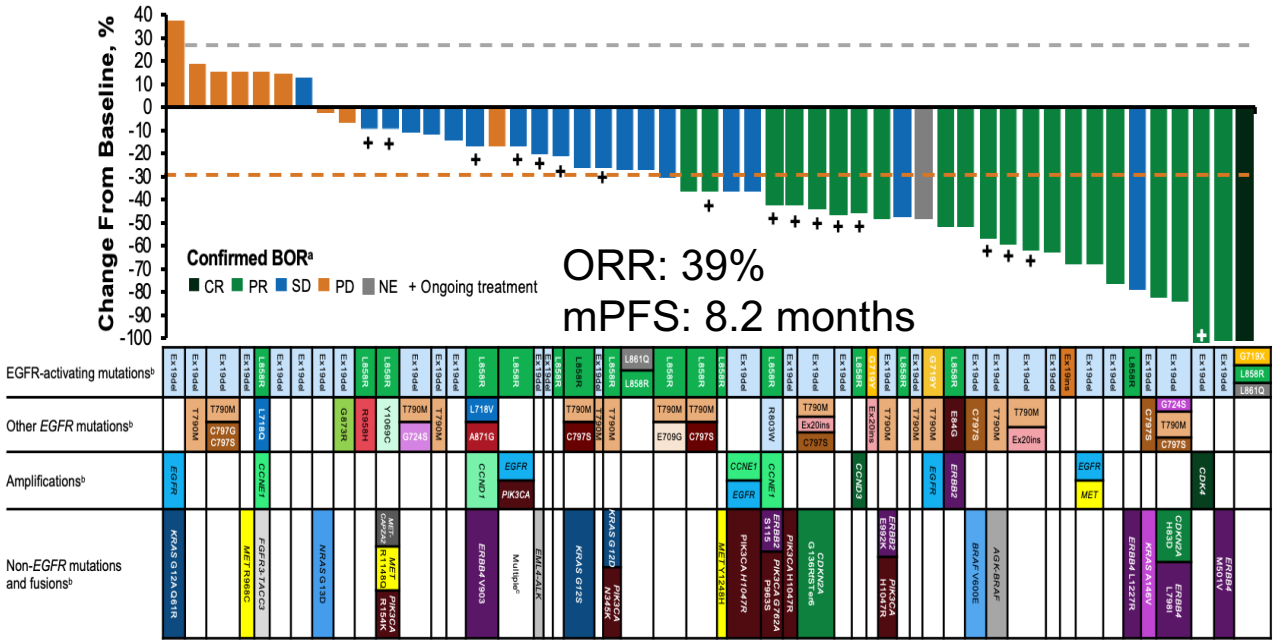
Antibody-drug conjugates and bispecific antibodies have broad activity post-osimertinib. I anticipate approval of these therapies in the future for the post-osimertinib setting.

CHRYSALIS-2: Amivantamab/Lazertinib



- 10 efficacy-evaluable patients did not have any evaluable post-baseline target lesion measurements

HERTHENA: Patritumab Deruxtecan



- Response rates are higher in pts with EGFR/MET-based resistance by NGS (29% vs 47%)

Shu ASCO 2022, Janne Cancer Discovery 2022

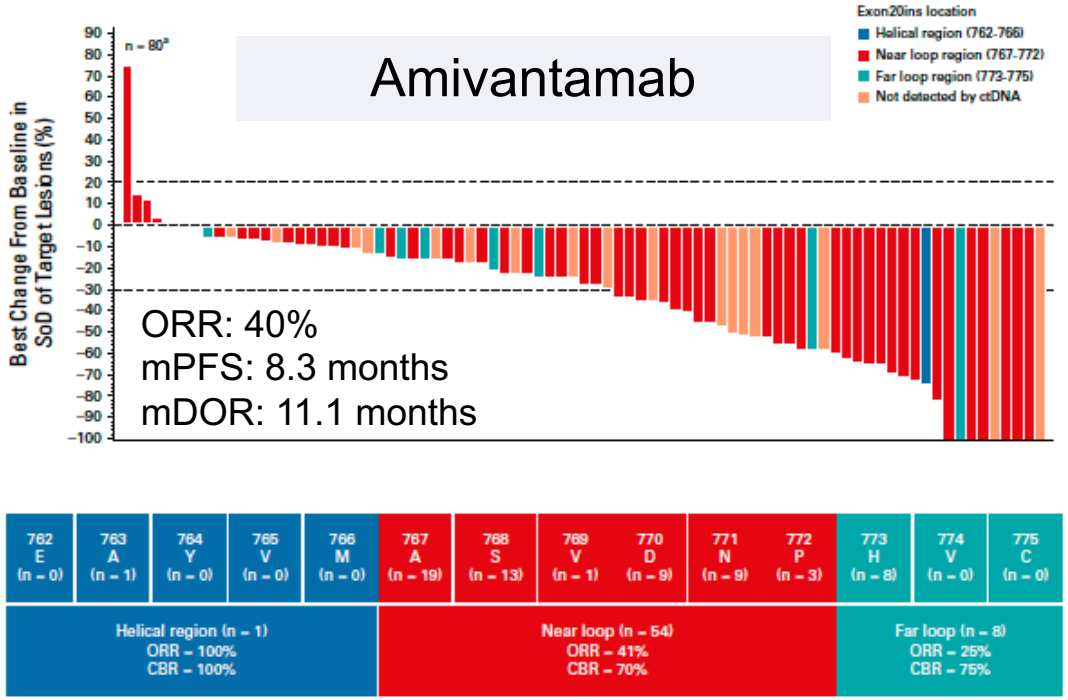
Discussion Question

In which line of treatment do you administer targeted therapy to your patients with metastatic NSCLC and EGFR exon 20 insertion mutations? How do you select between amivantamab and mobocertinib?

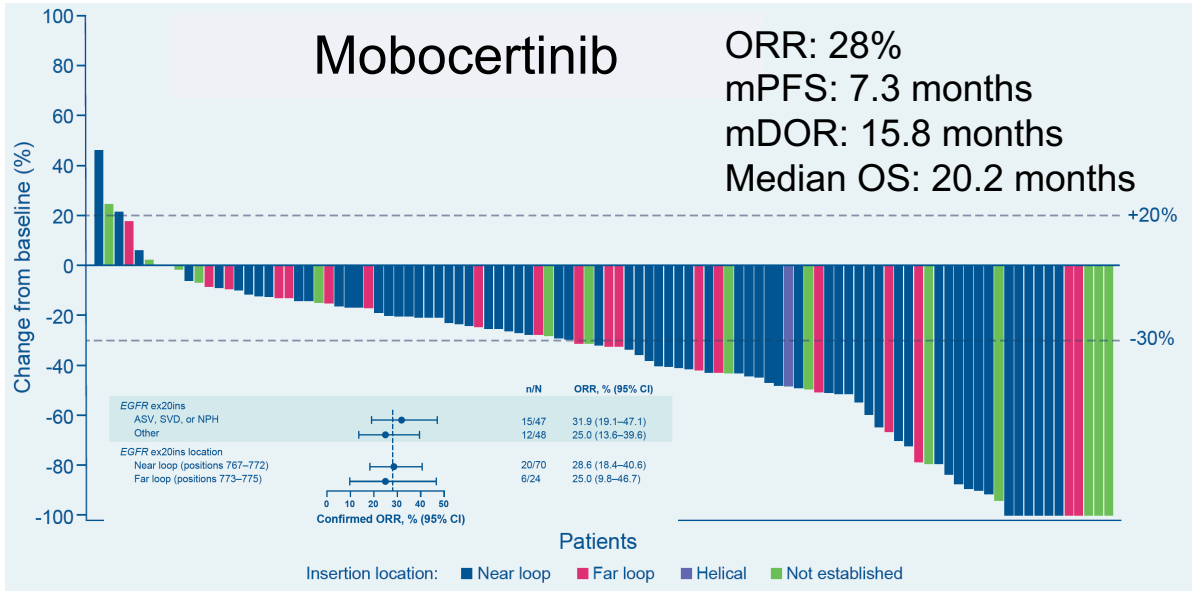
Chalk Talk — Ibiayi Dagogo-Jack, MD

Management of EGFR Exon 20+ NSCLC

- PCR assays miss ~50% of EGFR exon 20 insertions.
- Drug discontinuation for toxicity: Amivantamab (10%), Mobocertinib (17%). **I start with Amivantamab.**
- We need better targeted therapies for EGFR ex20 mutations with brain mets.
- Note: ~40% of pts had CNS as a site of 1st progression on Mobocertinib.



Toxicities: Infusion reactions (66%), rash (86%), paronychia (45%), edema (18%)



Toxicities: Diarrhea (91%, 21% grade >3), nausea (34%), rash (45%), paronychia (38%), QTC prolongation (11%), rare cardiomyopathy

Park JCO 2021; Zhou JAMA Oncology 2021; Ramalingam ESMO 2022; Ab 988P

Discussion Question

In which line of treatment do you administer targeted therapy to your patients with metastatic NSCLC and MET exon 14 mutations? How do you select between capmatinib and tepotinib?

Chalk Talk — Ibiayi Dagogo-Jack, MD

Management of NSCLC Harboring MET Exon 14 Skipping Alterations

- RNA-based NGS is the most optimal strategy for detecting MET skipping alterations.
- Tepotinib and Capmatinib are approved in a line-agnostic fashion. Both drugs have excellent CNS activity. I prioritize TKI therapy in the 1st line over chemotherapy + immunotherapy due to efficacy in the 1st line and potential toxicity of the reverse sequence.
- Side effects from these TKIs can impact QoL, including edema. **Both are great options, but I start with Capmatinib given the higher response rate, acknowledging lack of head-to-head data.**

	*Not A Formal Comparison			
Response & Toxicity	Capmatinib Tx Naive n = 28	Capmatinib Prior Tx n = 69	Tepotinib Tx Naive n = 69	Tepotinib Prior Tx n = 83
Confirmed ORR, %	68	41	44.9	44.6
Disease Control Rate, %	96	78	68.1	72.3
Median PFS, months	12.4	5.4	8.5	10.9
Dose Reduction, %	23 (Pooled cohort)		27.8 (Pooled cohort)	
Dose Discontinuation, %	11 (Pooled cohort)		10.6 (Pooled cohort)	

Wolf NEJM 2020, Wolf ASCO 2021, Le Clinical Cancer Research 2022

Discussion Question

In which line of treatment do you administer targeted therapy for your patients with metastatic NSCLC and HER2 mutations? What about for those with HER2 overexpression or amplification?

Chalk Talk — Ibiayi Dagogo-Jack, MD

Management of HER2-Mutant NSCLC

- Trastuzumab deruxtecan is approved for NSCLC with a HER2 mutation (not amplification).
- There are data supporting antibody-drug conjugates (T-DXd and T-DM1) for other HER2 alterations, but these are not FDA-approved indications. I currently do not check for HER2 overexpression.
- Brain metastases are common (as high as 47% of patients in a retrospective study!)
- The FDA-approved dose is 5.4 mg/kg. Higher doses are associated with more toxicity/pneumonitis.

DESTINY Lung-02

Response Assessment	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed Objective Response Rate, n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
Complete Response	1 (1.9)	1 (3.6)
Partial Response	27 (51.9)	11 (39.3)
Stable Disease	19 (36.5)	14 (50.0)
Progressive Disease	2 (3.8)	1 (3.6)
Not evaluable	3 (5.8)	1 (3.6)
Disease Control Rate, n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Interstitial Lung Disease, %	5.9	14.0
Dose Reduction/Drug Discontinuation, %	9.9/7.9	26/16

I reserve T-DXd for the 2nd-line setting

Stay tuned for DESTINY-Lung04!

Goto ESMO 2022

Discussion Question

In which line of treatment do you administer targeted therapy to your patients with metastatic NSCLC and KRAS G12C mutations? How do you select between sotorasib and adagrasib?

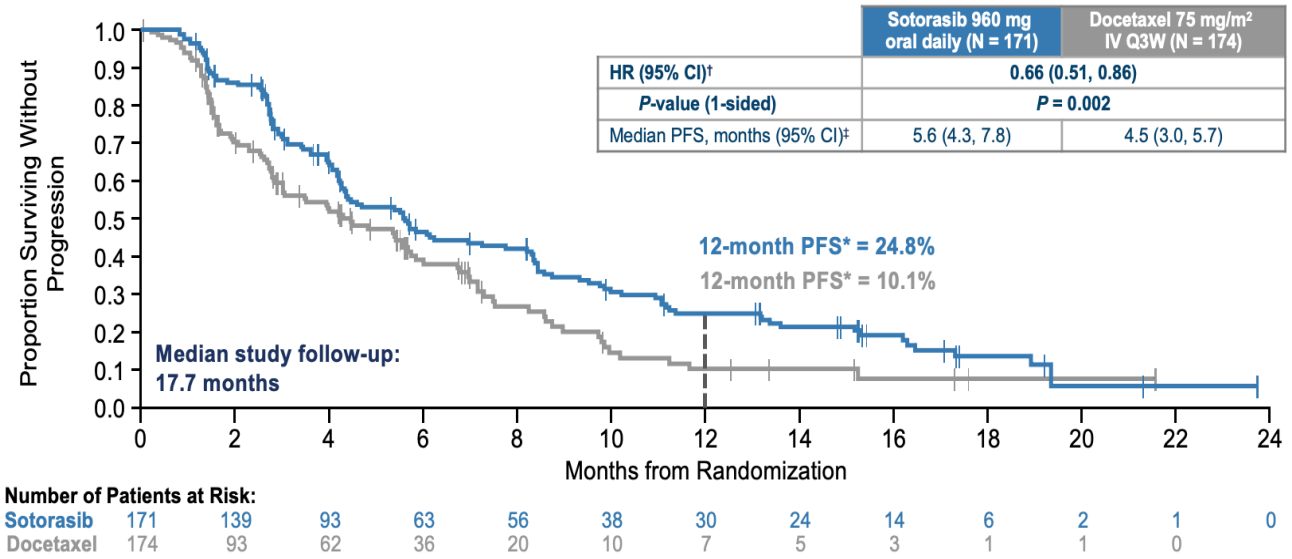
Chalk Talk — Ibiayi Dagogo-Jack, MD

Management of KRAS G12C-mutant NSCLC

- Sotorasib and Adagrasib have comparable antitumor activity. We don't have head-to-head studies but the safety profile of Sotorasib is slightly more favorable.
- We have more data for Adagrasib in patients with (treated) brain metastases.
- I reserve Adagrasib and Sotorasib for the 2nd-line setting. I would consider prioritizing Adagrasib over Sotorasib in a patient with brain metastases. I tend to use Sotorasib for all others.

Response & Toxicity	*Not A Formal Comparison Sotorasib n = 174	Adagrasib n = 112
Confirmed ORR, n (%)	41	48 (42.9)
Disease Control Rate, n (%)	84	89 (79.5)
Median PFS, months	6.3	6.5
Median OS, months	12.5	12.6
Intracranial ORR, %	---	33
Dose Reduction, %	22.2	51.7
Dose Discontinuation, %	7.1	6.9

CodeBreak 200: Sotorasib vs Docetaxel



ORR: 28.1% vs 13.2%, Median DOR: 8.6 vs 6.8 mo
Overall Survival: 10.6 vs 11.3 mo (not statistically significant)

de Langen Lancet 2023, Skoulidis NEJM 2021, Dy GK AACR 2022; Ab CT008, Janne NEJM 2022