MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

How to Rescue Patients from Osimertinib Resistance

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VANDERBILT UNIVERSITY
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Putting the Data in Context

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The clinic perspective

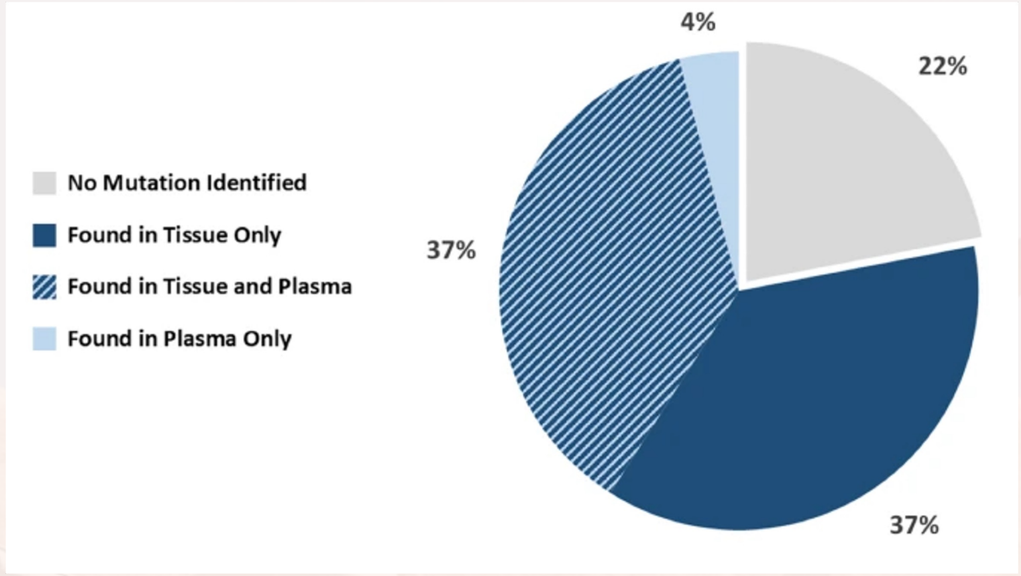
Carboplatin, pemetrexed +/- osimertinib

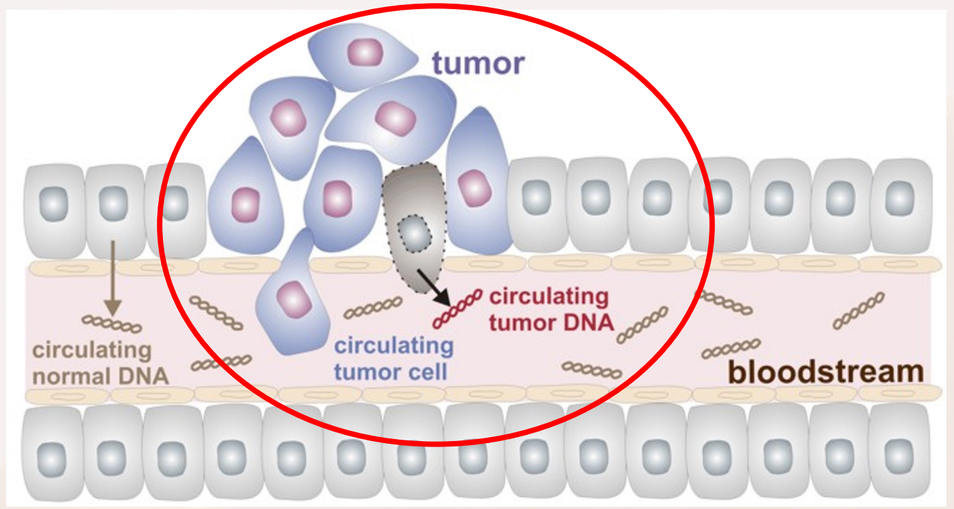
Primary Mission: Maximize *Quantity and Quality* of Life

Organization

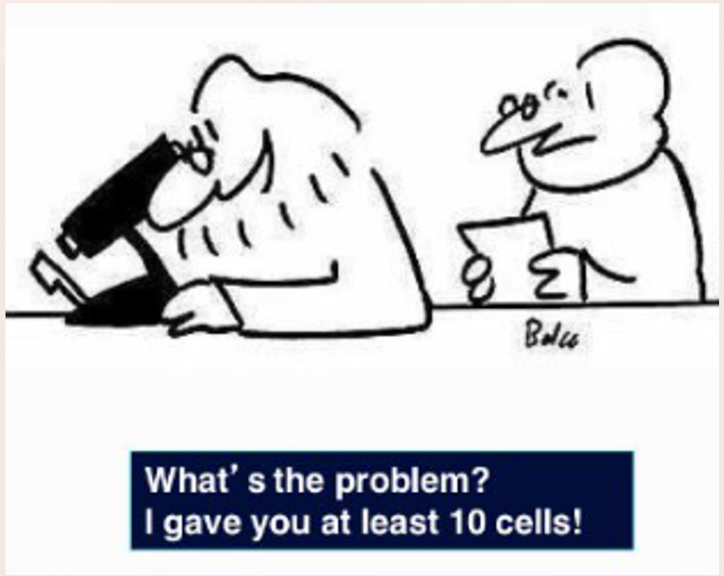
- Tissue and liquid biopsy
- Mechanisms of resistance to 1L osimertinib
- Targeting mechanisms of resistance to 1L osimertinib
- Future post osimertinib landscape

Obtain Both Tissue and Liquid Biopsy





***Tumor tissue, not NGS only liquid biopsy, is capable of identifying SCLC transformation**



Lin HL, et al. Comparison of tissue and liquid biopsy in clinically relevant mutations in lung adenocarcinoma. *Modern Pathology* 2021

Mechanisms of Resistance on FLAURA

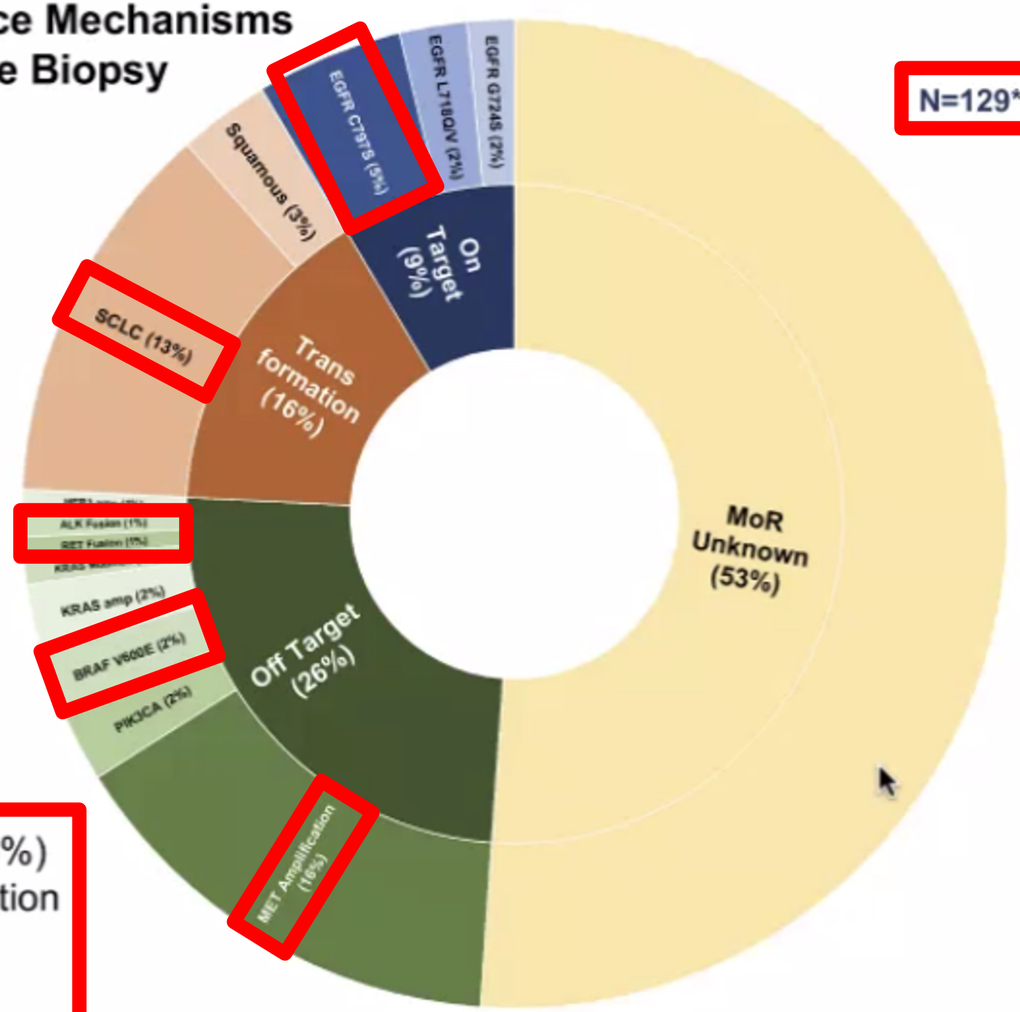
- FLAURA ctDNA analyzed at baseline and at the time of progression
- Why was SCLC transformation not observed?

Chmielecki J, et al. Mechanisms of resistance to 1L osimertinib. *Nat Comm* 2023

Tissue Resistance to 1L Osimertinib

Figure 1. Resistance Mechanisms Identified on Tissue Biopsy

Median Time, osi start to Tissue Biopsy:
14.5 mo (range, 1-52)



MET Amplification (16%) and SCLC transformation (13%) were the most common resistance mechanisms identified on tissue biopsy.

Piotrowska, et al. Mechanisms of resistance to 1L osimertinib in NSCLC. ASCO 2023; Abstr 9108

Targeting Mechanisms of Resistance

- *MET* amplification (15 - 25%)
  - Add MET inhibitor vs platinum doublet +/- IO (Phase III SAFFRON)

- SCLC transformation (15%)
  - Platinum etoposide plus osimertinib or immunotherapy (ECOG)

- *EGFR* C797S (5 – 10%)
  - Add earlier gen EGFR TKI (i.e. gefitinib) vs platinum doublet +/- IO

- Acquired targetable oncogenic mutations (< 5%)
  - Add relevant targeted therapy (*BRAF* V600E, *RET* fusion, etc.)

Tan DSW, et al. INSIGHT-2. ASCO 2023
Ramalingam SS, et al. Targeting osimertinib resistance. WCLC 2022; *JTO* 16(3): e15-20. OA03.05
Rotow J, et al. Osimertinib + selpercatinib in *EGFR* mutant and *RET* fusion NSCLC. *CCR* 2023.
Wei XW, et al. Treatment for *EGFR* mutant NSCLC with concomitant *BRAF* mutations. *JTO CRR* 2022.

No Targetable Mechanism of Resistance

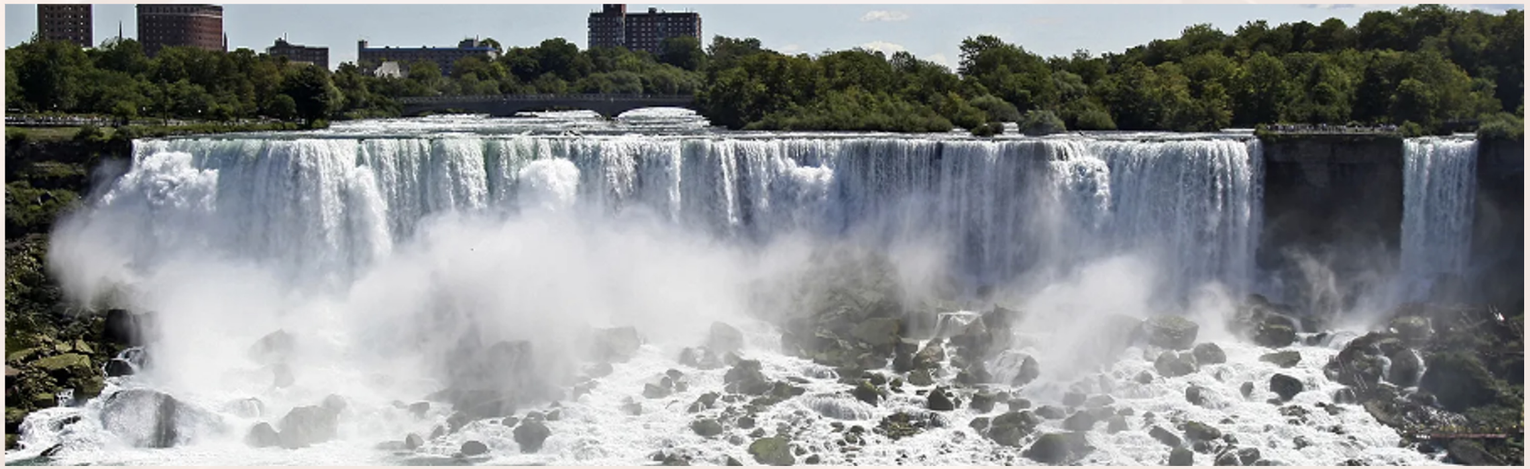
- Carboplatin, pemetrexed
  - With or without continuation of osimertinib (CNS disease?)

No Targetable Mechanism of Resistance

- Carboplatin, pemetrexed +/- immunotherapy
  - With or without continuation of osimertinib (CNS disease?)
- Patritumab deruxtecan (HER3 DXd)
- Amivantamab +/- chemotherapy +/- Lazertinib
- Datopotamab deruxtecan (Dato-DXd)

Yu H, et al. HERTHENA-Lung01, a phase II trial of patritumab deruxtecan (HER3-DXd) in *EGFR* mutant NSCLC after EGFR TKI and Platinum-Based Chemotherapy. *JCO* 2023
White MN, et al. Combining osimertinib with chemotherapy in EGFR-mutant NSCLC at progression. *Clin Lung Cancer* 2021
Besse B et al. Predictive Biomarkers of Amivantamab + Lazertinib. ASCO 2023.

Regimen Efficacy Results



Current **Regimen Efficacy Results**

Regimen / Trial	Patients	ORR	Median DOR	Median PFS	Median OS
Osimertinib + Tepotinib - INSIGHT 2	98	50%	8.5 months	5.6 months	17.8 months
Carboplatin + pemetrexed - ATTLAS / MARIPOSA2	74 (92% *EGFR*) / 263	42% / 36%	7 months / NA	5.6 months / 4.2 months	NA
Carboplatin + pemetrexed + atezolizumab + bevacizumab - ATTLAS	151 (95% *EGFR*)	70%	7 months	8.5 months	NA

Tim KM, et al. Tepotinib + Osimertinib with MET amp following Osimertinib. WCLC 2023; Ahn M-J, et al. ATTLAS. ESMO 2023

Future Regimen Efficacy Results

Regimen / Trial	Patients	ORR	Median DOR	Median PFS	Median OS
Carboplatin + pemetrexed - ATTLAS / MARIPOSA2	74 / 263	42% / 36%	7 months / NA	5.6 months / 4.2 months	NA
Platinum + pemetrexed + amivantamab + Lazertinib - MARIPOSA2	263	64%	NA	8.3 months	HR 0.96 (0.67-1.35)
Paritumab deruxtecan - HERTHENA-Lung01	225	30%	6.4 months	5.5 months	12 months
Platinum + pemetrexed + amivantamab - MARIPOSA2	131	63%	NA	6.3 months	HR 0.77 (0.49-1.21)
Amivantamab + Lazertinib - CHRYSALIS	101	30% (MET+ 61%)	10.8 months	5.7 months	NA
Datopotumab deruxtecan - TROPION-Lung05	78	44%	7 months	5.8 months	NA

Ahn M-J, et al. ATTLAS. ESMO 2023
Yu H, et al. HERTHENA-Lung01, a phase II trial of patritumab deruxtecan (HER3-DXd) in *EGFR* mutant NSCLC after EGFR TKI and Platinum-Based Chemotherapy. *JCO* 2023
Passaro A, et al. MARIPOSA 2. ESMO 2023; Paz Ares L, et al. Datopotumab deruxtecan with actionable alterations. ESMO 2023

Conclusions

- Tissue and liquid biopsy
  - Obtain both at progression on osimertinib
- Mechanisms of resistance to 1L osimertinib
  - *MET* amplification, SCLC >> *EGFR* C797S > targetable fusions or MAPK/cell cycle alterations
- Targeting mechanisms of resistance to 1L osimertinib
  - Resistance mechanism directed therapy
  - Carboplatin, pemetrexed +/- immunotherapy
  - Multiple new options, **awaiting mature survival results**

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Thank you for your attention