OVERCOMING EGFR TKI RESISTANCE

Jonathan W. Riess MD MS

Professor

UC Davis Comprehensive Cancer Center

Endorsed by

IASLC International Association for the Study of Lung Cancer — Conquering Thoracic Cancers Worldwide

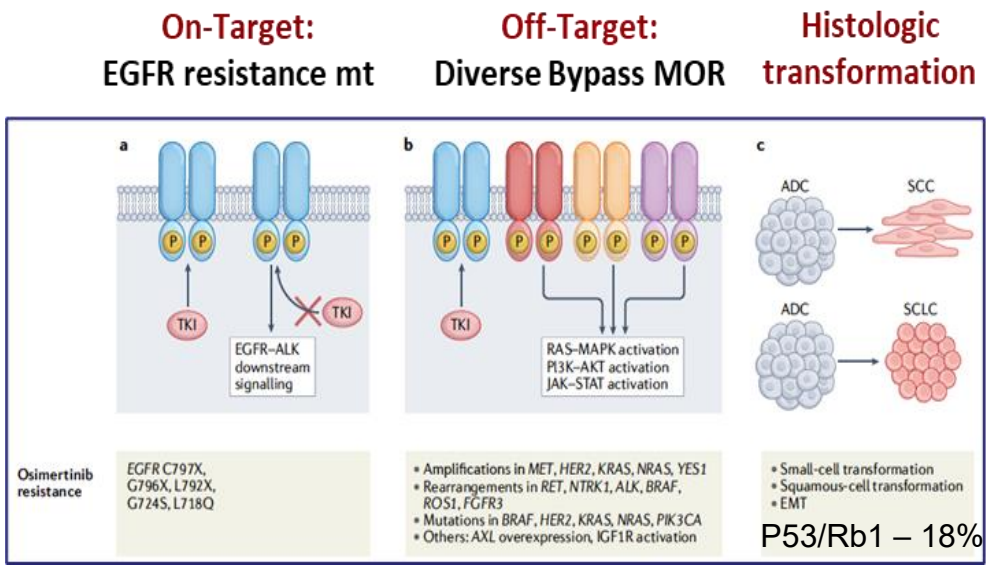
Accredited by

PIM Postgraduate Institute for Medicine — Professional Excellence in Medical Education

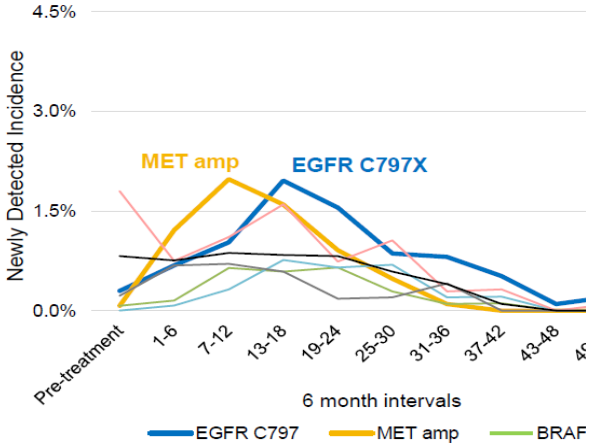
Presented by

IDEOlogy Health — Creating Aha! Moments In Healthcare

Broad Mechanisms of Resistance to EGFR-TKI and Temporal Occurrence

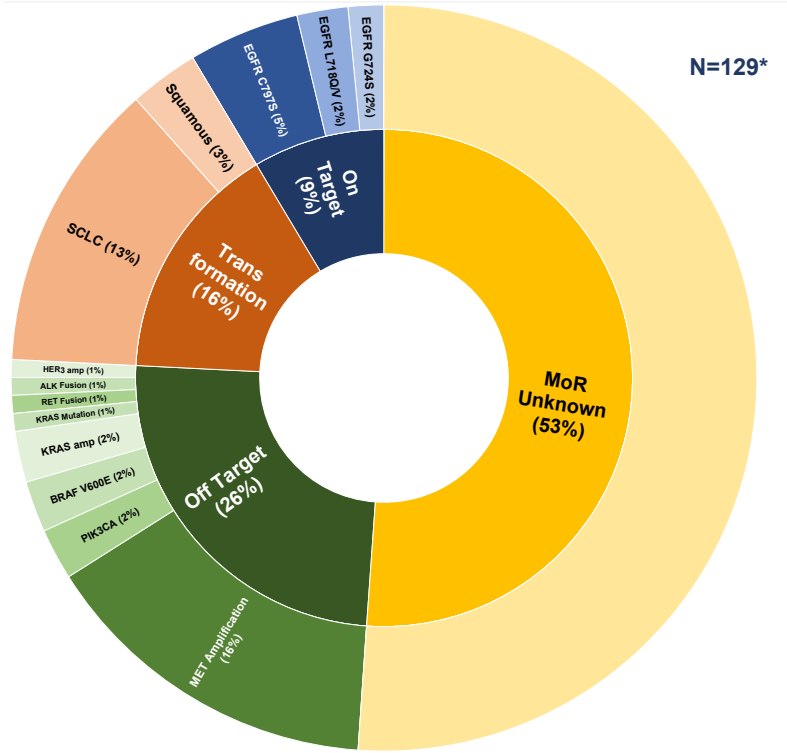


Cooper AS, et al, Nat Rev Clin Oncol 2022



Presented by S. Ramalingam WCLC 2022

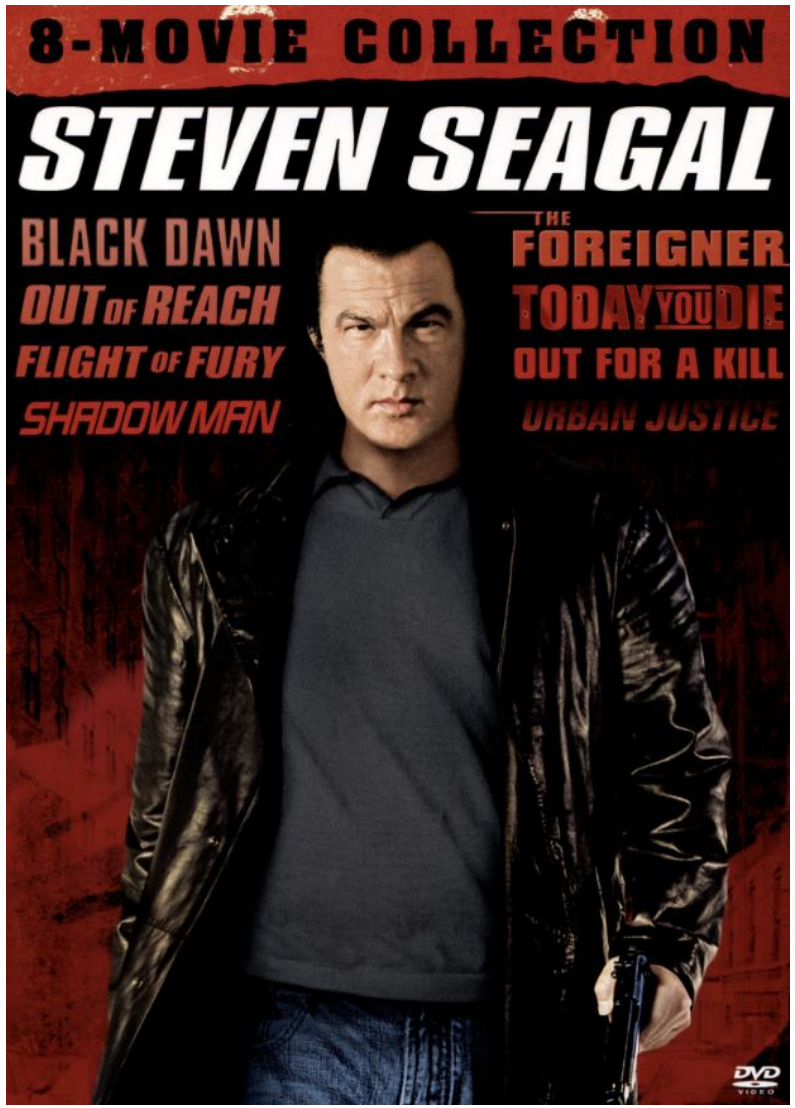
Osimertinib Resistance Mechanisms (Real World Tissue)



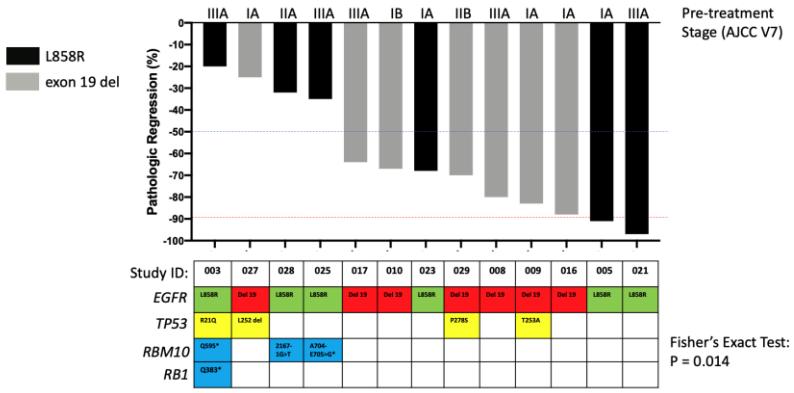
- **Pre-Existing Comutations Mediating Resistance (Impact for locally advanced/early stage treatment)**
- **Resistance to Immunotherapy**

Z. Piotrowska et al. ASCO 2023

Who are the bad actors? Co-mutations

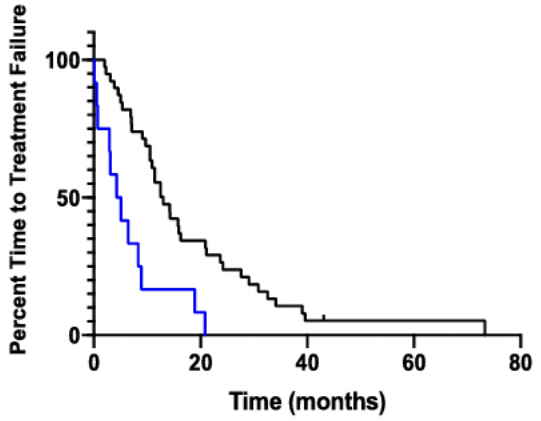


Co-occurring RBM10 mutations correlate with lack of pathological response



TTF with NRF2 Activating Genotypes In EGFR mut NSCLC (NFE2L2/KEAP1/CUL3)

A

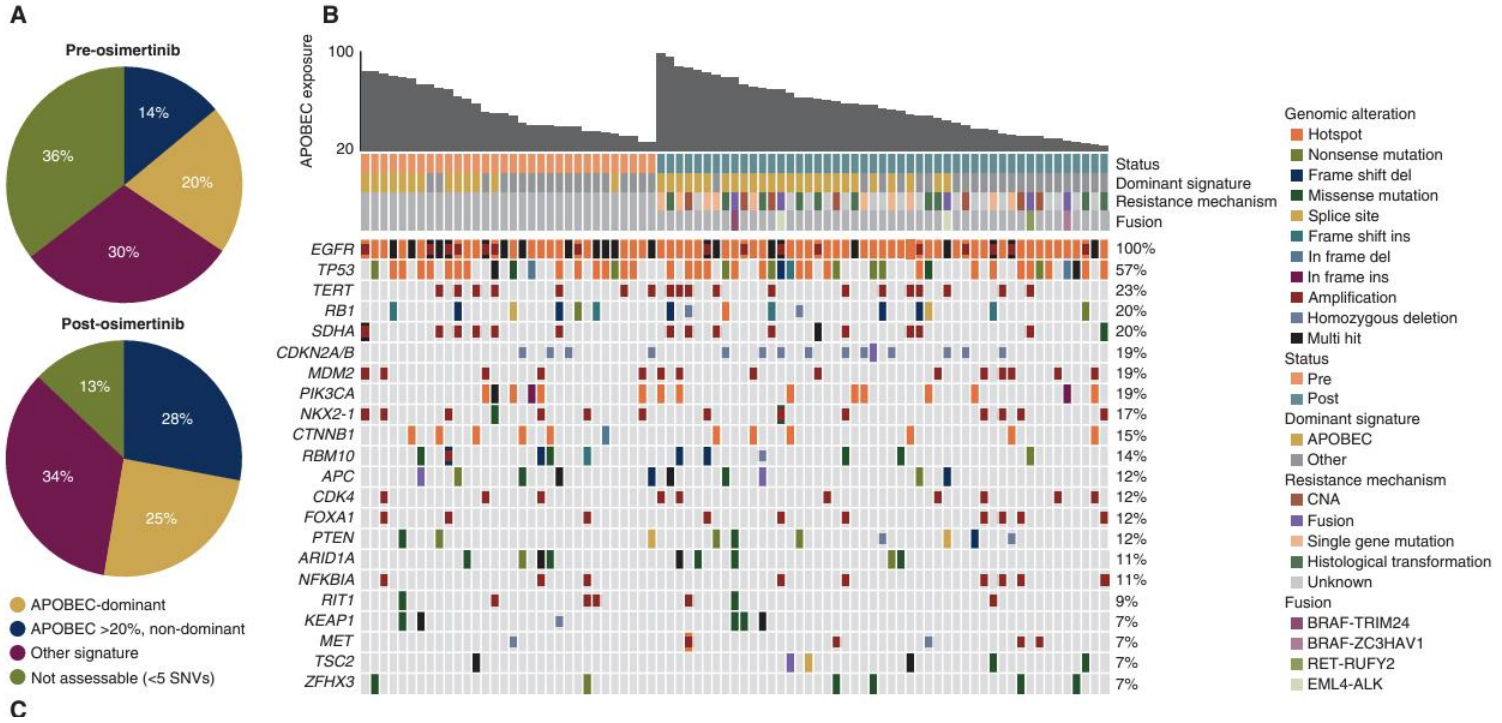


Median TTF 4.7 vs 13.0 months
HR = 2.8 (95% CI 1.1 – 7.2), *p= 0.0014*

P53/RB1 mutations 20x transformation to SCLC.

Aredo et al. ASCO 2023. Hellyer et al. CLC 2019.

Beyond the Usual Suspects: APOBEC Mutagenesis

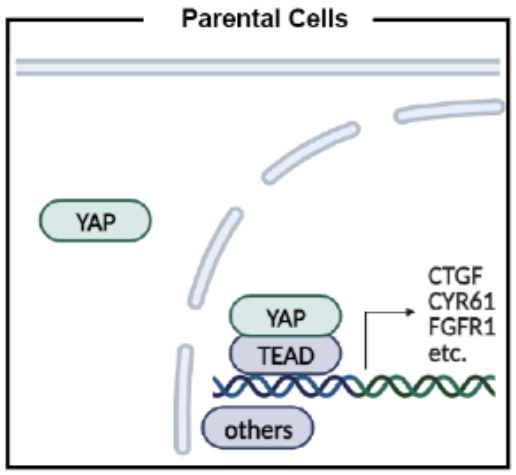


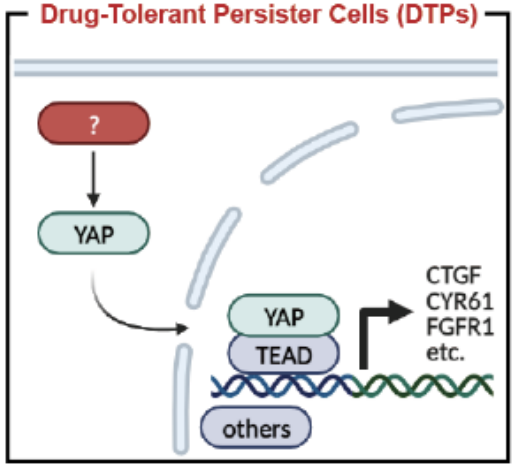
- APOBEC3 family of cytosine deaminases has been implicated in some of the most prevalent mutational signatures in cancer
- APOBEC Mutagenesis occurs at a higher frequency in the setting of osimertinib resistance.
- Inhibiting APOBEC3B mutagenesis may delay resistance to targeted therapies
- May contribute to fusion events driving resistance and lineage plasticity

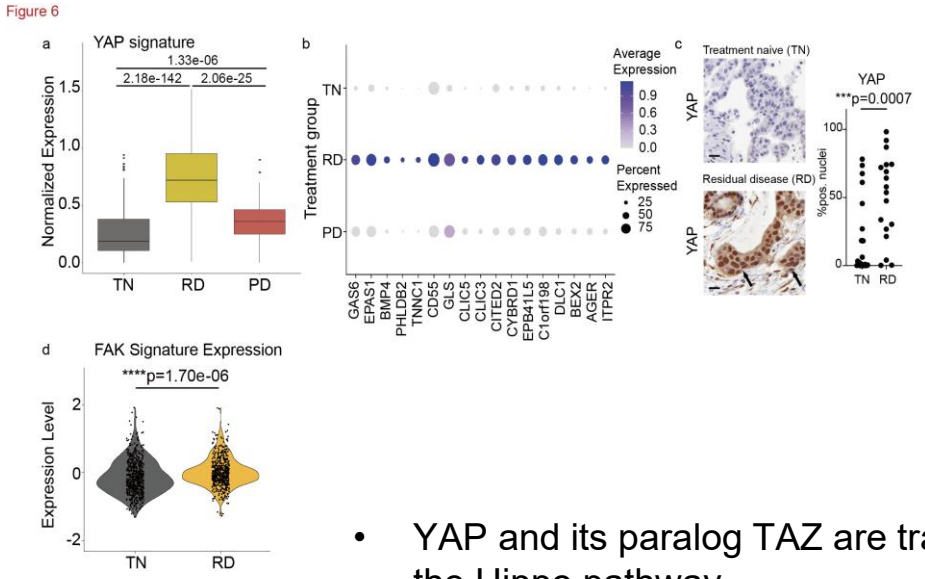
Upregulation of A3B and revealed therapy-induced activation of nuclear factor kappa B (NF-κB) as an inducer of A3B expression.

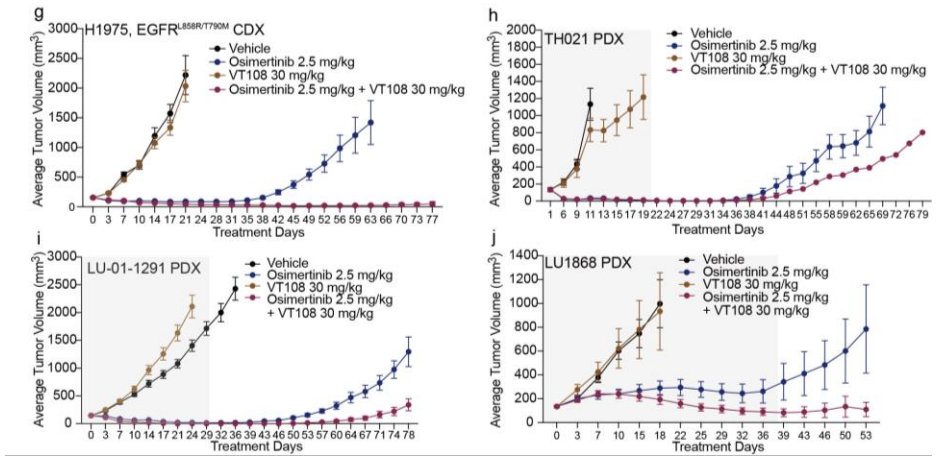
P. Seleneca et al Ann Oncol. 2022.

Beyond the Usual Suspects: HIPPO-YAP Pathway and Long-Term Drug Tolerant Persister Cells







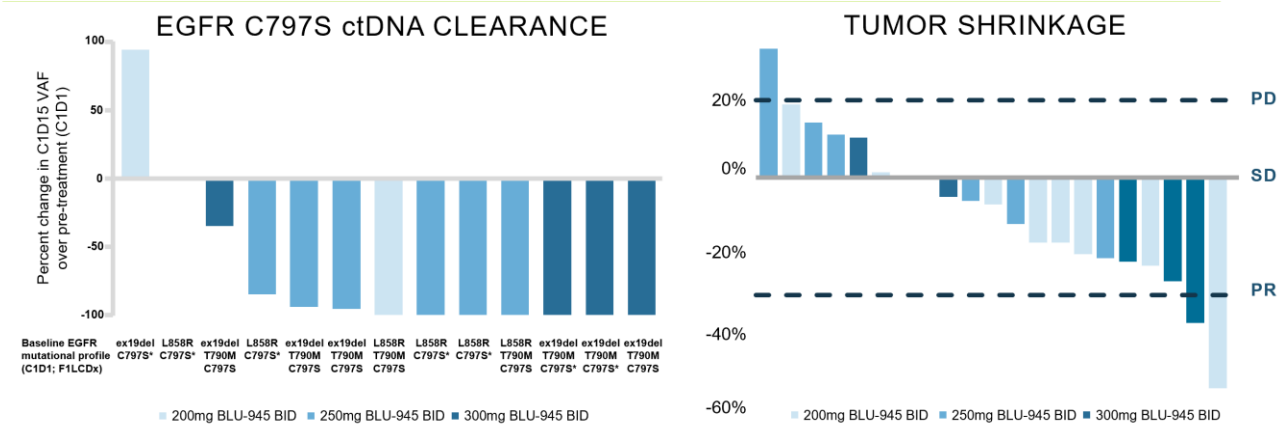


- YAP and its paralog TAZ are transcriptional coactivators and effector proteins of the Hippo pathway.
- The Hippo pathway is a serine/threonine kinase module that phosphorylates YAP thereby sequestering of YAP in the cytoplasm, limiting its coactivating transcriptional function
- TKI activity limited by drug-tolerant persister cells (DTPs) which withstand treatment and comprise residual disease.
- YAP signature increase in residual disease
- FAK-YAP signaling inhibition combined with TKI suppressed residual drug-tolerant cells and enhanced tumor responses.

F. Haderk et al. Nature Communications in press. Reproduced with permission.

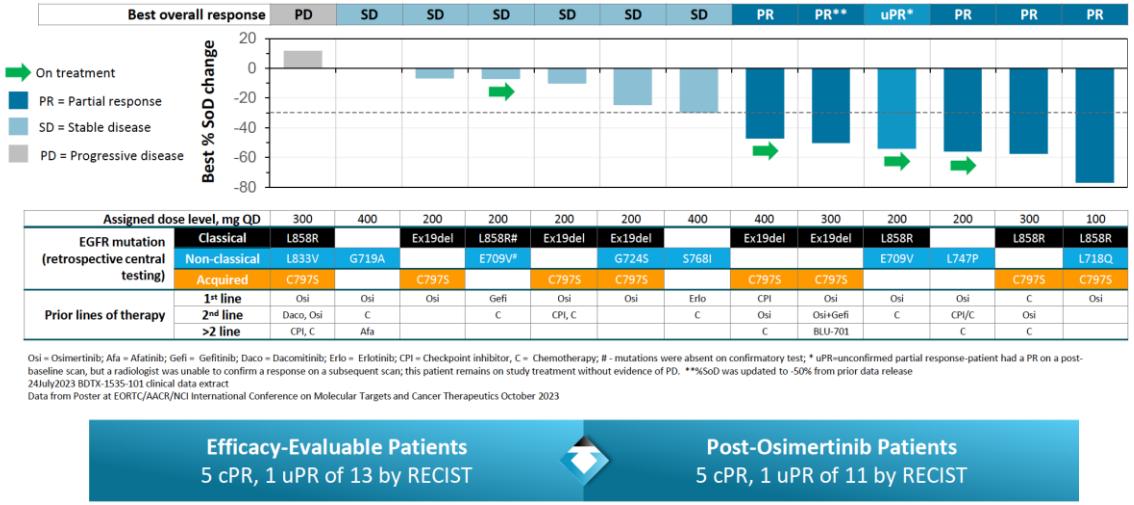
On-Target - 4th Generation C797S EGFR TKIs in the Clinic

BLU-945: Preliminary Efficacy Data Monotherapy Cohorts, Top Dose Levels



Adapted from: Mar, B. Presented to EGFR Exon 20 Research Consortium

BDTX-1535 in Efficacy Evaluable Population

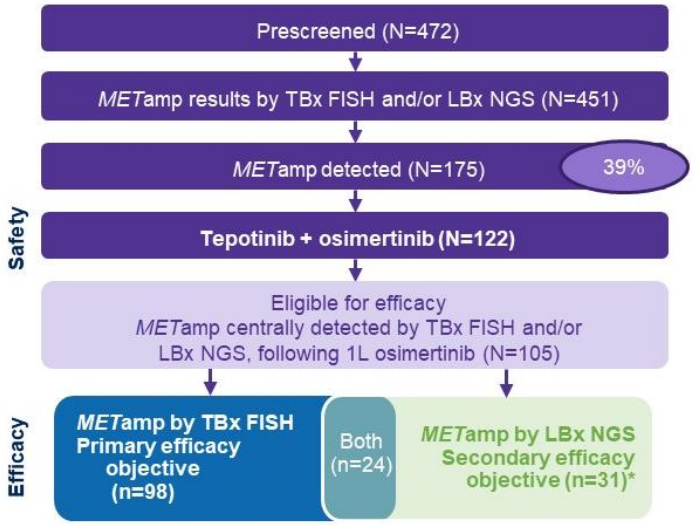


Adapted from Poster at EORTC/AACR/NCI Triple Meeting October 2023

- Tumor heterogeneity post osimertinib resistance and frequency less than T790M are considerations in development

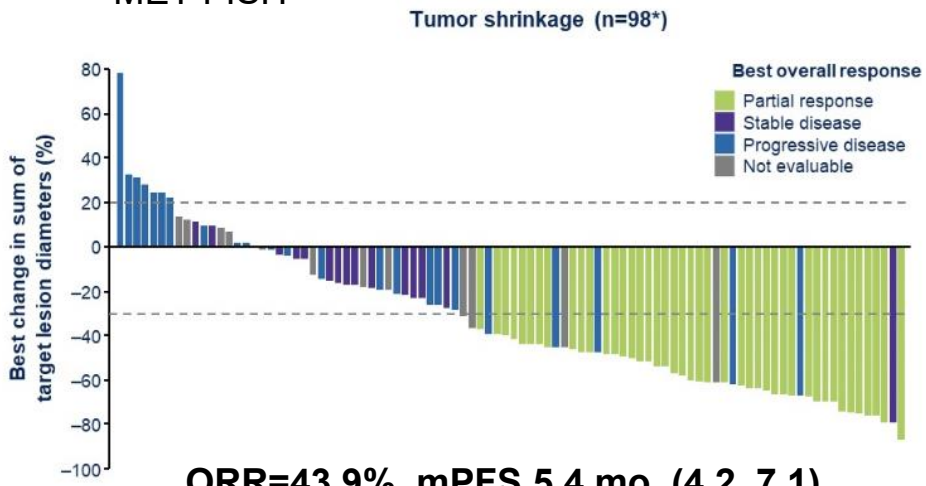
MET Inhibition - INSIGHT 2: Osimertinib + Tepotinib for MET-amplified EGFRm NSCLC

- ***MET*amp detected** by: **TBx FISH** (*MET* GCN ≥5 and/or *MET*/*CEP7* ≥2) and/or by **LBx NGS** (*MET* GCN ≥2.3; Archer®)
- Comprehensive analysis of prescreening *MET*amp by **TBx FISH** & **LBx NGS** is reported by Yu et al. (**Poster 9074, ASCO 2023**)
- **Primary endpoint:** objective response by IRC for patients with centrally detected *MET*amp by **TBx FISH**



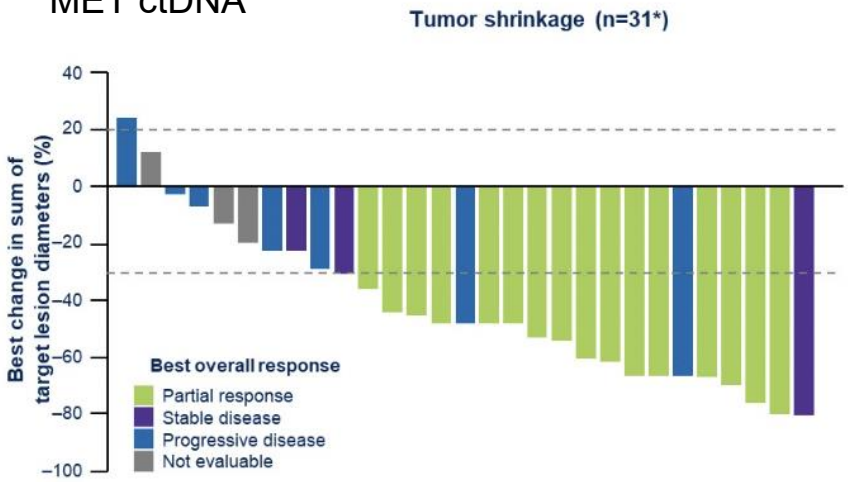
- At data cut-off (September 26, 2022), efficacy population had ≥3 months' follow-up
- Primary analysis will be conducted at ≥9 months' follow-up

MET FISH



ORR=43.9%, mPFS 5.4 mo. (4.2, 7.1)

MET ctDNA



ORR=51.6%, mPFS 4.6 mo. (2.7, 6.9)

D. Tan et al. ASCO 2023.

EGFR + MET TKI Combinations

Osimertinib + Savolitinib for MET+ s/p Osimertinib

TATTON Phase Ib
FISH MET/CEP7 2+ or MET 5x+; IHC 3+ in 50%+; NGS 5X CNG)

ORR 30% post 3rd gen EGFRTKI

SAVANNAH Phase II
Definition MET+: IHC 50+ or FISH 5+ (62% screened)
Definition MET-high: IHC 90+/FISH 10+ (34% screened)

ORR 49%, PFS 7.1 mo MET-high
ORR 9% if not MET-high

CoC AACR
Definition FISH 5+ (62% screened) or MET/CEP7 2+
Definition MET-high: IHC 90+/FISH 10+
ORR 49%, PFS 7.1 mo MET-high
N=14, ORR 57%, 7.4 months mPFS
Savo alone ORR=13%, mPFS 1.6 mo.

Osimertinib + Capmatinib for MET+ s/p Osimertinib

GEOMETRY-E Phase III
Randomized osimertinib + capmatinib vs platinum doublet
NCT 04816214 → study enrollment terminated

SAFFRON Phase III
NCT NCT05261399

Lung MAP S1900G
Randomized osimertinib + capmatinib +/- ramucirumab

Key Takeaways

- Biomarker Definition of MET high
- What does that mean in the patient?
- Tumor Heterogeneity and response
- Single agent MET TKI likely unhelpful

Sequist et al, Lancet Oncology, 2020; Ahn et al, IASLC 2022 EP08.01-140; McCoach et al J Precision Oncol. 2021. Yang et al AACR 2023.

Other Bypass Tracts That Are Potentially Actionable

ALK Fusions

Osimertinib + Alectinib
6 months DoR Case Reports

BRAF Fusions

Osimertinib + Trametinib
Response, D/c at 5 mo (Tox) Case Report

BRAF V600E

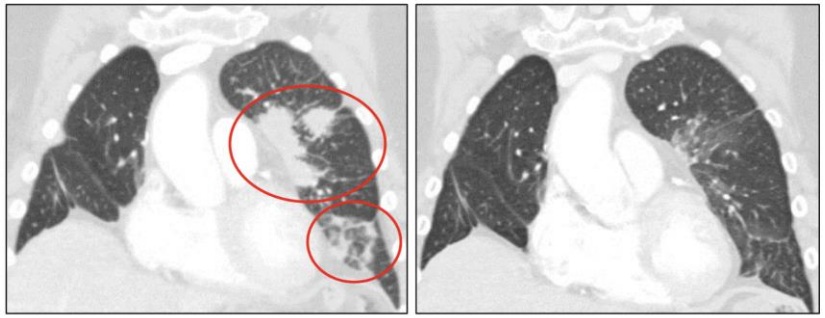
Osimertinib + Dabrafenib/Trametinib
7-8 months DoR

Osimertinib+Vemurafenib
7+ months DoR Case Reports

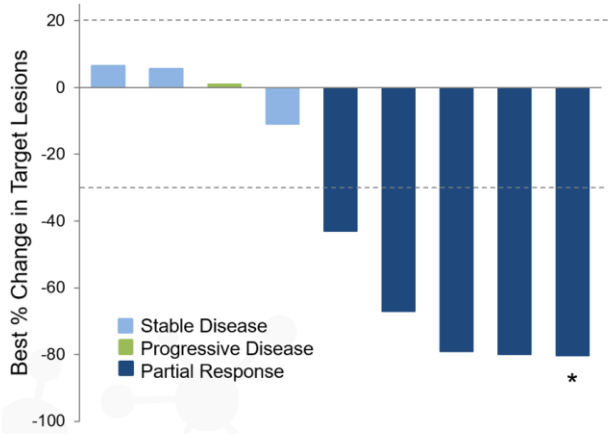
Osimertinib + RET TKI in Acquired Resistance Mediated by RET Fusion

Pralsetinib

B



Selpercatinib



Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

*One partial response unconfirmed

One patient with clinical progression without radiographic evaluation not shown

Jebbink et al. MA02.07. WCLC 2021; Schrock JTO 2018; Offin et al JCP Precis Oncol. 2018;
Ribero et al, npj precision oncology 2021; Huang et al JTO 2019; Sun et al Thorac Cancer 2022; Dagogo-Jack et al. JTO. 2019
J. Rotow et al. WCLC 2021
Z. Piotrowska et al. Cancer Discovery 2018.

MARIPOSA-2: Phase 3 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)*
- ECOG PS 0 or 1
- Stable brain metastases were allowed; radiation/definitive therapy was not required (untreated)

Stratification Factors
- Osimertinib line of therapy (1st vs 2nd)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 Randomization (N=657)

- **Amivantamab-Lazertinib-Chemotherapy (n=263)**
- **Chemotherapy (n=263)**
- **Amivantamab-Chemotherapy (n=131)**

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 Cycle 3 (week 7)

Lazertinib: 240 mg daily starting after completion of carboplatin[b]

Chemotherapy administered at the beginning of every cycle:
- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m² 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

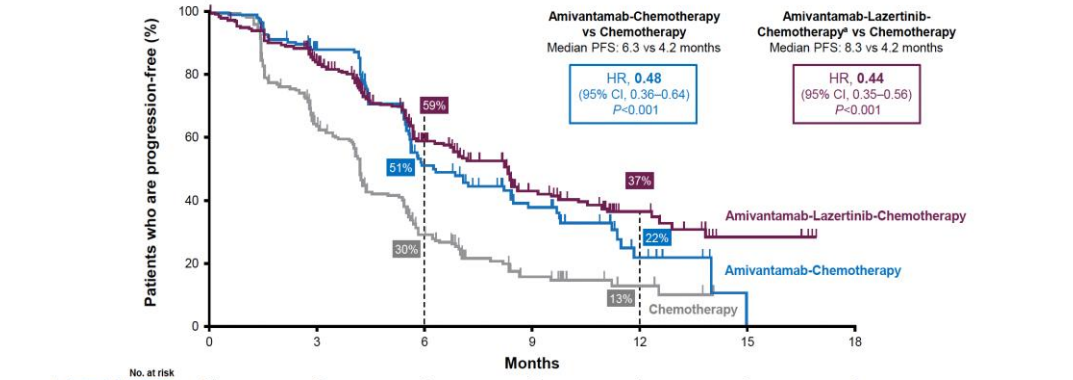
MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295) enrollment period: December 2021 to April 2023; data cut-off: 10-Jul-2023

[a]Patients who could not have MRI were allowed to have CT scans.
[b]All patients randomized before 7Nov2022 initiated lazertinib on the first day of Cycle 1 (see next slide).
[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 (median PFS of 8.5 months for amivantamab-containing arms vs 5.5 for chemotherapy). Statistical hypothesis testing included PFS, ORR, and then OS.
[d]These secondary endpoints (time to subsequent therapy, PFS2, and symptomatic PFS) will be presented at a future congress.

AUC, area under the curve; BICR, blinded independent central review; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletions; HR, hazard ratio; IDMC, independent data monitoring committee; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Primary Endpoint: Progression-free Survival by BICR

At a median follow-up of 8.7 months, amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of progression or death by 52% and 56%, respectively



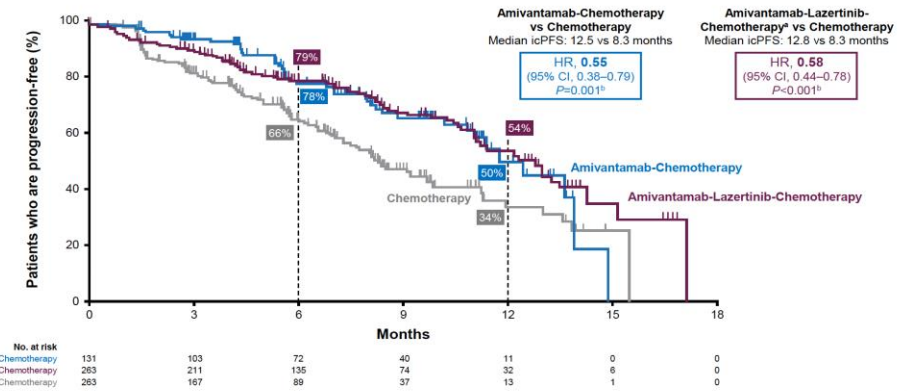
Consistent PFS benefit by investigator: HR, 0.41 (8.2 vs 4.2 mo; P<0.001[b]) & HR, 0.38 (8.3 vs 4.2 mo; P<0.001[b])

[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Intracranial Progression-free Survival by BICR

Amivantamab-chemotherapy and amivantamab-lazertinib-chemotherapy reduced the risk of intracranial progression or death by 45% and 42%, respectively

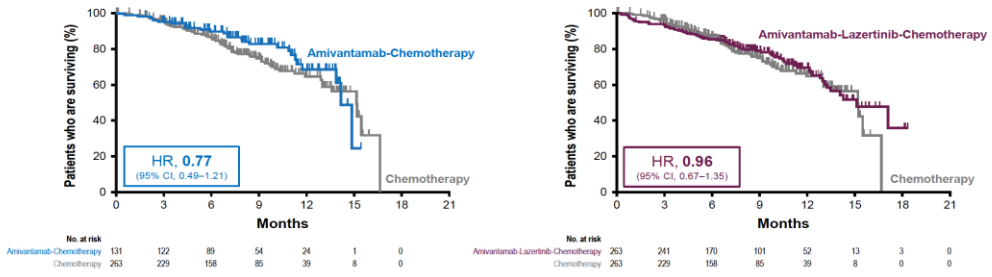


[a]Amivantamab-lazertinib-chemotherapy arm includes all patients regardless of the dosing regimen received. [b]Nominal *P*-value; endpoint not part of hierarchical hypothesis testing.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; icPFS, intracranial progression-free survival.

Early Interim Overall Survival[a]

At time of data cutoff, the median follow-up for the study was 8.7 months



Includes all randomized patients regardless of dosing regimen received
- Median follow-up for the modified amivantamab-lazertinib-chemotherapy regimen was 5.4 months

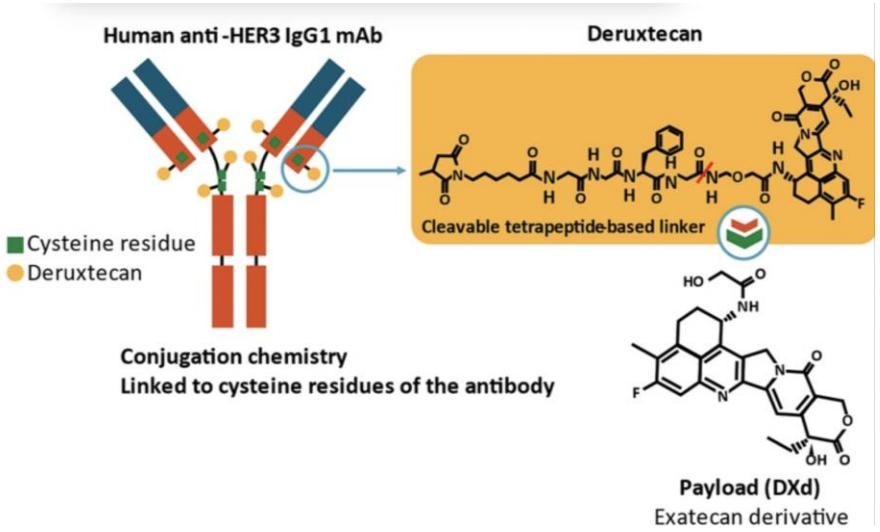
[a]There were 161 deaths in the study at the time of the prespecified interim OS analysis (representing 25% of all randomized patients and 40% of the 400 projected deaths for the final OS analysis). Median estimates at this time (median follow-up of 8.7 months) are not reliable.

CI, confidence interval; HR, hazard ratio; OS, overall survival.

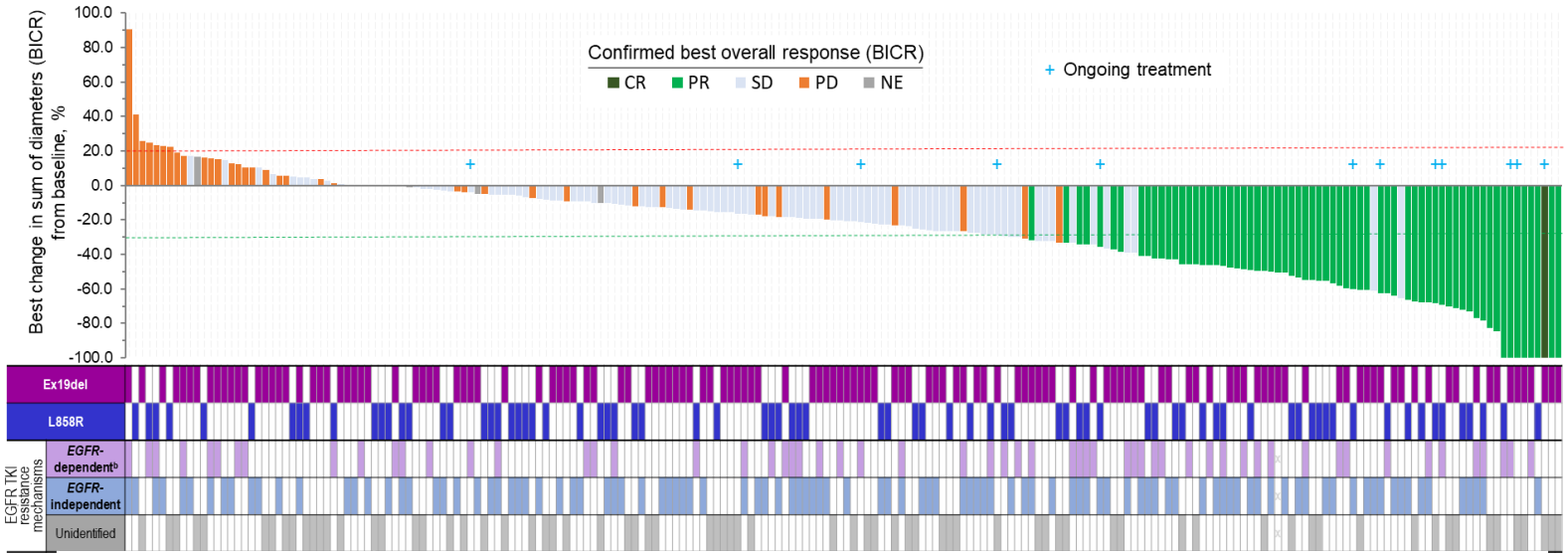
VTE=22% in ami/lazer

Passaro et al. Annals of Oncology 2024

Patritumab deruxtecan in EGFR-mutated NSCLC with PD on Prior EGFR-TKI



ORR=29.8 (23.9-36.2), mPFS=5.5 (5.1-5.9), mOS=11.9 (11.2-13.1)



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)

	Type of EGFR TKI resistance mechanism			
	EGFR-dependent, only (n=34)	*EGFR*-independent, only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

Tropion-Lung01 – Dato-Dxd vs Docetaxel. AGA mutations HR=0.35.

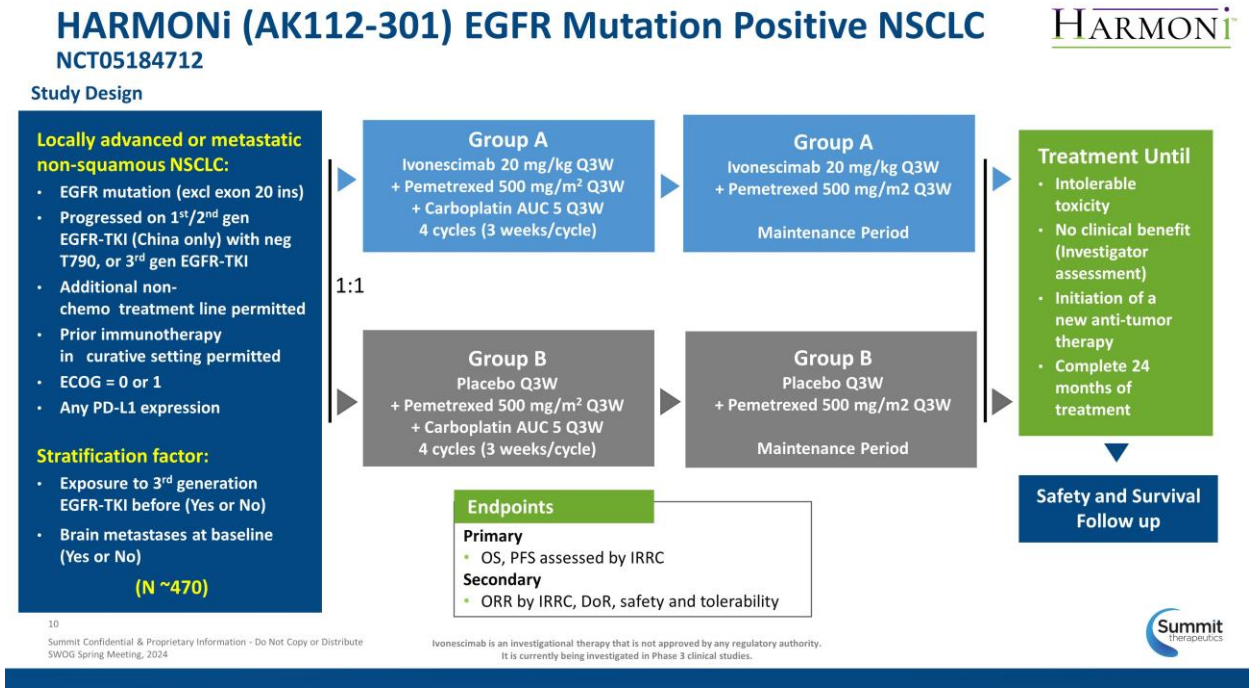
P. Janne et al. Cancer Discovery 2022.
H. Yu et al. JCO 2023/WCLC 2023.
N. Girard et al. ELCC 2024.

Major Combination Strategies to Enhance ICI Efficacy in EGFR mutated NSCLC

Chemo+ICI +/- Anti-Angiogenesis

Trial	Treatment	PFS	OS
KN789[7]	platinum-pemetrexed-pembrolizumab	0.8 (0.65-0.97)*	0.84 (0.69-1.02)*
CM722#[8]	platinum-pemetrexed-nivolumab	0.75 (0.56-1.0) p=0.052	0.82 (0.61-1.10)
ORIENT-31[9]	Cisplatin-Pemetrexed +/- Sintilimab (anti- PD-1)	0.72 (0.55-0.94)	0.97 (0.71-1.32)**
ORIENT-31[9]	Cisplatin-Pemetrexed+ Sintilimab + IBI305 (bevacizumab biosimilar) vs. chemo alone	0.51 (0.39-0.67)	0.98 (0.72-1.34)**
Impower 150 (EGFR-prior TKI)	carbo-paclitaxel-atezolizumab-bevacizumab (ACBP vs. CBP)	0.42 (0.22–0.80)	0.74 (0.38-1.46)

*Not statistically significant per statistical plan, ** adjusted for crossover
T790M+ allowed w/o prior osimertinib



But no clear OS benefit with IO + anti-angiogenesis in
In EGFR mutant NSCLC

S. Gettinger et al JTO 2018. 13:9 1363-1372. 2. MH Ahn et al. JTO. 2022 May;17(5):718-723. 3. G. Oxnard et al. Ann Oncol 2020 Apr;31(4):507-516. 4. JW Riess et al WCLC 2018. 5. BC Creelan et al. BJC 2021 Jan;124(2):383-390. 6. GGY Lai et al. JTO Clin Res Rep. . 2022 Sep 21;3(12):100416. 7. J. Yang et al. ASCO 2023. 8. T. Mok et al. ESMO Asia 2022. 9. S. Lu et al. Lancet Resp. Med. 2023. (online)10. N. Nogami et al. JTO 2022 Feb;17(2):309-323.
. 2022 Feb;17(2):309-323.

Summary

- **Targeted therapy approaches can overcome Osimertinib Resistance**
- **Tumor heterogeneity and suboptimal biomarker selection may limit activity of targeted agents**
- **Need to move beyond standard resistance mechanisms to target underlying mechanisms of long-term drug tolerant persister cells**
- **Need to study exceptional responders to ICI blockade and need new immunotherapy treatment approaches**