OVERCOMING EGFR TKI RESISTANCE

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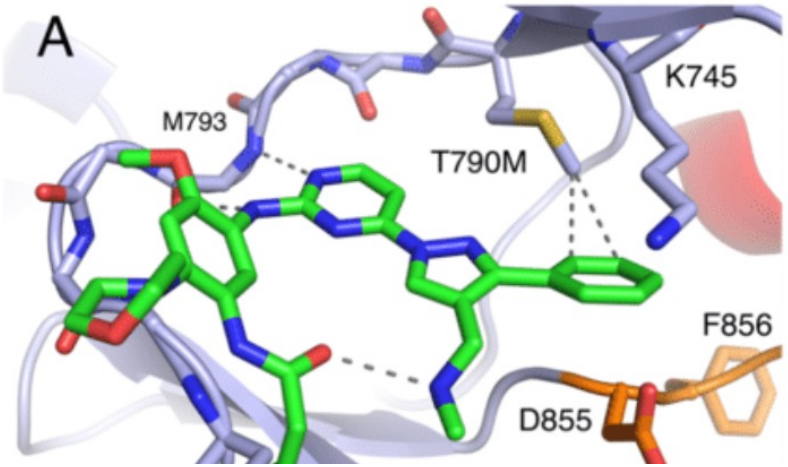
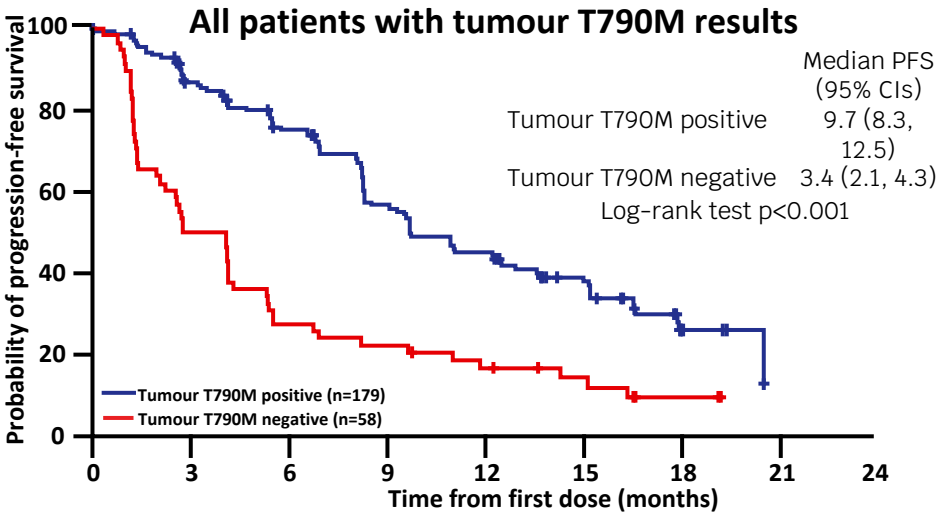
EGFR T790M The (Former) King of EGFR TKI Resistance Mechanisms





Oxnard et al. ELCC 2016

FLAURA: Osimertinib vs comparator EGFR-TKI as first-line treatment for EGFRm advanced NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria

- ≥18 years old
- WHO performance status 0/1
- Exon 19 deletion/L858R (enrollment by local or central *EGFR* testing)
- No prior systemic anticancer/ EGFR-TKI therapy
- Stable CNS metastases were allowed

→ Stratification by **mutation status** (exon 19 deletion/ L858R) and **race** (Asian/non-Asian)

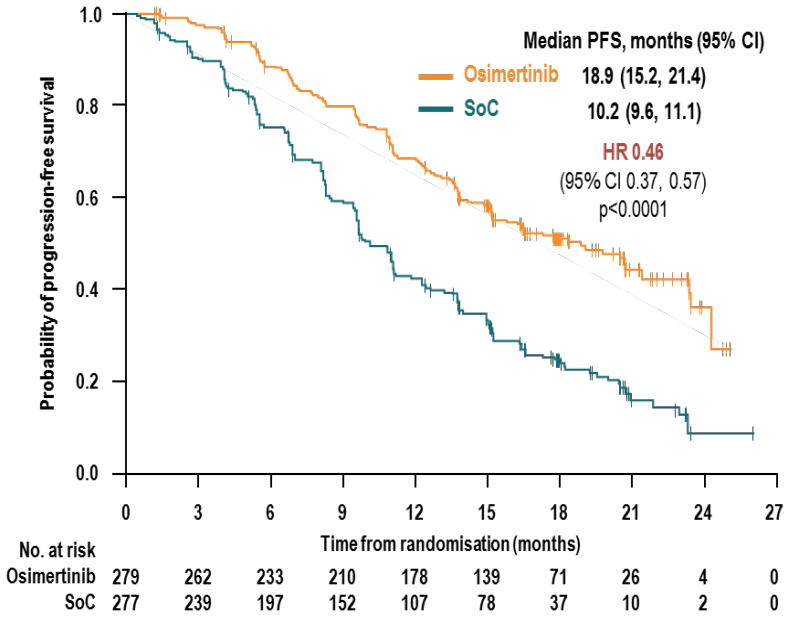
→ R 1:1

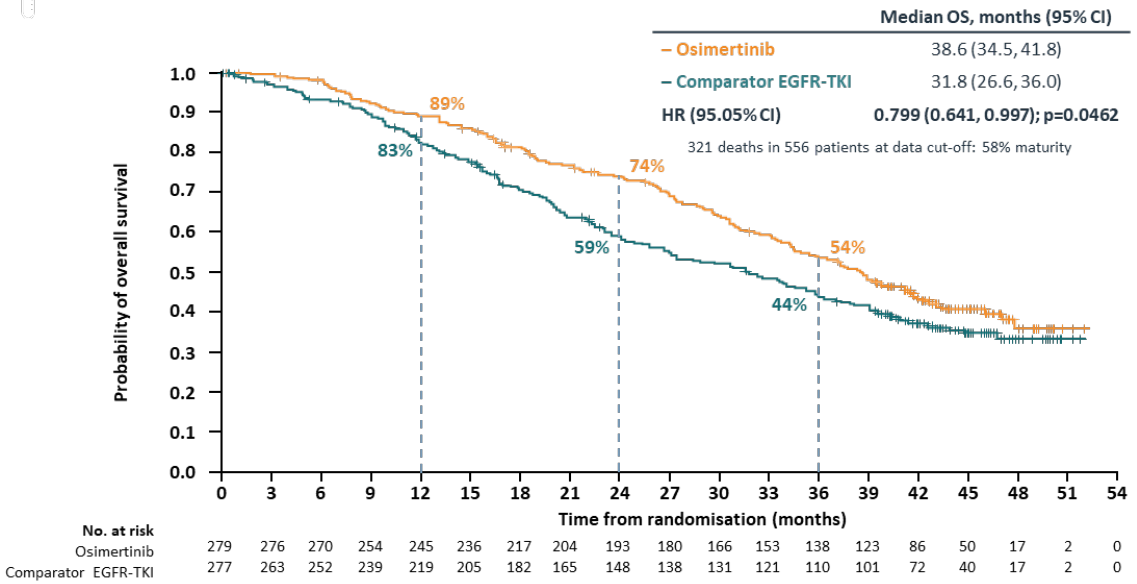
→ **Osimertinib** (80 mg po qd) (n=279)

→ **Comparator EGFR-TKI**; **Gefitinib** (250 mg po qd) or **Erlotinib** (150 mg po qd) (n=277)

→ RECIST v1.1 assessment every 6 weeks until objective progressive disease
Following the primary PFS analysis, progression events per RECIST 1.1 were no longer collected centrally

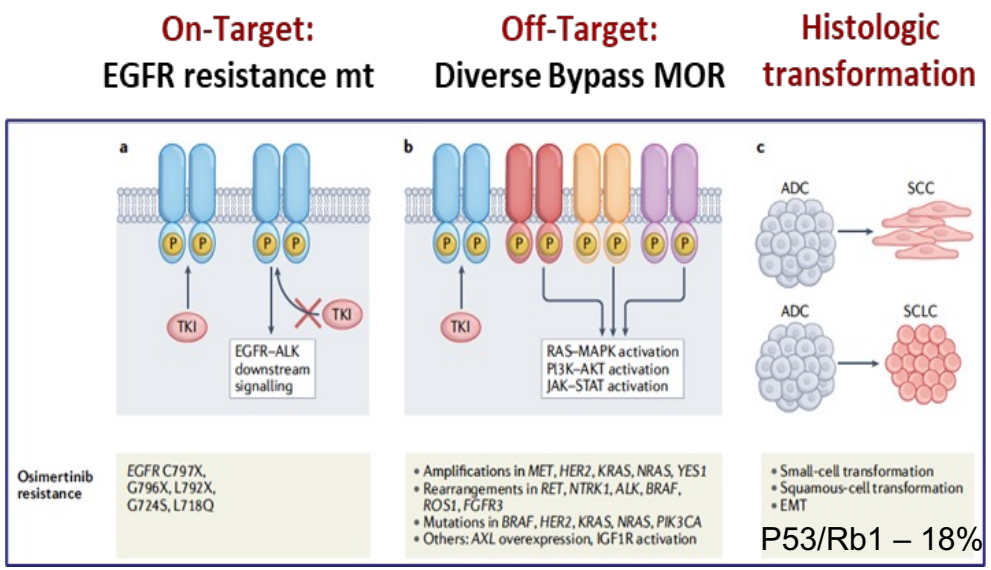
Crossover was allowed for patients in the **comparator** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity



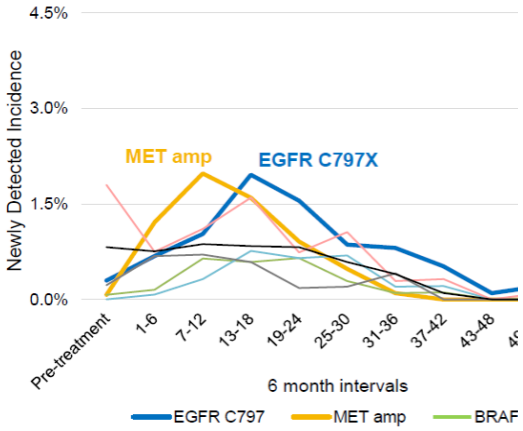


Ramalingam SS, et al. ESMO 2019. Abstract LBA5_PR.

Broad Mechanisms of Resistance to EGFR-TKI and Temporal Occurrence

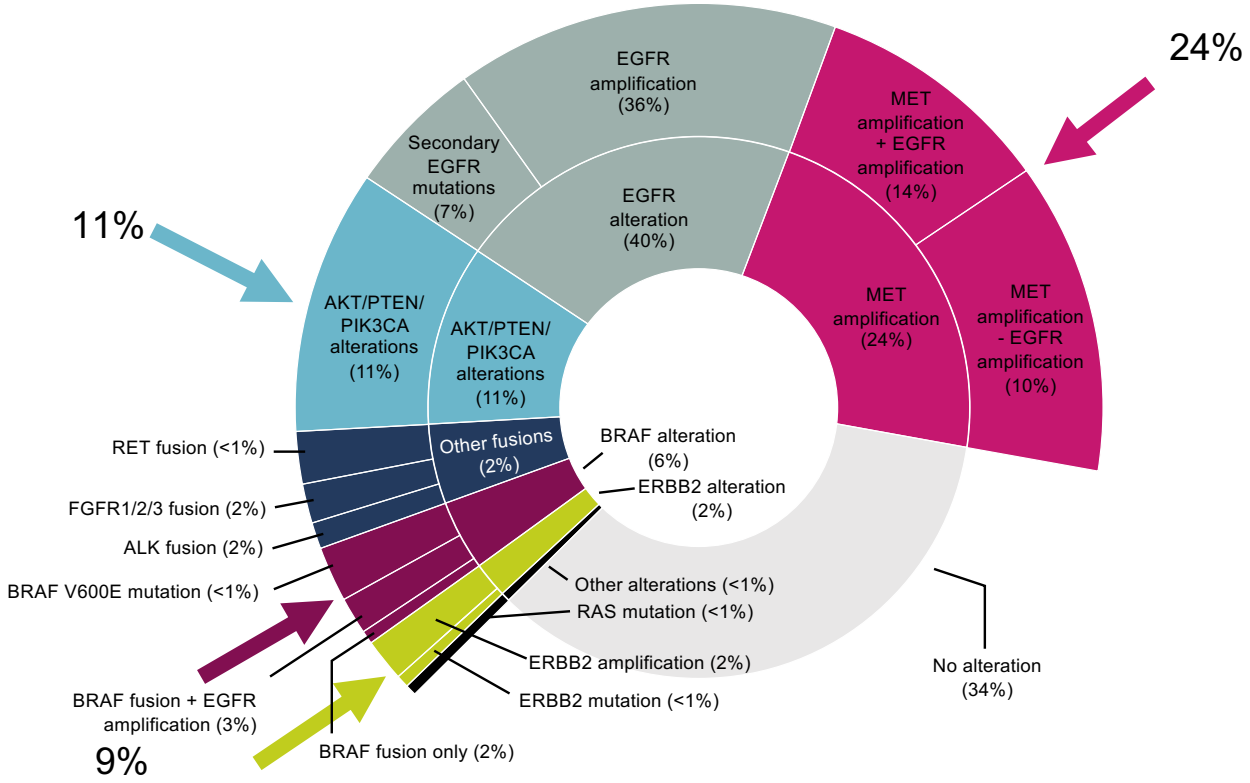


Cooper AS, et al, Nat Rev Clin Oncol 2022



Presented by S. Ramalingam WCLC 2022

Genomics from Orchard: N-174 tissue samples/concurrent Plasma ctDNA



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

C797S-Active Compounds in Development: Preclinical Data

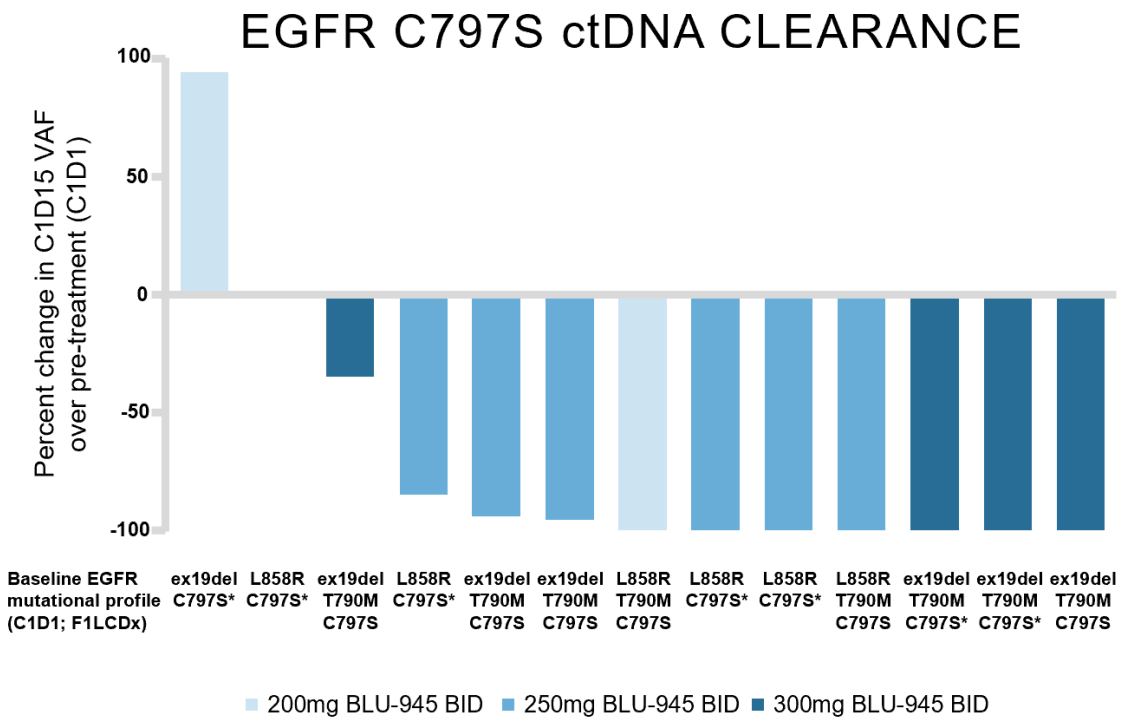
Compound	Del19	L858R	Del19/ T790M	L858R/ T790M	Del19/ C797S	L858R/ C797S	Triple Mutant	Other	CNS?	Status
BLU-945	-	X	X	X	-	X	X		-	Phase 1/2 (NCT04862780)
BLU-701	X	X	-	-	X	X	X		X	Discontinued
BLU-525	X	X	-	-	X	X	X		X	Preclinical
BDTX-1535	X	X	-	-	X	X	X	Uncommon	X	Phase 1 (NCT05256290)
THE-349	X	X	X	X	X	X	X		X	Preclinical
H002	X	X	X	X	X	X	X		X	Phase 1/2 (NCT05552781)
BAY 2927088	X	X			X	X		Ex20ins		Phase 1 (NCT05099172)
JIN-A02	X	X	X	X	X		X		X	Phase 1/2 (NCT05394831)
BBT-176	X	X	X		X	X	X		X	Phase 1/2 (NCT04820023)

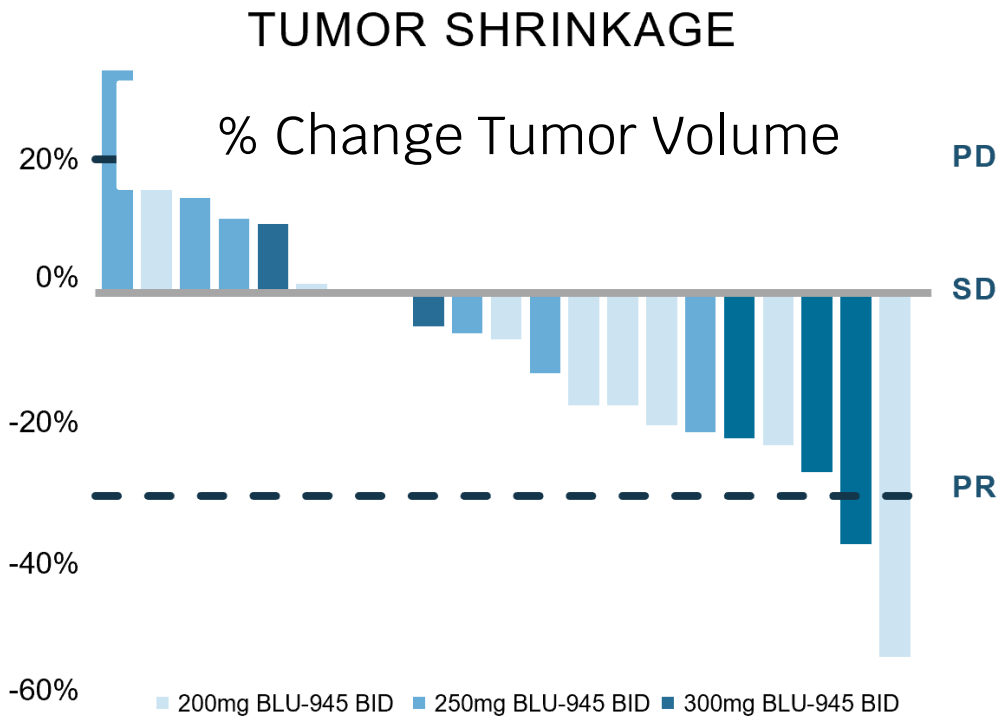
Predicted Not Active Predicted Active No available data

Shum et al, AACR 2022; Tavera-Mendoza et al ENA 2022 #177; Lucas et al. ENA 2022. Abstract #64; Zhang et eal. ENA 2022 #236; Siegel et al. ENA 2022 #17; Lim et al ESMO 2021; Yun et al ESMO 2022 #999P

Slide courtesy of Julia Rotow, MD

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

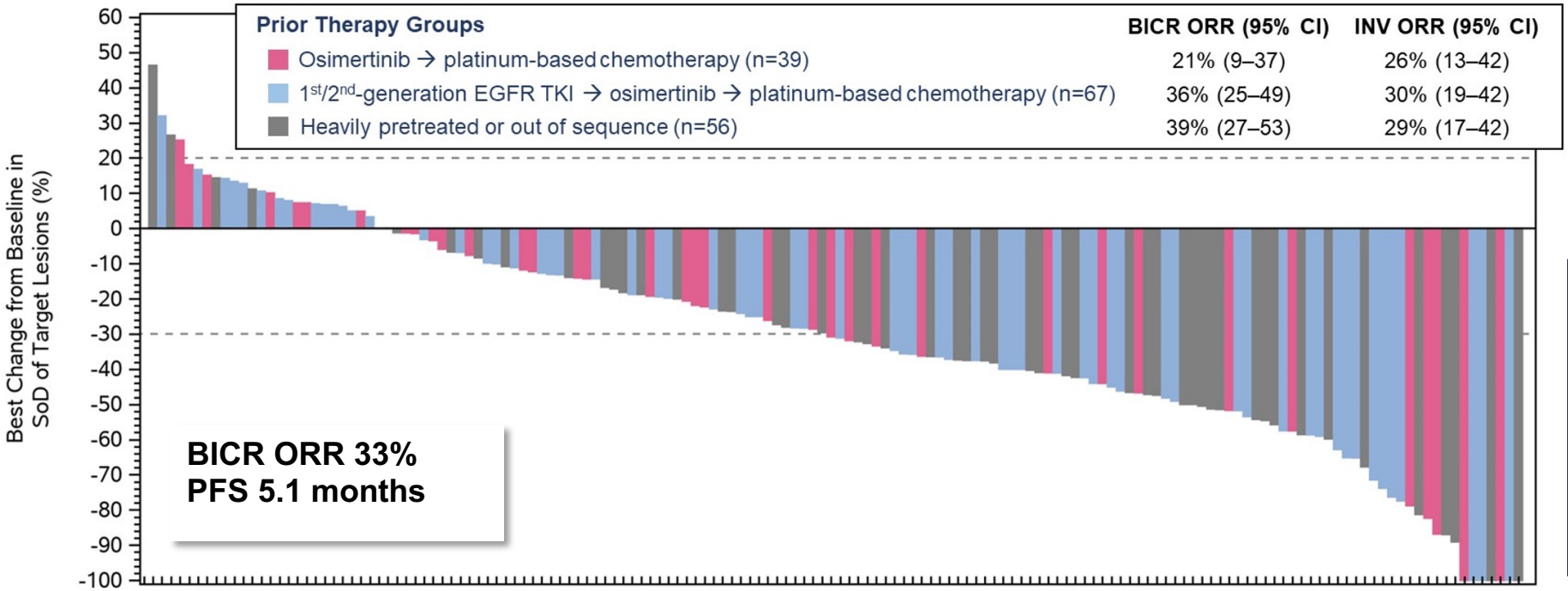




Adapted from: Mar, B. Presented to EGFR Exon 20 Research Consortium

Amivantamab + Lazertinib

EGFR/MET Bispecific +3rd Gen EGFR TKI CHRYSALIS-2

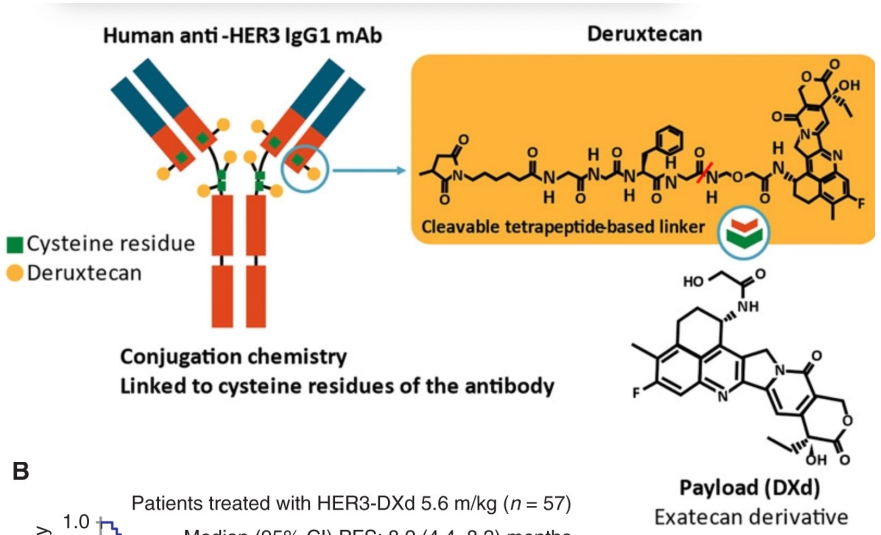


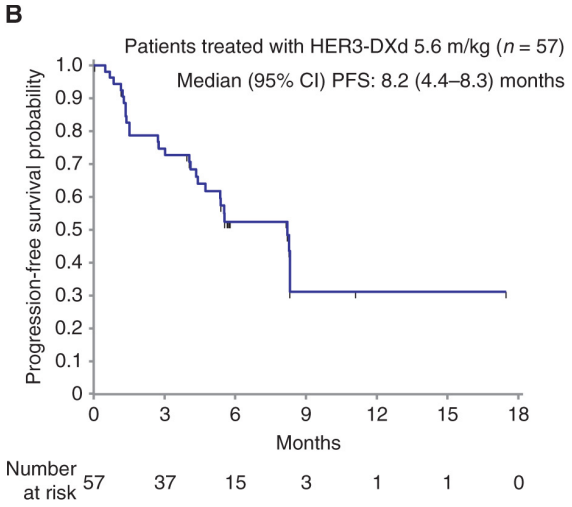
In CHRYSALIS-1, MET/EGFR IHC score correlated with response (n=20)

ORR 90% if IHC+
ORR 10% if IHC-

Shu et al. ASCO 2022. #9006.; Bauml et al ASCO 2021 #9006

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





P. Janne et al. Cancer Discovery 2022.

INSIGHT2: Tepotinib and Osimertinib

Key eligibility
- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by central/ local FISH testing (TBx) or central NGS testing (LBx)
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed

R 1:1

Tepotinib 500 mg QD + **osimertinib** 80 mg QD

Tepotinib monotherapy

Primary endpoint:
- ORR by IRC (patients with *MET*amp centrally confirmed by TBx FISH treated with tepotinib + osimertinib)

Secondary endpoints:
- ORR by IRC in patients with:
  - *MET*amp centrally confirmed by TBx FISH treated with tepolinib

Detection of *MET*amp

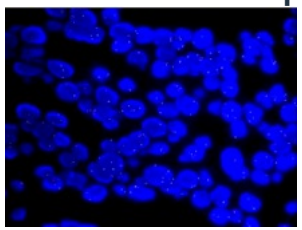
*MET*am definitions

TBx FISH: *MET* GCN ≥5 and/or *MET/CEP7* ≥2

and/or

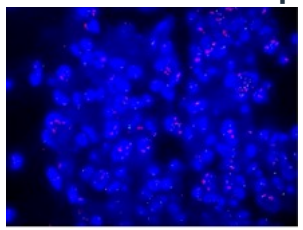
LBx NGS: *MET* GCN ≥2.3; Archer®

TBx FISH: *MET*amp -ve



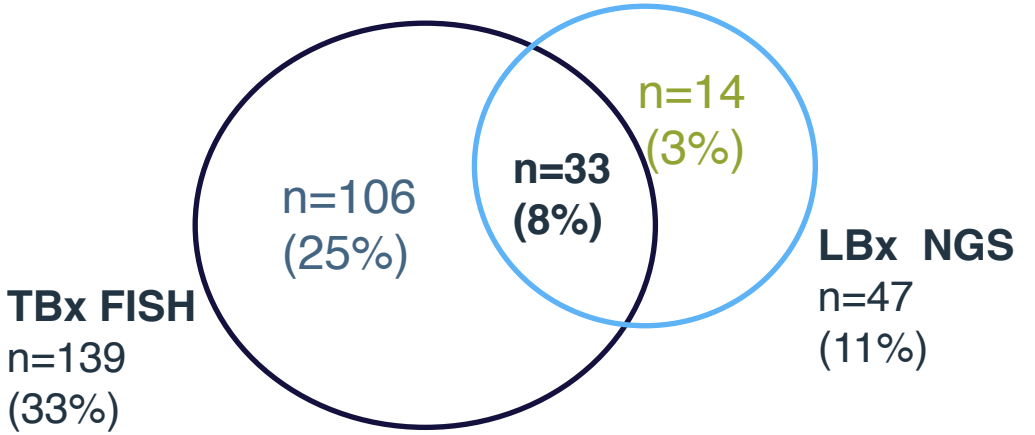
MET GCN, 2.33; *MET/CEP7*, 0.96

TBx FISH: *MET*amp +ve

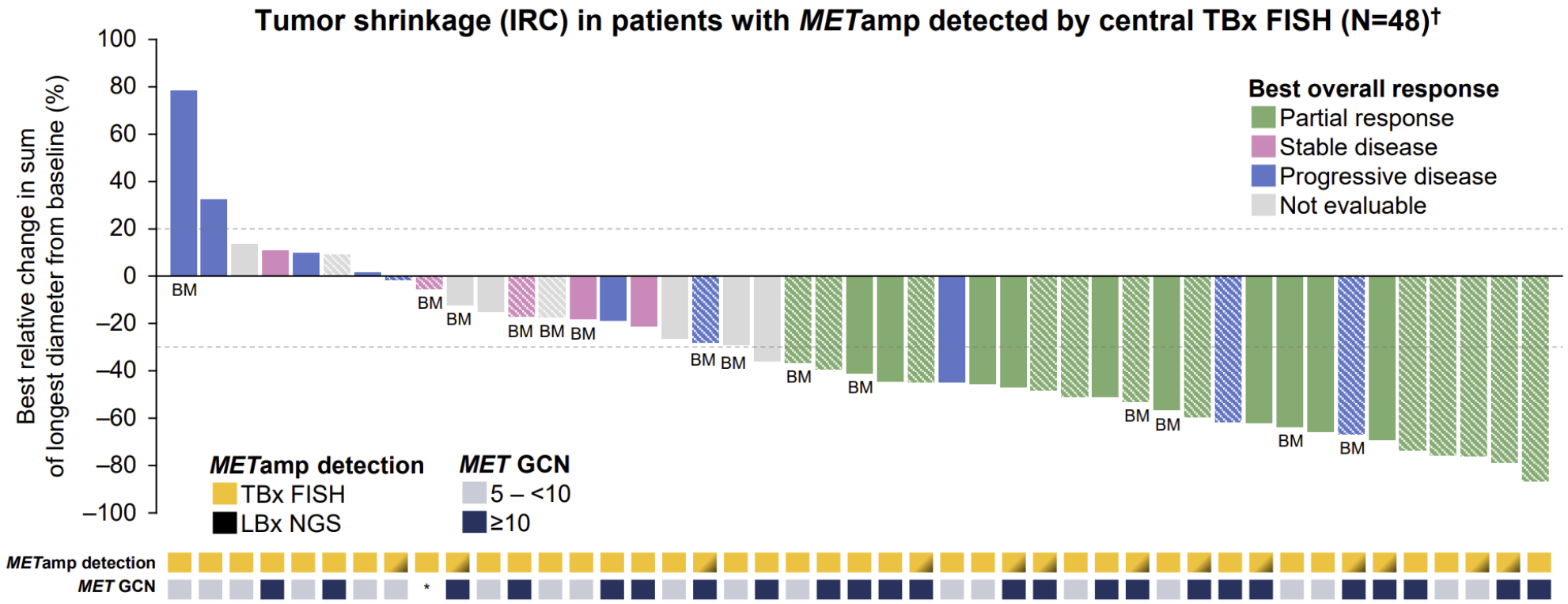


MET GCN, 17.4; *MET/CEP7*, 7.35

*MET*amp detected in 153/425 (36%) of pre-screened patients



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



ORR 45.8%-56.5% osimertinib + tepotinib
ORR 8.3% tepotinib monotherapy

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

Osimertinib + Capmatinib for MET+ s/p Osimertinib

SAFFRON Phase III
NCT NCT05261399

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

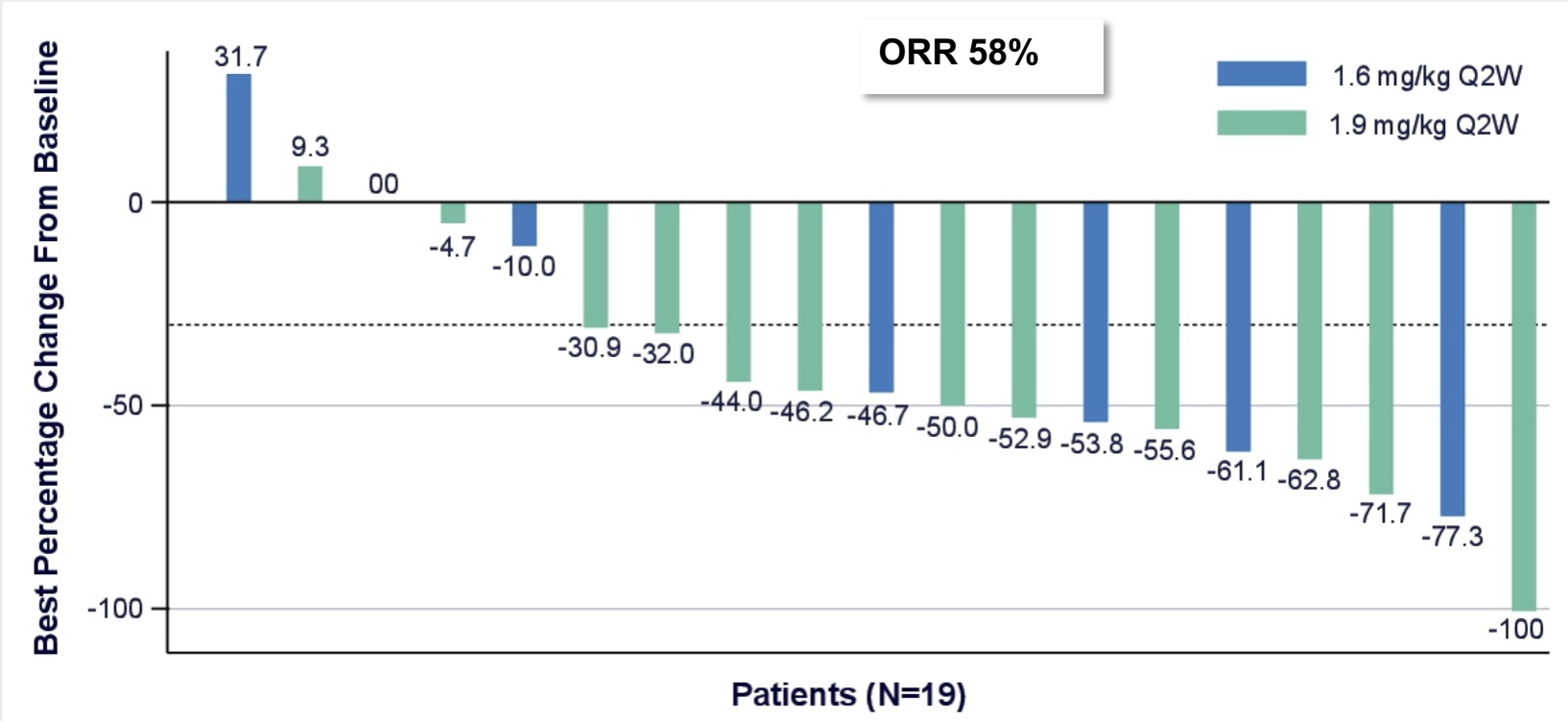
Key Takeaways

- 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.

Telisotuzumab vedotin + Osimertinib
MET-ADC + EGFR TKI

MET-overexpression: IHC 3+ in at 25% of tumor cells



Goldman et al. ASCO 2022. #9013

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

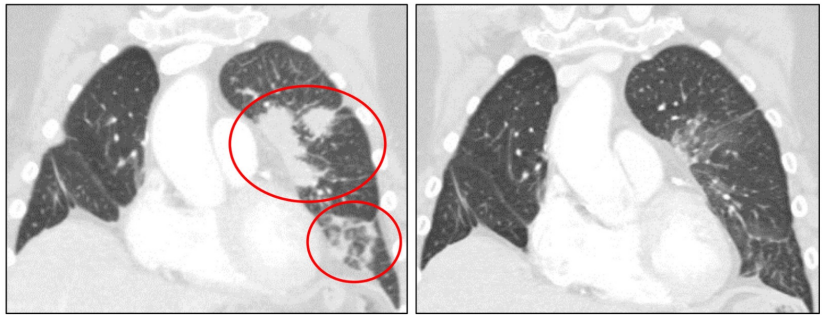
Osimertinib+Vemurafenib
7+ months DoR Case Reports

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.

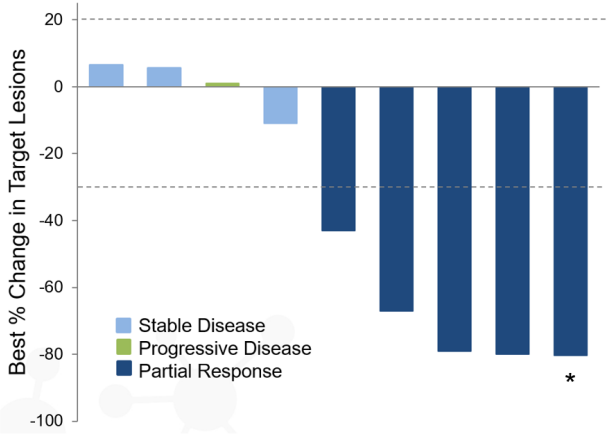
Osimertinib + RET TKI in Acquired Resistance Mediated by RET Fusion

Pralsetinib

B



Selpercatinib

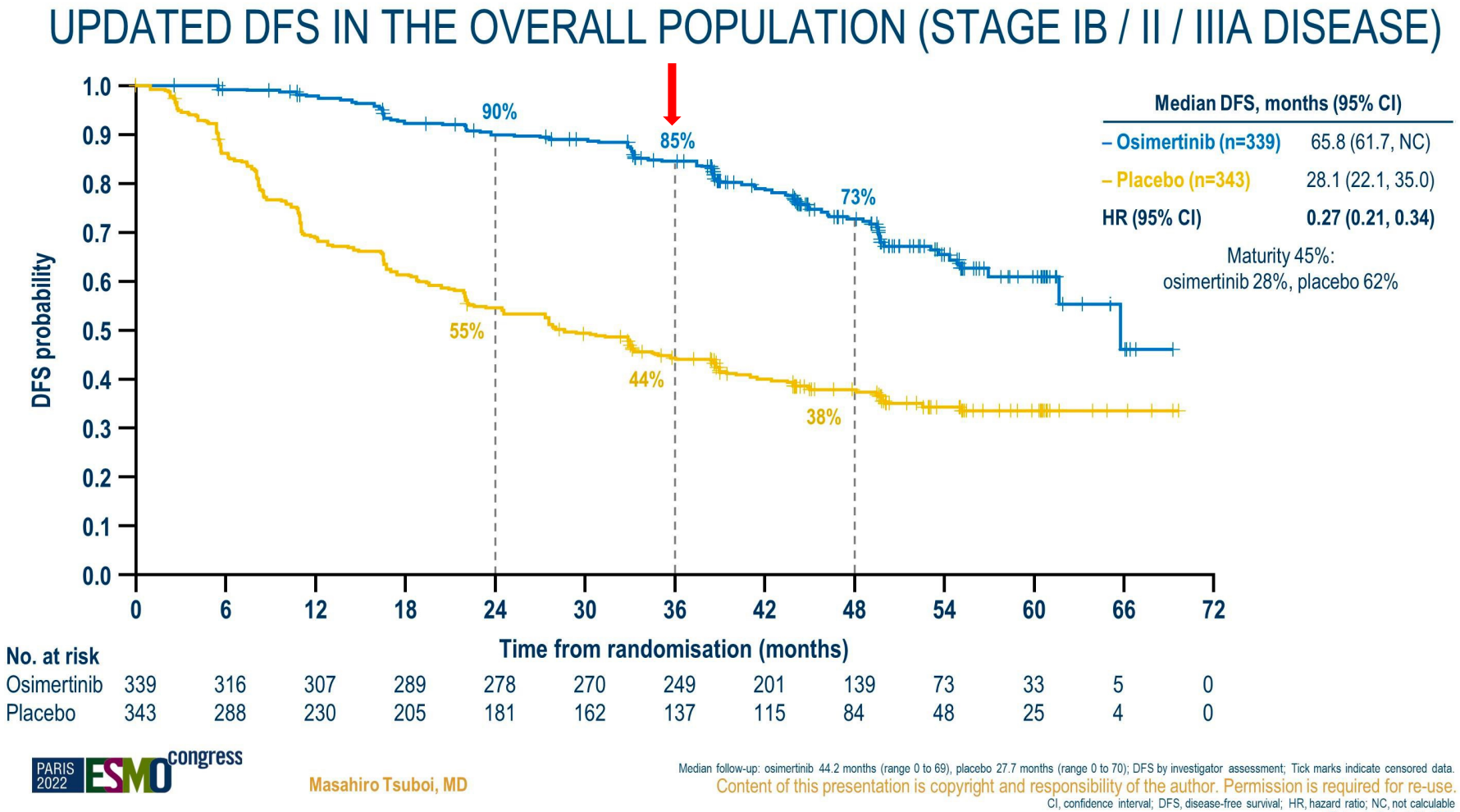


Best Response (n=10)	
Objective Response n (%)	**5 (50%)**
Partial Response*	5 (50%)
Stable Disease	3 (30%)
Progressive Disease	2 (20%)
Disease Control Rate n (%)	**8 (80%)**
Median Depth of Response (%)	**-43%**

*One partial response unconfirmed

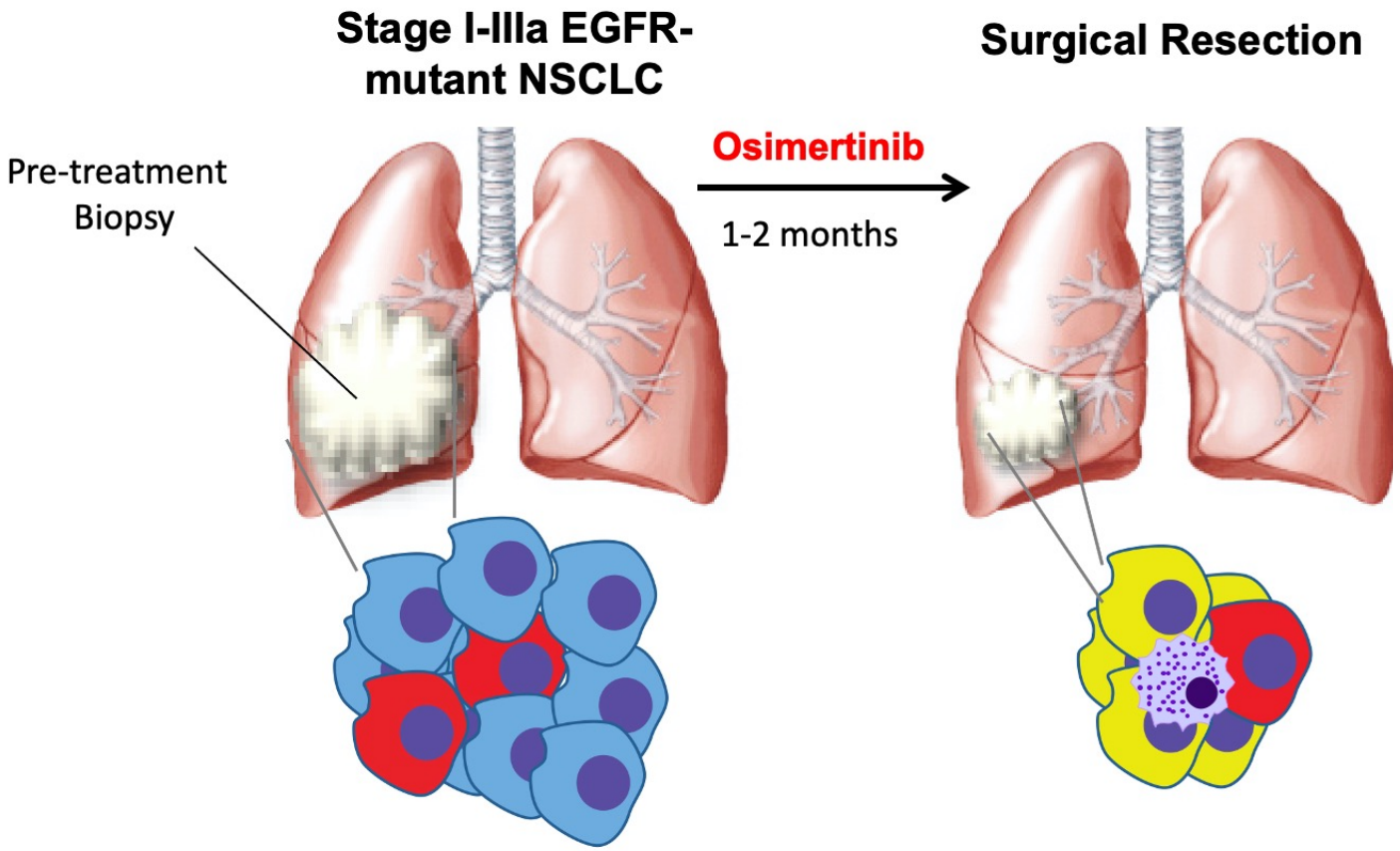
One patient with clinical progression without radiographic evaluation not shown

Overcoming Resistance in Earlier Stage Disease



Tsuboi. ESMO Paris 2022

Neoadjuvant Osimertinib in Stage I-IIIA NSCLC: Interim analysis of first 13 patients



Primary Endpoint:

MPR: ~15%

Safety:

Secondary Efficacy:

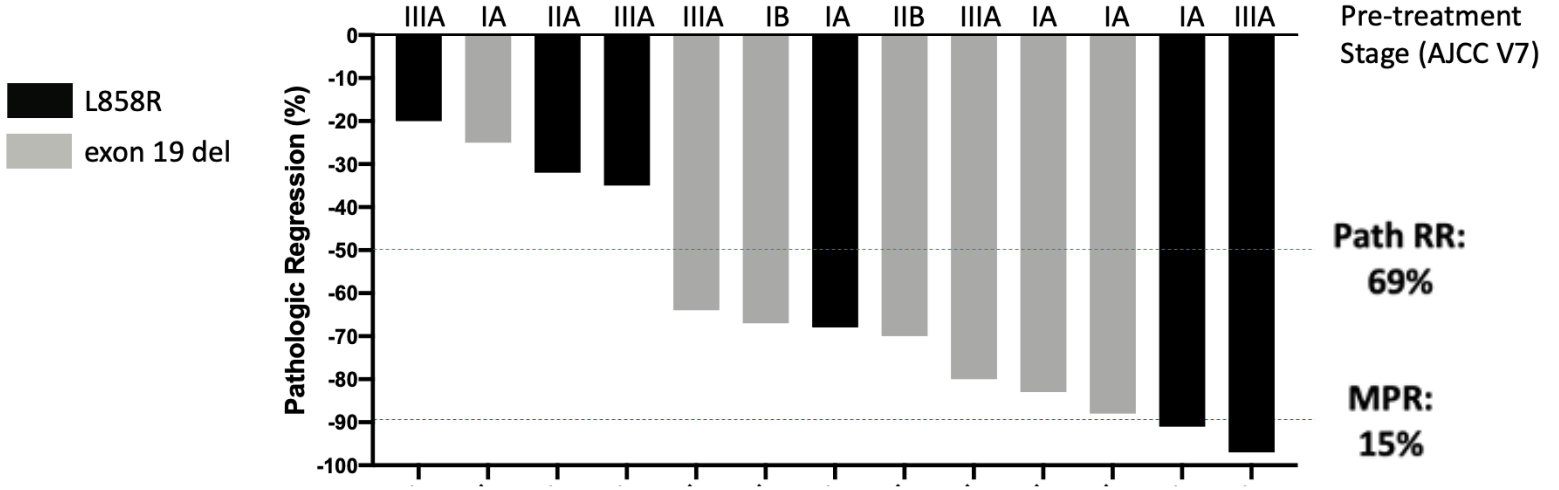
80% LN downstaging (4/5)
46% ORR
0% PCR
DFS/OS: TBD

Exploratory:

RBM10 commutations
AT2 – diff
WNT/b-catenin activation
T-Cell infiltration

Blakely, IASLC WCLC, 2021

Co-occurring RBM10 mutations correlate with lack of pathological response



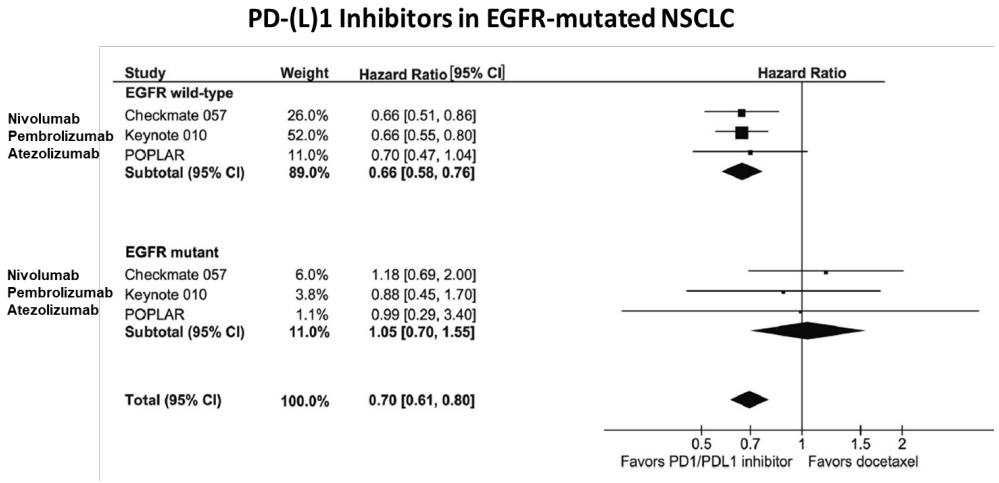
Study ID:	003	027	028	025	017	010	023	029	008	009	016	005	021
EGFR	L858R	Del 19	L858R	L858R	Del 19	Del 19	L858R	Del 19	Del 19	Del 19	Del 19	L858R	L858R
TP53	R21Q	L252 del						P278S		T253A			
RBM10	Q595*		2167-1G>T	A704-E705>G*									
RB1	Q383*												

Fisher's Exact Test: P = 0.014

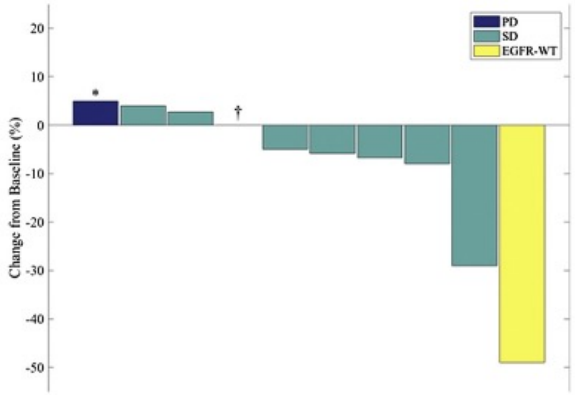
Collin Blakely, MD, PhD, UCSF, USA, @collin_blakely

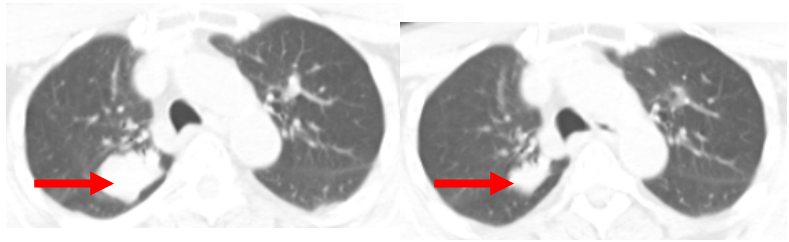
Blakely, IASLC WCLC, 2021

PD-(L)1 Blockade alone in EGFR-mut NSCLC is Suboptimal



1L Pembro PD-L1 positive





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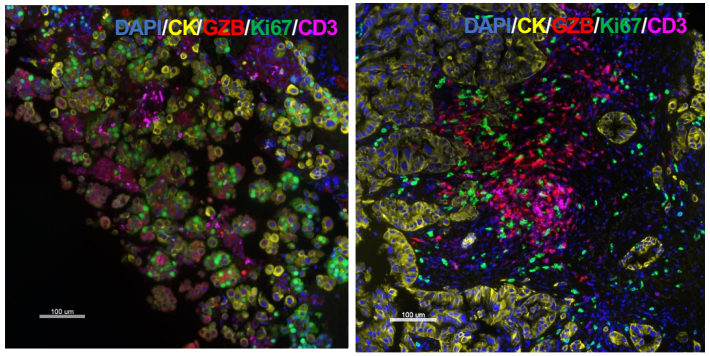

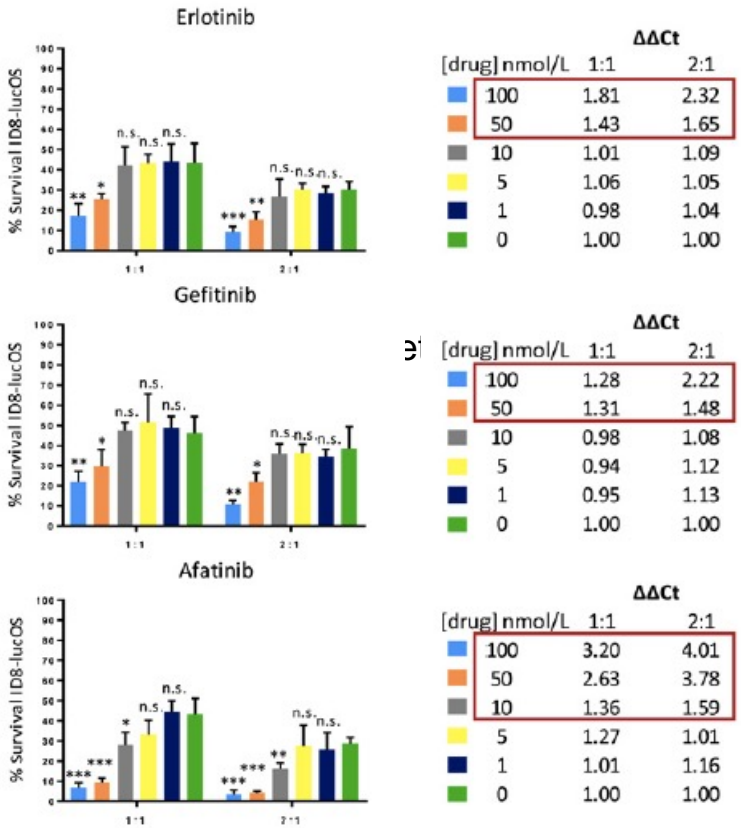

Baseline and Week 12 Scan with PR to treatment.
PD-L1 (22C3 40%) and PD-L1 and PD-L2 amp on NGS

Pt with 20% tumor shrinkage and PFS > 1 year.

Ovarian cancer cell line with luciferace reporter in setting of CD8 T-cell co-culture

A. Lisberg et al JTO 2018, CK Lee, et al. J Thorac Oncol 2016

JW Riess et al. WCLC 2018.

P. Lizotte et al. Cancer Imm Res. 2018.

Summary

- **Targeted therapy approaches can overcome Osimertinib Resistance (in some instances)**
- **Tumor heterogeneity and suboptimal biomarker selection may limit activity**
- **More work needs to be done regarding EGFR-TKI resistance in the neoadjuvant/adjuvant setting**
- **Need to study exceptional responders to ICI blockade and need new immunotherapy treatment approaches**