EGFR and Resistant Mechanisms

Edgardo S. Santos, M.D., FACP
Genesis Care USA
Medical Director of Research Services/GC Hematology-Oncology
Thoracic Oncology
Clinical Associate Professor
Charles E. Schmidt School of Medicine/Florida Atlantic University
Treasurer, FLASCO & President, FLASCO Foundation

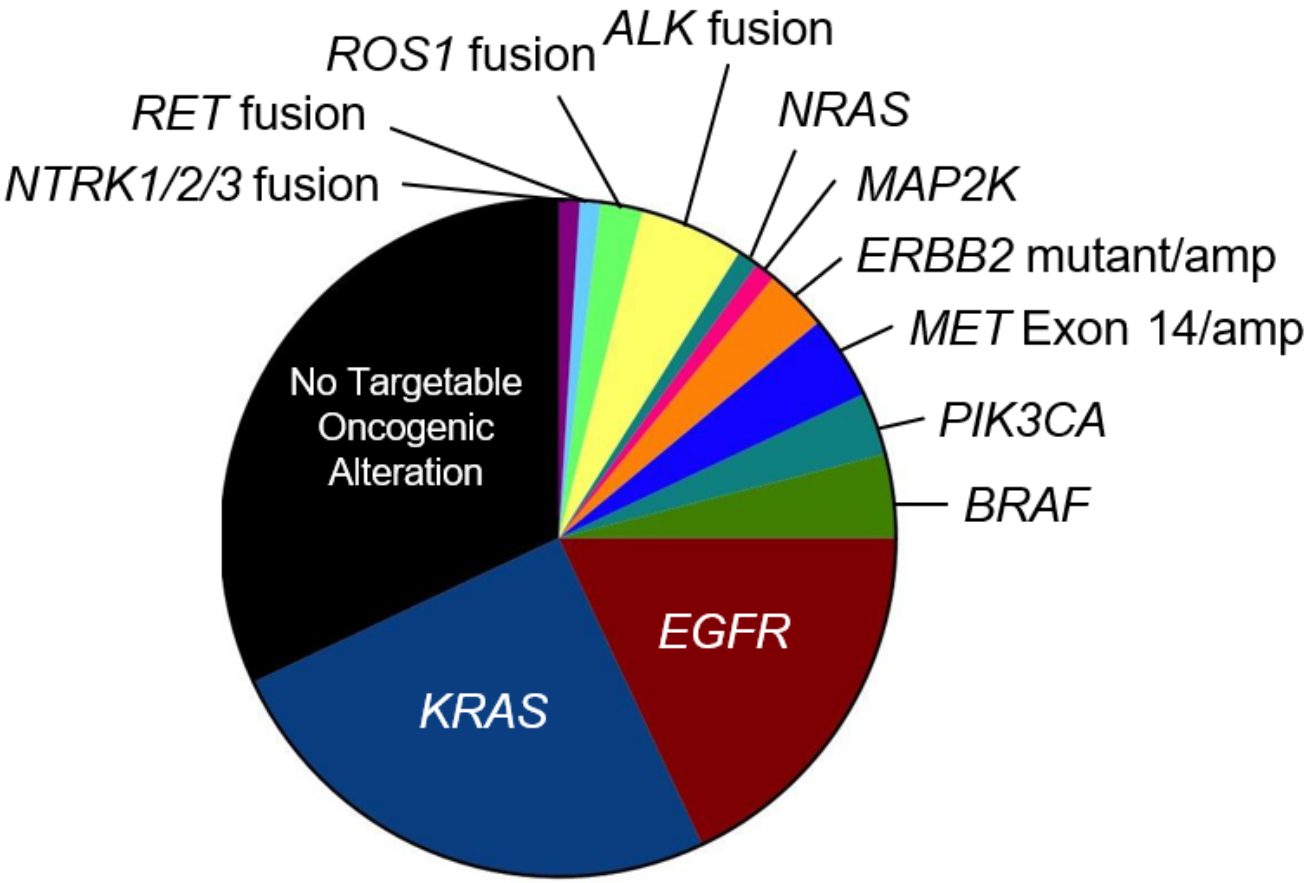
GenesisCare

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

FLASCO

OLA
Oncology Latin American Association

Precision Therapy for Lung Adenocarcinoma in 2023



Target	Approved Drug(s)
EGFR	Gefitinib, Erlotinib, Afatinib, Dacomitinib, Osimertinib, Erlotinib/Ramucirumab
EGFR Exon 20	Amivantamab, mobocertinib
ALK	Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib
ROS1	Crizotinib, Entrectinib
NTRK 1/2/3	Latrotrectinib, Entrectinib
RET	Selpercatinib, Pralsetinib
MET exon 14	Capmatinib, Tepotinib
BRAF V600E	Dabrafenib/Trametinib
KRAS G12C	Sotorasib, Adagrasib
HER-2	Trastuzumab deruxtecan

Epidermal Growth Factor Receptor Ex19del & L858R

GenesisCare

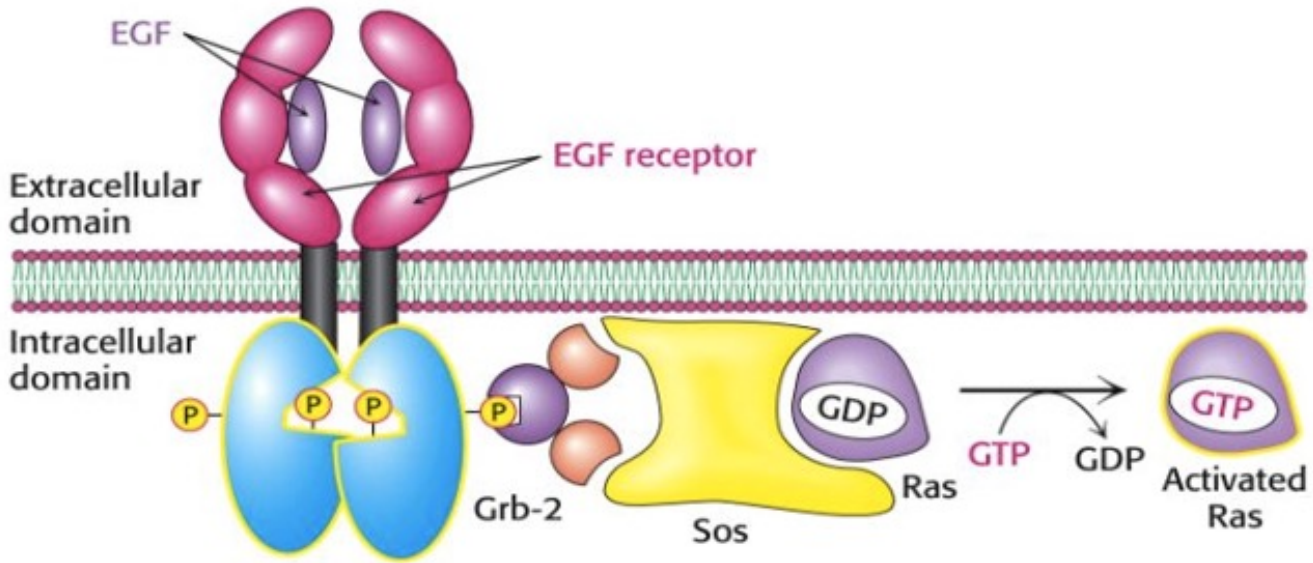
OLA

FLASCO

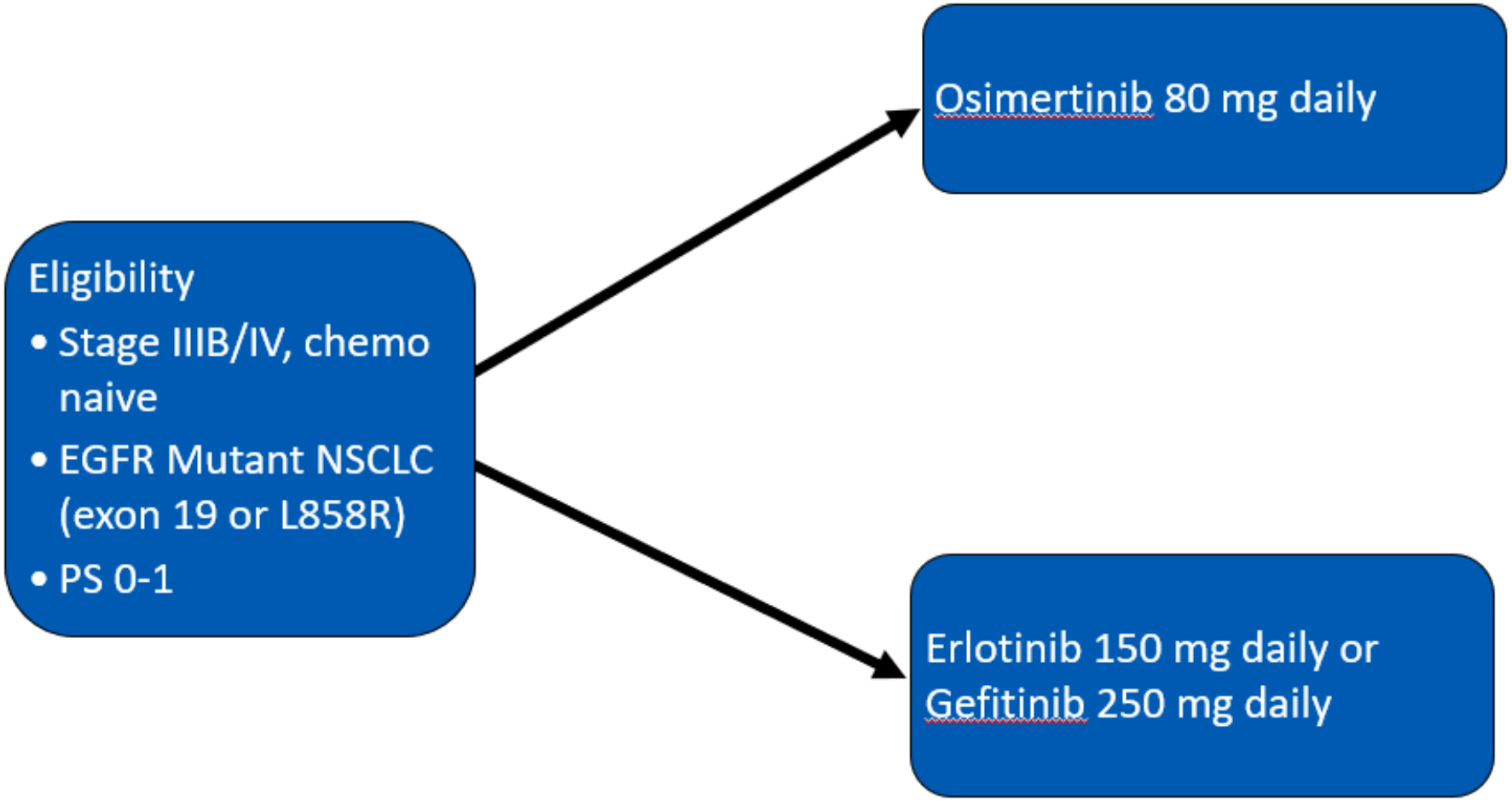
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

Epidermal Growth Factor Receptor

- Mutations seen 10-15% of Caucasians
  - 30-35% East Asians
- Strongly associated with epidemiology
  - Female
  - Never or light smokers (PY matters!)
- Exon 19 deletion and L8585R

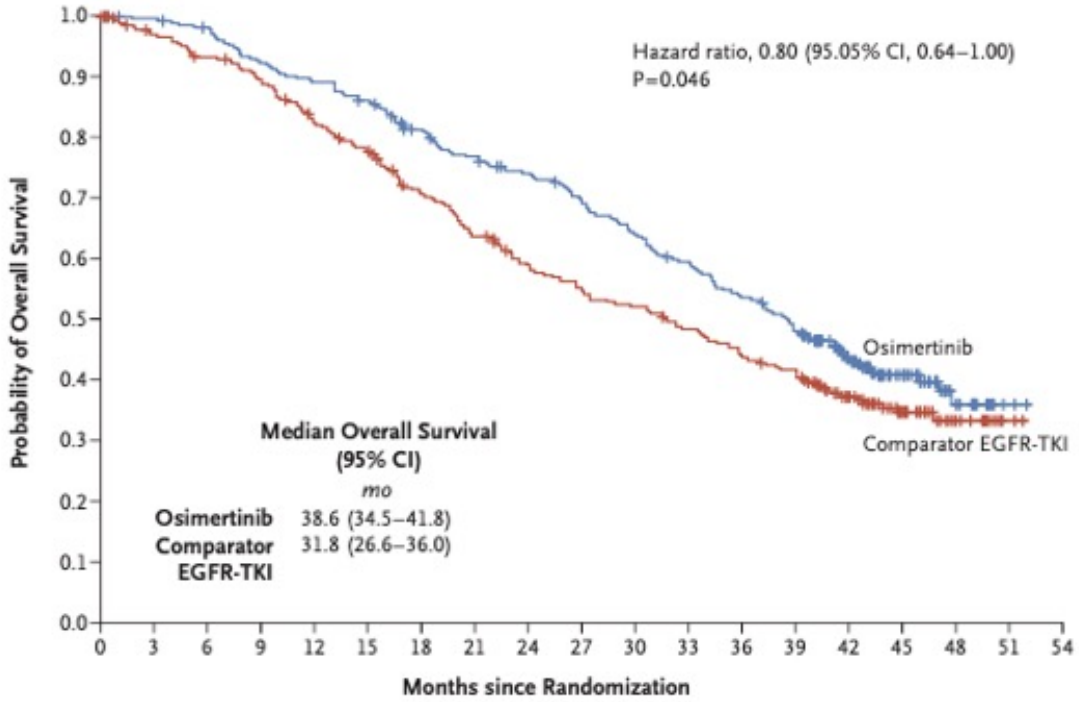


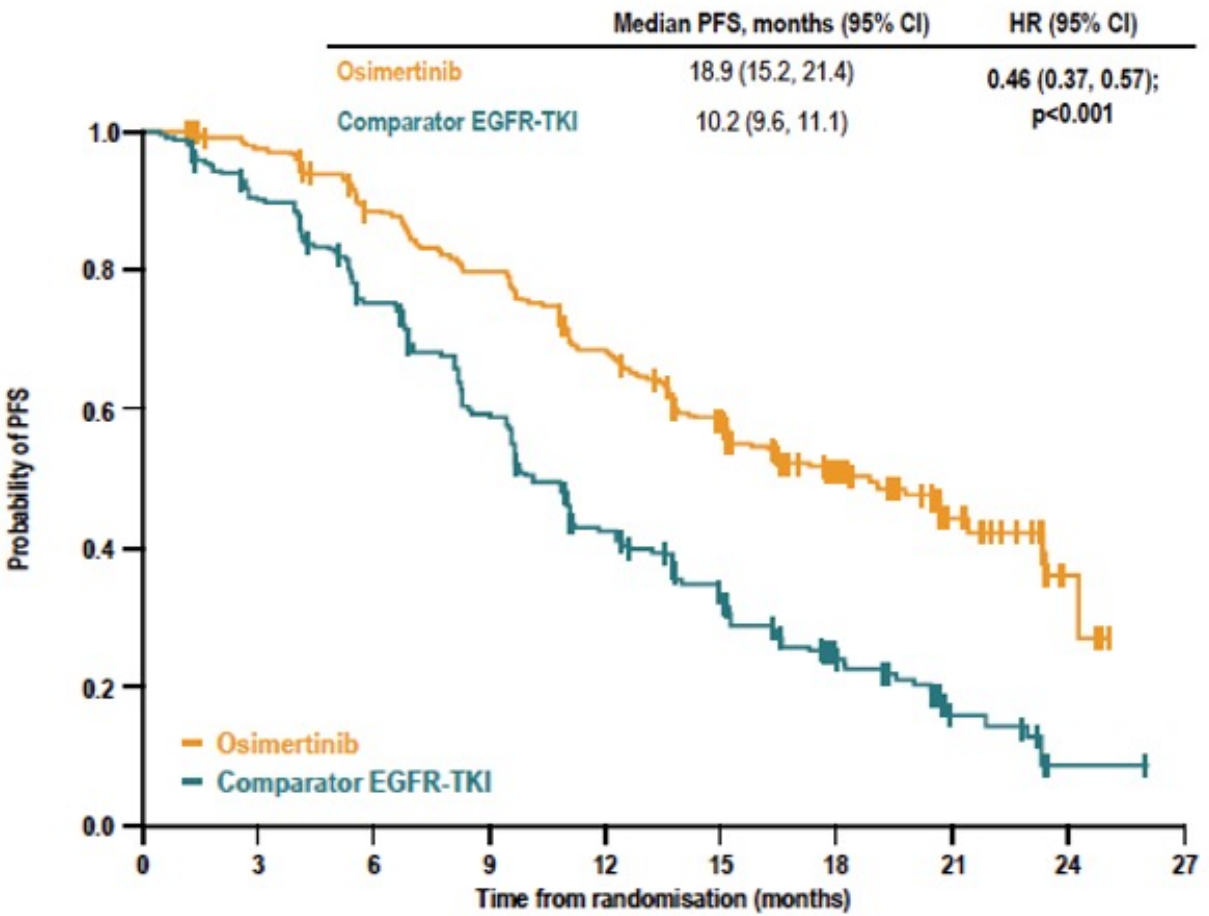
FLAURA: Osimertinib vs SOC in 1st Line EGFR Mutant NSCLC



Ramalingam et al ESMO 2017

FLAURA Results



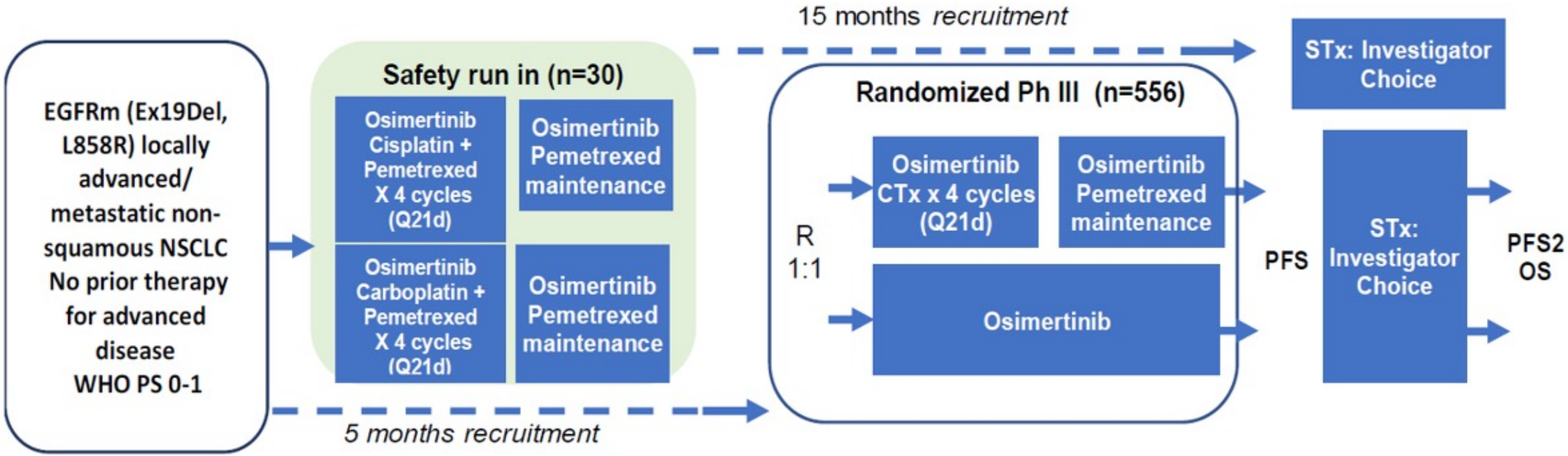


	Osimertinib	SOC
Rash	25%	48%
Diarrhea	58%	57%
Stomatitis	29%	20%

Ramalingam et al NEJM 2019.
Ramalingam et al ESMO 2019.

What's After FLAURA?

FLAURA2 Study Design



Stratification factors:

1) Central or local method for tissue testing for potential differences in EGFR mutation detection
2) Race Chinese/Asian vs. Non-Chinese/Asian vs. Non-Asian
3) Baseline performance status based on the WHO PS.

What's After Osimertinib Progression in the Real World Practice

GenesisCare

OLA

FLASCO

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

What Are We Doing In Real World Practice Post-Osimertinib Progression?

- Scant data from some studies
- Thoracic oncologist experience

RWP

- Research

RWP

Therapy Post-Progression on Osimertinib

1) Continue Osimertinib with Routine Surveillance for Asymptomatic Patients

- Patients best suited for this approach:
  - –No symptoms requiring palliation
  - –Growth in a single metastatic site
  - –"RECIST only progression", ie:19 to 24 mm
  - –No new metastases or site of metastases

- Plan routine follow-up imaging every 3 months

M. Kris. Hawaii Global Lung Cancer Summit 2022, July 6-9.

Therapy Post Progression on Osimertinib

RWP

2) Systemic Therapies Today

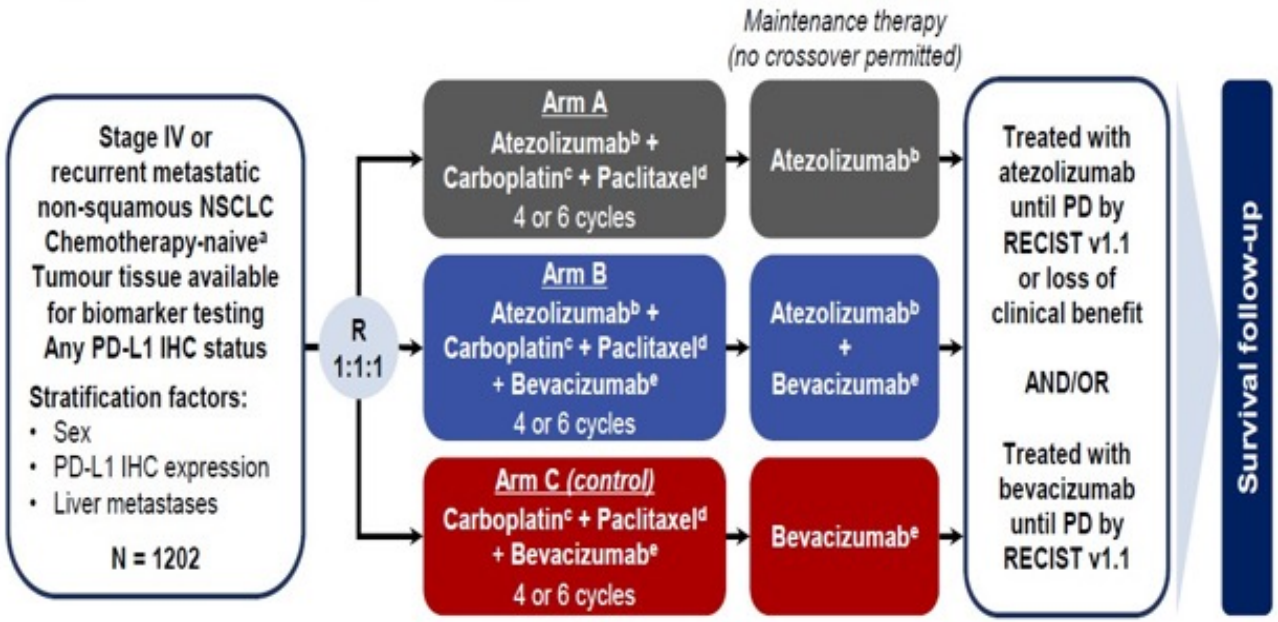
- Platinum-Based Chemotherapy
- Platinum-Based Chemotherapy +Bevacizumab
- Platinum-Based Chemotherapy +Bevacizumab + Atezolizumab
- Osimertinib 160 mg

M. Kris. Hawaii Global Lung Cancer Summit 2022, July 6-9.

Systemic Therapy
Platinum-based doublet + Bevacizumab + Atezolizumab (IO)

RWP

IMpower150 study design

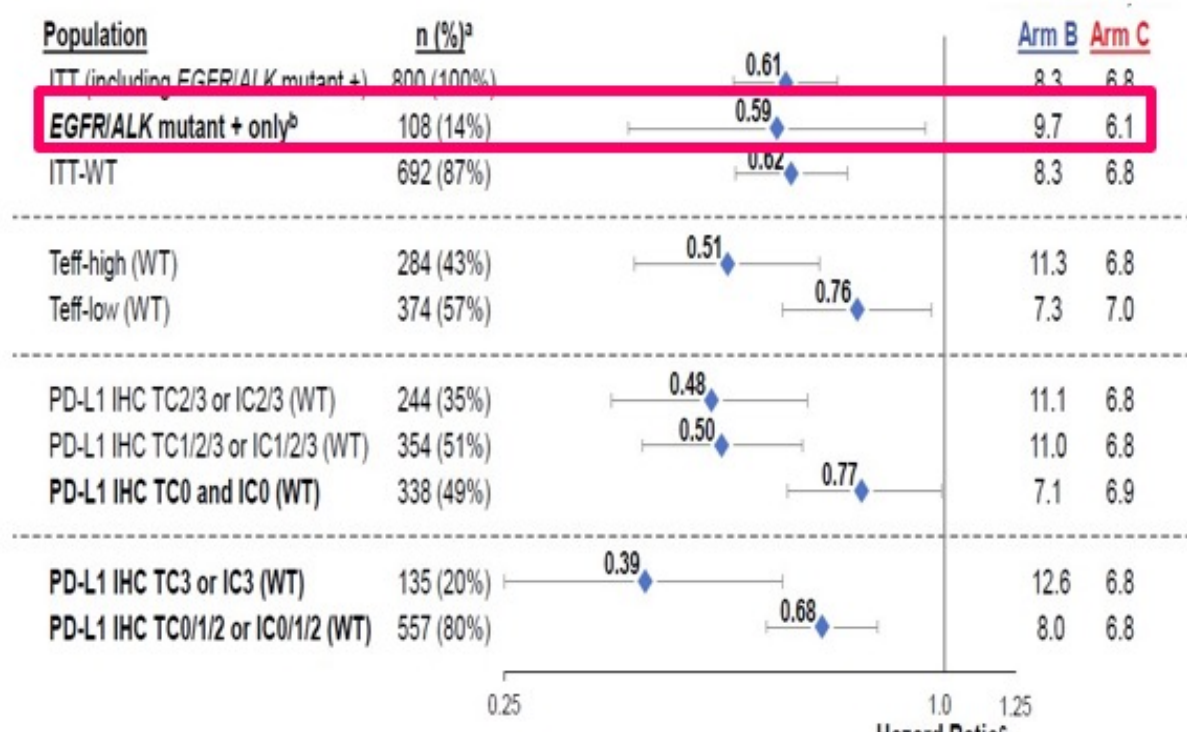


The principal question is to assess whether the addition of atezolizumab to Arm C provides clinical benefit

[a] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [b] Atezolizumab: 1200 mg IV q3w. [c] Carboplatin: AUC 6 IV q3w. [d] Paclitaxel: 200 mg/m² IV q3w. [e] Bevacizumab: 15 mg/kg IV q3w.

Reck M, et al. IMpower150 PFS analysis.

5



[a] ITT, *EGFR/ALK* mutants, and ITT-WT % prevalence out of ITT (n = 800); Teff % prevalence out those tested in ITT-WT (n = 658); PD-L1 IHC % prevalence out of ITT-WT (n = 692). [b] Patients with a sensitising *EGFR* mutation or *ALK* translocation must have disease progression or intolerance of treatment with one or more approved targeted therapies. [c] Stratified HRs for ITT, ITT-WT and Teff-high WT populations; unstratified HRs for all other subgroups.

Reck M, et al. IMpower150 PFS analysis.

18 Data cutoff: September 15, 2017

Therapy Post Progression on Osimertinib

T-Cell Checkpoint Inhibitors in Patients with *EGFR*-mutant NSCLC

- Patients with *EGFR*-mutant lung cancers excluded from pivotal clinical trials … scant data (CM-057, KN-010, OAK, etc).
- Tumors with *EGFR* mutations generally have a low mutational burden. PR in 4%, PD-L1 >50% in 11%, high level TILs in 2% (J Gainor. *Clin Cancer Res* 2016).
- Better PFS with docetaxel over nivolumab 2nd line (Borghaei et al. NEJM 2015).
- No consensus on what to do if a patient tumor has both *EGFRmut* and PD-L1 > 50%.
- Pulmonary toxicity with Osi + CPI.

M. Kris. Hawaii Global Lung Cancer Summit 2022, July 6-9.

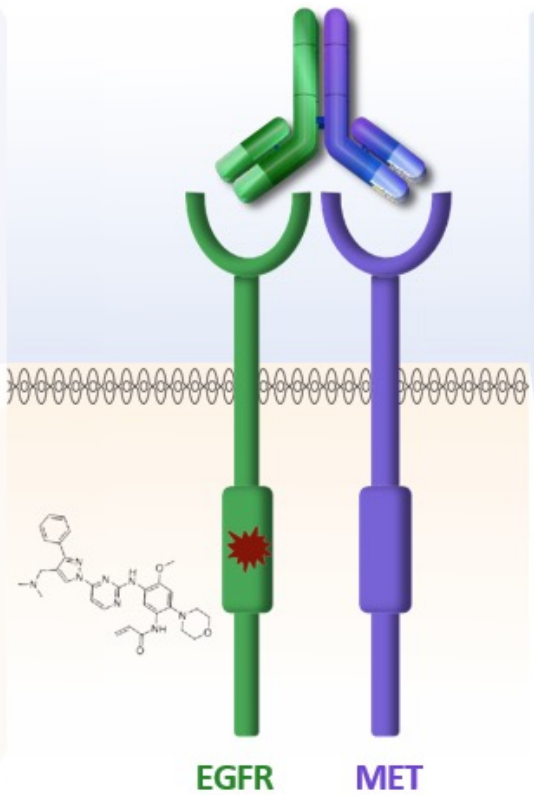
Amivantamab and Lazertinib

Amivantamab (am-e-van-tuh-mab)

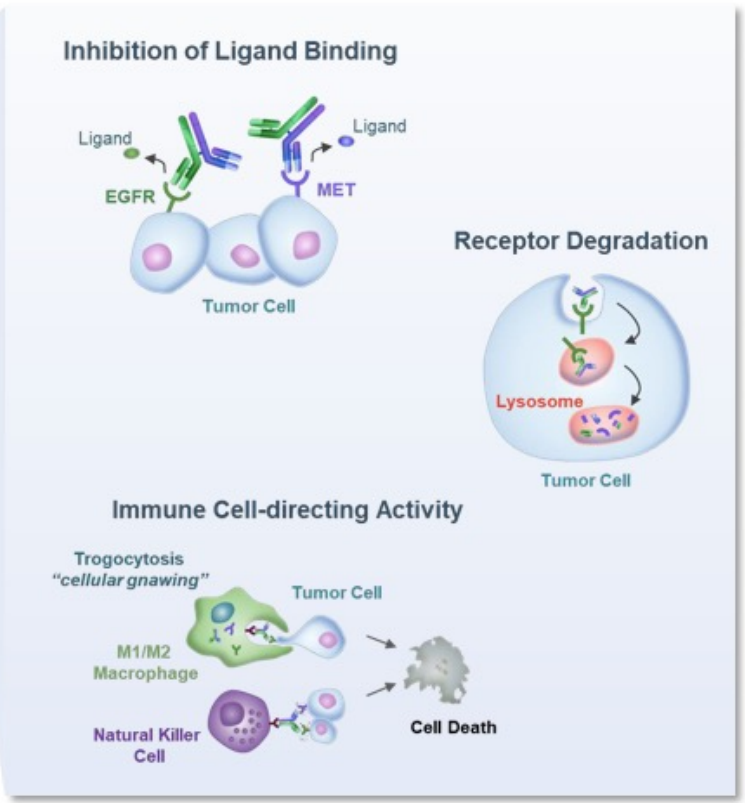
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules

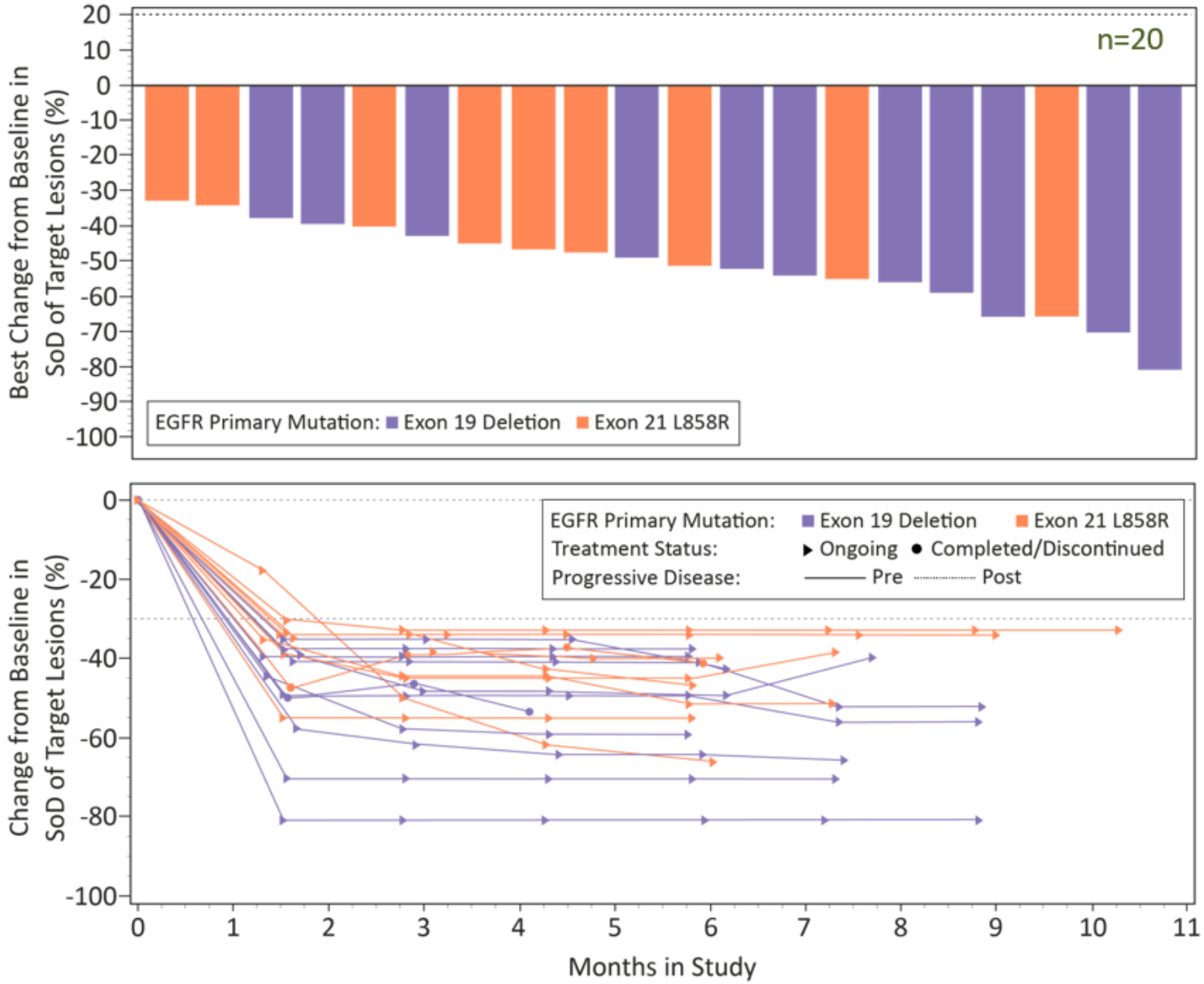


Amivantamab MOA



Cho et al. ASCO 2021

Combination Efficacy in Treatment-naïve Patients



- **ORR: 100% (95% CI, 83 – 100)**
  - 20 PR
- **CBR: 100% (95% CI, 83 – 100)**
- **mDOR: not estimable**

- **Median follow-up**: 7 mo (4 – 10)
- **Median treatment duration**: 7 mo (3 – 10)

Rapid time to first response: Median 1.5 months (1.2 – 2.6)

Responses w ere assessed by investigator per RECIST v1.1. mDOR, median duration of response.

Cho et al. ESMO 2019

Phase 3 MARIPOSA Study (NCT04487080)

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- EGFR Exon19del or L858R mutation

Stratification

- EGFR mutation (Exon19del/L858R)
- Asian race (yes/no)
- Brain metastases (yes/no)

Randomization (2:2:1; N~1000)

Arm A (n~400)	**Amivantamab** 1050/1400 mg **Lazertinib** 240 mg QD
Arm B (n~400)	**Osimertinib** 80 mg QD
Arm C (n~200)	**Lazertinib** 240 mg QD

Arms B & C are double-blinded

Primary Endpoint:
(Arm A vs Arm B)

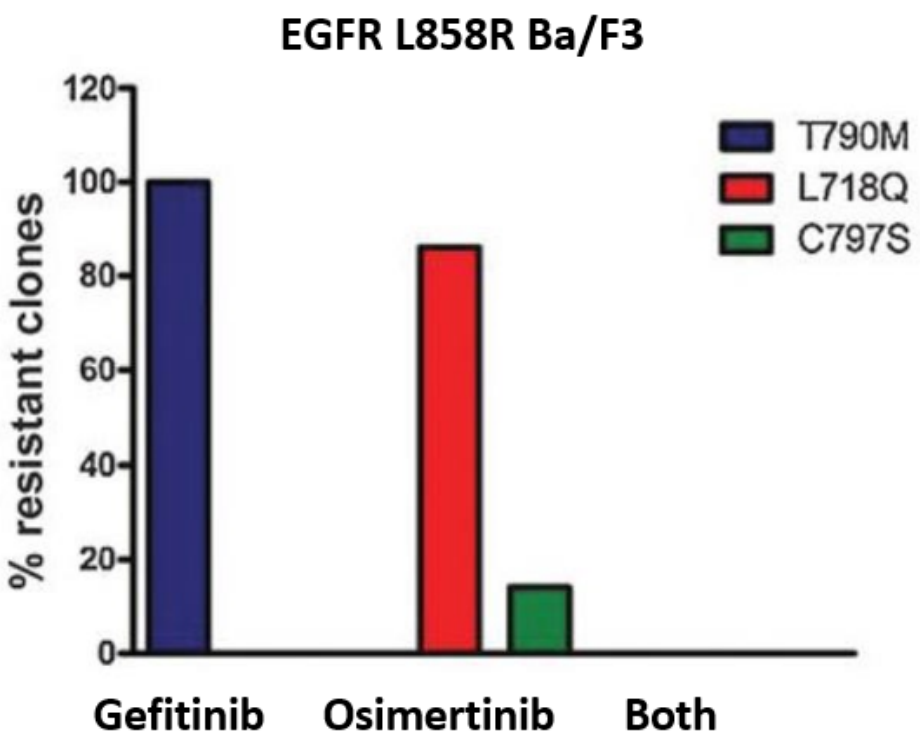
- PFS by BICR

Secondary Endpoint:
(Arm A vs Arm B)

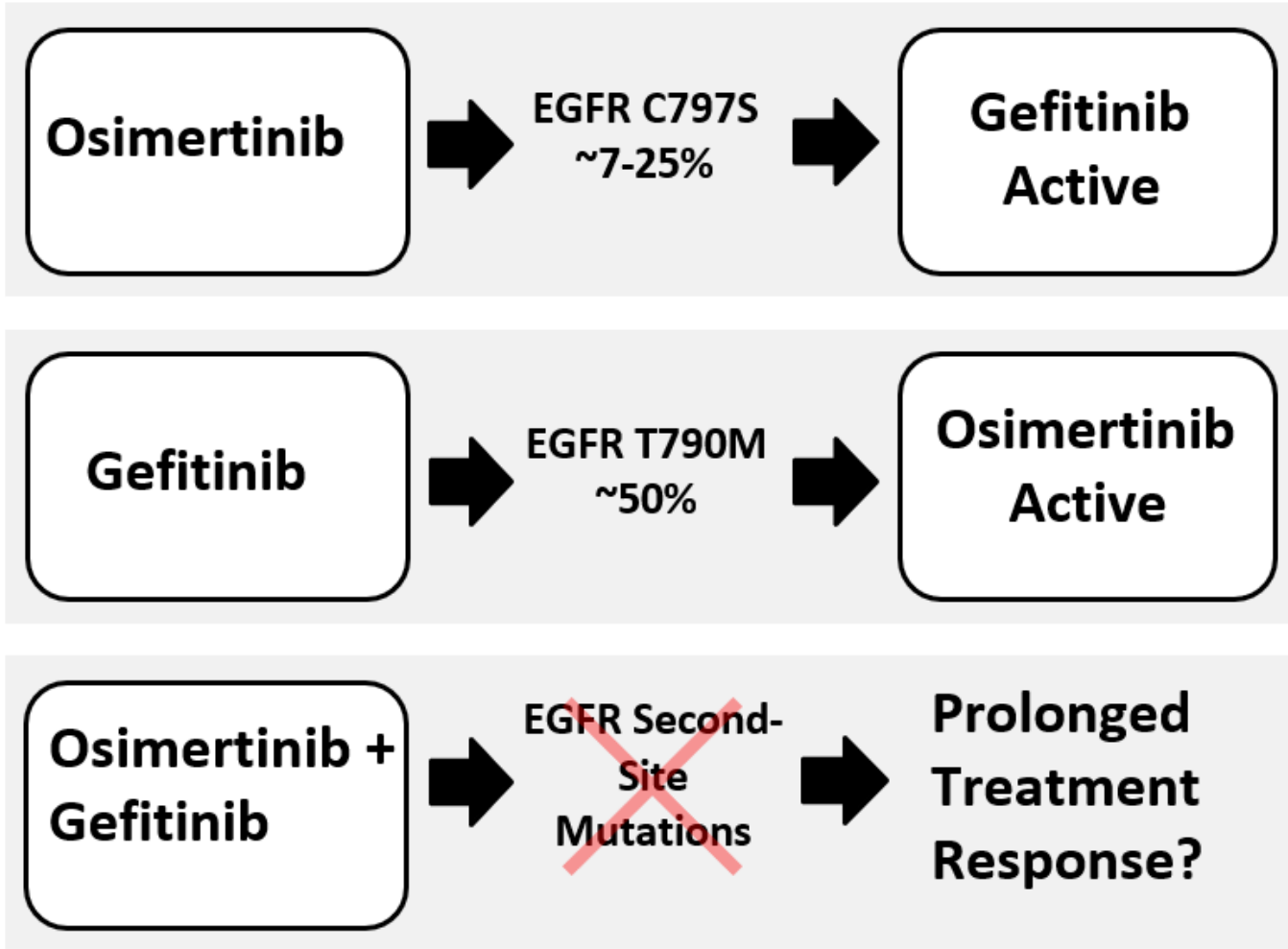
- Overall survival
- Objective response rate
- Duration of response
- PFS2
- Time to symptomatic progression
- Intracranial PFS
- Safety

BICR, blinded independent central review; PFS, progression-free survival; PFS2, PFS after first subsequent therapy; QD, once a day

In preclinical models combined treatment with osimertinib + gefitinib prevented development of acquired second-site EGFR resistance mutations

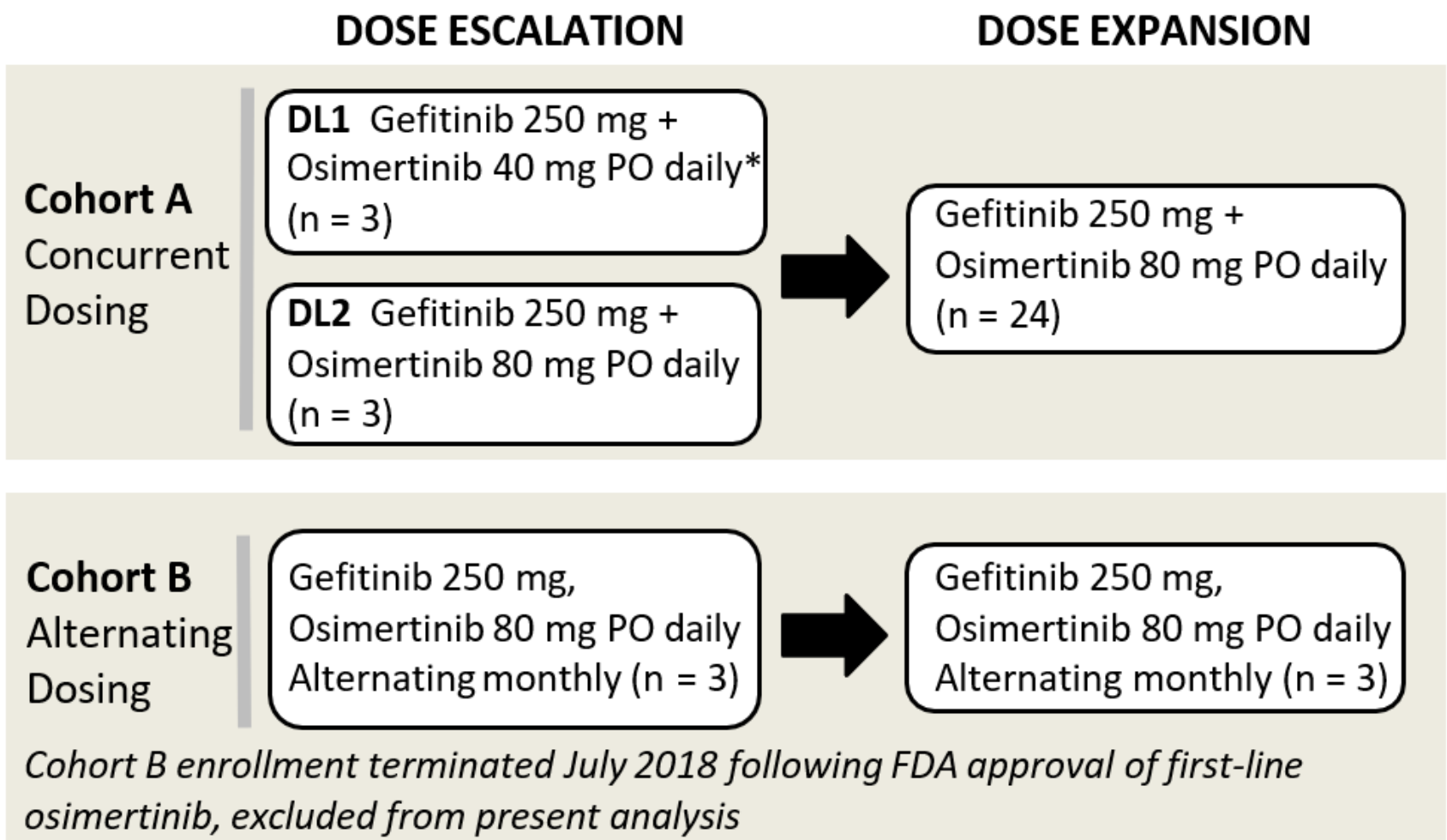


Adapted from Ercan et al. Clin Can Res. 2015. 21(17):3913-23



Rotow et al. ASCO 2020

Study Schema – Osimertinib & Gefitinib for treatment naïve EGFR mutant NSCLC



Primary Endpoints

- Dose Escalation: MTD
- Dose Expansion: Feasibility, defined as receipt of combination therapy for ≥ 6 28-day cycles

Secondary Endpoints

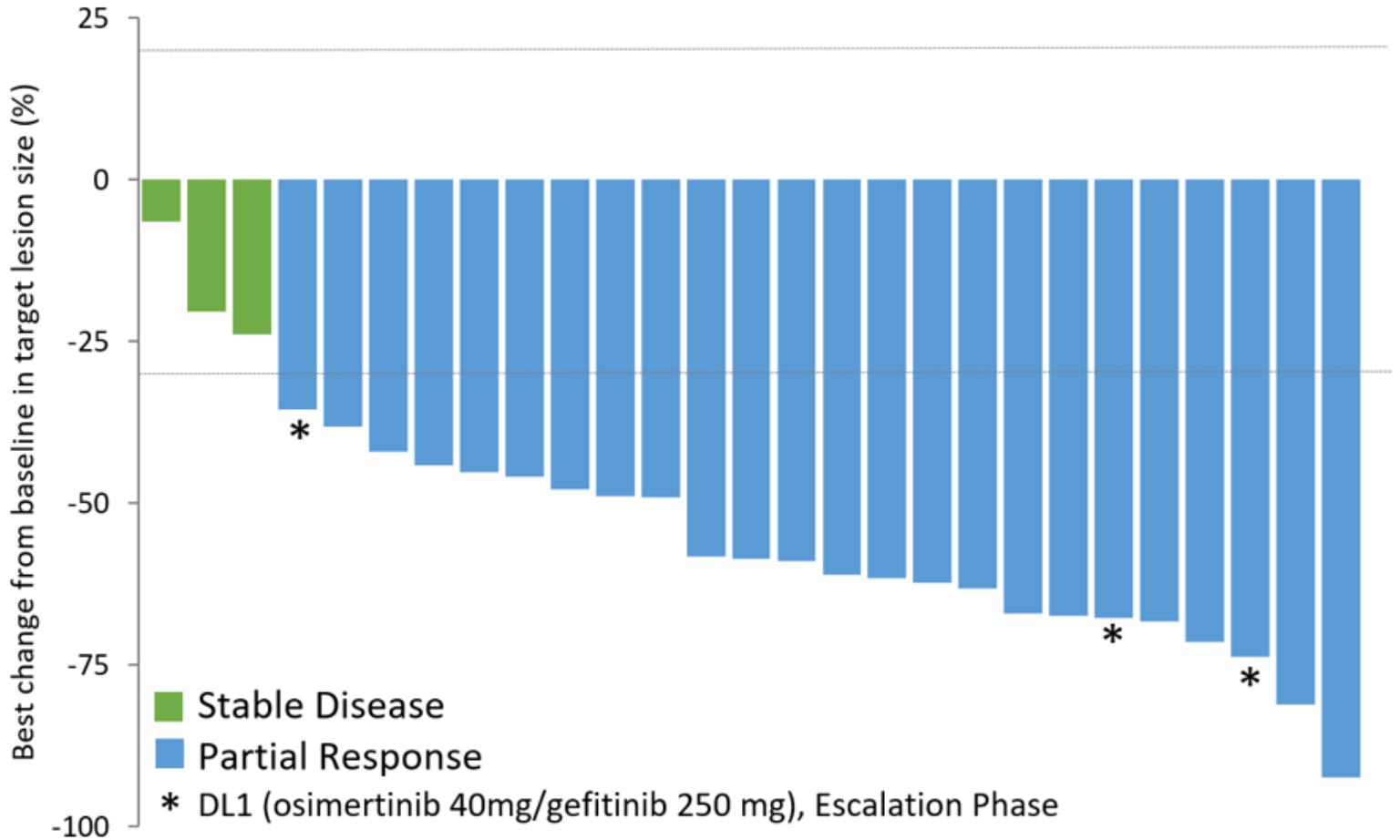
- Rate of G3-5 TRAEs
- ORR per RECIST 1.1
- Progression free survival
- Overall survival
- cfDNA clearance
- Genomic alterations at progression

*Intrapatient dose escalation to osimertinib 80 mg po daily following study amendment

Rotow et al. ASCO 2020

NCT03122717

Efficacy of Osimertinib/Gefitinib in EGFR Mutant NSCLC



Endpoint (n=27)	
Objective Response rate - % of patients (95% CI)*	88.9% (71.9% - 96.1%
Disease Control Rate - % of patients (95% CI)	100% (87.5% - 100.0%)
Type of Response – n(%)	
Complete	0 (0%)
Partial	24 (88.9%)
Stable Disease	3 (11.1%)
Progression	0 (0%)
Median Depth of Response – % (range)	58.6% (6.5% - 94.2%)

*All responses confirmed

Although sample size is still small; no EGFR secondary mutations have been identified at the time of acquired resistance

Rotow et al. ASCO 2020

12th Annual WCS™
WINTERCANCER SYMPOSIUM
MARCH 3–5, 2023
WYNDHAM GRAND RIO MAR
PUERTO RICO

PROGRAM DIRECTORS:
William Caceres, MD
Luis E. Raez, MD, FACP, FCCP
Edgardo S. Santos Castillero, MD, FACP

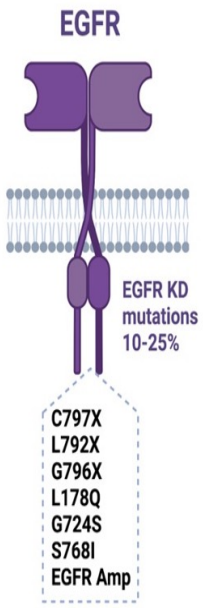
Accredited by: MEC THE MEDICAL EDUCATOR CONSORTIUM | FLASCO | CANCER EXPERT NOW | MECC GLOBAL MEETINGS MEETINGS • EVENTS • CONFERENCE • COORDINATORS

Resistant Mechanisms

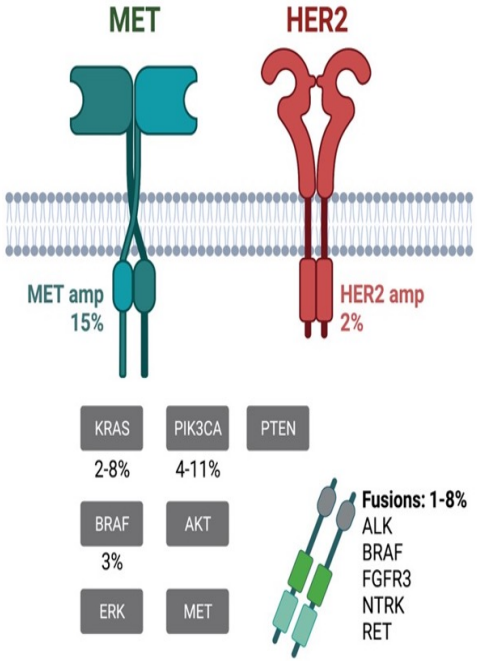
GenesisCare | OLA Oncology Latin American Association | FLASCO | FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

Novel Approaches in EGFR-Mutant Lung Cancer

On-Target resistance

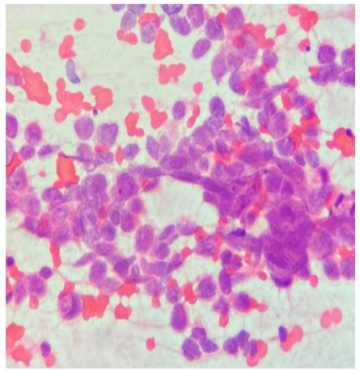


Bypass resistance



Histologic transformation

Small cell lung cancer: 5-15%



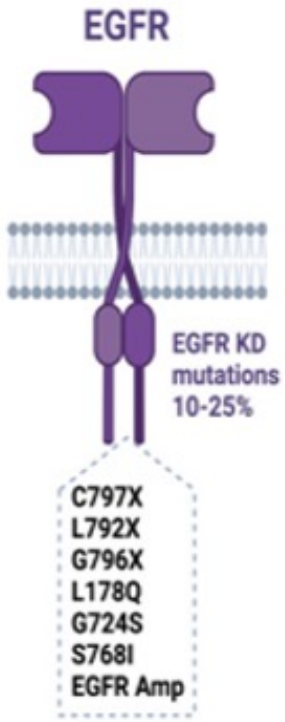
TP53 mutations
RB1 mutations

Apoptotic defects: BIM Deletion
Epigenetic modifications

A. Passaro et al. Nature Cancer 2021
A. Leonetti et al. British Journal of Cancer 2019

Osimertinib and Necitumumab in EGFR+ NSCLC

On-Target resistance



Osimertinib 80mg + Necitumumab 800mg D1, D8 q21 days

Dose Escalation of Osimertinib and Necitumumab in Advanced EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (1st-3rd gen)

MTD

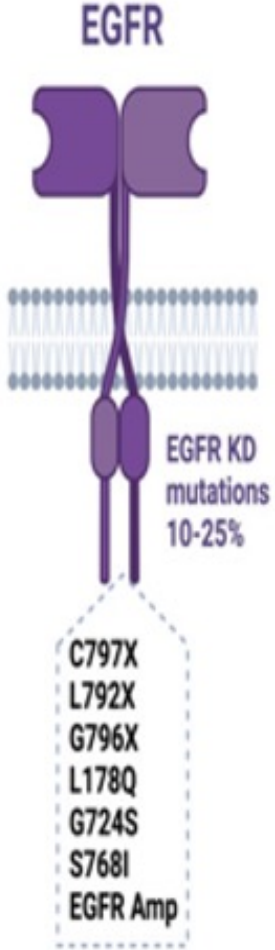
	Confirmed PR	mPFS (95%CI)	
Cohort A: T790M negative, PD on afatinib, gefitinib, erlotinib as last treatment (N=18)	3 **(16%)**	**3.9** (1.3 - 5.7)	
Cohort B: EGFR T790M negative, PD on osimertinib or other 3rd gen EGFR-TKI (N=18)	0 **(0%)**	**1.5** (1.2 - 2.6)	3rd Generation TKI T790M-
Cohort C: EGFR T790M positive, PD on osimertinib or other 3rd gen EGFR-TKI (N=18)	2 **(11%)**	**3.9** (2.4 - 5.6)	3rd Generation TKI T790M+
Cohort D: EGFR Exon 20 Insertion NSCLC with PD on platinum-based chemotherapy and no prior 3rd gen/Exon 20 ins TKI (N=18)	3 (16%)	6.9 (4.1 - 11.4)	
Cohort E: EGFR mut NSCLC with PD on first line osimertinib (N=18)	3 **(16%)**	**2.3** (1.4 - NR)	3rd Generation TKI 1st line

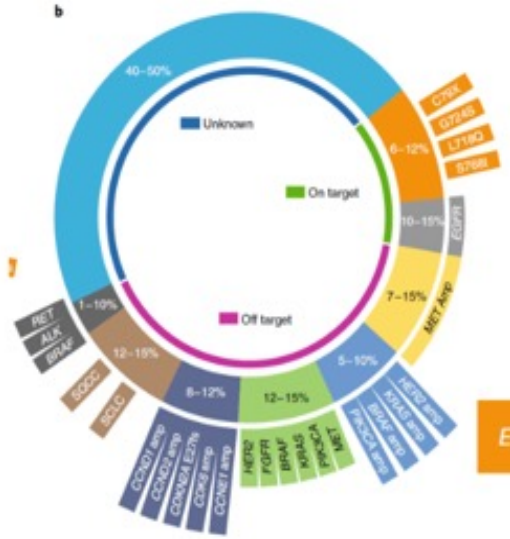
- Primary pre-specified efficacy endpoint for expansion cohorts ≥ **3/18 pts with confirmed PR** per RECIST per cohort.

JW Riess et al. 2022 ASCO, abstr 9014.

EGFR + EGFR – osimertinib + gefitinib: Inhibit On-Target EGFR Resistance?

On-Target resistance



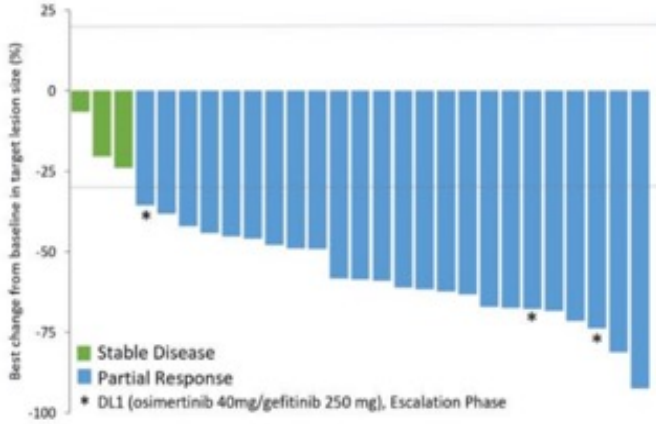


Resistance to First-Line Osimertinib

6-12% 'On-Target'

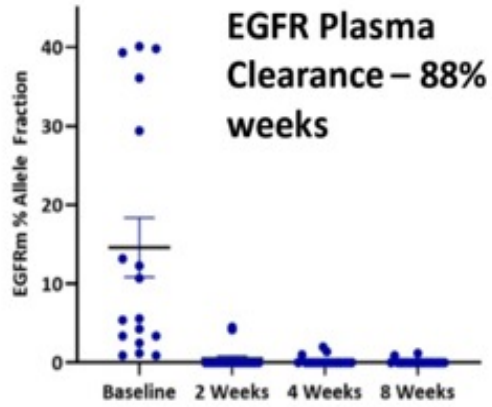
EGFR mutation	*EGFR* amplification	*MET* amplification	Other acquired amplifications	Acquired mutations	Cell cycle gene alterations	Histological transformation	Fusion

Single-arm study (n = 27 evaluable), phase I/II



Endpoint (n=27)	
Objective Response rate - % of patients (95% CI)*	88.9% (71.9% - 96.1%
Disease Control Rate - % of patients (95% CI)	100% (87.5% - 100.0%)
Type of Response - n(%)	
Complete	0 (0%)
Partial	24 (88.9%)
Stable Disease	3 (11.1%)
Progression	0 (0%)
Median Depth of Response - % (range)	58.6% (6.5% - 94.2%)

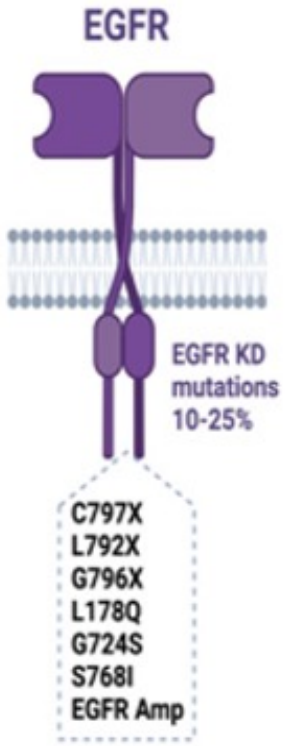
*All responses confirmed



EGFR Plasma Clearance – 88% at 2 weeks

Rotow et al. ASCO 2020. Abstract #9507; Passaro et al. Nature Cancer. 2021;2:377

On-Target resistance



Amivantamab and Lazertinib

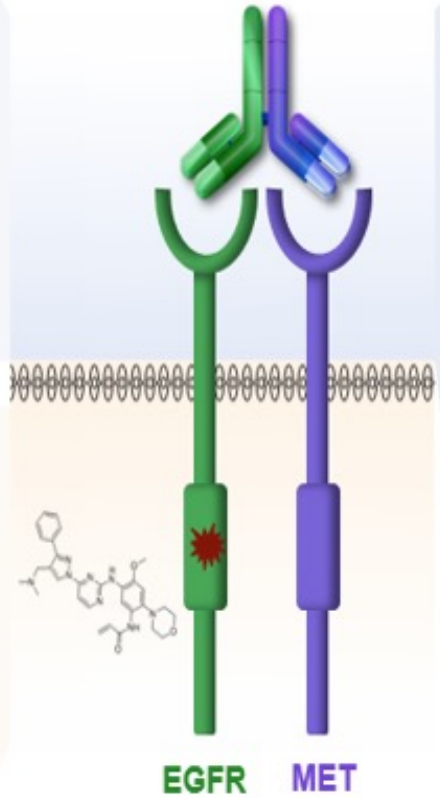
CHRYSALIS Study

Amivantamab (am-e-van-tuh-mab)

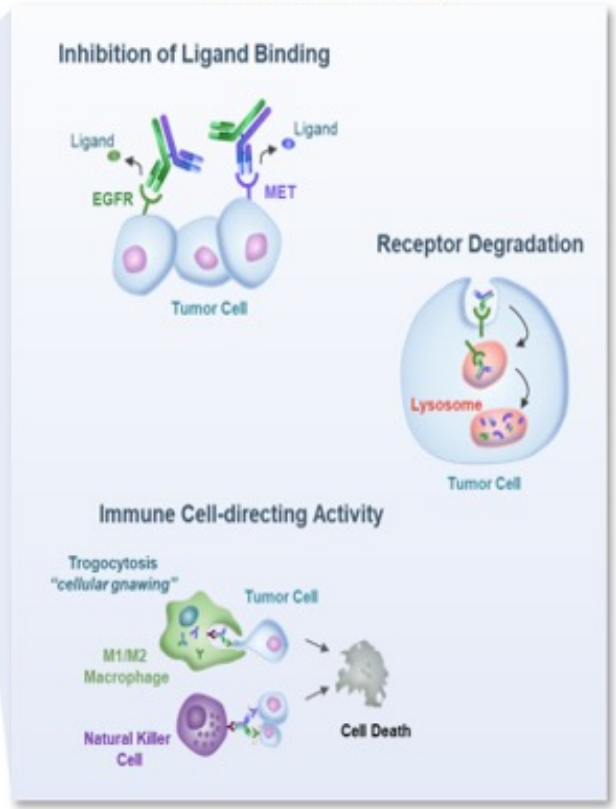
- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules



Amivantamab MOA



BC Cho et al. 2021 ASCO, abstr 9006.

CHRYSALIS Phase 1 Study Design: Combination Cohort (NCT02609776)

Key Objectives

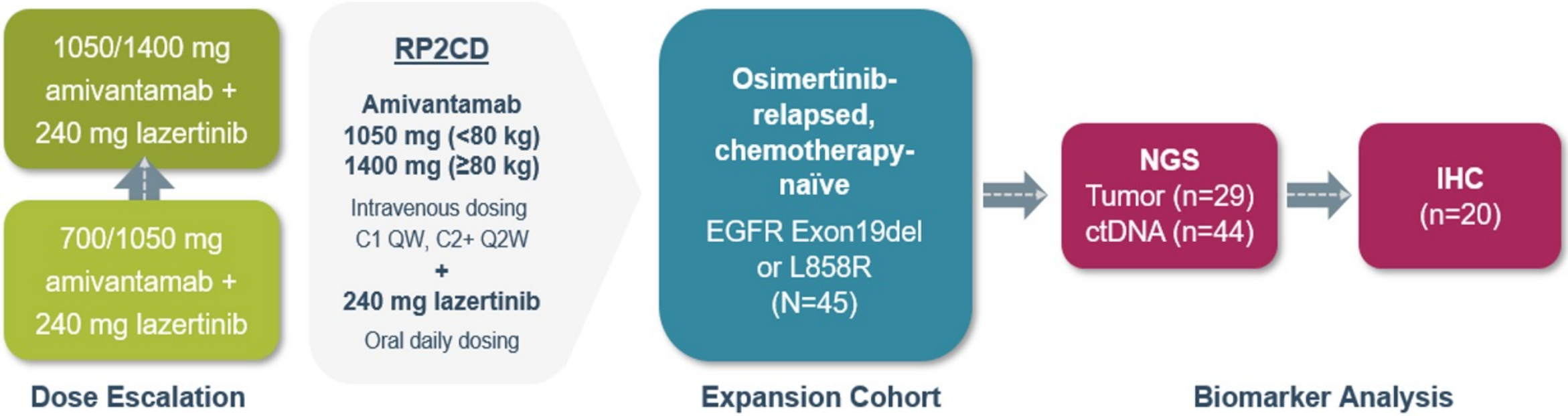
- Establish RP2CD
- Safety and efficacy at RP2CD

Key Eligibility Criteria

- Metastatic/unresectable NSCLC
- Measurable disease (expansion cohort)
- EGFR Exon19del or L858R mutation

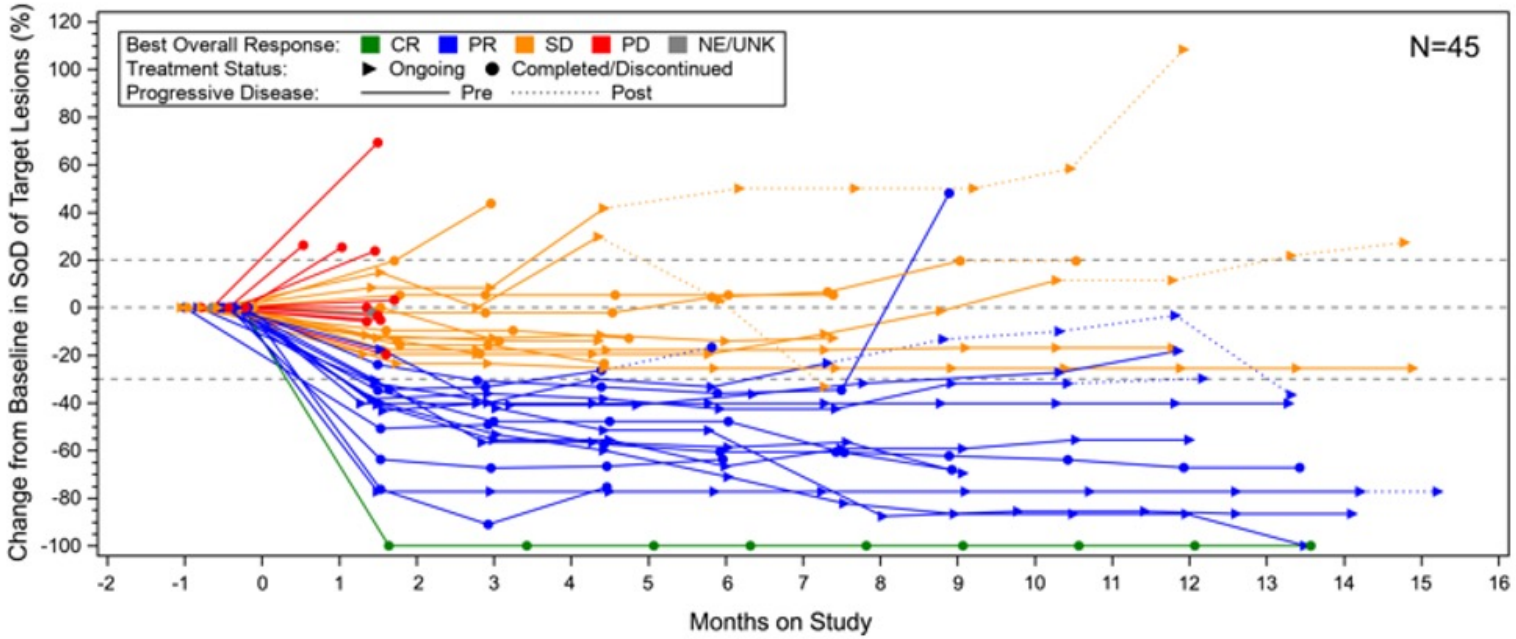
Biomarker Analysis[a]

- NGS of pretreatment tumor biopsy and ctDNA collected prospectively
- IHC for EGFR/MET expression



This presentation provides updated results with longer follow-up from the ESMO 2020 oral presentation (Cho *Ann Oncol* 31:S813 Oral #1258O). [a]≥1 alteration detected in 42/44 ctDNA and 29/45 tumor NGS analyses.
C, cycle; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; QW, weekly; Q2W, every 2 weeks; RP2CD, recommended phase 2 combination dose

Durable Responses Observed with Amivantamab + Lazertinib with Manageable Safety



Investigator-assessed Response (N=45)
mF/U: 11.0 months (range, 1.0–15.0)
mDOT: 5.6 months (range, 0.5–14.8)

ORR	36% (95% CI, 22–51)
mDOR, months	9.6 (95% CI, 5.3–NR)
DOR ≥6 months	69%
CBR	64% (95% CI, 49–78)
mPFS, months	4.9 (95% CI, 3.7–9.5)

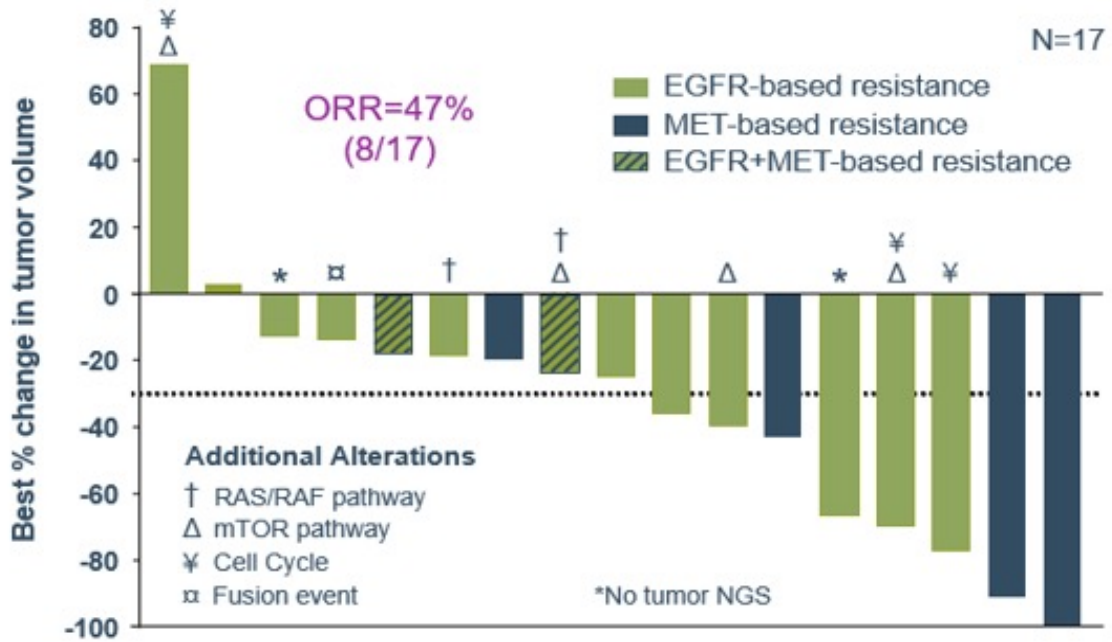
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

19 Apr 2021 clinical cutoff. Four patients did not have postbaseline disease assessments and are not included in the plot. [1]Cho *Ann Oncol* 31:S813 Oral #1258O.
AE, adverse event; CBR, clinical benefit rate (CR, PR, or SD ≥11 weeks); CR, complete response; IRR, infusion-related reaction; mDOR, median duration of response; mDOT, median duration of treatment; mF/U, median follow-up; mPFS, median progression-free survival; NE, not evaluable; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of target lesion diameters; UNK, unknown

BC Cho et al. 2021 ASCO, abstr 9006.

Response Among Patients with Identified EGFR/MET-based Resistance

- 17 of 45 patients were identified with either EGFR/MET-based resistance by NGS[a] (ctDNA/tissue)
- ORR in this subgroup was 47%, mDOR was 10.4 months, CBR was 82%, and mPFS was 6.7 months



Resistance[b]	Alterations[c]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)
Additional	PIK3CA E542X (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

[a]Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS; [b]EGFR amp (CNV ≥7) and MET amp (CNV ≥3) were based on tumor NGS; other amps were based on tumor NGS (CNV ≥7) or ctDNA NGS (CNV ≥3). Single nucleotide variants, insertion/deletions, and insertion call threshold was ≥1% allele frequency with >250 reads. [c]Eight patients had ≥1 alteration. Amp, amplification; CNV, copy number variation

BC Cho et al. 2021 ASCO, abstr 9006.

CHRYSALIS-2 (ClinicalTrails.gov Identifier: NCT04077463)
Study Design

Post-Osi Progression

Dose Expansion Cohorts

RP2CD: Lazertinib 240 mg PO +
Amivantamab 1050 mg (1400 mg for ≥80 kg) IV

Cohort A: EGFR ex19del or L858R
Post-osimertinib and platinum-based chemotherapy (n=162)

Cohort B: EGFR ex20ins
Post-standard of care and platinum-based chemotherapy

Cohort C: Uncommon EGFR mutations
Treatment naïve or post-1st or 2nd generation EGFR TKI

Cohort D: EGFR ex19del or L858R
Post-osimertinib, chemotherapy naïve, biomarker validation

Endpoints

- Overall response rate (primary)
- Duration of response
- Clinical benefit rate[a]
- Progression-free survival
- Overall survival
- Adverse events

Here we present updated **safety** and **efficacy** results
of the **amivantamab and lazertinib combination** from **fully enrolled Cohort A**

[a]Percentage of patients with confirmed response or durable stable disease (duration of ≥11 weeks).

EGFR, epidermal growth factor receptor; ex19del, exon 19 deletion; ex20ins, exon 20 insertion; IV, intravenous; PO, per oral; RP2CD, recommended phase 2 combination dose; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

Demographics and Baseline Characteristics

Post-Osi Progression

Characteristic, n (%)	n=162
Median age, years (range)	61.5 (31–83)
Male / female	57 (35) / 105 (65)
Race	
White	42 (26)
Asian	99 (61)
Black	1 (0.6)
Not reported	20 (12)
ECOG PS 0 /1	49 (30) / 113 (70)
Brain metastases at baseline[a]	66 (41)
Untreated	30 (19)
Treated	36 (22)

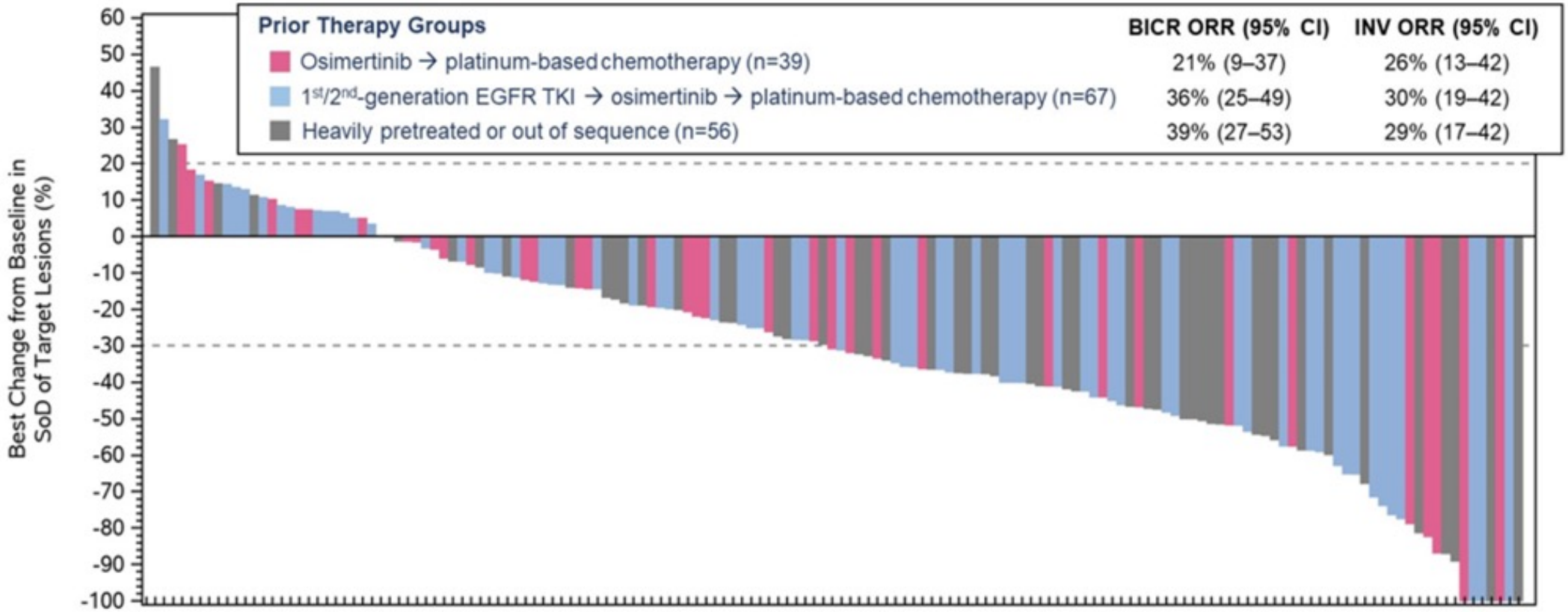
Characteristic, n (%)	n=162
Smoking history	
Non-smoker	111 (69)
Smoker	49 (30)
Unknown	2 (1)
Median number of prior therapy lines (range)	3 (2–14)
2–3	117 (72)
≥4	45 (28)
Prior therapy regimens	
Frontline osimertinib → platinum-based chemo	39 (23)
1st/2nd-gen EGFR TKI → osimertinib → platinum-based chemo	67 (42)
Heavily pretreated or out of sequence	56 (35)

[a]Study initially allowed stable/asymptomatic treated or untreated brain metastases at baseline and was later amended to allow for treated brain metastases only.

Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

CA Shu et al. ASCO 2022

Best Antitumor Response and ORR by Prior Therapy Group

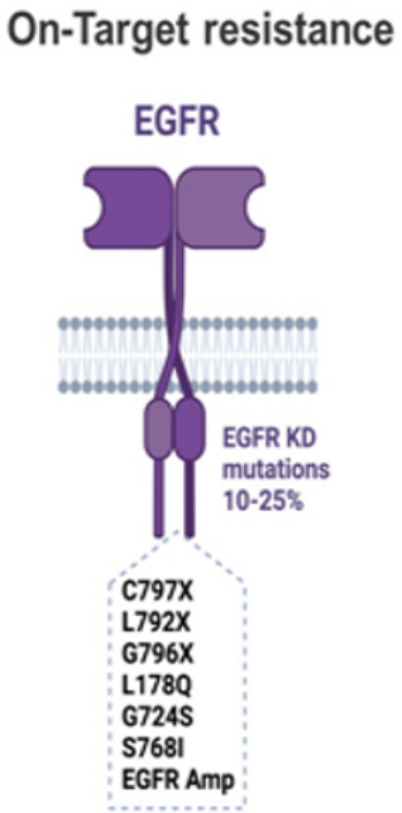


- 10 efficacy-evaluable patients did not have any evaluable post-baseline target lesion measurements

BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; INV, investigator-assessed; ORR, overall response rate; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

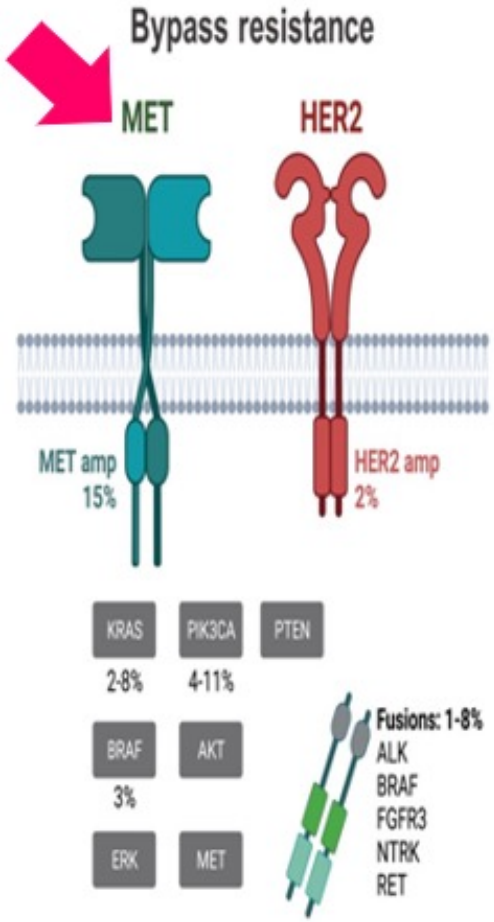
CA Shu et al. ASCO 2022

Overcoming "On" Target Resistance



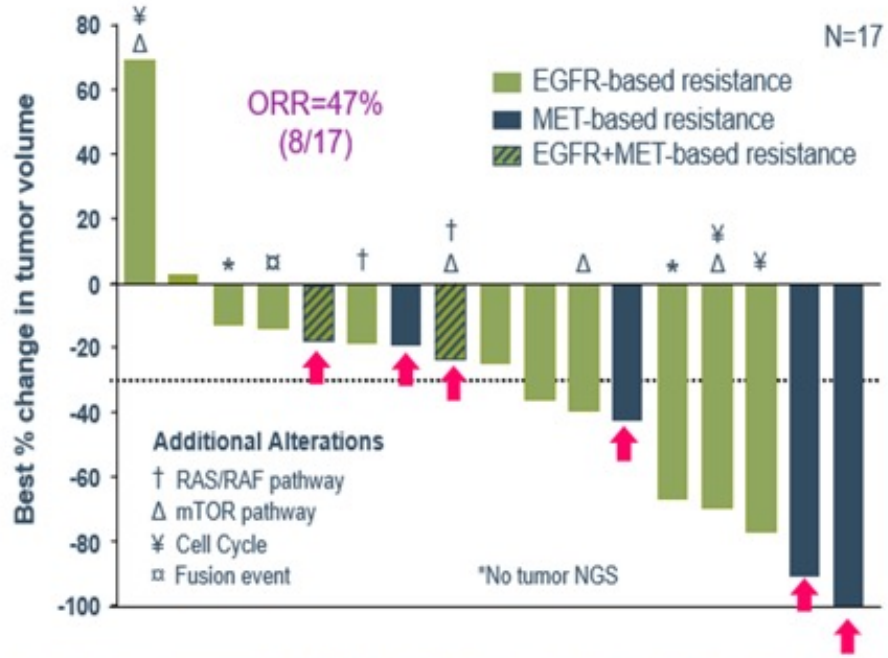
- Continue the same EGFR TKIs no matter what.
- Develop better EGFR inhibitors (4th generation; BLU-701, BLU-945)
- Combination therapies:
  - → 1st or 2nd generation EGFR TKIs + 3rd generation EGFR TKIs
  - → 3rd generation EGFR TKIs + 4th generation TKIs
  - → EGFR TKIs + mAB (eg, Lazertinib + Amivantamab)
  - → EGFR TKIs + agnostic agents (eg, Patritumab)
  - → Non-EGFR TKIs + mAB (eg, Brigatinib + Cetuximab)

CHRYSALIS Study



Response Among Patients with Identified EGFR/MET-based Resistance

- **17 of 45** patients were **identified with either EGFR/MET-based resistance** by NGS[a] (ctDNA/tissue)
- **ORR in this subgroup was 47%,** mDOR was 10.4 months, CBR was 82%, and mPFS was 6.7 months

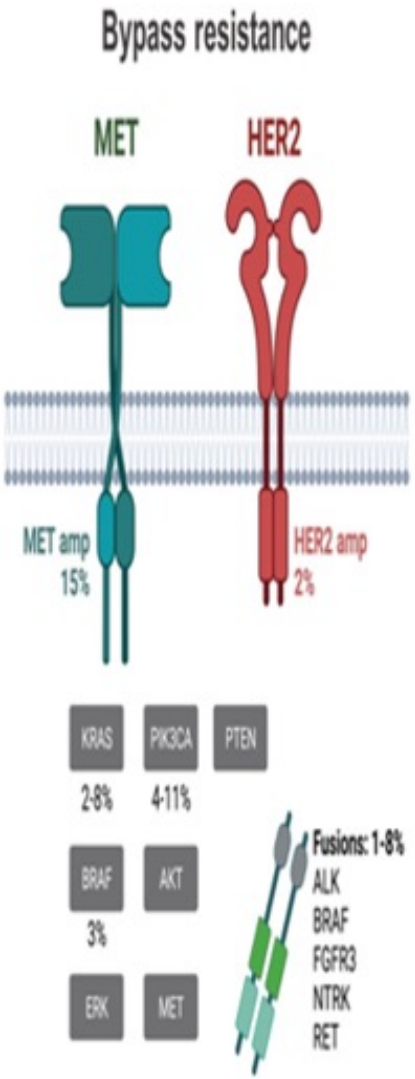


Resistance[b]	Alterations[c]	
EGFR-based	C797S (n=7) Amp (n=3) L718X (n=3) G724S (n=2)	L792H (n=1) G796S (n=1) E709K (n=1)
MET-based	Amp (n=5)	METex14 (n=1)
Additional	PIK3CA E542X (n=2) CCNE1 Amp (n=1) PIK3CA Amp (n=1) CCND1 Amp (n=1) CDK4 (n=1)	KRAS Amp (n=1) FGFR3-TACC3 fusion (n=1) KRAS G12D (n=1) CDKN2A G101W (n=1)

[a]Genomic analysis used Guardant360 for ctDNA NGS and ThermoFisher for tissue NGS; [b]EGFR amp (CNV ≥7) and MET amp (CNV ≥3) were based on tumor NGS; other amps were based on tumor NGS (CNV ≥7) or ctDNA NGS (CNV ≥3). Single nucleotide variants, insertion/deletions, and insertion call threshold was ≥1% allele frequency with >250 reads. [c]Eight patients had ≥1 alteration. Amp, amplification; CNV, copy number variation

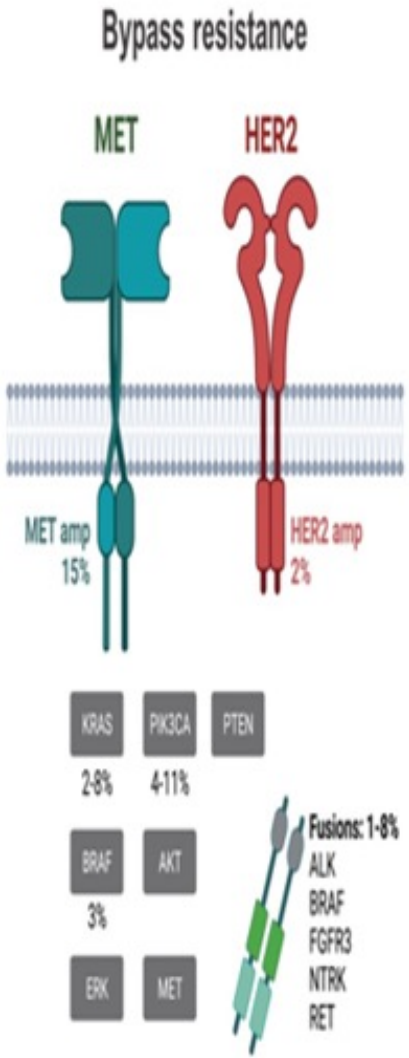
BC Cho et al. 2021 ASCO, abstr 9006.

Novel Therapies Post-Osimertinib w MET as Target

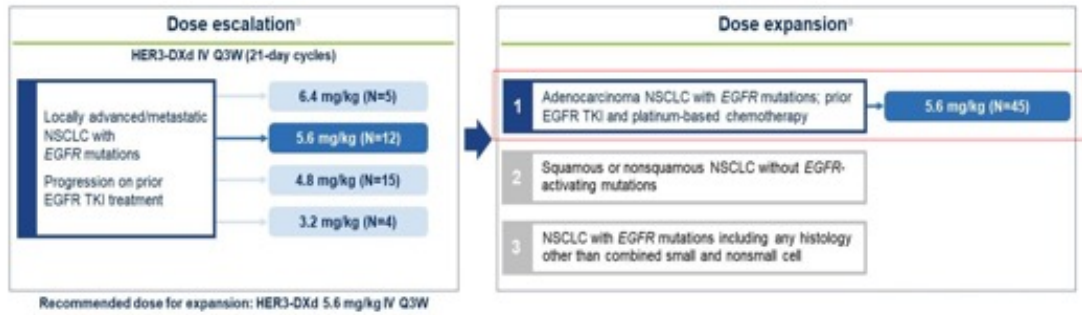


Outcomes	Amivantanab + Lazertinib N = 45	Amivantanab + Lazertinb PD Chemo N = 162	Osimertinib + Savolitinib N = 69	Teliso-V + Osimertinib N = 25
Trial	CHRYSALIS	CHRYSALIS-2 (A)	TATTON (B1)	NCT02099058
Target	EGFR + MET Post-Osi	EGFR + MET Post-Osi and Plat-based chemo	EGFR + MET Post 3RD Gen TKI	EGFR + MET Post-Osi
Biomarker	EGFR/MET resistance; unknown resistance; other resistance.	Without biomarker selection (underlying resistance mech. to be reported in the future)	MET Amplification	MET Expression
ORR	36%	33%	30%	58%
mDOR (months)	9.6 (95% CI: 5.3-NR)	9.6 (95% CI: 7.0-NR)	7.9 (95% CI: 6.9-11.2)	Not reported
mPFS (months)	4.9 (95% CI: 3.7-9.5)	5.1 (95% CI: 4.2-6.9)	5.4 (95% CI: 4.1-8.0)	Not reported
Grade ≥ 3 TRAE	16%	38%	57%	32%

BC Cho et al. Presented at ASCO 2021
C Shu et al. Presented at ASCO 2022
L Sequist et al. Lancet Oncology 2020
JW Goldman et al. Presented at ASCO 2022

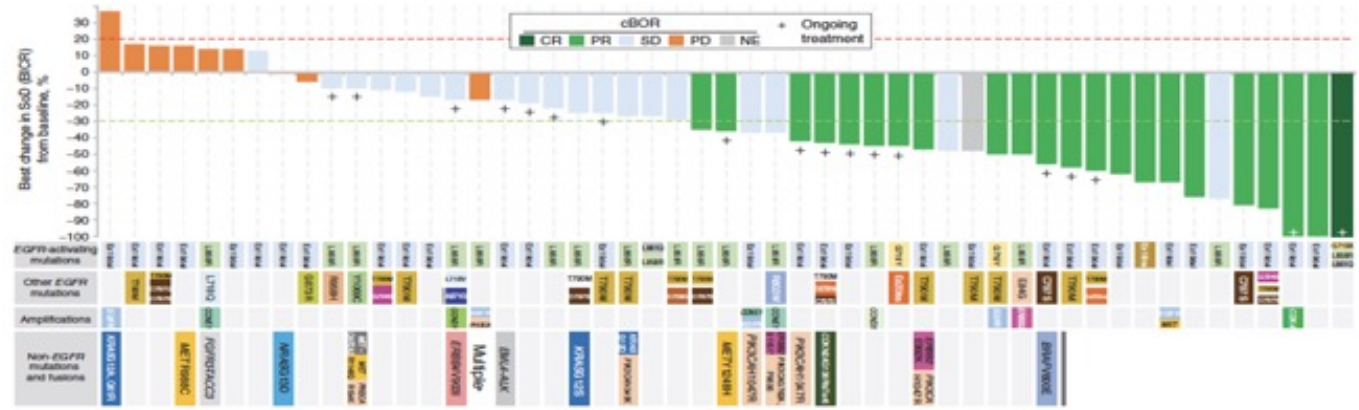


U31402-A-U102 Ph 1 Study of Patritumab Deruxtecan: Study Design

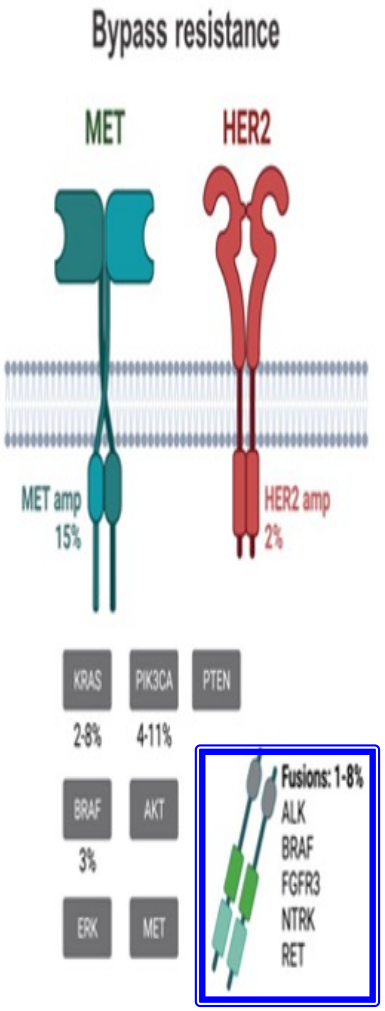


Patritumab Deruxtecan: Osimertinib-Resistant, EGFRm NSCLC

	All (n=57)	Prior PBC + Osi (n=44)
Confirmed ORR (BICR)	39%	39%
mDOR, mo (range)	6.9 (3.1-NE)	7.0 (3.1-NE)
mPFS, mo (range	8.2 (4.4-8.3)	8.2 (4.0-NE)



ORCHARD study: Treatment-based on resistance mechanism identified.



New arms:
Osimertinib + alectinib
Osimertinib + selpercatinib

Analysis of tumour biopsy from patients with EGFRm NSCLC progressing on first-line osimertinib monotherapy

Group A: Treatment based on resistance mechanism detected

MET amp	osimertinib (80 mg qd PO) + savolitinib (300 / 600 mg qd PO)
EGFR C797X	osimertinib (80 mg qd PO) + gefitinib (250 mg qd PO)
EGFR amp	osimertinib (80 mg qd PO) + necitumumab (800 mg IV*)
Future arms 1, 2, etc	Future treatments 1, 2, etc

Group B: Non-matched arm for patients without a resistance mechanism detected (to be filled sequentially)

Biomarker non-matched	1	For up to 6 cycles: durvalumab (1500 mg IV) + carboplatin ([AUC5] IV) + pemetrexed (500 mg / m² IV) q3w; followed by D (1500 mg IV) + P (500 mg / m² IV) q4w
	2	osimertinib (80 mg qd PO) + necitumumab (800 mg IV*)
	3+	Future treatments 1, 2, etc

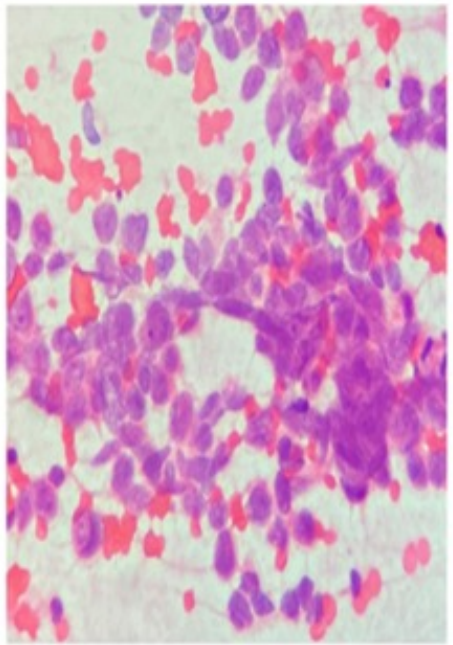
Disease progression → **Follow-up for overall survival**

Group C: For patients whose optimal treatment involves medication not available within the Group A or B cohorts (e.g. transformation to SCLC or squamous histology; presence of an actionable biomarker for which treatment is not currently available in ORCHARD+; pre-screen failure or Group A/B screen failure)

*On Days 1 and 8 of each 3-week cycle; +e.g. ALK fusion
ALK, anaplastic lymphoma kinase; amp, amplification; AUC, area under curve; EGFR, epidermal growth factor; EGFRm, EGFR-tyrosine kinase inhibitor sensitising mutation; IV, intravenous; MET, hepatocyte growth factor receptor (HGFR); NGS, next generation sequencing; NSCLC, non-small cell lung cancer; PO, orally; q3(4)w, once every 3(4)-week cycle; qd, once a day; SCLC, small cell lung cancer

Histologic transformation

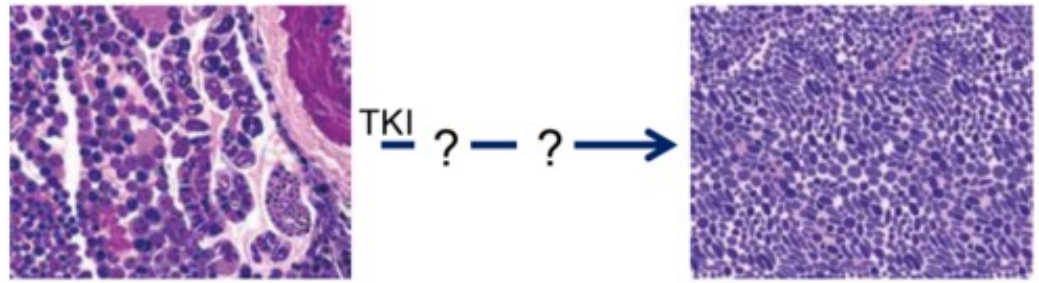
Small cell lung cancer: 5-15%



TP53 mutations
RB1 mutations

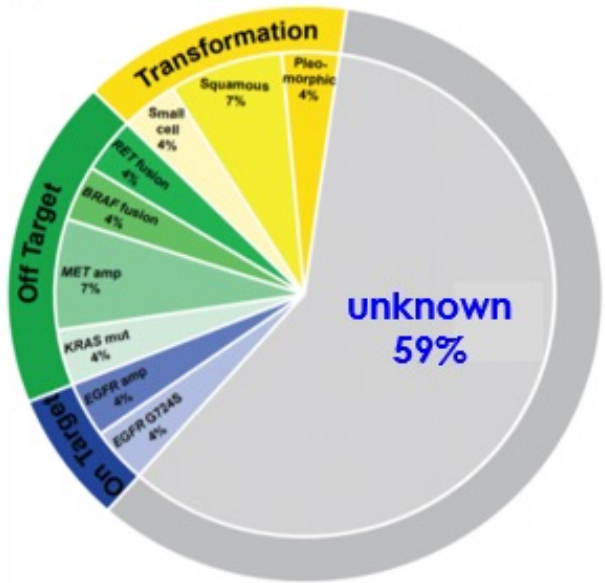
Apoptotic defects: BIM Deletion
Epigenetic modifications

Lineage plasticity as a mechanism of targeted drug resistance

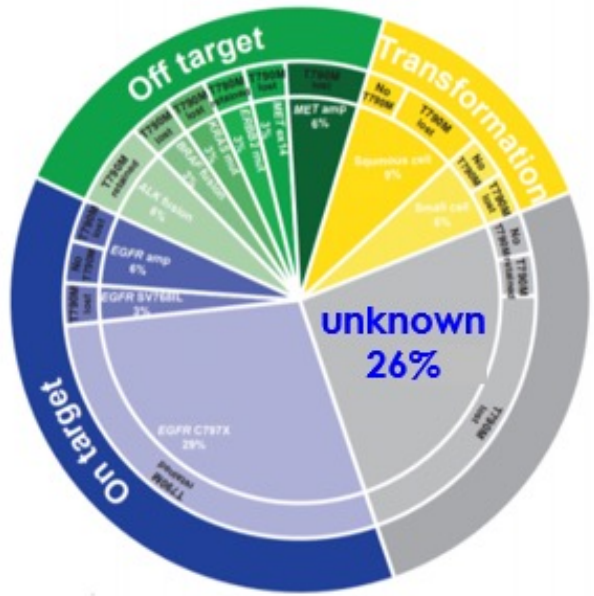


EGFR-mutant lung adeno

Small cell lung cancer



First line osimertinib

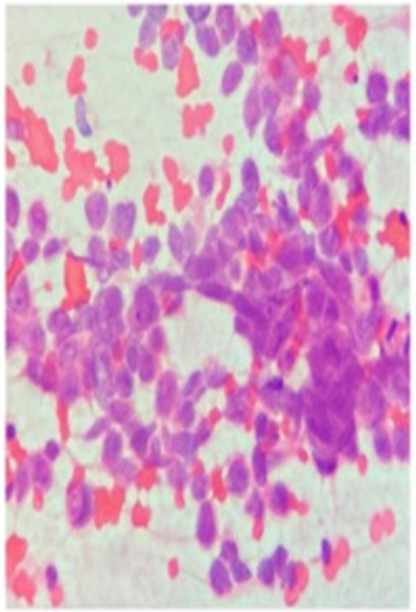


Later line osimertinib

Schoenfeld et al., Clin Cancer Res 2020.

Histologic transformation

Small cell lung cancer: 5-15%

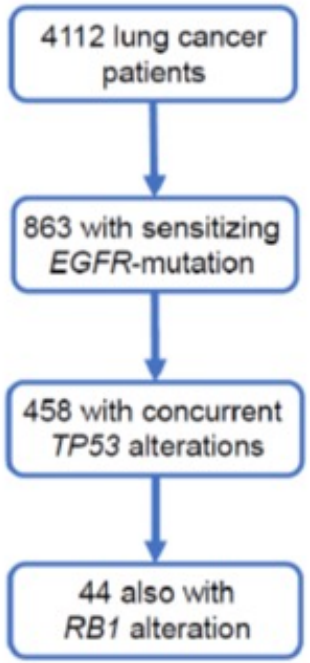


TP53 mutations
RB1 mutations

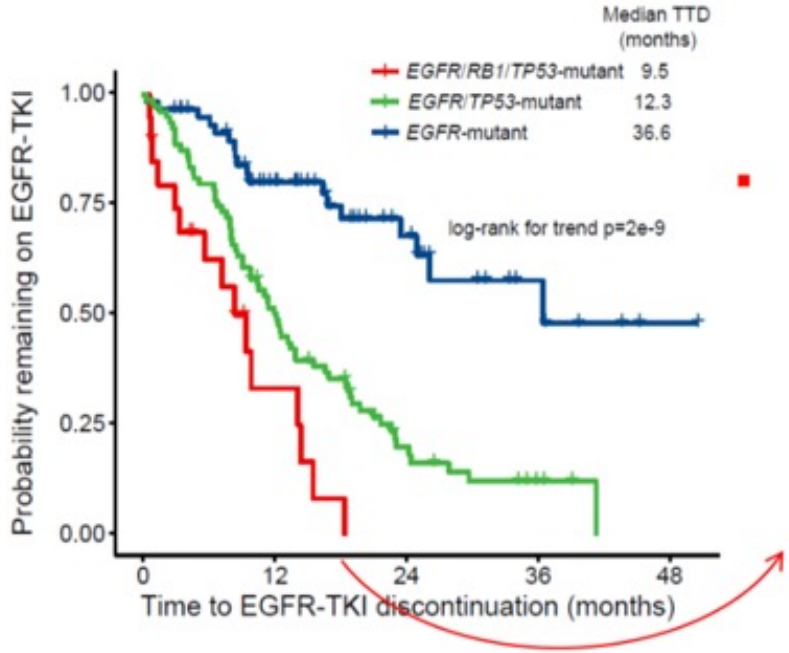
Apoptotic defects: BIM Deletion
Epigenetic modifications

MSK cohort – EGFR/TP53/RB1 mutant lung cancers

Inactivation of *RB1* and *TP53* is nearly universal in SCLC



Co-occurrence *TP53/RB1*
Adjusted p < 0.001



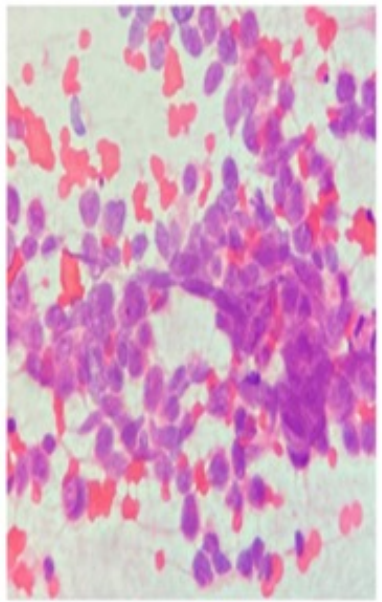
- All SCLC transformations have pre-existing detectable *TP53/RB1* LOF mutations
  - Differential co-mutations
  - APOBEC signature
  - Whole genome duplication

Offinet al.,J Thorac Oncol. 2019; George et al., Nature 2015; Niederstet al., Nature Commun 2015.

Open Questions Around First-Line Treatment for EGFR Mutant Lung Cancer Patients

Histologic transformation

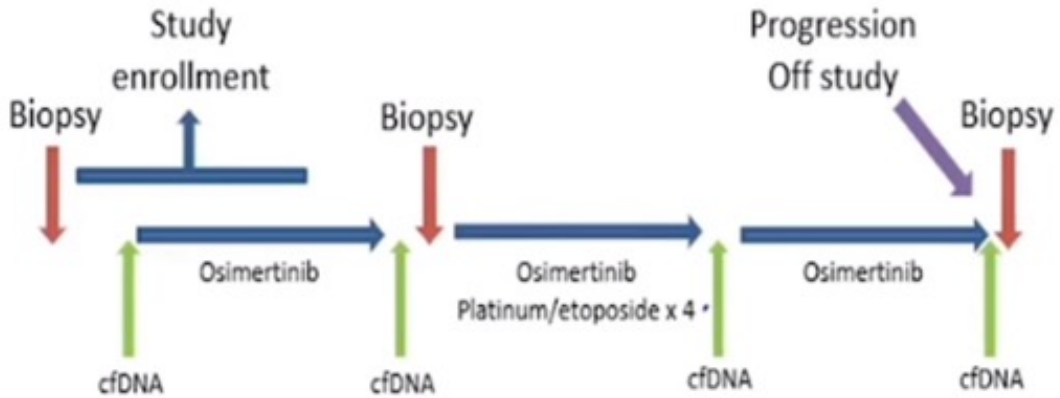
Small cell lung cancer: 5-15%

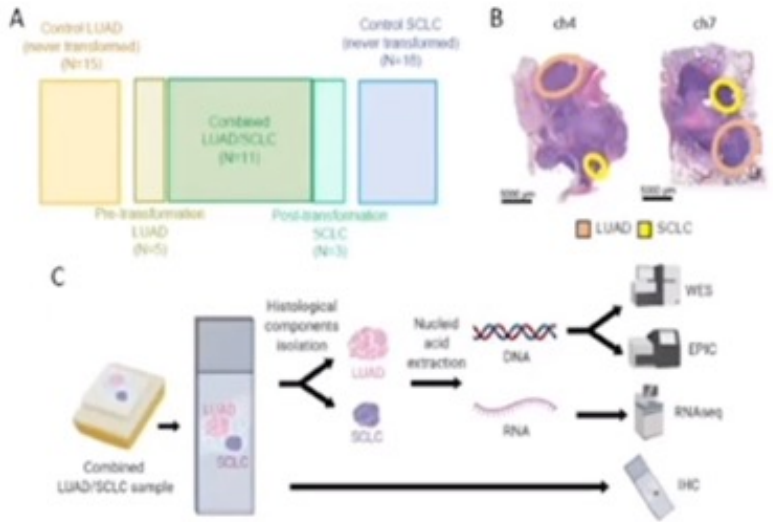


TP53 mutations
RB1 mutations

Apoptotic defects: BIM Deletion
Epigenetic modifications

Genomic-based treatment personalization





-Clinical trial that selects patients at risk (EGFR/RB1/TP53 genotype) for small cell transformation and adds in small-cell directed chemotherapy prior to transformation to try to eradicate small-cell subclone
-Comprehensive molecular analyses at different timepoints to identify changes in subclones over treatment and time.

Yu, H. 2022 Targeted Therapies in Lung Cancer Meeting, IASLC, February 22-26, 2022.

EGFR Exon 20ins

GenesisCare

OLA

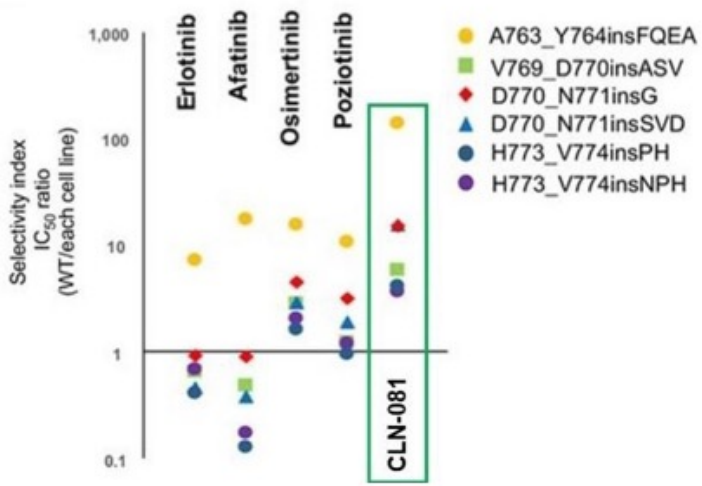
FLASCO

FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

Background

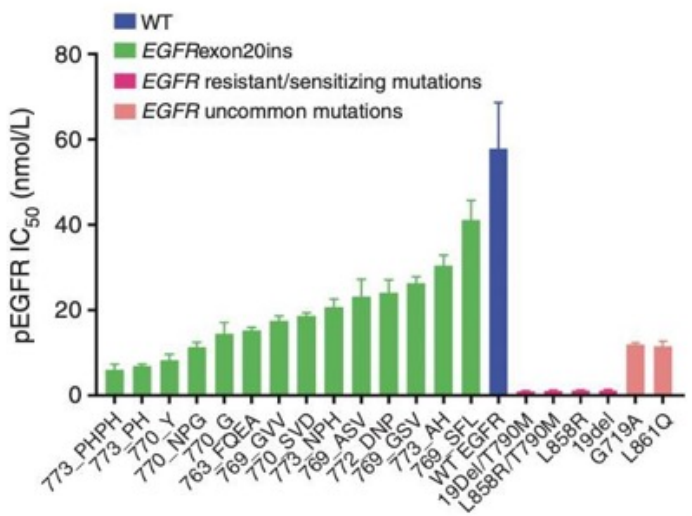
- Mobocertinib (EGFR TKI) and Amivantamab (bispecific EGFR/MET Ab) are now approved for NSCLC with EGFR exon 20 insertions after progression on chemotherapy, but activity is limited (ORR 28-40%).
- Both drugs are associated with high rates of toxicities associated with inhibition of wild-type EGFR (GI, skin tox).
- More potent and selective EGFR inhibitors are in development to improve efficacy and safety.

CLN-081



Yu HA, ASCO 2022
Wang M, Cancer Discov 2022.

Sunvozertinib (DZD9008)



CLN-081 Safety

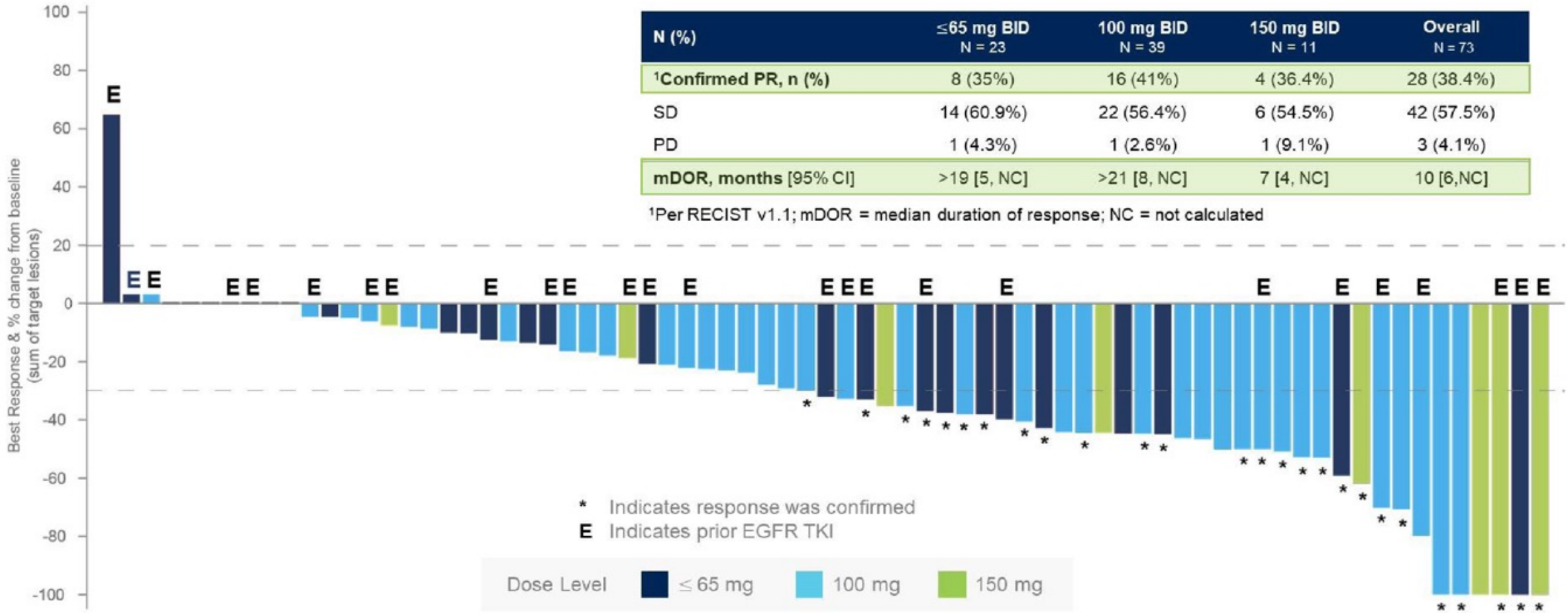
Dose BID	≤65 mg (N = 23)		100 mg (N = 39)		150 mg (N = 11)		Overall (N = 73)	
AE Term, n (%)	All grade[1]	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥3
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17)	5 (13)	1 (3)	2 (18)	2 (18)	14 (19)	7 (10)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4)	3 (8)	1 (3)	2 (18)	1 (9)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0
Dose Interruptions	5 (22)		13 (33)		6 (55)		24 (33)	
Dose Reductions	2 (9)		5 (13)		3 (27)		10 (14)	
Dose Discontinuations	2 (9)		2 (5)		2 (18)		6 (8)	

Yu HA, ASCO 2022

CLN-081 Efficacy

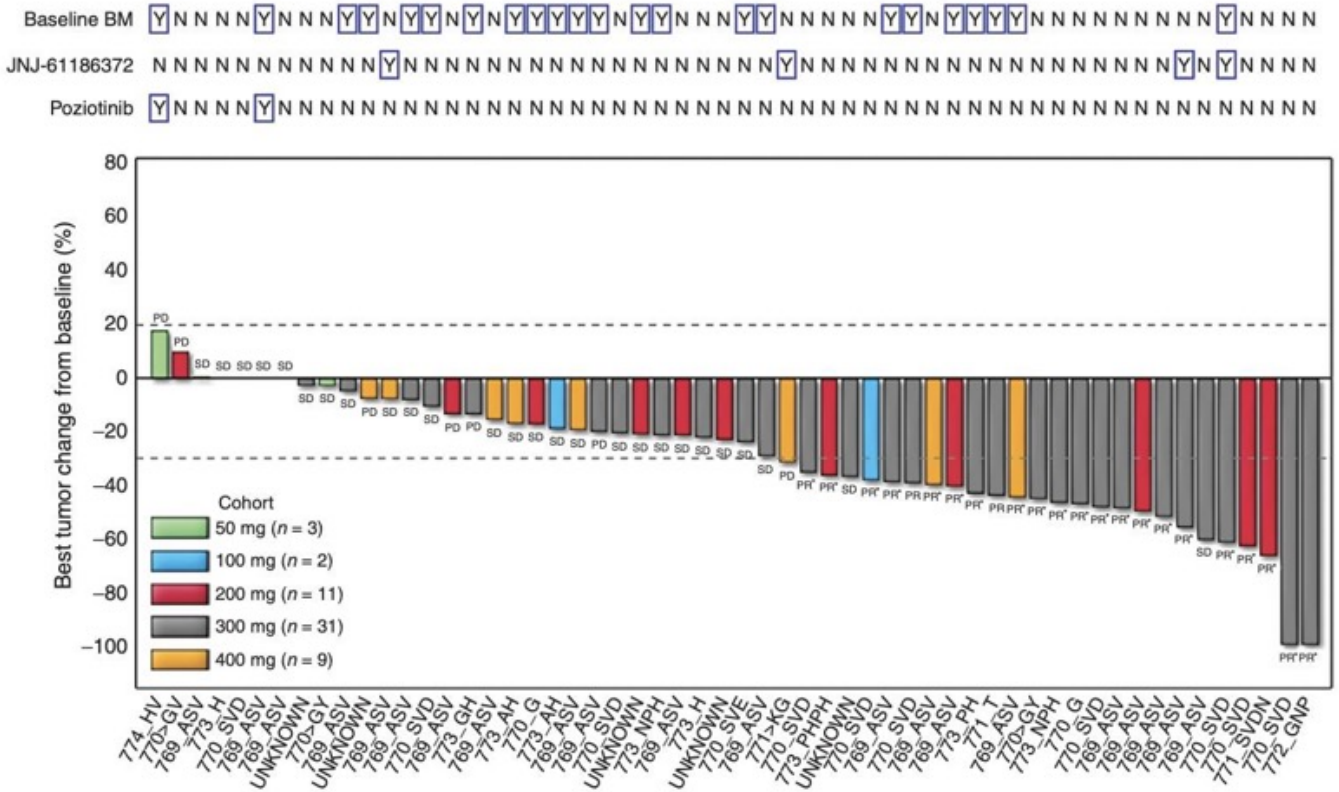
N (%)	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
[1]Confirmed PR, n (%)	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDOR, months [95% CI]	>19 [5, NC]	>21 [8, NC]	7 [4, NC]	10 [6,NC]

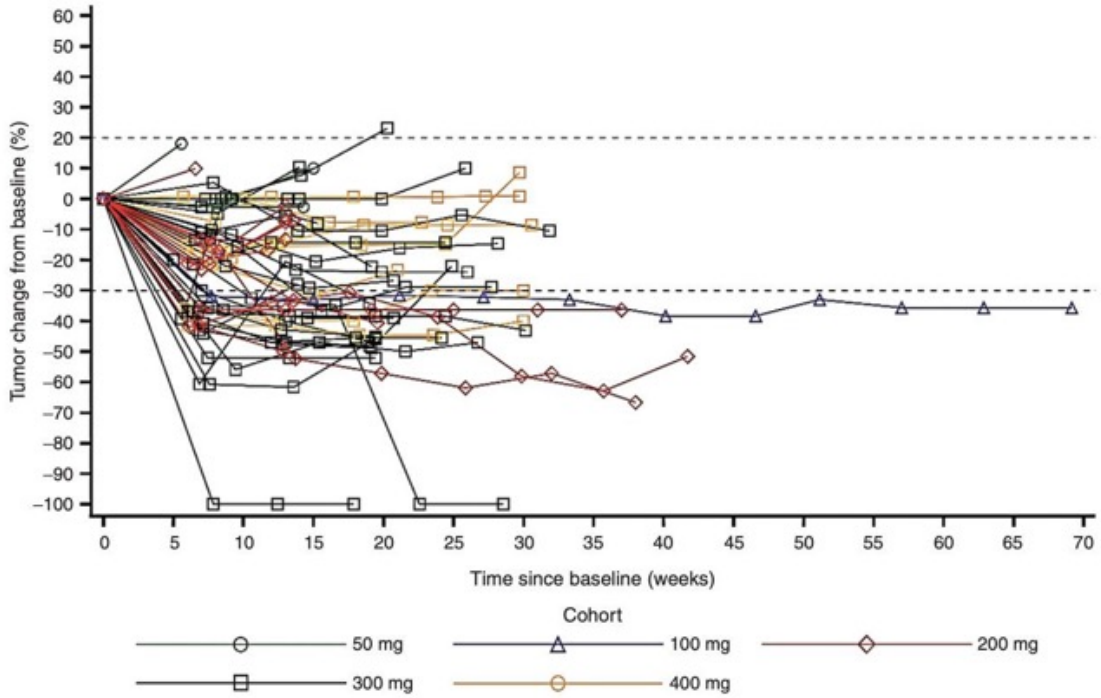
[1]Per RECIST v1.1; mDOR = median duration of response; NC = not calculated



Yu HA, ASCO 2022

Sunvozertinib Efficacy





	200 mg n=11	300 mg n=31	Total n=56
Confirmed ORR	5 (45.5%)	13 (41.9 %)	21 (37.5 %)
DCR	9 (82%)	28 (90.3 %)	48 (85.7%)

Wang M, Cancer Discov 2022.

Sunvozertinib Safety

	100 mg (n=9)	200 mg (n=16)	300 mg (n=51)	400 mg (N=20)	All (N=102)
Diarrhea	1 (11)	10 (62)	29 (57)	17 (85)	58 (57)
Rash	2 (22)	3 (19)	23 (45)	14 (70)	45 (44)
Anemia	3 (33)	4 (25)	16 (31)	11 (55)	36 (35)
Nausea	3 (22)	3 (19)	19 (37)	8 (40)	34 (33)
Vomiting	2 (22)	3 (19)	13 (26)	13 (65)	32 (31)
Decr. Appetite	3 (33)	2 (13)	17 (33)	9 (45)	32 (31)
Paronychia	1 (11)	4 (25)	15 (29)	8 (40)	29 (28)
CPK incr.	2 (22)	3 (19)	9 (18)	12 (60)	26 (26)
Fatigue	1 (11)	1 (6)	11 (22)	7 (35)	22 (22)
Cr incr.	1 (11)	1 (6)	9 (18)	8 (40)	19 (19)
Mouth ulcers	1 (11)	2 (13)	11 (22)	4 (20)	18 (18)

**All AE's seen in > 15% of entire population shown (50mg DL not shown)*

	100 mg (n=9)	200 mg (n=16)	300 mg (n=51)	400 mg (n=20)	All (n=102)
Any TRAE	8 (89)	16 (100)	49 (96)	20 (100)	99 (97)
Any TRAE gr $\geq$ 3	1 (11)	1 (6)	17 (33)	14 (70)	34 (33)
Any TRAE leading to death	0	0	1 (2)	0	1 (1)
TRAE leading to rx discontinuation	0	0	4 (8)	2 (10)	6 (6)
TRAE leading to dose reduction	0	0	6 (12)	10 (50)	16 (16)
TRAE leading to dose interruption	1 (11)	1 (6)	14 (28)	8 (40)	24 (24)

Recommended phase 2 dose = 200mg, 300mg QD

Wang M, Cancer Discov 2022.

GenesisCare OLA FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

Emerging Drugs in EGFR Exon 20

Drug	NCT	Most Recent REF	Notes
Sunvozertinib (DZD9008)	NCT03974022	Janne P, ASCO 2022	
CLN-081	NCT04036682	Yu HA, ASCO 2022	
BDTX-189	NCT04209465	Schram AM, ASCO 2020	*Clinical Development Halted*
BLU-451	NCT05241873	Spira AI, ASCO 2022	CNS Activity Predicted
ORIC-114	NCT05315700	Juntilla MR, AACR 2021	CNS Activity Predicted
HS-10376	NCT05435274		

REF: Clinicaltrials.gov search for "EGFR exon 20" (accessed July 1, 2022) – not an exhaustive list

Future Directions

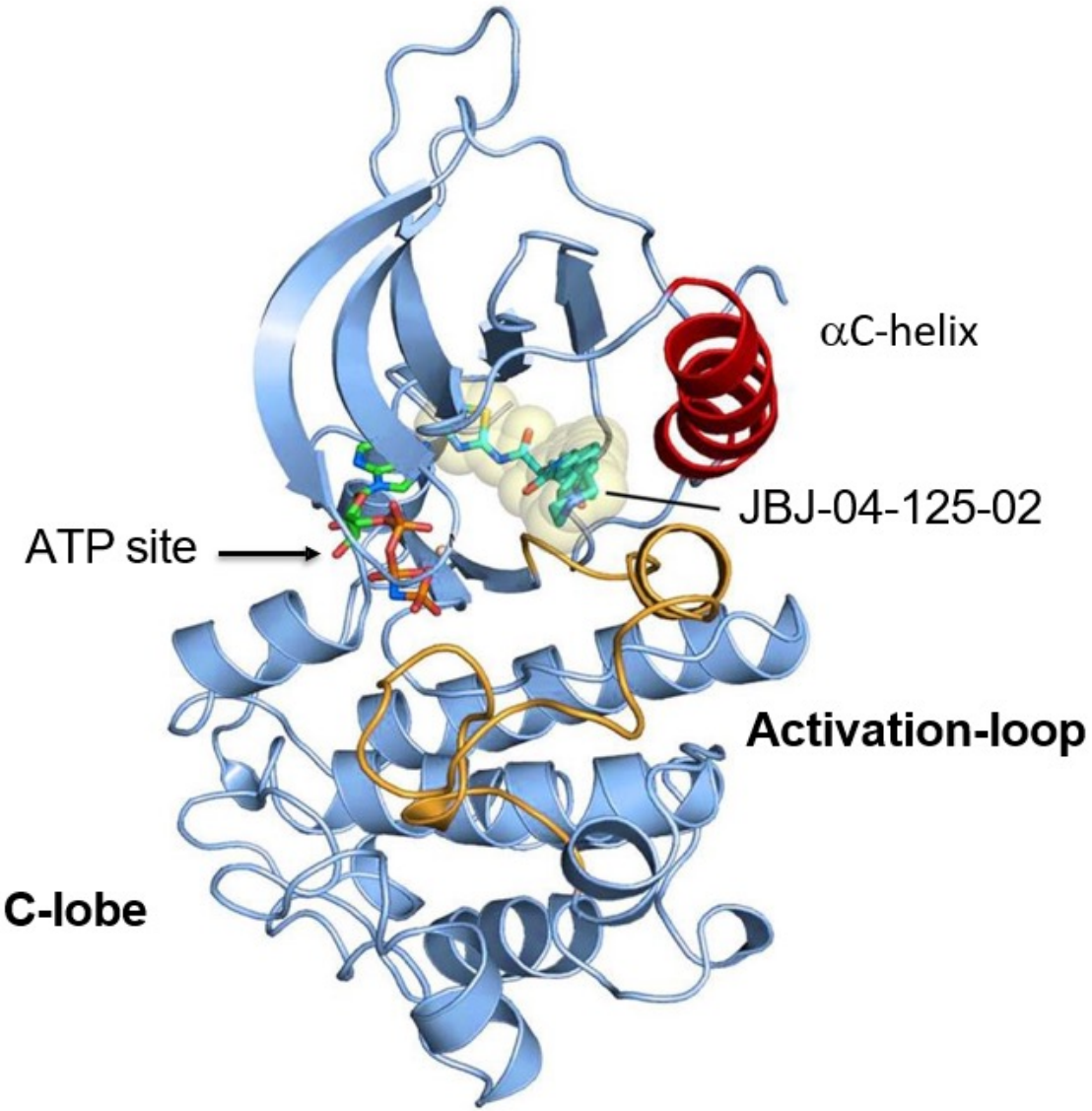
GenesisCare

OLA

FLASCO

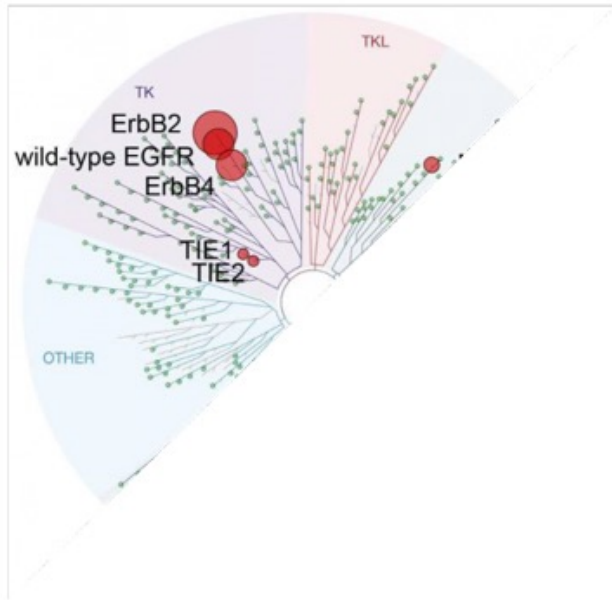
FAU MEDICINE
FLORIDA ATLANTIC UNIVERSITY

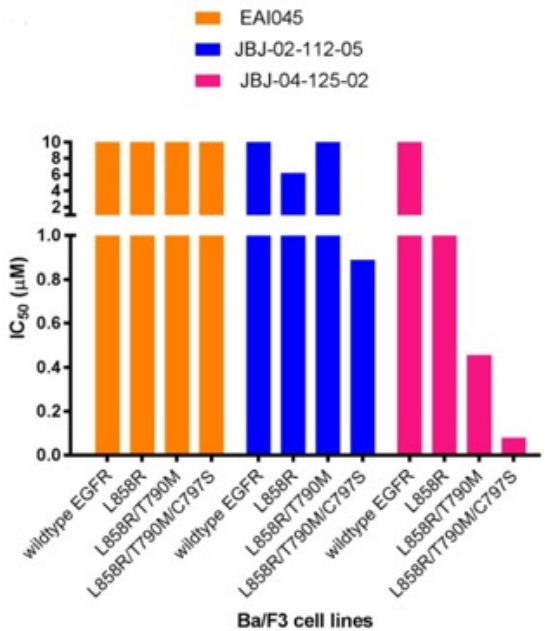
Allosteric EGFR Inhibitor JBJ-04-125-02

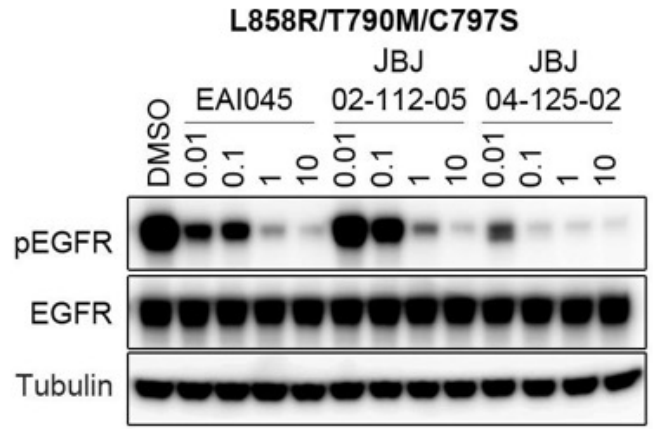


To, Jang et al. Cancer Discovery 2019

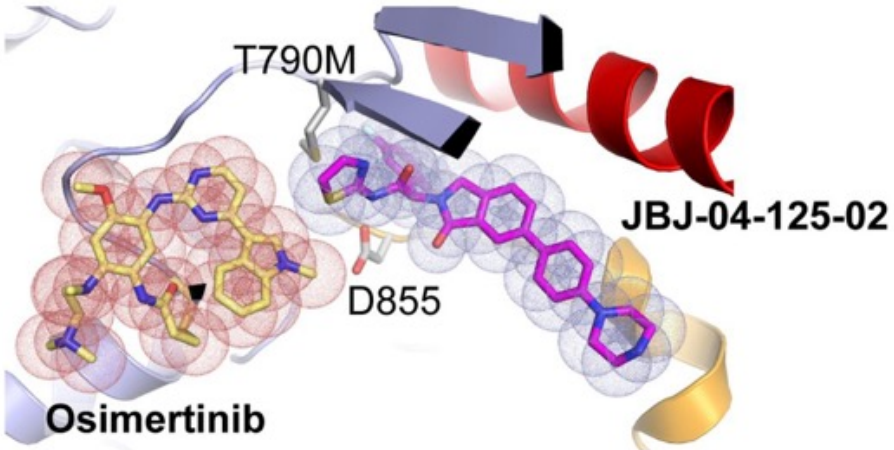
Allosteric pocket uniquely created in the presence of EGFR L858R

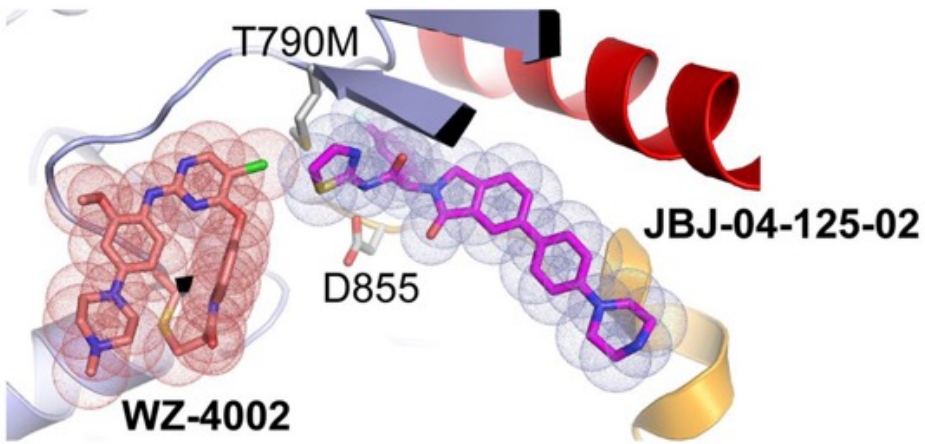


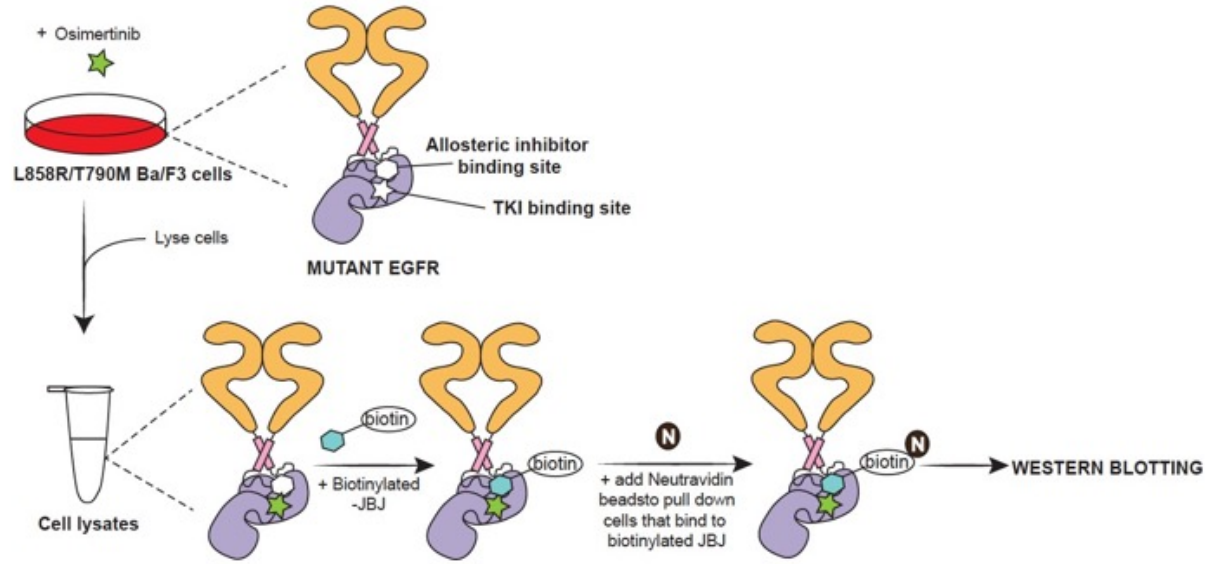


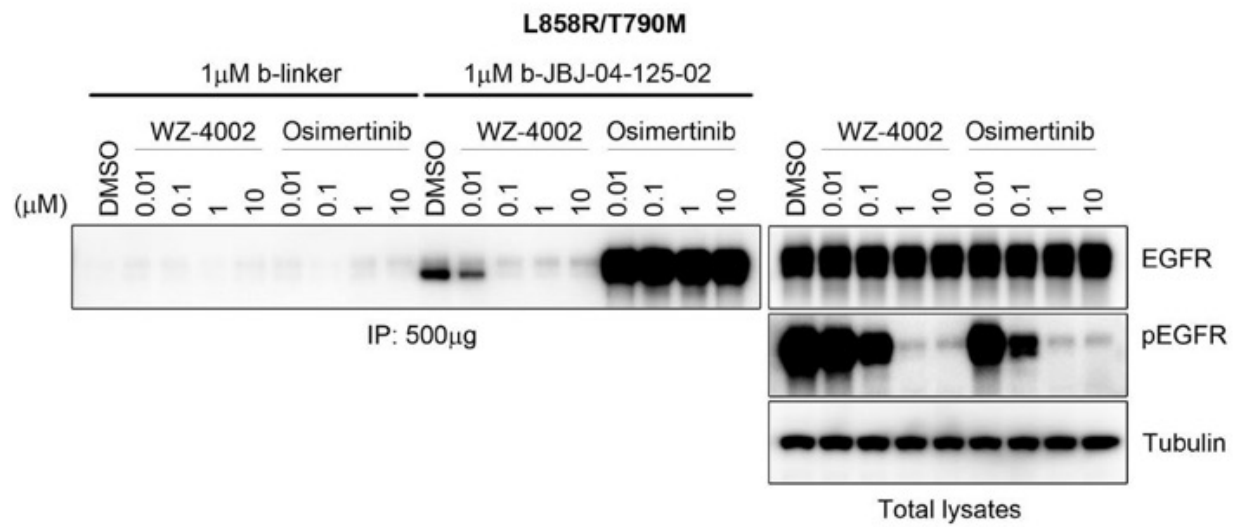


Can an allosteric and an ATP competitive EGFR inhibitor bind simultaneously to mutant EGFR ?



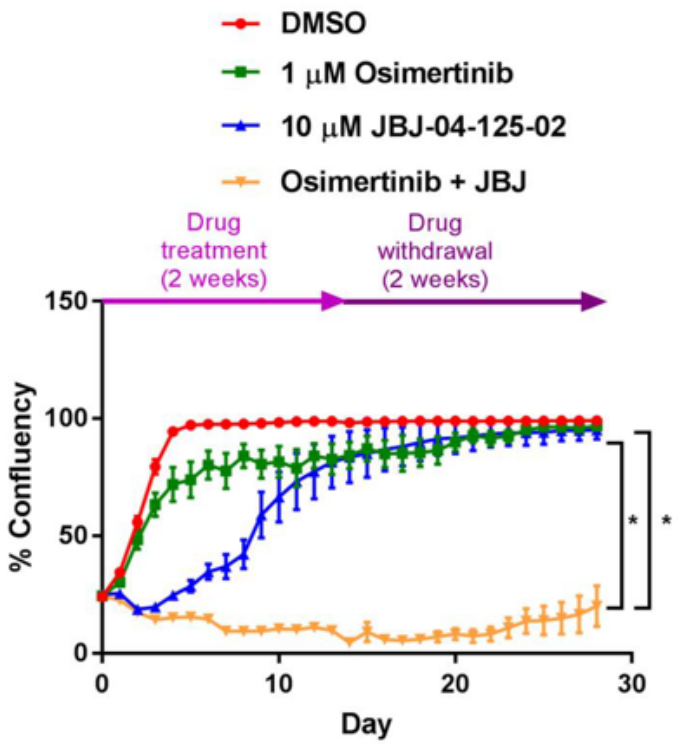


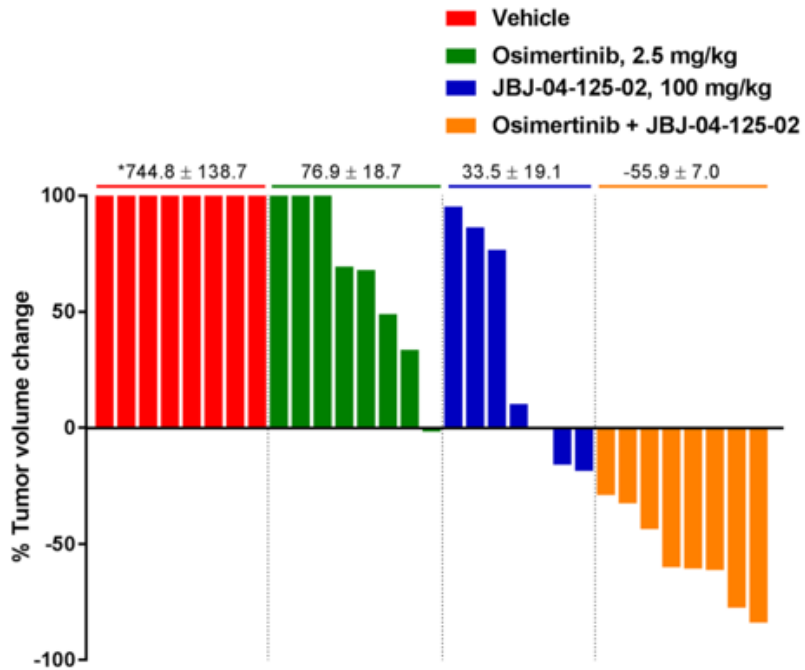


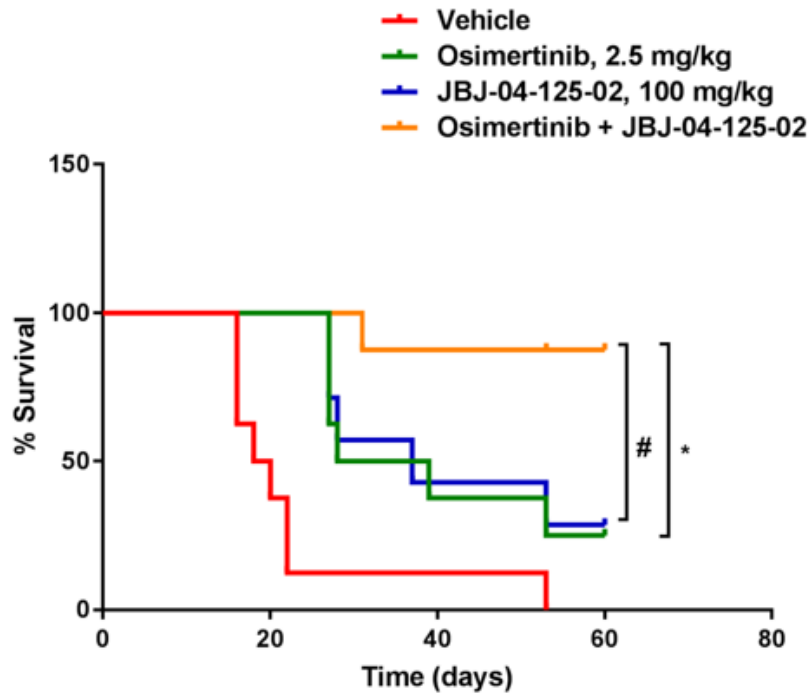


To, Jang et al. Cancer Discovery 2019

Enhanced efficacy of JBJ-04-125-02 with osimertinib compared to single agents in H1975 (L858R/T790M) cells







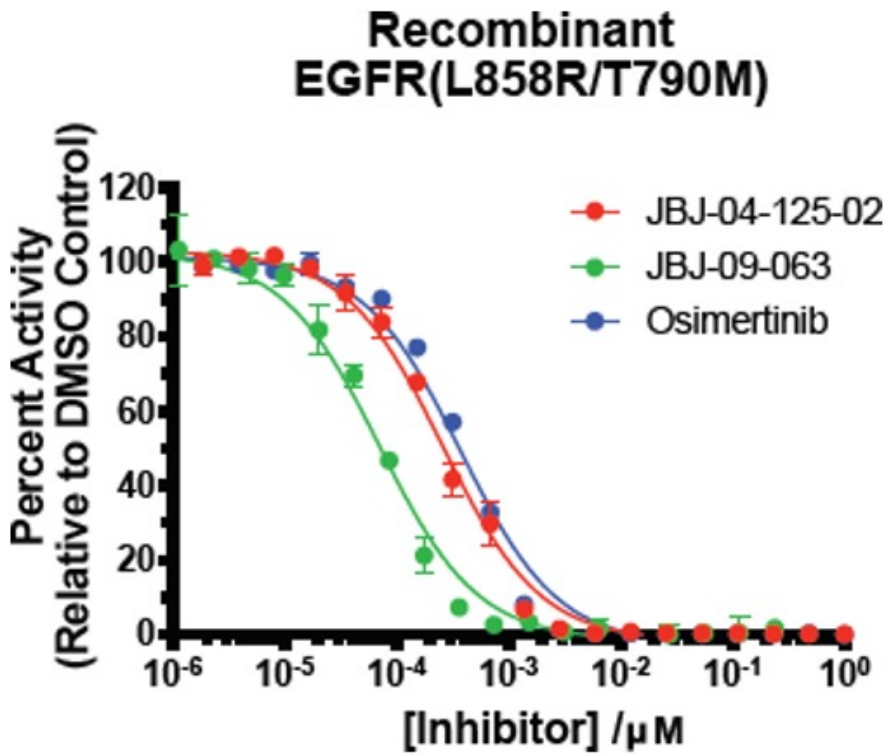
Enhanced *in vitro* efficacy

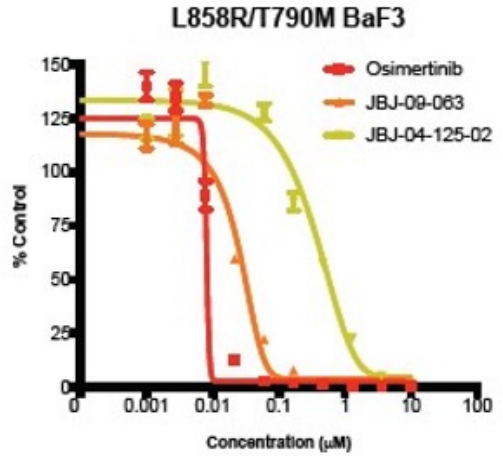
Enhanced *in vivo* efficacy

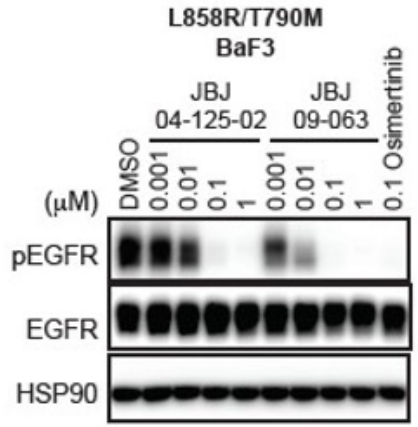
Improvement in survival

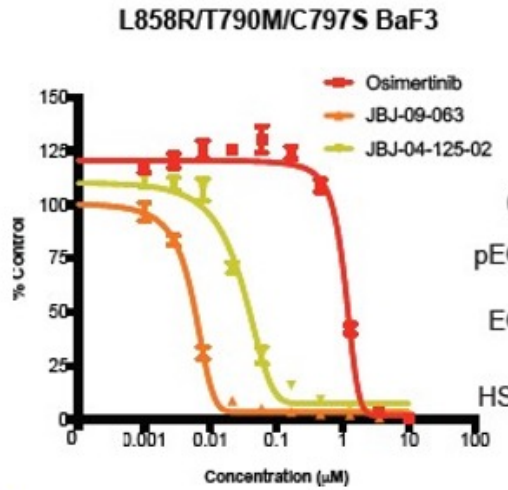
To, Jang et al. Cancer Discovery 2019

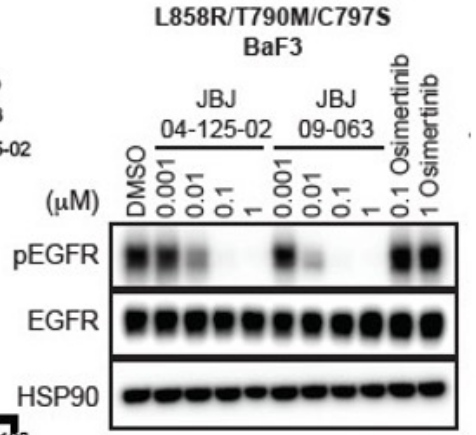
JBJ-09-063 – next generation allosteric EGFR Inhibitor





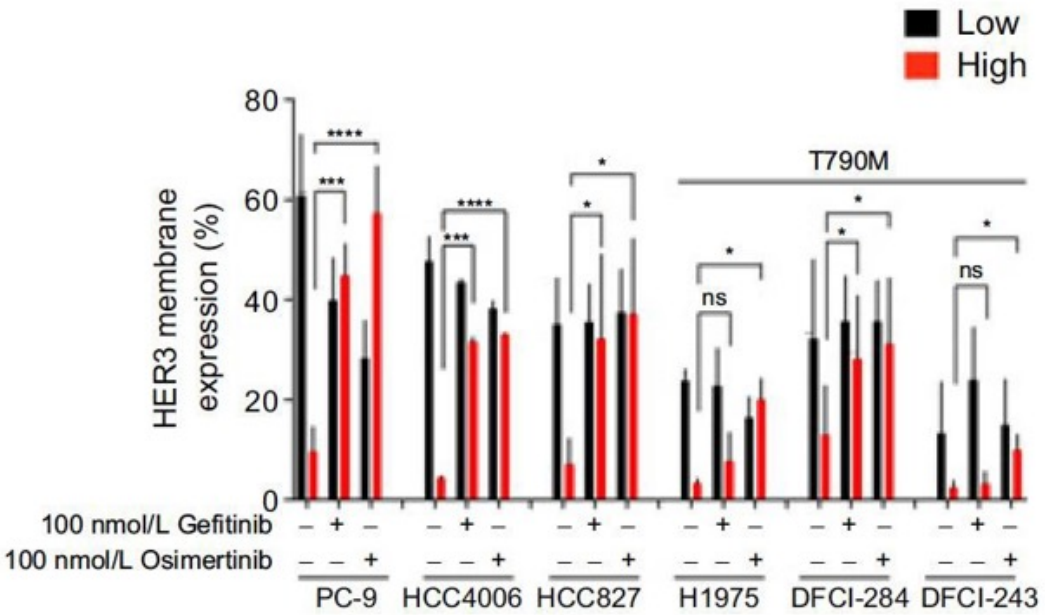




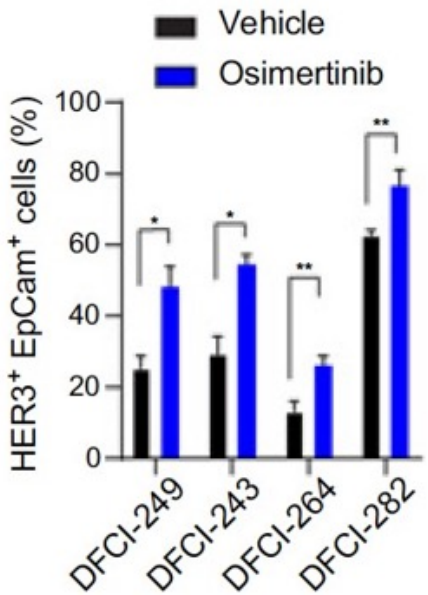


Ciric To, Tyler Beyett, Jaebong Jang et al. Nature Cancer 2022

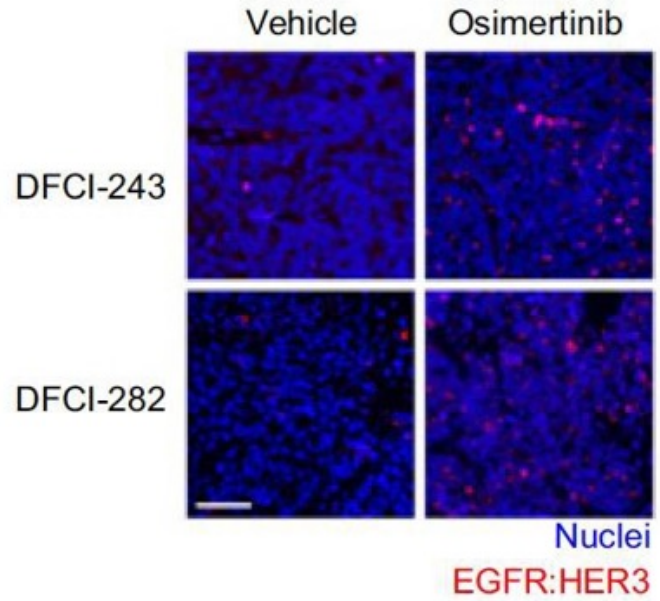
EGFR inhibition increases membrane bound HER3



In vitro



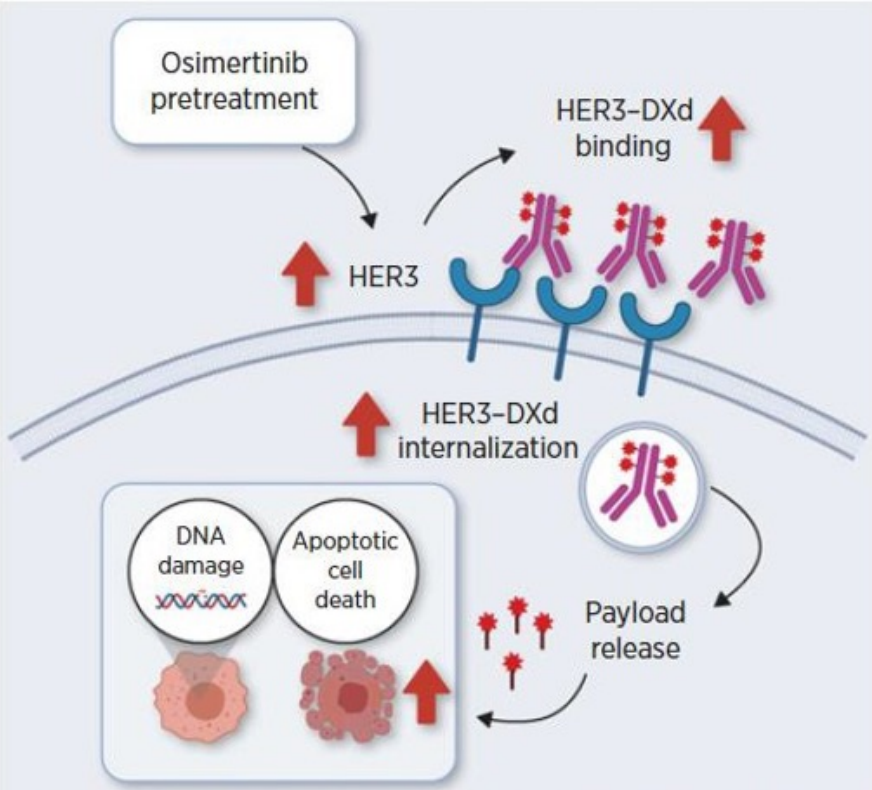
In vivo



EGFR:HER3 association increases after EGFR TKI treatment

Haikala et al. Cancer Research 2021

Clinical trial of osimertinib and HER3-DxD post- first line osimertinib



EGFR inhibition leads to feedback HER3 membrane expression promoting HER3–DXd antibody drug conjugate internalization and efficacy, supporting the clinical development of the EGFR inhibitor/HER3–DXd combination in EGFR-mutant lung cancer.

Phase 1 trial underway (NCT04676477)

Dose escalation of HER3-Dxd (3.2 mg/kg to 5.6 mg/kg) with osimertinib 80 mg

Dose expansion:

-Post first line osimertinib

-First line in TKI naïve patients

U31402-A-U103 (NCT04676477) Study Design

Eligibility criteria

Dose escalation; doseexpansion Arms 1 and 2 (second line)

- Metastatic/unresectable NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- Progression after treatment with osimertinib; no other prior systemic therapies in the locally advanced/metastatic setting

Dose expansion Cohort 3 (first line)[a]

- Metastatic/unresectable NSCLC with an *EGFR*-activating mutation (exon 19 deletion or L858R)
- No prior systemic treatment for locally advanced/metastatic disease
  - Patients may have received prior neoadjuvant or adjuvant therapy (except with osimertinib)

HER3-DXd (patritumab deruxtecan) IV Q3W + osimertinib PO QD

Dose escalation[b]

Starting dose:

HER3-DXd
3.2 mg/kg
+
osimertinib
80 mg

Guided by BLRM with EWOC

Dose expansion

Second line:

R 1:1 → *R 1:1:1*[c]
- Arm 1: HER3-DXd + osimertinib at RCD (n ≈ 60)
- Arm 1b[c]: HER3-DXd + osimertinib at RCD2 (n ≈ 60)
- Arm 2: HER3-DXd 5.6 mg/kg (n ≈ 60)

Cohort 3 (first line)[a]:

HER3-DXd + osimertinib at RCD (n ≈ 30)

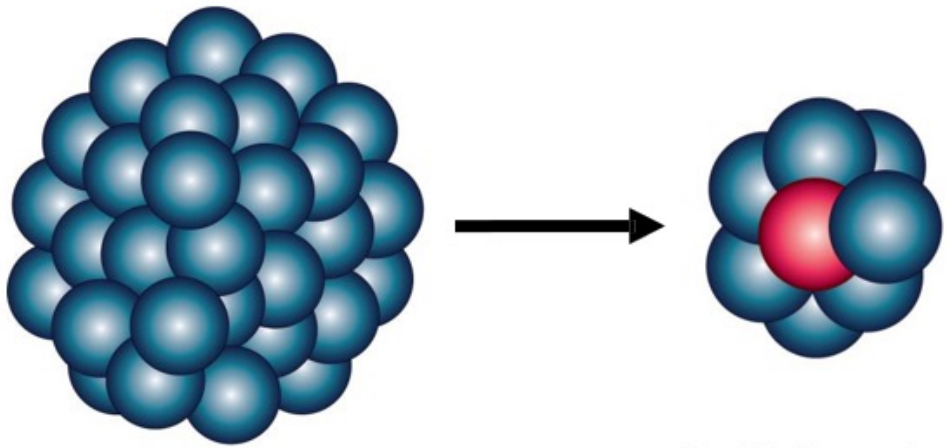
Primary objectives[d,e]

Dose escalation
- Determine RCD
- Safety and tolerability

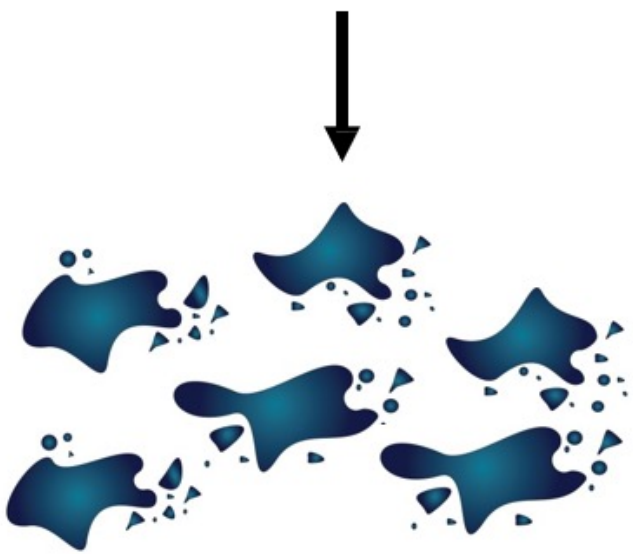
Dose expansion Arms 1 and 2
- ORR by BICR

Dose expansion Cohort 3
- Safety and tolerability

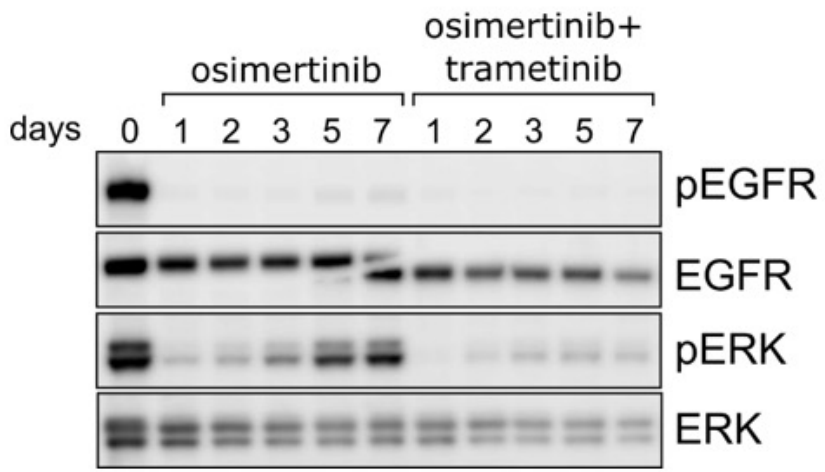
Why do some EGFR mutant cells not die despite EGFR inhibition?

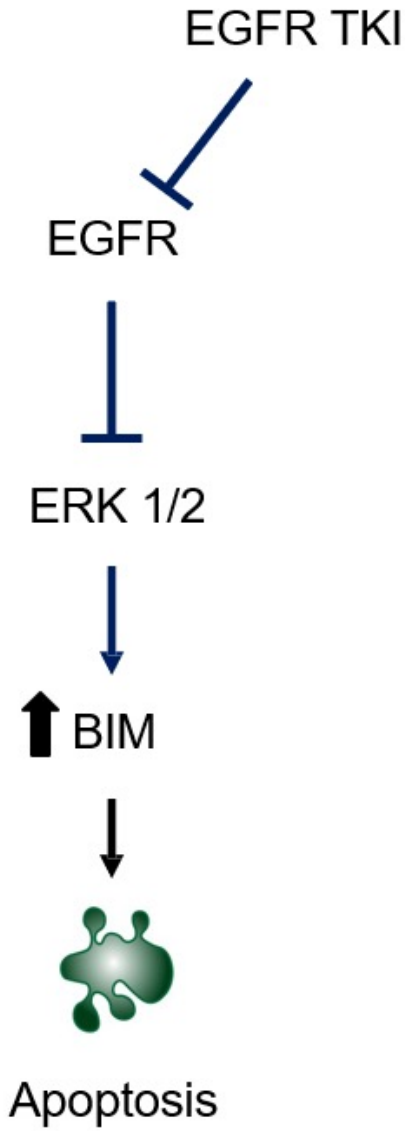


Cell Survival



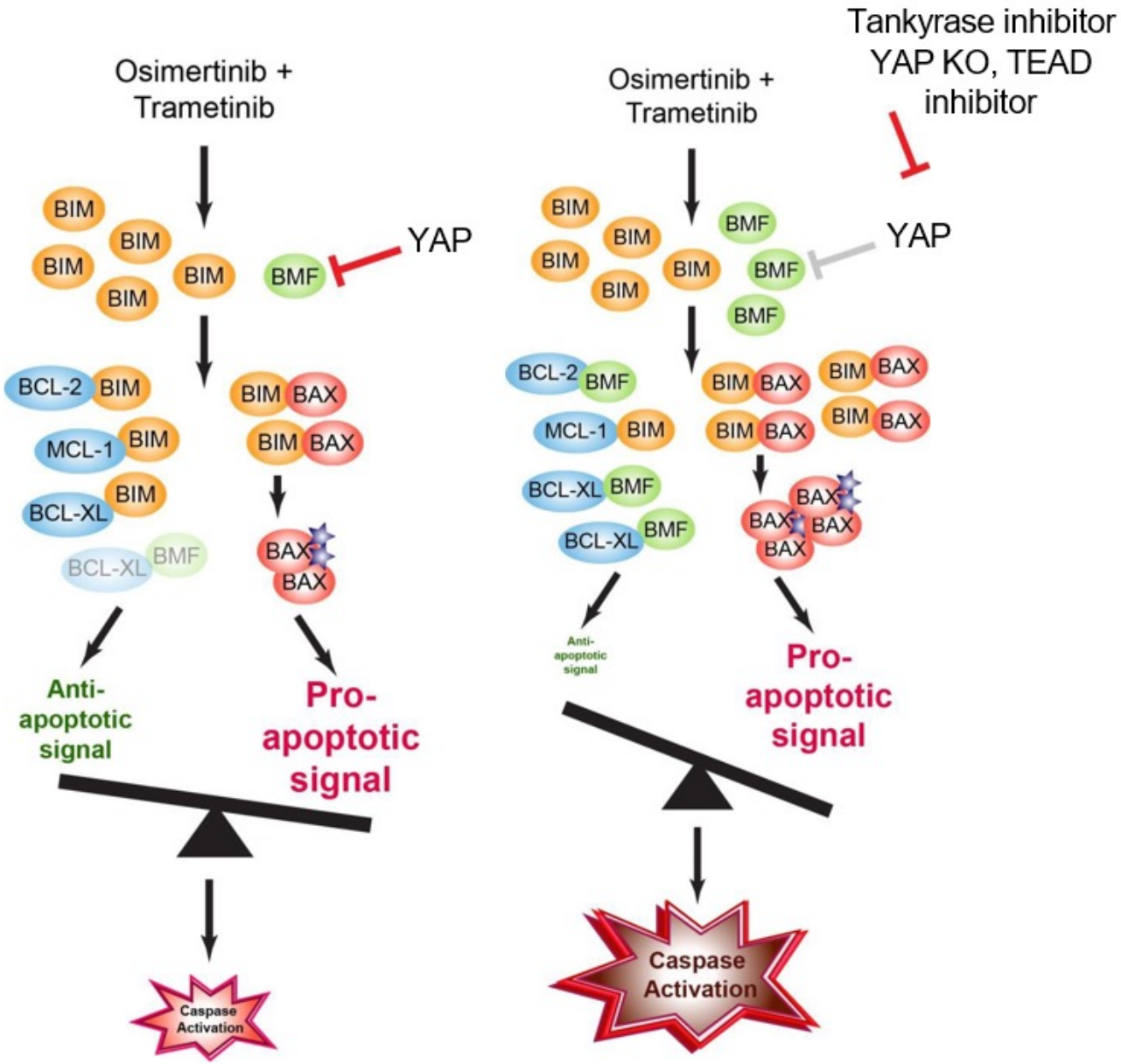
Cell Death

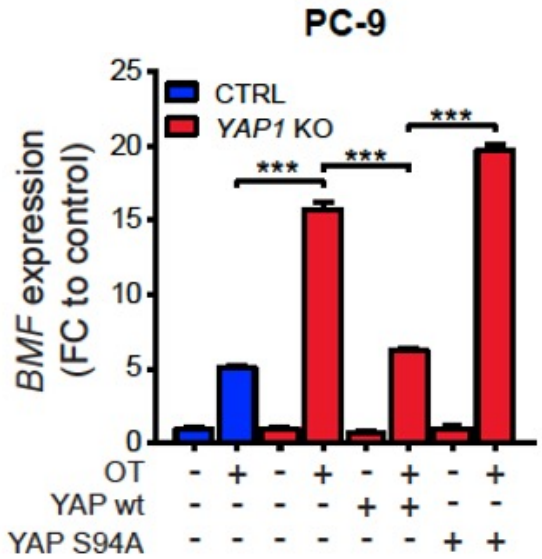


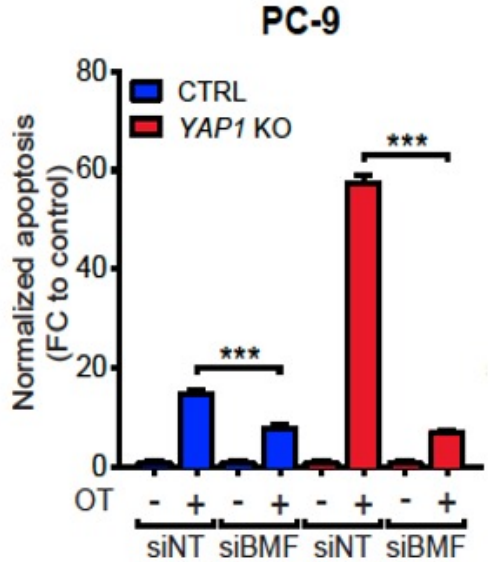


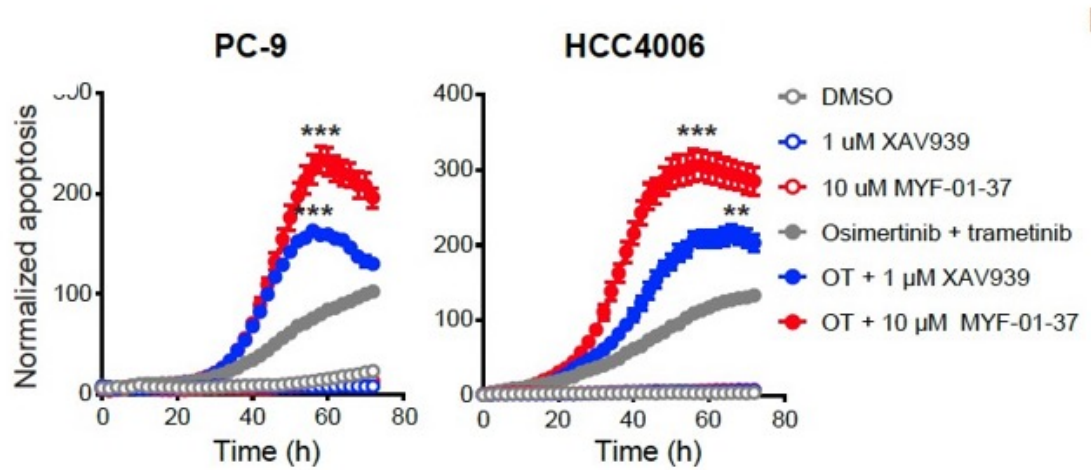
Tricker et al. 2015 Cancer Discovery; Kurppa et al. Cancer Cell 2020

YAP directly represses BMF transcription by binding to BMF locus









Multiple TEAD inhibitors in clinical development

Kurppa et al. Cancer Cell 2020

Phase II Trial of Osimertinib & Selumetinib in EGFR TKI naïve EGFR mutant NSCLC

Key eligibility:

- Stage IV NSCLC
- EGFR-activating mutation (Del 19/L858R)
- EGFR TKI and chemotherapy naive
- ECOG PS 0/1

→

Osimertinib 80 mg QD
Selumetinib 75 mg BID
4 days on/3 days off

N= 25

Primary endpoint:

- ORR

Secondary endpoints:

- PFS
- Tolerability
- OS

Correlative endpoints:

- cfDNA clearance
- Resistance mechanisms

PIs: Jänne and Stinchcombe

Funding: NCCN

NCT03392246

Conclusion

- Eagerly awaiting for FLAURA2 study results; see if it is superior to FLAURA.
- Ami + Laz yielded durable responses in patients who *progressed on osimertinib as prior line of therapy*:
  - 36% ORR, mDOR of 9.6 months, 64% CBR, and mPFS of 4.9 months
- CHRYSALIS-2 (Coh-A): Durable antitumor activity in pts with EGFRm NSCLC *after progression on both Osi and platinum chemotherapy* (Ami + Laz).
- Ami + Laz in front-line (MARIPOSA) and post-Osi, adding carbo/pemetrexed (MARIPOSA-2) ongoing [both are phase 3 trials].
- MET alteration (amplification) most common mechanism of resistance to EGFR TKIs; other: on-target, off-target, transformation.
- *MET-driven resistance to EGFR TKIs including 3rd Gen TKI* (TATTON B1); wait for final results of ORCHAD & SAVANNAH trials.
- Mobocertinib and amivantamab target EGFRex20ins; other inhibitors in development CLN-081 and sunvozertinib.
- Development of allosteric EGFR inhibitors; combining with EGFR TKIs.
- Targeting cells that survive by entering a senescence-like dormant state characterized by high YAP/TEAD activity during EGFR TKI inhibition is under investigation.