Mechanisms of Resistance to EGFR, ALK, and Other Relevant Pathways

Evolving Treatments for the Oncology Practice

October 8, 2022

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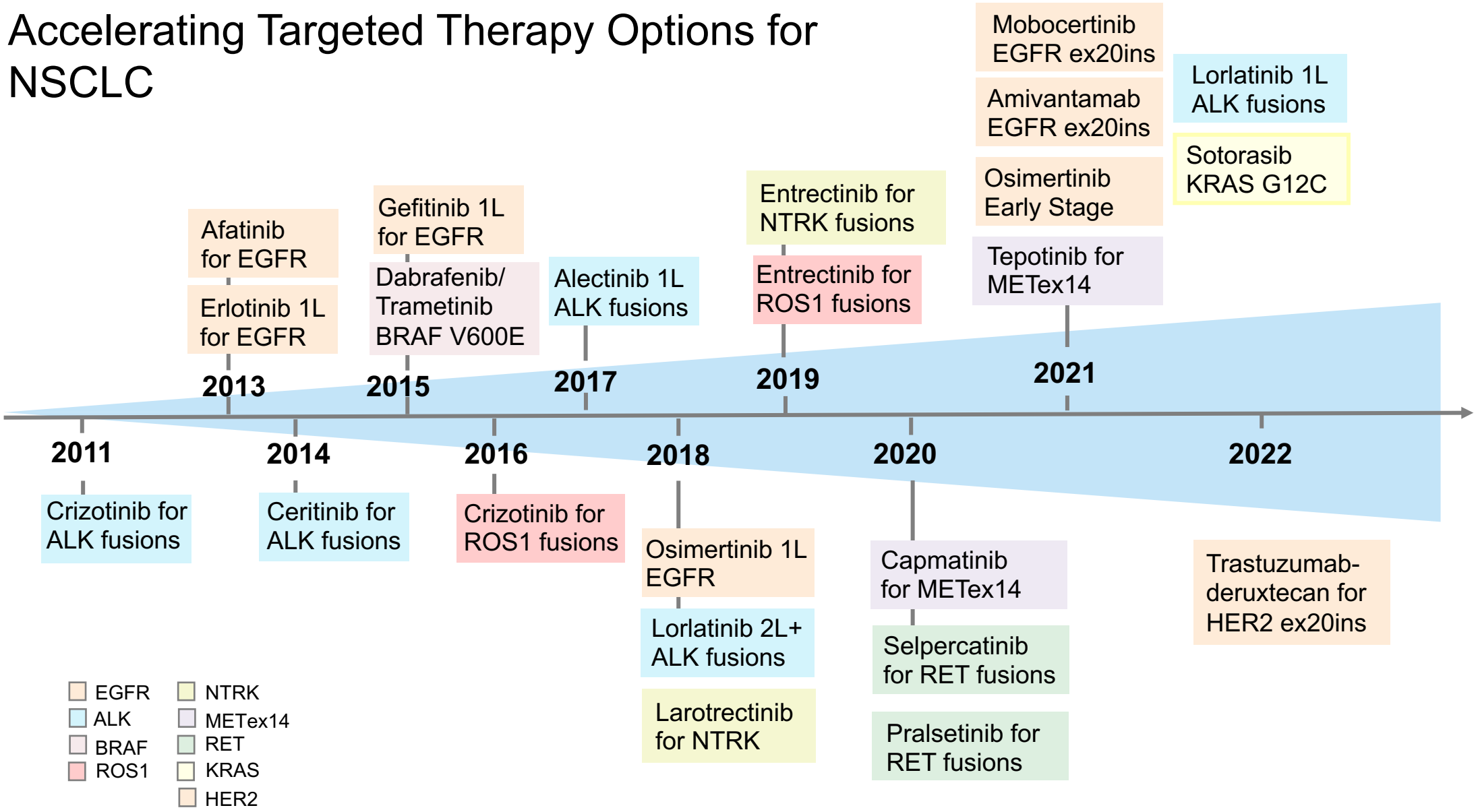
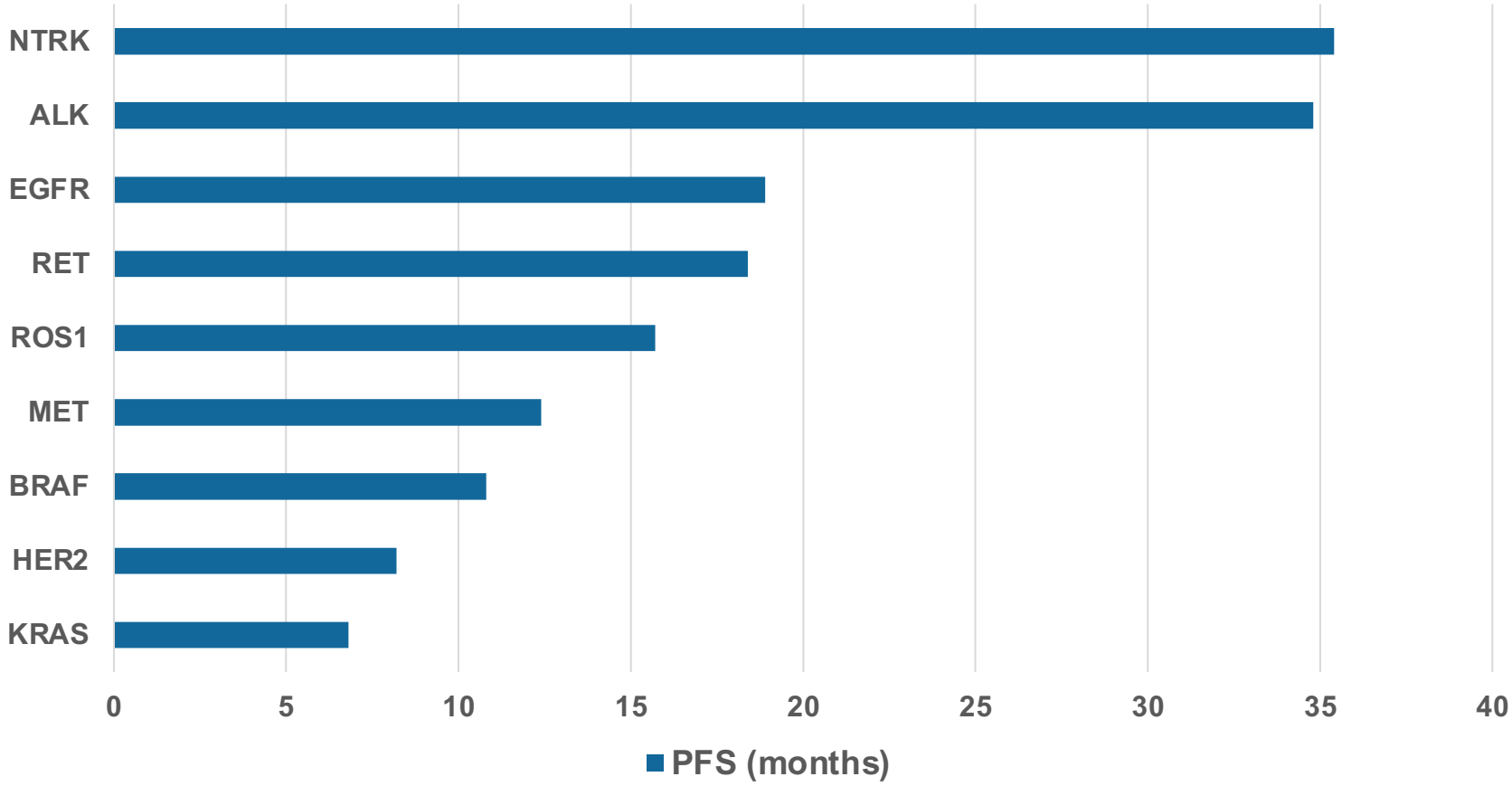
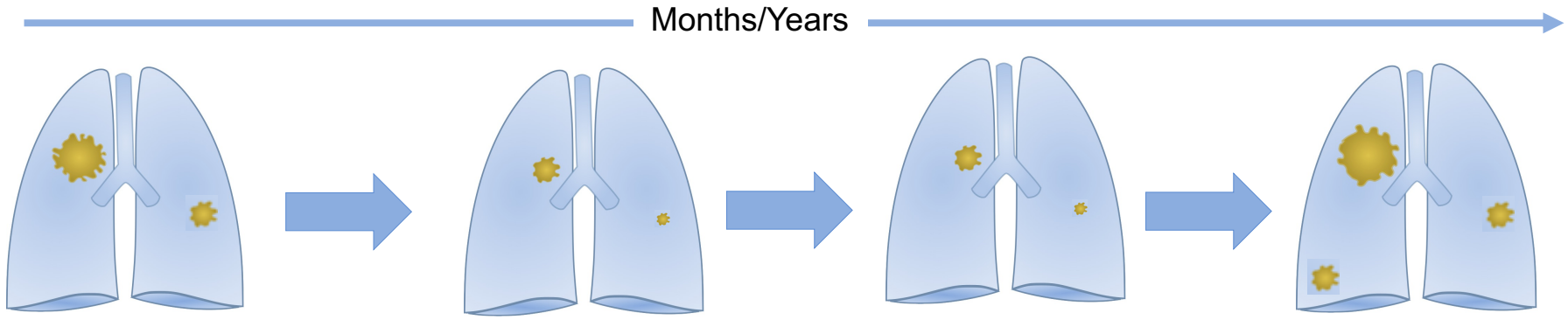
Accelerating Targeted Therapy Options for NSCLC



Median PFS is variable for actionable targets



Soria et al 2018, Wolf et al 2021, Mok et al 2020, Drilon et al 2020, Drilon et al 2022, Planchard et al 2022, Drilon et al 2022, Li et al 2022, Skoulidis et al 2021



Does local consolidation therapy delay resistance?

Do persister cells offer novel therapeutic targets?

Oligoprogression?

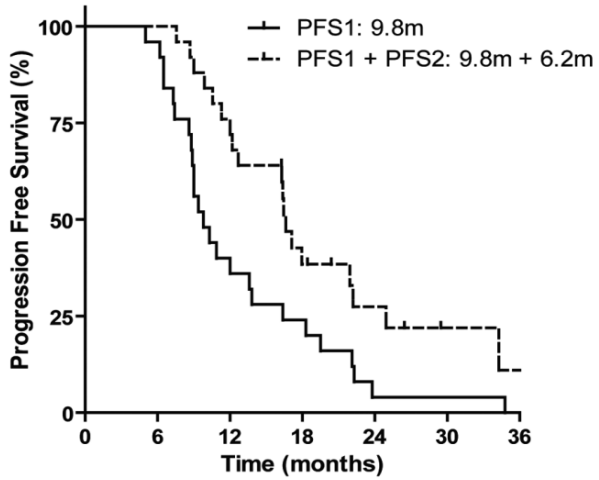
Multifocal Progression?

On-Target?

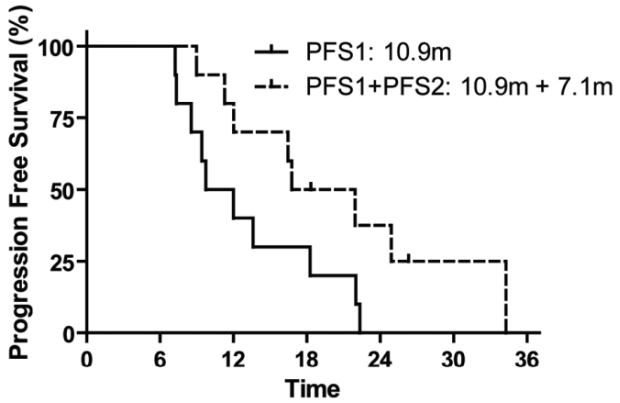
Off-Target?

Local Ablative Therapy for Oligoprogression

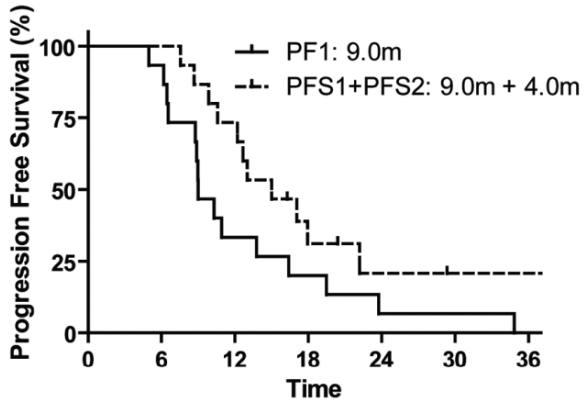
(A) PFS of all patients treated with LAT and continuation of TKI therapy



(B) CNS as site of first progression



(C) eCNS as site of first progression



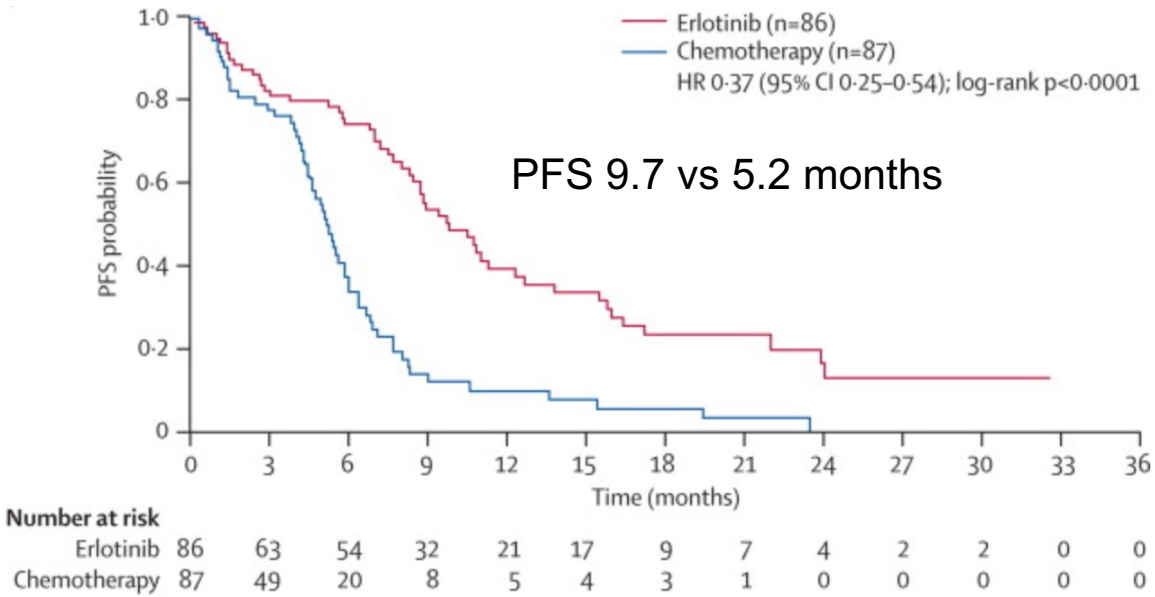
Local abalative therapy in oncogene driven NSCLC resulted in a median 6.2 month PFS2

Benefits greatest for CNS oligoprogresson in this study, which predated highly CNS active TKIs

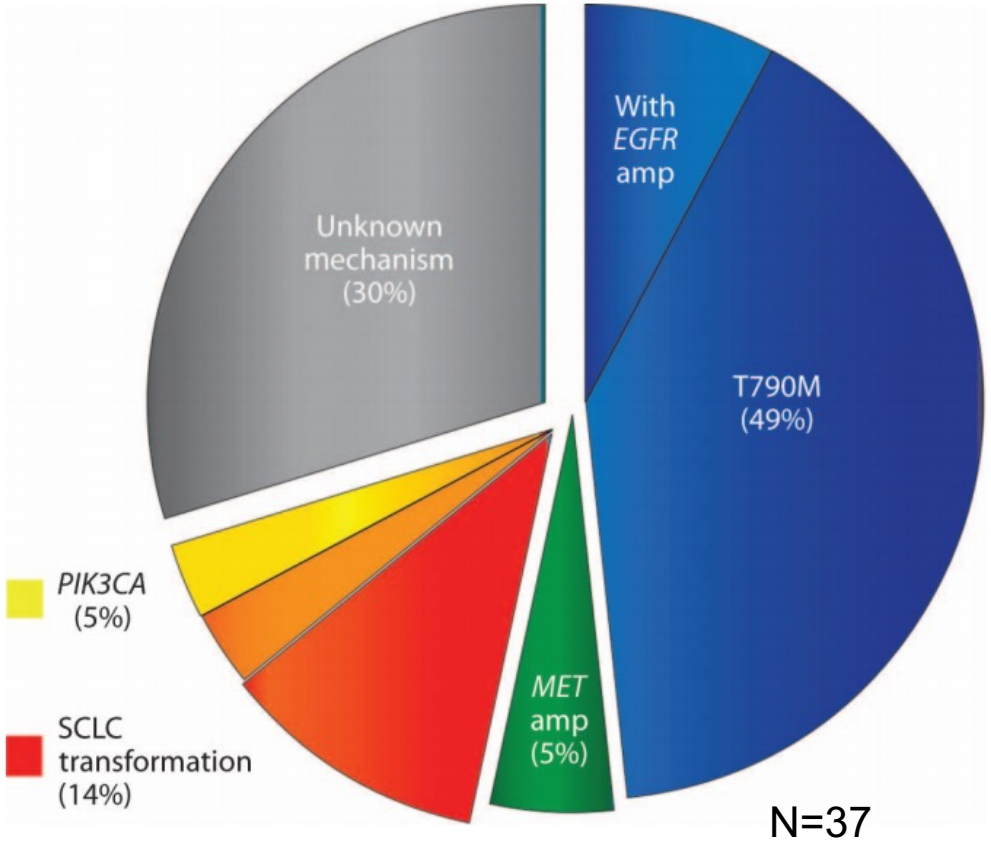
Weickhardt et al. JTO 2012

Resistance to 1st/2nd Generation EGFR Inhibitors

EURTAC: 1L erlotinib vs chemotherapy



PFS 9.7 vs 5.2 months



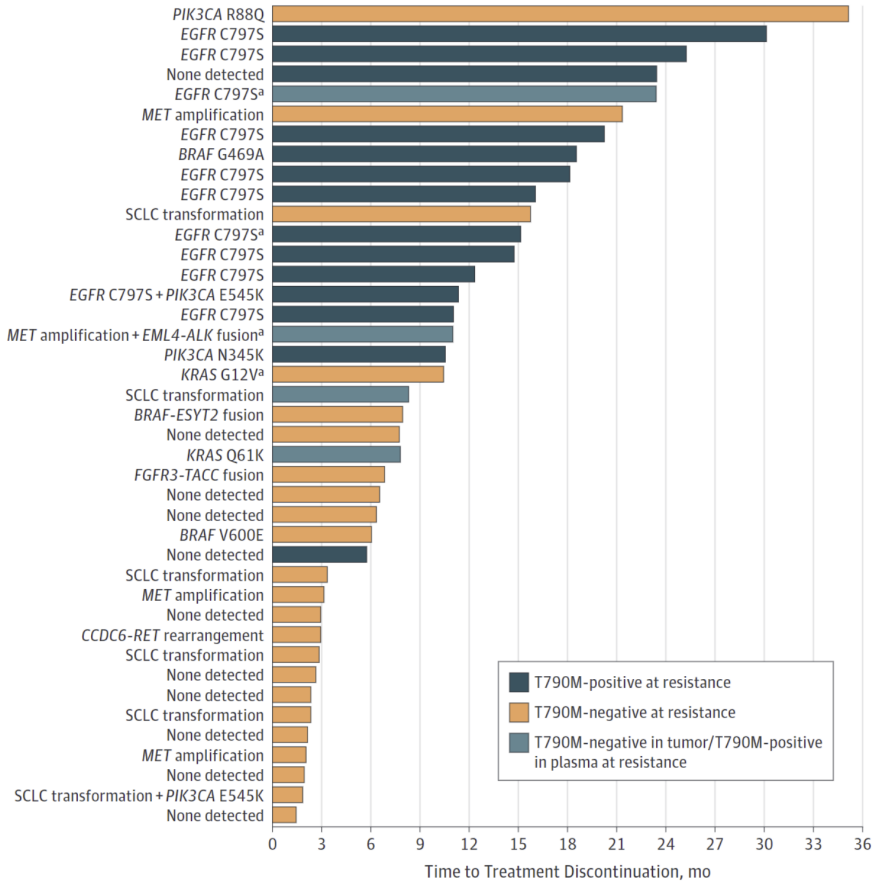
~50% Acquired EGFR T790M mutations at early generation TKI resistance

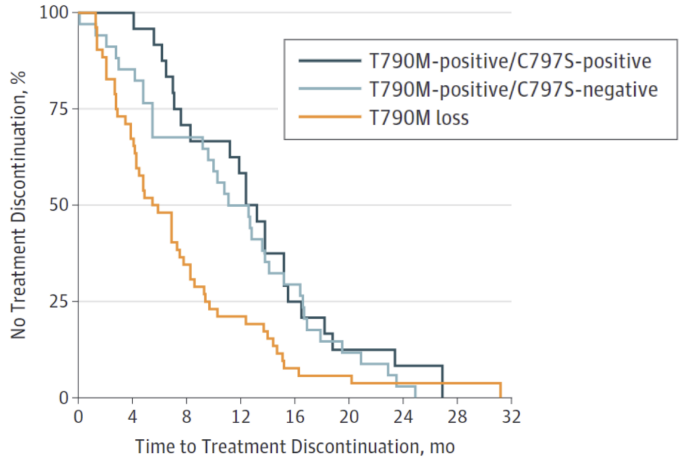
"Gatekeeper" steric interference

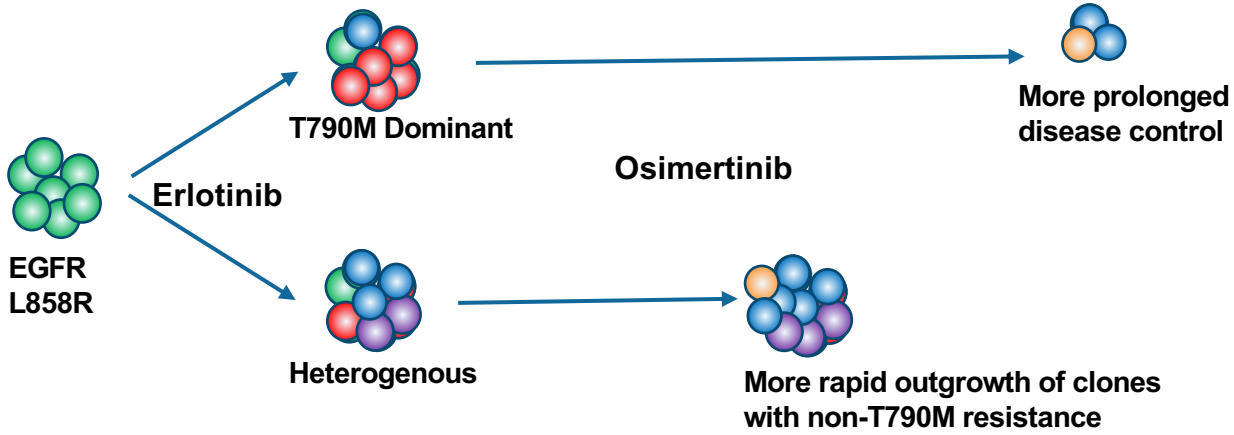
Third generation EKI therapy (osimertinib) 2L/T790M+ (AURA) and then frontline (FLAURA)

Sequist et al. Science Translational Med. 2011; 3(75):75ra26, Rosell et al. Lancet Oncol. 2012; 12(3):329

Patients who lost detectable T790M at acquired resistance to 2L+ osimertinib had worse outcomes



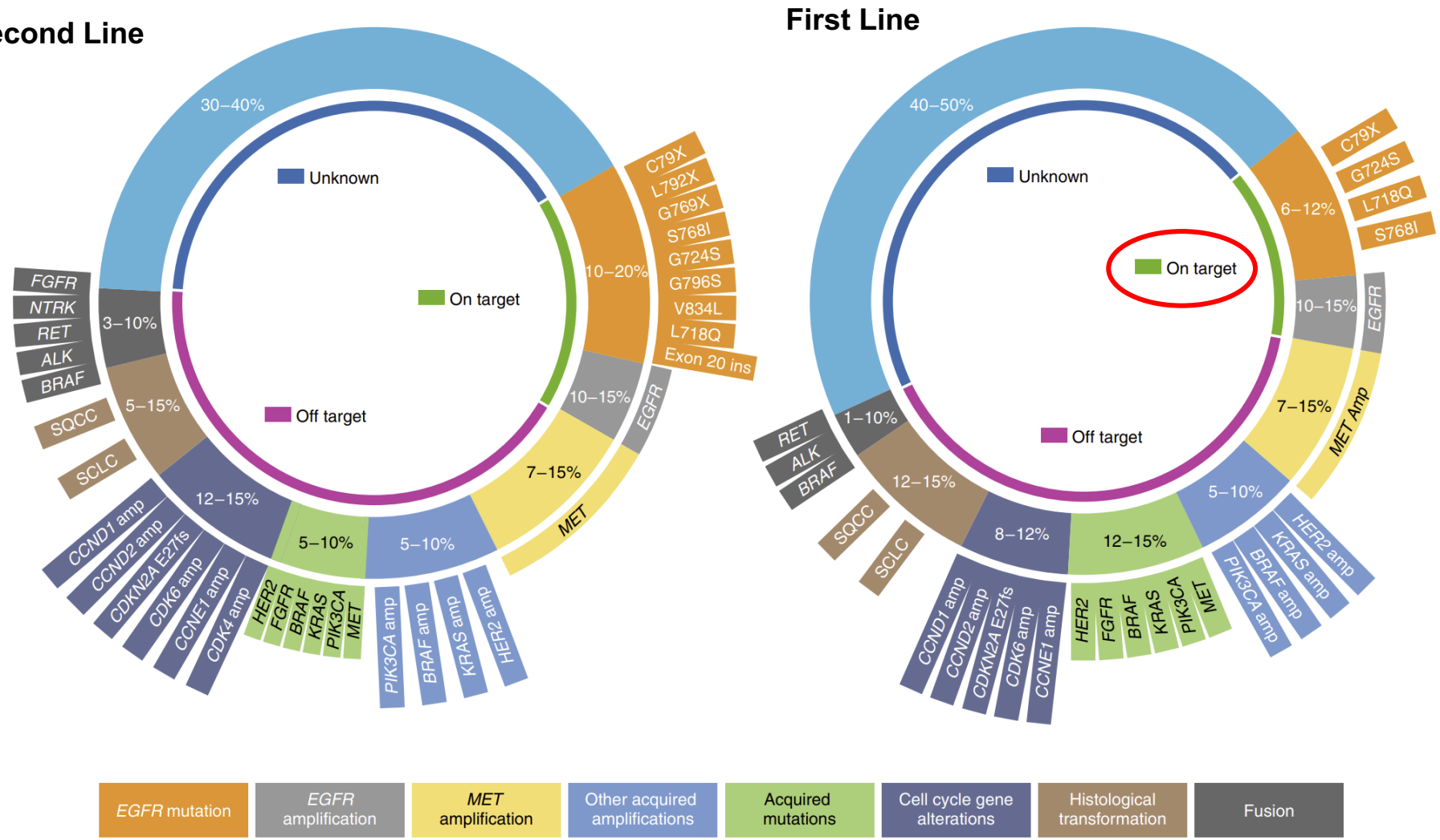




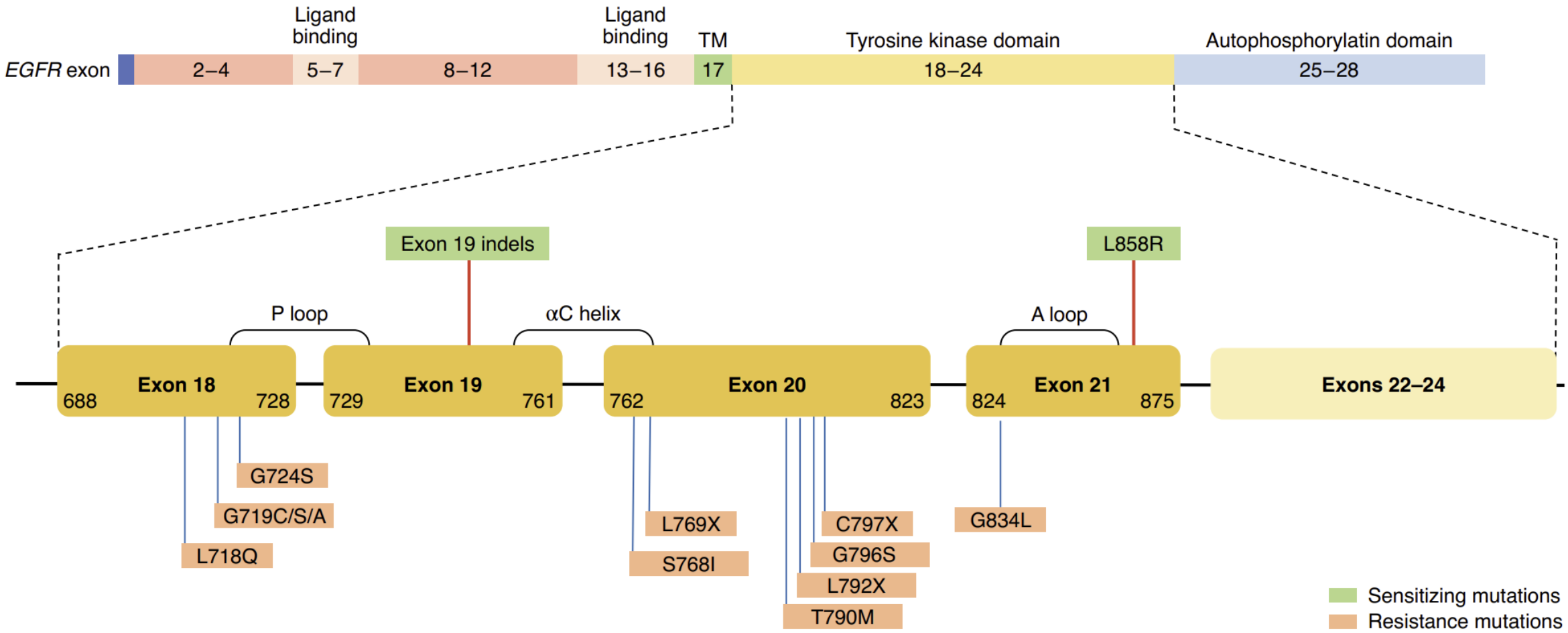
Suggests the T790M+ clones were less dominant and alternative resistance mechanisms more readily present to overcome osimertinib treatment

Oxnard et al, 2018

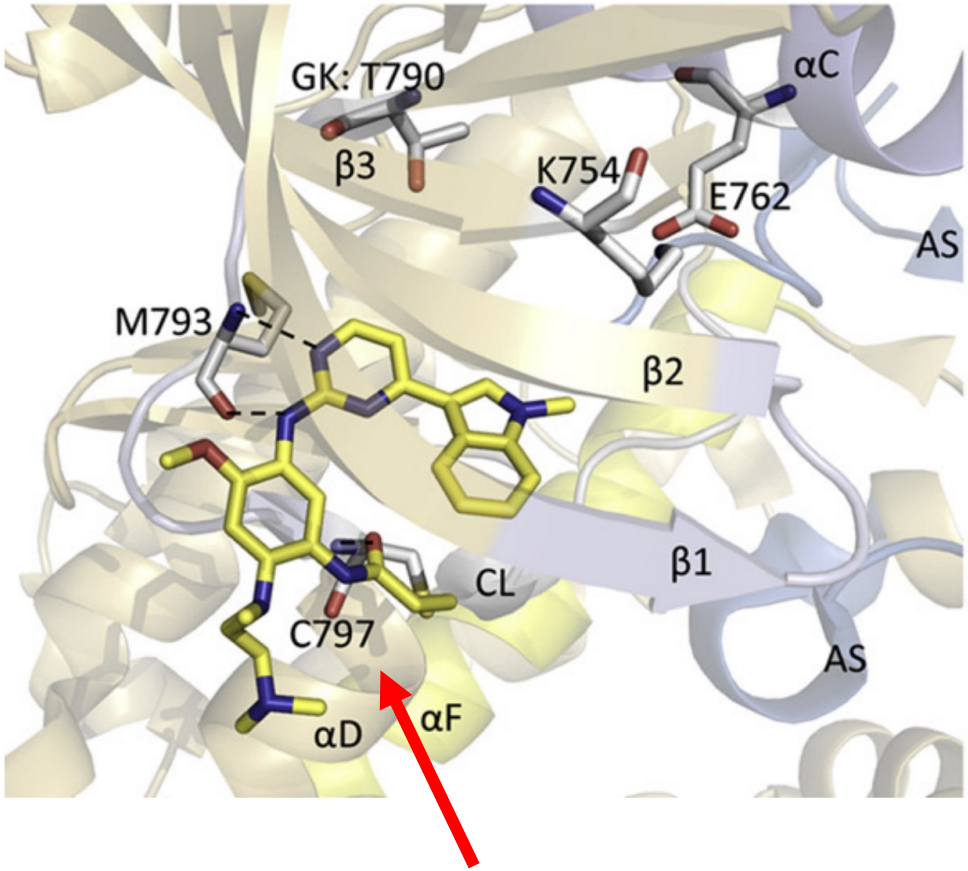
Resistance to Osimertinib



EGFR Second-Site Mutations



EGFR C797S



Residue C797 is the site of osimertinib covalent binding

C797S is the most common second-site EGFR mutation at osimertinib resistance

- 7% - 12.5% of acquired resistance

Roskoski et al, 2019; Ramalingam et al WCLC 2022 MA07.03

EGFR Triple Mutants, A Clinical Challenge

EGFR inhibitor	*EGFR* mutant type (preclinical model prediction)			
	Sensitizing Mutation (SM) exon 19 indels / L858R	SM / C797S	SM / T790M	SM / T790M / C797S
Gefitinib (1st gen. reversible)	sensitive	sensitive	resistant	resistant
Erlotinib (1st gen. reversible)	sensitive	sensitive	resistant	resistant
Afatinib (2nd gen. irreversible)	sensitive	resistant	resistant	resistant
Dacomitinib (2nd gen. irreversible)	sensitive	resistant	resistant	resistant
Osimertinib (3rd gen. irreversible)	sensitive	resistant	sensitive	resistant

resistant | sensitive

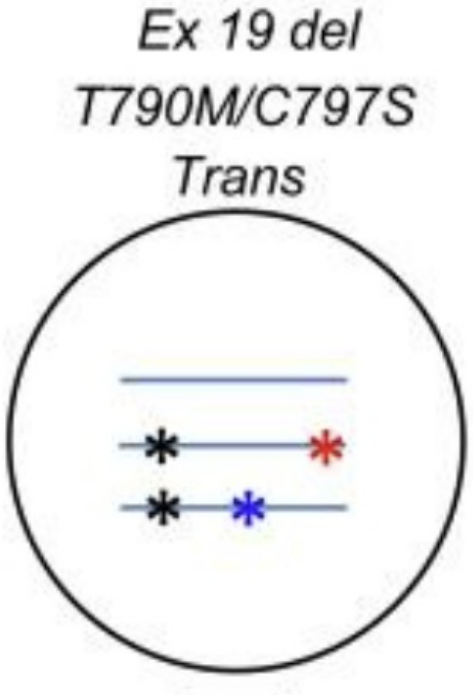
1st/2nd Generation **+T790M** → 3rd Generation **+C797S** →

3rd Generation **+C797S** → 1st/2nd Generation **+T790M** →

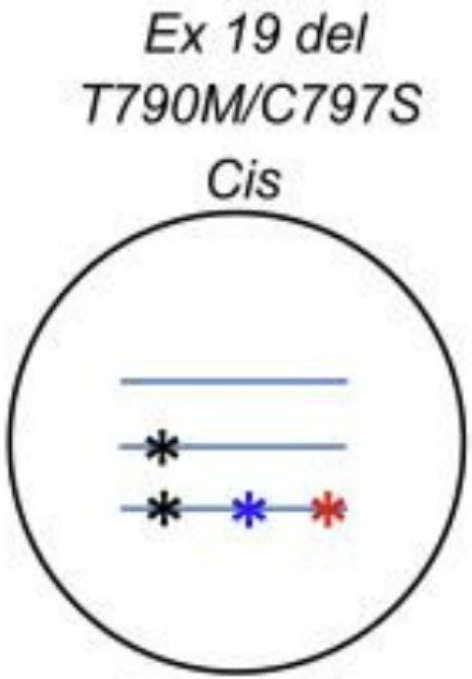
Triple Mutant SM/T790M/C797S

Rangachari et al, 2019

Triple Mutant EGFR – Allelic Context



- **T790M and CS97S on different alleles**
- **1st Generation + 3rd Generation EGFR TKI Active?**



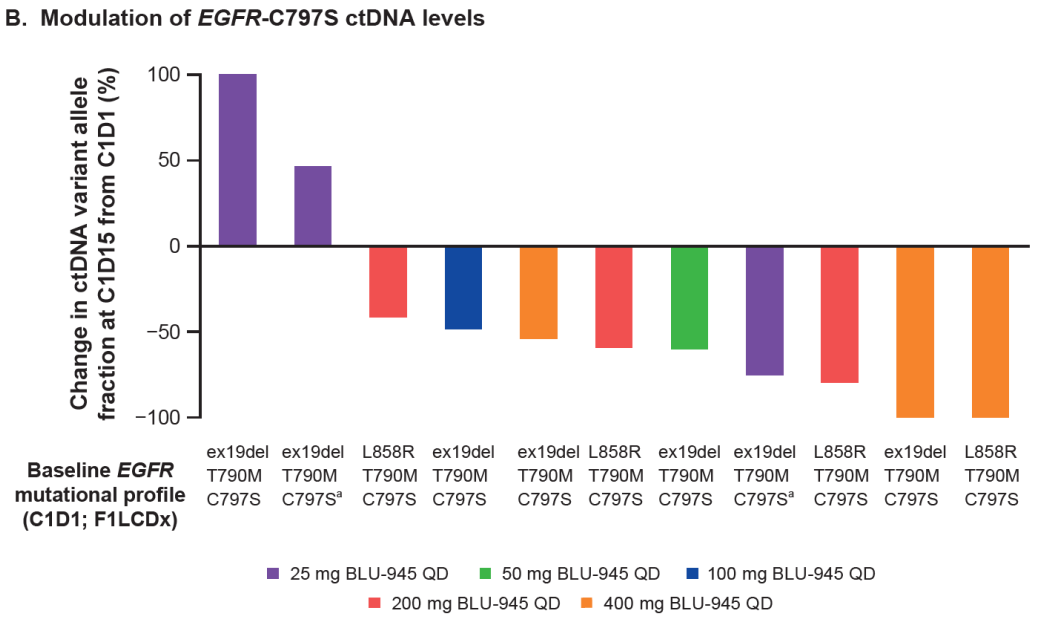
- **T790M and CS97S on same allele**
- **No active SOC TKI combination**

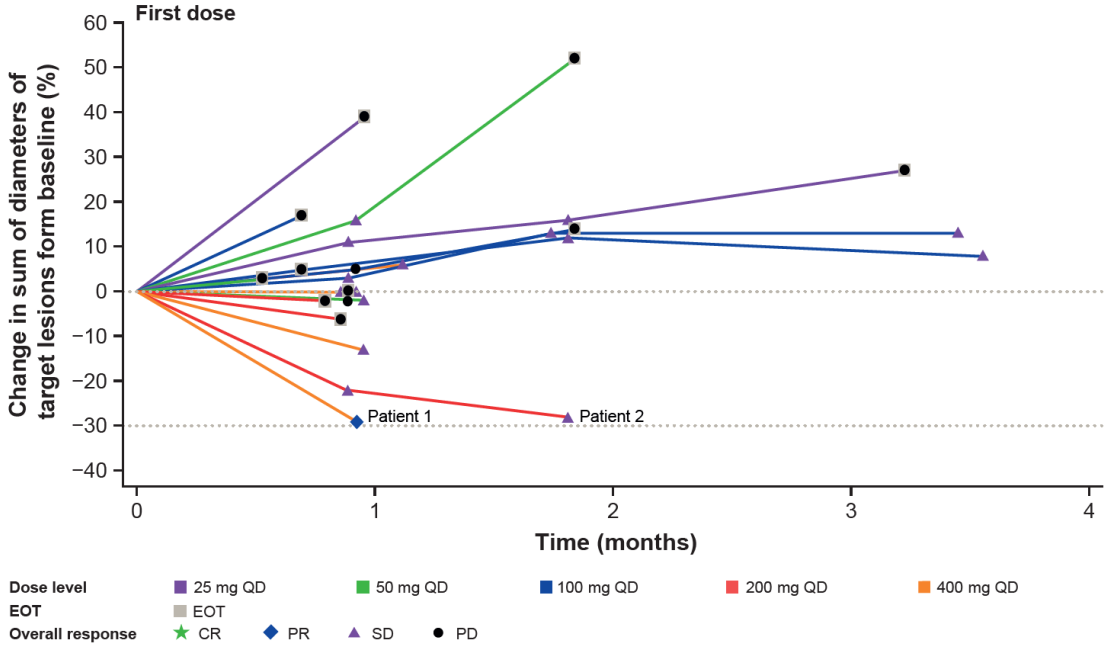
Triple-Mutant Active Inhibitors

- Catalytic-Site ATP Competitive Inhibitors
- Allosteric Inhibitors

Niederst et al, 2015

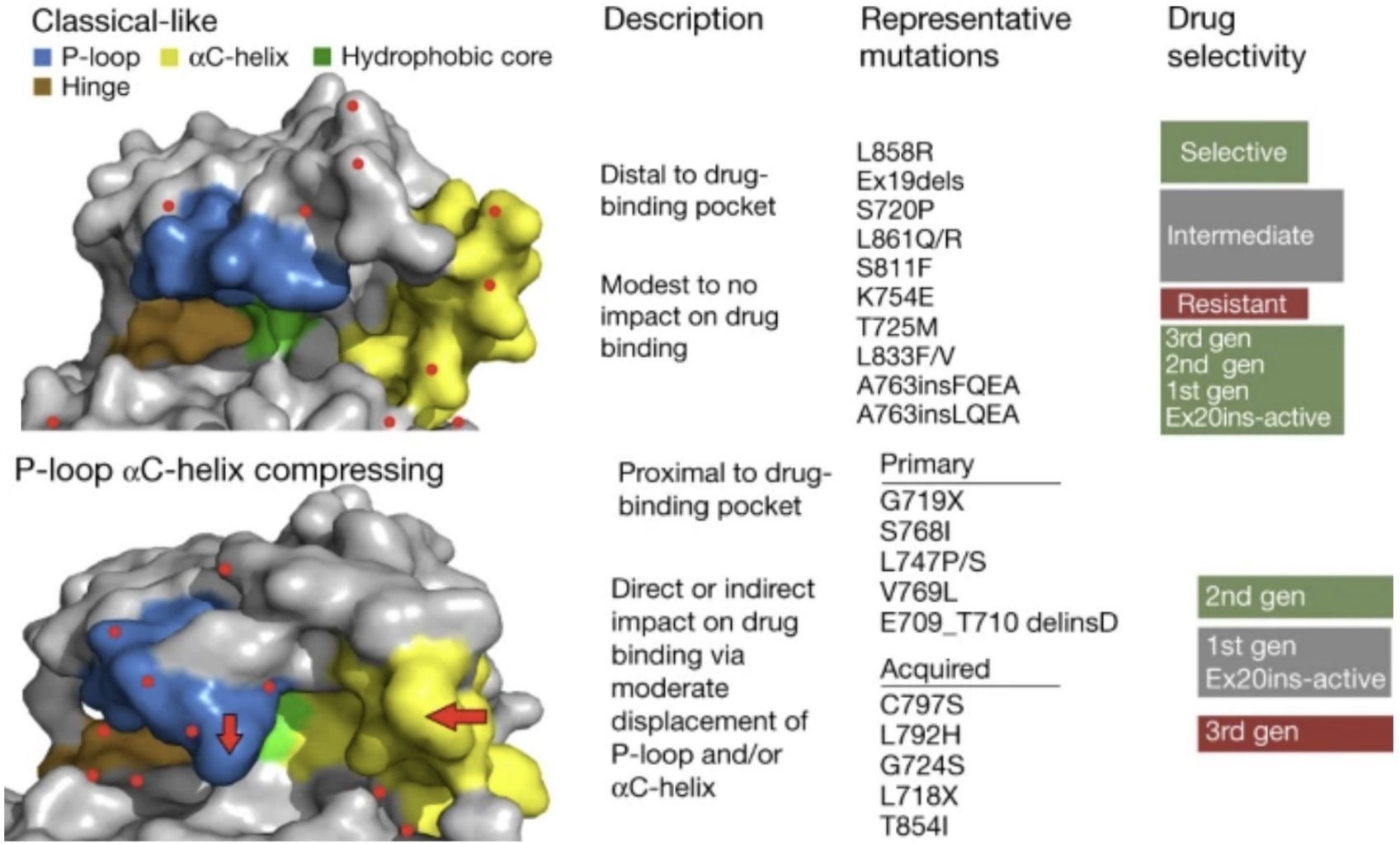
BLU-945, a Fourth Generation EGFR Inhibitor





Shum et al. AACR 2022

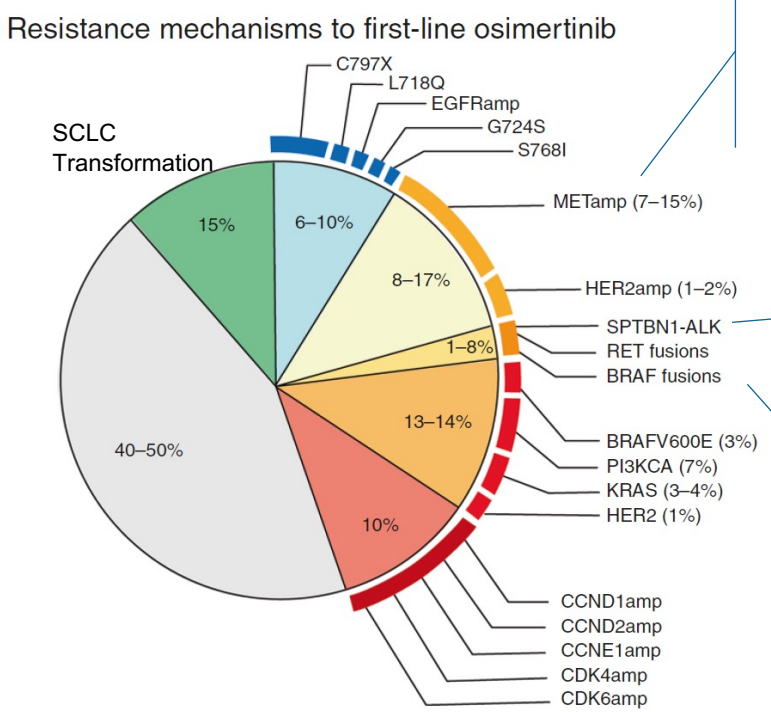
Modeling to predict 3rd generation TKI sensitivity



	Description	Representative mutations	Drug selectivity
Classical-like	Distal to drug-binding pocket	L858R Ex19dels S720P L861Q/R S811F	Selective Intermediate
	Modest to no impact on drug binding	K754E T725M L833F/V A763insFQEA A763insLQEA	Resistant 3rd gen 2nd gen 1st gen Ex20ins-active
P-loop αC-helix compressing	Proximal to drug-binding pocket	Primary G719X S768I L747P/S V769L E709_T710 delinsD	2nd gen 1st gen Ex20ins-active
	Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix	Acquired C797S L792H G724S L718X T854I	3rd gen

Robichaux et al. 2021

Off-Target or Unknown Mechanisms of Acquired Osimertinib Resistance



MET Amplification (~15%)
EGFR TKI + MET TKI
ORR 27%

ALK Fusions
Case Reports of Response To EGFR TKI + ALK TKI

BRAF V600E
Case Reports of Response to EGFR + BRAF/MEK inhibitor

RET Fusions (~5%)
Osimertinib + Selpercatinib ORR 50%

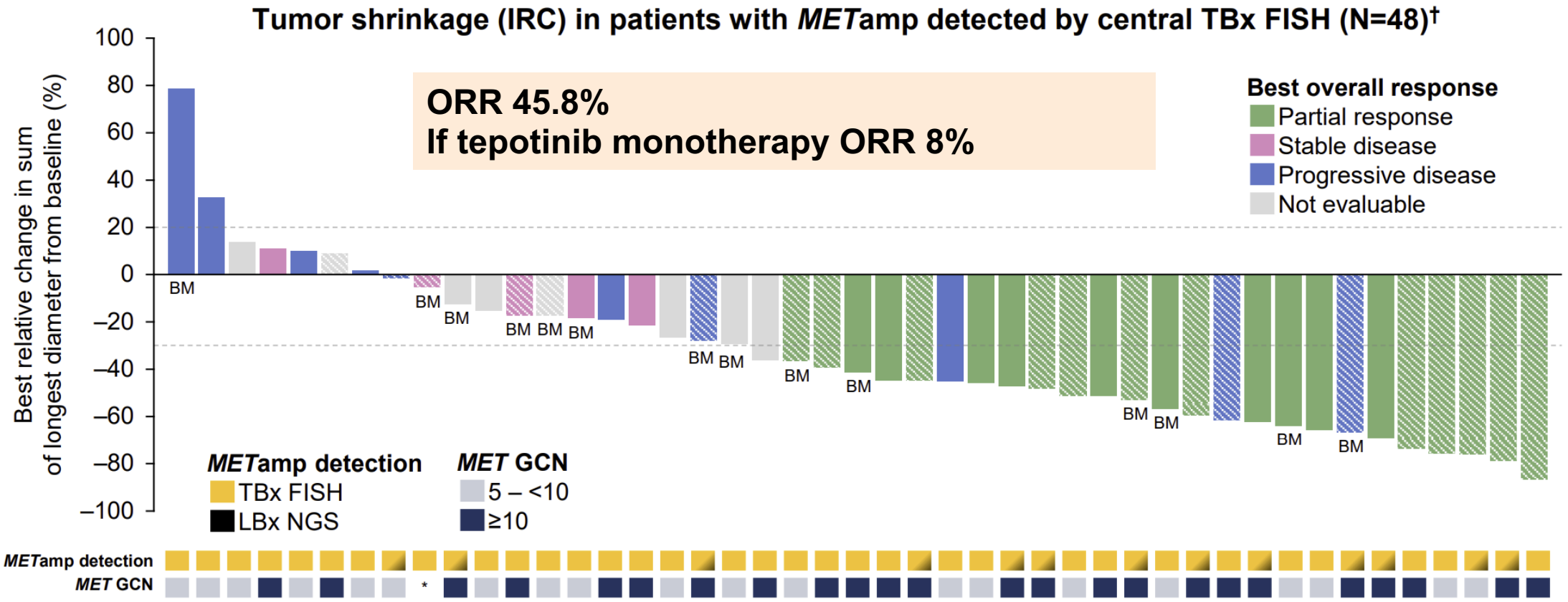
Prospective Studies Ongoing
ORCHARD Osimertinib + Multiple Targets (EGFR amplification, EGFR C797S, ALK fusion, RET fusion)
TATTON Osimertinib + selumetinib (MEK) or savolitinib (MET amplified)
SAVANNAH Osimertinib + savolitinib (MET)

Non-TKI Strategies

- **Lazertinib + Amivantamab** (EGFR TKI + EGFR/MET bispecific antibody)
- **Antibody-Drug Conjugates** (TROP2, HER3)

Leonetti et al. BJC. 2019, Wu et al 2020; Wang et al. Lung Cancer 2020, Piotrowska et al. Cancer Discovery. 2018; Meng et al. Lung Cancer. 2020; Ramalingam et al. AACR 2019 CT034; Rotow et al. IASLC WCLC 2020.

INSIGHT 2: Tepotinib + Osimertinib for Acquired MET amplification



*One patient had GCN 4.96 and enrolled through a *MET/CEP7* ratio ≥2. †Three patients were excluded due to a baseline/post-baseline measurement not being available.
Hashed bars indicate patients with ≥9 months' follow-up. BM, brain metastases at baseline.

PARIS 2022 ESMO congress

Julien Mazieres

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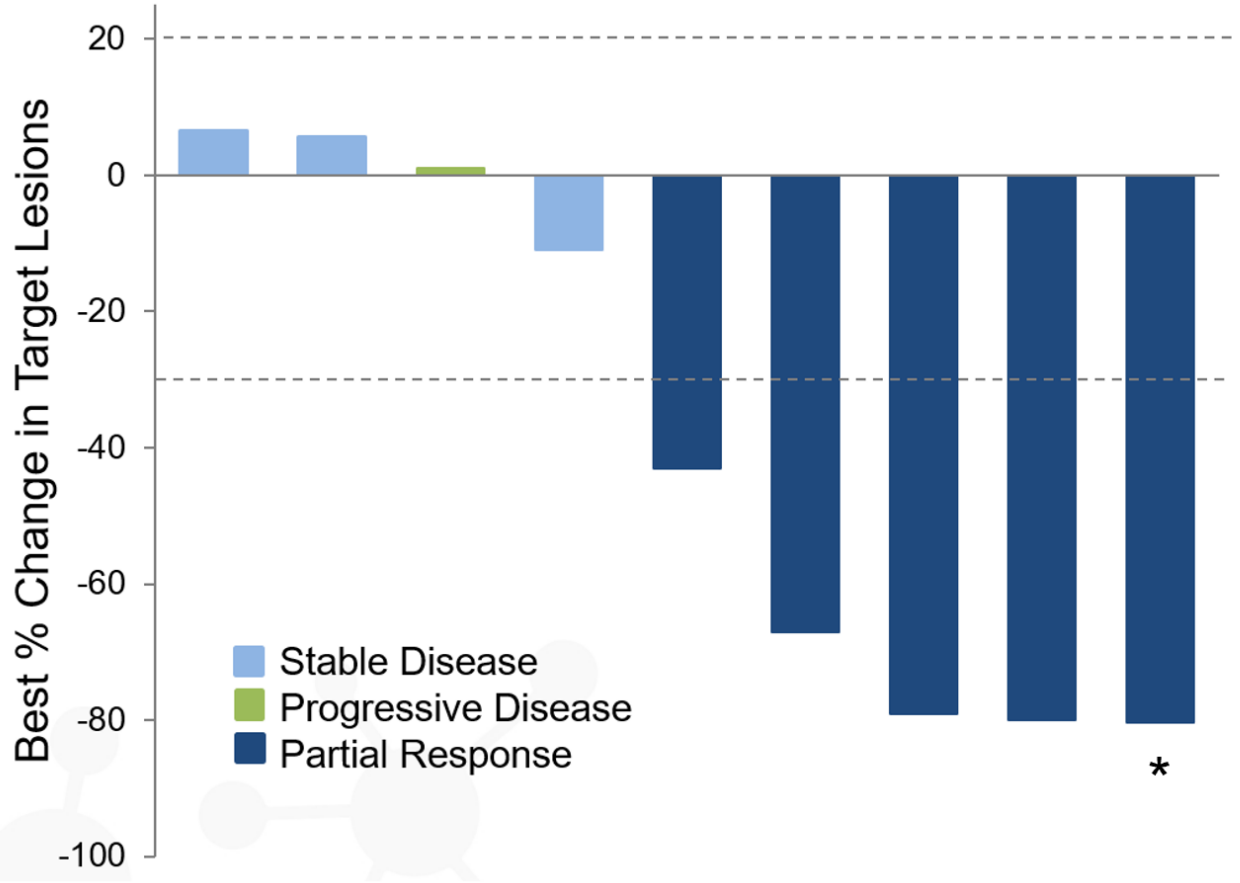
Acquired RET amplification



Compassionate selpercatinib access program

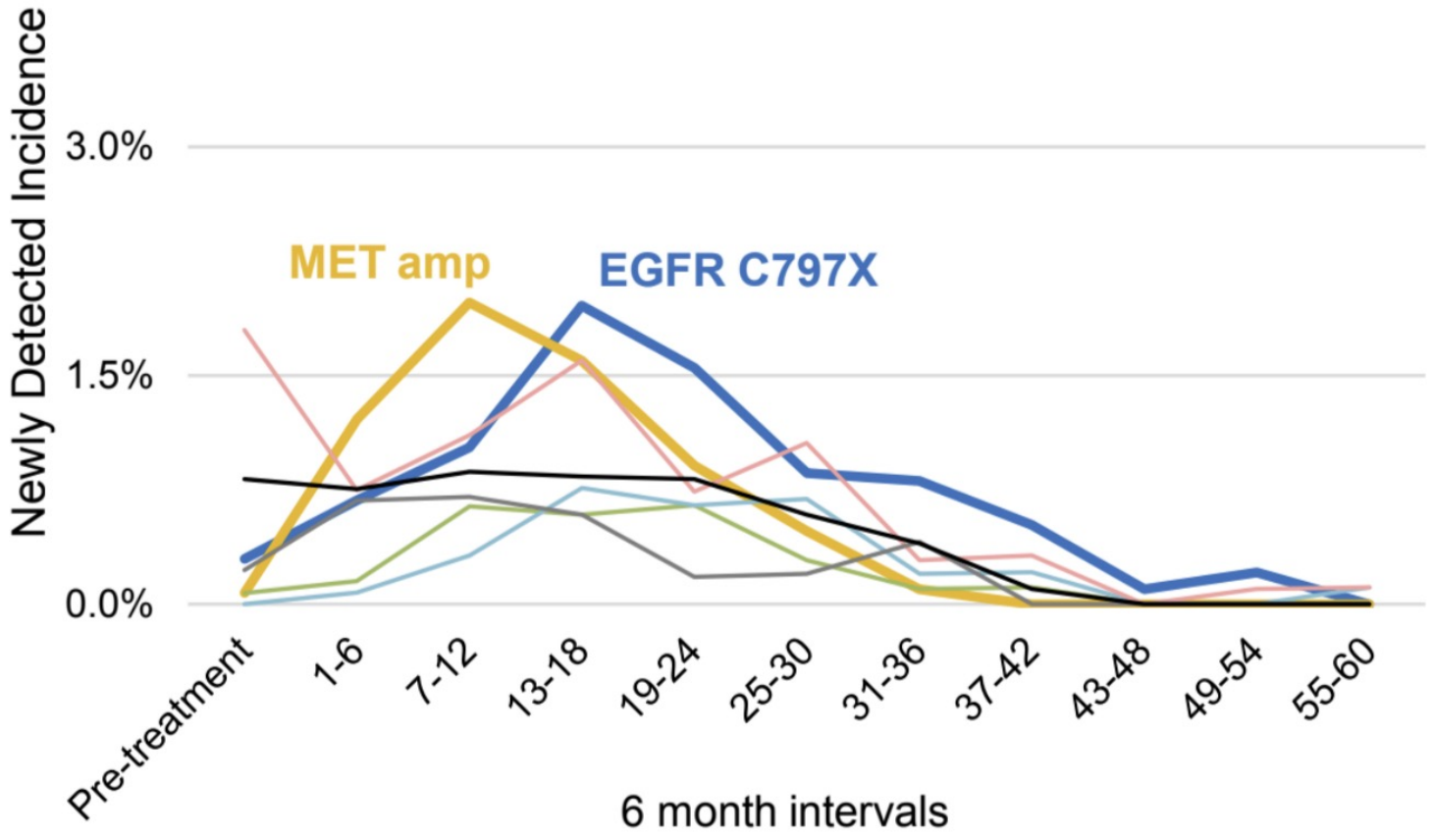
EGFRm NSCLC with acquired RET fusion

Unconfirmed ORR 50%

Median Duration of Treatment 7.4 months

Rotow et al. WCLC 2021

Dynamics of 1L Osimertinb Resistance

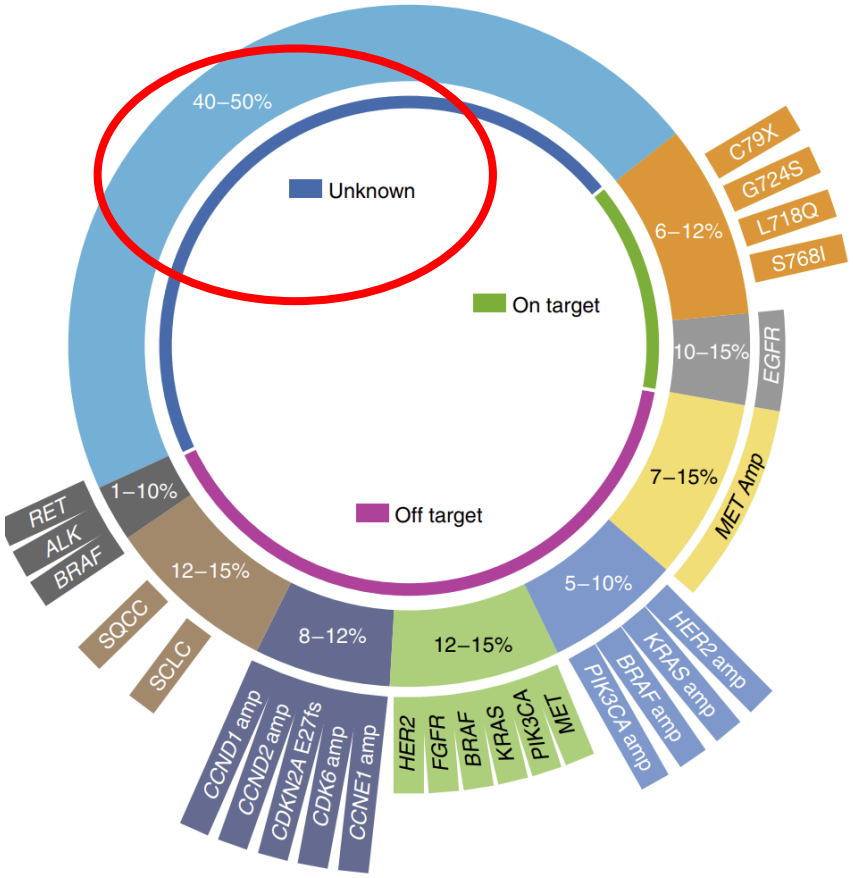


Resistance in 1st Year:
MET amp = most common

Resistance in 2nd Year: EGFR C797S = most common

Ramalingam et al. WCLC 2022 MA07.03

Novel Therapeutic Classes for EGFR TKI Resistance



Non-TKI Strategies

- **Lazertinib + Amivantamab** (EGFR TKI + EGFR/MET bispecific antibody)
- **Antibody-Drug Conjugates** (TROP2, HER3)

CHRYSALIS Phase 1 Study Design: Combination Cohort (NCT02609776)

Key Objectives

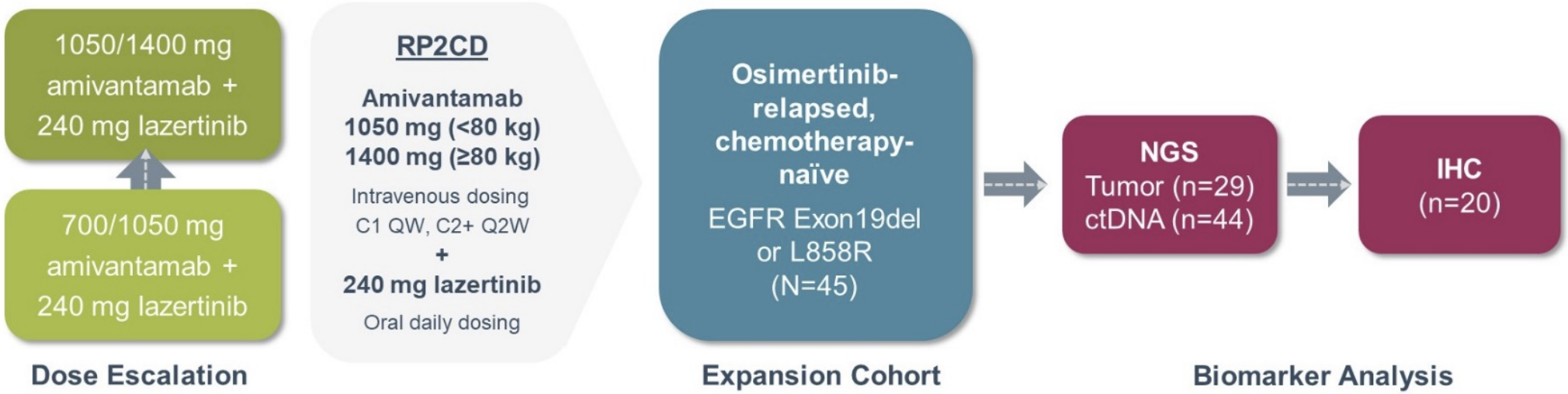
- Establish RP2CD
- Safety and efficacy at RP2CD

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

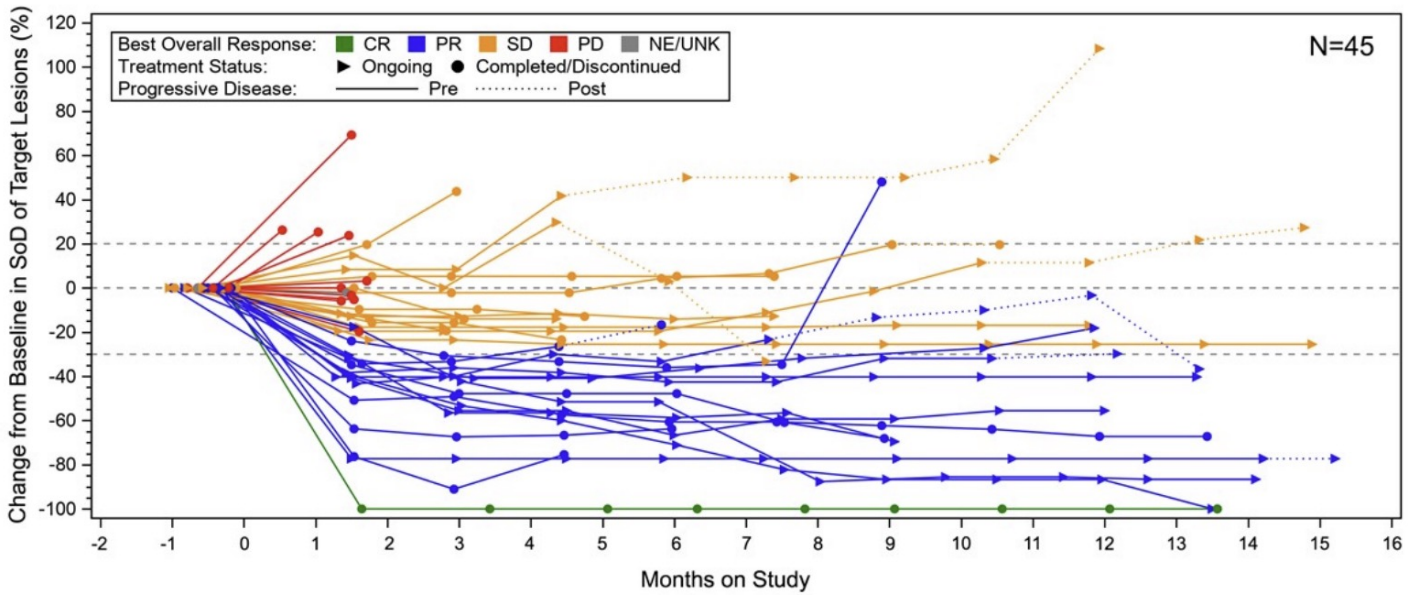


This presentation provides updated results with longer follow-up from the ESMO 2020 oral presentation (Cho *Ann Oncol* 31:S813 Oral #1258O). [a]≥1 alteration detected in 42/44 ctDNA and 29/45 tumor NGS analyses.
C, cycle; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; QW, weekly;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

Presented By: BC Cho
Abstract #9006

2021 ASCO ANNUAL MEETING

Amivantamb + Lazertinib at EGFR TKI Resistance



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)

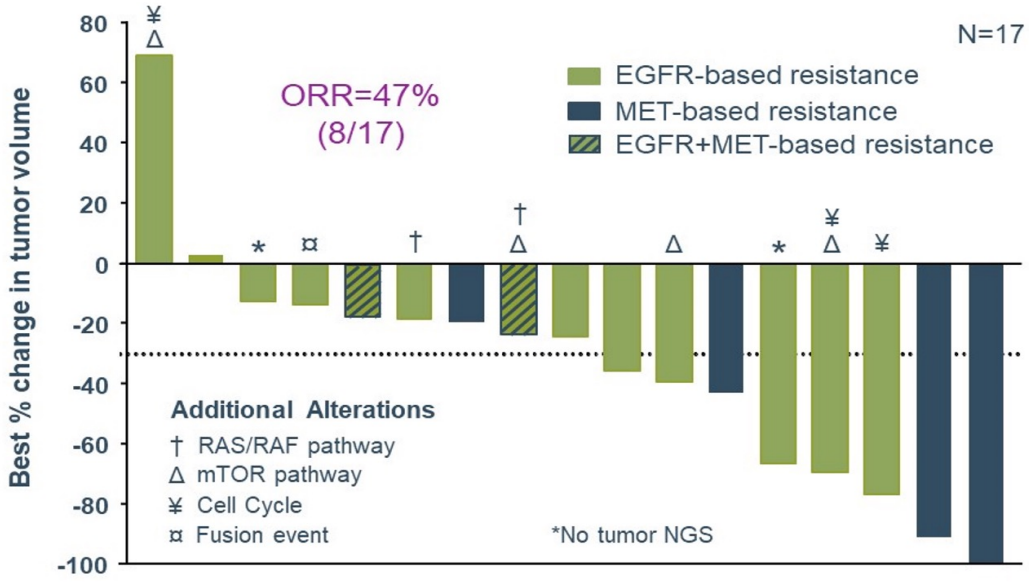
- Safety profile consistent with previous experience with amivantamab + lazertinib[1]
- Most common AEs were IRR (78%), rash (acneiform dermatitis, 51% + rash, 27%), and paronychia (49%)
  - Majority were grade 1–2
- Treatment-related: grade ≥3 AE (16%), discontinuations (4%), dose reductions (18%)

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

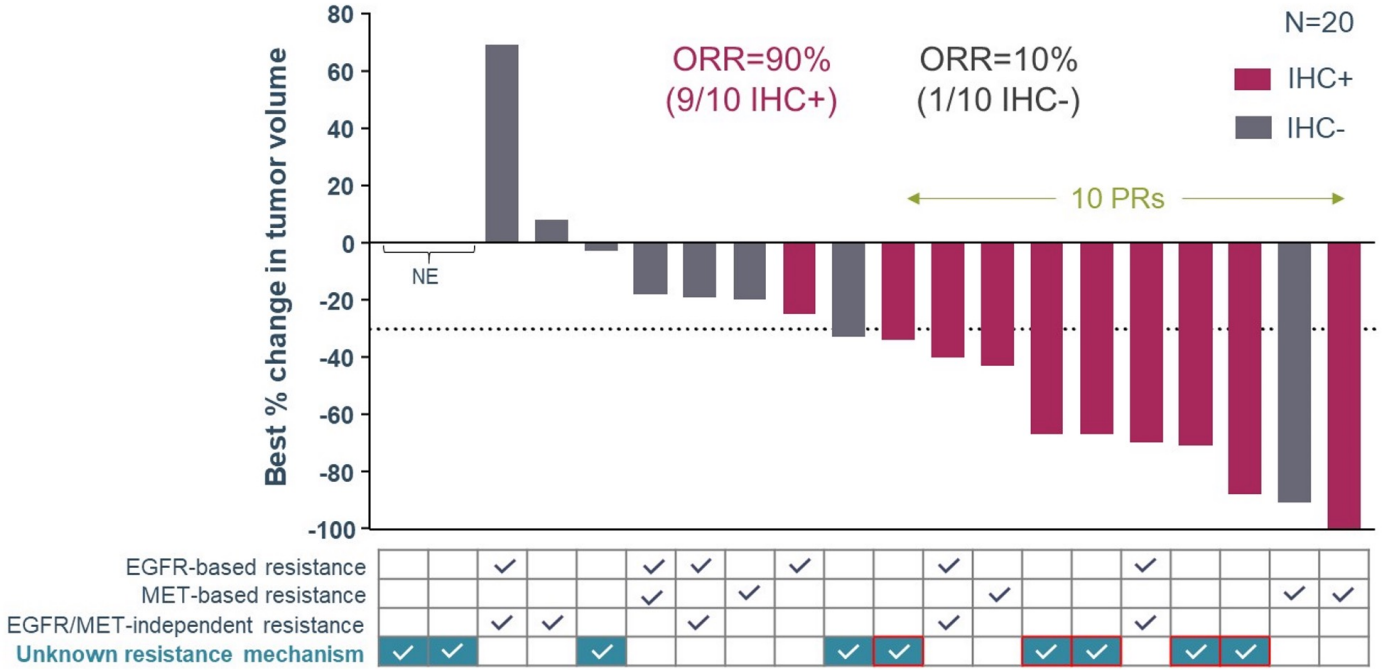
Presented By: BC Cho
Abstract #9006

2021 ASCO ANNUAL MEETING

EGFR/MET Biomarkers for Response

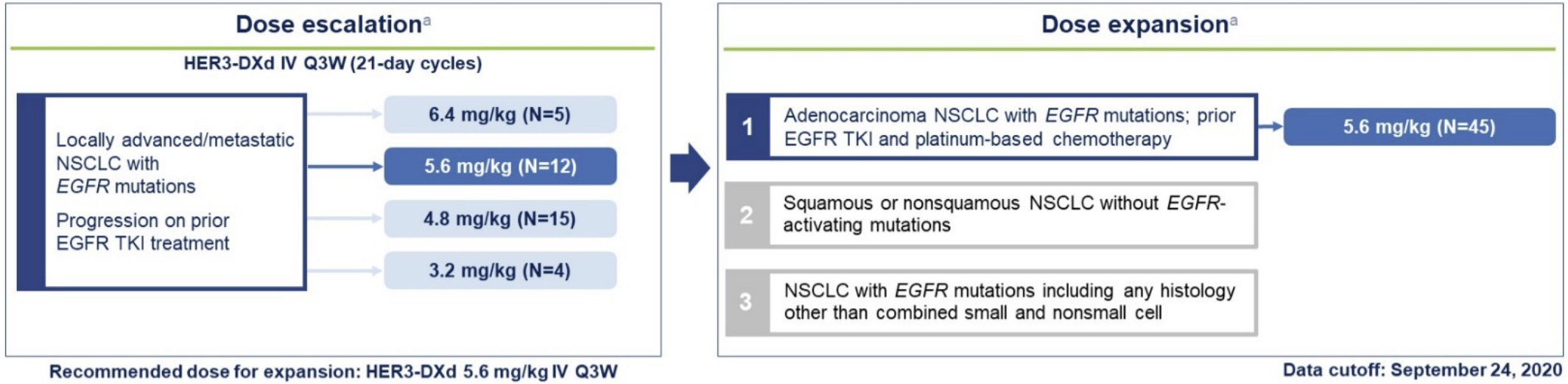


NGS Positive for EGFR/MET-Driven Resistance



ORR by EGFR/MET IHC STatus

U31402-A-U102 is a Phase 1 Dose Escalation and Dose Expansion Study in Patients With NSCLC



Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

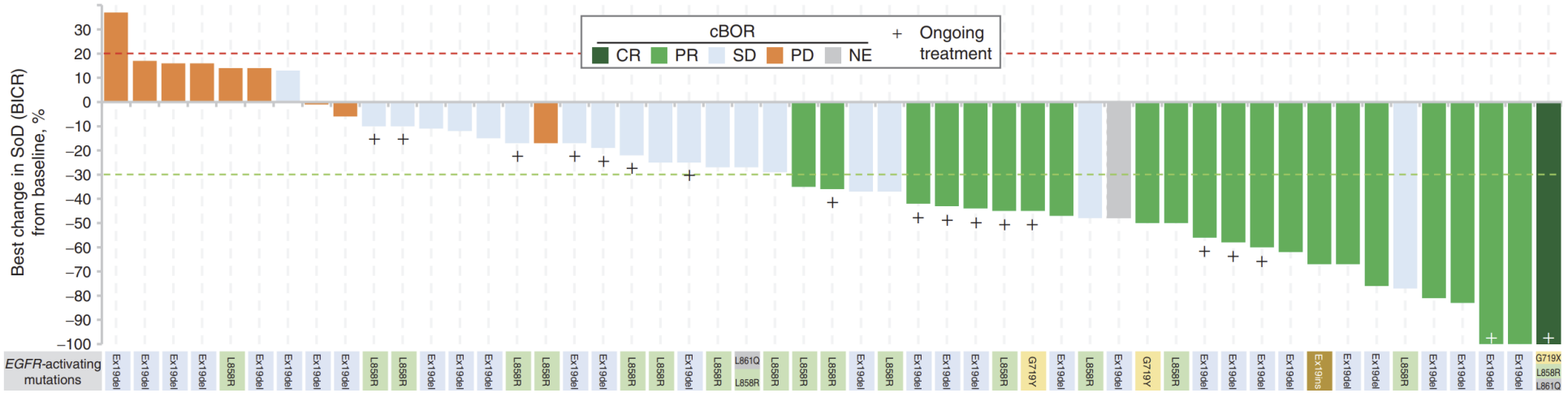
Data cutoff: September 24, 2020

57 patients with EGFR TKI–resistant, *EGFR*m NSCLC were treated with HER3-DXd 5.6 mg/kg in dose escalation (N=12) and dose expansion Cohort 1 (N=45)

- **Efficacy** evaluation in pooled patients with *EGFR*m NSCLC treated with HER3-DXd 5.6 mg/kg (**N=57**)
  (Median Follow Up: 10.2 mo; range, 5.2-19.9 mo)
- **Safety** evaluation in all patients in dose escalation and dose expansion Cohort 1 (**N=81**)

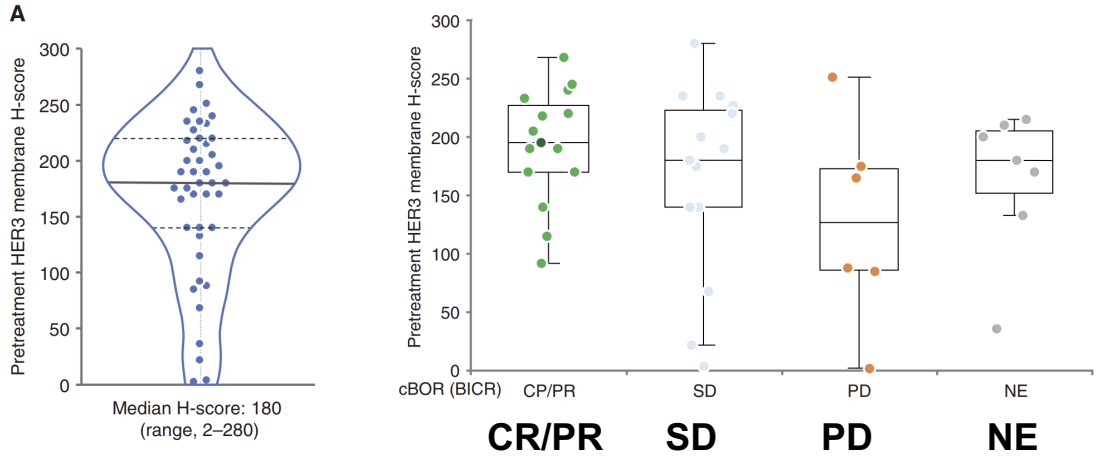
Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.
[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

Patritumab-deruxtecan (HER3-DXd) after EGFR TKI Resistance



ORR 39%
DCR 72%
PFS 8.2 months

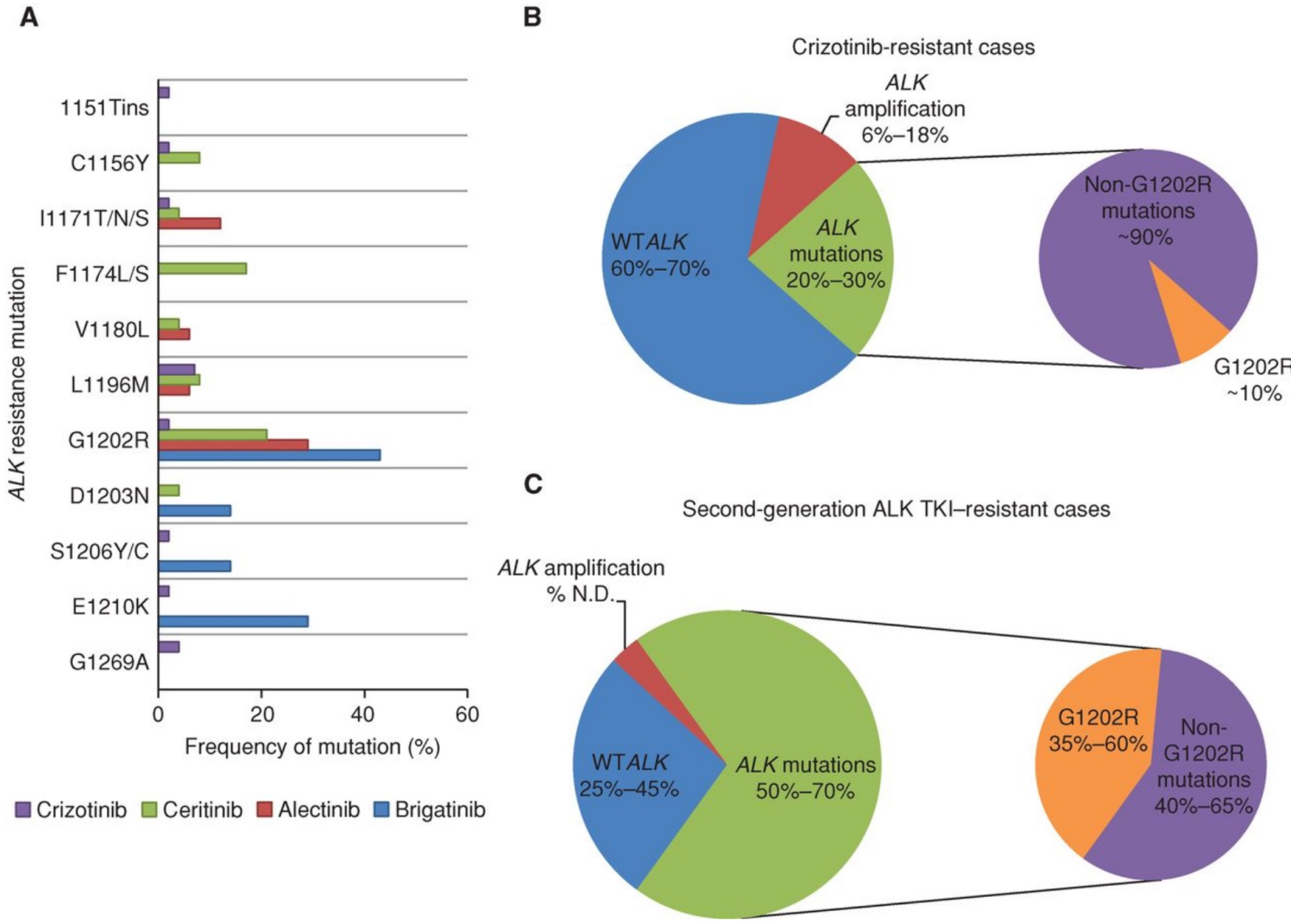
HER3 H-Score



Probability of response similar across wide range of HER3 expression

Jänne et al, 2022

Resistance to ALK TKI Therapy



~60% ALK-dependent Resistance

~40% ALK-independent

Lin et al. Cancer Discov. 2017; 7(2):137

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F					
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

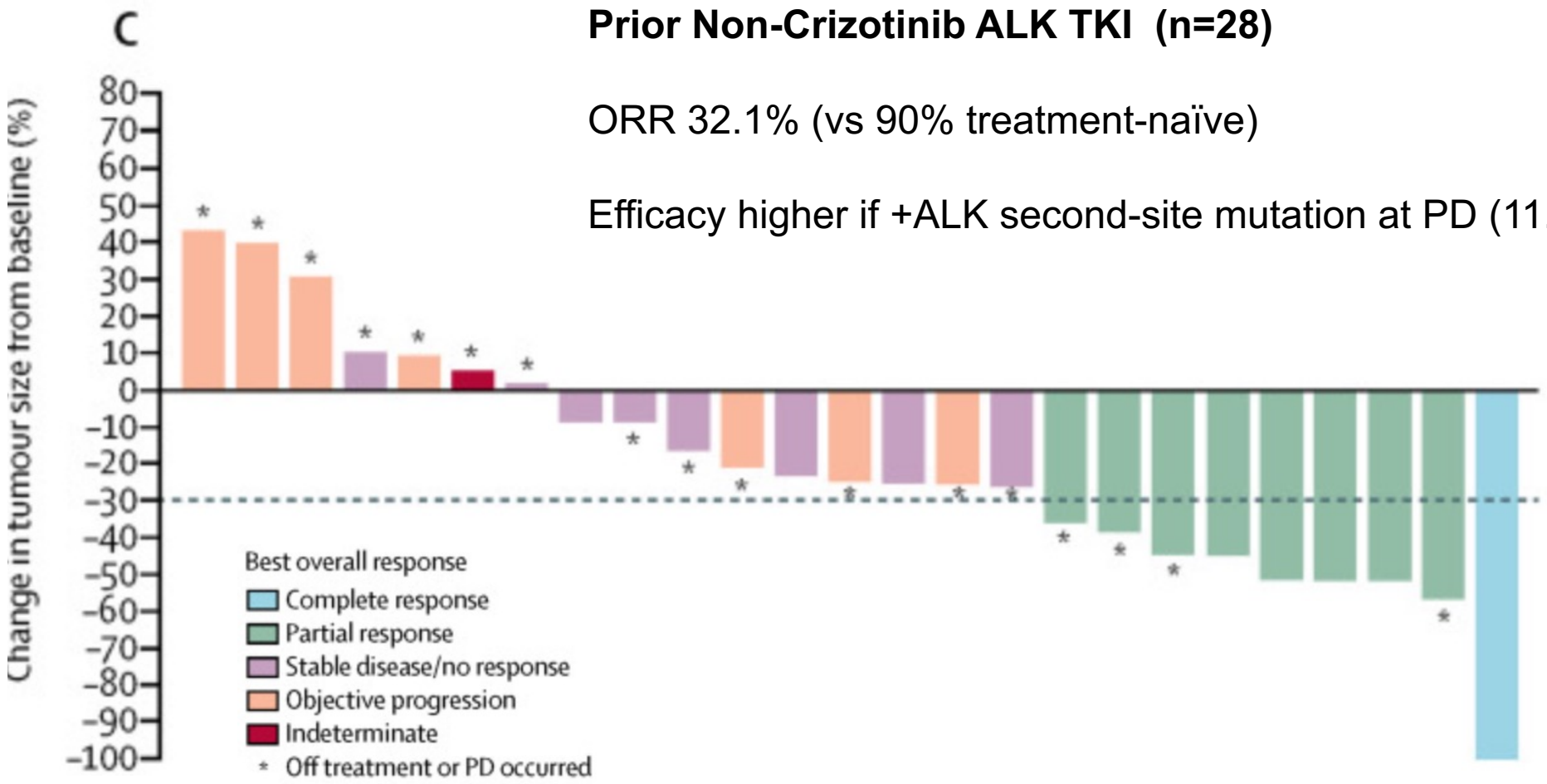
The ALK inhibitors vary in their activity against acquired ALK mutations

The G1202R produces resistance to all approved ALK inhibitors except lorlatinib

ALK G1202R Mutation

Gainor et al. Cancer Discovery. 2016

Lorlatinib, a G1202R active next-generation ALK inhibitor



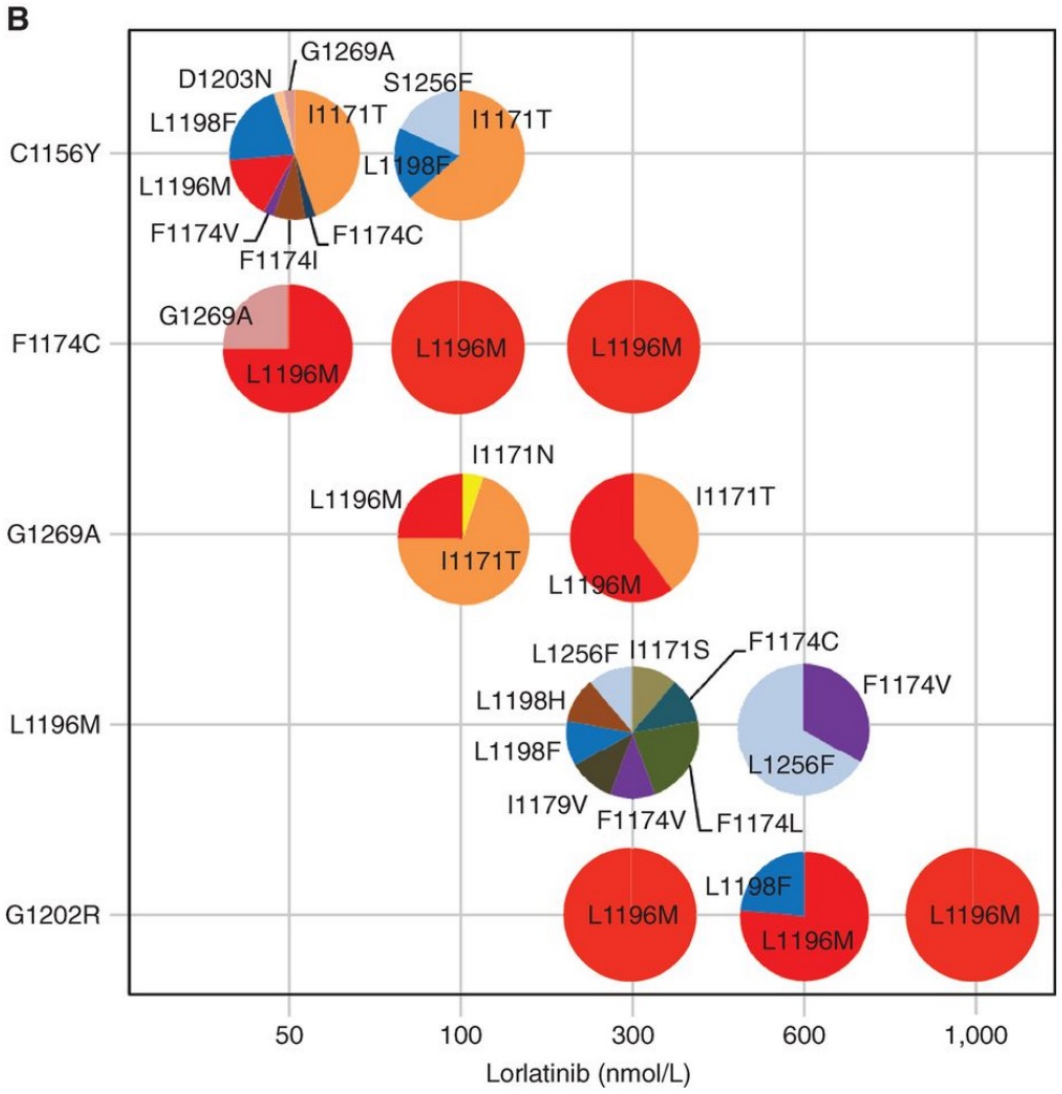
Prior Non-Crizotinib ALK TKI (n=28)

ORR 32.1% (vs 90% treatment-naïve)

Efficacy higher if +ALK second-site mutation at PD (11.0 vs 5.4 months)

Solomon et al. Lancet Oncol. 2018; 19(120):1654; Shaw et al. J Clin Oncol. 2019; 37(16):1370.

Lorlatinib Resistance

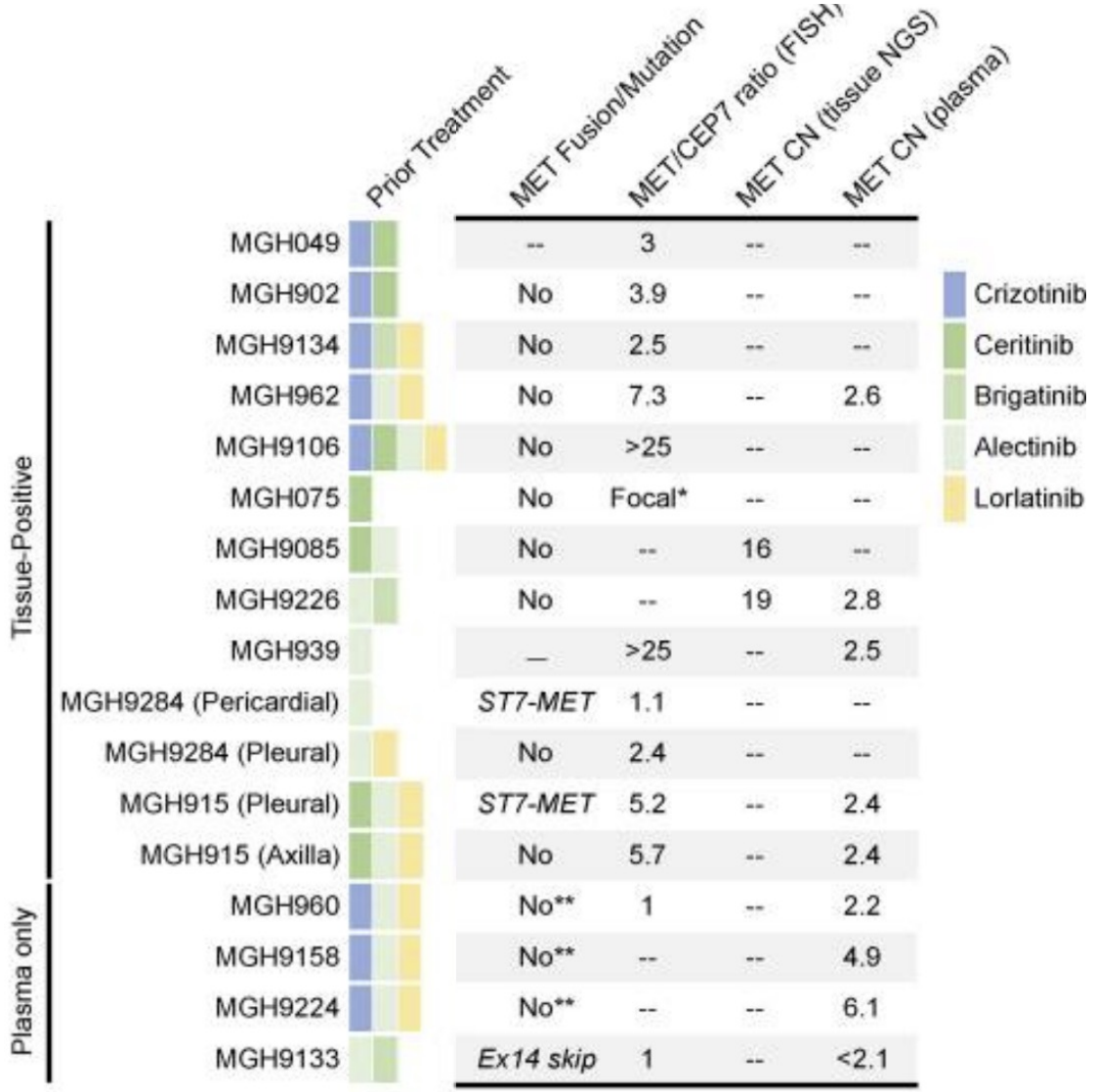


C1156Y (crizotinib resistance as single mutation)+ L1198F (lorlatinib resistance) resensitizes to crizotinib

I1171N compound mutations → Sensitive to the FLT3 inhibitor Gilteritinib in preclinical studies

L1196M + G1202R → resistance to all approved ALK TKIs

Yoda et al. Cancer Discovery. 2018; 8(6):714-29, Mizuta et al. Nature Communications. 2021;12:1261, Shaw et al. NEJM. 2016;374(1):54-61, Okada et al. EBioMedicine. 2019;41:105-19



MET Amplification at ALK Inhibitor Resistance

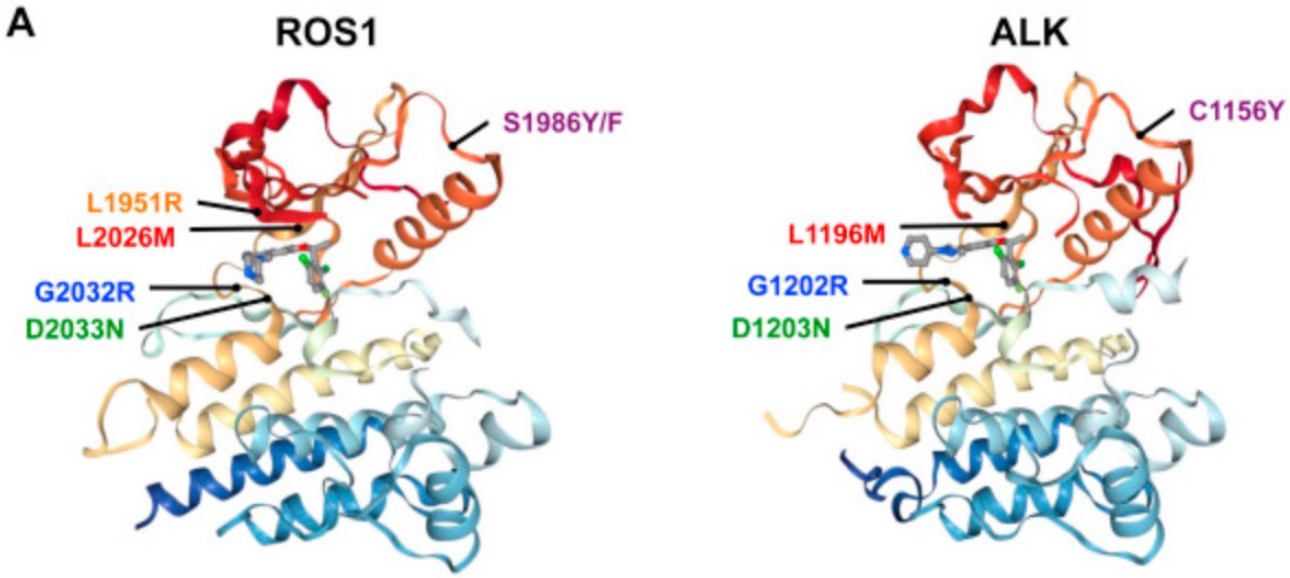
15% Rate of MET amplification

- 12% After 2nd Generation ALK Inhibitors
- 22% After lorlatinib

Two-patient case series with short duration responses to MET inhibition

- Crizotinib monotherapy 10 weeks PFS
- Crizotinib + Lorlatinib 3 months PFS

ROS1 Resistance



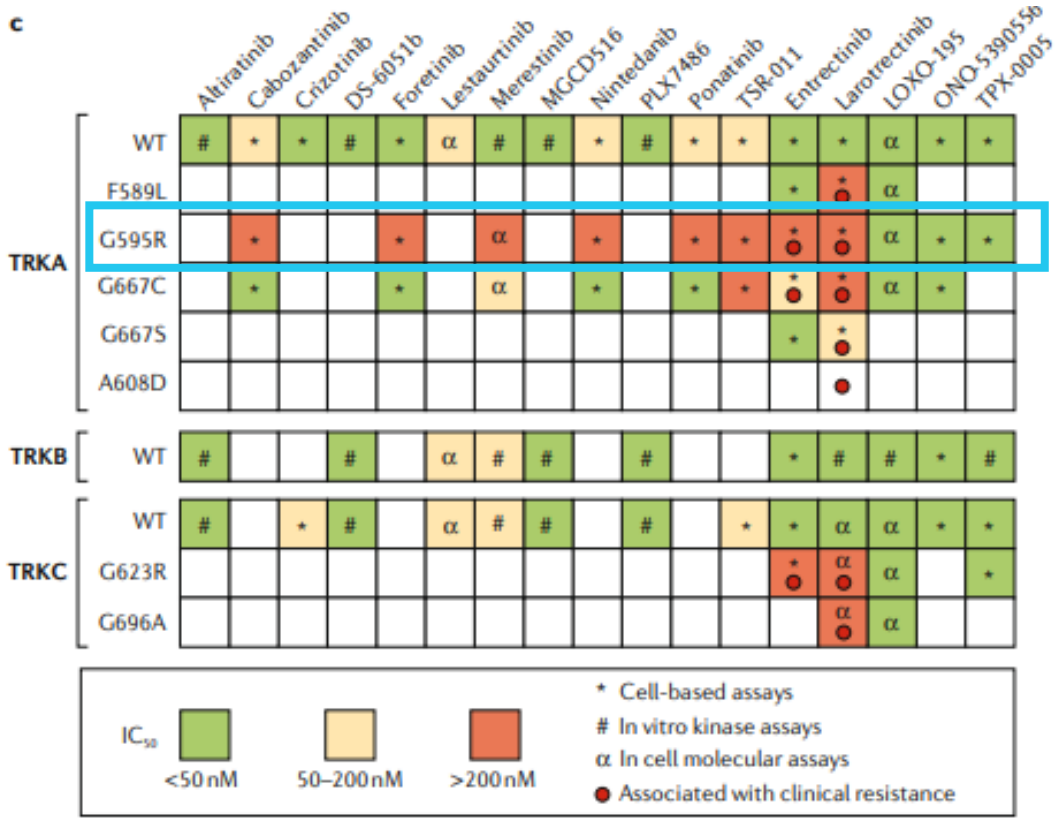
G2032R Solvent Front = dominant second site mutation
Repotrectinib clinical trials ongoing

IC_{50} (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Brigatinib	Taletrectinib	Alectinib
Parental	840.5	1801.0	>3000	1218.0	>3000	1117.0	>3000	>3000	1207.0
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	472.7	53.3	1091.0
L2086F	536.8	440.0	>3000	587.9	3.6	226.9	159.3	1265.0	672.5
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	62.5	20.3	1080.0
S1986F/L2086F	469.7	344.2	>3000	241.2	1.3	154.8	48.5	662.6	919.9
G2032R/L2086F	498.6	335.4	>3000	248.9	5.0	573.9	450.9	744.2	1254.0
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	717.0	105.4	1137.0
S1986F/G2032R/L2086F	562.8	1111.0	2131.0	1178.0	9.4	1116.0	1341.0	2432.0	1150.0

$IC_{50} \leq 50$ nmol/L
50 nmol/L < IC_{50} <200 nmol/L
$IC_{50} \geq 200$ nmol/L

Lin et al, 2017; Lin et al, 2021

TRK, RET Resistance



TRKA G595R Solvent Front Mutation

Repotrectinib (TPX-0005), LOXO-195
Clinical trials ongoing

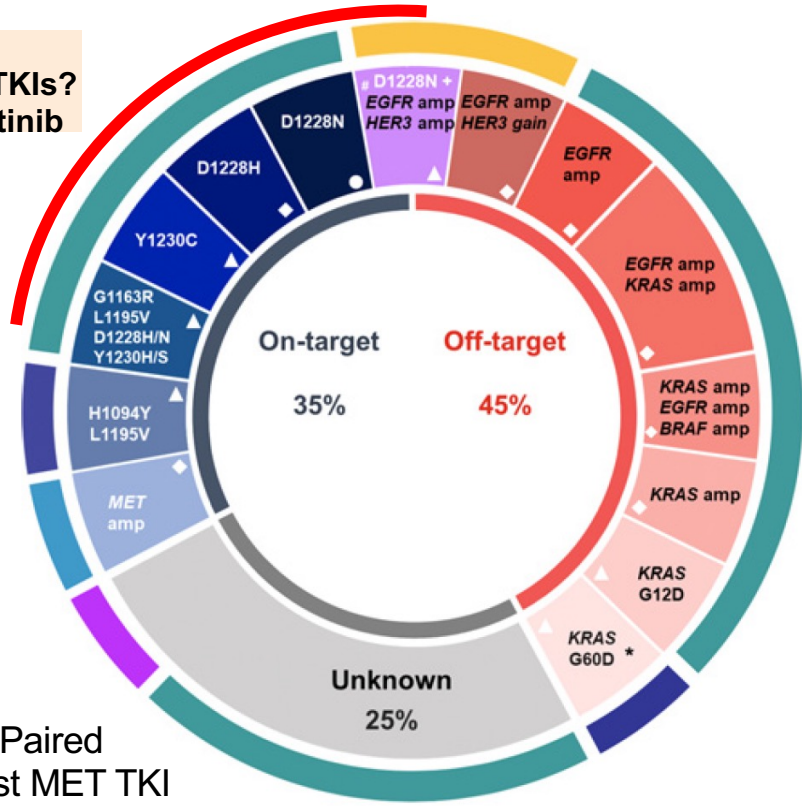
RET G810X Solvent Front Mutation
Next-generation RET inhibitors in clinical trials, eg LOXO-260, TPX-0046

Solvent Front	NTRK1 G595R	ALK G1202R	ROS1 G2032R	RET G810X
Gatekeeper	NTRK1 F589L	ALK L1196M	ROS1 L2026M	
xDFG	NTRK1 G667X	ALK G1269A		

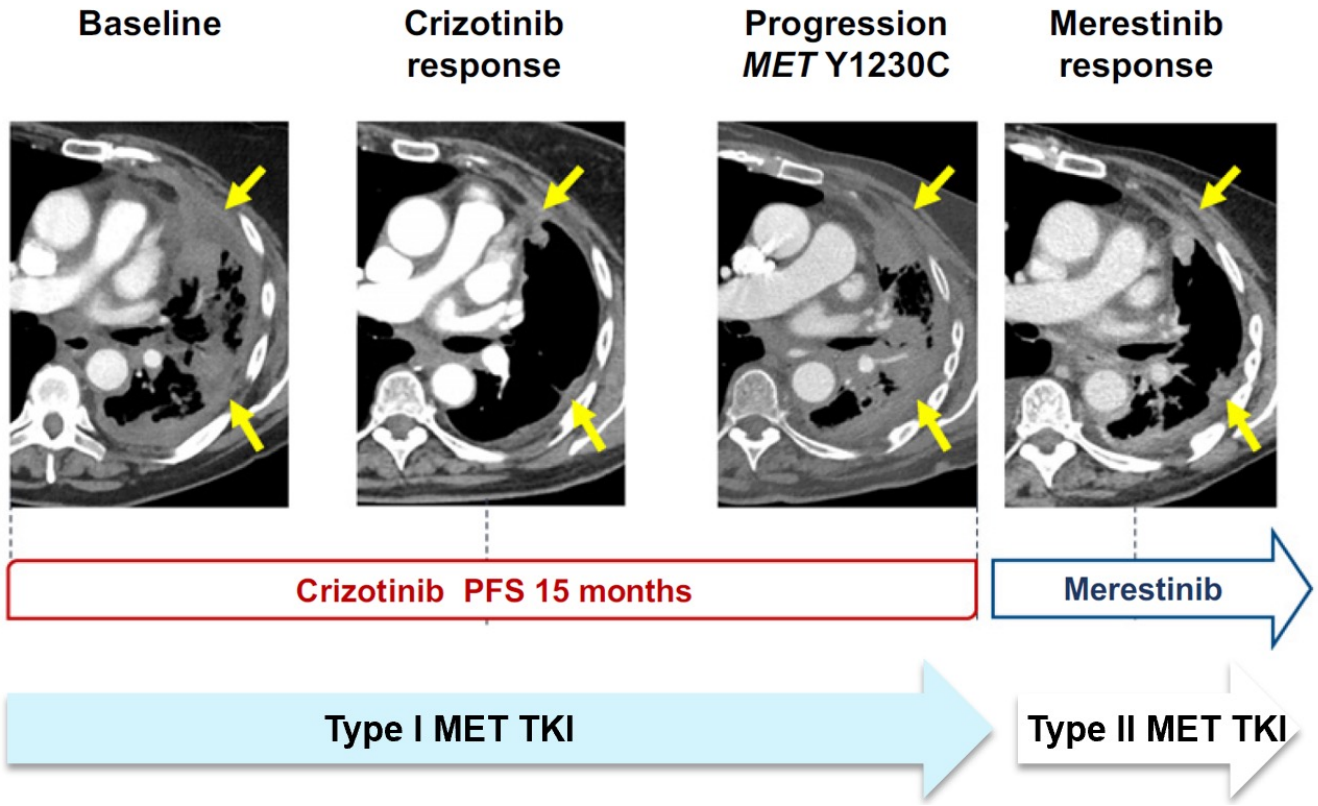
Cocco et al. 2018., Lin et al 2017, *Liu et al. 2018* .

Acquired Resistance to MET inhibitors

Type II MET TKIs?
e.g. cabozantinib



N= 20; Paired
Pre/Post MET TKI



Recondo et al. CCR. 2020;26(11):2615

- Resistance to targeted therapy is heterogenous and includes both on- and off-target mechanisms
- There is homology among acquired resistance to the fusion oncogenic drivers ALK, ROS, RET, NTRK
- Genomic profiling at resistance may offer sequential TKI and/or TKI combination strategies with clinical activity
- Bispecific antibodies and antibody drug conjugates offer antitumor activity independent of identifiable genomic mechanism of resistance