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Identifying and Targeting Mechanisms of Resistance to 3rd Generation EGFR Inhibitors

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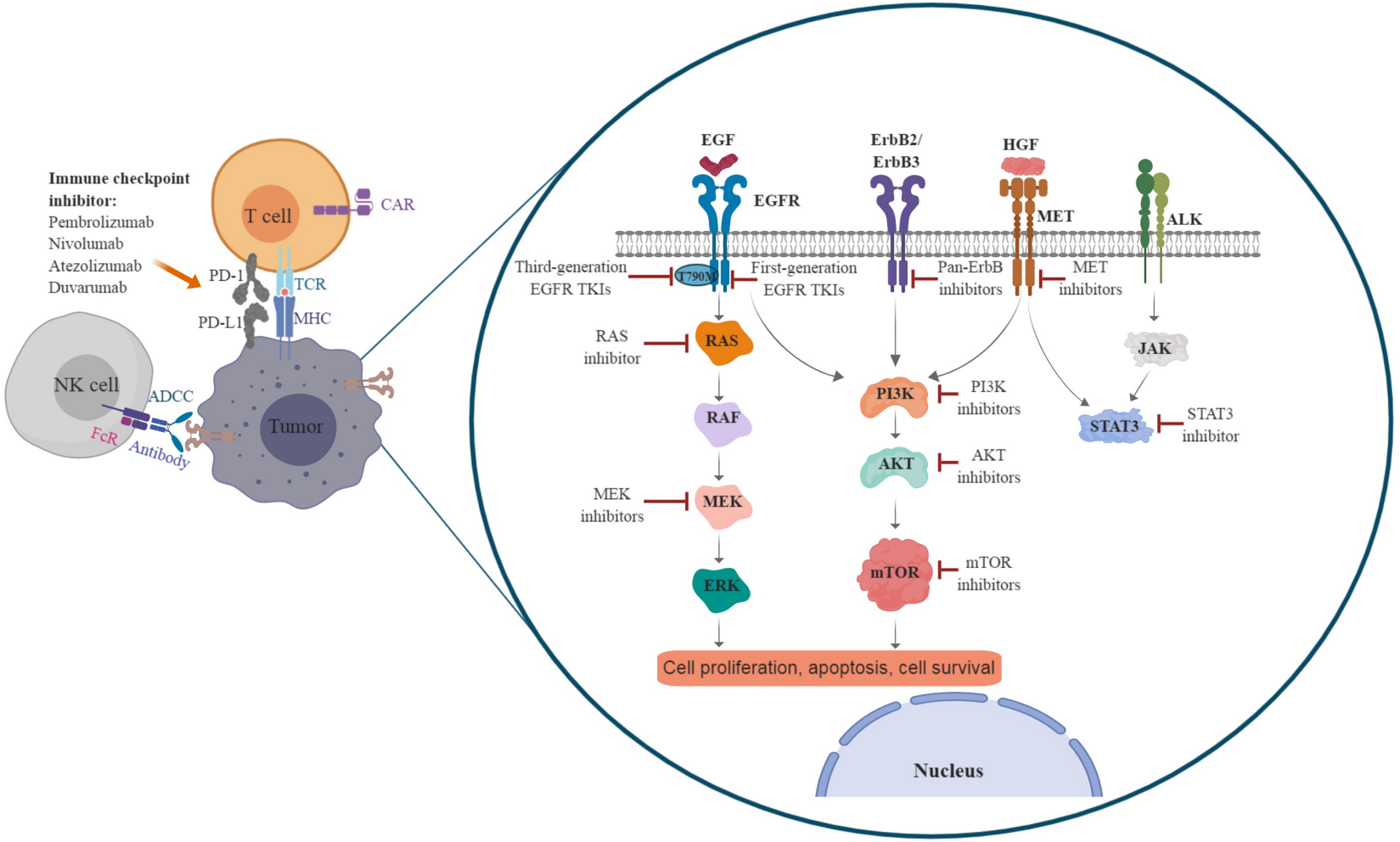
Professor and Chair

Department of Medical Oncology and Therapeutics Research

Objectives

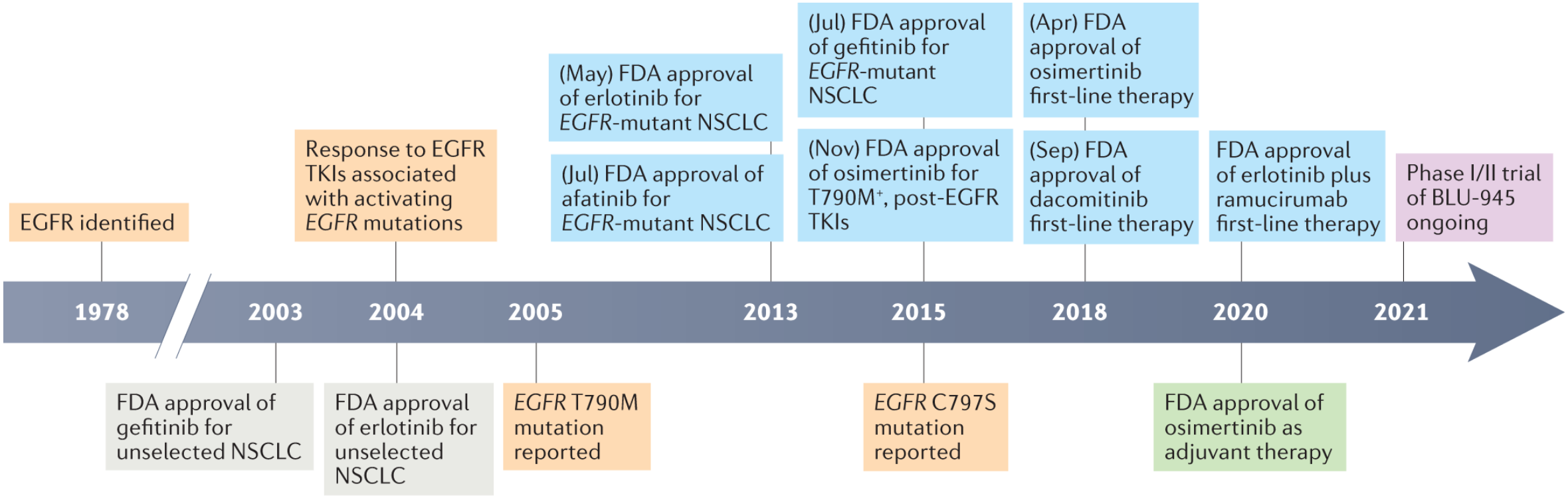
- EGFR
- EGFR Resistance
- ASCO23 Osimertinib Resistance Data
    - Phase II Trial of Neoadjuvant Osimertinib for Surgically Resectable EGFR-Mutated Non-Small Cell Lung Cancer
    - BLU-945 Monotherapy and in Combination with Osimertinib in Previously Treated Patients with Advanced EGFR-mutant NSCLC in the phase 1/2 SYMPHONY Study
    - Tepotinib + Osimertinib for EGFR Mutant NSCLC with MET Amplification After First-line Osimertinib
    - Predictive Biomarkers for Treatment with Amivantamab Plus Lazertinib Among EGFR-mutated Advanced NSCLC in the Post-Osimertinib Setting: Analysis of Tissue IHC and ctDNA NGS

EGFR Mechanism of Action



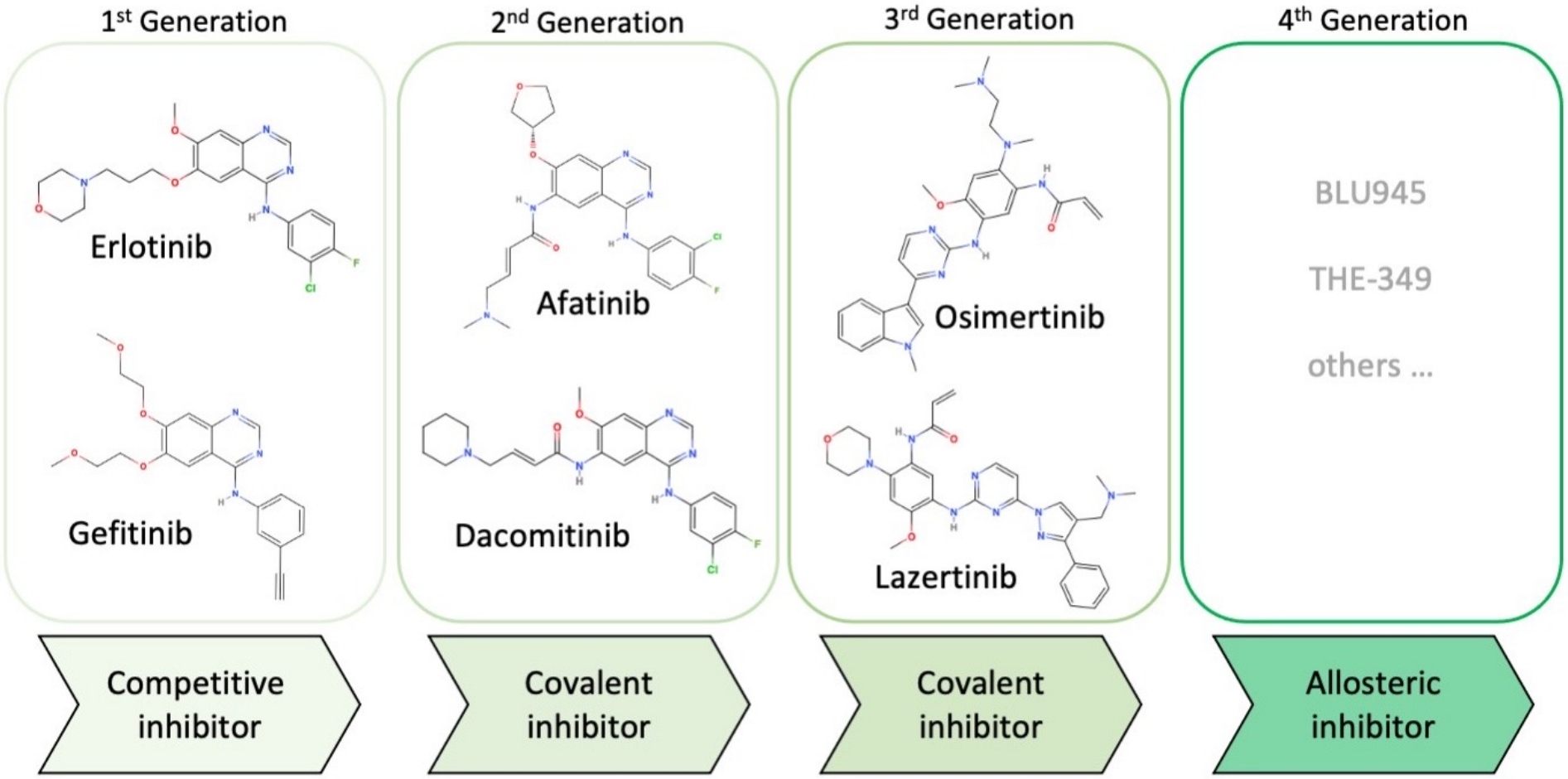
Malik, et int. Salgia, ACR 2020

EGFR Timeline of FDA Approvals



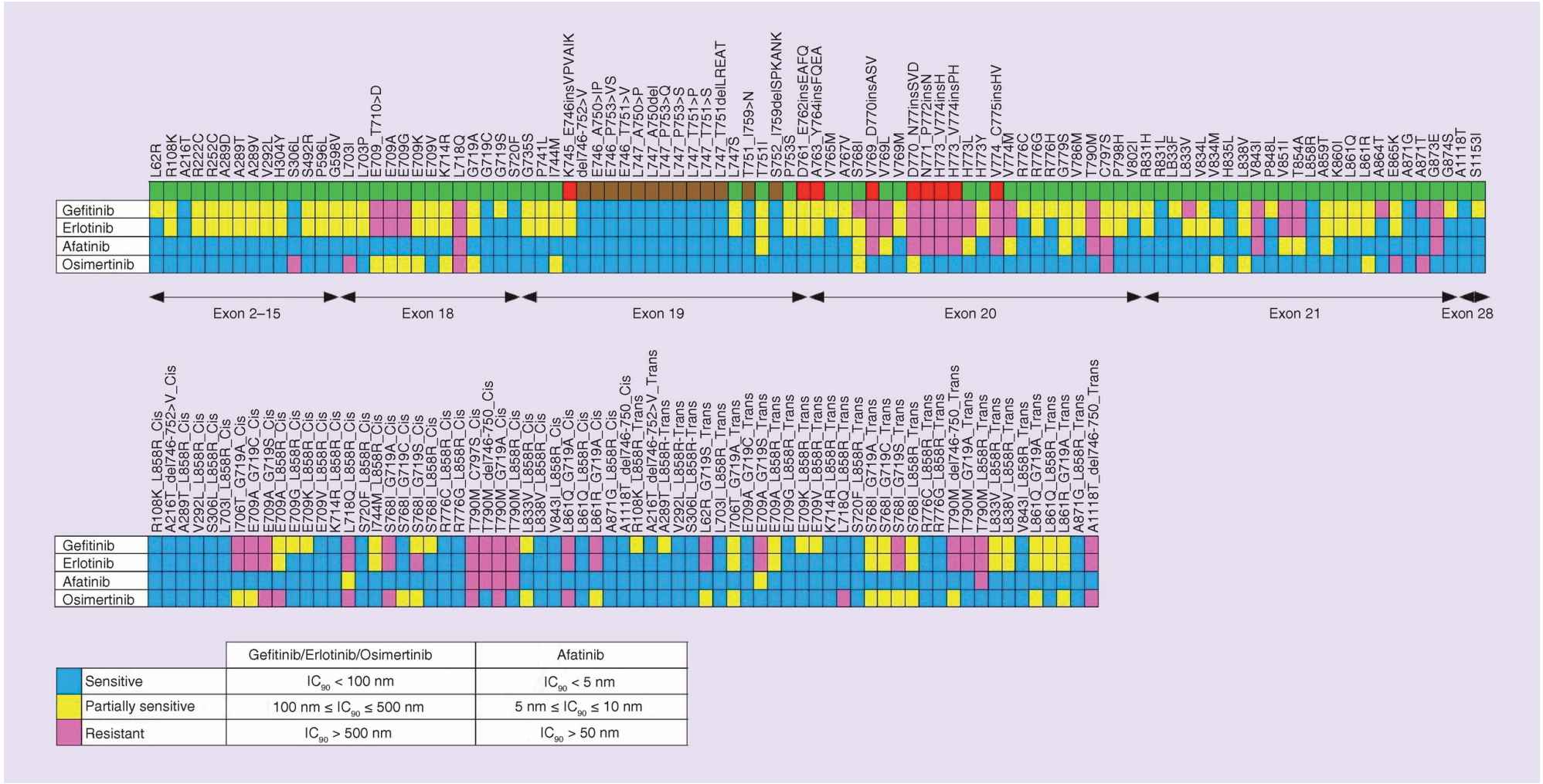
Cooper et al., Nature Reviews Clinical Oncology, 2022

EGFR Evolution of EGFR TKIs



Sattler et int. Salgia, JCM 2023

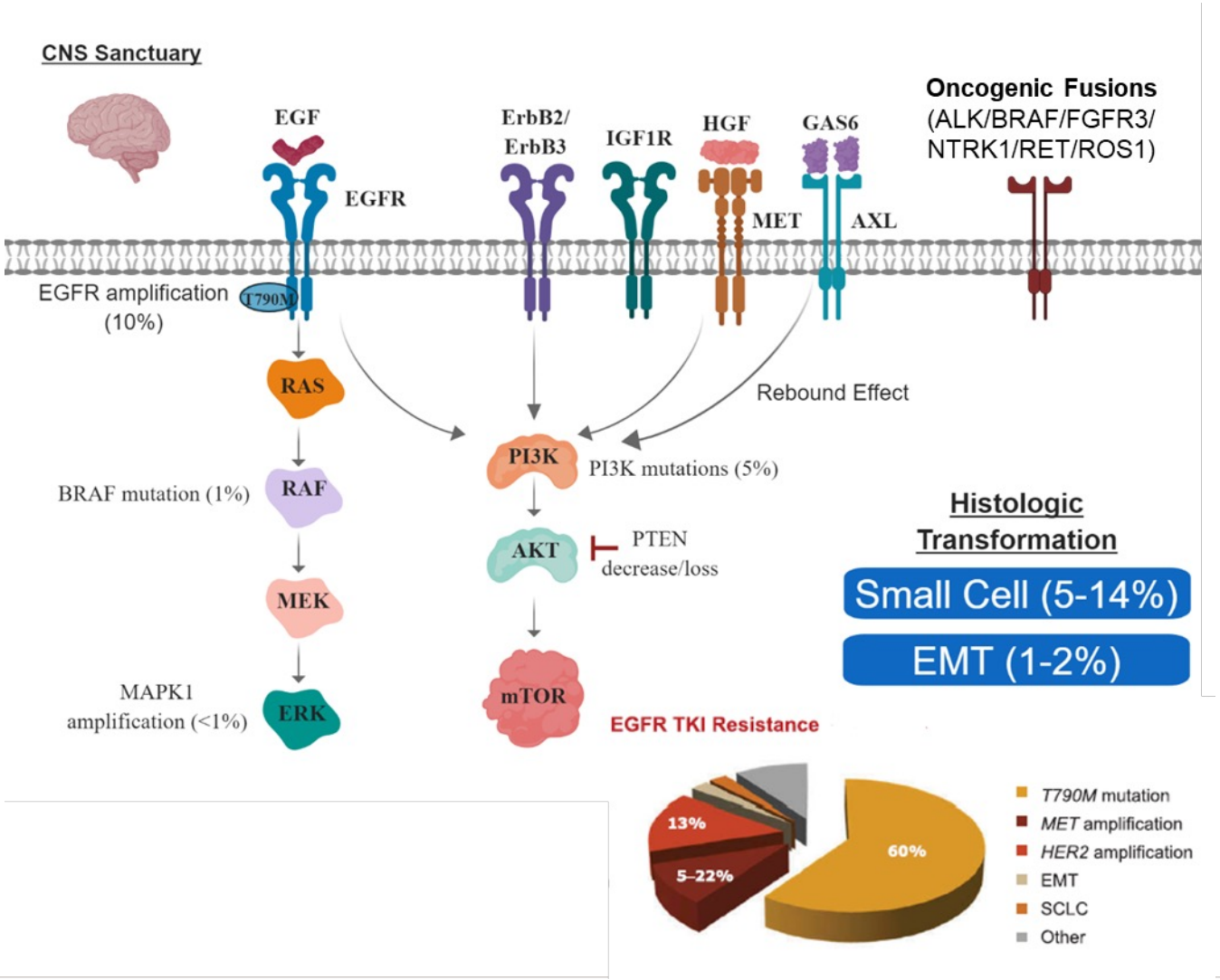
Predicted Clinical Benefit for EGFR Mutations



	Gefitinib/Erlotinib/Osimertinib	Afatinib
Sensitive	IC_{90} < 100 nm	IC_{90} < 5 nm
Partially sensitive	100 nm ≤ IC_{90} ≤ 500 nm	5 nm ≤ IC_{90} ≤ 10 nm
Resistant	IC_{90} > 500 nm	IC_{90} > 50 nm

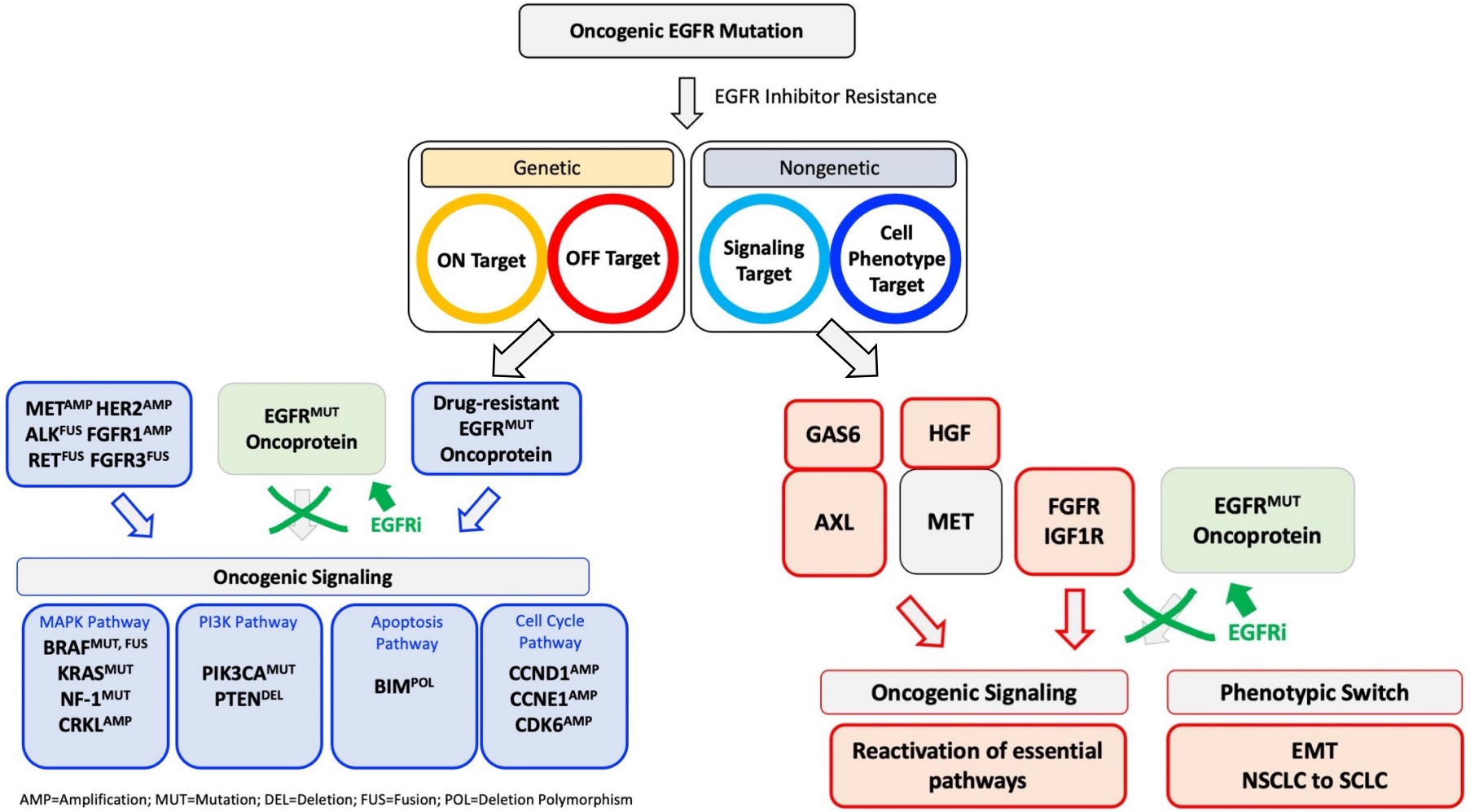
Kohsaka et al., Future Medicine, 2019

EGFR Mechanisms of Resistance



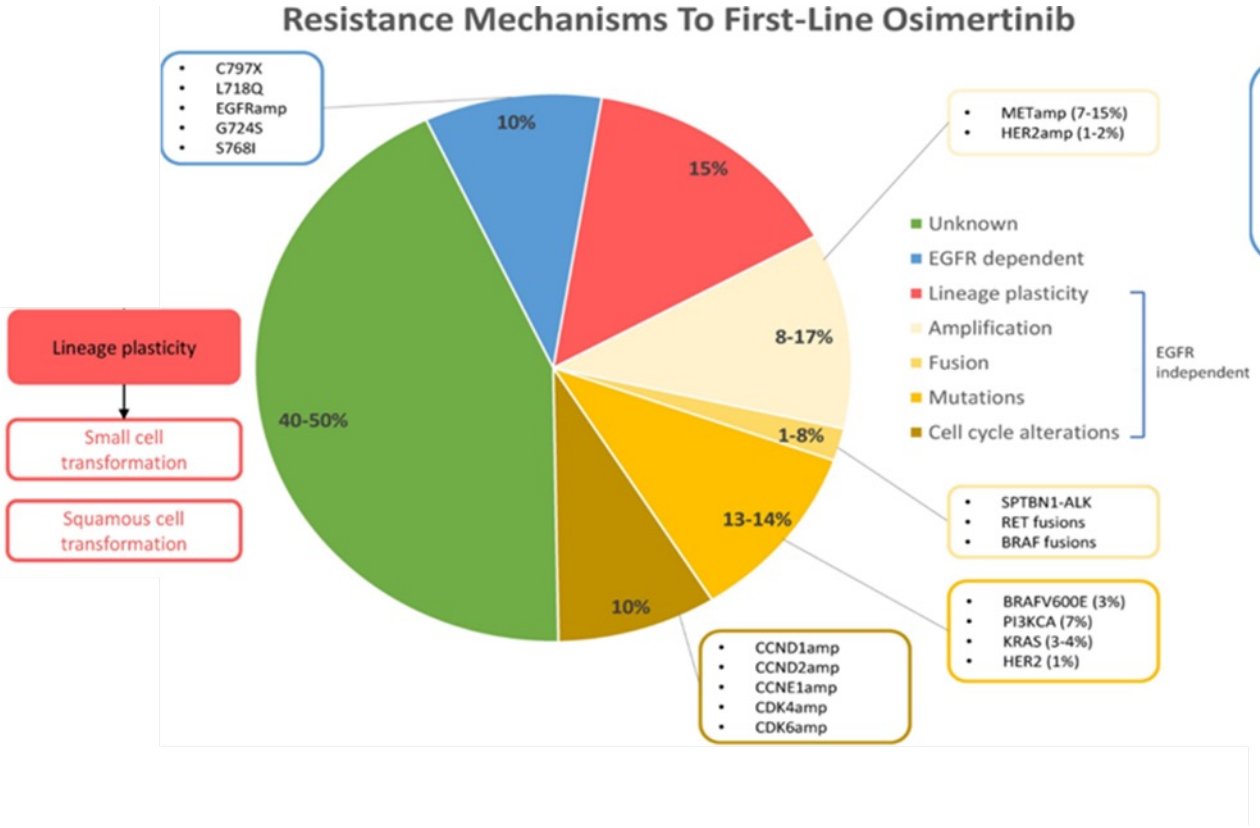
Adapted From Ke & Wu, Trends Pharmacol Sci. 2016

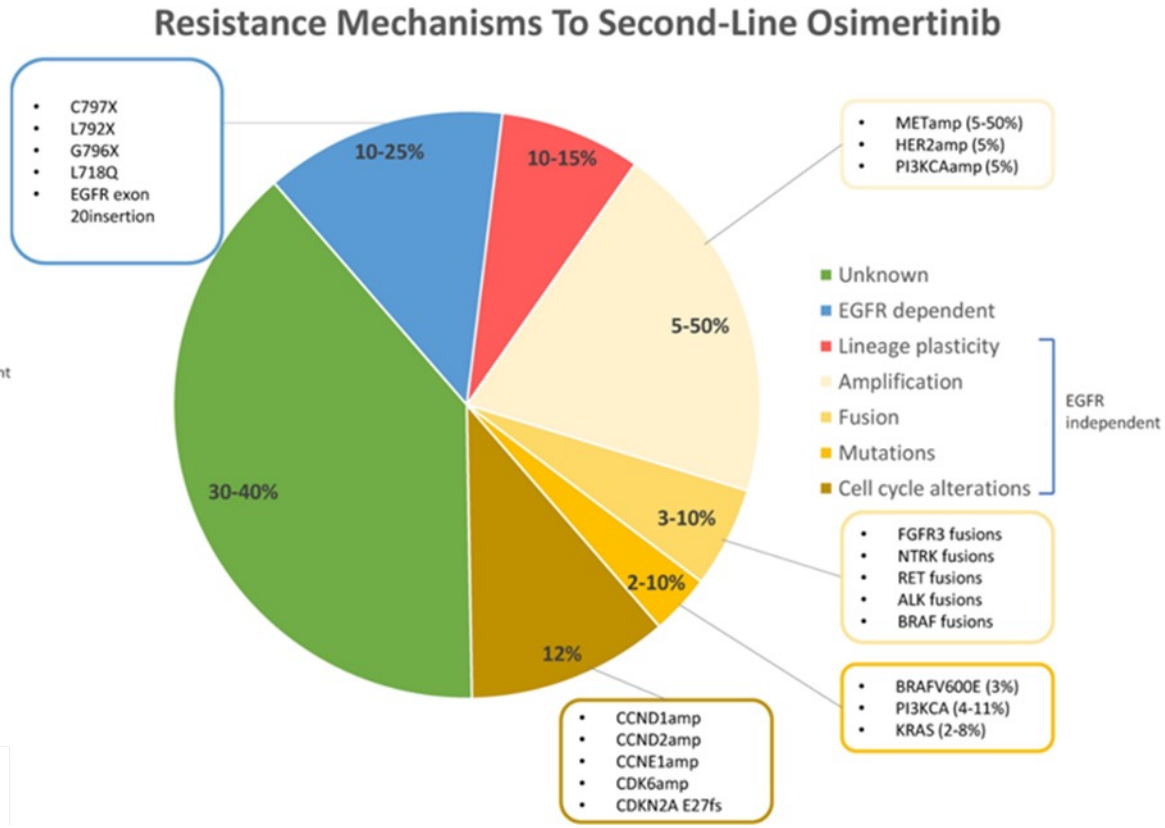
EGFR Genetic and Non-genetic Mechanisms of Resistance



Sattler et int. Salgia, JCM 2023

Resistance Mechanisms to Osimertinib





Schmid et al., Lung Ca., 2020

2023 ASCO ANNUAL MEETING

Phase II Trial of Neoadjuvant Osimertinib for Surgically Resectable *EGFR*-Mutated Non-Small Cell Lung cancer

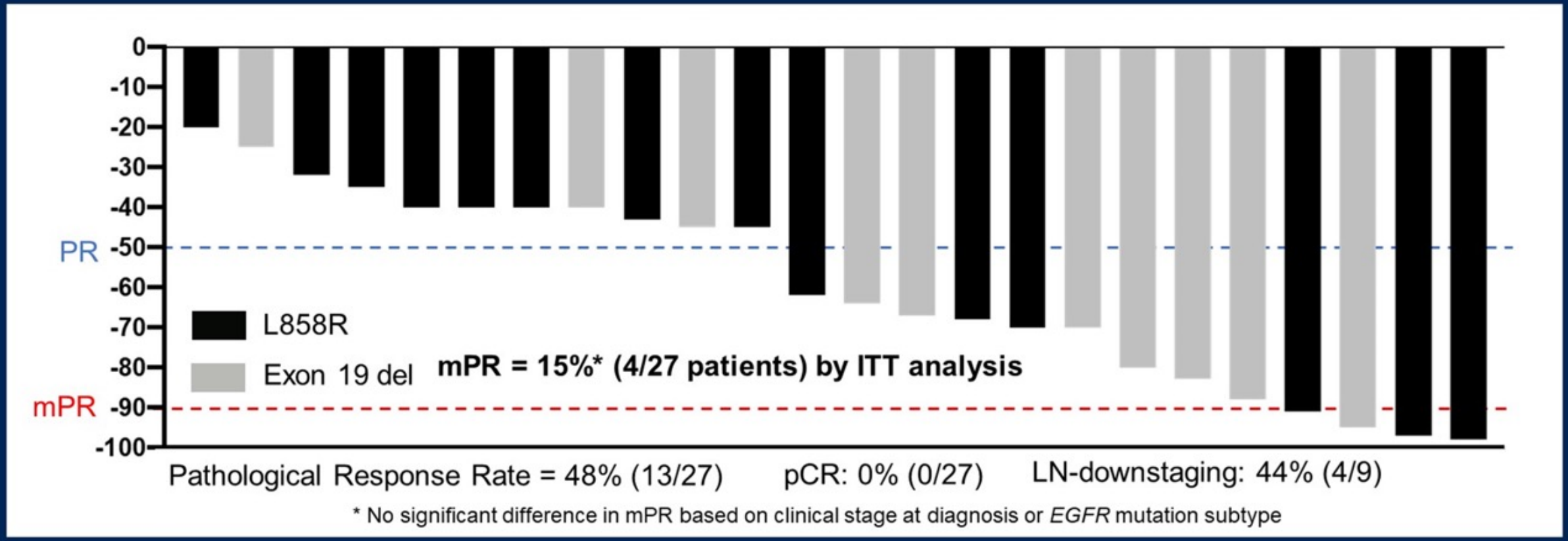
PI: Collin Blakely, MD, PhD, UCSF

Presented By: Jacqueline V. Aredo, MD, MS

University of California, San Francisco

USA

Primary Endpoint:
Major Pathologic Response Rate = 15%



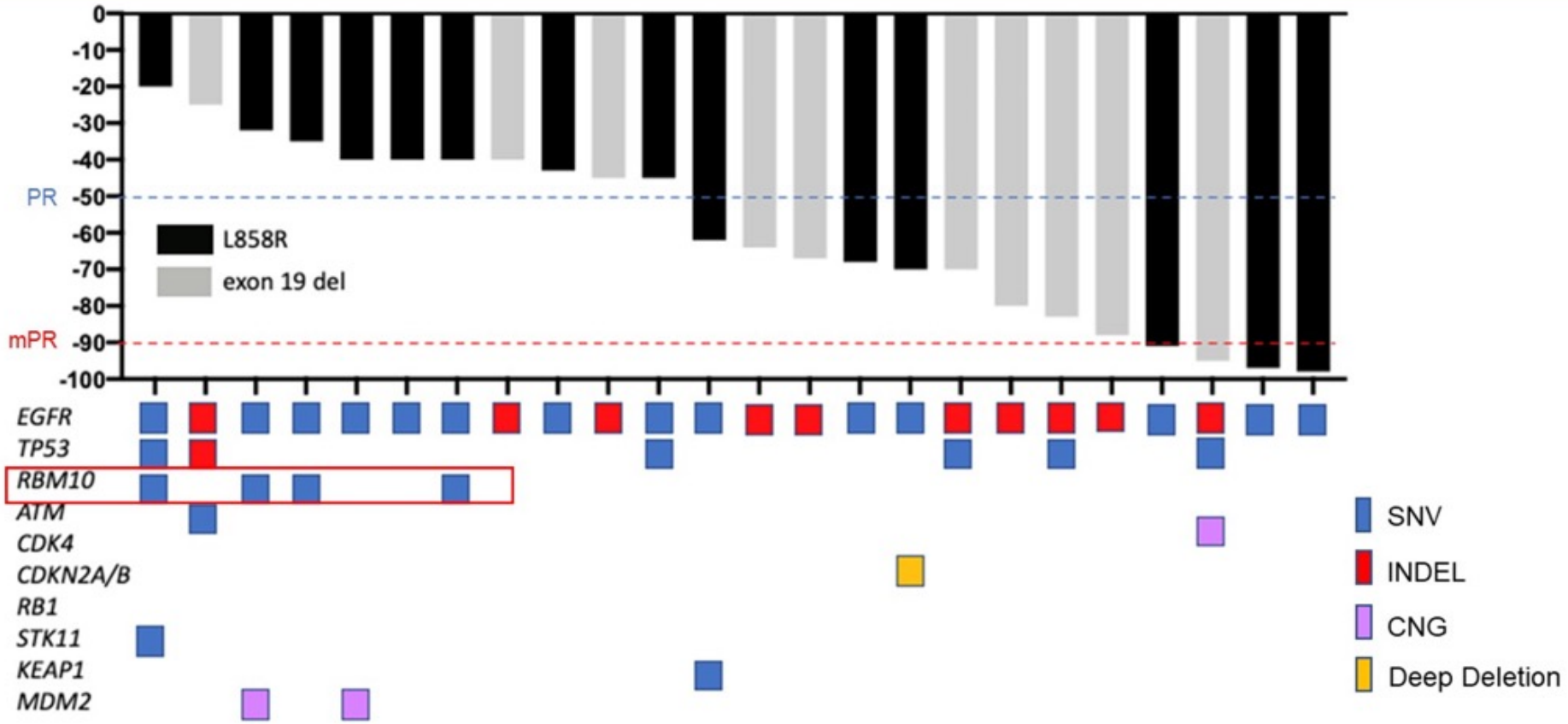
Median duration of neoadjuvant osimertinib: 56 days (IQR 41-62)

Efficacy and Safety Summary

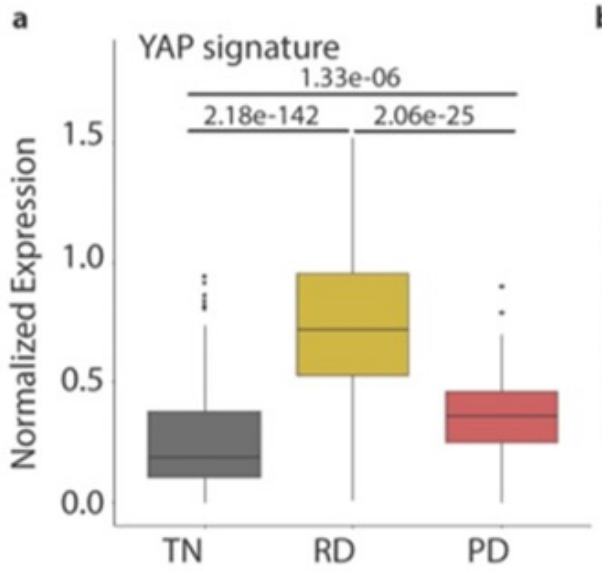
- Neoadjuvant osimertinib in surgically resectable *EGFR*-mutated NSCLC resulted in a 15% mPR, which did not meet the primary endpoint of an mPR of 50%.
- Complete R0 surgical resection was achieved in 89% of patients with no surgical complications.
- SAEs and perioperative complication rates were in line with predicted rates in this patient population.

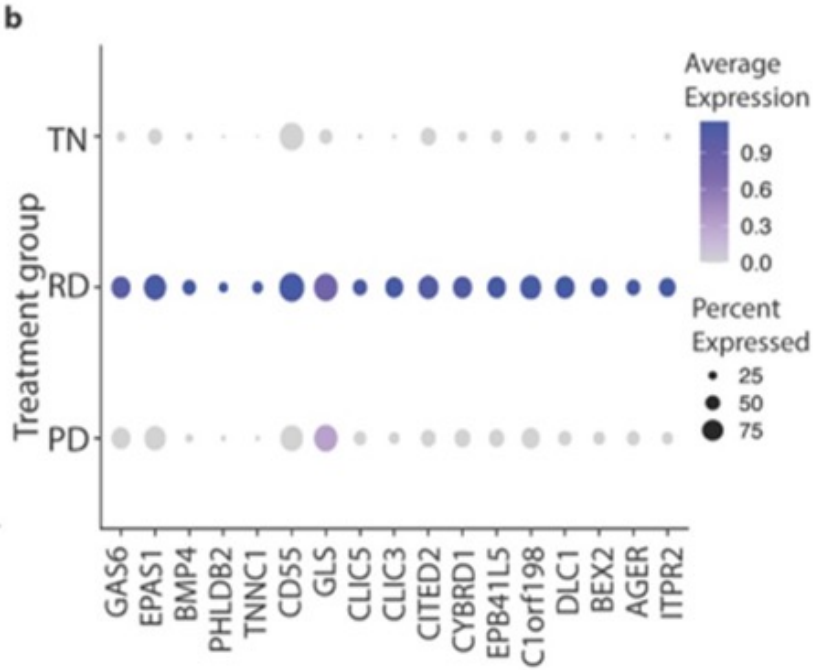
RBM10 Loss-of-function Mutations Identified in Non-responders by Targeted Exome Sequencing

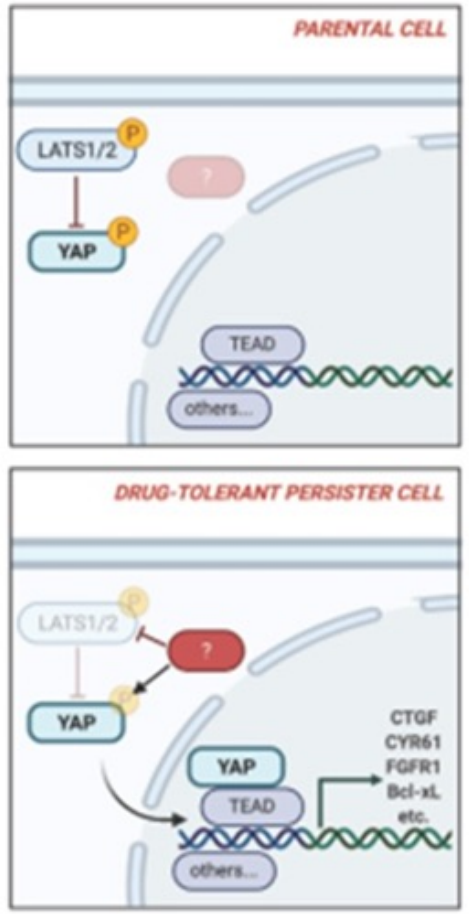
	Path response >50%	Fisher's Exact, P value
RBM10 mut	0% (0/4)	0.03
RBM10 wt	65% (13/20)	



Increased Expression of YAP Target Genes Identified at Residual Disease







Haderk et al., bioRxiv preprint doi: https://doi.org/10.1101/2021.10.23.465573

Bivona Lab, UCSF

Conclusions

- Neoadjuvant osimertinib in surgically resectable *EGFR*-mutated NSCLC achieved a 15% mPR.
- Co-occurring mutations in *RBM10* may limit response.
- YAP activation may drive tumor cell survival and offer a potential target for combination therapies to eliminate residual disease.

Limitations

- Pilot study with small sample size.
- Neoadjuvant osimertinib treatment limited to 2 months.

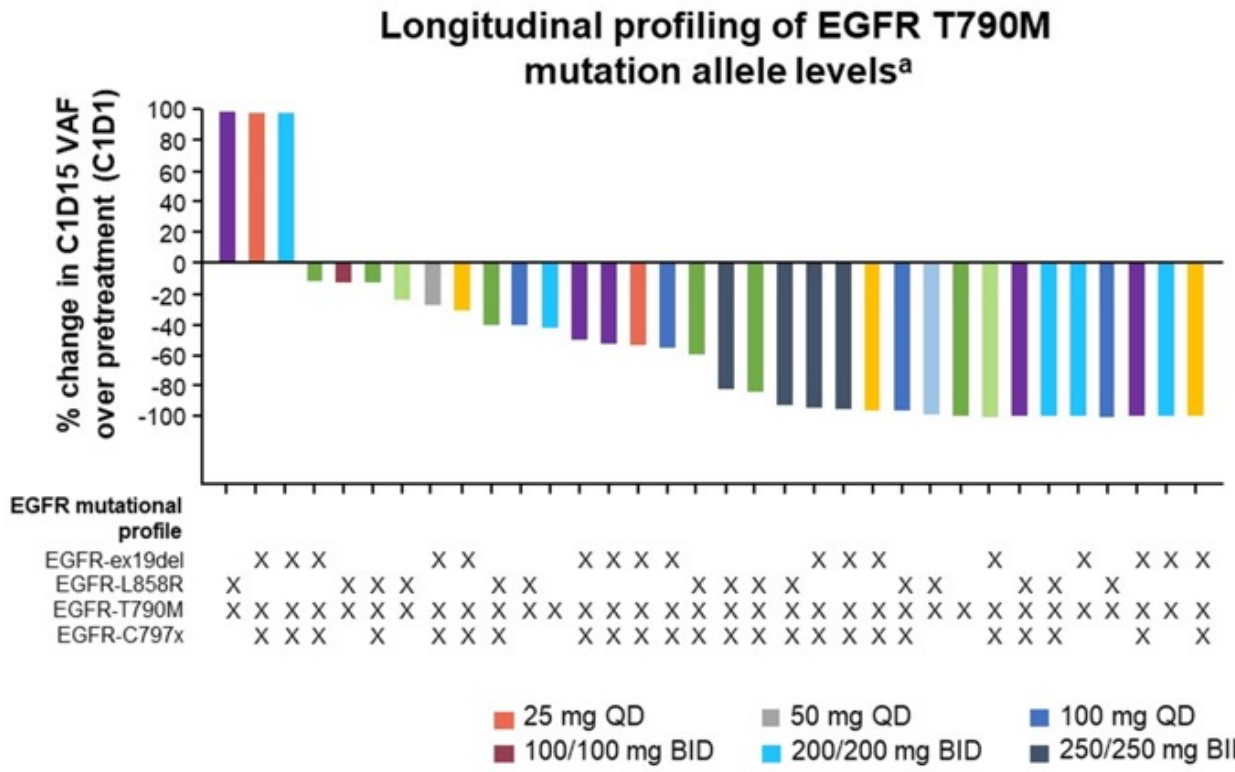
2023 ASCO ANNUAL MEETING

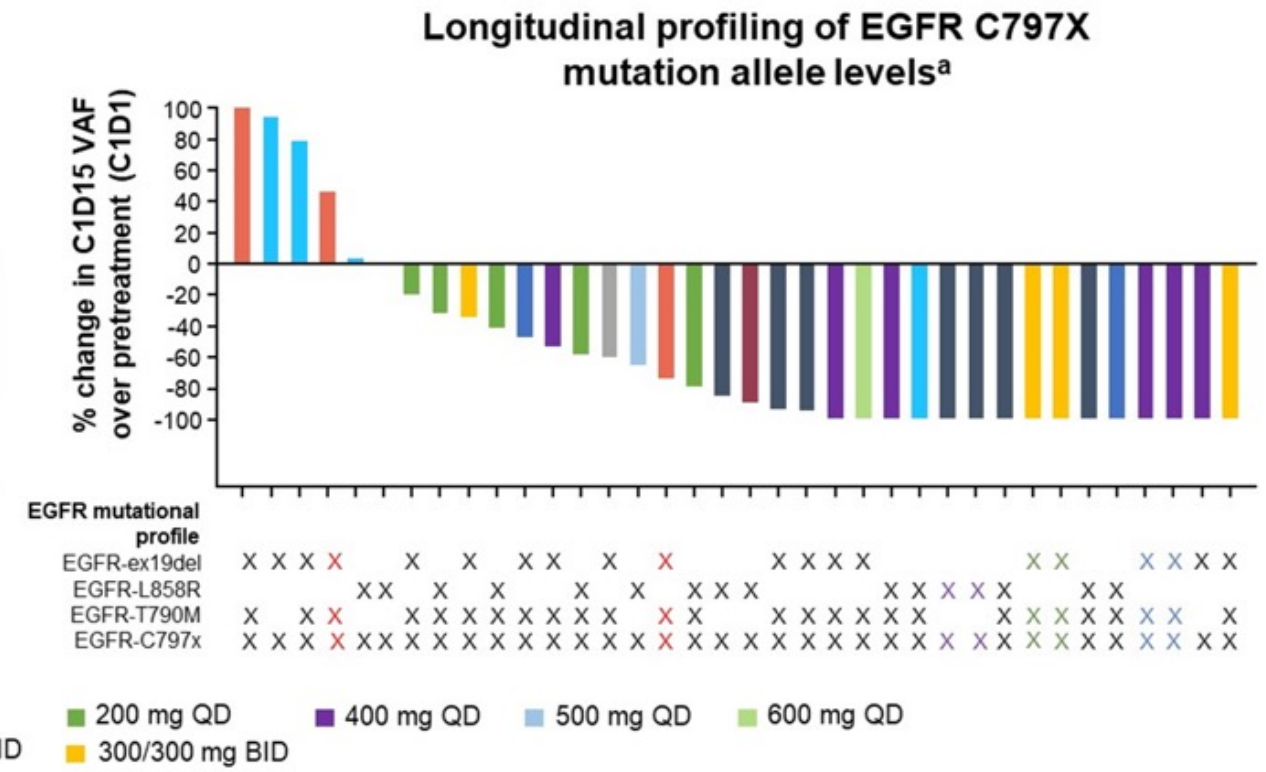
Lung Cancer Rapid Abstract Session
9011

BLU-945 monotherapy and in combination with osimertinib in previously treated patients with advanced *EGFR*-mutant NSCLC in the phase 1/2 SYMPHONY study

Yasir Elamin, MD,[1] Misako Nagasaka, MD, PhD,[2] Elaine Shum, MD,[3] Lyudmila Bazhenova, MD,[4] D. Ross Camidge, MD, PhD,[5] Byoung Chul Cho, MD, PhD,[6] Enriqueta Felip, MD, PhD,[7] Koichi Goto, MD, PhD,[8] Chia-Chi Lin, MD, PhD, [9] Zofia Piotrowska, MD,[10] David Planchard, MD, PhD,[11] Julia Rotow, MD,[12] David R. Spigel, MD[13] Daniel S. W. Tan, MD, PhD,[14] Tatsuya Yoshida, MD, PhD,[15] Anna Minchom, MD,[16] Adrianus Johannes de Langen, MD,[17] Terufumi Kato, MD,[18] Alena Zalutskaya, MD, PhD,[19] Karen L. Reckamp, MD[20]

BLU-945 monotherapy resulted in dose-dependent reduction and clearance of EGFR T790M and EGFR C797X ctDNA at Cycle 1 Day 15

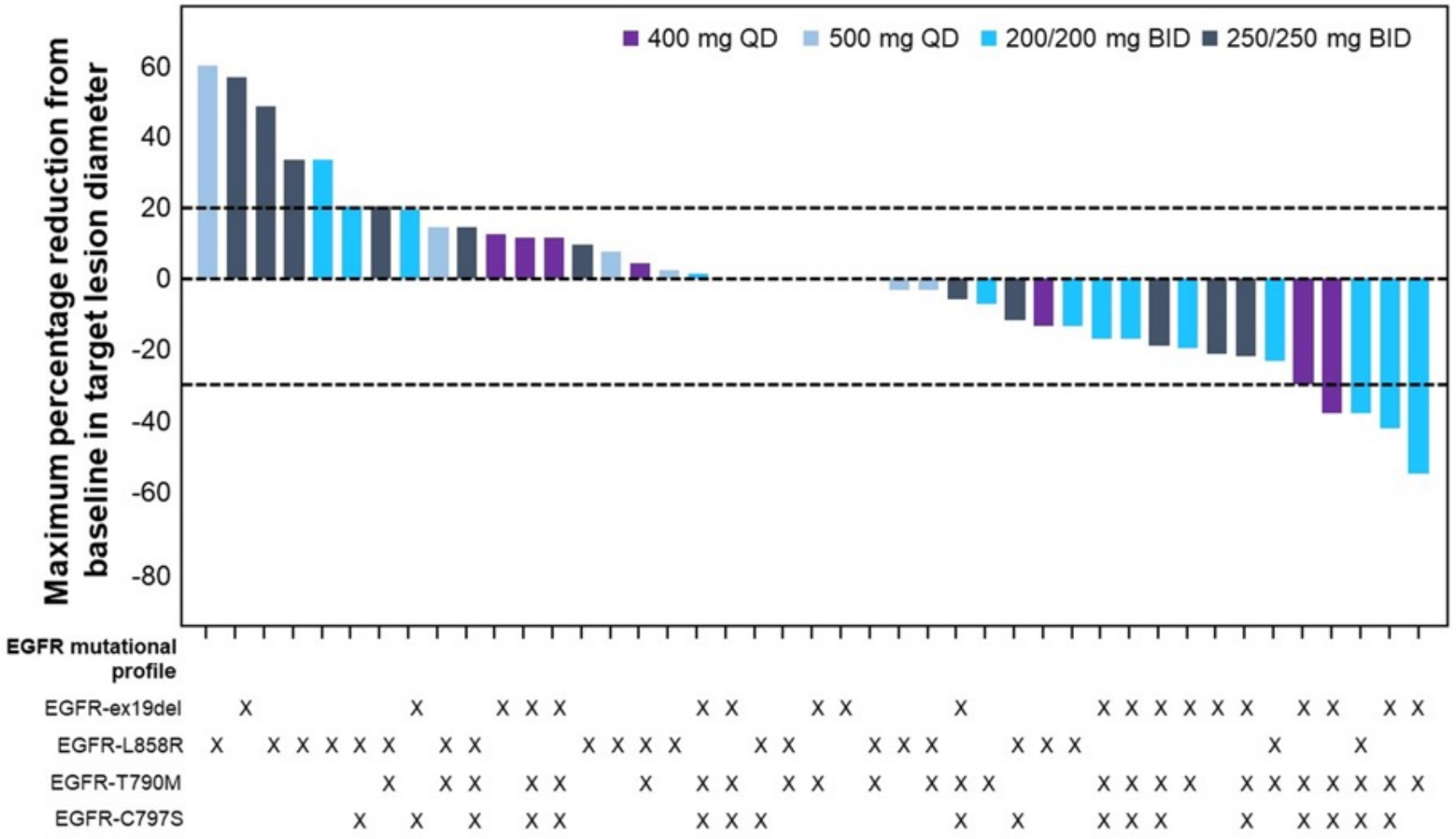




25 mg QD
50 mg QD
100 mg QD
200 mg QD
400 mg QD
500 mg QD
600 mg QD
100/100 mg BID
200/200 mg BID
250/250 mg BID
300/300 mg BID

[a]Percent change greater than 100% are displayed as 100% in the figure. EGFR mutational profile based on results from Foundation One Liquid CDx (F1CDx) baseline (C1D1) analysis
Note: Patient with multiple mutations for EGFR C797S in the same specimen are shown as a different colored X in the EGFR mutational profile.
BID, twice daily; EGFR, epidermal growth factor receptor; QD, once daily

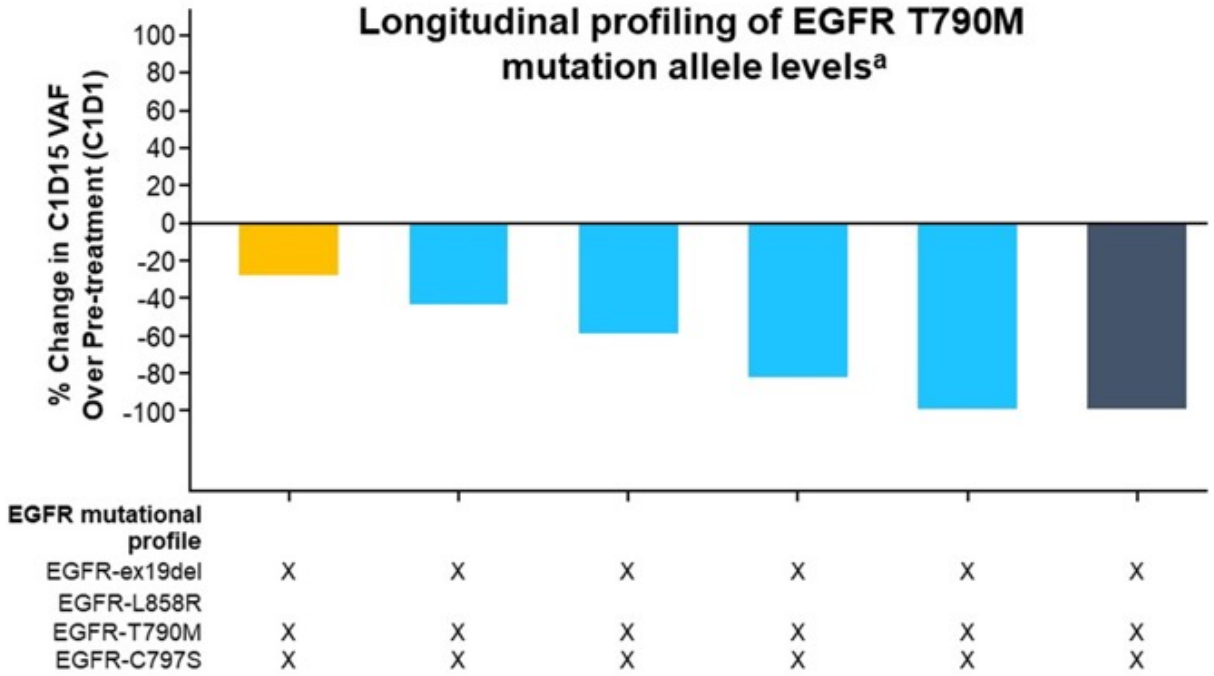
BLU-945 monotherapy antitumor activity[a]

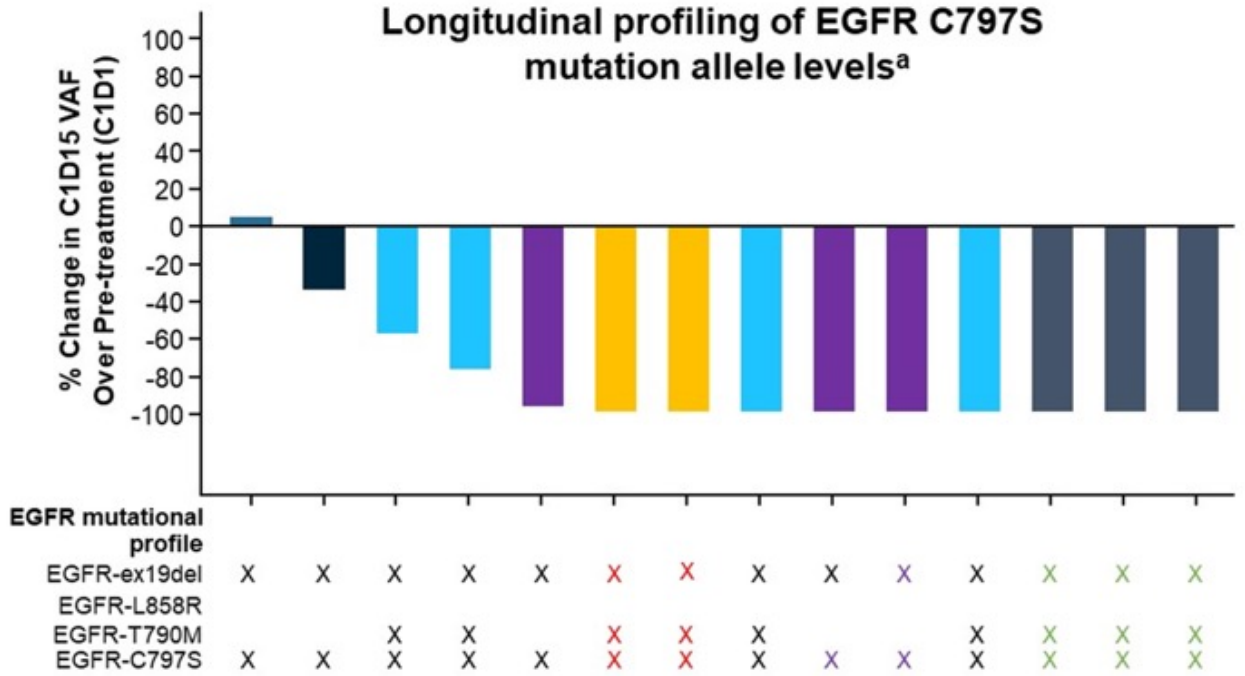


- Heavily pretreated population resulting in disease heterogeneity
- Tumor reduction and two confirmed partial responses were observed at higher dose levels of BLU-945 monotherapy
- Limited durability of clinical benefit observed, likely due to late-line disease heterogeneity and off-target resistance

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA (displayed) with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease.

BLU-945 + osimertinib combination therapy resulted in dose-dependent reduction of EGFR T790M and EGFR C797S mutant allele levels at Cycle 1, Day 15

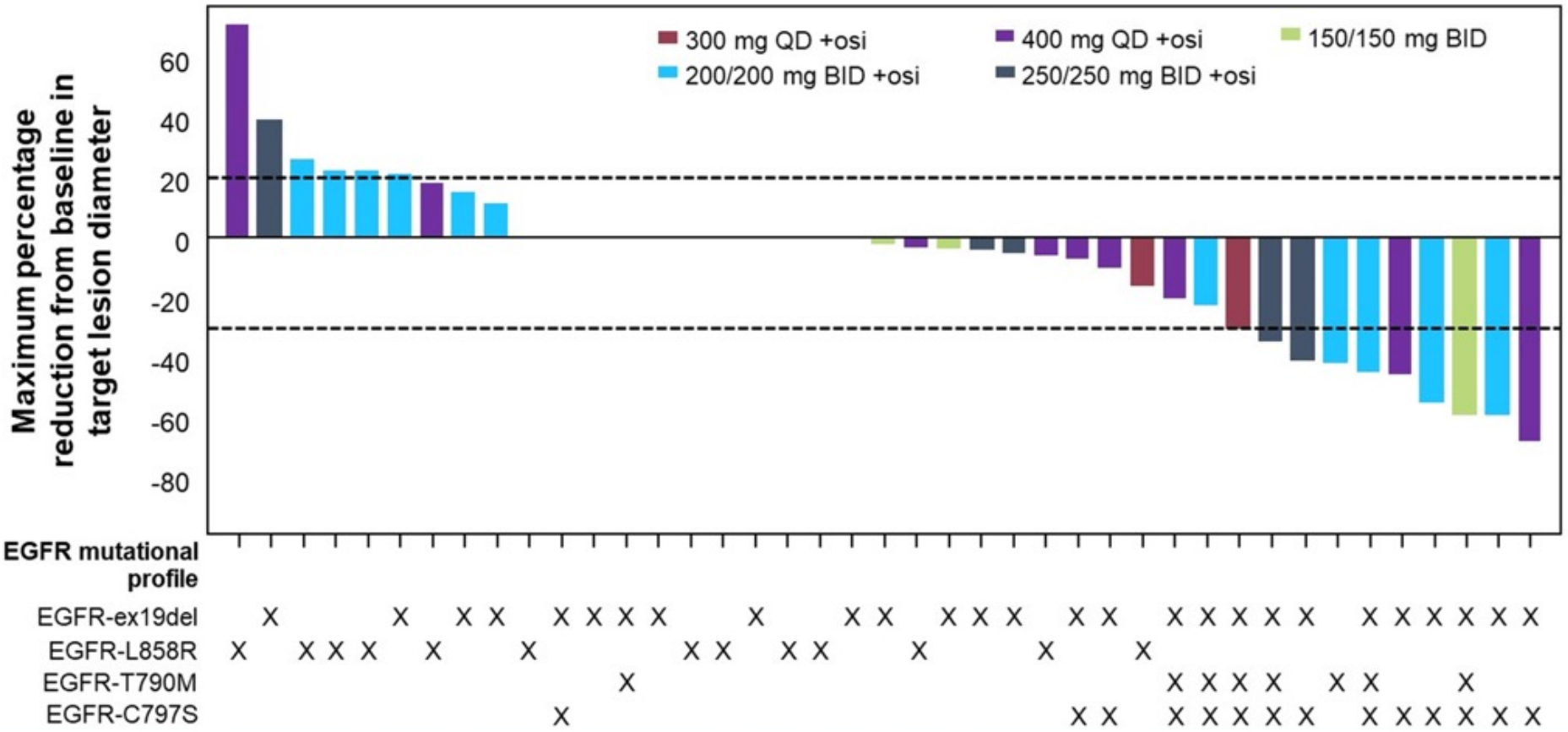




200 mg QD +osi
300 mg QD +osi
400 mg QD +osi
100/100 mg BID +osi
150/150 mg BID +osi
200/200 mg BID + osi
250/250 mg BID +osi

[a]Percent change greater than 100% are displayed as 100% in the figure. EGFR mutational profile based on results from Foundation One Liquid CDx baseline (C1D1) analysis.
Note: Patient with multiple mutations for EGFR C797S in the same specimen are shown as a different colored X in the EGFR mutational profile.

Early BLU-945 + osimertinib antitumor activity[a]



- In the ongoing dose-escalation, tumor shrinkage, including 4 confirmed PRs, was observed in patients who had progressed on osimertinib as the last therapy line

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor.

Conclusions

- In heavily pretreated EGFR-mutant NSCLC patients, BLU-945 monotherapy was active and well-tolerated; however, due to genomic heterogeneity, responses were not durable
- Emerging BLU-945 + osimertinib combination data demonstrated clinical activity post progression on osimertinib and was well tolerated with infrequent EGFR WT toxicity
- A correspondence between reduction of the resistance mutation alleles by ctDNA and tumor shrinkage was observed in both cohorts
- Phase 1 data support BLU-945 + osimertinib as a differentiated, fully oral, novel combination for treatment of EGFR-mutant NSCLC, warranting further clinical development
    - Combination escalation is ongoing with RP2D/MTD yet to be established

2023 ASCO ANNUAL MEETING

Tepotinib + osimertinib for *EGFR* mutant NSCLC with *MET* amplification after first-line osimertinib

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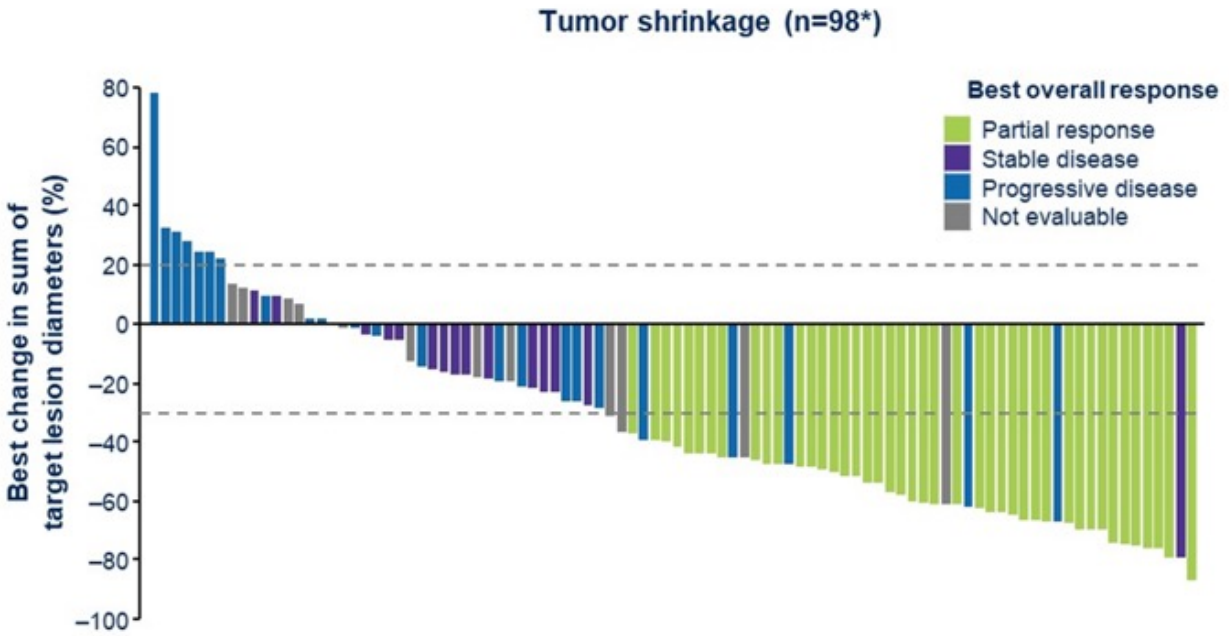
[1]Division of Medical Oncology, National Cancer Centre, Singapore; [2]Seoul National University Cancer Research Institute, Seoul, Republic of Korea; Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [3]Department of Surgery, Oncology and Gastroenterology, University of Padova, Oncology 2, IOV - Istituto Oncologico Veneto IRCCS -IOV, Padova, Italy; [4]Hospital Umum Sarawak, Kuching, Sarawak, Malaysia; [5]Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia; [6]Thoracic Oncology Unit, Service de Pneumologie, Hôpital Cochin, APHP, Université Paris Cité, France; [7]Department of Thoracic Oncology, Fujian Cancer Hospital, Fuzhou, China; [8]CHU de Toulouse, Pneumology Departement, Paul Sabatier University, Toulouse, France; [9]Department of Oncology, Pantai Hospital Kuala Lumpur, Kuala Lumpur, Malaysia; [10]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan; [11]National Lung Hospital, Hanoi, Viet Nam; [12]Department of Medical Oncology, Tan Tock Seng Hospital, Singapore; [13]Thoracic Oncology Division, European Institute of Oncology (IEO), IRCCS, Milan, Italy; [14]Department of Thoracic Head and Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [15]Division of Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [16]Global Clinical Development, the healthcare business of Merck KGaA, Darmstadt, Germany; [17]Global Development Operations, the healthcare business of Merck KGaA, Darmstadt, Germany; [18]Department of Biostatistics, the healthcare business of Merck KGaA, Darmstadt, Germany; [19]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Guangzhou, China

INSIGHT 2: Efficacy TBx FISH+

- Of 98 patients with **TBx FISH+** *MET*amp (primary analysis set), BOR was PR in 43 patients, for an ORR of 43.9% (95% CI: 33.9, 54.3)
- As the data matures, six additional PRs have been confirmed

		TBx FISH+ (n=98)
BOR, n (%)	PR	43 (43.9)
	SD	15 (15.3)
	PD	23 (23.5)
	NE	17 (17.3)
ORR	% (95% CI)	**43.9** (33.9, 54.3)
DOR	Median, months (95% CI)	**9.7** (5.6, ne)
	Events, n (%)	11 (25.6)
PFS	Median, months (95% CI)	**5.4** (4.2, 7.1)
	Events, n (%)	51 (52.0)
OS	Median, months (95% CI)	**ne** (11.1, ne)
	Events, n (%)	23 (23.5)



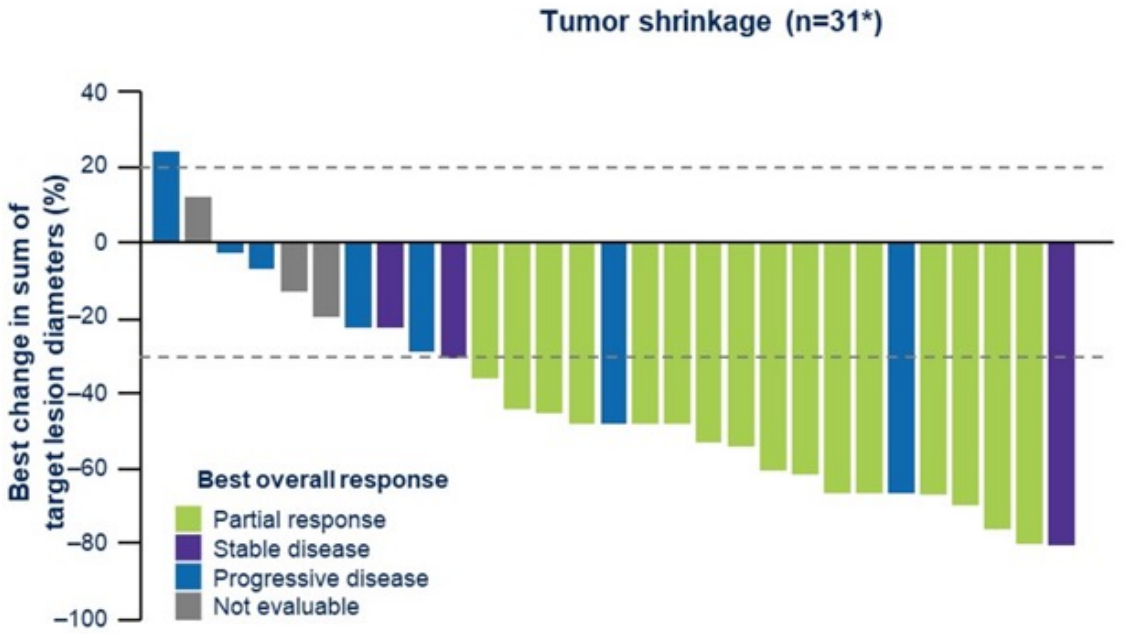
*Four patients were excluded due to baseline/post-baseline measurement not being available.

BOR, best overall response; CI, confidence interval; DOR, duration of response; FISH, fluorescent in situ hybridization; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; ne, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TBx, tissue biopsy.

INSIGHT 2: Efficacy LBx NGS+

- Of 31 patients with **LBx NGS+** *MET*amp, BOR was PR in 16 patients, for an ORR of 51.6% (95% CI: 33.1, 69.8)

		LBx NGS+ (n=31)
BOR, n (%)	PR	16 (51.6)
	SD	3 (9.7)
	PD	7 (22.6)
	NE	5 (16.1)
ORR	% (95% CI)	**51.6** (33.1, 69.8)
DOR	Median, months (95% CI)	**5.6** (2.9, ne)
	Events, n (%)	7 (43.8)
PFS	Median, months (95% CI)	**4.6** (2.7, 6.9)
	Events, n (%)	19 (61.3)
OS	Median, months (95% CI)	ne (6.8, ne)
	Events, n (%)	9 (29.0)



*Two patients were excluded due to baseline/post-baseline measurement not being available.

BOR, best overall response; CI, confidence interval; DOR, duration of response; LBx, liquid biopsy; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; ne, not evaluable; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

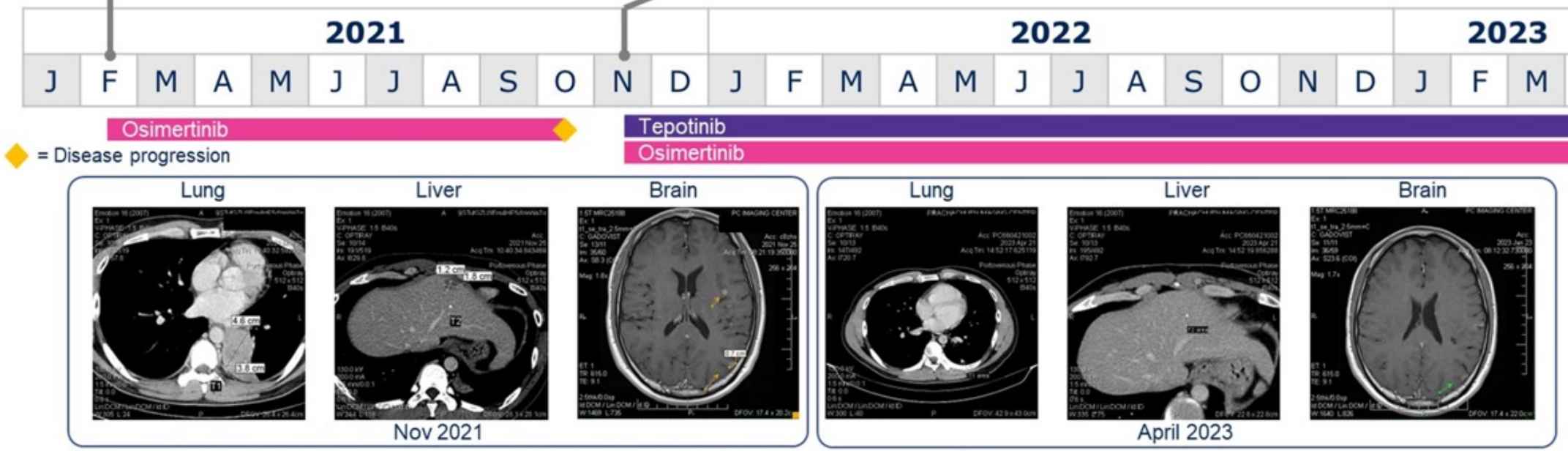
Case study: Control of brain metastases in a 33-year-old* Asian male with a durable response to tepotinib + osimertinib

Diagnosis
Stage IV adenocarcinoma
EGFR Del19
Bone and multiple intrapulmonary metastases

1L osimertinib†
PR with treatment duration (osimertinib monotherapy): 9 months

Enrolled in **INSIGHT 2‡**
TBx FISH *MET*amp
Brain metastases in the parietal lobe

2L tepotinib + osimertinib§
Treatment ongoing with total duration of treatment: 18 months
Overall PR with resolution of the target lesions and control of brain metastases

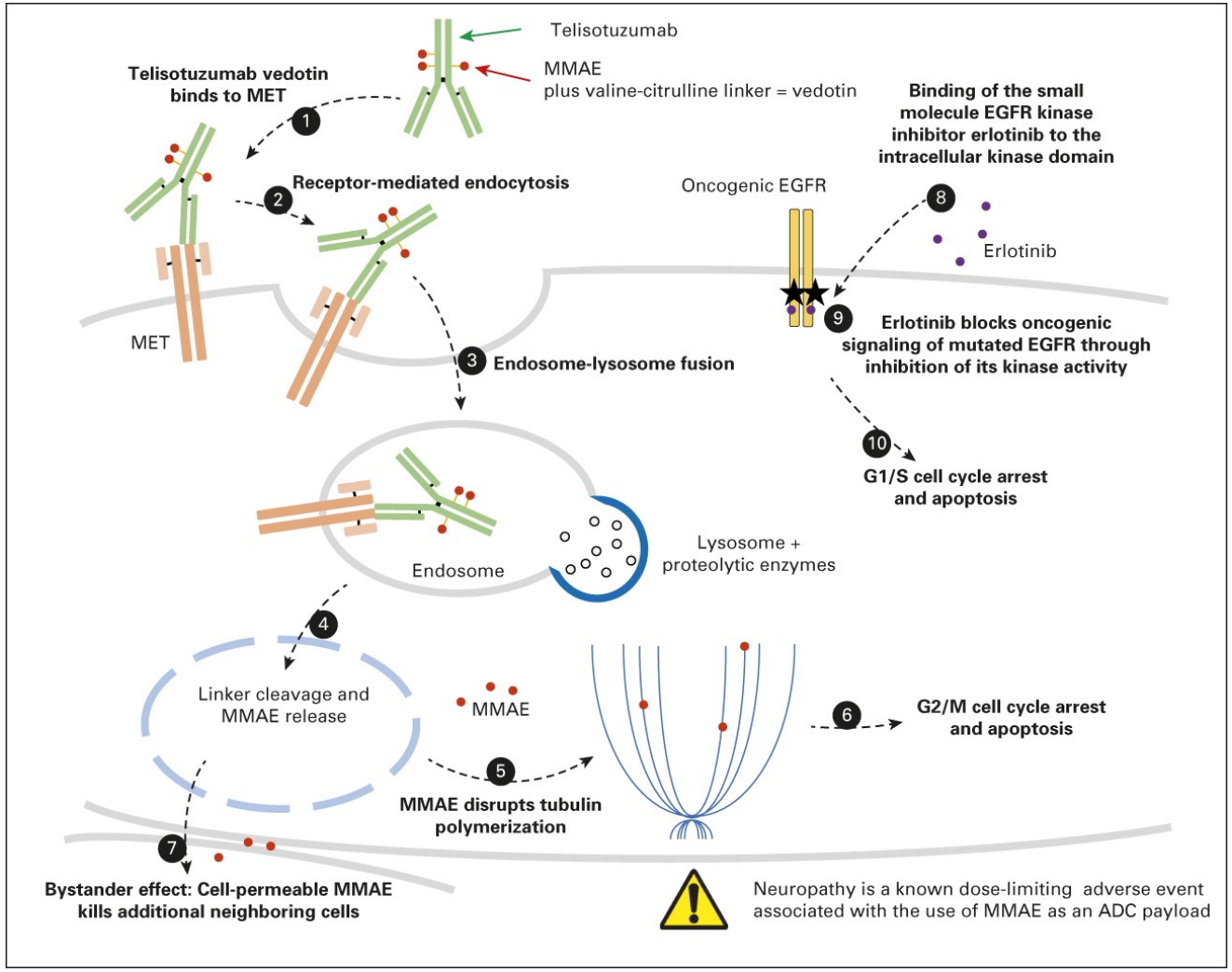


Courtesy of Pongwut Danchaivijitr. *Age at INSIGHT 2 study entry. †Osimertinib 80 mg QD. ‡RANO-BM analysis planned at the time of the primary analysis. §Tepotinib 500 mg QD plus osimertinib 80 mg QD.
1L, first line; 2L, second line; EGFR, epidermal growth factor receptor; Del19, exon 19 deletion; FISH, fluorescent in situ hybridization; MET, mesenchymal–epithelial transition factor; *MET*amp, *MET* amplification; PR, partial response; QD, once daily; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; TBx, tissue biopsy.

INSIGHT 2: Conclusions

- Tepotinib + osimertinib was highly active in patients with *EGFR*m NSCLC with acquired resistance to 1L osimertinib and *MET*amp
  - ORR was 43.9% in 98 patients with TBx FISH$^+$ *MET*amp; as the data matures, six additional PRs have been confirmed
  - Primary analysis will be conducted when all 98 patients have ≥9 months' follow-up
  - ORR was 51.6% in 31 patients with LBx NGS$^+$ *MET*amp
- The combination treatment was well tolerated with no new safety signals observed
- Tepotinib + osimertinib provides a potential chemotherapy-sparing oral targeted therapy option in this population with a high unmet need, regardless of the method used for detecting *MET*amp

Teliso-V Plus Erlotinib in High MET EGFRm NSCLC



Sattler & Salgia, JCO, 2022

2023 ASCO® ANNUAL MEETING

Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated advanced NSCLC in the post-osimertinib setting: Analysis of tissue IHC and ctDNA NGS

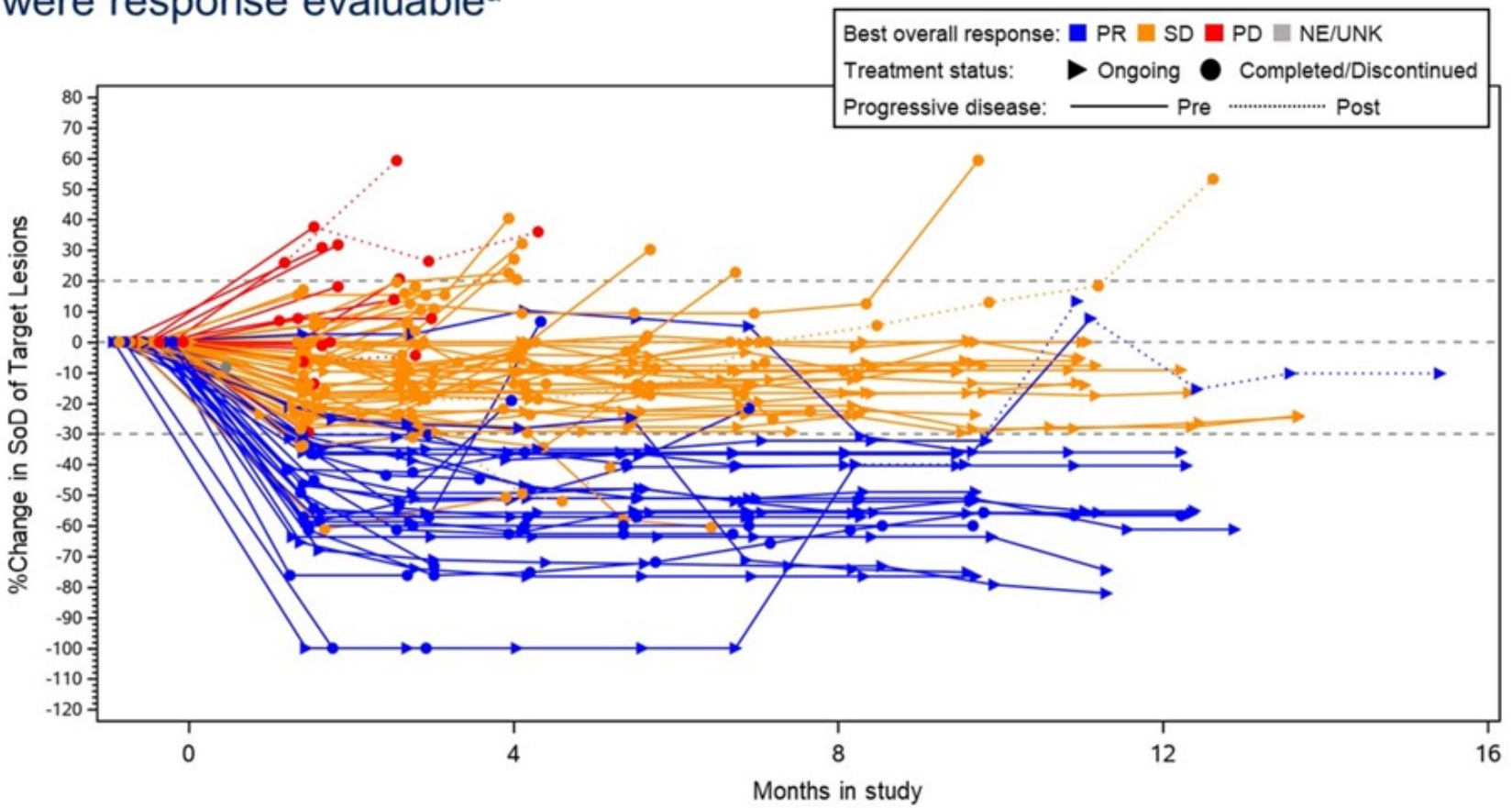
Benjamin Besse,[1] Christina S. Baik,[2] Melina E. Marmarelis,[3] Joshua K. Sabari,[4] Koichi Goto,[5] Catherine A. Shu,[6] Jong-Seok Lee,[7] Sai-Hong Ignatius Ou,[8] Byoung Chul Cho,[9] Saiama N. Waqar,[10] Aurélie Swalduz,[11] Pascale Tomasini,[12] Joshua M. Bauml,[13] Joshua C. Curtin,[13] Xuesong Lyu,[14] Songbai Wang,[15] Tim Jatkoe,[15] Michael Gormley,[13] Leonardo Trani,[13] Roland E. Knoblauch,[13] Enriqueta Felip[16]

[1]Paris-Saclay University, Institut Gustave Roussy, Villejuif, France; [2]University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [3]University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA; [4]NYU Langone Health, New York City, NY, USA; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Columbia University Irving Medical Center, New York City, NY, USA; [7]Seoul National University College of Medicine, Seoul, Republic of Korea; [8]University of California Irvine, Orange, CA, USA; [9]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [10]Division of Oncology, Washington University School of Medicine, St. Louis, MO, USA; [11]Centre Leon Bérard, Lyon, France; [12]CEPCM "CLIP2" & Multidisciplinary Oncology & Therapeutic Innovations Department, Aix Marseille University, CNRS, INSERM, CRCM, APHM, Marseille, France; [13]Janssen R&D, Spring House, PA, USA; [14]Janssen R&D, Shanghai, China;[15]Janssen R&D, Raritan, NJ, USA; [16]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain

Durable Responses Seen With Amivantamab Plus Lazertinib

- Among the 108 patients, 101 were response evaluable[a]

	n=101
ORR	30% (95% CI, 21–40)
Median DOR	10.8 months (95% CI, 5.5–NE)
CBR[b]	69% (95% CI, 59–78)
Median PFS	5.7 months (95% CI, 4.0–8.2)
Median OS	Not estimable

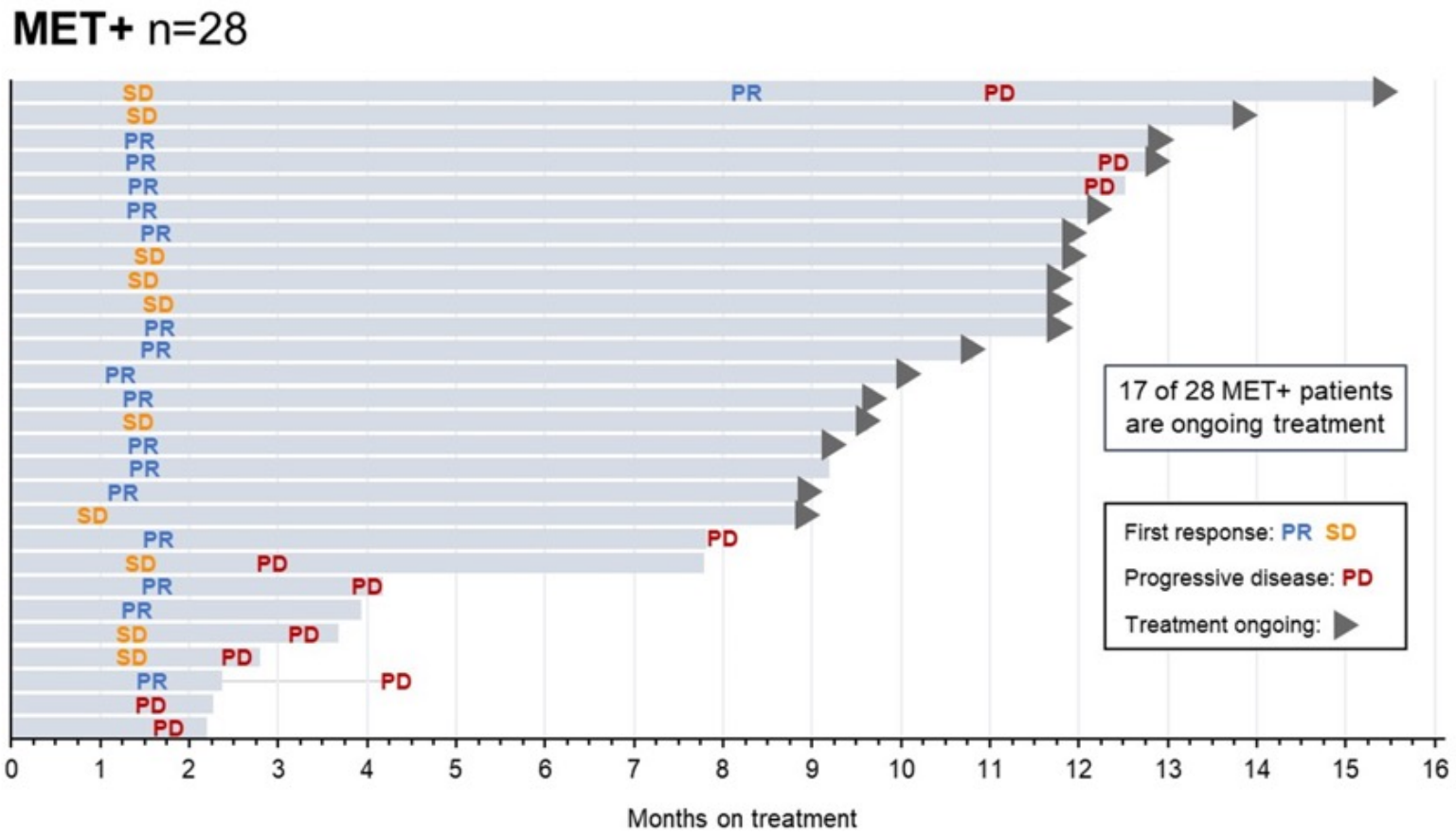


[a]Response-evaluable patients had ≥1 dose of study intervention and ≥1 post-baseline disease assessment, clinical progression, or died due to disease progression before the first post baseline disease assessment.
[b]CBR defined as the percentage of patients achieving confirmed complete/partial response or durable stable disease (duration ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; UNK, unknown.

Durable Responses Seen With Amivantamab Plus Lazertinib in the MET+ Subgroup

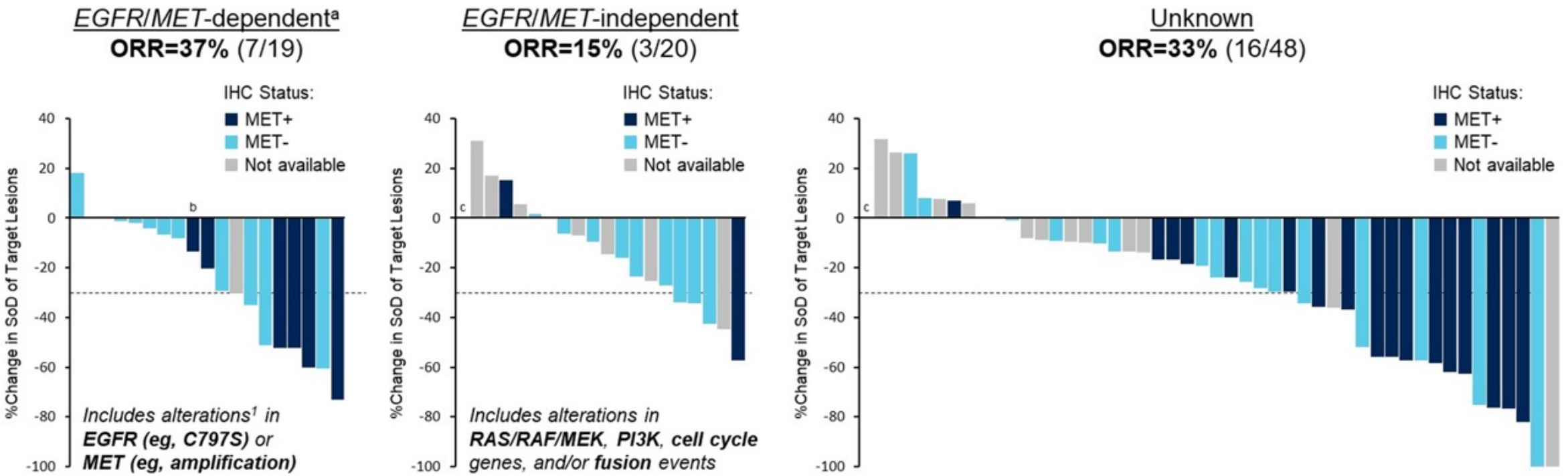
	MET+ (n=28)	MET- (n=49)
ORR	61% (95% CI, 41–79)	14% (95% CI, 6–27)
Median DOR	10.8 months (95% CI, 2.9–NE)	6.8 months (95% CI, 1.9–NE)
CBR[a]	86% (95% CI, 67–96)	61% (95% CI, 46–75)
Median PFS	12.2 months (95% CI, 8.0–NE)	4.2 months (95% CI, 2.8–6.4)



[a]CBR defined as the percentage of patients achieving confirmed complete/partial response or durable stable disease (duration ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; DOR, duration of response; MET, mesenchymal-epithelial transition factor; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Baseline NGS of ctDNA Does Not Predict Response to Amivantamab Plus Lazertinib



- MET+ IHC was predictive of response regardless of molecular resistance mechanism

[a]Includes co-occurring independent resistance mechanisms.
[b]*MET* amplification was detected in 1 patient.
[c]Two patients did not have any evaluable target lesion measurements in any post-baseline disease assessment.

ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor; NE, not evaluable or unknown; NGS, next-generation sequencing; ORR, objective response rate; SoD, sum of diameters.

1. Leonetti et al. Br J Cancer. 2019;121(9):725-737.

Conclusions

Treatment Benefit

- Consistent with prior reports, amivantamab plus lazertinib demonstrated activity in patients with *EGFR*-mutated advanced NSCLC whose disease progressed on or after osimertinib
- Based on rebiopsy after osimertinib resistance, **MET 3+ staining on ≥25% of tumor cells** by IHC (MET+) demonstrated:
  - ORR of 61% vs 14% in MET-
  - Longer PFS of 12.2 months in MET+ vs 4.2 months in MET-
- MET+ IHC was predictive of response regardless of molecular resistance mechanism

Safety

- Safety profile was consistent with prior reports

Key Takeaway & Next Step

- MET+ by IHC may be a predictive biomarker for response to amivantamab plus lazertinib in the post-osimertinib, chemotherapy-naïve setting
- This biomarker will be prospectively validated in CHRYSALIS-2 (NCT04077463)

EGFR: Ongoing or planned clinical trials with 3rd generation EGFR Resistance

Primary Target	Primary Therapeutic	Secondary Target	Secondary Therapeutic	ClinicalTrials.gov Identifier
EGFR	Osimertinib	CDK4/CDK6	Abemaciclib	NCT04545710
EGFR	Osimertinib	mTOR Aurora A	Sapanisertib Alisertib	NCT04479306
EGFR	Osimertinib	Anti-EGFR	Necitumumab	NCT02496663
EGFR	Osimertinib	MET	Tepotinib	NCT03940703
EGFR	Osimertinib	MET	Tepotinib	NCT05120960
EGFR	Osimertinib	COX1/COX2 (AKT/BIM)	Aspirin	NCT04184921
EGFR	Osimertinib - 	MET EGFR Anti-EGFR Antifolate + Anti-PD1 ALK RET Antifolate + + Platinum Chemotherapy MEK1/MEK2 TROP2 ADC Topoisomerase + Anti PD-L1 + Platinum Chemotherapy	Savolitinib Gefitinib Necitumumab Pemetrexed + Durvalumab Alectinib Selpercatinib Pemetrexed + Carboplatin or Cisplatin Selumetinib Datopotamab-deruxtecan Etoposide + Durvalumab + Carboplatin or Cisplatin	NCT03944772
EGFR	Osimertinib	BCL-2/BCL-xL	Pelcitoclax	NCT04001777
EGFR	Osimertinib	BCL-2/BCL-xL	Navitoclax	NCT02520778
EGFR	Osimertinib	SRC	Dasatinib	NCT02954523
EGFR	Osimertinib	α/δ Phosphatidylinositol 3-kinase	TQ-B3525	NCT05284994
EGFR	Osimertinib	EGFR HER2	Necitumumab + Trastuzumab	NCT04285671
EGFR, HER2, HER4	Dacomitinib	EGFR	Alone or + Osimertinib	NCT03755102
EGFR-MET bispecific antibody	Amivantamab	EGFR Antifolate Chemotherapy	Lazertinib or + Pemetrexed + Carboplatin	NCT05299125, NCT02609776, NCT04077463
EGFR-MET bispecific antibody	EMB-01			NCT03797391
Anti-HER3 ADC	Patritumab Deruxtecan	EGFR	Osimertinib	NCT04676477
EGFR	Nazartinib (EGF816)	MEK1/MEK2	Trametinib	NCT03516214
PARP	Olaparib	Anti-PD-L1	Durvalumab	NCT04538378
Antifolate + Chemotherapy	Pemetrexed + Platinum Chemotherapy	Anti-PD-1	Alone or + Pembrolizumab	NCT03515837
EGFR (C797X)	BLU-701	EGFR Antifolate Chemotherapy	Alone or + Osimertinib + Pemetrexed + Carboplatin	NCT05153408
EGFR (C797X)	BLU-945	EGFR	Alone or + Osimertinib	NCT04862780
EGFR (C797X)	WJ13405			NCT05662670
EGFR (C797X)	BAY2927088			NCT05099172
EGFR (C797X)	JIN-A02			NCT05394831
EGFR (C797X)	HS-10375			NCT05435248
EGFR (C797X)	QLH11811			NCT05555212
EGFR (C797X)	BPI-361175			NCT05393466
EGFR (C797X)	BDTX-1535			NCT05256290

Sattler et int. Salgia, JCM 2023

Summary

- EGFR therapeutics have revolutionized our treatment for a subset of NSCLC
- There are a large number of resistance with EGFR TKI
- There can be genetic and non-genetic mechanisms of resistance
- Based on the mechanism of resistance, we can rationally determine the next therapy

Acknowledgment

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