OSPEDALE SAN RAFFAELE

New drugs bypassing the anti-EGFR blockade

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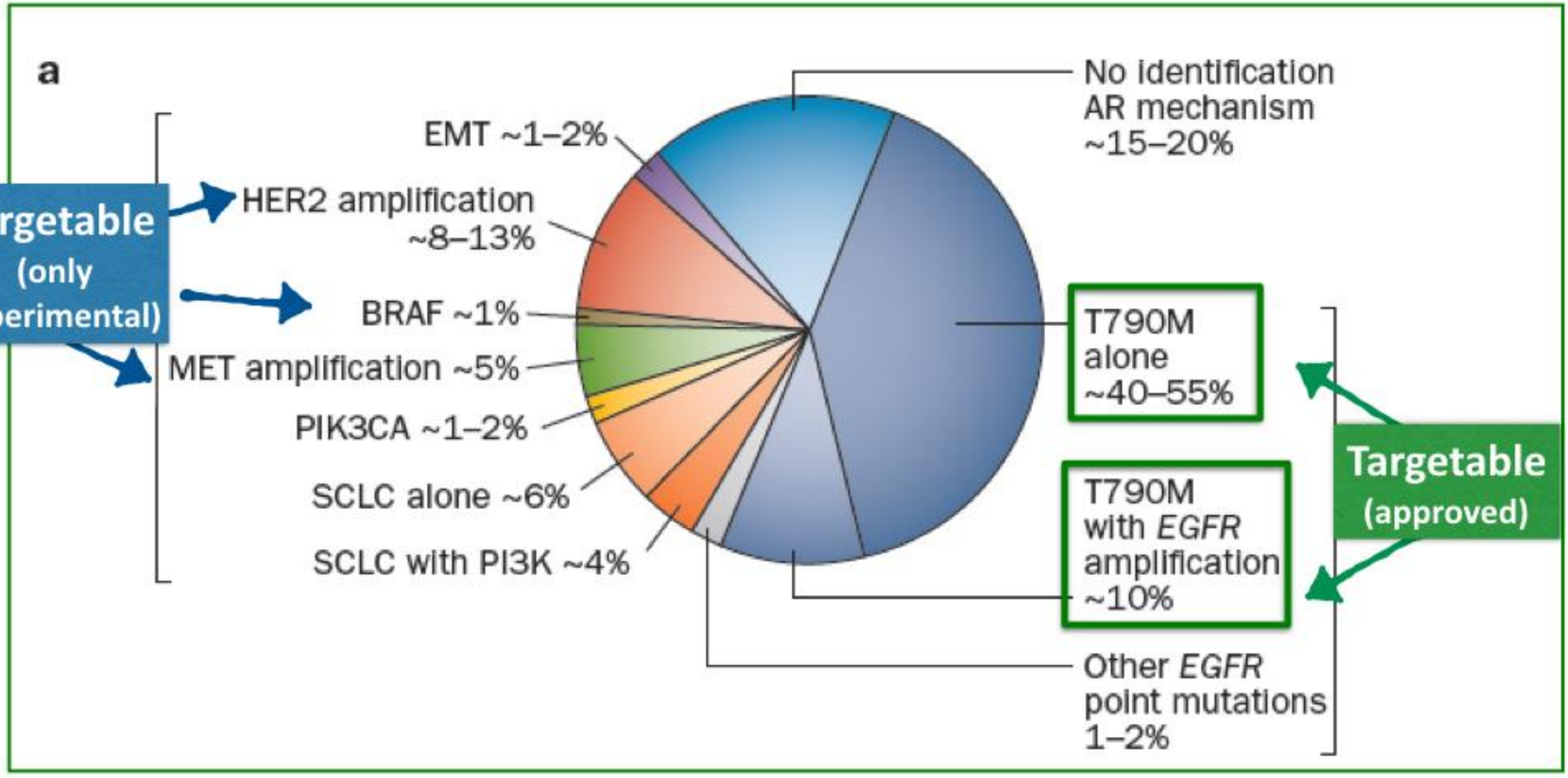
Heterogeneous acquired resistance mechanisms to EGFR-TKIs



Camidge et al, Nat Rev Clin Oncol 2014

Treatment strategies for patients developing EGFR T790M mutation

Osimertinib

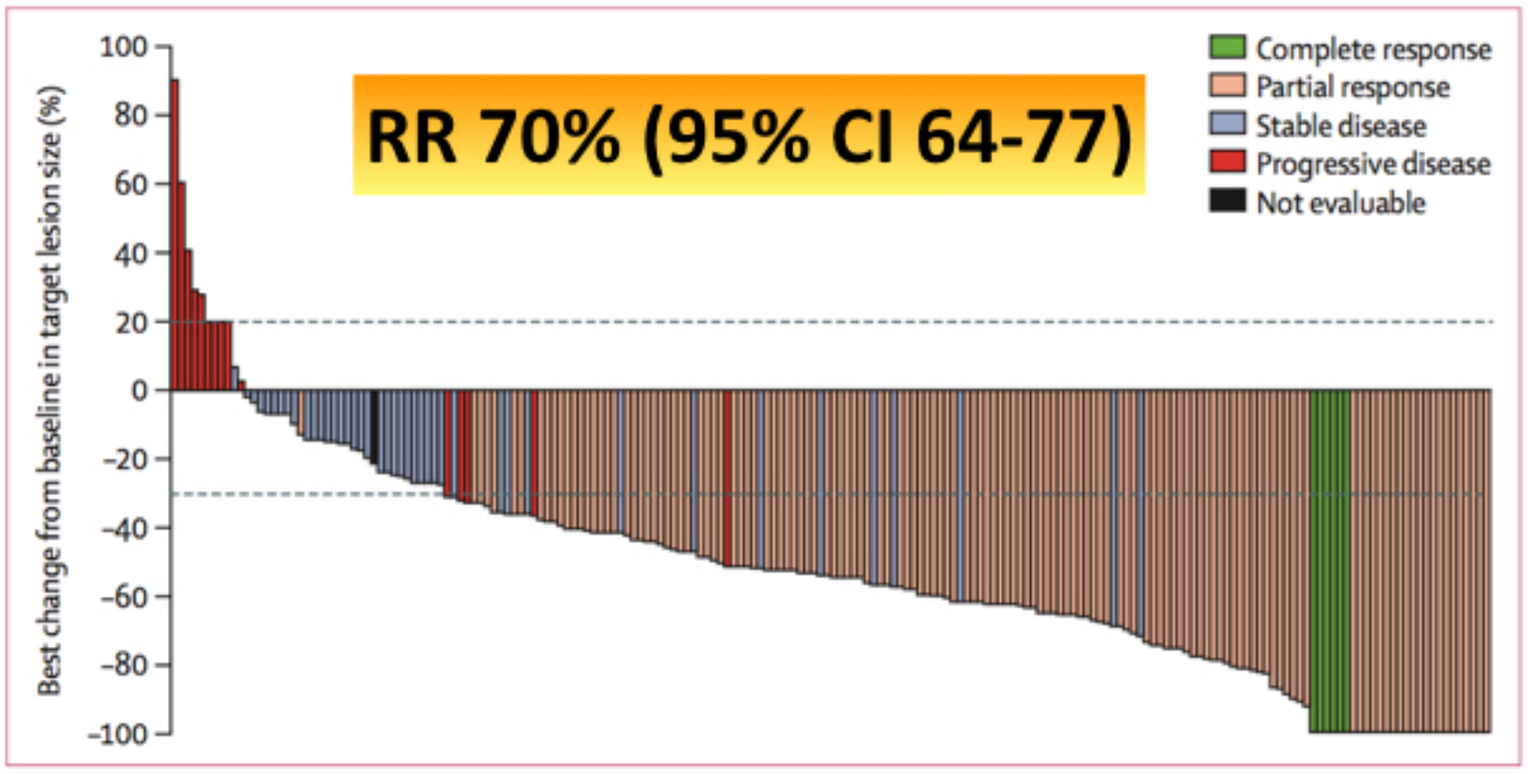
FDA and EMA approved

Rociletinib

Discontinued for poor efficacy

Olmutinib

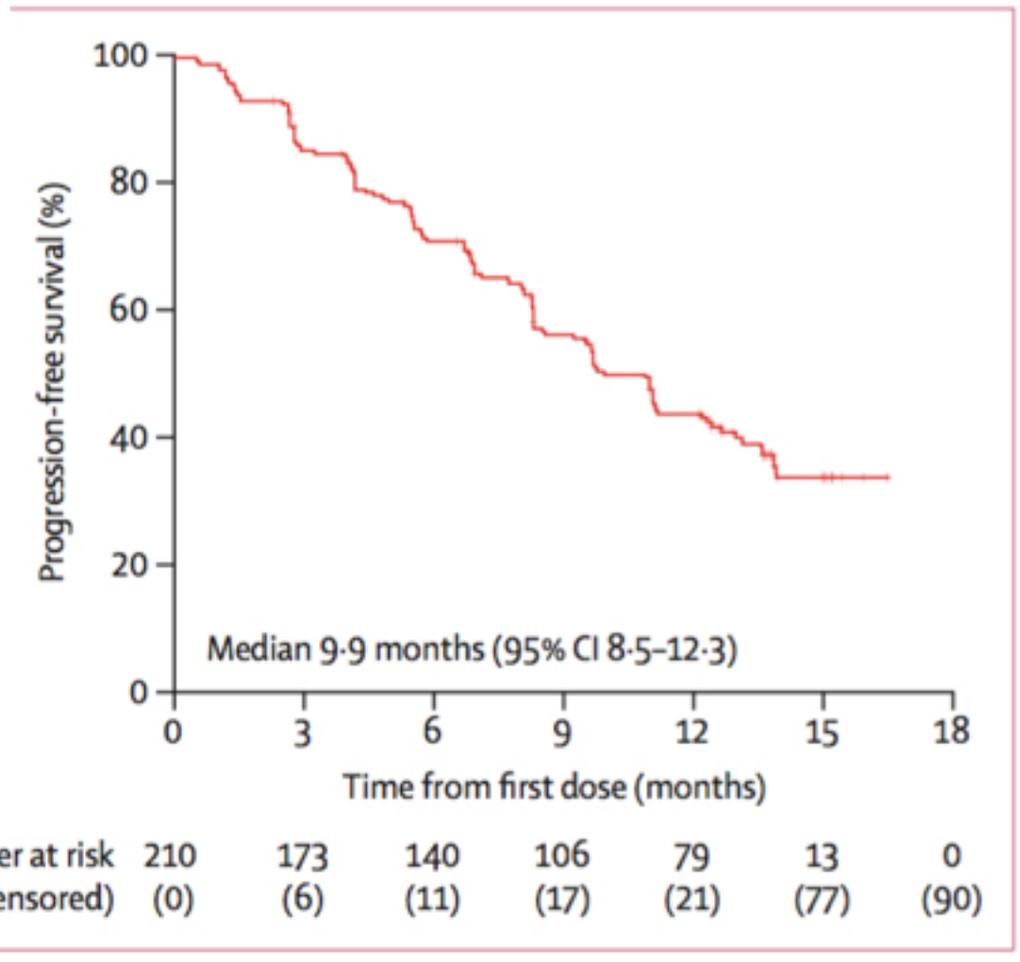
Osimertinib is a recommended targeted therapy for EGFR T790M+ NSCLC - Phase II AURA2 trial



210 EGFR mutated NSCLC carrying T790M

Median duration of response 11.4 months (95% CI 9.0 - not calculable)

Median PFS 9.9 months (95% CI 8.5 - 12.3)



Goss et al, Lancet Oncol 2016

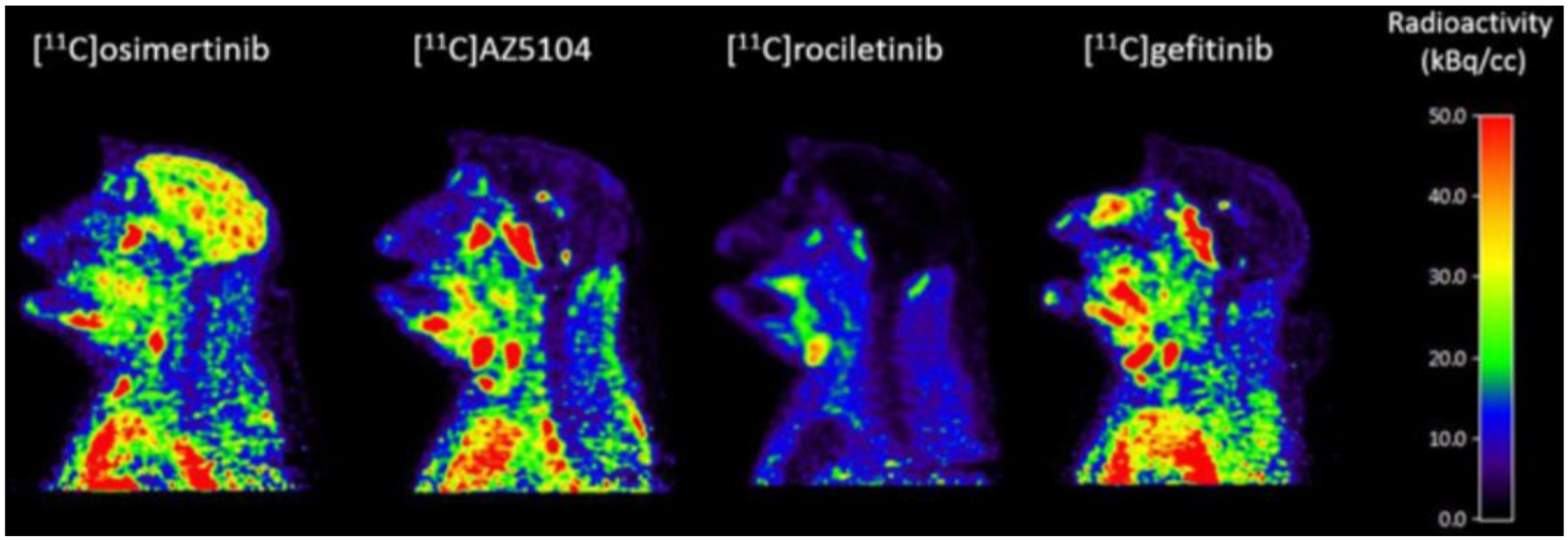
Osimertinib and brain metastases

30% of EGFR mutant patients develop brain lesions in the course of EGFR-TKis

Osimertinib and its metabolites AZ5104 and AZ7550 are substrates of Pgp and BCRP

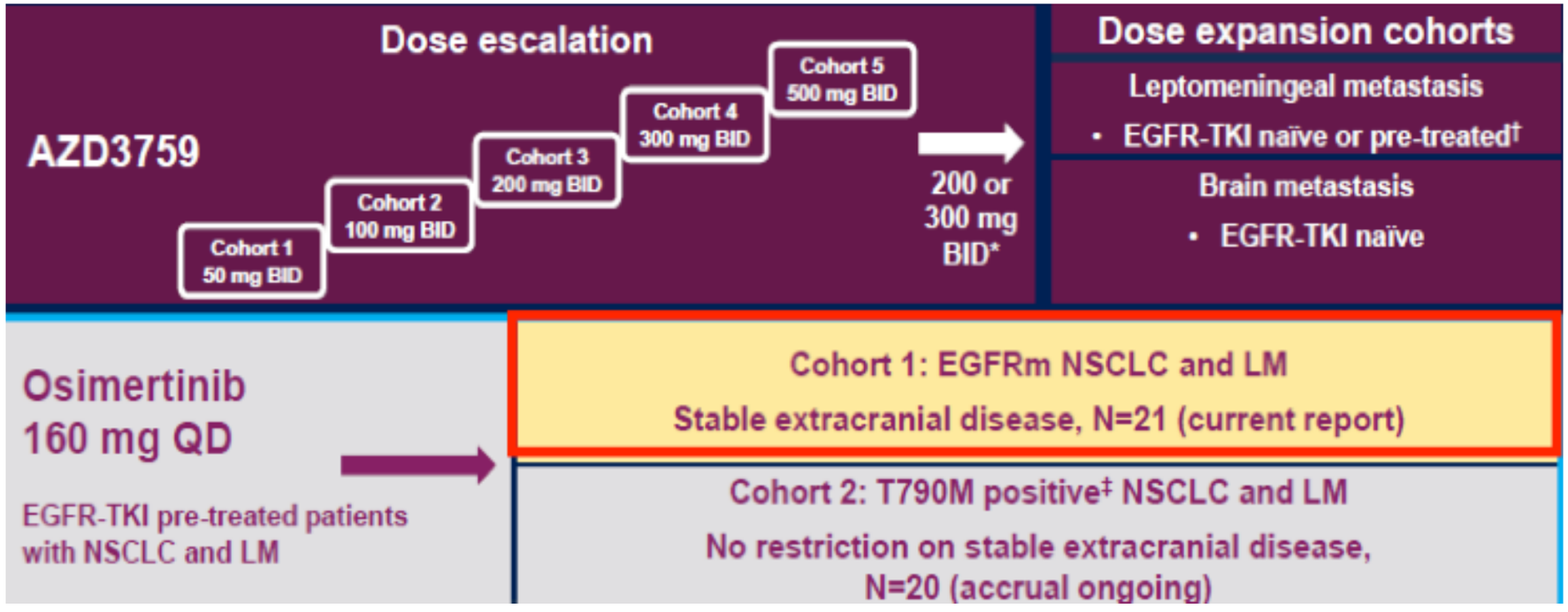
Table 2. Distribution to mouse brain of osimertinib, gefitinib, rociletinib, and afatinib following oral administration

	Osimertinib	Gefitinib	Rociletinib	Afatinib
Dose (mg/kg)	25	6.25	100	7.5
Plasma C_{max} (μmol/L)	0.82	0.82	3.32	0.14
Brain C_{max} (μmol/L)	2.78	0.17	BLQ	BLQ
Brain/plasma C_{max} ratio	3.41	0.21	<0.08	<0.36



Ballard et al, Clinical Cancer Research 2016

Strategies under investigation to overcome brain progression - BLOOM - Phase I



21 patients receiving osimertinib

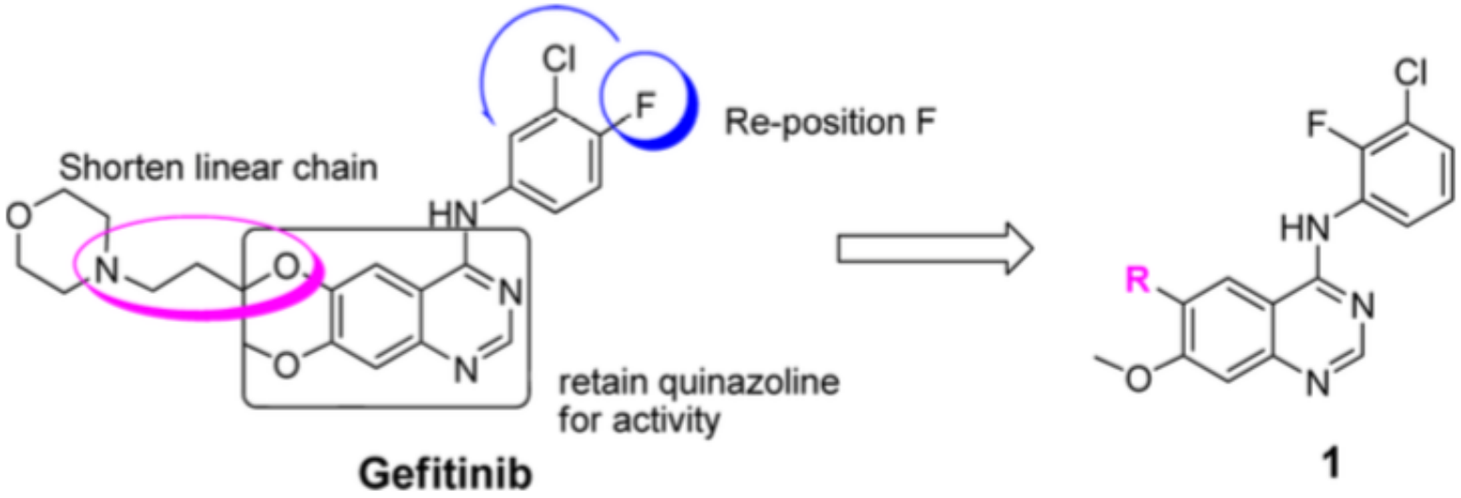
Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	

Yang et al, ASCO 2016

AZD3759 - synthesized to overcome blood brain barrier

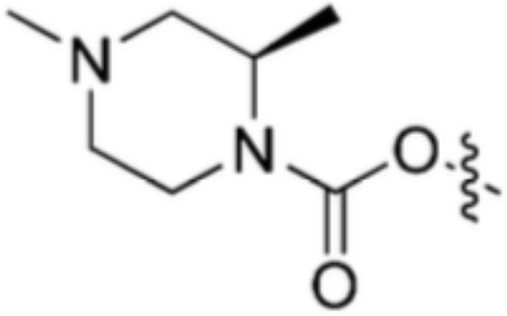


Gefitinib

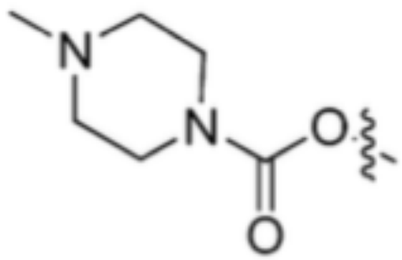
1

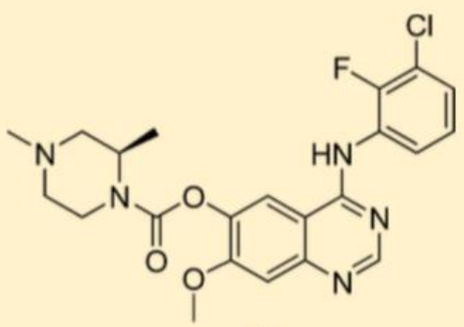
replacement of the methylene group with nitrogen to improve stability

permeability, solubility, efflux ratio



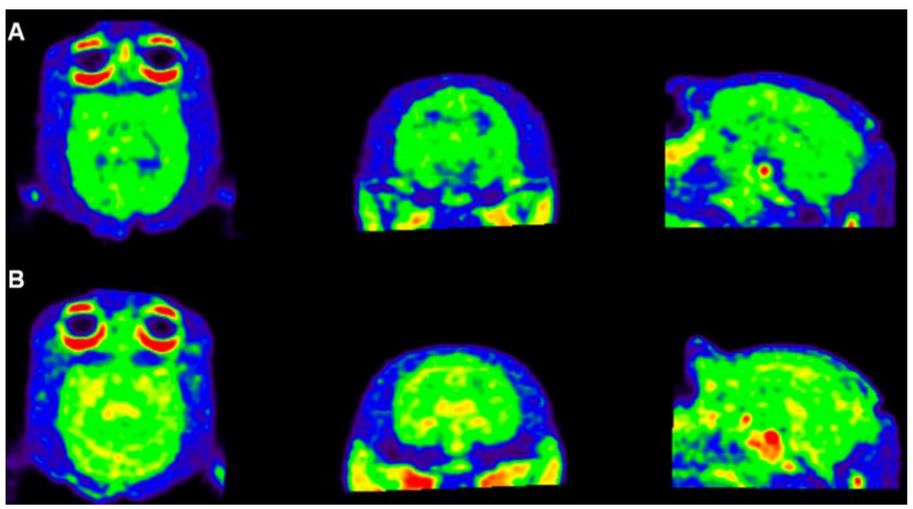
incorporation of a methyl group to increase PK





1m

L858R pEGFR IC_{50} = 7.2 nM
$K_{puu,brain}$ = 1.3
$K_{puu,CSF}$ = 1.3



Zeng et al, Journal of Medicinal Chemistry 2016

How to identify the emerging mechanisms of acquired resistance - Analysis of circulating tumor DNA

Retrospective analysis of EGFR mutant patients enrolled in the AURA trial

Table 1. Sensitivity and Specificity of Plasma Genotyping Assays Compared With Tumor Genotype As a Reference Standard

Plasma Genotype (BEAMing)	Tumor Genotype (cobas, Central Laboratory)	
	Exon 19 del+ (n = 136)	Exon 19 del− (n = 80)
Exon 19 del+ (n = 114)	112 (82.3% sensitivity)	2
Exon 19 del− (n = 102)	24	78 (97.5% specificity)
	L858R+ (n = 73)	L858R− (n = 143)
L858R+ (n = 68)	63 (86.3% sensitivity)	5
L858R− (n = 148)	10	138 (96.5% specificity)
	T790M+ (n = 158)	T790M− (n = 58)
T790M+ (n = 129)	111 (70.3% sensitivity)	18
T790M− (n = 87)	47	40 (69.0% specificity)

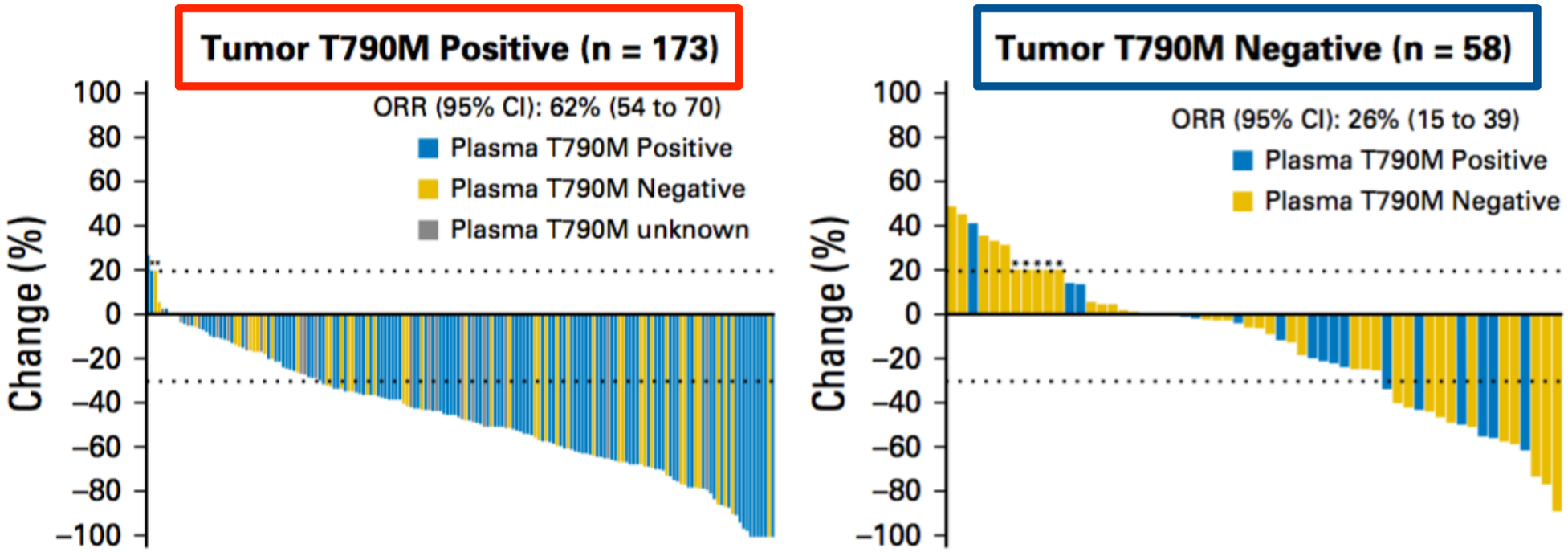
High specificity (~100%), good sensitivity (>80%) for EGFR sensitizing mutations

Good sensitivity and specificity for T790M (~70%)

false negative results for EGFR sensitizing mutations
false negative results for T790M

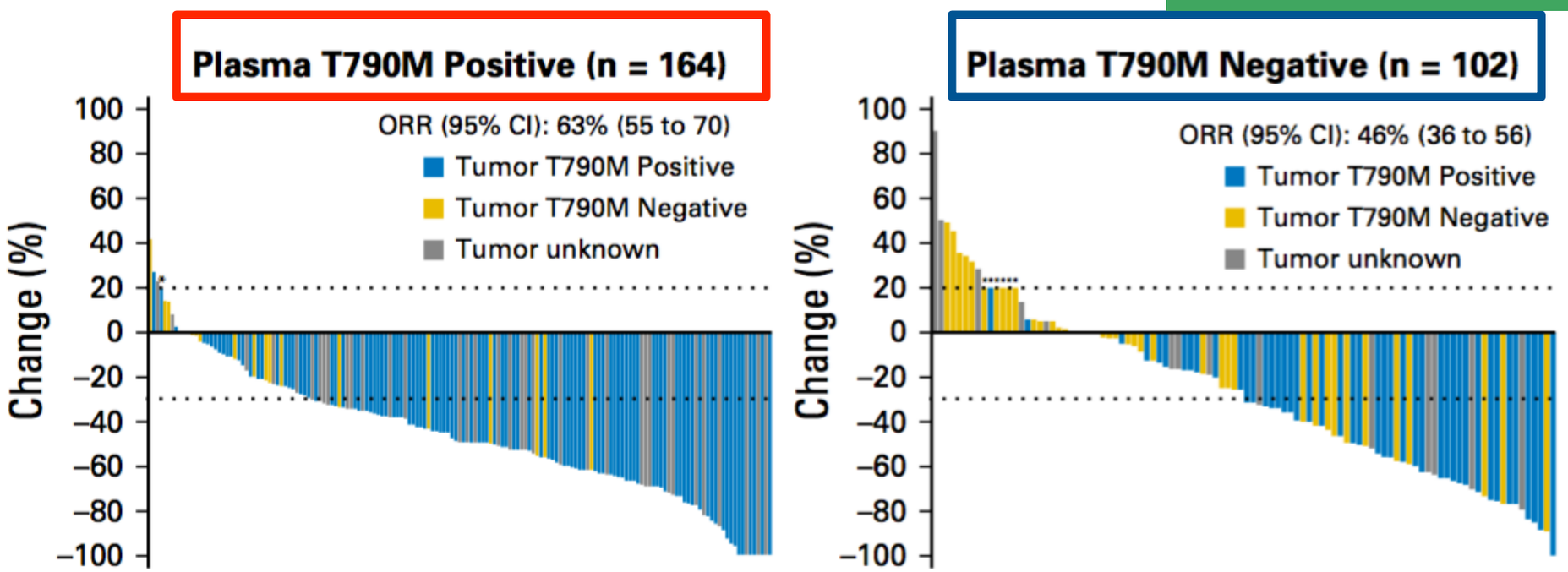
Oxnard et al, JCO 2016

Response rate in T790M+ : tumor = plasma



	ORR (95% CI)	*P*
Tumor T790M Positive	62% (54 to 70)	< .001
Tumor T790M Negative	26% (15 to 39)	

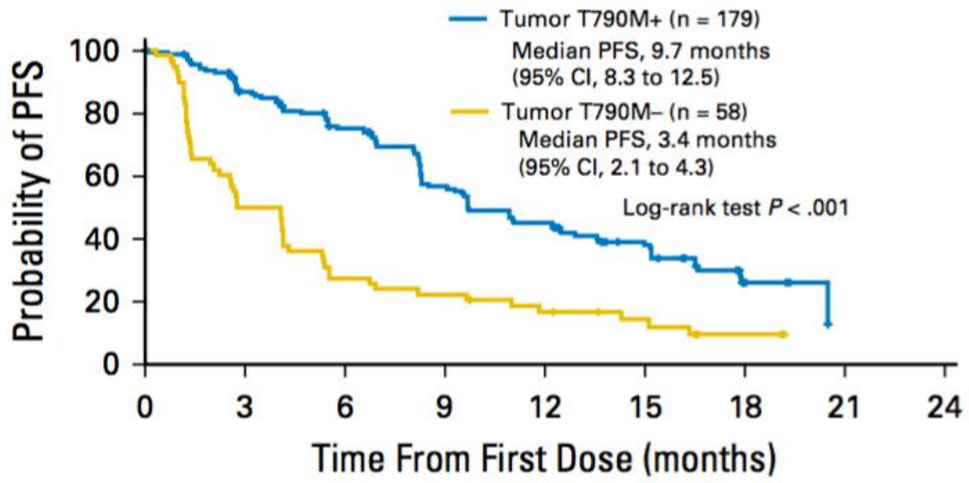
false negative results for T790M



	ORR (95% CI)	*P*
Plasma T790M Positive	63% (55 to 70)	.011
Plasma T790M Negative	46% (36 to 56)	

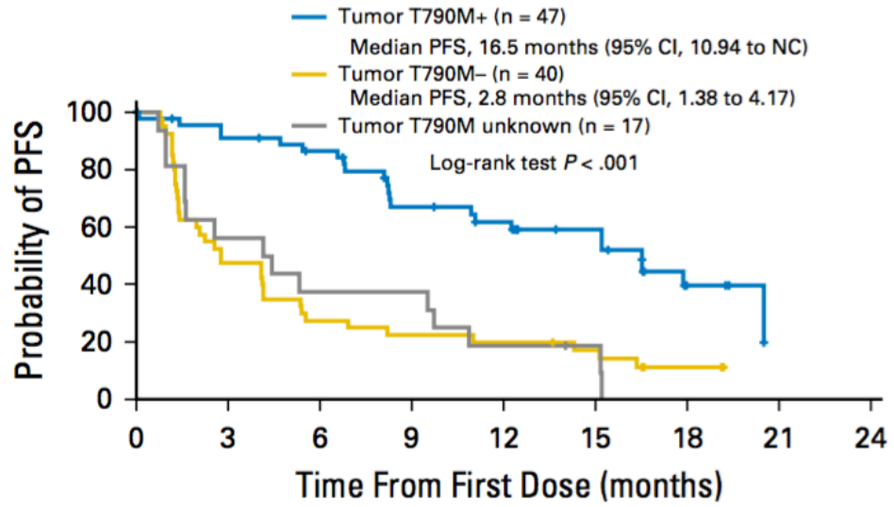
Oxnard et al, JCO 2016

Tumor



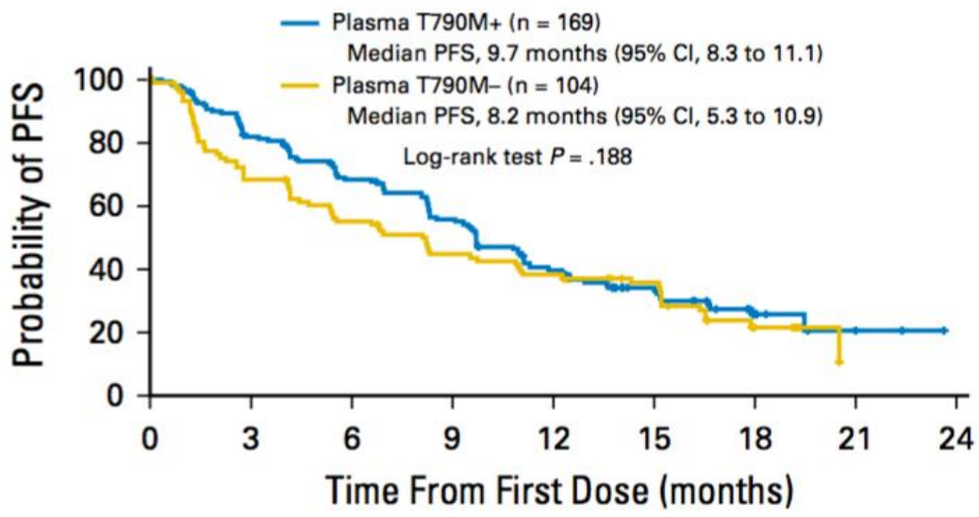
No. at risk							
Tumor T790M+	179	131	107	75	56	36	5
Tumor T790M–	58	29	16	13	9	6	2

Plasma T790M-



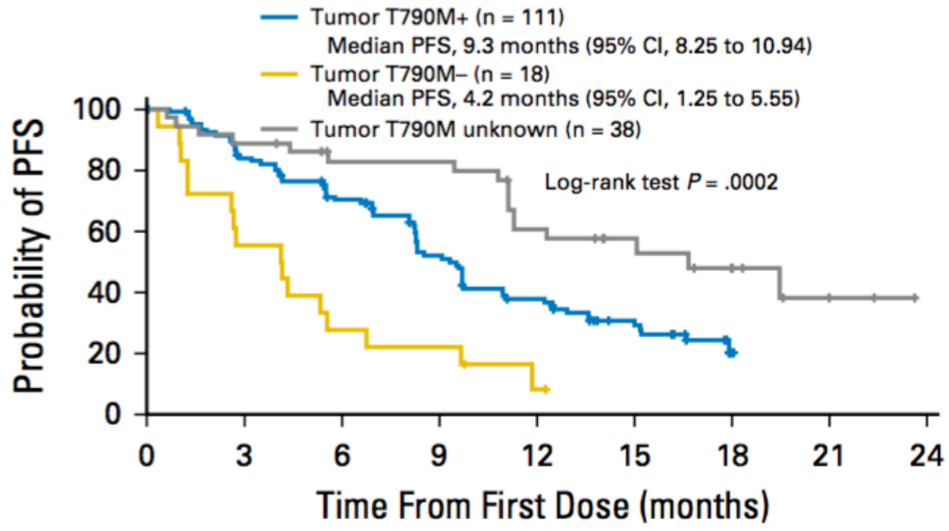
No. at risk							
Tumor T790M+	47	41	37	27	23	17	4
Tumor T790M–	40	19	11	9	8	6	2
Tumor unknown	17	9	6	5	3	2	

Plasma



No. at risk								
Plasma T790M+	167	130	102	79	53	31	9	2
Plasma T790M–	104	69	54	42	34	25	6	

Plasma T790M+



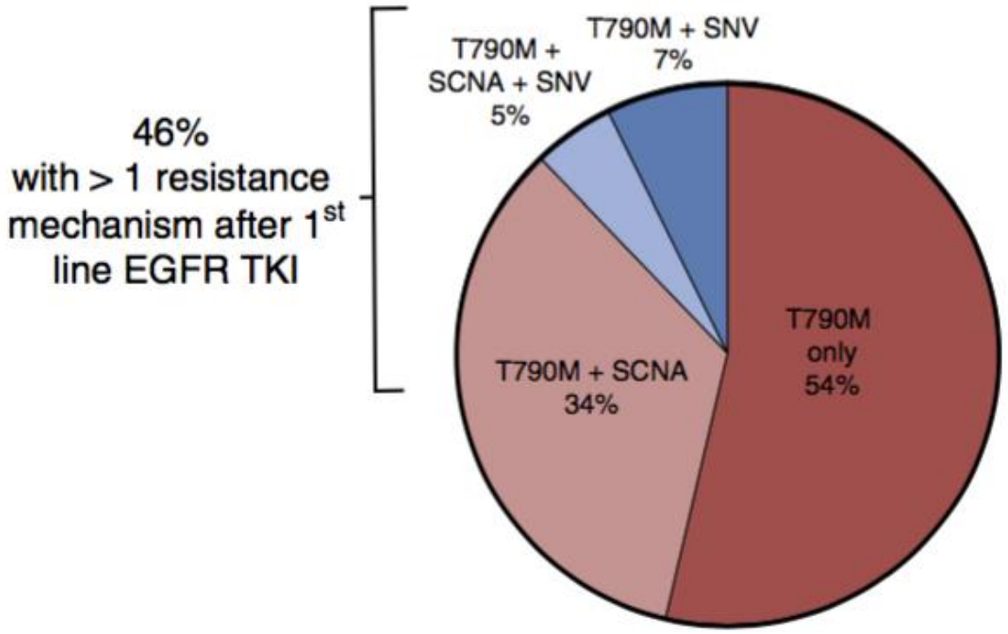
No. at risk								
Tumor T790M+	111	88	70	48	33	19	1	
Tumor T790M–	18	10	5	4	1			
Tumor unknown	38	32	27	26	19	12	8	2

Tumor positive, plasma negative (***16.5 months***) >
Tumor positive, plasma positive (***9.3 months***)>
Tumor negative, plasma positive (***4.2 months***)

Oxnard et al, JCO 2016

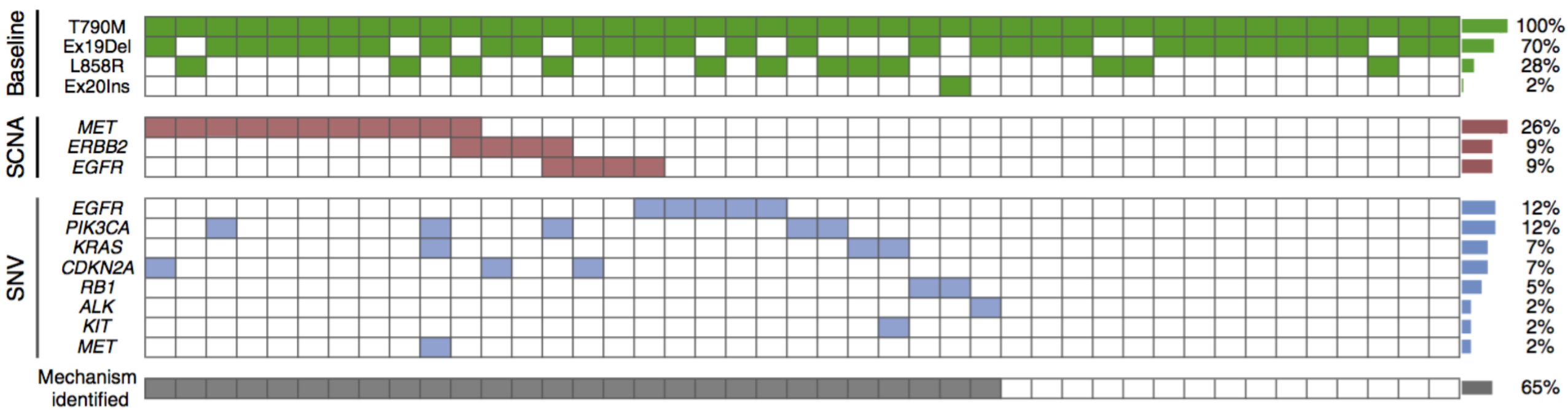
How to identify the emerging mechanisms of acquired resistance - Analysis of circulating tumor DNA

- Integrates contribution from many tumor deposits
- More accurate identification of the heterogeneous resistance mechanisms



SCNA: somatic copy number alterations

SNV: single nucleotide variants



Chabon et al, Nature communications 2016

How to define the emerging mechanisms of acquired resistance - Which methods?

38 patients enrolled in the AURA trial

	cobas® EGFR Mutation Test	therascreen™ EGFR ARMS-PCR	ddPCR™	BEAMingdPCR
Exon 19 deletion				
Sensitivity	86% (24/28)	82% (23/28)	–[b]	93% (26/28)
Specificity	100% (10/10)	100% (10/10)	–[b]	100% (10/10)
Concordance	89%	87%	–[b]	95%
L858R				
Sensitivity	90% (9/10)	78% (7/9)	90% (9/10)	100% (10/10)
Specificity	100% (28/28)	100% (28/28)	100% (28/28)	93% (26/28)
Concordance	97%	95%	97%	95%
T790M				
Sensitivity	41% (7/17)	29% (5/17)	71% (12/17)	71% (12/17)
Specificity	100% (6/6)	100% (6/6)	83% (5/6)	67% (4/6)
Concordance	57%	48%	74%	70%

72 patients enrolled in the AURA trial

	cobas® EGFR Mutation Test	BEAMing dPCR
Exon 19 deletion		
Sensitivity	82% (23/28)	82% (23/28)
Specificity	97% (30/31)	97% (30/31)
L858R		
Sensitivity	87% (20/23)	87% (20/23)
Specificity	97% (35/36)	97% (35/36)
T790M		
Sensitivity	73% (30/41)	81% (33/41)
Specificity	67% (16/24)	58% (14/24)

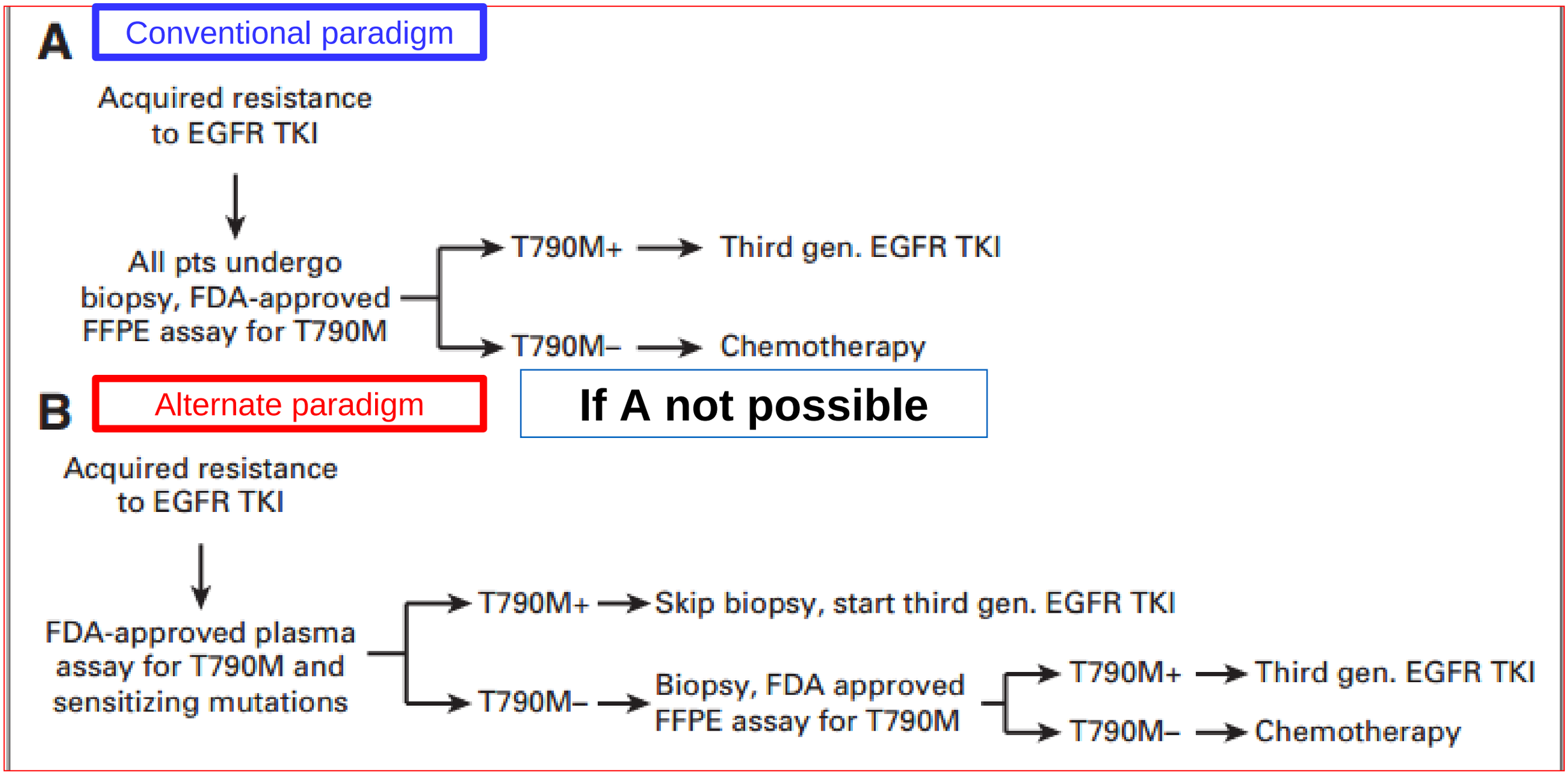
EGFR mutation	Concordance (cobas® EGFR Mutation Test and BEAMing dPCR)
Exon 19 deletion	90% (65/72)
L858R	93% (67/72)
T790M	90% (65/72)

Digital platforms are more ***sensitive*** and ***quantitative***, allowing quantification of longitudinal plasma samples

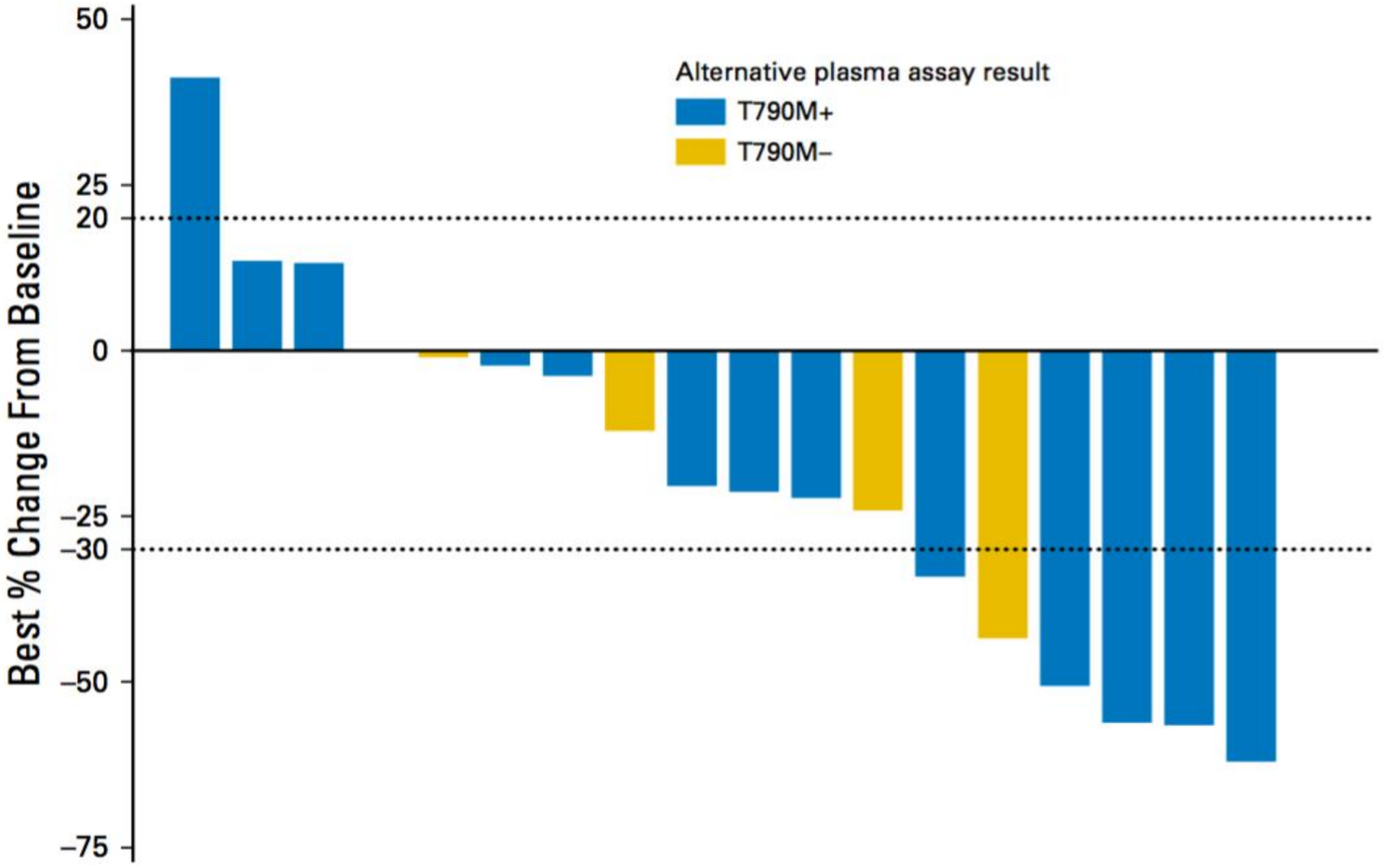
BUT CONSIDER biological FALSE POSITIVE

Thress et al, Lung Cancer 2015

A proposed paradigm for use of plasma genotyping



Oxnard GR, JCO 2016



Plasma T790M+, Tumor T790M+

Plasma T790M+, Tumor T790M-

↓

Heterogeneity and T790M is a minor clone

	pl T790M-/sens+	pl T790M-/sens-
ORR (%)	38 (26 - 50)	64 (45 - 79)
PFS (m)	4.4 (2.8 - 6.8)	15.2 (11.0 - 17.9)

← Lack of tumor DNA

Oxnard et al, JCO 2016

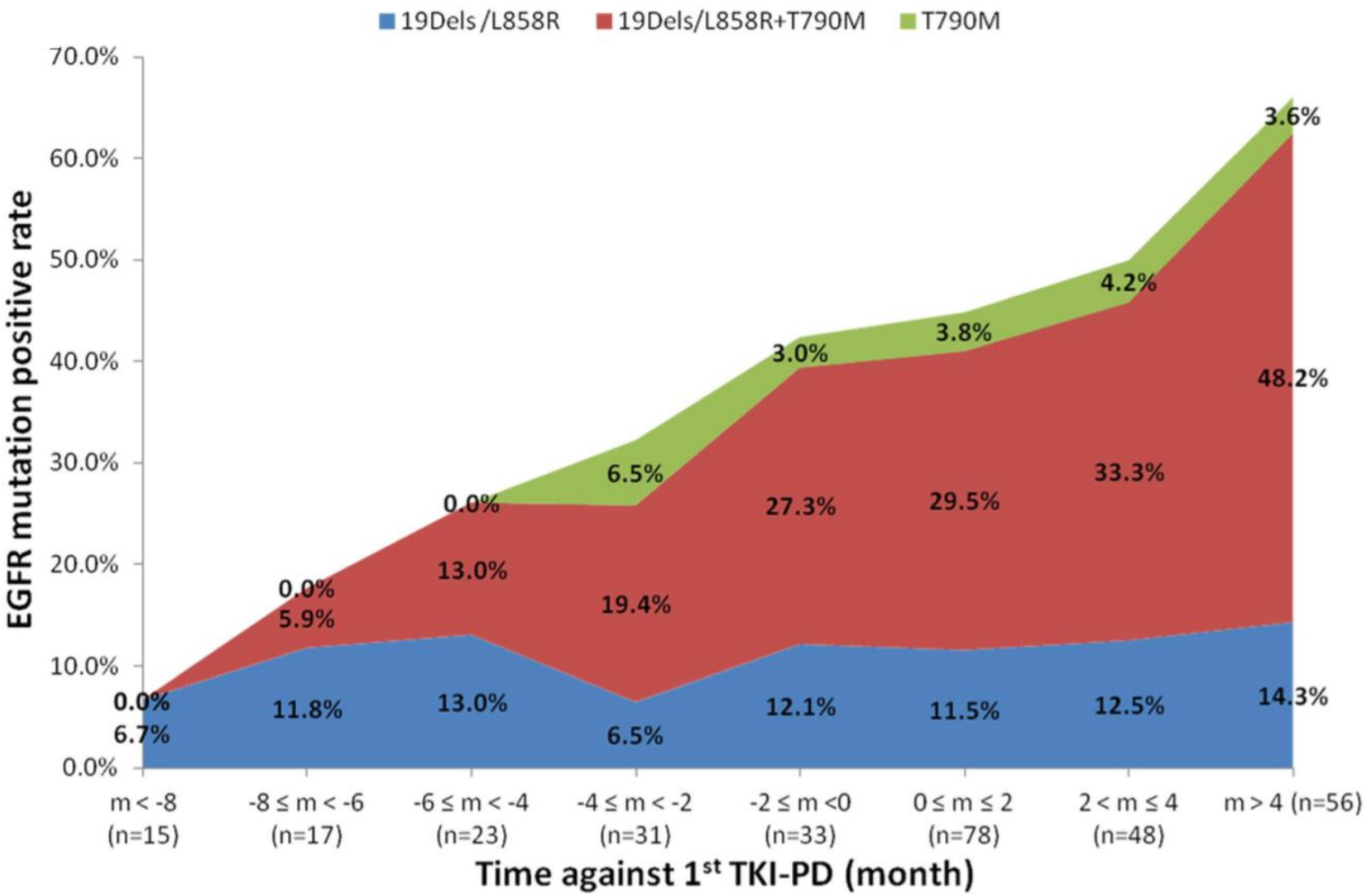
Longitudinal monitoring of EGFR sensitizing and T790M mutations

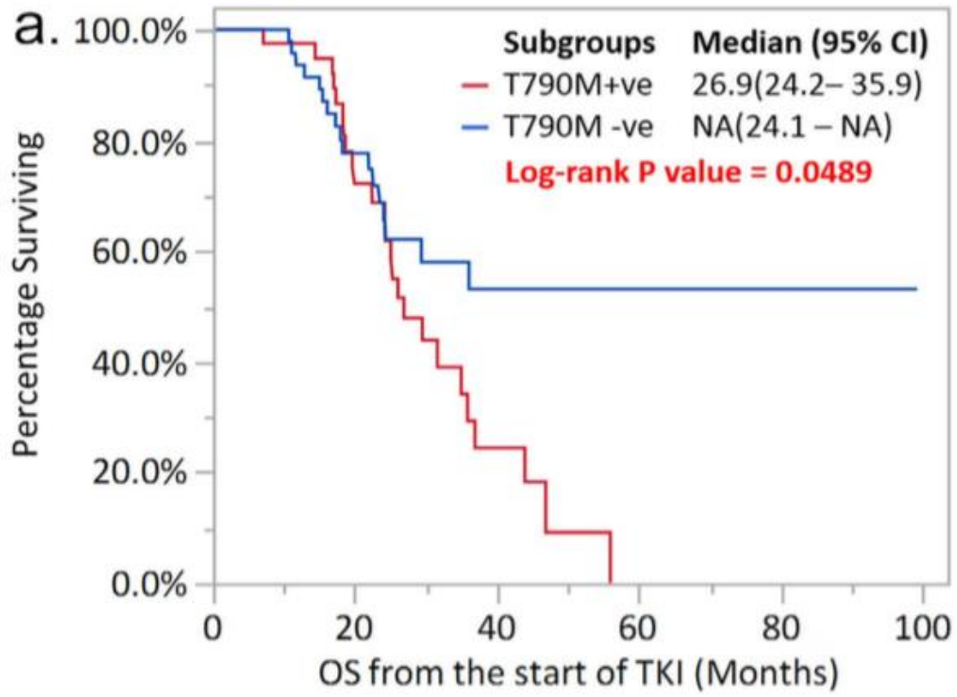
OPEN QUESTION

- How many patients develop EGFR T790M earlier than RECIST progression

- What is timing of EGFR T790M development and the clinical significance of early EGFR T790M detection?

Longitudinal monitoring of EGFR sensitizing and T790M mutations

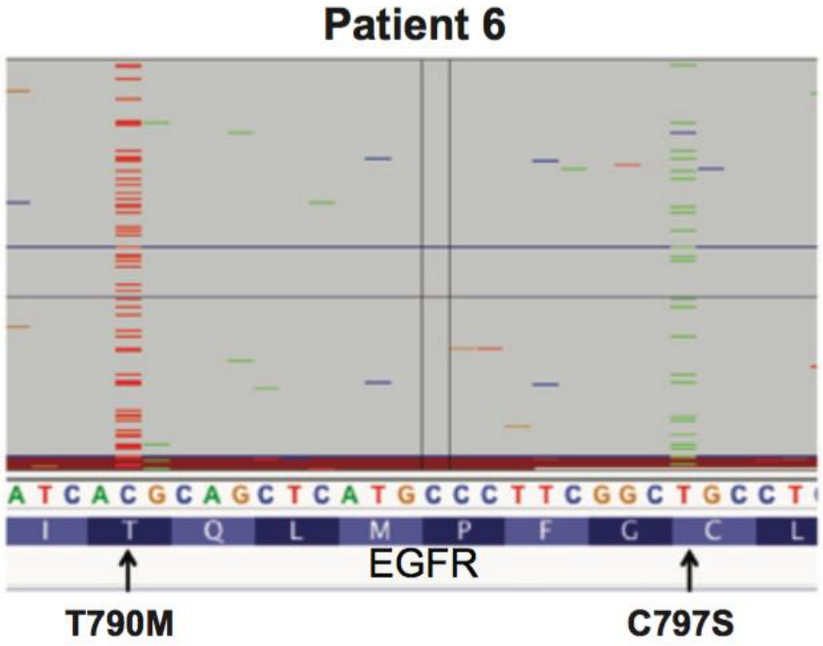




35 (46%) patients developed EGFR T790M, 16 (45%) of whom earlier than clinical progression (median time 2.2 months, increasing progressively from 6 months prior PD to 4 months beyond PD)

Zheng et al, Scientific Reports 2015

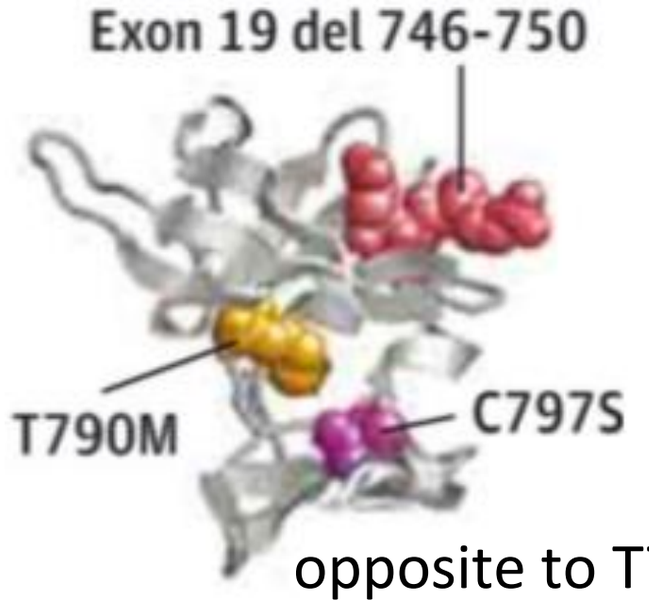
Acquired resistance mechanisms to third generation EGFR-TKIs - C797S



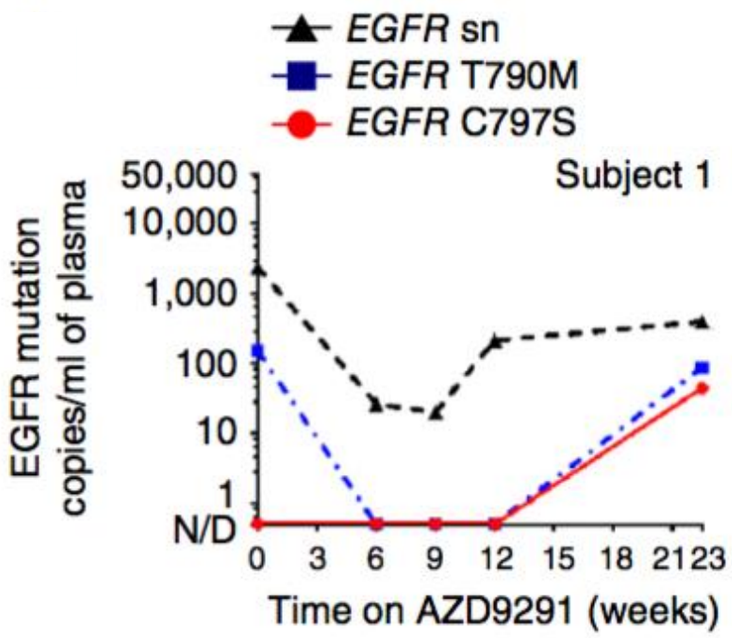
C797S in exon 20

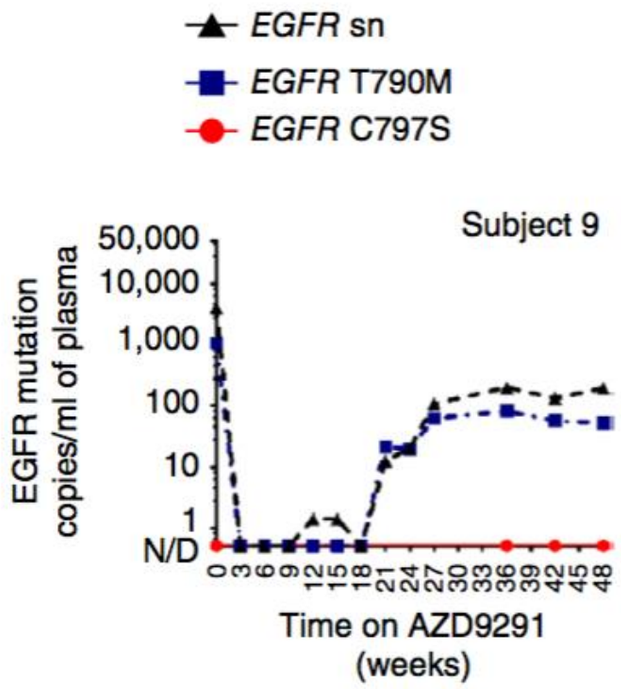
(abrogates the irreversible binding of third generation)

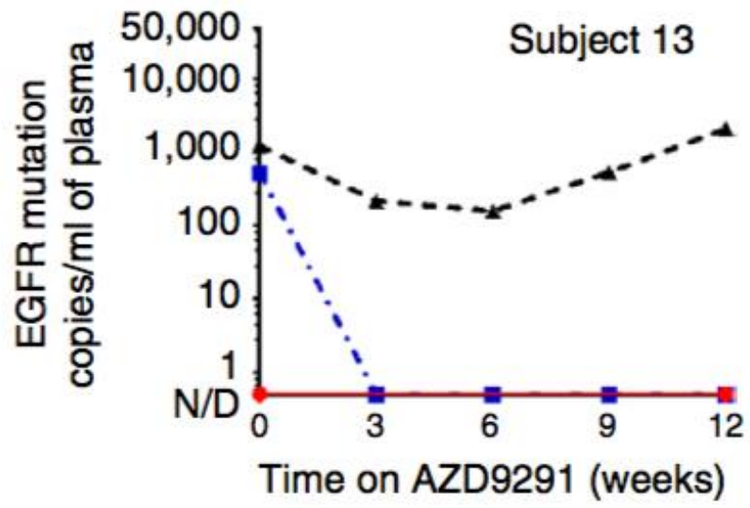
40% of cases



opposite to T790M
in the ATP binding pocket

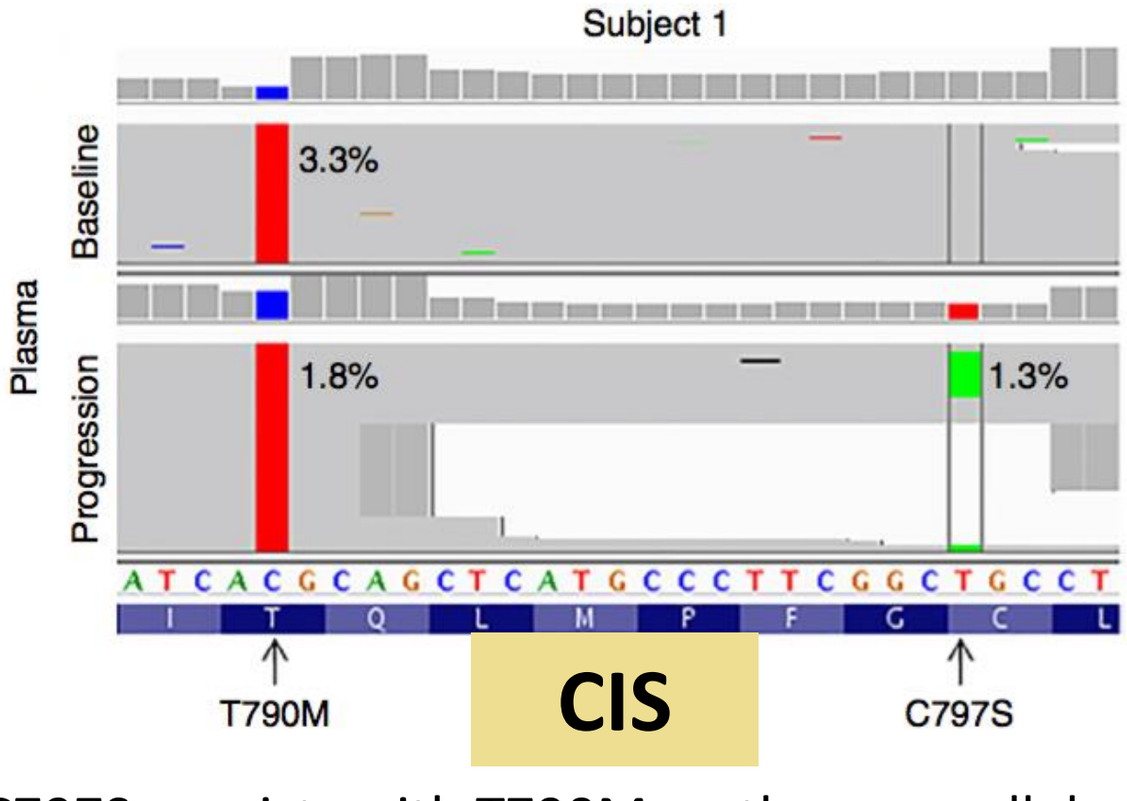






Ortiz-Charan et al; Clin Canc Res 2015. Thress et al; Nature Medicine 2015. Yu HA et al; JAMA 2015

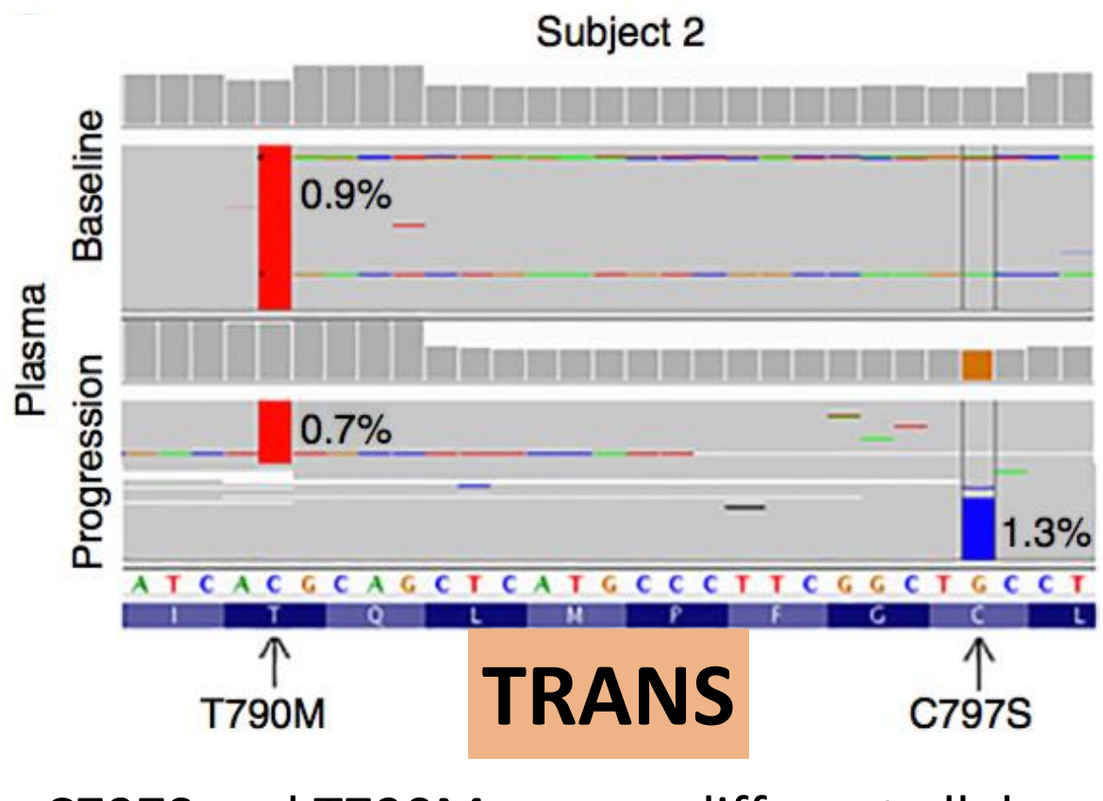
Acquired resistance mechanisms to third generation EGFR-TKIs - C797S



CIS

C797S coexists with T790M on the same alleles

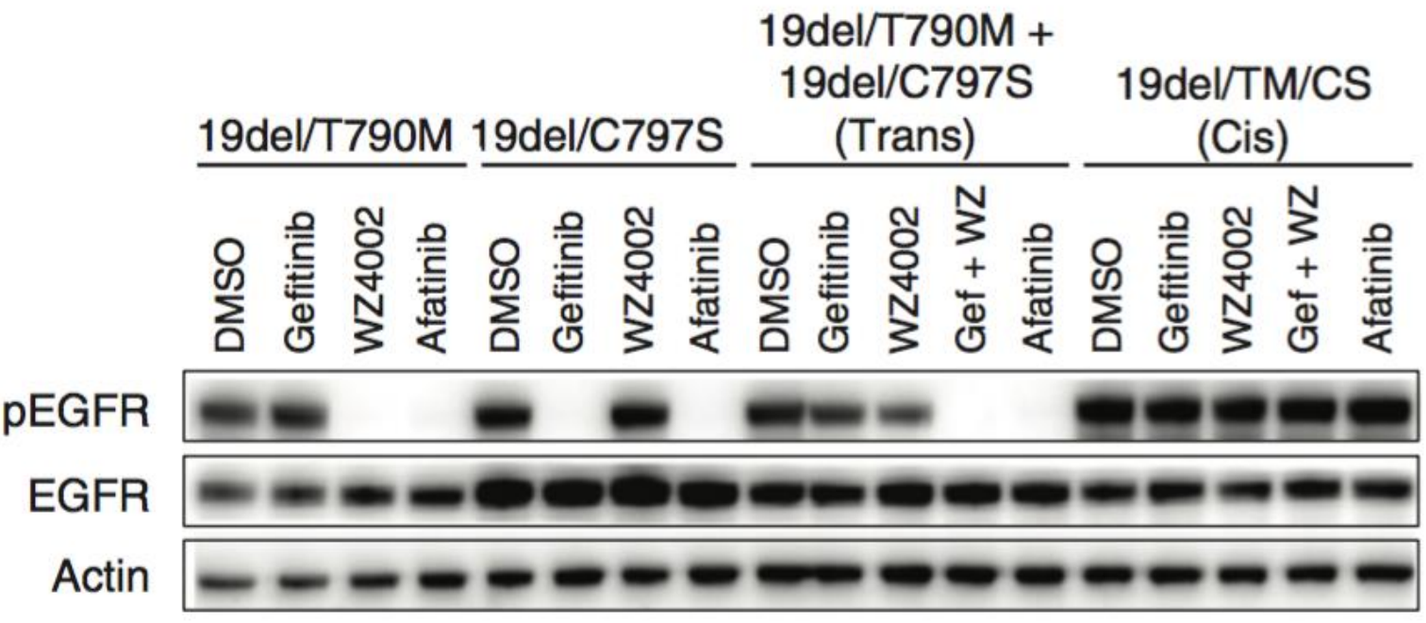
Resistance to all 3 generations EGFR-TKIs



TRANS

C797S and T790M are on different alleles

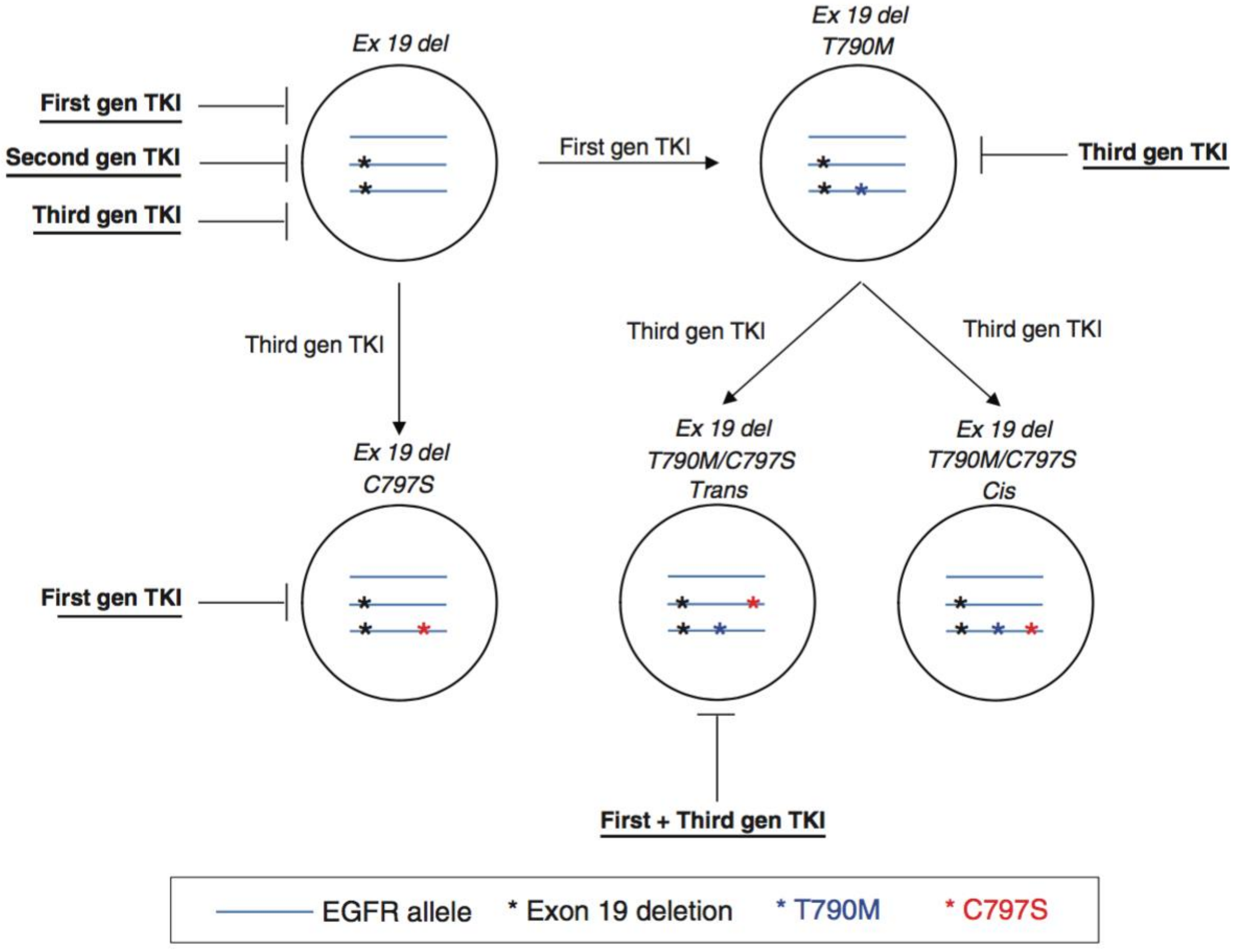
Sensitive to 1st/2nd generations EGFR-TKIs



Third generation require cyst for binding

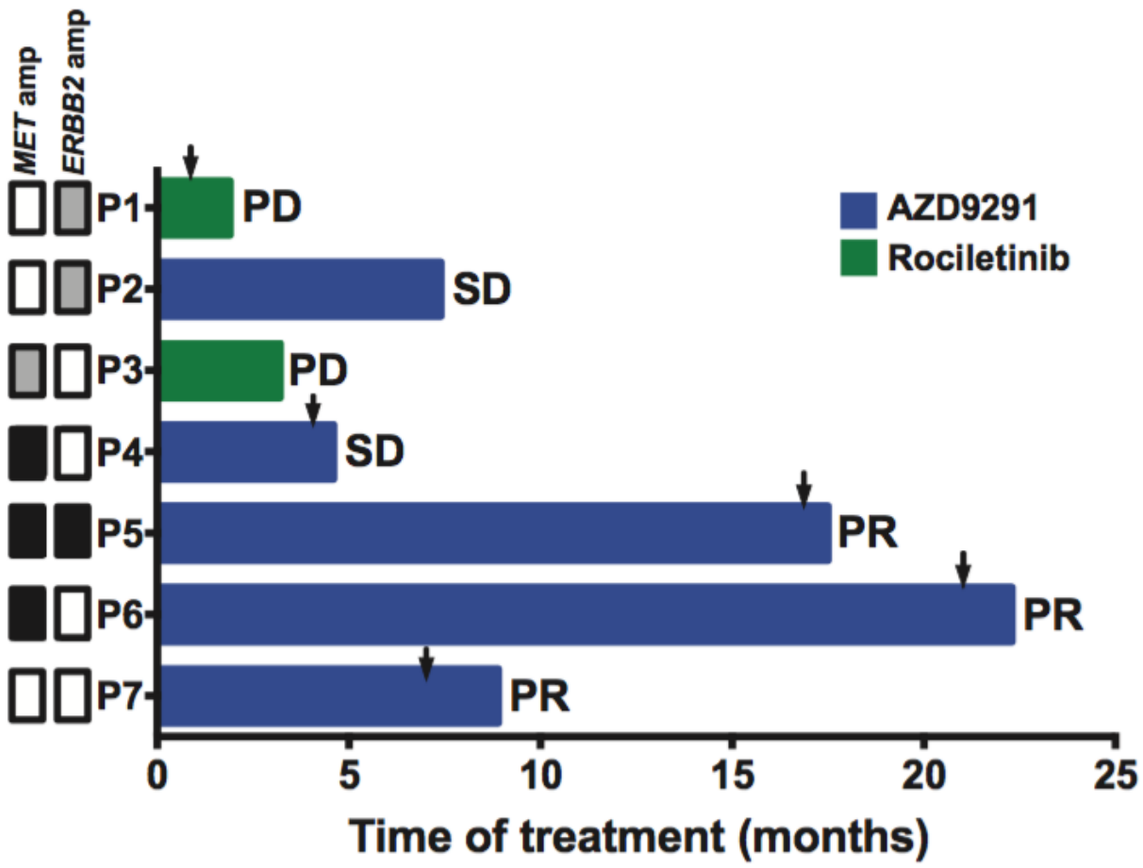
First and second generation do not bind cyst

Niederst et al; Clin Canc Res 2015



Niederst et al; Clin Canc Res 2015

Acquired resistance mechanisms to third generation EGFR-TKIs - MET and ERBB2



At baseline

At progression

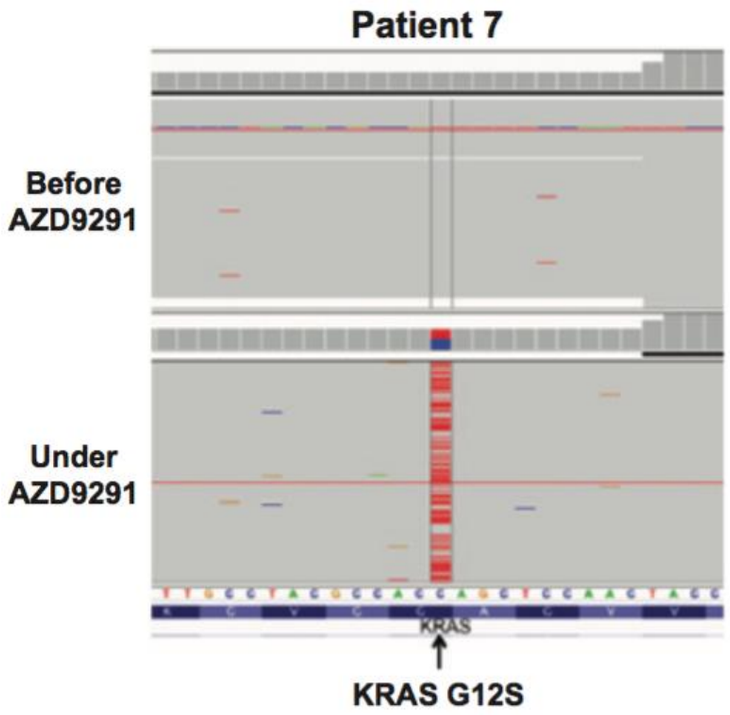
ERBB2 and **MET** amplification decrease sensitivity to third generation EGFR-TKIs

Ongoing studies:

- savolitinib + osimertinib (TATTON trial)

Ortiz-Charan et al; Clin Canc Res 2015

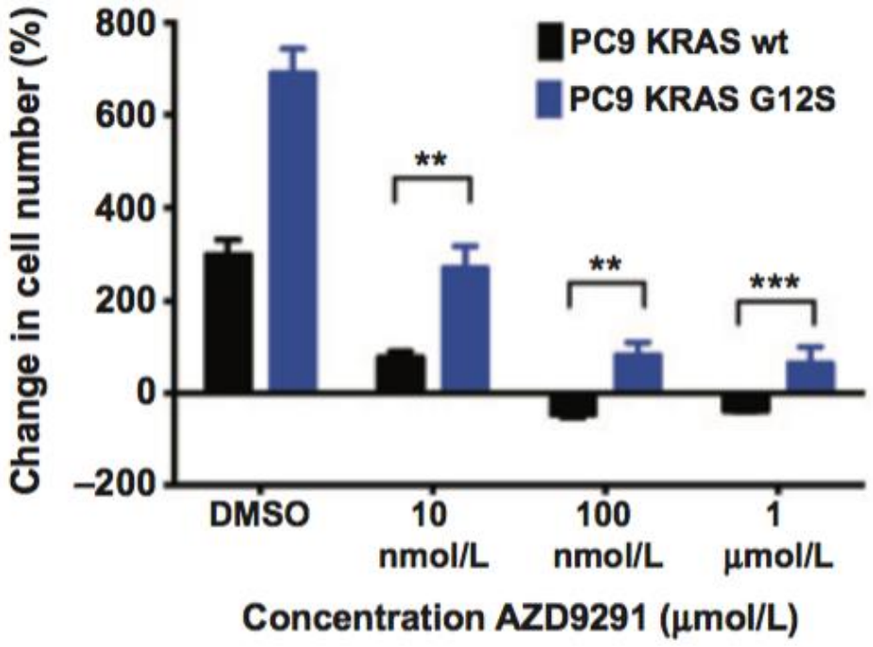
Acquired resistance mechanisms to third generation EGFR-TKIs - KRAS

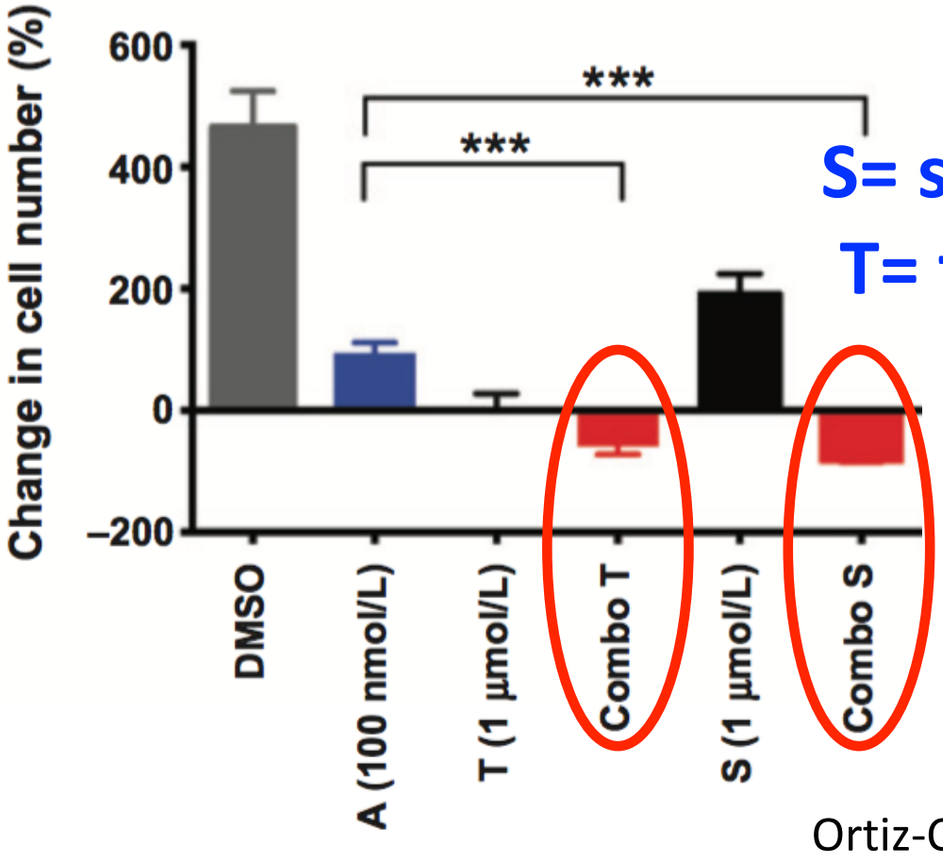


KRAS G12S in tissue

T790M - in tissue

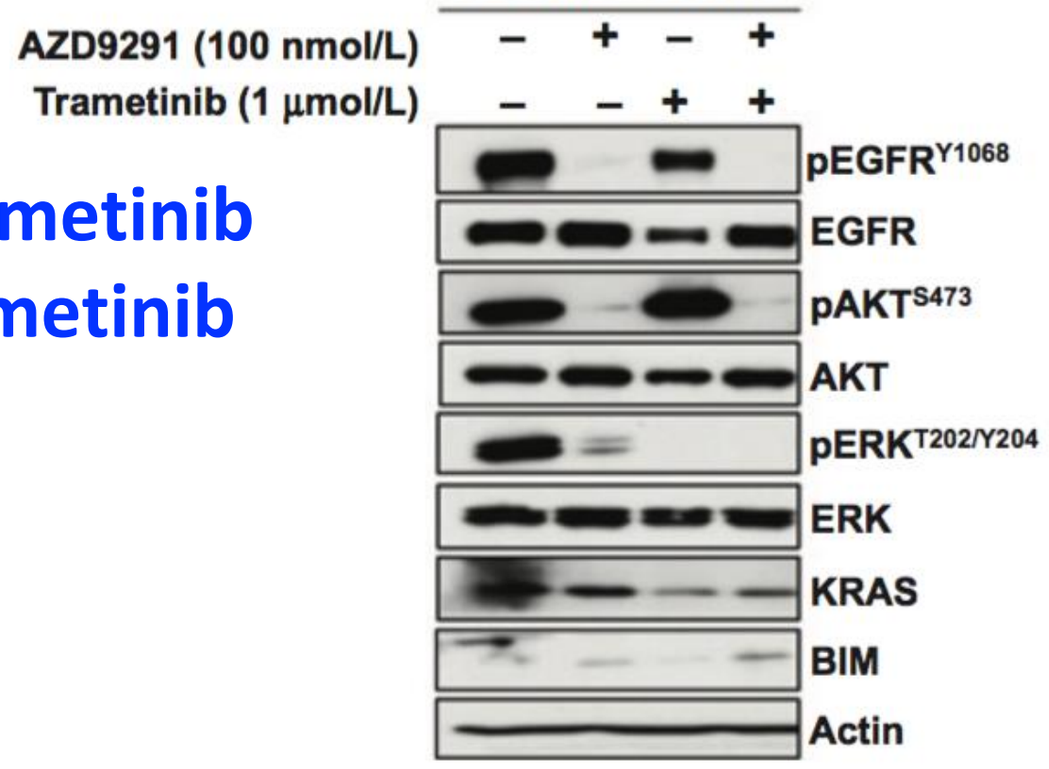
C797S + in blood





S= selumetinib

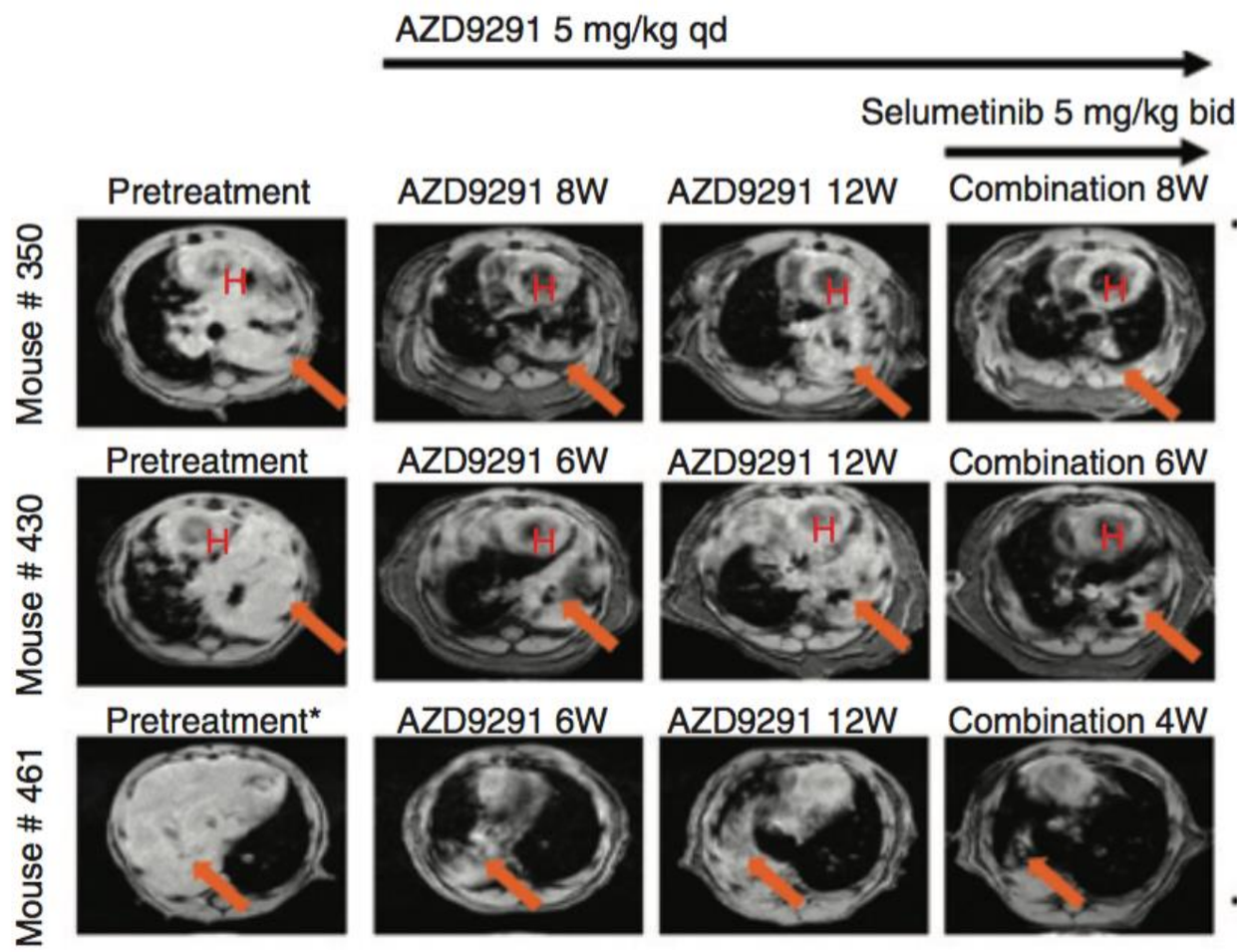
T= trametinib



Ortiz-Charan et al; Clin Canc Res 2015. Thress et al; Nature Medicine 2015

Acquired resistance mechanisms to third generation EGFR-TKIs - KRAS

Cell population	Genetic alterations detected within resistant populations	Selumetinib (MEK1/2)
PC9		6.95 (±2.5)
PC9 GR_1	EGFR T790M/KRAS gain (5.43-fold)	7.24 (±3.2)
PC9 GR_2	NRAS E63K	0.62 (±0.3)
PC9 GR_3	EGFR T790M	6.2 (±3.6)
PC9 GR_4	EGFR T790M	6.2 (±3.6)
PC9 GR_5	EGFR T790M	7.32 (±2.3)
PC9 GR_6	EGFR T790M	8.77 (±1.5)
PC9 GR_7	EGFR T790M	7.44 (±2.6)
PC9 GR_8	EGFR T790M/KRAS gain (7.06-fold)	3.7 (±0.99)
PC9 AR_1	KRAS gain (24.6-fold)	2.7 (±0.23)
PC9 AR_4	EGFR T790M	1.63 (±1.1)
PC9 AR_6	NRAS gain (4.23-fold)	0.89 (±0.6)
PC9 WZR_1	NRAS Q61K	0.23 (±0.04)
PC9 WZR_3	KRAS gain (2.64-fold)	0.22 (±0.1)
PC9 AZDR_1	NRAS gain (2.5-fold)/MAPK1 gain/CRKL gain	0.25 (±0.06)
PC9 AZDR_2	NRAS G12V	1.4 (±0.9)
PC9 AZDR_3	MAPK1 gain/CRKL gain	2.38 (±0.9)
PC9 AZDR_4	ND	0.19 (±0.1)
PC9 AZDR_5	NRAS E63K	0.17 (±0.05)
PC9 AZDR_6	NRAS E63K	0.11 (±0.03)
PC9 AZDR_7	NRAS G12R	0.14 (±0.03)
PC9 GR_1_AZDR_1	EGFR T790M/KRAS gain (6.23-fold)	3.6 (±0.7)
PC9 GR_1_AZDR_2	KRAS gain (5.66-fold)	6.7 (±1.4)
PC9 GR_1_AZDR_3	EGFR T790M/KRAS gain (4.44-fold)	3.4 (±0.5)
PC9 GR_1_AZDR_4	EGFR T790M/KRAS gain (5.46-fold)	3.6 (±2.6)
PC9 GR_6_AZDR_1	ND	0.28 (±0.2)
PC9 GR_6_AZDR_2	NRAS gain (2.4-fold)	0.54 (±0.3)
PC9 GR_6_AZDR_3	NRAS gain (3.68-fold)	0.13 (±0.06)
PC9 GR_6_AZDR_4	ND	0.73 (±0.5)
NCI-H1975	EGFR T790M	4.94 (±3)
NCI-H1975 AZDR_1	EGFR T790M	0.024 (±0.003)
NCI-H1975 AZDR_2	EGFR T790M	0.15 (±0.1)
NCI-H1975 AZDR_3	EGFR T790M	>10
NCI-H1975 AZDR_4	EGFR T790M/NRAS Q61K	5.46 (±3.7)



Ongoing studies:

- selumetinib + osimertinib (TATTON trial)

Eberlein et al; Canc Res 2015. Tricker et al; Cancer Discovery 2015

OSIMERTINIB + DURVALUMAB (Tatton trial)

Part A

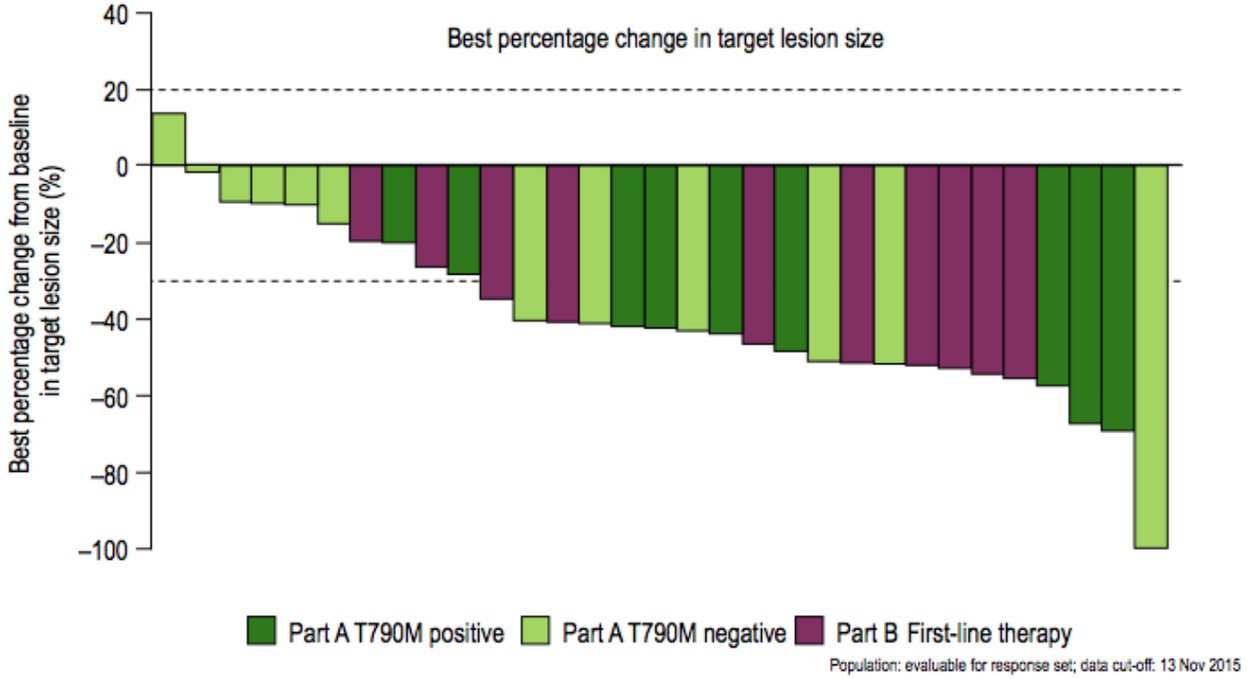
- EGFR mutated pre treated NSCLC patients
- No controindicazioni to immunotherapy
- No history of ILD

Dose escalation

Part B

- EGFR mutated naive NSCLC patients
- No controindicazioni to immunotherapy
- No history of ILD

Dose expansion



Increased percentage of ILD

Part A	6/23 (26%)
Dose 1: Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W	2/10 (20%)
Dose 2: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	4/13 (31%)
Part B: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	7*/11 (64%)
Part A and Part B	13/34 (38%; 95% CI 18, 52)†

†5 events were Grade 3/4 and there were no fatalities; most cases were managed using steroids

Entire osimertinib clinical programme (Phase I and II)	
Osimertinib monotherapy	35/1207 (3%)
Durvalumab monotherapy	23/1149 (2%)

23 patients in PART A (12 PR, 9 SD)
11 patients in PART B (8 PR, 2 SD)

Ahn et al; ELCC 2016

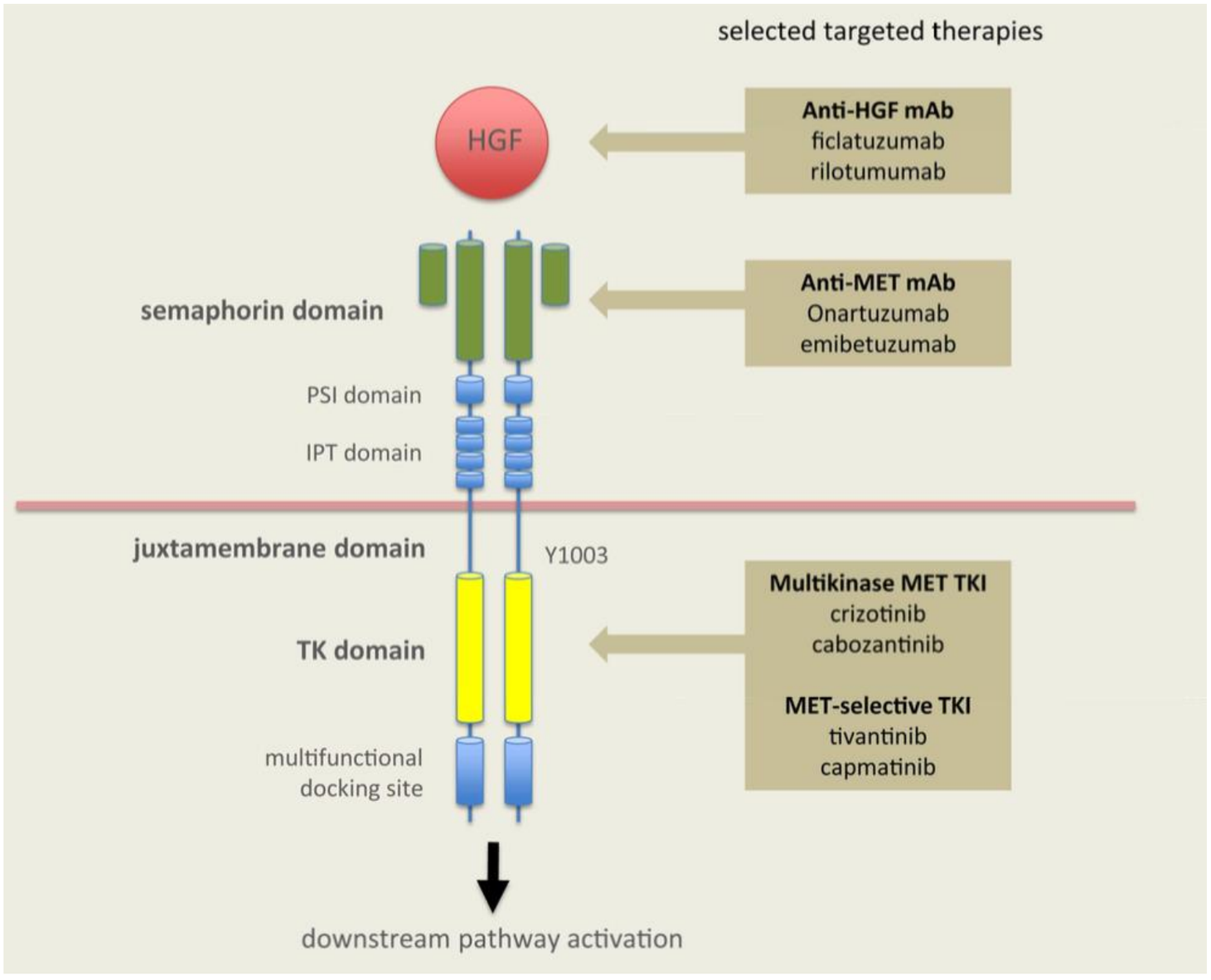
Treatment strategies for patients developing MET alterations

Type I MET inhibitors

Bind the active conformation of MET
(crizotinib)
(savolitinib)

Type II MET inhibitors

Bind the inactive conformation of MET
(cabozantinib)



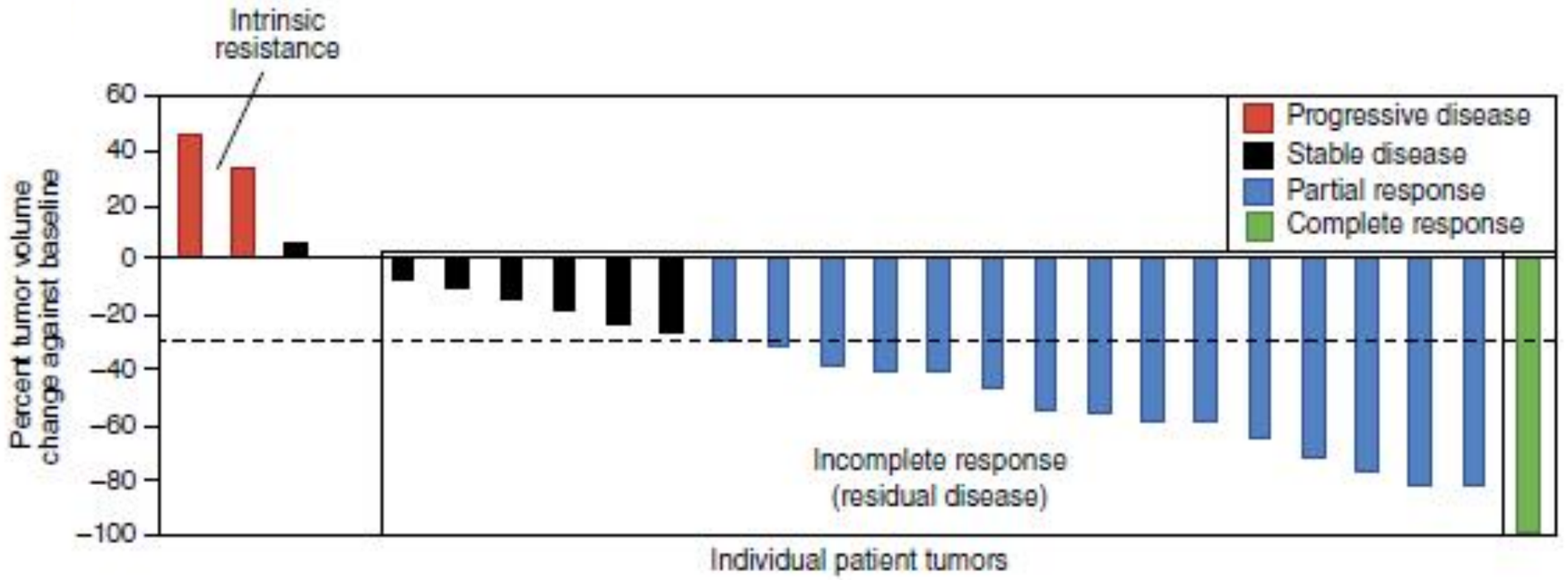
Resistance driven by ERBB3 dependent PI3K pathway activation

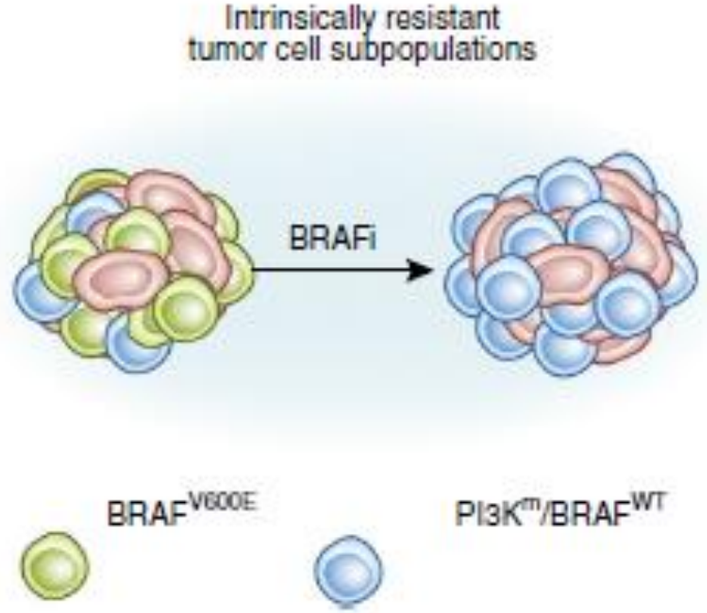
Drilon et al; JTO 2016

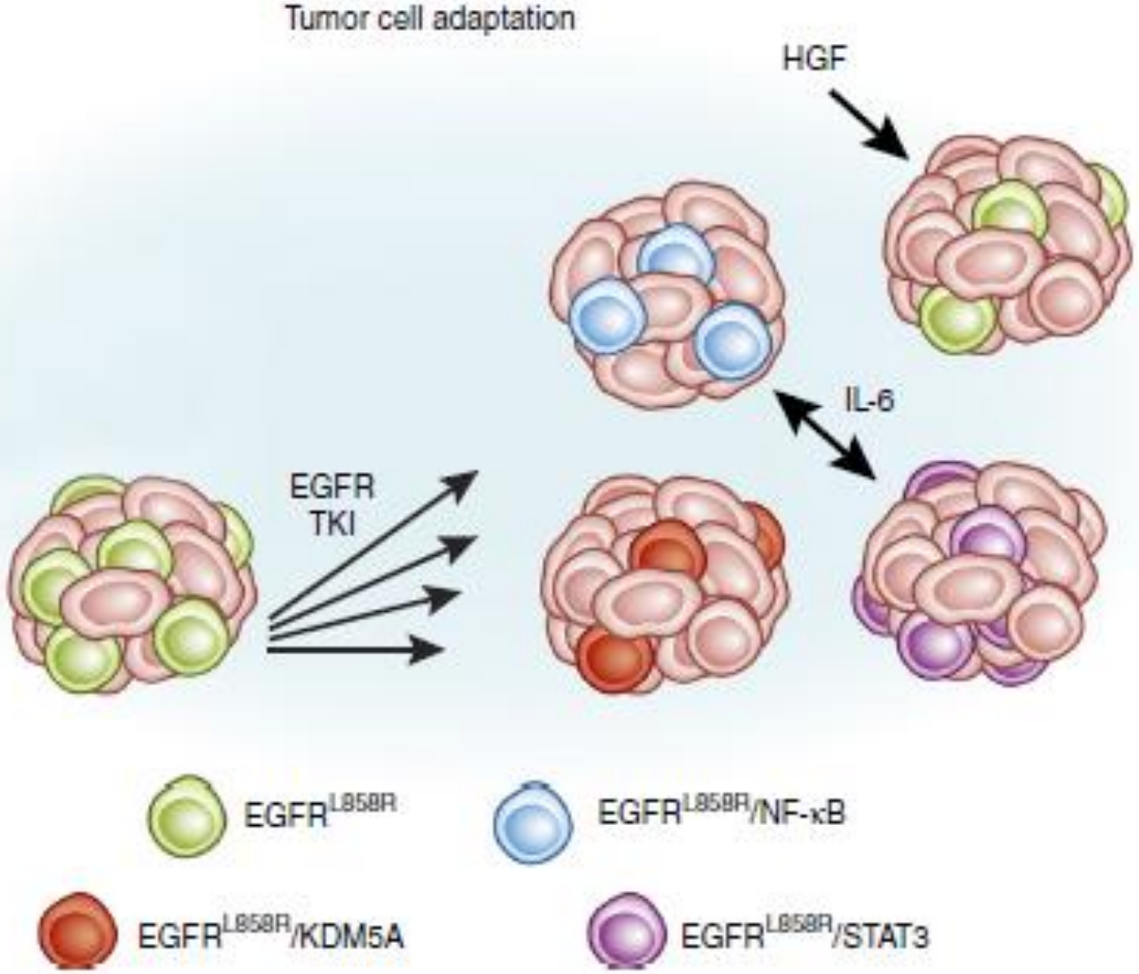
MET alteration

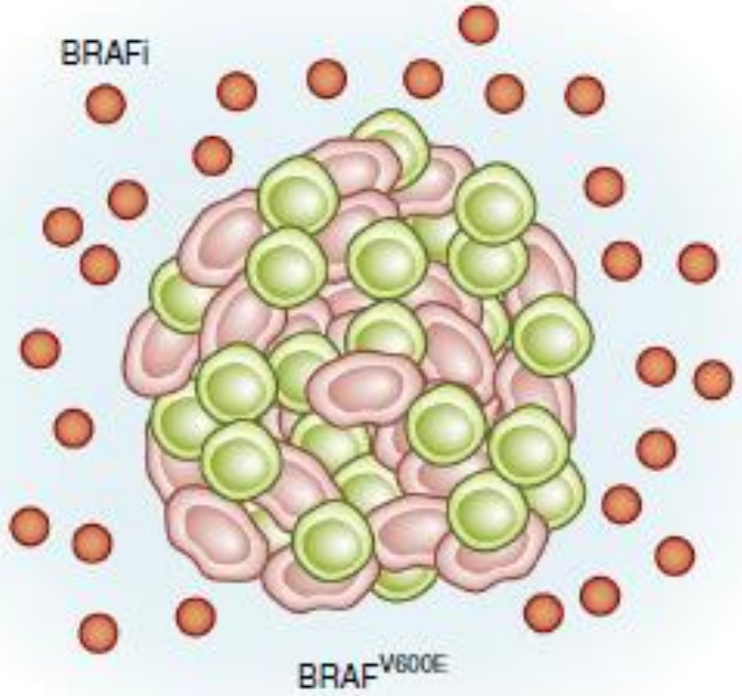
One challenge is defining the appropriate method and positivity cut point for identifying MET gene copy-number gain

In a phase II study, EGFR-mutant patients with acquired resistance to an EGFR TKI were treated with the combination of gefitinib and capmatinib (response rate 40% among those with a MET copy-number ≥5)









Bivona et al. Nature Med 2016