Mechanisms of resistance to HER targeting drugs Lung cancer

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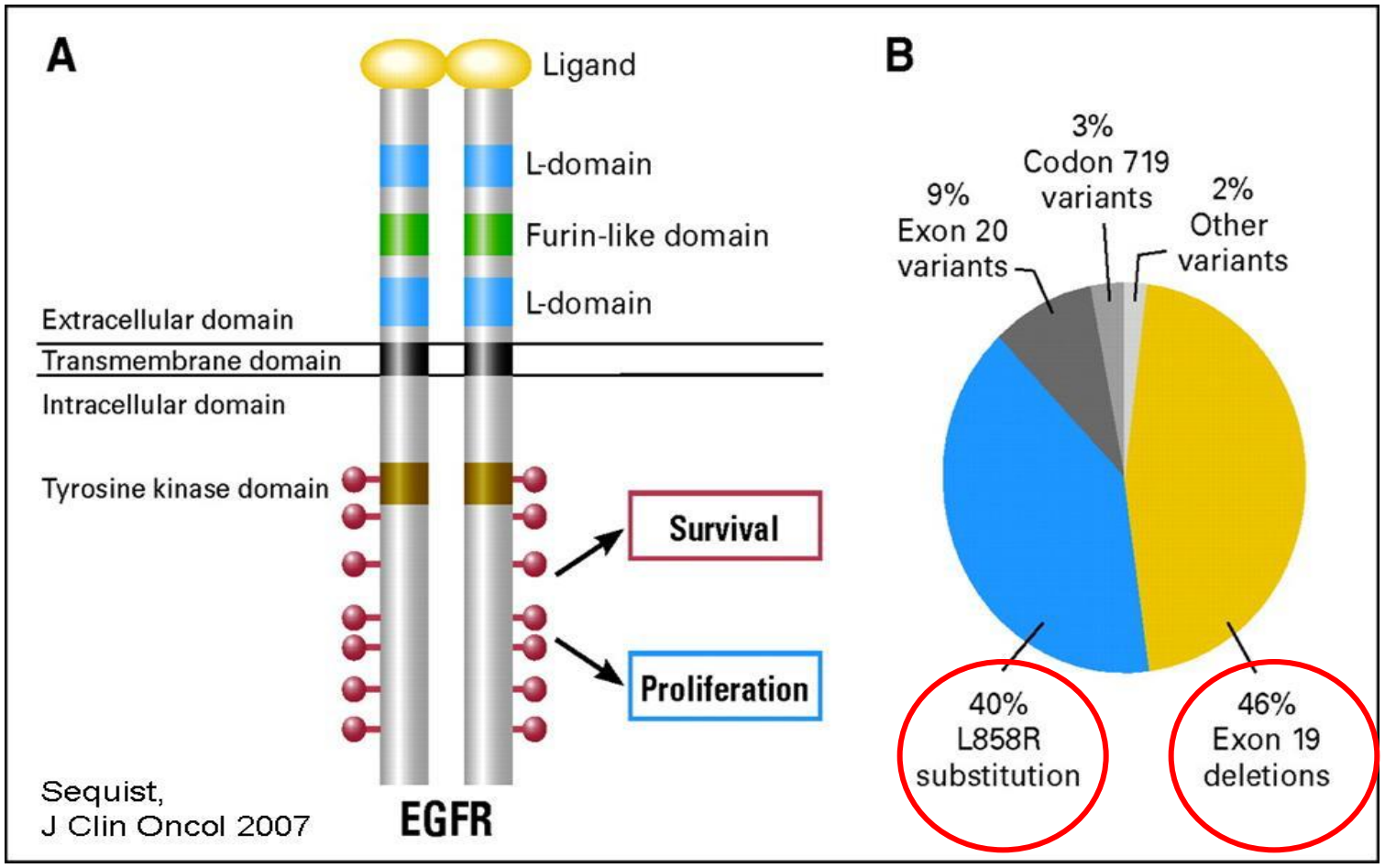
Second University of Naples

EGFR mutations



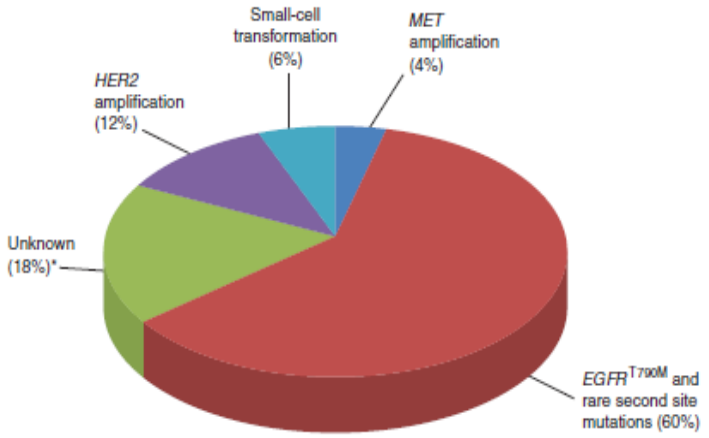
Sequist et al, JCO 2007

1st line: EGFR-TKIs vs CT

Author	Study	N (EGFR mut. +)	EGFR-TKI	Median PFS* (months)	PFS* HR
Mok	IPASS	261	Gefitinib	9.8 vs. 6.4	0.48
Lee	First-SIGNAL	42	Gefitinib	8.4 vs. 6.7	0.54
Mitsudomi	WJTOG 3405	177	Gefitinib	9.2 vs. 6.3	0.49
Maemondo	NEJGSG002	228	Gefitinib	10.8 vs. 5.4	0.30
Zhou	OPTIMAL	154	Erlotinib	13.1 vs. 4.6	0.16
Rosell	EURTAC	175	Erlotinib	9.7 vs. 5.2	0.37
Yang	LUX-Lung 3	345	Afatinib	11.1 vs. 6.9	0.58
Wu	LUX-Lung 6	364	Afatinib	11.0 vs 5.6	0.28
Yang	Pooled analysis LL3-LL6	1340	Afatinib		Median OS 27.3 vs 24.3 months
Shi	CONVINCE	296	Icotinib	NA	NA
Park	LUX-Lung 7	319	Afatinib vs Gefitinib	11 vs 10.9	0.73

Resistance to EGFR TKI

- Regardless of extent of initial response, resistance to TKI develops invariably due to
  - T790 mutation (~ 50% to 60%)
  - HER 2 mutation (8%-12%)
  - MET amplification (~ 5% to 20%)
  - Conversion to SCLC (< 5%)

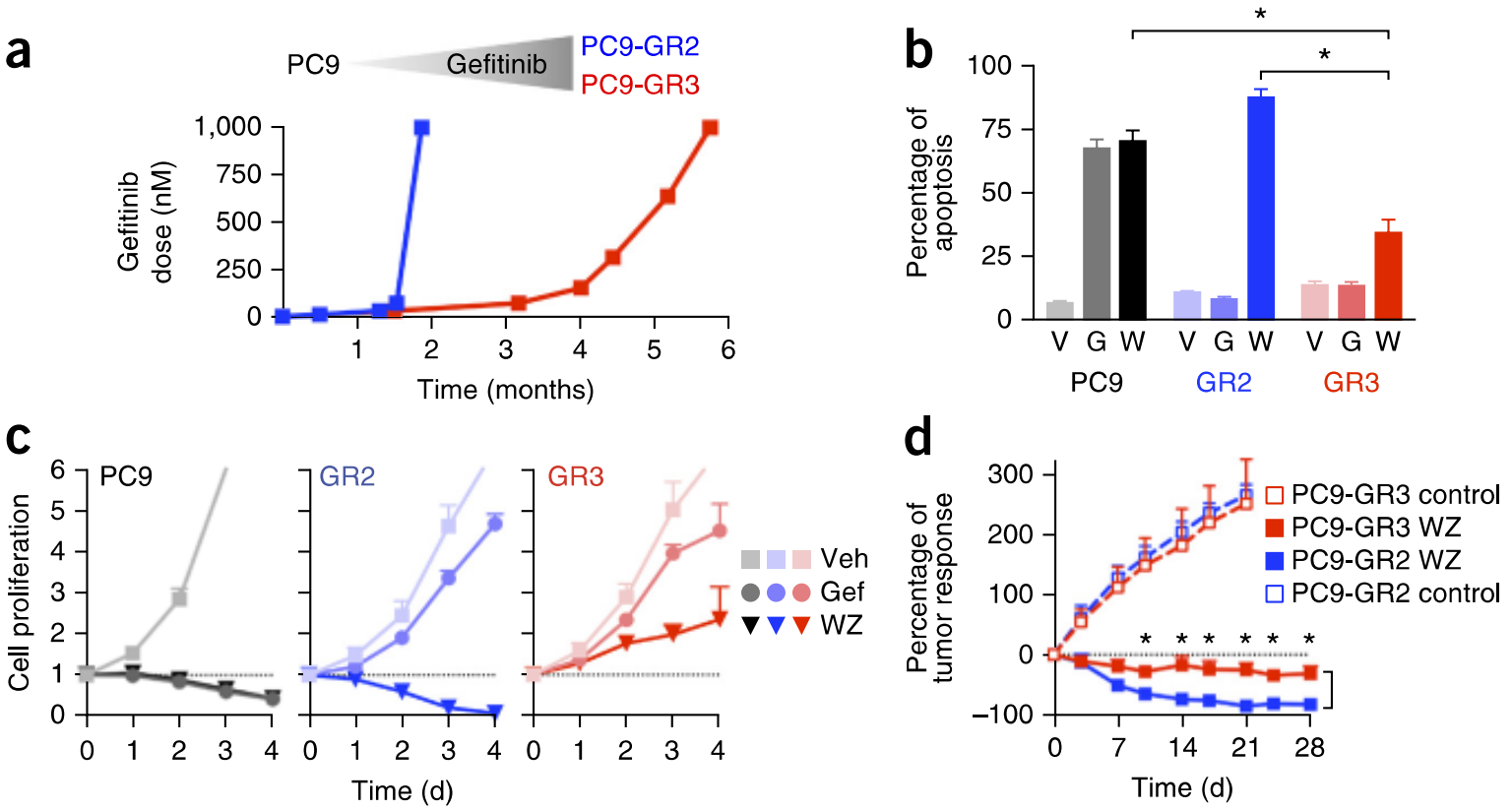


- EGFR mutated tumors might progress rapidly upon withdrawal of TKI
- Role of continuation of TKI beyond progression is under evaluation
- Afatinib, AZ9291, CO1686, HM-61713 targets T790 mutation

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

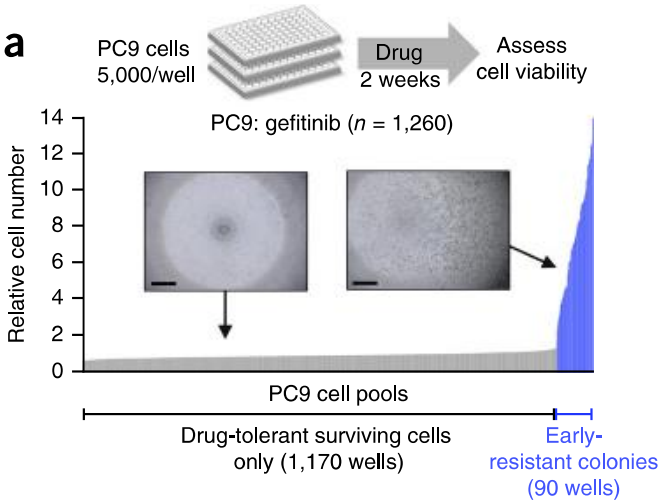
Sequist LV, et al. *Sci Transl Med*. 2011;3(75):75ra26 2011.
Pao W, et al. *PLoS Med*. 2005;2(3):e73.

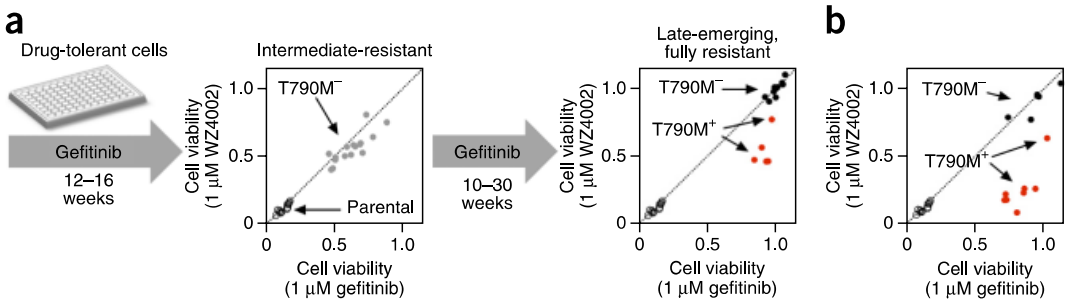
Variable sensitivity of gefitinib-resistant *EGFR*T790M-positive PC9 cell lines to EGFR inhibition

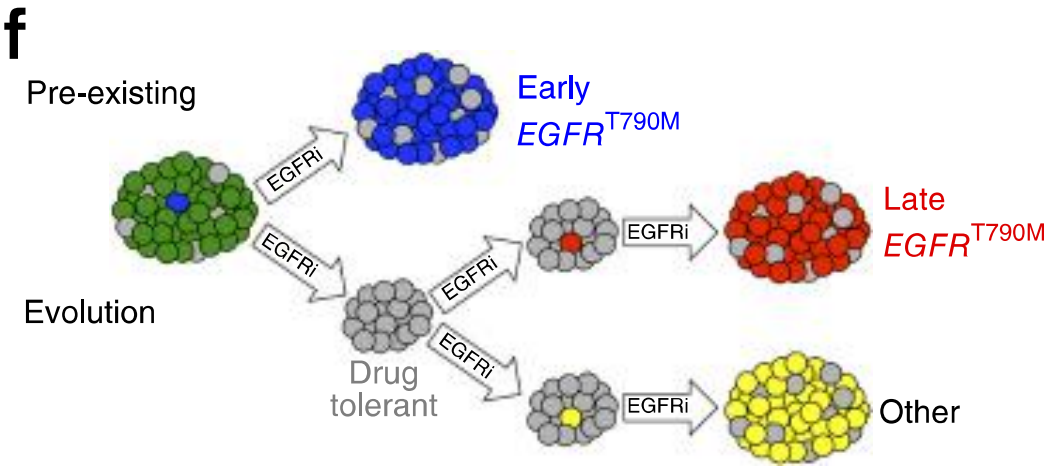


Hata A N et al, Nature Medicine 2016

Tumor cells can follow distinct evolutionary paths to become resistant to EGFR inhibition

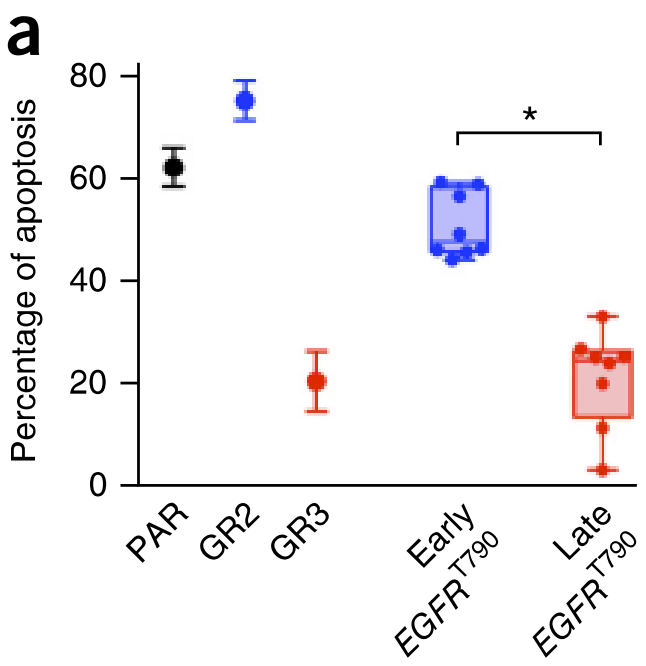


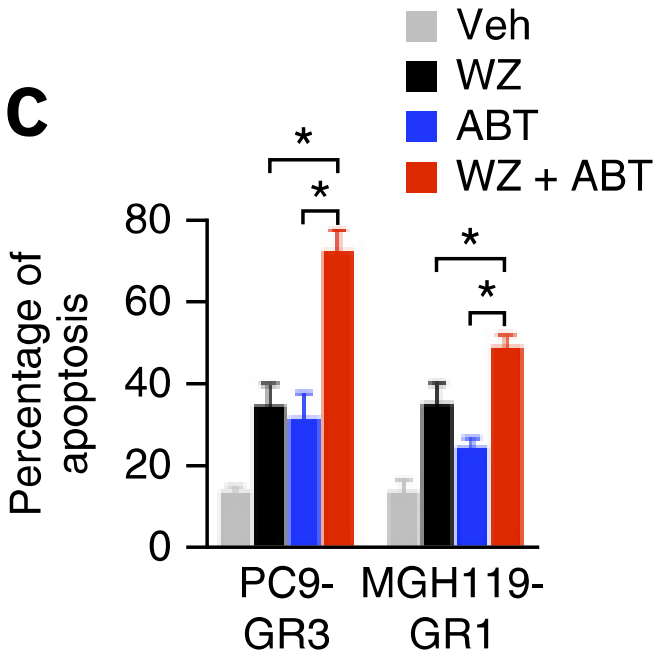




Hata A N et al, Nature Medicine 2016

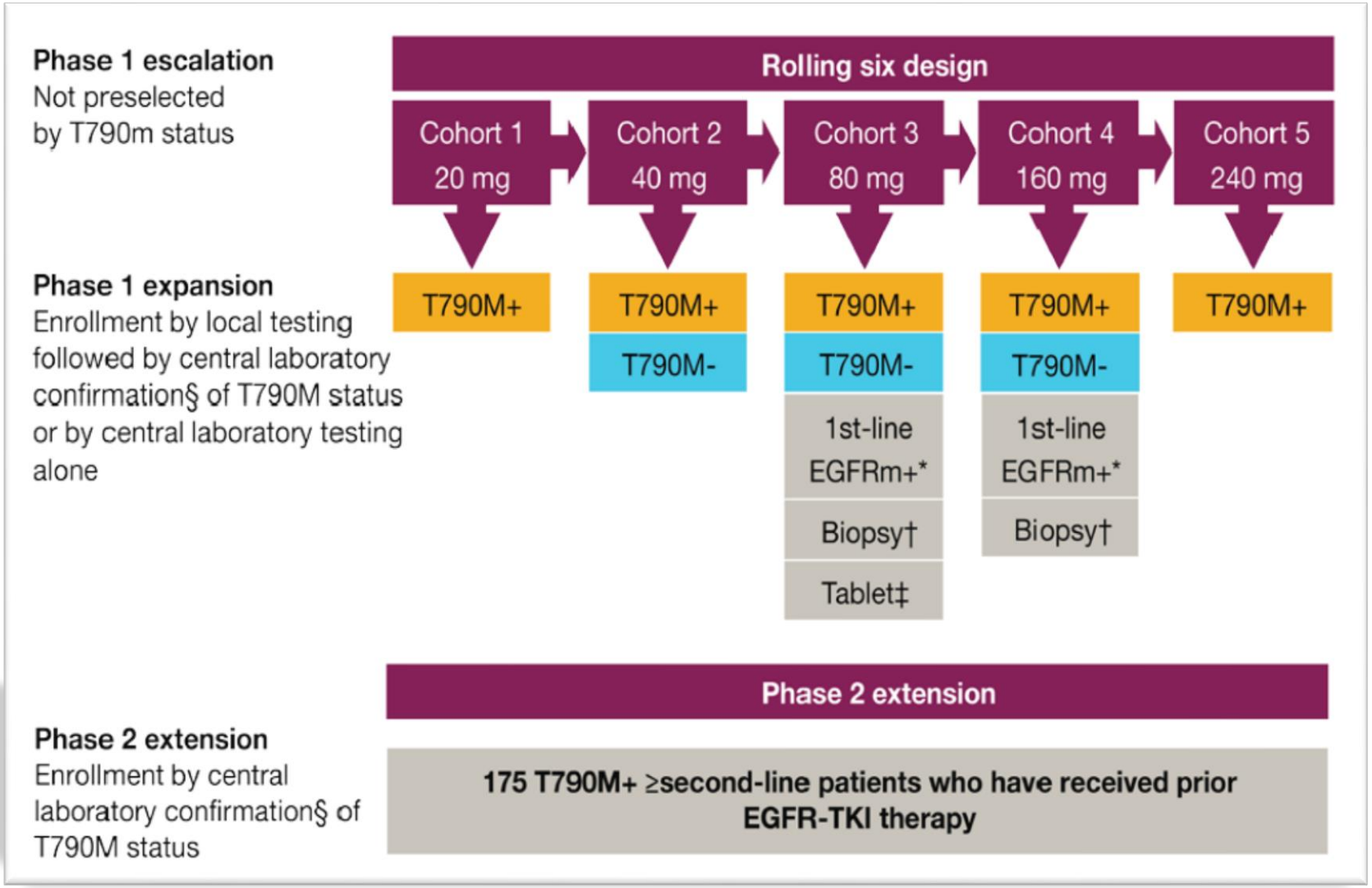
Inhibition of BCL-XL and BCL-2 restored sensitivity to third generation EGFR inhibitor





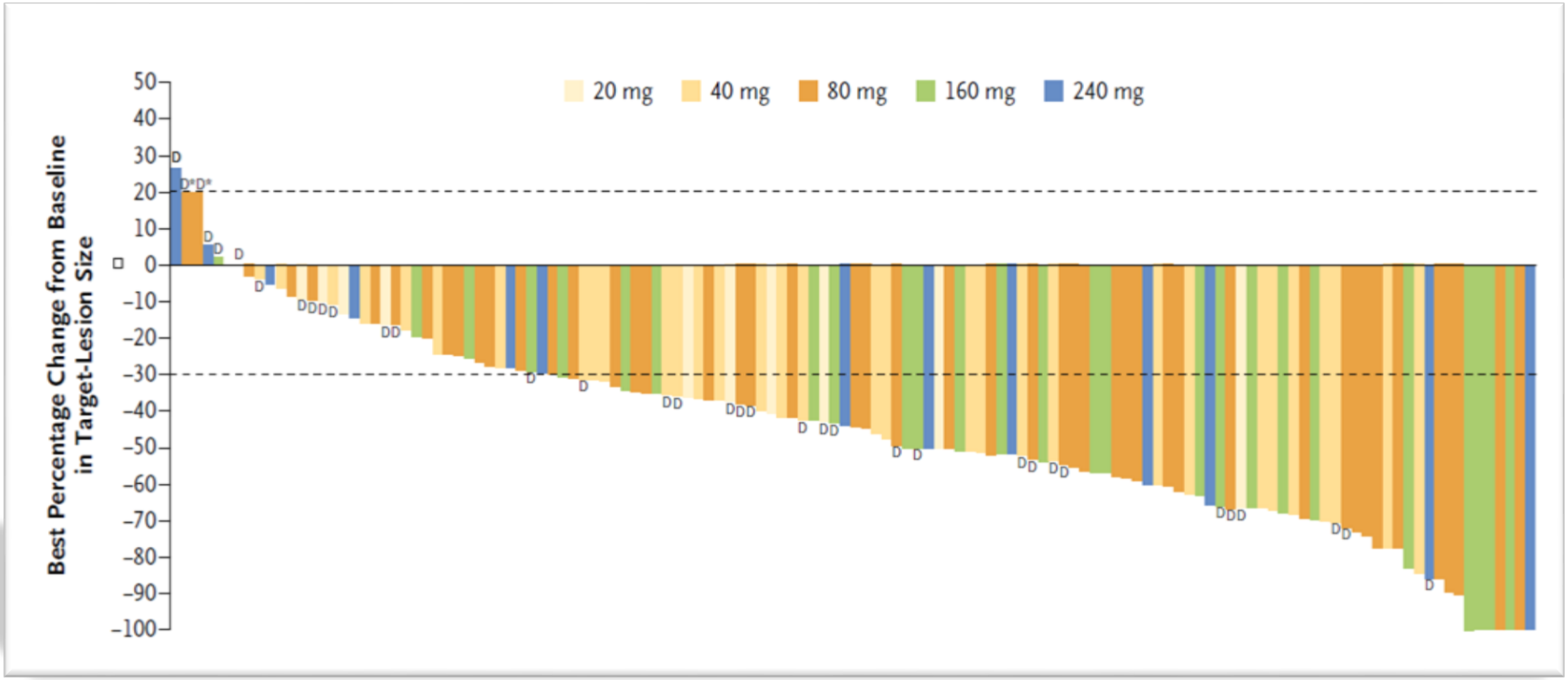
Hata A N et al, Nature Medicine 2016

AURA (AZD9291): *Overall study schema*



Janne PA, NEJM 2015

AURA (AZD9291):
Best % change in target-lesion size



Janne PA, NEJM 2015

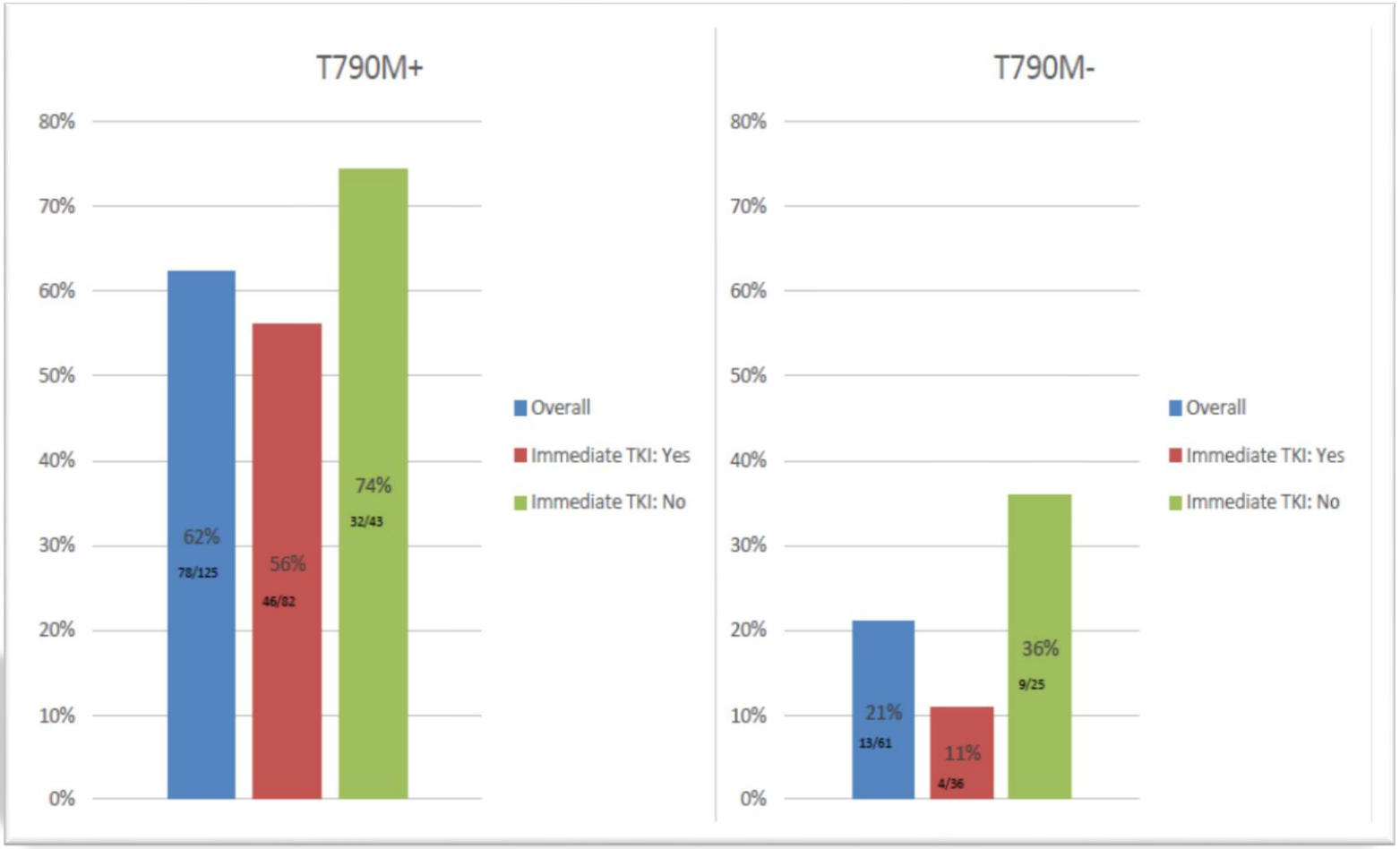
AURA (AZD9291):

RR in patients treated with 1 or >1 prior EGFR-TKI and centrally tested T790M status

Janne PA, NEJM 2015

AURA (AZD9291):

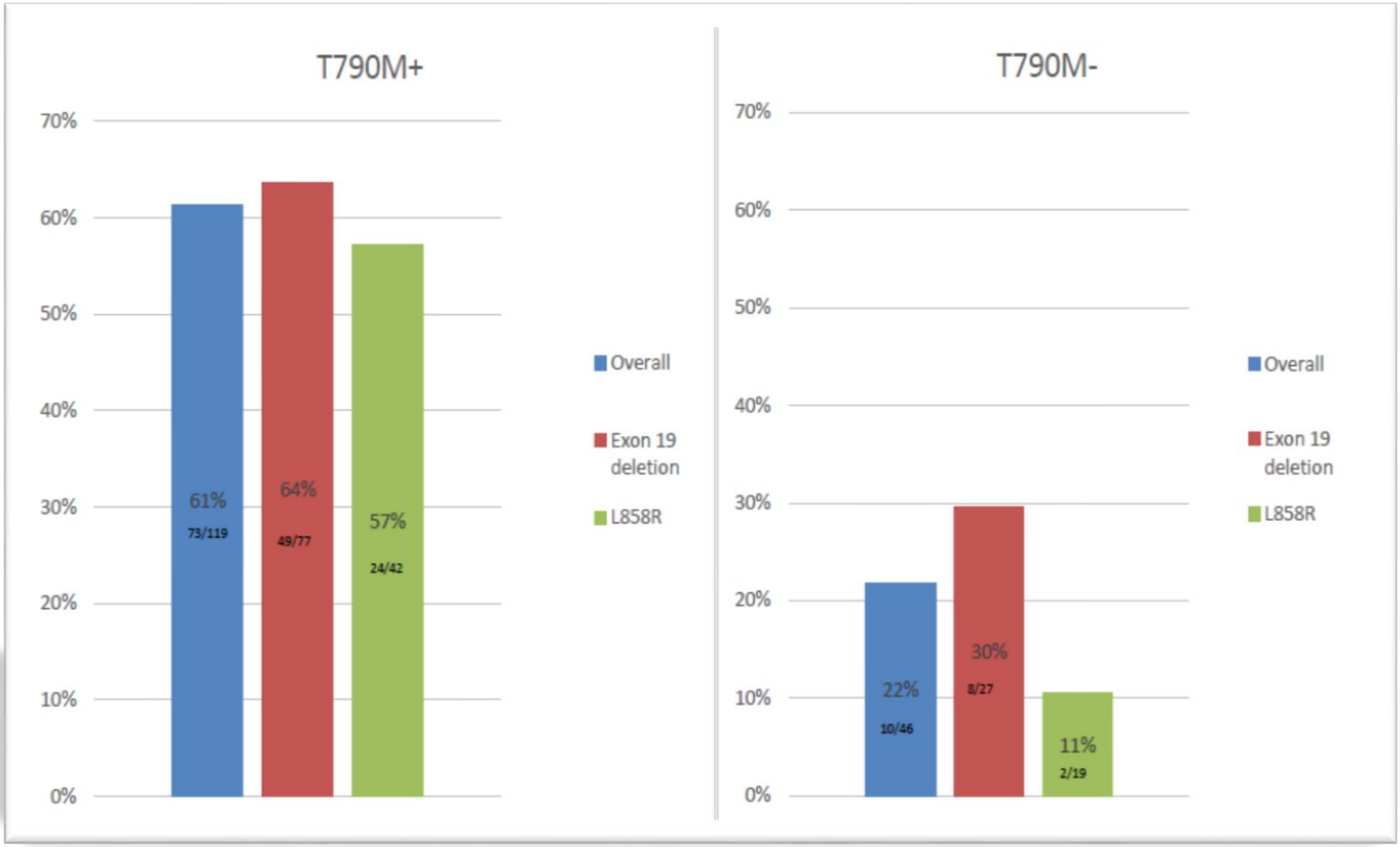
RR in treated patients immediate vs no immediate prior EGFR-TKI and centrally tested T790M status



Janne PA, NEJM 2015

AURA (AZD9291):

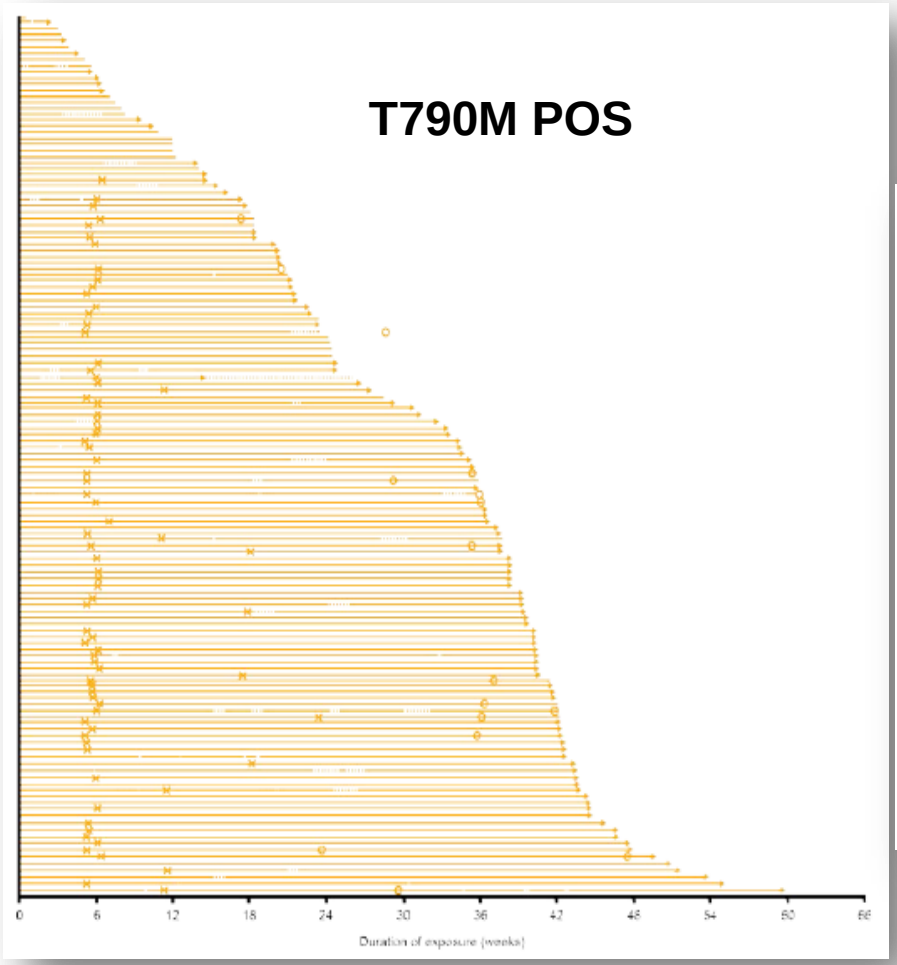
RR in patients with EGFR mutation type L858R versus exon 19 deletion and T790M status

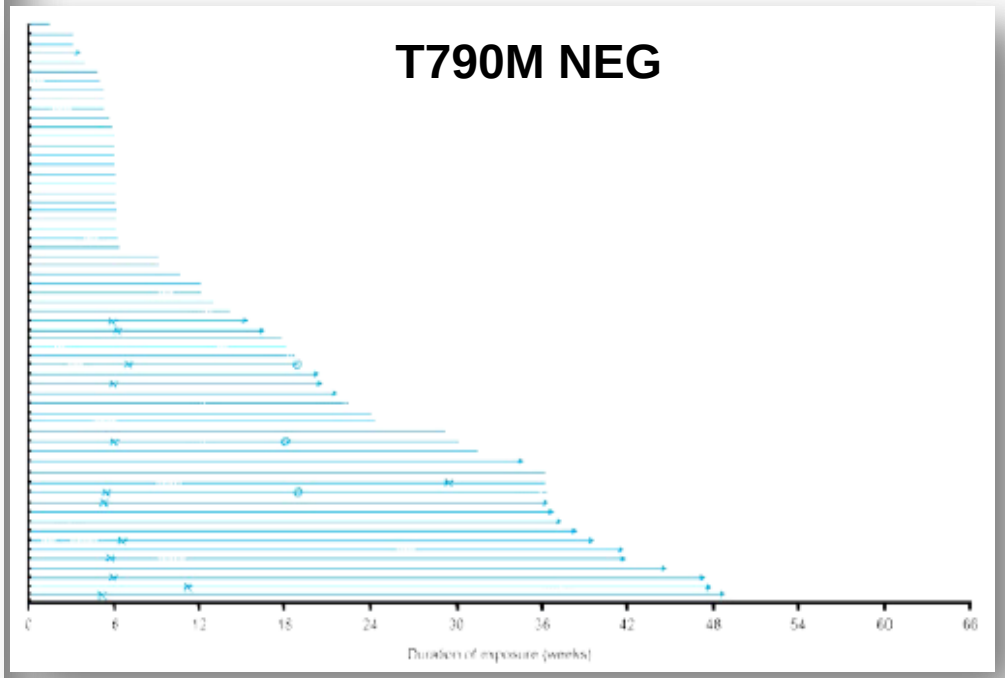


Janne PA, NEJM 2015

AURA (AZD9291):

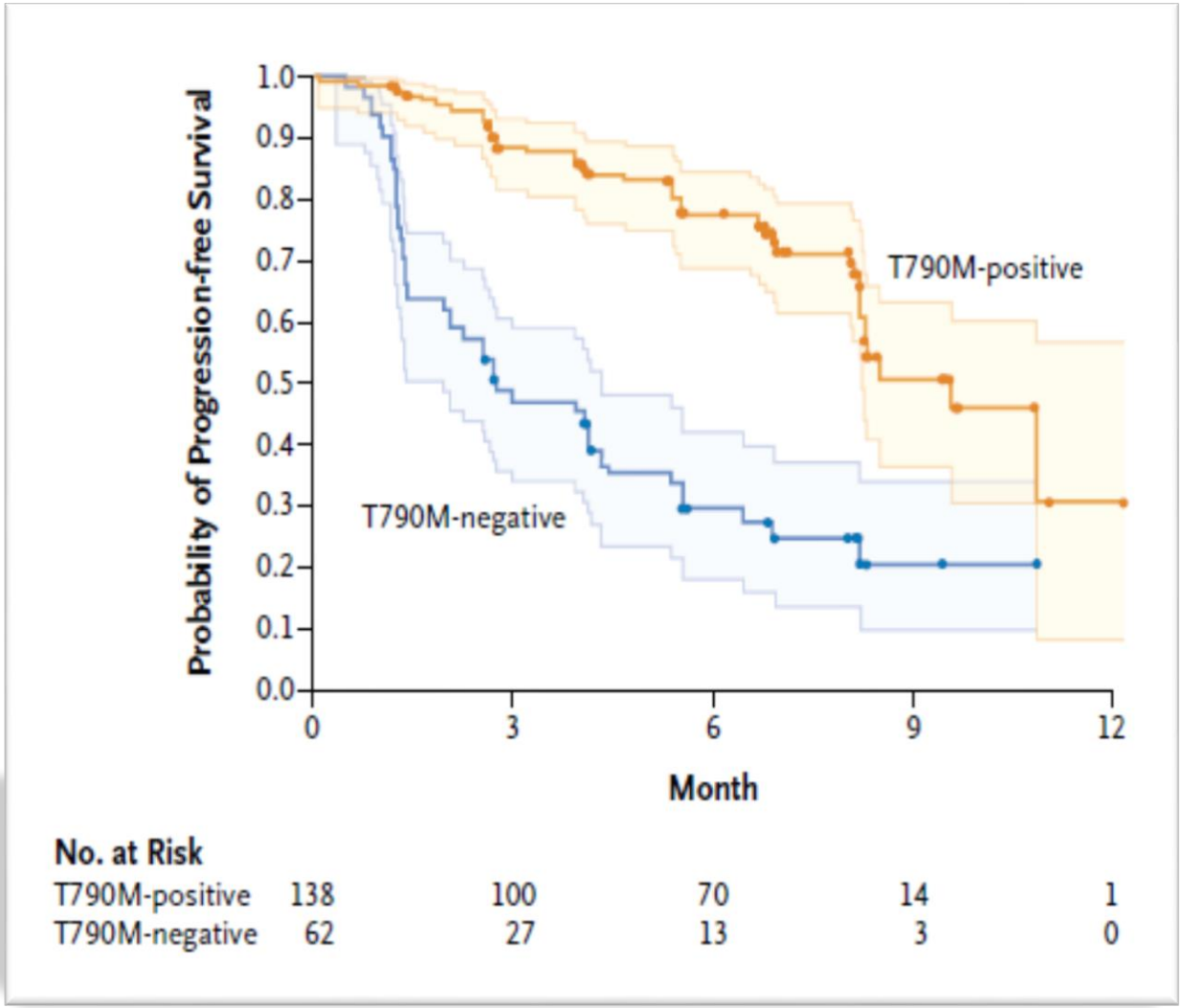
Duration of treatment and response by centrally tested T790M





Janne PA, NEJM 2015

AURA (AZD9291):
PFS according to status with respect to EGFR T790M



Janne PA, NEJM 2015

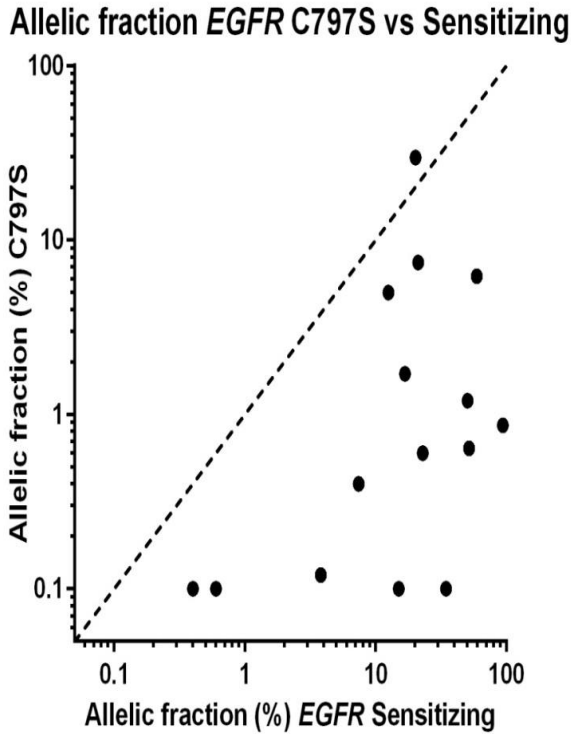
Osimertinib

Osimertinib

On November 13, 2015, the U. S. Food and Drug Administration granted accelerated approval to osimertinib (TAGRISSO) once daily tablets, AstraZeneca Pharmaceuticals LP, for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

C797S for acquired resistance to 3rd generation TKIs

- 67 patients met the following two eligibility criteria for acquired resistance analysis:
  - T790M positive on plasma or tumor genotyping at enrollment
  - Detectable EGFR-TKI-sensitizing mutation in plasma at progression on AZD9291
- Of those, **15 (22%) had detectable C797S on ddPCR**, all with detectable T790M
- C797S was more common with EGFR exon 19 del (13/43, 30%) vs those with L858R (2/24, 8%, p=0.06)

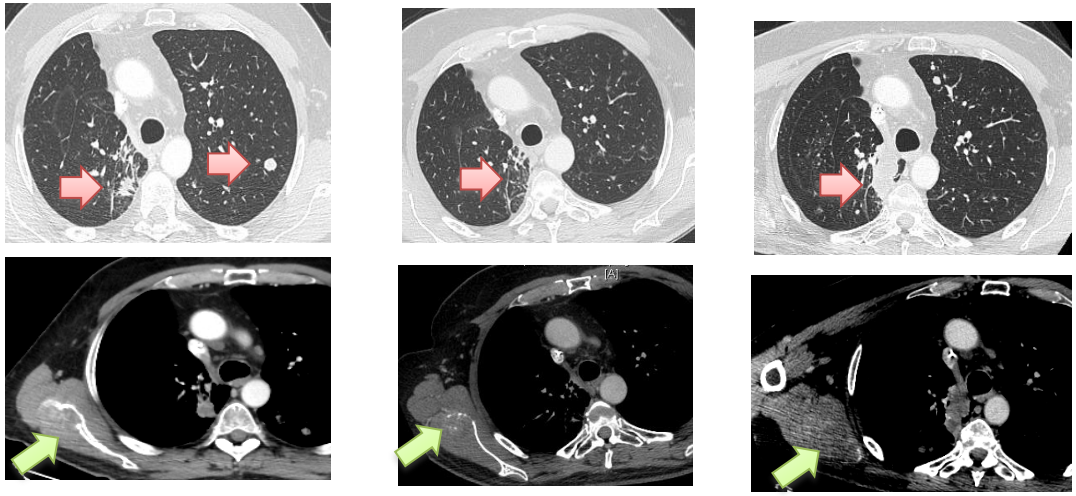


Oxnard GR, WCLC 2015

HER2 amplification at PD after AZD 9291

- 54-year-old man
- Former smoker (20 patient-years)
- Adenocarcinoma
- Metastatic to brain, bone
- EGFR Ex19del

PRE-GEFITINIB IMAGING UNAVAILABLE



at PD after AZD 9291

Gefitinib

LUNG

EGFR Ex19del
T790M negative

LUNG BIOPSY

EGFR Ex19del and
T790M positive
No HER2 amplification (CGH)

AZD9291 (80 mg)

SCAPULAR

EGFR Ex19del
T790M negative

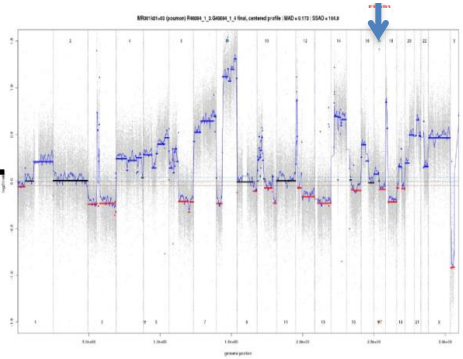
LUNG BIOPSY

EGFR Ex19del
T790M negative
C797S negative
HER2 amplification

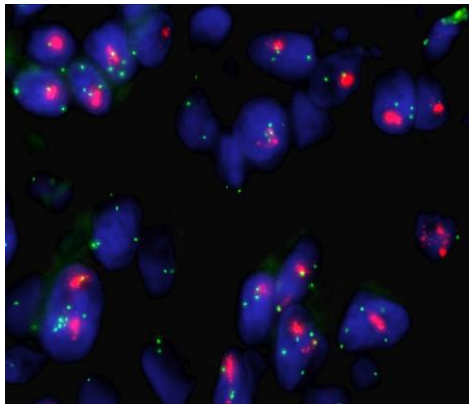
SCAPULAR BIOPSY

EGFR Ex19del
T790M negative

HER2



HER2 amplification by CGH: log ratio x3.32



HER2/CEP17: 6.65
HER2 in red; centromere 17 in green

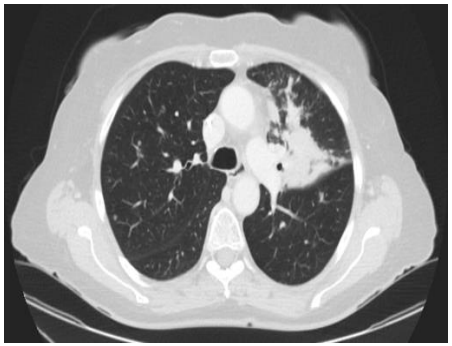
NGS: Ion Torrent Personal Genome Machine®
CGH: Agilent technology
HER2-FISH: Dako DNA probe kit

Oxnard GR, WCLC 2015

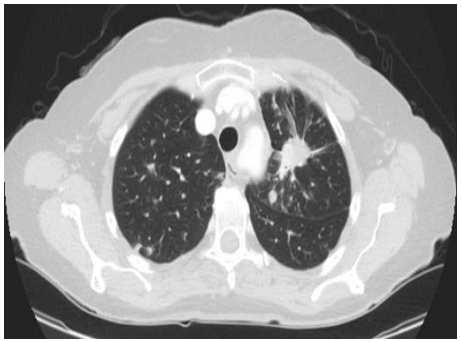
MET amplification at PD after AZD 9291

- 69-year-old female with EGFR-mutant NSCLC metastatic to liver, adrenal, bones who had progression after first-line chemotherapy and subsequent erlotinib
- Resistance biopsy was inadequate for genotyping, but plasma genotyping positive for L858R (26%) and T790M (4%)
- Initiated AZD9291 and responded on the first scan (-40%) but progressed after 24 weeks
- Resistance biopsy undergone for targeted NGS:
  - Positive for L858R, negative for T790M, positive for MET amplification
  - MET protein overexpression also seen on IHC

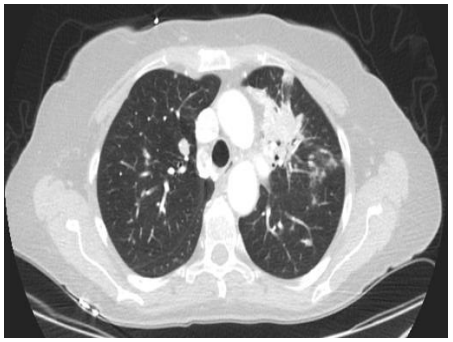
Pre-AZD9291 plasma genotype:
L858R (26%)
T790M (4%)



Baseline



4 months



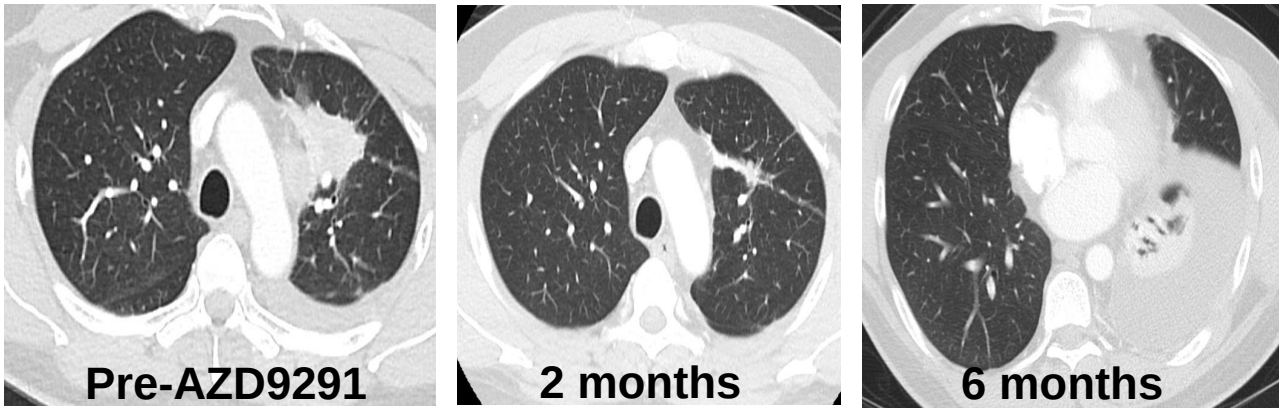
6 months

Progression tumor genotype:
L858R
T790M negative
MET amplified

Oxnard GR, WCLC 2015

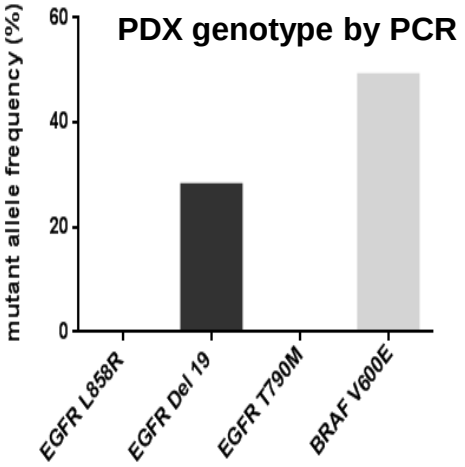
BRAF V600E at PD after AZD 9291

- 49-year-old male with metastatic NSCLC positive for EGFR exon 19 deletion
- Developed resistance to first-line erlotinib after 11 months, T790M positive biopsy
- Had a confirmed PR to AZD9291 but growth of lung mass, effusion after 5 months
- Targeted NGS of progression biopsy shows exon 19 deletion (8% of reads), no T790M, BRAF V600E (6% of reads)
  - A patient-derived xenograft is in development



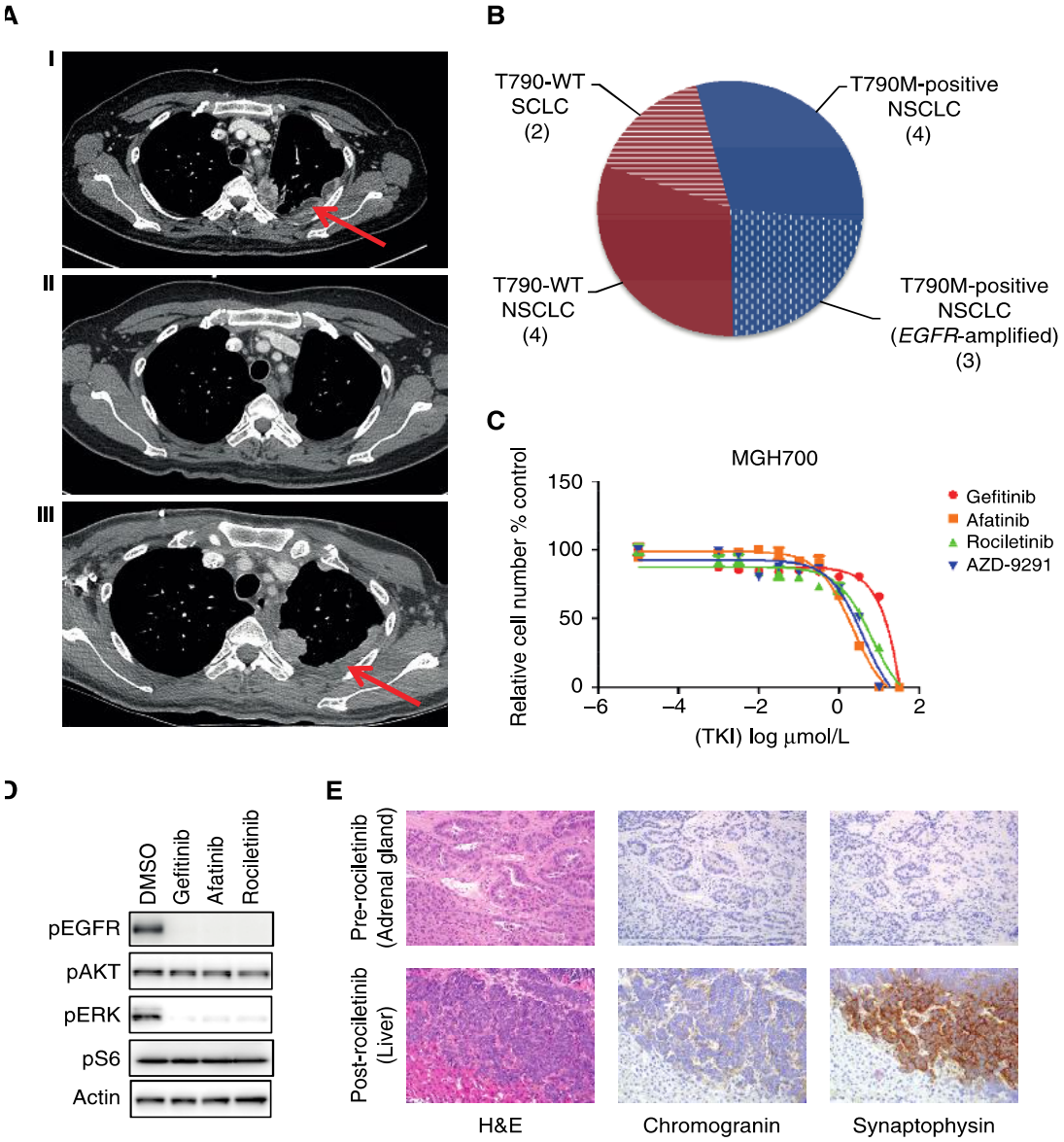
Ex19del/T790M

Ex19del/BRAF V600E



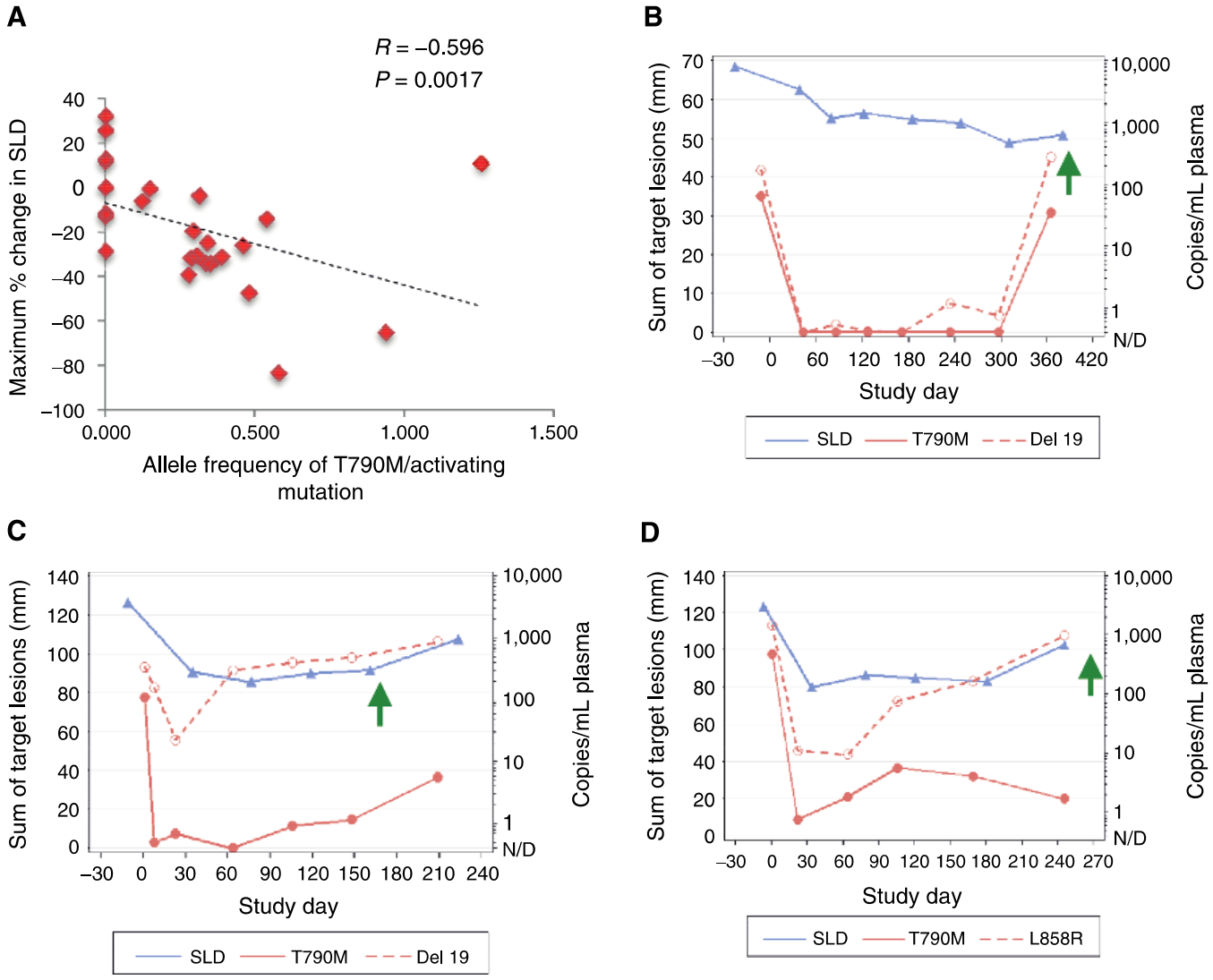
Oxnard GR, WCLC 2015

Rociletinib resistance: *12 case series*



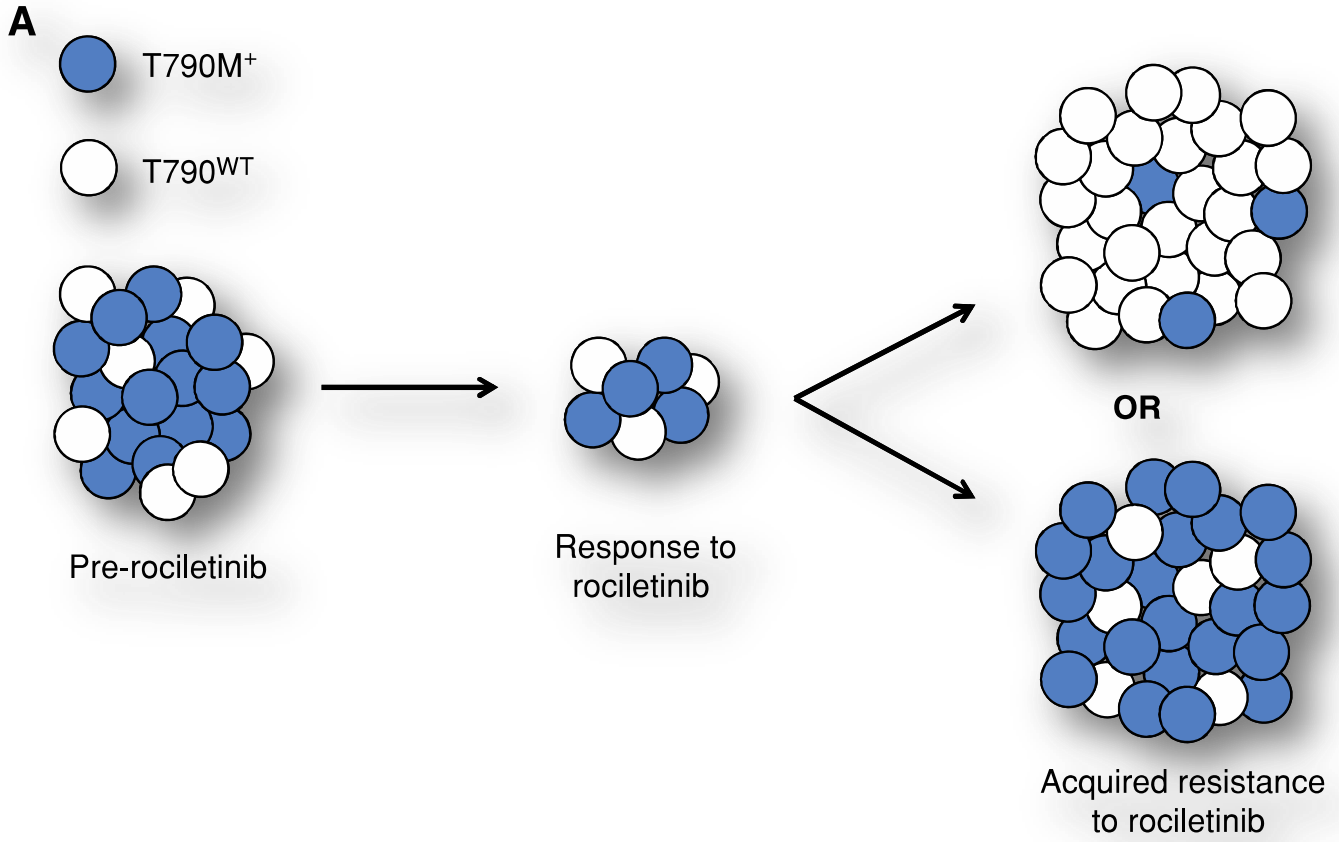
Piotrowska Z et al, Cancer Discovery 2015

Correlation with allelic fraction of T790M and maximum reduction in tumor volume



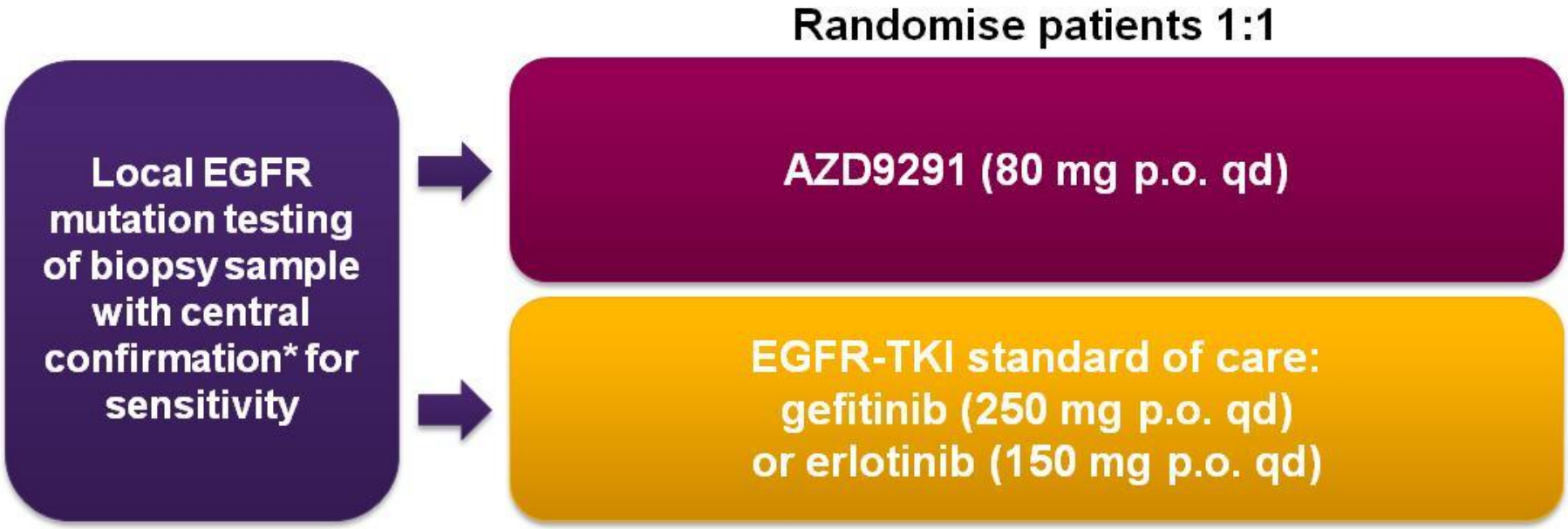
Piotrowska Z et al, Cancer Discovery 2015

Rociletinib resistance: intratumoral heterogeneity



Piotrowska Z et al, Cancer Discovery 2015

FLAURA:
Study design



Algorithm at PD during EGFR TKIs