The Biology Behind Oligometastatic Disease

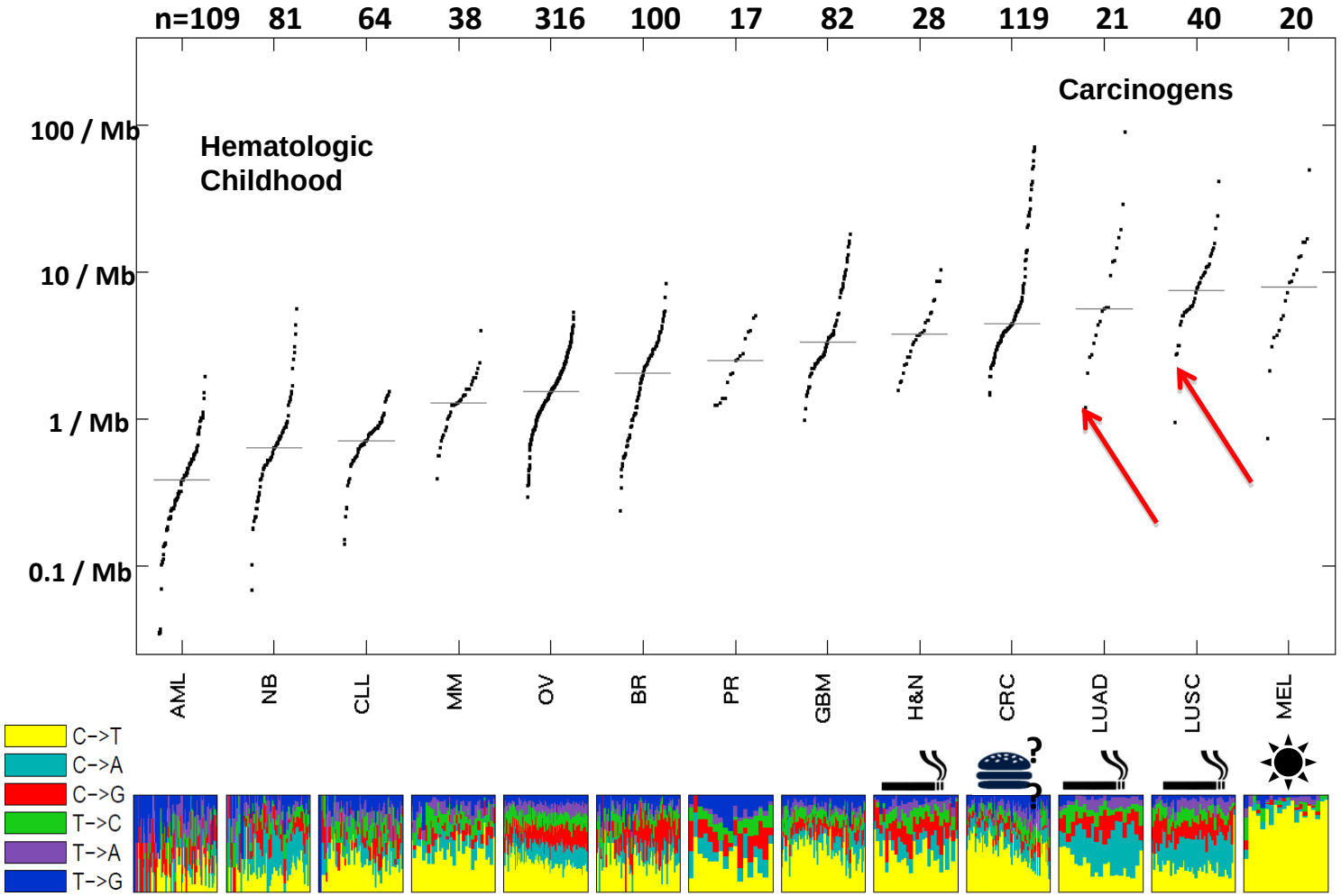
Federico Cappuzzo

Istituto Toscano Tumori

Ospedale Civile

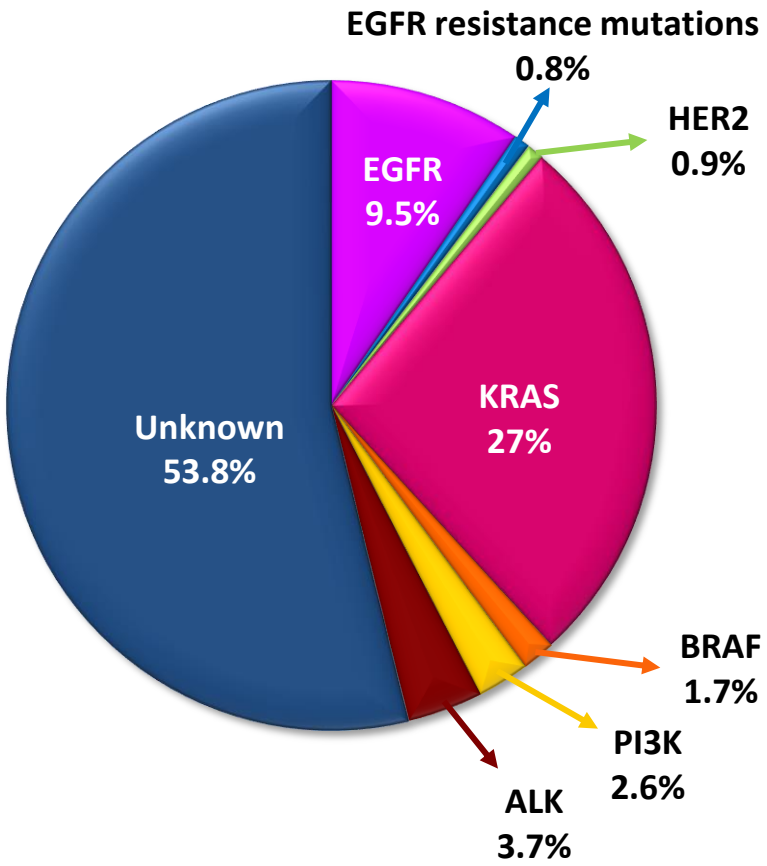
Livorno-Italy

Lung cancer has a very high rate of somatic mutations

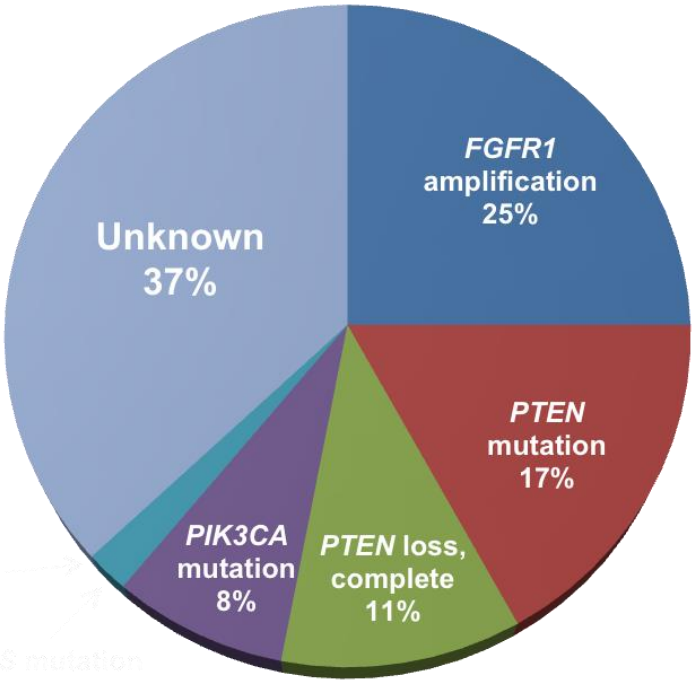


Molecular events in lung cancer

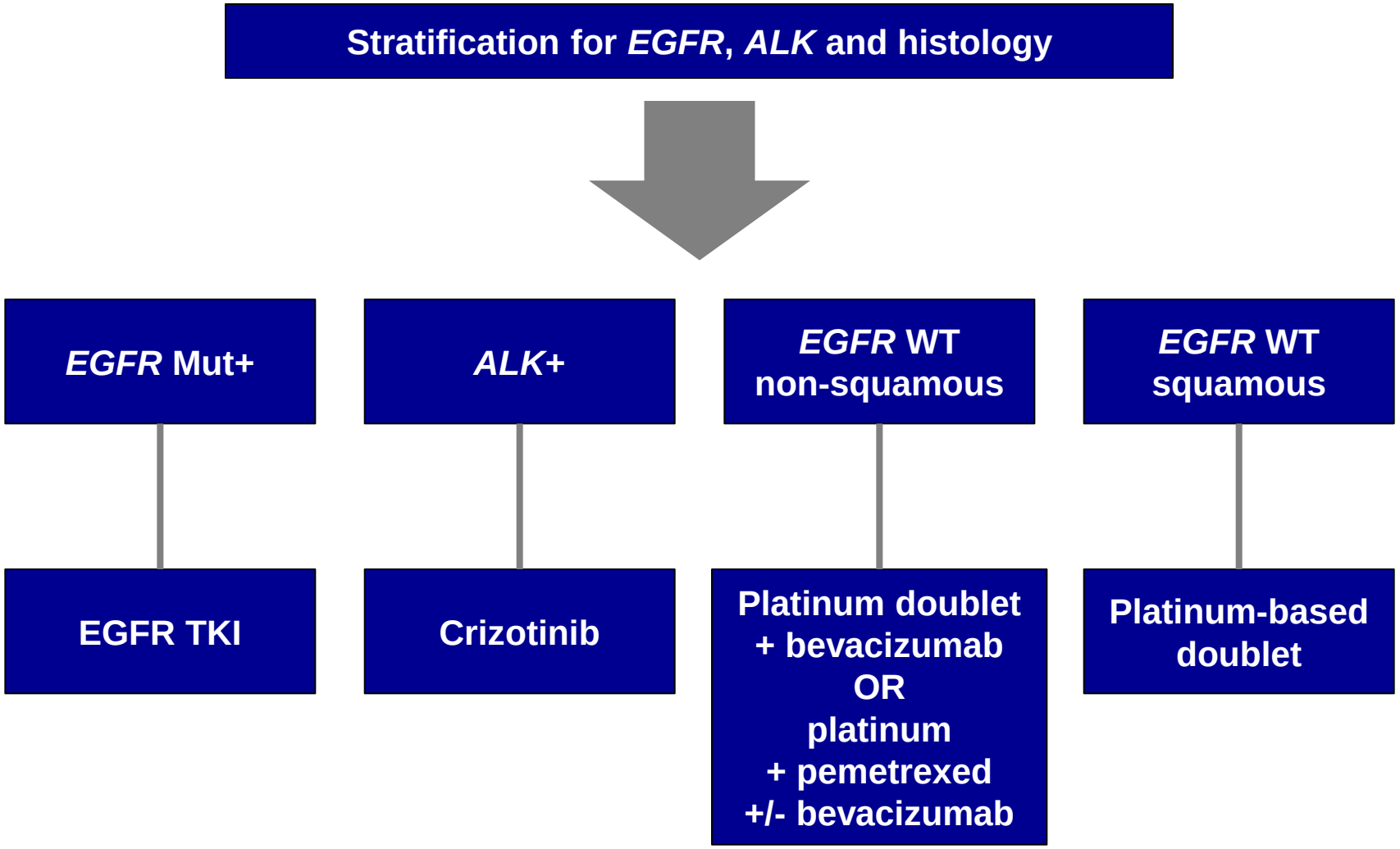
Adenocarcinoma



Squamous-cell carcinoma



First-line therapy for metastatic NSCLC in 2014



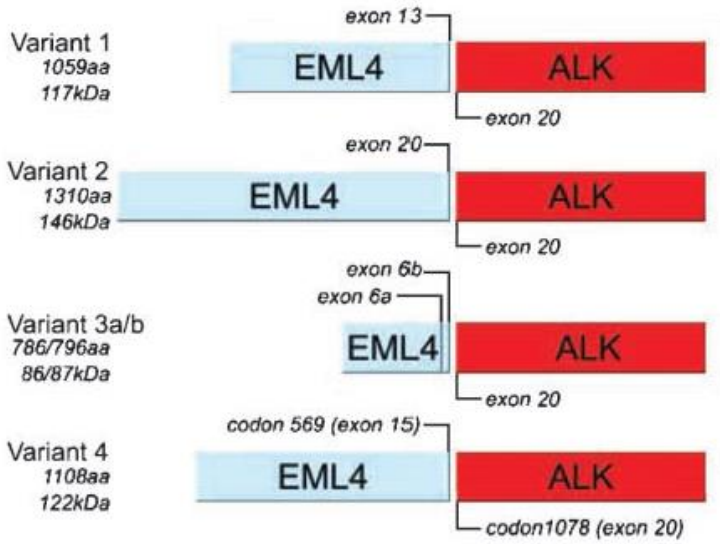
Studies of EGFR TKIs versus chemotherapy as first-line therapy in *EGFR* Act Mut+ NSCLC

Study	EGFR TKI	n	Median PFS in TKI arm (months)	P value	HR
OPTIMAL	Erlotinib	154	13.1	<0.0001	0.16
First Signal	Gefitinib	42	8.4	0.084	0.61
IPASS	Gefitinib	261	9.5	<0.0001	0.48
WJTOG 3405	Gefitinib	177	9.2	<0.001	0.48
NEJSG 002	Gefitinib	200	10.8	<0.001	0.36
EURTAC	Erlotinib	174	9.4	<0.0001	0.42
LUX-3	Afatinib	308	13.6	<0.0001	0.47
LUX-6	Afatinib	364	11.0	<0.0001	0.28

EML4-ALK fusion oncogene in NSCLC

Initially reported in 2007 as a result of an inversion in chromosome 2p, which results in the fusion of the N-terminal portion of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the kinase domain of *ALK*

- **3–7% of patients with NSCLC have an EML4-ALK gene fusion[1]**
- **detection test available (FISH the gold-standard)**
- **mainly seen in adenocarcinomas (mutually exclusive with EGFR mutations)**
- **phase I/II trial of crizotinib, oral c-MET and ALK inhibitor in selected patients: DCR = 70%[3]**
- **further potential for personalising therapy in NSCLC**



1. Koivunen, et al. Clin Cancer Res 2008
2. Shaw, et al. ASCO 2009; 3. Bang, et al. ASCO 2010

ALK translocations also occur in smokers

Smoking status	ALK positive (n=45) n (%)	ALK negative (n=176) n (%)
Never smoker	26 / 58	85 / 48
Ex-smoker (cessation ≥ 10 years)	4 / 9	22 / 13
Ex-smoker (cessation < 10 years)	3 / 7	16 / 9
Current Smoker	7 / 16	50 / 28
Unknown	5 / 11	3 / 2

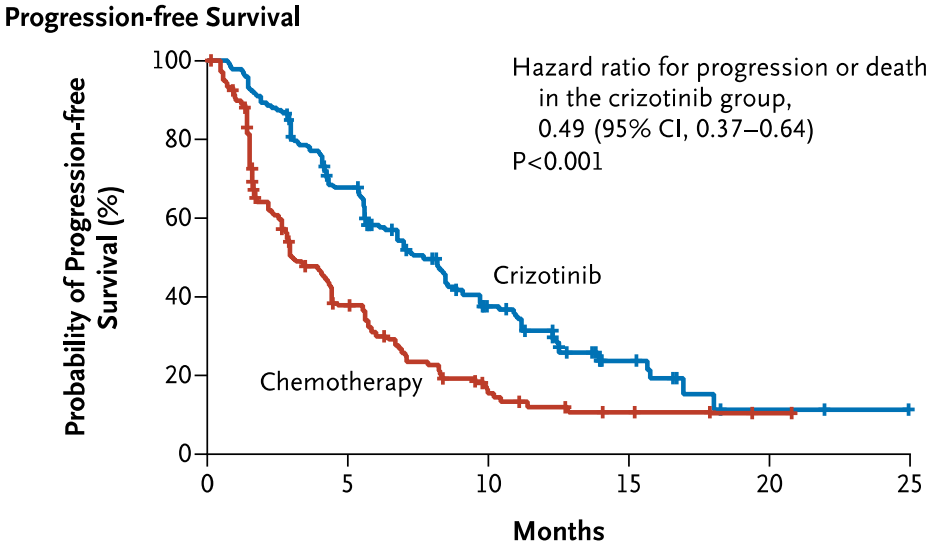
Koh Y, et al. *J Thorac Oncol* 2011;6:905–12

Comparison of FISH, IHC, and RT-PCR as screening modalities for *ALK* fusion

	FISH	IHC	RT-PCR
Current standard for *ALK* detection	Yes	No	No
Sensitivity	Break-apart signal can be subtle	High for some antibodies	High
Detection of unknown variants	Yes	Yes	Possible with some platforms
Labor intensive	Yes	No	No
Highly specialized training required	Yes	No	No
Simultaneous visualization of cell morphology	No	Yes	No

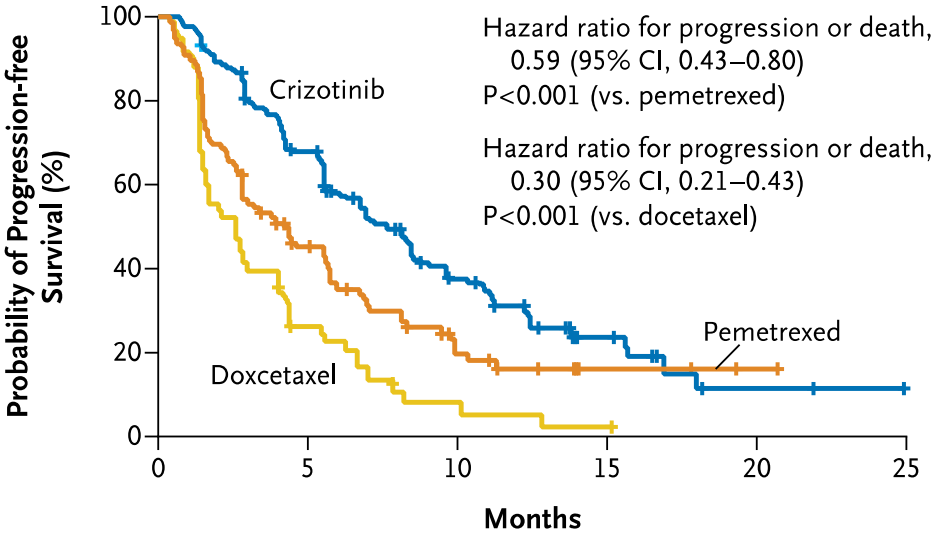
Adapted from
Mitsudomi, IASLC 2011; Abs #MTE22.1
Hirsch, IASLC 2011; Abs #O05.08

Profile 1007: PFS by Independent Radiologic Review (in overall population and according to chemotherapy)



Treatment	mPFS (mos)	HR/p value
Crizotinib	7.7	0.49/P<0.001
Chemotherapy	3.0	

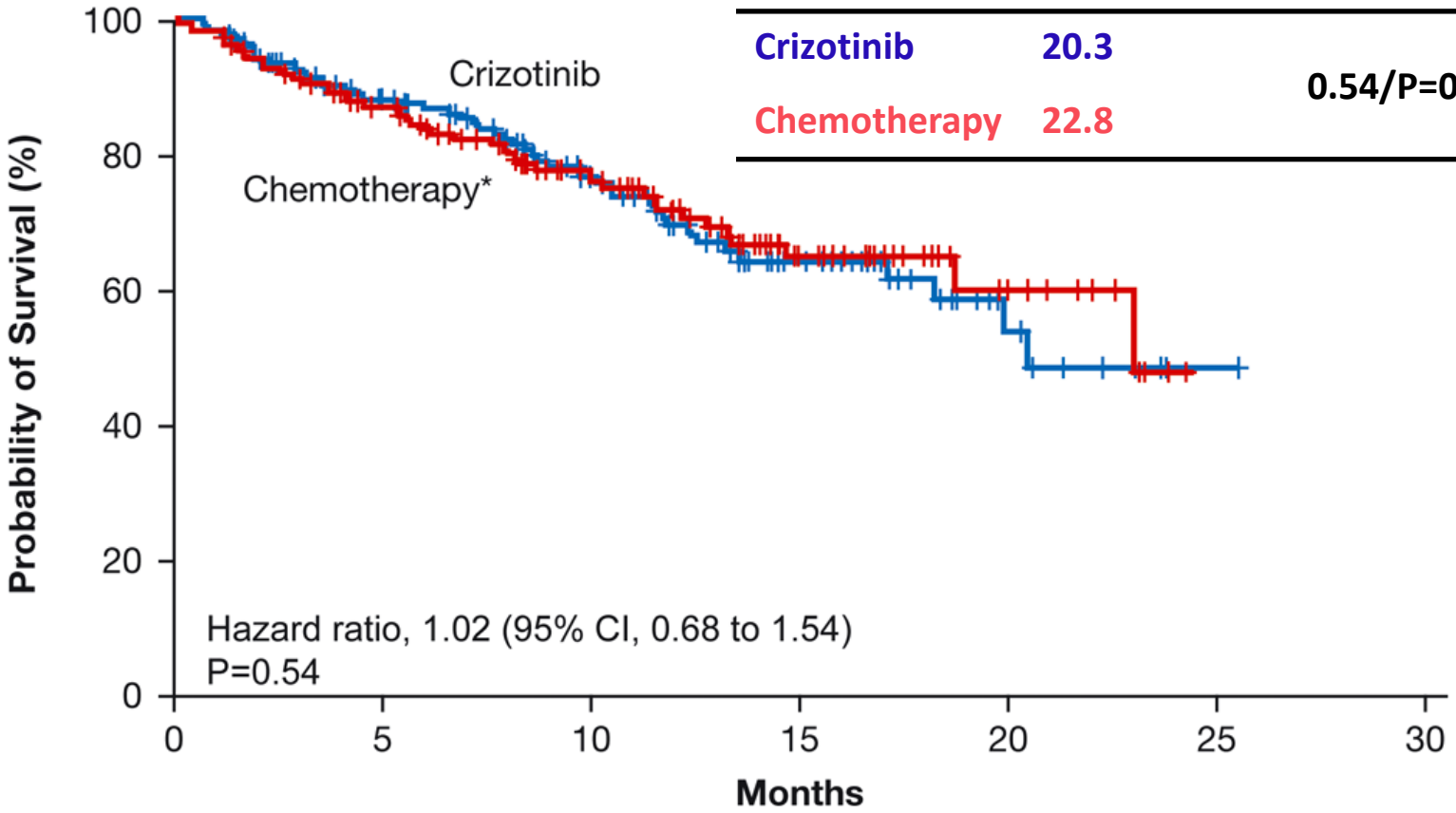
Treatment	mPFS (mos)	HR/p value
Crizotinib	7.7	
Pemetrexed	4.2	0.59/P<0.001
Docetaxel	2.6	0.30/P<0.001



Shaw AT., NEJM 2013

Overall Survival

Treatment	mOS (mos)	HR/p value
Crizotinib	20.3	0.54/P=0.54
Chemotherapy	22.8	

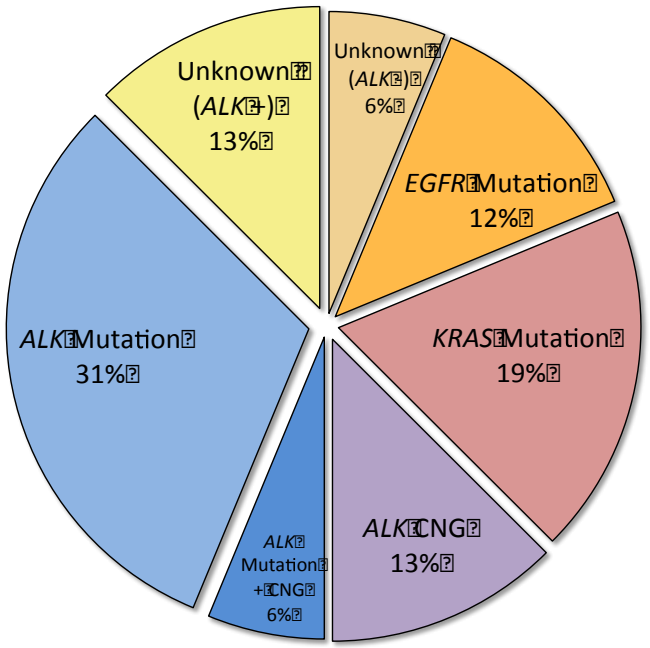


*** 112 patients crossed over to crizotinib**

Shaw AT., NEJM 2013

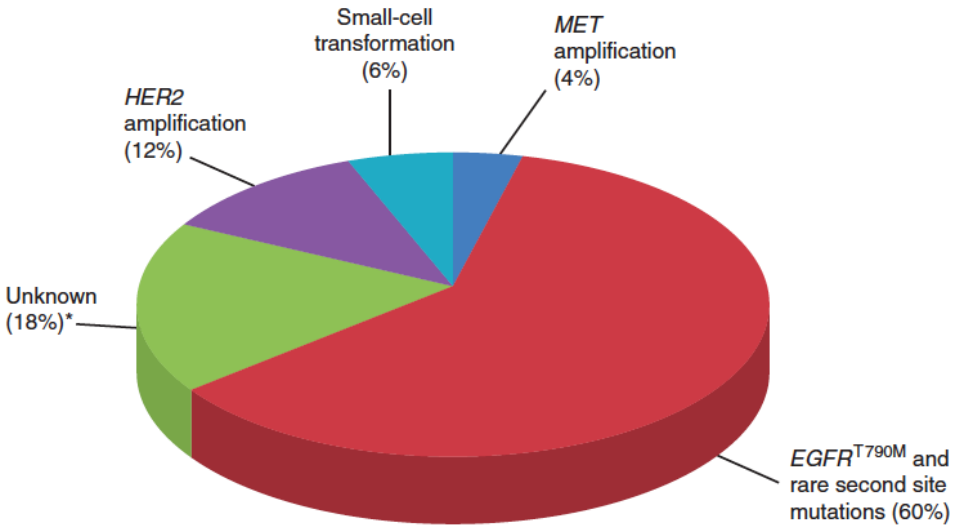
Mechanisms responsible for acquired resistance to crizotinib or EGFR-TKIs

Crizotinib resistance



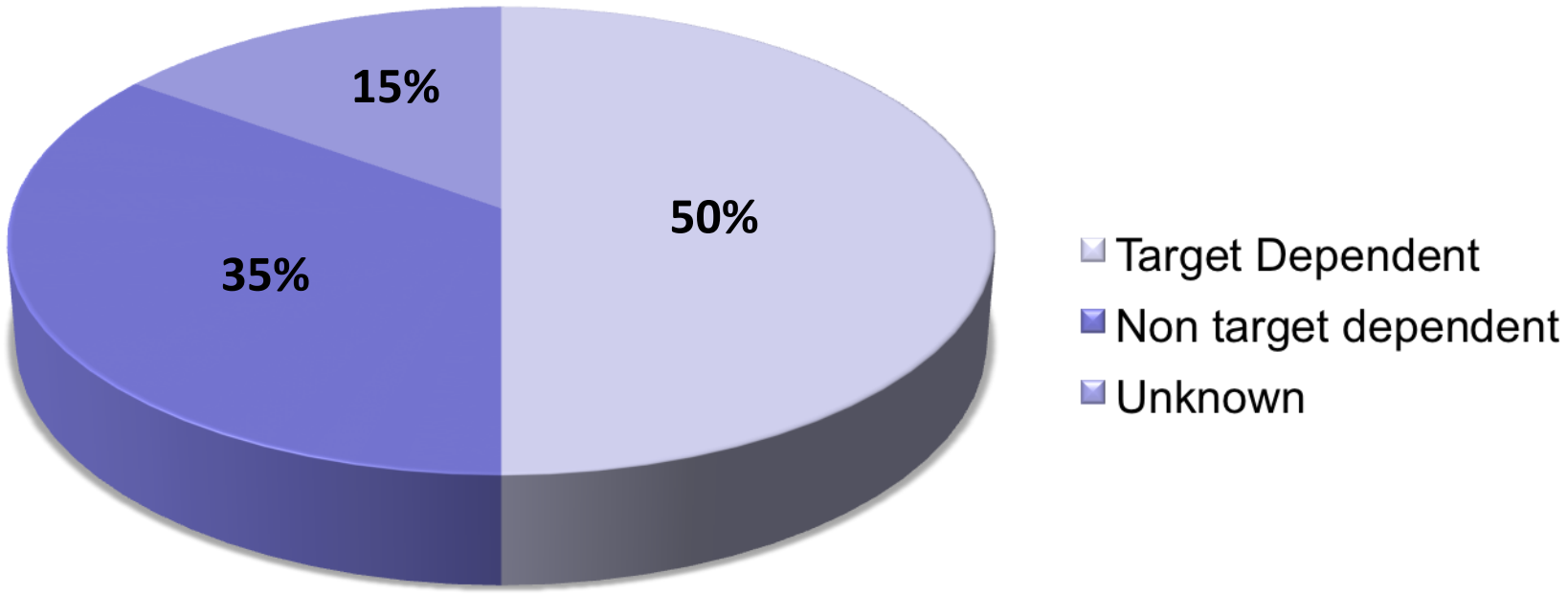
Camidge R, ASCO 2013

EGFR-TKI resistance



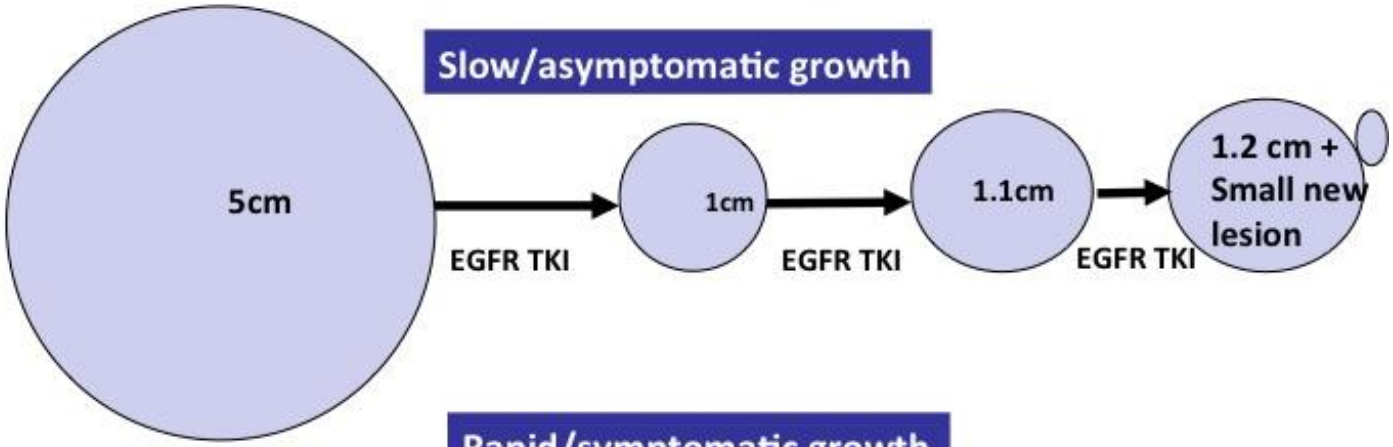
Takezawa et al. Cancer Discovery 2012

Mechanisms of acquired resistance

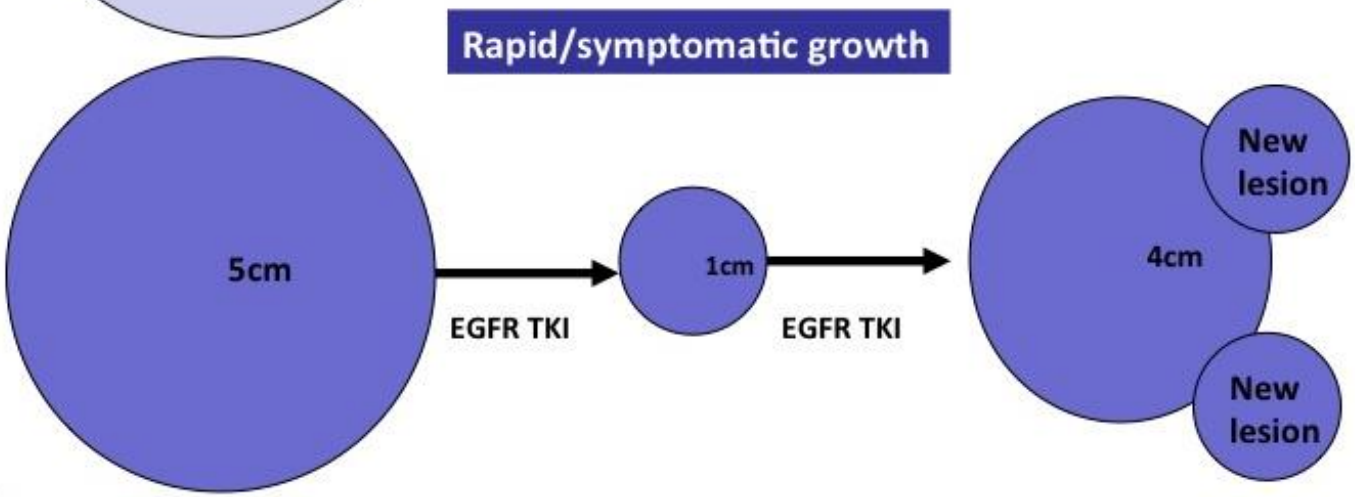


Clinical presentations of acquired resistance

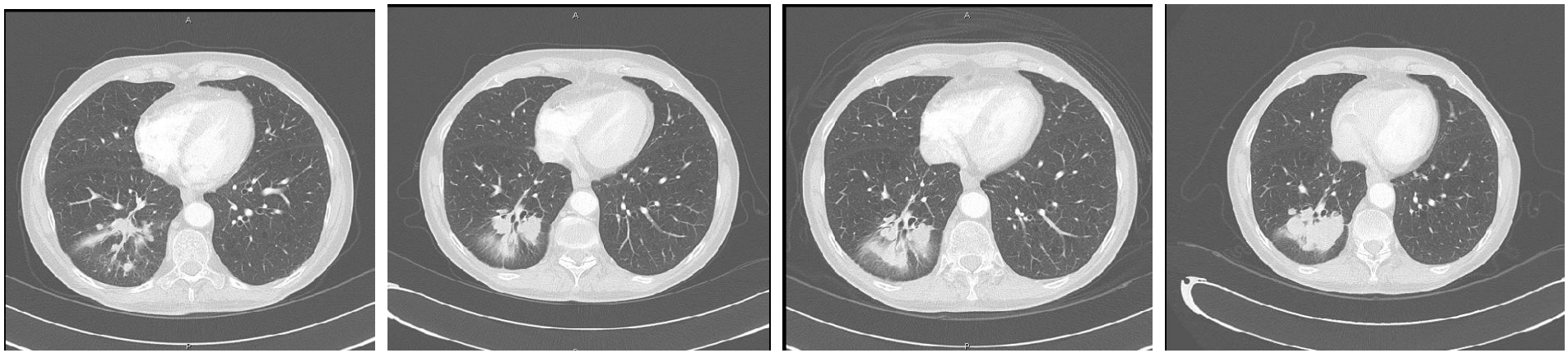
Target dependent



Target independent



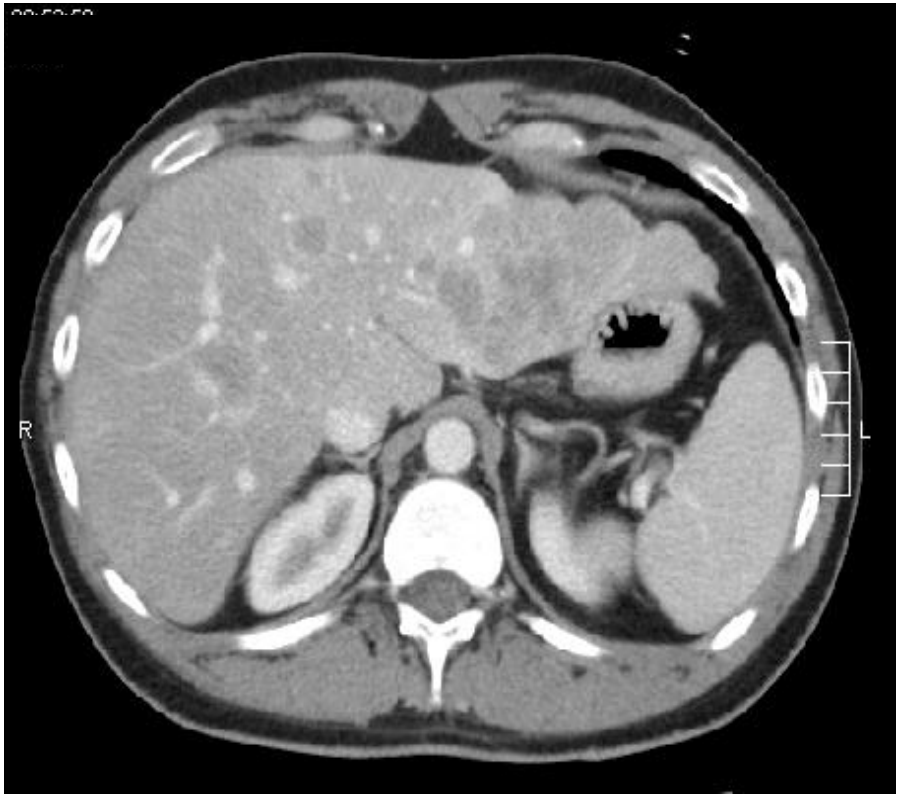
Target dependent tumor progression

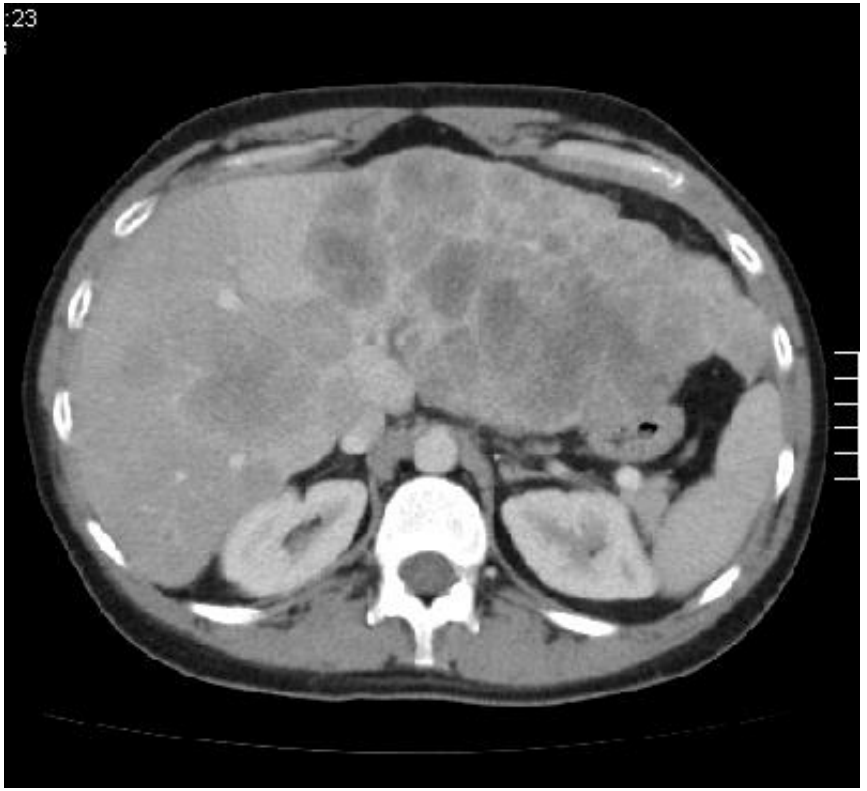


12 November 2012,
EGFR mut ex 19

20 February 2014
EGFR mut ex 19 + T790M

Target independent tumor progression



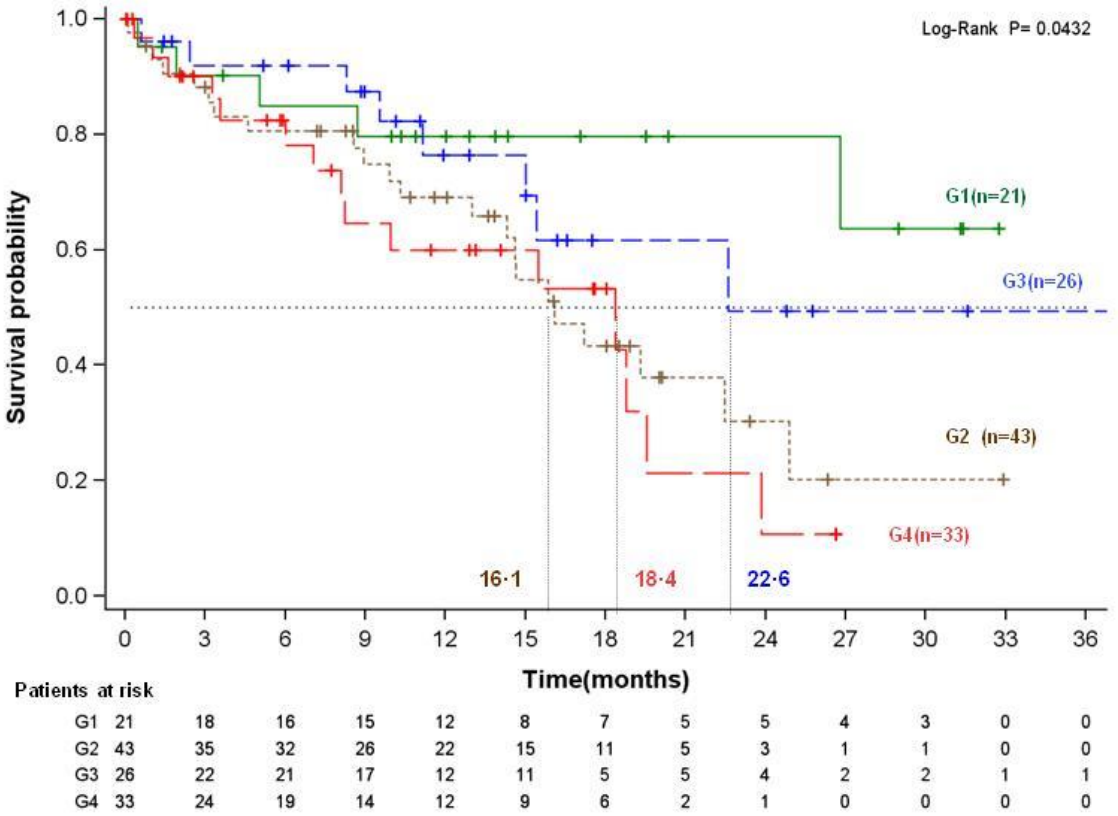


03 February 2012 EGFR mut ex 21 → **23 March 2012 EGFR wt-KRAS mut**

T790M mutation in NSCLC

- **Present in up to 50% of NSCLC with EGFR-TKI acquired resistance**
- **Rare event in EGFR-TKI naive NSCLC (<3%) using low sensitive methods**
- **Detected in up to 40% of EGFR-TKI naive patients using high sensitive methods**
- **Preclinical evidence that EGFR T790M decreases growth potential of lung tumor cells (Chmielecki et al AACR 2009)**

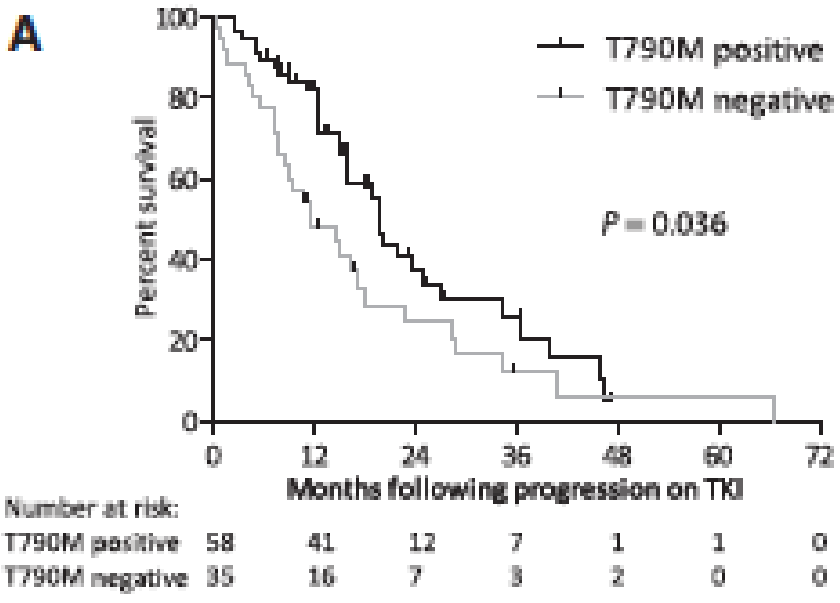
Overall survival according to pretreatment T790M

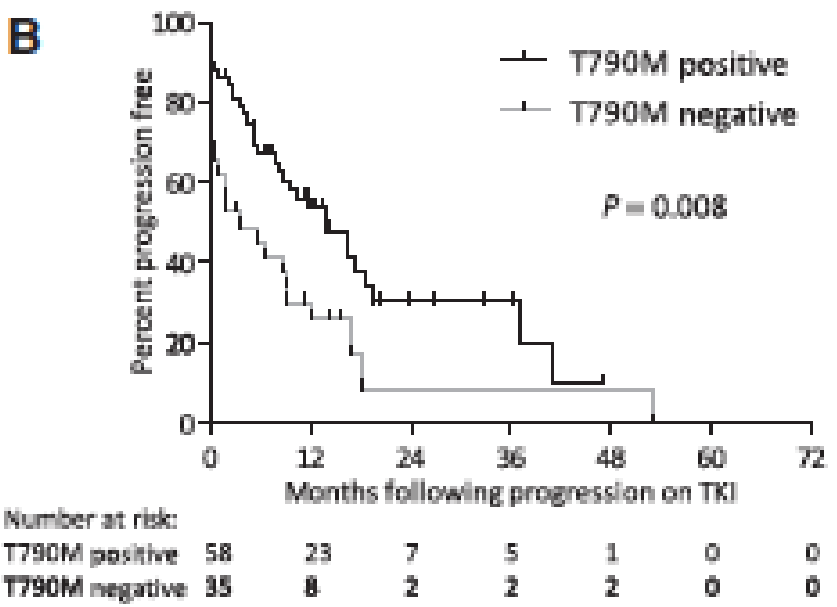


Strata	Median OS (95% CI)
G1: Patients on Erlotinib arm with T790M present	NA (26.8, NA)
G2: Patients on Erlotinib arm with T790M absent	16.1 (13.0, 24.9)
G3: Patients on Chemotherapy arm with T790M present	22.6 (15.0, NA)
G4: Patients on Chemotherapy arm with T790M absent	18.4 (8.1, 19.5)

Rosell ASCO 2012

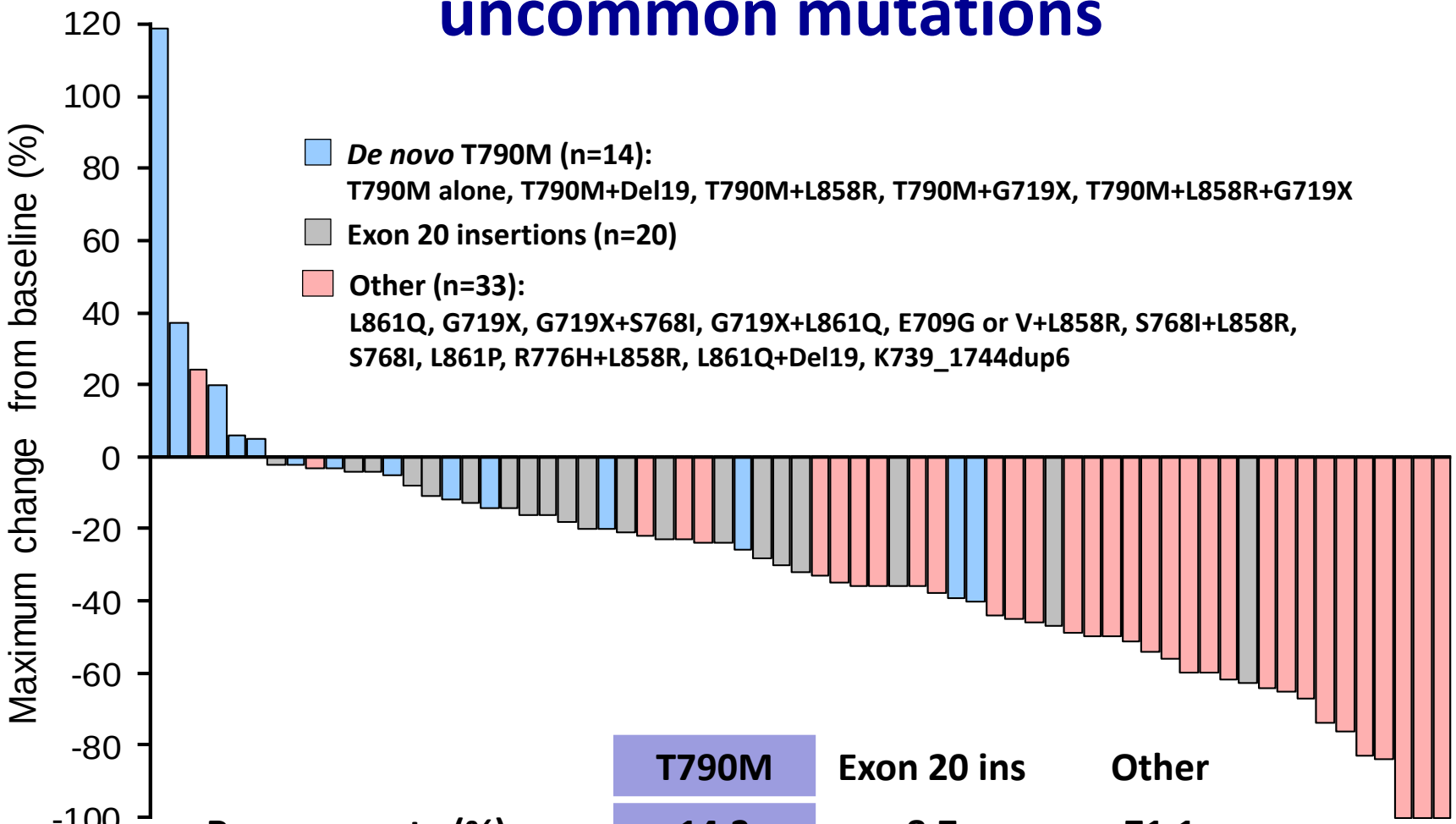
Presence of “acquired” T790M confers favorable prognosis





Oxnard Clin Cancer Res 2011

Outcome in patients treated with afatinib with uncommon mutations

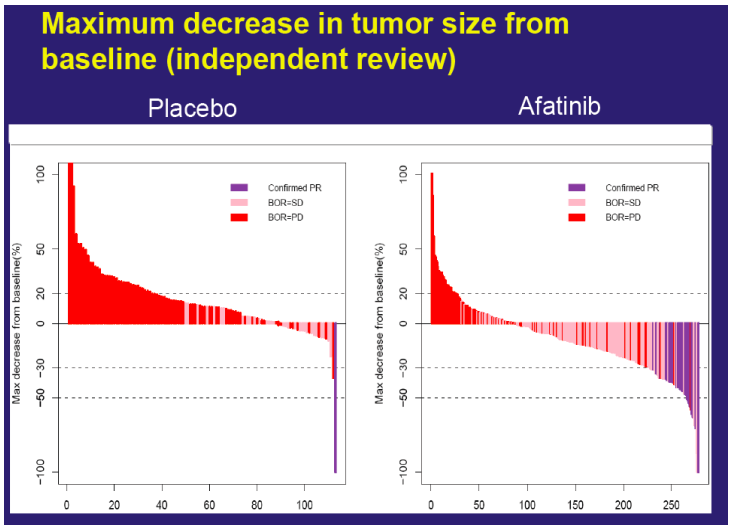


	T790M	Exon 20 ins	Other
Response rate (%)	14.3	8.7	71.1
PFS (months)	2.9	2.7	10.7
OS (months)	14.9	9.4	18.6

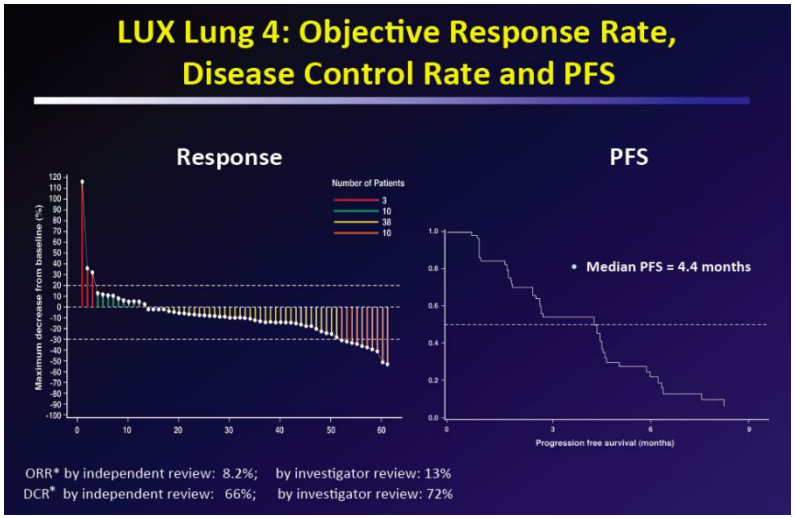
Young WCLC 2013

Modest efficacy of irreversible EGFR-TKIs Against “de novo” and “acquired” T790M

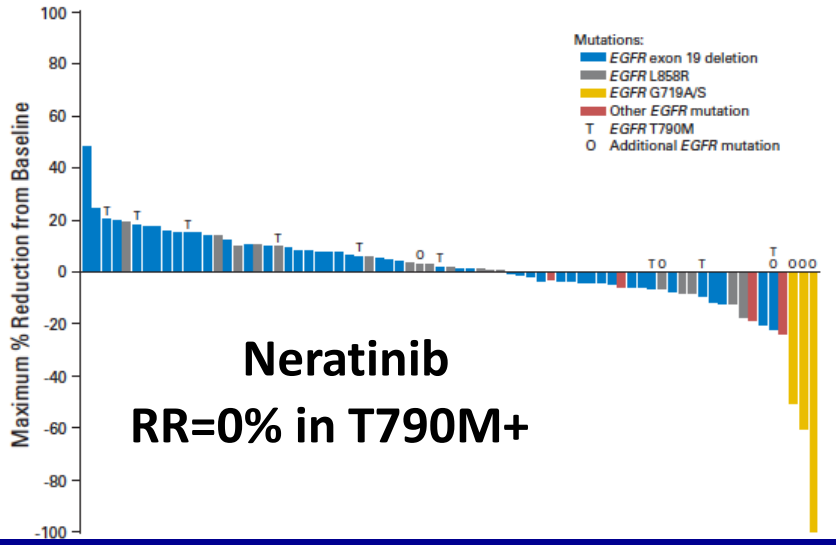
LUX LUNG 1: RR=7%



LUX LUNG 4: RR=8%



LUX-LUNG 2-3-6 trials	T790M
Response rate (%)	14.3
PFS (months)	2.9
OS (months)	14.9

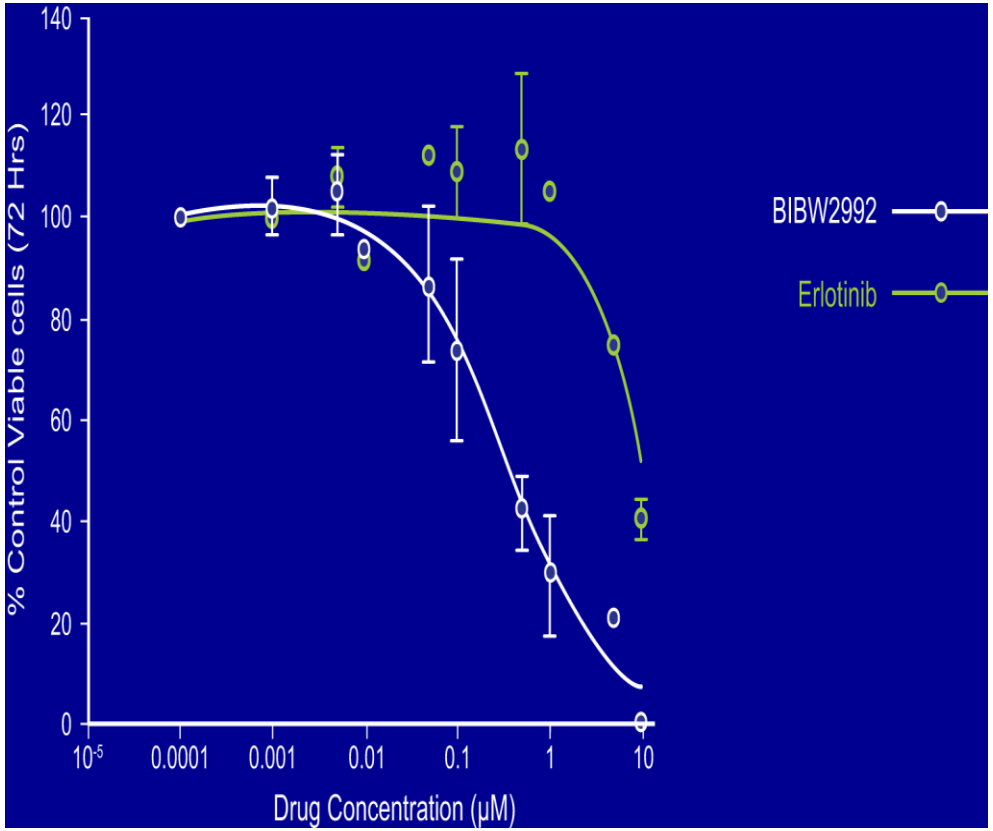


Neratinib

RR=0% in T790M+

Why irreversible inhibitors work against T790M in preclinical models only?

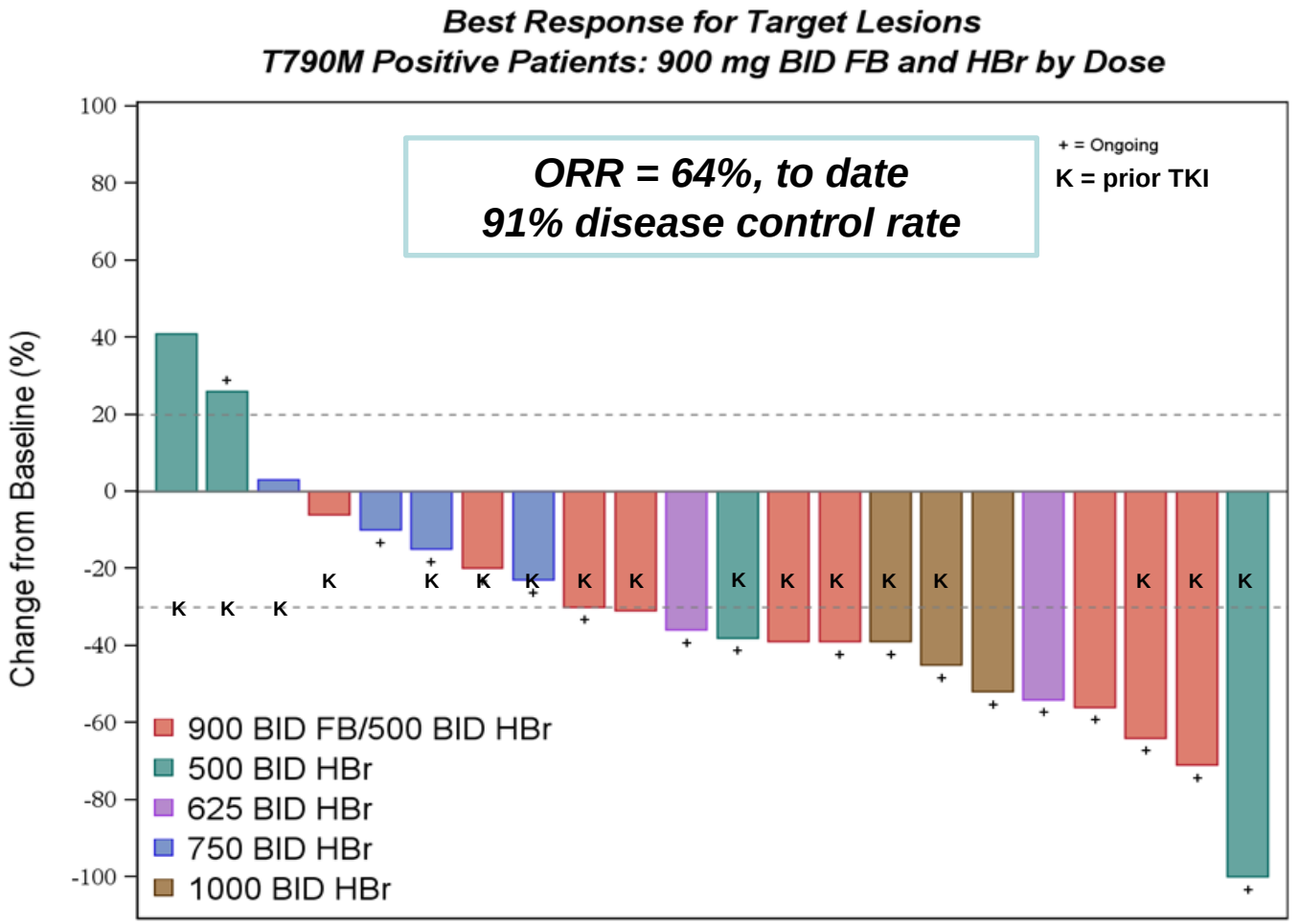
NCI-H1975



CO-1686 is a novel TKI specifically targeting mutated EGFR

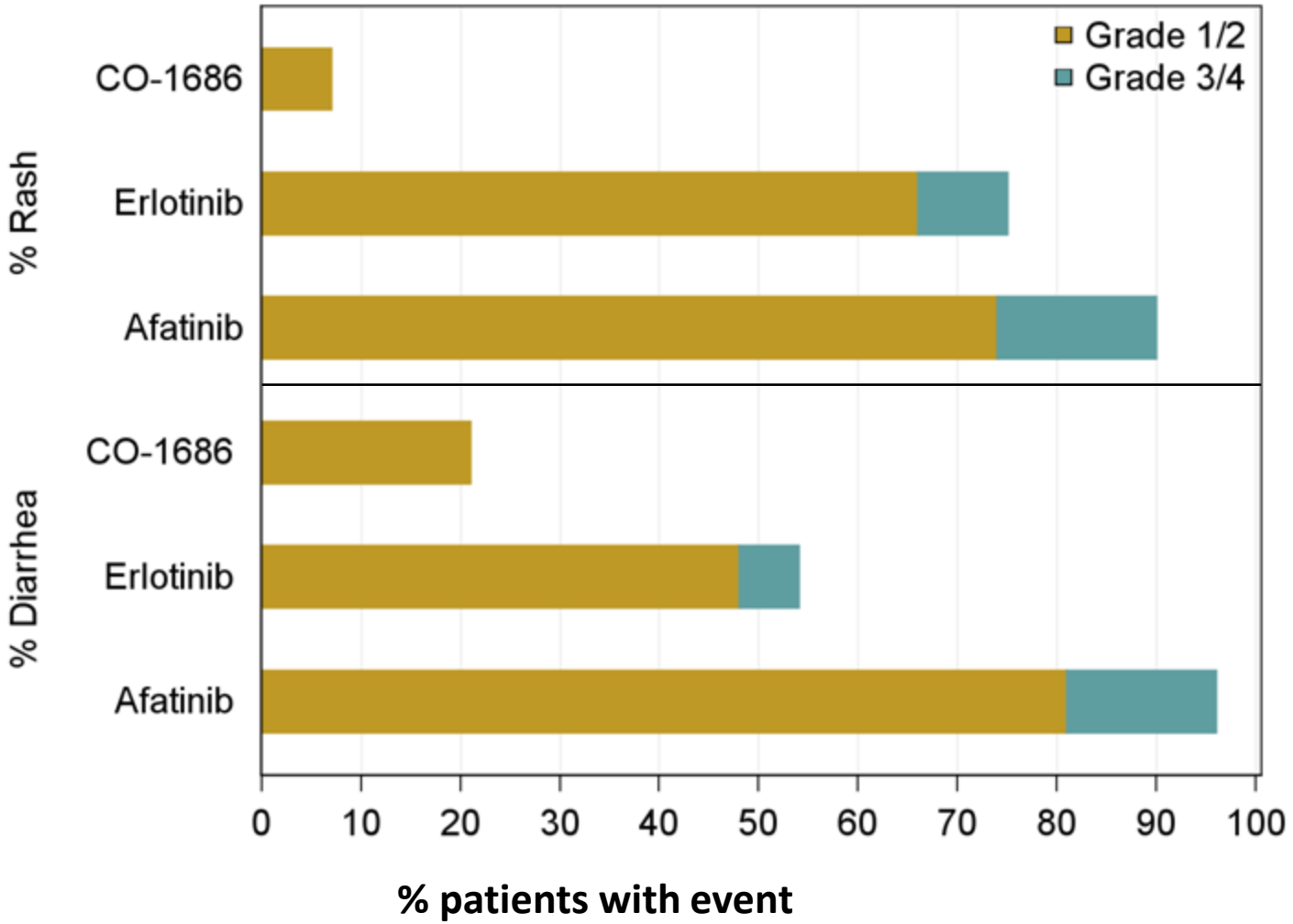
- **Novel, oral, selective covalent inhibitor of EGFR mutations in NSCLC**
  - **Inhibits key activating and T790M resistance mutations**
  - **Spares wild type receptor signaling**
- **First-in-human study ongoing in EGFR mutated patients with recurrent, advanced NSCLC**
  - **MTD has not yet been reached**
- **Hydrobromide salt form of CO-1686 with improved drug availability and reduced variability recently introduced**
  - **Dose escalation continuing**

Efficacy clear across dose levels in 22 centrally-confirmed T790M+ patients



Wakelee H, ELCC 2014

Classical AEs observed with WT-EGFR inhibition uncommon with CO-1686



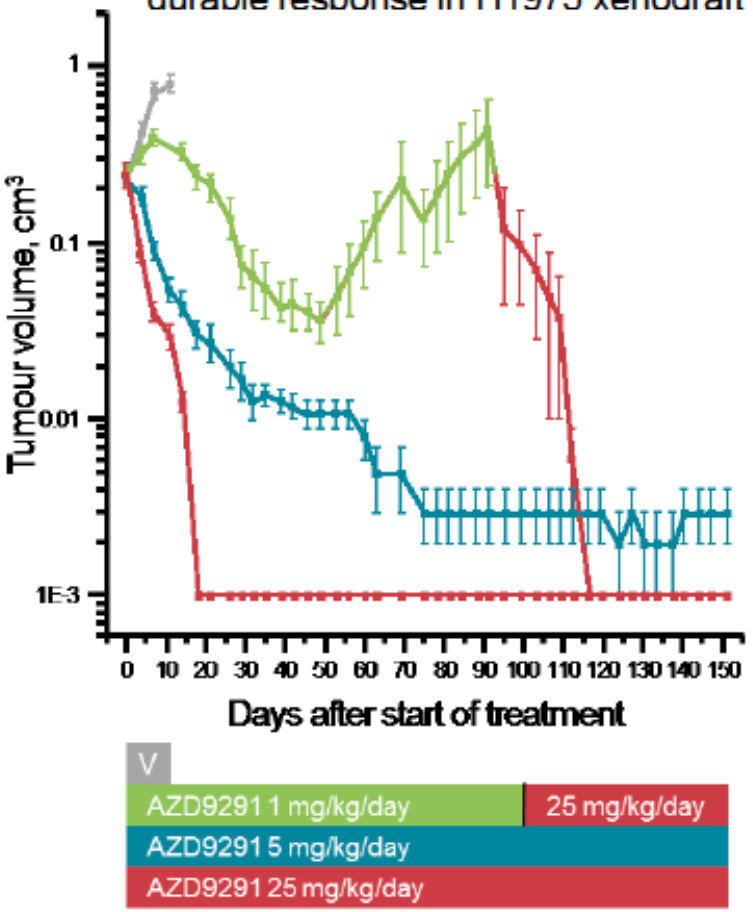
Comparator data from US prescribing information

AZD9291: another irreversible EGFR-TKI potentially effective against T790M

- AZD9291 is a potent oral, irreversible inhibitor of *EGFR* that contains EGFR-TKI-sensitising (*EGFR*m+) and resistance mutations (T790M)
- Good potency and high selectivity demonstrated in enzymatic and cellular *in vitro* assays

Model	Wild-type LoVo cells	*EGFR*m+ PC9 cells	*EGFR*m+/ T790M H1975 cells
AZD9291 phospho-EGFR IC_{50} µM	0.480	0.017	0.0115

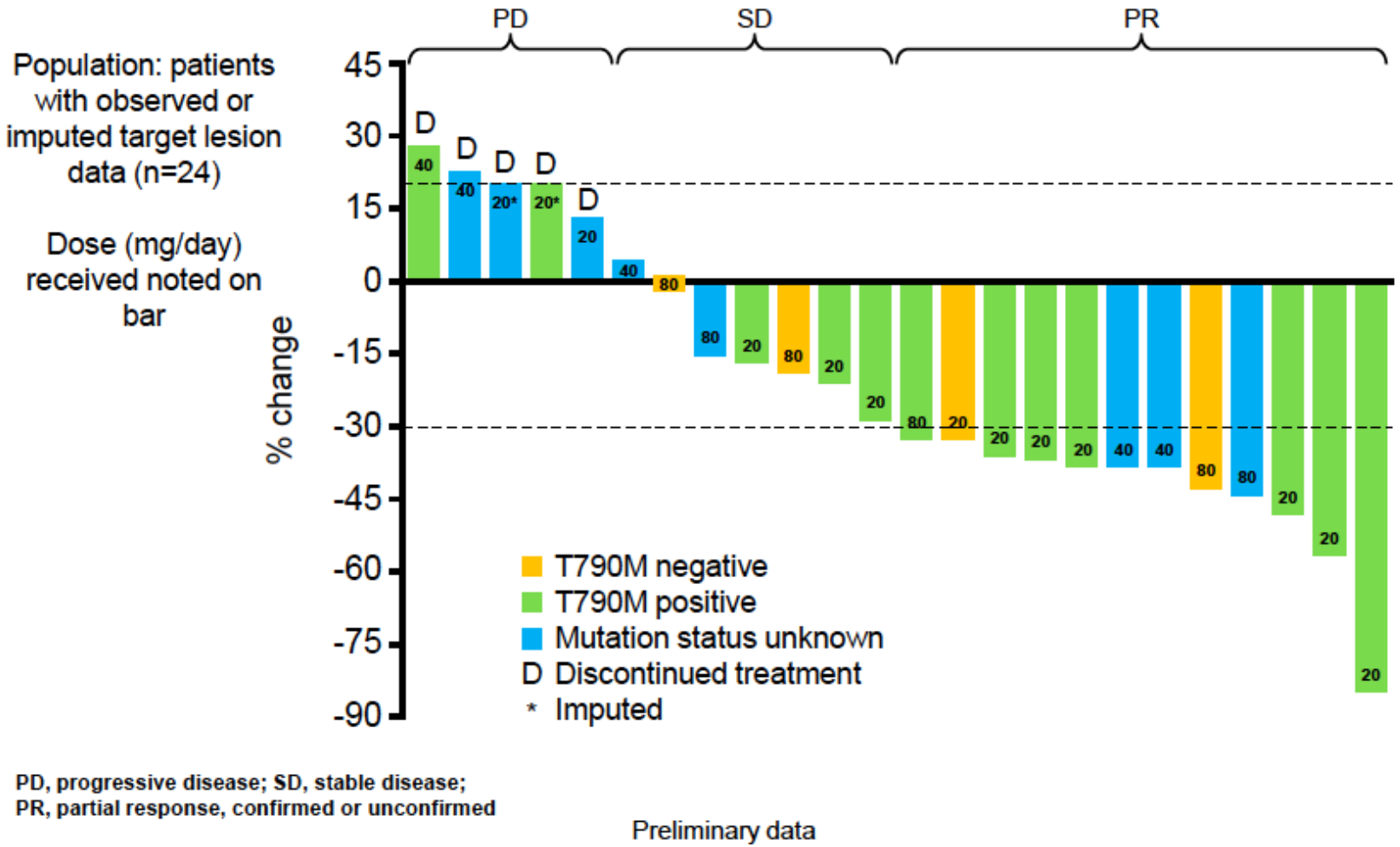
AZD9291 achieved complete and durable response in H1975 xenograft



AstraZeneca data on file

V, vehicle

AZD 9291: Evidence of efficacy against T790M even at the lowest dose



PD, progressive disease; SD, stable disease;
PR, partial response, confirmed or unconfirmed

Preliminary data