EGFR-TKIs for the treatment of advanced NSCLC with EGFR mutations

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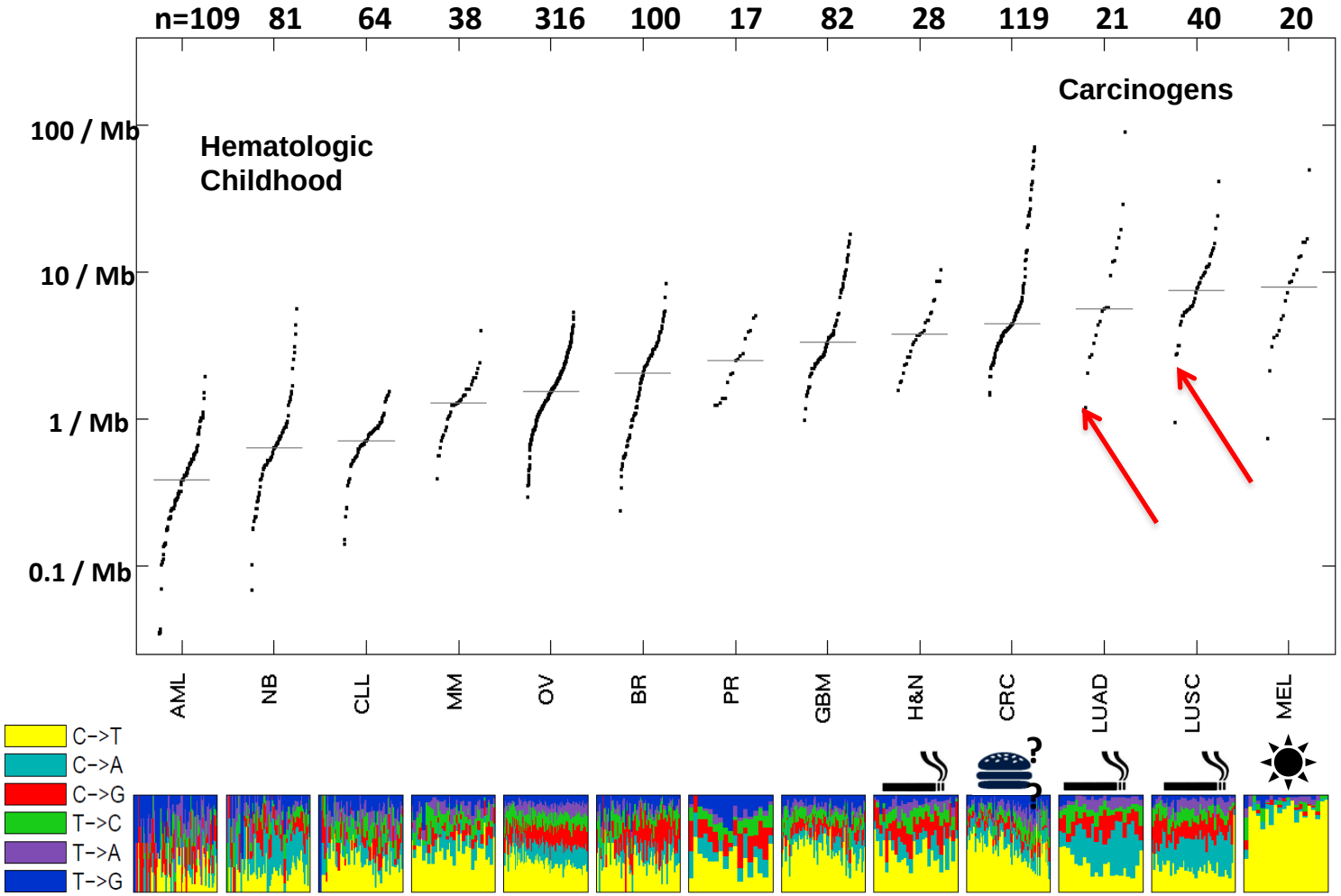
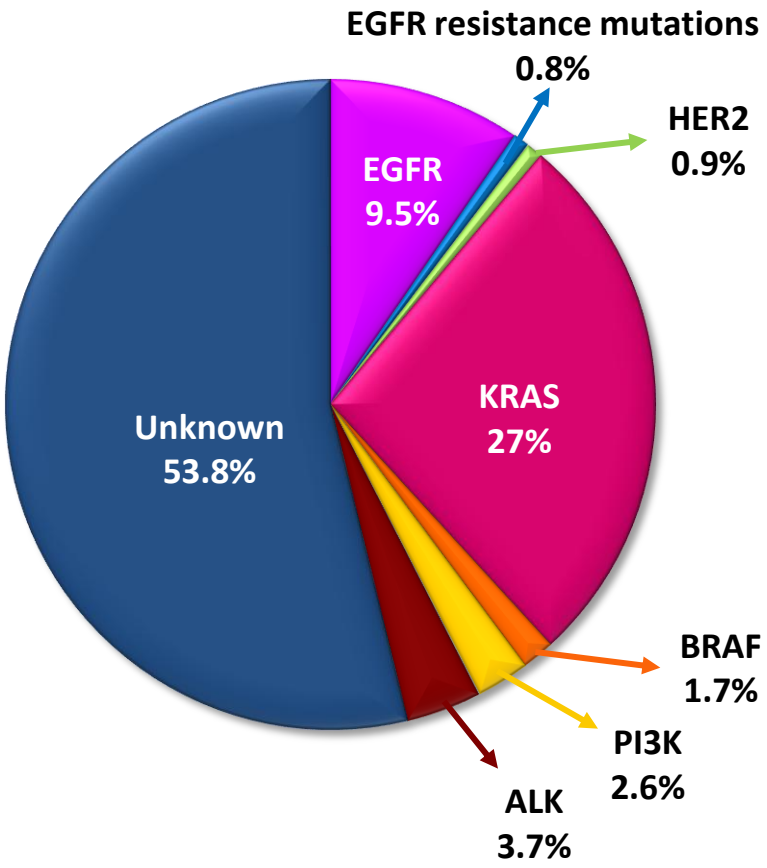
Negrar 12 marzo 2014

Lung cancer has a very high rate of somatic mutations

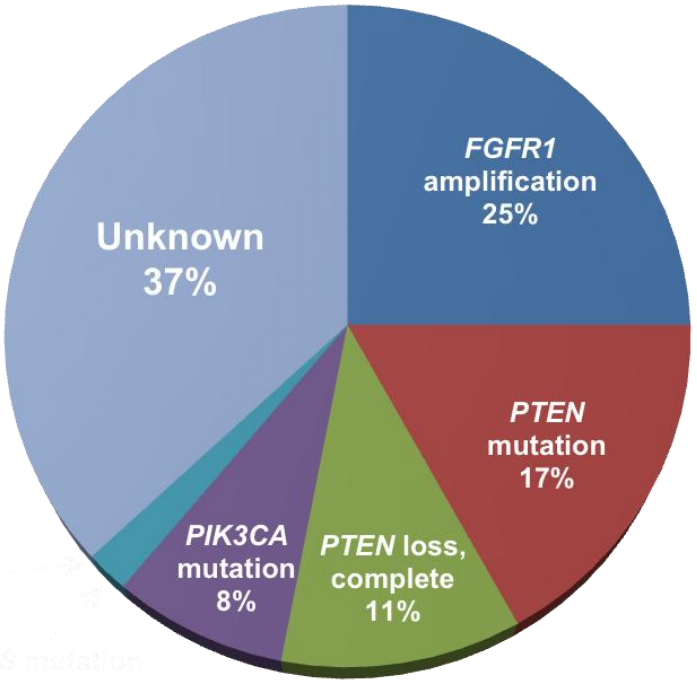


Molecular events in lung cancer

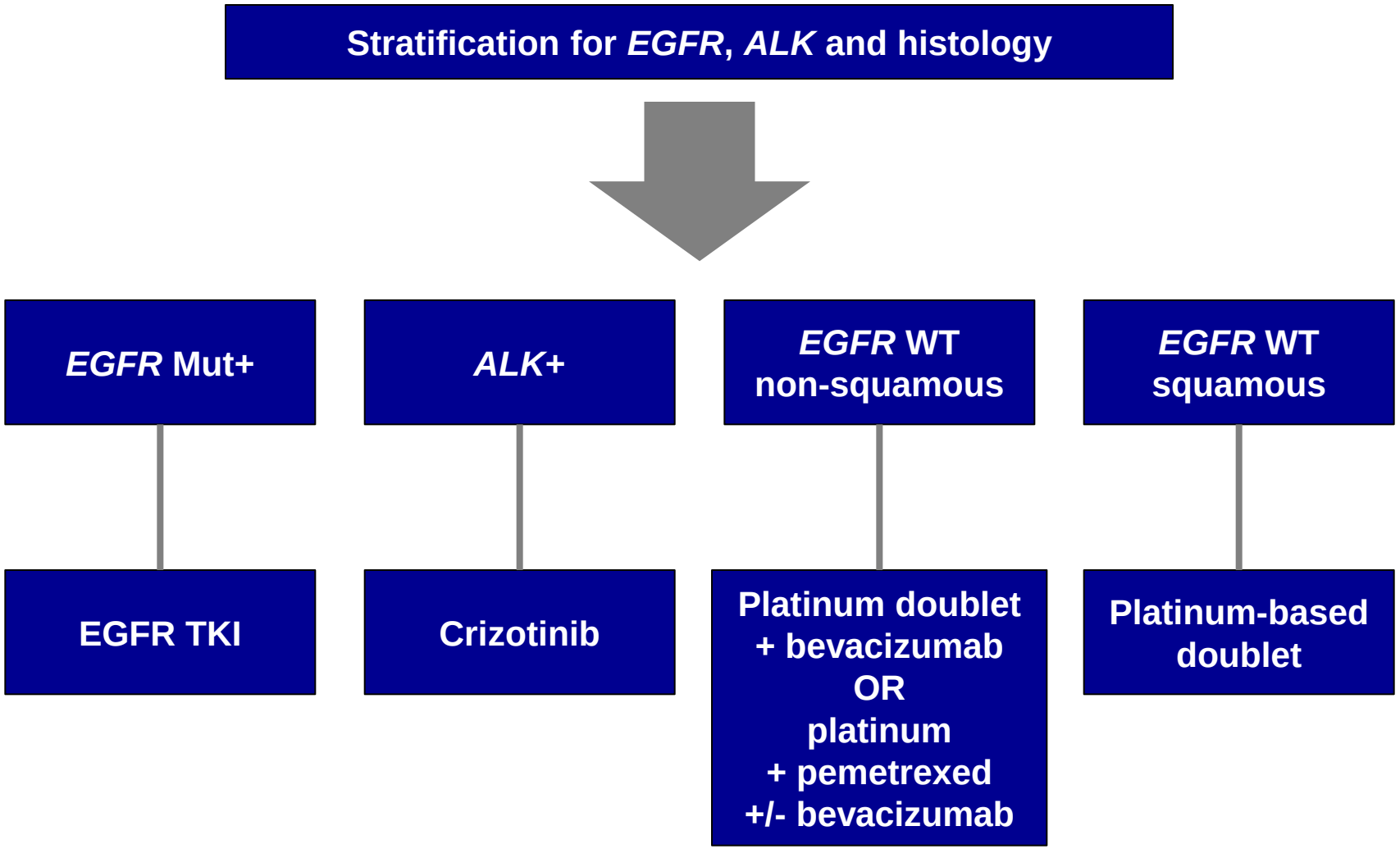
Adenocarcinoma



Squamous-cell carcinoma



First-line therapy for metastatic NSCLC in 2014

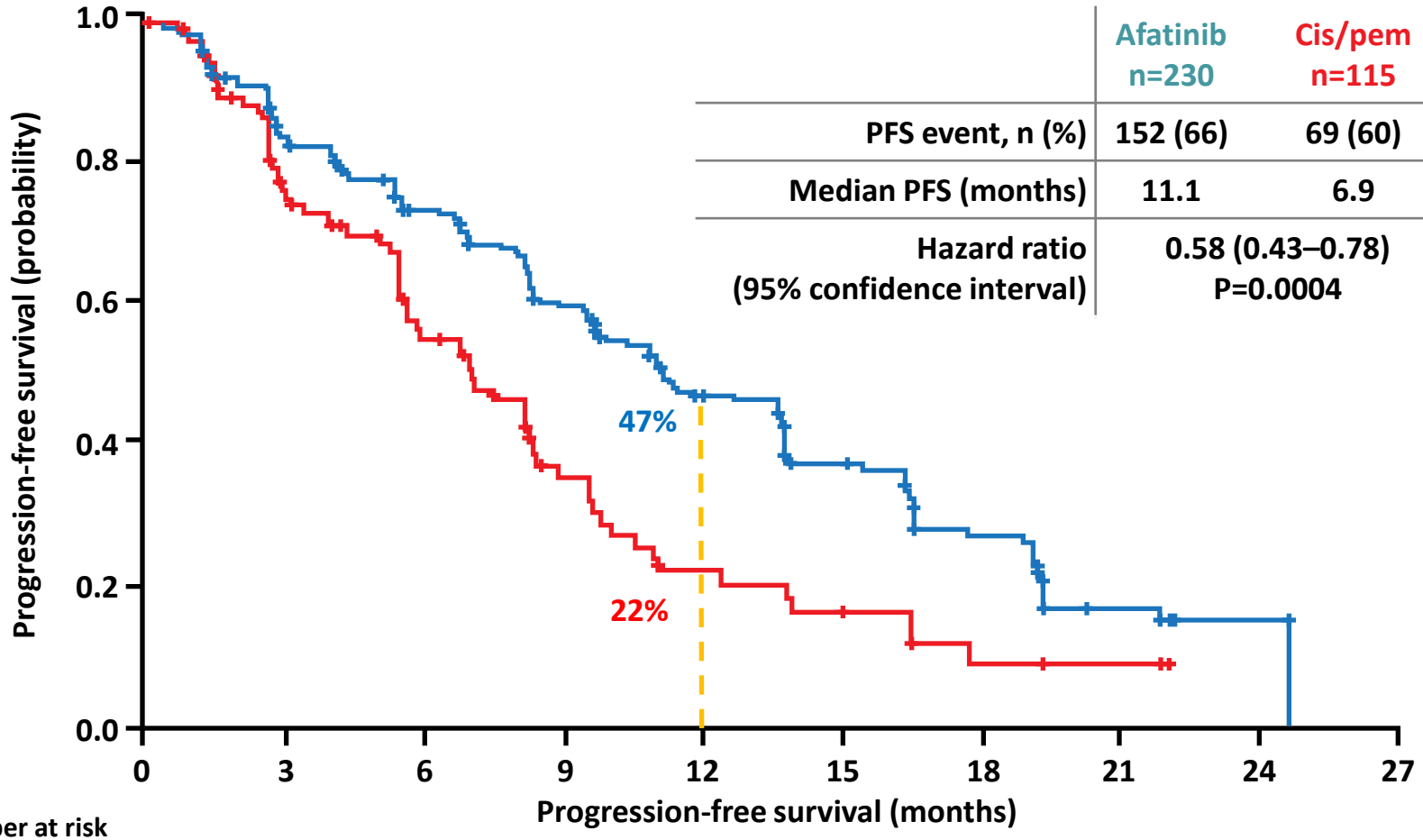


Studies of EGFR TKIs versus chemotherapy as first-line therapy in *EGFR* Act Mut+ NSCLC

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

LUX-3 study of afatinib versus CT: PFS results

Independent review – all randomized patients



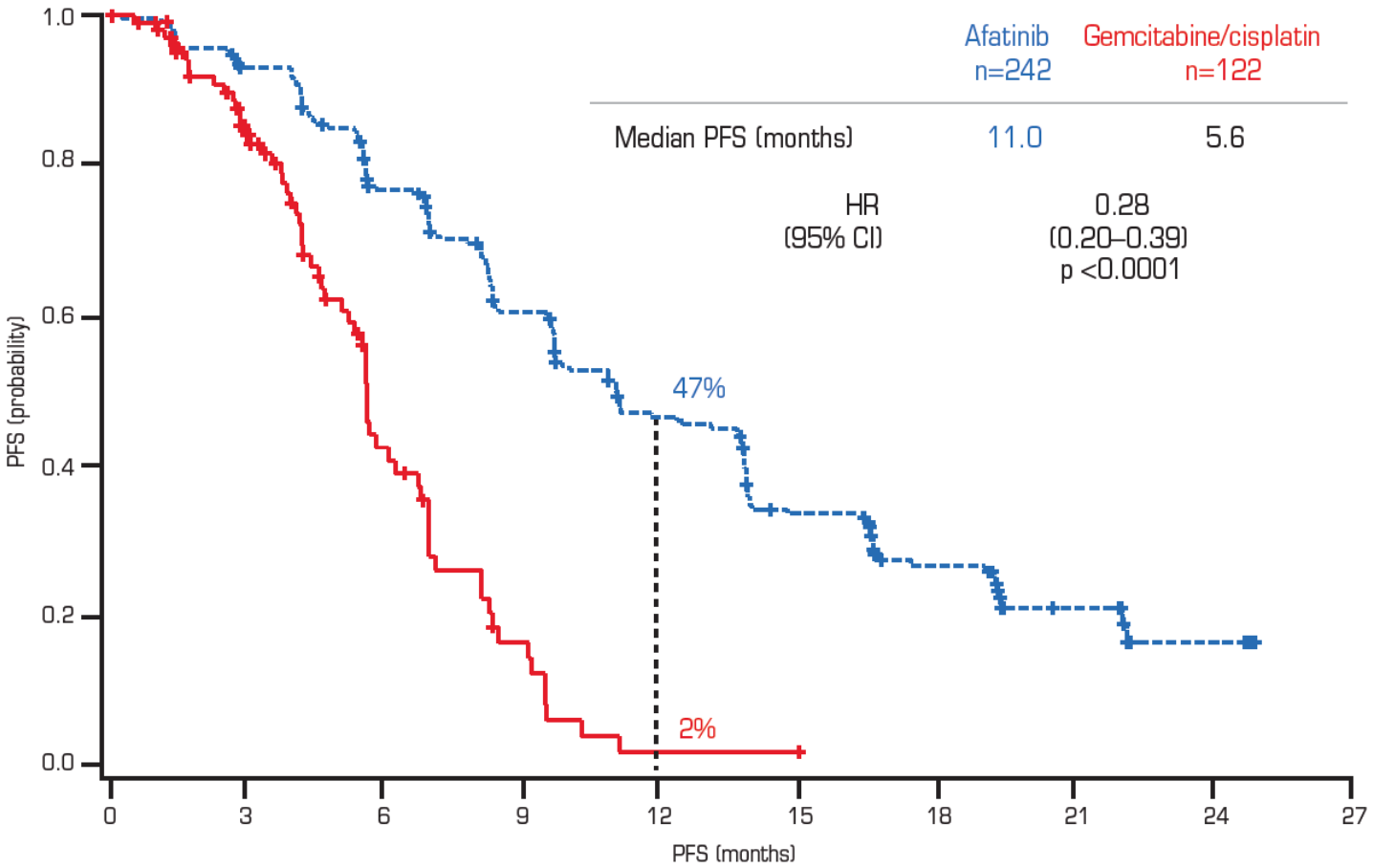
	Afatinib n=230	Cis/pem n=115
PFS event, n (%)	152 (66)	69 (60)
Median PFS (months)	11.1	6.9
Hazard ratio (95% confidence interval)	0.58 (0.43–0.78) P=0.0004	

Number at risk

Afatinib	230	180	151	120	77	50	31	10	3	0
Cis/Pem	115	72	41	21	11	7	3	2	0	0

Yang ASCO 2012

LUX-6: PFS by independent review



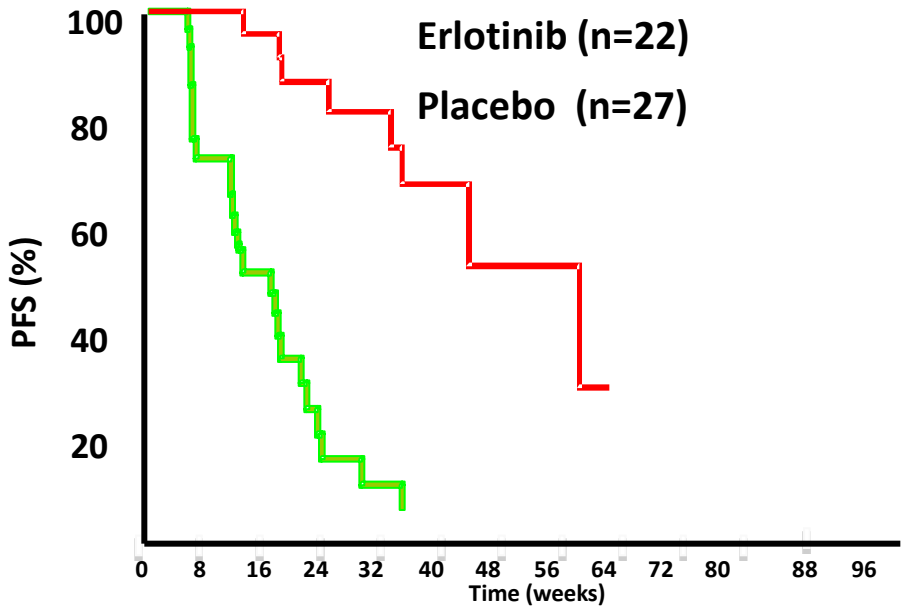
Wu YL. et al. 2013 ASCO Annual Meeting. Abs. 8016

EGFR-TKIs best option in maintenance

Progression-free Survival in mutated patients

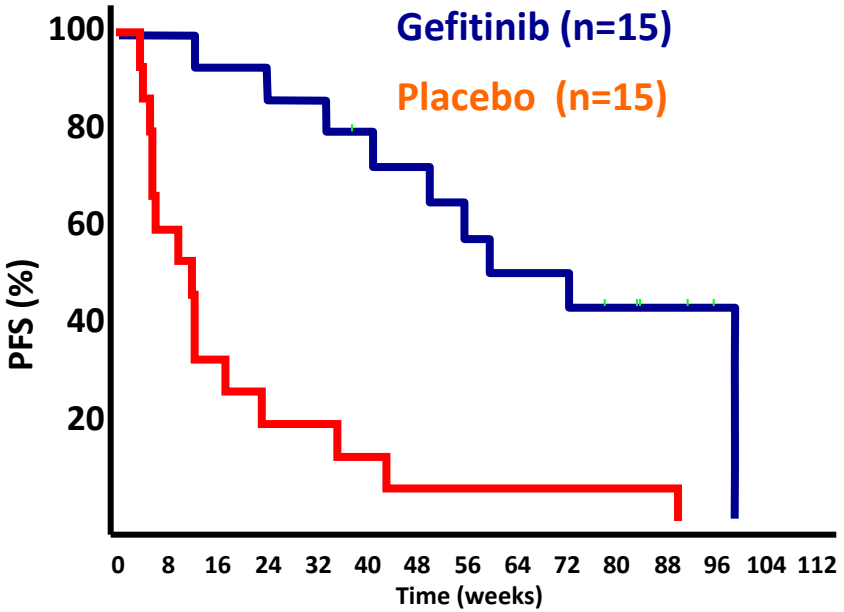
Erlotinib maintenance: SATURN

HR=0.10 (0.04–0.25)
P<0.0001



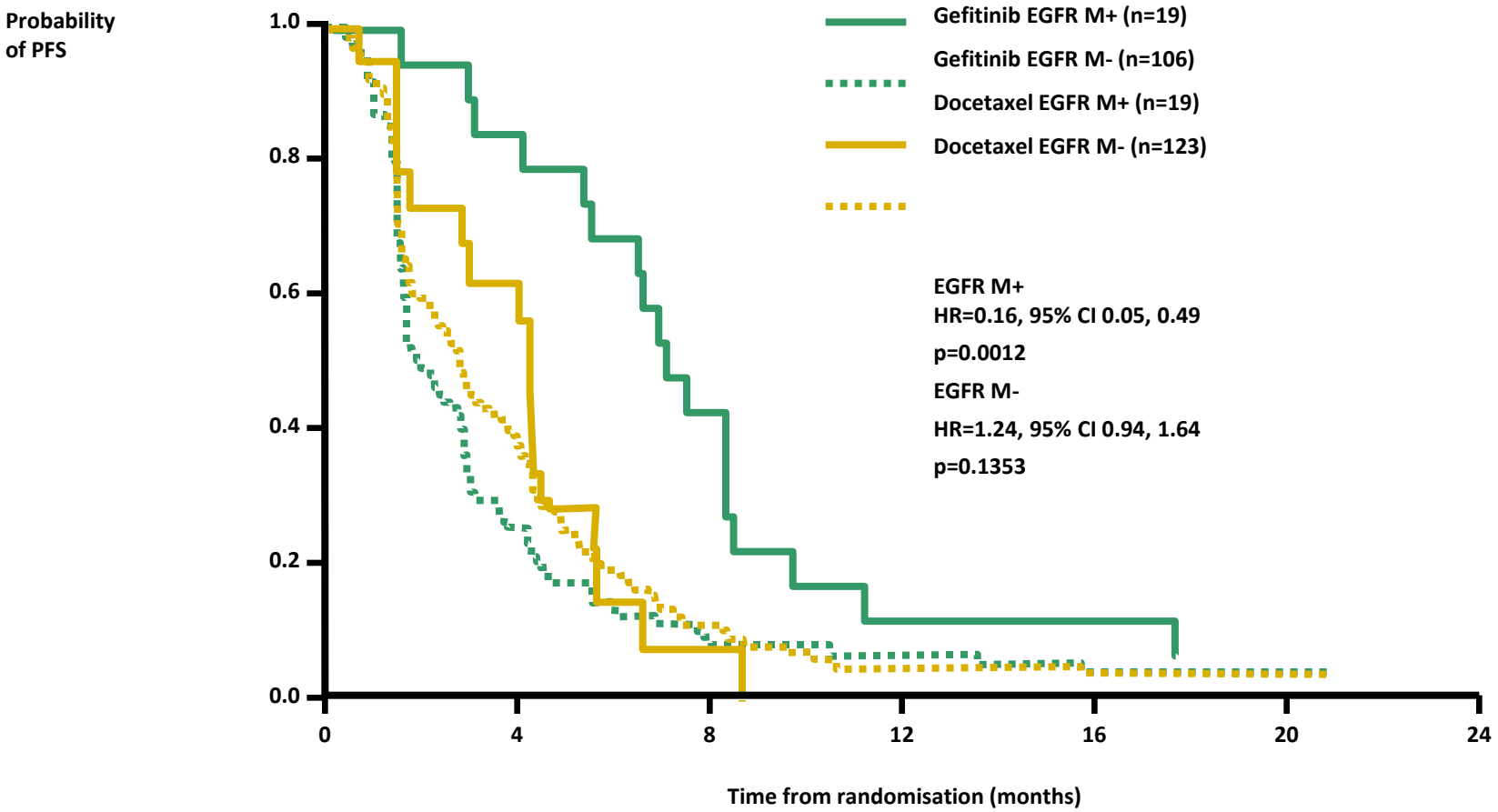
Gefitinib maintenance: INFORM

HR=0.17 (0.07–0.42)
P<0.0001



Cappuzzo et al, 2010; Zhang et al 2012

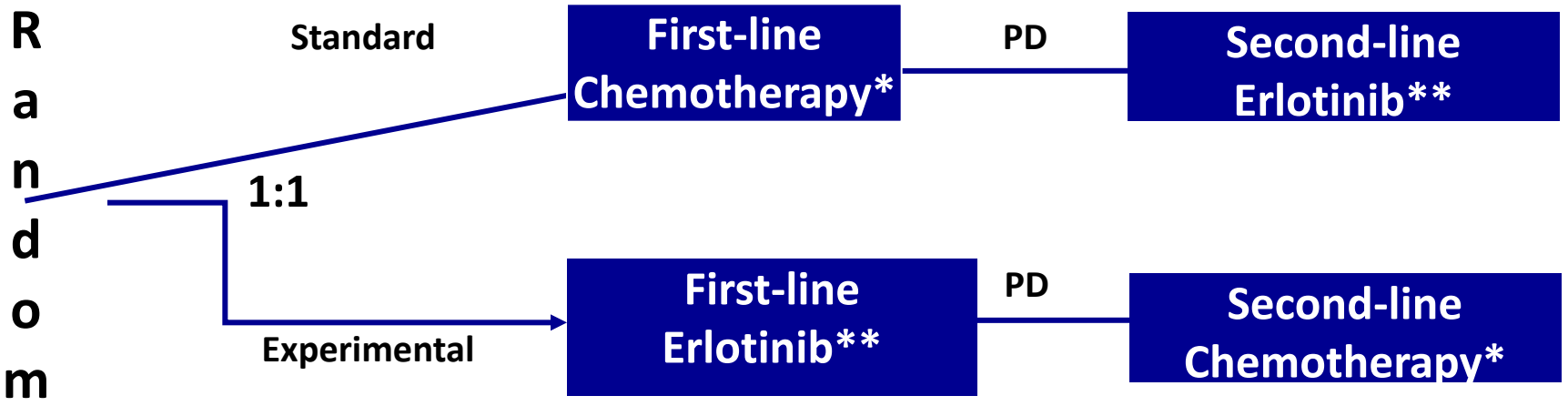
EGFR-TKIs superior to chemotherapy in second-line EGFR mutated NSCLC



M+, mutation positive; M-, mutation negative. EFR population

Douillard J-Y 2008

The risk of a wrong selection: the TORCH study



Strata:
- histology
- smoking status
- gender
- country (Italy, Canada)
- age
- ethnicity

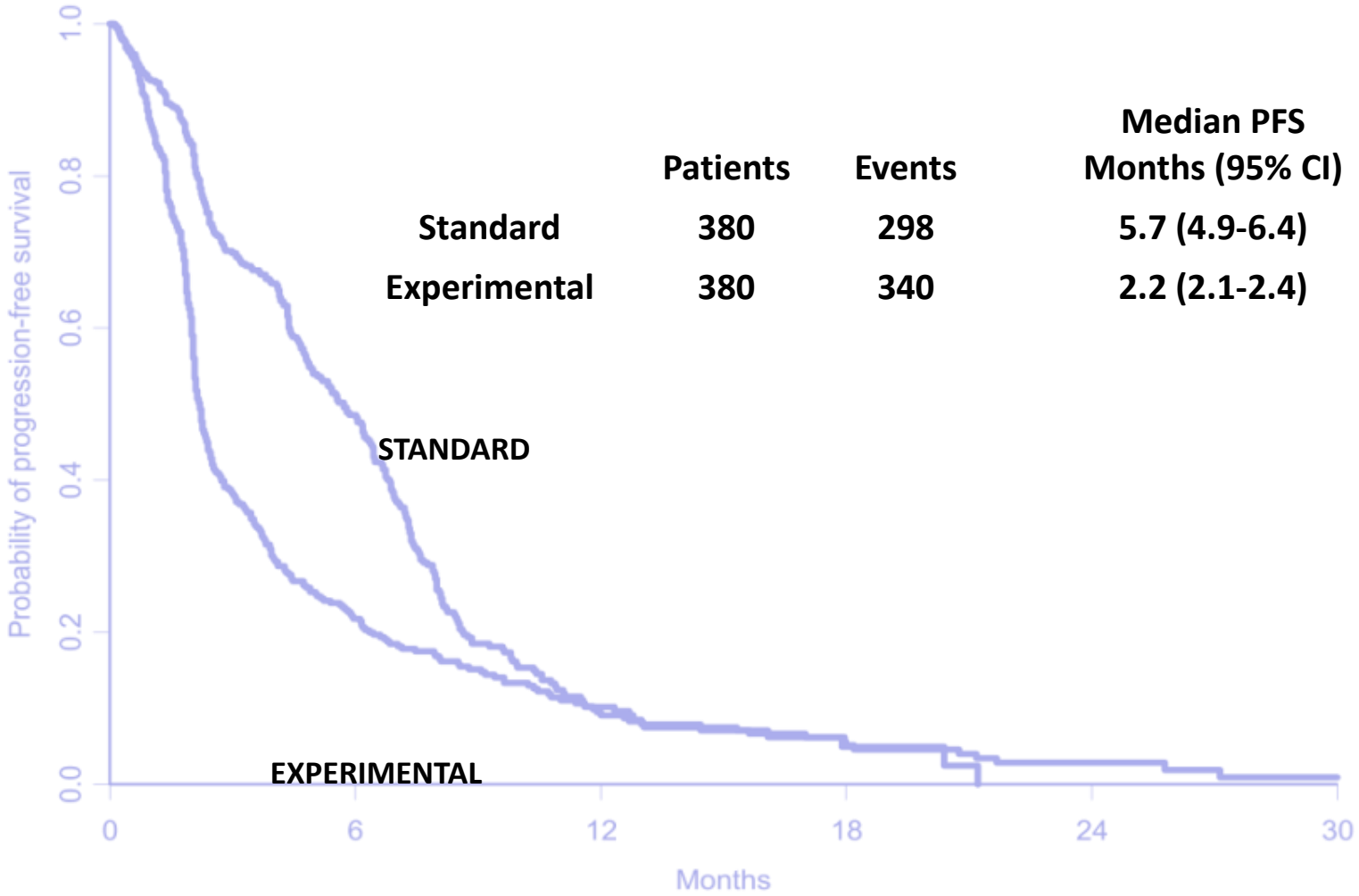
***Chemotherapy:**
- Cisplatin, 80 mg/m^2, day 1
- Gemcitabine, 1200 mg/m^2, day 1 and 8
- every 3 weeks, for 6 cycles

****Erlotinib:**
150 mg/day p.o. until progression

PRIMARY END-POINT: NON INFERIORITY FOR OS

Progression-free survival

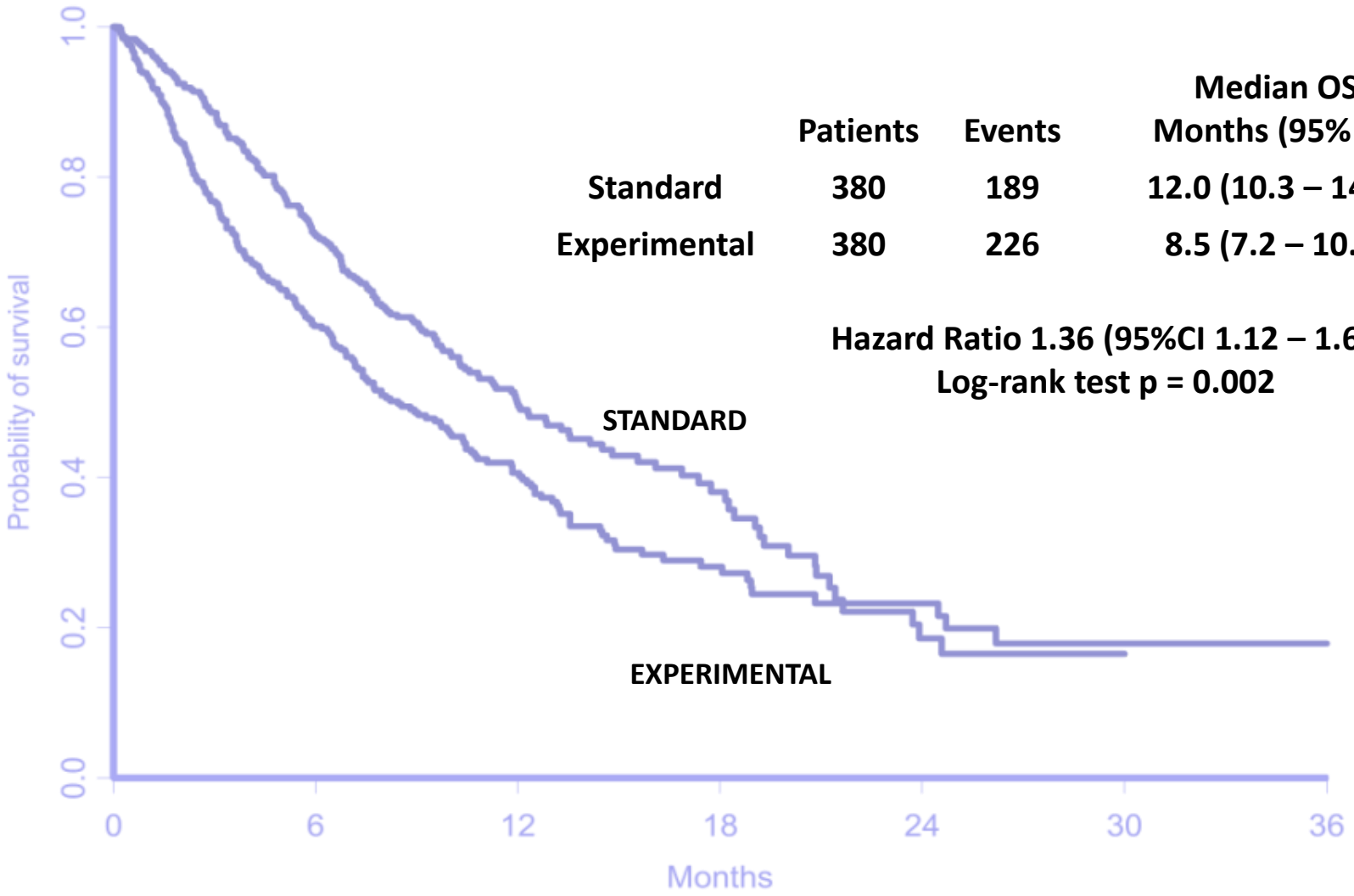
	Patients	Events	Median PFS Months (95% CI)
Standard	380	298	5.7 (4.9-6.4)
Experimental	380	340	2.2 (2.1-2.4)



Patients at risk						
Standard	380	151	23	5	-	-
Experimental	380	74	24	12	6	2

Gridelli C, et al. JCO 2012

Overall survival



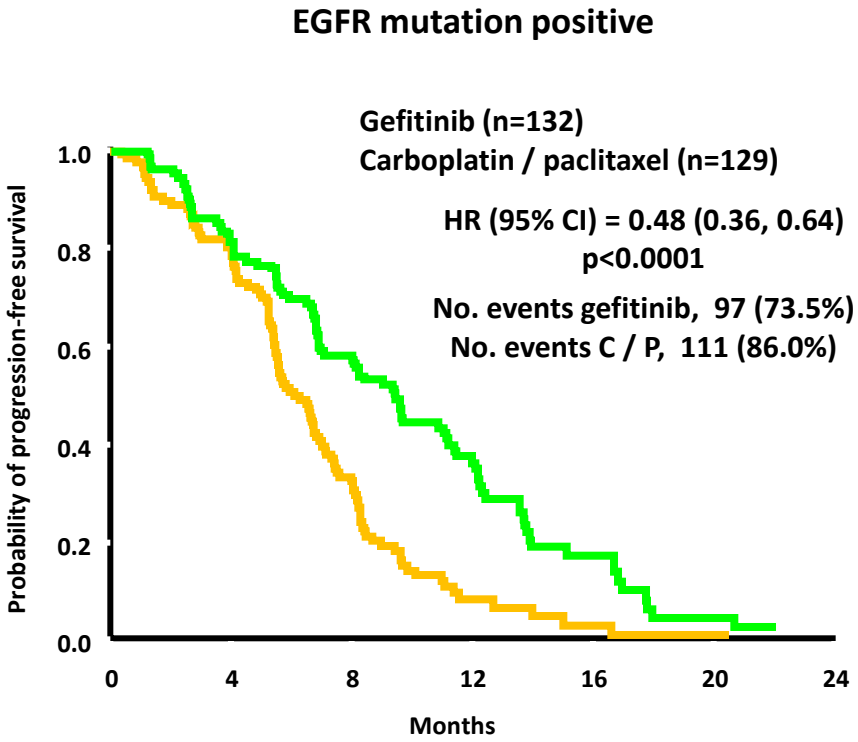
	Patients	Events	Median OS Months (95% CI)
Standard	380	189	12.0 (10.3 – 14.8)
Experimental	380	226	8.5 (7.2 – 10.5)

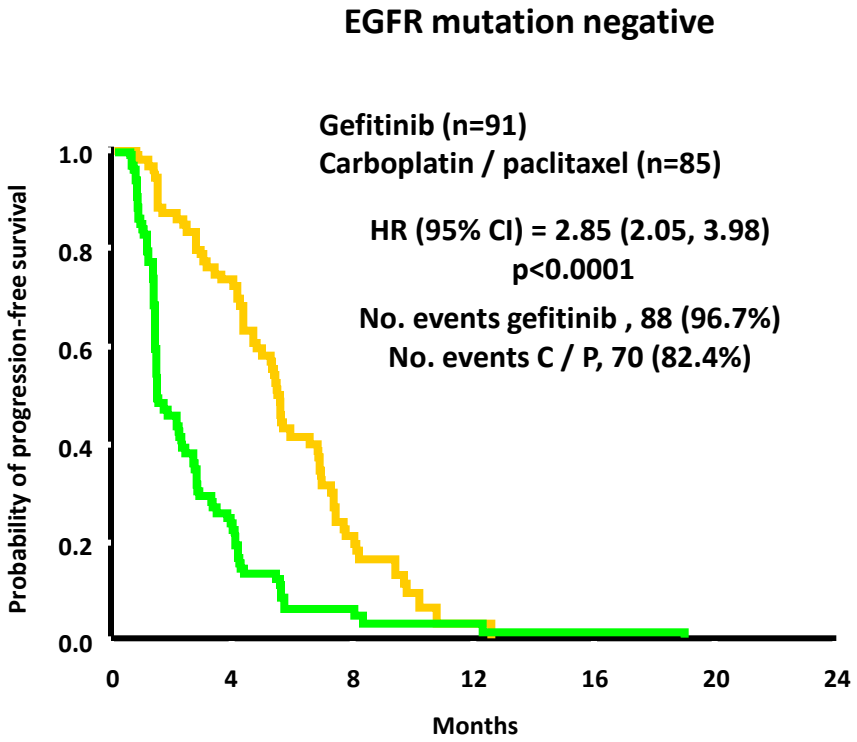
Hazard Ratio 1.36 (95%CI 1.12 – 1.65)
Log-rank test p = 0.002

Standard	380	226	108	34	11	1	
Experimental	380	197	88	34	16	4	2

Gridelli C, et al. JCO 2012

Detrimental effect of front-line gefitinib in EGFR wild-type NSCLC: IPASS results



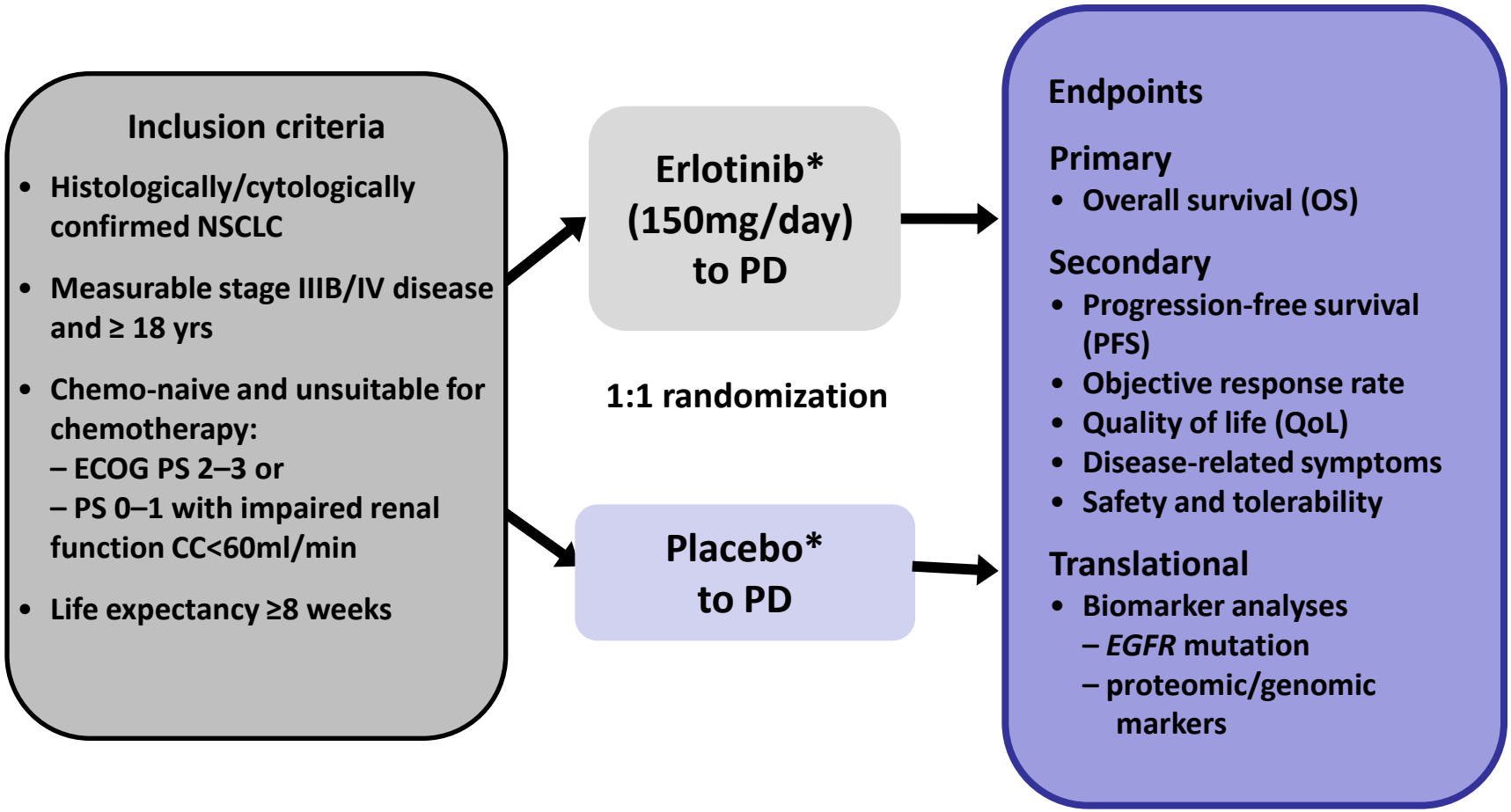


Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

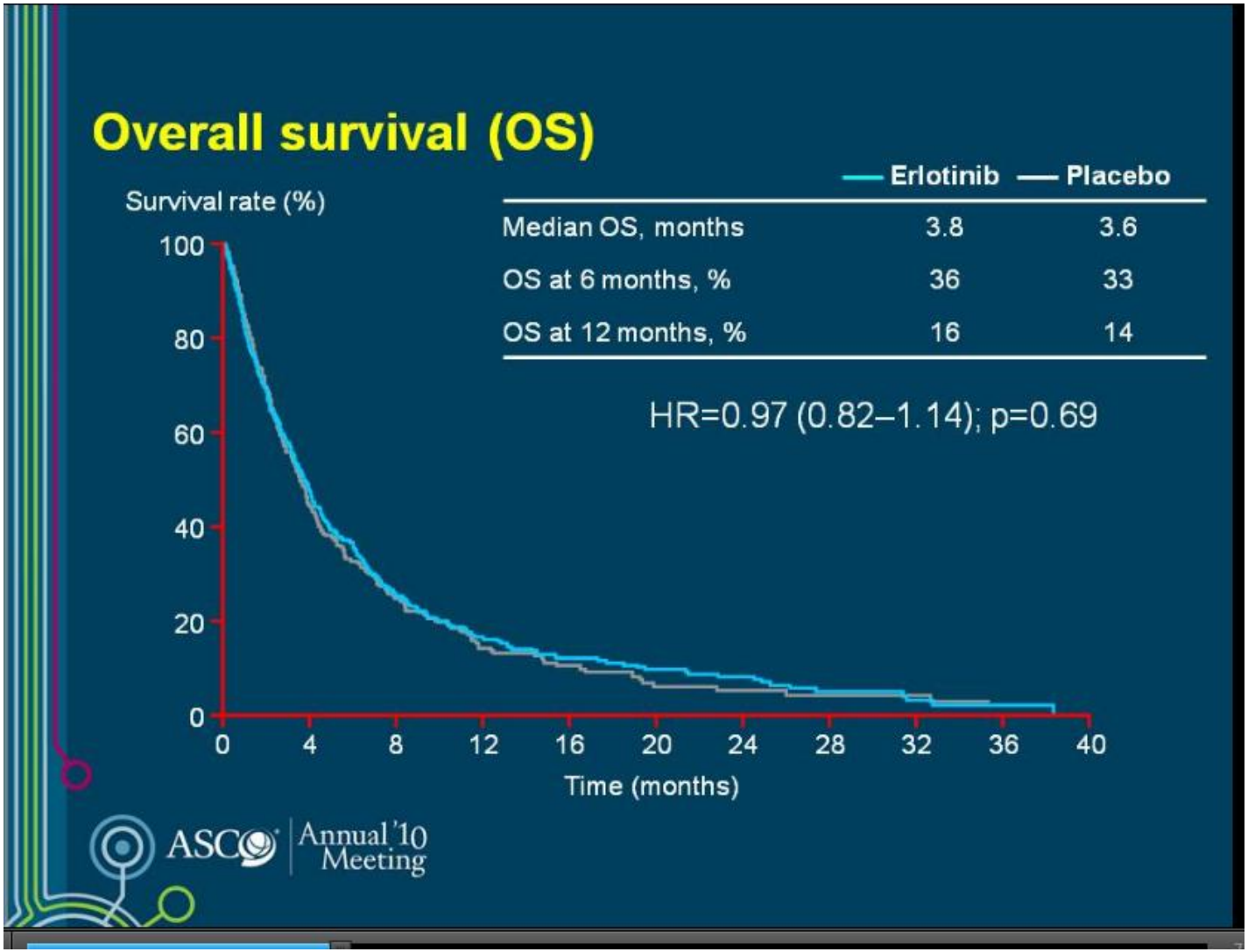
Mok TS, et al. NEJM 2009

Are EGFR-TKIs indicated front-line in unselected NSCLC unsuitable for standard CT? The TOPICAL study



Lee SM ASCO 2010

No survival difference versus placebo in unselected patients



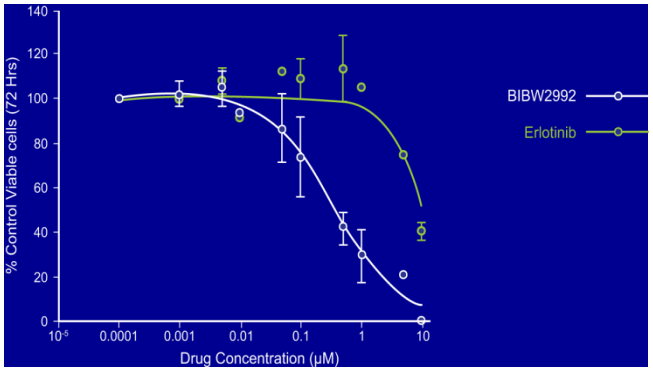
Lee SM ASCO 2010

Afatinib and Dacomitinib

Afatinib[1]

- Orally bioavailable, small molecule TKI
- Designed to irreversibly bind to the ATP binding pocket of EGFR and HER2
- Highly specific for EGFR and HER2
  - EGFR IC_{50}: 0.50nM
  - HER2 IC_{50}: 14nM

NCI-H1975



Dacomitinib[2]

- Irreversible inhibitor of the tyrosine kinases of EGFR (HER1), HER2, HER4
  - 'Pan-HER' inhibitor
- Preclinical activity against
  - *EGFR* sensitising mutations
  - *EGFR* T790M
  - wild-type HER2
  - mutant HER2

1. Li, et al. Oncogene 2008
2. Engleman, et al. Cancer Res 2008

Is response rate improved with irreversible EGFR-TKIs?

Comparison of best reported phase II results for EGFR TKIs in patients with *EGFR*-Mutant lung cancers (Exon 19 and Exon 21)

Agent	Entered, n	CR+PR Rate, %	Median PFS, months	Median OS, months
Dacomitinib	46	74	17	NR
Afatinib[1]	129[a]	66	15[b]	32–39
Erlotinib[2]	33	70	14	31
Gefitinib[3]	27	59		
Weighted pooled analysis median PFS in patients with EGFR-mutant lung cancers[4]				
Erlotinib (95% CI)	365[c]		13.2 (12.0–14.7)	
Gefitinib (95% CI)	1069[d]		9.8 (9.2–10.4)	

[a]51 treated first-line; [b]median PFS: 12 months on blind review;
[c]12 studies; [d]39 studies

NR, not reached; OS, overall survival

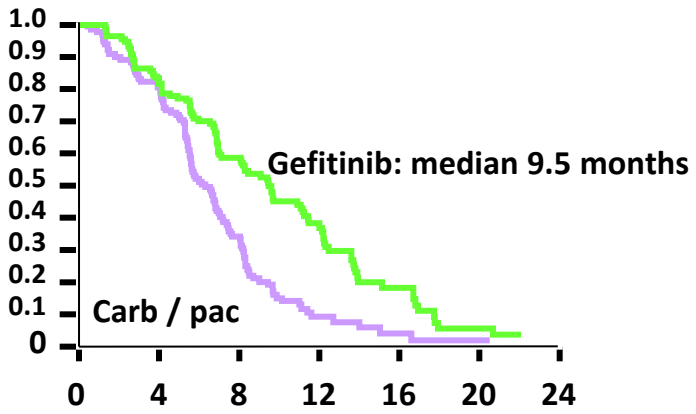
[1]Yang JC, *et al.* Lancet Oncol 2012;3: 539–48.
[2]Janne PA, *et al.* J Clin Oncol 2012;epub 30April.
[3]Sequist LV, *et al.* J Clin Oncol 2008;26: 2442–9
[4]Paz-Ares L, et al. *J Cell Mol Med* 2010;14:51–69.

Is PFS improved with irreversible EGFR-TKIs?

Indirect comparison in patients with classical EGFR mutations in first-line

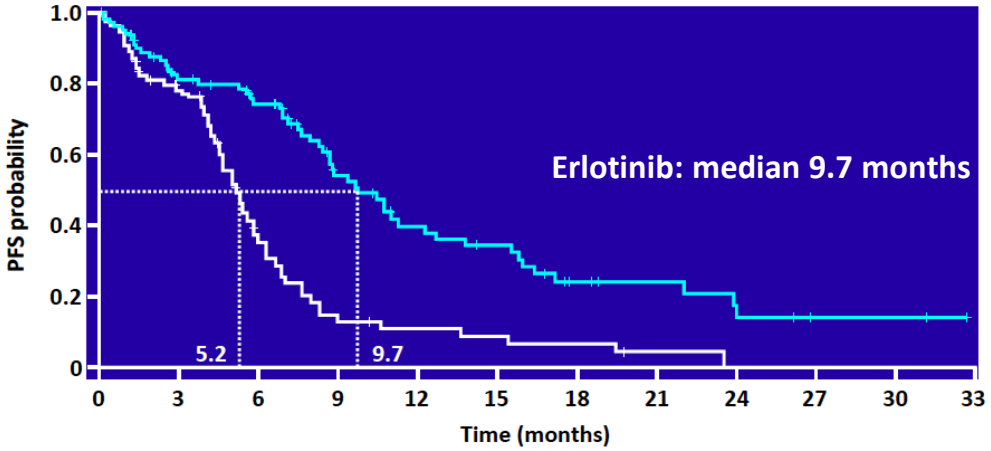
Gefitinib:IPASS

HR 0.48, p<0.0001

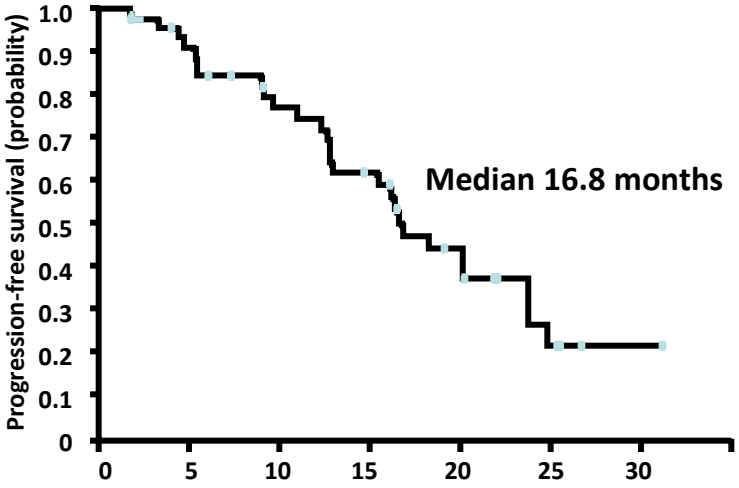


Erlotinib: EURTAC

HR 0.37, p<0.0001

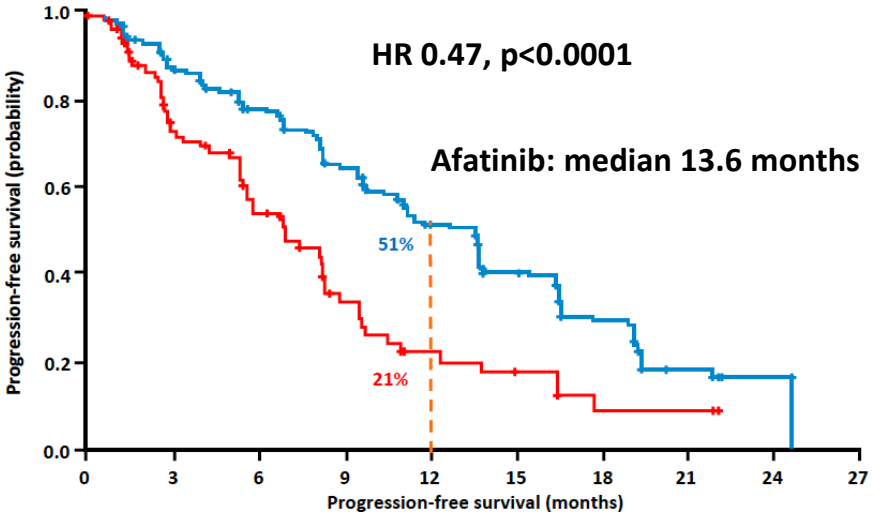


Dacomitinib:phase II



Afatinib:phase III

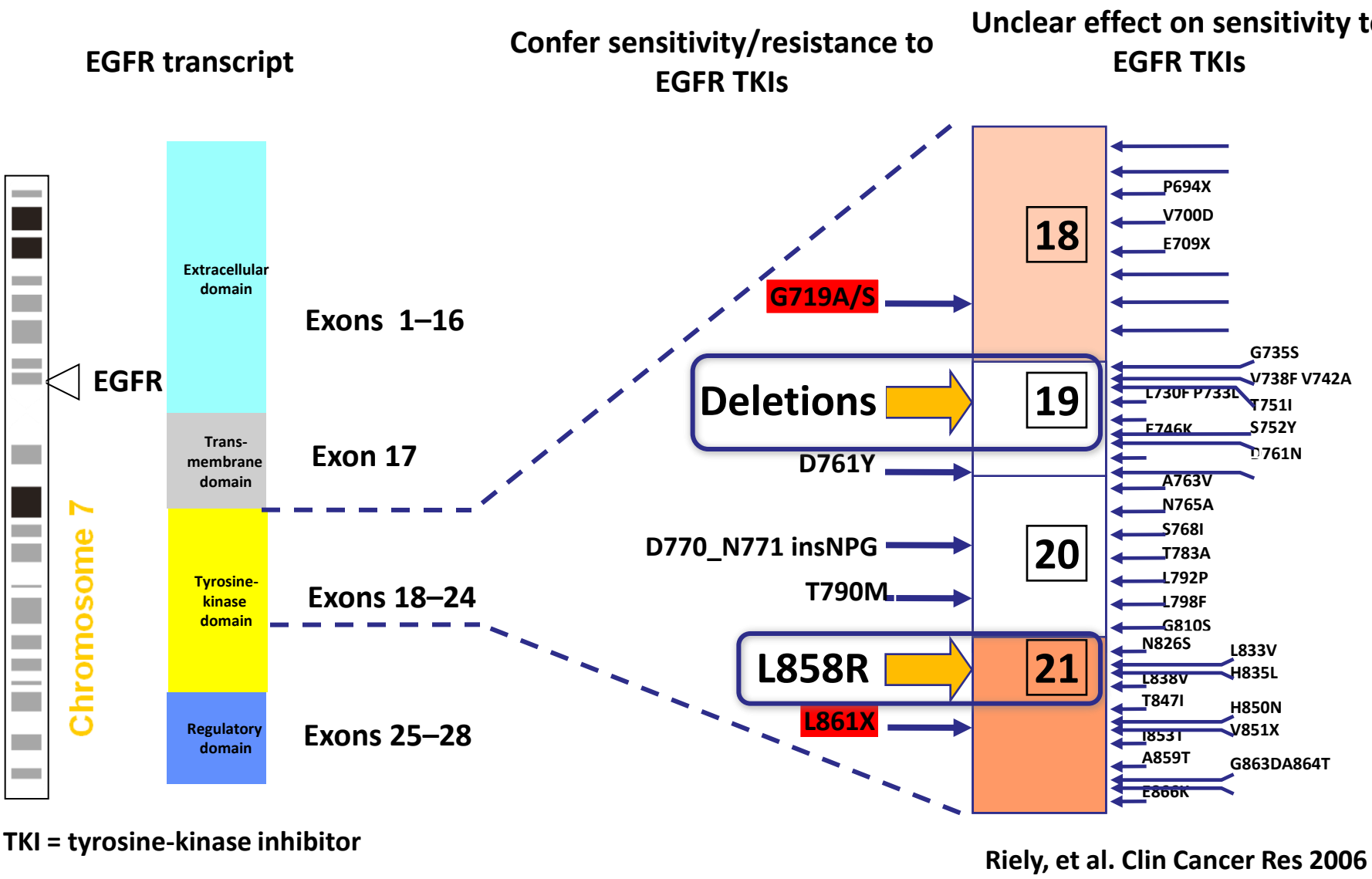
HR 0.47, p<0.0001



Indirect comparison of reversible versus irreversible EGFR-TKIs

	Gefitinib				Erlotinib		Afatinib
	NEJSG 002 n=114	IPASS n=607	First-SIGNAL n=159	WJTOG3405 n=87	OPTIMAL n=83	CALGB30406 n=81	LUX-3 n=229
Rash	71.0 (5.3)	66.2 (3.1)	72.3 (1.3)	74 (2)	73.5 (2.4)	NR (7.4)	37 (16.2)
Diarrhoea	34.2 (0.9)	46.6 (3.8)	NR	47(1)	25.3 (1.2)	NR (4.9)	33 (14.4)
Fatigue	10.5 (2.6)	NR	28.3 (0.6)	34 (2)	4.8 (0)	NR (1.2)	3 (1.3)
Anorexia	NR	21.9 (1.5)	44.7 (0)	NR	NR	NR	7 (3.1)
Stomatitis	9.6 (0)	17.0 (0.2)	NR	19 (0)	13.3 (1.2)	NR	20 (8.7)
Paronychia	NR	13.5 (0.3)	NR	28 (1)	3.6 (0)	NR	26 (11.4)
Vomiting	6.1 (0.9)	12.9 (0.2)	NR	NR	NR	NR	7 (3.1)

Mutations in the *EGFR* gene



TKI = tyrosine-kinase inhibitor

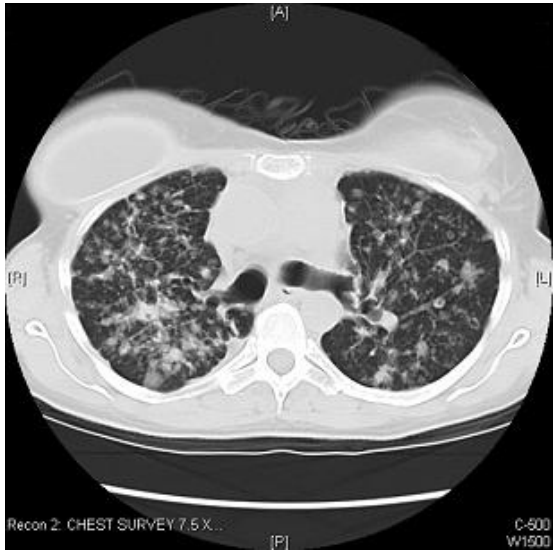
Riely, et al. Clin Cancer Res 2006

Efficacy of EGFR-TKIs in presence of uncommon mutations

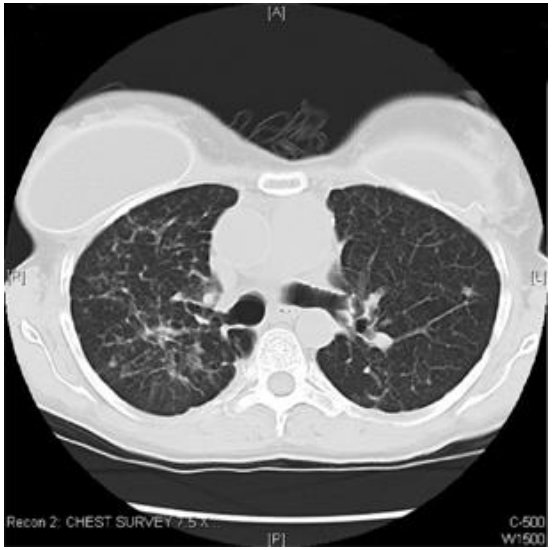
	Reversible EGFR-TKIs[1]				Afatinib [2,3,4]			
EGFR	N	RR (%)	PFS (months)	OS (months)	N	RR (%)	PFS (months)	OS (months)
Exon 19-21	278	74.1	8.5	19.6	308[4]	60.8	13.6	-
Wild-type	272	16.5	2.0	10.4	42[3]	0	1.0	7.2
Exon 20 insertion	11	0	1.4	4.8	20[2]	8.7	2.7	9.4
G719	15	53.3	8.1	16.4	18[2]	78.0	13.8	26.9
L861	15	60.0	6.0	15.2	16[2]	56.0	8.2	16.9
Other	15	20.0	1.6	11.1	1	100	-	-

[1]Wu J et al. Clin Cancer Res 2011;17:3812-3821; [2]Yang Y et al. WCLC 2013; [3] Ahn et al, ESMO 2012; [4]Sequist et al JCO 2013

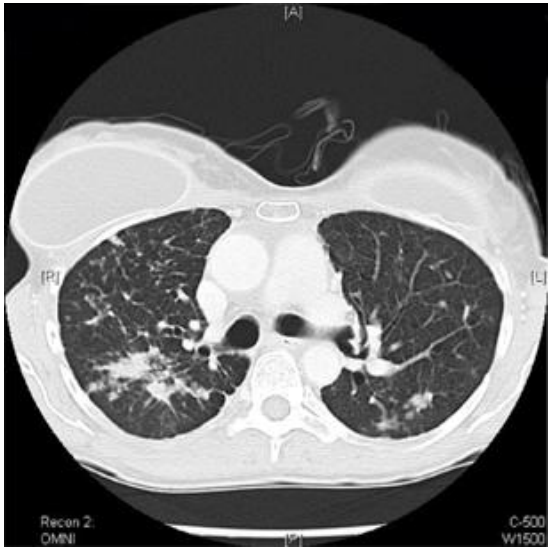
No cure with currently available targeted agents



Baseline



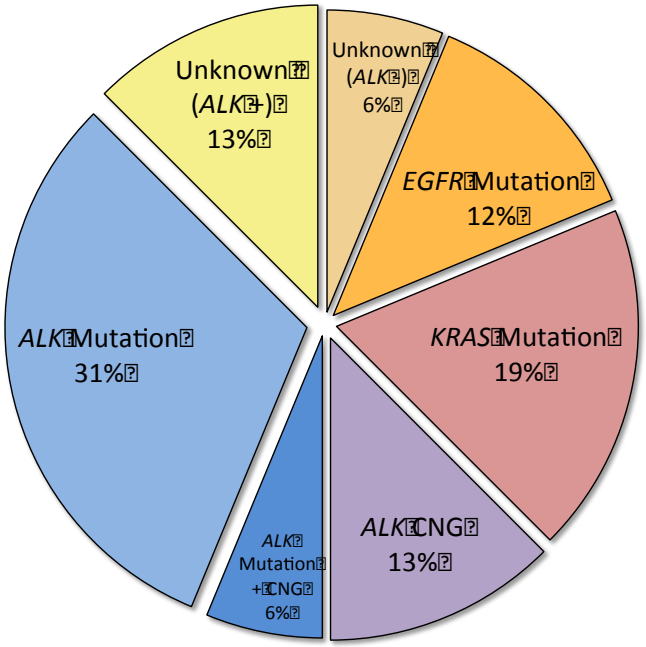
Tumor regression (RR up to 90%)



Progression (median 9 months)

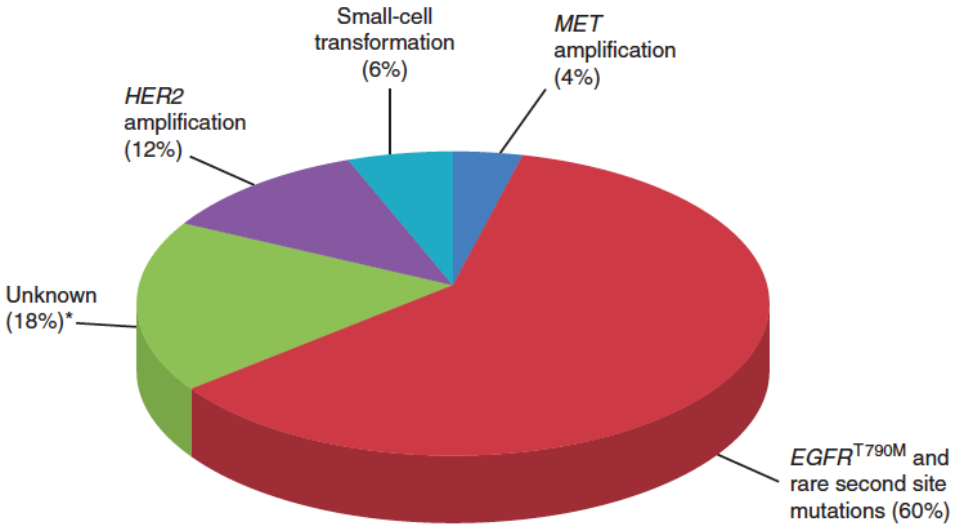
Mechanisms responsible for acquired resistance to crizotinib or EGFR-TKIs

Crizotinib resistance



Camidge R, ASCO 2013

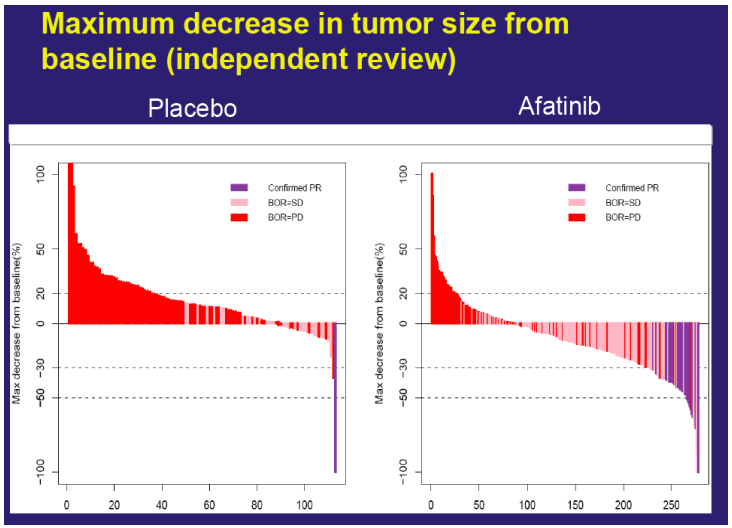
EGFR-TKI resistance



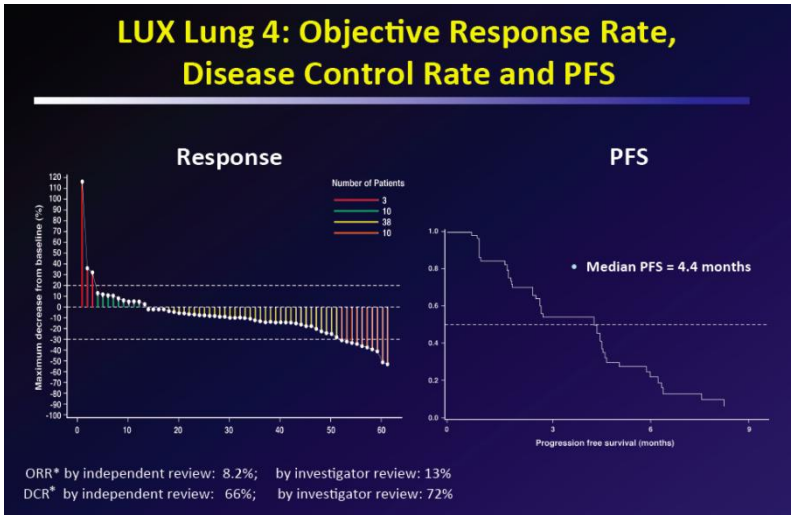
Takezawa et al. Cancer Discovery 2012

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

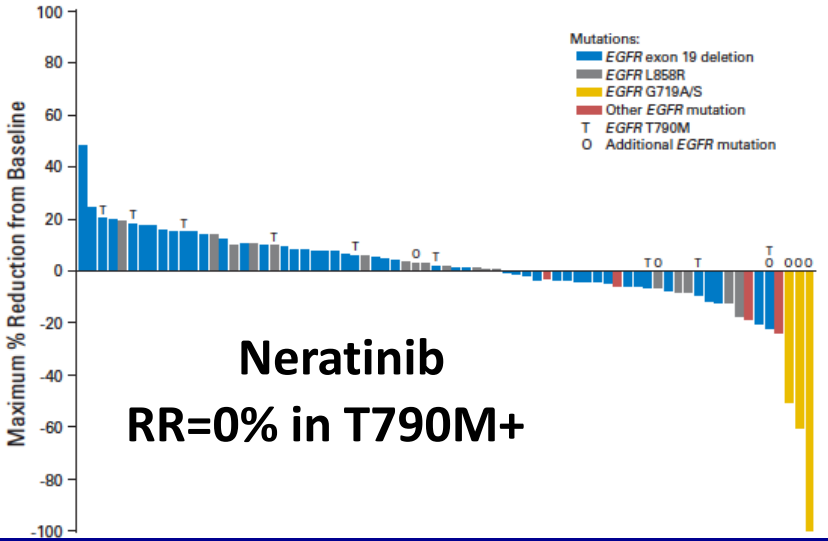
LUX LUNG 1: RR=7%



LUX LUNG 4: RR=8%

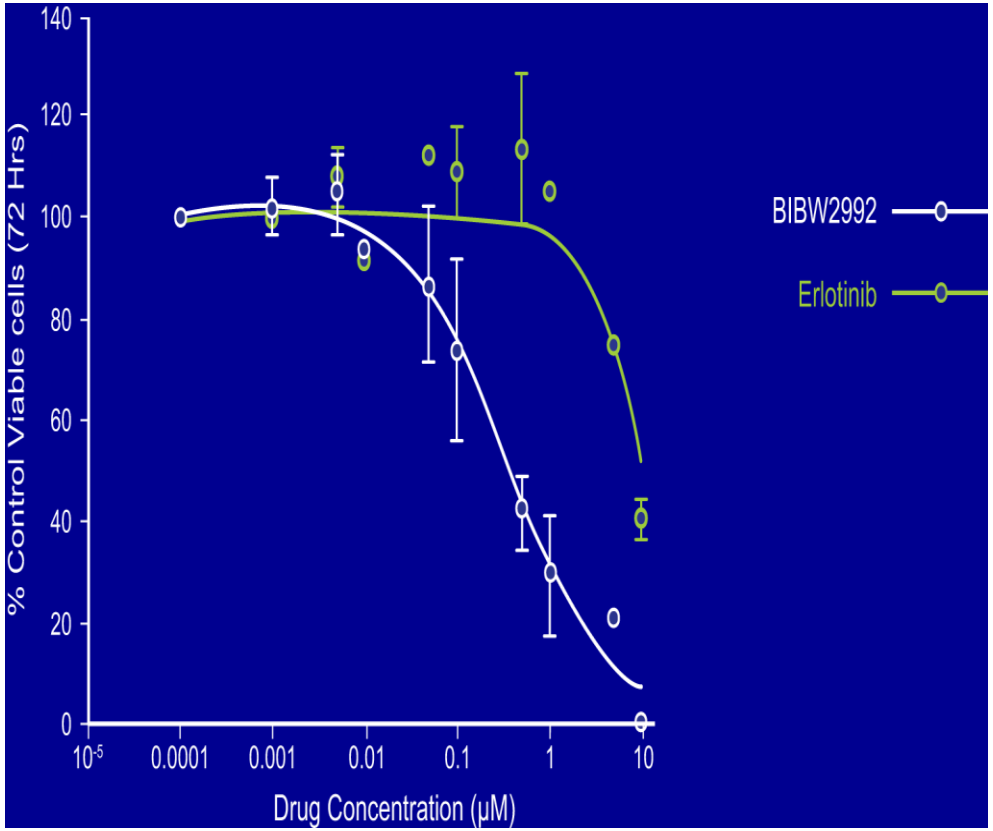


LUX-LUNG 2-3-6 trials	T790M
Response rate (%)	14.3
PFS (months)	2.9
OS (months)	14.9



Why irreversible inhibitors work against T790M in preclinical models only?

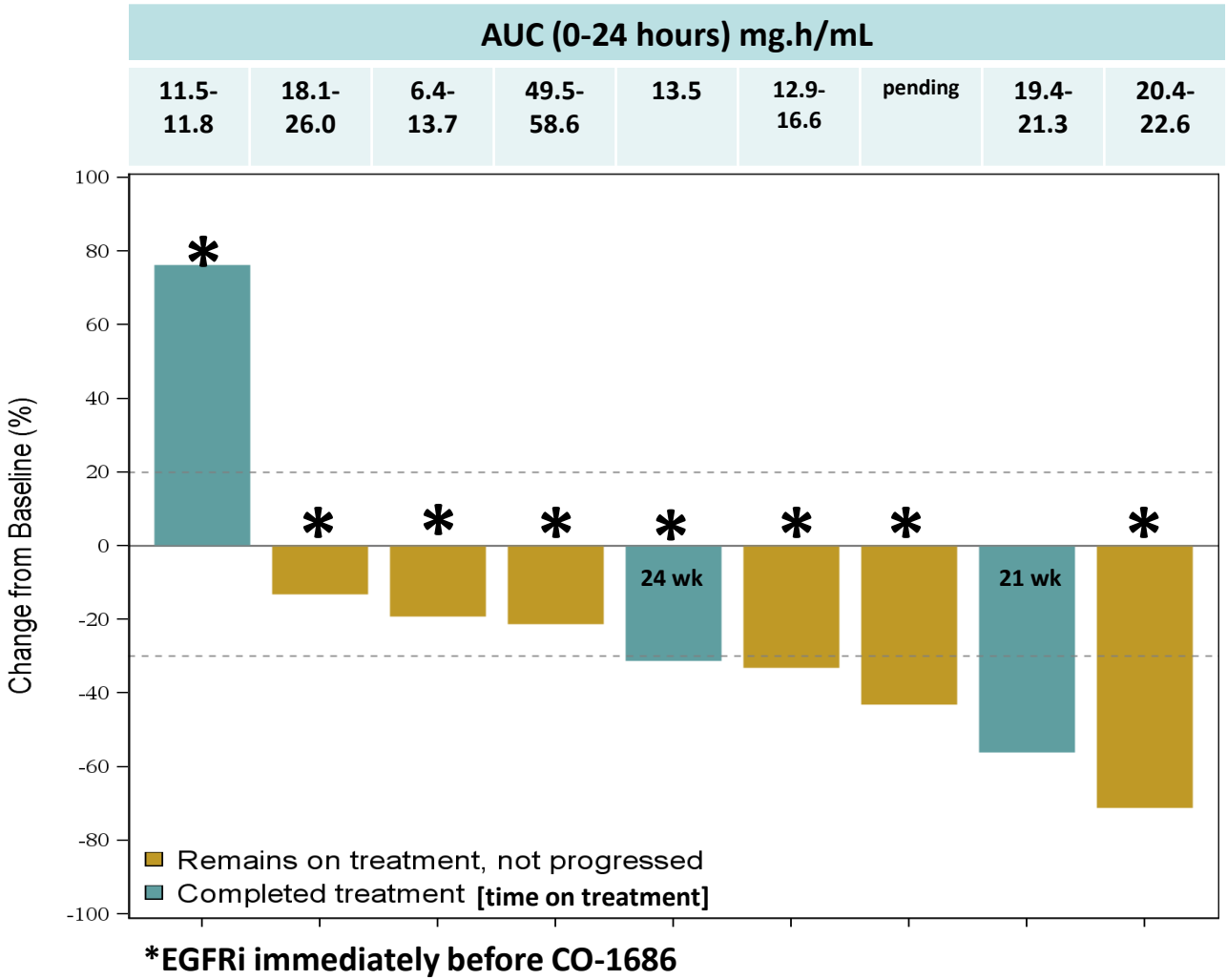
NCI-H1975



CO-1686 is a novel TKI specifically targeting mutated EGFR

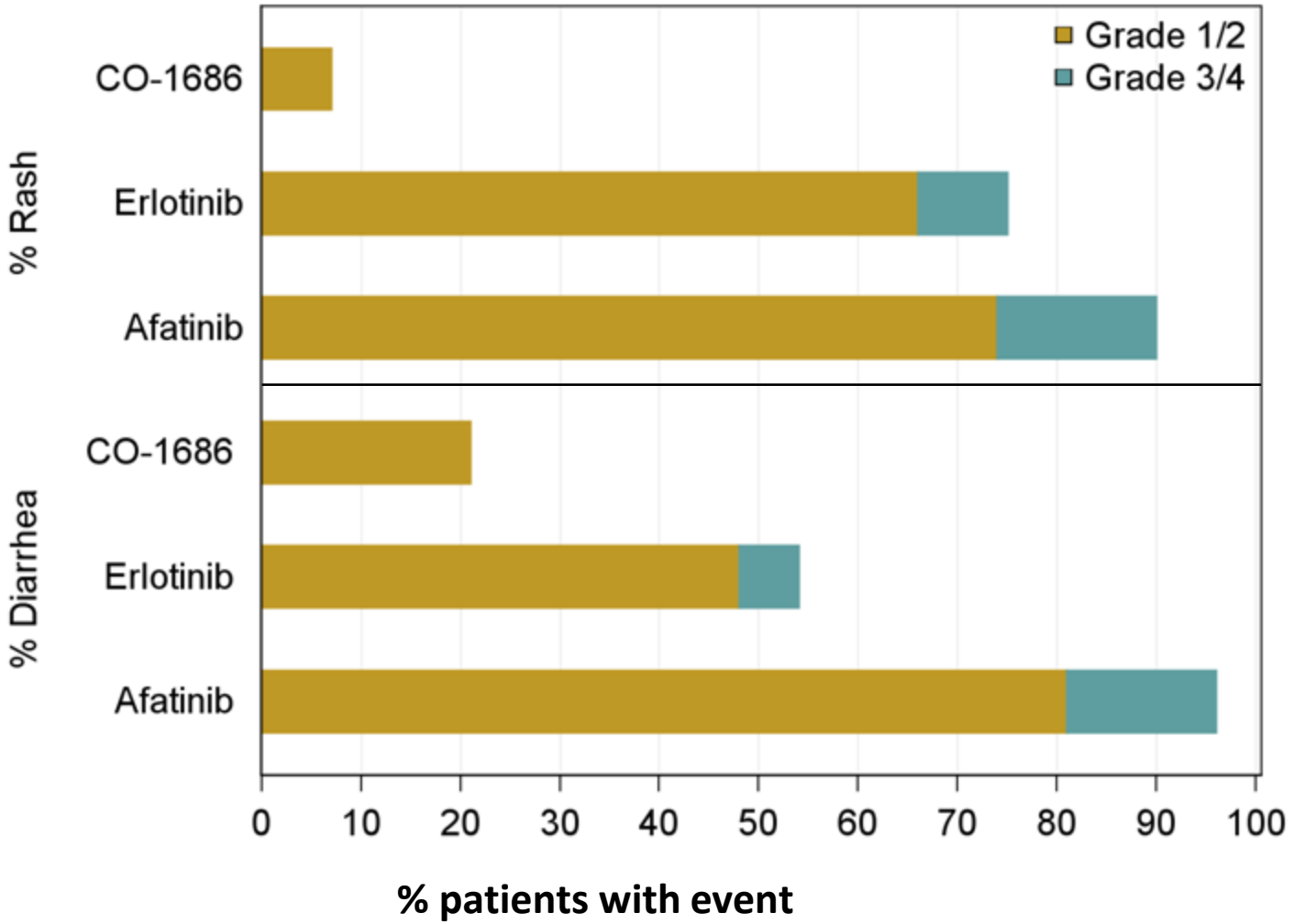
- **Novel, oral, selective covalent inhibitor of EGFR mutations in NSCLC**
  - **Inhibits key activating and T790M resistance mutations**
  - **Spares wild type receptor signaling**
- **First-in-human study ongoing in EGFR mutated patients with recurrent, advanced NSCLC**
  - **MTD has not yet been reached**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

RECIST PRs and significant tumor shrinkage in T790M+ patients at highest dose tested to date



*EGFRi immediately before CO-1686

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



Comparator data from US prescribing information

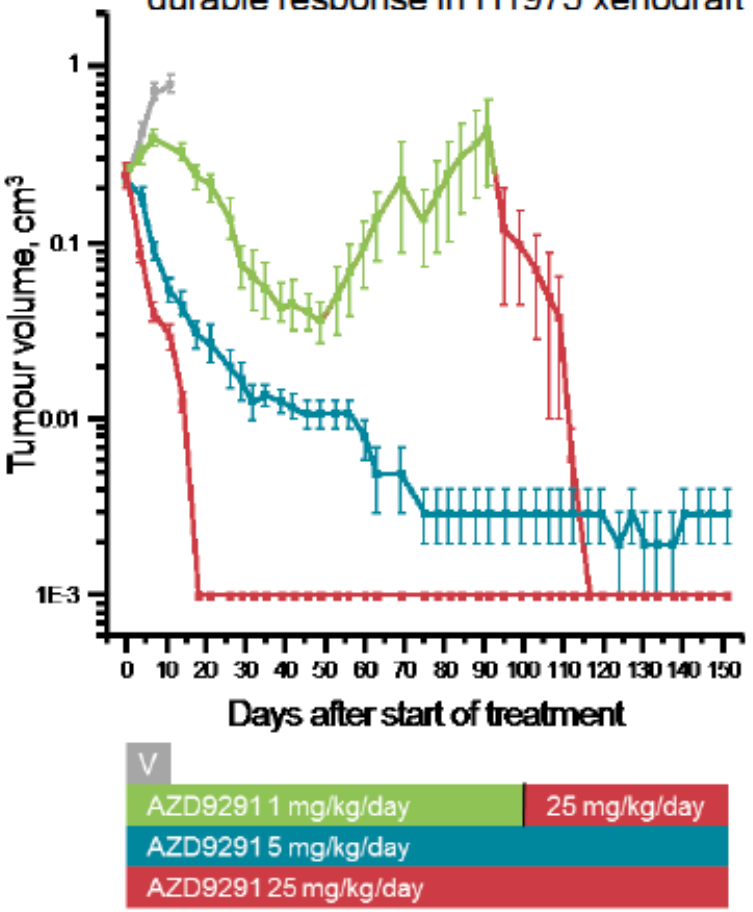
AZD9291: another irreversible EGFR-TKI potentially effective against T790M

- 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

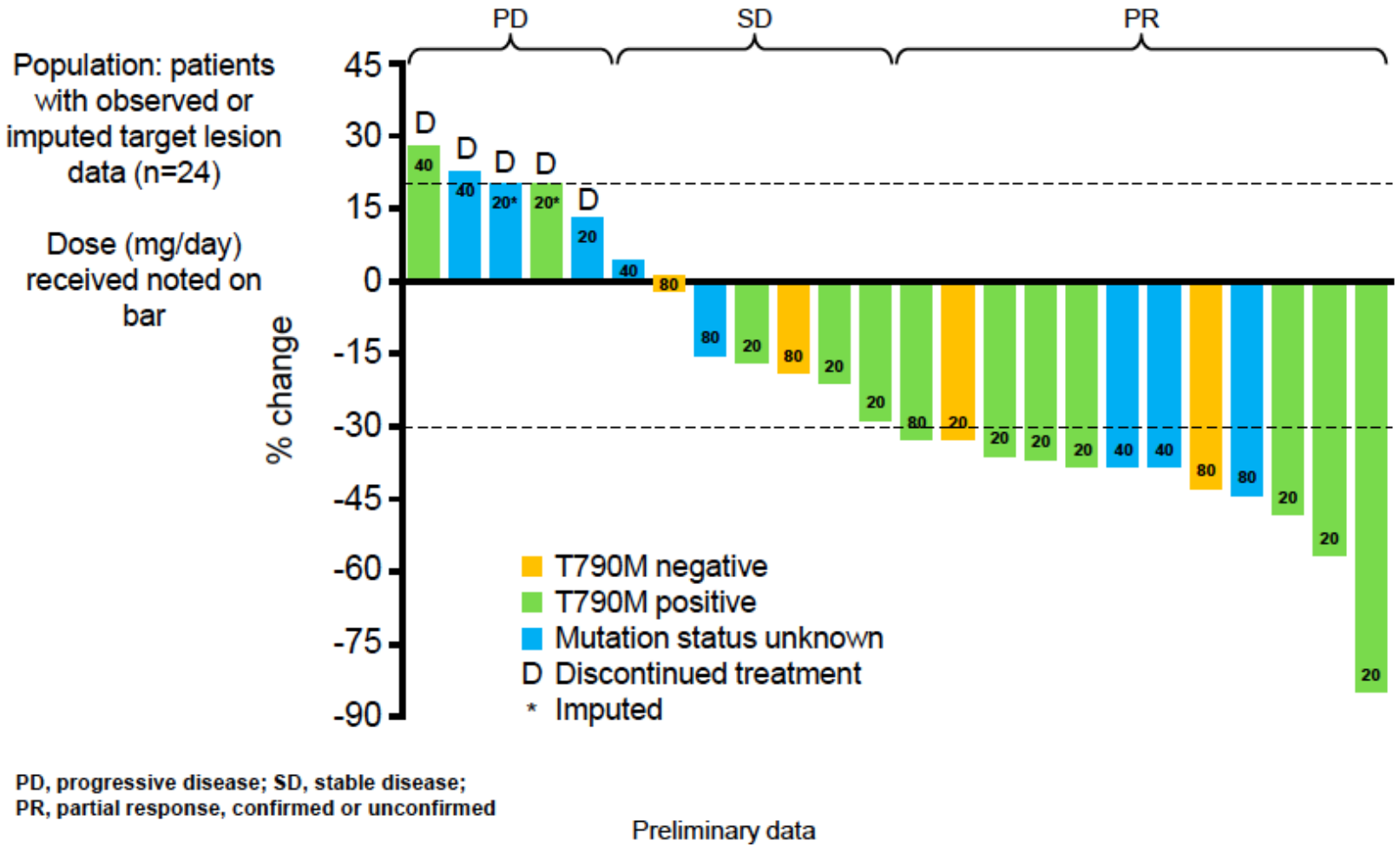
AstraZeneca data on file

AZD9291 achieved complete and durable response in H1975 xenograft



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

Clinical Development of Inhibitors of PD-1 Immune Checkpoint

Target	Agent	Molecule	Company	Development
PD-1	Nivolumab-BMS-936558	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II, III multiple tumors
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II multiple tumors
	Lambrolizumab MK-3475	Humanized IgG4 mAb	Merck	Phase I-II
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
PD-L1	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase I
	MedI-4736	Engineered human IgG1 mAb	MedImmune	Phase I
	MPDL-3280A	Engineered human IgG1 mAb	Genentech	Phase I-II

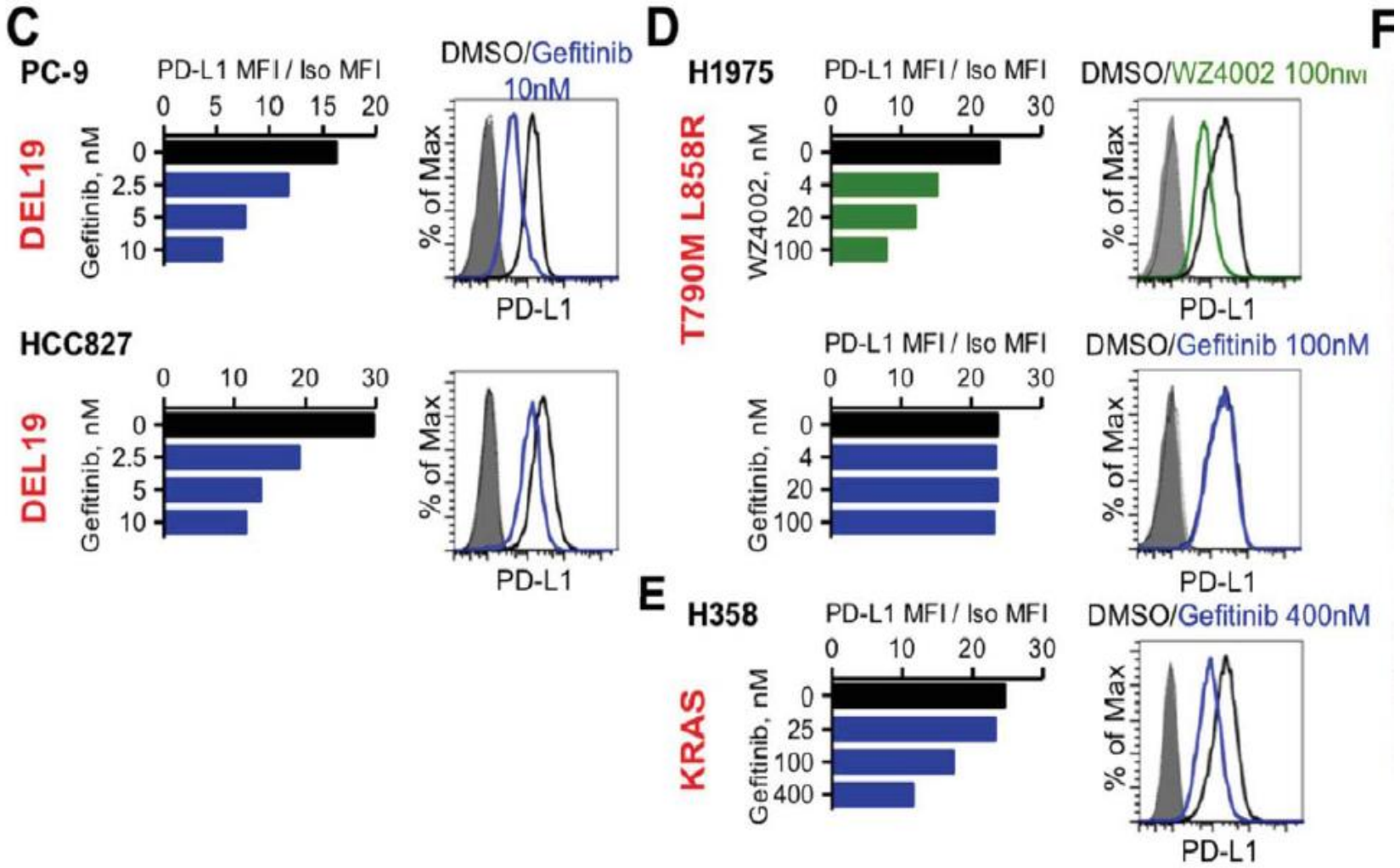
MPDL3280A Phase Ia: Best Response by PD-L1 IHC Status - NSCLC

Diagnostic Population[a] (n = 53)	ORR[b] % (n/n)	PD Rate % (n/n)
IHC 3	83% (5/6)	17% (1/6)
IHC 2 and 3	46% (6/13)	23% (3/13)
IHC 1/2/3	31% (8/26)	38% (10/26)
All Patients[c]	23% (12/53)	40% (21/53)

[a] IHC 3: ≥ 10% tumor immune cells positive for PD-L1 (IC+); IHC 2 and 3: ≥ 5% tumor immune cells positive for PD-L1 (IC+); IHC 1/2/3: ≥ 1% tumor immune cells positive for PD-L1 (IC+); IHC 0/1/2/3: all patients with evaluable PD-L1 tumor IC status.
[b] ORR includes investigator-assessed unconfirmed and confirmed PR.
[c] All patients includes patients with IHC 0/1/2/3 and 7 patients have an unknown diagnostic status.
Patients first dosed at 1-20 mg/kg by Oct 1, 2012; data cutoff Apr 30, 2013.

Soria et al et al. ESMO 2013

Reduction in PD-L1 expression in NSCLC cell lines exposed to EGFR-TKIs



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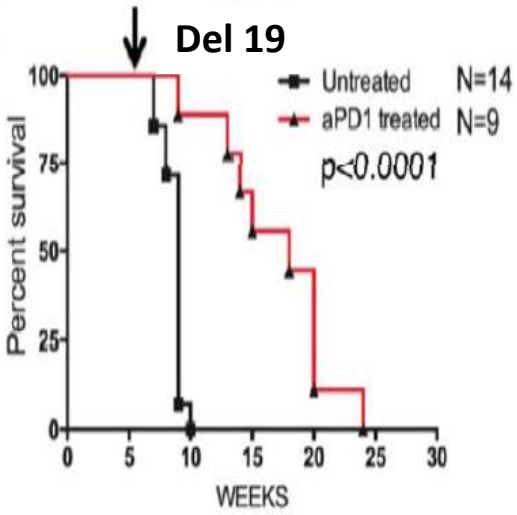
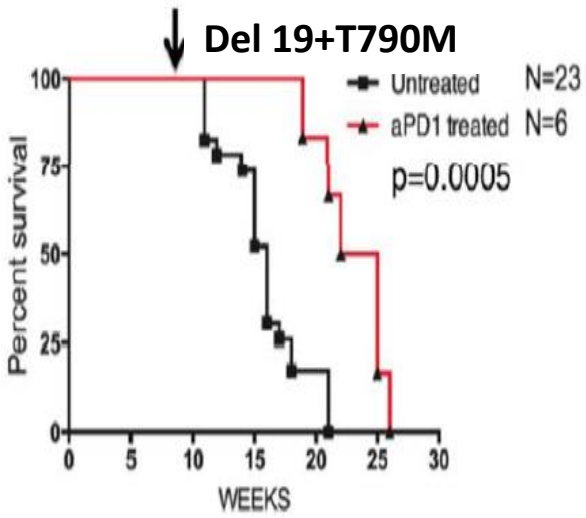
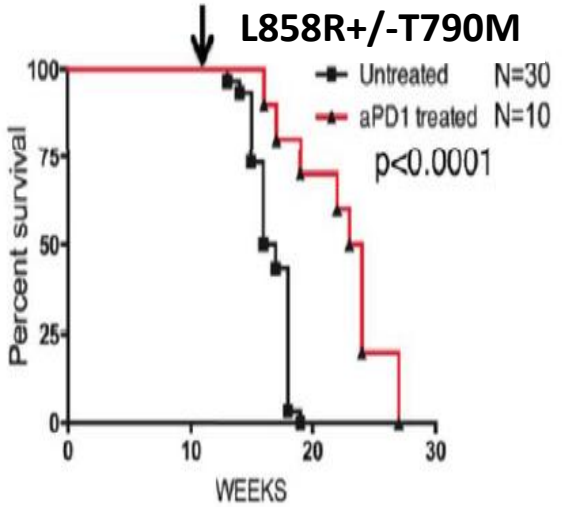
High efficacy of anti-PD1 agents in presence of EGFR mutations in mouse models







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Conclusions

- **EGFR-TKIs are the best option in patients with activating EGFR mutations irrespective of therapy line**
- **EGFR-TKIs are contraindicated front-line in unselected (EGFR wild-type or unknown) patients or in presence of mutations with unknown significance**
- **No agent currently available against T790M**
- **New drugs and new strategies currently under investigation to overcome acquired resistance**
- **Strong rationale for combining anti-EGFR agents with checkpoint inhibitors particularly in EGFR mutant NSCLC**