Challenges in the design of the next generation of clinical trials

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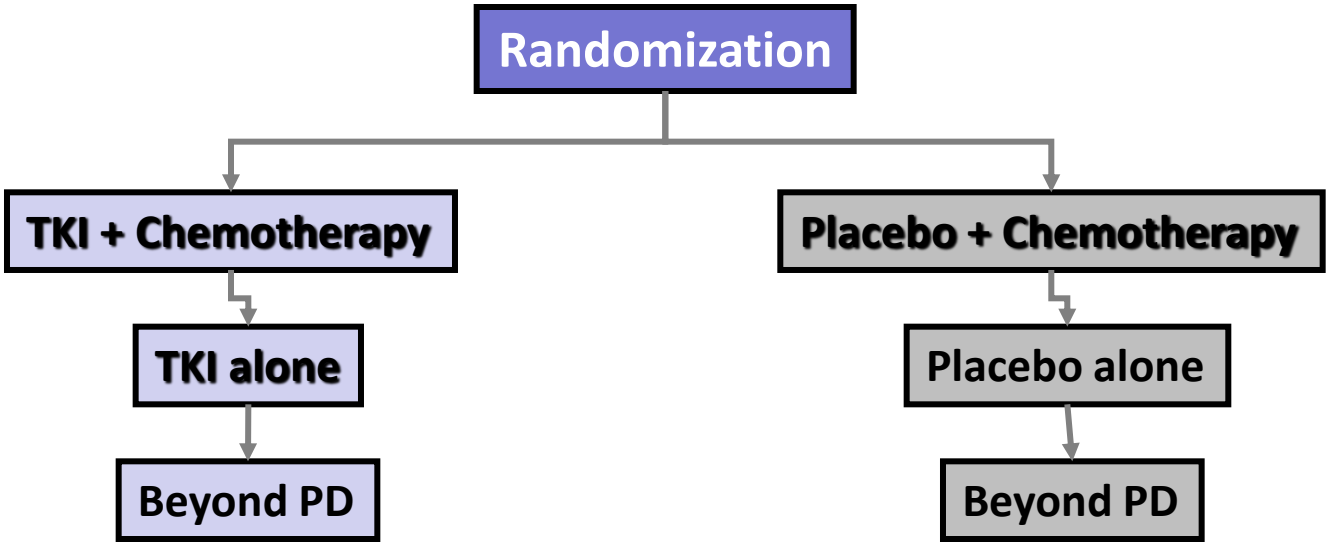
Example of phase III trials with new targeted agents in unselected NSCLC

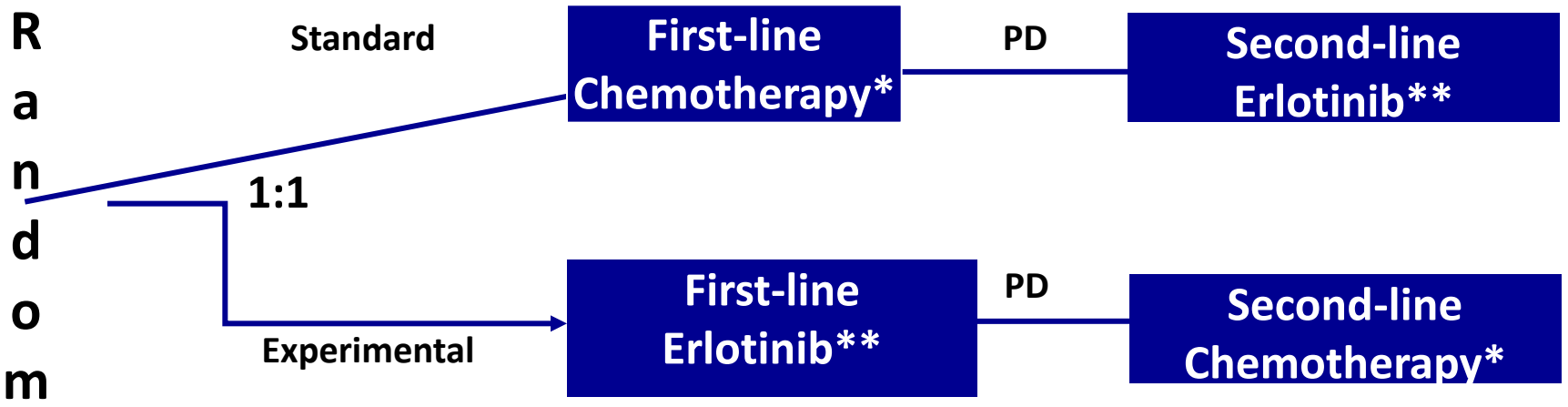
Agent	Phase	Effect on Survival
Gefitinib	III	No
Erlotinib	III	No
Cetuximab	III	Yes/minimal
Bevacizumab	III	Yes/no
Bexarotene	III	No
Sorafenib	III	No
Figitumumab	III	No
ASA 404	III	No

Chemotherapy alone versus Chemotherapy + EGFR TKI: Phase III Trials



- 4 trials so far conducted (INTACT 1&2, TRIBUTE, TALENT)
- More than 1000 patients enrolled in each study
- No survival advantage for TKI plus chemotherapy
- No patient selection

The risk of a wrong selection: the TORCH study



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

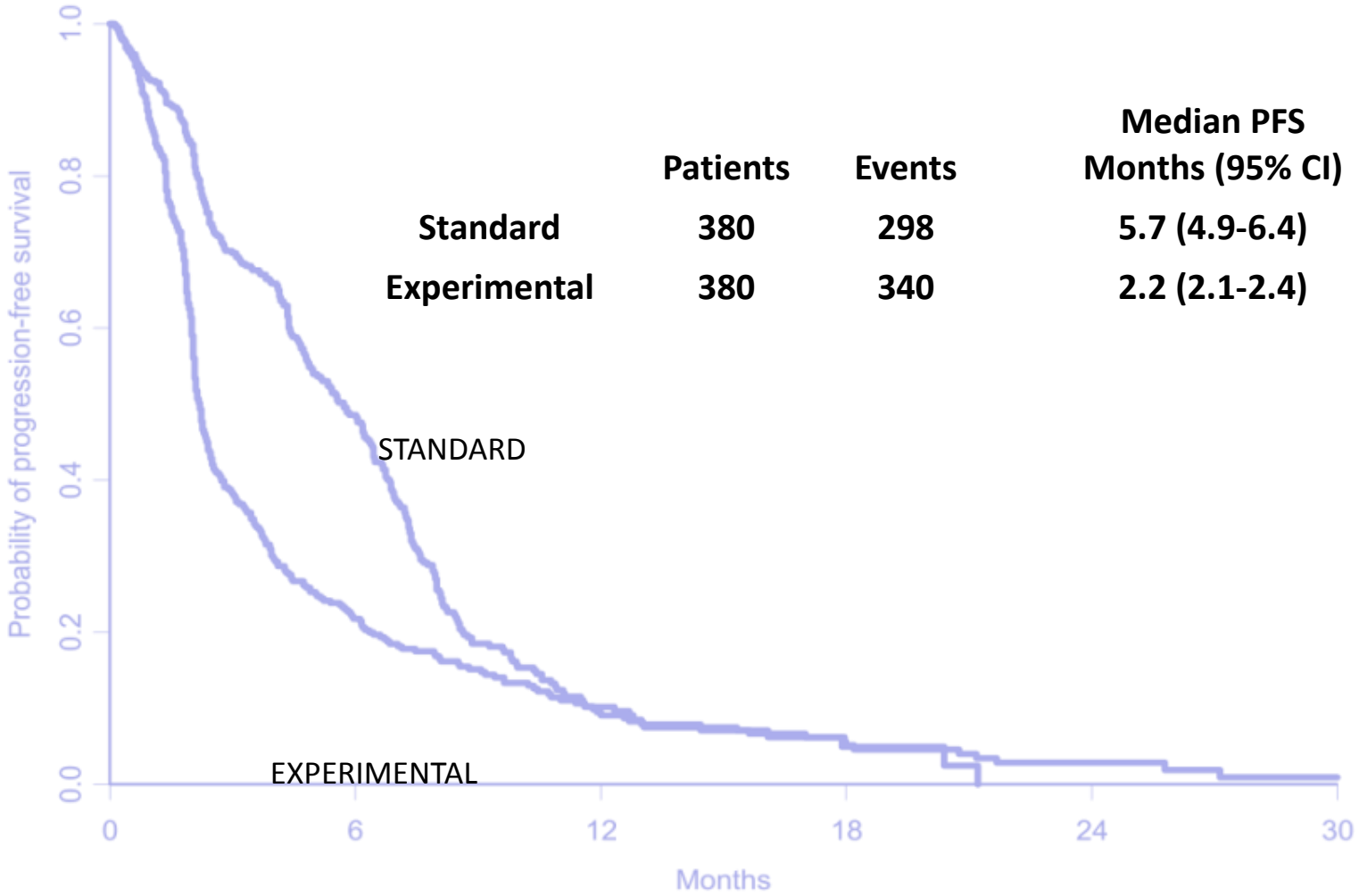
***Chemotherapy:**
- Cisplatin, 80 mg/m^2, day 1
- Gemcitabine, 1200 mg/m^2, day 1 and 8
- every 3 weeks, for 6 cycles

****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)



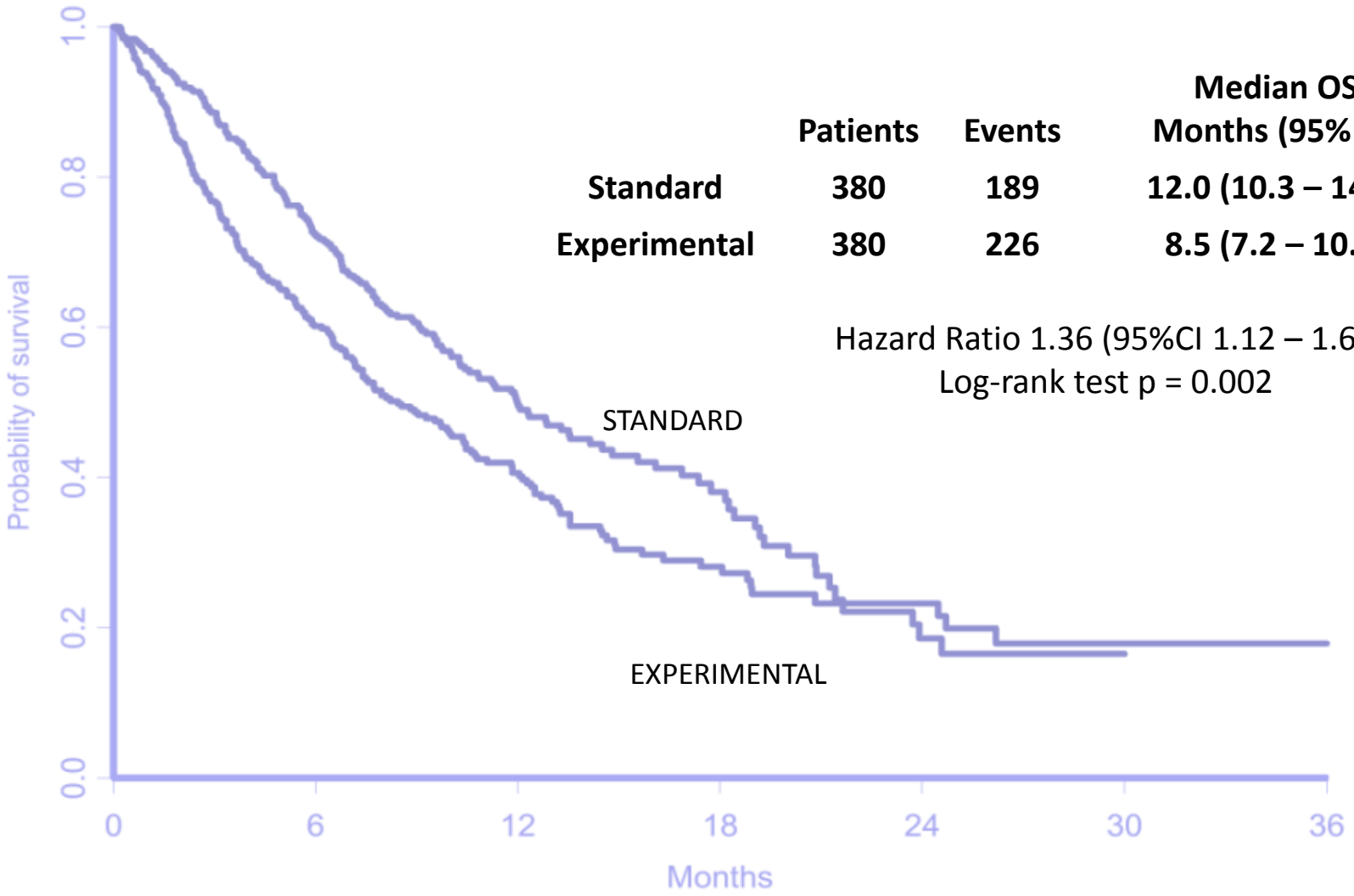
Patients at risk						
Standard	380	151	23	5	-	-
Experimental	380	74	24	12	6	2

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

IPASS: Study Design

Patients

- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

Gefitinib (250 mg / day)

1:1 randomization

Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m^2) 3 weekly#

Endpoints

Primary

- Progression-free survival (non-inferiority)

Secondary

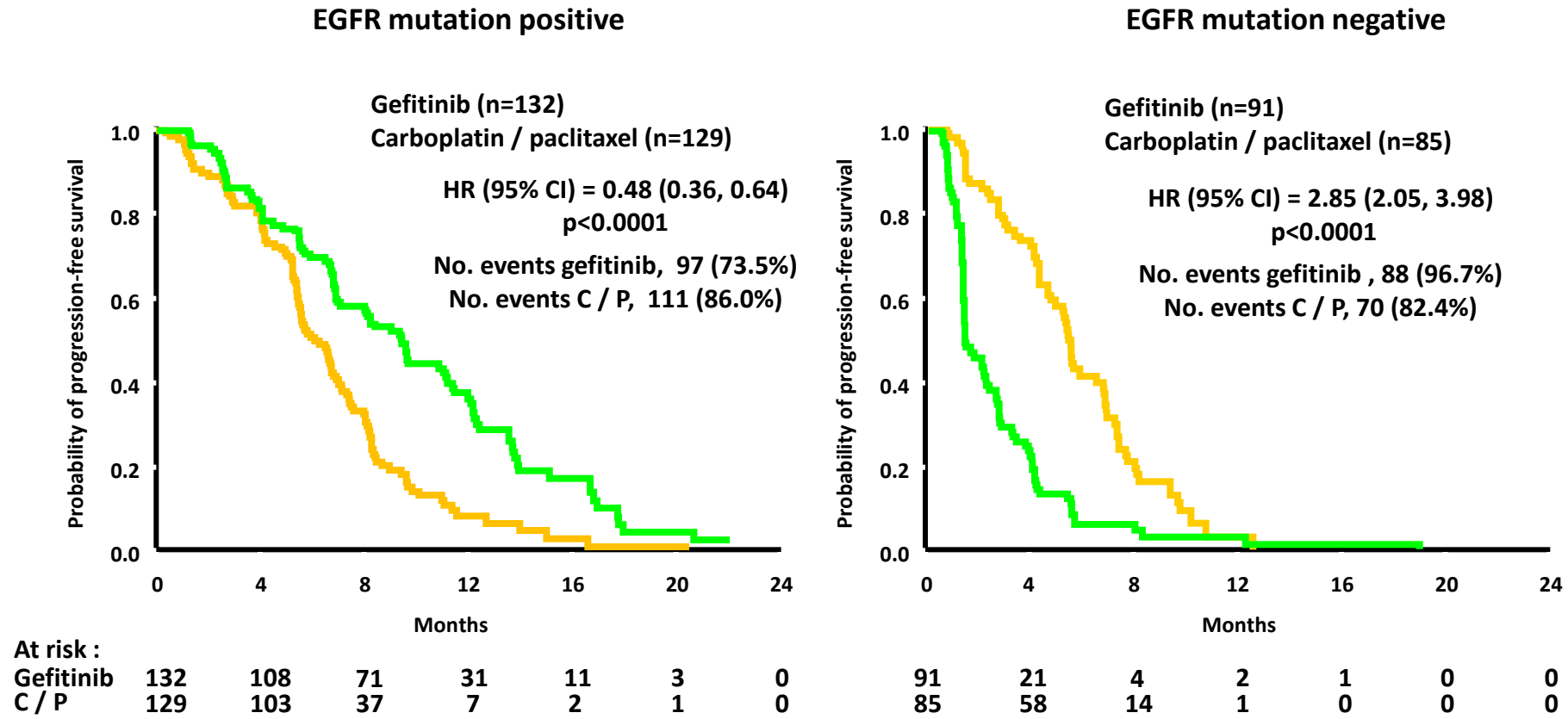
- Objective response rate
- Overall survival
- Quality of life
- Disease-related symptoms
- Safety and tolerability

Exploratory

- Biomarkers
  - EGFR mutation
  - EGFR-gene-copy number
  - EGFR protein expression

*Never smokers, <100 cigarettes in lifetime; light ex-smokers, stopped ≥15 years ago and smoked ≤10 pack years;
#limited to a maximum of 6 cycles
Carboplatin / paclitaxel was offered to gefitinib patients upon progression
PS, performance status; EGFR, epidermal growth factor receptor

Progression-free Survival in EGFR Mutation Positive and Negative Patients

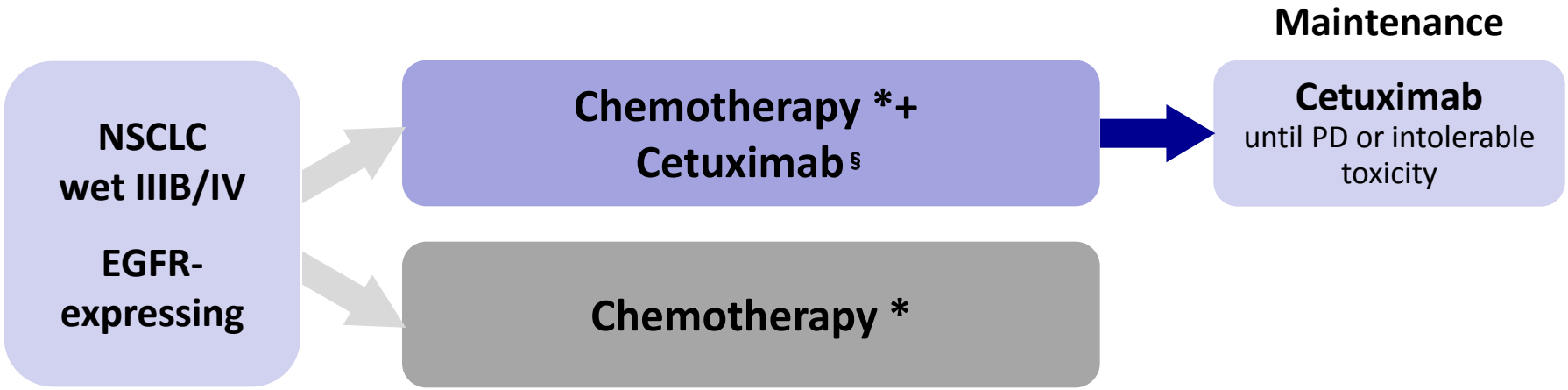


Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

Mok TS, et al. NEJM 2009

Cetuximab in NSCLC: FLEX Study Design



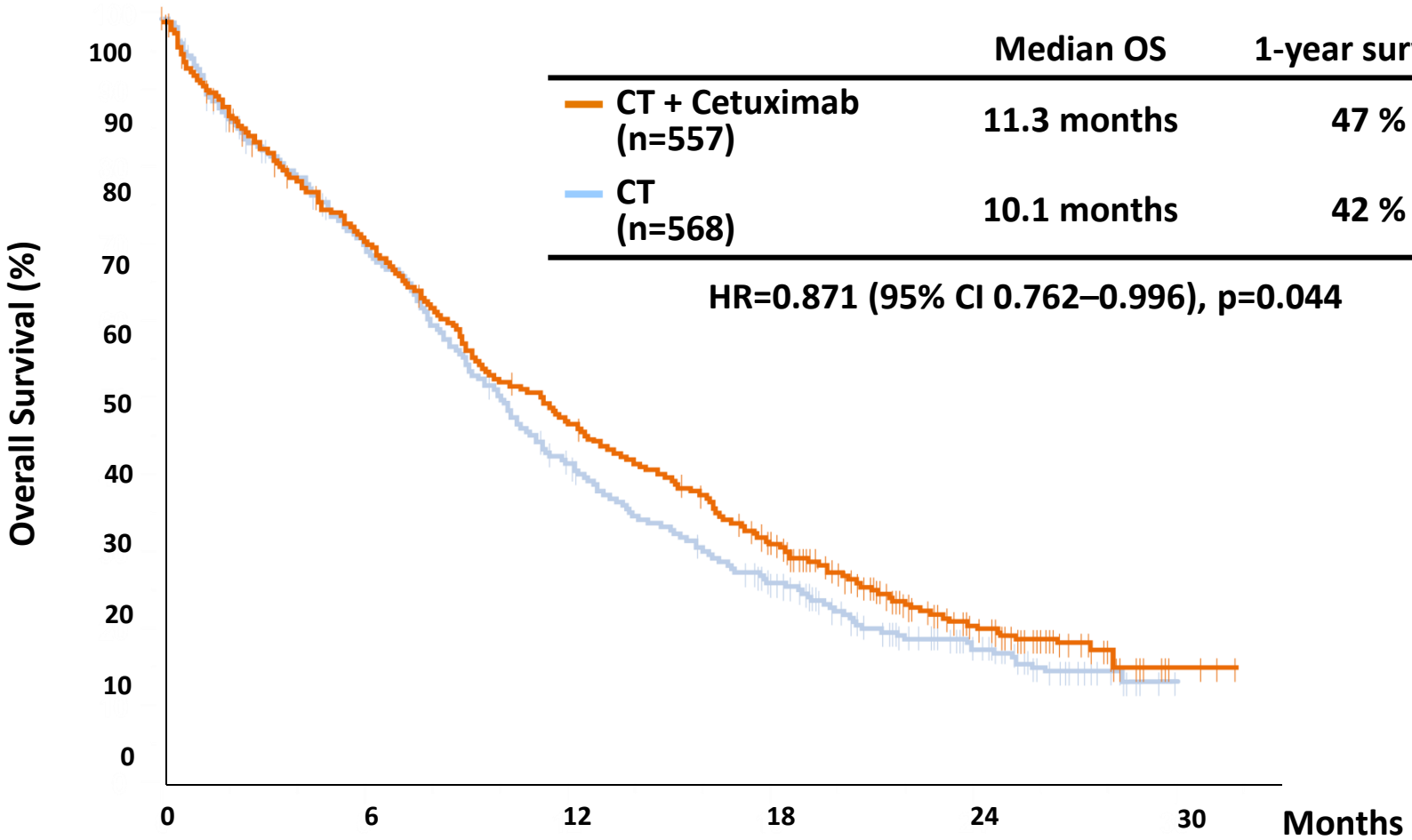
*Cisplatin 80 mg/m^2 day 1 + Vinorelbine 25 (30) mg/m^2 days 1, 8

Every 3 weeks, up to 6 cycles

§ Cetuximab initial dose 400 mg/m^2, then 250 mg/m^2 weekly

Pirker R, et al. Lancet 2009

FLEX: Overall Survival



	Median OS	1-year survival
CT + Cetuximab (n=557)	11.3 months	47 %
CT (n=568)	10.1 months	42 %

HR=0.871 (95% CI 0.762–0.996), p=0.044

Patients at risk						
CT + Cetuximab	557	383	251	155	53	3
CT	568	383	225	134	48	0

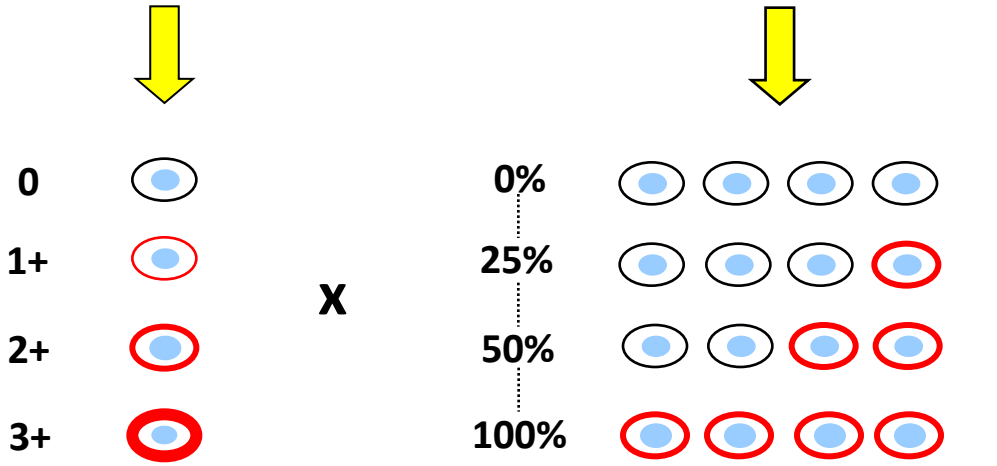
p-value = stratified log-rank test (2-sided)

Pirker R, et al. Lancet 2009

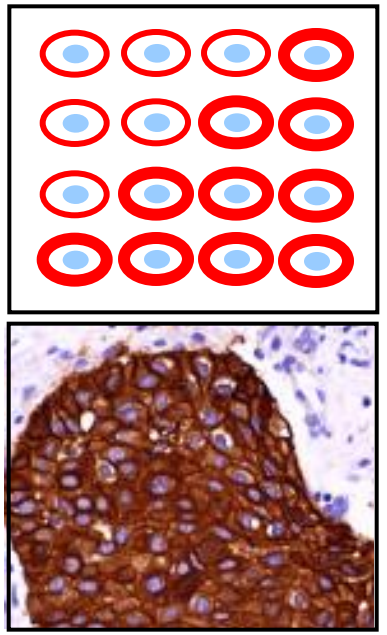
FLEX study: EGFR IHC score

DAKO pharmDx™ kit

Staining intensity and proportion of positive tumor cells



EGFR high expressing tumor (example)



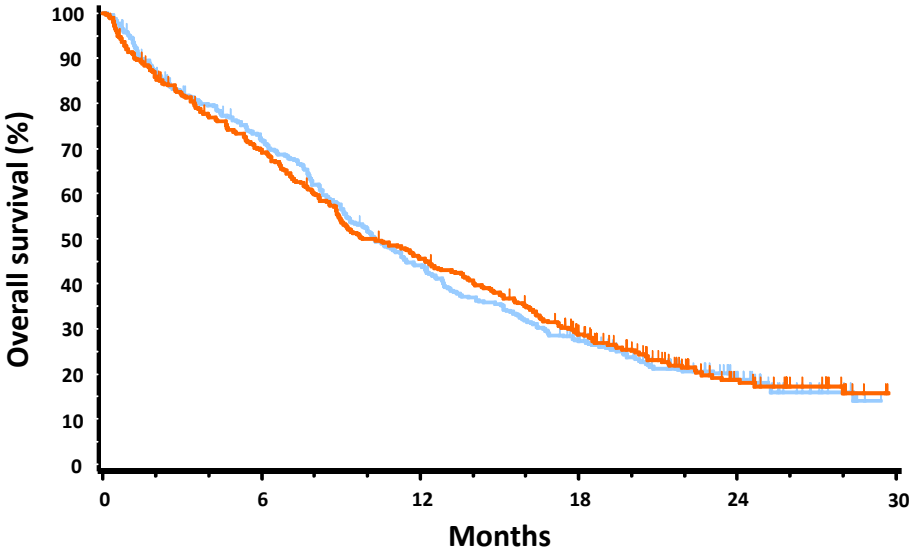
EGFR IHC score ranges from 0–300

[1]Hirsch FR, et al. J Clin Oncol, 2003; [2]Cappuzzo F, et al. J Natl Cancer Inst, 2005; [3]Hirsch FR, et al. Cancer, 2008; [4]Felip E, et al. Clin Cancer Res, 2008; [5]Gori S, et al. Ann Oncol, 2009; [6]Lee HJ, et al. Lung Cancer, 2010

Predictive value of high EGFR for survival benefit with CT + cetuximab

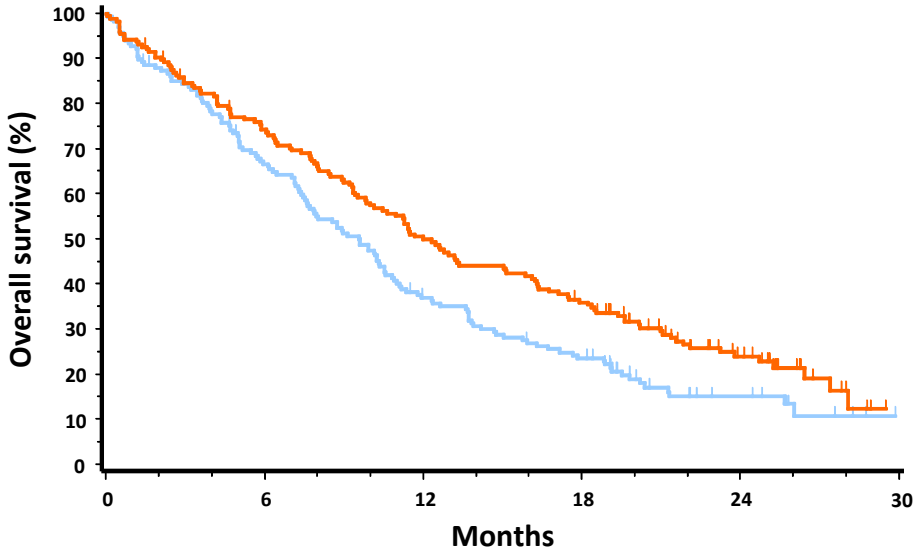
Low EGFR

HR 0.99 [95% CI 0.84–1.16]



High EGFR

HR 0.73 [95% CI 0.58–0.93]



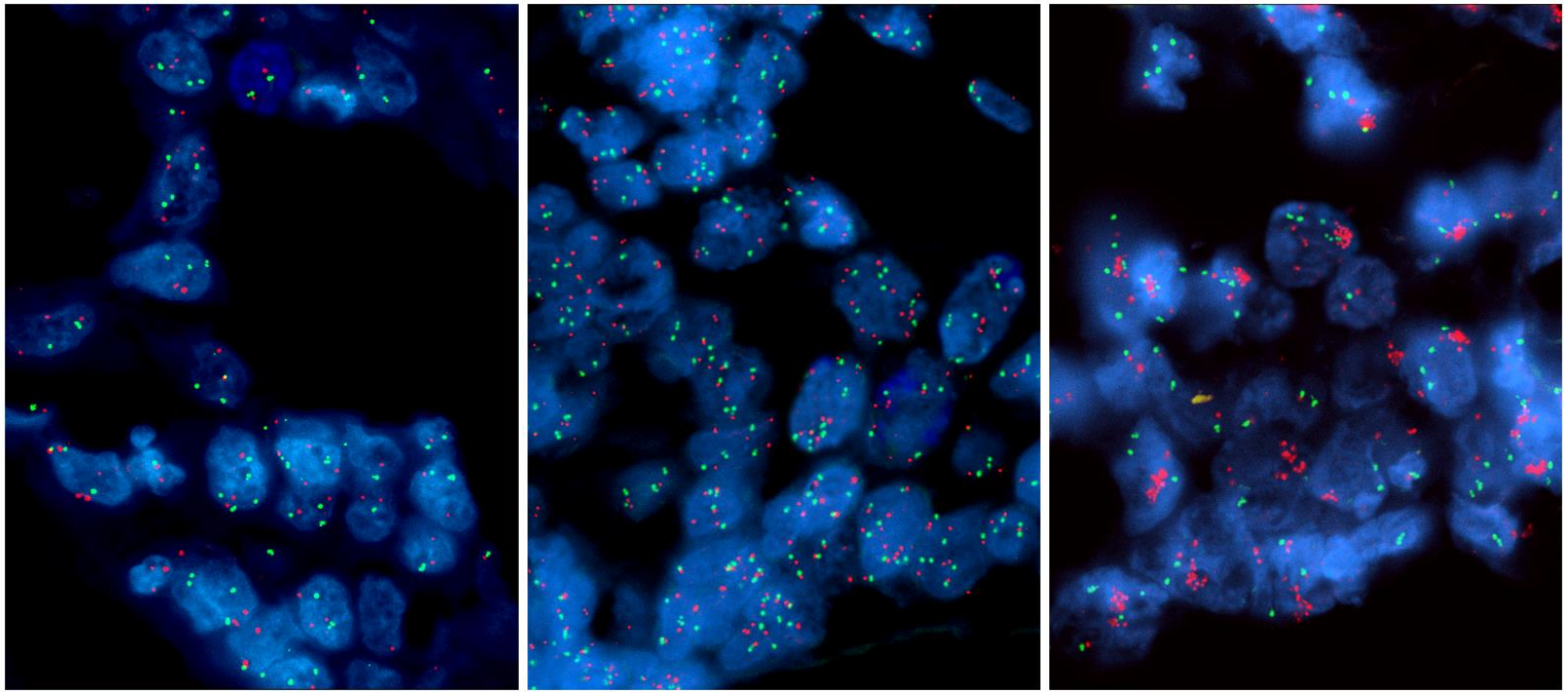
CT + cetuximab
CT

Interaction p-value=0.044

Pirker R, et al. Lancet Oncol 2012

MET gene copy number in unselected TKI naïve NSCLC

Total evaluated: 435



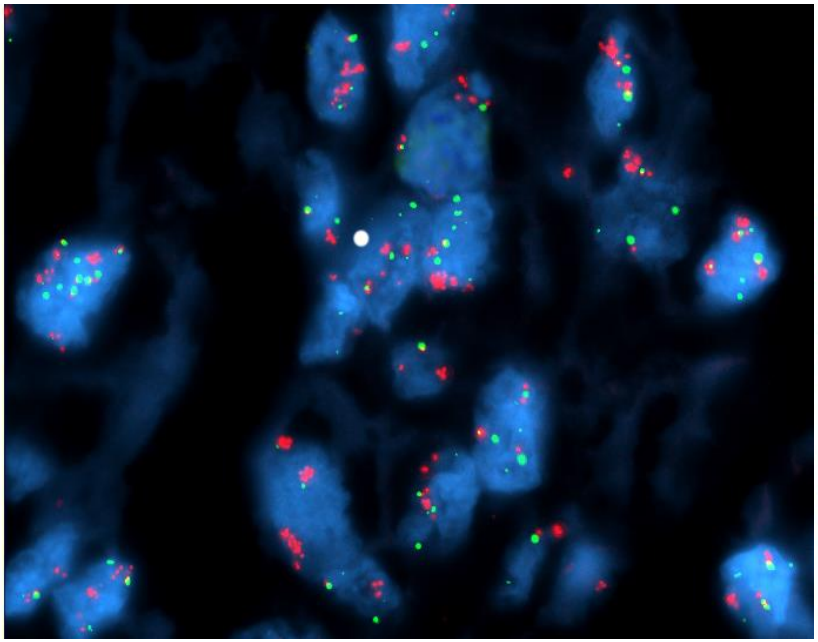
Low copy number: 383 (88.9%)

High polysomy: 30 (7.0%)

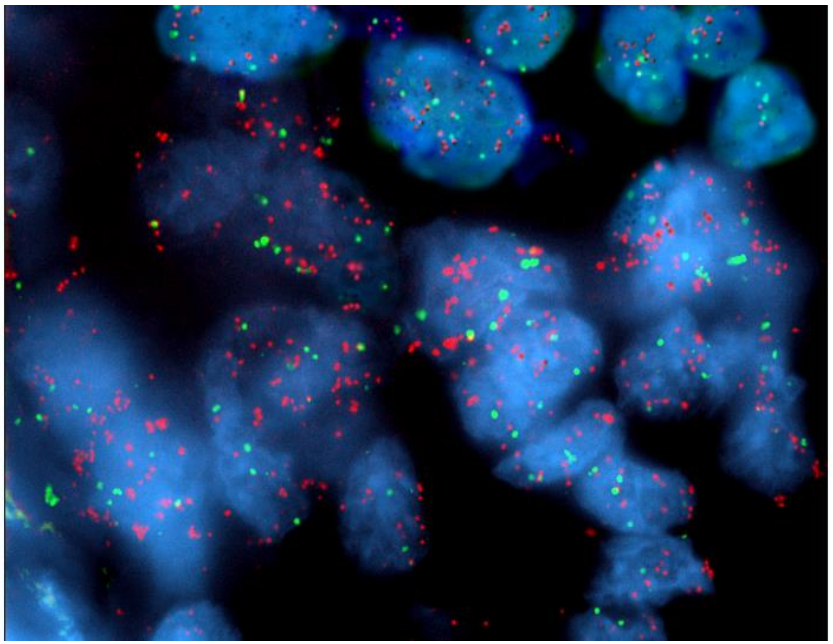
Gene amplification: 18 (4.1%)

Cappuzzo F et al, JCO 2009

MET and *EGFR* Co-amplification: a Rare Event



***EGFR* Gene Amplification**



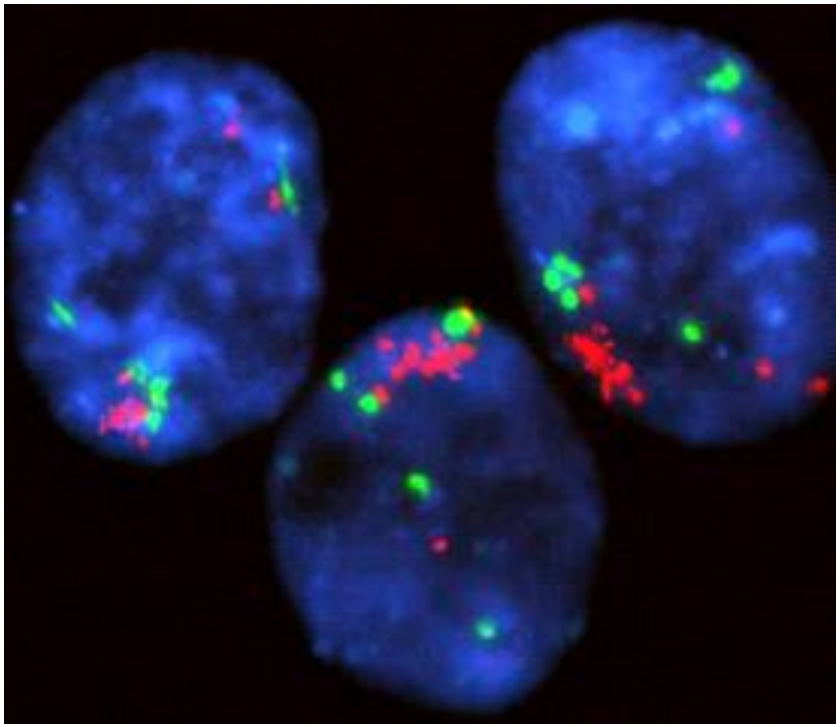
***MET* Gene Amplification**

Co-amplification observed in only 1.1%

Cappuzzo F et al, JCO 2009

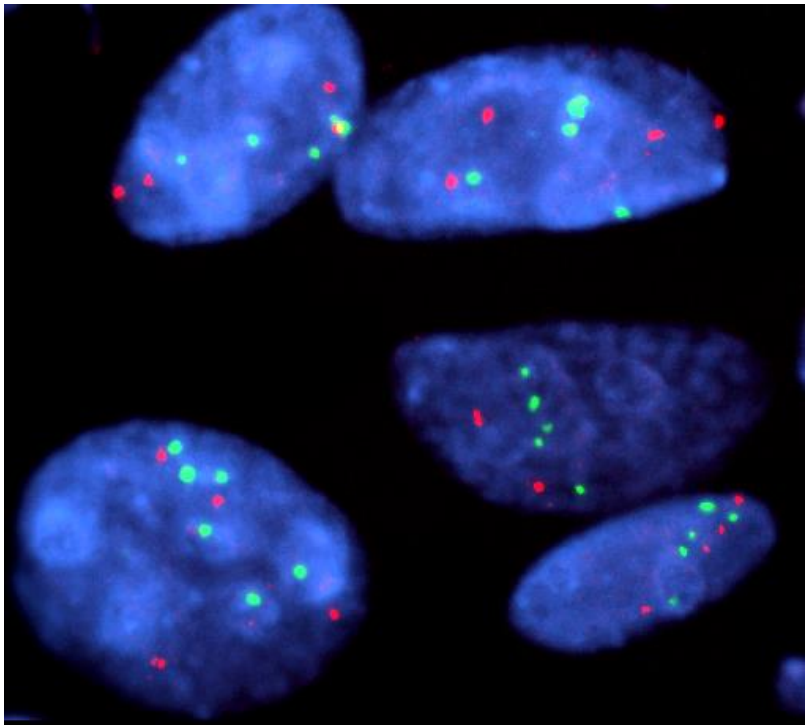
High levels of MET amplification in cell lines with EGFR-TKI acquired resistance

Gefitinib Resistant



MET amplification in HCC827 GR6
Mean MET gene copy number>12

Gefitinib Sensitive



NO MET amplification in HCC827
Mean MET gene copy number =4

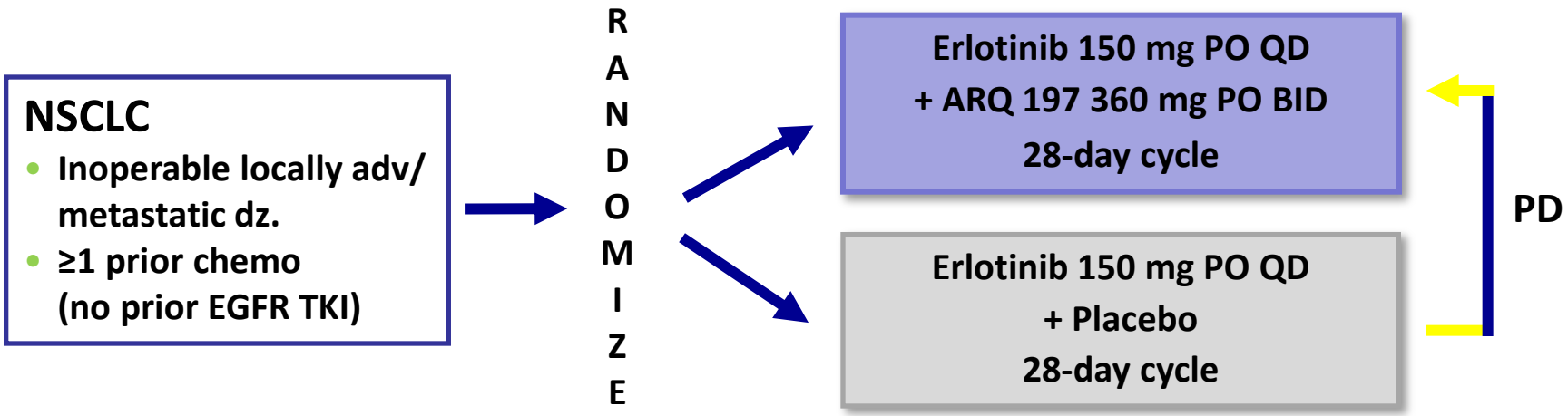
Cappuzzo et al., Ann Oncol 2008

Anti-MET agents in development in patients with NSCLC

Agent	Target	Type	Development phase
Ligand antagonists			
Ficlatuzumab (AV-299)	HGF	Monoclonal antibody	I and II
Rilotumumab (AMG-102)	HGF	Monoclonal antibody	II
TAK-701	HGF	Monoclonal antibody	I
Receptor inhibitors			
Onartuzumab (OA5D5)	MET	Monoclonal antibody	III completed
Receptor TKIs			
Tivantinib (ARQ-197)	MET	Non-ATP competitive TKI	III completed
Cabozantinib (XL-184)	MET, RET, VEGFR1-3, KIT, FLT3, TIE2	ATP competitive TKI	II
Foretinib (XL-880)	MET, RON, VEGFR1-3, PDGFR, KIT, FLT3, TIE2	ATP competitive TKI	II
Crizotinib (PF-02341066)	MET, ALK	ATP competitive TKI	II and III
MGCD-265	MET, RON, VEGFR1-2, PDGFR, KIT, FLT3, TIE2	ATP competitive TKI	II

Tivantinib: Study Design

Randomized, placebo-controlled, double-blind clinical trial



Endpoints

- 1° PFS
- 2° ORR, OS
- Subset analyses
- Crossover: ORR

33 sites in 6 countries

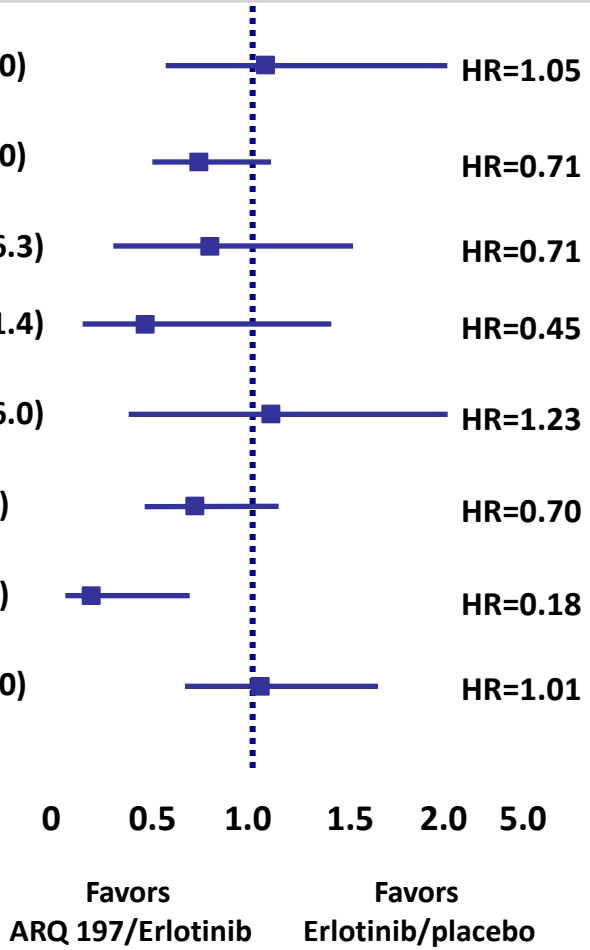
Study accrual over 11 months (10/08-9/09)

Randomization stratified by prognostic factors incl. sex, age, smoking, histology, performance status, prior therapy and best response, and geography (U.S. vs. ex-U.S.)

Sequist L, et al. JCO 2011

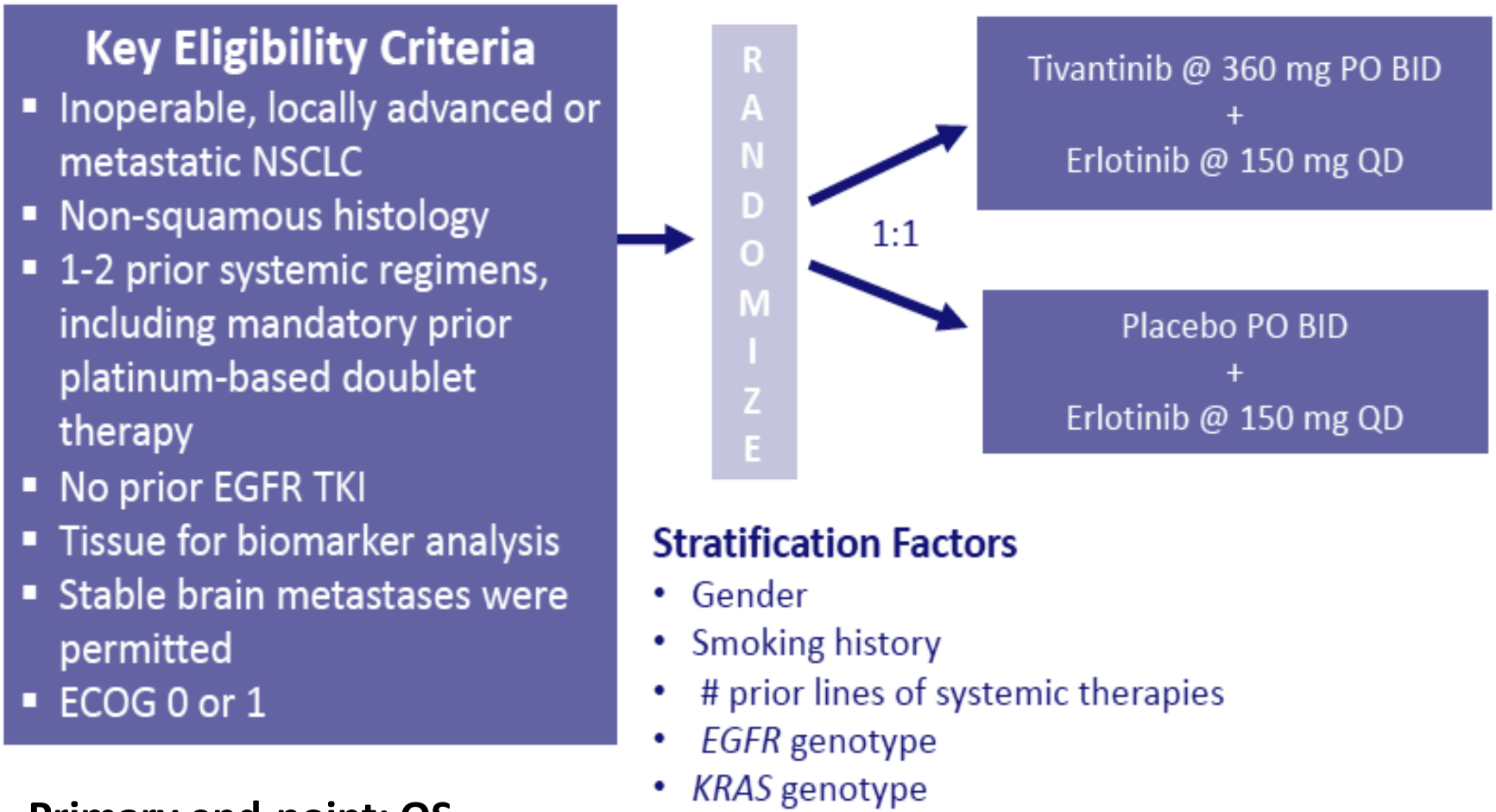
Tivantinib: PFS in Histologic and Molecular Subgroups

		ARQ197/erlotinib	Placebo/erlotinib	
	N	Median PFS (95% CI, weeks)		Unadjusted HR (95% CI)
Squamous Cell	26 / 24	13.7 (8.0–18.1)	8.4 (7.9–21.0)	HR=1.05
Non-Squamous Cell	58 / 59	18.9 (15.0–31.1)	9.7 (8.0–16.0)	HR=0.71
c-MET FISH >4	19 / 18	15.4 (8.1–24.4)	15.3 (7.1–16.3)	HR=0.71
c-MET FISH >5	8 / 11	24.1 (16.3–NE)	15.6 (7.9–31.4)	HR=0.45
EGFR mutant	6 / 11	24.1 (8.0–32.1)	21.0 (8.1–36.0)	HR=1.23
EGFR wt	51 / 48	13.7 (8.1–18.1)	8.1 (7.9–9.9)	HR=0.70
KRAS mutant	10 / 5	9.7 (7.9–NE)	4.3 (1.1–8.0)	HR=0.18
KRAS wt	49 / 45	15.4 (8.1–18.1)	9.9 (8.0–16.0)	HR=1.01



Sequist L, et al. JCO 2011

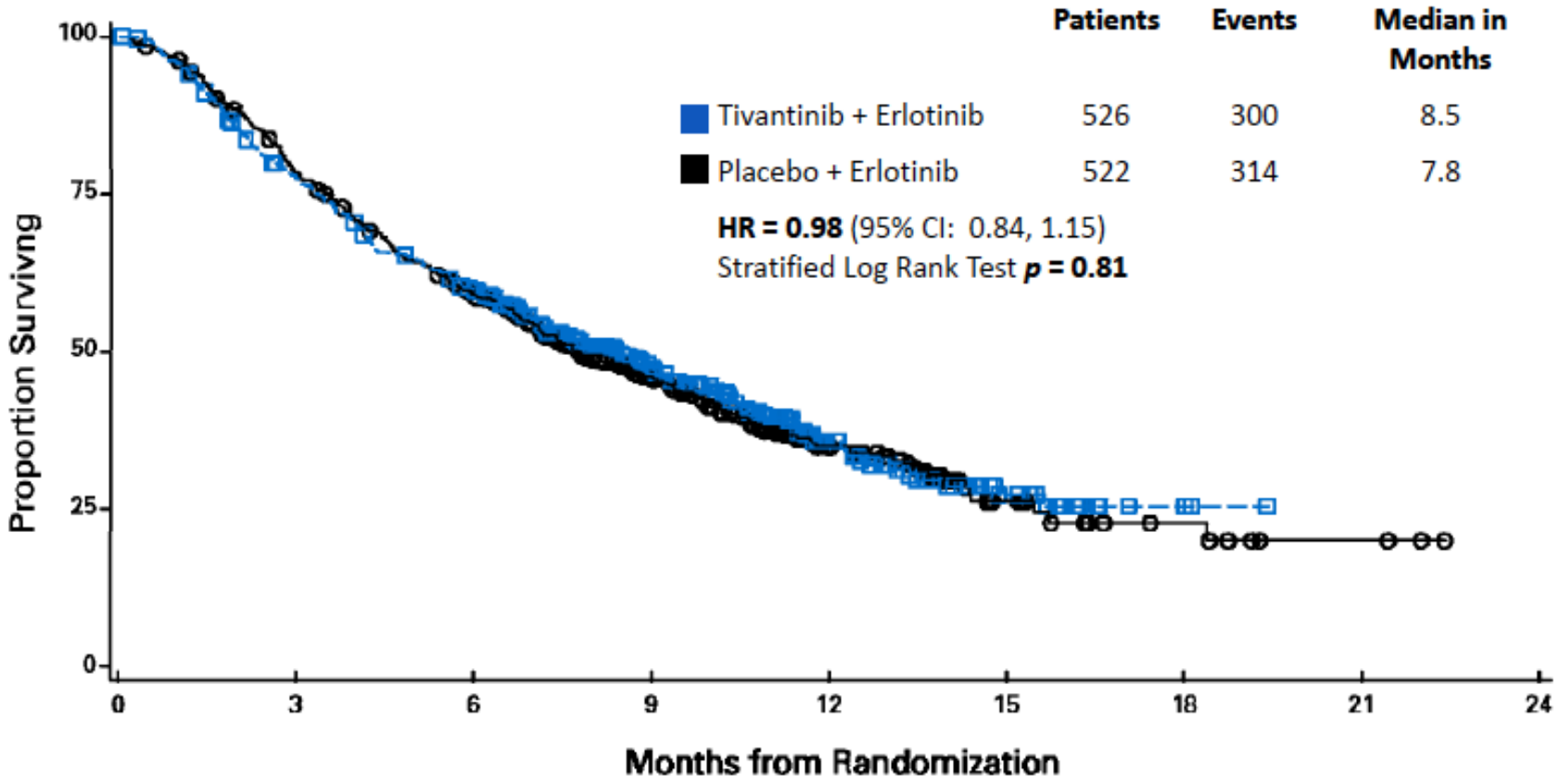
MARQUEE phase III study design



Primary end-point: OS

Scagliotti GV, ECCO 2013

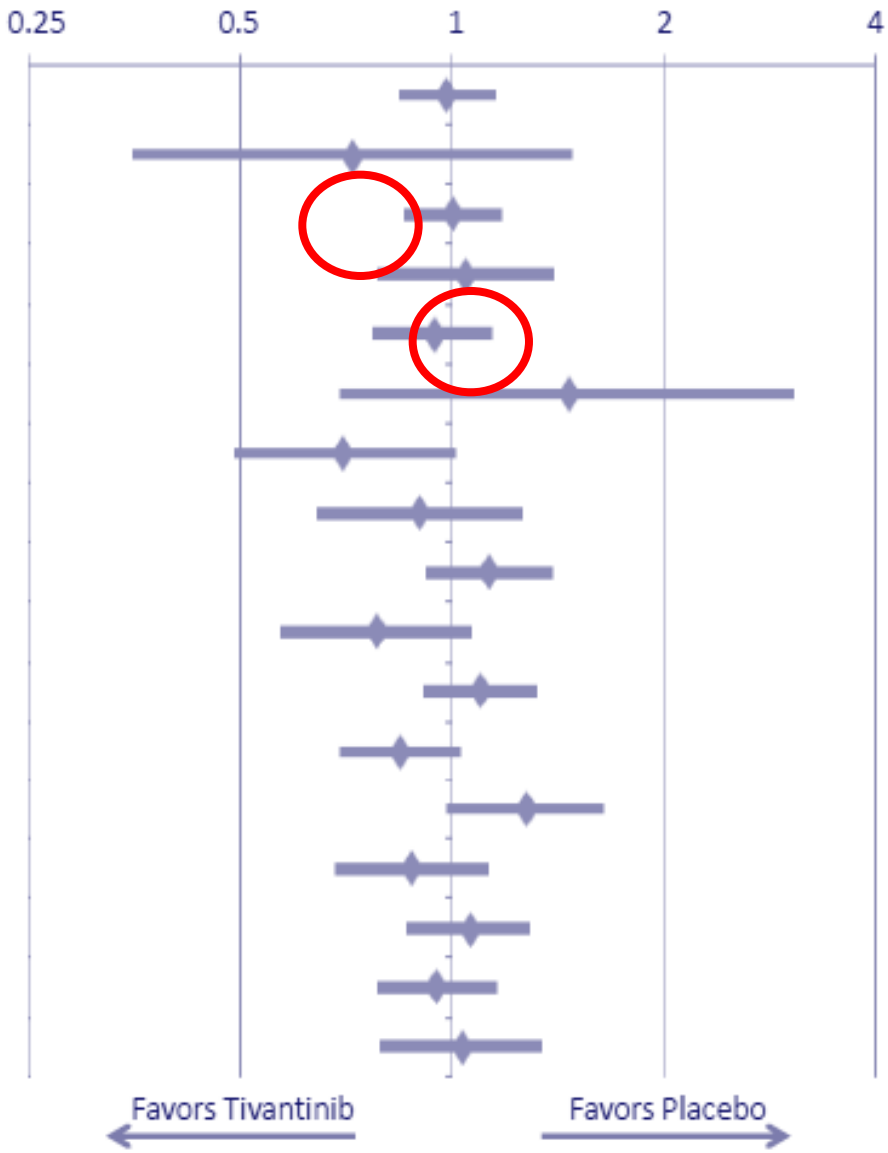
MARQUEE: OS in the study population



Scagliotti GV, ECCO 2013

MARQUEE: Forest plot for OS in key subgroups

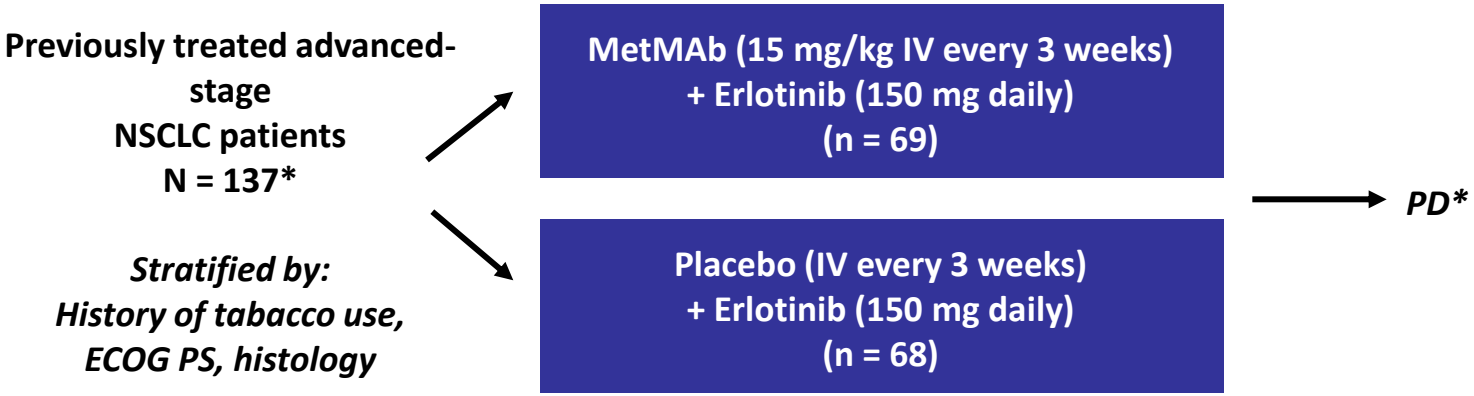
Factor	Group	N	HR (95% CI)
All	All	1048	.98 (.84-1.15)
EGFR	Mutant	109	.72 (.35-1.48)
	Non-Mutant	937	1.00 (.85-1.18)
KRAS	Mutant	284	1.04 (.78-1.40)
	Non-Mutant	702	.94 (.77-1.14)
	Indeterminate	62	1.46 (.69-3.07)
MET	High	211	.70 (.49-1.01)
	Low	234	.90 (.64-1.26)
	Not Assessable	603	1.13 (.92-1.39)
ECOG PS	0	336	.78 (.57-1.07)
	1	710	1.10 (.91-1.32)
Age	<65	646	.84 (.69-1.03)
	>=65	402	1.27 (.98-1.64)
Gender	Female	429	.87 (.68-1.13)
	Male	619	1.06 (.86-1.29)
Prior Regimens	1	694	.95 (.78-1.16)
	2	354	1.03 (.79-1.34)



Scagliotti GV, ECCO 2013

Onartuzumab (MetMAb): Randomized Phase II Trial

- **Onartuzumab (MetMAb): monovalent (single-arm) antibody to MET, prevents MET activation by HGF**

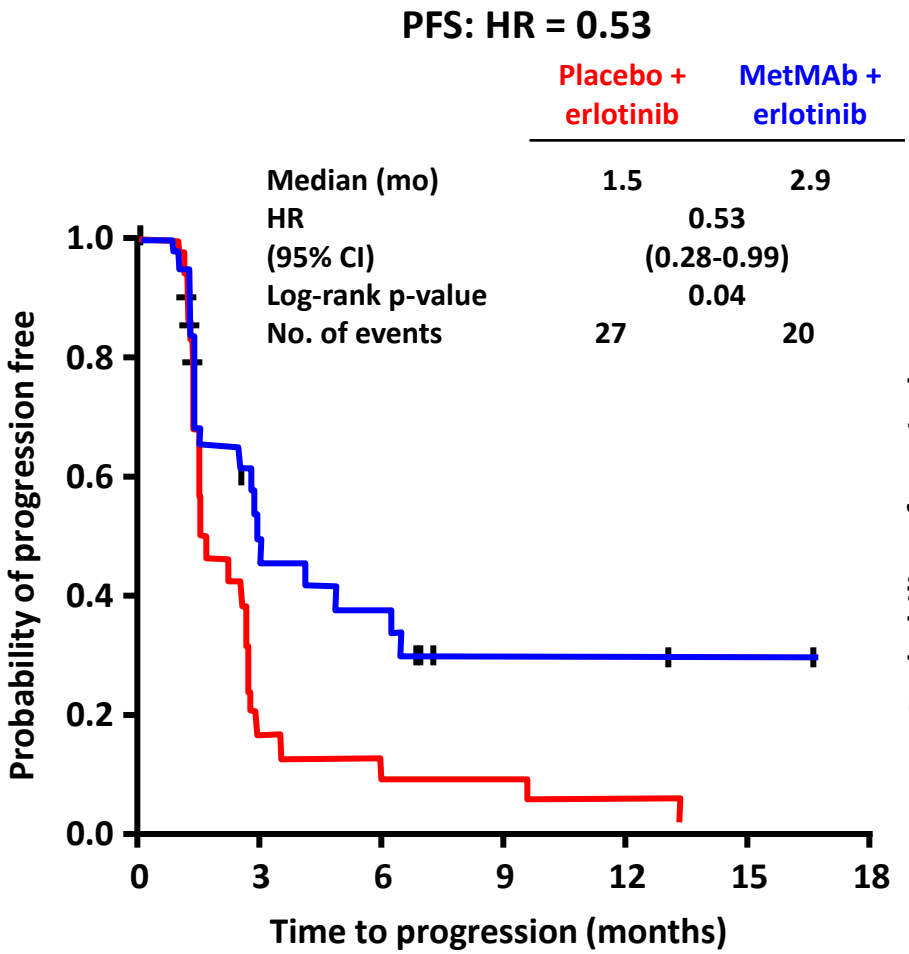


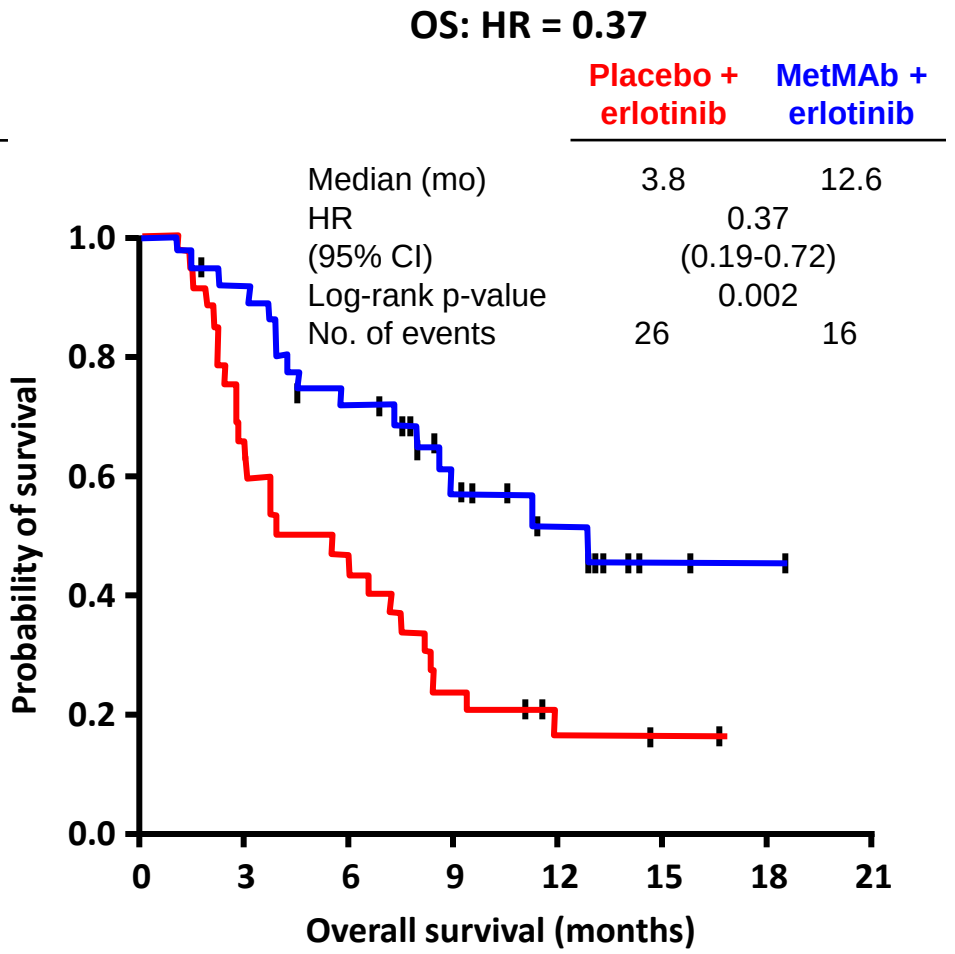
*Includes 9 patients with squamous cell histology
†Patients in placebo arm allowed to cross-over to receive MetMAb (n = 27)

- **Primary endpoint: PFS in Met-positive and ITT population**
- **Secondary endpoints: OS, ORR, safety**

Spigel, et al. ASCO 2011. Abstract 7505.

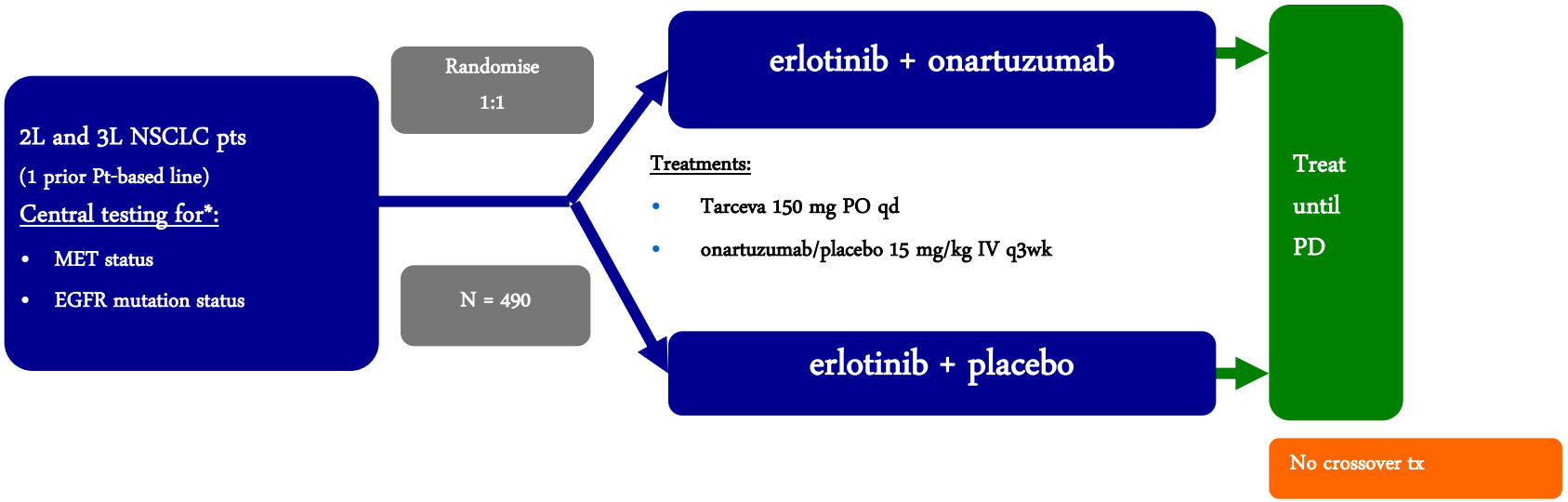
Onartuzumab (MetMAb): PFS and OS in MET Dx+ (High-Positive) Population





Spigel D, et al. ASCO 2011. Abstract 7505.

Onartuzumab (MetMAb) Phase III 2L/3L MET-positive NSCLC



Key eligibility criteria:

- Stage IIIB or IV Met diagnostic positive NSCLC
- 1-2 prior lines of tx
- No prior EGFR inhibitor
- ECOG PS 0 or 1

Stratification criteria:

- EGFR mut status
- MET 2+ or 3+ score
- # of prior lines of tx
- Histology

Primary endpoint:

- Overall survival (OS)

Secondary endpoints:

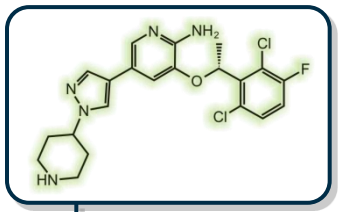
- Progression-free survival (PFS)
- Overall response rate (ORR)
- Quality of life (QoL)
- Safety

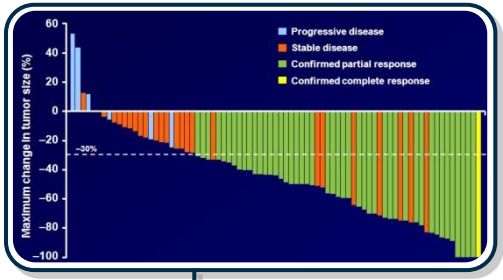
***PRE-SCREENING: Patients could submit tumor samples for testing prior to requiring treatment with 2L or 3L therapy**

Lesson from crizotinib studies: few years from compound identification to approval

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



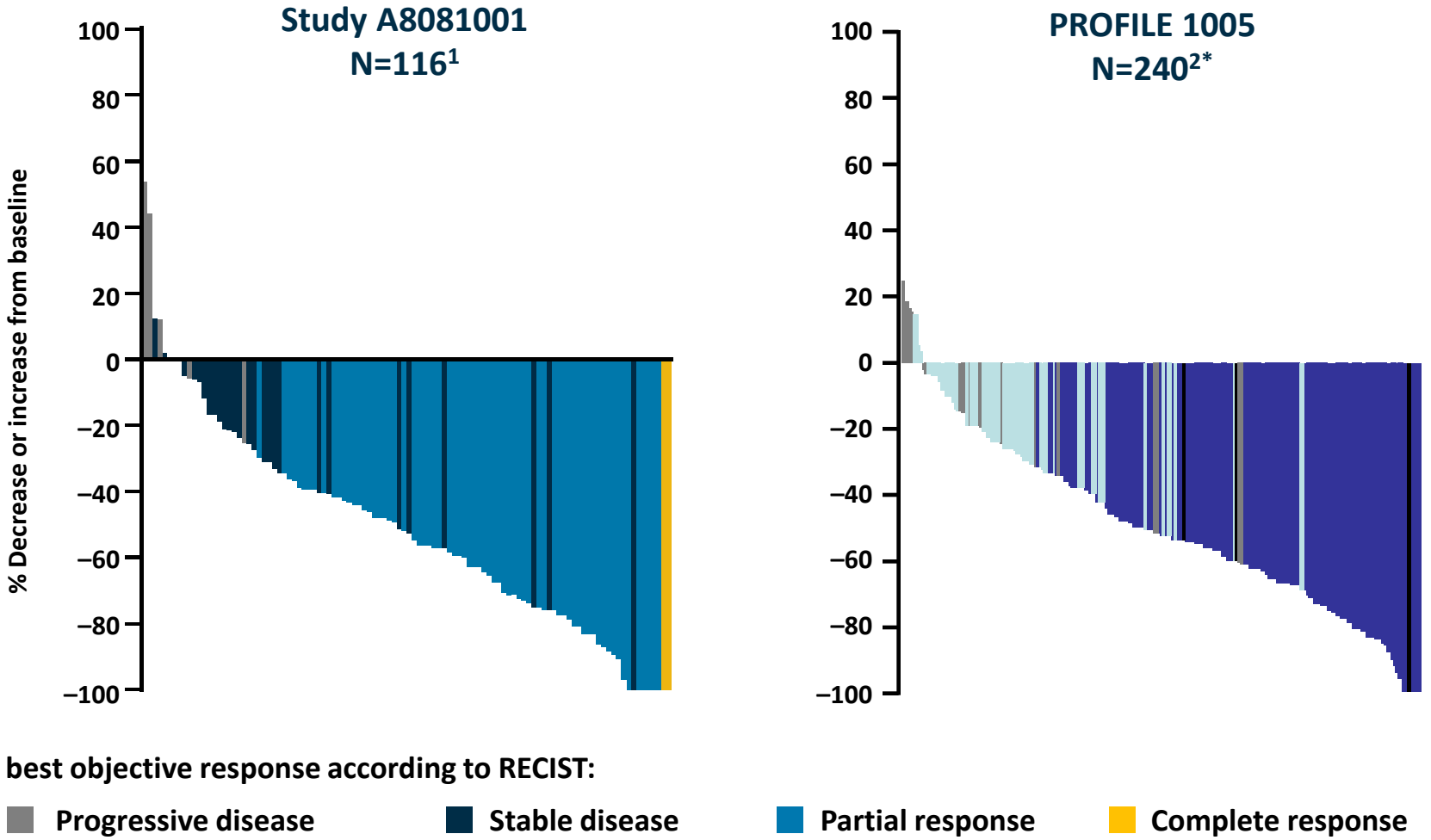


Lead compound identified	Clinical testing begins	Discovery of EML4-ALK fusion gene[1]	First clinical responses observed in ALK+ tumours	Phase 3 lung cancer trial initiated	ASCO plenary of expanded ALK+ cohort[2]	FDA approval	EMA approval
2005	2006	2007	2008	2009	2010	2011	2012

Rapid timeline from compound identification, target discovery and clinical results

1. Soda M, et al. *Nature* 2007;448:561–6
2. Bang JY, et al. Presented at ASCO 2010; Abstract 3

Lesson from crizotinib studies: High efficacy in the targeted population



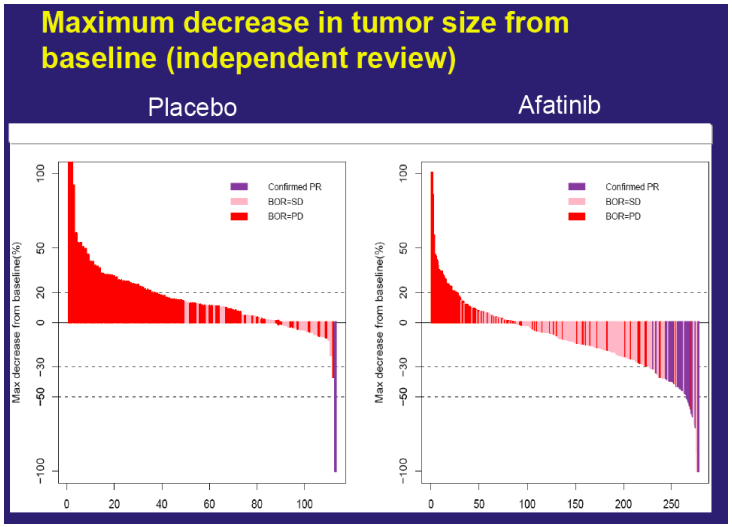
*Mature population, excluding those with early death, indeterminate response and non-measurable disease

1. Camidge R et al. Presented at ASCO 2011; Abstract 2501
2. Kim DW et al. Presented at ASCO 2012; Abstract 7533

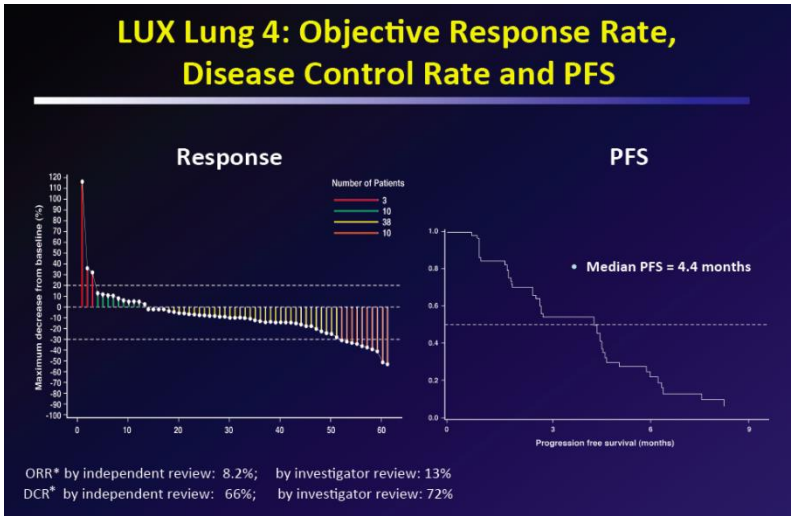
Right target and right patients could not be enough

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

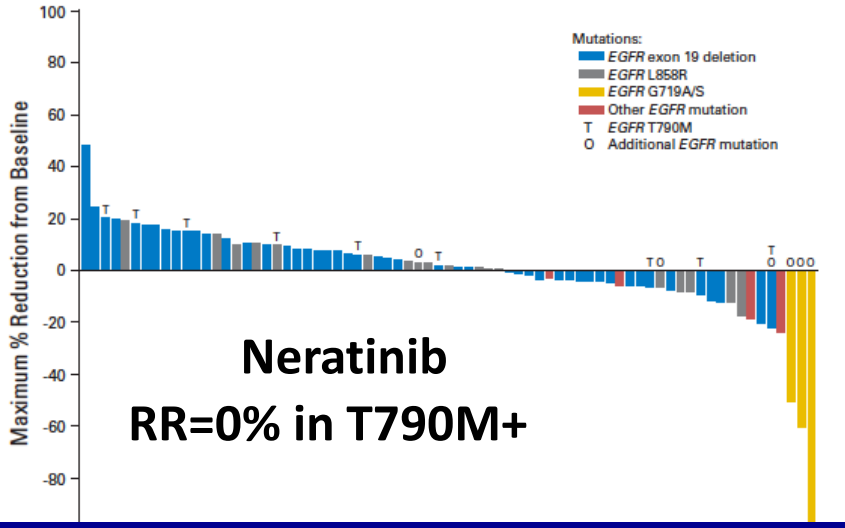
LUX LUNG 1: RR=7%



LUX LUNG 4: RR=8%



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

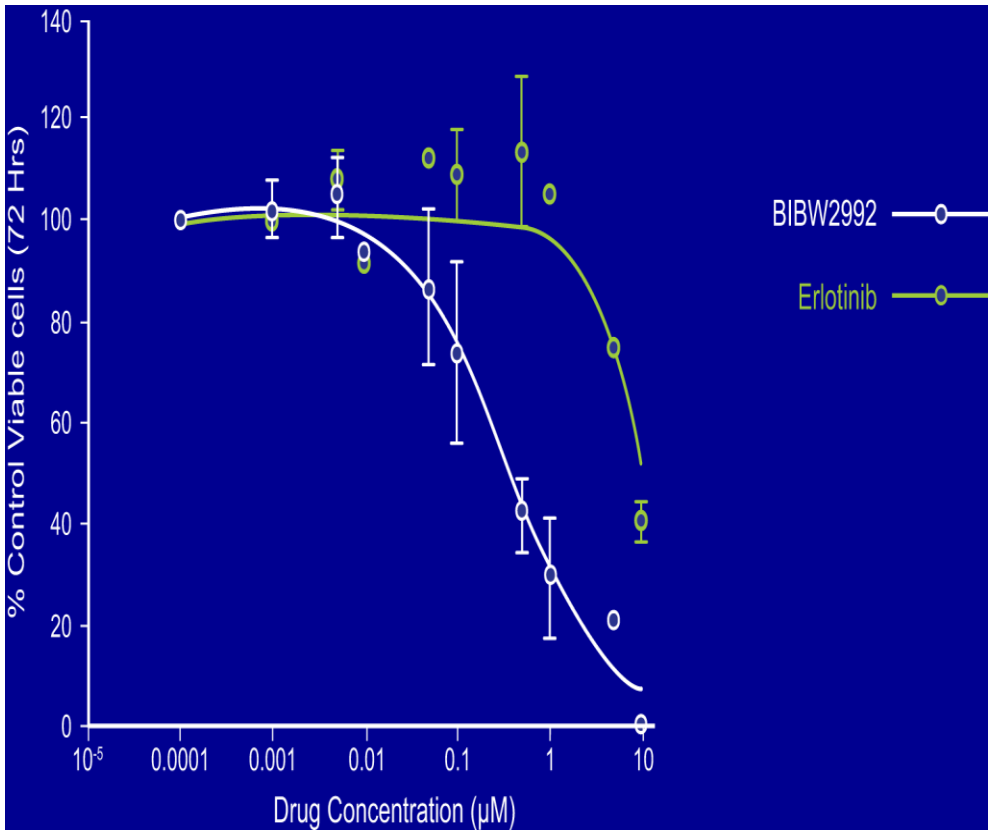


Neratinib

RR=0% in T790M+

Why irreversible inhibitors work against T790M in preclinical models only?

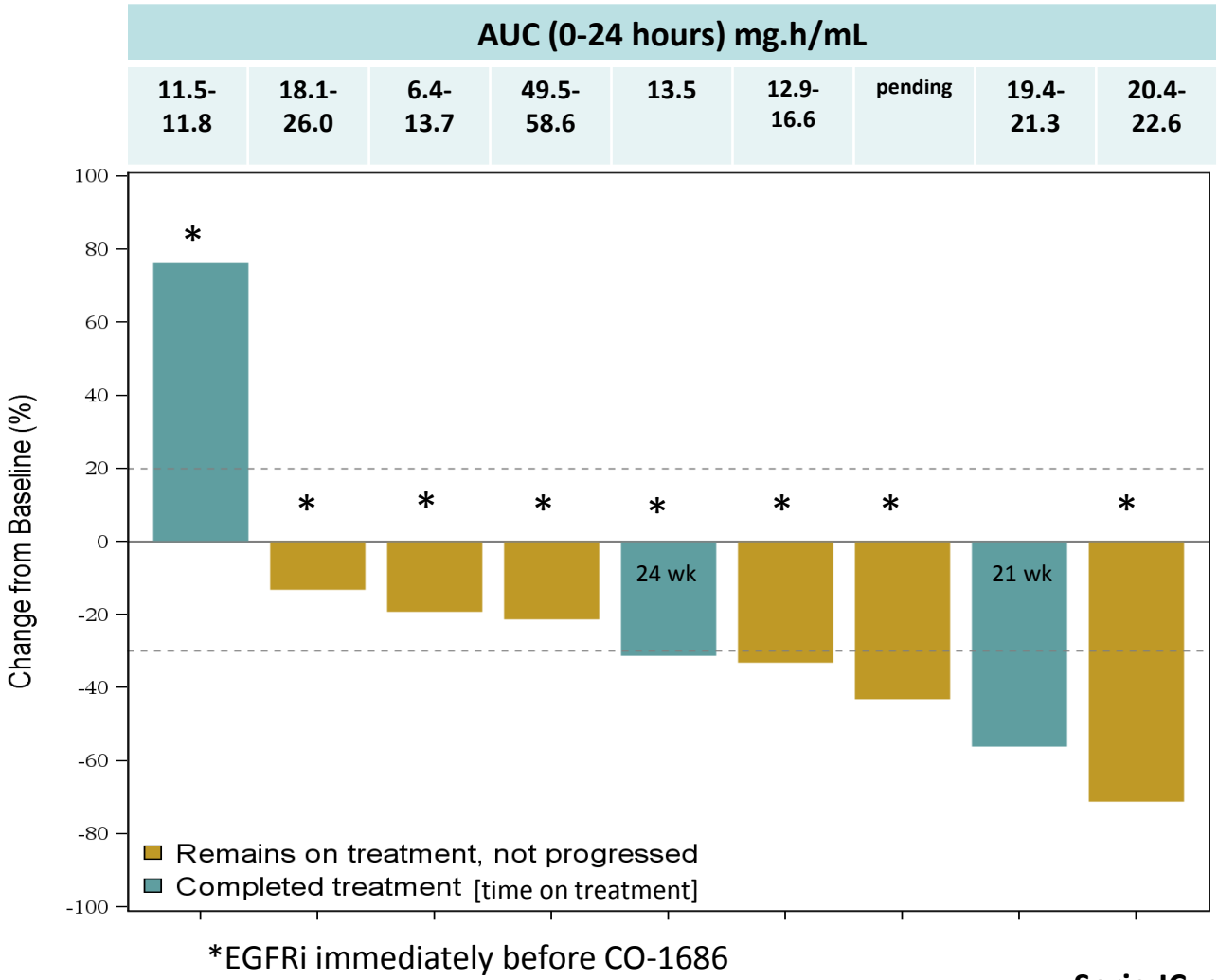
NCI-H1975



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**

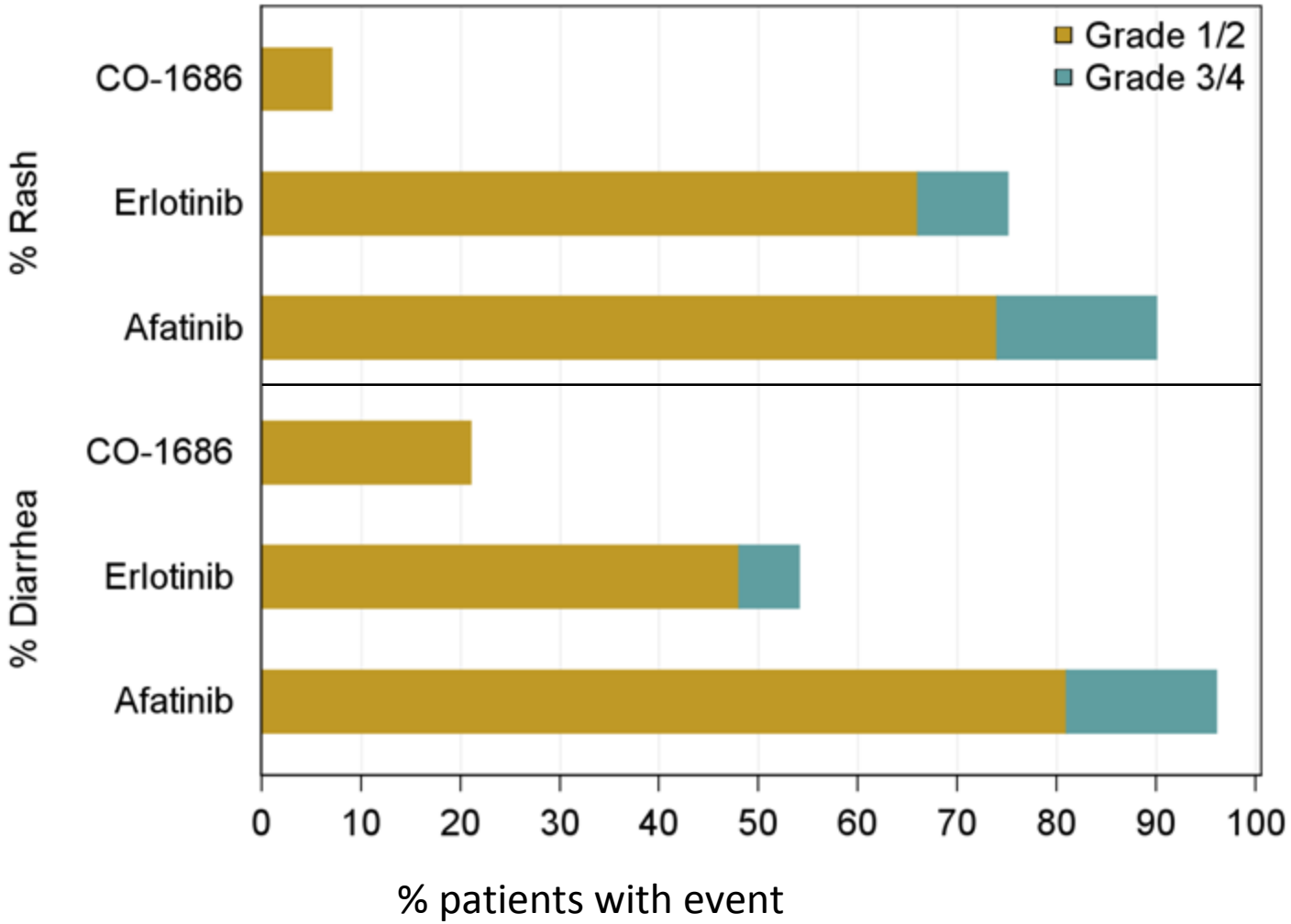
RECIST PRs and significant tumor shrinkage in T790M+ patients at highest dose tested to date



*EGFRi immediately before CO-1686

Soria JC, et al. WCLC 2013

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



Comparator data from US prescribing information

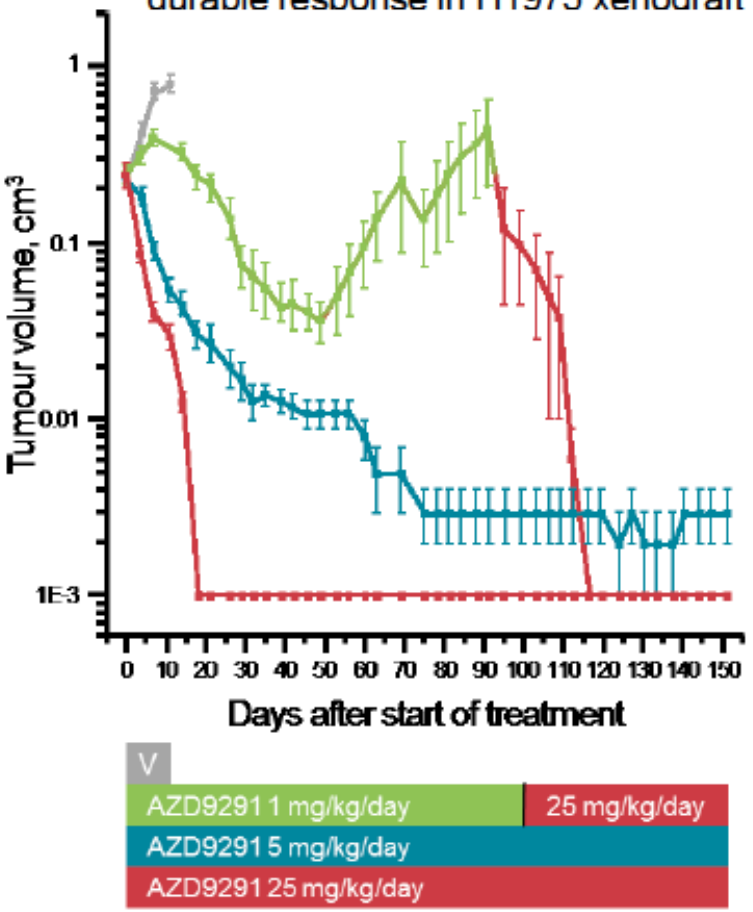
Soria JC, et al. WCLC 2013

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

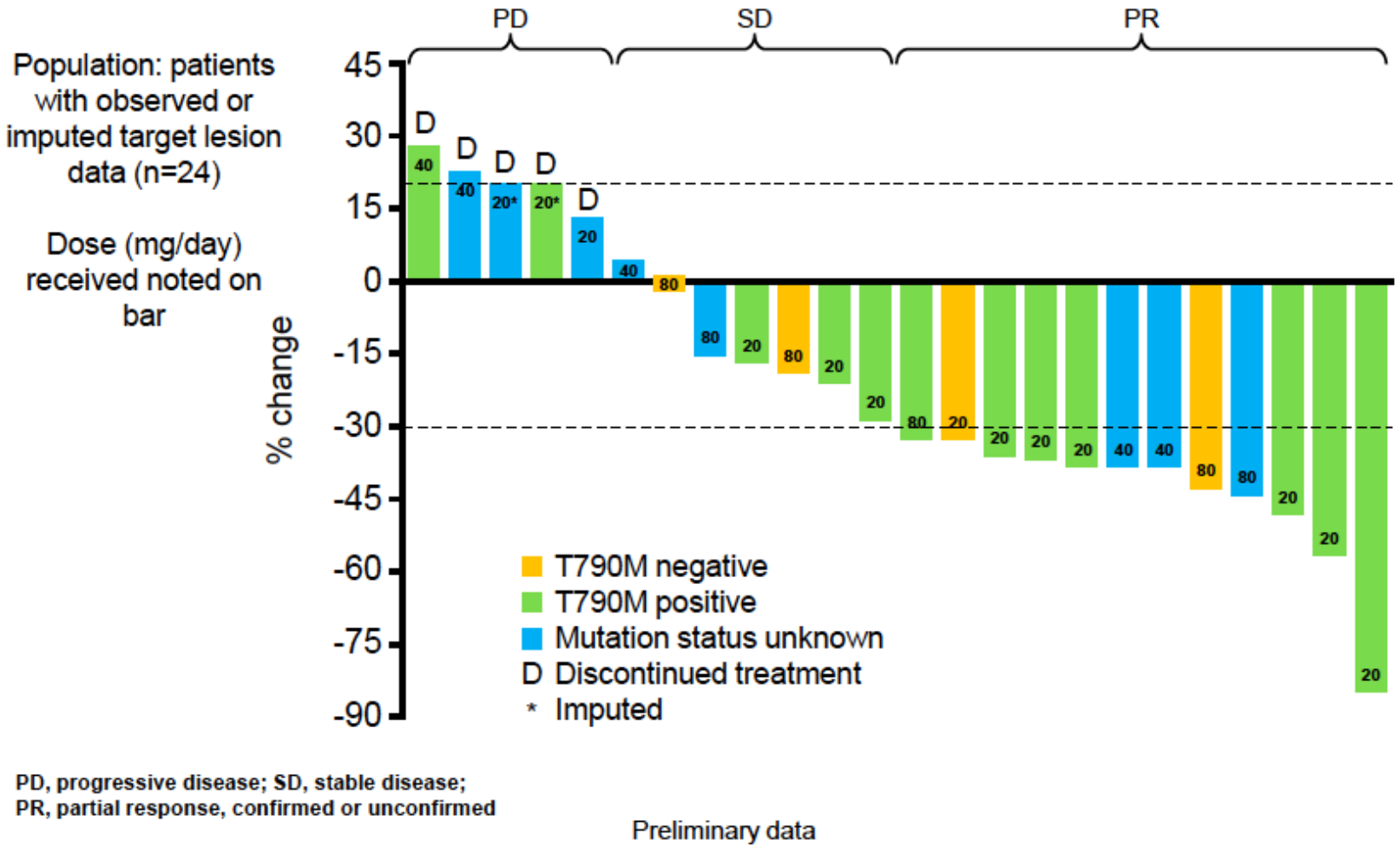
AZD9291 achieved complete and durable response in H1975 xenograft



AstraZeneca data on file

V, vehicle

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



Ranson M , et al. WCLC 2013

Conclusions

- Drug development should be fast
- Selection based on tumor biology-TARGETED
- Multicentric studies with mandatory tissue collection
- Contribution to clinical trials that mandate tissue is possible for most community sites
- Archival tissue (as opposed to new biopsy) is more likely to succeed in the community but new tissue is preferable
- New sources for biomarker testing are highly recommended (i.e plasma, effusions….)
- Drug toxicity remains a relevant issue when exploring the efficacy of targeted agents