Corso di Metodologia sulla Ricerca Clinica
Milano, 15 Novembre 2012

L'impiego dei biomarkers negli studi oncologici

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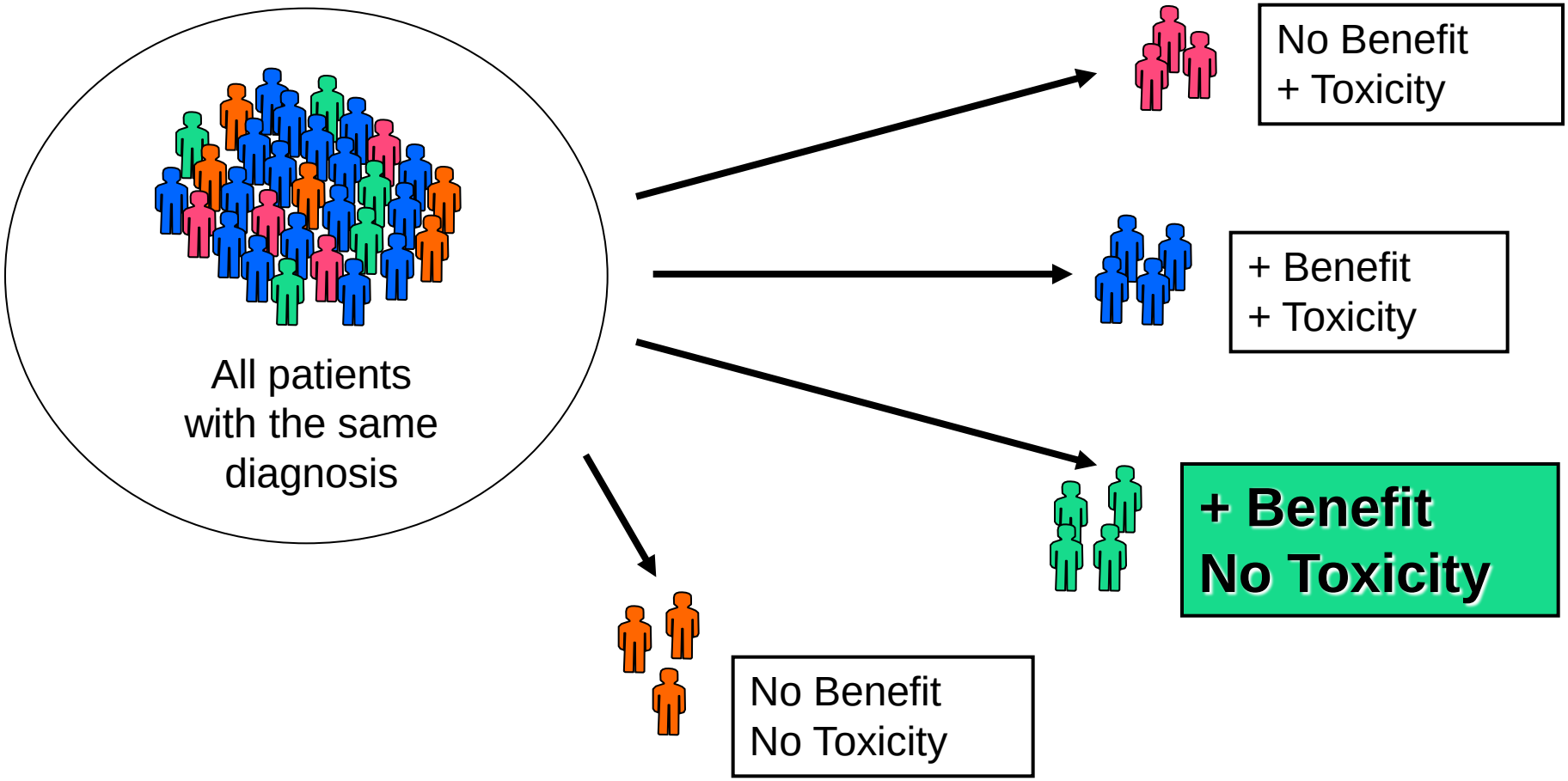
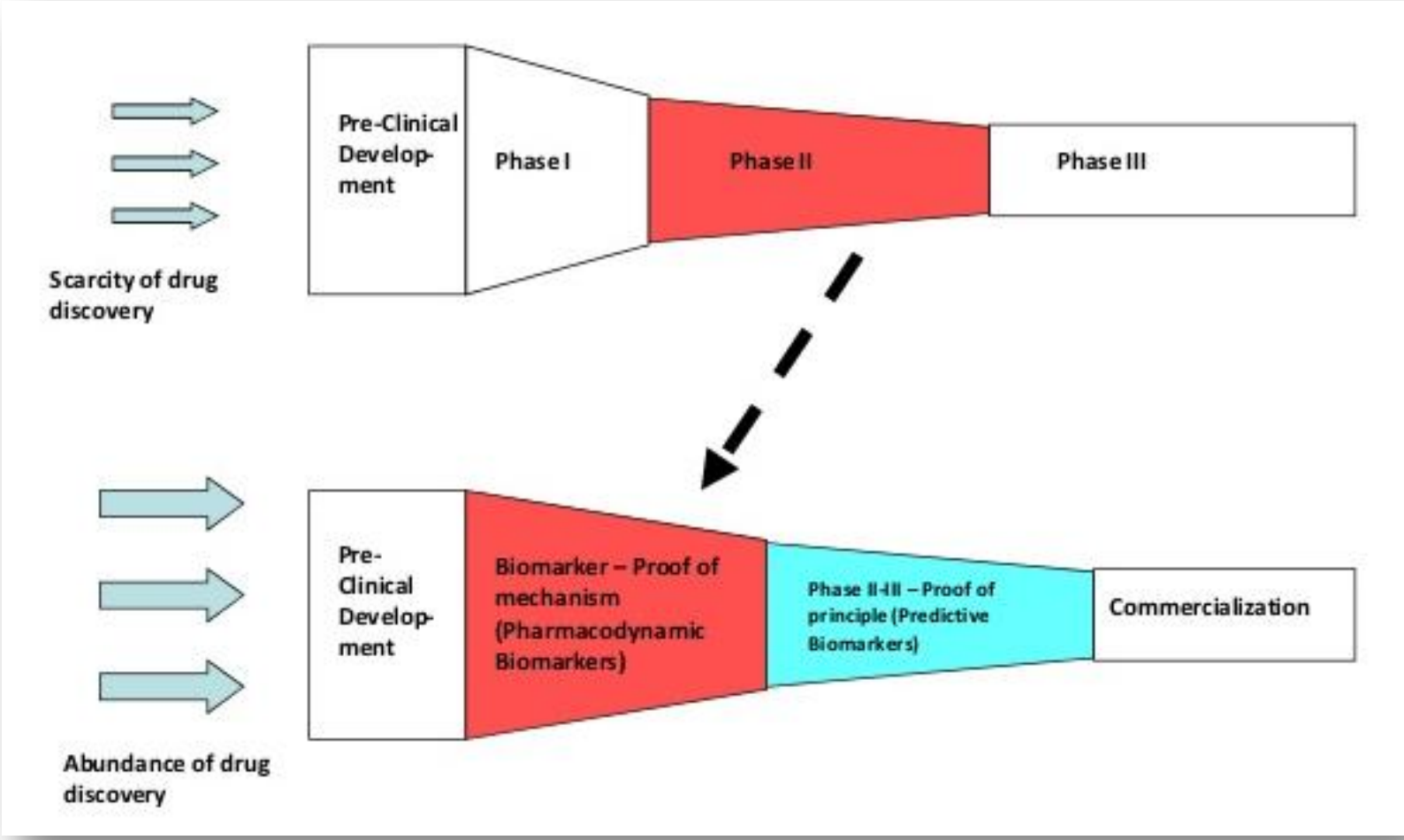
Genova

The promise of pharmacogenomic testing



Walgren RA, J Clin Oncol 2005

Changes in clinical trials



Agenda

- Why biomarkers are very important in clinical trials with targeted agents
- The limitations in the use of tumor biomarkers in clinical trials
- Methodological problems in trials with biomarkers
- One biomarker → One drug → One trial: is this approach correct?

Agenda

- Why biomarkers are very important in clinical trials
  - Prognostic vs predictive markers
  - The old approach (untargeted selection) to targeted therapies
  - A clinical pathological selection for targeted therapies based trials
  - The correct approach (target selection) to targeted therapies

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Prognostic versus predictive markers

Prognostic

Provides information on outcome, regardless of which treatment is used

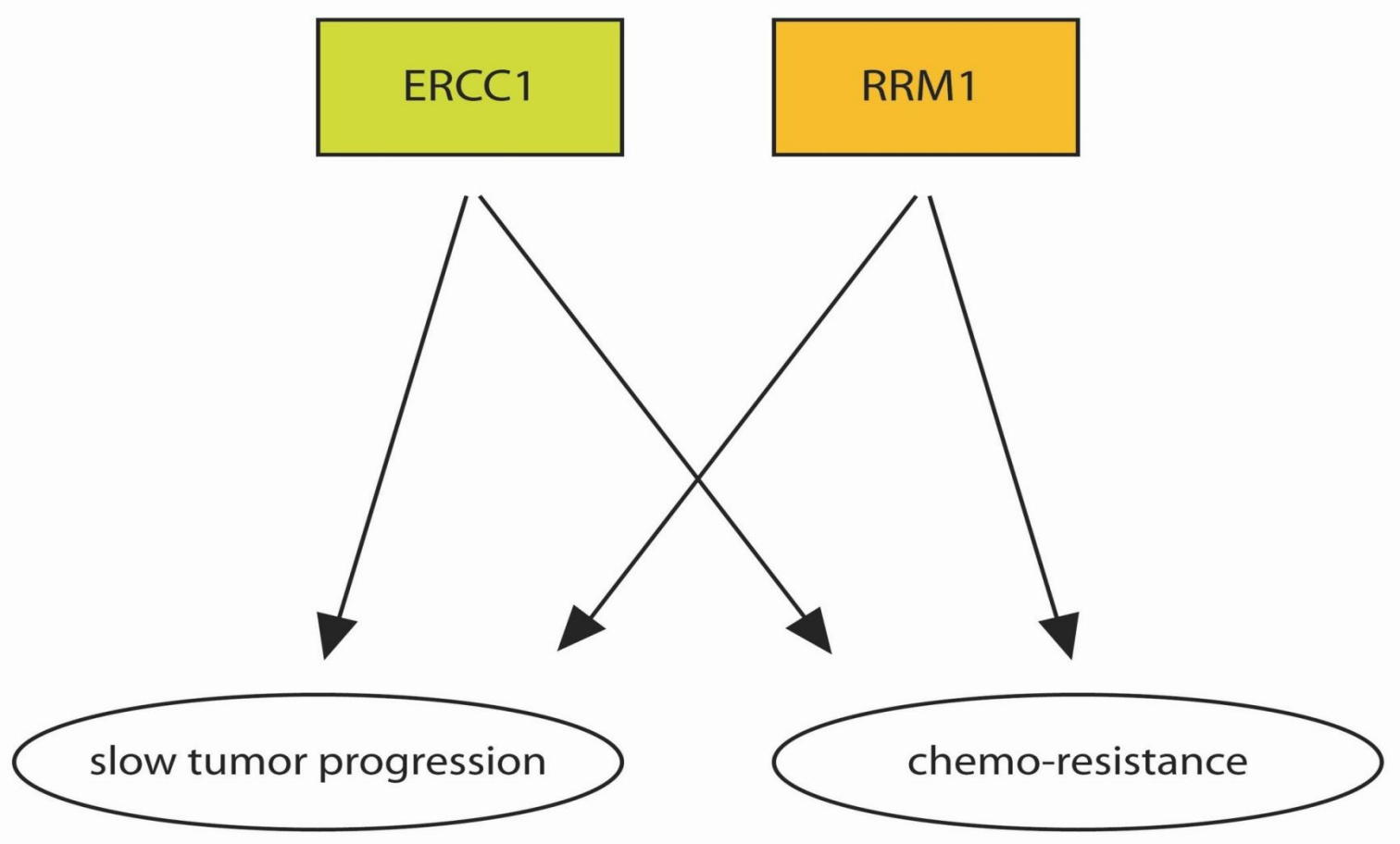
Predictive

Provides information on outcome with regards to a specific therapy

Many biomarkers have both predictive and prognostic value

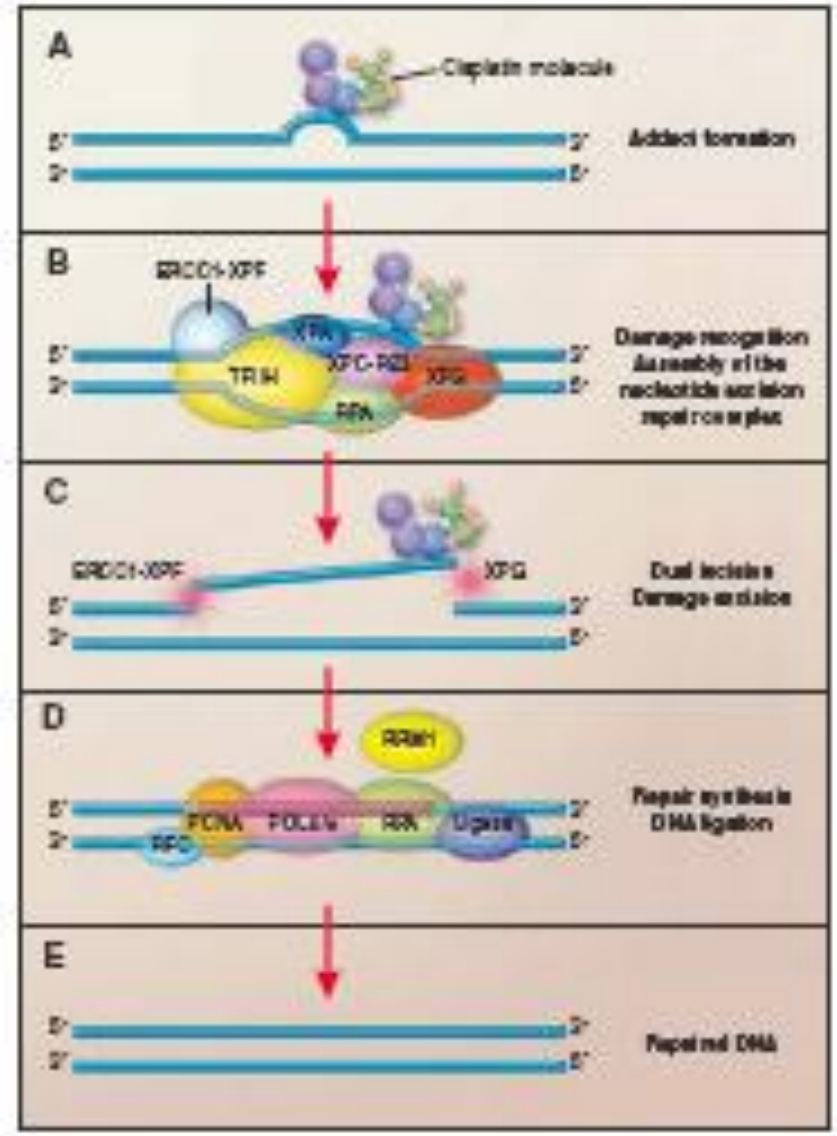
Controlled studies or meta-analyses are required to determine the prognostic and predictive contributions made by a particular marker

ERCC1 & RRM1: Clinical Significance



ERCC1 and RRM1 in DNA damage repair

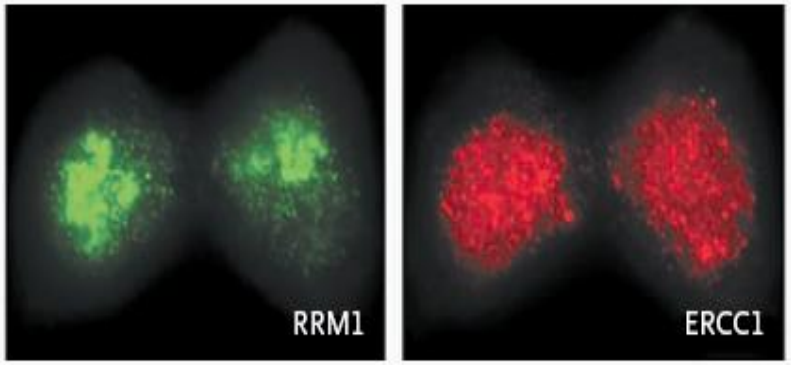
- Nucleotide excision repair (NER) plays a central role in DNA repair pathways
- ERCC1 enzyme plays a rate-limiting role in the NER pathway
- Overexpression of the excision repair cross complementing 1 (ERCC1) gene, which is crucial in the repair of cisplatin (CDDP)-DNA adducts
- Ribonucleotide reductase, although not an integral part of the repair complex, catalyzes the biosynthesis of deoxyribonucleotides from the corresponding ribonucleotides, providing the building blocks for reconstitution of the excised oligonucleotide.

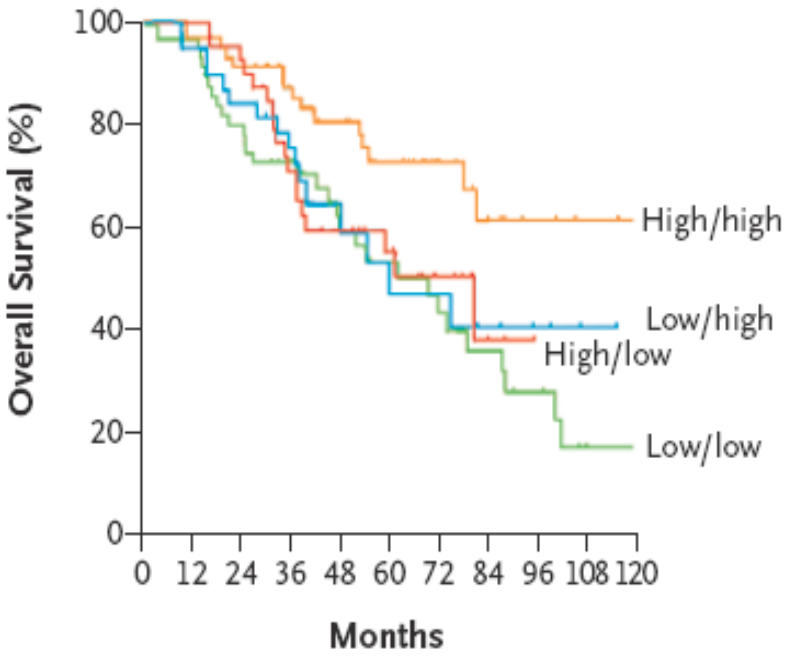


Friedberg EC, Nat Rev Cancer 2001

RRM1 & ERCC1 are determinants of survival after surgical treatment of early stage NSCLC

- RRM1 expression correlated with the expression of ERCC1 ($p<0.001$).
- High expression of RRM1 and ERCC1 defines a subgroup of patients with an excellent outcome.
- These pts accounted for approximately 30% of our pts (55 of 184) who underwent potentially curative lung cancer surgery.
- Although the high expression of either protein alone was associated with a good prognosis, coexpression of the two proteins characterized the group with an excellent outcome.

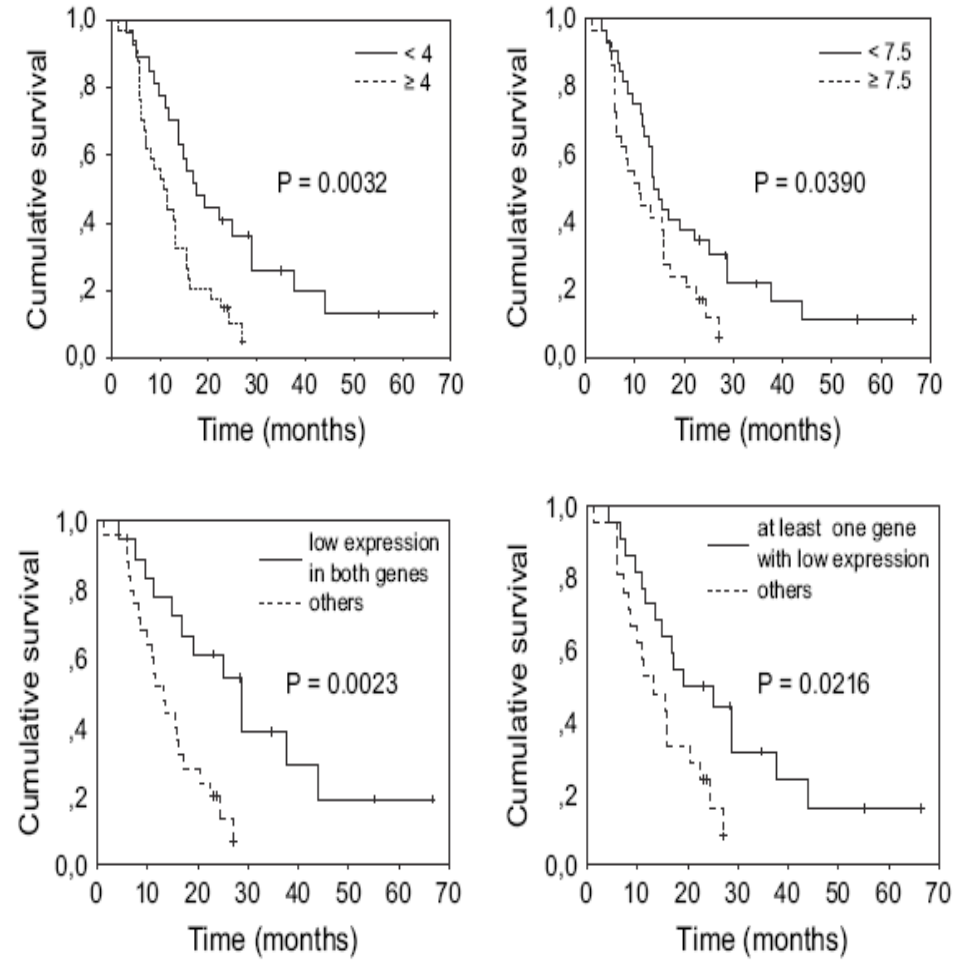




Zheng Z, NEJM 2007

Survival for ERCC1, RRM1 & for the combination of both in CDDP-treated pts

- Median survival time in patients with low ERCC1 was significantly longer (17.3 versus 10.9, p= 0.0032) as well as in patients with low RRM1 (13.9 versus 10.9, p= 0.039).
- Concomitant low expression levels of ERCC1 and RRM1 were predictive of a better outcome (14.9 versus 10.0, p= 0.0345).
- Among cisplatin treated patients, a low ERCC1 level was highly predictive of a longer survival (23.0 versus 12.4, p= 0.0001).



Ceppi P, Ann Oncol 2006

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Standard of treatment in 1990-2000: platinum doublets

	Efficacy			
	CDDP + TXT	CDDP + Gem	CBDCA + PTX	CDDP + VNB
n of trials	3	6	4	5
n of patients	863	1054	854	1,014
RR (%)	29	32	26.5	28
MS (mos)	10	9.5	9.7	8.8
1-yr survival (%)	41.5	40.5	41.5	39
Toxicity (%)				
Grade 3 or 4 neutropenia	73	46.5	64.5	77
Grade 3 or 4 thrombocytopenia	2	34.5	10	6
Grade 2–4 neuropathy	5	3.4	13	6.5
Grade 1 or 2 alopecia	NA	10	52	11

Grossi F, The Oncologist 2010

Negative phase III trials of new agents in NSCLC 2000-2010

Compound	Mechanism of action	N° trials	N	End point
Gefitinib	EGFR TKI	8	5975	OS
Erlotinib	EGFR TKI	4	3661	OS
Afatinib	EGFR/HER2 TKI	1	585	OS
Cetuximab	EGFR antibody	1	676	PFS
Prinomastat	Matrix metalloprotease inhibitor	2	1048	OS
Rebimastat	Matrix metalloprotease inhibitor	1	774	OS
PF-676	Toll-like receptor 9-activating oligodeoxynucleotide	2	1667	OS
Aprinocarsen	Protein kinase C-alpha antisense oligonucleotide	2	1286	OS
Bexarotene	Retinoid X receptor activator	2	1235	OS
Lonafarnib	Farnesyl-transferase inhibitor	1	675	OS
Figitumumab	IGF-1R antibody	1	681	OS
Celecoxib	Cox2 inhibitor	1	561	OS
IL-2	Cytokine	1	241	OS
Total		27	19 065	

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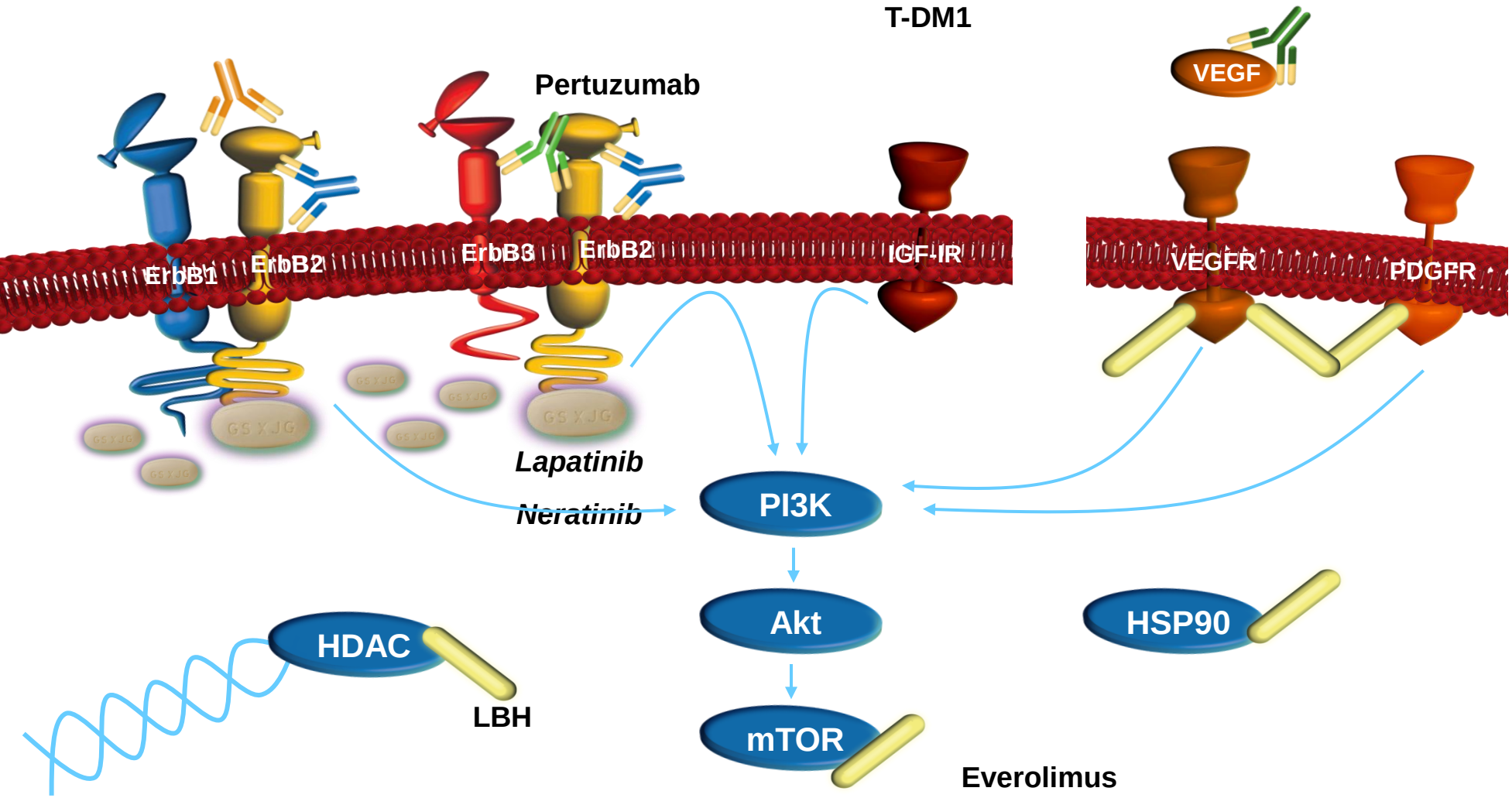
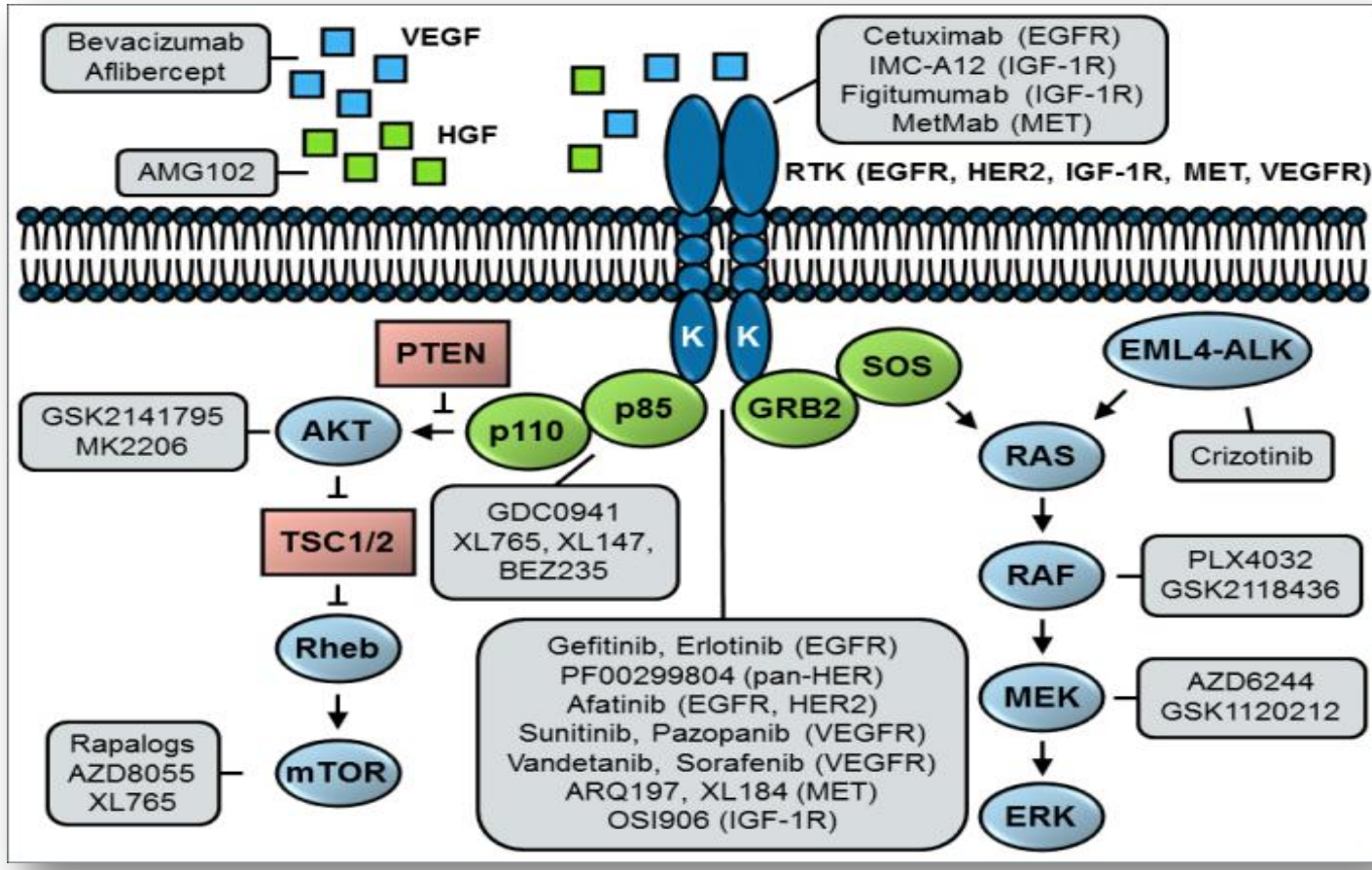
Targets and bullets in breast cancer



Molecular targets and agents affecting specific targets being studied as potential therapy for NSCLC



EGFR-TKIs in NSCLC patients with EGFR mutations

Reference	#	Selection criterion	Line	Drug	RR (%)	PFS (months)	OS (months)
Asahina	16	EGFR mutation	I	Gefitinib	75	8.9	Not reached
Inoue	30	EGFR mutation	I	Gefitinib	66	6.5	17.8
Inoue	16	EGFR mutation	I	Gefitinib	75	9.7	Not reported
Kimura	13	EGFR mutation	I	Gefitinib	53.8	3.2	10.1
Rosell	217	EGFR mutation	I/II	Erlotinib	70.6	14	27
Rosell	12	EGFR mutation	I	Erlotinib	90	13	>28.0
Sequist	34	EGFR mutation	I	Gefitinib	55	9.2	17.5
Yang	55	EGFR mutation	I	Gefitinib	69	8	24
Sugio	20	EGFR mutation	I/II	Gefitinib	63.2	7.1	20
Sunaga	21	EGFR mutation	I/II	Gefitinib	76	12.9	Not reached
Sutani	38	EGFR mutation	I/II	Gefitinib	78	9.4	15.4
Yoshida	27	EGFR mutation	I/II	Gefitinib	90.5	7.7	Not reached
Han	17	EGFR mutation	I/II+	Gefitinib	64.7	21.7	30.5
Tamura	28	EGFR mutation	I/II/III	Gefitinib	75	11.5	Not reached

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IPASS (Iressa Pan Asia Study)
Study design

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

Gefitinib 250 mg/day

1:1 randomization

Carboplatin AUC 5 or 6 and Paclitaxel 200mg/m^2 3 wkly

Endpoints

Primary
- Progression free survival (non-inferiority)

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

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

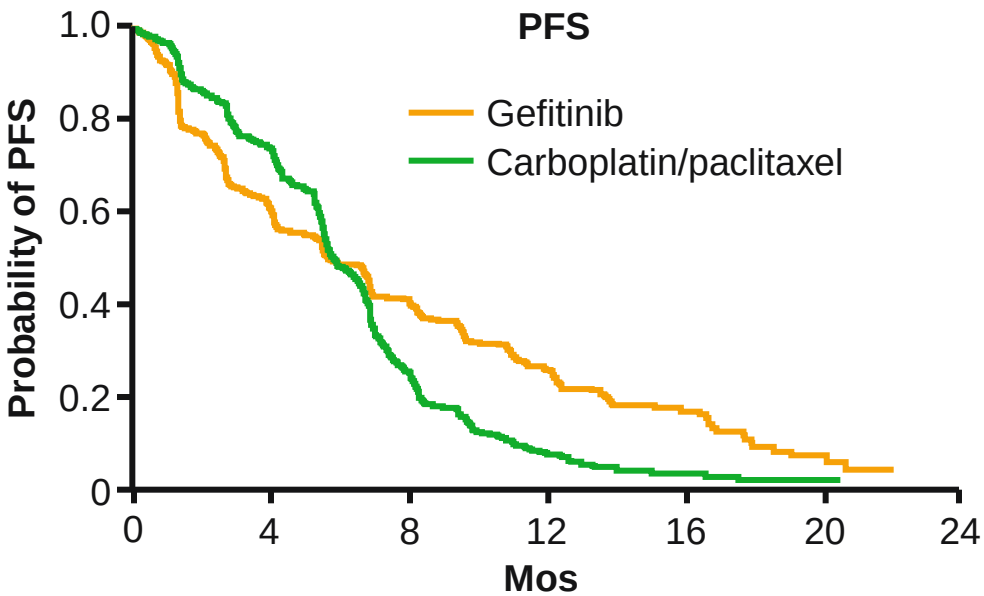
*Never smokers:<100 cigarettes in lifetime; light ex-smokers: stopped ≥15 years ago and smoked ≤10 pack yrs

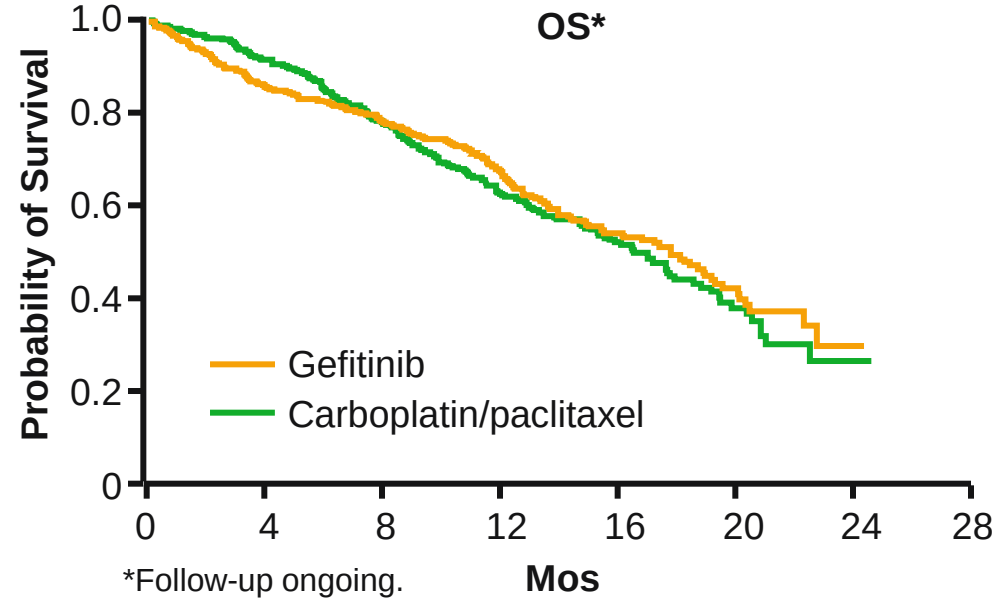
Carboplatin/paclitaxel was offered to gefitinib patients upon progression

Mok T, NEJM 2009

IST

IPASS: Results in ITT Population





*Follow-up ongoing.

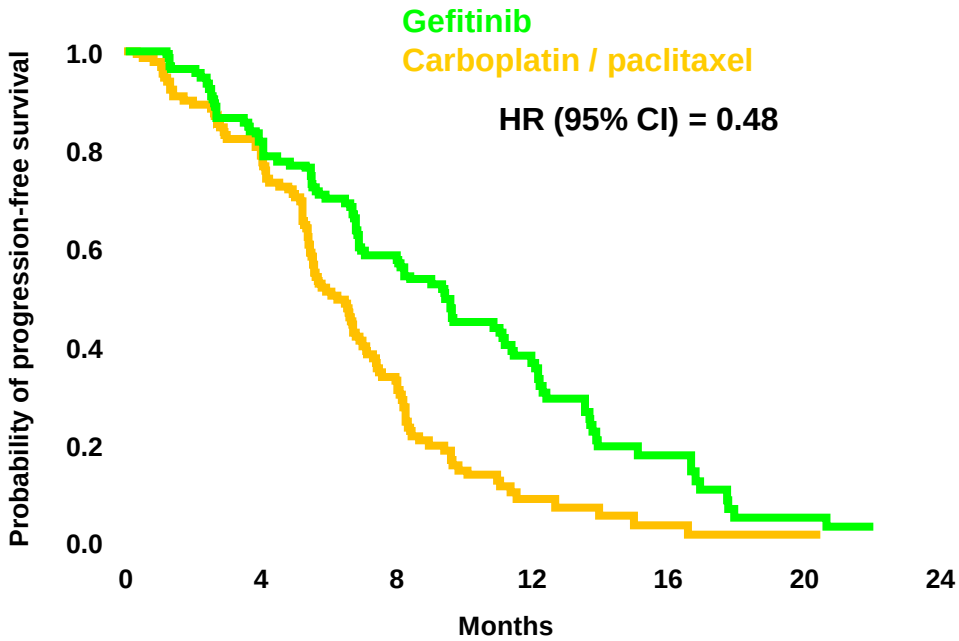
	G	C/P
n	609	608
Median PFS, mos	5.7	5.8
	HR: 0.74; *P* < .001	
12-mo PFS, %	25	7

	G	C/P
ORR, %	43.0	32.2
Median OS, mos	18.6	17.3
	HR: 0.91; *P* = NR	
12-mo OS, %	68	64

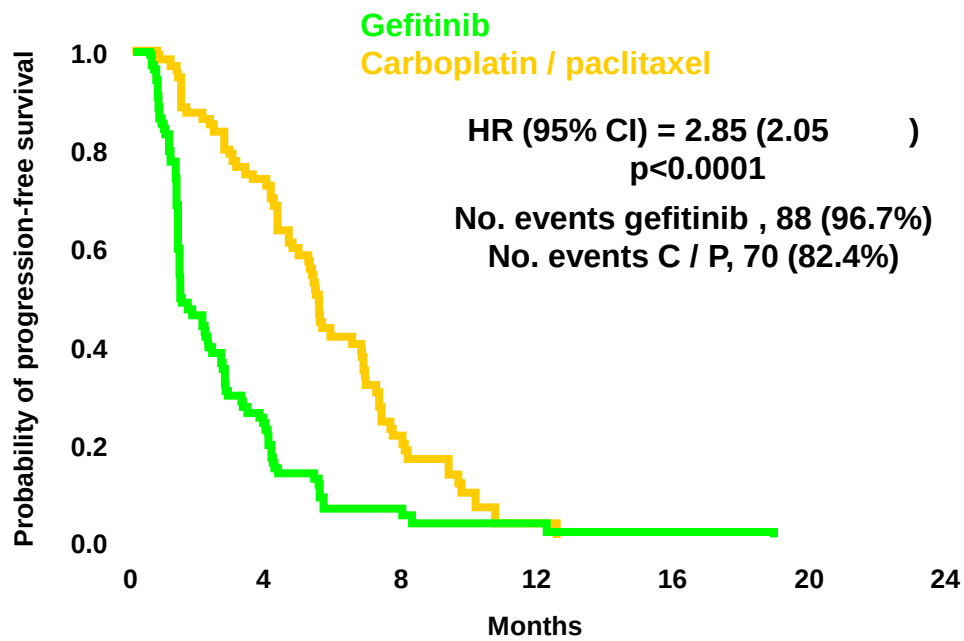
Mok T, NEJM 2009

PFS in EGFR mutation positive and negative patients

EGFR mutation positive



EGFR mutation negative



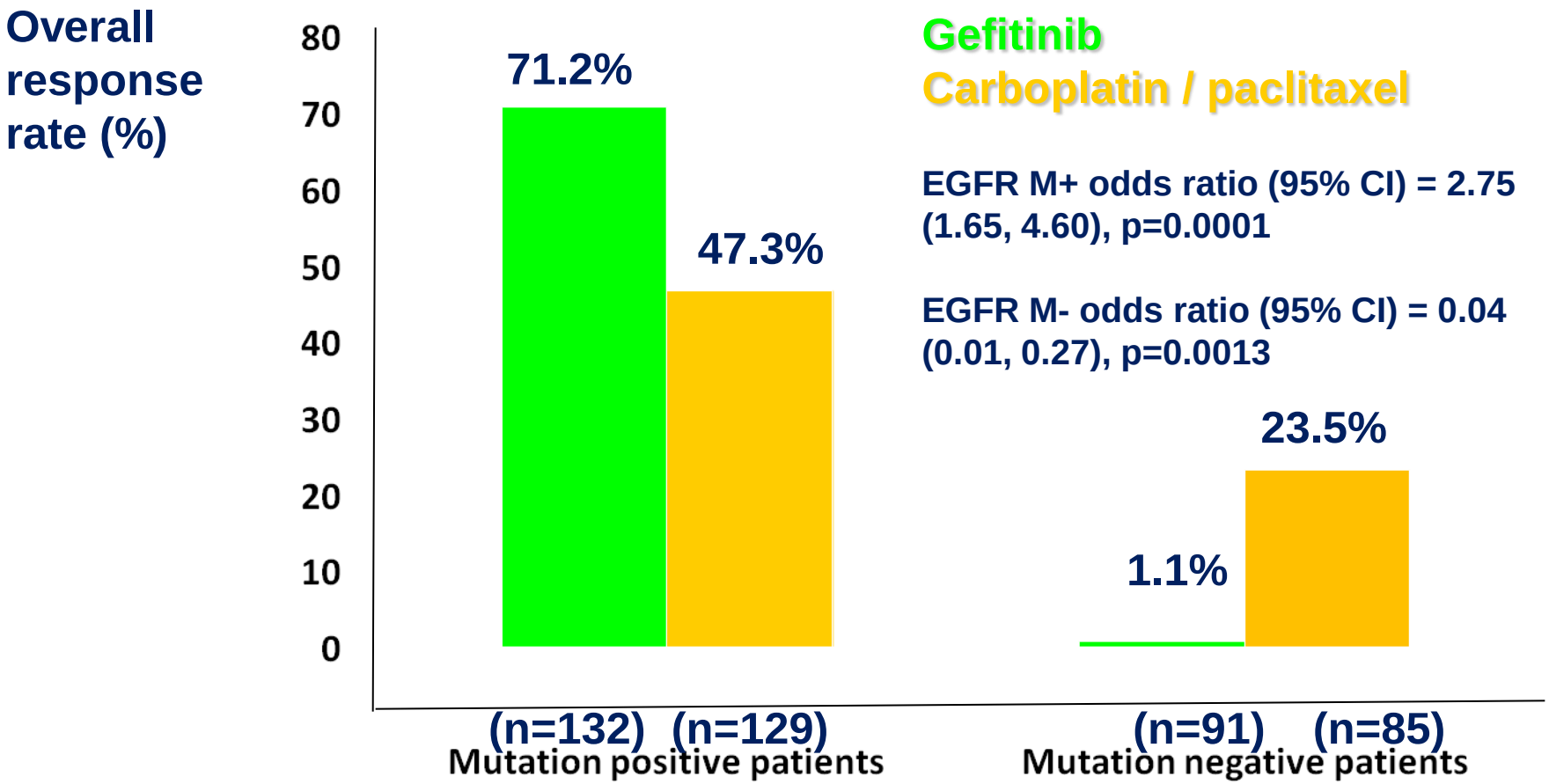
At risk :													
Gefitinib	132	108	71	31	11	3	0	91	21	4	2	1	0	0
C / P	129	103	37	7	2	1	0	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

Mok T, NEJM 2009

ITT population
Cox analysis with covariates

IPASS: objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Mok T, NEJM 2009

EURTAC & OPTIMAL: studies design

EURTAC; NCT00446225

- Chemonaïve
- Stage IIIB/IV NSCLC
- *EGFR* exon 19 deletion or exon 21 L858R mutation
- ECOG PS 0–2

(n=174)

R

- Mutation type
- ECOG PS (0 vs 1 vs 2)

Erlotinib 150mg/day → PD

Platinum-based doublet chemotherapy q3w x 4 cycles* → PD

- **Phase III, randomised, open-label, active-controlled**
- **Primary endpoint**
  - progression-free survival (PFS)
    - interim analysis planned at 88 events

*Cisplatin 75mg/m² d1/docetaxel 75mg/m² d1; cisplatin 75mg/m² d1/gemcitabine 1250mg/m² d1,8; carboplatin AUC6 d1/docetaxel 75mg/m² d1; carboplatin AUC5 d1/gemcitabine 1000mg/m² d1,8.

- **Secondary endpoints**
  - Objective response rate (ORR)
  - Overall survival (OS)
  - Location of progression
  - Safety
  - *EGFR* mutation analysis in serum
  - Quality of life (QoL)

- Phase III study initiated by Tongji University, Shanghai, China
- Recruitment in China

Chemonaïve advanced NSCLC

- *EGFR* mutation-positive (exon 19 or 21)
- ECOG PS 0–2
- n~150

R

Erlotinib 150 mg/day until PD

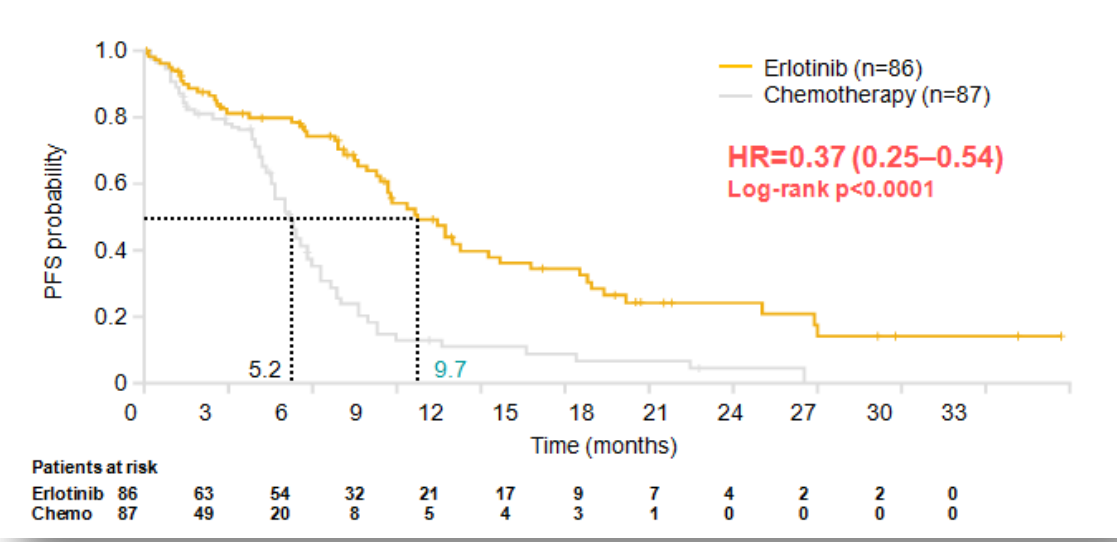
Gemcitabine (1,000 mg/m², IV, d1 and d8) plus carboplatin (AUC=5, IV d1) repeated every 3 weeks up to 4 cycles

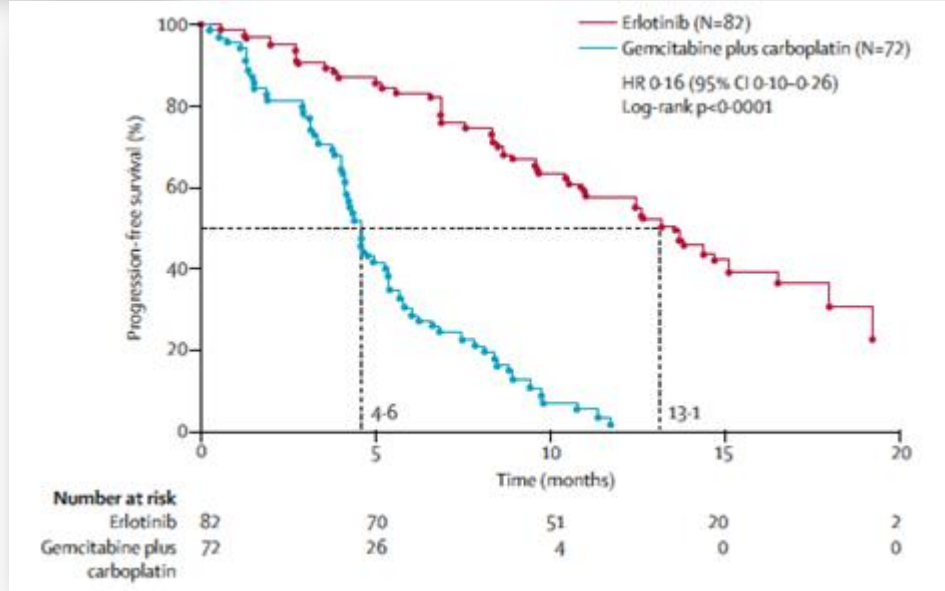
- **Primary endpoint: PFS**
- **Secondary endpoints: ORR, OS, QoL and safety**

gem/carb = gemcitabine/carboplatin; AUC = area under curve

Rosell R, ASCO 2011
Zhou C, Lancet Oncology 2011

EURTAC & OPTIMAL: PFS



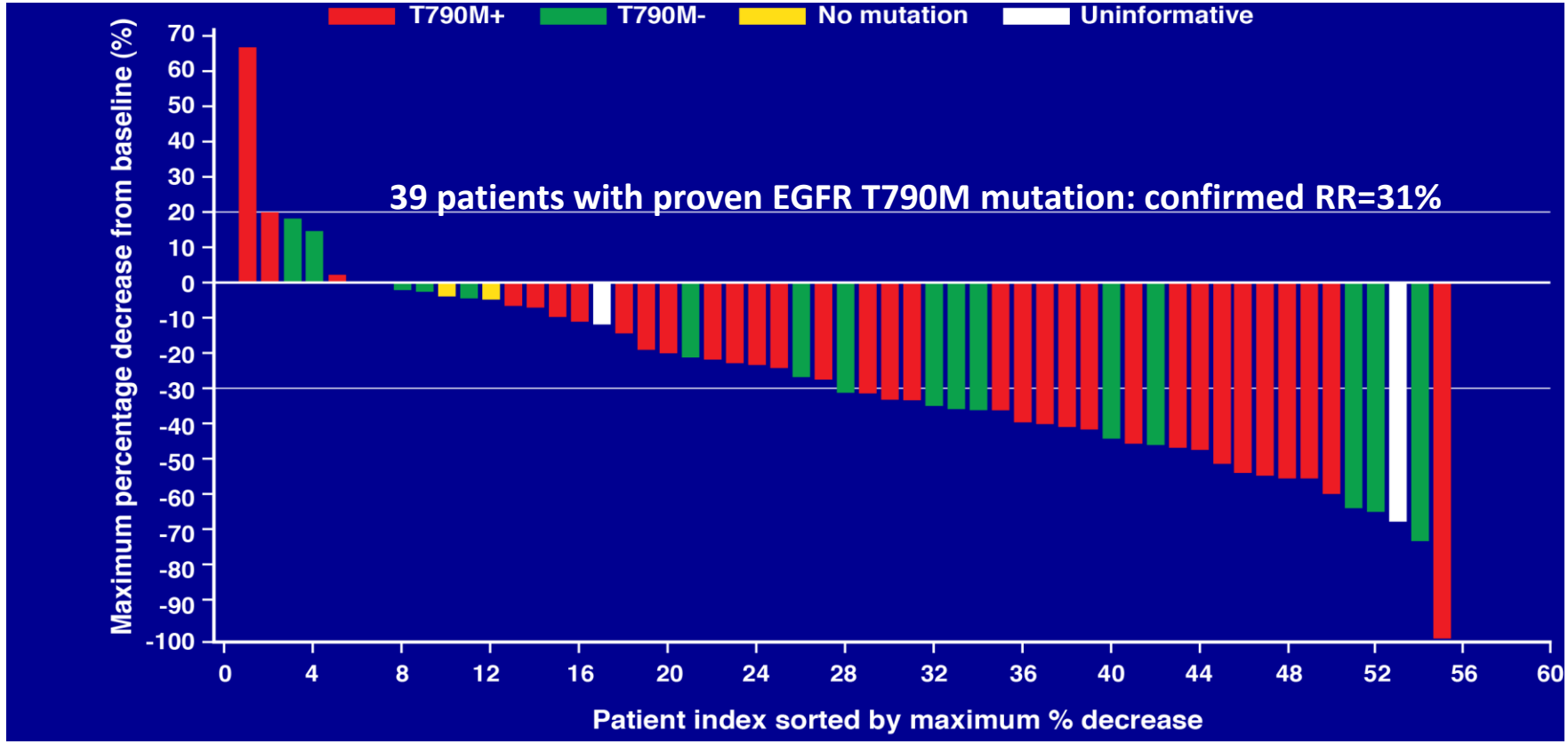


Rosell R, ASCO 2011
Zhou C, Lancet Oncology 2011

T790M mutations

- 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

Tumor regression by T790M mutation status at recommended dose of cetuximab+afatinib



Jangijian YY, ASCO 2011

LUX-Lung 1: Trial design

Patients with:

- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization 2:1
(Double Blind)

Oral afatinib 50 mg once daily
plus BSC

Oral placebo once daily
plus BSC

Primary endpoint: Overall survival (OS)

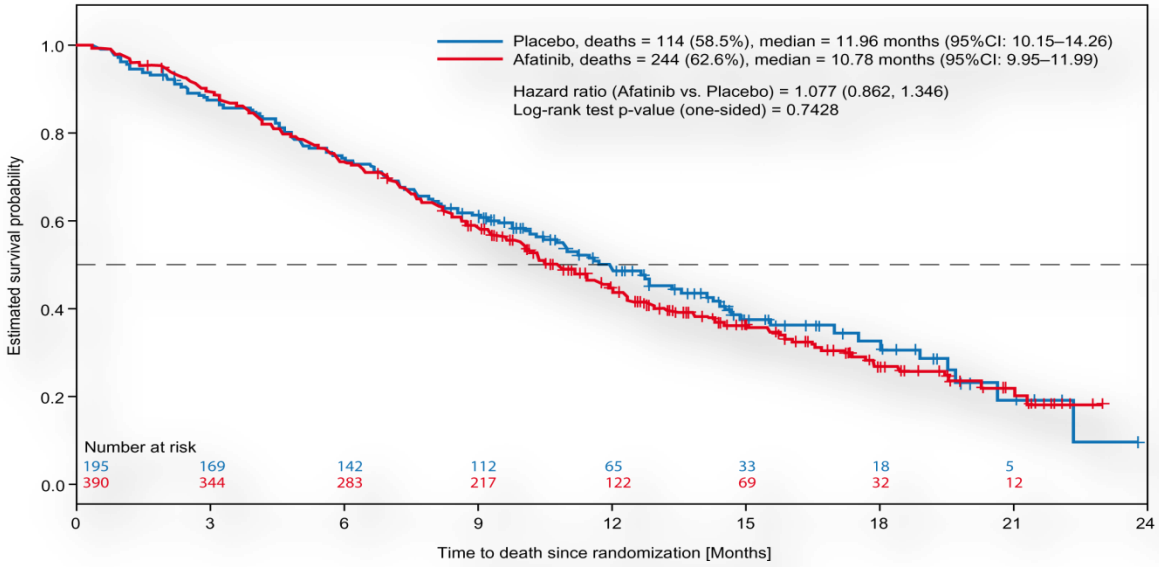
Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

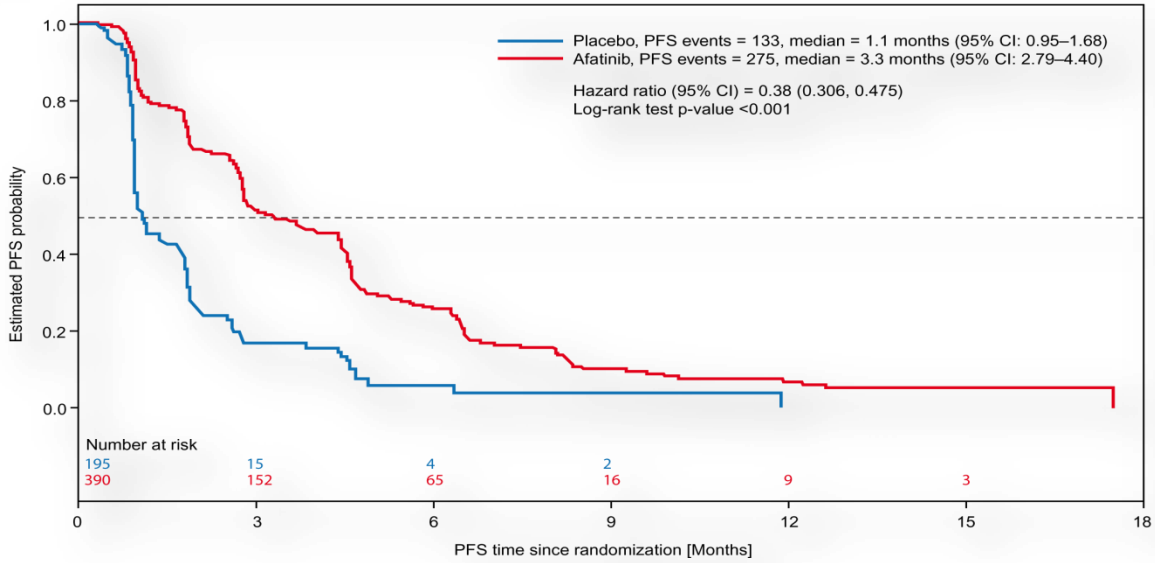
- Radiographic assessments at 4, 8, 12 wks and every 8 wks thereafter
- Exploratory biomarkers:

Archival tissue testing for EGFR mutations (optional; central lab)
Serum EGFR mutational analysis (all patients)

Miller VA, Lancet Oncol 2012

LUX-LUNG 1: OS & PFS

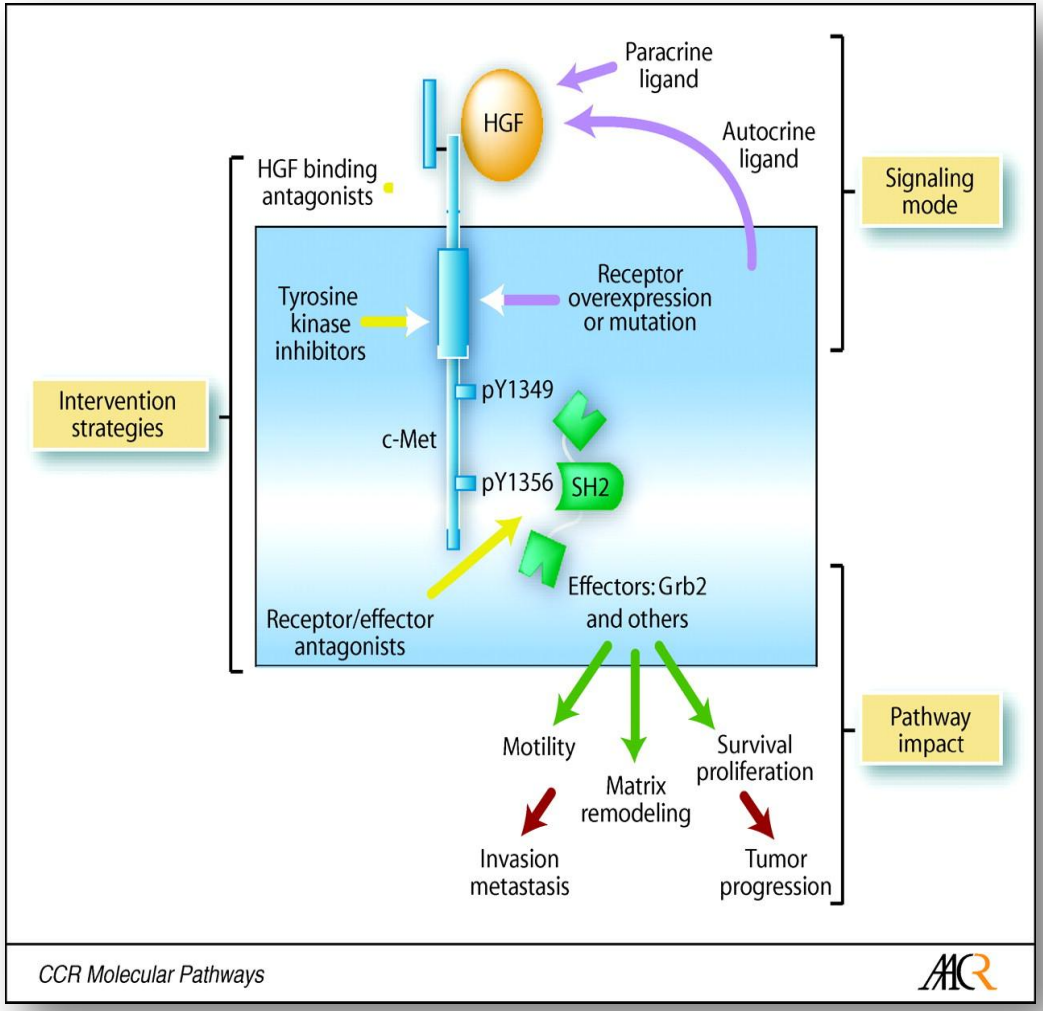




Miller VA, Lancet Oncol 2012

MET Signaling

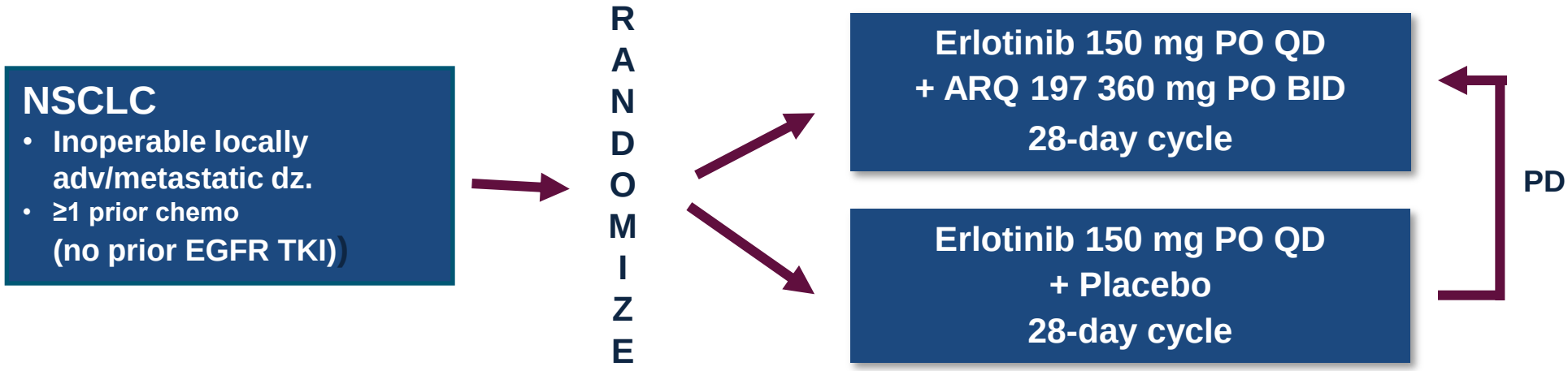
- MET is the receptor for hepatocyte growth factor (HGF)
- MET activation → cell-cell detachment, proliferation, invasion, angiogenesis, and survival – assoc w/ poor prognosis in NSCLC
- MET activation associated with EGFR TKI resistance
- MET activation results from:
  - Receptor overexpression (frequent in NSCLC)
  - Activating mutations (rare in NSCLC)
  - Gene amplification
  - Autocrine / paracrine (stromal) secretion of HGF



Peruzzi B, Clin Cancer Res 2006

Tivantinib: Study Design

Randomized placebo-controlled double-blind phase II trial

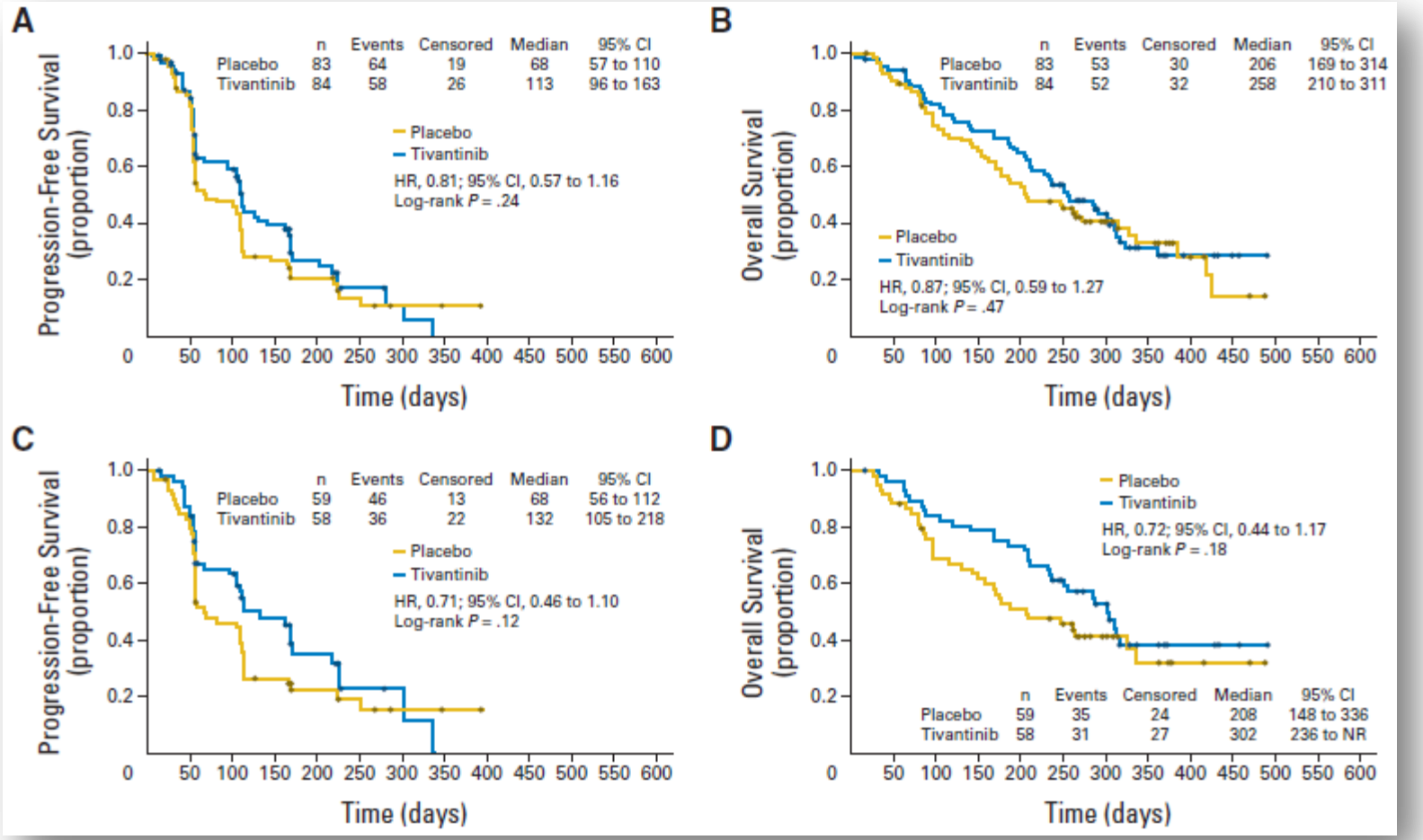


Endpoints
- 1 PFS
- 2 ORR, OS
- Subset analyses
- Crossover: ORR

- 33 sites in 6 countries
- Study accrual over 11 months (10/08-9/09)
- Randomization stratified by prognostic factors: gender, age, smoking, histology, PS, prior therapy, best response, and geography (U.S. vs. ex-U.S.)

Sequist LV, JCO 2011

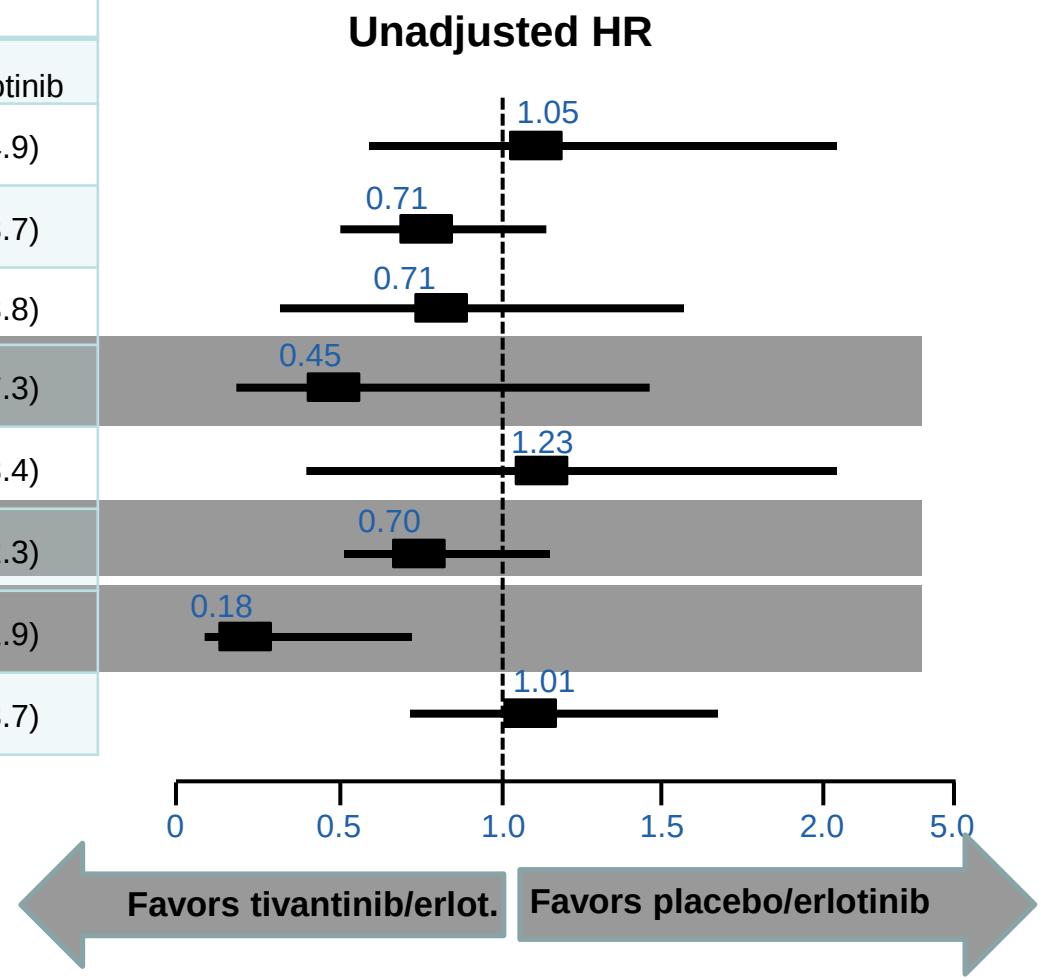
PFS & OS in the ITT population and in nonsquamous



Sequist LV, JCO 2011

Tivantinib: Phase II data

		Median PFS (95% CI), months	
	n/N	Tivantinib/Erlotinib	Placebo/Erlotinib
Squamous cell	26/24	3.2 (1.9 - 4.2)	2.0 (1.8 - 4.9)
Non-squamous cell	58/59	4.4 (3.5 - 7.3)	2.3 (1.9 - 3.7)
c-MET FISH > 4	19/18	3.6 (1.9 - 5.7)	3.6 (1.7 - 3.8)
c-MET FISH > 5	8/11	5.6 (3.8 - NE)	3.6 (1.8 - 7.3)
EGFR mutant	6/11	5.6 (1.9 - 7.5)	4.9 (1.9 - 8.4)
EGFR wt	51/48	3.2 (1.9 - 4.2)	1.9 (1.8 - 2.3)
KRAS mutant	10/5	2.3 (1.8 - NE)	1.0 (0.3 - 1.9)
KRAS wt	49/45	3.6 (1.9 - 4.2)	2.3 (1.9 - 3.7)



- **A PFS benefit associated with tivantinib plus erlotinib was observed in patients with tumors harboring amplified c-MET, wild-type EGFR, or mutant KRAS**

Cox proportional hazard ratio analysis of median progression-free survival by patient subgroup. Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; PFS, progression-free survival; wt, wild type

Sequist LV, JCO 2011

MARQUEE Phase III study design

A multicenter, phase 3, randomized, double-blind, placebo-controlled clinical trial

Phase III in NSCLC

- Inoperable, locally advanced or metastatic disease
- Non-squamous histology
- 1 - 2 regimens of prior chemo (no prior EGFR TKI)
- Prior platinum-based doublet therapy required

Endpoints

1 : OS (ITT population)

2 /Exploratory:

- PFS (ITT population)
- PK and PD analysis
- OS and PFS in EGFR wt patients
- Safety and toxicity
- QOL/FACT-L
- Biologic subgroup analysis

RANDOMIZE

Arm A: Tivantinib 360 mg PO BID + Erlotinib 150 mg PO QD

Arm B: Placebo PO BID + Erlotinib 150 mg PO QD

Stratification by EGFR and KRAS mutational status

Scagliotti GV, Clin Lung Cancer 2012

Tivantinib will not meet primary endpoint, phase III trial discontinued

By Jake King

Shares of ArQule (NASDAQ:ARQL) are being crushed in early trading on Tuesday following an announcement that the company and partner Daiichi Sankyo (OTC:DSNKY) will be discontinuing a Phase III non small-cell lung cancer (NSCLC) study of its lead product tivantinib. After a planned interim analysis of the MARQUEE trial, an independent safety monitoring committee advised that the drug would not meet its primary endpoint of improved overall survival in the 1,000 patient study, and the study should be discontinued. Tuesday's press release stated that the companies will continue to develop tivantinib for other oncology indications.

Most frustrating for ArQule shareholders is that their greatest fear, safety issues, were not the cause of the discontinuation, but rather efficacy. In August, enrollment for a separate, Asia-based Phase III trial (titled ATTENTION) of tivantinib for the same indication was suspended due to safety issues. A data safety monitoring committee raised concerns when the trial showed higher rates of interstitial lung disease (ILD). Analysts maintained that the concerns were unlikely to affect the drug and pointed to the domestic trial as the real determinant. At the time, PropThink advised against involvement in ARQL until safety issues were resolved.

The MARQUEE trial pitted tivantinib, which is a c-MET inhibitor, plus erlotinib against erlotinib plus placebo in previously-treated NSCLC patients. Marketed by Genentech, a subsidiary of Roche Holdings (OTC:RHHBY), and Astellas Pharma (OTC:ALPMY) as Tarceva in the U.S., erlotinib is a mainline treatment for NSCLC and is a tyrosine kinase inhibitor. Interestingly, MARQUEE's interim analysis did report a significant improvement in progression-free survival, but that data did not carry into overall survival. Tivantinib's near-term prospects now fall to a planned Phase III trial for the drug in hepatocellular carcinoma (HCC) and results from a Phase II trial for colorectal cancer, both due by early 2013. Already the drug showed promise in a Phase II trial for HCC, so many are pinning hopes on that indication, as well as the lack of safety issues in Western tivantinib trials. Shares of ARQL are off 55% to $2.20 in the late morning.

Onartuzumab (OAM4558g): study design

OAM4558g; NCT00854308

- **One or two prior chemotherapy regimens**
  - **Stage IIIB/IV NSCLC**
  - **ECOG PS 0–2**
  - **Tissue required**

  (n=128)

→ **R**

→ **Erlotinib 150mg/day + placebo** → **PD** → **Add MetMAb if eligible*** **(n=23)**

Stratification
- **Histology**
- **Smoking history**
- **ECOG PS**

→ **Erlotinib 150mg/day + MetMAb 15mg/kg IV q3w** → **PD**

- Second/third line advanced NSCLC
- Phase II, randomised, double-blind, placebo-controlled
- Primary endpoints
  - PFS in MET diagnostic positive (Met Dx+) patients
  - PFS in overall ITT population

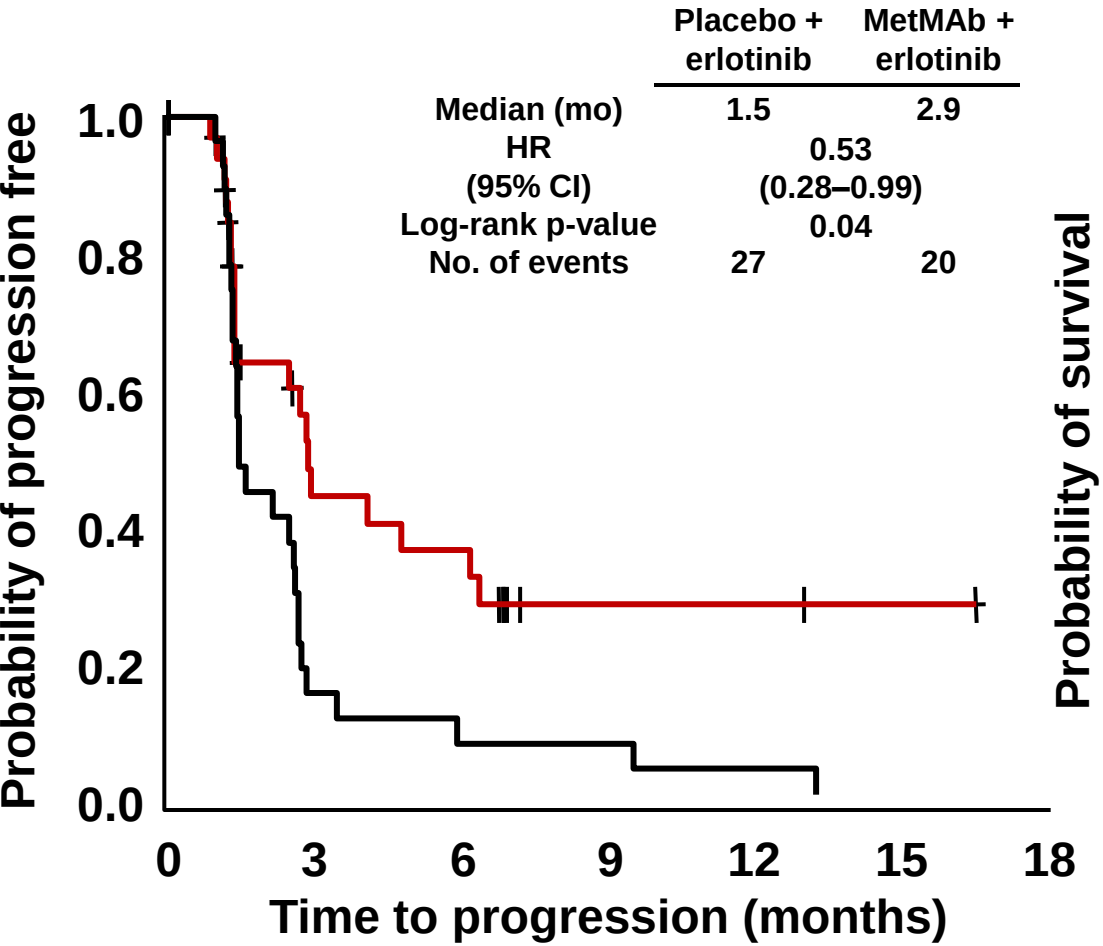
***Patient crossover permitted if eligible**

- Secondary endpoints
  - OS
  - ORR
  - TTP
  - duration of response
  - Safety
  - HRQoL (FACT-L, LCSS)
  - exploratory biomarker analyses

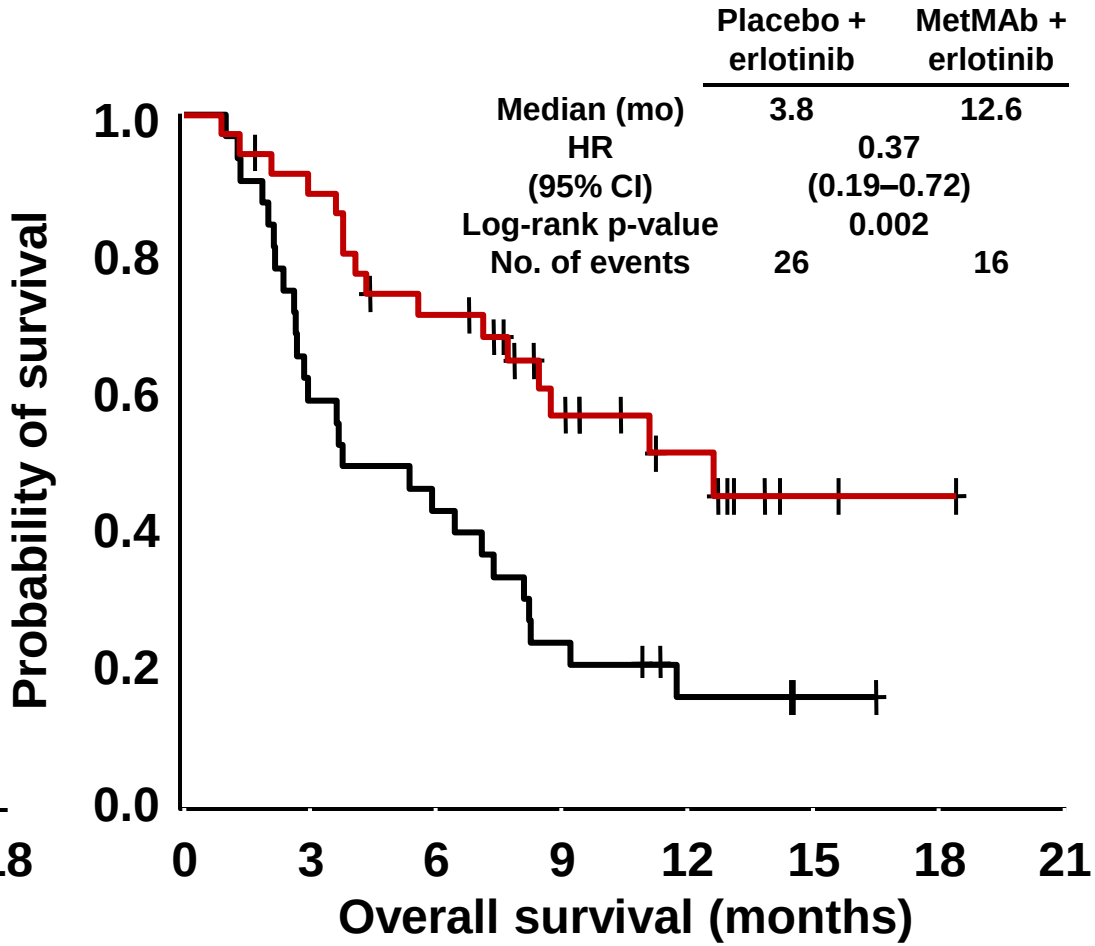
Spigel D, ASCO 2011

MetMAb plus Erlotinib in Met Dx+ Patients

PFS: HR=0.53



OS: HR=0.37



Spigel D, ASCO 2011

Phase III: Erlotinib +/- Onartuzumab in 2nd/3rd-line NSCLC

Study Population

Key eligibility:
- Stage IIIB/IV NSCLC
- MET Dx Positive*
- 2nd/3rd-line NSCLC
- Tissue required
- PS 0–1
- No prior EGFR inhib.

(N=480)

R
1:1

Onartuzumab
(15 mg/kg IV Q3W)
+
Erlotinib
(150 mg daily)

Placebo
+
Erlotinib
(150 mg daily)

Stratification factors:
- EGFR Mut Status
- MET IHC 2+ v. 3+
- No. of prior therapies
- Histology

*Central Testing for MET and EGFR

Primary objective:
OS

Secondary Objectives:
PFS QoL
ORR Safety

Agenda

- The limitations in the use of tumor biomarkers in clinical trials
  - Many biomarkers evaluations needs a lot of tissue
  - The heterogeneity of the tumor
  - The low expression of some biomarkers

Agenda

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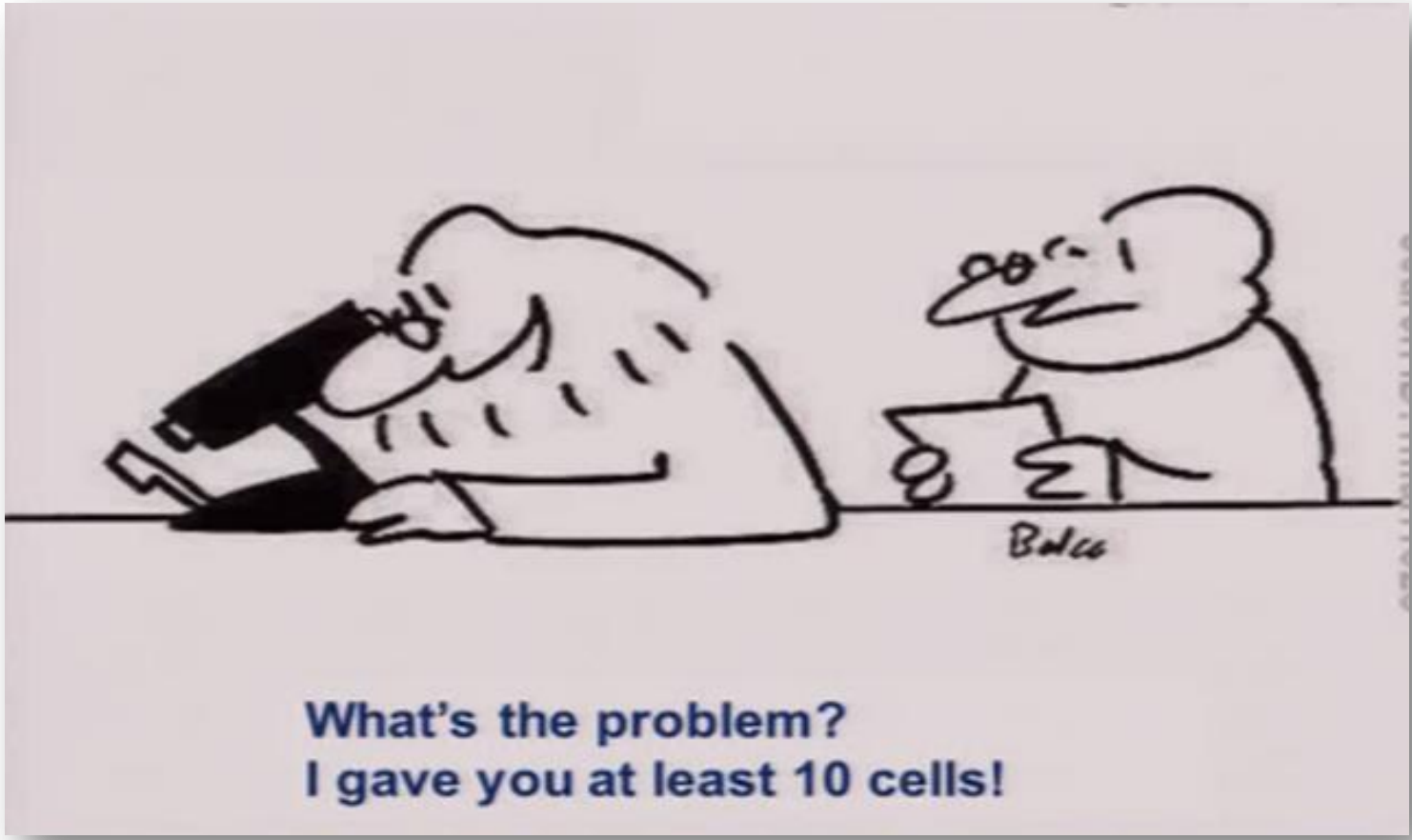
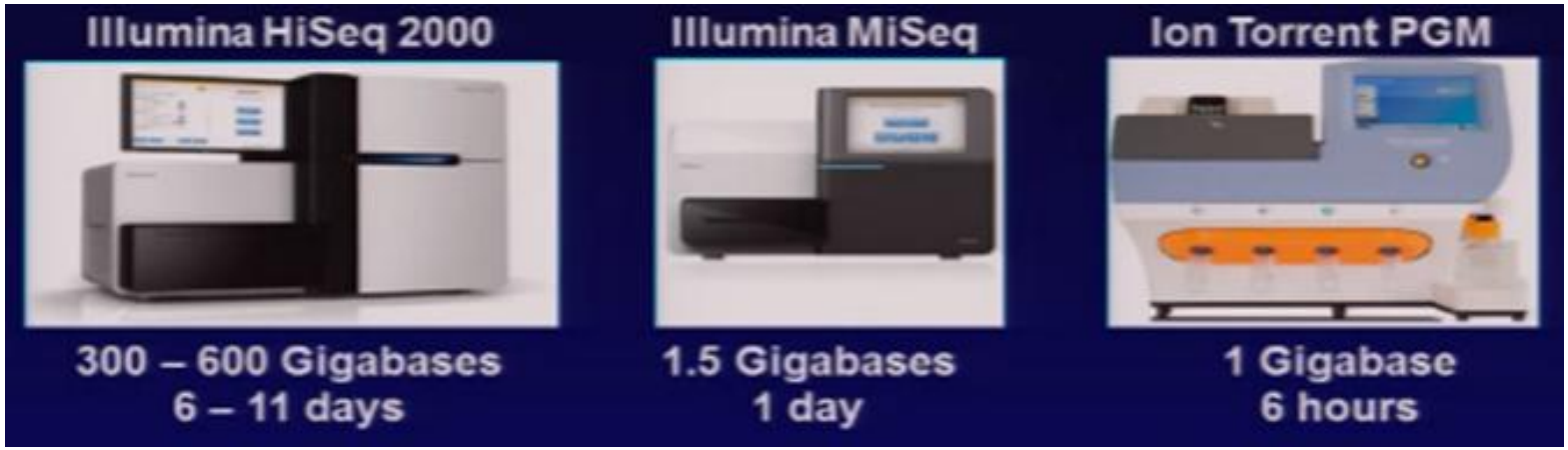
Pathologists vs Oncologists

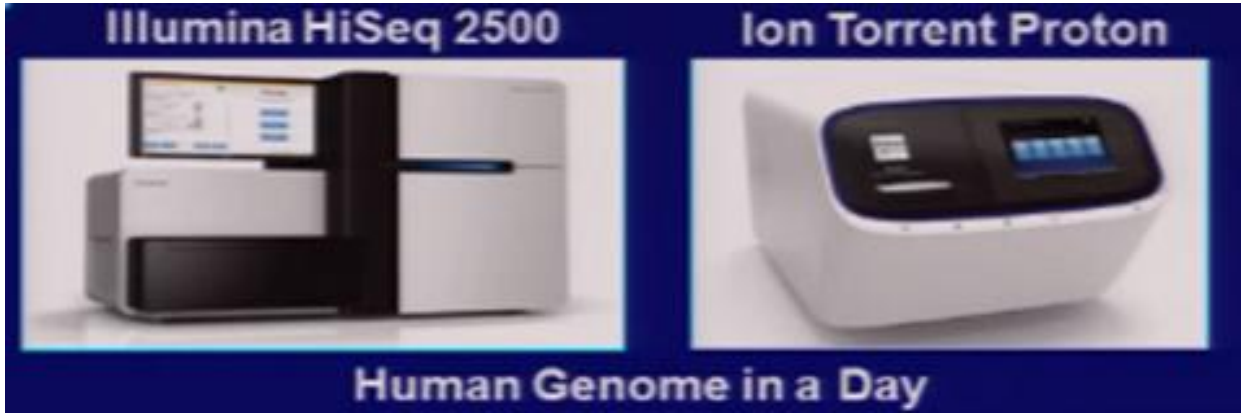


Next Generation of Sequencing

Current:



Emerging:



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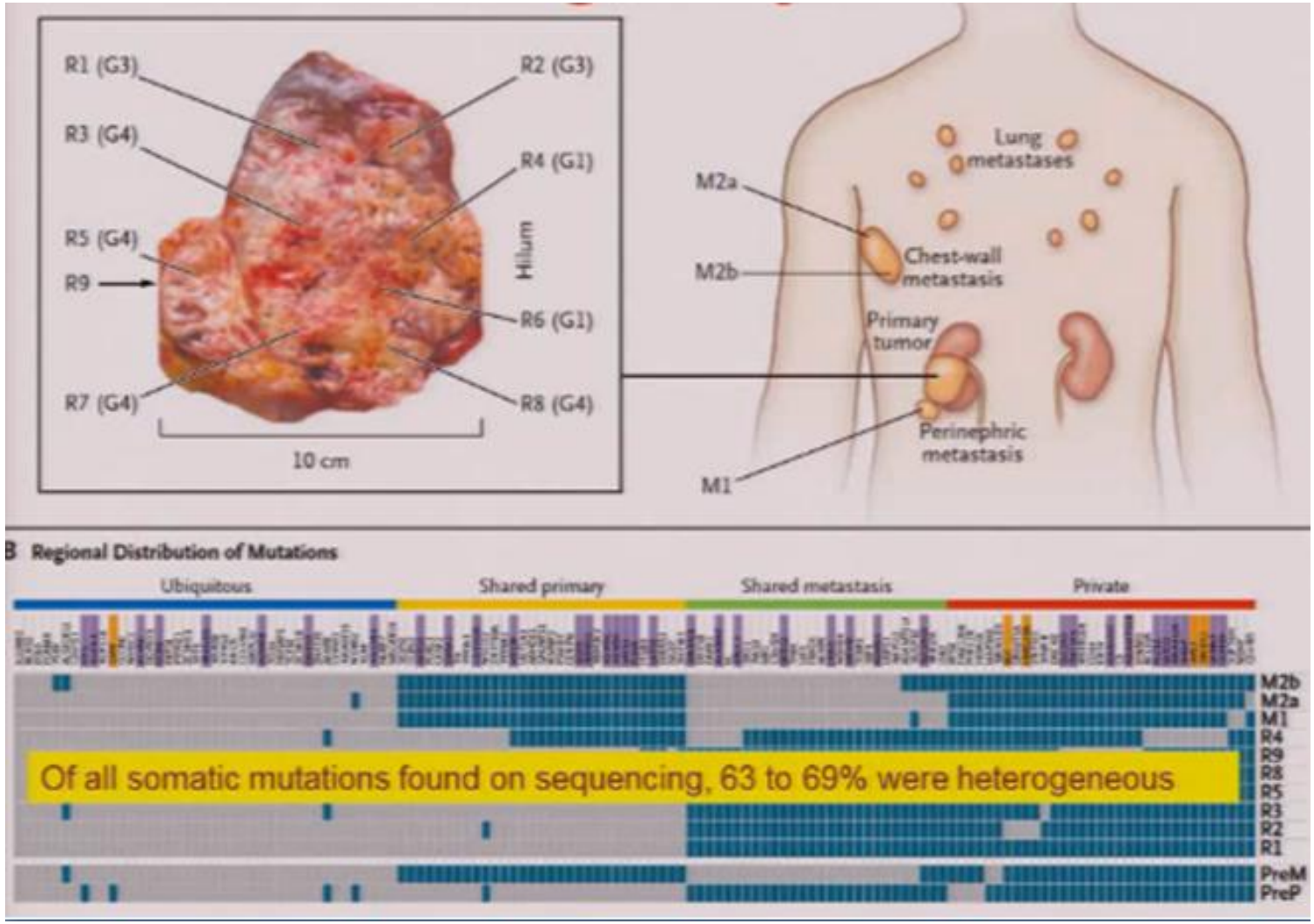
  - The heterogeneity of the tumor
  - The low expression of some biomarkers

Tumor heterogeneity



Reciprocal & complementary role of MET amplification & EGFR T790M mutation in acquired resistance to TKIs in lung cancer

EGFR mutational status and *MET* gene amplification in each primary or metastatic lesion

Patient	Primary	IM	LNs	Liver	Ad-G	Oment	Pleura
1	NA	DEL/T	DEL/T	DEL/m	—	DEL/T/M	—
2	DEL/T/m	—	DEL/M	DEL/T/m	DEL/T/m	—	—
3	DEL/M	DEL/M*	—	DEL/M	DEL/M	DEL/M	—
4	NE	—	—	—	—	—	DEL/T
5	L858R/T	—	—	—	—	—	L858R/T
6	DEL	DEL/T*	DEL/T†	—	—	—	—

Kidney	Chest	Ret-P	Skin	Thyroid	Bowel	Heart	Bone
	—	DEL/T	DEL/M	—	—	—	—
DEL/T/m	—	—	—	DEL/T	—	—	—
DEL/M	DEL/M	—	—	—	DEL/M	DEL/M	—
—	—	—	—	—	—	—	DEL/T
—	L858R/T	—	—	—	—	—	—
—	—	—	—	—	—	—	—

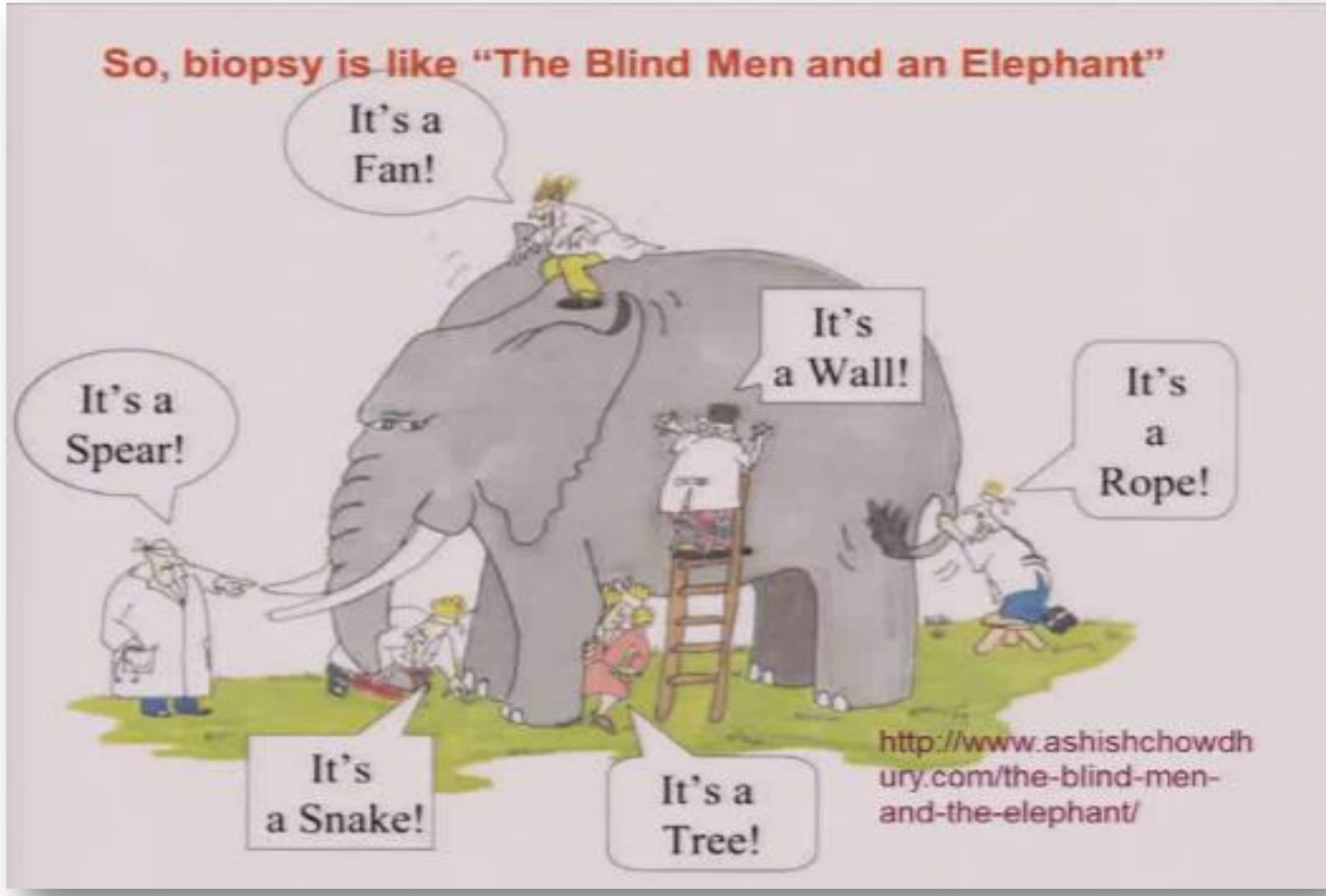
Suda K, Clin Cancer Res 2010

Intratumor heterogeneity

- Can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples
- May present major challanges to personalized medicine and biomarker development
- May foster tumor adaptation and therapeutic failure through Darwinian selection

Geringer, NEJM 2012

Heterogeneity of the tumor



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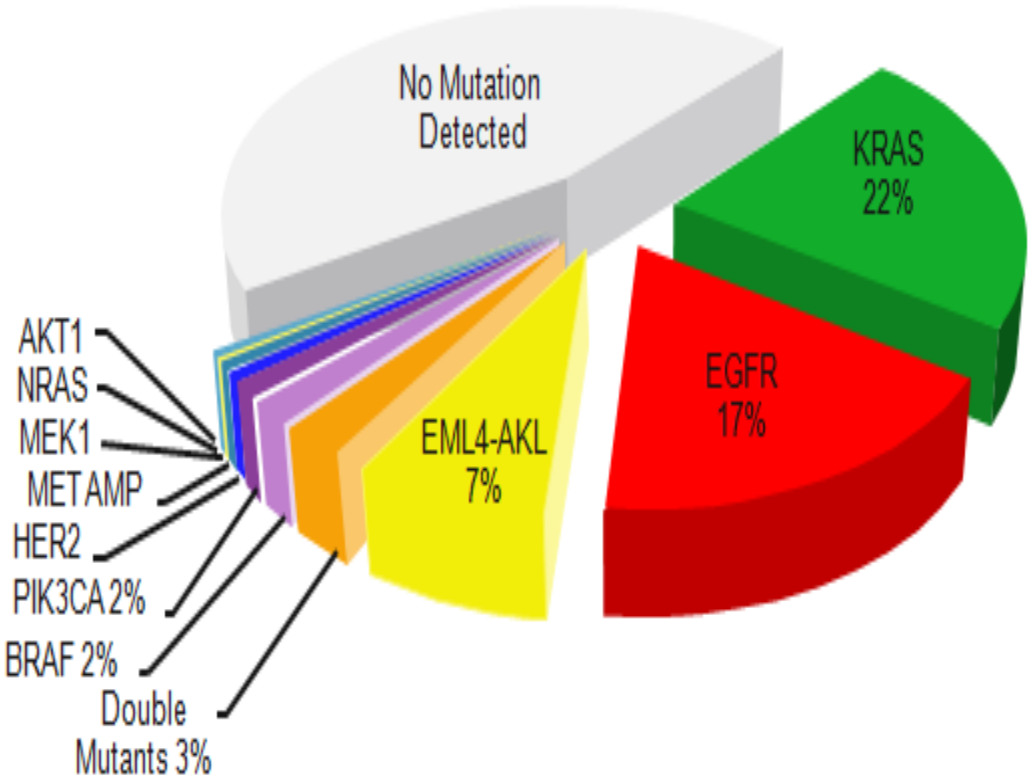
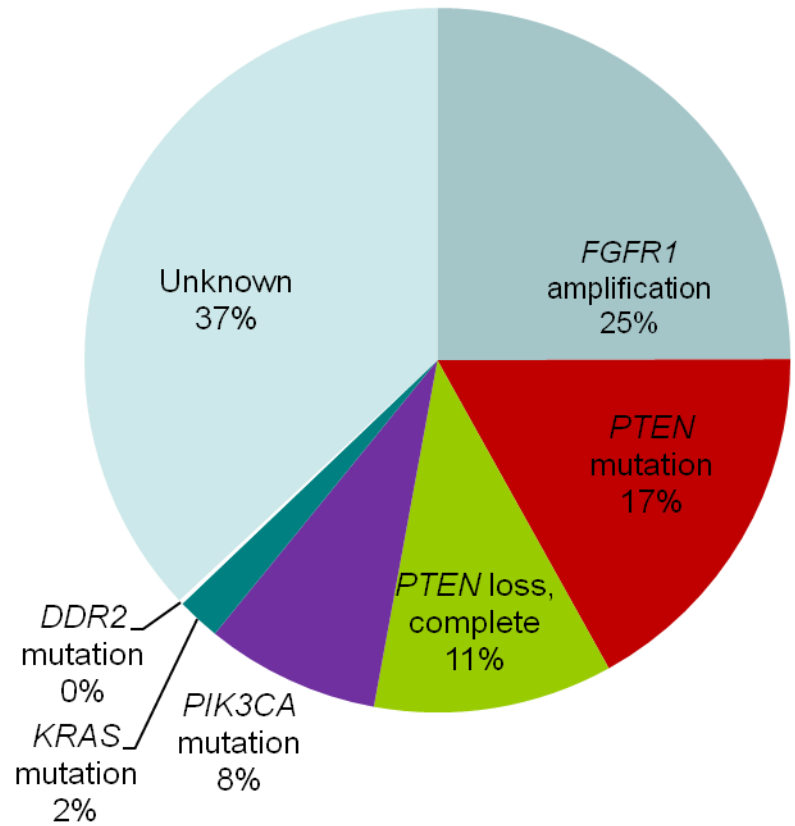
Adk & squamous driver mutations



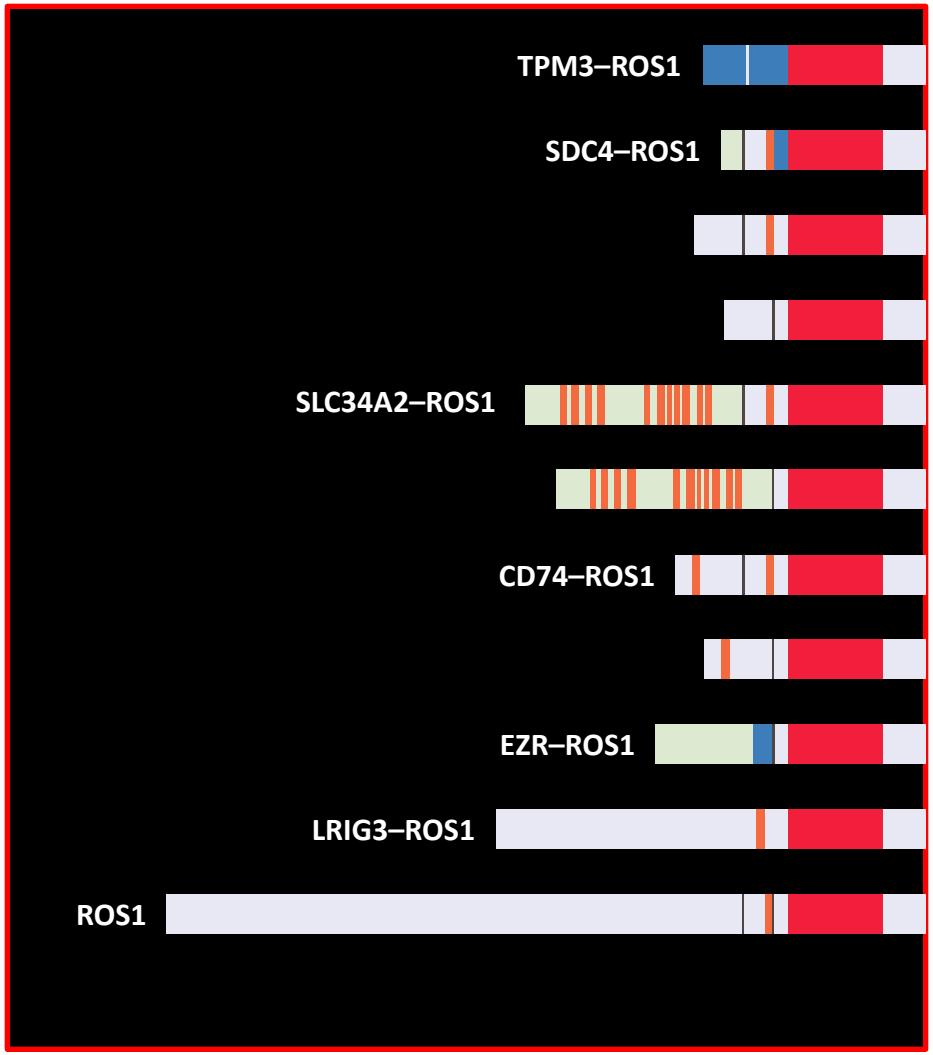


An actionable driver event was identified in the majority of adenocacinoma and squamous cell lung cancers

Next generation sequencing is feasible using ‘small biopsy’ and FFPE specimens

Summary of tumor responses in patients with advanced ROS1+ NSCLC (n= 14)

ROS1 Rearrangements in NSCLC



- ✓ ~1% of NSCLC cases
- ✓ More frequent in younger patients
- ✓ More frequent in never or light smokers with adenocarcinoma histology
- ✓ No overlap with other oncogenic drivers

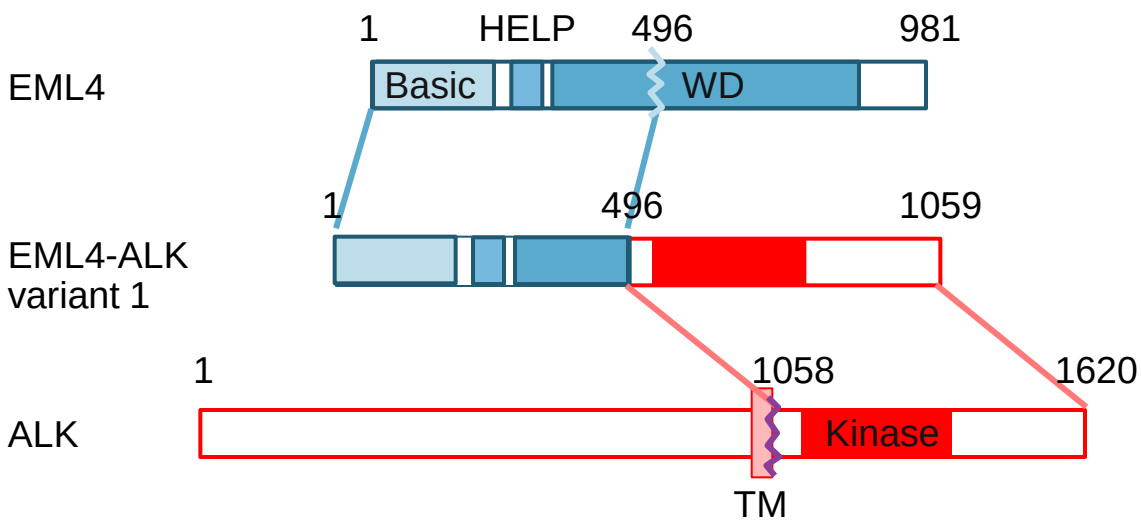
Bergethon, JCO 2012
Takeuchi, Nat Med 2012

EML4-ALK translocations in NSCLC

Vol 448 | 2 August 2007 | doi:10.1038/nature05945 nature

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]



***EML4-ALK* frequency:**

~ 4% (64/1709)

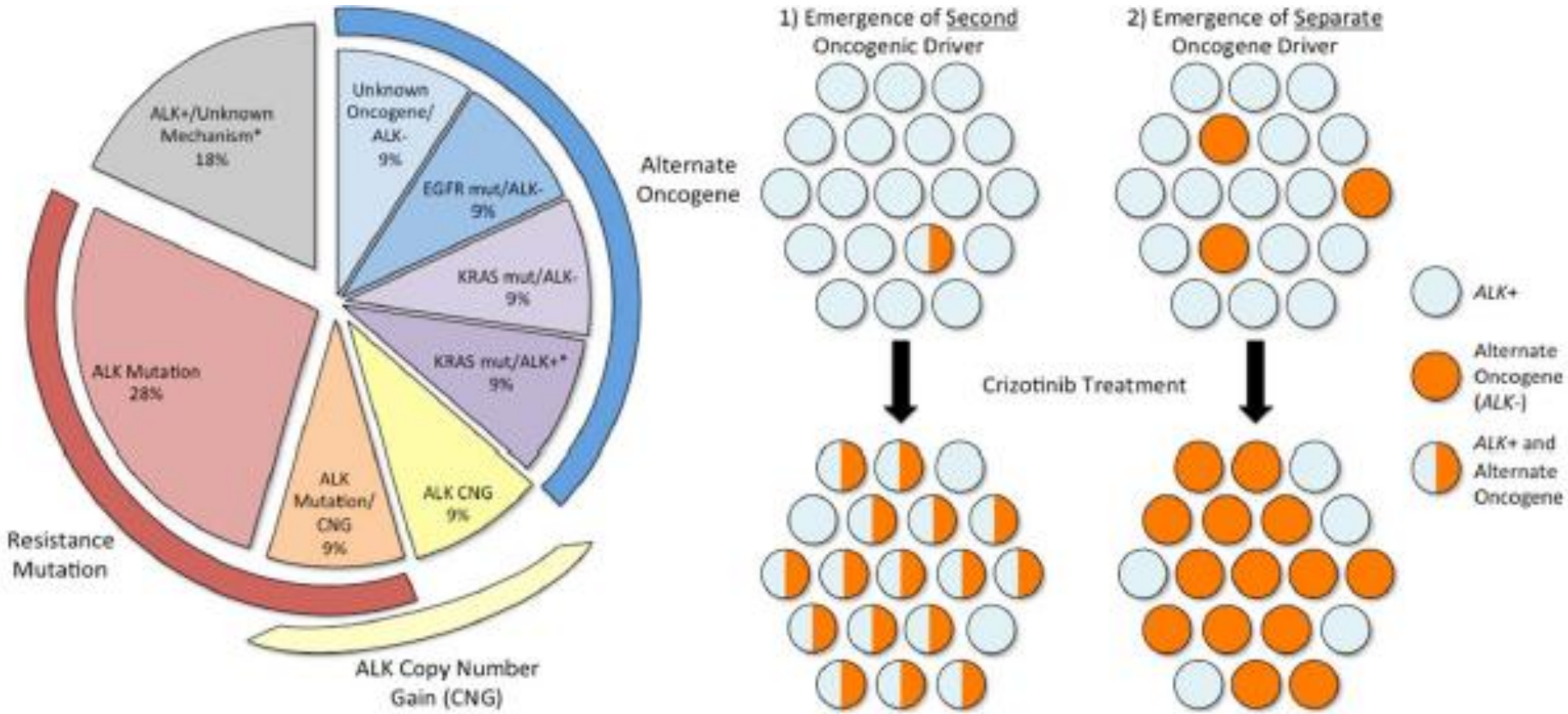
Primarily in adenocarcinoma

More common in younger patients

More common in never-smokers

Soda M, Nature 2007

Mechanism of crizotinib resistance



Doebele R, Clin Cancer Res 2012

Agenda

- Methodological problems in trials with biomarkers
  - Definition of progressive disease: RECIST vs others
  - The role of cross-over in biomarkers studies. What is the best endpoint in trials with high response agents?
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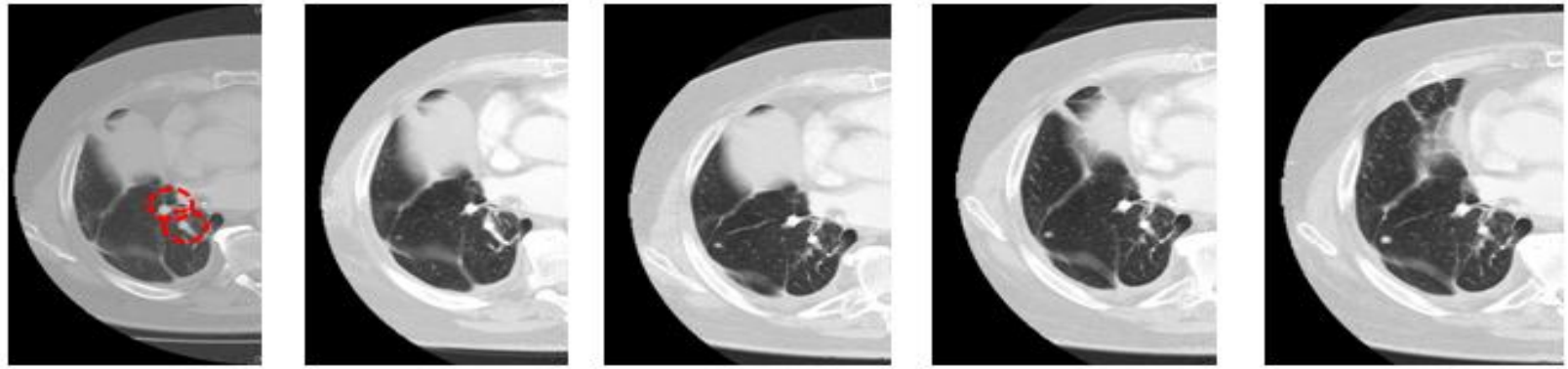
Definition of PD during EGFR TKIs treatment

- 56-year-old woman with exon 19 EGFR mutation. PD (2 new lung lesion less than 5 mm in diameter) after 15 months of gefitinib, asymptomatic.

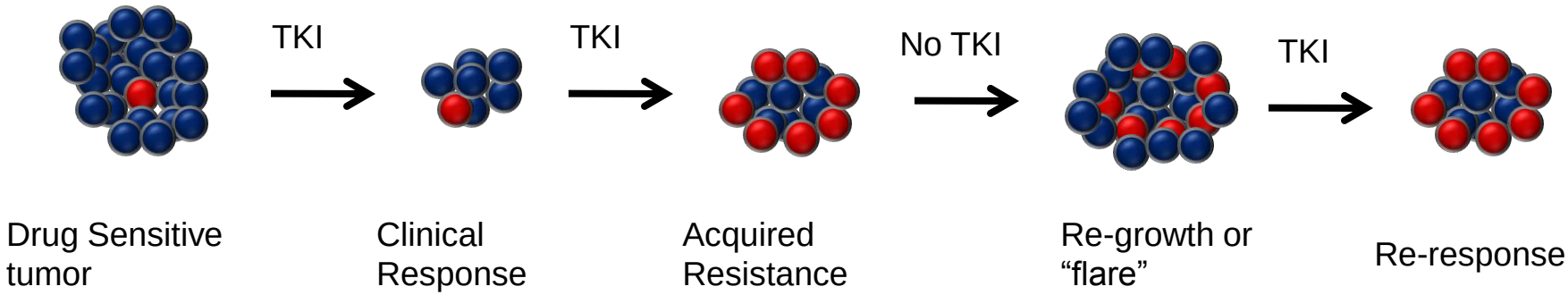


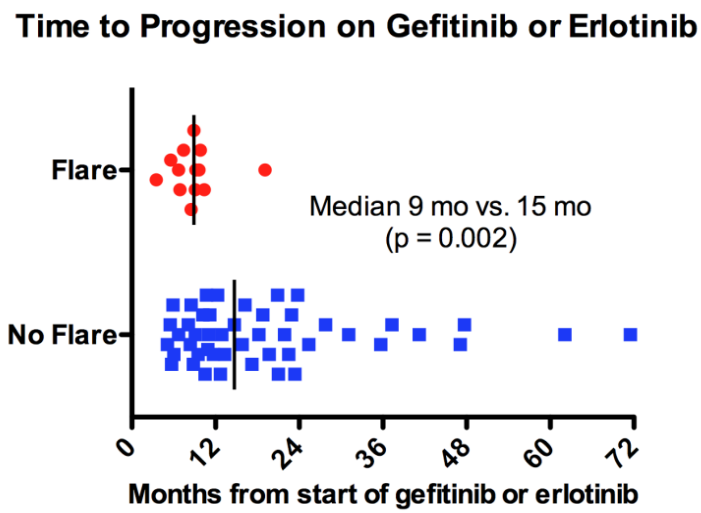
Dec 2009 Feb 2010 Apr 2010 Jun 2010 Aug 2010

RECIST PD

- 56-year-old woman with exon 19 EGFR mutation. PD (RECIST from 80 mm to 10 mm to 13 mm) after 15 months of gefitinib, asymptomatic.
- 56-year-old woman with exon 19 EGFR mutation. PD (progression in lung, 2 new liver lesions and 1 in left adrenal gland) after 15 months of gefitinib, symptomatic.

Risk of disease flare in EGFR mut+ NSCLC with acquired resistance





- 14 of 61 patients (23%, 95% CI 14-35%) had a disease flare (hospitalization or death)
- Flare & no flare group - same 30 day pretrial hospitalization rate
- Median time from last TKI to flare was 8 days (range 3-21 days)
- 3 patients went on to trial treatment

Chaft JE, Clin Cancer Res 2011

Pseudoprogression

- In studies of immunotherapies, durable CR, PR, or SD have occurred after initial PD by WHO or RECIST criteria
- Longer time may be necessary for immune response
- Discontinuation of immunotherapy after “early” PD by WHO or RECIST may not be appropriate unless confirmed
- In patients not showing clinical deterioration, confirm progression by another imaging study in 4 weeks or biopsy is recommended

PET for early prediction of erlotinib treatment outcome

ELIGIBILITY CRITERIA

- NSCLC
- STAGE IV
- PROGRESSION AFTER AT LEAST FIRST-LINE CT
- PS 0-1

Erlotinib 150 mg once daily continuously

TAC before treatment	Day 0 FDG-PET	Day 2* FDG-PET	Day 45 TAC or TAC-PET

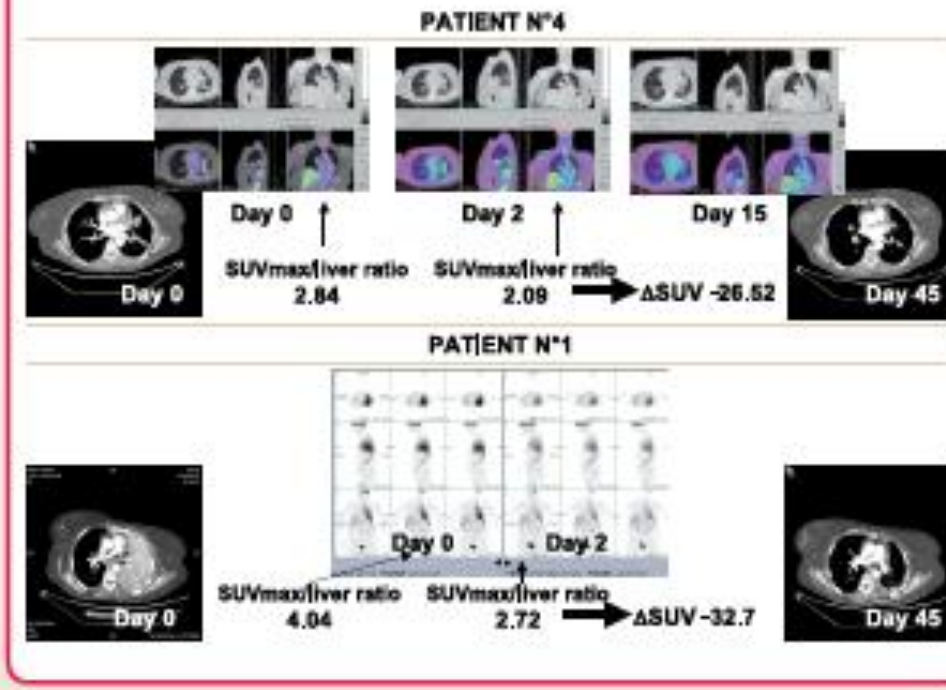
** 3 daily doses of TARCEVA before FDG PET*

FDG-PET 48 H VS TAC* DAY 45

		PET 48 hours		
		RP	SD	PD
Response evaluation day 45 (TAC*)	RP	4	-	-
	SD	4	-	-
	PD	-	8	7

** or TAC PET*

RESPONSIVE PATIENTS EARLY DETECTED BY FDG-PET



Soto-Parra H, WCLC 2009

The relevance of stable disease as a surrogate end-point

- An increasing number of experts have recently proposed that disease control rate should be used to predict survival, and prospective trials have shown that SD plays a clinically relevant role in the management of NSCLC.
- SD has, however, often been viewed as an equivocal result and is therefore of uncertain clinical value.
- SD patients are a heterogeneous group for whom tumour size fails to meet the criteria for either response or progression, in which patient with slight reduction do better compared with patient who have growth of their tumour although less than PD.
- Logic suggests that the SD definition is somewhat arbitrary, and that it is highly unlikely that these two patients would have similar outcomes.

Grossi F, Drugs 2012

Agenda

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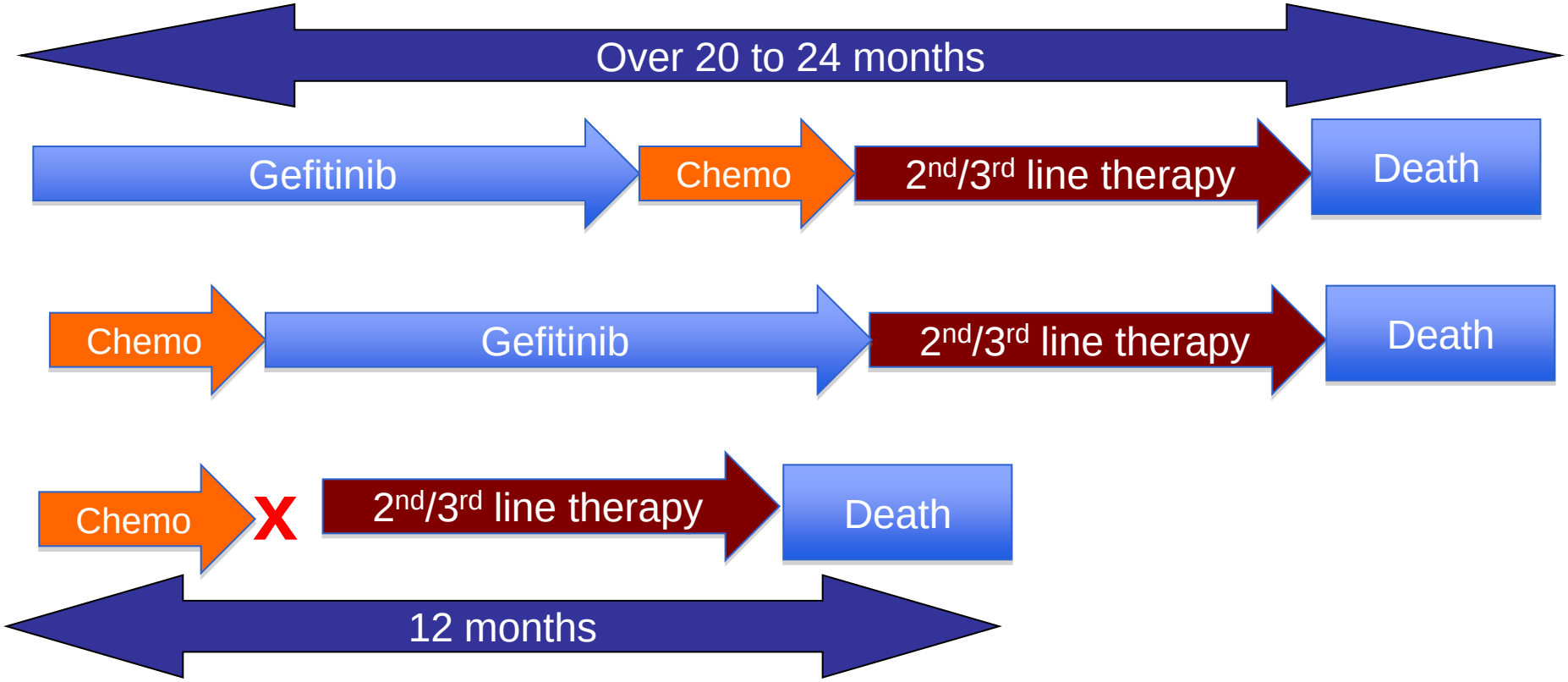
Cross-over explains the similar survival

Treatment sequence in patients with EGFR mutation.



EGFR TKIs vs chemotherapy as first-line therapy

Trial/Patient Group		EGFR Mut+, n	Median PFS, Mos			OS, Mos	
			EGFR TKIs	Chemo	HR (95% CI)	EGFR TKIs	Chemo
Selected by Clinical Factors							
I-PASS	East Asian, light/nonsmoker, adeno	261	9.8	6.4	0.48 (0.36-0.64)	21.6	21.9
First-SIGNAL	Korean, nonsmoker, adeno	42	8.4	6.7	0.61 (0.31-1.22)	30.6	26.5
Selected by Molecular parameter							
NEJ002	Japan, EGFR mutant	230	10.8	5.4	0.322 (0.236-0.438)	27.7	26.6
WJTOG3405	Japan, EGFR mutant	172	9.2	6.3	0.49 (0.34-0.71)	36	39
OPTIMAL	China, EGFR mutant	154	13.7	4.6	0.164	22.7	28.8
EURTAC	Caucasian, EGFR mutant	174	9.7	5.2	0.37	Not reached	Not reached
LUX-Lung 3	Asian/Caucasian EGFR mutant	345	11.1	6.9	0.58 (0.43-0.78)	Not available	Not available

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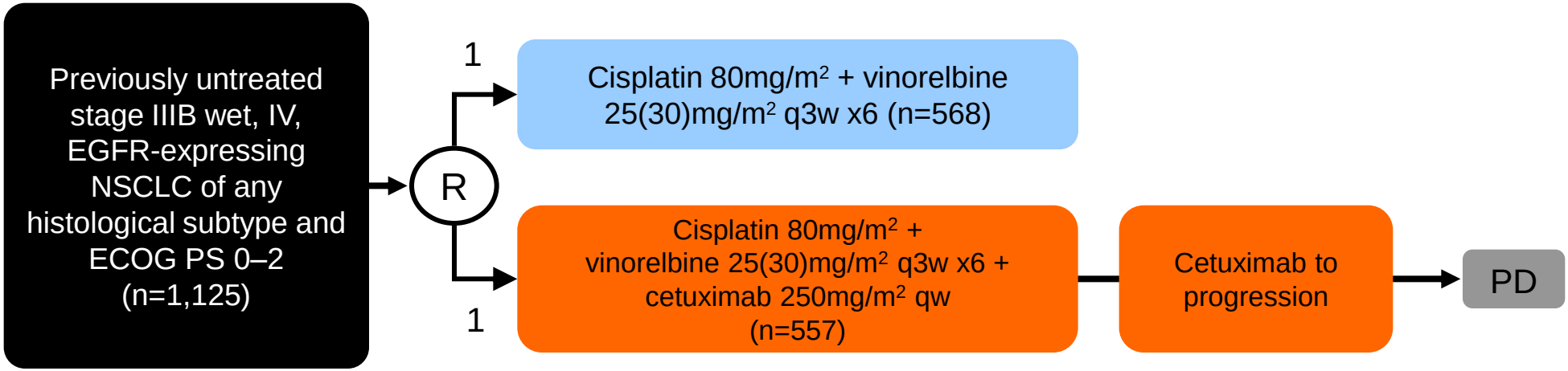
FLEX: trial design

Trial commenced 2004

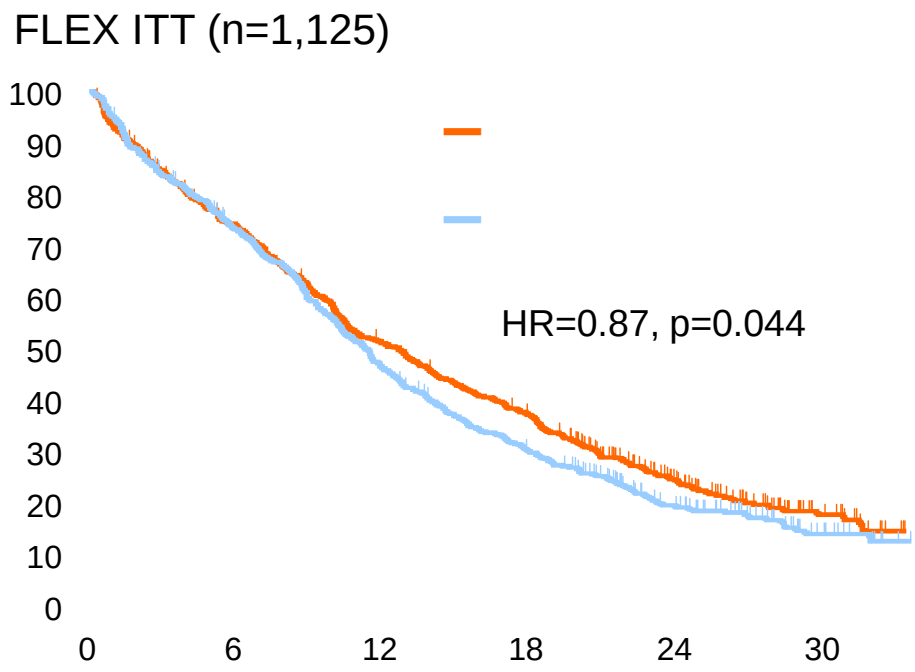


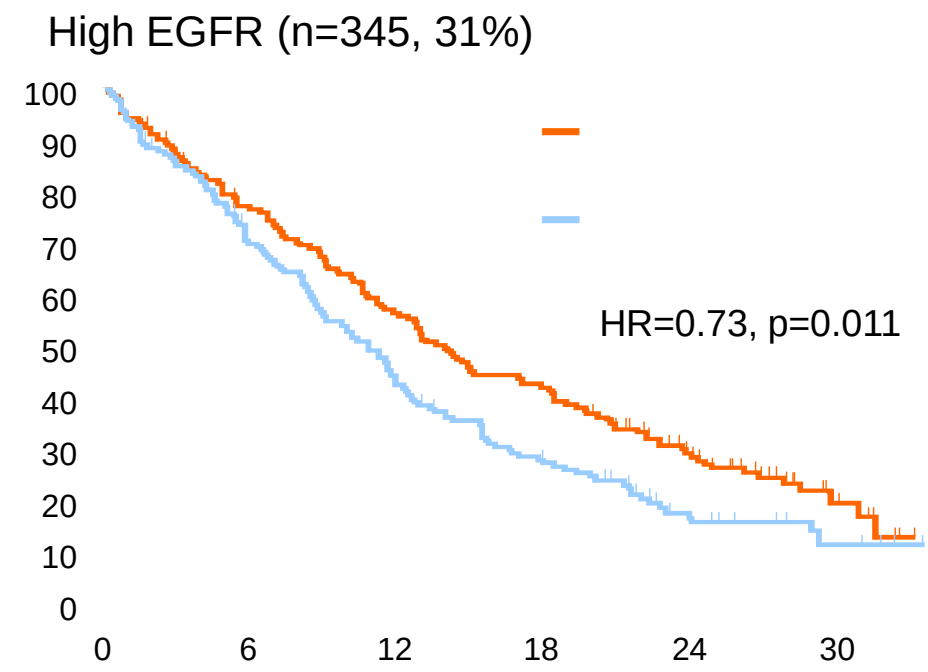
- Primary endpoint
  - overall survival (OS)
- Secondary endpoints
  - objective response rate (ORR)
  - progression-free survival (PFS)
  - disease control
  - quality of life
  - safety

- Key exclusion criteria
  - brain metastases
  - previous treatment with EGFR-targeted drugs or monoclonal antibodies
  - active infection
  - symptomatic peripheral neuropathy

Pirker R, Lancet 2009

FLEX survival: ITT population vs high EGFR expression

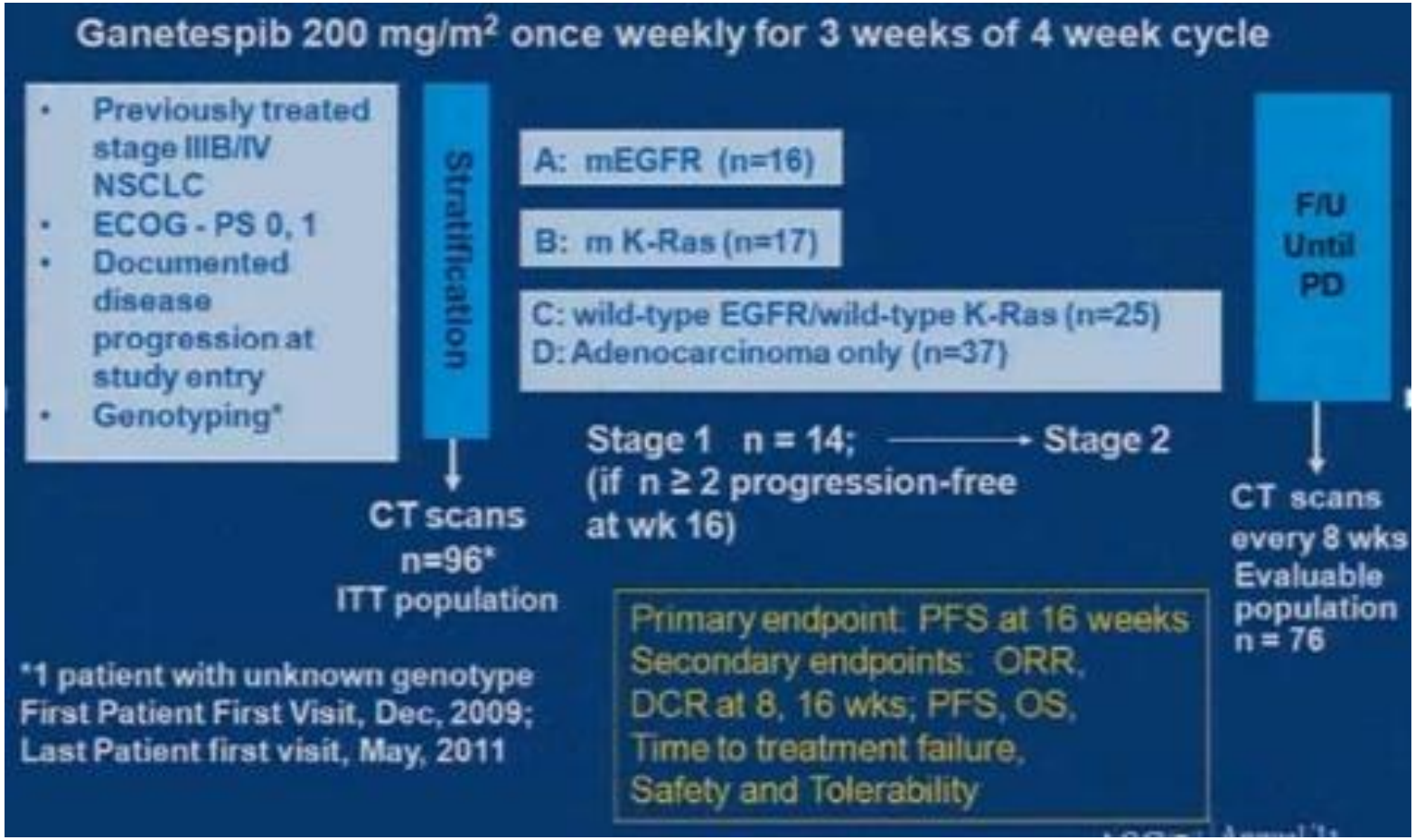




- OS improvement with cetuximab was 6 weeks in ITT population
- Patients with high tumour EGFR expression and receiving CT + cetuximab had a median OS of 12.0 months (vs 9.6 months)

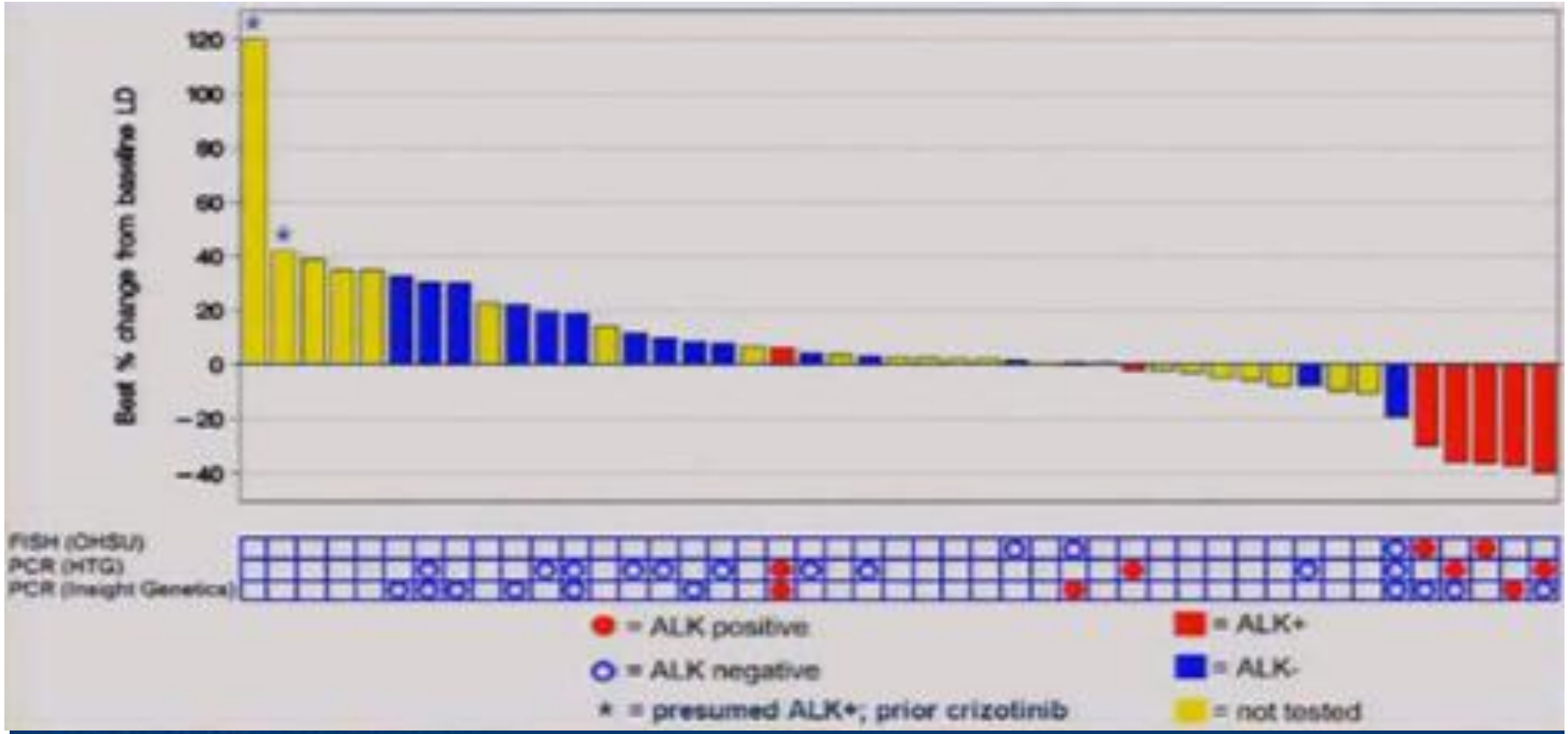
Pirker R, Lancet Oncology 2011

Phase II with Hsp 90 Ganetespib



Wong KK, ASCO 2011

ALK rearrangement (cohort C/D)



For crizotinib-naïve patients:
7 out of 8 (88%) patients with ALK-positive tumors had disease control lasting at least 16 weeks.
6 out of 8 (75%) patients with ALK-positive tumors had tumor shrinkage in target lesions.
4 out of 8 (50%) patients with ALK-positive tumors had objective response.

Wong KK, ASCO 2011

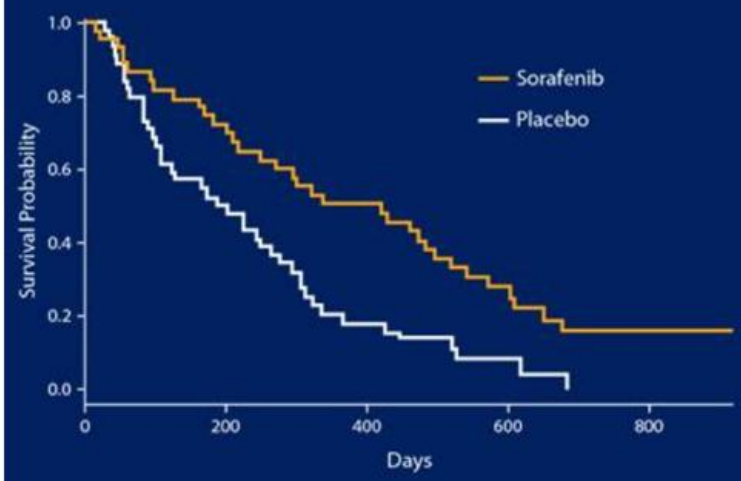
OS of patients with EGFR mutation and EGFR wild-type

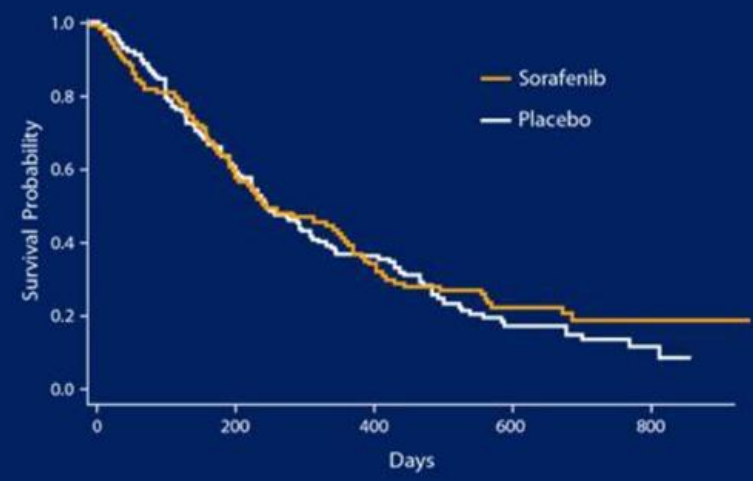
Pts with EGFR mut (in tumor or plasma)

- Sorafenib N=44; Placebo N=45
- HR=0.48 (95% CI 0.3,0.76)
- P-value=0.002
- Sorafenib median OS=423d
- Placebo median OS=197d

Pts with EGFR wt

- Sorafenib N=122; Placebo N=136
- HR=0.92 (95% CI 0.7,1.21)
- P-value=0.559
- Sorafenib median OS=253d
- Placebo median OS=256d





Biomarker*treatment interaction analysis: p-value=0.023

JMDB: Cis/pem vs cis/gem - study design

Randomization factors:

- Stage
- PS
- Gender
- Hysto vs cyto dx
- Brain mets

Vitamin B_{12} folate and dexamethasone given in both arm

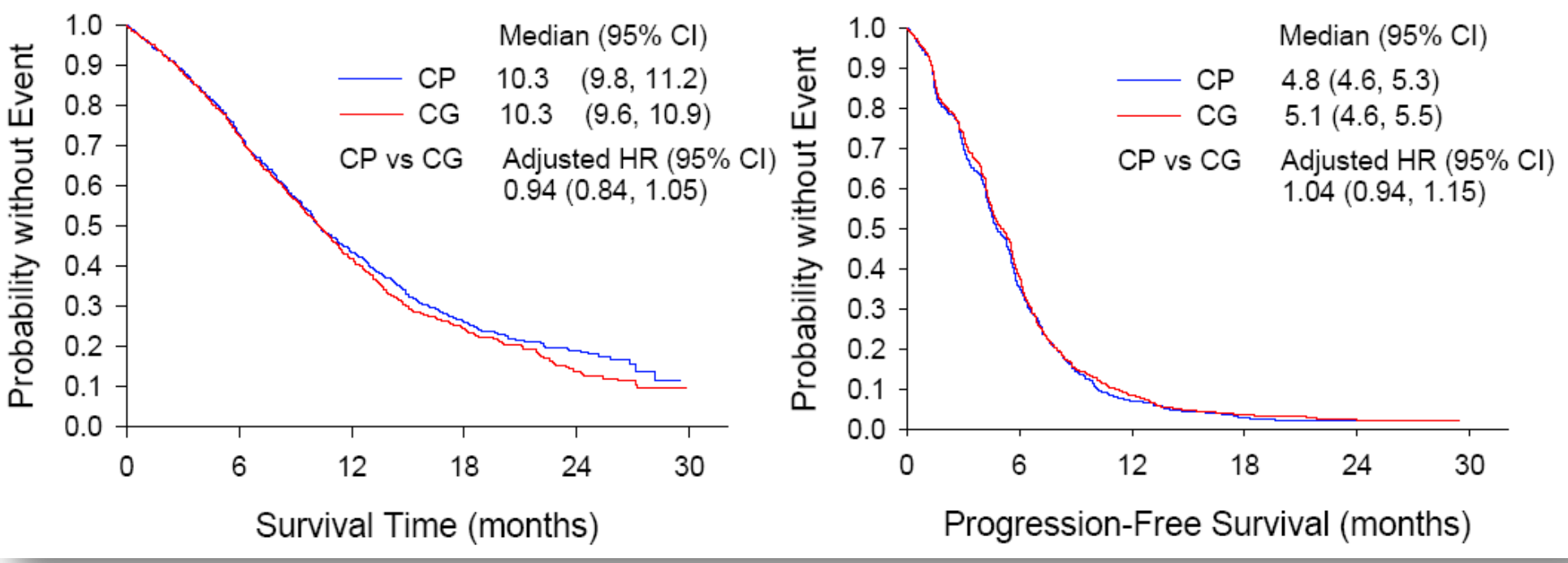
RANDOMISE

Cisplatin 75 mg/m^2
Pemetrexed 500 mg/m^2
d1 q 3 weeks up to 6 cycles

Cisplatin 75 mg/m^2
Gemcitabine 1250 mg/m^2
D1,8 q 3 weeks up to 6 cycles

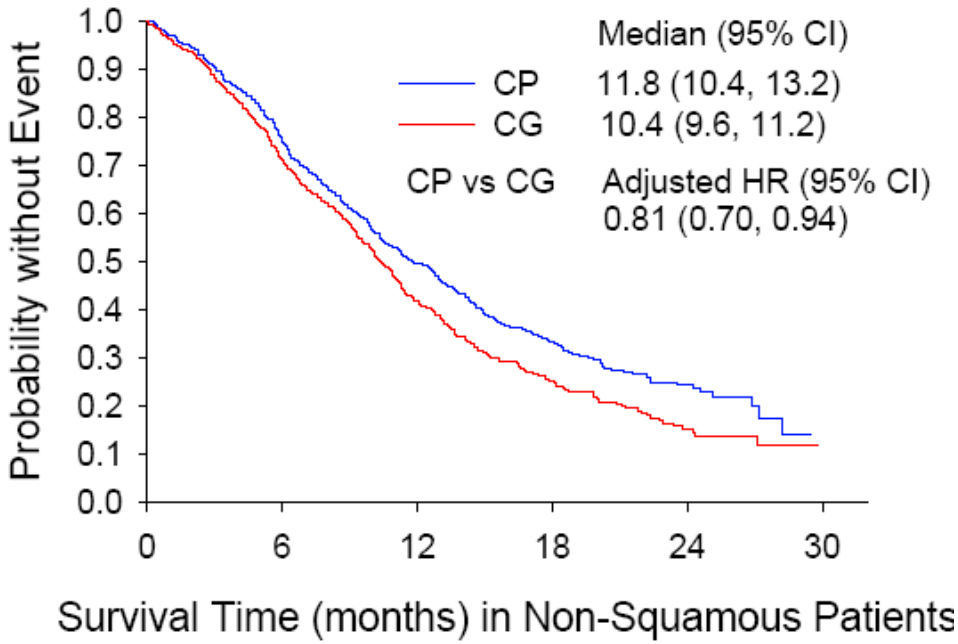
Scagliotti G, JCO 2008

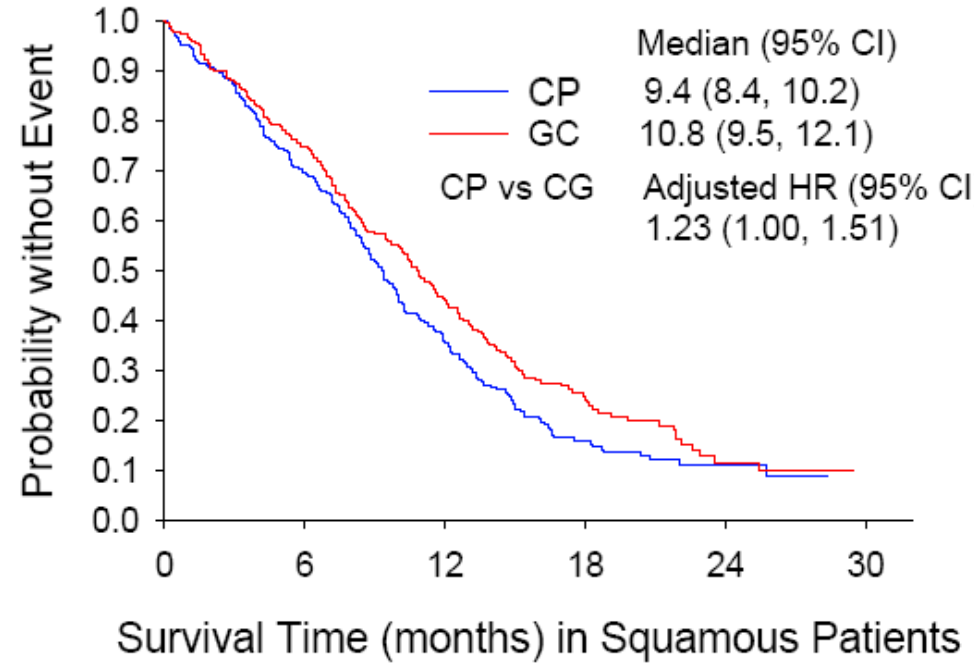
JMDB: OS & PFS



Scagliotti G, JCO 2008

JMDB: OS in non-squamous & squamous patients





Scagliotti G, JCO 2008

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EGFR-TKI resistance: from adenocarcinoma to SCLC

Histology	Adeno	SCLC	Adeno	SCLC
Genotype	L858R	L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI status	Sensitive	Resistant	Sensitive	Resistant
Tumor burden				
Treatment	Erlotinib	C+RT	Erlotinib	C+ RT
Timeline	2008	2009	2010	

Sequist L, Science Transl Med 2011

Agenda

- One biomarker → One drug → One trial: is this approach correct?
  - Probably YES in 2012
  - Probably NO in the next future

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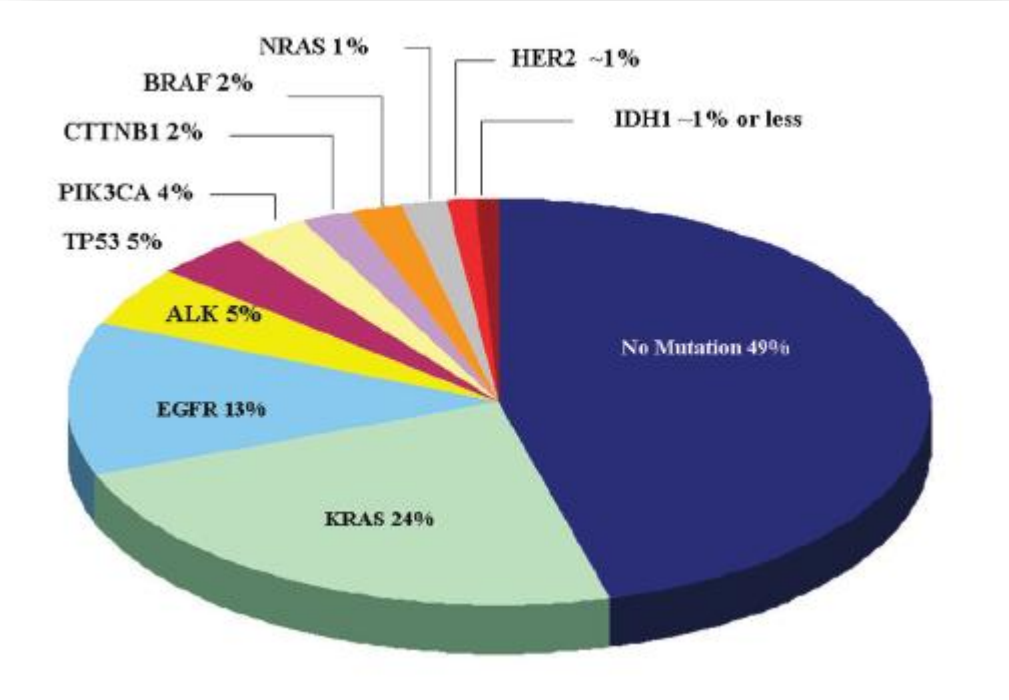
Lung Cancer Mutation Consortium 97% of mutations mutually exclusive

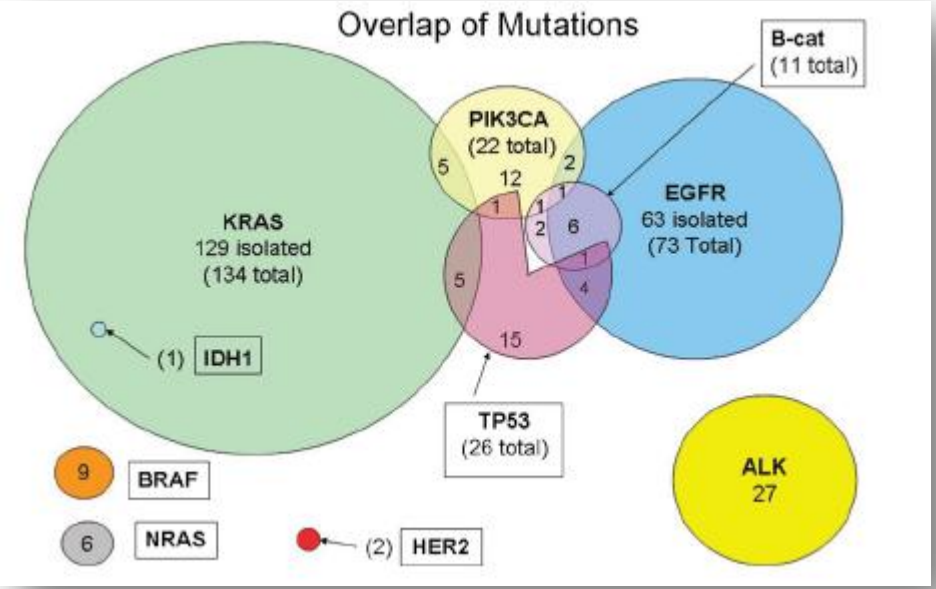
# Single Mutations	ALK	AKT	BRAF	EGFR	HER2	KRAS	MEK1	MET	NRAS	PIK3CA
ALK (38)	X		1	2		1		1		
AKT1 (0)		X								
BRAF (9)			X							1
EGFR (89)				X				1		3
HER2 (3)					X					
KRAS (114)						X		1		1
MEK1 (2)							X	1		1
MET AMP (3)								X		
NRAS (2)									X	
PIK3CA (6)										X

Number of patients with variants in indicated combination of genes, 3% (14/516)

Kris M, ASCO 2011

Distribution frequency and overlap of the genotypes observed





Sequist LV, Ann Oncol 2011

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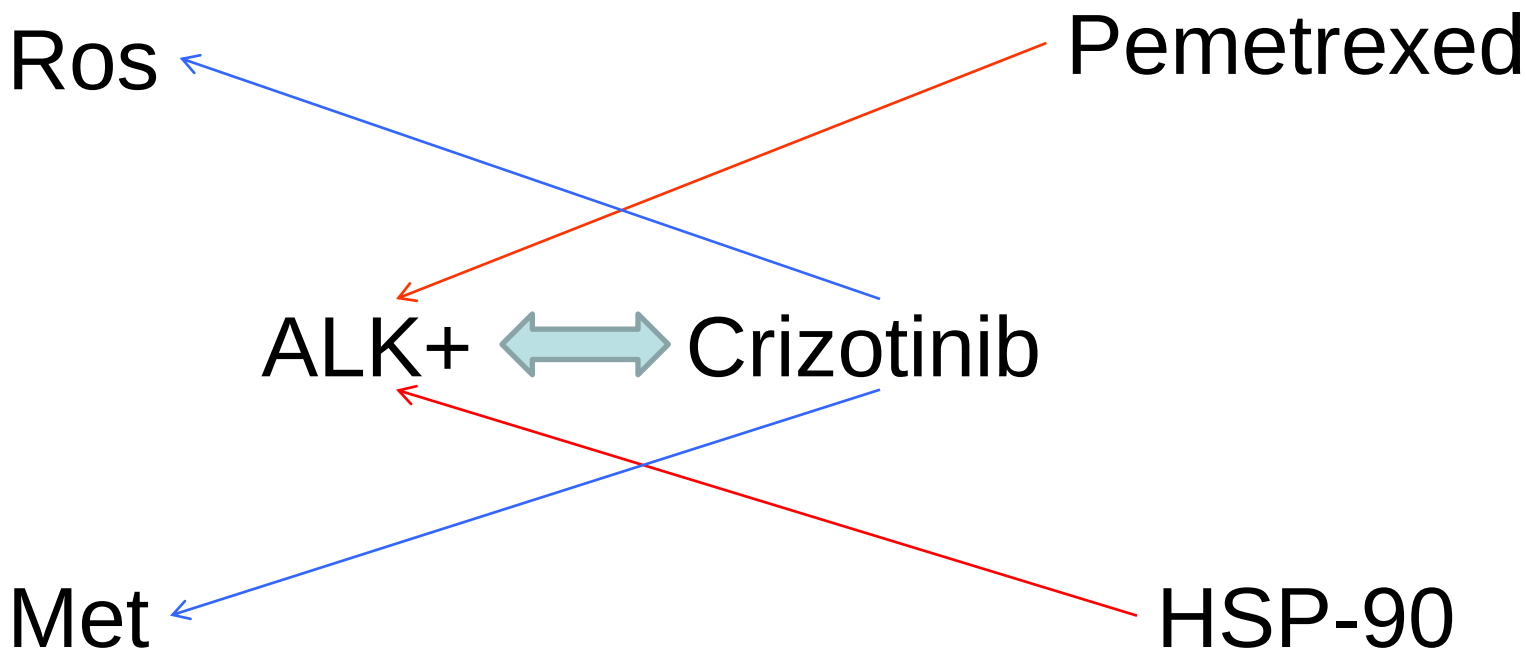
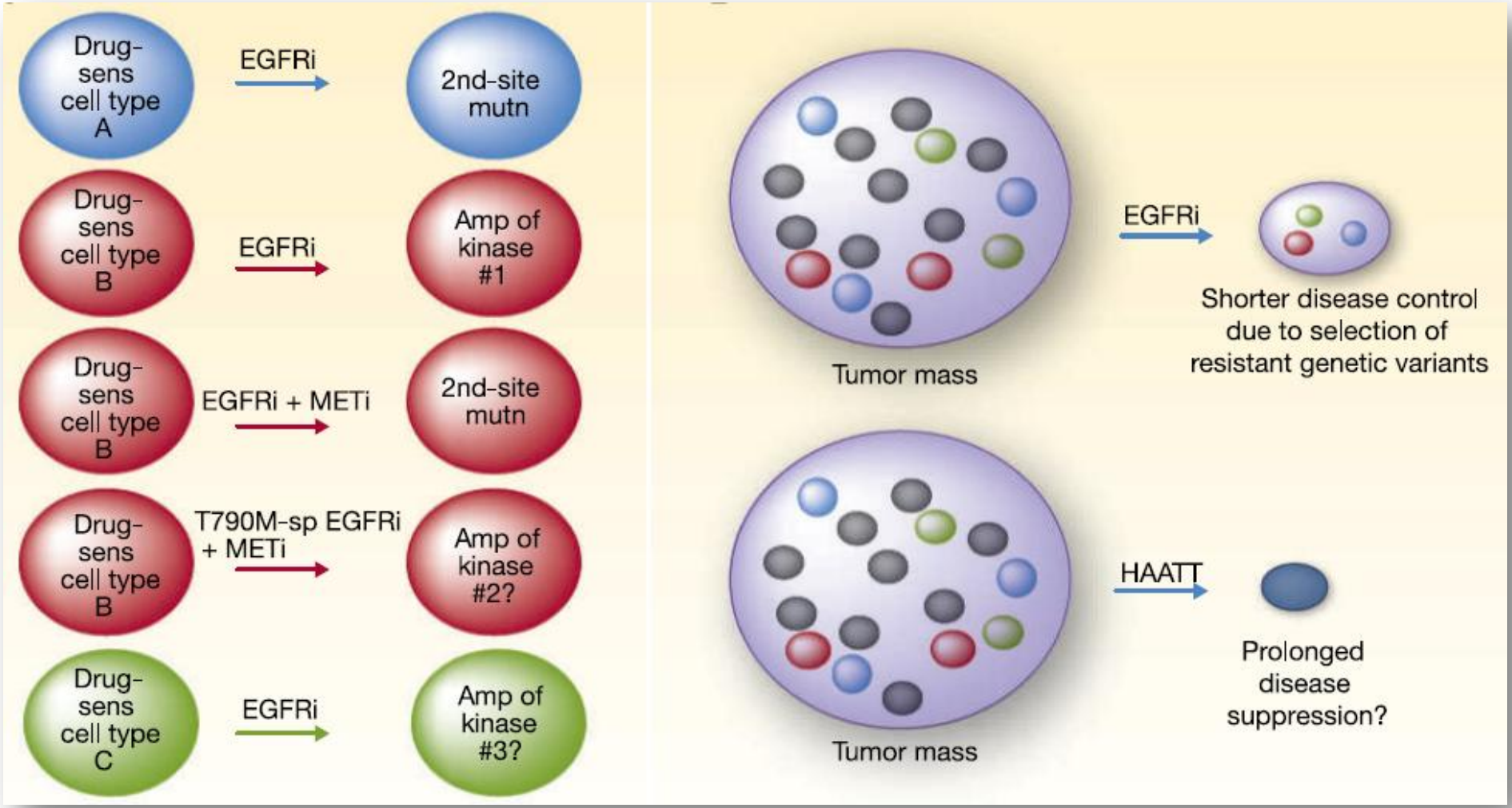
One target ⟺ One drug?



Highly Active Antitumor Therapy (HAATT) for EGFR-Mutant Lung Cancer



Chmielecki J, Clin Cancer Res 2010

Take home messages

- Biomarker based therapy is the future in oncology. Till now this strategy is generally available for few patients.
- Clinical trials based on predictive biomarkers should be designed correctly.
- The limitations in the use of tumor biomarkers in clinical trials should be considered in the study design.
- Methodological problems are important to consider in the correct evaluation of the trials results.
- Future trials should consider the heterogeneity of the tumor.

Grazie per l’attenzione!

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