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Special Symposia
NSCLC, metastatic, Oct. 1, 2012

# Personalized therapy and bio-molecular driven treatment in lung cancer

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# Disclosures: T. Mitsudomi

- I received honorarium from AstraZeneca, Chugai, Eli-Lilly, Pfizer, Daiichi-Sankyo and Taiho.
- I also served as an advisory board for Boehringer-Ingelheim, Pfizer, AstraZeneca, Chugai, Eli-Lilly, and Merck-Serono.

# Biomarkers in Lung cancer (example)

| | | Genetic… single gene | | Genomic… comprehensive |
|---|---|---|---|---|
| **Pharmacodynamic** (metabolism, detoxification) | | CYPs UGT1A1 | Various CPT-11 | Expression profiling / proteomics |
| **Pharmacokinetic** (predictive marker) | Driver gene mutation | EGFR | gefitinib/erlotinib | Expression profiling / proteomics / whole genome sequencing |
| | | ALK | crizotinib | |
| | | ROS1 | crziotinib | |
| | | RET | vandetanib | |
| | | DDR2 | dasatinib | |
| | Expression | ERCC1↓ | CDDP | |
| | | RRM1↓ | Gemcitabine | |
| | | TS↓ | pemetrexed | |

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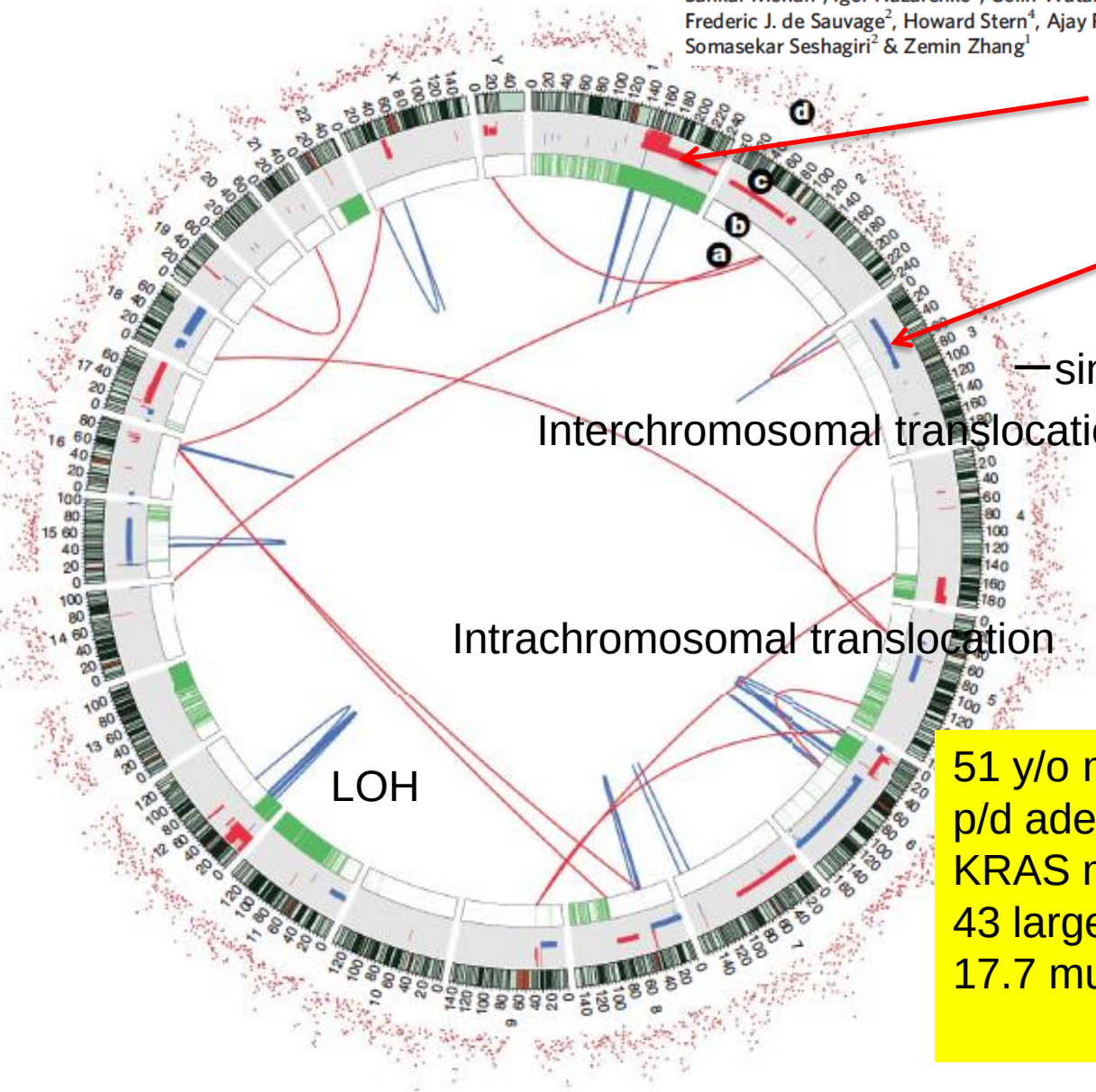
NATURE|Vol 465|27 May 2010

First adenocarcinoma genome

# The mutation spectrum revealed by paired genome sequences from a lung cancer patient

William Lee[1], Zhaoshi Jiang[1], Jinfeng Liu[1], Peter M. Haverty[1], Yinghui Guan[2], Jeremy Stinson[2], Peng Yue[1], Yan Zhang[1], Krishna P. Pant[3], Deepali Bhatt[2], Connie Ha[2], Stephanie Johnson[4], Michael I. Kennemer[3], Sankar Mohan[5], Igor Nazarenko[3], Colin Watanabe[1], Andrew B. Sparks[3], David S. Shames[5], Robert Gentleman[1], Frederic J. de Sauvage[2], Howard Stern[4], Ajay Pandita[5], Dennis G. Ballinger[3], Radoje Drmanac[3], Zora Modrusan[2], Somasekar Seshagiri[2] & Zemin Zhang[1]




Copy number gain

Copy number loss

single nucleotide variation

Interchromosomal translocation

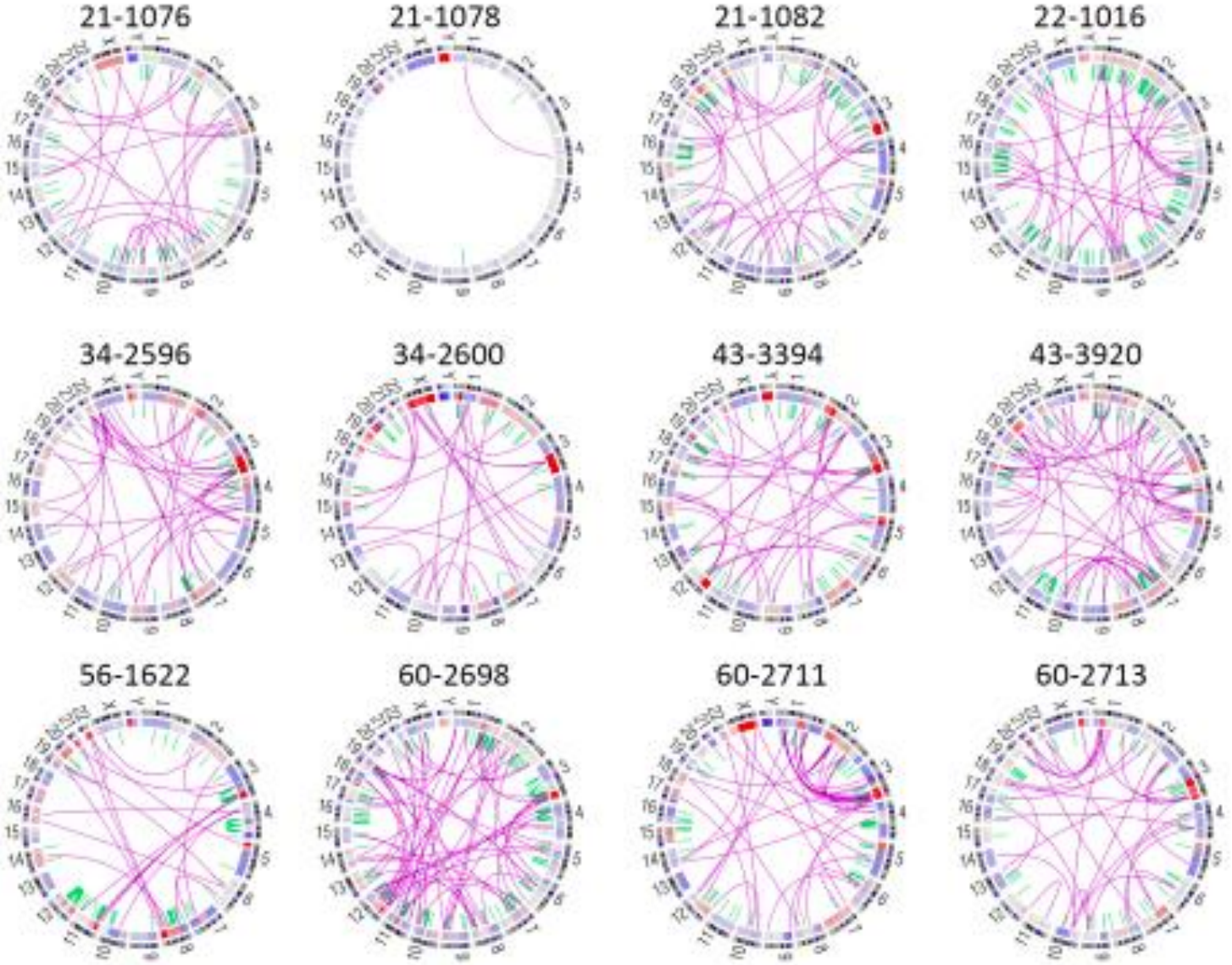
Intrachromosomal translocation

LOH

51 y/o male caucacian with smoking hx
p/d adenocarcinoma
KRAS mutation + 391 somatic mutation
43 large-scale structural variants
17.7 mutation/Mb

# CIRCOS plots of somatic alterations in whole genome of somatic alterations in whole genome sequencing data from squamous cell lung cancer

The Cancer Genome Atlas Network, Nature 2012



# Driver and Passenger

## Driver gene mutation

Gene mutations essential for cancer cell development, growth or survival

## Passenger gene mutation

Neutral genetic changes that are unrelated to cancer development caused by exposure to mutagens, or genetic instability or many mitoses

# Addiction to Oncogenes—the Achilles Heal of Cancer

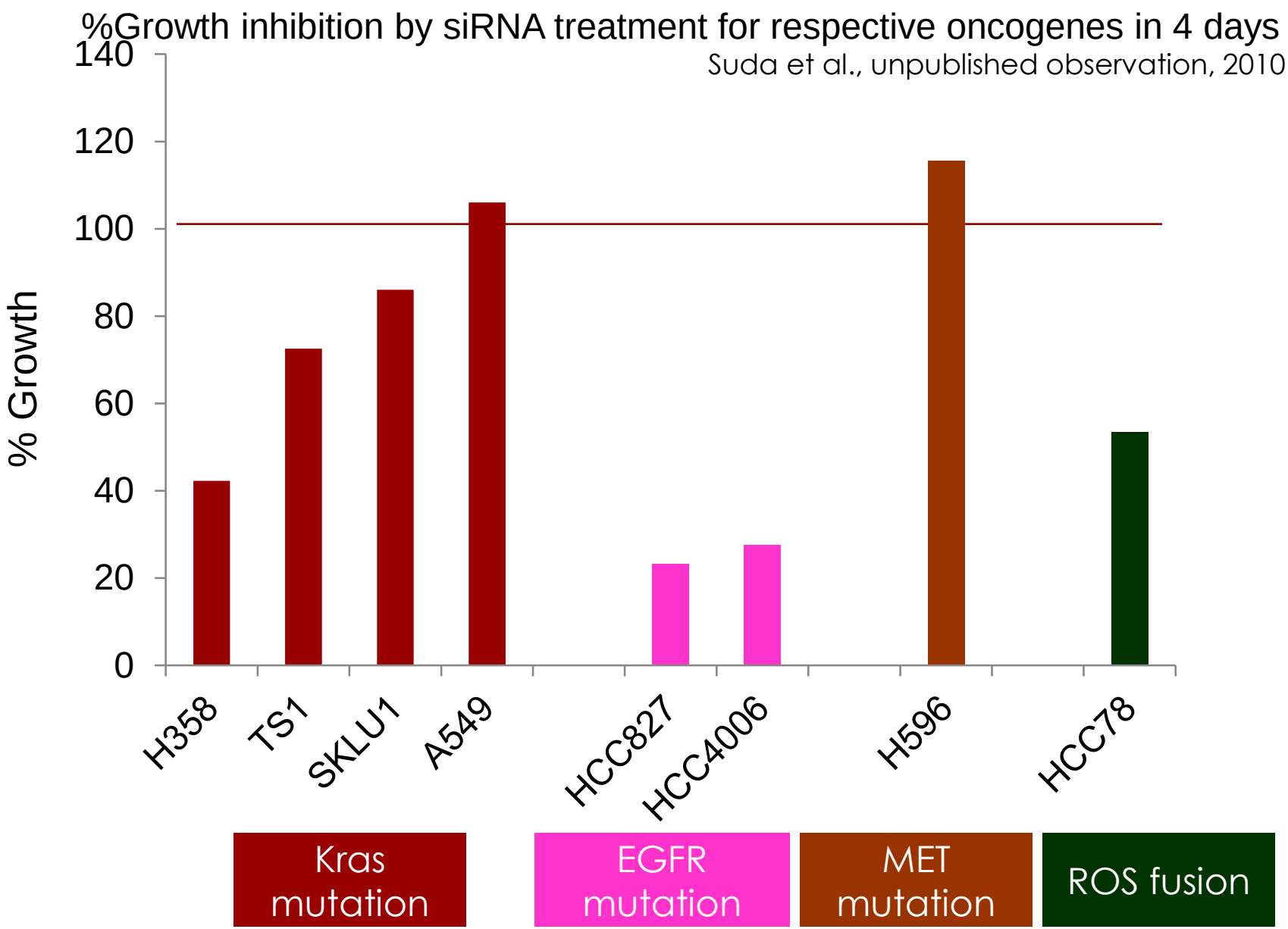
I. Bernard Weinstein

SCIENCE VOL 297 5 JULY 2002

*The phenomenon by which some cancers that contain multiple genetic and epigenetic abnormalities remain dependent on (addicted to) one or a few genes for both maintenance of the malignant phenotype and cell survival*

Weinstein and Joe, Nature Rev Clin Oncol, 2006

# Cancer cells are not equally addicted to respective driver oncogenes

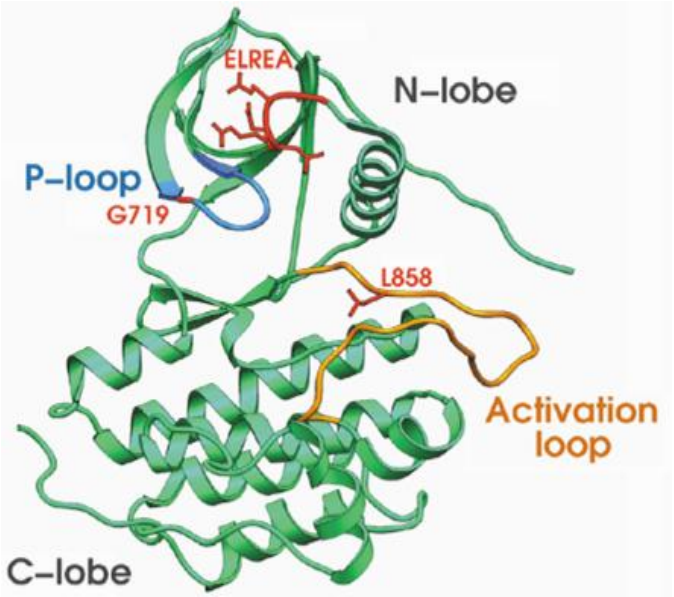


# How can driver gene / oncogene addiction be screened?

- Search for oncogenes whose inhibition result in induction of apoptosis
  - siRNA screen
  - Inhibitor screen
- Search for mutations that occur exclusively with known mutations of addicted oncogenes

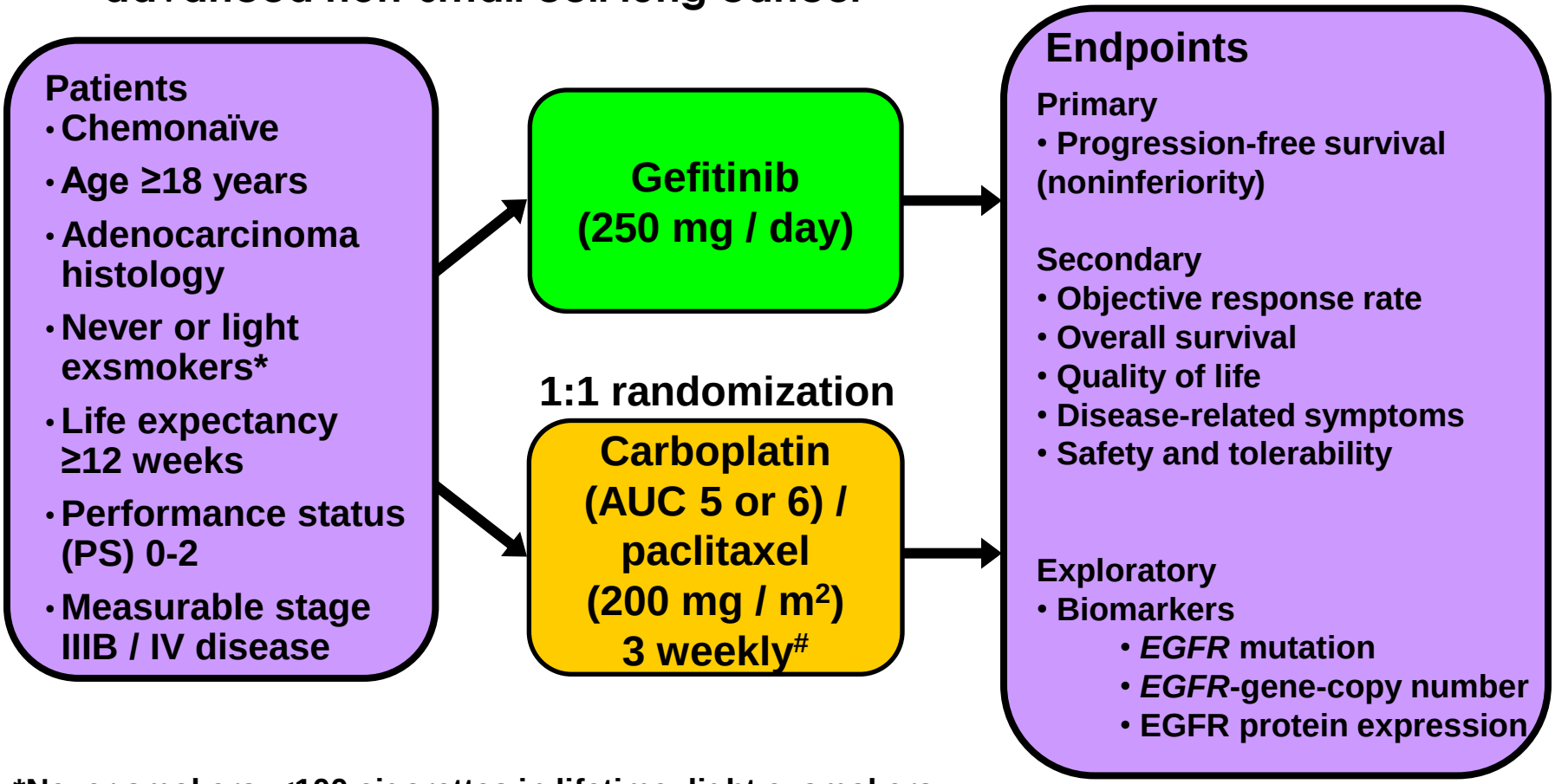
# April 2004,
# Activating mutations of the EGFR genes・・・
## A prototype of driver gene mutation of the lung

- lung cancer (adenocarcinoma) specific
- tyrosine kinase domain
  - In-frame deletions (exon 19)
  - L858R (exon 21)
- distinct subsets of patients
  - Adenocarcinoma
  - Non smoker
  - Asian
  - Female
- Mutually exclusive with KRAS mutation
- Oncogenic in vitro and in vivo
- Suppression by siRNA or small molecules results in massive apoptosis



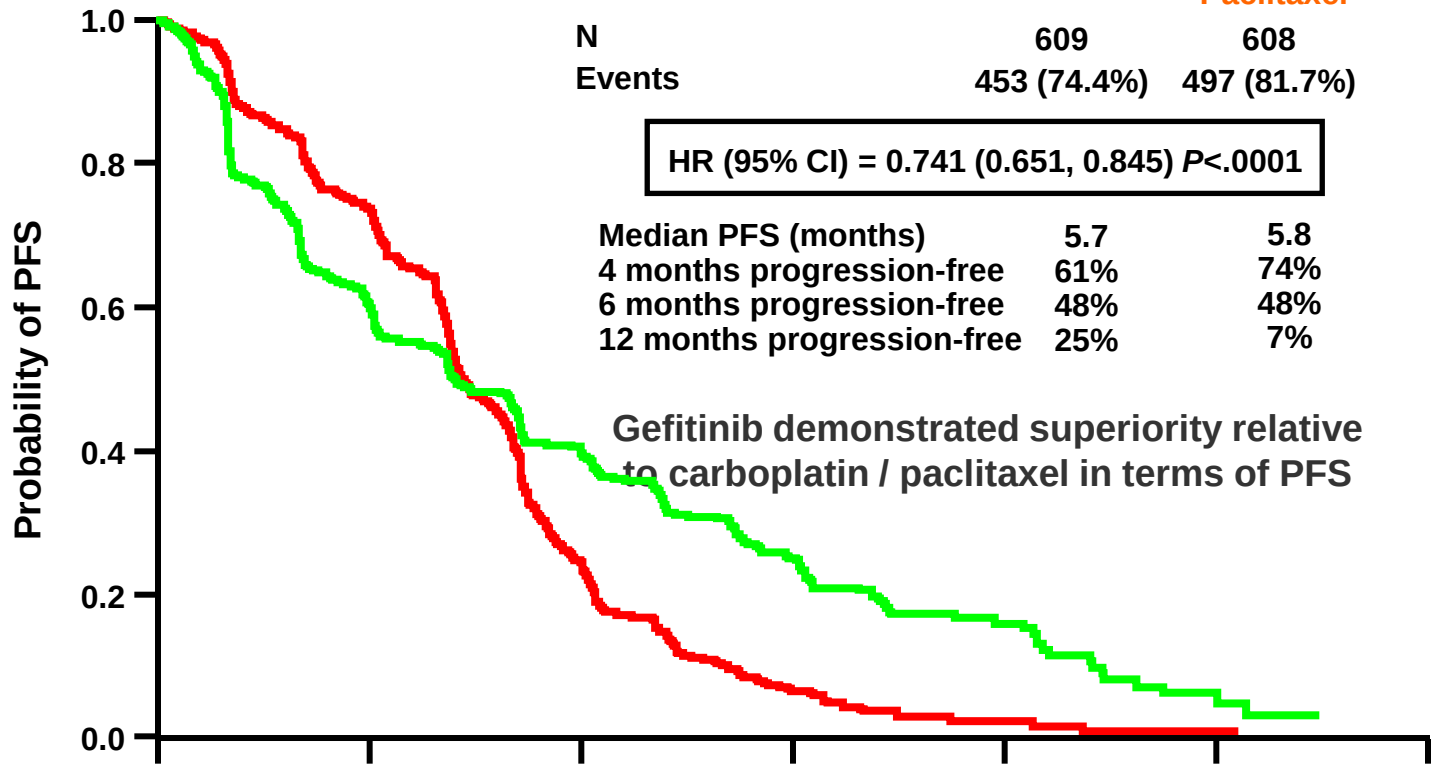
# IPASS: Iressa Pan-Asian Study

**Phase III, randomized, open-label, first-line study of gefitinib vs carboplatin / paclitaxel in clinically selected patients with advanced non-small cell lung cancer**




*Never smokers, <100 cigarettes in lifetime; light exsmokers, 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
AUC, area under the curve
Mok TS, et al., *N Engl J Med.* 2009; 361(10):947-957.

# IPASS: Progression-Free Survival in ITT Population

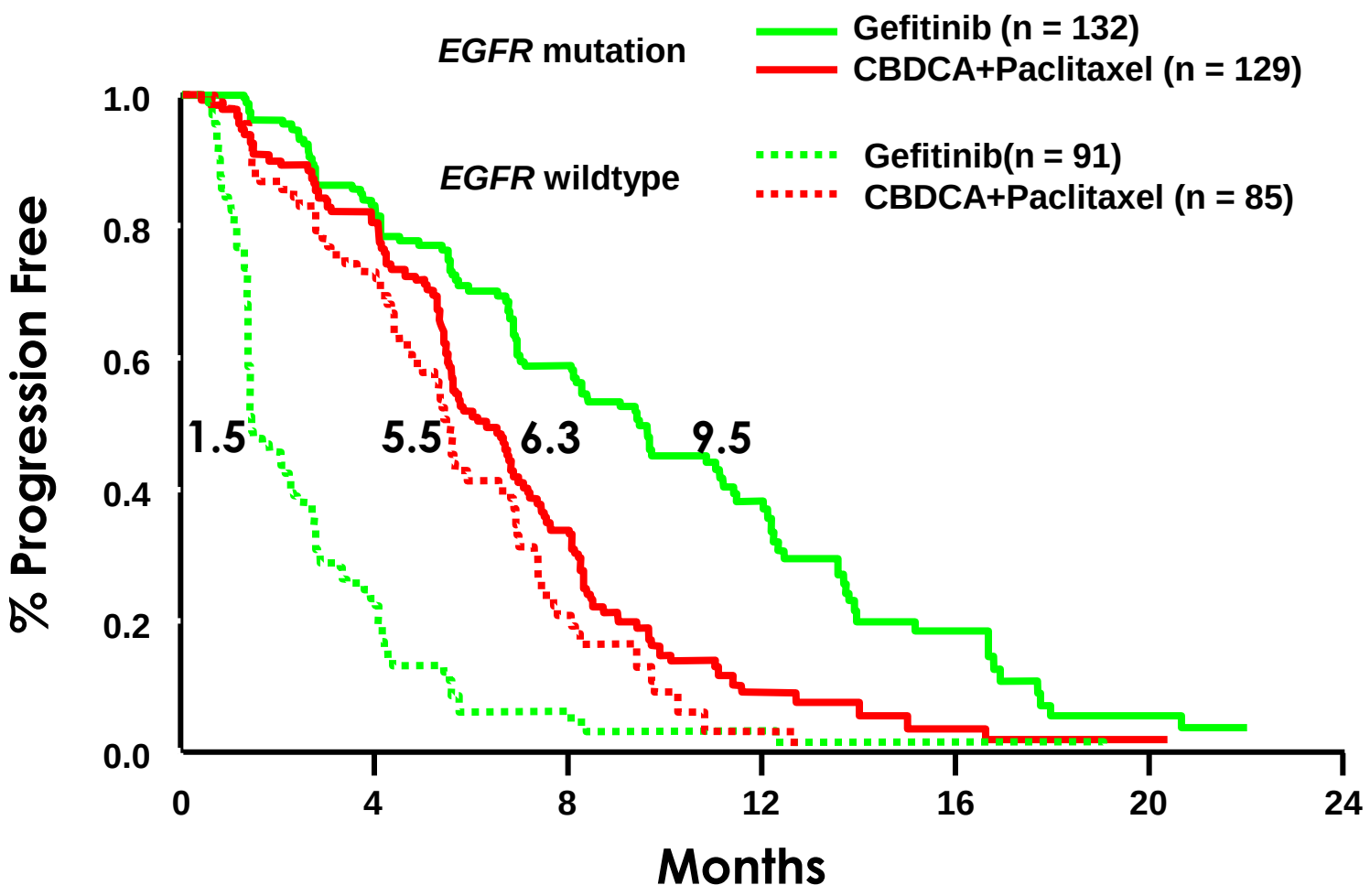



| At risk : | | | | | | | |
|---|---|---|---|---|---|---|---|
| Gefitinib | 609 | 363 | 212 | 76 | 24 | 5 | 0 |
| Carboplatin / paclitaxel | 608 | 412 | 118 | 22 | 3 | 1 | 0 |

Primary Cox analysis with covariates
HR <1 implies a lower risk of progression on gefitinib
CI, confidence interval; HR, hazard ratio; ITT, intent to treat; PFS, progression-free survival

361(10):947-957.

# IPASS: PFS by *EGFR* Mutation and Treatment Arms



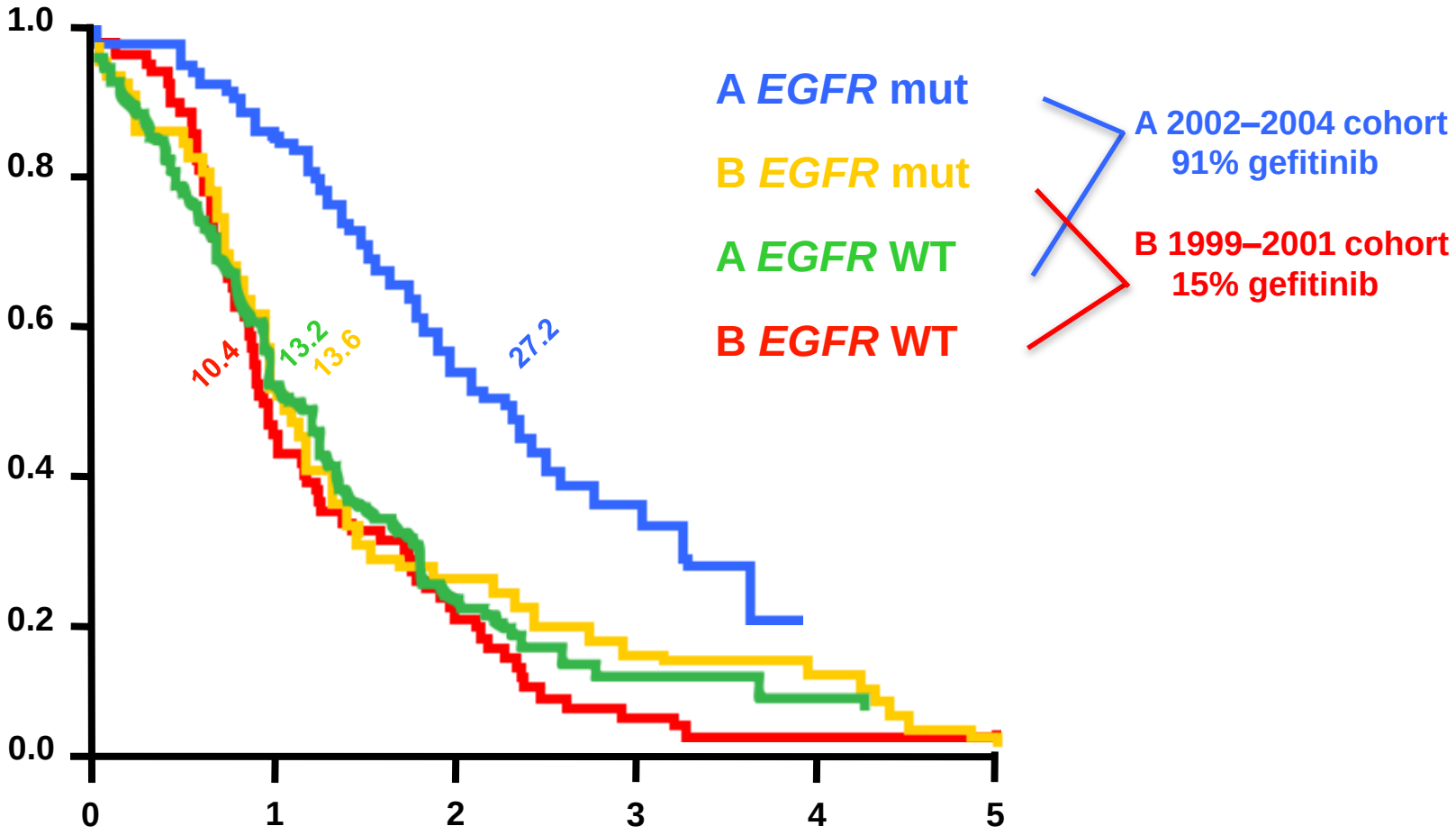

Mok TS, et al. *N Engl J Med.* 2009; 361(10):947-957.

# Phase III Trials for Patients Selected by *EGFR* Mutation (as of ASCO 2012)

| Study | Race | TKI | N | PFS | | | OS | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | TKI | CTx | HR | TKI | CTx | HR |
| NEJ002 | Japanese | Gefitinib | 228 | 10.8 | 5.4 | 0.32 (0.24-0.44) | 27.7 | 26.6 | 0.88 (0.63-1.24) |
| WJTOG 3405 | Japanese | Gefitinib | 172 | 9.6 | 6.6 | 0·52 (0·38-0·72) | 35.5 | 38.8 | 1.18 (0.77-1.83) |
| OPTIMAL | Chinese | Erlotinib | 154 | 13.7 | 4.6 | 0.16 (0.11-0.26) | 22.7 | 28.9 | 1.04 (0.69-1.58) |
| EURTAC | Caucasian | Erlotinib | 173 | 9.7 | 5.2 | 0.37 (0.25-0.54) | 19.3 | 19.5 | 1.04 (0.65-1.68) |
| Lux-Lung3 | Caucasian 26% Asian 72% | Afatinib | 345 | 11.1 | 6.9 | 0.58 (0.43-0.78) | N/A | | |

Inoue et al, ASCO 2011, Mitsudomi et al., ASCO 2012, Zhou et al., ASCO 2012, Rosell et al., ASCO 2012, Yang et al., ASCO 2012

# *EGFR* Mutations Predict Survival Benefit From Gefitinib in Patients With Advanced Lung Adenocarcinoma: A Historical Comparison of Patients Treated Before and After Gefitinib Approval in Japan

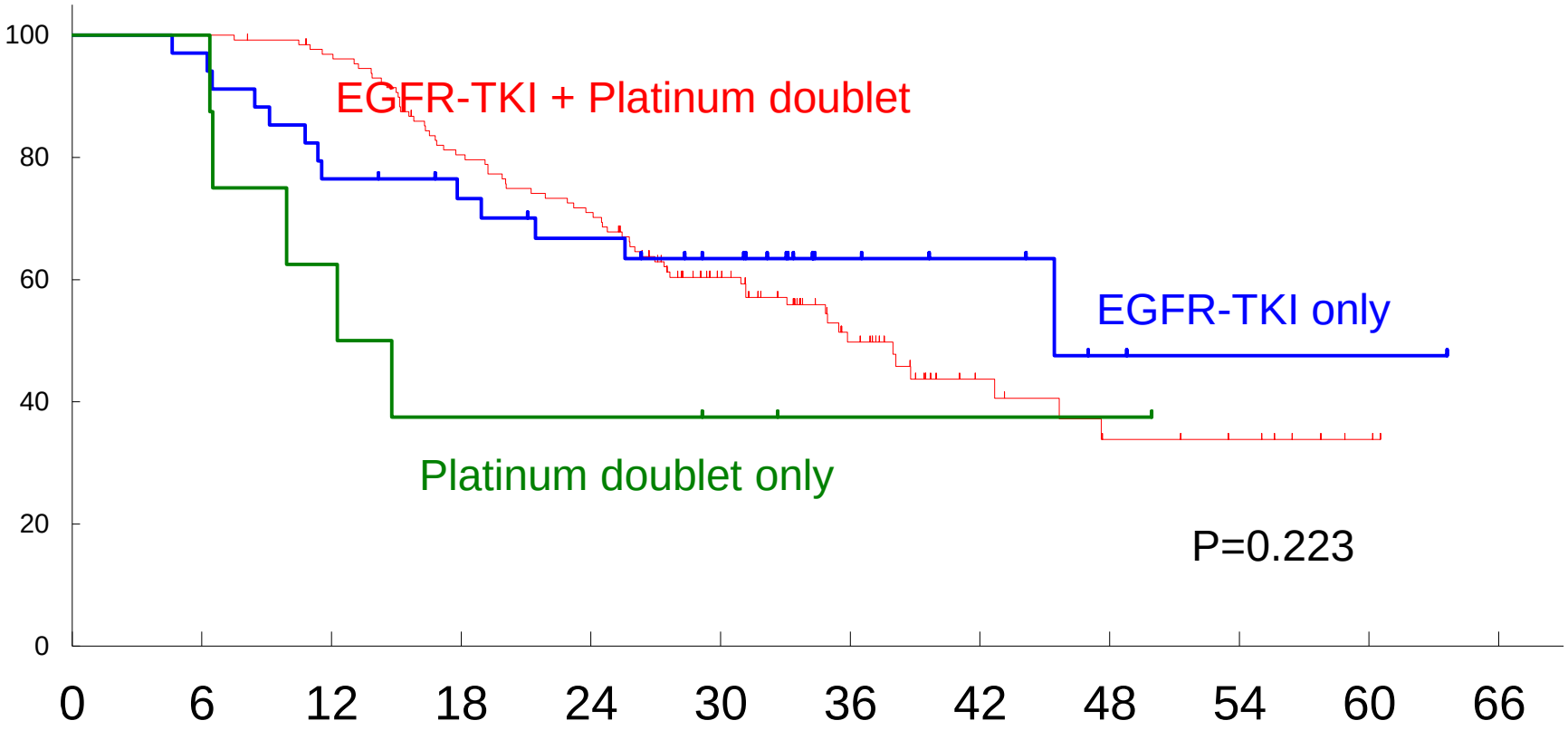



Takano T, et al. *J Clin Oncol.* 2008; 26(34):5589-5595.

# OS by entire treatment regimens in WJTOG 3405

Mitsudomi et al., 2012

EGFR-TKI + Platinum doublet (N=130) MST: 35.9 mo.
EGFR-TKI only (N=34) MST: 45.4 mo.
Platinum doublet only (N=8) MST: 13.5 mo.



# TORCH

Gridelli et al., JCO 2012

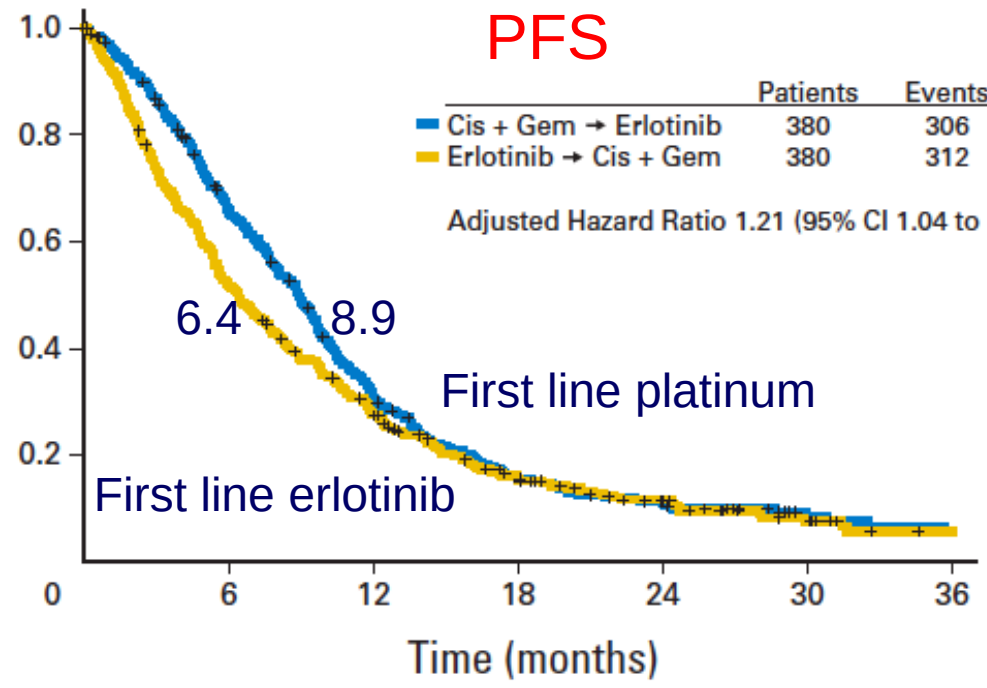
UNSELECTED patients

RANDOMIZE

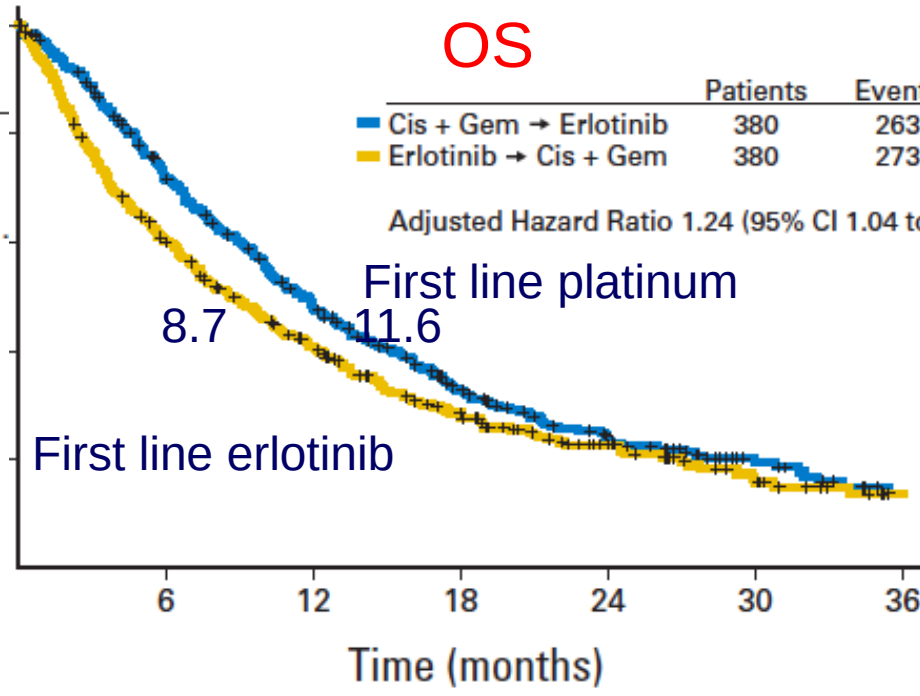
First-line CDDP+GEM → PD → First-line Erlotinib

First-line Erlotinib → PD → First-line CDDP+GEM

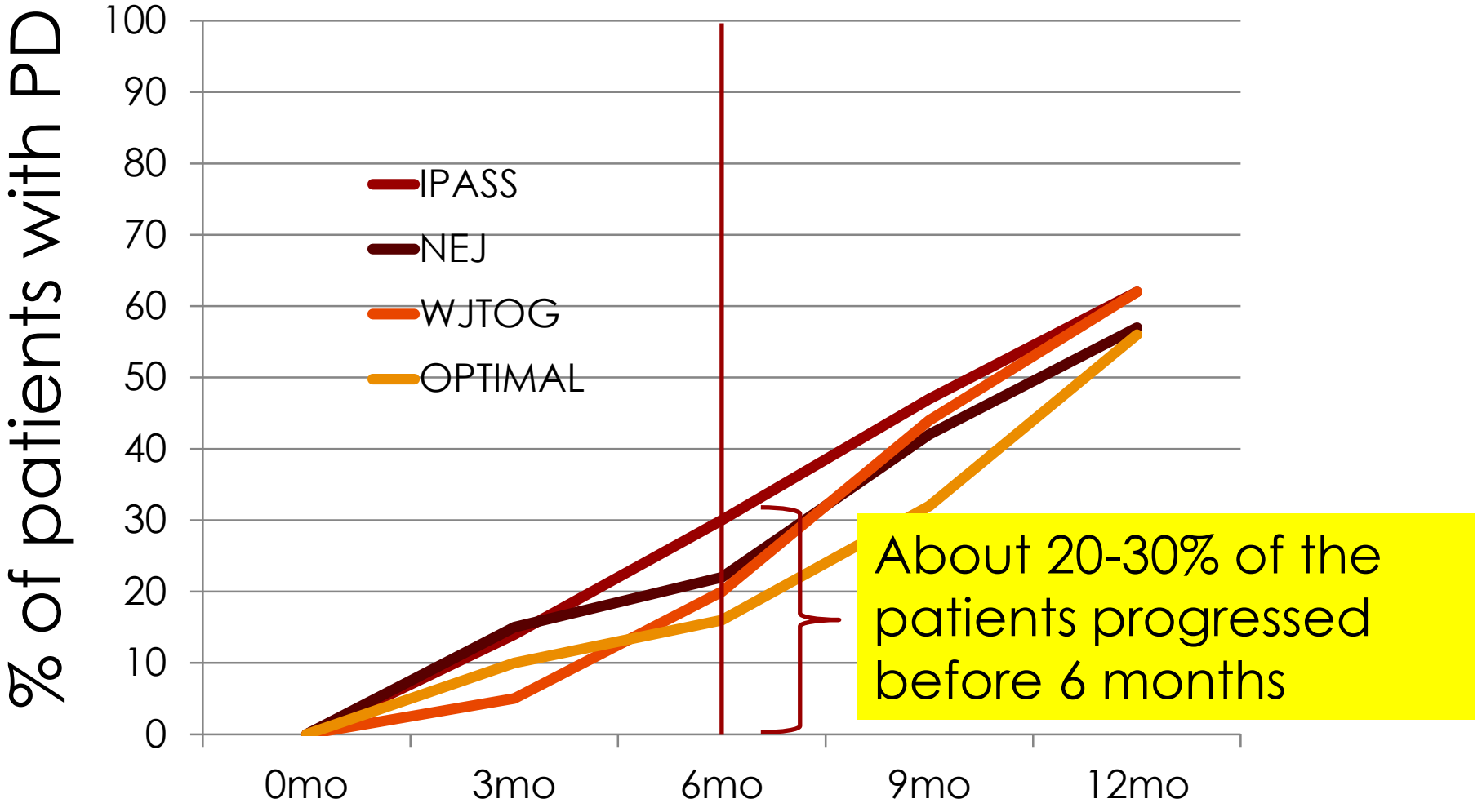
## PFS




## OS



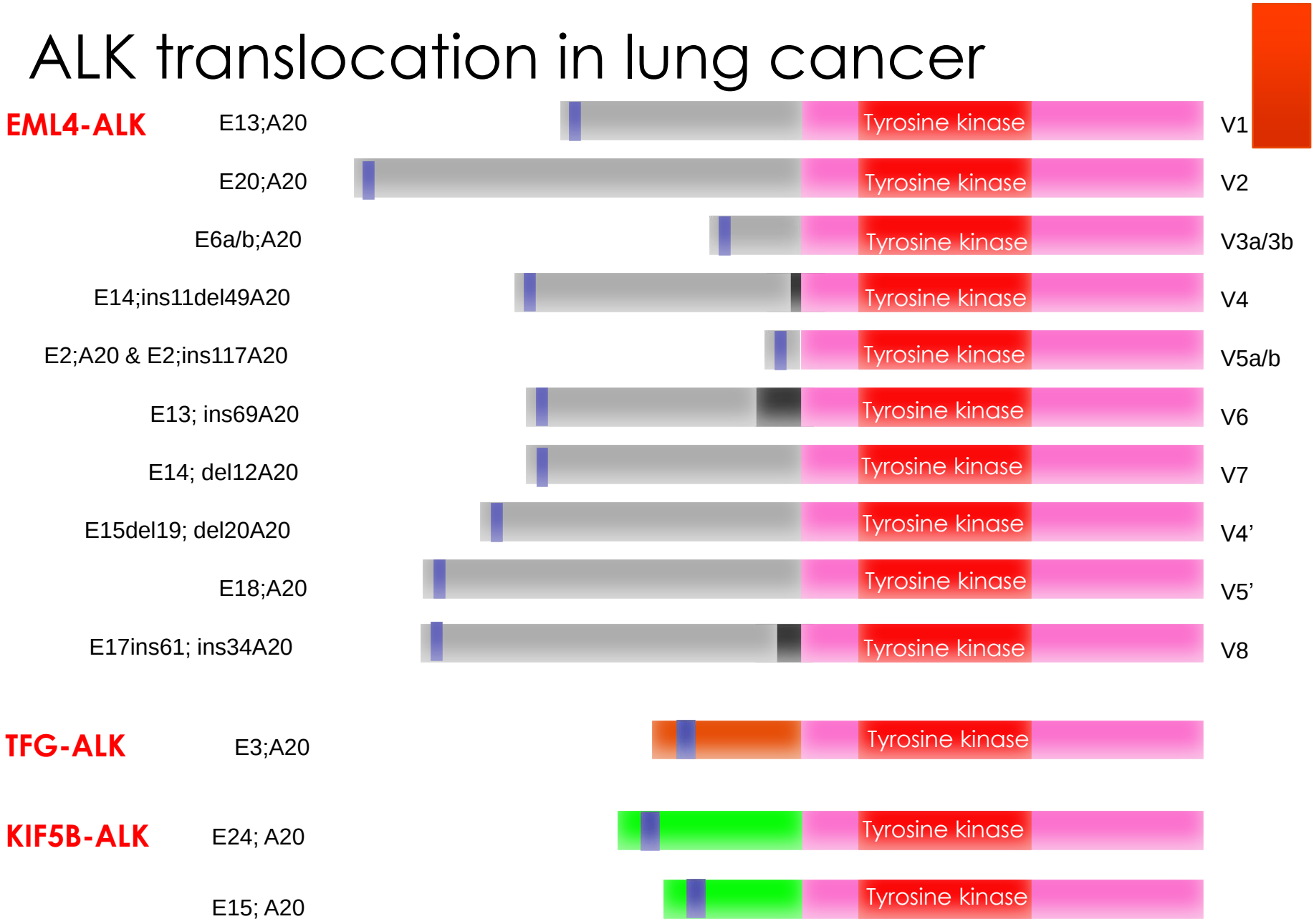
# Approx. % of patients with PD harboring sensitive EGFR mutation treated with EGFR-TKI



# Why is response or survival heterogenious?

- Mutation class
  - X19del ≥ L858R > G719X >>>> X20 ins = T790M
- Amount of T790M allele
- FAS, NFkB
- BIM
- CRKL
- Heterogeneity of driver?

# ALK translocation in lung cancer




Modified from Sasaki T et al., Eur J Cancer, 2010

# EGFR and ALK lung cancer

| | EGFR | ALK |
|---|---|---|
| discovery | 2004 | 2007 |
| Clinical background | Non-smoker、female,ad,Asian | Non-smoker, young |
| histology | Replacemt growth, non-mucinous | Acinar,cribriform, signet |
| Incidence in Ad | ~40%(Asians), ~15%(Caucacians) | 5-8% |
| Mechanism of activation | Mutation (deletion~point mutation) | tramnslocation |
| TKI | gefitinib/ erlotinib | crizotinib |
| RR | 60-80% | 50-60% |
| MST | 9~10~12 mo | 10 month |

# PROFILE 1005

Shaw et al., ESMO 2012

**Key entry criteria**

- *ALK*+ by central FISH testing[a]
- Stage IIIB/IV NSCLC
- 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

RANDOMIZE[b]

N=318

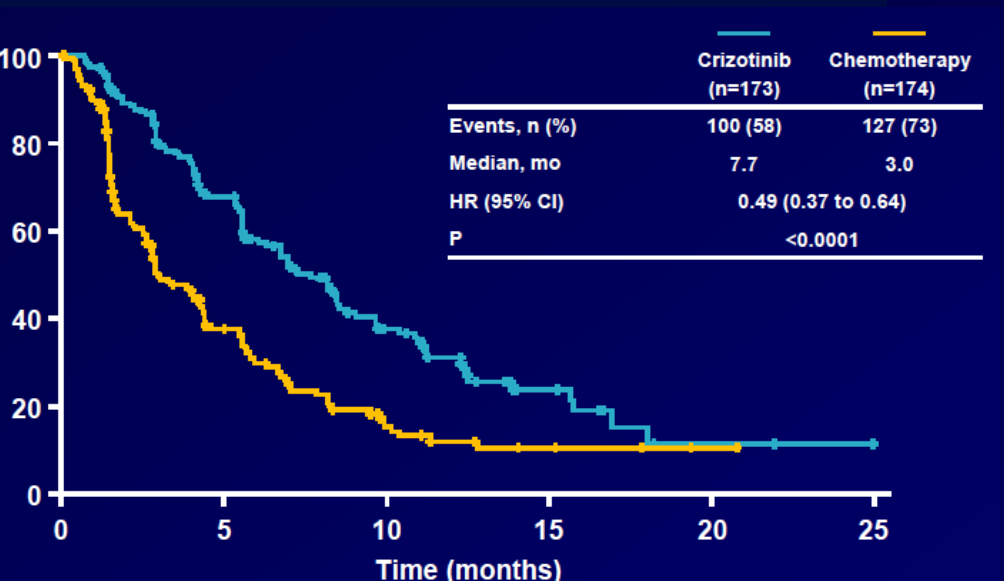
- Crizotinib 250 mg BID PO, 21-day cycle (n=159)
- Pemetrexed 500 mg/m² or Docetaxel 75 mg/m² IV, day 1, 21-day cycle (n=159)

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

**Endpoints**

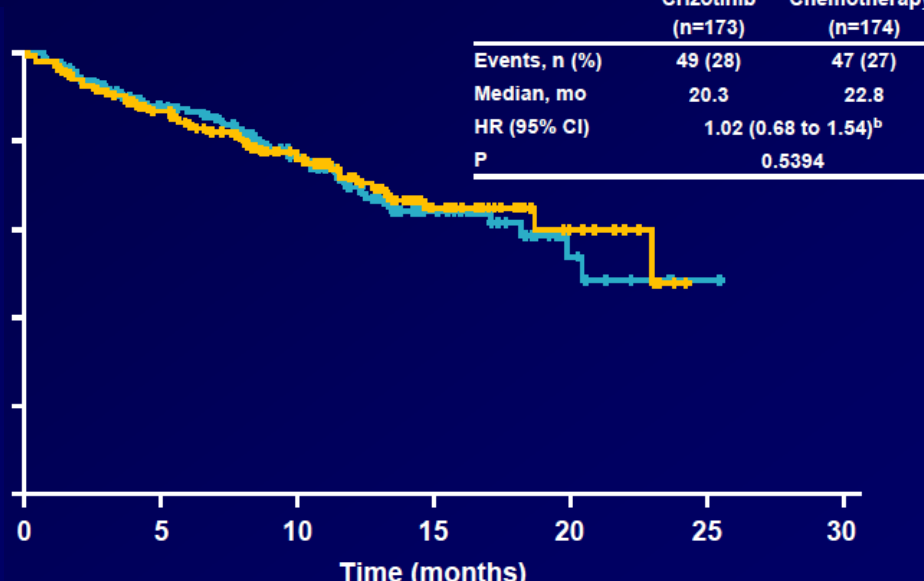
- Primary
  - PFS (RECIST 1.1, independent radiology review)
- Secondary
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

## PFS




| | Crizotinib (n=173) | Chemotherapy (n=174) |
|---|---|---|
| Events, n (%) | 100 (58) | 127 (73) |
| Median, mo | 7.7 | 3.0 |
| HR (95% CI) | 0.49 (0.37 to 0.64) | |
| P | <0.0001 | |

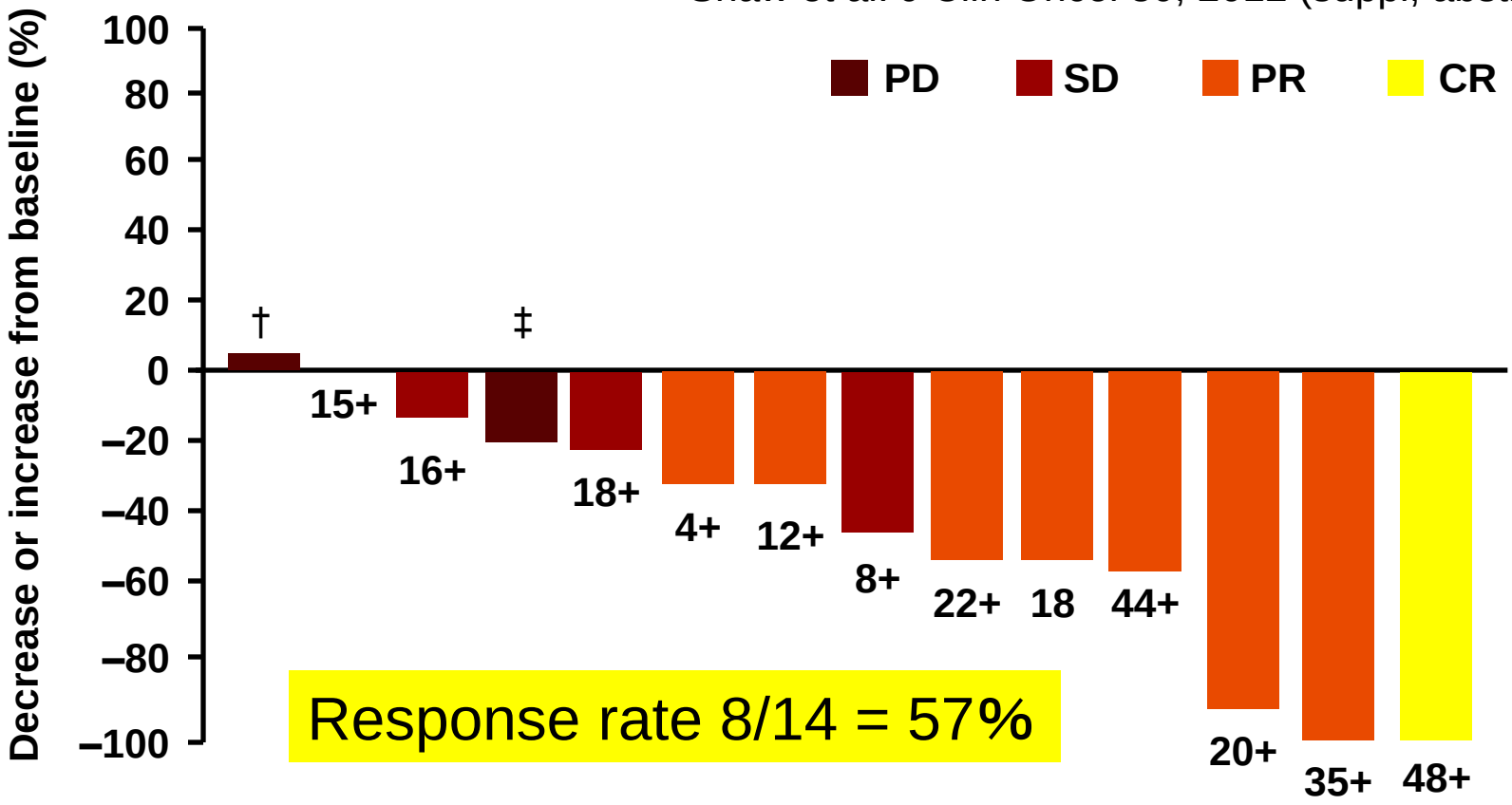
## OS




| | Crizotinib (n=173) | Chemotherap (n=174) |
|---|---|---|
| Events, n (%) | 49 (28) | 47 (27) |
| Median, mo | 20.3 | 22.8 |
| HR (95% CI) | 1.02 (0.68 to 1.54)[b] | |
| P | 0.5394 | |

# Tumor responses in patients with advanced ROS1+ NSCLC (n=14*)

Shaw et al. J Clin Oncol 30, 2012 (suppl; abstr 7508)




*Response-evaluable population

†Tumour ROS1 FISH-positive, but negative for ROS1 fusion gene expression

‡Crizotinib held for >6 wks prior to first scans which showed PD

+, treatment ongoing

# Other candidates of targeted therapies in lung cancer

| oncogene | activation | drug |
|---|---|---|
| **Adenocarcinoma** | | |
| RET | translocation | TKI: sunitinib, vandetanib, sorafenib, XL184 |
| HER2 | mutation | TKI: afatinib, dacomitinib<br>Ab: trastuzumab |
| MET | Amplification (mutation???) | TKI: crizotinib, tivantinib<br>Ab: MetMAb |
| **Squamous cell carcinoma** | | |
| FGFR1 | amplification | TKI |
| DDR2 | mutation | TKI: dasatinib |

# Summary(1)
# Bio-molecular-driven treatment in lung cancer

- Mutations of the driver oncogenes are most reliable for predicting efficacy of corresponding inhibitors
- All the driver genes so far identified are receptor tyrosine kinases activated either by mutation (EGFR, HER2, DDR2), amplification (MET, FGFR1) or translocation (ALK, ROS1, RET)
- Pharmacologic inhibition of the driver gene products typically achieves ORR of ~60-70% and PFS of ~10 month which are significantly longer than those of chemotherapy

# Summary(2)
# Bio-molecular-driven treatment in lung cancer

- Many of them are low in incidence (~1%). Efficient screening method/algorithm is awaited…Next Gen. Sequence technology?
- There is heterogeneity in response even within patients having driver gene mutation, which is probably due to additional genetic/epigenetic alterations
- Acquired resistance is inevitable, and its overcoming is of utmost importance.