Personalized therapy in lung cancer: The promise for the future

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DISCLOSURE

- I received honoraria for advisory boards and for lectures from: Eli Lilly, Abbott, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Genentech, GSK, Merck Serono, Novartis, Pfizer and Roche

Personlized therapy of lung cancer

Taking into account not only patient characteristics, but also molecular tumor characteristics and thus:

- **Moving away from empirism and serendipity to a biology-based therapy**
- **Matching the right drug with the right cancer type**
- **Defining on each patient's tumor the right biomarker of response**

Histological classification is necessary for today‘s decision making

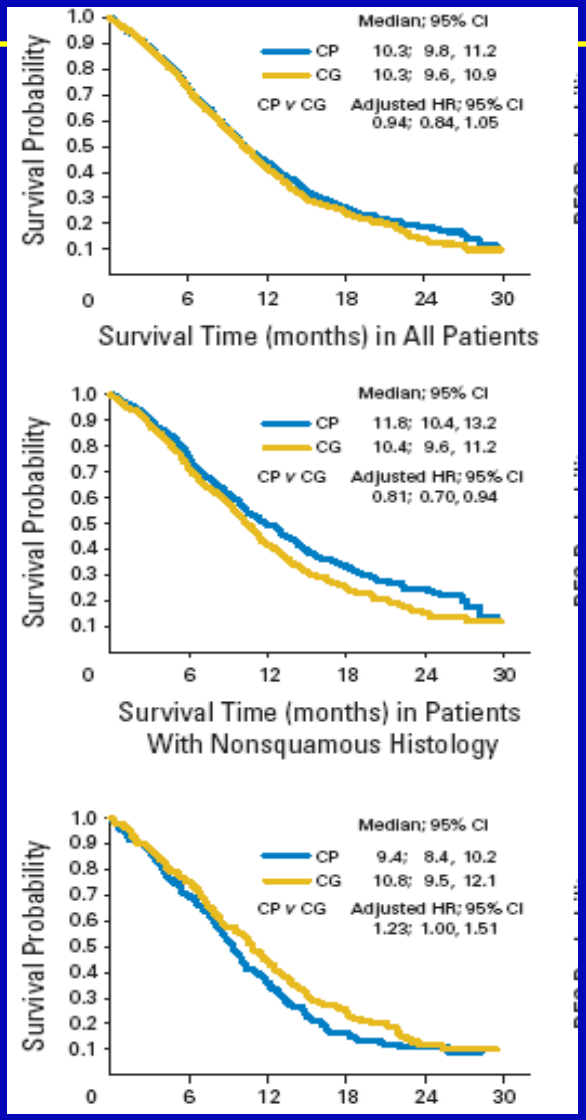
- **A diagnosis of “non-small cell lung cancer” is no longer acceptable as sufficient basis for treatment decisions:**
  - **Benefit of bevacizumab added to first line chemotherapy in non-squamous cell carcinoma** Sandler, JCO 2006; Reck JCO 2009
  - **Differential effect of pemetrexed in non-squamous vs squamous cell carcinoma** Scagliotti, JCO 2008
  - **Histology will help guide decision about which molecular analysis is performed**

Cisplatin-Pemetrexed vs Cisplatin-Gemcitabine in Advanced NSCLC

No difference in overall PFS or survival between study arms

Cis/pem improves survival over cis/gem in non-squamous cell carcinoma (HR 0.81, p=0.005)

Cis/gem improves survival over cis/pem in squamous cell carcinoma (HR 1.23, p=0.05)

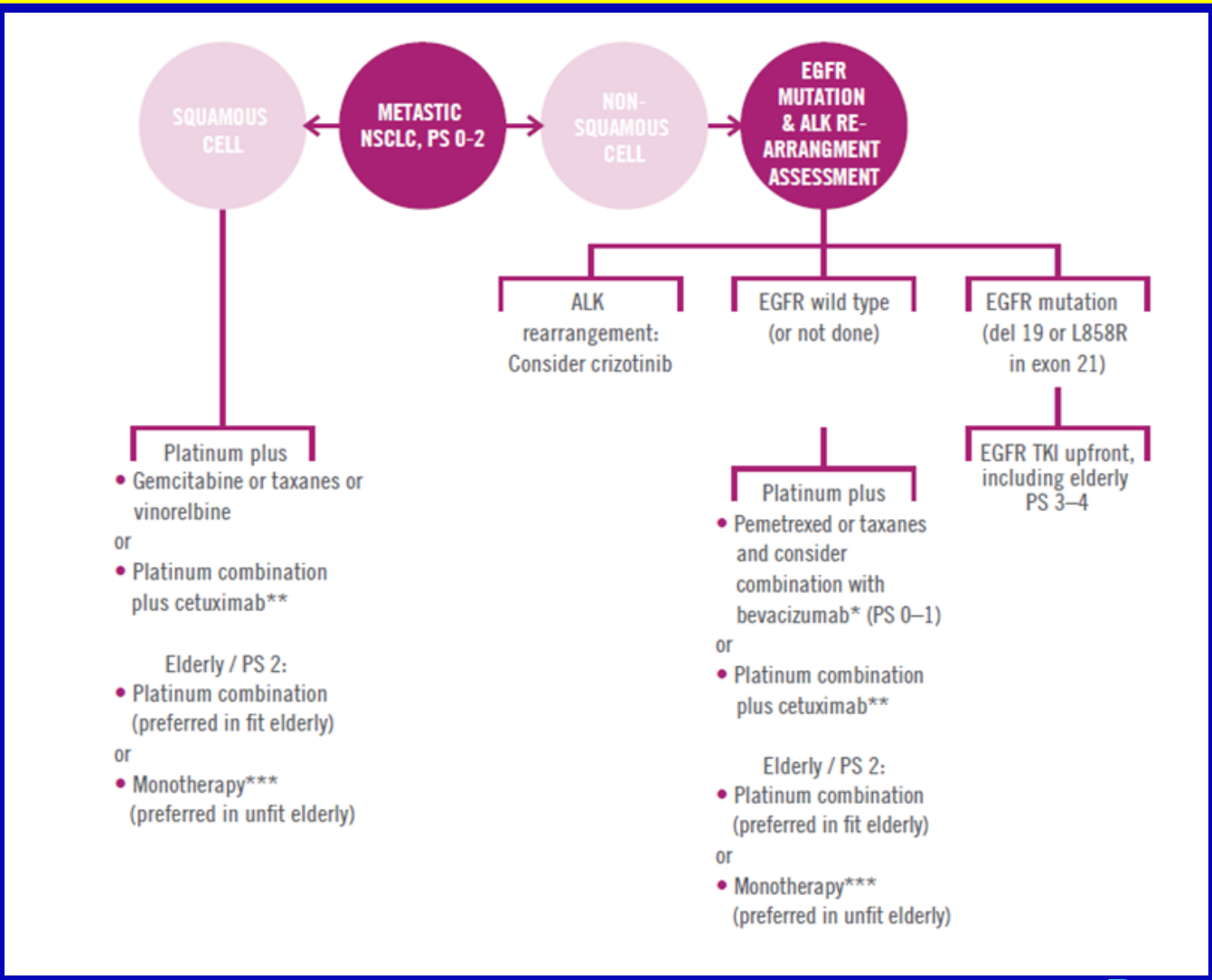


Scagliotti, JCO 2008

Molecular classification: Present necessities and future directions

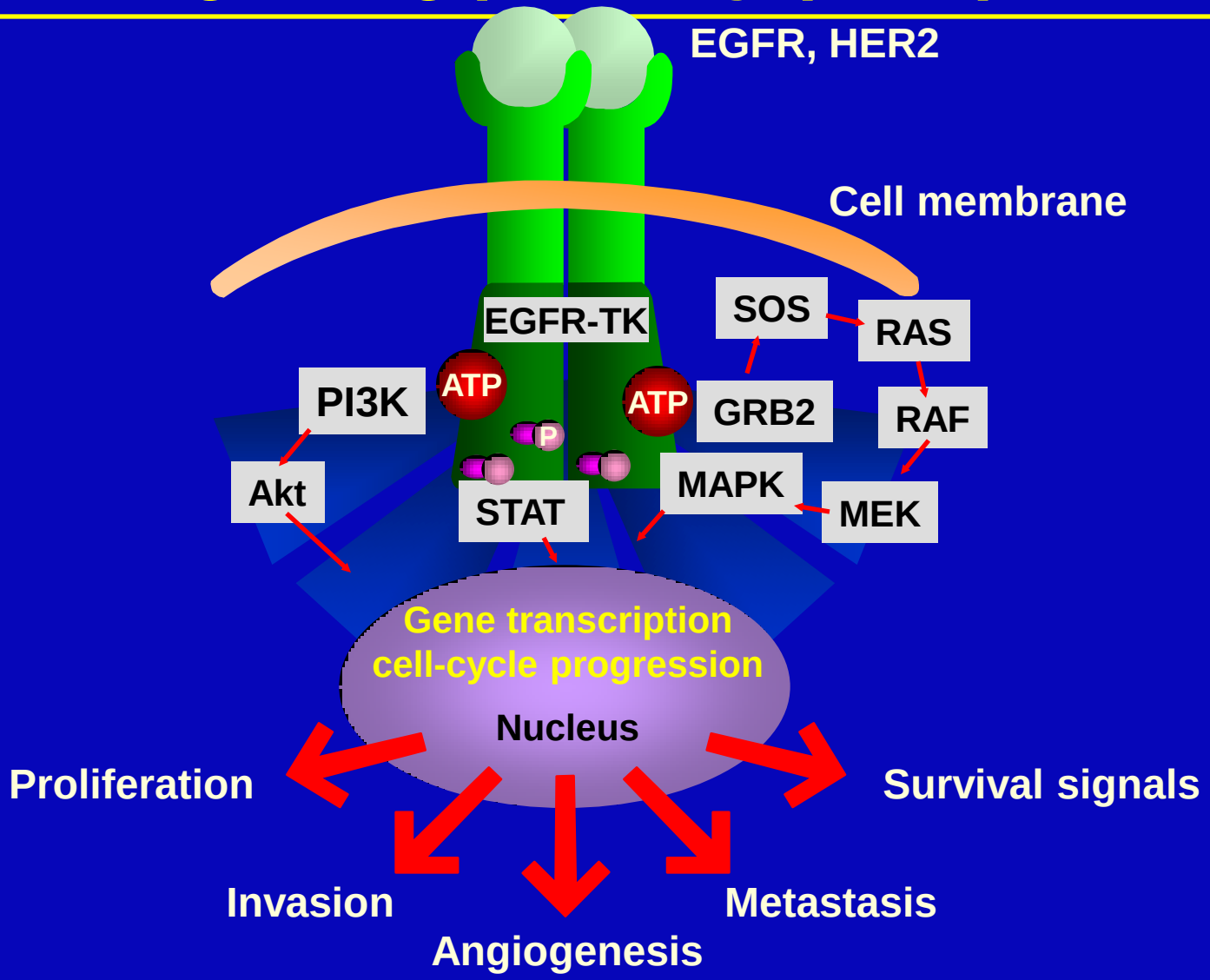
- Adenocarcinoma of the lung is not a uniform disease and needs to be classified by additional molecular analysis
  - Present needs include EGFR mutation status and determination of EML4-ALK fusion gene
  - Knowledge about resistance mechanisms to available agents and the opportunity of agents against new molecular targets mandate change in the trial design
- Potential driver mutations are also being identified in squamous cell lung cancer

The situation today: ESMO Pocket Guideline (2012 edition)

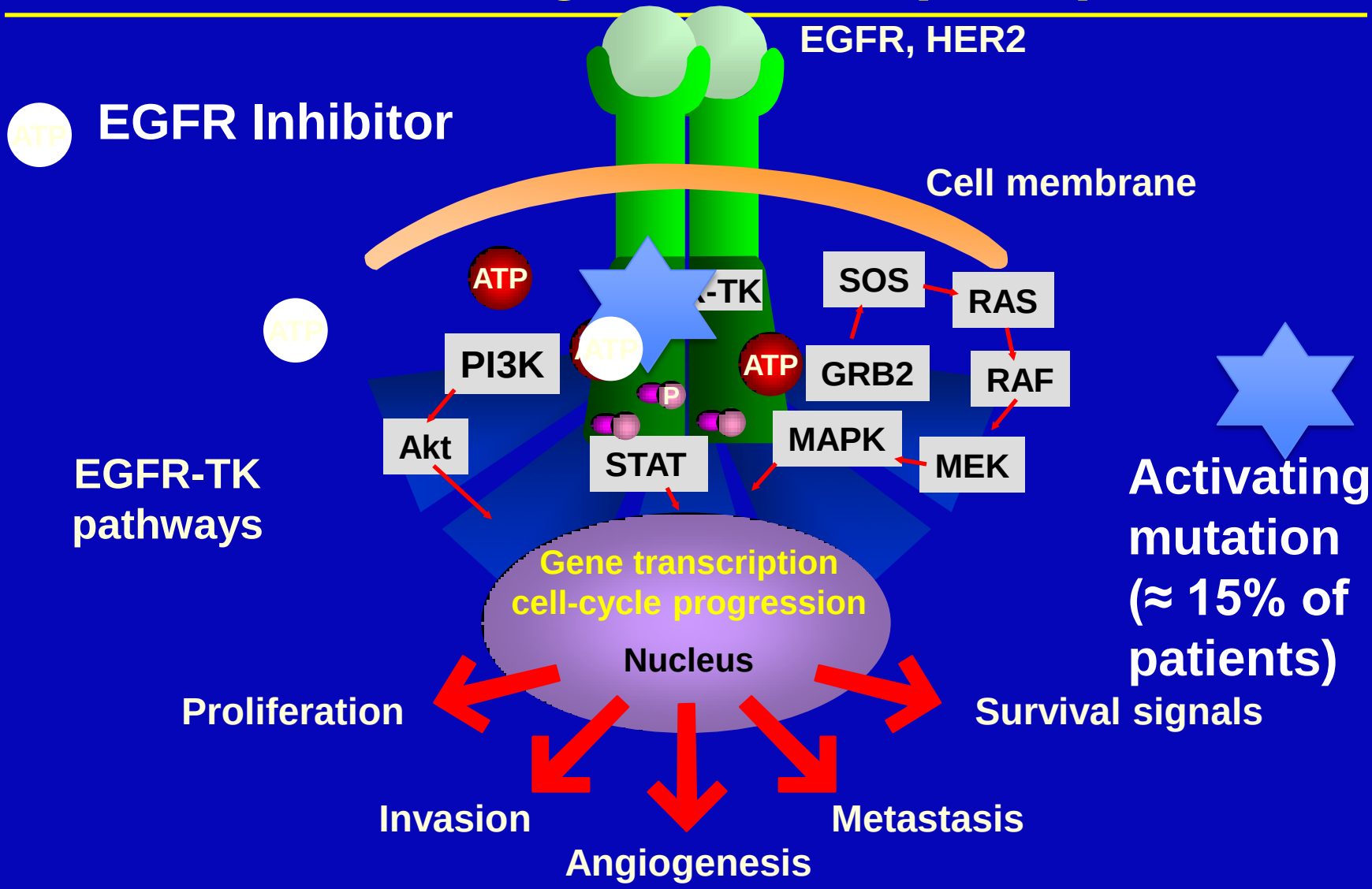


Peters et al, 2012

Epidermal growth factor receptor (EGFR) signaling pathway (1980)



Inhibition of EGFR signaling pathway with activating mutation (2004)



The NEW ENGLAND JOURNAL of MEDICINE

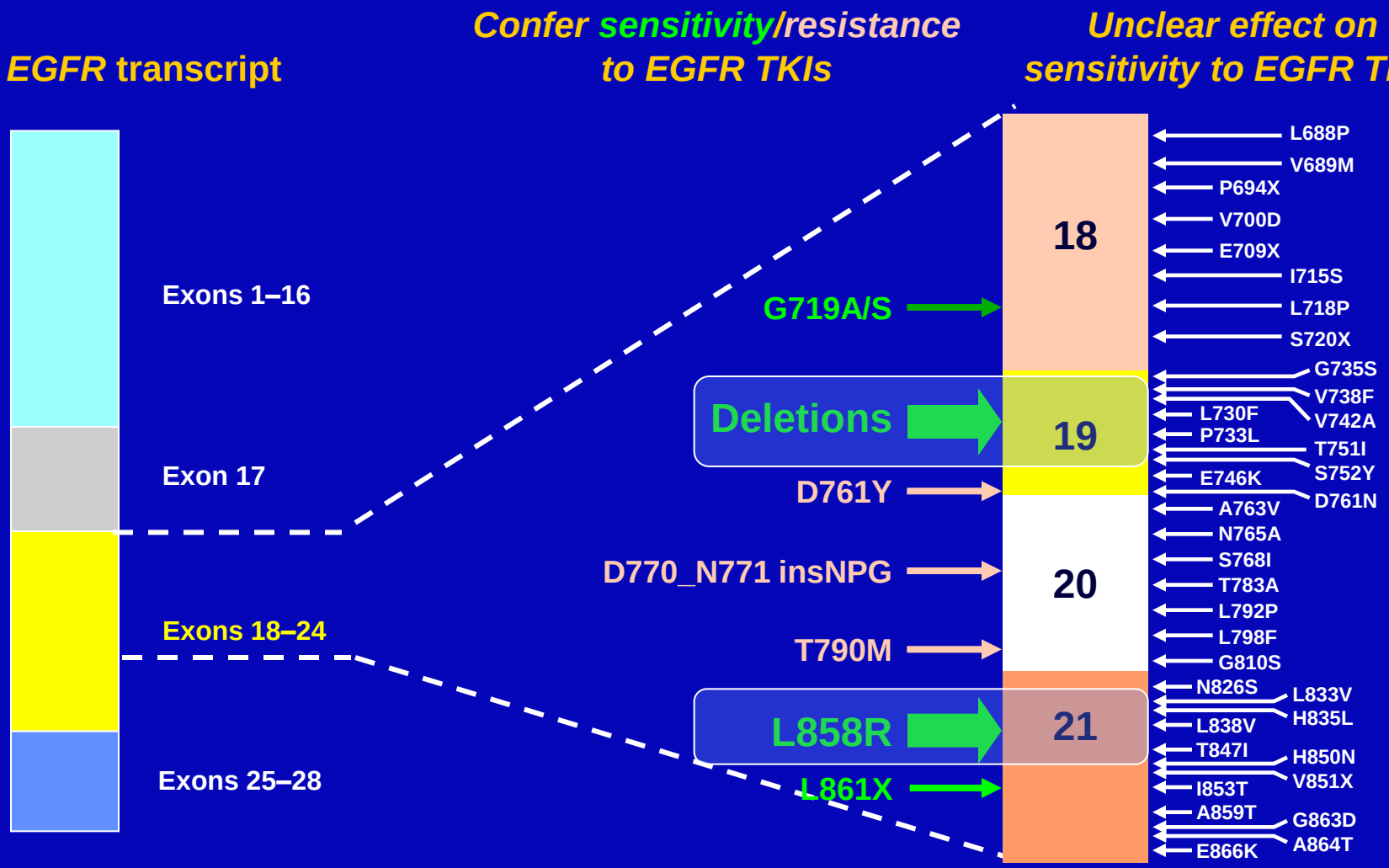
ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

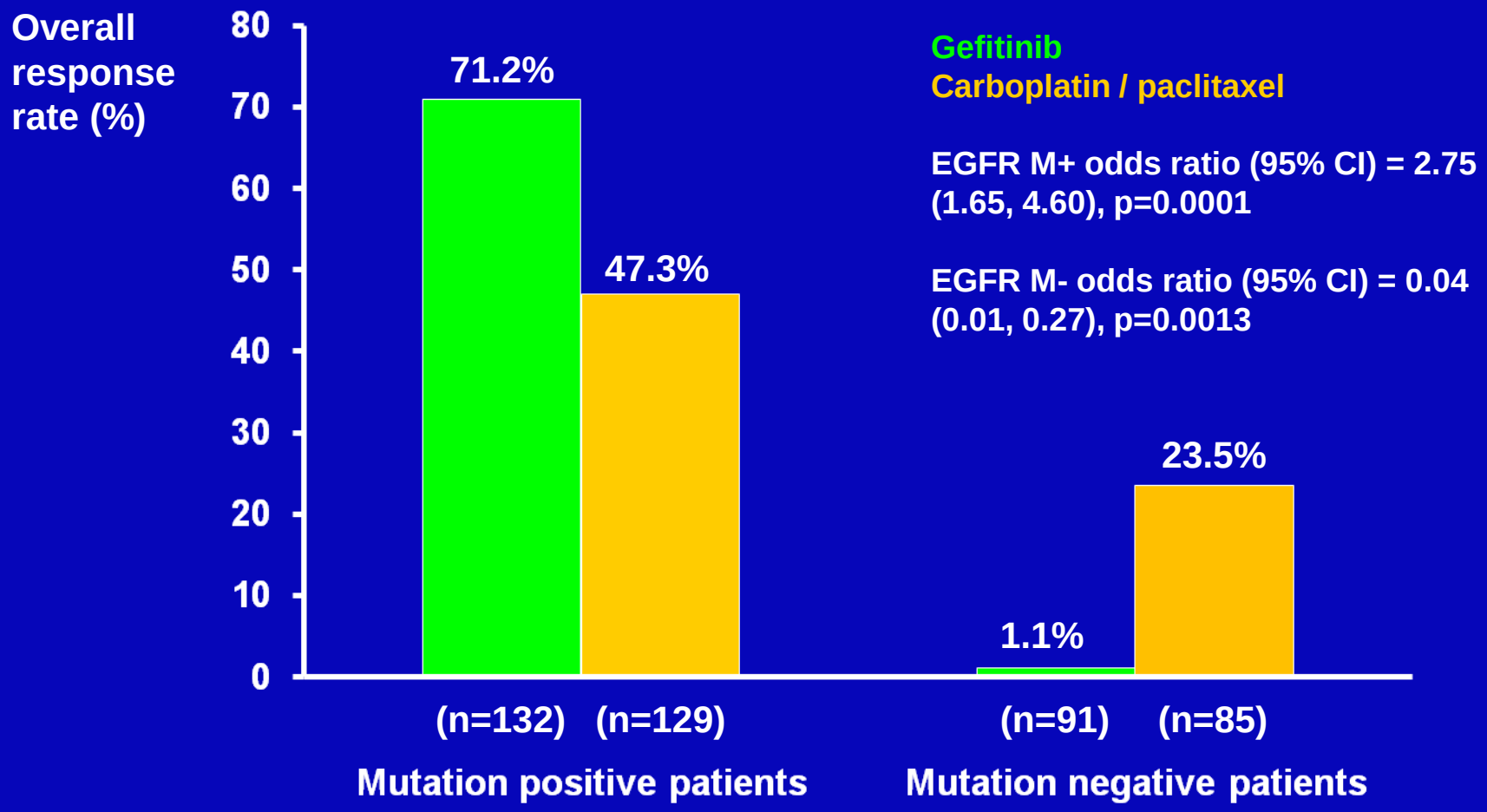
	EGFR mutations
Gefitinib responders	8/9
Non-responders	0/7

Mutations identified in *EGFR* gene



Riely, Clin Cancer Res 2006

IPASS: Objective RR in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

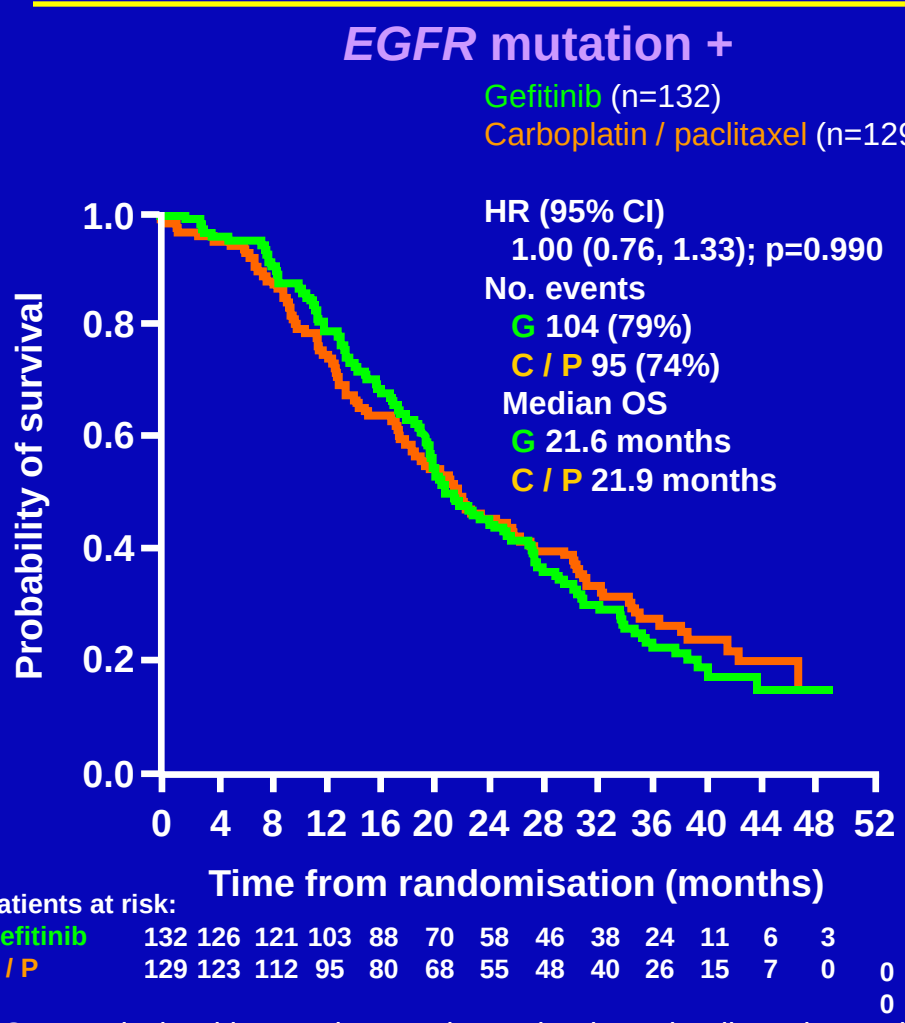
Mok, ESMO 2008; NEJM 2009

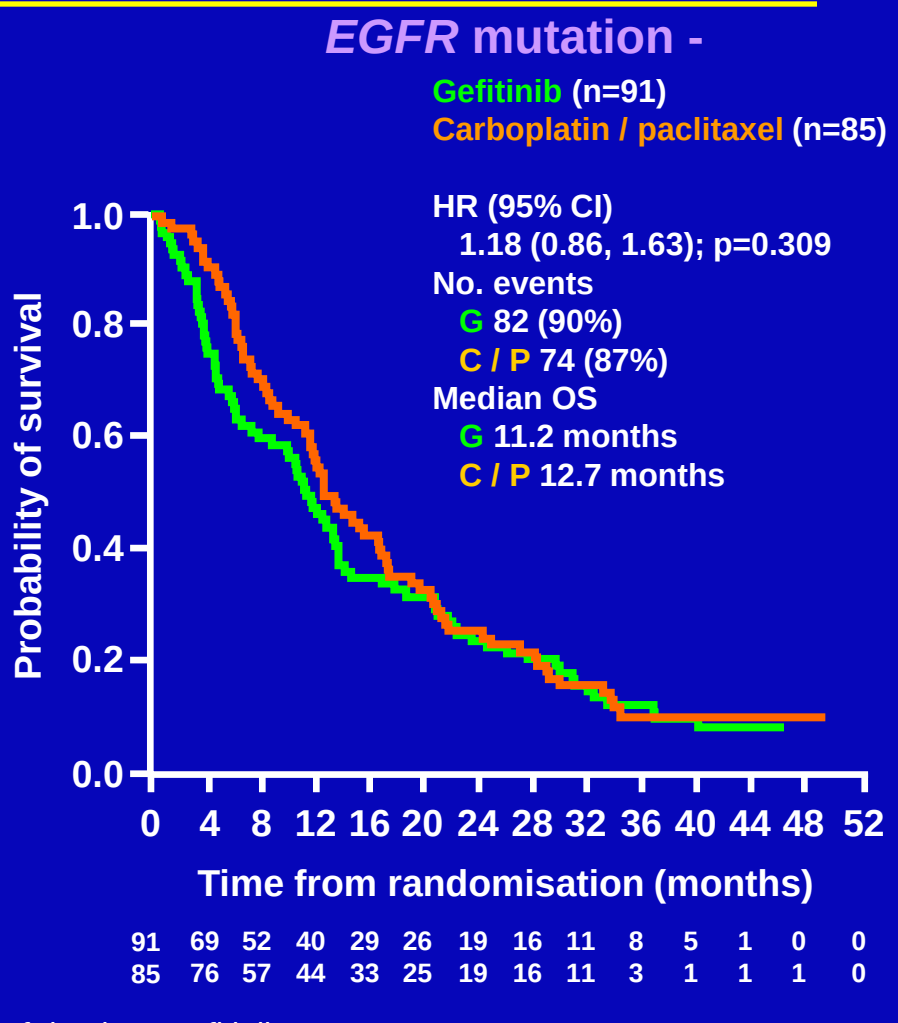
First line EFGR TKI or chemotherapy for non-squamous cell lung cancer harboring activating EGFR mutation

Author	Study	N	RR (TKI vs Chemo)	PFS (HR, 95%CI)
Mok	IPASS	261	71% vs 47%	0.48 (0.36, 0.64)
Lee	First-SIGNAL	42	85% vs 38%	0.61 (0.31, 1.22)
Mitsudomi	WJTOG 3405	198	62% vs 32%	0.49 (0.34, 0.71)
Kobayashi	NEJGSG002	177	75% vs 29%	0.36 (0.25, 0.51)
Zhou	Optimal	165	83% vs 36%	0.16 (0.10, 0.26)
Rosell	EUROTAC	174	58% vs 15%	0.42 (0.27, 0.64)
Yang	LUX-lung 3	345	56% vs 22%	0.58 (0-43. 0.78)

Mok, NEJM 2009; Lee, WCLC 2009; Mitsudomi,Lancet Oncology 2010; Kobayahsi, ASCO 2009; Yang, ESMO 2010; Rosell ASCO 2011, Yang ASCO 2012

IPASS: Overall survival in EGFR mutation positive and negative patients





Cox analysis with covariates; a hazard ratio <1 implies a lower risk of death on gefitinib

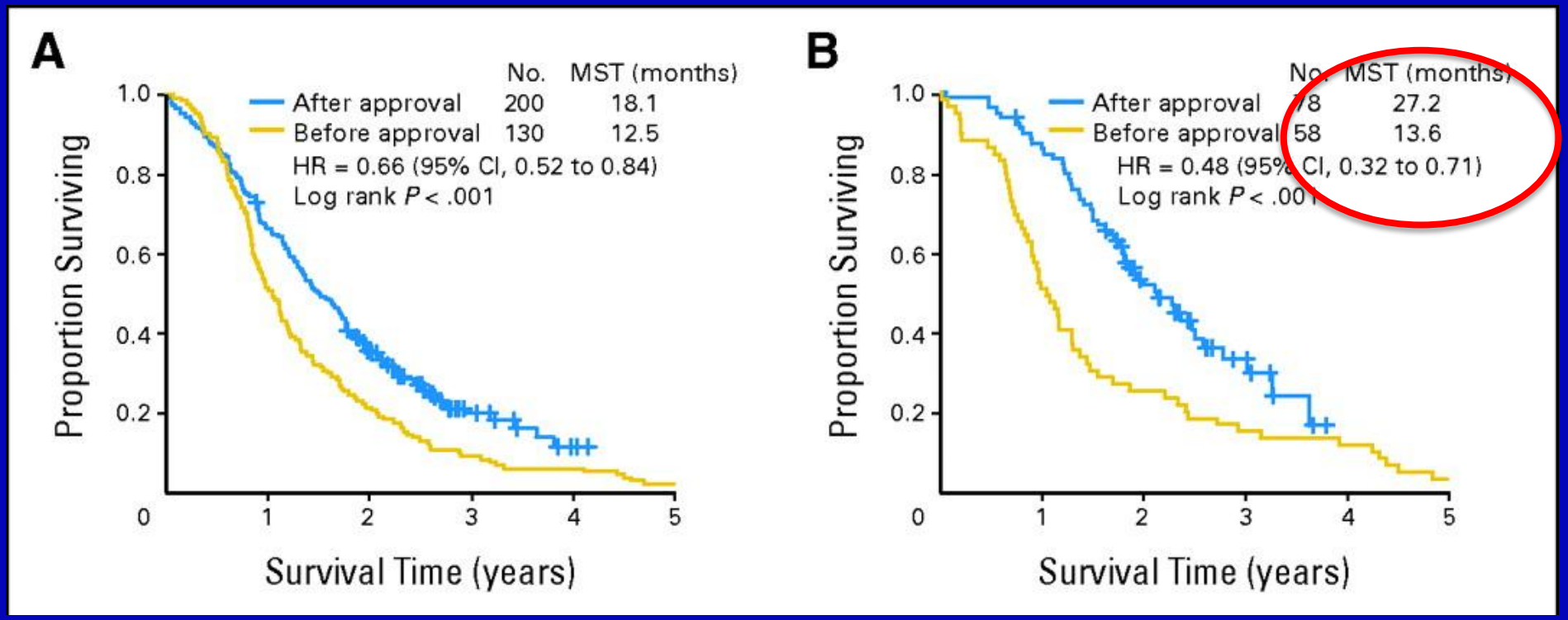
No formal adjustment for multiple testing was made, therefore statistical significance at the traditional 5% level cannot be claimed

Yang, ESMO 2010

Comparison of survival for patients with lung adenocarcinoma in Japan before and after gefitinib approval

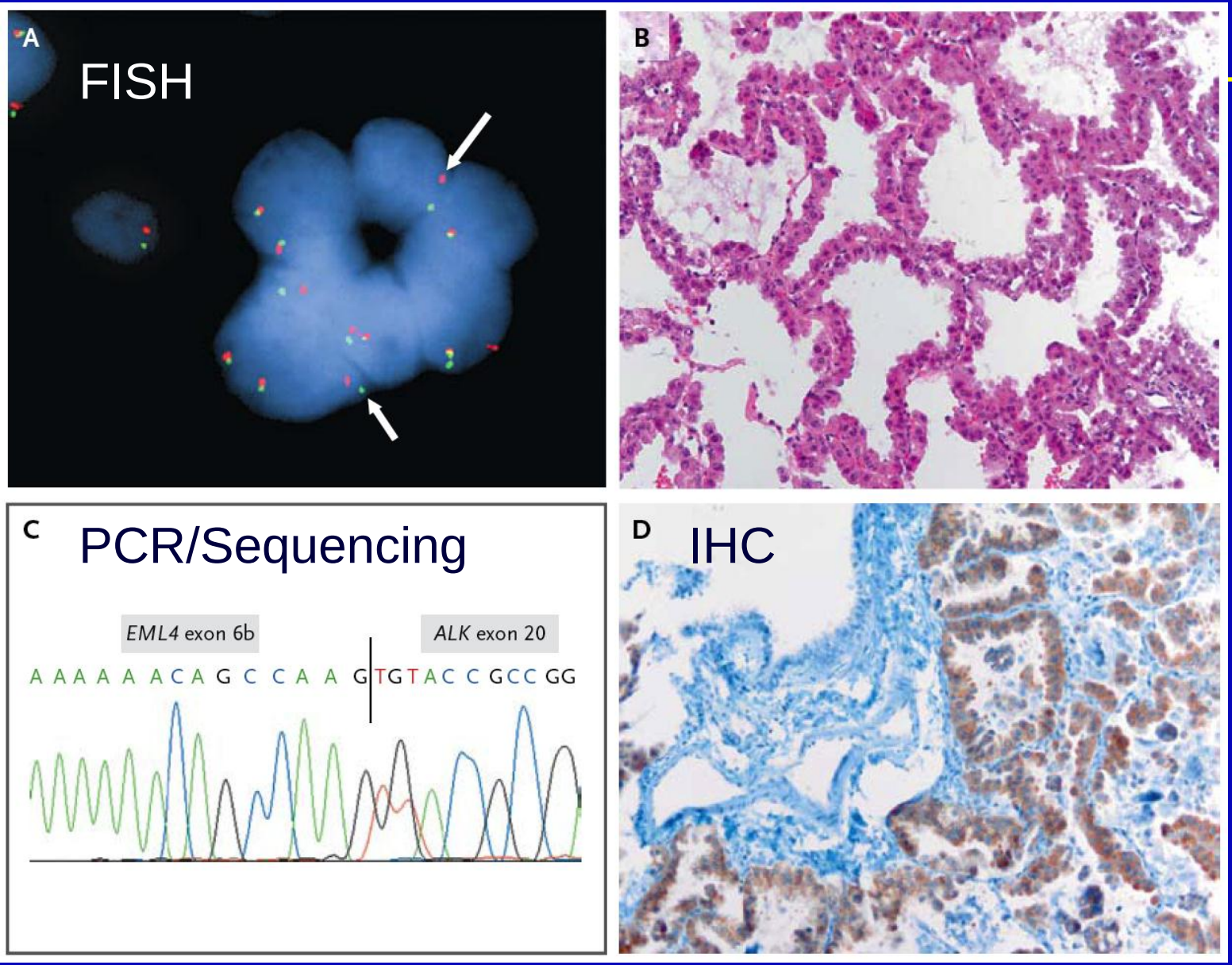
All patients

EGFR mut+ patients

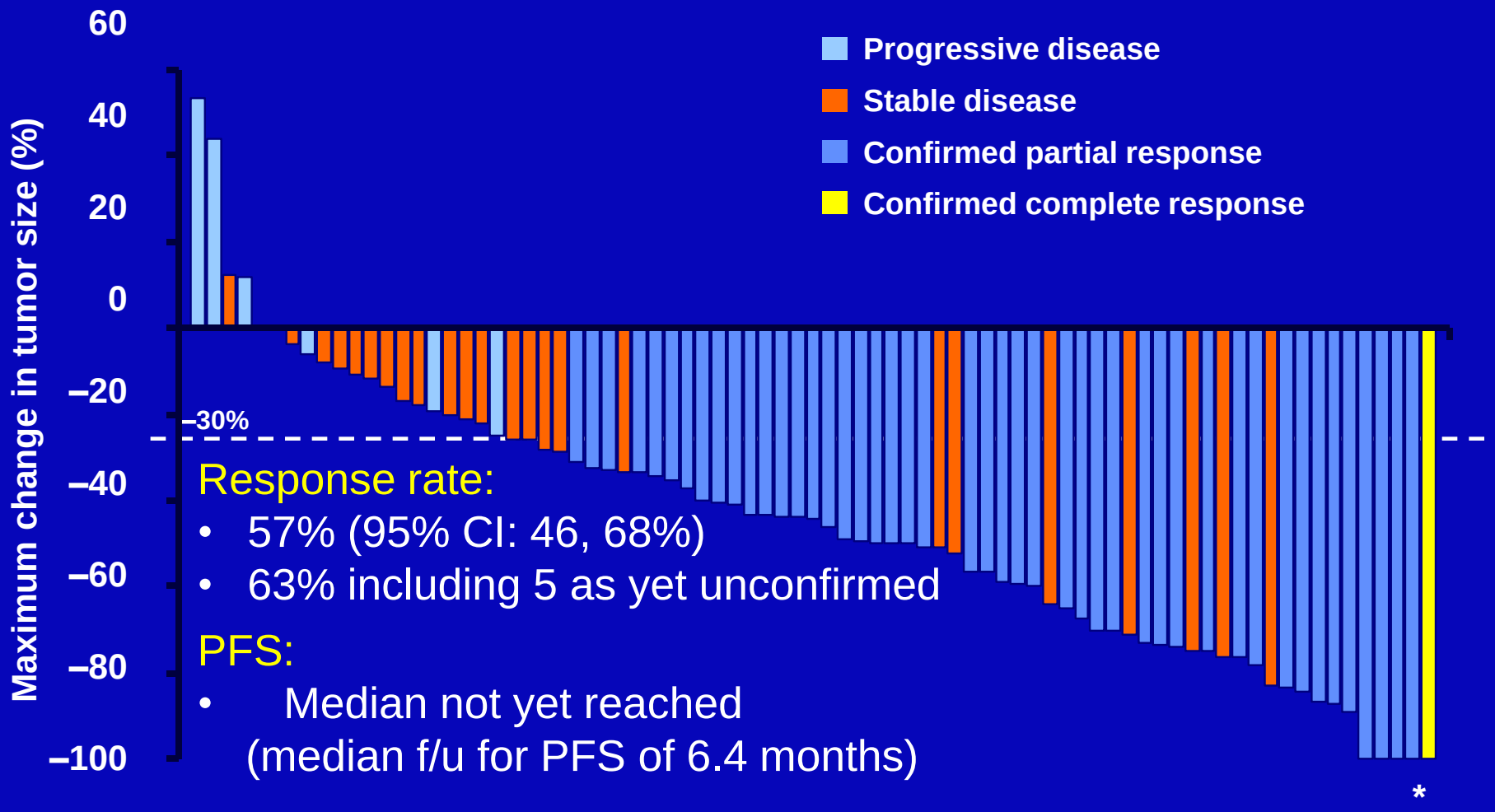


Takano, JCO 2008

Diagnosis of EML4-ALK positive NSCLC



Responses to crizotinib for patients with *ALK*-positive NSCLC



Response rate:

- 57% (95% CI: 46, 68%)
- 63% including 5 as yet unconfirmed

PFS:

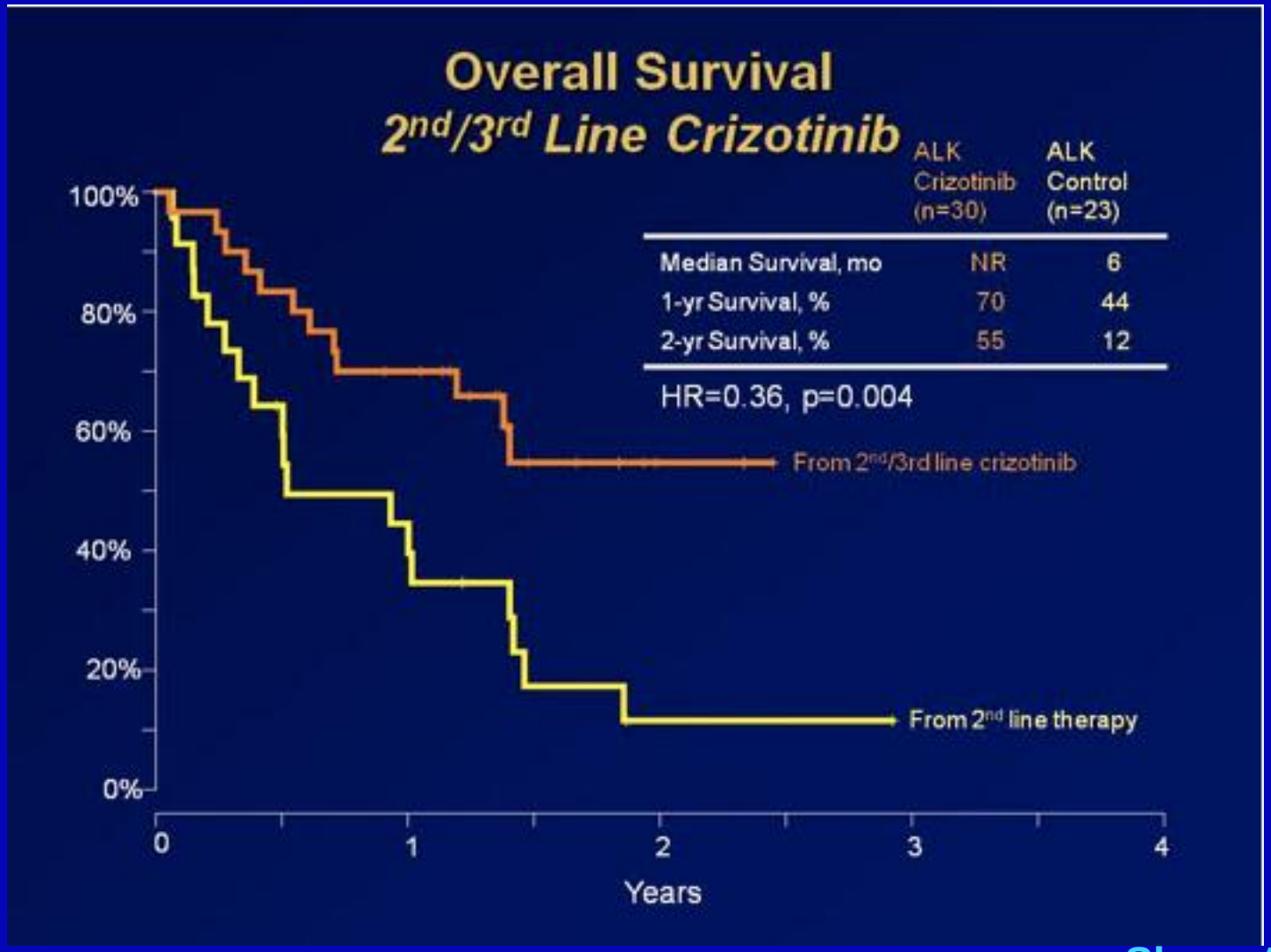
- Median not yet reached (median f/u for PFS of 6.4 months)

F1174L mutation associated with resistance

Sasaki, CR 2010

Bang, ASCO 2010: Kwak, NEJM 2010

Survival benefit with crizotinib?



Shaw, ASCO 2011

Crizotinib timeline

2007

First Report of EML4/ALK Fusion and Biology

2008

Crizotinib Phase I response in ALK+NSCLC Preclinical studies;FISH & PCR tests

2009

Efficacy Reports: clinical Reports; biomarker reports

2010

Type B mtg with FDA

Agreement A8081001 and A8081005 OK for accelerated approval

Orphan drug status

Type B mtg with FDA

Pre-NDA

Vysis FISH PMA completed by Abbott Molecular

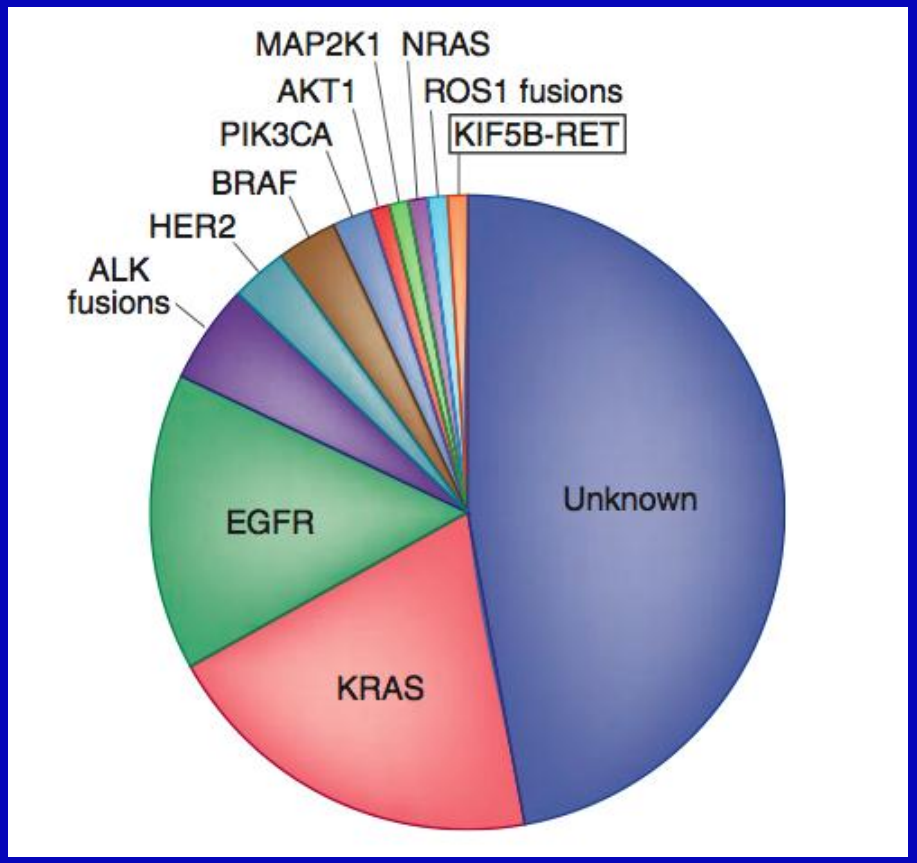
2011

Rolling NDA Submission completed

FDA Approval

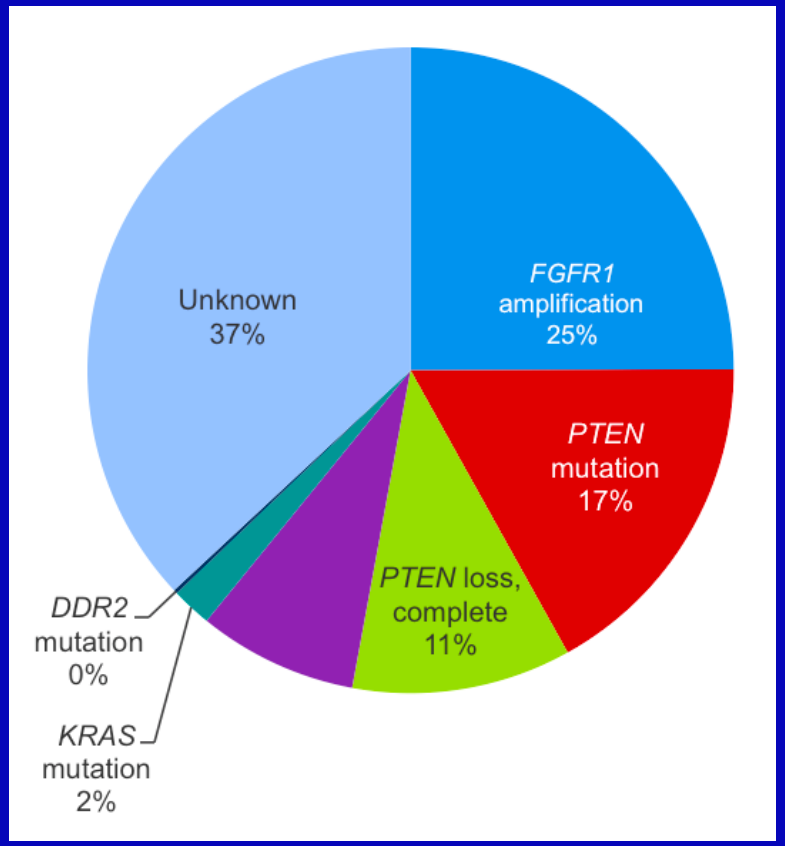
The situation tomorrow: Molecularly-based first line therapy

Adenocarcinoma



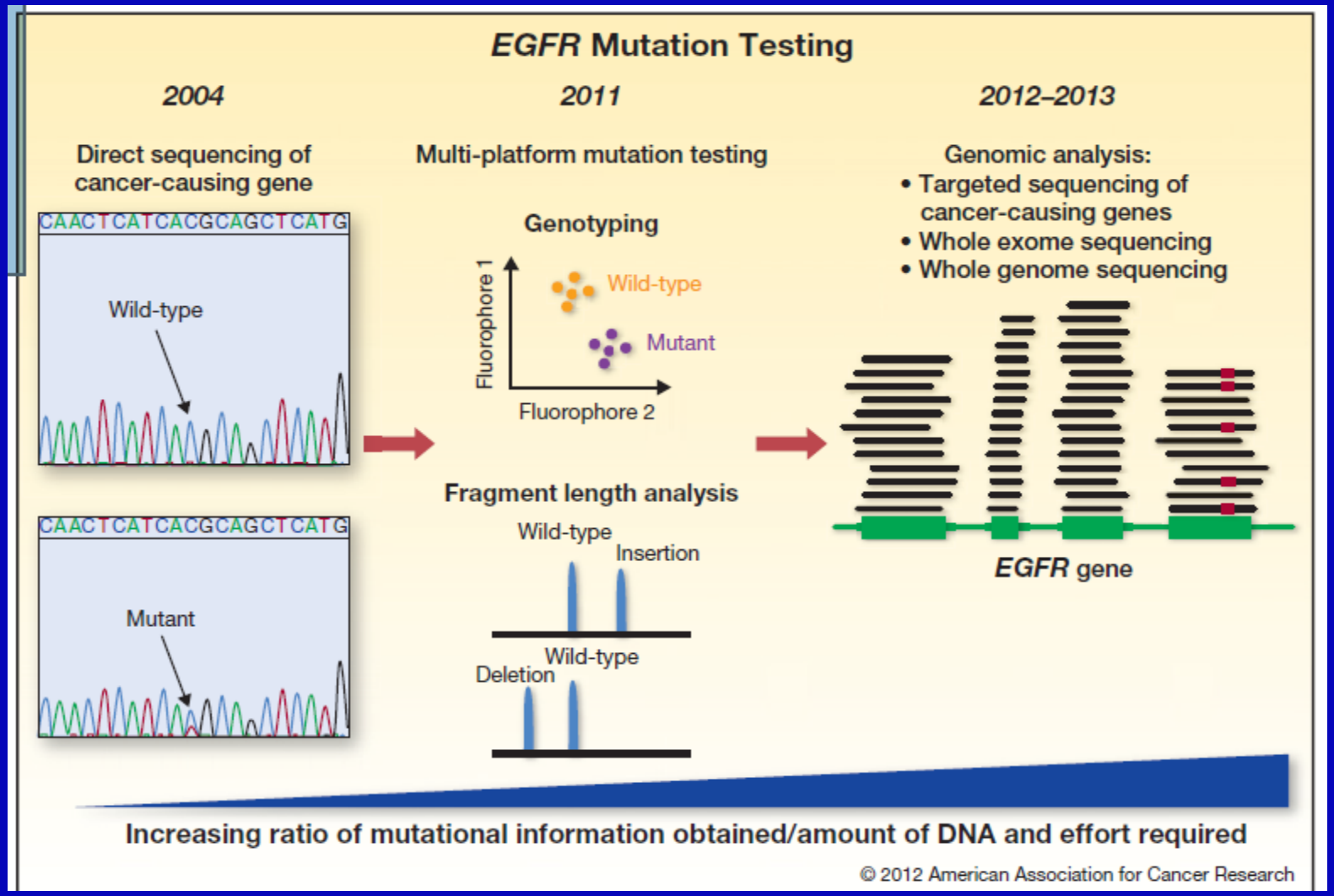
Pao, Nature Med 2012

Squamous cell carcinomaa



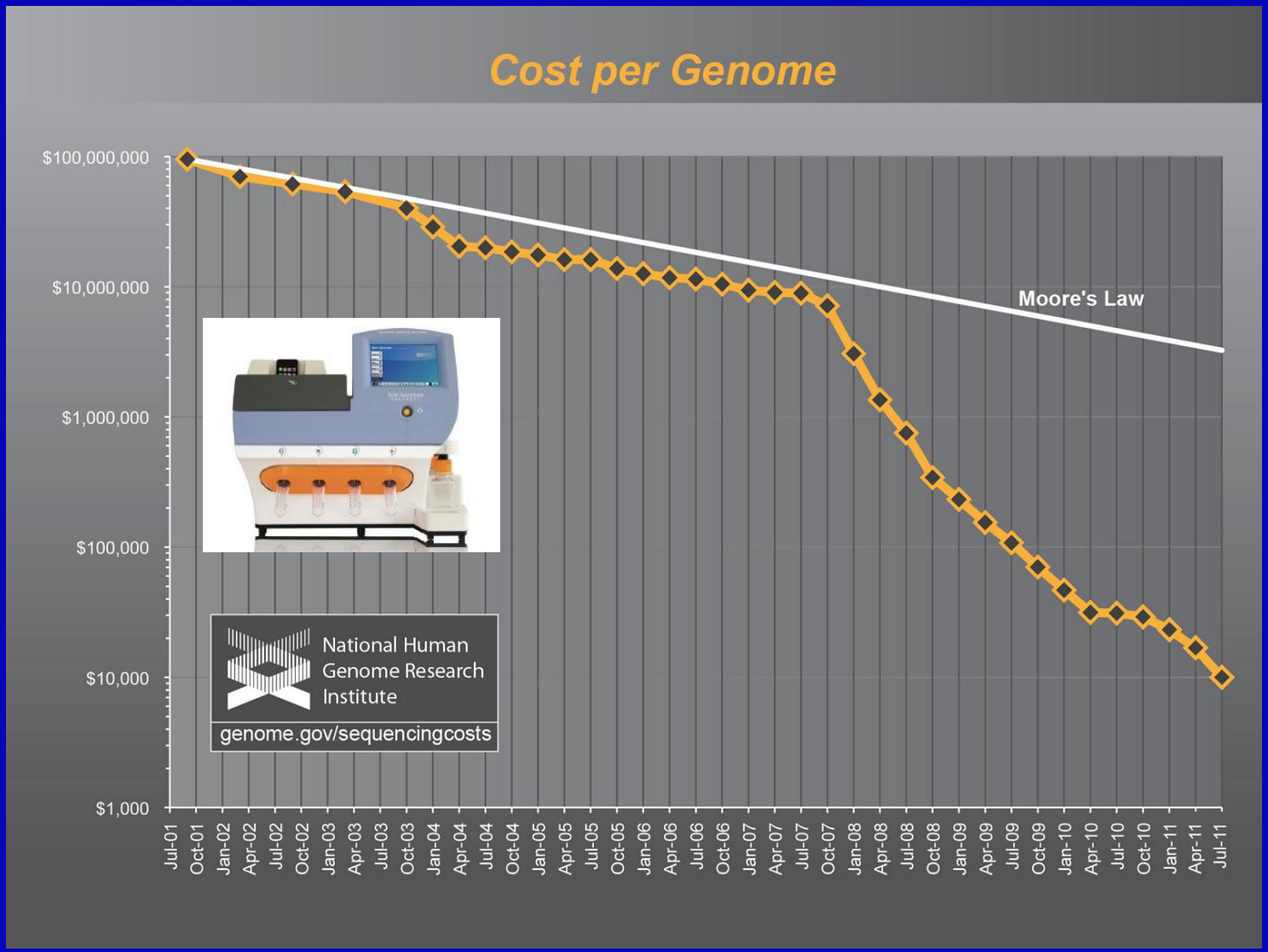
Paik, ASCO 2012

Evolution of mutation testing, example EGFR

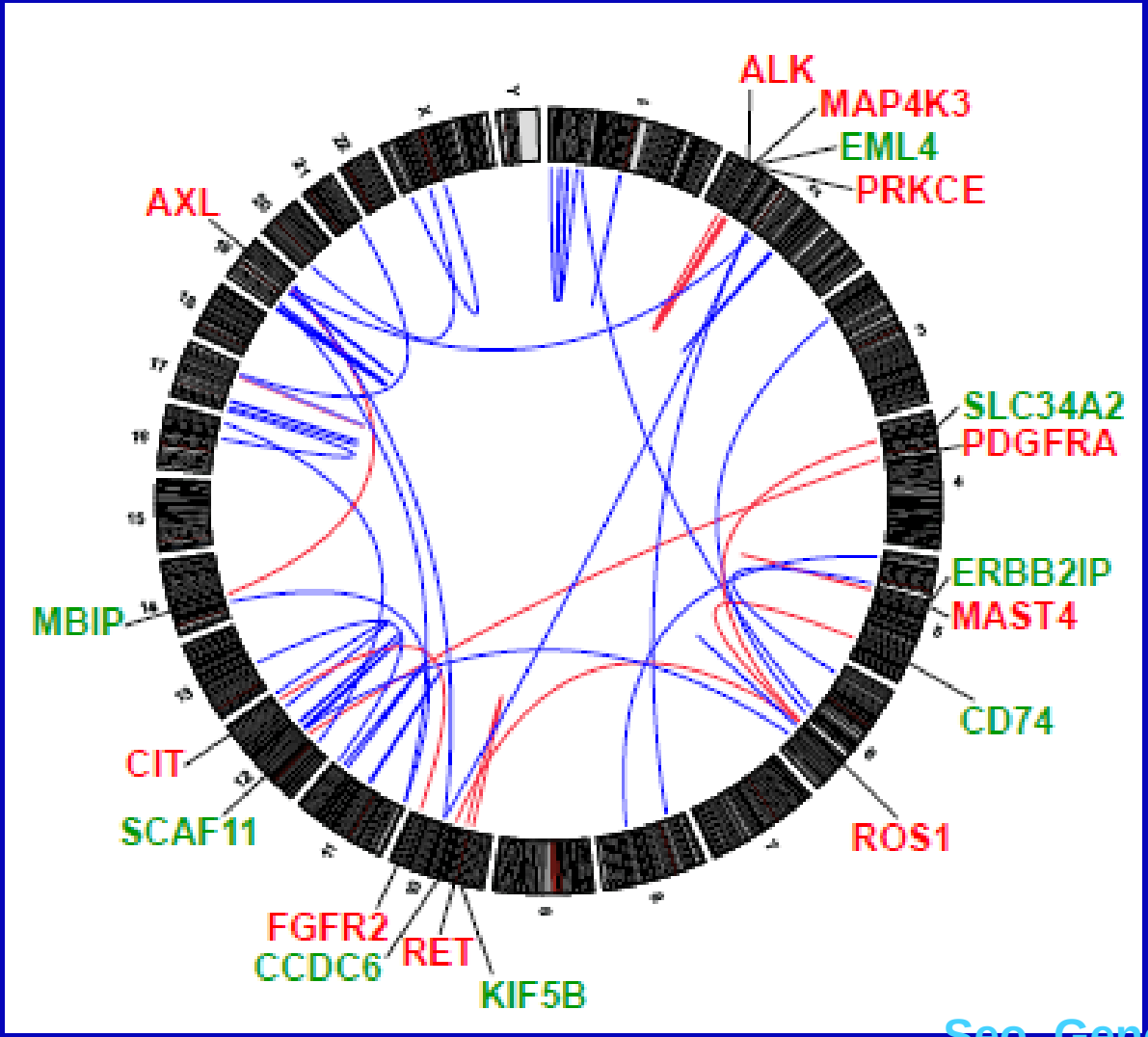


Politi, CCR 2012

The DNA sequencing revolution

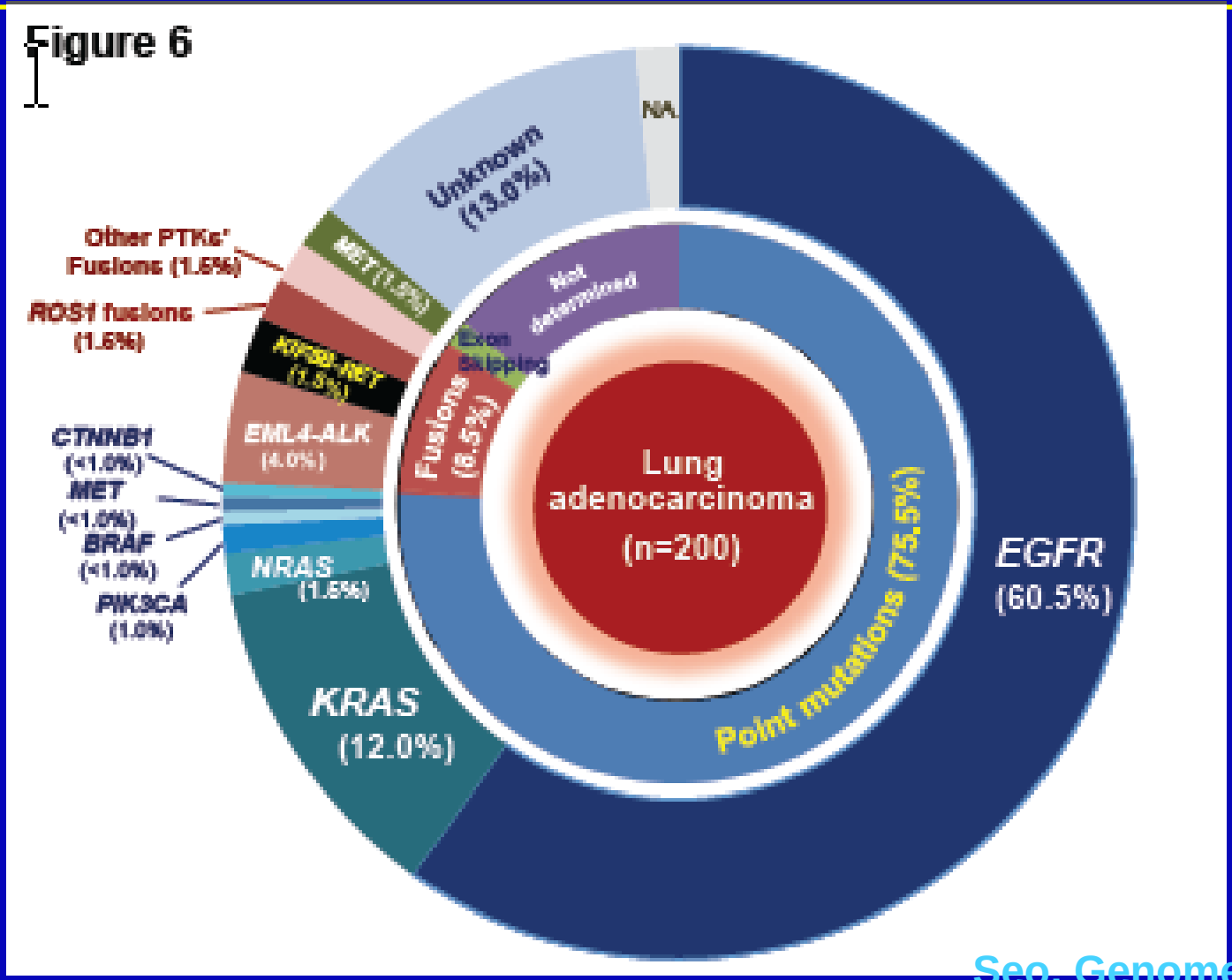


Graphical representation of 45 fusion genes from 87 adenocarcinomas from Korea



Seo, Genome Res 2012

Summary of mutational profiles for 200 adenocarcinomas from Korea



Seo, Genome Res 2012

Personalized therapy for lung cancer

- Personalized therapy for advanced non-small cell lung cancer has become a new reality
- As of today, about one third of lung adenocarcinoma in Western Societies do have actionable oncogenic mutations or gene rearrangements with approved therapies (EGFR and ALK) or therapies under investigation
- A similar picture is emerging on lung squamous cell carcinoma
- Further progress mandates a move from empiric trial designs based on clinical patient characteristics to molecularly-driven clinical trials

Personalized therapy for lung cancer

- In Western societies actionable molecular subgroups range between 1% and 15%, mandating large networks for molecular testing and patient selection for molecular-driven clinical trials
- The dramatic impact of specific targeted therapies would make it unethical for future trials not to include a crossover design. Thus new ways must be found leading to regulatory acceptance and to eventually document survival benefits
- The multitude of actionable molecular changes is leading to a change in the diagnostic work up from sequential testing to multiplex testing and next generation sequencing