Latest advances in Lung Cancer
Key facts & new therapies

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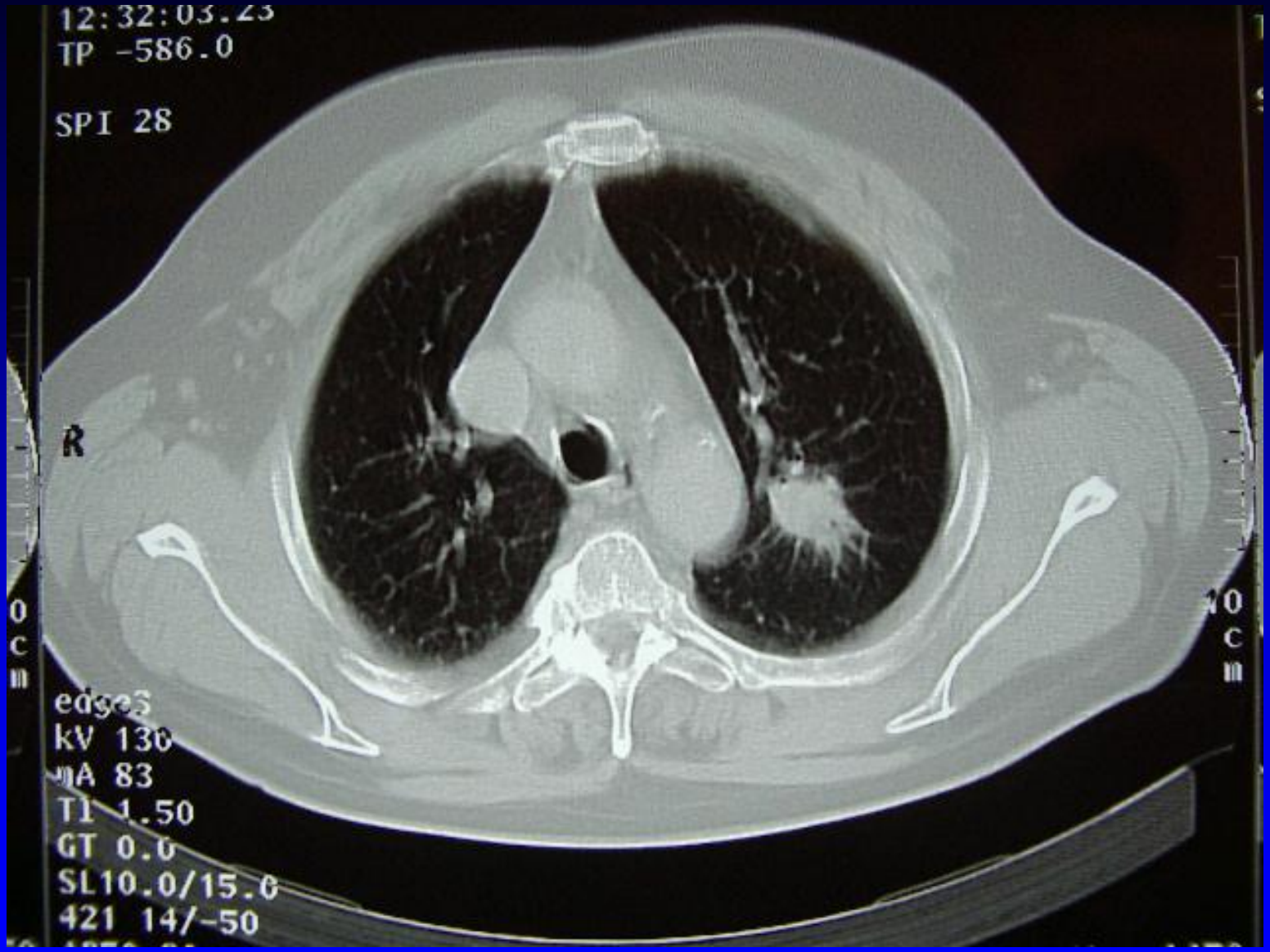
ESMO Patient Seminar
Vienna 2012

Lung Cancer

- High incidence: ~1.5 Mill new cases worldwide every year
- Exogen & endogen risk factors
- ~85% of cancers in smokers or former smokers
- Pathological classification
  - Non-small cell lung cancer (>80%)
  - Small cell lung cancer
- Asymptomatic in early stages !
  Cough, thoracic pain, dyspnea, pneumonia, hemoptoe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Pathology of Lung Cancer

- WHO classification 2004
  - Squamous cell carcinoma
  - Smalll cell lung cancer
  - Adenocarcinoma
  - Large cell carcinoma
  - Adenosquamous carcinoma
  - Sarcomatoid carcinoma
  - Carcinoid (typical, atypical)
  - Saliva gland carcinomas (mucoepidermoid, adenocystic, epithelial-myoepithelial)
- Predominant sites of metastasis

  Lymph nodes

  Lung Liver Adrenal Glands Bone Brain

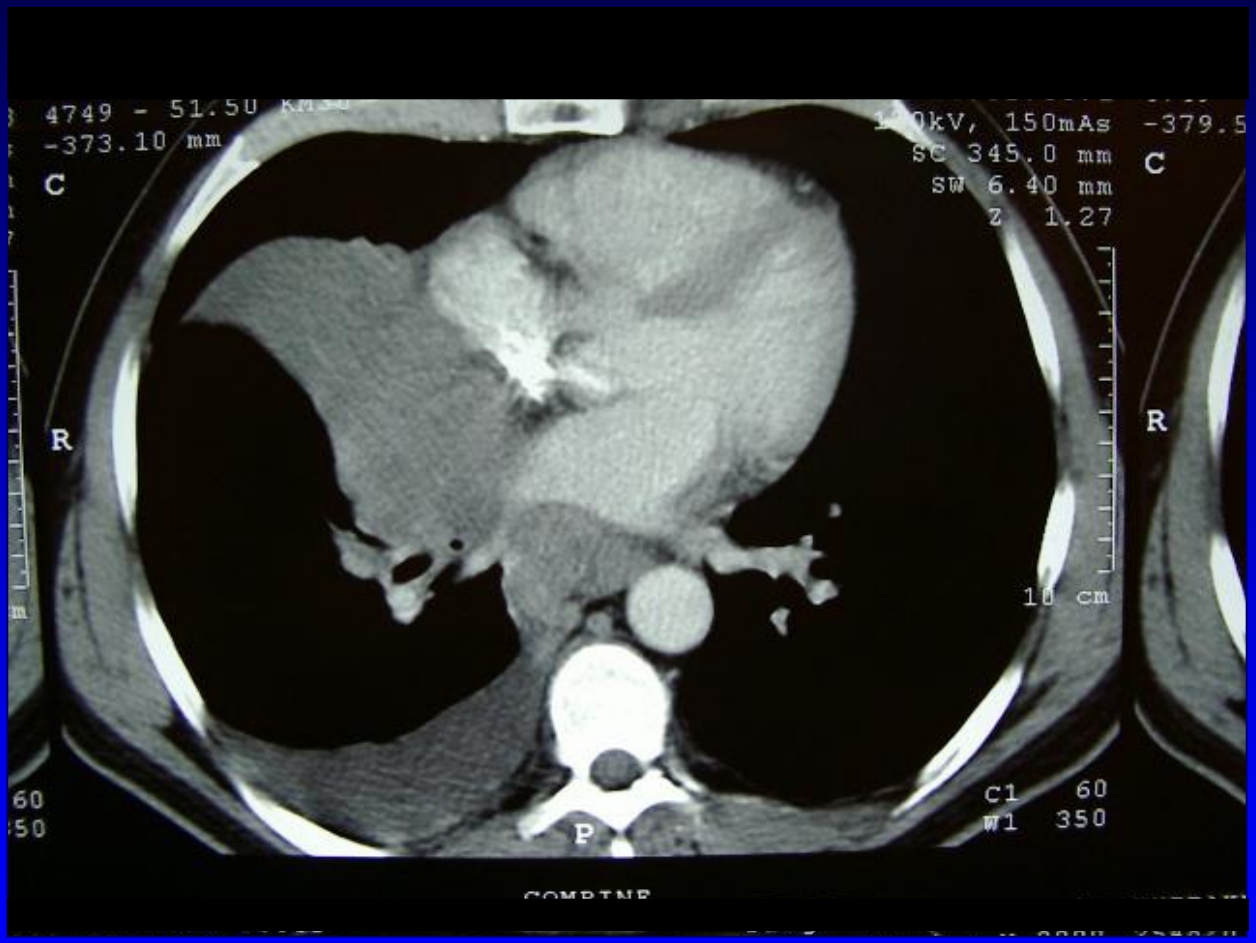
Non-small cell lung cancer

Stage	Standard therapy	Within trials
I, II	Surgery Adjuvant chemo	Adjuvant therapies
III	Local therapy + chemo	Multimodality therapies
IV	Chemotherapy Bevacizumab Gefitinib, Erlotinib	New drugs

Small cell lung cancer

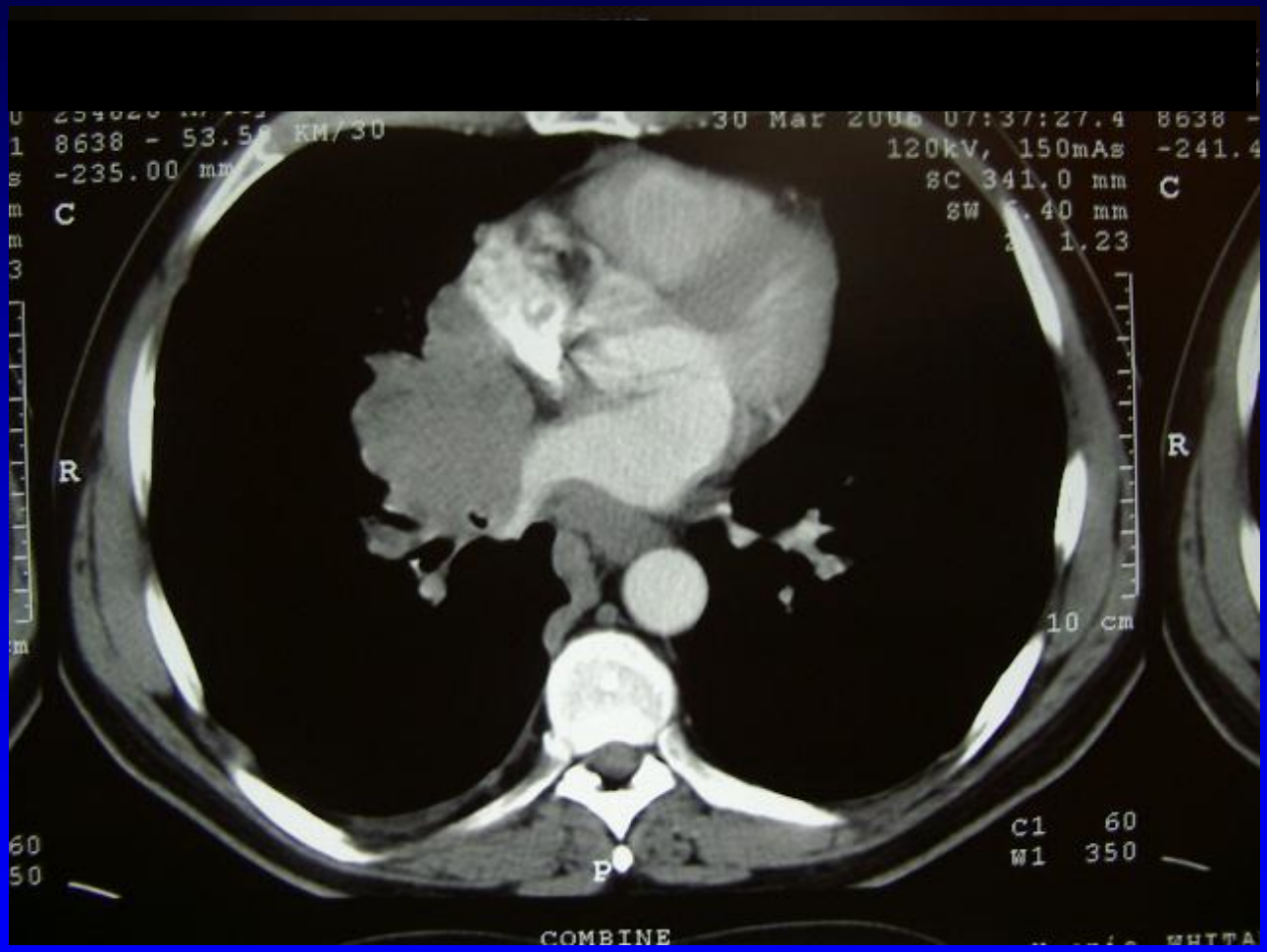
- Combination hemotherapy
  Cisplatin (or Carboplatin) + Etoposide
  Cyclophosphamide + Adriamycin + Vincristine
  others
- Thoracic radiotherapy simultan, sequentiell)
  Patients with limited disease
- Prophylactic cranial irradation
  Patients responding to chemo(radio)therapy
- Secondline chemotherapy
  Topotecan

Patient CT



Before Chemotherapy

Patient CT



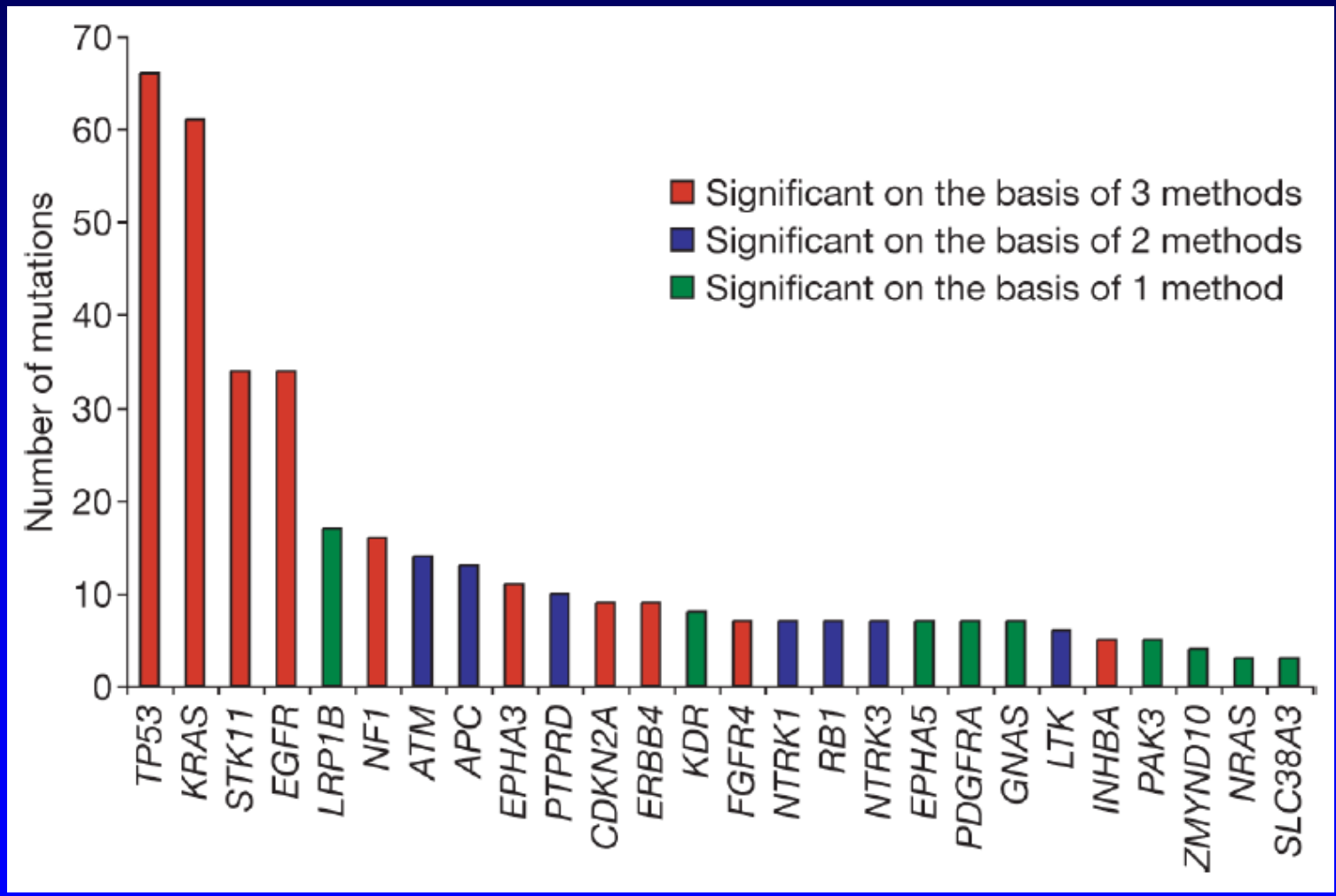
After Chemotherapy

New developments

- Molecular changes involved in tumor growth
  - Genes
  - Proteins
- Future classification based on classical histopathology and molecular features
- Screening
- Prevention
- New treatments based on molecular changes of tumor cells

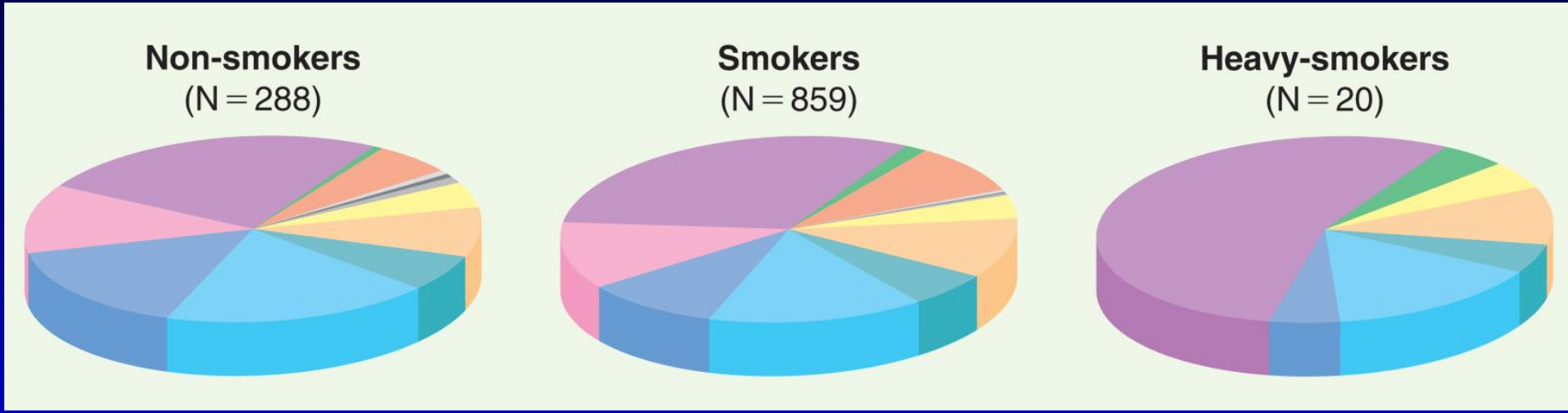
Somatic mutations in adenocarcinomas

Ding L et al. Nature 2008, 455, 1069



TP53 Mutation Spectra

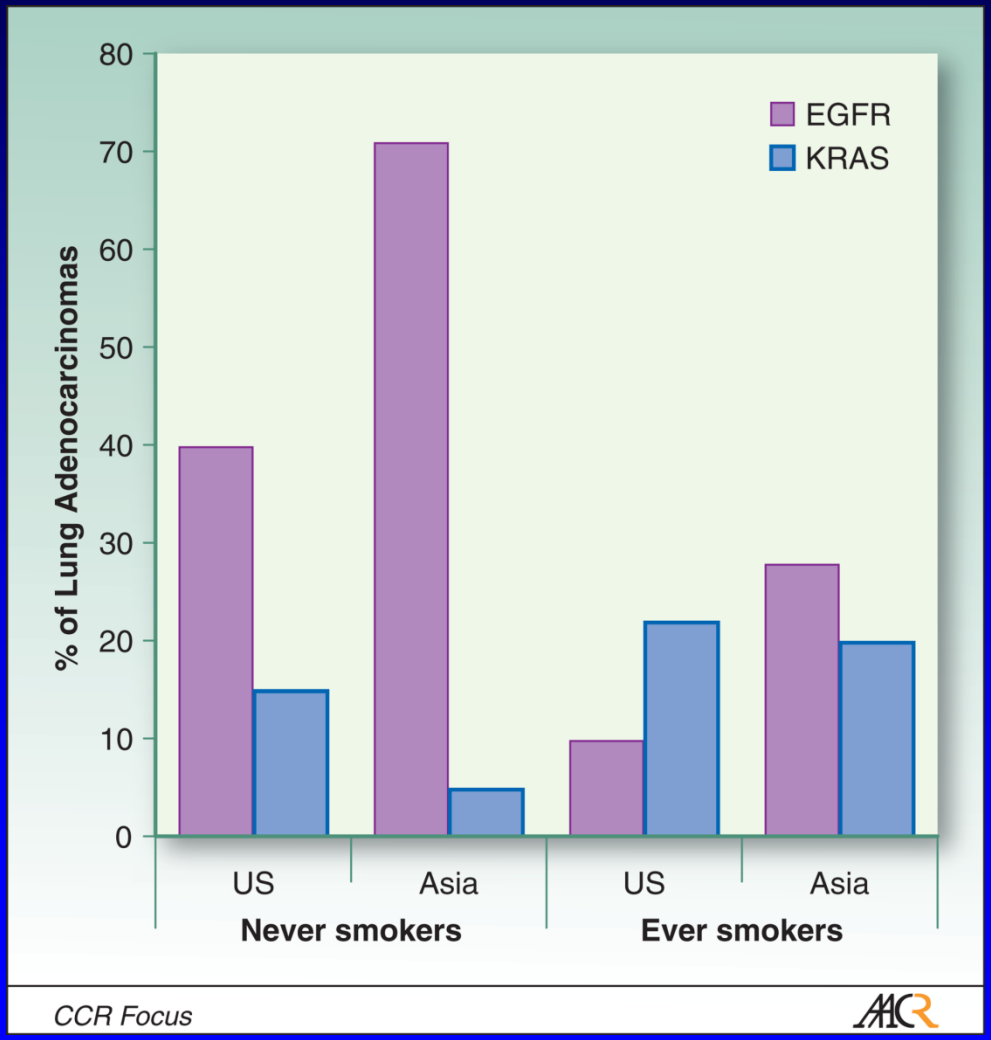
Rudin CM et al. CCR 2009, 15, 5646

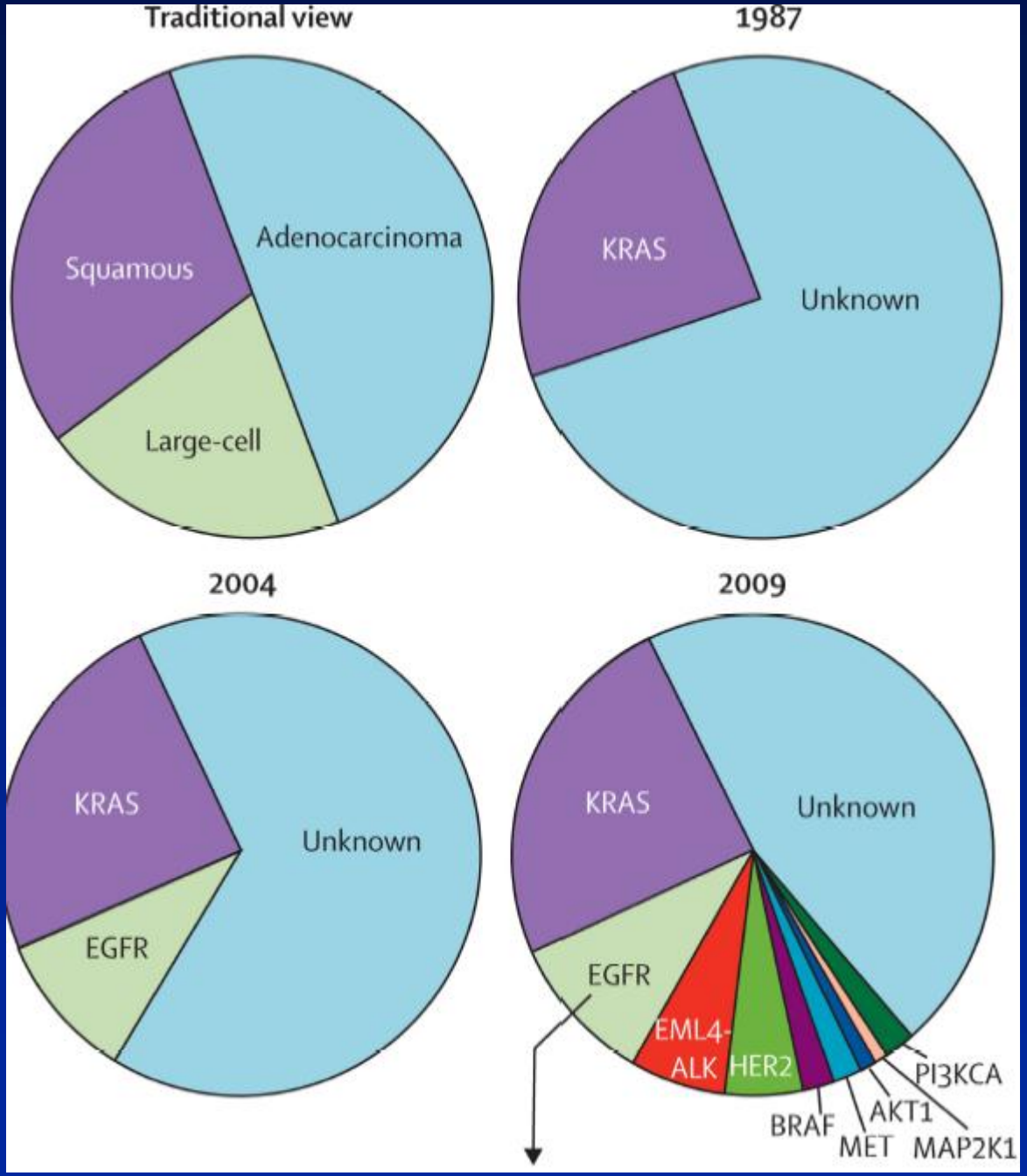


- ins-2 (0.69%)
- del-17 (5.90%)
- tandem-2 (0.69%)
- CC tandem-2 (0.69%)
- complex-3 (1.04%)
- A:T>C:G-13 (4.51%)
- A:T>G:C-25 (8.68%)
- A:T>T:A-18 (6.25%)
- G:C>A:T-54 (18.7%)
- G:C>A:T at CpG-46 (15.9%)
- G:C>C:G-34 (11.8%)
- G:C>T:A-72 (25%)

Lung adenocarcinoma

Rudin CM et al. CCR 2009, 15, 5646





New driver mutations in NSCLC

Pao W & Girard N. Lancet Oncol 2011, 12,175

NSCLC
Clinical relevance of molecular features

- Classification
  - Smoking-related cancers: KRAS-driven
  - Cancers in never-smokers: EGFR-driven
  - Subclassification based on classical histopathology & molecular tumor characteristics
- Prognostic significance
- Impact on treatment
  - Customized chemotherapy
  - Targeted therapy

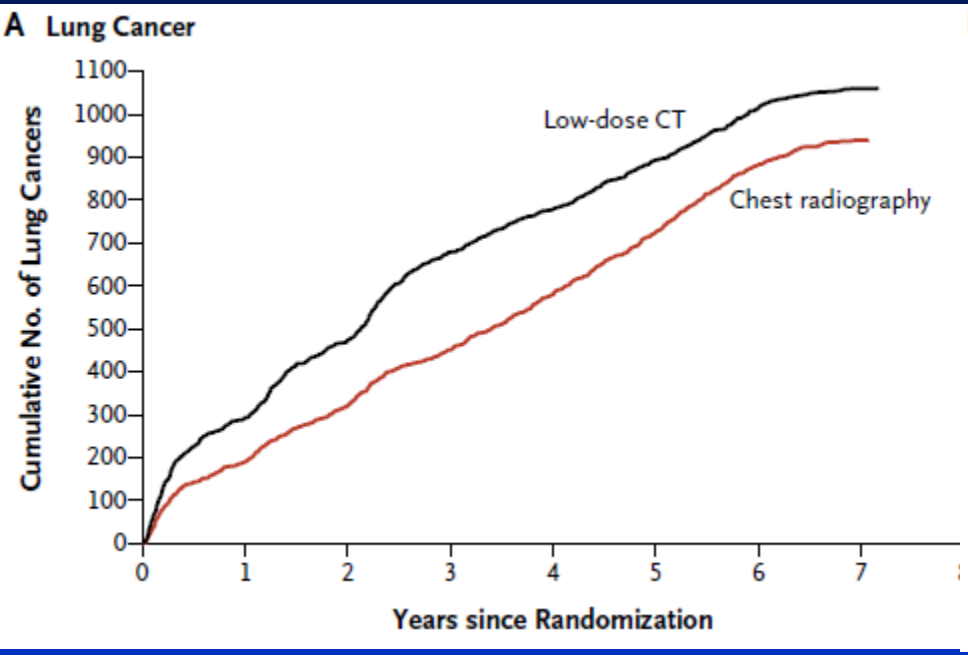
Screening

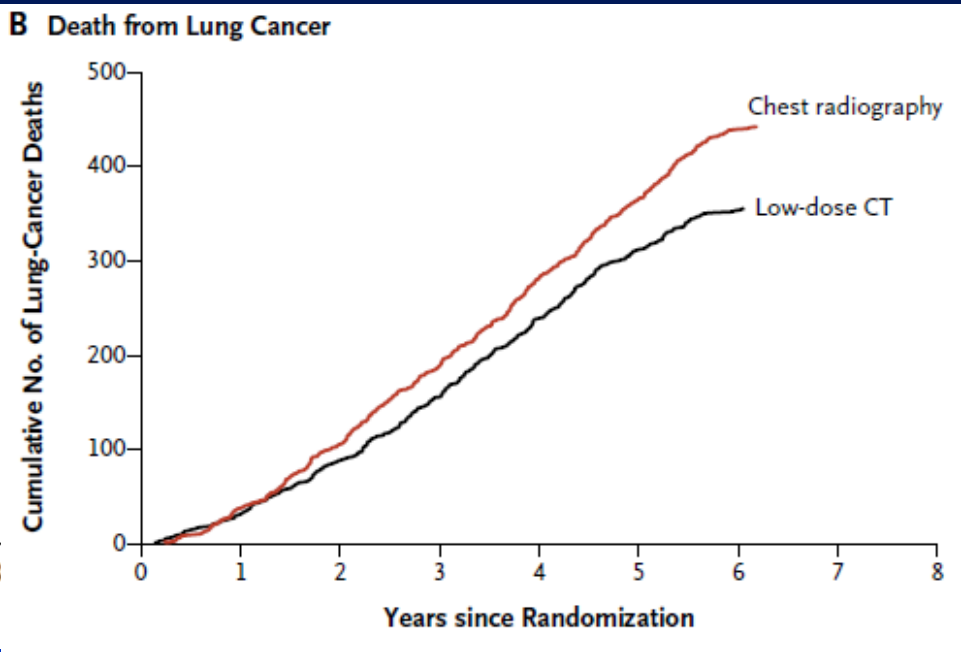
- Cure rates of up to 90% can be achieved in early stages of lung cancer.
- Screening aims at decreasing lung cancer mortality by diagnosing lung cancer at an early stage in which cure is still possible.
- Screening is preferentially done in persons at high risk (heavy smokers).
- Screening should always be combined with smoking cessation measures.
- Previous screening trials based on chest X ray and sputum analysis failed.
- Low-dose computer tomographic screening is promising.

Reduced lung-cancer mortality with low dose computed tomographic screening

The National Lung Screening Trial Team

N Engl J Med 2011, 365, 395





53.454 persons at high risk (08/2002-04/2004); 3 annual screens

	CT (26.277 persons)	X-ray (26.732 pers.)
Lung cancer cases	645	572
Lung cancer deaths	247	309

Relative risk reduction in lung cancer mortality of 20% with CT

Screening with low-dose computer tomography

- Mortality from lung cancer reduced by 20% and from any cause by 6.9%.
- Smokers, aged 55-74 years, who have smoked >30 pack years and are still smoking or have quit in the past 15 years.
- “Low dose CT may benefit individuals at an increased risk for lung cancer, but uncertainty exists about the potential harms of screening and the generalizability of results.”
- High false positive rate.
- Screening must be accompanied by smoking cessation measures.

Prevention
World Health Organization
Tobacco Free Initiative (TFI)

- **WHO Framework Convention on Tobacco Control (WHO FCTC)**
  http://www.who.int/tobacco/en/
  http://www.who.int/fctc/en/
  http://www.fctc.org

- **MPOWER**
  http://www.who.int/tobacco/mpower/en/

WHO Framework on Tobacco Control
http://www.fctc.org

- **„First ever global health treaty“**
- **Measures**
  - Higher prices, taxes
  - Avoid exposition (working place, public areas)
  - Regulation of cigarette composition
  - Information on packages
  - Information of the public, public awareness
  - Global ban on both advertising and sponsoring
  - International co-operation (laws, research)
  - others

World Health Organization
MPOWER

http://www.who.int/tobacco/mpower/en/

Monitor tobacco use

Protect people from tobacco smoke

Offer help to quit tobacco use

Warn about the dangers of tobacco

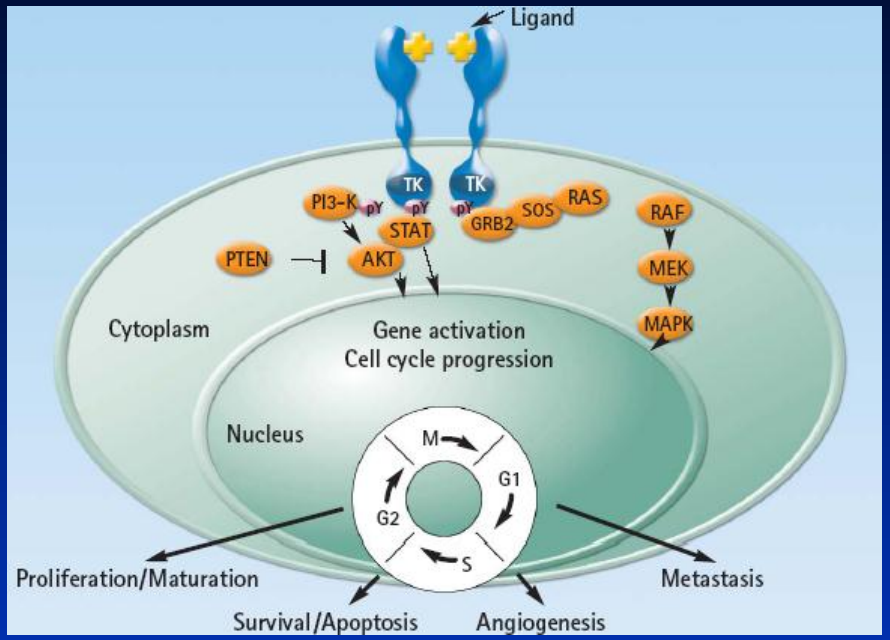
Enforce bans on tobacco advertsing, promotion

Raise taxes on tobacco products

Therapeutic Targets in Lung Cancer

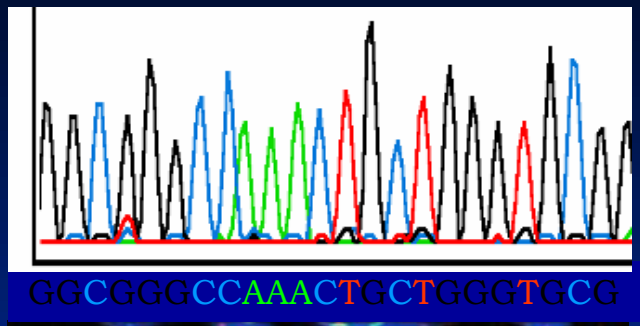
- Growth factors and their receptors
  - ✓ EGFR
  - ✓ HER-2/neu
  - ✓ IGF-1R
- Angiogenesis
- Cell cycle
  - ✓ Aurora kinases
  - ✓ Polo-like kinase 1
- Proteasome
- Farnesyltransferase
- Metalloproteinases
- Vaccines
- Others

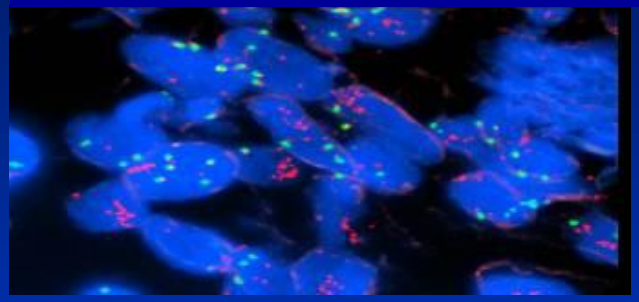
EGFR as a target

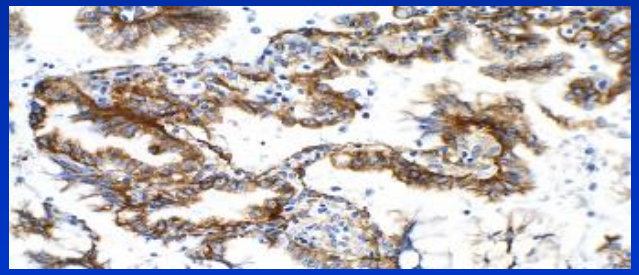


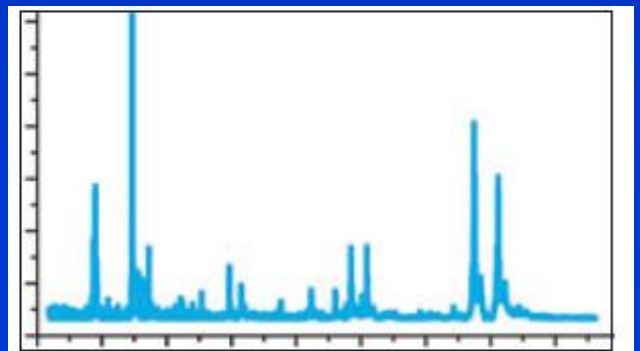
- EGFR expressed in many cancers including NSCLC (>80%)
- Expression is associated with tumor growth, metastasis and poor prognosis
- Blocking the EGFR has the potential to improve outcome

Assessment of EGFR Status





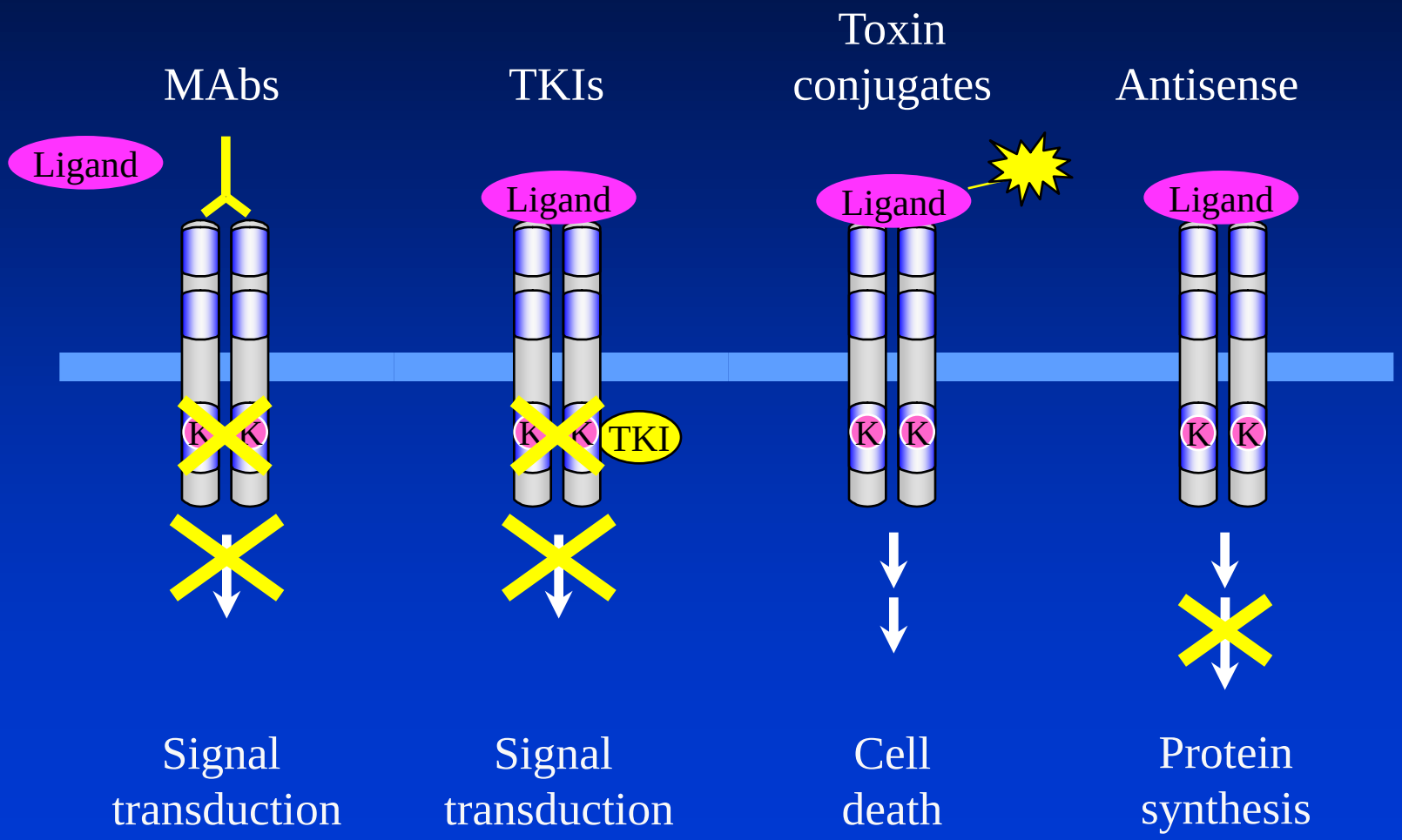




- EGFR mutation status by gene sequencing
- EGFR gene copy number by fluorescence in situ hybridization (FISH)
- EGFR protein expression by immunohistochemistry:
  - 85% positive in FLEX
- Serum Proteomics by MALDI MS

Modified from Courtesy D Gandara

EGFR-targeting Approaches

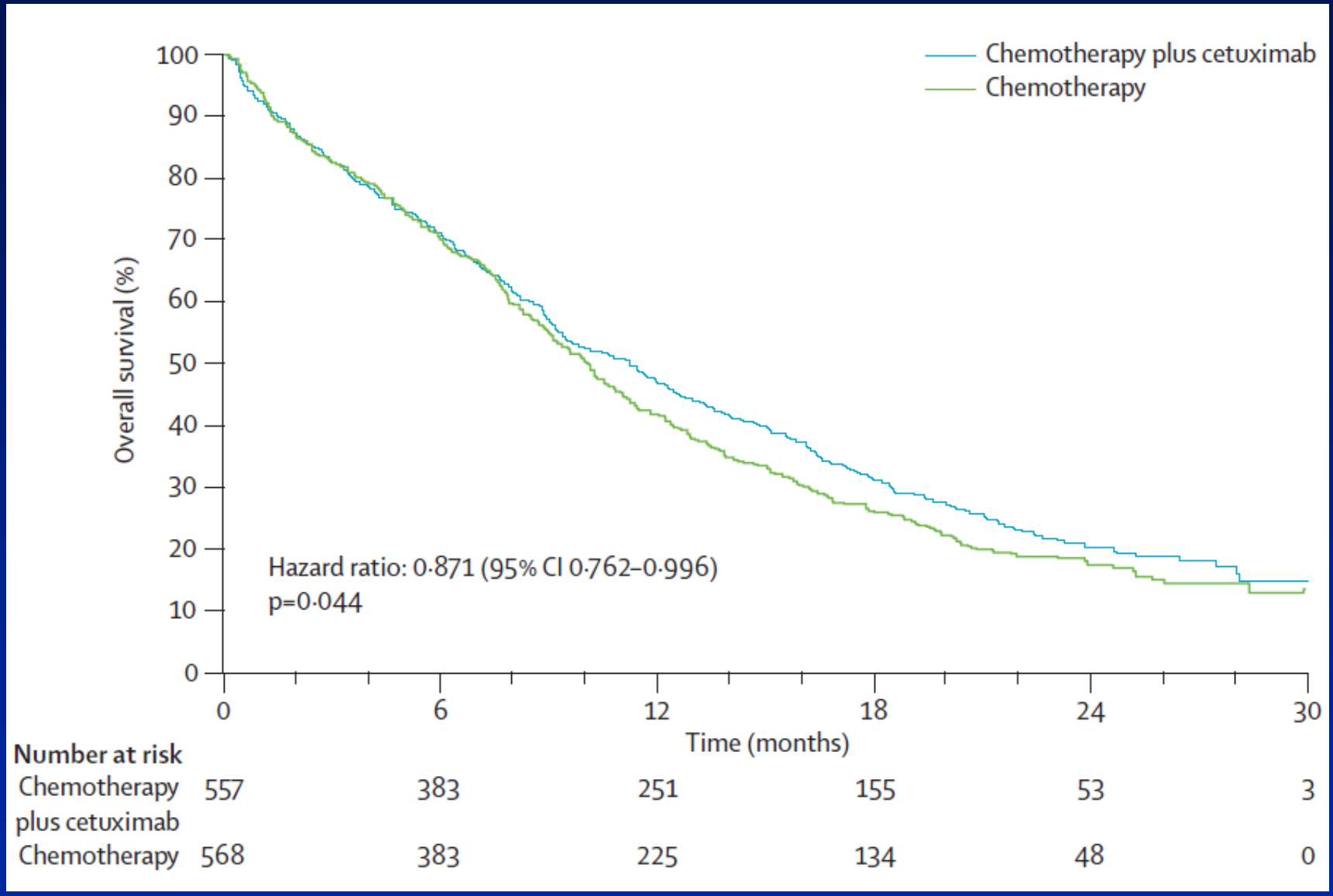


Courtesy Jose Baselga

EGFR inhibitors

- **Monoclonal antibodies**
  - Cetuximab
  - Matuzumab
  - Nimotuzumab
  - Panitumumab
  - Necitumumab (IMC-11F8)
- **Tyrosine kinase inhibitors**
  - Gefitinib
  - Erlotinib
  - Afatinib (ErbB Family Blocker)
  - Dacomitinib (PF-299804; pan-HER)
  - AZD8931 (EGFR, HER2, HER3)
  - Lapatinib (EGFR, HER2)
  - Vandetanib (EGFR, VEGFR)
  - Neratinib (HKI-272)
  - Icotinib

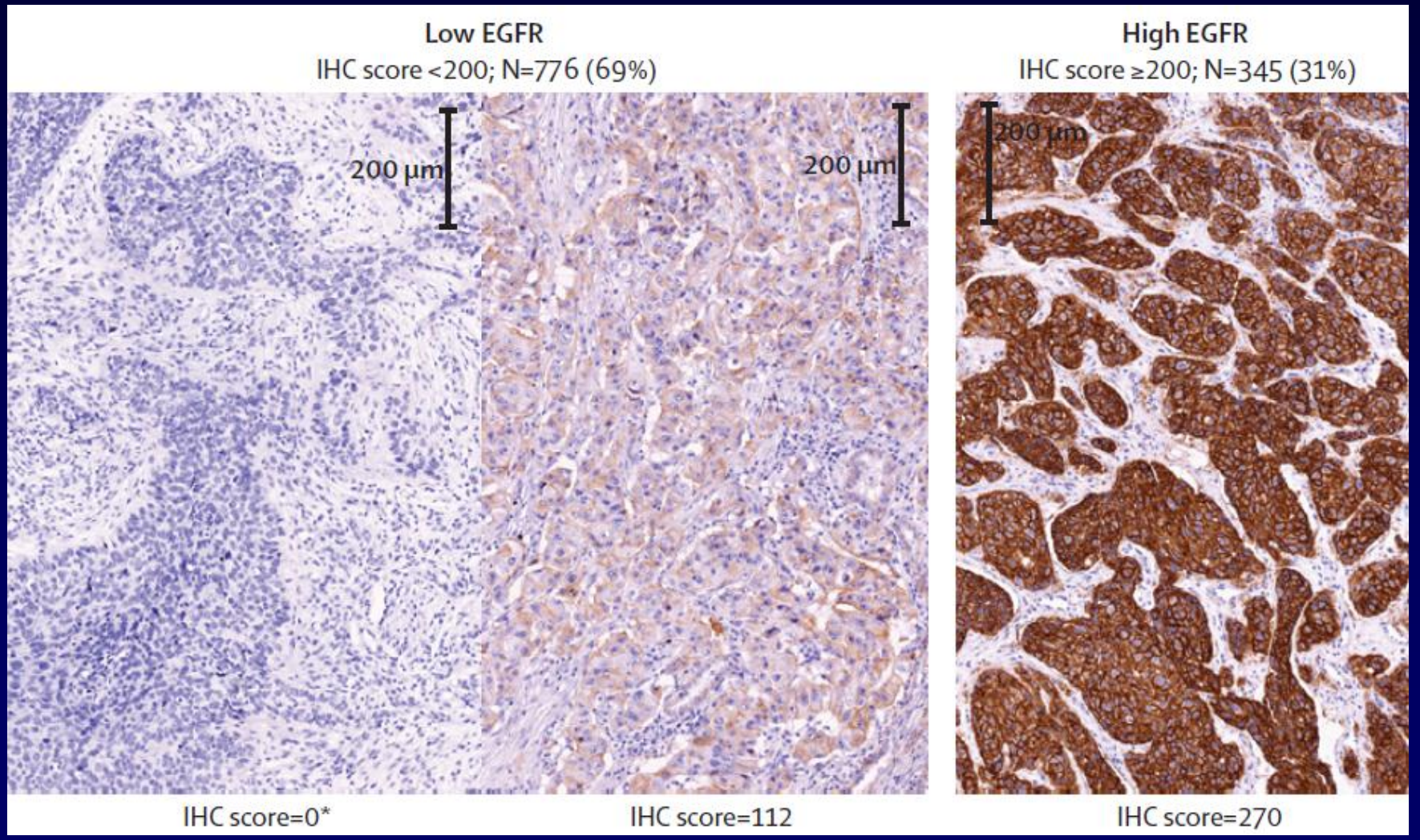
FLEX: Overall Survival



Pirker R et al. Lancet 2009, 373, 1525

Low and high EGFR expression in FLEX

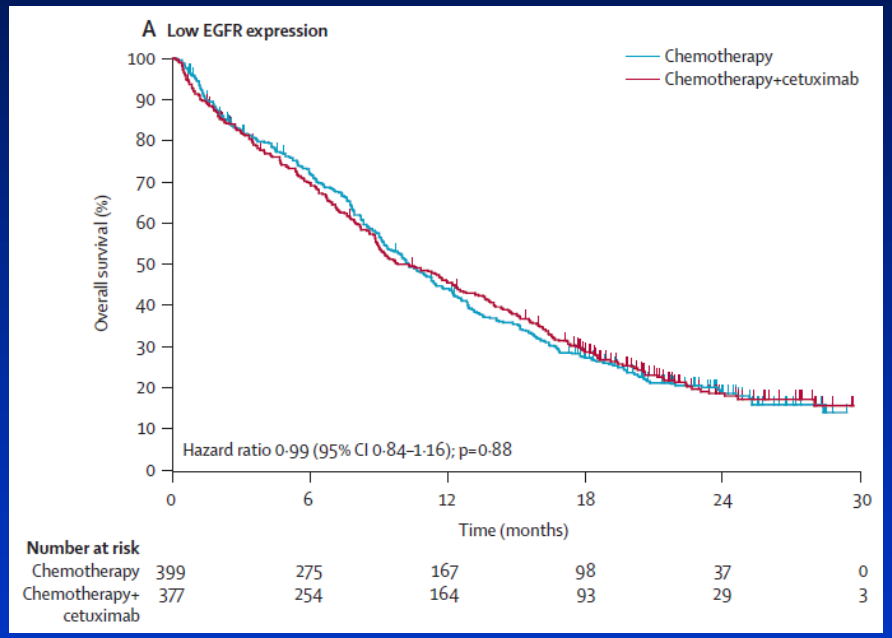
Pirker R et al. Lancet Oncology 2012, 13, 33



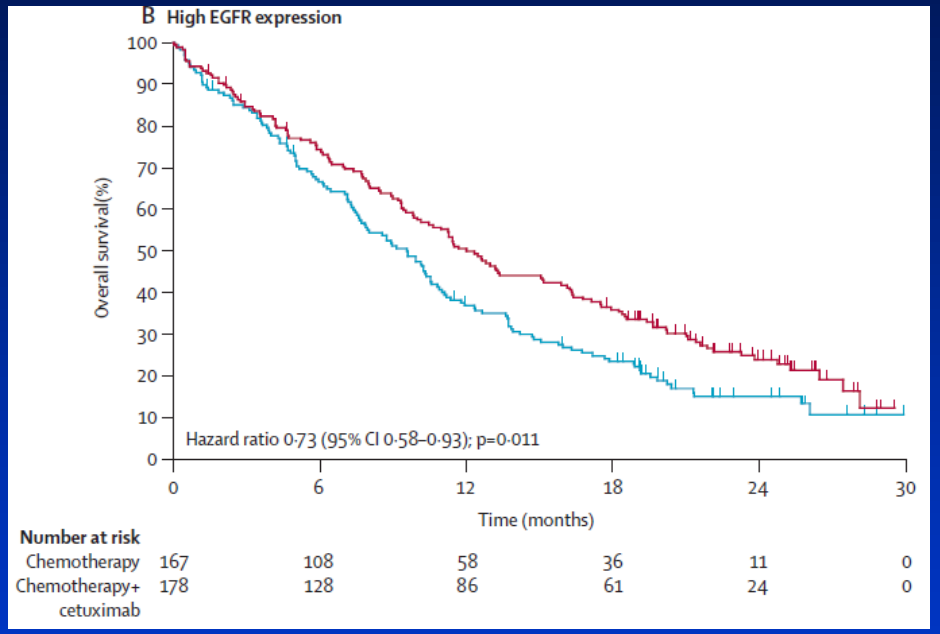
Low and high EGFR expression in FLEX

Pirker R et al. Lancet Oncology 2012, 13, 33

Low



High



HR 0.99 [95% CI 0.84–1.16]

HR 0.73 [95% CI 0.58–0.93]

Interaction p-value=0.044

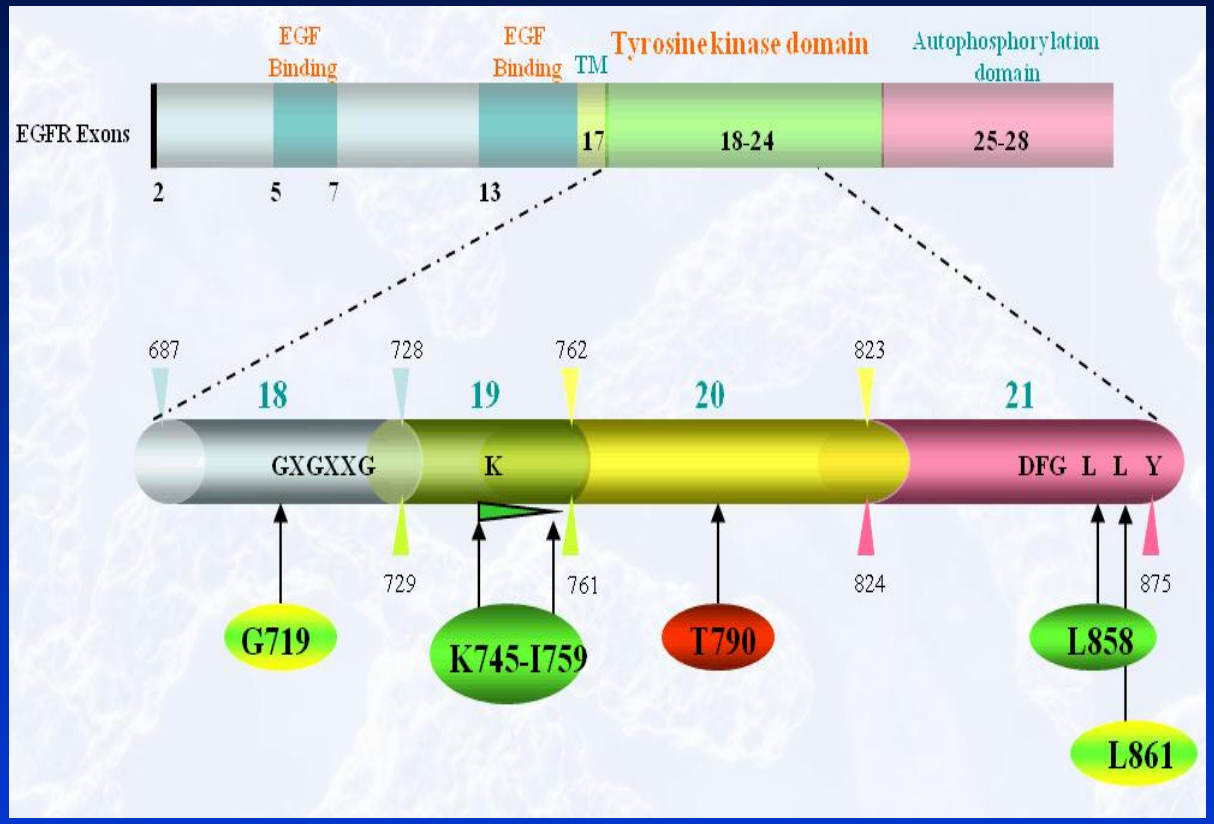
Gefitinib & Erlotinib

- Initially studied in unselected patients (IDEAL, ISEL, BR.21)
- Preferential efficacy in selected patients

Response rate	*Survival*
Adenocarcinoma	Never-smokers
Females	South-East Asians
Never-smokers	
South-East Asians	

- Efficacy in patients with EGFR-activating mutations
  - Exon 19 deletions, exon 21 point mutations (L858R)
- Studies in selected patients
  - Clinical selection
  - EGFR-activating mutations

EGFR mutations and response to TKIs

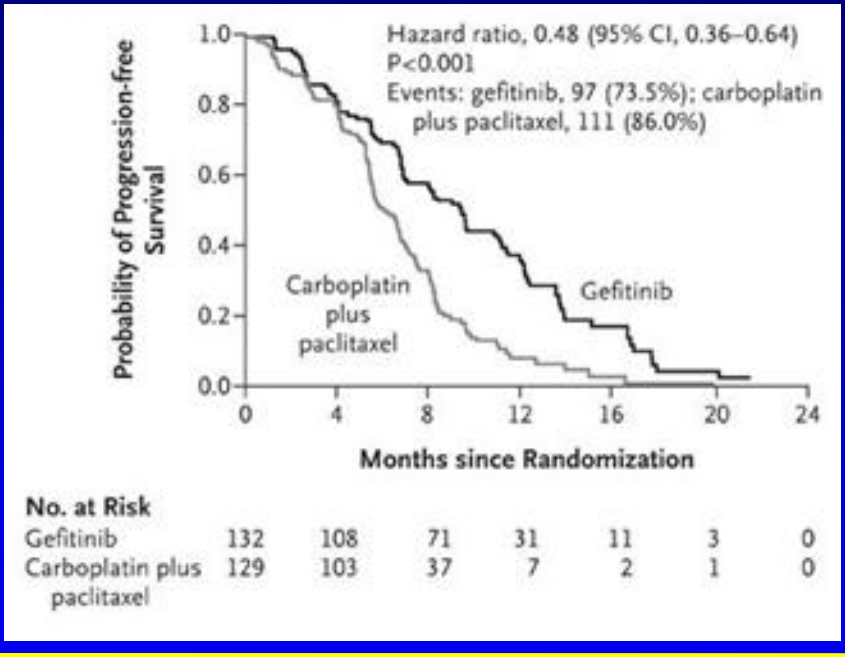


Green = responsive
Red = non-responsive
Yellow-green = mixed response outcomes

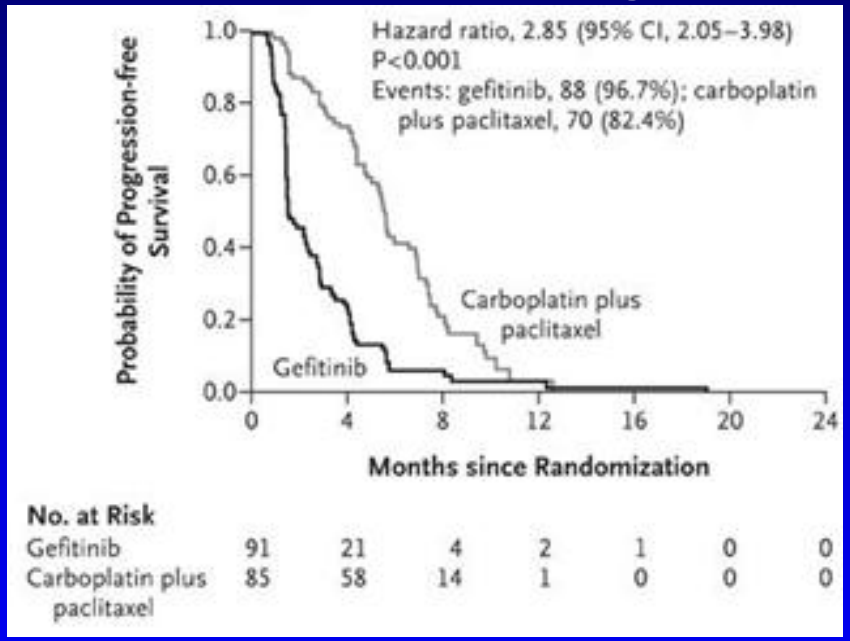
http://www.somaticmutations-egfr.info

IPASS: PFS by Mutation Status within Treatment Arm

EGFR Mutation Positive



EGFR Mutation Negative



Gefitinib, HR=0.19, 95%CI (0.13, 0.26), p<0.001
No. events M+ = 97 (73.5%), No. events M- = 88 (96.7%)

Carboplatin/paclitaxel, HR=0.78, 95%CI (0.57, 1.06), p=.1103
No. events M+ = 111 (86.0%), No. events M- = 70 (82.4)

Mok T, et al. ESMO 2008.
Mok T et al. N Engl J Med 2009;361:10.1056/NEJMoa0810699

EGFR-directed TKIs in advanced NSCLC

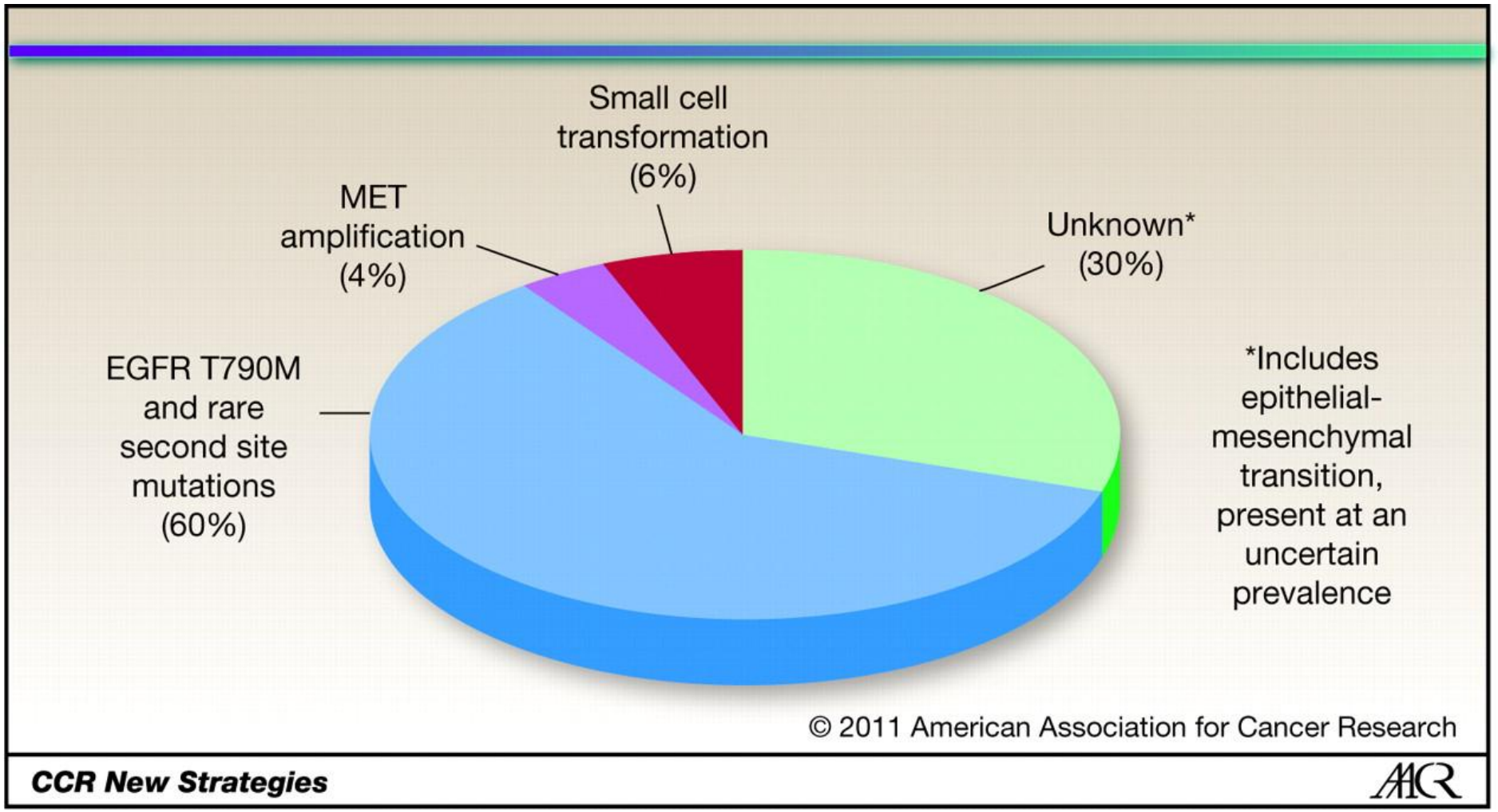
- Never-smokers or “light smokers” with adenocarcinomas
  - IPASS: Gefitinib vs. carboplatin/paclitaxel
    Mok T et al. NEJM 2009, 361, 947
  - First-SIGNAL: Gefitinib vs. cisplatin/gemcitabine
    Han JY et al. JCO 2012, 30, 1122
- Patients with EGFR-activating mutations
  - WJTOG 3405: Gefitinib vs. cisplatin/docetaxel
    Mitsudomi T et al. Lancet Oncology 2010, 11, 121
  - NEJ 002: Gefitinib vs. carboplatin/paclitaxel
    Maemondo M et al. NEJM 2010, 11, 121
  - OPTIMAL: Erlotinib vs. carboplatin/gemcitabine
    Zhou C et al. Lancet Oncology 2011, 12, 735
  - EU-TARC: Erlotinib vs. chemotherapy in Caucasians
    Rosell R et al. Lancet Oncol 2012, 13, 239

Recommendations from the IASLC-ETOP European Multidisciplinary Workshop
Who should be tested ?

- Some disagreement around this topic
- Focus should be on all NSCLC patients
  - It might be impossible to test every patient.
  - Pre-selection based on clinical parameters ?
  - Screening tests ?
  - There are some NSCLC subtypes that, if there is diagnostic certainty, would not be tested.
- If in doubt, test !
- Treating physician decides

Pirker R et al. JTO 2010, 5, 1706

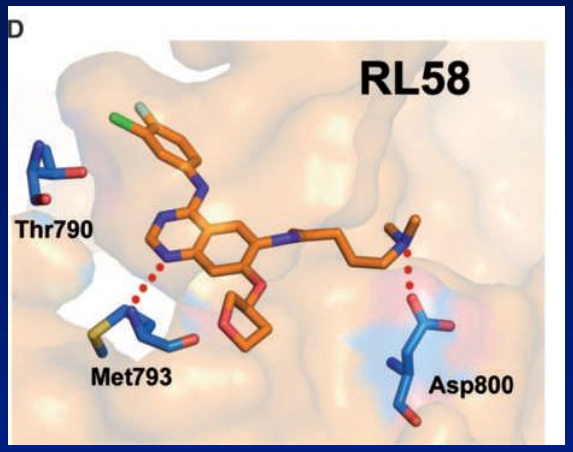
Frequency of acquired resistance mechanisms for EGFR-TKIs



Oxnard G R et al. Clin Cancer Res 2011;17:5530-5537

EGFR-directed TKIs
Reversal of Resistance

- Irreversibe TKIs
  - Afatinib
  - Dacomitinib (PF-00299804)

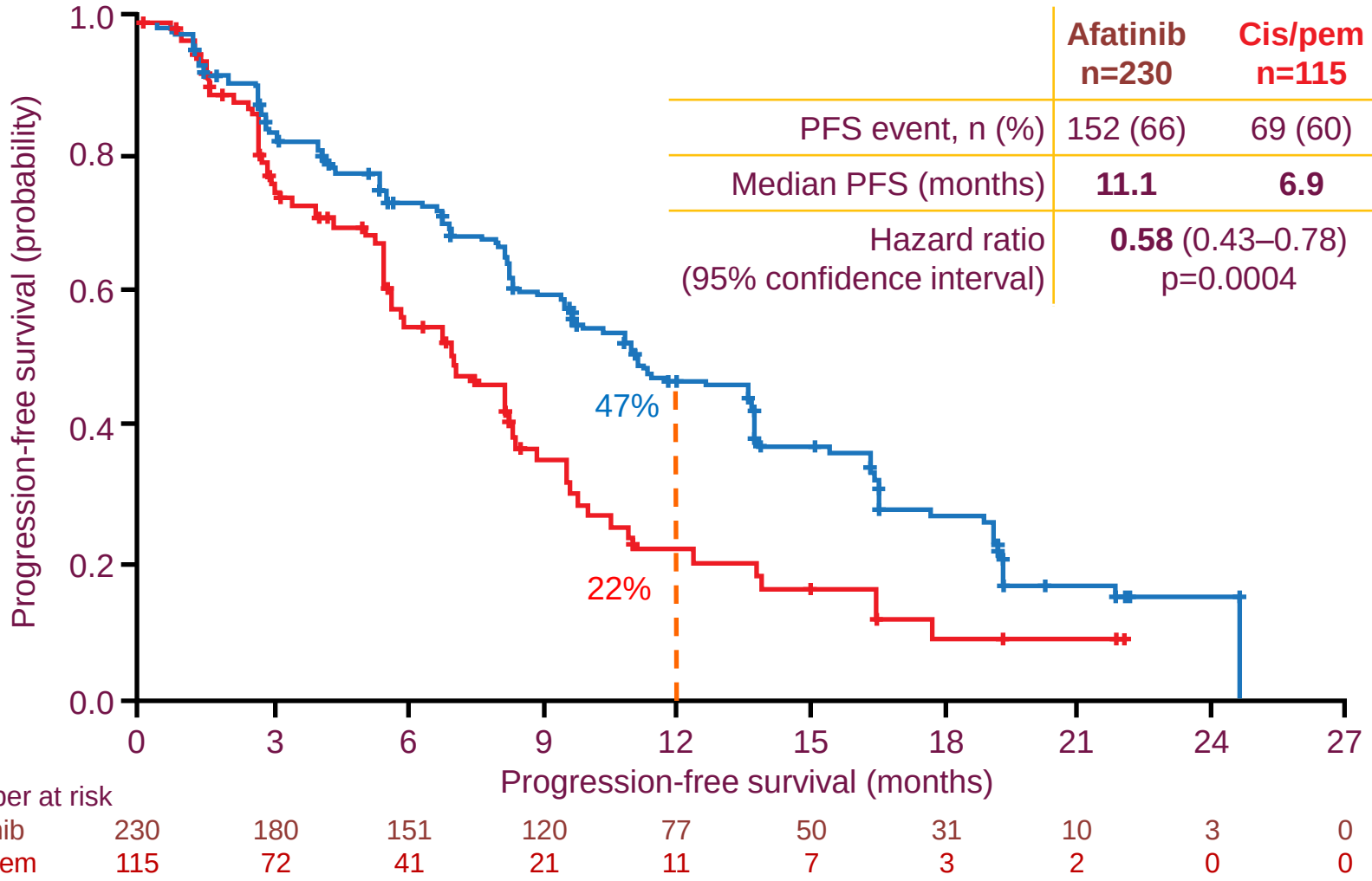


ML Sos et al. Cancer Res 2010, 70, 868

- MET inhibitors
  - Tivantinib (ARQ-197)
  - Onartuzumab (MetMAB)
  - Crizotinib (PF-02341066)
  - PHA665752 (TKI)
  - Anti-hepatocyte growth factor antibody (SCH-900105)

Primary endpoint: PFS

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	

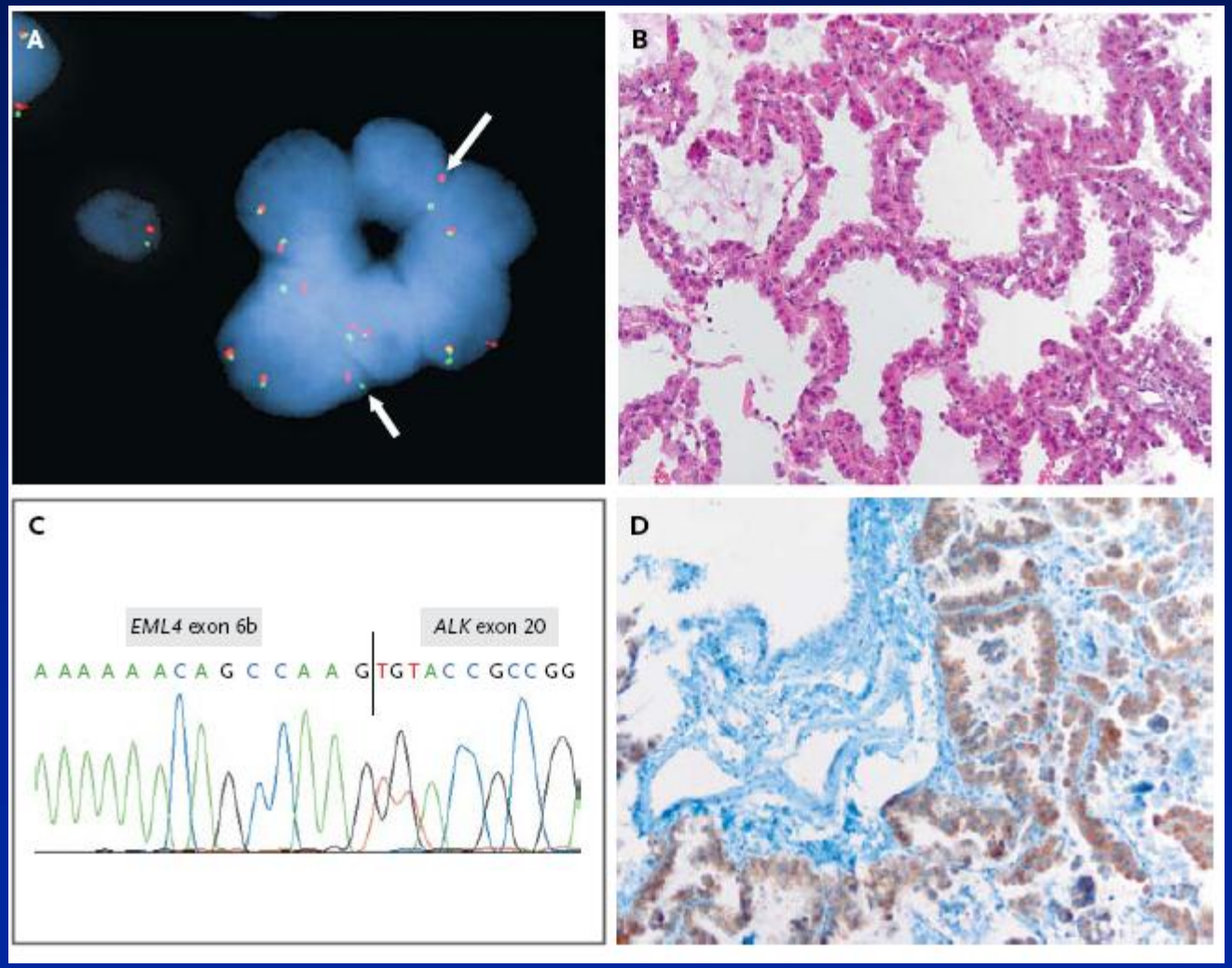
Number at risk

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

Crizotinib (PF-02341066) in advanced NSCLC

EL Kwak al. NEJM 2010, 363, 1693

EML4-ALK-positive NSCLC



Crizotinib (PF-02341066) in advanced NSCLC

EL Kwak al. NEJM 2010, 363, 1693

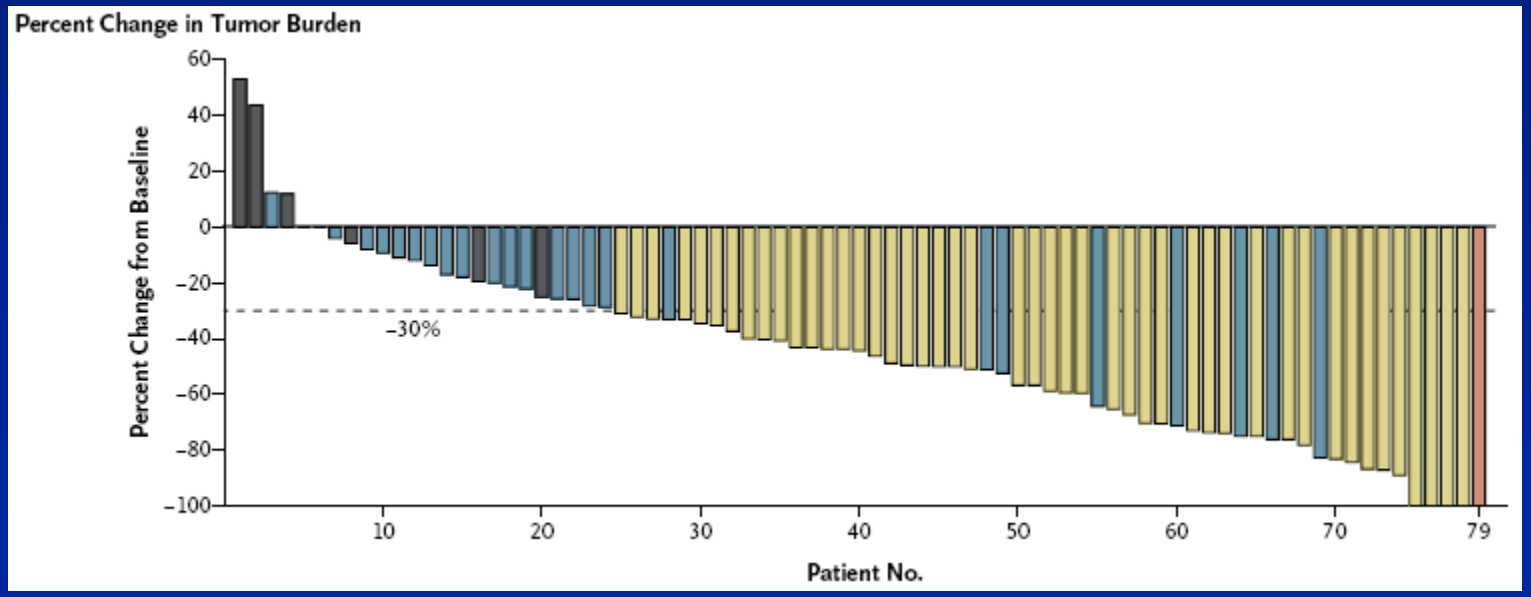
EML4-ALK fusion protein

82 patients (out of 1500 screened)

Crizotinib 250 mg twice daily

ORR: 57%

6-month progression-free survival: 72%

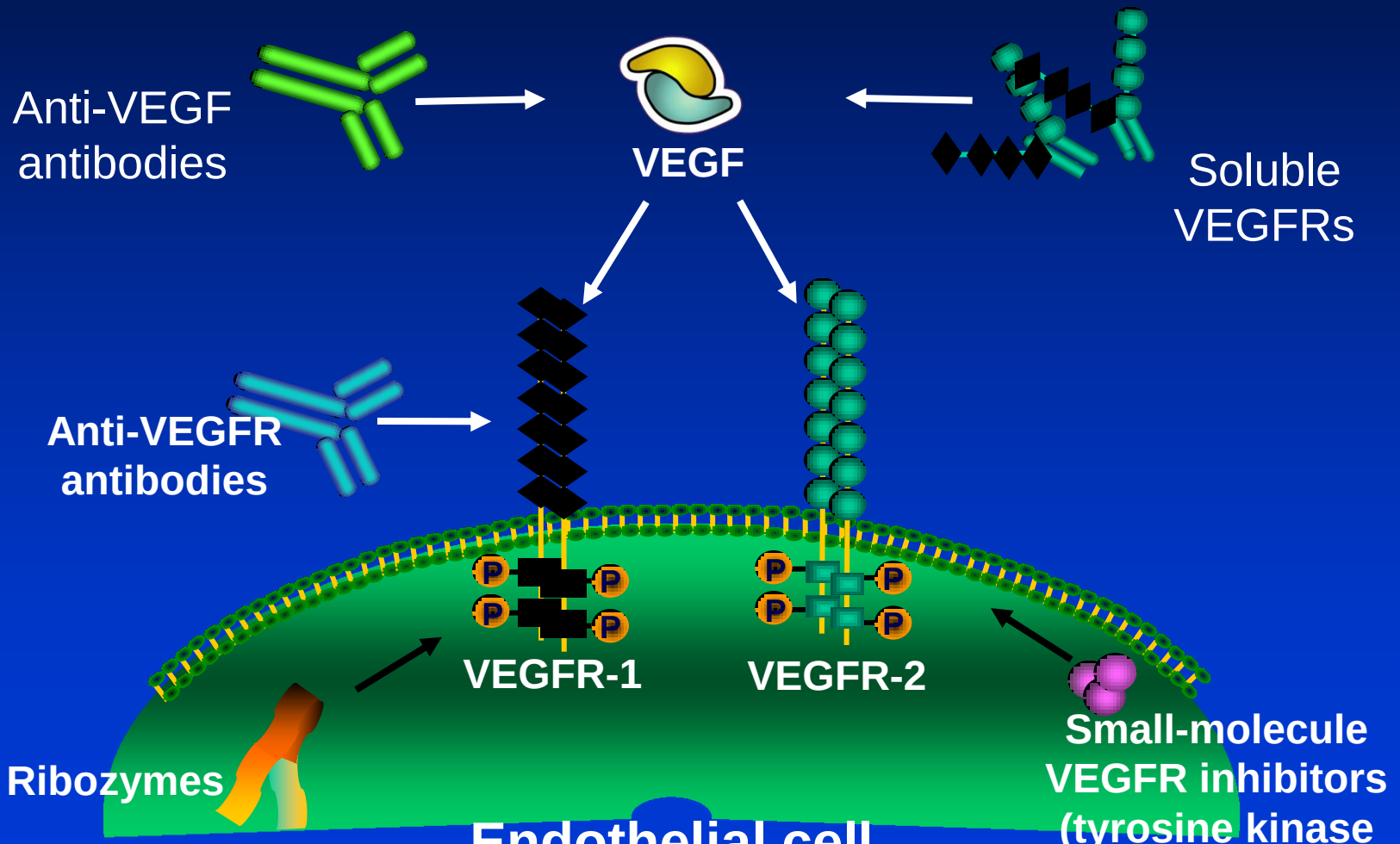


Angiogenesis inhibitors

- Bevacizumab
- Tyrosine kinase inhibitors

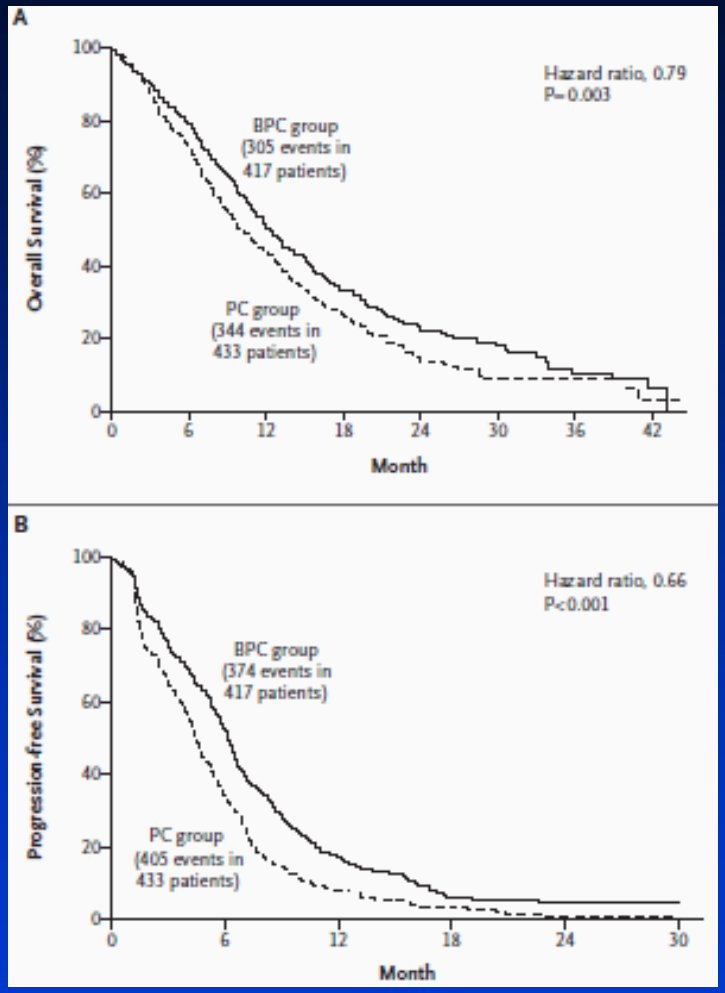
  Vargatef (BIBF1120) Vandetanib
  Sunitinib Sorafenib
  Pazopanib Motesanib
  Apatinib Cediranib
  Axitinib
- Ramucirumab (VEGFR inhibitor)
- Aflibercept (VEGF trap)
- Vascular disrupting agents
  - Vadimezan (ASA404): ATTRACT-1 halted
  - Fosbretabulin tromethamine
  - Plinabulin (NPI-2358)
  - Omrabuilin
- Thalidomide

Targeting the VEGF pathway



Courtesy of Roche

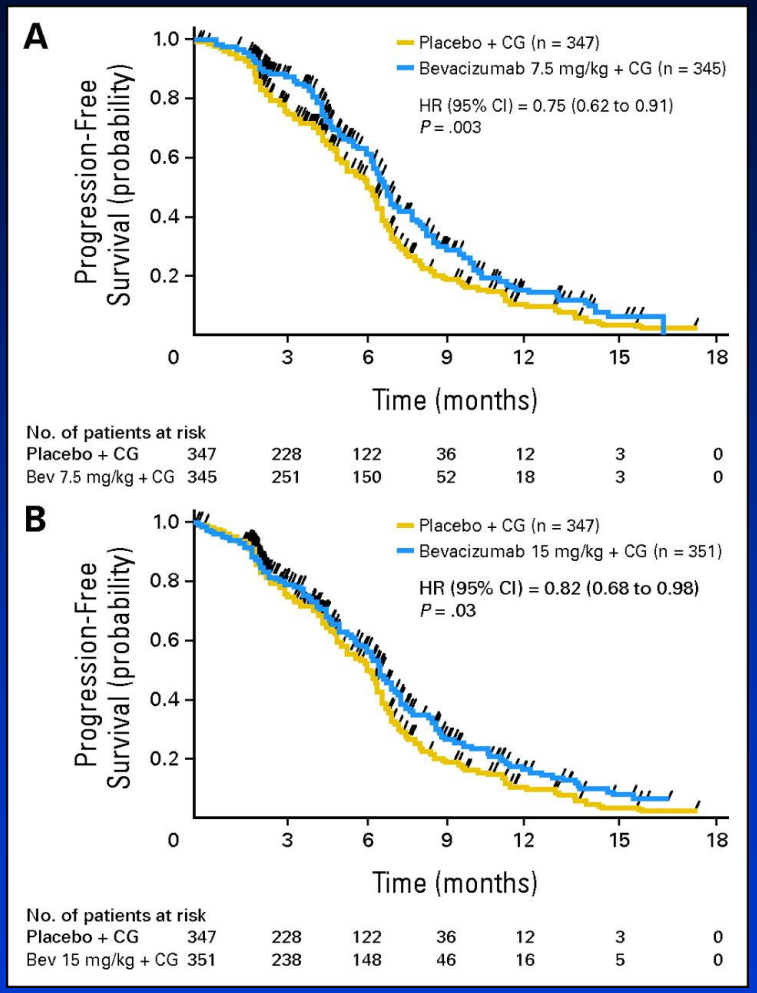
Bevacizumab in advanced non-squamous NSCLC



ECOG 4599

Sandler A et al.

NEJM 2006, 355, 2542



AVAiL

Reck M et al.

JCO 2009, 27, 1227



Welcome to Vienna

17th World Congress on Lung Cancer in 2016

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www.IASCL.org