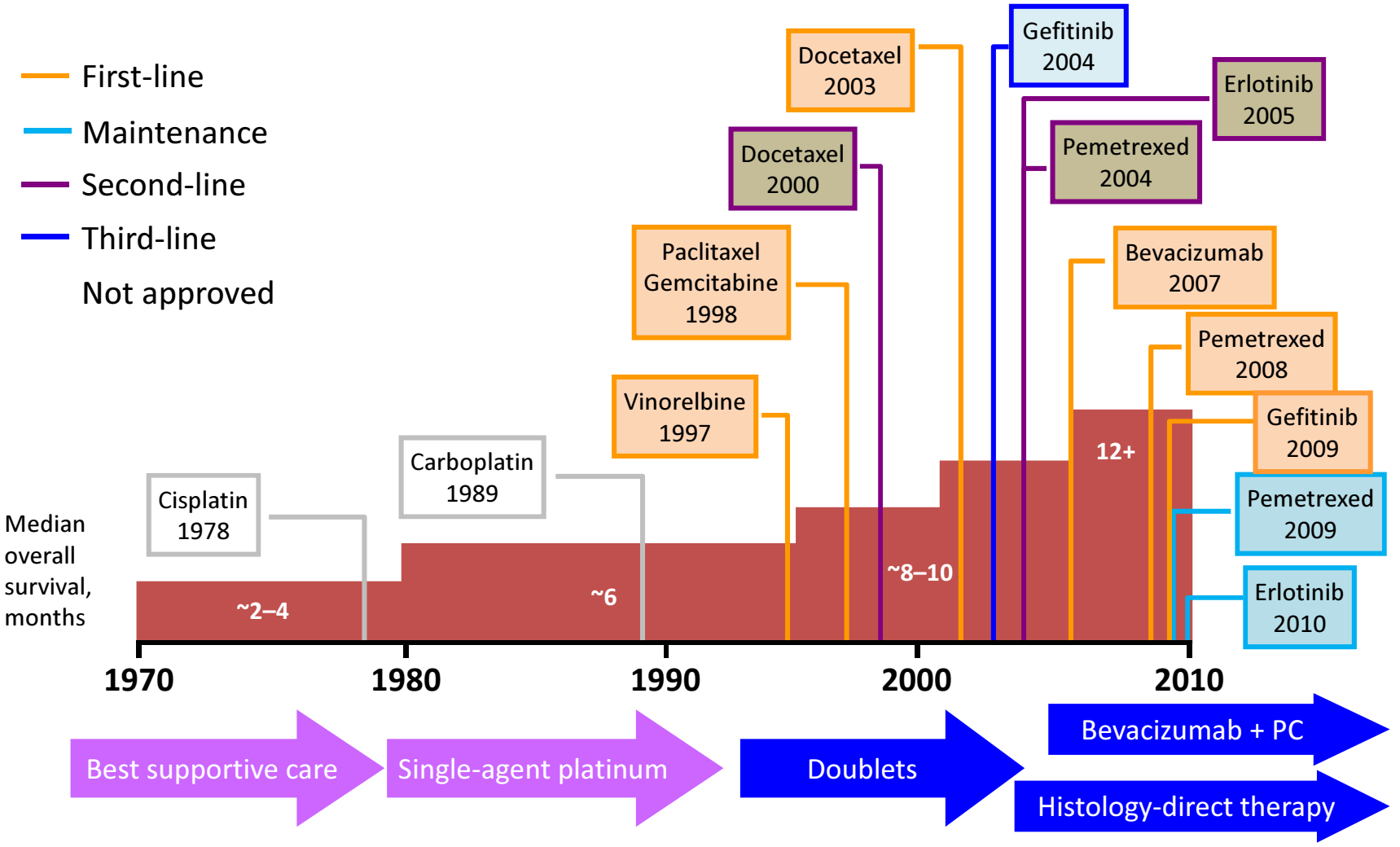
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Stato dell'arte e prospettive delle terapie a bersaglio molecolare nel carcinoma polmonare

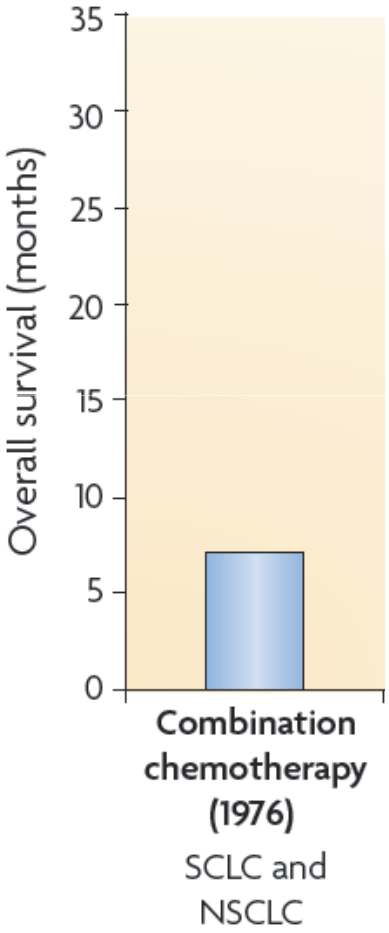
Giorgio V. Scagliotti
Università di Torino
Dipartimento di scienze cliniche & biologiche
giorgio.scagliotti@unito.it

Evolution of Systemic Therapy in Advanced NSCLC



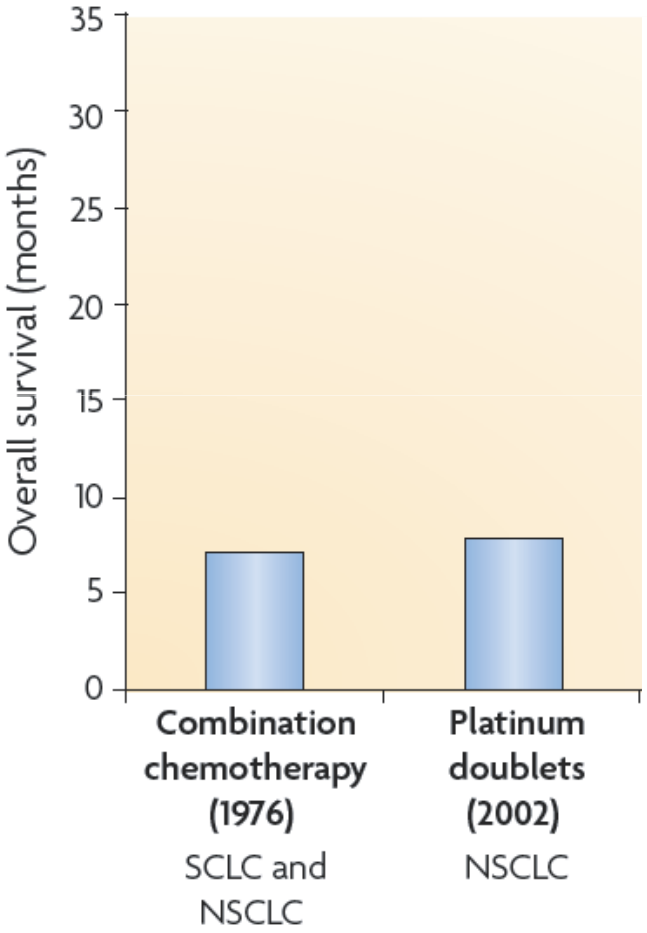
European Medicines Agency. http://www.ema.europa.eu/ema/index.jsp?curl=/pages/home/Home_Page.jsp

Progress in the treatment of metastatic lung cancer



Pao W. et al. *Nat. Rev. Cancer* 2010; 10;760

Progress in the treatment of metastatic lung cancer



Pao W. et al. *Nat. Rev. Cancer* 2010; 10;760

Randomized Trials with CT+/- Targeted Therapies in Treatment-naive NSCLC

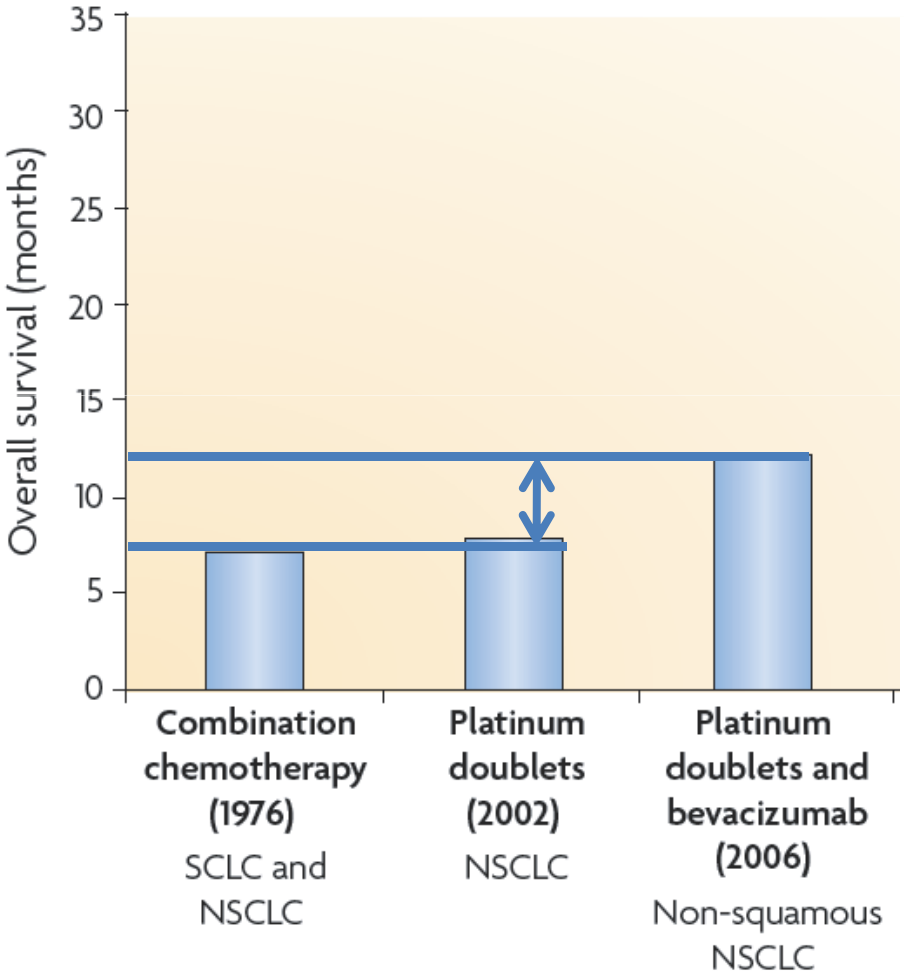
TRIAL	TARGET	CT	GROUP	COMMENT
INTACT-1	EGFR	GC	AstraZeneca	Closed, no benefit
INTACT-2	EGFR	PC	AstraZeneca	Closed, no benefit
TRIBUTE	EGFR	PC	Genentech/OSI	Closed, no benefit
TALENT	EGFR	GC	Genentech/OSI	Closed, no benefit
ABXEGFR	EGFR	PC	Amgen	Closed, no benefit
AG3340	MMP	PC	Agouron	Closed, no benefit
AG3340	MMP	GC	Agouron	Closed, no benefit
BMS275291	MMP	PC	BMSO	Closed, no benefit
Lonafarnib	FT (ras)	PC	Schering	Closed, no benefit
ISIS 3521	PKCα	PC	ISIS	Closed, no benefit
Targretin	RXR	PC	Ligand	Closed, no benefit
Sorafenib	raf-kinase,VEGFR2	PC	Bayer	Closed, no benefit
Figitumumab	IGFR-1	PC	Pfizer	Closed, no benefit
AZ2171	VEGFR	PC	Astra Zeneca	Closed, no benefit
ASA-404	VDA	PC	Novartis	Closed, no benefit

Bevacizumab in Non squamous NSCLC
Key Results

	ECOG 4599		AVAIL		
	PCB	PC	CGB (7.5)	CGB (15)	CG
RR	35%	15%	34.1%	30.4%	20.1%
P value	<.001			<.0001 (7.5) .0023 (15)	
PFS, months	6.2	4.5	6.7	6.5	6.1
HR / *P* value	0.66 (<.001)			0.75 (.003) / 7.5 0.82 (.03) / 15	
OS, months	12.3	10.3	13.6	13.4	13.1
HR / *P* value	0.79 (.003)			0.93 (ns) / 7.5 1.03 (ns) / 15	

Sandler A, et al. *N Engl J Med*. 2006;355(24):2542-2550.
Reck M, et al. *J Clin Oncol*. 2009;27(8):1227-1234.

Progress in the treatment of metastatic lung cancer



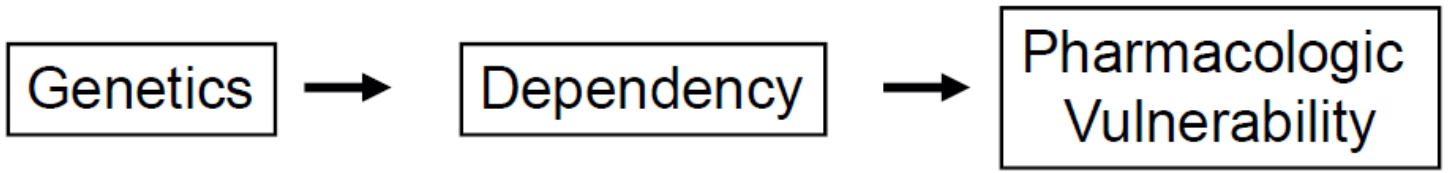
Pao W. et al. *Nat. Rev. Cancer* 2010; 10;760

Potential Surrogate Markers for the Evaluation of Anti-VEGF Agents

- Invasive
  - Tissue biopsy
  - Interstitial fluid pressure measurement
  - Measurement of tissue oxygenation
  - Skin wound healing
- Minimally Invasive
  - Circulating endothelial cells
  - Circulating progenitor cells
  - Protein levels in plasma
  - VEGF polymorphisms
- Non-Invasive
  - Imaging
    - *CT imaging*
    - *PET imaging ^{15}O FDG*
    - *MRI*
  - Clinical
    - *HTN*
    - *Gender*
    - *Urine protein (MMP, VEGF)*

Jain RK. *Nat Clin Practice* 2006;3:24–40; Davis DW. *Br J Cancer* 2003;89:8–14

Clinical relevance of oncogene addiction



- *ERBB2* gene amplification and response to herceptin in breast cancer
- *BCR/ABL* fusion gene and response to imatinib in CML
- *KIT* and *PDGFRA* gene mutations and response to imatinib in GIST
- *EGFR* gene mutations and response to EGFR inhibitors erlotinib and gefitinib in lung cancer
  - Response: Exon 19 deletions and L858R (exon 21)
  - Relapse: T790M resistance mutation (exon 20) acting *in-cis*
  - Relapse: amplification of *MET* as a *trans* mechanism

EGFR-TKIs and EGFR Mutation -Directed Front - Line Studies

Study	Entry Criteria	HR for PFS (EGFR mut +)	HR for OS (EGFR mut +)
IPASS Mok NEJM 2009	Asiatic, never- & light – smokers, adenocarcinoma (EGFR mut + 59.7%)	0.48 (0.36-0.66)	0.91 * (0.76-1.10) *overall population
First – SIGNAL Proc. IASLC 2009	Adenocarcinoma, Never-smokers (EGFR mut + 44%)	0.61 (0.30-1.22)	0.82 (0.35-1.92)

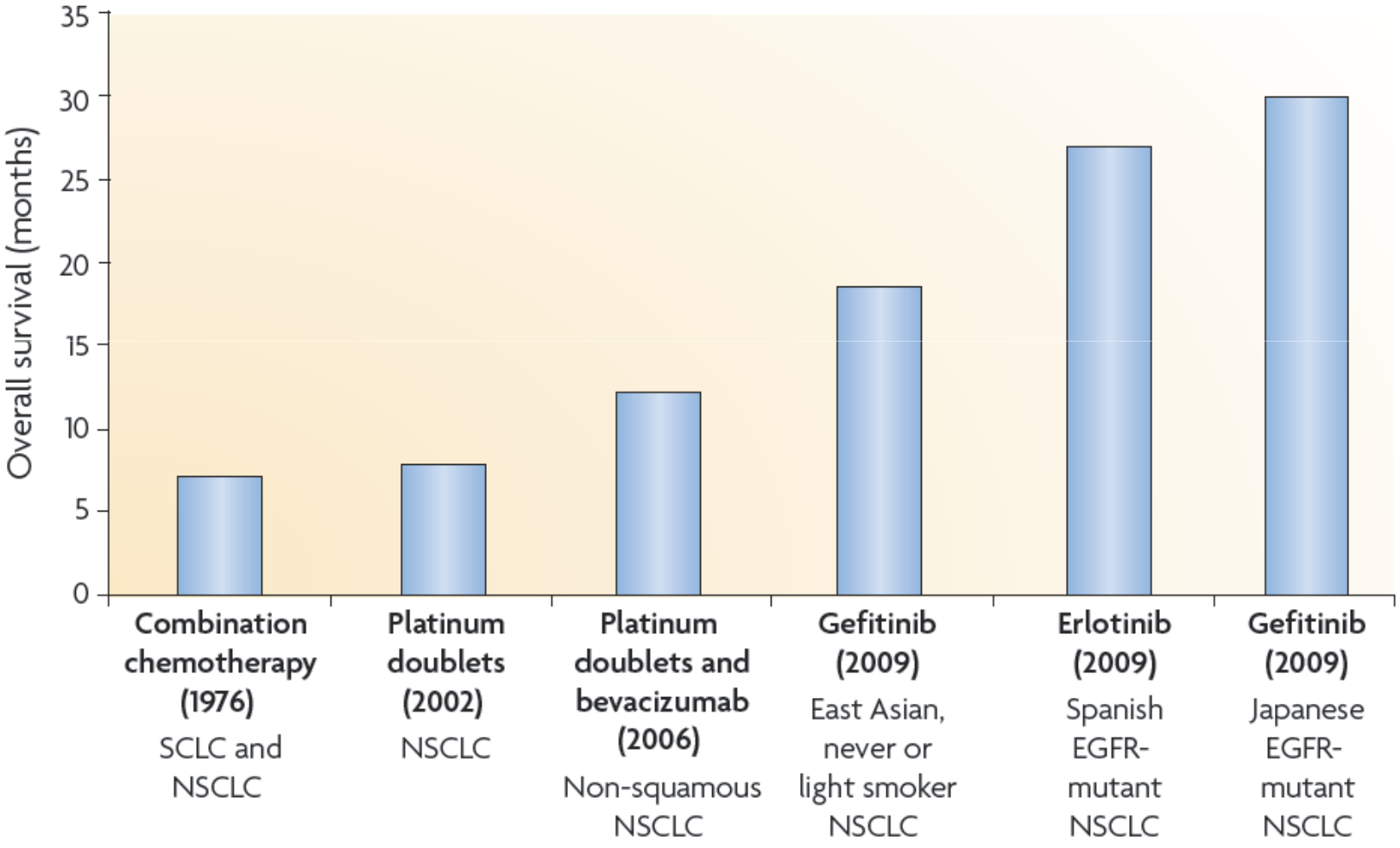
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NEJ002 NEJM 2010 Proc. ASCO 2011	EGFR Mutation + (all)	0.35 (0.25-0.50)	0.887 (0.634-1.241)
WJTOG3405 Lancet Onc. 2010	EGFR Mutation + (all)	0.489 (0.336-0.710)	
EURTAC (EU)	EGFR Mutation + (all)	0.42 (0.27-0.64)	?
OPTIMAL (China)	EGFR Mutation + (all)	0.16 (0.10-0.26)	?

Survival time of EGFR(mutant) NSCLC

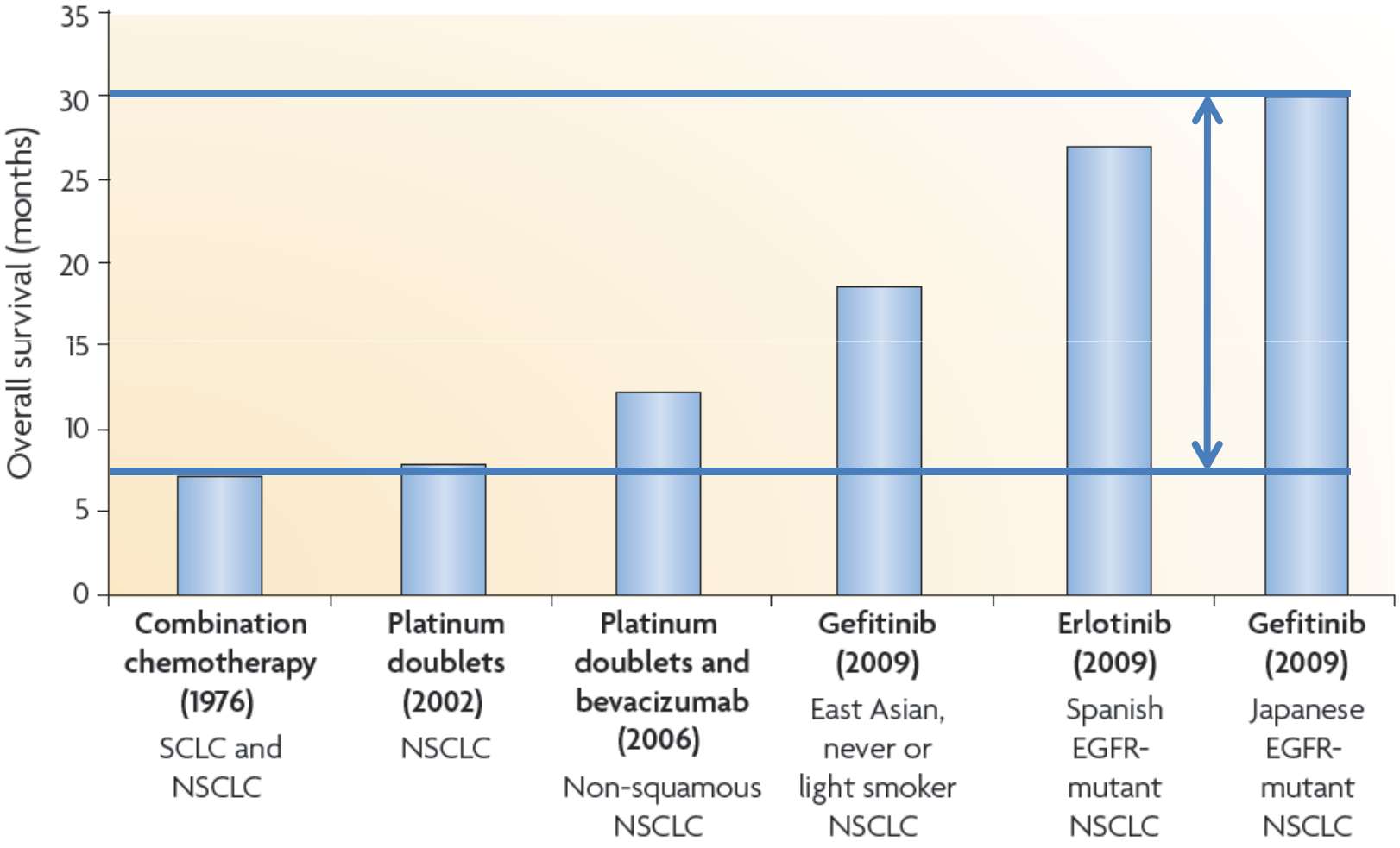
Study	First line	Median OS	Ref
IPASS	Gefitinib	21.6M	Yang CH et. al. Ann Oncol 2010:21;LBA2
	Pac/Car	21.9M	
NEJ002	Gefitinib	27.7M	Inoue A. et al. JCO 2011
	Pac/Car	26.6M	
WJOG3405	Gefitinib	30.9M	Lancet Oncology; 2010:11;121-8
	Doc/cis	Not reached	
First-SIGNAL	Gefitinib	30.6M	Lee JS. et.al. JTO;2009;4: PRS 4
	Gem/cis	26.5M	
I-CAMP	Gefitinib	27.7M	Morita S. et. al. CCR 2009;15:4493-98
	Chemotherapy	25.7M	
Spanish	Erlotinib	27.0M	Rosell R. et al. NEJM 2009;361;958-67

Progress in the treatment of metastatic lung cancer



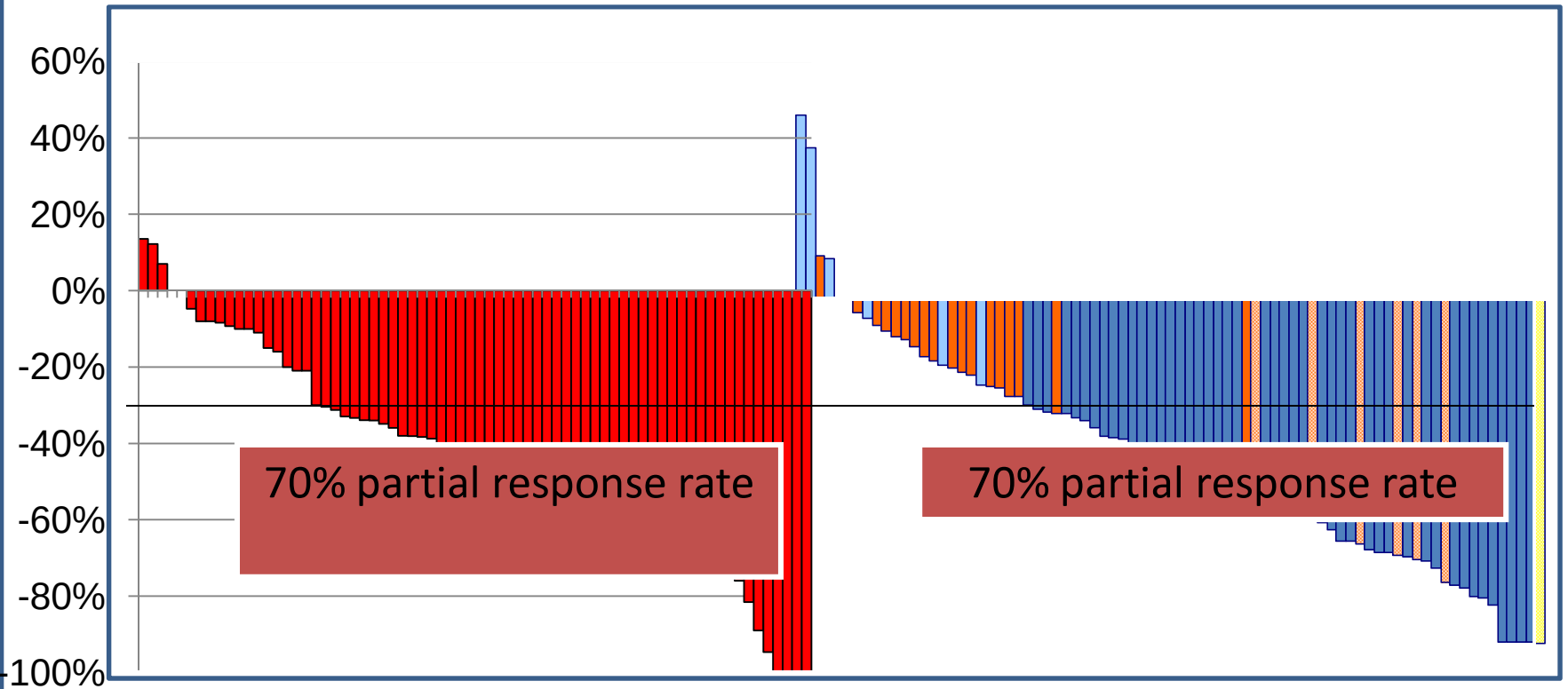
Pao W. et al. *Nat. Rev. Cancer* 2010; 10;760

Progress in the treatment of metastatic lung cancer



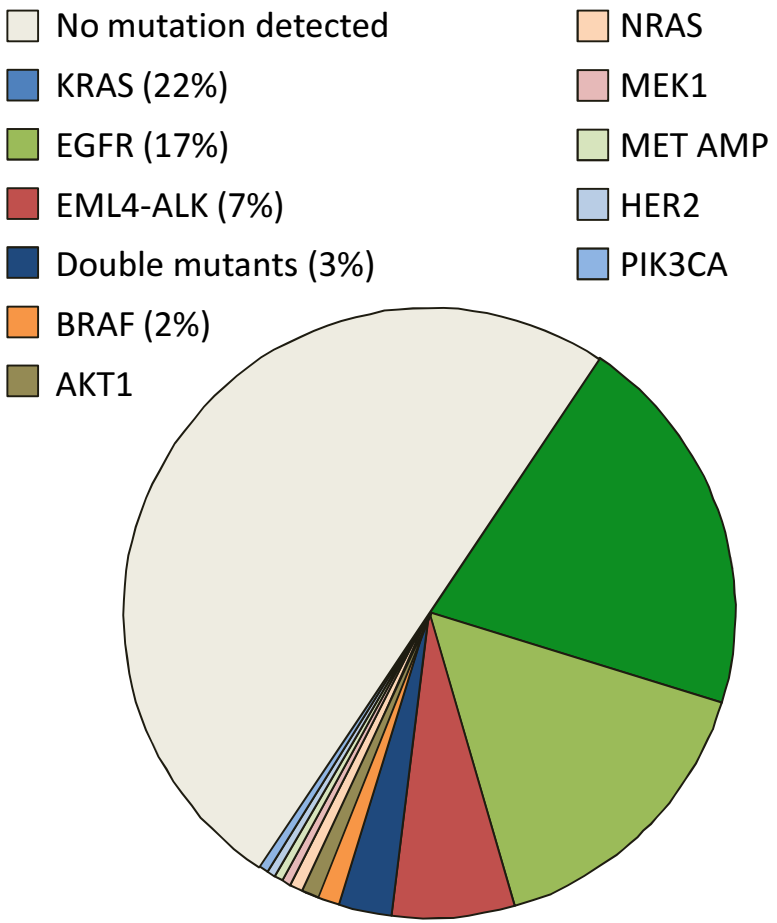
Pao W. et al. *Nat. Rev. Cancer* 2010; 10;760

Comparison of Responses *EGFR* mutations with erlotinib vs *EML4-ALK* translocations with Crizotinib



Jackman CCR 2009, Bang ASCO 2010

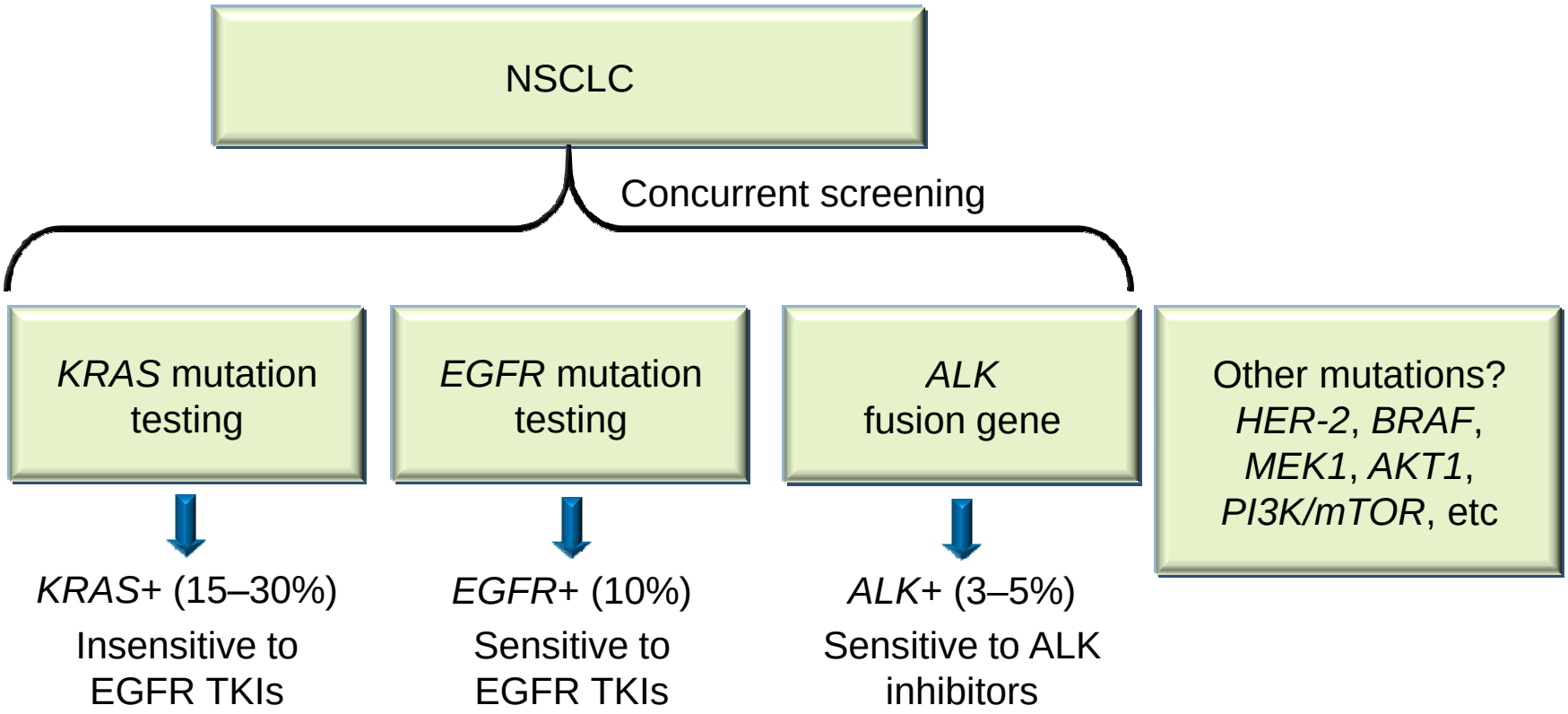
Status of Actionable Driver Mutations in Lung Adenocarcinoma Tumor Specimens



Kris MG, et al. ASCO 2011. Abstract CRA7506.

- Lung Cancer Mutation Consortium (LCMC) mutation testing
  - Performed in CLIA-certified laboratories at LCMC sites
- Physicians used data in real-time to guide therapeutic decisions for patients
  - If *EGFR* mutation: give erlotinib
  - If other mutation: recommend trial of agent specific for that target
- 54% incidence of single driver mutations among samples
  - *KRAS, EGFR,* and *EML4-ALK* most common

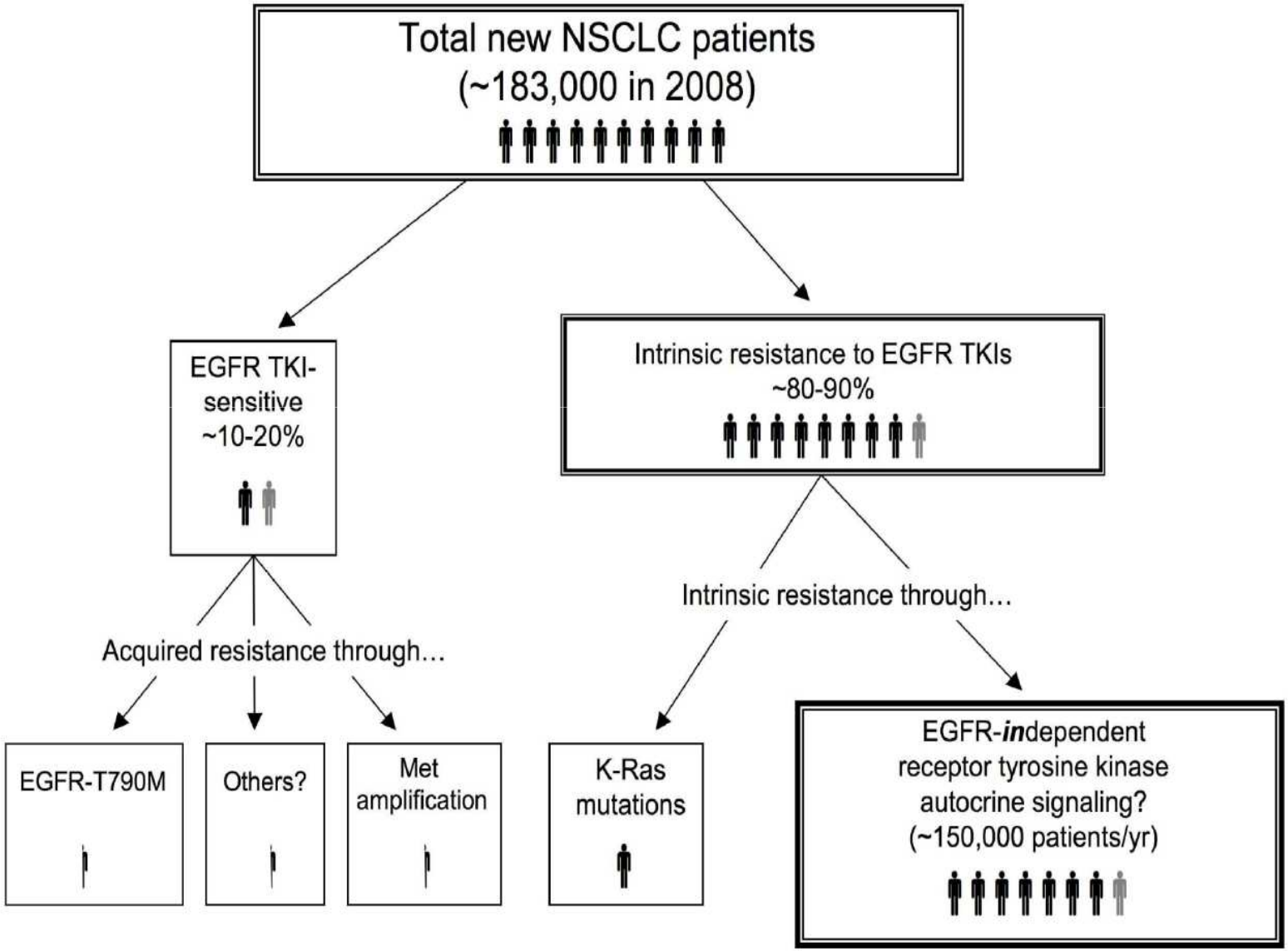
Molecular Screening in NSCLC

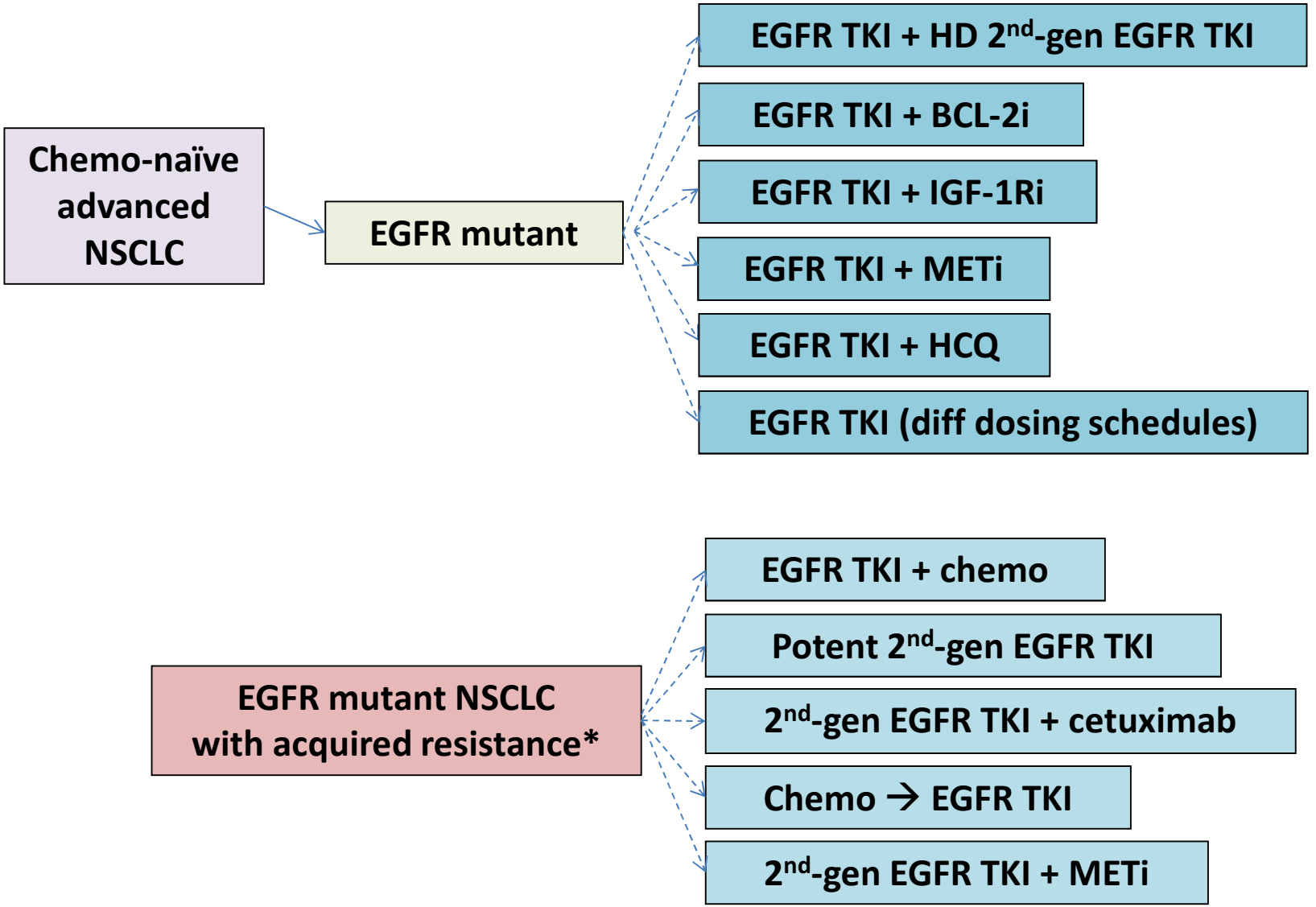


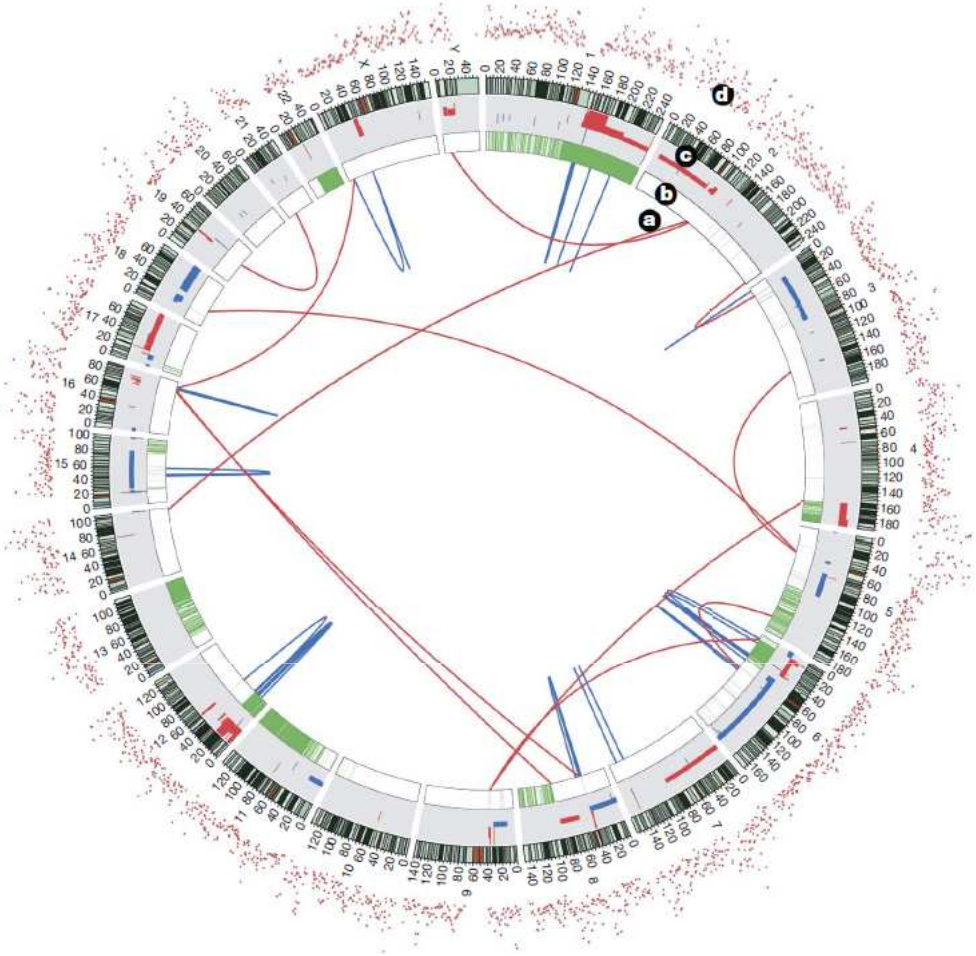
MEK1, mitogen activated protein kinase kinase 1; AKT1, v-akt murine thymoma viral oncogene homolog 1; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

Modified from Horn L, Pao W. *J Clin Oncol.* 2009;26:4232–35.
Shaw AT, et al. *J Clin Oncol.* 2009;27:4247–53.

Frequencies of Intrinsic Resistance to EGFR-TKIs relative to sensitivity/resistance in NSCLC

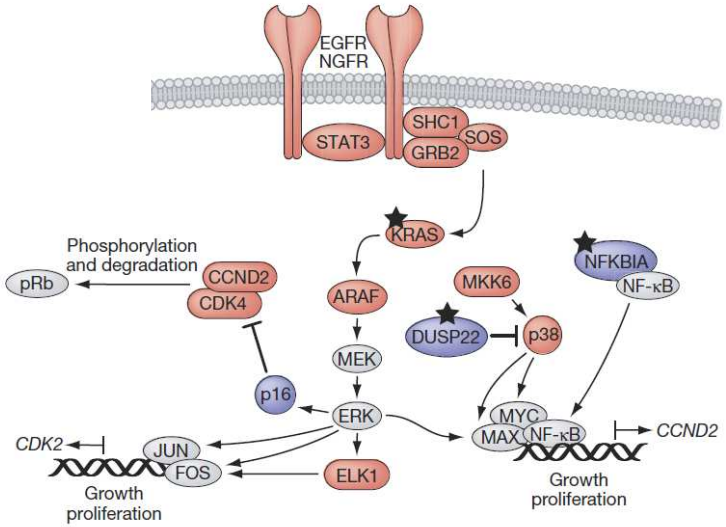



Chemo-naïve advanced NSCLC
EGFR mutant
EGFR TKI + HD 2nd-gen EGFR TKI
EGFR TKI + BCL-2i
EGFR TKI + IGF-1Ri
EGFR TKI + METi
EGFR TKI + HCQ
EGFR TKI (diff dosing schedules)
EGFR mutant NSCLC with acquired resistance*
EGFR TKI + chemo
Potent 2nd-gen EGFR TKI
2nd-gen EGFR TKI + cetuximab
Chemo → EGFR TKI
2nd-gen EGFR TKI + METi



A= inter-& intra-chromosomal rearrangements
B= LOH & allelic imbalance
C= copy number variations
D= single nucleotide variants

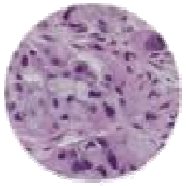
Red= amplification
Purple=LOH
Black* = mutation



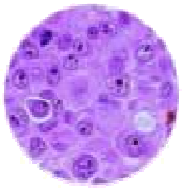
Lee et al. Nature 2010; 465:473-7

Treatment Selection Is Moving From Histology-Based to Targeting Oncogenic Drivers

1999-2006
Histology-driven selection



Adenocarcinoma

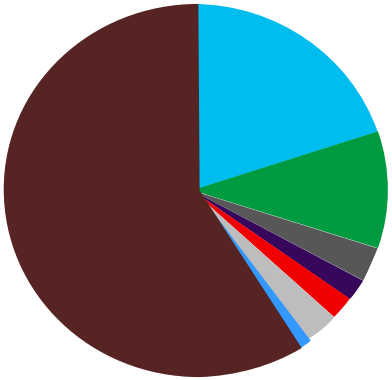


Squamous-cell carcinoma

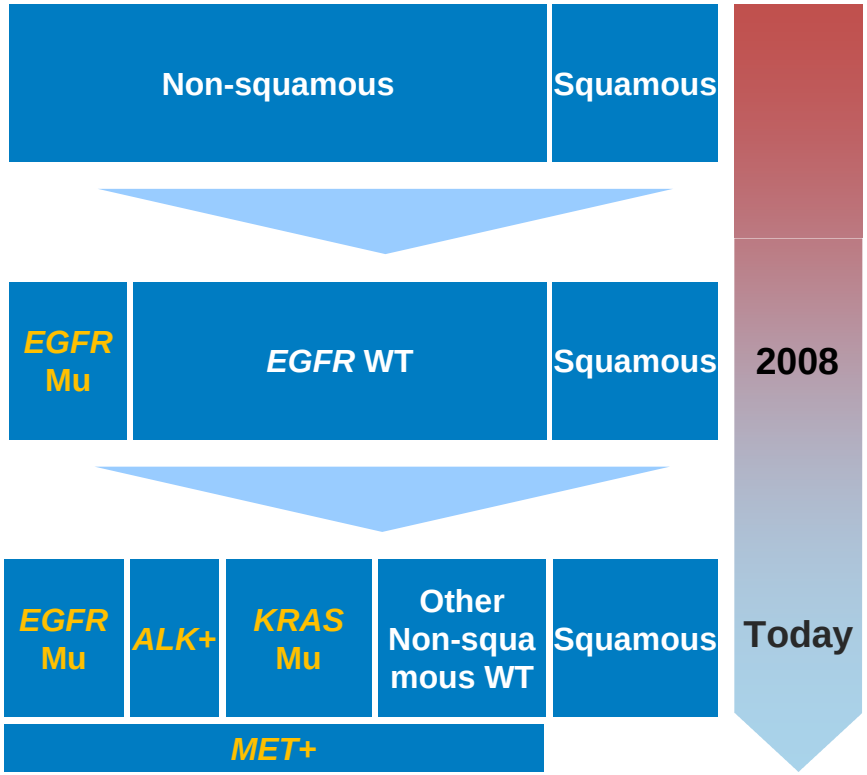


Large cell carcinoma

2010
Targeting oncogenic drivers*



Evolution of NSCLC treatment



*Incidence of mutations in adenocarcinoma provided as an example

Current Standard of NSCLC Care

Figure: Massachusetts General Hospital, data on file. Horn L, Pao W. *J Clin Oncol.* 2009;26:4232–4235.

What the Future Holds……

- Other histotypes of lung cancers
- Cancer Genome Projects
- Pivotal trials in genotype defined subgroups
- Cancer genome analysis is expected to have a far-reaching impact
- New comprehensive and biologically rational classification of human cancers based on genomic abnormalities → prognostic & predictive effectiveness of all mutated cancer genes present in a specific tumor type

Squamous Cell Carcinoma of the Lung

Gene	Event Type	Frequency
FGFR1	Amplification	20-25%
FGFR2	Mutation	5%
PIK3CA	Mutation	9%
PTEN	Mutation/Deletion	18%
CCND1	Amplification	8%
CDKN2A	Deletion/Mutation	45%
PDGFRA	Amplification/Mutation	9%
EGFR	Amplification	10%
MCL1	Amplification	10%
BRAF	Mutation	3%
DDR2	Mutation	4%
ERBB2	Amplification	2%

In 63% of lung SCCs we can now identify a possible therapeutic target

Targets will need to be validated
in pre-clinical models

FGFR1/2, PIK3CA and DDR2 inhibitor trials are planned or ongoing

Hammerman P. et al. Proc. IASLC 2011

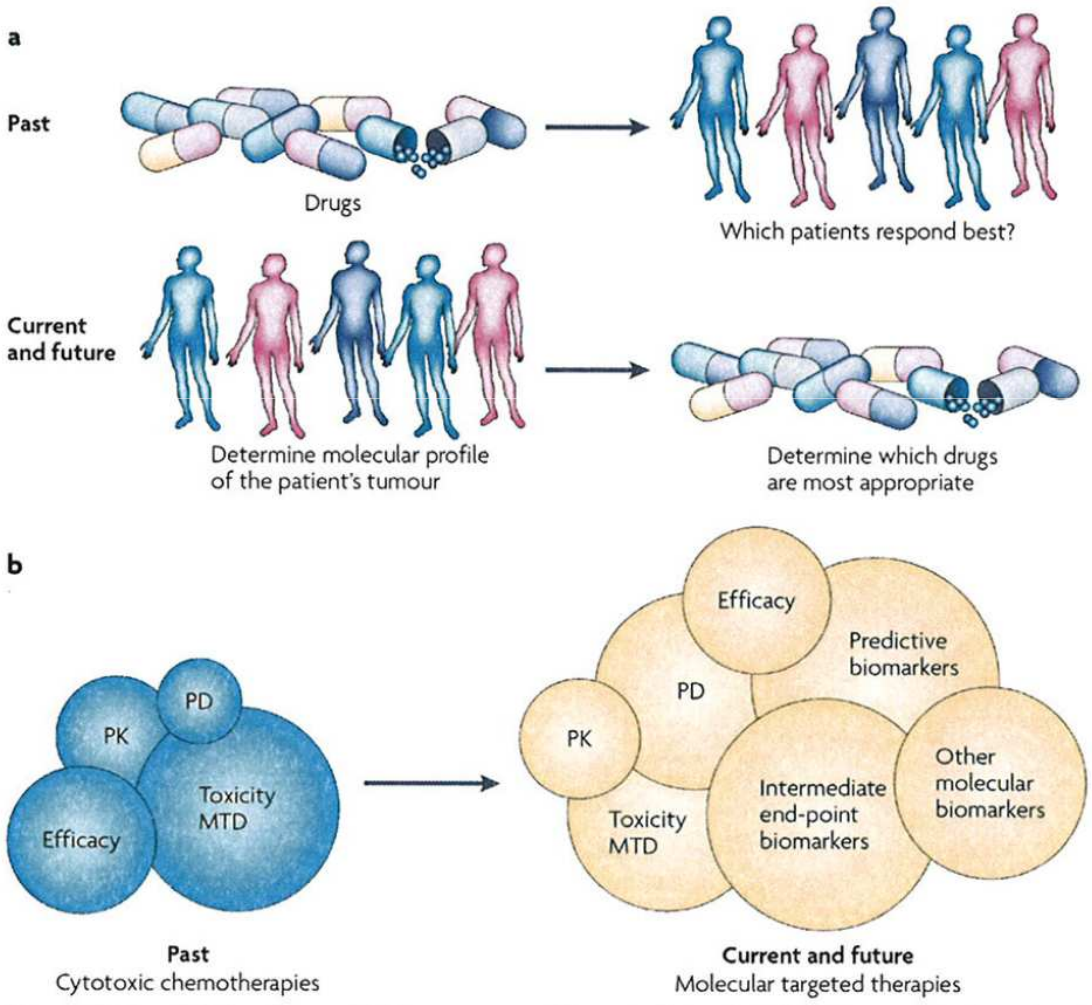
LCMC protocols linked to specific molecular lesions detected

Target	Agent(s)
EGFR	Erlotinib + OSI 906 Erlotinib + MM 121
KRAS	Tivantinib + Erlotinib
MET Amplification	GSK1120212
EML4-ALK	Crizotinib
NRAS	GSK1120212

Target	Agent
MEK1	GSK1120212
BRAF (V600E)	GSK2118434
BRAF (not V600E)	GSK1120212
HER2	Afatinib
PIK3CA	BKM120
AKT1	

Kris M. et al. Proc. ASCO 2011

From 'classical' Phase I (tumour type selection) to 'molecular profiling' Phase I (targeted drug selection)



Emerging new paradigm:

- Use of customized, adaptive, hypothesis-testing early trial designs
- Use of 'enrichment' biomarkers from earliest possible stage
- Use of intermediate endpoints of response

Yap et al. Nature Rev Cancer 2010;10:514–23

Summary

- EGFR-TKIs should be the preferred first line treatment choice for patients with tumours harbouring EGFR sensitizing-mutations. ALK inhibitors under investigations.
- Therapeutic choices based on histology are the current standard of care for the majority of our patients.
- In more than 50% of adenocarcinoma and squamous cell carcinoma of the lung a potential therapeutic target has been identified. Need to be verified in preclinical models.
- The definition of homogeneous genetic subgroups of tumors and the search for individualized approaches is the way to substiantially increase survival expectancy in this disease.

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ECOG 4599: Survival by Histology Subtype

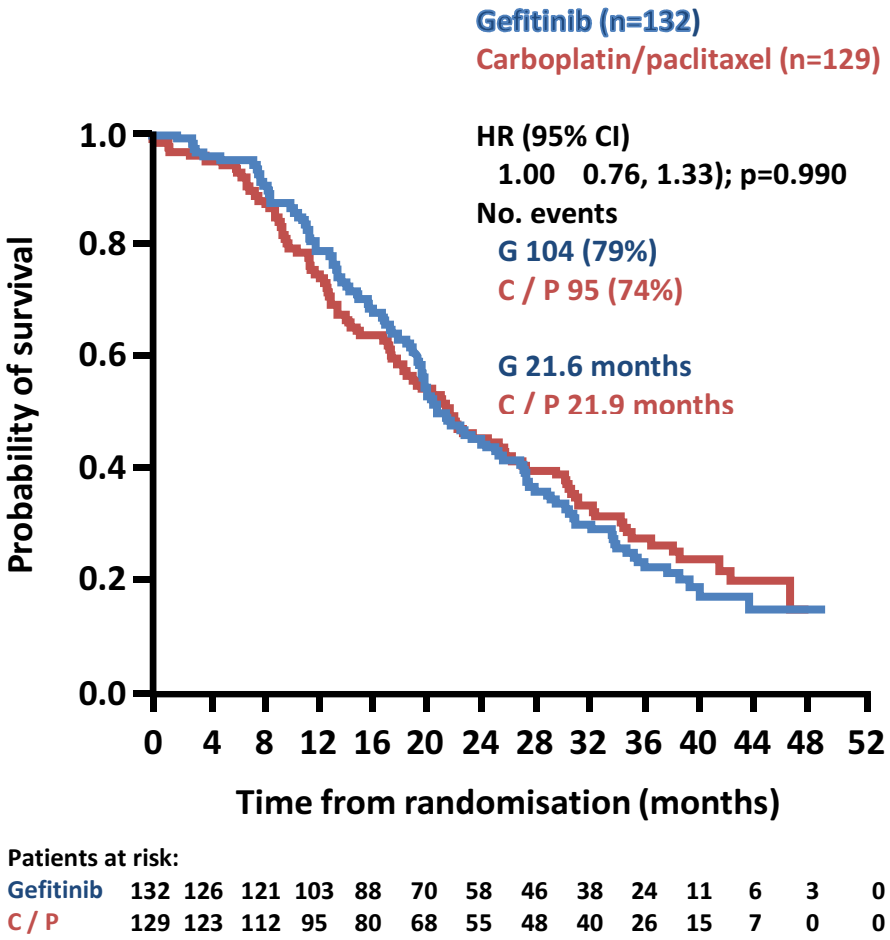
Baseline Characteristics	Total N	PC (n = 444)		PCB (n = 434)		Hazard Ratio	95% CI
		N	Median Months	N	Median Months		
All patients	878	444	10.3	434	12.3	0.80	0.69-0.93
Histologic type							
- Adenocarcinoma	602	302	10.3	300	14.2	0.69	0.58-0.83
- Large Cell	48	30	8.7	18	10.0	1.15	0.60-2.24
- Squamous	3	2	12.3	1	22.4	0.00	0.00-
- BAC	23	11	17.7	12	10.0	1.48	0.57-3.69
- NSCLC,NOS	165	86	10.0	79	9.5	1.16	0.84-1.61
- Other	34	11	12.6	23	8.4	0.92	0.43-1.98

Sandler A. et al. *J Thorac Oncol.* 2008;3(11 Suppl 4): Abstract 133.

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IPASS: 2010 OS by EGFR mutation status (ITT)

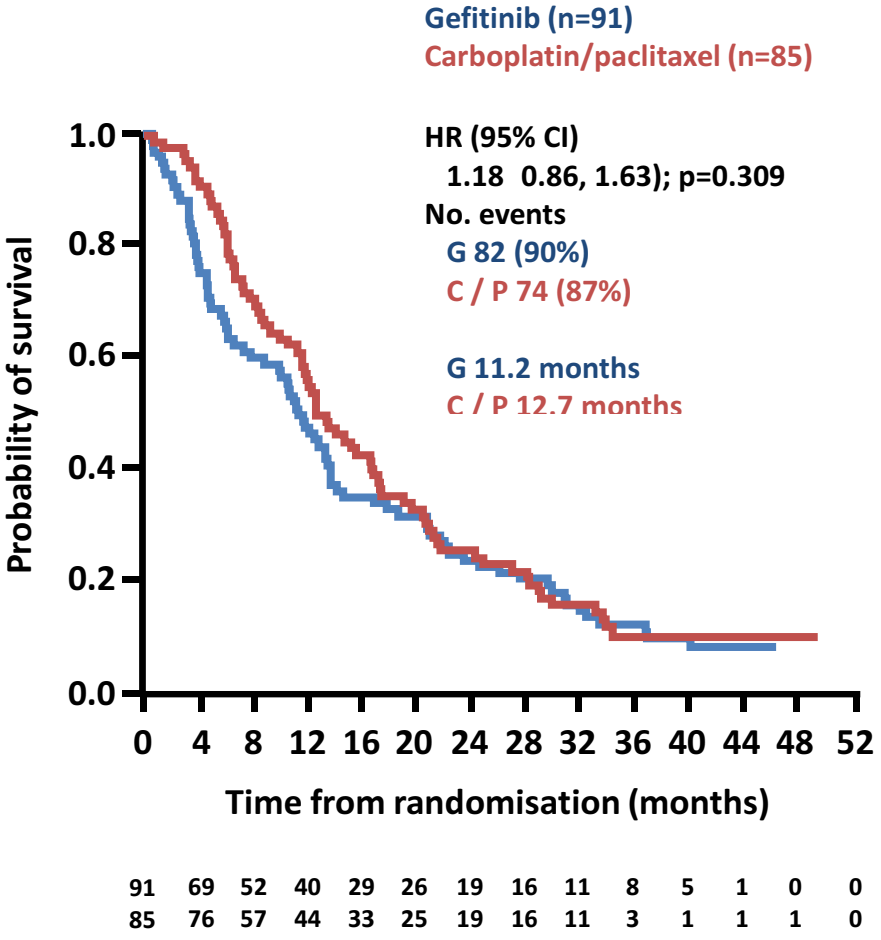
EGFR Mutation +



Patients at risk:

Gefitinib	132	126	121	103	88	70	58	46	38	24	11	6	3	0
C / P	129	123	112	95	80	68	55	48	40	26	15	7	0	0

EGFR Mutation -



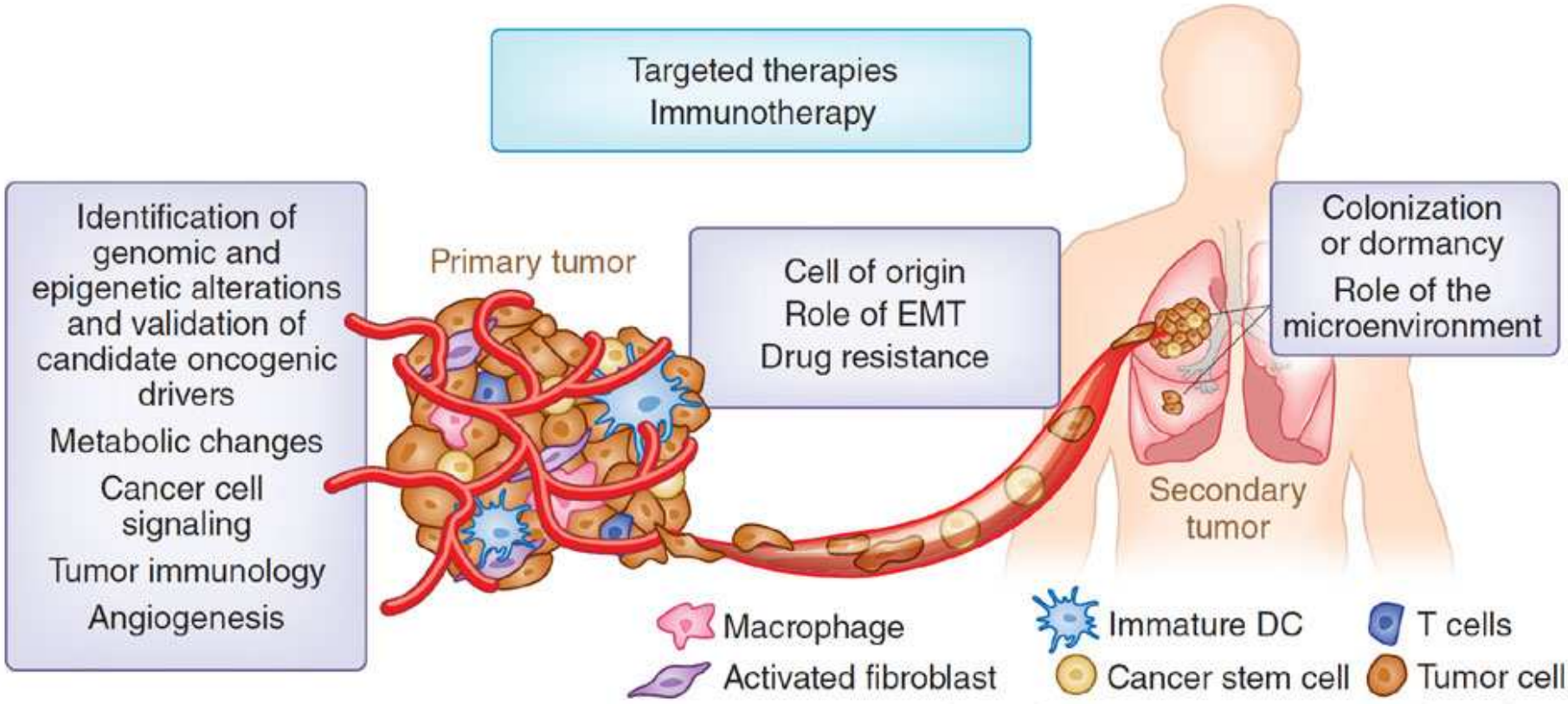
	91	69	52	40	29	26	19	16	11	8	5	1	0	0
	85	76	57	44	33	25	19	16	11	3	1	1	1	0

Treatment by subgroup interaction test p=0.480

Cox analysis with covariates; A hazard ratio < 1 implies a lower risk of death on gefitinib
No formal adjustment made for multiple testing

Yang et al. Proc. ESMO 2010

Notable Advances in Cancer Research in the last 2 years



Farrel A. Nat. Med. 2011; 17:262-264

Molecular Characteristics in NSCLC May Predict Response or Resistance

Molecular aberration	Frequency in NSCLC (%)	Comment
EGFR mutation	10–16.6	Indicates sensitivity to EGFR inhibitors
EGFR amplification	30.8–59.2	May be associated with response to EGFR inhibitors
ALK fusion gene	3–5*	Indicates sensitivity to ALK inhibitors
KRAS mutation	19–21	Usually in smokers Associated with poor prognosis irrespective of therapy Conflicting data with respect to resistance to EGFR inhibitors
PIK3CA mutation	2	May be involved in EGFR resistance
PIK3CA amplification	12–17.1	May be involved in EGFR resistance
MET mutation	12–14	Contributes to EGFR resistance
MET amplification	54†	Contributes to EGFR resistance

Janku F, et al. *Nat Rev Clin Oncol.* 2010;*7:*401–14.
(except *Garber J, et al. *Natl Cancer Inst.* 2010;102:672–675, †Spigel DR, et al. Presented at ESMO 2010; Abstract LBA15.)