Associazione Italiana Radioterapia Oncologica

LA RADIOTERAPIA PALLIATIVA CON TECNICHE SPECIALI DELLA MALATTIA METASTATICA

Polmone :

Integrazione radioterapia chemioterapia

e

farmaci biologici

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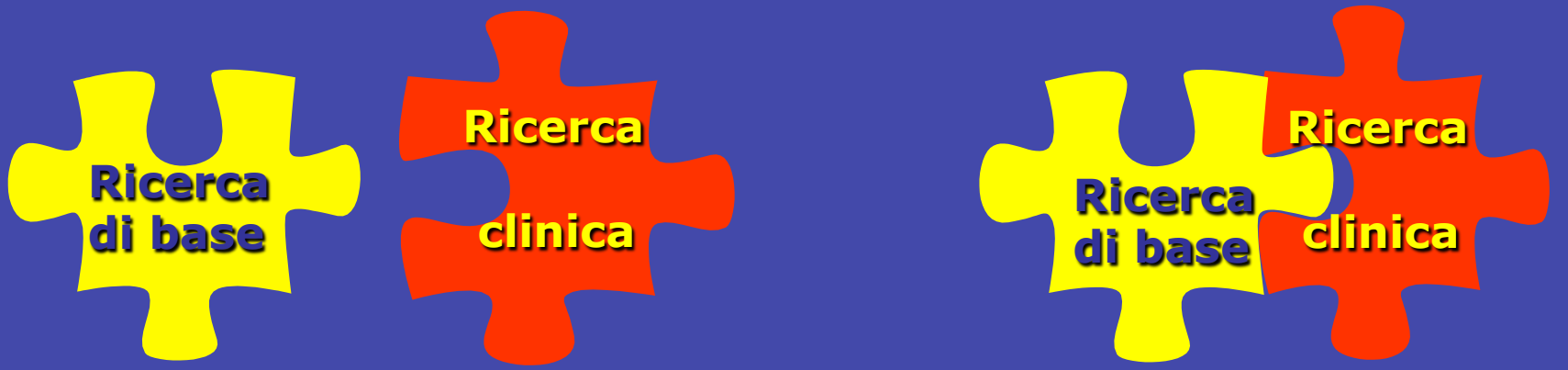
Evoluzione della metodologia scientifica nel trattamento medico del paziente affetto da neoplasia

1960 1990 2000

ONCOLOGIA EMPIRICA → ONCOLOGIA MOLECOLARE



Terapia standard applicata su tutta la popolazione

Sottogruppi di pazienti con differenti trattamenti

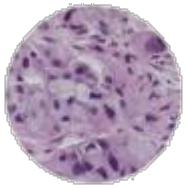
TERAPIA ANTIBLASTICA → TARGET THERAPY

Tumore polmonare metastatico
Evoluzione della strategia terapeutica in base all'istologia

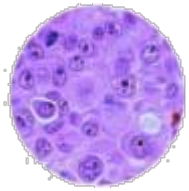
Meta-analysis .BMJ. 1995 Oct 7;311(7010):899-909.
Loehrer PJ Sr, Semin Oncol. 1988 Jun;15(3 Suppl 3):2-8. Review.
L. Einhorn, JCO 2008;26:3485-3486
FR Hirsch JTO 2008;3:1468-1481

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

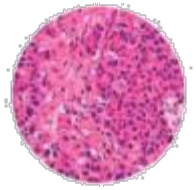
1999
Histology-driven selection



Adenocarcinoma

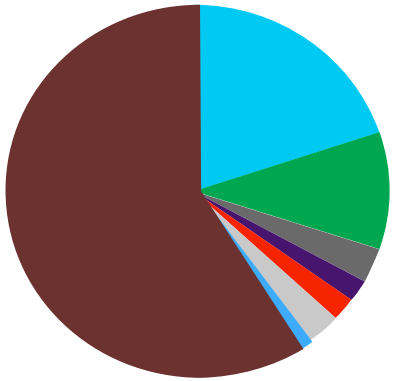


Squamous-cell carcinoma

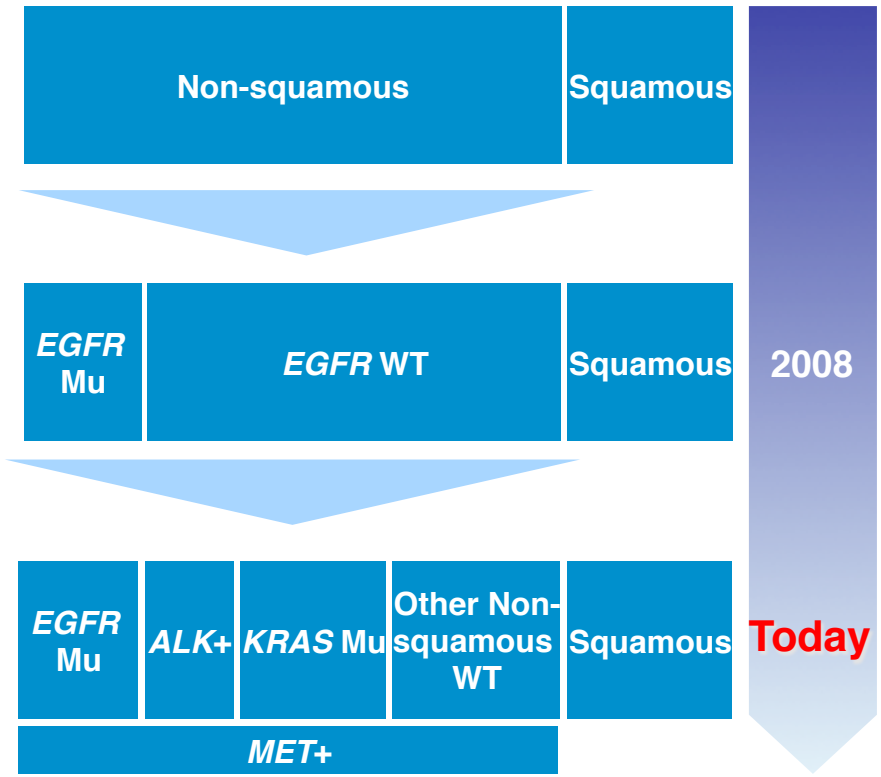


Large cell carcinoma

2010
Targeting oncogenic drivers*



Evolution of NSCLC treatment

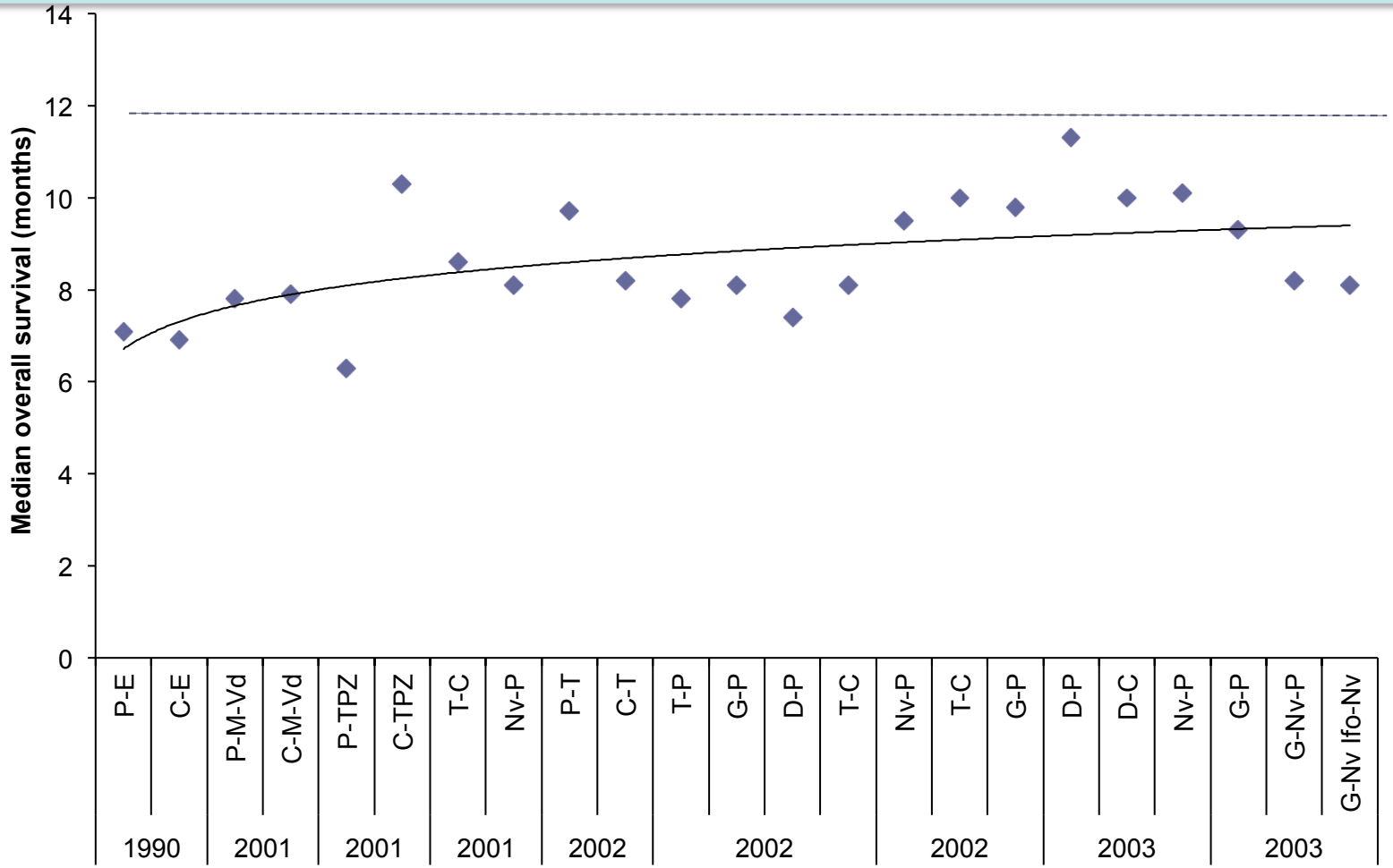


*Incidence of mutations in adenocarcinoma provided as an example

Current Standard of NSCLC Care

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

Chemotherapy in advanced NSCLC reached a plateau in efficacy



P = cisplatin; E = etoposide; C = carboplatin; M = mitomycin; Vd = vindesine; TPZ = tirapazamine; T = paclitaxel; G = gemcitabine; D = docetaxel; Vb = vinblastine; Nv = vinorelbine; Ifo = Ifosfamide

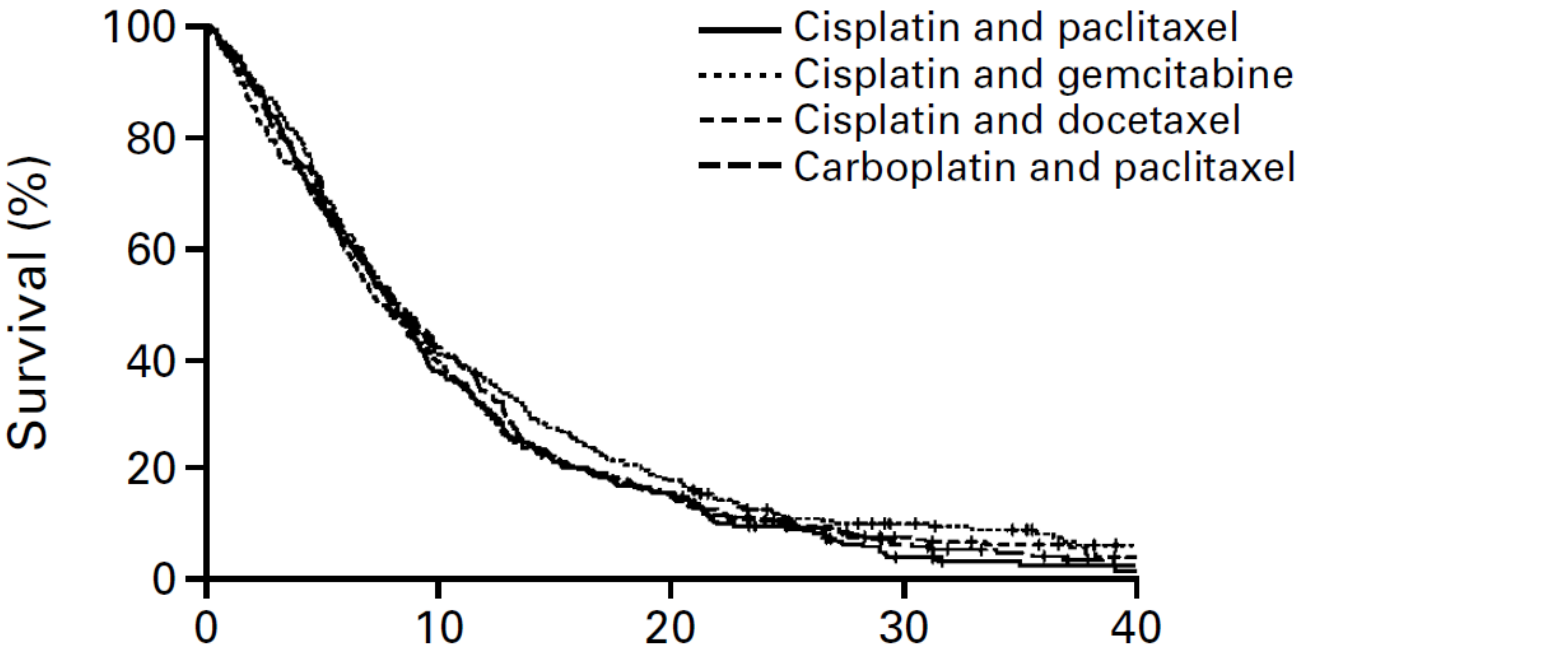
Reck M. Anticancer Res 2005;25:1501-1506; Ardizzoni et al. J Natl Cancer Inst 2007;99:847-857

Chemioterapia“classica”

The New England Journal of Medicine

COMPARISON OF FOUR CHEMOTHERAPY REGIMENS FOR ADVANCED NON–SMALL-CELL LUNG CANCER

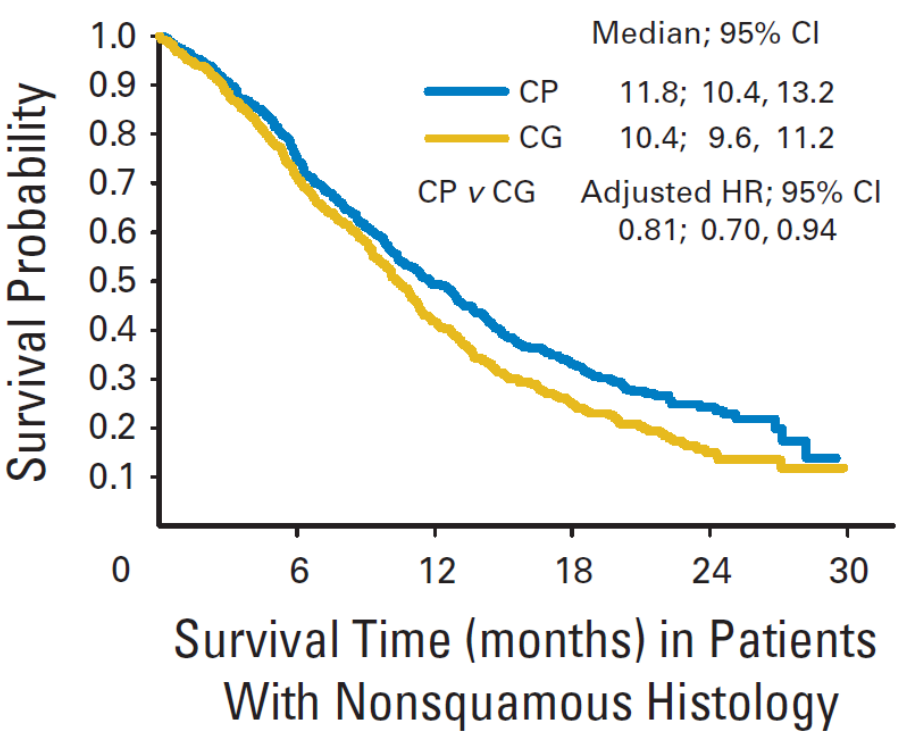
JOAN H. SCHILLER, M.D., DAVID HARRINGTON, PH.D., CHANDRA P. BELANI, M.D., COREY LANGER, M.D., ALAN SANDLER, M.D., JAMES KROOK, M.D., JUNMING ZHU, PH.D., AND DAVID H. JOHNSON, M.D., FOR THE EASTERN COOPERATIVE ONCOLOGY GROUP

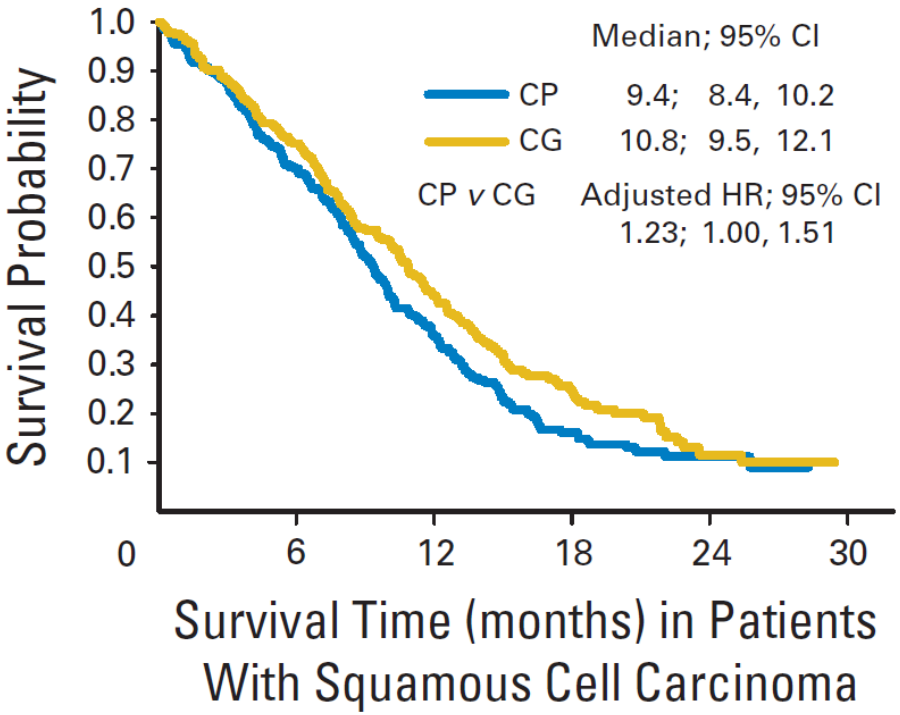


N Engl J Med 2002;346:92-8.

Chemioterapia “semi-personalizzata”

Cisplatin + pemetrexed vs. cisplatin + gemcitabine as 1st line treatment





Scagliotti GV et al, J Clin Oncol 2008; 26: 3543-3551

Efficacy by Histology in Pemetrexed Studies

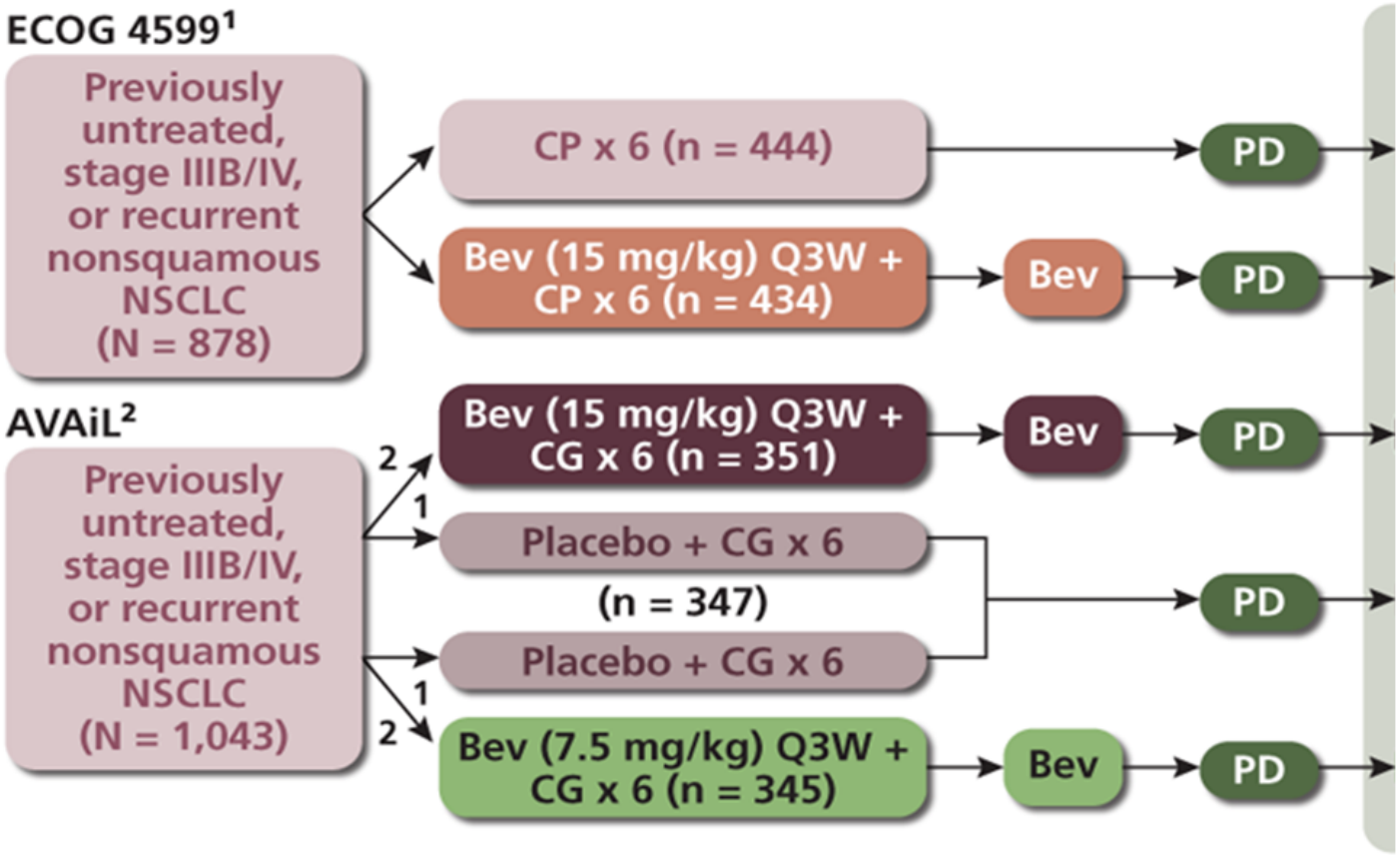
NSCLC Histologic Group	Second-line Pem vs. Docetaxel		First-line Pem/Cis vs. Gem/Cis		Maintenance Pem vs. Placebo	
	Pem	**Doc**	**Cis/Pem**	**Cis/Gem**	**Pem**	**Placebo**
Non-squamous	**n=205**	**n=194**	**n=618**	**n=634**	**n=325**	**n=156**
Median OS, months	9.3	8.0	11.0	10.1	15.5	10.3
Adjusted HR (95% CI)	0.78 (0.61–1.00)		0.84 (0.74–0.96)		0.70 (0.56–0.88)	
P value	0.048		0.011		0.002	
Squamous	**n=78**	**n=94**	**n=244**	**n=229**	**n=116**	**n=66**
Median OS, months	6.2	7.4	9.4	10.8	9.9	10.8
Adjusted HR (95% CI)	1.56 (1.08–2.26)		1.23 (1.00–1.51)		1.07 (0.77–1.50)	
P value	0.018		0.050		0.678	

Non-squamous = adenocarcinoma, large cell carcinoma, and other/indeterminate NSCLC histology

Scagliotti GV et al. *Oncologist* 2009

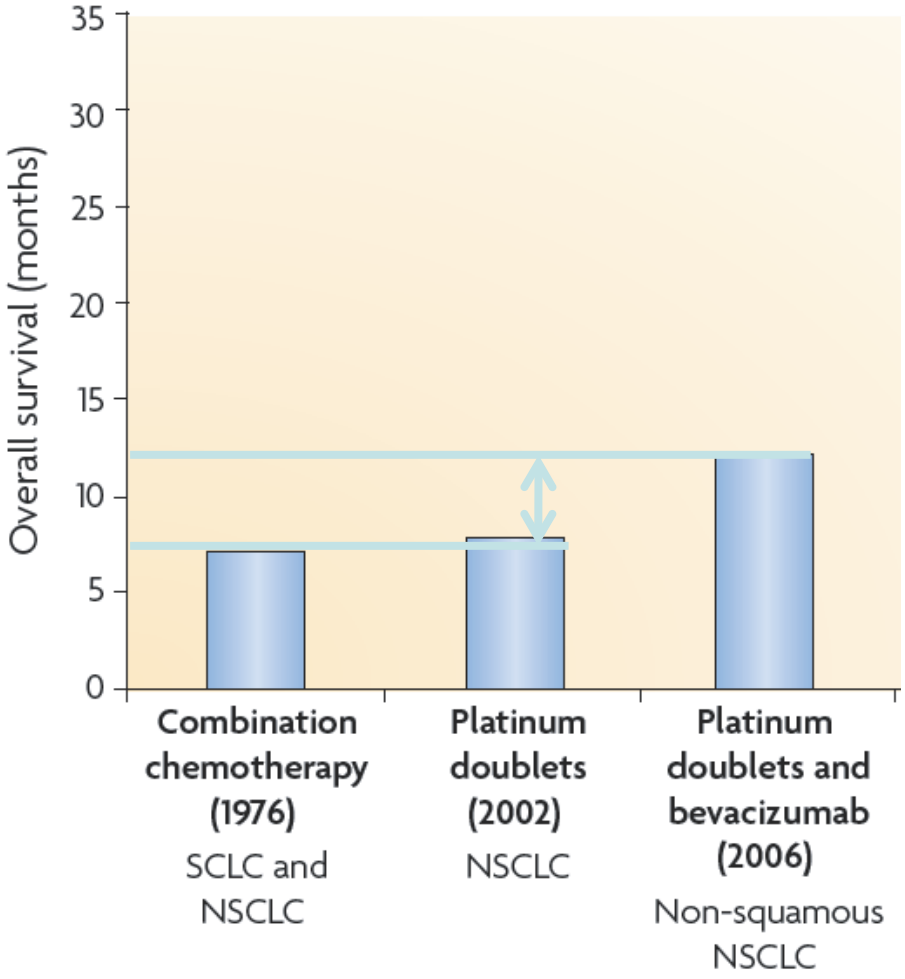
Farmaci biologici “non personalizzati”

Bevacizumab in 1st-line of advanced NSCLC
ECOG 4599 and AVAiL trials



[1] Sandler et al, N Engl J Med 355, 2542-2550, 2006
[2] Reck et al, J Clin Oncol 27, 1227-1234, 2009

Progress in the treatment of metastatic lung cancer



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

Classic RCT Design: CT* +/- Targeted Agent in 1st-line Advanced Stage NSCLC

Target	Agent	Survival benefit
MMPs	Prinomastat, others	No
EGFR (TKI)	Gefitinib or Erlotinib	No
FT (RAS)	Lonafarnib	No
PKCα	ISIS 3521	No
RXR	Bexarotene	No
VEGFR (TKI)	Sorafenib	No
VEGF (MAb)	Bevacizumab	Yes
EGFR (MAb)	Panitumumb	No
TLR9 agonist	PF-351 (2 phase III trials)	No
EGFR (MAb)	Cetuximab (FLEX)	Yes*
IGF1-R	Figitumumab	No
Vascular (VDA)	ASA-404	No

*In combination with platinum-based CT vs CT; **EGFR IHC positive

LUNG CANCER Major Advance

First-line treatment with cetuximab extends survival in NSCLC. Cetuximab is approved for treating advanced colorectal and head and neck cancers.

- A phase III study (called Cisplatin/Vinorelbine ± Cetuximab as First-Line Treatment of Advanced Non–Small-Cell Lung Cancer [FLEX]) found that adding cetuximab to initial chemotherapy with cisplatin and vinorelbine anticancer drugs conventionally used to treat patients with NSCLC**—extended overall survival by up to 21%** in patients with advanced NSCLC that expressed epidermal growth factor receptor (EGFR). Cetuximab works by targeting EGFR.
- This study adds to the body of evidence showing that EGFR plays a strong role in the progression of some lung cancers and that treatments targeting EGFR can improve survival. It also validates the continued exploration of the molecular biology of lung cancer, including studies identifying new therapeutic targets.

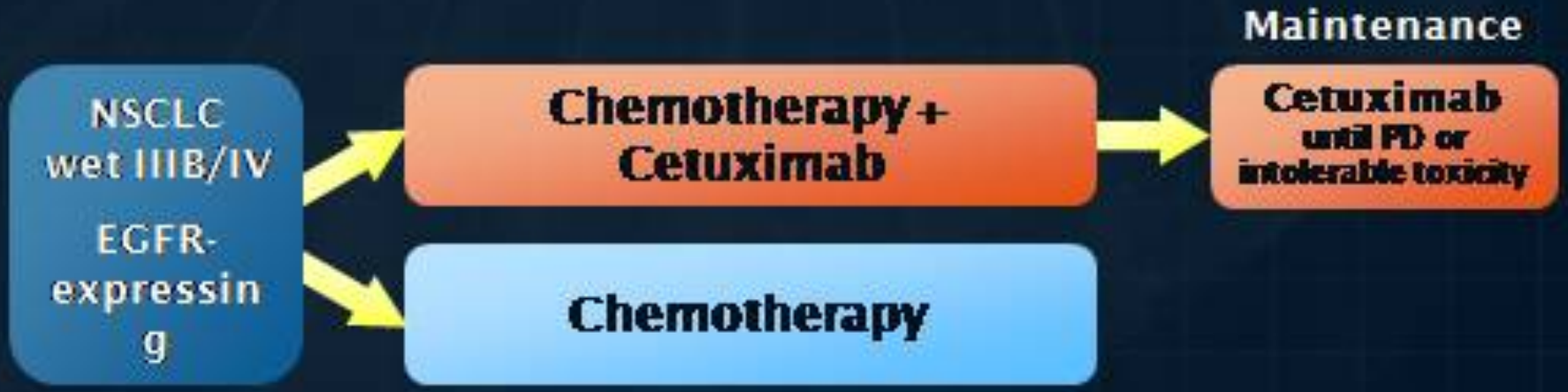
Pirker R, Szczesna S, von Powel J, et al: FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non–small-cell lung cancer (NSCLC). J Clin Oncol 26:6s; 2008 (suppl) abstr 3

FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non–small-cell lung cancer (NSCLC).

Background: Epidermal growth factor receptor (EGFR) dysregulation is common in NSCLC and is associated with poorer prognosis. This phase III study assessed the efficacy and safety of the EGFR-targeted monoclonal antibody cetuximab in combination with cisplatin/vinorelbine (CV) compared with CV alone in advanced NSCLC. **Methods:** Patients with EGFR-detectable advanced NSCLC were randomized 1:1 to cetuximab (400 mg/m2 initial dose, then 250 mg/m2/wk) plus C (80 mg/m2 d1) and V (25 mg/m2 d1, d8) q3w (arm A) or CV alone (arm B). The primary endpoint was overall survival (OS); secondary endpoints were progression-free survival, tumor response, disease control, and safety. Randomization was stratified by ECOG performance status (0/1 vs 2) and tumor stage (wet IIIb vs IV). Results: 1,125 patients were randomized: 557 to arm A, 568 to arm B, 70% male, median age 59 (18-83) years, 94% stage IV, 47% adenocarcinoma (AC), 34% squamous cell carcinoma (SCC), 83% ECOG 0/1. Survival analysis was performed after 868 events had occurred. OS was significantly improved in arm A (stratified log-rank test). Preliminary results of prespecified subgroup analyses suggest a greater benefit in Caucasians independent of histology and a general better prognosis in Asians. Analyses of secondary endpoints are ongoing. **Conclusions:** Cetuximab plus CV demonstrated superior survival over CV alone in patients with advanced EGFR-detectable NSCLC. There was a remarkable difference between the outcome of Asian and Caucasian patients. This is the first study to demonstrate a survival benefit of an EGFR-targeted agent in combination with platinum-based chemotherapy in advanced first-line NSCLC irrespective of histology and confirms the clinical relevance of cetuximab in NSCLC.

Pirker R,et al:J Clin Oncol 26:6s; ASCO 2008 (suppl) abstr 3

FLEX
Study design



Chemotherapy (CT)	Cetuximab
Cisplatin 80 mg/m² day 1	initial dose 400 mg/m²
Vinorelbine 25 (30) mg/m² days 1, 8	then 250 mg/m² weekly
Every 3 weeks, up to 6 cycles	

FLEX
Study endpoints

Primary endpoint: Overall survival

Secondary endpoints: Response
Progression-free survival
Disease control
Quality of life
Safety

ASCO Annual '08 Meeting

FLEX
Main eligibility criteria

- NSCLC wet IIIB / IV
- All histological subtypes
- EGFR expression by immunohistochemistry (≥1 positive tumor cell)
- Age ≥18 years
- ECOG PS 0/1 and 2
- No known brain metastases
- No prior chemotherapy or anti-EGFR therapy

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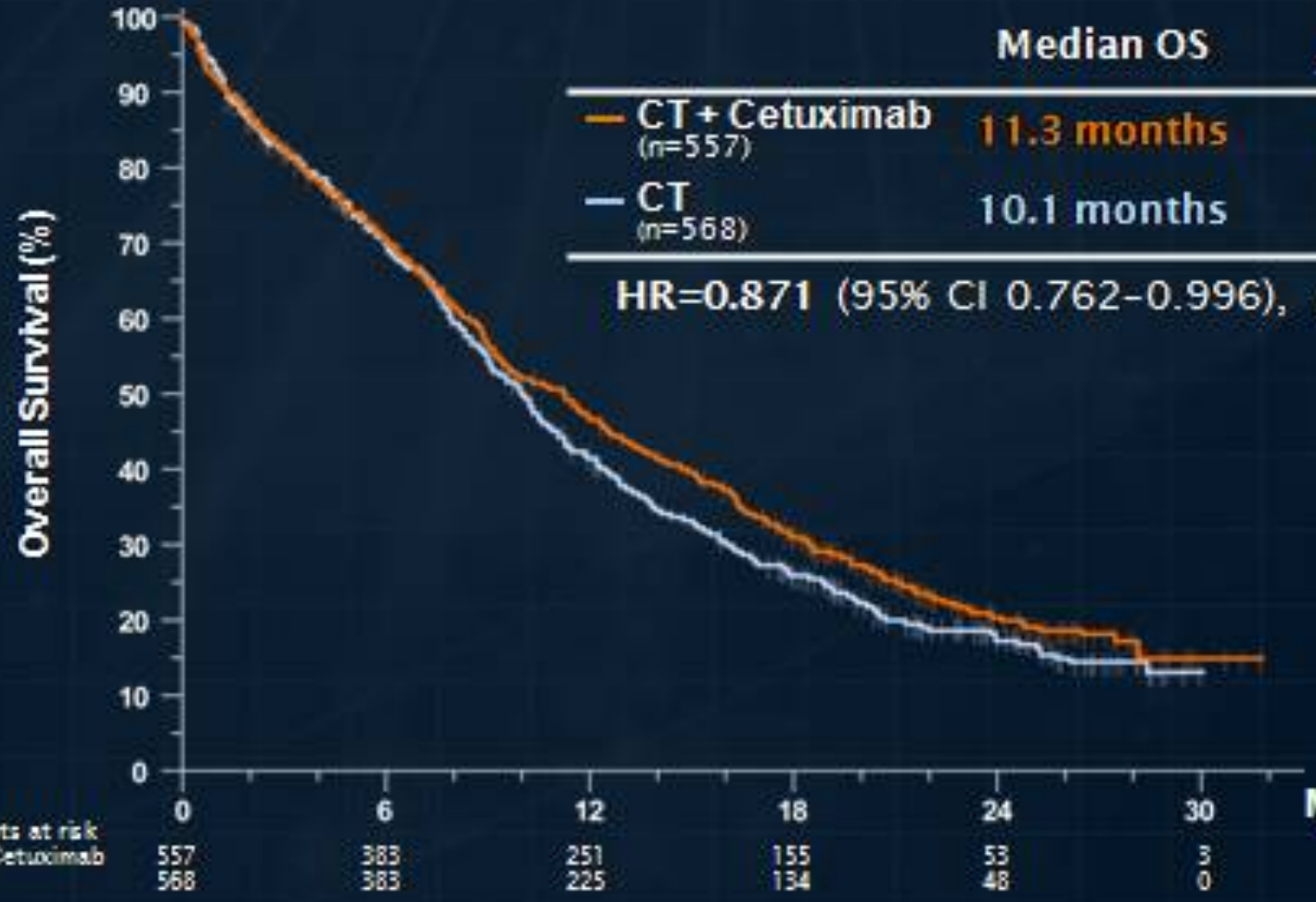
FLEX Overall survival



	Median OS	1-year survival
CT + Cetuximab (n=557)	11.3 months	47 %
CT (n=568)	10.1 months	42 %

HR=0.871 (95% CI 0.762–0.996), **p=0.044**

Patients at risk						
CT + Cetuximab	557	383	251	155	53	3
CT	568	383	225	134	48	0

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p-value = stratified log-rank test (2-sided)

FLEX
Differences in ethnicity

	Caucasian (n=946)	Asian (n=121)
Prognostic factors		
Adenocarcinoma	44 %	72 %
Female	27 %	46 %
Never smoked	17 %	52 %
ECOG Performance Status 0/1	81 %	94 %
Post-study treatment		
EGFR TKIs	17 %	61 %
Median OS	9.6 months	19.5 months
[95% CI]	[9.0-10.4]	[16.4-23.3]

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FLEX
Asian subgroup (n=121)

	CT + Cetuximab (n=62)	CT (n=59)	p-value
Baseline prognostic factors:			
Adenocarcinoma	65 %	80 %	
Post-study treatment:			
EGFR TKIs	50 %	73 %	
OS	17.6 months	20.4 months	ns
RR	50 %	44 %	ns

Small sample size (10% of total) and difference in histology and post-study EGFR TKI treatment do not allow to draw definitive conclusions

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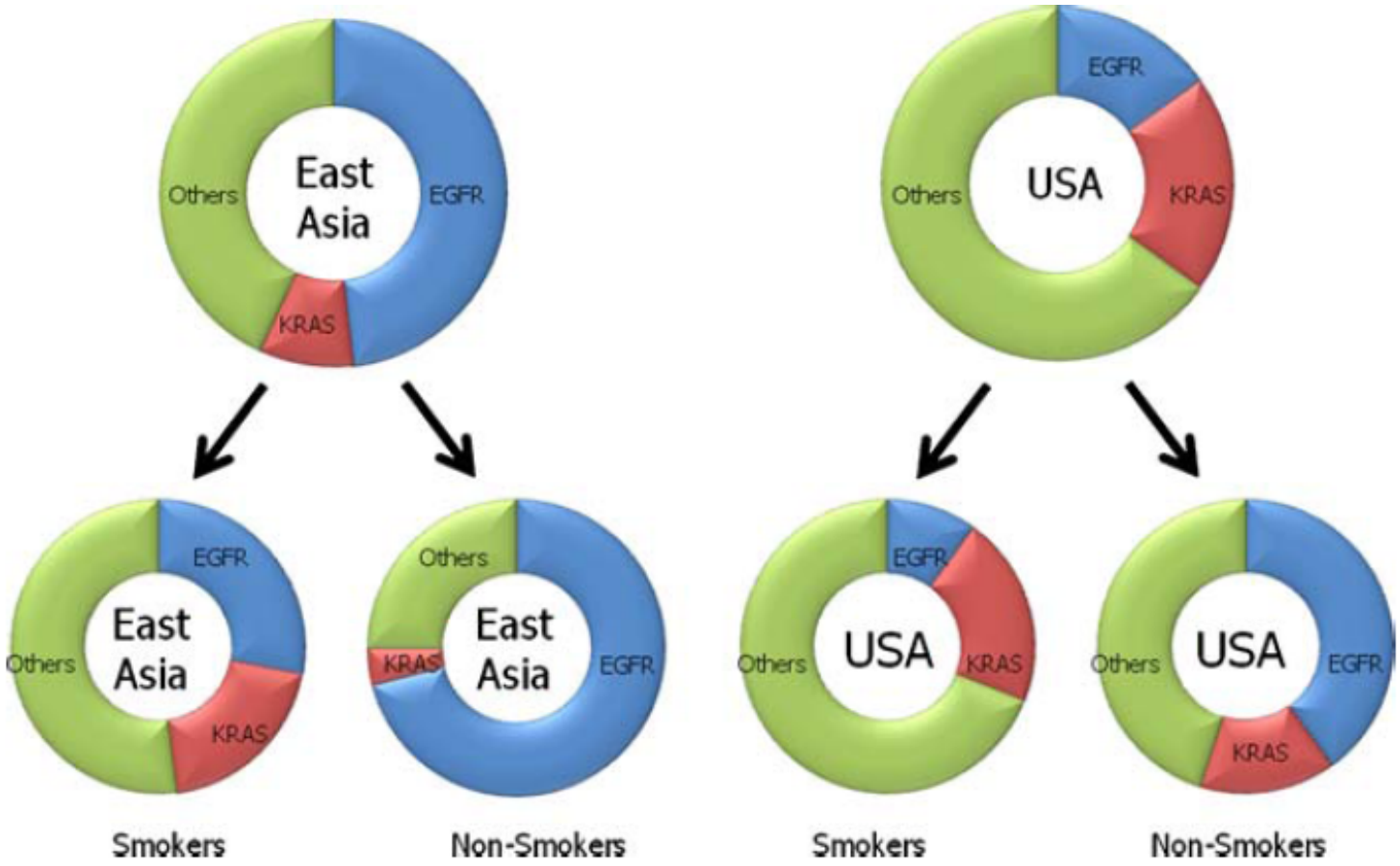
EGFR or K-*RAS* Mutations According to Ethnicity and Smoking Status



Suda K. et al. *Cancer Metastasis Rev.* 2010; 29:49

Combination Frontline Chemotherapy and EGFR TKIs in Unselected Populations

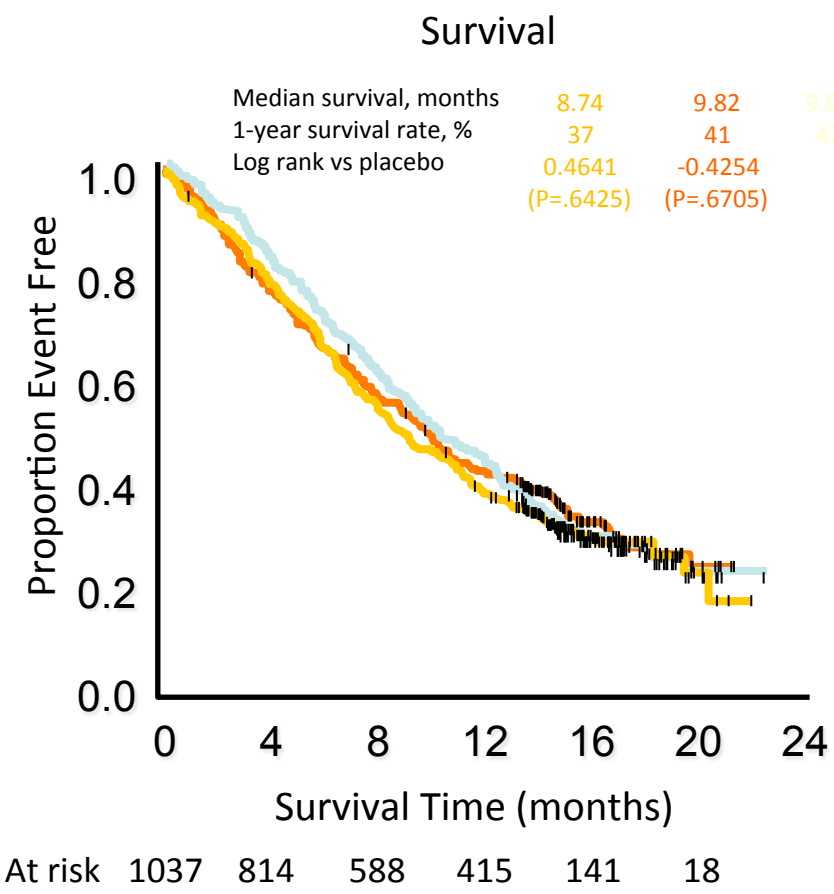
Trial	Agent	N	RR	TTP/PFS	OS
TALENT	E + CisG	580	32%	7.9 mos	10.0 mos
	CisG	579	30%	5.4 mos	10.2 mos
TRIBUTE	E + CbP	526	22%	5.1 mos	10.6 mos
	CbP	533	19%	4.9 mos	10.5 mos
INTACT-1	G + CisG	730	51%	5.7 mos	9.9 mos
	CisG	363	47%	6.0 mos	10.9 mos
INTACT-2	G +CbP	692	30%	5.0 mos	9.3 mos
	CbP	345	29%	5.0 mos	9.9 mos

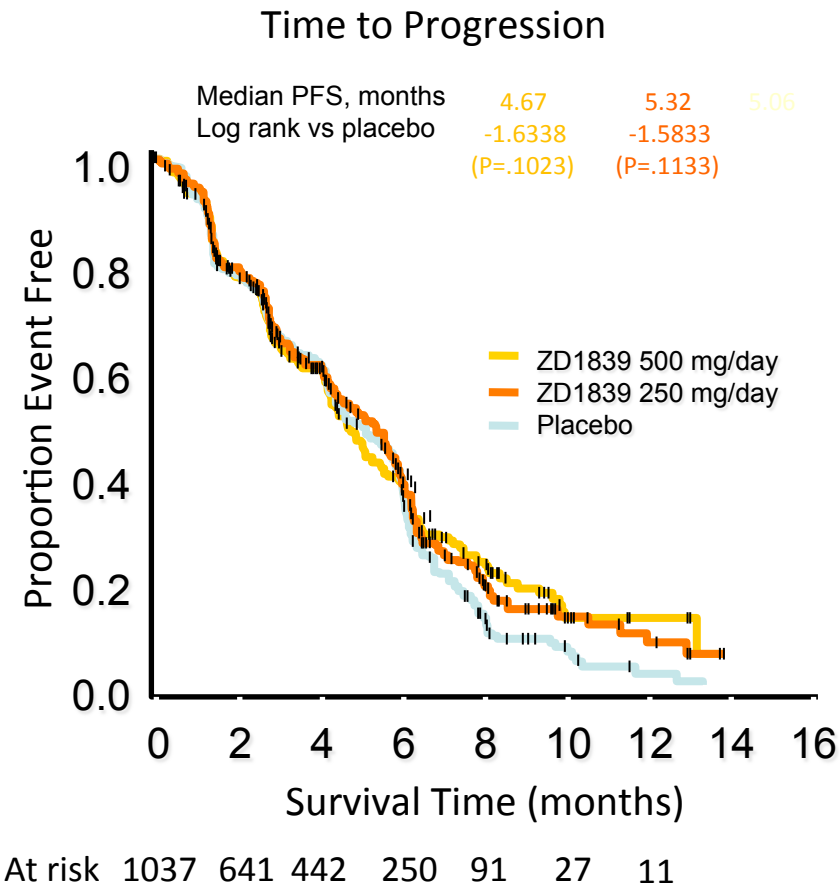
E=erlotinib; CisG=cisplatin/gemcitabine; CbP=carboplatin/paclitaxel; G=gefitinib.

Frontline EGFR TKIs provide no survival benefit in unselected populations

Fong. *J Thor Oncol.* 2008;3:303; Herbst. *J Clin Oncol.* 2005;23:5892; Gatzemeier. *J Clin Oncol.* 2007;25:1545; Giaccone. *J Clin Oncol.* 2004;22:777; Herbst. *J Clin Oncol.* 2004;22:785.

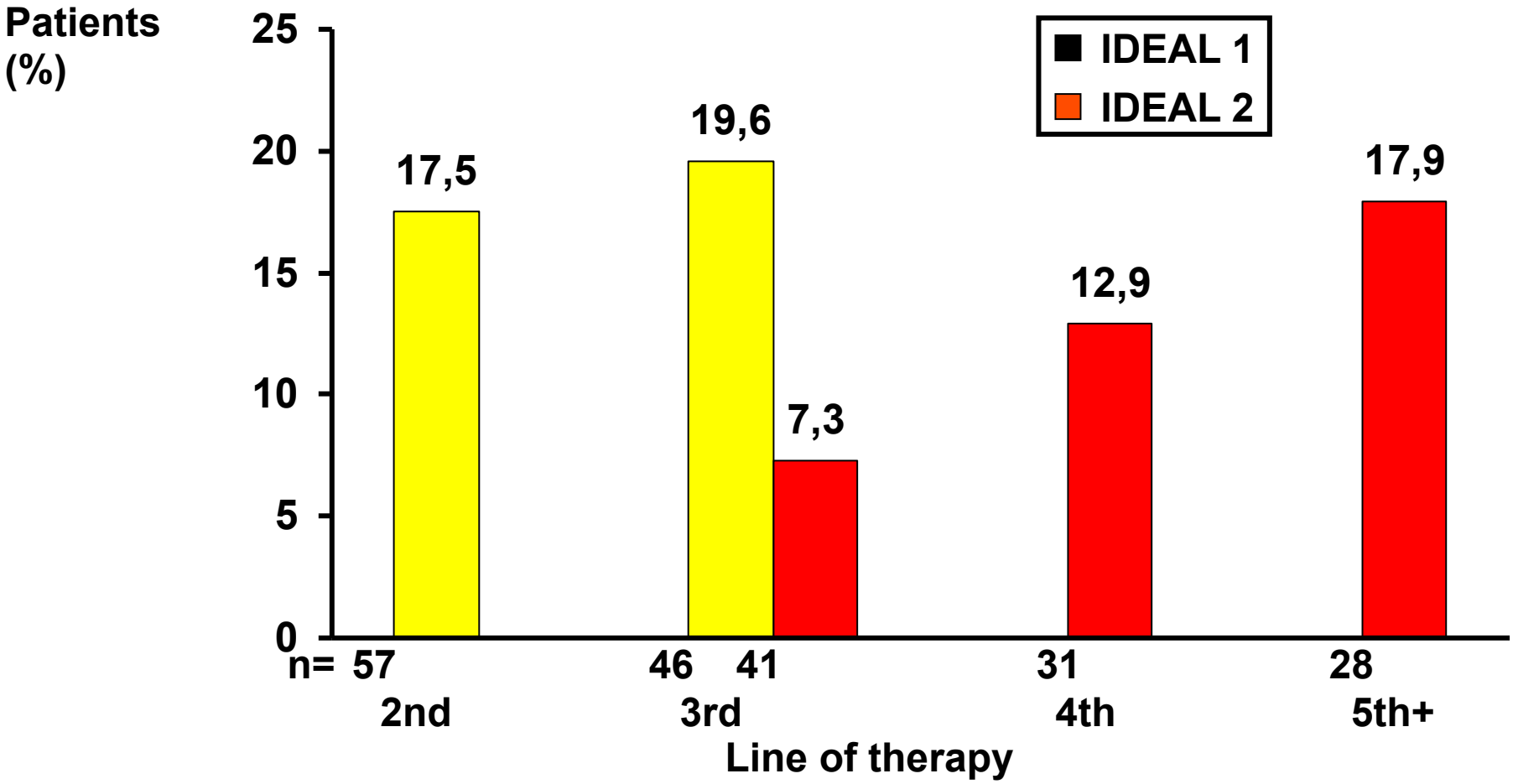
INTACT 2: Overall Survival and Time to Disease Progression Rate



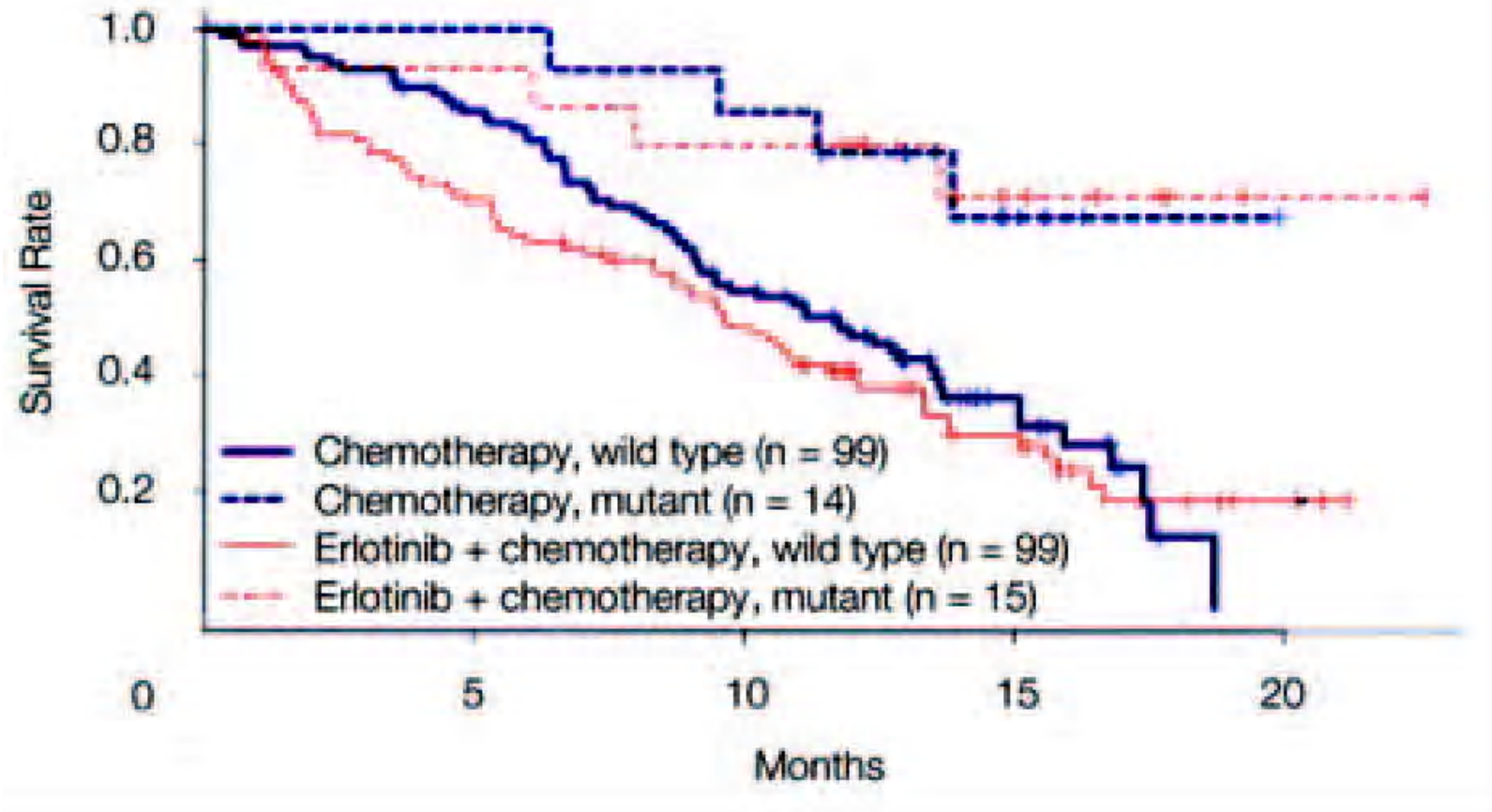


Johnson DH et al. *Ann Oncol*. 2002;13(suppl 5):127-128. Abstract 4680.

IDEAL 1 and 2: Objective response with gefitinib (250 mg/day)



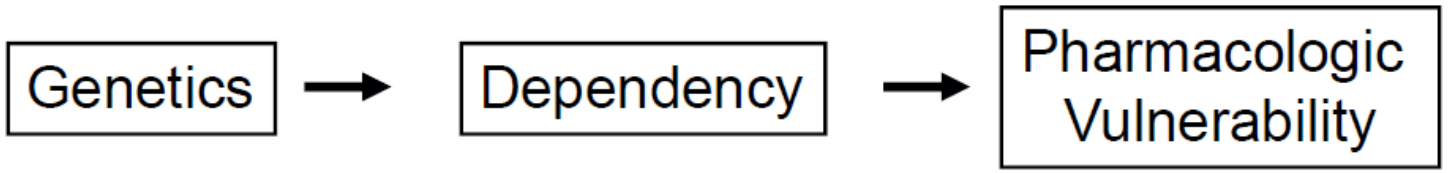
Prognostic vs. Predictive Biomarkers
The Tale of EGFR Mutations in NSCLC



Molecular analysis of TRIBUTE trial (CT vs. CT + erlotinib)

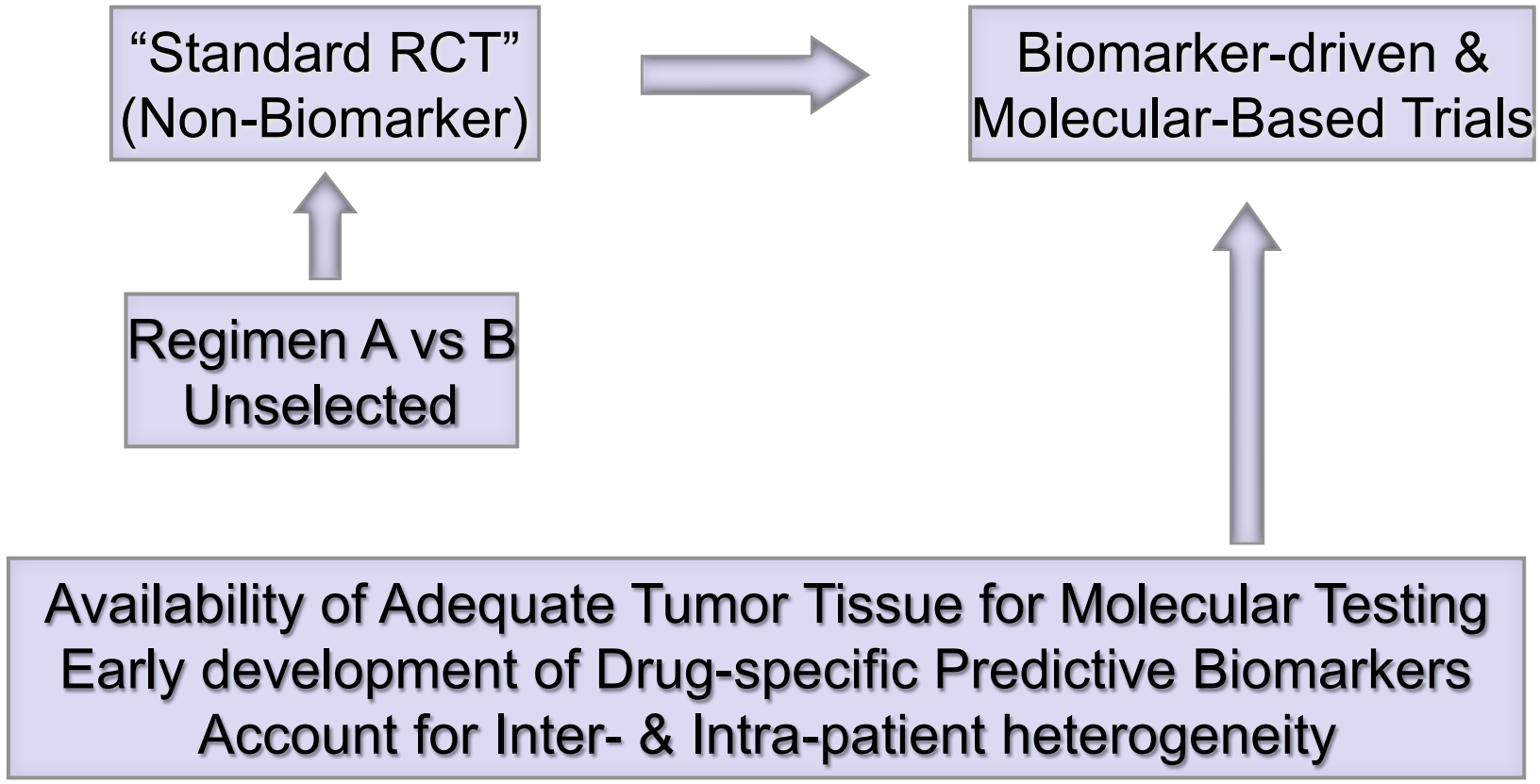
Eberhard al., JCO 2005

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

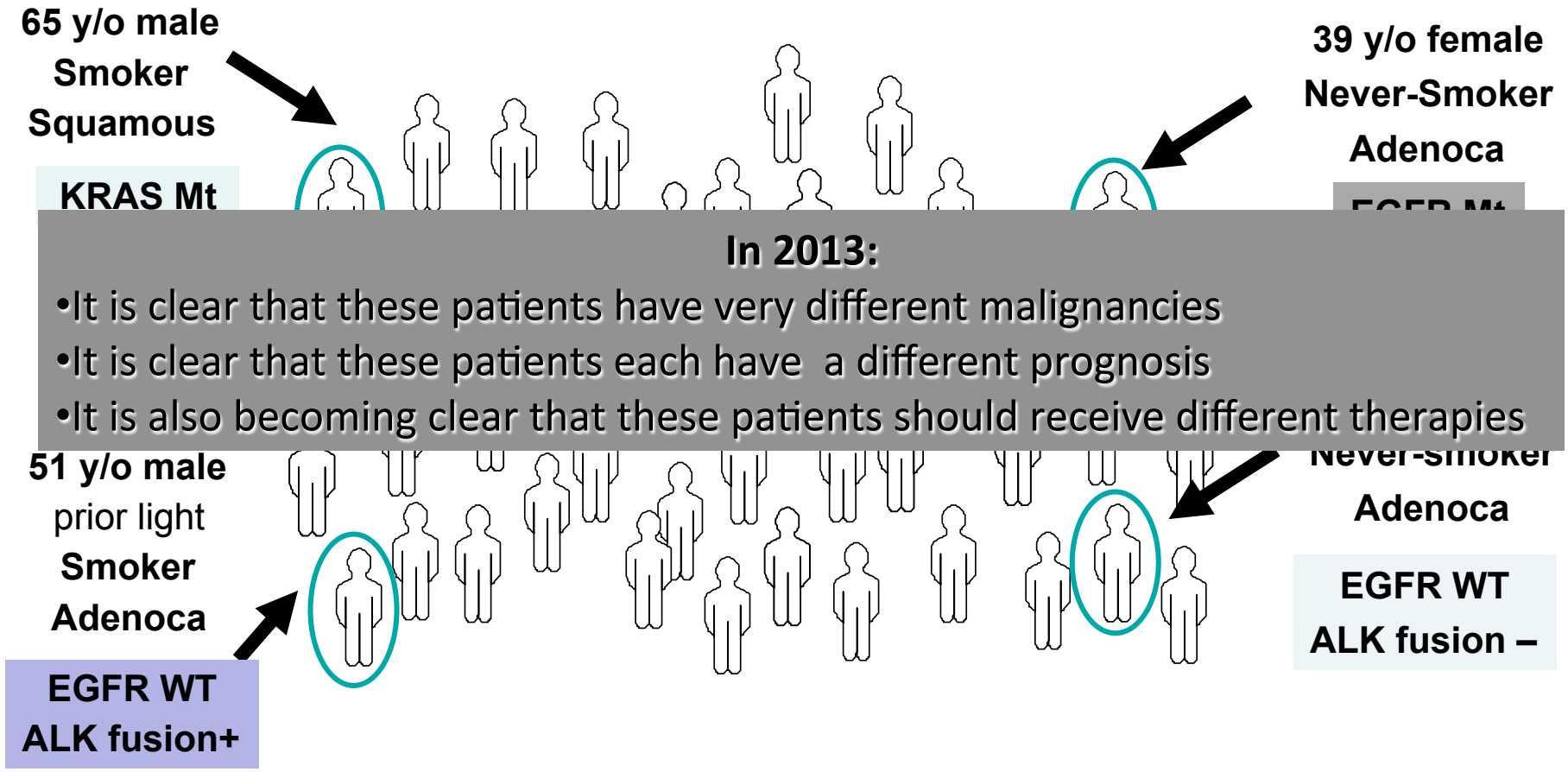
Transition from “Standard RCT” to Biomarker-driven & Molecular-based Clinical Trials



Gandara, Scagliotti et al: Clin Lung Cancer, 2009

Personalizing Therapy by Molecular Biomarker testing will Improve Outcomes for Cancer Patients

Patients with the same Diagnosis & Clinical Features
(Stage IV Non-small Cell Lung Cancer)

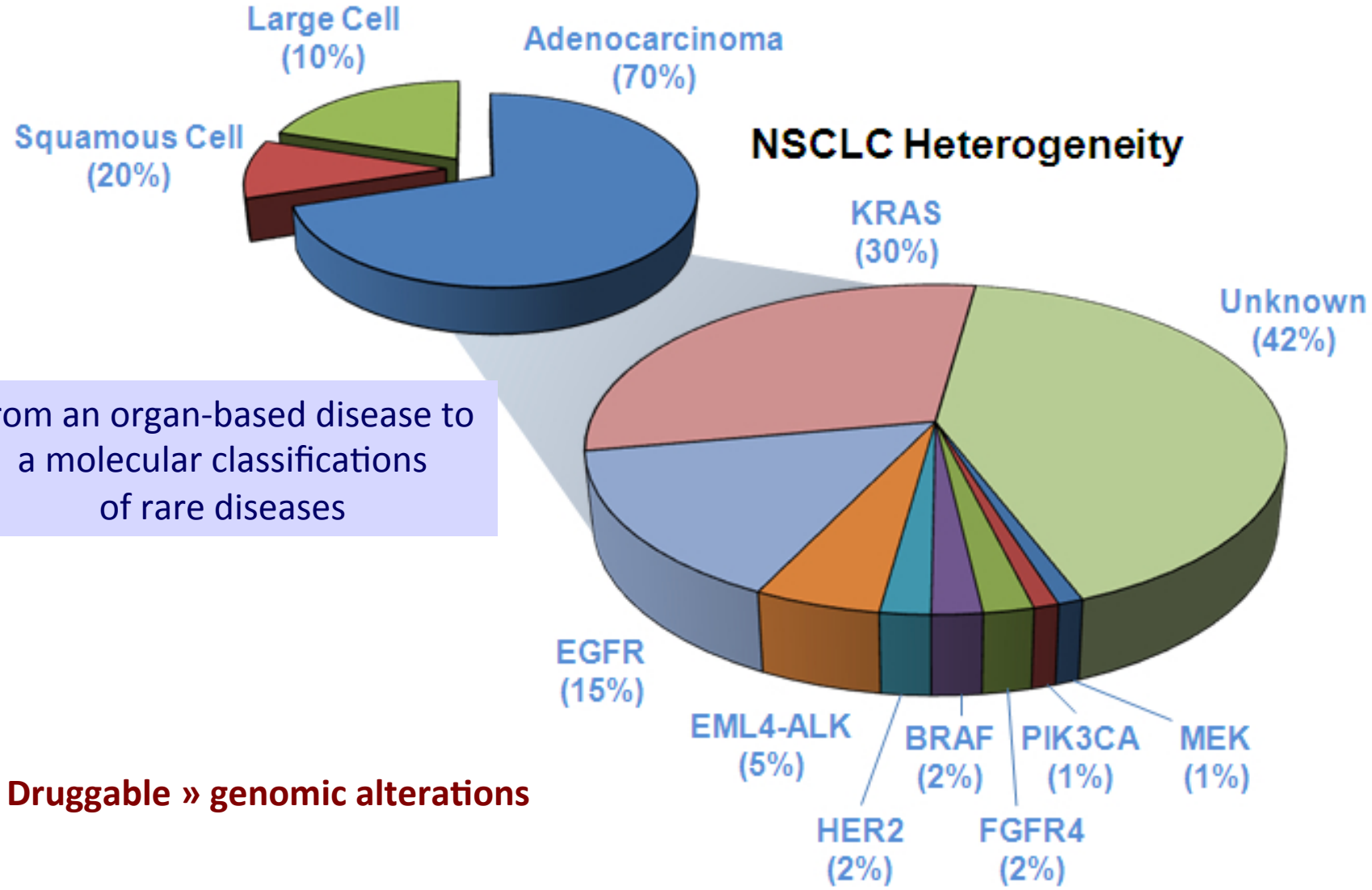


Cancer Research at the roundabout

1. Cancer is a genetic somatic disease (5% inherited)
2. (Very likely) originates from stem cells
3. It is caused by genetic alterations of a handful of genes (*Oncogenes* or '*Driver genes*')
4. It is often possible to identify these genetic lesions by molecular diagnosis
5. 'Target' Therapy is only effective when aimed at the alteration of the driver gene(s): '*Oncogenic Addiction*'

G.Scagliotti

Disease segmentation based on oncogenic events



From an organ-based disease to a molecular classifications of rare diseases

« Druggable » genomic alterations

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.)

Sensitivity to EGFR-TKI according to different EGFR mutations

N	EGFR	RR (%)	PFS (months)	OS (months)
278	Classical exon 19-21	74.1	8.5	19.6
272	Wild-type	16.5	2.0	10.4
11	Exon 20 insertion	0	1.4	4.8
15	G719	53.3	8.1	16.4
15	L861	60.0	6.0	15.2
15	Uncommon mutations	20.0	1.6	11.1

Wu J et al. Clin Cancer Res 2011;17:3812-3821

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)
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)	0.520 (0.378-0.715)	1.185 (0.767-1.829)
EURTAC (EU)	EGFR Mutation + (all)	0.42 (0.27-0.64)	?
OPTIMAL (China)	EGFR Mutation + (all)	0.16 (0.10-0.26)	1.04 (0.69–1.58)
LUX-LUNG 3	EGFR Mutation + (all)	0.58 (0.43–0.78)	?

Survival time of EGFR(mutant) NSCLC

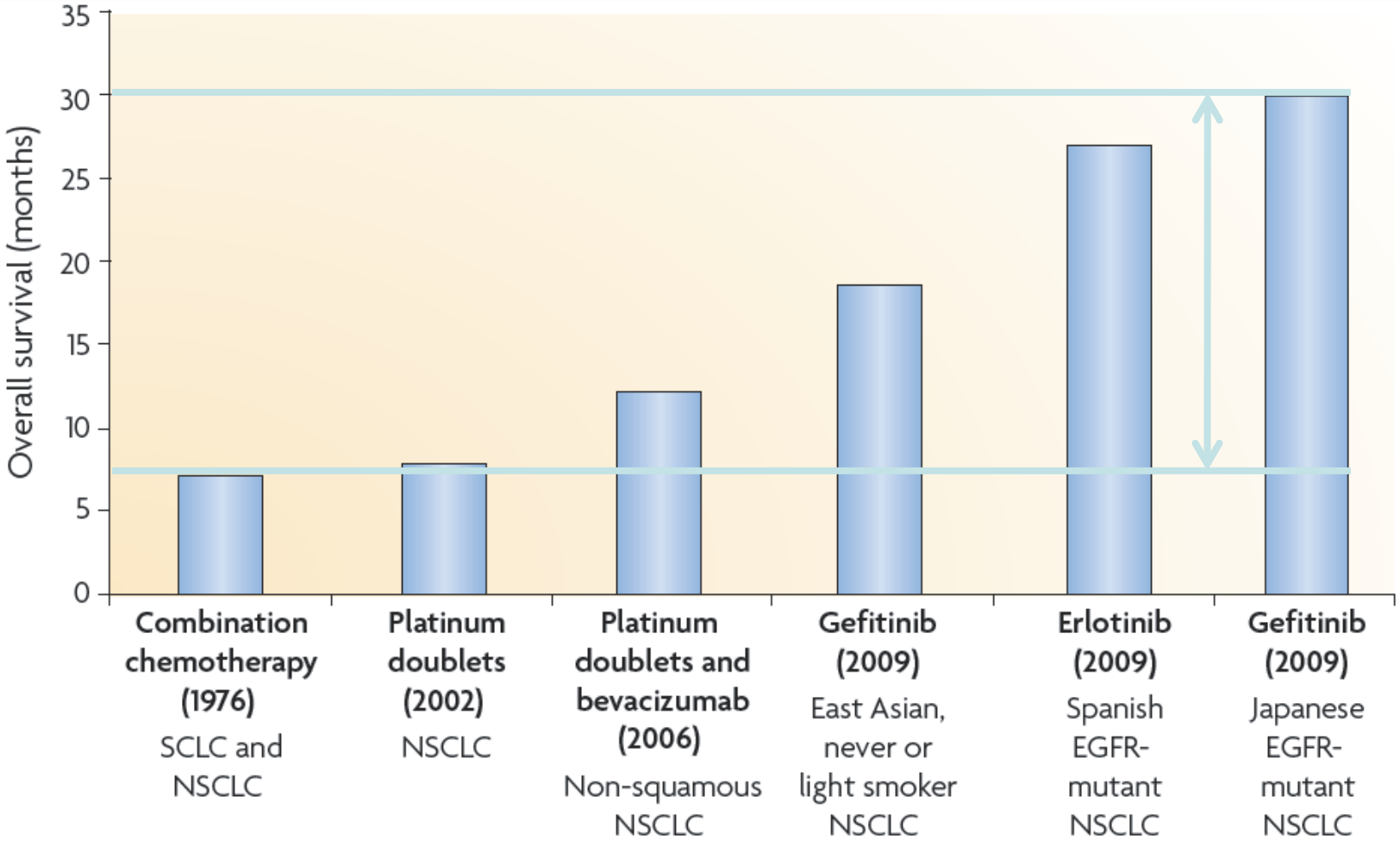
Study	First line	Median OS	Ref
IPASS	Gefitinib	21.6M	Yang CH et. al. Ann Oncol 2010:21;LBA2
	Pac/Car	21.9M	
NEJ002	Gefitinib	27.7M	Inoue A. et al. JCO 2011
	Pac/Car	26.6M	
WJOG3405	Gefitinib	30.9M	Lancet Oncology; 2010:11;121-8
	Doc/cis	Not reached	
First-SIGNAL	Gefitinib	30.6M	Lee JS. et.al. JTO;2009;4: PRS 4
	Gem/cis	26.5M	
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

For EGFR mutant (+) NSCLC
If OS is the same, why EGFR-TKI first?

EGFR-TKI may provide

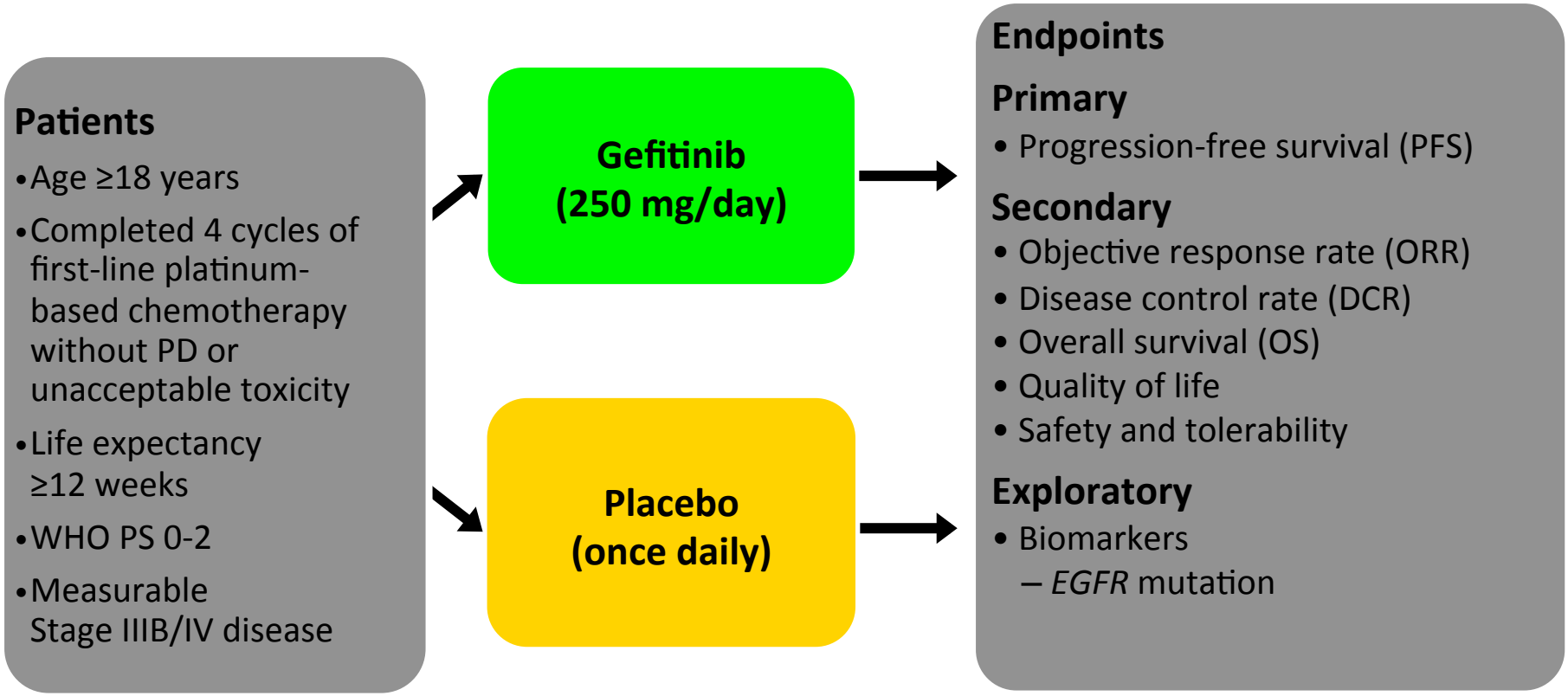
- Higher response
- Better progression-free survival
- Better quality of life and symptom improvement
- Some patients only have chance to use one line of treatment

Progress in the treatment of metastatic lung cancer



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

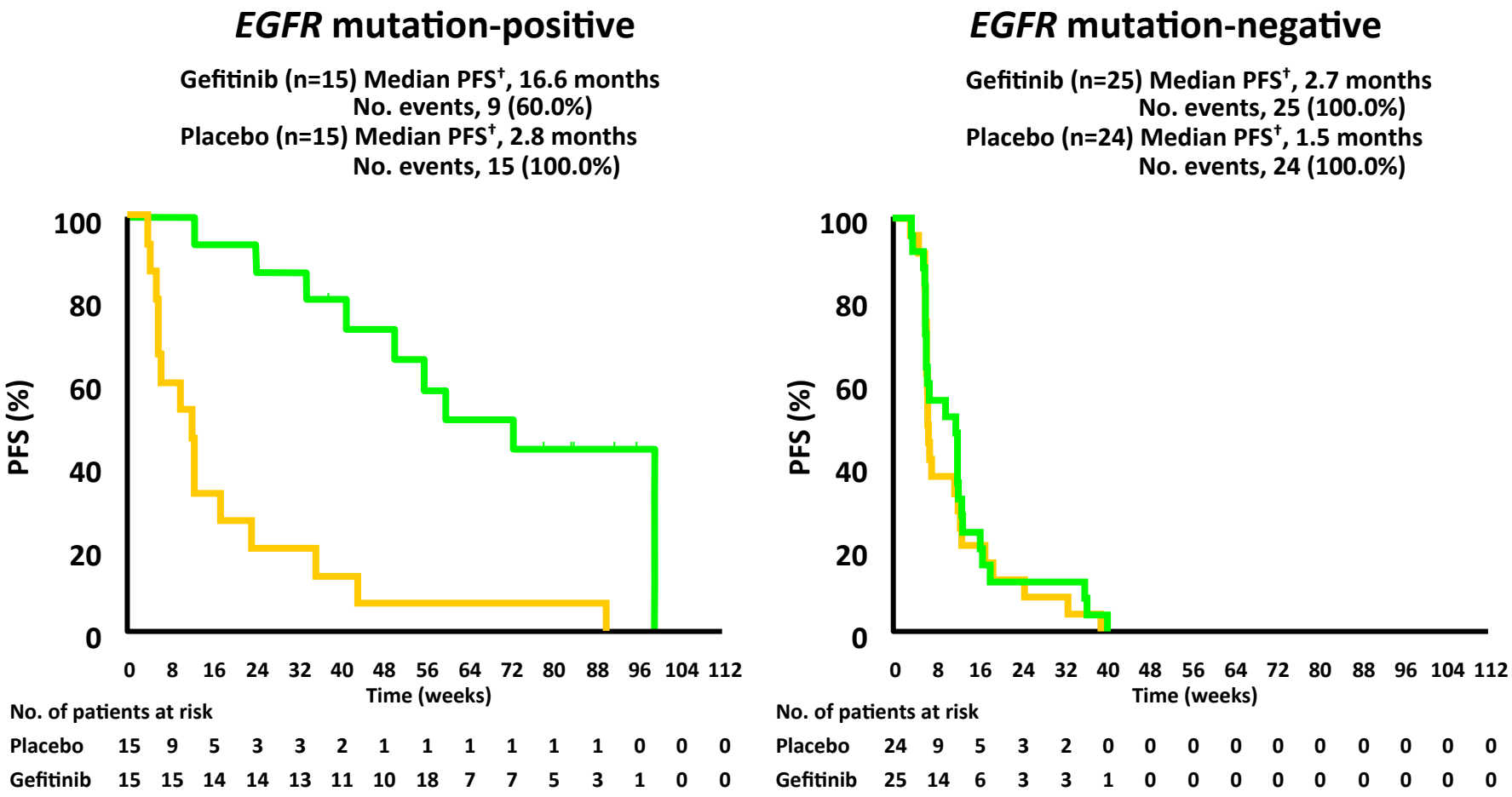
INFORM - Gefitinib as maintenance therapy in locally advanced or metastatic NSCLC



EGFR, epidermal growth factor receptor; PD, progressive disease
PS, performance status; WHO, World Health Organization

Zhang L. et al. Proc. ASCO 2011 # LBA 7511

Progression-free survival by *EGFR* mutation status

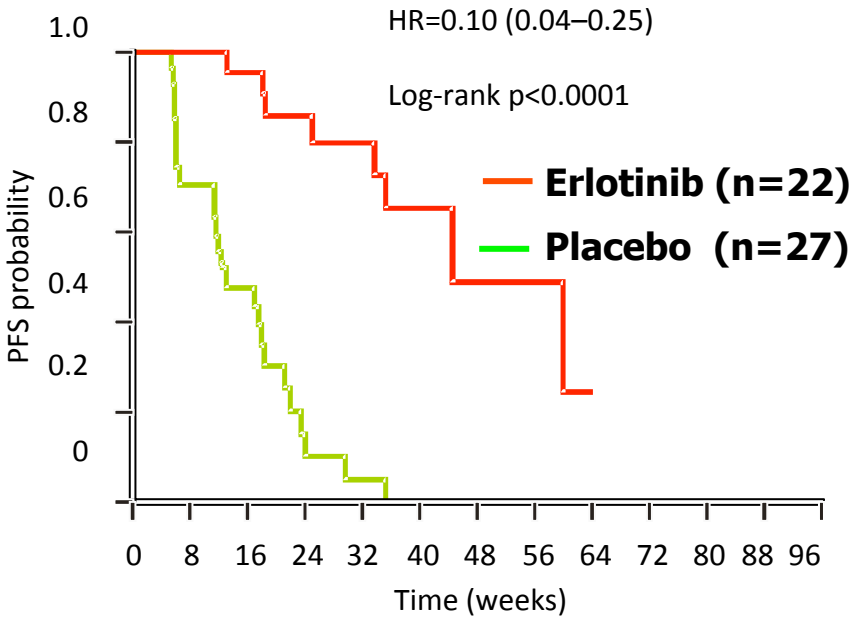


†Estimated using the Kaplan-Meier method
HR <1 implies a lower risk of progression on gefitinib

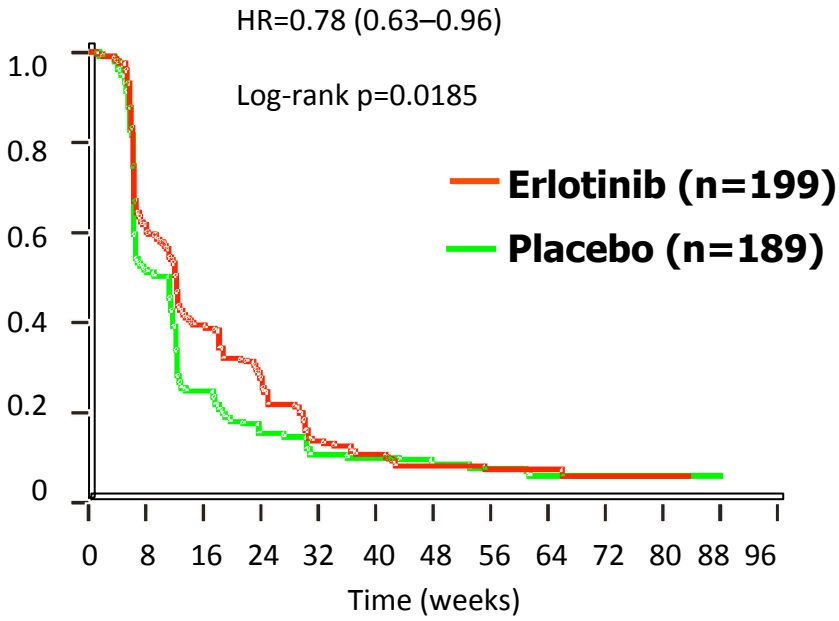
Zhang L. et al. Proc. ASCO 2011 # LBA 7511

SATURN : Largest PFS Benefit with Erlotinib in Patients with *EGFR* Mutated Tumours

EGFR mutation+



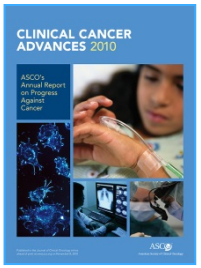
EGFR wild-type



Interaction p<0.001

LUNG CANCERS

Major Advances



Crizotinib shows high response rate in patients with lung adenocarcinoma with EML4-ALK translocations

A phase I trial showed that a high percentage of patients with lung adenocarcinoma with a specific *ALK* gene mutation responded to an investigational *ALK* inhibitor,crizotinib. 36 More than half of these patients experienced some tumor shrinkage.

Phase I trials are typically aimed at gauging toxicity of an experimental agent and rarely show dramatic clinical activity. When the *ALK* gene fisse with another gene, it promotes lung cancer cell growth by encoding the production of a tumor-specific protein called anaplastic lymphoma kinase (ALK), an enzyme that is instrumental to cancer cell growth and development.Crizotinib,which is taken orally, inhibits the *ALK* enzyme. About one in 20 patients with lung cancer, or approximately 11,000 people, in the United States are estimated to be diagnosed with *ALK*-positive lung cancer each year.

In the study, more than 90% of the 82 patients enrolled responded to the drug; either their disease stabilized, or there was some tumor shrinkage.

On the basis of these findings, phase III trials comparing crizotinib to chemotherapy are ongoing.

Bang Y, Kwak EL, Shaw AT, et al: Clinical activity of the oral *ALK* inhibitor PF-02341066 in *ALK*-positive patients with non-small cell lung cancer(NSCLC).
J Clin Oncol 28:6s, 2010 (suppl; abstr 3)

Crizotinib Selectivity Profile

Upstate 102 kinase

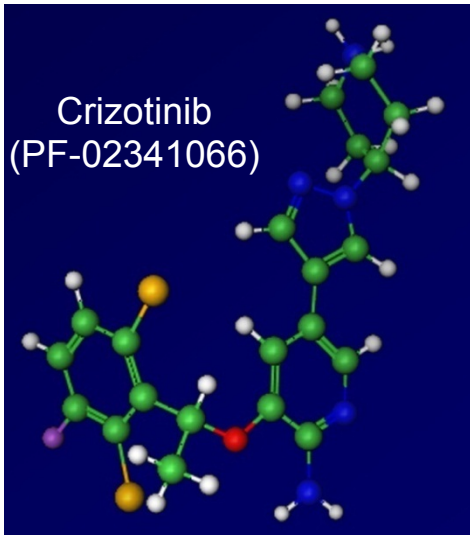
Kinase	% Inhibition
Met(h)	94
Tie2(h)	103
TrkA(h)	102
ALK(h)	100
TrkB(h)	100
Abl(T315I)(h)	98
Yes(h)	96
Lck(h)	95
Rse(h) [SKY]	94
Axl(h)	93
Fes(h)	93
Lyn(h)	93
Arg(m)	91
Ros(h)	90
CDK2/cyclinE(h)	87
Fms(h)	84
EphB4(h)	80
Bmx(h)	79
EphB2(h)	77
Fgr(h)	73
Fyn(h)	68
IR(h)	64
CDK7/cyclinH/MAT1(h)	58
cSRC(h)	58
IGF-1R(h)	56
Aurora-A(h)	54
Syk(h)	52
FGFR3(h)	50
PKCμ(h)	50
BTK(h)	35
CDK1/cyclinB(h)	25
p70S6K(h)	24
PRK2(h)	22
PAR-1Bα(h)	21
PKBß(h)	21
Ret(h)	21
GSK3ß(h)	18
FIt3(h)	17
MAPK1(h)	17
ZAP-70(h)	17
Abl(h)	16
c-RAF(h)	16
PKD2(h)	15
ROCK-II(h)	14
Rsk3(h)	14
GSK3α(h)	11
CDK5/p35(h)	10
PDGFRα(h)	10
Rsk1(h)	7
SGK(h)	6
CHK1(h)	5
ErbB4(h)	5
Rsk2(h)	5
JNK1α1(h)	4
PKBα(h)	4
Blk(m)	3
CDK3/cyclinE(h)	3
PKCι(h)	3
PKCδ(h)	3
CDK2/cyclinA(h)	2
PAK2(h)	2
PKCδl(h)	2
Pim-1(h)	1
PKCγ(h)	1
SAPK4(h)	1
CaMKII(r)	0
MKK7ß(h)	0
CaMKIV(h)	-1
CHK2(h)	-1
CK2(h)	-1
JNK2α2(h)	-1
MKK6(h)	-1
CK1δ(h)	-2
PKCα(h)	-2
MAPK2(h)	-3
MEK1(h)	-3
PKCδ(h)	-3
PKCε(h)	-3
Plk3(h)	-3
PKCδII(h)	-5
MSK1(h)	-6
PDGFRß(h)	-6
PKCζ(h)	-6
SAPK3(h)	-6
MAPKAP-K2(h)	-7
PKA(h)	-7
AMPK(r)	-9
CDK6/cyclinD3(h)	-9
CSK(h)	-9
SAPK2a(h)	-9
JNK3(h)	-10
PKBγ(h)	-10
IKKα(h)	-11
NEK2(h)	-11

13 kinase “hits” <100X selective for c-MET

Cellular selectivity on 10 of 13 relevant hits

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	20	2X
RON	298	34X
	189	22X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

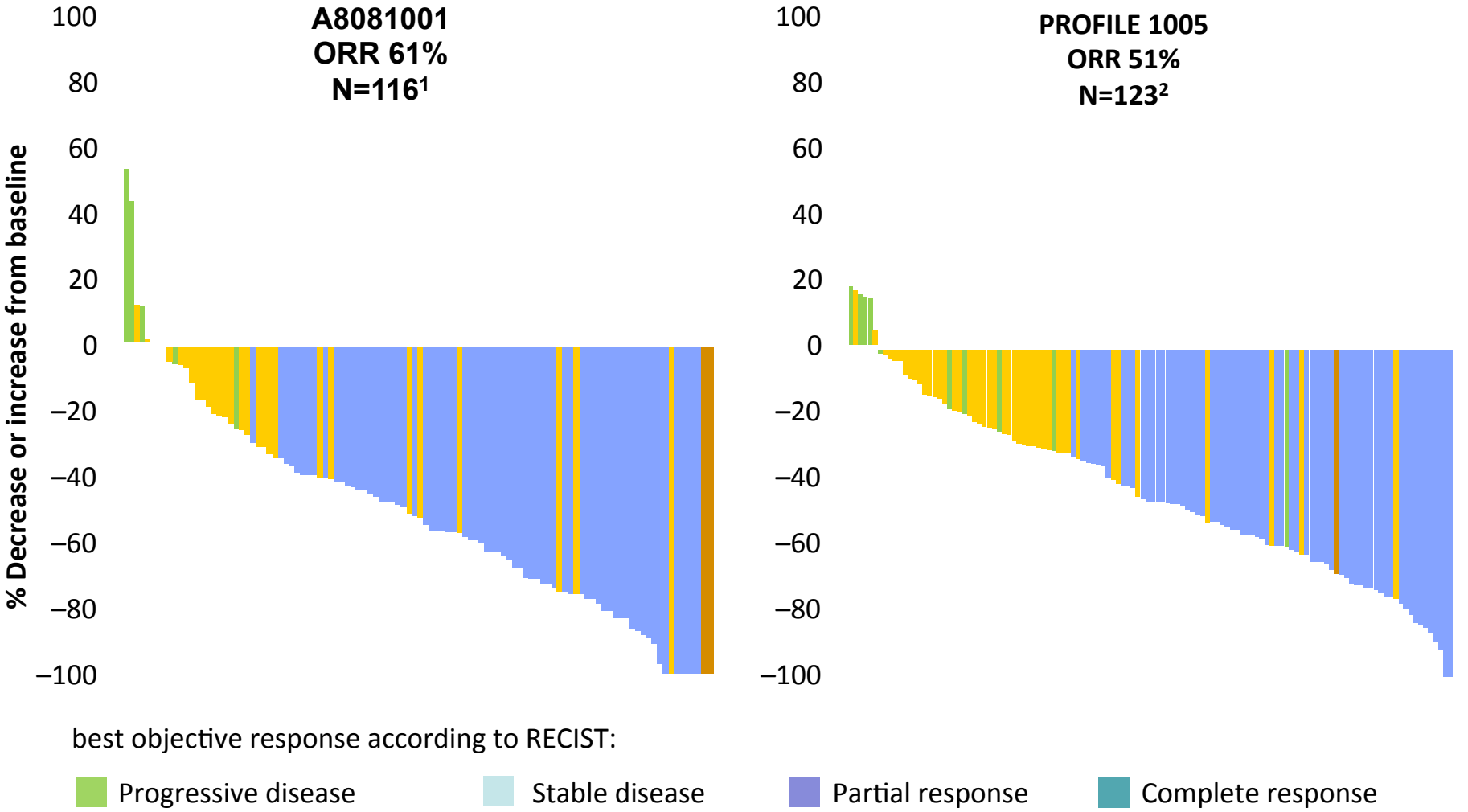
* The cellular kinase activities were measured using ELISA capture method



Selectivity findings

- **Crizotinib – ALK and c-MET inhibition at clinically relevant dose levels**
- **Crizotinib – low probability of pharmacologically relevant inhibition of any other kinase at clinically relevant dose levels**

Tumour responses to crizotinib by patient

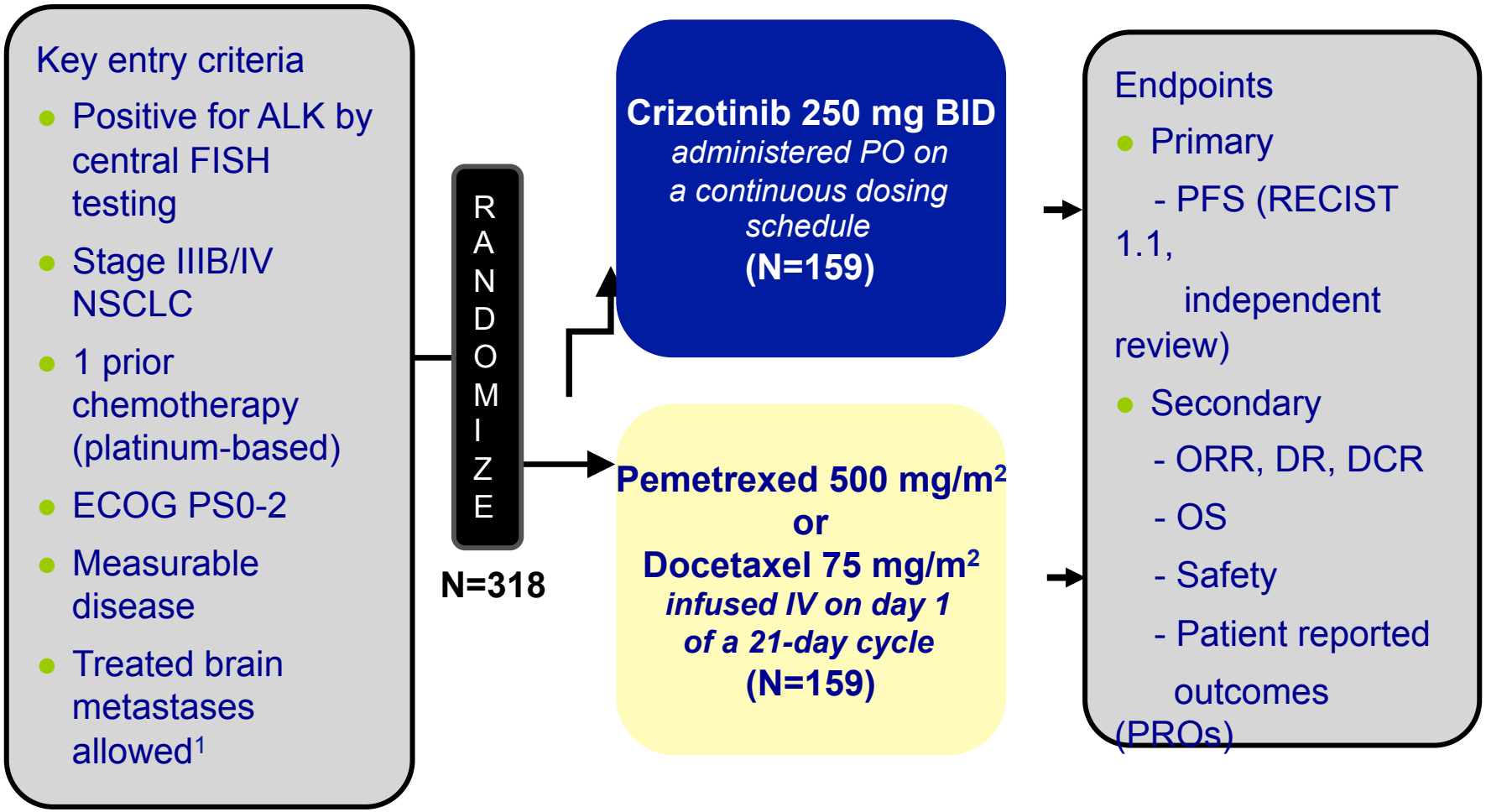


Progression-Free Survival (PFS) from a Phase 1 Study of Crizotinib (PF-02341066) in Patients with *ALK*-Positive Non-Small Cell Lung Cancer (NSCLC).

P

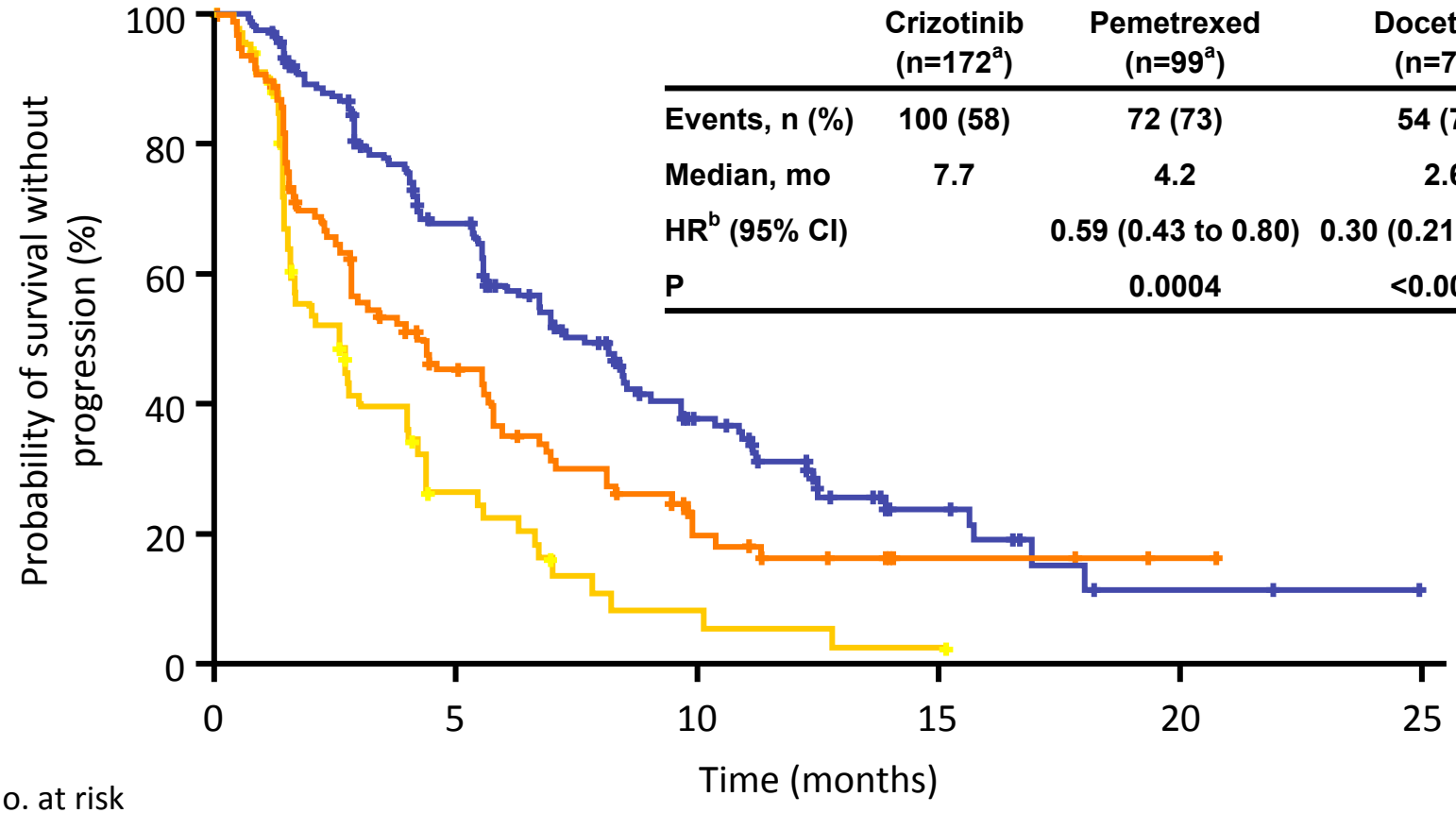
A Global Phase 2 Study Including Efficacy, Safety, and Patient-reported Outcomes with Crizotinib in Patients with ALK-positive Non-small Cell Lung Cancer.

Phase 3 Study: PROFILE 1007



Shaw A. et al. Proc. ESMO 2012

PFS of Crizotinib vs Pemetrexed or Docetaxel



	Crizotinib (n=172[a])	Pemetrexed (n=99[a])	Docetaxel (n=72[a])
Events, n (%)	100 (58)	72 (73)	54 (75)
Median, mo	7.7	4.2	2.6
HR[b] (95% CI)		0.59 (0.43 to 0.80)	0.30 (0.21 to 0.43)
P		0.0004	<0.0001

No. at risk						
Crizotinib	172	93	38	11	2	0
Pemetrexed	99	36	12	3	1	0
Docetaxel	72	13	3	1	0	

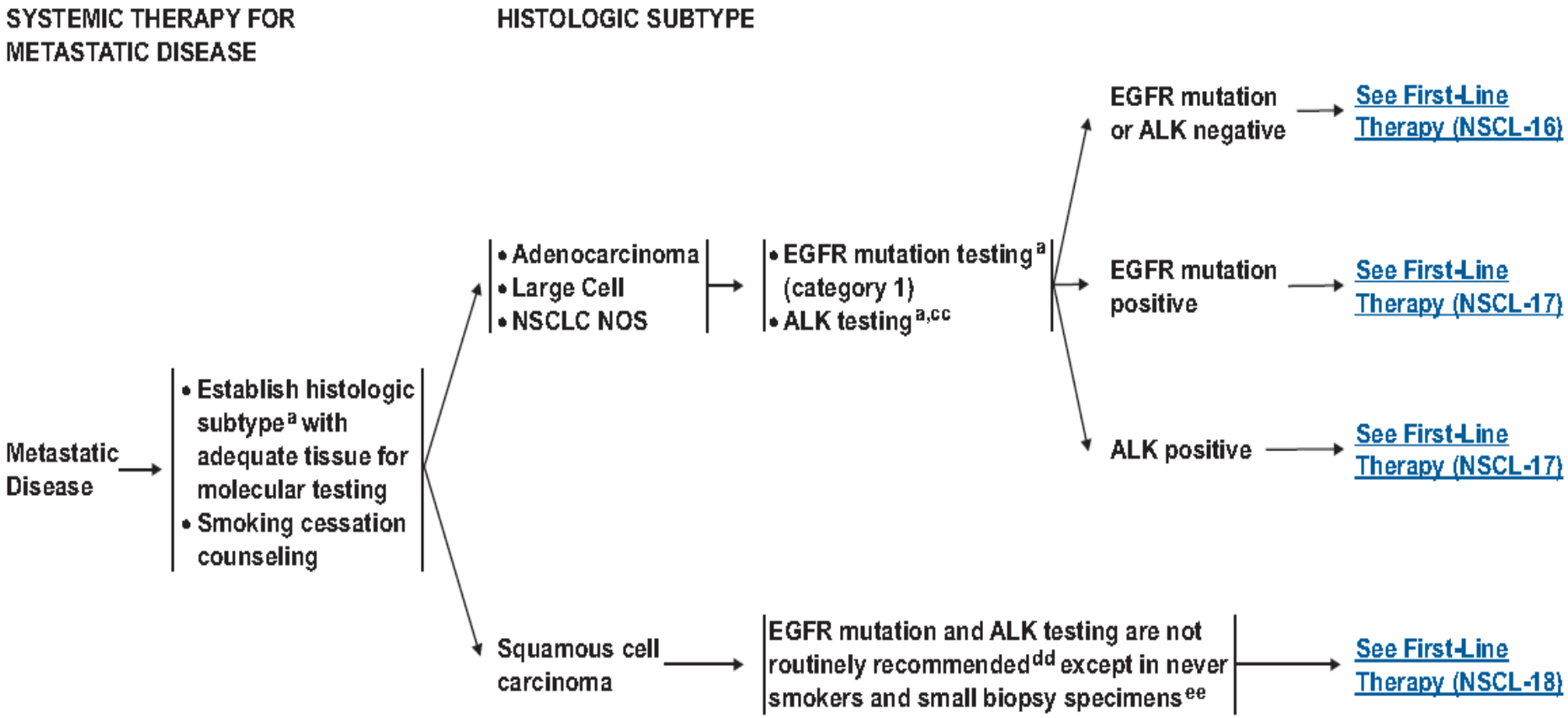
Shaw A. et al. ESMO 2012

New Molecular Targets in Lung Cancers discovered in 2012

Target	Author	Year	Sensitive to Kinase Inhibition ?	Mutually Exclusive?	Incidence
ROS1	Bergethon	2012	Yes	Yes	2%-18/1073
KIF5B-RET	Seok	2011	?	Yes	14%-5/21
HER2 Extracellular Domain Mutations	Gruelich	In press	Yes	Yes	?

National Comprehensive Cancer Network®

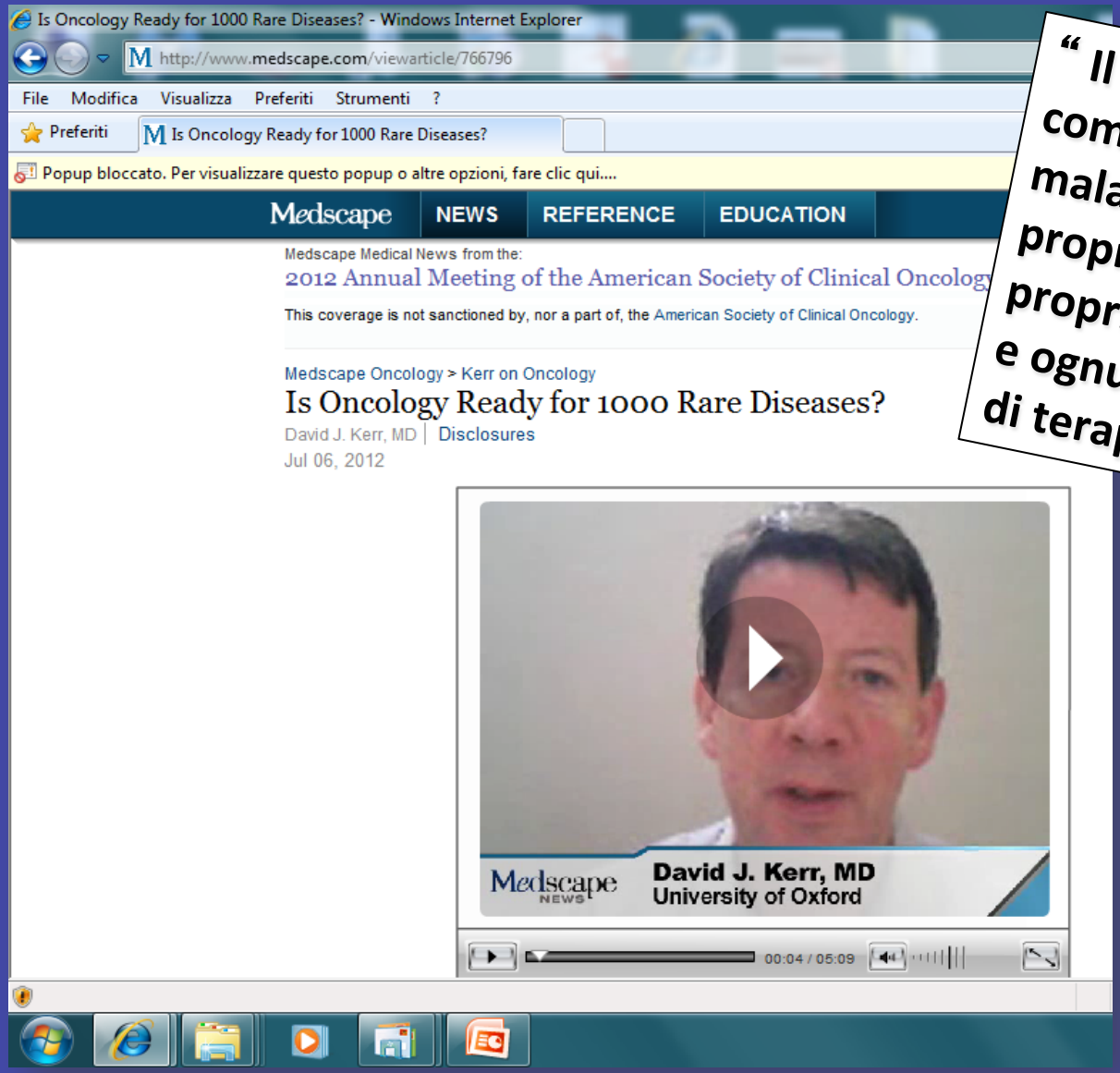
NCCN Guidelines Version 2.2013
Non-Small Cell Lung Cancer



Summary

- **Stopping smoking is the most cost-effective therapy in reducing lung cancer mortality**
- Growing evidence of genomic abnormalities in all the histotypes of non-small cell lung cancer, some of them already ‘drugable’
- *EGFR* Mut+ lung cancer should be treated with and EGFR TKI
- Therapeutic choices based on histology are the current standard of care for the majority of our patients
- The definition of homogeneous genetic subgroups of tumours and the search for individualised approaches is the way to substantially increase survival expectancy in this disease

Is Oncology ready for 1000 rare diseases?”



“ Il cancro sarà sempre più compartimentalizzato in 1000 malattie rare, ognuna con il suo proprio fenotipo, ognuna con il proprio insieme di biomarcatori, e ognuna con il proprio portfolio di terapie mirate. ”

Conversazione con Alberto Sobrero

Oncologia Medica San Martino ,Genova

Le sfide Future. Ovvero come e verso dove ,dovrebbe muoversi la ricerca clinica?

Ci sono due direzioni da perseguire :

la prima è l'identificazione di determinanti patogenetici della malattia verso cui è possibile indirizzare inibitori specifici.

Questa è la strategia più politicamente corretta.

E' quella del futuro che mira a dare fortissimi benefici per pochissimi pazienti.

Fuori moda ,ma finora molto più produttiva è la direzione di perseguire piccoli benefici per tutti i pazienti

www.oncologiacosenza.com

"Il minimo movimento interessa tutta la natura: il mare intero cambia per una pietra"
Blaise Pascal

Grazie per l'Attenzione

candida.mastroianni@alice.it