

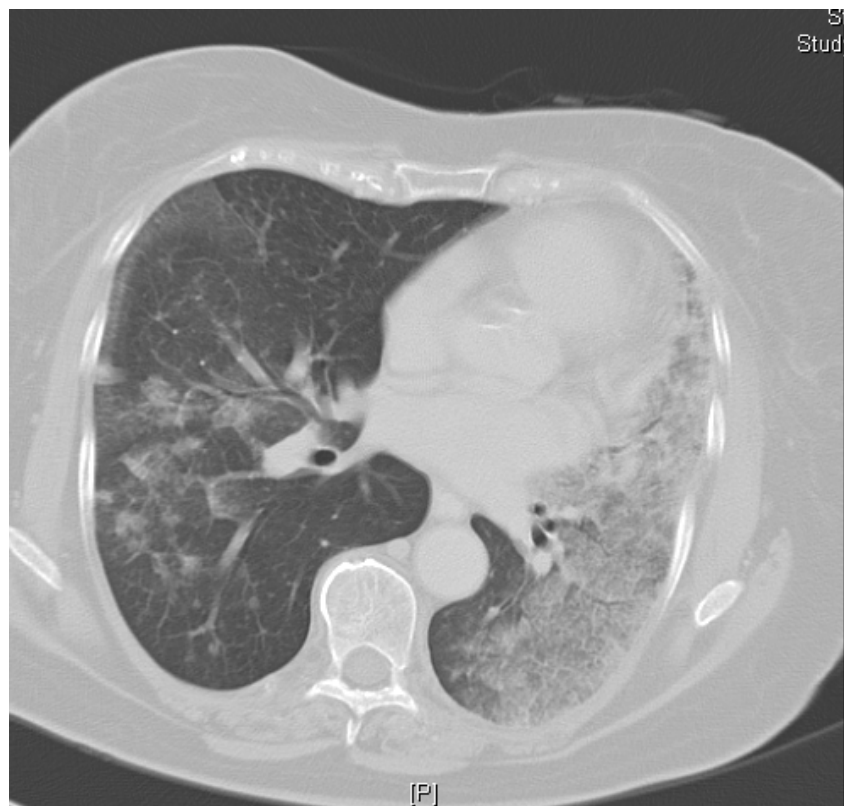
EGFR in Lung Cancer

Bruce E. Johnson, MD
Dana-Farber Cancer Institute,
Brigham and Women's Hospital and
Harvard Medical School

EGFR in Lung Cancer

- Discovery of the Association between Response to Gefitinib and Erlotinib and EGFR Mutations
- Validation in Prospective Phase II Clinical Trials
- Confirmation in Phase III Clinical Trials

Woman with Adenocarcinoma Treated with Gefitinib with Exon 19 EGFR Deletion Mutation



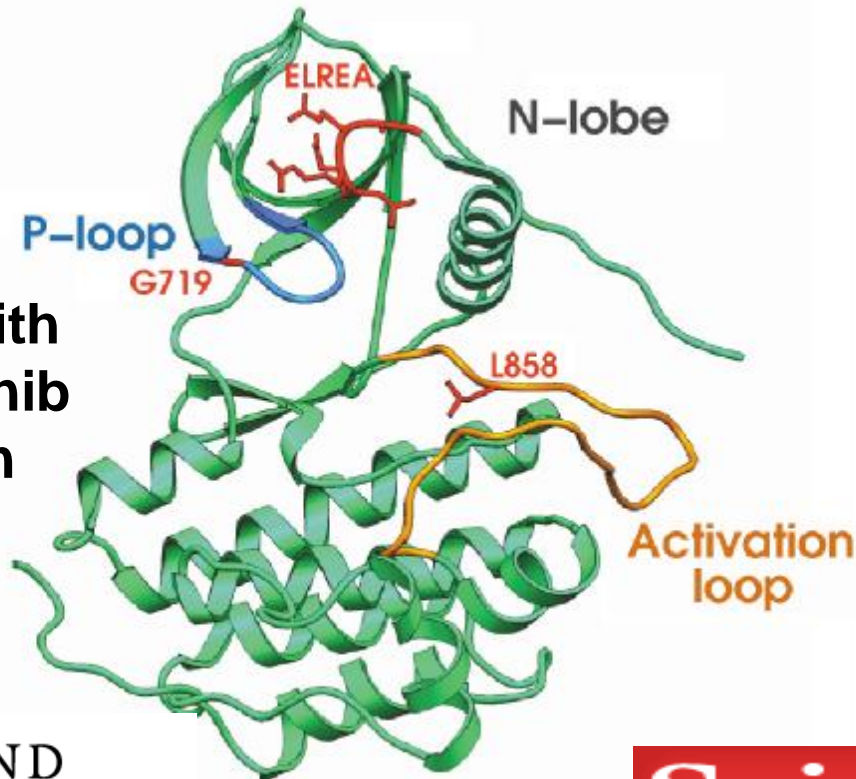
January 2002



October 2004

Epidermal Growth Factor Receptor Mutations

13 of 14 Patients with Response to Gefitinib Had EGFR Mutation



The NEW ENGLAND
JOURNAL of MEDICINE

Lynch et al 2004

Science

Paez et al. 2004

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Phase II Trial of Women with Adenocarcinoma with Minimal Smoking History

- Women
- Adenocarcinoma Histology
- Adequate Tissue for Analysis
- Stopped Smoking for More than 1 Year

Erlotinib

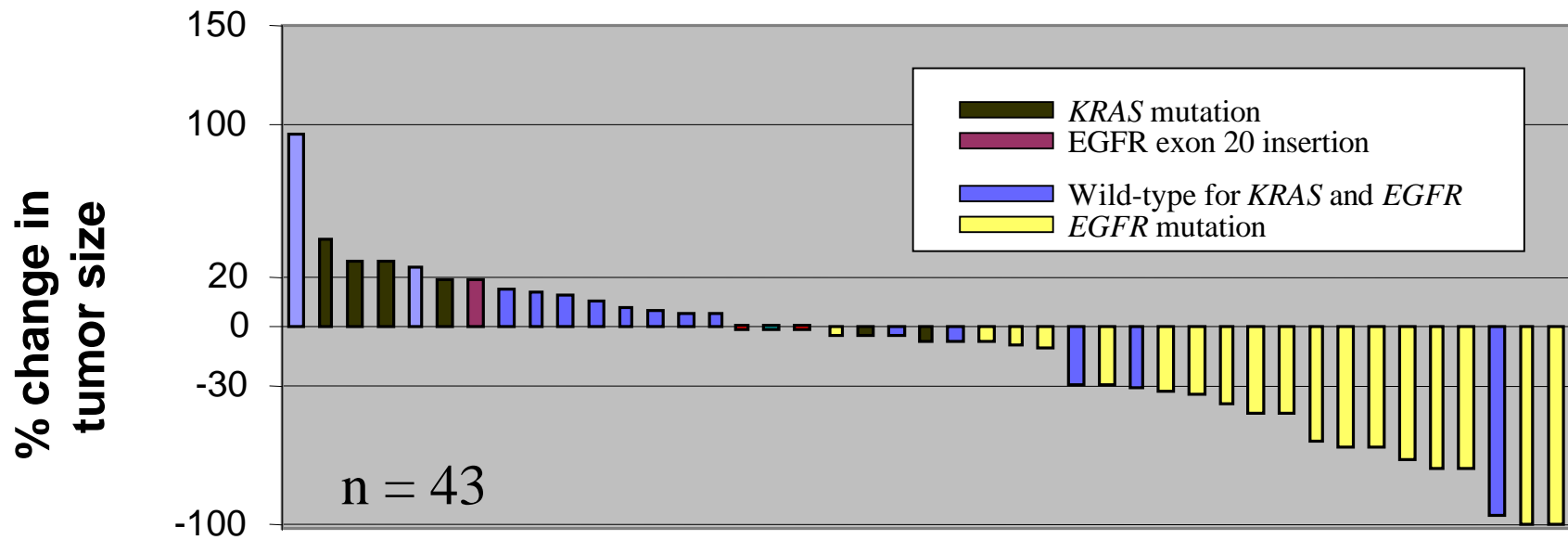


**150 mg
daily**

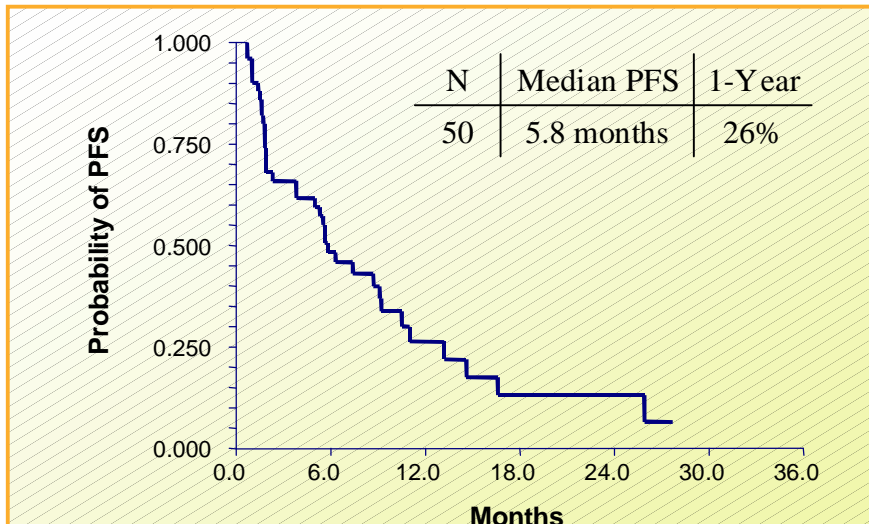
Continuous

Continue until
disease
progression or
development of
toxicity

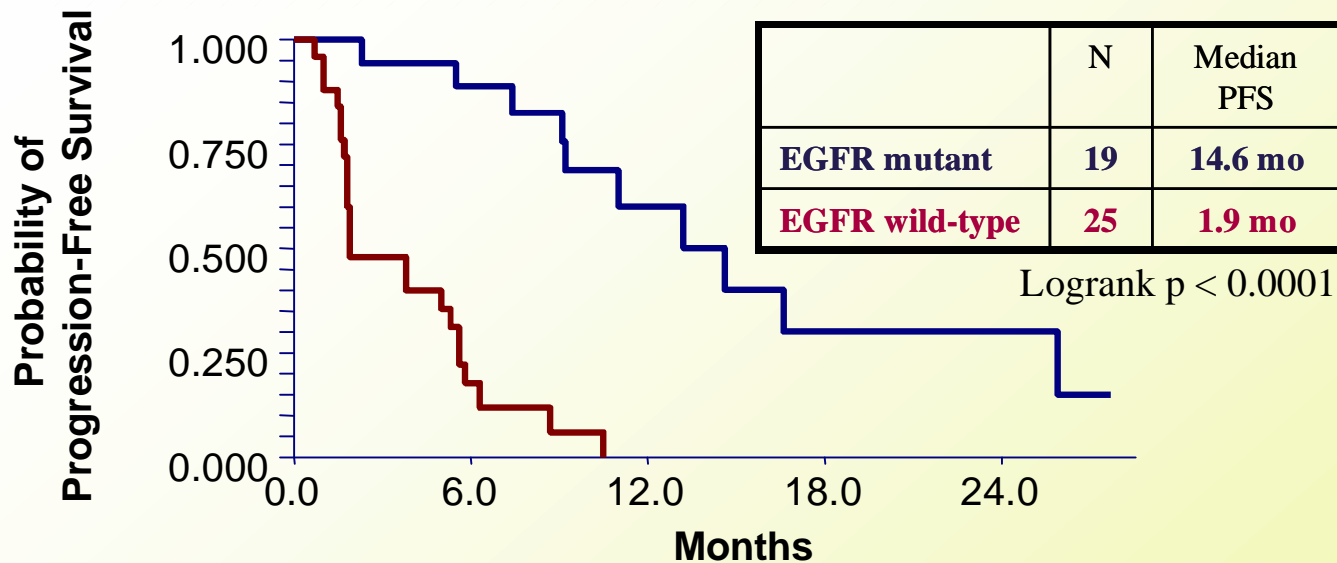
Waterfall Plot: Mutation Status



Clinical Versus Genomic Determinants



Clinically enriched patients



Genomically defined patients

Phase II Trials for Patients Given Gefitinib or Erlotinib as their Initial Therapy

- Non-Small Cell Lung Cancer
- No Previous Chemotherapy Treatment
- Tumor Tissue Available for Testing

Erlotinib 150 mg day



Gefitinib 250 mg day

Continue until disease progression or development of toxicity

EGFR Mutation Database

- Patients from five clinical trials that have explored the use of first-line therapy with an EGFR-tyrosine kinase inhibitor (erlotinib or gefitinib) were included in the database.
- Patients were eligible for inclusion in the database if they had undergone testing for *EGFR* and/or *KRAS* mutation analysis.

Trial/Author	Patient selection	1st-line pts treated, N	1st-line pts tested for <i>EGFR</i> , N	1st-line pts tested for <i>KRAS</i> , N
Giaccone et al ¹	Unselected	53	28	26
Jackman et al ²	Pts \geq age 70	80	43	41
Miller et al ³	BAC histology	75	57	56
Sequist et al ⁴	Known EGFR mutations	31	31	0
Jackman et al	Women, adenoCA, not current smokers	78*	63	52

¹Giaccone et al, Clin Canc Res 2006

²Jackman et al, JCO 2007

³Miller et al, JCO 2008

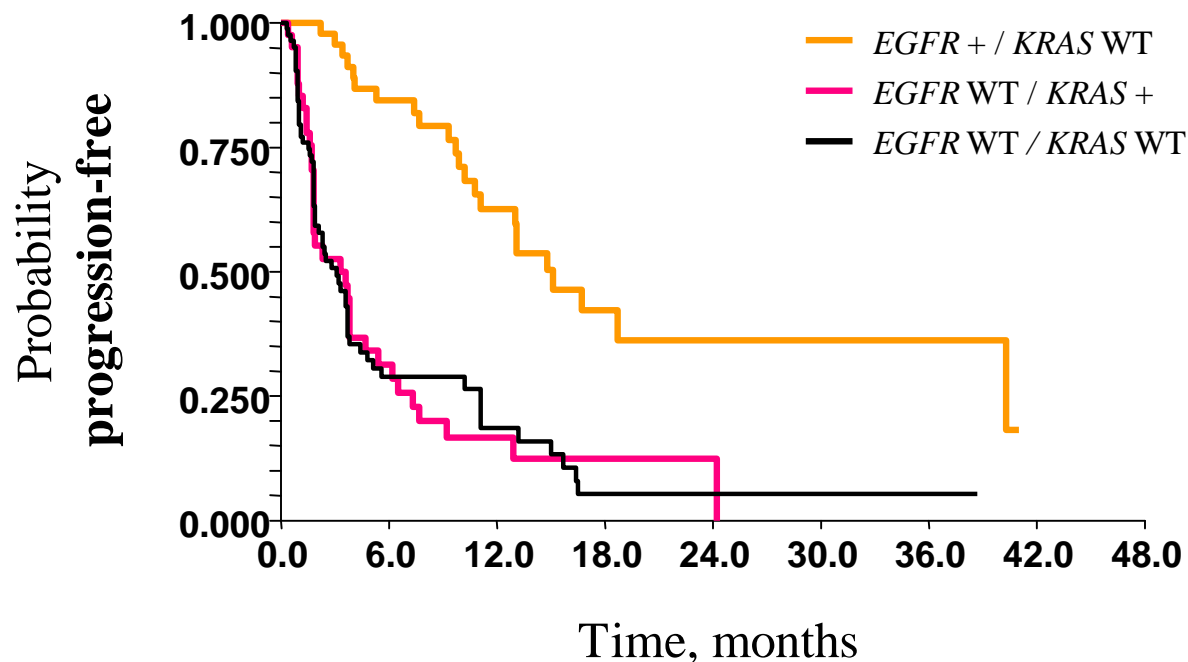
⁴Sequist et al, JCO 2008

⁵Jackman et al, ASCO 2007

Results: Outcomes based on *EGFR* and *KRAS* status

Clinical Outcomes: Time to Progression

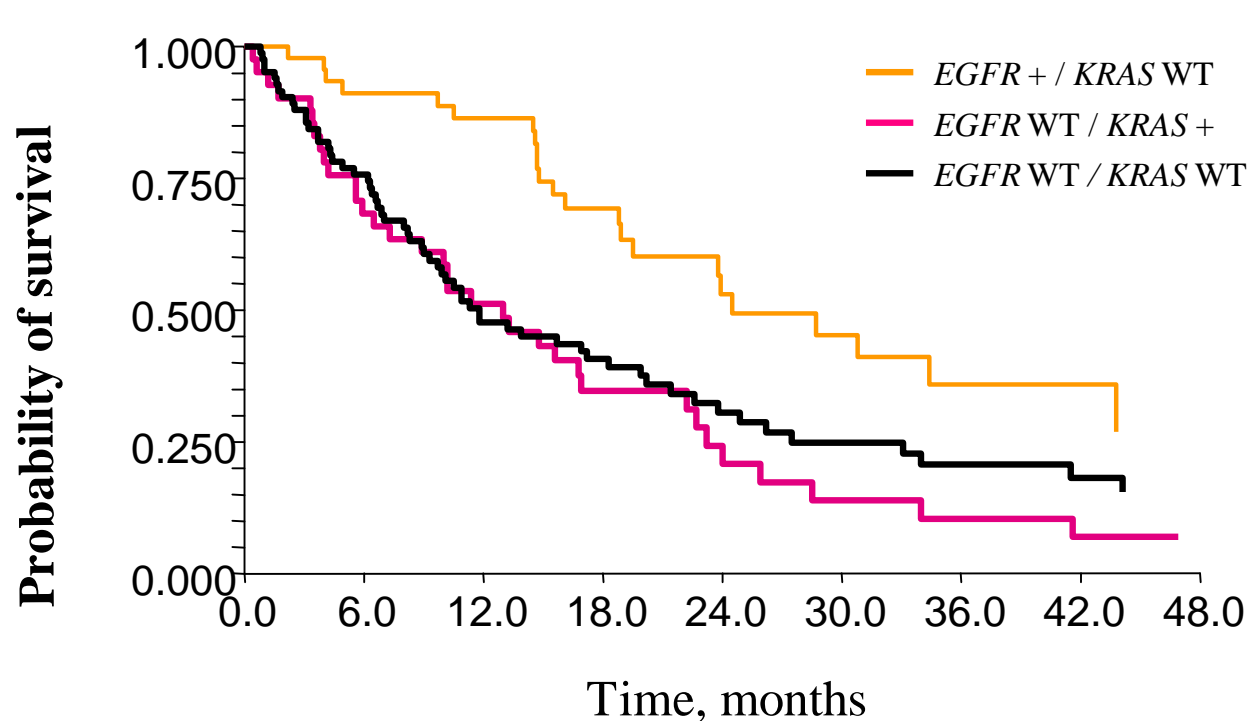
	<i>EGFR</i> + / <i>KRAS</i> WT	<i>EGFR</i> WT / <i>KRAS</i> +	<i>EGFR</i> WT / <i>KRAS</i> WT	
N	46	41	83	p
Median TTP	15.1	3.3	3.1	< .0001



Results: Outcomes based on *EGFR* and *KRAS* status

Clinical Outcomes: Overall Survival

	<i>EGFR</i> + / <i>KRAS</i> WT	<i>EGFR</i> WT / <i>KRAS</i> +	<i>EGFR</i> WT / <i>KRAS</i> WT	
N	46	41	83	P
Median OS	24.5	13.0	11.8	.002



Phase II Trials for Patients with EGFR Mutations

- Non-Small Cell Lung Cancer
- Prospectively Identified Mutation in EGFR Mutation

Erlotinib 150 mg day



Gefitinib 250 mg day

Continue until disease progression or development of toxicity

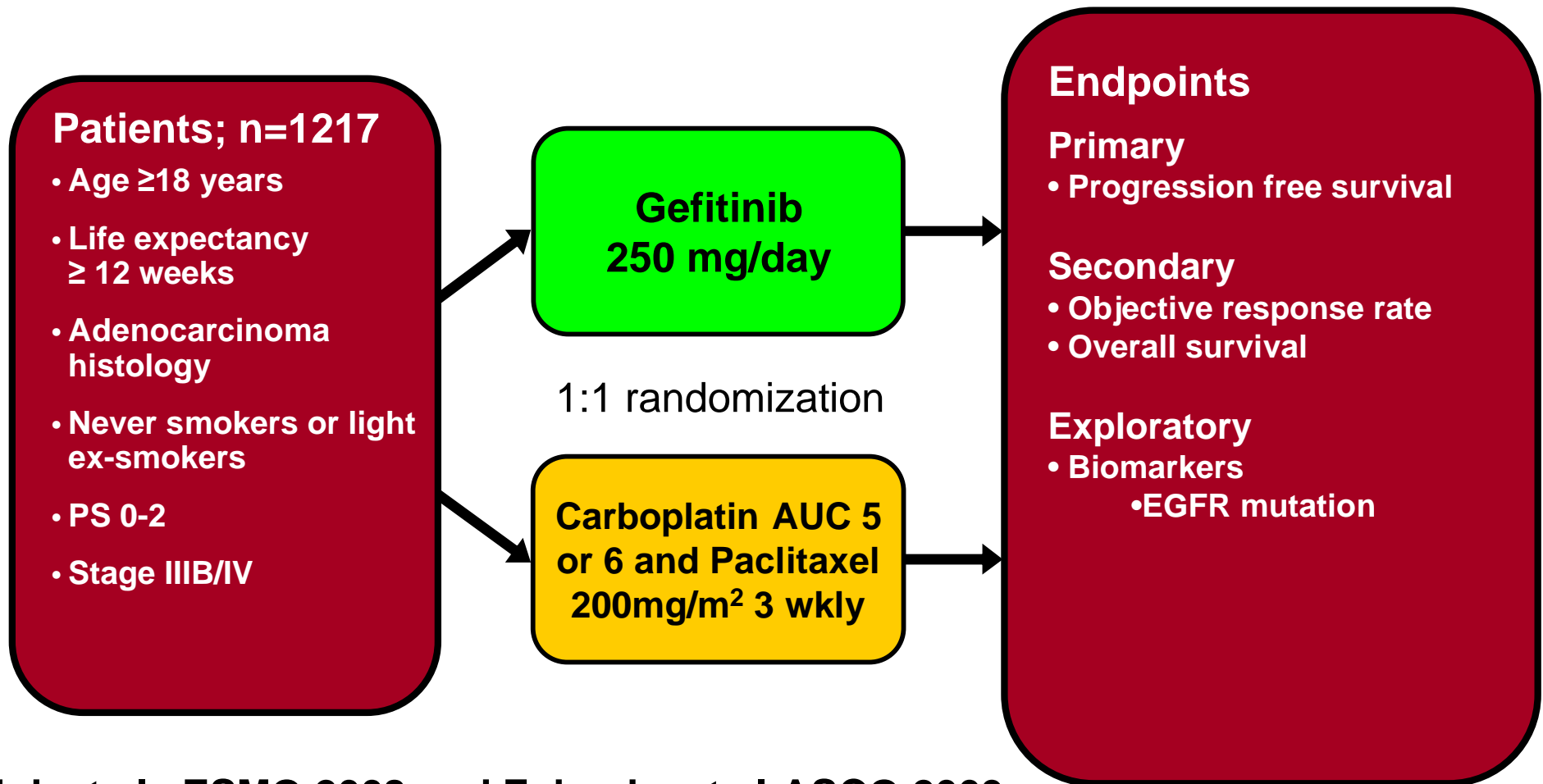
Phase II Trials for Patients with EGFR Mutations

Study	Total tested	Total treated	Drug	Response rates in mutants	Disease control rate in mutants	PFS/ TTP in mutants (months)	OS in mutants (months)
Sequist et al.	98	31	Gefitinib	55%	94%	9.2	17.5
Massuti et al	2507	217	Erlotinib	64%	82%	14	27
Inoue et al	75	25	Gefitinib	75%	88%	9.7	Not reported
Asahina et al.	82	16	Gefitinib	75%	81%	8.9	Not Reached

EGFR in Lung Cancer

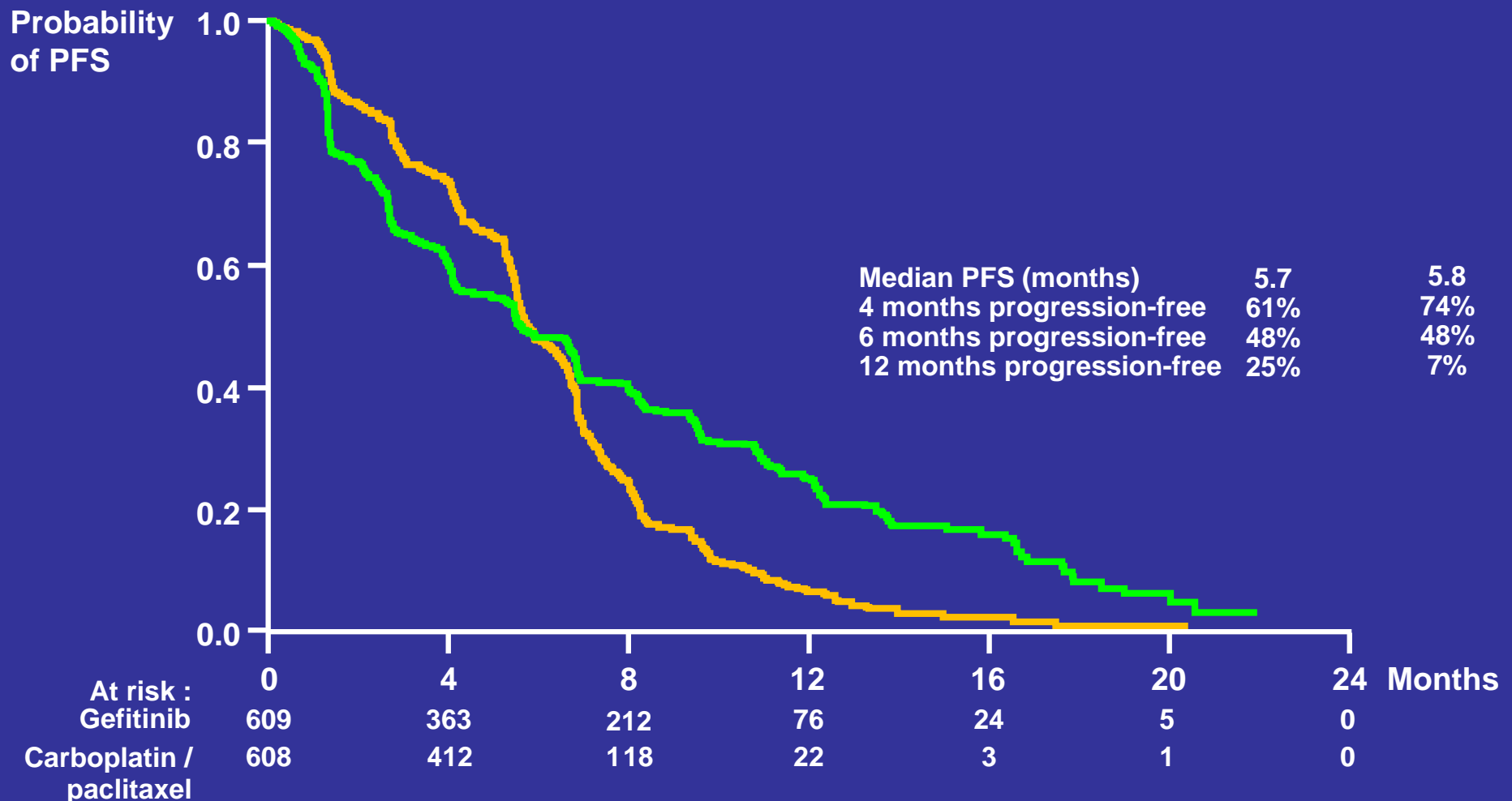
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IPASS Study Design



Mok et al. ESMO 2008 and Fukuoka et al ASCO 2009

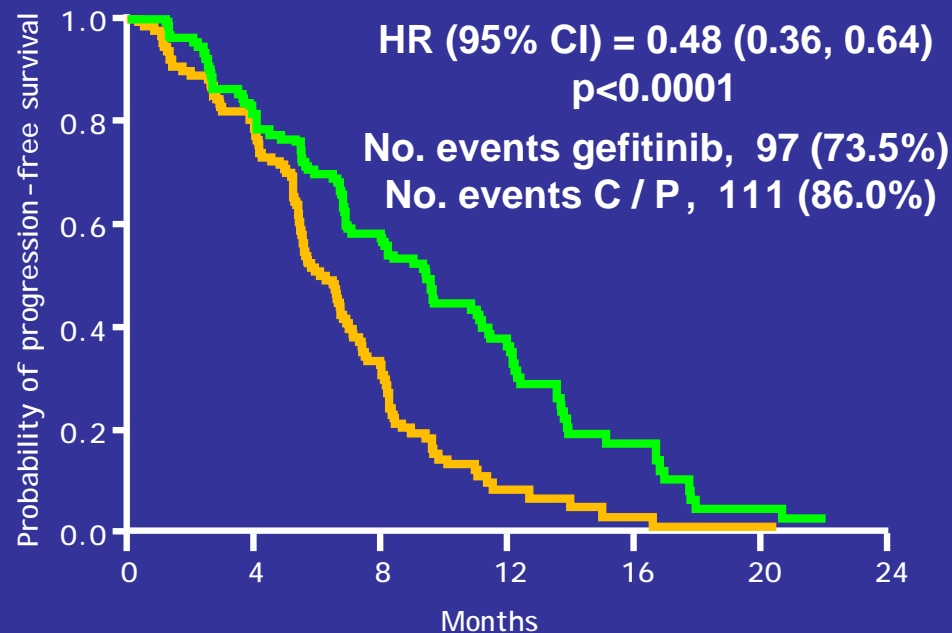
Progression-free survival in 1217 positive and negative patients



Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive

Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)

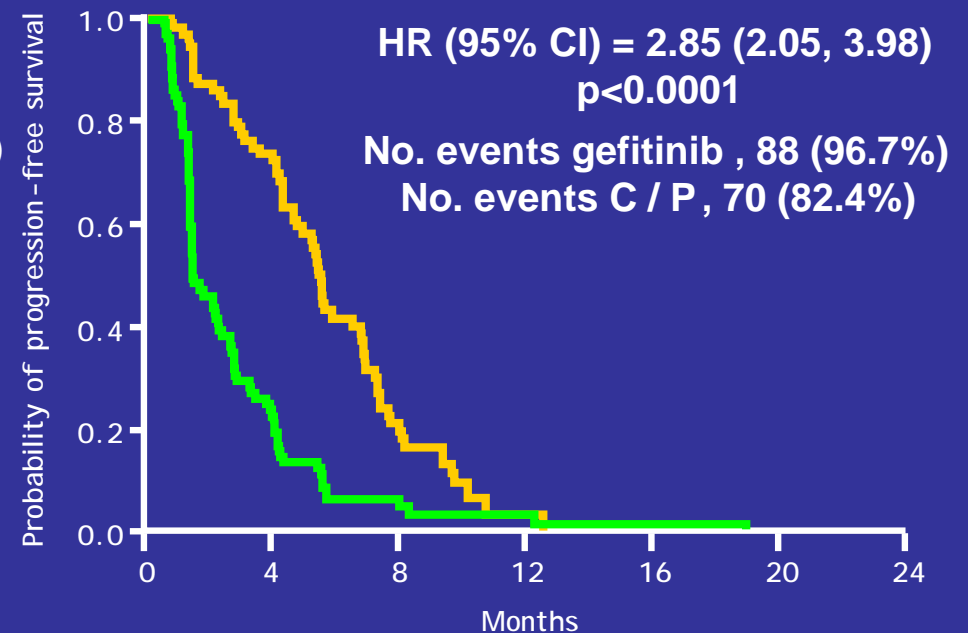


At risk :

Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

EGFR mutation negative

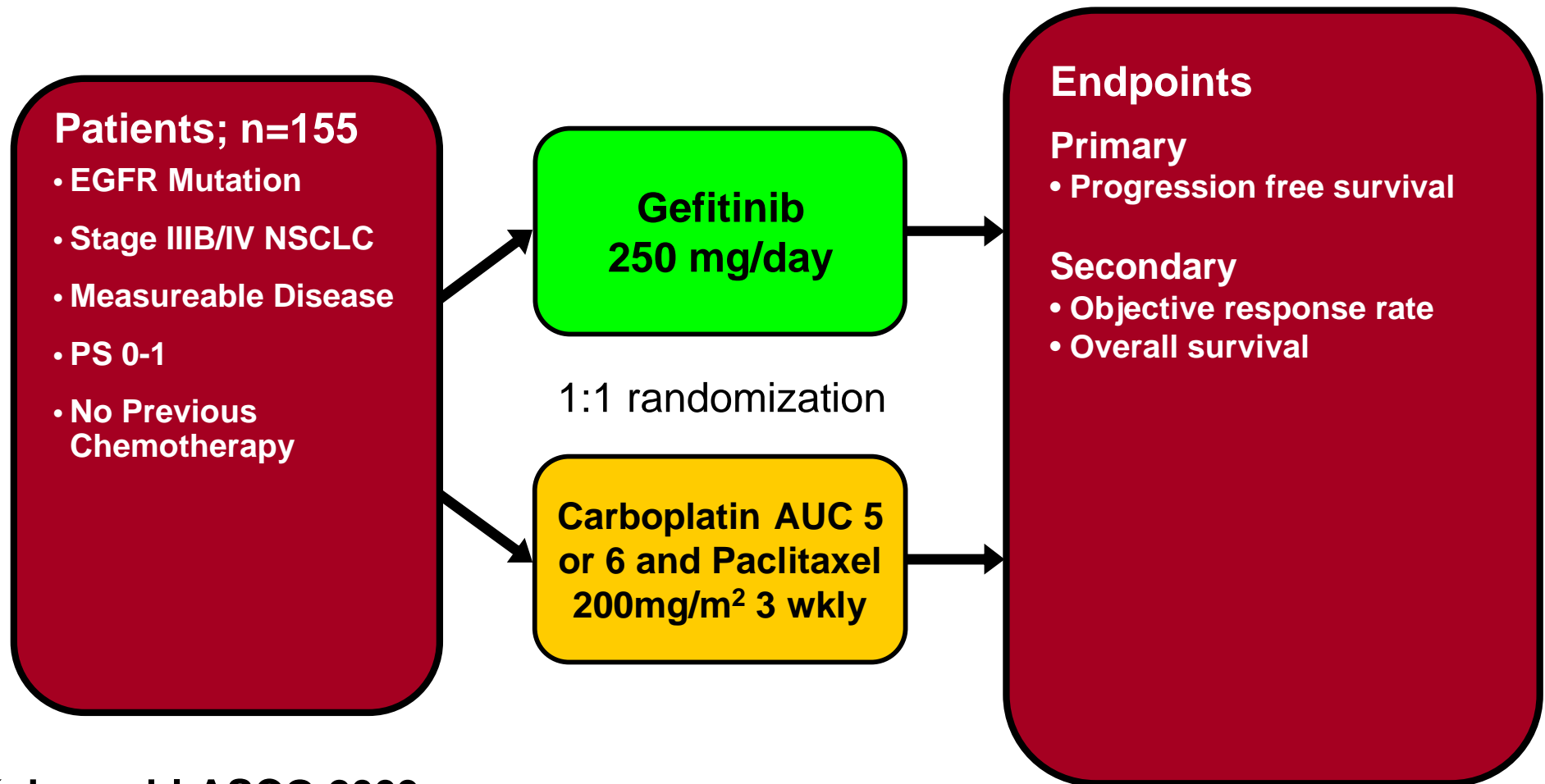
Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)



Gefitinib	91	21	4	2	1	0	0
C / P	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p < 0.0001

Gefitinib versus Combination Chemotherapy

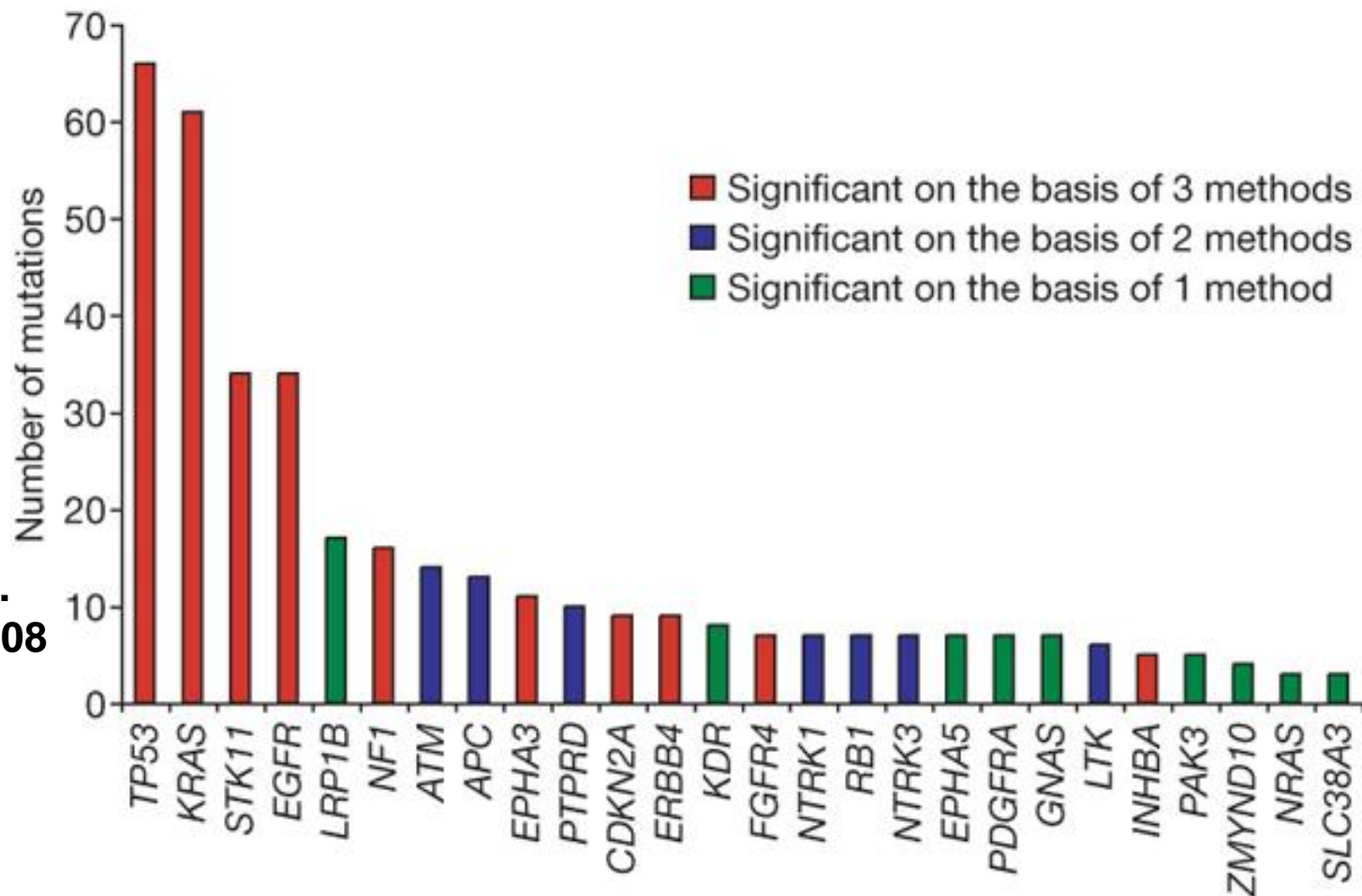


Kobayashi ASCO 2009

Impact of Genomic Changes on Treatment and Outcome of Patients with NSCLC

- **IRESSA (Gefitinib) Recommended for Approval for the Treatment of Non-Small Cell Lung Cancer in Europe**
- **Published date : 23 April 2009**
- **AstraZeneca announced today that the Committee for Medicinal Products for Human Use (CHMP), the scientific advisory committee of the European Medicines Agency (EMA), has issued a positive opinion supporting approval of the targeted oral anti-cancer drug, IRESSA (gefitinib).**
- **The CHMP has recommended the approval of IRESSA for adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (epidermal growth factor receptor-tyrosine kinase), in all lines of therapy**

Somatic Mutations in 188 Adenocarcinomas of Lung



Ding et al.
Nature 2008

Impact of Genomic Changes on Treatment and Outcome of Patients with NSCLC

Genomic Change	Drug	Percentage
EGFR Mutation	Erlotinib & Gefitinib	10
Ins 20 Mutations	PF-299804*	3
EML4-ALK Trans	PF-2341066*	3
MET Amplification	EGFRI +XL184	3
HER2 Amplification	Trastuzumab	2
TOTAL		>20%

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