EGFR en de long

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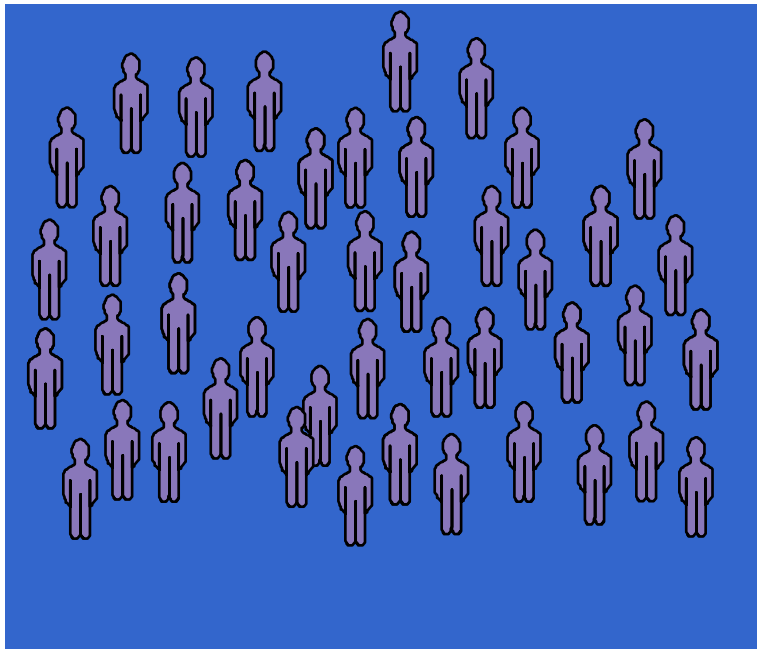
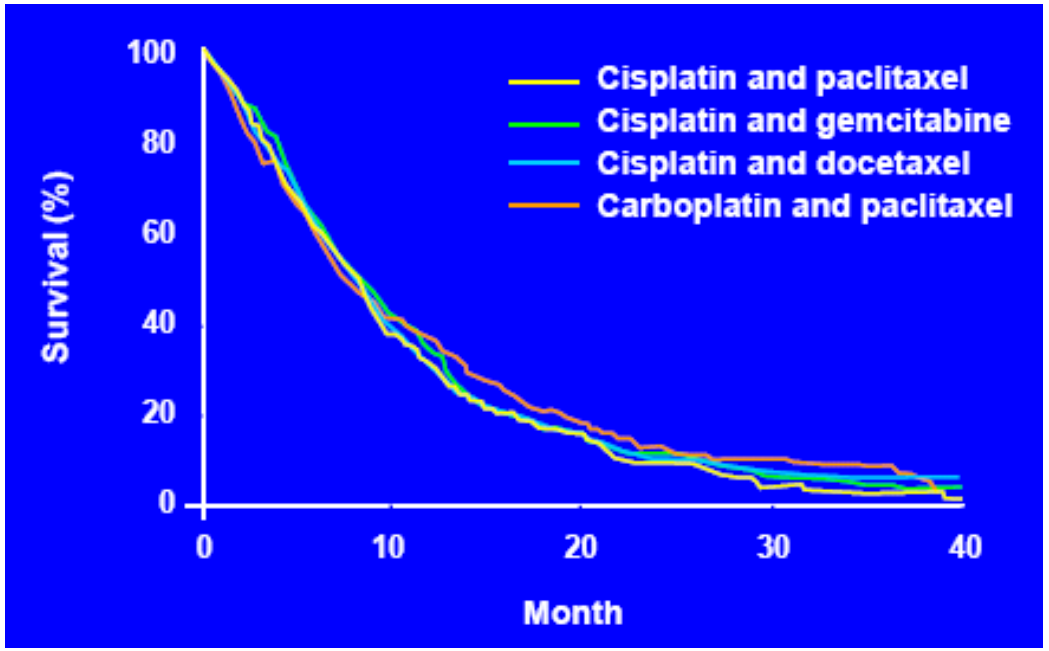
Advanced NSCLC : one disease, one treatment

Doublet chemotherapy is gold standard since years…



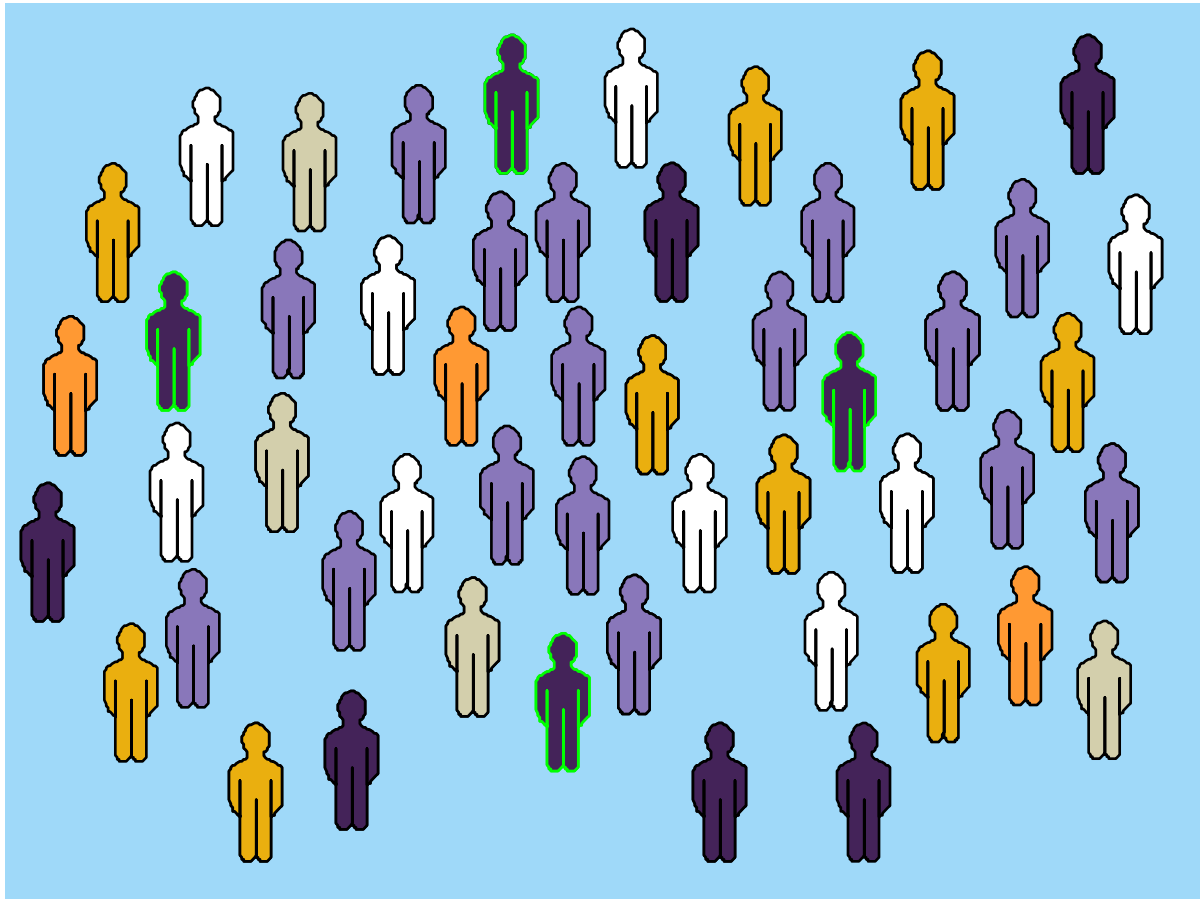


« one size fits all » therapy is not effective enough

Schiller JH, et al. NEJM 2002;346:92-98

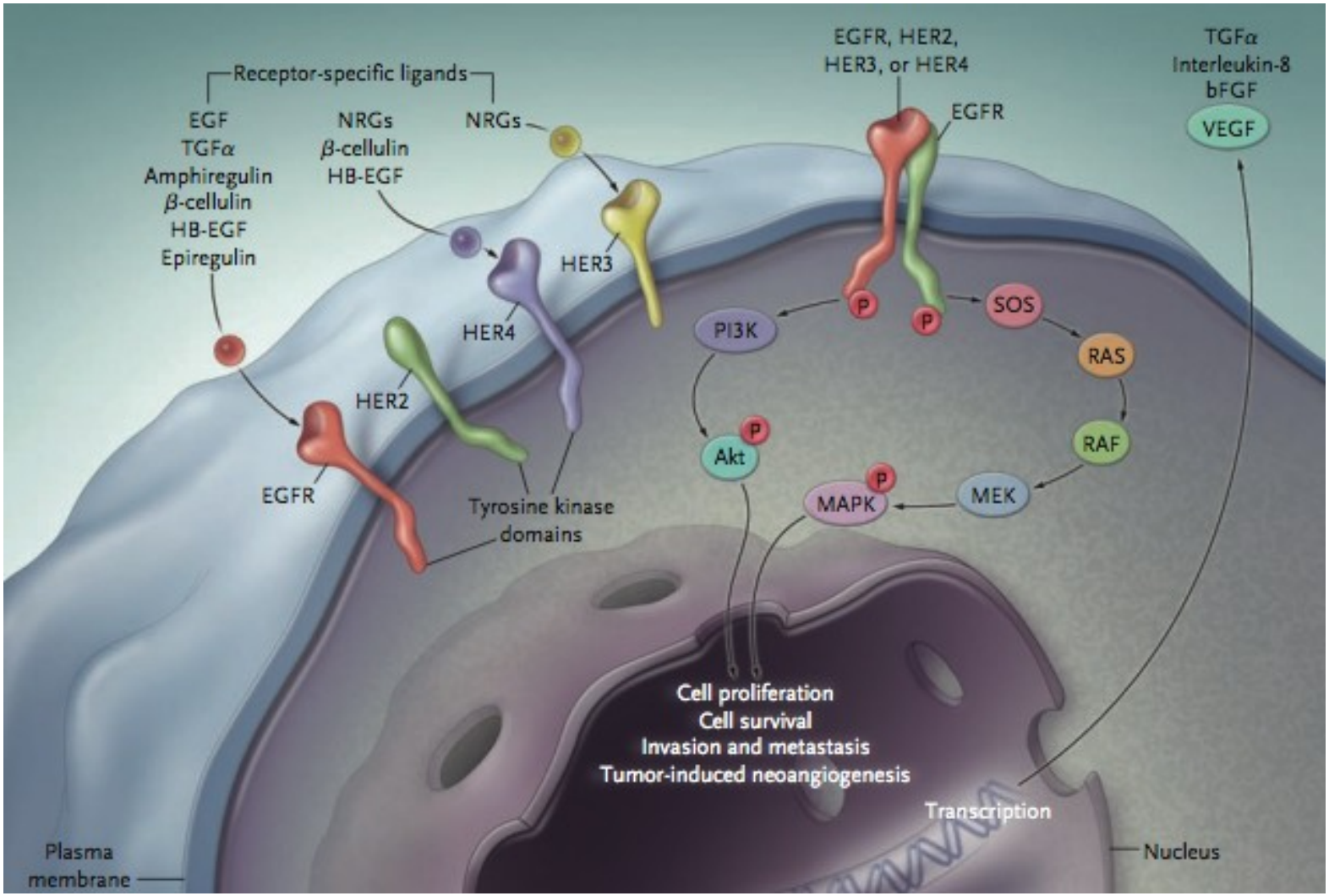
Using biomarkers to customize treatment

Patients with the same diagnosis (NSCLC),
but with different molecular profiles and biomarkers



They deserve customized treatment

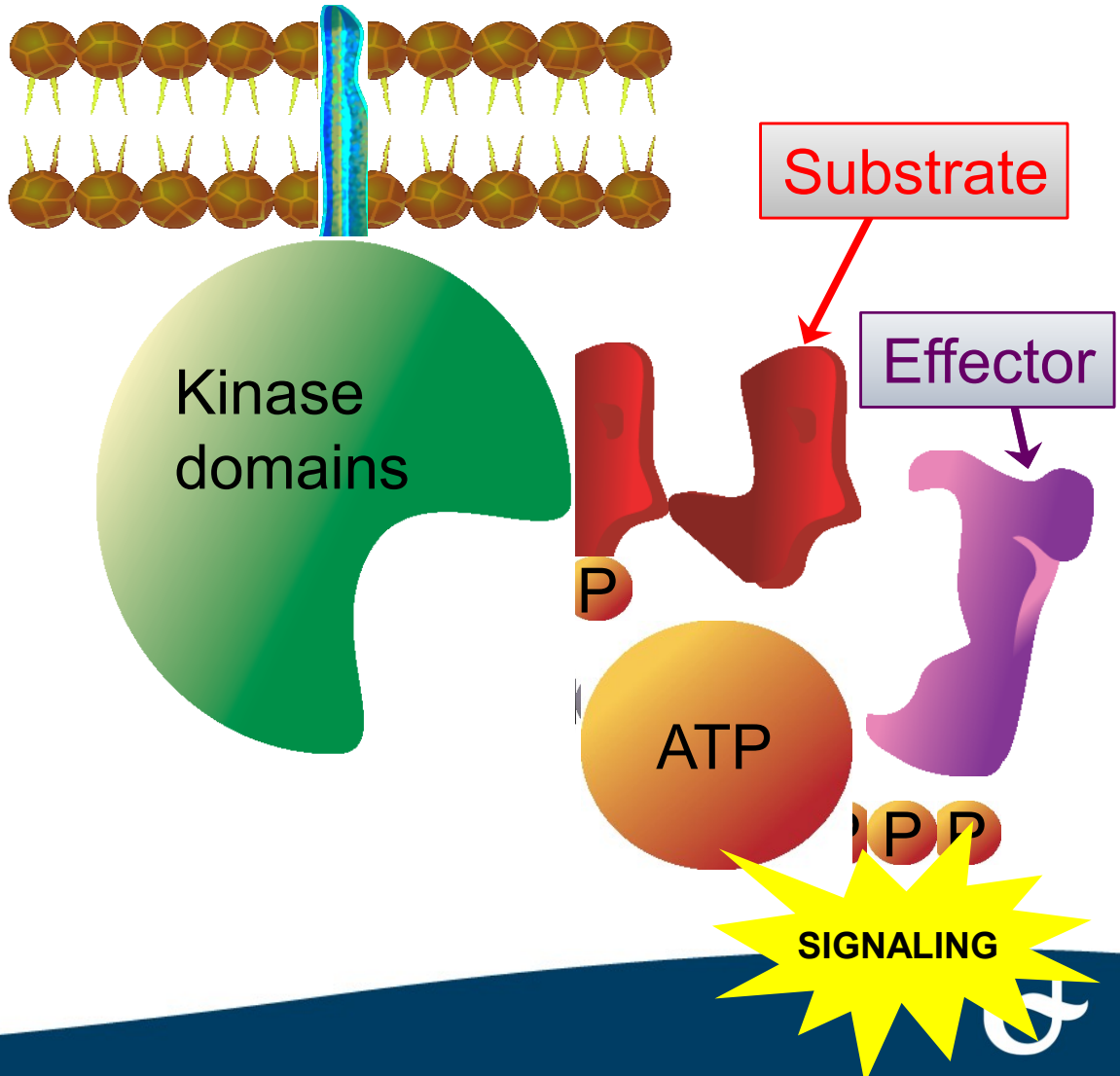
Signal Transduction Pathways Controlled by the Activation of EGFR



Ciardiello and Tortora. NEJM. 2008; 358:1160-74.

Signal transduction mechanism

- The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival

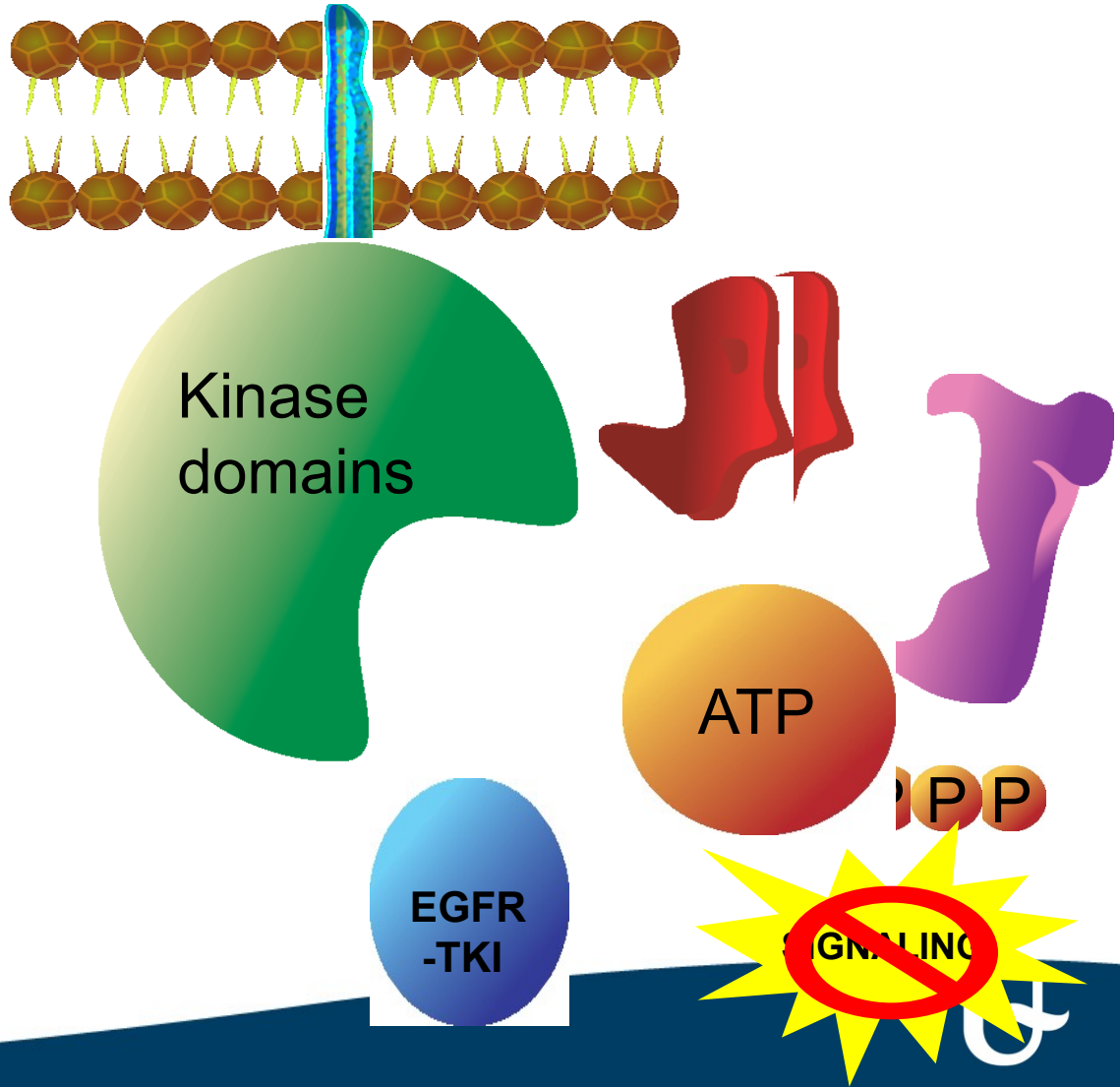


Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

Mechanism of action of EGFR-TKIs

The EGFR-TKI:

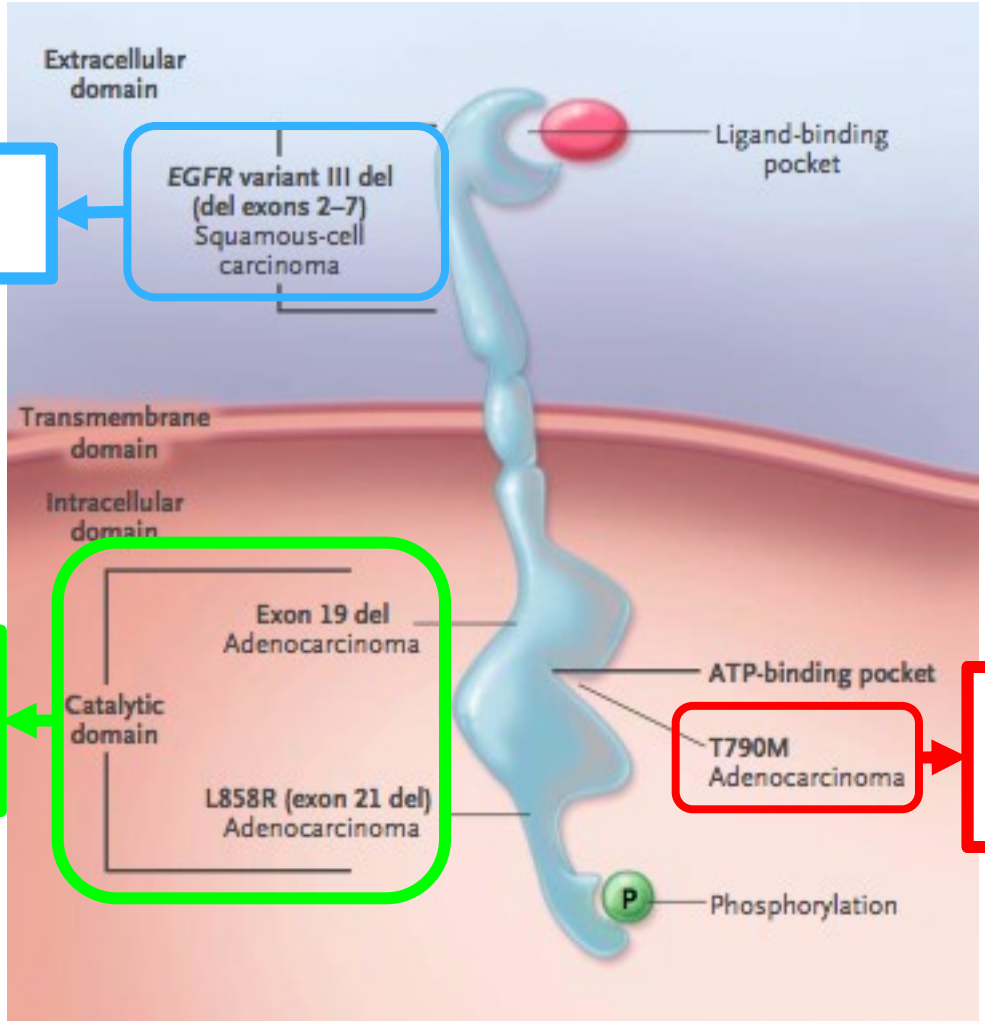
- Occupies the ATP binding pocket of the kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683.
Scheijen and Griffin. *Oncogene*. 2002;21:3314.

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

Constitutively active TK (ligand independent)

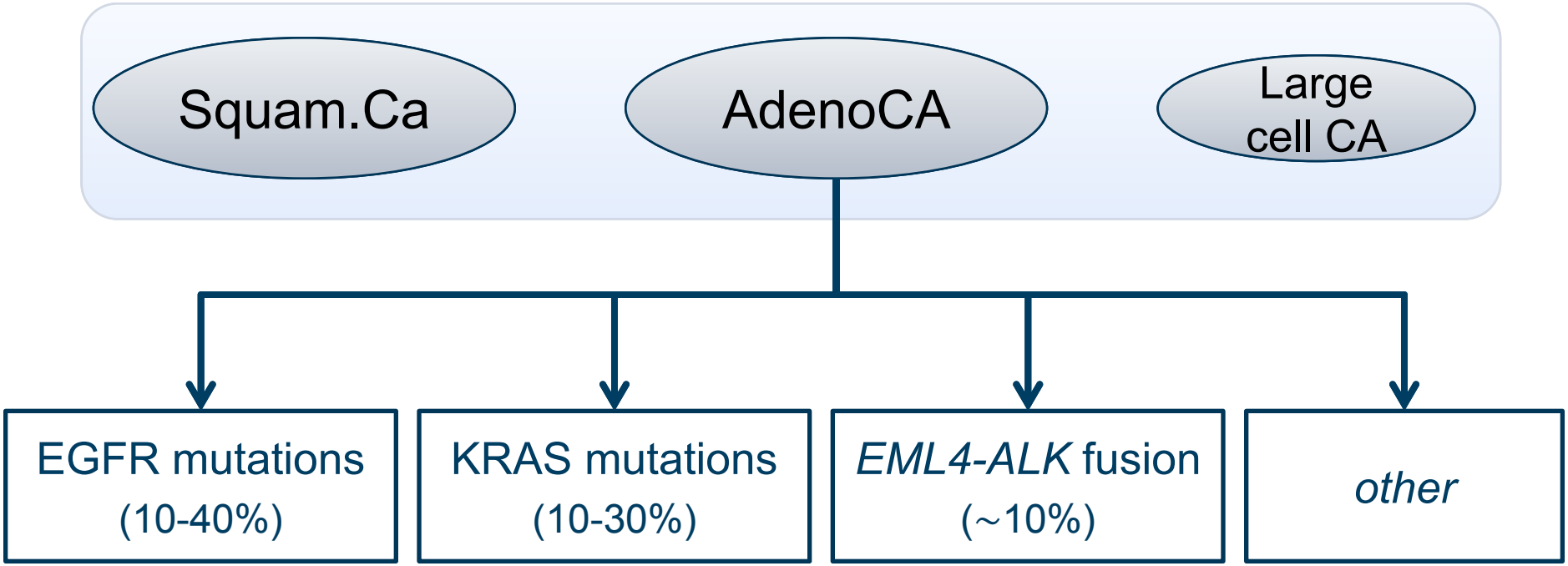


>80% of EGFR mutations; results in constitutive EGFR **activation**

associated with aquired **resistance** to EGFR-TKI

NSCLC: driver mutations

Genetic alterations responsible for initiating and maintaining lung cancer:



Using biomarkers to customize treatment

Patients with the same diagnosis (NSCLC),
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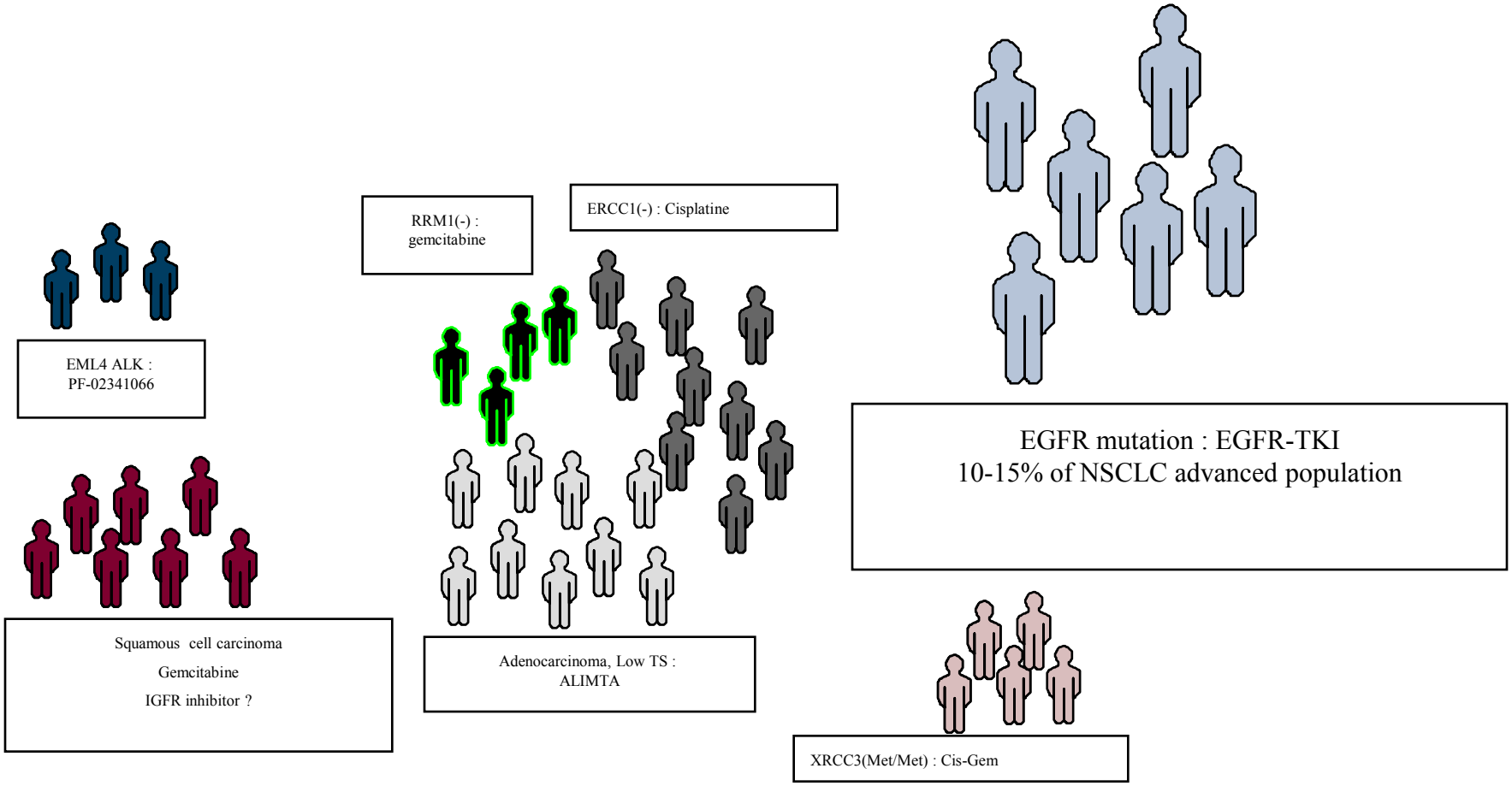
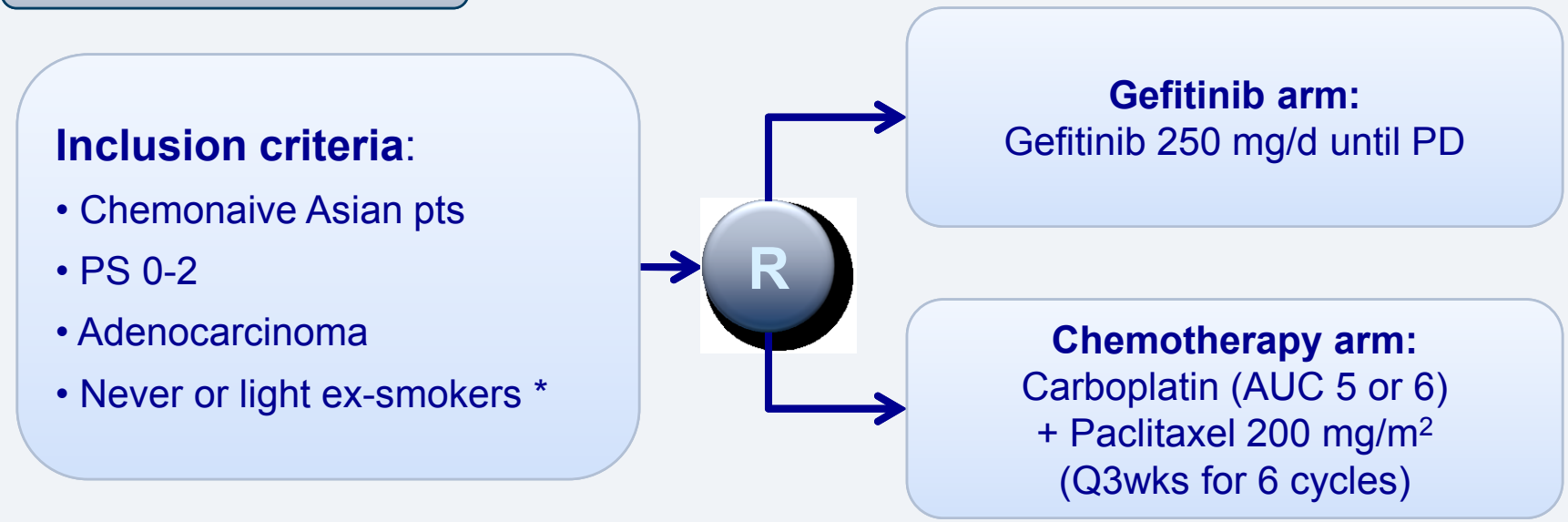


IPASS : 1st line EGFR-TKI *vs* chemotherapy in selected patients

Study design



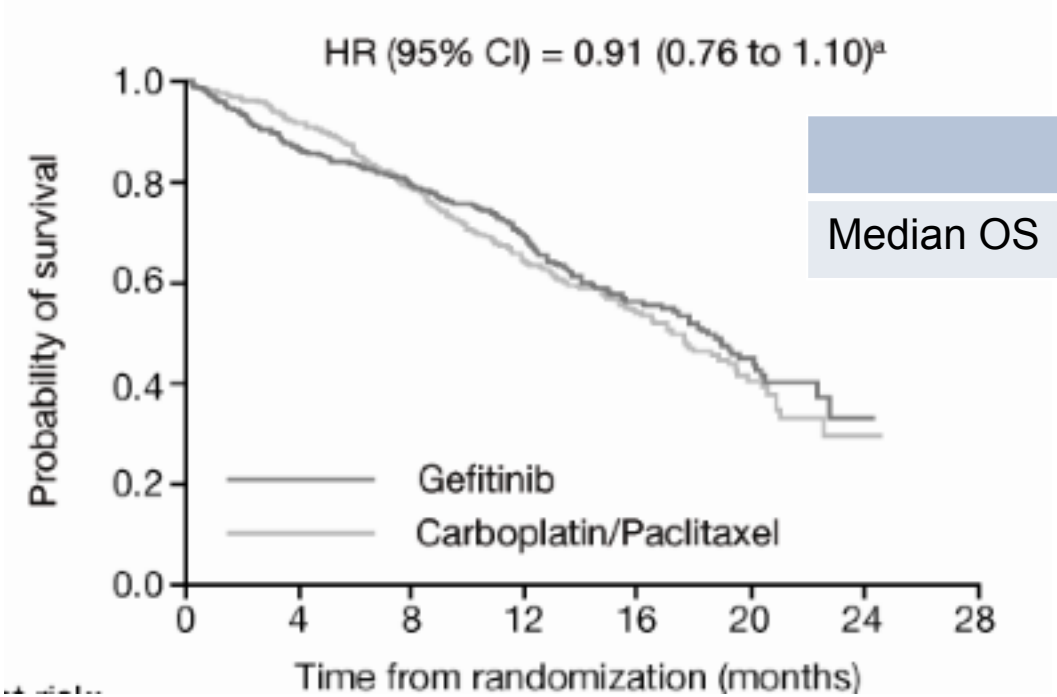
* Never smoker: <100 cigarettes in lifetime; light ex-smoker: stopped ≥15y ago and <10PY total

Statistics : Progression-free survival as primary endpoint

Mok et al. *NEJM* 2009; 361:947-57.

IPASS: Overall survival

All patients

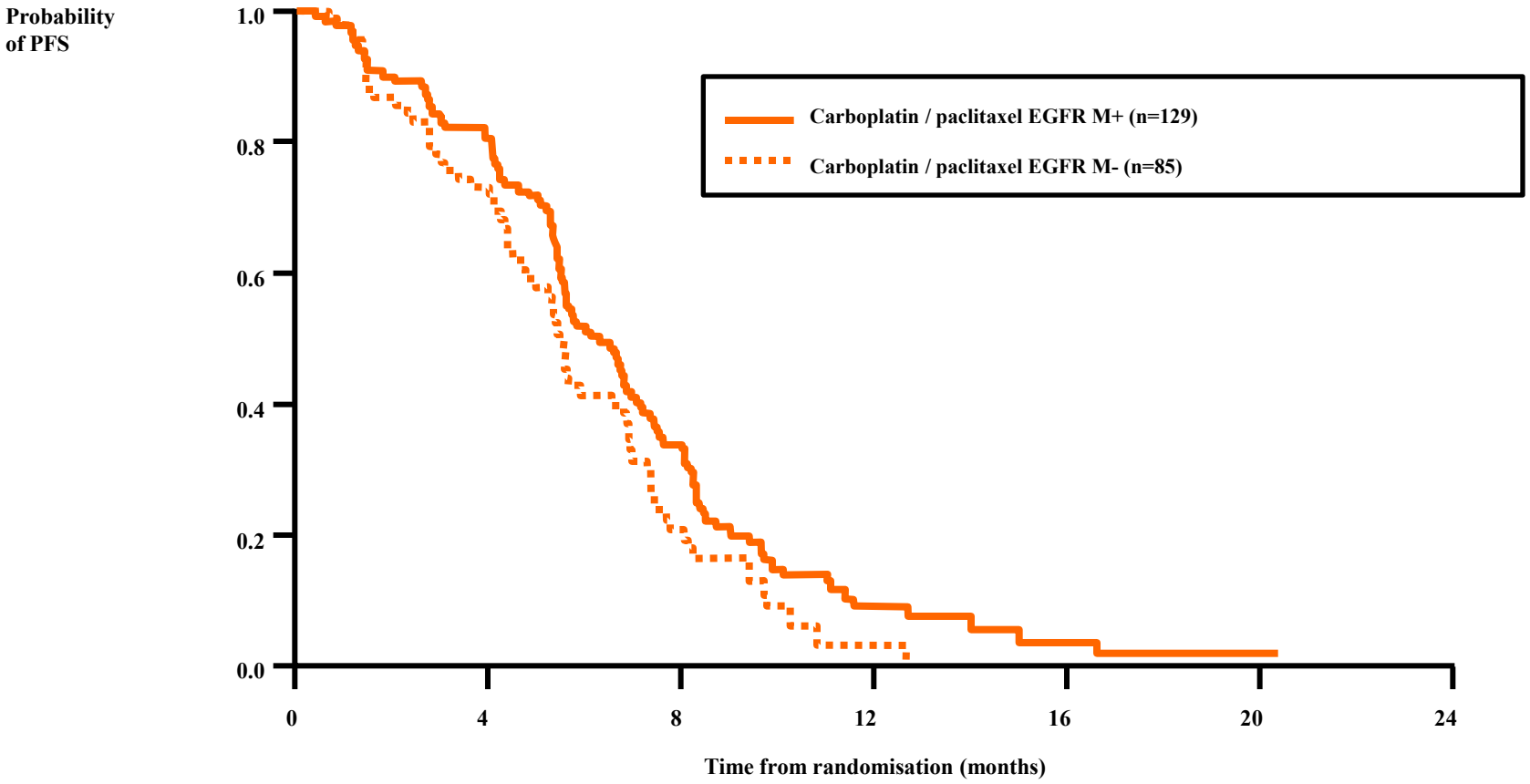


	Geftinib	CarboPacli
Median OS	18.6 m	17.3 m

At progression ~40% of patients in each arm crossed over to other treatment modality

Mok et al. *NEJM* 2009; 361:947-57.

IPASS: Progression Free Survival by mutation status



Primary Cox analysis with covariates; ITT population;
HR <1 implies a lower risk of progression on gefitinib

Mok et al N Engl J Med 2009; 361

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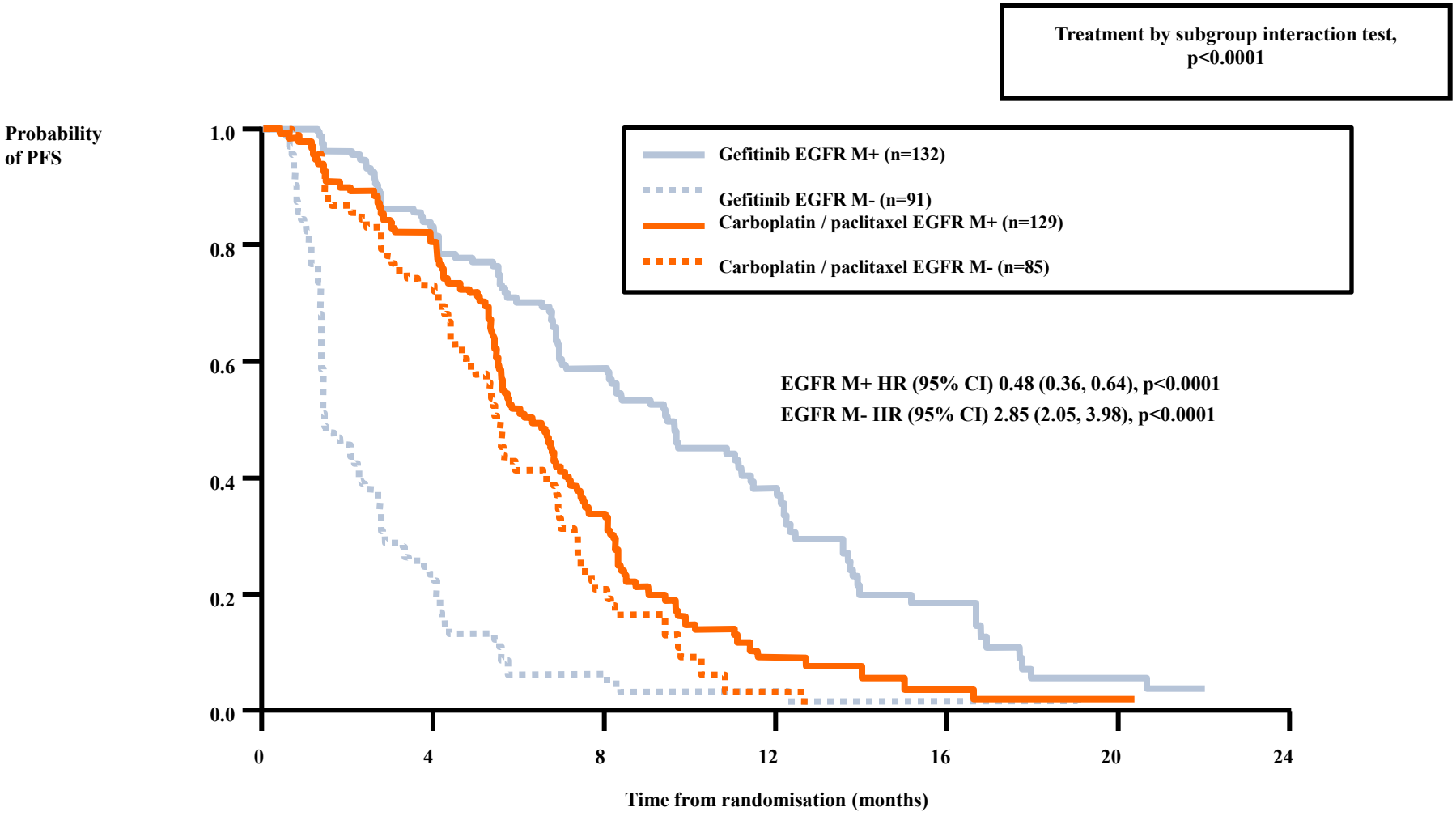

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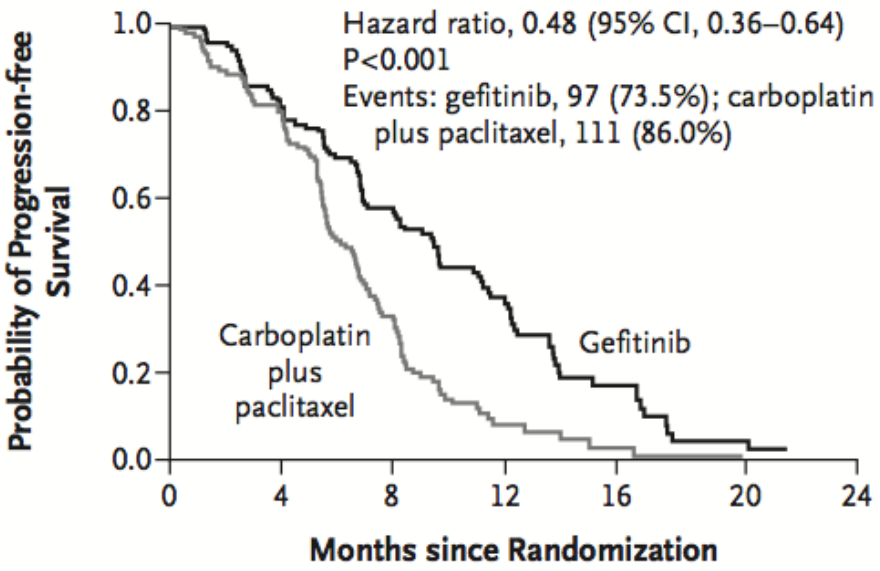
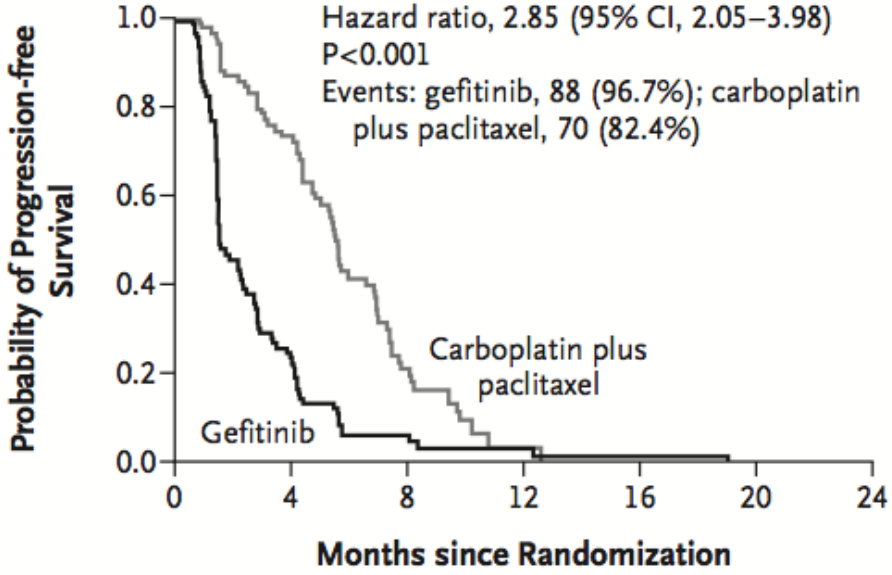
Mok et al N Engl J Med 2009; 361

IPASS: Progresion-free survival

EGFR-mutation positive



EGFR-mutation negative



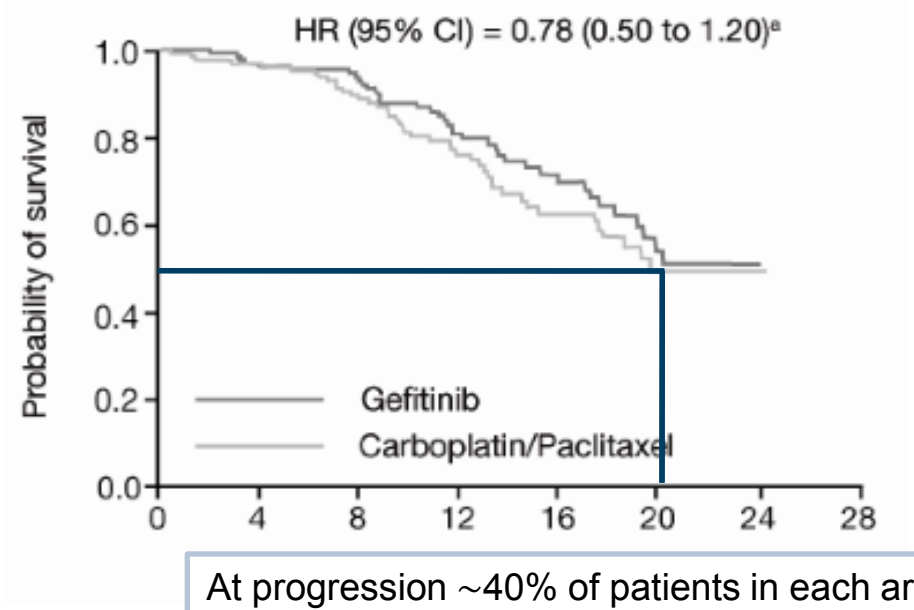
	EGFR-mutation pos.		EGFR-mutation neg.	
	Gefitinib	Carbo/Pacli	Gefitinib	Carbo/Pacli
Respose rate	71% *	47%	1%	23% *
Median PFS	9.6 m *	6.3 m	1.5 m	5.5 m *

* $P < 0.05$

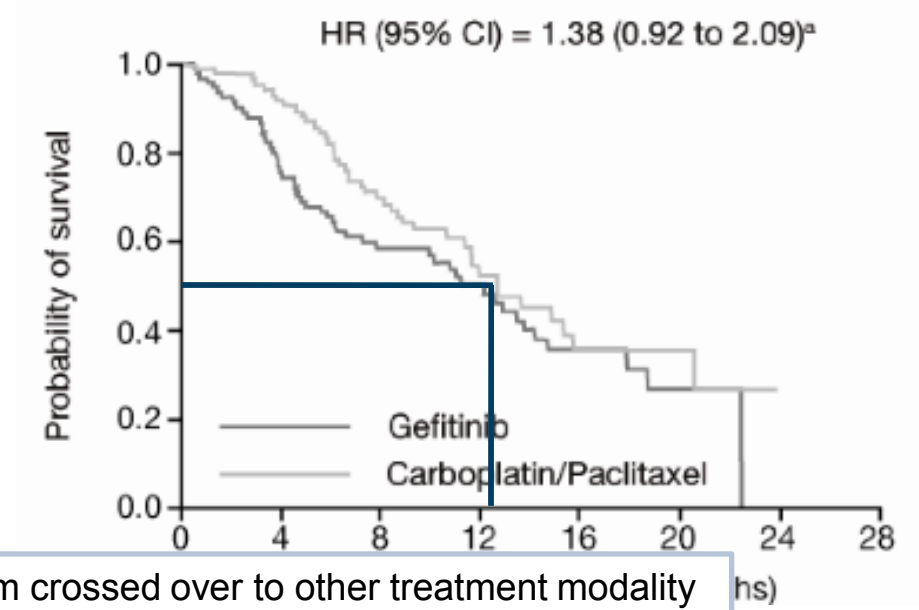
Mok et al. *NEJM* 2009; 361:947-57.

IPASS: Overall survival

EGFR-mutation positive



EGFR-mutation negative



At progression ~40% of patients in each arm crossed over to other treatment modality

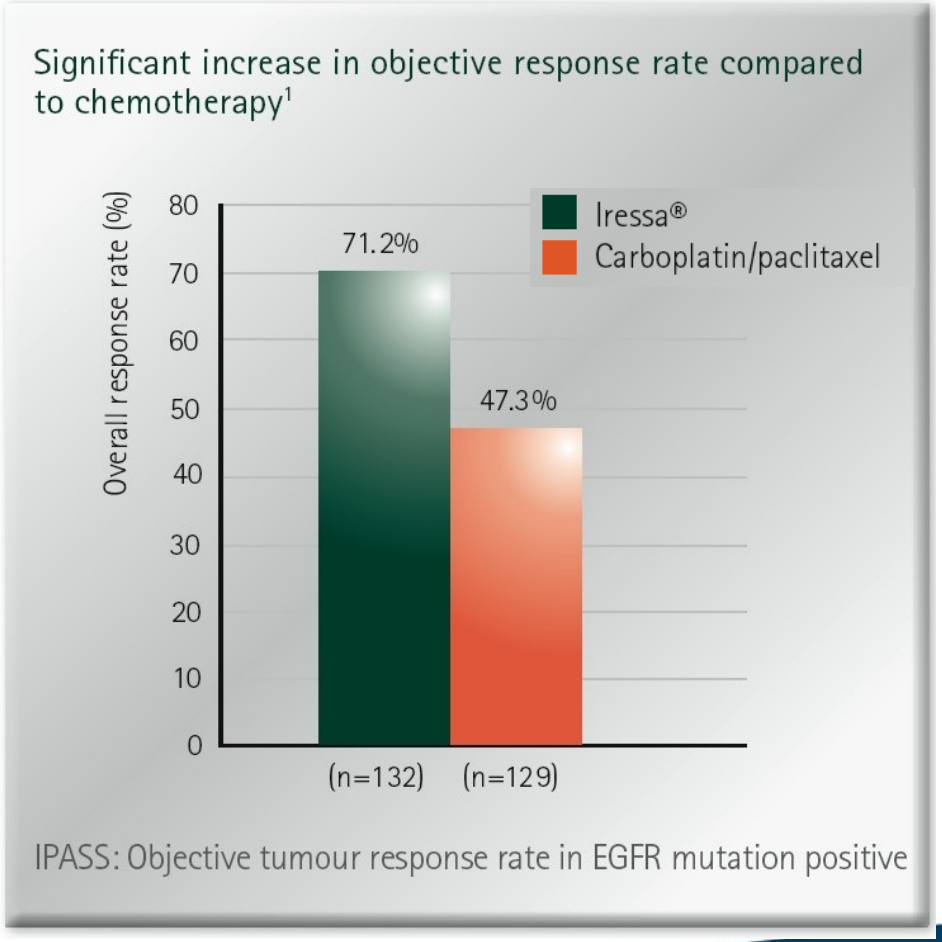
The presence of an EGFR mutation:

- is a strong predictive biomarker for ↗ response rate (both to chemotherapy and EGFR-TKI)
- is a strong predictive biomarker for ↗ PFS with EGFR-TKI *versus* chemotherapy
- is a favourable prognostic factor

Mok et al. *NEJM* 2009; 361:947-57.

Iressa®: Significant Greater Objective Response Rate

- 7/10 EGFR+ patients will respond* to Iressa® in 1st line. Less than 5/10 will respond to chemotherapy

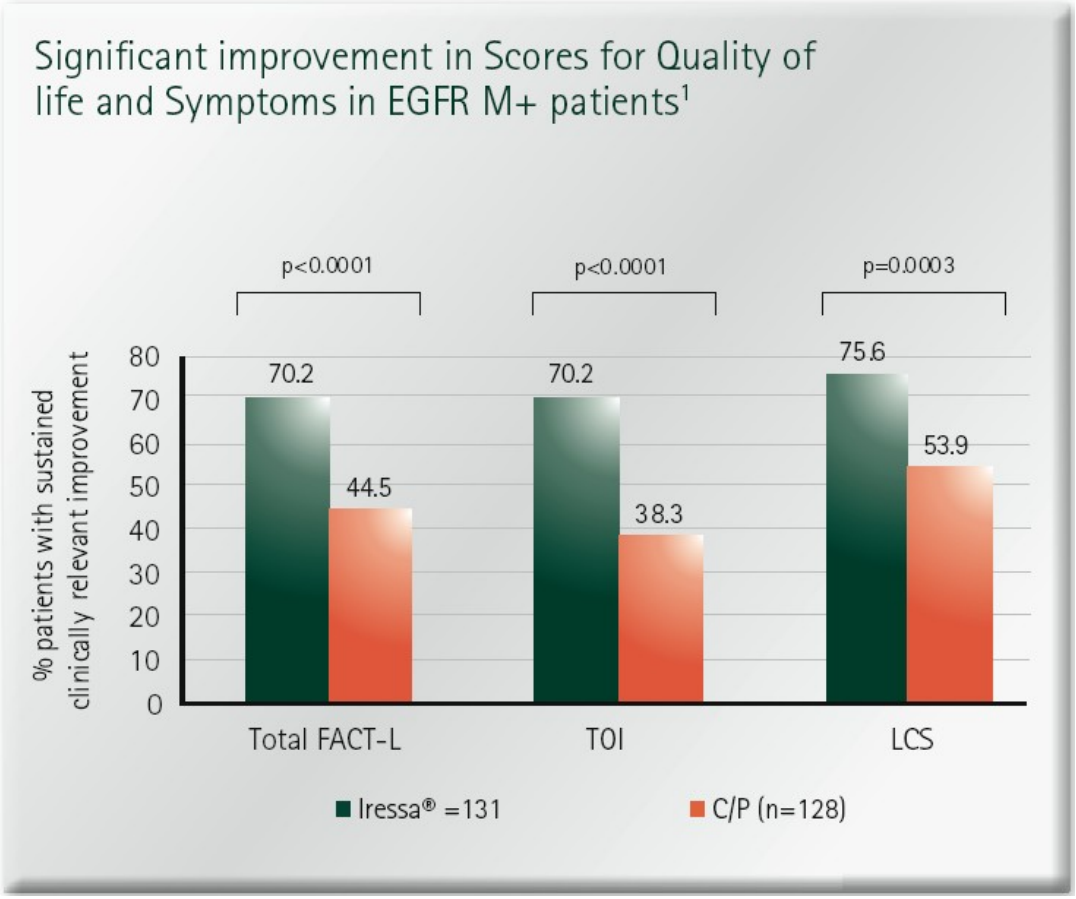


* Defined by ORR in EGFR M+ subgroup,

Adapted from Mok T et al. N Engl J Med 2009;361

Iressa®: Better Symptom Control*

- Iressa® in 1st line significantly improves lung cancer symptoms in EGFR M+ patients compared to chemotherapy

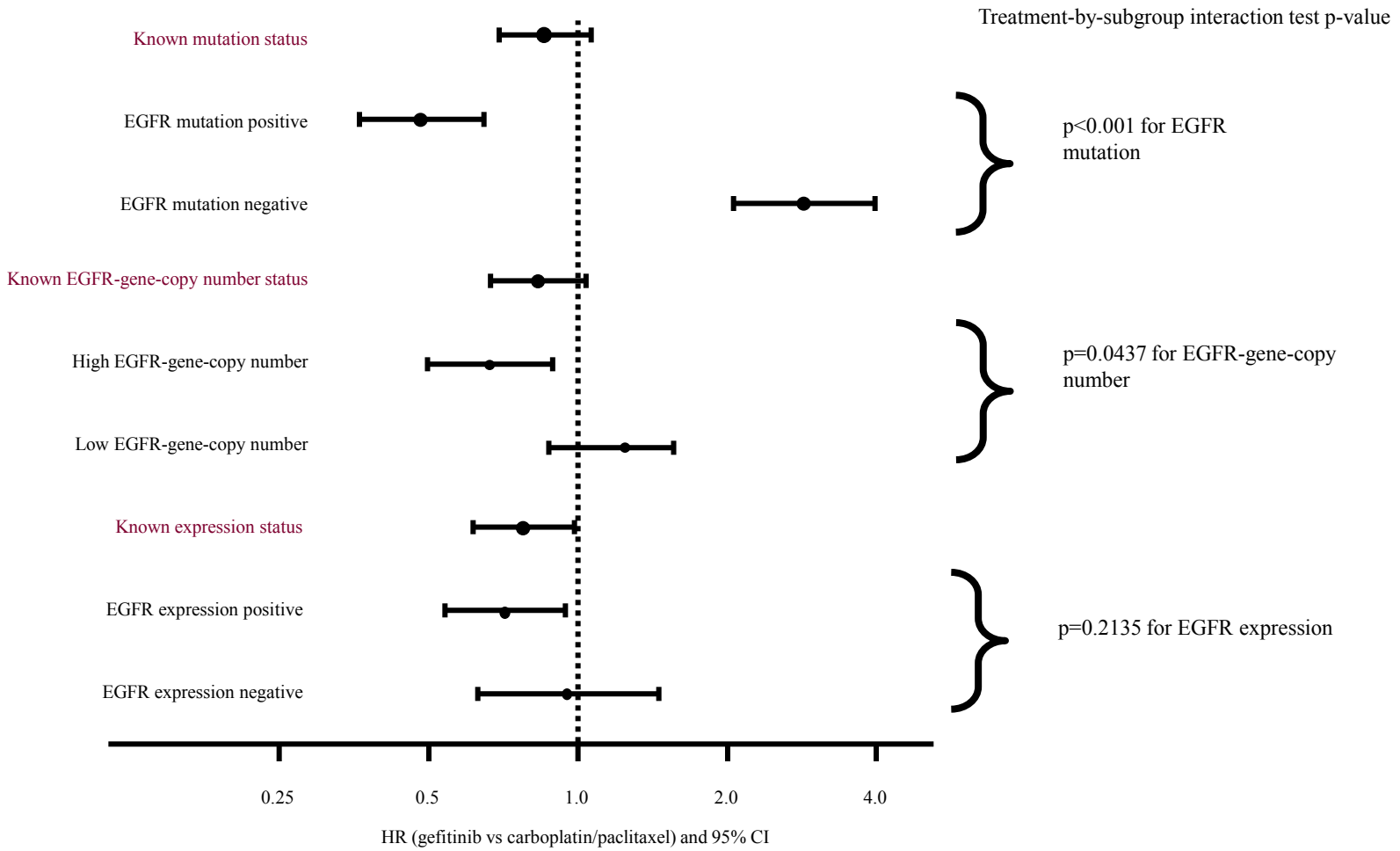


Fact-L: Functional Assessment of Cancer Therapy-Lung
TOI: Trial Outcome Index
LCS: Lung Cancer Subscale

*Defined by FACT-L, TOI and LCS scores in EGFR M+ subgroup,

Adapted from Mok T et al. N Engl J Med 2009; 361, supplementary appendix - fig. 3.

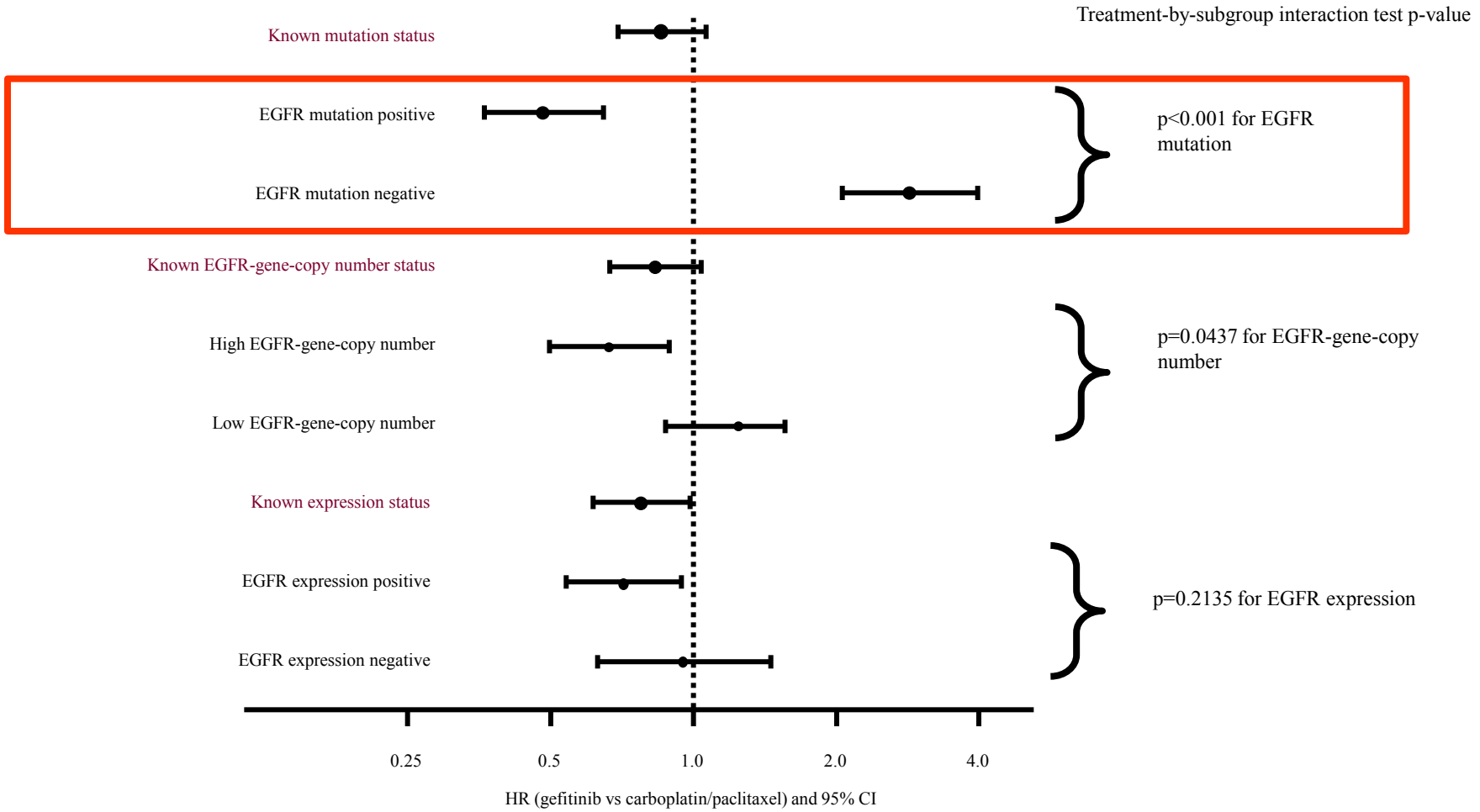
Progression-free survival by biomarkers



ITT population
Cox analysis with covariates
HR <1 implies a lower risk of progression/death on gefitinib

Mok et al 2009

Progression-free survival by biomarkers



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Mok et al 2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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Maemondo M et al. N Engl J Med 2010; 362: 2380-8.

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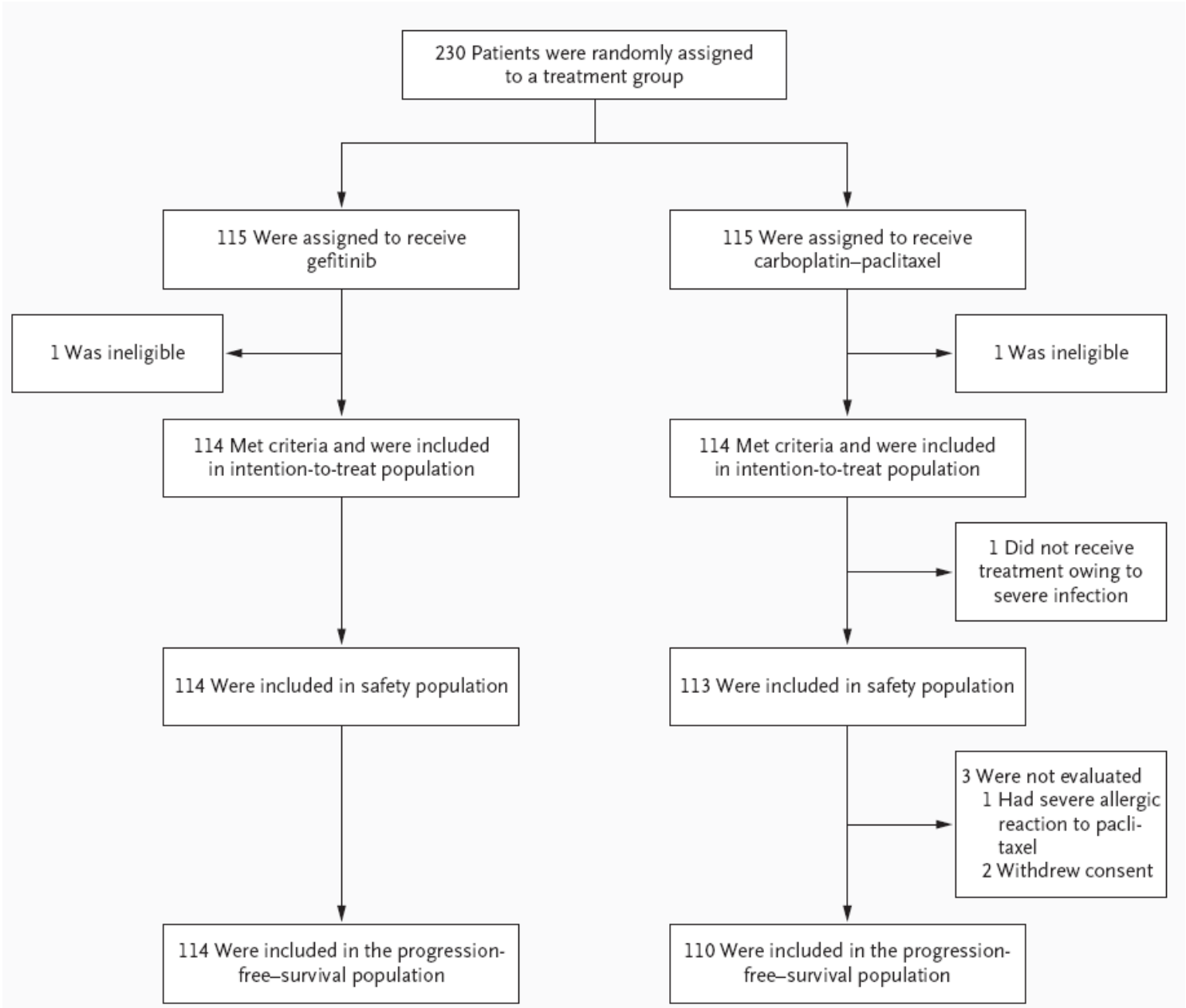


Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

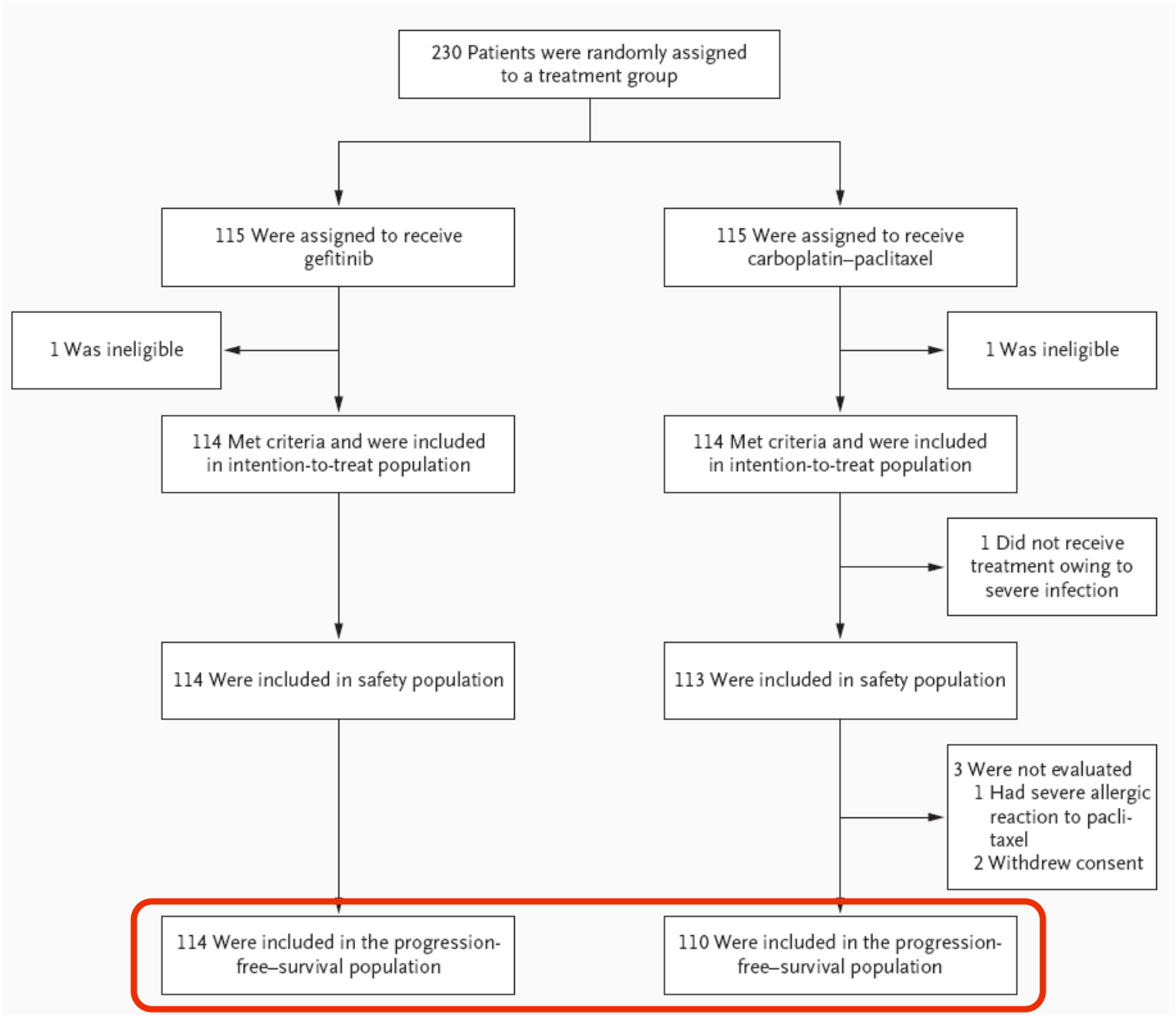


Figure 1. Randomization and Follow-up of the Study Patients, According to Treatment Group.

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

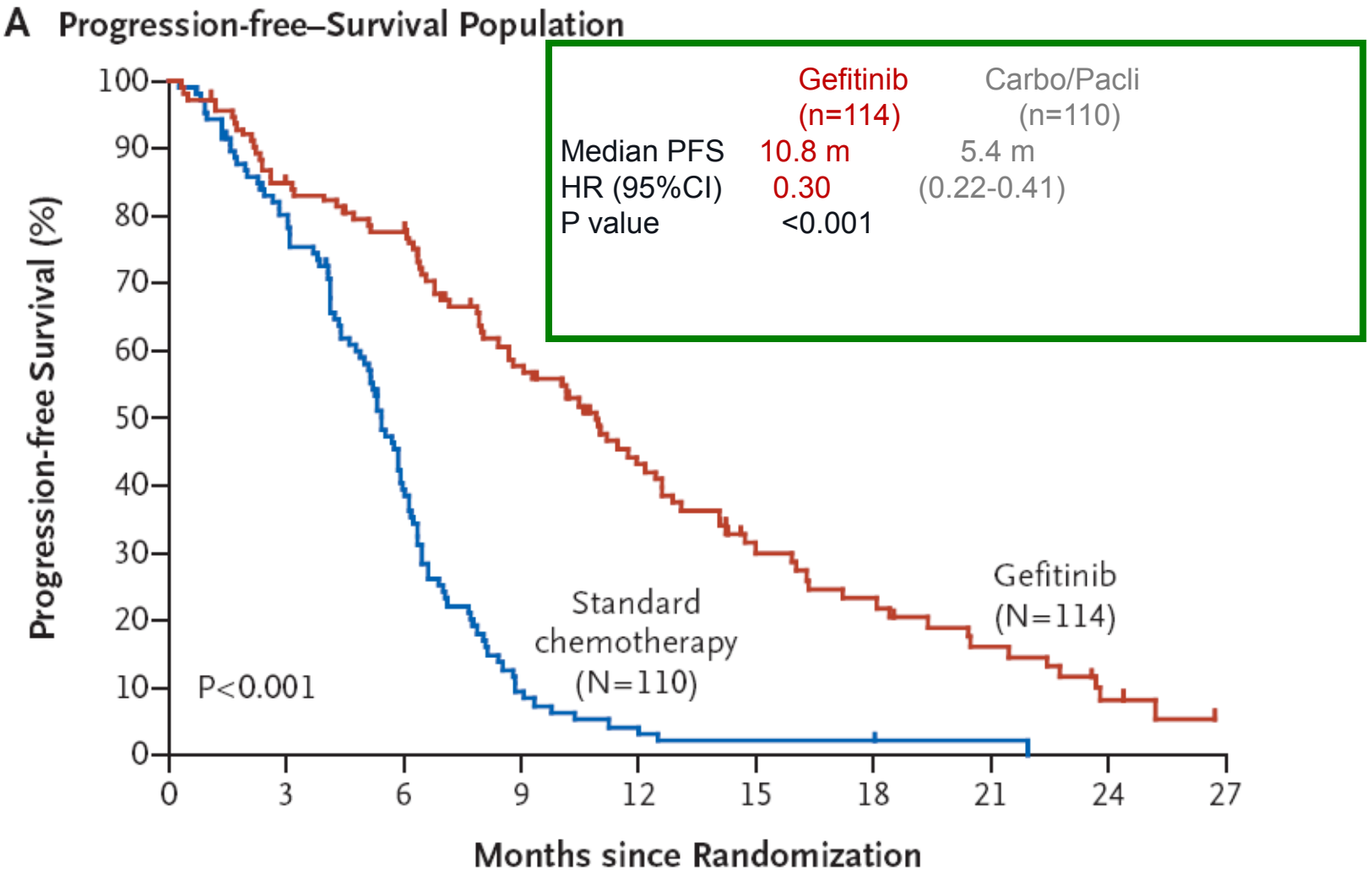
Characteristic	Gefitinib (N = 114)	Carboplatin–Paclitaxel (N = 114)
Sex — no. (%)		
Male	42 (36.8)	41 (36.0)
Female	72 (63.2)	73 (64.0)
Age — yr		
Mean	63.9±7.7	62.6±8.9
Range	43–75	35–75
Smoking status — no. (%)		
Never smoked	75 (65.8)	66 (57.9)
Previous or current smoker	39 (34.2)	48 (42.1)
ECOG performance status score — no. (%)		
0	54 (47.4)	57 (50.0)
1	59 (51.8)	55 (48.2)
2	1 (0.9)	2 (1.8)

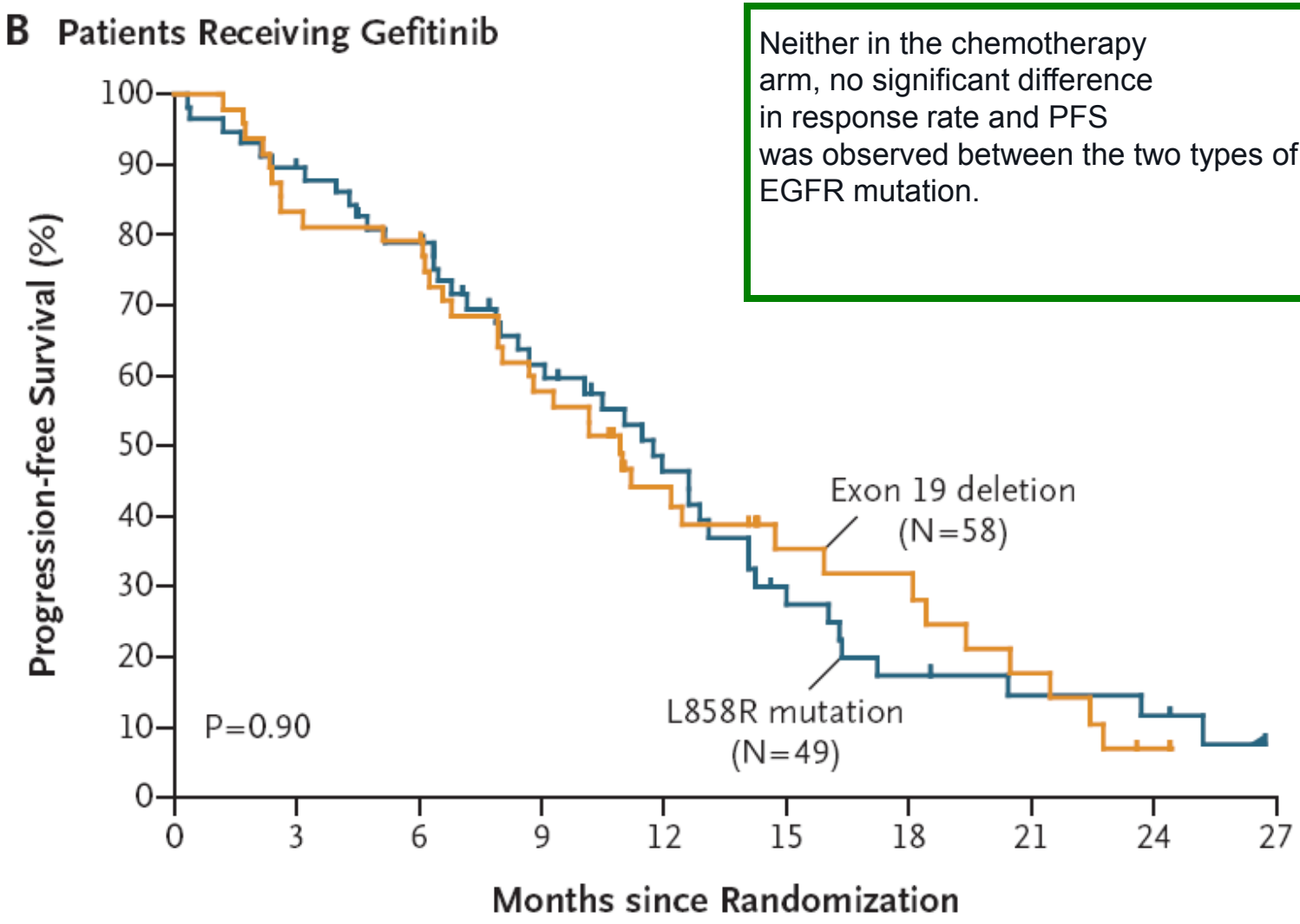
* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.

Table 1. Baseline Characteristics of the Intention-to-Treat Population, According to Treatment Group.*

Characteristic	Gefitinib (N = 114)	Carboplatin–Paclitaxel (N = 114)
Histologic diagnosis — no. (%)		
Adenocarcinoma	103 (90.4)	110 (96.5)
Large-cell carcinoma	1 (0.9)	0
Adenosquamous carcinoma	2 (1.8)	1 (0.9)
Squamous-cell carcinoma	3 (2.6)	2 (1.8)
Other	5 (4.4)	1 (0.9)
Clinical stage — no. (%)		
IIIB	15 (13.2)	21 (18.4)
IV	88 (77.2)	84 (73.7)
Postoperative relapse	11 (9.6)	9 (7.9)
Type of EGFR mutation — no. (%)		
Exon 19 deletion	58 (50.9)	59 (51.8)
L858R	49 (43.0)	48 (42.1)
Other	7 (6.1)	7 (6.1)

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group.


A Progression-free–Survival Population
Gefitinib (n=114)
Carbo/Pacli (n=110)
Median PFS 10.8 m 5.4 m
HR (95%CI) 0.30 (0.22-0.41)
P value <0.001
Progression-free Survival (%)
100
90
80
70
60
50
40
30
20
10
0
P<0.001
Standard chemotherapy (N=110)
Gefitinib (N=114)
0 3 6 9 12 15 18 21 24 27
Months since Randomization



Neither in the chemotherapy arm, no significant difference in response rate and PFS was observed between the two types of EGFR mutation.

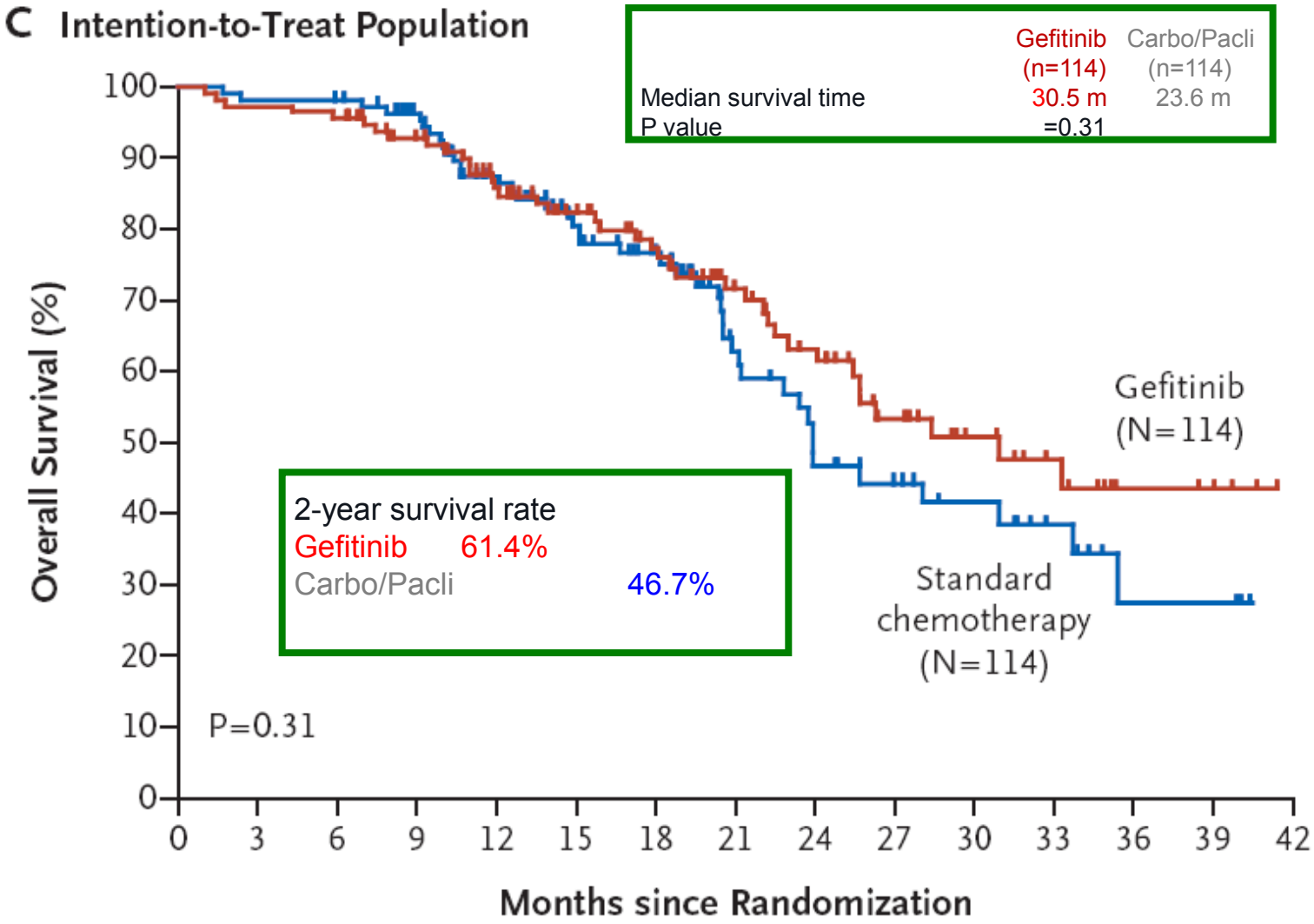

C Intention-to-Treat Population
Gefitinib (n=114)
Carbo/Pacli (n=114)
Median survival time
30.5 m
23.6 m
P value
=0.31
Overall Survival (%)
100
90
80
70
60
50
40
30
20
10
0
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
Months since Randomization
Gefitinib (N=114)
Standard chemotherapy (N=114)
2-year survival rate
Gefitinib 61.4%
Carbo/Pacli 46.7%
P=0.31

Table 1. Summary of presented gefitinib first-line efficacy data in patients with *EGFR* mutation-positive advanced non-small-cell lung cancer.

Trial	Patient origin and selection	Treatment and number of patients	Primary end point	Response rate (%)	PFS (HR or median [months])	Overall survival (HR or median [months])	Ref.
Phase III studies							
IPASS	Asia Never- or light ex-smoker, adenocarcinoma	Gefitinib (n = 609 total; n = 132 *EGFR* M+) Carboplatin/paclitaxel (n = 608 total; n = 129 *EGFR* M+)	PFS (overall population)	71.2 47.3 OR: 2.75; 95% CI: 1.65–4.60; p < 0.001	HR: 0.48 95% CI: 0.36–0.64 p < 0.001	HR: 0.78† 95% CI: 0.50–1.20	[15]
First-SIGNAL	Asia Never-smoker, adenocarcinoma	Gefitinib (n = 159 total; n = 26 *EGFR* M+) Gemcitabine (n = 150 total; n = 16 *EGFR* M+)	Overall survival (overall population)	84.6 37.5 OR: 9.17; 95% CI: 2.11–39.85; p = 0.002	HR: 0.61 95% CI: 0.31–1.22 p = 0.08	HR: 0.82 95% CI: 0.35–1.92 p = 0.65	[30]
NEJ002	Asia *EGFR* mutation	Gefitinib (n = 98 *EGFR* M+) Carboplatin/paclitaxel (n = 100 *EGFR* M+)	PFS	74.5 29.0 p < 0.001	HR: 0.36 95% CI: 0.25–0.51 p < 0.001	HR: 0.79 95% CI: 0.49–1.30 p = 0.35	[29]
WJTOG 3405	Asia *EGFR* mutation	Gefitinib (n = 86 *EGFR* M+) Cisplatin/docetaxel (n = 86 *EGFR* M+)	PFS	62.1 32.2 p < 0.001	HR: 0.49 95% CI: 0.34–0.71 p < 0.001	HR: 1.64‡ 95% CI: 0.75–3.58	[31]

†*Post-hoc* analysis (overall survival follow-up ongoing).
‡Overall survival follow-up ongoing.
§Projected median overall survival.
¶Time to treatment failure.
EGFR: EGF receptor; First-SIGNAL: First-Line Single Agent IRESSA Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; HR: Hazard ratio; I-CAMP: IRESSA Combined Analysis of Mutation Positives; IPASS: IRESSA Pan-Asia Study; M+: Mutation-positive; NEJ: North East Japan; OR: Odds ratio; ORR: Objective response rate; PFS: Progression-free survival; PS: Performance status; WJTOG: West Japan Thoracic Oncology Group.

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WJTOG 3405	Asia *EGFR* mutation	Gefitinib (n = 86 *EGFR* M+) Cisplatin/docetaxel (n = 86 *EGFR* M+)	PFS	62.1 32.2 p < 0.001	HR: 0.49 95% CI: 0.34–0.71 p < 0.001	HR: 1.64‡ 95% CI: 0.75–3.58	[31]

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§Projected median overall survival.
¶Time to treatment failure.
EGFR: EGF receptor; First-SIGNAL: First-Line Single Agent IRESSA Versus Gemcitabine and Cisplatin Trial in Never-Smokers with Adenocarcinoma of the Lung; HR: Hazard ratio; I-CAMP: IRESSA Combined Analysis of Mutation Positives; IPASS: IRESSA Pan-Asia Study; M+: Mutation-positive; NEJ: North East Japan; OR: Odds ratio; ORR: Objective response rate; PFS: Progression-free survival; PS: Performance status; WJTOG: West Japan Thoracic Oncology Group.

EGFR mutation & treatment with an EGFR-TKI in non-Asian patients

- In the INTEREST Subgroup analysis, in non-Asian patients only, has also shown that PFS was significantly longer with gefitinib compared with docetaxel in the non-Asian EGFR mutation-positive patients (HR: 0.12; 95% CI: 0.03–0.51; p = 0.005), although the patient numbers were low (Figure 3).
- The ORR and PFS achieved with gefitinib in patients with EGFR mutations from western populations in these studies are comparable to those observed in the Phase III studies already described and in other prospective Phase II studies of first-line gefitinib in Asian patients with EGFR mutation-positive tumors, in which ORRs of 51–78% have been reported (Table 1).

EGFR mutation & treatment with an EGFR-TKI in non-Asian patients

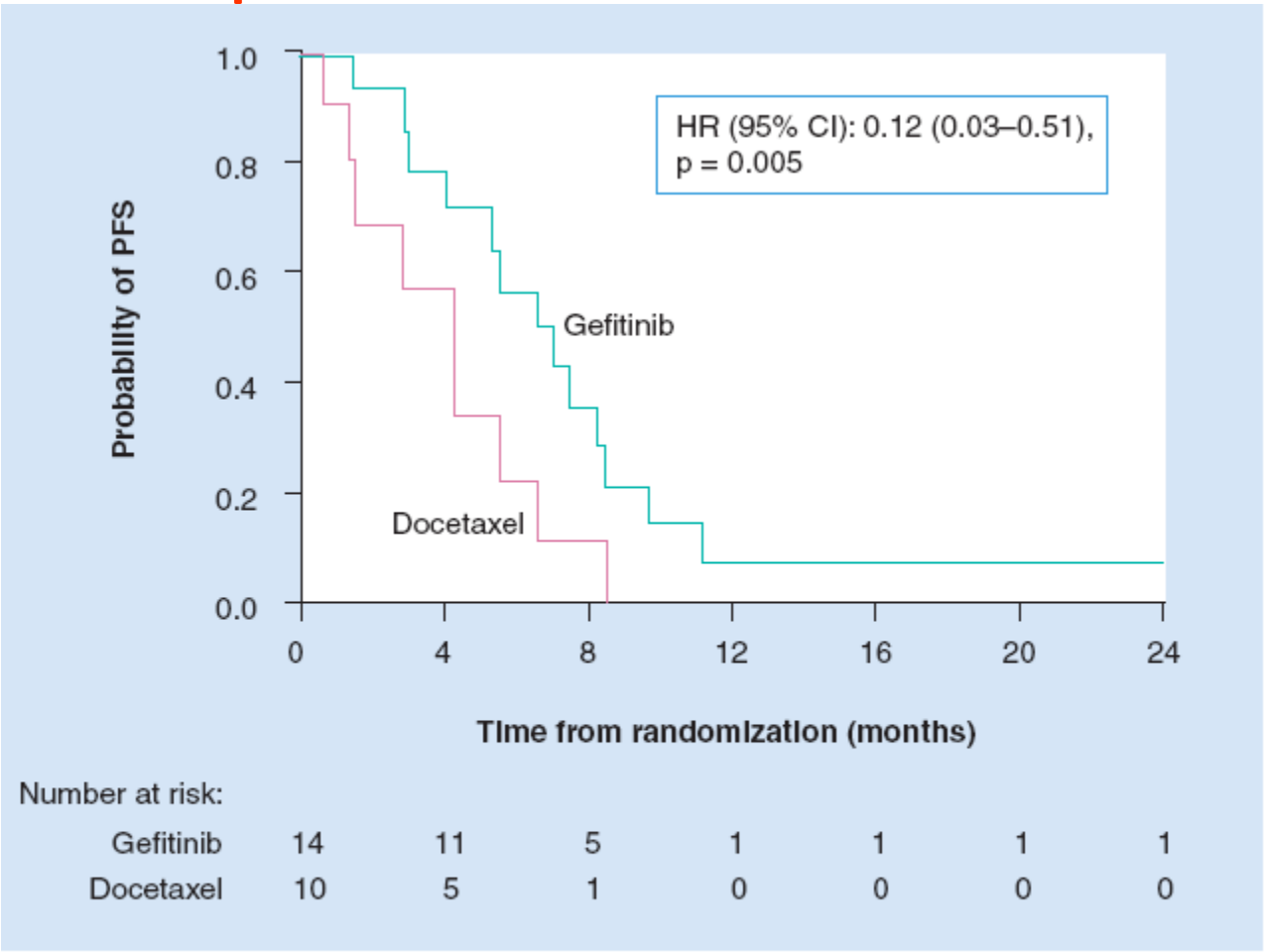
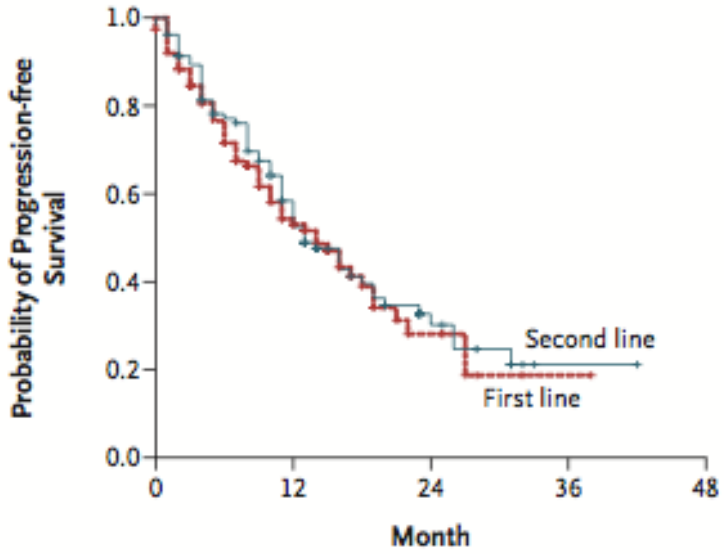


Figure 3. Kaplan–Meier curves for progression-free survival for non-Asian patients with *EGFR* mutation-positive status in INTEREST.
EGFR: EGF receptor; HR: Hazard ratio; INTEREST: IRESSA NSCLC Trial Evaluating Response and Survival Versus Taxotere; PFS: Progression-free survival.

Reck M Expert Rev. Anticancer Ther. 10(6), 955–965 (2010)

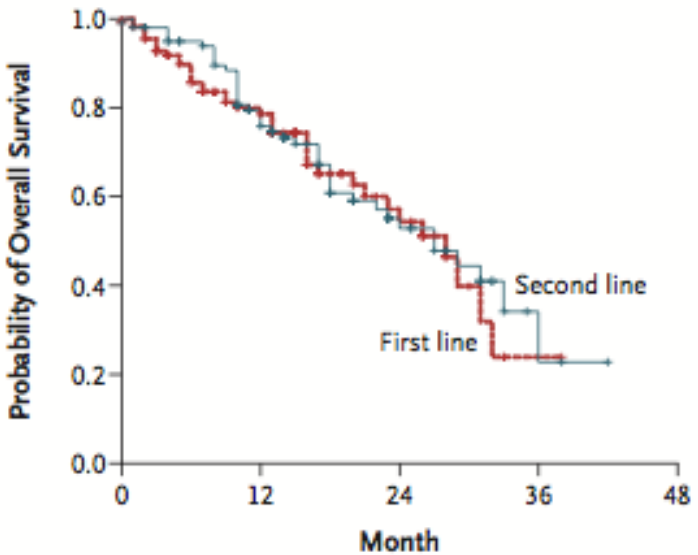
Survival of patients with activating EGFR-mutations who received erlotinib therapy

Progression-free Survival According to Therapy



First Line					
No. at risk	113	41	9	1	0
No. of events	0	46	58	60	60
Second Line					
No. at risk	104	48	12	1	1
No. of events	0	41	59	62	62

Overall Survival According to Therapy

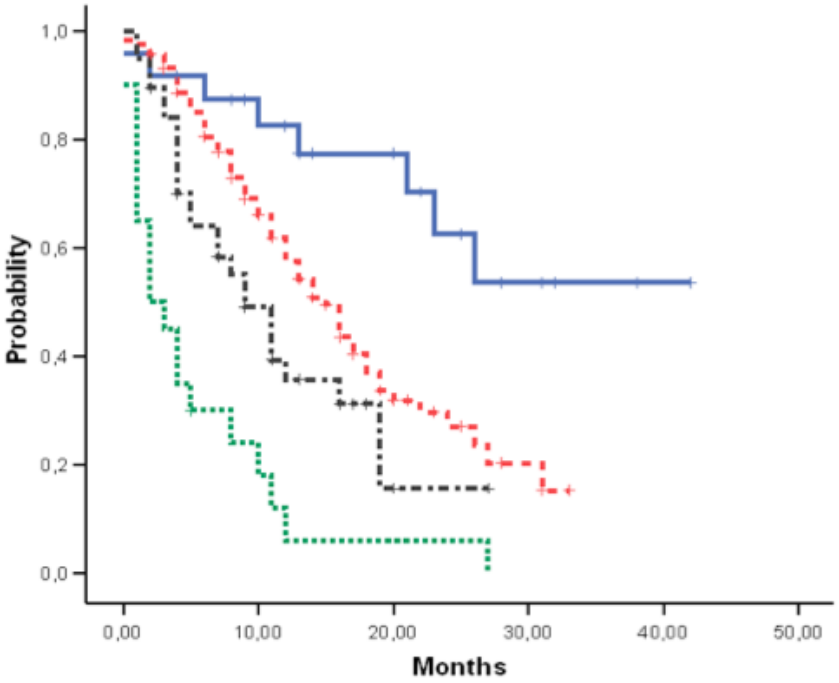


First Line					
No. at risk	113	58	19	1	0
No. of events	0	21	33	38	38
Second Line					
No. at risk	104	64	23	2	1
No. of events	0	20	36	42	42

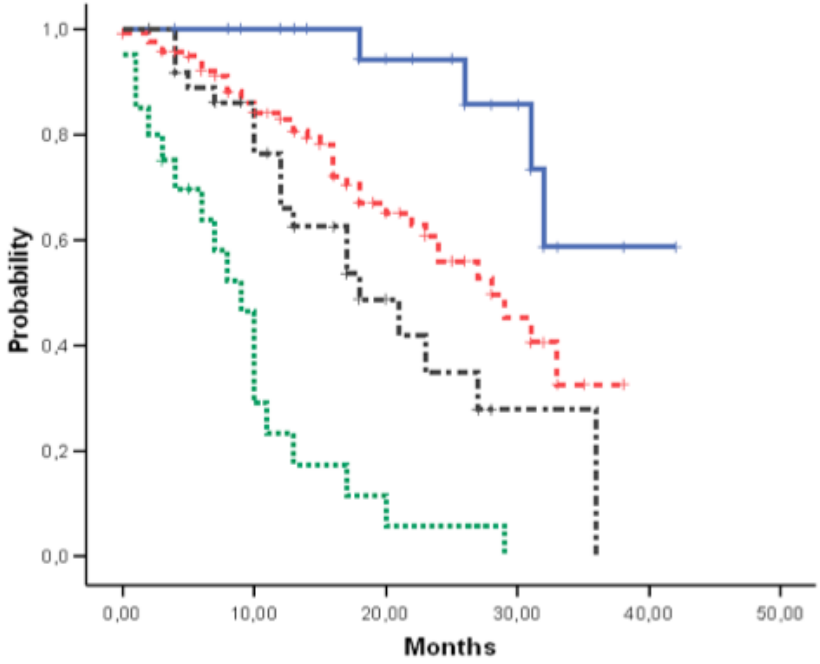
Rosell et al. *NEJM* 2009; 361: 958-67.

Survival of patients with activating EGFR-mutations who received erlotinib therapy

PFS



OS



:CR :PR :SD :PD

Rosell et al. *NEJM* 2009; 361: 958-67.

EGFR mutation & treatment with an EGFR-TKI in non-Asian patients

- These results indicate that the presence of an EGFR mutation is the driving factor that determines outcome rather than the ethnicity and that the efficacy of the EGFR-TKI in EGFR mutation-positive patients is independent from the line of therapy.

SATURN: erlotinib as maintenance in 1st-line treatment of advanced NSCLC

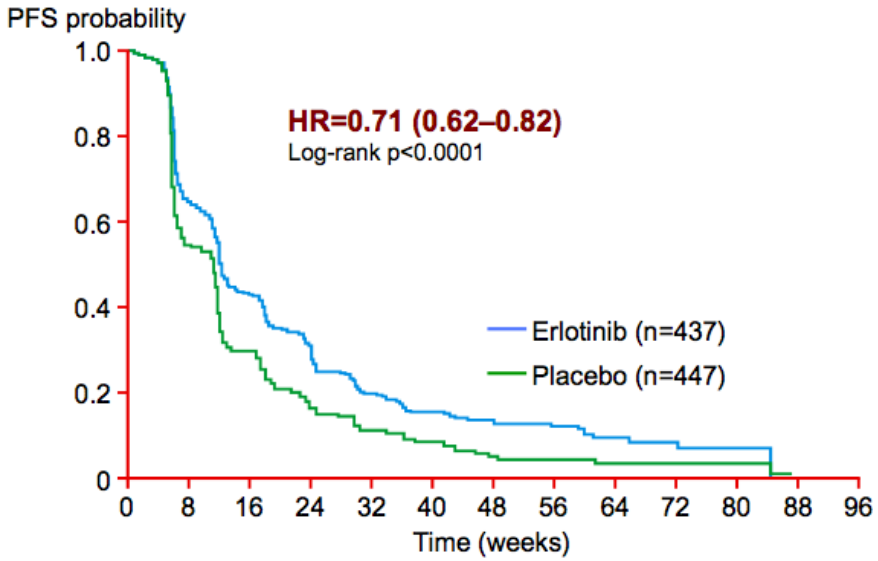
Inclusion criteria:
- Stage IIIB/IV NSCLC
- PS 0-1
- Non-PD following 4 cycles of platinum-based chemotherapy*

R 1:1

Maintenance arm (n=438):
Erlotinib 150 mg/d until PD

Control arm (n=451):
Placebo 1x/d until PD

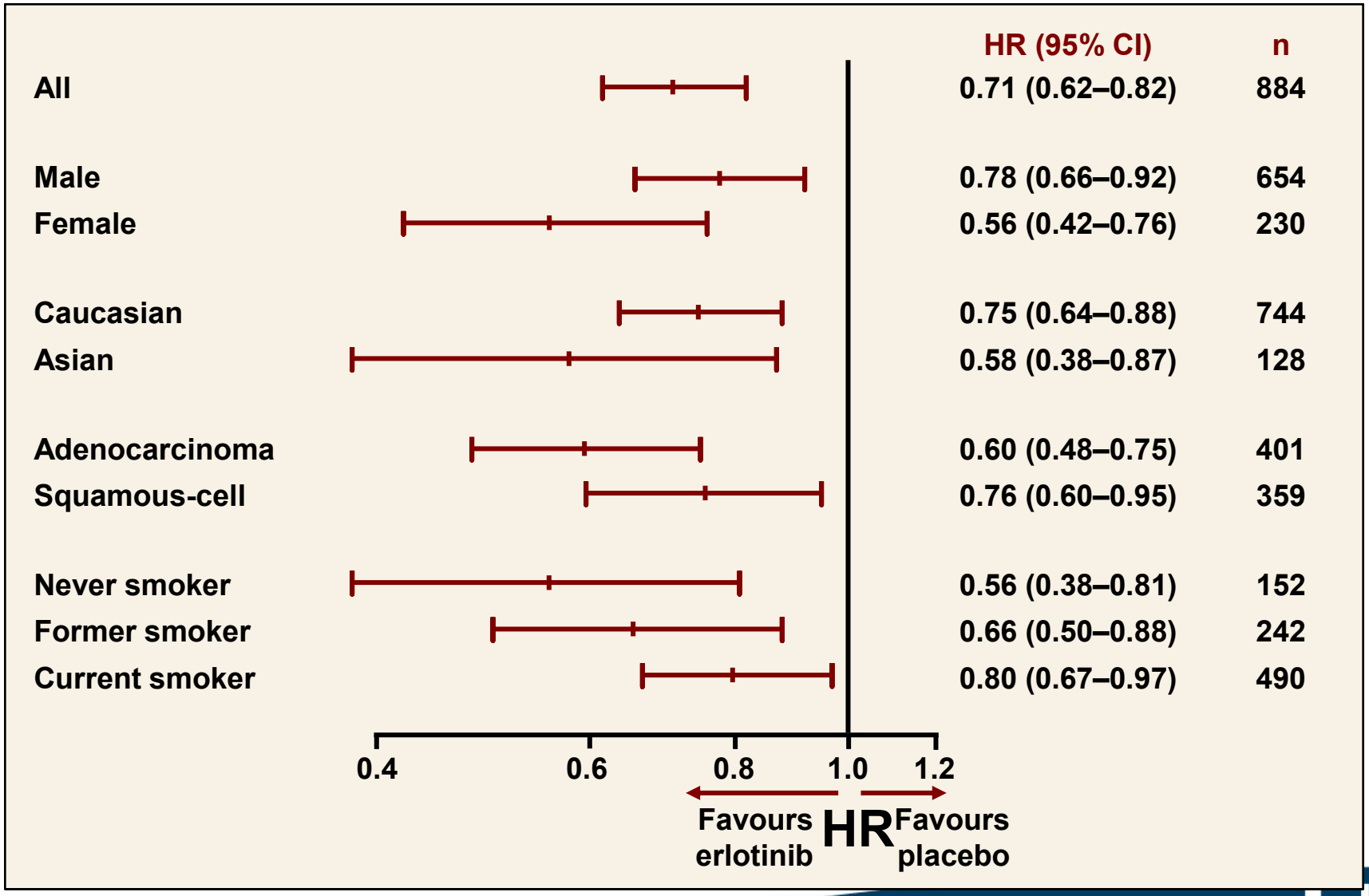
Statistics : PFS as primary endpoint



* 1st line chemotherapy: Cisplatin/Carboplatin + Docetaxel/Paclitaxel/Gemcitabine/Vinorelbine

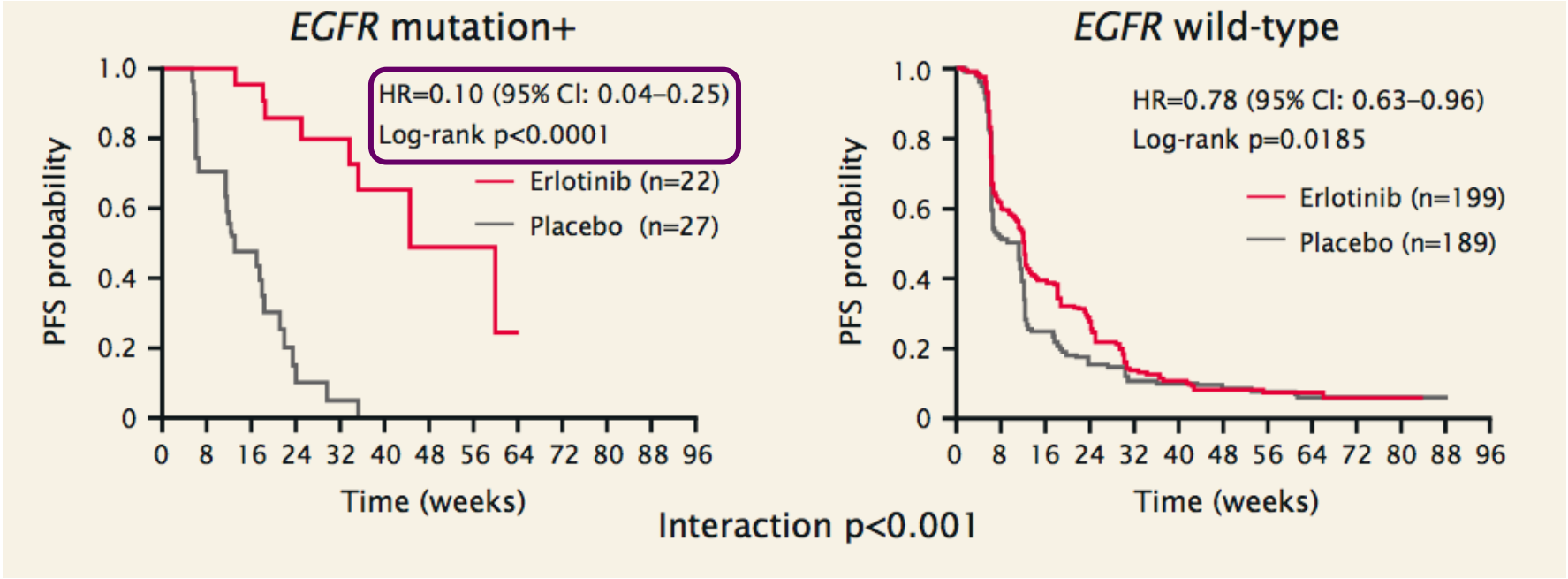
Cappuzzo et al. *ASCO 2009*: abstract 8001.

SATURN: PFS subgroup analysis



Cappuzzo et al. *ASCO 2009*: abstract 8001.

SATURN: PFS by biomarkers

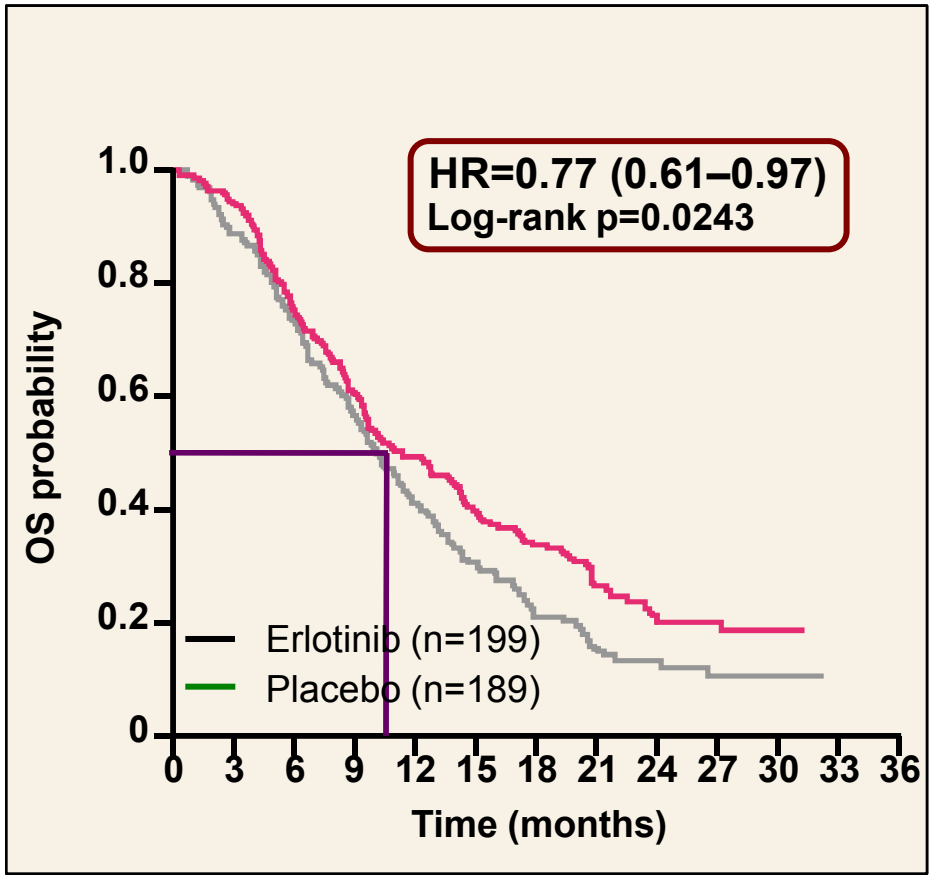


EGFR mutations identify patients who derive a greater PFS-benefit from erlotinib maintenance (median PFS 11m *vs* 3 m).

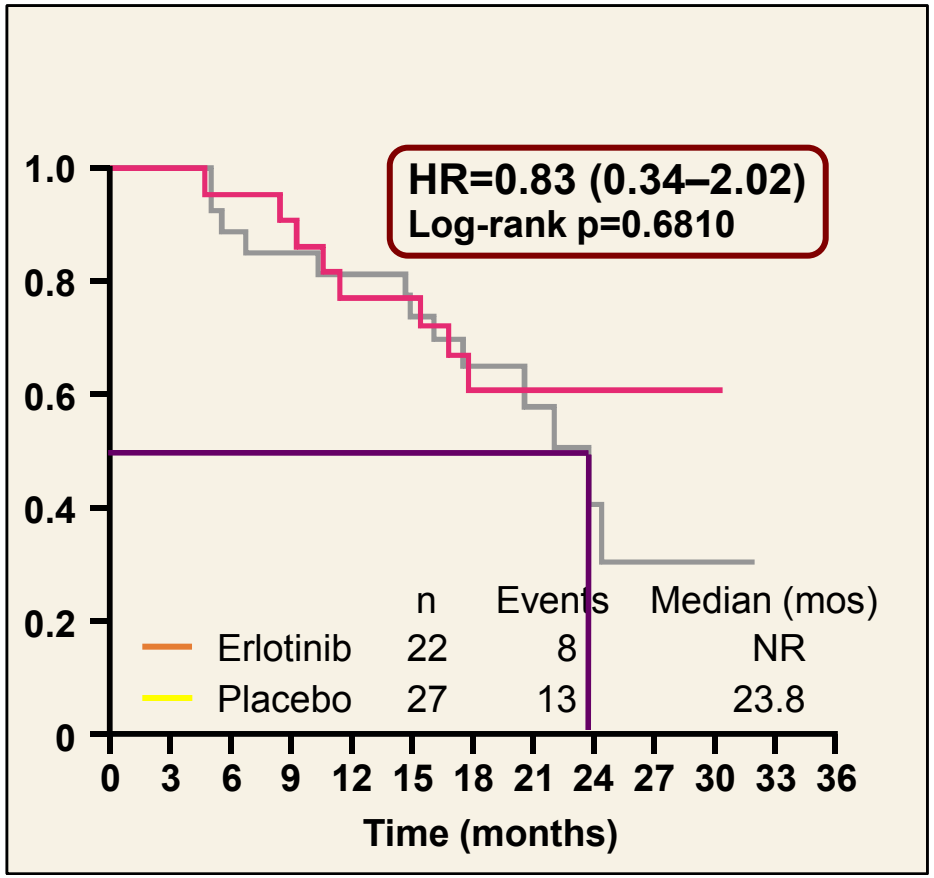
Brugger et al. *ASCO 2009*: abstract 8020.

SATURN: overall survival

EGFR-wild type



EGFR-mutation positive *



*67% of patients with *EGFR* mutation+ disease in the placebo arm received a second-line EGFR TKI

Brugger, et al. WCLC 2009

Erlotinib maintenance in NSCLC: SATURN trial

	EGFR wild type	EGFR mutation +
PFS	**HR 0.78** (0.63-0.96)	**HR 0.10** (0.04-0.25)
OS *	**HR 0.77** (0.61-0.97)	**HR 0.83** (0.34-2.02)
OS	**MST ~11 m**	**MST ~24m**

- **EGFR mutations** identify patients who derive a **greater PFS-benefit** from erlotinib maintenance (median PFS 11m *vs.* 3 m).
- The **EGFR mutation** is a **favourable prognostic factor**

*67% of patients with *EGFR* mutation+ disease in the placebo arm received a second-line EGFR TKI

Brugger et al. *ASCO 2009*: abstract 8020.

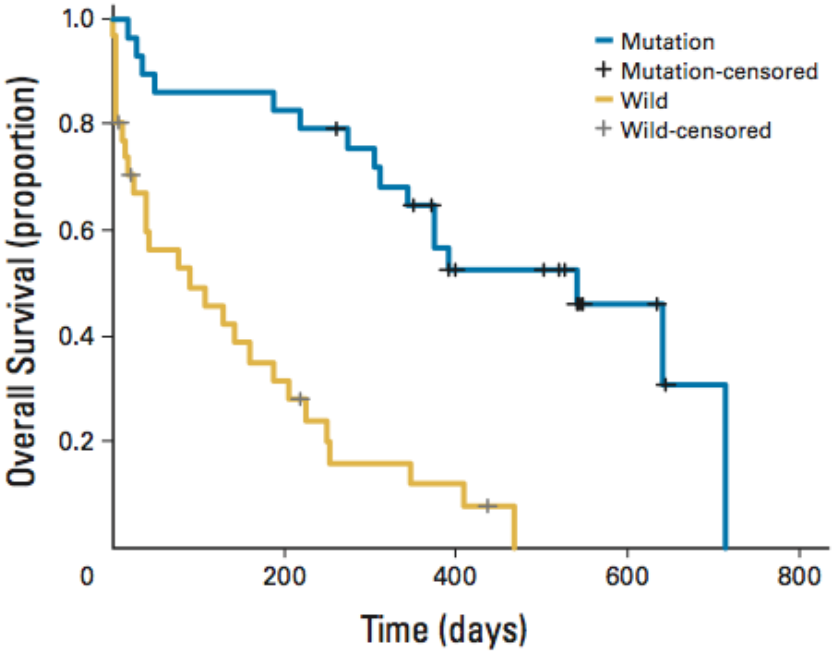
Phase II study of 1st-line gefitinib for poor PS pts with NSCLC harboring activating EGFR-mutations

- Chemo-naïve NSCLC
- Poor PS:
  - 20-74 yrs: PS 3- 4
  - 75-79 yr: PS 2-4
  - ≥80 yr: PS 1-4¶

EGFR-mutation

Activating EGFR-mutation:
Gefitinib (n 30)

Wildtype EGFR:
No Gefitinib (n 31)



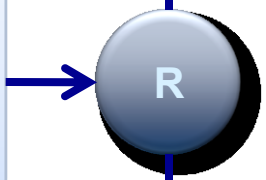
EGFR mutation +	
Objective response rate	66%
Disease control rate	90%
PS improvement rate	79%
median PFS	6.5 m
median OS	17.8 m
1-yr OS rate	63%

Inoue et al. *J Clin Oncol* 2009; 27:1394-1400.

Topical trial: erlotinib in pts unfit for chemo

- Advanced NSCLC
- Chemo-naïve
- Unfit for platinum chemo§

§ PS 2-3 or GFR <60ml/min



N = 670

Experimental arm:
Erlotinib 150 mg/d

Control arm:
Best Supportive Care

Trial demographics	
Median age	77y
PS 2-3	84%
Women	39%
AdenoCA	38%
Never smokers	5%

	Erlotinib	BSC
median PFS	2.8 m	2.7 m
median OS	3.8 m	3.6 m
↳ female	5.3 m *	4.3 m
↳ EGFR m+	11 m	2.8 m

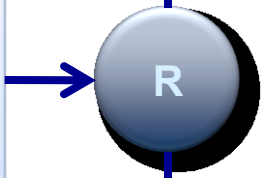
* p=0.025

Lee et al. *ASCO 2010*: abstract 7504.

Erlotinib ± CarboPacli in 1st line

- Chemo-naïve NSCLC
- Never or former light § smoker
- AdenoCA

§ ≤10PY and ≥1y stop smoking



Erlotinib
N = 82

Erlotinib + CarboPacli (6x)
N = 100

EGFR genotyping in 95% of pts → *EGFR* mutation in 39% of pts

Erlotinib	RR	PFS	OS
All	34%	6.7m	24.0m
EFGR mutant	66%	16.4m	27.6m
EGFR WT	8%	2.8m	15.4m

Erlot + CP	RR	PFS	OS
All	47%	6.0m	19.6m
EFGR mutant	69%	17.2m	39.0m
EGFR WT	31%	4.8m	13.7m

Janne et al. *ASCO 2010*: abstract 7503.

American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non–Small-Cell Lung Cancer

Christopher G. Azzoli, Sherman Baker Jr, Sarah Temin, William Pao, Timothy Aliff, Julie Brahmer, David H. Johnson, Janessa L. Laskin, Gregory Masters, Daniel Milton, Luke Nordquist, David G. Pfister, Steven Piantadosi, Joan H. Schiller, Reily Smith, Thomas J. Smith, John R. Strawn, David Trent, and Giuseppe Giaccone

The first-line use of gefitinib may be recommended for patients with known EGFR mutation; for negative or unknown EGFR mutation status, cytotoxic chemotherapy is preferred.

Azzoli CG et al. J Clin Oncol 2009; 27:6251-6266

2009 recommendation A7

- In unselected patients with stage IV NSCLC, erlotinib or gefitinib should not be used in combination with cytotoxic chemotherapy as first-line therapy.
- In unselected patients, evidence is insufficient to recommend single-agent erlotinib or gefitinib as first-line therapy.
- The first-line use of gefitinib may be recommended for patients with activating EGFR mutations.
- If EGFR mutation status is negative or unknown, then cytotoxic chemotherapy is preferred.

Azzoli CG et al. J Clin Oncol 2009; 27:6251-6266

Expert commentary

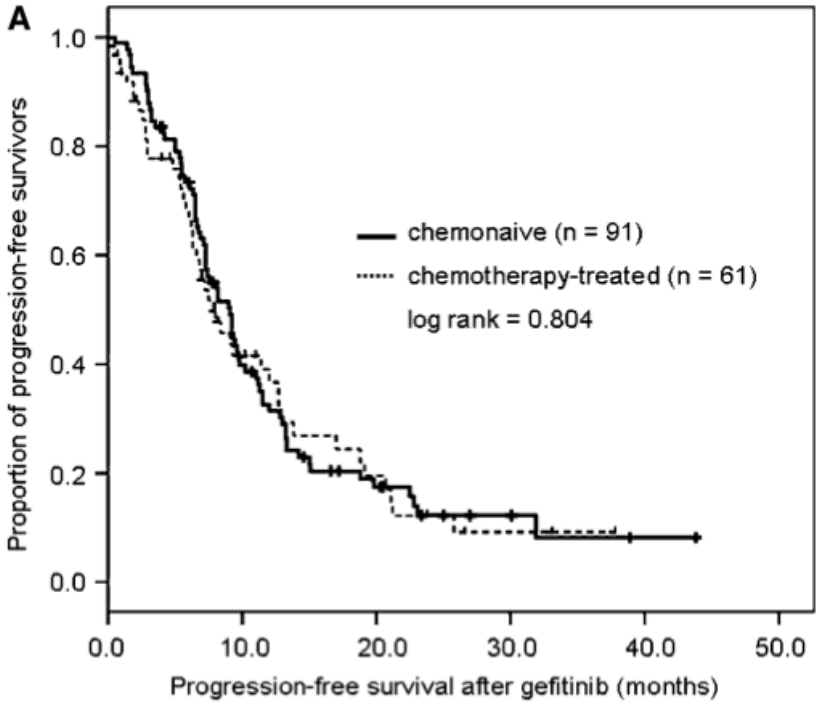
- EGF receptor mutation testing is likely to become used more routinely to select patients for treatment with an EGFR-TKI; therefore, limitations of the current techniques need to be addressed.
- Another limitation of EGFR mutation analysis is the availability of tissue for testing.
- In the lung cancer setting, diagnoses are often based on small biopsies or cytologic specimens; tumors are often inaccessible and the collection of sufficient good-quality tissue samples is difficult.
- The use of surrogate (non tumor) samples, including serum, plasma and cytology samples, has been explored; however, current methods have been found to lack sufficient sensitivity with a false-negative rate of approximately 50%.

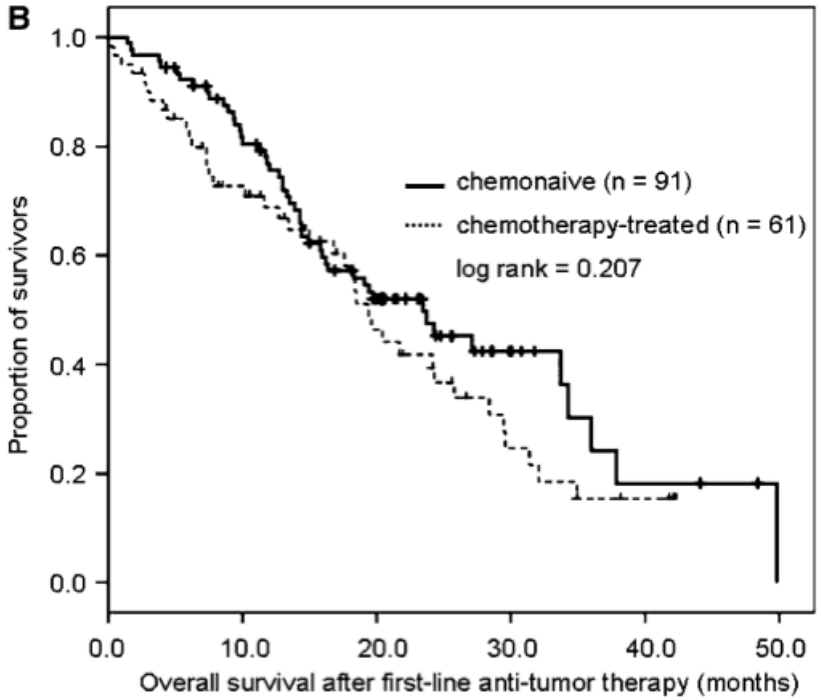
Expert commentary

- The detection of EGFR mutations is fundamental in identifying those patients who will benefit most from treatment with gefitinib.
- Results from the IPASS indicate that if patients with EGFR mutation-positive tumors are treated with gefitinib, they will have superior PFS and ORR than if they receive chemotherapy.
- The detection of EGFR mutations in patients with NSCLC is the first molecular predictive factor that offers patients a more effective and convenient targeted therapy than conventional chemotherapy regimens.
- This is the first step leading to individualized treatment for patients with advanced NSCLC that will improve both disease outcomes and QoL.

- Recommendation A7 supports the first-line use of gefitinib over carboplatin and paclitaxel in patients whose NSCLC tumors harbor EGFR mutation based on a clinically significant improvement in PFS, favorable toxicity profile, and improved quality of life.
- These data justify attempts to test NSCLC tumors for the presence of EGFR mutation.

Survival of patients with activating EGFR-mutations who received gefitinib therapy





Wu et al. *Am J Respir Crit Care Med* 2008; 178: 847–853.

WJTOG3405 : 1st line gefitinib *vs* chemotherapy

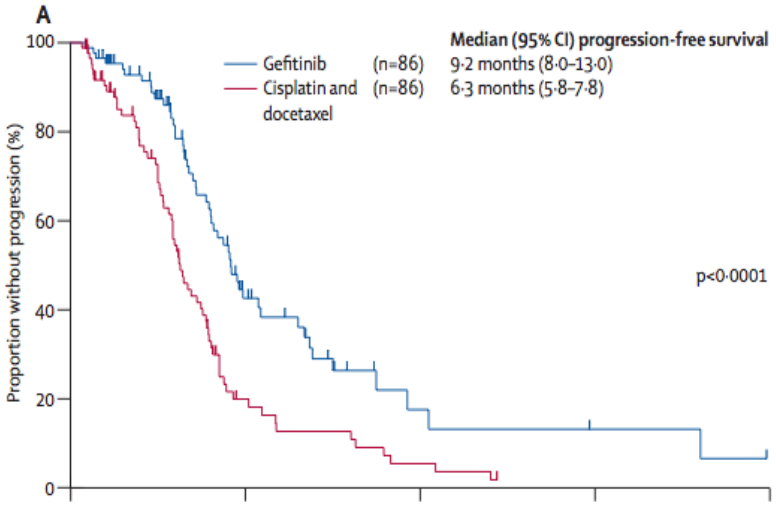
Inclusion criteria:
- Chemonaive Asian pts
- EGFR activating mutation

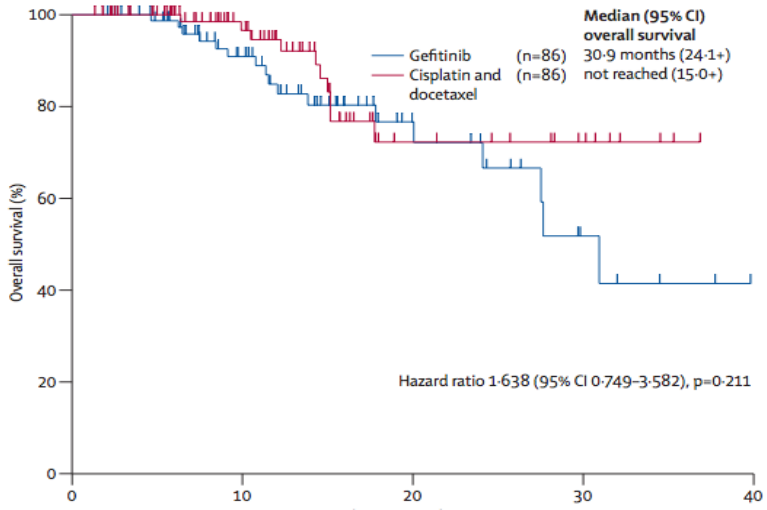
R

Gefitinib arm:
Gefitinib 250 mg/d until PD

Chemotherapy arm:
Cisplatin + Docetaxel (6 cycles)

Statistics : PFS as primary endpoint



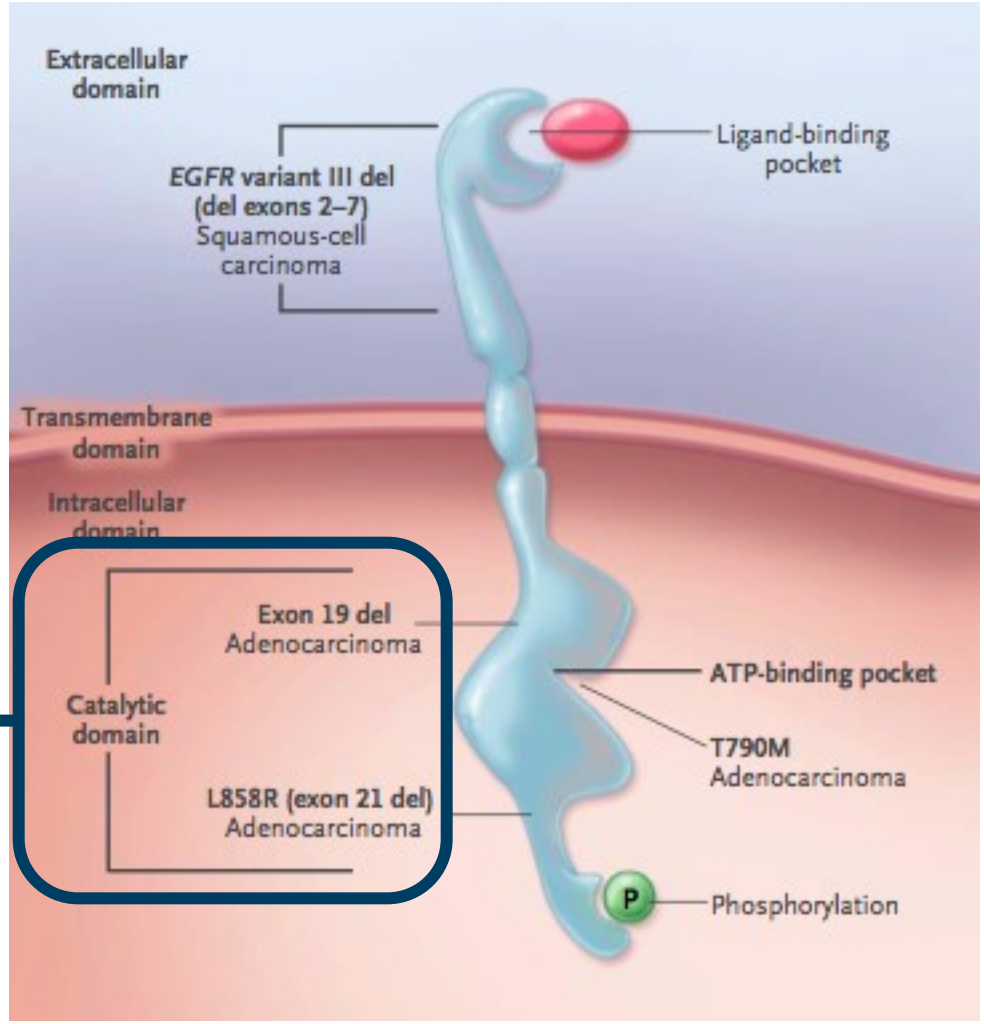


Mitsudomi et al. *The Lancet Oncology*. 2010 ; 11: 121-128.

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

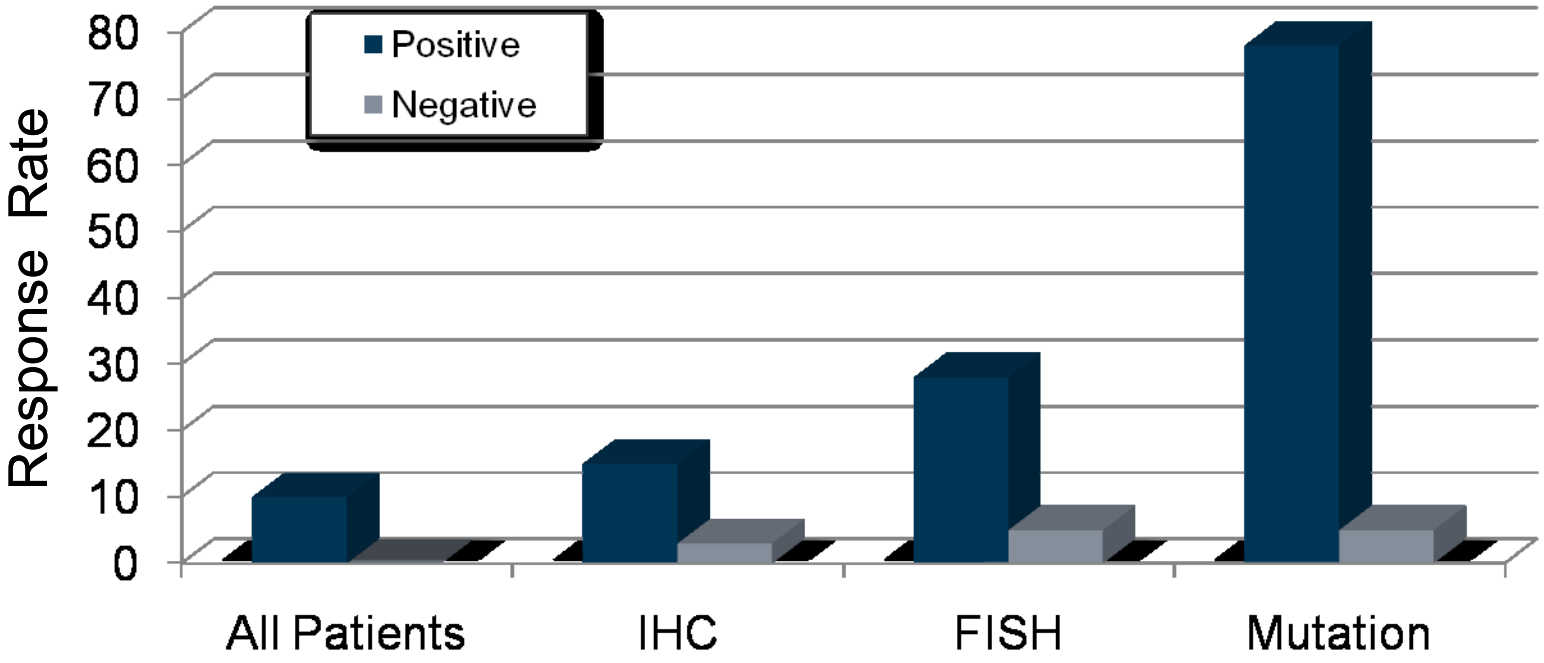
>80% of EGFR mutations; results in **constitutive EGFR activation**

Oncogene-addiction to activated EGFR-pathway



Herbst RS et al. *NEJM*. 2008; 359:1367-80.

Antitumorale activiteit van EGFR-TKI en EGFR-biomerkers



Tsao *NEJM* 2005; Capuzzo *JNCI* 2005; Hirsch *J Clin Oncol* 2005; Han *JCO* 2005; Takano *JCO* 2005; Cortes Funes *Ann Oncol* 2004; Taron *CCR* 2005