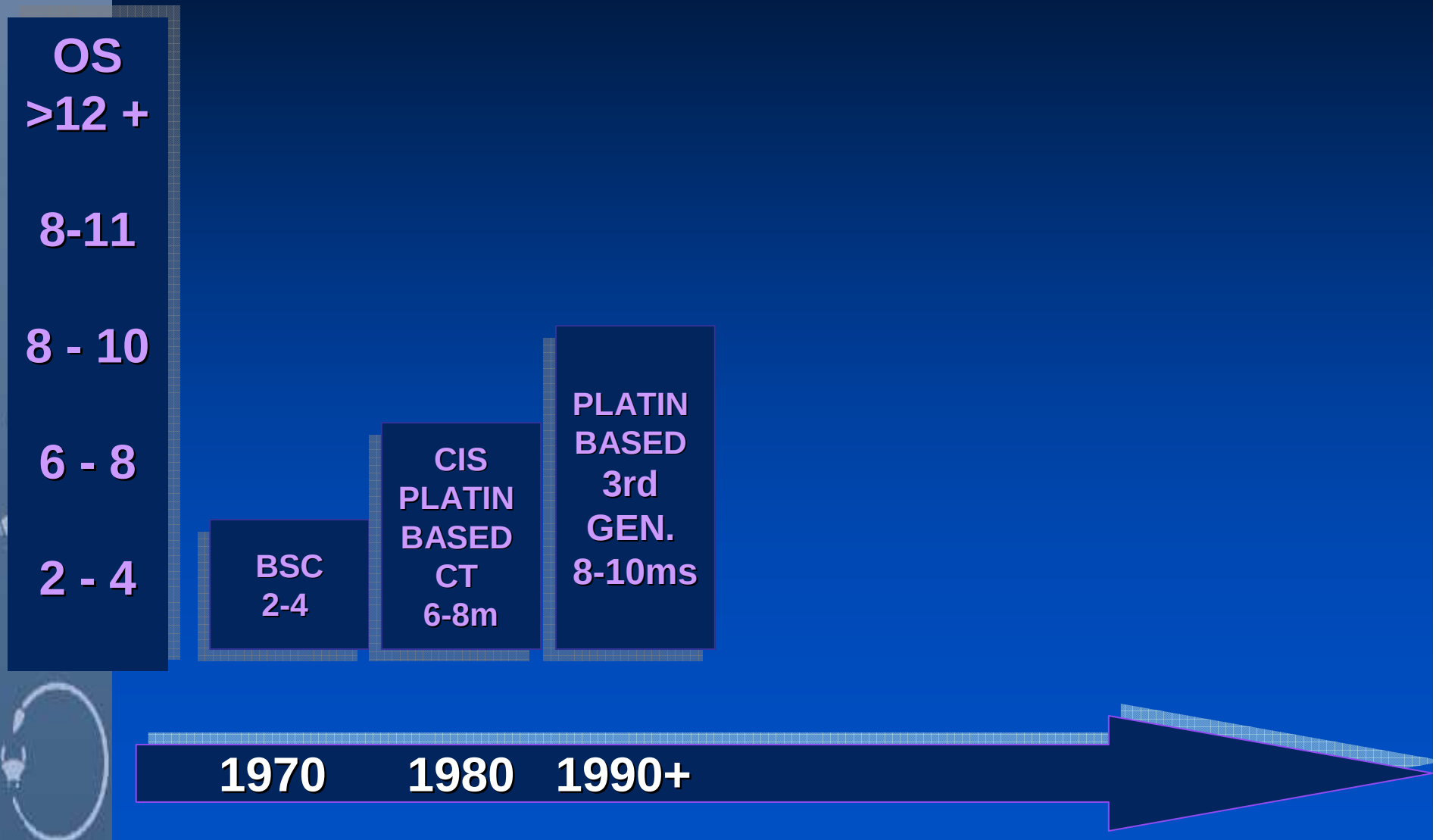
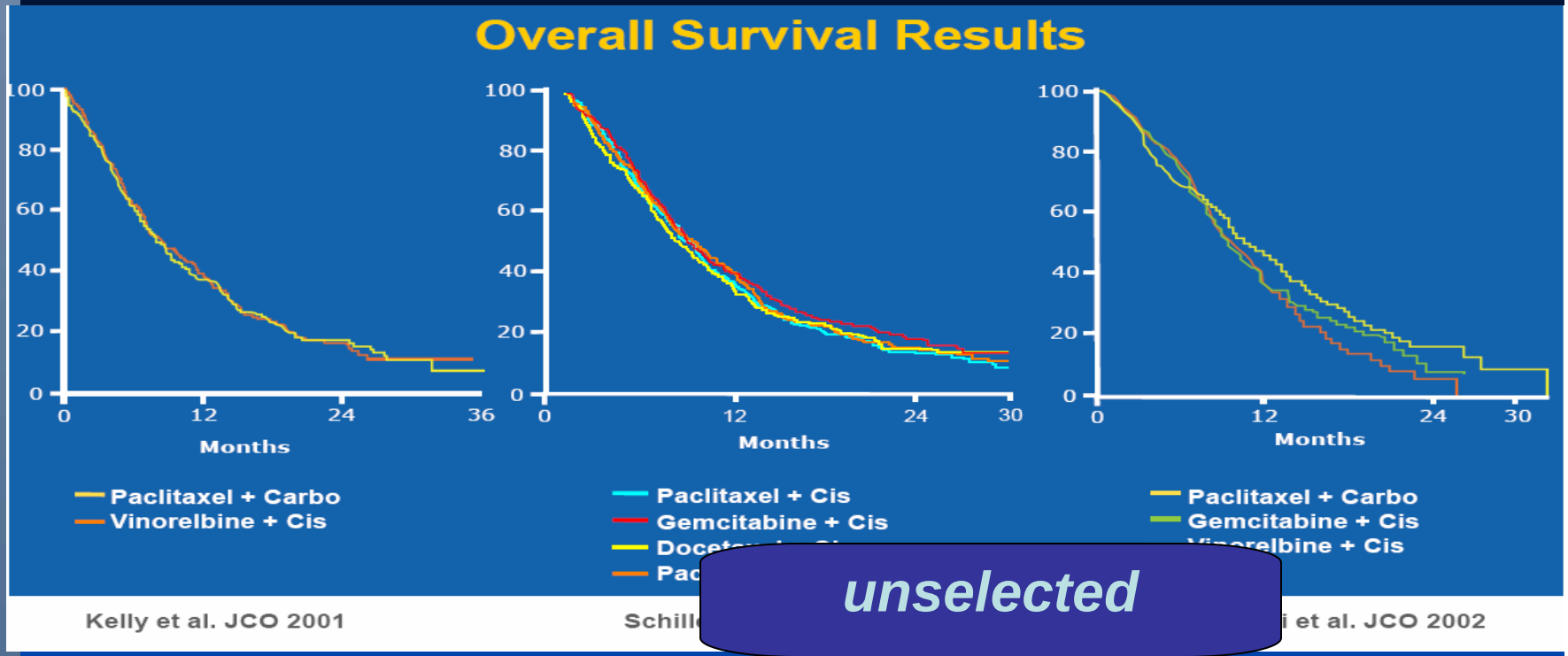
ΜΜΚΠ Πόσο μακριά είμαστε από την εξατομικευμένη θεραπεία;

Ανδριανή Γ. Χαρπίδου
Πνευμονολόγος
Διδάκτωρ Πανεπιστημίου Αθηνών
Ογκολογική Μονάδα,
Γ΄ΠΠ, ΝΝΘΑ «ΣΩΤΗΡΙΑ»

Platinum-based CTx: The Cornerstone of therapy in 1st line for advanced NSCLC



CTx in advanced NSCLC



unselected

What we can achieve in unselected patients?

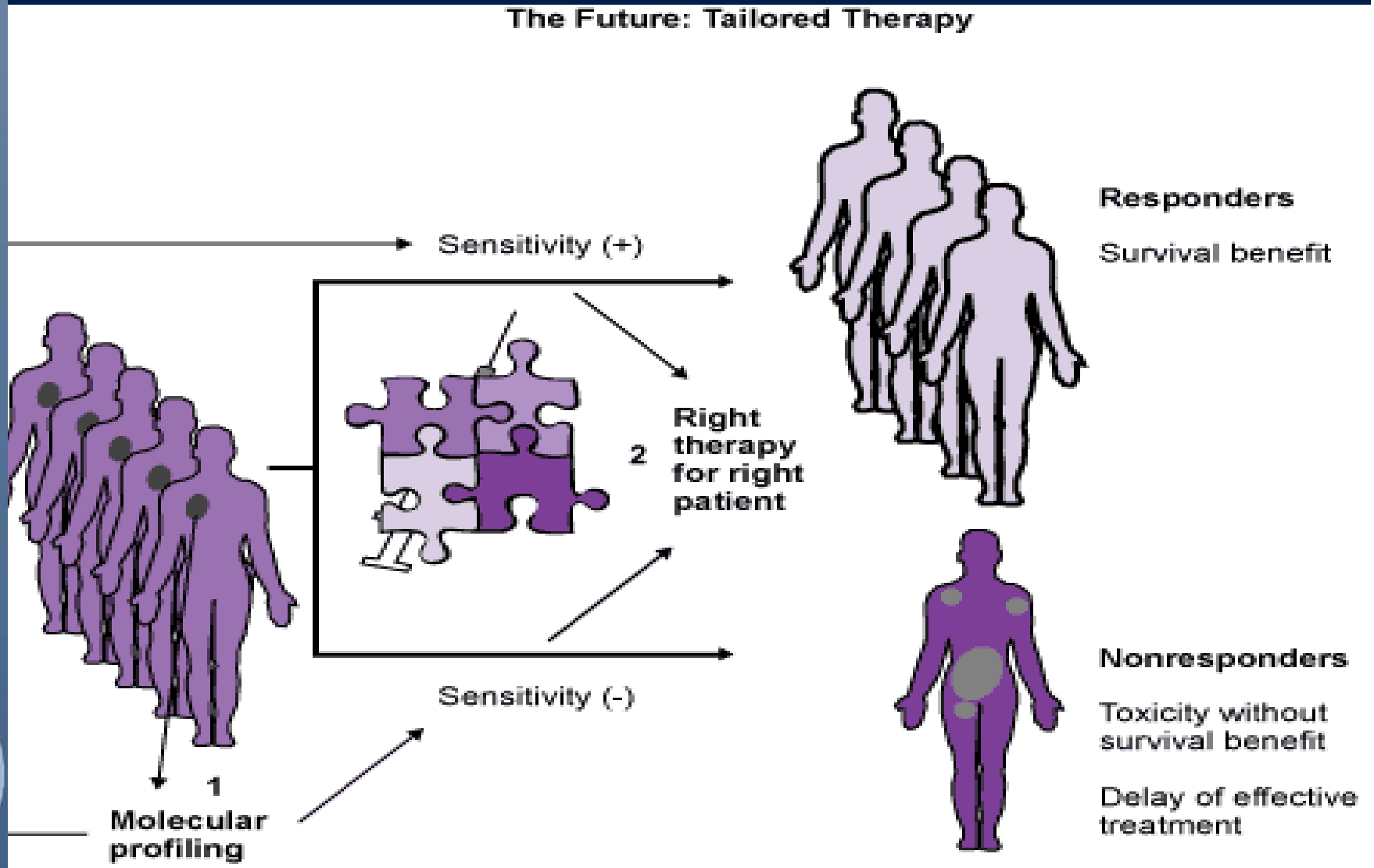
Response :19% - 32%

Progression Free Survival :3 -5 months

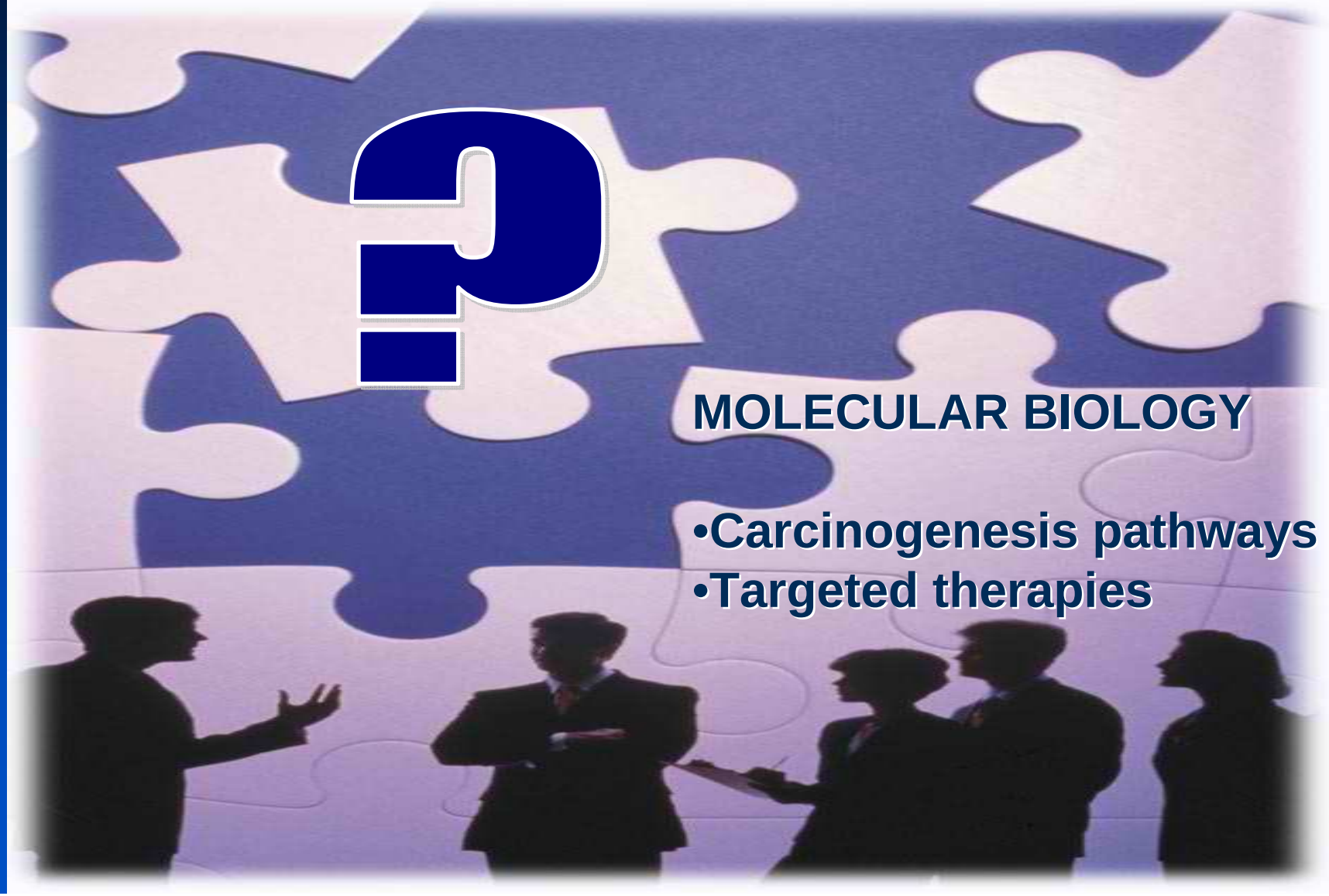
Median Survival :7.9-9.9 months

1y survival :33-43%

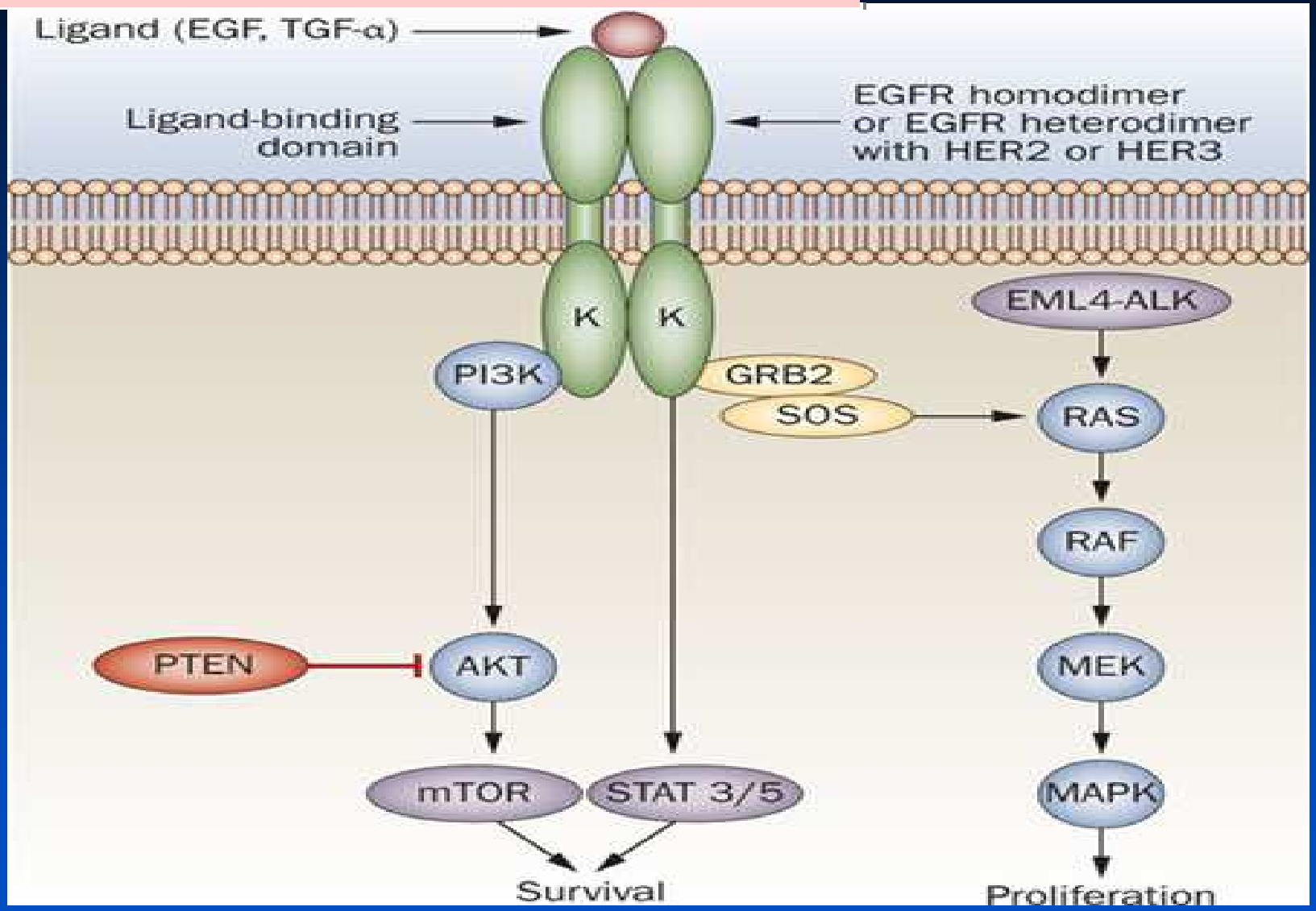
Individualized therapy



Individualized therapy

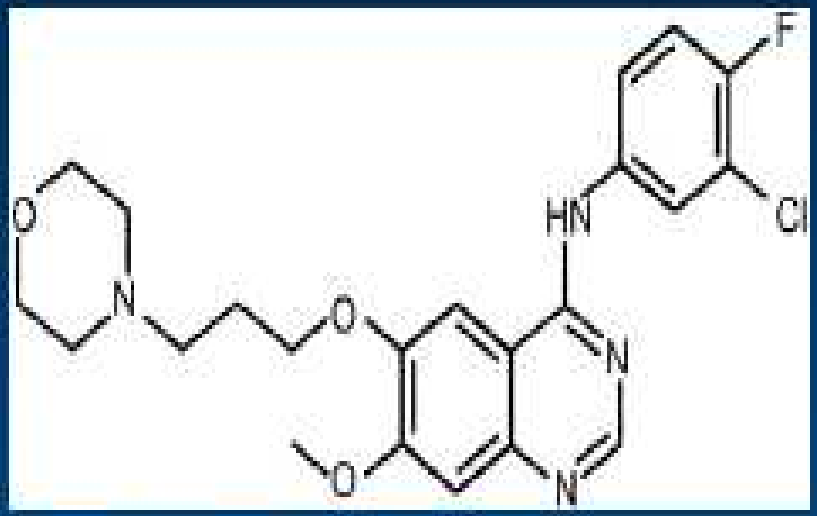


Epidermal Growth Factor Receptor (EGFR) signaling pathways

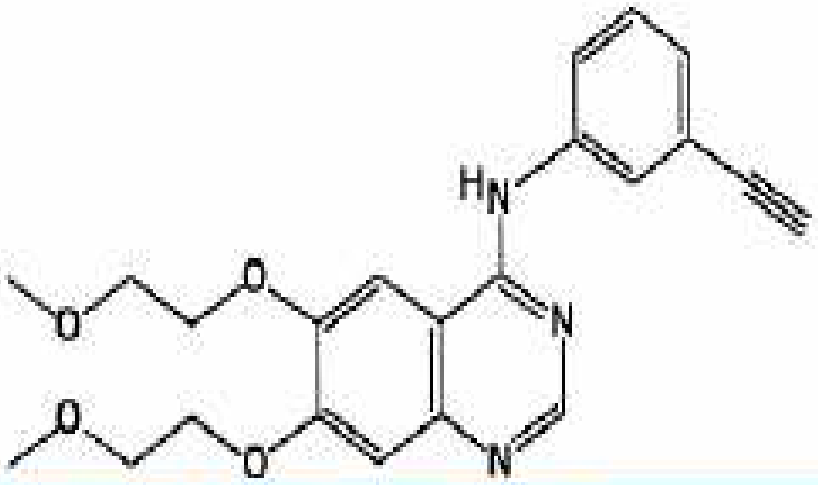


Janku, F. et al. Nat. Rev. Clin. Oncol. ;2010

1st Generation EGFR TKIs: Gefitinib, Erlotinib



ZD1839, Gefitinib, Iressa



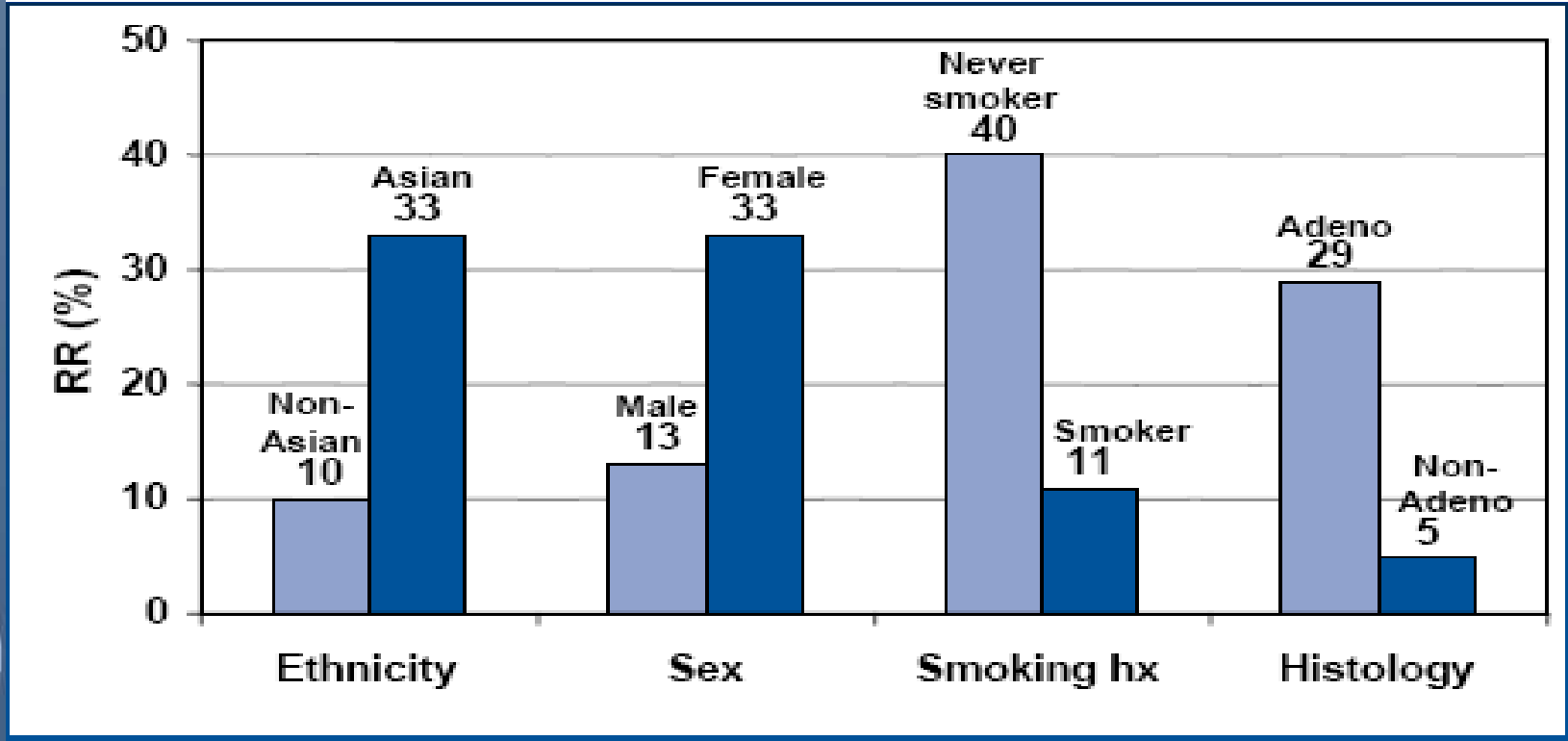
OSI-774, Erlotinib, Tarceva

Response Rate of EGFR-TKIs according to Clinical Backgrounds

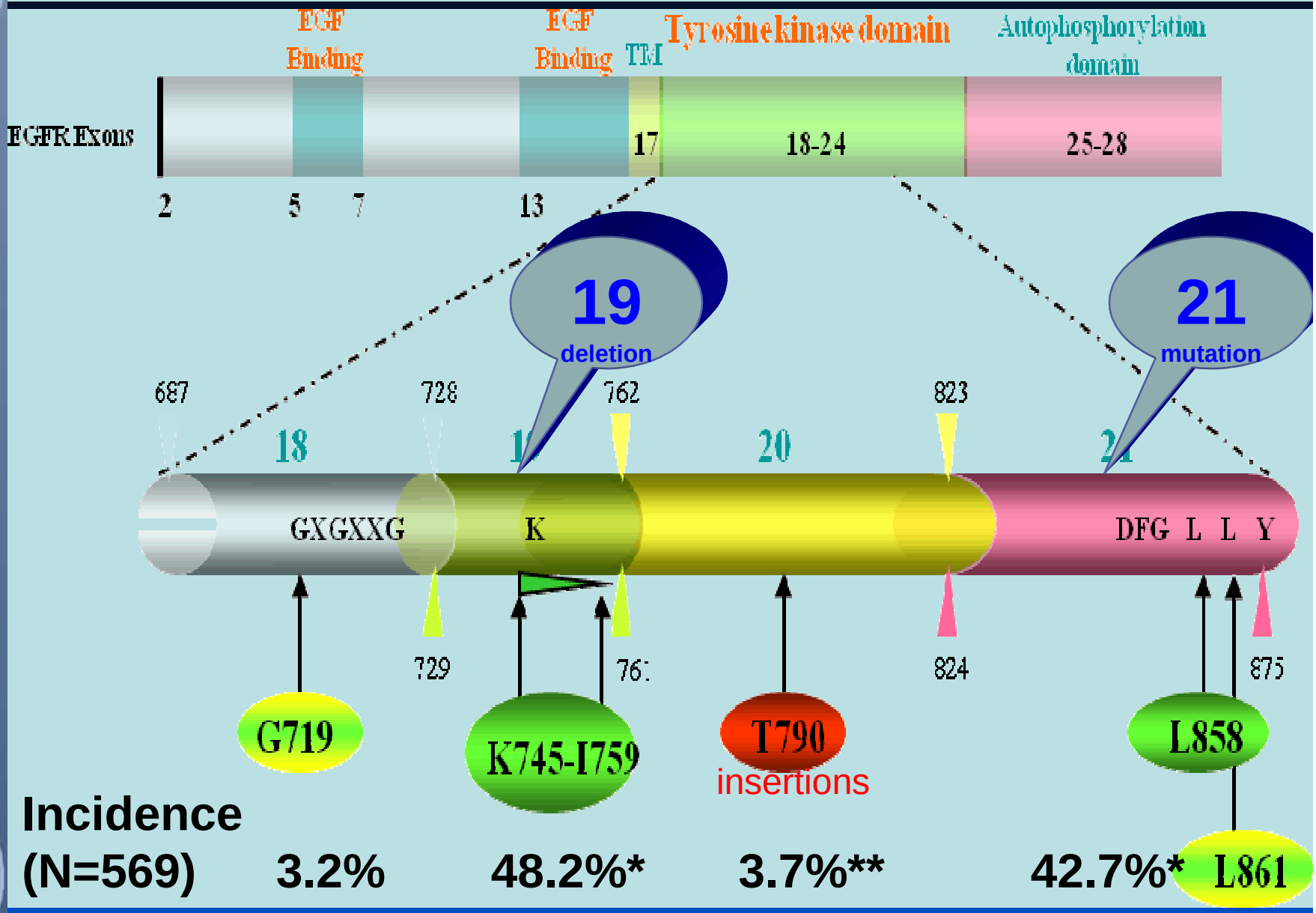
(compiled from the literature N=1974)

About 10% of unselected NSCLC pts have an objective response but

the frequency of response was related to clinical features

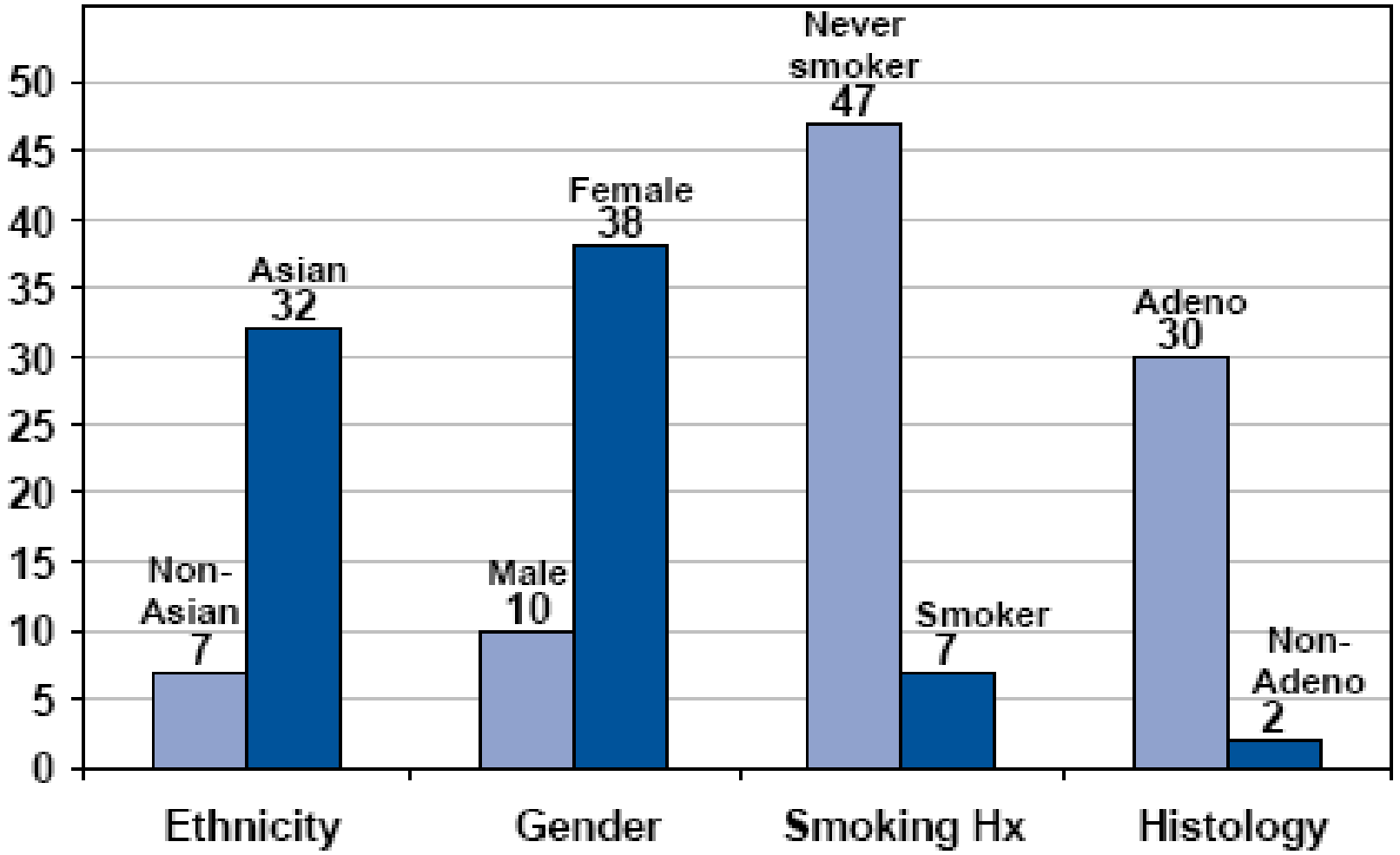


EGFR mutations: distribution and incidence



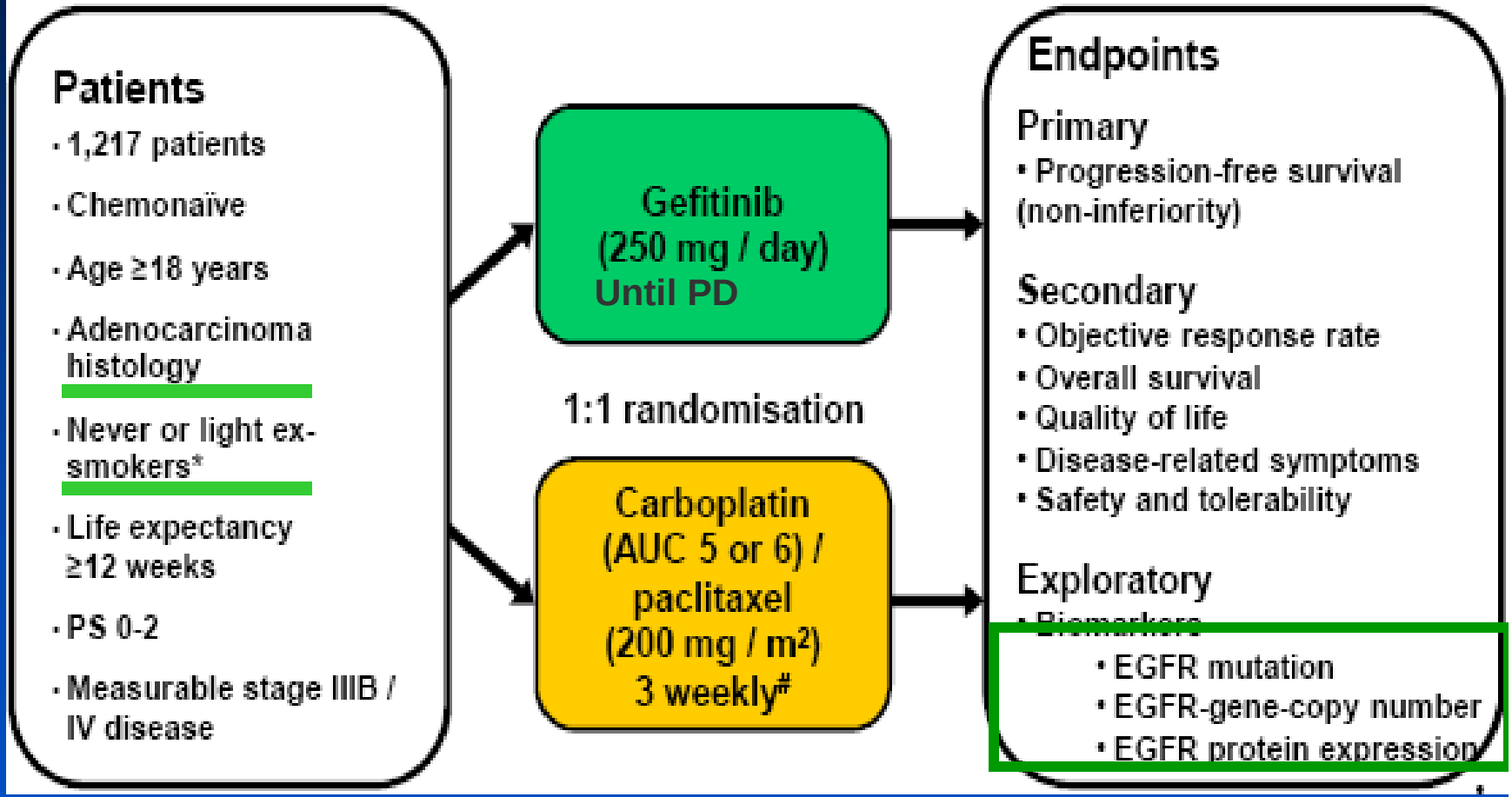
Lynch T et al N Engl J Med 2004
Mitsudomi et al. Cancer Science 2007.

Incidence of *EGFR* Mutations According to Patient Backgrounds (N=2880)



EGFR - TKIs

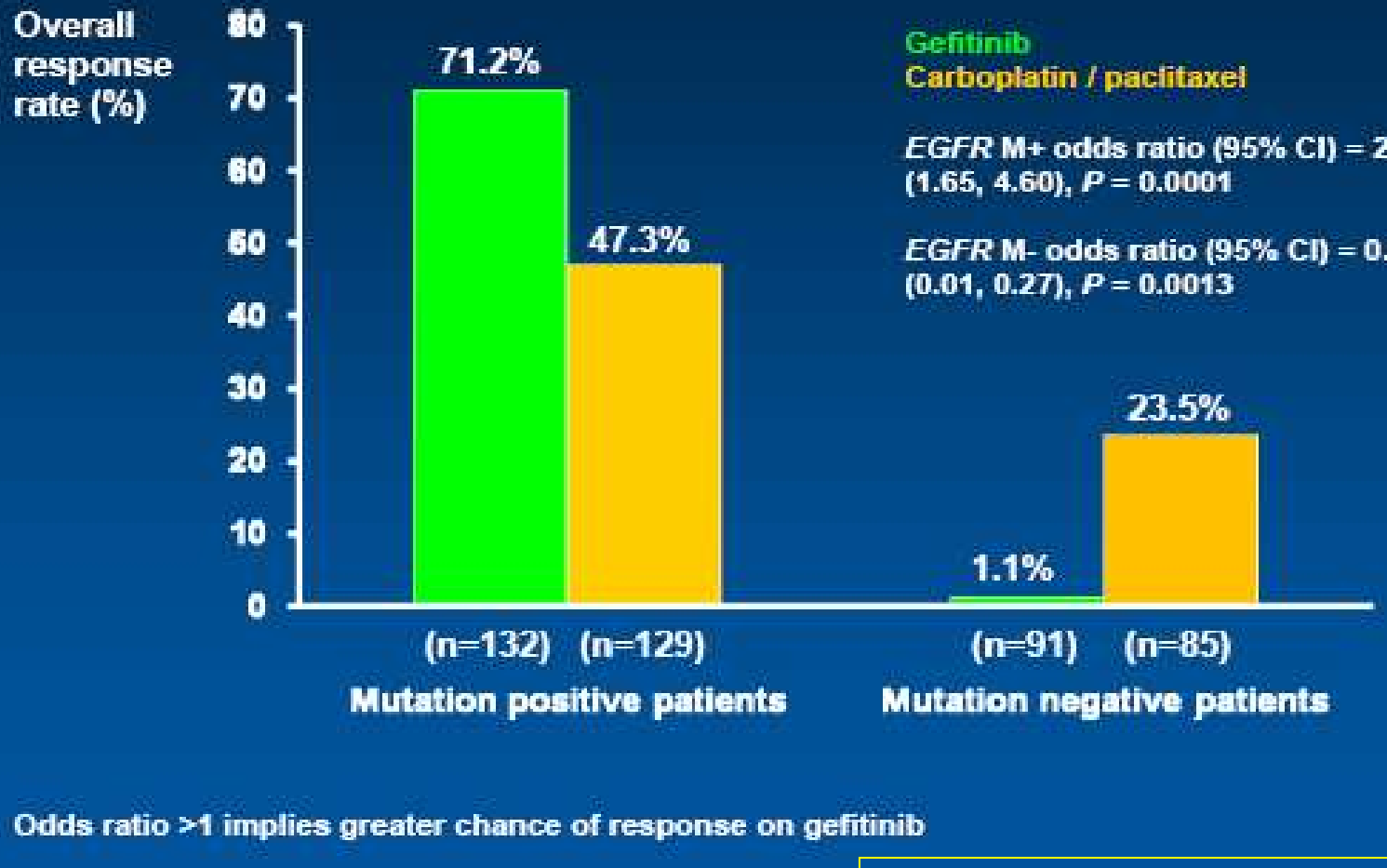
Iressa Pan-ASia Study (chemotherapy vs. gefitinib in first line therapy)



Mok T et al, NEJM 361:945-957, 2009

IPASS (chemotherapy vs. gefitinib in first line therapy)

Response Rate varied according to EGFR status

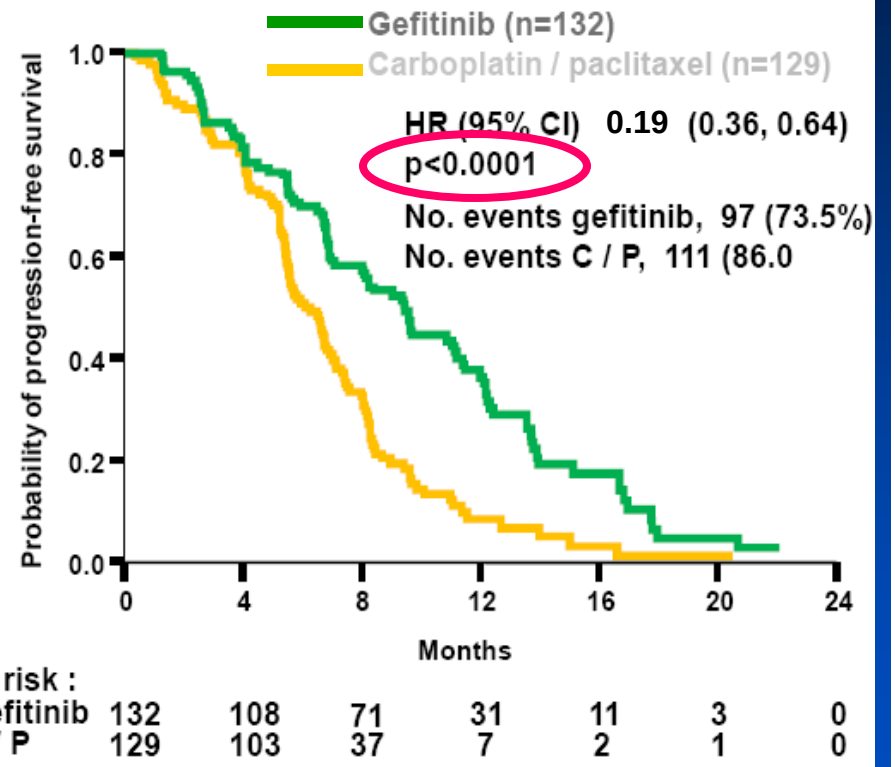


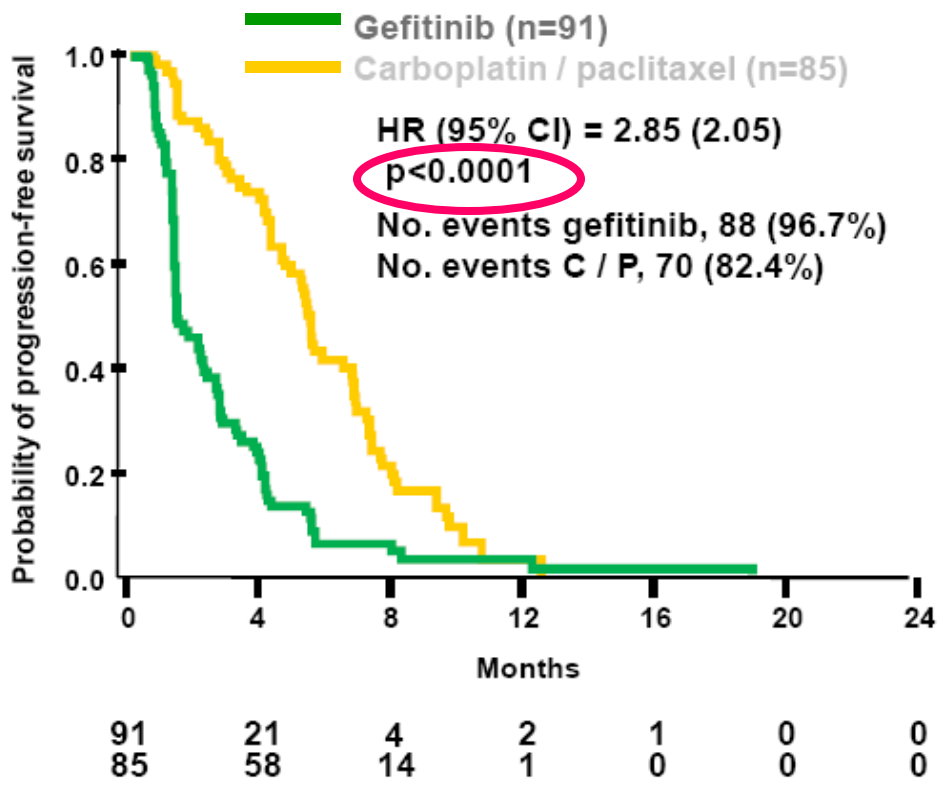
Odds ratio >1 implies greater chance of response on gefitinib

Mok T et al, NEJM 361:945-957, 2009

IPASS (chemotherapy vs. gefitinib in first line therapy)

PFS





Mok T et al, NEJM 361:945-957, 2009

IPASS (chemotherapy vs. gefitinib in first line therapy)

Hematological toxicity

Lab parameter, n (%)#	Gefitinib (N=599)	Carboplatin / paclitaxel (N=577)
Neutropenia	22 (3.7)	387 (67.1)
Leukopenia	9 (1.5)	202 (35.0)
Anaemia	13 (2.2)	61 (10.6)
Thrombocytopenia	6 (1.0)	32 (5.5)

IPASS (chemotherapy vs. gefitinib in first line therapy)

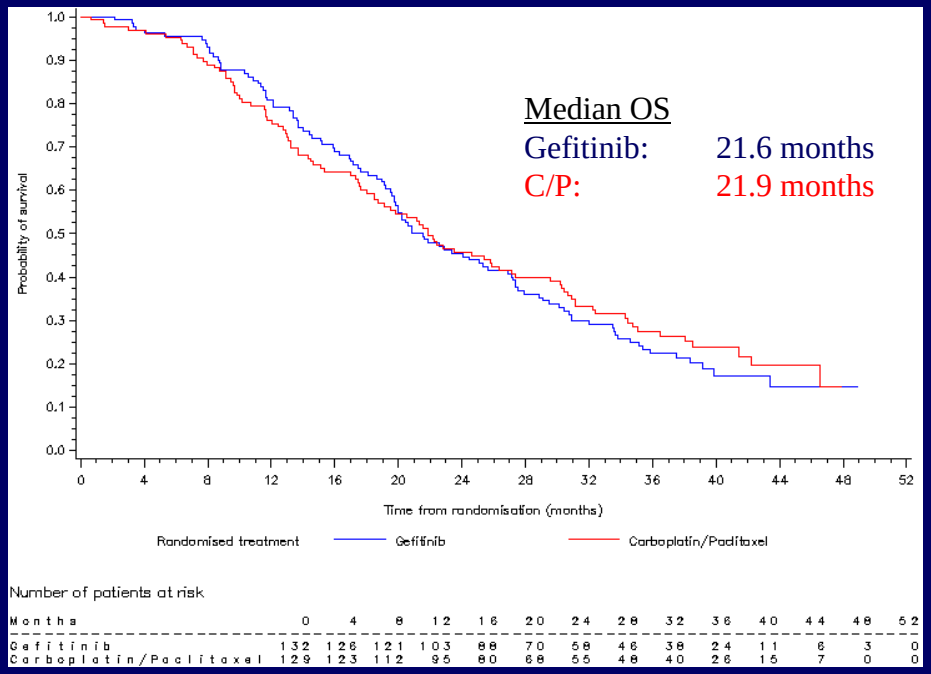
Summary of Adverse Events

	Treatment-related[a]	
n (%)	Gefitinib (N=607)	Carboplatin / paclitaxel (N=589)
SAE	21 (3.5)	53 (9.0)
AE leading to death	4 (0.7)	3 (0.5)
AE leading to discontinuation	24 (4.0)	67 (11.4)
CTC Grade 3, 4 or 5 AE	103 (17.0)	334 (56.7)

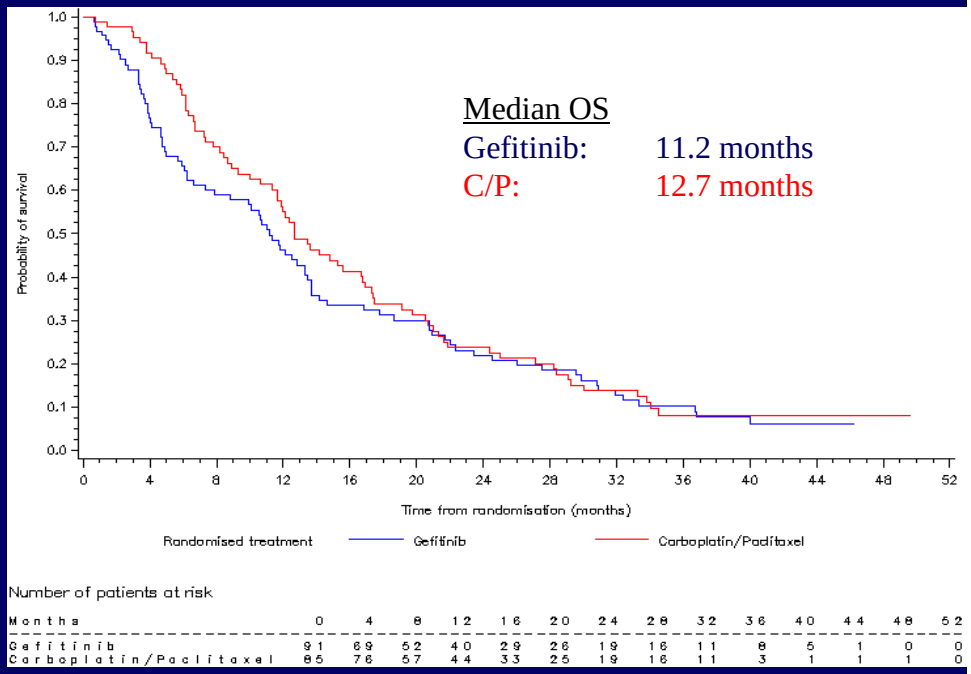
IPASS (chemotherapy vs. gefitinib in first line therapy)

OS

EGFR Mutation possitive



EGFR Mutation negative



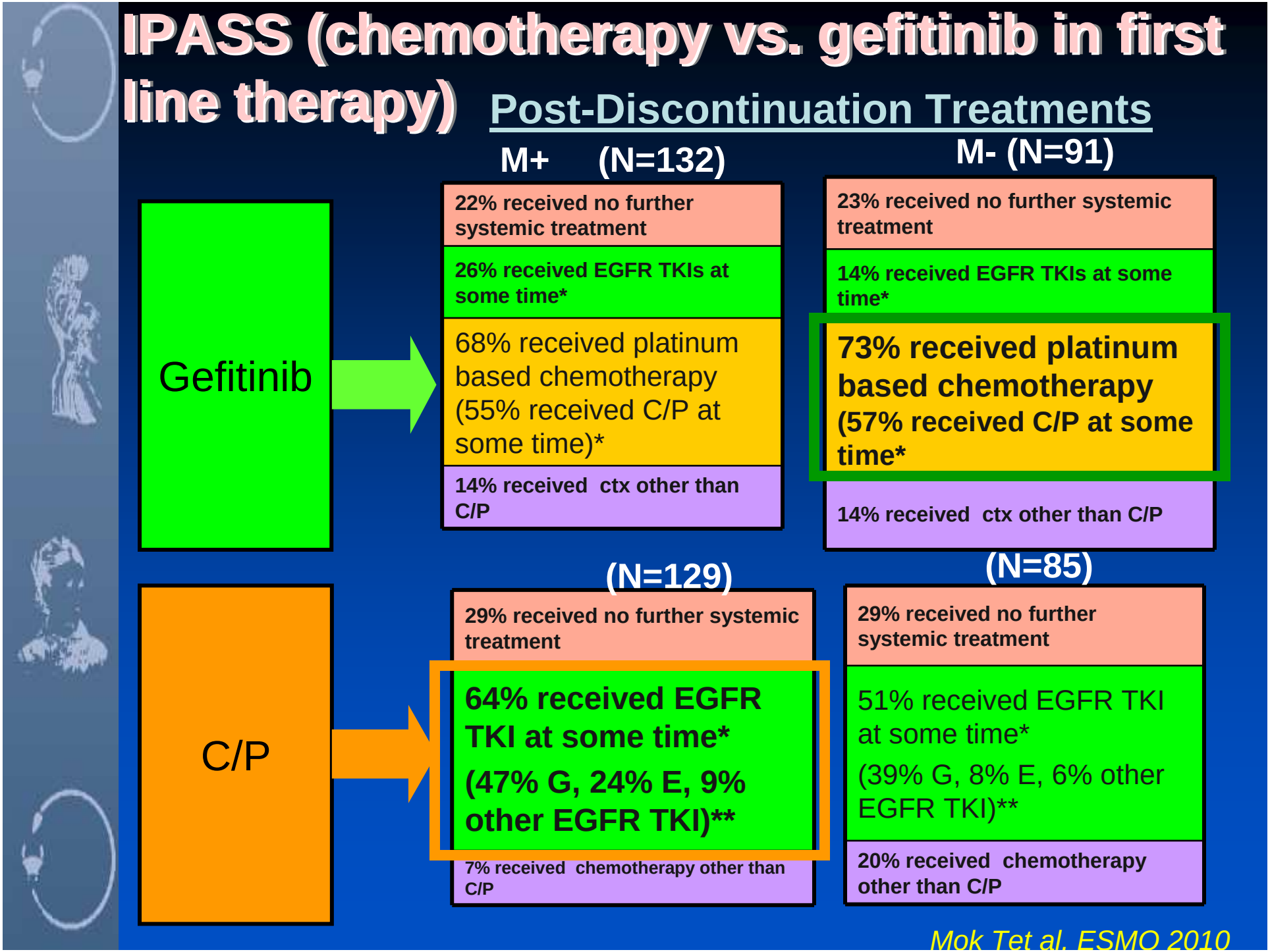
M+	Gefitinib	C/P
N	132	129
Events	104 (78.8%)	95 (73.6%)
HR (95% CI) = 1.00 (0.76, 1.33) p=0.990		

M-	Gefitinib	C/P
N	91	85
Events	82 (90.1%)	74 (87.1%)
HR (95% CI) = 1.18 (0.86, 1.63) p=0.309		

Mok Tet al. ESMO 2010

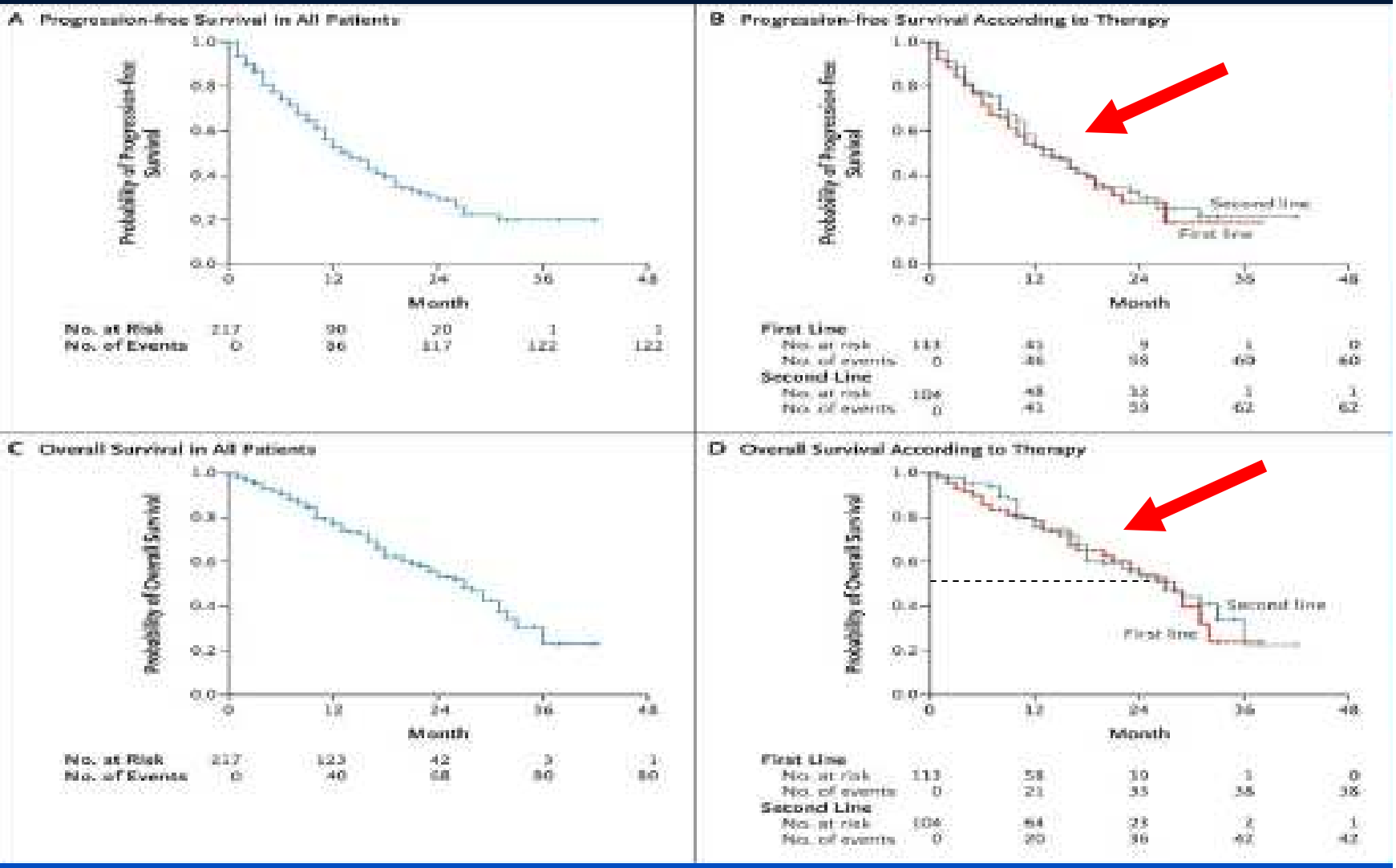
IPASS (chemotherapy vs. gefitinib in first line therapy)

Post-Discontinuation Treatments



Mok Tet al. ESMO 2010

Erlotinib in 1st and 2nd line NSCLC



Rosell R et al. N Engl J Med. 2009;10.1056.

EGFR-TKIs Resistance

Primary **Acquired**

In EGFR Wild Type patients

In EGFR Mutated patients

EGFR-TKIs Resistance

In EGFR Mutated patients

25% of mutated cases do not respond to EGFR-TKIs

Mutations that are less sensitive

D770, N771, insNPG, insSVQ, ins G, N771T

Resistant

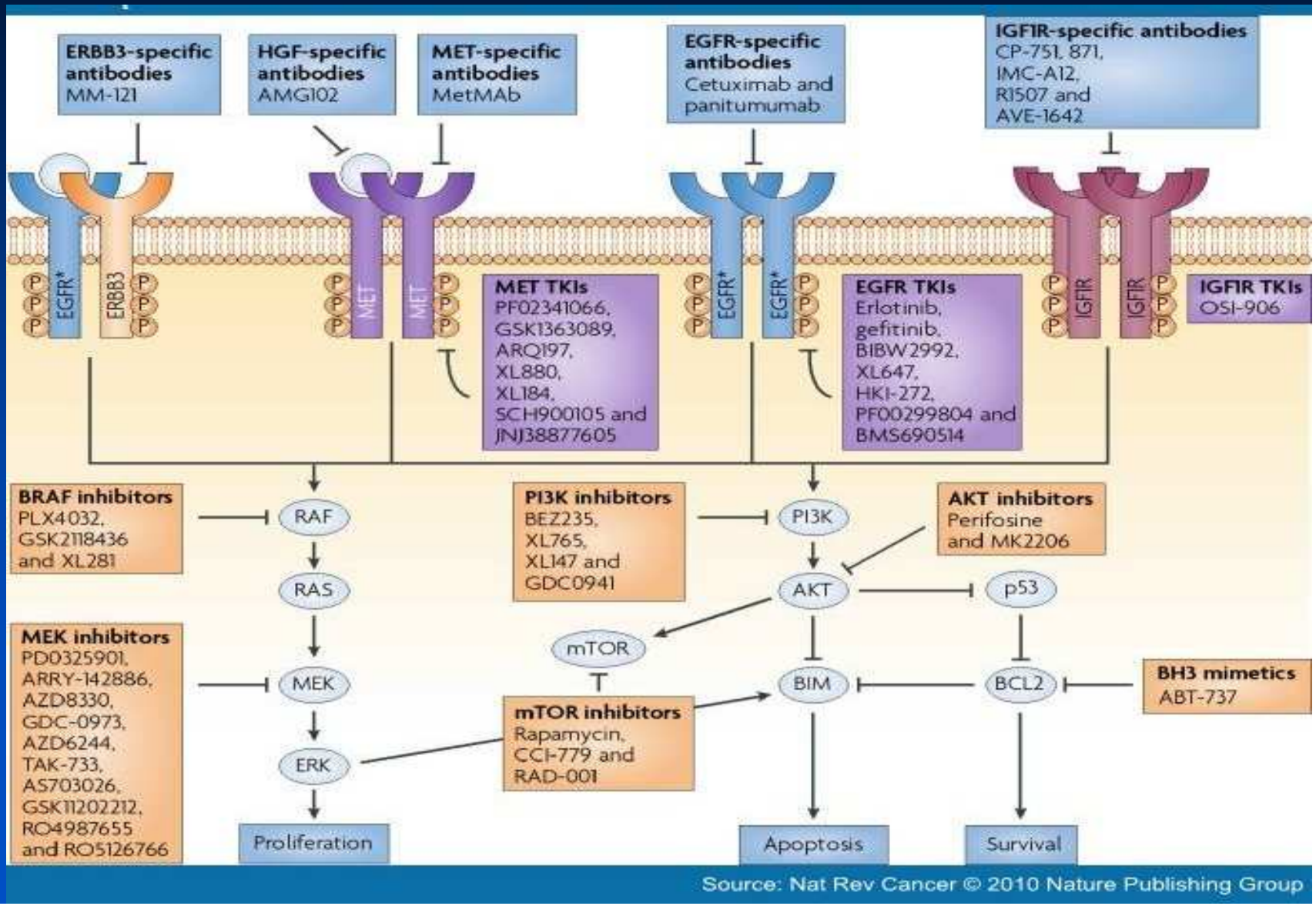
T790M

Co-existence of sensitive and resistant mutation

Other genomic alterations

IGF1R

Signaling pathways in lung cancer



EGFR-TKIs Resistance

In EGFR Wild Type patients

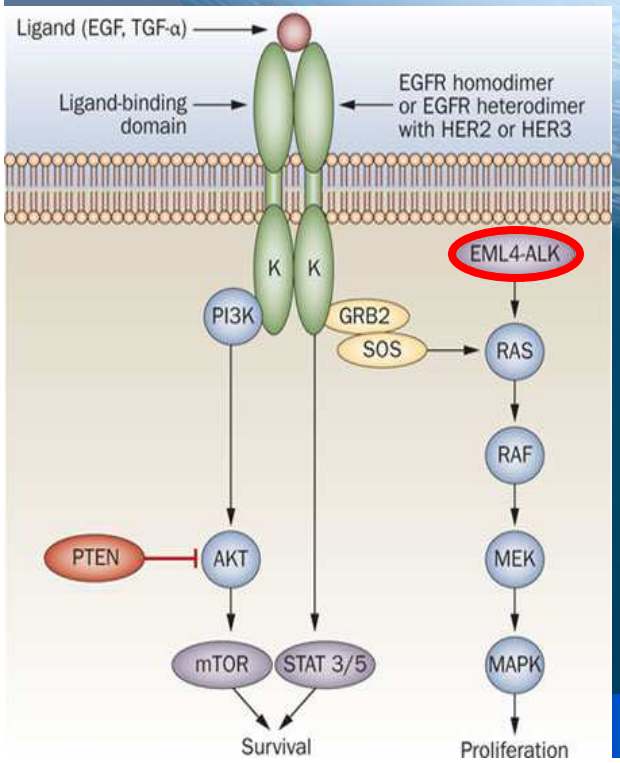
Absence of drug sensitizing mutations

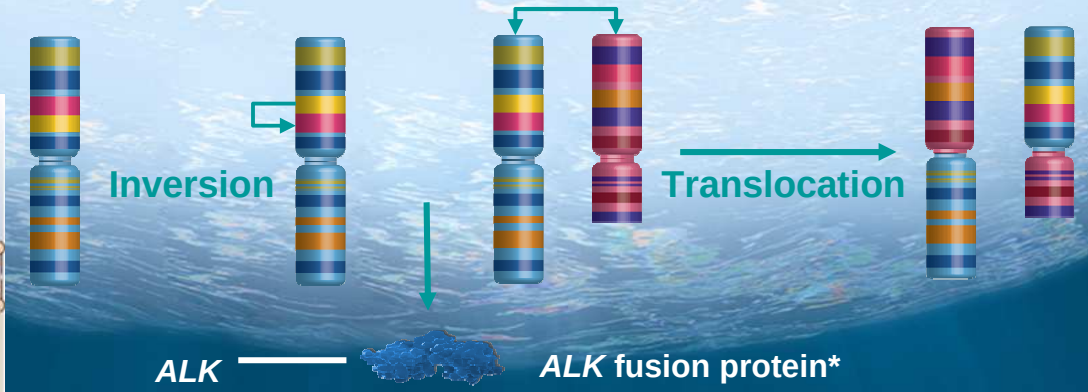
Presence of other mutations
KRAS, EML4-ALK

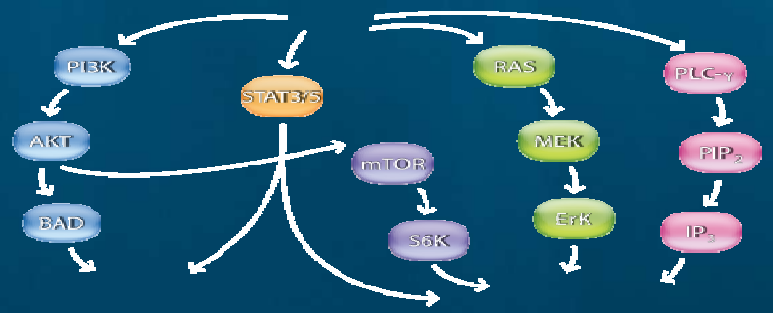
EML4-ALK Fusion in NSCLC

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Mamoru Enomoto[1,2], Shuji Takada[3], Yoshihiro Yamashita[3], Shunpei Ishikawa[3], Shin-ichiro Fujiwara[4], Hideki Watanabe[4], Kentaro Kurashina[4], Hisashi Hatanaka[4], Masashi Bando[5], Shoji Ohno[5], Yuichi Ishikawa[6], Hiroyuki Aburatani[1,2], Toshiro Niki[7], Yasunori Sohara[8], Yukihiko Sugiyama[8] & Hiroyuki Mano[1,2]







Nature 448; 561 (2007).

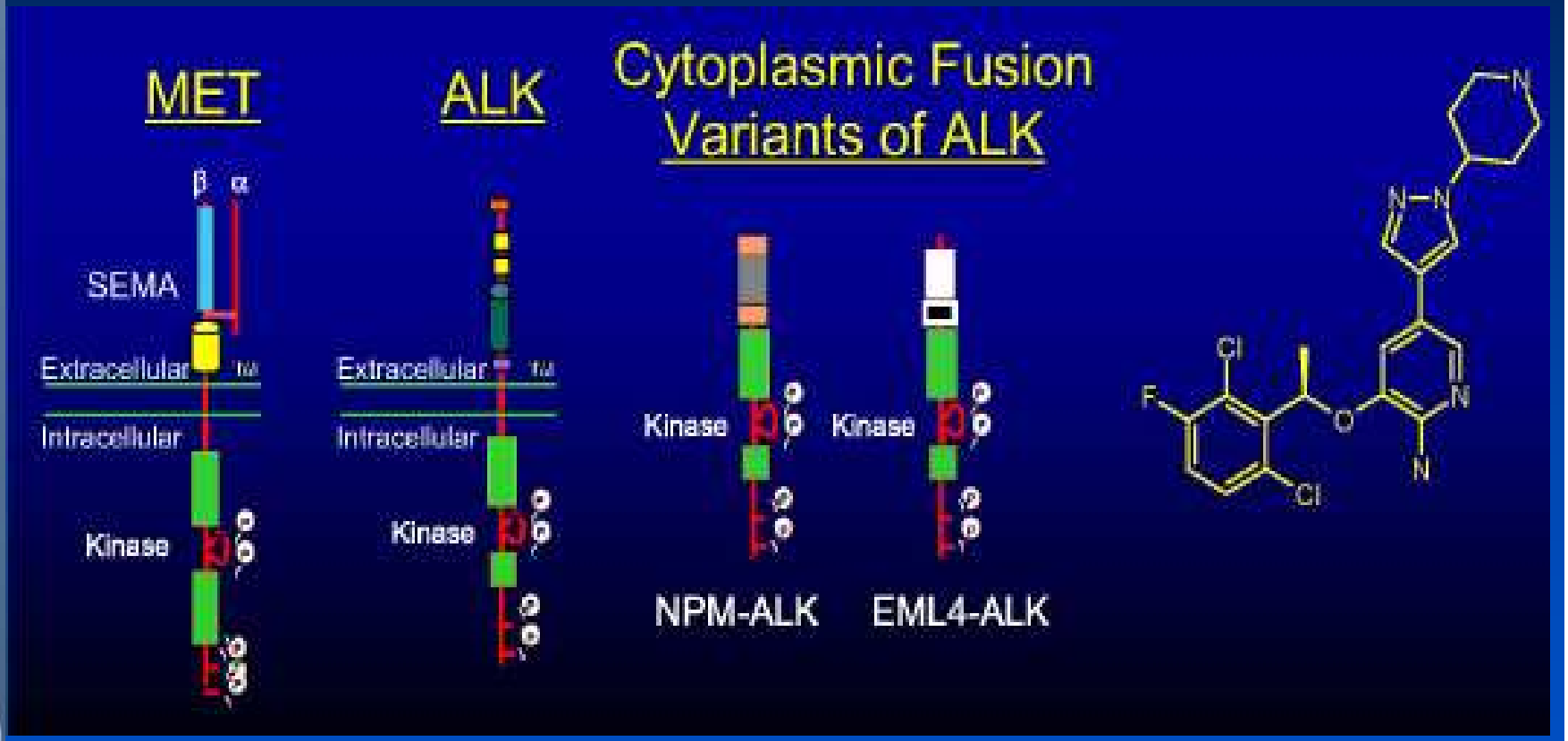
Frequency of ALK Translocations

Author	Total Number	Pos	%
Shaw, ASCO 2009	141	19	13%
Inamura, JTO 2008	149	5	3%
Takeuchi, CCR 2008	253	11	4%
Koivunen, CCR 2008	365	8	3%
Wong, Cancer 2009	266	13	5%
Takahashi, ASO 2009	313	5	1.6%

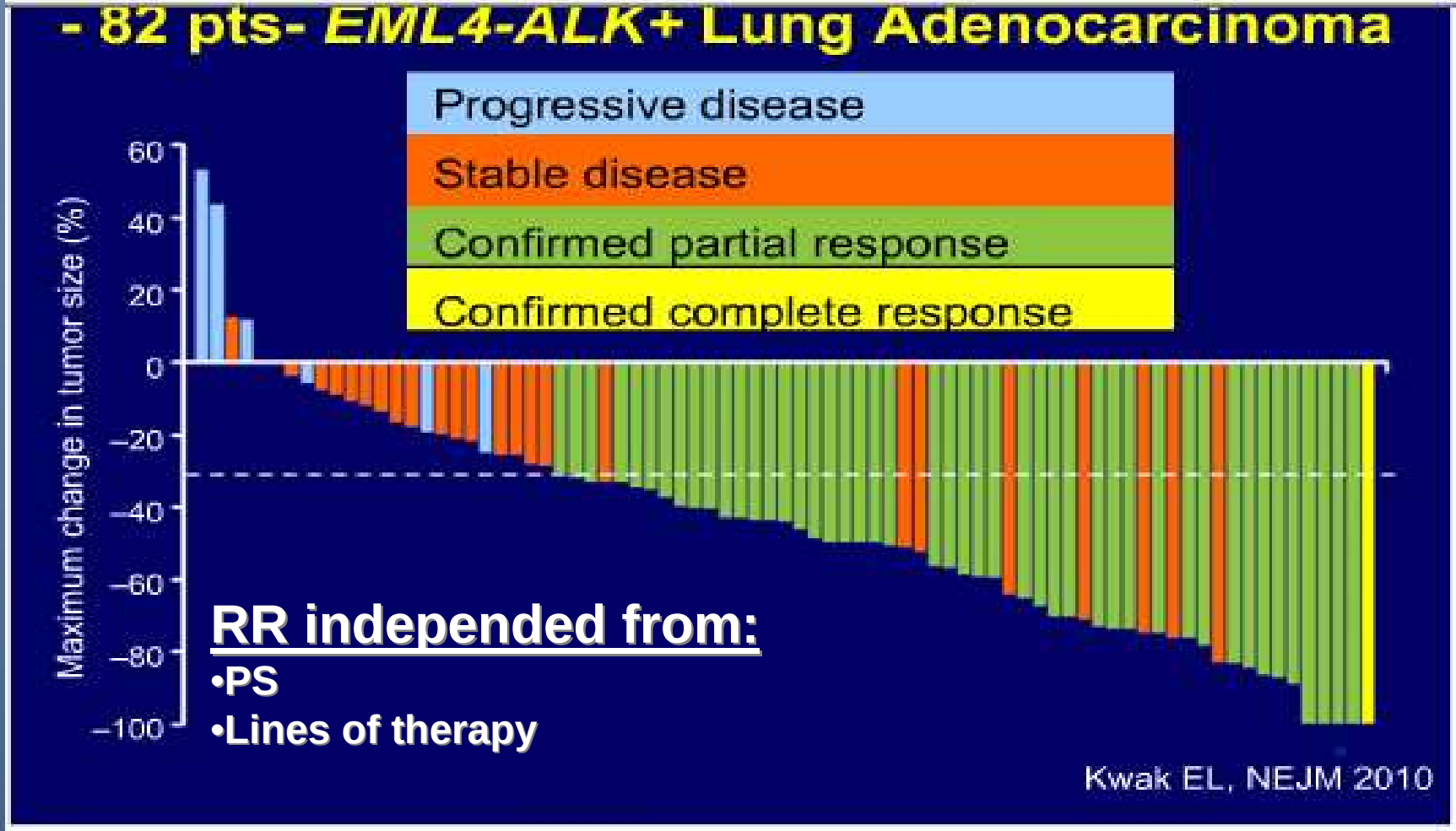
- Median age is low but can be in elderly.
- Frequency equivalent by sex, ethnicity and stage.
- More common in ADC histology but occurs in SCC.
- More common in never/light smokers but may occur in smokers.

Inhibitor of EML-ALK = Crizotinib (PF-02341066)

Potent & Selective ATP competitive oral inhibitor of MET and ALK kinases and their oncogenic variants



Tumor Responses to Crizotinib for pts with ALK-positive NSCLC



PFS 9.2 months

EGFR-TKIs Resistance

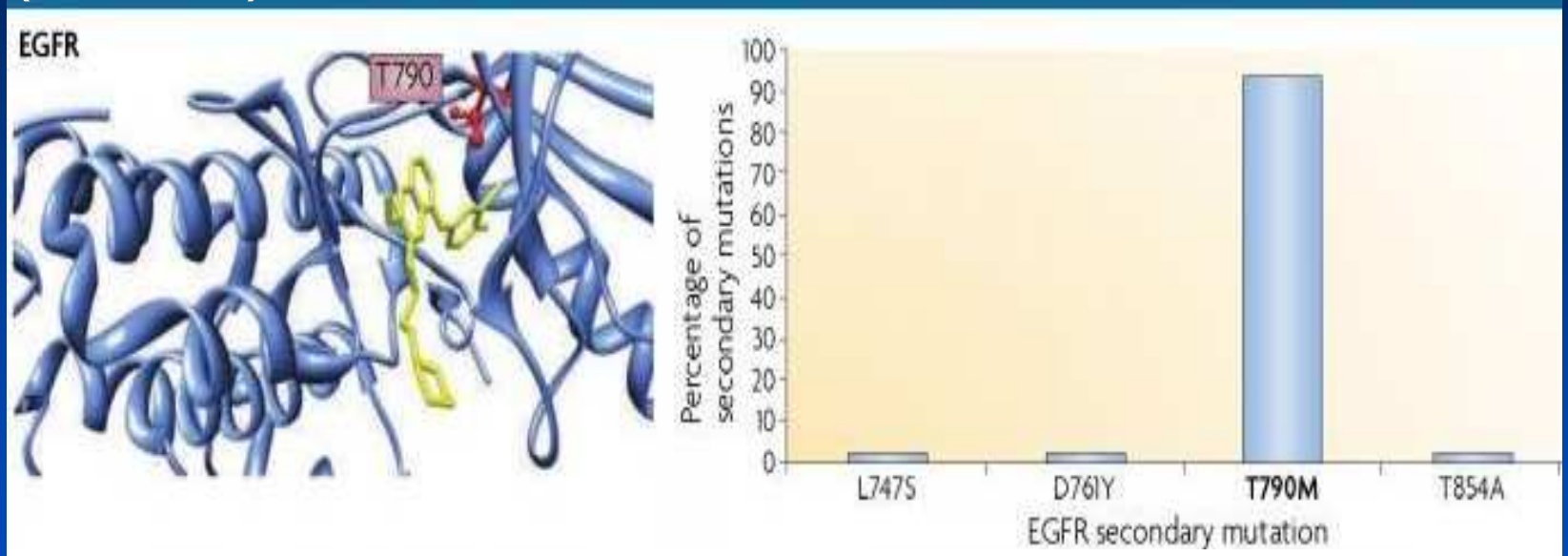
Acquired

... previous treatment with single agent, EGFRTKIs, in patients that harbors sensitizing mutations and had objective clinical bennefit from treatment with EGFR-TKIs ; systematic progression by RECIST /WHO while on continuous treatment with Gef or Erl

EGFR-TKIs Resistance

Acquired

50% of acquired resistance is due to T790M mutation (exon 20)



Why??????????????????????????

Several re-responses after short discontinuation have been reported

EGFR-TKIs Resistance Acquired

How we Overcome Resistance to TKIs?

With other TKIs

Generic name	Target
Pelitinib	EGFR >T790
Neratinib	EGFR and ERBB2 >T790
Carnetinib	Pan ERBB >T790

Afatinib*- LUX-Lung 1

Phase IIb/III trial of BIBW 2992 after 1st generation TKIs

Patients with:

- Adenocarcinoma of the lung
- Stage IIIB/IV
- **Progressed after one or two lines of chemotherapy (incl. one platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib**
- ECOG 0–2

N=585

Randomization 2:1
(double blind)

Oral afatinib 50 mg once daily
plus BSC

Oral placebo once daily
plus BSC

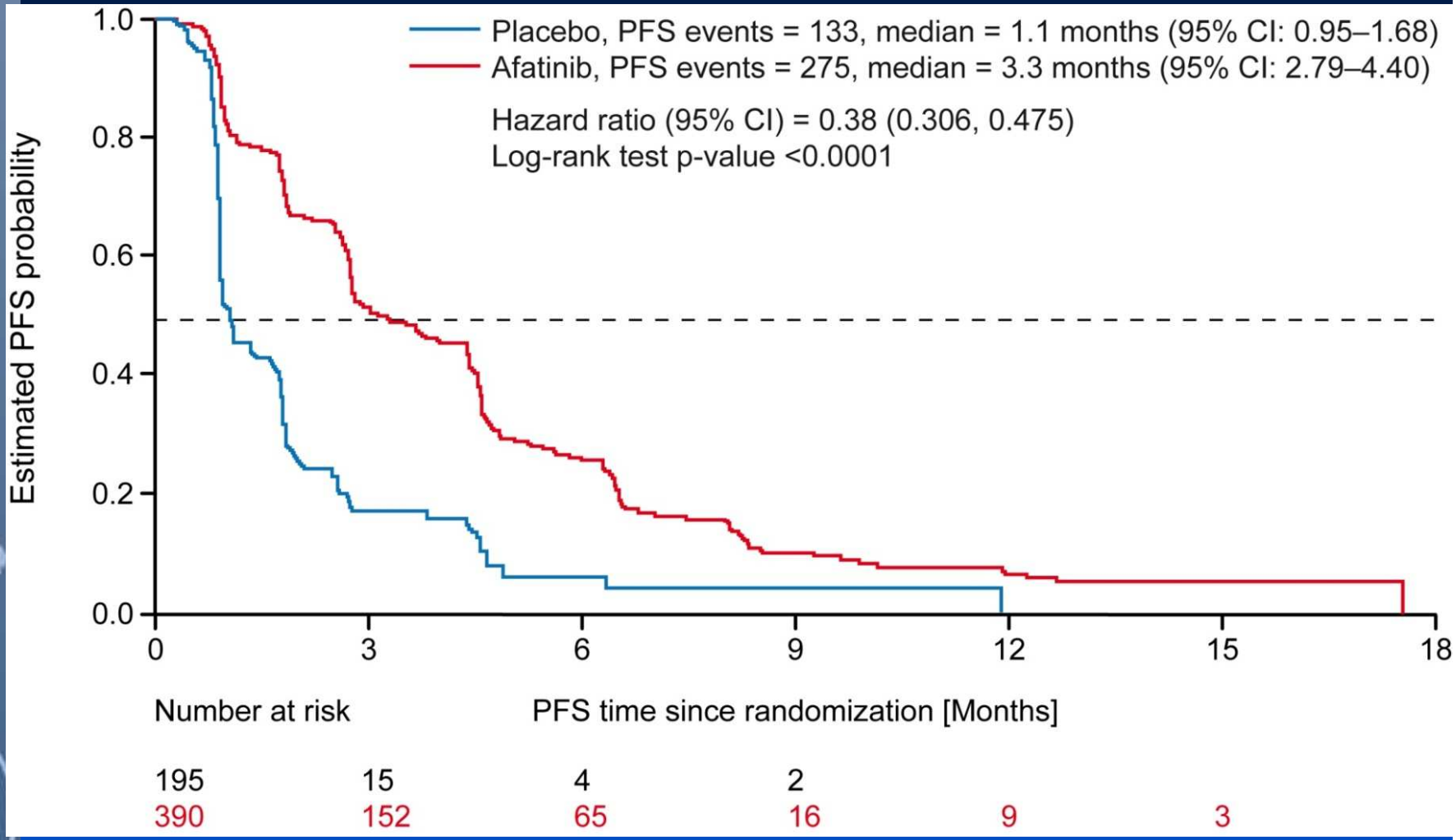
Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

- Radiographic assessments at 4, 8, 12 wks and every 8 wks thereafter
- Exploratory biomarkers:
  - Archival tissue testing for EGFR mutations (optional; central lab)
  - Serum EGFR mutational analysis (all patients)

**Afatinib (compound code BIBW 2992) is an investigational compound. Its safety and efficacy have not yet been fully established.*

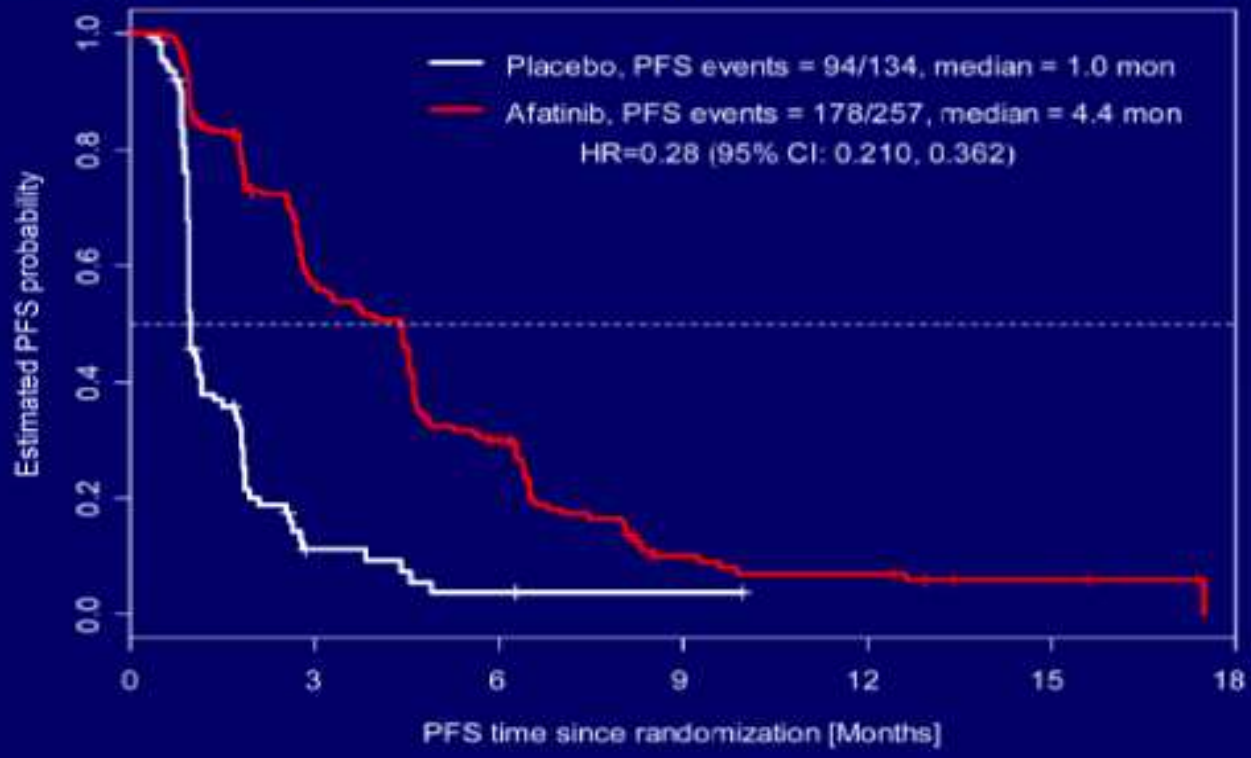
Afatinib- LUX-Lung 1
PFS by independent review (all patients)



Afatinib- LUX-Lung 1, Subgroup§ Analysis Significant prolongation of PFS

PFS* for a subgroup with a high likelihood of EGFR mutations

CR/PR on prior E/G and/or ≥48 wks on tx with prior E/G (67% of all pts)



Also, Jackman criteria: Median PFS 4.5 months vs. 1.0 months

§ Subgroup with a high likelihood of EGFR mutations*: CR/PR on prior E/G and/or ≥ 48 wks on tx with prior E/G (67% of all patients)

Afatinib*- LUX-Lung 3:

Ongoing Phase III trial in first line NSCLC with EGFR mutation

ONGOING




Patients (n=330) with:

- Stage IIIB/IV adenocarcinoma of the lung
- Presence of EGFR mutation in the tumour tissue
- Chemonaive
- ECOG 0 or 1

Randomization

2:1

Oral BIBW 2992 40 mg once-daily

Cisplatin/pemetrexed

Primary endpoint: PFS

Analysis is ongoing – Results to be presented soon at a scientific congress

**Afatinib (compound code BIBW 2992) is an investigational compound. Its safety and efficacy have not yet been fully established.*

Activity and tolerability of combined EGFR targeting with afatinib (BIBW 2992) and cetuximab in T790M+ NSCLC patients

Leora Horn[1], Harry J.M. Groen[2], Egbert F. Smit[3], Yelena Y. Janjigian[4], Yali Fu[5], Fei Wang[5], Mehdi Shahidi[6], Louis Denis[7], William Pao[1], Vincent A. Miller[4]

14th World Conference on Lung Cancer
IASLC
14TH WORLD CONFERENCE ON LUNG CANCER
JULY 3–7, 2011 AMSTERDAM RAI, THE NETHERLANDS

Afatinib + Cetuximab in mutant pts

Phase Ib, open-label, multicenter trial in the US and The Netherlands

NSCLC with *EGFR* mutation[1]

OR

SD ≥6 months with erlotinib/gefitinib

OR

Partial or complete response to erlotinib/gefitinib

Disease progression[2]

Stop erlotinib/ gefitinib for ≥72 hours[3]

Dose escalation schema 3–6 patients per cohort

Afatinib p.o. daily + escalating doses of i.v. cetuximab q 2 weeks

Dose levels starting at:
afatinib 40 mg +
cetuximab 250 mg/m^2

Predefined maximum dose:
afatinib 40 mg +
cetuximab 500 mg/m^2

MTD cohort expanded up to 80 *EGFR* mutation-positive patients[4]:
40 T790M+ and 40 T790M–

[1]EGFR G719X, exon 19 deletion, L858R, L861Q; [2]Progression of disease (Response Evaluation Criteria in Solid Tumors v1.1) on continuous treatment with erlotinib or gefitinib within the last 30 days; [3]Amended from original 14-day interval; [4]Acquisition of tumor tissue after the emergence of acquired resistance was mandated.

i.v.=intravenous; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; SD=stable disease

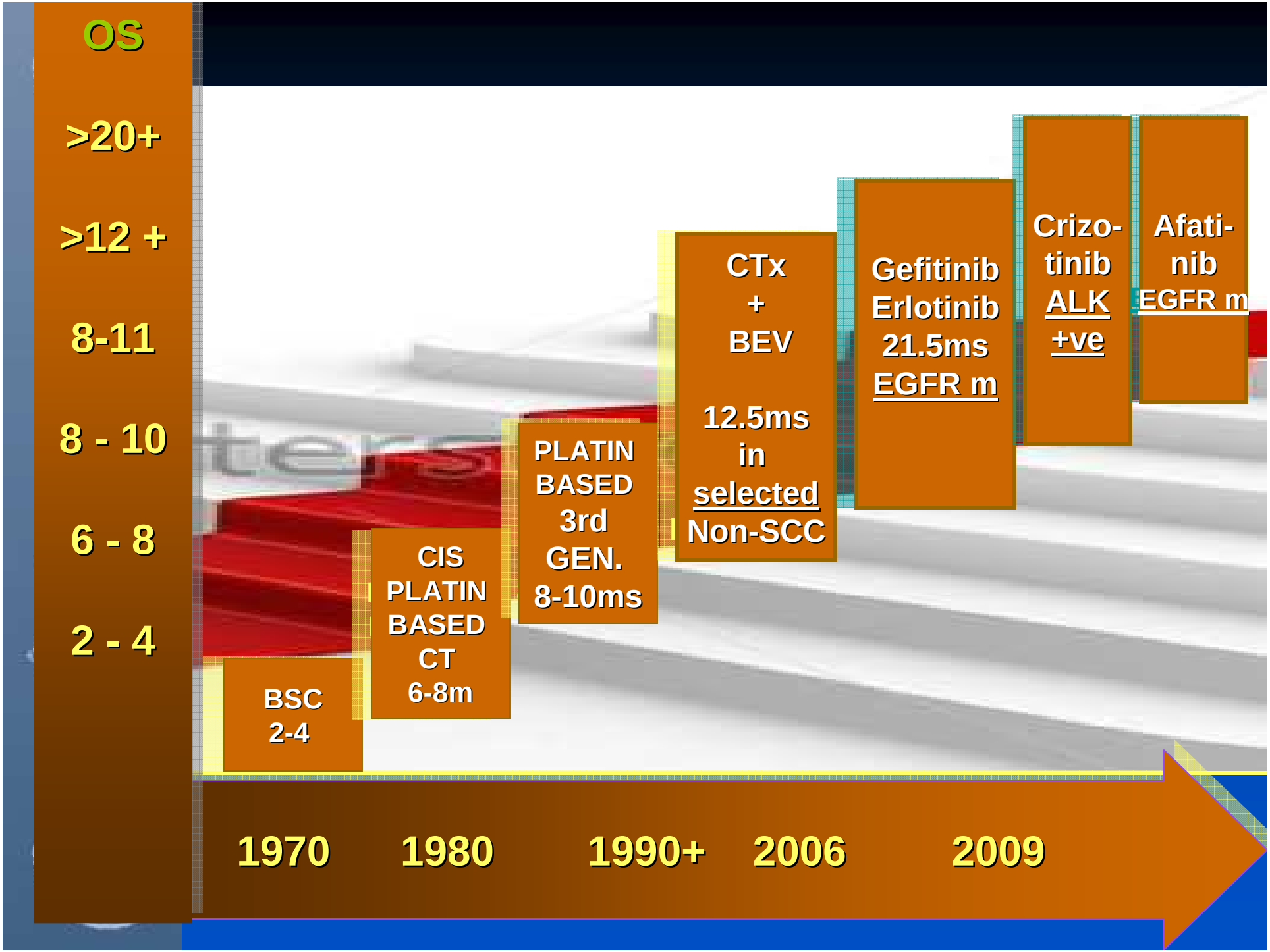
Treatment Responses by T790M Mutation Status at Recommended Dose

	T790M positive	T790M negative	T790M uninformative	No EGFR mutation	Total
Total treated		**18**	**2**	**2**	**61**
Evaluable for efficacy†		**16**	**2**	**2**	**55**
Best response					
Any PR, n(%), [95% CI]		9 (56) [30,80]	1 (50)		28 (51) [39,67]
Confirmed PR n(%), [95% CI]		7 (32) [20,70]	1 (50)		19 (35) [23,50]
SD, n(%)		6 (38)	1 (50)	2 (100)	24 (44)
Clinical response (any PR + SD), n(%)		**15 (94)**	**2 (100)**	**2 (100)**	**52 (95)**
Progression of disease, n(%)		1 (6)			3 (5)

†Six patients were not evaluable for efficacy.
PR=partial response; SD=stable disease.

Data were evaluated up to 06 June 2011

Πόσο μακριά είμαστε από την εξατομικευμένη θεραπεία;


OS
>20+
>12 +
8-11
8 - 10
6 - 8
2 - 4
BSC
2-4
CIS
PLATIN
BASED
CT
6-8m
PLATIN
BASED
3rd
GEN.
8-10ms
CTx
+
BEV
12.5ms
in
selected
Non-SCC
Gefitinib
Erlotinib
21.5ms
EGFR m
Crizo-
tinib
ALK
+ve
Afati-
nib
EGFR m
1970
1980
1990+
2006
2009

ΜΜΚΠ
Πόσο μακριά είμαστε από την εξατομικευμένη θεραπεία;

Ανδριανή Γ. Χαρπίδου
Πνευμονολόγος
Διδάκτωρ Πανεπιστημίου Αθηνών
Ογκολογική Μονάδα,
Γ΄ΠΠ, ΝΝΘΑ «ΣΩΤΗΡΙΑ»