
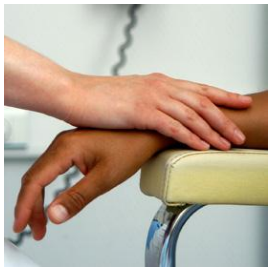
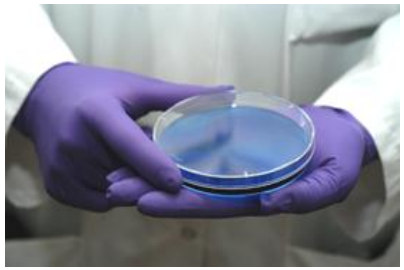
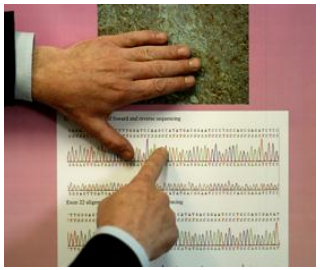

EGFR inhibitors are the best choice for first line treatment of EGFR mutated lung adenocarcinoma patients

NO

Benjamin Besse, MD., PhD.

VIENNA 2012 ESMO congress

Institut de cancérologie GUSTAVE ROUSSY
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Disclosures

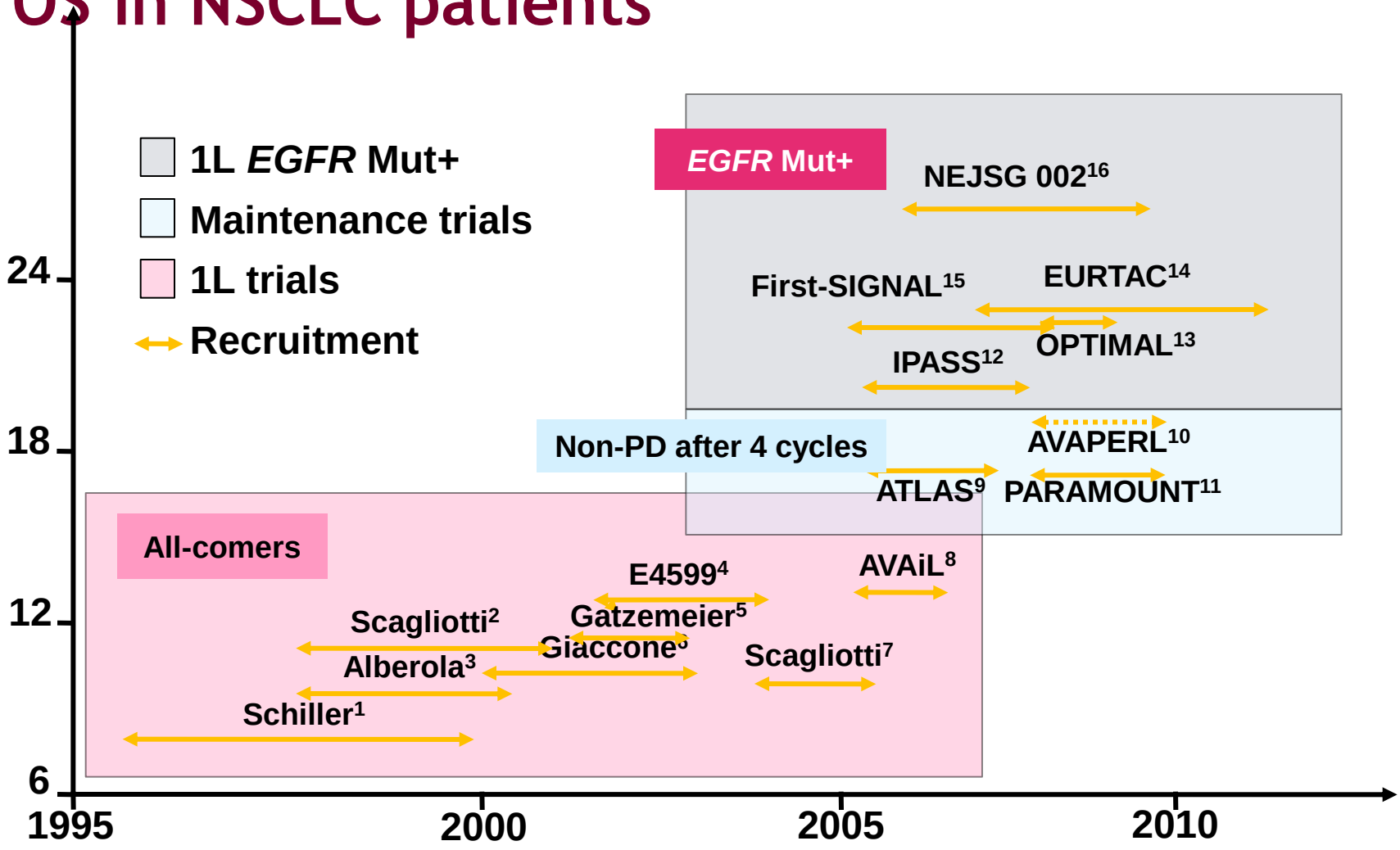
- **No personal financial disclosures**
- **Institutional grants for clinical and translational research**
  - **Abbott, Amgen, AstraZeneca, Boehringer-Ingelheim, Lilly, Pfizer, Roche-Genentech, Sanofi-Aventis, Clovis**


CAN YOU
HEAR
HIS
VOICE?


Robert Donaghey 2001

⇢ Who are the EGFR Mut patients ?

OS in NSCLC patients

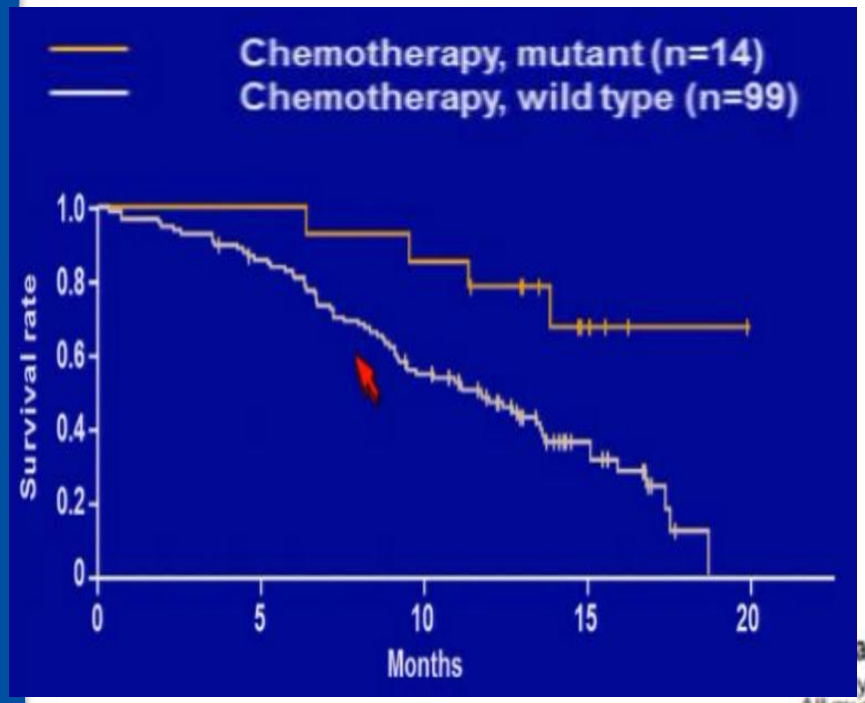


1. Schiller, et al. NEJM 2002; 2. Scagliotti, et al. JCO 2002; 3. Alberola, et al. JCO 2003; 4. Sandler, et al. NEJM 2006; 5. Gatzemeier, et al. JCO 2007 6. Giaccone, et al. JCO 2004; 7. Scagliotti, et al. Clin Cancer Res 2005; 8. Reck, et al. Ann Oncol 2010; 9. Kabbinavar, et al. ASCO 2010 10. Barlesi, et al. EMCC 2011; 11. Paz-Ares, et al. ASCO 2012; 12. Fukuoka, et al. JCO 2011; 13. Zhou, et al. ASCO 2012 14. de Marinis, et al. EMCC 2011; 15. Han, et al. JCO 2012; 16. Maemondo NEJM 2010

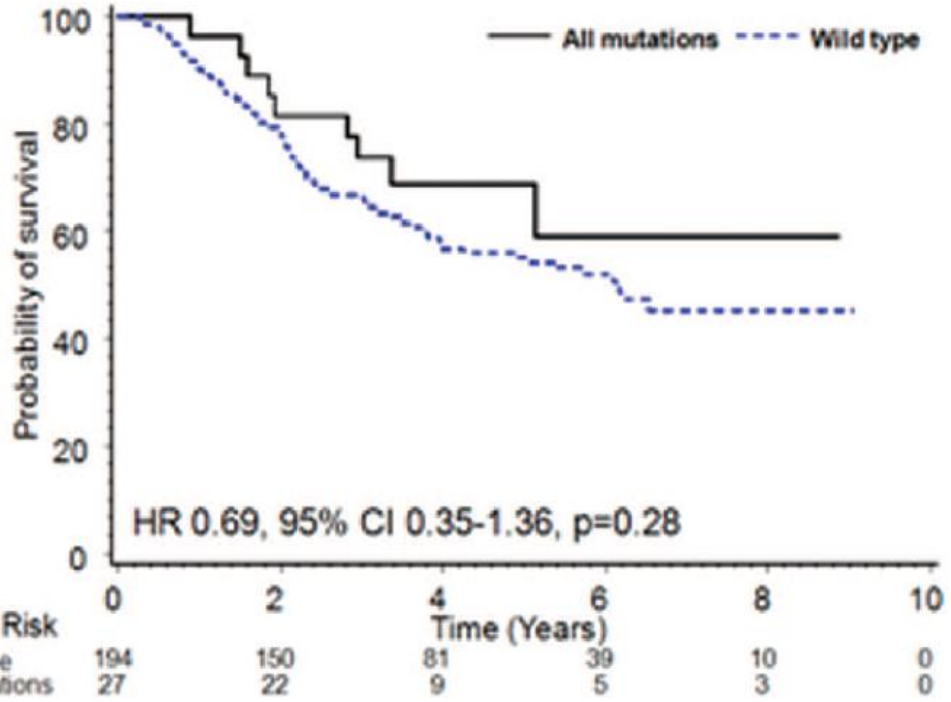
EGFR mutation : a good news !

Positive prognostic factor

STAGE IIIB/IV



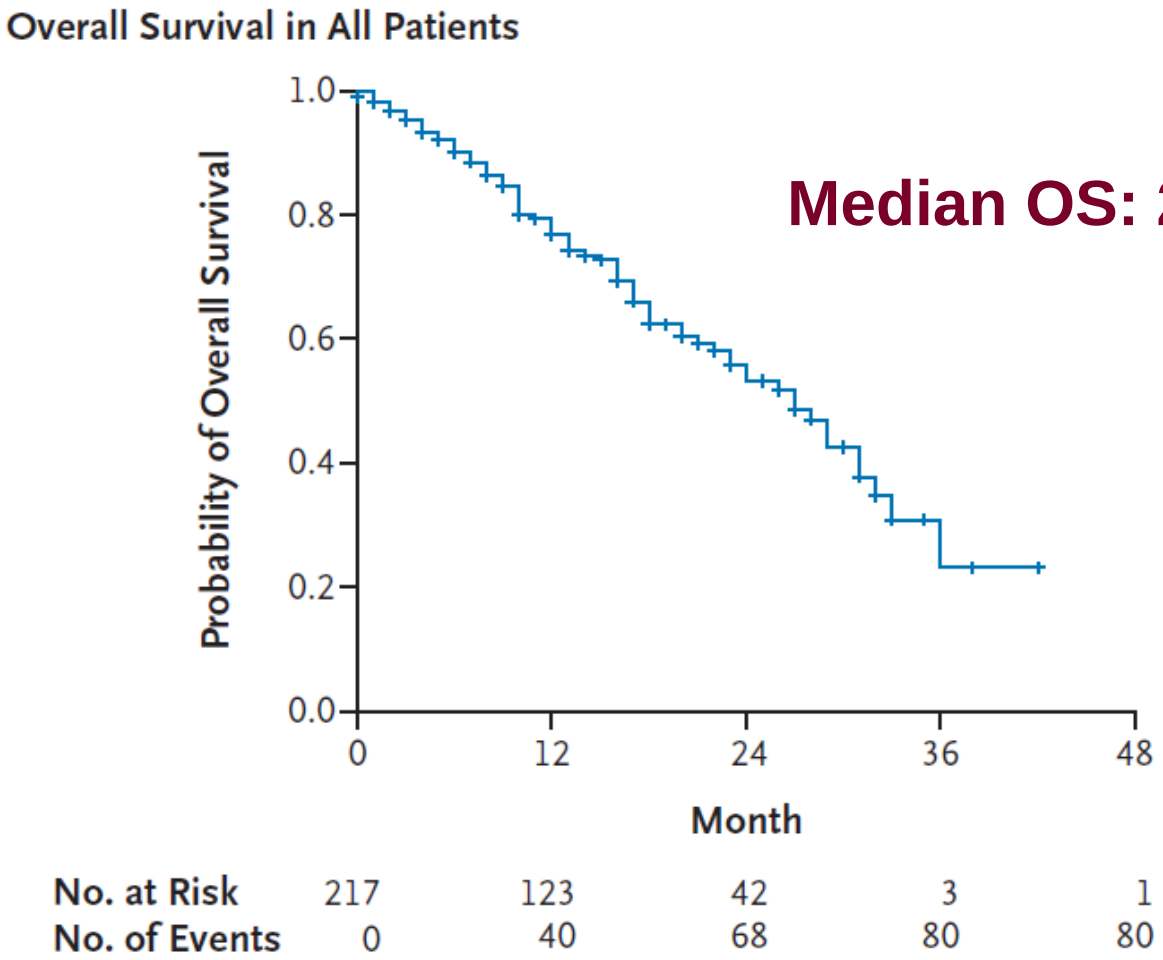
STAGE IB/II (resected)



Inclusion period : Jul 2001 – Aug 2002

Tsao, JTO 2011 - Eberhard JCO 2005

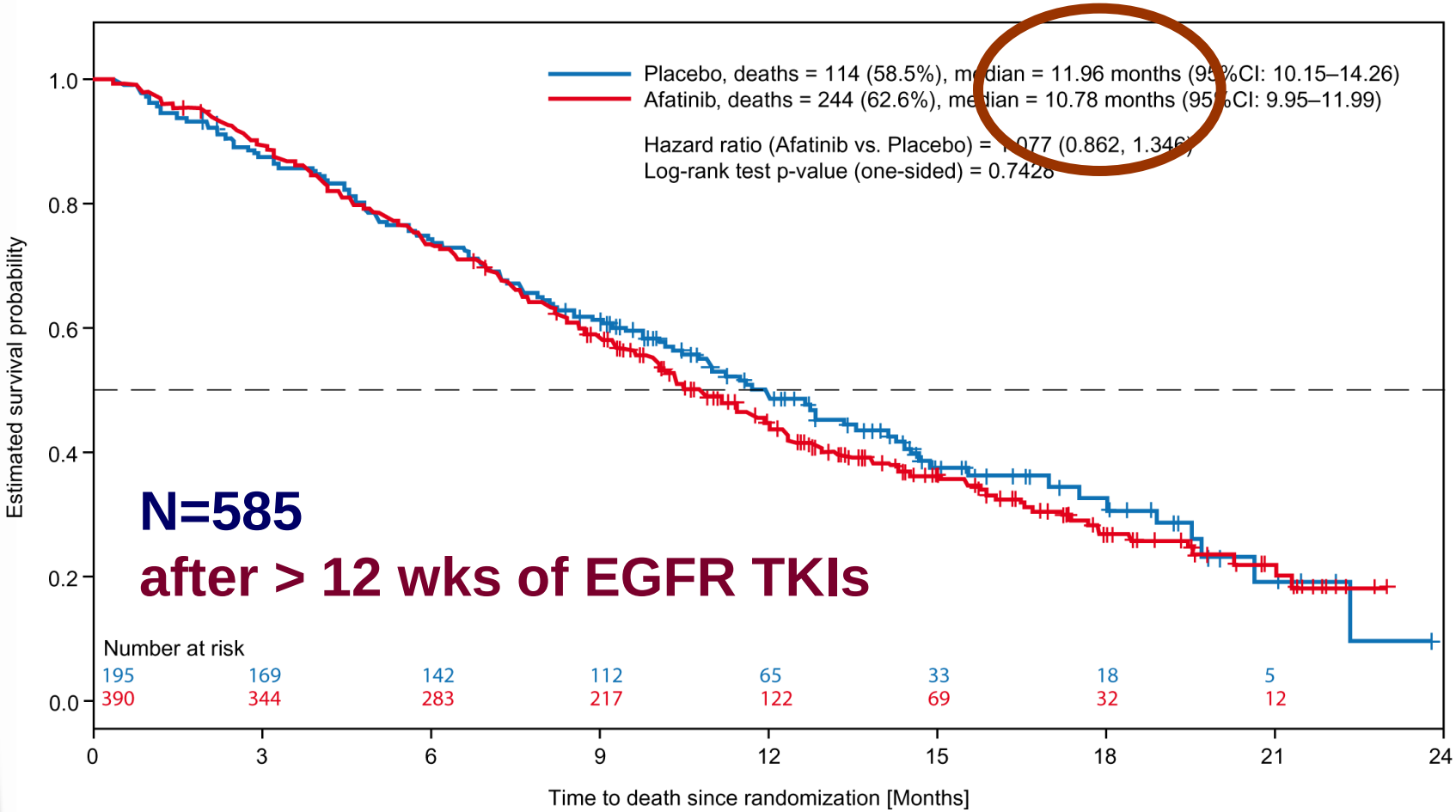
A unique disease history



Median OS: 27 months

Rosell et al, NEJM 2009

Afatinib vs placebo in 3rd/4th line



Post treatment (4/5th lines and more)

Anticancer therapy	Afatinib (%)	Placebo (%)
Any	**68**	**79**
Chemotherapy	**61**	**70**
Pemetrexed	**36**	**47**
Docetaxel	**21**	**26**
Vinorelbine	**15**	**19**
Other	**18**	**20**
EGFR TKI	**12**	**24**
Anti-angiogenesis	**4**	**6**
Radiotherapy	**9**	**14**

sensual, intense, unique ...

The hero,
of course is ...

TKIs. What else ?

⇢ The phase III trials

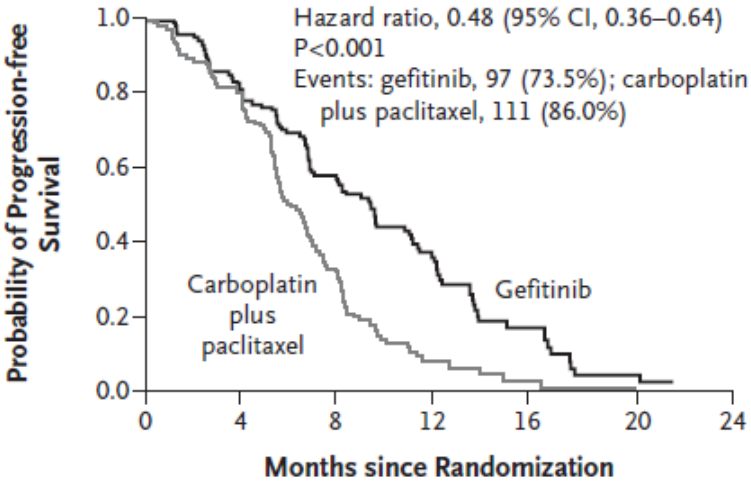
IPASS PFS in EGFRmut patients

Patients
- Chemonaïve
- Age ≥18 years
- Adenocarcinoma histology
- Never or light ex-smokers*
- Life expectancy ≥12 weeks
- PS 0-2
- Measurable stage IIIB / IV disease

→ **Gefitinib (250 mg / day)**

1:1 randomisation

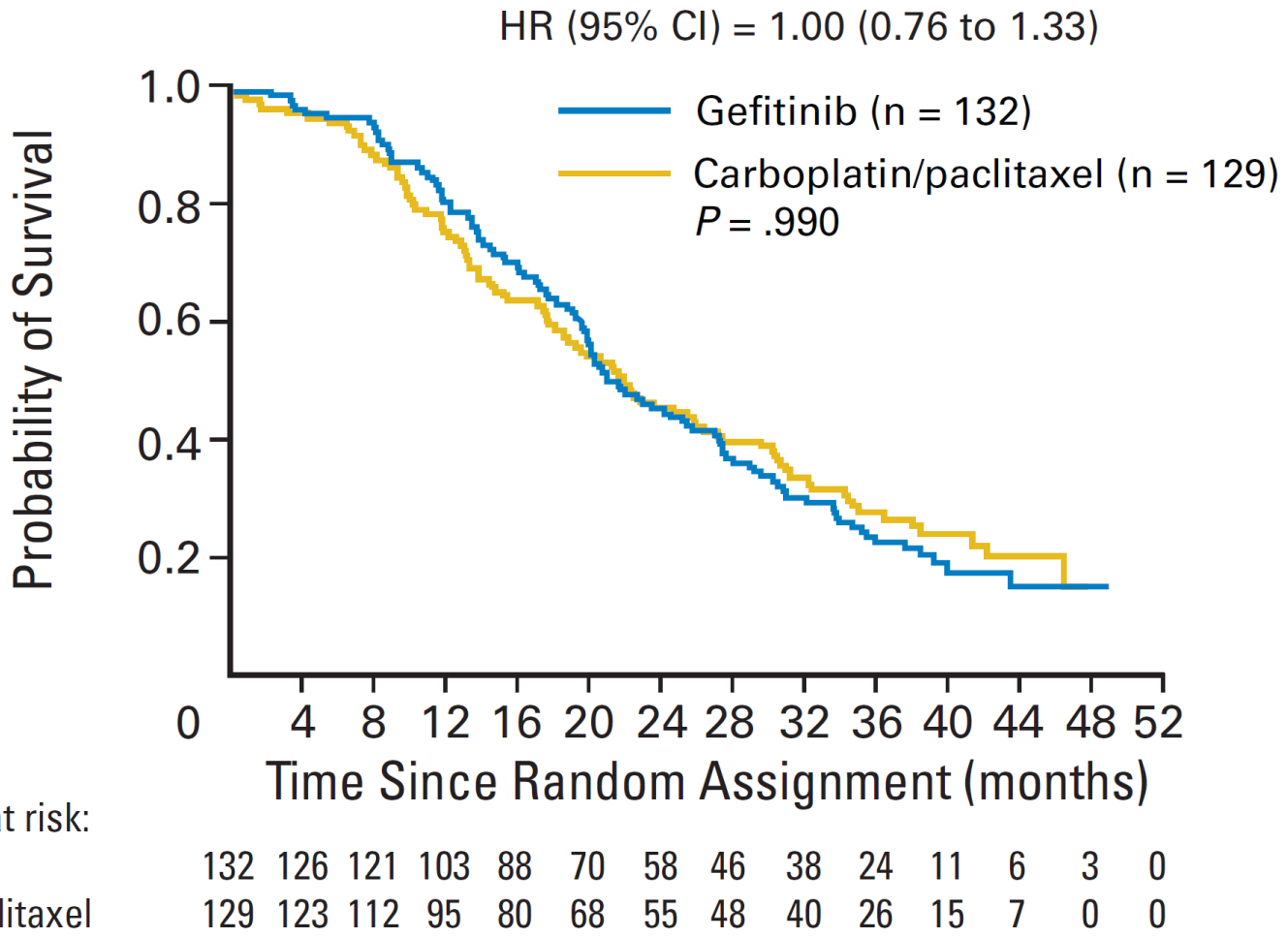
→ **Carboplatin (AUC 5 or 6) / paclitaxel (200 mg / m²) 3 weekly cycle 6 cycles**



EGFR mut patients (60%)
HR = 0.48
p<0.001

Mok NEJM 2009

IPASS OS in EGFRmut patients



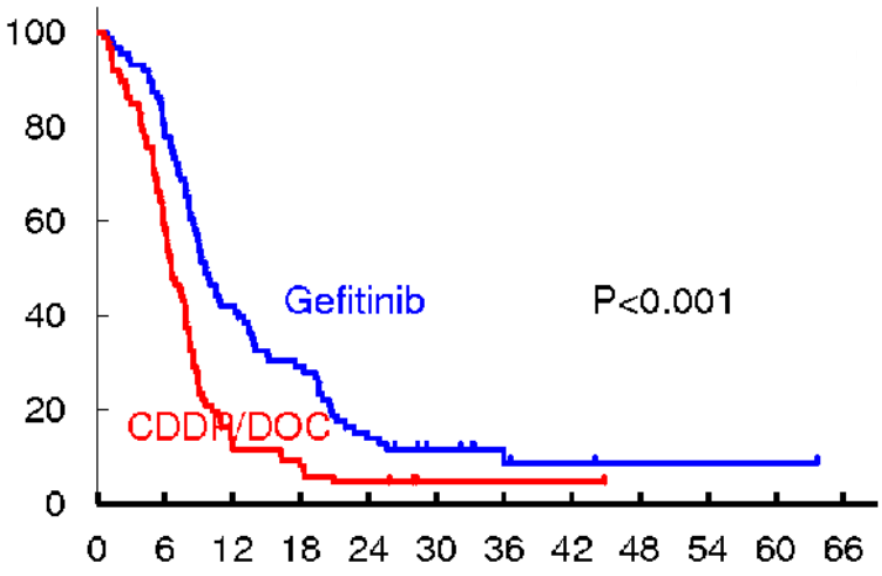
WJTOG3405 - PFS

Patients
- Chemonaïve
- Measurable stage IIIB / IV disease
- were aged 75 years or
- WHO performance status 0–1
- **EGFR mutated (either exon 19 deletion or L858R in exon 21)**

Gefitinib (250 mg / day)

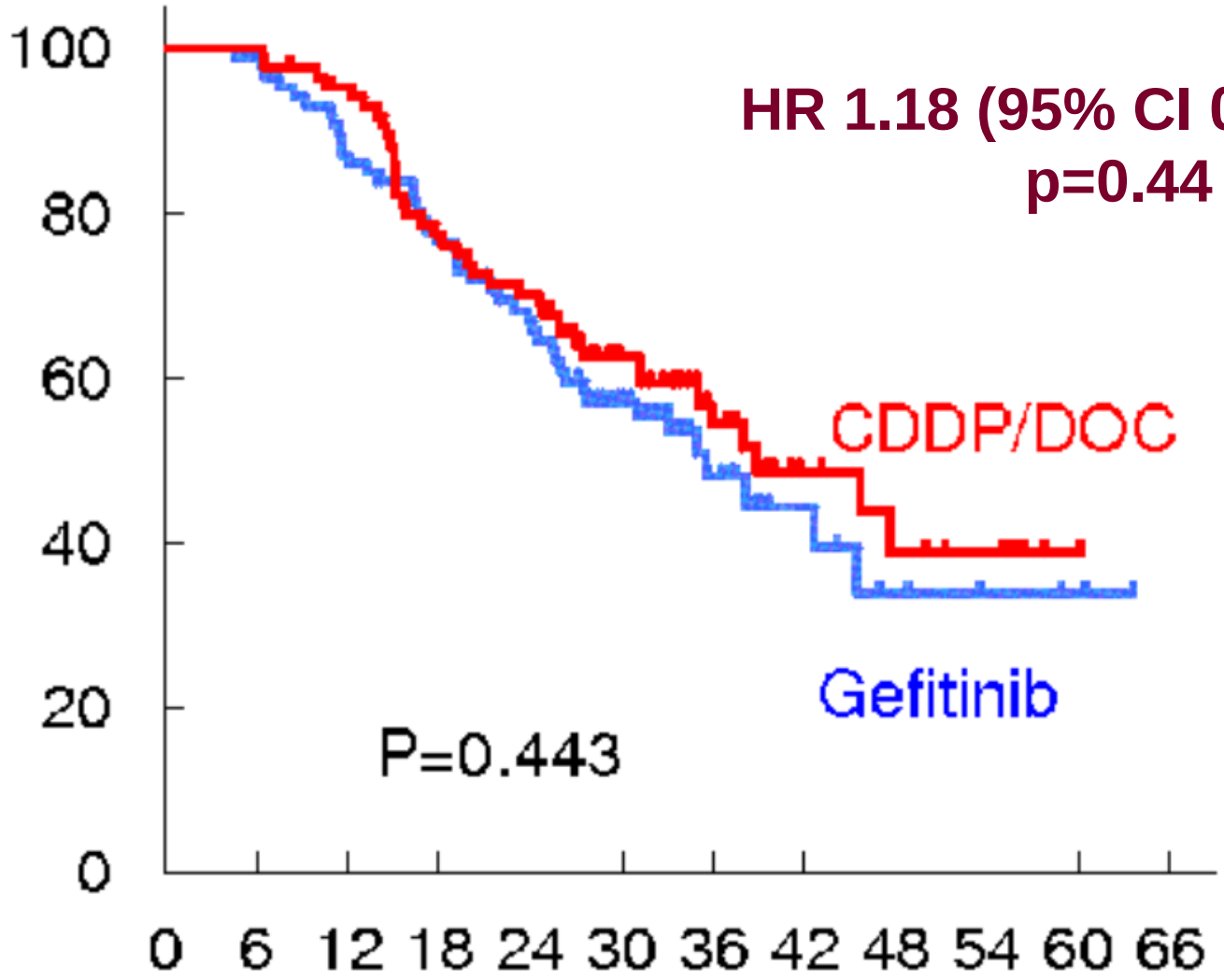
1:1 randomisation

Cisplatin (80 mg/m²) / docetaxel (60 mg / m²) 3 weekly 3 to 6 cycles



Primary objective : PFS
HR 0.52 (95% CI 0.37-0.71)
p<0.0001

WJTOG3405 - OS



HR 1.18 (95% CI 0.76−1.82)
p=0.44

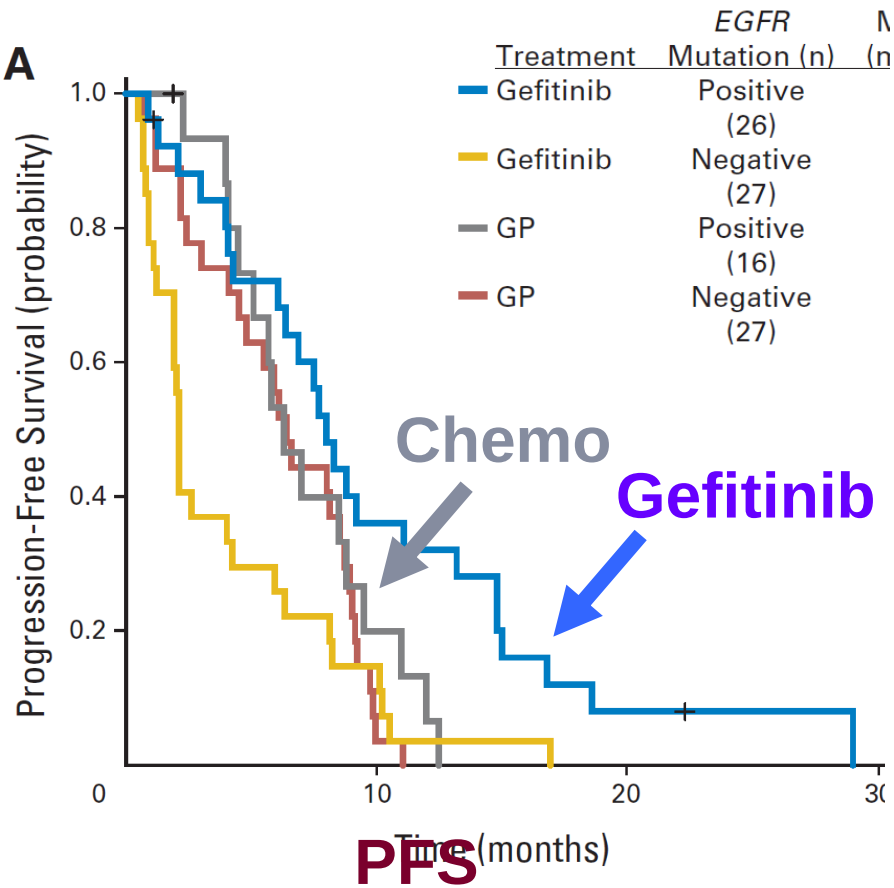
⇢ SIGNAL – PFS in EGFR mut

Patients (Korean)
- Chemonaïve
- Measurable or not stage IIIB / IV disease
- WHO performance status 0–2
- **Never smokers**

Gefitinib (250 mg / day)

1:1 randomisation

Cisplatin (75 mg/m²) / Gemcitabine (1250 mg / m²) d1,8 - 3 weekly Up to 9 cycles



PFS

HR=0.54 (95% CI 0.26-1.10)
p=0.086

Han JCO 12

SIGNAL - OS

Primary objective : OS
All patients

OS
EGFR patients (arrows)

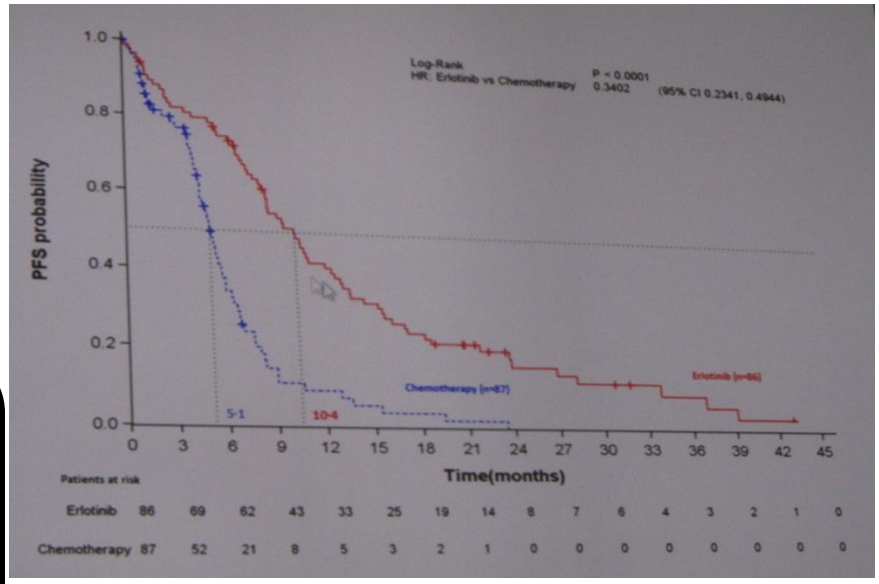
EURTAC - PFS

Patients (European)
- Chemonaïve
- Measurable stage IIIB / IV disease
- WHO performance status 0–2
- **activating EGFR mutations**

Erlotinib (150 mg / day)

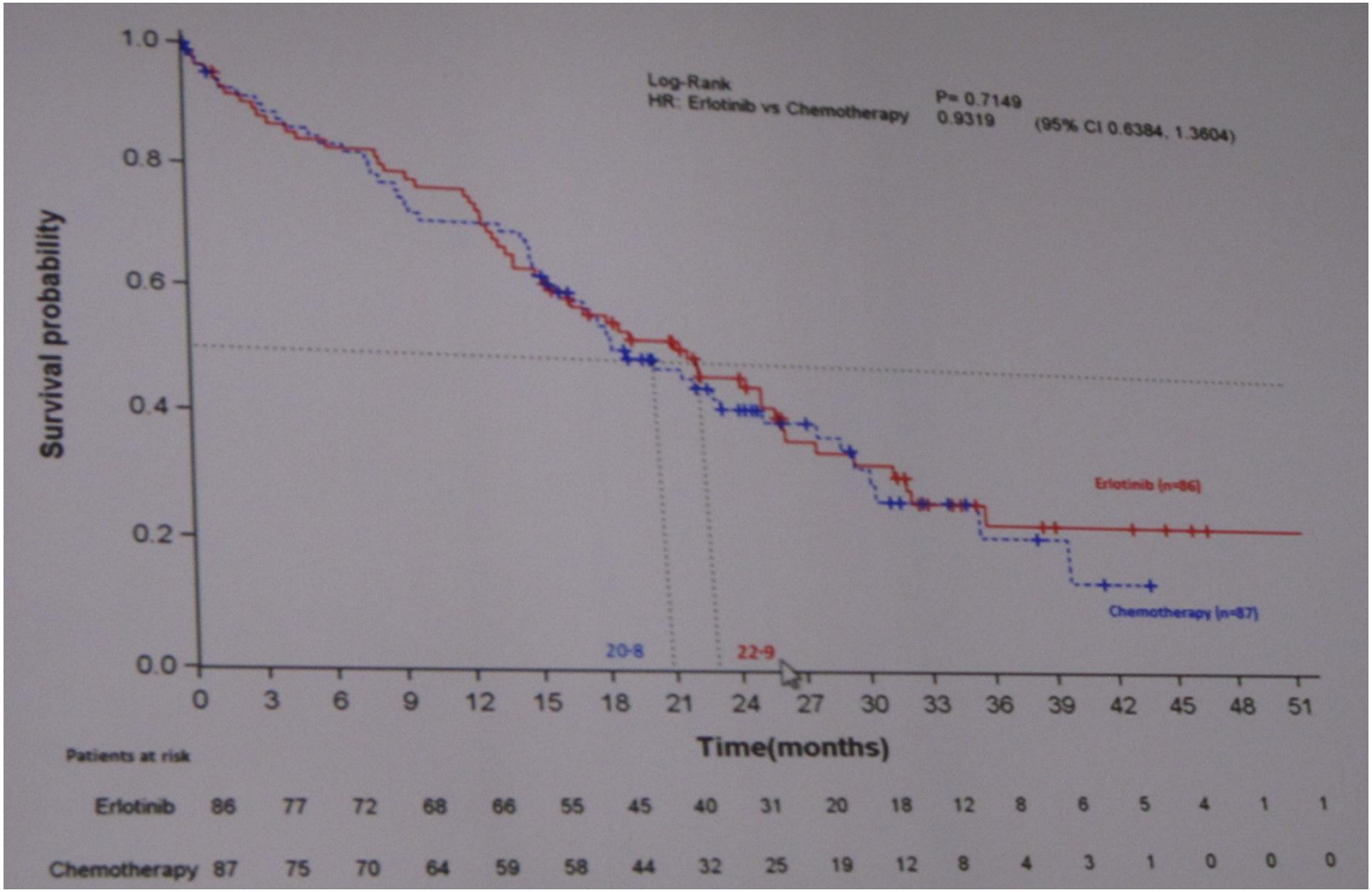
1:1 randomisation

Cisplatin (75 mg/m²) or Carboplatine (AUC 5-6) / Docetaxel (75 mg/m²) or Gemcitabine (1000-1250 mg / m²) d1,8 - 3 weekly 4 cycles



Primary objective : PFS
HR 0.34 (95% CI 0.23−0.49)
p<00001

EURTAC - OS


Log-Rank
HR: Erlotinib vs Chemotherapy
P= 0.7149
0.9319
(95% CI 0.6384, 1.3604)
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
Erlotinib (n=86)
Chemotherapy (n=87)
20-8
22-9
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Time(months)
Patients at risk
Erlotinib 86 77 72 68 66 55 45 40 31 20 18 12 8 6 5 4 1 1
Chemotherapy 87 75 70 64 59 58 44 32 25 19 12 8 4 3 1 0 0 0

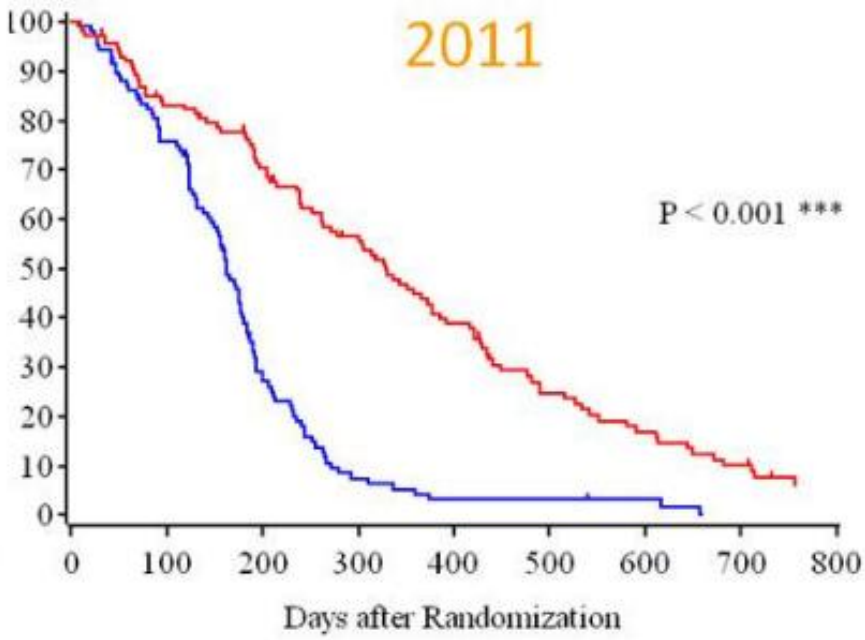
⇢ NEJ 002 - PFS

Patients (Japan)
- **Chemonaïve**
- **Measurable stage IIIB / IV disease**
- **WHO performance status 0–1**
- **activating EGFR mutations**

Gefitinib (250 mg / day)

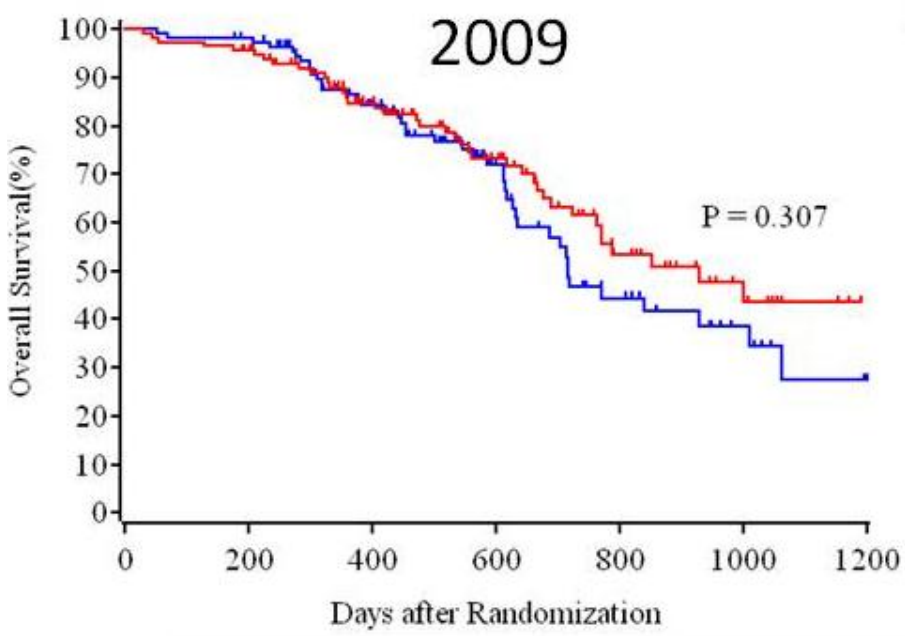
1:1 randomisation

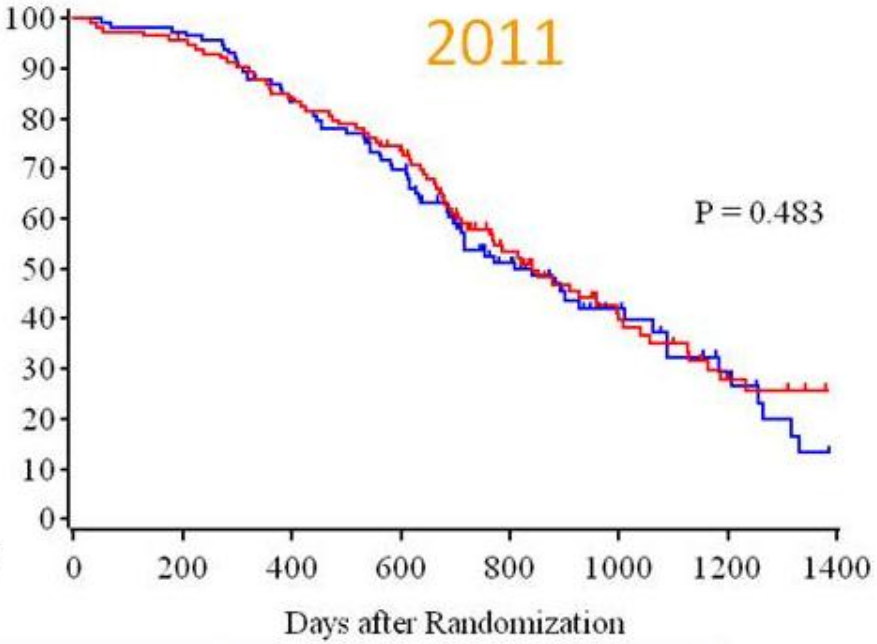
Carboplatin (AUC6) / Paclitaxel (200 mg/m²) - 3 weekly Cycles At least 3 cycles



Primary objective : PFS
HR 0.322 (95% CI 0.236−0.438)
p<0.001

NEJ 002 - OS





	2009		2011	
	Gefitinib	CBDCA/PTX	Gefitinib	CBDCA/PTX
Median OS (mo)	30.5	23.6	27.7	26.6
Hazard ratio (95%CI)	0.798 (0.517-1.232)		0.887 (0.634-1.241)	

PFS and OS in EGFRmut patients

Study	n	Drugs	HR PFS (95% CI)
NEJ 002	228	Gefitinib Pacli/carbo	0.32 (0.23-0.43) ; p<0.001
SIGNAL	96/ 309	Gefitinib Gem/Cis	0.54 (0.26-1.10) ; p=0.086
EURTAC	173	Erlotinib Gem-doc Cis-carbo	0.34 (0.23−0.49); p<0·0001
WJTOG 3505	177	Gefitinib Doc/Cis	0.52 (0.37-0.71) ; p<0.0001
iPass	261/ 1217	Gefitinib Pacli/carbo	0.48 (0.36–0.64) ; p<0.001
OPTIMAL	165	Erlotinib Gem/carbo	0.16 (0.10-0.26) ; p<0.0001
Lux Lung 3	345	Afatinib Pem/Cis	0.58 (0.43–0.78) : p=0.0004

Yang ASCO 12, Mitsudomi ASCO 12, Mok NEJM 07,
Rosell ESMO 12, Han JCO 12, Zhou ASCO 12, Inoue ASCO 11

PFS and OS in EGFRmut patients

Study	n	Drugs	HR PFS (95% CI)	HR OS (95% CI)
NEJ 002	228	Gefitinib Pacli/carbo	0.32 (0.23-0.43) ; p<0.001	0.88 (0.63-1.24) ; p=0.483
SIGNAL	96/ 309	Gefitinib Gem/Cis	0.54 (0.26-1.10) ; p=0.086	1.04 (0.49-2.18)
EURTAC	173	Erlotinib Gem-doc Cis-carbo	0.34 (0.23−0.49); p<0·0001	1.36 (0.73-1.36) ; p=0.71
WJTOG 3505	177	Gefitinib Doc/Cis	0.52 (0.37-0.71) ; p<0.0001	1.18 (0.76-1.82) ; p=0.44
iPass	261/ 1217	Gefitinib Pacli/carbo	0.48 (0.36–0.64) ; p<0.001	1.00 (0.76- 1.33) ; p=0.99
OPTIMAL	165	Erlotinib Gem/carbo	0.16 (0.10-0.26) ; p<0.0001	1.04 (0.69- 1.58) ; p=0.69
Lux Lung 3	345	Afatinib Pem/Cis	0.58 (0.43–0.78) : p=0.0004	Not Presented yet

Yang ASCO 12, Mitsudomi ASCO 12, Mok NEJM 07,
Rosell ESMO 12, Han JCO 12, Zhou ASCO 12, Inoue ASCO 11

Cross over

Study	n	Drugs	TKI ->platinum-based chemo	platinum-based CT arm -> TKI
NEJ 002	228	Gefitinib Pacli/Carbo	64%	98%
SIGNAL	96/ 309	Gefitinib Gem/Cis	65%	75%
EURTAC	173	Erlotinib Gem-doc Cis-carbo	Not presented	
WJTOG 3505	177	Gefitinib Doc/Cis	68%	64%
iPass	261/ 1217	Gefitinib Pacli/carbo	60%	91%
OPTIMAL	165	Erlotinib Gem/carbo	Not mature	
Lux Lung 3	345	Afatinib Pem/Cis	Not Mature	

Mitsudomi ASCO 12, Mok NEJM 07, Rosell Lancet Oncol 12, Han JCO 12, Zhou ASCO 12, Inoue ASCO 11

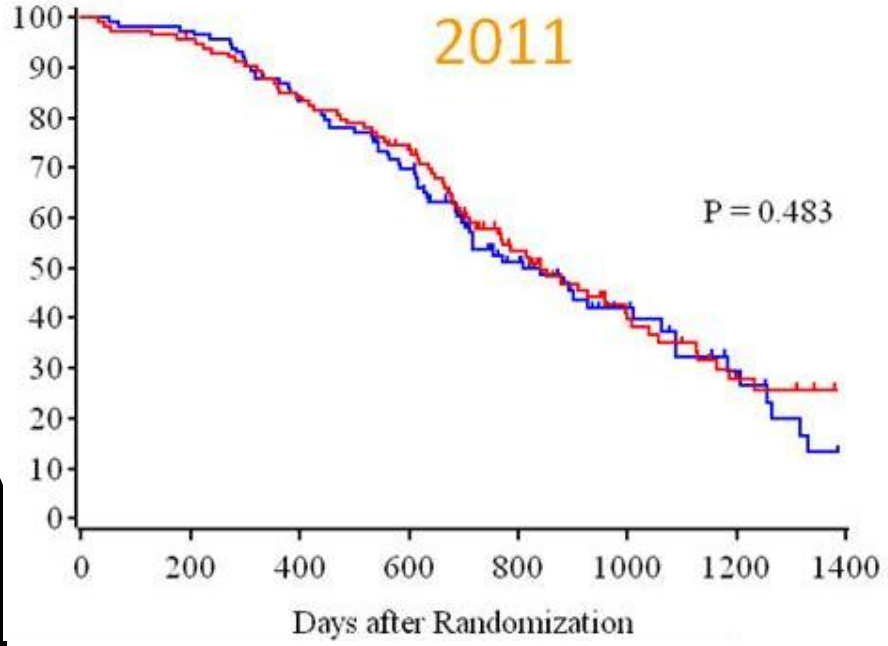
⇢ NEJ 002 - OS

Patients (Japan)
- **Chemonaïve**
- **Measurable stage IIIB / IV disease**
- **WHO performance status 0–1**
- **activating EGFR mutations**

Gefitinib (250 mg / day)

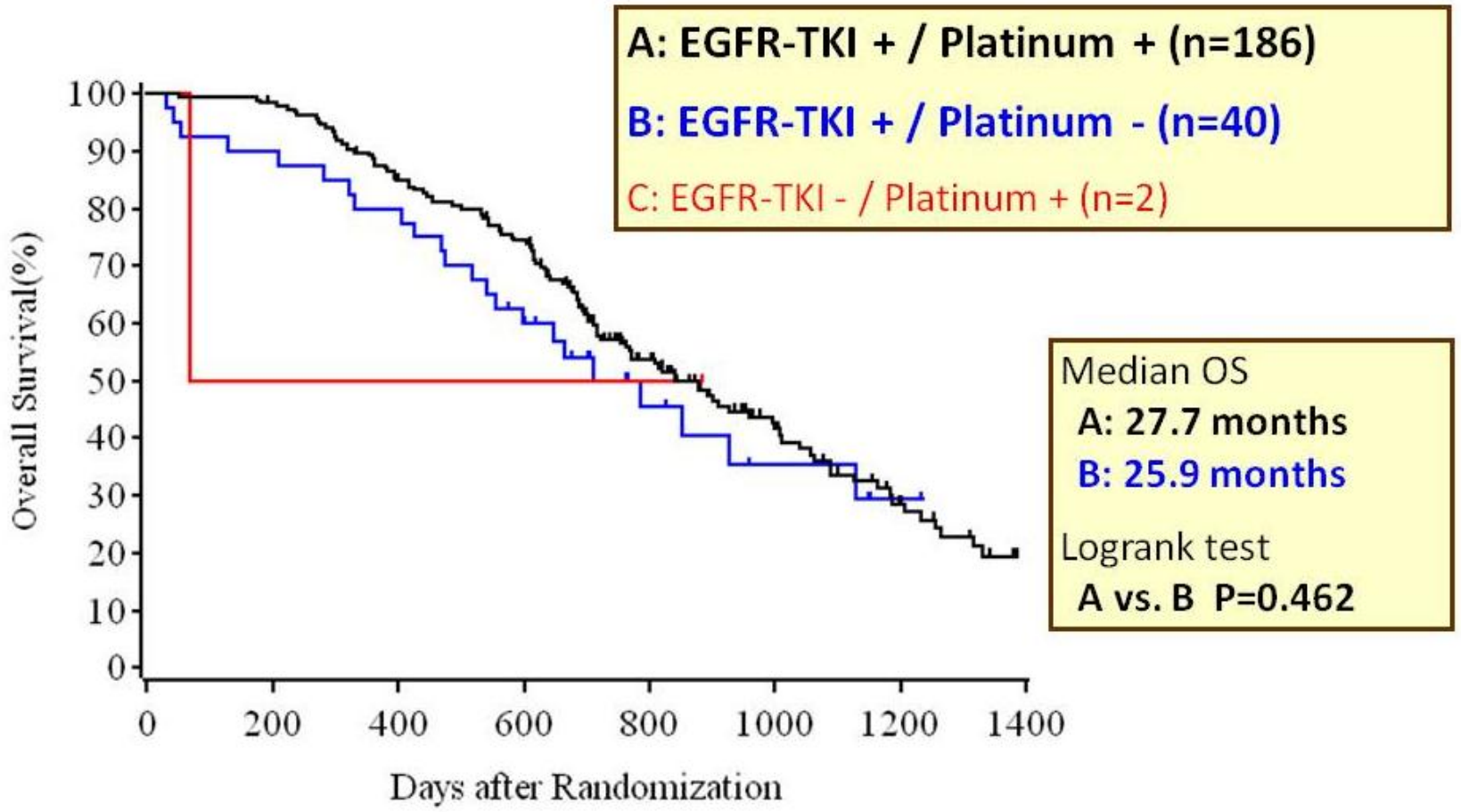
1:1 randomisation

Carboplatin (AUC6) / Paclitaxel (200 mg/m²) - 3 weekly Cycles At least 3 cycles

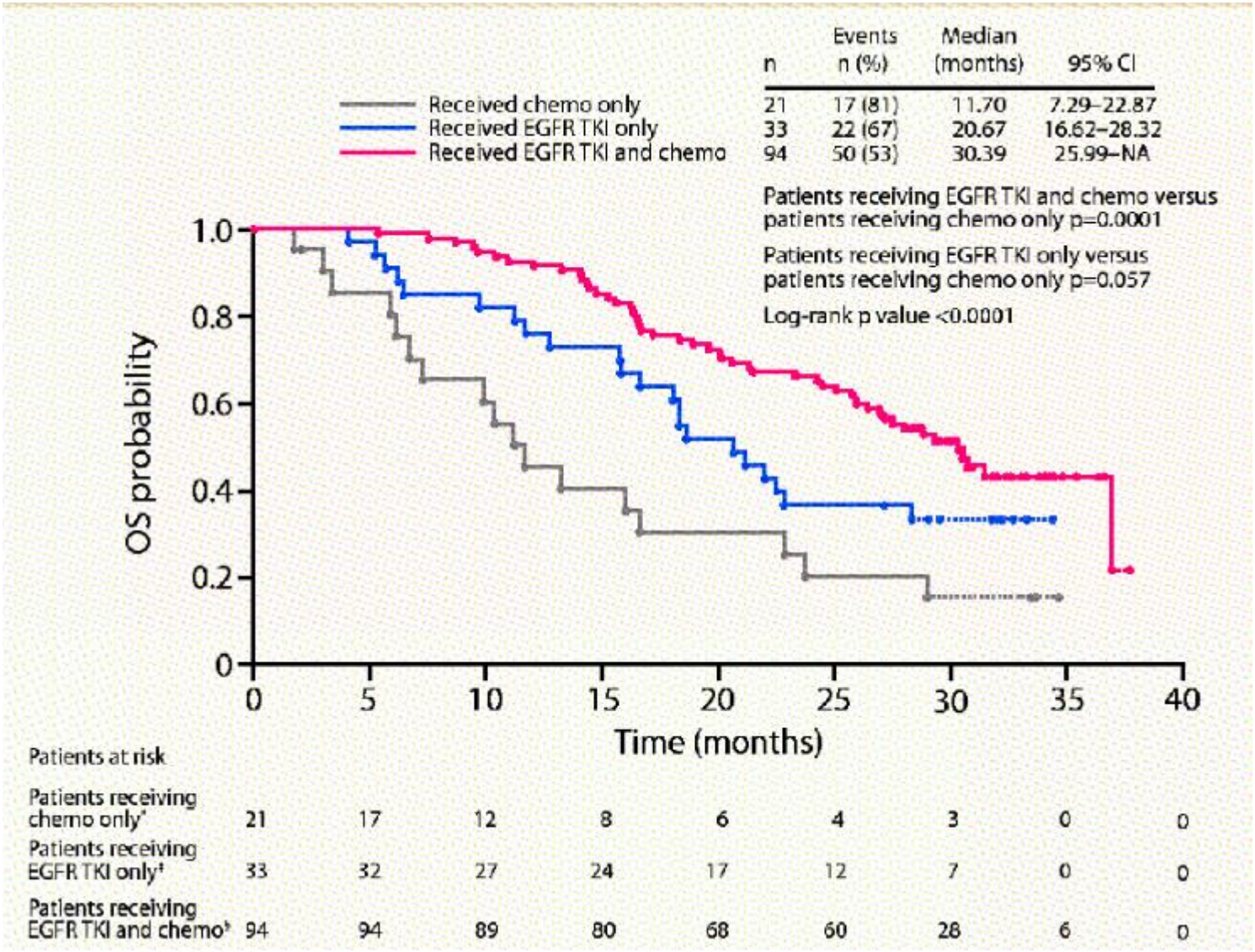


OS
HR 0.887 (95% CI 0.634−1.241)
p=0.483

Influence of Platinum regimen on OS



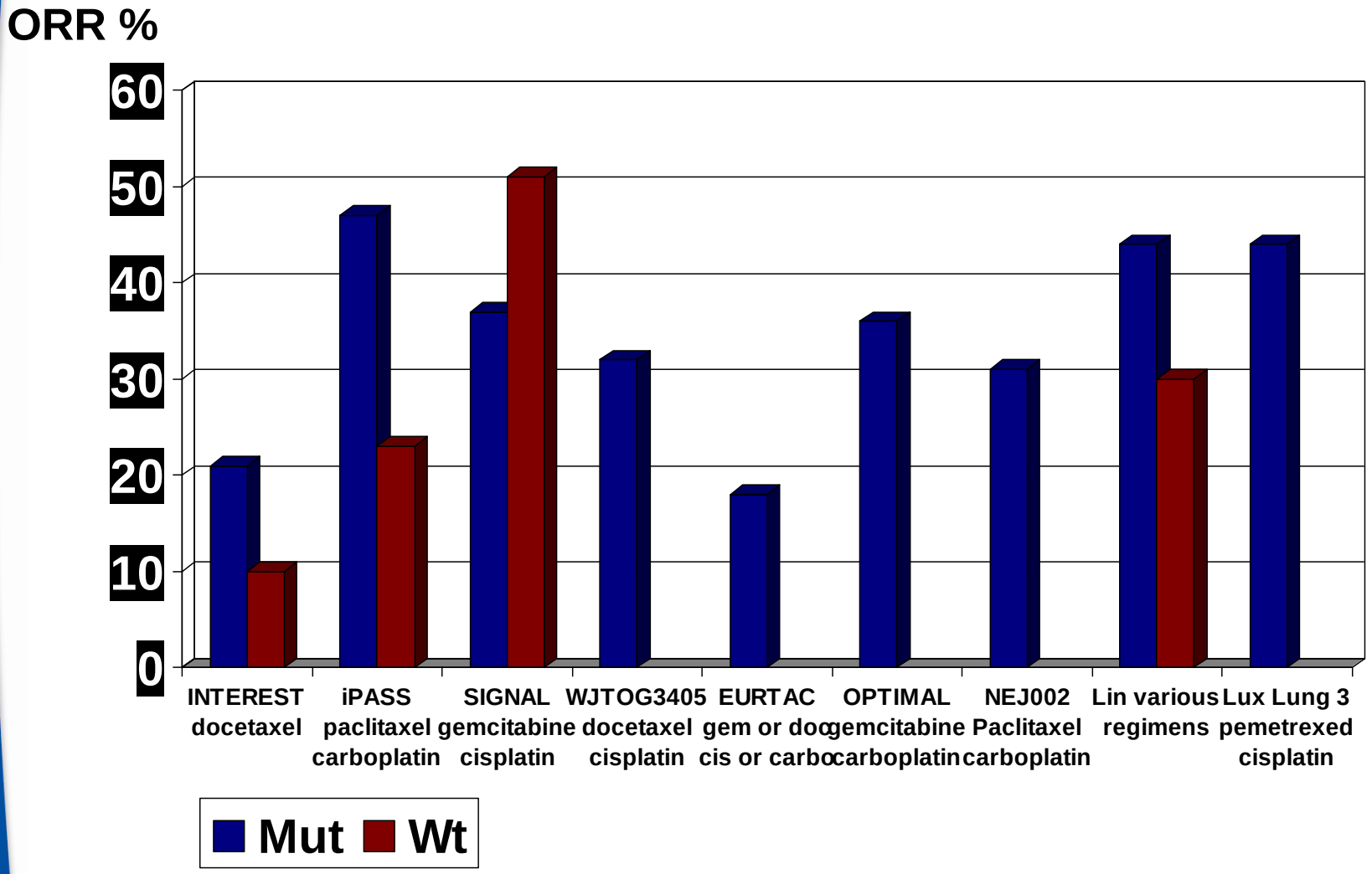
Chemotherapy does matter



EGFR are only one piece of the puzzle, not the whole picture !

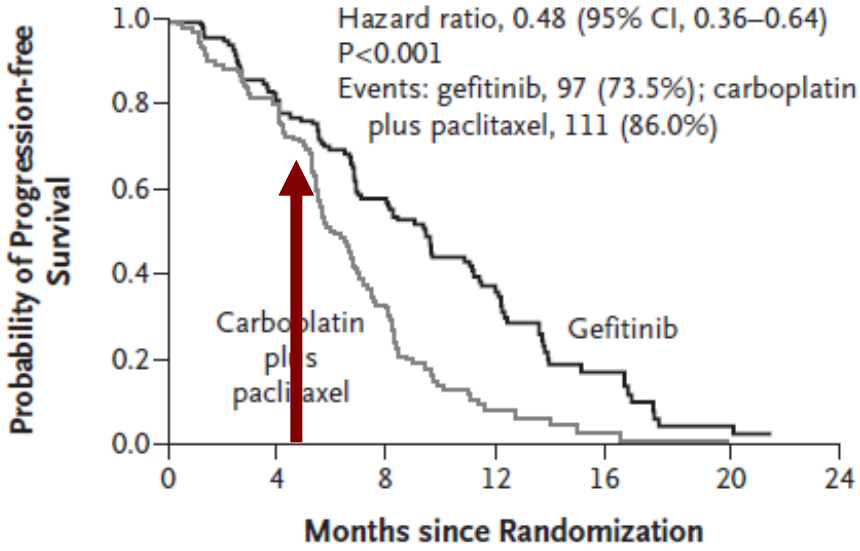
⇢ Are the control arms adequate ?

EGFRmut and response to CT



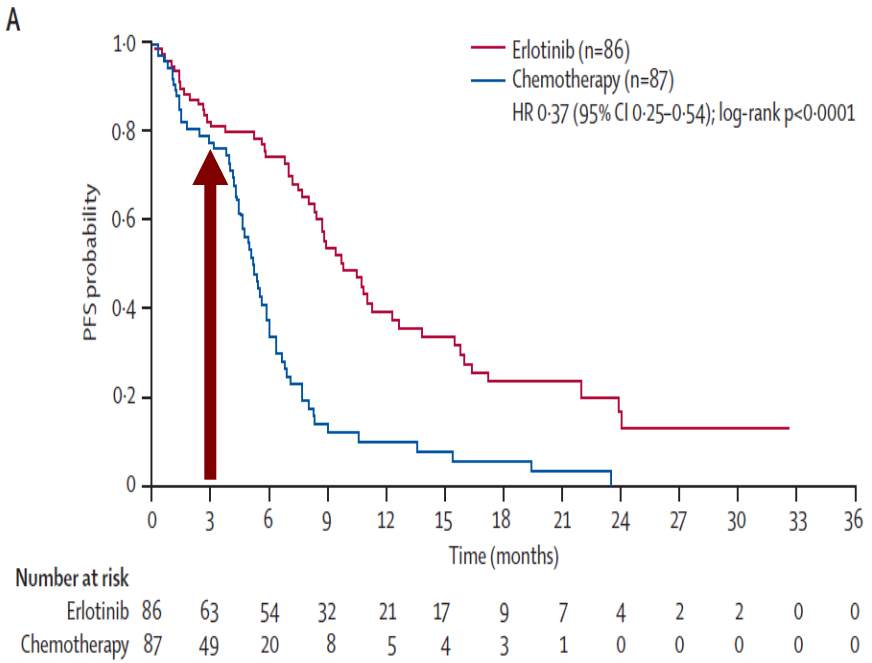
Duration of chemotherapy

- **iPASS**
  - 6X 3 weeks-cycles = 4.5 m



No. at Risk							
Gefitinib	132	108	71	31	11	3	0
Carboplatin plus paclitaxel	129	103	37	7	2	1	0

- **EURTAC**
  - 4X 3 weeks-cycles = 3 m



Number at risk													
Erlotinib	86	63	54	32	21	17	9	7	4	2	2	0	0
Chemotherapy	87	49	20	8	5	4	3	1	0	0	0	0	0

Continuation maintenance chemotherapy ?

Mok NEJM 07, Rosell Lancet Oncol 12

PFS AVAPERL : Pemetrexed/Cisplatin/bevacizumab X 4

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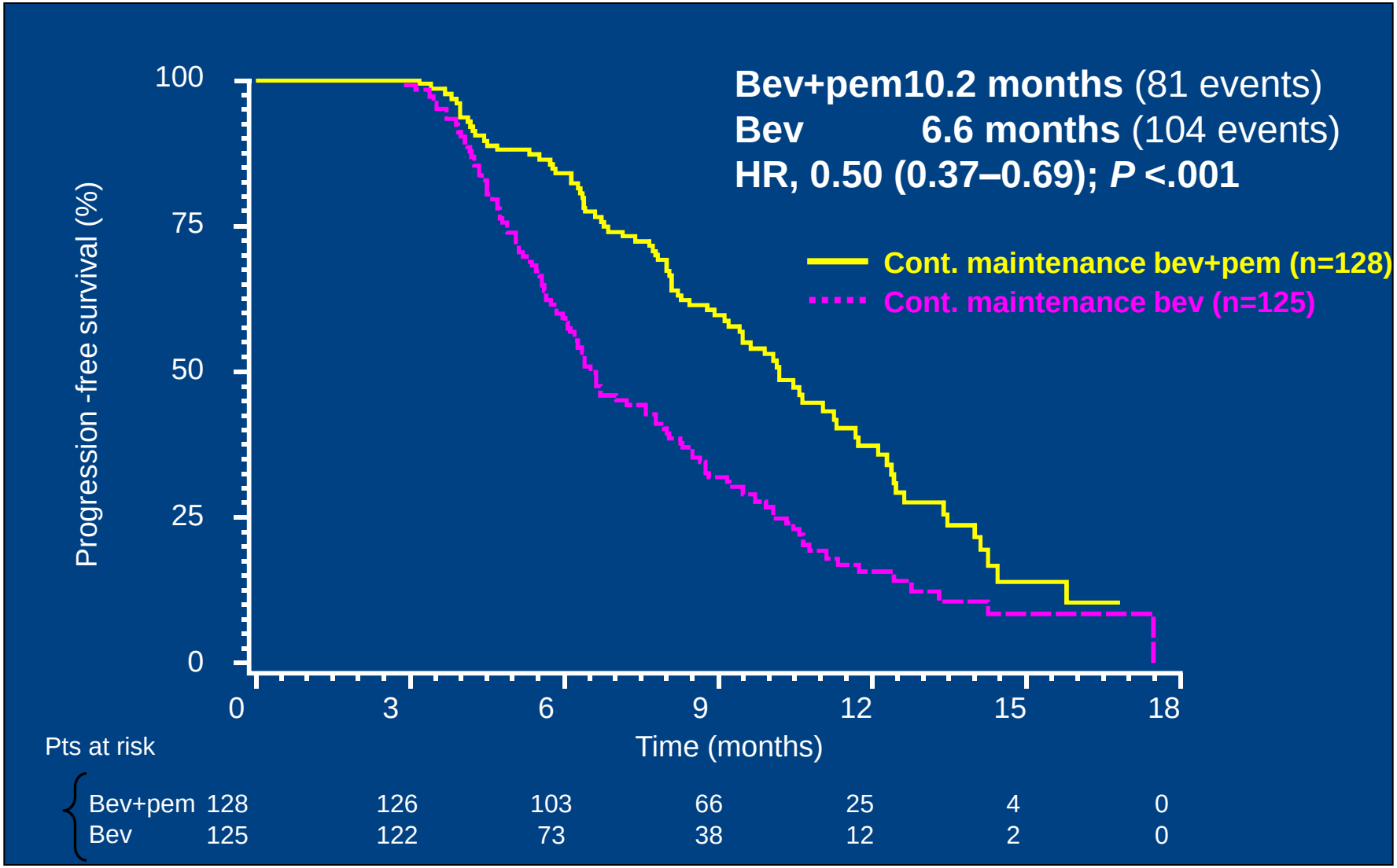
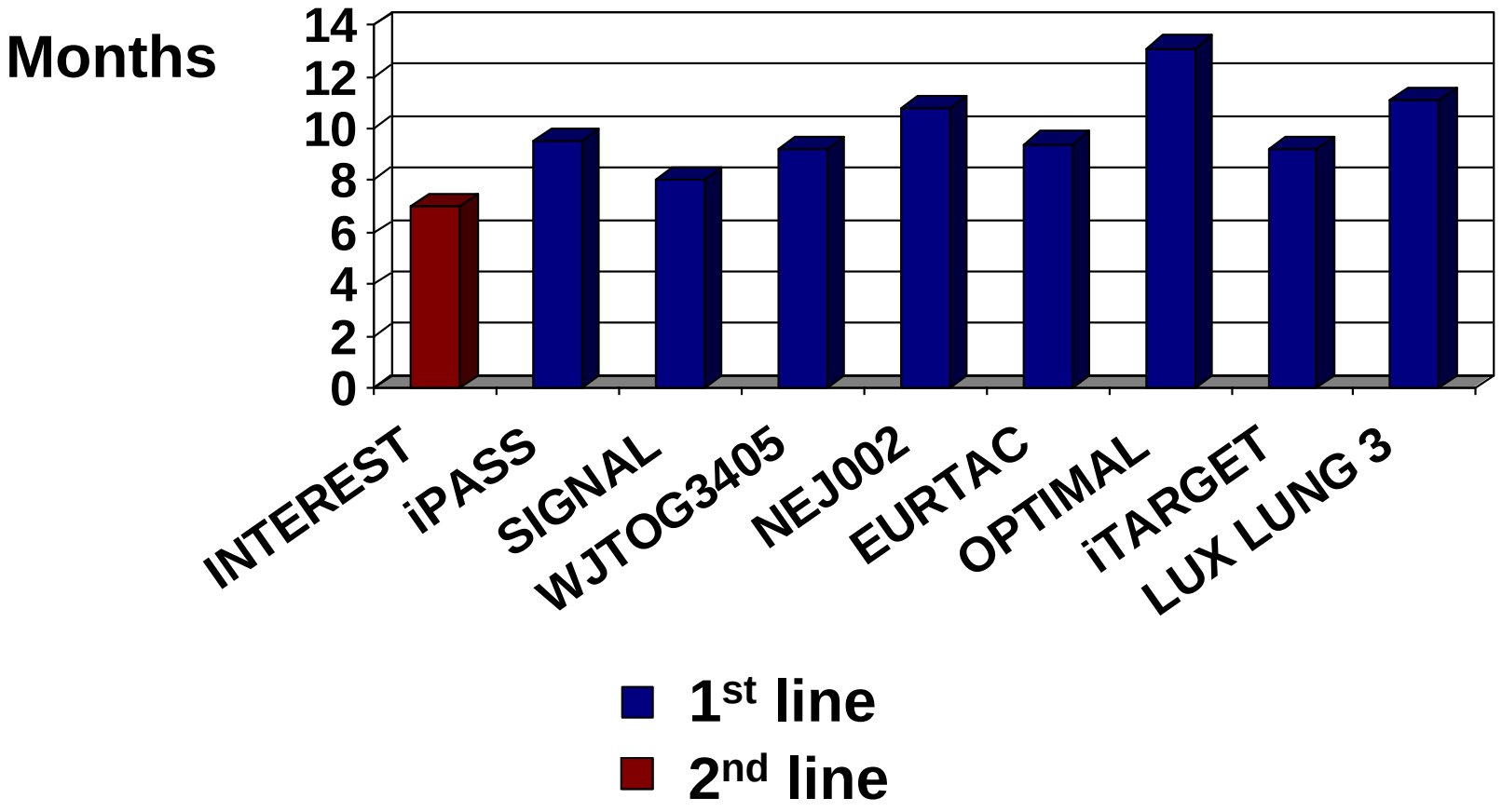


[a] Randomized pts, Intent-to-treat population

Bev, bevacizumab; HR, hazard ratio; Pem, pemetrexed; pts, patients.

VIENNA 2012 ESMO congress

EGFR TKIs : PFS in EGFR mut patients



Yang ASCO 12, Douillard JCO 10, Mitsudomi Lancet Oncol 10, Kobayashi ASCO 09, Mok NEJM 07, Rosell Lancet Oncol 12, Han JCO 12, Zhou Lancet Oncol 11, Inoue ASCO 11, Sequist JCO 08

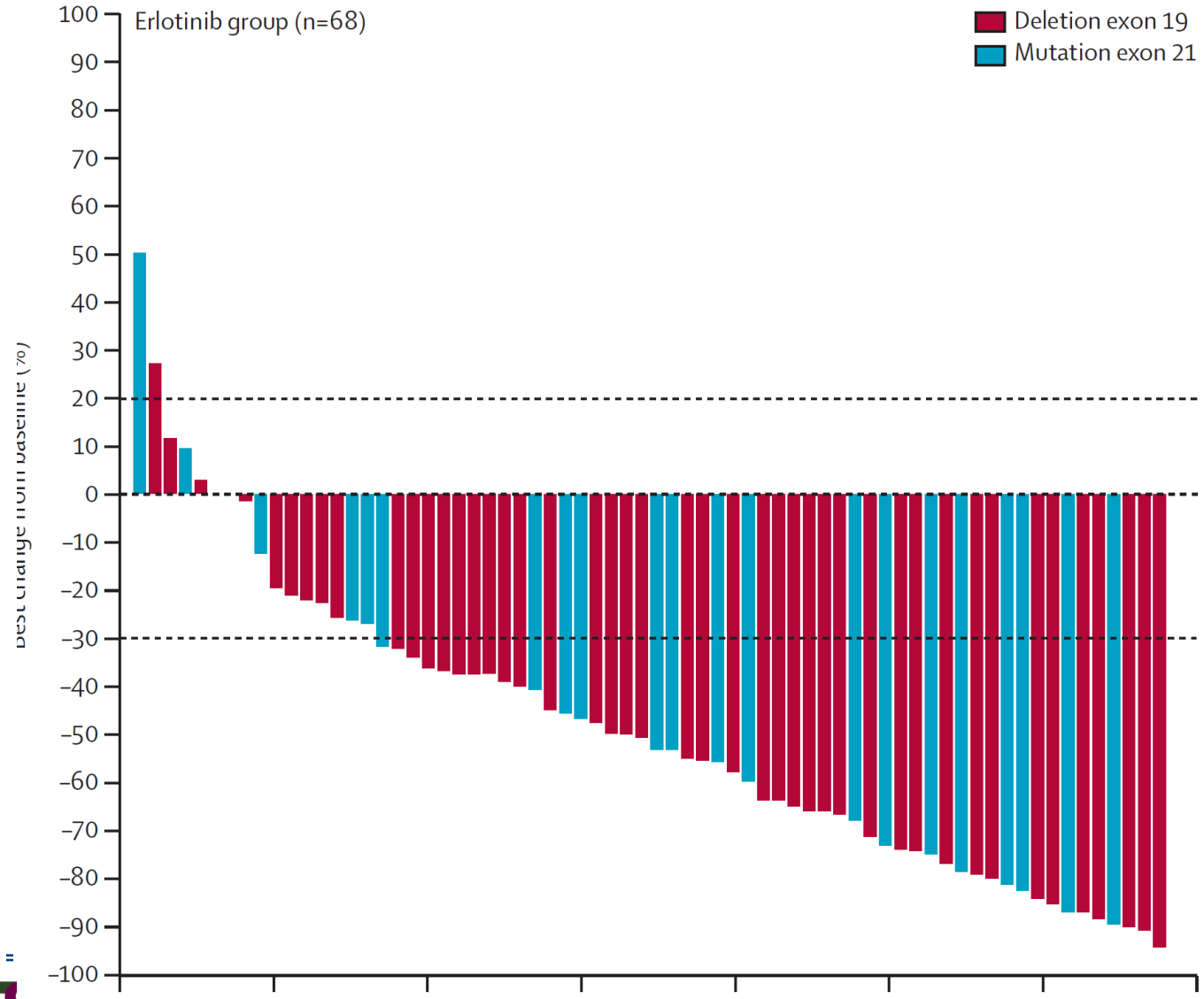
EGFR mutation in plasma (n=264) Before and after chemotherapy

Before -> after	n	PR	SD	PD
Mut -> WT	54	39%	48%	13%
No change	186	30%	46%	24%
WT -> mut	24	21%	54%	25%

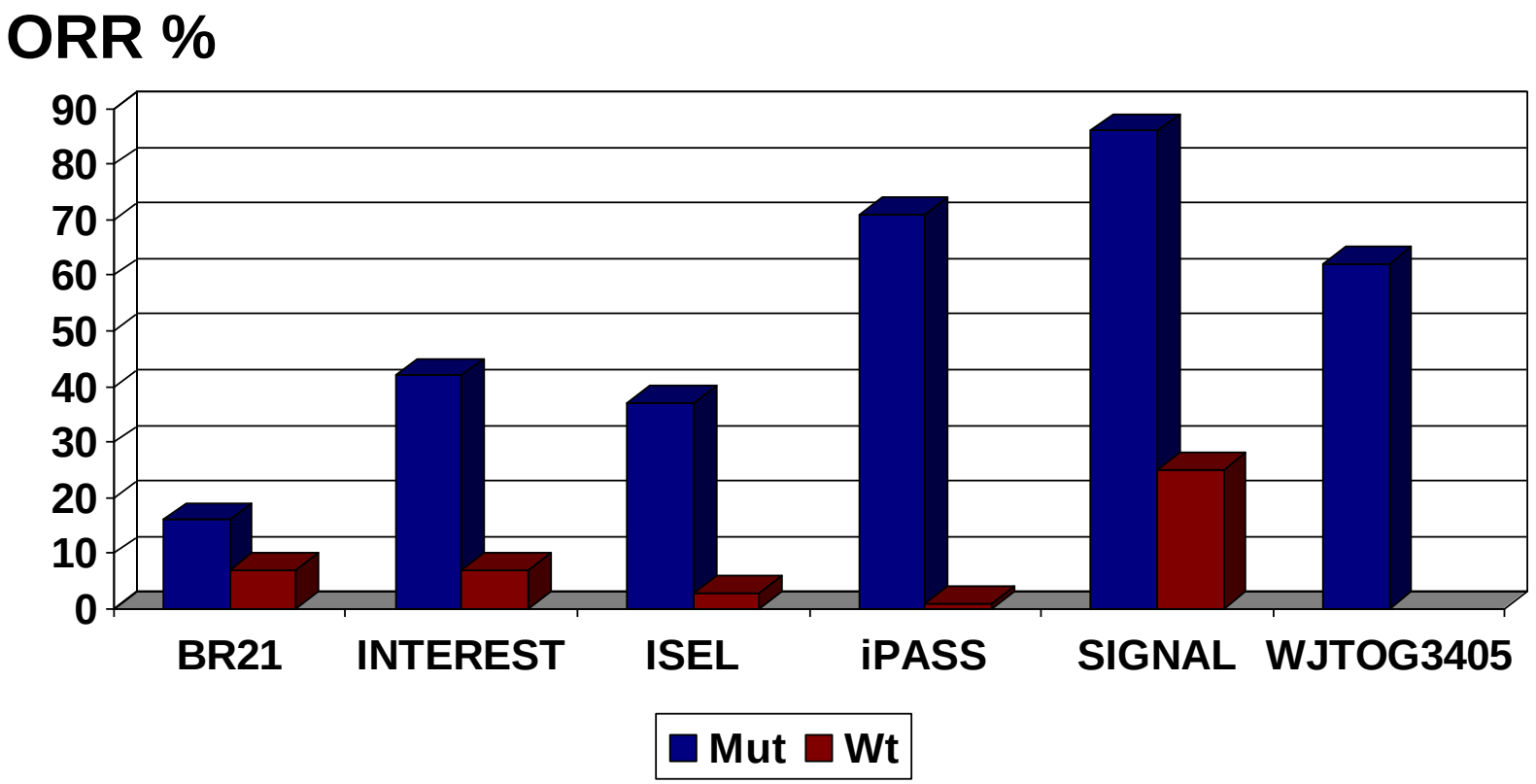
Chemotherapy induces EGFR mut ??

⇢ Oncogenic addition field: think new !

EURTAC - erlotinib arm

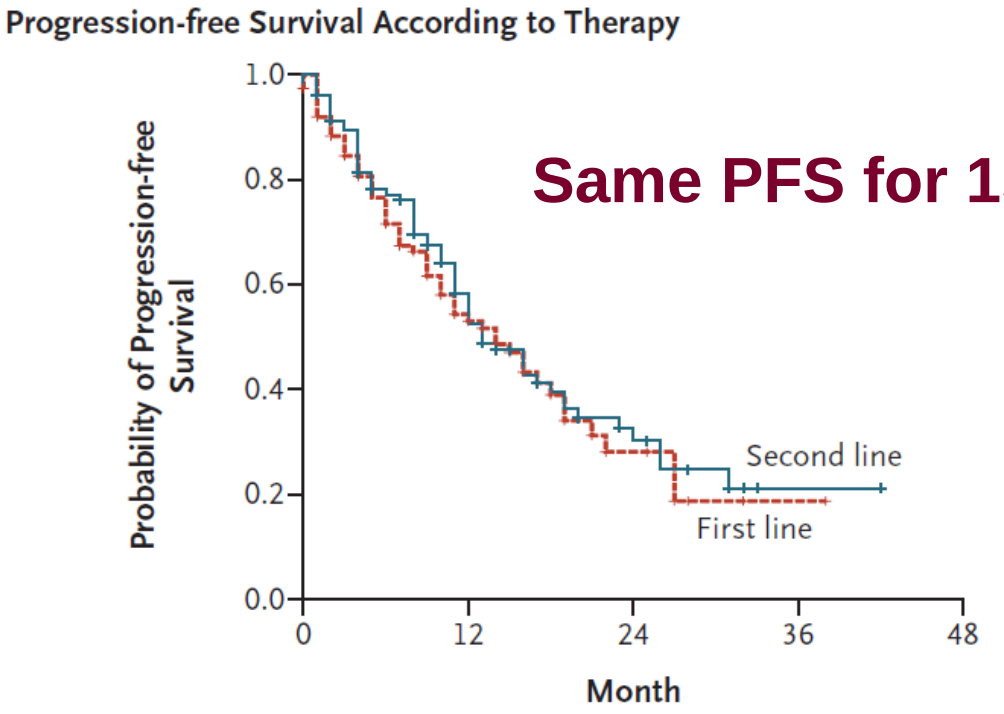


EGFR mut and response to EGFR TKIs



Tsao, NEJM 05, Douillard et al, JCO 10, Hirsch et al. JCO 2006, Mitsudomi et al. LANCET ONCOL 10, Kobayashi ASCO 2009

EGFR TKIs in EGFR mutated patients

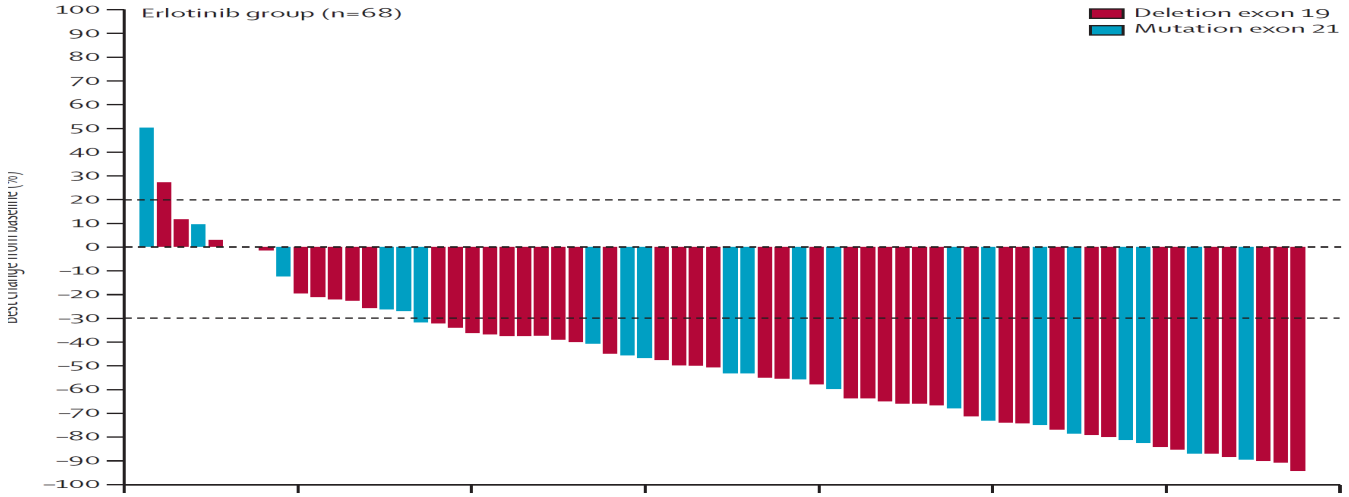


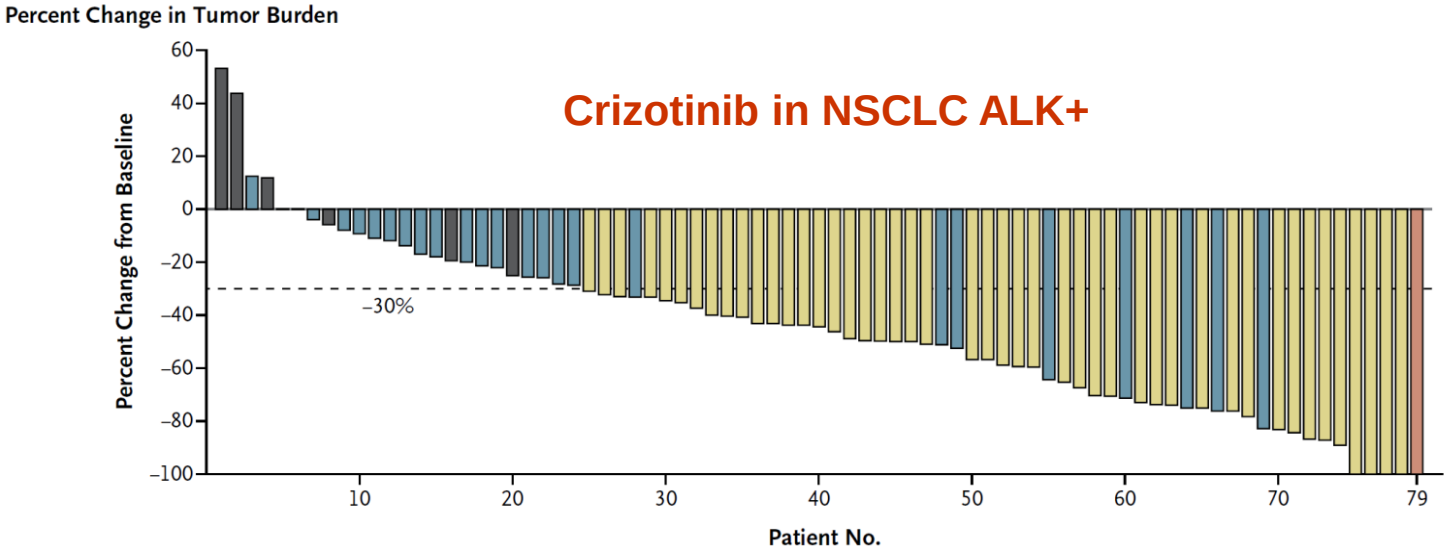
First Line					
No. at risk	113	41	9	1	0
No. of events	0	46	58	60	60
Second Line					
No. at risk	104	48	12	1	1
No. of events	0	41	59	62	62

Same PFS for 1st and 2nd line!

Rosell et al, NEJM 2009

EURTAC - erlotinib arm





Rosell Lancet Oncol 12, Kwak NEJM 10

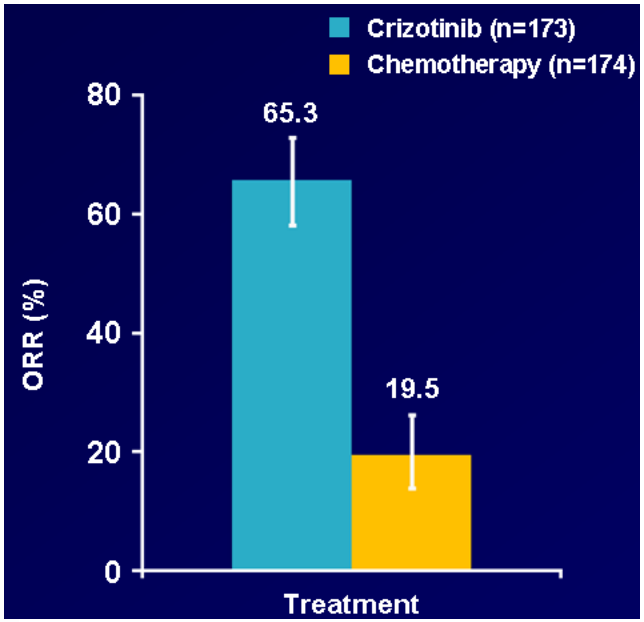
Response by subgroup

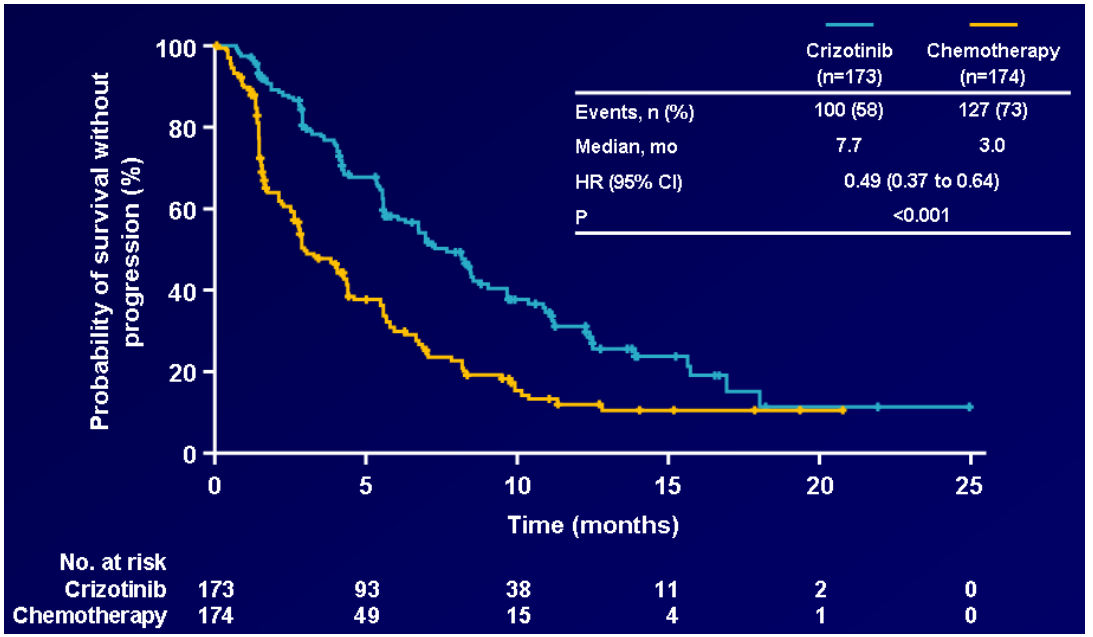
	Objective Response Rate % (n/N)	
No. of prior regimens*		
0	50	(3/6)
1	60	(18/30)
2	56	(10/18)
3	62	(10/16)
> 3	53	(18/34)
Performance status		
0	50	(17/34)
1	54	(30/56)
2	80	(12/15)
Age		
< 65 years	59	(53/90)
≥ 65 years	40	(6/15)
Gender		
Male	60	(31/52)
Female	53	(28/53)

- Median response duration was 36.3 weeks (95% CI: 32.1, 72.9) in patients with an objective response (n=59)

* Unknown for 1 patient

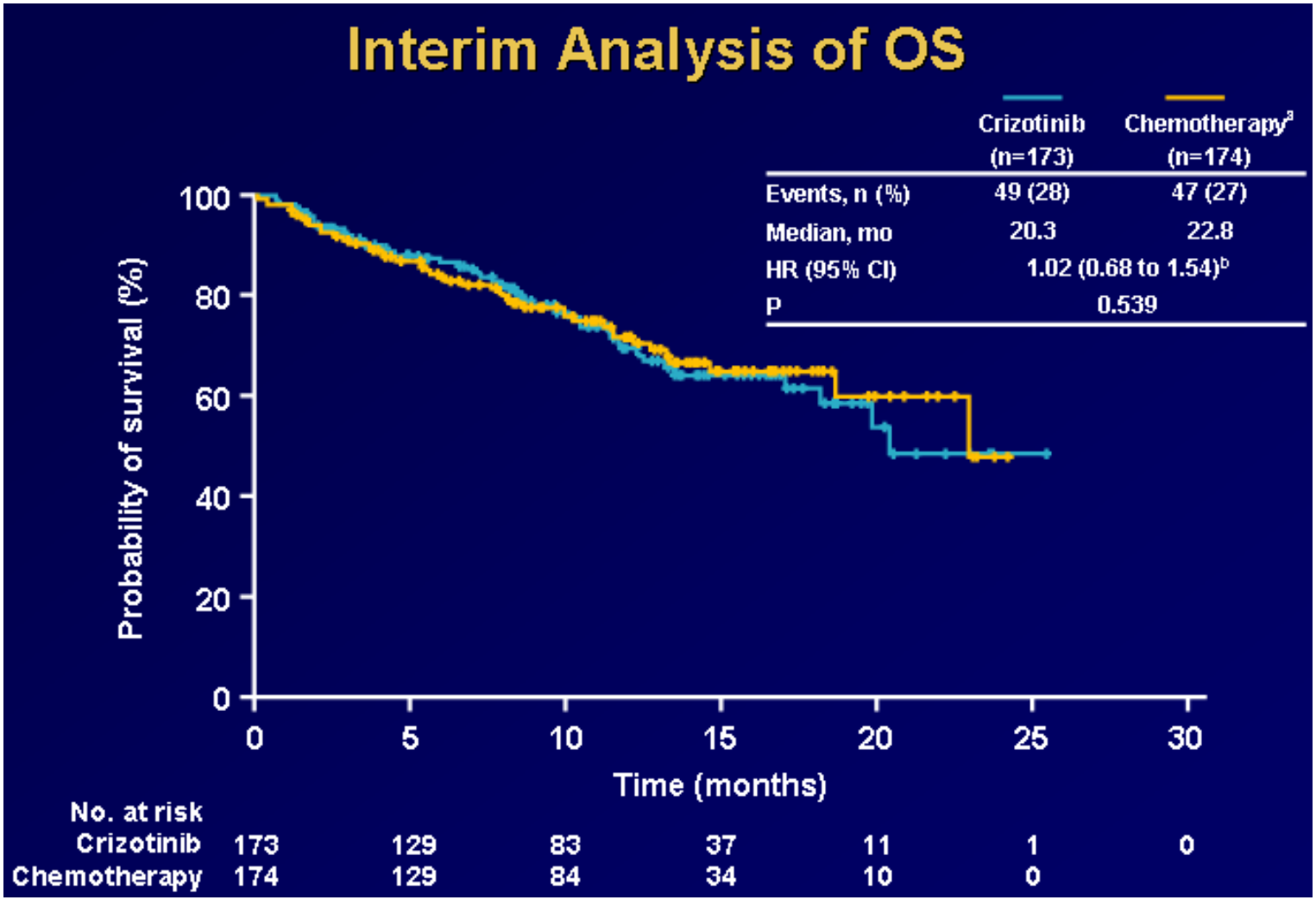
PROFILE 1007
Pemetrexed vs. pemetrexed/docetaxel





- **PFS is improved by** 4,7 months **(**HR of 0,49**)**

PROFILE 1005 : OS



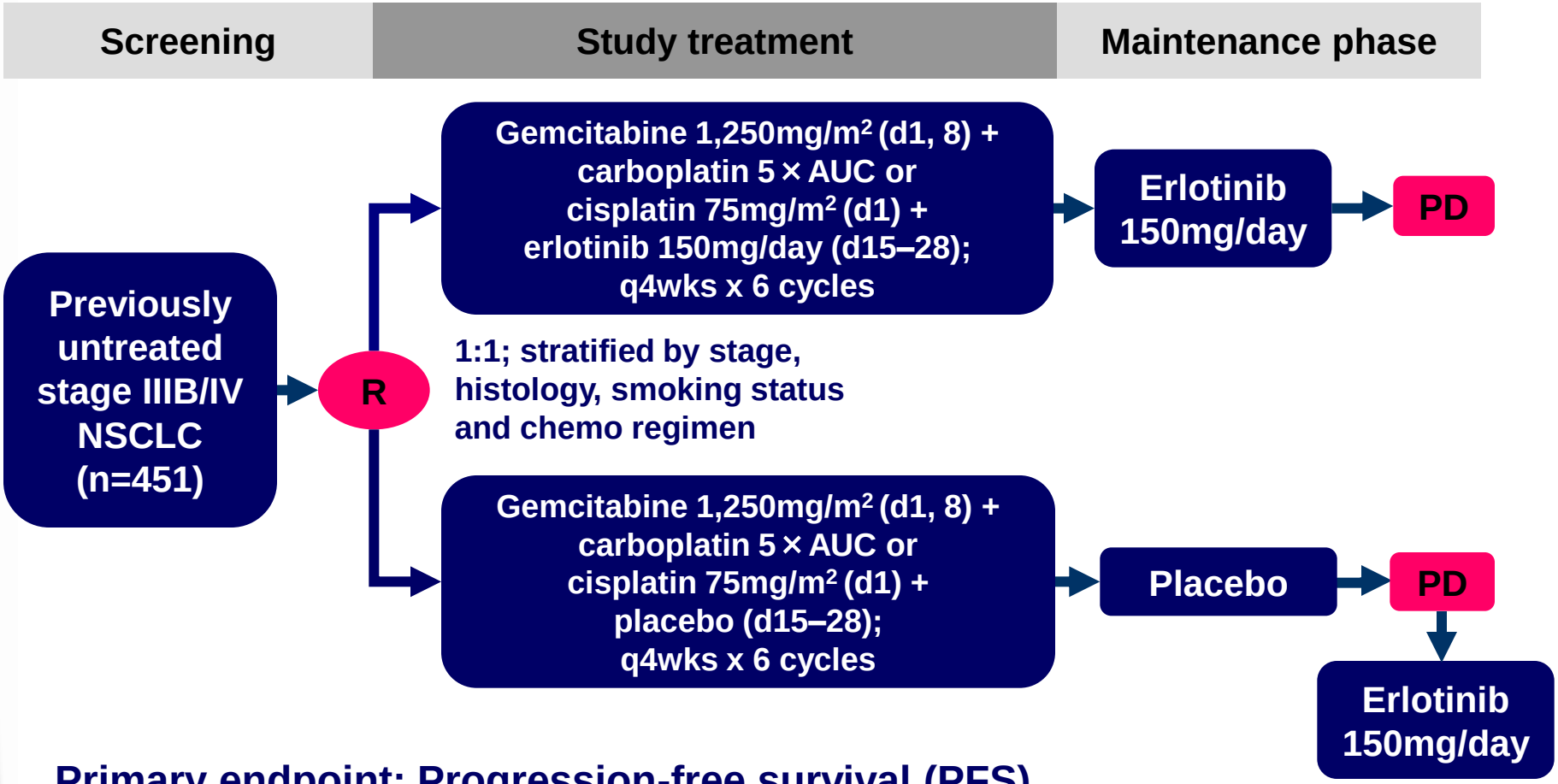
PFS and OS in EGFRmut/ALK+ pts

Study	n	Drugs	HR PFS (95% CI)	HR OS (95% CI)
NEJ 002	228	Gefitinib Pacli/carbo	0.32 (0.23-0.43) ; p<0.001	0.88 (0.63-1.24) ; p=0.483
SIGNAL	96/ 309	Gefitinib Gem/Cis	0.54 (0.26-1.10) ; p=0.086	1.04 (0.49-2.18)
EURTAC	173	Erlotinib Gem-doc Cis-carbo	0.34 (0.23−0.49); p<0·0001	1.36 (0.73-1.36) ; p=0.71
WJTOG 3505	177	Gefitinib Doc/Cis	0.52 (0.37-0.71) ; p<0.0001	1.18 (0.76-1.82) ; p=0.44
iPass	261/ 1217	Gefitinib Pacli/carbo	0.48 (0.36–0.64) ; p<0.001	1.00 (0.76- 1.33) ; p=0.99
OPTIMAL	165	Erlotinib Gem/carbo	0.16 (0.10-0.26) ; p<0.0001	1.04 (0.69- 1.58) ; p=0.69
PROFILE 5	347	Crizotinib Pem & Doc	0.49 (0.37–0.64) : p<0.001	1.02 (0.68- 1.54) ; p=0.53

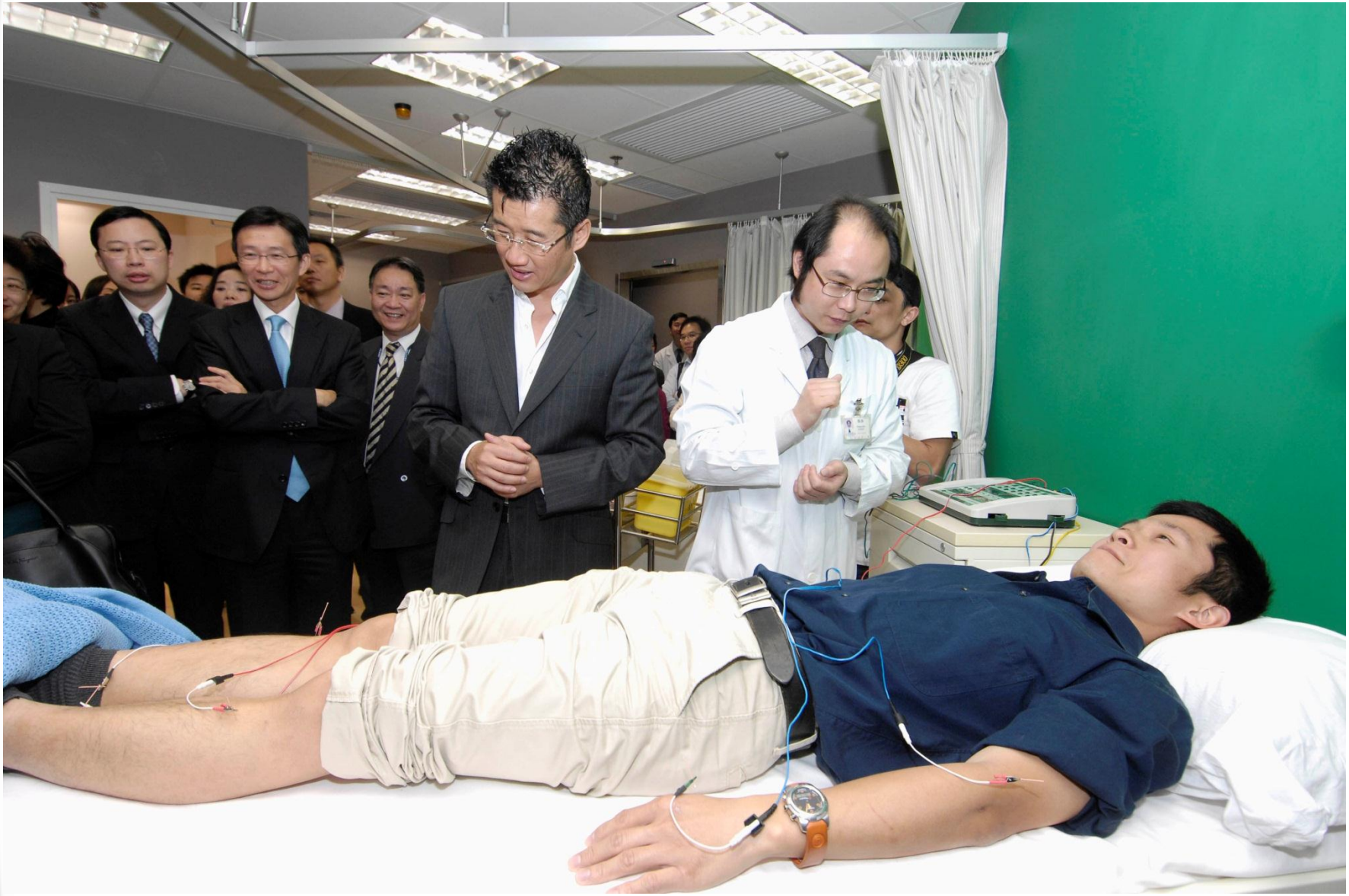
Yang ASCO 12, Mitsudomi ASCO 12, Mok NEJM 07;
Rosell ESMO 12, Han JCO 12, Zhou ASCO 12, Inoue ASCO 11

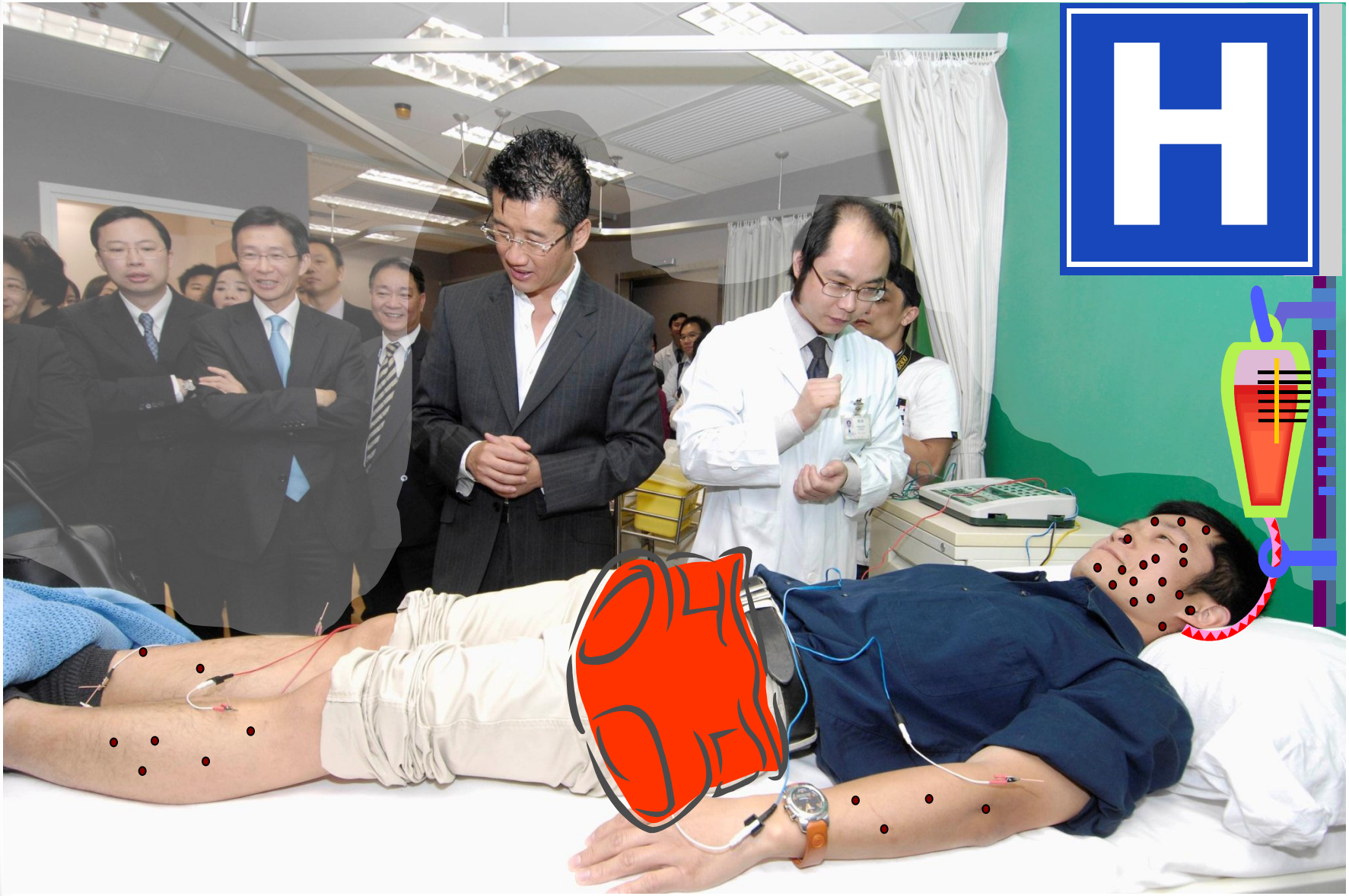
⇢ **We do not use RECIST when treating our patients**

FASTACT-II study design



Primary endpoint: Progression-free survival (PFS)

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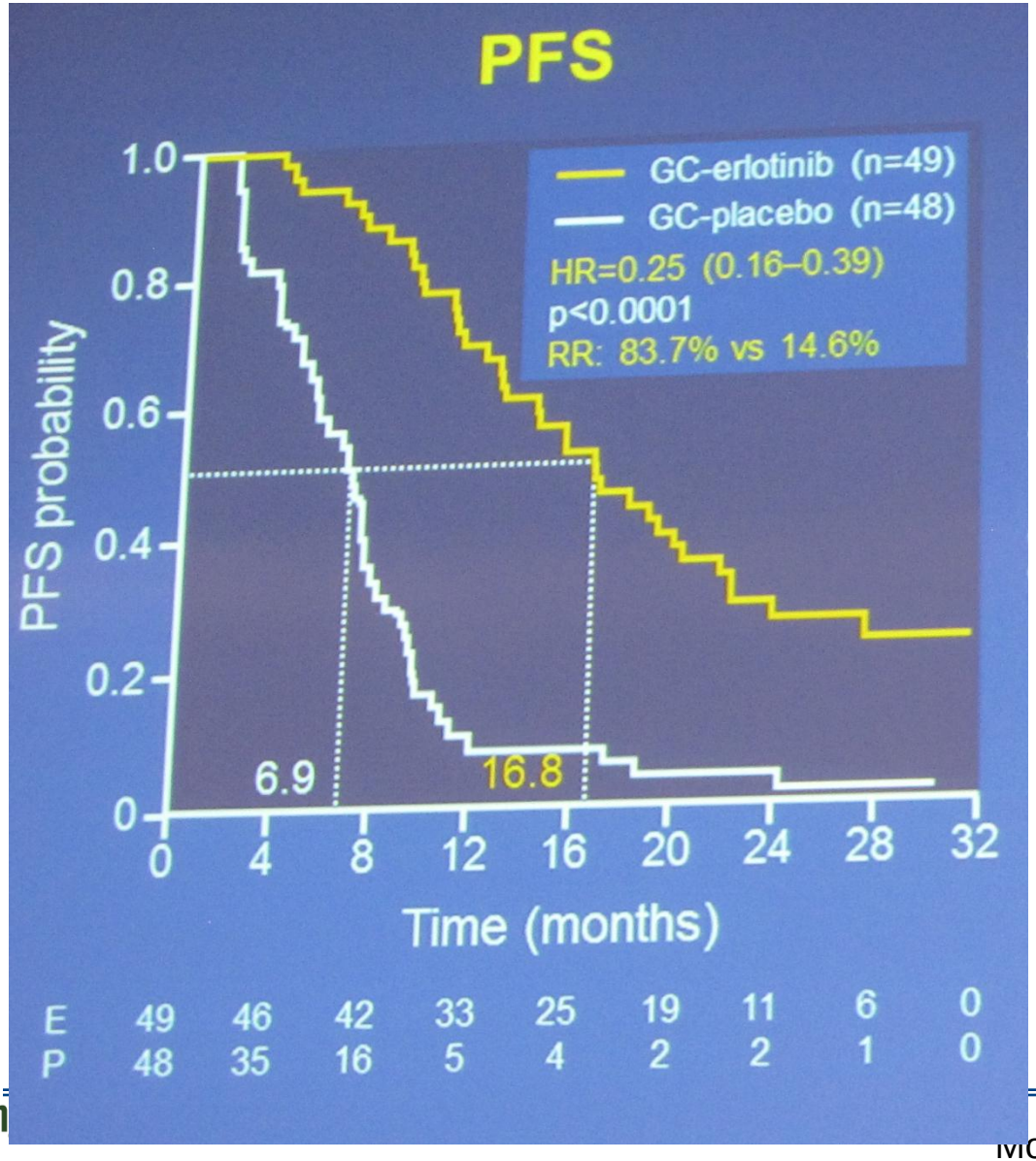
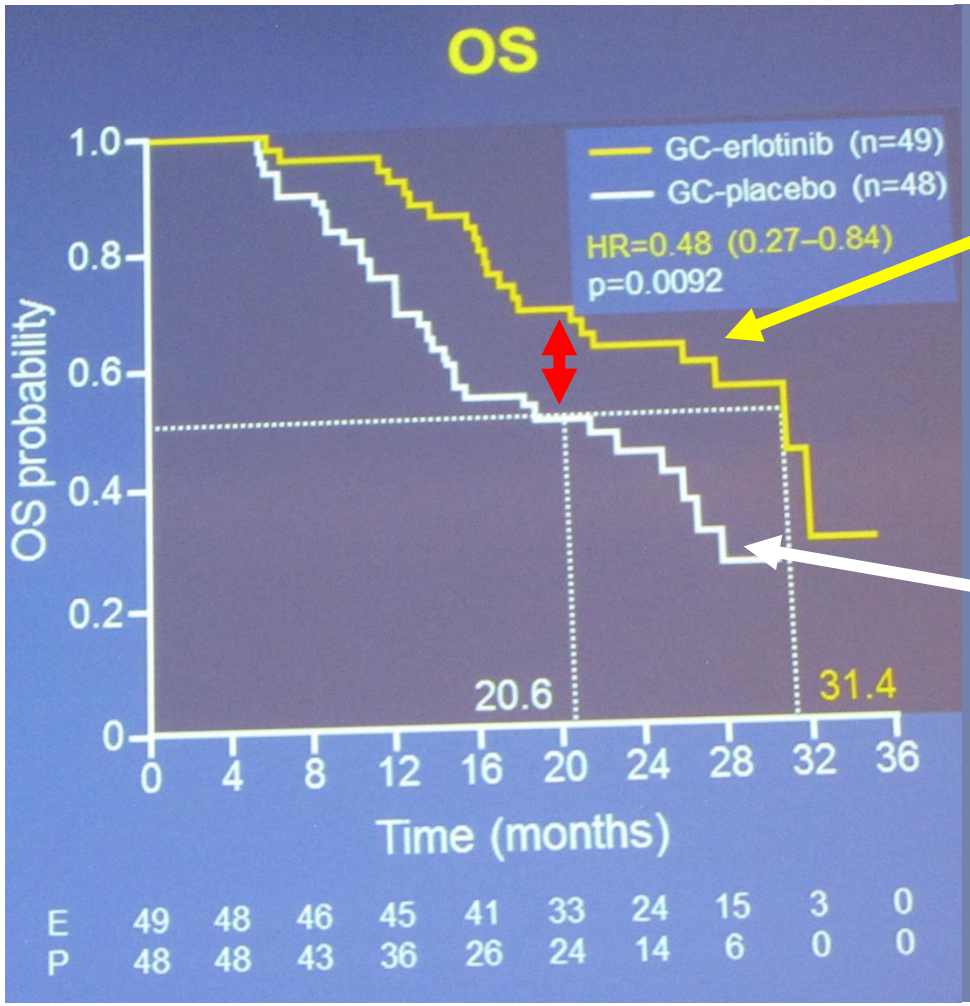
FASTACT-II study design – EGFRmut subgroup



FASTACT-II study design – EGFRmut subgroup

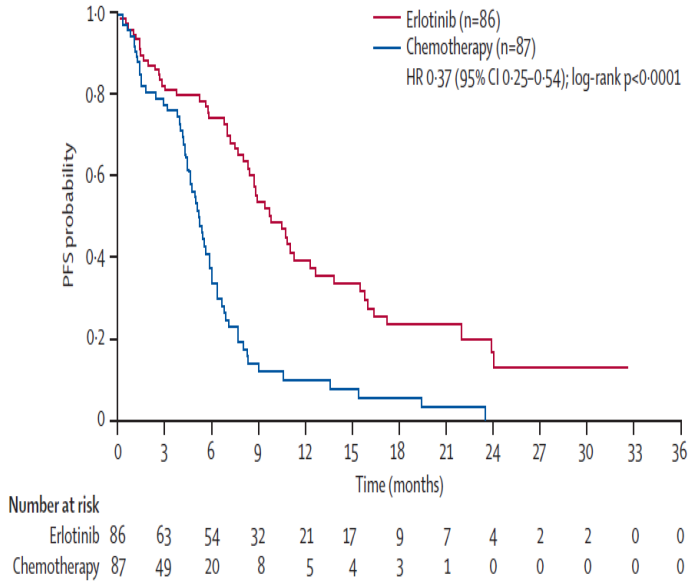


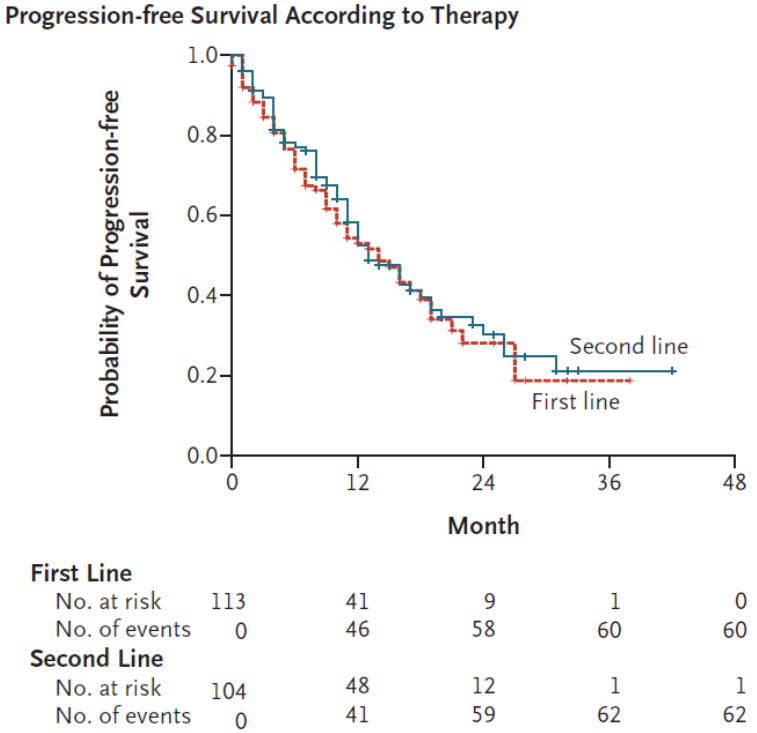
100% received TKIs

11 patients !!

85% received TKIs

⇢ PFS EURTAC VS Rosell's cohort





PFS = 9.7 months

PFS = 14 months

Rosell NEJM 09, Rosell Lancet Oncol 12

Conclusion in EGFRmut patients

- Same OS with upfront TKI or upfront chemo
- Platinum-based therapy is beneficial
- Patients have to received both sequentially
- CT toxicity > TKI toxicity
- I start with the more toxic treatment


EGFR
MUT
Think different.