EGFR TKI is the best choice for first line treatment of EGFR mutated lung adenocarcinoma

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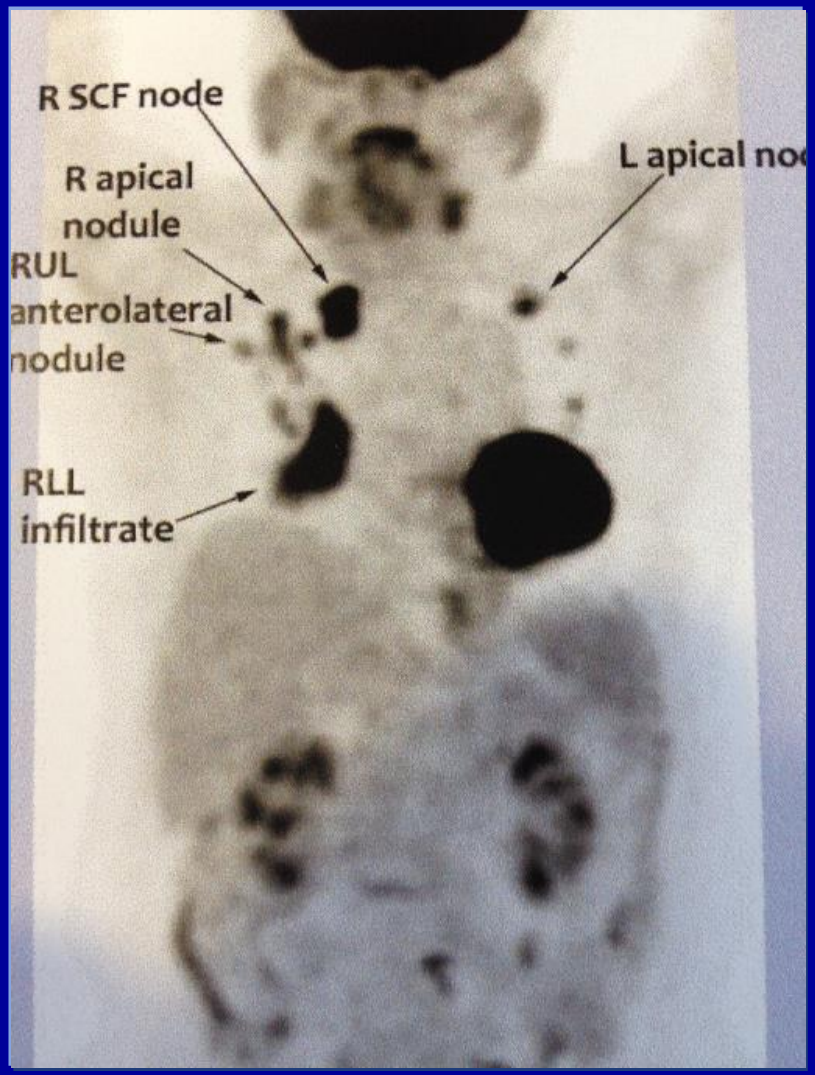
Miss Lee, 44 year old female non-smoker

- Present with 3 months history of cough
- Recent increase in shortness of breath
- CXR showed RLL infiltrate and hilar mass
- Biopsy confirmed adenocarcinoma
- EGFR mutation sent



“Congratulation, Miss Lee. EGFR mutation is positive and I shall start you on CHEMOTHERAPY immediately!” Doctor said.

“Congratulation, Miss Lee. EGFR mutation is positive and I shall start you on EGFR TKI immediately!” Doctor said.

EGFR Mutation is the most significant pathophysiologic event in this type of adenocarcinoma

Definition of oncogenic addiction:

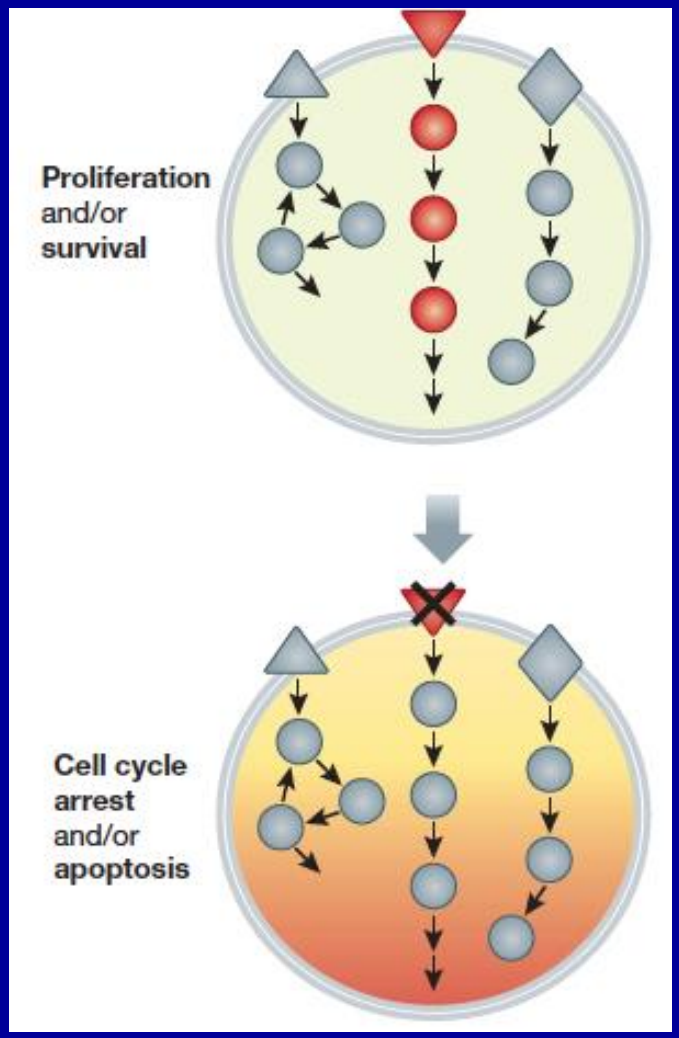
The phenomenon by which some cancers that contain multiple genetic and epigenetic abnormalities remain dependent on (addicted to) one or a few genes for both maintenance of the malignant phenotype and cell survival

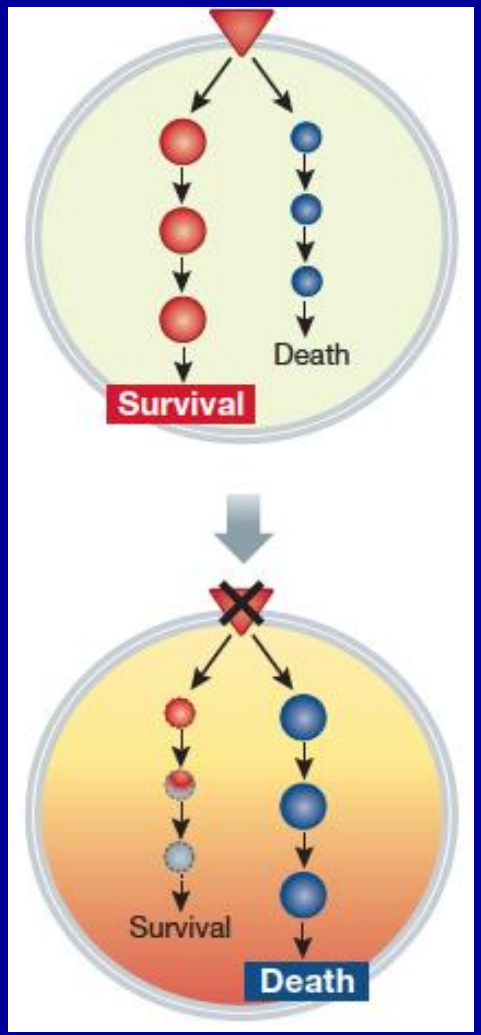
Weinstein et al Science July 2002

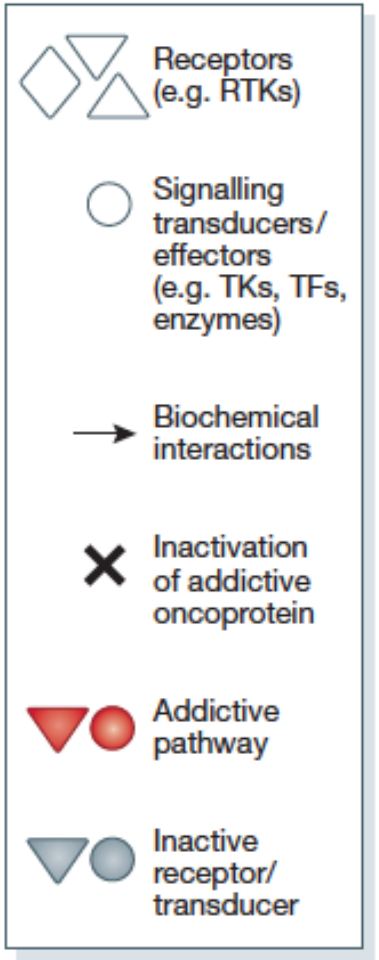
Models of driver oncogene

Genetic streamlining

Oncogenic shock



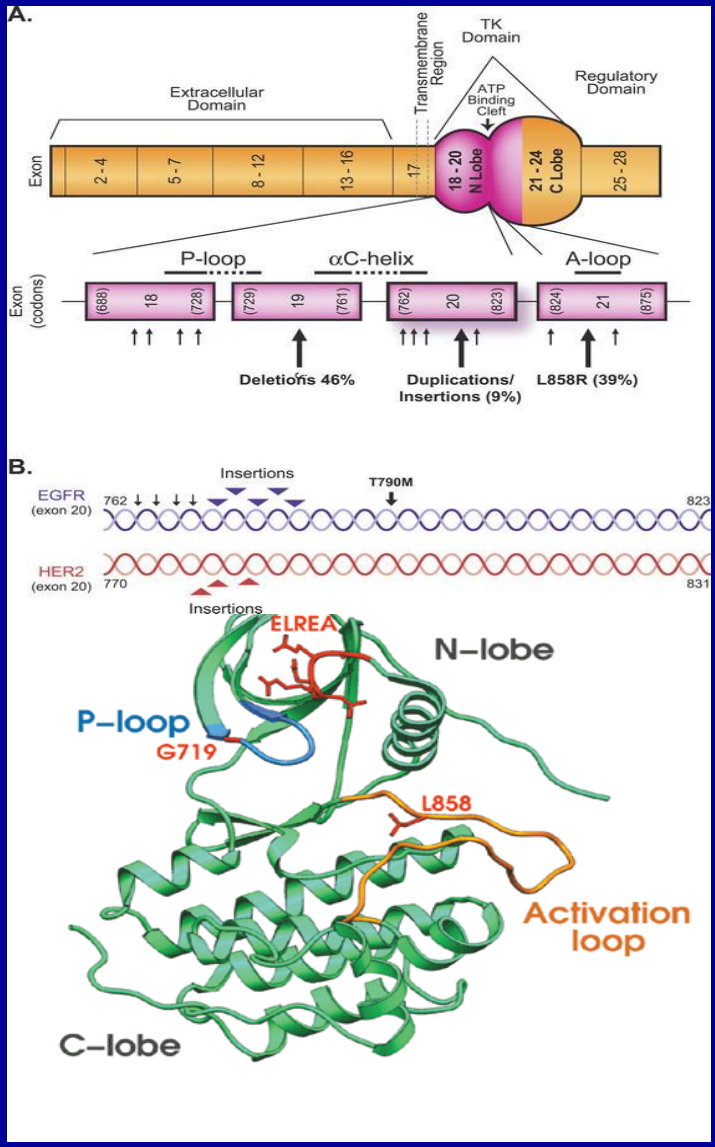




Torti and Trusolino, EMBO Mol Med: 623, 2011

EGFR Oncogenic Addiction

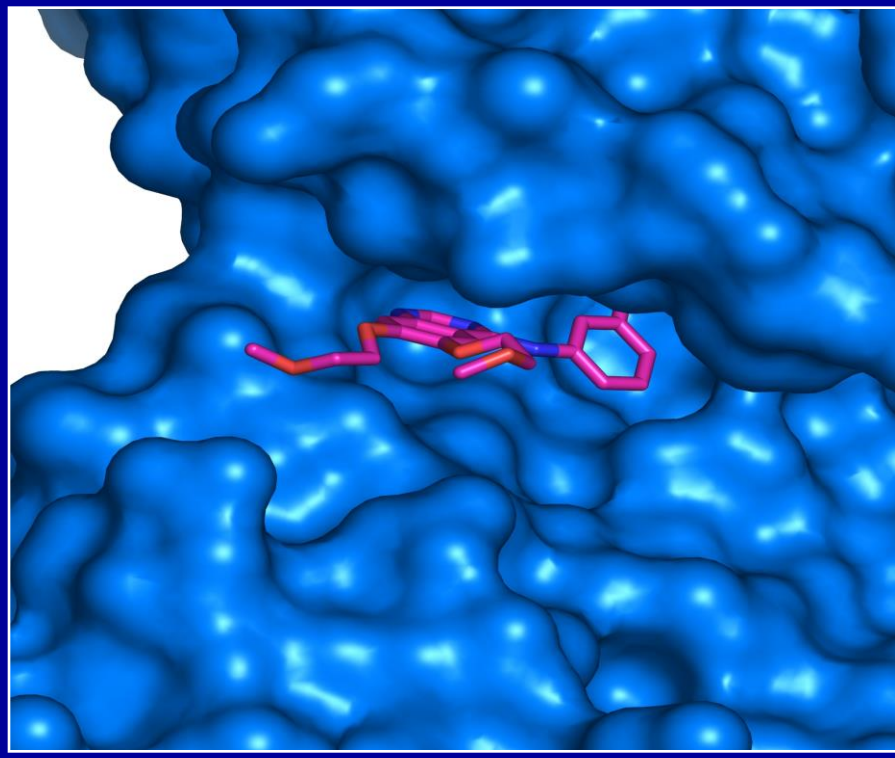
- Exon 21 lies within the activation loop while exon 19 remove residue from the C-helix
- Mutation at this sites shift the equilibrium such that it favors the activated states
- Activated states induce downstream pro-survival and pro-apoptotic activity
- As result tumor cell depends on EGFR signal for survival



Kumar et al J Clin Oncol 2008;26(10):1742-51.

EGFR Tyrosine Kinase Inhibitors (TKI)

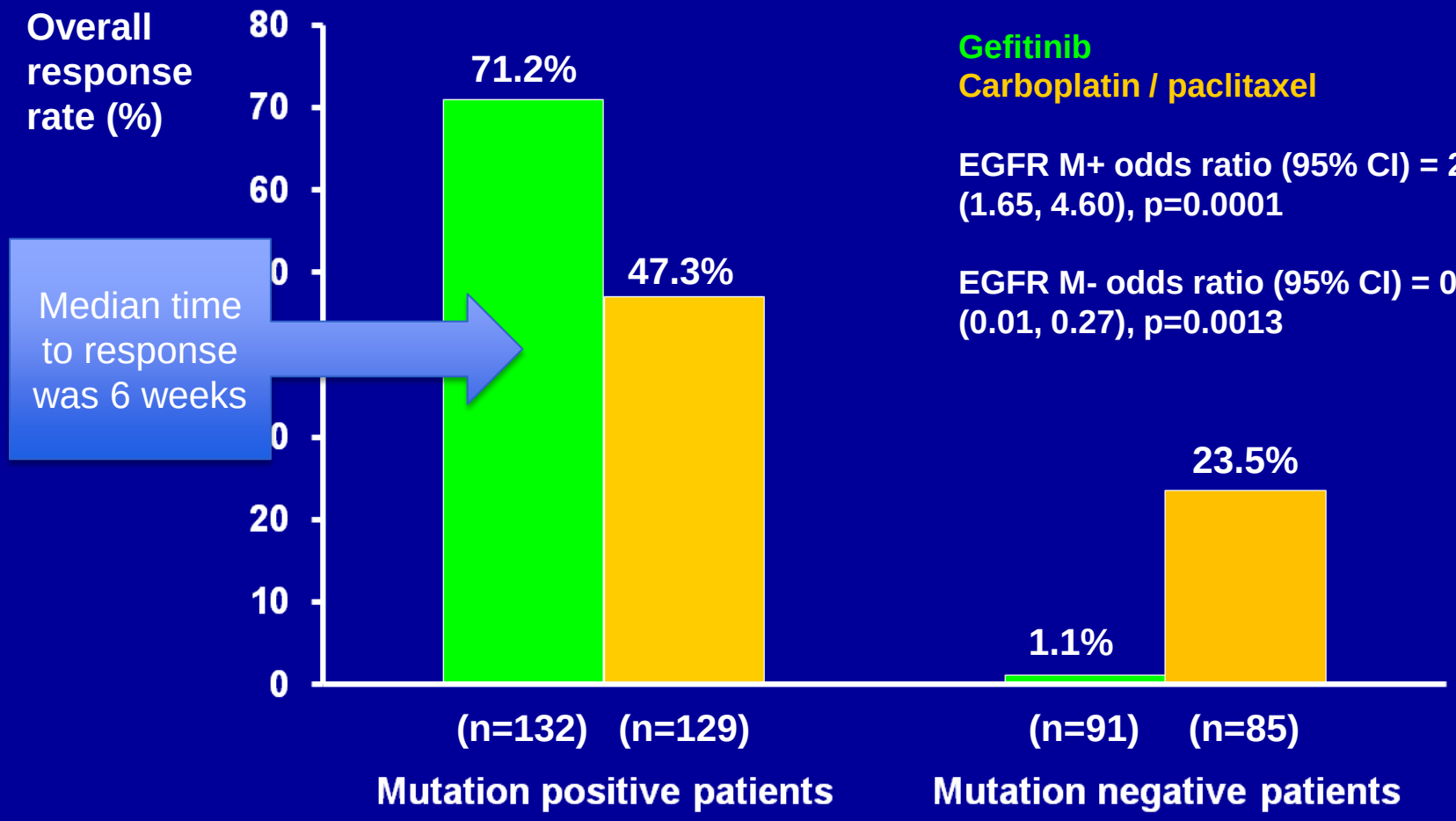
- Mutated EGFR has increased binding ATP thus highter affinity (5-10 fold) to gefitinib or erlotinib than wild type
- Functional inhibition of EGFR signal dependent cancer cell induces dramatic tumor response



Eck et al Biochim.Biophys.Acta 2010;1804(3):559-66

Miss Lee will have better chance of clinical improvement quickly

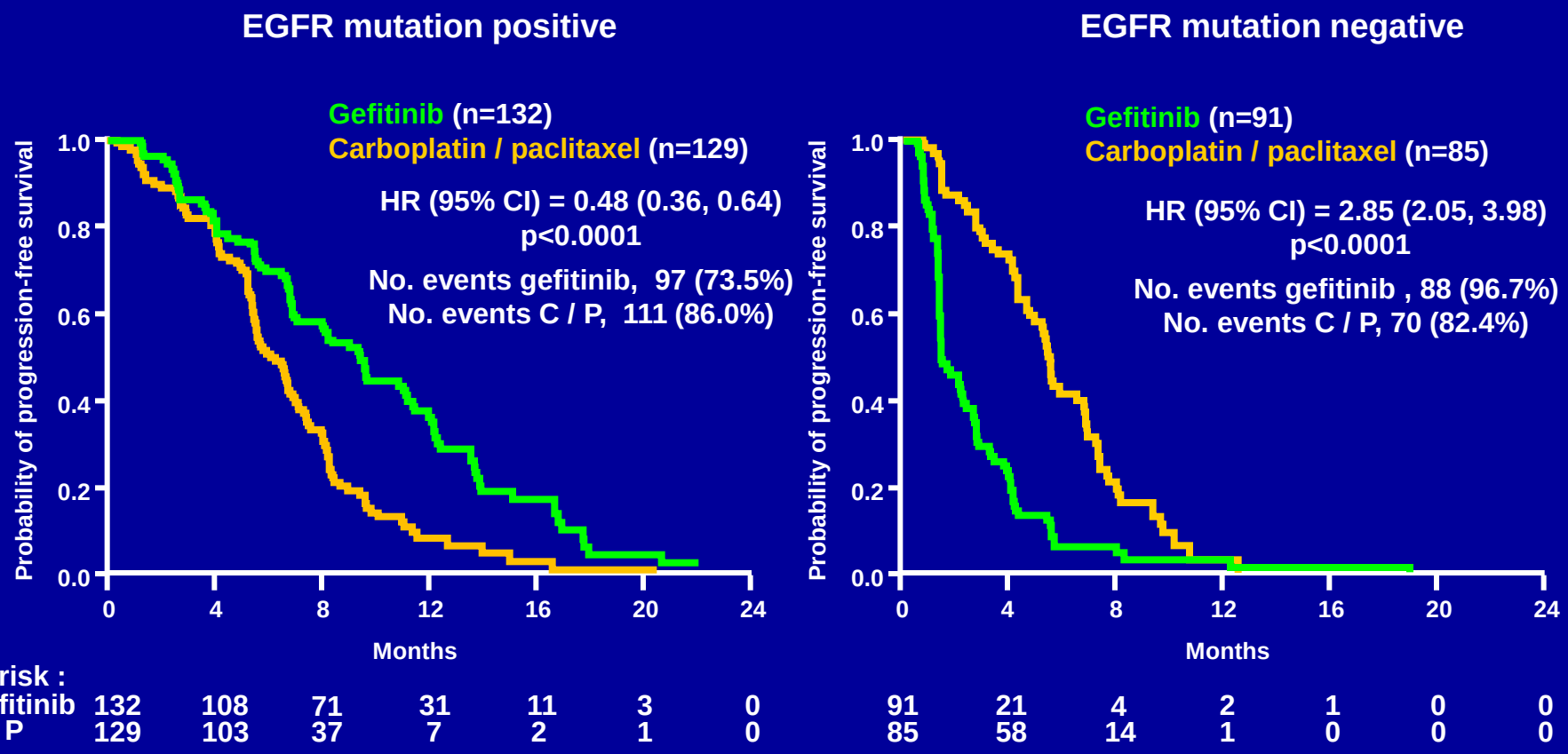
IPASS: Objective response rate in EGFR mutation positive and negative patients



Odds ratio >1 implies greater chance of response on gefitinib

Mok et al NEJM 361:947 2009

Progression-free survival in EGFR mutation positive and negative patients



Treatment by subgroup interaction test, p<0.0001

ITT population
Cox analysis with covariates

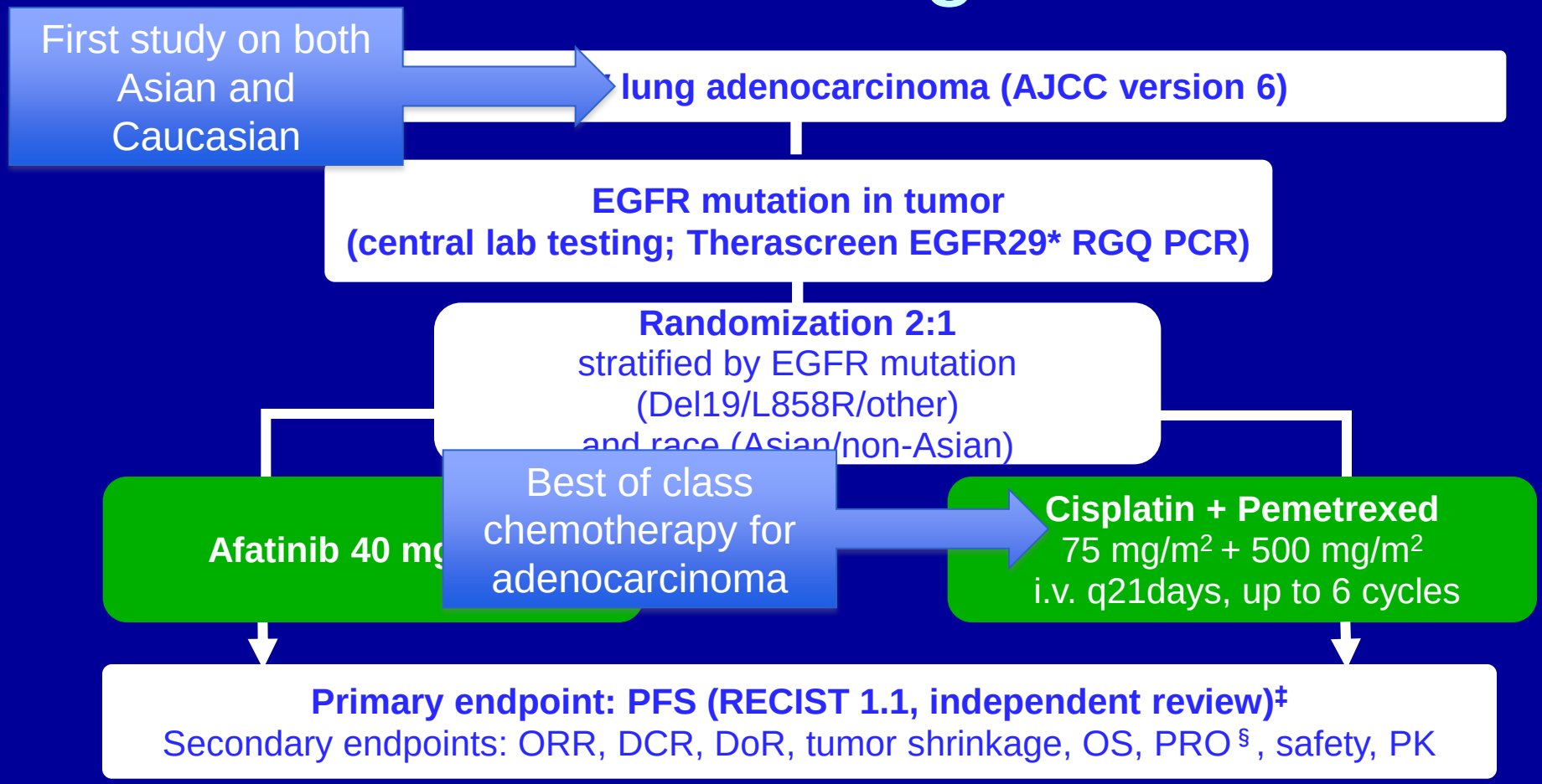
Mok et al NEJM 361:947 2009

Six Randomized studies on first line EGFR TKI in patients with EGFR mutation

Author	Study	N (EGFR mut +)	RR	Median PFS
Mok et al	IPASS	132	71.2% vs 47.3	9.8 vs 6.4 months
Lee et al	First-SIGNAL	27	84.6% vs 37.5%	8.4 vs 6.7 months
Mitsudomi et al	WJTOG 3405	86	62.1% vs 32.2%	9.2 vs 6.3 months
Maemondo et al	NEJGSG002	114	73.7% vs 30.7%	10.8 vs 5.4 months
Zhou et al	OPTIMAL	154	83% vs 36%	13.1 vs 4.6 months
Rosell et al	EURTAC	175	58% vs 15%	9.7 vs 5.2 months

Mok et al NEJM 2009, Lee et al WCLC 2009, Mitsudomi et al Lancet Oncology 2010, Maemondo NEJM 2010 Zhou et al ESMO 2010, Rossell et al Lancet Oncology 2012,

LUX Lung 3



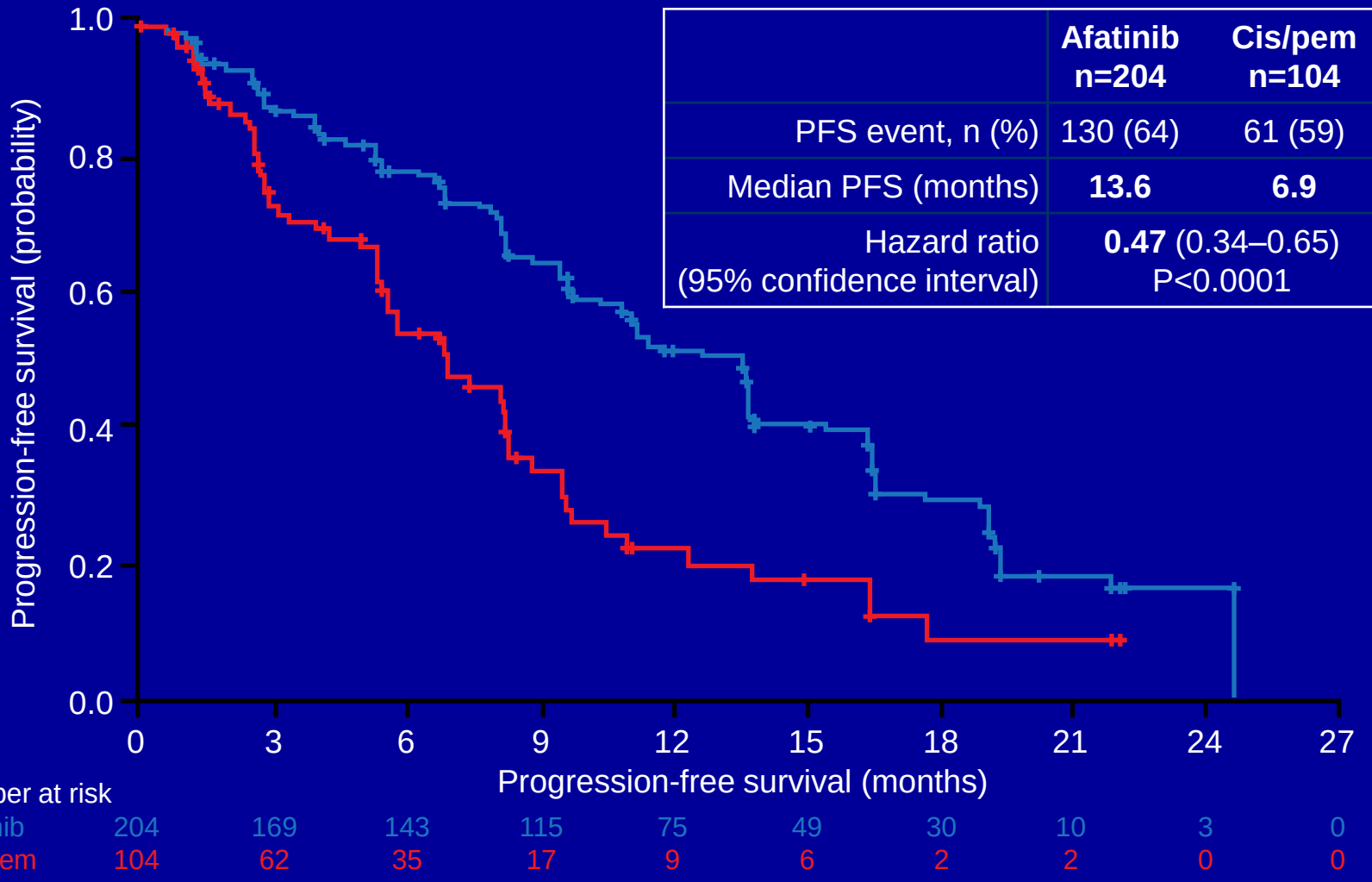
Primary PFS analysis (independent review)

Sample size: 217 independent events needed to detect HR of 0.64 (or median increase in PFS from 7 to 11 months) at two-sided 5% significance level with 90% power

Yang et al ASCO 2012

PFS: Common mutations (Del19/L858R)

Independent review – patients with Del 19/L858R (n=308)



	Afatinib n=204	Cis/pem n=104
PFS event, n (%)	130 (64)	61 (59)
Median PFS (months)	**13.6**	**6.9**
Hazard ratio (95% confidence interval)	**0.47** (0.34–0.65) P<0.0001	

Number at risk

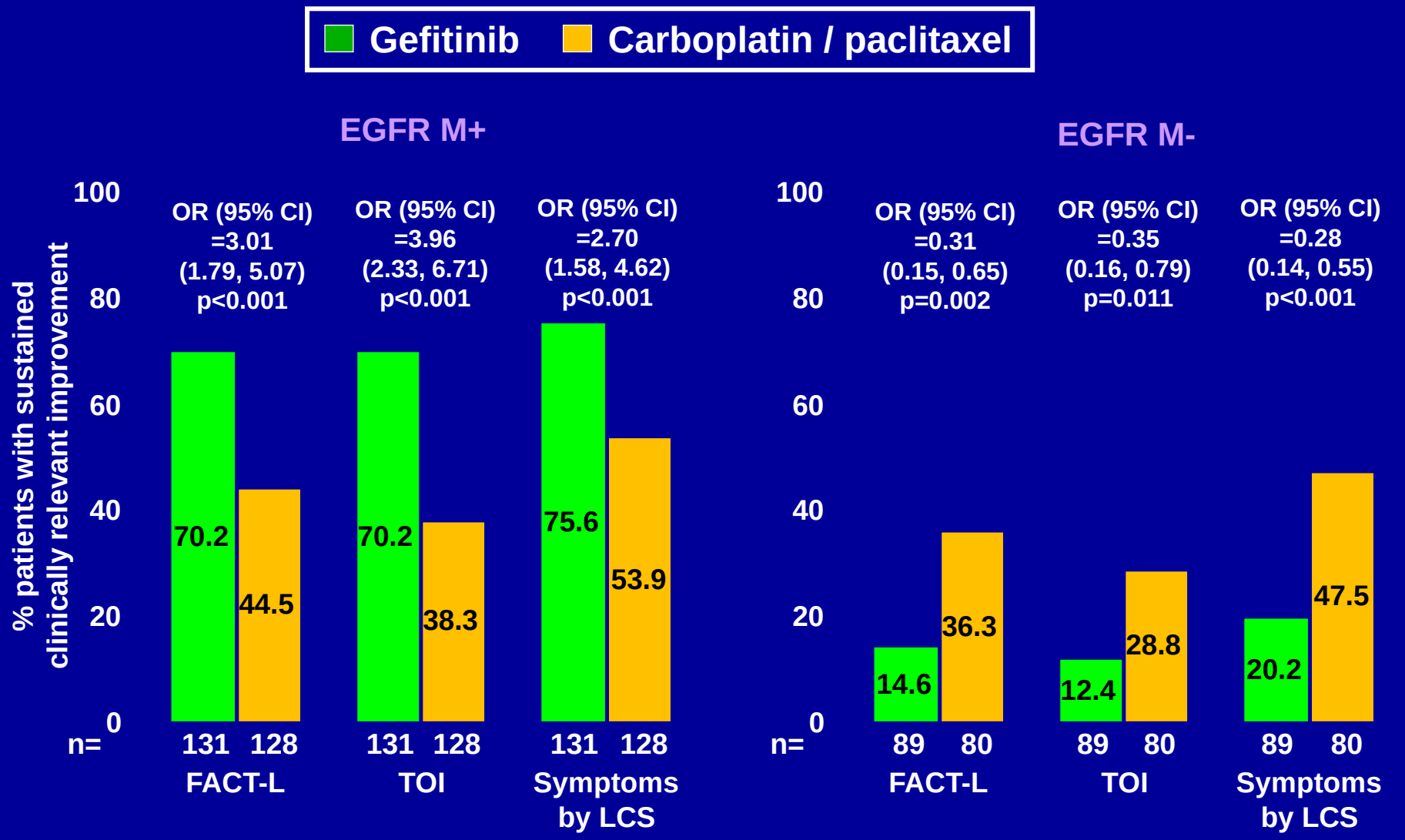
Afatinib	204	169	143	115	75	49	30	10	3	0
Cis/Pem	104	62	35	17	9	6	2	2	0	0

Total of 7 randomized study confirming the role of first line EGFR TKI in patients with EGFR mutated adenocarcinoma

	No. of positive randomized phase III studies
Pemetrexed as first line chemotherapy	1
Pemetrexed as maintenance therapy	1
Bevacizumab as first line therapy	2
Concurrent chemo-RT for stage III lung cancer	2

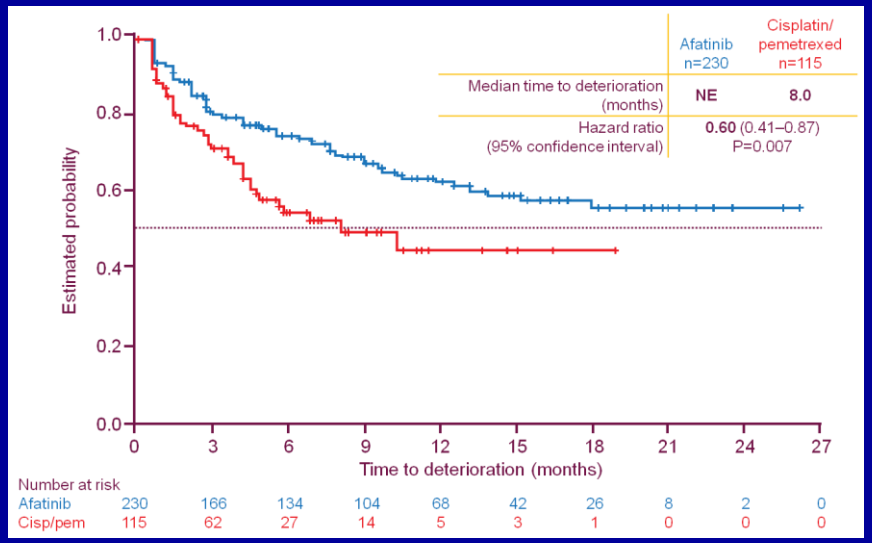
Miss Lee will feel a lot better

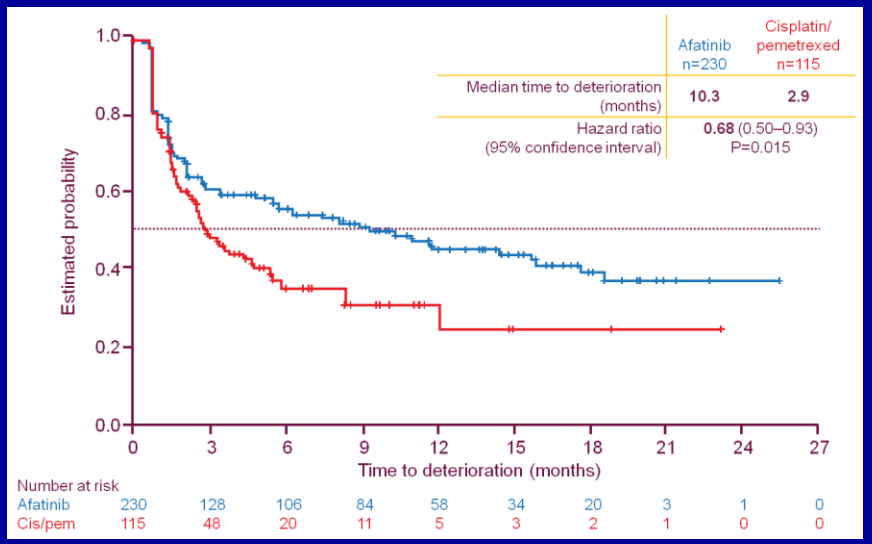
IPASS: First line Gefitinib improves QOL

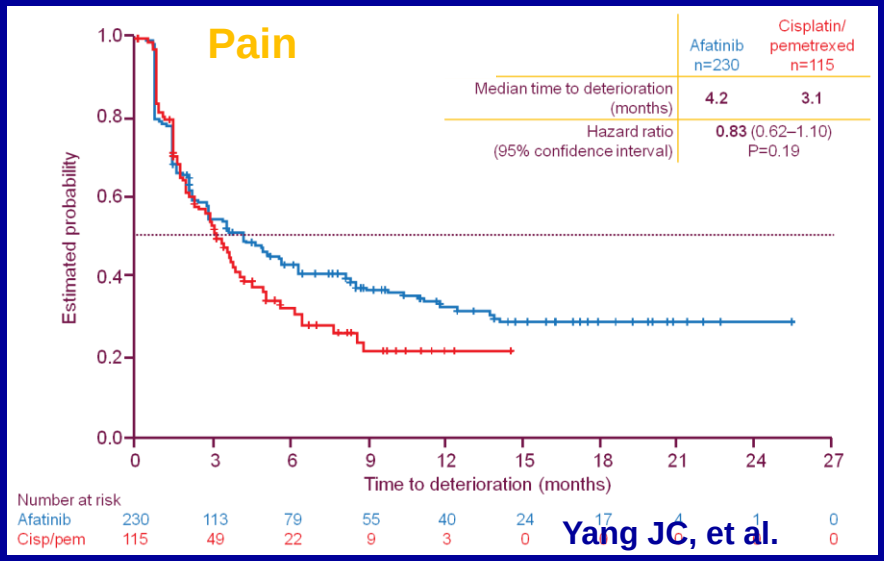


Post hoc analyses
p-values are derived from logistic regression analysis with covariates WHO PS, smoking history and gender

LUX Lung 3: Time to deterioration in lung cancer-related symptoms



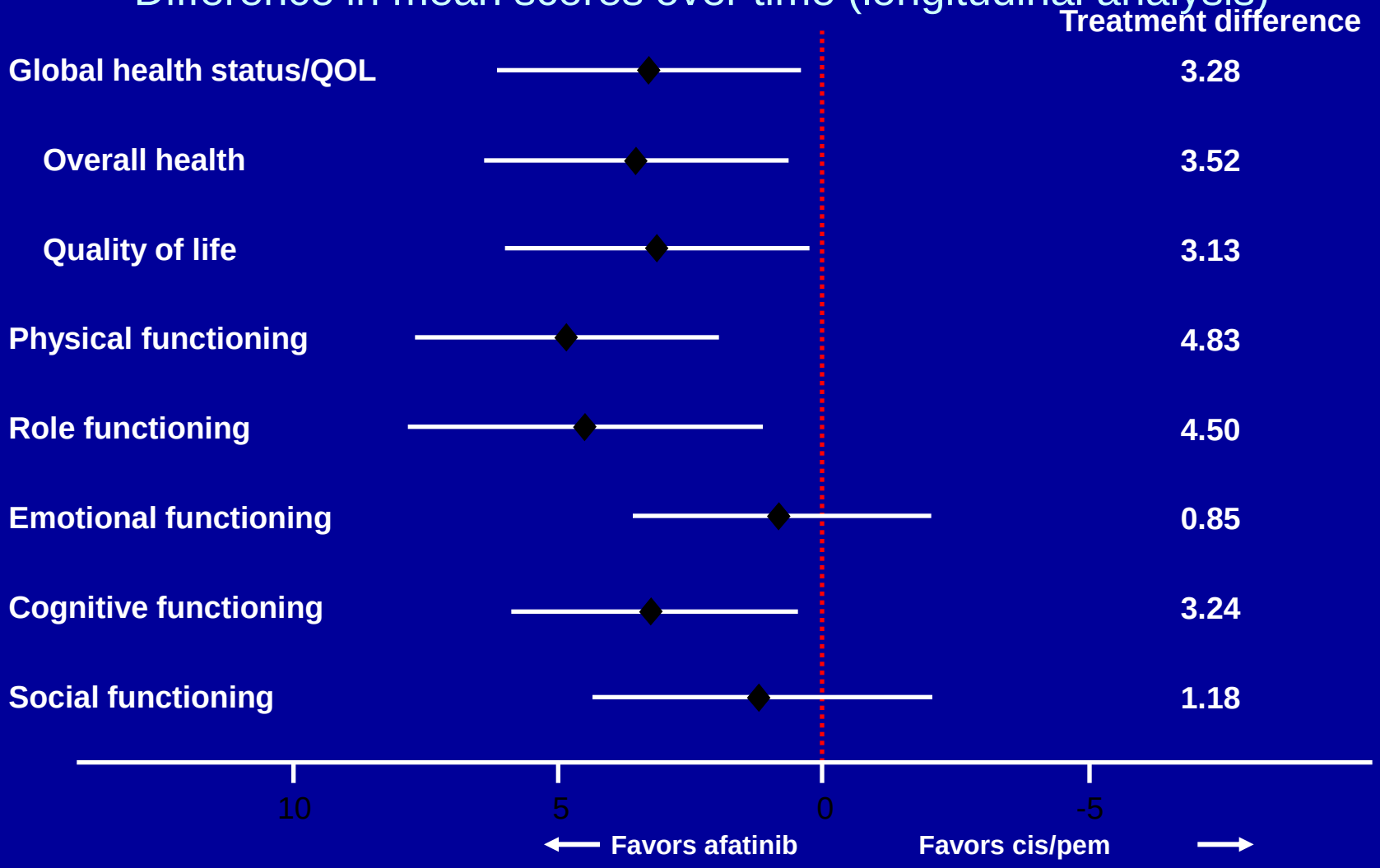




Yang JC, et al.

LUX Lung 3: First line Afatinib improves QOL (EORTC QoL C-30)

Difference in mean scores over time (longitudinal analysis)



Miss Lee will get better and feel better with EGFR TKI, but doctor may still use first line chemotherapy?

EGFR TKI for patients with EGFR mutations

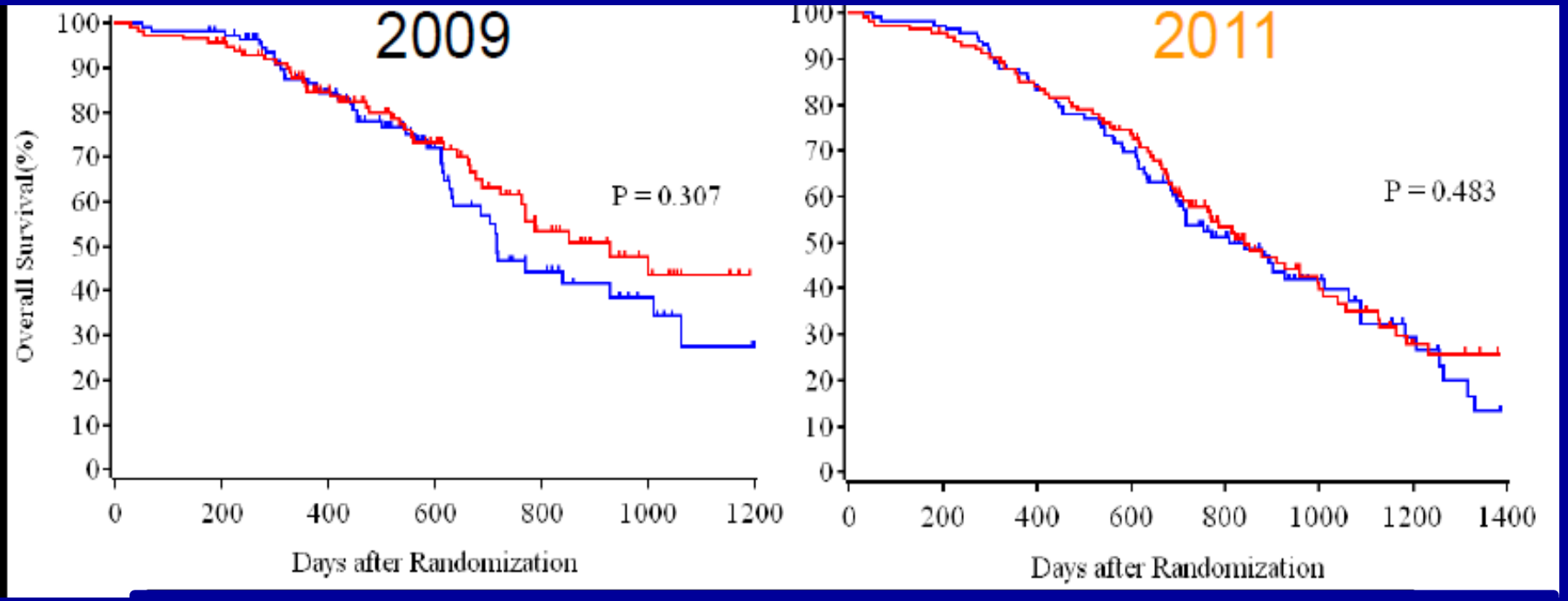
Study	Patient group	N	PFS(months) TKI	PFS(months) Chemotx	OS(months) G	OS(months) Chemotx
IPASS	Asian, light-non-smoker, adenocarcinoma	261	G	6.3	21.6	21.9
First SIGNAL	Kor					26·5
NEJ002					27.7	23·6 ↓ 26.6
WJTOG3405	Japanese,	17	↓ **9.6**	6·3 ↓ **6.6**	30.9 ↓ 35.5	N/A ↓ 38.8
OPTIMAL	Chinese	154	E 13.1	4.6	22.7	28.8
EURTAC	Caucasian EGFR mutation	173	E 9.7	5.2	19.3	19/5

No difference in overall survival thus it doesn't matter when to give EGFR TKI

DOES IT??

All patients with EGFR mutated adenocarcinoma should have exposure to both EGFR TKI and chemotherapy

Final OS results of NEJ002

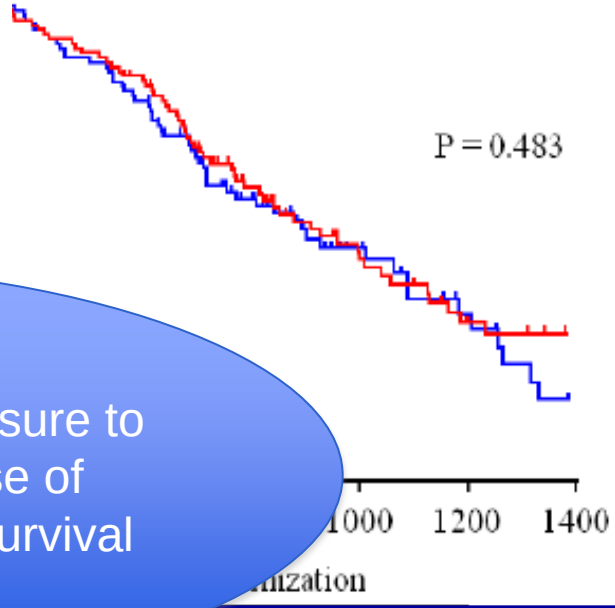


	2009		2011	
	Gefitinib	CBDCA/PTX	Gefitinib	CBDCA/PTX
Median OS (mo)	30.5	23.6	27.7	26.6
Hazard ratio (95%CI)	0.798 (0.517-1.232)		0.887 (0.634-1.241)	
1-year OS rate	84.7%	86.4%	85.0%	86.8%
2-years OS rate	61.4%	46.7%	57.9%	53.7%
Number of Event	39	43	69	69

Final OS results of NEJ002

	Gefitinib	CBDCA/PTX
EGFR-TKI	100%	98.2%
Gefitinib	100%	98.2%
Erlotinib	27.2%	28.9%
BIBW2992	0	1.8%
Chemotherapy	64.[illegible]	
Platinum based		
CBDCA/P[illegible]		
Pemetrexed		
Docetaxel		
Others		

2011



Patients who missed the exposure to chemotherapy during course of treatment may have shorter survival

Days after Randomization

	2009		2011	
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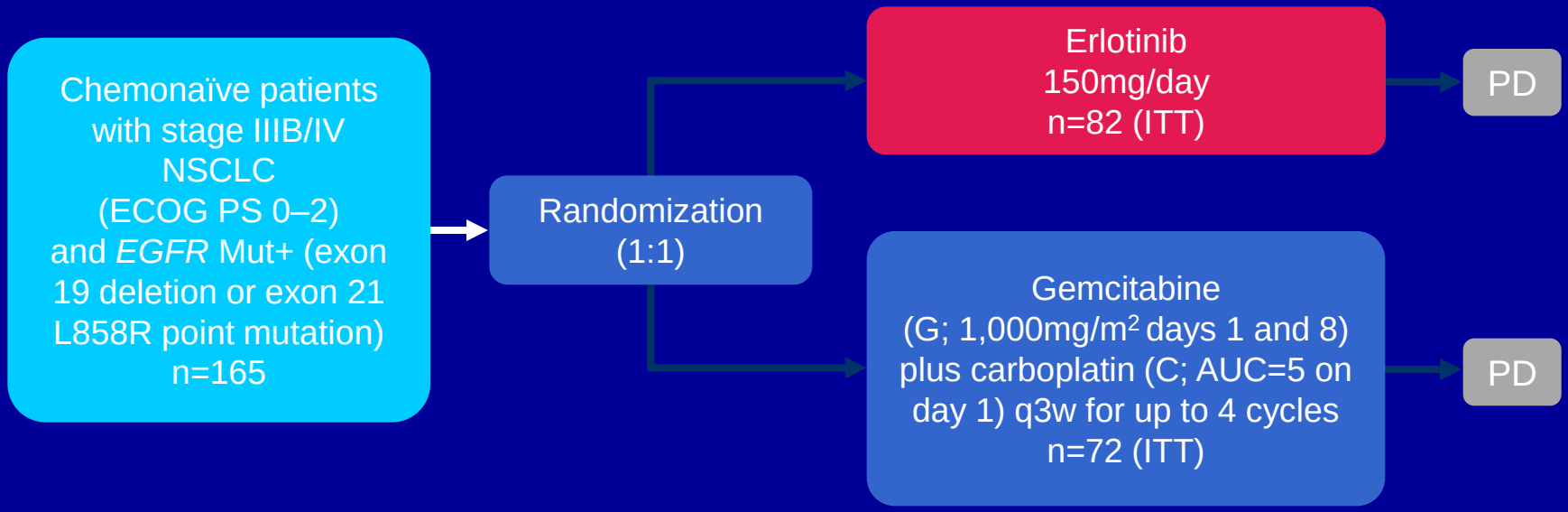
OPTIMAL study design



Stratification factors:

- *EGFR* mutation type (exon 19 mutation vs exon 21 L858R point mutation)
- Histology (adenocarcinoma vs non-adenocarcinoma)
- Smoking status* (current or former smoker vs non- smoker)

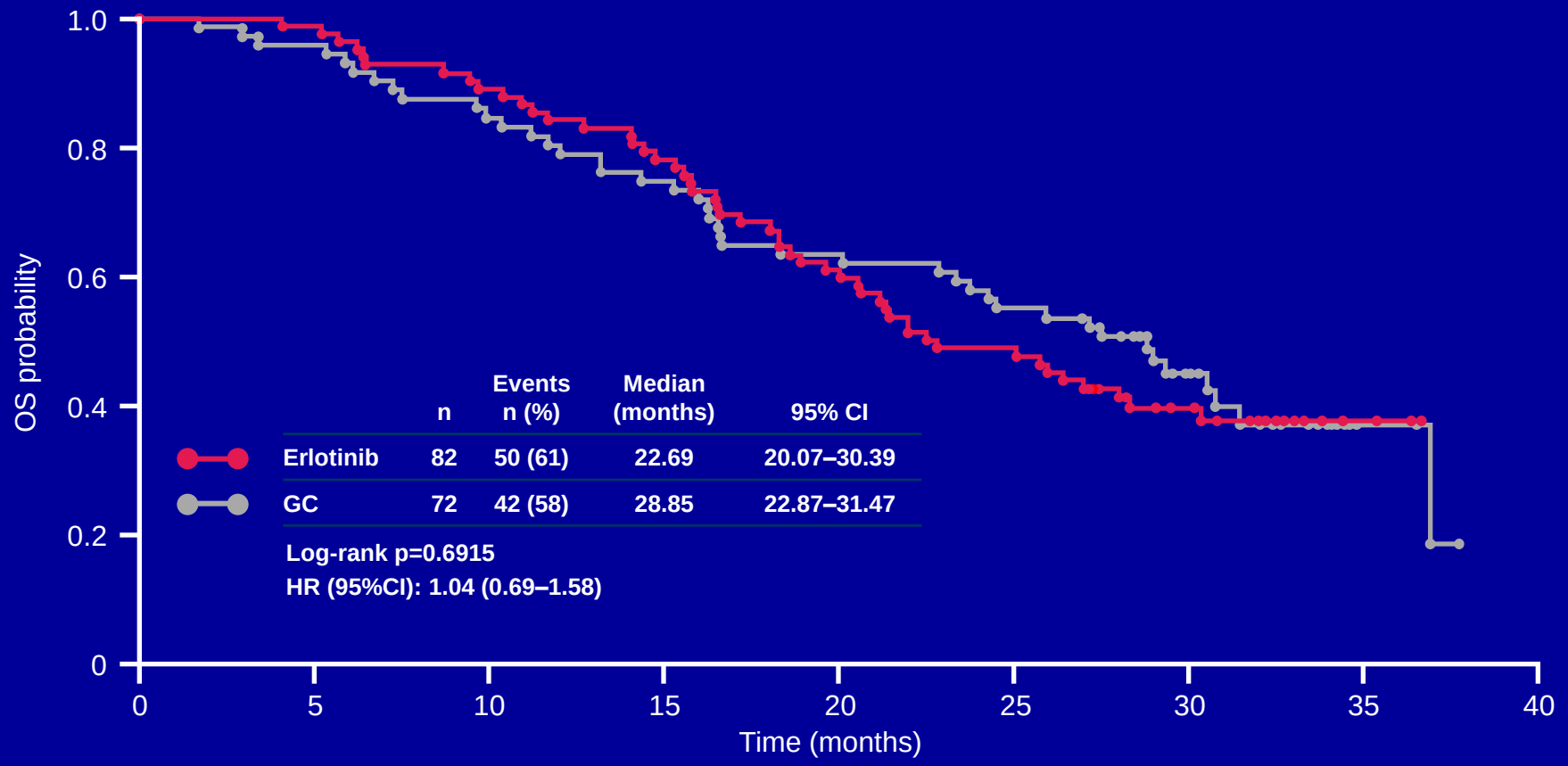
Endpoints:

- PFS (primary endpoint)
- OS, ORR, TTP, biomarker analyses; safety; QoL (secondary endpoints)

*Current smoker: >100 cigarettes in their lifetime and either currently smoking or had stopped smoking <1 year ago; former smoker: >100 cigarettes in their lifetime and stopped ≥1 year ago; non-smoker: ≤100 cigarettes in their lifetime or never smoked. ECOG PS = Eastern Cooperative Oncology Group performance status; PD = progressive disease; q3w = every 3 weeks; ORR = overall response rate; TTP = time to progression, ITT = Intent to treat population

Zhou et al Lancet Oncology 2011

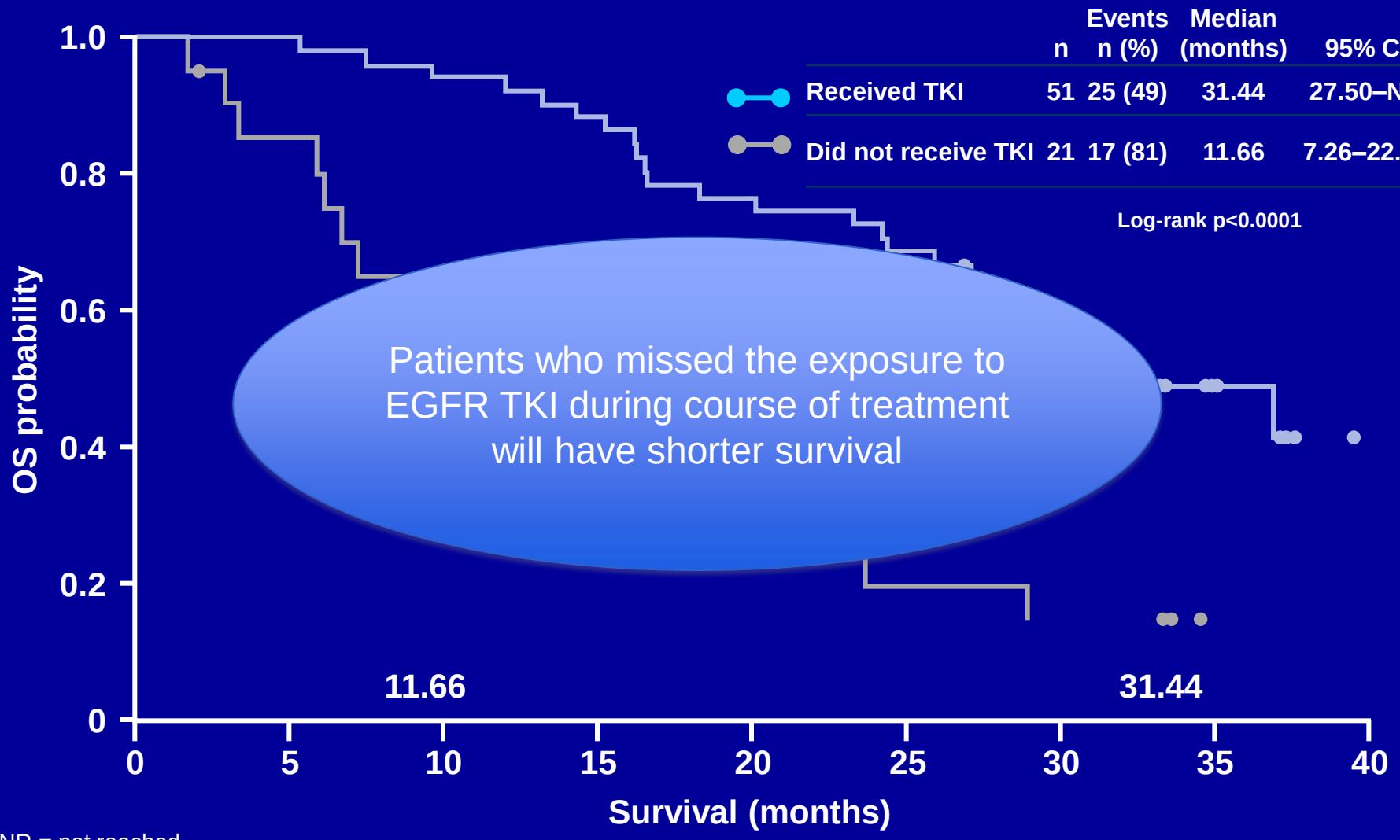
Overall survival (ITT)



Patients at risk

Erlotinib	82	81	73	64	50	40	20	3	0
GC	72	68	60	53	45	39	19	3	0

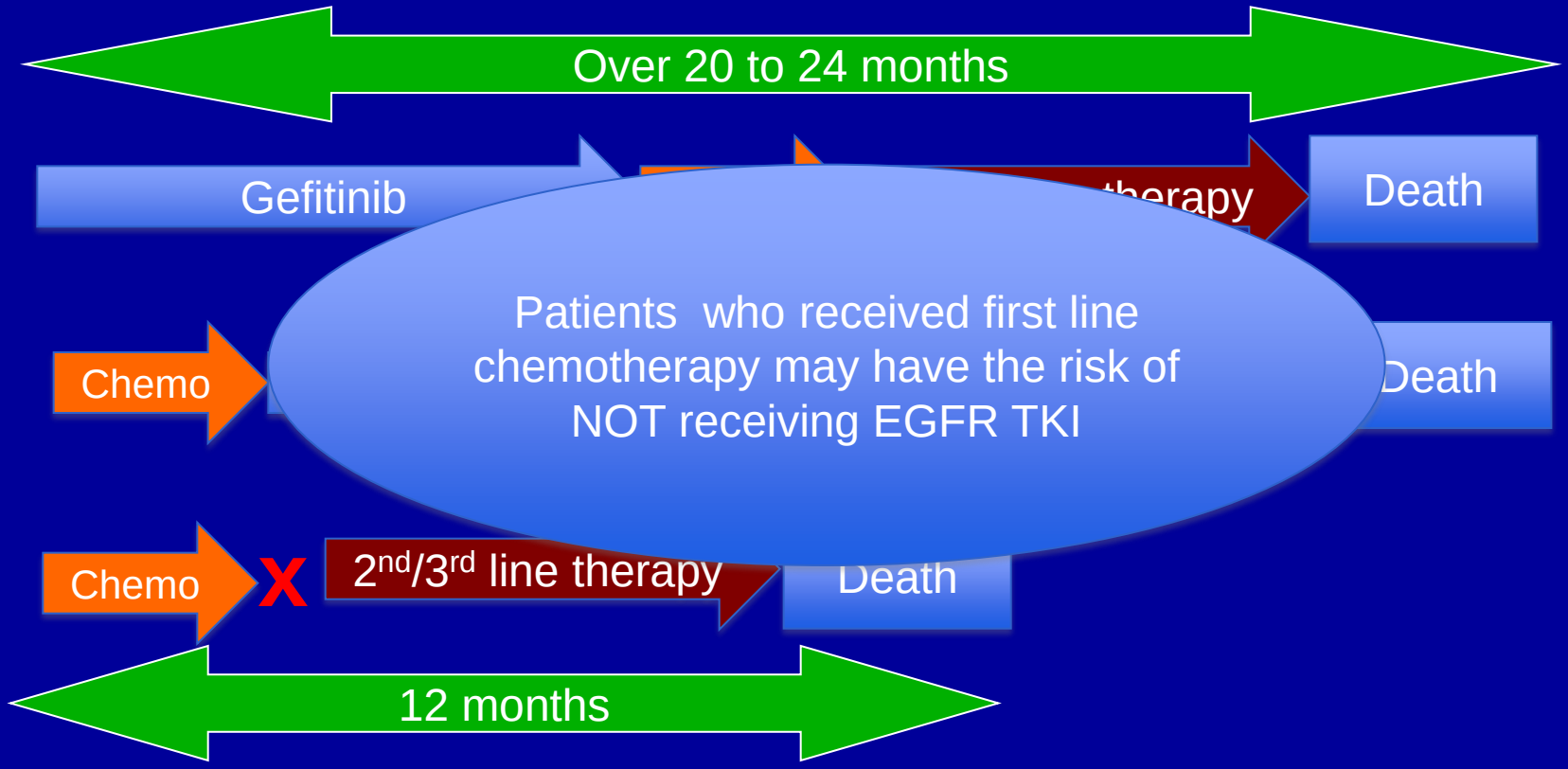
OS (GC arm) stratified by post-study EGFR TKI therapy



NR = not reached

Zhou et al ASCO 2012

Which one will you rather miss?



SUMMARY

- EGFR mutation is the major oncogenic driver in this type of adenocarcinoma
- 7 randomized studies confirmed higher response rate and long PFS
- Quick tumor response and better QOL
- Patients who missed the exposure to EGFR TKI will have shorter survival

EGFR TKI is the best choice of first line treatment for EGFR mutated adenocarcinoma

IT IS NOT A MATTER OF “MAY”

BUT A MATTER OF “SHOULD”