Case #4—*EGFR*-Mutant Advanced NSCLC: Evaluating Treatment Options

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What would be your treatment approach for this patient with stage IV *EGFR*-mutant adenocarcinoma?

1. First-generation EGFR TKI (eg, erlotinib, gefitinib)
2. Second-generation EGFR TKI (afatinib)
3. Chemotherapy → EGFR TKI maintenance
4. Intercalated combination of chemo and erlotinib
5. Clinical trial of erlotinib + bevacizumab, if available

Metastatic NSCLC: ESMO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-Up

- **First-line treatment with a TKI (erlotinib, gefitinib, or afatinib) is the preferred treatment of patients with tumors bearing an activating (sensitising) *EGFR* mutation [I, A]**

- **Patients with *EGFR* mutation and PS 3-4 may also be offered an EGFR TKI [II, A]**

Reck M, et al. *Ann Oncol.* 2014;25 Suppl 3:iii27-iii39.

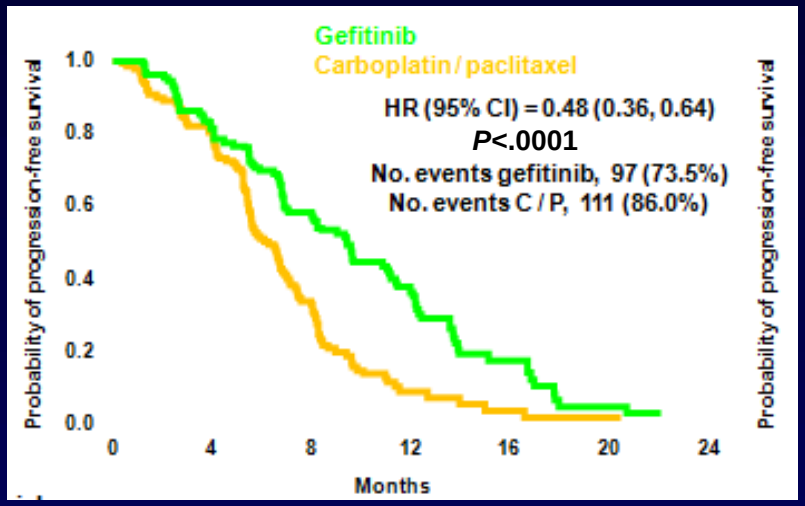
Clinical Efficacy of First Generation EGFR-TKIs vs Chemotherapy as First-Line Therapy

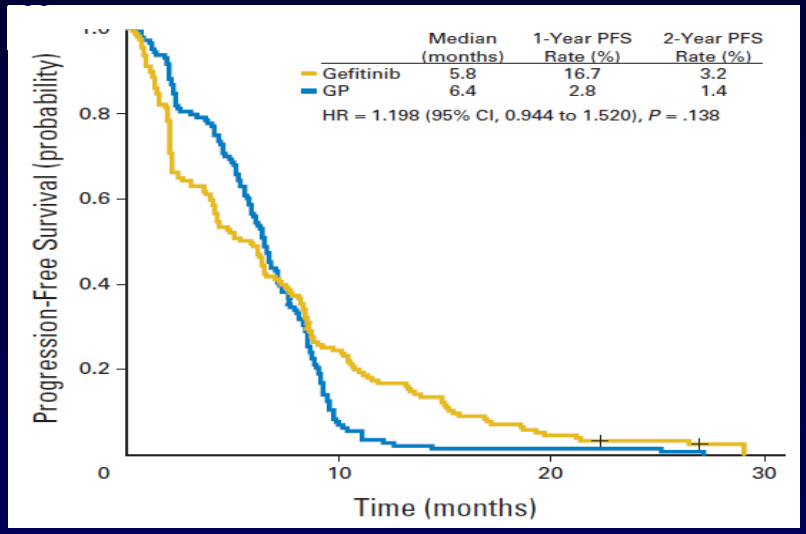
Trial	Pop.	Experimental Drug	*EGFR* Mut +, N	ORR, % TKI vs Chemo	PFS TKI vs Chemo, Months (HR, 95% CI)
IPASS	Asia	Gefitinib	261	71.2 vs 47.3	9.8 vs 6.4 0.48 (0.36, 0.64)
First-SIGNAL	Asia	Gefinitib	42	84.6 vs 37.5	8.4 vs 6.7 0.61 (0,31, 1.22)
WJTOG 3405	Asia	Gefitinib	172	62.1 vs 32.2	9.2 vs 6.3 0.49 (0.34, 0.71)
NEJGSG002	Asia	Gefitinib	224	73.7 vs 30.7	10.8 vs 5.4 0.32 (0.22, 0.41)
OPTIMAL	Asia	Erlotinib	154	83 vs 36	13.7 vs 4.6 0.16 (0.10, 0.26)
EURTAC	Europe	Erlotinib	174	58.1 vs 14.9	9.7 vs 5.2 0.37 (0.25, 0.54)

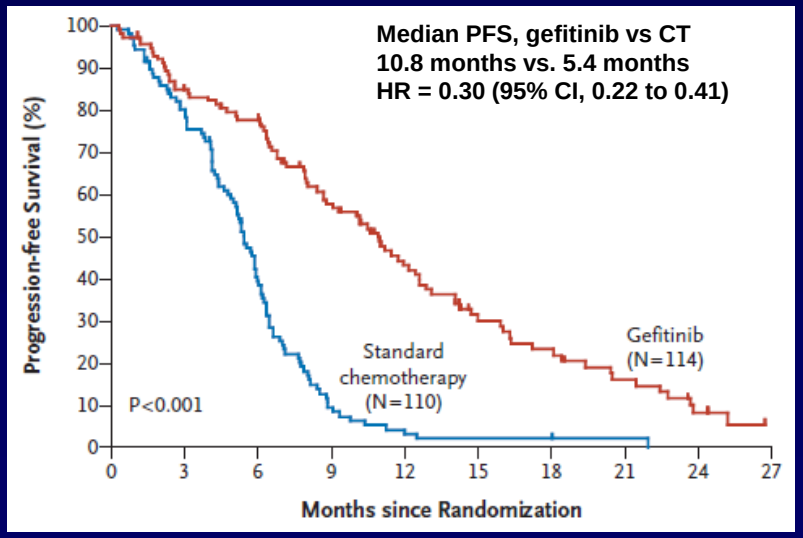
ORR, overall response rate

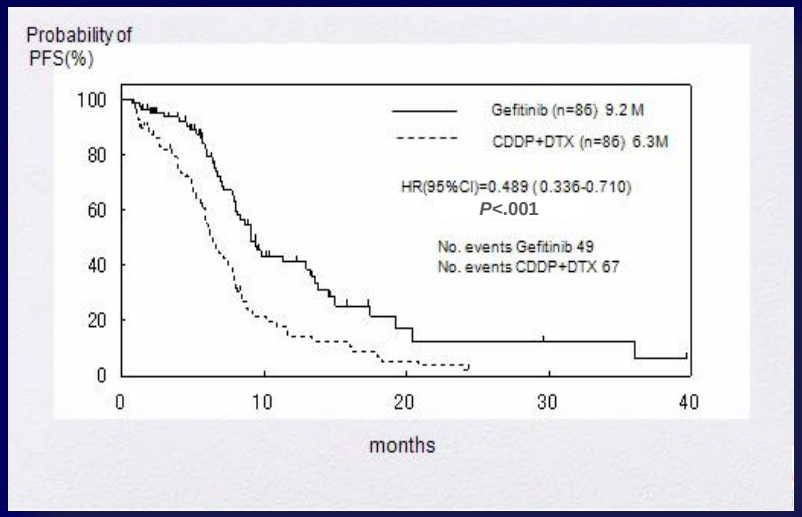
Mok T, et al. *N Engl J Med.* 2009;361(10):947-957. Han JY, et al. *J Clin Oncol.* 2012;30(10):1122-1128. Mitsudomi T, et al. *Lancet Oncol*. 2010;11(2):121-128. Maemondo M, et al. *N Engl J Med.* 2010;362(25):2380-2388. Zhou C, et al. *Lancet Oncol*. 2011;12(8):735-742. Rosell R, et al. *Lancet Oncol.* 2012;13(3): 239-246.

PFS in Phase III Trial With Gefitinib in *EGFR* Mut+ NSCLC





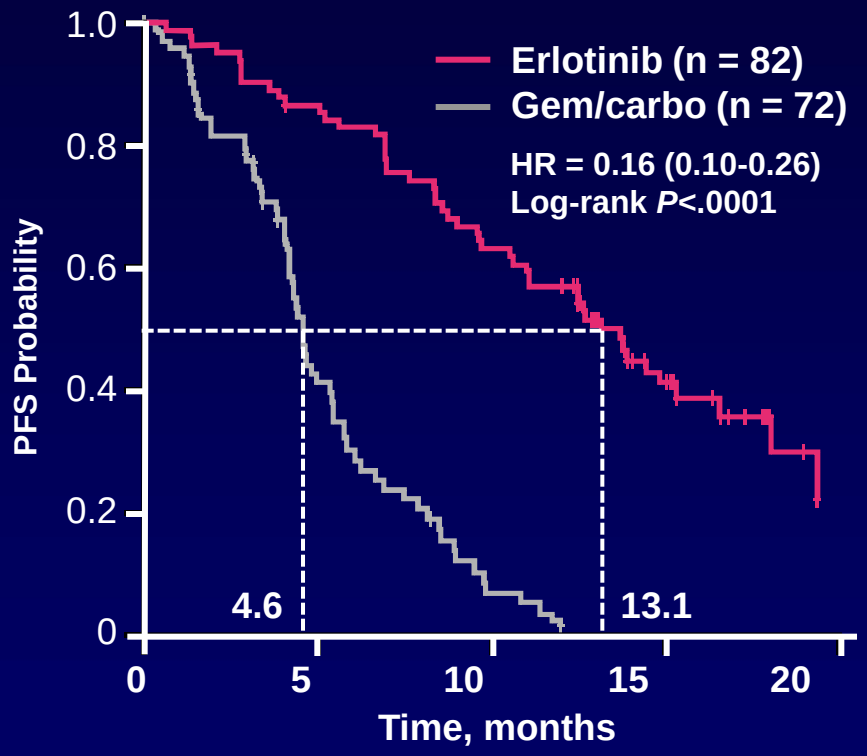




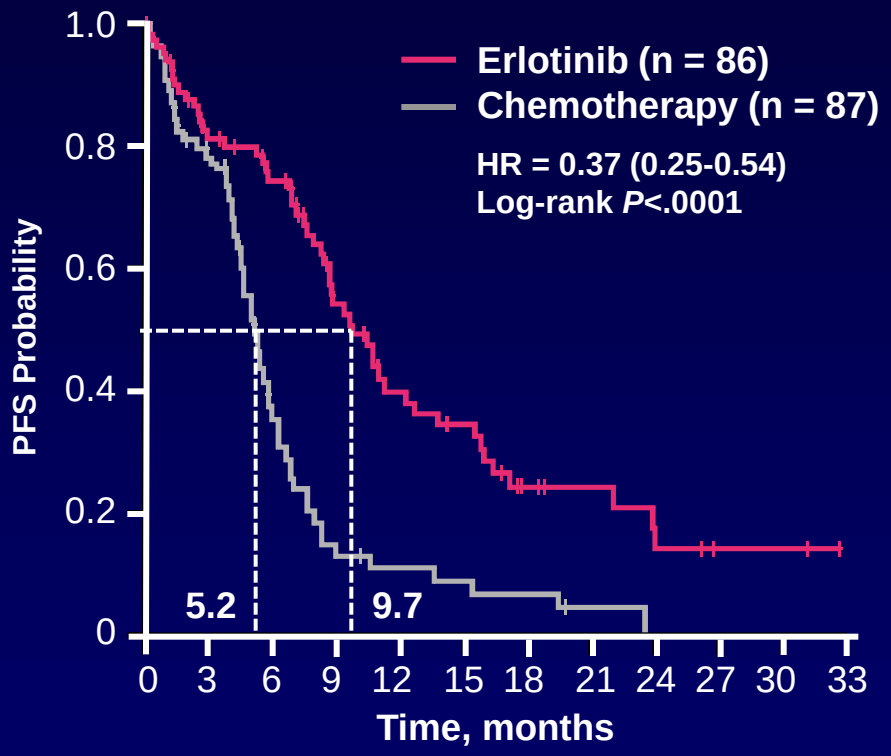
Mok T, et al. *N Engl J Med.* 2009;361(10):947-957. Han JY, et al. *J Clin Oncol.* 2012;30(10):1122-1128. Maemondo M, et al. *N Engl J Med.* 2010;362(25):2380-2388. Mitsudomi T, et al. *Lancet Oncol*. 2010;11(2):121-128.

PFS in Phase III Trial With Erlotinib in *EGFR* Mut+ NSCLC

Asian Patients (OPTIMAL study)[1]



Caucasian Patients (EURTAC study)[2]

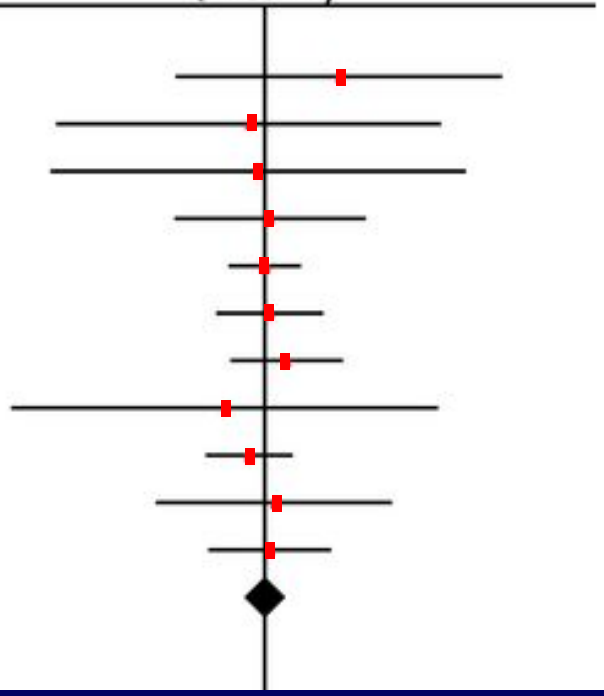


Pivotal phase III EURTAC study resulted in erlotinib first-line *EGFR* Mut+ label (EU)

1. Zhou C, et al. *Lancet Oncol.* 2011;12(8):735-742. 2. Rosell R, et al. *Lancet Oncol.* 2012;13(3):239-246.

First-Line EGFR-TKI Does Not Result in Improved OS

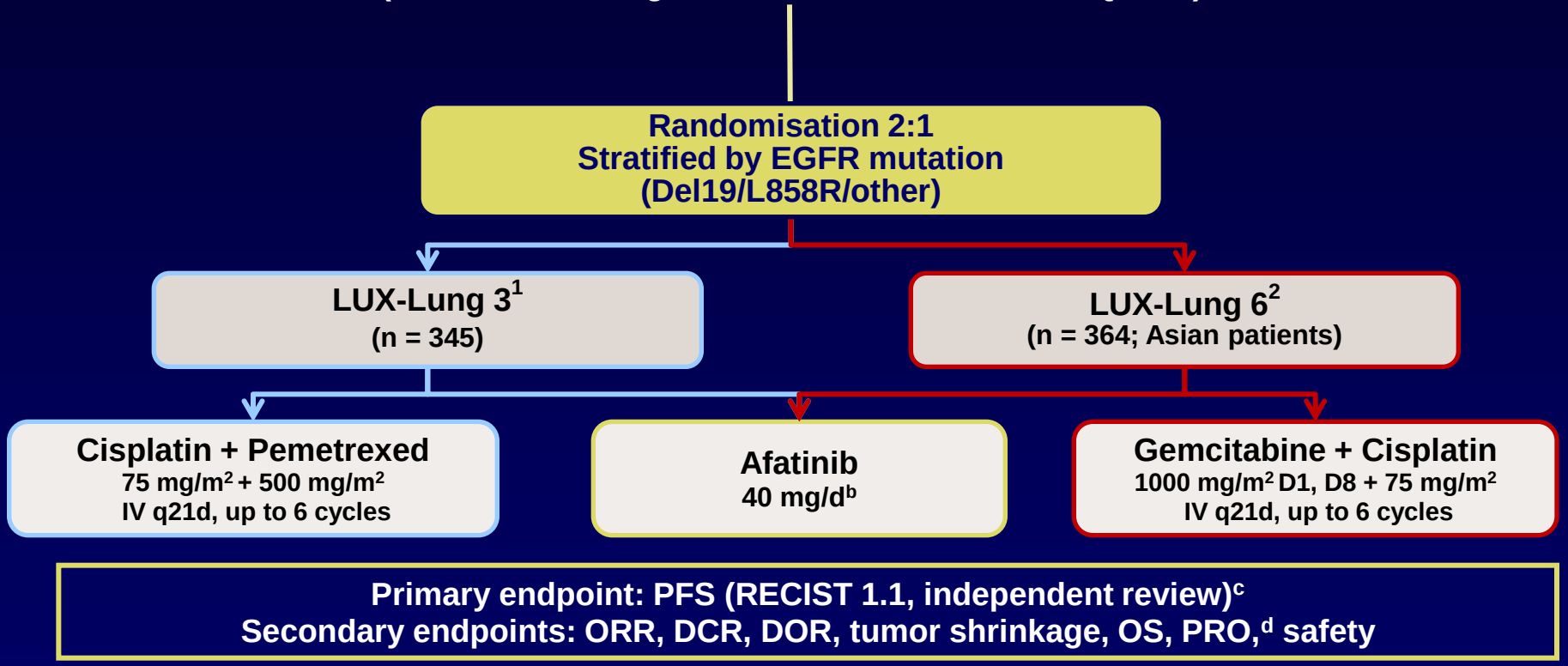
Study	Hazard ratio (95% CI)
EGFRmut+ (front-line therapy)	
INTACT1-2	1.77 (0.50 to 6.25)
TRIBUTE	0.88 (0.20 to 3.90)
TALENT	0.95 (0.19 to 4.72)
First-SIGNAL	1.04 (0.50 to 2.18)
IPASS	1.00 (0.76 to 1.32)
OPTIMAL	1.04 (0.69 to 1.57)
WJTOG3405	1.19 (0.77 to 1.83)
GTOWG	0.73 (0.14 to 3.82)
NEJ002	0.89 (0.63 to 1.24)
TOPICAL	1.07 (0.43 to 2.67)
EURTAC	1.04 (0.65 to 1.67)
Subtotal (95% CI)	**1.01 (0.87 to 1.18)**



Lee CK, et al. *J Natl Cancer Inst.* 2013;105(9):595-605.

LUX-Lung 3 and 6 Phase III Trials

Stage IIIB (wet)/IV lung adenocarcinoma, with *EGFR* mutation in tumor (central lab testing; Therascreen® EGFR29[a] RGQ PCR)

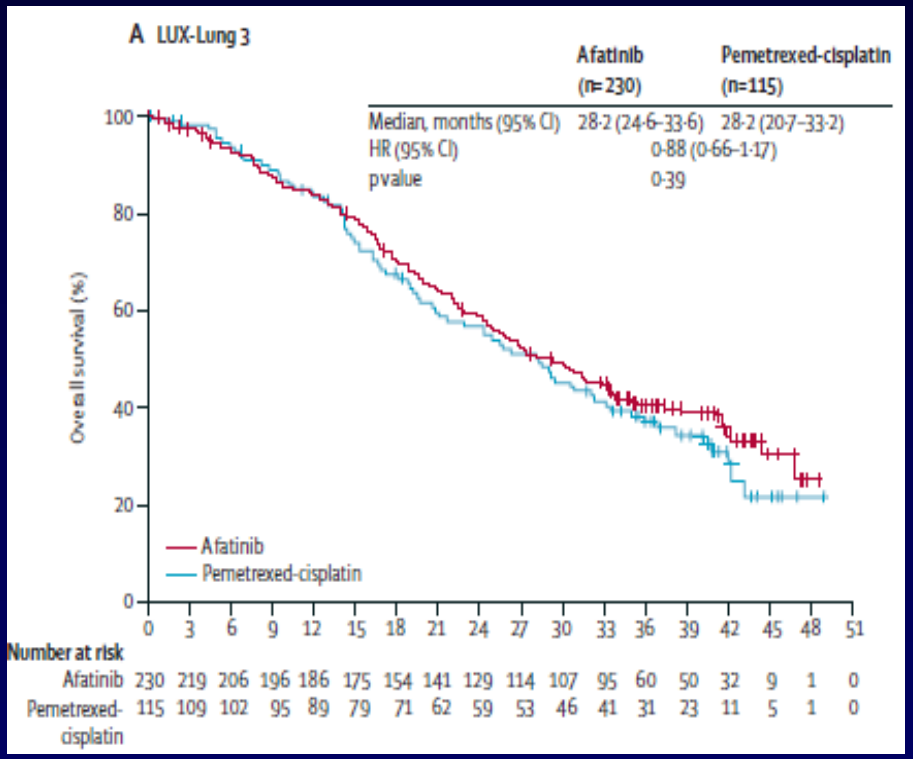


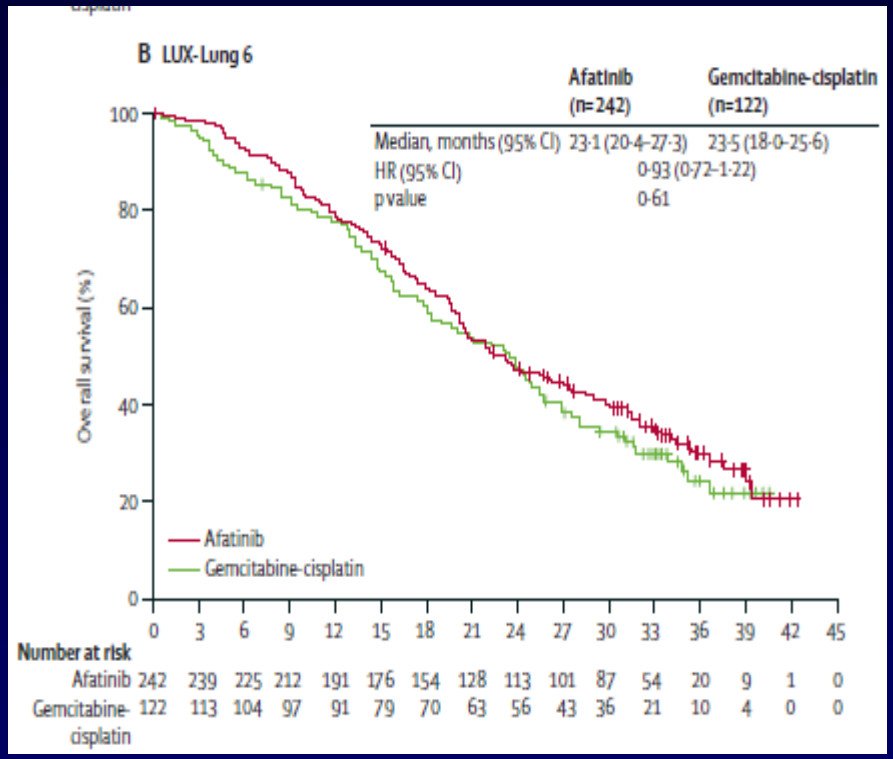
Primary endpoint: PFS (RECIST 1.1, independent review)[c]
Secondary endpoints: ORR, DCR, DOR, tumor shrinkage, OS, PRO,[d] safety

RESIST, Response Evaluation Criteria in Solid Tumours; DOR, duration of response; OS, overall survival; PRO, patient-reported outcomes.
[a]EGFR29:19 deletions in exon 19, 3 insertions in exon 20, L858R, L861Q, T790M, G719S, G719A, and G719C (or G719X), S768I.
[b]Dose escalated to 50 mg if limited AE observed in cycle 1. Dose reduced by 10 mg decrements in case of related G3 or prolonged G2 AE.
[c]Tumour assessments: q6wk until week 48 and q12wk thereafter until progression/start of new therapy.
[d]EQ-5D, EORTC QLQ-C30 and QLQ-LC13 at randomisation and q3wk until progression or new anticancer therapy.

1. Sequist LV, et al. *J Clin Oncol.* 2013;31(27):3327-3334. 2. Wu YL, et al. *Lancet Oncol.* 2014;15(2):213-222.

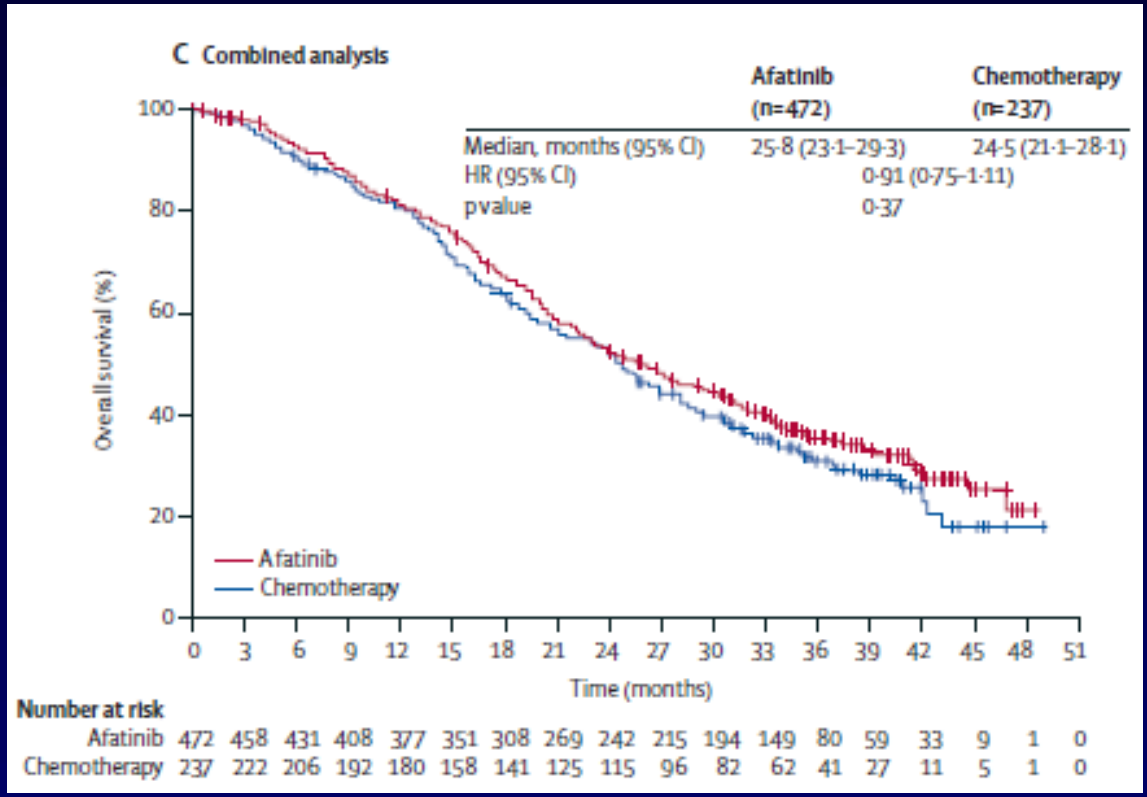
Lux Lung 3 and 6: Overall Survival





Yang JC, et al. *Lancet Oncol*. 2015;16(2):141-151.

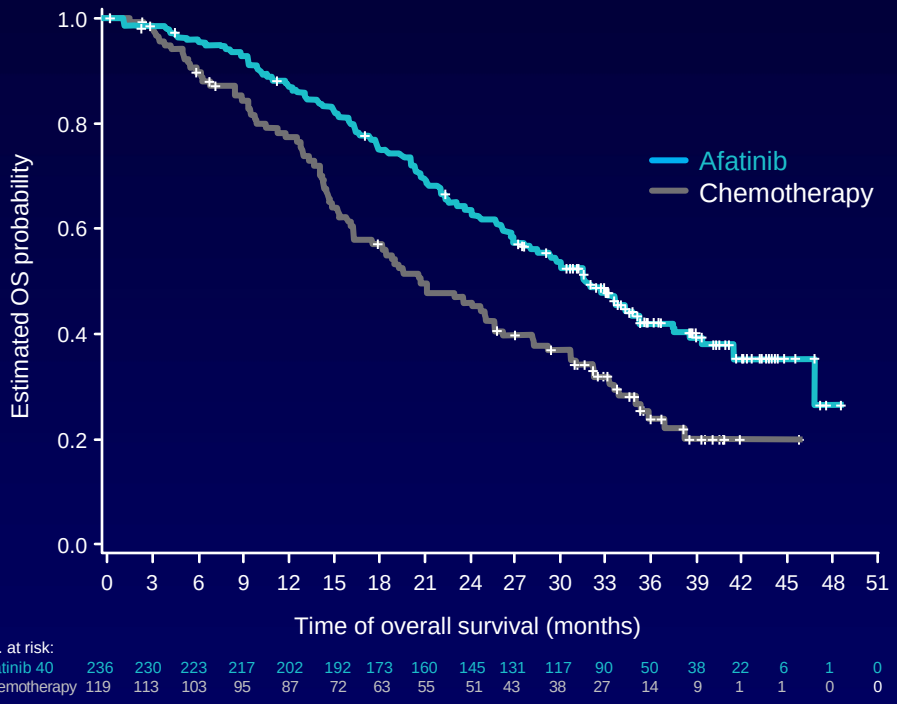
Lux Lung 3 and 6: Overall Survival



Yang JC, et al. *Lancet Oncol*. 2015;16(2):141-151.

LUX-Lung 3 and 6 Exploratory Combined OS Analysis: Del19 and L858R

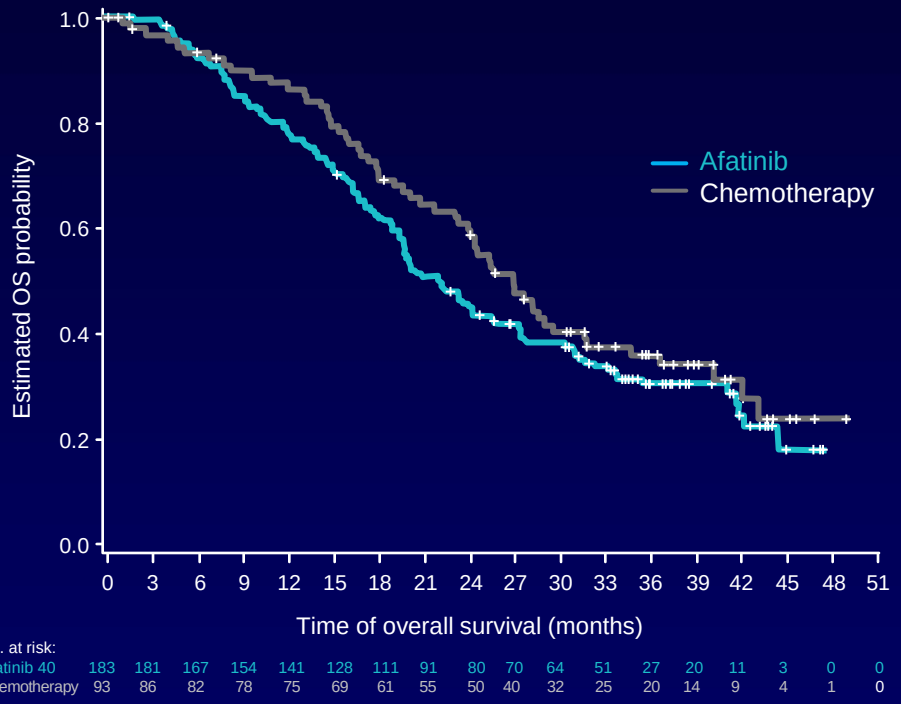
Del19



No. at risk:

Afatinib 40	236	230	223	217	202	192	173	160	145	131	117	90	50	38	22	6	1	0
Chemotherapy	119	113	103	95	87	72	63	55	51	43	38	27	14	9	1	1	0	0

L858R



No. at risk:

Afatinib 40	183	181	167	154	141	128	111	91	80	70	64	51	27	20	11	3	0	0
Chemotherapy	93	86	82	78	75	69	61	55	50	40	32	25	20	14	9	4	1	0

	Del19		L858R	
	Afatinib (n=236)	Chemo (n=119)	Afatinib (n=183)	Chemo (n=93)
Median, months	31.7	20.7	22.1	26.9
HR (95% CI), *P*-value	0.59 (0.45-0.77), *P*=.0001		1.25 (0.92-1.71), *P*=.1600	

Yang JC, et al. *Lancet Oncol*. 2015;16(2):141-151.

LUX-Lung 3, EURTAC, IPASS: Safety

	% of Patients		
	LUX-Lung 3[1] Afatinib (n = 229)	EURTAC[2] Erlotinib (n = 84)	IPASS[3] Gefitinib (n = 607)
Adverse Events	**Grade ≥3**	**Grade ≥3**	**Grade ≥3**
Diarrhea	14.4	5	3.8
Rash/acne[a]	16.2	13	3.1
Stomatitis/mucositis[a]	8.7	NR	0.2
Paronychia	11.4	NR	0.3

[a]Group term in at least 1 of the trials included in the table. NR, not reported

1. Sequist LV, et al. *J Clin Oncol.* 2013;31(27):3327-3334. 2. Rosell R, et al. *Lancet Oncol.* 2012;13(3):239-246. 3. Mok TS, et al. *N Engl J Med.* 2009;361(10):947-957.

LUX-Lung 3, EURTAC, IPASS Safety (Drug Discontinuation)

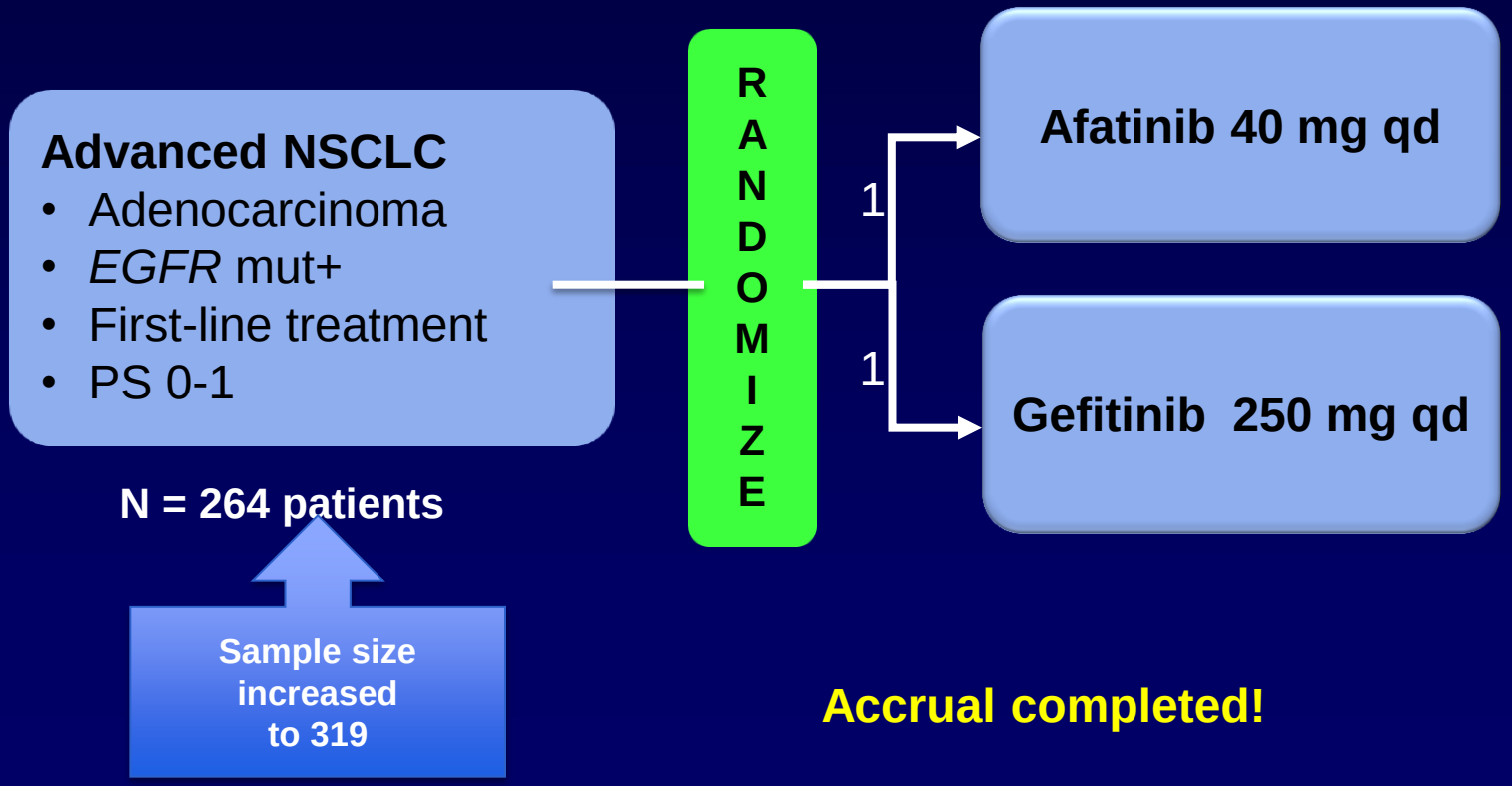
	% of Patients		
	LUX-Lung 3[1] Afatinib (n = 229)	EURTAC[2] Erlotinib (n = 84)	IPASS[3] Gefitinib (n = 607)
Treatment-related AEs	99.6	93	NR
Any grade ≥3	60.7	45	28.7
Dose reduction due to AE	57.2	21	16.1 (modification)
Discontinuation due to AE	7.9 (related)	6 (related)	6.9
Any serious AE	28.8	32	16.3
Fatal serious AE	1.7 (related)	1 (related)	3.8
ILD-like	1.3	1	2.6

ILD, interstitial lung disease

1. Sequist LV, et al. *J Clin Oncol.* 2013;31(27):3327-3334. 2. Rosell R, et al. *Lancet Oncol.* 2012;13(3):239-246. 3. Mok TS, et al. *N Engl J Med.* 2009;361(10):947-957.

Second or First Generation TKI? LUX Lung 7 Randomized Phase IIb Study

- **Is afatinib better than gefitinib in patients with *EGFR* mutation?**

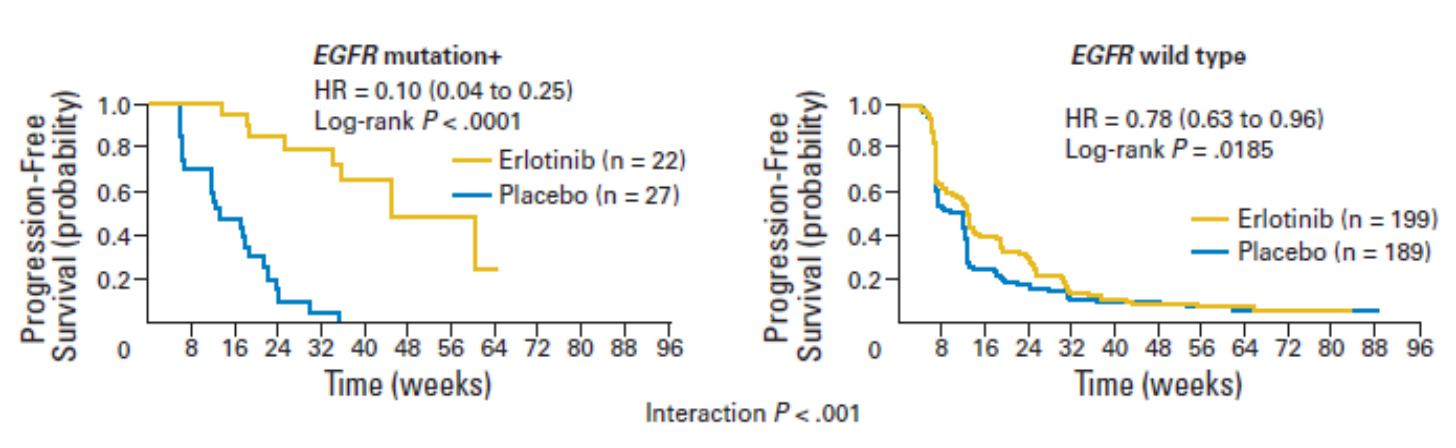


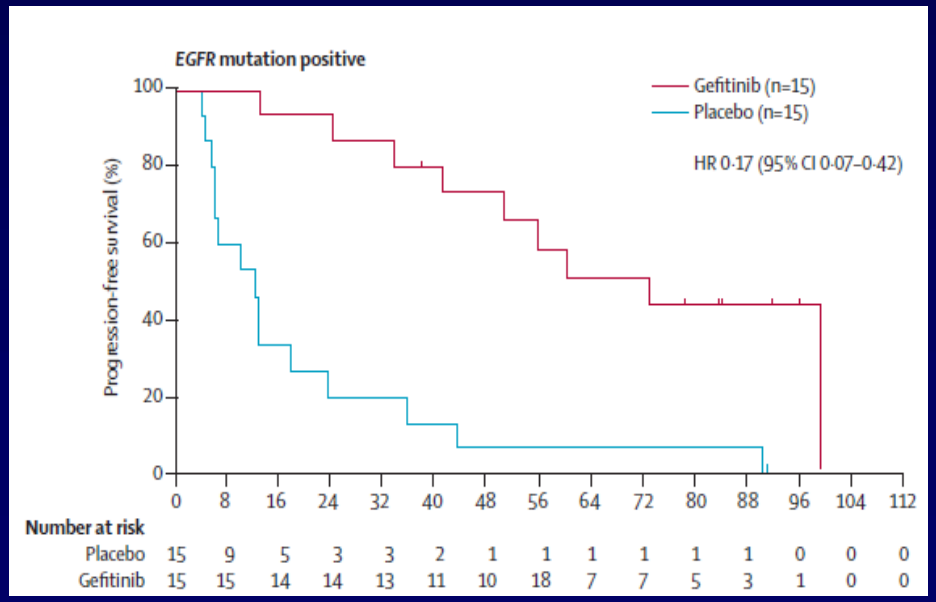
National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT01466660. Accessed 4 March 2015.

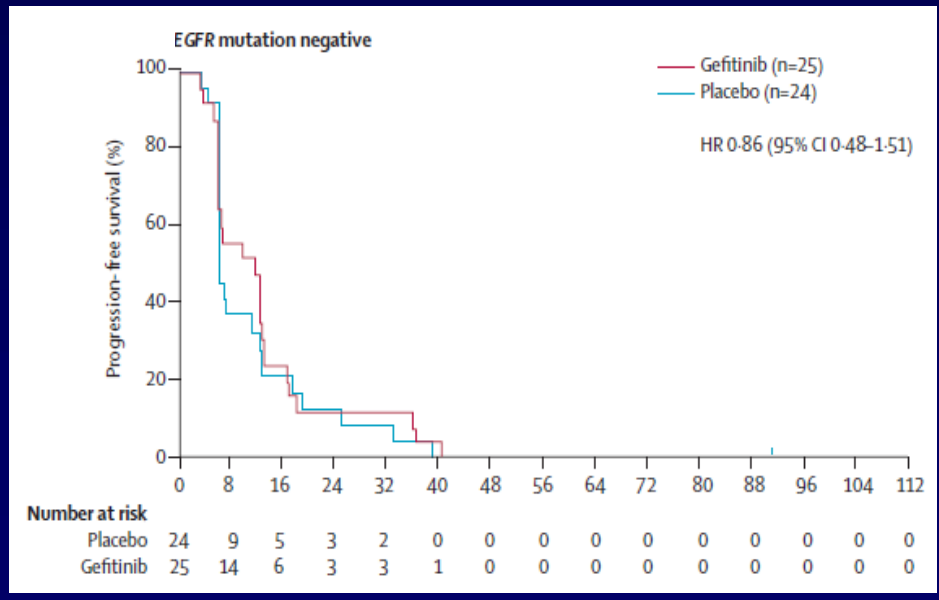
How to Improve Outcome?

- Chemotherapy → EGFR TKI maintenance
- Intercalating: FASTACT 2
- Adding bevacizumab

Switch Maintenance in NSCLC: Bio-SATURN and INFORM

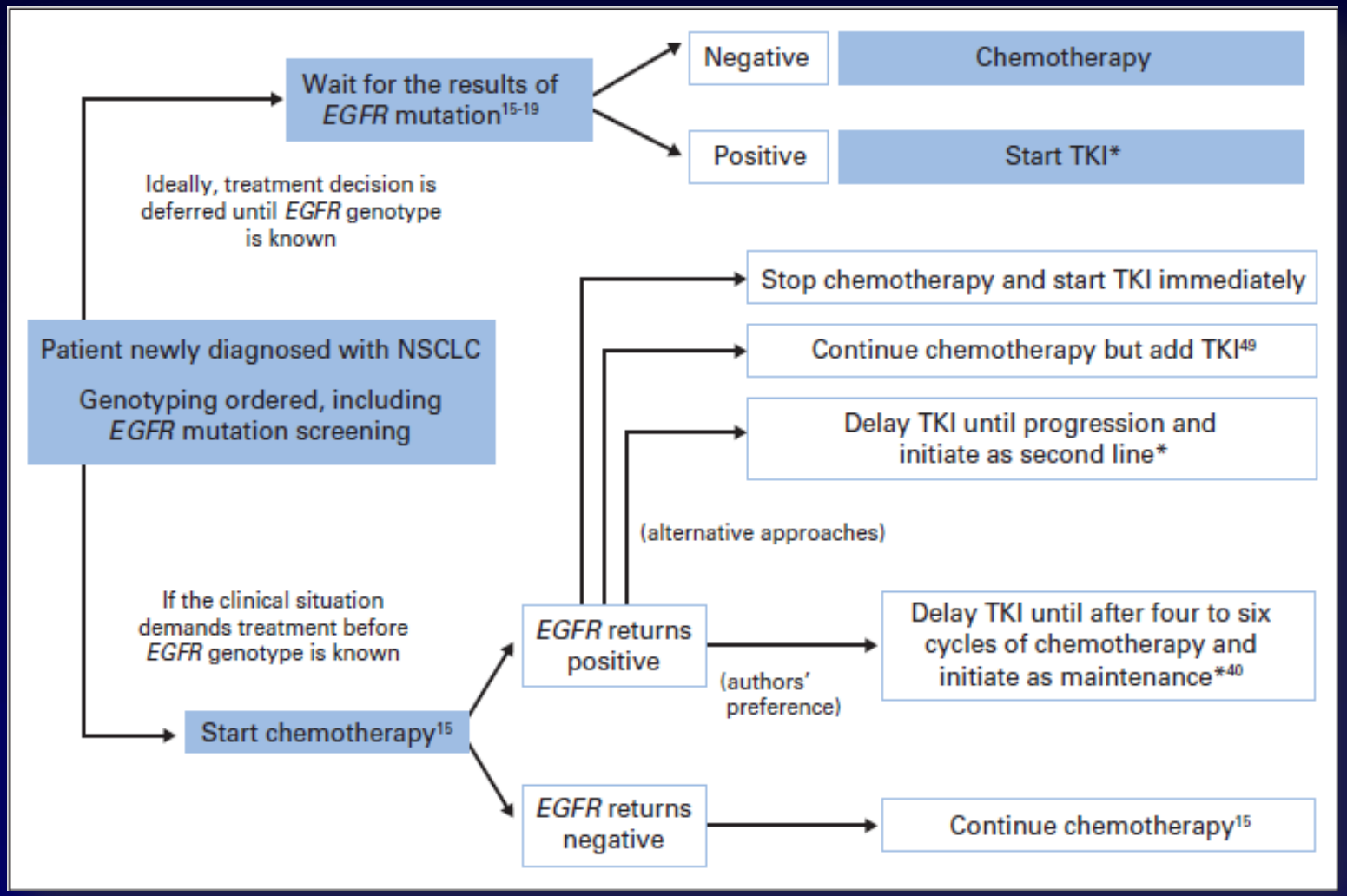






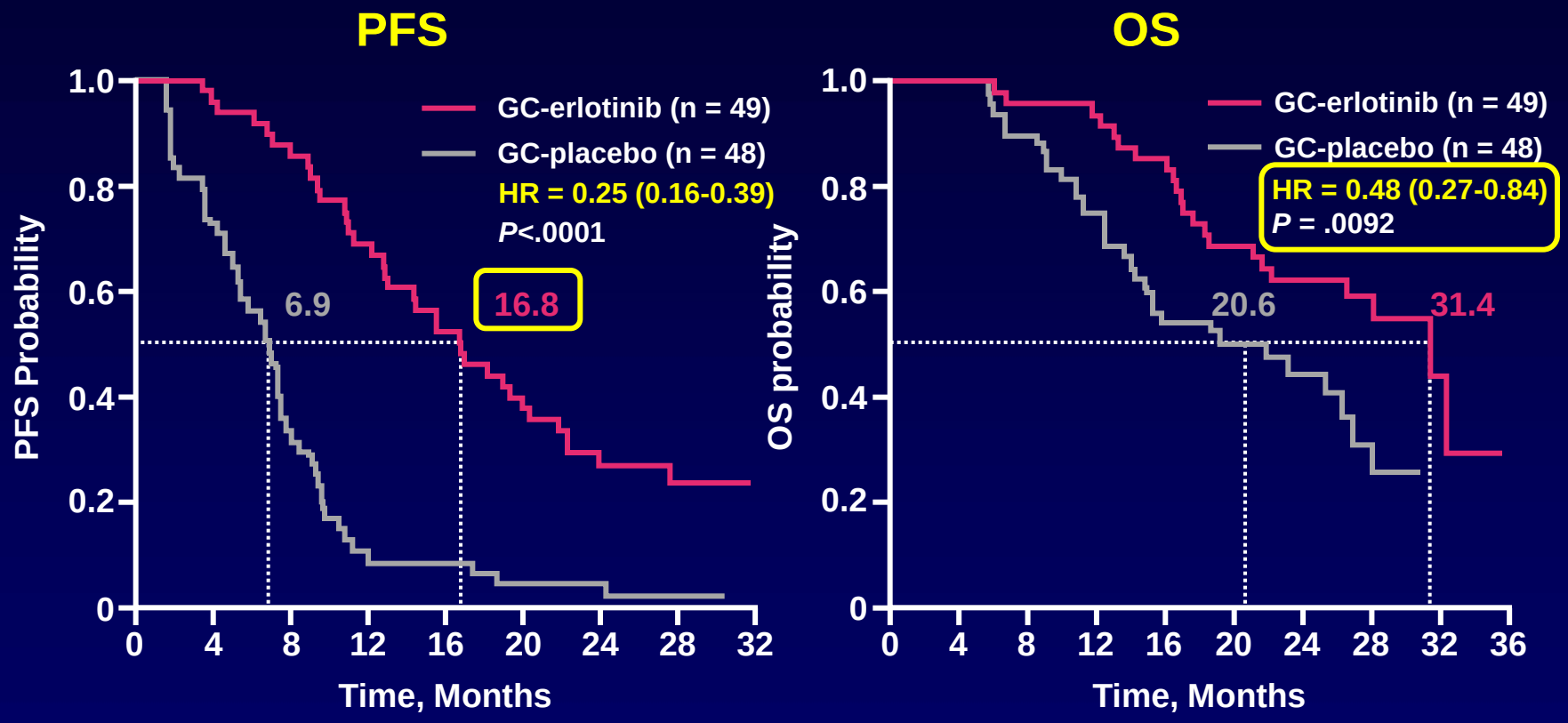
Brugger W, et al. *J Clin Oncol.* 2011;29(31):4113-4120. Zhang L, et al. *Lancet Oncol.* 2012;13(5):466-475.

Timing of EGFR TKI Therapy in Patients With *EGFR* Mutation



Moran T, et al. *J Clin Oncol.* 2012;30(27):3330-3336.

FASTACT-2: PFS and OS Benefit With Intercalated Erlotinib in *EGFR* Mut+ Disease (N = 97)



OS benefit with GC-erlotinib vs GC-placebo despite high rate of crossover (85%) from GC-placebo to second-line EGFR TKI

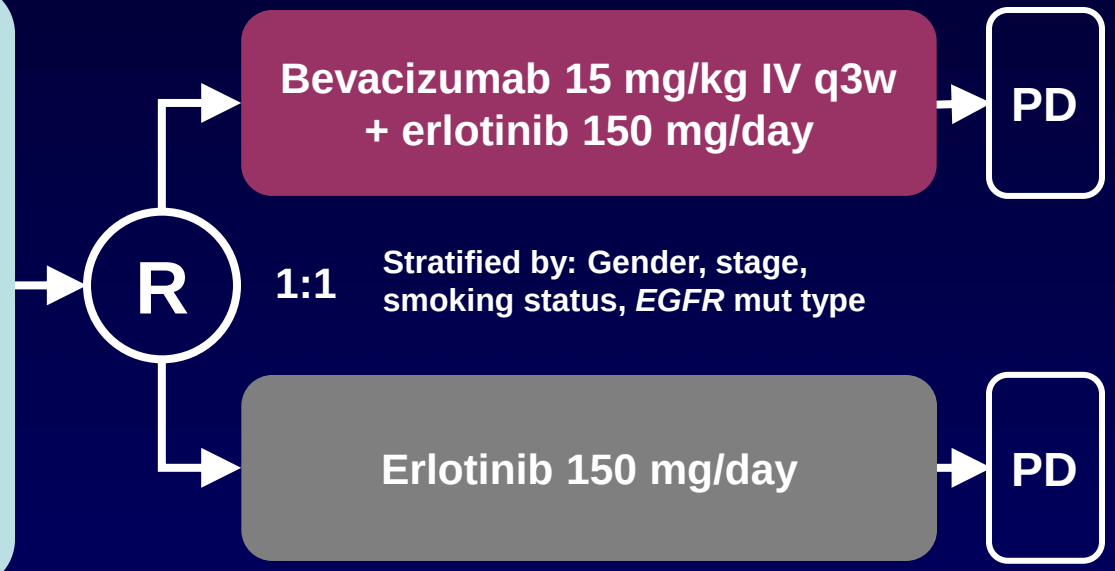
GC, gemcitabine, platinum

Wu YL, et al. *Lancet Oncol.* 2013;14(8):777-786.

Adding Bevacizumab?
JO25567 Trial

- Stage IIIB/IV or recurrent NSCLC
- Nonsquamous histology
- *EGFR* Mut+
  - Exon 19 deletion / L858R*
- No prior treatment
- ECOG PS 0-1

(n = 150)



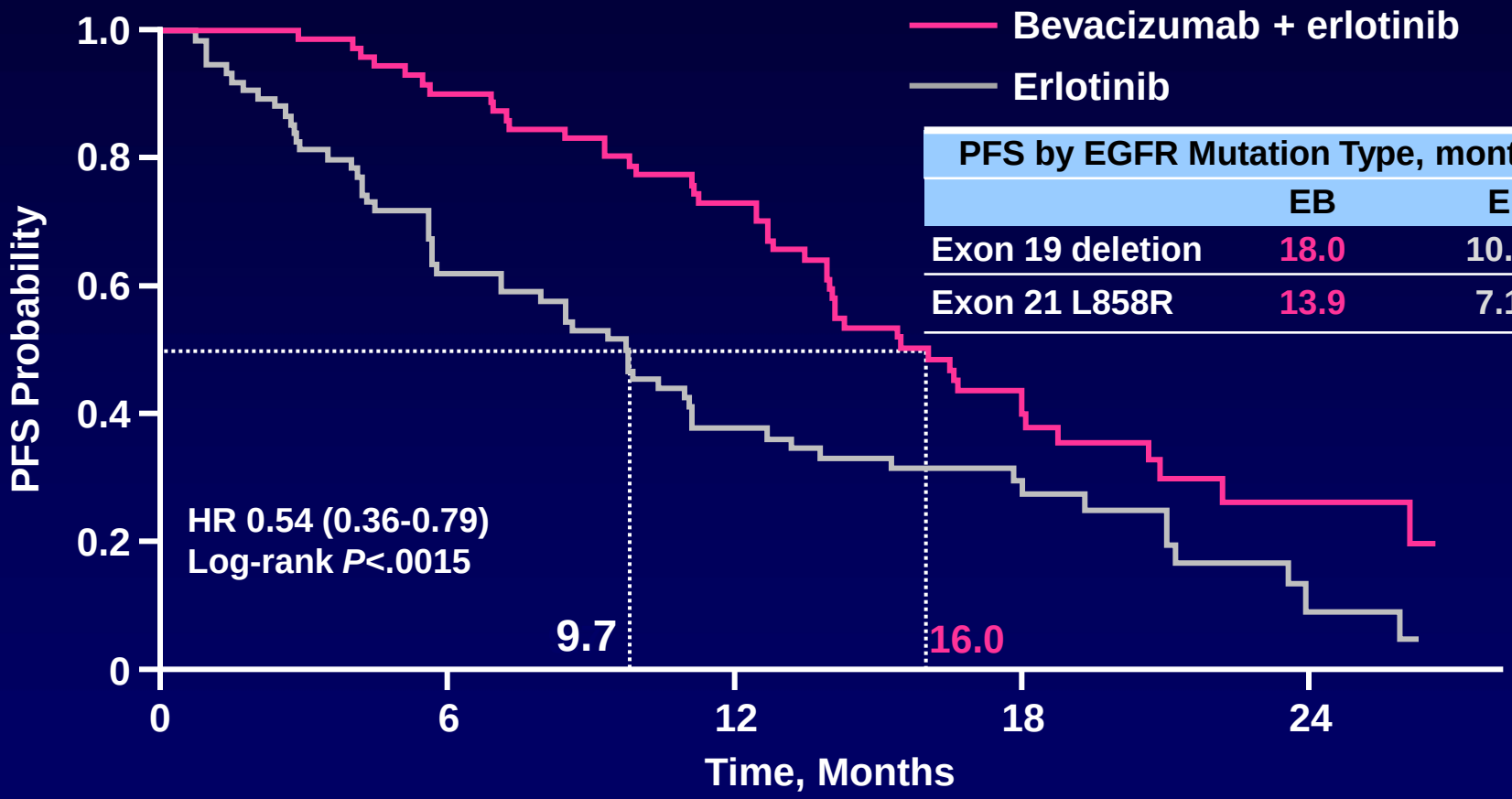
Primary endpoint
- PFS by independent review

Secondary endpoints
- OS
- ORR
- DCR
- Response duration
- QoL
- Safety

Exploratory endpoints
- Biomarkers

Kato T, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8005.

Prolonged PFS When Bevacizumab Is Added to Erlotinib



PFS by EGFR Mutation Type, months		
	EB	E
Exon 19 deletion	18.0	10.3
Exon 21 L858R	13.9	7.1

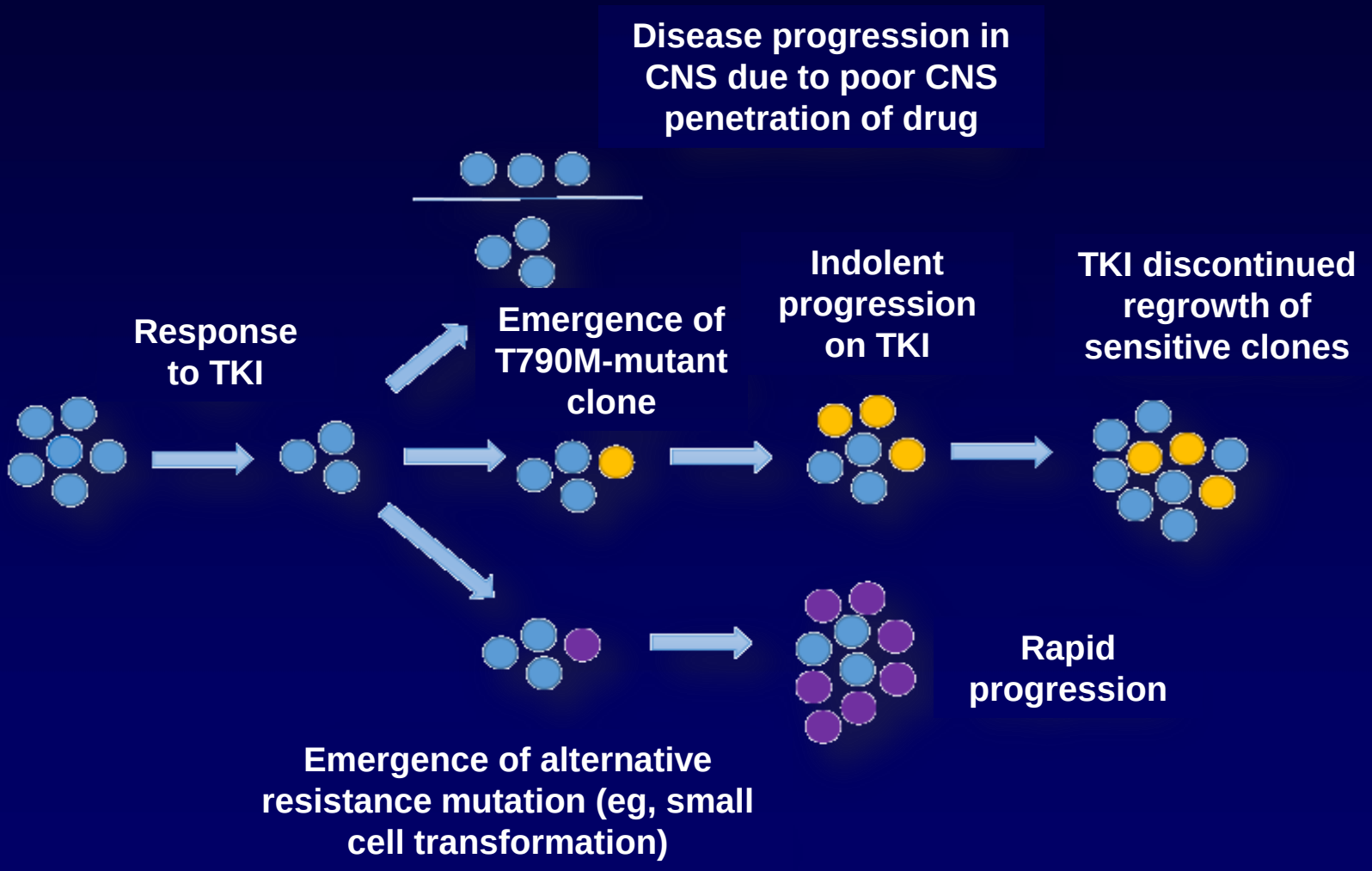
RESULTS of BELIEF Trial AWAITED!

Kato T, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8005.

After 11 Months: Slight progression/asymptomatic
Which of the following would you recommend now?

1. Continue erlotinib and perform close follow-up
2. Local radiotherapy and continue erlotinib
3. Change to second generation TKI
4. Continue erlotinib and add platinum-based chemotherapy
5. Discontinue erlotinib and start platinum-based chemotherapy
6. Clinical trial of afatinib + cetuximab
7. Rebiopsy to determine the type of resistance and include patient in a clinical trial with a third generation TKI

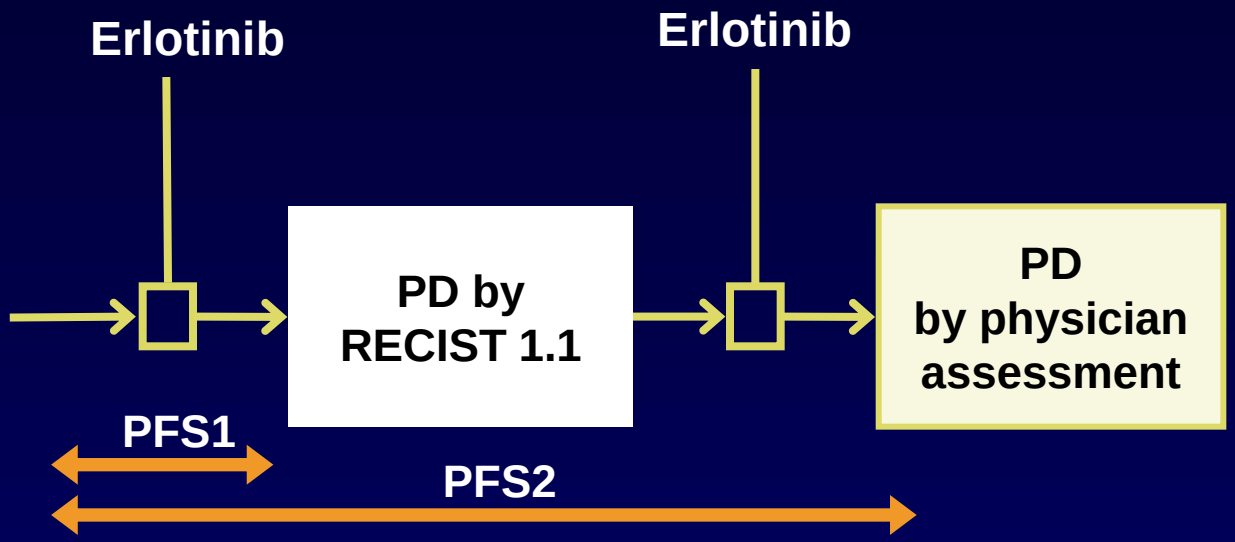
PD After Response to TKI in Patients With *EGFR* Mutations



Sacher AG, et al. *Cancer.* 2014;120(15):2289-2298

ASPIRATION: Study Design

- Stage IV or recurrent NSCLC
- Chemonaïve
- *EGFR* Mut+ NSCLC*
  - exon 18-21
- ECOG PS 0-2 (n = 207)



* Except for T790M

Primary endpoint

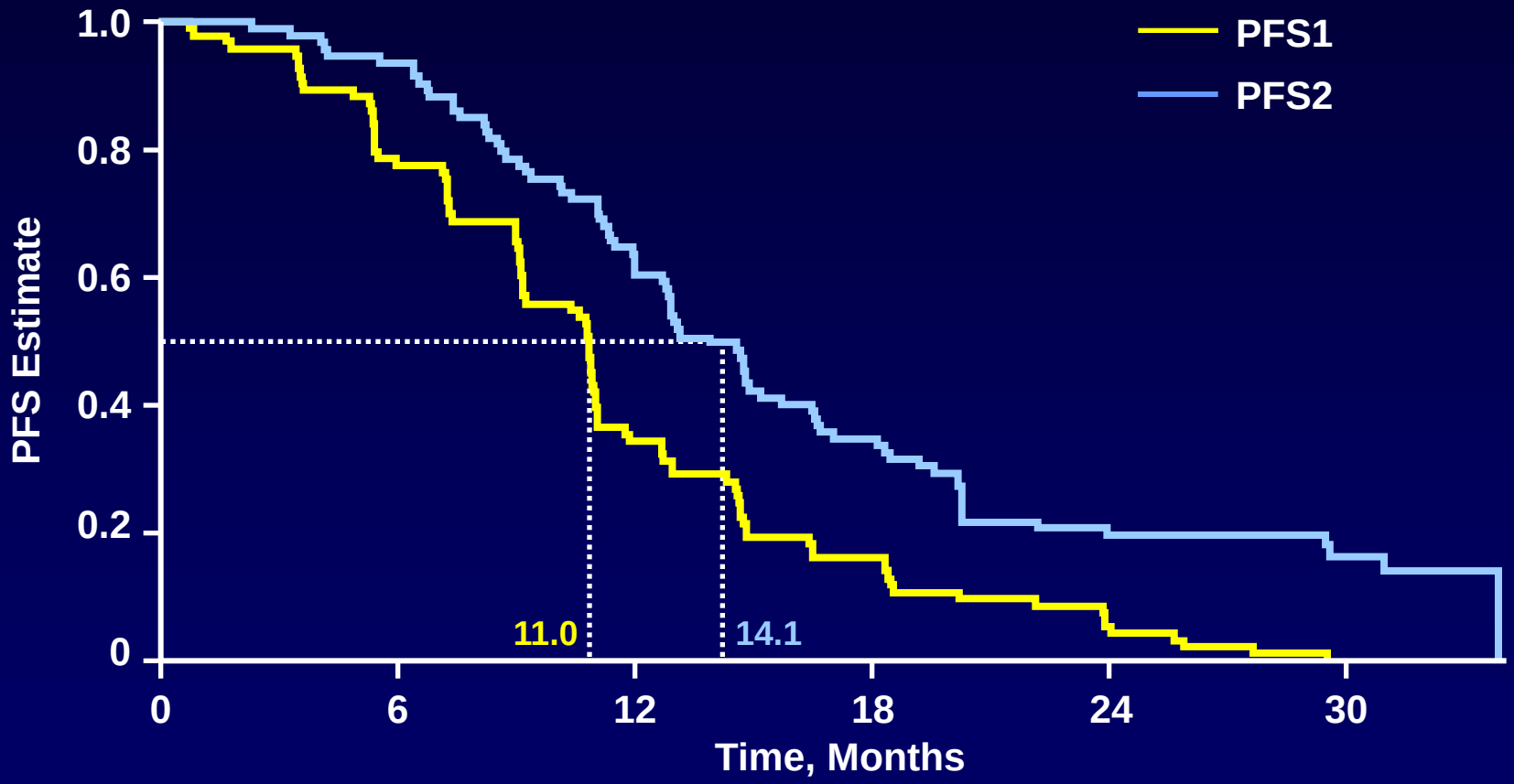
- PFS1 (time to RECIST PD or death)

Secondary endpoints

- PFS2 (time to off-erlotinib PD if erlotinib was extended beyond RECIST PD)
- OS
- ORR/DCR/BOR
- Safety

Park K, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1223O.

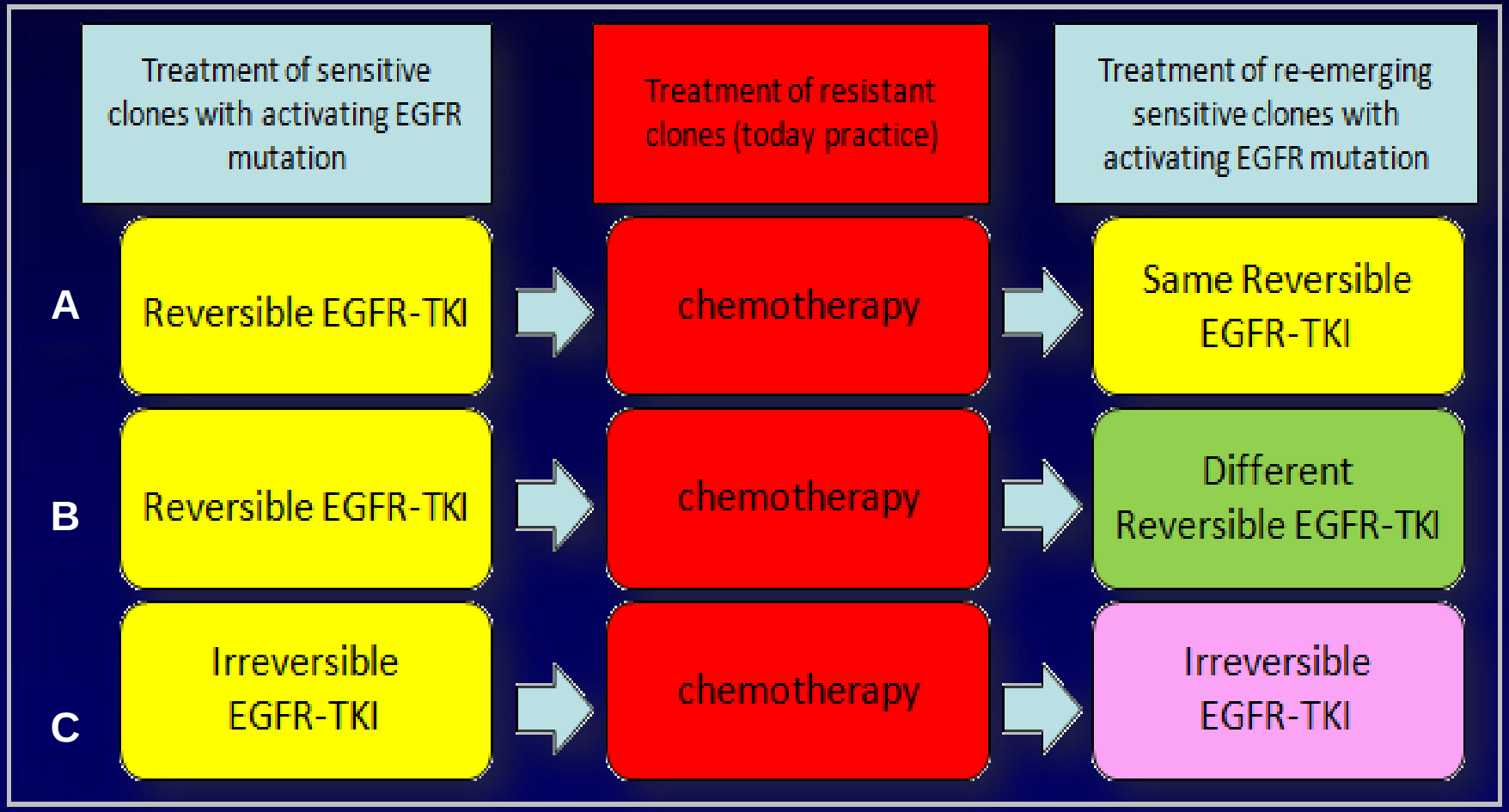
ASPIRATION: PFS in Patients Receiving Erlotinib Post-PD (n = 93/207)



The difference between PFS1 and PFS2 was an additional 3.1 months

Park K, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract 1223O.

Strategies in Patients With EGFR Mutation After First-Line EGFR-TKI



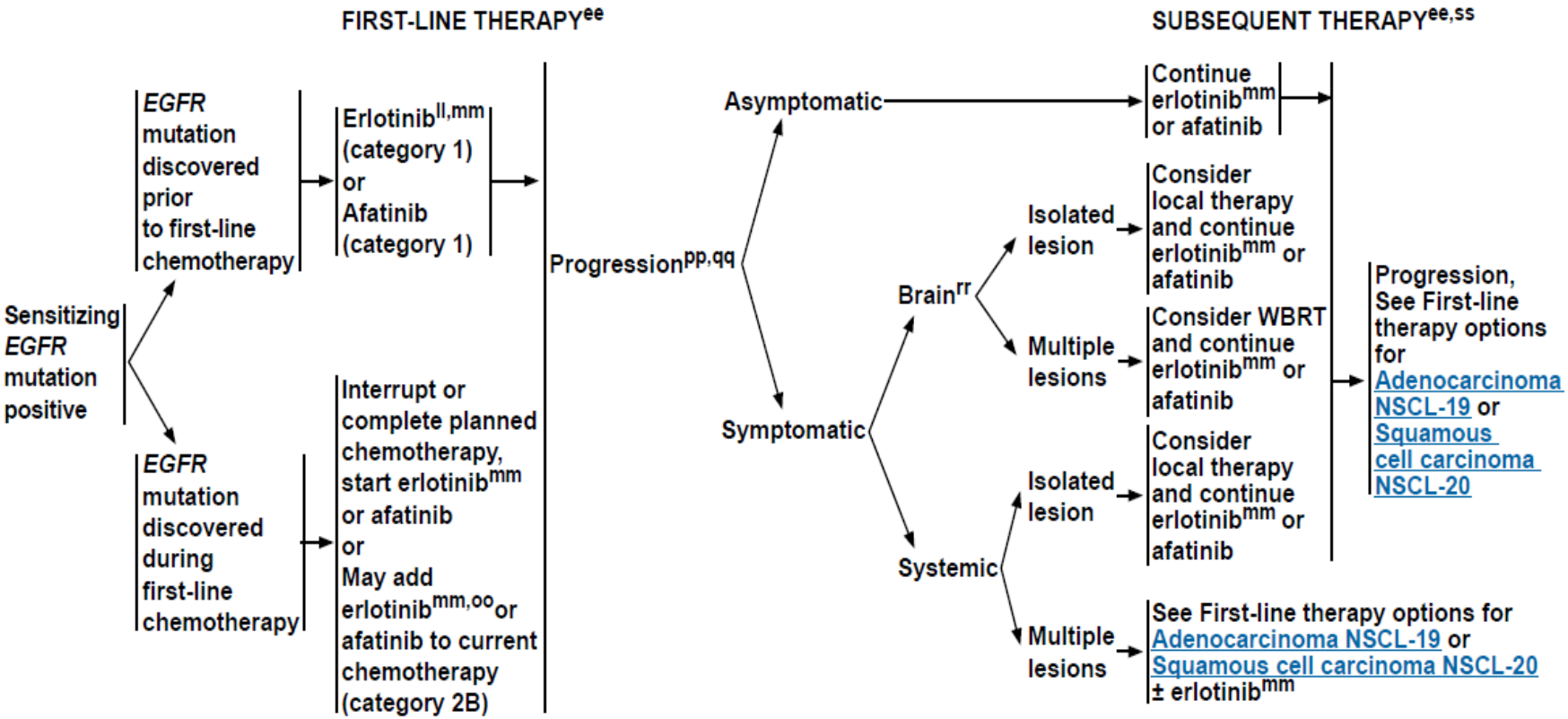
Strategies in Patients With EGFR Mutation After First-Line EGFR-TKI

National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2015
Non-Small Cell Lung Cancer

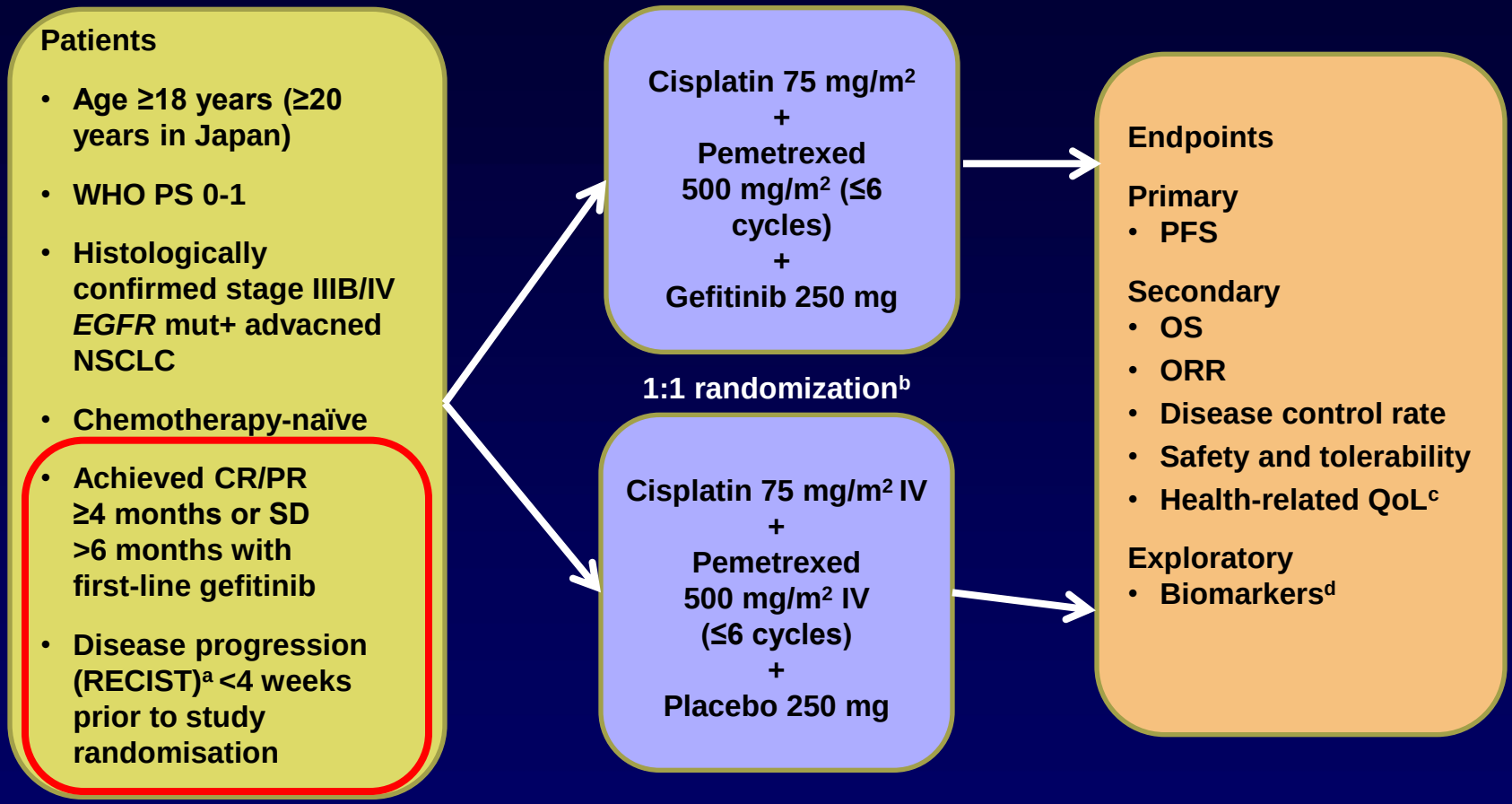
NCCN Guidelines Index
NSCLC Table of Contents
Discussion

SENSITIZING EGFR MUTATION POSITIVE[a]



National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 11 March 2015.

IMPRESS: Study Design



[a] Progressive disease based on radiologic evaluation (modified Jackman's criteria[1]) and RECIST v 1.1. Tumor assessments were performed ≤4 weeks before the start of treatment (baseline), and every 6 weeks (±7 days) after randomization until progressive disease;

[b] Randomization did not include stratification factors; analyses were adjusted for 2 covarietes; age (<64 years vs ≥65 years) and prior response to gefitinib (SD vs PR+CR)

[c] will be reported seperately

[d] Analyses not yet completed and will be reported seperately

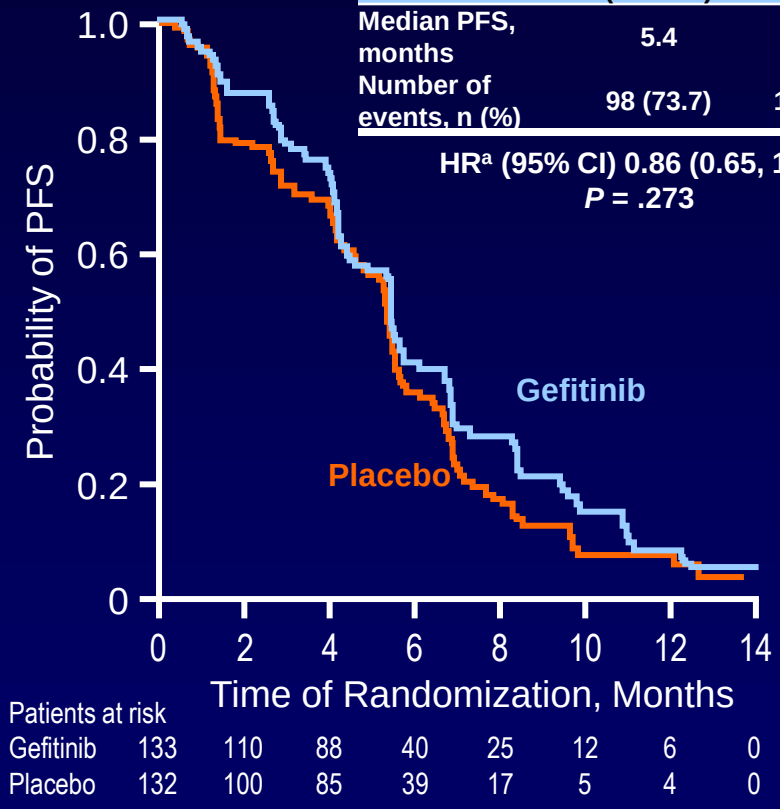
Mok T, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA2_PR.

IMPRESS: PFS and OS

PFS

	Gefitinib (n = 133)	Placebo (n = 132)
Median PFS, months	5.4	5.4
Number of events, n (%)	98 (73.7)	107 (81.1)

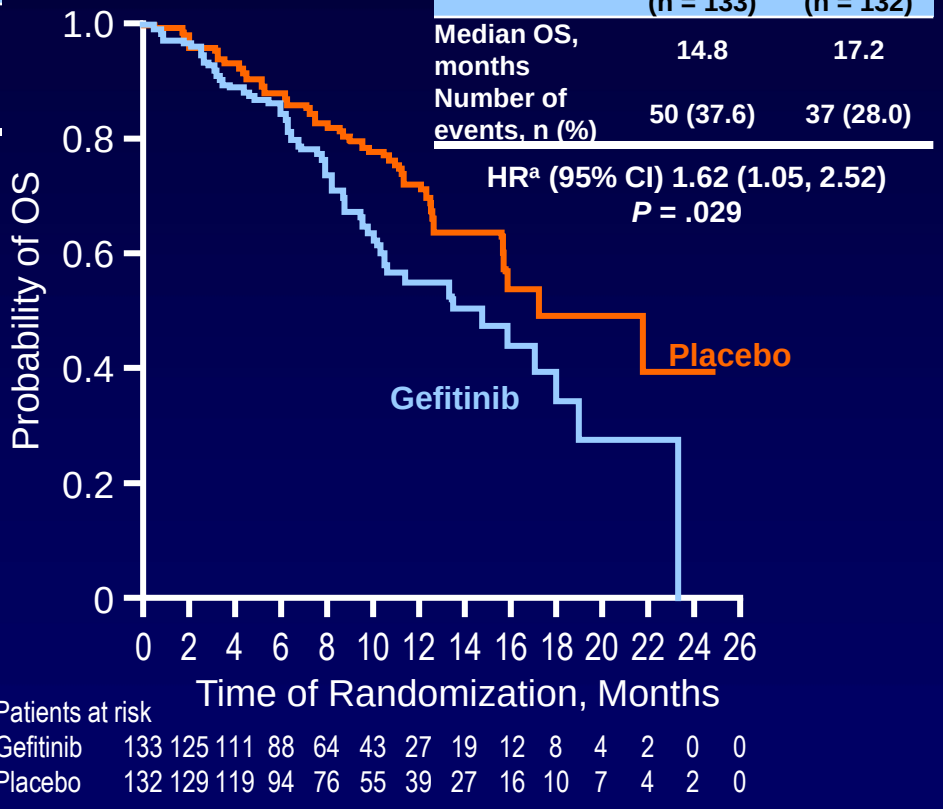
HR[a] (95% CI) 0.86 (0.65, 1.13)
P = .273



OS (33% of events)

	Gefitinib (n = 133)	Placebo (n = 132)
Median OS, months	14.8	17.2
Number of events, n (%)	50 (37.6)	37 (28.0)

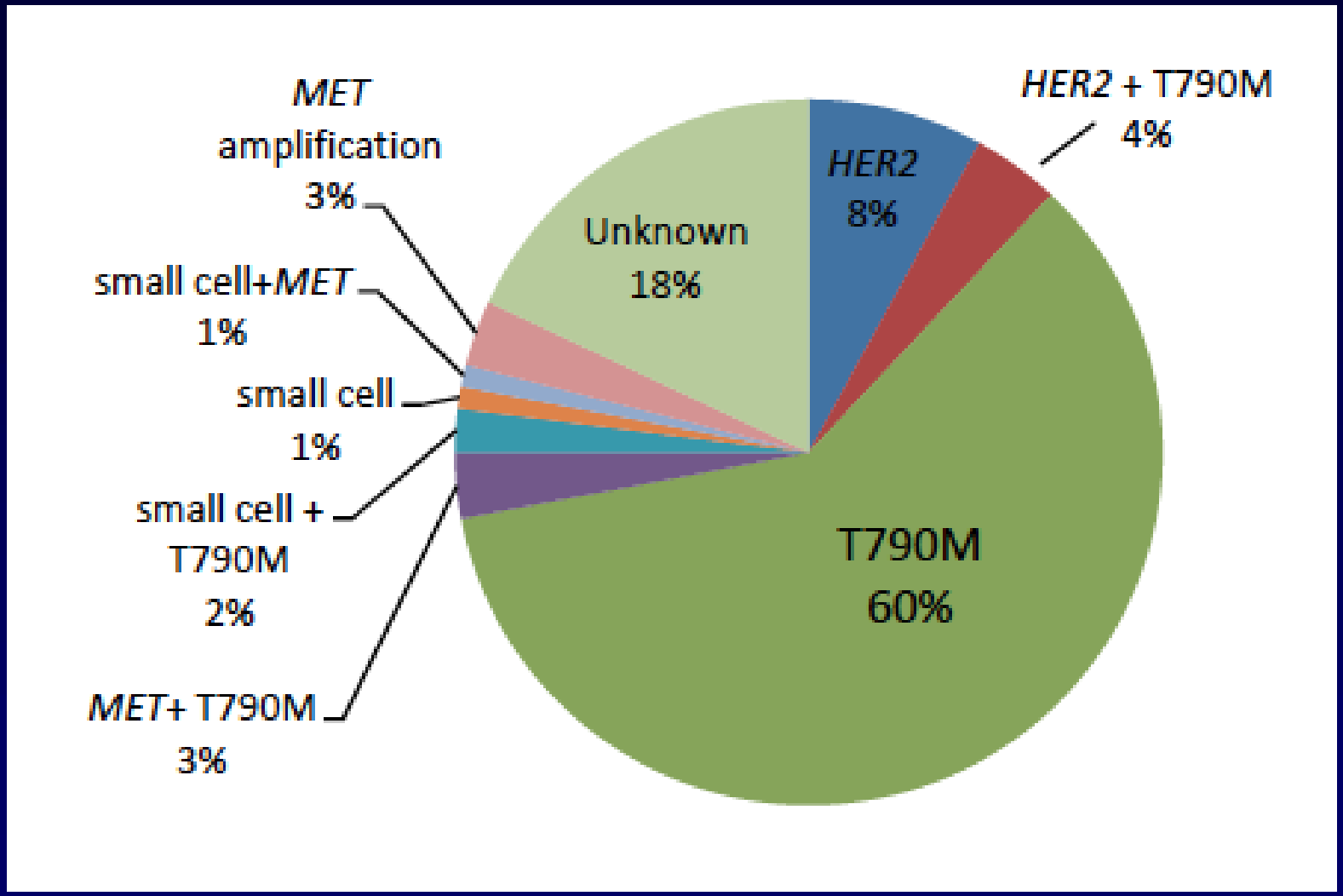
HR[a] (95% CI) 1.62 (1.05, 2.52)
P = .029



[a]Primary Cox analysis with covariates

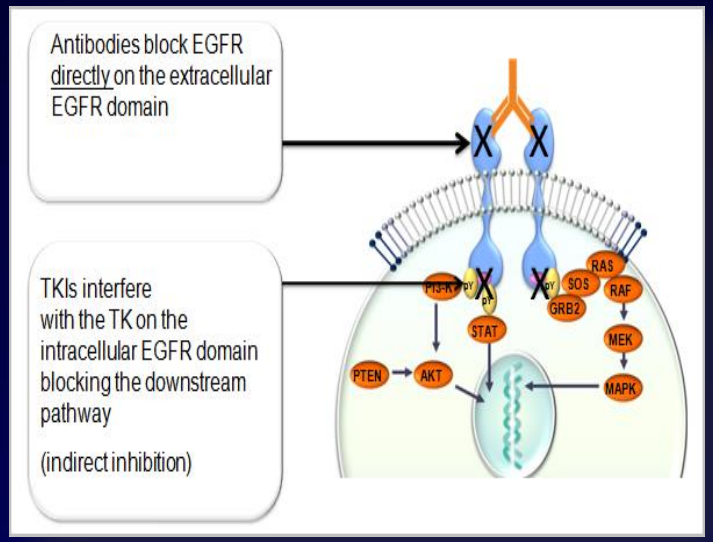
Mok T, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA2_PR.

Resistance Mutations



Yu HA, et al. *Clin Cancer Res*. 2013;19(8):2240-2247.

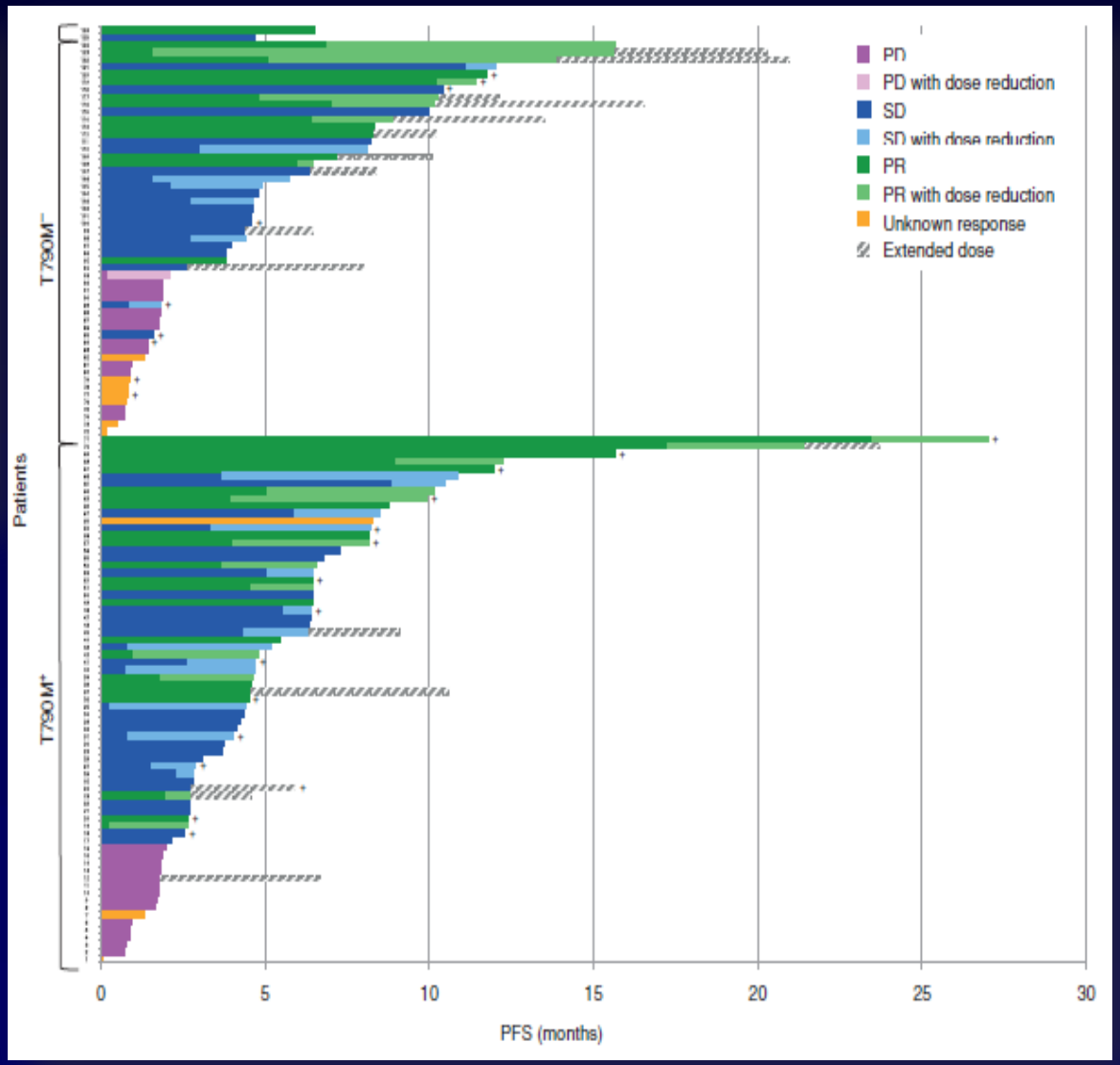
Afatinib + Cetuximab: Response and PFS by T790M Mutation Status



71 patients with proven *EGFR T790M* mutation: confirmed RR = 32%

PFS 4.7 months

Grade 3/4 AEs 44%



Janjigian YY, et al. *Cancer Discov.* 2014;4(9):1036-1045

EGFR Inhibitors Following PD on EGFR-Directed Therapy

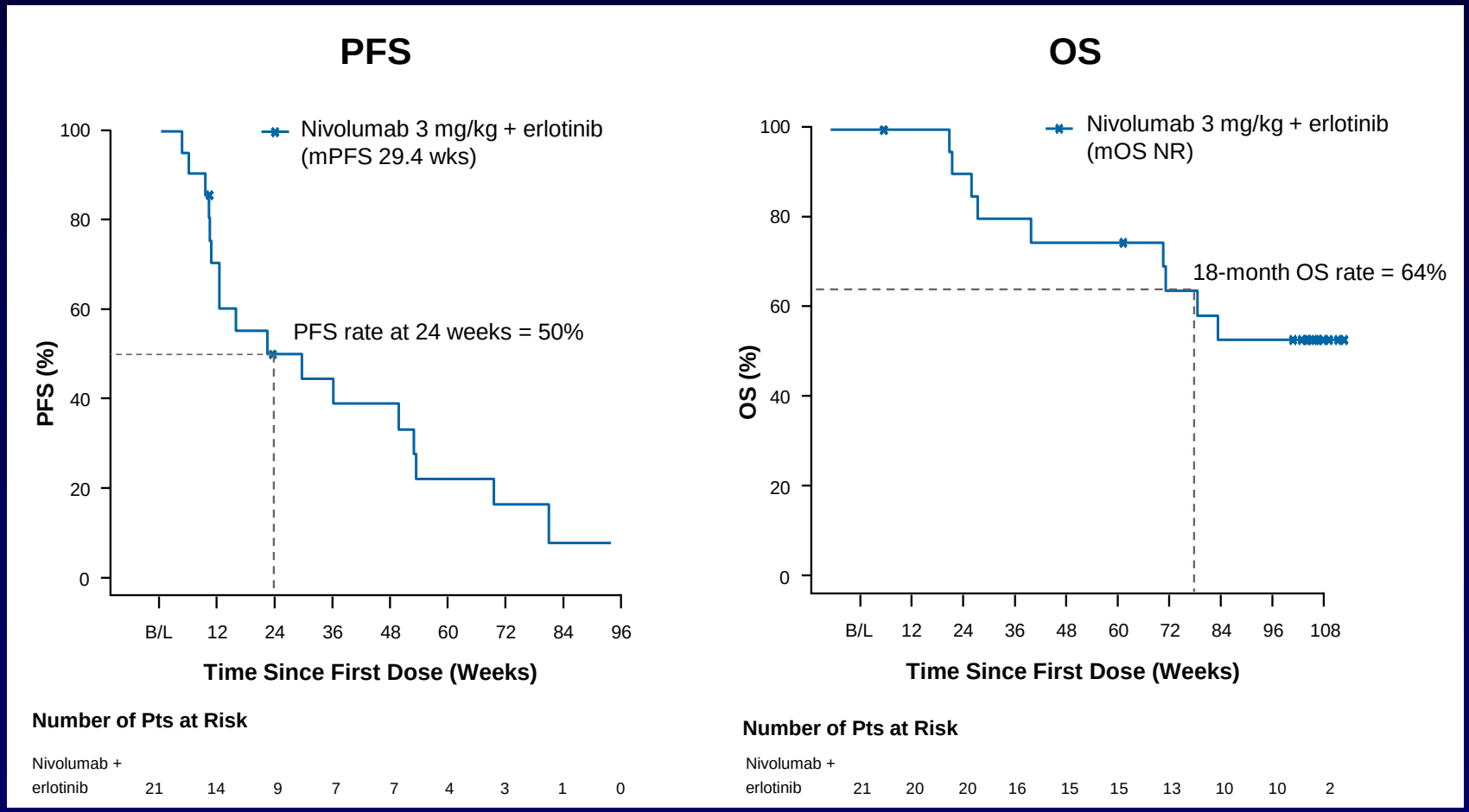
	RR T790M+	RR T790M-	PFS
Afatinib/cetuximab	32%	25%	4.7
HM-61713	29%	12%	4.34
CO-1686 (rociletinib)	58%	Inc	↑
AZD 9291	65%	22%	↑

- T70M EGFR mutation predictive for 3rd generation TKIs benefit
- Ongoing AURA trials (AZD9291) and TIGER trials (CO-1686)

1.Janjigian YY, et al. Cancer Discov. 2014;4(9):1036-1045; 2. Kim DW, et al. *J Clin Oncol* 2014;32 (suppl; abstr 8011); 3. Sequist L, et al *J Clin Oncol* 2014; 32:(suppl; abstr 8010^); 4 Janne PA, *J Clin Oncol* 2014;32 (suppl; abstr 8009^);

PFS and OS in EGFR+ NSCLC Treated With Nivolumab Plus Erlotinib

20 refractory after TKI failure, 1 naïve EGFR Mut+ patients; ORR 19%



Gettinger S, et al. Presented at: 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology; 30 October - 1 November 2014; Chicago, Illinois. Abstract 171.

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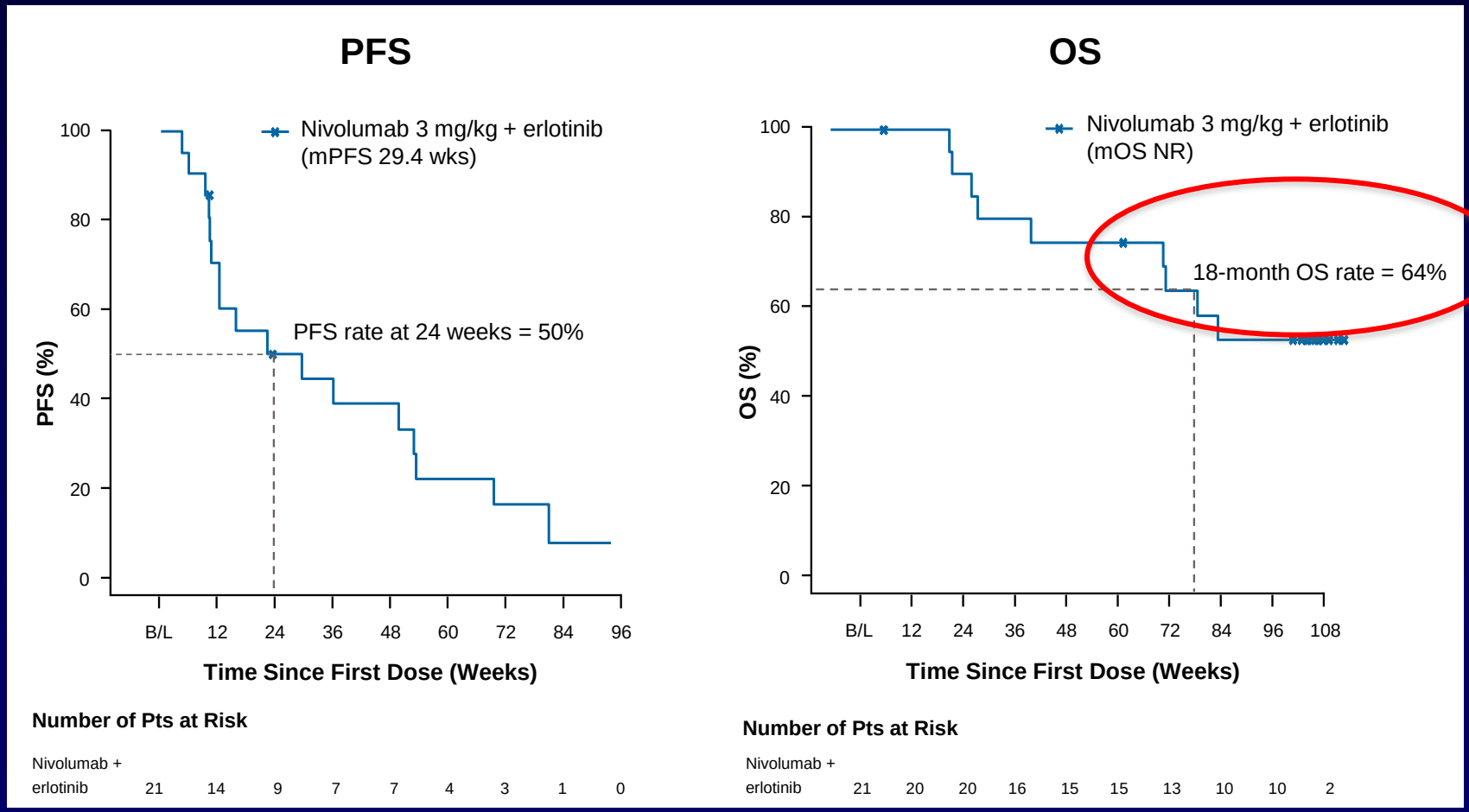

Gettinger S, et al. Presented at: 2014 Chicago Multidisciplinary Symposium in Thoracic Oncology; 30 October - 1 November 2014; Chicago, Illinois. Abstract 171.

Conclusions

- First-line treatment with first or second generation EGFR-TKI, taking into account efficacy and toxicity
- At slow PD proceed with EGFR-TKI until symptomatic progression
- Symptomatic PD: Platinum-based CT (present)
- Rebiopsy if T790M proceed with T790M inhibitors (future)