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

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Metastatic NSCLC: Consensus on Pathology and Molecular Test, First-Line, Second-Line, and Third-Line Therapy

12. What is the preferred first-line treatment in patients with a tumor harboring an activating *EGFR* mutation

Recommendation 12: **An EGFR TKI is the preferred first-line treatment in patients whose tumor harbors an activating *EGFR* mutation**

Strength of recommendation: A

Level of evidence: I

Felip E, et al. *Ann Oncol.* 2011;22(7):1507-1519

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

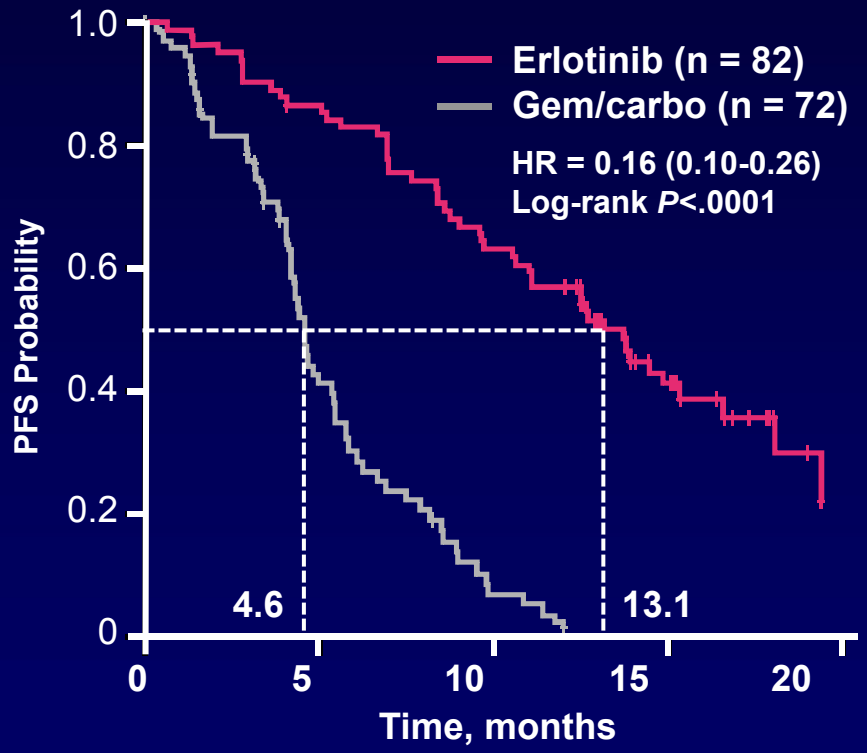
Trial	Pop.	Experimental Drug	*EGFR* Mut +, N	ORR, % TKI vs Chemo	PFS TKI vs Chemo, Months (HR, 95% CI)
IPASS	Asia	Gefitinib	261	71.2 vs 47.3	9.8 vs 6.4 0.48 (0.36, 0.64)
First-SIGNAL	Asia	Gefinitib	42	84.6 vs 37.5	8.4 vs 6.7 0.61 (0,31, 1.22)
WJTOG 3405	Asia	Gefitinib	172	62.1 vs 32.2	9.2 vs 6.3 0.49 (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

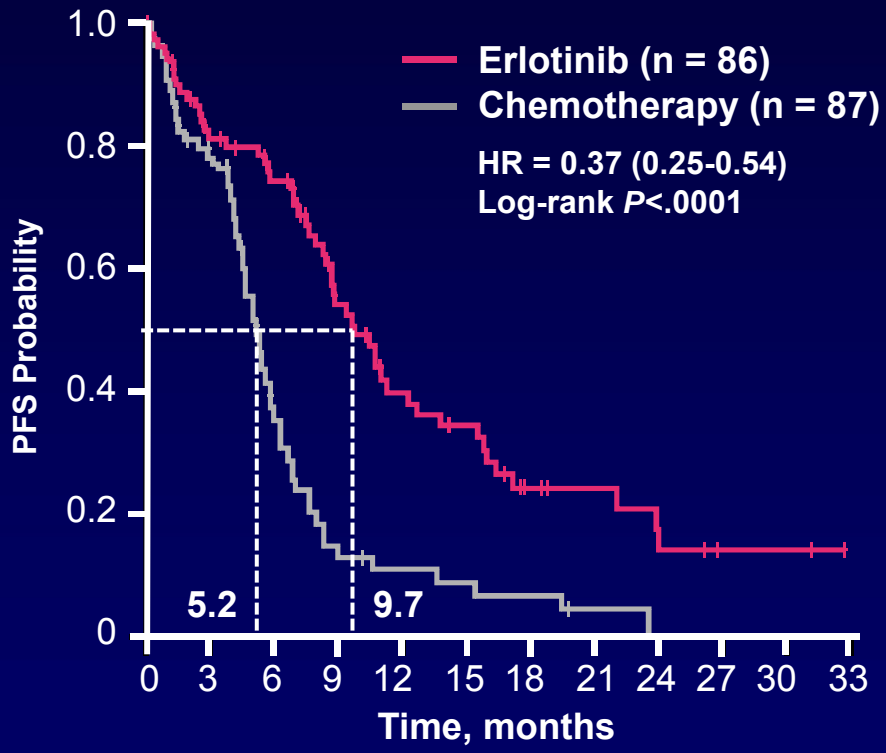
Mok T, et al. *N Engl J Med.* 2009;361(10):947-957. Han JY, et al. *J Clin Oncol.* 2012;30(10):1122-1128. Mitsudomi T, et al. *Lancet Oncol*. 2010;11(2):121-128. Maemondo M, et al. *N Engl J Med.* 2010;362(25):2380-2388. Zhou C, et al. *Lancet Oncol*. 2011;12(8):735-742. Rosell R, et al. *Lancet Oncol.*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

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

Asian Patients (OPTIMAL study)[1]



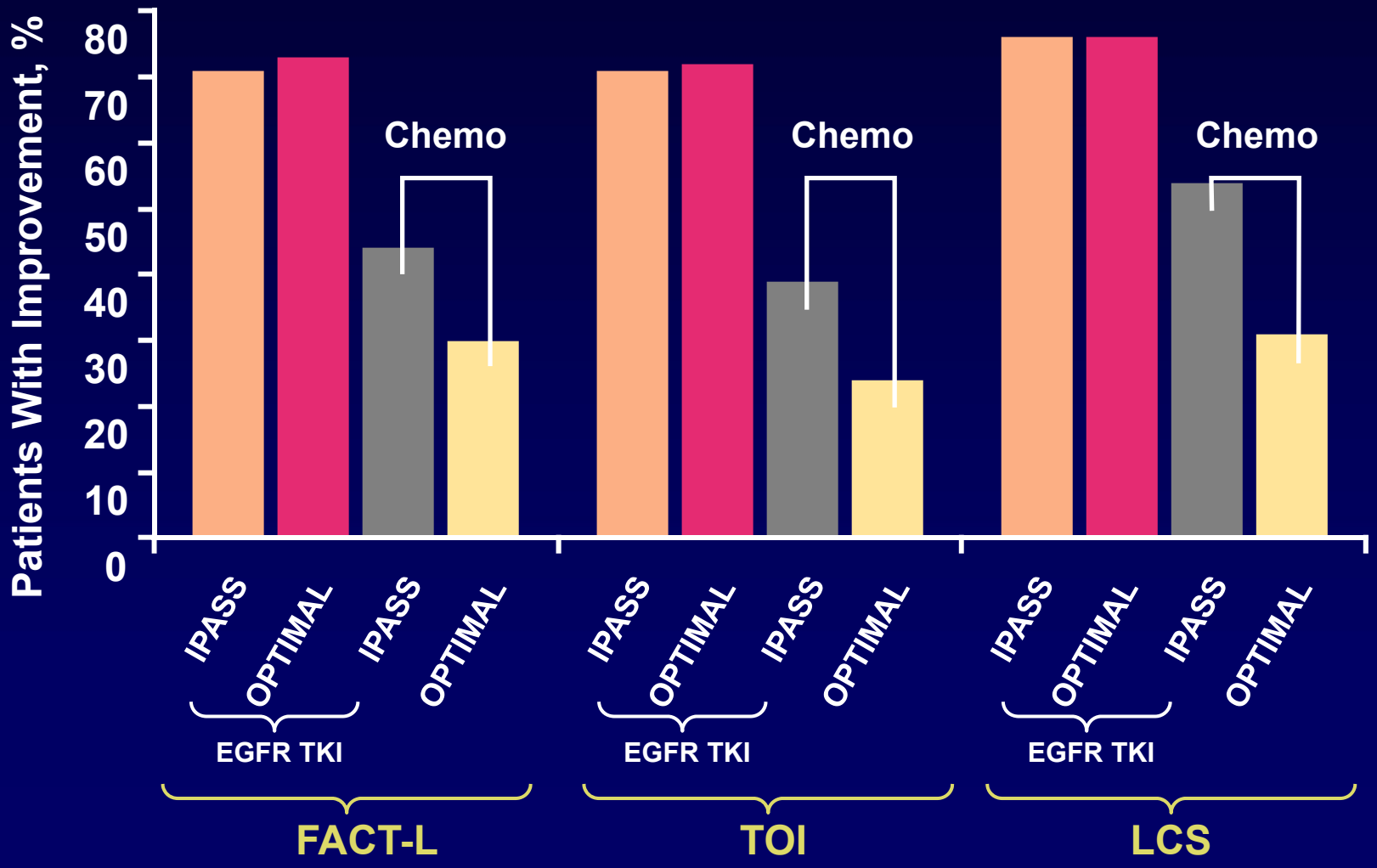
Caucasian Patients (EURTAC study)[2]



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.

Better QoL With First-Line EGFR-TKI



Mok TS, et al. *N Engl J Med.* 2009;361(10):947-957. Zhou C, et al. *J Clin Oncol.* 2011;29(Suppl): Abstract 7520.

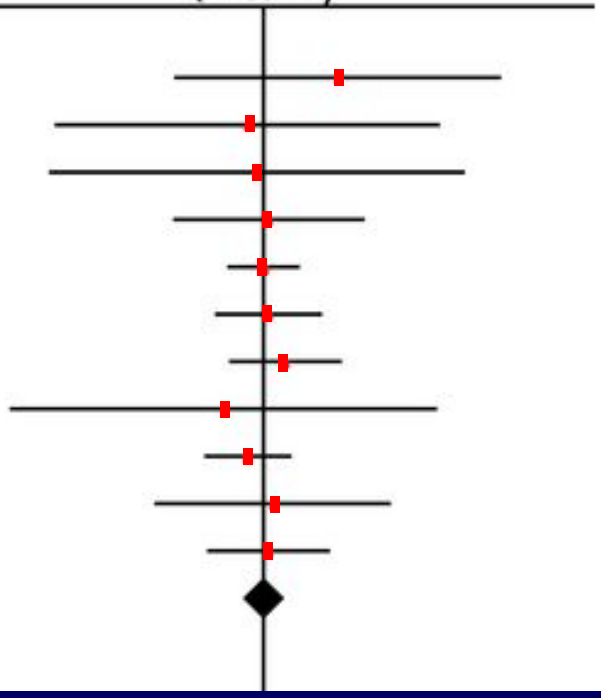
EURTAC: Tolerability

Adverse event (AE) (Grade 3/4, CTC 3.0)	EURTAC	
	Erlotinib	Chemotherapy
Grade 3/4 AEs	45%	67%
Rash	13%	0%
Diarrhea	5%	0%
Fatigue	6%	0%
Neutropenia	0%	22%
Febrile neutropenia	0%	3%
Anemia	1%	4%
Interstitial lung disease like events	1%	1%
Treatment-related AEs leading to discontinuation	6%	20%

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)**



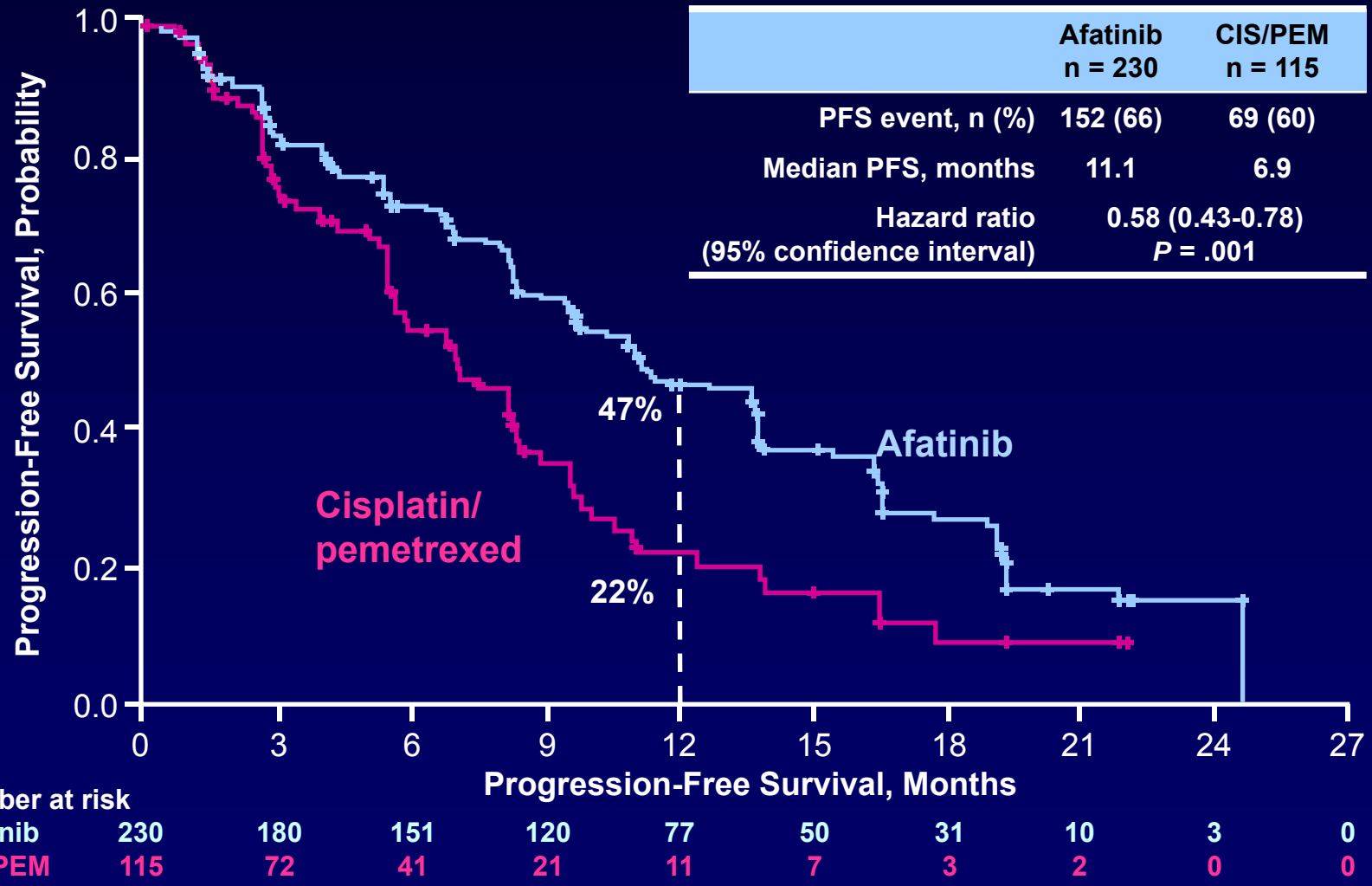
Lee CK, et al. *J Natl Cancer Inst.* 2013;105(9): 595-605

How to Improve Outcome?

Investigated Strategies:

- **Second generation: Afatinib**
- **Intercalating?: FASTACT 2**
- **Adding bevacizumab?**

LUX Lung 3: Afatinib Improves PFS in *EGFR*-Mutant NSCLC



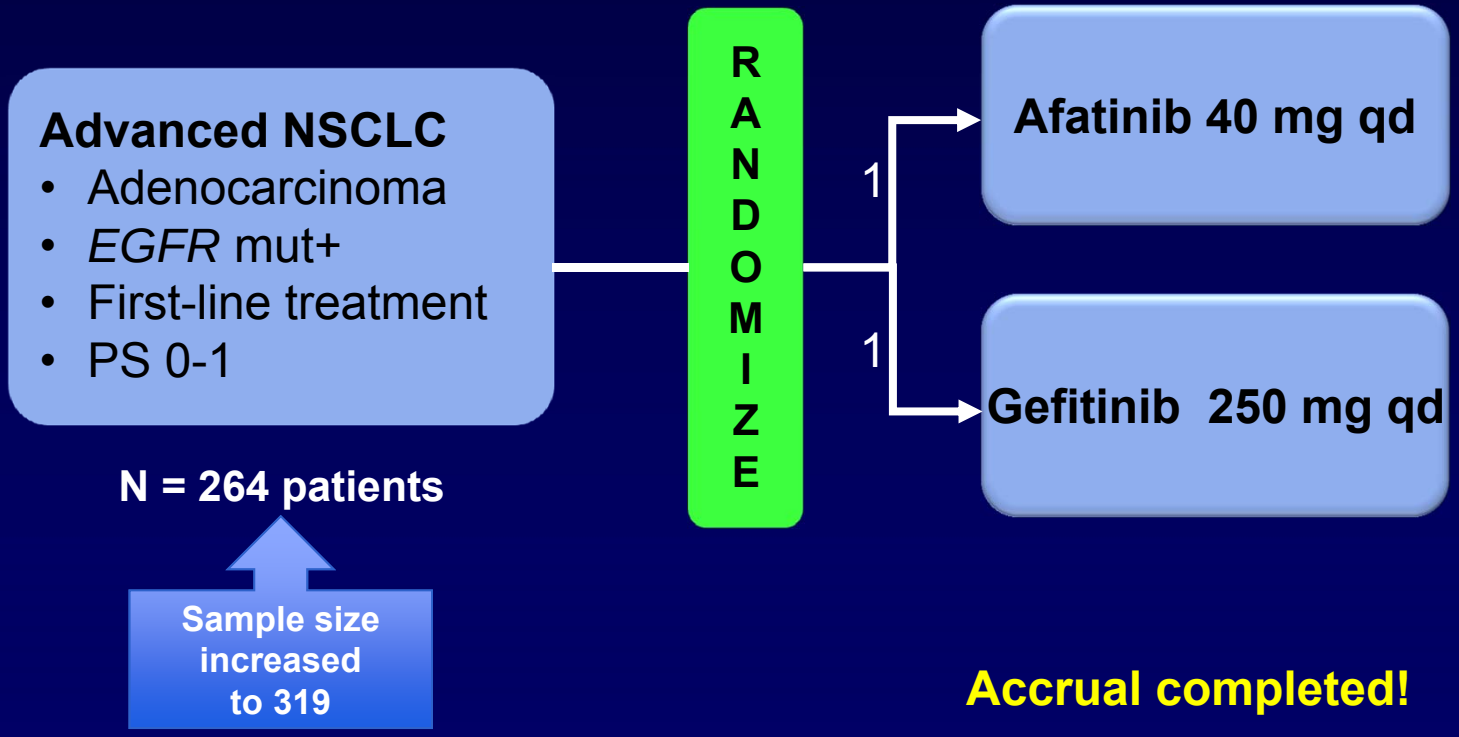
	Afatinib n = 230	CIS/PEM n = 115
PFS event, n (%)	152 (66)	69 (60)
Median PFS, months	11.1	6.9
Hazard ratio (95% confidence interval)	0.58 (0.43-0.78) *P* = .001	

Number at risk										
Afatinib	230	180	151	120	77	50	31	10	3	0
CIS/PEM	115	72	41	21	11	7	3	2	0	0

Sequist LV, et al. *J Clin Oncol*. 2013;31(27):3327-3334.

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

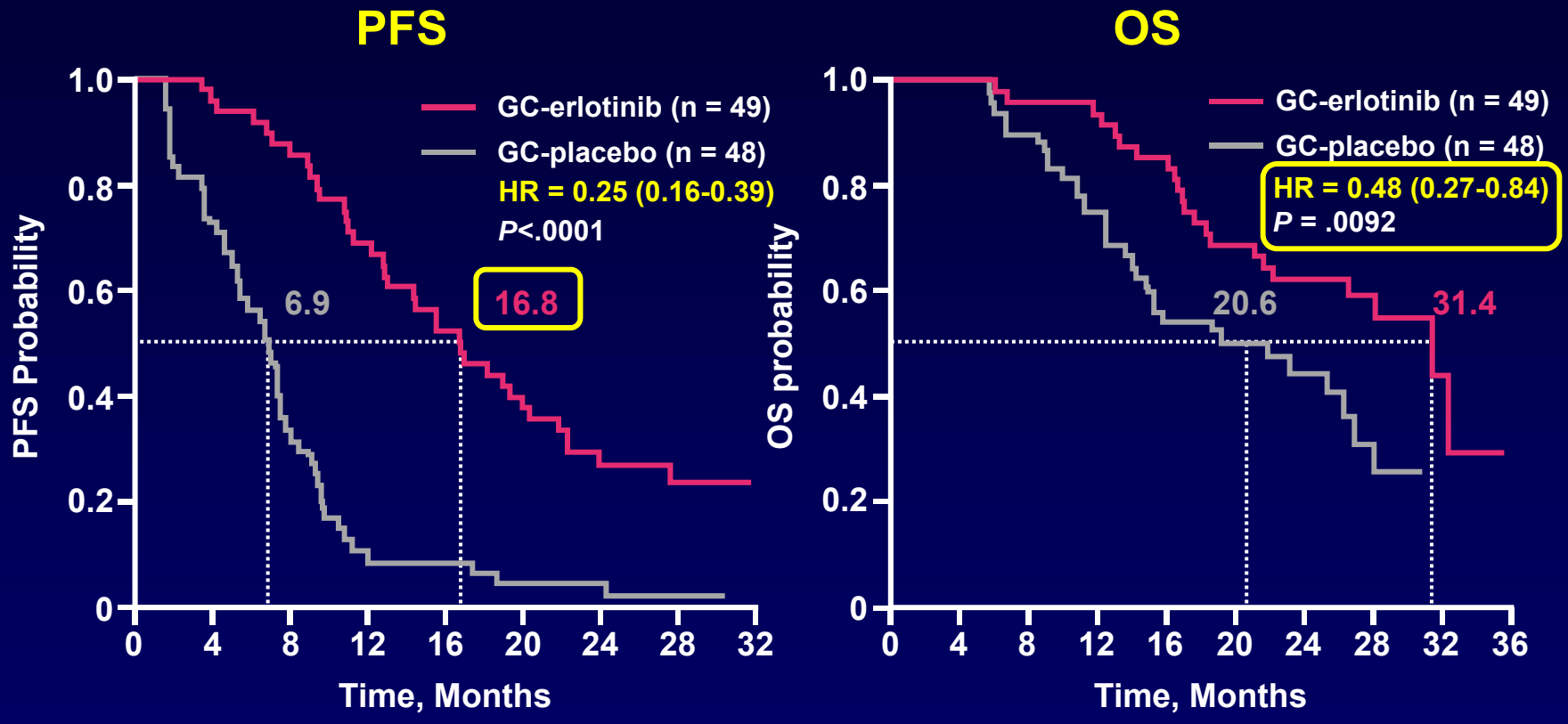
- **Is afatinib better than gefitinib in patients with EGFR mutation?**



Accrual completed!

National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT01466660. Accessed 11 December 2014.

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

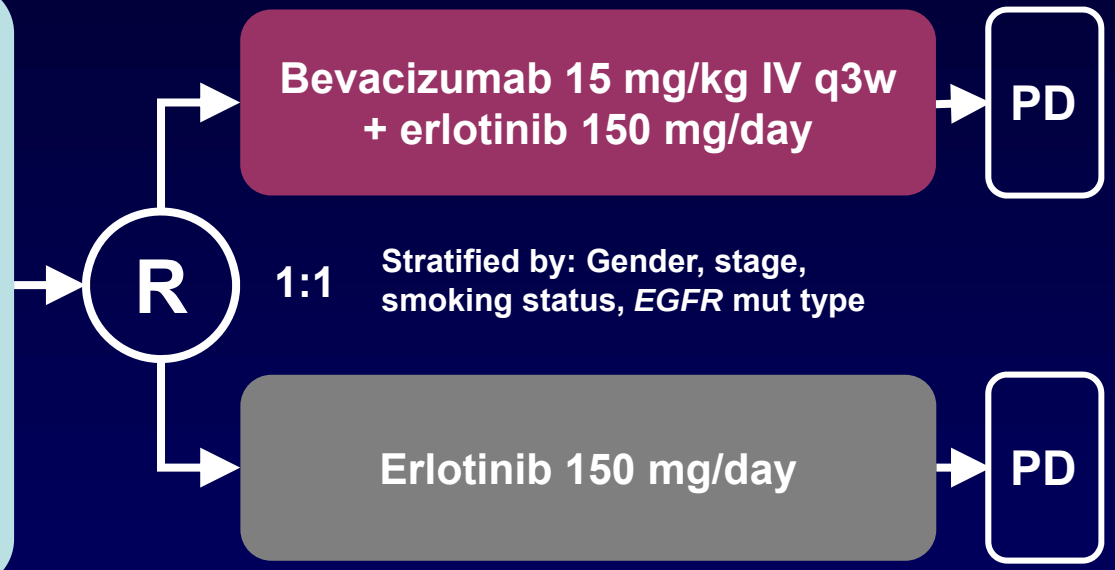
GC, gemcitabine, platinum

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)



Stratified by: Gender, stage, smoking status, *EGFR* mut type

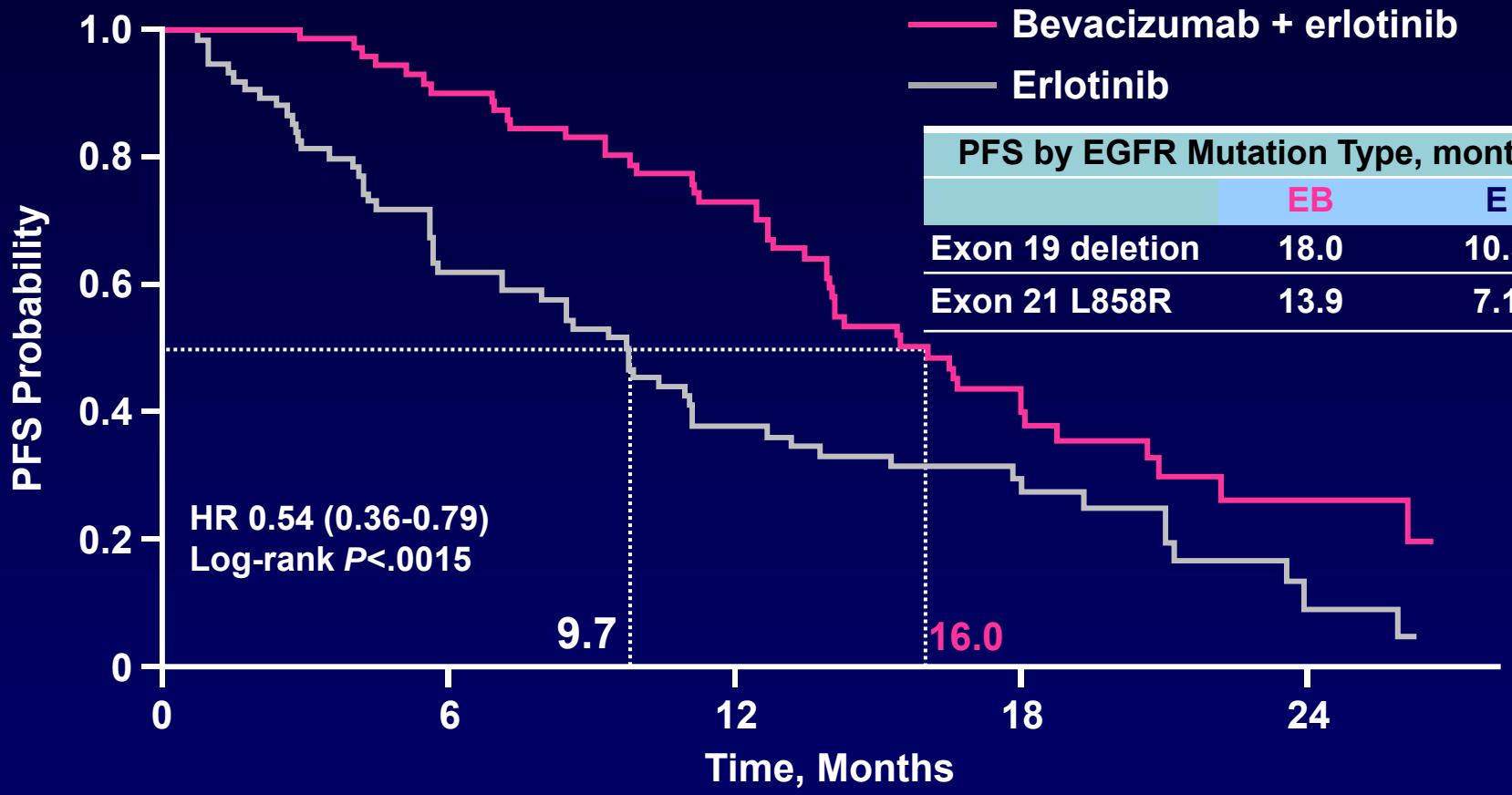
Primary endpoint
- PFS by independent review

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

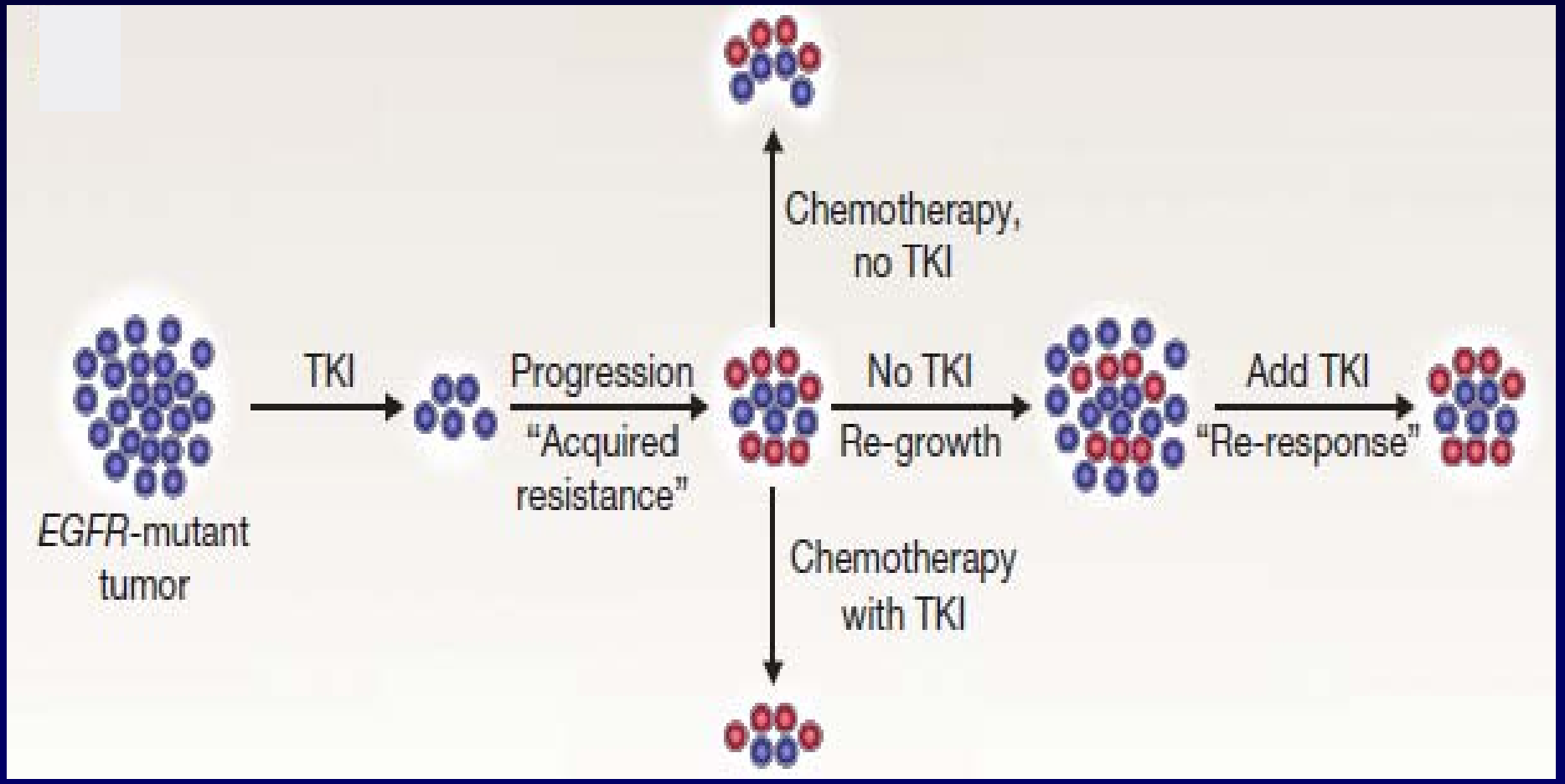
RESULTS of BELIEF Trial AWAITED!

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

Secondary Resistance—Clinically Distinct Patterns

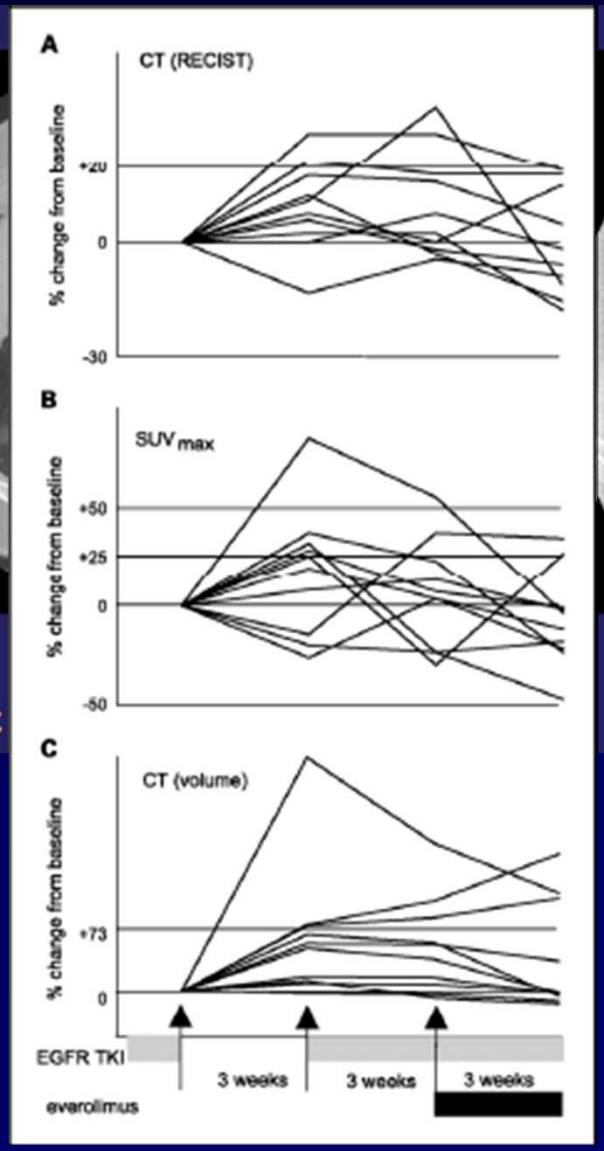
- Oligometastatic progression
  - Decreased tumor burden compared to initial presentation
- Slow, minimal multifocal progression
  - Decreased tumor burden compared to initial presentation
- Rapid multifocal progression

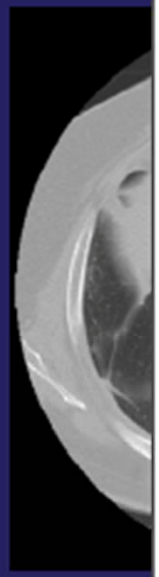
Evolutionary Modeling Based on Growth Kinetics

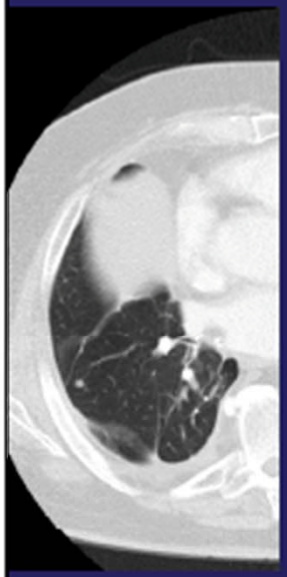


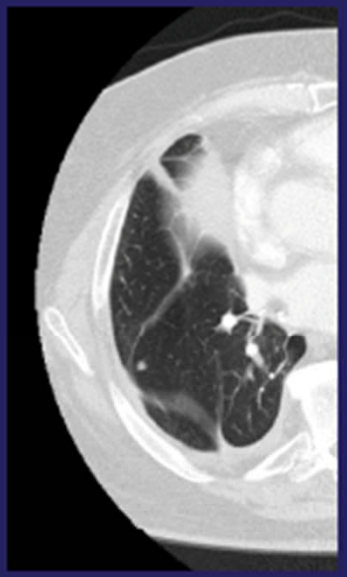
Chmielecki J, et al. *Sci Transl Med.* 2011;3(90):90ra59.

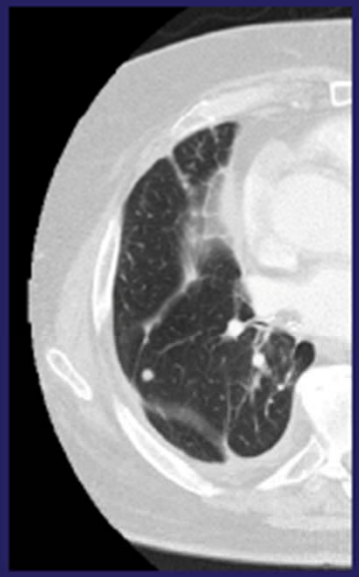
Resistance to EDFR-TKIs Can Be Indolent…But Not When the Drug Is Stopped











Dec

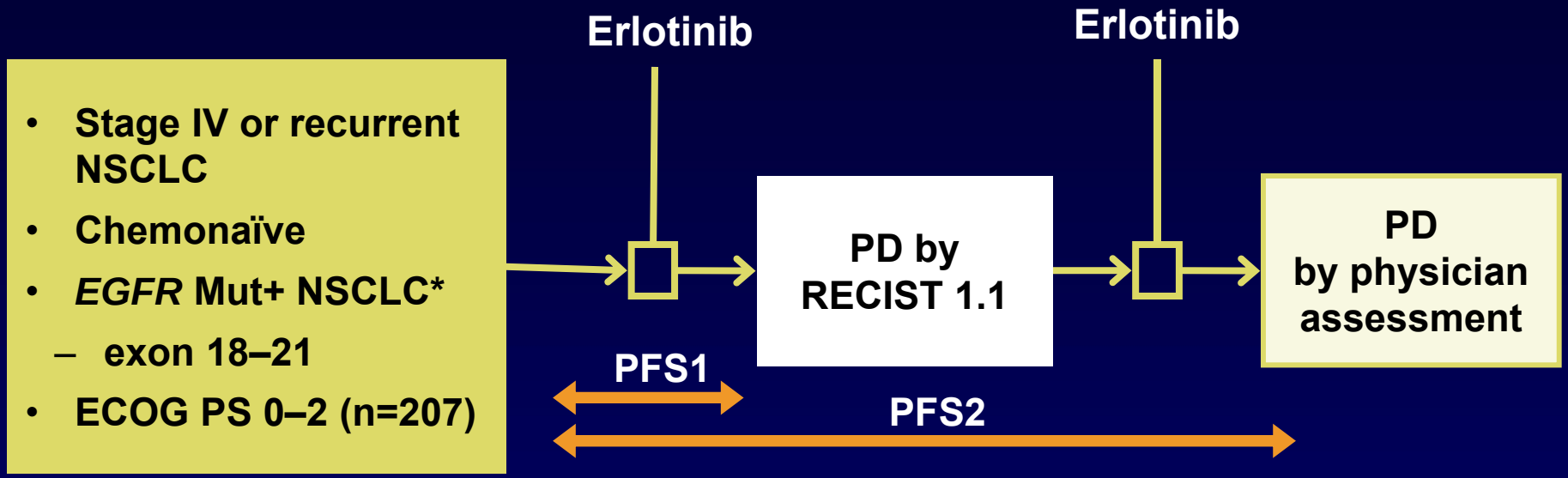
Apr 2010

Jun 2010

Aug 2010

Riely GJ, et al. *Clin Cancer Res*. 2007;13(7):5150-5155.

ASPIRATION: Study Design



* Except for T790M

Primary endpoint

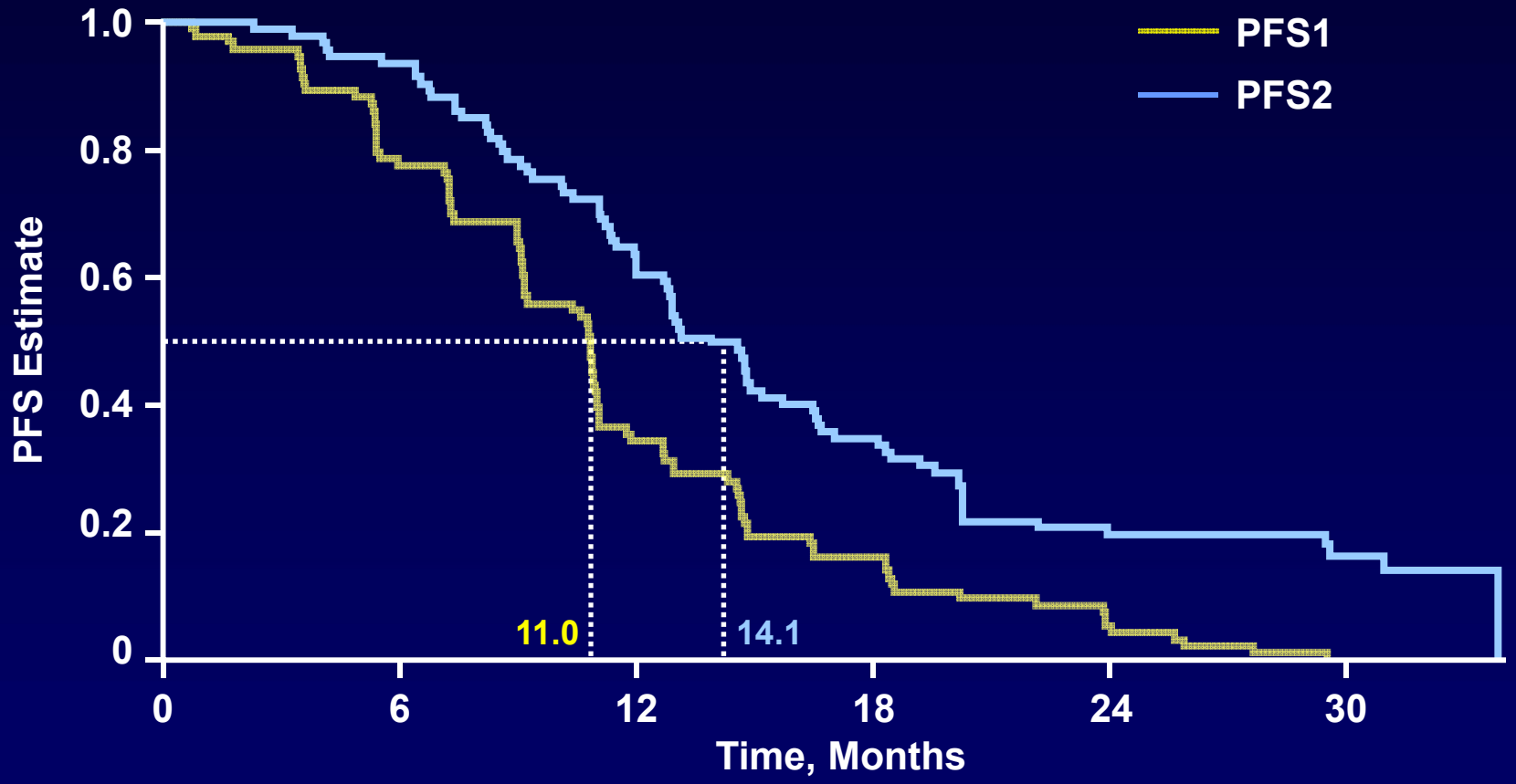
- PFS1 (time to RECIST PD or death)

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.

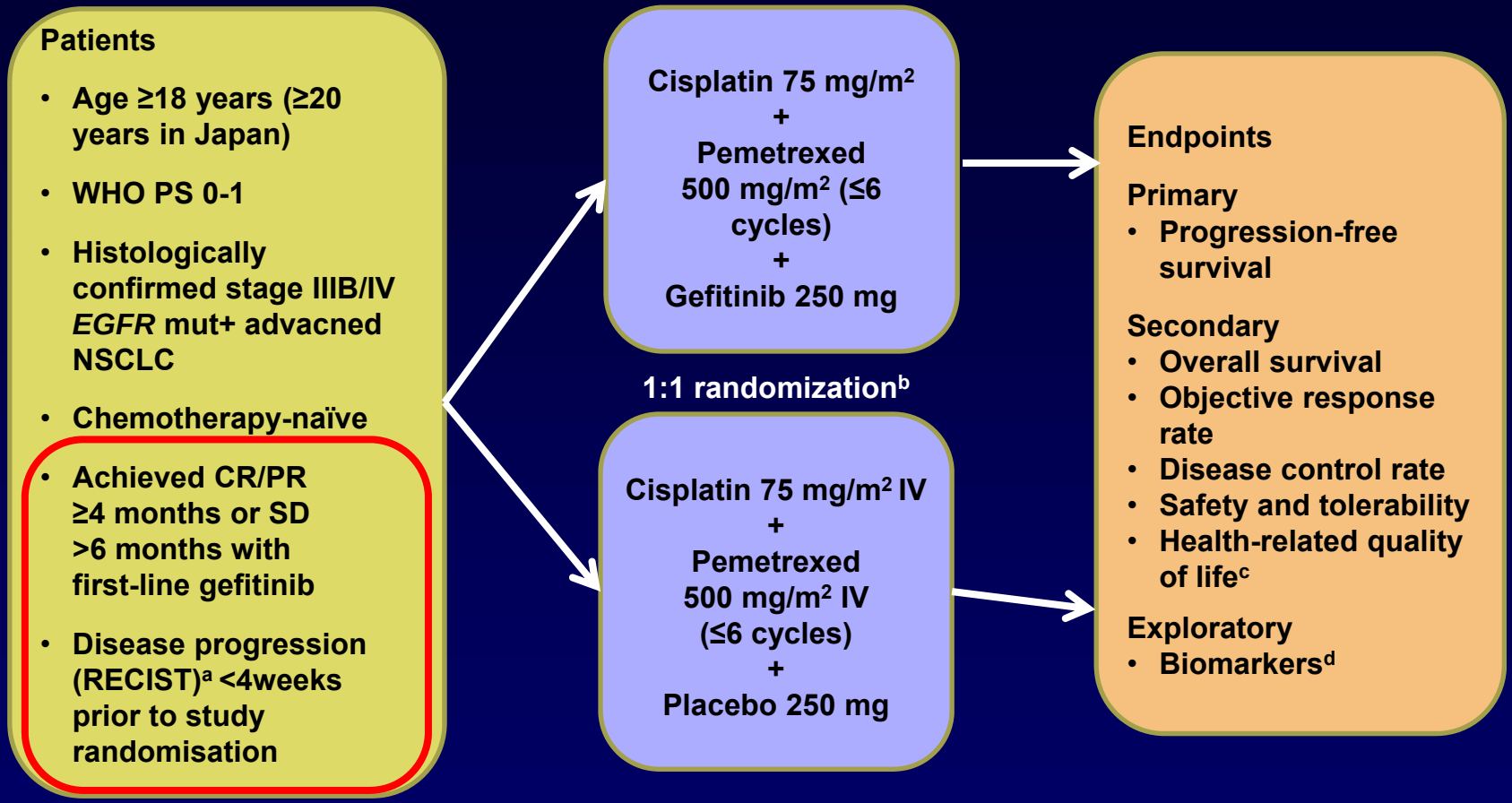
ASPIRATION: PFS in Patients Receiving Erlotinib Post-PD (n = 93/207)



The difference between PFS1 and PFS2 was an additional 3.1 months

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

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

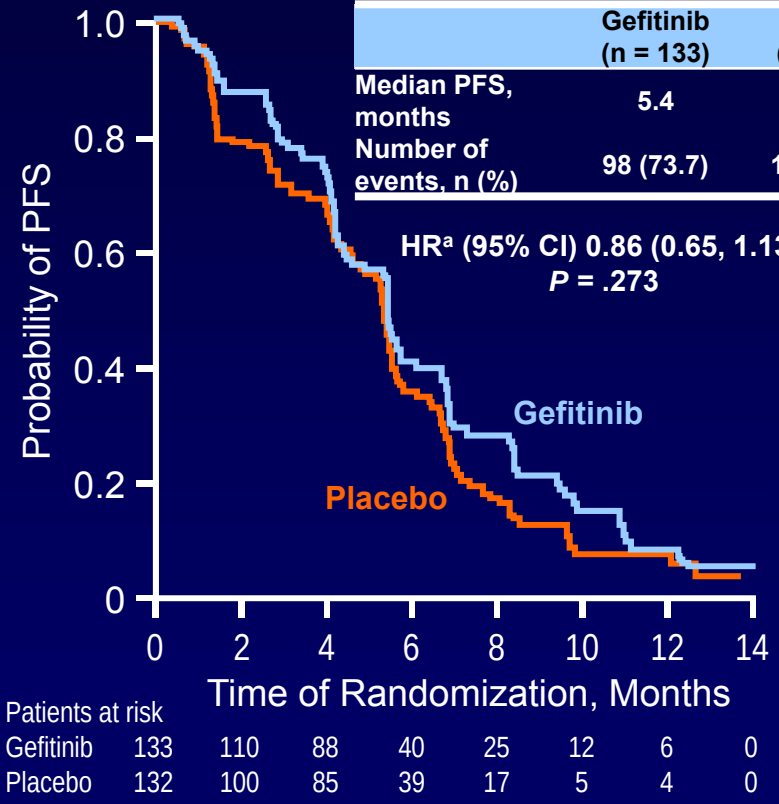
Mok T, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA2_PR.

IMPRESS: No statistically significant improvement in PFS with continuation of gefitinib; OS in favour of placebo arm but analysis was immature

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



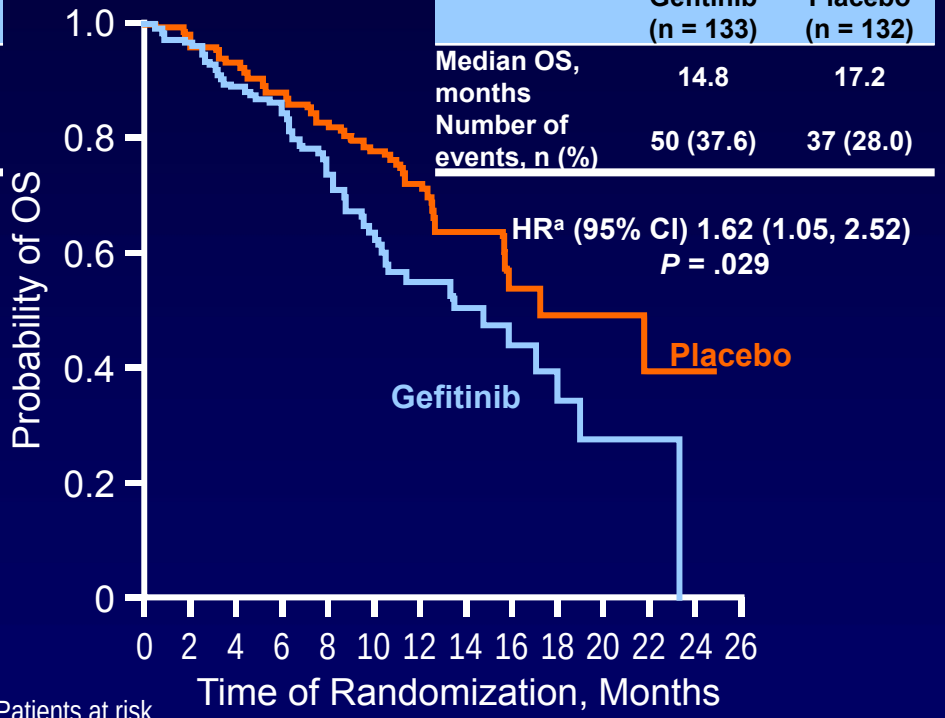
Patients at risk

Gefitinib	133	110	88	40	25	12	6	0
Placebo	132	100	85	39	17	5	4	0

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



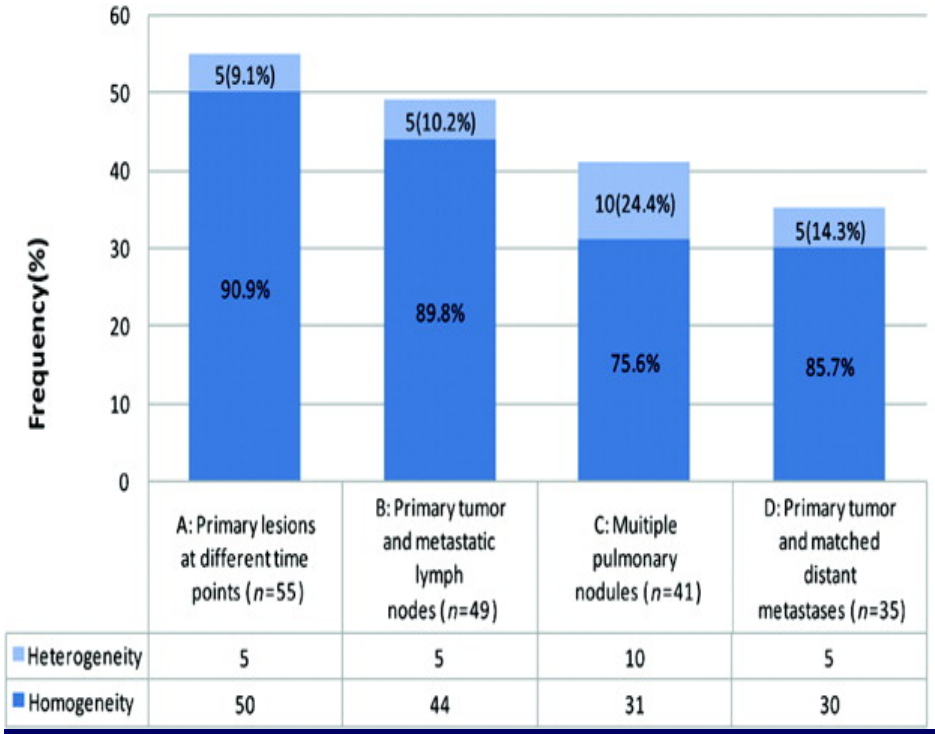
Patients at risk

Gefitinib	133	125	111	88	64	43	27	19	12	8	4	2	0	0
Placebo	132	129	119	94	76	55	39	27	16	10	7	4	2	0

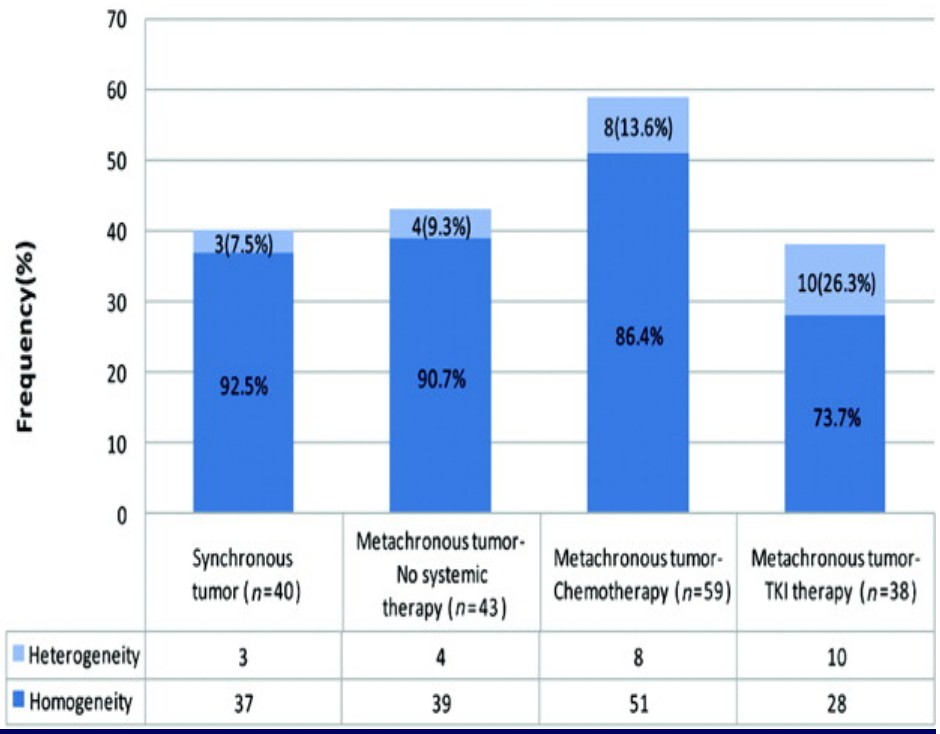
[a]Primary Cox analysis with covariates

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

EGFR: Primary vs Metastatic Sites



	A: Primary lesions at different time points (*n*=55)	B: Primary tumor and metastatic lymph nodes (*n*=49)	C: Muitiple pulmonary nodules (*n*=41)	D: Primary tumor and matched distant metastases (*n*=35)
Heterogeneity	5	5	10	5
Homogeneity	50	44	31	30

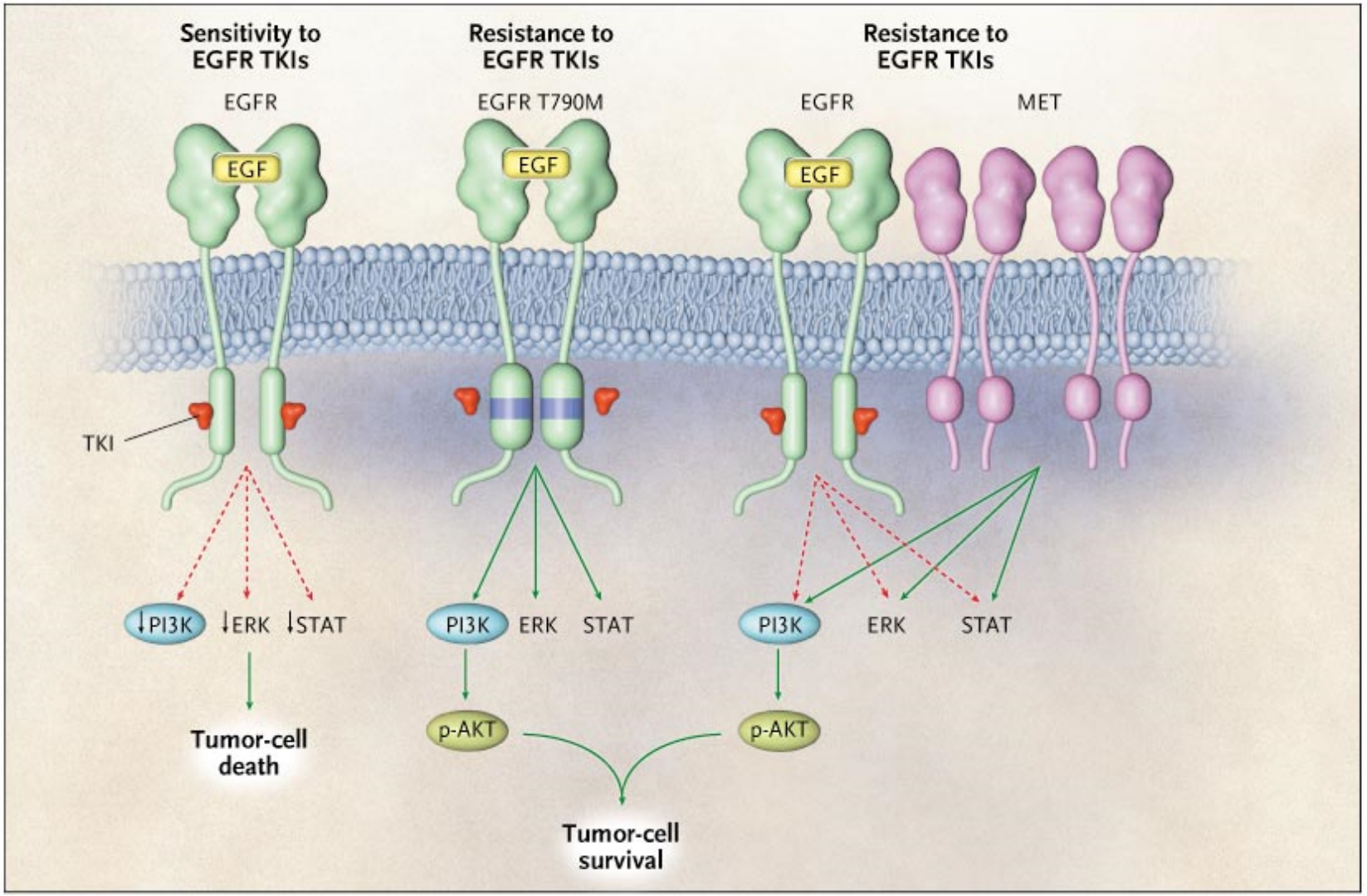


	Synchronous tumor (*n*=40)	Metachronous tumor-No systemic therapy (*n*=43)	Metachronous tumor-Chemotherapy (*n*=59)	Metachronous tumor-TKI therapy (*n*=38)
Heterogeneity	3	4	8	10
Homogeneity	37	39	51	28

Heterogeneity *EGFR* mutations is low, except for multiple pulmonary nodules

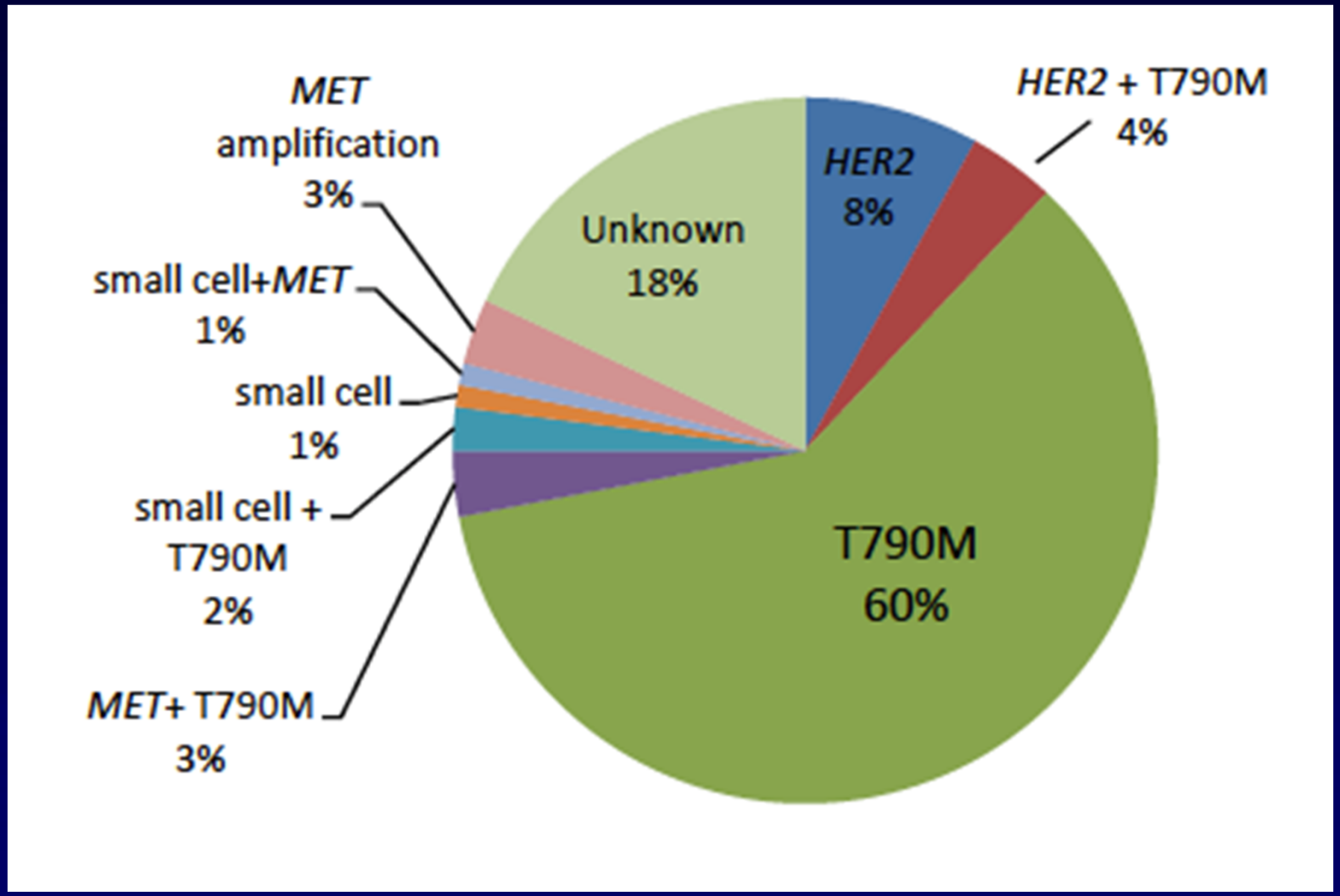
Chen ZY, et al. *Oncologist*. 2012;17(7):978-985.

Effect of Mutations on the Signaling Pathway



Sequist LV, et al. *N Engl J Med.* 2008;359(4):405-414.

Resistance Mutations



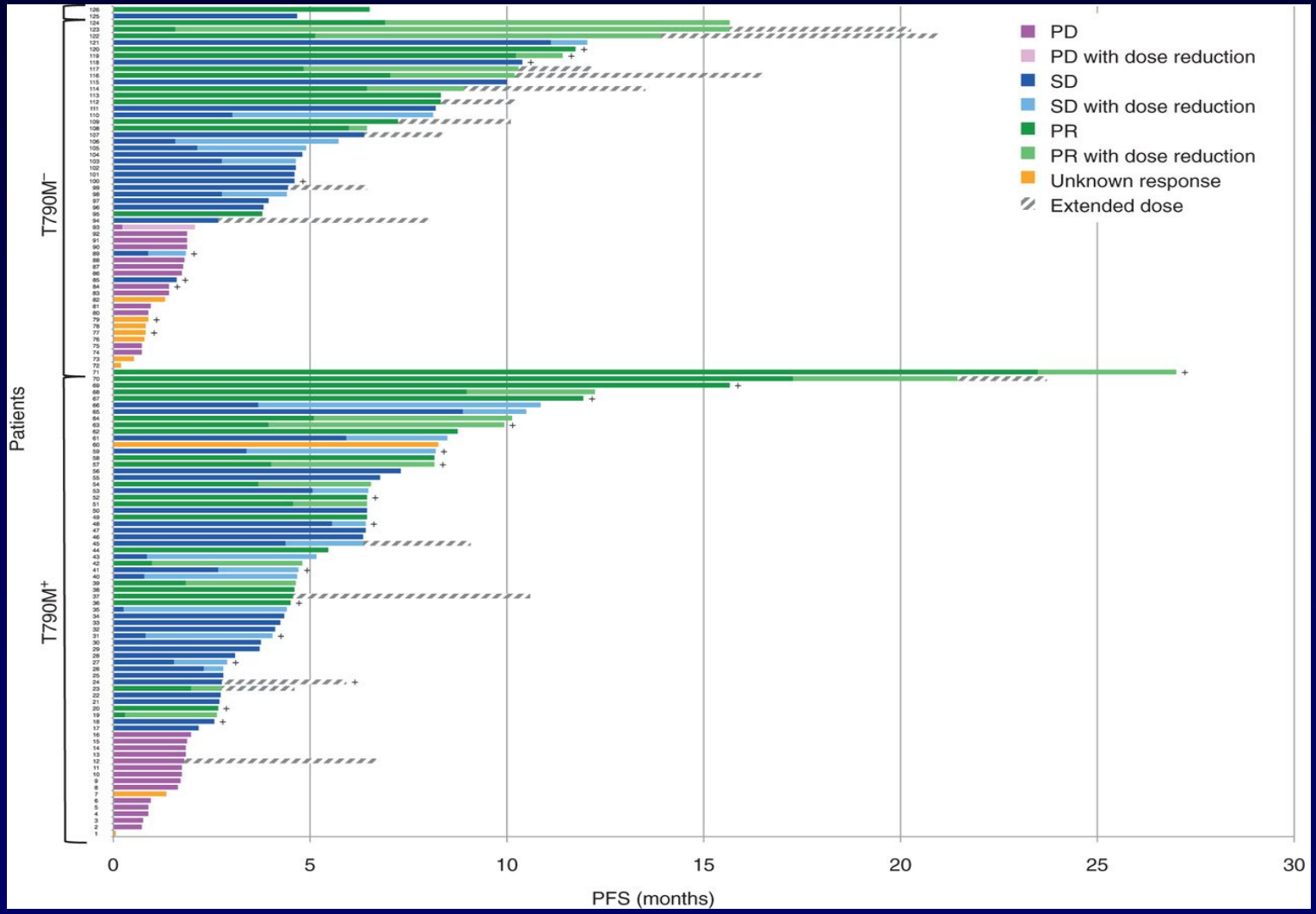
Yu HA, et al. *Clin Cancer Res*. 2013;19(8):2240-2247.

Irreversible TKIs (Pan-HER Inhibitors): Not Highly Effective for T790M

- Neratinib[1]
  - RR 2%, PFS 15 weeks in TKI-resistant patients
- Afatinib[2]
  - RR 7%, PFS ~13 weeks in TKI-resistant patients
- Dacomitinib[3]
  - RR 7% in TKI-resistant patients

1. Sequist LV, et al. *J Clin Oncol.* 2010;28(18):3076-3083. 2. Miller VA, et al. *Lancet Oncol.* 2012;13(5):528-538.
3. Janne PA, et al. *Clin Oncol.* 2009;15s(Suppl): Abstract 8063.

Afatinib and Cetuximab in First Generation EGFR TKI Resistant Patients



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

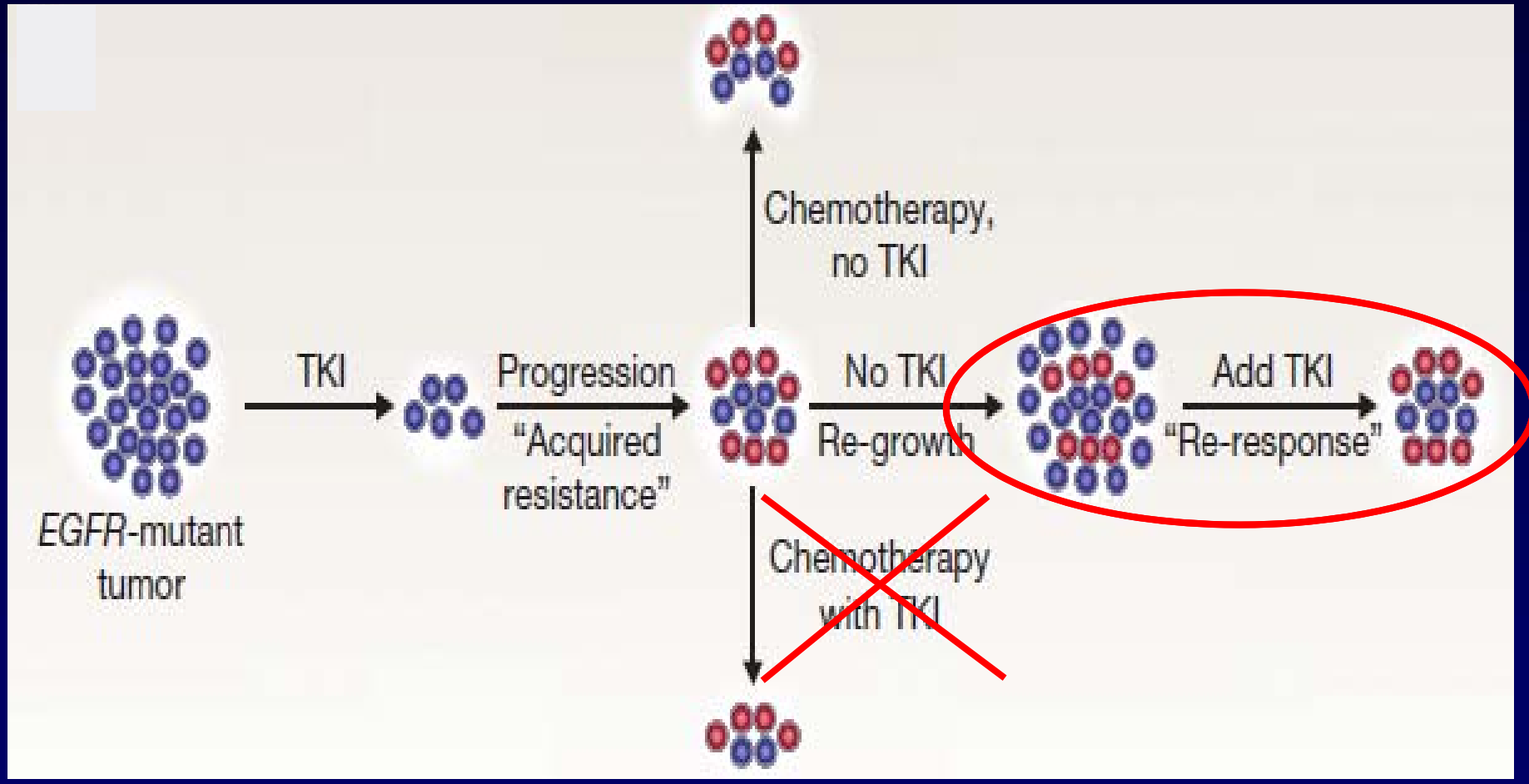
Preliminary Efficacy of EGFR Inhibitors Following Progression on EGFR-Directed Therapy

	RR T790M+	RR T79M-	PFS
Afatinib / cetuximab	32%	25%	4.7
HM 61713	29%	12%	4.34
CO-1686 (Rociletinib)	58%	Inc.	↑
AZD9291	65%	22%	↑

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

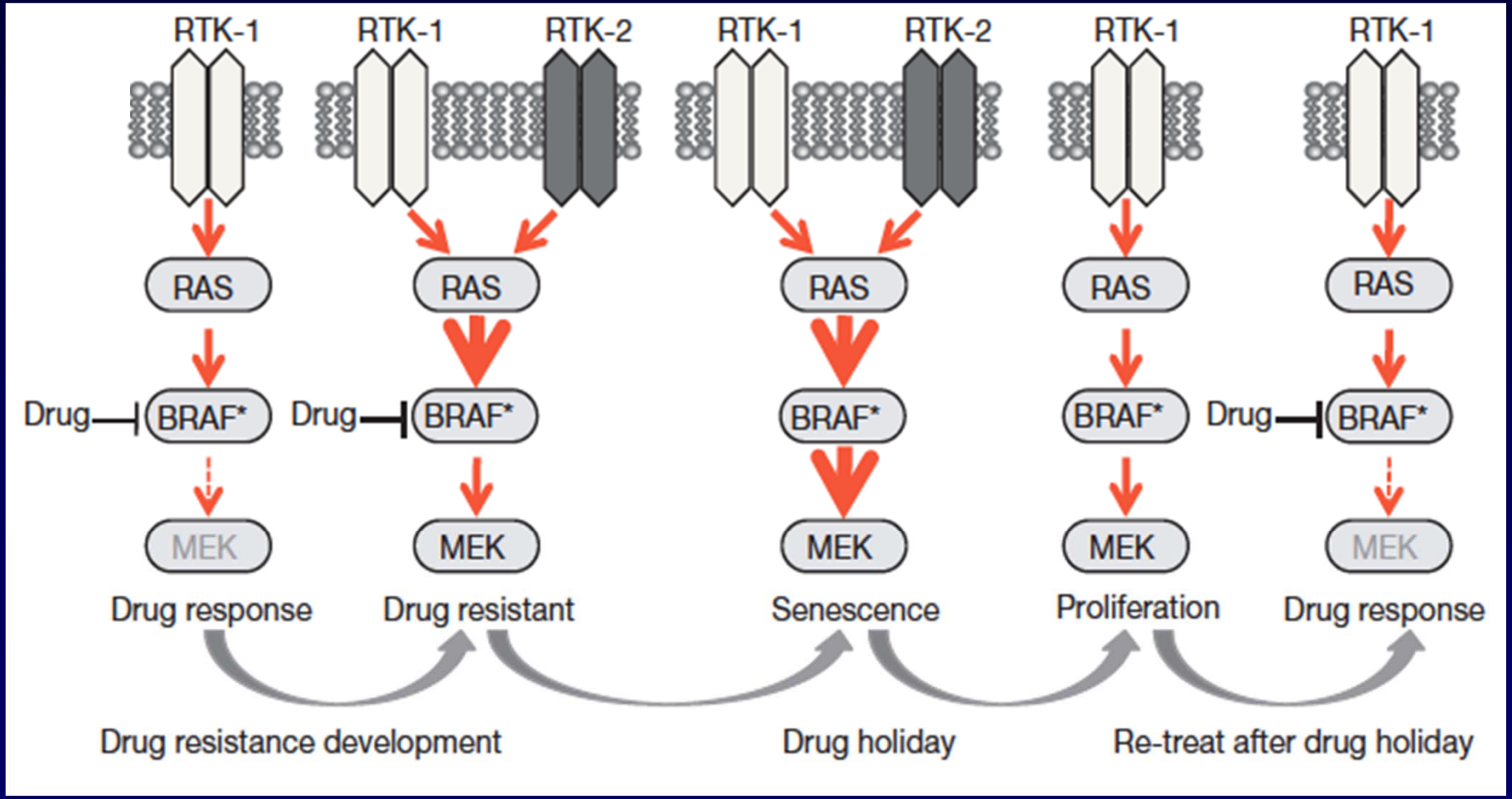
1.Janjigian YY, et al. *Cancer Discov*. 2014;4(9):1036-1045. 2. Kim DW, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8011. 3. Sequist LV, et al *J Clin Oncol.* 2014;32:(5s): Abstract 8010. 4. Janne PA, *J Clin Oncol.* 2014;32(5s): Abstract 8009.

Evolutionary Modeling Based on Growth Kinetics



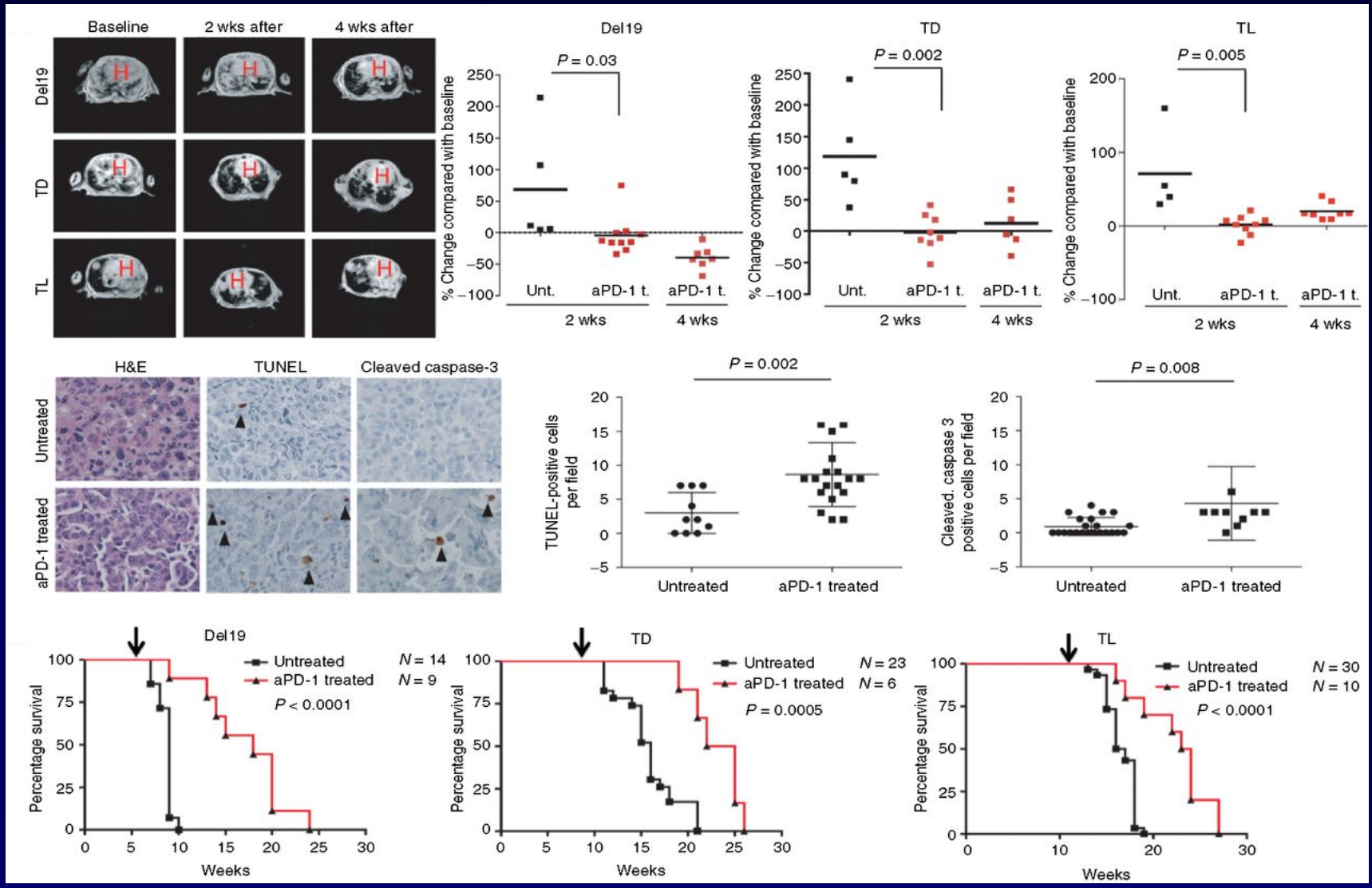
Chmielecki J, et al. *Sci Transl Med.* 2011;3(90):90ra59.

The Biology Behind Retreatment?



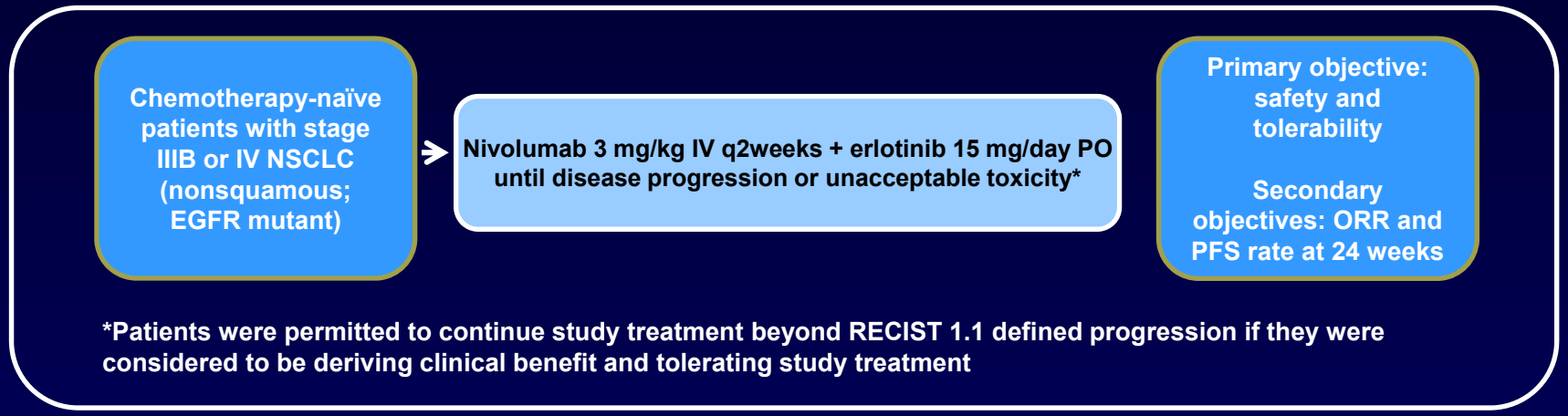
Sun C, et al. *Nature.* 2014;508(7494):118-122.

Promising: *In Vivo* Efficacy of PD-1 Antibody Blockade in EGFR-Mutant Murine Lung Cancer Models



Akbay EA, et al. *Cancer Discov.* 2013;3(12):1355-1363.

Phase I Nivolumab + Erlotinib: Encouraging Results



21 patients; 20 prior treatment with erlotinib

- ORR 19%; SD 45% (responses also in T790M patients
- PFS at 24 weeks 51%
- 1-year OS rate 73%
- Grade 3/4 toxicity 24% (diarrhea, ALT and AST elevation)
- No pneumonitis

Studies evaluating anti-PD-L1 in combination with erlotinib are ongoing

Rizvi NA, et al. *J Clin Oncol.* 2014;32(5s): Abstract 8022.

My Personal View (Today!)

- First-line treatment with first generation EGFR-TKI, taking into account toxicity/ motivating patient to maintain on treatment
- At slow PD proceed with EGFR-TKI until symptomatic progression
- Oligo PD: RT/surgery
- Symptomatic PD: Platinum based CT/rebiopsy