Mechanism of Resistance and Treatment Strategies

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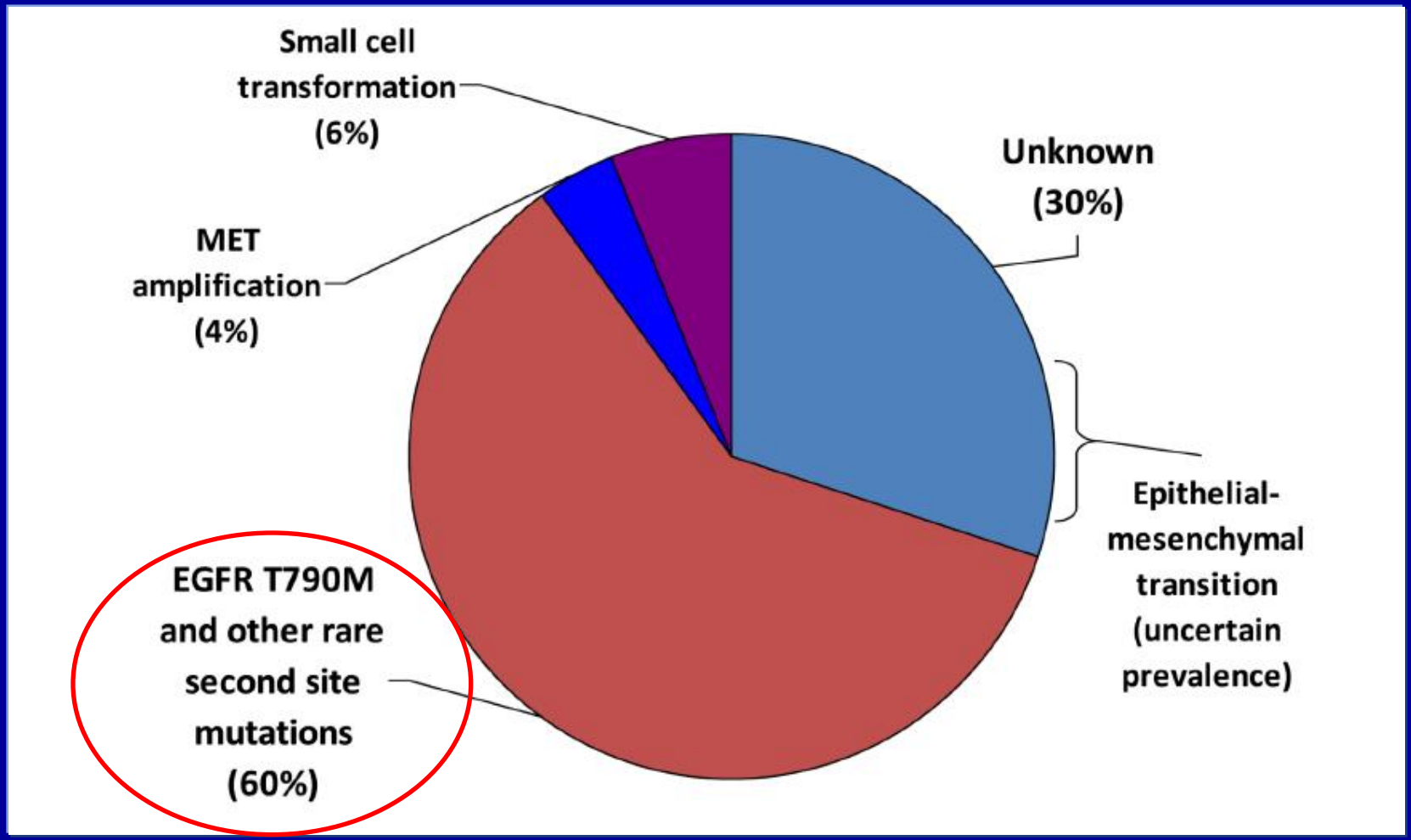
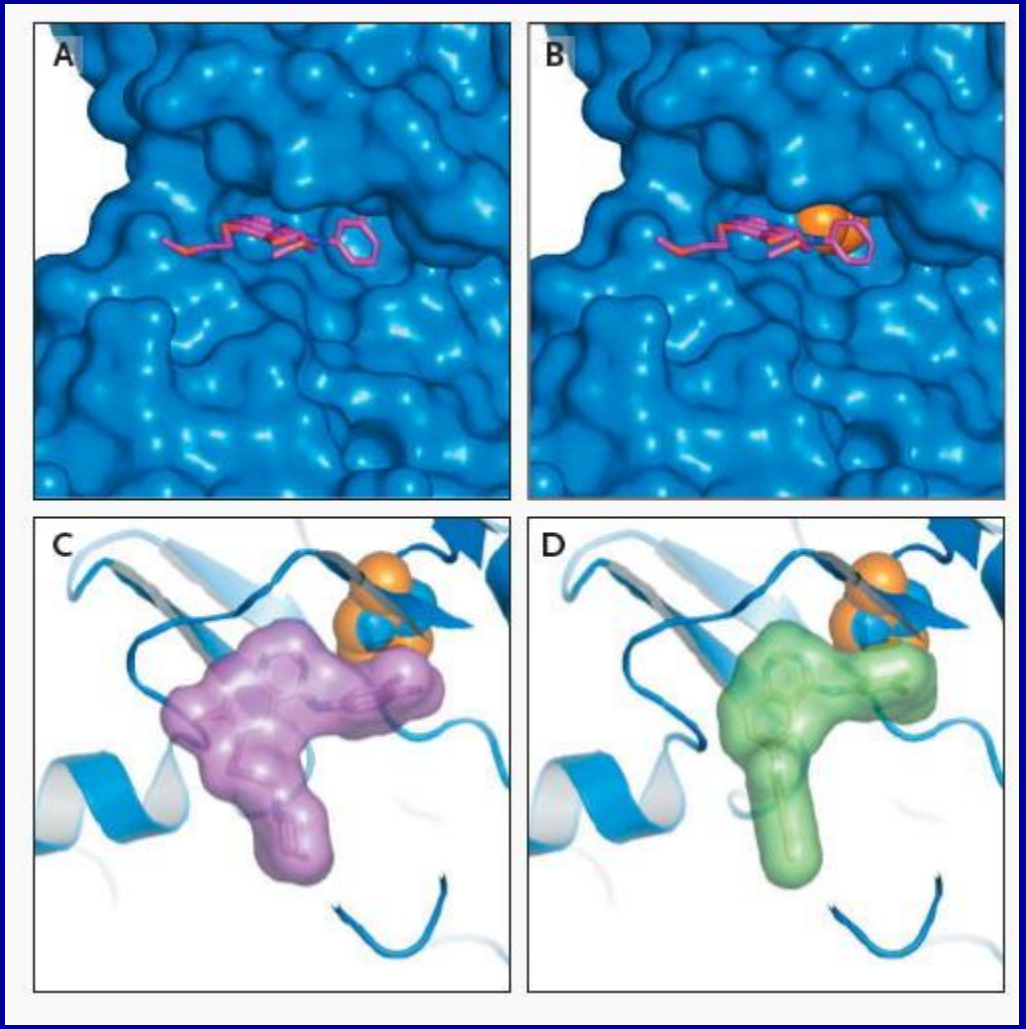
What we know about the mechanism of resistance?



Oxnard et al CCR 17:5530, 2011

Gatekeeper Mutation: T790M

- Acquired point mutation resulting in threonine-to-methioine amino acid change at positive 790



Kobayashi S NEJM 352:786, 2006

Incidence of de-novo T790M

Study	Technique	# cases / #EGFRm
Inukai , CR 2006	Sequencing Enriched PCR	1/98 (1%) 4/98 (4%)
Sequist, JCO 2008	Sequencing	2/34 (6%)
IPASS, NEJM 2009	SARMS	7/261 (3%)
Maheswaran, NEJM 2009	SARMS	10/36 (28%)
Rossell ASCO 2010	Taqman + PNA probe	45/129 (35%)
Hata, JTO, 2010	PNA-LNA clamp	3/318 (1%)

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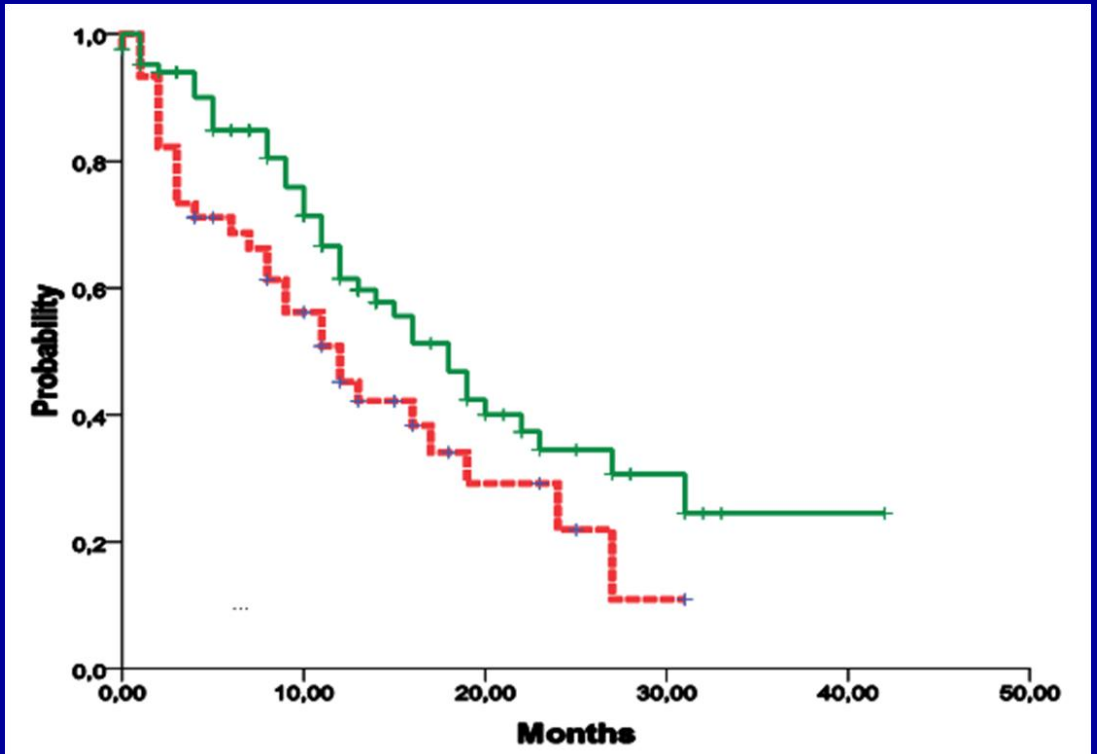
Is the difference in incidence explained by sensitivity of testing methods?

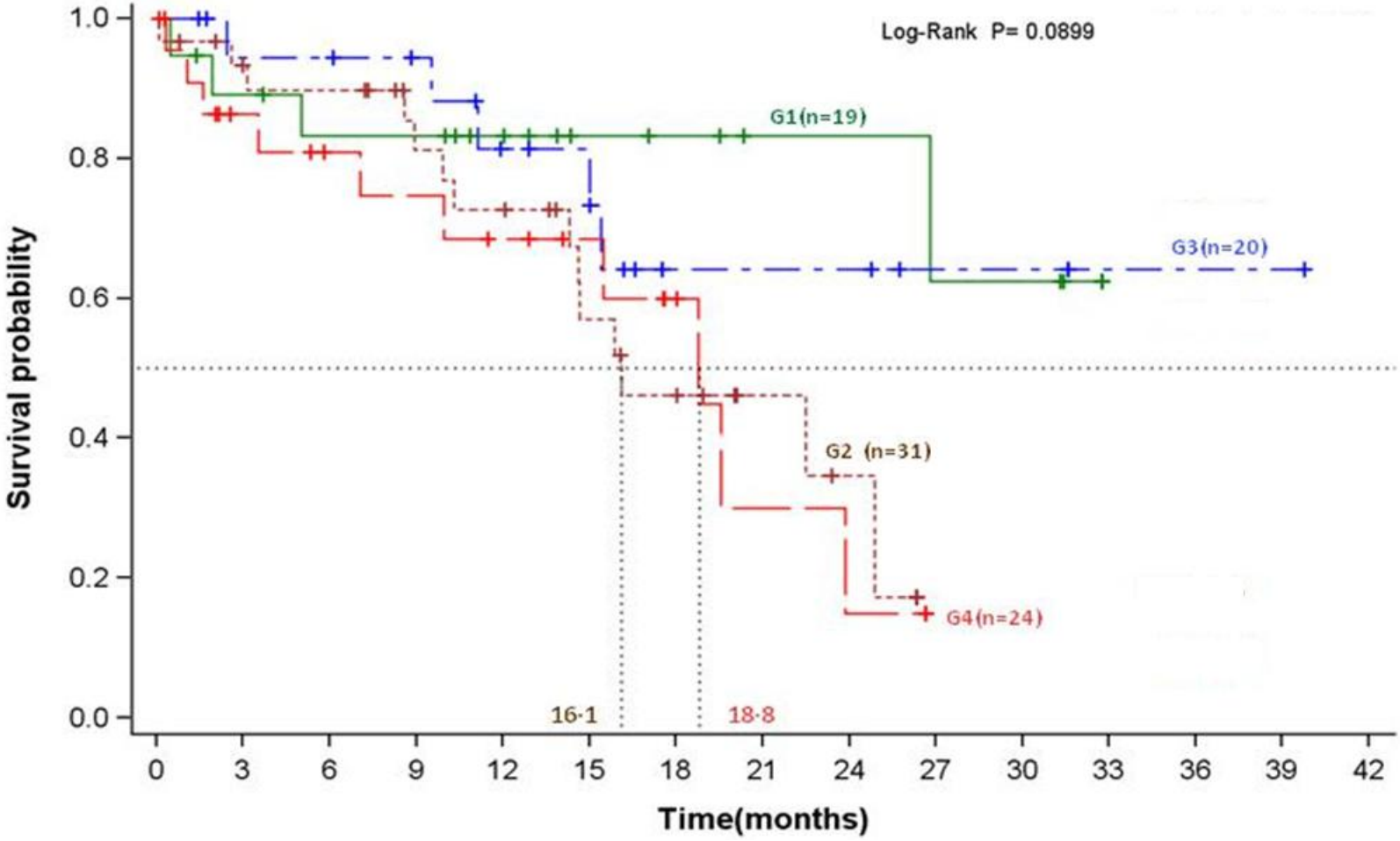
SLCG: Implication of de-novo T790M



	N	Median	95% CI	P Value
T790M positive	45	12	7.6-16.4	0.05(*)
T790M negative	84	18	14.1-21.9	

Rosell et al ASCO 2010

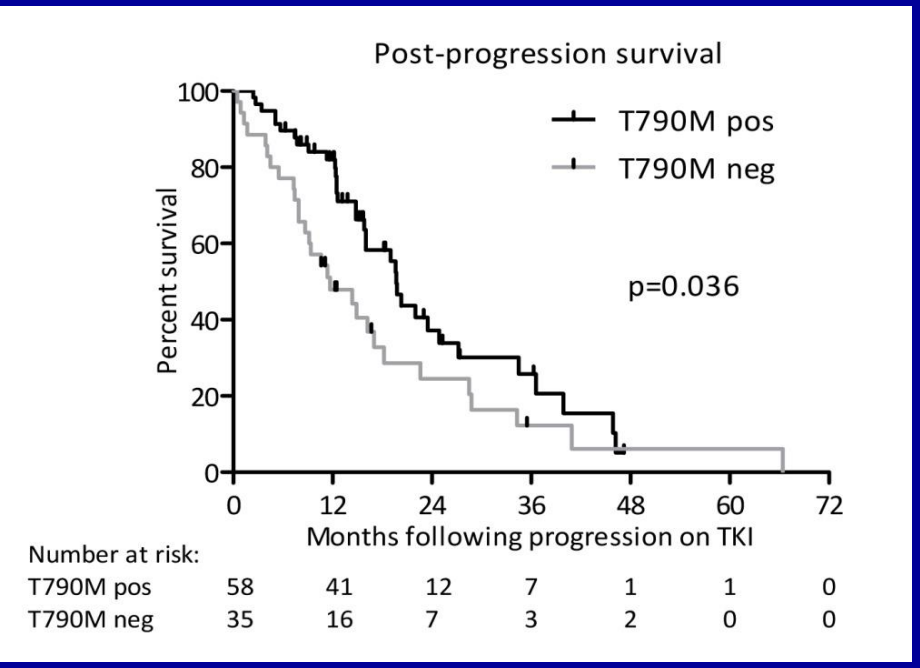
EURTAC: More favorable outcome in patients with de Novo T790M



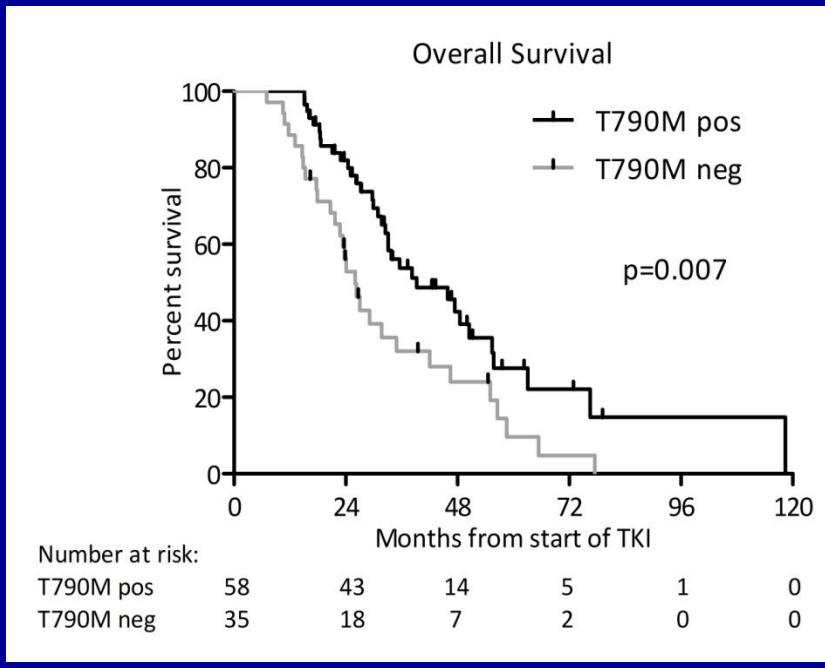
G1: patients on Erlotinib with	**T790M**	NA
G2: patients on Erlotinib with	**T790M absent**	16.1(14.3, 24.9)
G3: patients on Chemotherapy with	**T790M**	NA (15.0, NA)
G4: patients on Chemotherapy with	**T790M absent**	18.8 (7.1, 23.9)

Rosell ASCO 2012

Implication of “acquired T790M”



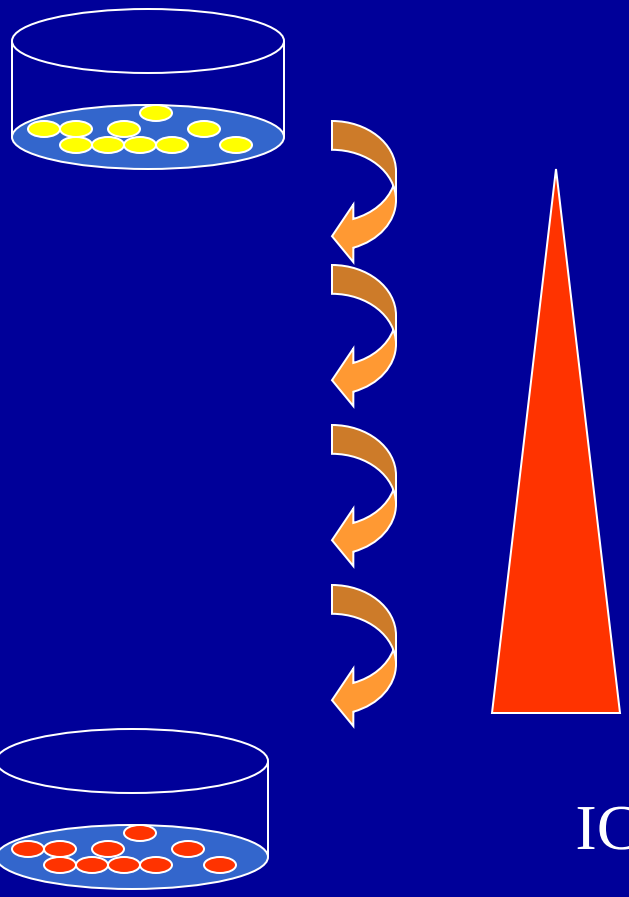
Median T790M pos = 19 months
Median T790M neg = 12 months



Median T790M pos = 39 months
Median T790M neg = 26 months

Oxnard et al CCR 17:1616, 2011

How we learnt about CMET overexpression: Generation of gefitinib *in vitro* resistant H3255



IC_{50} = 40 nM

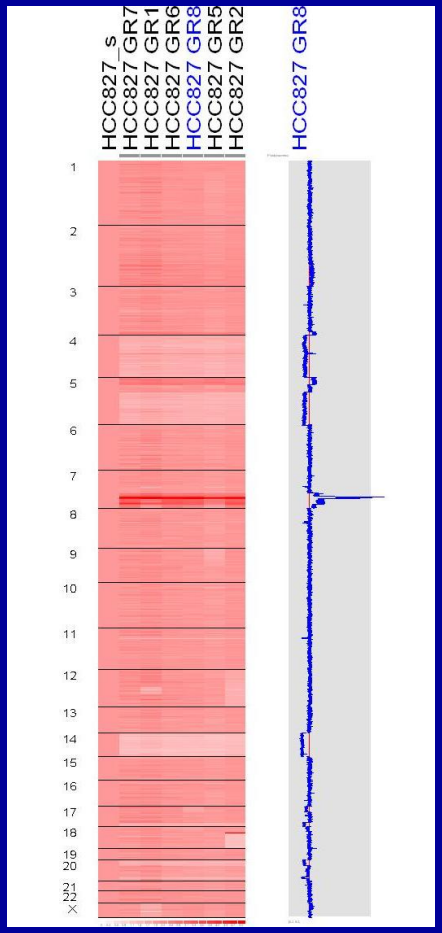
EGFR amplification ~20 fold

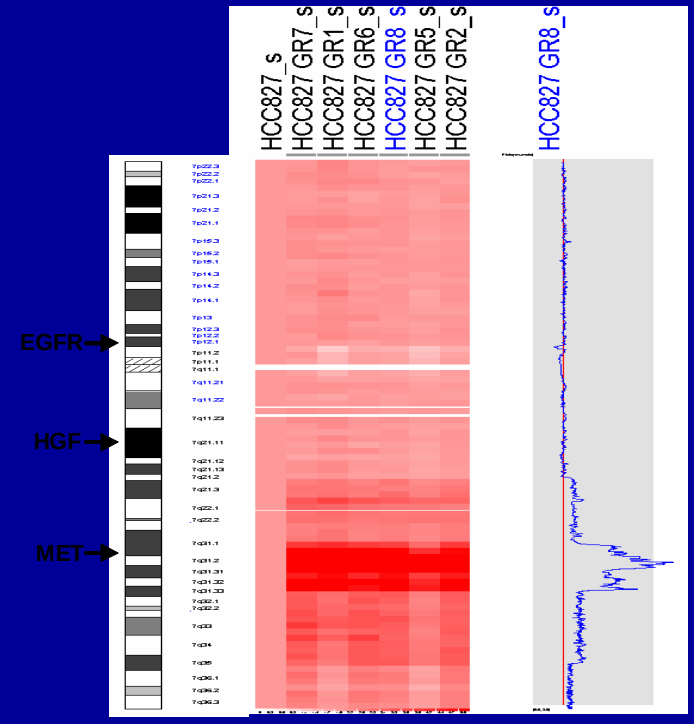
EGFR L858R mutation

Increasing gefitinib dose

IC_{50} > 10 μM

MET amplification



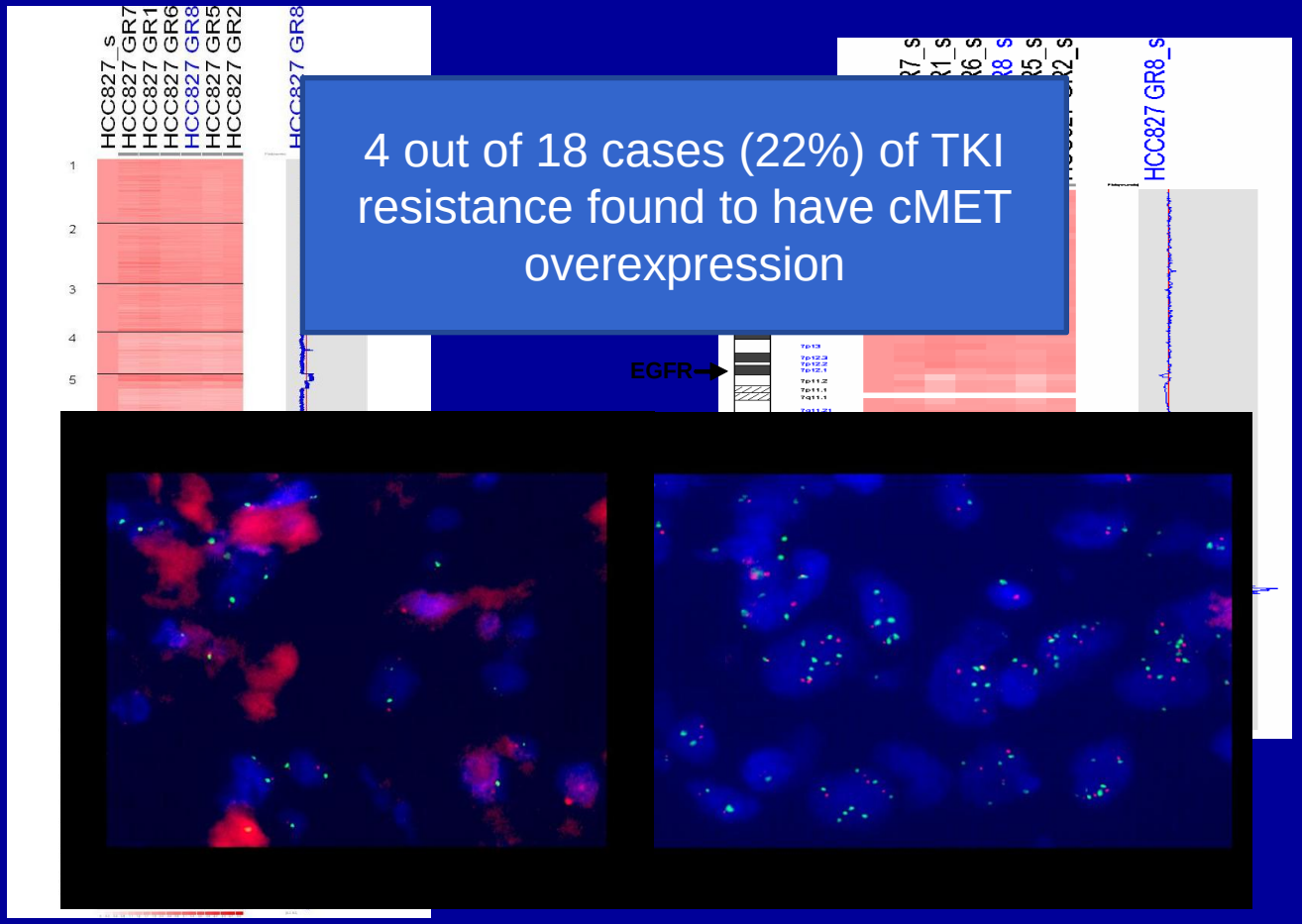


Chromosome 7

Confirmed by QPCR; no mutations detected in MET

Engelman et al. Science 2007

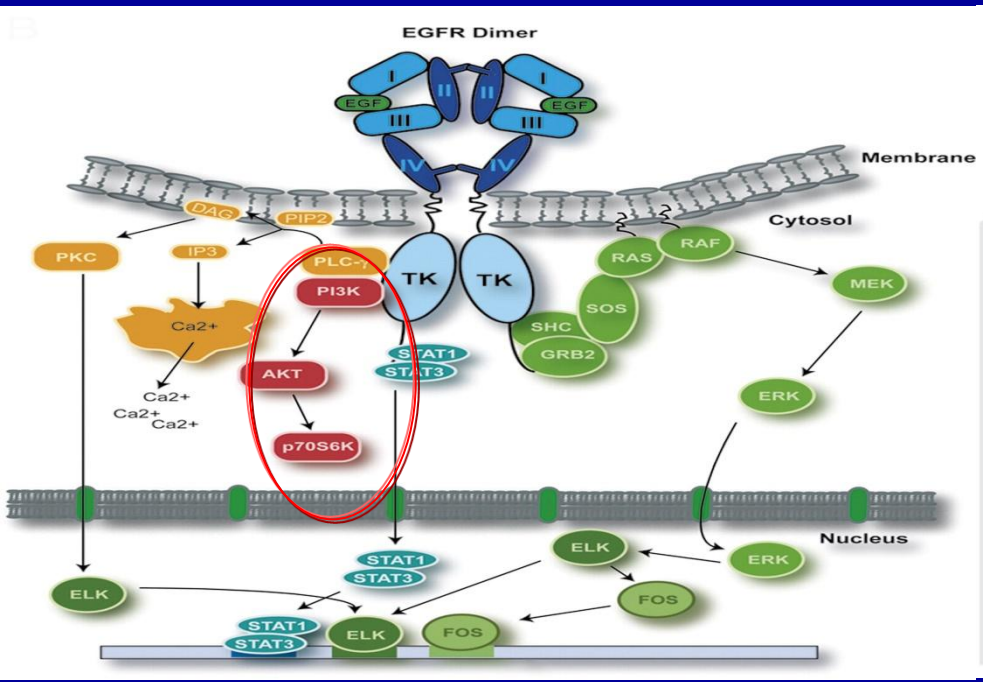
MET amplification

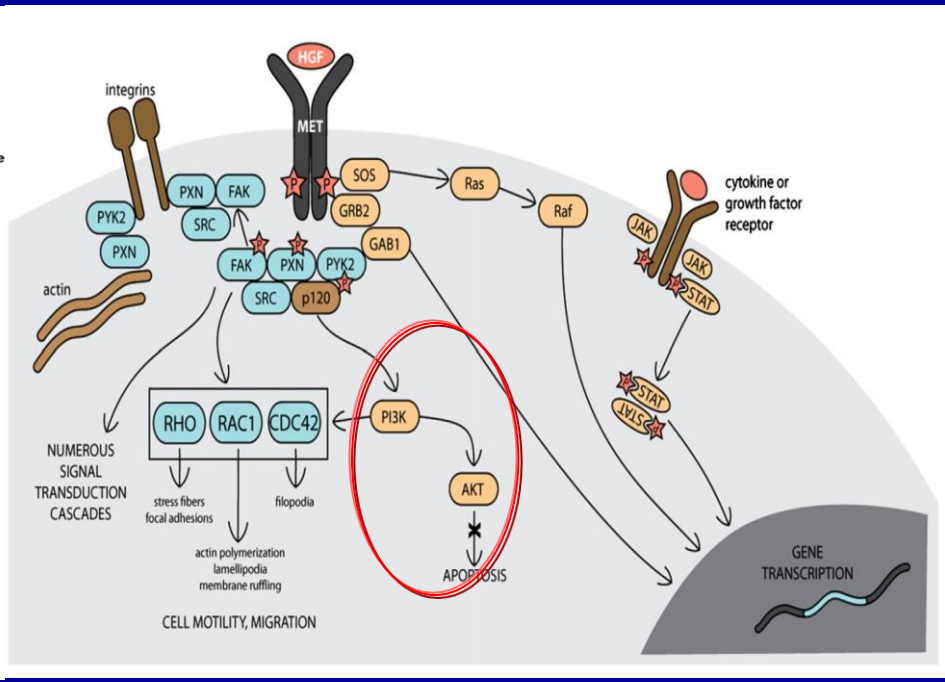


Confirmed by QPCR; no mutations detected in MET

Engelman et al. Science 2007

c-MET Receptor



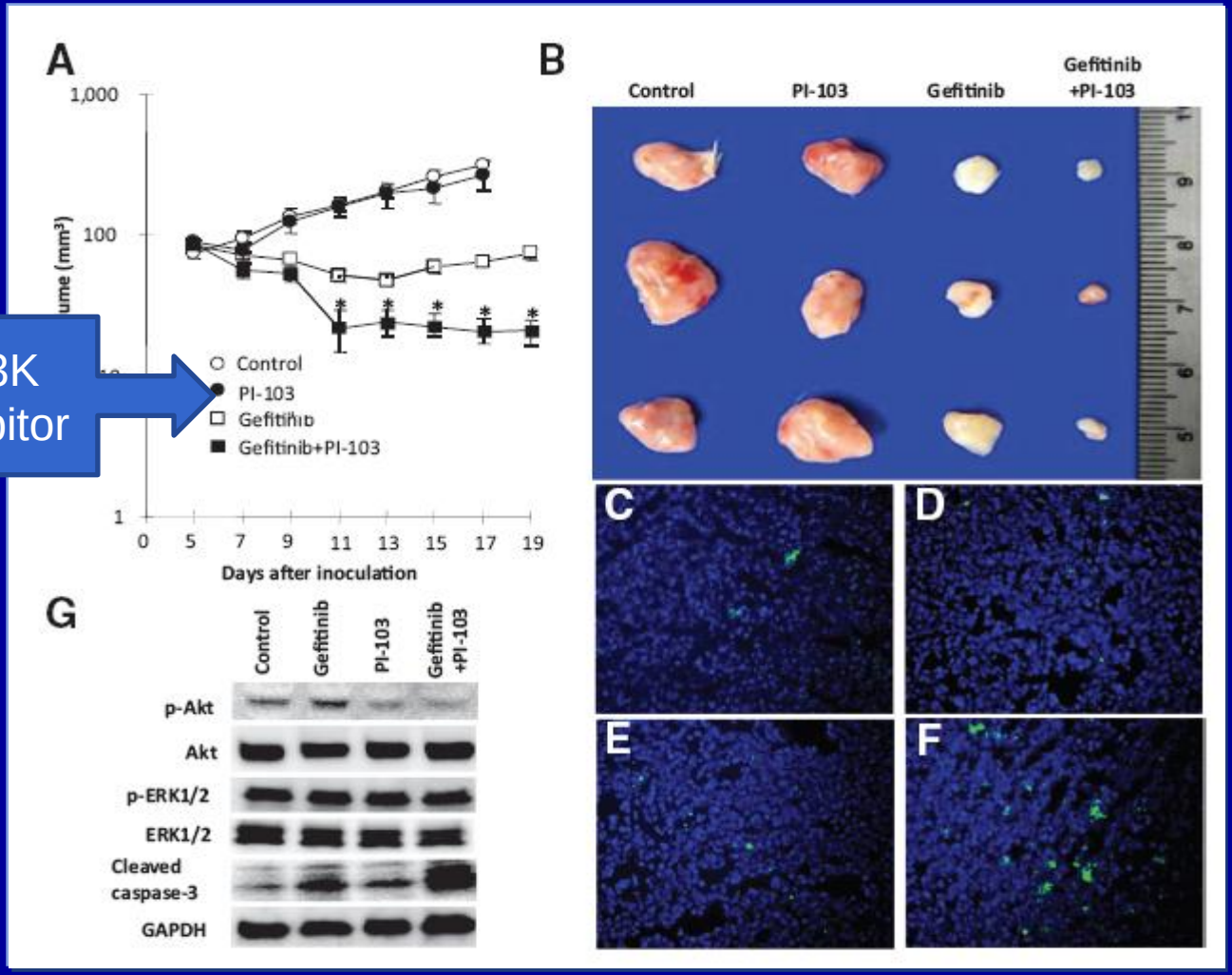


Abbreviations: EGFR, epidermal growth factor receptor; Grb2, growth factor receptor-bound protein 2; NSCLC, non-small cell lung cancer; SH2, src homology 2.

1. Birchmeier C and Gherardi E. *Trends Cell Biol.* 1998;8:404-410; 2. Cappuzzo F, et al. *J Clin Oncol.* 2009;27:1667-1674; 3. Engelman JA, et al. *Science.* 2007;316:1039–1043; 4. Bean J *et al*. *PNAS.* 2007;104:20932–20937.

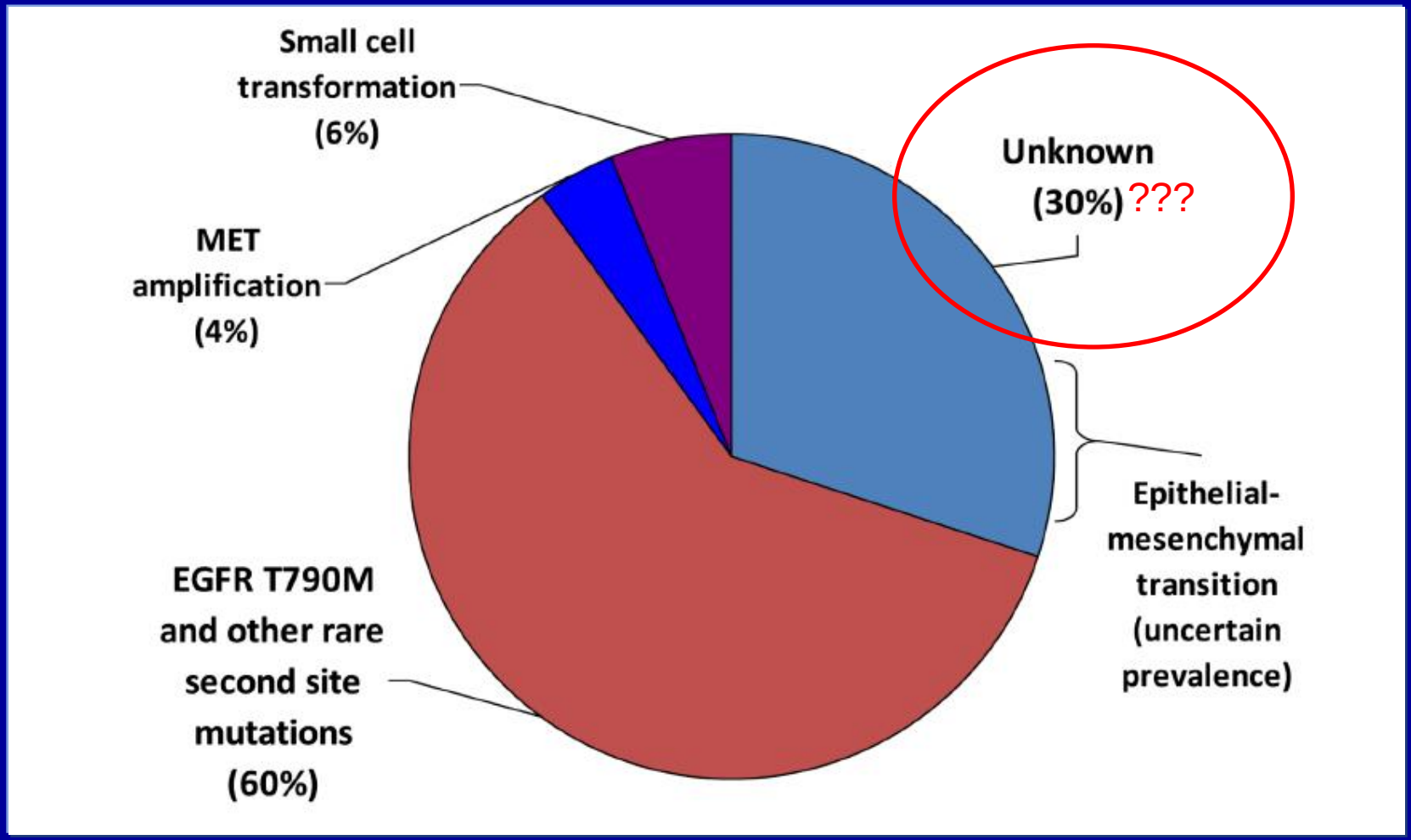
PI3K inhibition may overcome MET-induced resistance

PI3K inhibitor



Xu et al CCR 17:2260, 2011

What we know about the mechanism of resistance?



Oxnard et al CCR 17:5530, 2011

nature medicine

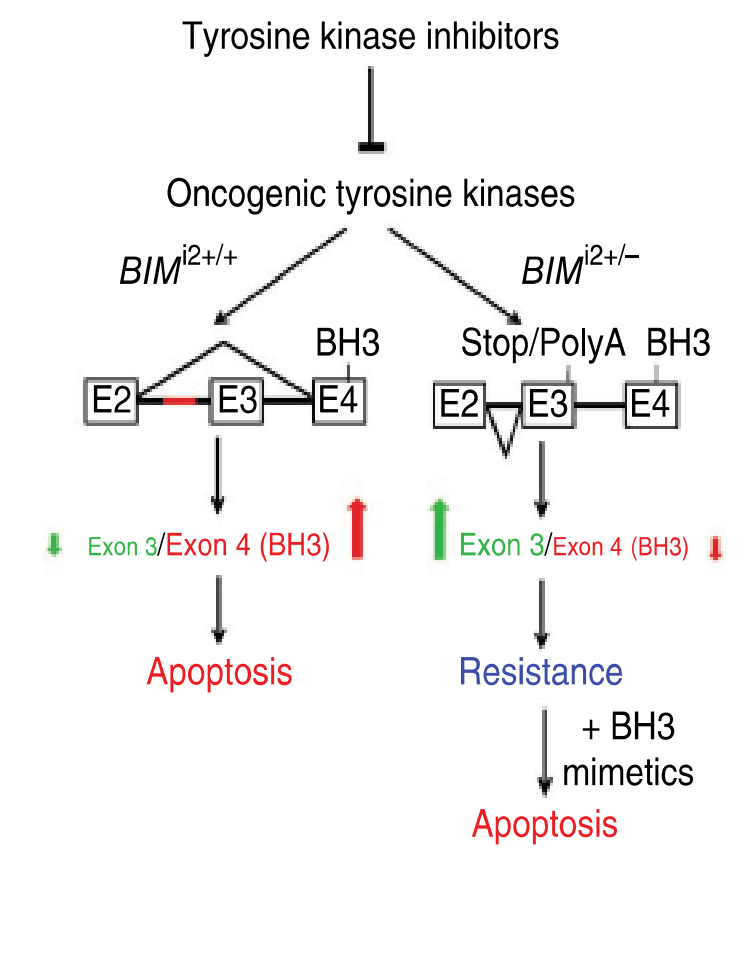
A common *BIM* deletion polymorphism mediates intrinsic resistance and inferior responses to tyrosine kinase inhibitors in cancer

King Pan Ng[1,23], Axel M Hillmer[2,23], Charles T H Chuah[1,3,23], Wen Chun Juan[1,23], Tun Kiat Ko[1], Audrey S M Teo[2], Pramila N Ariyaratne[2], Naoto Takahashi[4], Kenichi Sawada[4], Yao Fei[2,5], Sheila Soh[1], Wah Heng Lee[2], John W J Huang[1], John C Allen Jr[6], Xing Yi Woo[2], Niranjan Nagarajan[2], Vikrant Kumar[2], Anbupalam Thalamuthu[2], Wan Ting Poh[2], Ai Leen Ang[3], Hae Tha Mya[3], Gee Fung How[3], Li Yi Yang[3], Liang Piu Koh[7], Balram Chowbay[8], Chia-Tien Chang[1], Veera S Nadarajan[9], Wee Joo Chng[7,10,11], Hein Than[3], Lay Cheng Lim[3], Yeow Tee Goh[3], Shenli Zhang[1], Dianne Poh[1], Patrick Tan[1,2,11], Ju-Ee Seet[12], Mei-Kim Ang[13], Noan-Minh Chau[13], Quan-Sing Ng[13], Daniel S W Tan[13], Manabu Soda[14], Kazutoshi Isobe[15], Markus M Nöthen[16], Tien Y Wong[17], Atif Shahab[2], Xiaoan Ruan[2], Valère Cacheux-Rataboul[2], Wing-Kin Sung[2], Eng Huat Tan[13], Yasushi Yatabe[18], Hiroyuki Mano[14,19], Ross A Soo[7,11], Tan Min Chin[7], Wan-Teck Lim[13,20], Yijun Ruan[2,21] & S Tiong Ong[1,3,13,22]

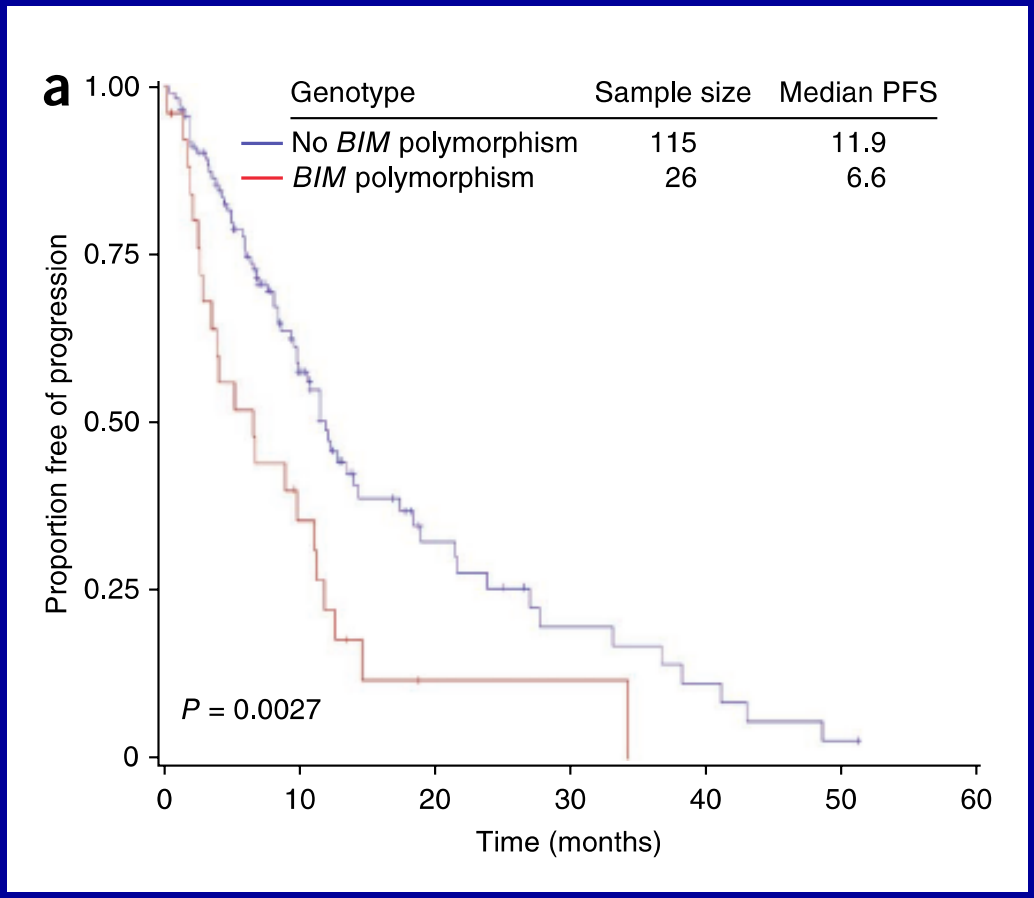
Nature Medicine 18(8):521, 2012

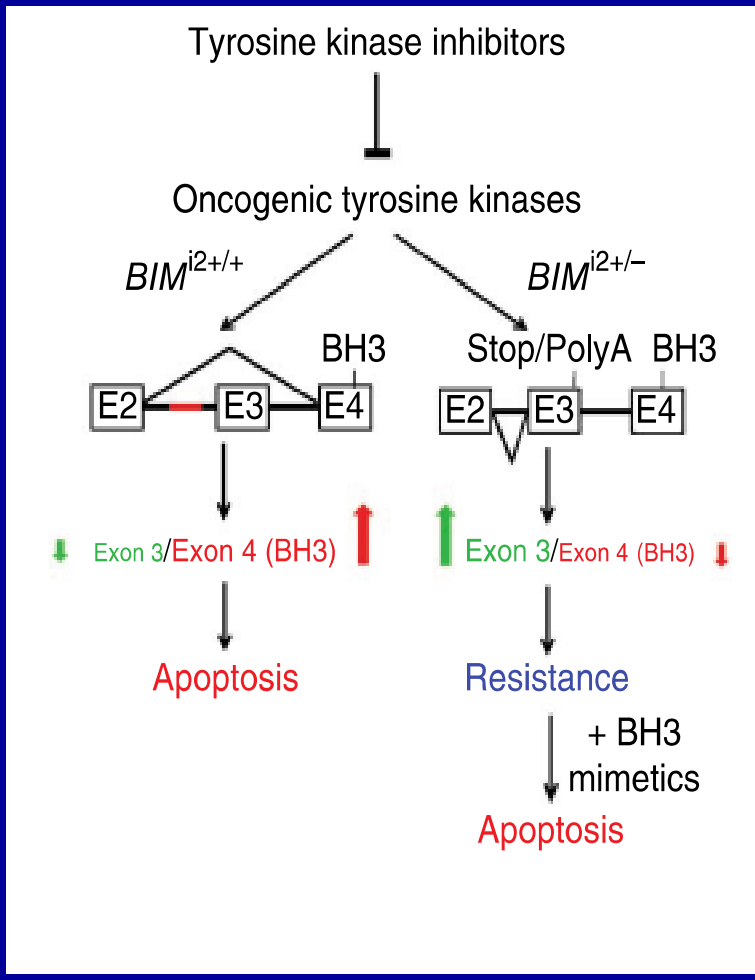
BIM (BCL-2 Like 11)

- BIM is a member of the pro-apoptotic protein
- BIM is essential in TKI induced apoptosis
- Polymorphism existed and may splice from exon 4 to exon 3, and result in low expression of the functional isoform (BH3)
- Reduced BH3 implies less apoptosis, thus resistance to TKI



BIM (BCL-2 Like 11)

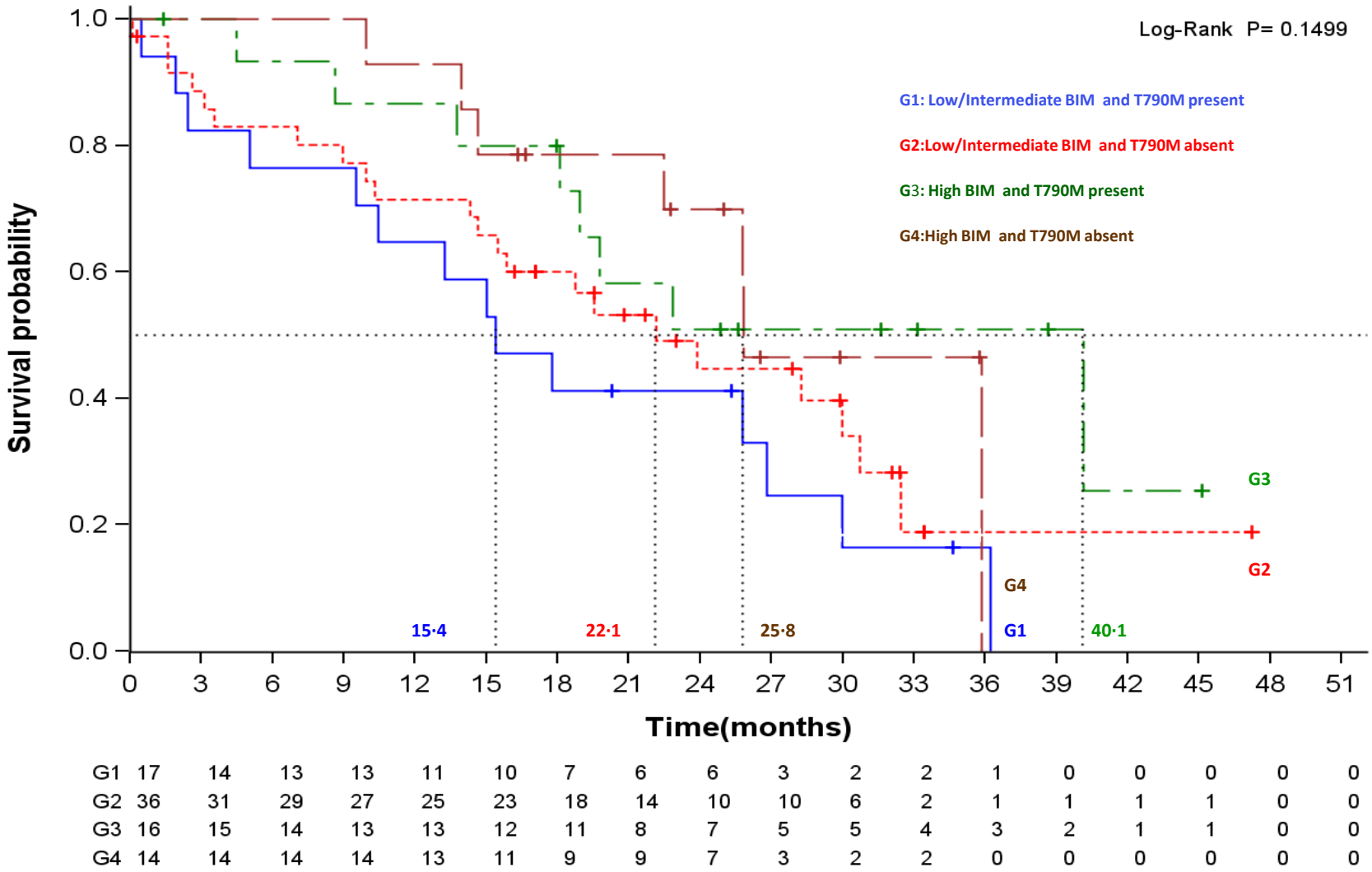




EURTAC Biomarker Study

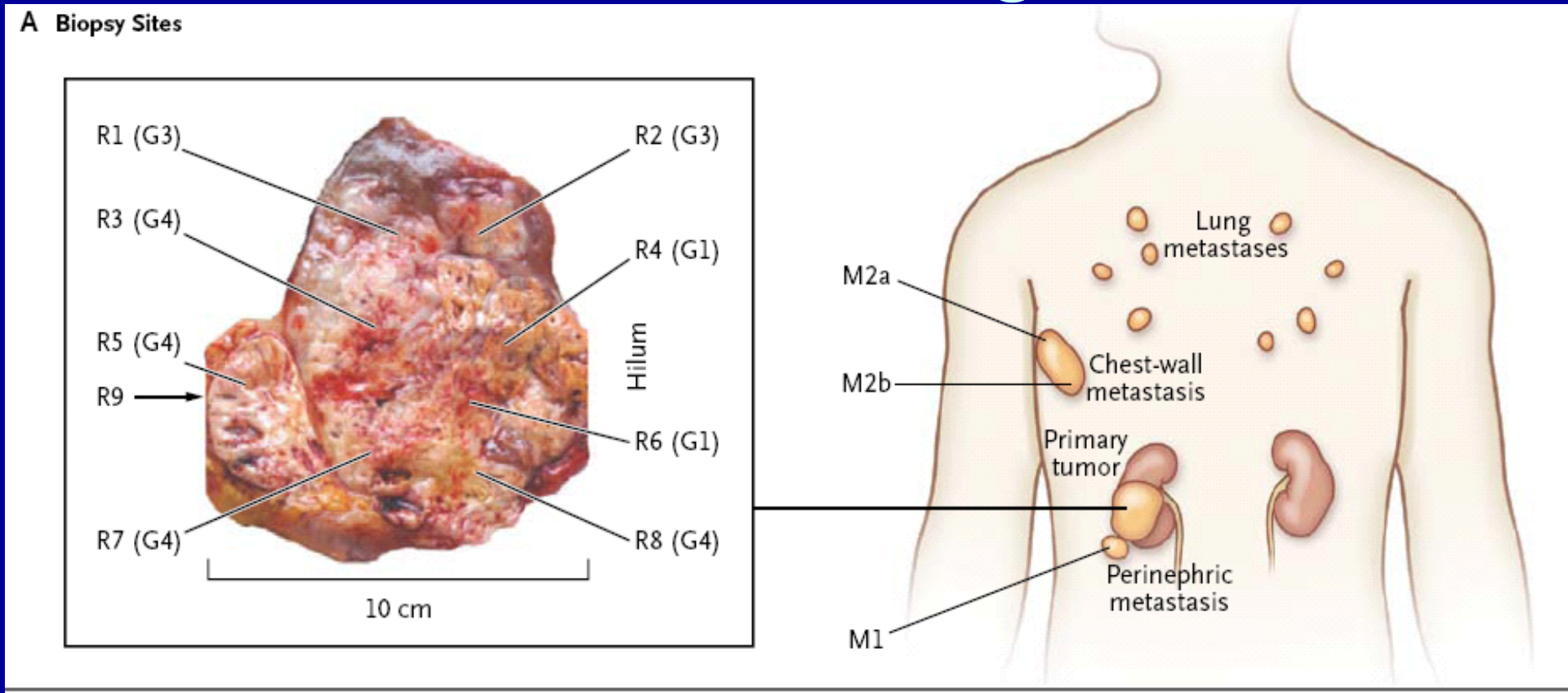
- 95 patients from EURTAC (EGFR Mutation) with available samples
- Biomarkers: ELM4 ALK, T790M, TP53, BIM

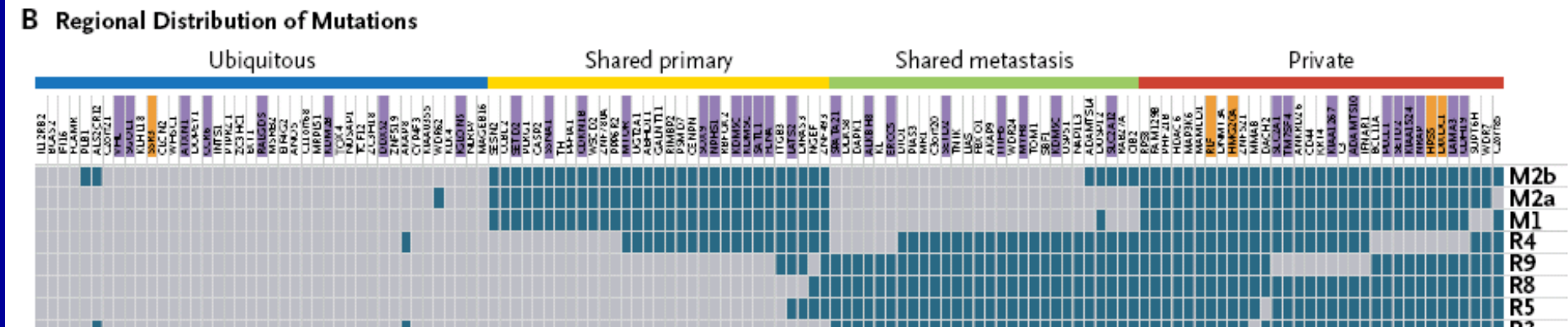
Potential biomarker of a biomarker selected population: T790M mutation status and BIM mRNA levels



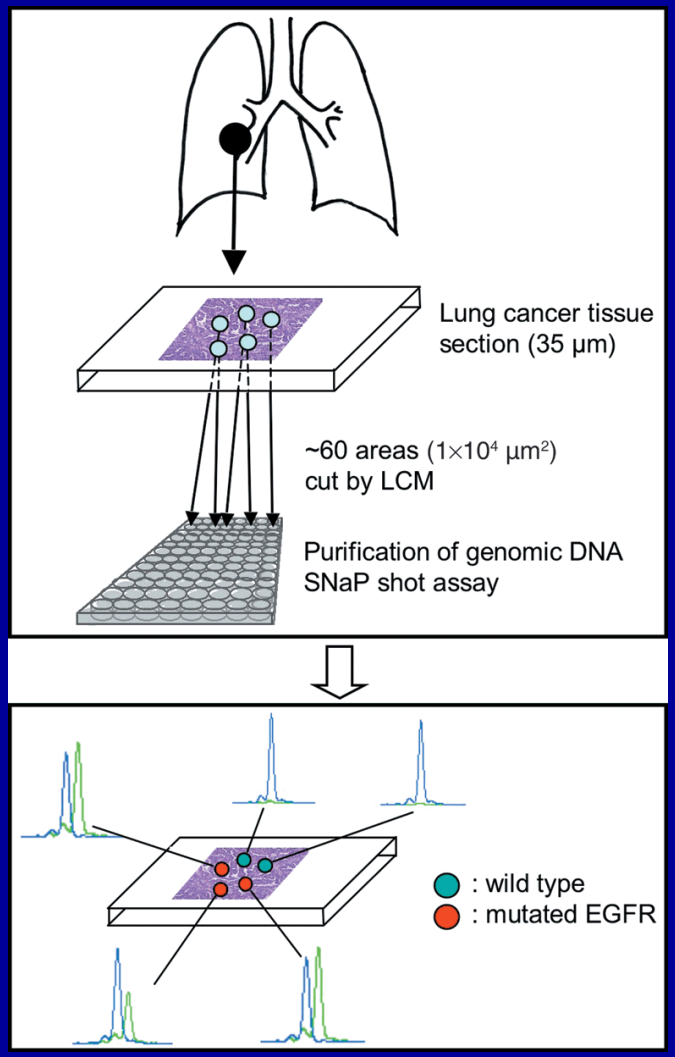
Rosell et al ESMO 2012

Cancer is heterogenous





Early finding of intratumor heterogeneity in lung cancer



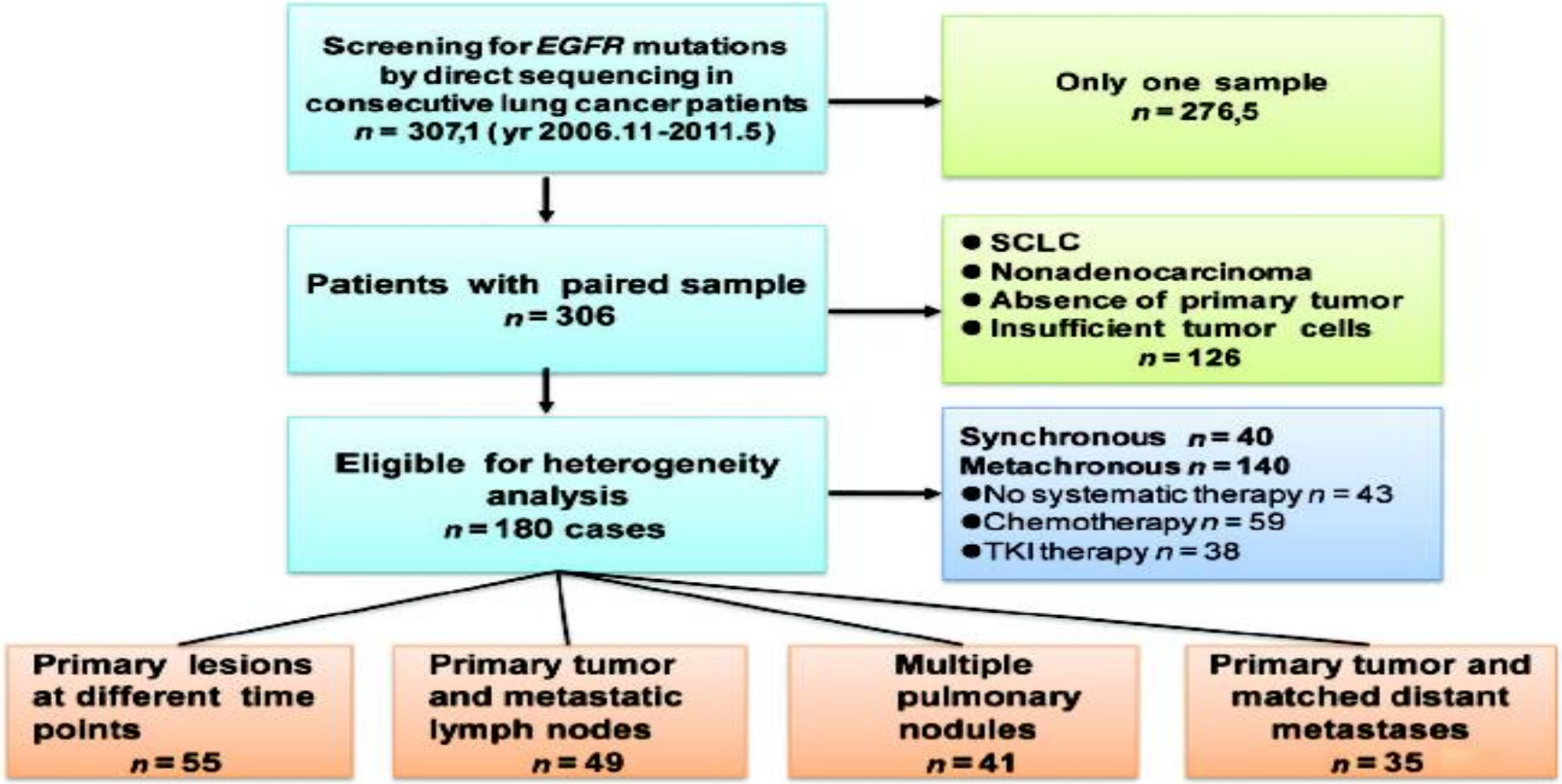
- **Twenty-one patients with recurrent EGFR mutation positive lung cancer**
- **Surgical specimens were retrieved from archive**
- **Using laser capture microdissection and analyzed 50–60 areas from each tissue**
- **Fifteen tissues consisted only of cells with EGFR mutations**
- **Six tissues contained both mutated and non-mutated cells.**

Taniguchi K, Cancer Sci, 2008 May;99(5):929-35

The Oncologist®

EGFR Mutation Heterogeneity and the Mixed Response to EGFR Tyrosine Kinase Inhibitors of Lung Adenocarcinomas

ZHI-YONG CHEN,[a] WEN-ZHAO ZHONG,[a] XU-CHAO ZHANG,[a] JIAN SU,[a] XUE-NING YANG,[a] ZHI-HONG CHEN,[a] JIN-JI YANG,[a] QING ZHOU,[a] HONG-HONG YAN,[a] SHE-JUAN AN,[a] HUA-JUN CHEN,[a] BEN-YUAN JIANG,[a] TONY S. MOK,[b] YI-LONG WU[a]

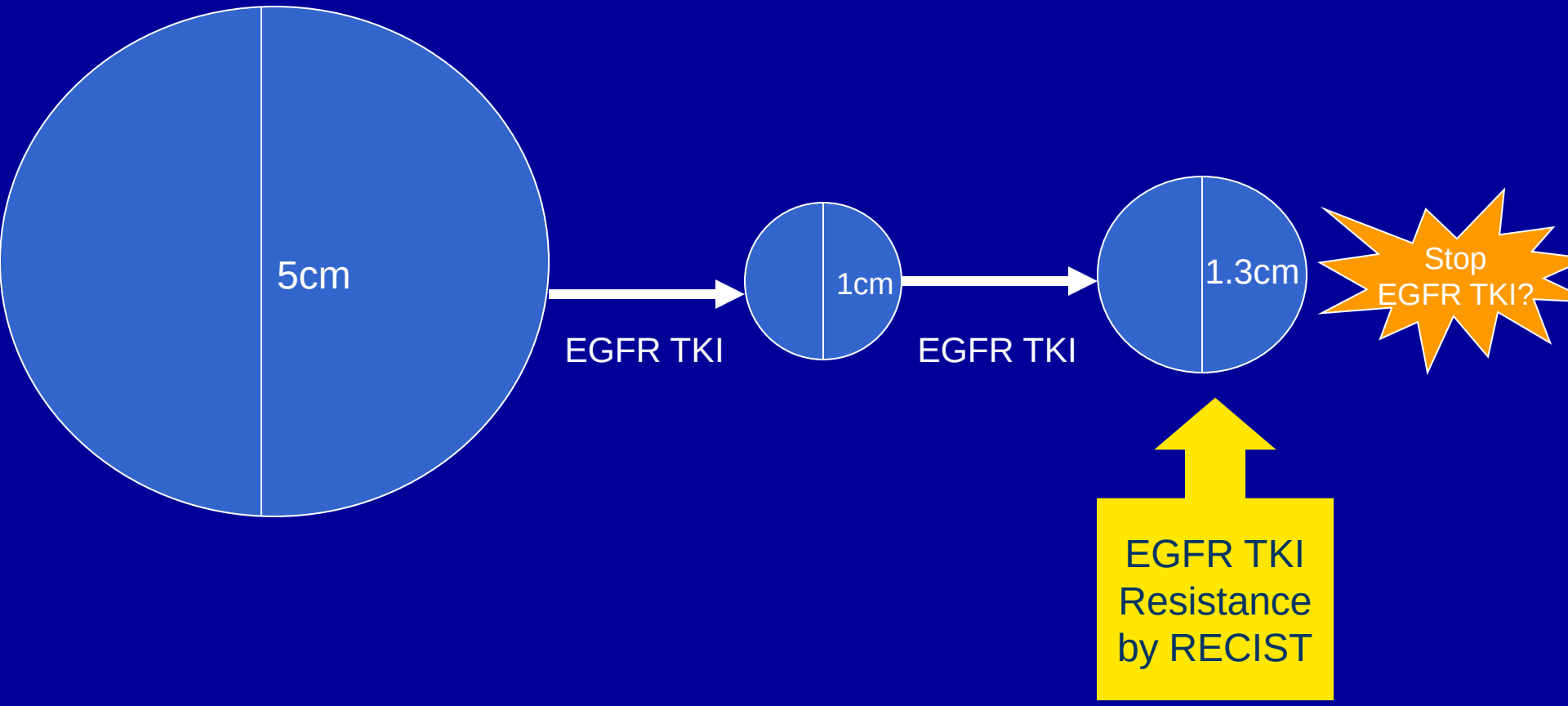


A.

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

How to manage TKI resistance?

Problem with RECIST Criteria as definition of resistance



Cessation of EGFR TKI upon progression

Table 3. Changes in tumor on CT and FDG-PET

	After stopping gefitinib or erlotinib	After restarting gefitinib or erlotinib	3 wks after adding everolimus
Median change in tumor diameter	+9%	-1%	-8%
Mean change in tumor diameter	+9%	1%	-9%
Range in change in tumor diameter	-13% to +29%	-14% to +23%	-34% to +15%
Median change in tumor volume	+50%	-1%	-11%
Mean change in tumor volume	+61%	-4%	-10%
Range in change in tumor volume	-4% to +260%	-27% to 15%	-40% to +26%
Median change in SUV_{max}	+18%	-4%	-18%
Mean change in SUV_{max}	+23%	-11%	-11%
Range in change in SUV_{max}	-17% to +87%	-45% to +62%	-39% to +82%

Riely et al Clin Can Res 13:5150, 2007

Cessation of EGFR TKI upon progression

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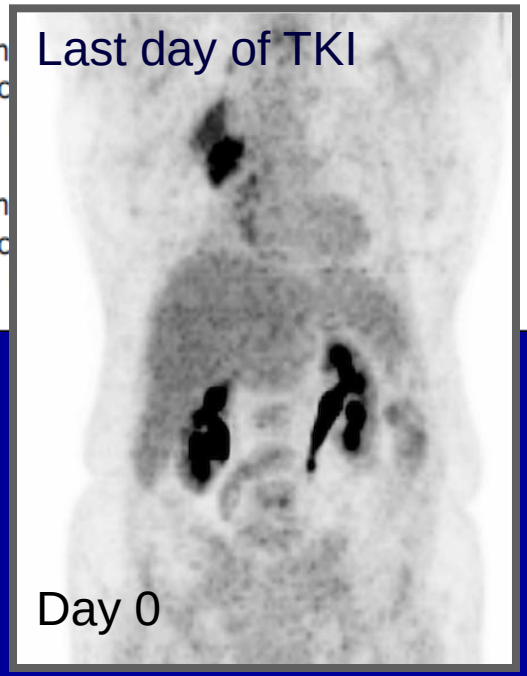
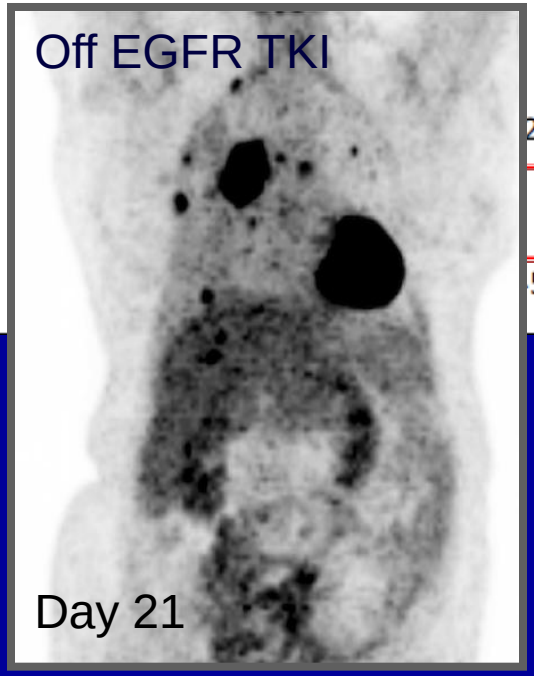
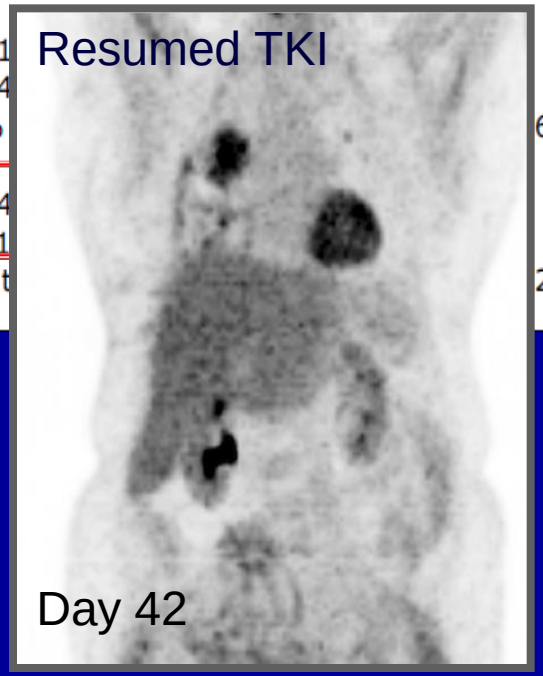
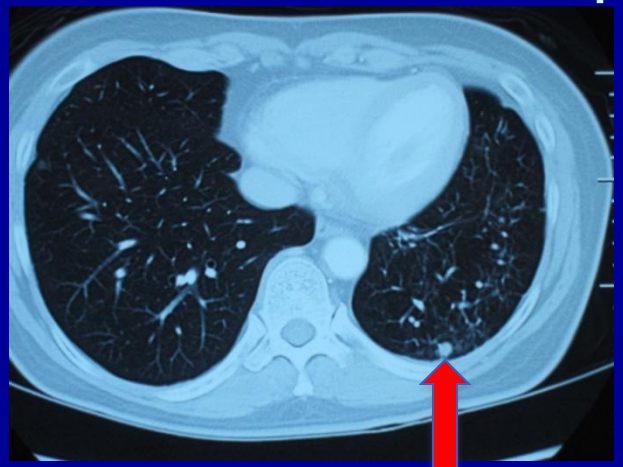




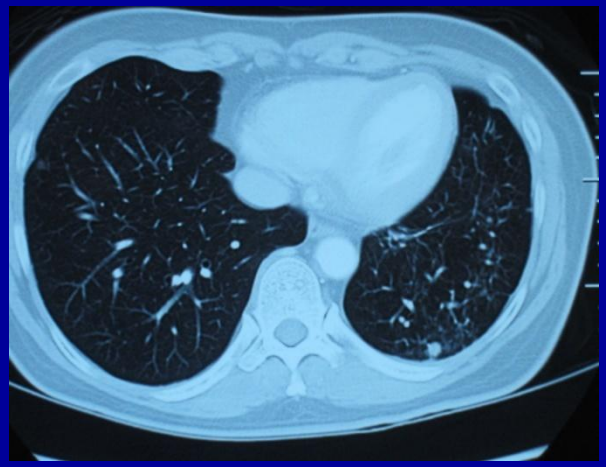


Riely et al Clin Can Res 13:5150, 2007

45 Female treated with Geftinib for exon 19 mutation positive disease since 2005



Aug 2008



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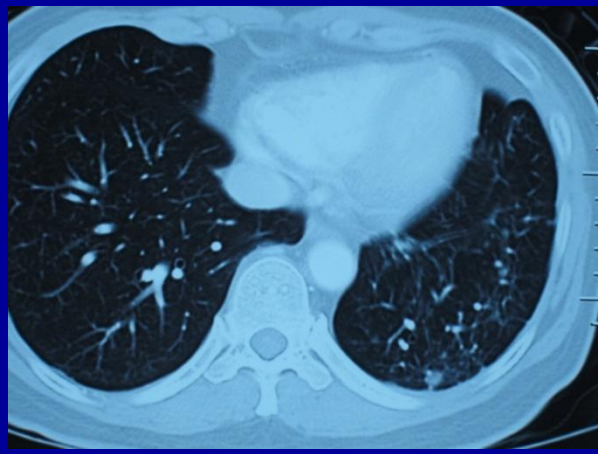
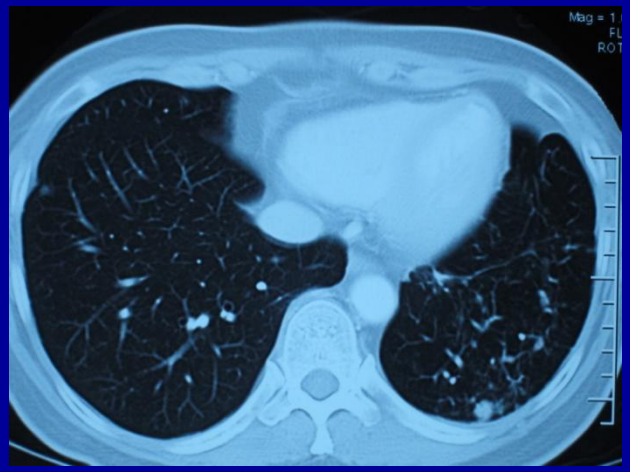
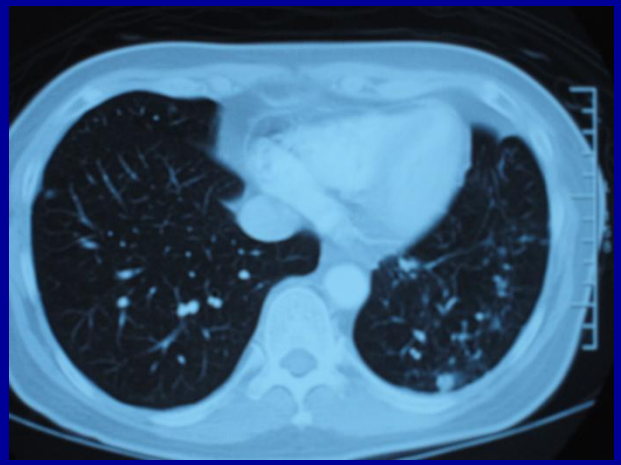


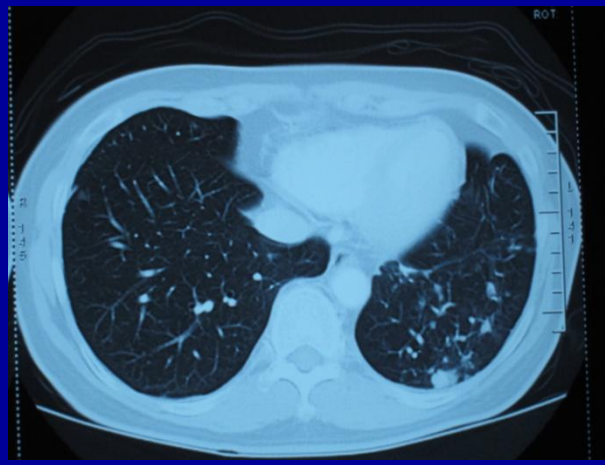
Apr 2009



Aug 2009

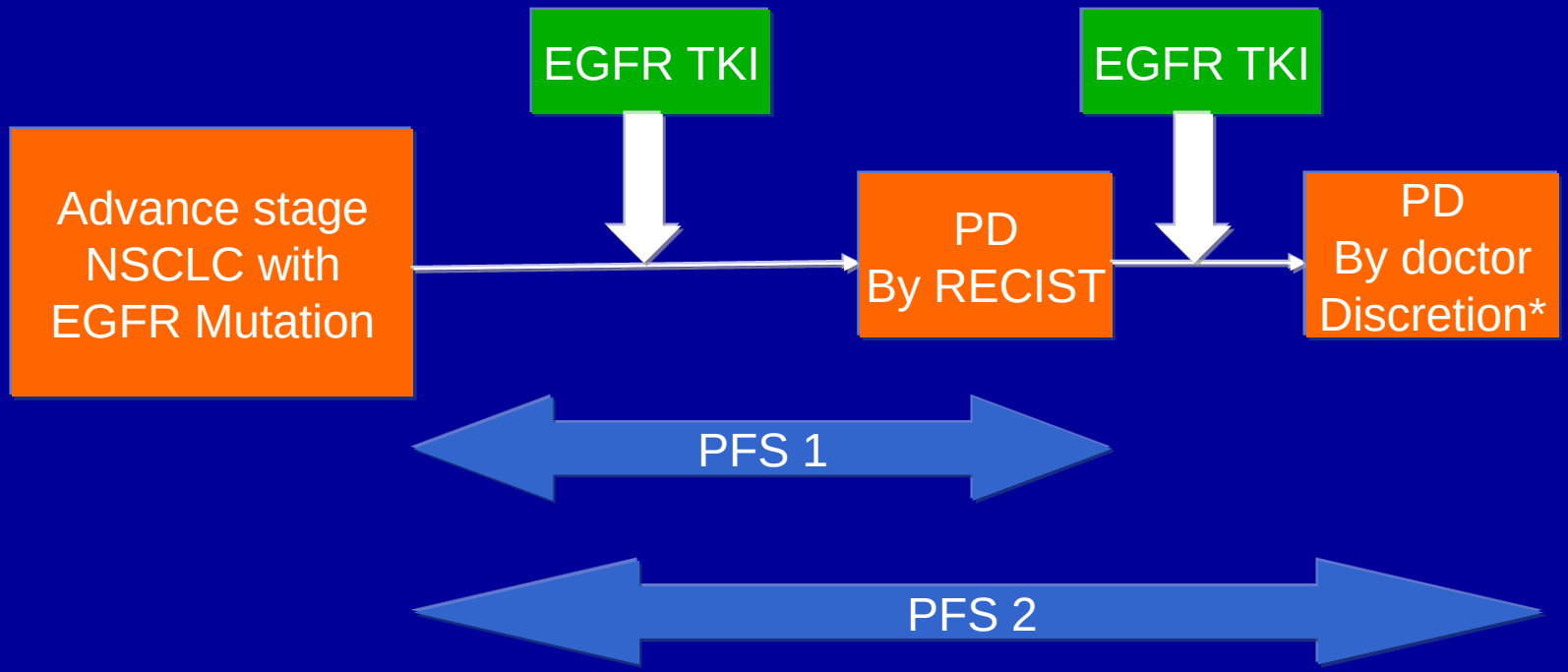


Dec 2009



May 2010

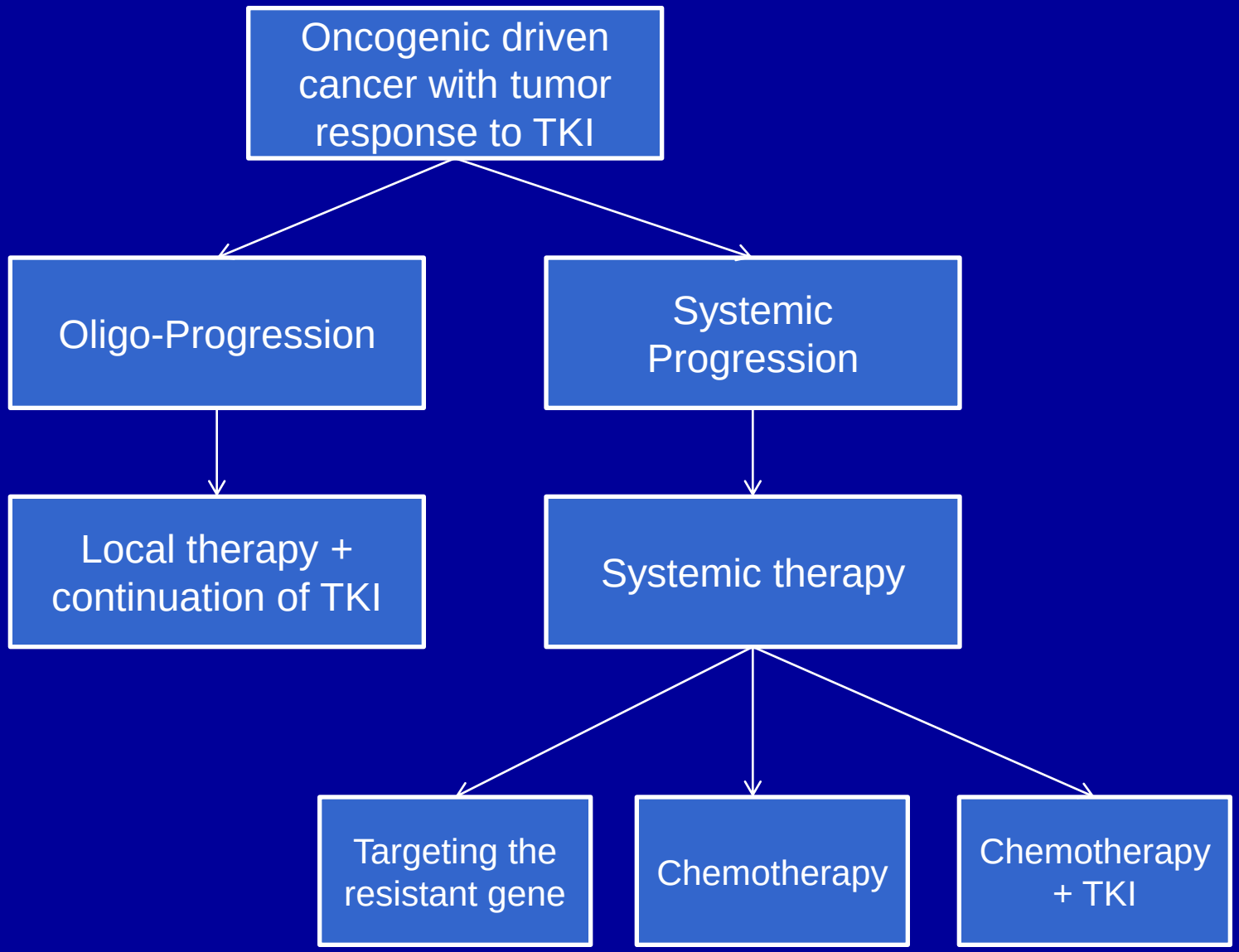
ASPIRATION: To optimize treatment duration



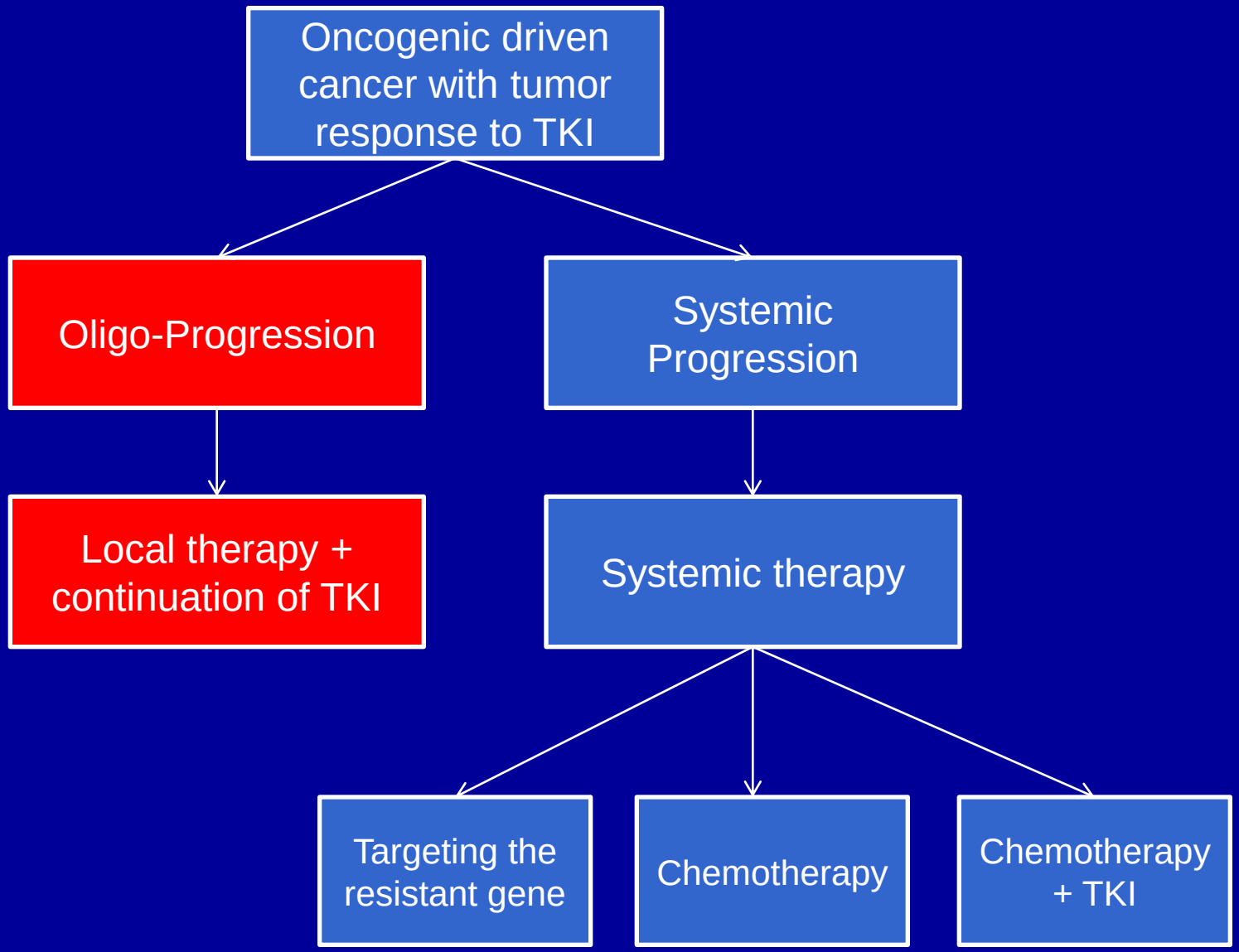
*Doctor Discretion: Symptomatic progression, multiple progression
Threat to major organ…etc

PI: K Park

Treatment of TKI Resistance

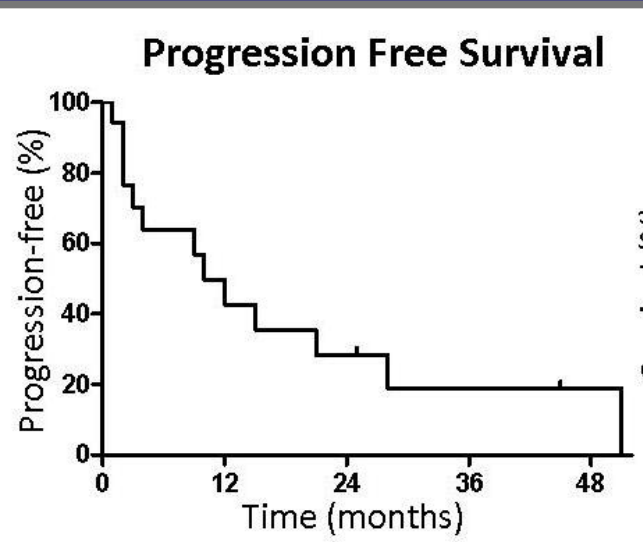


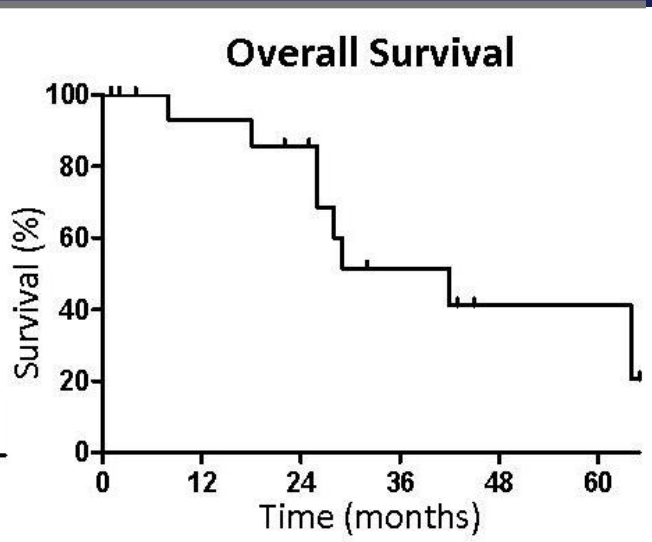
Treatment of TKI Resistance



Local Therapy in Acquired Resistance: MSKCC

- 18/184 pts/7+ yrs underwent local therapy for extracranial PD
  - CNS PD excluded
- From time of local therapy
  - Median TTP: 10 months
  - Median time to new systemic Rx: 22 months
  - Median OS: 41 months





Local Therapy Procedures	
Procedures Performed	18
Lung	15
Radiofrequency ablation	2
Radiation	2
Lobectomy	7
Wedge resection	1
Pneumonectomy	3
Lymph node- Radiation (mediastinum, supraclavicular lymph nodes)	1
Adrenals- Adrenalectomy	2

Yu, ASCO 2012, Abst#7527

Local treatment to oligo-progression plus continuation of TKI

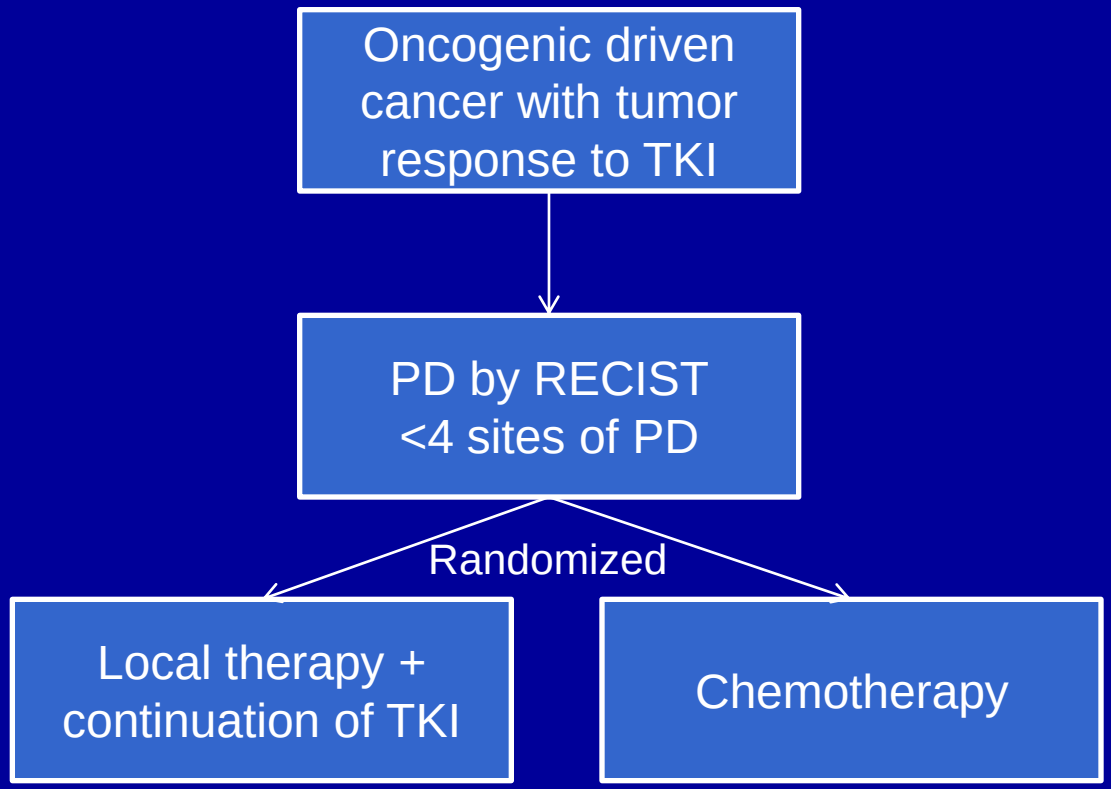
- Colorado University collection of 65 patients with oncogenic driven cancer (EGFR mutation or ALK positive)
- All received EGFR TKI or Crizotinib
- PFS 1 defined as <4 sites of progression
  - Local ablative therapy offered to all sites of involvement and continue TKI
- PFS 2 defined as from time of local therapy to second progression

PFS of patients treated with LAT and continuation of TKI therapy

Site of first progression	Number of patients	PFS1 (months)(95% CI)	PFS2 (months)(95% CI)	Site of 2nd progression	
CNS	10	10.9 7.3 – 18.3	**7.1** 1.7 – 11.3	2 (20%)	no prog
				3 (30%)	CNS
				5 (50%)	eCNS
eCNS†	15	9.0 6.5 – 13.8	**4.0** 2.7 -7.4	4 (27%)	no prog
				3 (20%)	CNS
				8 (53%)	eCNS
All patients	25	9.8 8.8 – 13.8	**6.2** 3.7 – 8.0	6 (24%)	no prog
				7 (28%)	CNS
				12 (48%)	eCNS

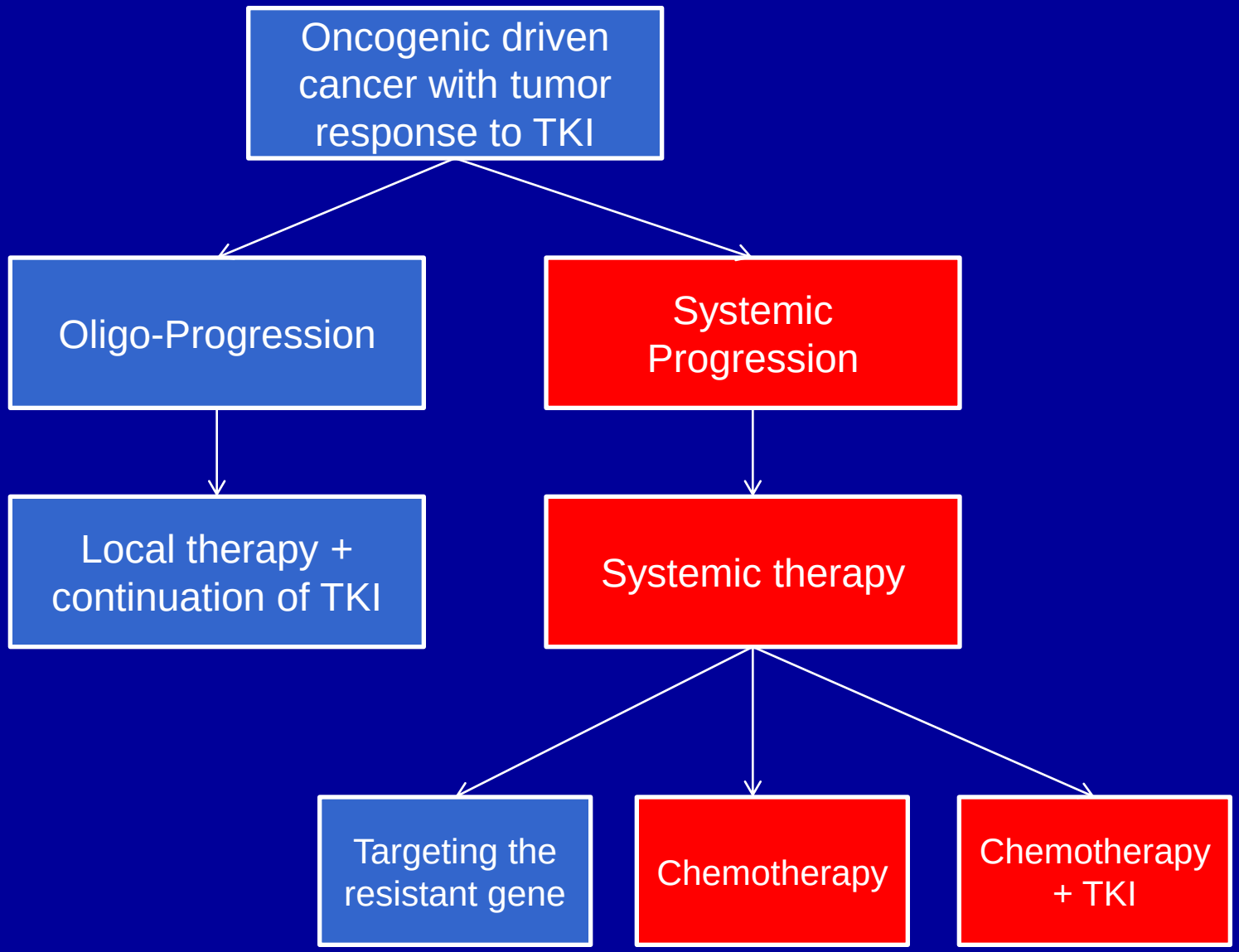
† Includes 3 patients who progressed systemically (eCNS) and simultaneously within the CNS

Future Prospective Study?

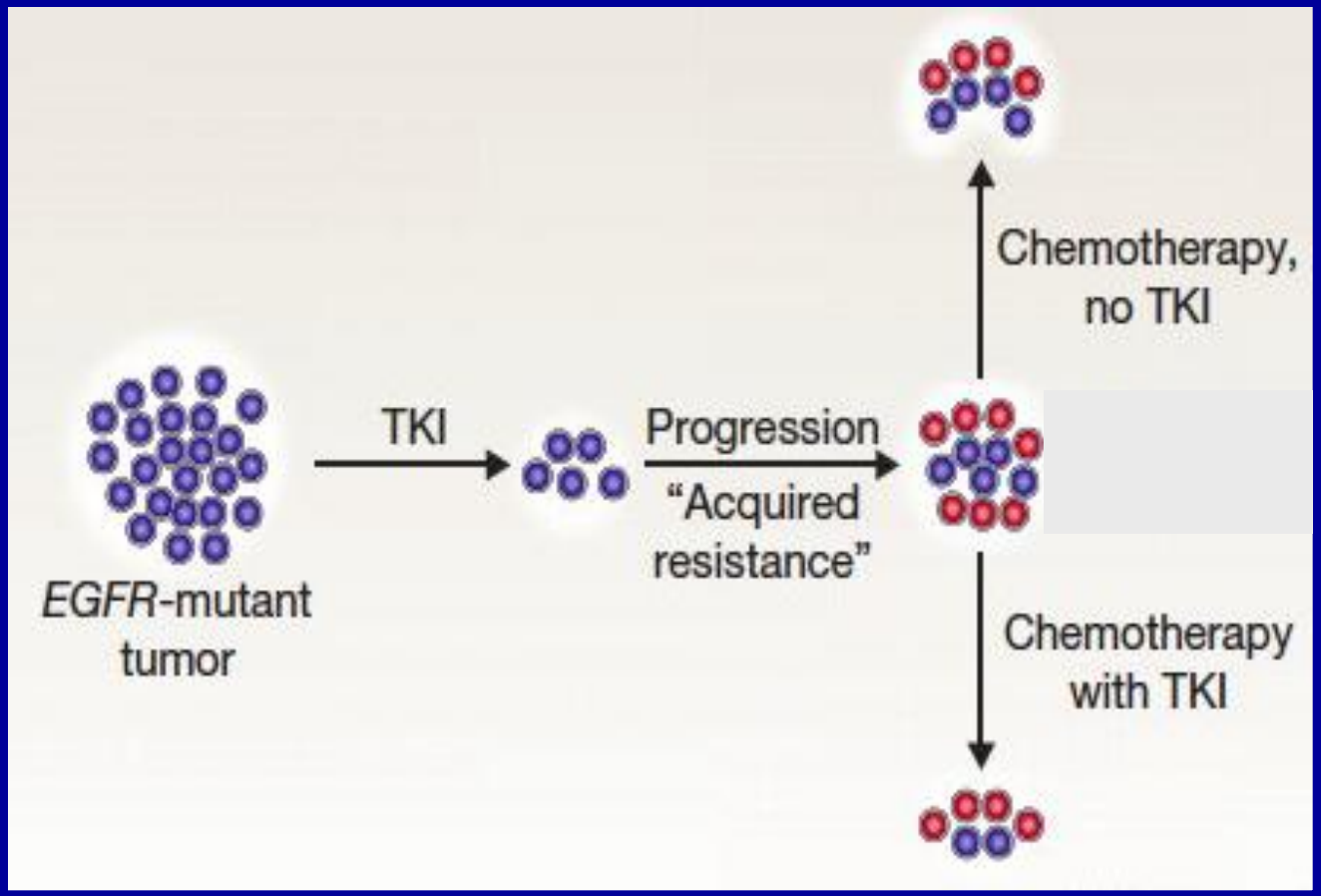


Primary endpoint: PFS
Secondary endpoint: OS, RR, QOL

Treatment of TKI Resistance



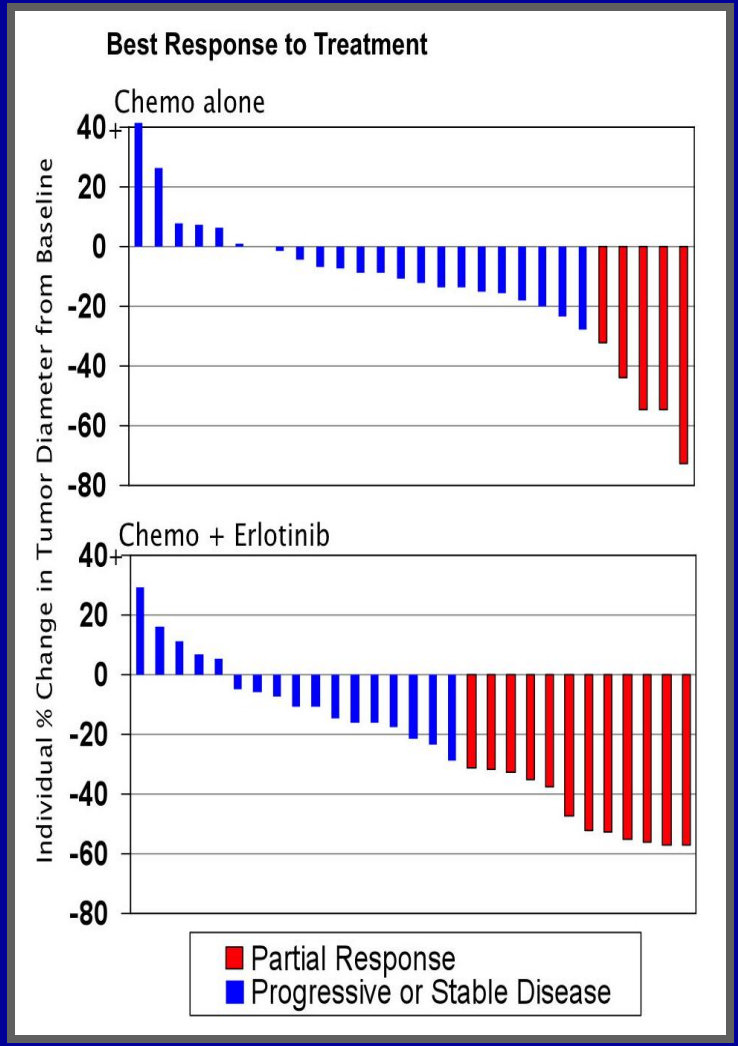
Treatment Options after Acquired Resistance to EGFR TKI



Oxnard, *Clin Cancer Res*, 2011

Chemo/Erlotinib vs. Chemo Alone at Progression after Acquired Resistance

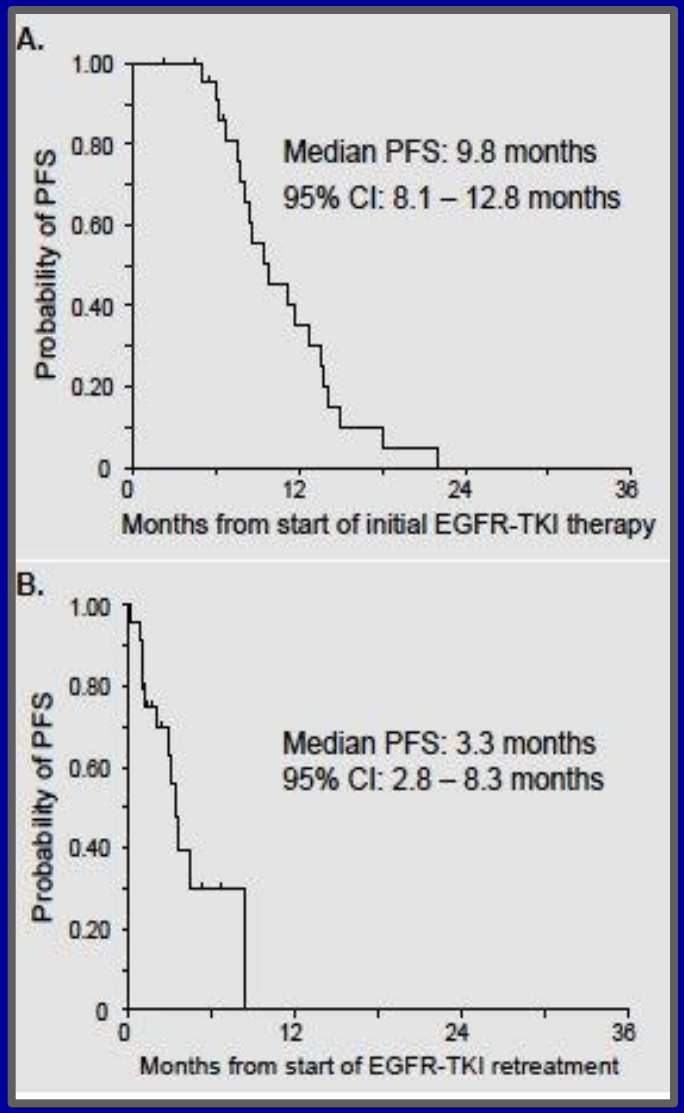
- N = 78 retrospective review of outcomes
  - chemo alone (N = 44) or
  - chemo/erlotinib (N = 34)
- RR 18% (chemo) vs. 41% with chemo/erlotinib)
- No differences in PFS or OS between these two strategies



Goldberg, ASCO 2012, Abst#7524

EGFR TKI Re-treatment after Acquired Resistance: DFCI/MGH Experience

- Retrospective, 24 pts (over 9.5 yrs) with activating EGFR mutation after AR to gefitinib (30%) or erlotinib (70%)
- RR 4%, SD 63%
- Median interval off EGFR TKI 5 mo (range 2-46 mo)
- Greater benefit w/longer interval of EGFR TKI (PFS 4.4 vs. 1.9 mo for 6 mo interval off EGFR TKI)



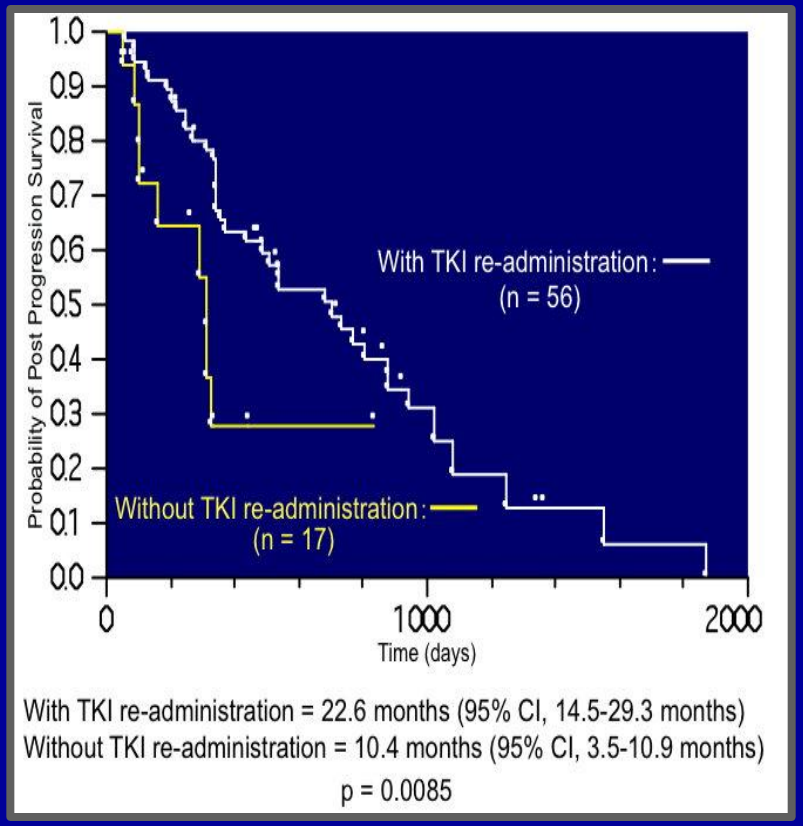
Heon, ASCO 2012, Abst#7525

Re-challenge with EGFR TKI after Acquired Resistance

- N = 73 pts with acquired resistance
- OS post-PD better for 56 who had EGFR TKI re-treatment vs. 17 who did not

Variable		P-value	HR (95%CI)
Re-administration	(with/without)	0.0003	0.45 (0.30-0.68)
T790M	(with/without)	0.0024	0.57 (0.37-0.82)
PS	(0-1/2-4)	0.0003	3.65 (1.77-8.33)
Brain metastases	(with/without)	0.3266	0.86 (0.63-1.16)
Leptomeningeal metastases	(with/without)	0.2592	1.20 (0.87-1.68)

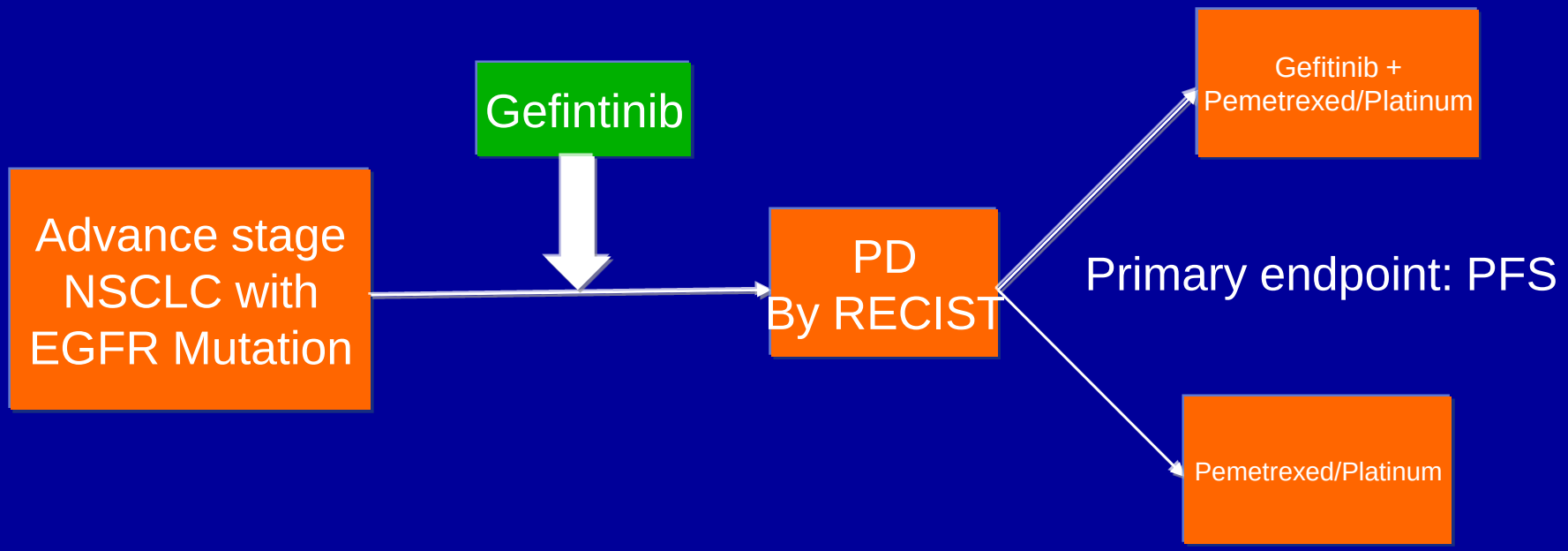
※Proportional hazards model was used in the analysis.



- No correlation of benefit w/interval off EGFR TKI seen

Hata, ASCO 2012, A#7528

IMPRESS: Chemotherapy with or with gefitinib at progression

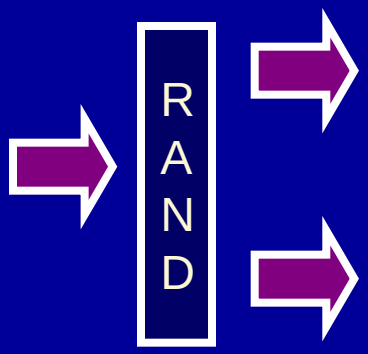


Co-PI: Soria J; Mok T

Chemotherapy +/- Ongoing EGFR TKI for Acquired Resistance, with Retreatment

PI: Leora Horn (Vanderbilt)

Advanced NSCLC
Activating EGFR TKI
Resp to EGFR TKI>4 mo
No prior chemotherapy
PS 0/1
N= 120



Cis or Carbo/Pemetrexed
+ ongoing erlotinib

Cis or Carbo/Pemetrexed

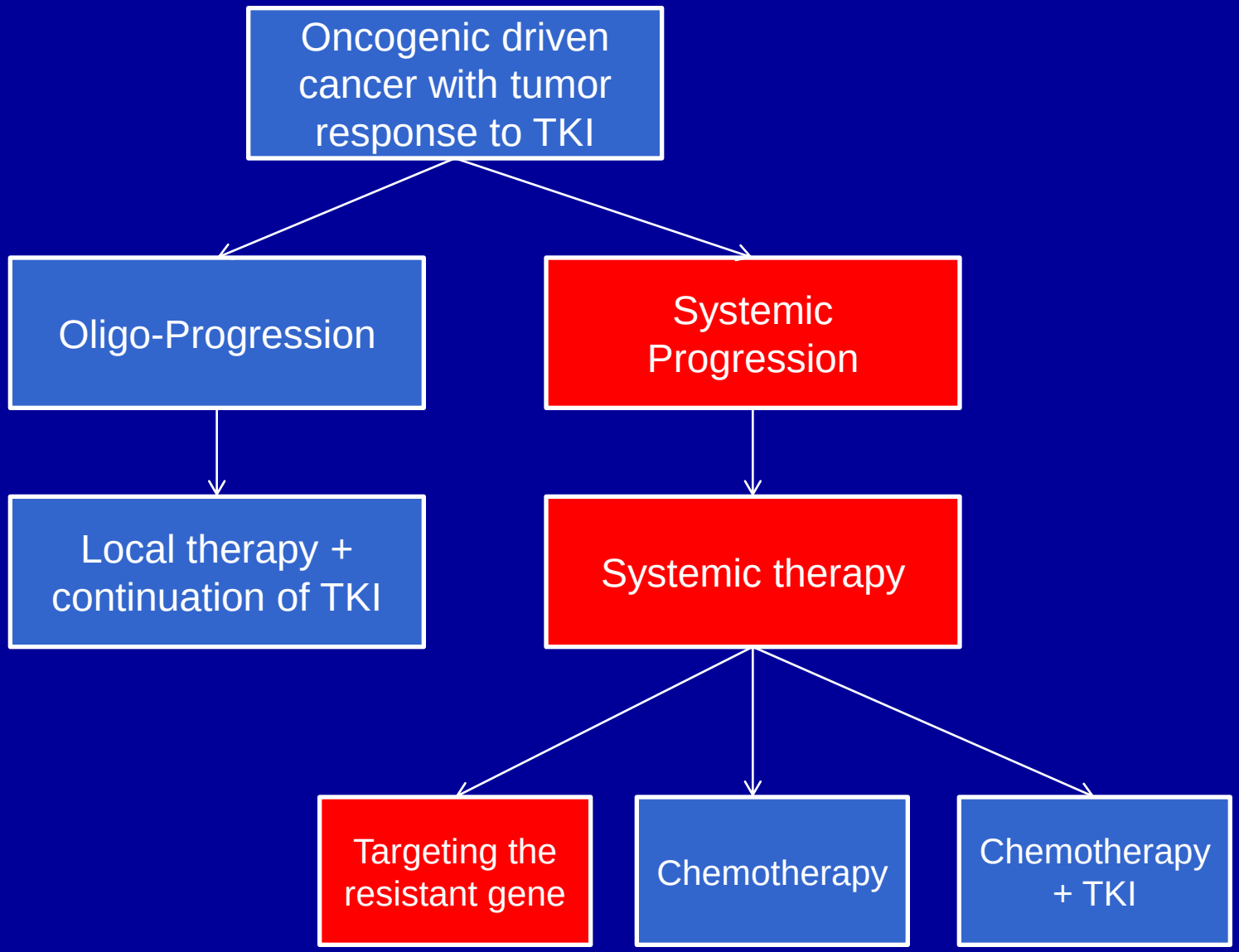
Erlotinib re-treatment

Stratification by:

- EGFR mut'n exon 19 vs. exon 21
- Time to progression on EGFR TKI ≤1 yr vs. >1 yr
- PS 0 vs. 1

Primary endpoint: progression-free survival

Treatment of TKI Resistance



Disappointing experiences

Author	Treatment for resistance	Sample size (%EGFR mutation)	RR	Efficacy
Riely et al CCR 2007	Gefitinib + everolimus	13(62)	0	TTP 3 m
Soria et al Ann Onco 2009	Everolimus	43 (0)	2%	TTP 2.7 m
Sequist et al JCO 2010	Neratinib	91 (100)	3%	PFS 3.6 m
Janjigian et al CCR 2011	Erlotinib + cetuximab	19 (84)	0	PFS 3 m
Sequist et al JCO 2010	IPI-504	28(100)	4%	NR
Johnson et al JTO 2011	Dasatinib	12 (100)	0	PFS 3 m
Miller et al ASCO 2008	XL647	23	12%	NR

Oxnard et al CCR 17:5530, 2011

LUX-Lung 1 – trial design

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

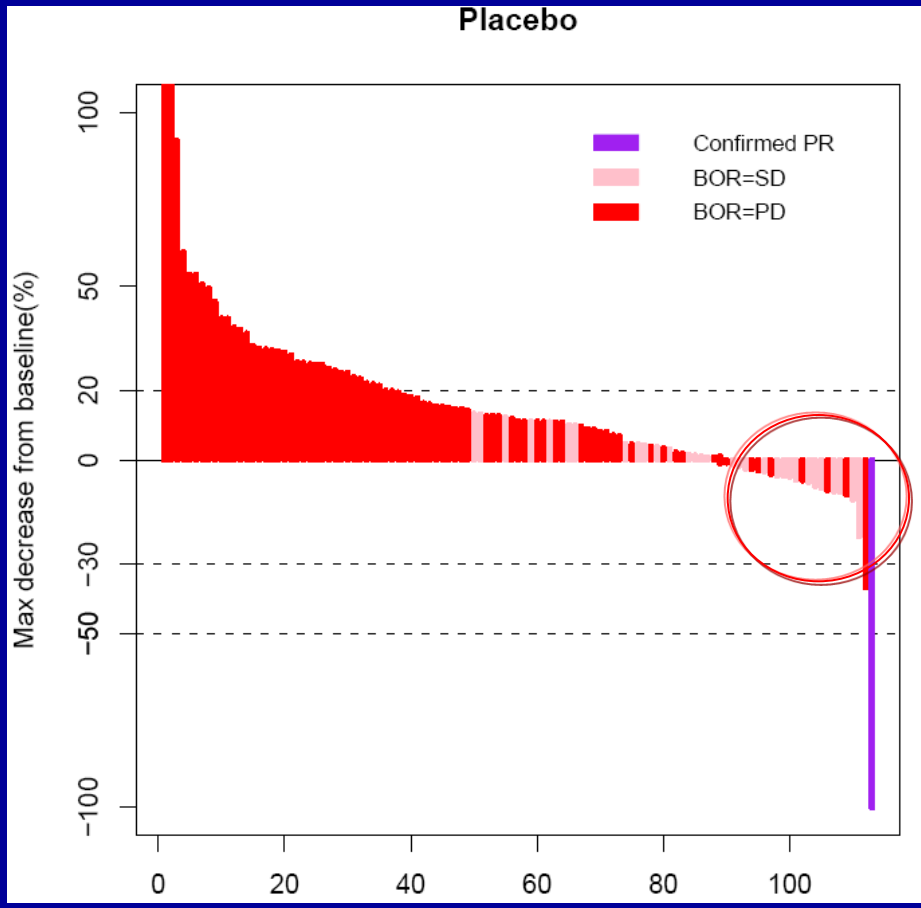
Oral BIBW 2992 50 mg once daily plus best supportive care	Oral placebo once daily plus best supportive care

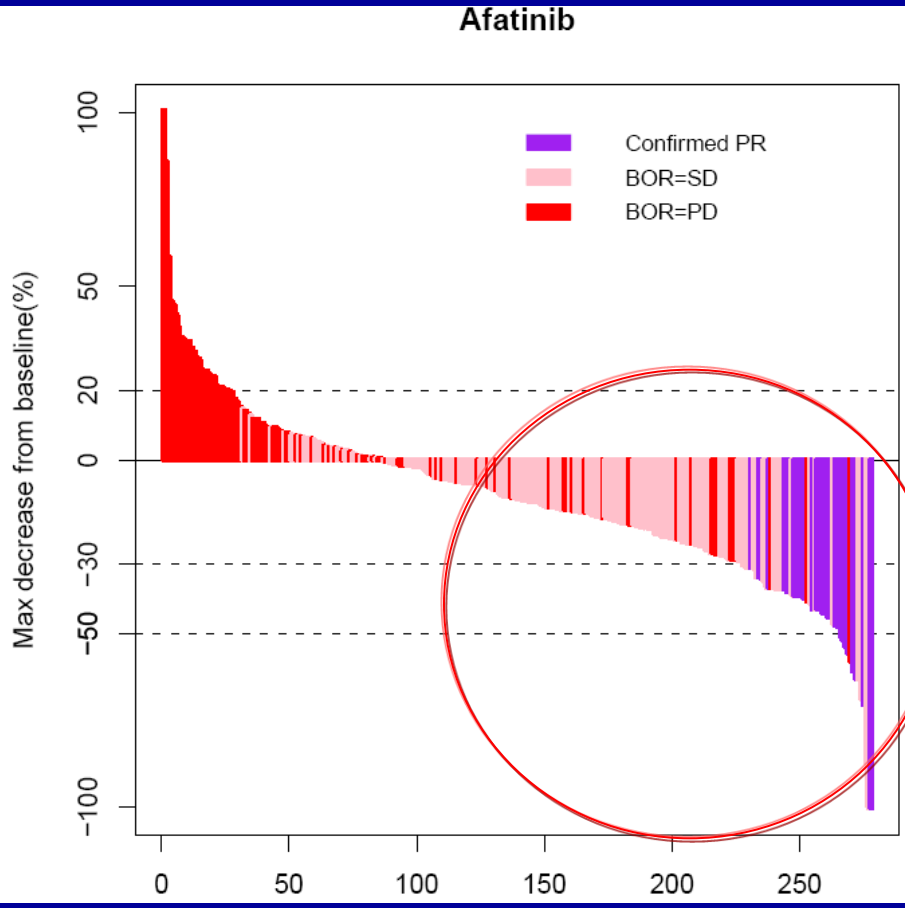
Primary endpoint: Overall survival (OS)

Secondary: PFS, RECIST response, QoL, safety

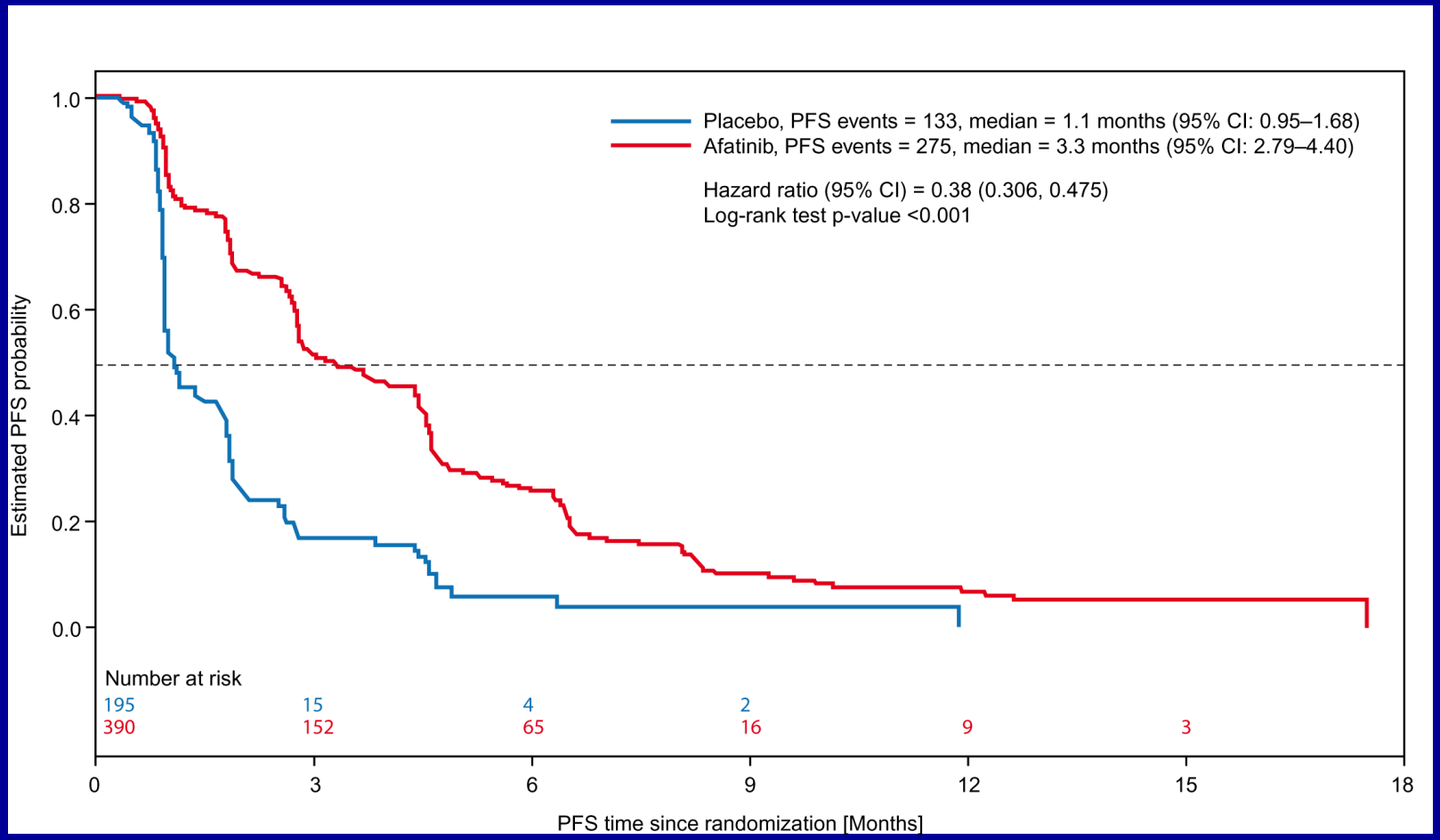
Countries: North America, Europe, Asia
Status: Recruitment complete, DBL for primary analysis 6 July 2010

Waterfall plots by independent review



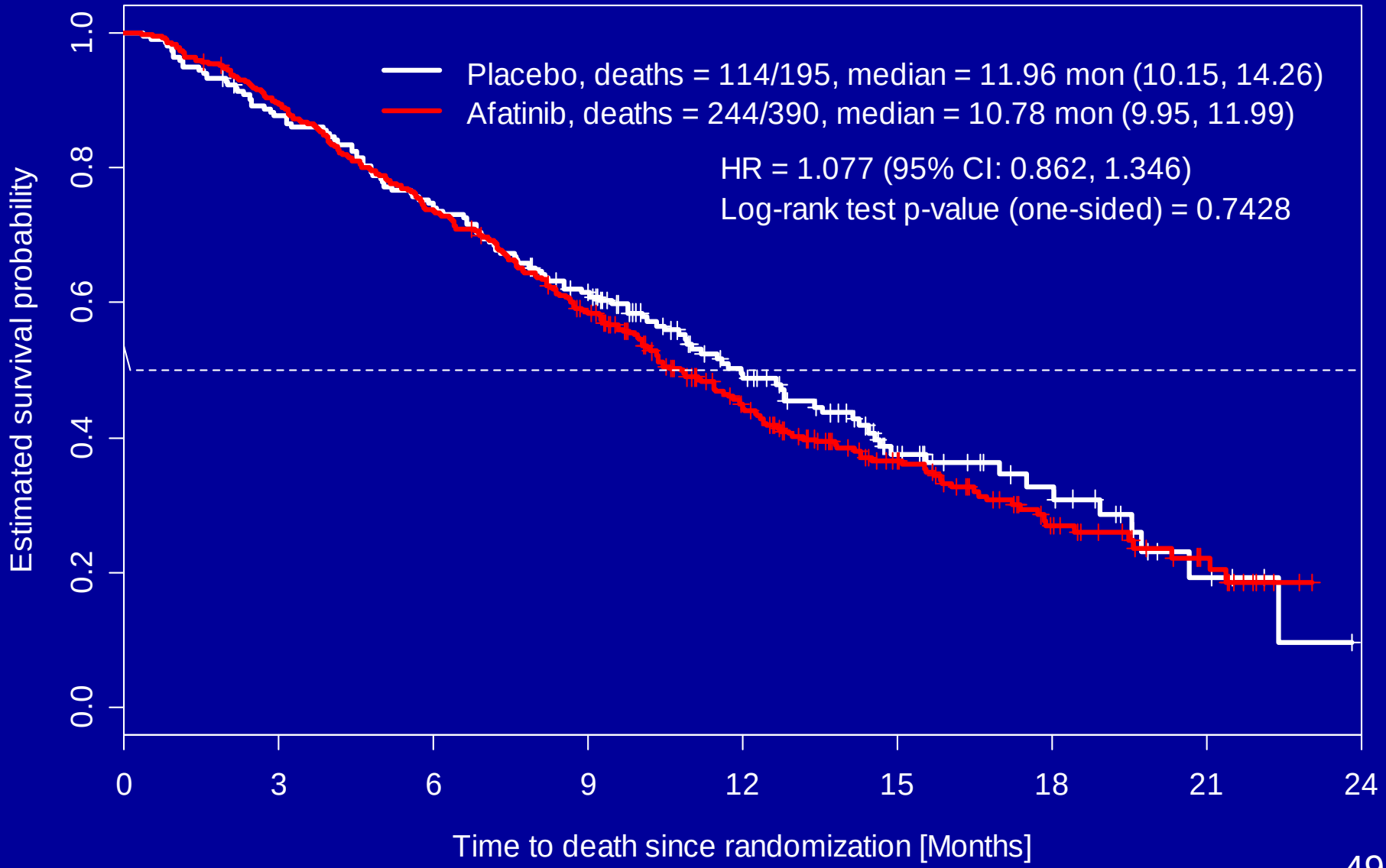


PFS by independent review

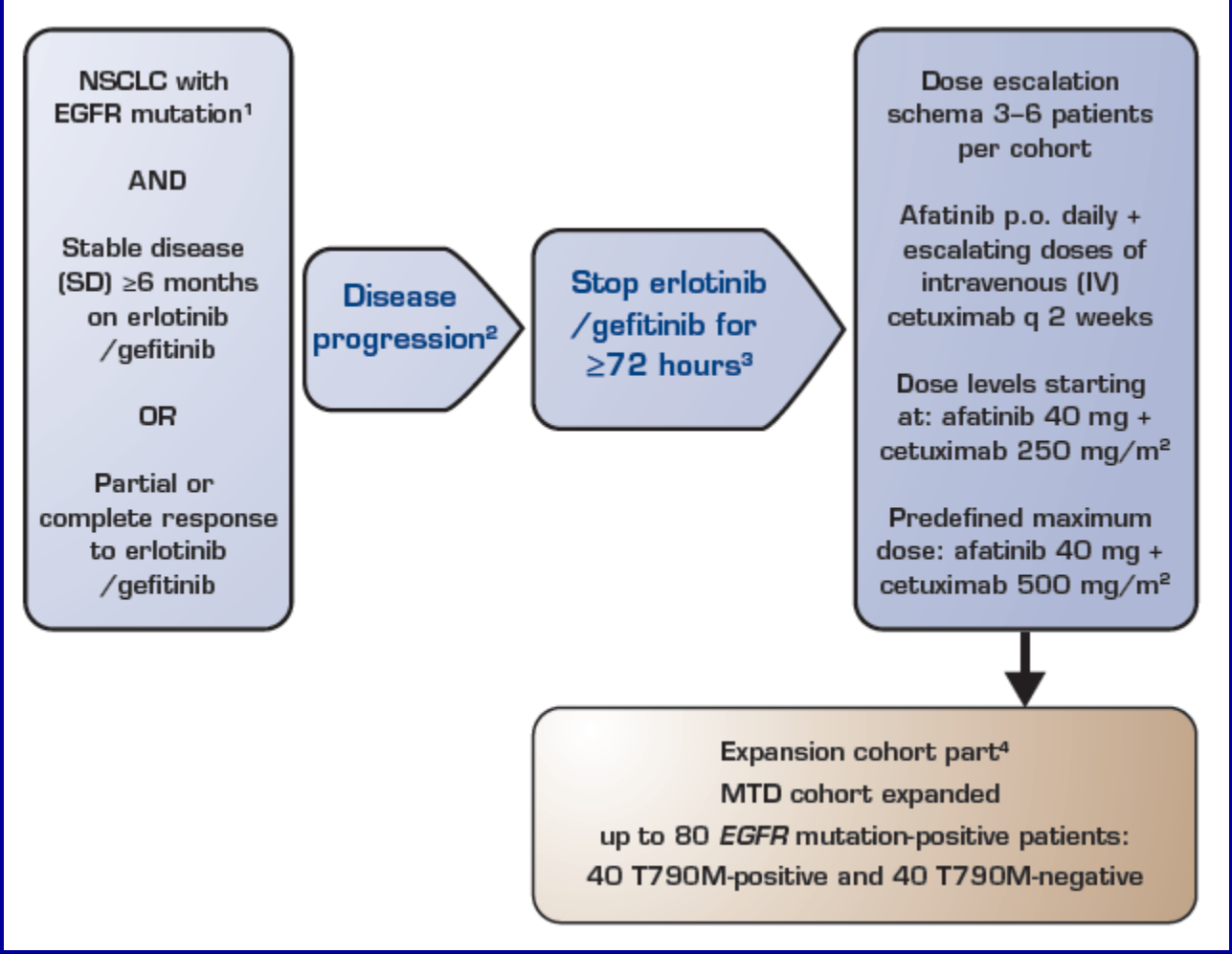


Statistically significant across almost all subgroups

Overall survival

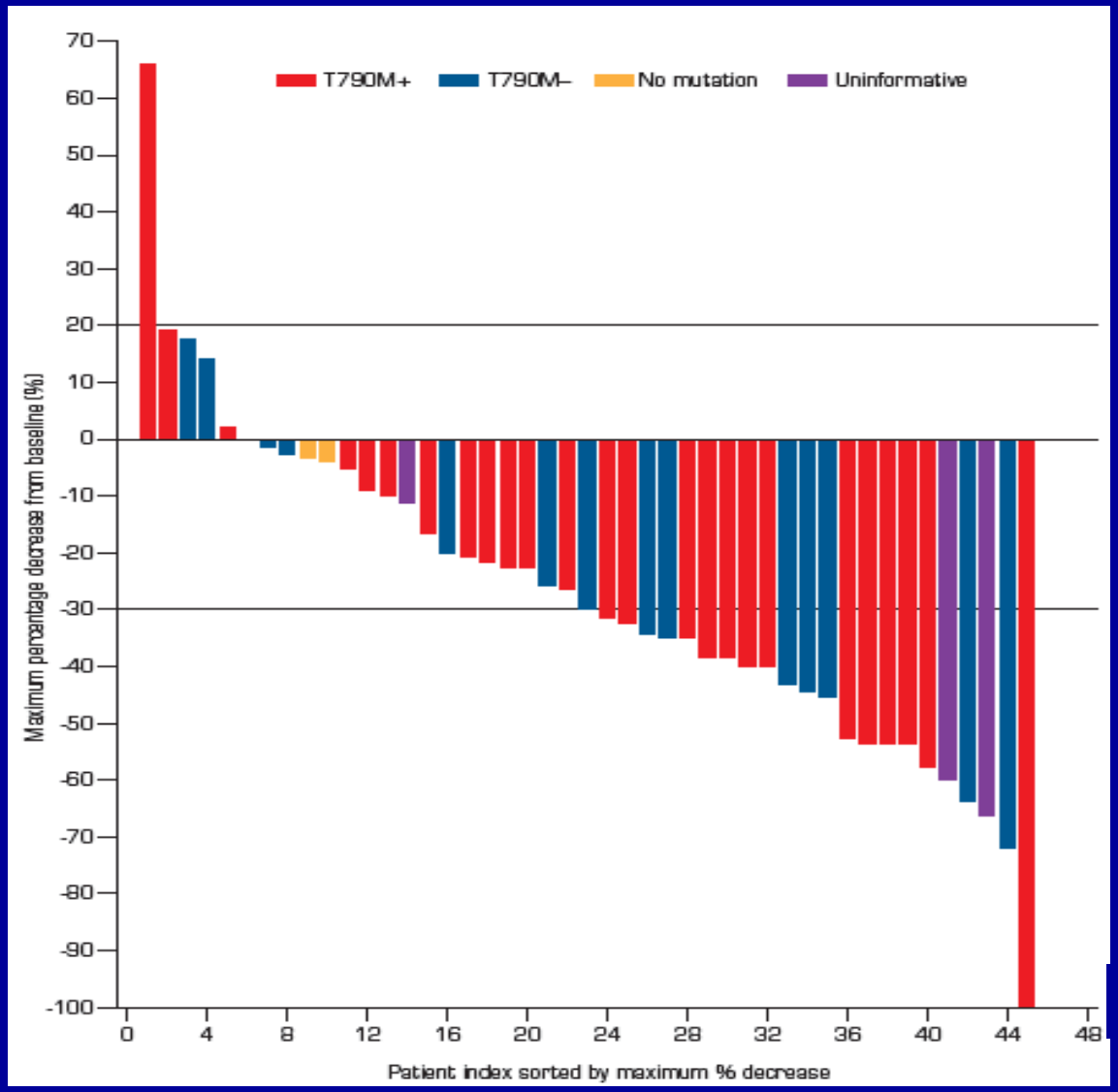


BIBW 2992 + Cetuximab

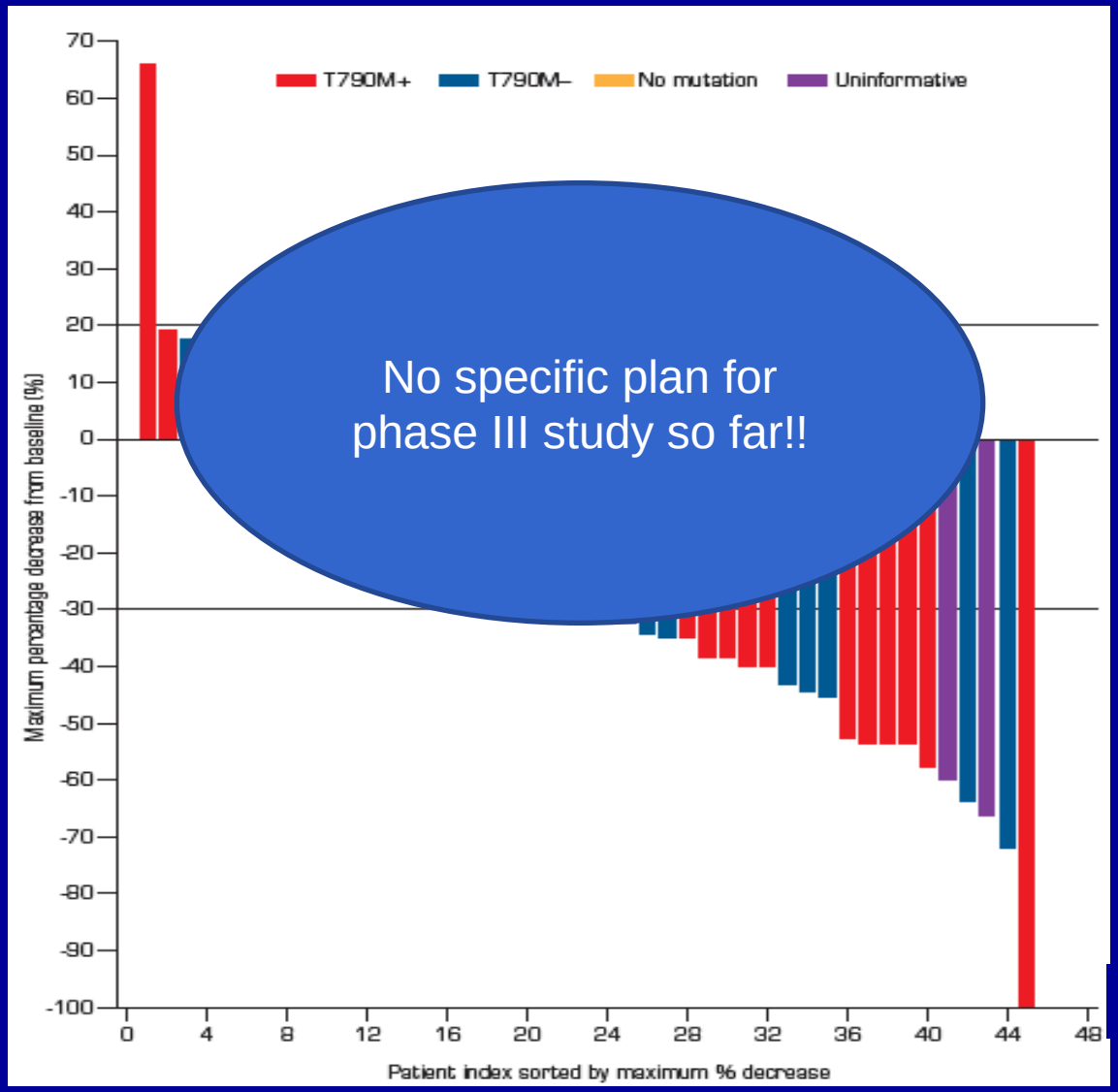


Jangijian et al ASCO 2011 Abst# 7525

Afatinib + cetuximab at MTD responses by mutation



Afatinib + cetuximab at MTD responses by mutation



No specific plan for phase III study so far!!

Summary

- Mechanism of TKI resistance
  - Gatekeeper mutation (T790M)
  - C-MET
  - Others (BIM, tumor heterogeneity)
- Oligo-progression
  - Retrospective studies suggested longer PFS
  - Need prospective study to confirm
- Systemic progression
  - IMPRESS: ongoing trial comparing chemo + TKI vs chemotherapy
  - Afatinib+/-Cetuximab for T790M