Secondary resistance to systemic treatment

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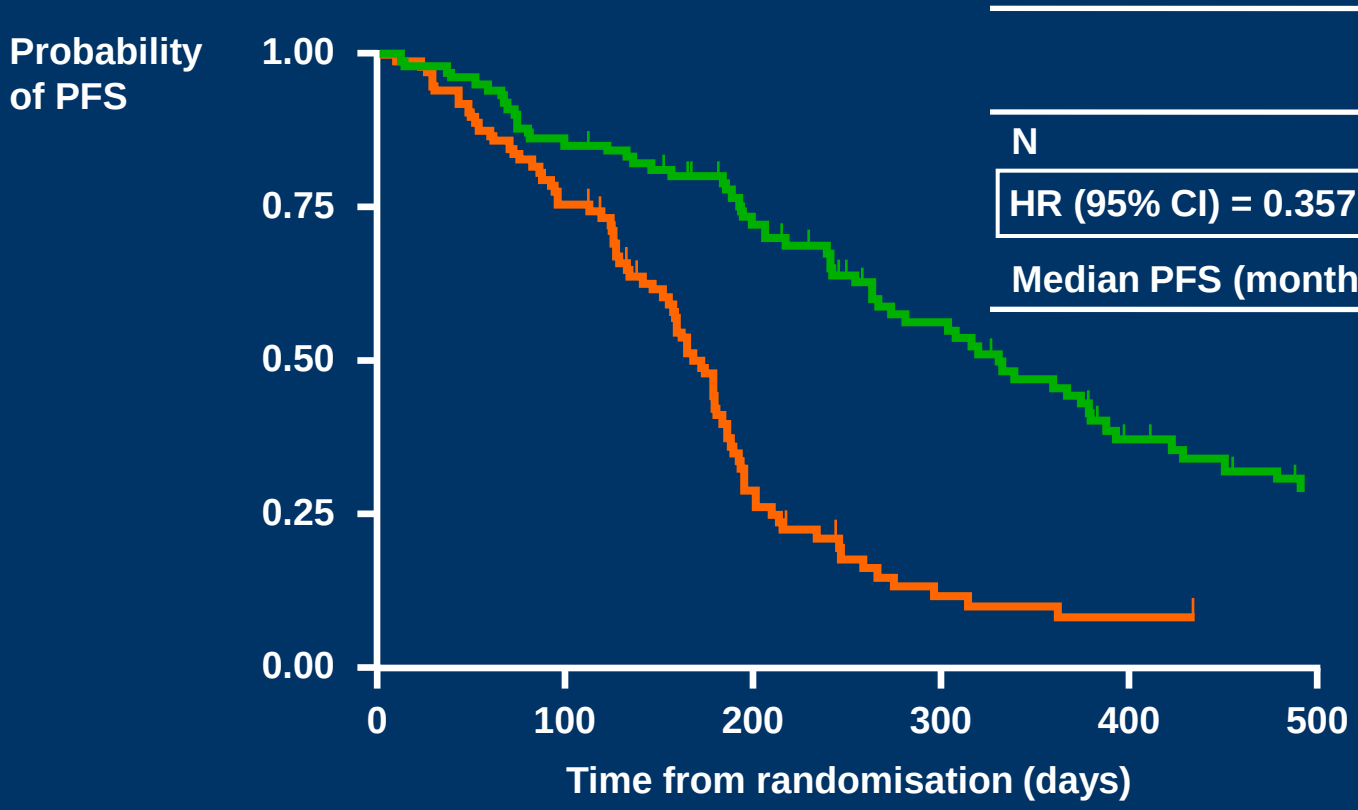
Disclosures

- Advisory role: Astra Zeneca, BMS, Clovis, Daiichi, MSD, Lilly, Roche, BI, Bayer, Pfizer, Ariad, Novartis.
- Testimony: None
- Will discuss off label use of Trastuzumab

NEJ002: study of first-line gefitinib versus carboplatin / paclitaxel in EGFR mutation positive patients: PFS



	Gefitinib	Carboplatin / paclitaxel
N	96	98
HR (95% CI) = 0.357 (0.25, 0.51) p<0.001		
Median PFS (months)	10.4	5.5

Log rank test
HR <1 implies a lower risk of progression on gefitinib

Kobayashi et al 2009

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

Secondary resistance Pharmacology

Journal of Neuro-Oncology
September 2010, Volume 99, Issue 2, pp 283-286

High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer

Jennifer L. Clarke, William Pao, Nian Wu, Vincent A. Miller, Andrew B. Lassman

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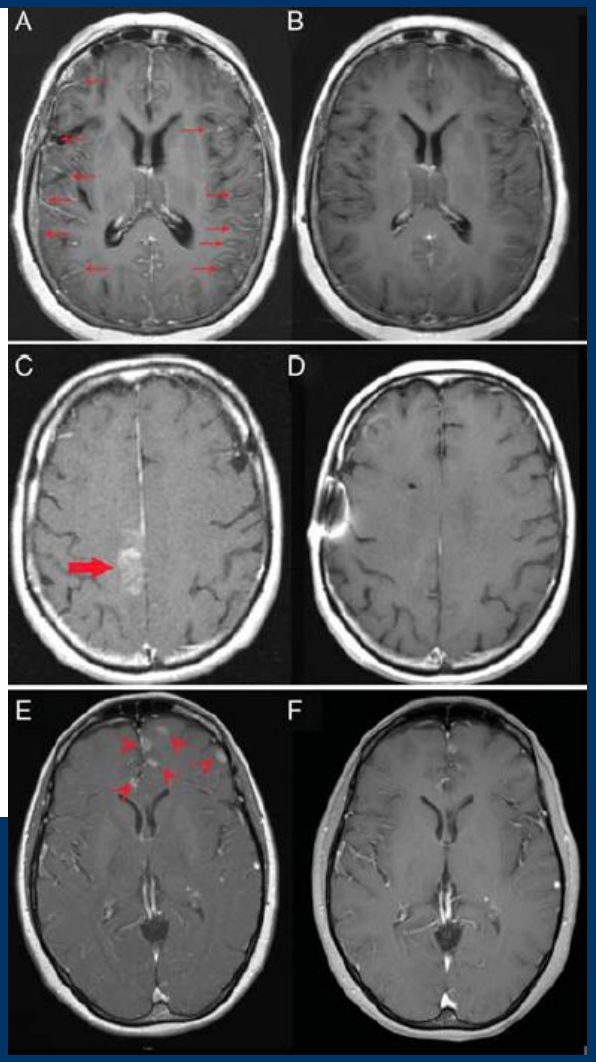
Abstract

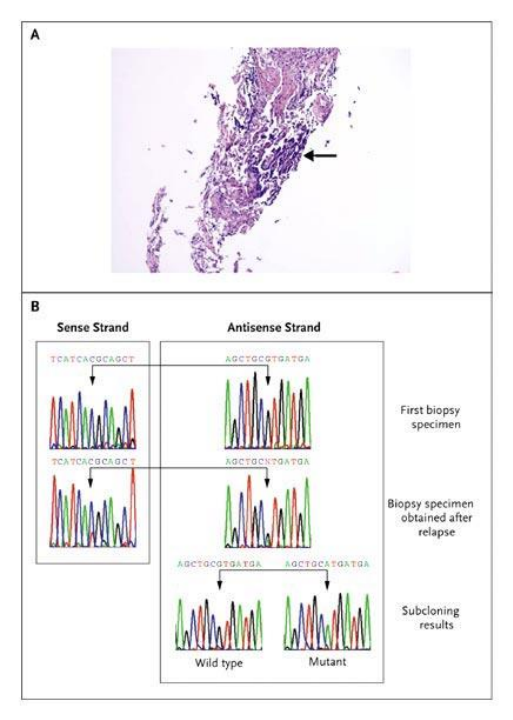
Leptomeningeal metastases (LM) occur in 5–10% of patients with solid tumors and are associated with a dismal prognosis. We describe LM from lung adenocarcinoma harboring a mutation in the epidermal growth factor receptor (EGFR) gene that confers sensitivity to the EGFR tyrosine kinase inhibitors (EGFR-TKIs) erlotinib and gefitinib. The CSF concentration of EGFR-TKIs achieved by standard daily dosing may be insufficient for therapeutic effect. However, intermittent (pulsatile) high dose administration (1000–1500 mg/week) achieves a higher CSF concentration than standard dosing, and successfully controlled LM in this patient.

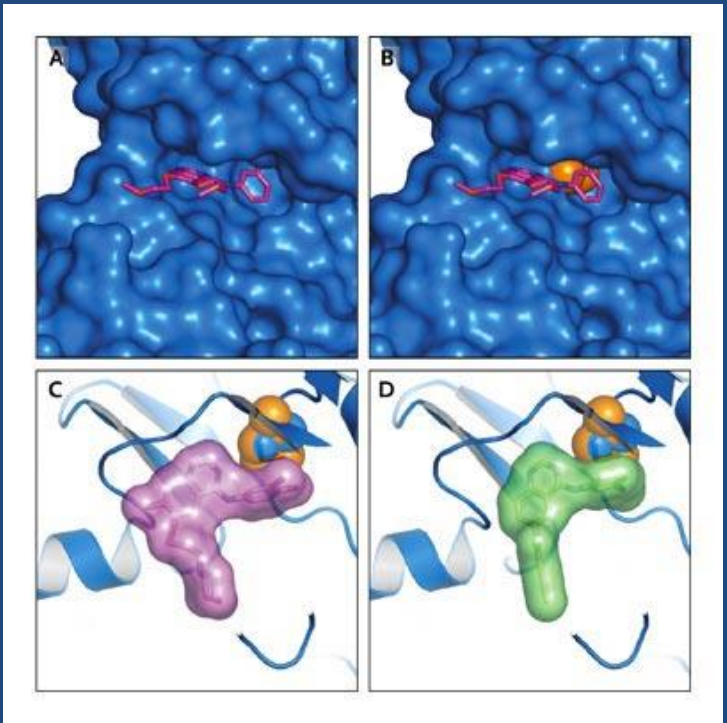


Secondary Resistance
Common themes

- Oligoprogression
- Gatekeeper mutations

EGFR mutation associated with resistance to Gefitinib.

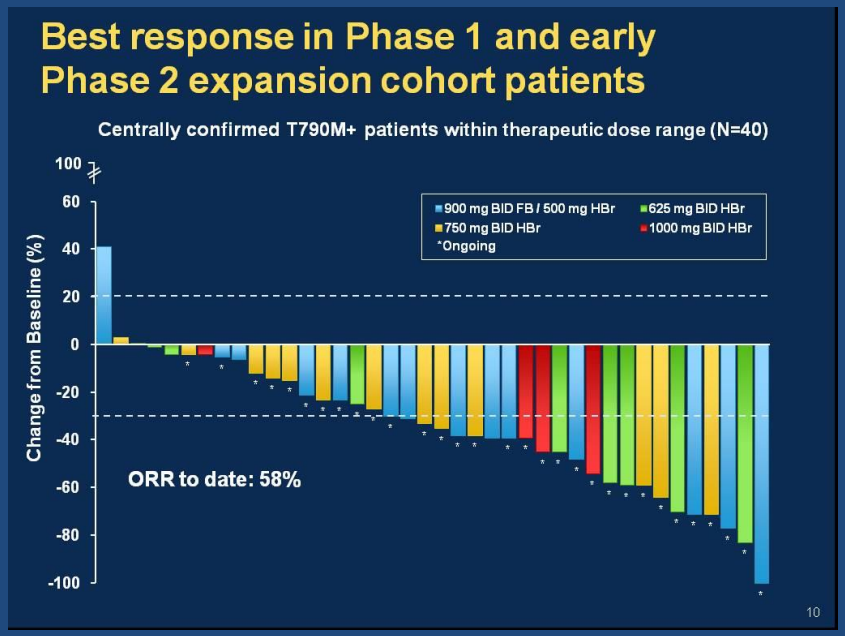


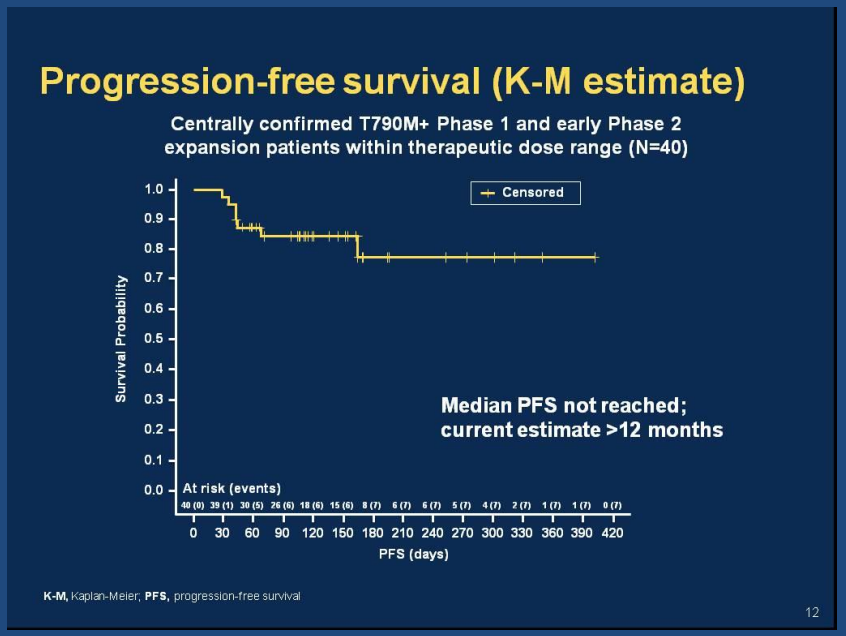


Left: sequencing of exon 20 demonstrates a novel C-to-T (antisense G-to-A) base-pair change leading to steric hindrance in the predicted complex of gefitinib and EGFR (right)

Kobayashi et al. New Eng. J. Med. 352;786,2005.

CO-1686





Presented By Lecia Sequist at 2014 ASCO Annual Meeting

T790M EGFR Mutation Predictive for 3rd generation TKI Benefit

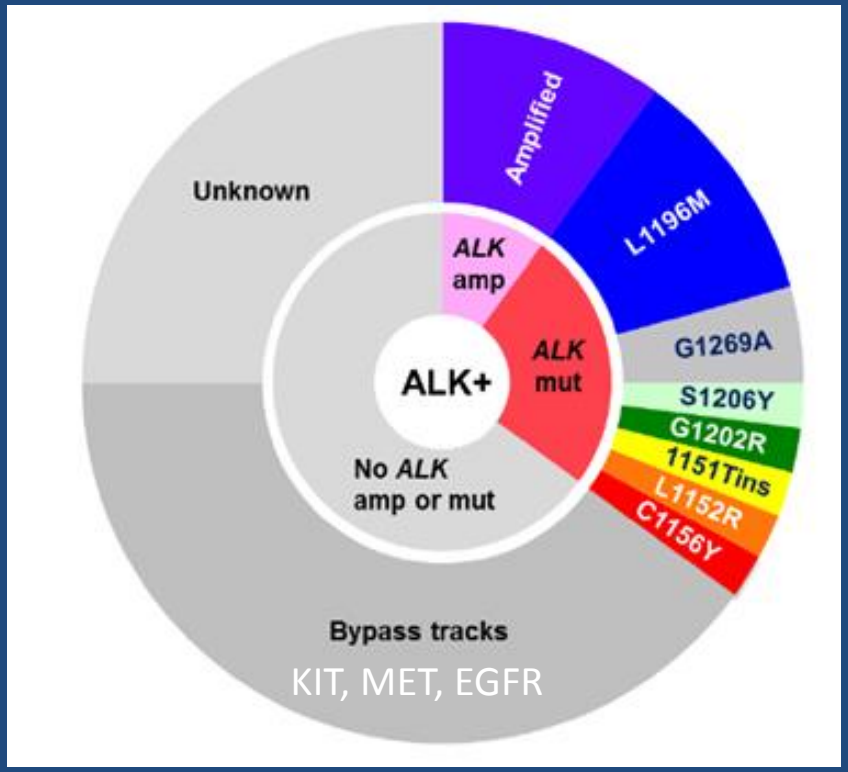
	RR T790M +	RR T790M -	PFS
Afatanib/Cetux	32%	28%	4.66
HM 61713	29%	12%	4.34*
CO-1686	58%	Inc.	↑
AZD 9291	65%	22%	↑

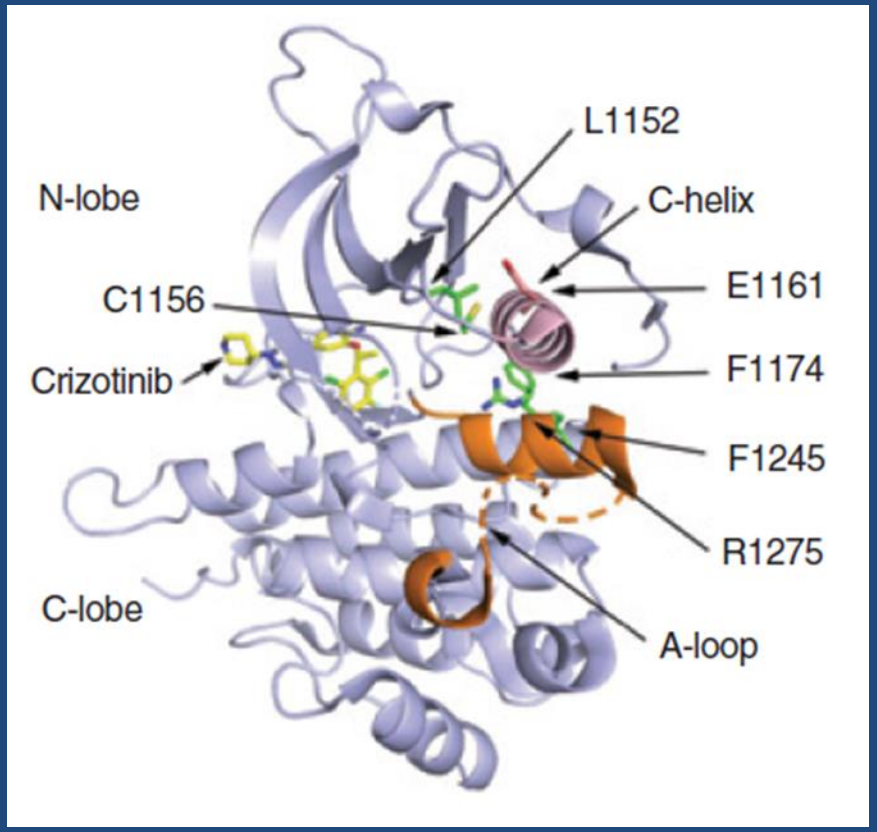
Lynch et al. ASCO 2014

Toxicity Comparison

Any Grade (Gr3)	Diarrhea	Rash	ILD/SOB *	Inc BS	QTc
Erlotinib	57%	80%	1%	NR	NR
Afatanib/Cetux	71%	97%	NR	NR	NR
CO-1686	23%	4%	NR	55% (22%)	15% (7%)
AZD 9291 80mg	20%	27%	3%	1%	1%
HM 61713	21%	24%	10%*	0%	3%

ALK Mechanisms of resistance

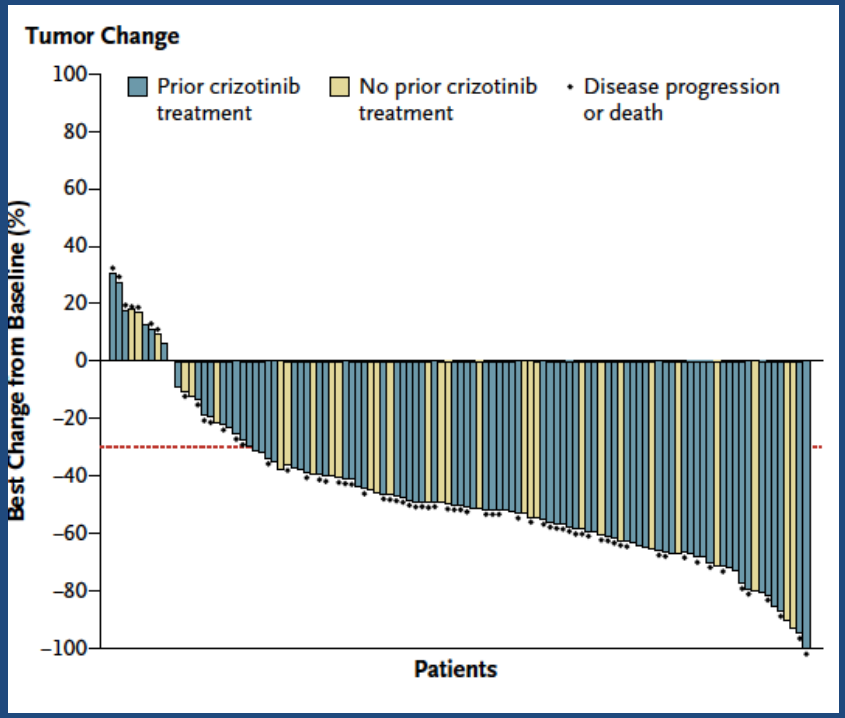


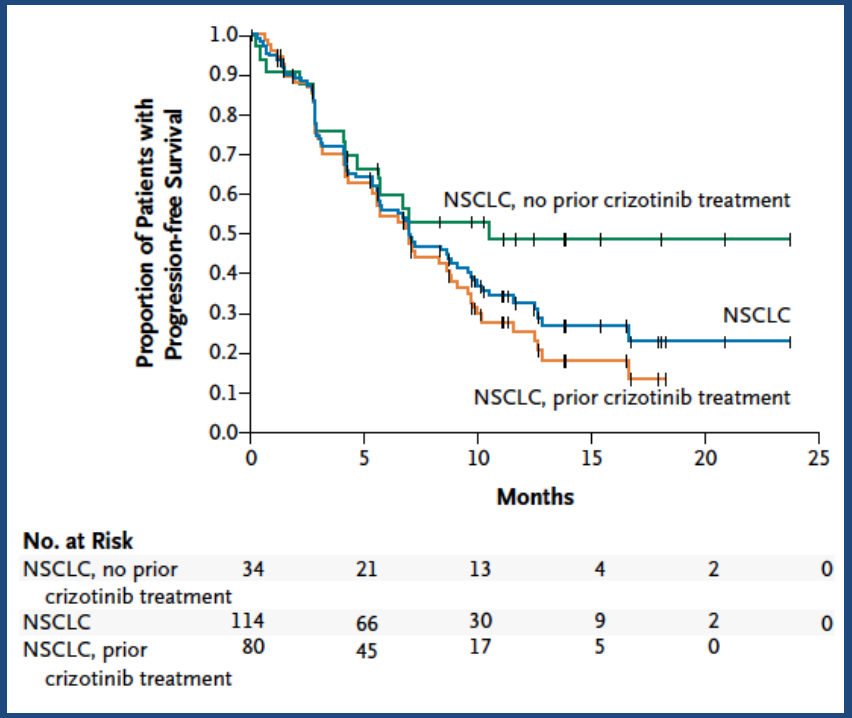


Choi NEJM 2010; Sasaki CR 2011; Doebele CR 2012; Yu CR 2013

Mutation	Localization in kinase	Proposed mechanism of resistance	Cross-resistance with other ALK inhibitors
C1156Y	N-terminal of αC-helix	Unknown	Yes
L1196M	Gatekeeper	Crizotinib binding	Yes
L1152R	N-terminal of αC-helix	Unknown	Yes
F1174L	C-terminal of αC-helix	Affinity for ATP	Sensitive to other ALK inhibitors
G1202R	Solvent front	Crizotinib binding	different degrees of resistance
S1206Y	Solvent front	Crizotinib binding	different degrees of resistance
1151Tins	N-terminal of αC-helix	Affinity for ATP	different degrees of resistance
G1269A	ATP binding pocket	Affinity for ATP	?

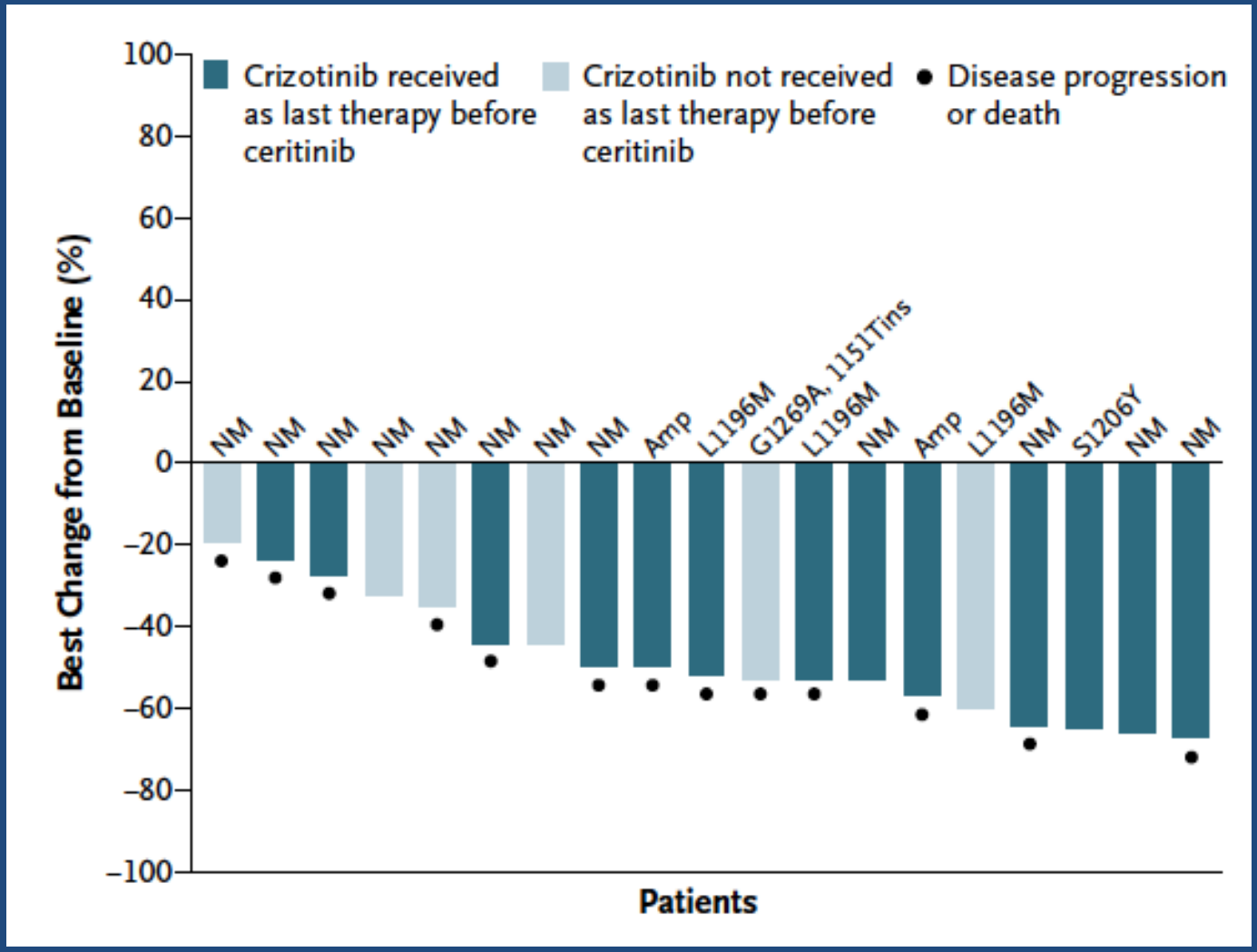
2nd Line Ceritinib – Phase II





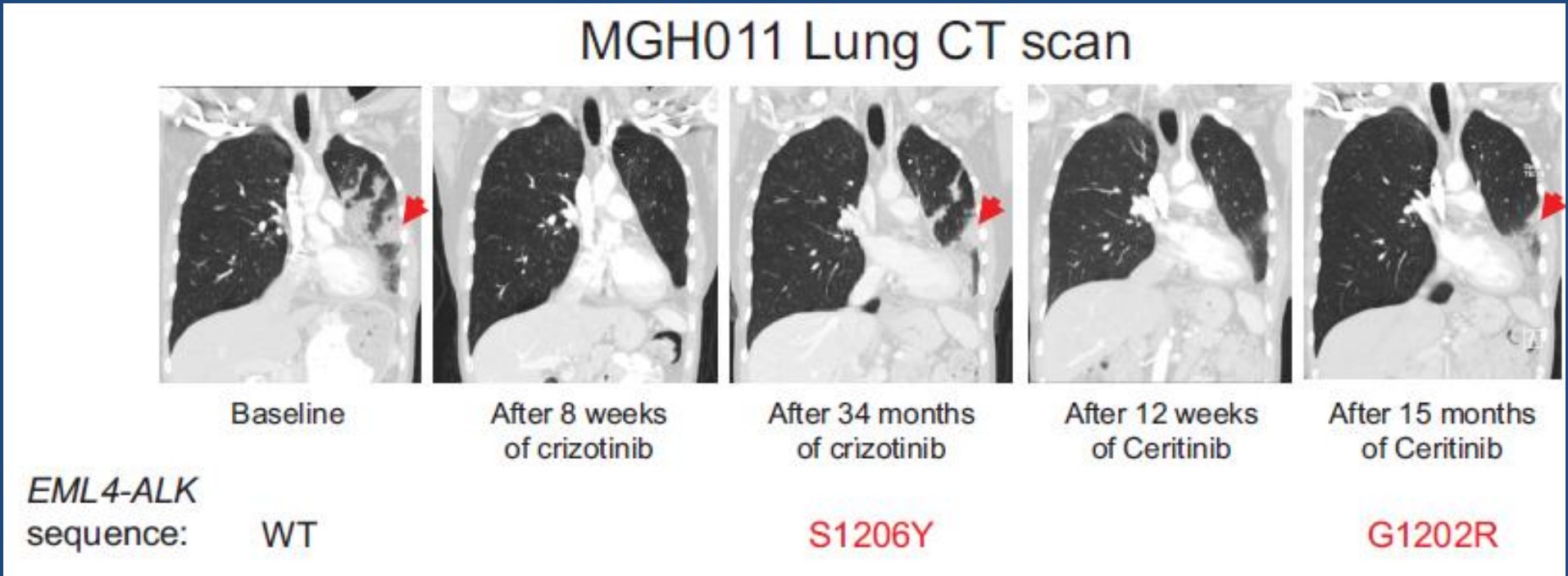
Shaw et al. NEJM 370,1189,2014

Rebiopsies



Shaw et al. NEJM 370,1189,2014

Ceritinib resistance is associated with ALK G1202R



Friboulet, Cancer Disc 2014

Next-Generation ALK Inhibitors

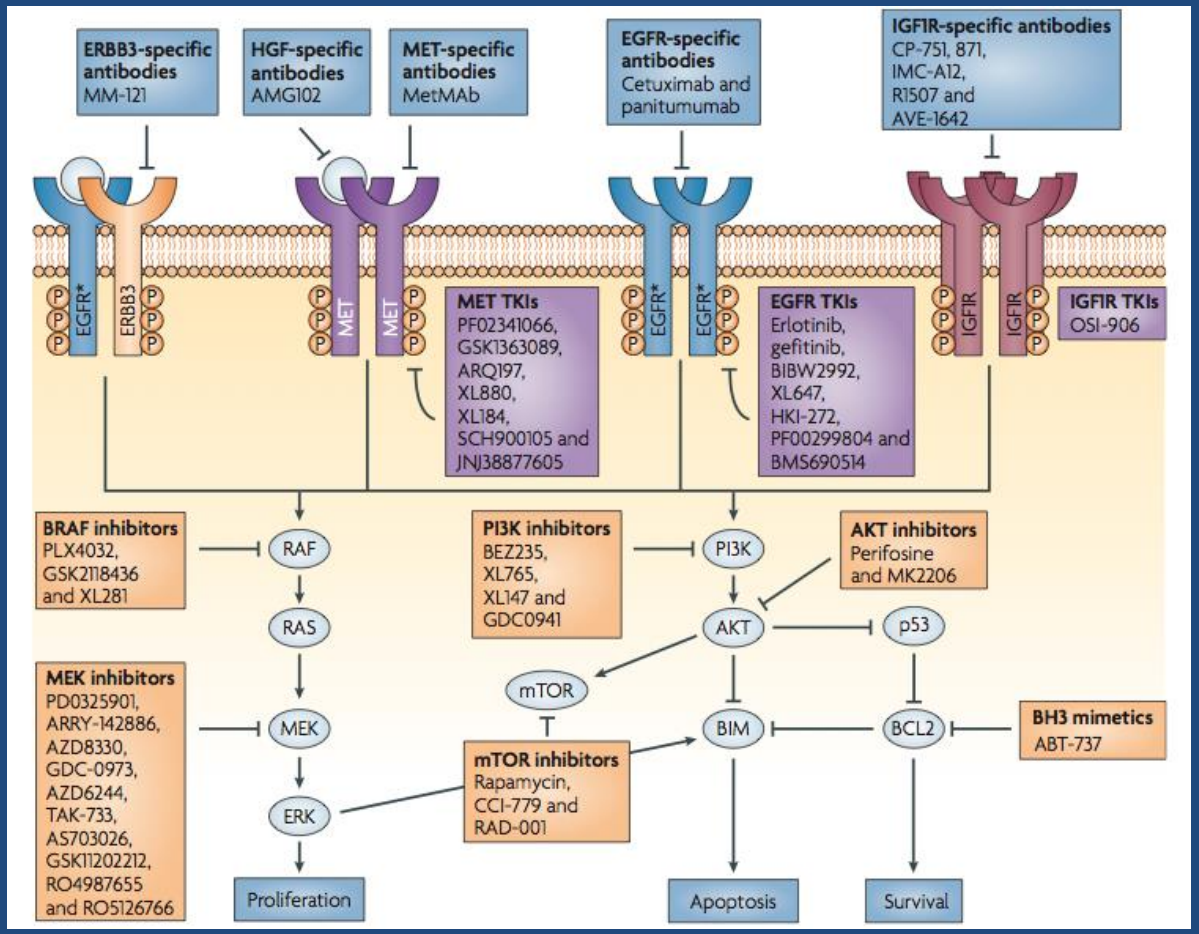
Inhibitor	Targets	Development stage	Recent reports
Ceritinib	ALK/ROS	FDA approved Phase III/CUP	Shaw, NEJM 2014 Kim, ASCO 2014
Alectinib	ALK	Approved in Japan FDA fast-track Phase III/CUP	Seto, Lancet Oncol 2014 Gadgeel, Lancet Oncol 2014 Nakagawa, ASCO 2014
AP26113	ALK/EGFR/ROS	Phase I/II	Gettinger, ASCO 2014
TSR-011	ALK/TRK	Phase I/II	Weiss, ASCO 2014
X-396	ALK/ROS	Phase I/II	Horn, ASCO 2014
RXDX-101	ALK/ROS/TRK	Phase I/II	De Braud, ASCO 2014
PF-06463922	ALK/ROS/TRK	Phase I/II	Johnson, J Med Chem 2014
CEP-37440	ALK/FAK	Phase I/II	-

Secondary Resistance

Common themes

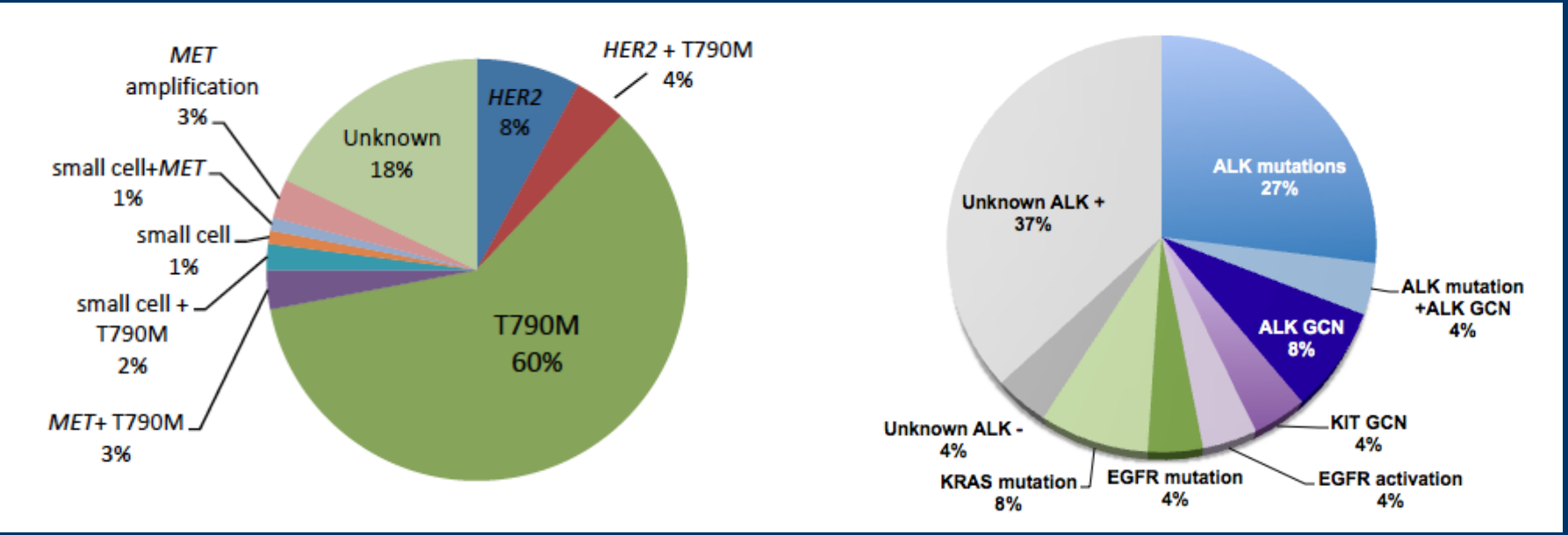
- Local treatments
- Gatekeeper mutations
- Side road resistance

Side-road resistance



Pao, Nat Rev Cancer, 2010

Characteristics of tumours with acquired resistance to TKI's



EGFR

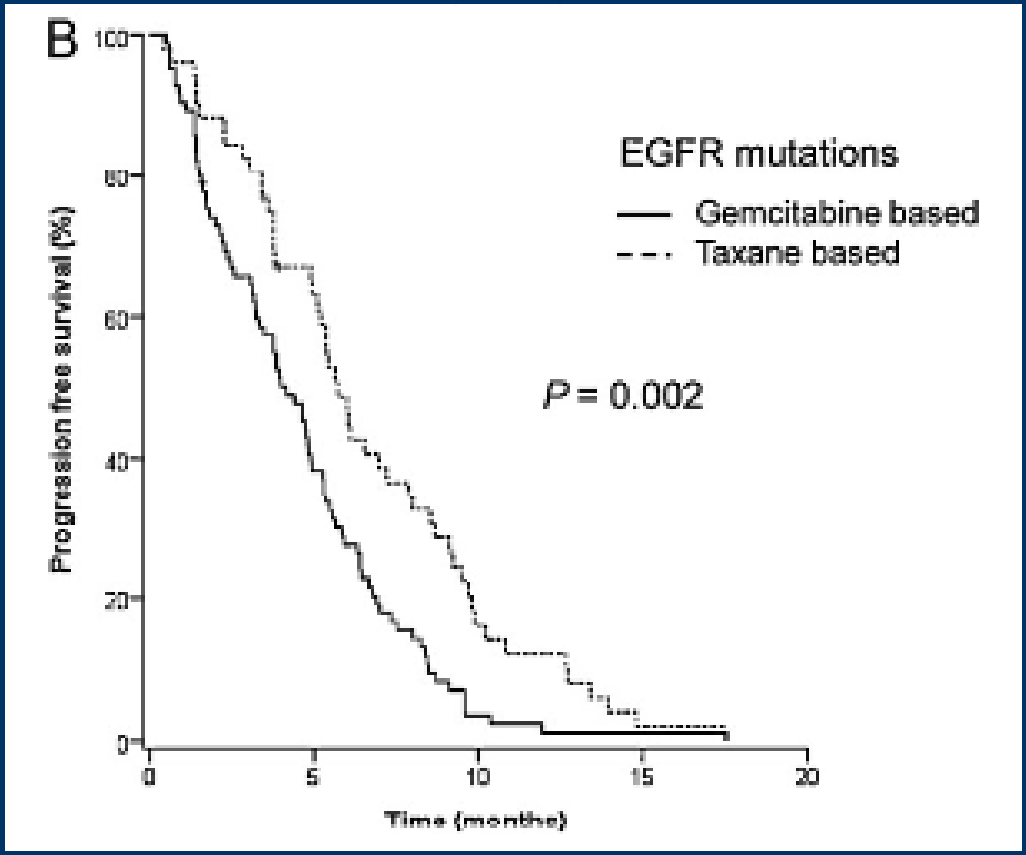
Alk

Yu CCR, 2013; Katayama Sci Transl Med 2012, Doebele CCR 2012

Strategies at Progression

- Cytotoxic Chemotherapy

What is the optimal chemotherapy post-progression on EGFR TKIs?

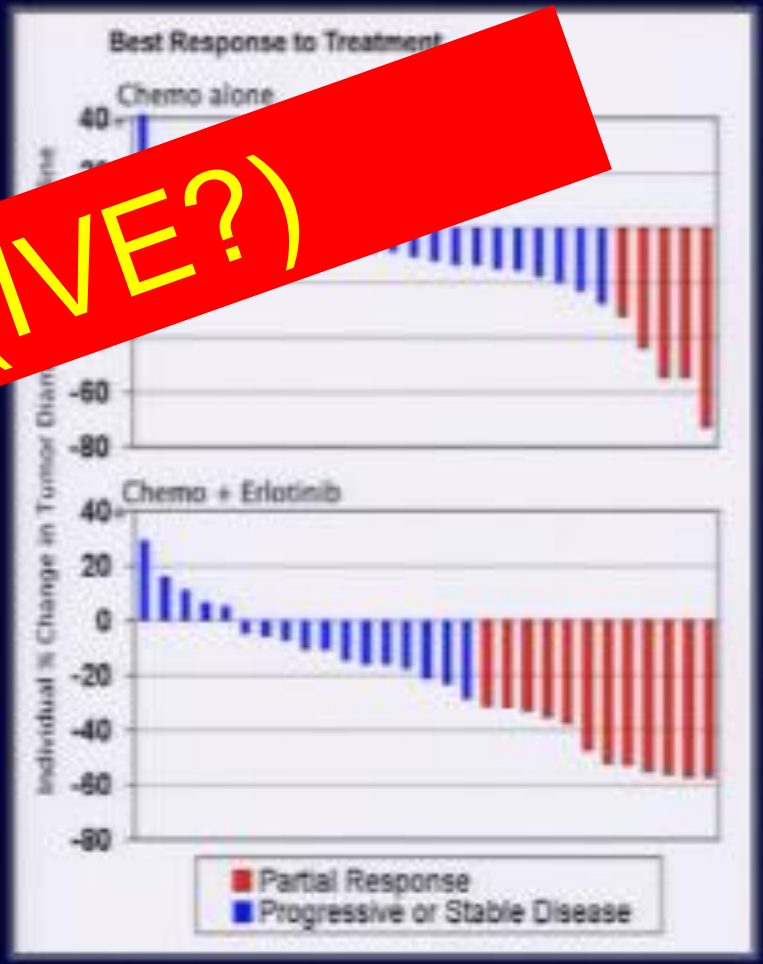


J.H. Park et al. Lung Cancer 77: 433– 437, 2012

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

- N = 78 retrospective review of outcomes
  - chemo alone (N = 44) or
  - chemo/erlotinib (N =
- RR [illegible]% with chem[illegible])
- No differences in PFS or OS between these two strategies

IMPRESS(IVE?)

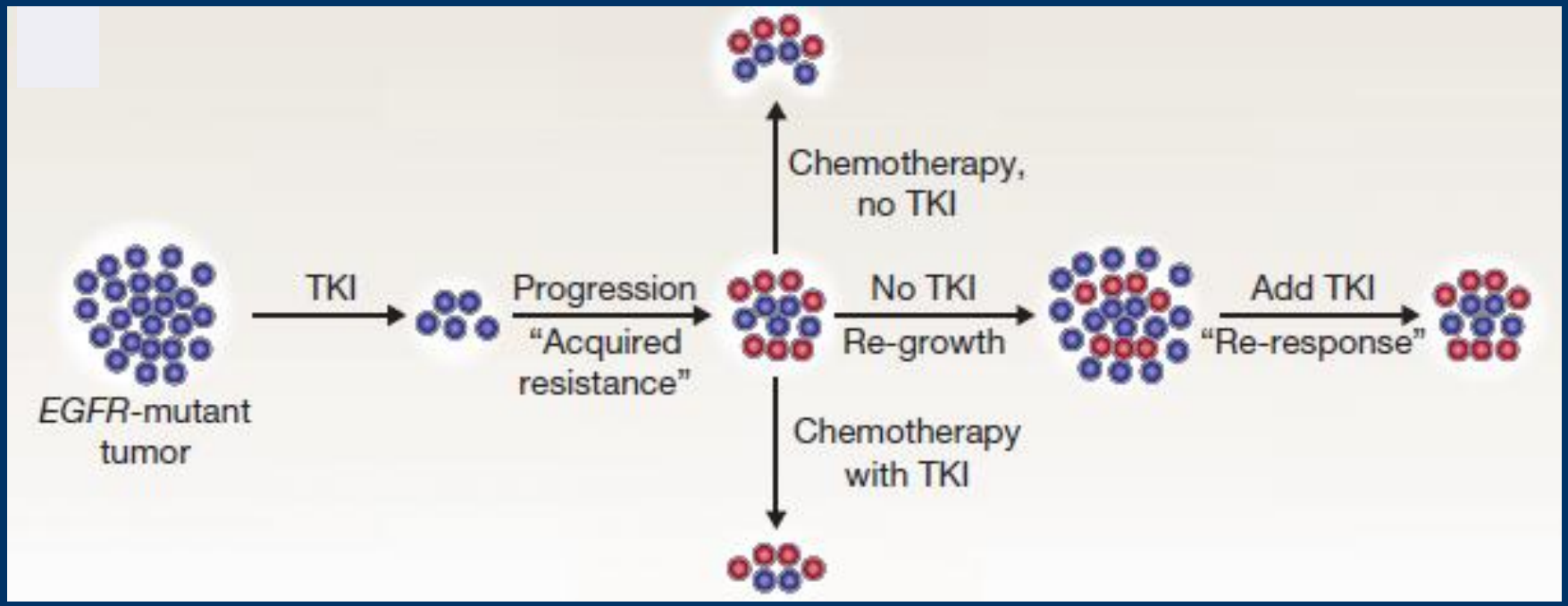


Goldberg, ASCO 2012, A#7524

Strategies At Progression

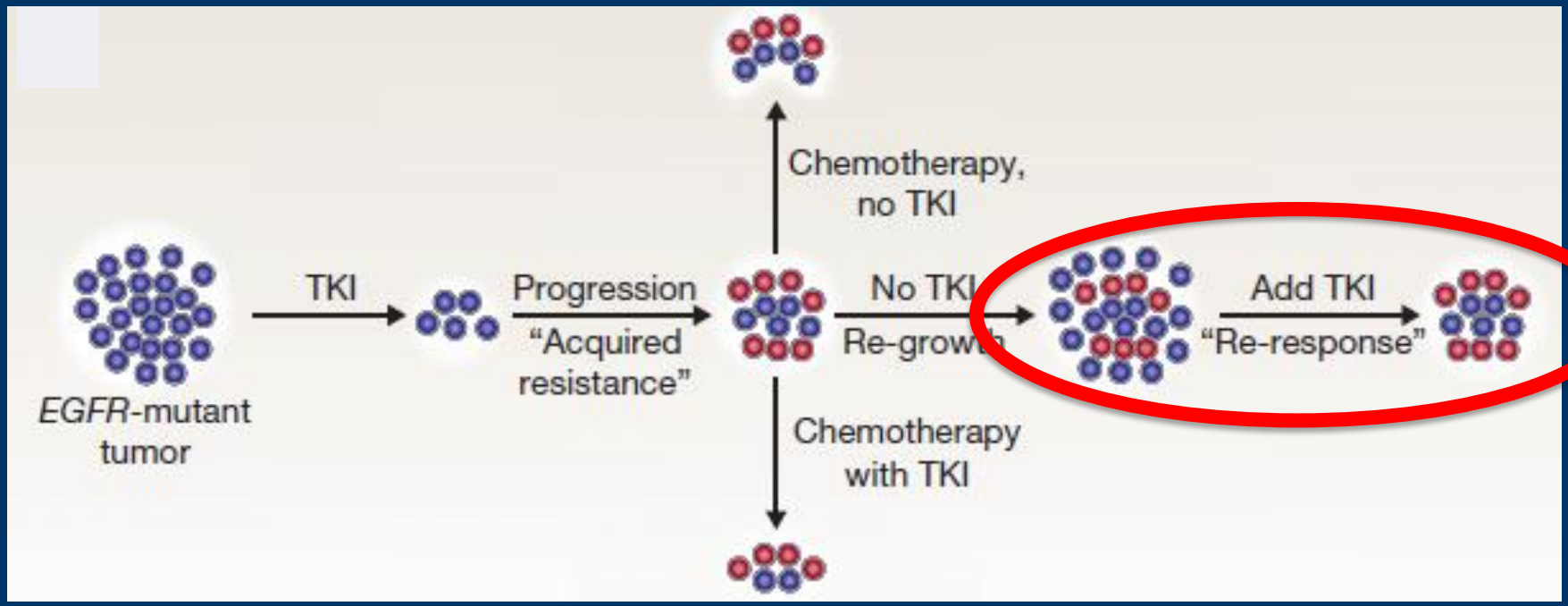
- Chemotherapy (w/wo EGFR TKI)
- Retreatment with “first” EGFR-TKI

Evolutionary modeling based on growth kinetics



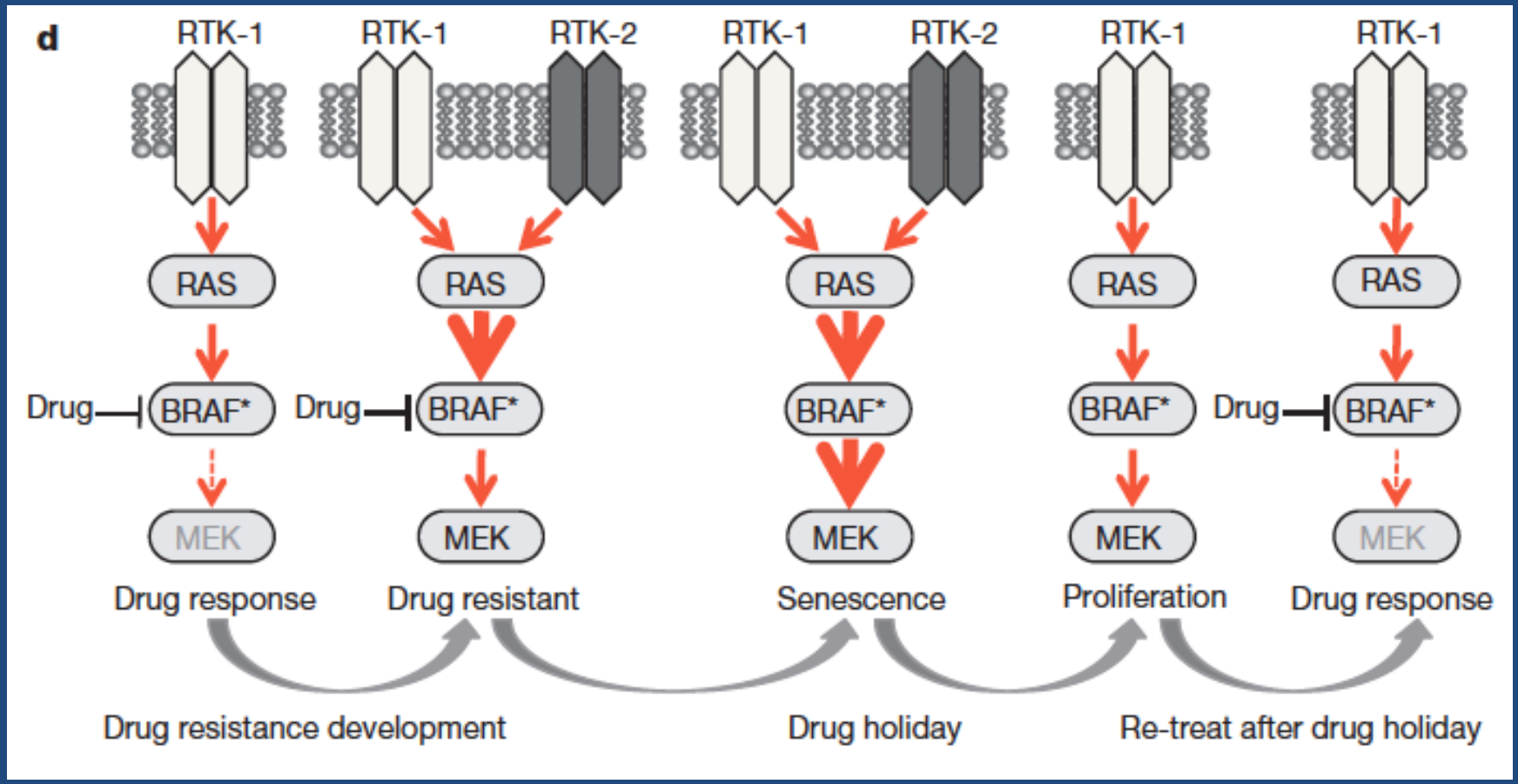
Chmielecki J, Sci Transl Med 2011

Evolutionary modeling based on growth kinetics



Chmielecki J, Sci Transl Med 2011

The biology behind retreatment?



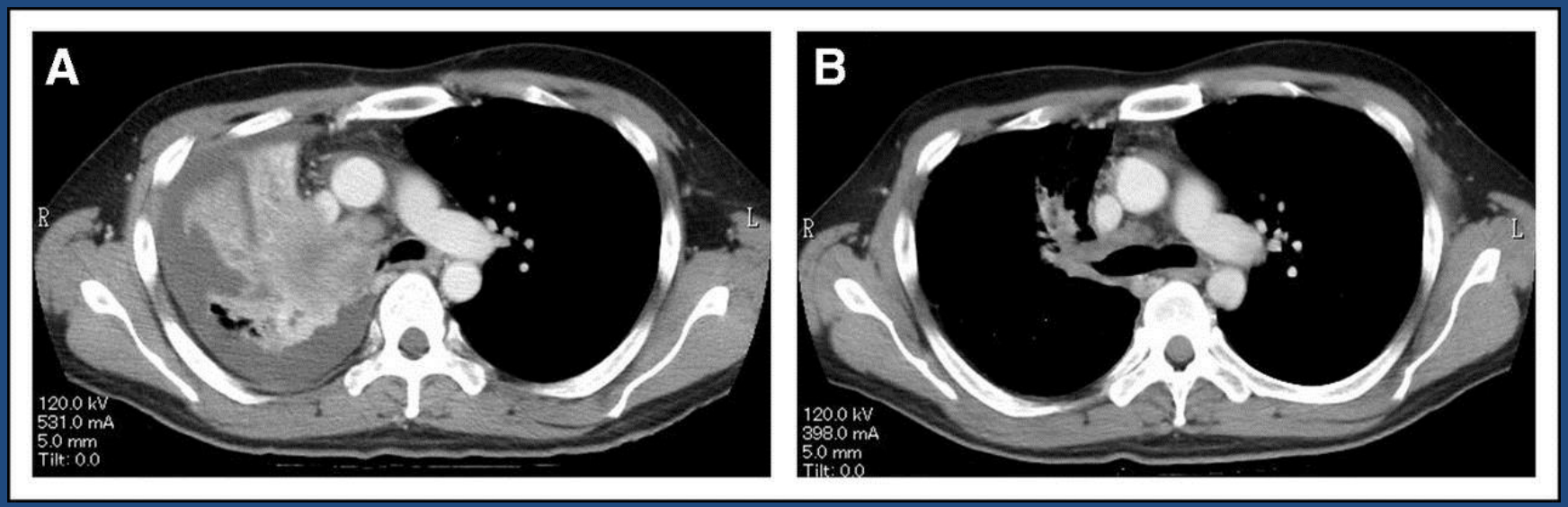
Sun et al. Nature 508,118,2014

Results of EGFR-TKI retreatment

	Median (range)
Length of TKI ‘holiday’	9.5 months (3-36)
Follow-up after retreatment	9 months (1.5-16^{+})
Progression free survival	6.5 months (1-16^{+})
	Number of patients (%)
Response to reintroduction TKI	
Partial remission	5 (36)
Stable disease	7 (50)
Progressive disease	2 (14)

Becker et al. Eur. J. Cancer 2012

Crizotinib retreatment

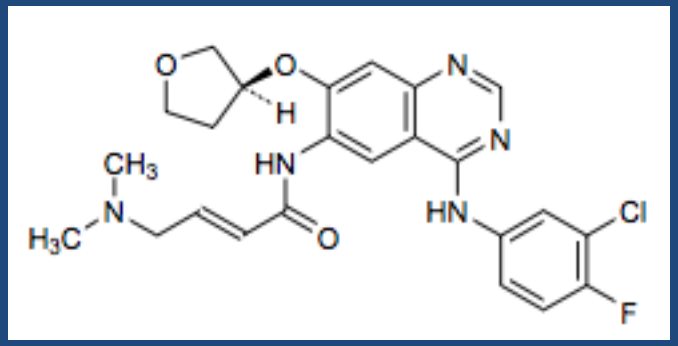


Matsuoka et al. J. Clin. Oncol. 2013

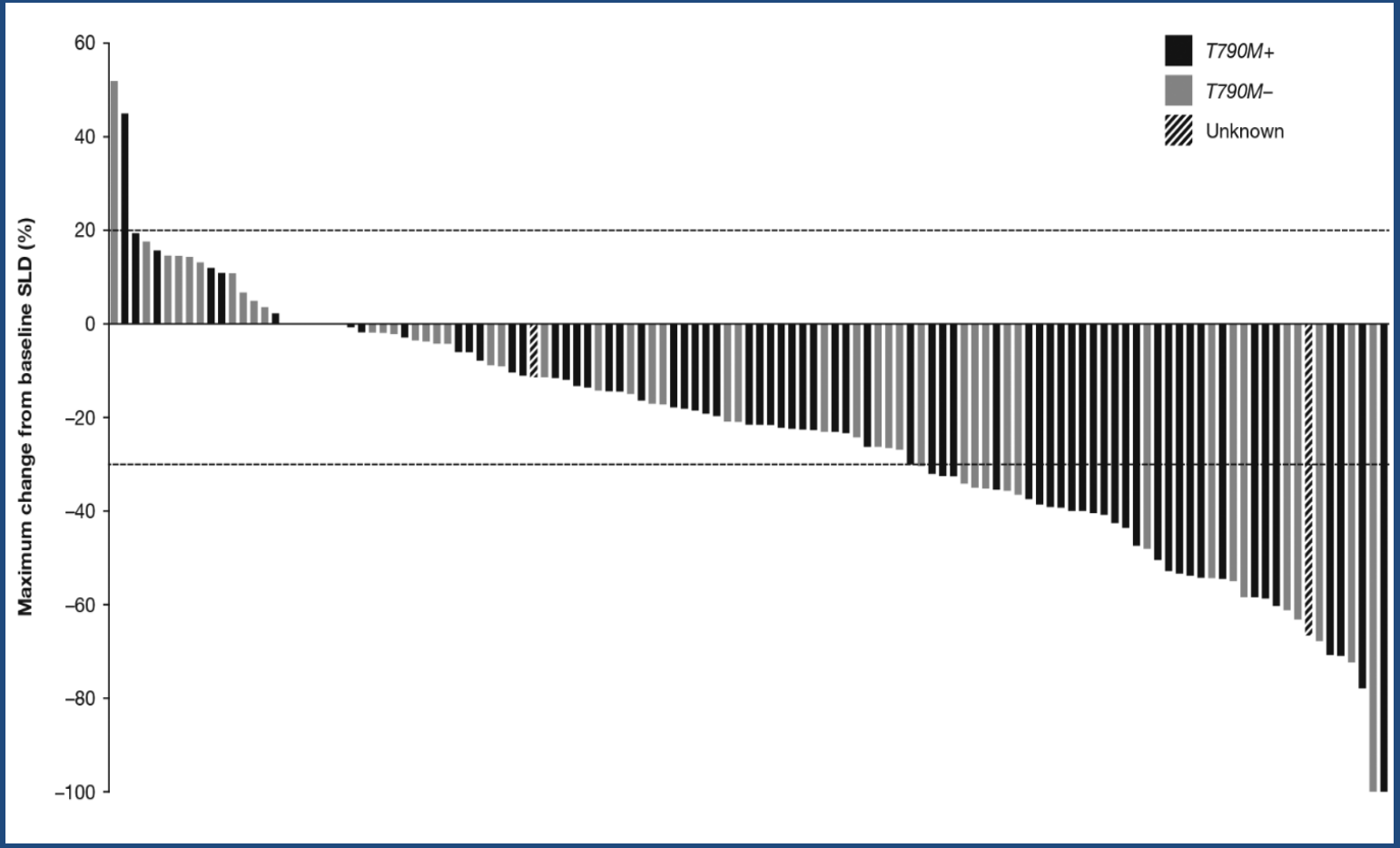
Strategies At Progression

- Chemotherapy (w/wo EGFR TKI)
- Retreatment with “first” EGFR-TKI
- “Dual blockade”

Strategies At Progression
Dual Blockade

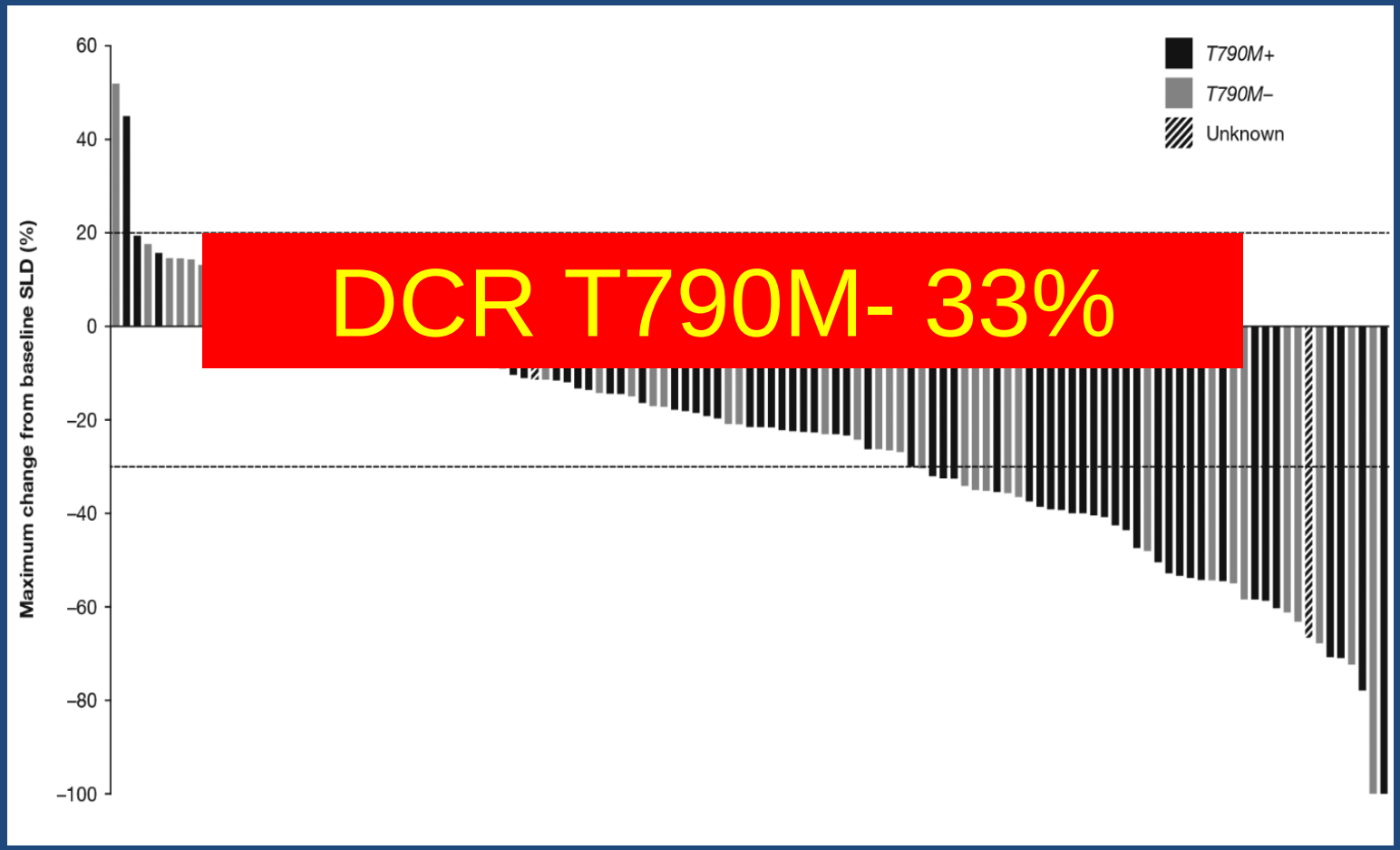


Afatinib + Cetuximab Responses by mutation



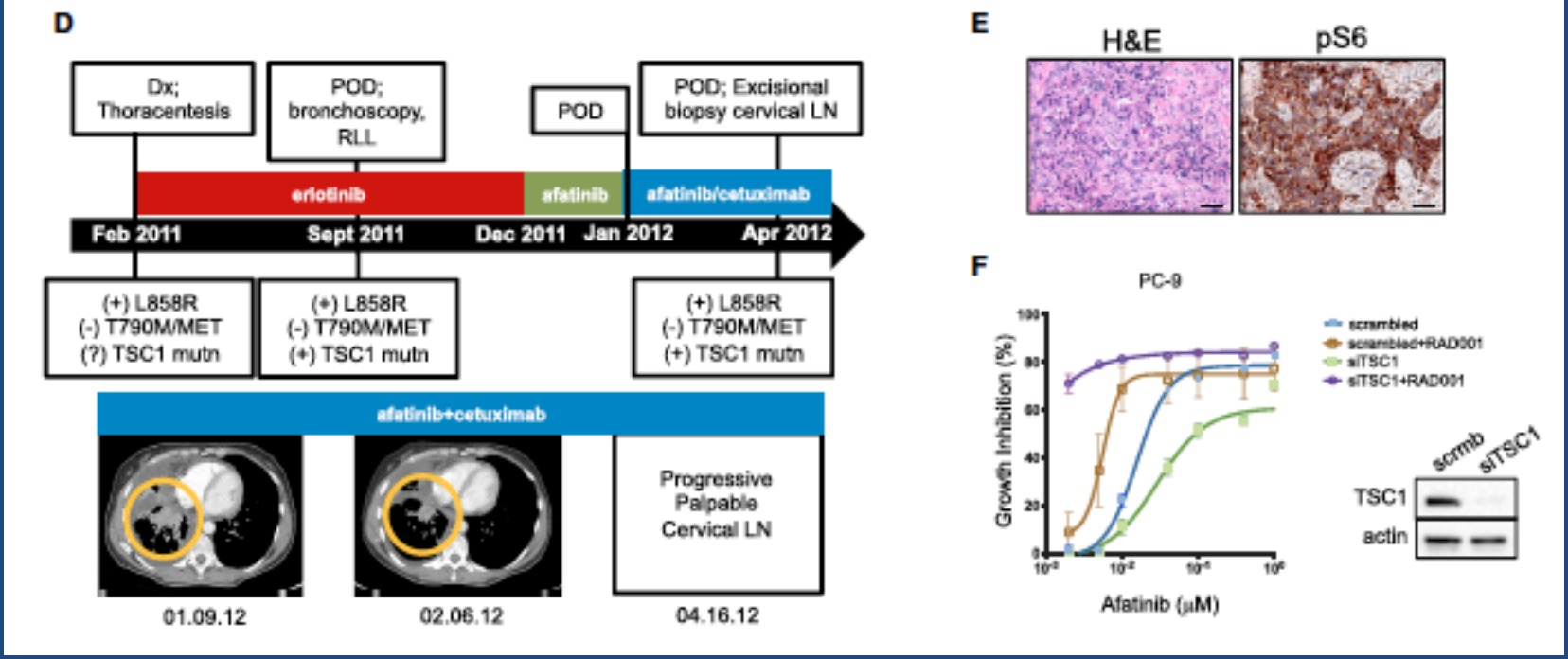
Janjigian Cancer Discovery 2014

Afatinib + Cetuximab Responses by mutation



Janjigian Cancer Discovery 2014

Resistance to Afa-Cetuximab mediated by mTORC1

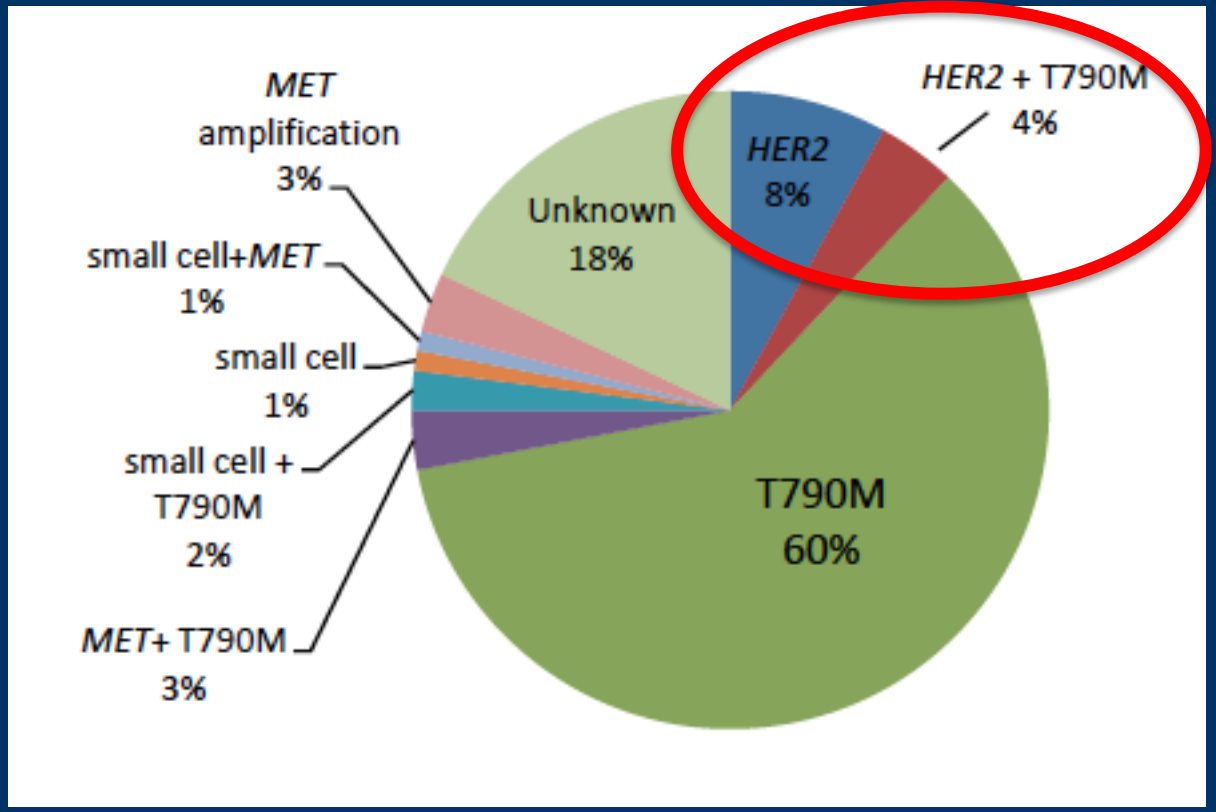


Pirazzoli. Cell Reports 2014

Strategies At Progression

- Chemotherapy (w/wo EGFR TKI)
- Retreatment with “first” EGFR-TKI
- “Dual blockade”
- Attack side road resistance

Heterogenity at EGFR TKI resistance

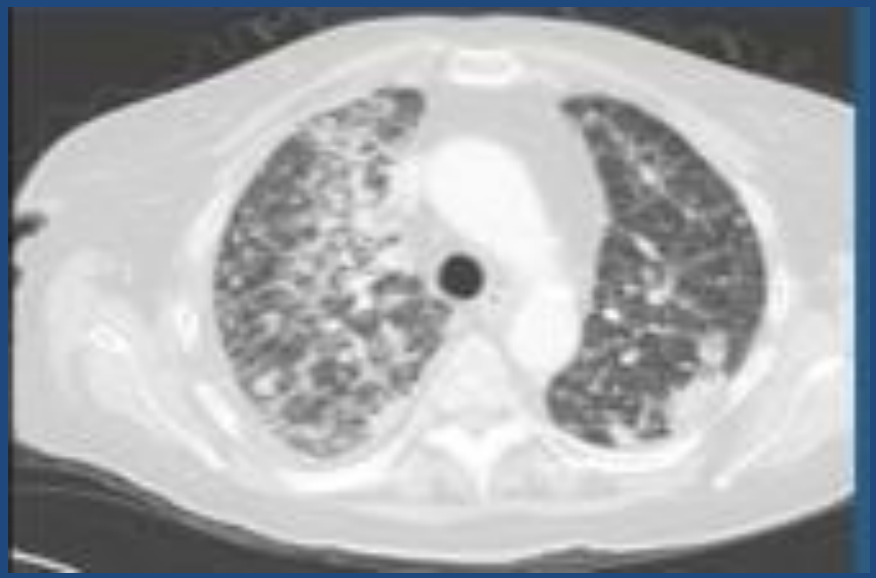


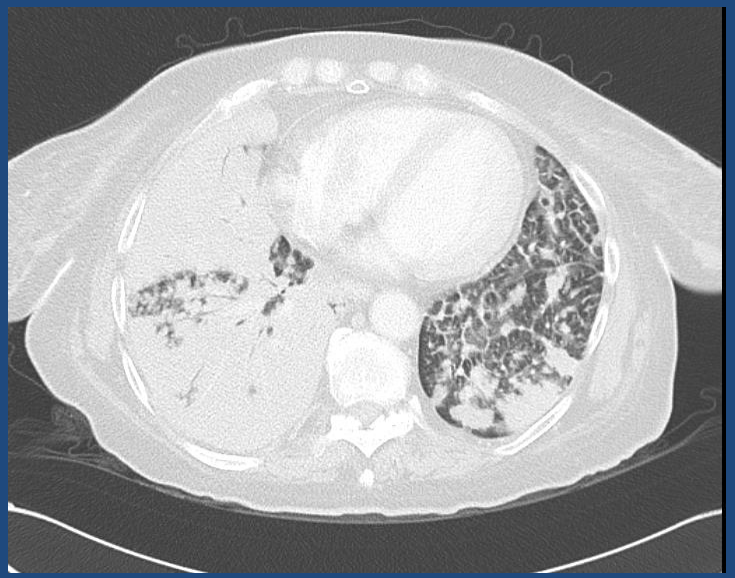
Yu et al. Clin. Cancer Res. 2013

Case

- Female 66 y 2007 Stage IV NSCLC
  - Cisplatin-gemcitabine, erlotinib, carboplatin-gemcitabine
- 2010 referral; biopsy revealed EGFR exon 19 del.
  - Placebo, carboplatin-pemetrexed, afatinib-cetuximab, pemetrexed, erlotinib
- August 2012: dyspnea.

CT scan

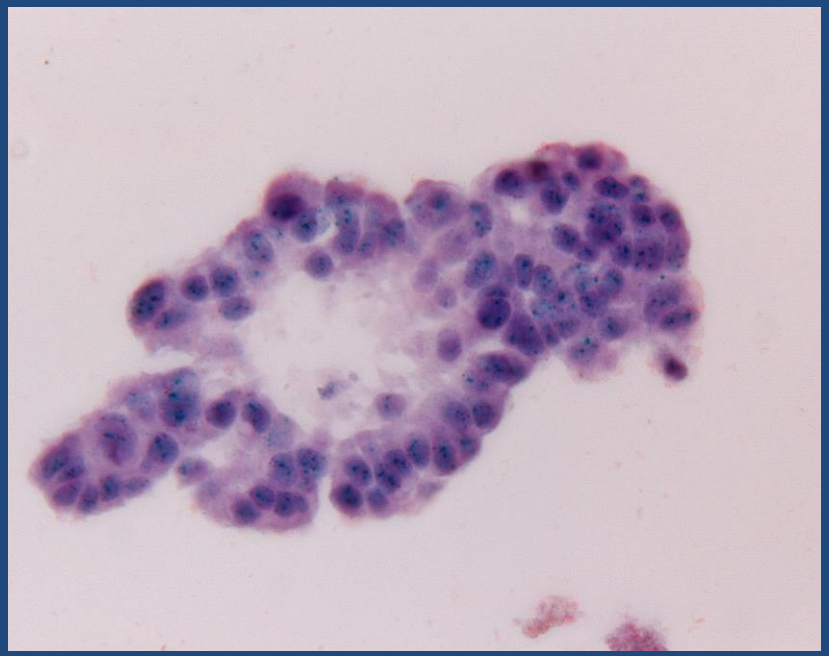




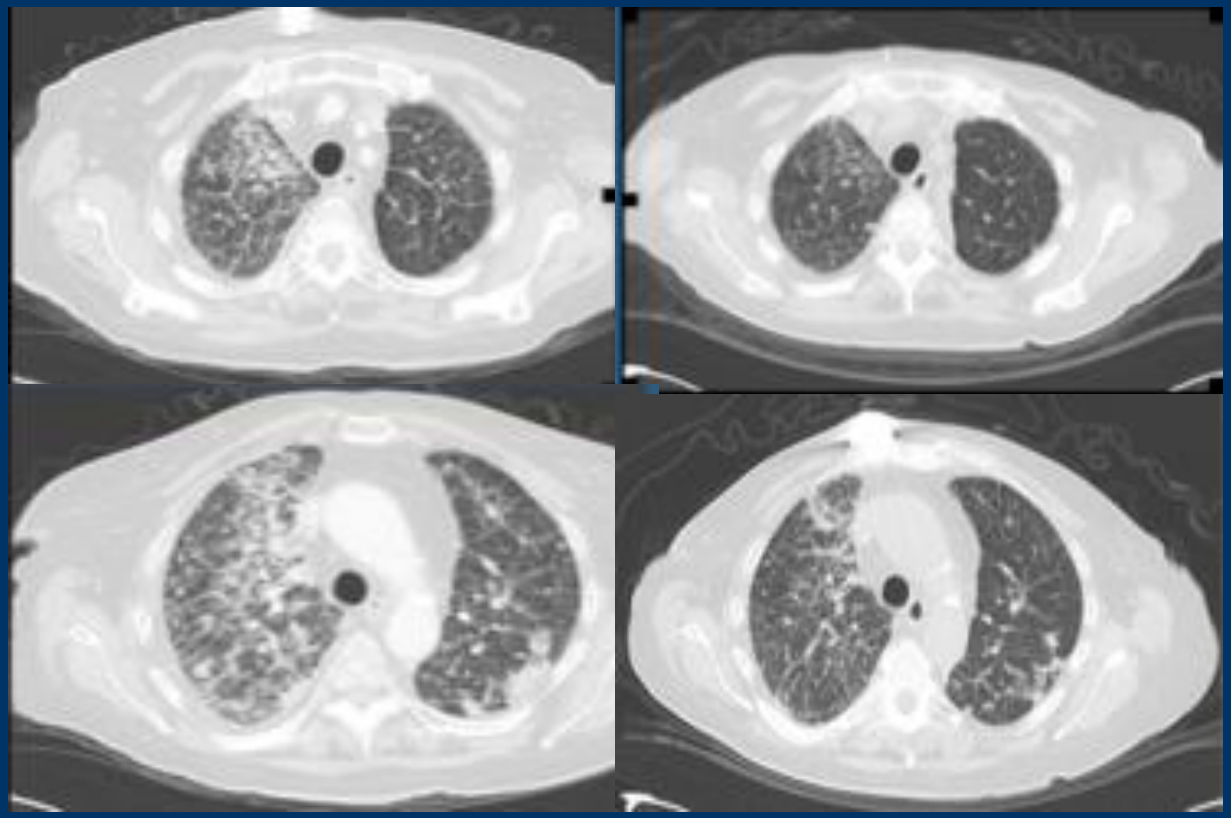
VUmc – unpublished data

Reassesment of pathology

- Biopsy taken at progression on erlotinib 2012
- EGFR exon 19 del
- HER2 IHC 2+
- HER2 CISH



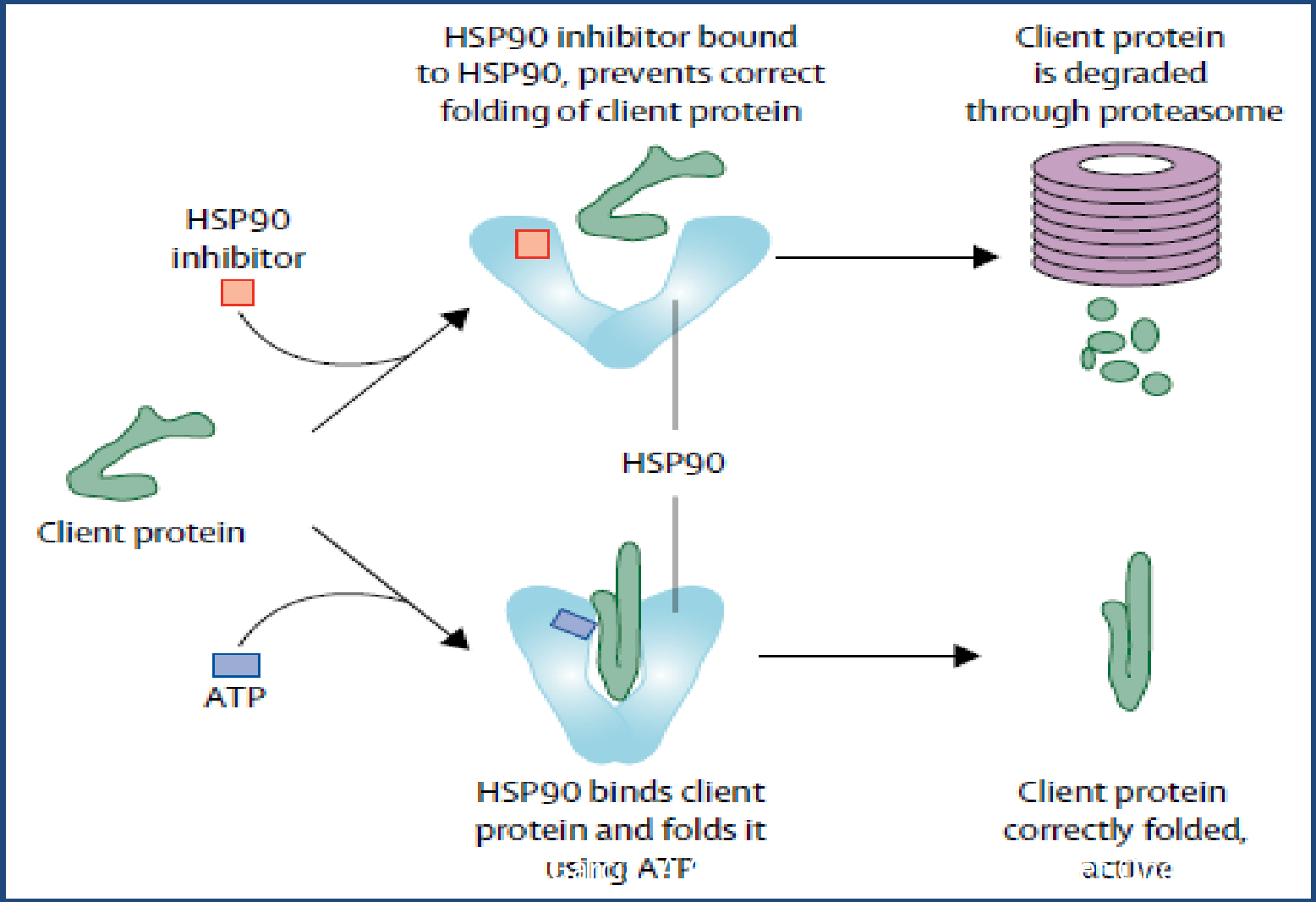
Trastuzumab at progression after Cetuximab-Afatinib



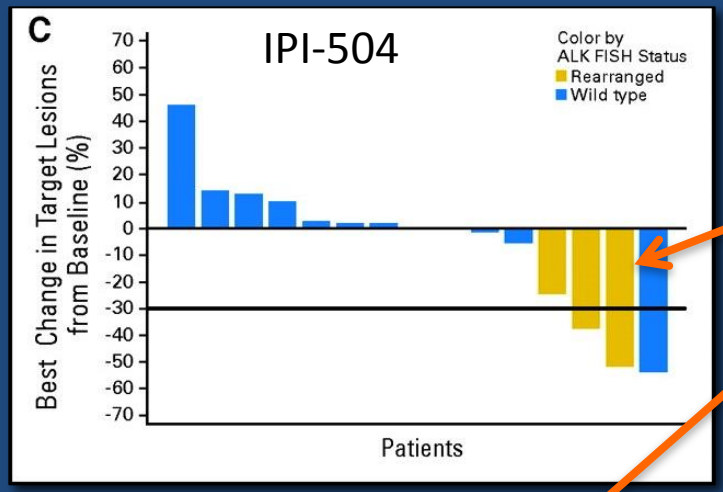
Strategies At Progression

- Chemotherapy (w/wo EGFR TKI)
- Retreatment with “first” EGFR-TKI
- “Dual blockade”
- Attack side road resistance
- Novel untargeted drugs

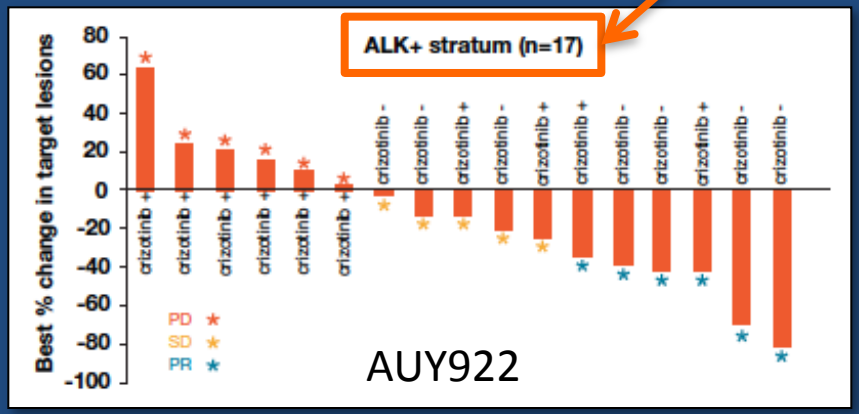
HSP90 Inhibition
Simultaneous inhibition of multiple molecular pathways



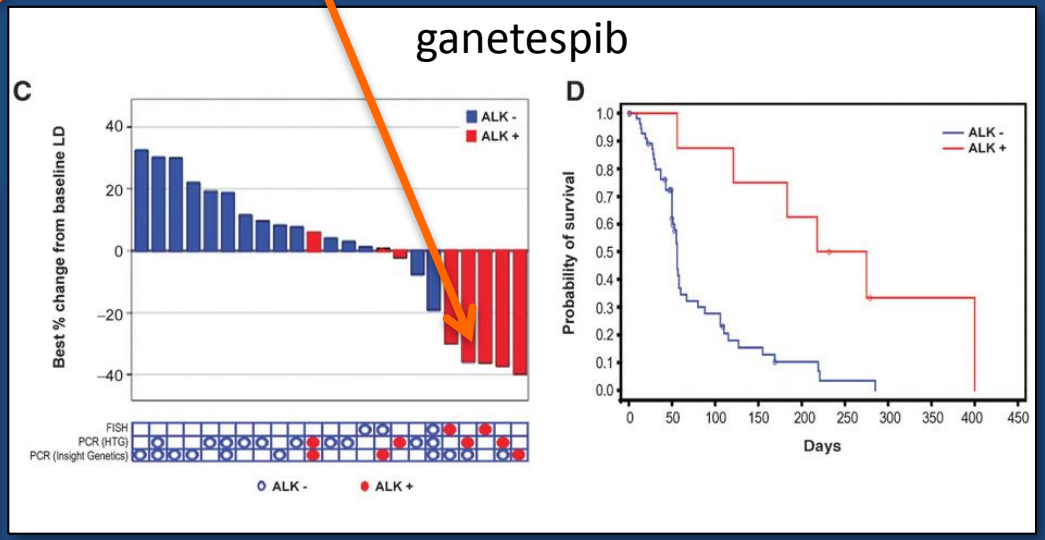
ALK + NSCLC
HSP90 Inhibitors



ALK+ patients



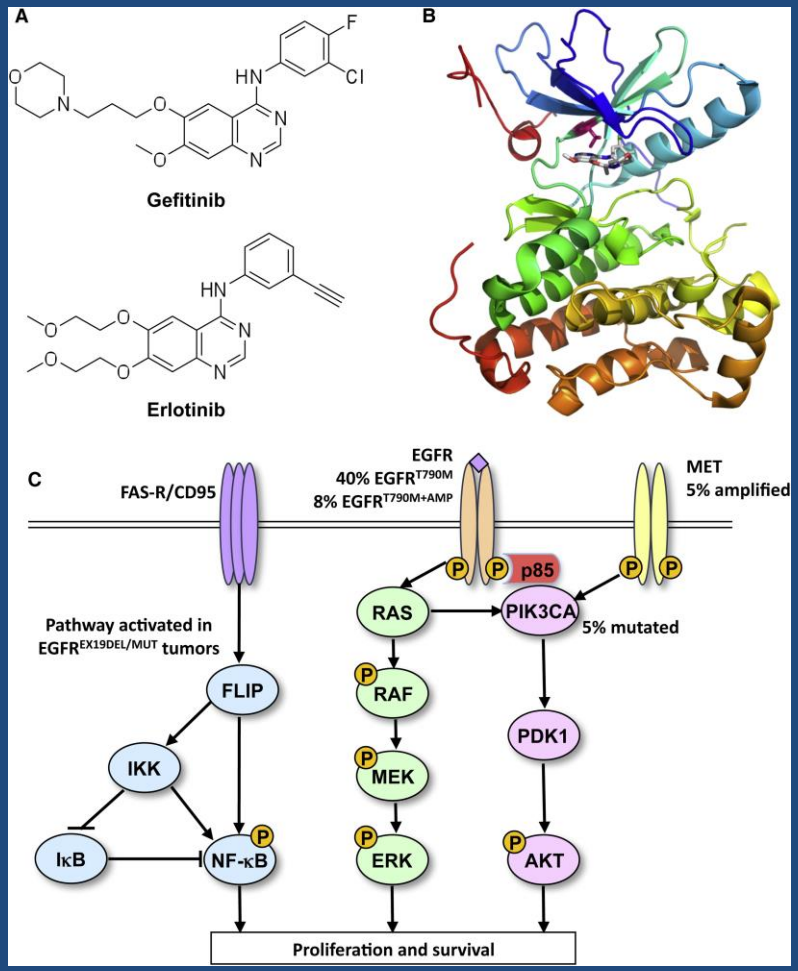
ganetespib



*2 patients with crizotinib-resistance had PD on ganetespib

Sequist et al., *J Clin Oncol*., (2010)
Garon et al., ASCO 2012
Socinski et al., *Clin Can Res* 2013

50 ways to leave (EGFR) inhibition



Workman and Clarke. Cancer Cell 19,437,2011

Some ways

- Met amplification
- NF-1 downregulation
- Stromal components
  - HGF
  - Amphiregulin
- NFK beta downregulation
- Axl overexpression

Donald Rumsfeld

“There are known knowns. These are things we know that we know. There are known unknowns. That is to say, these are things that we know we don't know. But there are also unknown unknowns. These are things we don't know we don't know.”

Leading Edge
Essay

Cell

It's Diagnostics, Stupid

René Bernards[1,*]
[1]Division of Molecular Carcinogenesis, Center for Biomedical Genetics and Cancer Genomics Center, The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
*Correspondence: r.bernards@nki.nl
DOI 10.1016/j.cell.2010.03.018

To stem the spiraling cost of cancer treatment, a concerted effort is urgently needed to develop molecular diagnostics to better identify the patients that respond to expensive targeted therapies. Opportunities and obstacles in the development of such drug response biomarkers are discussed here.

“Playing chess with cancer”:

only feasible through

multidisciplinary approach