UNIVERSITY OF TORINO – DEPARTMENT OF ONCOLOGY

WALCE
Women Against Lung Cancer in Europe

Mechanisms of primary/secondary resistance to EGFR inhibitors

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www.womengainstlungcancer.eu

- How we define PD/resistance in a patient treated with EGFRTki
- Is there a role for chemotherapy?
- Do we accept a different approach for OLIGO and SYSTEMIC PD?
- Primary and Acquired resistance: quick overview
- Target the Resistance

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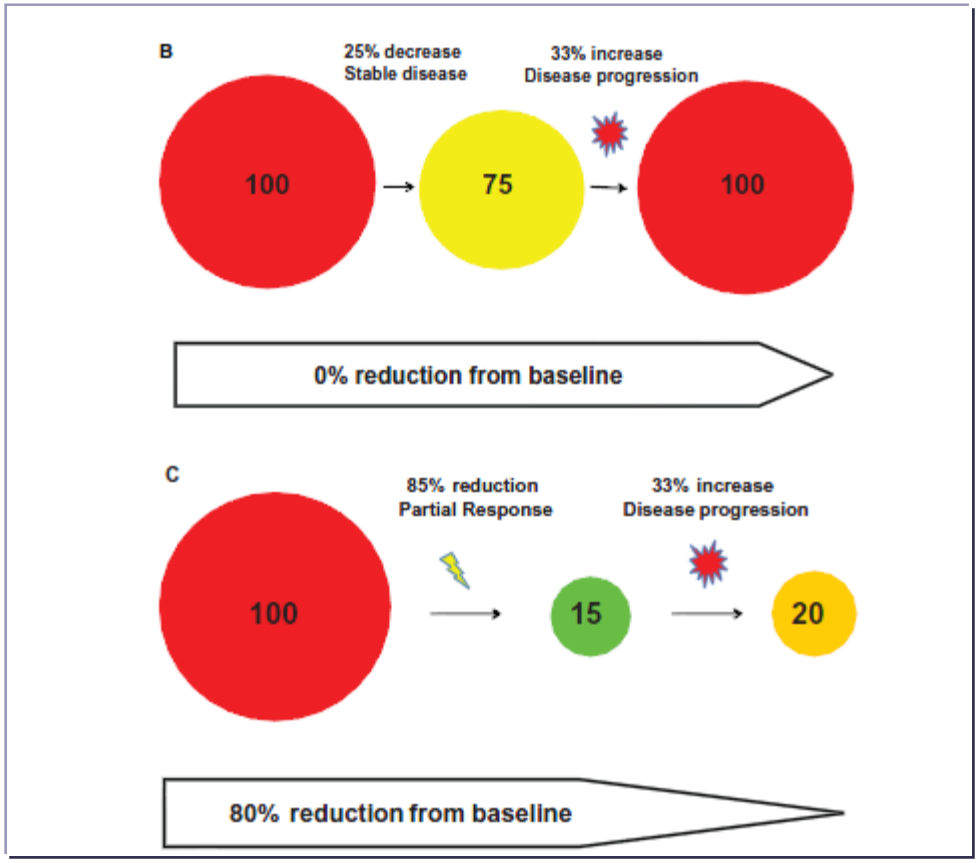
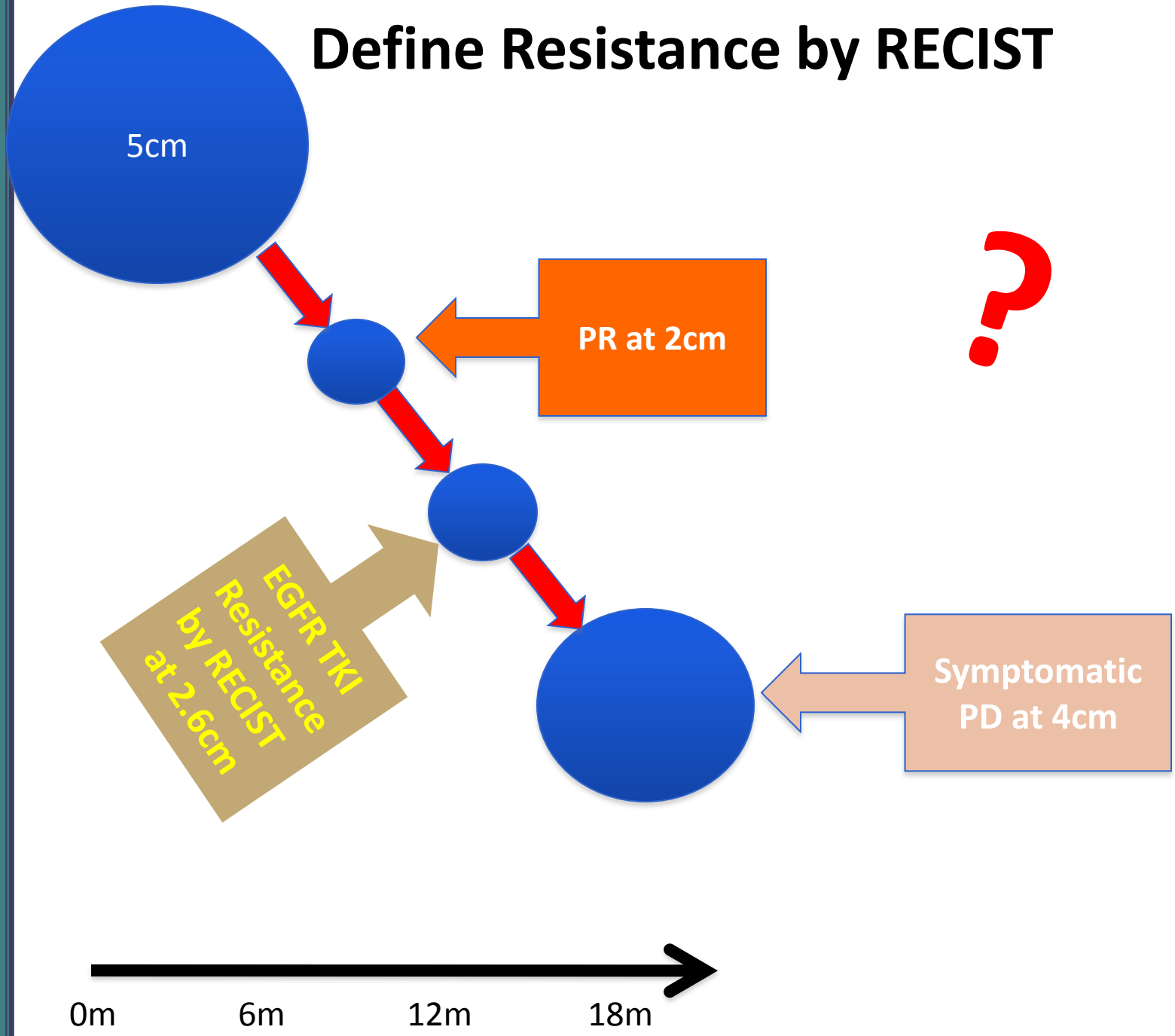
Some considerations for patients who progress on targeted therapy

- **The definition of disease progression in the context of EGFR inhibition may differ from RECIST criteria and "requires" further refinement.**



Ou S-H I, Drug Design, Development and Therapy 2011

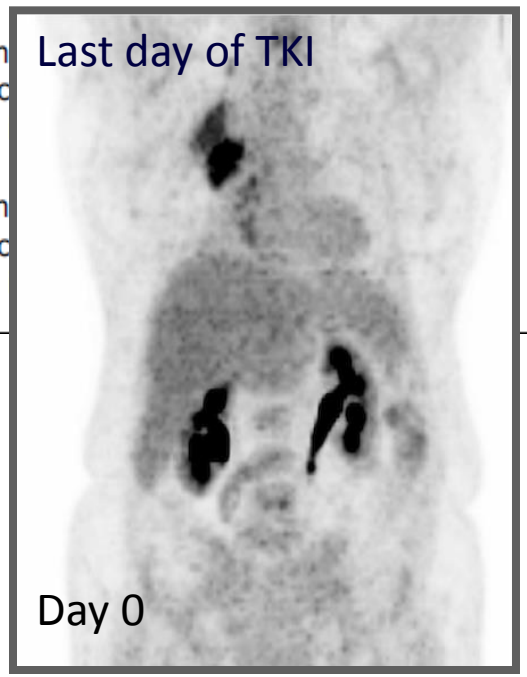
Define Resistance by RECIST

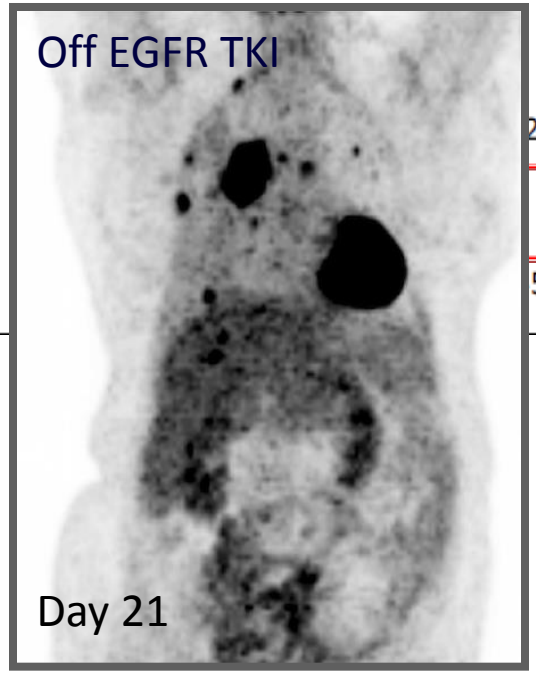


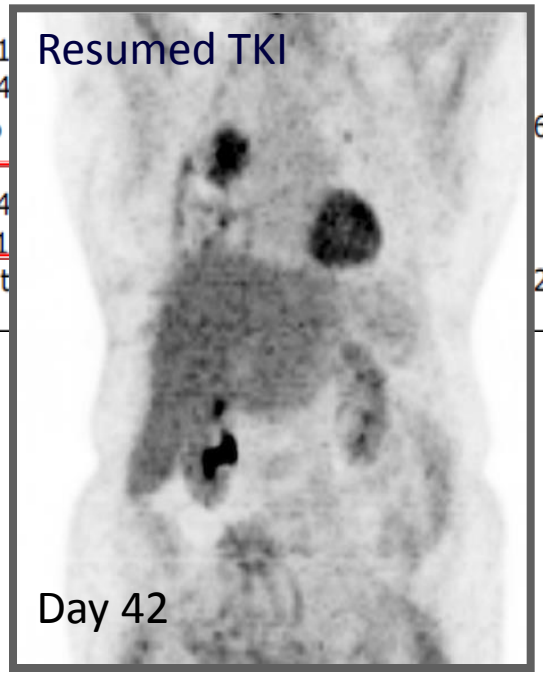
Cessation of EGFR TKI upon progression

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%



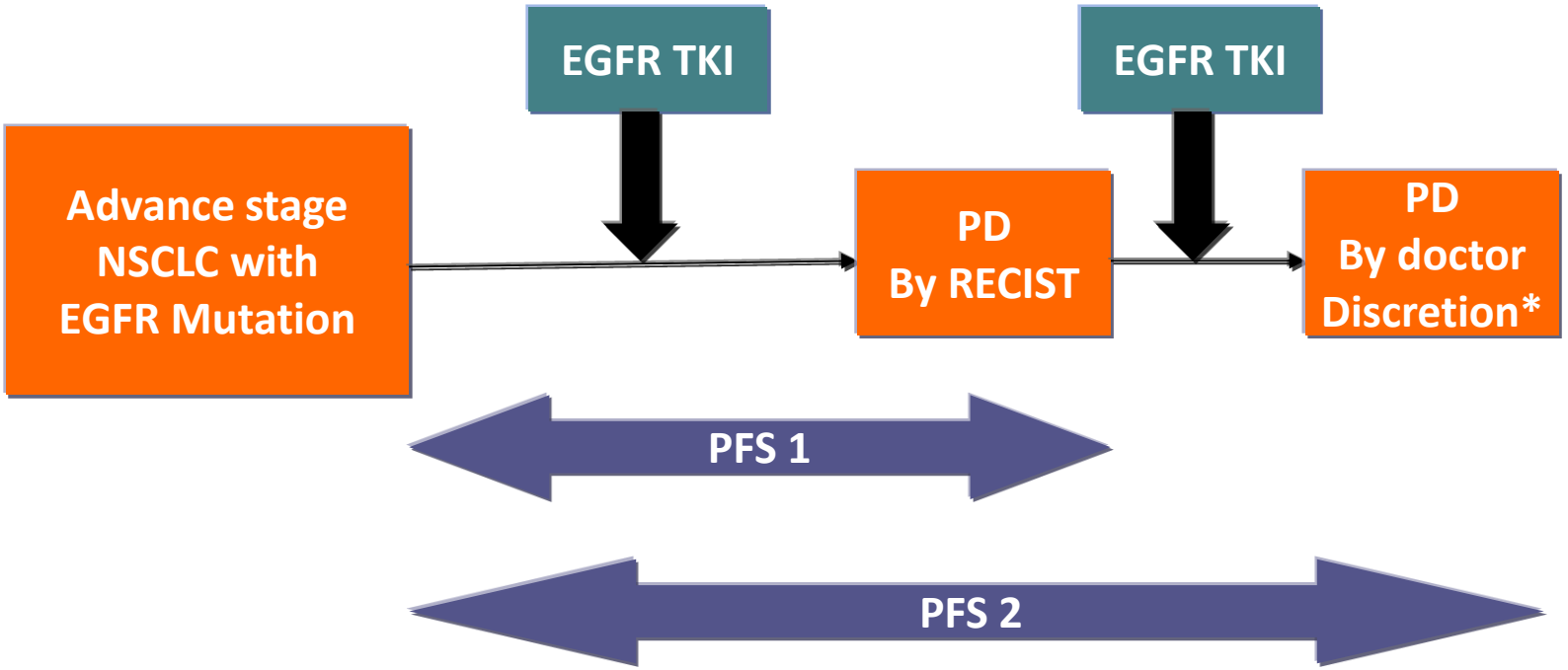




Riely et al Clin Can Res 13:5150, 2007

Defining resistance by RECIST may lead to premature termination of TKI

ASPIRATION: To optimize treatment duration



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

PI: K Park

Annals of Oncology 23 (Supplement 7): vii56–vii64, 2012
doi:10.1093/annonc/mds226

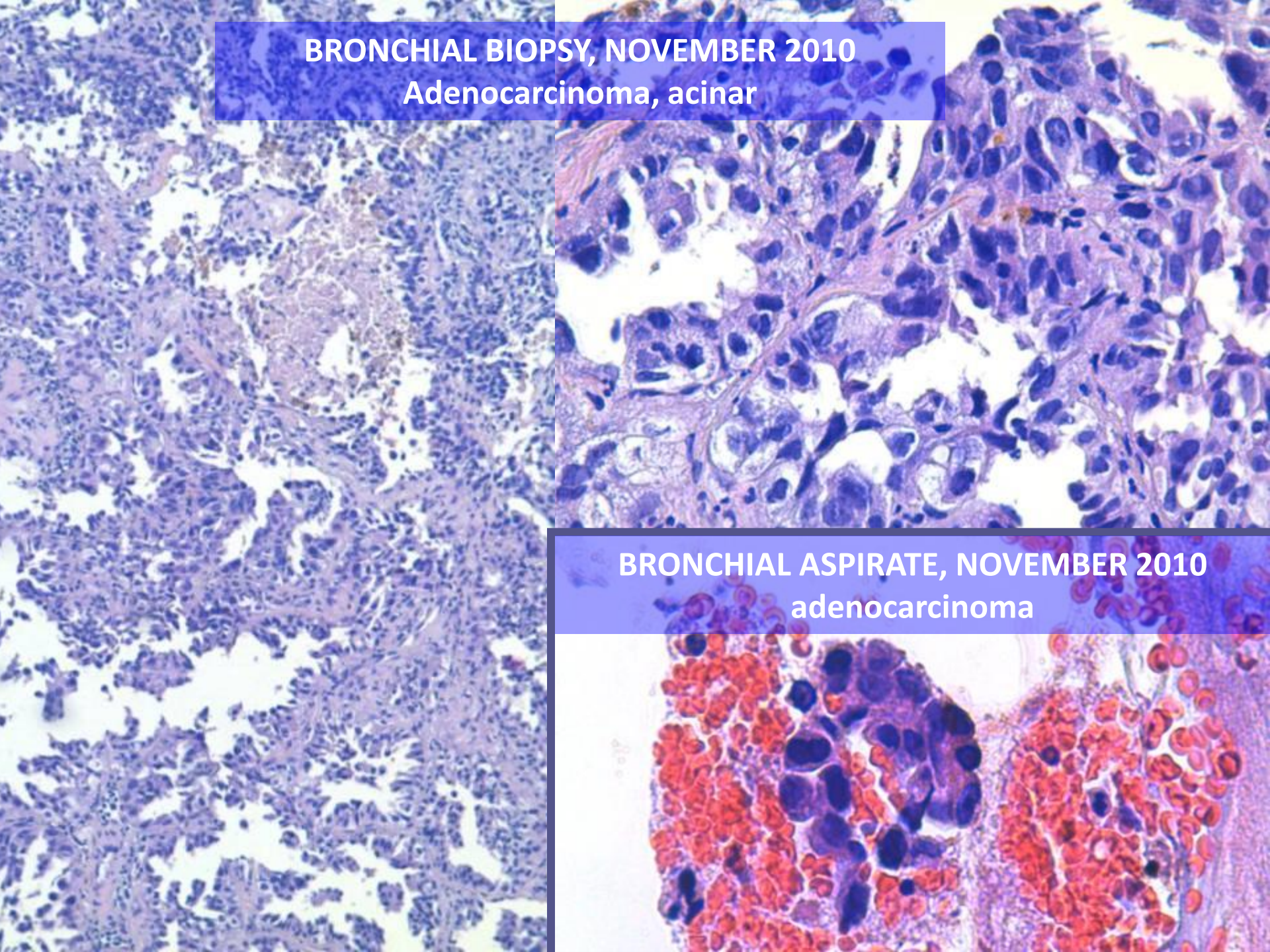
Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

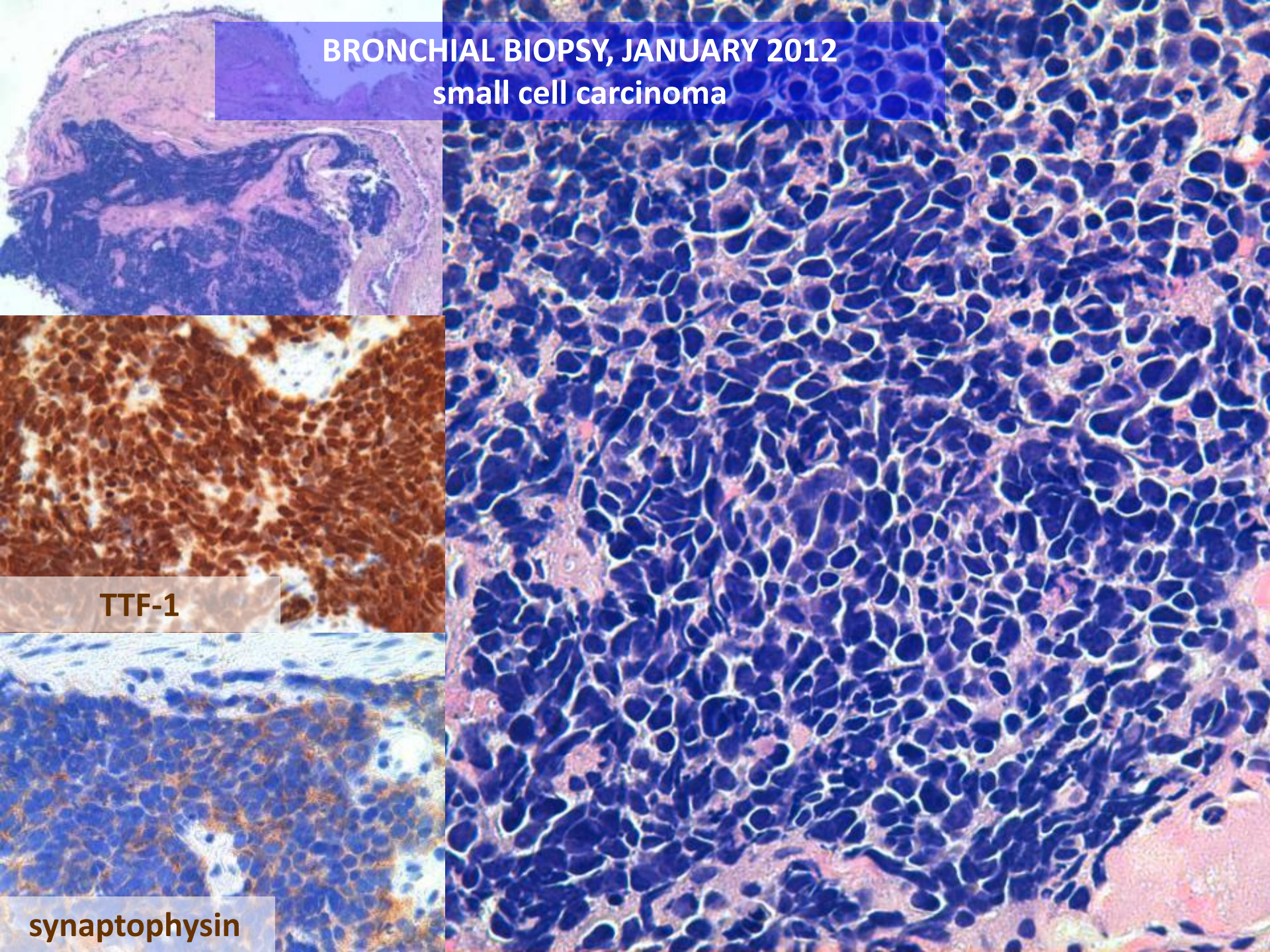
S. Peters[1], A.A. Adjei[2], C. Gridelli[3], M. Reck[4], K. Kerr[5] & E. Felip[6] on behalf of the ESMO Guidelines Working Group*

[1]Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [2]Department of Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA; [3]Department of Medical Oncology, 'S.G. Moscati' Hospital, Avellino, Italy; [4]Department of Thoracic Oncology, Hospital Grosshansdorf, Grosshansdorf, Germany; [5]Aberdeen Royal Infirmary, Aberdeen, UK; [6]Vall d'Hebron University Hospital, Barcelona, Spain

Re-biopsy at disease progression should be considered [7].

Diagnosis (and tests) do not end at the time of diagnosis


BRONCHIAL BIOPSY, NOVEMBER 2010
Adenocarcinoma, acinar
BRONCHIAL ASPIRATE, NOVEMBER 2010
adenocarcinoma


BRONCHIAL BIOPSY, JANUARY 2012
small cell carcinoma
TTF-1
synaptophysin

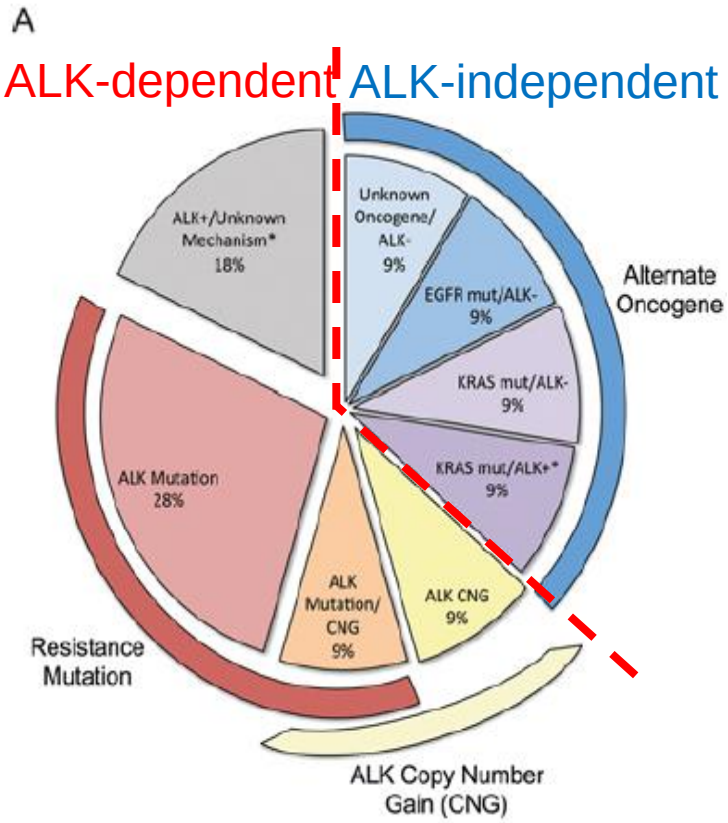
Emergence of EGFR&ALK Resistance Mechanisms:
Rebiopsy of EGFRm&ALK+ tumors at progression

A

Histology	Adeno		Adeno		Adeno
Genotype	L858R TP53		L858R TP53 T790M		L858R TP53
EGFR TKI status	Sensitive		Resistant		Sensitive
Tumor burden					
Treatment	Chemo	Erlotinib		Chemo	Chemo	Erlotinib*
Timeline	2007	2008		2009		2010

B

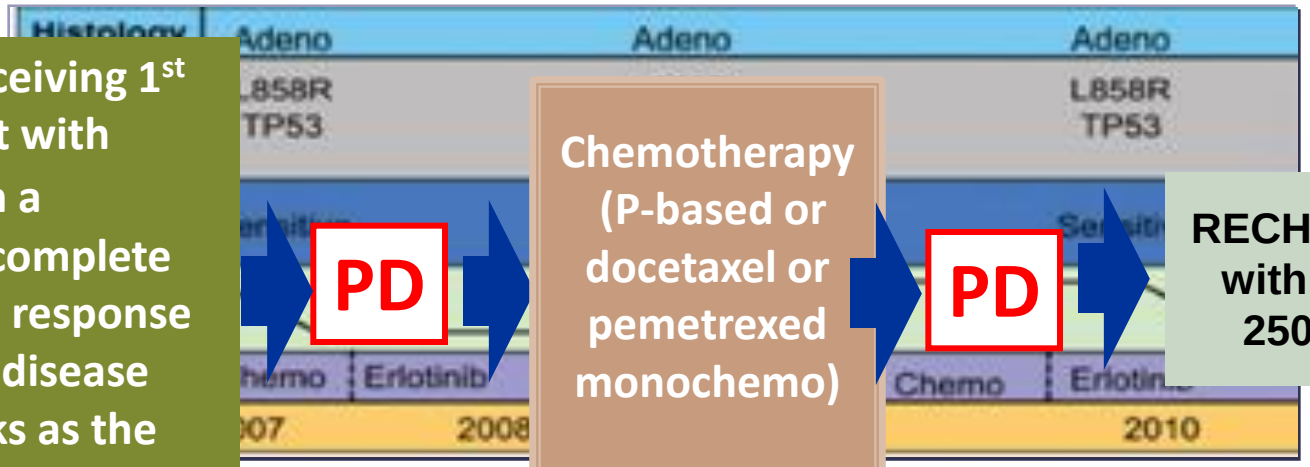
Histology	Adeno		SCLC	Adeno	SCLC
Genotype	L858R		L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI status	Sensitive		Resistant	Sensitive	Resistant
Tumor burden					
Treatment	Erlotinib		C+RT	Erlotinib	C+ RT
Timeline	2008	2009		2010	



Doebele et al, CCR 2012

Sequist L et al, Sci Transl Med 2011
Zakowski MF et al NEJM 2006
Morinaga R et al, Lung Cancer 2007

Is there a room for rechallenge?

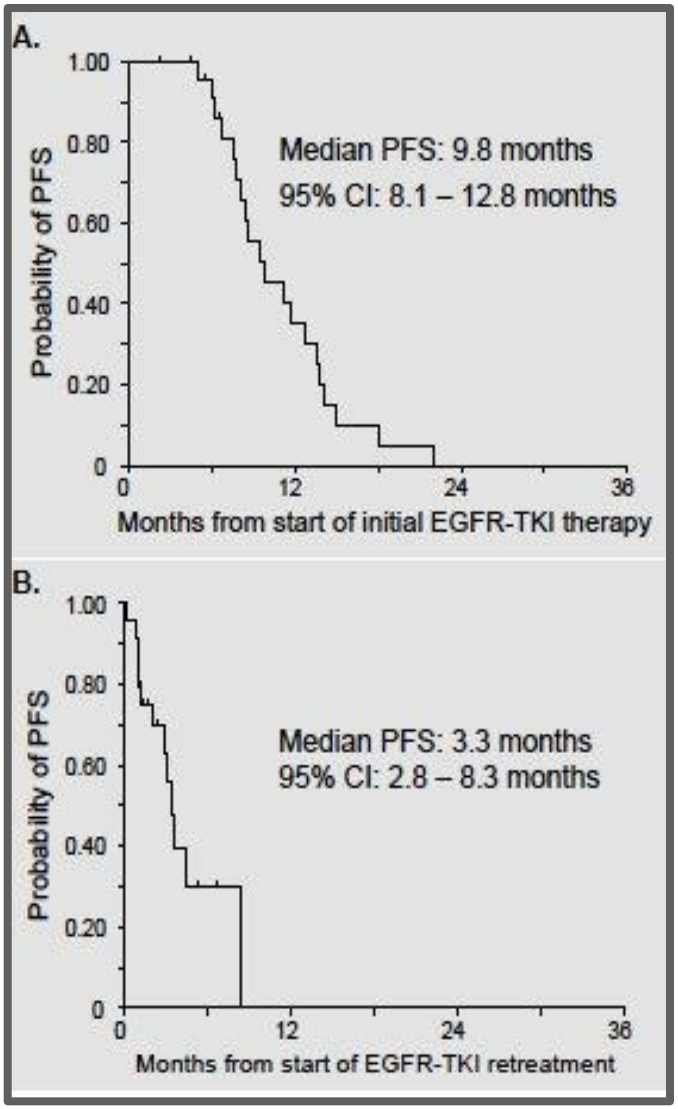


EGFRm+ pts receiving 1st line treatment with **gefitinib** with a documented complete (CR) or partial response (PR) or stable disease (SD) >12 weeks as the best response

Ph II trial; PI: F De Marinis

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

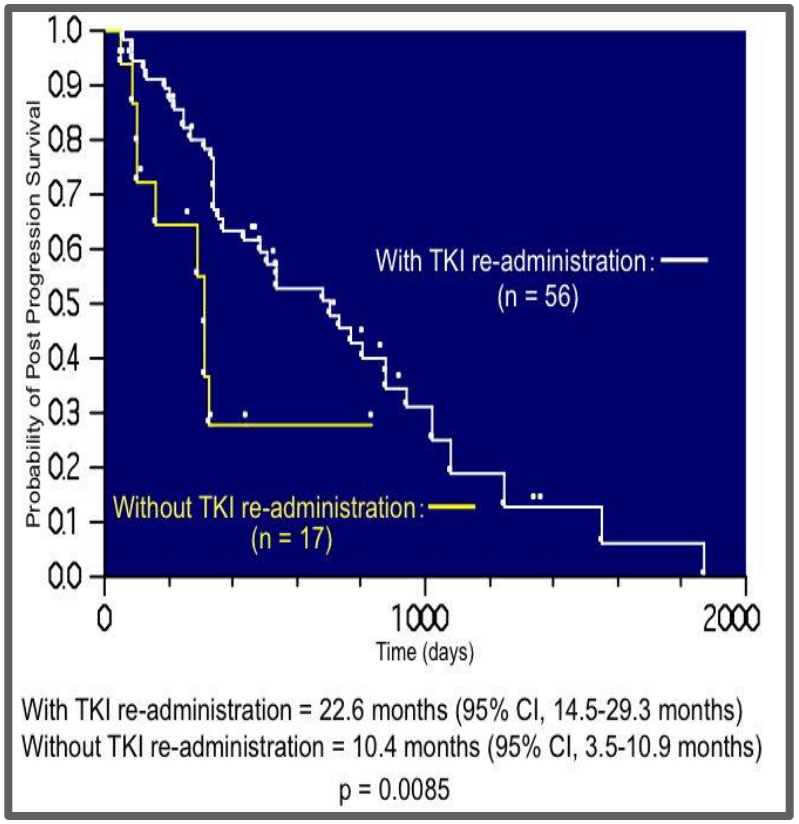
- Retrospective, 24 pts (over 9.5 yrs) with activating EGFR mutation after AR to gefitinib (30%) or erlotinib (70%)
- RR 4%, SD 63%
- Median interval off EGFR TKI 5 mo (range 2-46 mo)
- Greater benefit w/longer interval of EGFR TKI (PFS 4.4 vs. 1.9 mo for 6 mo interval off EGFR TKI)



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

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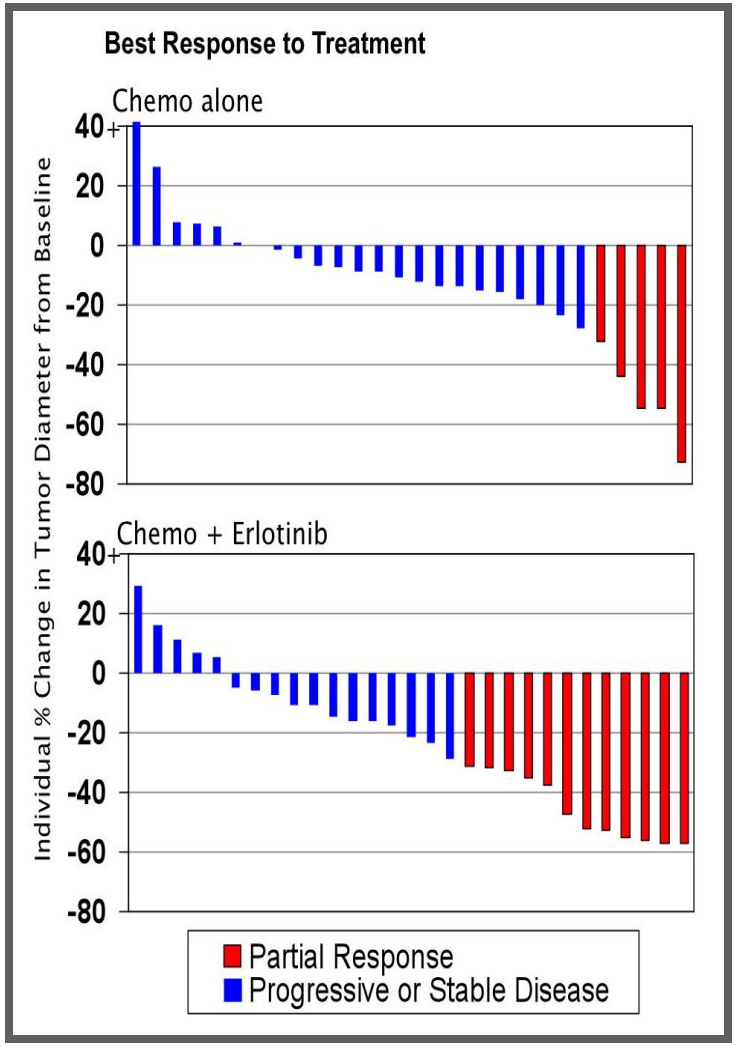
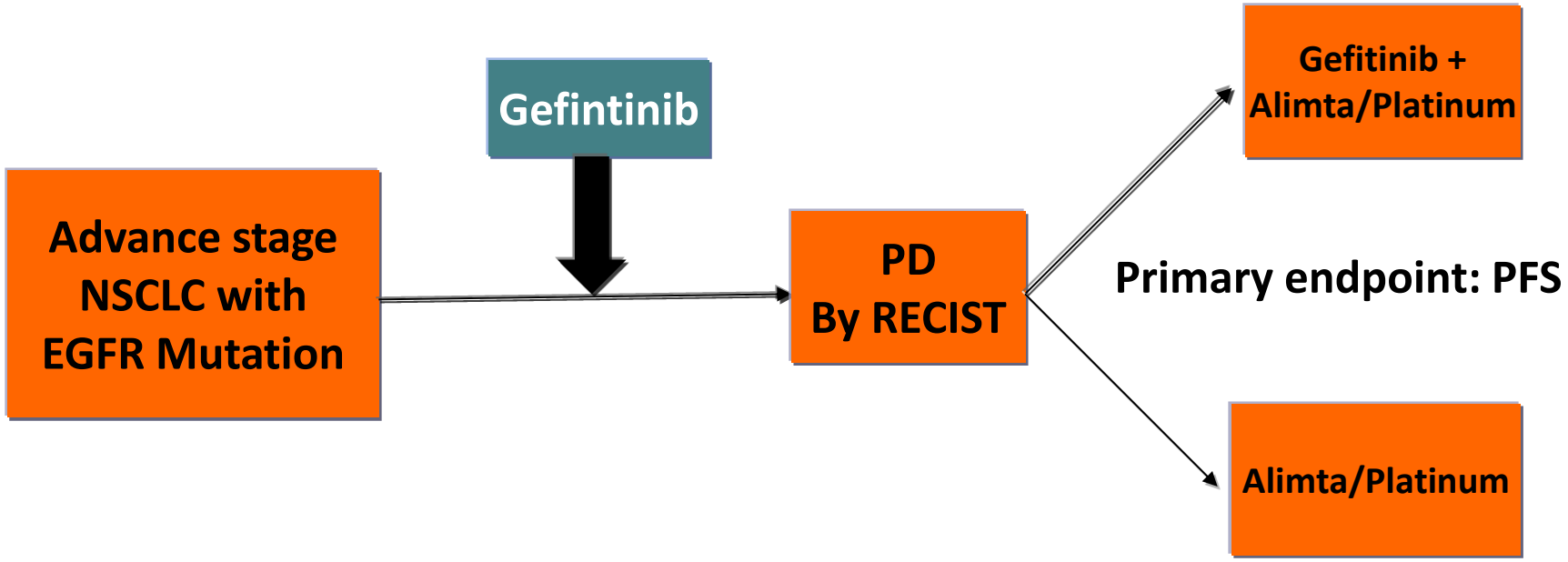
Chemo/Erlotinib vs. Chemo Alone at Progression after Acquired Resistance

- 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

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

RAND

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

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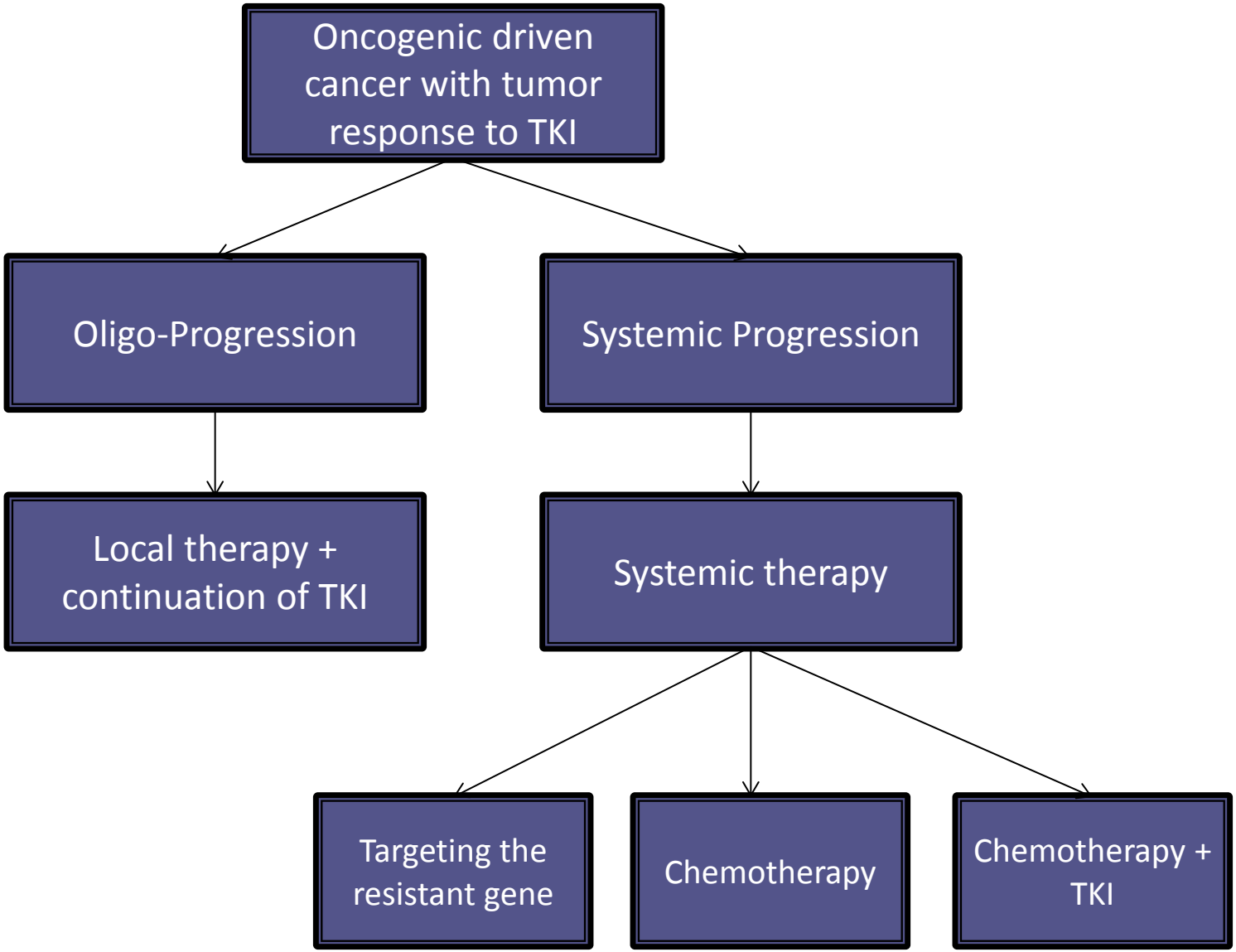
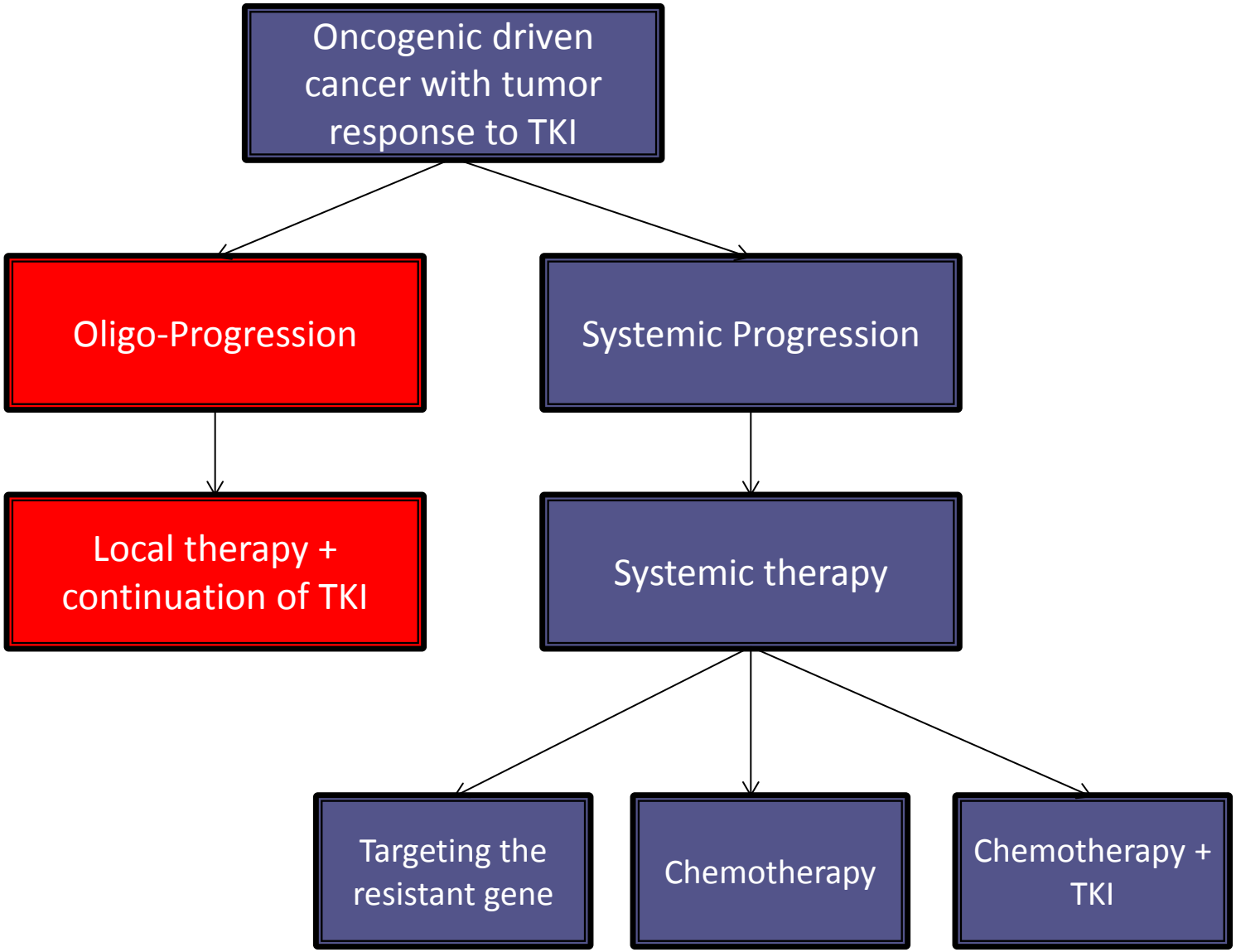
Treatment of TKI Resistance

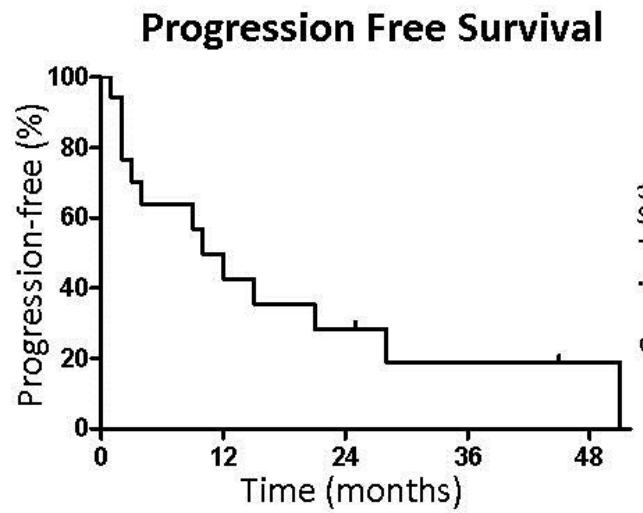


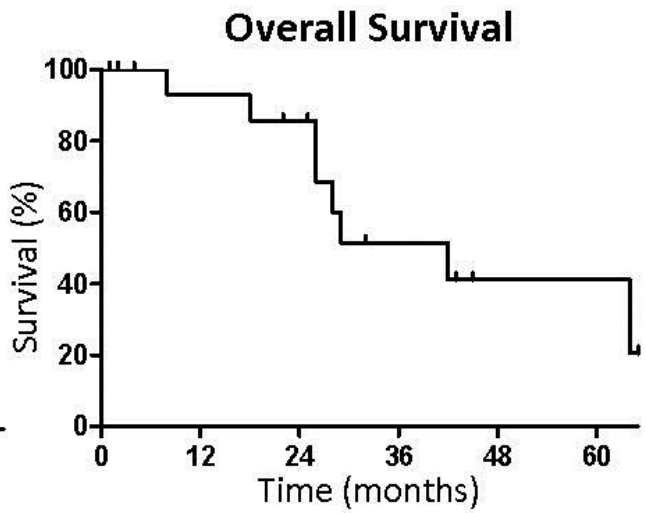
Treatment of TKI Resistance



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

Weickhardt A et al, Proc ASCO 2012 # 7526

PFS of patients treated with local therapy and continuation of TKI therapy

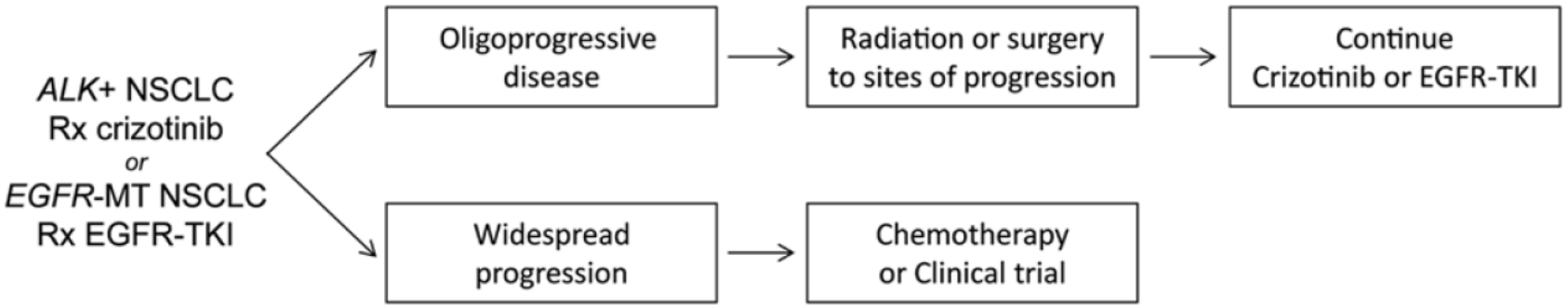
Site of first progression	Number of patients	PFS1 (months)(95% CI)	PFS2 (months)(95% CI)	Site of 2nd progression	
CNS	10	10.9 7.3 – 18.3	**7.1** 1.7 – 11.3	2 (20%)	no prog
				3 (30%)	CNS
				5 (50%)	eCNS
*eCNS†	15	9.0 6.5 – 13.8	**4.0** 2.7 -7.4	4 (27%)	no prog
				3 (20%)	CNS
				8 (53%)	eCNS
All patients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

* bone, lung, lymph node, adrenal, liver

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

Weickhardt A et al, JTO Dec 2012

Future Prospective Study?



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

Weickhardt A et al, JTO Dec 2012

- How we define PD/resistance in a patient treated with EGFRTki
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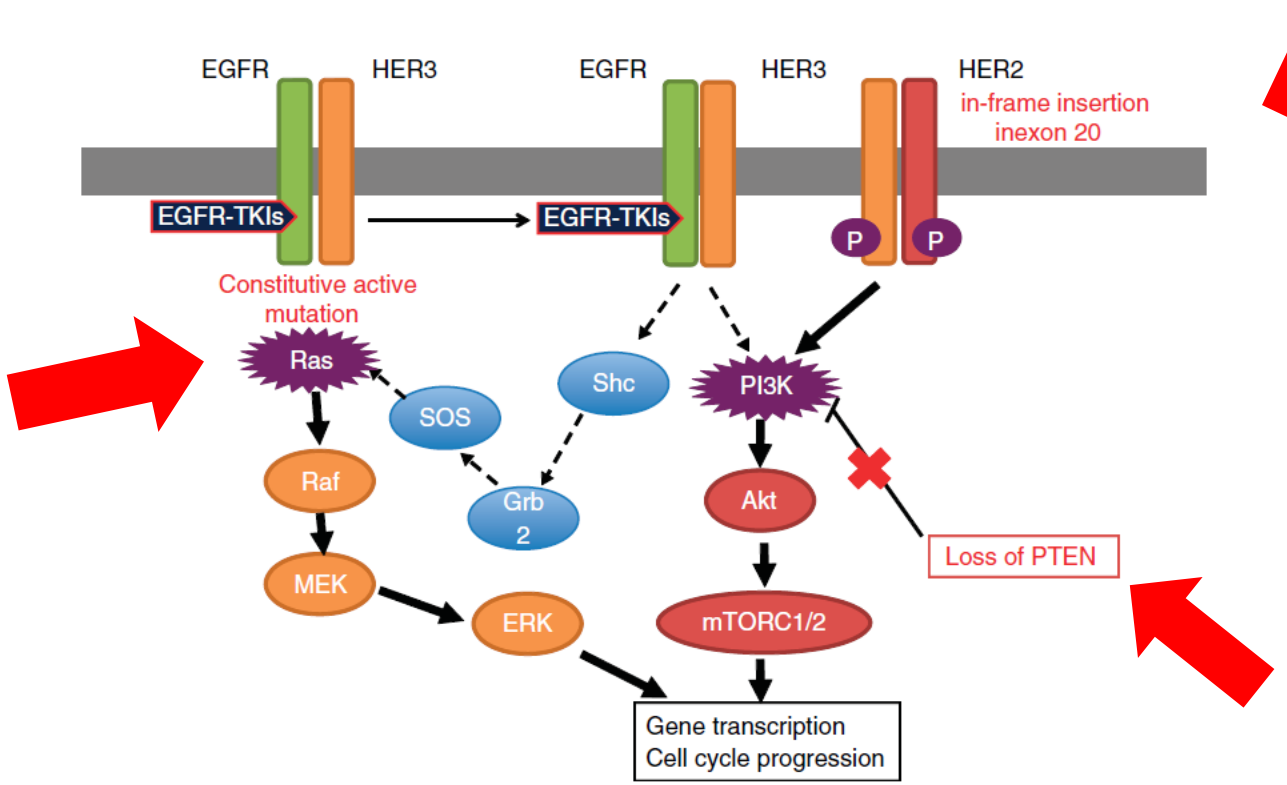
Primary Resistance



- [illegible] resistance to EGFR-TKI

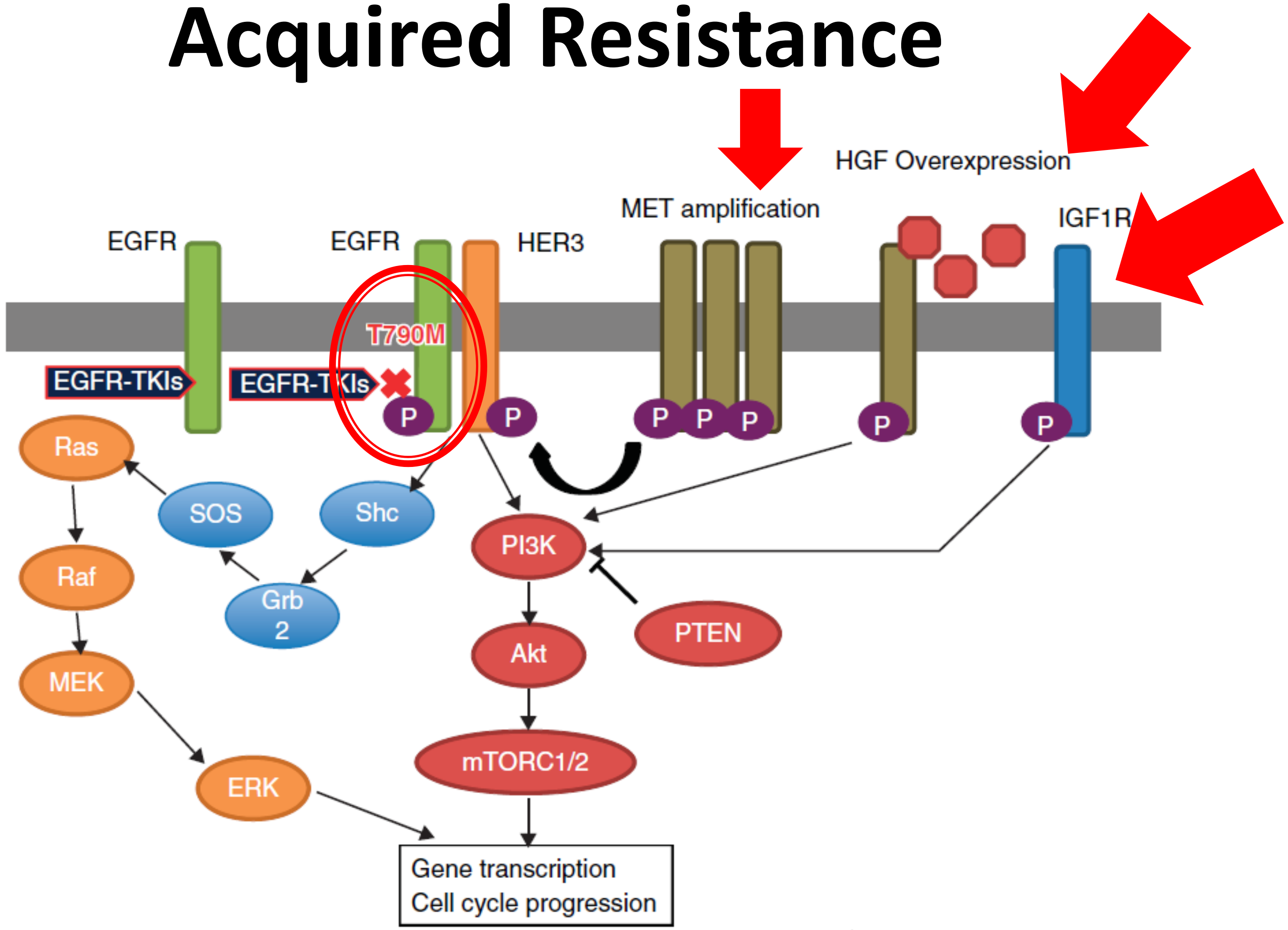
Ayoola A et al Cancer Invest 2012;
Nakata A& N Gotoh, Expert Opinion 2012

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%)

Acquired Resistance

D761Y
L747S
T854A



- IGF seems to be involved in some cases of resistance (probably a reversible mechanism) in NSCLC cell lines that have been continuously exposed to a first-generation TKI, an increased activation of the IGF-1R has led to cell growth
- MET seems to provide an alternative signaling pathway in the presence of EGFR inhibition, through MET amplification (5-20%) and overexpression of HGF (10-20%)

Ayoola A et al Cancer Invest 2012;
Nakata A& N Gotoh, Expert Opinion 2012

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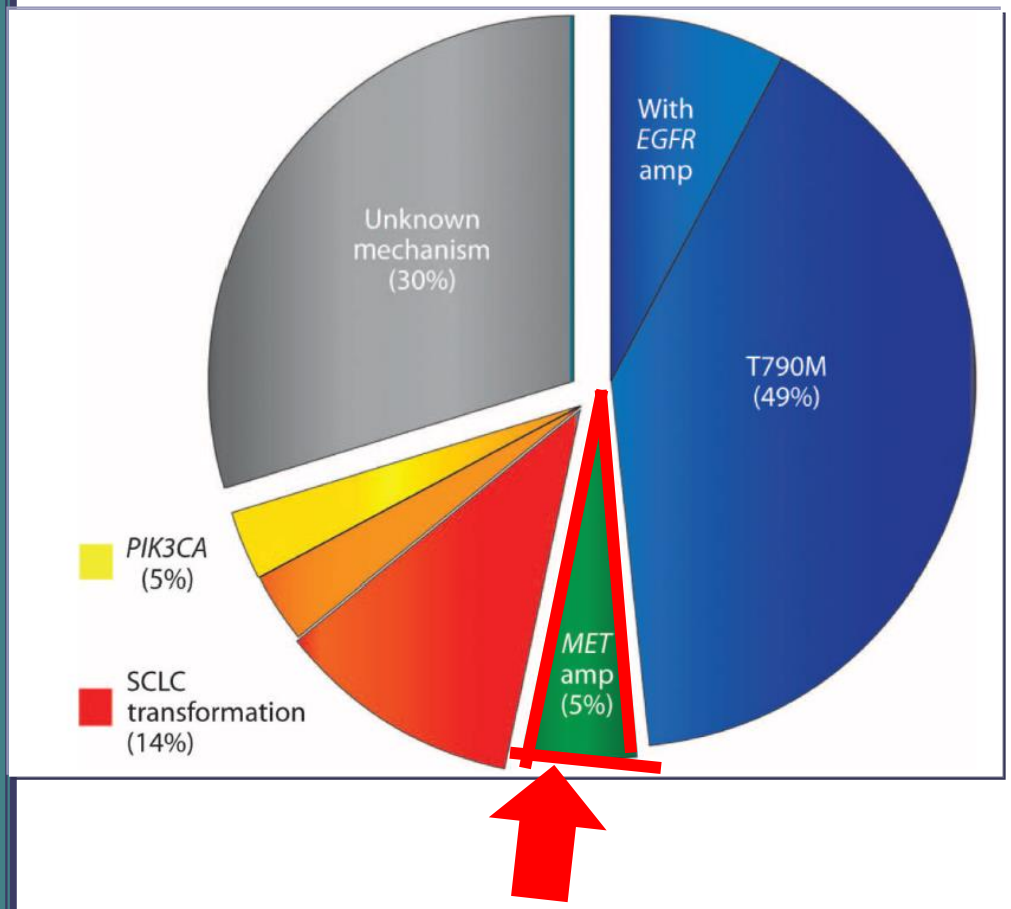
Sequist L et al, Sci Transl Med 2011

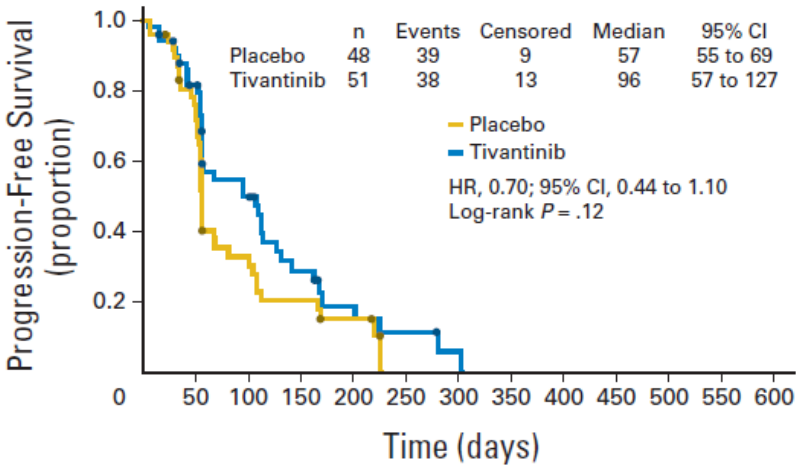


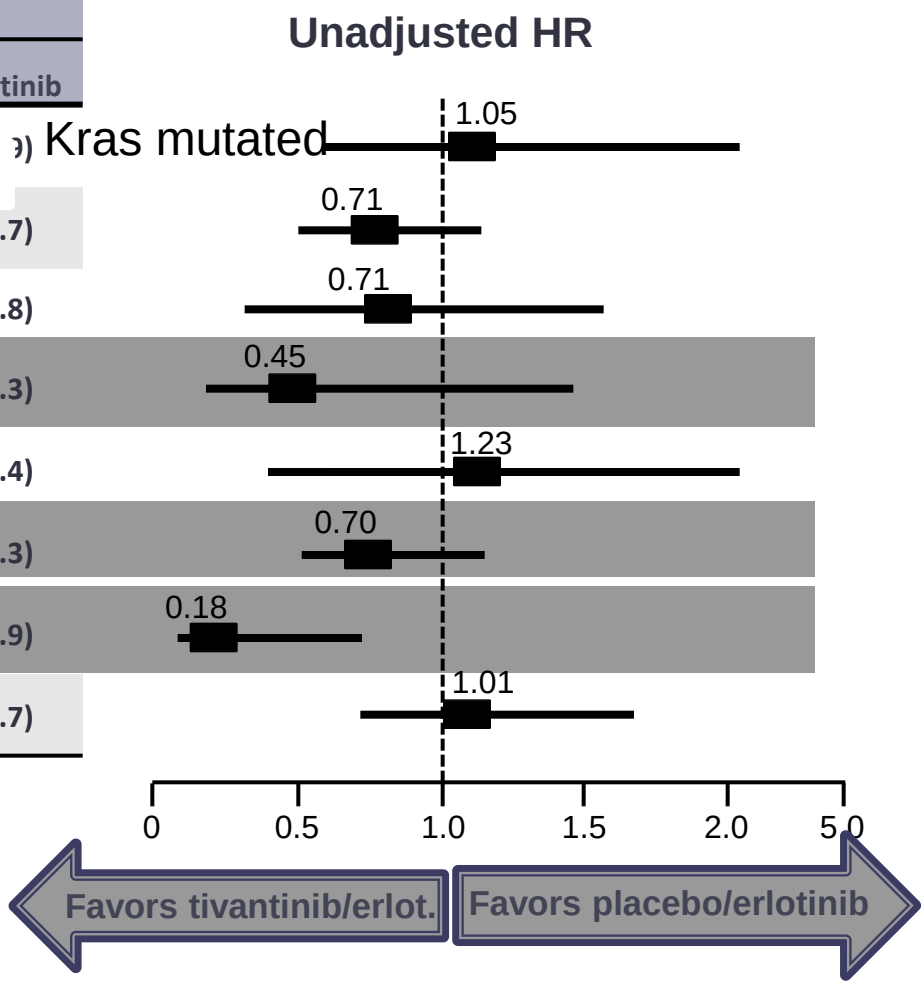
- MET activates PI3K/Akt signaling in the presence of EGFR-TKI
  Engelman Science 2007, Bean PNAS 2007
- Concomitant inhibition of both EGFR and MET is required to kill resistant cells
- Targeting of Both the c-Met and EGFR Pathways Results in Additive Inhibition of Lung Tumorigenesis in Transgenic Mice
  Stabile L et al, Cancer 2010
- *MET* amplification: 4-22% of NSCLC with acquired EGFR TKI resistance

Engelman Science 2007, Bean PNAS 2007, Sequist Sci Transl Med 2011, Oxnard Clin Ca Res 2011

Tivantinib: Phase II data

	n/N	Median PFS (95% CI), months: Tivantinib/Erlotinib	Median PFS (95% CI), months: Placebo/Erlotinib
EGFR wt			
			3.7)
			3.8)
			7.3)
			8.4)
			2.3)
			1.9)
KRAS wt	49/45	3.6 (1.9 - 4.2)	2.3 (1.9 - 3.7)





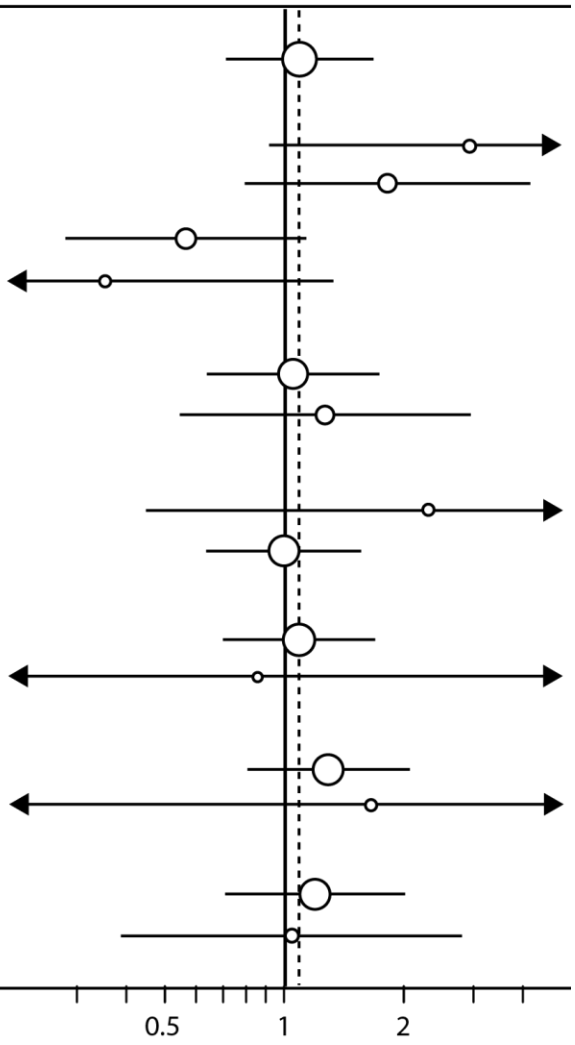
- **A PFS benefit associated with tivantinib plus erlotinib was observed in patients with tumors harboring amplified c-MET, wild-type EGFR, or mutant KRAS**

Cox proportional hazard ratio analysis of median progression-free survival by patient subgroup. Abbreviations: CI, confidence interval; FISH, fluorescence in situ hybridization; HR, hazard ratio; PFS, progression-free survival; wt, wild type

Sequist L, Shiller J et al, JCO 2011

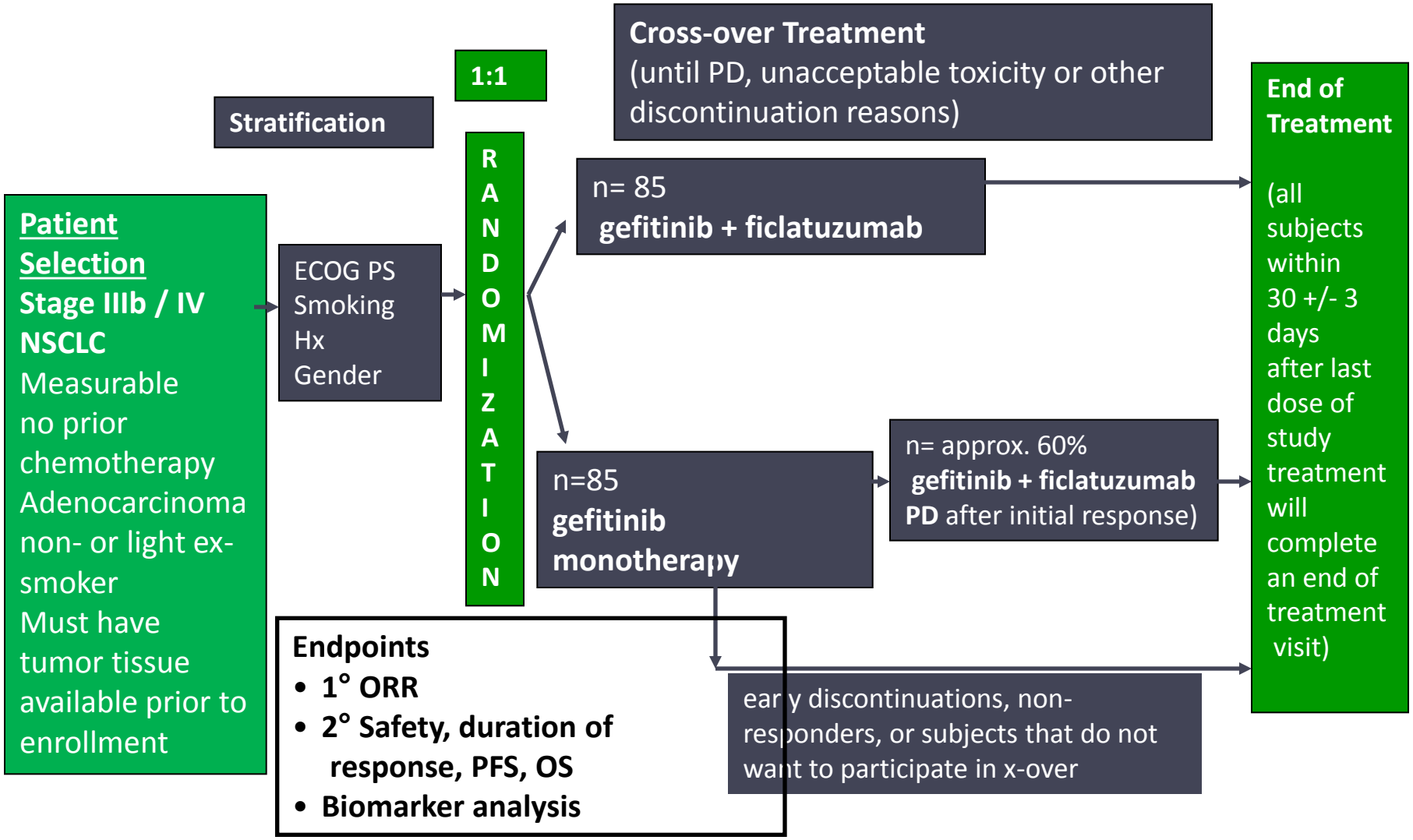
Onartuzumab: Phase II data

Baseline Risk Factor	Erlotinib +Placebo Median (wk)	Erlotinib +MetMAb Median (wk)	Hazard Ratio	(95% CI)	p-Value
All Subjects (n=128)	11.1	9.6	1.09	(0.71–1.67)	0.699
Met IHC Scheme II Score					
0 (n=18)	8.8	5.9	2.94	(0.92–9.40)	0.058
1 (n=38)	11.4	6.1	1.82	(0.79–4.18)	0.151
2 (n=51)	6.4	12.9	0.57	(0.28–1.14)	0.105
3 (n=14)	6.3	11.6	0.36	(0.09–1.33)	0.108
Histology Category					
Non-Squamous Cell (n=97)	9.4	9.6	1.05	(0.64–1.74)	0.836
Squamous Cell (n=31)	11.4	6.3	1.27	(0.55–2.95)	0.579
Tobacco History					
<100 Cigarettes (n=18)	11.7	5.9	2.30	(0.44–11.87)	0.308
≥100 Cigarettes (n=110)	10.9	9.6	0.99	(0.63–1.55)	0.967
ECOG					
0/1 (n=122)	11.3	9.7	1.08	(0.70–1.68)	0.727
2+ (n=6)	6.0	5.9	0.85	(0.14–5.24)	0.863
EGFR Mutation					
Wildtype (n=99)	10.9	6.1	1.28	(0.80–2.05)	0.308
Mutant (n=13)	na	na	1.63	(0.10–26.5)	0.728
KRAS Mutation					
Wildtype (n=86)	11.3	6.3	1.19	(0.71–2.00)	0.517
Mutant (n=26)	11.4	6.0	1.04	(0.38–2.79)	0.945



Spigel et al: WCLC 2011

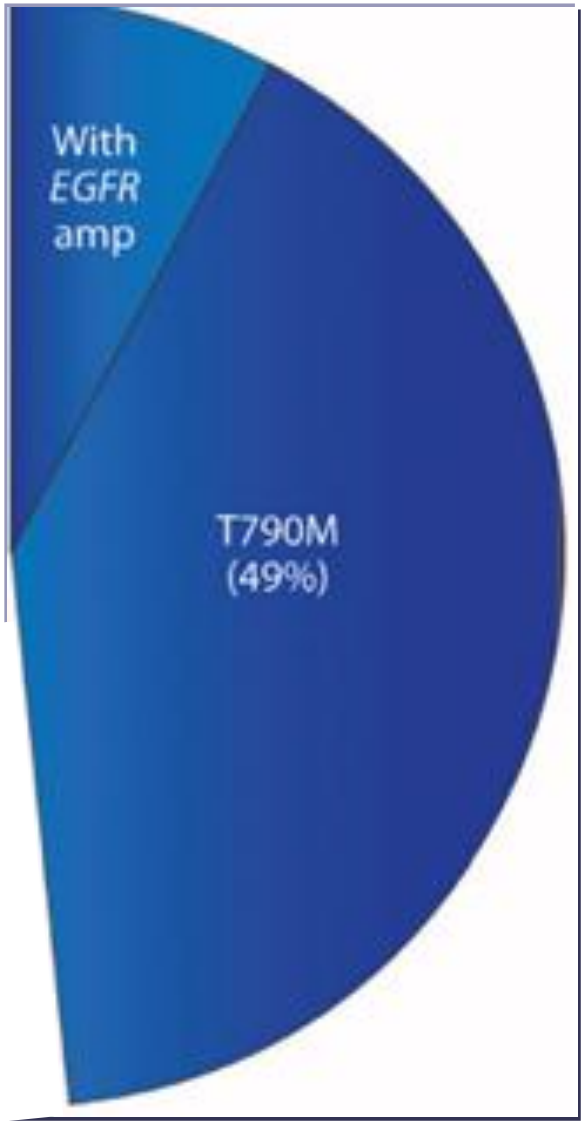
Phase II Ficlatuzumab in Combination with Gefitinib in Asian Subjects with Non-Small Cell Lung Cancer

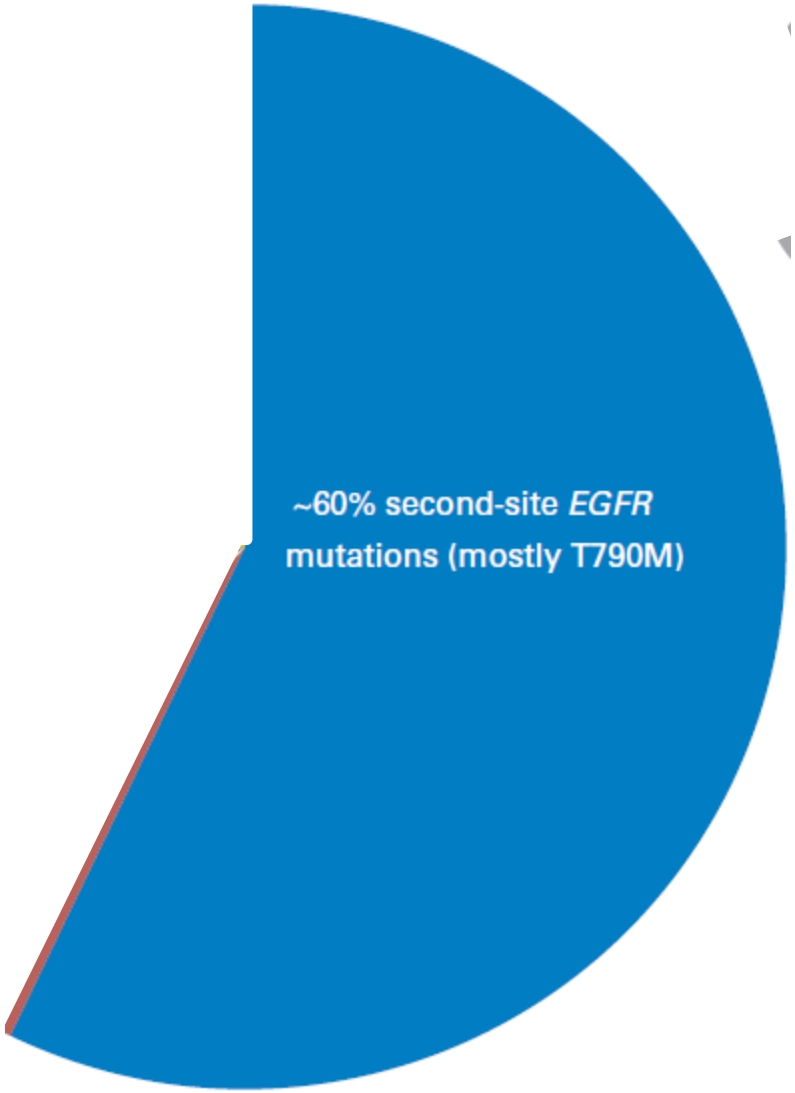


Adequate tissue for central IHC assay of Met receptor, and EGFR testing if EGFR status is unknown

Mok ASCO 2011, NCT01039948

T790M





Sequist L et al, Sci Transl Med 2011

Ohashi K et al, JCO 2013

Second- and Third-generation EGFR TKIs

Drug Name	Generic Name	Target	Recommended dose	Status
EKB-569	Pelitinib	EGFR	50 mg once per day	Phase I*
CI-1033	Canertinib	EGFR/ERBB2/ERBB4	150 mg once per day	Phase II*
HKI-272	Neratinib	EGFR/ERBB2	320 mg once per day (than 240 within trial)	Phase II*
BIBW2992	Afatinib	EGFR/ERBB2/ERBB4	50 mg once per day	Phase III
PF-00299804	Dacomitinib	EGFR/ERBB2/ERBB4	45 mg once per day	Phase III
CO-1686	NA	EGFR T790M	NA	Phase I/II
WZ4002	NA	EGFR T790M	NA	Preclinical

*no additional trials planned in lung cancer

Ohashi K et al, JCO 2013

Irreversible EGFR TKIs

Mutation:	WT	Activated	Resistance		
	wild type H1666	L858R H3255	L858R+T790M NCI1975	Target	Binding mode
BIBW 2992[1]	60	0.7	99	EGFR/HER2	Irreversible
Gefitinib[1]	157	5	>4000	EGFR	Reversible
Erlotinib[1]	110	40	>4000	EGFR	Reversible
Lapatinib[1]	534	63	>4000	EGFR/HER2	Reversible
CP 724,714[2]	>4000	561	>4000	HER2	Reversible

IC50 values (nM) for the inhibitory activities of different compounds on the proliferation of NSCLC cells with *EGFR* mutations

EGFR mutation	Gefitinib IC_{50}	PF299 IC_{50}
Del E746_A750	4.8 nM	<1 nM
Del S752_I759	35 nM	2.0 nM
Del L747_A750InsP	7.4 nM	1.6 nM
L858R	26 nM	2.6 nM
L858R/T790M	>10000	300 nM

LUX-Lung 1 – Trial Design

LUX-Lung 1

A multicentre, randomized, double-blind Phase IIb/III trial of BIBW 2992* plus best supportive care (BSC) versus BSC in patients with non-small cell lung cancer (NSCLC) who have progressed after chemotherapy and erlotinib or gefitinib

Patients with:

- Adenocarcinoma of the lung
- Stage IIIB/IV
- Progressed after 1 or 2 lines chemotherapy (incl. 1 platinum-based regimen) and ≥12 weeks of treatment with erlotinib or gefitinib
- ECOG 0–2

N=585

Randomization

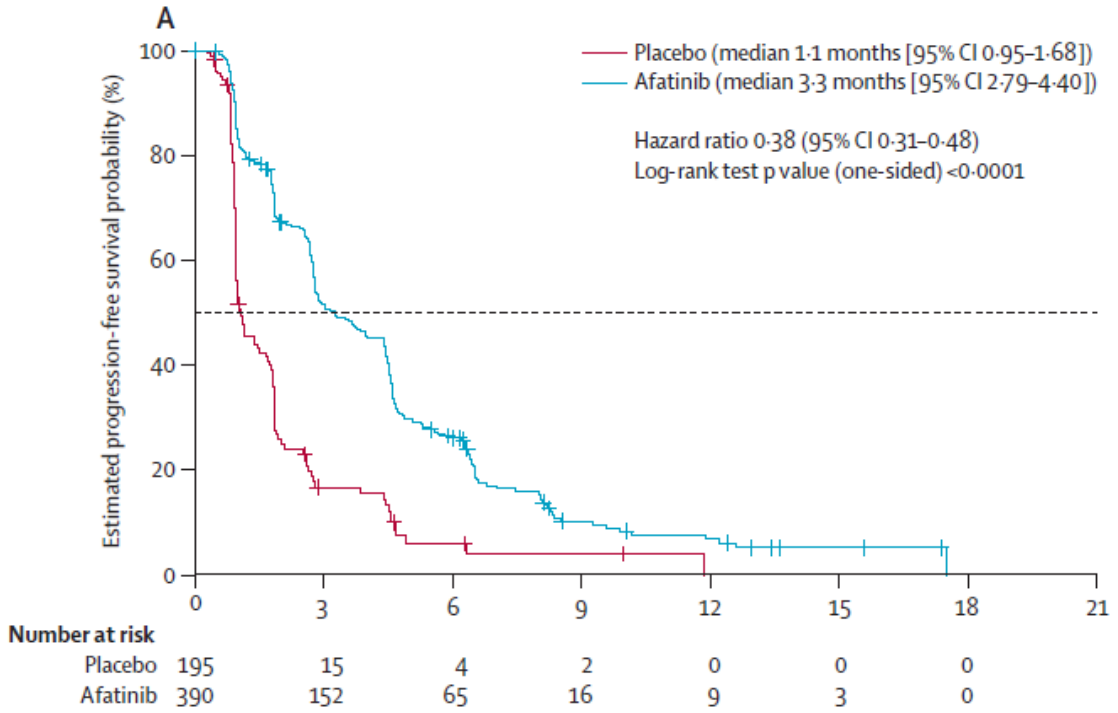
2:1

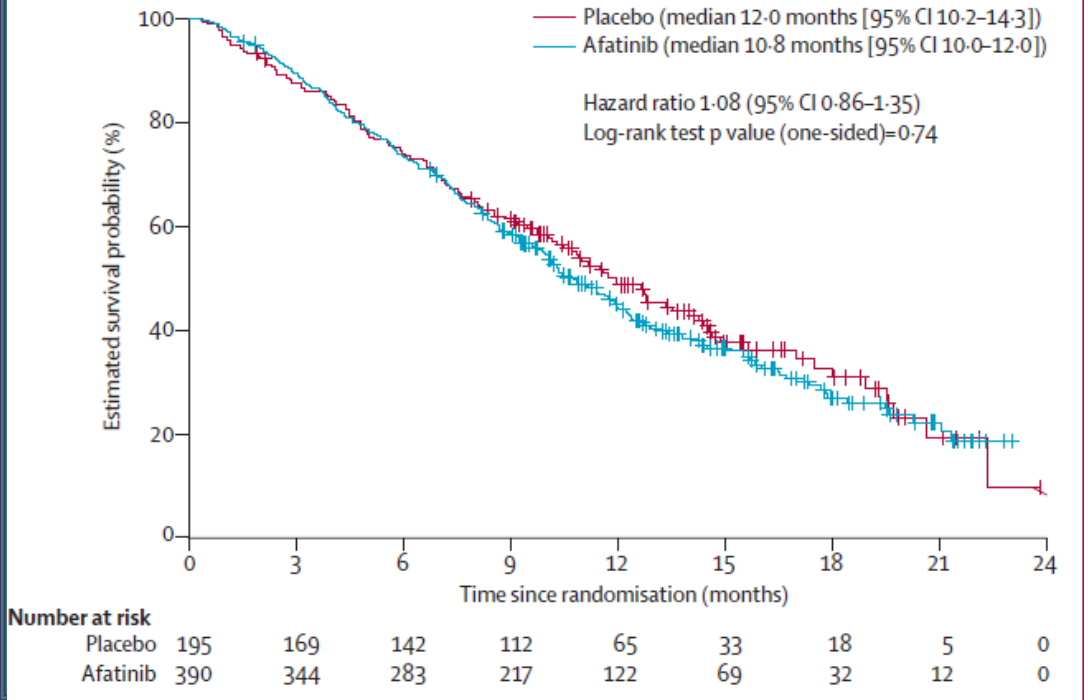
Oral BIBW 2992 50 mg once-daily plus best supportive care	Oral placebo once-daily plus best supportive care

Primary endpoint: Overall survival (OS)
Secondary: PFS, RECIST response, QoL (LC13 & C30), safety

Miller VA, et al, Lancet Oncol 2012

PFS (independent review)





OS

Miller VA, et al, Lancet Oncol 2012

PF299 (dacomitinib)- Phase II Trial

- PF299804 was self-administered at a dose of 45 mg once daily, continuously

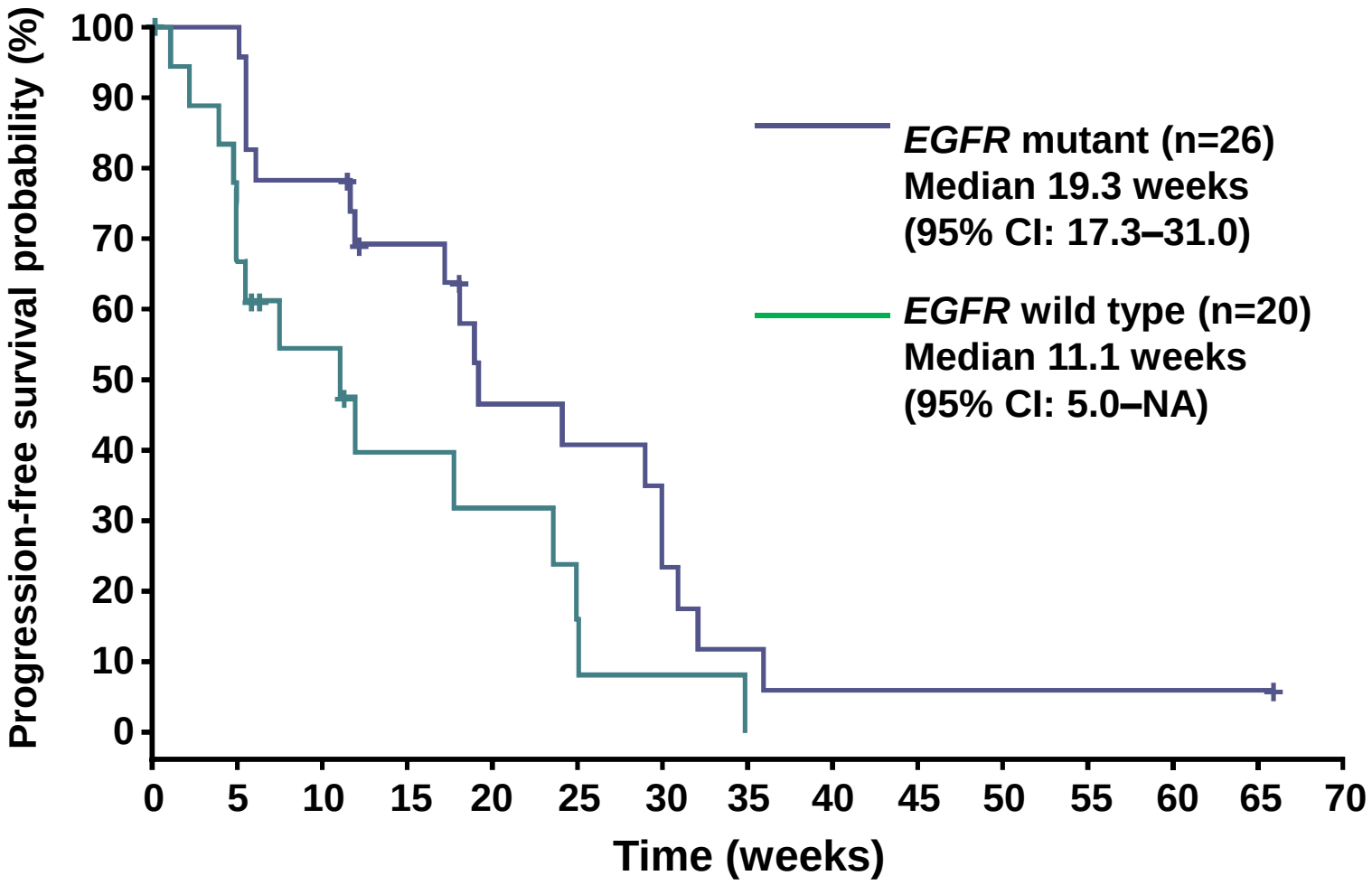
- Pts with advanced NSCLC previously treated with one or two chemotherapy regimens **and erlotinib**

Janne P et al, ASCO 2010 abst 7596

PF299 Patients Characteristics

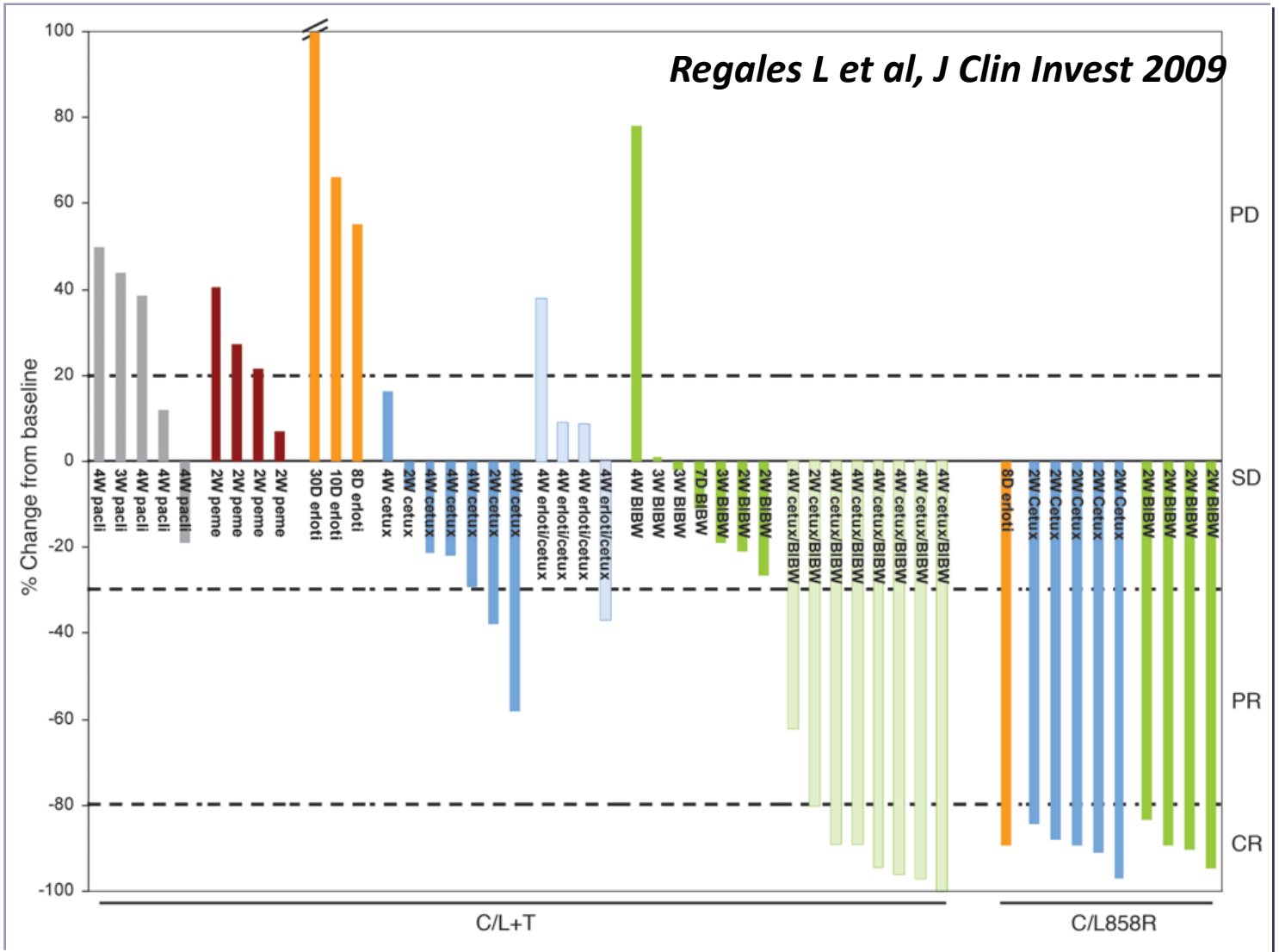
Characteristic	N=66 Adenocarcinoma n=50	N=66 Nonadenocarcinoma n=16
Mean (range) age, years	60.7 (37–79)	65.0 (50–84)
Gender (male/female), n	15/35	14/2
Smoking history, n (%)		
Never-smoker	27 (54)	3 (19)
Current smoker	1 (2)	2 (13)
Ex-smoker	22 (44)	11 (69)
Mutational status, n (%)		
KRAS wt	50 (100)	16 (100)
EGFR wt	11 (22)	9 (56)
EGFR exon 19	13 (26)	1 (6)
EGFR exon 20	3 (6)	1 (6)
EGFR exon 21	7 (14)	0
EGFR sensitizing mutation and *T790M*	7 (14)	0
EGFR mutation not specified	1 (2)	0
EGFR unknown	8 (16)	5 (31)
Prior chemotherapy treatment, n (%)		
1 regimen	4 (8)	1 (6)
2 regimens	18 (36)	8 (50)
≥3 regimens	28 (56)	7 (44)

Progression-free Survival According to *EGFR* Mutation Status

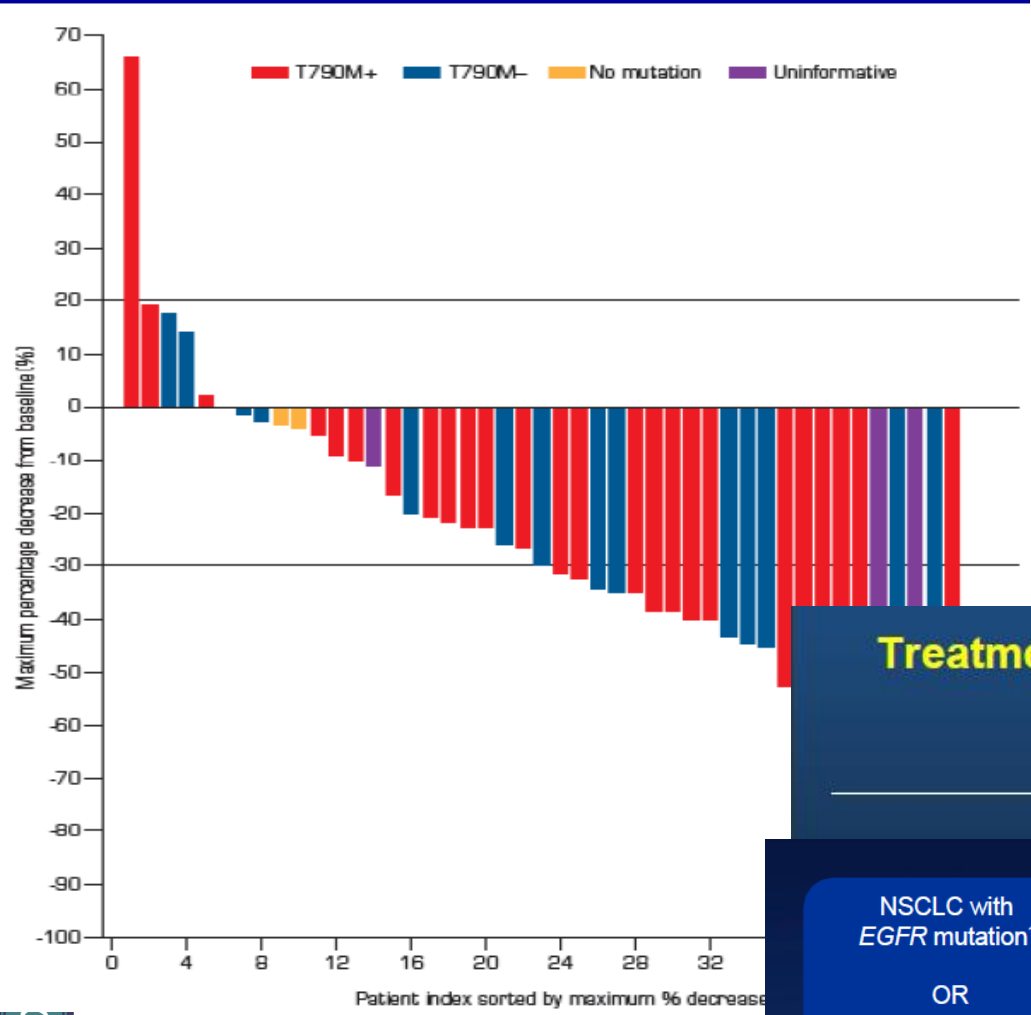


Janne P et al, ASCO 2010 abst 7596

Dual Targeting of EGFR



Phase IB Afatinib and Cetuximab



Treatment Responses by T790M Mutation Status
at Recommended Dose

T790M	T790M	T790M	No EGFR	Total

NSCLC with *EGFR* mutation[1]

OR

SD ≥6 months with erlotinib/gefitinib

OR

Partial or complete response to erlotinib/gefitinib

→ Disease progression[2] → Stop erlotinib/gefitinib for ≥72 hours[3]

Dose escalation schema 3–6 patients per cohort

Afatinib p.o. daily + escalating doses of i.v. cetuximab q 2 weeks

Dose levels starting at:
afatinib 40 mg +
cetuximab 250 mg/m²

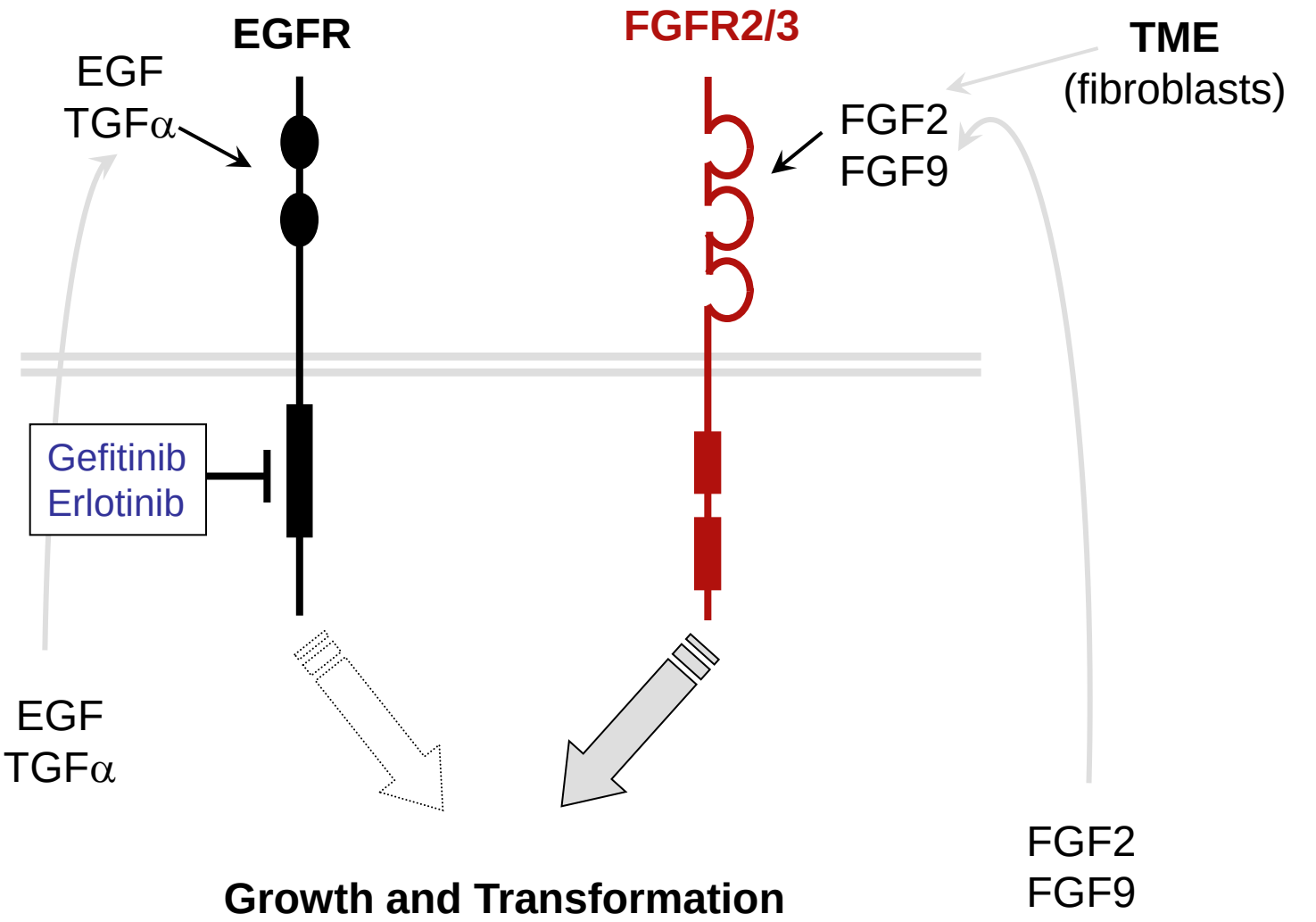
Predefined maximum dose:
afatinib 40 mg +
cetuximab 500 mg/m²

MTD cohort expanded up to 80 *EGFR* mutation-positive patients[4]:
40 T790M+ and 40 T790M–

Horn L et al, IASLC 2011

Other targets

FGFR Autocrine/Paracrine Loop



Courtesy P. Bunn

Three of nine EGFR mutant NSCLC cell lines acquire EGFR TKI-resistance through induction of FGF2 and FGFR1

Cell Line	EGFR genotype	Resistance	Resistance Mechanism
H1650	E746-A750 del	Gefitinib resistant	FGF2 and FGFR1 induction
H1975	L858R, T790M	BIBW2992 resistant	IGF1R?
H3255	L858R	Gefitinib resistant	Multi-clonal
HCC827	E746-A750 del	Gefitinib resistant	MET amplification
HCC2279	E746-A750 del	Gefitinib resistant	FGF2 and FGFR1 induction
HCC2935	E746-S752 del, I insert	In process	
HCC4006	L747-A750 del, P insert	Gefitinib resistant	FGF2 and FGFR1 induction
HCC4011	L858R	In process	
PC9	E746-A750 del	Gefitinib resistant	T790M

Courtesy P. Bunn

Phase I Study of FGFR TKI + Erlotinib Study: Design

Part 1: MTD determination

Patients:

- Clinically selected
  - ➢ Advanced solid malignancies
  - ➢ Refractory to SoC or no SoC available

PK data collected

Escalating doses of erlotinib (50-150mg/day po) and FGFR TKI up to RP2D

1 cycle = 4 weeks
Scans every 2 cycles

Part 2:

Patients: advanced stage adenocarcinoma

- Molecularly defined
- No limit on prior regimens

Efficacy and single-/multi-dose PK data collected

***EGFR* activating mutations**

***EGFR* wt (excluding *KRAS* mut and *ALK*+)**

Study sites are Univ. Colorado, one or more sites in Asia and one or more other SPORE sites.

Rationale for Hsp90 inhibition in NSCLC

- NSCLC with activating mutations in EGFR
  - Mutated EGFR is a sensitive client protein of Hsp90
  - Both T790M and Met amplification are susceptible to Hsp90 inhibition (Park et al, Abstract 2450 AACR Annual Meeting 2008)
- NSCLC containing wild type EGFR
  - Many NSCLC cell lines are sensitive to Hsp90 inhibitors in vitro
  - Multiple proteins important in the progression of NSCLC are client proteins of Hsp90
    - HER2
    - p-AKT
    - EML4-ALK
    - c-RAF

Study Design

NCT01124864

Phase II Study Population

- ► Previously treated stage IIIb or IV NSCLC
- ► ≥2 lines of chemotherapy
- ► Prior EGFR TKI therapy if *EGFR* is mutated
- ► WHO PS ≤2

AUY922 70 mg/m^2	AUY922 70 mg/m^2	AUY922 70 mg/m^2	AUY922 70 mg/m^2
KRAS-activating mutation	**EGFR-activating mutation**	**EGFR/KRAS/ALK wild type**	**ALK+**
n=28	**n=35**	**n=33**	**n=22**

Bayesian design:
Primary endpoint – efficacy classified as 3 categories (mutually exclusive):
1. Response (CR or PR) or 2. SD at 18 weeks or 3. No clinical benefit (NCB)
Secondary endpoints – efficacy (OS, or PFS) and PK, safety/tolerability

Null hypothesis (no efficacy): response ≤5%, and NCB ≥85%
Alternative hypothesis (efficacious): response ≥10% (≥20% for ALK+ arm), or NCB ≤60% (≤40% for ALK+ arm)

CR, complete response; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

Shaw A et al, ESMO 2012

Results: Patient Demographics and Disease Characteristics

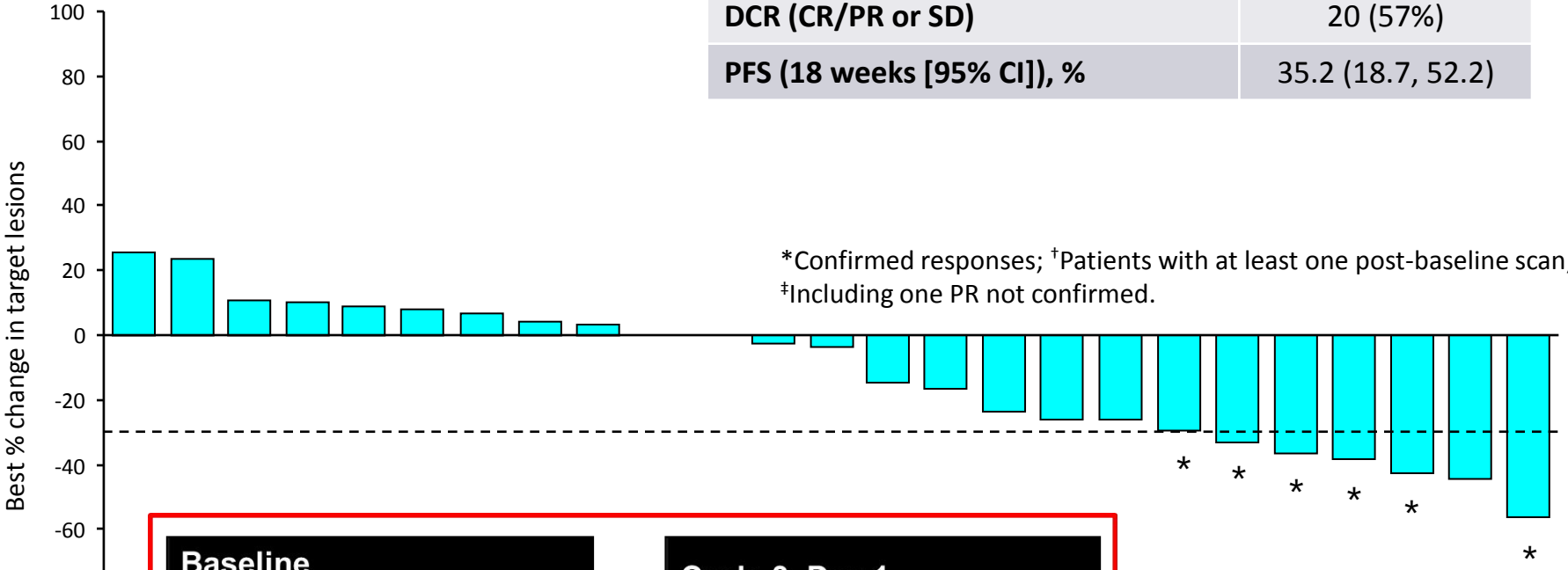
Demographic or characteristic	*KRAS*-mut (n=28)	*EGFR*-mut (n=35)	*EGFR*/*KRAS*/ *ALK* wt (n=33)	ALK+ (n=22)	All* (N=121)
Age (median), years	60	63	63	53	60
Sex (male), %	17 (61)	10 (29)	15 (45)	7 (32)	52 (43)
WHO PS					
0	10 (36)	13 (37)	10 (30)	9 (41)	43 (36)
1	18 (64)	19 (54)	20 (61)	11 (50)	70 (58)
2	0 (0)	3 (9)	3 (9)	2 (9)	8 (7)
Histology					
Adenocarcinoma	23 (82)	32 (91)	27 (82)	20 (91)	105 (87)
Squamous cell carcinoma	1 (4)	0 (0)	2 (6)	0 (0)	3 (2)
Other	4 (14)	3 (9)	4 (12)	2 (9)	13 (11)
Prior regimens					
1	1 (4)	3 (9)	0 (0)	1 (5)	5 (4)
2	8 (29)	13 (37)	16 (48)	5 (23)	42 (35)
3	14 (50)	11 (31)	4 (12)	7 (32)	38 (31)
≥4	5 (18)	8 (23)	13 (39)	9 (41)	36 (30)
Prior ALK inhibitor (crizotinib)	NA	NA	NA	14 (64)	NA
Prior EGFR TKI	NA	34 (97)	NA	NA	NA
Erlotinib		30 (86)			
Gefitinib		4 (11)			
None		1 (3)			

Shaw A et al, ESMO 2012

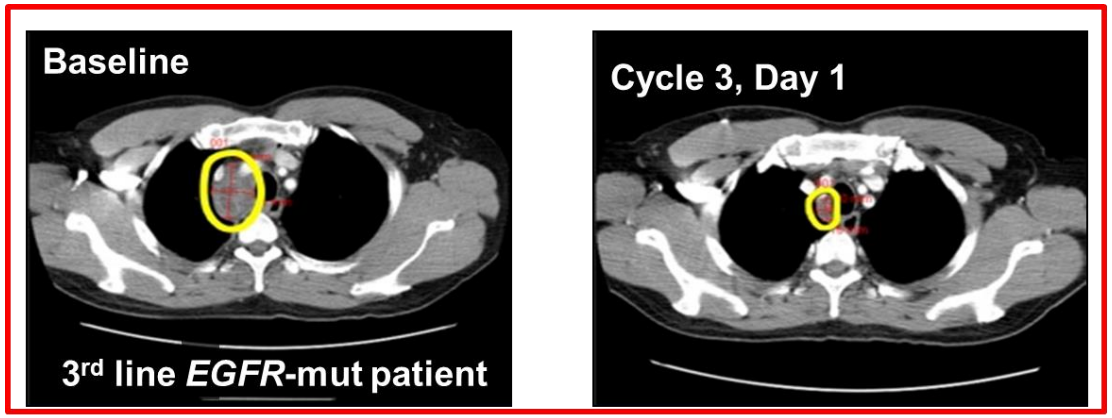
*Includes unknown genotype patients (n=3; stratum not listed); NA, not applicable; wt, wild type.

Best CT Response: *EGFR*-mutant Patients (n=25†/35)

EGFR-mutant (n=35)	
ORR (any PR)	7 (20%)‡
DCR (CR/PR or SD)	20 (57%)
PFS (18 weeks [95% CI]), %	35.2 (18.7, 52.2)



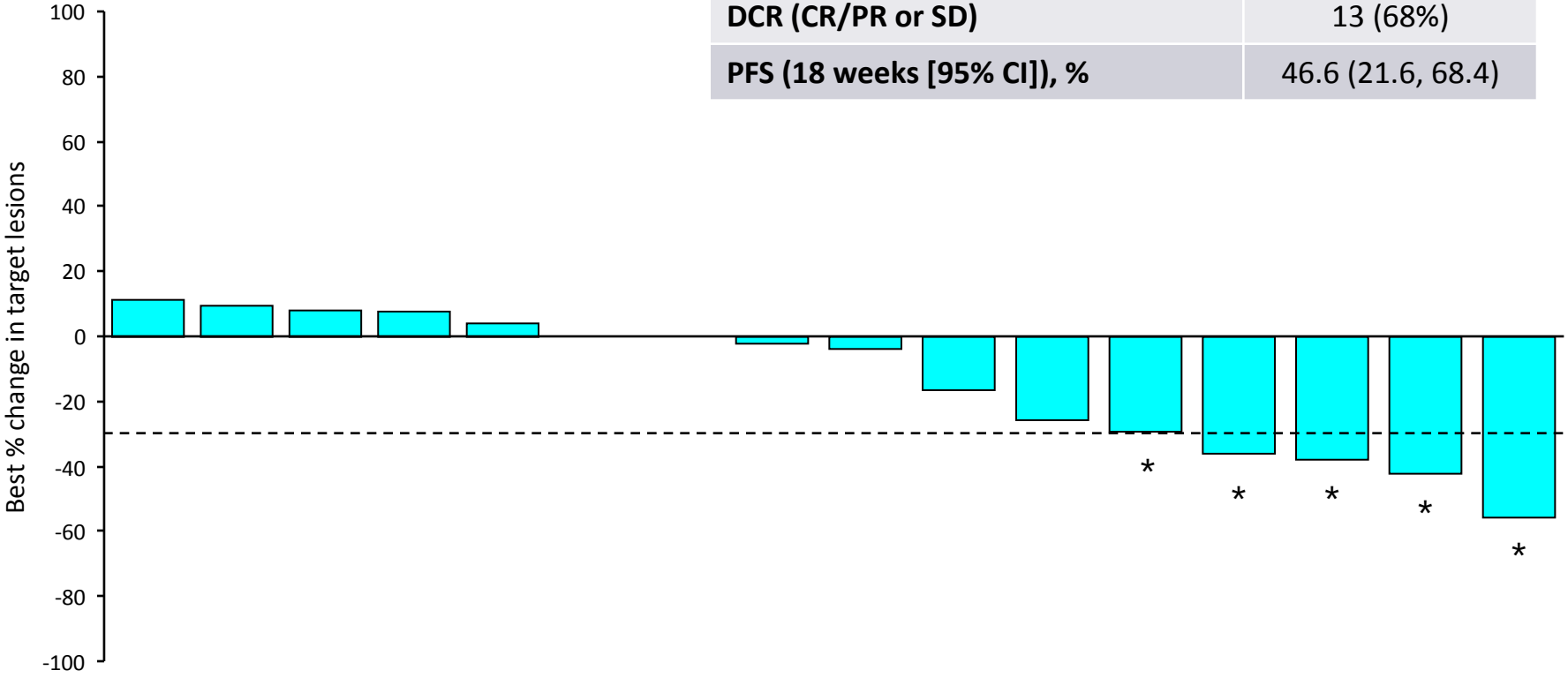
*Confirmed responses; †Patients with at least one post-baseline scan; ‡Including one PR not confirmed.



Shaw A et al, ESMO 2012

Best CT Response: *EGFR*-mutant Patients with EGFR TKI as Part of Their Last Regimen (n= 16†/19)

EGFR-mutant with TKI as part of last regimen (n=19)	
ORR (any PR)	5 (26%)
DCR (CR/PR or SD)	13 (68%)
PFS (18 weeks [95% CI]), %	46.6 (21.6, 68.4)



*Confirmed responses; †Patients with at least one post-baseline scan.

Shaw A et al, ESMO 2012

Conclusion

- More information and details are needed about this issue
- Unfortunately, at the present time, only chemotherapy is approved in this setting
- Whenever is possible, please contribute to implement knownledge increasing re-biopsies at the time of resistance and including pts in dedicated trials

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