A Teaching Affiliate of Harvard Medical School

Acquired Resistance to EGFR TKIs: Clinical obstacles and recent progress

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Chair, Thoracic Clinical Trials Committee, Dana-Farber/Harvard Cancer Center

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MGH 1811 MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

Disclosure Slide

- Paid advisory consulting: Clovis, Celgene
- Unpaid advisory consulting: Boehringer-Ingelheim, Merrimack Pharmaceuticals, Daiichi-Sankyo

- Thanks to Alice Shaw, Jeff Engelman, Ross Camidge for sharing slides

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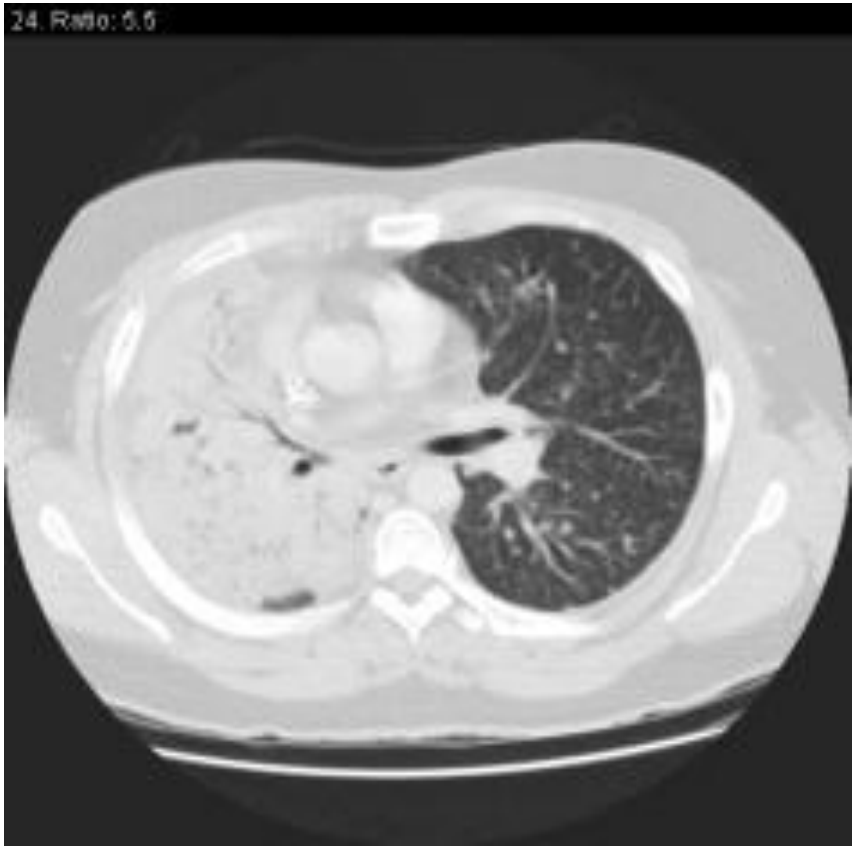
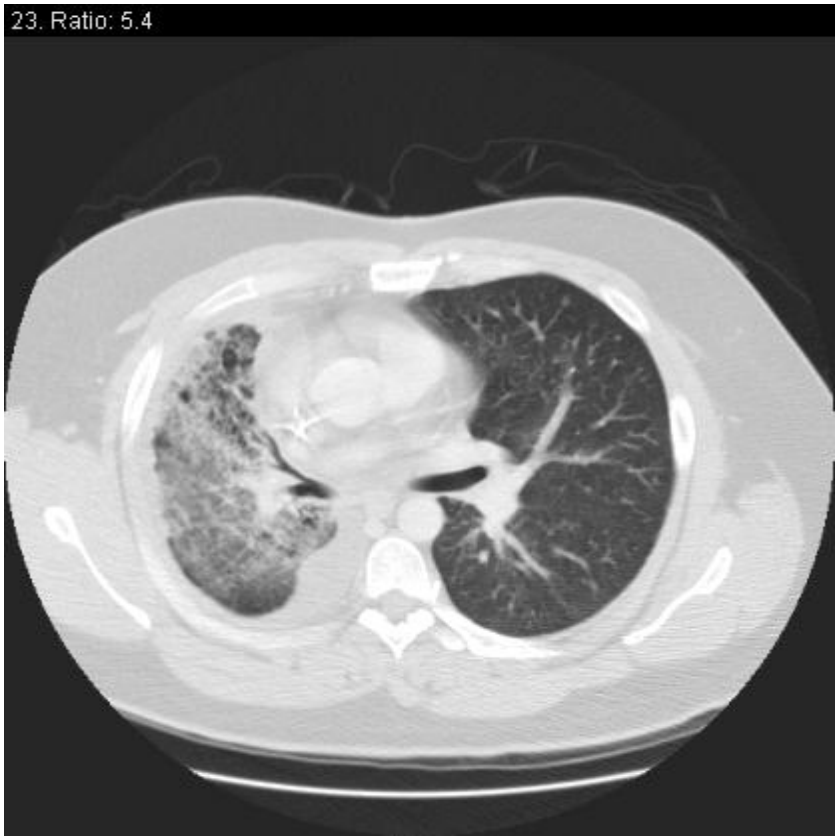
Before….



…and After



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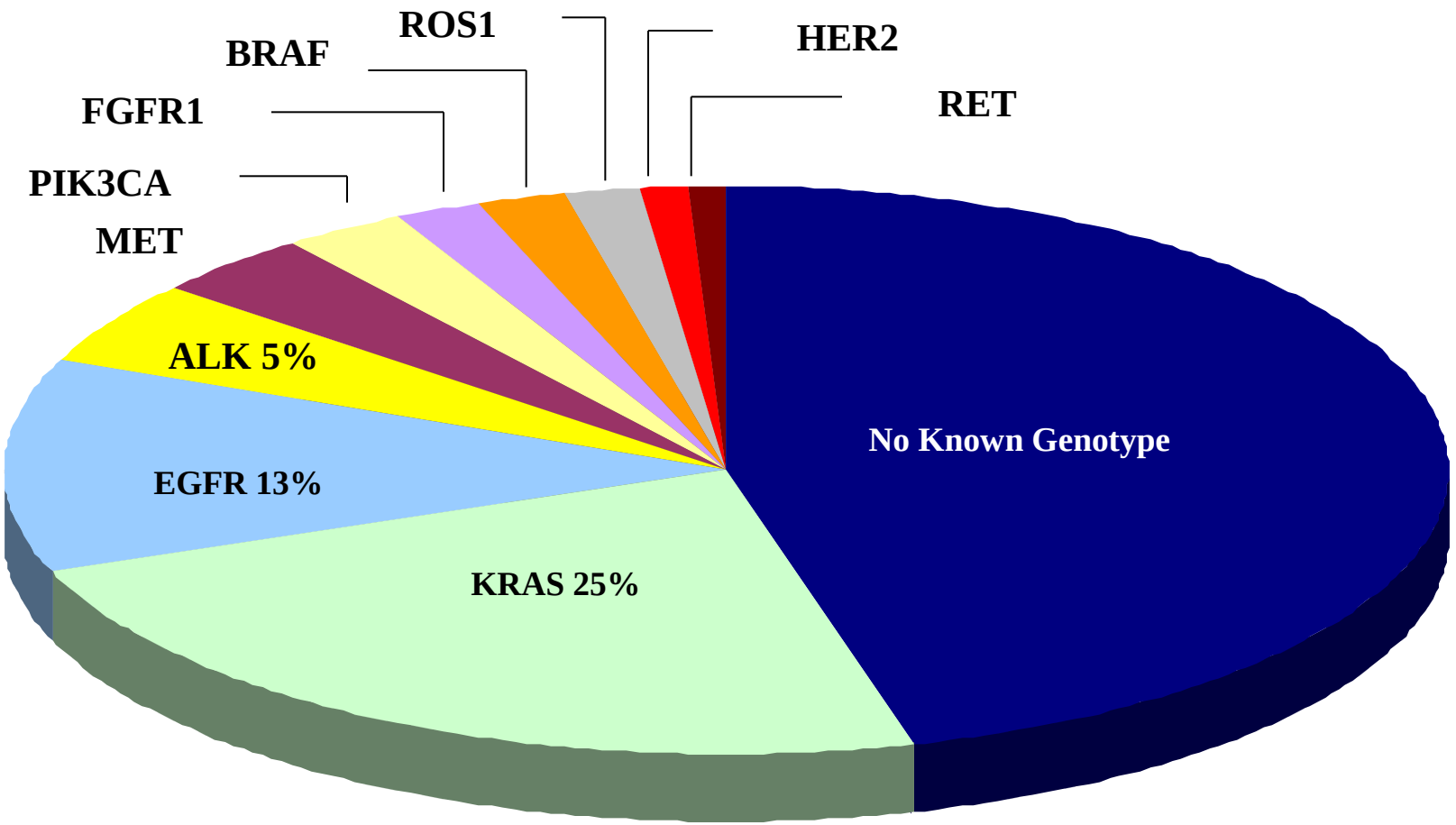
Over 50% of NSCLC have an Identifiable Driver Genotype



Sequist et al, Ann Oncol 2011, adapted

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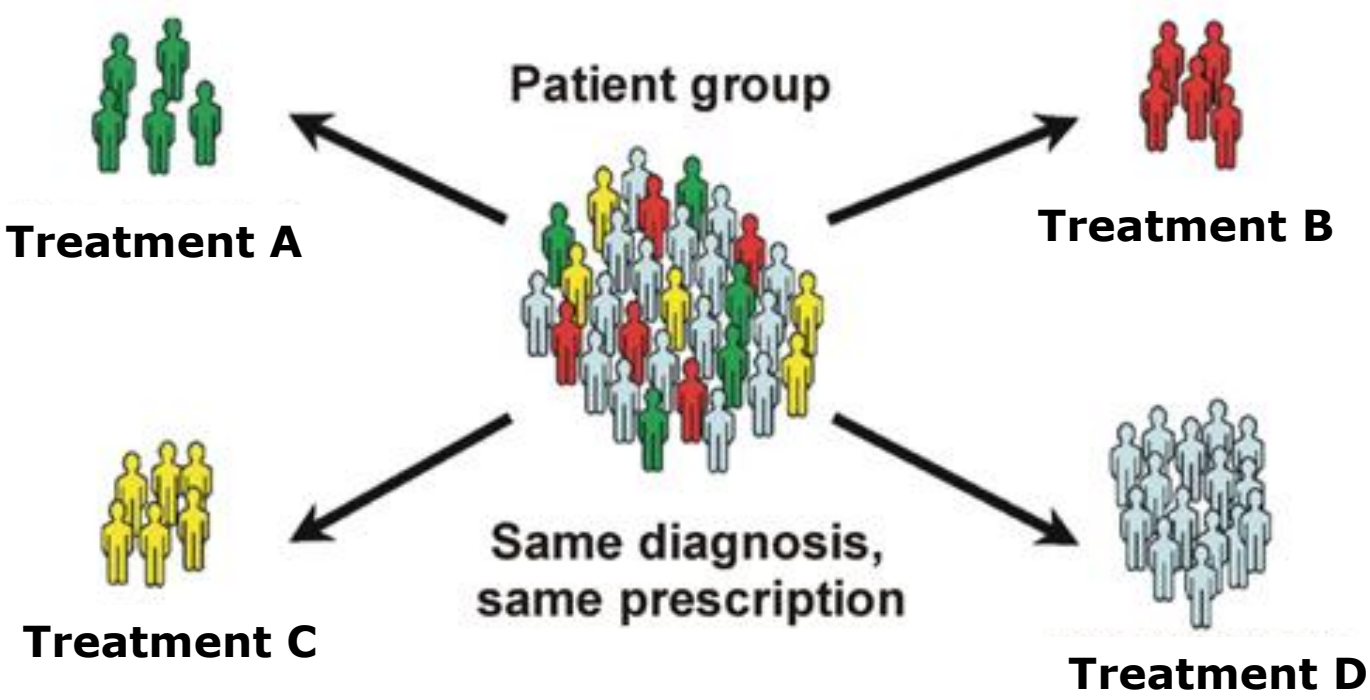
The reality of genotype-directed therapy



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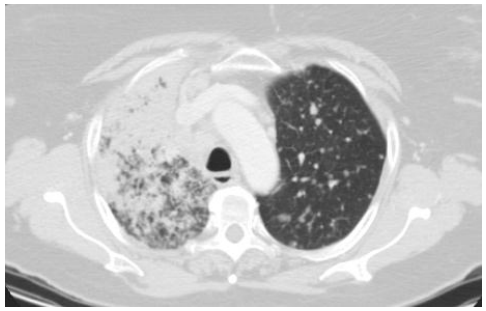
……But responses are short lived

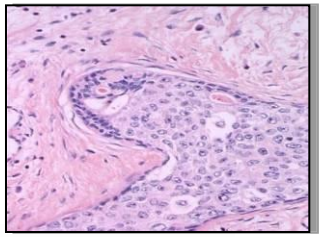
Study	Median PFS
IPASS (EGFR mutants, gefitinib)	9.6 months
NEJ002 (EGFR mutants, gefitinib)	10.4 months
EURTAC (EGFR mutants, erlotinib)	9.7 months
LUX Lung 3 (EGFR mutants, afatinib)	13.6 months
PROFILE 1001, 1005 (ALK, crizotinib)	8-10 months
Preliminary data ASCO ’12 Shaw (ROS, crizotinib)	Not known but appears similar

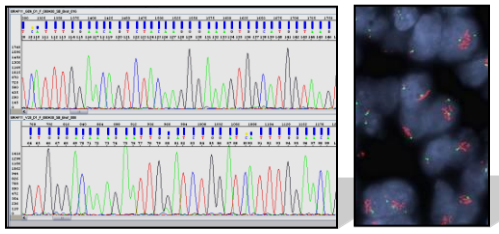
Clinical Information



Targeted Therapy

Biopsy





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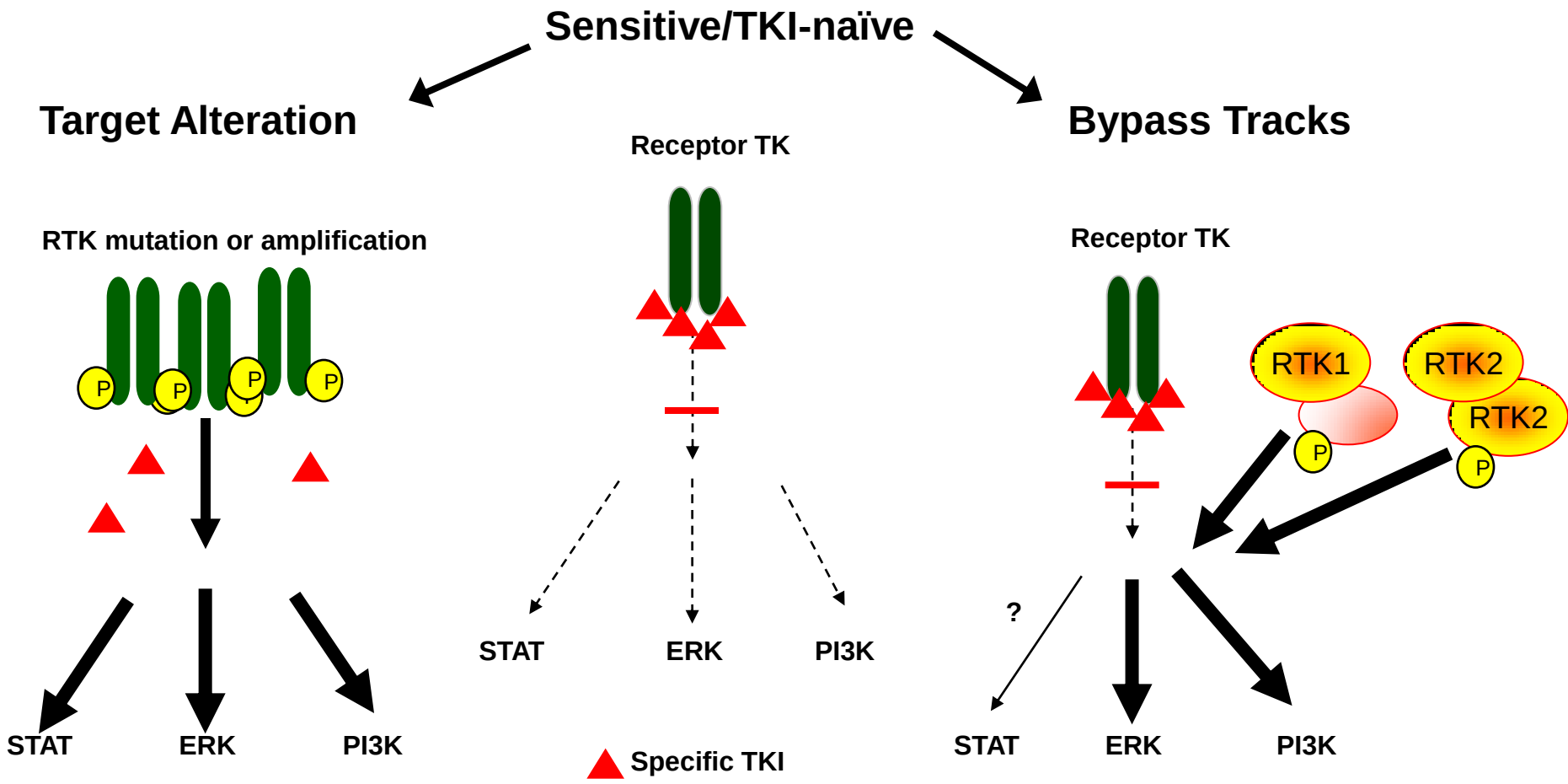
Routine and Molecular Pathology

Two General Classes of TKI Resistance



Slide courtesy of Alice Shaw

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Sci Transl Med; March 2011

RESEARCH ARTICLE

CANCER

Genotypic and Histological Evolution of Lung Cancers Acquiring Resistance to EGFR Inhibitors

Lecia V. Sequist,[1,2*†] Belinda A. Waltman,[2*] Dora Dias-Santagata,[2,3*] Subba Digumarthy,[2,4] Alexa B. Turke,[1,2] Panos Fidias,[1,2] Kristin Bergethon,[3] Alice T. Shaw,[1,2] Scott Gettinger,[5] Arjola K. Cosper,[1] Sara Akhavanfard,[2,3] Rebecca S. Heist,[1,2] Jennifer Temel,[1,2] James G. Christensen,[6] John C. Wain,[1,2,7] Thomas J. Lynch,[5] Kathy Vernovsky,[1] Eugene J. Mark,[2,3] Michael Lanuti,[1,2,7] A. John Iafrate,[2,3] Mari Mino-Kenudson,[2,3] Jeffrey A. Engelman[1,2†]

- 37 consecutive samples with paired pre- and post- AR tissue
- Comparative analyses for:
  - Histology with IHC
  - SNaPshot (most common mutations in 13 genes)
  - FISH for EGFR and MET amplification

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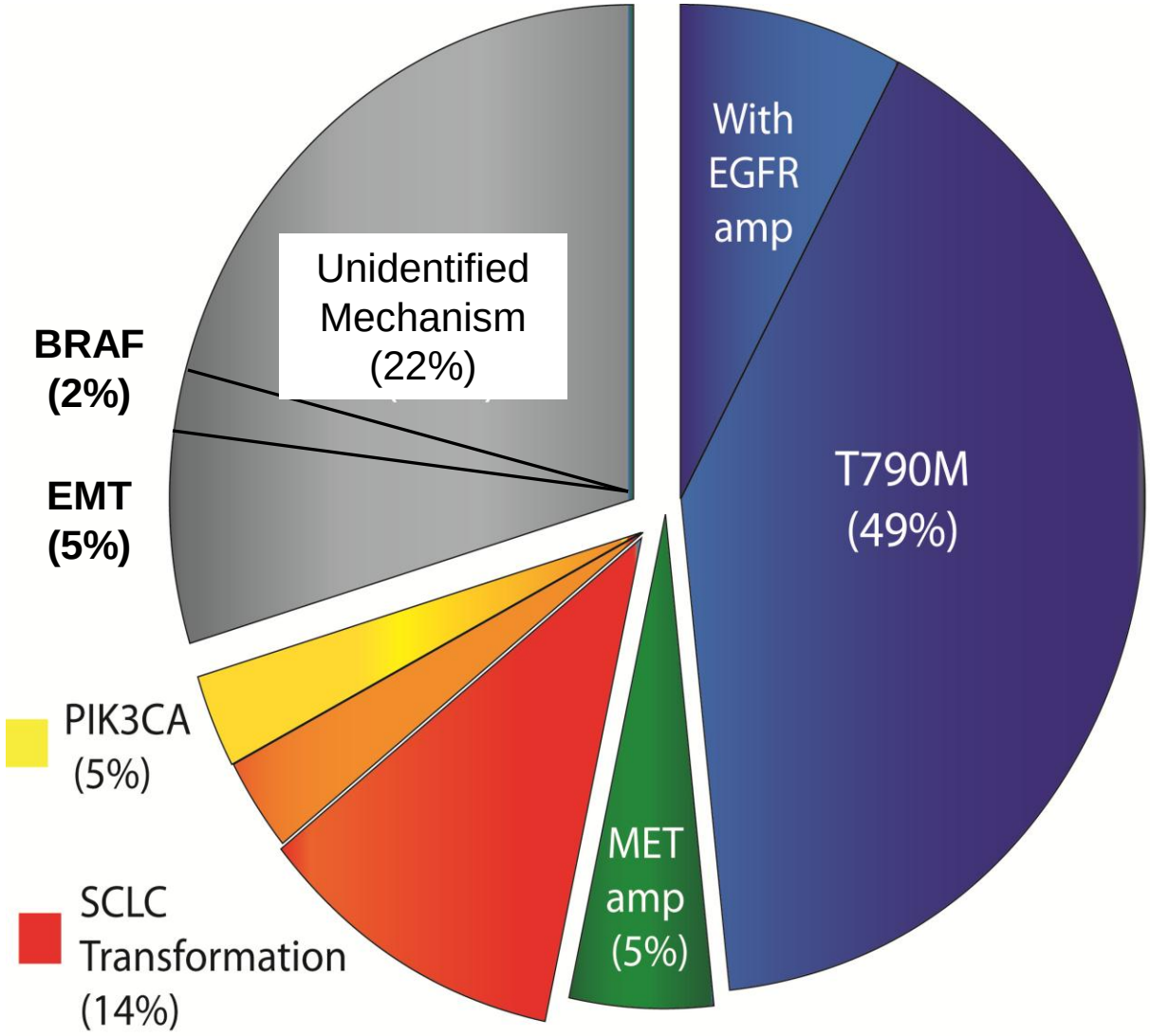
Repeat Biopsies: EGFR mutants with AR to gefitinib, erlotinib



Sample size now 98, distribution of findings overall stable

Sequist et al Sci Transl Med 2011, adapted; Ohashi et al, PNAS 2012

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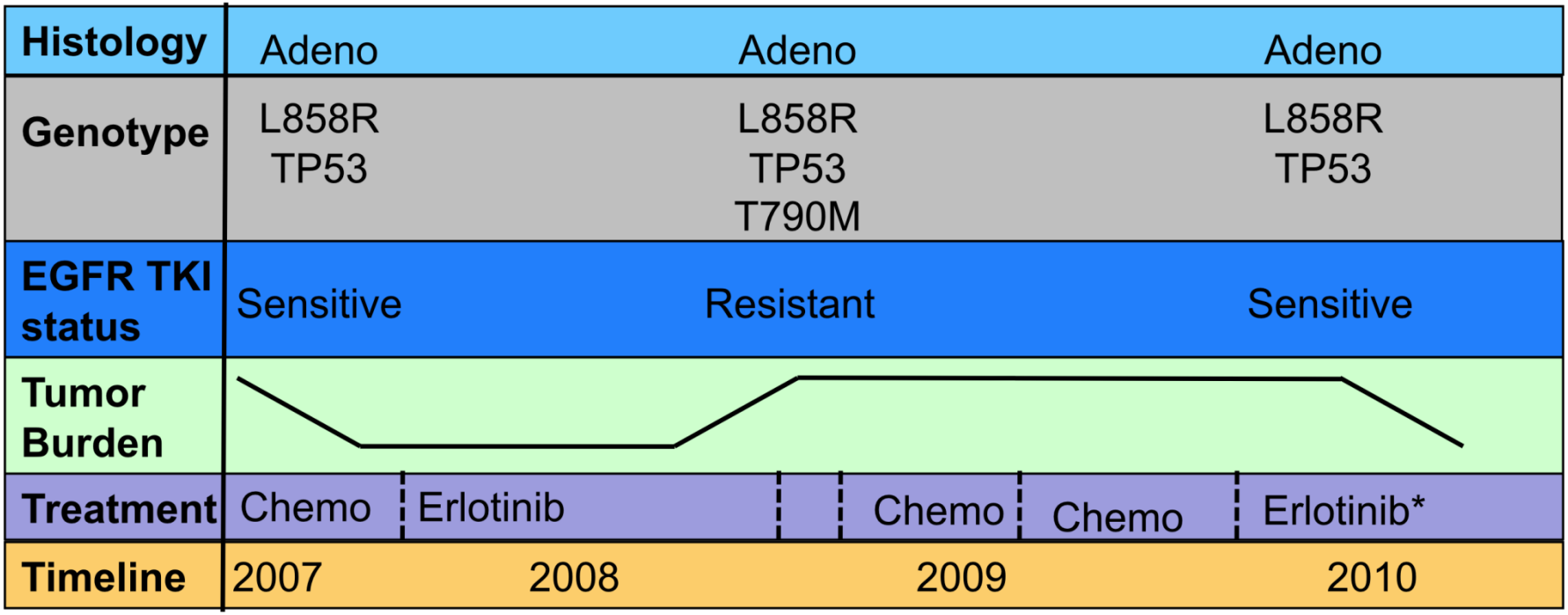
Waxing/waning resistance in response to TKI selective pressure



Sequist et al, Sci Transl Med 2011

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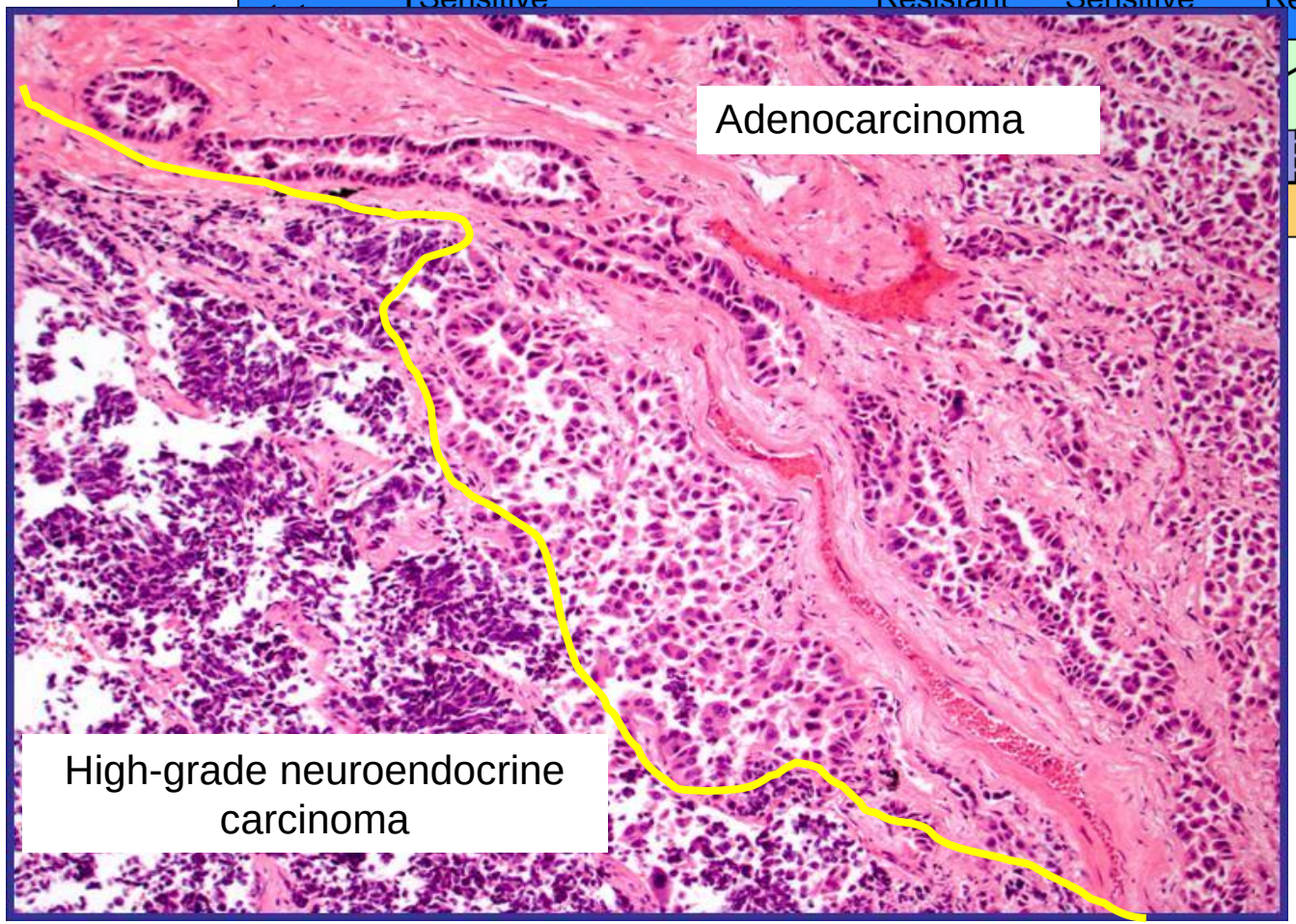
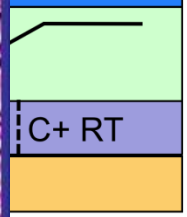
Waxing/waning resistance in response to TKI selective pressure

Histology	Adeno	SCLC	Adeno	SCLC
Genotype	L858R	L858R PIK3CA	L858R	L858R PIK3CA
EGFR TKI	Sensitive	Resistant	Sensitive	Resistant





Sequist et al, Sci Transl Med 2011

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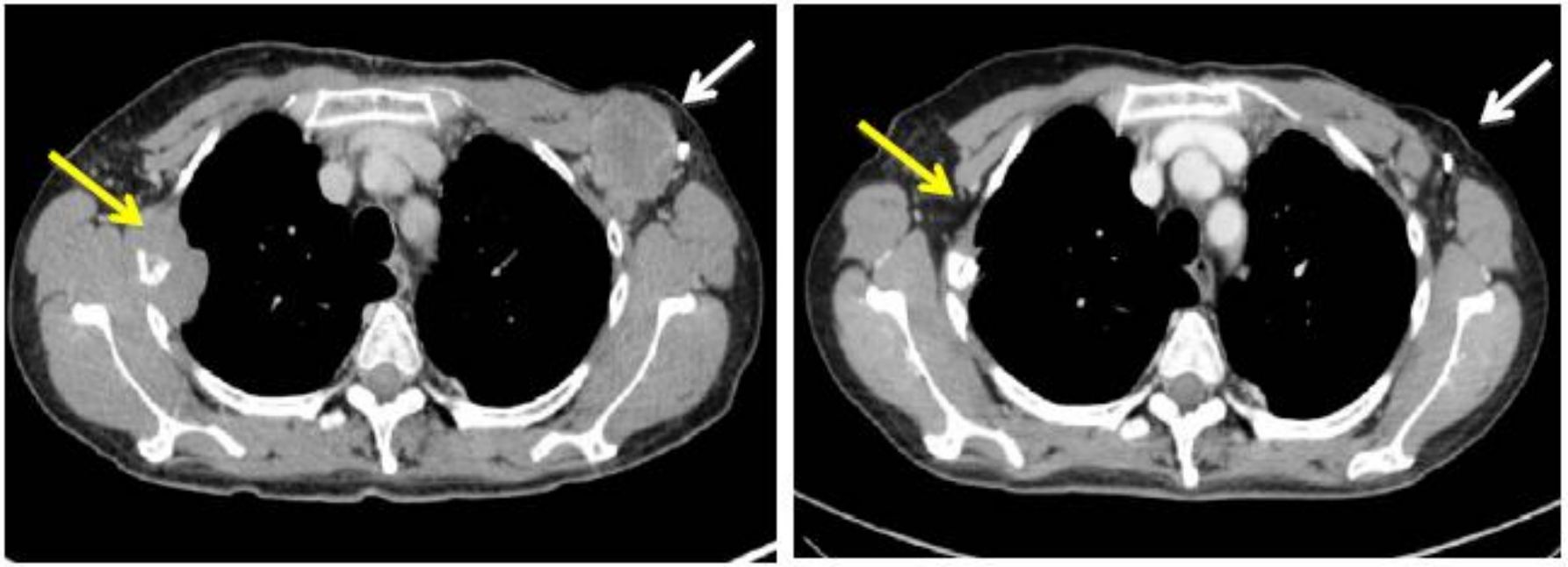
EGFR transformed to SCLC is responsive to SCLC chemo



Patient received carboplatin, etoposide and erlotinib

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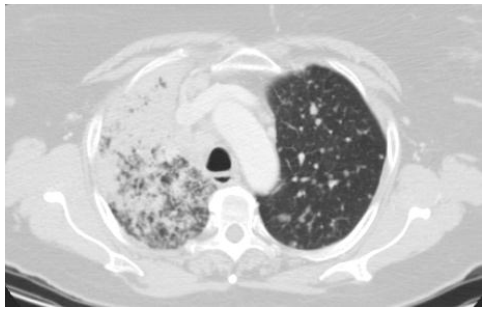
Clinical Information



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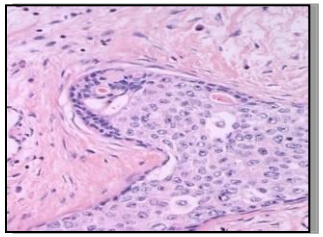

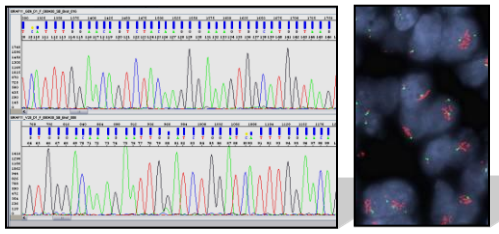

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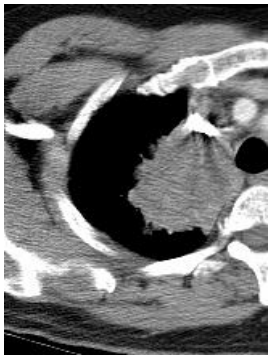
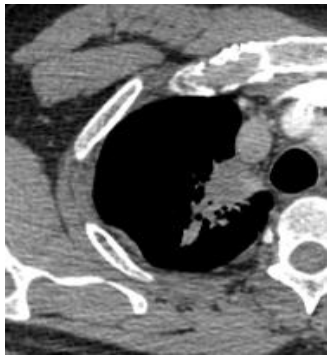
Routine and Molecular Pathology

Proof of principle: 63 year old man with an EGFR mutant lung cancer



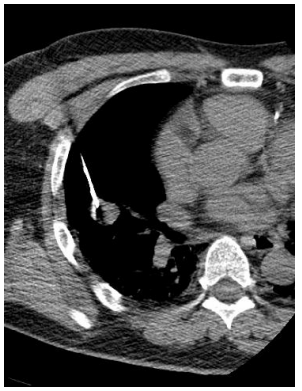
1/30/08

erlotinib



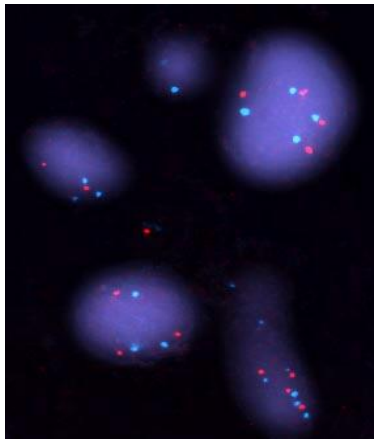
3/31/08

Developed Resistance

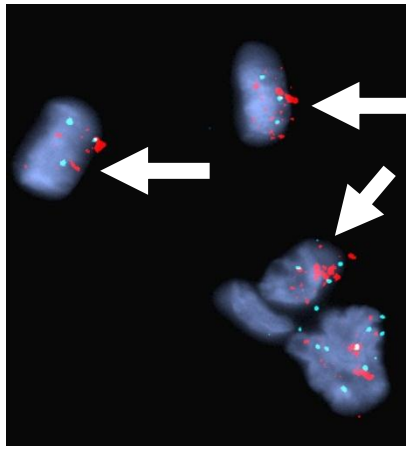


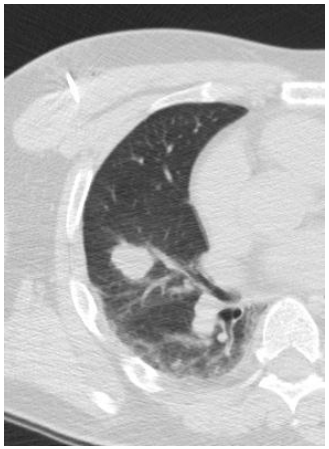
2/25/09

Pre-Rx ‘08

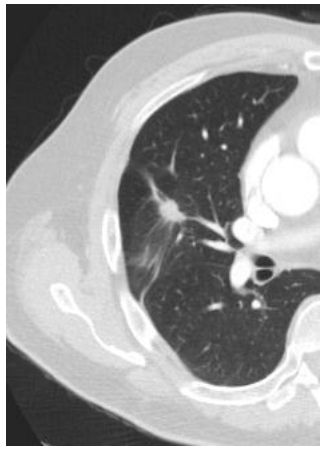


Resistant ‘09





Rx on clinical trial



Irreversible TKIs (Pan-HER Inhibitors): Not highly effective for T790M

- Neratinib (HKI-272)
  - RR 2%, PFS 15 weeks in TKI-resistant patients (Sequist, JCO 2010)
- Afatinib (BIBW-2992)
  - RR 7%, PFS ~13 weeks in TKI-resistant pts (Miller, Lan Onc '12)
- Dacomitinib (PF-299804)
  - RR 7% in TKI-resistant patients (Janne, ASCO '09)

….novel T790M-specific TKIs are entering clinical trials

- CO-1686
- AP26113

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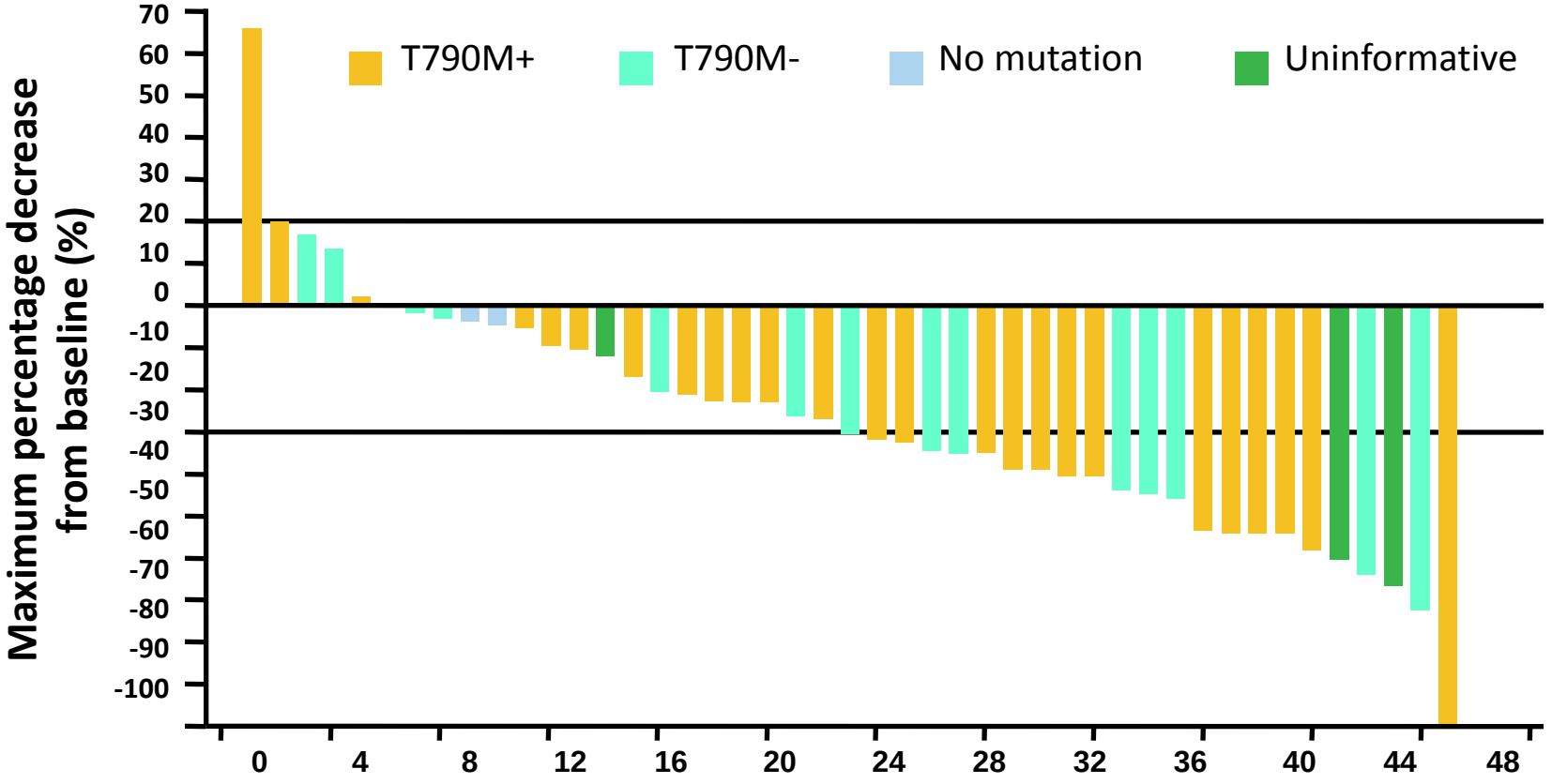
Afatinib/Cetuximab has been most active treatment, regardless of mechanism of AR



Janjigian YY et al. *ASCO* 2011;Abstract 7525.

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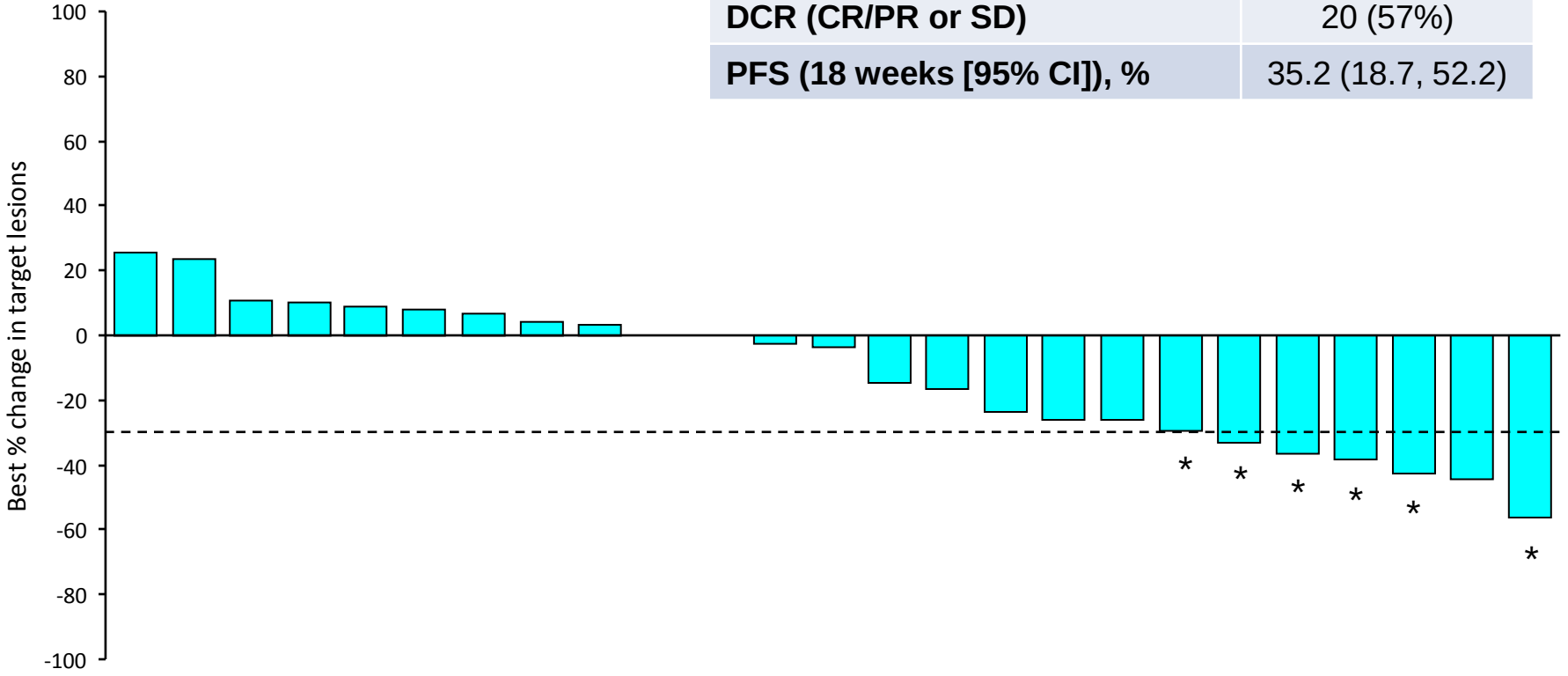
AUY922 (Hsp90): best CT response: *EGFR*-mutant patients (n=25†/35)

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)

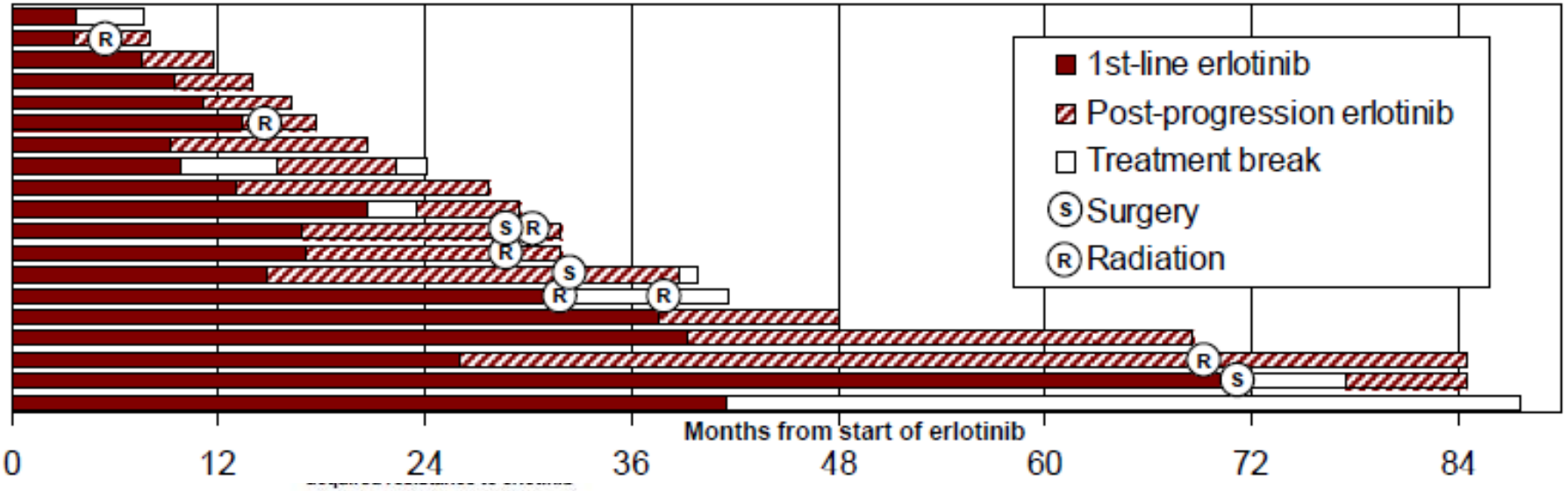


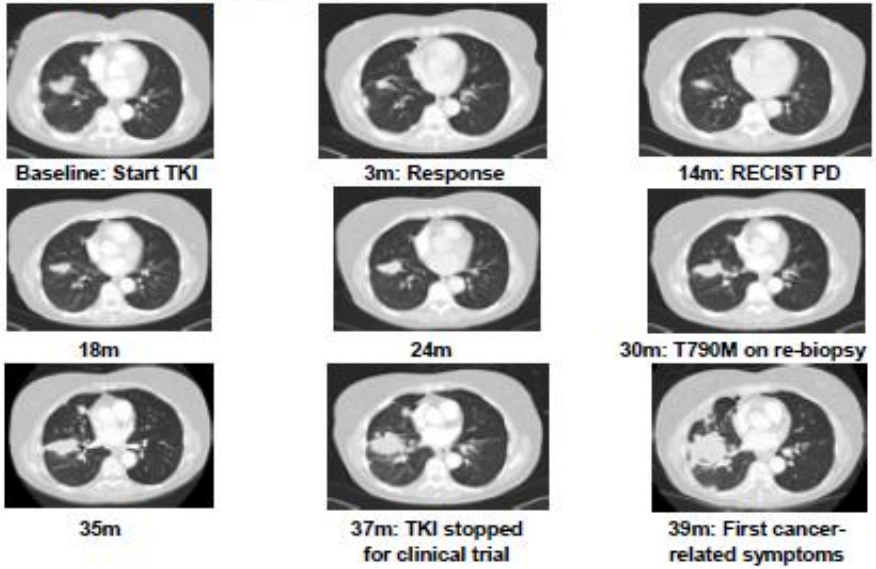
*Confirmed responses; †Patients with at least one post-baseline scan;
‡Including one PR not confirmed.

Felip, et al. ESMO '12

Treatment Beyond Progression: appealing if PD is slow

Figure 1: Management of the 19 patients able to delay alternate systemic therapy for more than 3 months





Oxnard, et al ASCO'12

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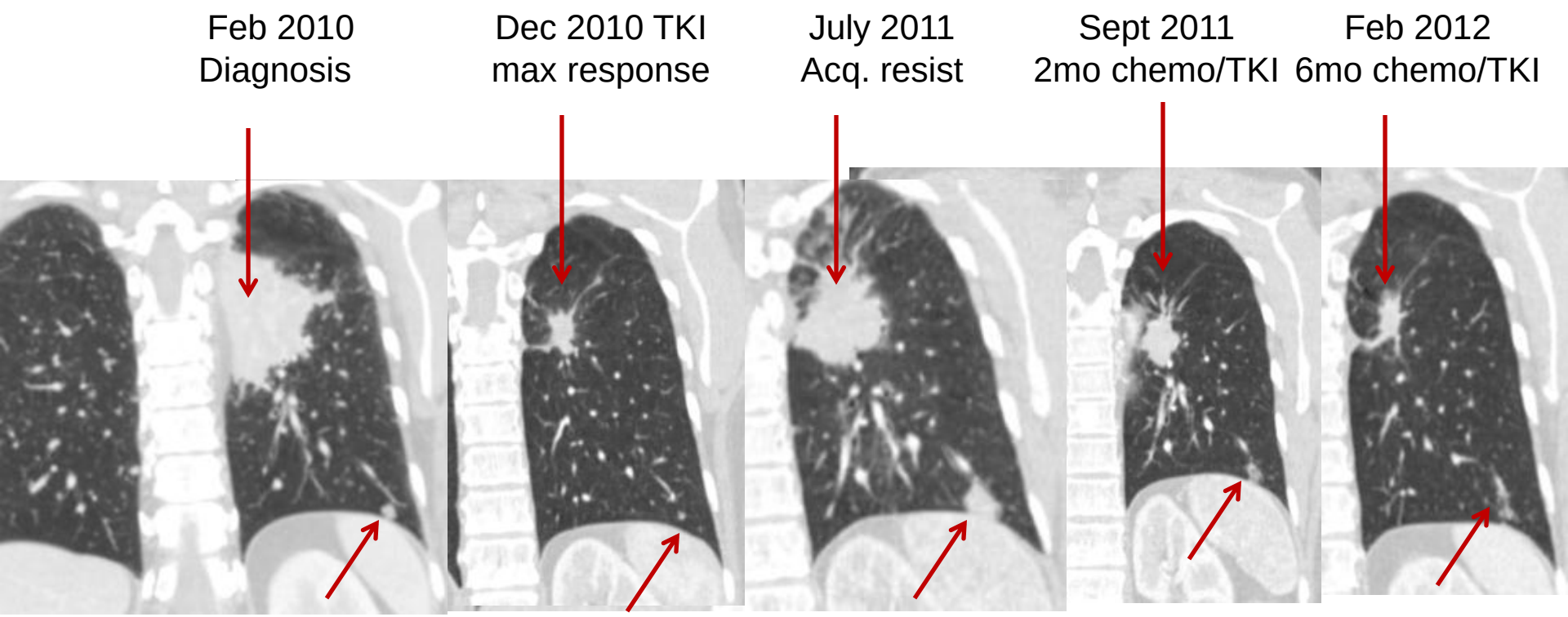
Chemotherapy plus EGFR TKI: Example Patient



Goldberg, et al ASCO ’12 showed RR higher than chemo alone
Ongoing randomized trials in US (Horn) and Asia (Mok)

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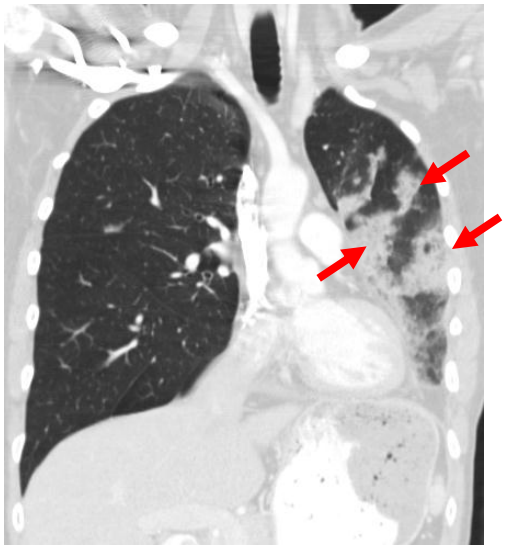
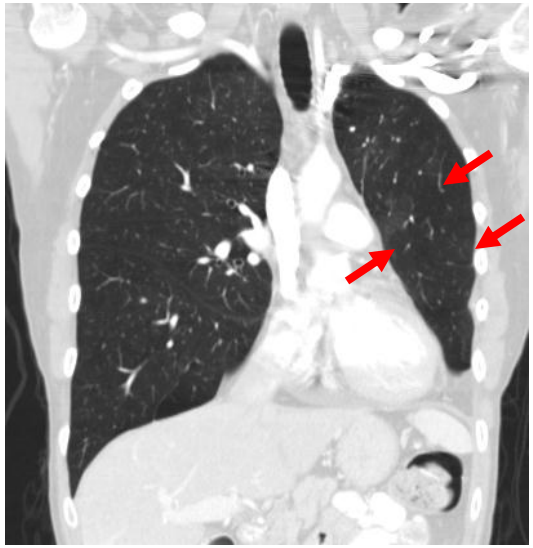
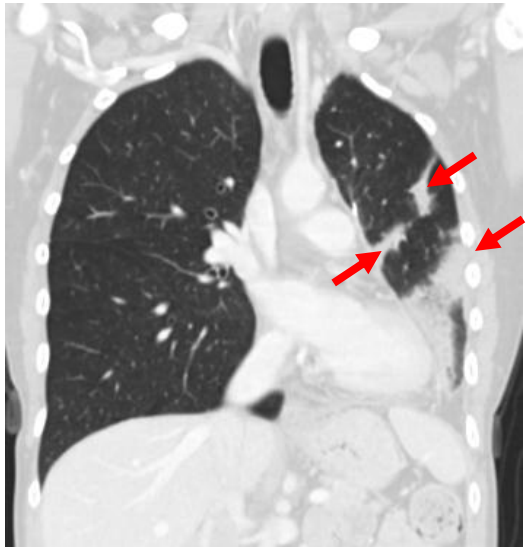
Disease Relapses on Crizotinib



Baseline



After 8 weeks of crizotinib



After 34 months of crizotinib

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Patients with Crizotinib-Resistant ALK+ NSCLC

Patient	Duration (months)*	Timing (months)†	Histology	ALK fusion
MGH0NZ	20	0	Adeno	Positive
MGH001	4	3.5	Adeno	Positive
MGH010	8	0	Adeno	Positive
MGH011	34	0	Adeno	Positive
MGH013	9	0	Adeno	Positive
MGH016	6	6	Adeno	Positive
MGH017	23+	0	Adeno	Positive
MGH018	10	0.5	Adeno	Positive
MGH019	8	<0.5	Adeno	Positive
MGH020	13	0	Adeno	Positive
MGH021	12	3	Adeno	Positive
MGH022	6	0	Adeno	Positive
MGH023	12	0	Adeno	Positive
MGH024	15	0	Adeno	Positive
MGH025	11	0	Adeno	NA
MGH027	4	1	Adeno	NA
MGH028	14	1	Adeno	NA
MGH029	8	0	Adeno	Positive

- **All patients had *acquired* TKI resistance**
- **No evidence of SCLC transformation**
- **All evaluable repeat biopsy specimens were ALK$^+$ by FISH**

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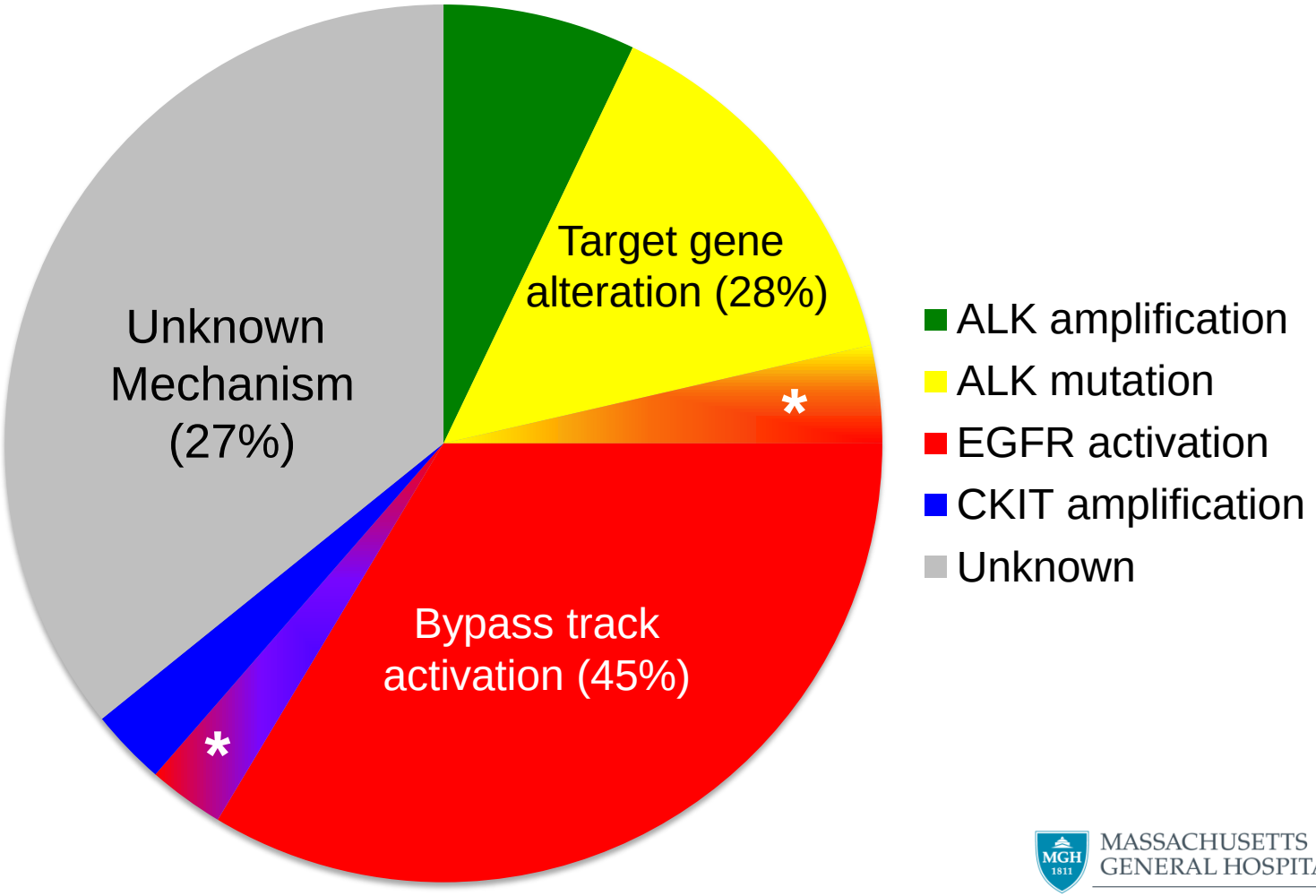
Katayama et al. Sci Transl Med 2012;4(120):120ra17

Mechanisms of Crizotinib Resistance



Katayama et al. Sci Transl Med 2012;4(120):120ra17

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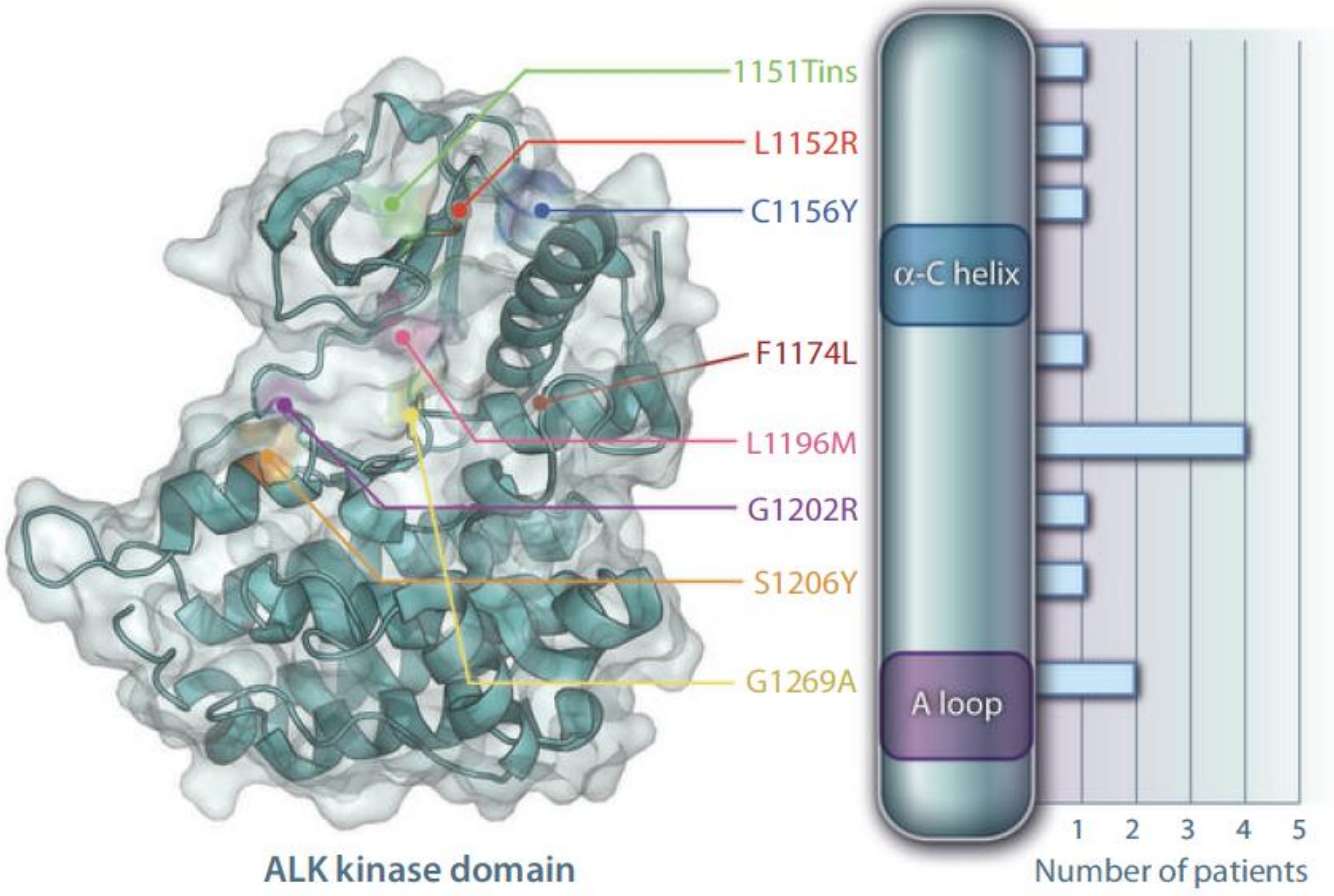
Many Different ALK Resistance Mutations



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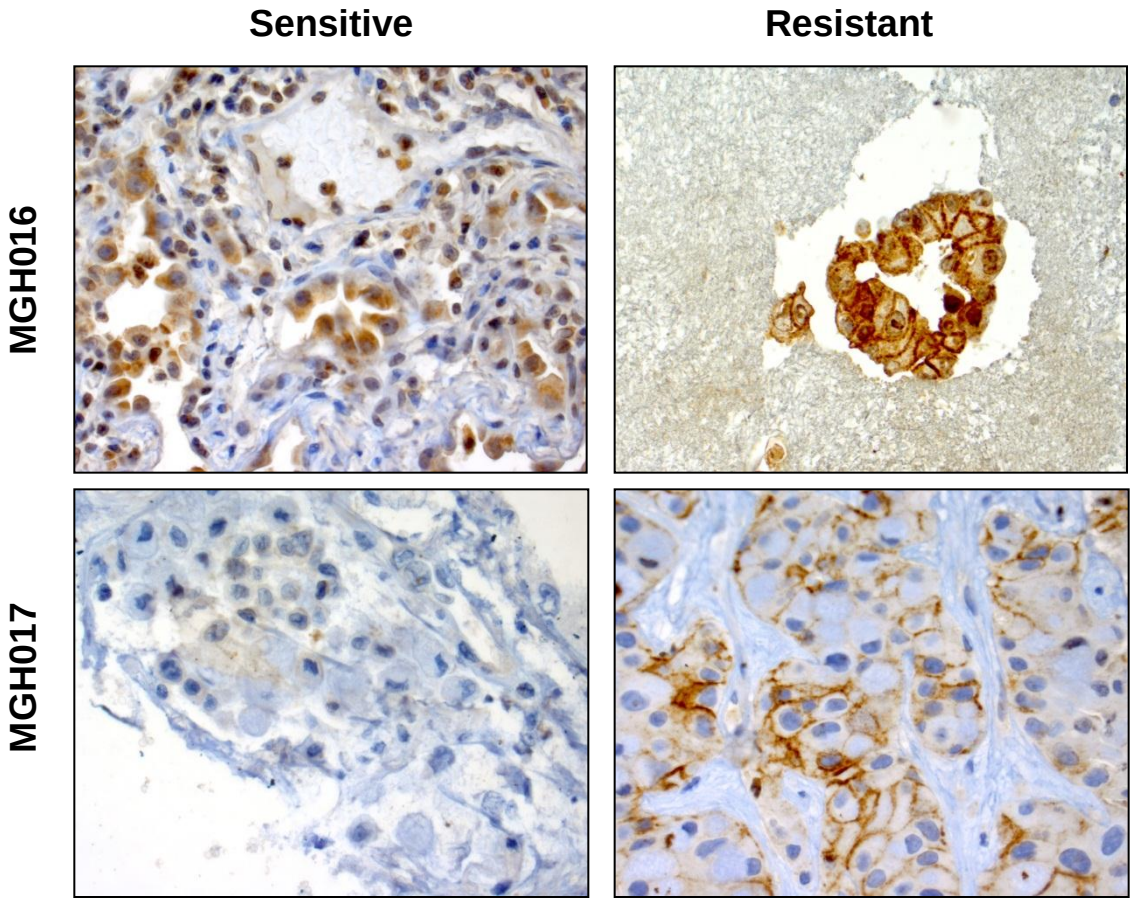
Lovly and Pao, Sci Transl Med 2012;4(120):120ps2

EGFR Activation in Crizotinib-Resistant NSCLC



No EGFR mutations

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Katayama et al., Sci Transl Med 4(120): 120ra17, 2012

Emergence of Other “Drivers”

	Doebele et al	Katayama et al
Addition of other driver mutations	**1/11 EGFR mt** **2/11 KRAS mt**	**0/6 EGFR or KRAS mt**
Loss of ALK translocation	**Absence of ALK = 2/11** (EGFR mt, unknown)	**Absence of ALK = 0/15**

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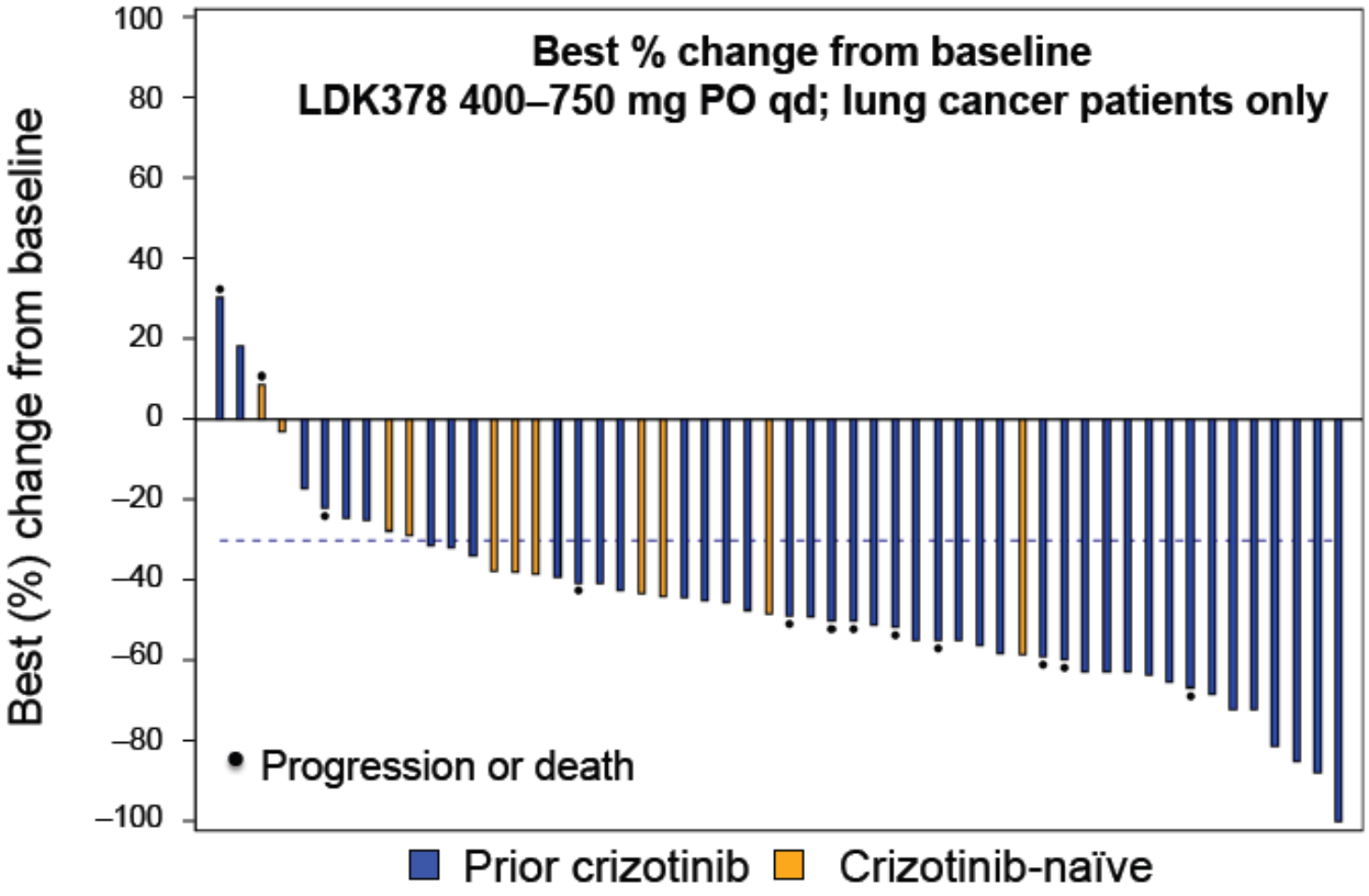
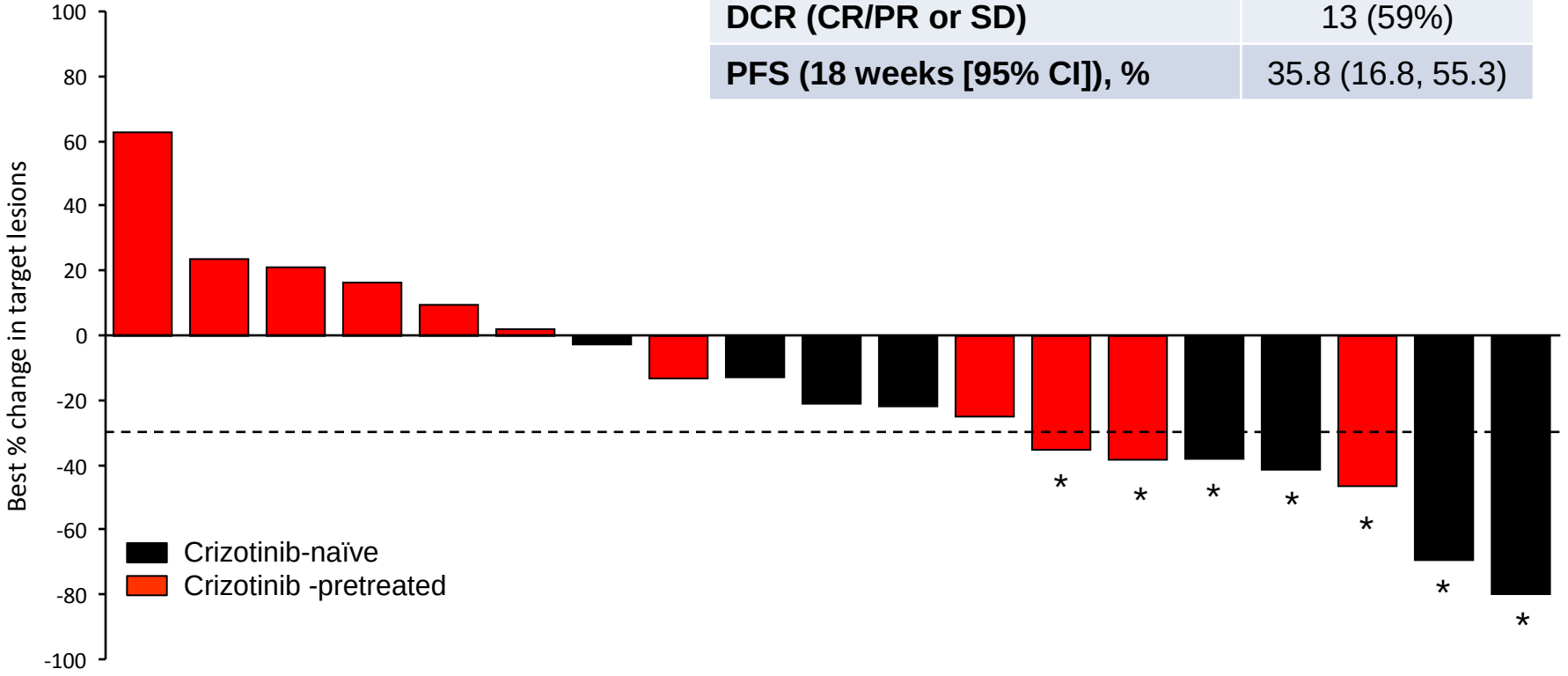
Marked activity of LDK378 in advanced ALK+ NSCLC



AUY922: best CT Response: ALK+ Stratum Patients (n=19†/22)

ALK+ (n=22)	
ORR (any PR)	7 (32%)
DCR (CR/PR or SD)	13 (59%)
PFS (18 weeks [95% CI]), %	35.8 (16.8, 55.3)



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Felip, et al. ESMO ‘12

Comparison of EGFR and ALK Resistance

EGFR Mutations	ALK Translocations
Dominant mechanism = T790M gatekeeper	**No clear dominant mechanism** **Multiple ALK mutations observed**

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EGFR amp has been seen with T790M but unclear if it is sufficient for AR	**ALK amp seems to cause AR**

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1º EGFR mutation is not lost at AR	ALK can possibly be lost at AR

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1º EGFR mutation is not lost at AR	ALK can possibly be lost at AR
Effective therapies for AR have been challenging to find	LDK378 looks promising for AR

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Summary and Conclusions

- Genotype-directed therapy paradigm has revolutionized NSCLC landscape
- Treatment of resistance has proven complicated
- Repeat biopsies of patients with AR will continue to greatly supplement lab-based research
- Prevention may be a potent strategy, especially since pre-disposition toward certain mechanisms may be identifiable
- Need less invasive alternatives to biopsies

Acknowledgments

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Subba Digumarthy
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Engelman Lab
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Tony Faber
Matt Niederest
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Vicente Morales

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Shannon Stott
John Walsh
James Sullivan
Mike Rothenberg

Yale
Tom Lynch
Scott Gettinger
Sarah Goldberg
Katie Politi

Germans Trias i Pujol, Barcelona
Teresa Moran

Stanford
Joel Neal

Vanderbilt
William Pao
Kadaoki Ohashi

Dana-Farber
Geoff Oxnard
Pasi Janne
Bruce Johnson

UCSF
Belinda Waltman

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MGH Thoracic Oncology
MGH Pathology

And Our Patients!!!

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