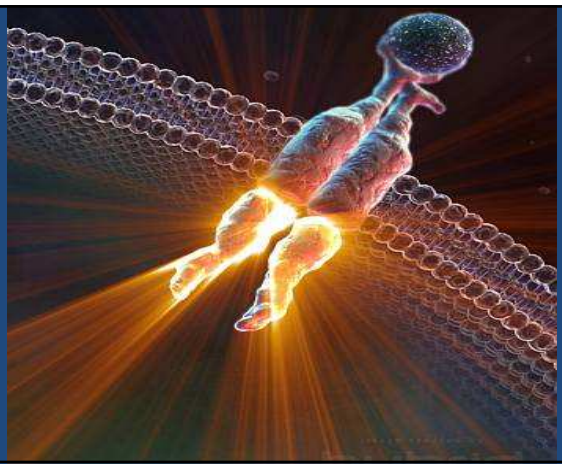
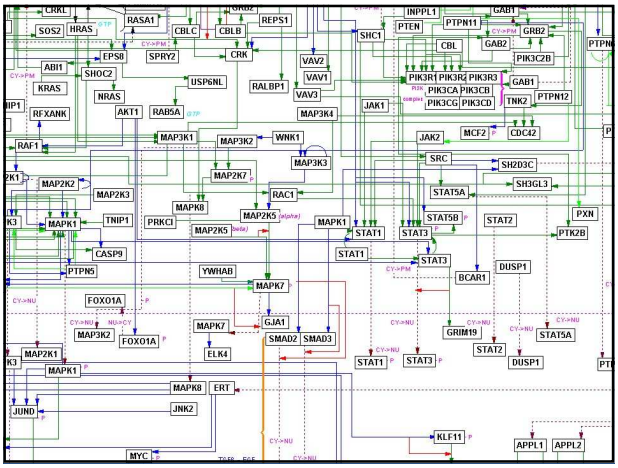
Molecular testing in NSCLC.

P.Pauwels (UZA/UZG)





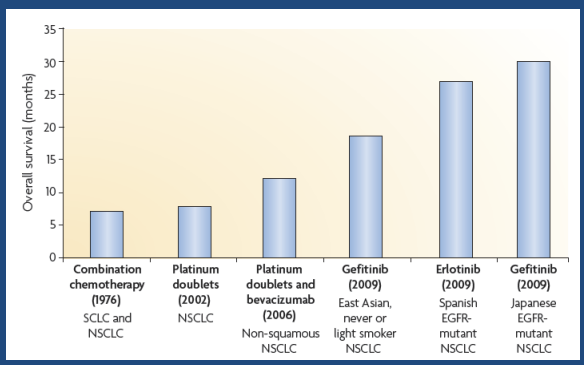
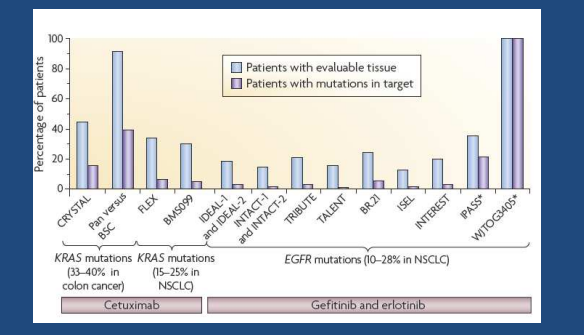
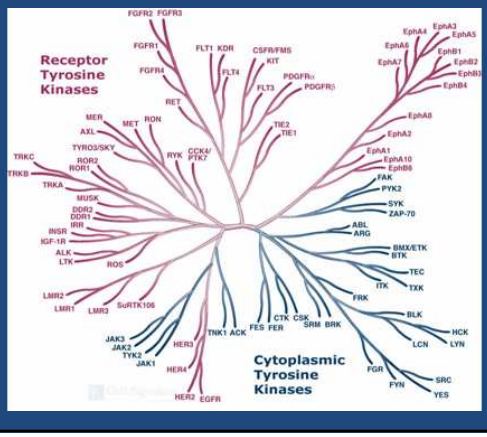
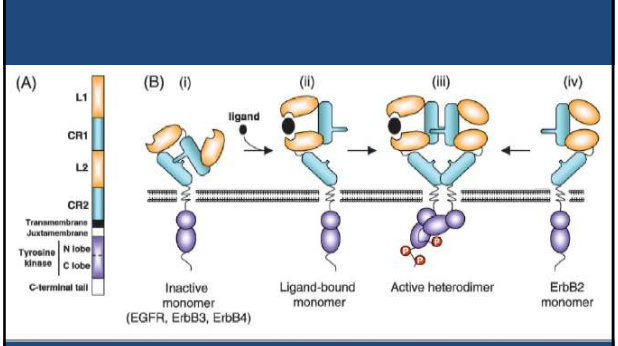


Table 1 | **Select clinical trials in lung cancer involving anti-EGFR therapies**

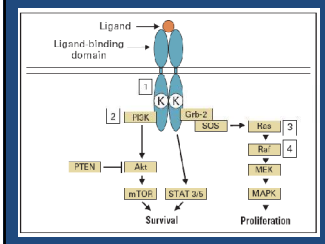
Trial	Type	Drugs	Enrollment criteria	RR (%) (EGFR TKI versus other)	Median time to treatment failure (months) (EGFR TKI versus other therapy)	Re
Gefitinib						
IDEAL-1, IDEAL-2	Phase II	Gefitinib (250 mg versus 500 mg)	Unselected previously treated NSCLC	18.4–19.0 (IDEAL-1) and 9–12 (IDEAL-2)	2.7–2.8 (IDEAL-1) and 1.5–1.7 (IDEAL-2)	1
ISEL	Phase III	Gefitinib versus placebo	Unselected previously treated NSCLC	8.0 versus 1.3	3.0 versus 2.6	
INTACT-1, INTACT-2	Phase III	Chemotherapy ± gefitinib (250 mg versus 500 mg)	Unselected chemotherapy-naive NSCLC	50.3–51.2 versus 47.2 (INTACT-1) and 30 versus 28.7 (INTACT-2)	5.5–5.8 versus 6.0 (INTACT-1) and 4.6–5.3 versus 5.0 (INTACT-2)	16 16
INTEREST	Phase III	Gefitinib versus docetaxel	Unselected previously treated NSCLC	9.1 versus 7.6	2.2 versus 2.2	15
IPASS	Phase III	Gefitinib versus chemotherapy	East Asian never or light smokers with chemotherapy-naive lung adenocarcinoma	43.0 versus 32.2* 71.2 versus 47.3*	5.7 versus 5.8* 9.5 versus 6.3*	
WJTOG3405	Phase III	Gefitinib versus chemotherapy	Japanese *EGFR*-mutant chemotherapy-naive NSCLC	62.1 versus 32.2	9.2 versus 6.3	
NEJ002	Phase III	Gefitinib versus chemotherapy	Japanese *EGFR*-mutant chemotherapy-naive NSCLC	73.7 versus 30.7	10.8 versus 5.4	
Erlotinib						
NA	Phase II	Erlotinib	NSCLC with BAC features	22	4	
BR.21	Phase III	Erlotinib versus placebo	Unselected previously treated NSCLC	8.9 versus <1	2.2 versus 1.8	
TALENT	Phase III	Chemotherapy ± erlotinib	Unselected chemotherapy-naive NSCLC	31.5 versus 29.9	6.4 versus 6.0	15
TRIBUTE	Phase III	Chemotherapy ± erlotinib	Unselected chemotherapy-naive NSCLC	21.5 versus 19.3	5.1 versus 4.9	12
SLCG	Single arm	Erlotinib	Spanish *EGFR*-mutant NSCLC	70.6	14	
Cetuximab						





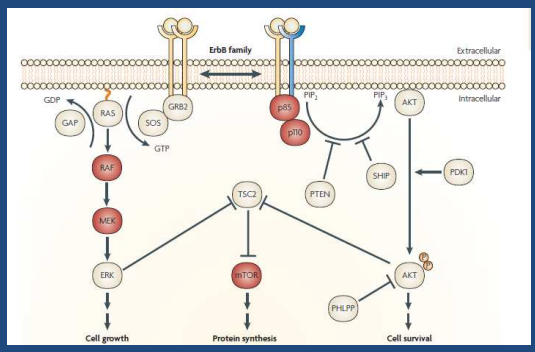


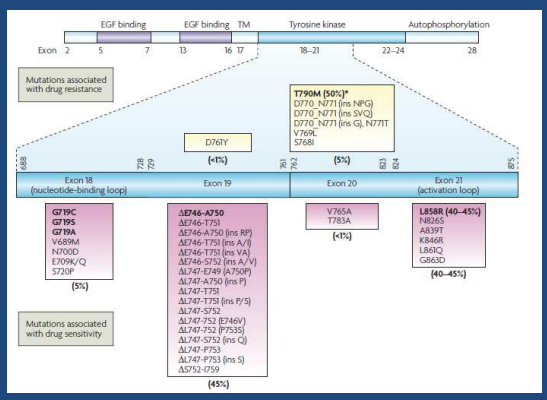
EGFR

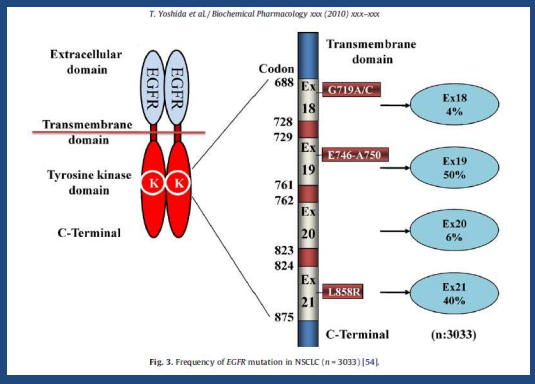


Pao & Miller JCO 2005;23:2556-2568

- Exist as monomers
- Binds ligand, changes shape and homo/hetero-dimerize
- Autophosphorylation of tyrosine residues
- Recruitment of adaptor/signaling molecules
- Downstream signaling



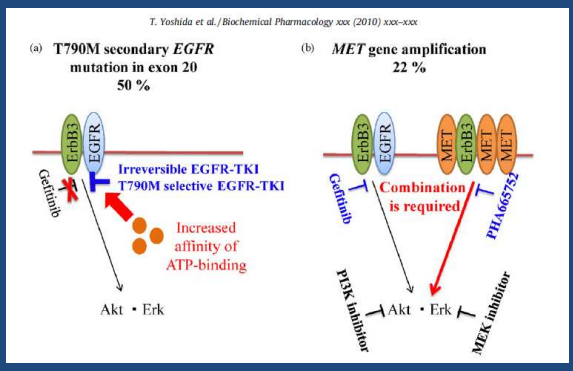




INTERESTing Biomarker to Select IDEAL Patients for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors: Yes, for *EGFR* Mutation Analysis, Others, I PASS

Ramaswamy Govindan, *Division of Oncology, Department of Medicine, and the Alvin J Siteman Cancer Center at Washington University School of Medicine, St Louis, MO*

T. Yoshida et al. / Biochemical Pharmacology xxx (2010) xxx–xxx



Oncogene (2010) 29, 2346–2356

www.nature.com/onc

ORIGINAL ARTICLE

Amplification of *EGFR* T790M causes resistance to an irreversible EGFR inhibitor

D Ercan[1,2], K Zejnullahu[1,2], K Yonesaka[1,2], Y Xiao[3], M Capelletti[1,2], A Rogers[1,2], E Lifshits[4], A Brown[5], C Lee[5], JG Christensen[6], DJ Kwiatkowski[7], JA Engelman[4] and PA Jänne[1,2,8]

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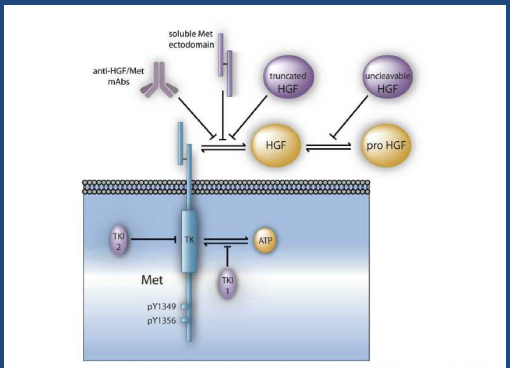

Fig. 1 – Agents currently under development as HGF/Met pathway inhibitors can be broadly subdivided into biologicals and low molecular weight synthetic compounds.

Cancer Cell
Article

Preexistence and Clonal Selection of *MET* Amplification in *EGFR* Mutant NSCLC

Alexa B. Turke,[1,2,10] Kreshnik Zejnullahu,[3,4,10] Yi-Long Wu,[5] Youngchul Song,[1] Dora Dias-Santagata,[1] Eugene Lifshits,[1] Luca Toschi,[3,4] Andrew Rogers,[3,4] Tony Mok,[6] Lecia Sequist,[1] Neal I. Lindeman,[7] Carly Murphy,[7] Sara Akhavanfard,[1] Beow Y. Yeap,[1,2] Yun Xiao,[4,7] Marzia Capelletti,[3,4] A. John Iafrate,[1] Charles Lee,[7] James G. Christensen,[8] Jeffrey A. Engelman,[1,2,11,*] and Pasi A. Jänne[2,3,4,9,11,*]

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DOI 10.1016/j.ccr.2009.11.022

Consensus for *EGFR* Mutation Testing in Non-small Cell Lung Cancer

Results from a European Workshop

Robert Pirker, MD, Felix J. F. Herth, MD, PhD, FCCP,† Keith M. Kerr, MD, FRCPath,‡ Martin Filipits, PhD,* Miquel Taron, PhD,§‖ David Gandara, MD,¶ Fred R. Hirsch, MD,# Dominique Grunenwald, MD,** Helmut Popper, MD,†† Egbert Smit, MD, PhD,‡‡ Manfred Dietel, MD,§§ Antonio Marchetti, MD, PhD,‖‖ Christian Manegold, MD,¶¶ Peter Schirmacher, MD,## Michael Thomas, MD, PhD,† Rafael Rosell, MD, PhD,§‖ Federico Cappuzzo, MD,*** and Rolf Stahel, MD†††; on Behalf of the European EGFR Workshop Group*

Can Cytology Samples Be Used?

Cytology samples may be suitable for analysis but further research is needed to fully understand the clinical reliability of mutational data obtained from these samples. Until then, clinicians should be encouraged to provide tissue biopsy samples whenever possible.

TABLE 3. Recommendations for *EGFR* Mutation Testing in NSCLC

Which patient?	NSCLC patients[a]
Time point	At diagnosis
	When possible at disease progression
Sample source	Most easily accessible
	Biopsy preferred over cytology
Fixation	10% neutral-buffered formalin
	Bouin's fluid should not be used
Tumor cell content	≥50% Tumor cells for DNA sequencing
	Lower % acceptable with higher sensitivity techniques
EGFR mutation analysis method	No gold standard yet
Report to include	Detail of biopsy sample and tissue extracted
	Type of mutation analysis
	Mutation present/absent
	Interpretation

[a] Local policy may determine which patients are tested. In European studies, the prevalence of *EGFR* mutation in definitively diagnosed squamous cell carcinoma, neuroendocrine carcinomas, and mucinous bronchioloalveolar-pattern adenocarcinomas is effectively zero.[45] A pragmatic approach could be to exclude from testing those patients with a confident diagnosis of the above tumor types, but to test all those with other NSCLC subtypes, and all "never smokers," regardless of tumor type. In cases in which subtype is unclear, testing is indicated.

NSCLC, non-small cell lung cancer.

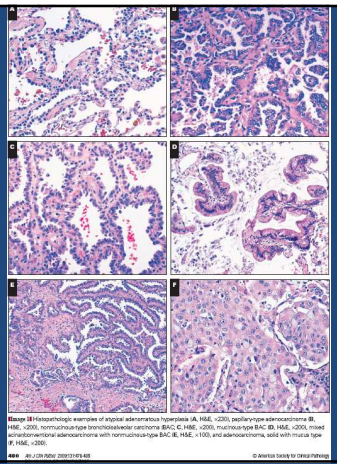

Image 1 Histopathologic examples of atypical adenomatous hyperplasia (A, H&E, ×200), papillary-type adenocarcinoma (B, H&E, ×200), nonmucinous-type bronchioloalveolar carcinoma (BAC) (C, H&E, ×200), mucinous-type BAC (D, H&E, ×200), mixed acinar/papillary/mucinous adenocarcinoma with nonmucinous-type BAC (E, H&E, ×100), and adenocarcinoma, solid with mucus type (F, H&E, ×200).

Human Pathology (2010) 41, 94–102

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Original contribution

A comparison of *EGFR* and *KRAS* status in primary lung carcinoma and matched metastases

Sara E. Monaco MD*, Marina N. Nikiforova MD, Kathleen Cieply BS, Lisa A. Teot MD, Walid E. Khalbuss MD, PhD, Sanja Dacic MD, PhD

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Received 13 May 2009; revised 29 June 2009; accepted 30 June 2009

Clinical Activity Observed in a Phase 1 Dose-Escalation Trial of an Oral MET and ALK Inhibitor, PF-02341066

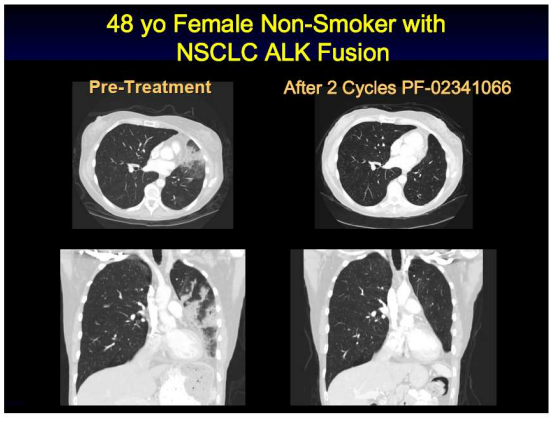
EL Kwak[1], DR Camidge[2], J Clark[1], GI Shapiro[3], RG Maki[4], MJ Ratain[5], B Solomon[6], Y-J Bang[7], S-H Ou[8], R Salgia[5]

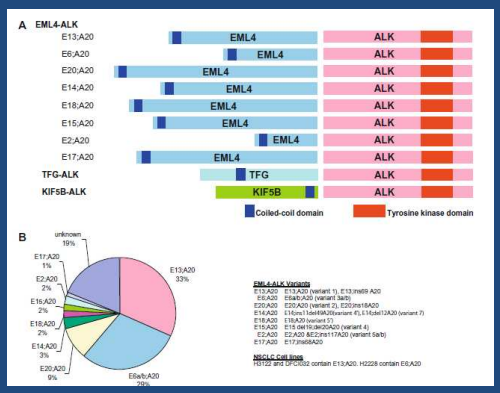
1. Massachusetts General Hospital
2. University of Colorado Cancer Center
3. Dana-Farber Cancer Institute
4. Memorial Sloan-Kettering Cancer Center
5. University of Chicago Cancer Center
6. Peter MacCallum Cancer Centre
7. Seoul National University
8. University of California at Irvine

48 yo Female Non-Smoker with NSCLC ALK Fusion

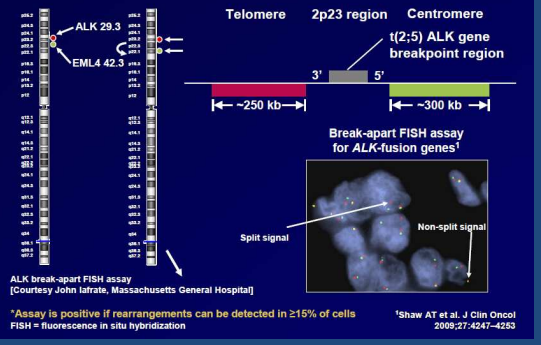
Pre-Treatment

After 2 Cycles PF-02341066





FISH Assay for *ALK* Rearrangement*



*Assay is positive if rearrangements can be detected in ≥15% of cells
FISH = fluorescence in situ hybridization

[1]Shaw AT et al. J Clin Oncol 2009;27:4247–4253

Summary

- Treatment with crizotinib resulted in impressive clinical activity in patients with *ALK*-positive advanced NSCLC
  - ORR: 57%
  - DCR at 8 weeks: 87%
  - PFS probability at 6 months: 72%
- Crizotinib was well tolerated
  - The most frequent adverse events were mild and moderate gastrointestinal events and mild visual disturbances

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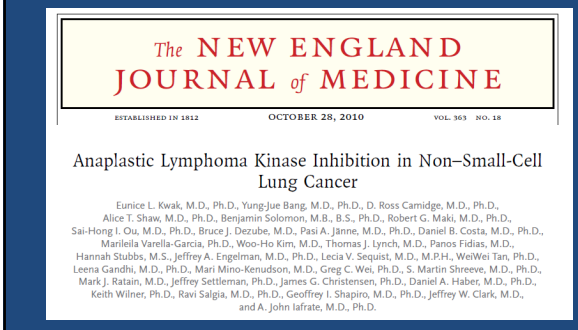
JOURNAL OF CLINICAL ONCOLOGY | EDITORIAL

EML4-ALK: Honing In on a New Target in Non–Small-Cell Lung Cancer

Leora Horn and William Pao, *Vanderbilt-Ingram Cancer Center, Nashville, TN*

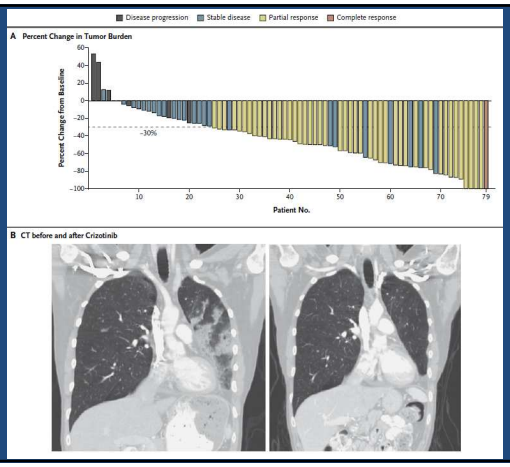


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.



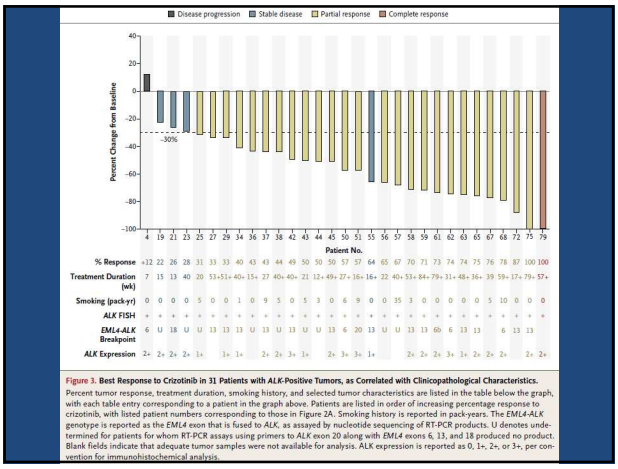


Figure 3. Best Response to Crizotinib in 31 Patients with *ALK*-Positive Tumors, as Correlated with Clinicopathological Characteristics.
Percent tumor response, treatment duration, smoking history, and selected tumor characteristics are listed in the table below the graph, with each table entry corresponding to a patient in the graph above. Patients are listed in order of increasing percentage response to crizotinib, with listed patient numbers corresponding to those in Figure 2A. Smoking history is reported in pack-years. The *EML4-ALK* genotype is reported as the *EML4* exon that is fused to *ALK*, as assayed by nucleotide sequencing of RT-PCR products. U denotes undetermined for patients for whom RT-PCR assays using primers to *ALK* exon 20 along with *EML4* exons 6, 13, and 18 produced no product. Blank fields indicate that adequate tumor samples were not available for analysis. ALK expression is reported as 0, 1+, 2+, or 3+, per convention for immunohistochemical analysis.

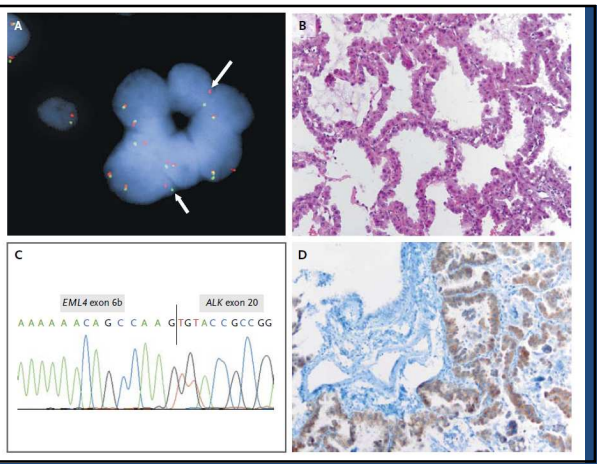
Table 1. Demographic and Clinicopathological Characteristics of the 82 Patients.

Characteristic	Value
Male sex — no. (%)	43 (52)
Age — yr	
Mean	51
Range	25–78
Race — no. (%)*	
White	46 (56)
Asian	29 (35)
Other	7 (9)
ECOG performance status — no. (%)†	
0	24 (29)
1	44 (54)
2	13 (16)
3	1 (1)
No. of previous therapies — no. (%)	
0	5 (6)
1	27 (33)
2	15 (18)
≥3	34 (41)
Not reported	1 (1)
Histologic analysis — no. (%)	
Adenocarcinoma	79 (96)
Squamous-cell carcinoma	1 (1)
Other	2 (2)
Smoking history — no. (%)‡	
Never	62 (76)
≤10 pack-yr	15 (18)
>10 pack-yr	5 (6)

Table 2. Adverse Events in the 82 Patients.*

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Total
			no. of patients (%)		
Any adverse event†					
Nausea	43 (52)	1 (1)	0	0	44 (54)
Diarrhea	38 (46)	1 (1)	0	0	39 (48)
Vomiting	35 (43)	1 (1)	0	0	36 (44)
Visual disturbance	34 (41)	0	0	0	34 (41)
Constipation	18 (22)	2 (2)	0	0	20 (24)
Peripheral edema	13 (16)	0	0	0	13 (16)
Dizziness	12 (15)	0	0	0	12 (15)
Decreased appetite	11 (13)	0	0	0	11 (13)
Fatigue	8 (10)	0	0	0	8 (10)
Grade 3 or 4 adverse events‡					
ALT elevation			4 (5)	1 (1)	
AST elevation			5 (6)	0	
Lymphopenia			2 (2)	0	
Hypophosphatemia			1 (1)	0	
Neutropenia			1 (1)	0	
Hypoxia			1 (1)	0	
Pneumonitis			1 (1)	0	
Pulmonary embolism			1 (1)	0	

* ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† These adverse events occurred in at least 10% of the 82 patients. The adverse events that occurred in two patients who received crizotinib during dose escalation are included. The remaining patients started treatment at 250 mg of crizotinib twice daily.
‡ These grade 3 or 4 adverse events were evaluated in 82 patients; laboratory data were not always available for all 82 patients.



Crizotinib — Latest Champion in the Cancer Wars?

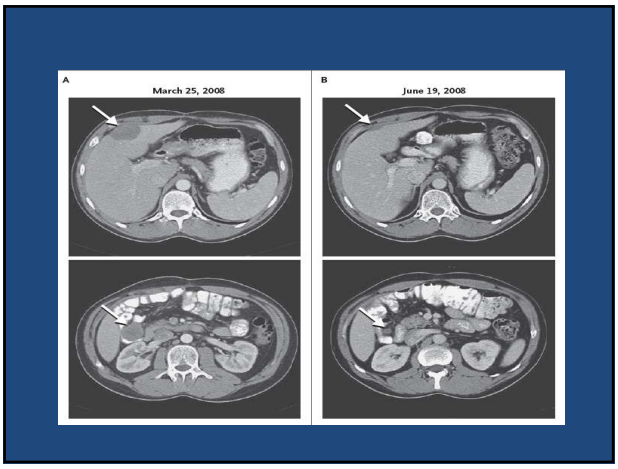
Bengt Hallberg, Ph.D., and Ruth H. Palmer, Ph.D.

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Crizotinib in *ALK*-Rearranged Inflammatory Myofibroblastic Tumor

James E. Butrynski, M.D., David R. D'Adamo, M.D., Ph.D., Jason L. Hornick, M.D., Ph.D., Paola Dal Cin, Ph.D., Cristina R. Antonescu, M.D., Suresh C. Jhanwar, Ph.D., Marc Ladanyi, M.D., Marzia Capelletti, Ph.D., Scott J. Rodig, M.D., Ph.D., Nikhil Ramaiya, M.D., Eunice L. Kwak, M.D., Jeffrey W. Clark, M.D., Keith D. Wilner, Ph.D., James G. Christensen, Ph.D., Pasi A. Jänne, M.D., Ph.D., Robert G. Maki, M.D., Ph.D., George D. Demetri, M.D., and Geoffrey I. Shapiro, M.D., Ph.D.


A
March 25, 2008
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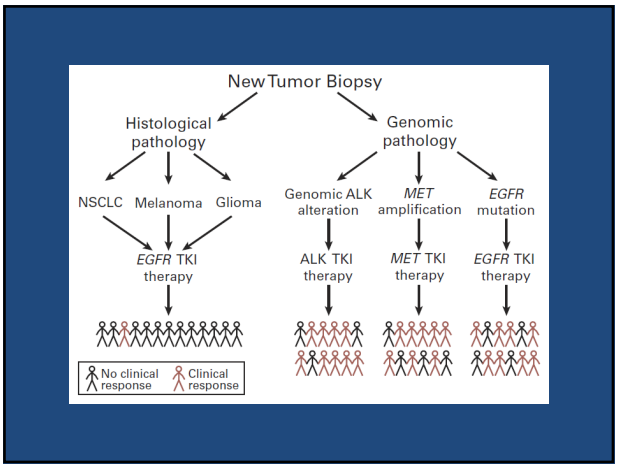
June 19, 2008


New Tumor Biopsy
Histological pathology
Genomic pathology
NSCLC
Melanoma
Glioma
Genomic ALK alteration
MET amplification
EGFR mutation
EGFR TKI therapy
ALK TKI therapy
MET TKI therapy
EGFR TKI therapy
No clinical response
Clinical response