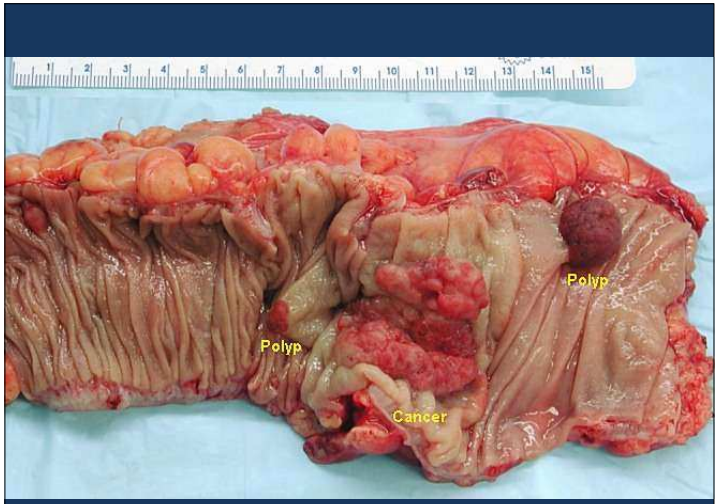

Daniele Pellegrini/Photo Researchers, Inc.


Polyp
Polyp
Cancer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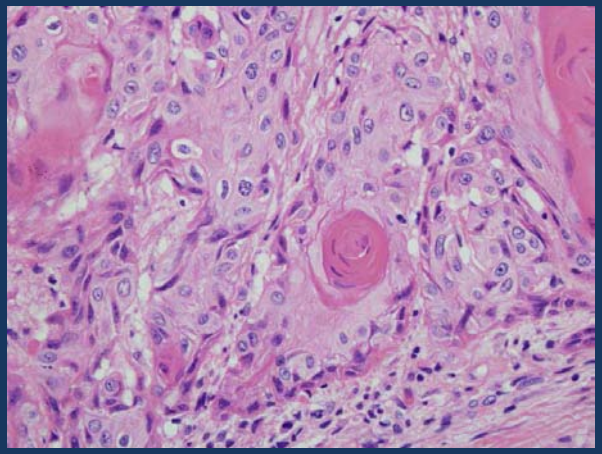
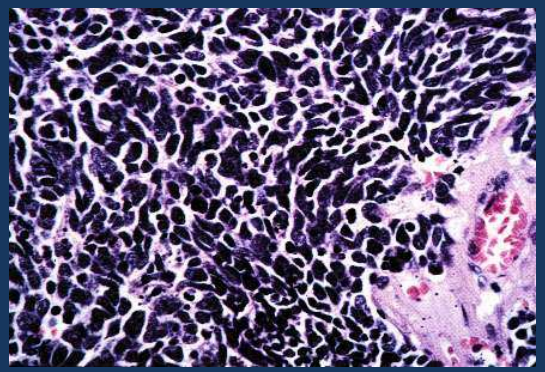
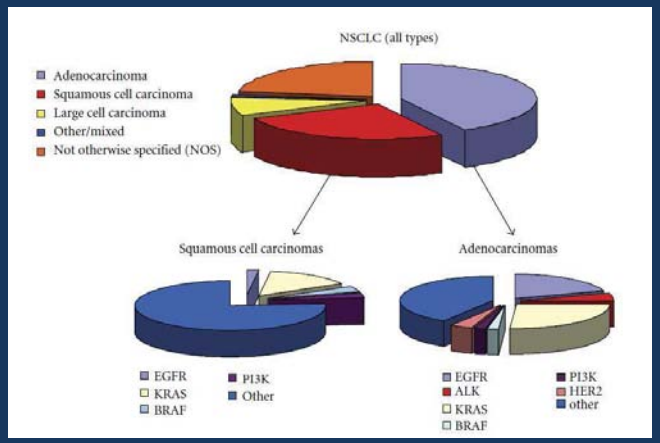
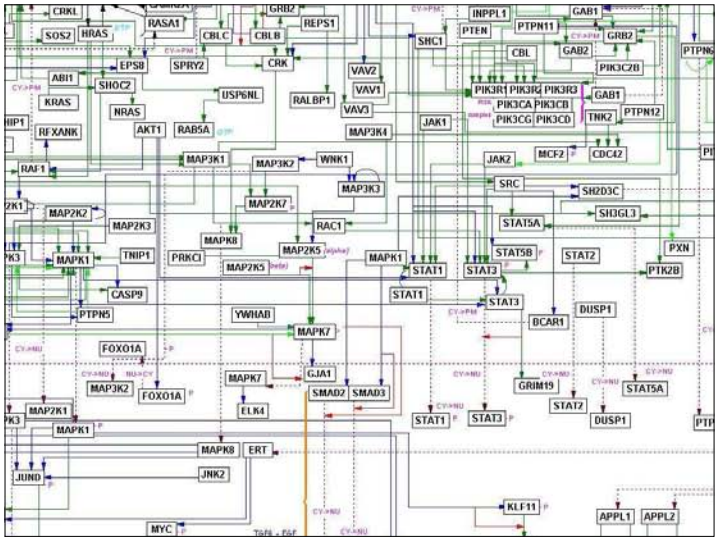
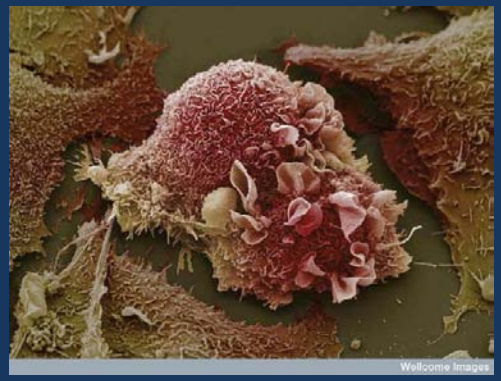


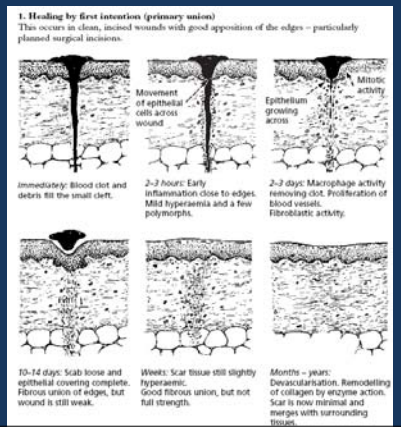


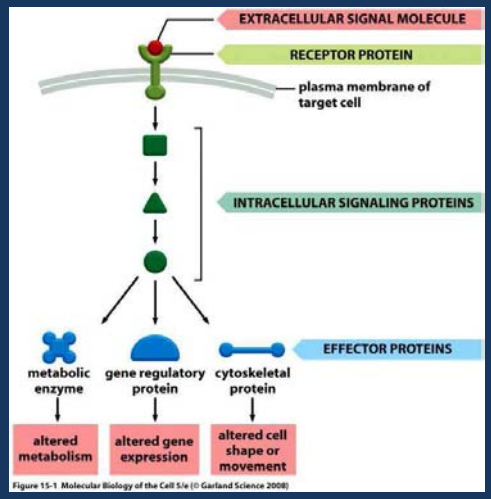

NSCLC (all types)
Adenocarcinoma
Squamous cell carcinoma
Large cell carcinoma
Other/mixed
Not otherwise specified (NOS)
Squamous cell carcinomas
Adenocarcinomas
EGFR
PI3K
KRAS
Other
BRAF
EGFR
PI3K
ALK
HER2
KRAS
other
BRAF

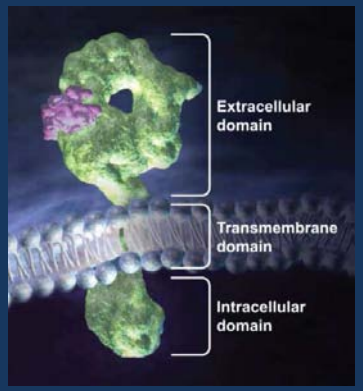

CRKL
RASA1
GRB2
REPS1
INPPL1
GAB1
SOS2
HRAS
CBLC
CBLB
PTEN
PTPN11
GRB2
SHC1
CBL
GAB2
EPS8
SPRY2
CRK
VAV2
PIK3C2B
ABI1
SHOC2
VAV1
PIK3R1 PIK3R2 PIK3R3
GAB1
KRAS
USP6NL
RALBP1
VAV3
PIK3CA PIK3CB
NRAS
PIK3CG PIK3CD
TNK2
PTPN12
RFXANK
AKT1
RAB5A
MAP3K4
JAK1
MAP3K1
MAP3K7
WNK1
JAK2
MCF2
CDC42
RAF1
SRC
MAP3K3
SH2D3C
MAP2K2
MAP2K7
SH3GL3
MAP2K3
RAC1
STAT5A
MAPK8
TNIP1
PRKCI
MAP2K5
MAPK1
STAT1
STAT3
STAT5B
STAT2
PXN
PIK2B
CASP9
PTPN5
YWHAB
MAPK7
BCAR1
DUSP1
FOXO1A
GJA1
MAP3K2
FOXO1A
SMAD2
SMAD3
GRIM19
STAT5A
MAP2K1
ELK4
STAT2
MAPK1
DUSP1
MAPK8
ERT
JUND
JNK2
KLF11
APPL1
APPL2
MYC



Types of healing







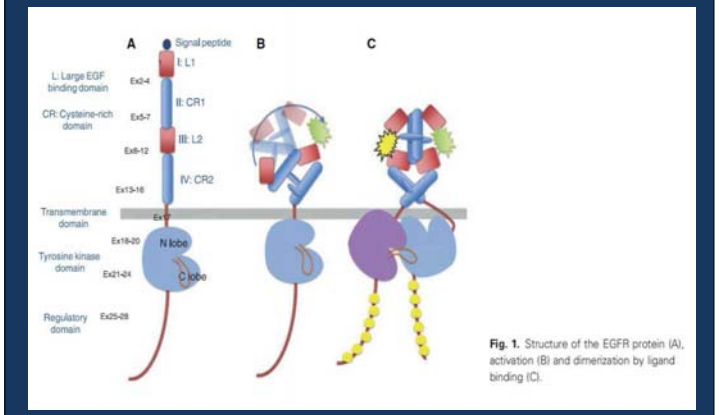
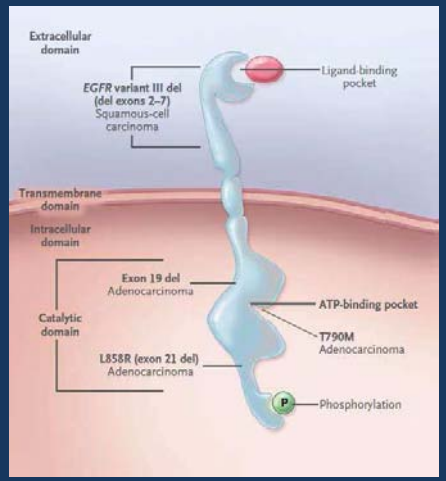
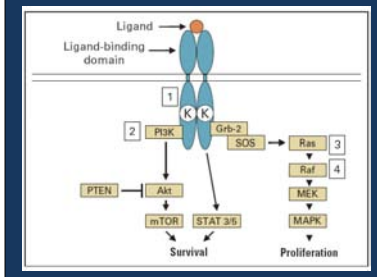


Fig. 1. Structure of the EGFR protein (A), activation (B) and dimerization by ligand binding (C).

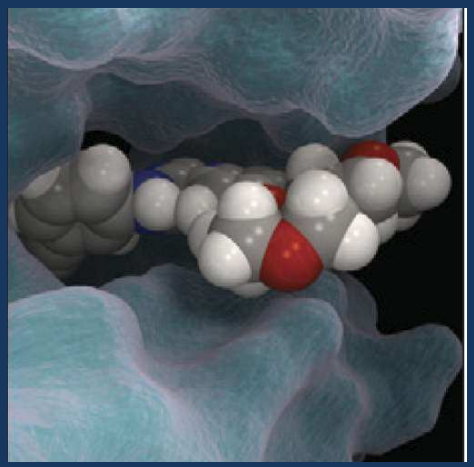


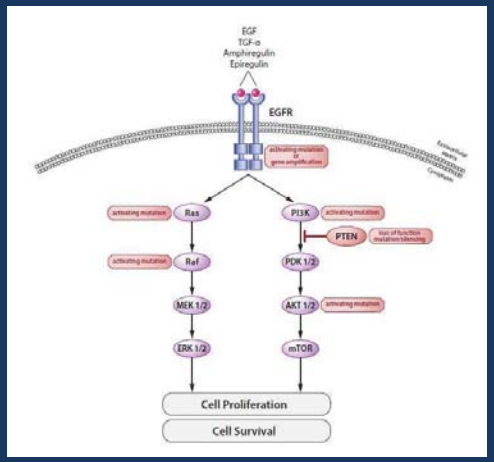
EGFR

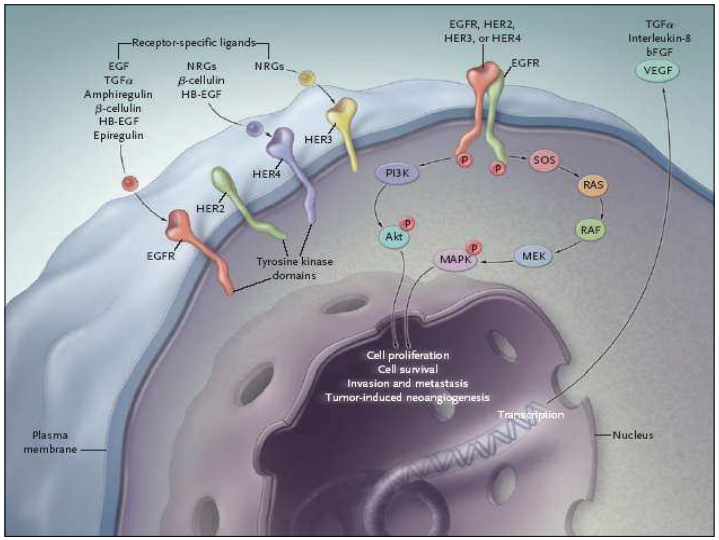


- Exist as monomers
- Binds ligand, changes shape and homo/hetero-dimerize
- Autophosphorylation of tyrosine residues
- Recruitment of adaptor/signaling molecules
- Downstream signaling

Pao & Miller JCO 2005;23:2556-2568







NEWS & VIEWS

TARGETED THERAPIES

Front-line therapy in lung cancer with mutations in *EGFR*

Lorenza Landi and Federico Cappuzzo

Large randomized phase III trials conducted in patients with non-small-cell lung cancer (NSCLC) harboring activating mutations in *EGFR* have demonstrated that erlotinib or gefitinib are superior to platinum-based chemotherapy. Zhou *et al.* have now confirmed that these agents represent the best treatment we can offer today as front-line therapy for *EGFR*-mutant NSCLC.

Landi, L. & Cappuzzo, F. *Nat. Rev. Clin. Oncol.* 8, 571–573 (2011); published online 30 August 2011; doi:10.1038/nrclinonc.2011.135

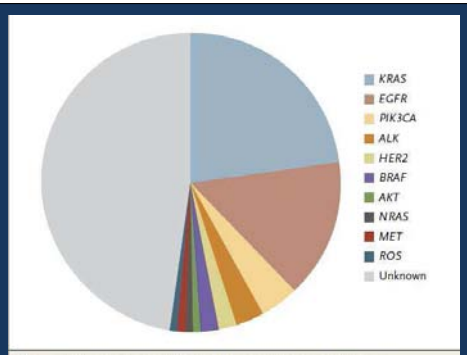


Figure 4. Genetic Abnormalities in Adenocarcinomas of the Lung.

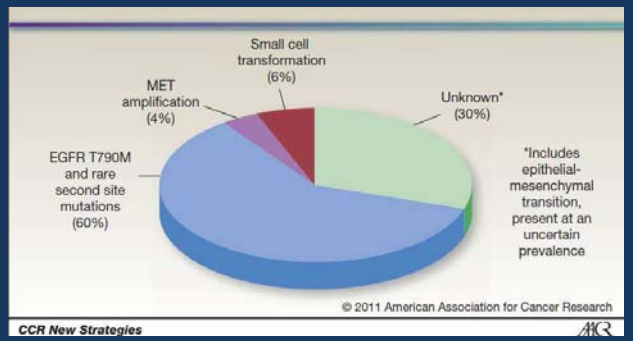
The pie chart depicts the approximate frequency of each oncogenic alteration. Results are based on the screening of 650 lung adenocarcinomas at Massachusetts General Hospital. The genotyping platform detects activating mutations in *KRAS, EGFR, PI3K, HER2, BRAF, AKT,* and *NRAS*. In addition, fluorescence in situ hybridization is used to identify chromosomal rearrangements involving *ALK* or *ROS* and gene amplification of *c-MET*. In nearly half of lung adenocarcinomas, no genetic abnormality can be identified by these methods.

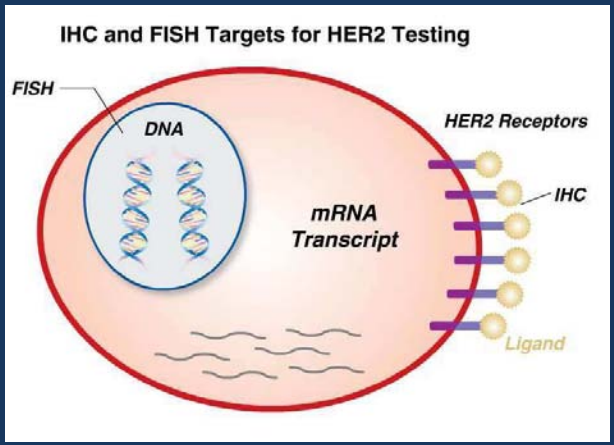
RESEARCH ARTICLE

CANCER

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

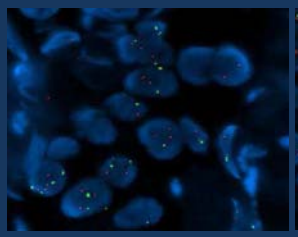
Lecia V. Sequist,[1,2*†] Belinda A. Waltman,[2*] Dora Dias-Santagata,[2,3*] Subba Digumarthy,[2,4] Alexa B. Turke,[1,2] Panos Fidias,[1,2] Kristin Bergethon,[3] Alice T. Shaw,[1,2] Scott Gettinger,[5] Arjola K. Cosper,[1] Sara Akhavanfard,[2,3] Rebecca S. Heist,[1,2] Jennifer Temel,[1,2] James G. Christensen,[6] 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†]



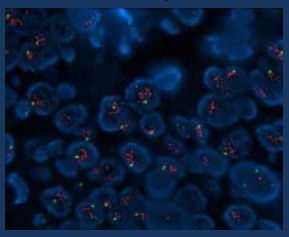


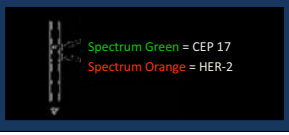
Standard HER-2 FISH patterns

HER-2 not amplified



HER-2 amplified





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.

EML4–ALK is a Potent "Oncogenic" Driver

Inhibition of ALK leads to dramatic *in vivo* tumor regression

EML4 = echinoderm microtubule-associated protein-like 4; NPM = nucleophosmin

Soda M et al. Nature 2007;448:561–567
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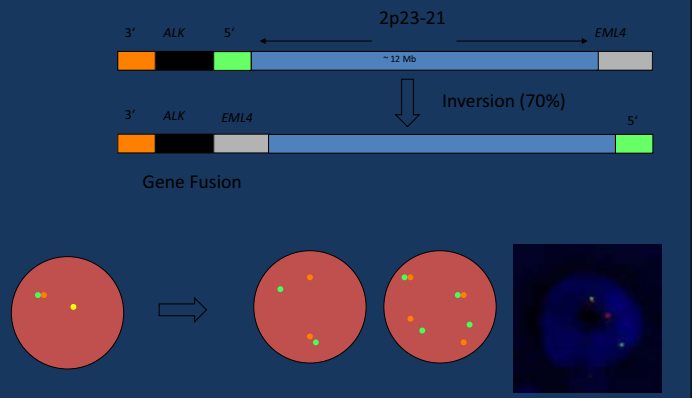
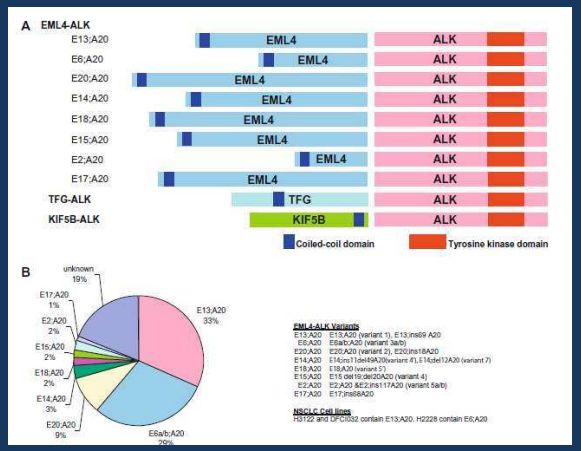
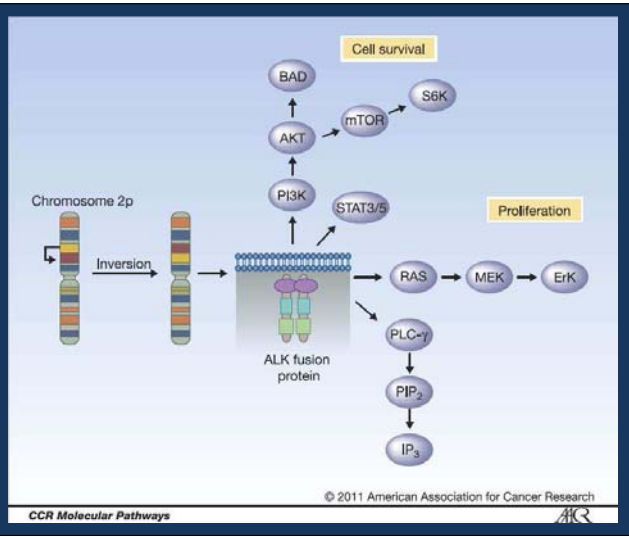
Fluorescence in situ Hybridization



Negative

Positive (break-apart - inversion)





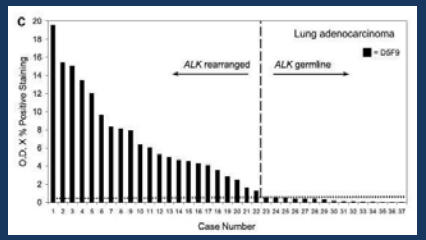
Imaging, Diagnosis, Prognosis

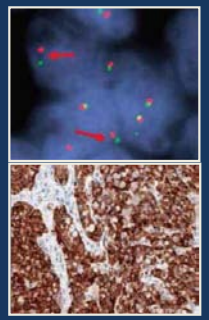
Clinical Cancer Research

March 2010

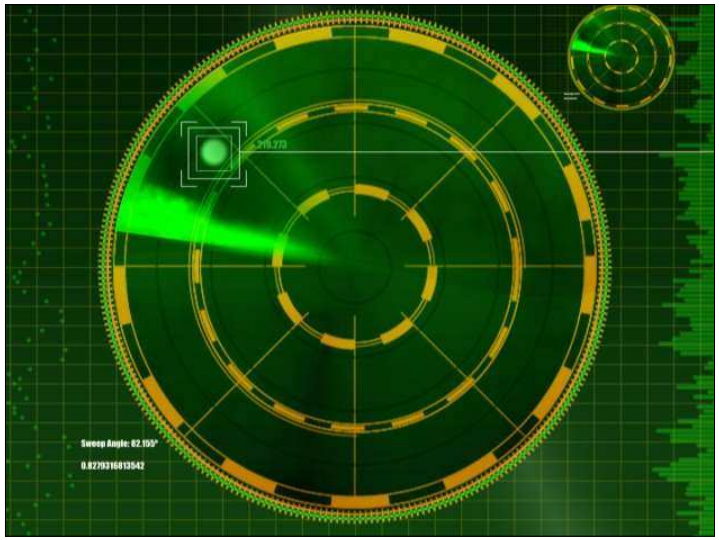
A Novel, Highly Sensitive Antibody Allows for the Routine Detection of *ALK*-Rearranged Lung Adenocarcinomas by Standard Immunohistochemistry

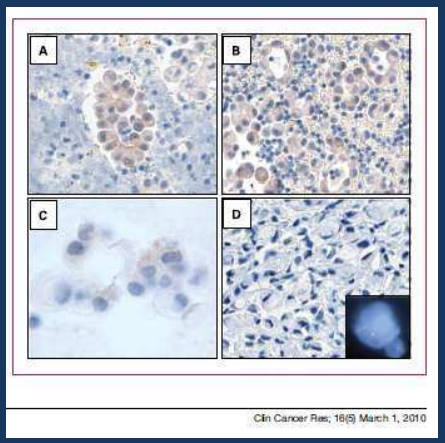
Mari Mino-Kenudson[1], Lucian R. Chirieac[2], Kenny Law[2], Jason L. Hornick[2], Neal Lindeman[2], Eugene J. Mark[1], David W. Cohen[3], Bruce E. Johnson[4], Pasi A. Jänne[4], A. John Iafrate[1], and Scott J. Rodig[2]



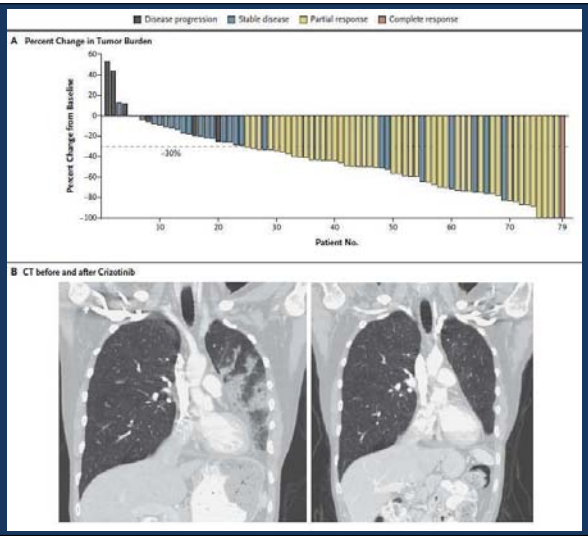


Novel ALK IHC with
....excellent sensitivity and specificity
....may obviate the need for FISH





Clin Cancer Res; 16(5) March 1, 2010



Pathway From Compound Identification to Discovery of ALK Target and Clinical Results

2005	2006	2007	2008	2009	2010
Lead Compound Identified	Clinical Testing Begins	Discovery of *EML4-ALK* Fusion Gene	First Clinical Responses Observed in *ALK+* Tumours	Phase 3 Lung Cancer Trial Initiated	ASCO plenary of expanded *ALK+* cohort[1]
					NEJM publication of *ALK+* cohort[2]

Rapid Timeline from Compound Identification, Target Discovery and Clinical Results

Clinical Results to Date

- Objective response rate = 61%[3]
- Median duration of response = 48 weeks[3]*
- Median PFS = 10 months[†3]

*in responding patients
†Fifty-four (47.8%) patients remain in follow-up for PFS

[1]Bang JY, et al. Presented at ASCO 2010.
[2]Kwak et al. *N Engl J Med.* 2010;363:1693–03.
[3]Camidge DR, et al. Presented at ASCO 2011; Abstract 2501.