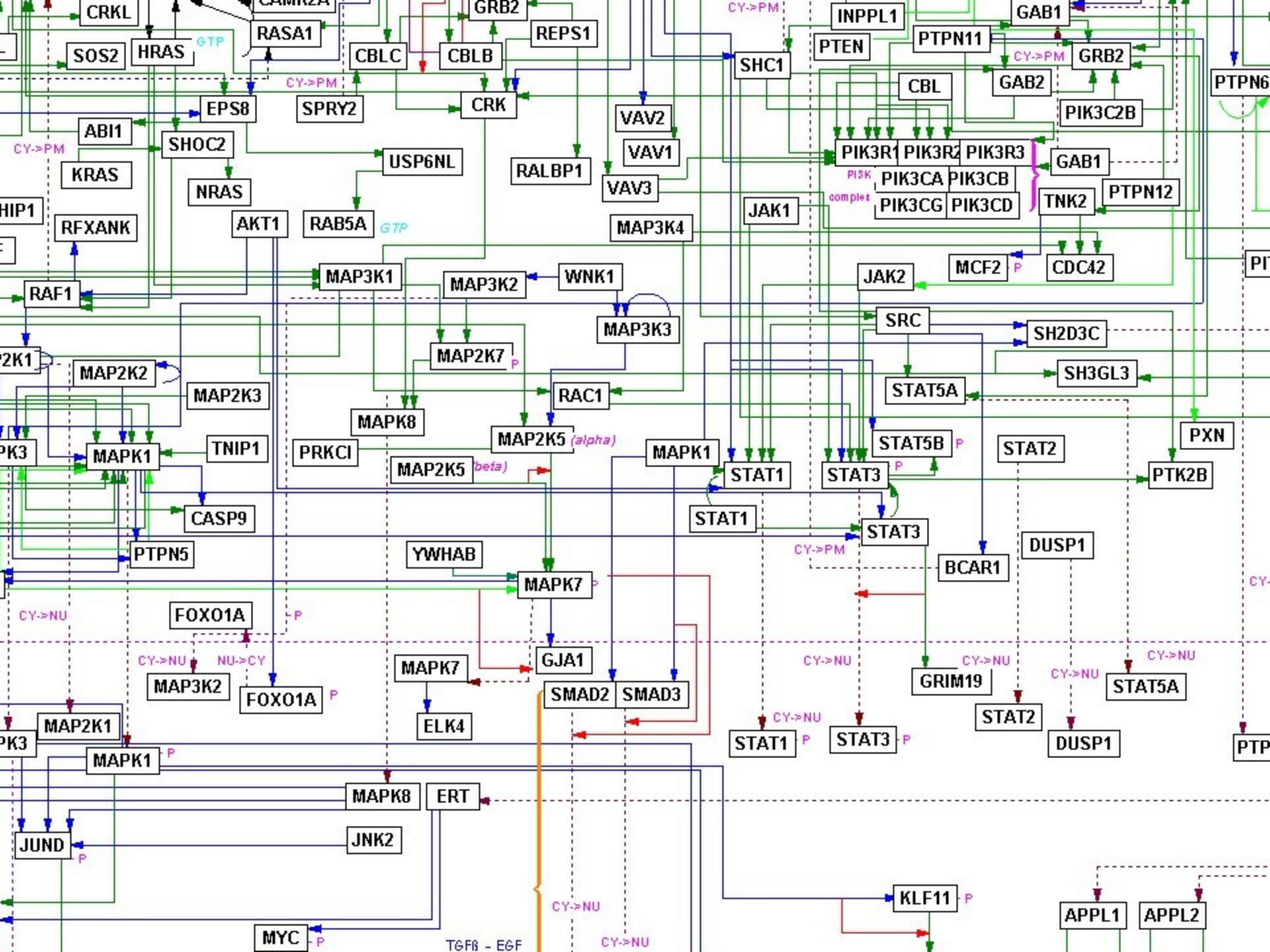
Molecular testing in NSCLC.

P.Pauwels (UZA/UZG)


CRKL
RASA1
SOS2
HRAS
GTP
CBLC
CBLB
GRB2
REPS1
CY->PM
SPRY2
CRK
EPS8
ABI1
SHOC2
KRAS
NRAS
USP6NL
RALBP1
RAB5A
GTP
AKT1
RFXANK
HIP1
RAF1
MAP3K1
MAP3K2
WNK1
MAP3K3
MAP2K7
P
MAP2K2
MAP2K3
RAC1
MAPK8
MAP2K5
(alpha)
PRKCI
MAP2K5
(beta)
TNIP1
MAPK1
CASP9
PTPN5
YWHAB
MAPK7
P
CY->NU
FOXO1A
P
CY->NU
NU->CY
MAP3K2
FOXO1A
P
MAPK7
GJA1
ELK4
SMAD2
SMAD3
MAP2K1
MAPK1
P
MAPK8
ERT
JUND
P
JNK2
MYC
P
TGFß - EGF
CY->NU
CY->NU
KLF11
P
SHC1
VAV2
VAV1
VAV3
JAK1
MAP3K4
MAPK1
STAT1
STAT1
STAT3
CY->PM
INPPL1
PTEN
GAB1
PTPN11
CY->PM
GRB2
CBL
GAB2
PIK3C2B
PIK3R1
PIK3R2
PIK3R3
GAB1
PI3K
complex
PIK3CA
PIK3CB
PIK3CG
PIK3CD
TNK2
PTPN12
MCF2
P
CDC42
JAK2
SRC
SH2D3C
SH3GL3
STAT5A
STAT5B
P
STAT2
PXN
PTK2B
STAT3
P
BCAR1
DUSP1
CY->PM
CY->NU
GRIM19
CY->NU
STAT2
CY->NU
DUSP1
CY->NU
STAT5A
CY->NU
STAT1
P
STAT3
P
APPL1
APPL2
PTPN6

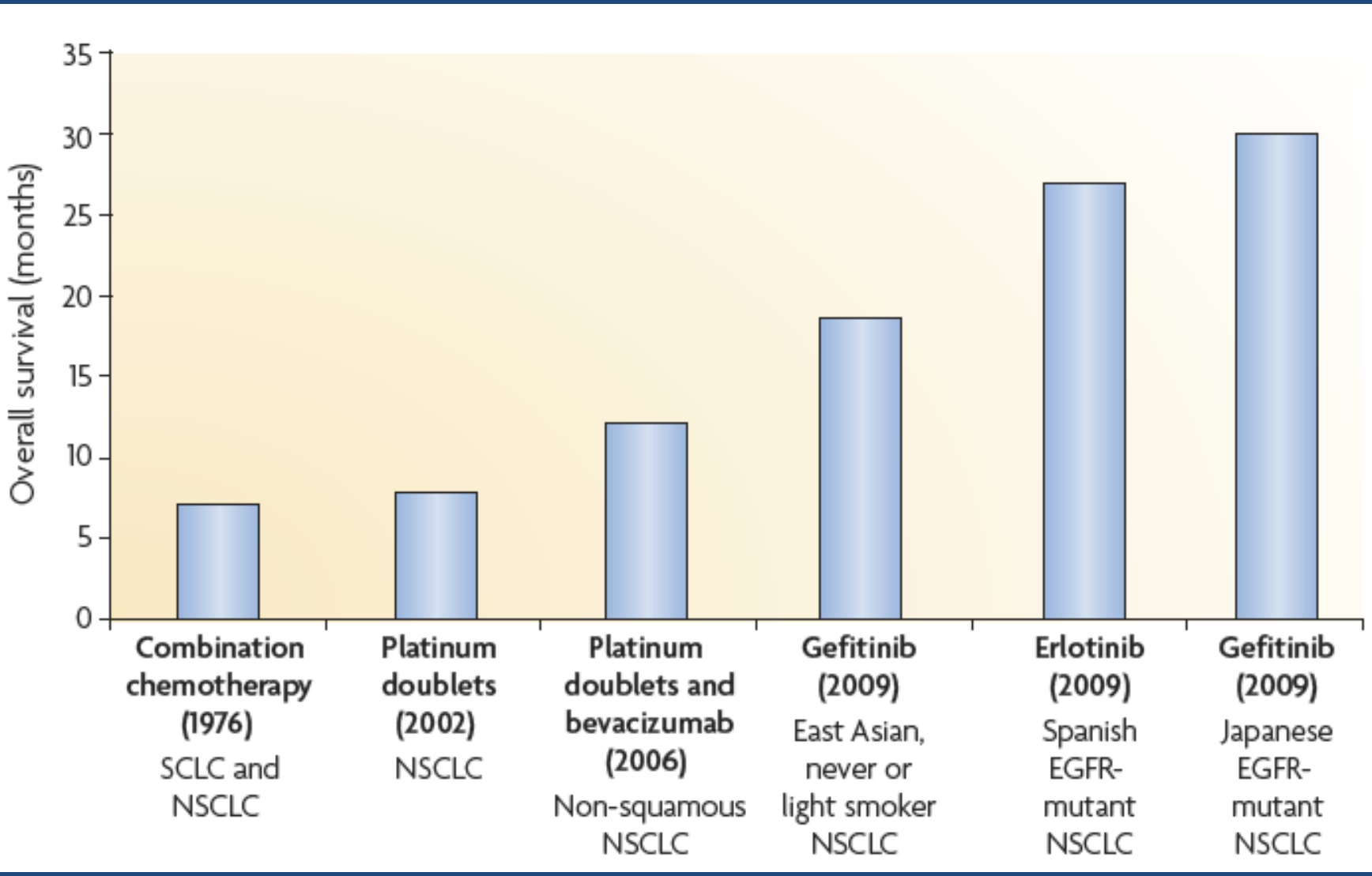
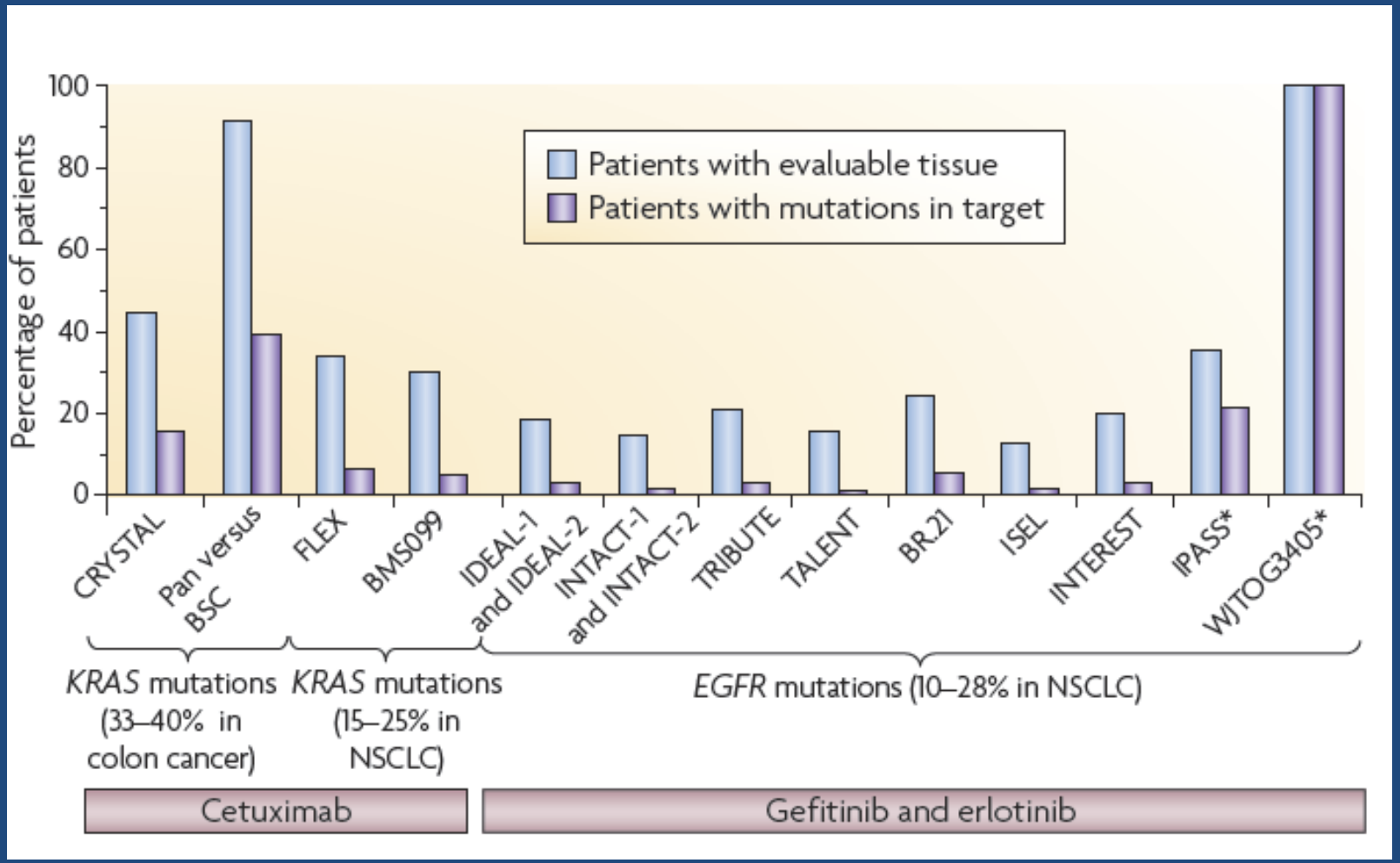
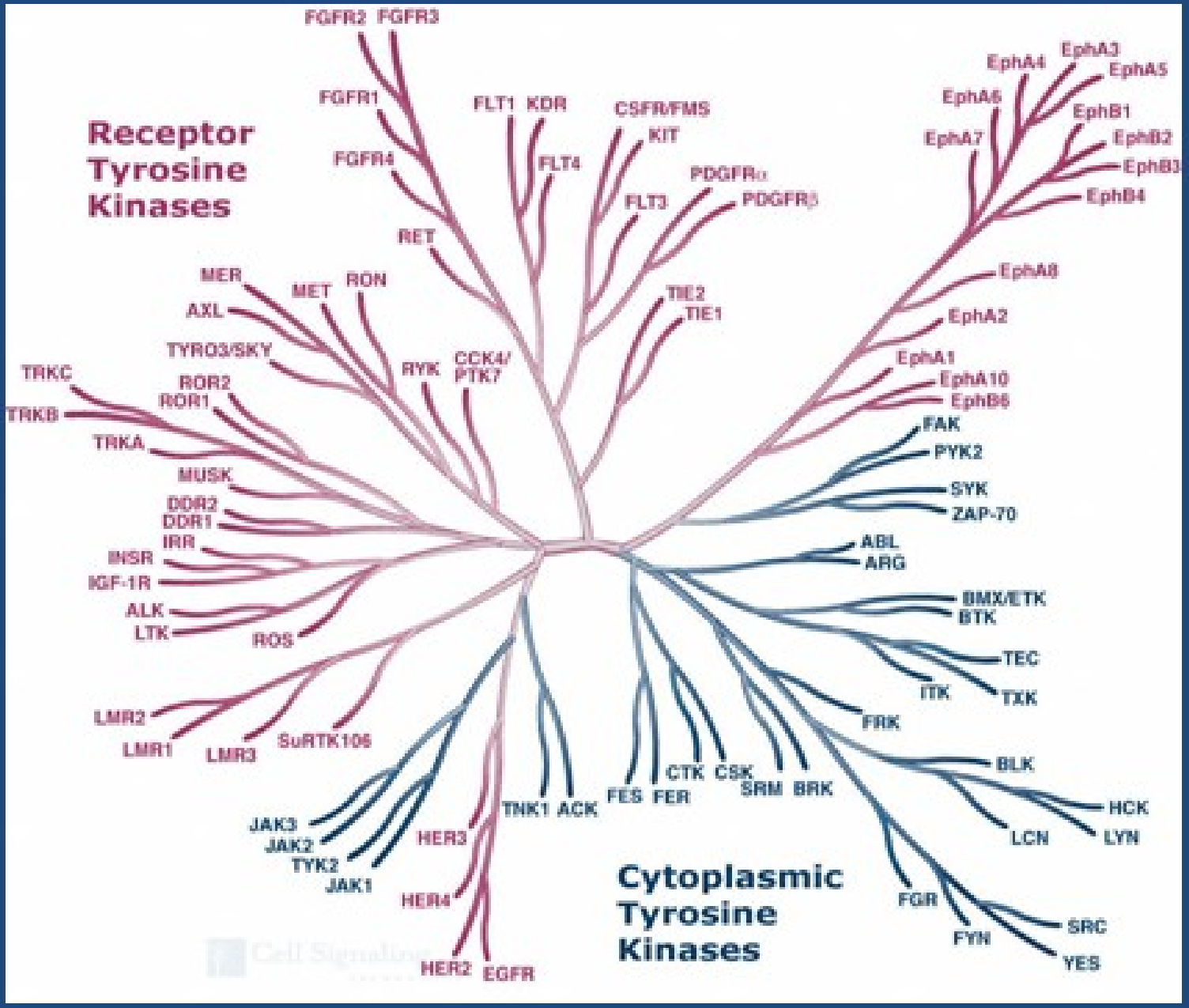
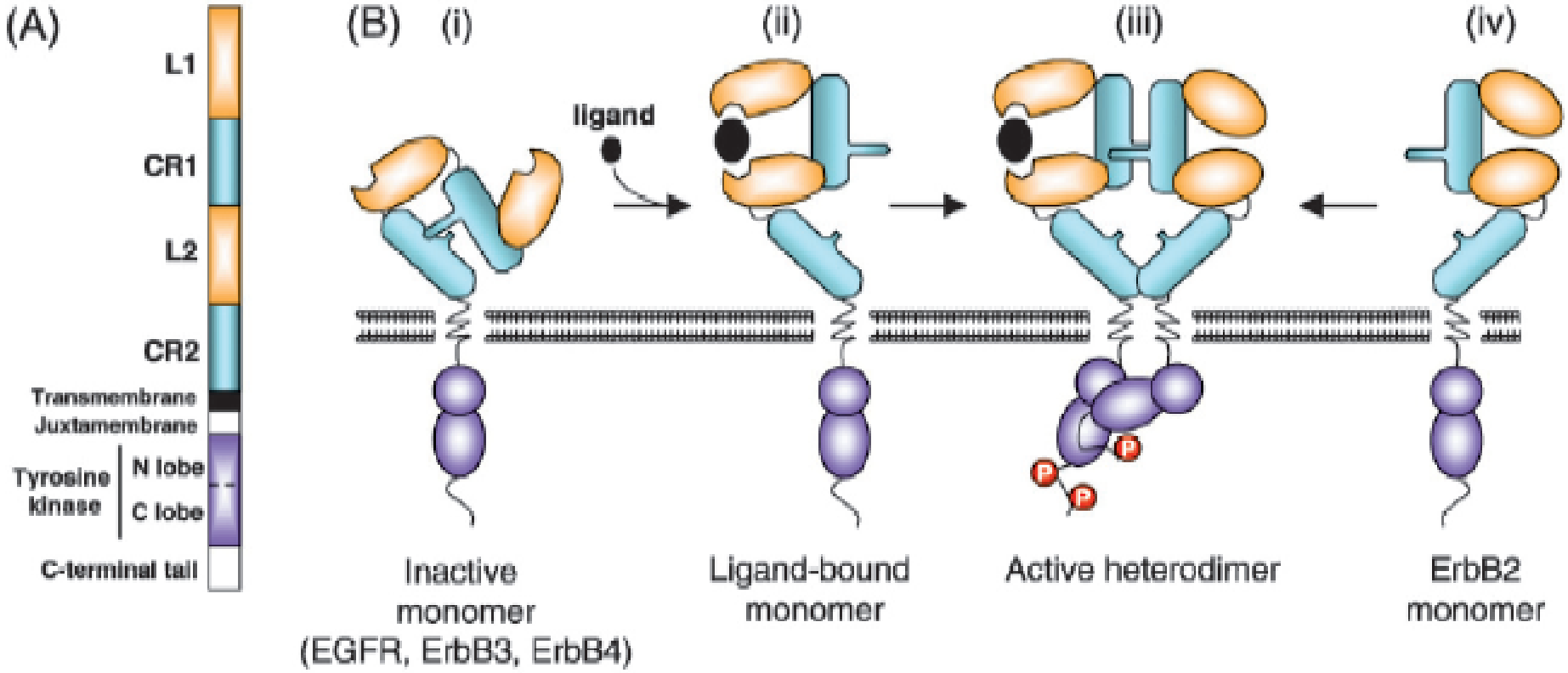

Overall survival (months)
35
30
25
20
15
10
5
0
Combination chemotherapy (1976)
SCLC and NSCLC
Platinum doublets (2002)
NSCLC
Platinum doublets and bevacizumab (2006)
Non-squamous NSCLC
Gefitinib (2009)
East Asian, never or light smoker NSCLC
Erlotinib (2009)
Spanish EGFR-mutant NSCLC
Gefitinib (2009)
Japanese EGFR-mutant NSCLC

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

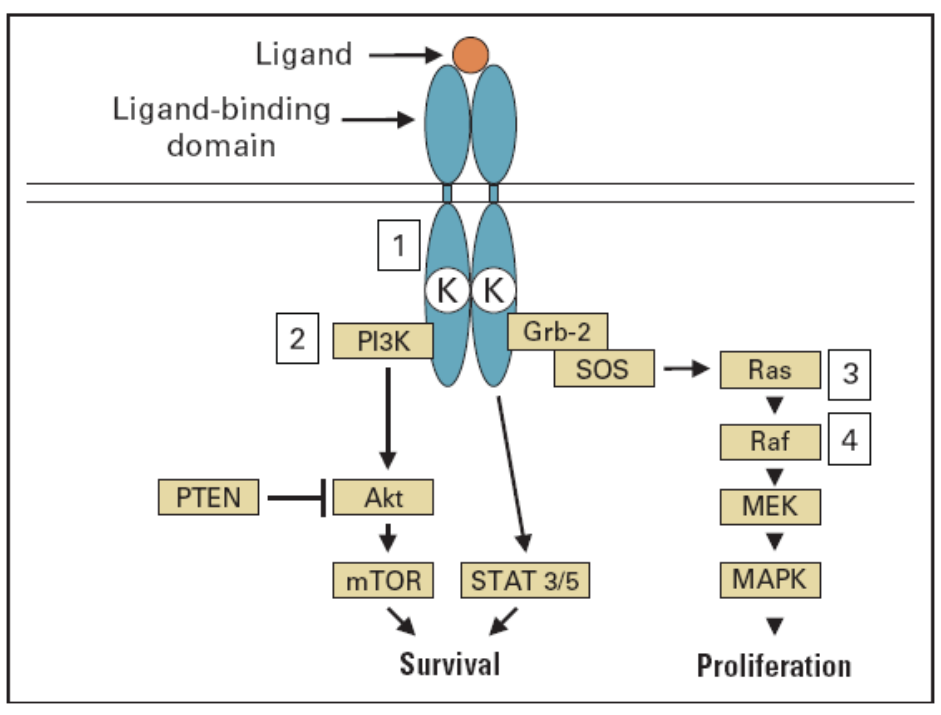
Trial	Type	Drugs	Enrollment criteria	RR (%) (EGFR TKI versus other)	Median time to treatment failure (months) (EGFR TKI versus other therapy)	Ref
Gefitinib						
IDEAL-1, IDEAL-2	Phase II	Gefitinib (250 mg versus 500 mg)	Unselected previously treated NSCLC	18.4–19.0 (IDEAL-1) and 9–12 (IDEAL-2)	2.7–2.8 (IDEAL-1) and 1.5–1.7 (IDEAL-2)	11 1
ISEL	Phase III	Gefitinib versus placebo	Unselected previously treated NSCLC	8.0 versus 1.3	3.0 versus 2.6	1
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)	168 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‡	2
WJTOG3405	Phase III	Gefitinib versus chemotherapy	Japanese *EGFR*-mutant chemotherapy-naive NSCLC	62.1 versus 32.2	9.2 versus 6.3	2
NEJ002	Phase III	Gefitinib versus chemotherapy	Japanese *EGFR*-mutant chemotherapy-naive NSCLC	73.7 versus 30.7	10.8 versus 5.4	2
Erlotinib						
NA	Phase II	Erlotinib	NSCLC with BAC features	22	4	1
BR.21	Phase III	Erlotinib versus placebo	Unselected previously treated NSCLC	8.9 versus <1	2.2 versus 1.8	1
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	17
SLCG	Single arm	Erlotinib	Spanish *EGFR*-mutant NSCLC	70.6	14	2
Cetuximab						


Percentage of patients
100
80
60
40
20
0
Patients with evaluable tissue
Patients with mutations in target
CRYSTAL
Pan versus BSC
FLEX
BMS099
IDEAL-1 and IDEAL-2
INTACT-1 and INTACT-2
TRIBUTE
TALENT
BR.21
ISEL
INTEREST
IPASS*
WJTOG3405*
KRAS mutations (33–40% in colon cancer)
KRAS mutations (15–25% in NSCLC)
EGFR mutations (10–28% in NSCLC)
Cetuximab
Gefitinib and erlotinib


Receptor Tyrosine Kinases
FGFR2
FGFR3
FGFR1
FGFR4
FLT1
KDR
FLT4
CSFR/FMS
KIT
FLT3
PDGFRα
PDGFRβ
RET
MER
MET
RON
AXL
TYRO3/SKY
RYK
CCK4/ PTK7
TIE2
TIE1
TRKC
TRKB
TRKA
ROR2
ROR1
MUSK
DDR2
DDR1
IRR
INSR
IGF-1R
ALK
LTK
ROS
LMR2
LMR1
LMR3
SuRTK106
EphA4
EphA3
EphA5
EphA6
EphB1
EphA7
EphB2
EphB3
EphB4
EphA8
EphA2
EphA1
EphA10
EphB6
FAK
PYK2
SYK
ZAP-70
ABL
ARG
BMX/ETK
BTK
TEC
ITK
TXK
FRK
BLK
HCK
LCN
LYN
FGR
FYN
SRC
YES
JAK3
JAK2
TYK2
JAK1
HER3
HER4
HER2
EGFR
TNK1
ACK
FES
FER
CTK
CSK
SRM
BRK
Cytoplasmic Tyrosine Kinases

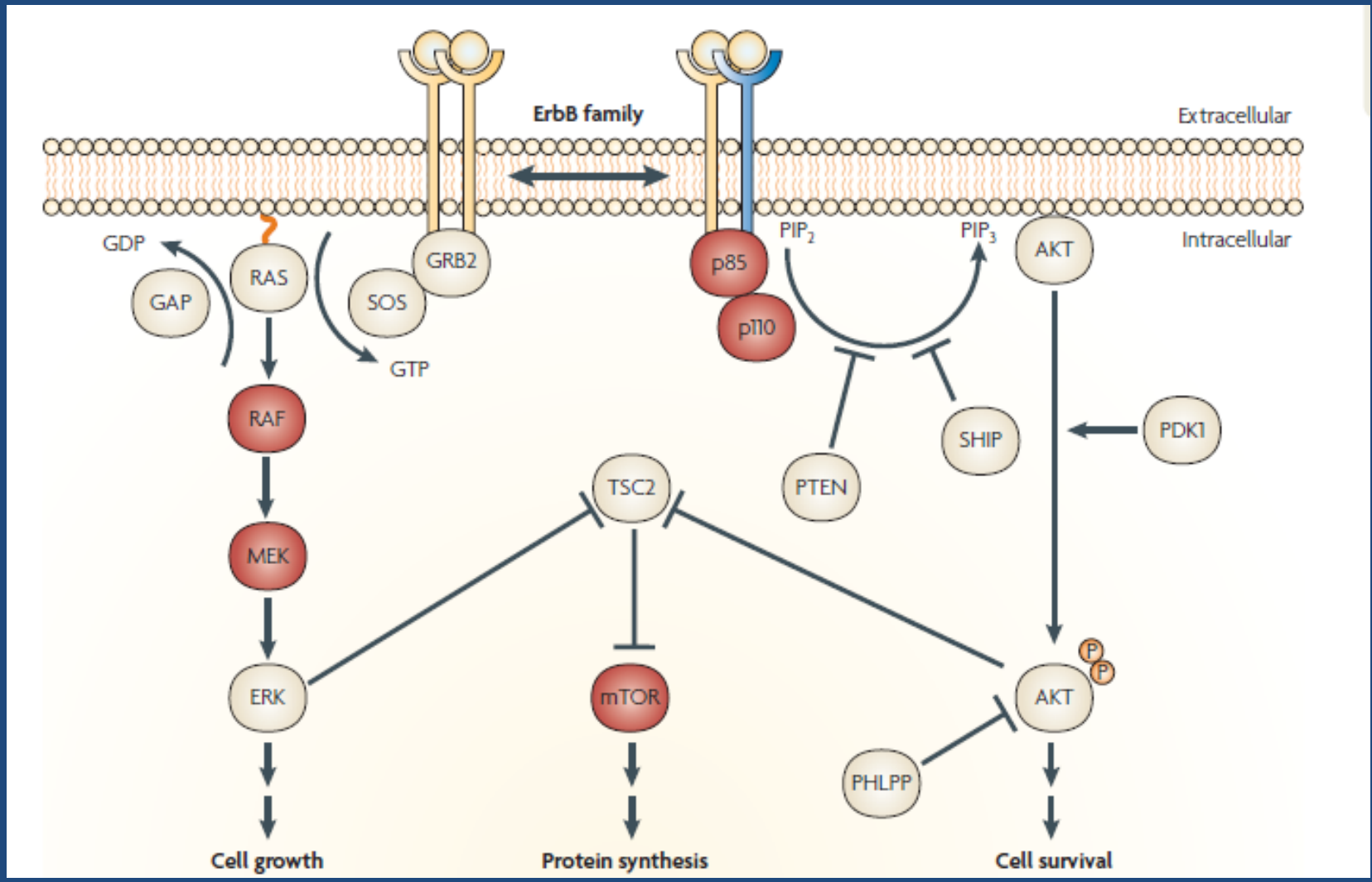

(A)
L1
CR1
L2
CR2
Transmembrane
Juxtamembrane
Tyrosine kinase
N lobe
C lobe
C-terminal tail
(B)
(i)
(ii)
(iii)
(iv)
ligand
P
Inactive monomer (EGFR, ErbB3, ErbB4)
Ligand-bound monomer
Active heterodimer
ErbB2 monomer

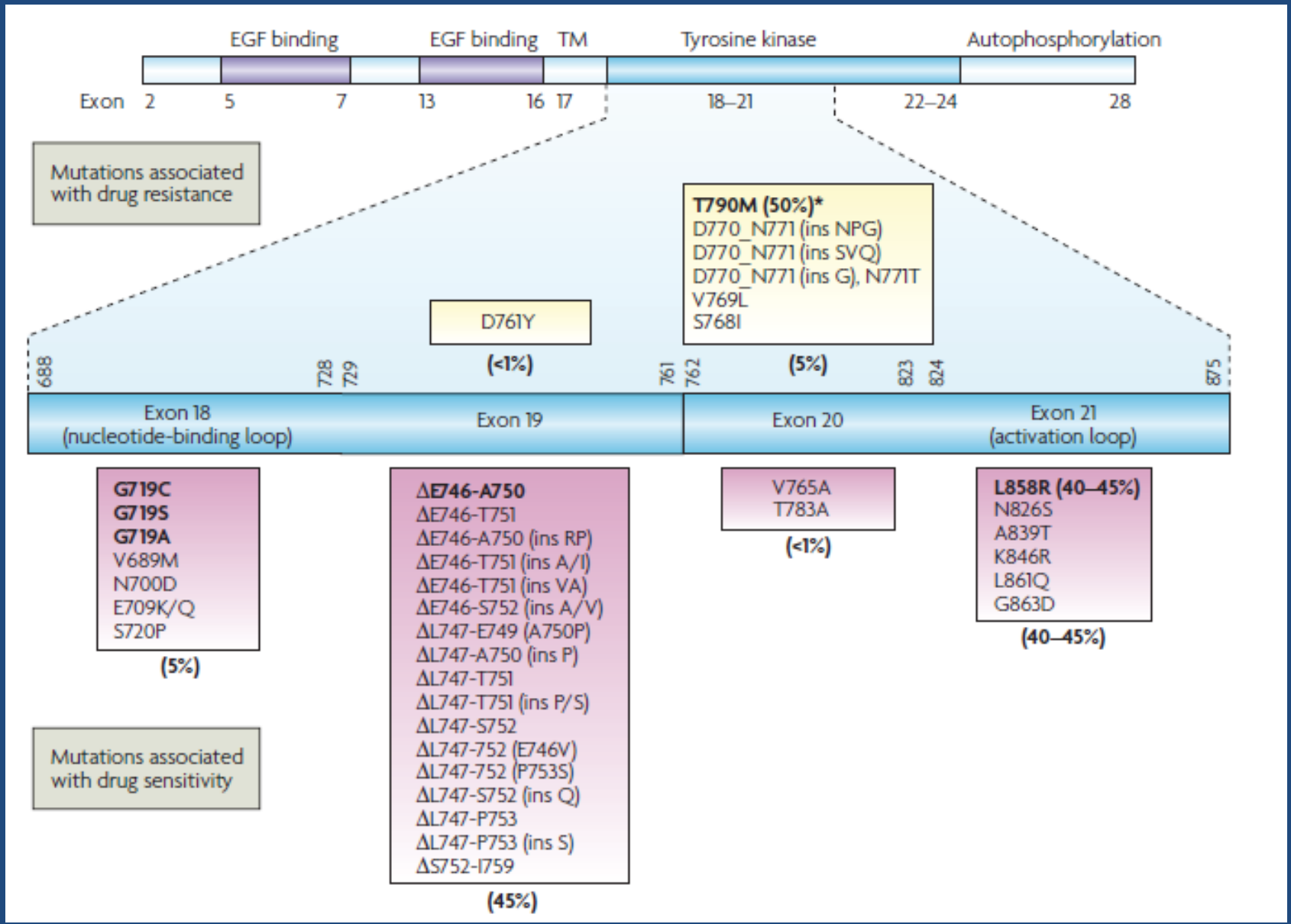
EGFR



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


ErbB family
Extracellular
Intracellular
GDP
GAP
RAS
GRB2
SOS
GTP
p85
p110
PIP2
PIP3
AKT
RAF
MEK
ERK
TSC2
mTOR
PTEN
SHIP
PDK1
PHLPP
P
P
Cell growth
Protein synthesis
Cell survival


EGF binding
EGF binding
TM
Tyrosine kinase
Autophosphorylation
Exon 2 5 7 13 16 17 18–21 22–24 28
Mutations associated with drug resistance
T790M (50%)*
D770_N771 (ins NPG)
D770_N771 (ins SVQ)
D770_N771 (ins G), N771T
V769L
S768I
(5%)
D761Y
(<1%)
688 728 729 761 762 823 824 875
Exon 18 (nucleotide-binding loop)
Exon 19
Exon 20
Exon 21 (activation loop)
G719C
G719S
G719A
V689M
N700D
E709K/Q
S720P
(5%)
ΔE746-A750
ΔE746-T751
ΔE746-A750 (ins RP)
ΔE746-T751 (ins A/I)
ΔE746-T751 (ins VA)
ΔE746-S752 (ins A/V)
ΔL747-E749 (A750P)
ΔL747-A750 (ins P)
ΔL747-T751
ΔL747-T751 (ins P/S)
ΔL747-S752
ΔL747-752 (E746V)
ΔL747-752 (P753S)
ΔL747-S752 (ins Q)
ΔL747-P753
ΔL747-P753 (ins S)
ΔS752-I759
(45%)
V765A
T783A
(<1%)
L858R (40–45%)
N826S
A839T
K846R
L861Q
G863D
(40–45%)
Mutations associated with drug sensitivity

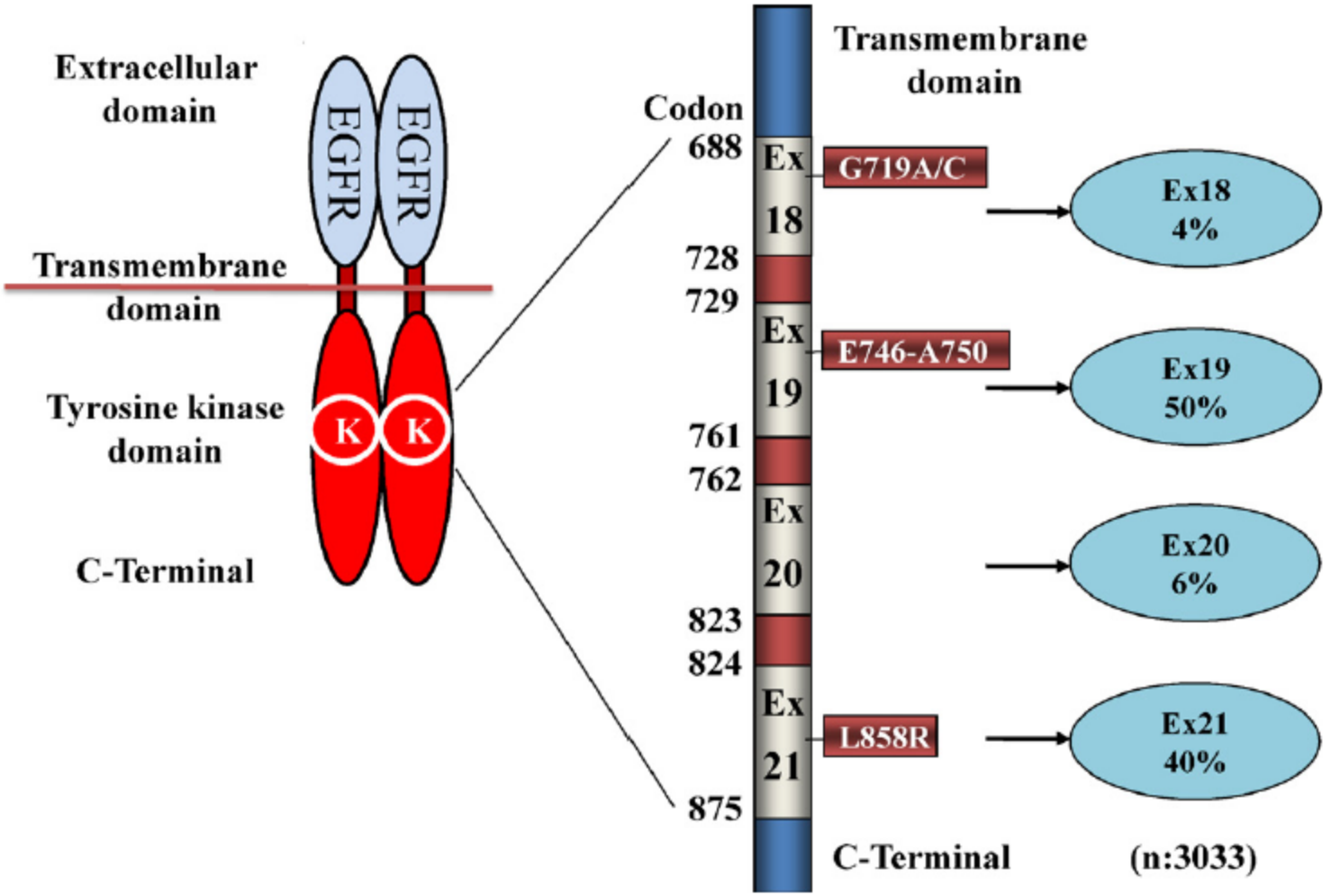
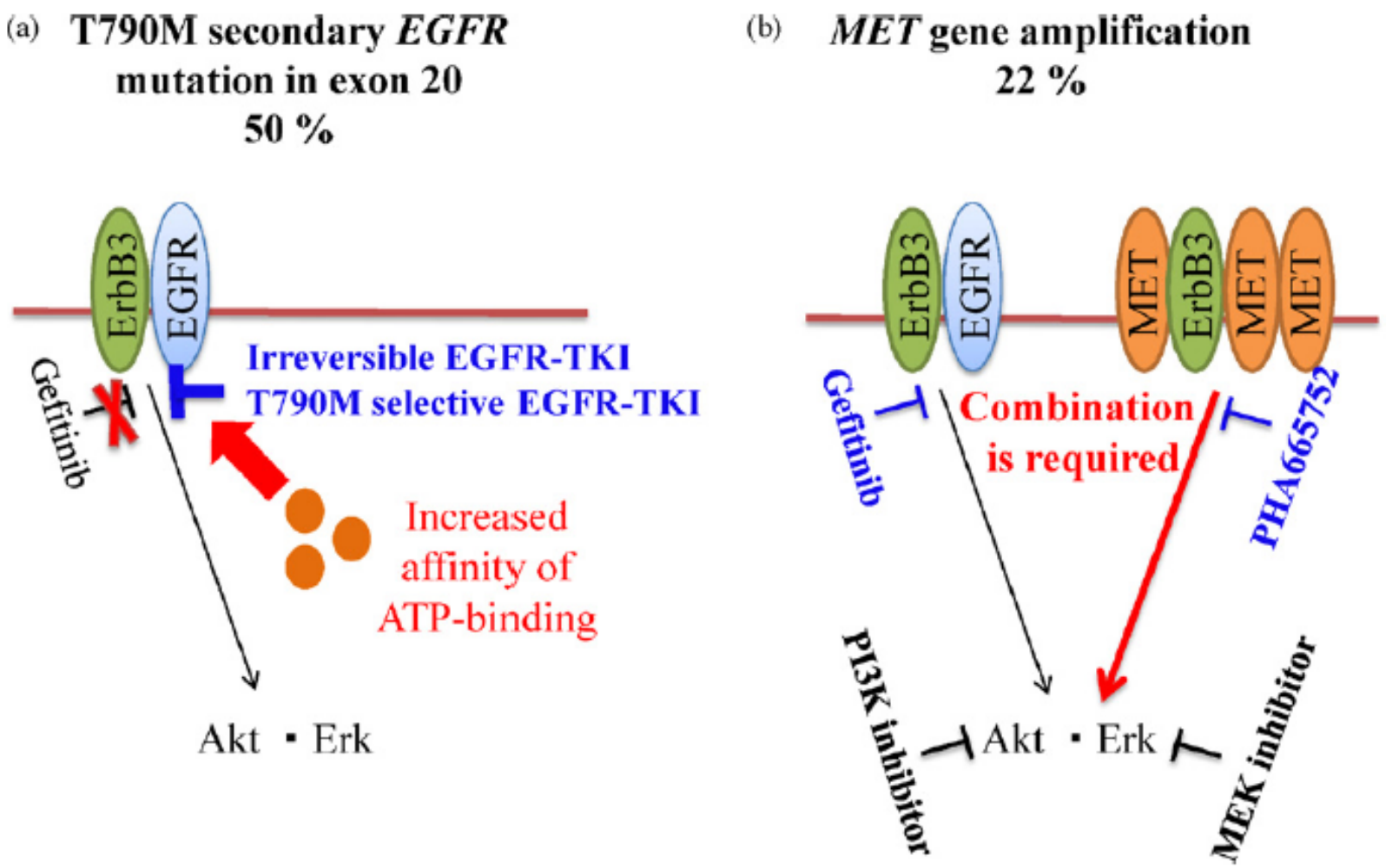


Fig. 3. Frequency of *EGFR* mutation in NSCLC ($n = 3033$) [54].

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*


(a) T790M secondary *EGFR* mutation in exon 20 50 %
ErbB3
EGFR
Gefitinib
Irreversible EGFR-TKI
T790M selective EGFR-TKI
Increased affinity of ATP-binding
Akt ▪ Erk
(b) *MET* gene amplification 22 %
ErbB3
EGFR
MET
ErbB3
MET
MET
Gefitinib
Combination is required
PHA665752
PI3K inhibitor
Akt ▪ Erk
MEK inhibitor

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[3], JG Christensen[6], DJ Kwiatkowski[7], JA Engelman[4] and PA Jänne[1,2,8]

[1]Lowe Center for Thoracic Oncology, Dana–Farber Cancer Institute, Boston, MA, USA; [2]Department of Medical Oncology, Dana–Farber Cancer Institute, Boston, MA, USA; [3]Department of Pathology, Brigham and Women's Hospital, Boston, MA, USA; [4]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [5]Harvard Partners Center for Genetics and Genomics, Harvard Medical School, Cambridge, MA, USA; [6]Pfizer Global Research and Development, Department of Research Pharmacology, La Jolla Labs, La Jolla, CA, USA; [7]Division of Translational Medicine, Brigham and Women's Hospital, Boston, MA, USA and [8]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

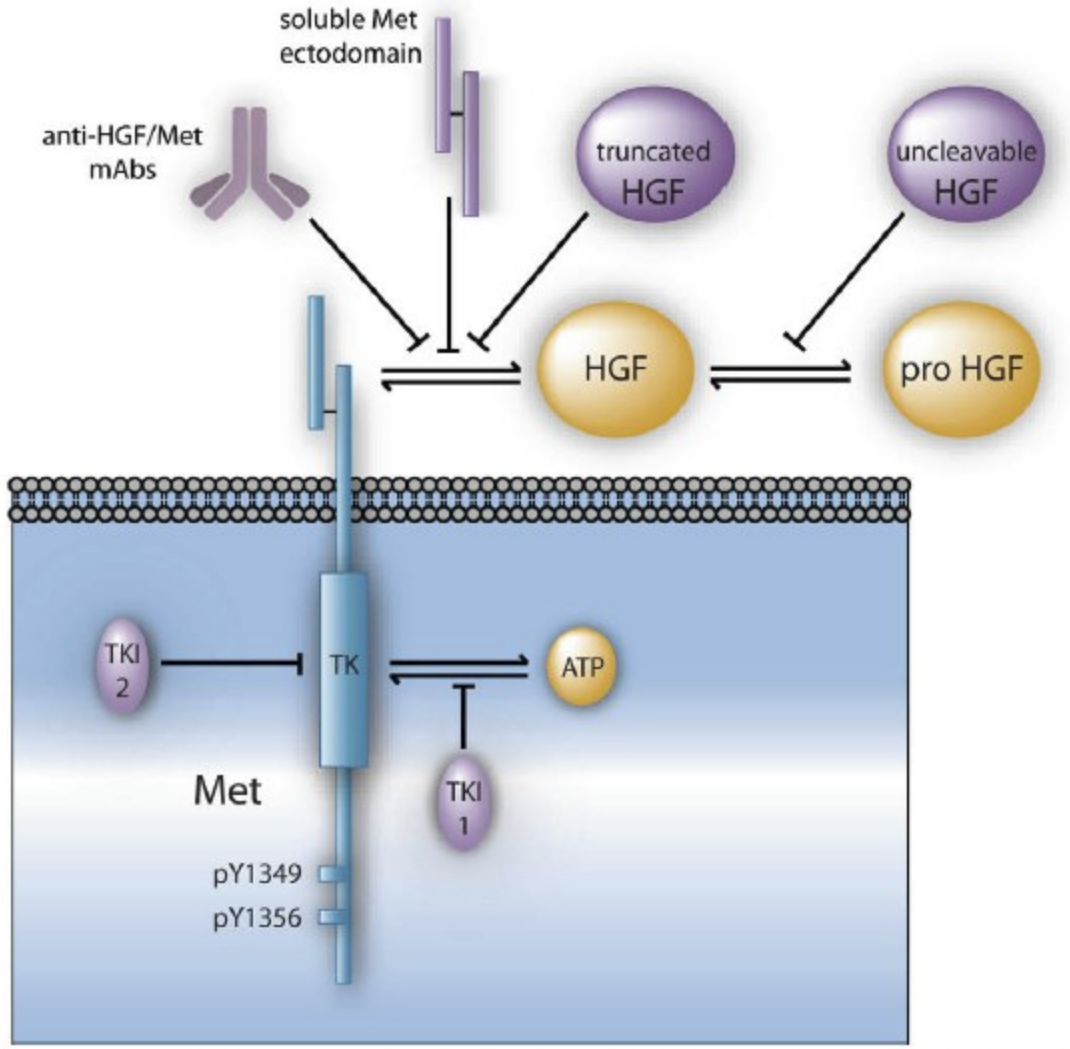


Fig. 1 – Agents currently under development as HGF/Met pathway inhibitors can be broadly subdivided into biologicals and low molecular weight synthetic compounds.

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,*]

[1]Massachusetts General Hospital Cancer Center, Boston, MA 02129, USA
[2]Department of Medicine, Harvard Medical School, Boston, MA 02115, USA
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[4]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02115, USA
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[10]These authors contributed equally to this work
[11]These laboratories contributed equally to this work
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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.

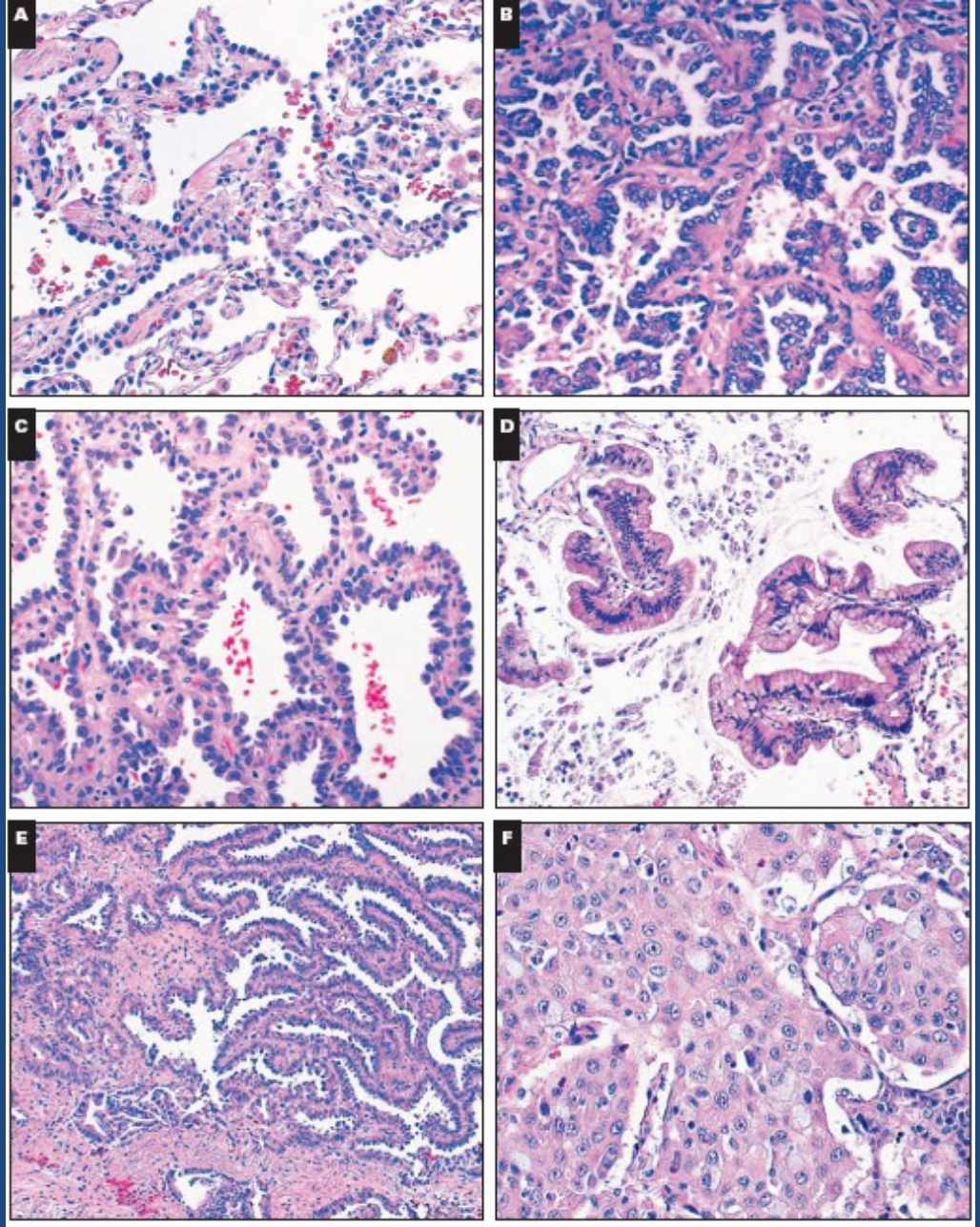

Image 1 Histopathologic examples of atypical adenomatous hyperplasia (**A**, H&E, ×230), papillary-type adenocarcinoma (**B**, H&E, ×200), nonmucinous-type bronchioloalveolar carcinoma (BAC; **C**, H&E, ×200), mucinous-type BAC (**D**, H&E, ×200), mixed acinar/conventional adenocarcinoma with nonmucinous-type BAC (**E**, H&E, ×100), and adenocarcinoma, solid with mucus type (**F**, H&E, ×200).

DOI: 10.1309/AJCPH0TRMPXVZW2F

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

Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA 15232, USA

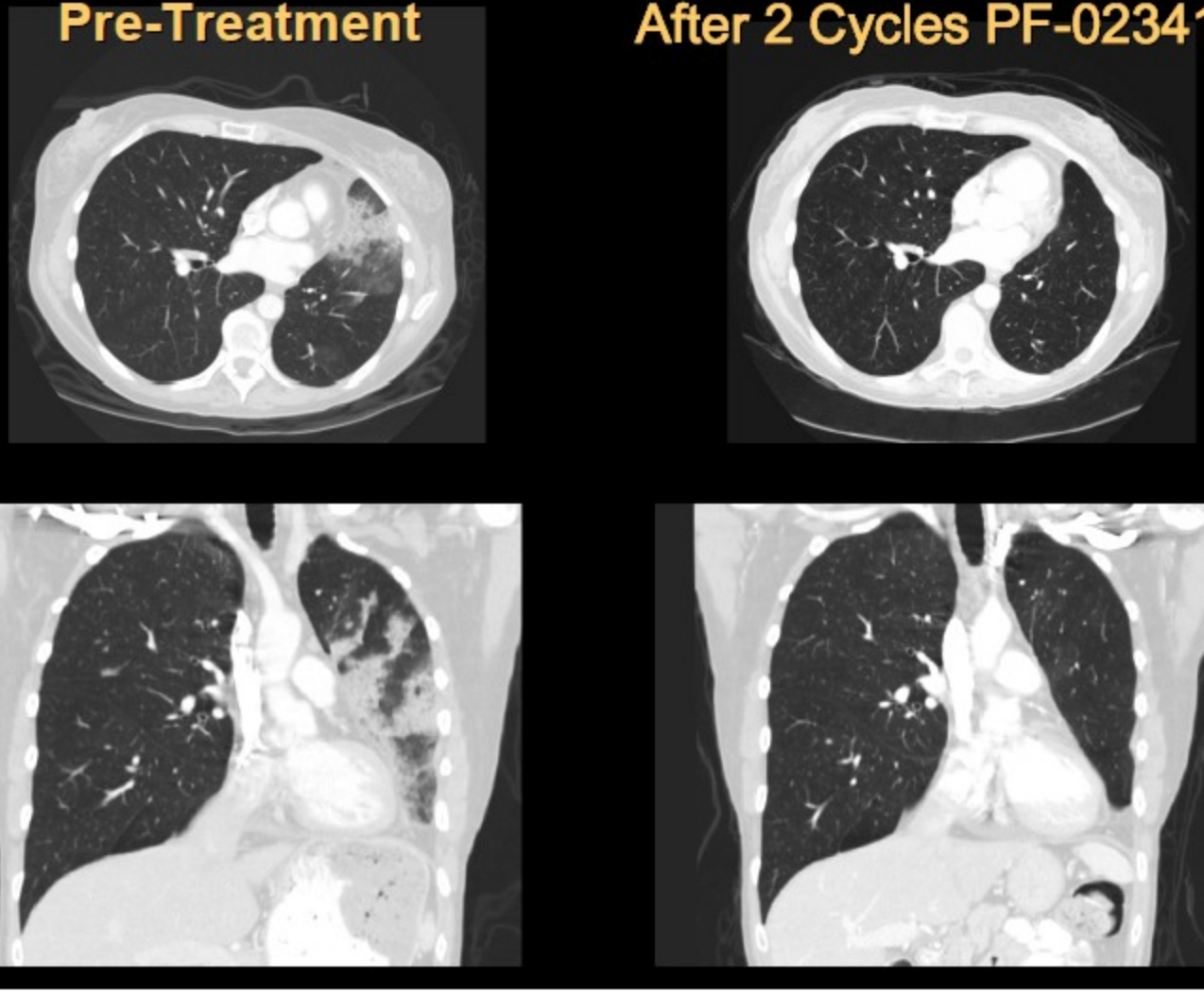
Received 13 May 2009; revised 29 June 2009; accepted 30 June 2009

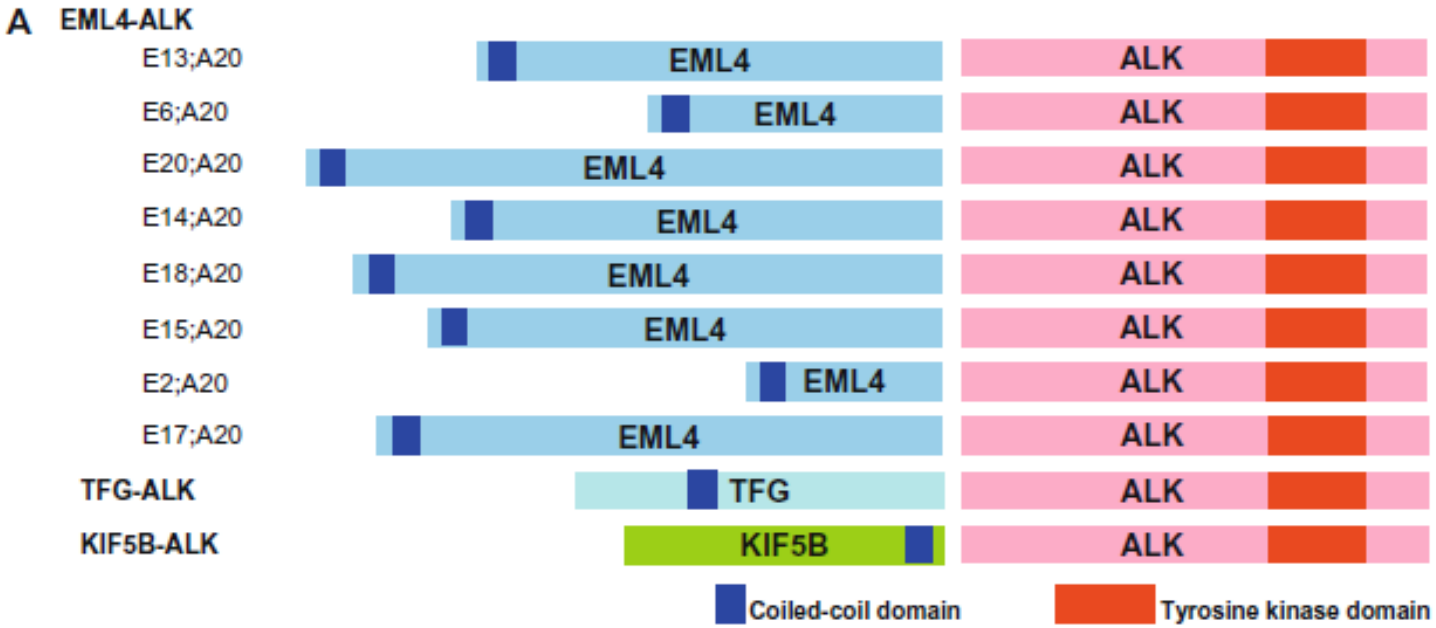
Clinical Activity Observed in a Phase 1 Dose-Escalation Trial of an Oral MET and ALK Inhibitor, PF-02341066

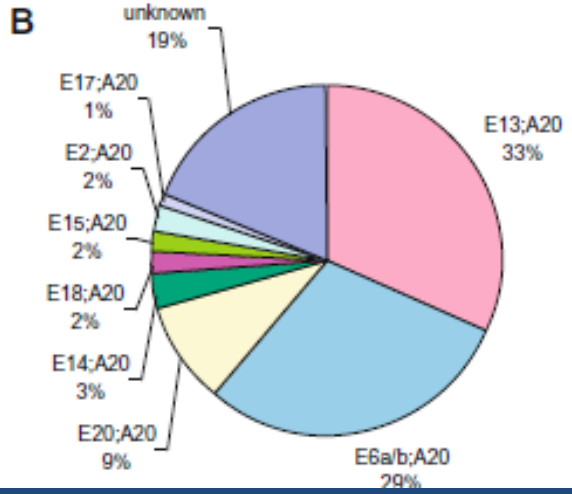
EL Kwak[1], DR Camidge[2], J Clark[1], GI Shapiro[3], RG Maki[4], MJ Ratain[5], B Solomon[6], Y-J Bang[7], S-H Ou[8], R Salgia[5]

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







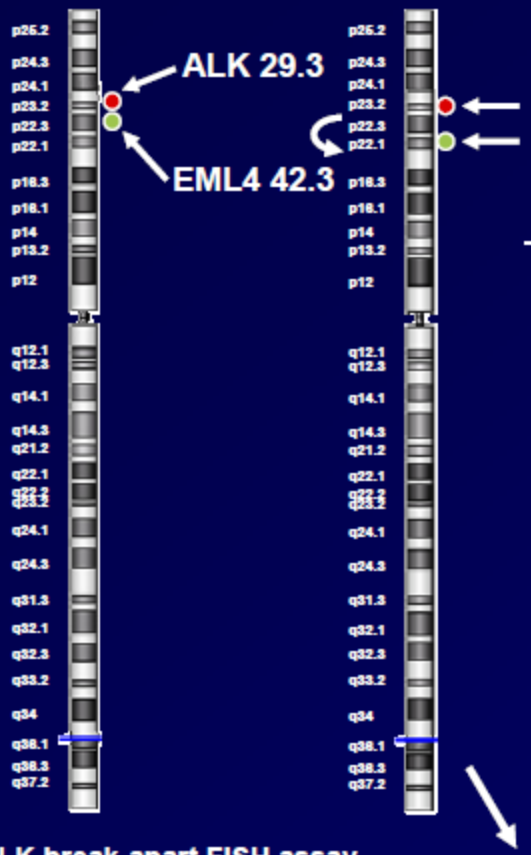
EML4-ALK Variants

E13;A20	E13;A20 (variant 1), E13;ins69 A20
E6;A20	E6a/b;A20 (variant 3a/b)
E20;A20	E20;A20 (variant 2), E20;ins18A20
E14;A20	E14;ins11del49A20(variant 4'), E14;del12A20 (variant 7)
E18;A20	E18;A20 (variant 5')
E15;A20	E15 del19;del20A20 (variant 4)
E2;A20	E2;A20 &E2;ins117A20 (variant 5a/b)
E17;A20	E17;ins68A20

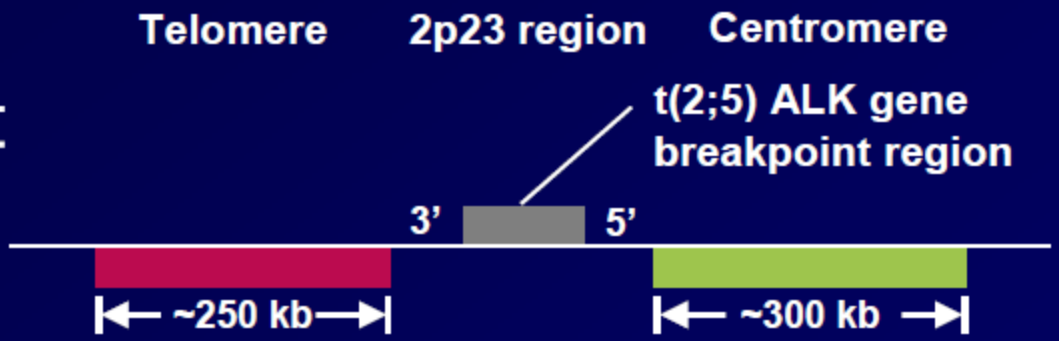
NSCLC Cell lines

H3122 and DFCI032 contain E13;A20. H2228 contain E6;A20

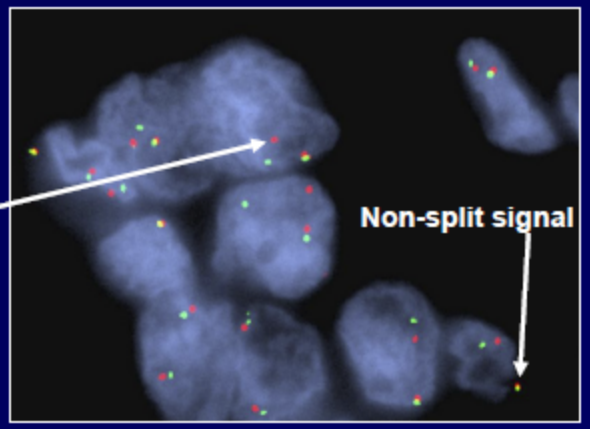
FISH Assay for *ALK* Rearrangement*



ALK break-apart FISH assay
[Courtesy John Iafrate, Massachusetts General Hospital]



Break-apart FISH assay for *ALK*-fusion genes[1]



*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

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

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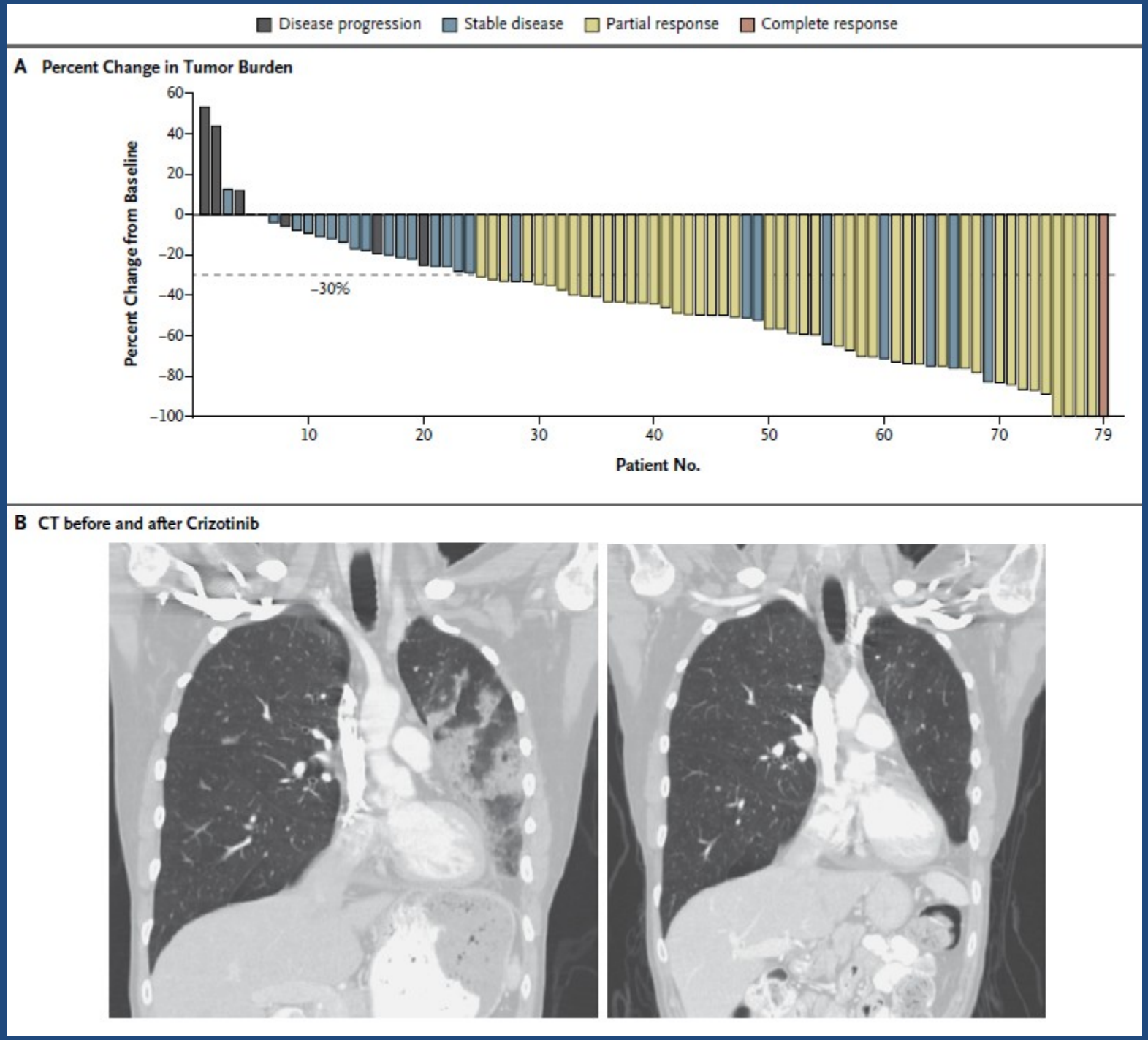

Disease progression
Stable disease
Partial response
Complete response
A Percent Change in Tumor Burden
Percent Change from Baseline
60
40
20
0
−20
−40
−60
−80
−100
−30%
10
20
30
40
50
60
70
79
Patient No.
B CT before and after Crizotinib

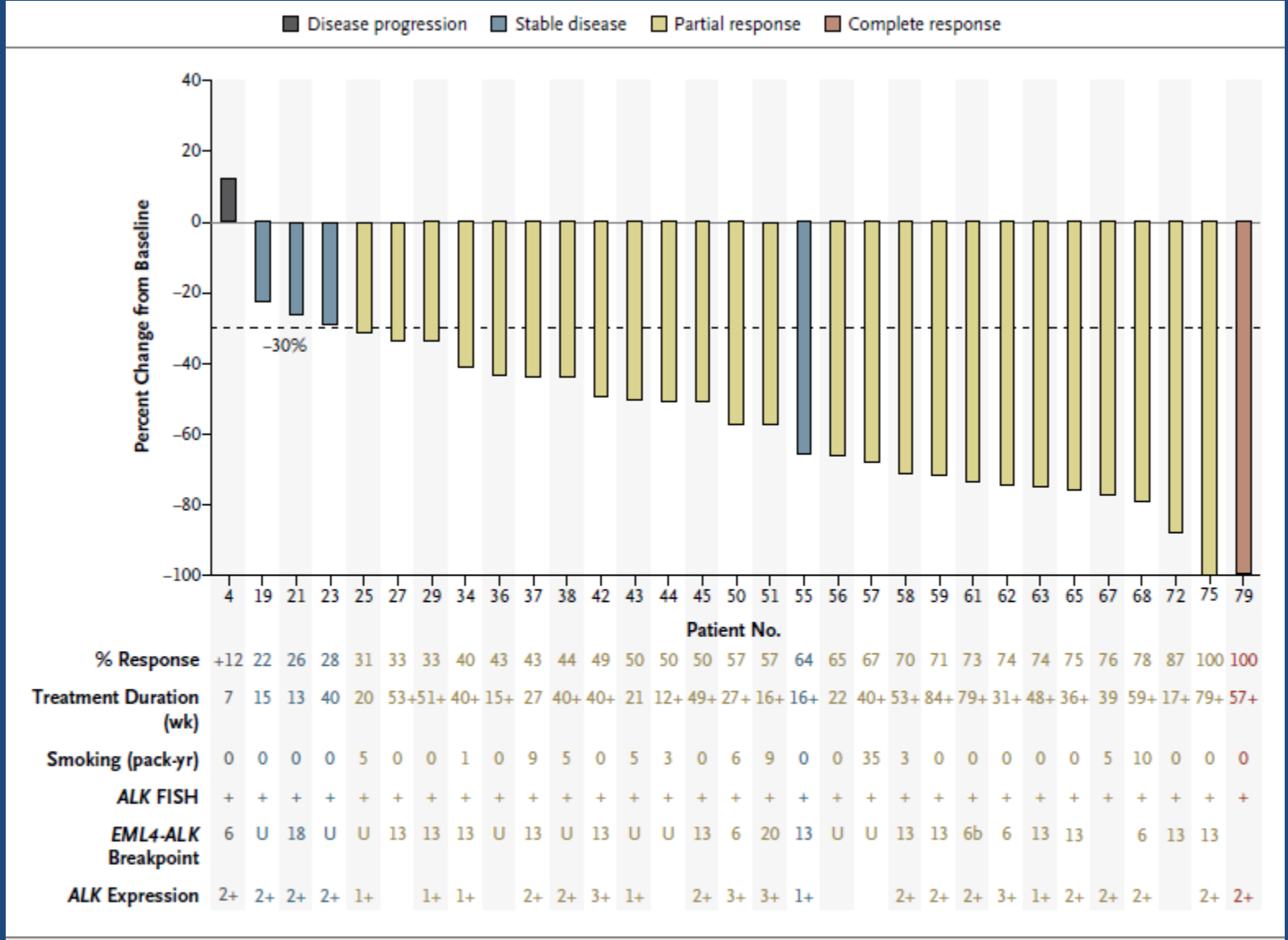


Figure 3. Best Response to Crizotinib in 31 Patients with *ALK*-Positive Tumors, as Correlated with Clinicopathological Characteristics.

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.

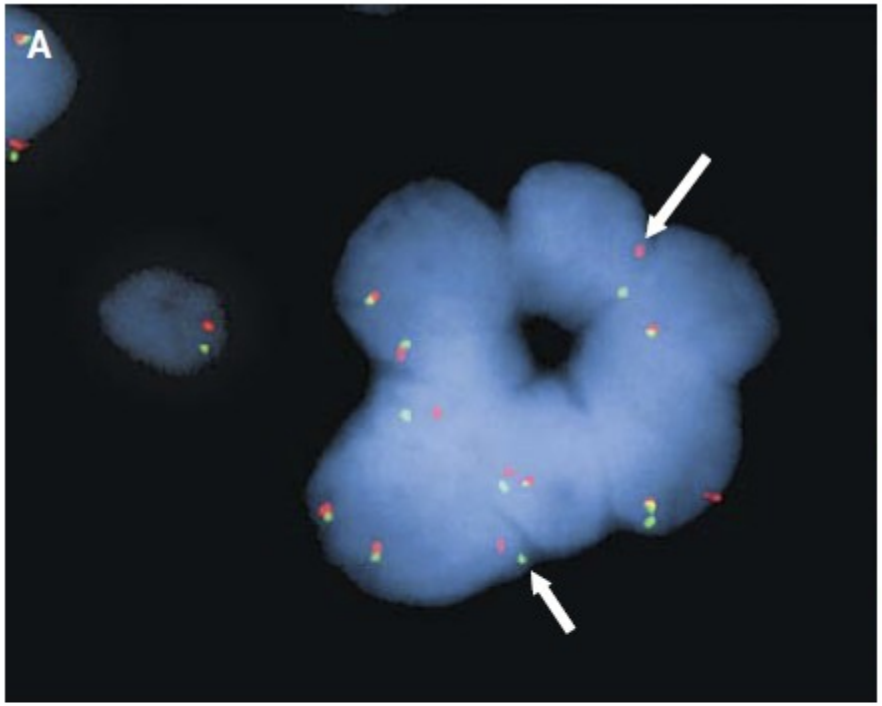
Table 1. Demographic and Clinicopathological Characteristics of the 82 Patients.

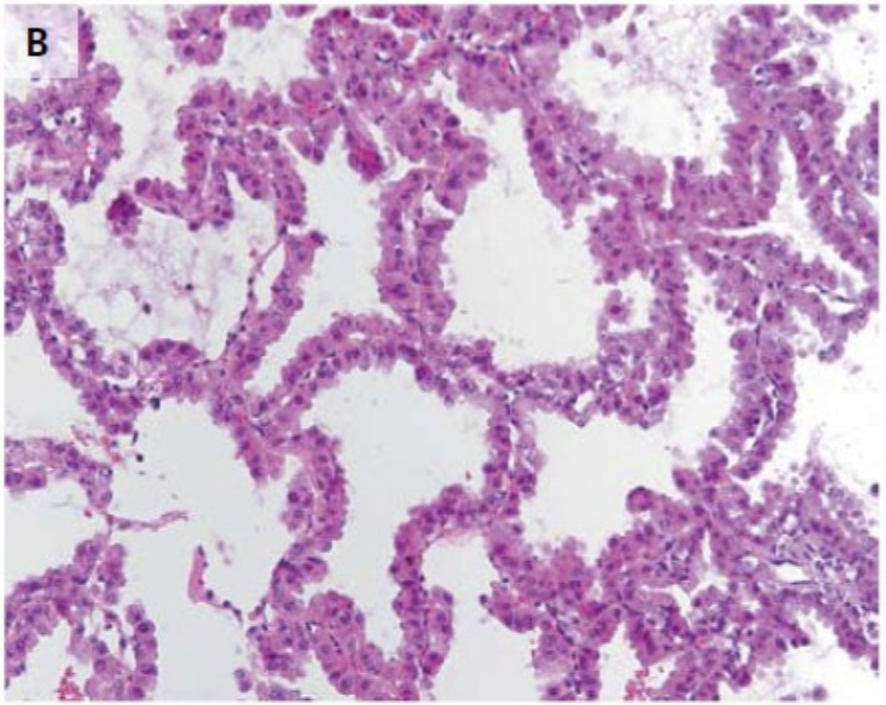
Characteristic	Value
Male sex — no. (%)	43 (52)
Age — yr	
Mean	51
Range	25–78
Race — no. (%)*	
White	46 (56)
Asian	29 (35)
Other	7 (9)
ECOG performance status — no. (%)†	
0	24 (29)
1	44 (54)
2	13 (16)
3	1 (1)
No. of previous therapies — no. (%)	
0	5 (6)
1	27 (33)
2	15 (18)
≥3	34 (41)
Not reported	1 (1)
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.


A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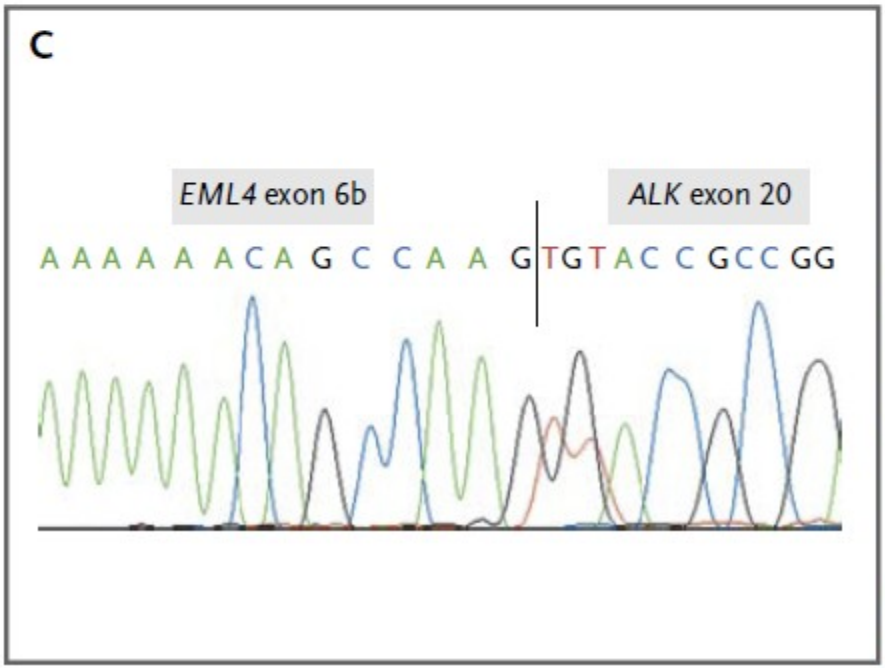
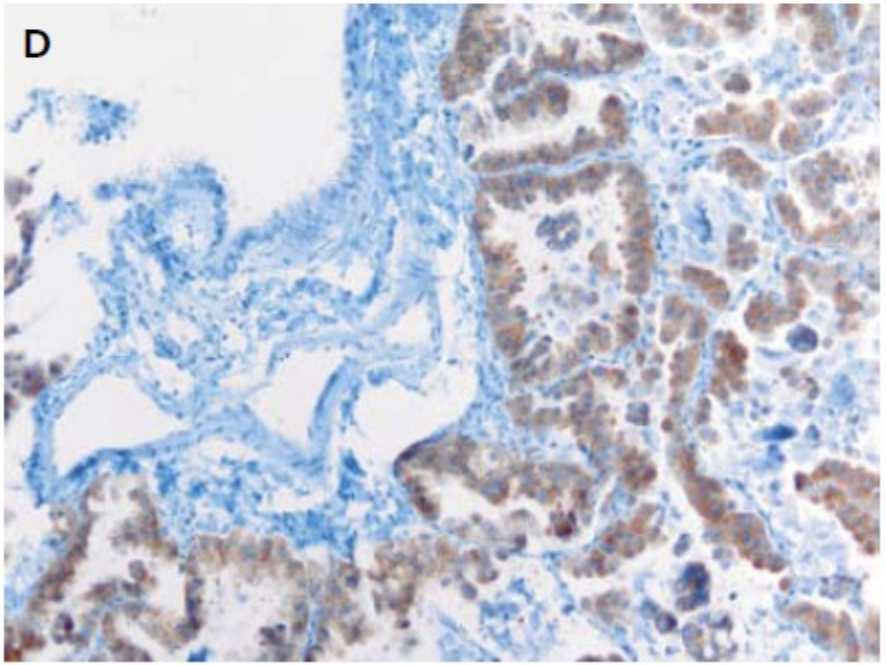

C
EML4 exon 6b
ALK exon 20
A A A A A A C A G C C A A G T G T A C C G C C G G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Crizotinib — Latest Champion in the Cancer Wars?

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

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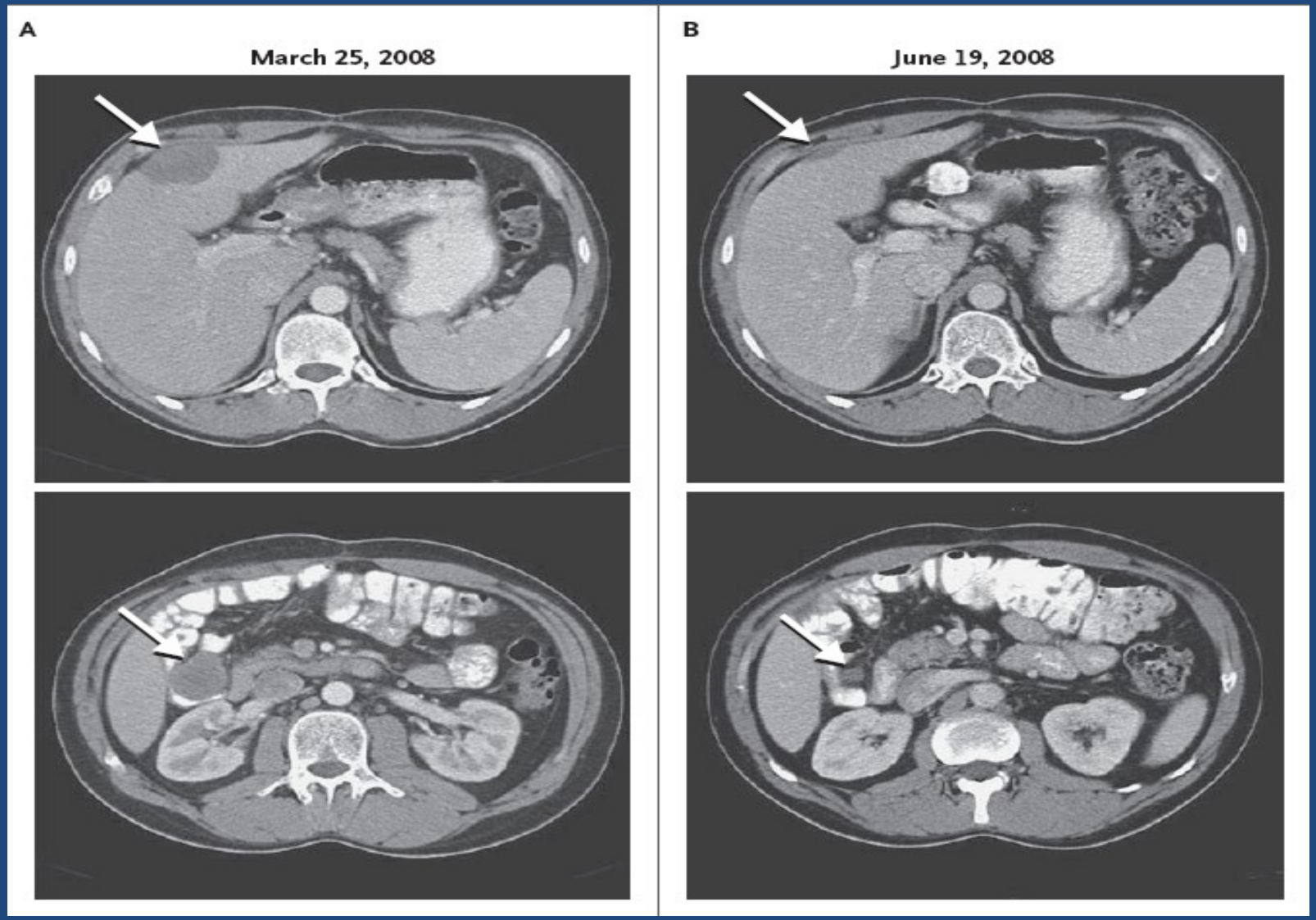
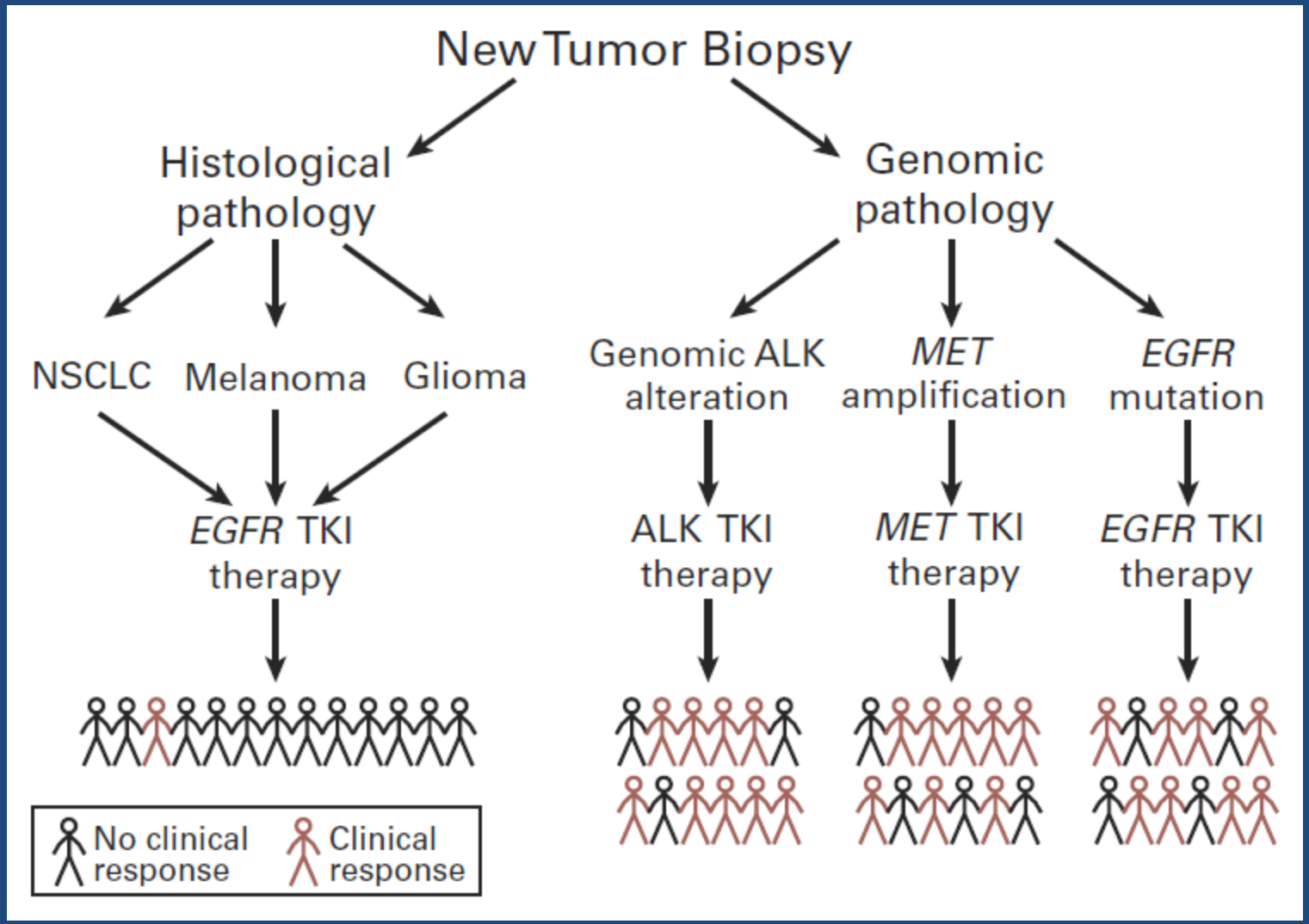

A
March 25, 2008
B
June 19, 2008


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