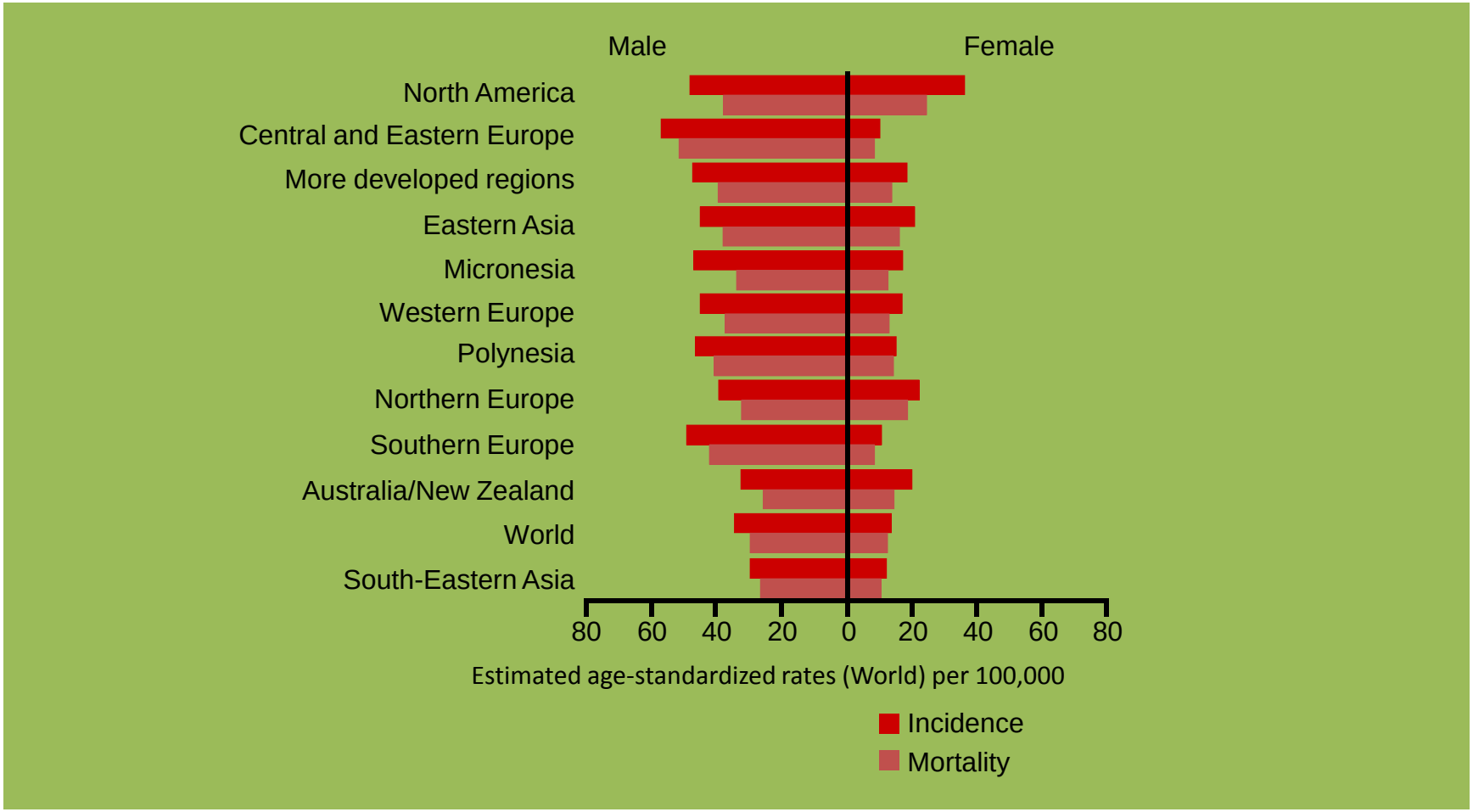
Hedefe yönelik tedaviler, yönlendirici rolümüz ve artan sorumluluğumuz

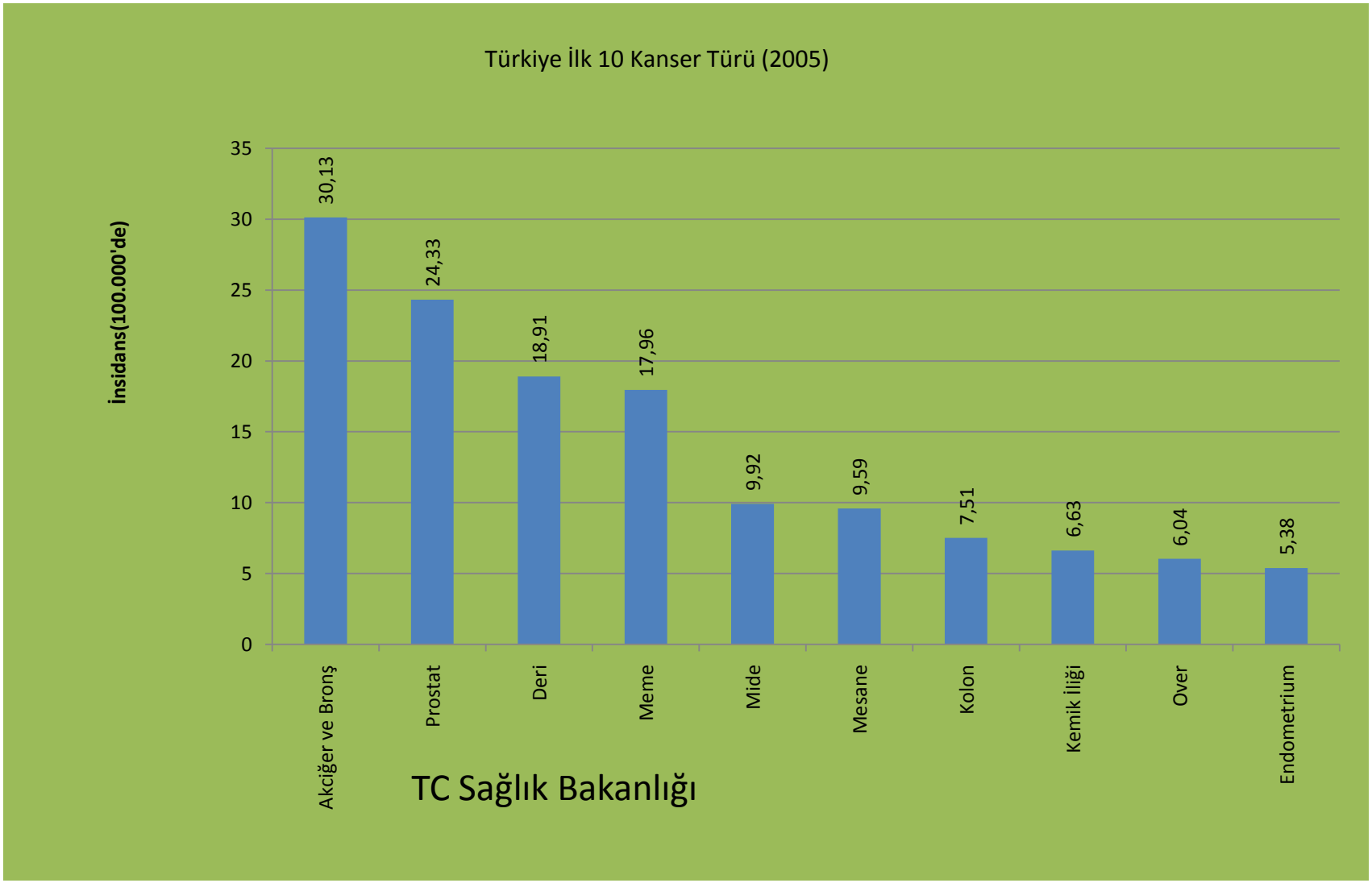
Serpil Dizbay Sak
Ankara Üniversitesi Tıp Fakültesi
Patoloji ABD

1. Akciğer kanseri tüm dünyada büyük bir sorun



GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet] Lyon, France: International Agency for Research on Cancer 2010. Available from: http://globocan.iarc.fr. Accessed February 3, 2011

Türkiyede’de



2. Tanı anında genellikle inoperable

KHDAK tanı anında evreler

Evreler	Hasta sayısı	Yüzde (%)
IA	72	1.8
IB	336	8.3
IIA	21	0.5
IIB	234	5.8
IIIA	446	11.0
IIIB	1248	30.8
IV	1696	41.8
Toplam	4053	100.0

% 72.6

Türkiye'nin Akciğer Kanseri Haritası Projesi
Türk Toraks Derneği/ Akciğer ve Plevra Maligniteleri Çalışma Grubu
T.C. Sağlık Bakanlığı Kanserle Savaş Dairesi
(Yayınlanmamış ön veri)

3.Olguların çoğunda sistemik tedavi gereklidir

SİTOTOKSİK TEDAVİLER

Sitotoksik tedaviler normal hücreler ile kanser hücrelerini birbirinden ayırmaz

Hedefe yönelik tedavi

- Kanser hücresini diğer hücrelerden ayıran genetik farklılıkların tespiti (mutasyonlar)
- Bu mutant yolaklar üzerinde bir hedef belirleme
- Bu hedefe yönelik ilaç geliştirme
  - Mutasyonu bulunduran hücrelerin büyüme/çoğalmasının engellenmesi
  - Tümörün regresyona uğratılması

EGFR Gen Mutasyonu: TK bölgesinde aktivasyon -2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

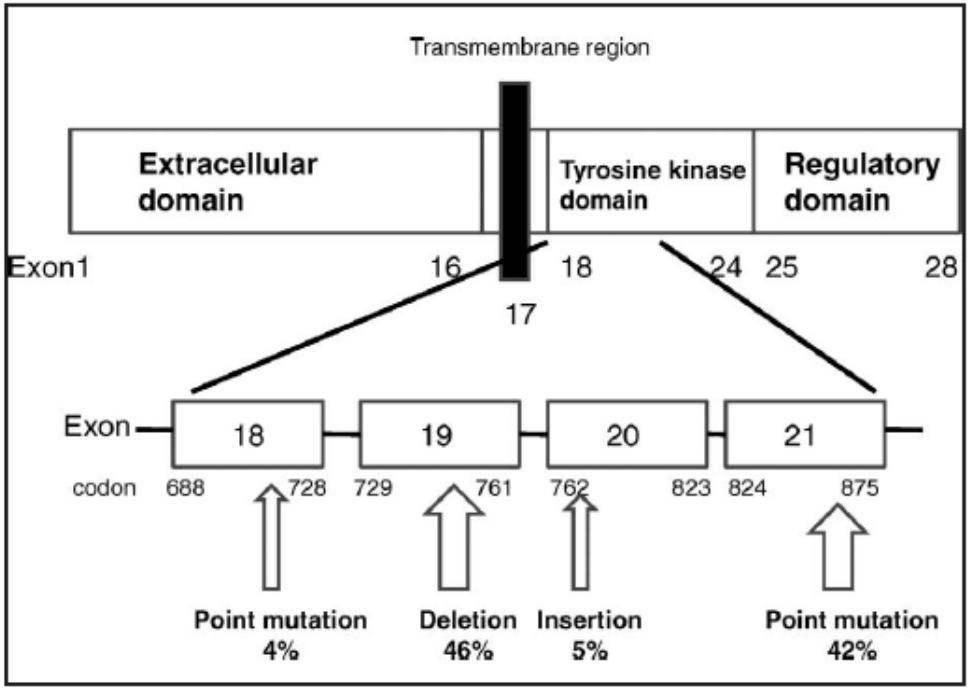
J. Guillermo Paez,[1,2]* Pasi A. Jänne,[1,2]* Jeffrey C. Lee,[1,3]* Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4]† Bruce E. Johnson,[1,2]† Matthew Meyerson[1,3,4]†

SCIENCE VOL 304 4 JUNE 2004

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*††, Vincent Miller†§, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†§, and Harold Varmus*

13306–13311 | PNAS | September 7, 2004 | vol. 101 | no. 36



- Mutasyonların yaklaşık %90'ı ekzon 19 ve 21'de

- Ekzon 19'da in-frame delesyon
- Ekzon 21'de nokta mutasyonu CTG- CGG dönüşümü (L858R)

Tirozin Kinaz İnhibitörleri

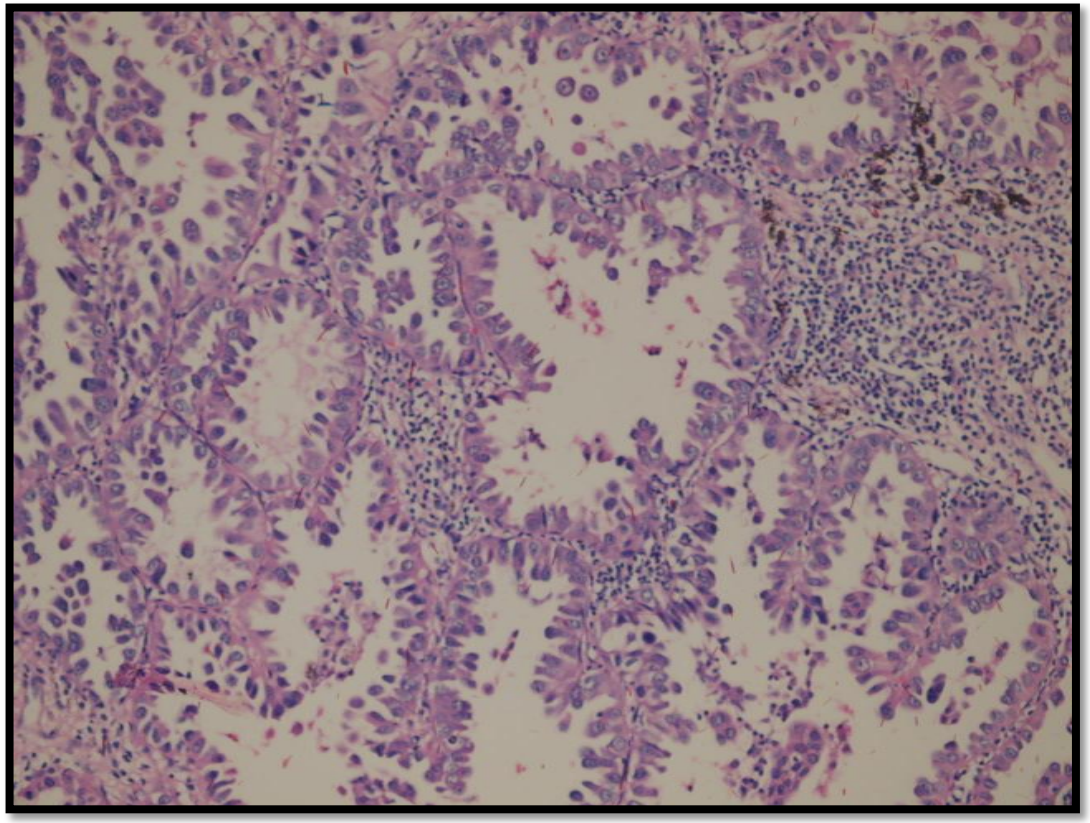
- Gefitinib (Iressa®)
- Erlotinib (Tarceva®)

- Oral
- *Nispeten* düşük toksisite

➢EGFR tedavisine yanıt veren tümörler:

-İyi-orta differansiye , periferik adenokarsinomlar

- TTF1 pozitif
- Saf (non müsinöz) BAK ya da BAK komponentli adenoca.



EGFR Mutasyonu pozitif olgularda 'First-Line' EGFR TKI tedavisi: Randomize çalışmalar

Yazar	Çalışma	N (EGFR mut+)	Median PFS (Ay)
Mok *et al.*	IPASS	261	9.8 *vs.* 6.4
Lee *et al.*	First-SIGNAL	27	8.4 *vs.* 6.7
Mitsudomi *et al.*	WJTOG 3405	86	9.2 *vs.* 6.3
Maemondo *et al.*	NEJGSG002	114	10.8 *vs.* 5.4
Zhou *et al.*	OPTIMAL	154	13.1 *vs.* 4.6
Rosell et al.	EURTAC	174	9.7 *vs. 5.2*

1. Mok *et al. NEJM* 2009; 2. Lee *et al. WCLC* 2009 3. Mitsudomi *et al. Lancet Oncology* 2010;
4. Maemondo *et al. NEJM* 2010; 5. Zhou *et al. ESMO* 2010; 6. Rosell *et al. ASCO 2011*

Technique	Limit of detection (% mutant DNA)	Mutations identified
Direct sequencing	10–20	All – known and new
*Taq*man PCR	10	Limited – specific known only
Loop-hybrid mobility shift assay	10	Limited – specific known only
dHPLC	10	All – known and new
Cycleave PCR	5	Limited – specific known only
Pyrosequencing	5	All – known and new
PCR-RFLP and length analysis	5	Limited – specific known only
MALDI-TOF MS-based genotyping	5	Limited – specific known only
PCR-SSCP	5	All – known and new
WAVE surveyor	3–5	All – known and new
High-resolution melting (HRM)	3–5	All – known and new
PNA-LNA PCR clamp	1	Limited – specific known only
Scorpion ARMS	1	Limited – specific known only
Single molecule sequencing	0.1	All – known and new
Mutant-enriched sequencing	0.1	Limited – specific known only
SMAP	0.1	Limited – specific known only

SMAP: smart amplification process; ARMS: amplification-refractory mutation system; PNA-LNA: peptide nucleic acid-locked nucleic acid; PCR: polymerase chain reaction; SSCP: single-MALDI-TOF: matrix-assisted laser desorption/ionization-FLP: restriction fragment length polymorphism; dHPLC: omatography; MS: mass spectometry; WAVE® (SUR-HPLC Platform, Transgenomics, Glasgow, UK).

Histopathology 2011 DOI: 10.1111/j.1365-2559.2011.03854.x

REVIEW

Personalized medicine for lung cancer: new challenges for pathology

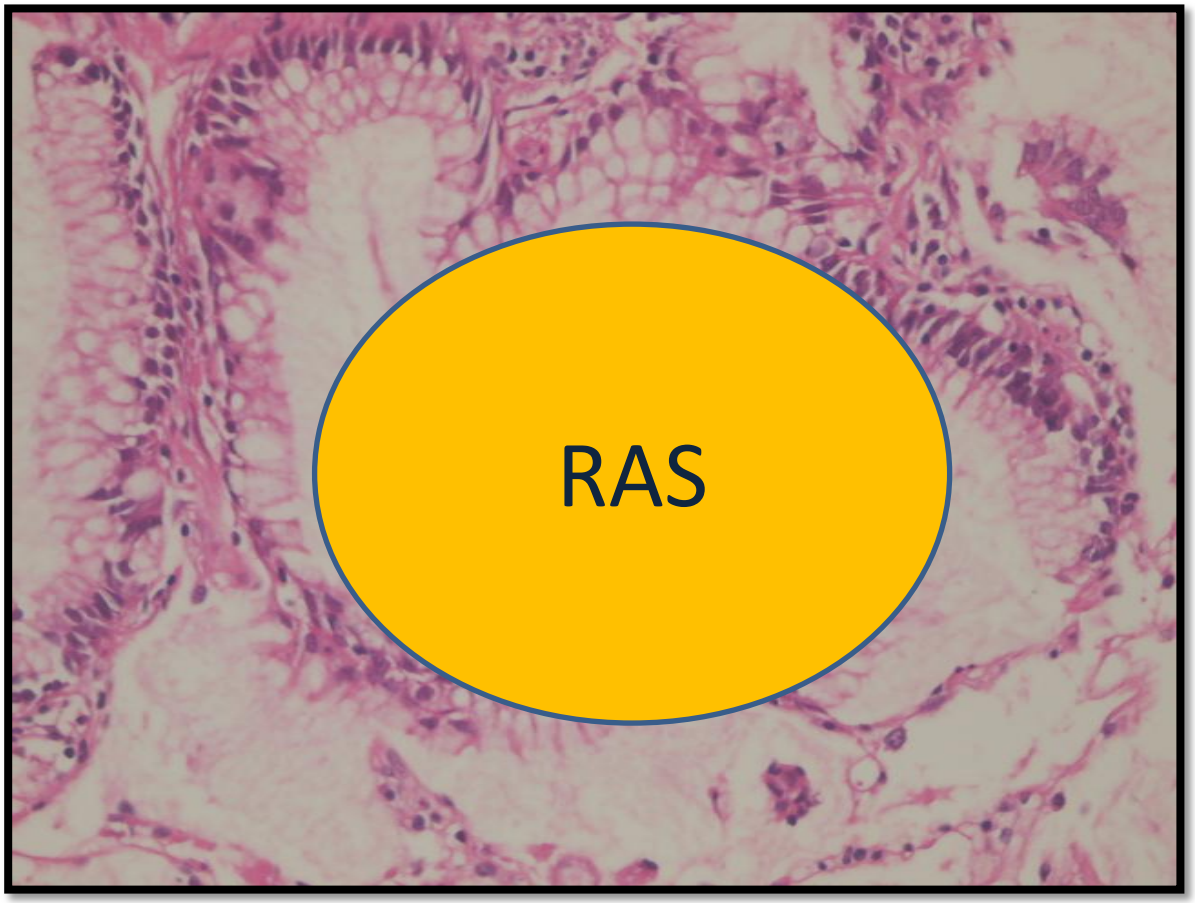
Keith M Kerr
Aberdeen University Medical School, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, UK

➢EGFR tedavisine yanıt vermeyenler:

-Az differansiye TTF-1 negatif tümörler

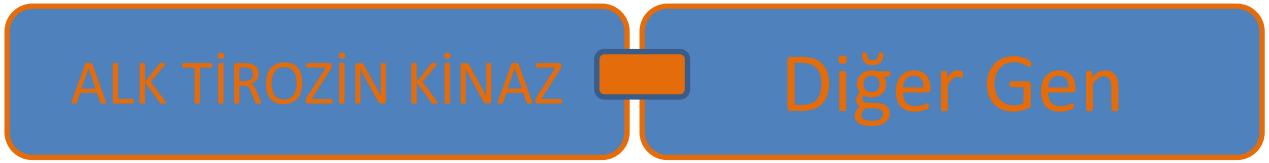
- Saf yassı hücreliler

- Müsinöz BAK



ALK

- Anaplastik lenfoma kinaz: 2. chr yerleşimli transmembran tirozin kinaz
- Kromozomal rearranjmanlar (inversiyon/translokasyon) ile aktive olur.



- ALK&EML4 (ekinoderm michrotubule-associated protein-like 4)
- ALK&KIF5B
- ALK&TFG

ALK Mutasyonları

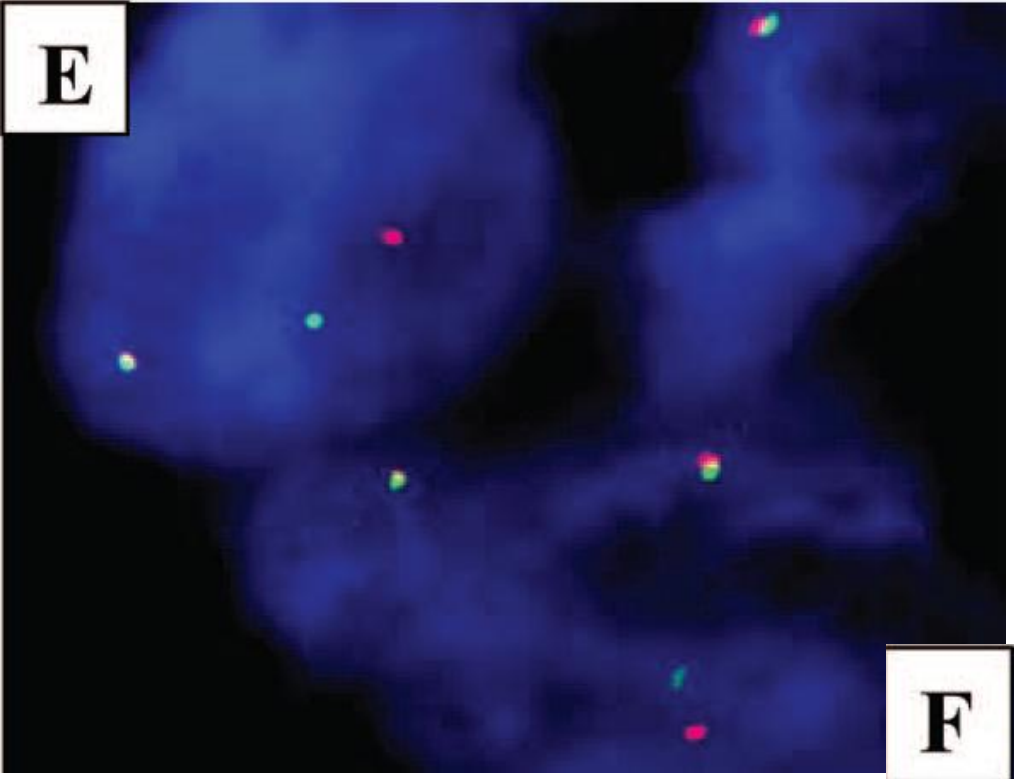
- Colorado serisi:

  Adenokarsinoma; <10 paket-yıl sigara; EGFR ve ras wild type ise % 45 ALK pozitif (Camidge et al.)
- Hiç sigara kullanmamış adenokarsinoma: %9.9 (Yi et al.)
- Küçük hücreli dışı: %4.2 (Paik et al)

- Crizotinib: MET/ALK inhibitörü:
- ALK rearranjmanı gösteren hastalarda etkin
- ALK rearranjmanı %4 kadar

ALK- nasıl saptamalı?

- FISH
- Immünhistokimya
- RT-PCR: Füzyon partnerine spesifik test gerekli



Screening of Anaplastic Lymphoma Kinase Rearrangement by Immunohistochemistry in Non-small Cell Lung Cancer

Correlation with Fluorescence In Situ Hybridization

Jin Ho Paik, MD, PhD, Gheeyoung Choe, MD, PhD,* Hyojin Kim, MD,* Ji-Young Choe, MD,* Hyun Ju Lee, MD,* Choon-Taek Lee, MD, PhD,† Jong Seok Lee, MD, PhD,† Sanghoon Jheon, MD, PhD,‡ and Jin-Haeng Chung, MD, PhD**

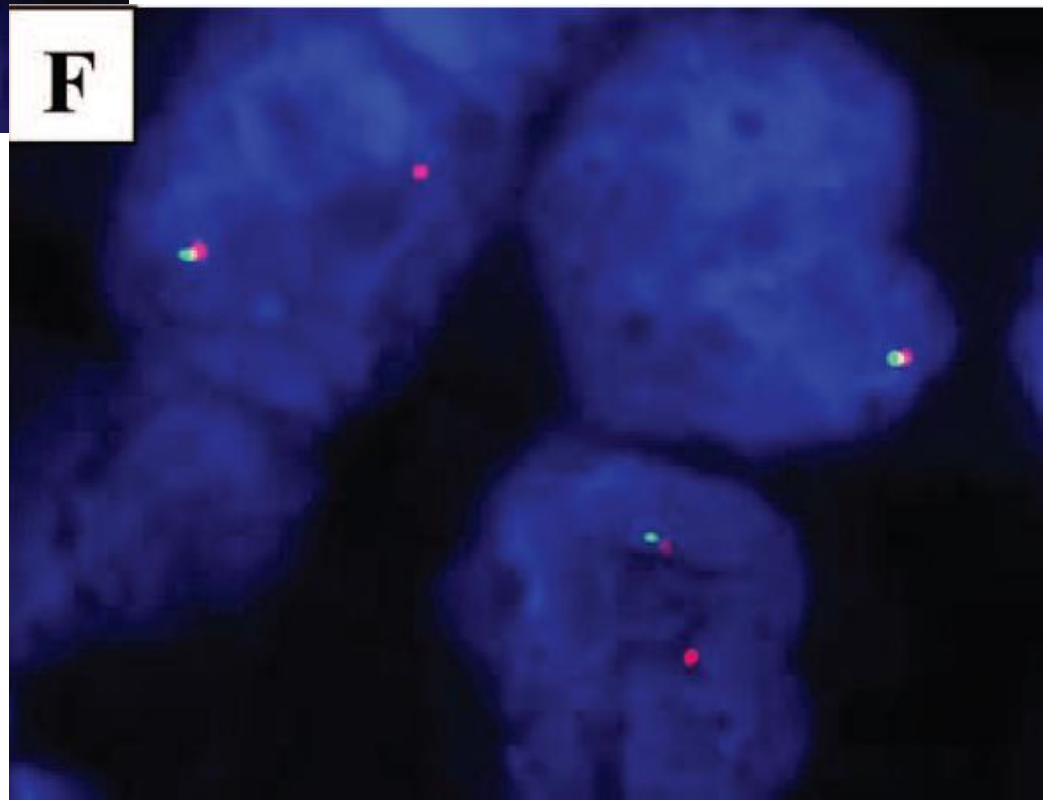
Background: The use of a standard immunohistochemistry (IHC) assay to detect the anaplastic lymphoma kinase (ALK) protein in lung cancer is challenging. There are no universally accepted, evidence-based guidelines on identifying patients with *ALK*-rearranged lung cancer using IHC.

Methods: We retrospectively reviewed 465 resected specimens of non-small cell lung cancer using a tissue microarray as a test set. ALK protein expression using IHC with 5A4 monoclonal antibody (Novocastra) and *ALK* gene rearrangement using fluorescence in situ hybridization (FISH) with dual-color break-apart probes (Abbott molecular) were examined. Immunoreactivity was scored as 0, 1, 2,

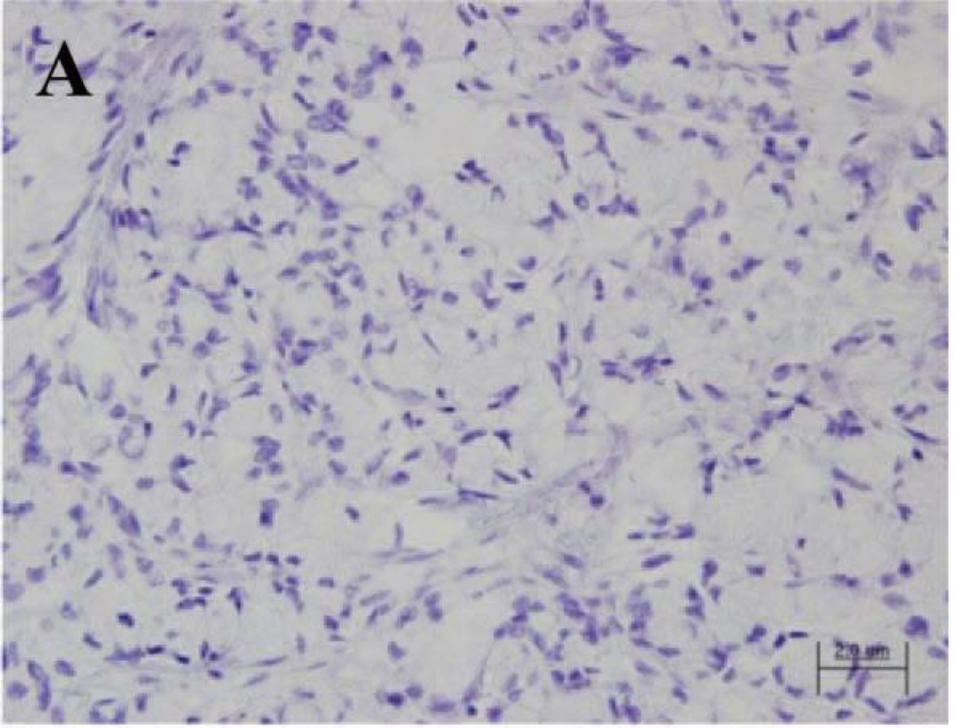
Conclusions: The sensitivity and specificity of IHC was 100% and 95.8%, respectively. These data supported an IHC scoring algorithm in which ALK IHC scores of 0, 1, or 3 were highly compatible with FISH results, and IHC scores of 2 were variable. Based on these findings, the IHC assay using the 5A4 antibody reliably detected non-small cell lung cancer with *ALK* rearrangement and may be useful as a screening method to identify these tumors.

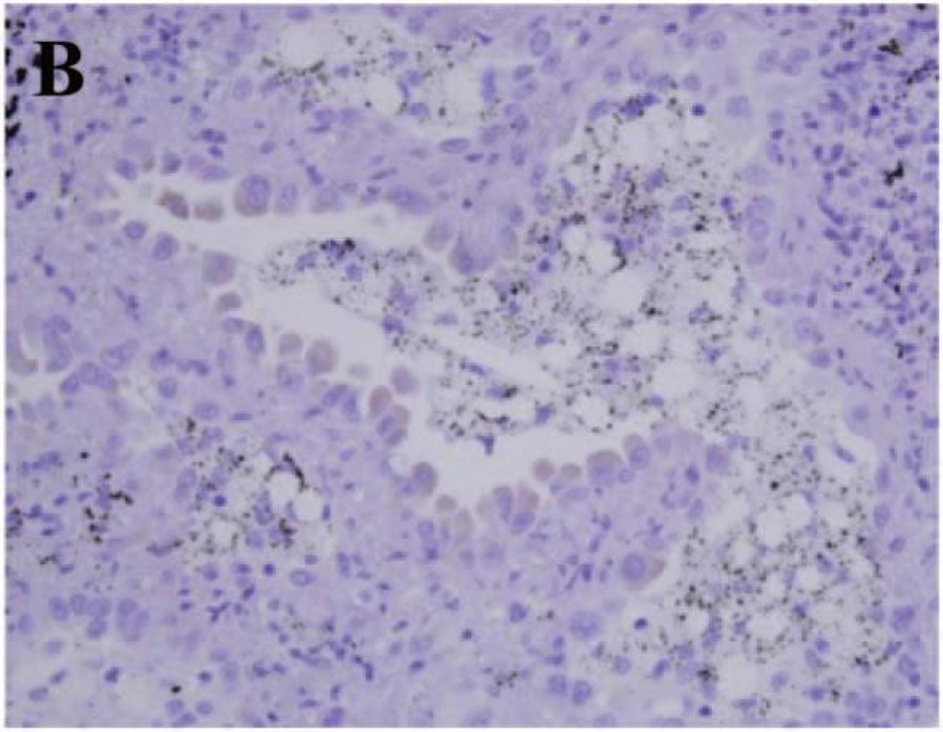
Key Words: *EML4-ALK*, Non-small cell lung cancer, Immunohistochemistry, Fluorescence in situ hybridization.

(*J Thorac Oncol.* 2011;6: 466–472)



Break-apart problar





Screening of Anaplastic Lymphoma Kinase Rearrangement by Immunohistochemistry in Non-small Cell Lung Cancer

Correlation with Fluorescence In Situ Hybridization

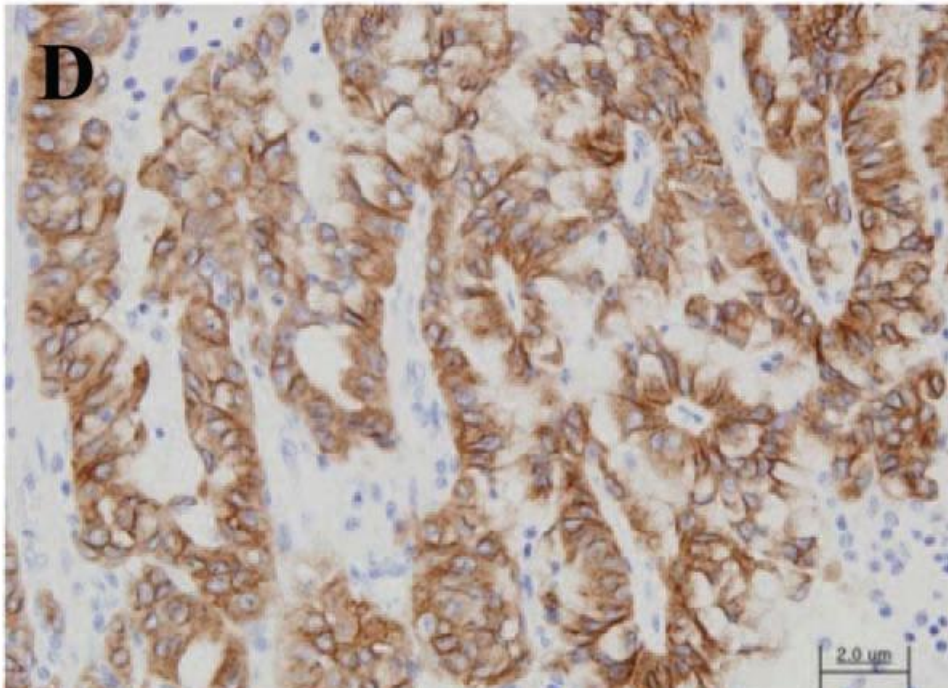
Jin Ho Paik, MD, PhD, Gheeyoung Choe, MD, PhD,* Hyojin Kim, MD,* Ji-Young Choe, MD,* Hyun Ju Lee, MD,* Choon-Taek Lee, MD, PhD,† Jong Seok Lee, MD, PhD,† Sanghoon Jheon, MD, PhD,‡ and Jin-Haeng Chung, MD, PhD**

Background: The use of a standard immunohistochemistry (IHC) assay to detect the anaplastic lymphoma kinase (ALK) protein in lung cancer is challenging. There are no universally accepted, evidence-based guidelines on identifying patients with *ALK*-rearranged lung cancer using IHC.

Methods: We retrospectively reviewed 465 resected specimens of non-small cell lung cancer using a tissue microarray as a test set. ALK protein expression using IHC with 5A4 monoclonal antibody

Conclusions: The sensitivity and specificity of IHC was 100% and 95.8%, respectively. These data supported an IHC scoring algorithm in which ALK IHC scores of 0, 1, or 3 were highly compatible with FISH results, and IHC scores of 2 were variable. Based on these findings, the IHC assay using the 5A4 antibody reliably detected non-small cell lung cancer with *ALK* rearrangement and may be useful as a screening method to identify these tumors.

Key Words: *EML4-ALK*, Non-small cell lung cancer, Immunohistochemistry, Fluorescence in situ hybridization.



Screening of Anaplastic Lymphoma Kinase Rearrangement by Immunohistochemistry in Non-small Cell Lung Cancer

Correlation with Fluorescence In Situ Hybridization

Jin Ho Paik, MD, PhD, Gheeyoung Choe, MD, PhD,* Hyojin Kim, MD,* Ji-Young Choe, MD,* Hyun Ju Lee, MD,* Choon-Taek Lee, MD, PhD,† Jong Seok Lee, MD, PhD,† Sanghoon Jheon, MD, PhD,‡ and Jin-Haeng Chung, MD, PhD**

Background: The use of a standard immunohistochemistry (IHC) assay to detect the anaplastic lymphoma kinase (ALK) protein in lung cancer is challenging. There are no universally accepted, evidence-based guidelines on identifying patients with *ALK*-rearranged lung cancer using IHC.

Methods: We retrospectively reviewed 465 resected specimens of non-small cell lung cancer using a tissue microarray as a test set. ALK protein expression using IHC with 5A4 monoclonal antibody (Novocastra) and *ALK* gene rearrangement using fluorescence in situ hybridization (FISH) with dual-color break-apart probes (Abbott molecular) were examined. Immunoreactivity was scored as 0, 1, 2,

Conclusions: The sensitivity and specificity of IHC was 100% and 95.8%, respectively. These data supported an IHC scoring algorithm in which ALK IHC scores of 0, 1, or 3 were highly compatible with FISH results, and IHC scores of 2 were variable. Based on these findings, the IHC assay using the 5A4 antibody reliably detected non-small cell lung cancer with *ALK* rearrangement and may be useful as a screening method to identify these tumors.

Key Words: *EML4-ALK*, Non-small cell lung cancer, Immunohistochemistry, Fluorescence in situ hybridization.

(*J Thorac Oncol.* 2011;6: 466–472)

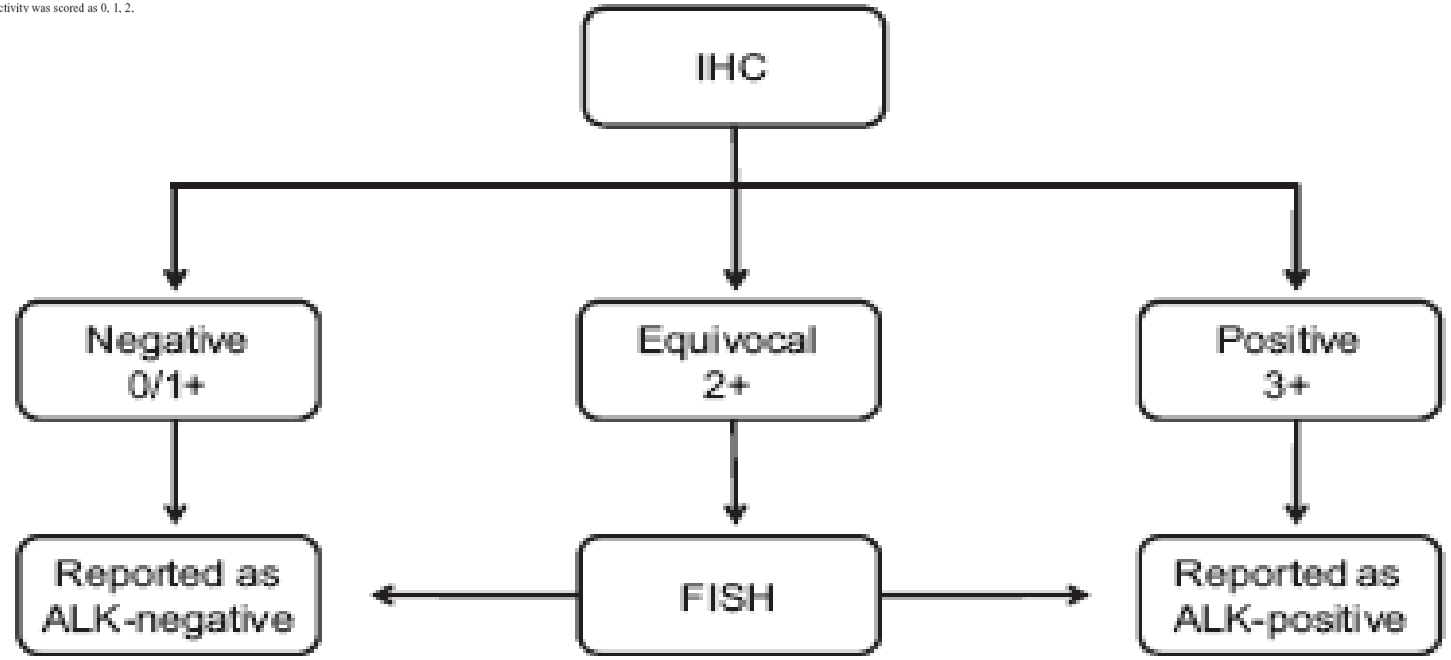
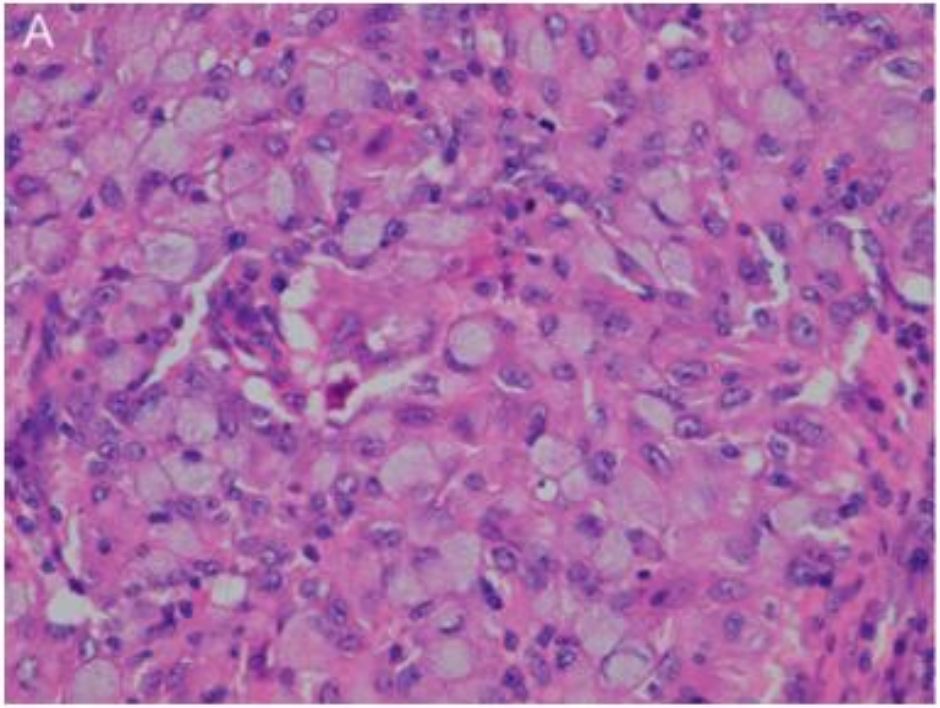
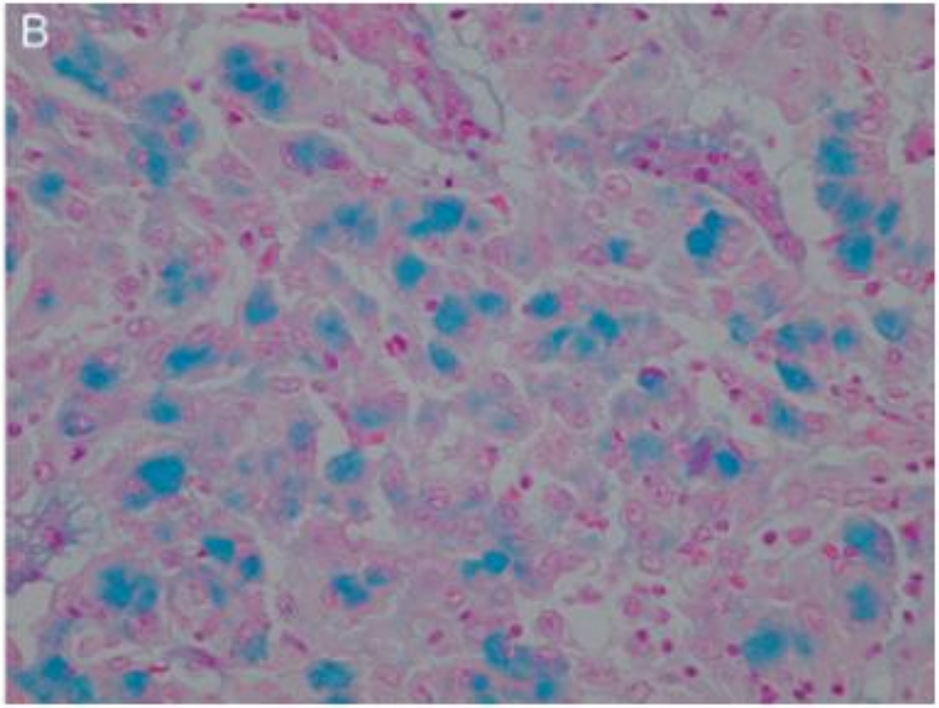


FIGURE 2. Diagnostic algorithm using anaplastic lymphoma kinase (ALK) immunohistochemistry and fluorescence in situ hybridization in non-small cell lung cancer.

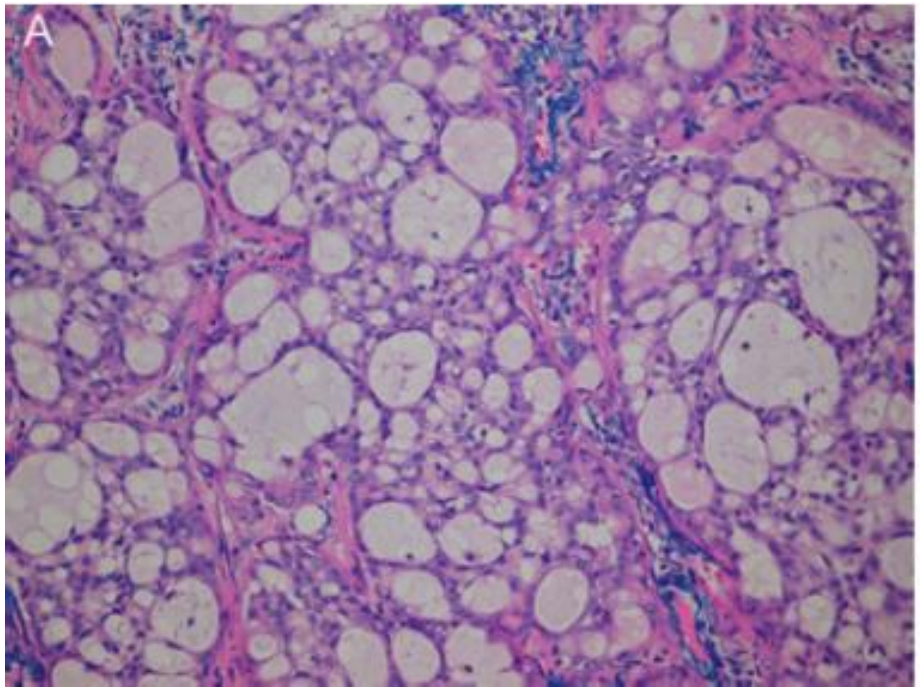


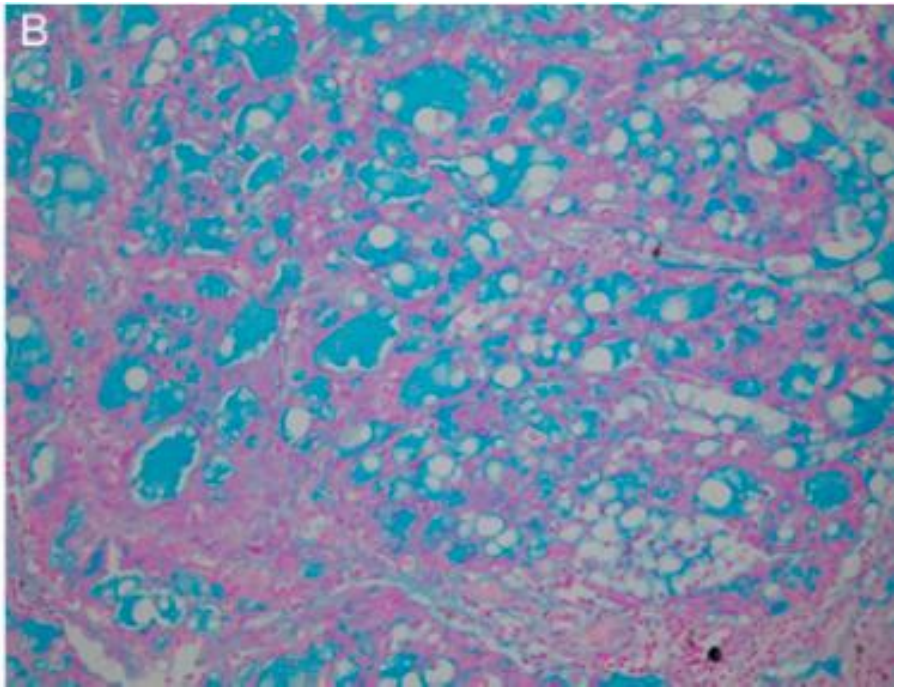


Taşlı Yüzük Hücreleri

Combination of morphological feature analysis and immunohistochemistry is useful for screening of EML4-ALK-positive lung adenocarcinoma

Ryu Jokoji,[1] Takashi Yamasaki,[1] Seigo Minami,[2] Kiyoshi Komuta,[2] Yasushi Sakamaki,[3] Kengo Takeuchi,[4] Masahiko Tsujimoto[1]



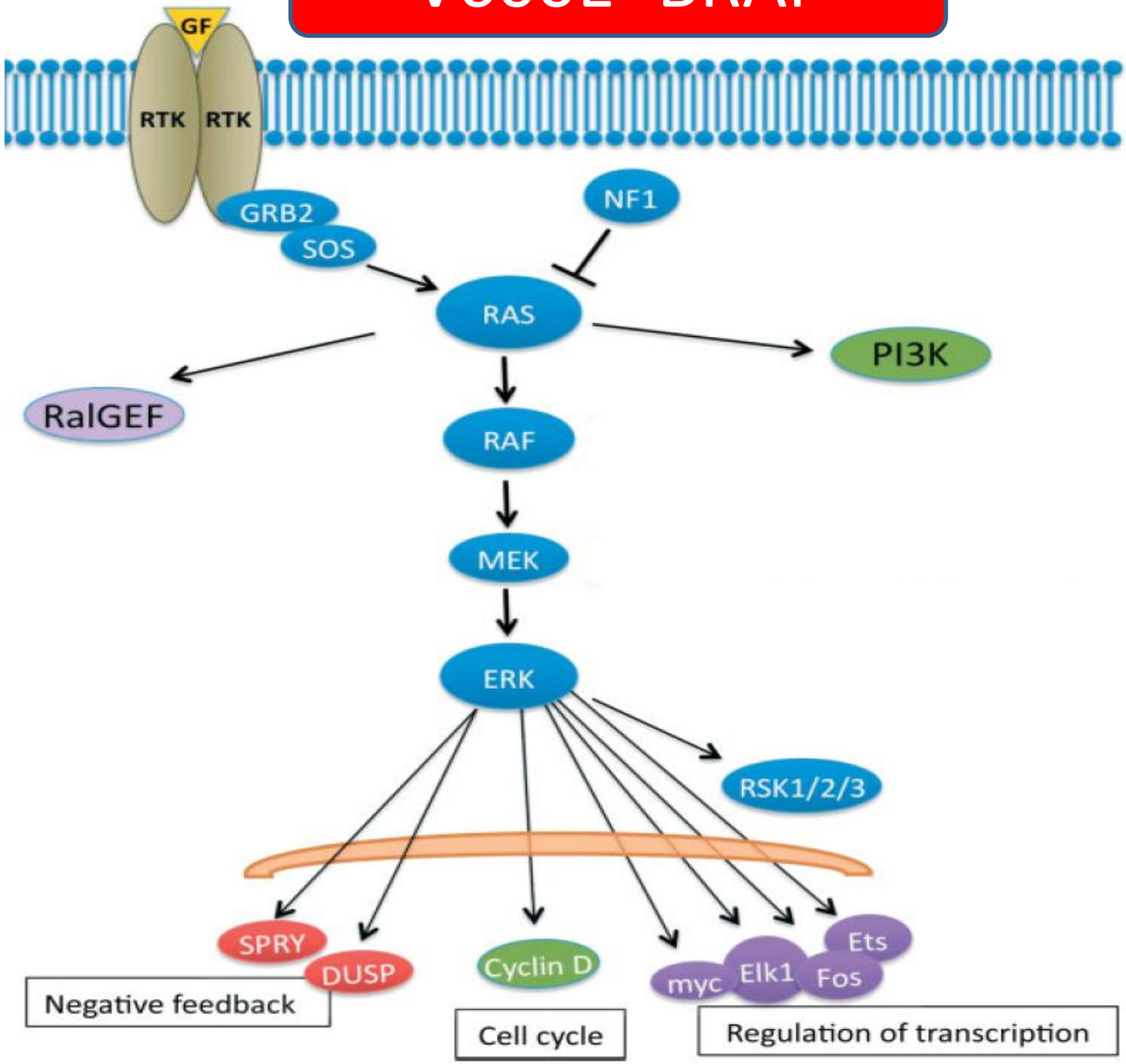


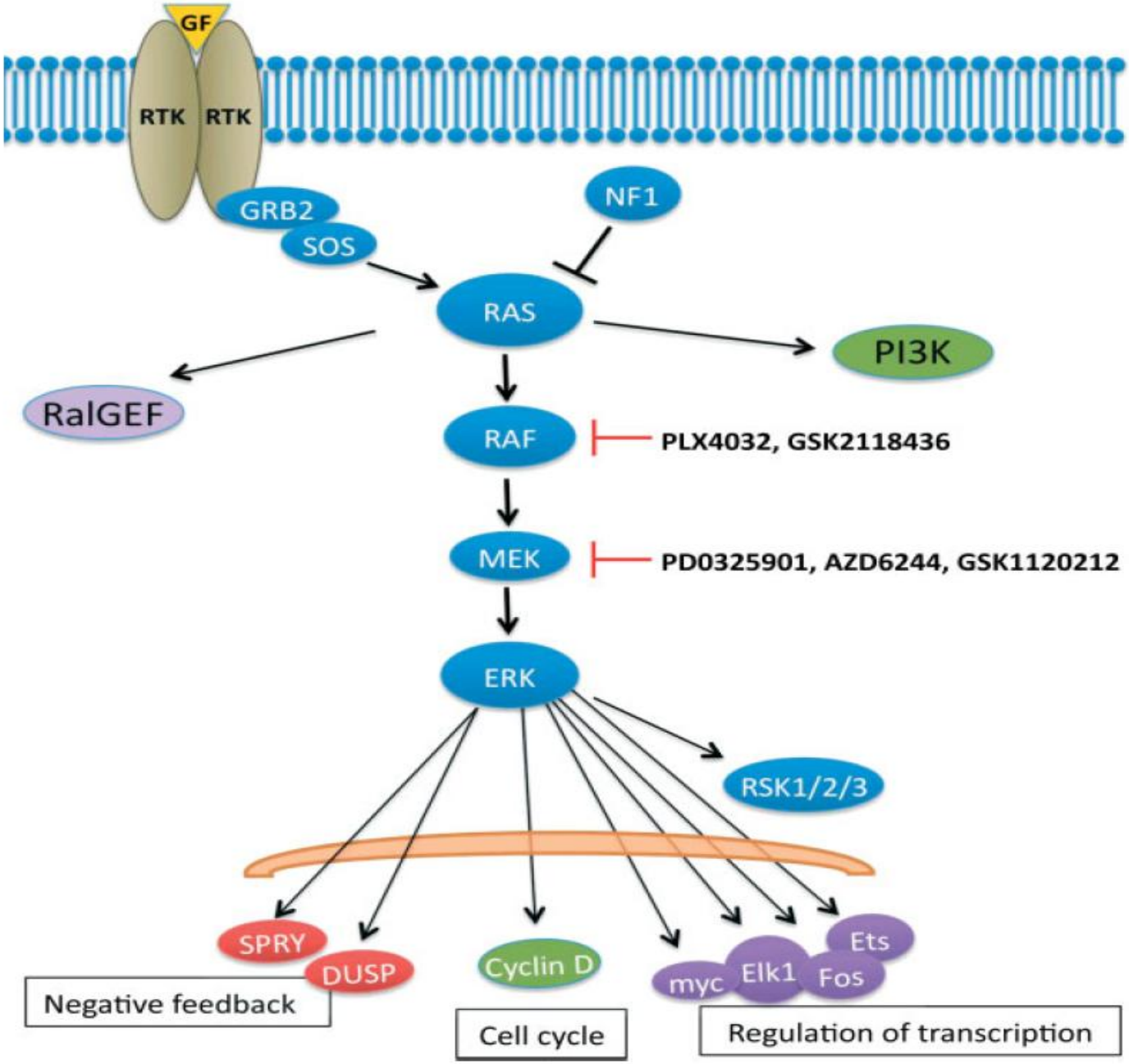
Kribriform/müsinöz pattern

Combination of morphological feature analysis and immunohistochemistry is useful for screening of EML4-ALK-positive lung adenocarcinoma

Ryu Jokoji,[1] Takashi Yamasaki,[1] Seigo Minami,[2] Kiyoshi Komuta,[2] Yasushi Sakamaki,[3] Kengo Takeuchi,[4] Masahiko Tsujimoto[1]

V600E- BRAF


GF
RTK
RTK
GRB2
SOS
NF1
RAS
PI3K
RalGEF
RAF
MEK
ERK
RSK1/2/3
SPRY
DUSP
Cyclin D
myc
Elk1
Fos
Ets
Negative feedback
Cell cycle
Regulation of transcription


GF
RTK
RTK
GRB2
SOS
NF1
RAS
PI3K
RalGEF
RAF
PLX4032, GSK2118436
MEK
PD0325901, AZD6244, GSK1120212
ERK
RSK1/2/3
SPRY
DUSP
Negative feedback
Cyclin D
Cell cycle
myc
Elk1
Ets
Fos
Regulation of transcription

BRAF ve MEK inhibitörleri

RAF inhibitörleri

- PLX4032 (Plexxikon/Roche)
  - V600E mutant BRAF'ı selektif olarak inhibe eder
  - Minimal toksisite, %81 yanıt
- GSK2118436

MEK inhibitörleri

- CI-1040 (Pfizer Oncology)
  - MEK'e bağlanarak inaktif hale getirir
- PD0325901
- AZD6244 (AstraZeneca)

The Histopathology of *BRAF*-V600E–mutated Lung Adenocarcinoma

Samuel A. Yousem, MD, Marina Nikiforova, MD, and Yuri Nikiforov, MD, PhD

Abstract: *BRAF* mutations in lung adenocarcinoma are much less common than the more frequently reported and mutually exclusive mutations of *KRAS* and *EGFR* genes, and the clinical and histologic phenotype of *BRAF* adenocarcinomas has not been described. We analyzed 222 adenocarcinomas of lung lacking *KRAS* and *EGFR* mutations and identified 10 adenocarcinomas with *BRAF*-V600E mutation. All *BRAF*-V600E mutations were heterozygous. There was a slight female predilection (6:4) in these elderly patients (average age 67 y) who were found to have a greater than expected incidence of intralobar satellite nodules and N2 node involvement. The adenocarcinomas were largely of mixed type with a high incidence of papillary (80%) and lepidic growth (50%). Adenocarcinomas with this clinicopathologic phenotype may be worthwhile investigating for *BRAF*-V600E mutation as more genetically oriented drug therapies emerge.

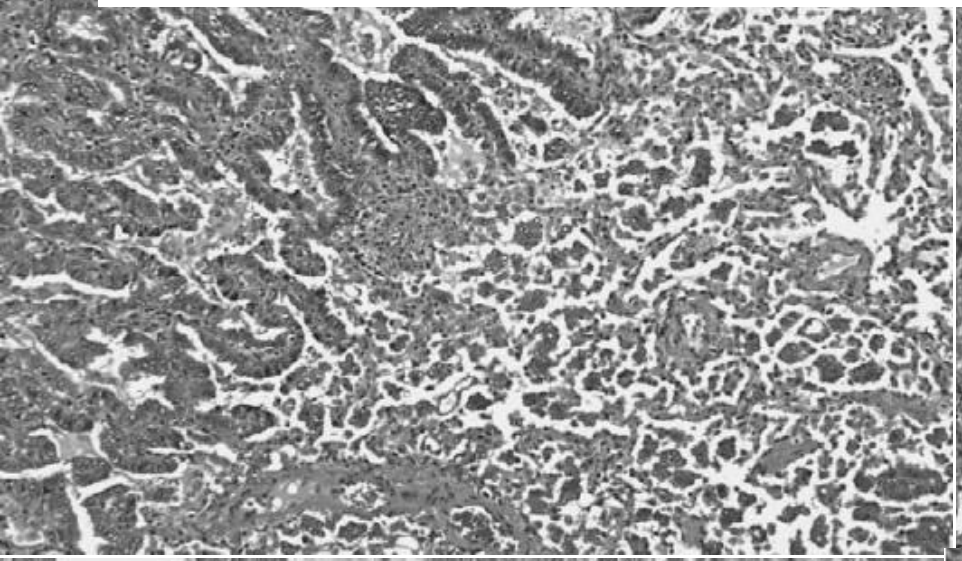
Key Words: lung, adenocarcinoma, *BRAF*, V600E, *KRAS*, EGFR, papillary

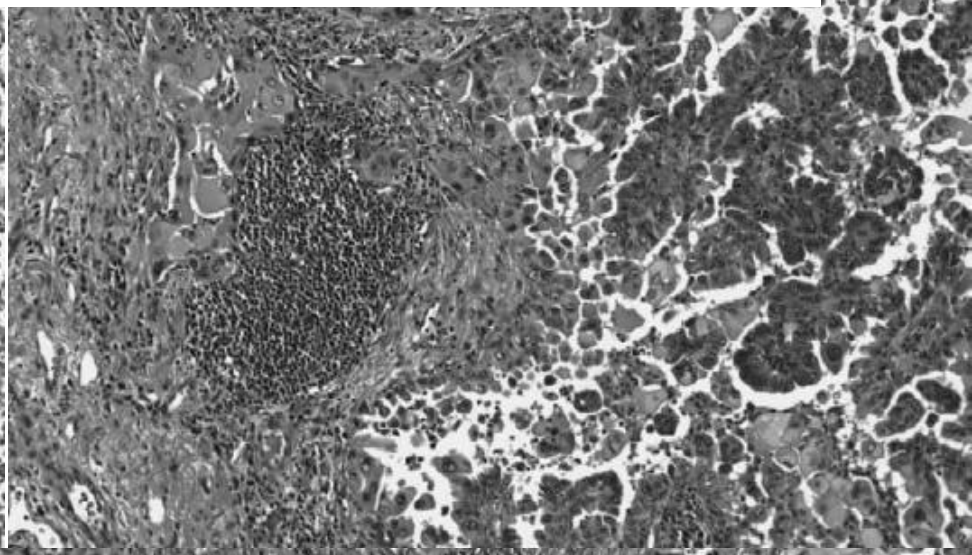
(*Am J Surg Pathol* 2008;32:1317–1321)

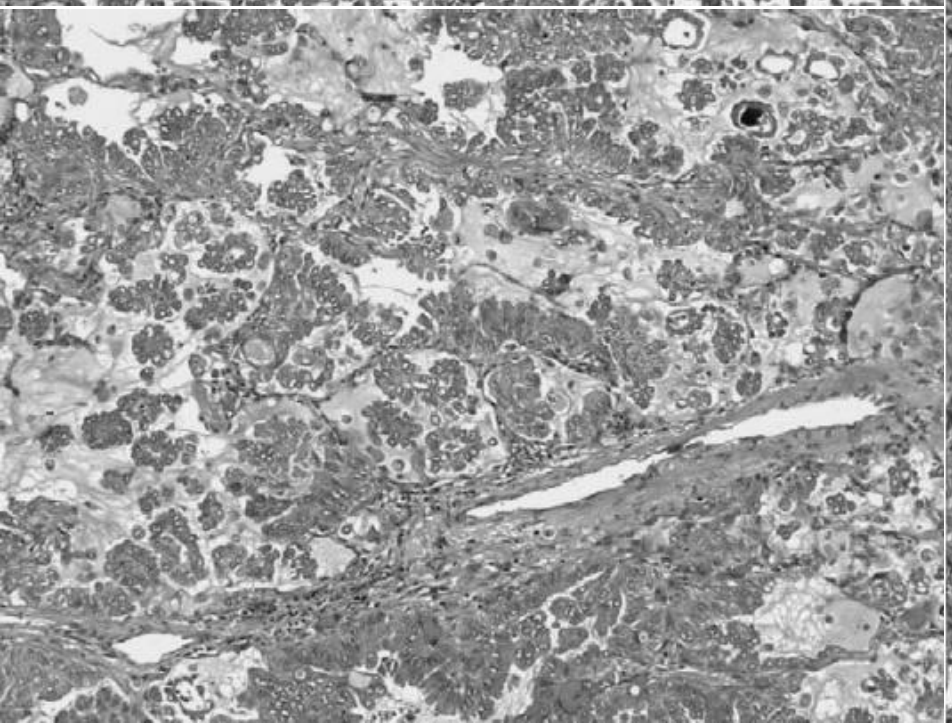
BRAF mutations have been reported in 3% to 10% of lung adenocarcinomas, although they are more frequently observed in papillary thyroid carcinoma, malignant melanoma, colorectal adenocarcinoma, and ovarian serous adenocarcinoma.[3,5–7,13] *BRAF* is one of 3 isoforms of the *RAF* gene, a serine–threonine-specific protein kinase that is activated downstream of RAS. RAF activates the MAP kinase extracellular signal regulated kinase (MEK) which in turn stimulates the extracellular signal-regulated kinase (ERK).[3,7,13,17,19] Mutations of *BRAF* constitutively activate ERK signaling through hyperactivation of the RAS-ERK pathway stimulating proliferation and augmented cell survival.[1,13,14] The most common *BRAF* mutation in human cancer is a glutamic acid for valine substitution at position 600 on exon 15 (V600E). In mouse models, *BRAF*-V600E can induce pulmonary adenomas and adenocarcinomas, although it is believed that oncogenic *BRAF* acts early in the mutation process and requires additional mutagenic events for these epithelial proliferations to achieve a full malignant state.[5,6,8] *BRAF*-V600E mutations are exclusive of coexistent *KRAS* and *EGFR*

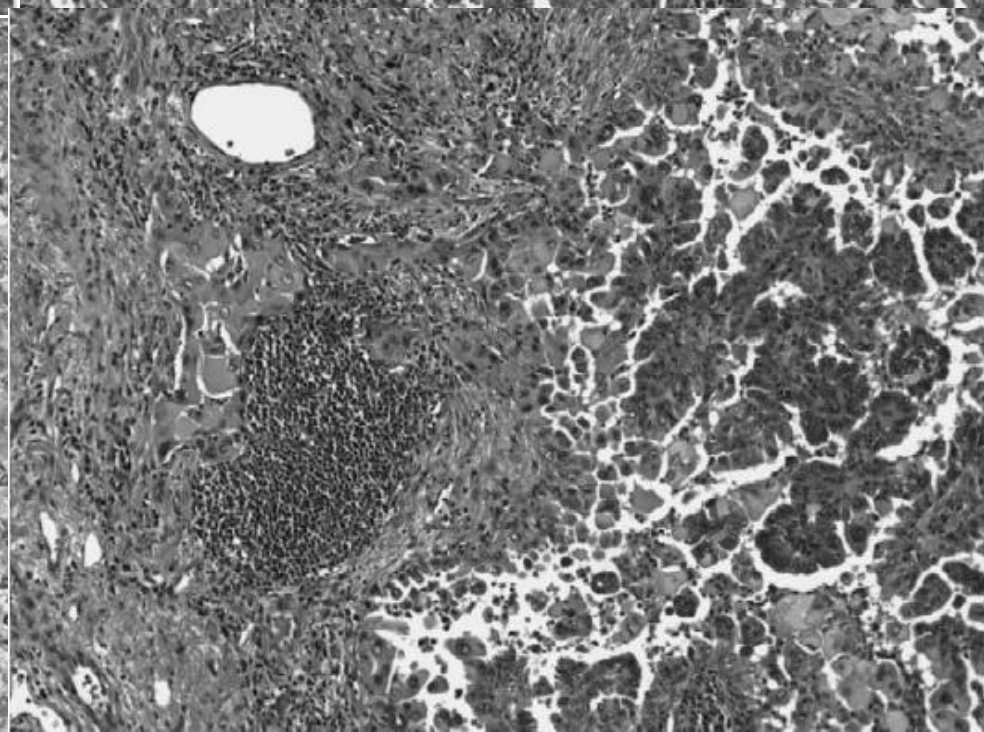
The Histopathology of *BRAF*-V600E–mutated Lung Adenocarcinoma

Samuel A. Yousem, MD, Marina Nikiforova, MD, and Yuri Nikiforov, MD, PhD









The Histopathology of *BRAF*-V600E–mutated Lung Adenocarcinoma

Samuel A. Yousem, MD, Marina Nikiforova, MD, and Yuri Nikiforov, MD, PhD

TABLE 1. Clinicopathologic Data in *BRAF*-V600E Mutated Lung Adenocarcinoma

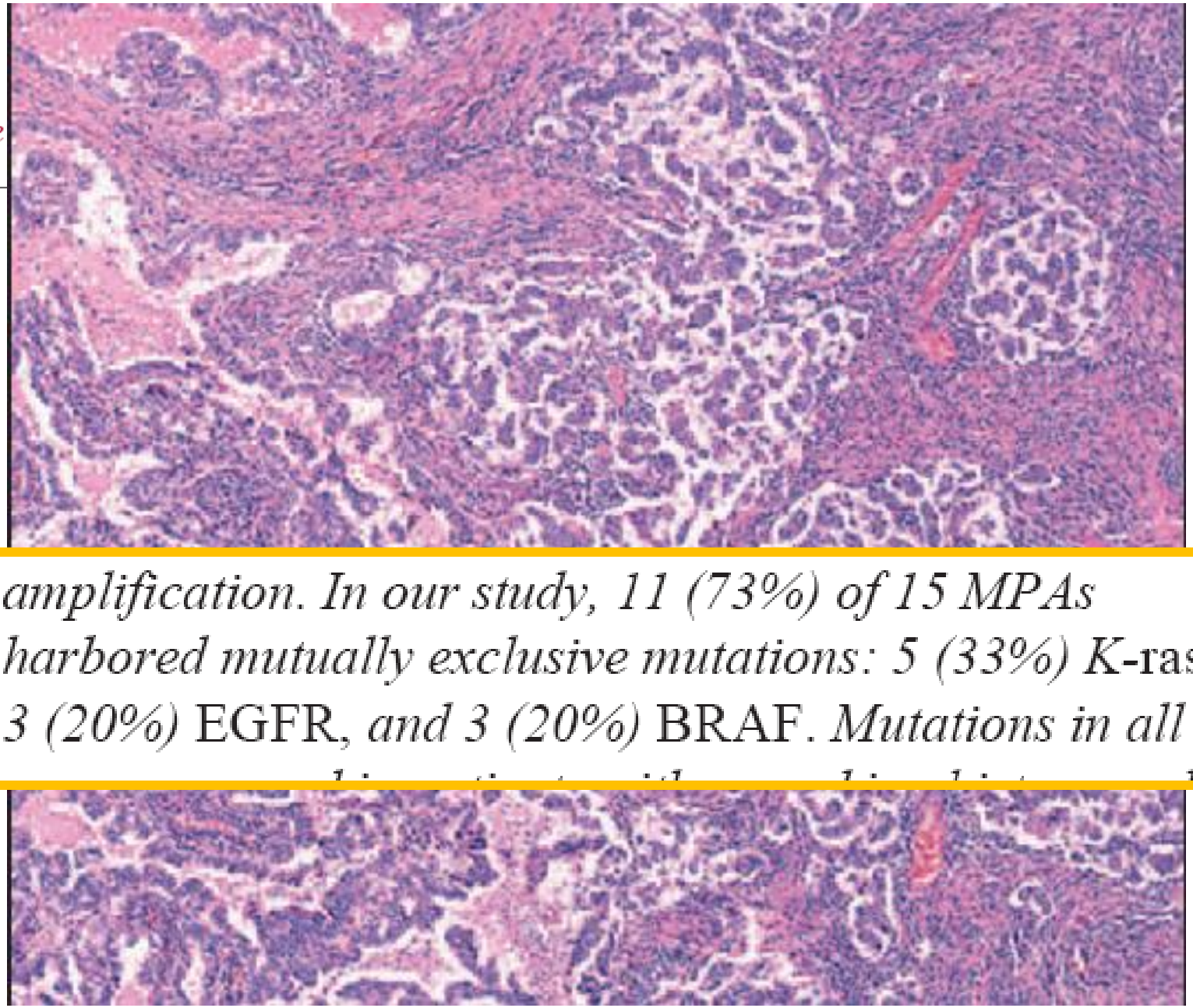
Case	Age/Sex	Location	P	Diameter (cm)	Diagnosis	Growth Patterns			VPI	ALI	Pathologic Stage (TNM)	Clinical Stage	Status (mo)
						BAC	Papillary	Solid					
1	52F	LUL	L	2.5	ADCA	+	+	–	+	–	T2NOMX	1B	ANED 24
2	69F	LUL	S	1.5	ADCA	+	–	–	+	+	T2NOMX	1B	AWD 25
3	66M	LLL	L	3.0	ADCA	–	+	+	–	+	T4NOMX	IIIB	ANED 4
4	64M	LUL	L	3.0	ADCA	+	+		+	+	T4N2MX	IIIB	DOD 8
5	80F	RUL	L	6.5	ADCA	–	+	+	+	+	T4N0MX	IIIB	ANED 3
6	62F	LLL	S	1.5	ADSQ	+	+	–	+	+	T2N2M1	IV	AWD 2
7	56M	RLL	L	5.0	ADCA	–	+	+	–	+	T2N2MX	IIIA	LOST
8	68F	LUL	L	1.5	ADCA	–	+	+	–	+	T1N2MX	IIIA	DOD 9
9	81M	LUL	Bx	N/A	ADCA	–	–	+	–	+	–	N/A	DOD 6
10	72F	RLL	S	1.5	ADCA	+	+	–	+	–	T2NX	N/A	ANED 21

Micropapillary Lung Adenocarcinoma

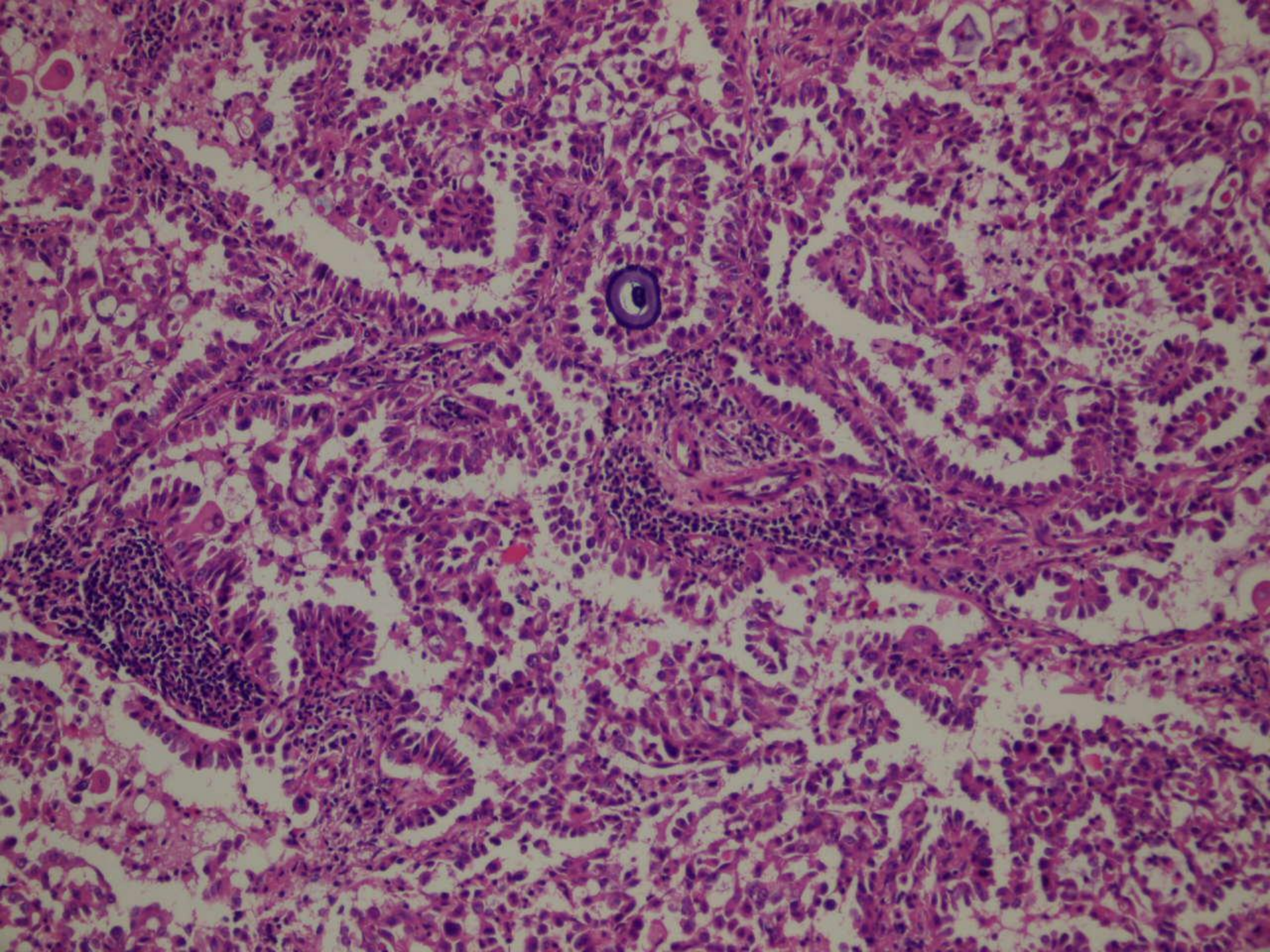
EGFR,

Rosane De

Key Words:



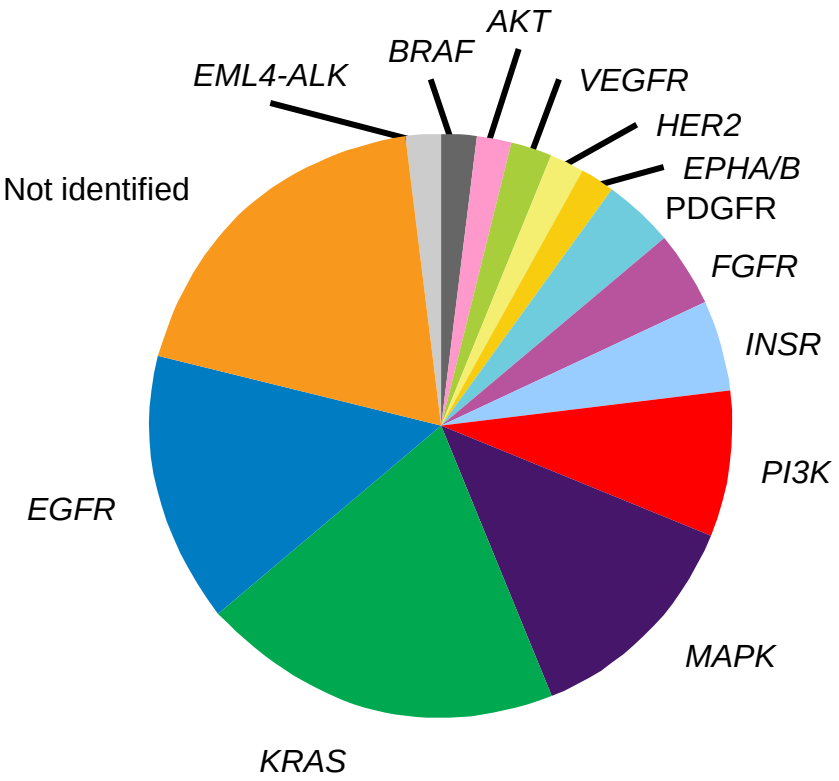
*amplification. In our study, 11 (73%) of 15 MPAs harbored mutually exclusive mutations: 5 (33%) K-*ras, *3 (20%)* EGFR, *and 3 (20%)* BRAF. *Mutations in all 3*



Başka Hangi Tümörlerde BRAF Mutasyonu Var?

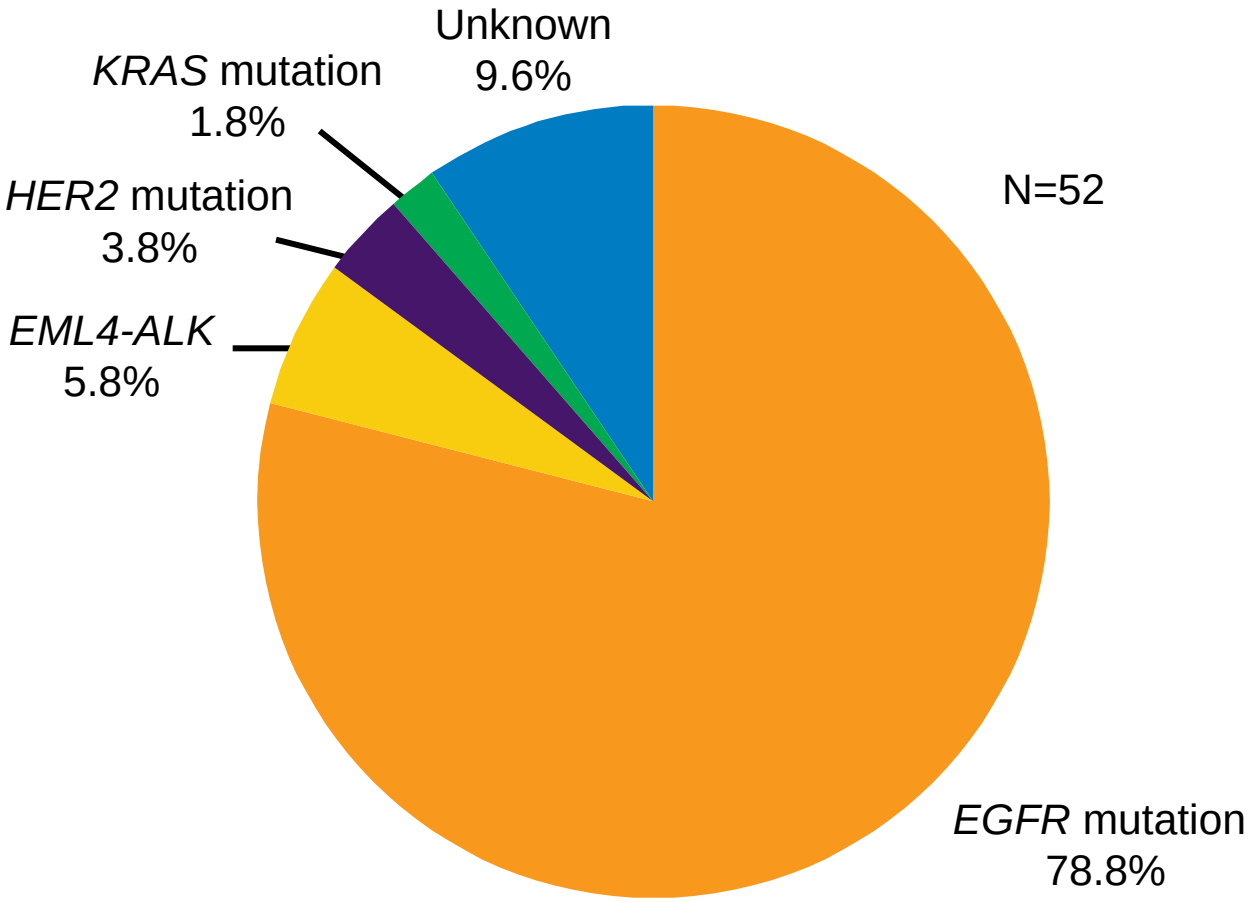
Akciğer adenokanserinde genetik değişiklikler

- 188 olguda karsinogenezle ilgili 623 gen sekanslanmış
- Akciğer adenokanserinde bunların 26’ sı sıklıkla mutant



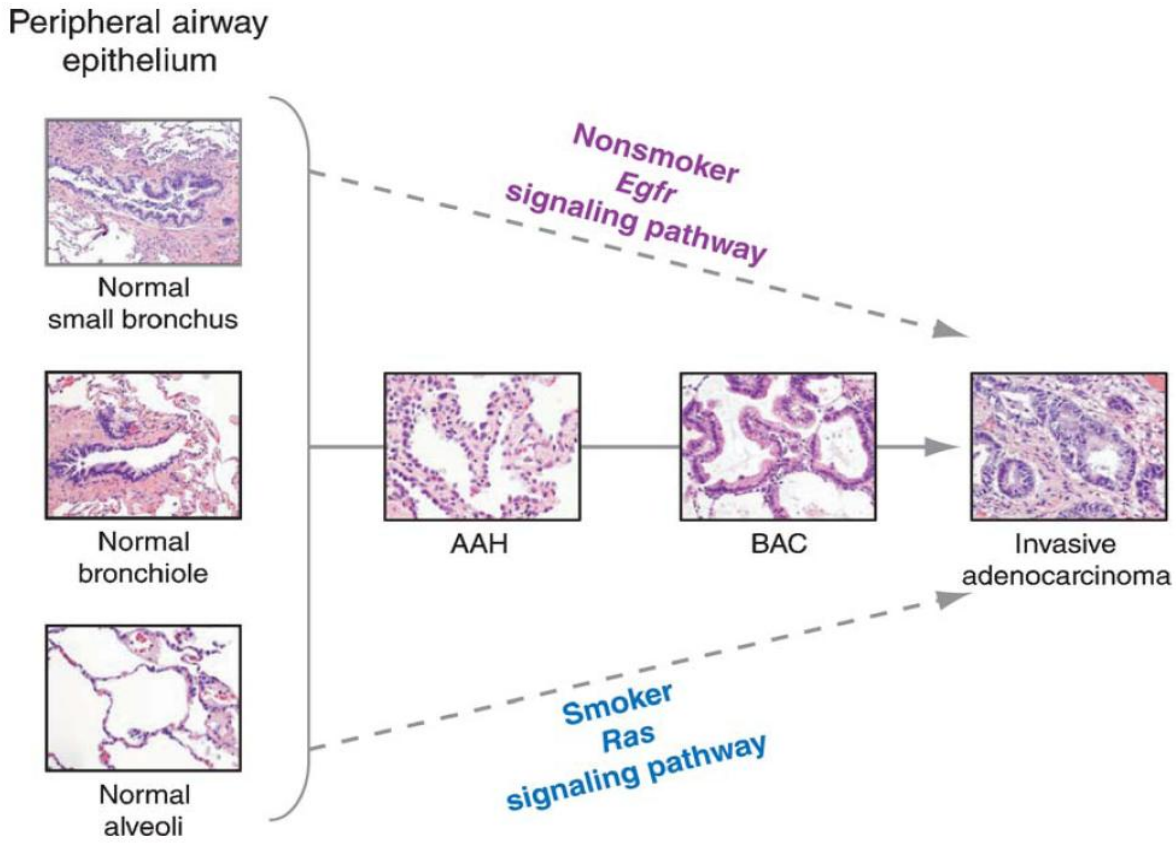
Ding L, et al. *Nature* 2008;455:1069–1075

Asyalı hiç sigara kullanmamış adenokarsinom olgularında



Sun Y, et al. *J Clin Oncol* 2010 28:4616–4620

EGFR ve KRAS mutasyonları “exclusive”



Küçük Hücre Dışı Akciğer Kanserinde EGFR ve KRAS Mutasyonu: Bir grup Türk hastada pilot çalışma (Bircan S ve arkadaşları)

- 14 Adenokarsinom (AK)
- 11 Skuamöz hücreli karsinom (SHK)
- 4 Adenokarsinom metastazı*EGFR Ekzon 19*

Adenokarsinom Olguları

EGFR %35.7 KRAS %21.4
EGFR 19 %21.4
EGFR 21 %21.4

Bircan ve arkadaşları

	Yaş	Cins	Doku	Evre	Sigara	EGFR 19	EGFR 21	KRAS
1	79	K	Trukat	IV	**Hayır**	*Wt*	**M**	*Wt*
2	61	E	WB	IV	**Hayır**	**M**	**M**	*Wt*
3	61	E	Lobek.	IIIA	İçiyor	*Wt*	*Wt*	*Wt*
4	81	E	Biyopsi	IV	**Hayır**	*Wt*	**M**	**M**
5	66	E	Biyopsi	IV	Bırakmış	**M**	*Wt*	**M**
6	61	E	Biyopsi	IV	İçiyor	*Wt*	*Wt*	*Wt*
7	67	E	Biyopsi	IIIB	İçiyor	*Wt*	*Wt*	*Wt*
8	85	K	Trukat	IV	**Hayır**	*Wt*	*Wt*	**M**
9	77	E	Trukat	II	Bırakmış	**M**	*Wt*	*Wt*
10	70	K	Trukat	Bilinmiyor	Bilinmiyor	*Wt*	*Wt*	*Wt*
11	52	E	Trukat	IV	İçiyor	*Wt*	*Wt*	*Wt*
12	28	E	Lobek.	IIB	Bilinmiyor	*Wt*	*Wt*	*Wt*
13	76	K	Biyopsi	IV	**Hayır**	*Wt*	*Wt*	*Wt*
14	57	E	Lobek.	IV	İçiyor	*Wt*	*Wt*	*Wt*

KÜÇÜK HÜCRELİ DIŞI AKCİĞER KANSERİNDE SIK GÖRÜLEN MUTASYONLARININ TEDAVİYE YANIT VE PROGNOZLA İLİŞKİSİ

Ankara Üniversitesi Tıp Fakültesi
Uzman. Dr. Mutlu Doğan
Prof Dr. Ahmet Demirkazık

Ocak 2004 – Kasım 2009
Retrospektif, doku tanısı / sitoloji (hücre bloğu) olan 513 hasta

•**DIŞLANANLAR:** erken evre, dış merkez tanı, sitoloji (hc blk-),

•tedavileri planlandıktan sonra tüm tedavileri baska merkezlerde alanlar

68

PATOLOG/SİTOPATOLOG TARAFINDAN DIŞLANANLAR: parafin bloklarda yeterli doku olmayanlar,

53

KESİTLERİNİN HAZIRLANMASI SIRASINDA DIŞLANANLAR:
parafin bloktan kesit hazırlanırken DNA izolasyonu için yeterli materyal elde edilemeyenler

DNA İZOLASYONU SIRASINDA DIŞLANANLAR: parafin blokta yeterli materyale sahip ancak yeterli DNA izolasyonu yapılamayanlar

52

SAĞKALIM VE EGFR-TKI YANITI DEĞERLENDİRMELERİ SIRASINDA DIŞLANANLAR (LOF):
Takipte kayıp hasta

42

41 hasta

•EGFR
•RAS
•BRAF

y	E K	pat	evre		PS	**mutasyon**	erlot	Erlot bas	yanıt	toksisite	DFS TTP	Erlotinib TTP	OS	Ex/sağ
70	K	adeno	Lok il			**EGFR ekzon 19 del**	1	2 (16 ay)	PR	G2 dokuntu	25	16	59	Ex
63	E	adeno	Lok il		0	**Braf V600E mut**	0	N/A	N/A	N/A	21 (Tr)	N/A	22	Sag
44	K	adeno	4		0	**EGFR ekzon 19 del**	LOF	LOF	LOF	LOF	LOF	LOF	LOF	LOF
65	E	adeno	Lok il		1	**EGFR ekzon 19 del**	1	2 (8 ay)	TR	G2 dokuntu	9	8	28	Sag
53	K	Musin adeno	4		1	**Kras kod 61 del**	1	2 (7 ay)	SD	G2 dokuntu G1 diyare	11	7	28	Ex
57	E	yassı	Lok il		1	**Kras kod 61 del**	0	N/A	N/A	N/A	9	N/A	19	ex

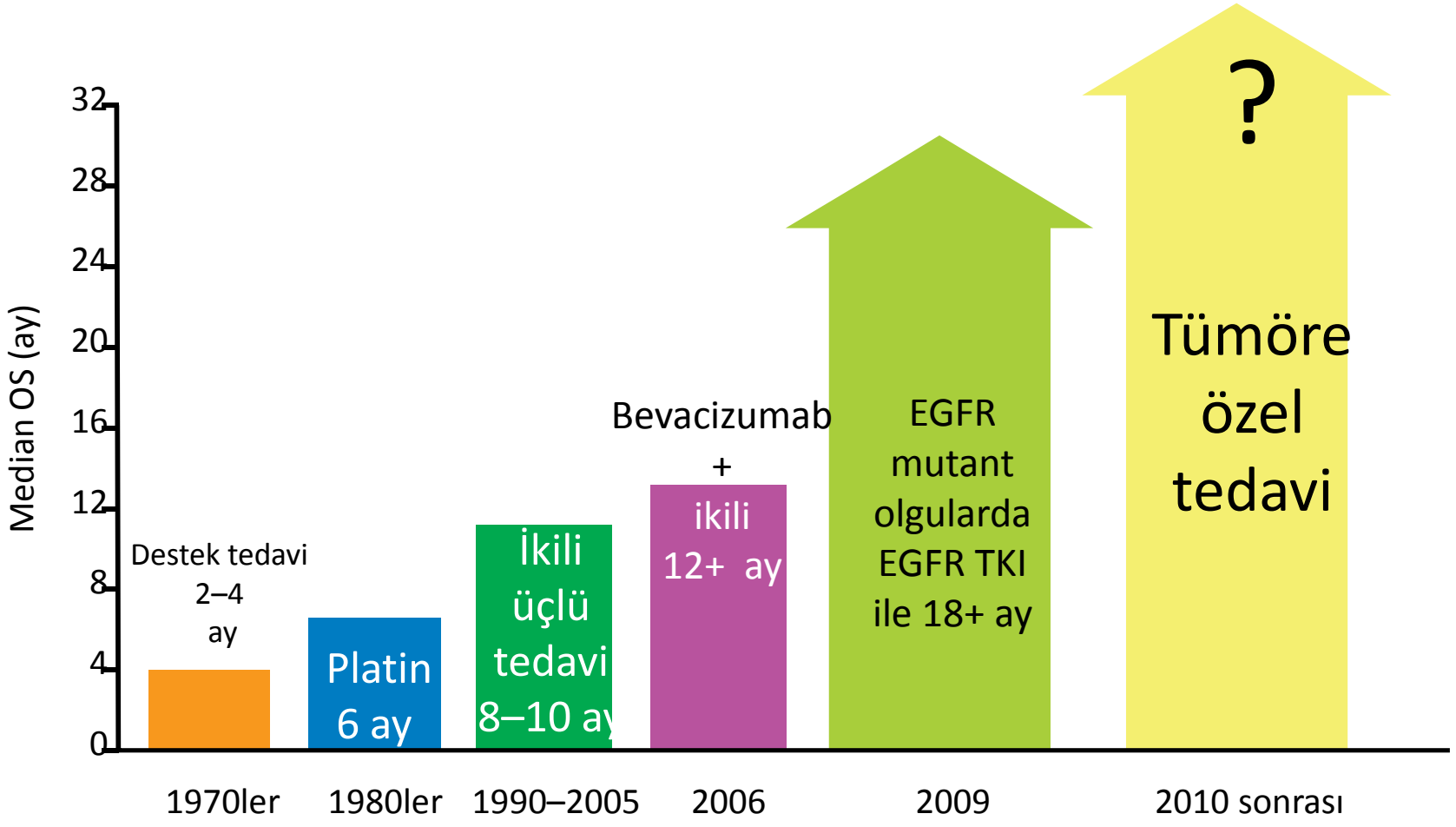
Gelecek nasıl olacak?

- Küçük hücreli dışı akciğer kanserinin tedavisi giderek tümöre özel bir yaklaşım halini almaktadır.
- Moleküler hedefleri saptamak ve bunlara yönelik ilaçları geliştirmek kişiselleştirilmiş tedavinin temelini oluşturmaktadır.
- Bugün için akciğer kanserinde en ön planda olan hedefler:
  - EGFR -KRAS
  - EML4/ALK -BRAF

Spesifik moleküler hedeflere yönelik tedavi protokolleri

- *EGFR*
  - Erlotinib + OSI 906 (IGF1R)
  - Erlotinib + MM 121 (HER3)
- Pan-HER inhibitors
  - Dacomitinib
  - Afatinib
- *KRAS*
  - Tivantinib + erlotinib
- *MET* amplification
  - Crizotinib
- *EML4-ALK*
  - Crizotinib
- *MEK1*
  - GSK1120212
- *BRAF (V600E)*
  - GSK2118434
- *BRAF (not V600E)*
  - GSK1120212
- *HER2*
  - Trastuzumab
- *PIK3CA*
  - BKM120

Akciğer kanserinde sağkalımda uzama



Patolog ne yapmalı?- 1

- HE kesitler ile verilmiş KHDK tanısı artık yeterli değildir.
- Tanı immünhistokimya kullanılarak mümkün olduğunca spesifiye edilmelidir.
- Net morfolojik bulgu içeren olgular dışındaki olgularda immünhistokimya kullanmak tanısal doğruluğu artıracaktır.

Galiba adeno, galiba yassı diyorsanız:
İHK' ya ihtiyacınız var demektir

IHK

Adeno

- TTF1
- Napsin
- CK7
- Sulfaktan

Skuamöz

- CK5/6
- P63
- Desmokollin

•Gerekli olduğu durumlarda NE markerlar

•Metastazı ekarte etmeye yönelik markerlar

Patolog ne yapmalı?- 2

- Bu dokunun özgürce harcanabileceği anlamına gelmez:
  - Aksine doku mümkün olan en pinti biçimde kullanılmalıdır.
  - Sıvılardan ve aspirasyonlardan her durumda hücre bloğu hazırlanmasına çalışılmalıdır

•Çünkü bu materyal muhtemelen hastanın tedavisini yönlendirecek olan tek materyal olacaktır.

•Moleküler testler için kullanılacaktır

Patolog ne yapmalı?-3

- Yapılacak moleküler testlerin duyarlılığını artırmak ve false negatifleri önlemek için patolog örnek içerisindeki tümör miktarını artırmaya çalışmalıdır.
  - Makrodisseksiyon