DM Seminar

ALK gene rearrangements & ALK-targeted therapy in NSCLC

Dr Sarat

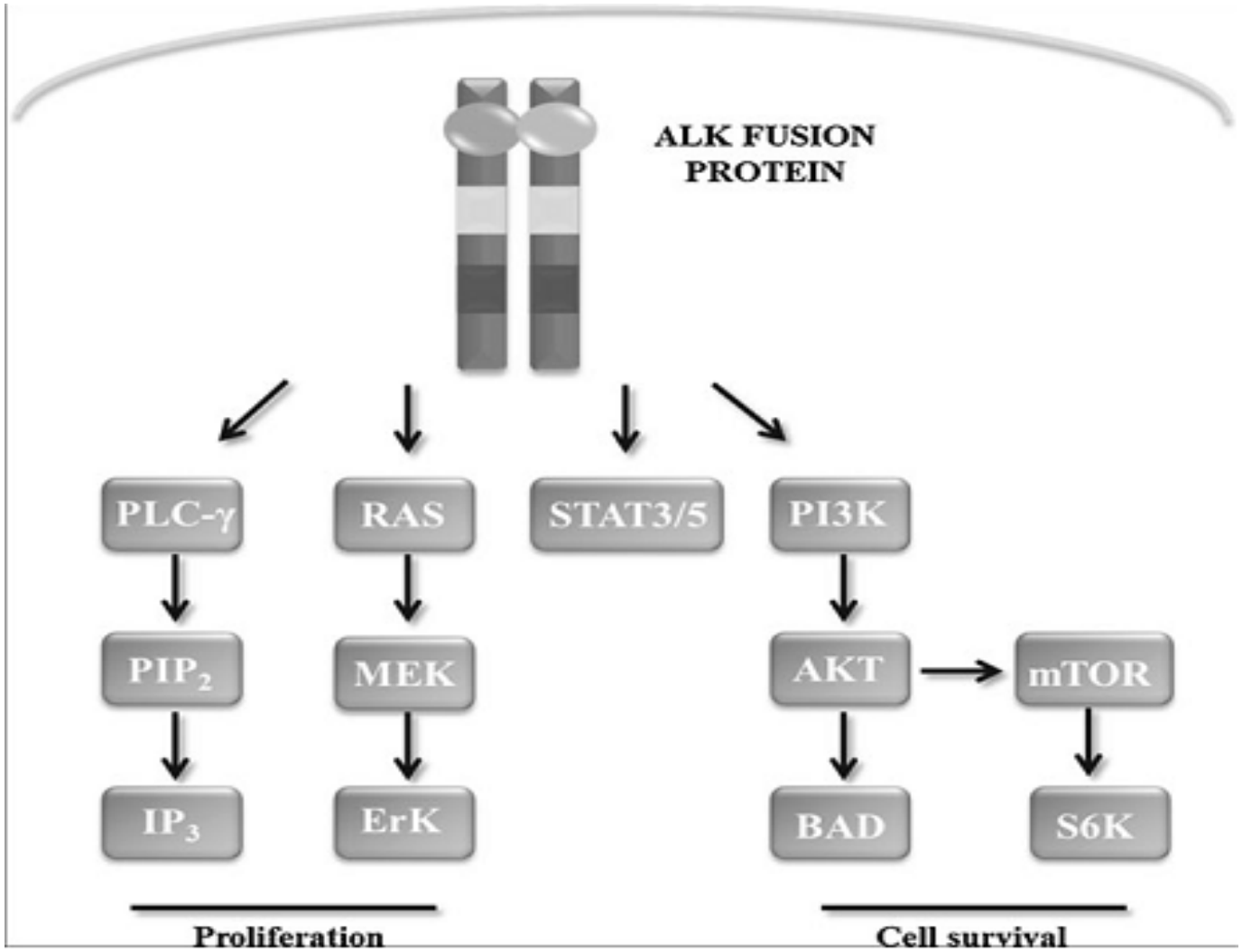
Introduction

- Discovery of activating mutations in kinase domain of epidermal growth factor receptor (EGFR) opened a new era of targeted therapy in NSCLC
- Soda (2007)identified a fusion gene between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) genes
- Inversion in short arm of chromosome 2 resulted in ligation of EML4 and ALK,to form a fusion protein consisting of the amino-terminal portion of ELM4 and the intracellular region of the protein tyrosine kinase ALK
- The coiled-coil domain within this portion of ELM4 mediated constitutive dimerization & activation of ELM4–ALK, resulting in oncogenic activity

ALK rearrangement in NSCLC

- ALK identified in 1994 in anaplastic large-cell lymphoma (ALCL) with t(2;5) chromosomal translocation as a fusion protein to nucleophosmin (NPM)
- A member of insulin receptor tyrosine kinases
- EML4 essential for formation of microtubules & its binding protein
- Closely located genes on short arm of chromosome 2 (2p21 & 2p23, resp)
- The fusion gene joining exons 1–13 of EML4 to exons 20–29 of ALK
- The EML4–ALK protein contained amino-terminal half of EML4, and the intracellular catalytic domain of ALK
- This dimerization induces aberrant activation of down-stream signaling involved in inhibition of apoptosis & promotion of cell proliferation

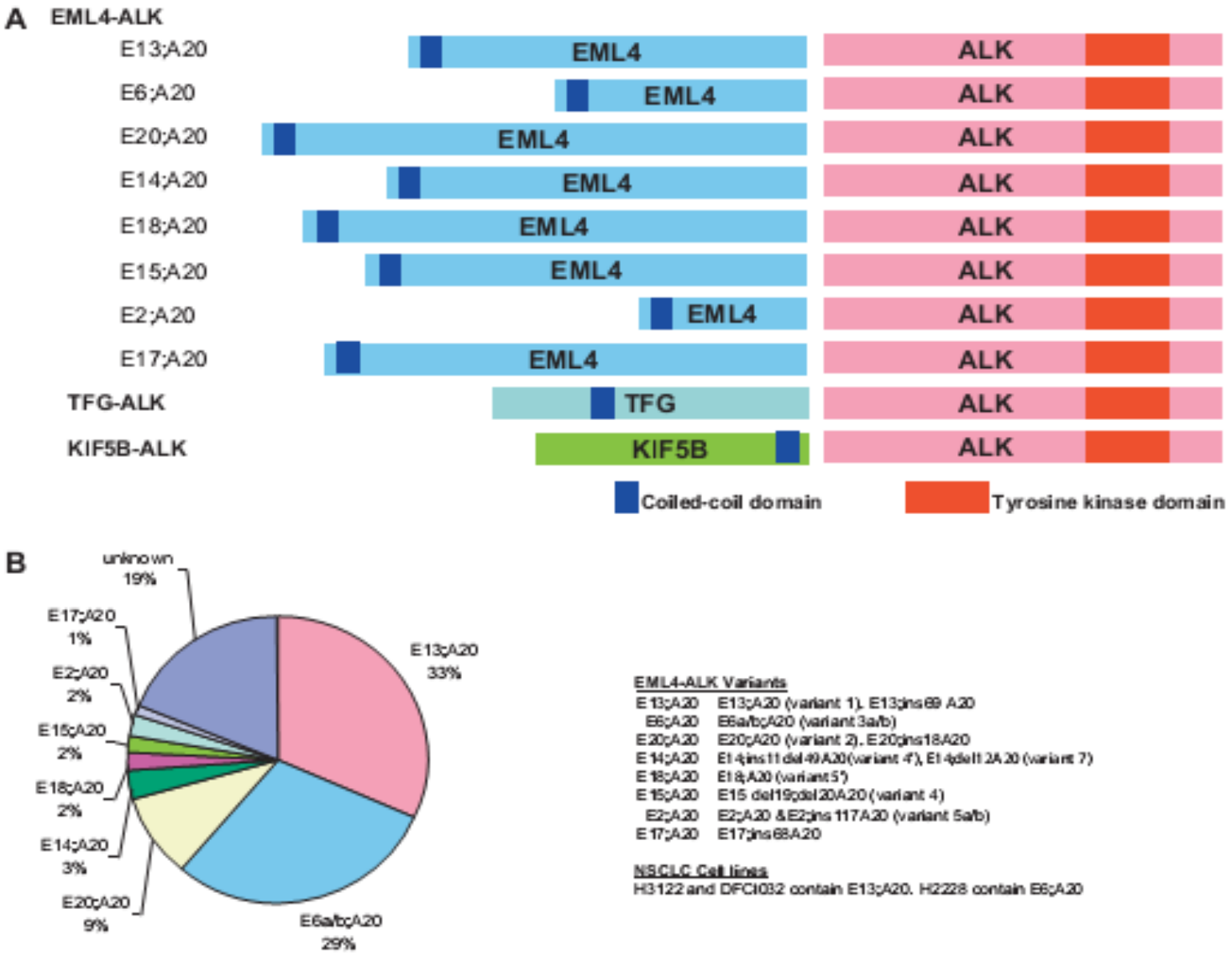
ALK downstream signaling



Targ Oncol jan 2013

VARIANTS OF ALK FUSION

- At least 11 variants reported and most of them are oncogenic
- Common variants are 1 (detected in 33% of NSCLC patients) (E13;A20) and 3a/b (29 %) (E6a/b;A20)
- All encode same intracellular tyrosine kinase domain of ALK, but contain different truncations of EML4 (its coiled-coil domain necessary and sufficient for the transforming activity of EML4–ALK)
- EML4 is not the exclusive fusion partner with ALK in NSCLC
- TFG-ALK & KIF5B-ALK complicates clinical detection of ALK-translocations



Different variants of EML4-ALK and non-EML4 fusion partners.
(A) The nomenclature refers to the exon in EML4 translocated to the exon in ALK.
(B) The most common variants are E13;A20 (variant 1) and E6a/b; A20 (variant 3)

EUROPEAN JOURNAL OF CANCER 46 (2010)

Methods of detection for ALK fusion gene

- Break-apart Fluorescence in situ hybridization (FISH) is the recommended method(gold standard)) for detecting ALK gene rearrangement (FDA)
- IHC, fluorescence in situ hybridization (FISH), and reverse transcriptase-polymerase chain reaction (RT-PCR)--each has strengths and weaknesses
- Because of cost and ease of performance tumors for IHC may be done to screen patients--score of 1 or 2 considered for confirmatory FISH for ALK

Test	Advantages	Disadvantages
Break-apart FISH	Can detect any rearrangement	Cost
	Performed on FFPE tissue	Expertise required
	Used clinically in crizotinib trials	Often difficult to interpret
CISH	Cost	Expertise required
	Performed on FFPE tissue	Often difficult to interpret
	Simultaneous histology evaluation	
Reverse transcriptase PCR	Needs minimal material	Will not identify new fusions
	Can identify fusion partners	RNA degradation
		Possibility of contamination
IHC	Cost	Low-level ALK expression
	Can be performed in any laboratory	No preferred antibody as yet
	Performed on FFPE tissues	

Abbreviations: FFPE, formalin-fixed paraffin-embedded; IHC, immunohistochemistry.

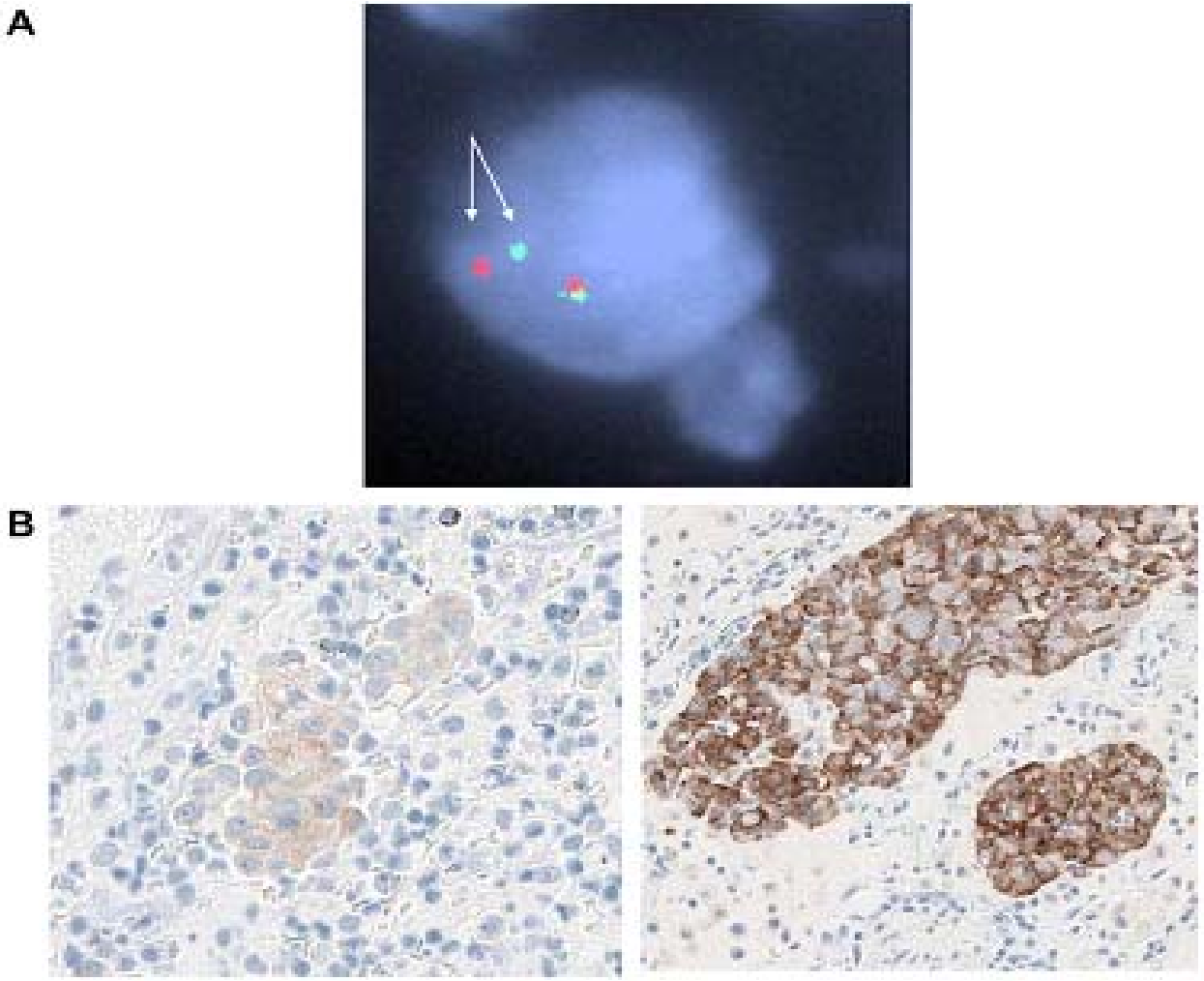
Methods to diagnose ALK rearrangements

Clin Cancer Res; July 15, 2012

Item	Estimated unit cost	Effectiveness relative to FISH (%)
Validated FISH	$1400	100
Validated RT–PCR	$875	70
Validated IHC assay (3+ cutpoint only)	$600	80

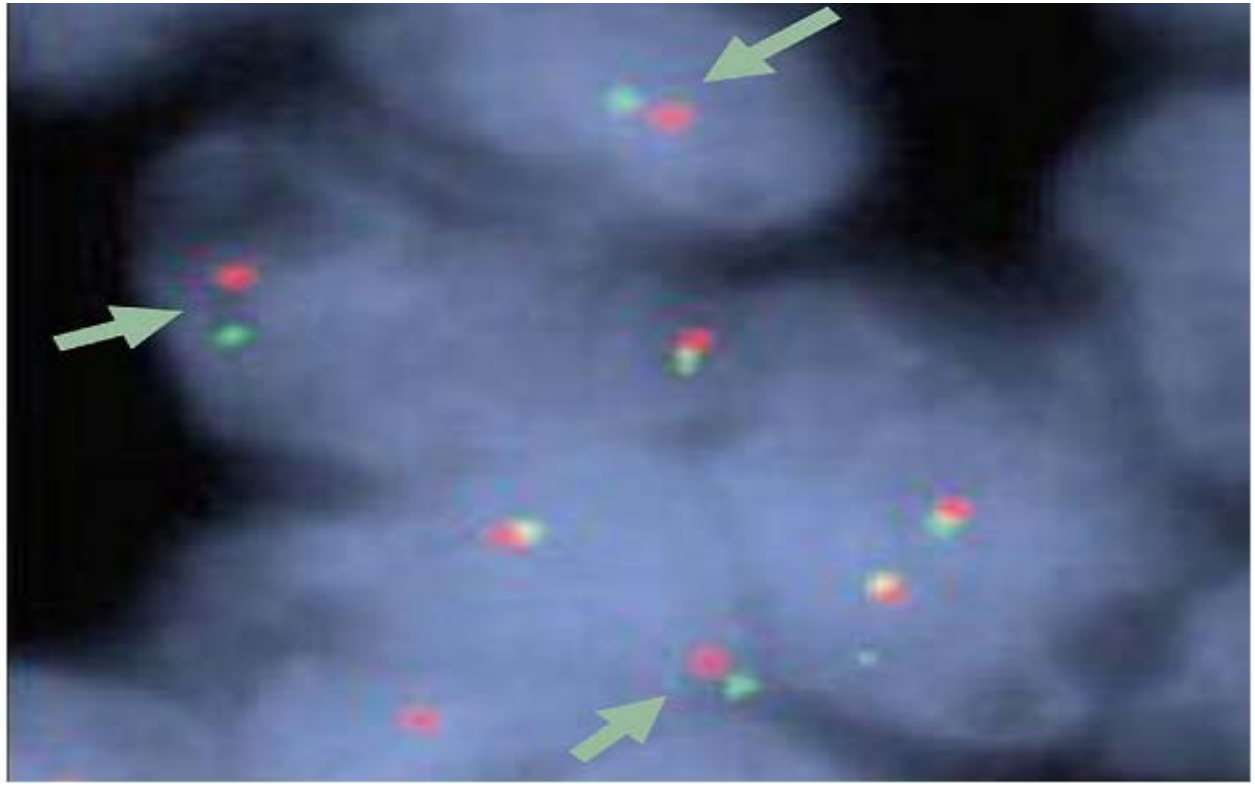
Costs associated with different screening tests and their ability to detect true positives with 100% specificity(anaplastic lymphoma kinase-estimated example)

British Journal of Cancer (2012)



(A) FISH analysis using the ALK break apart probe.Arrows depict split signals indicative of a chromosome 2 inversion. Tumour is heterozygous – signals remain together on other allele. (B) IHC analysis for ALK using the D5F3 (Cell Signalling Technology) antibody. Shown are examples of low (left) and high (right) ALK expressing tumours

EUROPEAN JOURNALOFCANCER 46 (2010)



Break Apart FISH Probe kit (Abbott Molecular, Abbott Park, IL, U.S.A.)
A red & green probe are hybridized to region flanking ALK translocation breakpoint
Probes separated by an intervening fusion of translocated fragment (eg. EML4)
That intervening fusion can be clearly seen here in several cells (arrows)
In normal allele,they are not separated,may be yellow (artefact of visual overlap)
Positive if ≥15% of ≥ 50 cell nuclei demonstrate split signal or isolated red signal

Current Oncology June 2012

Prevalence of ALK fusion genes in NSCLC

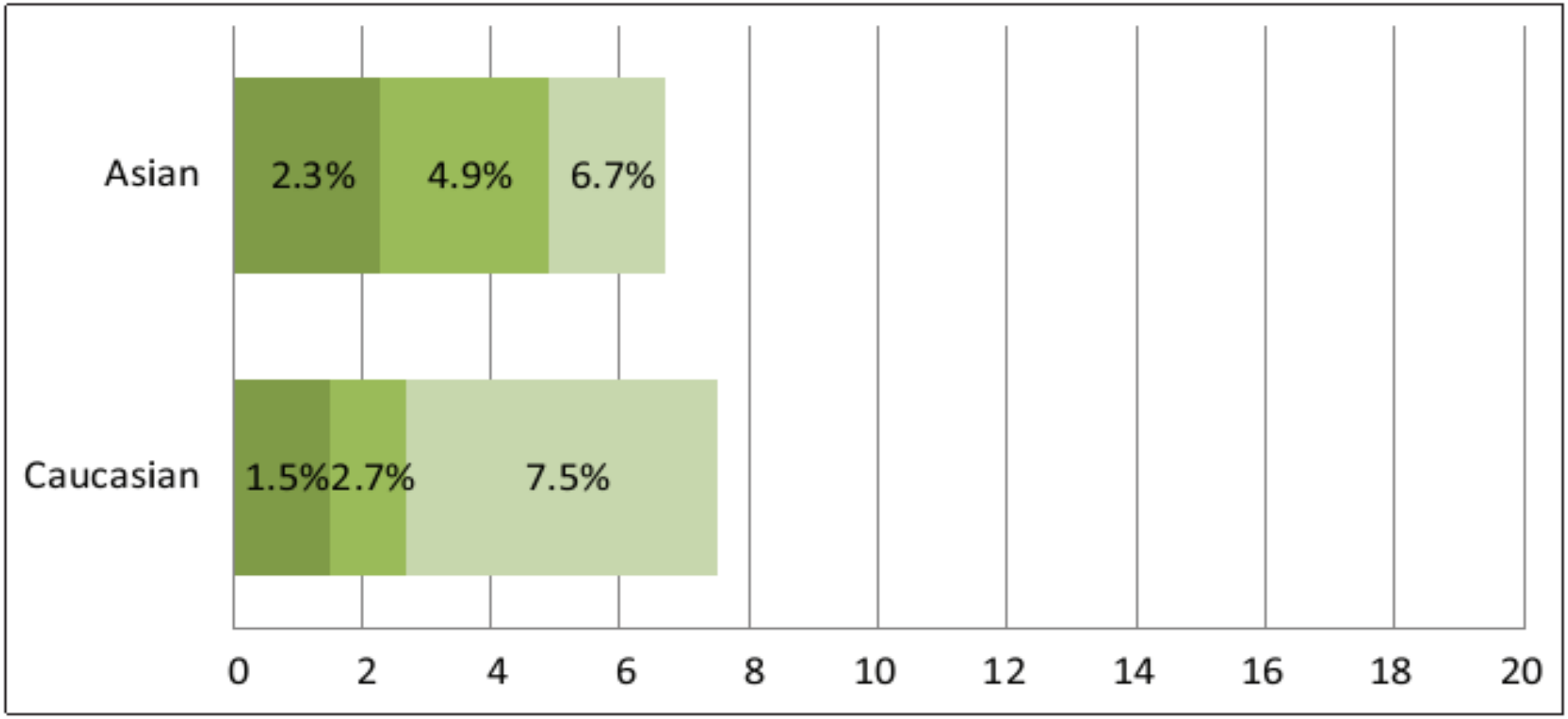
- First screen for EML4–ALK(Soda et al 2007), using RT-PCR in 75 patients of NSCLC yielded 5 cases of fusion genes, with a frequency of 6.7 %
- In subsequent studies,it is found in about 1.6–11.6 % of NSCLC in unselected patient populations
- After adjustment for sample size, enrichment prior to preselection, screening methods, and ethnic differences, true incidence closest to 2–7%

Author	Method of Testing	Population of Origin	ALK Gene Rearrangements Identified	Total Number of NSCLC Tumors Tested	Percentage
Soda et al.[2]	RT-PCR	Japan	5	75	6.7
Rikova et al.[11]	RT-PCR	China	4[a]	103	3.9
Shinmura et al.[48]	RT-PCR	Japan	2	77	2.6
Perner et al.[46]	FISH	Switzerland, USA	16	603	2.7
Inamura et al.[47]	RT-PCR	Japan	5	200	2.5
Koivunen et al.[7]	FISH	USA (138), Korea (167)	8	305	2.6
Takeuchi et al.[5]	RT-PCR	Japan	11	253	4.3
Wong et al.[9]	RT-PCR	China	13	266	4.9
Boland et al.[41]	IHC, FISH	USA	6	335	1.9
Martelli et al.[42][b]	RT-PCR	Italy, Spain	9	120	7.5
Rodig et al.[44][c]	IHC, FISH	USA	1	227	0.4
Shaw et al.[45][d]	FISH	USA	19	141	13.5
Takeuchi et al.[8]	IHC, RT-PCR	Japan	8[e]	130	6.2
Total			107	2835	3.8

Frequency of ALK Gene Rearrangements in NSCLC

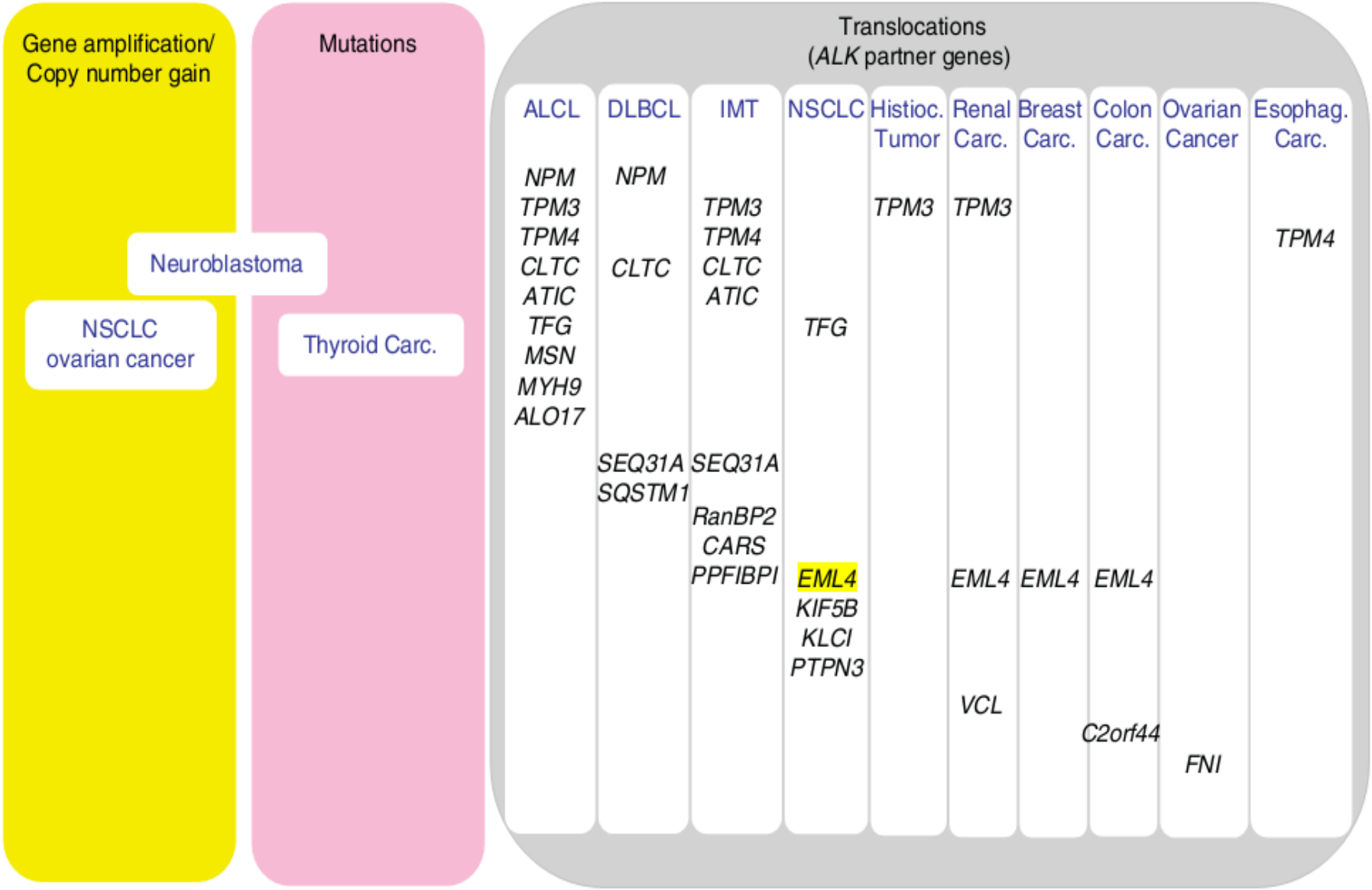
a-Includes one tumor with TRG-ALK fusion.
b-542 patients who had testing by IHC only are not included.
c-Patients in the original report that are described in another series are excluded.
d-Patients tested were preselected for factors associated with EGFR mutation positivity, enriching the tested population for factors that included adenocarcinomas and low/never smoking status.
e-Includes one tumor with KIF5-ALK fusion

J Thorac Oncol.2009;4: 1450–1454



Spectrum of EML4-ALK oncogenic driver fusions among different racial groups with NSCLC.
The different color shades represent EML4-AL Krates reported by different studies.
Data among human populations other than white and Asian are lacking thus far

Genes & Cancer/ vol 3 no 7-8 (2012)

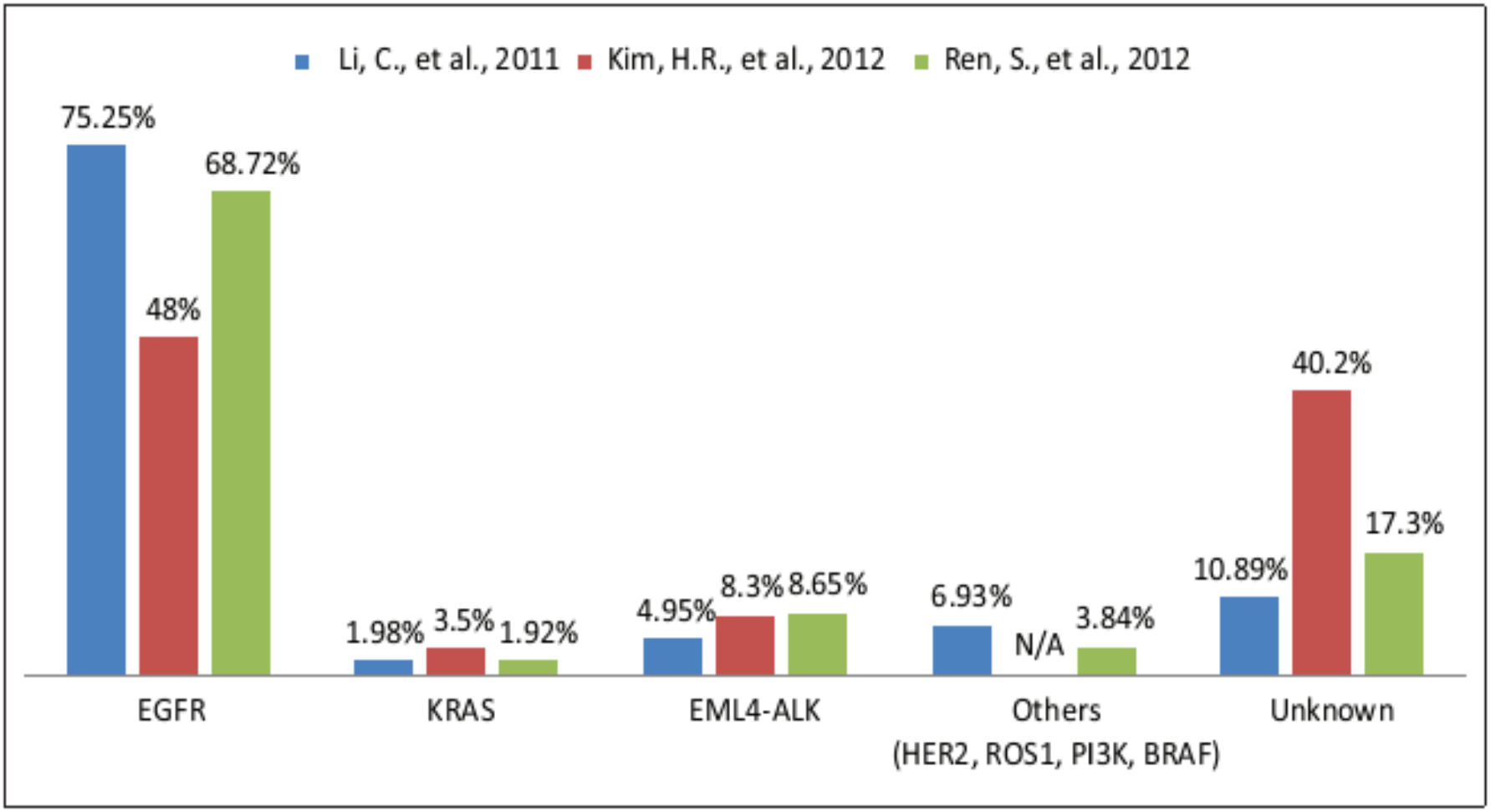


ALK abnormalities in tumors

Expert Opin. Ther. Targets(2012) 16(11)

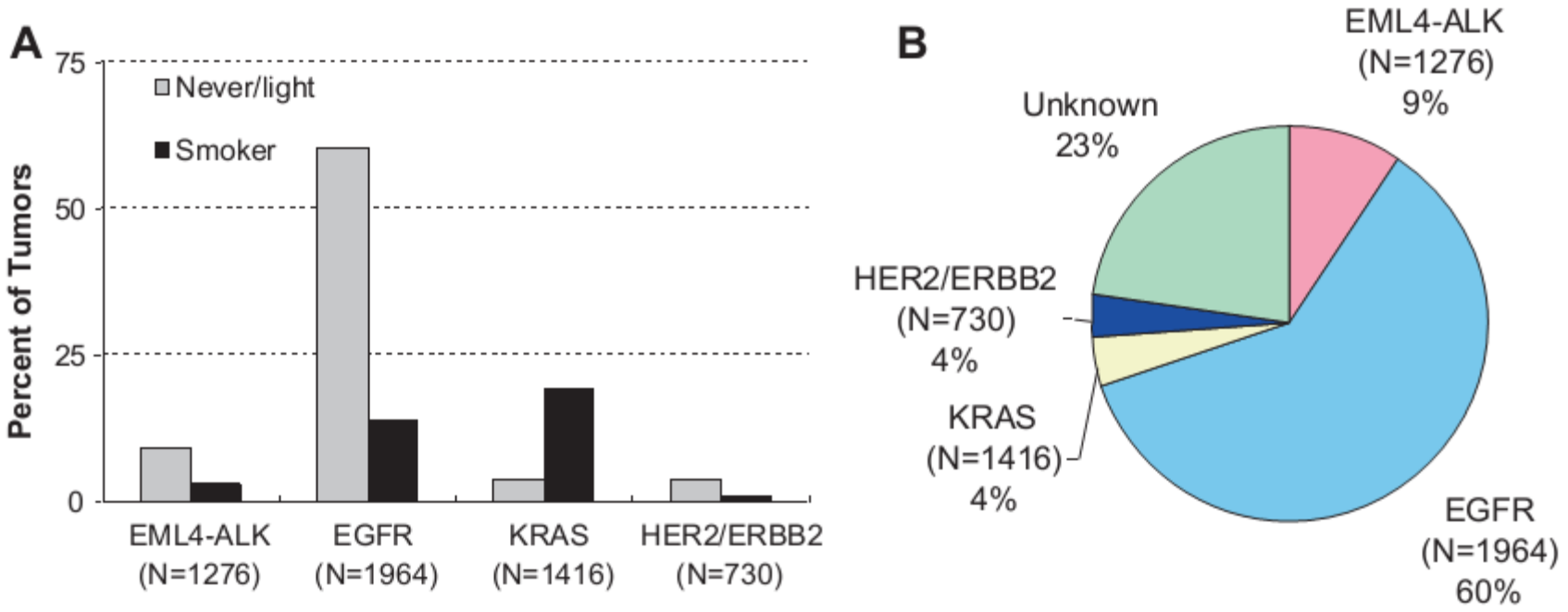
Clinicopathologic features associated with EML4–ALK NSCLC

- Pts with ALK fusion gene occur more in
  - adenocarcinoma histology , rarely (<1 %) in squamous cell carcinoma
  -tend to occur in light (≤10 pack years) or never smokers
  -younger age
  - no gender predilection
  -mutually exclusive with EGFR and KRAS mutations
  -strong positive relationship with TTF-1 protein expression
  - predominantly the signet ring cell subtype(caucasian)
  -



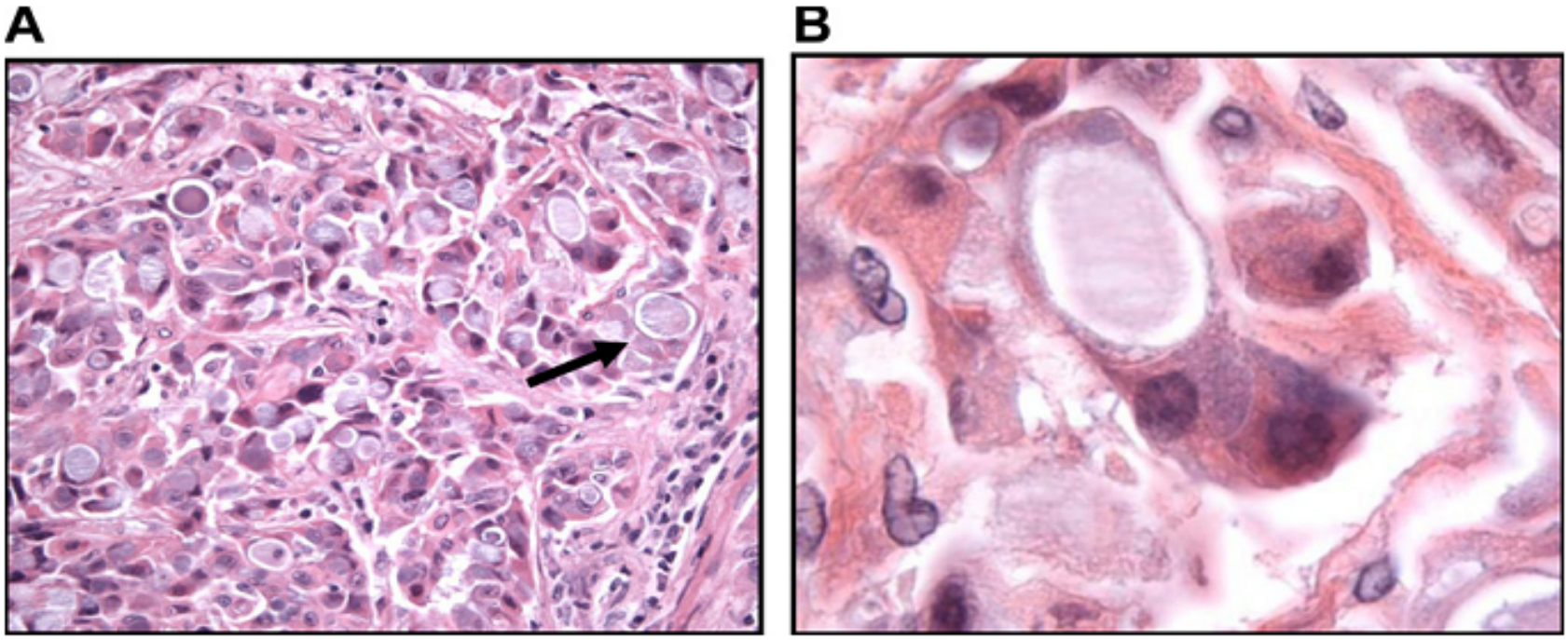
Spectrum of oncogenic driver mutations in Asian never smokers with lung adenocarcinoma. The data were collected from 3 different studies to represent the mutational frequency range of different genes among the same population

Genes & Cancer/ vol 3 no 7-8 (2012)



Frequency of somatic genetic changes in NSCLC.
(A) EML4-ALK translocations,EGFR, KRAS and ERBB2 mutation frequencies broken down by smoking history
(B) Frequency of somatic mutations in never or former light (<10 pack years; Quit >1 year ago) smokers
The somewhat higher EGFR mutation frequency is likely a reflection of the predominance of studies from East Asian countries
The EGFR mutation frequency in Caucasian never/former light smokers is 35%

EUROPEAN JOURNALOFCANCER 46 (2010)



Pathologic characteristics ofEML4-ALKNSCLC.EML4-ALKNSCLC demonstrates a signet cell features (arrow). (A) 40·magnification, (B) 1000·magnification

EUROPEAN JOURNALOFCANCER 46 (2010)

ALK inhibitors: role in NSCLC

- Crizotinib(Crizalk,Pfizer India):

  -Crizotinib (PF-02341066) is the first in human ALK inhibitor developed

  - A derivate of aminopyridine,developed as orally bioavailable, ATP-competitive small molecule inhibitor of mesenchymal epithelial transition growth factor (c-MET), and hepatocyte growth factor receptor

  -Inhibits ALK phosphorylation & signal transduction with G1–S phase cell cycle arrest and induction of apoptosis in NPM–ALK-positive ALCL cells

Crizotinib

- ALK-positive advanced NSCLC, ≥ 60 % of patients had objective response (ORR), responses rapid (median 7.9 weeks) & durable (median 49.1 wks)

  -The greatest OR were noted in treatment-naive patients, those with the lowest performance status score, and Asian patients

--Showed in vitro activity and early evidence of clinical activity in NSCLC with chromosomal rearrangements of the ROS1 receptor tyrosine kinase gene detected by FISH assay

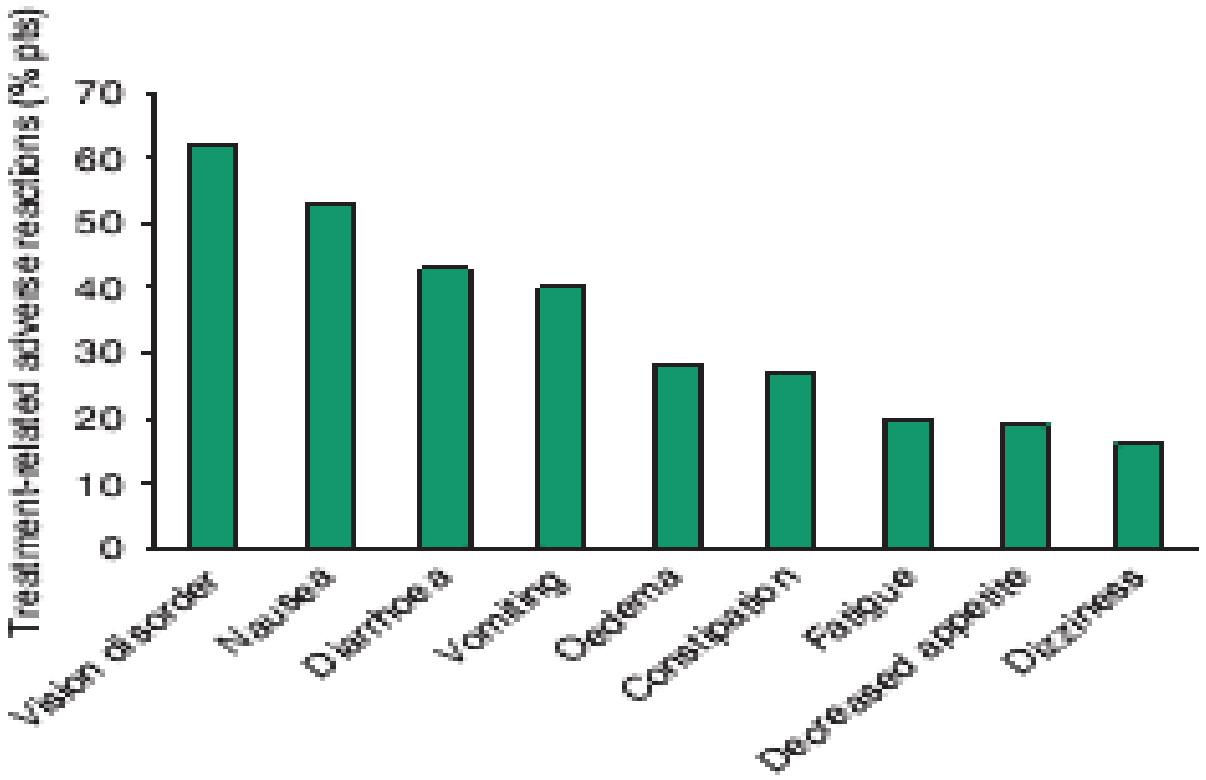
Features and properties of crizotinib (Xalkori®)	
Indication	
Anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC) [as detected by an FDA-approved test, according to the US prescribing information]	
Mechanism of action	
Inhibitor of receptor tyrosine kinases (including ALK and mesenchymal epithelial growth factor/hepatocyte growth factor receptor)	
Dosage and administration	
Recommended dose	250 mg
Route of administration	Oral
Frequency of administration	Twice daily with or without food
Dose interruption or reduction (based on individual tolerability)	200 mg twice daily; then 250 mg once daily if further dose reduction is still required
Pharmacokinetic parameters at steady state after 250 mg twice daily for 15 days in patients with NSCLC	
Median time to peak plasma concentration (single dose)	4–6 h
Mean plasma terminal elimination half-life (single dose)	42 h
Time to reach steady state	<15 d
Most common treatment-related adverse reactions (≥25% of crizotinib recipients in phase I and II trials)	
Vision disorder, nausea, diarrhoea, vomiting, oedema, constipation	

Drugs 2012; 72 (1)

Drug	Crizotinib (PF-02341066)
Phase	Launched
Indication	Locally advanced or metastatic NSCLC that is ALK-positive
Mechanism of action	Competitive ATP tyrosine kinase inhibitor
Route of administration	Oral
Chemical formula	$C_{21}H_{22}Cl_2FN_5O$
Pivotal trials	Ongoing Phase III studies in first-line and second-line metastatic and recurrent ALK-positive NSCLC

Drug summary:Crizotinib

Expert Opin. Pharmacother.(2012) 13(8)



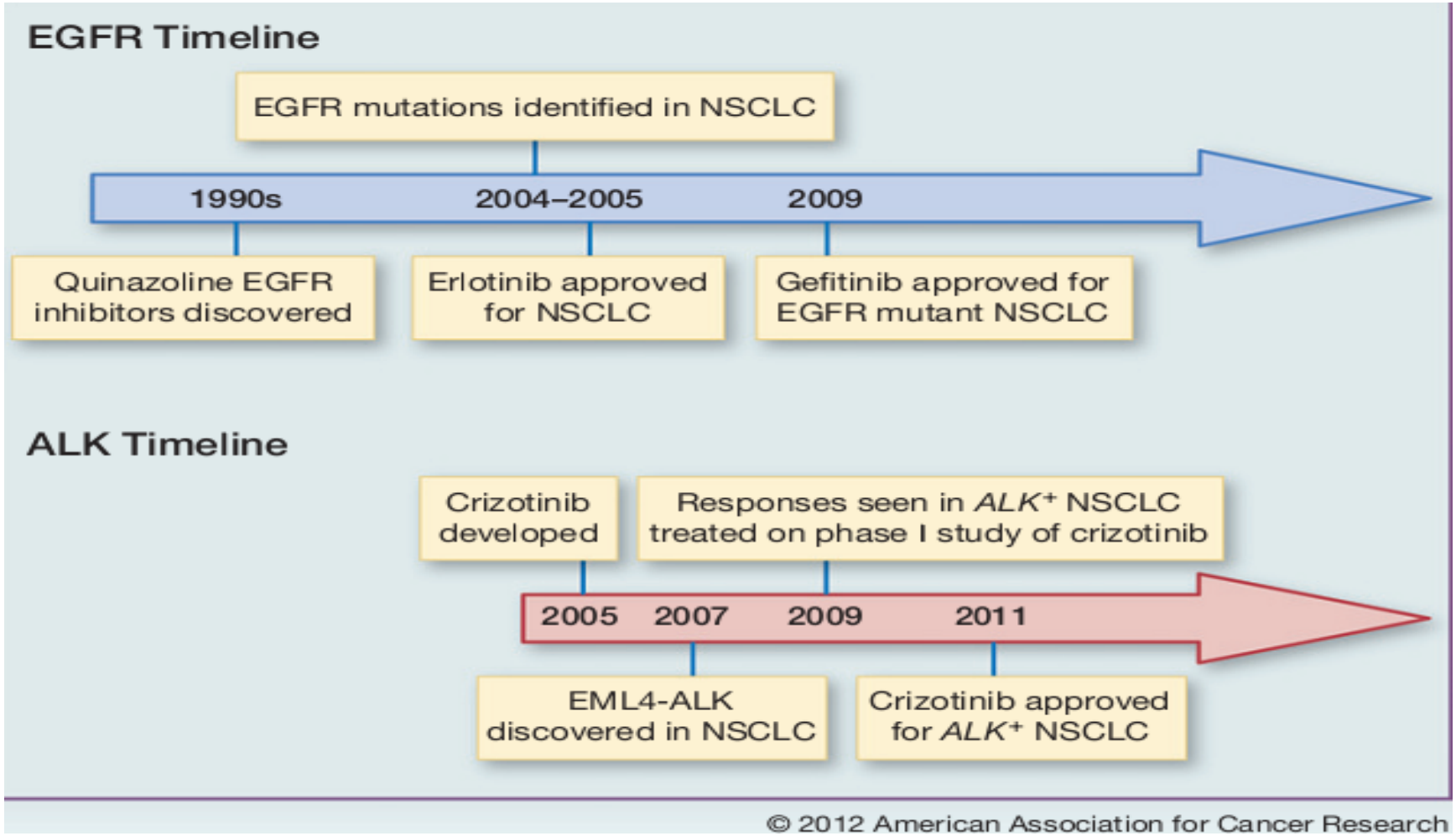
Tolerability profile of crizotinib. Treatment-related adverse reactions (all grades) occurring in 15%of 255 patients with anaplastic lymphoma kinase-positive, locally advanced or metastatic,non-small cell lung cancer treated with oral crizotinib 250 mg twice daily in a phase I trial and a phase II open-label trial.

Drugs 2012; 72 (1)

	Kwak et al.	Crino et al.
Sample size	82 patients	136 patients
Response rate	57% (47 of 82 patients)	83% (63 of 133 patients)
PFS	72% estimated 6-month PFS	73.7% disease control rate at 12 weeks
Salient toxicities	Nausea/vomiting, visual disturbance	Nausea, vomiting, diarrhea, visual disturbance

Clinical data with crizotinib

Curr Oncol Rep (2012) 14

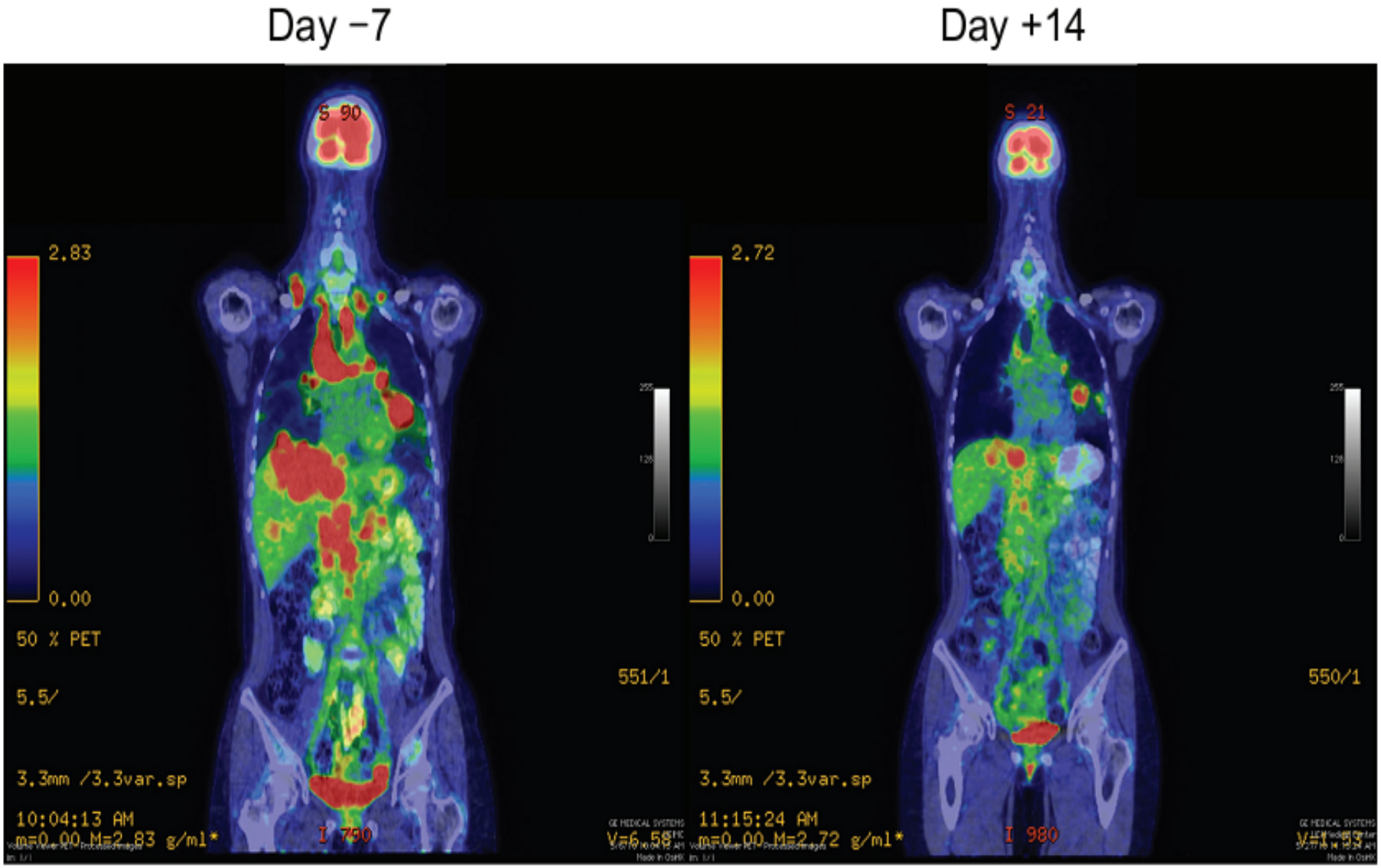


Timeline for approval of kinase inhibitors for molecular subsets of NSCLC. EGFR inhibitors were approved initially for a broader population and subsequently forEGFR-mutant patients with NSCLC.In contrast, clinical development and approval of crizotinib have been limited to ALK-positive patients withNSCLC

Clin Cancer Res; July 15, 2012

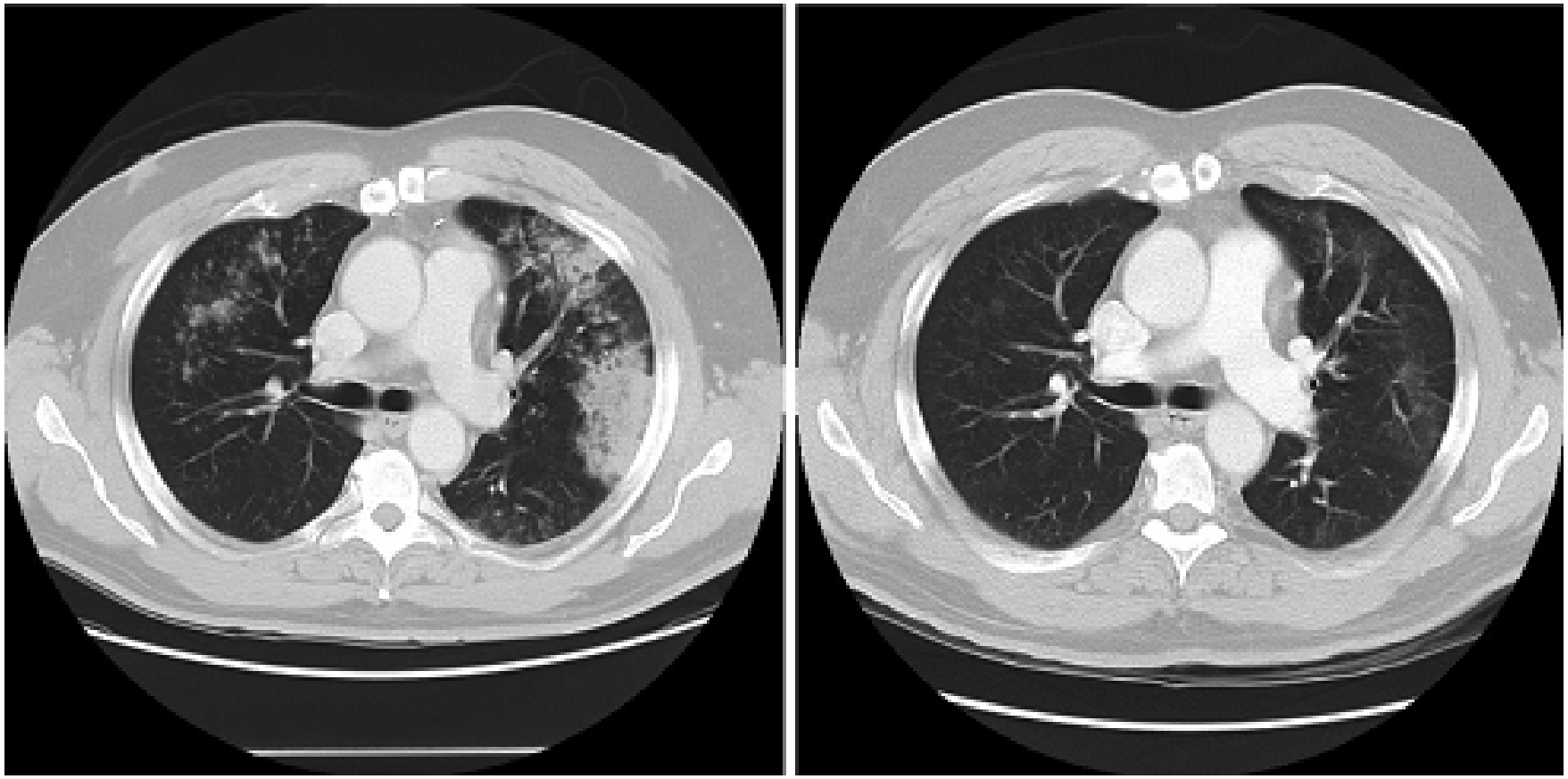
Patient characteristics (n = 255)	
Median (range) age (years)	51 (21–82)
Gender (%)	
Male	123 (48)
Female	133 (52)
Eastern Cooperative Oncology Group performance status (%)	
0	78 (30)
1	137 (54)
2–3	40 (16)
Race (%)	
Caucasian	161 (63)
African-American	8 (3)
Asian	77 (30)
Other	9 (4)
Smoking status (%)	
Never-smoker	178 (70)
Former smoker	71 (28)
Current smoker	6 (2)
Histology (%)	
Adenocarcinoma	246 (96.5)
Squamous cell carcinoma	2 (1)
Large cell carcinoma	1 (0.5)
Adenosquamous carcinoma	3 (1)
Other	3 (1)
Disease stage (%)	
Locally advanced	14 (5.5)
Metastatic	241 (94.5)
Number of prior regimens of systemic therapy (%)	
0	15 (6)
1	47 (18)
2	57 (22)
3	54 (21)
≥4	82 (32)

Clinicopathologic characteristics of 255 patients with ALK-rearranged NSCLC, the data for whom were used for conditional approval of crizotinib



Dramatic response to crizotinib in a ALK-rearranged NSCLC patient.

Drug Design, Development and Therapy 2011:5



Response of ALK-rearranged NSCLC after 2 months of crizotinib

Drug Design, Development and Therapy 2011:5

Ongoing Crizotinib trials

- PROFILE 1005 –Phase II trial,open label single arm in adv NSCLC

  --Preliminary report of 261/901

  -- majority had adenocarcinoma histology

  --median age 52 years,

  -- >95 % of the patients were never or former smokers

  --53 % of the patients had received ≥3 prior therapies

  --Crizotinib demonstrated an ORR of 59.8 %

  --responses within first 8 wks of treatment in 71 % patients

  --with a median time to response of 6.1 weeks

  --Median PFS was 8.1 months (95 % CI 6.8-9.7)

  -- AEs were gastrointestinal effects (nausea, vomiting, and diarrhea) and vision disorder (visual impairment, photopsia, vision blurred, vitreous floaters,photophobia, and diplopia),

  --grade≥3 AEs were reported in 25.6 % of patients neutropenia, increased alanine aminotransferase, fatigue

Ongoing Crizotinib trials

- PROFILE 1007 --first phase III, randomized, open-label study evaluated the efficacy and safety of crizotinib versus standard single-agent chemotherapy (pemetrexed or docetaxel)
  --347 EML4–ALK-positive adv NSCLC-pretreated patients
  --Crizotinib was superior to standard single-agent chemotherapy(docetaxel or pemetrexed) in terms of response and PFS (median 7.7 versus 3.0 months,P<0.0001)
  --no significant difference in OS between crizotinib and chemo-therapy, but interim analysis was immature
  -- AEs with crizotinib were diarrhea, nausea,vomiting, and
  --elevated transaminases, while nausea, fatigue,neutropenia, decreased appetite, alopecia were in pemetrexed/docetaxel
  --crizotinib is associated with significantly greater improvement from baseline in both lung cancer symptoms and QOL

- PROFILE 1014 -- ongoing phase III, randomized, open-label study
  --efficacy and safety of crizotinib versus pemetrexed/cisplatin or pemetrexed/carboplatin in previously untreated patients with NSCLC rearrangement at ALK gene locus
- The primary endpoint of this study is PFS
- Result by 2013 end

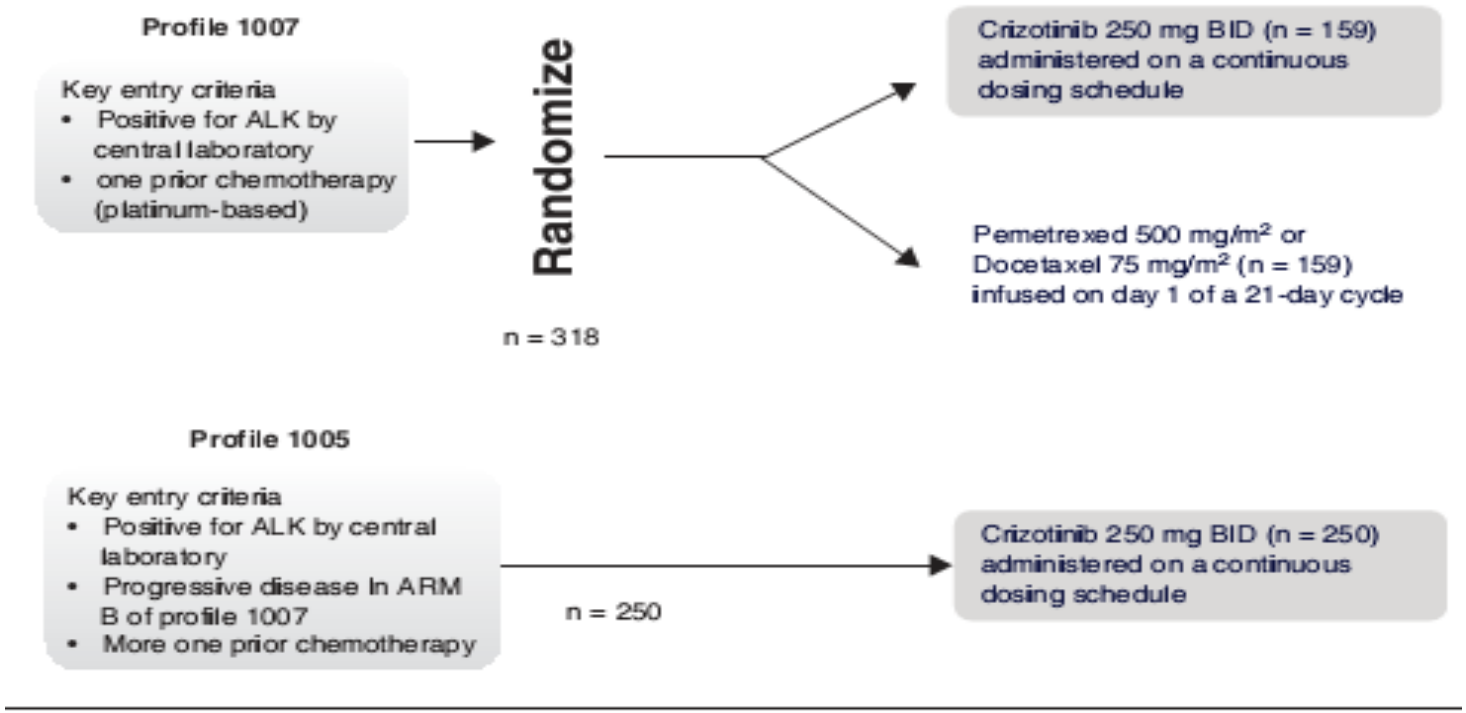


Figure 1. Ongoing trials investigating crizotinib in previously treated NSCLC patients.

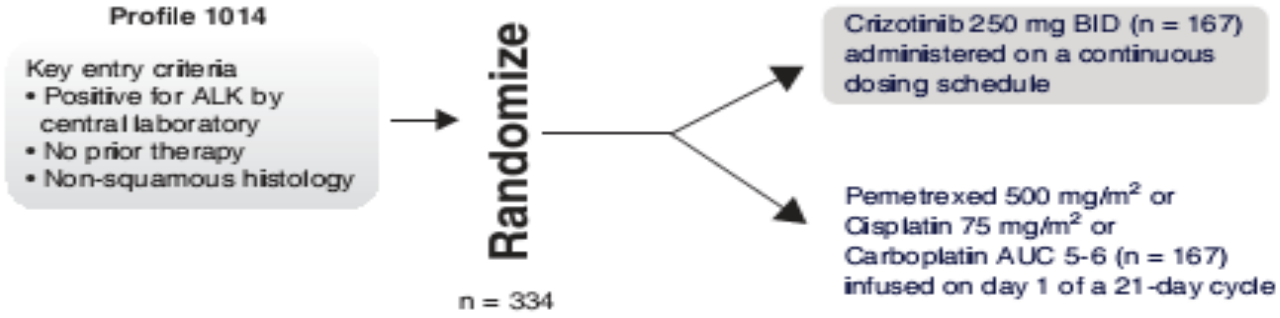


Figure 2. Ongoing trial investigating crizotinib as first-line therapy of NSCLC patients.

Expert Opin. Ther. Targets(2011) 16(Suppl.2)

Crizotinib problems:

Cost

Resistance-ALK dominant

-non ALK dominant

Crizotinib with Erlotinib

- Ongoing phase I/II clinical trial is evaluating the safety, efficacy, and pharmacokinetics of erlotinib with or without crizotinib
- erlotinib plus crizotinib at the MTD (erlotinib 100 mg QD plus crizotinib 150 mg BID) was well tolerated, with no unexpected AEs,
- showed signs of activity in a pretreated population (treated with one or two prior chemotherapy regimens and none previous MET-directed therapy) with advanced NSCLC

ESMO 2012 abstract

	Condition	End point	Combinations	Phase	Ref.
Crizotinib	Healthy	Bioavailability of liquid vs capsule formulation	-	I	NCT01297595
	Healthy	Bioavailability	-	I	NCT01168934
	Healthy	Effect of ketoconazole on pharmacokinetics	-	I	NCT01149785
	Healthy	Effect of rifampin on pharmacokinetics	-	I	NCT01147055
	Healthy	Food effect	-	I	NCT01154218
	Healthy	Safety and pharmacokinetics	-	I	NCT01250730
	Healthy	Absorption, metabolism and excretion	-	I	NCT01082380
	Healthy	Taste of liquid formulation	-	I	NCT01125904
	Renal impairment	Pharmacokinetics in subjects with renal impairment	-	I	NCT01419041
	ALK+ tumors except NSCLC	Safety and efficacy	-	I	NCT01121588
	RCC, glioblastoma, HCC	Safety and pharmacokinetics	VEGFR inhibitors	I	NCT01441388
	ALK+ or MET+sensitive tumor	Safety, pharmacokinetics and efficacy	-	I	NCT00585195
	ALCL, IMT, other	Efficacy	-	II	NCT01524926
	Brain tumors, ALCL	Efficacy	-	III	NCT00939770
	ALCL, NSCLC	Safety and efficacy	-	II	NCT01500824
	NSCLC	Safety and efficacy	Erlotinib	III	NCT00965731
	NSCLC	Safety and efficacy	PF-00299804	I	NCT01121575
	NSCLC	Efficacy vs pemetrexed or docetaxel	-	III	NCT00932893
	NSCLC	Efficacy	-	II	NCT00932451
	NSCLC	Determinants of acquired clinical resistance	-	nd	NCT01300429
	NSCLC	Bioavailability of powder-in-capsule vs immediate-release tablet	-	I	NCT00939731
	Non-squamous lung cancer	Efficacy vs pemetrexed + platinum	-	III	NCT01154140
	NSCLC	Safety, pharmacokinetics and efficacy	PF-00299804	I	NCT01441128
LDK378	ALK+ tumors	Safety and pharmacokinetics	-	I	NCT01283516
ASP3026	ALK+ or ROS+ tumor	Safety and pharmacokinetics	-	I	NCT01284192
AP26113	ALK+ tumors	Safety, pharmacokinetics and efficacy	-	I/II	NCT01449461
AF802	NSCLC	Safety, pharmacokinetics and efficacy	-	I/II	JapicCTI-101264

Current clinical trials evaluating ALK inhibitors in cancer

Company	Name	Target	Development status
Pfizer	Crizotinib (Xalkori®)	ALK and c-MET	Approved by FDA for the treatment of late-stage ALK-positive NSCLC in the USA Companion diagnostic kit 'ALK break apart FISH probe' for patient selection
Hoffmann-La-Roche/Chugai	AF-802	ALK	Phase I/II
Ariad Pharmaceuticals	AP-26113	ALK and EGFR	Phase I/II
Novartis	LDK-378	ALK	Phase I
Astellas	ASP-3026	ALK	Phase I
Xcovery	X-396	ALK	Preclinical
Amgen/TesaroBio	TSR-011	ALK	Preclinical
Nerviano medical sciences	NMS-E628	ALK	Preclinical
Teva	1. Cephalon-2 2. CEP-37440	1. ALK 2. ALK and FAK	Preclinical
Sareum		ALK and Aurora	Preclinical
PharmaDesign		ALK	Preclinical
Infinity Pharmaceuticals	Retaspimycin (IPI-504)	HSP-90	Phase II
Synta Pharmaceuticals	Ganetespib	HSP-90	Phase III

ALK inhibitors in various stages of development

Expert Opin. Ther. Targets(2012) 16(11)

Drug	Company
AP26113	Ariad Pharmaceuticals
LDK378	Novartis
AF802	Chugai Pharmaceuticals
ASP3026	Astellas
X-396	Xcovery
NMS-E628	Nerviano Medical Sciences
GSK1838705A	GlaxoSmithKline
CEP-28122	Cephalon

Cancer Genes in Lung Cancer: Racial Disparities: Are There Any?

Genes & Cancer
3(7-8) 467–480

DOI: 10.1177/1947601912465177
http://ganc.sagepub.com
SAGE

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Abstract

Cancer is now known as a disease of genomic alterations. Mutational analysis and genomics profiling in recent years have advanced the field of lung cancer genetics/genomics significantly. It is becoming more accepted now that the identification of genomic alterations in lung cancer can impact therapeutics, especially when the alterations represent "oncogenic drivers" in the processes of tumorigenesis and progression. In this review, we will highlight the key driver oncogenic gene mutations and fusions identified in lung cancer. The review will summarize and report the available demographic and clinicopathological data as well as molecular details behind various lung cancer gene alterations in the context of race. We hope to shed some light into the disparities in the incidence of various genetic mutations among lung cancer patients of different racial backgrounds. As molecularly targeted therapy continues to advance in lung cancer, racial differences in specific genetic/genomic alterations can have an important impact in the choices of therapeutics and in our understanding of the drug sensitivity/resistance profile. The most relevant genes in lung cancer described in this review include the following: *EGFR, KRAS, MET, LKB1, BRAF, PIK3CA, ALK, RET,* and *ROS1*. Commonly identified genetic/genomic

Characteristic	Genotype						P	
	ALK (n = 19)		*EGFR* (n = 31)		WT/WT (n = 91)			
	No.	%	No.	%	No.	%	*ALK* v *EGFR*	*ALK* v WT/WT
Age, years								
Median	52		66		64		≤ .001	.005
Range	29-76		36-90		29-87			
Sex								
Male	11	58	8	26	29	32	.036	.039
Female	8	42	23	74	62	68		
Smoking history								
Never smoker	14	74	21	68	24	26	.366	≤ .001
Light smoker	5	26	6	19	15	16		
Smoker	0	0	4	13	52	57		
Ethnicity								
Asian	0	0	2	6	7	8	.519	.602
Non-Asian	19	100	29	94	84	92		
Pathology								
Adeno	16	84	24	77	49	54	.380*	.696*
BAC†	2	11	7	23	32	35		
Adenosquamous	1	5	0	0	3	3		
Squamous	0	0	0	0	2	2		
Large cell/NOS	0	0	0	0	5	6		
Stage								
IA	2	11	2	6	10	11		
IB	0	0	1	3	10	11		
IIA	0	0	0	0	1	1		
IIB	0	0	0	0	0	0		
IIIA	0	0	2	6	3	3		
IIIB	0	0	0	0	4	4		
IV	17	89	26	84	53	58	.695‡	.051‡
Multifocal BAC	0	0	0	0	10	11		

Clinical Characteristics of Genotype-Specific Subsets of Patients With Non–Small-Cell Lung Cancer

J Clin Oncol 27:4247-4253

Analysis	Genotype		
	ALK	*EGFR*	WT/WT
ALK rearrangement			
Positive	19	0	0
Total	19	31	91
EGFR mutation			
Positive	0	31	0
Total	19	31	74
KRAS mutation*			
Positive	0	0	6
Total	11	10	23

Abbreviation: WT, wild type.
**KRAS* mutation testing was not performed on all patients because of limited amounts of tissue.

Mutation Analysis of Screened Patients With Non–Small-Cell Lung Cancer

J Clin Oncol 27:4247-4253

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ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Who Harbor *EML4-ALK*

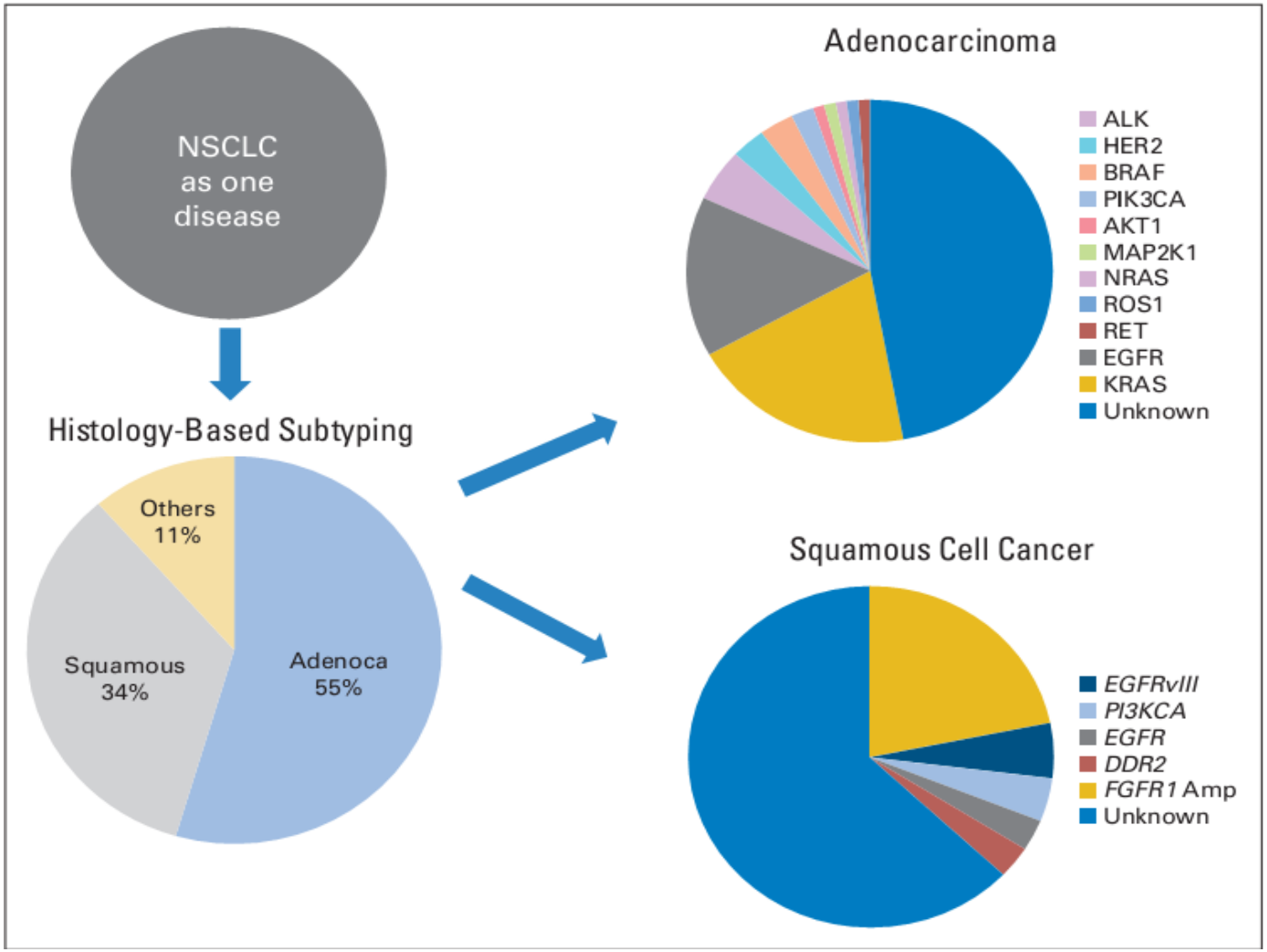
Alice T. Shaw, Beow Y. Yeap, Mari Mino-Kenudson, Subba R. Digumarthy, Daniel B. Costa, Rebecca S. Heist, Benjamin Solomon, Hannah Stubbs, Sonal Admane, Ultan McDermott, Jeffrey Settleman, Susumu Kobayashi, Eugene J. Mark, Scott J. Rodig, Lucian R. Chirieac, Eunice L. Kwak, Thomas J. Lynch, and A. John Iafrate

Results

Of 141 tumors screened, 19 (13%) were *EML4-ALK* mutant, 31 (22%) were *EGFR* mutant, and 91 (65%) were wild type (WT/WT) for both *ALK* and *EGFR*. Compared with the *EGFR* mutant and WT/WT cohorts, patients with *EML4-ALK* mutant tumors were significantly younger ($P < .001$ and $P = .005$) and were more likely to be men ($P = .036$ and $P = .039$). Patients with *EML4-ALK*–positive tumors, like patients who harbored *EGFR* mutations, also were more likely to be never/light smokers compared with patients in the WT/WT cohort ($P < .001$). Eighteen of the 19 *EML4-ALK* tumors were adenocarcinomas, predominantly the signet ring cell subtype. Among patients with metastatic disease, *EML4-ALK* positivity was associated with resistance to EGFR tyrosine kinase inhibitors (TKIs). Patients in the *EML4-ALK* cohort and the WT/WT cohort showed similar response rates to platinum-based combination chemotherapy and no difference in overall survival.

Conclusion

EML4-ALK defines a molecular subset of NSCLC with distinct clinical characteristics. Patients who harbor this mutation do not benefit from EGFR TKIs and should be directed to trials of ALK-targeted agents.



Evolution of non–small-cell lung cancer (NSCLC) subtyping from histologic to molecular based. EGFR,epidermal growth factor receptor; HER2,human epidermal growth factor receptor2; MAP2K1, mitogen-activated protein ki-nase kinase 1

Lancet Oncol 12:175-180, 2011

Oncogene	Mutation Prevalence	Mutation-Predicted Therapeutic Response	Predicted Response Rate
EGFR	Asians: 30%-40%; whites: 10%-20%	Sensitive to EGFR TKIs (most mutations)*	Erlotinib: 60%-83%[11,12]; gefitinib: ~71%[8-10]
KRAS	Asians: 10%; whites: 30%	Resistant to EGFR TKIs†; sensitive to MEK inhibitors?	Data are limited[40,41]
EML4-ALK	1%-7%; no clear racial difference	Sensitive to ALK inhibitors†; resistant to EGFR TKIs	Crizotinib: 50%-60%[13]; data are limited regarding resistance to EGFR TKIs[42]
ROS1	1.7%; more in Asians?	Sensitive to ALK inhibitors†	Crizotinib: unknown[43]
HER2	More in Asians?	Sensitive to HER2 inhibitors	Trastuzumab: unknown; lapatinib, afatinib, and dacomitinib: unknown

Oncogene Mutations Predict Likelihood of Response or Resistance to Current Targeted Therapies in Patients With NSCLC

Common mutations (exon 19 deletions,L858R,L861Q,&G719A/C/S) a/w response to EGFR TKIs;
Rare mutations such as T790M and exon 20 insertion are associated with resistance to TKIs.
KRAS mutations and ALK2p23 rearrangements may also predict resistance
Alternative therapies should be considered when resistance is predicted

J Clin Oncol 2013(31):1039-1049

Anaplastic Lymphoma Kinase Translocation

A Predictive Biomarker of Pemetrexed in Patients with Non-small Cell Lung Cancer

Jeong-Ok Lee, MD, Tae Min Kim, MD,†‡ Se-Hoon Lee, MD,†‡ Dong-Wan Kim, MD,†‡ Soyeon Kim, MS,‡ Yoon-Kyung Jeon, MD,§ Doo Hyun Chung, MD,§ Woo-Ho Kim, MD,§ Young Tae Kim, MD,‡‖ Seok-Chul Yang, MD,† Young Whan Kim, MD,† Dae Seog Heo, MD,†‡*

Results: Ninety-five NSCLC patients were genotyped as follows: 43 (45%) *EGFR* mutation, 15 (16%) *ALK* translocation, and 37 (39%) WT. The overall response rate was superior in *ALK*-translocated patients compared with *EGFR* mutant or WT patients (46.7 versus 4.7 versus 16.2%, $p = 0.001$). *ALK*-positive patients showed longer time to progression than *EGFR* mutant or WT patients (9.2 versus 1.4 versus 2.9 months, $p = 0.001$). *ALK* positivity alone was a significant predictor for overall response rate (hazard ratio [HR] = 0.07, 95% confidence interval [CI]: 0.01–0.32; $p = 0.001$) and time to progression (HR = 0.44, 95% CI: 0.24–0.80; $p = 0.007$). *ALK* positivity remained independently significant regardless of treatment line (HR = 0.43, 95% CI: 0.24–0.77; $p = 0.005$). Thymidylate synthase mRNA levels in *ALK*-positive cells were significantly lower compared with control cells ($p < 0.05$).

Conclusion: Pemetrexed is an effective treatment in patients with *ALK*-positive NSCLC. *ALK* positivity was independently predictive of pemetrexed efficacy in NSCLC patients.

J Thorac Oncol.2011;6: 1474–1480

- Pemetrexed may have exceptional activity in ALK-rearranged NSCLC, with a response (in monotherapy or in combination with a platin) of 42% and a PFS of 9 months
- Other publications have appeared in support, but more recently, those findings have been questioned
- The ongoing PROFILE studies should be informative

J Thorac Oncol 2011;6:1474–80

•The discovery of EML4–ALK brings us one step closer to personalized lung cancer therapy with crizotinib and other drugs

• A never or light-smoking patient presenting with NSCLC adenocarcinoma should be screened first for EGFR mutation

•If EGFR mutation is absent, patients screened for ALK rearrangement by IHC

•If IHC reveals moderate staining for ALK, a FISH confirmatory test is required.