ALK AND ROS1 TARGETED THERAPY IN LUNG CANCER

Ankan Bandyopadhyay

SR Pulmonary Medicine

Lung cancer is the leading cause of cancer-related death worldwide.

For certain patients with non– small-cell lung cancer (NSCLC), molecularly targeted therapies have changed treatment and improved outcomes.

In patients with NSCLC targeted therapies represent the standard of care, with superior efficacy and improved tolerability, as compared with cytotoxic chemotherapy.

Chromosomal rearrangements of the gene encoding ROS1 proto-oncogene receptor tyrosine kinase (*ROS1*) is a distinct molecular subgroup of non–small-cell lung cancers (NSCLCs) susceptible to therapeutic ROS1 kinase inhibition.

Crizotinib is a small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), ROS1, and MET.

The dual inhibition of ALK and ROS1 by the same small molecule is probably due to structural similarities between these two closely related tyrosine kinases.

The three-dimensional structures of the sites of crizotinib binding with ALK and ROS1 are similar. Most of the amino acid differences between ALK and ROS1 are conservative or do not contact crizotinib.

Clin Cancer Res. 2013 August 1; 19(15): 4040–4045.

Chromosomal rearrangements involving the *ROS1* receptor tyrosine kinase gene present in glioblastoma, NSCLC and cholangiocarcinoma.

ROS1 rearrangements have been identified in approximately 1%–2% of patients with NSCLC .

J Clin Oncol 2012;30:863– 870

ROS1 rearrangements associated with
younger age,
 never smoking history,
 Asian ethnicity
and advanced stage adenocarcinoma histology

- J Clin Oncol 2012;30:863– 870

Table 1. Prevalence of *ROS1* rearrangements in non-small cell lung cancer screening studies

Study	Screening/validation techniques	Prevalence of *ROS1* fusions	Rearrangements identified by fusion partner (no.)
Arai et al. [29]	Transcriptome sequencing, RT-PCR	4/569 (0.7%)	(4) *EZR*
Bergethon et al. [25]	FISH, RT-PCR	18/1073 (1.7%)	(5) *CD74* (1) *SLC34A2* (8) *Unknown partner* (4) *Insufficient tissue*
Davies et al. [27]	FISH, RT-PCR	5/428 (1.2%)	(2) *CD74* (2) *SLC34A2* (1) *SDC4*
		1/48 (2.1%)	(1) *SDC4*
Govindan et al. [30]	Whole-genome and transcriptome sequencing	1/17 (5.9%)	(1) *KDELR2*
Li et al. [26]	RT-PCR, direct sequencing	2/202 (1%)[a]	(2) *CD74*
Rikova et al. [24]	Phosphoproteomics screen, RT-PCR	1/150 (0.7%)	(1) *CD74* (1) *SLC34A2*[b]
Rimkunas et al. [28]	IHC, RT-PCR, FISH	9/556 (1.6%)	(4) *CD74* (2) *SLC34A2* (1) *FIG* (1) *Unknown partner* (1) *Insufficient tissue*
Seo et al. [31]	Whole-transcriptome sequencing, RT-PCR	3/200 (1.5%)	(1) *CD74* (1) *SLC34A2* (1) *CCDC6*
Suehara et al. [32]	Messenger RNA screen, RT-PCR	1/69 (1.4%)[c]	(1) *FIG*
Takeuchi et al. [33]	FISH, RT-PCR	13/1476 (0.9%)	(3) *CD74* (3) *SDC4* (2) *TPM3* (2) *EZR* (1) *SLC34A2* (1) *LRIG3* (1) *Unknown partner*
Yoshida et al. [34]	RT-PCR, FISH	15/799 (1.9%)	(10) *CD74* (4) *EZR* (1) *SLC34A2*

ROS1 rearrangements do not overlap with mutations in other oncogenic drivers, such as *EGFR* or *ALK*.

ROS1 and *ALK* rearrangements are mutually exclusive.

ROS1 rearrangement Identified in the early 1980s

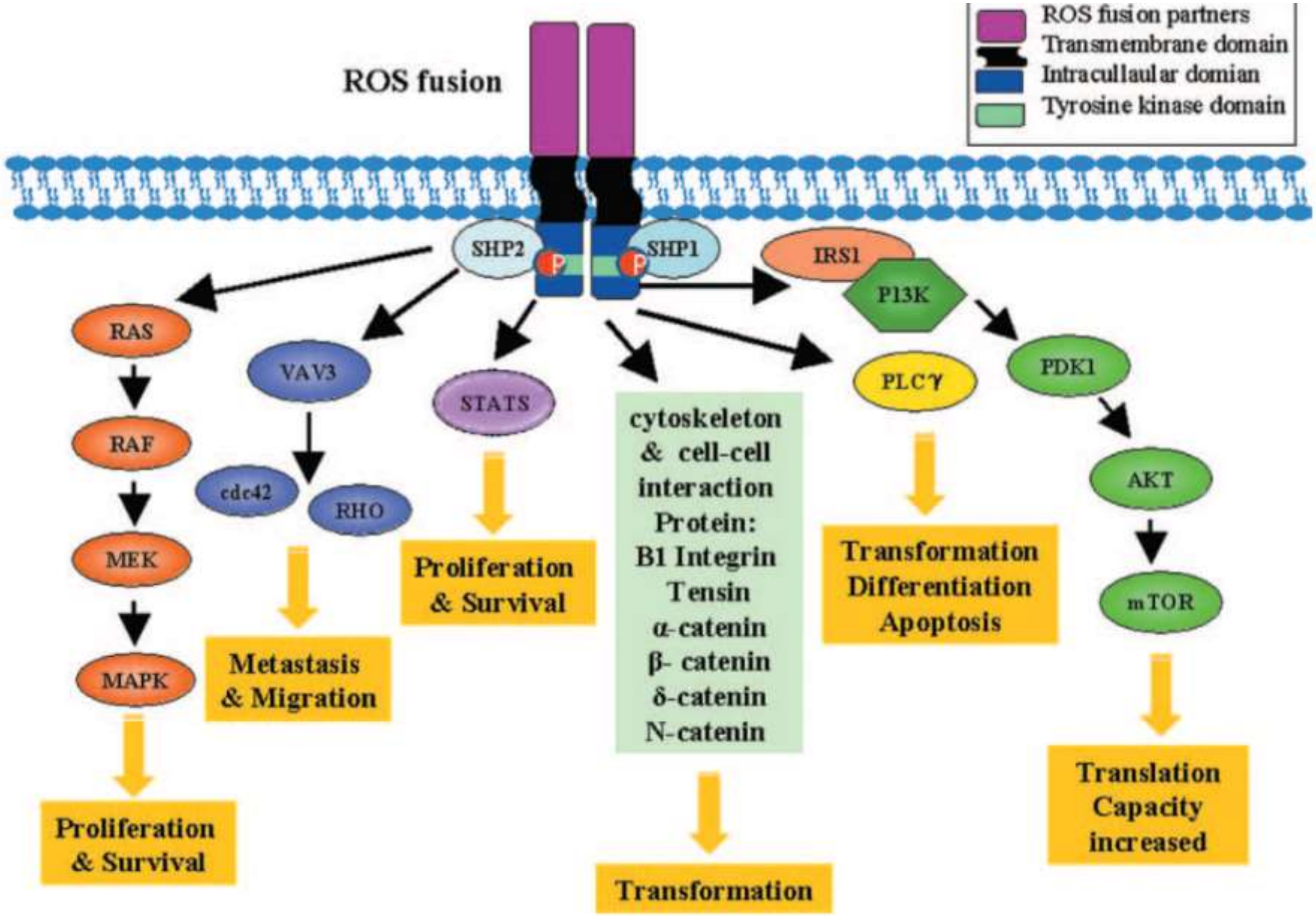
ROS1 is located on chromosome 6, where it encodes an orphan receptor tyrosine kinase.

ROS1 consists of

(a) a glycoprotein-rich extracellular domain,

(b) a transmembrane domain, and

(c) an intracellular tyrosine kinase


ROS fusion partners
Transmembrane domain
Intracullaular domian
Tyrosine kinase domain
ROS fusion
SHP2
SHP1
P
P
RAS
RAF
MEK
MAPK
Proliferation & Survival
VAV3
cdc42
RHO
Metastasis & Migration
STATS
Proliferation & Survival
cytoskeleton & cell-cell interaction Protein:
B1 Integrin
Tensin
α-catenin
β- catenin
δ-catenin
N-catenin
Transformation
IRS1
P13K
PLCγ
Transformation Differentiation Apoptosis
PDK1
AKT
mTOR
Translation Capacity increased

Deregulated ROS1 may occur as a result of *ROS1* gene fusion, overexpression or mutations.

Aberrant ROS1 kinase activity leads to activated downstream signaling of several oncogenic pathways .

TABLE 1. *ROS1* Fusion Variants Described in Non–Small-Cell Lung Cancer

Fusion Variant	Chromosomal Translocation	Lung Tumor Type	*ROS1* Exon Breakpoint	Partner Exon Breakpoint
CD74-ROS1	t(5;6) (q32;q22)	Non–small-cell lung cancer	32	6
			34	6
EZR-ROS1	Inv(6) (q22;q25.3)	Adenocarcinoma	34	10
LRIG3-ROS1	t(6;12) (q22;q14.1)	Adenocarcinoma	35	16
SDC4-ROS1	t(6;20) (q22;q12)	Adenocarcinoma	32	2
			34	2
SLC34A2-ROS1	t(4;6) (p15.2;q22)	HCC78 cell line	32	4
			34	4
TPM3-ROS1	t(1;6) (q21.2;q22)	Adenocarcinoma	35	8

Detection of ROS1 rearrangements by FISH-

Red and green fluorescent probes used to hybridize with sequences adjacent to or including a portion of the *ROS1* gene.

In the absence of a *ROS1* rearrangement, the overlapping probes produce a fused or yellow signal.

When a *ROS1* gene rearrangement is present the two probes become separated, resulting in a “split” signal.

Isolated red 3 signals can also be observed in the setting of *ROS1* rearrangements

Specimens considered FISH positive if more than15% of tumor cells demonstrate split or isolated 3 signals.

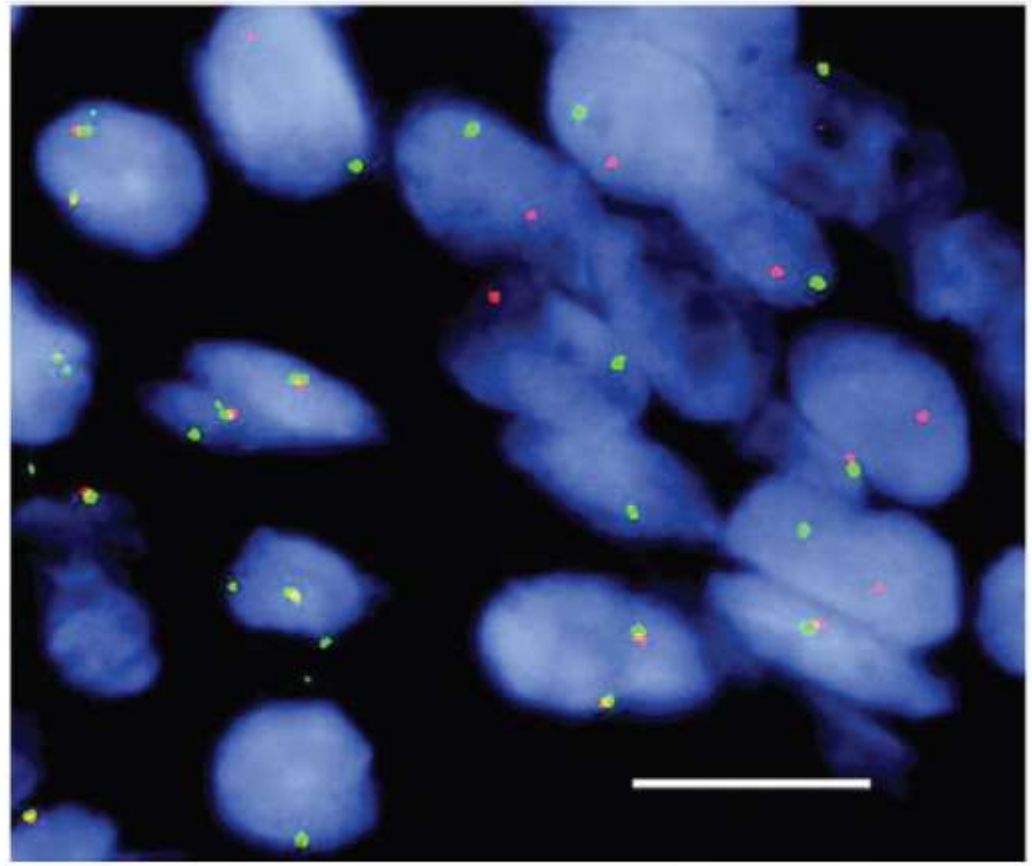


Figure 2. A ROS1 break-apart fluorescent in situ hybridization (FISH) assay. FISH reveals separation of the 5′ ROS1 probe (green) from the 3′ ROS1 probe (red), indicative of a *ROS1* rearrangement in a patient with non-small cell lung cancer. Size bar = 10 μm. Re-

- In addition to FISH, RT-PCR and IHC has also been used to screen for ROS1 rearrangements.

Methods for the detection of *ALK* gene rearrangement.

	FISH	IHC	RT-PCR
Pros	• Validated in clinical trials • Validated kit with standard procedures available • Can detect unusual variants	• User friendly • Simultaneous evaluation of morphology • Cost effective • Suitable as screening method for selecting patients for FISH test	• High sensitivity • High specificity • Can identify specific variants
Cons	• Cannot distinguish among different fusion variants • Rather subjective • Requires specialized training • Expensive method	• Cannot distinguish among different fusion variants • Lack of kit with standard procedure • Not validated in clinical trials	• High quality samples needed • Based on complex multiple PC • Not validated in clinical trials

VOLUME 30 · NUMBER 8 · MARCH 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers

Kristin Bergethon, Alice T. Shaw, Sai-Hong Ignatius Ou, Ryohei Katayama, Christine M. Lovly, Nerina T. McDonald, Pierre P. Massion, Christina Siwak-Tapp, Adriana Gonzalez, Rong Fang, Eugene J. Mark, Julie M. Batten, Haiquan Chen, Keith D. Wilner, Eunice L. Kwak, Jeffrey W. Clark, David P. Carbone, Hongbin Ji, Jeffrey A. Engelman, Mari Mino-Kenudson, William Pao, and A. John Iafrate

Using a *ROS1* fluorescent in situ hybridization (FISH) assay, 1,073 patients with NSCLC were screened and correlated *ROS1* rearrangement status with clinical characteristics, overall survival and when available, *ALK* rearrangement status.

Of 1,073 tumors screened, 18 (1.7%) were *ROS1* rearranged by FISH, and 31 (2.9%) were *ALK* rearranged.

Compared with the *ROS1*-negative group, patients with *ROS1* rearrangements were significantly younger and never-smokers (each $P < .001$).

All of the *ROS1*-positive tumors were adenocarcinomas, with a tendency toward higher grade.

ROS1-positive and -negative groups showed no difference in overall survival.

Patient treated with crizotinib showed tumor shrinkage, with a near complete response.

Table 1. Demographics and Clinical Characteristics of Patients With *ROS1*-Positive NSCLC

Demographic or Clinical Characteristic	All Patients (n = 1,073)		*ROS1* Positive (n = 18)		*ALK* Positive (n = 31)		*ROS1* Negative (n = 1,055)		*P* (*ROS1* positive *v* *ROS1* negative)
	No.	%	No.	%	No.	%	No.	%	
Age, years									
Median	62.0		49.8		51.6		62.3		< .001
Range	32-87		32-79		29-73		32-87		
Sex									
Male	523	49	7	39	17	55	516	49	.480
Female	550	51	11	61	14	45	539	51	
Smoking history									
Never-smoker	239	22	14	78	13	42	225	21	< .001
Light smoker	62	6	1	6	1	3	61	6	
Smoker	695	65	2	11	3	10	693	66	
NA	77	7	1	6	14	45	76	7	
Ethnicity									
Asian	45	4	5	28	2	6	40	4	< .001
Non-Asian	942	88	13	72	18	58	929	88	
NA	86	8	0	0	11	35	86	8	
Pathology									
Adenocarcinoma	694	65	18	100	16	52	676	64	.019
Squamous	200	19	0	0	1	3	200	19	
NSCLC, NOS	59	5	0	0	0	0	59	6	
Adenosquamous	10	1	0	0	0	0	10	1	
Other	38	4	0	0	0	0	38	4	
NA	72	7	0	0	14	45	72	7	
Stage									
IA	218	20	1	6	1	3	217	21	NS
IB	140	13	1	6	1	3	139	13	NS
IIA	44	4	1	6	2	6	43	4	NS
IIB	87	8	0	0	1	3	87	8	NS
IIIA	139	13	2	11	5	16	137	13	NS
IIIB	73	7	2	11	2	6	71	7	NS
IV	327	30	11	61	12	39	316	30	.010
NA	45	4	0	0	7	23	45	4	

Abbreviations: NA, not available; NOS, not otherwise specified; NS, not significant; NSCLC, non–small-cell lung cancer.

Table 2. Clinical Details of 18 Patients With *ROS1*-Positive NSCLC

Patient No.	Age (years)	Sex	Ethnicity	Smoking (No. of pack-years)	RT-PCR	Stage	Histology	Subtype
1	42.0	Male	Asian	0	Negative	1A	AdCA	Acinar (50%), solid (40%); high grade
2	37.0	Female	Asian	0	Negative	1B	AdCA	BAC, mucinous (90%), acinar (10%)
3	53.0	Male	White	0	Positive, CD74 exon 6, ROS exon 34	IIA	AdCA	Acinar (60%), papillary (30%), BAC nonmucinous (10%); high grade
4	39.0	Female	White	0	Negative	IIIA	AdCA	Papillary (60%), acinar (40%); high grade
5	32.0	Female	White	0	Negative	IIIA	AdCA	Acinar (100%); high grade
6	39.0	Female	White	0	ND	IIIB	AdCA	Acinar (100%)
7	51.0	Female	Asian	0	Positive, CD74 exon 6, ROS exon 34	IIIB	AdCA	Papillary (60%), acinar (40%)
8	71.0	Female	White	0	Positive, SLC34A2 exon 4., ROS exon 32	IV	AdCA	Solid (100%); high grade
9	43.0	Male	Asian	0	Negative	IV	AdCA	Papillary (60%), acinar (40%)
10	79.0	Male	White	75	Negative	IV	AdCA	Solid (100%)
11	68.0	Male	White	0	Negative	IV	AdCA	Solid (100%)
12	55.0	Female	White	23	Positive, CD74 exon 6, ROS exon 34	IV	AdCA	Papillary (60%), acinar (40%)
13	65.0	Female	White	10	ND	IV	AdCA	Acinar (90%), papillary (10%); high grade
14	47.0	Male	White	0	Negative	IV	AdCA	Acinar (100%)
15	39.0	Male	Asian	0	ND	IV	AdCA	Papillary (100%); high grade
16	44.0	Female	White		Positive, CD74 exon 6, ROS exon 34	IV	AdCA	Solid (100%)
17	35.0	Female	White	0	ND	IV	AdCA	Solid (100%); high grade
18	57.0	Female	White	0	Positive, CD74 exon 6, ROS exon 34	IV	AdCA	Acinar (60%), papillary (30%), BAC nonmucinous (10%)

Abbreviations: AdCA, adenocarcinoma; BAC, bronchioloalveolar carcinoma; ND, not determined; NSCLC, non–small-cell lung cancer; RT-PCR, reverse transcriptase polymerase chain reaction.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 20, 2014 VOL. 371 NO. 21

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

50 patients with advanced NSCLC who tested positive for *ROS1* rearrangement enrolled in an expansion cohort of the phase 1 study of crizotinib.

Patients were treated with crizotinib with oral dose of 250 mg twice daily and assessed for safety, pharmacokinetics, and response to therapy.

ROS1 fusion partners were identified with the use of next-generation sequencing or reverse-transcriptase– polymerase-chain-reaction assays.

Table 1. Characteristics of the Patients at Baseline.

Characteristic	ROS1 Cohort (N = 50)
Age — yr	
Median	53
Range	25–77
Sex — no. (%)	
Male	22 (44)
Female	28 (56)
Race — no. (%)*	
White	27 (54)
Asian	21 (42)
Other	2 (4)
Smoking status — no. (%)	
Never smoked	39 (78)
Former smoker	11 (22)
Histologic type — no. (%)	
Adenocarcinoma	49 (98)
Squamous-cell carcinoma	1 (2)
ECOG performance status — no. (%)†	
0	22 (44)
1	27 (54)
2	1 (2)
Previous regimens for advanced disease — no. (%)	
0	7 (14)
1	21 (42)
>1	22 (44)

Among the 50 study patients-

3 patients (6%) had a complete response

33 patients (66%) had a partial response

9 patients (18%) had stable disease .

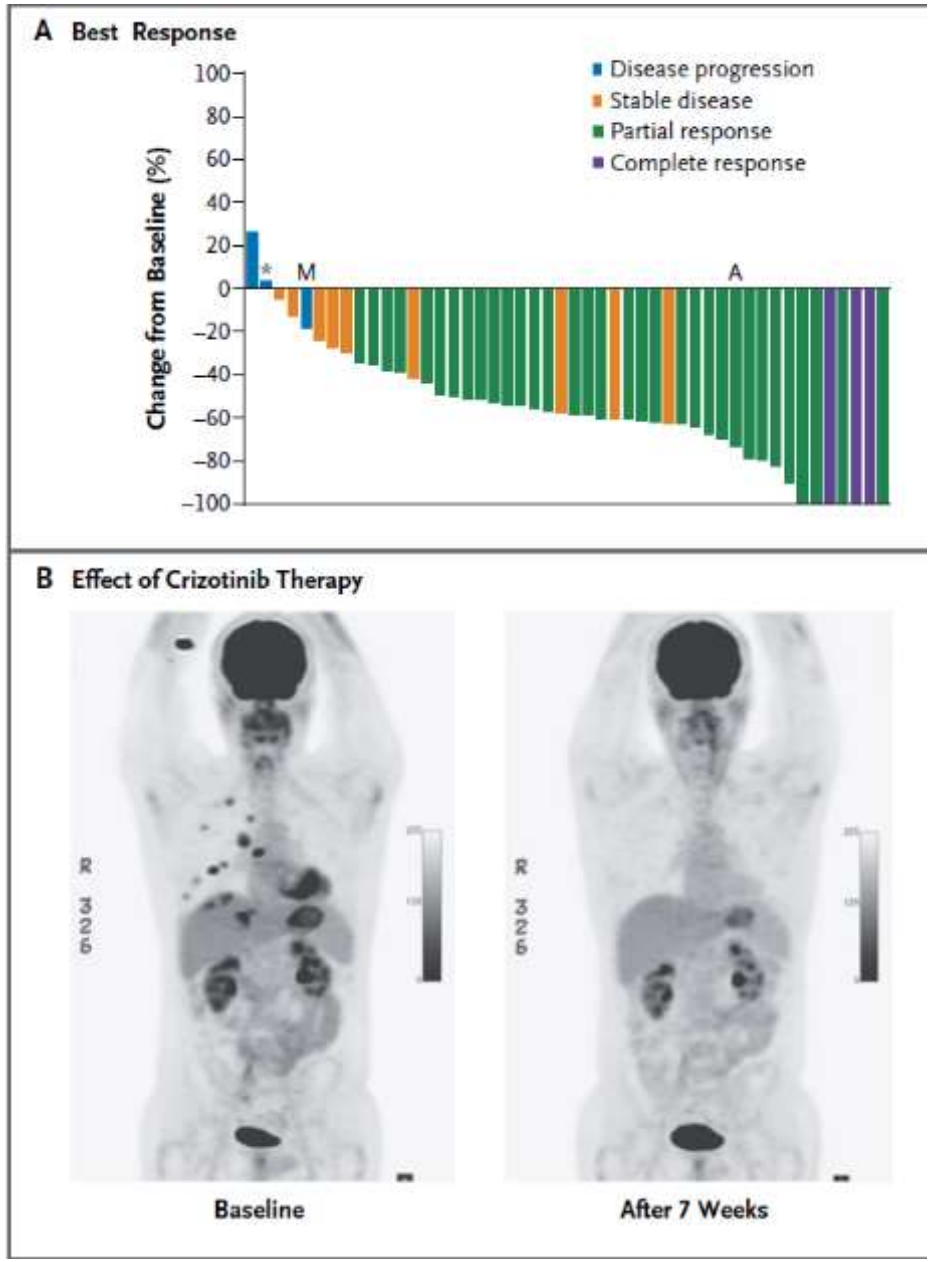
Overall response rate - 72% (95% confidence interval [CI], 58 to 84).

The median time to the first response - 7.9 weeks (range, 4.3 to 32.0)

Three of the 50 patients (6%) had evidence of progressive disease on the first restaging scans

Among the 50 patients- median duration of treatment was 64.5 weeks (range, 2.3 to 182.0), and 30 patients (60%) continued to receive crizotinib after the data cutoff date.

Median progression-free survival was 19.2 months (95% CI, 14.4 to NR)


A Best Response
Disease progression
Stable disease
Partial response
Complete response
Change from Baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
*
M
A
B Effect of Crizotinib Therapy
Baseline
After 7 Weeks

Median follow-up for overall survival was 16.4 months (95% CI, 13.8 to 19.8).

The overall survival rate at 12 months was 85%

Table 2. Adverse Events.*

Adverse Event	Grade 1	Grade 2	Grade 3	All Grades
	number of patients (percent)			
Visual impairment	41 (82)	0	0	41 (82)
Diarrhea	21 (42)	1 (2)	0	22 (44)
Nausea	18 (36)	2 (4)	0	20 (40)
Peripheral edema	15 (30)	5 (10)	0	20 (40)
Constipation	16 (32)	1 (2)	0	17 (34)
Vomiting	15 (30)	1 (2)	1 (2)	17 (34)
Elevated aspartate aminotransferase	9 (18)	1 (2)	1 (2)	11 (22)
Fatigue	9 (18)	1 (2)	0	10 (20)
Dysgeusia	9 (18)	0	0	9 (18)
Dizziness	8 (16)	0	0	8 (16)
Elevated alanine aminotransferase	3 (6)	2 (4)	2 (4)	7 (14)
Hypophosphatemia	0	2 (4)	5 (10)	7 (14)
Decreased testosterone†	2 (9)	1 (5)	0	3 (14)
Neutropenia	1 (2)	0	5 (10)	6 (12)
Dyspepsia	5 (10)	0	0	5 (10)
Sinus bradycardia	5 (10)	0	0	5 (10)

Resistance to crizotinib develops in patients with *ROS1*-rearranged NSCLC.

Mechanism-

1.secondary mutation that hinders drug binding

2.activation of epidermal growth factor receptor, which enables cancer cells to bypass crizotinib-mediated inhibition of ROS1 signaling.

N engl j Med 368;25 NEJM. ORG June 20, 2013

Resistance to crizotinib developed in a patient with metastatic lung adenocarcinoma harboring a *CD74–ROS1* rearrangement who had initially shown a dramatic response to treatment.

Biopsy of a resistant tumor identified an acquired mutation leading to a glycine-to-arginine substitution at codon 2032 in the ROS1 kinase domain.

. **www.pnas.org/cgi/doi/10.1073/pnas.1420785112**

Foretinib is a more potent ROS1 inhibitor than crizotinib in vitro and in vivo and remains effective against crizotinib-resistant ROS1 kinase domain mutations, including ROS1 G2032R.

PNAS | November 26, 2013 | vol. 110 | no. 48 | 19519–19524

PF-06463922 is the most potent and the most selective ROS1 inhibitor .

PF- 06463922 effectively inhibit the catalytic activity of recombinant ROS1G2032R and the CD74- ROS1G2032R fusion kinase .

www.pnas.org/cgi/doi/10.1073/pnas.1420785112

SUMMERY-

ROS1 rearrangement defines a second molecular subgroup of NSCLC for which crizotinib is highly active.

In the majority of patients with Ros1 rearrangement crizotinib produces durable clinical responses and associated with grade 2 or lower toxic effects.

Screening for ROS1 in patients with advanced NSCLC is important.

Second-generation ALK inhibitors ceritinib and alectinib, and the multitargeted kinase inhibitor foretinib, PF-06463922 exhibits improved ROS1 potency in both biochemical and cell based assays as compared to crizotinib.

- ALK REARRANGEMENT IN LUNG CANCER-

ALK comprises 4% cases of NSCLC.

EGFR mutations are found in 10% to 15% of NSCLCs.

Two other targets of crizotinib—ROS1 and c-MET—are less common than ALK; each present in 1% to 2% of NSCLCs.

4% of patients with ALK lung cancer represent potentially 40,000 new cases worldwide each year.

J Clin Oncol 30:863-870, 2012

Patients with *ALK* rearrangements are younger with no gender predilection .

Pathologically, *ALK*-positive tumors are predominately adenocarcinomas and contain signet ring cells.

ALK rearrangements and activating epidermal growth factor receptor (*EGFR*) mutations are mutually exclusive.

Among patients with *ALK*-positive lung cancer, more than 90% are never- or light smokers (light smoking is defined as < 10 pack-years).

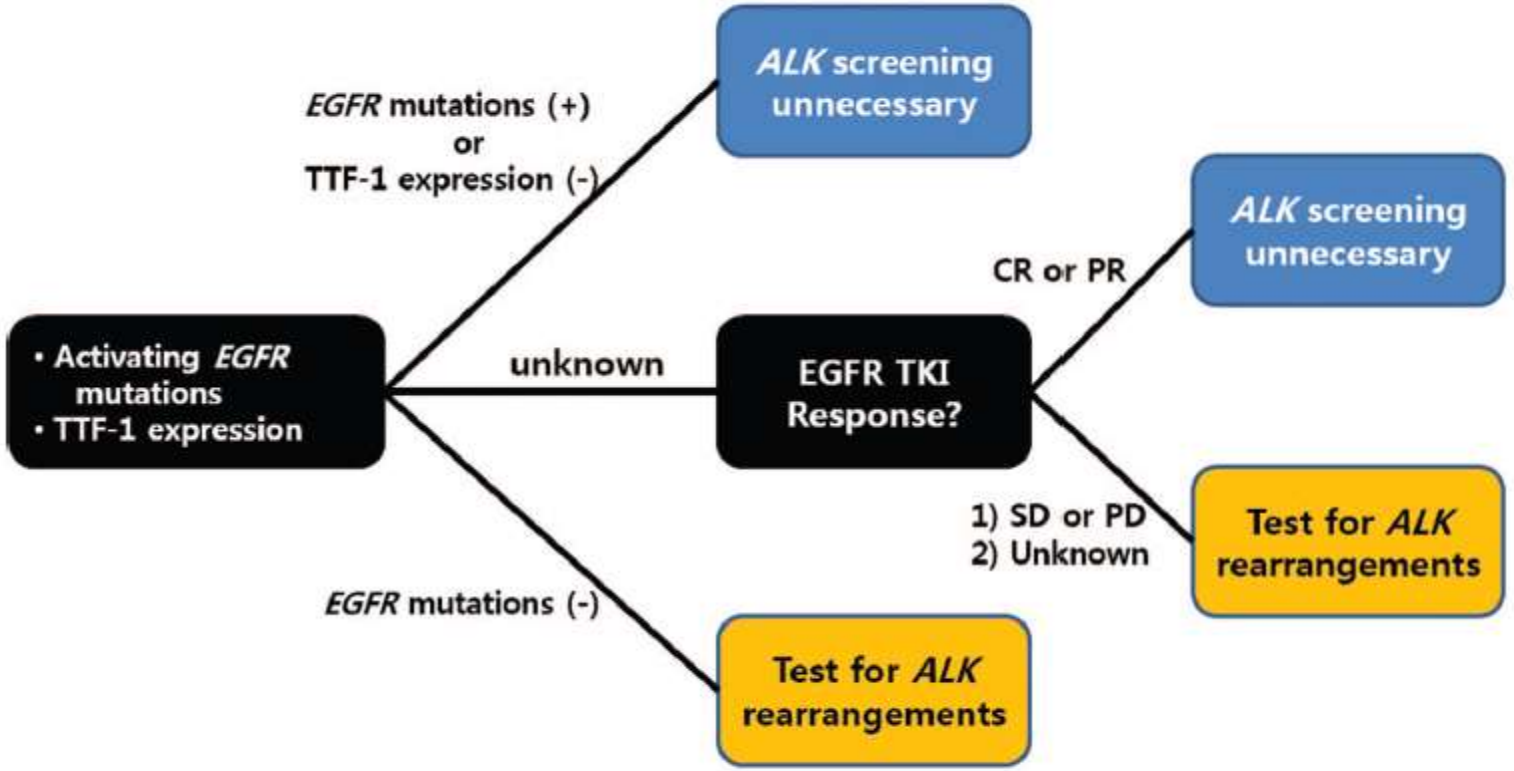
J Clin Oncol 2009;27:4247– 4253

Cancer 2009;115:1723–1733

27 ALK fusion variants are present

Most common of which EML4-ALK fusion tyrosine kinase .

Algorithm for ALK screening in advanced Adeno CA lung



Crizotinib a multi targeted TKI with activity against MET, ALK, and ROS1

It is the first molecule approved for the treatment of patients with ALK-positive advanced NSCLC.

Crizotinib got Food and Drug Administration(FDA) approval for ALK-positive patients in August 2011 .

N engl j med 368;25 nejm.2400 org june 20, 2013

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

Benjamin J. Solomon, M.B., B.S., Ph.D., Tony Mok, M.D., Dong-Wan Kim, M.D., Ph.D., Yi-Long Wu, M.D., Kazuhiko Nakagawa, M.D., Ph.D., Tarek Mekhail, M.D., Enriqueta Felip, M.D., Ph.D., Federico Cappuzzo, M.D., Jolanda Paolini, B.Sc., Tiziana Usari, B.Sc., Shrividya Iyer, Ph.D., Arlene Reisman, M.P.H., Keith D. Wilner, Ph.D., Jennifer Tursi, M.Sc., and Fiona Blackhall, M.D., Ph.D., for the PROFILE 1014 Investigators*

This open-label, phase 3 trial compared crizotinib with chemotherapy in 343 patients with advanced *ALK*-positive non squamous NSCLC who received no previous systemic treatment for advanced disease..

Patients randomly assigned to receive oral crizotinib at a dose of 250 mg twice daily or

received intravenous chemotherapy every 3 weeks for upto 6 cycles. (pemetrexed, 500 mg per square meter of body surface area, plus either cisplatin, 75 mg per square meter, or carboplatin, target area under the curve of 5 to 6 mg per milliliter per minute)

Crossover to crizotinib treatment after disease progression permitted for patients receiving chemotherapy.

Primary end point – progression free survival

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

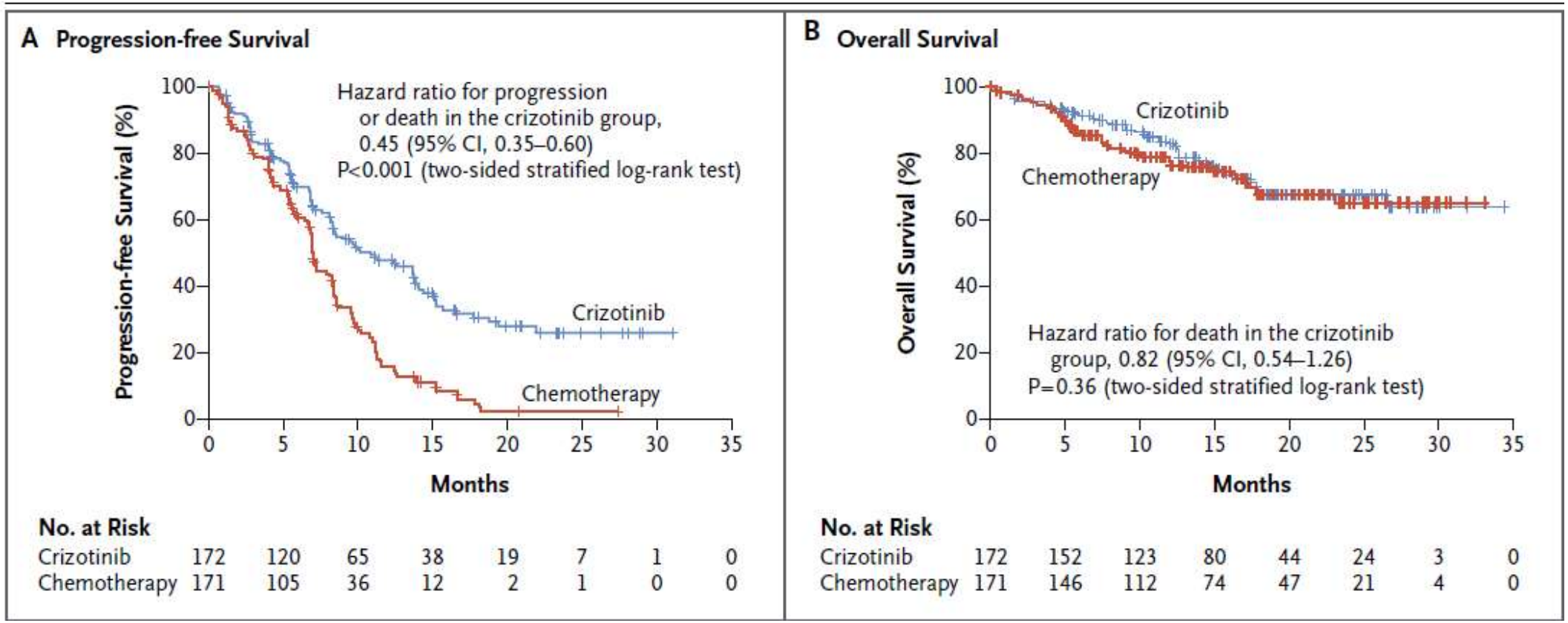
Characteristic	Crizotinib (N = 172)	Chemotherapy (N = 171)
Age — yr		
Median	52	54
Range	22–76	19–78
Male sex — no. (%)	68 (40)	63 (37)
Race — no. (%)†		
White	91 (53)	85 (50)
Asian	77 (45)	80 (47)
Other	4 (2)	6 (4)
Smoking status — no. (%)		
Never smoked	106 (62)	112 (65)
Former smoker	56 (33)	54 (32)
Current smoker	10 (6)	5 (3)
Histologic characteristic of tumor — no. (%)		
Adenocarcinoma	161 (94)	161 (94)
Nonadenocarcinoma	11 (6)	10 (6)
ECOG performance status — no. (%)‡		
0 or 1	161 (94)	163 (95)
2	10 (6)	8 (5)
Extent of disease — no. (%)		
Locally advanced	4 (2)	3 (2)
Metastatic	168 (98)	168 (98)
Time since first diagnosis — mo		
Median	1.2	1.2
Range	0–114.0	0–93.6
Brain metastases present — no. (%)	45 (26)	47 (27)

Table 2. Response to Treatment in the Intention-to-Treat Population.*

Response	Crizotinib (N = 172)	Chemotherapy (N = 171)
Type of response — no. (%)		
Complete response	3 (2)	2 (1)
Partial response	125 (73)	75 (44)
Stable disease	29 (17)	63 (37)
Progressive disease	8 (5)	21 (12)
Could not be evaluated†	7 (4)	10 (6)
Objective response rate — % (95% CI)‡	74 (67–81)	45 (37–53)
Time to response — mo§		
Median	1.4	2.8
Range	0.6–9.5	1.2–8.5
Duration of response — mo¶		
Median	11.3	5.3
95% CI	8.1–13.8	4.1–5.8

Progression-free survival significantly longer with crizotinib than with chemotherapy (median, 10.9 months vs. 7.0 months; hazard ratio for progression or death with crizotinib, 0.45; 95% confidence interval [CI], 0.35 to 0.60; P<0.001).

Objective response rates of crizotinib vs chemotherapy- 74% and 45% (P<0.001)


A Progression-free Survival
Progression-free Survival (%)
100
80
60
40
20
0
Hazard ratio for progression or death in the crizotinib group, 0.45 (95% CI, 0.35–0.60)
P<0.001 (two-sided stratified log-rank test)
Crizotinib
Chemotherapy
0 5 10 15 20 25 30 35
Months
No. at Risk
Crizotinib 172 120 65 38 19 7 1 0
Chemotherapy 171 105 36 12 2 1 0 0
B Overall Survival
Overall Survival (%)
100
80
60
40
20
0
Crizotinib
Chemotherapy
Hazard ratio for death in the crizotinib group, 0.82 (95% CI, 0.54–1.26)
P=0.36 (two-sided stratified log-rank test)
0 5 10 15 20 25 30 35
Months
No. at Risk
Crizotinib 172 152 123 80 44 24 3 0
Chemotherapy 171 146 112 74 47 21 4 0

C Progression-free Survival, According to Subgroup

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Crizotinib vs. chemotherapy	343	0.45 (0.35–0.60)
Age		
≥65 yr	55	0.37 (0.17–0.77)
<65 yr	288	0.51 (0.38–0.68)
Sex		
Male	131	0.54 (0.36–0.82)
Female	212	0.45 (0.32–0.63)
Race		
Non-Asian	186	0.53 (0.36–0.76)
Asian	157	0.44 (0.30–0.65)
Smoking status		
Smoker or former smoker	125	0.64 (0.42–0.97)
Nonsmoker	218	0.41 (0.29–0.58)
Time since diagnosis		
>1 yr	35	0.14 (0.04–0.51)
≤1 yr	308	0.52 (0.40–0.68)
ECOG performance status		
2	18	0.19 (0.05–0.76)
0 or 1	324	0.47 (0.36–0.62)
Adenocarcinoma		
Yes	322	0.49 (0.37–0.64)
No	21	0.37 (0.12–1.10)
Type of disease		
Metastatic	336	0.48 (0.37–0.63)
Locally advanced	7	0.54 (0.07–3.91)
Brain metastases		
Yes	92	0.57 (0.35–0.93)
No	251	0.46 (0.34–0.63)

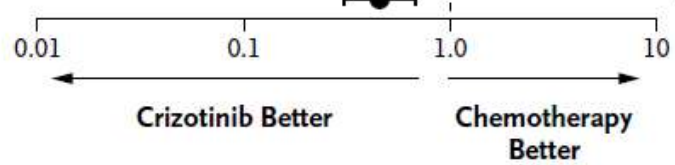


Table 3. Adverse Events from Any Cause in the As-Treated Population.*

Adverse Event	Crizotinib (N = 171)		Chemotherapy (N = 169)†	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Higher frequency in crizotinib group				
Vision disorder‡	122 (71)	1 (1)	16 (9)	0
Diarrhea	105 (61)	4 (2)	22 (13)	1 (1)
Edema§	83 (49)	1 (1)	21 (12)	1 (1)
Vomiting	78 (46)	3 (2)	60 (36)	5 (3)
Constipation	74 (43)	3 (2)	51 (30)	0
Elevated aminotransferases§	61 (36)	24 (14)	22 (13)	4 (2)
Upper respiratory infection§	55 (32)	0	21 (12)	1 (1)
Abdominal pain§	45 (26)	0	20 (12)	0
Dysgeusia	45 (26)	0	9 (5)	0
Headache	37 (22)	2 (1)	25 (15)	0
Pyrexia	32 (19)	0	18 (11)	1 (1)
Dizziness§	31 (18)	0	17 (10)	2 (1)
Pain in extremity	27 (16)	0	12 (7)	0
Higher frequency in chemotherapy group				
Fatigue	49 (29)	5 (3)	65 (38)	4 (2)
Neutropenia§	36 (21)	19 (11)	51 (30)	26 (15)
Stomatitis§	24 (14)	1 (1)	34 (20)	2 (1)
Asthenia	22 (13)	0	41 (24)	2 (1)
Anemia§	15 (9)	0	54 (32)	15 (9)
Leukopenia§	12 (7)	3 (2)	26 (15)	9 (5)
Thrombocytopenia§	2 (1)	0	31 (18)	11 (7)
Similar frequency in the two treatment groups				
Nausea	95 (56)	2 (1)	99 (59)	3 (2)
Decreased appetite	51 (30)	4 (2)	57 (34)	1 (1)
Cough§	39 (23)	0	33 (20)	0
Neuropathy§	35 (20)	2 (1)	38 (22)	0
Dyspnea§	30 (18)	5 (3)	26 (15)	4 (2)

Conclusion-

Patients with previously untreated *ALK*-positive NSCLC, crizotinib treatment is superior to pemetrexed-plus-platinum chemotherapy with respect to

1. Progression-free survival
2. Objective response rate,
3. Reduction of lung-cancer symptoms
4. Improvement in quality of life.

Results are independent of -

type of platinum treatment administered

performance status of the patient

patient’s race and

the presence or absence of brain metastases

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced *ALK*-Positive Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Ph.D., Takashi Seto, M.D., Lucio Crinó, M.D., Myung-Ju Ahn, M.D., Tommaso De Pas, M.D., Benjamin Besse, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Fiona Blackhall, M.D., Ph.D., Yi-Long Wu, M.D., Michael Thomas, M.D., Kenneth J. O'Byrne, M.D., Denis Moro-Sibilot, M.D., D. Ross Camidge, M.D., Ph.D., Tony Mok, M.D., Vera Hirsh, M.D., Gregory J. Riely, M.D., Ph.D., Shrividya Iyer, Ph.D., Vanessa Tassell, B.S., Anna Polli, B.S., Keith D. Wilner, Ph.D., and Pasi A. Jänne, M.D., Ph.D.

This phase 3, open-label trial compared crizotinib with chemotherapy in 347 patients with locally advanced or metastatic *ALK*-positive lung cancer who had received one prior platinum-based regimen.

Patients randomly assigned to receive oral treatment with

crizotinib (250 mg) twice daily

or

intravenous chemotherapy with either pemetrexed (500 mg per square meter of body-surface area) or docetaxel (75 mg per square meter) every 3 weeks.

The primary end point was progression-free survival

The median progression-free survival was 7.7 months in the crizotinib group and 3.0 months in the chemotherapy group (hazard ratio for progression or death with crizotinib, 0.49; 95% confidence interval [CI], 0.37 to 0.64; P<0.001).

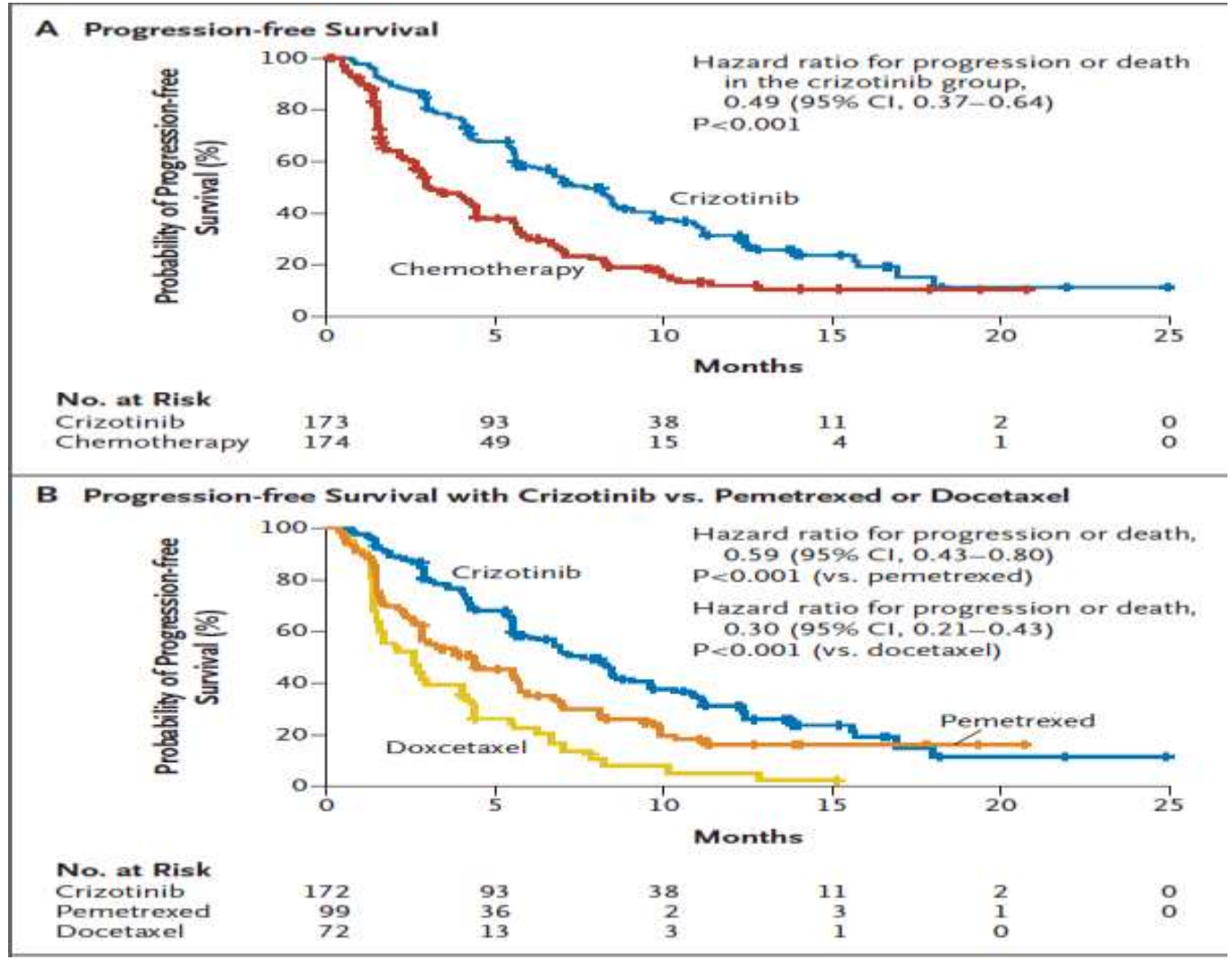
The response rates were 65% (95% CI, 58 to 72) with crizotinib, as compared with 20% (95% CI, 14 to 26) with chemotherapy (P<0.001).

Response rate to pemetrexed was higher than expected — 29%, as compared with 12.8% in the general population of patients with lung adenocarcinoma who had previously been treated with chemotherapy.

The incidence of treatment-related serious adverse events was similar in the crizotinib and chemotherapy groups.

Table 2. Summary of Responses in the Intention-to-Treat Population.*

Response	Crizotinib (N = 173)	Chemotherapy (N = 174)
Type of response — no. (%)		
Complete response	1 (1)	0
Partial response	112 (65)	34 (20)
Stable disease	32 (18)	63 (36)
Progressive disease	11 (6)	60 (34)
Could not be evaluated†	17 (10)	17 (10)
Rate of objective response — % (95% CI)‡	65 (58–72)	20 (14–26)
Duration of response — wk§		
Median	32.1	24.4
Range¶	2.1–72.4	3.0–43.6
Time to response — wk‖		
Median	6.3	12.6
Range	4.4–48.4	5.0–37.1


A Progression-free Survival
Probability of Progression-free Survival (%)
100
80
60
40
20
0
Hazard ratio for progression or death in the crizotinib group, 0.49 (95% CI, 0.37–0.64)
P<0.001
Crizotinib
Chemotherapy
0
5
10
15
20
25
Months
No. at Risk
Crizotinib 173 93 38 11 2 0
Chemotherapy 174 49 15 4 1 0
B Progression-free Survival with Crizotinib vs. Pemetrexed or Docetaxel
Probability of Progression-free Survival (%)
100
80
60
40
20
0
Hazard ratio for progression or death, 0.59 (95% CI, 0.43–0.80)
P<0.001 (vs. pemetrexed)
Hazard ratio for progression or death, 0.30 (95% CI, 0.21–0.43)
P<0.001 (vs. docetaxel)
Crizotinib
Pemetrexed
Doxcetaxel
0
5
10
15
20
25
Months
No. at Risk
Crizotinib 172 93 38 11 2 0
Pemetrexed 99 36 2 3 1 0
Docetaxel 72 13 3 1 0

Discovery of a novel ALK fusion—

Echinoderm microtubule-associated protein-like 4 (*EML4*)–*ALK*—as a somatic gene rearrangement found in a small percentage of lung cancers.

EML4-ALK fusions result from small inversions within chromosome 2p that fuse differing portions of the *EML4*gene with a portion of the *ALK* gene.

EML4-ALK is the predominant ALK fusion in lung cancer

Despite the marked antitumor activity of crizotinib, ALK-driven cancers become resistant to crizotinib.

In case of *ALK* positive & *EGFR* mutant lung cancer, resistance develops on average within the first year or two of TKI therapy

N Engl J Med 363:1734-1739, 2010

Up to one third of relapsing patients, crizotinib resistance is mediated by secondary resistance mutations located in the *ALK* TK domain.

Most commonly identified resistance mutation is the gatekeeper mutation L1196M in the TK domain of EML4–ALK involves –

Substitution of leucine for a methionine at position 1196 (L1196M) of the kinase domain of ALK- creating a mutant bulky amino-acid side chain in the ATP-binding pocket of the receptor interfere binding of crizotinib to its receptor

- **N Engl J Med 363:1734-1739, 2010**

- Other mutation causing crizotinib resistance-

1.G1269A substitution lies directly in the ATP-binding pocket.

2.G1202R and S1206Y, are located in the solvent-exposed region of the kinase domain and decrease the binding affinity of crizotinib.

3. 1151 threonine insertion –through conformational changes they compromise crizotinib binding

- **Sci Transl Med 4:120ra17, 2012**

To overcome the problem of crizotinib resistance, second-generation ALK inhibitors are developed .

Based on phase I/II data, ceritinib has gained accelerated FDA approval for the treatment of crizotinib resistant ALK-rearranged lung cancer.

The clinical development of alectinib has already reached phase III.

The toxicity profile of these drugs seems manageable, although side-effects still require attention and optimized supportive care.

Table 3. Activity of different second generation ALK inhibitors against ALK mutant isoforms conferring resistance against crizotinib

Resistance mutations	Ceritinib	Alectinib	AP26113	ASP3026	TSR-011	PF-06463922	X-396
L1196M	Yes	Yes	Yes	Yes	Yes	Yes	Yes
C1156Y	No	Yes	?	?	?	Yes	Yes
L1152R	No	Yes	?	?	?	Yes	?
F1174L	No	Yes	Yes	?	?	Yes	?
G1269A	Yes	Yes	Yes	?	?	Yes	?
G1202R	No	No	?	?	?	Yes	?
S1206Y	Yes	?	No	?	?	Yes	?
1151T	No	Yes	?	?	?	Yes	?
I1171T	Yes	?	?	?	?	?	?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

Ceritinib (LDK378) is a new ALK inhibitor that has shown greater antitumor potency than crizotinib in preclinical studies.

Oral ceritinib used in doses of 50 to 750 mg once daily to patients with advanced cancers harboring genetic alterations in *ALK*

.

The primary objective was to determine the MTD of ceritinib in adult patients with tumors harboring a genetic alteration in *ALK*.

Key secondary objectives were to characterize the safety and side effect profile, pharmacokinetic profile, and antitumor activity of ceritinib.

The study included a dose-escalation phase, followed by an expansion phase in which all the patients received treatment at the maximum dose established in the dose escalation phase.

Daily dosing of ceritinib was continued in 21-day cycles. The starting dose was 50 mg daily, on the basis of preclinical safety data

- Patients in the dose-escalation phase of the study were treated at dose levels of 50 to 750 mg daily.

For the expansion phase, patients received treatment with the MTD of ceritinib that had been established in the dose-escalation phase.

Patients continued treatment with ceritinib until

the disease progressed

an unacceptable level of toxic events developed

or the patient withdrew consent.

Treatment after disease progression was not permitted, unless the sole site of progression was the central nervous system.

Dose-limiting toxic events occurred in six patients at daily doses of 400 mg or more .

Dose-limiting toxic events included

diarrhea (at a daily dose of ≥600 mg),

vomiting (at 750 mg daily)

nausea (at 750 mg daily),

dehydration (at 600 mg daily)

elevated alanine aminotransferase level (at 400 mg daily)

hypophosphatemia (at 400 mg daily)

four cases of interstitial lung disease

All dose-limiting toxic events resolved on discontinuation of treatment.

114 patients with NSCLC received at least 400 mg of ceritinib daily

1 (1%) had a confirmed complete response

65 (57%) had a confirmed partial response

25 (22%) had stable disease.

12 patients (11%) had progressive disease on the first restaging scans, and for 11 patients (10%) the response was not known owing to early withdrawal from the study.

The overall response rate was 58% (95% confidence interval [CI], 48 to 67).

Among the 78 patients with NSCLC who received 750 mg daily, 46 had a confirmed partial response, for an overall response rate of 59% (95% CI, 47 to 70).

Among patients previously treated with crizotinib the overall response rate -

56% (95% CI, 45 to 67) among those who received ceritinib at a dose of 400 mg or more daily (45 of 80 patients) and

56% (95% CI, 41 to 70) among those treated with ceritinib at a dose of 750 mg daily (28 of 50 patients).

Among the 66 patients with NSCLC who had a response and who had been treated with at least 400 mg of ceritinib daily, 64% (95% CI, 50 to 74) had a duration of response of 6 months or longer.

Median duration of response was 8.2 months

Median progression free survival was 7.0 months

CONCLUSION-

Ceritinib at a dose of 400 mg or more daily similarly effective in patients who had received prior crizotinib treatment and in those who had not received crizotinib previously.

Overall response rate & median progression free survival observed with ceritinib were similar to those seen after initial crizotinib treatment.

.

Table 1 | Ongoing clinical trials involving novel ALK- and HSP90-inhibitors in NSCLC.

ONGOING CLINICAL TRIALS INVOLVING NOVEL ALK-INHIBITORS						
Drug	**Company**	**Activity against other kinases**	**Activity against L1196M mutation**	**Ongoing trials**	**Study phase**	**Previous treatment**
LDK378 (ceritinib)	Novartis	IFG-1R c-MET	Yes	NCT01772797 NCT02040870 NCT01685138 NCT01685060 NCT01947608 NCT01964157 NCT01828099 NCT01828112	Phase I Phase I/II Phase II Phase II Phase II Phase II Phase III Phase III	None Crizotinib/chemotherapy 0-3 lines of chemotherapy Crizotinib or 1-3 lines of chemotherapy Crizotinib 1 line of chemotherapy None Crizotinib
CH5424802/ RO5424802 (alectinib)	Roche/Chugai	ROS1	Yes	NCT01588028 NCT01871805 NCT01801111 NCT02075840	Phase I Phase II Phase II Phase III	 Crizotinib Crizotinib
AP26113	Ariad	EGFR ROS1	Unknown	NCT01449461 NCT02094573	Phase I/II Phase II	Refractory to standard therapy Crizotinib
ASP3026	Astellas	ROS1	Yes	NCT01401504 NCT01284192	Phase I Phase I	Refractory to standard therapy Refractory to standard therapy
TSR-001	Tesaro	Unknown	Yes	NCT02048488	Phase I	None
PF-06463922	Pfizer	EGFR ROS1	Unknown	NCT01970865	Phase I/II	None
X-396	Xcovery	Unknown	Yes	NCT01625234	Phase I	None

More potent ALK inhibitors with CNS activity and good tolerability like Alectinib shown clinical activity in patients with crizotinib resistant *ALK*-rearranged NSCLC including those with CNS metastasis.

Alectinib is active against most of the known resistance-mediating ALK mutations, except G1202R .

Cancer Lett 2014; **351:** 215–21.

Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant *ALK*-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase 1/2 study

Shirish M Gadgeel, Leena Gandhi*, Gregory J Riely, Alberto A Chiappori, Howard L West, Michele C Azada, Peter N Morcos, Ruey-Min Lee, Linta Garcia, Li Yu, Frederic Boisserie, Laura Di Laurenzio, Sophie Golding, Jotaro Sato, Shumpei Yokoyama, Tomohiro Tanaka, Sai-Hong Ignatius Ou*

Lancet Oncol 2014; 15: 1119–28

Published Online
August 19, 2014

Patients with *ALK*-rearranged NSCLC who progressed on or were intolerant to crizotinib were enrolled.

oral doses of alectinib (300–900 mg twice a day) was given

Response Evaluation Criteria in Solid Tumors criteria (version 1.1) used to investigate the activity of alectinib in all patients with a baseline scan and at least one post-treatment scan (CT or MRI), with central radiological review of individuals with brain metastases.

Safety was assesed in all patients who received at least one dose of alectinib.

	Alectinib dose cohort					Total (n=47)
	300 mg (n=7)	460 mg (n=7)	600 mg (n=13)	760 mg (n=7)	900 mg (n=13)	
Assessable patients*	7	7	10	7	13	44
Confirmed complete response†	0	0	0	0	1 (8%)	1 (2%)
Confirmed partial response†	2 (29%)	5 (71%)	4 (40%)	0	3 (23%)	14 (32%)
Unconfirmed partial response	0	0	3 (30%)	2 (29%)	4 (31%)	9 (20%)
Stable disease	4 (57%)	1 (14%)	3 (30%)	4 (57%)	4 (31%)	16 (36%)
Progressive disease	1 (14%)	1 (14%)	0	1 (14%)	1 (8%)	4 (9%)

Data are number of patients (%). *Had either a baseline scan and at least one post-treatment scan from which response could be measured or an investigator-assessed best response of progressive disease (based on symptomatic progression). †Per-protocol, clinical responses were confirmed by follow-up radiological imaging at 4 weeks or longer after the initial documentation of complete or partial response.

***Table 3*: Best systemic response**

Of 21 patients with CNS metastases at baseline, 11 (52%) had an objective response; six (29%) had a complete response and five (24%) had a partial response

eight (38%) patients had stable disease and the remaining two (10%) had progressive disease.

Most common adverse events –

fatigue (14 [30%]; all grade 1–2),

myalgia (eight [17%]; all grade 1–2),

peripheral edema (seven [15%] grade 1–2, one [2%] grade 3).

Dose-limiting toxic effects(headache, neutropenia) were recorded in two patients receiving alectinib 900 mg twice a day;

Most common grade 3–4 adverse events –

increased levels of γ-glutamyl transpeptidase (two [4%])

reduction in the number of neutrophils (two [4%]), hypophosphataemia (two [4%]).

	Grade 1–2*	Grade 3	Grade 4
Fatigue	14 (30%)	0	0
Myalgia	8 (17%)	0	0
Peripheral oedema	7 (15%)	1 (2%)	0
Increase in creatine kinase	7 (15%)	0	0
Nausea	7 (15%)	0	0
Increase in alanine aminotransferase	6 (13%)	0	0
Photosensitivity	6 (13%)	0	0
Constipation	5 (11%)	0	0
Rash	4 (9%)	1 (2%)	0
Dyspnoea	3 (6%)	1 (2%)	0
Headache	3 (6%)	1 (2%)	0
Hyperglycaemia	2 (4%)	1 (2%)	0
Hypophosphataemia	1 (2%)	2 (4%)	0
Decrease in neutrophil count	1 (2%)	2 (4%)	0
Abdominal pain	1 (2%)	1 (2%)	0
Increase in γ-glutamyl transpeptidase	0	2 (4%)	0
Brain metastasis of NSCLC	0	0	1 (2%)
Hypertriglyceridaemia	0	1 (2%)	0
Peripheral effusion	0	0	1 (2%)
Acute renal failure	0	0	1 (2%)
Syncope	0	1 (2%)	0

Data are number of patients (%). NSCLC=non-small-cell lung cancer. *Only those grade 1–2 adverse events with an incidence greater than 10% in the total study population are reported. Some grade 1–2 adverse events with an incidence less than 10% are provided for completeness, if grade 3–4 adverse events were also recorded.

Table 2: **Adverse events**

Conclusion-

Alectinib is well tolerated,

Have promising antitumour activity in patients with *ALK* rearranged NSCLC who are resistant or intolerant to crizotinib, including those with CNS metastases.

EML4-ALK gene products and their mutant subtypes are known clients of chaperones like HSP90 which ensure adequate folding necessary for protein function and prevent preterm degradation . Clinical activity of HSP90 inhibitors against ALK rearranged NSCLC shown in clinical trials

In vitro, this activity is directed against the wild-type ALK and against most of the known mutant forms of ALK conferring resistance against crizotinib.

In a phase II trial of the HSP90 inhibitor ganetespib, partial responses were detectable in four of eight patients with ALK rearranged NSCLC.

Clin Cancer Res 2013; 19:3068–3077

Efficacy and manageable toxicity were also reported for the HSP90-inhibiting compound AUY922 in a phase II trial .

Based on these results, further clinical development of HSP90 inhibitors in the ALK rearranged subtype of lung adenocarcinoma is ongoing.

- **Ann Oncol 2012; 23 (suppl 9):abstract 4380**

Difference between *ALK* rearrangement and *ROS1* rearrangement in patients with NSCLC is in the durability of the response to crizotinib.

Factors account for the longer responses observed in *ROS1*-rearranged NSCLC-

1.crizotinib may be a more potent inhibitor of ROS1 than of ALK, leading to more effective target inhibition and more durable responses.

2. In vitro measurements of the equilibrium dissociation constant (Kd) with the use of isothermal titration calorimetry indicated that **crizotinib binds significantly more tightly to ROS1 than to ALK**

INDIAN DATA OF ALK IN NSCLC

OncoTargets and Therapy

Dovepress

open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Clinical and epidemiological study of EGFR mutations and EML4-ALK fusion genes among Indian patients with adenocarcinoma of the lung

This article was published in the following Dove Press journal:
OncoTargets and Therapy
5 January 2015
Number of times this article has been viewed

DC Doval[1]
K Prabhash[2]
S Patil[3]
H Chaturvedi[4]
C Goswami[5]
AK Vaid[6]
S Desai[2]
S Dutt[7]
VH Veldore[8]
N Jambhekar[2]
A Mehta[1]
D Hazarika[8]
S Azam[1]
S Gawande[9]
S Gupta[10]

[1]Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, [2]Tata Memorial Hospital, Mumbai, [3]Bangalore Institute of Oncology, HCG Group, Bengaluru, [4]Max Super Speciality Hospital, New Delhi, [5]B. P. Poddar Hospital, Kolkata, [6]Medanta The Medicity, Gurgaon, [7]Oncquest Laboratories Ltd., New Delhi, [8]Triesta Reference Laboratory, HCG Group, Bengaluru, [9]Pfizer India Ltd., Mumbai, [10]Catalyst Clinical Services Pvt. Ltd., New Delhi, India

Patients with NSCLC, adenocarcinoma histology, whose tumors had been tested for EGFR mutational status-included in this study.

ALK gene rearrangement detected by fluorescence in situ hybridization using the Vysis ALK Break Apart Rearrangement Probe Kit.

ALK mutation was tested in EGFR mutation negative samples .

A total of 500 NSCLC adenocarcinoma patients enrolled across six centers.

337 (67.4%) men and 163 (32.6%) women with a median age of 58 years.

One hundred and sixty-four (32.8%) blocks positive for EGFR mutations,

336 (67.2%) were EGFR wild-type.

Of the 336 EGFR-negative blocks, EML4-ALK fusion gene was present in 15 (4.5%) patients & 321 (95.5%) tumors were EML4-ALK negative.

The overall incidence of EML4-ALK fusion gene was 3% (15/500)

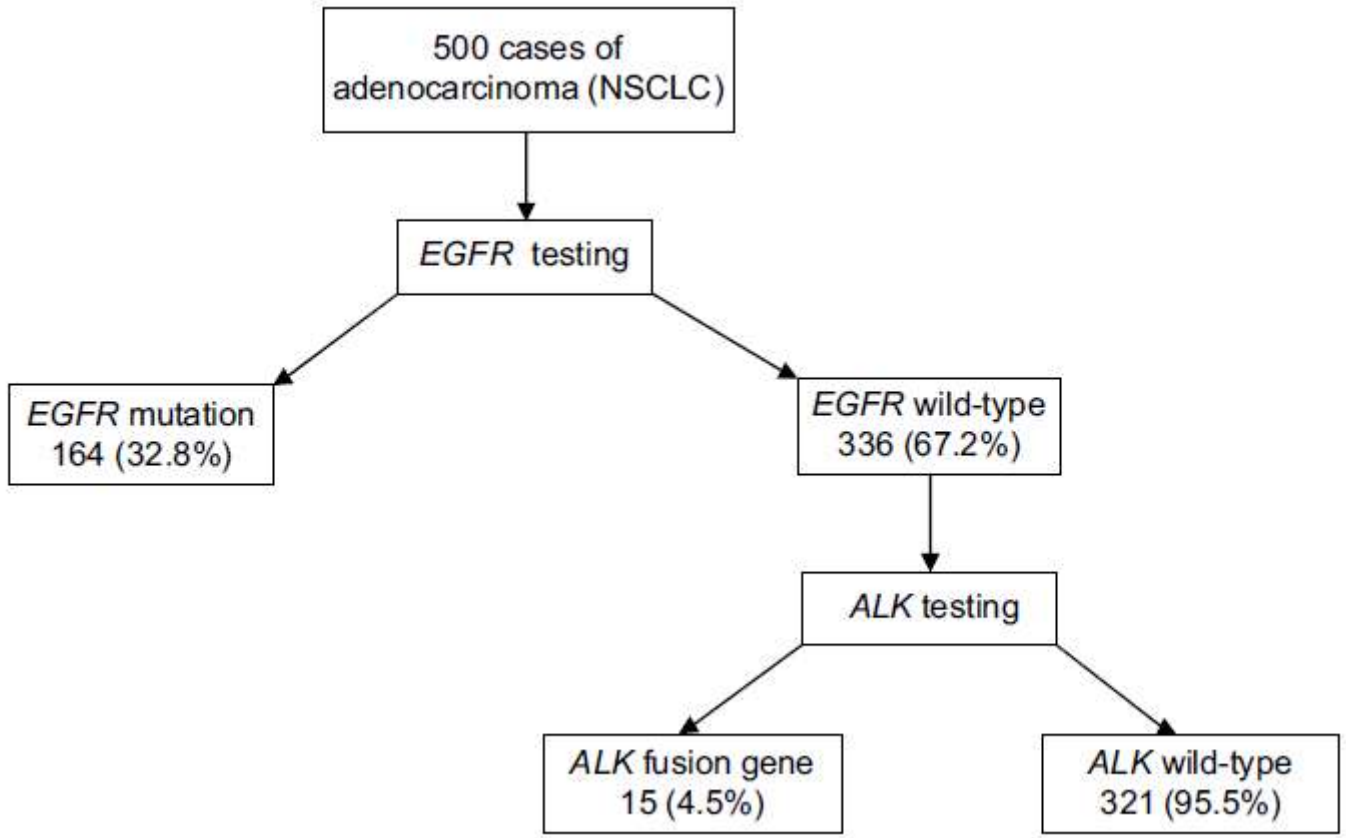

500 cases of adenocarcinoma (NSCLC)
EGFR testing
EGFR mutation 164 (32.8%)
EGFR wild-type 336 (67.2%)
ALK testing
ALK fusion gene 15 (4.5%)
ALK wild-type 321 (95.5%)

Table 4 Distribution of EGFR and EML4-ALK gene mutations

Variable	EGFR			EML4-ALK fusion gene		
	Wild-type n (%)	Mutated n (%)	*P*-value	Wild-type n (%)	Mutated n (%)	*P*-value
Sex			0.003			0.009
Female	95 (58.3)	68 (41.7)		86 (90.5)	9 (9.5)	
Male	241 (71.5)	96 (28.5)		235 (97.5)	6 (2.5)	
Age, years			0.549			0.0006
20–40	25 (67.6)	12 (32.4)		19 (76)	6 (24)	
40–60	153 (64.8)	83 (35.2)		146 (96.1)	6 (3.9)	
>60	158 (69.6)	69 (30.4)		156 (98.1)	3 (1.9)	
Smoking history			<0.001			0.151
Never-smokers	142 (56.8)	108 (43.2)		134 (94.4)	8 (5.6)	
Smokers	135 (82.3)	29 (17.7)		132 (97.1)	4 (2.9)	
Unknown	59 (68.6)	27 (31.4)		53 (91.4)	5 (8.6)	
Stage			0.346			0.644
I	4 (80)	1 (20)		4 (100)	0	
II	6 (54.5)	5 (45.5)		6 (100)	0	
III	60 (81.1)	14 (18.9)		59 (98.3)	1 (1.7)	
IV	246 (63.6)	141 (36.4)		236 (95.9)	10 (4.1)	
Unknown	20 (87)	3 (13)		16 (80)	4 (20)	

EML4-ALK gene fusions are present in lung adenocarcinomas from Indian patients

3% incidence of EML4-ALK gene fusion in EGFR mutation-negative cases is similar to other Western and Asian populations.

PGI DATA

- Out of 171 patients of adenocarcinoma of lung tested for ALK rearrangement in LCC 3 cases are positive.
- None of them received crizotinib treatment because of financial reasons.

TAKE HOME MESSAGE

- All patients of adenocarcinoma lung should be tested for EGFR & ALK mutation and should be offered targeted therapy accordingly.
- ROS1 mutation test can be offered to adenocarcinoma patients who are EGFR & ALK negative .
- Targeted therapy of NSCLC has better progression free survival and overall response rate and manageable toxicity profile as compared to chemotherapy.
- Second generation ALK inhibitors are equally effective as 1st generation ALK inhibitors and effective even when resistance to 1st generation ALK inhibitors develops.
- High cost of crizotinib in our country make it difficult to use in patients of NSCLC who are ALK& ROS1 positive.

- Govt of India should make necessary steps to ensure availabalility of crizotinib at a reasonable price in Indian market so that benefit of targeted therapy of lung cancer in Indian patients can be achived.
- At the present moment this drug is not cost effective.