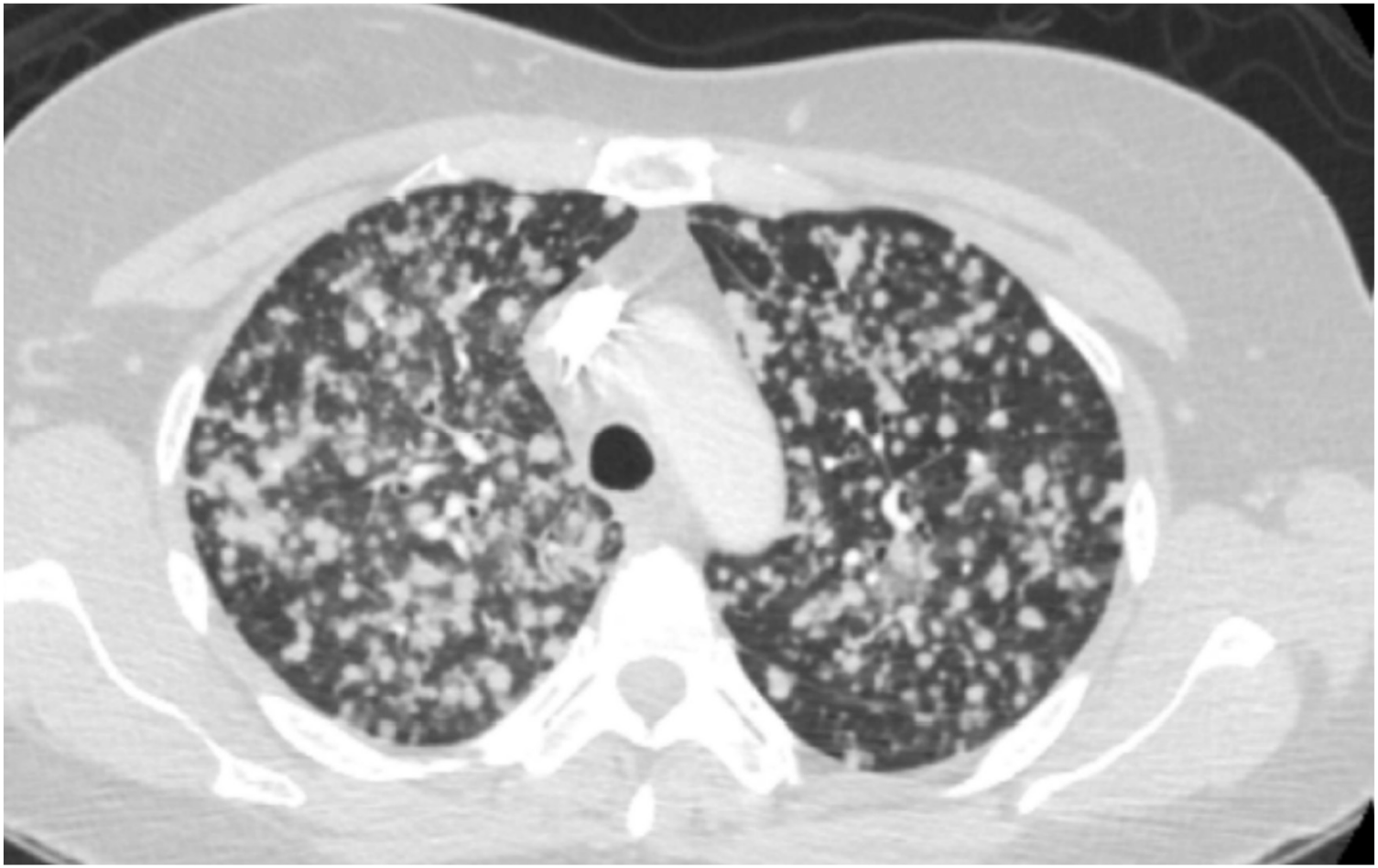
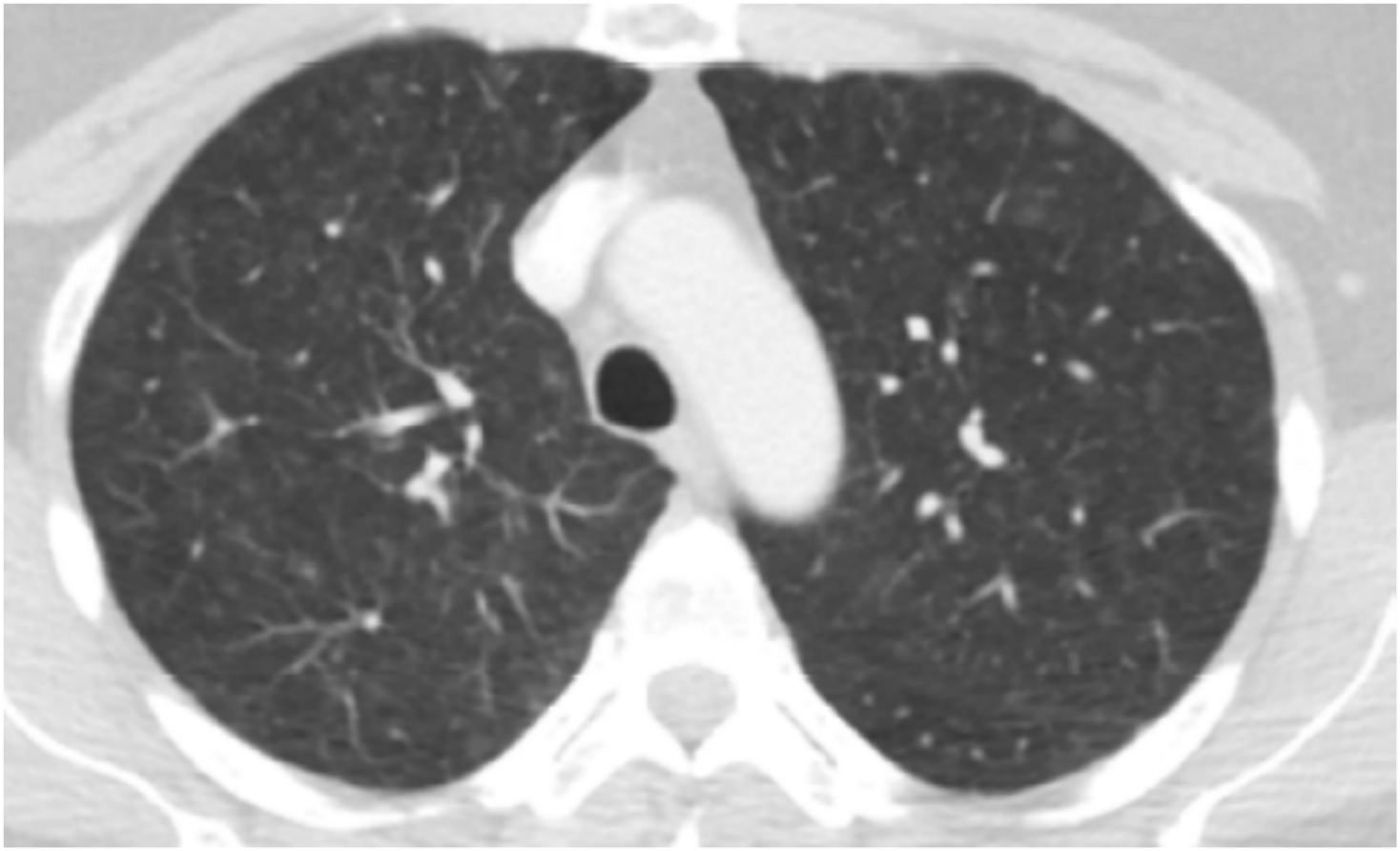
EGFR and ALK Inhibitors for Mutated Lung Cancer Tumors

Miguel A. Villalona-Calero, MD, FACP, FAAAS

Overview

1. Discovery and Tumor Association
2. Diagnostics
3. First Line
4. Resistance and Treatments Focused on Resistance
5. Utility of Cell Free DNA





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.

Sciencexpress Report

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†]

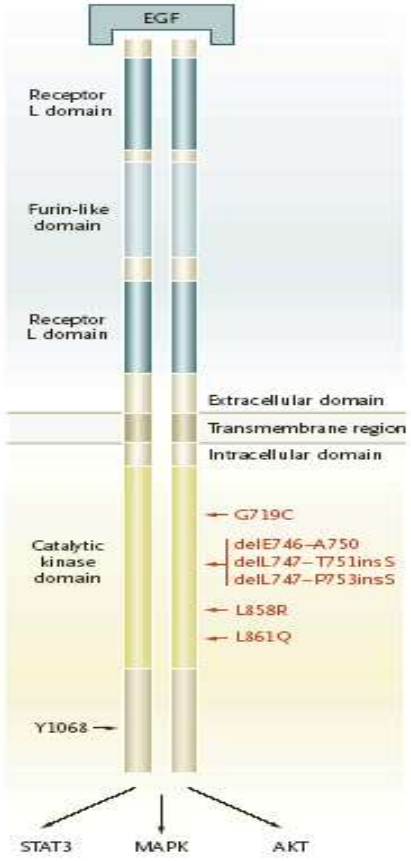
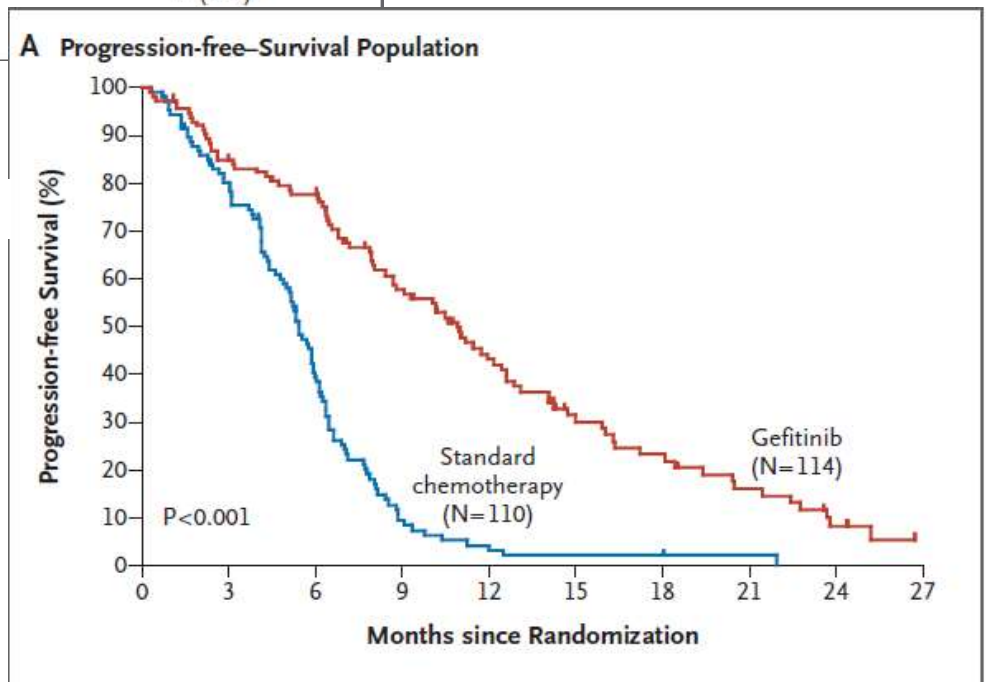

EGF
Receptor L domain
Furin-like domain
Receptor L domain
Extracellular domain
Transmembrane region
Intracellular domain
Catalytic kinase domain
G719C
delE746–A750
delL747–T751insS
delL747–P753insS
L858R
L861Q
Y1068
STAT3
MAPK
AKT

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

Response	Gefitinib (N=114)	Carboplatin–Paclitaxel (N=114)
	number of patients (percent)	
Complete response	5 (4.4)	0
Partial response	79 (69.3)	35 (30.7)
Complete or partial response†	84 (73.7)	35 (30.7)
Stable disease	18 (15.8)	56 (49.1)
Progressive disease	11 (9.6)	16 (14.0)
Response that could not be evaluated	1 (0.9)	7 (6.1)



Fusion of a Kinase Gene, *ALK*, to a Nucleolar Protein Gene, *NPM*, in Non-Hodgkin's Lymphoma

SCIENCE • VOL. 263 • 4 MARCH 1994

Stephan W. Morris,* Mark N. Kirstein, Marcus B. Valentine, Kristopher G. Dittmer, David N. Shapiro, David L. Saltman, A. Thomas Look

The 2;5 chromosomal translocation occurs in most anaplastic large-cell non-Hodgkin's lymphomas arising from activated T lymphocytes. This rearrangement was shown to fuse the *NPM* nucleolar phosphoprotein gene on chromosome 5q35 to a previously unidentified protein tyrosine kinase gene, *ALK*, on chromosome 2p23. In the predicted hybrid protein, the amino terminus of nucleophosmin (NPM) is linked to the catalytic domain of anaplastic lymphoma kinase (ALK). Expressed in the small intestine, testis, and brain but not in normal lymphoid cells, ALK shows greatest sequence similarity to the insulin receptor subfamily of kinases. Unscheduled expression of the truncated ALK may contribute to malignant transformation in these lymphomas.

Vol 448|2 August 2007|doi:10.1038/nature05945

nature

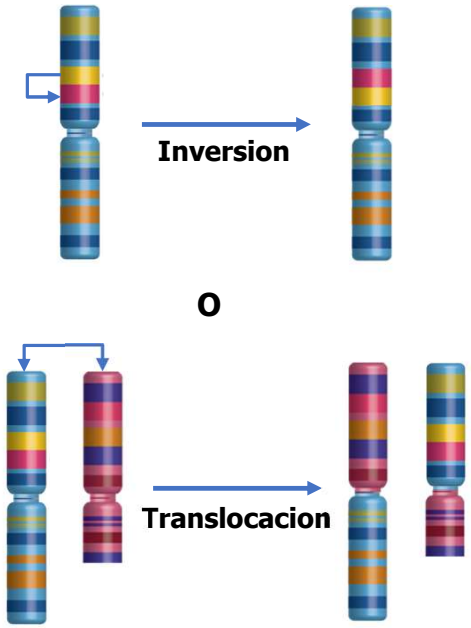
ARTICLES

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]

Improvement in the clinical outcome of lung cancer is likely to be achieved by identification of the molecular events that underlie its pathogenesis. Here we show that a small inversion within chromosome 2p results in the formation of a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*) gene in non-small-cell lung cancer (NSCLC) cells. Mouse 3T3 fibroblasts forced to express this human fusion tyrosine kinase generated transformed foci in culture and subcutaneous tumours in nude mice. The *EML4–ALK* fusion transcript was detected in 6.7% (5 out of 75) of NSCLC patients examined; these individuals were distinct from those harbouring mutations in the epidermal growth factor receptor gene. Our data demonstrate that a subset of NSCLC patients may express a transforming fusion kinase that is a promising candidate for a therapeutic target as well as for a diagnostic molecular marker in NSCLC.

Re-arrangements of ALK in NSCLC



Shaw AT, et al. J Clin Oncol 29:15s, 2011 (suppl; abstr 7507)

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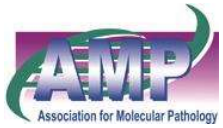


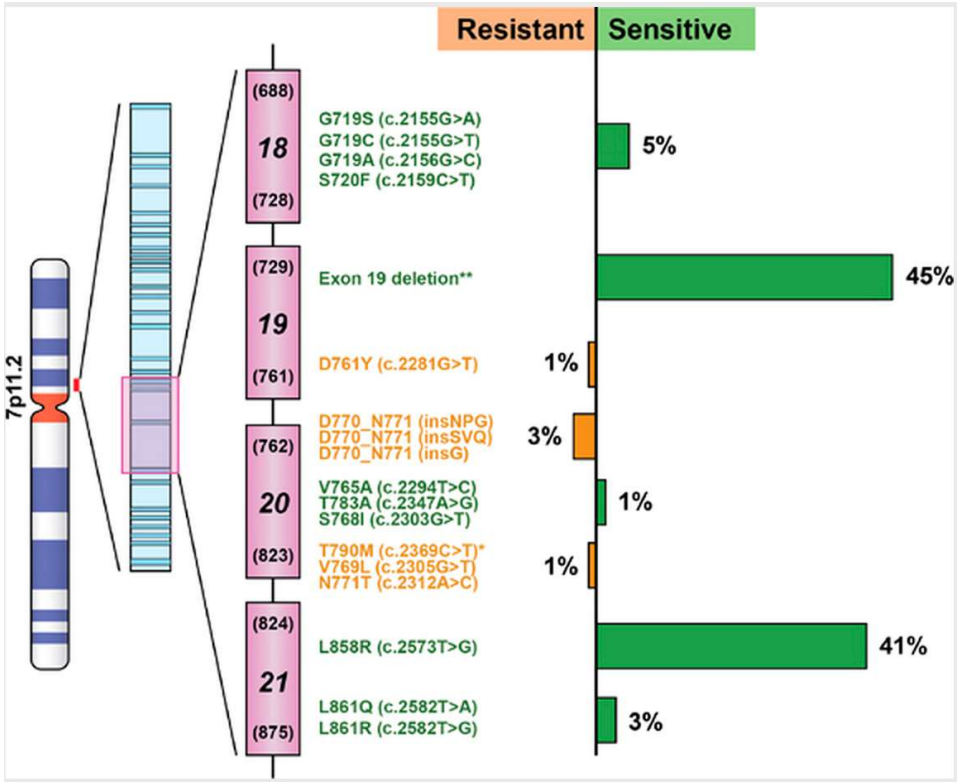
- **1.1a: Recommendation: *EGFR* molecular testing should be used to select patients for EGFR-targeted TKI therapy**, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.
- **1.1b: Recommendation: *ALK* molecular testing should be used to select patients for ALK-targeted TKI therapy**, and patients with lung adenocarcinoma should not be excluded from testing on the basis of clinical characteristics.

Ways to do Molecular Testing

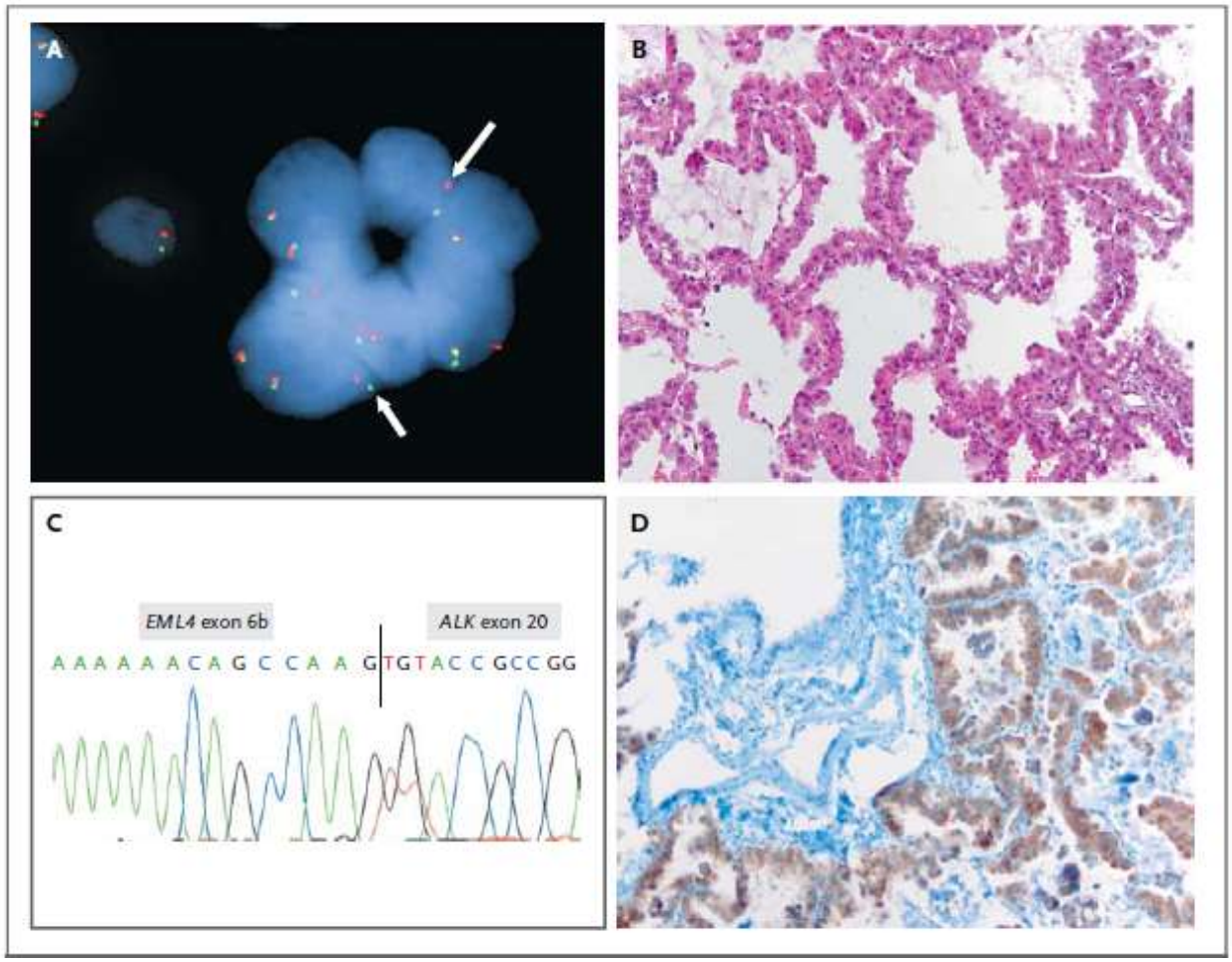
- PCR
- FISH
- IHC
- NGS
  - Limited
  - Extensive Panels

Complete Exon Sequencing vs. Hotspot Testing - *EGFR*

Testing for the Two Most Common Hotspots Misses 15% of the Targets



Cheng et al. 2012 Modern Pathology. Note that *EGFR* T790M is 1% of the total but after TKIs may be 50% of the total.


A
B
C
EML4 exon 6b
ALK exon 20
A A A A A A C A G C C A A G T G T A C C G C C G G
D

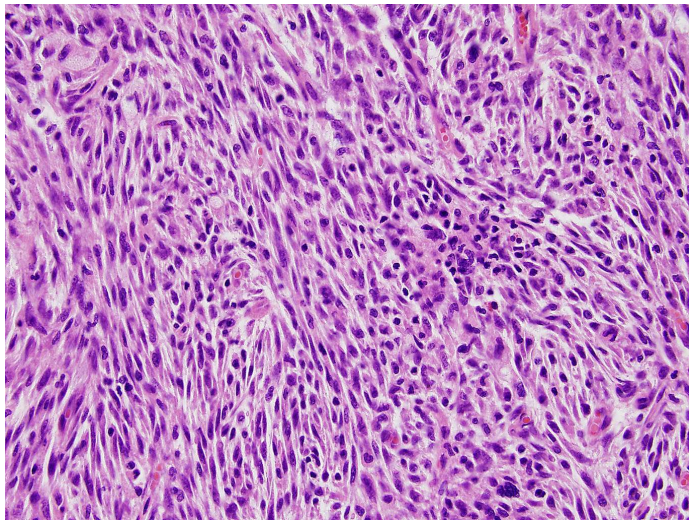


Fig. 3A

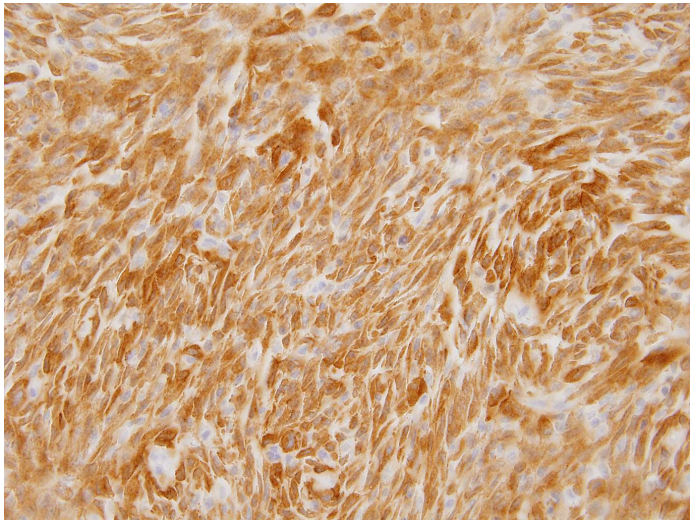


Fig. 3B

Figure 3. (A) H&E of inflammatory myofibroblastic tumor. Streaming fascicles of spindle cells admixed with few lymphocytes. (B) ALK antibody clone 5A4 from Leica Biosystems – at 1:100 with pressure cooker antigen retrieval. Diffuse cytoplasmic positivity

The Oncologist®

Precision Medicine Clinic: Molecular Tumor Board

EML4-ALK Rearrangement and Its Therapeutic Implications in Inflammatory Myofibroblastic Tumors

Fernando Vargas-Madueno,[a,b] Edwin Gould,[c] Raul Valor,[d] Nhu Ngo,[e] Linsheng Zhang,[e] Miguel A. Villalona-Calero[a,b]

Memorial Sloan Kettering Cancer Center

Memorial Hospital For Cancer & Allied Diseases

Molecular Diagnostics Service, Department of Pathology

1275 York Avenue New York, NY, 10065

Tel: (212) 639-8280 | Fax: (212) 717-3515

MSK-IMPACT Testing Report

[redacted]

Date of Birth	[redacted]/1999	**Accession #**	[redacted]
Gender	Female	**Specimen Submitted**	Left pleural biopsy #3
Tumor Type	Lung Adenocarcinoma	**Surgical Path. #**	-
Ref. Physician	- M.D.	**Account #**	[redacted]
Date of Receipt	6/21/2018	**Date of Report**	7/13/2018 12:46
Date of Procedure	6/21/2018		

Summary	no mutations, no copy number alterations, 1 structural variant detected. 1 alteration has an OncoKB treatment interpretation.
MSI Status	MICROSATELLITE STABLE (MSS). See MSI note below.[β]
Tumor Mutation Burden	Tumor mutation burden (TMB) for this sample is 0 mutations per Megabase.[γ]
Comments	Low tumor content (approximately 20% or less). Negative mutation, copy number and structural variant results, as well as low (stable) MSIsensor scores, should be interpreted with caution.

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Structural Variants				
EML4-ALK	Fusion	c.1490-288:EML4_c.3172+830:ALKinv	EML4 exons 1-12 and ALK exons 20-29	1 a

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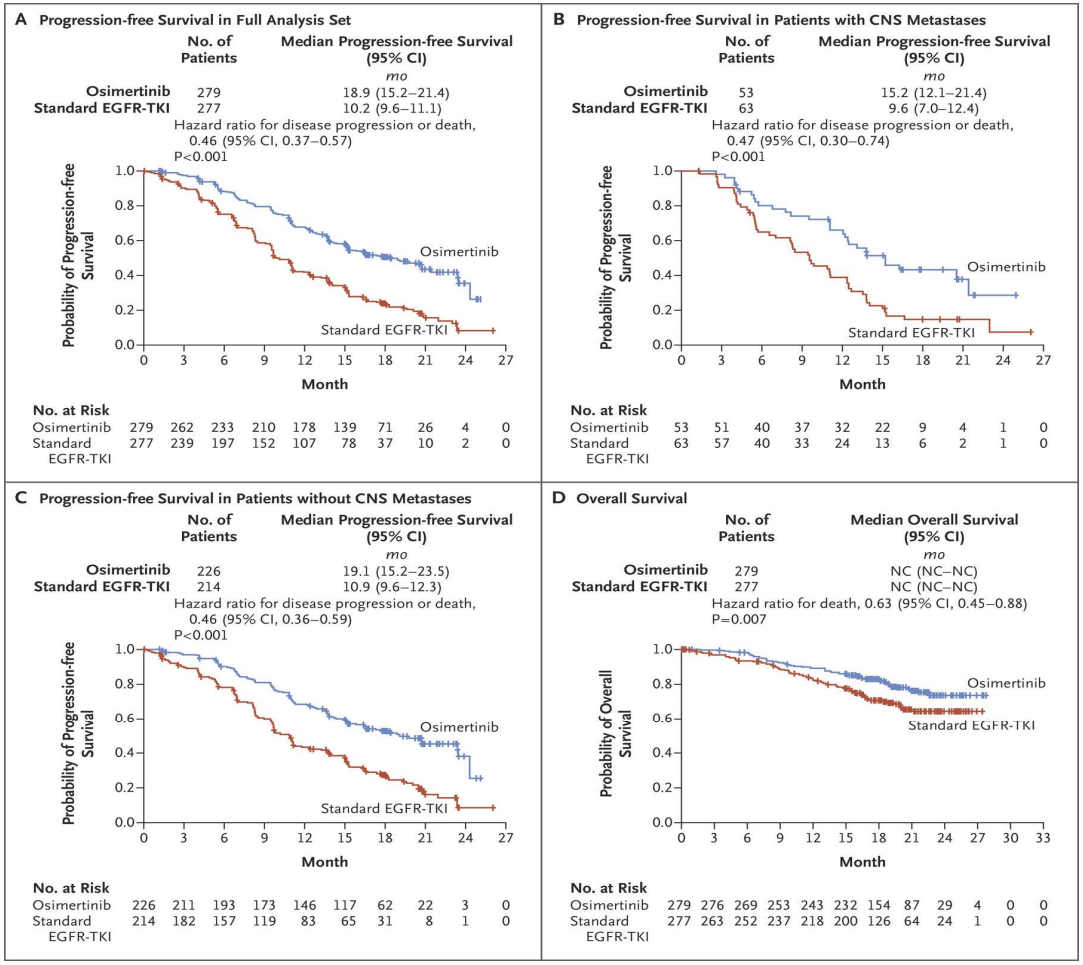
Available EGFR TKIs

- Gefitinib
- Erlotinib
- Afatinib
- Dacomitinib
- Osimertinib

Osimertinib vs. 1st Generation TKI

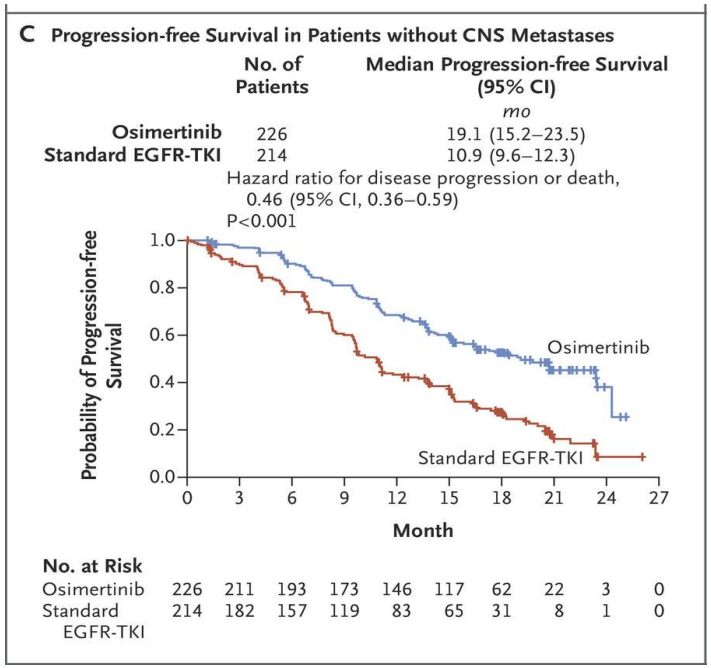


N Engl J Med 2018; 378:113-125

Alternatives to Osimertinib as First Line

- Sequencing
  - EGFR 1st or 2nd generation TKI followed by osimertinib if T790m+ or by chemo if T790 neg.
- Combination with VEGF inhibition
  - 1st generation TKI + Bevacizumab
  - 1st generation TKI + Ramucirumab
- Combination with Chemotherapy
  - 1st generation TKI + Pemetrexed/Carbo

Ramucirumab Plus Erlotinib



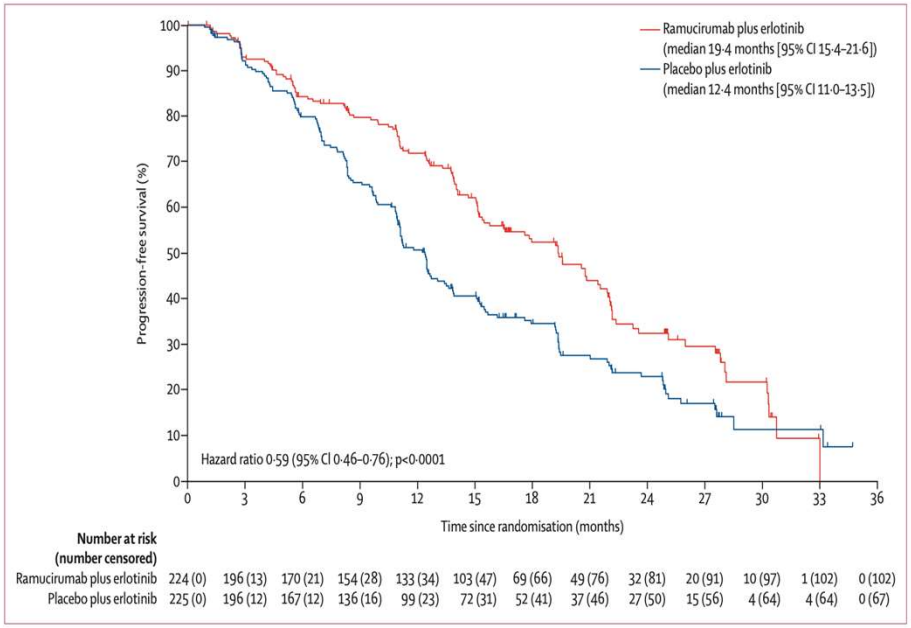
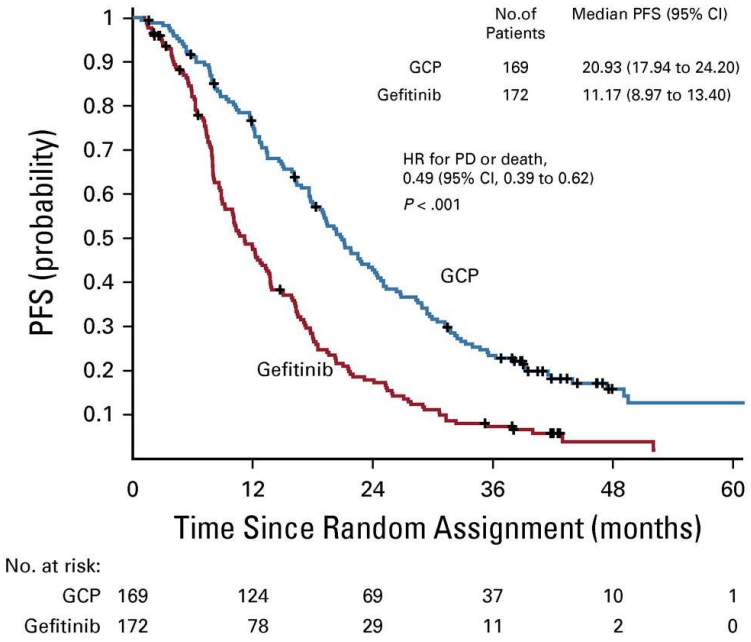
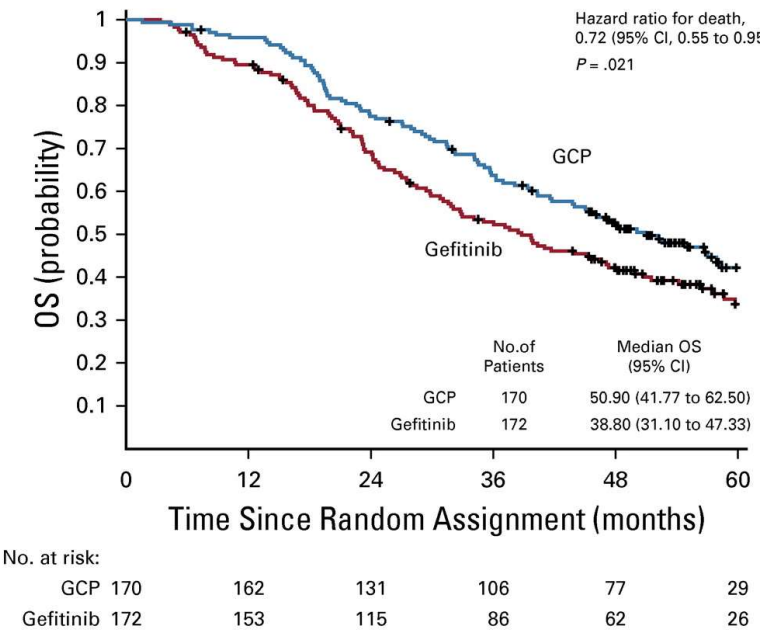


Figure 2: Kaplan-Meier estimates of investigator-assessed progression-free survival

Gefinitib Plus Chemotherapy





*Journal of Clinical Oncology*38, no. 2 (January 10, 2020) 115-123.

Available ALK TKIs

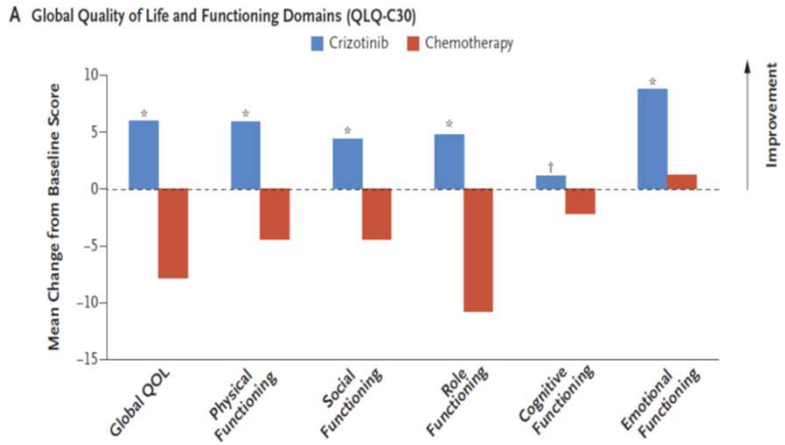
- Crizotinib
- Ceritinib
- Alectinib
- Brigatinib
- Lorlatinib

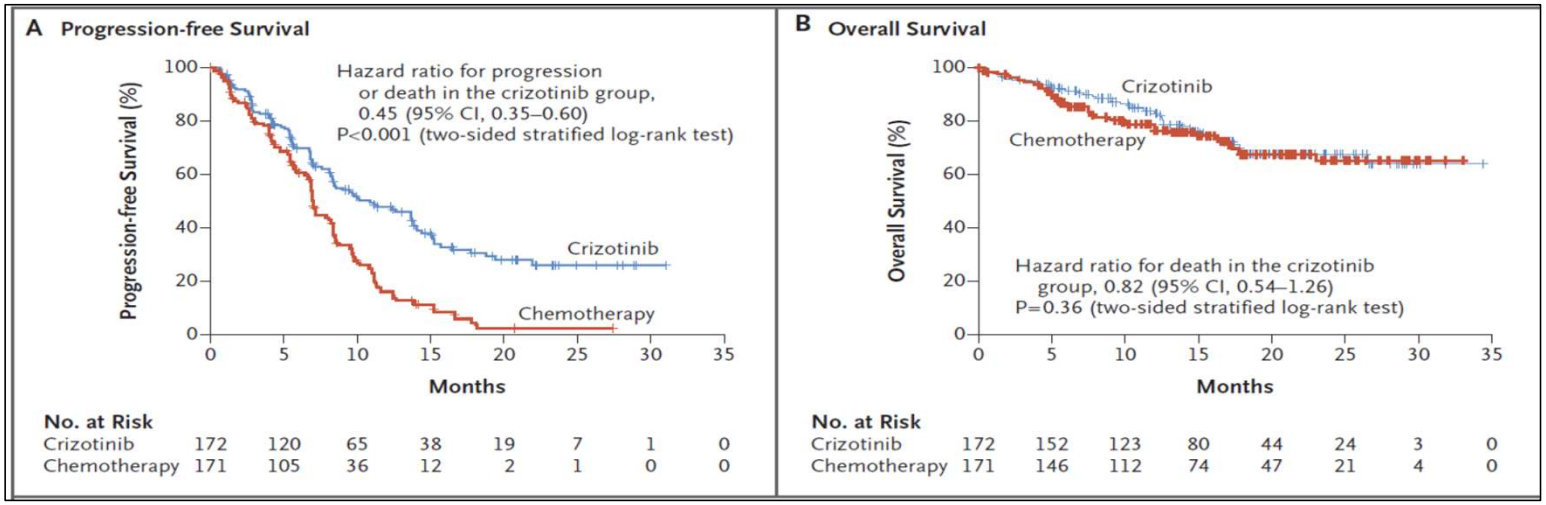
First-Line Crizotinib versus Chemotherapy in *ALK*-Positive Lung Cancer

N Engl J Med 2014;371:2167-77.
DOI: 10.1056/NEJMoa1408440

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

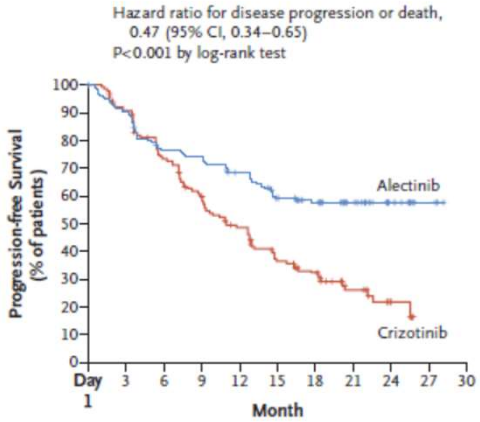




The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2017;377:829-38.
DOI: 10.1056/NEJMoa1704795
ORIGINAL ARTICLE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

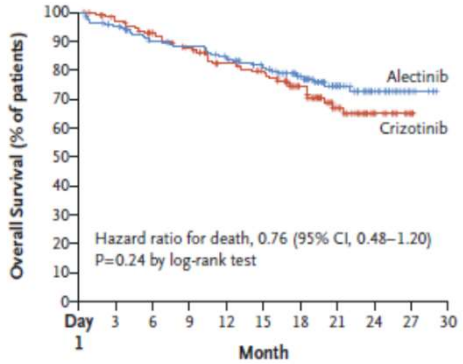
A Progression-free Survival



No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

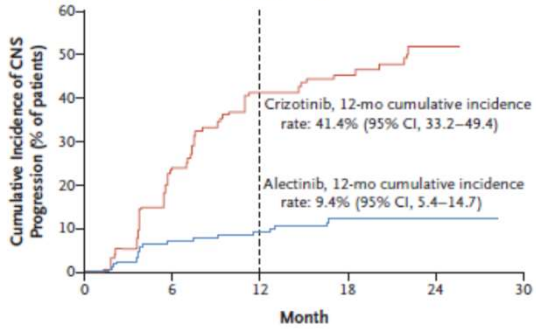
D Overall Survival



No. at Risk

Alectinib	152	142	131	127	119	107	87	51	24	5
Crizotinib	151	141	127	115	103	95	73	33	13	1

C Cumulative Incidence of CNS Progression



Adverse events that occurred at a higher incidence with alectinib than with crizotinib by 5 percentage points or more were anemia (20% vs. 5%), myalgia (16% vs. 2%), increased blood bilirubin (15% vs. 1%), increased weight (10% vs. 0%), musculoskeletal pain (7% vs. 2%), and photosensitivity reaction (5% vs. 0%) (Table 3). Adverse events that were more common with crizotinib included nausea (48% vs. 14% with alectinib), diarrhea (45% vs. 12%), and vomiting (38% vs. 7%)

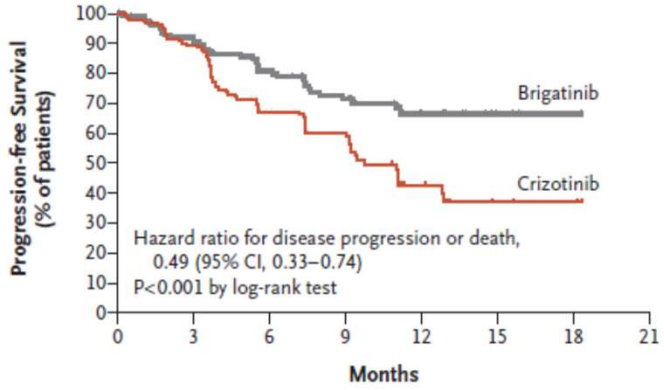
The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2018;379:2027-39.
DOI: 10.1056/NEJMoa1810171

ORIGINAL ARTICLE

Brigatinib versus Crizotinib in *ALK*-Positive Non–Small-Cell Lung Cancer

A Progression-free Survival

	Median (95% CI)	At 1 Yr (95% CI)
	mo	%
Brigatinib	NR	67 (56–75)
Crizotinib	9.8 (9.0–12.9)	43 (32–53)

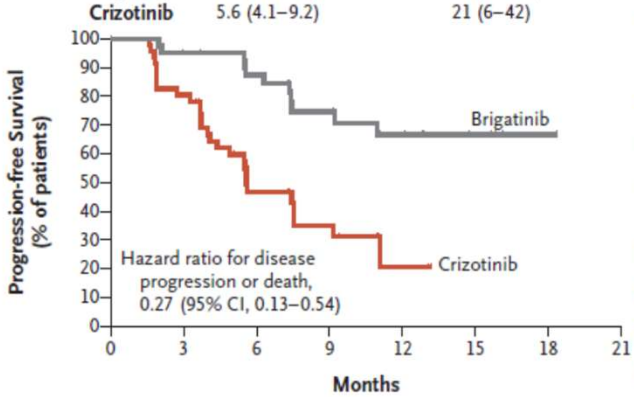


No. at Risk

Brigatinib	137	114	90	64	26	3	1
Crizotinib	138	117	75	50	18	3	2

D Survival without Intracranial Disease Progression among Patients with Brain Metastases at Baseline

	Median (95% CI)	At 1 Yr (95% CI)
	mo	%
Brigatinib	NR (11–NR)	67 (47–80)
Crizotinib	5.6 (4.1–9.2)	21 (6–42)



No. at Risk

Brigatinib	43	39	32	22	9	5	1
Crizotinib	47	37	16	9	2	0	0

Adverse events that occurred at a higher incidence by more than 5 percentage points with brigatinib than with crizotinib included an increased creatine kinase level (brigatinib [39%] vs. crizotinib [15%]), cough (25% vs. 16%), hypertension (23% vs. 7%), and an increased lipase level (19% vs. 12%). Adverse events that were more common with crizotinib than with brigatinib included nausea (crizotinib [56%] vs. brigatinib [26%]), diarrhea (55% vs. 49%), constipation (42% vs. 15%), peripheral edema (39% vs. 4%), vomiting (39% vs. 18%), an increased alanine aminotransferase level (32% vs. 19%), decreased appetite (20% vs. 7%), photopsia (20% vs. 1%), dysgeusia (19% vs. 4%), and visual impairment (16% vs.

Preferences for First Line

- EGFR mutant
  - Osimertinib
  - Afanitib for rare EGFR mutations
  - 1st generation TKI + Chemo or + Bev if osimertinib not available

- ALK Rearranged
  - Alectinib
  - Alternative Brigatinib

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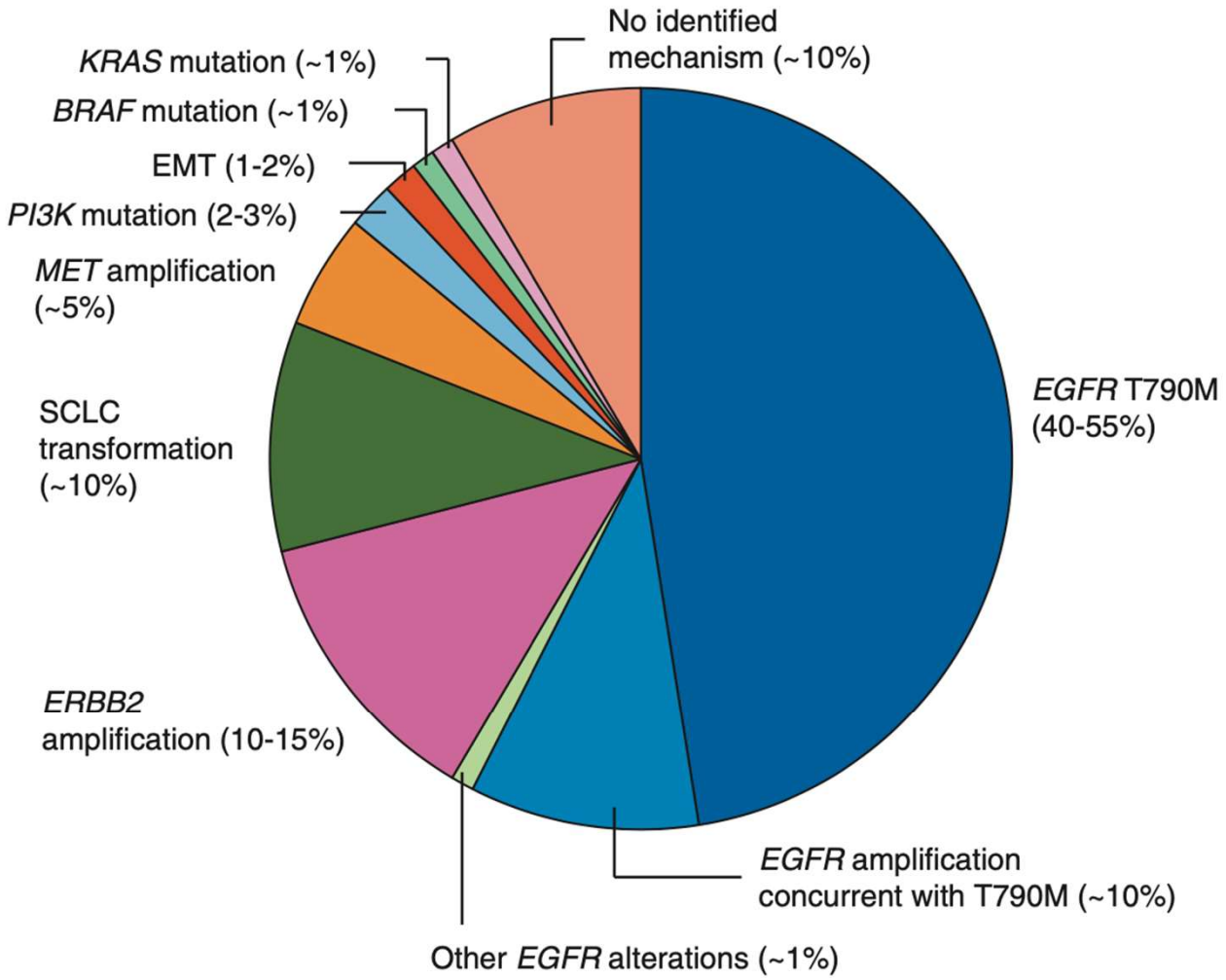
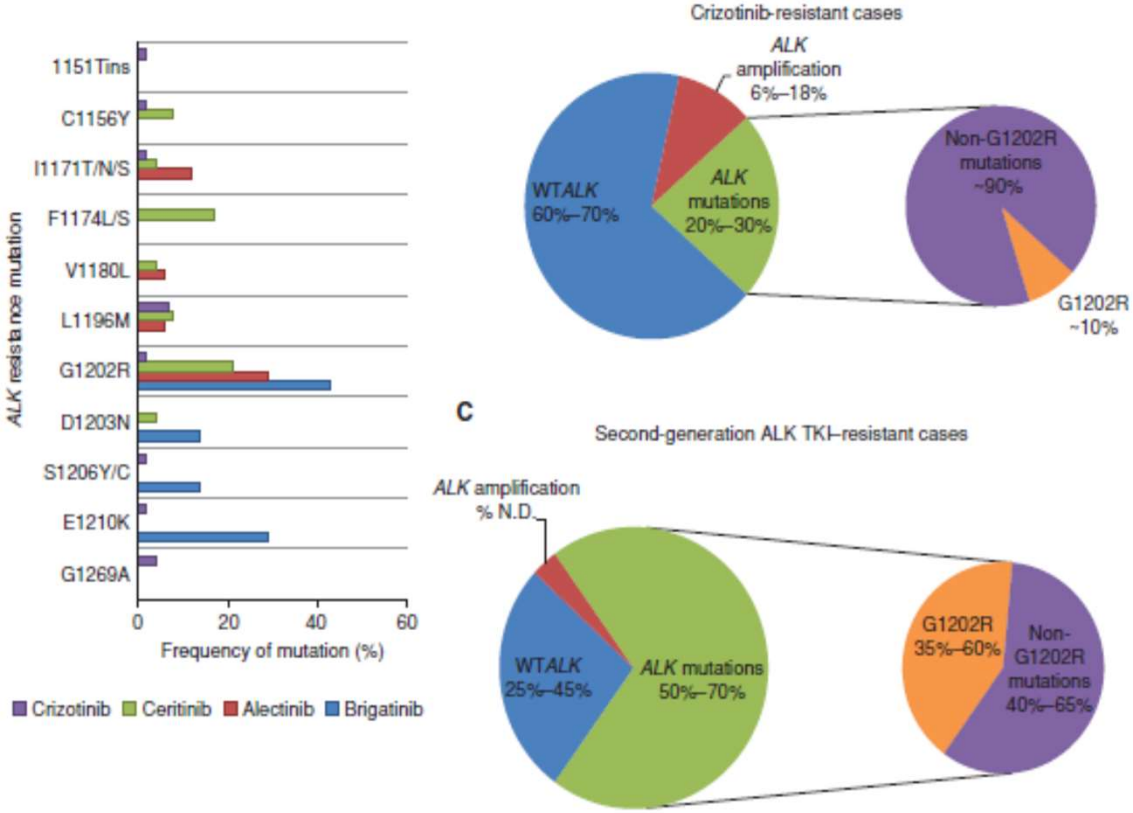


Annals of Oncology 29 (Supplement 1): i10–i19, 2018
doi:10.1093/annonc/mdx703

Preferences for Second Line and Beyond in EGFR mutants

- Biopsy of a Progressive Site, Highly recommended
- If no TKIs were previously used, add a TKI. Osimertinib preferred, especially if brain mets or T790m.
- If 1st or 2nd generation TKI used in first line, osimertinib is recommended if T790m present or brain mets are only progressing site. Otherwise, either add chemo to the TKI or use chemo alone.
- Adding a VEGF interacting agent can be considered if above fails.
- Chemo as per small cell, if small cell transformation.

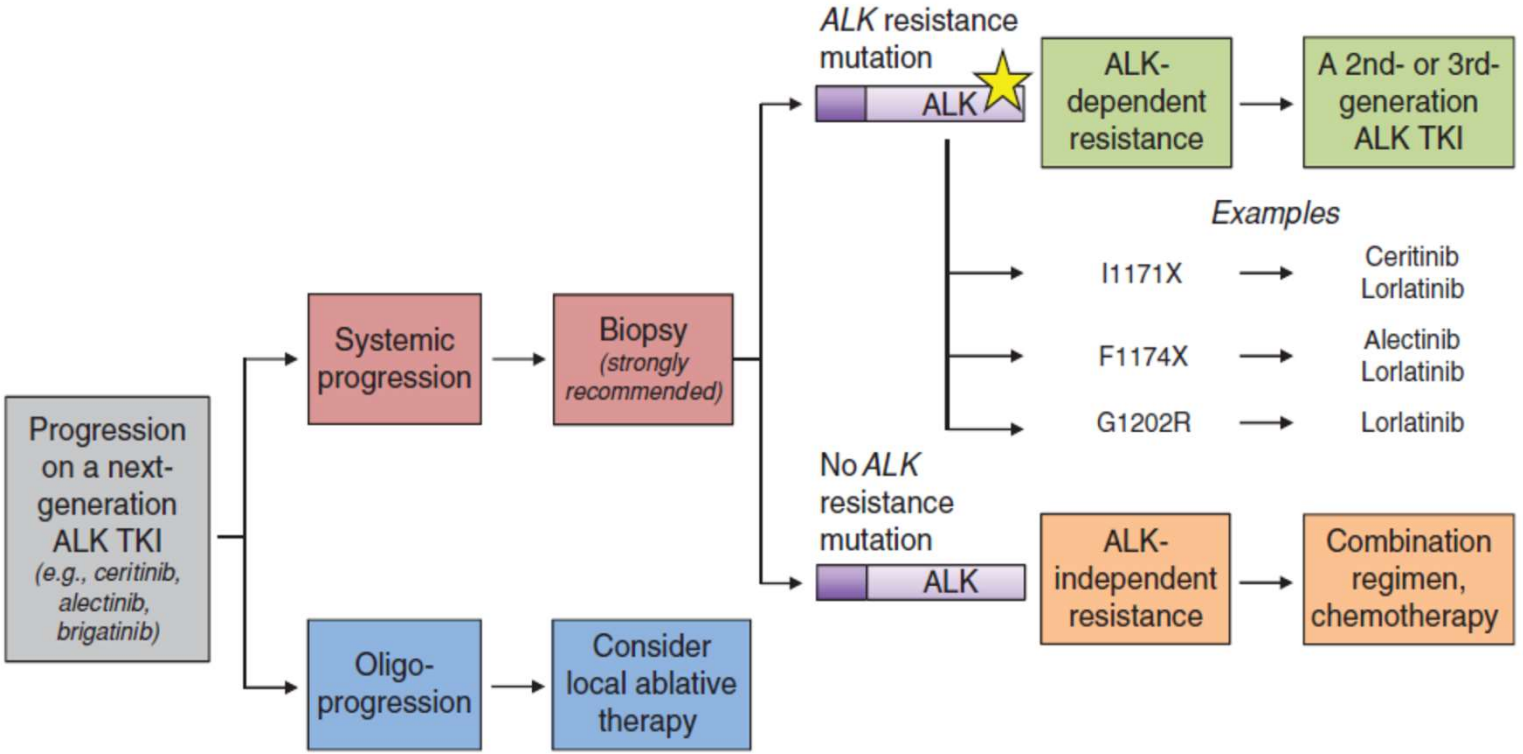
Resistance to ALK Inhibitors



Cancer Discovery 7(2); 1-19, 2017

ALK TKI	Crizotinib (PF-02341066)	Ceritinib (LDK378)	Alectinib (RO/ CH5424802)	Brigatinib (AP26113)	Lorlatinib (PF-06463922)	Entrectinib (RXDX-101)	Ensartinib (X-396)
Manufacturer	Pfizer	Novartis	Genentech	Ariad	Pfizer	Ignyta	Xcovery
Targets other than ALK	ROS1 MET	ROS1 IGF1R IR	GAK LTK RET	ROS1	ROS1	NTRK1 NTRK2 NTRK3 ROS1	ROS1 MET AXL
Resistance mutations known to be targeted by TKI	L1198F	I1171T/N L1196M S1206C/Y G1269A/S	L1152P/R C1156Y/T F1174C/L/V L1196M S1206C/Y G1269A/S	I1151Tins L1152P/R C1156Y/T F1174C/L/V L1196M G1202R[a] G1269A/S	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V L1196M G1202R[b] S1206C/Y E1210K G1269A/S	C1156Y/T L1196M	C1156Y/T L1196M
Reported resistance mutations to the TKI	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V V1180L L1196M G1202R S1206C/Y E1210K G1269A/S	I1151Tins L1152P/R C1156Y/T F1174C/ L/V G1202R	I1171T/N/S V1180L G1202R	G1202R[a] E1210K + S1206C E1210K + D1203N	L1198F + C1156Y[c]	G1202R	N.D.

Cancer Discovery 7(2); 1-19, 2017



Cancer Discovery 7(2); 1-19, 2017

ALK TKI	Crizotinib (PF-02341066)	Ceritinib (LDK378)	Alectinib (RO/CH5424802)	Brigatinib (AP26113)	Lorlatinib (PF-06463922)	Entrectinib (RXDX-101)	Ensartinib (X-396)
Manufacturer	Pfizer	Novartis	Genentech	Ariad	Pfizer	Ignyta	Xcovery
Targets other than ALK	ROS1 MET	ROS1 IGF1R IR	GAK LTK RET	ROS1	ROS1	NTRK1 NTRK2 NTRK3 ROS1	ROS1 MET AXL
Resistance mutations known to be targeted by TKI	L1198F	I1171T/N L1196M S1206C/Y G1269A/S	L1152P/R C1156Y/T F1174C/L/V L1196M S1206C/Y G1269A/S	I1151Tins L1152P/R C1156Y/T F1174C/L/V L1196M G1202R[a] G1269A/S	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V L1196M G1202R[b] S1206C/Y E1210K G1269A/S	C1156Y/T L1196M	C1156Y/T L1196M
Reported resistance mutations to the TKI	I1151Tins L1152P/R C1156Y/T I1171T/N/S F1174C/L/V V1180L L1196M G1202R S1206C/Y E1210K G1269A/S	I1151Tins L1152P/R C1156Y/T F1174C/L/V G1202R	I1171T/N/S V1180L G1202R	G1202R[a] E1210K + S1206C E1210K + D1203N	L1198F + C1156Y[c]	G1202R	N.D.

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Overview

1. Discovery and Tumor Association
2. Diagnostics
3. Front-Line Therapy
4. Resistance and Resistant Mutation Focused Treatments
5. Utility of cell Free DNA Analyses

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Precision Medicine and Imaging

Clinical Cancer Research

Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non–small Cell Lung Cancer

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FDA Approved Targets		Tissue +	Tissue -	Tissue Not Assessed/ QNS	Total		
EGFR Exon 19 del	cfDNA+	18	0	1	19	Sensitivity	81.8%
	cfDNA-	4	201	44	249	PPV	100.0%
	cfDNA cancelled / TND	0	11	3	14	Specificity	100.0%
	Total	22	212	48	282	NPV	98.0%
						Concordance	98.2%
EGFR L858R	cfDNA+	9	0	2	11	Sensitivity	90.0%
	cfDNA-	1	213	43	257	PPV	100.0%
	cfDNA cancelled / TND	0	11	3	14	Specificity	100.0%
	Total	10	224	48	282	NPV	99.5%
						Concordance	99.6%
ALK Fusion (ORIGINAL)	cfDNA+	5	0	1	6	Sensitivity	62.5%
	cfDNA-	3	207	52	262	PPV	100.0%
	cfDNA cancelled / TND	1	11	2	14	Specificity	100.0%
	Total	9	218	55	282	NPV	98.6%
						Concordance	98.6%
ALK Fusion (Re-analysis)	cfDNA+	6	0	1	7	Sensitivity	75.0%
	cfDNA-	2	207	52	261	PPV	100.0%
	cfDNA cancelled / TND	1	11	2	14	Specificity	100.0%
	Total	9	218	55	282	NPV	99.0%
						Concordance	99.1%
ROS1 Fusion	cfDNA+	0	0	0	0	Sensitivity	-
	cfDNA-	2	151	115	268	PPV	-
	cfDNA cancelled / TND	0	8	6	14	Specificity	100.0%
	Total	2	159	121	282	NPV	98.7%
						Concordance	98.7%
BRAF V600E mutation	cfDNA+	2	0	0	2	Sensitivity	100.0%
	cfDNA-	0	90	176	266	PPV	100.0%
	cfDNA cancelled / TND	0	5	9	14	Specificity	100.0%
	Total	2	95	187	282	NPV	100.0%
						Concordance	100.0%

Conclusions

- The Identification of EGFR mutations and ALK rearrangements in NSCLC has led to significant advances for the survival and quality of life of a substantial fraction of lung cancer patients.

- Several therapeutic alternatives are available for the frontline treatment and for patients experiencing subsequent progression.

- Technological advances in tissue and cell free DNA sequencing have poised us for a more informed choice of these alternatives.

MOC Question

Which one of the statements below is less likely to be true

1. Treatment with first generation or second generation tyrosine kinase inhibitors can be considered for first line treatment in patients with EGFR mutated lung cancer and metastatic disease.
2. Immuno histochemistry can be used as a method to diagnose ALK rearranged lung cancer.
3. Biopsy is not necessary in the recurrence setting for patients with ALK rearranged and EGFR mutated lung cancer previously treated with a tyrosine kinase inhibitor, as advances in cell free DNA testing can provide guidance to the next strategy of treatment in a less invasive way.
4. Given the approval of several second and third generation ALK inhibitors, there is no reason no consider the use of crizotinib either in the first line or recurrence setting.