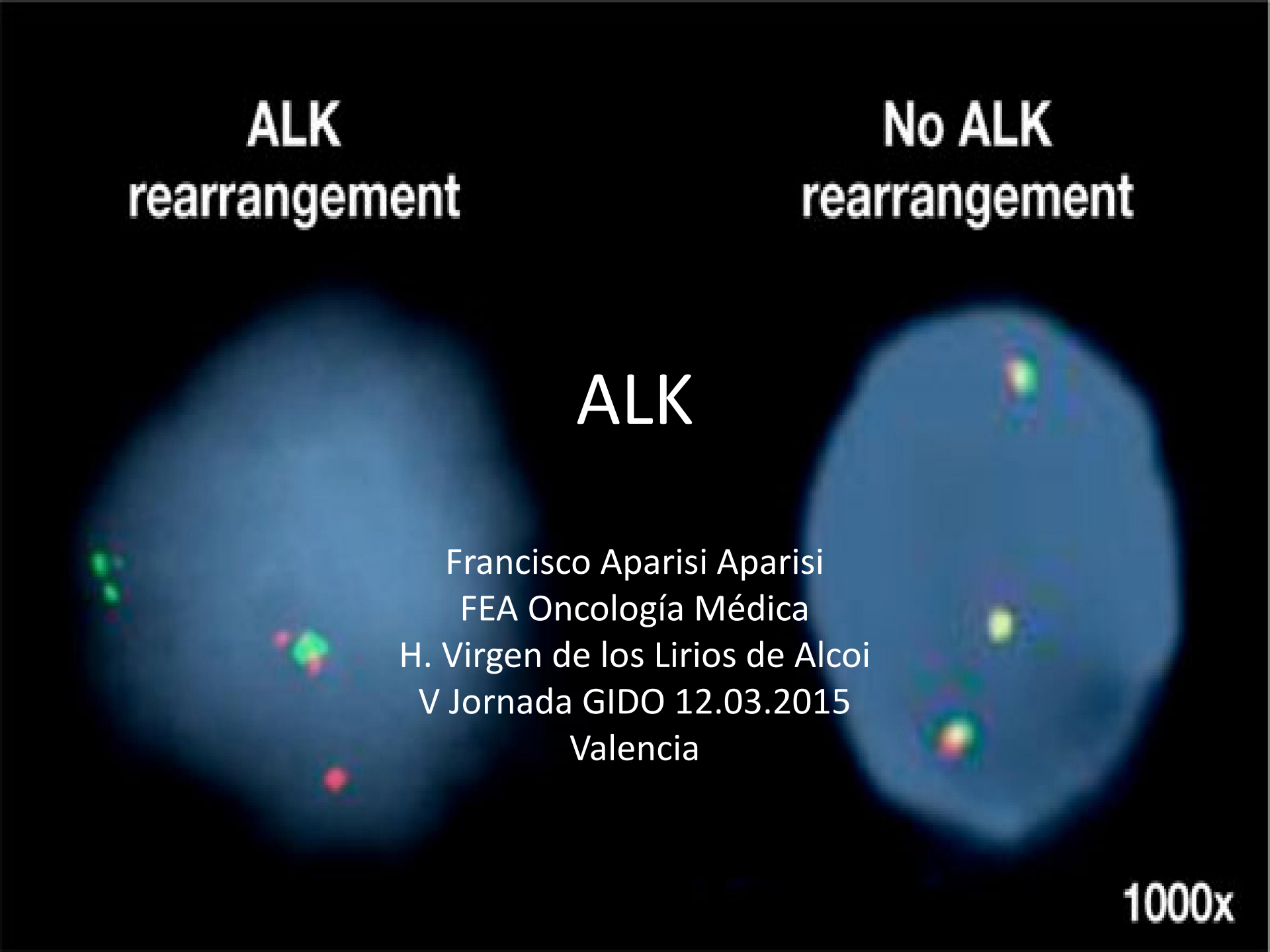

ALK

Francisco Aparisi Aparisi
FEA Oncología Médica
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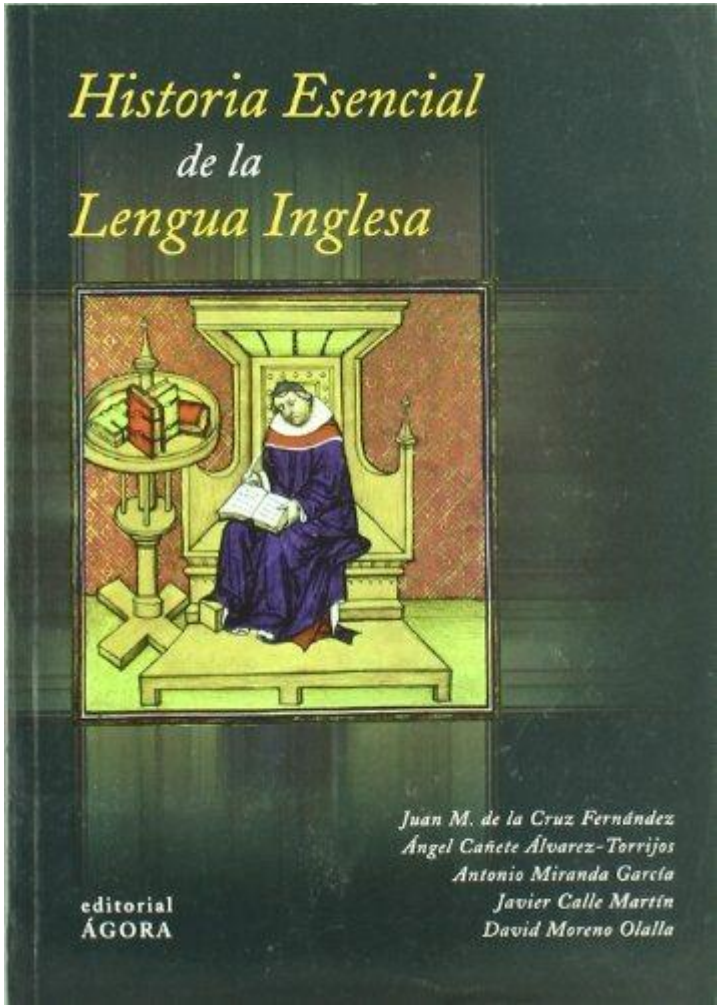
V Jornada GIDO 12.03.2015
Valencia

Translocaciones y mutaciones en otras circunstancias



INGLES ANTIGUO

Base Germana

Aleman: Tochter

I.Antiguo: dohtor

INGLES MEDIO

Influencia Francesa

I. Medio Doughter

INGLES MODERNO

Influencia Latina

I. Moderno: daughter

Translocaciones y mutaciones en otras circunstancias

Otto Jespersen (1860–1943)

GREAT VOWEL SHIFT

Explicar ALK como una clase de Historia

INTERNATIONAL JOURNAL OF ONCOLOGY 45: 509-515, 2014

Diagnostic and therapeutic issues for patients with advanced non-small cell lung cancer harboring anaplastic lymphoma kinase rearrangement: European vs. US perspective (Review)

MASSIMO DI MAIO[1], FILIPPO DE MARINIS[2], FRED R. HIRSCH[3] and CESARE GRIDELLI[4]

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Abstract. The recent availability of crizotinib in clinical practice, for the treatment of patients with advanced non-small cell lung cancer (NSCLC) selected by the presence of anaplastic lymphoma kinase (ALK) rearrangement, has relevant implications for both the diagnostic phase and the treatment choices. In the United States, crizotinib was approved by the Food and Drug Administration (FDA) in 2011 for patients with ALK positivity detected by FDA-approved companion diagnostic test. As of January, 2014, the only FDA-approved diagnostic test is Vysis ALK Break-Apart FISH Probe Kit. In Europe, European Medicines Agency (EMA) approved crizotinib for ALK-positive patients in 2012, without specifying the type of test used for determining the positivity. FISH remains the reference technique for ALK determination, but, if fully validated, immunohistochemistry could challenge the current ALK screening practice. Given the robust evidence of activity of crizotinib in ALK-positive patients both pretreated and chemotherapy-naïve, and the favourable tolerability profile of the drug, many oncologists would prefer to administer the drug as early as possible. This is technically feasible in the United States, where crizotinib was approved well before the availability of the results of the randomized phase III trial comparing the drug with standard second-line chemotherapy, and the use of crizotinib in ALK-positive patients is not restricted to a specific line of treatment. On the contrary, in Europe, differently from the FDA decision, crizotinib cannot be used in chemotherapy-naïve patients. In both realities, a deeper knowledge of mechanisms of resistance, the role of repeated biopsies, the treatment strategy for patients experiencing disease progression with crizotinib, the choice of the best chemotherapy regimen are challenging topics for the management of ALK-positive patients in clinical practice.

Contents

1. Introduction

In 2007, a small inversion within chromosome 2p, resulting in a fusion gene comprising portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*), was described in a subgroup of patients with advanced NSCLC and was immediately considered a promising candidate for a therapeutic target as well as for a diagnostic molecular marker (1). *EML4-ALK* translocation can be detected in a limited percentage of advanced NSCLC, representing about 5-6% of adenocarcinomas (2). Although ALK-positive cases are a small proportion of patients with advanced NSCLC, they represent a non-negligible number in absolute terms. In the United States, considering that about 228,190 new cases of lung cancer (both small cell and non-small cell) were expected for 2013 (3), it can be estimated that between 2,700 and 8,100 cases of ALK+ advanced NSCLC (representing 2-6% of all cases of advanced NSCLC) are diagnosed every year. Similarly, in Europe, where about 480,000 new lung cancer cases are diagnosed every year (4), between 5,000 and 14,500 cases of ALK+ advanced NSCLC are expected every year.

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Key words: crizotinib, non-small cell lung cancer, ALK rearrangement

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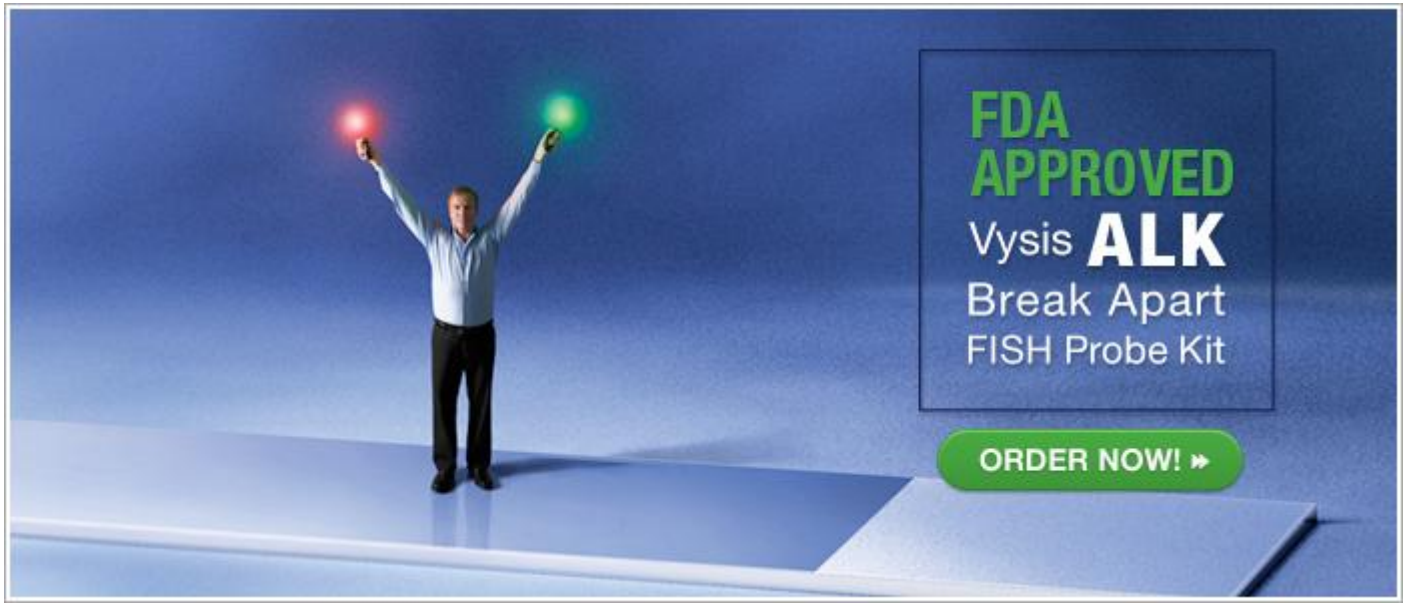
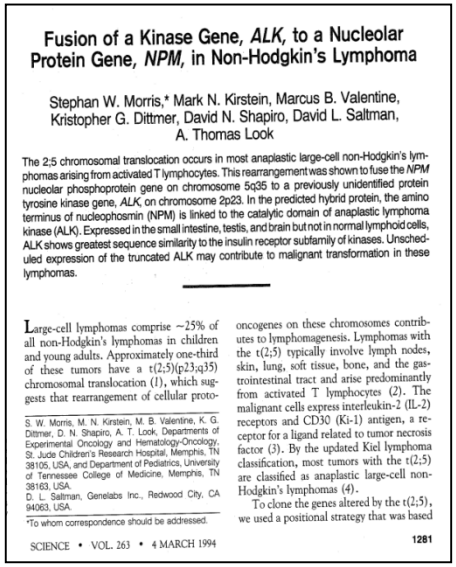
2. Capítulo 2: cómo se desarrolló crizotinib
3. Capítulo 3: aprobación de crizotinib por EMA y FDA
4. Capítulo 4: resistencias
5. Capítulo 5: tratamiento a la progresión de crizotinib
6. Capítulo 6:Rol de la QT en ALK +
7. Capítulo 7: Tratamiento de ALK en estadios tempranos

Capítulo 1: cómo se descubrió ALK



Historia

1994 → 2000 → 2007 → 2008



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

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

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D. L. Saltman, Genelabs Inc., Redwood City, CA 94063, USA.
*To whom correspondence should be addressed.

TPM3-ALK and *TPM4-ALK* Oncogenes in Inflammatory Myofibroblastic Tumors

Brandon Lawrence,* Antonio Perez-Atayde,† Michele K. Hibbard,* Brian P. Rubin,* Paola Dal Cin,* Jack L. Pinkus,* Geraldine S. Pinkus,† Sheng Xiao,* Eunhee S. Yi,§ Christopher D. M. Fletcher,* and Jonathan A. Fletcher*‡

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Accepted for publication May 8, 2000.
The sequences reported in this paper have been deposited in the GenBank database (accession nos. AF199105 and AF199106).

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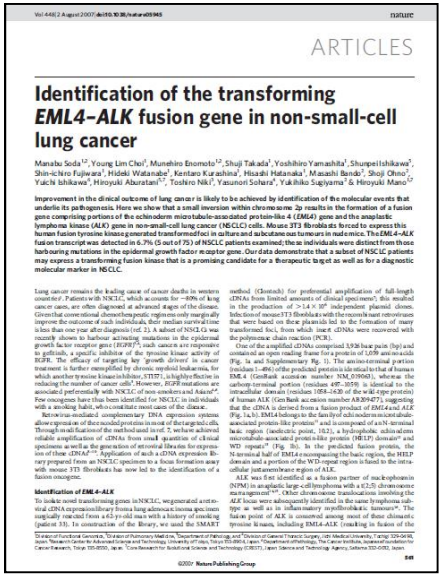

ARTICLES

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

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2Translational Pediatric Oncology, National Institute for Cancer Research and Italian Neuroblastoma Foundation, National Institute for Cancer Research, Genoa, Italy
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5The Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, USA
6Scripps Genomic Medicine and the Scripps Research Institute, La Jolla, California, USA
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9Abramson Family Cancer Research Institute, University of Pennsylvania School of Medicine, Philadelphia, PA USA

SUMMARY

Survival rates for the childhood cancer neuroblastoma have not substantively improved despite dramatic escalation in chemotherapy intensity. Like most human cancers, this embryonal malignancy can be inherited, but the genetic etiology of familial and sporadically occurring neuroblastoma was largely unknown. Here we show that germline mutations in the anaplastic lymphoma kinase gene (*ALK*) explain the majority of hereditary neuroblastomas, and that activating mutations can also be somatically acquired. We first identified a significant linkage signal at the short arm of chromosome 2 (maximum nonparametric LOD=4.23 at rs1344063) using a whole-genome scan in neuroblastoma pedigrees. Resequencing of regional candidate genes identified three separate missense mutations in

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AUTHOR CONTRIBUTIONS
Y.P.M and J.M.M designed the experiments and wrote the manuscript. Y.P.M, M.L., J.M.M, G.L, F.S, P.P., and G.P.T. collected the families for the linkage analysis. Y.P.M, M.L., L.L., E.R. and M.D. performed the genome-wide genotyping and linkage analysis. M.L. performed the DNA sequencing and analyses. K.A.C., A.W., and M.J.L. performed the siRNA experiments. E.F.A., H.H. and Y.P.M. performed the tumor SNP genotyping by marker analyses. J.E.L., K.A.C. and A.W. performed the expression analyses. K.A.C, R.S. and M.L. performed the protein work. G.M.B. initiated the collection of neuroblastoma pedigrees. AT and NJS performed the structural analysis of *ALK* coding mutations.
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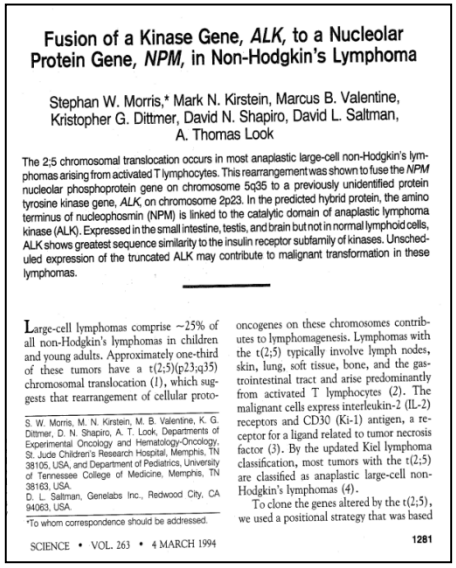

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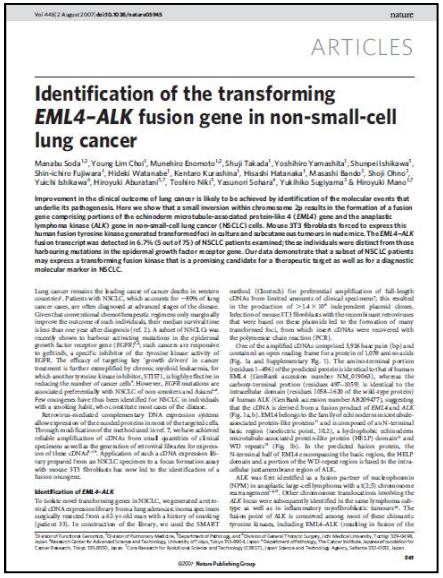

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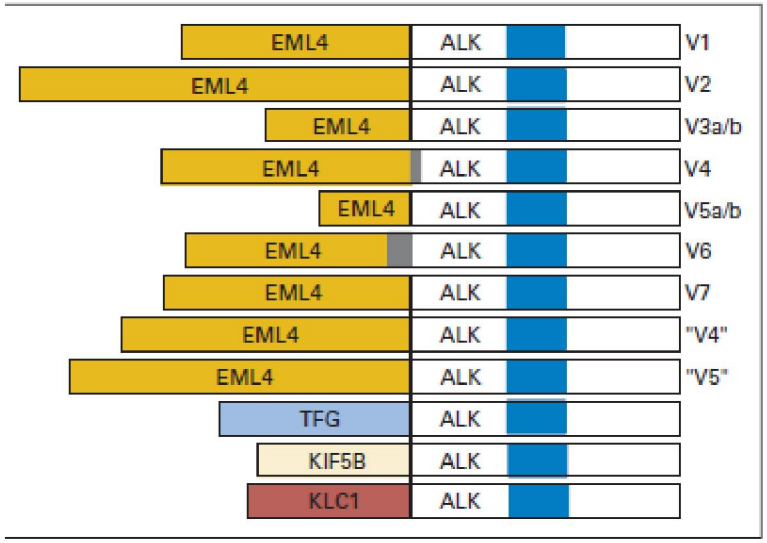
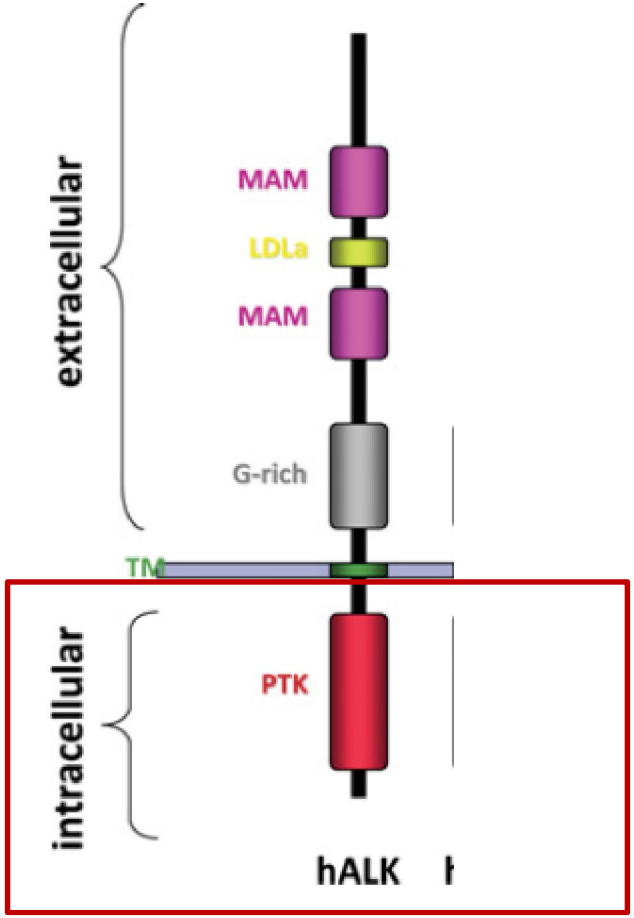
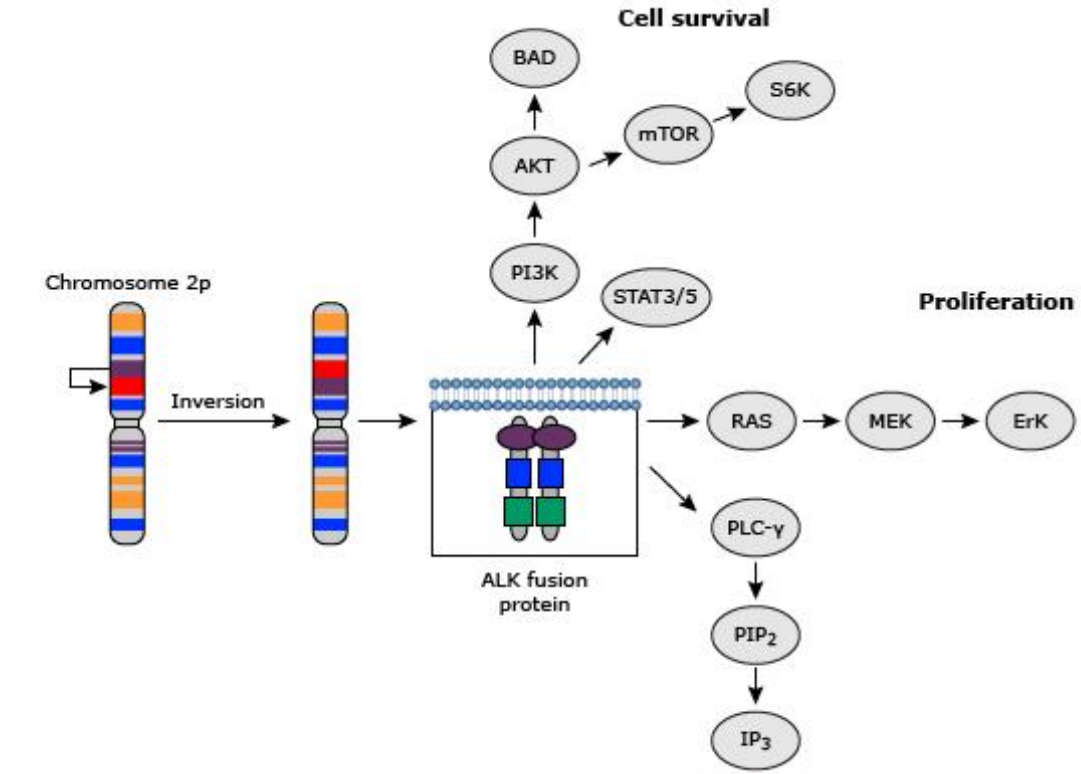


Fig 1. Schematic diagram depicting some of the anaplastic lymphoma kinase (ALK) fusion proteins identified in non–small-cell lung cancer (NSCLC). Echinoderm microtubule-associate protein-like 4 (EML4) –ALK variants are the predominant ALK fusions in NSCLC. More than 20 EML4-ALK variants have been identified, nine of which are shown here. Three other partner proteins have been identified in NSCLC: TFG, KIF5B, and KLC1. Three different KIB5B-ALK variants have been identified (not shown). The blue rectangles within each fusion protein symbolize the ALK tyrosine kinase domain. Adapted.[7a]

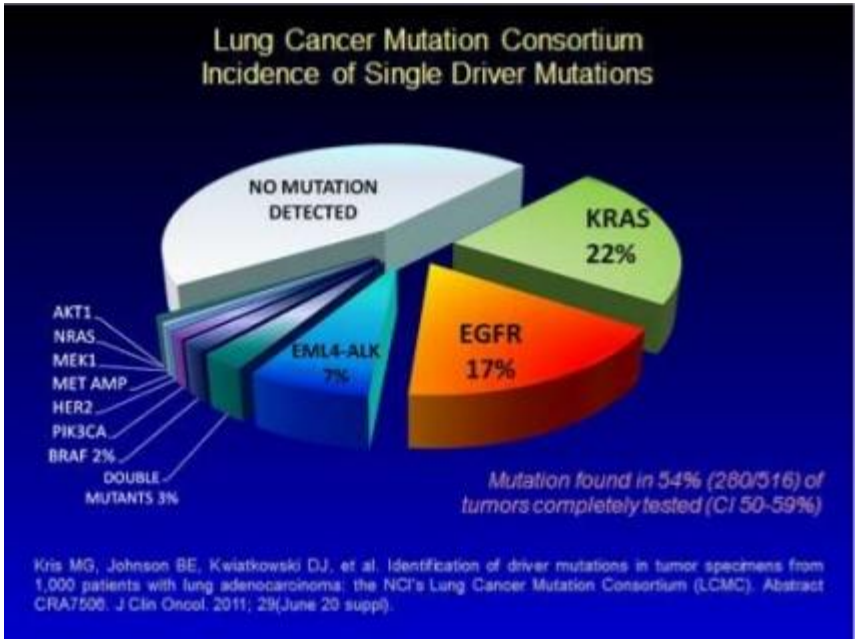


Palmer RH, et al. Biochem J 2009;420:345–61
Shaw AT JCO 2013



Shaw AT JCO 2013

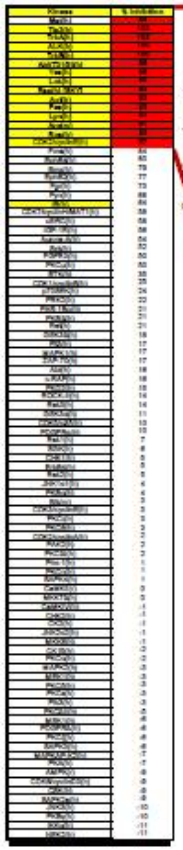
- Current estimates suggest the EML4–ALK fusion protein is present in approximately 3–5% of NSCLC tumors, which depends on the population studied and ALK detection methods used



Capítulo 2: cómo se ha desarrollado Crizotinib

Crizotinib (PF-02341066)

Upstate 102 kinase

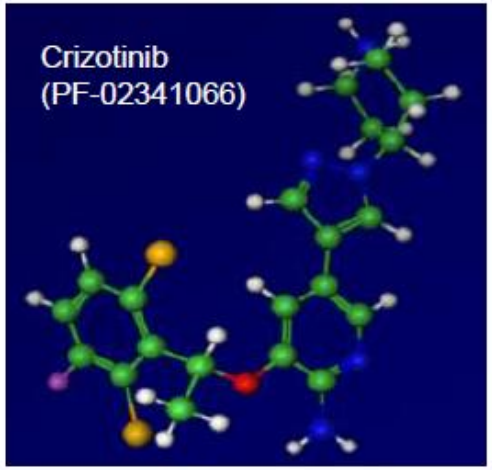


13 kinase "hits" <100X selective for c-MET

Cellular selectivity on 10 of 13 relevant hits

Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	20	2X
RON	298	34X
	189	22X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

*The cellular kinase activities were measured using ELISA capture method



Selectivity findings

- Crizotinib – ALK and c-MET inhibition at clinically relevant dose levels
- Crizotinib – low probability of pharmacologically relevant inhibition of any other kinase at clinically relevant dose levels

Fase I: PROFILE 1001

The NEW ENGLAND JOURNAL of MEDICINE

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

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

ABSTRACT

BACKGROUND

Oncogenic fusion genes consisting of *EML4* and anaplastic lymphoma kinase (*ALK*) are present in a subgroup of non–small-cell lung cancers, representing 2 to 7% of such tumors. We explored the therapeutic efficacy of inhibiting ALK in such tumors in an early-phase clinical trial of crizotinib (PF-02341066), an orally available small-molecule inhibitor of the ALK tyrosine kinase.

METHODS

After screening tumor samples from approximately 1500 patients with non–small-cell lung cancer for the presence of *ALK* rearrangements, we identified 82 patients with advanced *ALK*-positive disease who were eligible for the clinical trial. Most of the patients had received previous treatment. These patients were enrolled in an expanded cohort study instituted after phase 1 dose escalation had established a recommended crizotinib dose of 250 mg twice daily in 28-day cycles. Patients were assessed for adverse events and response to therapy.

RESULTS

Patients with *ALK* rearrangements tended to be younger than those without the rearrangements, and most of the patients had little or no exposure to tobacco and had adenocarcinomas. At a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients, with 46 confirmed partial responses and 1 confirmed complete response); 27 patients (33%) had stable disease. A total of 63 of 82 patients (77%) were continuing to receive crizotinib at the time of data cutoff, and the estimated probability of 6-month progression-free survival was 72%, with no median for the study reached. The drug resulted in grade 1 or 2 (mild) gastrointestinal side effects.

CONCLUSIONS

The inhibition of ALK in lung tumors with the *ALK* rearrangement resulted in tumor shrinkage or stable disease in most patients. (Funded by Pfizer and others; ClinicalTrials.gov number, NCT00585195.)

From the Massachusetts General Hospital Cancer Center (E.L.K., A.T.S., T.J.L., P.F., H.S., J.A.E., L.V.S., M.M.-K., J.S., D.A.H., J.W.C., A.J.I.), Beth Israel Deaconess Medical Center (B.J.D., D.B.C.), and Dana–Farber Cancer Institute (P.A.J., L.G., G.I.S.) — all in Boston; Seoul National University College of Medicine, Seoul, Korea (Y.-J.B., W.-H.K.); the University of Colorado Cancer Center, Aurora (D.R.C., M.V.-G.); Peter MacCallum Cancer Centre, Melbourne, Australia (B.S.); Memorial Sloan-Kettering Cancer Center, New York (R.G.M.); the University of California, Irvine (S.-H.I.O.); Pfizer Pharmaceuticals, La Jolla, CA (W.T., G.C.W., S.M.S., J.G.C., K.W.); and the University of Chicago, Chicago (M.J.R., R.S.). Address reprint requests to Dr. Kwak at the Massachusetts General Hospital Cancer Center, 55 Fruit St., Yawkey 7E-238, Boston, MA 02114, or at ekwak@partners.org.

N Engl J Med 2010;363:1693-703.

Activity and safety of crizotinib in patients with *ALK*-positive non-small-cell lung cancer: updated results from a phase 1 study

D Ross Camidge, Yung-Jue Bang, Eunice L Kwak, A John Iafrate, Marileila Varella-Garcia, Stephen B Fox, Gregory J Riely, Benjamin Solomon, Sai-Hong I Ou, Dong-Wan Kim, Ravi Salgia, Panagiotis Fidias, Jeffrey A Engelman, Leena Gandhi, Pasi A Jänne, Daniel B Costa, Geoffrey I Shapiro, Pasikanti L Rosso, Katherine Ruffner, Patricia Stephenson, Yiyun Tang, Keith Wilner, Jeffrey W Clark, Alice T Shaw

Summary

Background *ALK* fusion genes occur in a subset of non-small-cell lung cancers (NSCLCs). We assessed the tolerability and activity of crizotinib in patients with NSCLC who were prospectively identified to have an *ALK* fusion within the first-in-man phase 1 crizotinib study.

Methods In this phase 1 study, patients with *ALK*-positive stage III or IV NSCLC received oral crizotinib 250 mg twice daily in 28-day cycles. Endpoints included tumour responses, duration of response, time to tumour response, progression-free survival (PFS), overall survival at 6 and 12 months, and determination of the safety and tolerability and characterisation of the plasma pharmacokinetic profile of crizotinib after oral administration. Responses were analysed in evaluable patients and PFS and safety were analysed in all patients. This study is registered with ClinicalTrials.gov, number NCT00585195.

Findings Between Aug 27, 2008, and June 1, 2011, 149 *ALK*-positive patients were enrolled, 143 of whom were included in the response-evaluable population. 87 of 143 patients had an objective response (60·8%, 95% CI 52·3–68·9), including three complete responses and 84 partial responses. Median time to first documented objective response was 7·9 weeks (range 2·1–39·6) and median duration of response was 49·1 weeks (95% CI 39·3–75·4). The response rate seemed to be largely independent of age, sex, performance status, or line of treatment. Median PFS was 9·7 months (95% CI 7·7–12·8). Median overall survival data are not yet mature, but estimated overall survival at 6 and 12 months was 87·9% (95% CI 81·3–92·3) and 74·8% (66·4–81·5), respectively. 39 patients continued to receive crizotinib for more than 2 weeks after progression because of perceived ongoing clinical benefit from the drug (12 for at least 6 months from the time of their initial investigator-defined disease progression). Overall, 144 (97%) of 149 patients experienced treatment-related adverse events, which were mostly grade 1 or 2. The most common adverse events were visual effects, nausea, diarrhoea, constipation, vomiting, and peripheral oedema. The most common treatment-related grade 3 or 4 adverse events were neutropenia (n=9), raised alanine aminotransferase (n=6), hypophosphataemia (n=6), and lymphopenia (n=6).

Interpretation Crizotinib is well tolerated with rapid, durable responses in patients with *ALK*-positive NSCLC. There seems to be potential for ongoing benefit after initial disease progression in this population, but a more formal definition of ongoing benefit in this context is needed.

Funding Pfizer.

Introduction

Activation of the *ALK* gene has been described in several human cancers, including non-small-cell lung cancer (NSCLC), inflammatory myofibroblastic tumours, neuroblastomas, and diffuse large B-cell lymphomas, suggesting that ALK-mediated signalling might play a part in the development or progression of these tumours.[1–3] Activation of the *ALK* gene is usually through chromosomal rearrangement resulting in the placement of one of several different 5′ fusion partners and their associated promoter region upstream of the kinase domain of *ALK*.

ALK rearrangements in NSCLC were first described in 2007[4] and have an estimated prevalence of 3–5% in series mostly dominated by adenocarcinoma on histology.[5,7] *EML4–ALK* is the most common *ALK* fusion gene in NSCLC and occurs as several variants with different breakpoints in the *EML4* gene.[4,8] Other, more rare non-*EML4* fusions, including *KIF5B–ALK* and *TFG–ALK*, have also been described in lung cancer.[5,9] Their exact frequency and clinical significance remain under investigation but, by analogy with *EML4* and other oncogenic *ALK* fusions,[8] they also probably represent targets for therapeutic ALK inhibition in NSCLC. *ALK* fusions typically occur independently of *EGFR* and *KRAS* gene mutations,[5,8] although these aberrations are not mutually exclusive.[10,11] In the recent Lung Cancer Mutation Consortium series,[7] 8% of *ALK*-positive adenocarcinomas were also positive for either an *EGFR* or *KRAS* mutation.

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See Comment page 967

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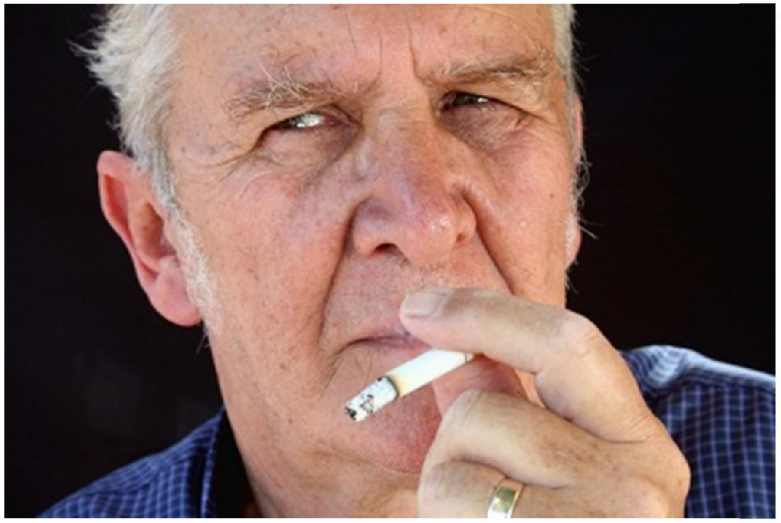
ross.camidge@ucdenver.edu

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

Characteristic	Value
Male sex — no. (%)	43 (52)
Age — yr	
Mean	51
Range	25–78
Race — no. (%)*	
White	46 (56)
Asian	29 (35)
Other	7 (9)
ECOG performance status — no. (%)†	
0	24 (29)
1	44 (54)
2	13 (16)
3	1 (1)
No. of previous therapies — no. (%)	
0	5 (6)
1	27 (33)
2	15 (18)
≥3	34 (41)
Not reported	1 (1)
Histologic analysis — no. (%)	
Adenocarcinoma	79 (96)
Squamous-cell carcinoma	1 (1)
Other	2 (2)
Smoking history — no. (%)‡	
Never	62 (76)
≤10 pack-yr	15 (18)
>10 pack-yr	5 (6)

Características 82 pacientes

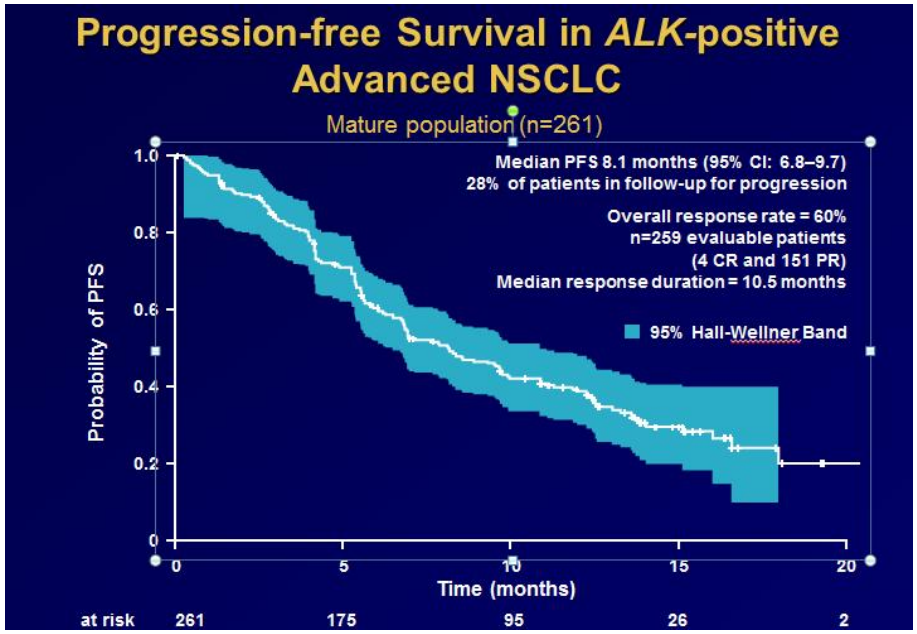
- Varones
- Jóvenes
- Adenocarcinoma
- No fumadores o < 10 paq/año



Fase II

- Profile 1005
- Diferentes Abstracts.

ASCO American Society of Clinical Oncology
Making a world of difference in cancer care



ESMO
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BETTER MEDICINE
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European Society for Medical Oncology

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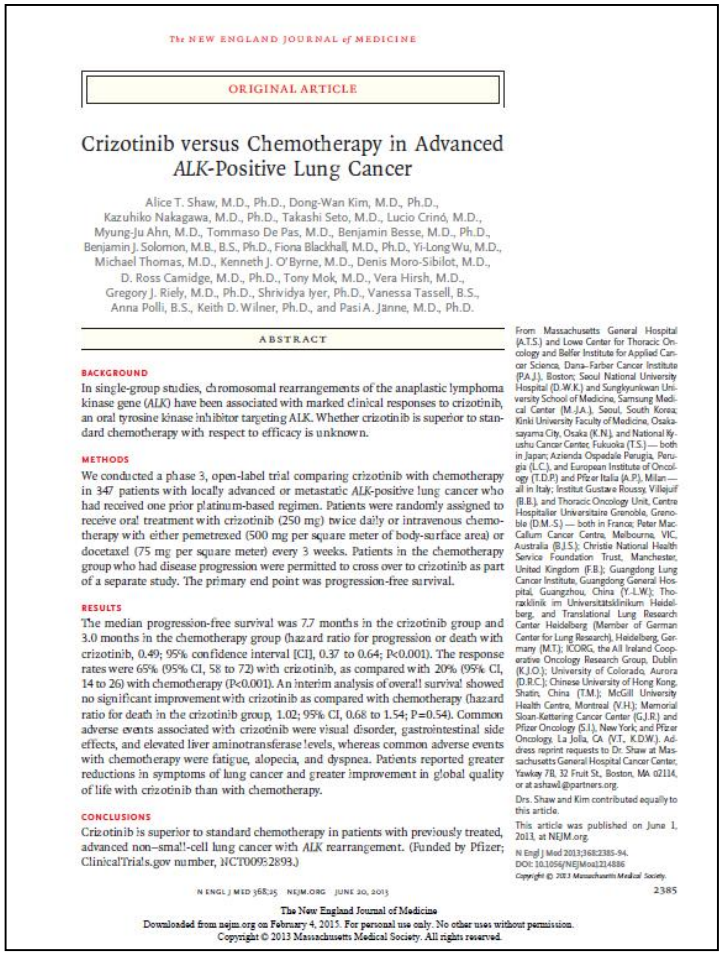

The NEW ENGLAND JOURNAL of MEDICINE

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.

ABSTRACT

BACKGROUND

In single-group studies, chromosomal rearrangements of the anaplastic lymphoma kinase gene (*ALK*) have been associated with marked clinical responses to crizotinib, an oral tyrosine kinase inhibitor targeting ALK. Whether crizotinib is superior to standard chemotherapy with respect to efficacy is unknown.

METHODS

We conducted a phase 3, open-label trial comparing crizotinib with chemotherapy in 347 patients with locally advanced or metastatic *ALK*-positive lung cancer who had received one prior platinum-based regimen. Patients were 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. Patients in the chemotherapy group who had disease progression were permitted to cross over to crizotinib as part of a separate study. The primary end point was progression-free survival.

RESULTS

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). An interim analysis of overall survival showed no significant improvement with crizotinib as compared with chemotherapy (hazard ratio for death in the crizotinib group, 1.02; 95% CI, 0.68 to 1.54; P=0.54). Common adverse events associated with crizotinib were visual disorder, gastrointestinal side effects, and elevated liver aminotransferase levels, whereas common adverse events with chemotherapy were fatigue, alopecia, and dyspnea. Patients reported greater reductions in symptoms of lung cancer and greater improvement in global quality of life with crizotinib than with chemotherapy.

CONCLUSIONS

Crizotinib is superior to standard chemotherapy in patients with previously treated, advanced non–small-cell lung cancer with *ALK* rearrangement. (Funded by Pfizer; ClinicalTrials.gov number, NCT00932893.)

From Massachusetts General Hospital (A.T.S.) and Lowe Center for Thoracic Oncology and Belfer Institute for Applied Cancer Science, Dana–Farber Cancer Institute (P.A.J.), Boston; Seoul National University Hospital (D.W.K.) and Sungkyunkwan University School of Medicine, Samsung Medical Center (M.-J.A.), Seoul, South Korea; Kinki University Faculty of Medicine, Osakasayama City, Osaka (K.N.), and National Kyushu Cancer Center, Fukuoka (T.S.) — both in Japan; Azienda Ospedale Perugia, Perugia (L.C.), and European Institute of Oncology (T.D.P.) and Pfizer Italia (A.P.), Milan — all in Italy; Institut Gustave Roussy, Villejuif (B.B.), and Thoracic Oncology Unit, Centre Hospitalier Universitaire Grenoble, Grenoble (D.M.-S.) — both in France; Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); Christie National Health Service Foundation Trust, Manchester, United Kingdom (F.B.); Guangdong Lung Cancer Institute, Guangdong General Hospital, Guangzhou, China (Y.-L.W.); Thoraxklinik im Universitätsklinikum Heidelberg, and Translational Lung Research Center Heidelberg (Member of German Center for Lung Research), Heidelberg, Germany (M.T.); ICORG, the All Ireland Cooperative Oncology Research Group, Dublin (K.J.O.); University of Colorado, Aurora (D.R.C.); Chinese University of Hong Kong, Shatin, China (T.M.); McGill University Health Centre, Montreal (V.H.); Memorial Sloan-Kettering Cancer Center (G.J.R.) and Pfizer Oncology (S.I.), New York, and Pfizer Oncology, La Jolla, CA (V.T., K.D.W.). Address reprint requests to Dr. Shaw at Massachusetts General Hospital Cancer Center, Yawkey 7B, 32 Fruit St., Boston, MA 02114, or at ashawl@partners.org.

Drs. Shaw and Kim contributed equally to this article.

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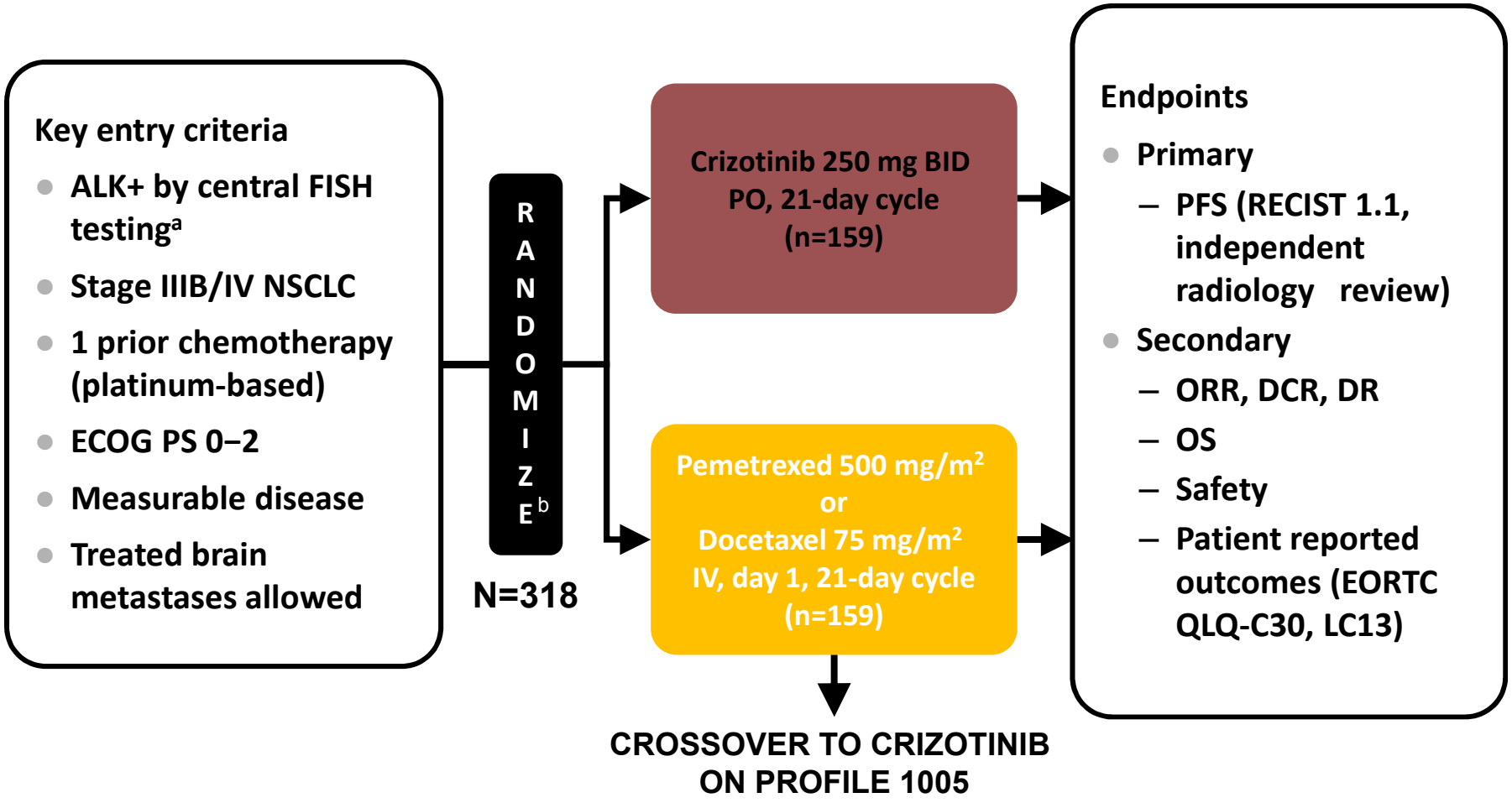
N Engl J Med 2013;368:2385-94.
DOI: 10.1056/NEJMoa1214886

Estudio PROFILE 1007

PROFILE 1007

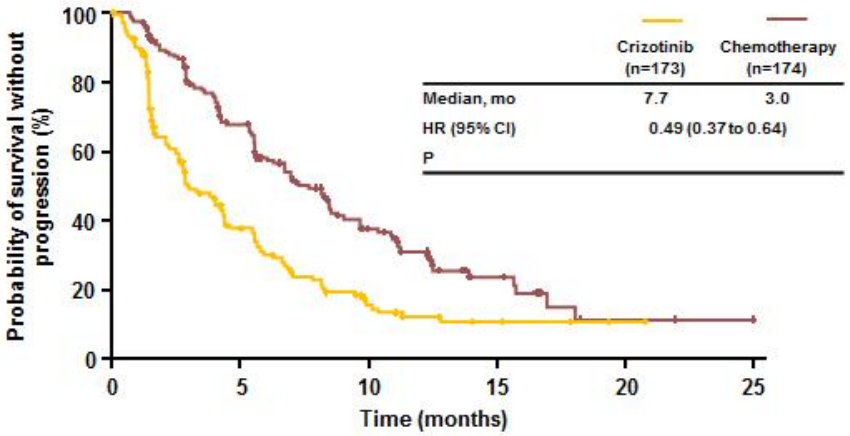
PROFILE 1007 Study Design



[a]ALK status determined using standard ALK break-apart FISH assay [b]Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

PROFILE 1007: NCT00932893

Primary Endpoint: PFS



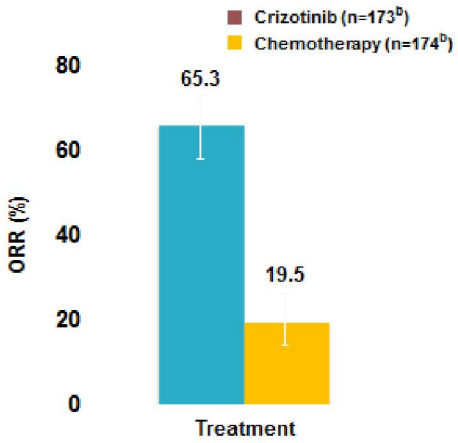
No. at risk						
Crizotinib	173	93	38	11	2	0
Chemotherapy	174	49	15	4	1	0

Shaw AT, et al. N Engl J Med 2013;368:2385–94

7.7 meses vs 3 meses

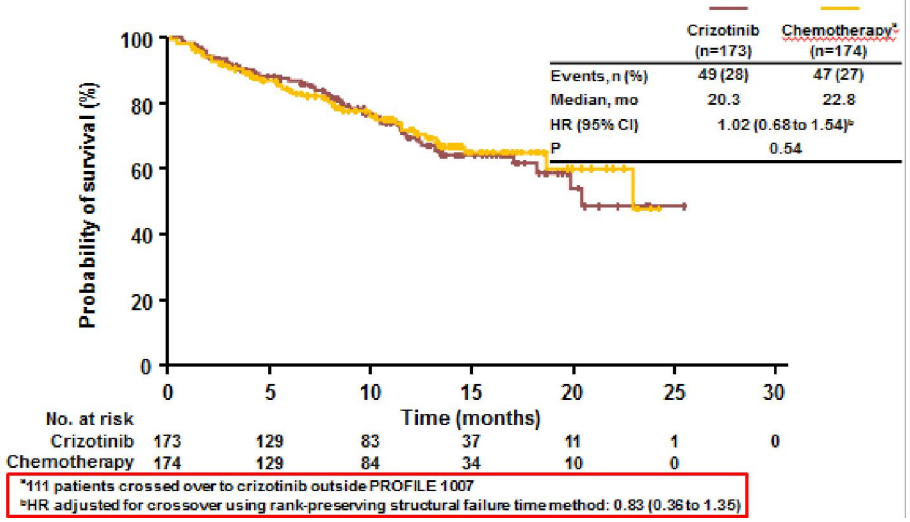
PROFILE 1007 ORR[a] by Independent Radiologic Review

ORR ratio: 3.4 (95% CI: 2.5 to 4.7); P<0.0001



TR: 65.3%

Interim Analysis of OS



OS: 20.3 m

Efectos adversos

Table 3. Adverse Events of Any Cause.*

Adverse Event	Crizotinib (N=172)		Chemotherapy (N=171)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	no. of patients (%)			
Vision disorder†‡	103 (60)	0	16 (9)	0
Diarrhea	103 (60)	0	33 (19)	1 (1)
Nausea§	94 (55)	2 (1)	64 (37)	1 (1)
Vomiting§	80 (47)	2 (1)	30 (18)	0
Constipation	73 (42)	4 (2)	39 (23)	0
Elevated aminotransferase levels†	66 (38)	27 (16)¶	25 (15)	4 (2)
Edema†	54 (31)	0	27 (16)	0
Fatigue	46 (27)	4 (2)	57 (33)	7 (4)
Upper respiratory infection†	44 (26)	0	22 (13)	1 (<1)
Dysgeusia	44 (26)	0	16 (9)	0
Dizziness†	37 (22)	1 (1)	14 (8)	0
Dyspnea†‖	23 (13)	7 (4)	32 (19)	5 (3)
Rash	15 (9)	0	29 (17)	0
Alopecia	14 (8)	0	35 (20)	0

	n (%)	
	Crizotinib (n=172)	Chemotherapy (n=171)
Elevated transaminases[a]	27 (16)	4 (2)
Pulmonary embolism[a]	9 (5)	3 (2)
Dyspnea[a]	7 (4)	5 (3)
Pneumonia	6 (4)	3 (2)
Hypokalemia	6 (4)	0
ECG QTc prolonged	6 (4)	0 [b]
Neutropenia[a]	23 (13)	33 (19)
Febrile neutropenia	1 (1)	16 (9)
Anemia[a]	4 (2)	9 (5)
WBC decreased	2 (1)	8 (5)
Fatigue	4 (2)	7 (4)

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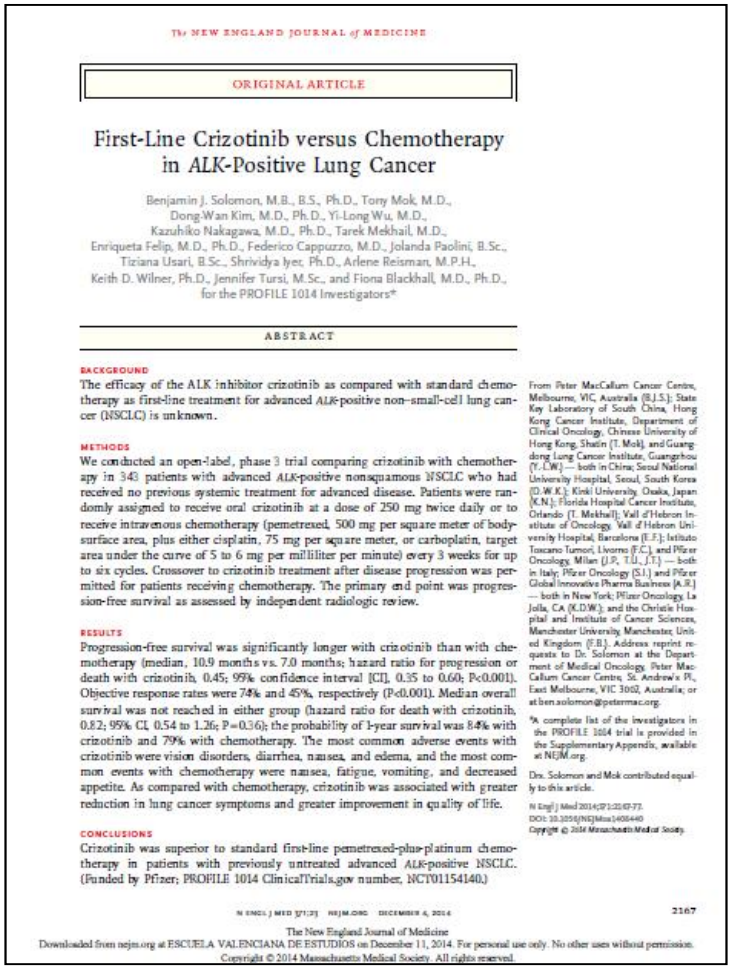

The NEW ENGLAND JOURNAL of MEDICINE

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*

ABSTRACT

BACKGROUND

The efficacy of the ALK inhibitor crizotinib as compared with standard chemotherapy as first-line treatment for advanced *ALK*-positive non–small-cell lung cancer (NSCLC) is unknown.

METHODS

We conducted an open-label, phase 3 trial comparing crizotinib with chemotherapy in 343 patients with advanced *ALK*-positive nonsquamous NSCLC who had received no previous systemic treatment for advanced disease. Patients were randomly assigned to receive oral crizotinib at a dose of 250 mg twice daily or to receive intravenous chemotherapy (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) every 3 weeks for up to six cycles. Crossover to crizotinib treatment after disease progression was permitted for patients receiving chemotherapy. The primary end point was progression-free survival as assessed by independent radiologic review.

RESULTS

Progression-free survival was 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 were 74% and 45%, respectively (P<0.001). Median overall survival was not reached in either group (hazard ratio for death with crizotinib, 0.82; 95% CI, 0.54 to 1.26; P=0.36); the probability of 1-year survival was 84% with crizotinib and 79% with chemotherapy. The most common adverse events with crizotinib were vision disorders, diarrhea, nausea, and edema, and the most common events with chemotherapy were nausea, fatigue, vomiting, and decreased appetite. As compared with chemotherapy, crizotinib was associated with greater reduction in lung cancer symptoms and greater improvement in quality of life.

CONCLUSIONS

Crizotinib was superior to standard first-line pemetrexed–plus-platinum chemotherapy in patients with previously untreated advanced *ALK*-positive NSCLC. (Funded by Pfizer; PROFILE 1014 ClinicalTrials.gov number, NCT01154140.)

From Peter MacCallum Cancer Centre, Melbourne, VIC, Australia (B.J.S.); State Key Laboratory of South China, Hong Kong Cancer Institute, Department of Clinical Oncology, Chinese University of Hong Kong, Shatin (T. Mok), and Guangdong Lung Cancer Institute, Guangzhou (Y.-L.W.) — both in China; Seoul National University Hospital, Seoul, South Korea (D.-W.K.); Kinki University, Osaka, Japan (K.N.); Florida Hospital Cancer Institute, Orlando (T. Mekhail); Vall d'Hebron Institute of Oncology, Vall d'Hebron University Hospital, Barcelona (E.F.); Istituto Toscano Tumori, Livorno (F.C.), and Pfizer Oncology, Milan (J.P., T.U., J.T.) — both in Italy; Pfizer Oncology (S.I.) and Pfizer Global Innovative Pharma Business (A.R.) — both in New York; Pfizer Oncology, La Jolla, CA (K.D.W.); and the Christie Hospital and Institute of Cancer Sciences, Manchester University, Manchester, United Kingdom (F.B.). Address reprint requests to Dr. Solomon at the Department of Medical Oncology, Peter MacCallum Cancer Centre, St. Andrew's Pl., East Melbourne, VIC 3002, Australia; or at ben.solomon@petermac.org.

*A complete list of the investigators in the PROFILE 1014 trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Solomon and Mok contributed equally to this article.

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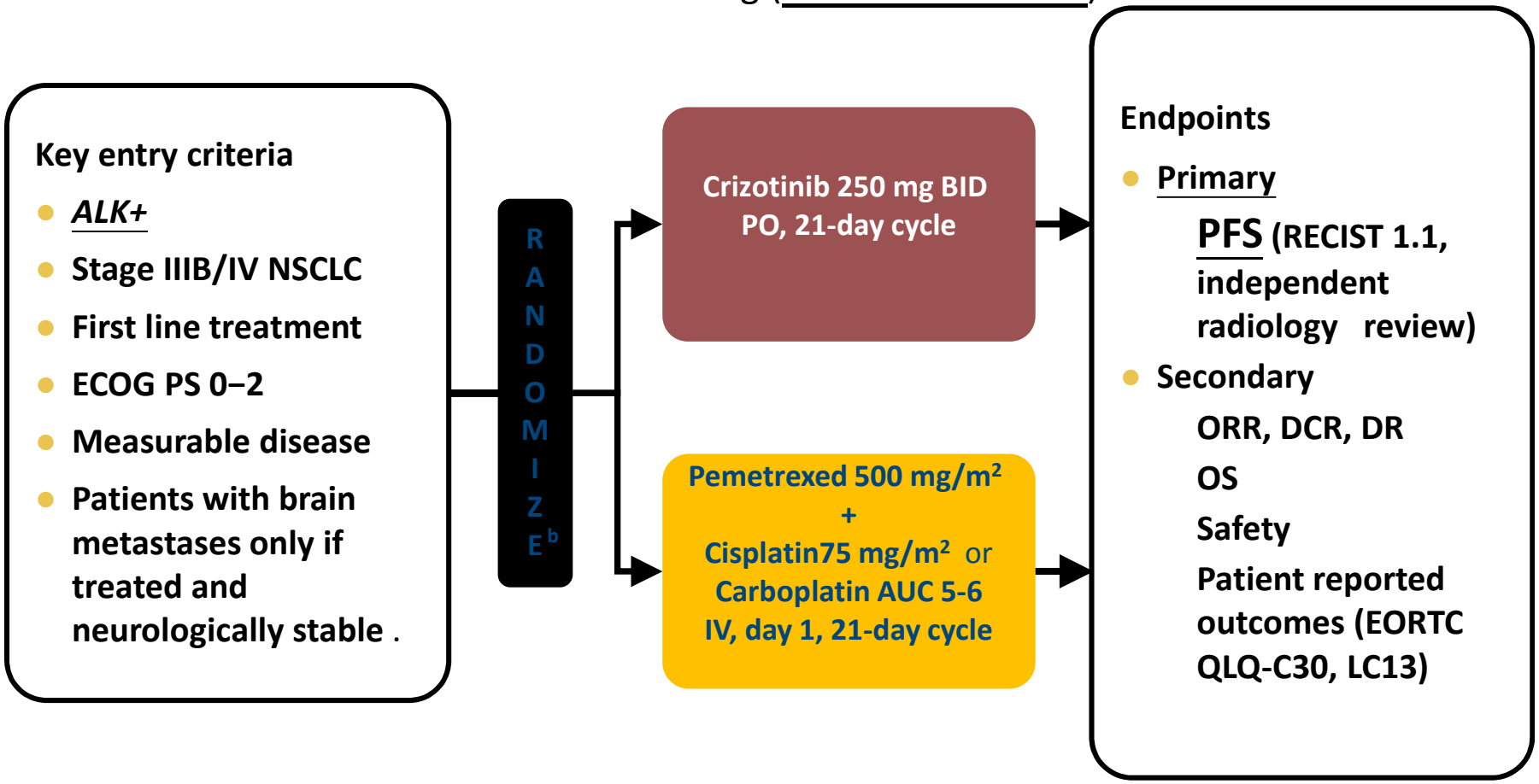
DOI: 10.1056/NEJMoa1408440

PROFILE 1014

A Clinical Trial Testing The Efficacy of Crizotinib Versus Standard Chemotherapy Pemetrexed Plus Cisplatin or Carboplatin in Patients With ALK Positive Non Squamous Cancer of The Lung (PROFILE 1014)



Estimated Enrollment:334

Study Start Date:January 2011

Estimated Study Completion Date:February 2015

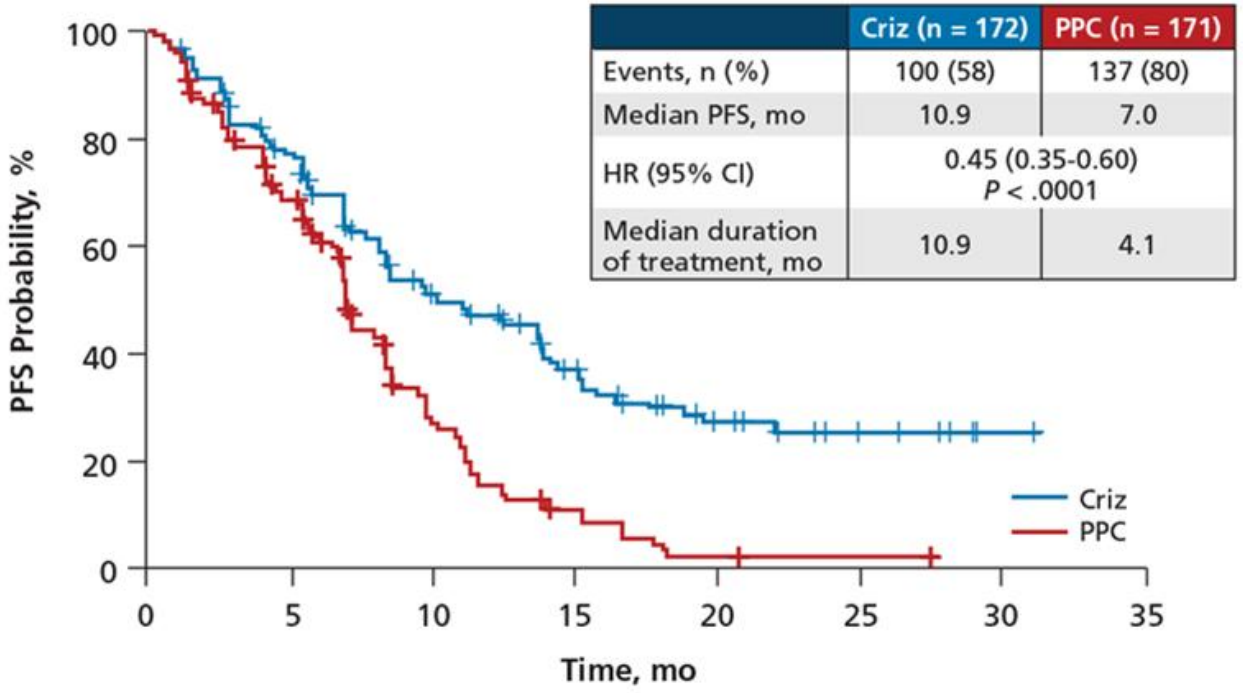
Primary Completion Date:November 2013

Salomon .NEJM Dec. 2014

SLP

PROFILE 1014: Progression-Free Survival

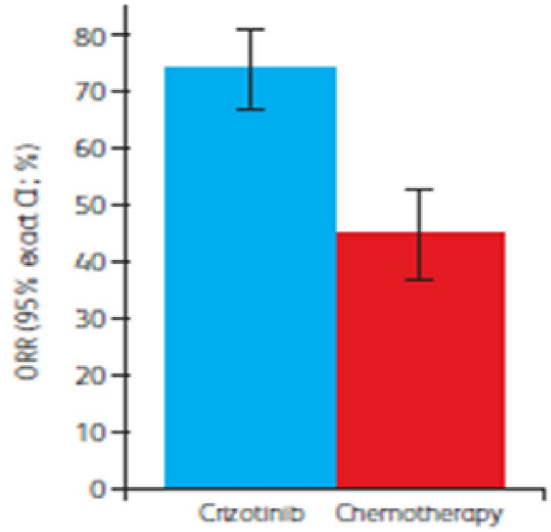
Primary Endpoint: PFS by IRR (ITT Population)



	Criz (n = 172)	PPC (n = 171)
Events, n (%)	100 (58)	137 (80)
Median PFS, mo	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60) $P < .0001$	
Median duration of treatment, mo	10.9	4.1

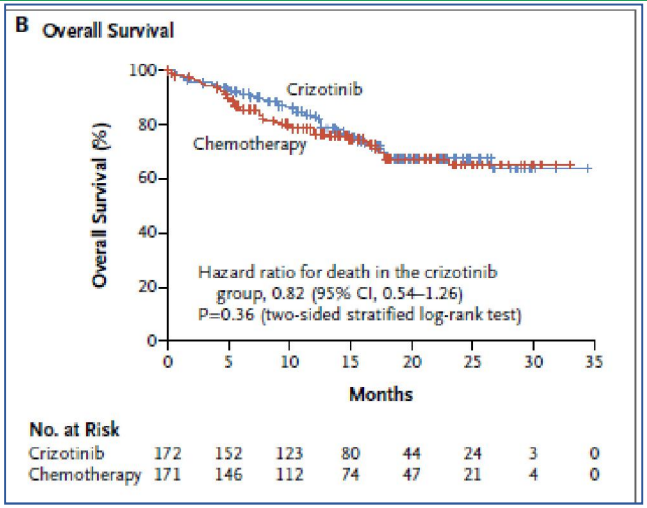
ORR y SG

Figure 3. ORR by Independent radiologic review.



	Crizotinib (N=172)		Chemotherapy (N=171)
Objective responses, n (%)	128 (74)		77 (45)
95% exact CI of ORR	67–81		37–53
Treatment difference, %		29	
95% CI[a]		20–39	
p[a]		<0.0001	
Median time to response,[b] weeks	6.1		12.1
Range	2.7–41.4		5.1–36.7
Median duration of response,[b,c] weeks	49.0		22.9
95% CI[d]	35.1–60.0		18.0–25.1

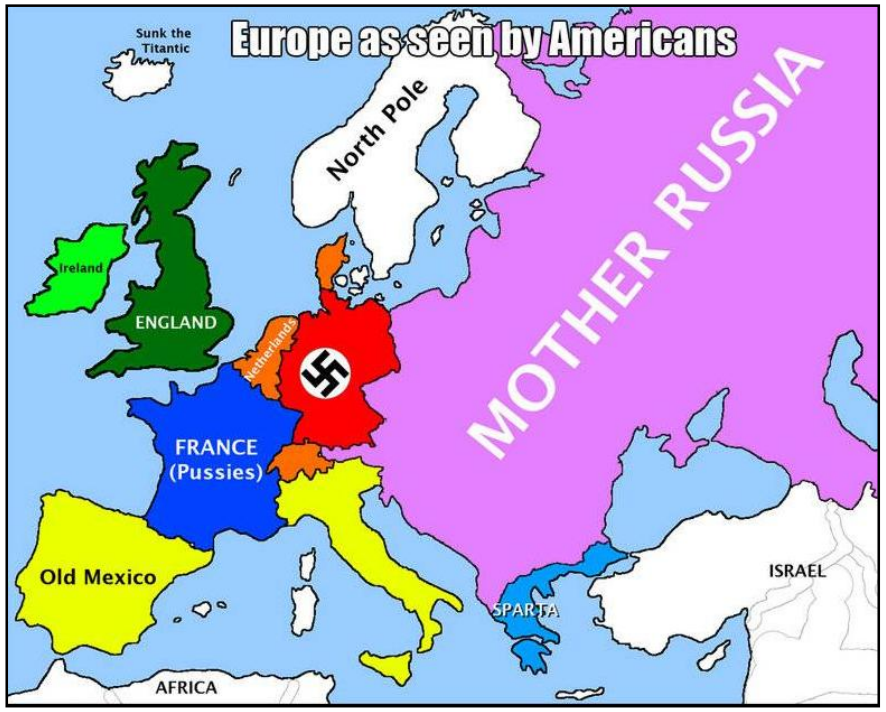
[a]Pearson χ^2 test.
[b]In patients with an objective response.
[c]Kaplan–Meier method.
[d]Brookmeyer–Crowley method.



Conclusiones

	Fase	n	Tratamientos previos	ORR	PFS
PROFILE 1001	Fase I seguido de Cohorte expandida	143	Pretratados	60.8%	9.7 m
PROFILE 1005	Fase II	259	Pre-tto + 2 líneas	53%	8.1 m
ROFILE 1007	Fase III	173	2º línea	65%	7.7 m
PROFILE 1014	Fase III	343	1º línea	74%	10.9 m

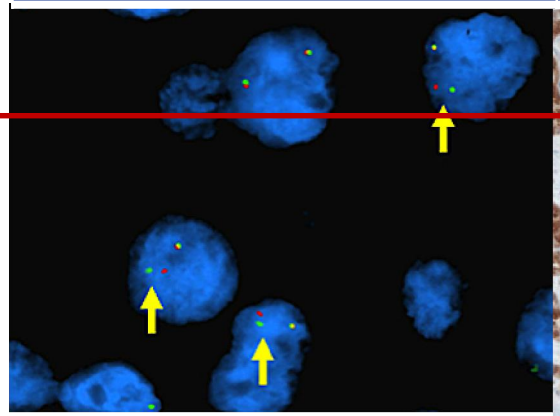
Capítulo 3: aprobación de crizotinib por FDA y EMA

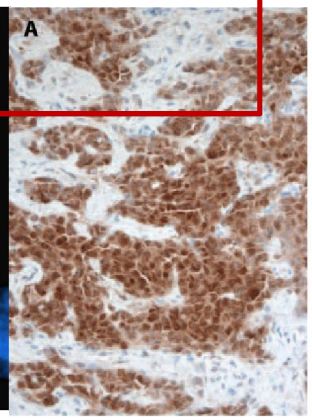


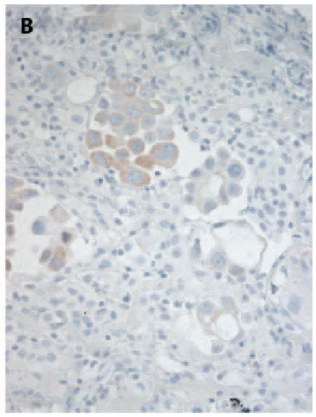
FDA	EMA
Su autorización se basa en la actividad demostrada	Su autorización se basa en los datos del 1º estudio Fase III
26.08.2011	23.10.2012
Indicada en pacientes ALK + independientemente de la línea	Indicada en Pacientes ALK + (2º línea) Tras los datos del ensayo Profile 1007
Detectada por Vysis ALK Break-Apart FISH Prove kit	No especifica el test a usar

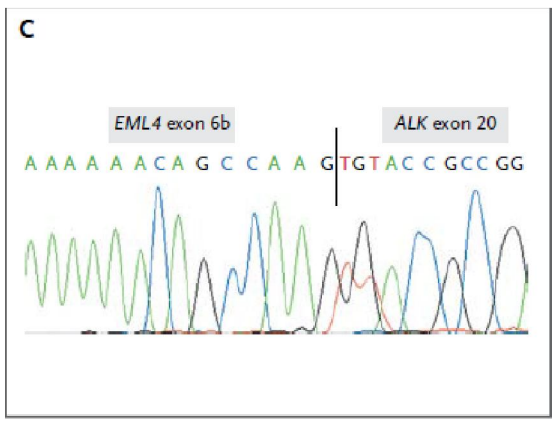
Cómo se diagnostica

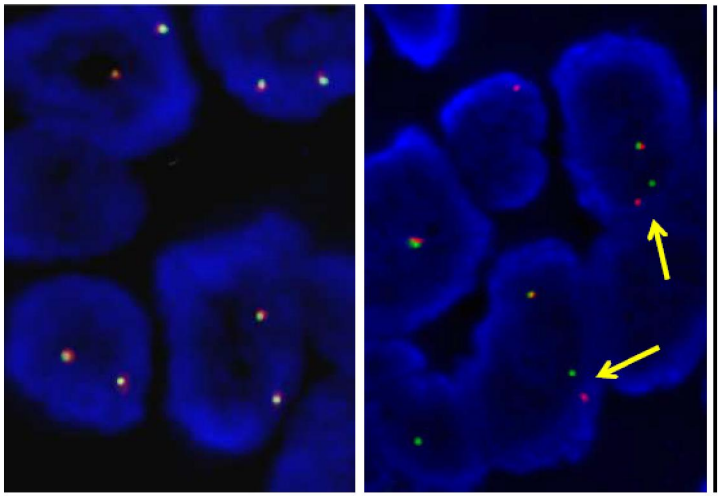
FISH	IHC	RT-PCR











Negativo Positivo

FISH positivo si se detectan señales separadas o señales rojas solas, en >15% de células

El problema del FISH

FISH	IHQ
Es más caro	Es más barato
Requiere mayor infraestructura	Menor infraestructura
Es más subjetivo	Es más objetivo
Personal entrenado	Es más reproducible

Correlation Between *ALK* IHC and *ALK* FISH

- Review of 11 studies involving 2,908 NSCLC cases studied by both IHC and FISH
- Majority of studies were retrospective or single-institution analyses

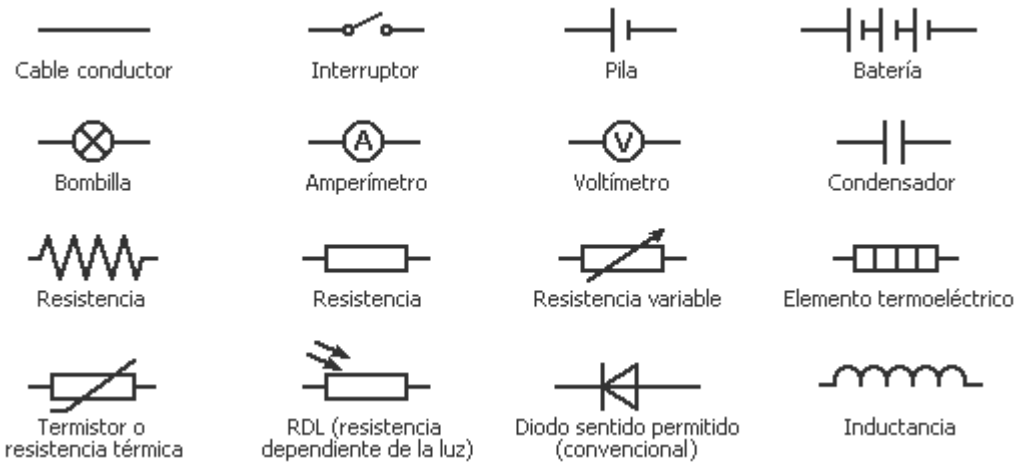
Correlation Between *ALK* IHC and *ALK* FISH in 2,908 Cases Studied by Both Techniques (Current and Published Studies)

IHC Status	Cases, n	
	FISH-	FISH+
IHC-	2,687	3
IHC+	73	172
IHC equivocal	0	2

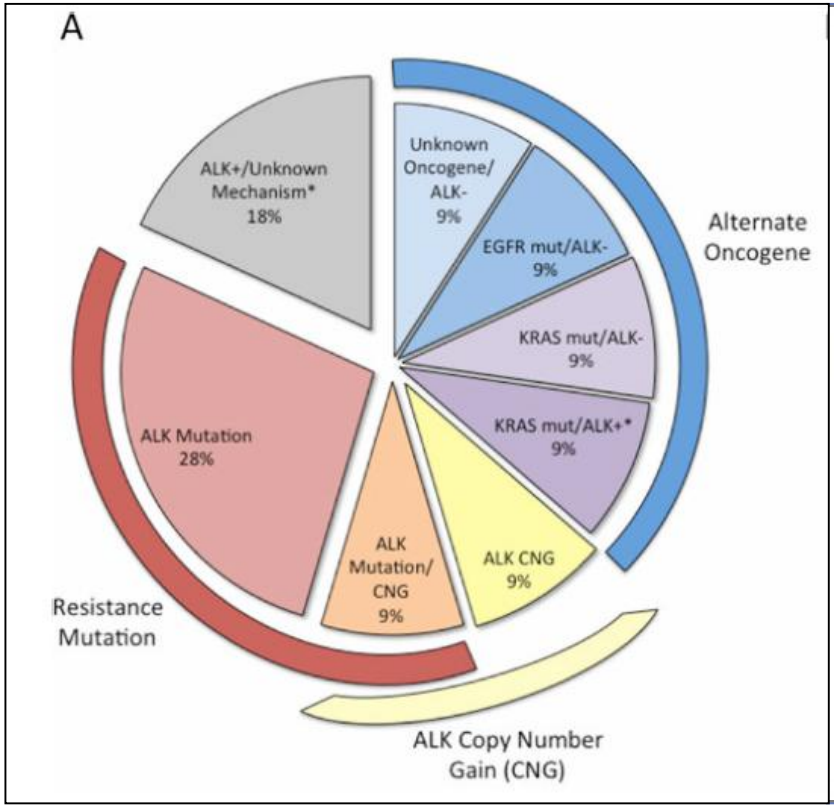
- **A false-negative rate of ~0.1% was found for IHC**

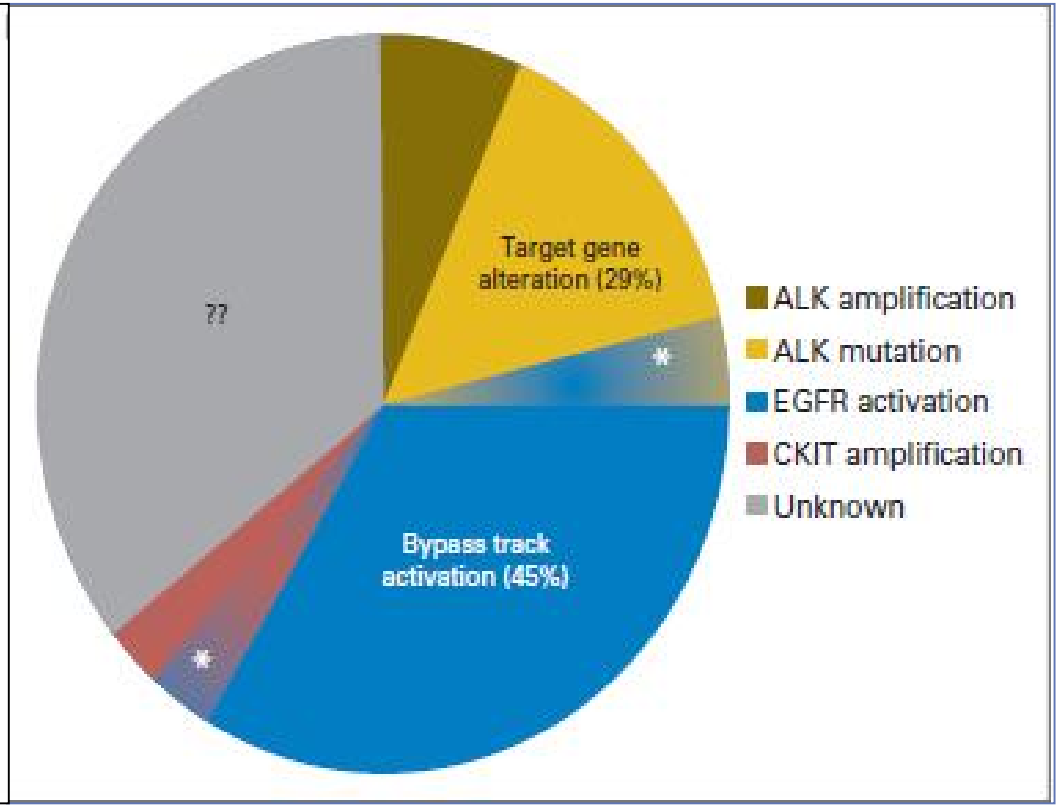
Deschen J ASCO 2014 Abstract 8070

Capítulo 4. Resistencias



Mecanismos de resistencia

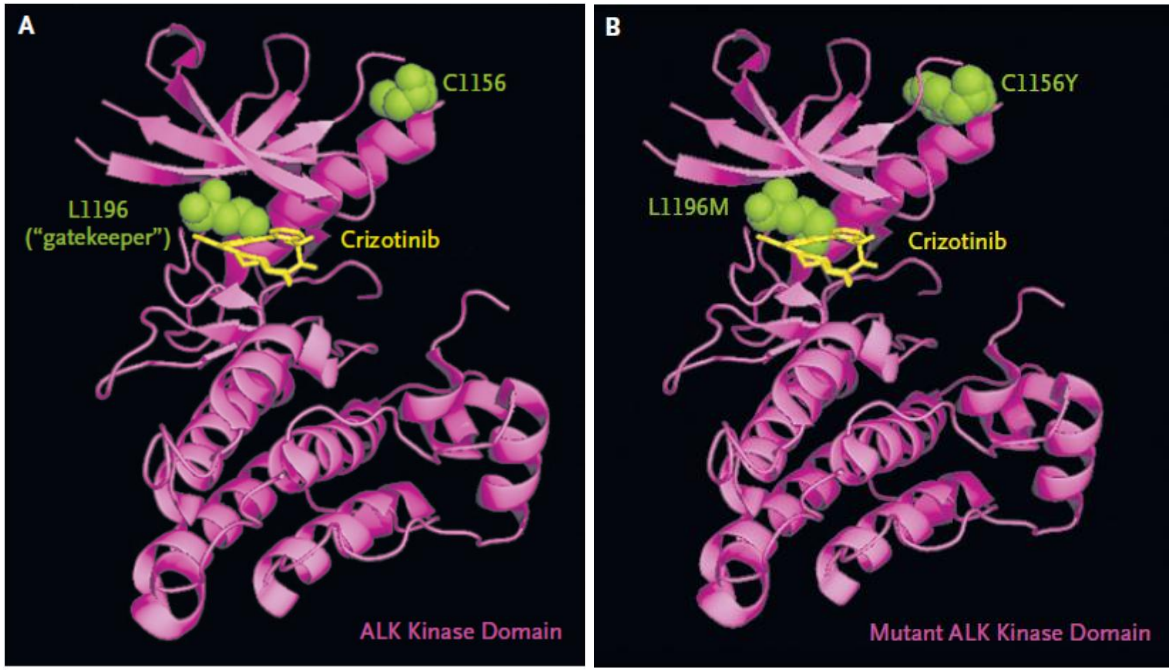




Doebele RC
Clinic Cancer Research 2012

Alice T JCO 2013

Mutaciones puntuales



Las más frecuentes

25%

Afectan el lugar de ligamiento del ATP

La más frecuente:L1196 sustitución de Leucina por Metionina en la posición 1196 del dominio Kinasa de ALK Colocando un Aminoácido voluminoso en el Gatekeeper del Crizotinib

Menos común es C1156Y: sustituye a una Cisteina por una Tirosina en la posición 1156

NEJM 2010 Choi YL

Amplificaciones

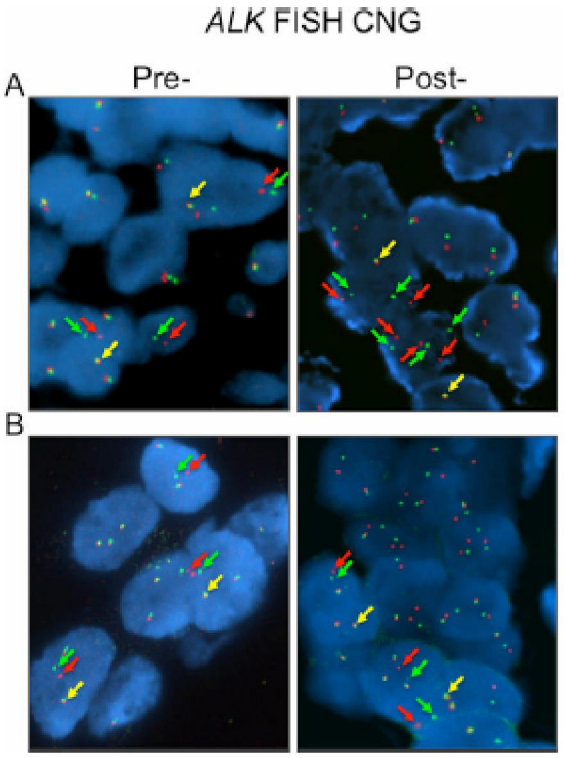
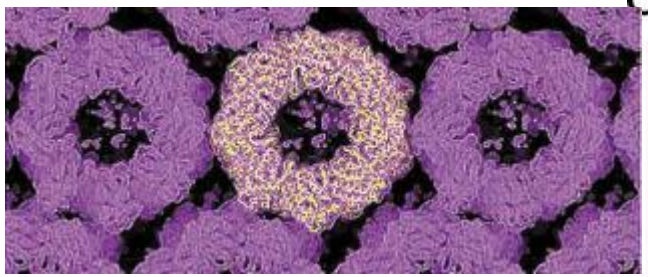


Figure 2. ALK FISH pattern changes from pre- to post-crizotinib tumor samples
FISH analysis of patients #6 (A) and #7 (B) before crizotinib treatment (left) and following progression on crizotinib (right) demonstrating a gain of split green (5') and red (3') *ALK* signals per each tumor cell. FISH analysis of patients #8a (C) and 11 (D) before crizotinib treatment (left) and following progression on crizotinib (right) demonstrating loss of split green (5') and red (3') *ALK* signals.

Katayama R Transl Med
Doebele RC Clin Cancer Research 2012

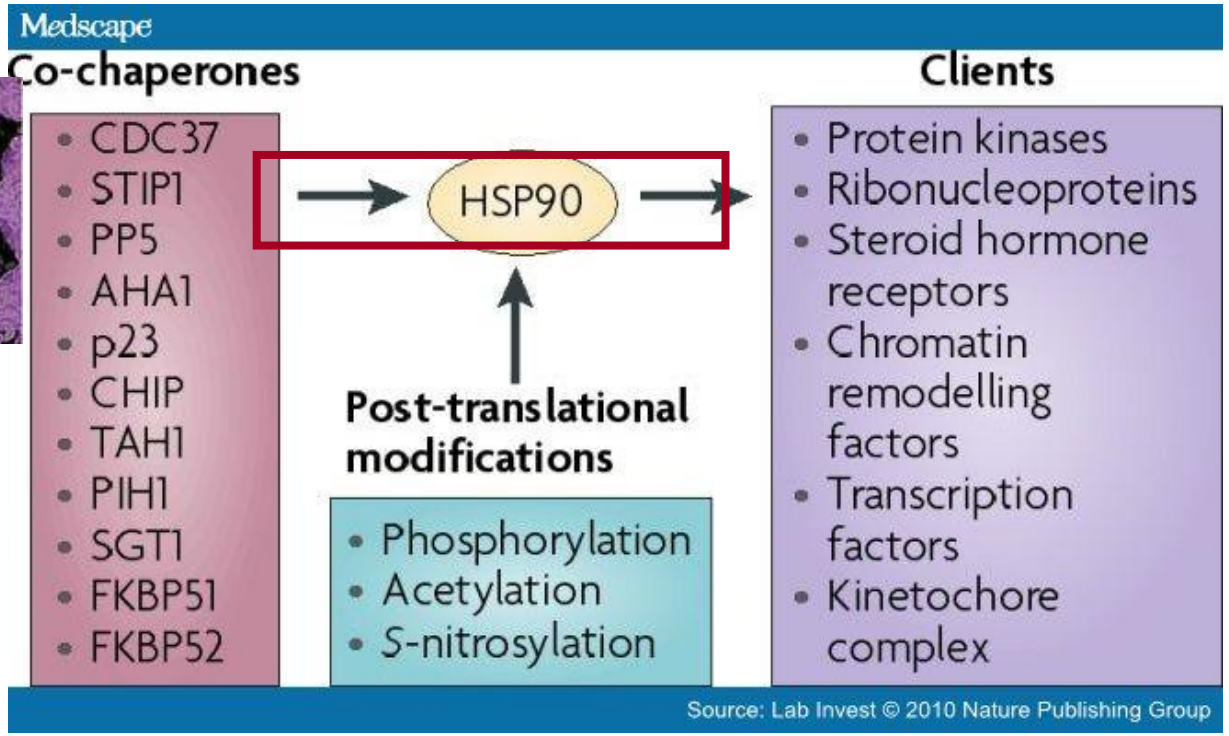
Uso de otras vías alternativas

HSP90



EGFR

KRAS



Sang J, Cancer Discov 2013
Chen Z. Cancer Res

Capítulo 5 Tratamiento a la progresión de Crizotinib

1. Asistencialmente: QT
2. Oligoprogresión: mantener crizotinib y hacer técnica local
3. Rebiopsia→ identificar mecanismo de resistencia y adaptar tratamiento
4. Inhibición de alk de 2º o 3º generación
5. Continuar crizotinib

Continuar crizotinib

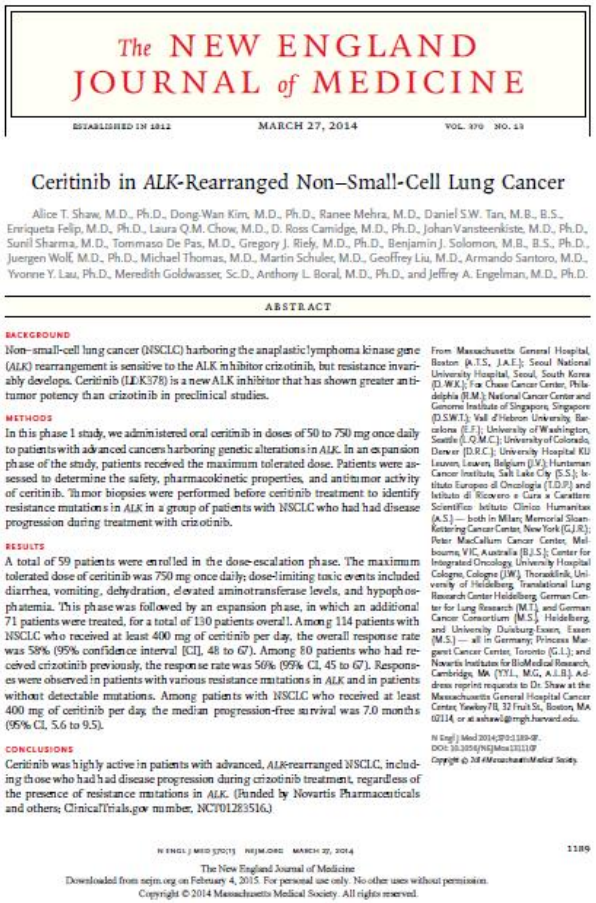
- Overall survival was significantly longer for patients who continued crizotinib beyond progression (120 patients, 62%) than for those who stopped the drug (74 patients, 38%): median overall survival from disease progression was 16.4 vs. 3.9 months, respectively (hazard ratio 0.27; 95% CI, 0.17-0.42; p<0.0001).

- The SouthWest Oncology Group is conducting a randomized phase II trial (SWOG 1300) testing the role of continuing crizotinib beyond progression in addition to chemotherapy. In that trial, patients assigned to the control arm receive pemetrexed alone, while patients assigned to the experimental arm receive pemetrexed plus crizotinib

Ou SH, Jänne PA, Bartlett CH, Tang Y, Kim DW, Otterson GA, Crinò L, Selaru P, Cohen DP, Clark JW and Riely GJ: Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. Ann Oncol 25: 415-422, 2014.

Ceritinib

Ascend 1



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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.

ABSTRACT

BACKGROUND

Non–small-cell lung cancer (NSCLC) harboring the anaplastic lymphoma kinase gene (*ALK*) rearrangement is sensitive to the ALK inhibitor crizotinib, but resistance invariably develops. Ceritinib (LDK378) is a new ALK inhibitor that has shown greater antitumor potency than crizotinib in preclinical studies.

METHODS

In this phase 1 study, we administered oral ceritinib in doses of 50 to 750 mg once daily to patients with advanced cancers harboring genetic alterations in *ALK*. In an expansion phase of the study, patients received the maximum tolerated dose. Patients were assessed to determine the safety, pharmacokinetic properties, and antitumor activity of ceritinib. Tumor biopsies were performed before ceritinib treatment to identify resistance mutations in *ALK* in a group of patients with NSCLC who had had disease progression during treatment with crizotinib.

RESULTS

A total of 59 patients were enrolled in the dose-escalation phase. The maximum tolerated dose of ceritinib was 750 mg once daily; dose-limiting toxic events included diarrhea, vomiting, dehydration, elevated aminotransferase levels, and hypophosphatemia. This phase was followed by an expansion phase, in which an additional 71 patients were treated, for a total of 130 patients overall. Among 114 patients with NSCLC who received at least 400 mg of ceritinib per day, the overall response rate was 58% (95% confidence interval [CI], 48 to 67). Among 80 patients who had received crizotinib previously, the response rate was 56% (95% CI, 45 to 67). Responses were observed in patients with various resistance mutations in *ALK* and in patients without detectable mutations. Among patients with NSCLC who received at least 400 mg of ceritinib per day, the median progression-free survival was 7.0 months (95% CI, 5.6 to 9.5).

CONCLUSIONS

Ceritinib was highly active in patients with advanced, *ALK*-rearranged NSCLC, including those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in *ALK*. (Funded by Novartis Pharmaceuticals and others; ClinicalTrials.gov number, NCT01283516.)

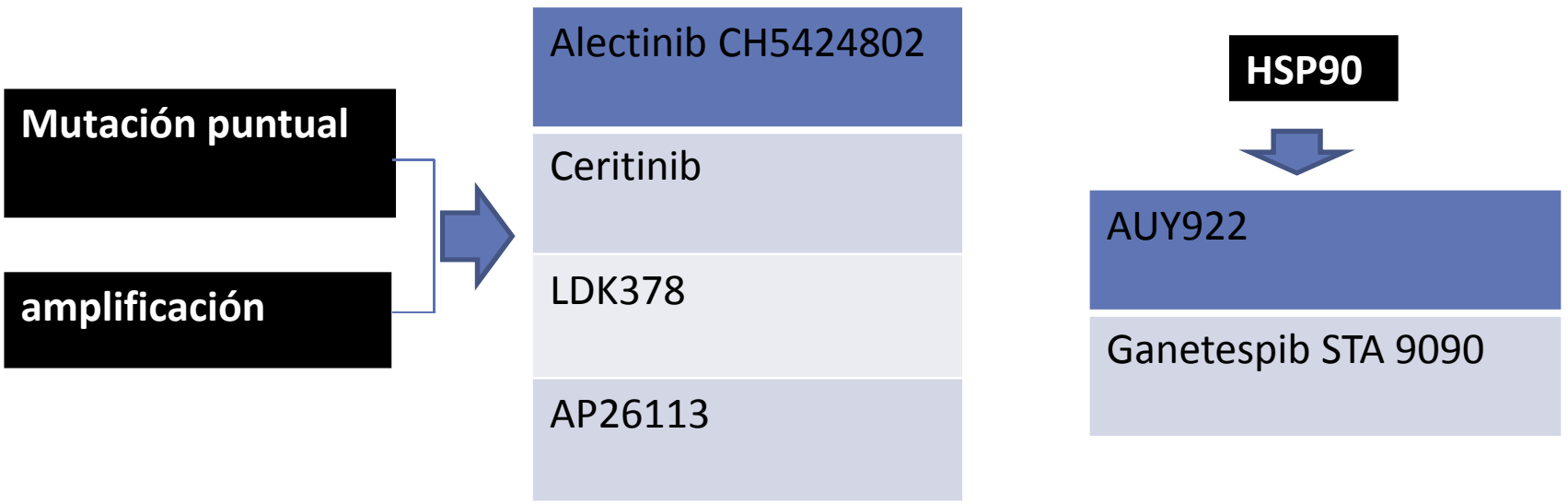
From Massachusetts General Hospital, Boston (A.T.S., J.A.E.); Seoul National University Hospital, Seoul, South Korea (D.-W.K.); Fox Chase Cancer Center, Philadelphia (R.M.); National Cancer Center and Genome Institute of Singapore, Singapore (D.S.W.T.); Vall d'Hebron University, Barcelona (E.F.); University of Washington, Seattle (L.Q.M.C.); University of Colorado, Denver (D.R.C.); University Hospital KU Leuven, Leuven, Belgium (J.V.); Huntsman Cancer Institute, Salt Lake City (S.S.); Istituto Europeo di Oncologia (T.D.P.) and Istituto di Ricovero e Cura a Carattere Scientifico Istituto Clinico Humanitas (A.S.) — both in Milan; Memorial Sloan-Kettering Cancer Center, New York (G.J.R.); Peter MacCallum Cancer Center, Melbourne, VIC, Australia (B.J.S.); Center for Integrated Oncology, University Hospital Cologne, Cologne (J.W.), Thoraxklinik, University of Heidelberg, Translational Lung Research Center Heidelberg, German Center for Lung Research (M.T.), and German Cancer Consortium (M.S.), Heidelberg, and University Duisburg-Essen, Essen (M.S.) — all in Germany; Princess Margaret Cancer Center, Toronto (G.L.); and Novartis Institutes for BioMedical Research, Cambridge, MA (Y.Y.L., M.G., A.L.B.). Address reprint requests to Dr. Shaw at the Massachusetts General Hospital Cancer Center, Yawkey 7B, 32 Fruit St., Boston, MA 02114, or at ashaw1@mgh.harvard.edu.

N Engl J Med 2014;370:1189-97.
DOI: 10.1056/NEJMoa1311107

- ITK 20 veces más potente que crizotinib.
- Actúa sobre mutaciones L1196M y G1269A
- FDA aprueba a Resistencia o intolerancia a crizotinib
- Resultados:
  - TR: 58%
  - SLP 8,2 meses (6,9 meses con crizotinib previo)
- 2 fases III en marcha

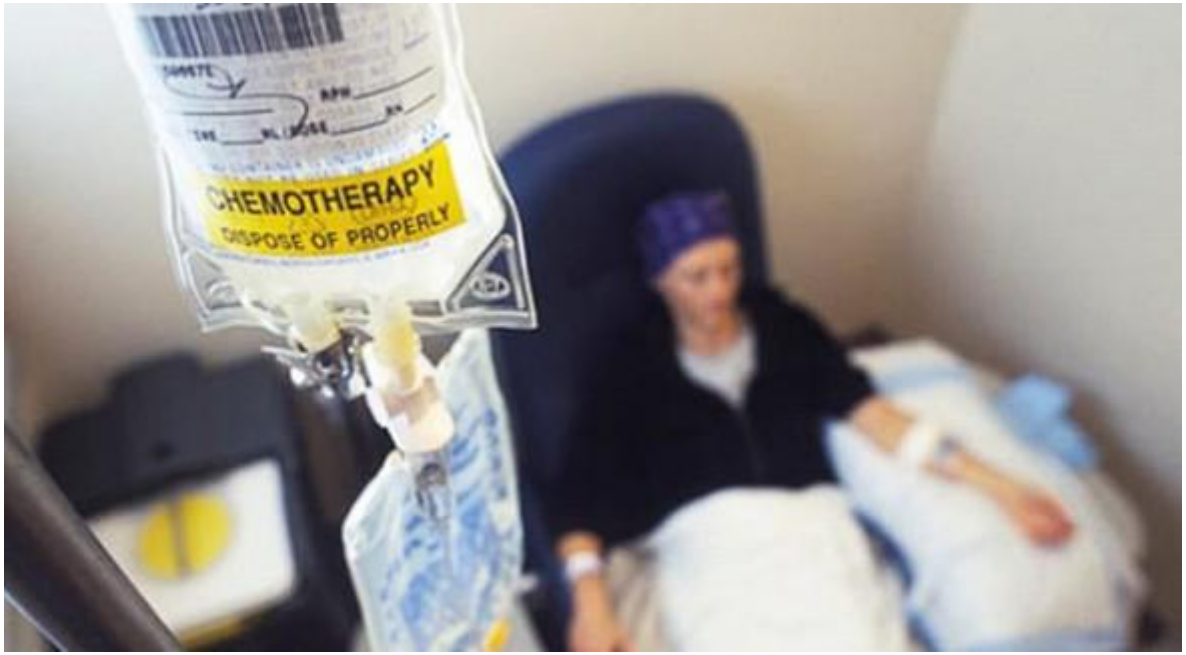
Alectinib

- Inh TK de 2º generacion
  - Fase I-II Seto T Lancet oncol 2013
    - pacientes naive a crizotinib.
    - Tasa de Respuesta del 93%.
  - Fase I/II: Gadgeel SM. Lancet Oncol. 2014
    - 47 pacientes a progresión a crizotinib
    - TR: 55%



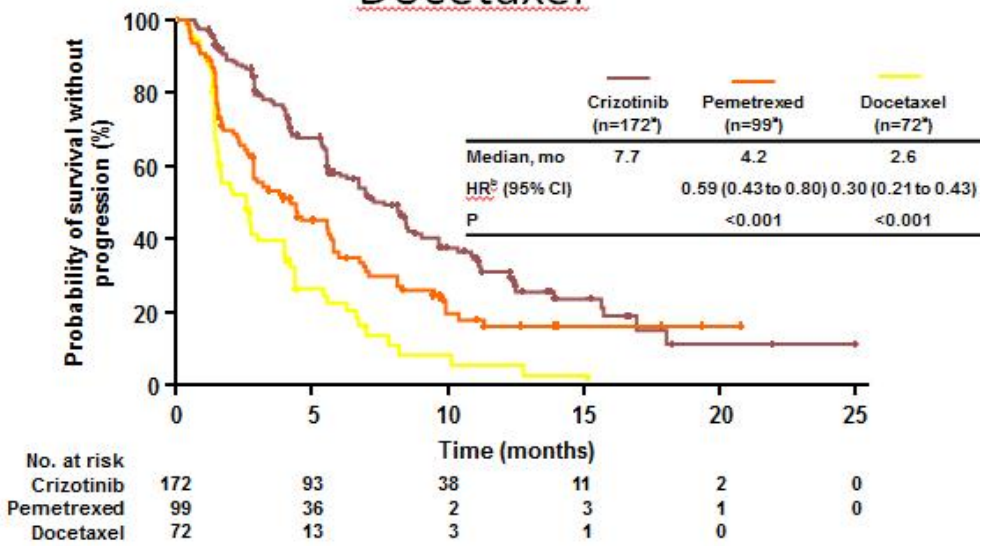
Drug	Phase	Compared drug	Treatment setting	Status	Clinical trial number
Crizotinib	III	PEM or DOC	Second line	Published[23]	NCT00932893
	III	Platinum + PEM	First line	Ongoing*[,25]	NCT01154140
Alectinib	I/II		ALK inhibitor-naive	Published[38]	AF-001JP
	III	Crizotinib	ALK inhibitor-naive	Ongoing[39]	JapicCTI-132316
LDK378	III	Platinum + PEM	First line	Ongoing[45]	NCT01828099
	III	PEM or DOC	Both platinum and crizotinib failure, third line	Ongoing[44]	NCT01828112
AP26113	I/II		ALK inhibitor-naive or failure	Ongoing[47]	NCT01449461
ASP-3026	I		ALK inhibitor-naive or failure	Ongoing[64]	NCT01401504
X-396	I		ALK inhibitor-naive or failure	Ongoing[65]	NCT01625234
CEP-37440	I		ALK inhibitor-naive or failure	Ongoing[66]	NCT01922752

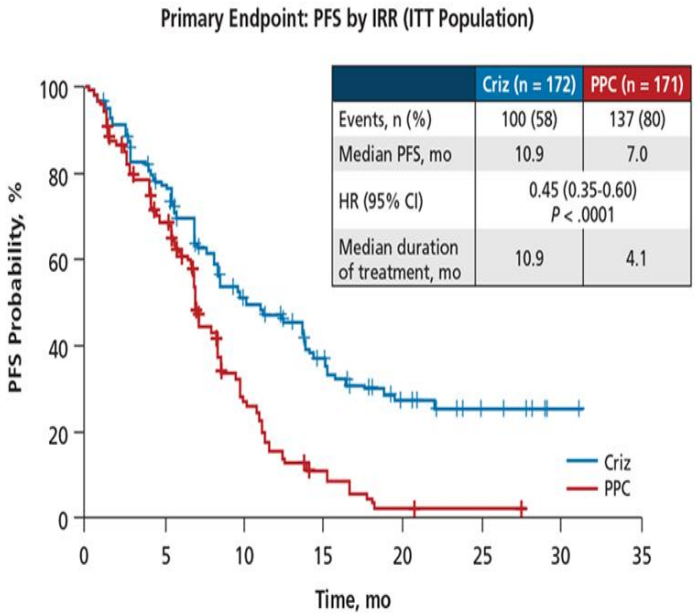
Capítulo 6: Rol de la QT en ALK +



- Modelos animales: Pemetrexed ofrece mas SG que docetaxel en ALK +. Chen . Clin cancer research. 2014
- Niveles de Timidilato Sintetasa en ALK +, es menor respecto a celulas control. Puede explicar la mayor sensibilidad a Pemetrexed en estos pacientes. Lee JO JTO 2011

PFS Crizotinib vs Pemetrexed or Docetaxel



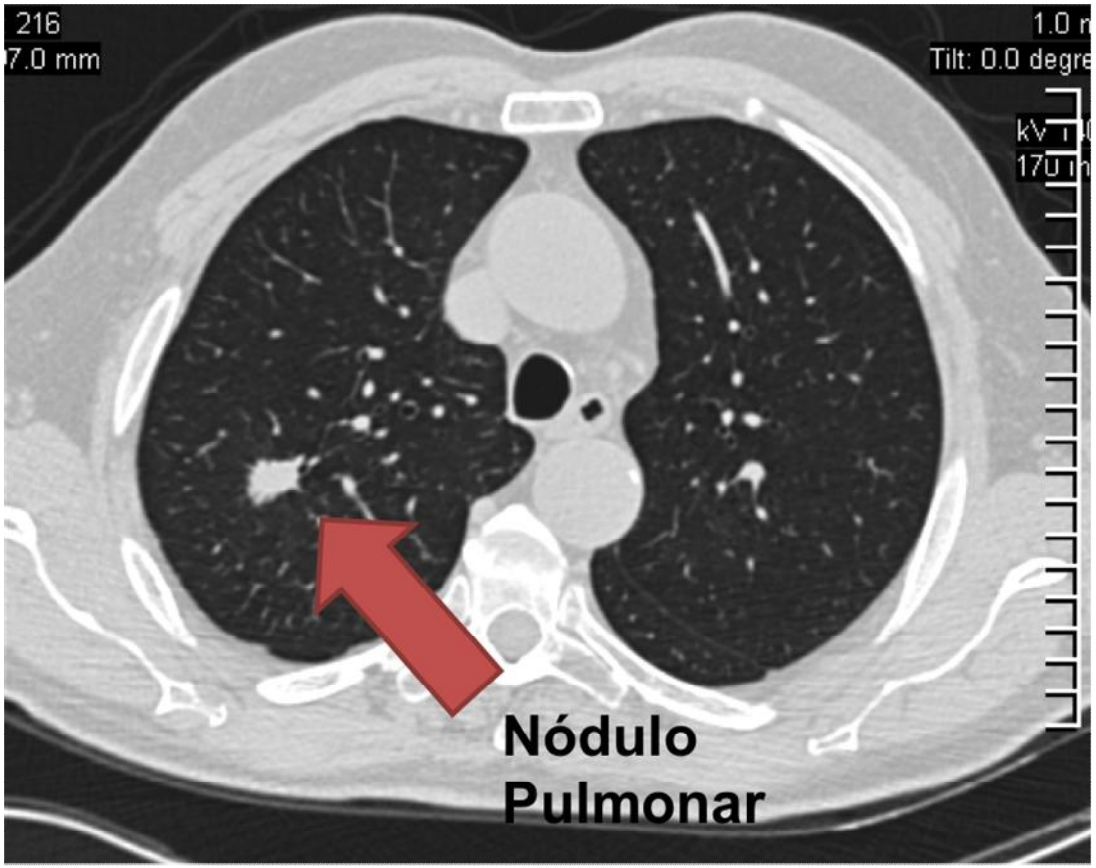


Mayor respuesta en Pemetrexed

PROFILE 1007

PROFILE 1014

Capítulo 7:Tratamiento de ALK en estadios tempranos

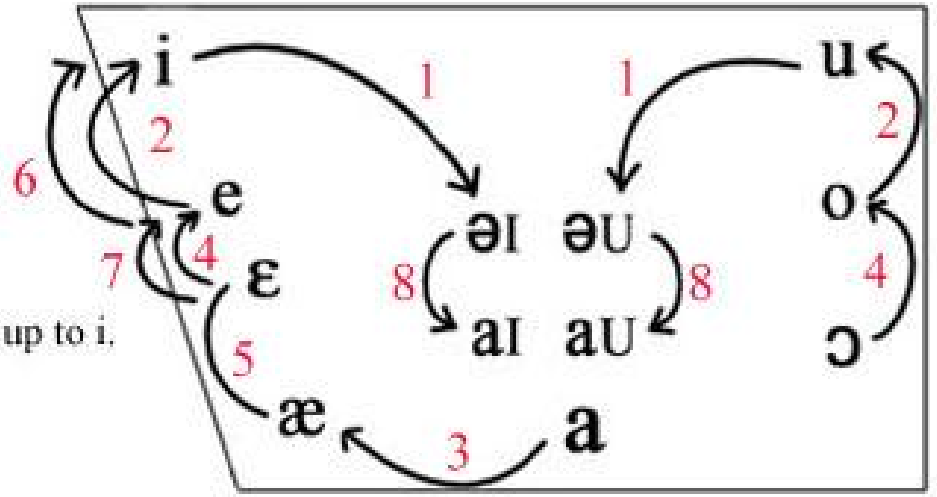


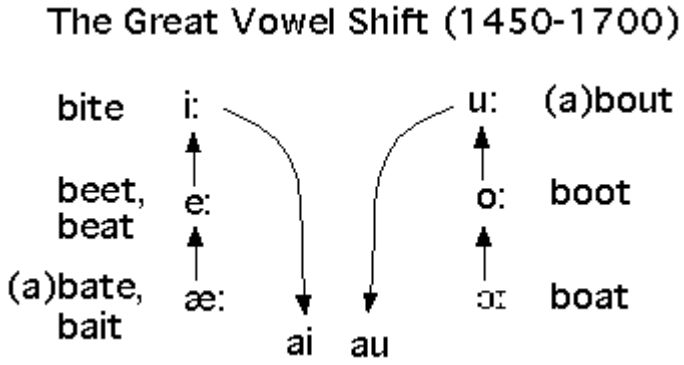
Capítulo 7:Tratamiento de ALK en estadios tempranos

- Difícil reclutamiento por el bajo porcentage de casos.
- Alchemist Protocol: screening of 6000-8000 pacientes con CPNCP resecable. Si hay reordenamiento de ALK se incluirá en el Ensayo ECOG 4517 trial: randomiza crizotinib 2 años vs placebo.

Great Vowel Shift

Step 1: i and u drop and become əɪ and əʊ
Step 2: e and o move up, becoming i and u
Step 3: a moves forward to æ
Step 4: ɛ becomes e, ɔ becomes o
Step 5: æ moves up to ɛ
Step 6: e moves up to i
A new e was created in Step 4; now that e moves up to i.
Step 7: ɛ moves up to e
The new ɛ created in Step 5 now moves up.
Step 8: əɪ and əʊ drop to aɪ and aʊ





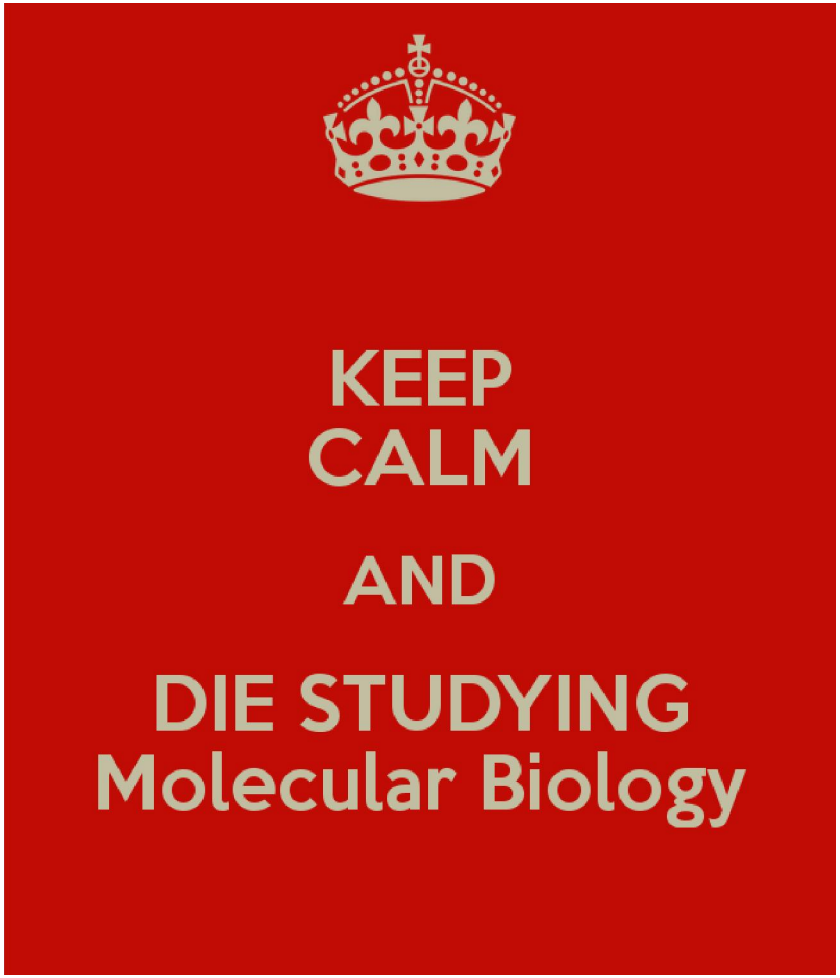
Great Vowel Shift

Inglés moderno temprano

Con el inglés moderno temprano se cree que hubo una evolución vocálica del inglés (*Great Vowel Shift*), cosa que pasó principalmente en el siglo XV. El inglés fue estandarizado a partir del dialecto deLondres y se extendió por el gobierno y la administración así como por los efectos de la imprenta. Hacia la época de William Shakespeare (mediados del siglo XVI), la lengua ya se reconoce como inglés moderno. En 1604 se publicó el primer diccionario en inglés (*Table Ahphabeticall).*

El inglés continuó adoptando palabras extranjeras, especialmente del latín y del griego desde el Renacimiento (en el siglo XVII las palabras latinas eran usadas a menudo con la declinación original pero esta práctica acabó desapareciendo).


KEEP
CALM
AND
LEARN
ENGLISH


KEEP
CALM
AND
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Molecular Biology