Review Article

Targeting EML4-ALK driven non-small cell lung cancer (NSCLC)

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Introduction

Recently, due to key discoveries relating to the molecular biology of many cancers and the development of effective and specific targeted treatments, the ability to personalize cancer therapy based on individual patient genotypes has become a reality in clinical practice (1). Some examples of this genotype-specific approach to anti-cancer therapeutics are BCR-ABL targeted therapy in chronic myelogenous leukemia, C-KIT inhibition in gastrointestinal stromal tumors, the use of Kristen rat sarcoma (KRAS) to negatively select EGFR inhibitors in colon cancer, HER2-directed therapy in breast cancer, and BRAF inhibitors in melanoma (2-13). Several other therapies are currently under investigation in clinical trials and will likely soon broaden this list further.

We have learned that there are different subsets of lung cancers that can be molecularly defined, targeted-treated and which exhibit differential outcomes in terms of response and survival when compared with tumors not harboring any specific mutations. The discovery of *EGFR* mutations in lung cancer represented the first event that marked this tremendous change in our understanding and management of lung cancer. Moreover, the discovery of the implications of *Anaplastic Lymphoma Kinase* (*ALK*) rearrangements in lung cancer has changed the paradigm of how we treat different subgroups of non-small cell lung cancer (NSCLC) patients (11,14).

ALK inhibitors are able to disrupt the signaling cascade related to cell survival, producing an apoptotic response (15,16). Crizotinib, an oral ALK inhibitor, has demonstrated a clinical benefit in this subset of patients that exceeds the usual expectations for this disease (13). Therefore, the inclusion of ALK screening in the molecular diagnosis of lung cancer is mandatory, considering that the frequency of ALK alterations has been reported to range from 2% to 25% of lung cancer patients between different series (1,2,17-24).

Some questions still remain a matter of debate. Firstly, which technique is most suitable to detect ALK alterations? Secondly, which patients should be included in screening programs? Thirdly, how should the sequence of available therapies be administered to these patients and, lastly, how can we understand the mechanisms of resistance that all patients invariably ultimately develop to ALK inhibitors?

ALK in lung cancer

Although *ALK* mutations do occur, the majority of ALK-positive tumors induce the aberrant signal through the formation of fusion genes. *ALK* rearrangements were initially identified in anaplastic large cell lymphoma. Since then, this alteration has been described in other tumors such as inflammatory myofibroblatic tumors, neuroblastoma and NSCLC, among others (11,25-29). These rearrangements induce a chimeric protein with ligand-independent tyrosine kinase activity that acts through different signaling pathways, such as RAS/MEK/ERK which are related to the proliferative effect, and PI3K/AKT y JAK3/STAT3 which are involved in cell survival (16,30,31).

Up to eleven different variants of *ALK* chromosomic rearrangement have been described. *Echinoderm microtubule associated protein like-4* (*EML4*) represents the most frequent partner for ALK in lung cancer. *Figure 1* shows the general

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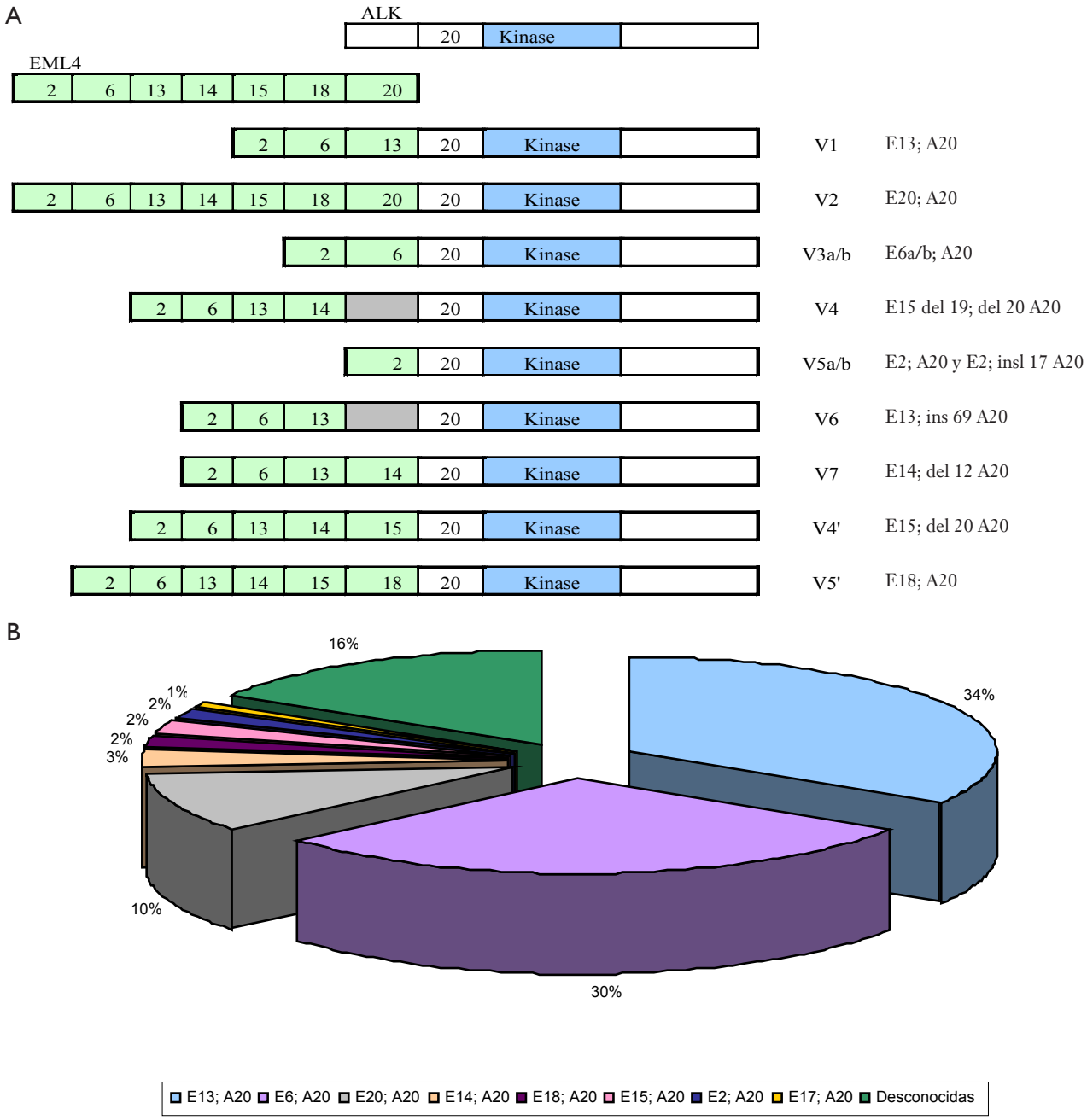

Figure 1 A. Distribution of different fusion gene variants of EML4-ALK described up to date. ALK fusion emerges on exon 20 of the kinase. Alternative variants depend on different EML4 cut points; B. Frequency of different EML4-ALK variants (11,15,17-21,32). Ins, insertion; V, variant

distribution of *EML4-ALK* rearrangement depending on different exons of *EML4* present in the fusion forms. Other partners for *ALK* are *TFG* and *KIF5B* (30,32,33).

The presence of *ALK* rearrangements has more frequently been associated with certain clinical and pathological features, including adenocarcinoma histology (especially cribiform, signet-ring cells and solid patterns), never or light smoking history and male gender (*Table 1*). More importantly, wild type (WT) status for *EGFR* and *KRAS* mutations represents a more suitable criteria for ALK screening since simultaneous overlapping with other oncogenic driver mutations is uncommon (37,38). When considering these features,

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Table 1 Summary of different studies reporting ALK positive results: results considering clinical, pathological and molecular criteria

	Clinical and pathological features	General frequencies	ALK + results by subgroups
Soda 2007 (11)	Never smokers *vs.* smokers	27.3% *vs.* 72.7%	11.1% *vs.* 8.3%
n=33	Adenocarcinoma *vs.* other	54.5% *vs.* 45.4%	5.5% *vs.* 13.3%
Japanese population	Male *vs.* female	66% *vs.* 33%	9.15% in both groups
	Age	NR	NR
Inamura 2008 (17)	Never smokers *vs.* smokers	43.6% *vs.* 56.4%	4.6% *vs.* 2.4%
n=149	Adenocarcinoma *vs.* other	67.4% *vs.* 32.6%	3.4% *vs.* 0%
Japanese population	Male *vs.* female	54% *vs.* 46%	2.5% *vs.* 4.3%
	Age	63.4	59.4
Shinmura 2008 (18)	Never smokers *vs.* smokers	35% *vs.* 65%	0% *vs.* 4.8%
n=77	Adenocarcinoma *vs.* other	65% *vs.* 35%	2% *vs.* 0%
Japanese population	Male *vs.* female	50.6% *vs.* 49.4%	2.9% *vs.* 2.6 %
	Age	64.3	54
Inamura 2009 (20)	Never smokers *vs.* smokers	41.5% *vs.* 58.1%	5.7% *vs.* 3.4%
n=363	Adenocarcinoma *vs.* other	69.7% *vs.* 30.3%	4.3% *vs.* 0%
Japanese population	Male *vs.* female	53% *vs.* 47%	3.7% *vs.* 5.1%
	Age	64	56
Shaw 2009 (12)	Never smokers *vs.* smokers	60% *vs.* 40%	23.7% *vs.* 6.1%
n=141	Adenocarcinoma *vs.* other	63% *vs.* 37%	17.9% *vs.* 5.8%
Clinical selection	Male *vs.* female	66% *vs.* 34%	22.9% *vs.* 8.6%
	Age	63	52
Wong 2009 (19)	Never smokers *vs.* smokers	53% *vs.* 47%	8.5% *vs.* 0.8%
n=266	Adenocarcinoma *vs.* other	78.6% *vs.* 21.4%	6.2% *vs.* 0%
Chinese population	Male *vs.* female	50.4% *vs.* 49.6%	1.9% *vs.* 3%
	Age	64	59
Rodig 2009 (34)	Never smokers *vs.* smokers	25.4% *vs.* 74.6%	15.4% *vs.* 6%
n=358	Adenocarcinoma *vs.* other	100% *vs.* 0%	5.6% *vs.* 0%
US	Male *vs.* female	25.9% *vs.* 74.1%	11.8% *vs.* 8.4%
	Age	66	51
Martelli 2009 (21)	Never smokers *vs.* smokers	13.3% *vs.* 86.7%	6.25% *vs.* 7.9%
n=120	Adenocarcinoma *vs.* other	52.5% *vs.* 47.5%	4.76% *vs.* 10.5%
Italy, Spain	Male *vs.* female	80% *vs.* 20%	8.3% *vs.* 4.1%
	Age	67	64
Camidge 2010 (23)	Never smokers *vs.* smokers	60% *vs.* 40%	39.4% *vs.* 0%
n=66	Adenocarcinoma *vs.* other	92.4% *vs.* 7.5%	21.3% *vs.* 0%
Caucasian, Hispanic	Male *vs.* female	NR	5M, 9F
	Age	NR	53
Salido 2011 (24)	Never smokers *vs.* smokers	15% *vs.* 85%	0% *vs.* 3.2%
n=107	Adenocarcinoma *vs.* other	65% *vs.* 35%	2.8% *vs.* 2.6%
Spain and US	Male *vs.* female	77% *vs.* 23 %	2.43% *vs.* 4%
	Age	66	73
Paik 2011 (35)	Never smokers *vs.* smokers	37.7% *vs.* 62.3%	5.8 % *vs.* 3.2%
n=465	Adenocarcinoma *vs.* other	58.1% *vs.* 41.9%	6.8% *vs.* 0.8%
Chinese population	Male *vs.* female	68.2% *vs.* 31.8%	3.6% *vs.* 5.5%
	Age	NR	48.7
Yi 2011 (36)	Never smokers *vs.* smokers	NR	NR
n=101	Adenocarcinoma *vs.* other	NR	100%
Japanese population	Male *vs.* female	NR	5M, 5F
	Age	NR	56
Kwak 2010 (13)	Never smokers *vs.* smokers	NR	76% *vs.* 24%
n=82	Adenocarcinoma *vs.* other	NR	96% *vs.* 4%
Molecular selection	Male *vs.* female	NR	52% *vs.* 48%
	Age	NR	43
Shaw 2011 (30)	Never smokers *vs.* smokers	42.5% *vs.* 54.5%	40% *vs.* 9.2%
n= 412	Adenocarcinoma *vs.* other	91.5% *vs.* 8.5%	23.3% *vs.* 11.42%
Molecular selection	Male *vs.* female	41.5% *vs.* 58.5%	27% *vs.* 19.6%
	Age	59.3	51

n, number of patients included; NR, not reported; *vs.*, versus

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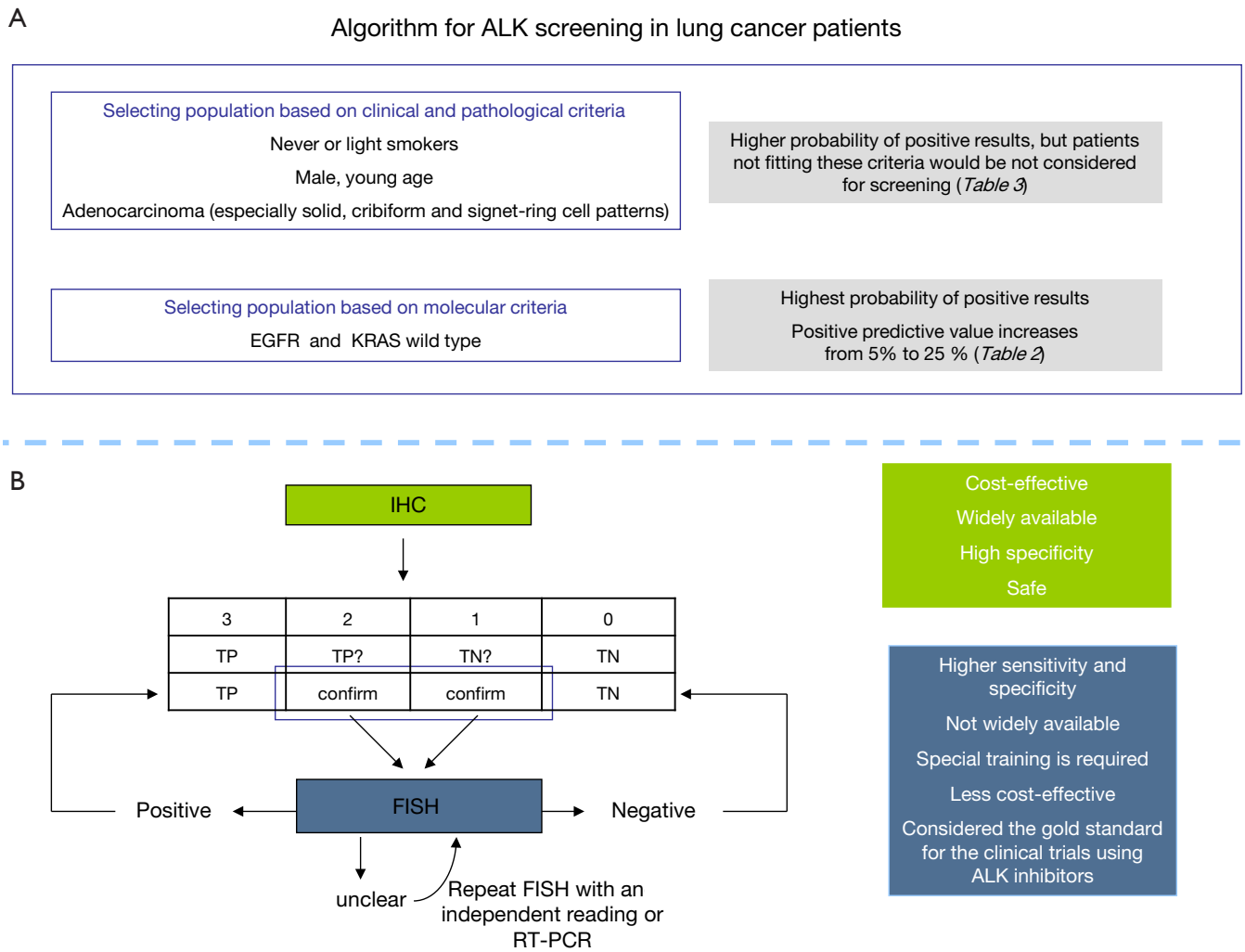

Figure 2 Algorithm for ALK screening in lung cancer patients. A. Selection of patients to be included in the screening, based on clinical-pathological and molecular criteria. B. Proposal for different techniques to be used in a large screening program. EGFR, Epidermal Growth Factor Receptor; PPV, positive predictive value; RT-PCR, Reverse transcription polymerase chain reaction; TN, true negative; TP, true positive

especially molecular selection, the likelihood of detecting an *ALK* rearrangement increases from 2-10% in the general population to 24-40% in this molecularly selected population, according to different series (see References and data in *Table 1*). Thus, the criteria for ALK screening should include the prior negative result of screening for *EGFR* and *KRAS* mutations, primarily avoiding the use of clinical and pathological characteristics (*Figure 2A*). Importantly, we should consider that frequencies of *ALK* rearrangements in other subgroup of patients, such as heavy smokers and other histology subtypes different to adenocarcinoma, are still only anecdotic.

Currently, three different techniques are available for detecting *ALK* rearrangement, though which of these is the most convenient is still a matter of debate. Consideration needs to be given to the characteristics required for a diagnostic tool to become the technique of choice for large scale screening programs, such as high sensitivity and especially high specificity to detect real true positive cases and thus avoid the need for additional procedures. Moreover, this technique needs to be cost-effective and widely available (*Table 2*). However, when considering the specific use of the ALK inhibitor crizotinib in ALK-positive patients, fluorescence in situ hybridization (FISH) has been considered to be the gold standard for detecting ALK rearrangements, using the ALK Vysis LSI ALK Dual Color

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Table 2 Advantages and disadvantages of different techniques used to detect ALK rearrangements

	RT-PCR	FISH	IHC
Advantages	High sensitivity	High specificity	Easy reading
	Quick method	PETT is suitable for this technique	Quick method
		Possibility of detection of new promoters	Lower cost
		Gold standard technique for the clinical trials using ALK inhibitors	Possibility of detection of new variants
			Detection of all rearrangements, no specific promoter is required
			Widely available
			Commercialized antibodies
Disadvantages	High quality and enough RNA quantity is required	Lower sensitivity	The fusion gene is indirectly detected by the protein expression
	Difficult to obtain RNA from small biopsies	Expertise in interpreting the results	Risk of false negative results
	Potential degradation of RNA in PETT	Risk of false negative results	Results can vary according to type and dilution of the antibody and reading method
	No new promoters are detected	No widely available	Compared to other tumors, the protein expression can be weaker in lung cancer (risk of false negative)
	No widely available	More time consuming	Reading method has been adapted from EGFR and HER2 score systems
		Higher cost	

PETT, paraffin embedded tumor tissue

Break Apart Rearrangement Probe (Abbott Molecular, Abbott Park, IL). Other regulatory agencies admit the use of other diagnostic techniques, as in Japan and Europe.

FISH confers higher sensitivity and specificity when compared to real time-PCR (RT-PCR) and immunohistochemistry (IHC). However, FISH is not widely available and is less cost-effective than other techniques. The algorithm these authors propose would include the use of IHC for the first analysis; results scored as 0 and 3 could be considered as true negative and true positive, respectively. However, for results scored as 2 and 1, a confirmatory test should be performed since these two groups accumulate the highest rates of false negative and false positive results (*Table 3*). This algorithm includes confirmation by FISH and RT-PCR (*Figure 2B*).

Current status of ALK inhibition in lung cancer: crizotinib trials (*Table 4*)

Since clinical practice currently differs from country to country, it is necessary to review data from different clinical trials to understand these differences, in particular how access to different drugs depends on patients' regional backgrounds.

Crizotinib (PF-2341066; XALKori, Pfizer, New York, NY) is an oral small-molecule with tyrosine kinase inhibitor (TKI) properties of both *MET* and ALK (46). The fast approval of crizotinib in the US was based on the results of a phase I trial expansion cohort which included ALK-positive NSCLC patients (13) in which a total of 82 patients were treated. This trial demonstrated that crizotinib was an effective agent in this subset of patients with an overall response rate of 57% (56% confirmed partial responses and 33% stable disease). The estimated probability of 6 months progression-free survival (PFS) was 72%. Additionally, crizotinib was confirmed as a safe drug. The majority of adverse events were grade 1 and 2 gastrointestinal disorders (13). Based on these results, the FDA approved the use of crizotinib in NSCLC patients harboring *ALK* rearrangements independently of any prior treatment the patient had received. A more recent analysis of patients included in this expansion cohort (n=119) confirmed the previous findings: response rate was 61% and response occurred independently of clinical features such as age, gender, number of previous therapies and performance status. The median PFS was 10 months, and the estimated overall survival rates at 6 and 12 months were

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Table 3 Summary of trials reporting the results of different techniques used for detecting ALK rearrangements

	Number of samples	Population	Technique	Positive results for ALK	Confirmation	Other interesting data
Soda 2007 (11)	33	Japanese, no other criteria	RT-PCR	9.10%	No	Detection of other variants, utility of cytology samples
	42	Japanese, no other criteria	RT-PCR	4.80%	No	Detection of other variants, utility of cytology samples
Inamura 2008 (17)	149 adeno (221 NSCLC)	Japanese, no other criteria	RT-PCR	3.4% in adeno; 2.3% in NSCLC	IHC, DAKO ALK1 1:20	100% of concordance with IHC; 2 variant 1 y 3 variant 2 Variant 1 in a mixed adeno (papillary and BAC) Variant 2 in acinar adenocarcinoma Exclusion of *EGFR* and *KRAS* mutations
Shinmura 2008 (18)	77	Japanese, no other criteria	RT-PCR	2.60%	No	No other variants Variant 1 y variant 2 (2 cases) Both positive results in adeno and smoking history Exclusion of *EGFR* and *KRAS* mutations, one case associated with *p53* mutation
Inamura 2009 (20)	253 adeno (363 NSCLC)	Japanese, no other criteria	IHC, DAKO ALK1 1:20	4.3% in adeno: 3.1% in NSCLC	RT-PCR	5 cases in adeno and 0 cases in other histologies Predominance in acinar adeno (54.5%) Predominance in never smokers (63.6%) Exclusion of *EGFR* and *KRAS* mutations, one case associated with *p53* mutation IHC SE 100%, SP N/R
Wong 2009 (19)	266	Chinese, no other criteria	RT-PCR	6.2% adeno, 4.9% in NSCLC	IHC, DAKO ALK1 1:1000	All cases adeno, 90,9% never smokers Exclusion of *EGFR* and *KRAS* mutations, one case associated with *p53* mutation *EGFR* and *KRAS* mutations are negative, the proportion of ALK positive results is 1.8% in never smoker males and 6.5% in never smoker females
Shaw 2009 (12)	141	Clinical selection	FISH Vysis	11.1%	IHC, DAKO ALK1, RT-PCR	At least 2 clinical criteria for selection: Asian population, adenocarcinoma, female, never smoking history. More frequent in male, adenocarcinoma (predominance in signet-ring cells), younger patients and never smoking history. Similar response to chemotherapy and lower response to TKI compared to *EGFR* and *KRAS*-mutant patients. 89% of ALK positive results in stage IV NSCLC Exclusion of *EGFR* and *KRAS* mutations
Rodig 2009 (34)	358	Clinical and pathological selection	DAKO ALK1 ALK1 1:2	5.6%	FISH	ALK positive results more frequent in younger patients, solid and signet-ring adenocarcinoma and more advanced stages. IHC SE 80 an 40% with and without tiramin amplification *vs.* FISH S 95% Exclusive with *EGFR* mutations
Martelli 2009 (21)	120	Italy, Spain	DAKO ALK1 ALK1, ALKc (SP8) y 5A4	7.5%	FISH, RT-PCR	IHC SE 0% and SP 0% (ALK detection in areas distant to the tumor)
Boland 2009 (39)	35	Clinical and pathological selection	DAKO ALK1, ALK1 1:100	2%	FISH, RT-PCR	SE100% and SP100% (validated in an independent cohort of 335 NSCLC cases)

Table 3 *(continued)*

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Table 3 *(continued)*

	Number of samples	Population	Technique	Positive results for ALK	Confirmation	Other interesting data
Takeuchi 2009 (32)	130	Japanese, no other criteria	ALK1, 5A4	6.15%	RT-PCR	IHC SE 100% and SP 100% for both techniques iAEP method used for interpreting the IHC results iAEP and PCR improve the detection rates for new ALK variants.
Mino-Kenudson 2010 (40)	153	US	DAKO ALK1 ALK1 1:50, 1:2	14.4%	FISH, RT-PCR	ALK-protein expression is lower in lung adenocarcinoma, risk of FN results.
		Clinical and pathological selection	D5F3			Use of new Ab at a higher concentrations improves SE with no effect in SP. ALK1 SE 67% y SP 97% *vs.* D5F3 SE 100% y SP 99%
Ros-Camidge 2010 (23)	61 adeno (66 NSCLC)	Caucasian, Hispanic	FISH Vysis	21.3% (19.7%)	No	Positive results in 100% adeno and 60% never smokers 1 case with concomitant *EGFR* mutation (exon 20) 0% concomitant *KRAS* mutations No concomitant MET amplification. FISH SE and SP improve to100% when at least 4 tumor areas are analyzed ALK positive result in 54% of cases when sampling tumor area *vs.* 6.8 % in areas adjacent to the tumor area, in ALK positive tumors. ALK positive result in 6% of cases when sampling tumor area *vs.* 6 % in areas adjacent to the tumor area, in ALK negative tumors.
Kwak 2010 (13)	82 de 1500	Molecular selection	FISH Vysis	5.4%	RT-PCR, IHQ (retrospective)	Clinical benefit of crizotinib: RR 57%, SD 33%, PFS rate at 6 m72%
Salido 2011 (24)	107	Spain, US, no other criteria	FISH Vysis	3%	IHQ, DAKO ALK1	2 cases EML4-ALK, 1 case ?-ALK IHC positive in 2 cases EML4-ALK and negative in ?-ALK case FISH: 63% increase GCN y 17% ALK amplification. Unknown predictive value
Paik 2011 (35)	465	Korean	IHQ, 5A4 1:30	8.6%	FISH Vysis	FISH positive in 19/453 (4.2%) FISH is concordant with IHC when score 3, 1 and 0. FISH is variable with score 2. SE and SP of IHC 100% and 95.8%, respectively. FP IHC 1.5% Exclusion of *EGFR* and *KRAS* mutations
Yi 2011 (36)	101	Japanese, clinical selection	DAKO ALK11 1:100	9.9%	FISH Vysis	IHC SE 90% and SP 97. 8% FN rate 10% and FP rate 2.2% using IHC IHC is a good initial screening technique but intermediate scores need to be confirmed

Table 3 *(continued)*

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Table 3 *(continued)*

	Number of samples	Population	Technique	Positive results for ALK	Confirmation	Other interesting data
Shaw 2011 (41)	92 ALK+ *vs.* 320 ALK-	Molecular selection	FISH Vysis	22.3%	RT-PCR, IHQ (retrospective)	ALK predictive but not prognostic value ALK positive results are more frequent in male, adenecarcinoma, younger patients, never smokers and Caucasian population

Adeno, adenocarcinoma; ALK+, presence of ALK rearrangement; BAC, bronquioloalveolar carcinoma; FN, false negative; FP, false positive; GCN, gene copy number; IHC, inmunohistochemistry; m, months; N/R, no reported; RT-PCR, reverse transcription polymerase chain reaction; PFS, progression-free survival; RR, response rate; SE, sensitivity; SD, stable disease; SP, specificity; TKI, tyrosin kinase inhibitors. Brand names for different antibodies and probes: DAKO Mouse Monoclonal Anti-Human CD246, ALK Protein Clone ALK1 (Dako, Dermank and CA); D5F3 Rabbit monoclonal anti-human CD246, clones D5F3 and D9E4, Cell Signaling Technology, Danvers, MA; 5A4 Mouse monoclonal anti CD246, clone 5A4, Novocastra, Newcastle, UK; LSI ALK (Abbott) ALK Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL

Table 4 Summary of the clinical trials reporting the efficacy results with crizotinib in ALK positive patients

	pI (12,42)	pII (43,44)	pIII (45)		
	crizotinib	crizotinib	crizotinib	Chemotherapy (PEM+DOC)	
n	82 [119]	135 [261]	173	174	
Overall RR (%)	61%	51%	65%	20% (PEM29%; DOC6.9%)	P<0.001
Duration of response (median, weeks)	48	42.9			
Duration of treatmente (median, weeks or cycles)	32 w	22 w	11 cycles	4 cycles	
6 months PFS	72%	NR	NR	NR	
mPFS (median, months)	NR	8.1 (6.8-9.7)	7.7	3 (PEM4.2; DOC2.6)	HR 0.49 (0.37-0.64), P<0.0001
mOS	NR	NR	20.3	22.8	HR 1.02 (0.68-1.5), P=0.5394
OS rates 6 m, 12 m	NR	90%, 81%	NR	NR	

DOC, docetaxel; m, months; m-PFS, median progression-free survival; mOS, median overall survival; n, number of patients included; PEM, pemetrexed; NR, no reported; RR, response rate; w, weeks

90% and 81%, respectively (42).

Similar results were obtained from patients included in the PROFILE 1005, a phase II single-arm study to evaluate the efficacy and safety of crizotinib in pretreated NSCLC patients harboring *ALK* rearrangements. A total of 136 patients received crizotinib in second line (9.6%), third line (27.2%) and forth line (27.2%). Thirty six percent of patients had received more than 4 previous lines of treatment. This study demonstrated an overall response rate of 50% for a heavily pretreated population. Except for Asian patients, no other clinical characteristics influenced response, with similar benefit regardless of smoking history, performance status and previous treatment exposure (43).

Notably, standard, second line, single-agent treatments for unselected patients with advanced NSCLC achieve an overall response rate of less than 10% and PFS of less than 3 months (47,48).

An up-to-date analysis for patients included in the PROFILE 1005 trial, in which more than 900 patients were treated, has been reported (44). The first 261 patients had received treatment with a median duration of 48 weeks and had been considered as mature population. The results were consistent with those previously reported. The overall response rate was 60% (54-66%) with median duration of response of 46 weeks (35-54 weeks) and PFS was 8.1 months (6.8-9.7 months). Fifteen percent of patients discontinued crizotinib and 10% had a dose reduction due to an adverse event. The most frequent adverse events were vision disorders (54%), nausea (51%), diarrhea (44%), vomiting (44%), and constipation (37%), which were mostly grade 1 and 2 (44).

Since most of ALK-positive patients currently receive crizotinib at some point during treatment, in the absence of data from a randomized controlled trial, the effect

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of this drug on overall survival remains unclear. Thus, a retrospective comparison to evaluate the impact of crizotinib on overall survival has been reported. Patients with advanced NSCLC from 3 patient cohorts were included in this analysis: 82 ALK-positive patients treated with crizotinib from the expansion cohort of a phase I trial of crizotinib, 36 ALK-positive controls who did not receive crizotinib and 253 ALK-negative/*EGFR*-negative patients. Among the ALK-positive patients treated with crizotinib, median overall survival from initiation of crizotinib was not reached and overall survival did not differ with age, gender, smoking exposure, or ethnic background. Overall survival in the ALK-positive crizotinib-naïve controls was similar to that in the entire cohort. However, overall survival was significantly improved in patients receiving crizotinib as second or third line therapy, compared with crizotinib-naïve patients receiving any other second line therapy (49).

Patient-reported outcomes of disease- and treatment-related symptoms, quality of life (QoL), and health status have been reported in the PROFILE 1005 trial (50). Data for symptom scores and QoL from the first 136 patients for whom efficacy and safety data are available have been presented (43,50,51). The results indicate that patients receiving crizotinib presented clinically meaningful and statistical (≥10-point change and P≤0.05, respectively) improvements in some symptoms from baseline. There were clinically meaningful improvements in pain, dyspnea, and cough from cycle 2, and in fatigue from cycle 5, and these improvements were maintained through subsequent cycles (49). Moreover, global QoL was maintained throughout treatment with crizotinib with clinically meaningful improvement at cycle 7 (51). Significant reductions in pain (50), dyspnea, cough, fatigue, insomnia, and alopecia symptom scales were maintained with therapy (51). Improvement in mean QoL was also reported but changes were not clinically significant, indicating that QoL was stable with more cycles of treatment (50). Clinical meaningful improvements were observed for physical, role and social functioning and for global QoL (51,52).

Recently, results for the PROFILE 1007 study have been reported (45). This large phase III trial (n=347) compared crizotinib *vs.* chemotherapy in ALK-positive patients previously treated with a prior chemotherapy regimen including a platinum-doublet. Patients were randomized to receive crizotinib or chemotherapy (pemetrexed or docetaxel, depending on the previous therapy). Those patients assigned to the chemotherapy arm were allowed to receive crizotinib when progression occurred. This crossover occurred in 62% of patients initially assigned to receive chemotherapy. The study met its primary endpoint, with a difference in PFS in favor of crizotinib [7.7 *vs.* 3 m, HR (95% CI), 0.49 (0.37-0.64), P<0.0001]. Response rate significantly favored crizotinib, with 65% of responses in the crizotinib arm *vs.* 20% in the chemotherapy arm (pemetrexed 29% and docetaxel 6.9%, P<0.0001). Interim analysis of overall survival (when 28% of survival events had occurred) showed no statistically significant difference between crizotinib and chemotherapy with a preliminary estimated median OS of 20.3 *vs.* 22.8 months; HR 3.02; 95% CI 0.68-1.5, P=0.5394), but not adjusted for crossover. The most frequent adverse events related to crizotinib were visual disturbances (59%), diarrhea (53%), nausea (52%), vomiting (44%), and elevated transaminases (36%). Frequent adverse events with chemotherapy were nausea (35%), fatigue (29%), decreased appetite (21%), and alopecia (20%). The incidence of grade 3-4 adverse events was similar in both arms (31%). Duration of treatment was longer for crizotinib *vs.* chemotherapy with a median number of administered cycles of 11 *vs.* 4, respectively (45). Crizotinib offered clinically meaningful and statistical (P<0.001) improvements in some symptoms from baseline. There were improvements in cough, dyspnea, fatigue, alopecia, insomnia, and pain. Moreover, global QoL as well as physical, role, emotional, cognitive and social functioning favored crizotinib over chemotherapy (P<0.001) (45).

This data clearly establish that crizotinib is superior to standard second line chemotherapy, usually with docetaxel and pemetrexed which were the comparators in this trial. This superiority was confirmed in terms of prolonging PFS and improving response rate, as well as improving patient symptoms and QoL.

Results from the currently ongoing PROFILE 1014 study (Clinicaltrials.gov identifier NCT01154140) comparing first line crizotinib *vs.* chemotherapy are expected to elucidate whether, mirroring the experience with EGFR-TKIs in *EGFR*-mutant lung cancer, the ALK inhibitor is a better strategy when administered upfront (53-57).

Beyond crizotinib

Despite the good activity and tolerability profile of crizotinib for treating ALK-positive patients, several molecules have been being tested to evaluate newer regimens with a more desirable toxicity profile and more convenient administration schedules for patients, though

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without jeopardizing clinical activity. Moreover, patients with initial good responses to crizotinib invariably develop resistance. Therefore, further therapies are required when resistance occurs.

Based on the previous experience with *EGFR*-mutant NSCLC, mutations affecting the kinase domain of ALK were expected to mediate resistance to crizotinib. In fact, the first report of the presence of such mutations was published along with the first results of crizotinib activity in ALK-positive NSCLC (13,58). The presence of two different kinase domain mutations, L1196M and C1156Y, occurred in different clones from the same patient. Other resistant mutations have been reported to date (L1152R, G1269A, S1206Y, G1202R and 1151 Tins) with further mutations already identified. Collectively these mutations can mediate crizotinib resistance in ALK-positive tumors (59-61). These findings are in contrast with the experience in EGFR, in which resistance is mainly mediated by the emergence of a predominant mutation, T790M, and other secondary mutations are rare (62,63). Furthermore, different *ALK* mutations identified so far have shown a differential spectrum of sensitivity to crizotinib and other ALK inhibitors, suggesting that not all the newer ALK inhibitors may be equally effective in treating ALK-positive patients who develop resistance to crizotinib (60,64,65).

Other mechanisms implicated in ALK resistance have been described. These include, firstly, the copy number gain of the ALK gene fusion, which occurs simultaneously with resistant mutations (61,66). Secondly, the presence of other oncogenes that may become active via mutation or other mechanism and coexist with ALK, such as EGFR, HER2 or KIT (59-61,63). Thirdly the emergence of a separate clone that harbors other oncogenes different to ALK, such as *EGFR* or *KRAS* (61). Additionally, the underexposure of the Central Nervous System (CNS) to crizotinib may partly underlie this resistance and warrants consideration for the development of newer ALK inhibitors that can attain optimal concentration in the cerebrospinal fluid (67).

LDK378 is a next generation ALK inhibitor able to inhibit both ALK and the C1156Y variant. Results of the first in-human phase I trial have been recently reported (68). Fifty-six ALK-positive patients were included (50 patients with ALK-positive lung cancers). LDK378 was administered orally once-daily, starting at 50 mg/day. Of 47 patients evaluable for response, 24 (51%) responded and all responses were in ALK-positive NSCLC patients. Twenty one (81%) of 26 patients who had progressed to crizotinib and were treated at a dose level of ≥400 mg/day responded. The maximum tolerated dose was 750 mg/day. Dose limiting toxicities included diarrhea, vomiting, nausea, dehydration, and ALT elevation. The most frequent grade 3 side effect was diarrhea, which occurred in 5 (9%) patients. However, the most common side effects (all grades) were nausea (59%), vomiting (54%) and diarrhea (48%). Some activity has been reported in CNS metastases, which suggests good penetration in the cerebrospinal fluid.

CH5424804 is a next generation ALK inhibitor able to inhibit ALK as well as the C1156Y and L1196M variants. Recently communicated results of a phase I/II trial demonstrated very promising activity in crizotinib-naïve ALK-positive NSCLC with a response rate of 85% and range of duration of treatment from 2-46 weeks. Thirty four patients were enrolled in the trial and CH5424804 was administered at 300 mg twice-daily. The majority of patients remain on treatment at the time of this communication. The main treatment-related adverse events were ALT, AST and bilirrubin elevation (7, 6 and 3 patients, respectively), neutropenia (5 patients, 2 grade 3), rash (4 patients), nausea (4 patients), and myalgia (3 patients) which were mostly grade 1 except for neutropenia (2 cases were grade 3). Only one patient presented a treatment-related eye disorder and was grade 1. No dose reductions were necessary due to side effects. Activity in CNS metastases was shown (69).

AP26113 is a novel, synthetic, orally-active TKI that inhibits mutant forms of ALK and EGFR, as well as TKI-resistant forms such as L1196M (ALK) and T790M (EGFR) (66). This drug does not inhibit the native form of EGFR. Results of the first in-human phase 1/2 trial have been recently reported (70). A total of 34 patients were included in the dose-finding phase, starting at a dose of 30 mg/day. Twenty-seven patients had lung cancer (11 ALK-positive patients, 11 *EGFR*-mutant patients and 5 WT for ALK and EGFR). Nine ALK-positive patients were crizotinib-resistant, while 2 were crizotinib-naïve. Among the ALK patients, 8 partial responses were recorded, 6 among the crizotinib-resistant patients and 2 among crizotinib-naïve patients. The initial doses of 60 and 90 mg/day were sufficient to achieve some of these partial responses. The more frequent side effects were nausea (32%), diarrhea (18%, 3% of grade 3), loss of appetite (12%), fatigue (26%, 3% of grade 3), and vomiting (12%). Four (12%) patients presented pneumonia, in all cases grade 3. Notably, no rash or visual disturbances were reported. Similarly to previous next generation ALK inhibitors, activity in CNS disease has been reported. The phase 2 expansion will include 4 cohorts: ALK-positive lung cancers

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Table 5 Current clinical investigation in ALK positive patients

clinicaltrials.gov identifier	Status	Phase	Drug(s)		Target population (ALK+)
NCT 01228435	terminated	II	IPI 504	HSP90i	both
NCT01562015	recruiting	II	STA-9090	HSP90i	C-N
NCT01752400	not yet recruitinig	II	ST-9090	HSP90i	C-R
NCT01772797	recruiting	I	LDK 378 plus AUY922	HSP90i	both
NCT 0157994	recruiting	I/II	STA-9090 plus crizotinib	HSP90i plus ALKi	C-N
NCT01801111	not yet recruitinig	I/II	RO5452802	HSP90i	C-R
NCT01712217	recruiting	I/II	AT13387+ crizotinib	HSP90i plus ALKi	C-R
			criztinib *vs.* crizo plus AT13387	HSP90i plus ALKi	C-R
			AT13387 *vs.* AT13387 plus crizotinib	HSP90i plus ALKi	C-R
NCT01288430	recruiting	I	DS-2248	HSP90i	C-R
NCT01625234	recruiting	I	X-396	ALK i	C-R

ALKi, ALK inhibitor; C-N, crizotinib-naïve; C-R, crizotinib-resistant; HSP90i, Heat Shock Protein 90 inhibitor

naïve to crizotinib, crizotinib-resistant ALK-positive lung cancers, *EGFR* mutant lung cancers resistant to reversible TKIs, and other cancers harboring ALK abnormalities.

Another strategy to try to overcome ALK resistance consists of targeting the chaperone pathway. Results of Heat-Shock-Protein 90 (HSP90) inhibition in a cohort of ALK-positive patients have been reported (71). AUY992 is a potent, non-geldanamycin, HSP90 inhibitor. Its activity as a once-weekly, 1-hour infusion has been tested in a specific cohort of 22 ALK-positive lung cancer patients. The overall response rate was 32%, with a disease control rate of 59% and an estimated PFS at 18 weeks of 35.8%. The overall response rate in ALK-positive crizotinib-naïve patients (8) was 50%, with a disease control rate of 100% and an estimated PFS of 62.5% at 18 weeks. The most frequent treatment related side effects were eye disorders (74%), diarrhea (68%), nausea (39%), vomiting (26%), and fatigue (21%). Grade 3-4 side effects included eye disorders (7%), diarrhea (6%), and fatigue (4%). AUY922 had an acceptable safety profile. Activity was demonstrated both in crizotinib-naïve and crizotinib-resistant patients.

Other ALK inhibitors, as well as HSP90 inhibitors and different combinations are being currently tested in clinical trials to evaluate the safety profile and the activity in patients harboring *ALK* rearrangement (*Table 5*).

Conclusions

Lung cancer harboring *ALK* rearrangements has emerged as a relevant subtype of this disease, based both on its particular natural history and on the success of crizotinib in efficaciously treating this specific population. However, some challenges remain, such as a how to better manage adverse events related to treatment, more convenient therapeutic schedules for our patients, how to effectively treat CNS disease and overcome or delay the emergence of resistance. Newer strategies including next generation ALK inhibitors or novel drugs may help to address some of these questions.

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