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EDITORIAL

First-line alectinib for ALK-positive lung cancer: is there room for further improvement?

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Abstract

In the present editorial we describe the therapeutic achievements in the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). We focus on the major breakthroughs we have been witnessing in this context, from the introduction of crizotinib as the first approved targeted drug, to the meaningful improvement in terms of clinical benefit that alectinib, a second generation ALK-inhibitor, has recently provided over crizotinib. Finally, we address major trends of clinical research in this setting, and whether this might translate into further clinical improvement in the near future.

Keywords: alectinib, ALK, brain metastases, brigatinib, ceritinib, crizotinib, non-small cell lung cancer.

Citation

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The discovery of anaplastic lymphoma kinase (*ALK*) gene rearrangement in non-small cell lung cancer (NSCLC) has unveiled a crucial signaling pathway for lung tumorigenesis [1]. In fact, *ALK* rearrangements, which are present in roughly 5% of NSCLCs, encode a deregulated fusion oncoprotein that promotes ALK dependency by constitutive activation of ALK tyrosine kinase through autophosphorylation. Importantly, they more commonly consist of a chromosomal inversion within the short arm of chromosome 2, which results in the formation of the echinoderm microtubule-associated protein-like 4 (*EML4*)–*ALK* fusion oncogene [2]. Various *EML4*–*ALK* fusion variants have been identified so far, based on the truncated site of *EML4*, which undergoes chromosomal inversion, with variant 1 (exon 13 of *EML4* fused to exon 20 of *ALK* [E13;A20]) and variant 3a/b (exon 6a/b of *EML4* fused to exon 20 of *ALK* [E6a/b;A20]) representing 60 to 80% of all variants [3]. From a clinical standpoint, the detection of an *ALK* gene rearrangement in a newly diagnosed advanced NSCLC patient is of utmost importance, as it associates with a response to treatment with an ALK-inhibitor in approximately three quarters of cases [4–9]. Consistently, available clinical data strongly suggest that the most optimal up-front therapy for these patients is an ALK-inhibitor, with crizotinib being the first ALK-targeted drug approved for use in this setting [4]. Of note, long-term outcomes of ALK-positive patients initially treated with crizotinib within the randomized phase 3 PROFILE 1014 trial of crizotinib versus platinum/pemetrexed chemotherapy are becoming available, and they indicate an exceptional 4-year survival rate of 56.6% [10]. Unfortunately, resistance to crizotinib is virtually inevitable, usually occurring after a median of approximately 11 months [4,5]. The mechanisms that underlie acquired resistance to crizotinib have been divided into biological and pharmacokinetic ones. In the first case, on-target (*ALK* gene amplification, *ALK* gene secondary mutations) and off-target (bypass tracks, histological transformation) mechanisms have been identified [11]. In the second, resistance is the result of disease progression in the central nervous system (CNS), which reflects the poor CNS penetration of crizotinib [12,13].

Against this background, second-generation ALK-inhibitors have been developed, namely alectinib, ceritinib, and brigatinib, with the aim of overcoming resistance to crizotinib [14]. Common features of these drugs are higher potency than crizotinib against ALK, activity against some, but not all, *ALK* secondary mutations that are responsible for acquired resistance to crizotinib, and superior clinical efficacy in the CNS compared to crizotinib. Such characteristics have justified the clinical development of this new generation of ALK-inhibitors as up-front treatment instead of crizotinib. Alectinib was among the first agents to be tested in this setting, and AF-001JP was a

Table 1. Cross comparison of clinical activity in alectinib and ceritinib phase 3 trials for ALK-inhibitor-naïve ALK-positive advanced NSCLC patients.

Trial	J-ALEX [7,17]	ALEX [8,9]	J-ALEX [7,17]	ALEX [8,9]	ASCEND-4 [6]
Drug	Crizotinib	Crizotinib	Alectinib	Alectinib	Ceritinib
Number of patients	104	151	103	152	189
Median PFS	10.2 months	10.9 months	NR (>21 months)	34.8 months	16.5 months
PFS HR (95% CI)	-	-	0.34* (0.17–0.71)	0.43* (0.32–0.58)	0.55** (0.42–0.73)
ORR (%)	79	75.5%	92	82.9	73
Median PFS with BM	10.2 months	7.4 months	NR (>21 months)	27.7 months	10.7 months
Median PFS without BM	10.0 months	14.7 months	20.3 months	34.8 months	26.3 months

BM, brain metastases; HR, hazard ratio; NR, Not reported; ORR, overall response rate; PFS, progression-free survival.
*_Versus_ crizotinib.
**_Versus_ chemotherapy.

phase 1/2 trial that evaluated alectinib as the first ALK-inhibitor treatment in ALK-positive advanced NSCLC patients from Japan [15]. The results of the phase 2 part of this study showed that alectinib at a dose of 300 mg twice daily provides an outstanding overall response rate (ORR) of 93.5% with a median progression-free survival (PFS) that has not been reached after a median follow-up of 3 years (3-year PFS rate=62%) [16].

On this basis, alectinib was subsequently tested in a phase 3 study, the Japanese-ALEX (J-ALEX) trial, in which ALK-inhibitor-naïve ALK-positive advanced NSCLC patients were randomized to standard crizotinib at a dose of 250 mg twice daily or alectinib 300 mg twice daily, the primary endpoint being PFS as assessed by an independent review facility (IRF) (Table 1) [7]. Under an assumption of expected hazard ratio (HR) of 0.643, 164 events were required to have 80% power for a superiority hypothesis at a two-sided alpha of 0.05. Three interim analyses for early stopping due to efficacy were planned after 33, 50, and 75% of required PFS events had occurred. Overall survival, ORR, time to progression in the brain, and safety were among key secondary endpoints. Initially presented at the American Society of Clinical Oncology (ASCO) 2016 meeting, the results of this study have been recently published by Hida and colleagues in *Lancet*. Overall, 207 patients were allocated to either alectinib (n=103) or crizotinib (n=104). Randomization was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 *versus* 2), treatment line (first *versus* second), and disease stage (IIIB or IV *versus* postoperative recurrence), but not for brain metastases, which resulted in a disproportionate prevalence of brain metastases in the crizotinib arm (28% for crizotinib *versus* 14% for alectinib). Remarkably, the study met its primary endpoint, as at the second planned interim analysis, the HR for IRF-assessed PFS was 0.34 (99.7% CI: 0.17–071) in favor of alectinib (median not estimable [NE], 95% CI: 20.3-NE, *versus* 10.2 months, 95% CI: 8.2–12.0; $p<0.0001$). A multiple stratified Cox regression analysis, adjusting for the potential of imbalance in the distribution of prognostic factors between treatment groups on IRF-assessed PFS, showed a similar HR as the primary analysis (HR=0.34). Therefore, it can be concluded that the superior efficacy observed with alectinib was independent of the different distribution of patients with baseline brain metastases between the two arms of the study. Benefits in terms of IRF-assessed PFS were seen across different subsets, including patients with brain metastases (HR=0.08) as well as those who had received prior chemotherapy (HR=0.39). Notably, the total number of patients with at least one grade 3 or 4 adverse event was higher in the crizotinib arm (52 *versus* 26%). Also, significant more patients interrupted crizotinib due to an adverse event (29 *versus* 20%), and drug discontinuation rate was higher with crizotinib (20 *versus* 9%). Therefore, the results of J-ALEX suggested for the first time a superior efficacy and tolerability of alectinib compared to crizotinib, although it should be noted that previous data have shown that the rate of crizotinib-associated toxicities might be higher in the Japanese population, accounting for a higher rate of discontinuation with crizotinib [18].

To put the results of J-ALEX in context, we should compare them with those of the global phase 3 ALEX trial, which similarly randomized a larger population of ALK-inhibitor-naïve ALK-positive advanced NSCLC patients (n=303) to either crizotinib (n=152) or alectinib (n=151) (Table 1) [8]. However, unlike J-ALEX, the ALEX trial had a doubled dose of alectinib (600 mg twice daily), which was based on a previous dose finding study conducted in a Northern American population, while in Japan dose escalation beyond 300 mg twice daily was not possible due to restrictions on the quantity of an additive present in alectinib capsules [15,19]. Secondly, the ALEX trial only allowed patients who were treatment-naïve as opposed to J-ALEX, which could include also patients who had received one prior chemotherapy regimen. Thirdly, the eligibility for ALEX was based on ALK-positivity by immunohistochemistry (IHC) as assessed through VENTANA ALK (D5F3) assay, while in

Table 2. Ongoing phase 3 randomized trials of ALK-inhibitors first-line treatment of ALK-positive advanced NSCLC.

	Brigatinib	Lorlatinib	Ensartinib
Acronym	ALTA-1L	CROWN	eXalt3
ClinicalTrials.gov identifier	NCT02737501	NCT03052608	NCT02767804
Comparator	Crizotinib	Crizotinib	Crizotinib
Expected data availability	April 2019	February 2020	April 2020

J-ALEX ALK positivity was assessed by IHC and confirmed by fluorescence *in situ* hybridization or by reverse transcription polymerase chain reaction (RT-PCR). Finally, although both trials shared the same primary PFS endpoint, this was investigator-assessed in ALEX and not based on an IRF as it was for J-ALEX. However, despite these few differences, alectinib was consistently found to be more active than crizotinib also in ALEX, with a recently updated analysis showing a huge HR for PFS of 0.43 (95% CI: 0.32–0.58) (median 34.8 months, 95% CI: 17.7-NE, *versus* 10.9 months, 95% CI: 9.1–12.9) in favour of alectinib [9]. Table 1 shows the superiority of up-front alectinib over crizotinib in terms of ORR and PFS in the overall population as well as in patients with or without brain metastases, with an indirect comparison with another second-generation ALK-inhibitor, namely ceritinib. Apparently, the superior efficacy of alectinib over ceritinib seems to be mainly driven by the higher activity exerted by alectinib in the group of patients with brain metastases at baseline, which represent approximately 20 to 30% of newly diagnosed ALK-positive advanced NSCLC patients who are seen in daily clinical practice [14].

Based on these results, it can be reasonably stated that alectinib has replaced crizotinib as standard of care in ALK-positive advanced NSCLC. Particularly attractive features that favor the up-front use of alectinib are the clinically meaningful PFS benefit over crizotinib, the higher activity against brain metastases as well as the lower rate of progression in the CNS [7–9,17,20]. Also, alectinib is associated with a more favorable toxicity profile compared to crizotinib, despite the fact that treatment duration with alectinib is more than tripled [8–9]. In addition, a recent meta-analysis of studies evaluating crizotinib, alectinib, ceritinib, and brigatinib for the treatment of ALK-positive advanced NSCLCs has suggested a relevant difference in terms of select toxicities among these ALK-inhibitors. Importantly, with regard to second-generation ALK-inhibitors, toxicity significantly favored alectinib over ceritinib for grade 3/4 gastrointestinal adverse events (diarrhea, nausea, vomiting), fatigue, and alanine transaminase (ALT)/aspartate transaminase (AST) elevation [21]. On the downside, the use of up-front alectinib leaves no established treatment options at progression, mainly due to the lack of characterization of the resistance mechanisms to alectinib when this drug is used as first-line. In fact, we could only assume that they resemble those that have been observed in patients who have received alectinib as subsequent line of therapy after crizotinib. If this is the case, it can be anticipated that G1202R secondary mutation is among the most common on-target resistance mechanism [22]. In fact, G1202R, which affects the solvent-exposed region of ALK, resulting in steric hindrance of most ALK-inhibitors, has been found in approximately 30% of patients who progress on alectinib when this drug is used in a post-crizotinib setting. Of note, alectinib-resistant tumors bearing a G1202R mutation may respond to lorlatinib, a third-generation ALK-inhibitor with proven preclinical and clinical activity against this form of *ALK*-mutant disease [22,23]. Therefore, in the near future it can be hypothesized a sequence of treatment in which patients progressing on first-line alectinib could be switched to lorlatinib, especially in cases with biopsy-proven G1202R resistance mechanism.

Nevertheless, a crucial point for the time being is whether we can further improve in the future the outcome of ALK-positive NSCLC patients treated with first-line alectinib. Currently, three phase 3 randomized trials are investigating novel, more potent ALK-inhibitors as up-front treatment of ALK-positive advanced NSCLC patients (Table 2). However, based on their design, which includes crizotinib in the comparator arm, these trials will likely yield positive results in favor of the experimental treatment. This, in turn, will produce a crowded environment in terms of newly approved ALK-inhibitors besides alectinib, without providing direct evidence on the superiority of any of these novel ALK-inhibitors over alectinib.

Against this scenario, the outcome of ALK-positive patients can only be improved by selecting the most appropriate ALK-inhibitor based on the predicted resistance mechanism that may develop according to the type of *EML4–ALK* fusion variant. Recent evidence suggests that resistance of ALK fusion variant 3 NSCLC patients is more often mediated by the G1202R mutation compared to other variants [3]. This finding, coupled with the notion that G1202R is commonly observed in alectinib-resistant patients, may support the fact that ALK-positive variant 3 NSCLC patients could benefit from the use of up-front lorlatinib (in order to prevent the onset of G1202R). Similarly, the up-front use of an ALK-inhibitor with a high CNS penetration rate could prevent/delay the onset of pharmacokinetic failure of treatment, and again, lorlatinib is a good candidate based on both preclinical and clinical findings [24,25].

Table 3. Selected overview of ALK-inhibitor combinatorial trials that are ongoing in ALK-positive advanced NSCLC patients.

	Drugs	ClinicalTrials.gov identifier
Immunotherapy combination	Crizotinib + nivolumab or ipilimumab	NCT01998126 (completed)
	Crizotinib + pembrolizumab	NCT02511184 (terminated, slow accrual)
	Alectinib + atezolizumab	NCT02013219 (active, not recruiting)
	Lorlatinib or crizotinib + avelumab	NCT02584634 (recruiting, Javelin Lung 101)
	Ensartinib + durvalumab	NCT02898116 (active, not recruiting)
Targeted treatment combination	Ceritinib + trametinib	NCT03087448 (recruiting)
	Alectinib + cobimetinib	NCT03202940 (recruiting)
	Ceritinib + ribuciclib	NCT02292550 (active, not recruiting)
	Ceritinib + everolimus	NCT02321501 (recruiting)
Antiangiogenic combination	Alectinib + bevacizumab	NCT03202940 (recruiting)

On the other hand, ALK-inhibitor combination strategies represent an appealing treatment approach in this context (Table 3). A strategy could be that of combining an ALK-inhibitor with immune checkpoint inhibitor(s), termed immunotherapy, although there are still limited preclinical data to support this combination [26]. In addition, recent data on the combination of crizotinib with the anti-programmed death-1 (PD-1) agent nivolumab have produced a poor ORR of 38%, with safety concerns because of a high rate of hepatic toxicity [27]. Therefore, combinations of an ALK-inhibitor with immunotherapy need to be more extensively studied and schedules optimized, before being utilized in clinical practice.

At the same time, combinations of an ALK-inhibitor with the antiangiogenic agent, bevacizumab, are also under clinical evaluation.

In conclusion, with the current knowledge of the complex and heterogeneous mechanisms behind ALK resistance, multiple next-generation ALK-inhibitors and combinatorial treatment approaches can be envisioned beyond alectinib. These new therapeutic strategies have the potential to improve further the results of treatment for an increasing portion of patients with ALK-positive advanced NSCLC.

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