Editorial

Editorial on the article entitled "brigatinib efficacy and safety in patients with anaplastic lymphoma kinase (*ALK*)-positive non-small cell lung cancer in a phase I/II trial"

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Anaplastic lymphoma kinase (*ALK*)-rearrangements occur in 3–7% of patients with non-small cell lung cancer (NSCLC) and are more common among patients with a never/light smoking history, adenocarcinoma histology, youngers and in tumors wild-type for *EGFR* and *KRAS* genes (1-4). Crizotinib (Xalkori®; PF-02341066; Pfizer), a small molecule inhibitor of *ALK*, *ROS1* and *MET* (5-7), was the first tyrosine kinase inhibitor (TKI) approved by the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for patients with NSCLC who have the *ALK* gene rearrangement, because it induces rapid tumor regression and objective responses around 70% in the majority of such patients, both in first and second line settings (8,9). Unfortunately, as occurred with other TKIs, the disease progressed within the first 12 months and the central nervous system (CNS) is one of the most common first sites of progression. Within different mechanisms of resistance, the emergence of acquired crizotinib-resistance mutations, such as the 'gate-keeper' L1196M, the G1269A, C1156Y and G1202R mutations, among others, are the main cause of crizotinib-resistant disease (10-15). In light of its limitations, several next-generation *ALK*-inhibitors were rapidly developed. Ceritinib (Zykadia™; LDK378; Novartis) was the first FDA and EMA drug approved for patients who have experienced progression on or are intolerant to crizotinib. Ceritinib has shown objective response rates (ORR) around 60% across its "ASCEND" development (16-19). Unlike crizotinib, ceritinib exhibited higher incidence of gastrointestinal adverse events. While the majority of crizotinib-resistant patients respond to ceritinib, acquired secondary resistance has been reported (20). Within the most developed second-generation *ALK*-inhibitors beyond ceritinib, alectinib (Alecensa™; CH5424802/RO5424802; Chugai-Roche), based on two phase II trials, was approved by the FDA: one was performed in a global population (21), and the other one was conducted in the United States and Canada (22). In addition, alectinib is the first *ALK*-inhibitor that has demonstrated superior efficacy against crizotinib in a head to head phase III trial. A multicenter randomized, open-label phase III trial (J-ALEX; JapicCTI-132316) was conducted in Japan by Nokihara and colleagues, to compare alectinib (300 mg twice daily) versus crizotinib (250 mg twice daily) in 207 *ALK*+ NSCLC patients who had received ≤1 prior chemotherapy regimen and no prior *ALK*-inhibitors. Of note, Japan regulates alectinib to a lower dose than does the rest of the world, which uses alectinib at 600 mg twice daily (23). Results from a pre-specified interim analysis showed an increased progression-free survival (PFS) by 66% compared with crizotinib [hazard ratio (HR) =0.34; 99% confidence interval (CI), 0.17–0.70, P<0.0001]. Median PFS was not reached in patients who received alectinib (95% CI, 20.3 months-not estimable) versus 10.2 (95% CI, 8.2–12.0) months in patients who received crizotinib. The ORR determined by an independent review favored alectinib (91.6% *vs.* 78.9%). Otherwise, alectinib reduced significantly the risk of progression by 92% compared with crizotinib in patients with brain metastases at baseline (HR =0.08; 95% CI, 0.01–0.61) (23). Moreover, alectinib is being compared with crizotinib in chemotherapy-naïve *ALK*+ NSCLC patients in the global phase III ALEX trial (NCT02075840). As it happens during crizotinib and ceritinib treatments, patients treated with alectinib develop

resistance and progress invariably (13,24,25).

Taken into account that up to 50% of patients with *ALK*+ NSCLC develop CNS metastases during the course of their disease (26,27), is of extreme interest to promote the development of drugs with an increased blood-brain barrier penetration. Indeed, lorlatinib (PF-06463922; Pfizer), a third-generation *ALK* and *ROS1* inhibitor, was specifically designed to increase tumor and CNS penetration by ensuring an increased lipophilicity and a decreased molecular weight (28). Among the 54 patients included in the phase I/II trial (NCT01970865), 39 patients (72%) had brain metastases at baseline. For patients with intra- and extra-cranial disease, the ORR was 50% (26/52 evaluable patients) and the intra-cranial ORR was 60% (12/20) in patients with target lesions (29).

Brigatinib (AP26113, Ariad) is a novel potent third-generation, orally available *ALK*-inhibitor, that appears to inhibit *ALK*-resistance mutations from first- and second-generation *ALK*-inhibitors, including G1202R, not yet approved for clinical use. Brigatinib also showed activity against *ROS1* (30,31) and mutant *EGFR*, including T790M resistant mutation (32). Results from the ongoing phase I/II, single-arm, open-label, multicenter trial in advanced malignancies, including *ALK*+ NSCLC, has been reported by Rosell and colleagues (NCT01449461) (33). A total of 137 patients received brigatinib at once-daily doses of 30 to 300 mg. Safety was reported in all patients and efficacy in 78 out of 79 *ALK*+ NSCLC patients. Among 79 *ALK*+ NSCLC patients whose median age was 54 (range, 29–83) years, 49% were female, and 90% had previously received crizotinib. At the date of cut-off on February 17th, 2015, 45/79 (57%) patients remained on study and the median time on treatment was 12.6 months (range, 1 day to 35.5 months). The ORR was 74% (58/78 patients) (95% CI, 63% to 84%) with a median PFS of 13.4 months. Among 70 evaluable *ALK*+ NSCLC patients with prior crizotinib therapy, the ORR was 71% (50/70) (95% CI, 59% to 82%) compared to 100% (8/8) (95% CI, 63% to 100%) in the crizotinib-naïve subgroup, including 3 complete responses. The median PFSs were not reached in either subgroup. In a post hoc independent radiological review of patients with brain metastases (BM) at baseline, 8/15 (53%) with measurable lesions (≥10 mm) achieved an intracranial objective response with an intracranial disease control rate of 87%. The toxicity profile described in all 137 patients (all grades) was nausea (52%), fatigue (42%) and diarrhea (40%). Grade ≥3 treatment-related adverse events (AEs) included elevated lipase (9%), dyspnea (7%), hypertension (5%), hypoxia (5%), pneumonia (5%), elevated amylase (4%), fatigue (4%), pulmonary embolism (3%), elevated ALT (2%), hyponatremia (2%) and hypophosphatemia (2%) (33).

Kim and colleagues recently presented the first report on efficacy and safety of brigatinib in the pivotal randomized phase II trial (ALTA; NCT02094573) including 222 crizotinib-treated *ALK*+ NSCLC patients. Prior chemotherapy was allowed, and 180 patients (69%) had baseline brain metastases. Patients were randomized to brigatinib at 90 or 180 mg once daily. In the 180 mg arm, patients were started at 90 mg for 1 week before increasing to 180 mg. Patients in the 180 mg arm versus the 90 mg arm had superior ORR (54% *vs.* 45%), disease control rate (86% *vs.* 82%), and median PFS (12.9 *vs.* 9.2 months). The median overall survival (OS) was not reached in either arm, but the 1-year OS rate was higher in the 180 mg arm (80% *vs.* 71%; HR, 0.57). In addition to provide a better systemic efficacy, the 180 mg dose was associated with a higher intracranial response rate (67% *vs.* 36%), although the intracranial disease control rate was similar in the 180 mg and 90 mg arms (83% and 88%, respectively). Intracranial PFS was prolonged in the 180 mg arm (not reached *vs.* 15.6 months) (34). The toxicity profile of the 180 mg dose showed more grade 1 or 2 AEs. Brigatinib, at 90 mg and 180 mg was associated with (any grade) nausea (33%/40%), diarrhea (19%/38%), headache (28%/27%), fatigue (20%/27%), vomiting (24%/23%), and dyspnea (21%). The dose-reduction rate was higher in the 180 mg arm (20% *vs.* 7%), as well as the dose-interruption rate (36% *vs.* 18%). Six percent of patients experienced early-onset pulmonary adverse events (hypoxia, dyspnea, cough, pneumonia, pneumonitis), and 3% had grade ≥3 toxicity (34).

Unlike crizotinib, ceritinib and alectinib, to date, no single secondary *ALK* kinase domain mutations that confer primary or secondary resistance to brigatinib has been identified (35). *Table 1* summarized the systemic and intracranial efficacies of second and third-generation *ALK* TKIs.

Based on the available single-arm studies of ceritinib and alectinib in crizotinib-resistant disease, alectinib appears with potential advantages over ceritinib, mainly in its higher intracranial activity and favorable toxicity profile. Despite the preliminary results from the Japanese J-ALEX trial (23), to date is unknown whether frontline alectinib improves survival outcomes compared with the strategy of frontline

Table 1 Systemic and intracranial efficacies of second- and third-generation *ALK* TKIs in *ALK*+ NSCLC patients

Trial	Ceritinib		Alectinib			Brigatinib			Lorlatinib
	ASCEND-2 Phase II N=140	ASCEND-3 Phase II N=124	NP28673 Phase II N=138	NP28761 Phase II N=87	J-ALEX Phase III N=207	NCT01449461 Phase I/II N=79	ALTA Phase II N=222		NCT01970865 Phase I/II N=54
Population	Prior CRZ Prior CT	CRZ naïve Prior CT	Prior ALKi Prior CT	Prior ALKi Prior CT	ALKi naïve Prior CT	Prior CRZ Prior CT	Prior CRZ Prior CT		Prior ALKi Prior CT
Dose	750 mg qd		600 mg bid		300 mg bid*	30–300 mg qd	90 mg qd	180 mg qd	10–200 mg qd
ORR (%)	38.6	63.7	50	48	91.6	74	45	54	50
iORR (%)	45	20	57	75	NA–HR: 0.08	53	36	67	60
mPFS (mo)	5.7	11.1	8.9	8.1	NR (20.3-NE)	13.4	9.2	12.9	-
References	(17)	(18)	(21)	(22)	(23)	(33)	(34)		(29)

*, Japan regulates alectinib to a lower dose. For the rest of the world alectinib is prescribed at 600 mg bid. ALKi, anaplastic lymphoma kinase inhibitor; bid, twice daily; CT, chemotherapy; CRZ, crizotinib; HR, hazard ratio; iORR, intracranial objective response rate; mo, months; mPFS, median progression-free survival; NA, not available; NE, not estimable; NR, not reached; ORR, objective response rate; qd, once daily.

crizotinib followed by alectinib upon progression. While is true that the global (ALEX) trial of first-line alectinib *vs.* crizotinib could support the benefit of alectinib in this setting, the crossover was not included in the design, precluding a direct comparison of first-line alectinib *vs.* sequential crizotinib/alectinib. If alectinib become as the recommended *ALK*-inhibitor, the subsequent point is which third-generation *ALK* TKI should be prescribed beyond alectinib progression. Unfortunately, to date there are no randomized trials comparing next-generation *ALK*-inhibitors in the setting of crizotinib resistance, limiting our ability to compare these agents directly.

Brigatinib is of major interest, as it has been shown in preclinical models to target known first- and second-generation *ALK*-resistant mutations, and nowadays it has demonstrated in clinical trials high activity in crizotinib/ceritinib/alectinib-refractory *ALK*+ NSCLC patients. The ALTA trial demonstrated higher efficacy with the 180 mg daily dose, which will move forward for development. In general, brigatinib was well tolerated, but in a proportion of cases, early onset pulmonary events were seen in 14% (6/44) of patients treated at starting dose of 180 mg, but in only 4% (2/50) of patients who started at 90 mg (including patients escalating to 180 mg after one week of treatment). Digestive toxicity seems to be independent of the dose level. Indeed, grade ≥3 increased amylase and lipase were most common at 90 mg than 90 mg → 180 or 180 mg. Nausea only was reported in 4% of patients at 180 mg (33). The toxicity profile reported for lorlatinib included any-grade hypercholesterolemia (54%) and peripheral edema (37%) as the most frequent drug-related AEs. Hypercholesterolemia was the most common (9%) grade ≥3 AE and the most frequent reason for dose delay/reduction (29).

To date, based on the safety data reported in clinical trials, and due to the lack of head to head studies comparing new *ALK*-inhibitors, it is difficult to know which is the best treatment in first-line setting. If ALEX trial confirms the benefit on efficacy and tolerability of alectinib against crizotinib, it would become as a major option in first- line for *ALK*+ NSCLC. All of these drugs have demonstrated robust efficacy results treating CNS disease. The ongoing phase III ALTA-1L trial (NCT02737501) randomized patients to receive either brigatinib, 90 mg once daily for 7 days, then 180 mg once daily, or crizotinib, 250 mg twice daily. Crossover to brigatinib is allowed at crizotinib progression. This trial could clarify the optimal approach to targeting *ALK* in first-line treatment.

In summary, brigatinib may have a place in the sequence for *ALK*+ NSCLC targeting *ALK*-resistant mutations that crizotinib, ceritinib, and alectinib may not. Until now, the optimal sequence of *ALK*-inhibitors needs to be individualized according to the type of resistant mutations and the presence of CNS disease. In *Figure 1* we propose an algorithm to treat patients with *ALK*+ NSCLC.

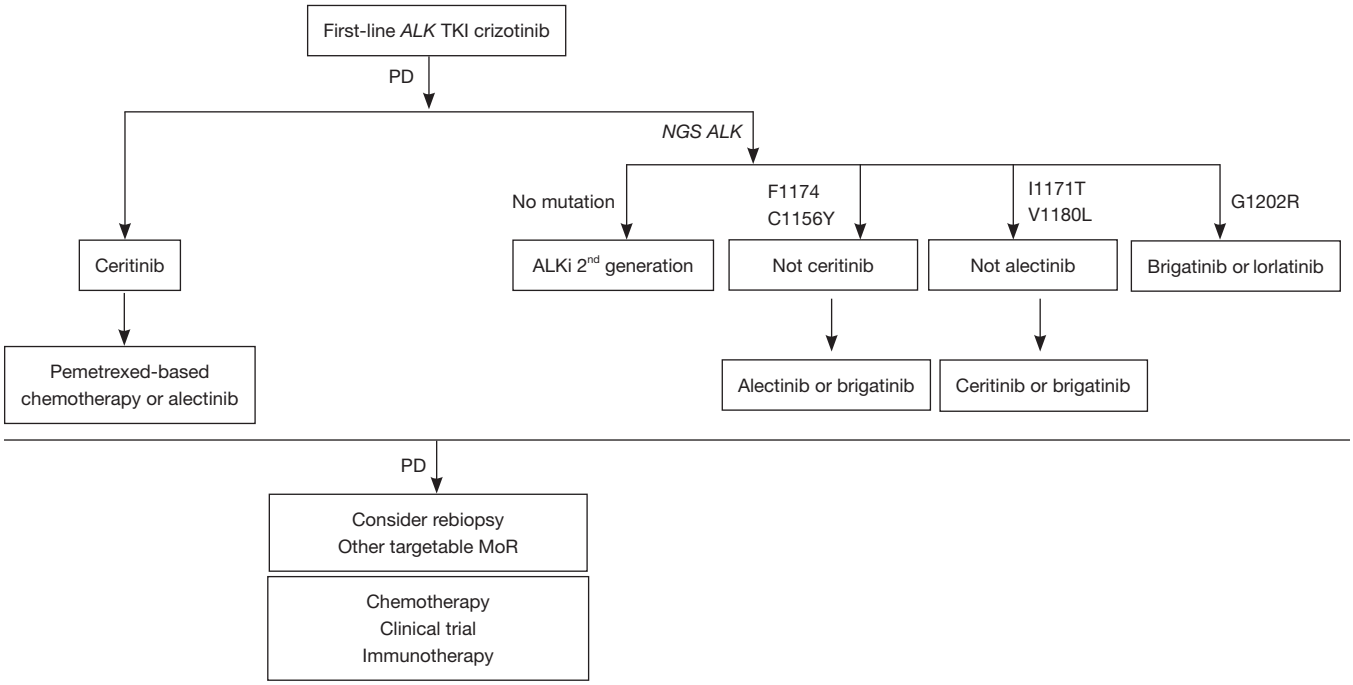

Figure 1 Potential treatment algorithm for *ALK*+ advanced NSCLC patients. ALKi, anaplastic lymphoma kinase inhibitor; MoR, mechanism of resistance; NGS, next generation sequencing; PD, progressive disease; TKI, tyrosine kinase inhibitor.

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Footnote

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Comment on: Rosell R, Gettinger SN, Bazhenova LA, *et al.* 1330: Brigatinib efficacy and safety in patients (Pts) with anaplastic lymphoma kinase (*ALK*)-positive (*ALK*+) non-small cell lung cancer (NSCLC) in a phase 1/2 trial. J Thorac Oncol 2016;11:S114.

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