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REVIEW

Profile of alectinib for the treatment of ALK-positive non-small cell lung cancer (NSCLC): patient selection and perspectives

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Abstract: Discovered in 2007, anaplastic lymphoma kinase (ALK) gene rearrangements positive (ALK+) lung cancers compose a small subset of non-small cell lung cancer (NSCLC), with rapidly expanded treatments. There are currently several ALK inhibitors, including crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib which have been licensed by the US Food and Drug Administration or the European Medicines Agency for the treatment of ALK+ NSCLC patients. Along with the multiple therapies, the survival of this subtype of NSCLC has been significantly expanded, even for patients whose disease has spread in the brain. Alectinib (Alecensa), a specific ALK and rearranged during transfection tyrosine kinase inhibitor is approved as first-line therapy for metastatic ALK+ NSCLC patients. It is additionally approved for ALK+ NSCLC previously treated with crizotinib. The main aim of this review is to assemble on the efficacy of alectinib for the treatment of ALK+ NSCLC, to elaborate the activity of the drug in the central nervous system, and to debate on which is the position of this compound in the treatment course of ALK+ lung cancer patients.

Keywords: anaplastic lymphoma kinase, alectinib, lung cancer

Introduction

Precision medicine has made a great impact in the survival of patients with advanced non-small cell lung cancer (NSCLC), particularly those with epidermal growth factor receptor (*EGFR*) mutations or echinoderm microtubule-associated protein-like 4 (*EML4*)-anaplastic lymphoma kinase (*ALK*) fusions (ALK+).[1,2] Alterations of the *ALK* gene were initially described in anaplastic large cell lymphoma (hence the name of the gene).[3,4] ALK alterations have a role in the pathogenesis of inflammatory myofibroblastic tumors and neuroblastomas.[4,5] In NSCLC, *ALK* fusions, which join the exons 1–13 of the *EML4* gene to exons 20–29 of *ALK* gene,[6] were discovered in 2007.[7,8]

ALK fusions are present in 3–5% of NSCLC and are more common in young patients with lung adenocarcinoma and non-smoking history.[9,10] Initially ALK+ patients were treated with chemotherapy until the discovery of crizotinib, an ALK, MET and ROS1 tyrosine kinase inhibitor (TKI), which has demonstrated its superiority compared to standard platinum-based chemotherapy in several clinical trials in ALK+ patients.[11–13] As happens with other targeted therapies, resistance to crizotinib soon appears due to ALK-dependent or ALK-independent mechanisms.[14–16] Furthermore, the central nervous system (CNS) is a frequent site of metastases in ALK+ NSCLC patients with approximately 26% of them having CNS metastases at the time of the diagnosis.[17] The

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incidence of CNS metastases increases during the course of the disease to as high as 60% for crizotinib-resistant ALK+ patients.[17] Still, stage IV ALK+ NSCLC patients have prolonged survival.[18] Median survival of 6.8 years can be achieved with the appropriate medical care in stage IV ALK+ NSCLC patients.[19] This is due to the development of several second- and third-generation ALK TKIs, like ceritinib,[20–21] alectinib,[22–24] brigatinib,[25] and lorlatinib[26,27] which have expanded the treatment options of ALK+ NSCLC (Figure 1). Ensartinib, entrectinib and repotrectinib are under clinical investigation.[28–30] It is worth mentioning that ALK+ NSCLC patients have better clinical outcome with pemetrexed chemotherapy, compared to wild-type NSCLC patients or those with other genetic alterations like *KRAS* mutations.[31] The differential outcome to pemetrexed chemotherapy may be attributed to the lower levels of thymidylate synthase in ALK+ compared to wild-type NSCLC patients.[31]

Alectinib (marketed as Alecensa) was created at Chugai Kamakura Research Laboratories, which is part of the Hoffmann-La Roche group, as an oral ALK inhibitor. Alectinib is approved for the first-line therapy of ALK+ NSCLC patients as well as for patients pretreated with crizotinib (Figure 1).[32] In preclinical studies, alectinib was able to inhibit the growth of *EML4-ALK* positive tumor cells. It has also shown activity against ALK+ cells with the gatekeeper *ALK* L1196M mutation, which confers resistance to crizotinib.[33,34] However, this activity has not been reconfirmed in the clinical setting.[35] Alectinib inhibits ALK autophosphorylation as well as the phosphorylation of signal transducer and activator of transcription 3 (STAT3).[33]

Alectinib is also a highly selective rearranged during transfection (RET) inhibitor.[36] Fusions of the *RET* gene, such as KIF5B (the kinesin family 5B gene)-RET, CCDC6 (coiled-coil domain containing 6)-RET, and others are driver oncogenes in 1–2% of lung adenocarcinomas.[37,38] Alectinib inhibits RET phosphorylation and the tumor growth in xenograft models with *RET* fusions.[36,39] It also has activity against *RET* gatekeeper mutations, like V804L and V804M.[36,39] Currently, alectinib is in clinical trials for *RET*-rearranged NSCLC. In this review, we will not focus on the activity of alectinib on *RET*-rearranged tumors, especially because other more specific RET inhibitors are in clinical development.[40–43]

In this review, we will discuss the clinical status of alectinib in ALK+ NSCLC patients, outline its clinical development, and CNS activity, and comment on the place of alectinib in the management of ALK+ NSCLC patients. Mechanisms of resistance to alectinib will be also revised.

Alectinib in the second-line setting of ALK+ NSCLC patients

The Phase I/II study AF-002JG study was performed in crizotinib-resistant ALK+ NSCLC patients, and established 600 mg of alectinib twice daily as the recommended Phase II dose.[44] The study showed promising antitumor activity of alectinib including in patients with brain metastases.[44] Indeed, the AF-002JG study confirmed the alectinib CNS penetration. Specifically, a 52% objective response rate (ORR) was observed among 21 patients with baseline brain metastases. In all patients who underwent CNS sampling, measurable

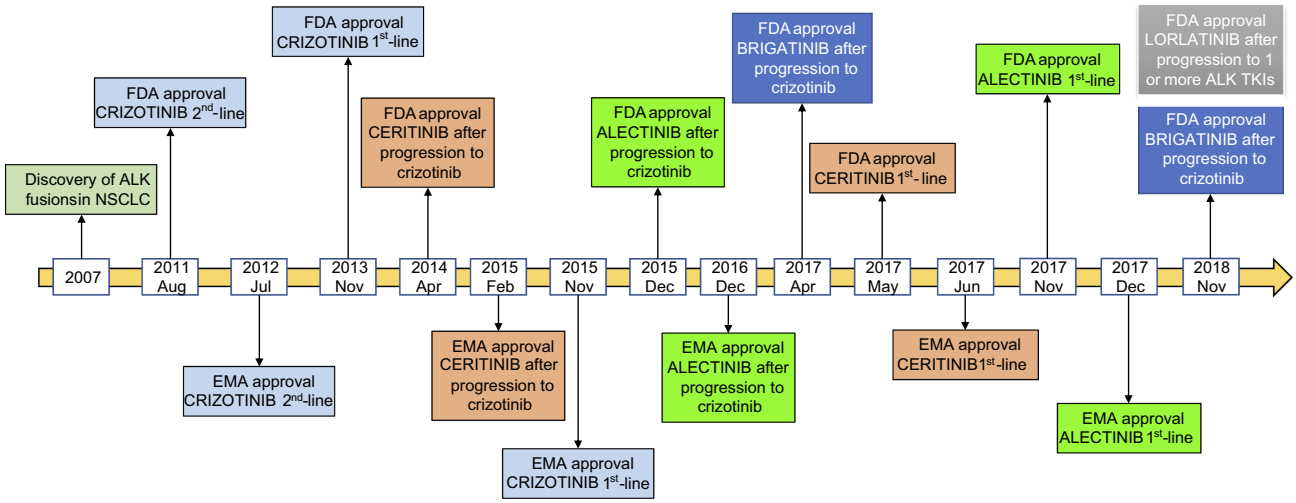

Figure 1 ALK inhibitors approved for the treatment of ALK+ NSCLC patients.
Abbreviations: NSCLC, non-small cell lung cancer; FDA, Food and Drug Administration; EMA, European Medicines Agency; TKI, Tyrosine kinase inhibitor; ALK, Anaplastic lymphoma kinase.

concentrations of alectinib were detected.[44] In Japan, 300 mg twice daily was tested in ALK+ NSCLC patients who had progressed to previous chemotherapy (Phase I/II AF-001JP study).[45] In an updated analysis of the AF-001JP study, median progression-free survival (PFS) was not reached (3-year PFS rate, 62%; 95% CI 45, 75) and the 3-year overall survival (OS) rate was 78%.[46]

Two Phase II studies evaluated the effect of alectinib in ALK+ NSCLC patients who had progressed on crizotinib (Table 1).[47,48] Most of the patients in both studies had received chemotherapy before crizotinib and had brain metastases at inclusion.[47,48] ORRs of 49 (95% CI 40, 58) and 48% (95% CI 36, 40) were observed in the global NP28673 and the North American NP28761 studies, respectively.[47,48] An updated analysis of the NP28673 with a longer follow-up of 21 months confirmed the ORR of 51% (95% CI 42, 60) with a duration of response (DoR) of 15.2 months (95% CI 11.2, 24,9). Median PFS to alectinib was 8.9 months (95% CI 5.6, 12,8), and median OS was 26 months (95% CI 11.2, not estimable) (Table 1).[49] Similarly, an updated analysis of NP28761 with a follow-up of 17 months reported an ORR of 52% (95% CI 40, 65), with a DoR of 15 months. Median PFS and OS were 8 and 22.7 months, respectively.[50] A pooled analysis of the NP28673 and NP28761 studies demonstrated an ORR of 51% (95% CI 44, 59), a disease control rate of 79% (95% CI 72, 84), and a median DoR of 14.9 months (95% CI 11.1, 20.4).[51] Median PFS was 8.3 months (95% CI 7.0, 11.3) and median OS was 26.0 months (95% CI 21.4, not estimable).[51] Based on the results of the NP28673 and NP28761 studies, on 11 December 2015, the US Food and Drug Administration (FDA) granted accelerated approval to alectinib for the treatment of ALK+ NSCLC patients who have progressed on or are intolerant to crizotinib. One year later, on 15 December 2016, the European Medicines Agency (EMA) approved alectinib for the same indication.

The Phase III ALUR clinical trial compared alectinib versus chemotherapy in ALK+ metastatic NSCLC patients whose disease had progressed after platinum-based chemotherapy and after crizotinib (Table 1).[22] One hundred seven patients were randomized 2:1 to receive alectinb or chemotherapy (pemetrexed or docetaxel). More than three-thirds of the patients had brain metastases at baseline.[22] Median PFS was significantly longer with alectinib compared to chemotherapy, as assessed both by the investigators (9.6 months [95% CI 6.9, 12.2; alectinib] and 1.4 months [95% CI 1.3,1.6; chemotherapy], HR 0.15 [95% CI 0.08, 0.29]; P< 0.001) and by an independent review committee (IRC) (7.1 months [95% CI 6.3,10.8, alectinib] and 1.6 months [95% CI 1.3,4.1, chemotherapy], HR 0.32 [95% CI 0.17, 0.59]; P< 0.001) (Table 1).[22] The ORR was 38% with alectinib versus 3% with chemotherapy. Median investigator-assessed DoR was 9.3 months (95% CI 6.9, not estimable; alectinib) versus 2.7 months (95% CI not estimable; chemotherapy) (Table 1).[22] No significant differences were observed in OS between the two treatment arms of the ALUR study, probably due to the trial design, which was permitting patients in the chemotherapy arm to cross over to alectinib therapy once disease progression was noted.[22]

Alectinib penetrates through the blood–brain barrier,[44] and it is retained within the CNS. The brain protective effect of alectinib has been attributed to the fact that alectinib is not a substrate of the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein).[32] In the ALUR study, those patients who had brain metastases at baseline had an ORR in CNS of 54% in the alectinib arm, compared to 0% in the chemotherapy arm.[22] Alectinib was able to reduce 86% the risk of progression in patients with baseline brain metastases. The 6-month cumulative incidence rate of CNS progression was 11% with alectinib and 48% with chemotherapy. A significantly higher CNS disease control rate of 80% was observed in the alectinib-treated patients compared to 27% for those who received chemotherapy (P<0.001).[22] Overall, the ALUR study showed a striking benefit of alectinib versus standard second-line chemotherapy in ALK+ NSCLC patients.

Alectinib in the first-line setting of ALK+ NSCLC patients

The first Phase III trial which compared alectinib (at the dose of 300 mg twice daily) with crizotinib in the first-line setting of ALK+ NSCLC patients took place in Japan (J-ALEX). ALK inhibitor-naïve Japanese patients, who may have received or not previous chemotherapy, were included in the study.[23] Overall, median PFS was not estimable (95%CI 20.3, not estimable) at the time of the analysis in the alectinib group compared to 10.2 months (95% CI 8.2, 12.0) in the crizotinib group (HR 0.34 [99.7% CI 0.17, 0.71]; P<0.0001).[23] For treatment-naïve patients, median PFS was not estimable (95% CI 17.5, not estimable) with alectinib versus 10.2 months (95% CI 8.3, 13.9) for those receiving crizotinib (HR 0.31 [95% CI 0.17, 0.57]). For patients previously treated with chemotherapy, median PFS was 20.3 months (95% CI 20.3, not estimable) in the alectinib group versus 8.2 months

Table 1 Clinical trials of alectinib

Study	Phase	Design	Population	Results			
				PFS (mo)	OS (mo)	ORR (%)	Ref
NP28673	II	Alectinib, single arm	Pretreated with crizotinib	8.9	26	51	49
NP28761	II	Alectinib, single arm	Pretreated with crizotinib	8	22.7	52	50
ALUR	III	Alectinib vs chemotherapy	Pretreated with platinum-based chemotherapy and crizotinib	7.1 vs 1.6* HR 0.32, P<0.001	12.6 vs NE	38 vs 3	22
ALEX	III	Alectinib vs crizotinib	First-line (treatment naïve)	34.8 vs 10.9, HR 0.43, P<0.001	–	83 vs 75	24,54
ALEX J	III	Alectinib (300 mg) vs crizotinib	ALK-inhibitor naïve	25.9 vs 10.2, HR 0.38, P<0.0001	–	85 vs 70	23,52

Note: *Independent review committee.
Abbreviations: PFS, Progression-free survival; OS, Overall survival; ORR, Objective Response Rate; mo, months vs, versus; NE, not estimable.

(95% CI 6.4, 15.7 in the crizotinib group (HR 0.40 [95% CI 0.19, 0.87]).[23] Patients treated with alectinib obtained an ORR of 85% versus 70% for those receiving crizotinib.[23] Updated data from the J-ALEX study showed median PFS of 25.9 months (95% CI 20.3, not estimable) with alectinib and 10.2 months (95% CI 8.3, 12.0) with crizotinib (HR 0.38 [95% CI 0.26, 0.55, P<0.0001)].[52] In the J-ALEX study, in 164 patients without brain metastasis at baseline, alectinib prevented CNS progression with a HR of 0.19 (95% CI 0.07, 0.53) compared to crizotinib. The same occurred for the 43 patients with brain metastasis at baseline, who had a lower risk for CNS progression with alectinib compared to crizotinib (HR=0.51, 95% CI 0.16, 1.64).[52]

The Phase III ALEX trial was conducted in non-Asiatic and Asiatic population.[24] A total of 303 ALK+ treatment-naïve NSCLC patients were treated with either 600 mg of alectinib twice daily or 250 mg of crizotinib twice daily. The investigator-assessed median PFS was not reached (95% CI 17.7, not estimable) with alectinib versus 11.1 months (95% CI 9.1, 13.1) with crizotinib (HR 0.47 [95% CI 0.34, 0.65], P<0.001 (Table 1).[24] Median PFS as assessed by an IRC was longer with alectinib compared to crizotinb (25.7 months [95% CI 19.9, not estimable) versus 10.4 months [95% CI 7.7, 14.6], HR, 0.50 [95% CI 0.36, 0.70], P<0.001).[24] No statistically significant differences occurred in terms of responses with a response rate of 83% (95% CI 76, 88) and 75% (95% CI 68, 82) for alectinib and crizotinib, respectively (P=0.09) (Table 1).[24] Finally, in the ALEX study, patients with measurable baseline brain metastases and prior radiotherapy had a CNS ORR of 85.7% with alectinib and 71.4% with crizotinib.[53] For those patients who had not received prior radiotherapy, the CNS ORR was 78.6% and 40.0% for alectinib and crizotinib, respectively. Importantly, alectinib significantly delayed CNS progression, independent of the existence or not of baseline brain metastases or the treatment or not with prior radiotherapy.[53] Patients with baseline brain metastases had median PFS of 24.7 months (95% CI 9.2, not estimable) with alectinib compared to 7.4 months (95% CI 6.6, 9.6) for crizotinib (HR=0.35, 95% CI 0.22, 0.56).[54] With a longer follow-up, median PFS of 34.8 months (95% CI 17.7, not estimable) for alectinib versus 10.9 months (95% CI 9.1, 12.9) for crizotinib (HR 0.43, 95% CI 0.32, 0.58) was reported.[54] Patients treated with alectinib had a longer median DoR compared to crizotinib (33.1 [95% CI 31.3, not estimable] versus 11.1 months [95% CI 7.9, 13.0], HR 0.36 [95% CI 0.24; 0.53]).[24,54] These updated data consolidate alectinib as the standard-of-care for first-line treatment of ALK+ NSCLC patients. Based on the data of the ALEX study, on 7 November 2017, FDA approved alectinib for the first-line treatment of patients with ALK+ NSCLC. One month later, on 21 December 2017, alectinib was also EMA approved.

Alectinib is a well-tolerated drug. The most frequent of any grade adverse events are gastrointestinal disorders, hepatobiliary disorders, edema, rash, myalgia, anemia and increased body weight.[32] This information is derived from a pooled analysis of three alectinib trials (ALEX, NP28673 and NP28761).[32] Adverse events of grade more than 3 occurred only in <4% of the patients.[32] Liver function disorders are the most common grade ≥3 adverse events, that are transient and resolved, when alectinib is interrupted or when it is given in a lower dose. Grade 1–2 bradycardia has been reported in almost 9% of patients receiving alectinib. Interstitial lung disease (ILD) is uncommon, but grade ≥3 ILD which led to treatment discontinuation, occurred in one patient. Elevated blood creatinine phosphokinase (CPK) and anemia are also

common grade ≥3 adverse events. For the above reasons, liver function, heart rate and blood pressure, pulmonary symptoms, CPK blood levels and anemia should be monitored in patients who are treated with alectinib.

Mechanisms of resistance to alectinib

As happens with all targeted therapies, resistance inevitably emerges after treatment with alectinib or other ALK inhibitors. ALK resistant mutations appear to be the main mechanism of resistance to second-generation ALK inhibitors. We have combined data available from three previous publications[14,35,55] to summarize the activity of alectinib and other ALK inhibitors against various resistant mutations (Table 2). *ALK* I1171 mutations are reported to be the second (after *ALK* G1202R) most common *ALK* resistance mutations in post-alectinib specimens. Alectinib is also inactive against L1196M, V1180L and T1151Tins mutations (Table 2).

Maintained mitogen-activated protein kinase (MAPK) activation through alternate kinases, including EGFR, KIT, Src, insulin growth factor 1 or the src homology 2 domain-containing phosphatase 2 [56] has been also described as a mechanism of resistance to ALK inhibitors.[57–60] We have found that *KRAS* wild-type copy number gain decreased of the dual specificity phosphatase 6 phosphatase reactivates the MAPK pathway in the presence of ALK inhibitors and therefore leads to tumor resistance.[61] To this end, a clinical trial with the combination of alectinib with the MEK inhibitor cobimetinib is ongoing in ALK+ NSCLC patients (Table 3).

Discussion – sequencing of treatment for ALK+ NSCLC patients

A main point of discussion for ALK+ NSCLC patients is the optimal sequencing of the available agents. More precise diagnosis for identifying the *ALK* fusion partner is also of great relevance, considering that fusion partners affect the sensitivity to different ALK inhibitors.[62] Therefore, in situ hybridization (FISH) or immunohistochemistry are not enough for the accurate diagnosis of ALK+ NSCLC patients. Next-generation sequencing technologies must come to the forefront of clinical diagnostics for the clinicians to know the fusion partner.[62] On the other hand, next-generation sequencing platforms allow us to know whether the resistance comes from acquired resistant mutations or from activation of bypass signaling pathways. This is important for selecting next therapeutic options. The activation of bypass signaling pathways may require a tissue re-biopsy as in circulating-free DNA alterations such as small cell transformation or epithelial-mesenchymal transition cannot be easily defined.[63] Therefore, liquid biopsies serve for the detection of ALK

Table 2 Half-maximal inhibitory concentrations (IC50) of first-, second- and third-generation ALK inhibitors on mutant EML4-ALK (data derived from[14,35,55])

ALK resistant mutations	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
G1269A					
E1210K					
S1206Y					ND
S1206F					ND
D1203N					
G1202del					
G1202R					
L1196M					
V1180L					ND
F1174C					ND
F1174L					ND
F1174V					ND
C1156Y					
I1171N					
I1171S					
I1171T					
F1174C					
L1152R	ND				ND
L1152P					ND
L1198F					
T1151Tins					ND
D1203N +F1174C					
D1203N +E1210K	ND				
			IC50≤50 nmol/L		
			>50, <200 nmol/L		
			≥200 nmol/L		

Abbreviation: ND, not determined.

Table 3 Ongoing clinical trials with alectinib

ClinicalTrials.gov Identifier	Phase	Treatment	Objective
NCT03194893	III, open	Alectinib, crizotinib	To provide continued treatment with alectinib or crizotinib as applicable to patients with ALK- or RET-positive cancer who were previously enrolled in any Roche-sponsored alectinib study and who are deriving continued clinical benefit from alectinib or crizotinib in the parent trial at the time of parent trial closure
–	II, open (Japan)	Alectinib	To evaluate the efficacy and safety of alectinib in patients with rare cancer harboring ALK alterations
NCT03596866	III, planned	Alectinib versus brigatinib	To compare the efficacy of brigatinib versus alectinib in participants with ALK+ locally advanced or metastatic NSCLC who have progressed on crizotinib
NCT03456076	III, open	Alectinib versus platinum-based chemotherapy (adjuvant)	To evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected stage IB (tumors equal to or larger than 4 cm) to stage IIIA ALK+ NSCLC
NCT03445000	II, open	Alectinib	To investigate the efficacy of alectinib in patients with advanced stage RET-rearranged NSCLC, treated with at least one platinum-based systemic chemotherapy regimen
NCT03202940	I/II, open	Alectinib plus cobimetinib	To study the combination of alectinib and cobimetinib as a possible treatment for ALK+ NSCLC
NCT03779191	II, planned	Alectinib plus bevacizumab	To assess alectinib plus bevacizumab in untreated and previously treated patients with advanced or metastatic non-squamous ALK+ NSCLC
NCT02521051	I/II, open	Alectinib plus bevacizumab	To evaluate the safety and tolerability of alectinib and bevacizumab in patients with ALK+ NSCLC
NCT02091141 (My pathway)	II, open	Alectinib, atezolizumab, vemurafenib/cobimetinib, erlotinib, pertuzumab/trastuzumab, vismodegib	To evaluate trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib and atezolizumab in patients who have advanced solid tumors with mutations or gene expression abnormalities predictive of response to one of these agents

Abbreviations: NSCLC, non-small cell lung cancer; ALK, anapestic lymphoma kinase.

acquired mutations, but if resistant mutations are not detected, then a tissue biopsy is necessary.[63]

Alectinib together with crizotinib and ceritinib are approved as first-line therapies for ALK+ NSCLC patients. Brigatinib is expected to gain soon first-line approval. We still do not know whether median PFS with brigatinib will be longer than what has been achieved with alectinib in the first-line setting.[25] Lorlatinib is approved for ALK+ NSCLC patients after progression to 1 or 2 prior lines of ALK TKIs. The ongoing clinical trials are comparing the second-generation ALK TKIs with crizotinib in the first-line setting and therefore we speculate that all of them will be positive studies. However, the key question is what the correct second-line therapy after a second-generation ALK inhibitor is? If this is the third-generation inhibitor, lorlatinib, then what comes next? Whether the combination of chemotherapy with immunotherapy is an option, is still debatable? In the subgroup analysis of the IMpower150 study, the combination of carboplatin, paclitaxel, bevacizumab and atezolizumab improved PFS compared to chemotherapy plus bevacizumab alone in ALK+ NSCLC patients.[64] Overall, only 34 ALK+ patients were included in the study and therefore the results of this subgroup analysis cannot be conclusive. Furthermore, many doubts have been raised on the design of this study, as well as on the way that the results were presented, especially because they exclude the comparison of carboplatin, paclitaxel, bevacizumab, and atezolizumab versus carboplatin, paclitaxel and atezolizumab.[65,66] Therefore, the IMpower150 study did not address the question whether vascular endothelial growth factor blockade enhances the efficacy of immunotherapy.[64,65]

Crizotinib probably will have no role in the treatment of ALK+ patients in the future. May be at the time that lorlatinib will come in the first-line setting, crizotinib will become useful again as it overcomes some of the lorlatinib-resistant mutations, like the double C1156Y–L1198F.[67] Right now,

alectinib and ceritinib are the only second-generation ALK inhibitors with CNS activity, approved in the first-line setting. Ceritinib is a very potent ALK inhibitor but with serious toxicity issues, at least when it was given at the initial approved fasting dose of 750 mg daily. Now, 450 mg of ceritinib given with food is the new FDA and EMA approved regimen, and ceritinib becomes again a very relevant compound for the first-line therapy of ALK+ NSCLC patients.[68] Brigatinib, which we anticipate that it will be soon approved for the same indication, has shown the longest intracranial PFS of 18 months in the 90–180 mg cohort.[69] Therefore, it is possible that soon, neither alectinib nor ceritinib, but brigatinib will be the ALK TKI to be used for the first-line therapy of ALK+ NSCLC patients. Lorlatinib, due to each side effects, is mostly preferred after two second-generation (alectinib and ceritinib, or alectinib and brigatinb) ALK TKIs. It will soon become the second ALK TKI to be used when medical oncologists are familiar with the management of the side effects of lorlatinib.[70,71] In the case that an ALK+ NSCLC patient progresses to several ALK TKIs, a chemotherapy regimen, like carboplatin with pemetrexed with or without bevacizumab may control the disease for a certain period and give space for ALK TKIs to regain activity after a "targeted therapy break".

Conclusion

We searched the Citeline Pharma Intelligence (https://citeline.informa.com/trials/results) for clinical trials with alectinib, that are open or ongoing (Table 3). A Phase III clinical trial plans to compare alectinib versus brigatinib for ALK+ NSCLC patients who have progressed to crizotinib. Alectinib is currently under comparison with adjuvant platinum-based chemotherapy for stage IB-IIIA completely resected ALK+ NSCLC patients. Two studies are planned to test the efficacy of alectinib in combination with bevacizumab in ALK+ NSCLC patients. Considering its efficacy and tolerability, alectinib is the best first-line approach for ALK+ NSCLC patients, especially those with CNS metastasis at the time of the diagnosis. Alectinib is an important treatment option for ALK+ NSCLC patients who have progressed to crizotinib.

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Disclosure

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