Editorial

Should alectinib or ceritinib be given as first line therapy for ALK positive non-small cell lung cancer patients instead of crizotinib?

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For patients with ALK positive non-small cell lung cancer (NSCLC), various treatment options are currently available. Crizotinib was the first drug with proven activity for these patients (1), followed by ceritinib (2,3) and alectinib (4-6) for patients progressing on crizotinib treatment. Most recently brigatinib was also approved for crizotinib-resistant patients, while lorlatinib received breakthrough status from the FDA and may be the next ALK inhibitor to be approved. These alternatives appear to be active against mutations in the *ALK* gene associated with crizotinib resistance.

Tamura *et al*. (7) recently published the outcome data of a 3-year follow-up of Japanese patients treated continuously with alectinib, albeit at a lower total dose (300 mg BID) than the FDA and EMA approved dose (600 mg BID). The survival data are from a group of patients that were ALK-positive, ALK-inhibitor naive, and who had progressed on previous chemotherapy regimens. The study consisted of a phase II population of 46 patients and 12 patients of the Phase I cohort that received 300 mg (twice daily) of alectinib, the registered regimen in Japan.

The study is interesting for several reasons: (I) included patients were ALK inhibitor negative; (II) 25 of the 46 patients were still receiving alectinib after the 3-year follow-up, therefore a long-term safety profile could be established; (III) the drug proved to be tolerable in this long period, while the most severe toxicity was found in the first 6 months; (IV) the median progression-free survival (PFS) was not yet reached [3-year PFS 62% and overall survival (OS) was 78%]; (V) the survival data compare favorably with that of (first-line) treatment with other drugs registered for ALK positive patients, crizotinib, ceritinib and most recently brigatinib; and (VI) the drug was effective at lower doses than FDA and EMA approved regimens.

This Japanese study (AF-001JP) was initiated as a single-arm, open label, multicenter phase I–II study in Japan (8). In the phase I part, patients received 2–300 mg given twice daily, in the extended phase II part, 46 patients received 300 mg twice daily (in contrast to the 600 mg BID FDA and EMA approved drug dosing). One concern of this study could be the question whether this dose would be sufficient to be biologically effective (9). However, at the 300-mg dose, the maximal (c_{max}) plasma levels of about 550 ng/mL and the trough level (c_{trough}) of about 440 ng/mL seem high enough to inhibit activity of the ALK-EML4 fusion protein (8), although several patients had lower levels that might not be sufficient These values compare favorably to the steady state levels (c_{ss} of 665 ng/mL) found at the 600 mg dose (4).

Another concern of the initial study was whether the proposed activity against brain metastases would sustain (9). Crizotinib does not accumulate in the brain (10) since brain penetration is poor because it is an excellent substrate for the efflux pump P-glycoprotein (3). Patients with brain metastasis were progressive on crizotinib treatment (11,12).

In the initial study (8), there were indications that alectinib showed activity against brain metastases, but follow-up time was too short. However, in the 3-year follow-up group 6 of the 14 patients with brain metastases remained in the study without CNS and systemic progression (7). Similar data were reported for other clinical studies (5,6). With alectinib the possibilities to treat brain metastases have been extended.

In the AF-001JP study, tumors of the patients were also investigated by ALK immunohistochemistry to determine positivity for the ALK-fusion protein (13). This was performed by using immunohistochemistry and FISH, which showed a good concordance. However, the authors did not report the presence of mutations. It is unlikely that the patients would have had crizotinib induced resistance mutations since the patients were crizotinib-naïve, but these aberrations cannot be excluded, and should be evaluated in stored samples. Alectinib has shown *in vitro* efficacy against crizotinib-resistant mutations in ALK, including: L1196M, F1174L, R1275Q, and C1156Y (14,15). Especially L1196M is considered as the gatekeeper mutation in crizotinib-resistant mutants, and alectinib can selectively inhibit growth of L1196M-driven tumors. However, alectinib is also effective against crizotinib sensitive ALK tumors. In order to determine whether patients with crizotinib-sensitive wild-type ALK would also be sensitive to alectinib, randomized studies are ongoing comparing first-line crizotinib and alectinib in ALK inhibitor-naive patients (16-19). In the ongoing Japanese J-ALEX study with 207 patients enrolled, alectinib (300 mg BID) was compared with crizotinib (250 mg BID). The most recent update showed a median PFS of 25.9 months for alectinib, while patients receiving crizotinib had a median PFS of 10.2 months (16) (HR 0.34; P<0.0001). Alectinib prevented onset of brain metastases (HR =0.19; 95% CI: 0.07–0.53), while progression was prevented compared to crizotinib. In the worldwide ALEX study, 303 patients were randomized to receive alectinib at 600 mg BID and crizotinib at 250 mg BID (19). A similar difference was found as in the J-ALEX study; the median PFS for alectinib was not yet reached and that for crizotinib was 11.1 months, while alectinib was more effective against brain metastases. Alectinib showed a favorable toxicity profile compared to crizotinib in both studies, with no major differences

These studies raise another important question, whether 600 mg alectinib BID is required for all patients? The survival data of these schedules seem to be in the same range, although the data are not mature. The population pharmacokinetics (PK) analysis showed that one third of the J-ALEX patients might benefit from a higher exposure (20) and it was concluded that a 600 mg BID would ensure that the exposure will maximize the expected PFS benefit. However, one might also consider to perform a limited PK analysis in the 300 mg BID schedule and increase the dose in patients with inadequate PK; this would reduce toxicity and costs for the drug.

The question now arises whether alectinib (or ceritinib) should replace crizotinib as first line treatment for ALK-positive NSCLC. There are several reasons to substitute crizotinib for the novel inhibitors, such as the poor activity of crizotinib against brain metastases, while alectinib and ceritinib (as well as brigatinib) have a much better brain penetration. Moreover, the novel inhibitors are active against crizotinib-resistant and -sensitive tumors. On the other hand, one might keep crizotinib as first line treatment (for patients without brain metastases), since it also has activity against cMET and ROS positive tumors; upon development of resistance to crizotinib, additional gain in disease control can be obtained by the novel compounds including alectinib. In order to make a balanced choice between the various alternatives, an extensive genetic analysis of the primary tumor before treatment and of the resistant variant, should be standard practice. The value of this has recently been demonstrated by the report of a patient treated with crizotinib (21), that became resistant and was subsequently treated with chemotherapy and ceritinib, but appeared to be resistant to ceritinib. Thereafter the patient responded to lorlatinib, but became resistant with a L1198F mutation in ALK and became sensitive to crizotinib again. This study shows that treatment choice at progression should be guided by analysis of underlying resistance mutations. Both alectinib and ceritinib are able to overcome most common crizotinib resistance mutations, but ceritinib is also active against some mutations conferring resistance to alectinib (3,14,15). However, secondary ALK mutations can lead to ceritinib resistance. On the other hand the F1174 mutation conferring resistance to ceritinib, is still sensitive to alectinib, while the G1202R mutation is resistant to most next-generation ALK inhibitors, except to lorlatinib.

Therefore, it is of utmost importance to perform both a retrospective analysis of the concluded studies such as AF-00JP and a prospective analysis of tumors of new patients. This will help to stratify future patients for the most effective drug, or possibly the most effective sequence of drugs. However, a serious drawback of this approach is the cost-effectiveness of the analysis, while access to the

tumor is not always possible. The latter can be solved by using alternative non-invasive surrogate biosources usually summarized as liquid biopsies (22,23) including plasma, exosomes, circulating-free DNA, circulating tumor cells (CTCs) and even platelets (24). However, these analyses are usually only feasible in specialized institutions and not available for most patients, especially those patients in countries with no access to these facilities. Moreover, this type of personalized treatment is too expensive for many healthcare providers. Therefore, alternatives to optimize treatment should be investigated, such as limited PK to select the optimal dose, and simplified genetic analysis for predictive biomarkers on easily available non-invasive liquid biopsies. With current possibilities to optimize methods, both approaches seem feasible cost-effectively for larger populations, enabling selection of the right drug and the right dose for the right patient.

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References

1. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. New Engl J Med 2014;371:2167-77.
2. Khozin S, Blumenthal GM, Zhang L, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res 2015;21:2436-9.
3. Muller IB, De Langen AJ, Honeywell RJ, et al. Overcoming crizotinib resistance in ALK-rearranged NSCLC with the second-generation ALK-inhibitor ceritinib. Expert Rev Anticancer Ther 2016;16:147-57.
4. Larkins E, Blumenthal GM, Chen H, et al. FDA Approval: Alectinib for the Treatment of Metastatic, ALK-Positive Non-Small Cell Lung Cancer Following Crizotinib. Clin Cancer Res 2016;22:5171-6.
5. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17:234-42.
6. Ou SH, Ahn JS, De Petris L, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol 2016;34:661-8.
7. Tamura T, Kiura K, Seto T, et al. Three-Year Follow-Up of an Alectinib Phase I/II Study in ALK-Positive Non-Small-Cell Lung Cancer: AF-001JP. J Clin Oncol 2017;35:1515-21.
8. Seto T, Kiura K, Nishio M, et al. CH5424802 (RO5424802) for patients with ALK-rearranged advanced non-small-cell lung cancer (AF-001JP study): a single-arm, open-label, phase 1–2 study. Lancet Oncol 2013;14:590-8.
9. Yang JC. A selective ALK inhibitor in ALK-rearranged patients. Lancet Oncol 2013;14:564-5.
10. Honeywell RJ, Avan A, Giovannetti E, et al. Tissue distribution of crizotinib and gemcitabine combination in a patient-derived orthotopic mouse model of pancreatic cancer. ADMET and DMPK 2017;4:327-34.
11. Gainor JF, Ou SH, Logan J, et al. The central nervous system as a sanctuary site in ALK-positive non-small-cell lung cancer. J Thorac Oncol 2013;8:1570-3.
12. Costa DB, Shaw AT, Ou SH, et al. Clinical Experience With Crizotinib in Patients With Advanced ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastases. J Clin Oncol 2015;33:1881-8.
13. Takeuchi K, Togashi Y, Kamihara Y, et al. Prospective and clinical validation of ALK immunohistochemistry: results

from the phase I/II study of alectinib for ALK-positive lung cancer (AF-001JP study). Ann Oncol 2016;27:185-92.
14. Sakamoto H, Tsukaguchi T, Hiroshima S, et al. CH5424802, a selective ALK inhibitor capable of blocking the resistant gatekeeper mutant. Cancer Cell 2011;19:679-90.
15. Kodama T, Tsukaguchi T, Yoshida M, et al. Selective ALK inhibitor alectinib with potent antitumor activity in models of crizotinib resistance. Cancer Lett 2014;351:215-21.
16. Takiguchi K, Hida T, Nokihara H, et al. Updated efficacy and safety of the j-alex study comparing alectinib (ALC) with crizotinib (CRZ) in ALK-inhibitor naïve ALK fusion positive non-small cell lung cancer (ALK+ NSCLC). J Clin Oncol 2017;35:abstr 9064.
17. Rossi A. Alectinib for ALK-positive non-small-cell lung cancer. Expert Rev Clin Pharmacol 2016;9:1005-13.
18. Dagogo-Jack I, Shaw AT. Crizotinib resistance: implications for therapeutic strategies. Ann Oncol 2016;27 Suppl 3:iii42-50.
19. Shaw AT, Peters S, Mok T, et al. Alectinib versus crizotinib in treatment-naive advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study. J Clin Oncol 2017;35:abstr LBA9008.
20. Hsu JC, Jaminion F, Guerini E, et al. Population pharmacokinetics (popPK) and exposure-response (ER) analyses bridge J-ALEX to the global population with an alectinib (ALC) 600mg bid dosing regimen. J Clin Oncol 2017;35:abstr e20616.
21. Shaw AT, Friboulet L, Leshchiner I, et al. Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F. New Engl J Med 2016;374:54-61.
22. Santarpia M, Karachaliou N, González-Cao M, et al. Feasibility of cell-free circulating tumor DNA testing for lung cancer. Biomark Med 2016;10:417-30.
23. Aguado C, Giménez-Capitán A, Karachaliou N, et al. Fusion gene and splice variant analyses in liquid biopsies of lung cancer patients. Transl Lung Cancer Res 2016;5:525-31.
24. Nilsson RJ, Karachaliou N, Berenguer J, et al. Rearranged EML4-ALK fusion transcripts sequester in circulating blood platelets and enable blood-based crizotinib response monitoring in non-small-cell lung cancer. Oncotarget 2016;7:1066-75.

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