Editorial

A few pills twice a day keep ALK-positive non-small-cell lung cancer at bay

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Non-small-cell lung cancer (NSCLC) represents the paradigm of personalized treatment of human cancer. A number of oncogenic druggable alterations have been so far identified, with anaplastic lymphoma kinase *(ALK)* gene rearrangements being one of the most attractive (1). In the past 10 years, we have learned that the presence of such molecular event is associated with some specific pathological and clinical features, including a preferential seeding into the central nervous system (CNS) and, most importantly, anticipates response to anti-ALK agents (2-4). Front-line crizotinib, the first-in-class ALK-inhibitor, prolonged median progression-free survival (PFS) of 4 months respect to standard platinum-pemetrexed (11.9 *vs.* 7.0 months; HR =0.45, P<0.001), nearly doubling the probability of achieving responses [response rate (RR): 75% *vs.* 45%] and preserving quality of life, as demonstrated in the PROFILE 1014 trial (5). However, the drug does not definitively cure any patient and, within the first year of therapy, cancer eventually re-growths due to the occurrence of acquired resistance, with the CNS as the dominant site of progression (6). The new generation and FDA-approved ALK-inhibitors, ceritinib, alectinib and brigatinib, are more potent and brain-penetrable than crizotinib and retain activity against a wide spectrum of *ALK* resistance mutations (6). In single-arm studies, all these drugs resulted effective in crizotinib-failure setting, particularly in patients with brain metastases (BMs) (7-11). Furthermore, sequential use of crizotinib followed by ceritinib or alectinib produced a combined PFS exceeding 18 months (12,13). This is the reason why, the standard of care for advanced ALK positive NSCLC should include crizotinib followed by a second generation ALK inhibitor. However, it remains unclear whether upfront use of a second-generation ALK inhibitor could translate into a more durable benefit than the one observed with sequential approach.

In a recent issue of *The Lancet*, Hida and colleagues reported results of the J-ALEX, a phase 3 randomized Japanese trial directly comparing alectinib to crizotinib in 207 *ALK* rearranged NSCLCs who had never received an ALK inhibitor (14). Notably, the study also included individuals previously exposed to one line of chemotherapy and with asymptomatic BMs, regardless of prior radiation therapy (RT). Stratification was done according to ECOG performance status (0/1 *vs.* 2), treatment line (first *vs.* second) and disease stage (IIIB *vs.* IV). The study met its primary end-point of PFS by independent review, demonstrating an impressive reduction in the risk of progression of 66% for patients treated with alectinib (PFS: not reached, NR *vs.* 10.2 months; HR =0.34, P<0.0001). In addition, alectinib had greater intracranial activity (HR for PFS 0.16) also delaying the onset of BMs (HR for time to BMs onset 0.41), had a numerically higher RR (92% *vs.* 79%) and a more favorable safety profile than crizotinib [grade 3–4 adverse events (AEs): 26% *vs.* 52%]. Importantly, the PFS improvement equally emerged in all groups of subjects, irrespective of age, sex, line of therapy, or disease stage.

Collectively, these results support the upfront use of alectinib. Particularly, even if the PFS has been not yet reached, it exceeded 20 months at the lower limit, more than expected with first line crizotinib—with a median PFS of 10–11 months—followed by alectinib -with a median PFS in the range of 7–8 months (5,9,10). On this perspective, front-line alectinib could actually translate into an overall survival advantage. In addition, note that there is a not negligible fraction of patients for which disease progression after crizotinib occurs with rapid clinical deterioration, precluding the opportunity of receiving a more effective drug.

Therefore, are J-ALEX findings sufficient to change current practice in non-Japanese populations? It is not possible to exclude that the remarkable activity of alectinib could simply reflect racial differences or a more squeezing patient selection. Indeed, in the study, the dose of alectinib is half than the one used outside Japan (300 mg twice daily *vs.* 600 mg twice daily), suggesting some imbalance in drug metabolism. In addition, *ALK* positivity was confirmed in parallel by immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) in 93% of cases or, by real time polymerase-chase reaction (RT-PCR) in the remaining 7%, potentially magnifying the sensitivity of a more potent ALK-inhibitor in a super-selected population. Furthermore, beyond constitutive and molecular characteristics, the number of patients having BMs at baseline is higher in the crizotinib arm (29 *vs.* 14 patients), and the presence of intracranial lesions was not a stratification factor. Finally, although crizotinib similarly performed with the PROFILE 1014 and 1029 (5,15) in terms of RR and PFS, the consistent proportion of subjects requiring dose interruption (74%) or reduction (20%) for AEs could have negatively affected the efficacy of the comparator arm.

Fortunately, all these points have been addressed by the global ALEX trial, a phase III, head-to-head study of alectinib 600 mg twice daily *vs.* standard-dose crizotinib (16). Overall, 303 ALK-IHC positive and untreated NSCLCs were included onto the study. Baseline characteristics were well balanced between the two arms. Particularly, 45% of subjects were Asians, 40% had BMs and among them, more than 80% did not receive prior brain radiation. Primary end-point was PFS by investigator assessment, whereas key secondary end point was time to CNS progression. Treatment with alectinib was associated with longer PFS (NR *vs.* 11.1 months, HR =0.47; P<0.001) and better safety profile (incidence of grade 3 to 5 AEs, 41% *vs.* 50%) and, most importantly, it prevented the occurrence of BMs (cause-specific HR =0.16, P<0.001). These findings indirectly confirmed those produced in the J-ALEX, thus placing alectinib instead of crizotinib as the new standard of care worldwide. Nevertheless, this change will have two immediate consequences. The first one is how alectinib could re-define the current management of BMs (17,18). Evidences from J-ALEX and ALEX demonstrate that the drug obtains an excellent intracranial control and prevents metastatic spread into the CNS, reinforcing the conviction that RT—especially whole brain RT—could be deferred as salvage treatment with a favorable impact in preserving neurocognitive functions. The second one concerns the molecular pattern of alectinib failure. Both target-dependent and non-target-dependent mechanisms of resistance have been described for alectinib, but they mainly refer to second line setting, for example at crizotinib progression (6). It is conceivable that a more potent and selective ALK-inhibitor such as alectinib, when used early, could shift the spectrum of resistance mechanisms in favour of non-target-dependent events, including *MET* amplification or histologic transformation. The knowledge of the resistance pattern will be crucial to design the optimal sequential strategy.

Beyond alectinib, two other second generation ALK-inhibitors have been tested in first-line setting (19,20). In the currently ongoing ALTA-1L trial, brigatinib is compared to crizotinib as front-line or after-chemo treatment and results are expected for 2018 (19). In the recently published ASCEND 4, whose trial design was quite similar to PROFILE 1014 and 1029, ceritinib has been compared to platinum-pemetrexed combination (20). Not surprisingly, ceritinib did better than chemotherapy, prolonging PFS in overall population (16.6 *vs.* 8.1 months, HR =0.55, P<0.00001), as well as in the subgroup of patients with or without CNS involvement (26.3 *vs.* 8.3 months; HR =0.48 and 10.7 *vs.* 6.7 months; HR =0.70, respectively). Unfortunately, the drug safety profile emerged as a major limitation. Dose interruption or reduction due to AEs was required in 80% of patients compared with 45% in chemo-arm, a "hard-to-justify" percentage especially for a targeted agent and in metastatic setting. Further, the efficacy of ceritinib in presence of BMs was not so convincing, as the differential PFS improvement produced by ceritinib *vs.* chemo for patients with BMs was less shocking than the one observed in individuals without CNS involvement (4 *vs.* 18 months), with no clear neuroprotective effect. For such reasons, the optimal positioning of ceritinib should

probably remain the crizotinib-failure context.

In conclusion, J-ALEX and ALEX findings coupled with all the available data firmly place alectinib as the new standard of care in untreated *ALK* positive NSCLC, representing the second watershed in the treatment of this disease.

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Footnote

Conflicts of Interest: Dr. Cappuzzo declares consultancy role for Roche, Pfizer, Novartis and Takeda. Dr. Landi declares consultancy role for Pfizer.

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