Editorial

# J-ALEX trial will crown alectinib as the standard choice for anaplastic lymphoma kinase positive untreated non-small cell lung cancer patients?

**Cesare Gridelli[1], Francesca Casaluce[1], Assunta Sgambato[1], Giovanni Palazzolo[2], Paolo Maione[1]**

[1]Division of Medical Oncology, 'S. G. Moscati' Hospital, Avellino, Italy; [2]Division of Medical Oncology, ULSS15 'Alta Padovana', Cittadella, Italy

*Correspondence to:* Cesare Gridelli. Division of Medical Oncology, 'S. G. Moscati' Hospital, Contrada Amoretta, Avellino, Italy.
Email: cgridelli@libero.it.

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About 4–5% of advanced non-small cell lung cancer (NSCLC) patients are diagnosed with an oncogene-addicted disease, due to the presence of echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion gene (1). Before August 2011, chemotherapy was the only option for those patients. The exquisite sensitivity to ALK targeted tyrosine kinase inhibitors (TKIs) in presence of this rearrangement shortly changed the standard of treatment of those patients. To date, standard first-line therapy for advanced ALK positive NSCLC is the multi-targeted ALK/ROS1/MET inhibitor crizotinib, followed by more potent second-generation ALK inhibitors, like ceritinib and alectinib, upon progression (2-5).

Alectinib is a high selective ALK inhibitor with activity against secondary ALK mutations that confer resistance to crizotinib. Unlike crizotinib, alectinib is also a central nervous system (CNS) penetrant, with the potential increase of brain metastases control, the most common site of disease progression in ALK rearranged tumors (6). After the significant activity in both ALK-inhibitor naïve and crizotinib-resistant patients emerged from phase I–II trials (4,5,7), the J-ALEX phase III is the first randomized trial directly comparing two ALK inhibitors—alectinib and crizotinib—in Japanese untreated population (8).

In this multicenter study, 207 patients with stage IIIB/IV ALK positive NSCLC who had previously received 0–1 lines of chemotherapy, but no prior ALK-TKI were randomly assigned to receive alectinib 300 mg twice daily (n=103) or crizotinib 250 mg twice daily (n=104). ALK positivity was confirmed by central immunohistochemistry (IHC) and fluorescence *in-situ* hybridization (FISH) in parallel, or by real time polymerase chain reaction (RT-PCR). Baseline characteristics were well balanced between the groups, except for the proportion of patients with baseline brain metastases which was higher in the crizotinib group (28% *vs.* 14% in the alectinib group). The study met its primary endpoint of showing superiority of alectinib than crizotinib in independent review facility-assessed progression-free survival (IRF-PFS) in both first- [median PFS: not estimable *vs.* 10.2 months, hazard ratio (HR): 0.31] and second-line setting (median PFS: 20.3 *vs.* 8.2 months, HR: 0.40). Interestingly, alectinib reduced the risk for progression of brain metastasis lesions or death in patients with brain metastasis at baseline (HR: 0.16) and the risk for metastasis to the brain or death in those free of intracranial lesions at baseline (HR: 0.41). Objective response (ORR) assessed by the investigator also favored alectinib in all population (85% *vs.* 70%), as well as in the subgroup of patients with brain metastases (92% *vs.* 79%). Alectinib showed a more favorable tolerability profile, with lower grade 3–4 adverse events (26% *vs.* 2%), treatment interruption (29% *vs.* 74%) and treatment discontinuation (9% *vs.* 20%). With a further 10 months of follow up, the

updated analysis confirmed the consistent superior efficacy of alectinib than crizotinib in systemic disease (median PFS: 25.9 *vs.* 10.2 months, HR: 0.38) and prevention of CNS progression (HR: 0.19 for CNS metastasis onset; HR: 0.51 for baseline CNS metastasis progression) (9).

No significant assessment bias was found, with similar results of IRF- and investigator-assessed-PFS. However, several important questions were moved, regarding statistical analysis (early release of study results with potential overestimation of HR; the addition of interim analysis after 33% of required PFS events during the course of study), and the generalizable findings to non-Japanese population. The ALEX trial confirmed the results of the J-ALEX on the global scale, but these studies were different in trial design.

First, the J-ALEX participants received alectinib at a lower dose than that used outside of Japan (600 mg twice daily), with comparable response rates and lower severe AEs (grade ≥3 AEs: 26% *vs.* 41% in J-ALEX an ALEX). Second, the J-ALEX required ALK positivity (by RT-PCR or by both IHC and FISH) might have theoretically selected for a subgroup of patients (such as high ALK fusion expression) with greater benefit from the more potent ALK inhibitor alectinib. Of note, a recent retrospective analysis of ALEX trial reported a clinical benefit from alectinib also in those patients with ALK IHC positive/FISH negative (median PFS: 7.8 *vs.* 3.8 months; P=0.41) (10). Third, a lower CNS ORR was reported in J-ALEX than ALEX trial (13.6% *vs.* 42%), despite the smaller sample size of brain metastatic patients at baseline in J-ALEX (14 *vs.* 64 patients in ALEX) might have influenced these data. Based on the success of alectinib over crizotinib in front-line setting in both trials, a key question is whether the use of alectinib upfront, rather than sequential therapy with crizotinib followed by a second-generation ALK inhibitors at the time of progression, will translate into long-term survival benefit. To data, there is a lack of prospective trials on this issue and overall survival data from ALEX and J-ALEX are still immature. Sequential treatment of crizotinib followed by ceritinib or alectinib reported a combined PFS no longer than 19 months (17.4–18.2 months) in retrospective analyses (11-12). Ceritinib as upfront in the ASCEND-4 trial (13) seemed to work better than crizotinib in the PROFILE 1014, reporting a median PFS of 16.6 months rather than 10.9 months, despite limited by higher gastrointestinal toxicities. Recently, the median PFS achieved by alectinib as first-line was 25.9 months, associated with a more favorable tolerability. These data suggested the greater efficacy of second-generation ALK inhibitors as upfront than crizotinib alone and potentially than sequential strategy. The availability of increasing number of ALK-TKIs, the better knowledge of acquired mechanisms of resistance, feasibility of re-biopsies at progression with aim to guide the choice of the best ALK inhibitor, as well as pending data from ongoing phase III trials comparing head-to head next generation ALK inhibitors, could help the definition of the best sequential approach in ALK positive advanced NSCLC patients. To date, the findings of J-ALEX and ALEX might support alectinib as new standard of care for untreated ALK positive NSCLC.

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## Footnote

*Conflicts of Interest:* Cesare Gridelli as consultant for Roche. The other authors have no conflicts of interest to declare.

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