Editorial

Lorlatinib in ALK- and ROS1-positive NSCLC: the future has a start

Francesco Facchinetti[1], **Luc Friboulet**[2]

[1]Medical Oncology Unit, University Hospital of Parma, Parma, Italy; [2]INSERM, U981, Gustave Roussy Cancer Campus, Université Paris Sud, Villejuif, France

Correspondence to: Luc Friboulet, PhD. INSERM, U981, Gustave Roussy Cancer Campus, 114 rue Edouard Vaillant, 94805 Villejuif, France.
Email: luc.friboulet@gustaveroussy.fr.

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In the last decade huge improvements in prognosis and quality of life have been provided by the molecular characterization of non-small cell lung cancer (NSCLC). With particular regard to ALK- and ROS1-positive tumors, the sequential development of oral tyrosine kinase inhibitors (TKIs) has allowed survival outcomes unconceivable before their availability (1-3). *ALK* and *ROS1* are usually approached together as lung cancer oncogenes due to their similitudes arising from the phylogenic origin, structural similarities and way of activation (i.e., by gene rearrangement) (4). The first-in-class molecule crizotinib, initially developed as a MET inhibitor, has fully shown its role in ALK- and ROS1-positive diseases. Second-generation inhibitors ceritinib, alectinib (not retaining anti-ROS1 activity) and brigatinib, administered after the onset of the unavoidable crizotinib resistance, dramatically concur to the extended patients' survival. More recently, the third generation molecule lorlatinib (PF-06463922) has been designed to encompass at the best level the main characteristics of an ALK/ROS1 inhibitor (5). Indeed, initial preclinical studies clearly revealed that (I) lorlatinib acts strictly against the two tyrosine kinases (thus creating a high therapeutic index by minimizing potential off-target toxicities), (II) harbors the highest on-target potency (III) with the widest spectrum of activity towards secondary resistant mutations, and (IV) shows an utmost blood-brain barrier penetration in mouse models (6). The first-in man trial of lorlatinib in ALK- and ROS1-positive NSCLC patients mirrored the promising results from its preclinical development (7).

The manuscript by Shaw and colleagues (7) presented the definitive results of the dose-escalating phase 1 study of lorlatinib in the specific setting of *ALK*- and *ROS1*-rearranged lung cancer. The trial itself (NCT01970865) contained a phase 2 cohort, whose initial results have already been presented at international congresses; the present commentary refers only to the phase 1 data.

Interestingly, the recommended phase 2 dose (RP2D, primary objective of the study) of 100 mg once daily emerges as a consequence of toxicity together with pharmacokinetics/pharmacodynamics features and clinical activity. Indeed, the dose of 200 mg daily was defined as toxicity-limiting and the twice daily schedule of 35 mg was deemed as not active. Fixing the RP2D at 100 mg once daily allowed a good tolerability profile while guaranteeing that plasma concentration of the drug would allow the inhibition of ALK mutants harboring the G1202R mutation, the most frequent resistant mutation to second-generation inhibitors and the most challenging to overcome (8). The frequent onset of hypercholesterolaemia and hypertriglyceridemia toxicities does not represent an issue, considering they can be managed pharmacologically. Gastrointestinal side effects, hampering the tolerability of some first-/second-generation compounds, have a lower impact.

Nevertheless, if as anticipated, lorlatinib is going to be the new standard of care in ALK- and ROS1-positive NSCLC, the development of neurological symptoms should deserve peculiar attention. Prescribing physicians will need to be aware of the neurocognitive and mood effects triggered by the drug, as they can be managed by drug dose interruption and reduction.

Regarding lorlatinib activity, two meaningful elements emerged in the study. First, lorlatinib maintained its clinical activity regardless of the number of previous TKI administered (including after acquired resistance to previous generations). Among the 41 ALK-positive cases, confirmed complete and partial responses were achieved in 3 (7%) and 16 (39%) patients. Focusing on the 11 (27%) patients experiencing disease progression, three had received insufficient lorlatinib dose (35 mg twice daily). Most of the patients (n=23) had previously received a sequence of crizotinib followed by a second-generation inhibitor. Importantly, the 9.2 months of estimated median progression-free survival (PFS) for the 26 patients who had previously received two or more ALK TKI, increased to 13.5 months in patients pretreated with one inhibitor. Importantly, the three patients who had previously received the sequence of crizotinib, ceritinib and alectinib achieved tumor shrinkage, with one complete and one partial response documented. Albeit the lack of systematic pre-lorlatinib biopsies does not allow definite conclusions, the molecular study of 12 samples obtained after the progression to a second-generation TKI sustains what was anticipated by preclinical findings: a divergent lorlatinib efficacy in tumors harboring wild-type rearranged *ALK* compared to *ALK*-mutated ones (6,8). The presence of mutations in the ALK kinase domain (whose occurrence is more frequent after second-generation compounds rather than after crizotinib) does not impair lorlatinib activity. This involves the G1202R mutation, the most challenging to overcome (7). On the other hand, if resistance to previous inhibitors is mediated by off-target mechanisms, providing lorlatinib does not translate into clinical benefit, as the signal directly depending on ALK is already fully compensated by activation of alternative kinases (8). If we dare a molecular parallelism, the actions of the respective EGFR and ALK third-generation TKIs can be simplified as being similar: both osimertinib and lorlatinib are effective in 50–60% of patients in which on-target mutations explaining resistance to previous inhibitors are detected. However, we cannot conclude yet that lorlatinib should be given only to patients with *ALK* secondary mutations. In line with T790M EGFR mutants, the detection of *ALK* mutations would likely require the development of liquid biopsy strategies, to which the trial aimed (7). In this sense, detection of *ALK* mutations in plasma samples has been recently proven feasible and clinically meaningful (9).

The second important feature in the study is the impressive intracranial disease responses achieved by lorlatinib, regardless of the number of previous TKIs administered. Brain and meningeal sites of disease both at diagnosis and after first- and second-generation inhibitors represent a critical issue in ALK-positive patients and, to a lower extent, in ROS1-positive ones (10). Although the sites of disease progression before lorlatinib were not recorded in the study, we can easily speculate that a significant proportion of ALK-rearranged NSCLC patients had previously developed central nervous system (CNS) progression. Out of 24 ALK/ROS1-positive patients with measurable target CNS lesions, 7 (29%) and 4 (17%) achieved a confirmed complete or partial response. These results are of strong interest when considering, again, that the majority of patients had received two or three TKIs. These data clearly demonstrate that lorlatinib, as predicted by *in vivo* studies (6), display an impressive capability to cross the blood-brain barrier, as its cerebrospinal fluid (CSF) concentration achieved 75% of the plasma concentration (7). Intracranial/leptomeningeal disease progression to second-generation inhibitors could therefore, in a close future, no longer be considered as an unequivocal dramatic event.

Together, the two abovementioned points constitute the backbone of the significant efficacy outcomes reported, and when adding the optimal tolerability, lorlatinib becomes a real option for the next future even on the basis of a phase 1 study. The activity and efficacy estimations provided in the manuscript will nevertheless require the confirmation from the lorlatinib phase 2 (whose recruitment is completed) and the ongoing phase 3 trials.

With regard to *ROS1*-rearranged cases, an opposite behavior to the one observed with crizotinib has been documented with lorlatinib. If the first-generation inhibitor allows longer-term disease control (4), this does not seem to be the case for lorlatinib (estimated median PFS of seven months). We can speculate that the putative emergence of the *ROS1* G2032R mutation [corresponding to the *ALK* G1202R (11)], before or after lorlatinib initiation (10), could account for the relative efficacy of the drug. Albeit preclinical studies reported that lorlatinib could be active in presence of G2032R *ROS1* mutation (12), our group and others have labeled this frequent *ROS1* substitution

as responsible for lorlatinib resistance (11,13). No clinical reports of response to the third-generation inhibitor against ROS1 G2032R mutants are indeed available so far. Besides the mentioned similarities between *ALK* and *ROS1* oncogenes, the exact therapeutic approaches to treat these malignancies seem slightly different. Ceritinib, active as a first-line ROS1 inhibitor, does not seem to be a suitable option after crizotinib exhaustion (4,14), as well as alectinib, entrectinib or brigatinib, not retaining sufficient potency against ROS1 mutants (13,15). Therefore, potential options of treatment sequence involve crizotinib (or ceritinib) followed by lorlatinib, taking into account its inefficiency on G2032R *ROS1* mutation. Additional "large spectrum" inhibitors such as cabozantinib have shown their role in crizotinib-resistant ROS1-positive NSCLC, with a relevant toxicity and without strict documentation of clinical effectiveness against G2032R mutant (13,16).

As seen for EGFR-driven NSCLC, the clinical strategies for ALK inhibition in NSCLC have been recently revolutionized by the marked PFS benefit obtained with second-generation inhibitors administered first-line (i.e., without prior crizotinib treatment) (17,18). Discussing the pros and cons of sequencing versus "next-generation first" TKIs administration goes beyond the scope of the current commentary. However, the head-to-head phase III trial comparing first-line lorlatinib versus crizotinib in *ALK*-rearranged NSCLC patients (NCT03052608), will allow determination of lorlatinib PFS given upfront compared to sequential TKIs (the cross-over of patients from the crizotinib arm to the lorlatinib arm being permitted).

Acknowledging we are still dealing with early signs of activity, the presented results place lorlatinib as a sure concrete option as a standard of care, regardless of previously administered inhibitors. We think that we now have to move on figuring out what will be the next options for patients after lorlatinib resistance. At least for the *ALK*-rearranged model, having fulfilled the characteristics of a *non plus ultra* inhibitor, we do not see any additional ALK inhibitors as a suitable option [with the remarkable exceptions of specific sensitization mutations (19)]. As lorlatinib activity is relatively hampered by the onset of bypass track resistance and is globally well tolerated as a monotherapy, putative scenarios of combining targeted-agents are of particular interest (20). Concerning ROS1-positive disease, on-target direct inhibition of G2032R mutation remains an issue and development of adequate inhibitors is needed.

In conclusion, lorlatinib is expected to actively contribute to the prolonged survival already observed in patients suffering from ALK- and ROS1-positive NSCLC. The enthusiasm following these presented results encompasses the constant hunt of improving patients' outcomes by means of molecularly driven approaches. From this perspective, lorlatinib defines the new playground. Counteracting both primary and acquired resistance to this new drug represents the real challenge.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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