Looking for a new panacea in ALK-rearranged NSCLC: may be Ceritinib?

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In the past decade, the advent of targeted therapy led to a silent revolution in the war against lung cancer and a significant evolution on the concept of Phase I clinical trials design. Thanks to the specificity of their target, the new drugs have radically changed NSCLC treatment, leading to the development of personalized strategies. The accelerated approval of the first ALK-inhibitor, Crizotinib and more recently Ceritinib, without a Phase III randomized, clinical trial, has been an amazing success story in lung cancer research, marking the beginning of a new decade of targeted drugs development, characterized by modern, biomarker-driven, early clinical trial design and shorter times for clinical approval. Is Ceritinib a new panacea for the treatment of ALK-rearranged NSCLC? We aimed to discuss the reasons of such success, including the new emerging questions, regarding mechanisms of acquired resistance, and the best treatment algorithm for ALK-rearranged NSCLC patients.

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The discovery of the EML4-ALK fusion gene, reported in about 3 – 7% of overall NSCLC patients [1,2], and the subsequent clinical development of the first ALK-inhibitor, Crizotinib, has been an amazing success story in lung cancer clinical and translational research. Its accelerated approval by FDA in October 2011, without a Phase III randomized, clinical trial, was absolutely uncommon, but it was the result of the impressive responses (~60%), and median progression-free survival (PFS: 8 – 10 months), observed in the early Phase I/II clinical trials [3], recently confirmed by the Phase III, randomized trials, both in second [4,5] and in first-line settings (biblio). The early approval of Crizotinib has benefited many NSCLC patients, whose tumors harbor this novel EML4/ALK translocation, marking the beginning of a new decade of targeted drugs development, characterized by new ethical and scientific considerations. Unfortunately, despite of a dramatic initial activity of Crizotinib in this, molecularly selected, NSCLC population, acquired resistance inevitably occurs during the first year of treatment, leading to a clinical progression of the disease, commonly involving the CNS. Data suggest that additional genetic alterations in the target, such as secondary mutations or amplification of the ALK fusion gene, seems to be responsible of the so-called ‘ALK- dependent’ acquired resistance to Crizotinib in about one-third of the patients [6,7]. The activation of other oncogenic drivers, such as, K-RAS mutations, KIT amplification and increased EGFR autophosphorylation and mutations, may cause resistance in another 30% of them, through reactivation of downstream signaling pathways via bypass tracts [6,7]. Thus, new drugs capable to overcome mechanisms of acquired resistance to Crizotinib are urgently needed. Second-generation ALK-inhibitors, including LDK378, CH5424802, AP26113 and others molecules, are currently
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under investigation in early Phase I/II clinical studies [8]. One of these compound, LDK378 (Ceritinib), has shown a great activity in ALK-rearranged, NSCLC patients. In the recent, Phase I trial by Shaw et al., including a total of 163 patients with metastatic, ALK-positive, NSCLC who had progressed on or were intolerant to Crizotinib, Ceritinib induced a 60% response rate, with a median PFS of 7.0 months (95% CI, 5.6–9.5) [9]. The benefit was similar in both patients who had received prior Crizotinib treatment and in those who had not. In addition, responses were seen in untreated CNS lesions, in patients treated with Crizotinib. The most common terminology criteria for adverse events grade 3 – 4 adverse reactions (≥ 5%) were diarrhea, fatigue, hyperglycemia, hypophosphatemia, increased transaminases and lipase levels and anemia. Therefore, a new, more potent ALK-inhibitor is emerging for ALK-rearranged NSCLC patients, who could benefit from a second chance of treatment, after progression to Crizotinib occurs. What are the reasons of such success? First, modifications in the chemical structure of the compound, promotes a more favorable interaction of Ceritinib with the mutant lipophilic residues, at the gatekeeper position of the kinase domain. The new chemical architecture could explain the activity of this drug against both the gatekeeper L1196M, and the non-gatekeeper G1296A mutations, which are the two most common secondary mutations identified in Crizotinib resistant tumors [10]. Second, as reported in the clinical trial, Ceritinib seems to be effective also in those ‘ALK-independent’ resistant patients, who develops resistance to Crizotinib without ALK mutation or amplification [9]. These findings suggest that the activity of Ceritinib in patients whose tumors had progressed during Crizotinib treatment may be independent of the underlying mechanism of acquired resistance. In this subset of patients, tumor cells probably preserve their sensitivity to ALK inhibition, but, because of a sub-therapeutic inhibition of the target, during Crizotinib treatment, may survive, through re-activation of bypass tracks, such as EGFR [10]. Thanks to its higher potency, Ceritinib completely inhibits the target, stopping the activity of by-pass track, and restoring full tumor cells sensitivity to ALK-inhibition. Third, the Phase I study of Ceritinib represent an excellent example of modern, biomarker driven, early clinical trial design. Such trial included a proven oncogenic driver as biomarker, a really effective drug in modulating the target, and a large, molecular selected, patients cohort. This made the results of the study even more reliable and attractive, leading to the accelerated approval by the FDA on 29 April 2014, for the treatment of patients with ALK-rearranged NSCLC, with disease progression on, or who are intolerant to Crizotinib. Furthermore, two Phase III, ongoing, randomized trials are currently investigating the role of Ceritinib both in Crizotinib treated (NCT01828112), and untreated (NCT01828099), NSCLC patients. Despite several strengths in favor of Ceritinib, some questions remain open. The evidence of equal efficacy of Ceritinib treatment, reported in both Crizotinib resistant and naive patients cohorts, led to a new debate regarding the best use of this new compound in the treatment of ALK-rearranged NSCLC patients. Even if most of the patients included in the trial had previously received Crizotinib, the similar efficacy and tolerability profile of the two drugs, the higher median PFS achieved in the Crizotinib-naive cohort, and the early activity on CNS disease, are findings which would support the use of Ceritinib as front-line treatment. A direct comparison trial between these two compounds is needed, in order to draw up the best treatment algorithm for the ALK-rearranged NSCLC patients. Common to other tyrosine kinase inhibitors already in use, including its precursor Crizotinib, after a variable period of response to Ceritinib, tumors inevitably develop resistance. This has been clearly shown in the study by Friboulet et al., which revealed the development of mutations at either G1202 or F1174, in 5 of 11 biopsed, Ceritinib-resistant tumors [10]. In addition, the authors reported an inferior activity of Ceritinib against less common ALK-resistant mutations, such as C1156Y, 1151T-ins and L1152P, which would confer resistance to both Crizotinib and Ceritinib, in cell-lines models [10]. Future studies will identify the exact mechanism behind such resistant mutations, allowing us to understand whether Ceritinib and new ALK-Inhibitors will be the new panacea for ALK-rearranged NSCLC.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


★★ It is the first, published, scientific evidence of the high activity/efficacy of Crizotinib in ALK-rearranged NSCLC, giving the basis for its approval by FDA.


★★ It is the first, randomized, phase III trial showing significant superiority of Crizotinib compared to standard platinum-chemotherapy in first-line treatment of ALK-rearranged NSCLC.


★★ It is the first, published, scientific evidence of the high activity/efficacy of Ceritinib in both Crizotinib treated, and untreated, ALK-rearranged, NSCLC patients, giving the basis for its approval by FDA.


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