Editorial

Ceritinib as a promising therapy for ALK related diseases

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Abstract: Ceritinib, also known as LDK-378 or Zykadia (Novartis), is a second generation inhibitor able to specifically target the anaplastic lymphoma kinase (ALK). In the last five years the interest for ALK small inhibitors grew rapidly, mainly because it was discovered that a small but significant percentage of non-small cell lung cancer (NSCLC) patients carries the oncogenic fusion protein EML4-ALK, in addition to about half percent of anaplastic large cell lymphoma (ALCL) patients, an aggressive but definitely rarer non Hodgkin's T cell lymphoma, and other malignancies. Moreover the first ALK inhibitor, crizotinib (Xalkori or PF02341066) was successfully approved for the treatment of late stages or metastatic ALK+ NSCLC, giving a new, safer therapeutic option for those patients. As predicted from previous clinical experience with other kinase inhibitors, crizotinib resistance inevitably occurred, so the clinical availability of new compounds able to overcome crizotinib resistance became a priority. Recently the first clinical data from the phase I trial on ceritinib were published (N Engl J Med 2014;370:1189-97): 59 patients were enrolled in the dose-escalation phase while additional 71 patients were treated in the following expansion phase. For 19 patients relapsed upon crizotinib treatment, ceritinib was used as second line therapy. Collectively, ORR was 58%, 56% for patients who received crizotinib before. Maximum tolerated dose (MTD) was established at 750 mg daily, but more than half patients had to reduce the drug dose because of adverse events. Finally PFS was 7.0 months. Here we discuss the clinical data presented in this article, comparing ceritinib with the first line inhibitor crizotinib and another second generation ALK inhibitor, alectinib (Chugai-Roche).

Keywords: Anaplastic lymphoma kinase (ALK); non-small cell lung cancer (NSCLC); crizotinib; drug resistance

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The journal article "Ceritinib in ALK-rearranged non-small-cell lung cancer", published last 27th of March on the *New England Journal of Medicine* (*N Engl J Med*), reports for the first time the clinical data from the phase 1 study on the anaplastic lymphoma kinase (ALK) inhibitor ceritinib, also known as LDK-378 (Novartis).

In this study authors describe a first, dose-escalation phase, where also pharmacokinetic was evaluated after a single administration followed by a 3-day of evaluation period, and a second expansion phase in which a larger cohort of patients was evaluated upon the maximum tolerated dose (MTD) administration, 750 mg once daily. The study comprised a total of 130 patients, including 122 non-small cell lung cancer (NSCLC), 4 breast cancer, 1 alveolar rhabdomyosarcoma, 1 rectal adenocarcinoma, 1 anaplastic large cell lymphoma (ALCL) and 1 inflammatory myofibroblastic tumor (IMT). Among these, only patients affected by NSCLC, ALCL and IMT had a response as a consequence of ceritinib treatment. Because the ALK related diseases different from NSCLC were only a few cases, it is difficult to hypothesize a correlation between the kind of disease and the response to the treatment, nonetheless the absence of drug response in all four breast cancer patients is notably and these data should be expanded in the future with a larger cohort of patients whose breast tumor should be better characterized from a molecular point of view. About side effects, authors report that 49% of patients had Grade 3 or 4 adverse events, and 6% of them were forced to suspend therapy, while 62% of patients treated at 750 mg required at least one dose reduction.

Comparison with clinical data available on crizotinib and the Chugai-Roche pharmaceutical compound alectinib (1,2) revealed that patients treated with ceritinib underwent the highest percentage of grade 3 or 4 adverse events (49% compared to 24% for crizotinib and 37% for alectinib), that most commonly are increased alanine or aspartate aminotransferase levels, diarrhea and increased lipase levels. One of the most diffused crizotinib related adverse effects are visual disturbances, maybe due to ALK physiological expression in the central nervous system and in retina, followed by gastrointestinal events. Surprisingly visual effects were not observed upon ceritinib treatment, and this unlikely is due to the inhibition of the other crizotinib target, Met, since it is expressed mostly in hepatocytes and in basal keratinocytes surrounding the gastrointestinal trait. Almost half percent of patients treated with ceritinib were forced to reduce the dose, and 62% of those who received the MTD did. This percentage is extremely high, especially if compared to the one observed for other drugs (7% for crizotinib and none for alectinib). On the other hand the overall response rate for ceritinib was evaluated at 58%, almost similar to the one observed for crizotinib (60.8%), and the percentage of partial responses and complete responses comprised in this subset of patients were similar. Interestingly, the median progression free survival does not seem to be affected by the presence of brain metastasis, meaning that ceritinib is able to cross the blood brain barer and to act at the site of metastasis, while crizotinib ability to penetrate into the central nervous system is poor. As shown by the authors, the shrinkage in tumor burden and the likelihood of relapse are not correlated with previous crizotinib treatment, meaning that the mechanisms of resistance occurred upon any ALK inhibitor treatment may vary in response to the positive selection applied to the tumor. Again, tumor heterogeneity is the most difficult issue to deal with, so, despite promising data related to new tyrosine kinase inhibitors, many other drugs or new association with different compounds need to be explored. More than half percent of patients previously treated with crizotinib alone or crizotinib followed by common systemic agent before relapsed after ceritinib administration. Two of them carried ALK amplification, other two the gatekeeper L1196M mutation and in one case the G1269A and 1151Tins were detected, meaning that other ALK inhibitors or other strategies need to be considered in these cases. Notably ceritinib was active against the S1206Y mutation. All substitution mentioned are already known as crizotinib resistance conferring (3,4), so in this case ceritinib would not be recommended as a second line therapy. Notably in one L1196M case ceritinib caused tumor shrinkage of about 60% and the patient did not relapsed at time of cut-off. This mutation was probably the cause of crizotinib relapse, while during the administration of the following systemic therapy other mechanisms of resistance were positively selected and residual L1196M clones never counter-selected, so still present in the tumor bulk. It would be interesting to know which was the percentage of gatekeeper mutated clones at the time when the first ceritinib administration occurred, since we cannot exclude that this mutation could be again positively selected by the drug, causing the new relapse. Finally, S1206Y mutation seems to be sensitive to ceritinib. Authors report also that PFS in patients never treated with Crizotinib was not reached at time of cut-off, while for those who already received crizotinib was 6.9 months. Despite this impressive data, maybe crizotinib is still the better option for a first line therapy, mainly because of the high frequency and severity of side effects. However crizotinib used as first line therapy had a PFS of 18 months in a study whose cut-off was established at 21 months, while ceritinib data were collected before, at no more than 15 months, so it is still too early to compare these data. Together, all these results support the idea that ceritinib can be considered as a valid therapeutic alternative, especially in case of brain metastasis or in the presence of a crizotinib resistance conferring mutation that is proven to be sensitive to this drug, like the S1206Y, even if a long term follow-up is required. In any case, considering the high incidence and the severity of known side effect, the general status of the patient and the dose to be administered should be strictly assessed by the clinician before starting ceritinib treatment, since the ratio risk/benefits may not be always favourable.

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