Commentary

Ceritinib in second and further lines of therapy in advanced ALK mutant adenocarcinoma

György Losonczy

Department of Pulmonology, Semmelweis University, Budapest, Hungary

Correspondence to: György Losonczy, MD, PhD, DSc, professor of pulmonology and clinical oncology. Department of Pulmonology, Semmelweis University, Diós árok 1/c, 1125 Budapest, Hungary. Email: losonczygyrgy@gmail.com.

Submitted Apr 24, 2016. Accepted for publication May 05, 2016.
doi: 10.21037/jtd.2016.05.53
View this article at: http://dx.doi.org/10.21037/jtd.2016.05.53

Crizotinib is the first approved ALK inhibitor in advanced, ALK-positive non-small cell lung cancer (NSCLC). When administered in first line, median progression-free survival (mPFS) was 10.9 months (ms) with crizotinib versus 7.0 ms with best cytostatic chemotherapy. Overall response rate was 74% with crizotinib versus 45% with chemotherapy (1). In second line mPFS of 7.7 ms has been reported with crizotinib versus 3.0 ms with chemotherapy (2). Thus, crizotinib has proved to be more effective than chemotherapy in advanced, ALK-positive NSCLC. But there are limitations: (I) majority of patients develop resistance to this drug within 1–2 years from initiation of treatment and (II) crizotinib has poor activity against central nervous system (CNS) metastasis of ALK-positive NSCLC. CNS concentration of crizotinib is three orders of magnitude less than the plasma concentration (3). While crizotinib treatment has been documented to provide median overall survival (OS) as long as 49.5 ms, within this same patient population the median intracranial progression-free interval was only 11.9 ms (4). Crizotinib is relatively weak against CNS metastasis formation or progression, therefore close CNS observation seems to be critical during crizotinib treatment.

Ceritinib is a more potent ALK inhibitor than crizotinib *in vitro* (5), crosses the blood-brain barrier *in vivo* (6) and shows clinical responses in patients with crizotinib-resistant disease (7). In the currently commented paper of Shaw *et al.* the whole-body activity of ceritinib was assessed in crizotinib-naive and crizotinib-pretreated patients with ALK-rearranged advanced NSCLC (8). This was an open-label, phase 1, dose-escalation and expansion phase study that recruited 255 patients in three continents. In most patients ceritinib was administered in 2nd or further line of treatment. The recommended dose of oral ceritinib was 750 mg/day and data were analysed of all patients who received at least one 750 mg dose of the drug. Frequency of brain metastasis was 31% and 60% among crizotinib-naive and crizotinib-pretreated patients, respectively. Many of them have undergone brain radiotherapy before inclusion. CNS metastasis was under control and symptomless in all patients at entering the ceritinib study.

Patient enrollment lasted for 30 ms, the median duration of response to ceritinib was 17.0 ms in crizotinib-naive as compared to 8.3 ms in crizotinib-pretreated patients. A similar difference was demonstrated between the two groups concerning mPFS, 18.4 and 6.9 ms, respectively (the median OS has not been reached, yet). Intracranial disease control rate was 79% among those who had MRI or CT assessed metastasis at the time of entering the study. There were 11 patients with measurable CNS metastasis and treated only with ceritinib afterwards (no previous irradiation). Six out of these 11 patients responded with MRI/CT documented partial regression of the brain metastasis. The most common grade 3–4 non-laboratory adverse events were diarrhoea and nausea, both of which occurred in 6% of ceritinib-treated patients. One case of interstitial lung disease and an other of infection and ischaemic hepatatitis were the two deaths deemed to be study-drug related.

Thus, 2nd or further line ceritinib can provide (I) an additional 6.9 ms of mPFS in crizotinib-pretreated and 17.0 ms mPFS in crizotinib-naive patients and (II) potent control of intracranial metastasis formation or progression in both crizotinib-naive and pretreated patients suffering

from advanced NSCLC. The results of this study identify ceritinib as a new targeted biological therapy of advanced, ALK-mutated NSCLC. In these advanced lung cancer patients ceritinib may be more potent than crizotinib in slowing down not only the extra- but the intracranial progression, as well.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Long Jiang (Second Affiliated Hospital, Institute of Respiratory Diseases, Zhejiang University School of Medicine, Hangzhou, China).
Conflicts of Interest: The author has no conflicts of interest to declare.

Comment on: Kim DW, Mehra R, Tan DS, *et al*. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452-63.

References

1. Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med 2014;371:2167-77.
2. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-94.
3. Metro G, Lunardi G, Floridi P, et al. CSF Concentration of Crizotinib in Two ALK-Positive Non-Small-Cell Lung Cancer Patients with CNS Metastases Deriving Clinical Benefit from Treatment. J Thorac Oncol 2015;10:e26-7.
4. Johung KL, Yeh N, Desai NB, et al. Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. J Clin Oncol 2016;34:123-9.
5. Friboulet L, Li N, Katayama R, et al. The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. Cancer Discov 2014;4:662-73.
6. NOVARTIS. Novartis personalized cell therapy CTL019 receives FDA Breakthrough Therapy designation. 2014. Available online: https://www.novartis.com/news/media-releases/novartis-personalized-cell-therapy-ctl019-receives-fda-breakthrough-therapy
7. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-97.
8. Kim DW, Mehra R, Tan DS, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452-63.

Cite this article as: Losonczy G. Ceritinib in second and further lines of therapy in advanced ALK mutant adenocarcinoma. J Thorac Dis 2016;8(7):E584-E585. doi: 10.21037/jtd.2016.05.53

