Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC

We read with interest the article published by Ou et al. [1] exploring the benefit of continuing anaplastic lymphoma receptor (ALK) inhibition with crizotinib beyond disease progression (CBPD) in patients with advanced ALK-positive non-small-cell lung cancer (NSCLC). Patients continuing CBPD had significantly longer overall survival from the time of progressive disease (PD) (median 16.4 versus 3.9 months; hazard ratio 0.27; 95% confidence interval 0.17–0.42; P < 0.0001). This is an important message for patient’s management but the article may be discussed on several points.

First, results are retrospectively extrapolated from two trials (PROFILE 1001 and PROFILE 1005) which were not designed for this end point. This is not a randomized comparison and there is an imbalance on Eastern Cooperative Oncology Group performance status (ECOG PS) at progression in favor of CBPD: only 3.3% of patients are ECOG PS 2–3 in CBPD group, versus 19% in the other group. This may reflect different biological mechanisms of resistance, indolent disease in one hand, highly aggressive disease in the other hands. In EGFR-mutated NSCLC, occurrence of T790M reflects a more indolent disease with a better outcome [2]. Furthermore, authors underline that the control group may have been undertreated but the type of subsequent treatments was not captured, in particular the exposure to pemetrexed, an effective cytotoxic in this setting.

Second, Response Evaluation Criteria In Solid Tumor (RECIST) uses only unidimensional measurements and does not include functional imaging methods such as [18F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET), volumetric assessment and advanced magnetic resonance techniques which may provide additional value in early assessment. Moreover, low disease burden has been correlated to a higher progression free survival, a criteria that has not been collected here [3].

Third, trials 1001 and 1005 were not designed to be holistic in the way they capture PD. The management of patient progressing with crizotinib could be based on recommendations for patients with epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKI) acquired resistance: patients with asymptomatic and indolent growth should continue TKI; patients with symptomatic multiple sites should be rebiopsied and receive chemotherapy and TKI or be included in a clinical trial; patients with single site of progression should be treated locally and resume TKI [4].

Fourth, some patients experience acute exacerbation, known as disease flare, after withdrawal of EGFR-TKI [5]. A few cases have recently been reported with crizotinib, but the incidence of disease flare is unknown, and difficult to anticipate. Although rechallenge is reportedly effective for disease flare after discontinuation of EGFR-TKI and maybe after ALK inhibitor, rapid disease progression may deprive the patients of a second chance.

Finally, management of patient with advanced ALK-positive NSCLC developing PD with crizotinib is a relevant question and remains unclear. Continuing CBPD may be a reasonable option in some cases as shown in Ou et al. study. A randomized prospective trial would be mandatory to validate this hypothesis. Such a trial is unlikely to be developed now that there are second-generation ALK TKIs in the field. The real question is: will patients continuing CBPD have the same benefit to second-generation inhibitors that the ones that are switched immediately after RECIST progression?

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disclosure

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references


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