



Crizotinib in ROS1-positive non-small cell lung cancer: an Asian large phase II trial confirms its key-role

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The *ROS1* oncogene encodes an orphan receptor tyrosine kinase related to anaplastic lymphoma kinase (ALK), along with members of the insulin-receptor family (1). *ROS1* rearrangement can be found in several human cancers as cholangiocarcinoma, gastric cancer, ovarian cancer, glioblastoma multiforme, and with therapeutic implications in non-small cell lung cancer (NSCLC) (2-4). As a consequence of the rearrangement, a portion of *ROS1*, that includes the entire tyrosine kinase domain, is fused with 1 of 12 different pattern proteins (5). The *ROS1* fusion kinases resulting from rearrangement are constitutively activated and drive cellular neoplastic transformation.

The incidence of *ROS1* rearrangements in NSCLC is not high, resulting about 1%, but if we considered only the never smoking population, it would be certainly higher (6). Clinical characteristics of patients with *ROS1* rearrangements are similar to those of ALK positive patients (adenocarcinoma histology, younger age at diagnosis, never or light smokers). However, *ROS1* rearrangements are mutually exclusive with ALK translocations as with *EGFR*, *HER2*, *KRAS* and *BRAF* mutations (7), but their prognostic role remains to be defined. Patterns of metastatic spread in *ROS1* positive NSCLC are different from ALK-positive NSCLC. In fact at diagnosis ROS-positive patients have lower rates, compared with ALK-positive patients, of extrathoracic metastases (59% versus 83%) including brain metastases (19% versus 39%), but experience similar overall survival (3 versus 2.5 years) (6).

Importantly, *ROS1* is phylogenetically related to the ALK receptor tyrosine kinase. Thus, like ALK

rearrangements in NSCLC, *ROS1* fusions confer sensitivity to the ALK/*ROS1*/MET inhibitor crizotinib (7). Moreover, in preclinical models, crizotinib seems more effective in *ROS1*-positive than in ALK-positive NSCLC. However, crizotinib was originally developed as a MET inhibitor, and subsequently approved for ALK-positive NSCLC. A very relevant phase I study named PROFILE 1001 enrolled also 50 patients with advanced *ROS1*-positive NSCLC that were treated with crizotinib. The authors reported in this patient population a very high antitumor activity with an objective response rate (ORR) of 72% and a median progression-free survival (PFS) of 19.2 months (8). Also the median duration of response was relevant, resulting 17.6 months. Moreover, the authors did not report any correlations between the type of *ROS1* rearrangement and the duration of treatment with crizotinib. Some retrospective analyses and prospective phase II trials reported similar response rates compared with PROFILE 1001, although shorter median PFS outcomes (range, 9.1–13.4 months) (9-12). Based upon this activity, the U.S. Food and Drug Administration, Europe and Asian countries expanded crizotinib's approval to patients with advanced *ROS1*-positive NSCLC, also without a randomized phase III trial because of the low incidence of this molecular subgroup of NSCLC.

Wu *et al.* very recently confirmed in a large prospective phase II, open-label, single-arm trial, the role of crizotinib in the treatment of ROS-1 positive advanced NSCLC (13). The authors enrolled, in East Asia, patients with advanced NSCLC harbouring a *ROS1* rearrangement and that were pretreated with three or less lines of systemic therapies.

In this trial *ROS1* rearrangements were found through validated AmoyDx assay (Amoy Diagnostics, Xiamen, China). Crizotinib was administered orally at the dose of 250 mg twice daily and continued until progression or unacceptable toxicity. The primary end point of the study was ORR, and in 16 months, 127 patients with *ROS1*-positive NSCLC were enrolled at 37 sites in China, Japan, South Korea, and Taiwan. An ORR of 30% was considered by the authors a clinically meaningful threshold for this study, and a lower limit of the two-sided 95% CI around the observed ORR greater than this threshold would have demonstrated the efficacy of crizotinib. The antitumor activity was clinically meaningful and consistent with previous reports. In fact the authors reported an ORR of 71.7% (95% CI, 63.0–79.3%). Moreover, in 17 patients a complete response was reported, while the remaining 74 patients experienced a partial response. Thus, the primary end point ORR met the statistical prospectively defined criteria, and the positive treatment outcomes were reported both in patients with and without brain metastases and irrespective of the number of previous lines of systemic therapies. Moreover, treatment outcomes were also independent of enrollment country, age, sex, smoking status, or ECOG performance status. The onset of antitumor activity was also rapid, with a reported median time to response of 1.9 months (range, 1.6–15.8 months). Moreover responses were durable as expected from previous studies (median duration of response, 19.7 months; 95% CI, 14.1 months to not reached). It is clinically relevant that among the 63 patients whose disease progressed during treatment with crizotinib, 43 (68.3%) were treated beyond progression with crizotinib for 3 or more weeks (median duration, 20.7; range, 3.3–92.7 weeks). The other very important clinical outcome reported by Wu *et al.* for crizotinib in patients with *ROS1*-positive NSCLC was a long median PFS, resulted 15.9 months (95% CI, 12.9–24.0 months). Moreover, it is to be considered that 45 (35.4%) of 127 patients were still in follow-up for PFS at data cutoff. As stated before, clinical benefit was reported both for patients with (n=23) and without (n=104) baseline brain metastases, and median PFS resulted 10.2 months (95% CI, 5.6–13.1 months) and 18.8 months (95% CI, 13.1 months to not reached), respectively in the two patient subgroups. Although median survival was not a primary endpoint of this trial, the reported median overall survival of 32.5 months (95% CI, 32.5 months to not reached) is very promising, also considering that 59.8% of patients were still in follow-up at data cutoff. This study is relevant

considering that it is not only the first prospective phase II trial in East Asian patients but also the largest phase II trial of crizotinib in patients with advanced NSCLC harbouring a *ROS1* rearrangement. The antitumor activity reported in this trial (ORR 71.7%), is to be considered a clinically relevant outcome and similar to that reported by Shaw *et al.* in the PROFILE 1001 trial (69.8%) (8) and to antitumor activity data from two prospective European phase II trials (10,11). Also the timing of the response onset was early and similar in PROFILE 1001 and in the Asian study by Wu *et al.* Although the primary endpoint of the Asian trial was response rate, the result in terms of PFS is impressive (median, 15.9 months) and confirming the previous outcome reported in the PROFILE 1001 trial (19.2 months) (8). It is relevant that also Wu *et al.* reported clinical benefit achieved with crizotinib irrespective of the clinical characteristic of the patients as observed previously by other authors. In particular, antitumor activity was demonstrated independently of the number of previous lines of systemic therapies administered. Intracranial response was not assessed and this was considered also by the authors a limitation of this trial. Overall, the current results demonstrate that crizotinib is clinically effective and should be considered the standard of care for the treatment of patients with *ROS1*-positive NSCLC. In PROFILE 1001, in 49 of 50 patients (98%) *ROS1* rearrangement was identified using break-apart fluorescence *in situ* hybridization (FISH), while *ROS1* fusion partners were identified with the use of next-generation sequencing or reverse transcriptase-polymerase chain reaction (RT-PCR) assays (8). Wu *et al.* assessed *ROS1* rearrangements through an RT-PCR assay (AmoyDx) that is able to detect the majority of *ROS1* rearrangements in lung cancer (14). The other widely used technique to detect *ROS1* rearrangements and consequently to select patients to be treated with crizotinib is FISH. Another approach is to screen patients for *ROS1* rearrangement by immunohistochemistry, as performed in the European trial, *acsè* (secured access to crizotinib for patients with tumors harboring a genomic alteration on one of the biological targets of the drug) (10). However, the AmoyDx RT-PCR diagnostic test used by Wu *et al.* in the Asian trial, guarantees a sensitivity of 100% and a specificity of 85% to 100% to detect *ROS1* rearrangements when compared to FISH (15,16). Thus, this test can be considered very effective to select patients with tumors harbouring *ROS1* rearrangements and to be consequently treated with crizotinib. In terms of toxicity profile, Wu *et al.* did not report for crizotinib in this patient

population unexpected toxicities (8,17,18). Most adverse events reported by Wu *et al.* were mild, with no grade 5 treatment related adverse events observed, which indicates that the safety profile of crizotinib was generally good. Adverse events related to crizotinib treatment were easily managed by dosing interruptions and or reductions, and the rate of definitive treatment discontinuation due to toxicity was extremely low. Another relevant clinical outcome reported by Wu *et al.* was a trend toward an improvement in patient-reported global quality of life and reduction of lung cancer-related symptoms. Although the impressive treatment outcomes achieved with crizotinib in patients with ROS1-positive NSCLC, resistance to crizotinib finally occurs, as reported also by Wu *et al.* Secondary mutations, epidermal growth factor receptor activation, and epithelial-to mesenchymal transition are the main molecular mechanisms leading to resistance (19). Thus, although the excellent results achievable with crizotinib in this patient population, acquired resistance is a relevant clinical issue yet to be solved (6). Seven secondary ROS1 resistance mutations have been reported (19-21), and up-regulation of bypass signaling pathways (e.g., EGFR, RAS, and KIT) have also been observed (22).

Gainor *et al.* recently presented a large study on the mechanisms of resistance to crizotinib in patients with ROS1-positive NSCLC (6). The authors reported a secondary ROS1 resistance mutation as the main finding, especially when they considered the non-central nervous system (CNS) progressions during crizotinib treatment. Probably this reflects the low CNS penetration of crizotinib. Interestingly, a majority of these alterations were concentrated at one residue (G2032R). The frequency and spectrum of on-target mechanisms of crizotinib resistance in ALK- and ROS1-positive NSCLC is different. Indeed, ROS1-positive patients have a much higher frequency of on-target resistance mutations, but such mutations are concentrated in a narrower segment of the kinase, perhaps reflecting the greater activity of crizotinib against ROS1-compared to ALK-positive NSCLC.

Data on cabozantinib, a multi-targeted TKI, and on lorlatinib, a next-generation ALK/ROS1 inhibitor have been accumulating, and clinical trials are ongoing, as potential drugs overcoming the resistance of ROS1-positive NSCLC to crizotinib (23,24). In the next future, we can hope to have the possibility to administer sequentially more than one targeted agents against ROS1-positive NSCLC as we can already do for patients with ALK-positive NSCLC, in order to further improve the treatment outcomes in this

patient population. In conclusion, Wu *et al.* have confirmed that crizotinib offers impressive treatment outcomes in terms of antitumor activity, quality of life, lung cancer symptoms control and safety profile in patients with ROS1-positive advanced NSCLC, also in Asian patients, to the extent to be considered the standard first-line treatment in this molecular subgroup of NSCLC. Moreover, this Asian trial stimulates further prospective clinical trials with drugs aimed at overcoming resistance to crizotinib in this specific patient population.

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Footnote

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