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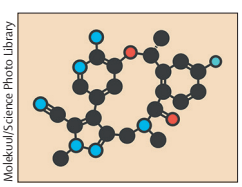
Lorlatinib: a new treatment option for *ROS1*-positive lung cancer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Published **Online**
October 25, 2019
https://doi.org/10.1016/S1470-2045(19)30716-8

See **Articles** page 1691

Chromosomal rearrangements of *ROS1* occur in 1–2% of patients with non-small-cell lung cancer (NSCLC). The ROS1 tyrosine kinase inhibitor (TKI) crizotinib provides a marked clinical efficacy in TKI-naive *ROS1*-positive patients in clinical trials, with an overall response of 65–72% and an expected median progression-free survival of 19 months.[1–4] Crizotinib is recommended in the first-line setting for *ROS1*-positive patients.[5] However, the majority of crizotinib-treated *ROS1*-positive patients will experience disease progression. Two main mechanisms of resistance have been described: on-target mutations, the most common of which is Gly2032Arg, and progression in the CNS, which occurs in 30–50% of patients.[6] The development of resistance to crizotinib and the scarcity of next-line treatment options represent an unmet medical need.

Lorlatinib is a potent, orally available, CNS-penetrant, selective ROS1 TKI. In preclinical models, lorlatinib can inhibit the Gly2032Arg resistance mutation.[7] In the phase 1 portion of an ongoing phase 1–2 study (NCT01970865), lorlatinib showed preliminary antitumour activity in *ROS1*-positive patients. In *The Lancet Oncology*, Alice T Shaw and colleagues[8] report the clinical activity, safety results, and molecular analysis from the phase 1–2 expansion part of this ongoing study that evaluates lorlatinib in *ROS1*-positive patients. The primary endpoints were the proportions of patients achieving an objective response and an intracranial response. Lorlatinib was evaluated in 21 TKI-naive patients and 48 TKI-pretreated patients, of whom 40 received crizotinib as their only TKI. Lorlatinib was administered orally at a dose of 100 mg daily in continuous 21-day cycles, with the exception of ten patients in phase 1 of the study who received doses ranging from 10 mg daily to 100 mg twice daily.

Among TKI-naive patients, 13 (62%, 95% CI 38–82) had an objective response; the median duration of response was 25·3 months (95% CI 7·5–31·9) and median progression-free survival was 21·0 months (95% CI 4·2–31·9). Waterfall plots summarising the best percentage change from baseline showed deep responses in the majority of patients. Among crizotinib-pretreated patients, 14 (35%, 95% CI 21–52) had an objective response; the median duration of response was 13·8 months (95% CI 9·7 to not reached) and the median progression-free survival was 8·5 months (95% CI 4·7–15·2). Deep responses were also reported in the majority of these patients. Lorlatinib showed potent intracranial activity, in both TKI-naive and TKI-pretreated patients.

The results from this study help to define a sequencing strategy for ROS1 TKIs. Lorlatinib does not seem to be superior to crizotinib in TKI-naive patients. Overall response, duration of response, and progression-free survival with lorlatinib are similar to those observed with crizotinib in the PROFILE 1001 trial.[1] The efficacy of the ROS1 TKIs ceritinib (overall response 67%, median duration of response 21·0 months, median progression-free survival 19·3 months) and entrectinib (overall response 77%, median duration of response 24·6 months, median progression-free survival 19·0 months) are also similar to that of crizotinib.[9,10] The safety profile of crizotinib is more favourable than that of lorlatinib. Therefore, we can conclude that crizotinib is still our first-line treatment of choice.

The clinical activity of lorlatinib in crizotinib-resistant patients is meaningful. This study represents the first clinical trial showing ROS1 TKI activity in crizotinib-resistant patients. The overall response with lorlatinib is likely to be similar to that achievable with chemotherapy, and the responses are durable. Of note,

CNS progression was delayed compared with non-CNS progression, whether or not baseline CNS metastasis was present. Because lorlatinib is likely to be better tolerated than platinum-pemetrexed chemotherapy and is able to effectively treat and prevent CNS progression, it represents a good treatment option in the case of crizotinib failure.

The analysis of baseline *ROS1* resistance mutations in the study by Shaw and colleagues provides an insight into resistance mechanisms to crizotinib. *ROS1* mutations were detected in 15% of plasma samples and in 24% of tumour tissue samples. Gly2032Arg was the most common mutation detected. The response was lower in patients with *ROS1* mutations detected in plasma samples (none of six patients) compared with those without mutations detected (nine [27%] of 33 patients), and higher in patients with *ROS1* mutations detected in tissue samples (two [40%] of five patients) compared with those without (one [9%] of 11 patients). Of note, no responses to lorlatinib were observed in the six patients with Gly2032Arg mutations. We must be cautious in interpreting the results from this small dataset. Nevertheless, preclinical evidence of lorlatinib activity on Gly2032Arg does not seem to translate to the clinic.[7] The proportion of *ROS1* mutations in plasma samples was lower than previously reported, highlighting the limitations of plasma genotyping in this setting. The detection of *ROS1* mutations is not yet a reliable biomarker of lorlatinib clinical activity and further dedicated studies are needed.

This study establishes lorlatinib as an effective treatment option after crizotinib failure in *ROS1*-positive patients. A chemotherapy-free crizotinib-lorlatinib sequence is emerging as a treatment strategy of choice, with an expected cumulated progression-free survival of up to 27–28 months. Combined with the median overall survival of 51·4 months seen in crizotinib-treated patients in the PROFILE 1001 trial,[1] these data highlight the importance of systematic, reliable ROS1 molecular testing in all patients with non-squamous advanced NSCLC. Many other ROS1 TKIs with promising activity, such as entrectinib, brigatinib, repotrectinib, and DS-6051b, are being investigated and could extend the survival of *ROS1*-positive patients.

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I report personal fees and non-financial support from Roche, Bristol-Myers Squibb, Takeda, and Boehringer Ingelheim; non-financial support from Nanostring and Blueprint; and personal fees from Merck Sharp & Dohme, AstraZeneca, and AbbVie, outside the submitted work.

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Tumour Treating Fields for mesothelioma: controversy versus opportunity

The challenge of improving standard-of-care chemotherapy with pemetrexed and cisplatin for mesothelioma has proven to be virtually insurmountable since 2004. The addition of novel agents to standard chemotherapy in phase 3 trials has not succeeded in changing practice. Therefore, the front-line treatment setting remains a formidable hurdle for drug developers.

Published **Online** October 15, 2019 https://doi.org/10.1016/S1470-2045(19)30642-4
See **Articles** page 1702