Review Article



# ROS1 non-small cell lung cancer patients treatment approach

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**Abstract:** Initially described in glioblastomas, *ROS1* rearrangements have been later found in multiple tumors as NSCLC, cholangiocarcinoma, ovarian cancer, gastric cancer, colorectal cancer, angiosarcoma, inflammatory myofibroblastic tumor and spitzoid melanoma. Detection of *ROS1* rearrangements identified a subgroup of patients with clinical characteristics similar to *ALK*-rearranged NSCLC. Since the identification of *ROS1* as an oncogenic driver in NSCLC, treatment in this population has radically changed with the rising development of targeted therapy. Although *ROS1*-rearranged tumors only represent around 1–2% of NSCLC, impact of targeted therapy in this population makes essential to identify them. Regulatory agencies initially approved crizotinib as first *ROS1* targeted treatment in 2016. Since then, development of new therapeutic agents has multiplied. Ceritinib, lorlatinib, brigatinib and entrectinib have also been tested in this population, with the approval of the last one as first line treatment in *ROS1* rearranged NSCLC. Other therapeutic agents as repotrectinib are currently under investigation. Some studies have also reviewed the efficacy of other therapies as chemotherapy or immunotherapy in this specific population. Increasing interest in the biology underlying resistance mechanisms has also emerged, as well as means to improve CNS disease control. This article aims to review the different available therapies for *ROS1* rearranged NSCLC patients.

**Keywords:** ROS1; non-small cell lung cancer (NSCLC); targeted therapy

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## Introduction

Successful development of targeted therapies in *EGFR* and *ALK*-driven tumors led to substantial improvement of outcomes in these oncogenic-driven populations. Later on, new oncogenic targets have been identified such as the rearranged proto-oncogene *ROS1*.

Presence of *ROS1* fusion leads to expression of ROS1 tyrosine kinase receptor (TKR) and subsequent activation of MAPK/EPK, PI3K/AKT, JAK/STAT3 and SHP1/2 pathways, resulting in cell growth signals. Interestingly, ROS1 TKR shares a large part of its amino acid sequence with ALK TKR, with whom an evolutionarily relation has been established (1).

Initially described in glioblastomas, *ROS1* rearrangements have been later found in multiple tumors as NSCLC, cholangiocarcinoma, ovarian cancer, gastric cancer, colorectal cancer, angiosarcoma, inflammatory myofibroblastic tumor and spitzoid melanoma.

Detection of *ROS1* rearrangements identified a subgroup of patients with clinical characteristics similar to *ALK*-rearranged NSCLC: younger patients, never-smokers, with adenocarcinoma histology (2) and a higher incidence of CNS metastases, reaching between 18% and 46% of the patients at the time of diagnosis (3).

Although *ROS1*-rearranged tumors only represent around 1–2% of NSCLC, impact of targeted therapy in this population makes essential to identify them.

There is not a unique option to detect *ROS1* rearrangements, but several different tests. Early studies

of *ROS1* tyrosine kinase inhibitors (TKIs) used single-gene assays as fluorescence *in situ* hybridization (FISH) and RT-PCR. However, they can under-detect some rearrangements. In recent years, there has been an increasing use of DNA-based or RNA-based next-generation sequencing, as they enable to detect *ROS1* rearrangements undetectable by other techniques. Immunohistochemistry assays have a low specificity, and their use should be limited to screening purposes, always followed by confirmation tests (4).

The introduction of *ROS1* TKIs as standard care has also increased interest in the biology underlying resistance mechanisms. Data about both exact frequency of resistance mutations in pre-treated patients is scarce, as well as about primary resistance mechanisms. One study analyzed mechanisms of resistance in *ROS1* tumors after progression to crizotinib, identifying *ROS1* resistance mutations in 9 (53%) of 17 patients, including G2032R (41%), D2033N (6%) and S1986F (6%) (5). Both G2032R and D2033N are known solvent-front mutations that prevent crizotinib binding. Interestingly, one specimen contained characteristics consistent with epithelial-to-mesenchymal transition.

Since the first approval in 2016, development of new therapeutic agents has multiplied. Here we summarize the different therapeutic options in this population.

## Crizotinib

Crizotinib is a multiple TKI, with affinity for ROS1, MET and ALK. Originally developed as MET inhibitor, PROFILE 1001 (6) was the first clinical trial to assess its efficacy in patients with *ROS1*-rearranged non-small cell lung cancer (NSCLC). Initially designed to test crizotinib in *ALK*-rearranged tumors, the protocol was amended to include *ROS1*-rearranged tumors in an expansion cohort due to favorable results of preclinical activity and reported clinical responses in case reports.

Fifty patients were included and received crizotinib 250mg twice daily after identifying *ROS1* rearrangement by fluorescence *in situ* hybridization (FISH) or reverse-transcriptase-polymerase-chain-reaction assay (RT-PCR). Most of them were women (56%), Caucasian (54%), never-smokers (78%) with adenocarcinoma histology (98%). Baseline brain imaging was no mandatory and they had received a median of one line of treatment previously.

Overall response rate (ORR) was 72%, with 66% of patients having a partial response and 6% a complete response. Median progression-free survival (PFS) was 19.2 months and overall survival (OS) rate at 12 months was 85%. Updated results (7) at a median follow up time of 62.6 months showed a PFS of 19.3 months and a median OS of 51.4 months.

Treatment-related adverse events were mostly (94%) grade 1 or 2 using common terminology criteria for adverse events (CTCAE). Most common events were visual impairment (82%), diarrhea (44%), nausea (40%), peripheral edema (34%), constipation (34%) and vomiting (34%). Grade 3 treatment-related adverse events consisted of vomiting (2%), elevated aspartate aminotransferase (2%) or alanine aminotransferase (4%), hypophosphatemia (10%) and neutropenia (10%). Only one patient discontinued treatment because of grade 3 nausea.

Afterwards, a French group evaluated the efficacy of crizotinib in *ROS1* rearranged NSCLC patients in a multiple-cohort phase II trial (8). Of 5,606 tumor samples tested, 78 *ROS1* translocated tumors were identified using immunochemistry (IHC) and FISH as confirmatory assay. Thirty-seven patients were enrolled in the *ROS1* cohort and received crizotinib 250 mg twice a day. Most of the patients were women (70%), with an Eastern Cooperative Oncology Group (ECOG) performance status 1 (44%) and never smokers (70%). They had received a median of 2 lines of treatment previously and mostly had adenocarcinoma histology (89%). Baseline brain imaging was mandatory, with 21% of patients having brain metastases at inclusion.

In the *ROS1* cohort, ORR was 47.2%, median PFS 5.5 months and median OS 17 months. Differences respect the phase I study results were possibly due to differences between population characteristics of both studies. Safety profile was consistent with previous reports, with mostly grade 1 or 2 treatment-related adverse events.

An additional phase II trial was carried out in East Asian patients (9). In this study, 127 patients were enrolled after finding *ROS1* rearrangement by RT-PCR. They were mostly women (57.5%), non-smokers (71.7%), ECOG PS 1 (73.2%) with adenocarcinoma histology (97.6%). At baseline, 18.1% of patients had brain metastases, and had received a median of one line of treatment previously. ORR was 71.7%, with 17 patients achieving a complete response. Median PFS was 15.9 months and median OS 32.5 months. Patients with brain metastases had similar ORR (73.9%) but shorter PFS (10.2 *vs.* 18.8 months in patients without intracranial disease), although these differences were not statistically significant. Consistent with previous studies, only 22% of grade 3 treatment-related adverse events were observed and

a 3.1% of grade 4, mostly abnormal laboratory findings.

Based on the results of the phase one study, crizotinib was the first *ROS1* approved targeted therapy in March 2016 by the Food and Drug Administration (FDA) and subsequently by the European Medicines Agency (EMA).

## Entrectinib

Entrectinib is a multiple kinase inhibitor, with affinity to ROS1, ALK, and tropomyosin receptors (TRK) A, B and C. Compared to crizotinib, it has achieved better inhibition activity on preclinical assays, as well as a compelling ability to cross the blood-brain barrier.

Patients with *ROS*1-rearranged advanced NSCLC included in three phase one or two trials (ALKA-372-001, STARTRK-1, STARTRK-2) have been examined in an integrated analysis (10). Fifty-three patients of the three trials were included in this efficacy analysis. They had not received previous treatment with *ROS1* targeted treatment, and they received entrectinib 600 mg or more once daily. Comparable to previous trials, most of the patients were women (64%), never smokers (59%), Caucasian (59%), ECOG PS 1 (51%) and with adenocarcinoma histology (98%). Interestingly, the percentage of patients with brain disease at baseline (43%) exceeded similar trials, even though brain imaging was not mandatory at baseline. They had received at least one line of systemic treatment in 68% of the patients, and 35% had required central nervous system radiotherapy.

Among the 53 patients, 77.3% had an objective response, with 3 (5.6%) complete responses and 38 (71.7%) partial responses. The overall intracranial response was 55% in patients with CNS disease. Median PFS was 19 months and median OS was not reached.

Regarding safety, 59% of adverse events were grade 1 or 2. Grade 3 and 4 represented 34 and 4% respectively, being the most common treatment-related adverse events neutropenia and weight increase. A small percentage (2%) of the patients required dose reduction due to confusion or mental status change, as well as another 15% due to other neurological symptoms such as paresthesia or dizziness.

Based on these results, FDA approved entrectinib as *ROS1* rearranged treatment on 2019. On May 2020, EMA's committee granted a conditional marketing authorization (11).

## Ceritinib

Ceritinib, a second-generation *ALK*, *ROS1*, insulin-like growth factor 1 receptor (IGF1R) and insulin receptor (INSR) inhibitor, has been tested in *ROS1*-rearranged NSCLC in a phase II Korean study (12). Thirty-two patients with *ROS1* fusion detected by FISH were included and received ceritinib 750 mg daily. Of them, 75% were females, 84% never-smokers and 100% with adenocarcinoma histology. They had received a median of 3 previous lines of treatment and, at baseline, 25% had asymptomatic or controlled brain metastases. Of note, two patients (6%) had received previously crizotinib.

Twenty-eight patients were evaluable for response. Four patients were excluded due to early progression, death or withdrawal related with toxicity, including both who had received crizotinib previously. In this evaluable population, ORR was 67%. Median PFS was 19.3 months and median OS 24 months. Overall intracranial response was 25%.

Concerning toxicity, all patients suffered at least one treatment-related adverse event. Most of them were grade 1 or 2, with 37% being grade 3 or higher. Excluding abnormal laboratory results, most common adverse events consisted of diarrhea, nausea and anorexia. One patient had to discontinue treatment with ceritinib due to treatment-related weakness and 68% required at least one dose adjustment.

## Lorlatinib

Lorlatinib is a third generation ALK and ROS1 TK inhibitor. It was tested in patients with *ROS1* rearranged metastatic NSCLC in a phase 1–2 trial (13). Sixty-nine patients were included after detection of ROS1 rearrangement by FISH, RT-PCR or next generation sequencing (NGS) techniques. Inclusion criteria admitted patients with asymptomatic brain metastases, treated or untreated, as well as leptomeningeal carcinomatosis. Patients received lorlatinib ranging from 10 mg daily to 100 mg twice a day if they were included in the phase one trial or 100 mg daily if they were in the phase two.

Among the 69 patients, 57% were females, 52% Caucasian and 32% Asian, with a PS1 (58%). A high number of the patients (57%) had brain metastases at baseline, which had been treated with radiotherapy in 49% of them. Only for 22% of the patients lorlatinib was the first line of treatment. In the previous-treated population, 40 patients had received crizotinib as only TKI previously, and 8 patients had received either another TKI or two or more TKI.

Of the 69 patients, 41% had an objective response. In the TKI-naive population, ORR was 62%, with 10%

of complete responses. Median PFS was 21 months and, among patients with brain metastases, intracranial response rate was 64%.

Responses were lower in the patients who had received crizotinib previously, with an ORR of 35% and a 5% of complete responses. Median PFS was 8.5 months and intracranial response rate 50%. Median duration of intracranial response was not reached neither in the TKI-naïve nor previous-crizotinib group.

Almost all patients (96%) suffered a treatment-related adverse event, mostly grade 1 or 2 (46%). Most common toxicity consisted of elevated levels of triglycerides and cholesterol, edema, peripheral neuropathy, and cognitive effects. Grade 3 was present in 43% of patients (mostly elevated levels of cholesterol or triglycerides), and grade 4 (6%) consisted on hypercholesterolemia, increase in AST or GGT and thrombocytopenia.

Clinical activity of lorlatinib is similar to other agents, with an interesting control of CNS disease and efficacy in a group of patients treated previously with crizotinib. Thus, lorlatinib represents an interesting option as second-line treatment, still neither approved by FDA nor EMA.

## Other tyrosine kinase inhibitors

### *Repotrectinib*

Repotrectinib is a ROS-1, TRK and ALK TK inhibitor. Its safety and efficacy in multiple tumors are being tested at the ongoing clinical trial TRIDENT-1. Preliminary results of the NSCLC ROS1 cohort have been reported (14).

Until July 2019, forty patients with ROS1 rearranged NSCLC were evaluable. They included 65% of females, 53% Asians, 50% of patients with CNS metastases, a median of two lines of previous treatments, and 28% of patients ROS1 TKI naïve.

Of the eleven TKI-naïve patients, ORR was 91%, with an intracranial response rate of 100% in the three patients with CNS disease. Median duration of response was not reached at the median follow up time of 20.1 months. Responses were lower in the group of patients who had received one ROS1 TKI (ORR 39% and intracranial ORR 75%) or at least two ROS1 TKI (ORR 29%).

Treatment-related adverse events most commonly reported were dizziness, dysgeusia, anemia, fatigue and constipation. Only 3.2% of grade 3 and no grade 4 were reported. A sudden death possibly related to treatment was reported.

### *Brigatinib*

Data about brigatinib in *ROS1* NSCLC is limited. A series of six patients (15) treated with brigatinib after progression to crizotinib showed an ORR of 25%. Three of the patients continued on treatment at 7.5 months. Three patients with *ROS1*-rearranged NSCLC were also included in a cohort of the phase 1–2 of brigatinib in *ALK*-rearranged NSCLC (16), two had received crizotinib previously. Only the crizotinib-naïve patient achieved a partial response, ongoing at 21.6 months of follow-up.

## Chemotherapy

Chemotherapy remains a standard treatment for *ROS1*-driven NSCLC. Specific activity of chemotherapy in *ROS1*-rearranged tumors in Asian population have been studied in one study, which retrospectively evaluated response to platinum-pemetrexed combination or pemetrexed monotherapy in different oncogenic-driven NSCLC (17). Nineteen patients with *ROS1* NSCLC were included. Of them, eleven patients had received treatment with platinum-pemetrexed (81% as first-line) with an ORR of 72.7%. Pemetrexed monotherapy obtained an ORR of 27.3% in the rest of them, who had a median of 2.8 previous lines of treatment. Median PFS of 7.5 months in the ROS1-rearranged NSCLC was superior to other molecular subgroups.

There are no direct comparisons between chemotherapy and TKI regimens. In a one-center retrospective study, they compared differences between their patients who had received crizotinib as first-line treatment (30 patients) and platinum-pemetrexed (47 patients) (18). Clinical characteristics were similar between both groups. Responses were higher in the crizotinib group, with an ORR of 86.7% compared with a 44.7%, and median PFS of 18.4 and 8.6 months, respectively. At the data cutoff, median OS in the crizotinib group was not reached and, in the platinum-pemetrexed group was 28.4 months. Interestingly, 37 patients received the other therapy at progression without differences in OS if they had received first crizotinib (7 patients, median OS 38.6 months) or platinum-pemetrexed (30 patients, median OS 32.8 months).

## Immunotherapy

The activity of immune checkpoint inhibitors in patients with oncogenic-driven NSCLC has also been evaluated.

One retrospective study included 551 patients of 10 different countries, of which 7 had *ROS1*-rearranged NSCLC. They mostly received anti-PD-1 treatment after at least one line of treatment. Regarding *ROS1*-rearranged cohort, patients were females (28.6%), never smokers (71.4%) and median PD-L1 expression was 90%. Except one patient, who showed an objective response, best response was progressive disease (19).

Unlike other oncogenic-driven NSCLC, there are no evidence to support the use of combination immunotherapy and chemotherapy in *ROS1* rearranged tumors.

## Conclusions

Many effective therapies have been developed in the last years after the discovery of *ROS1* as an oncogenic alteration. Despite excellent initial responses, most patients experience disease progression after some months, making development of newer agents a priority. Crizotinib and entrectinib are both effective first line treatments for patients with ROS1 rearranged tumors, being entrectinib a preferred option in those patients with brain metastases. Lorlatinib represents a reasonable option as second line treatment after any previous TKI. The final results of newer agents such as repotrectinib are eagerly awaited, both in the TKI-naïve and TKI-pretreated setting. Increasing interest in the biology underlying resistance mechanisms has also emerged, as well as means to improve CNS disease control; both being important challenges to overcome in this population.

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