

Taltrectinib: Transforming Outcomes in ROS1-Positive Non-Small Cell Lung Cancer

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Introduction

ROS1-rearranged non-small cell lung cancer (NSCLC) affects around 1–2% of patients globally and initially responds to crizotinib and entrectinib. However, both therapies face critical limitations: crizotinib shows poor brain penetration and fails against the G2032R resistance mutation, leading to frequent CNS relapse; entrectinib, despite improved intracranial activity, also cannot overcome G2032R. These shortcomings highlight a strong need for a next-generation Tyrosine Kinase Inhibitor (TKI) with potent ROS1 inhibition, effective CNS activity, and the ability to overcome resistance mutations [1].

Taltrectinib (AB-106/DS-6051b) is an oral, brain penetrant inhibitor selectively targeting ROS1 and NTRK fusions while sparing TRKB, potentially reducing neurologic toxicity. Preclinical studies confirmed potent activity against wild-type ROS1 and key resistance mutations, including G2032R [2]. In the phase II TRUST-I study involving 173 Chinese patients, taltrectinib delivered high systemic and intracranial confirmed objective response rates (cORR) 91% and 88% in TKI-naïve, and 52% and 73% in crizotinib-pretreated cohorts, with 67% of G2032R-positive patients responding. Toxicity was manageable: common side effects were mild Aspartate Aminotransferase/Aminotransferase (AST/ALT) elevations and diarrhea, while neurologic events like dizziness occurred in just 23% of patients [1, 2].

The TRUST-I (NCT04395677, China) and TRUST-II (NCT04919811, worldwide) Phase II trials were conducted to evaluate the effectiveness of taltrectinib in treating ROS1-positive non-small cell lung cancer (NSCLC). Tyrosine kinase inhibitor (TKI)-naïve and TKI-pretreated individuals were included in these open-label, single-arm investigations [3].

TKI-naïve patients had a median duration of response (DOR) of 44.2 months, a median progression-free survival (PFS) of 45.6 months, and an objective response rate

(ORR) of 88.8% in the pooled analysis. However, in TKI-pretreated patients, a median PFS of 9.7 months, a DOR of 16.6 months, and an ORR of approximately 55.8% were noticed [3].

Strong intracranial action was shown by taltrectinib. In TKI-naïve patients, the intracranial ORR was 76.5%, while in TKI-pretreated patients, it was 65.6%. This addresses an essential therapeutic need, as ROS1-positive NSCLC has a high rate of central nervous system (CNS) metastases. It also showed activity against the G2032R resistance mutation in TKI-pretreated patients with a confirmed ORR of 61.5% [3].

Taltrectinib is well tolerated and primarily causes grade 1-2 treatment-related side effects that include minor liver enzyme elevation and gastrointestinal (GI) symptoms, with a very low frequency of neurological side effects, such as dysgeusia and dizziness [2, 3].

Taltrectinib has dual activity against both systemic and intracranial disease. It showed great clinical significance by addressing the limitations of previous ROS1 inhibitors by showing robust intracranial activity, efficient central nervous system (CNS) penetration, and also demonstrating efficacy against resistance mutations, such as G2032R, making it a potential therapy for long-term control of CNS diseases [2].

Its use as a first-line therapy in ROS1-rearranged NSCLC is supported by its prolonged PFS, high response rate, and tolerable toxicity profile [3]. The information has resulted in revisions to treatment protocols and highlights the vital role of comprehensive molecular testing in NSCLC at both initial diagnosis and upon progression to enable the appropriate application of targeted treatments [4, 5].

In conclusion, taltrectinib is a promising therapeutic choice for front-line treatment of ROS1+NSCLC due to its potent intracranial activity, efficacy against resistance mutations, and favorable safety profile. As current data

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is largely based on the Chinese and North American population, its efficacy across backgrounds with different ethnicities and genetic make-up might be validated by conducting South Asian cohorts. Although the efficacy results are promising, further studies are still needed to declare taletrectinib a definitive treatment for ROS1.

Keywords:Antineoplastic agents, carcinoma, non-small-cell lung carcinoma, receptor protein tyrosine kinases, proto-oncogene proteins c-ros, blood-brain barrier treatment outcome, clinical trials, TRUST-I clinical trial, TRUST-II clinical trial

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None

Competing interests

None

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