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Letter to the Editor
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Efficacy of Taletrectinib to treat ROS1-positive non-small cell lung carcinoma

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INTRODUCTION:

Lung cancer represents the leading cause of death by cancer worldwide[1]. ROS-1 rearrangement is found in 0.9–2.6% of non-small-cell lung cancers (NSCLCs), most of which are adenocarcinomas of the lungs, with a significantly higher rate of women, non-smokers, and also tending to occur at a younger age[2]. Tyrosine kinase inhibitors, including crizotinib, entrectinib, lorlatinib[3], and repotrectinib, are FDA-approved therapies. Resistance mutations (most importantly G2032R) and brain metastases shorten long-term benefit[4].

In July 2024, the U.S. Food and Drug Administration (FDA) approved taletrectinib in adults with ROS1-positive metastatic NSCLC, both TKI-naïve and TKI-pretreated (following crizotinib or entrectinib). Approval was granted based on the TRUST-I (China) and TRUST-II (global) phase II studies, with efficacy powered by lasting systemic and intracranial responses by blinded independent central review (BICR)[5].

MECHANISM AND PHARMACOLOGY:

Taletrectinib is an oral, CNS-penetrating next-generation ROS1 and TRK inhibitor with activity against known resistance mutations. Preclinical studies have shown strong potency against G2032R, the most clinically relevant resistance mutation to date, and promising brain-to-plasma ratios consistent with CNS activity[6,7] . Although these observations are preclinical, they establish a mechanical rationale for the strong systemic and intracranial responses in clinical trials.

EFFICACY DATA:

In the TRUST-I and TRUST-II trials, taletrectinib demonstrated substantial clinical activity. Among TKI-naïve patients, the confirmed overall response rate (ORR) by BICR was 90% with a 95% confidence interval (CI) of 81–96, a median duration of response (DOR) of 44.2 months (95% CI, 27 months to not reached), and a median progression-free survival (PFS) of 36.8 months (95% CI, 24 months to not reached). Median follow-up was approximately 30 months[8]. In pretreated patients who received TKIs, primarily crizotinib and entrectinib in a minority, the established ORR according to BICR was 47.6% (95% CI, 36–59), the median DOR was 12.0 months (95% CI, 8–16), and the median PFS was 7.6 months (95% CI, 5–10), with a median follow-up of approximately 20 months[9]. Notably, in patients with measurable brain metastases, intracranial ORR according to RANO-BM was 65.6%, with some complete responses, establishing

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clinically relevant CNS activity. These results were observed in all patient subgroups irrespective of the history of prior radiotherapy[10].

CROSS-TRIAL CONTEXT:

The relative positioning of taletrectinib among currently available ROS1 inhibitors is instructive, although variations in design, patient selection, and assessment methodology inevitably constrain cross-trial comparisons. With a median PFS of 19 months and an ORR of roughly 72%, crizotinib demonstrated limited intracranial efficacy in PROFILE 1001 and later studies[11]. With higher intracranial penetration, entrectinib showed a median PFS of 19 months and an ORR of 68%[12]. In the TRIDENT-1 trial, repotrectinib produced an intracranial ORR of roughly 38% and an ORR of 79% in patients who had never taken a TKI and 39% in patients who had already received treatment[13]. On the other hand, taletrectinib resulted in longer DORs and higher CNS response rates in resistant settings, with ORRs of 90% in TKI-naïve patients and 48% in pretreated patients[14]. Although conclusive head-to-head data are still pending, these data support its role as an emerging preferred next-generation ROS1 inhibitor, especially for patients with CNS disease or G2032R resistance mutations[15].

SIDE EFFECTS AND COMPLICATIONS:

Most treatment-related adverse events (TRAEs) were manageable, though dose modifications were common.

Adverse Event (≥10%)	Any Grade (%)	Grade ≥3 (%)	Discontinuation (%)	Monitoring Guidance
ALT/AST elevation	40-45	7-9	3-4	Baseline + monthly LFTs; hold/reduce if ≥3× ULN
Diarrhea	35	2	<1	Supportive care; dose adjust if persistent
Nausea/vomiting	25-30	<2	<1	Antiemetics PRN
Fatigue	20	3	1	Assess for reversible causes
QTc prolongation	5	1	<1	Baseline + periodic ECGs
Interstitial lung disease	2	1	1	Educate on cough; hold drug immediately if suspected

Overall, grade ≥3 TRAEs occurred in ~30%, with permanent discontinuation in 5–7% of patients.

PLACE IN THERAPY:

Taletrectinib has several benefits over previous ROS1 inhibitors. Its potent systemic and intracranial activity in both treatment-naïve and resistant disease, even against the solvent front mutation G2032R, makes it a favorable first-line choice as well as a valuable second-line option after progression on crizotinib or entrectinib. The favorable safety profile and mild adverse event profile further enhance its place within

standard practice. Although an ongoing phase III trial directly comparing taletrectinib with crizotinib, the overall existing evidence makes taletrectinib a preferred option for ROS1-positive NSCLC[16].

CONCLUSION:

The FDA approval of taletrectinib is a welcome milestone for ROS1-positive NSCLC patients. With notable response rates, long-lasting systemic and intracranial activity, and an acceptable safety profile, taletrectinib fills critical gaps left by previous ROS1 inhibitors. While cross-trial comparisons should be interpreted with caution, available data indicate that taletrectinib will change the treatment paradigm in this uncommon oncogenic subset. Additional outcomes of phase III studies will further establish its position in the treatment order and validate its long-term efficacy.

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