Review

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Repotrectinib: a promising new therapy for advanced nonsmall cell lung cancer

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Abstract

Nonsmall cell lung cancer (NSCLC) is the major cause of cancer-related mortality worldwide, accounting for 84% of lung cancer cases. The newly FDA-approved kinase inhibitor, repotrectinib (AUGTYRO), offers a promising option for treating advanced or metastatic NTRK/ROS1-positive Nonsmall cell lung cancer. Repotrectinib has demonstrated significant efficacy in clinical trials. Notably, the phase 1/2 TRIDENT-1 study showed impressive progression-free survival and intracranial activity in both TKI-naïve and pretreated patients. With its high response rates and manageable side effects, repotrectinib is set to play a significant role in treating ROS1+ and NTRK+advanced solid tumors, highlighting the ongoing need for research and clinical application.

Keywords: FDA, nonsmall cell lung carcinoma, NTRK gene fusions, oncology, reprotrectinib, solid tumors

Introduction

Repotrectinib, marketed under Augtyro, is a breakthrough cancer medicine primarily used to treat nonsmall cell lung cancer (NSCLC). As an advanced tyrosine kinase inhibitor (TKI), riprectinib targets the proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Its approval by the U.S. Food and Drug Administration (FDA) in November 2023 marks an important milestone in cancer treatment, especially for patients with locally advanced or metastatic ROS1-positive NSCLC[1].

Early ROS1 TKIs have demonstrated antitumor activity; however, their effectiveness is often limited by the development of resistance and suboptimal intracranial activity. Repotrectinib is a next-generation ROS1 TKI designed to overcome these limitations. Preclinical studies have demonstrated efficacy against ROS1 fusion-positive cancers, including those with resistance mutations such as ROS1 G2032R. Unlike earlier TKIs like crizotinib, which often fail due to resistance, repotrectinib addresses solvent-front mutations such as ROS1 G2032R, this highlights the potential of repotrectinib to achieve more durable, more comprehensive responses in patients.

HIGHLIGHTS

- Nonsmall cell lung cancer (NSCLC), a malignant tumor of the epithelial cells of the lung, is the major cause of cancer-related mortality worldwide, accounting for 84% of lung cancer cases.
- Current treatment options for ROS1/NTRK-rearranged NSCLC includes: crizotinib (Xalkori), entrectinib (Rozlytrek), ceritinib (Zykadia), lorlatinib (Lorbrena), cabozantinib, ensartinib, and larotrectinib.
- Repotrectinib (AUGTYRO) is a next-generation tyrosine kinase inhibitor approved by the FDA in November 2023. It targets ROS1 and TRKs and is used primarily for treating ROS1-positive NSCLC by binding to specific sites on the tyrosine kinase receptor, preventing hyperactivation and promoting durable patient responses.
- It demonstrated a significant progression-free survival rates and overall efficient clinical activity in patients with ROS1 fusion-positive NSCLC and other solid tumors. It is well-tolerated with manageable side effects.
- Its consumed initial dose is 160 mg once daily for 14 days, followed by 160 mg twice daily as a maintenance dose.

The development of TKIs for the treatment of ALK-rearranged and ROS1-rearranged NSCLC has highlighted the importance of receptor tyrosine kinase fusions as targetable oncogenic drivers in a variety of solid malignancies[2–5].

This article reviews the preclinical activity and clinical potential of repotrectinib (TPX-0005), a rationally developed next-generation TKI. Repotrectinib has potent inhibitory activity against clinically persistent solvent-front substitutions involving ROS1, TRKA-C, and ALK, as well as other clinically relevant nonsolvent-front mutations. This brief provides a comprehensive overview of the development of repotrectinib, its mechanism of action, and its potential to revolutionize the treatment landscape of NSCLC and other solid tumors by targeting oncogenic drivers.

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Current treatment options

The treatment of NSCLC varies based on the disease stage at diagnosis and the therapies available to target specific tumor genetic alterations[6]. For NTRK/ROS1-rearranged advanced or metastatic NSCLC (aNSCLC), apart from repotrectinib (AUGTYRO), clinical guidelines recommend several options, including crizotinib, entrectinib, cabozantinib, ceritinib, ensartinib, lorlatinib, and larotrectinib.

Crizotinib

Crizotinib, the first-in-class ALK TKI, was FDA-approved in March 2016 for treating advanced ROS1-positive NSCLC. Also known as Xalkori, it is approved in many countries for frontline treatment[7,8]. When taken orally at 250 mg as per the recommended dose, Xalkori blocks the activity of ROS1 protein in tumors. This potentially prevents NSCLC growth and spread[9]. Studies underline its efficacy in prolonging overall survival and managing disease progression, but resistance through secondary mutations can limit its long-term effectiveness[7].

A recent meta-analysis confirms its safety and efficacy, supporting crizotinib as a reliable treatment for ROS1-positive aNSCLC in the real-world setting[8].

Entrectinib

In 2019, the FDA-approved entrectinib for adults with ROS1-positive metastatic NSCLC. When its efficacy was investigated, the overall response rate was 78%. Notably, 55% had responses lasting 12 months or longer. Entrectinib is a TKI targeting tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC, as well as proto-oncogene tyrosine-protein kinase ROS1 and ALK. The recommended dosage of ROZLYTREK (Entrectinib) in adults is 600 mg orally once daily until disease progression or unacceptable toxicity[10,11].

Ceritinib

Ceritinib (ZYKADIA) is a kinase inhibitor targeting ALK, insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1, with the highest activity against ALK. Ceritinib inhibits ALK autophosphorylation of ALK, STAT3 phosphorylation, and proliferation of ALK-dependent cancer cells[12].

In a phase II trial, ceritinib showed an overall response rate (ORR) of 62%, with a median progression-free survival (PFS) of 9.3 months. In the subgroup of crizotinib-naïve patients, PFS was 19.3 months, while in patients with brain metastases, the brain ORR was 63%. Grades 3–4 adverse events occurred in 37% of the patients. While not approved for first-line treatment, 750 mg ceritinib orally once daily may be used postcrizotinib progression[13,14].

Lorlatinib

Lorlatinib (Lorbrena) is a targeted therapy for ALK and ROS1 gene-mutated NSCLC, developed by Pfizer and FDA-approved in 2018. When taken orally once daily at 100 mg, it inhibits ALK and ROS1 kinases, blocking cancer cell growth and survival pathways, and can penetrate the blood-brain barrier, making it effective against brain metastases. Preclinical studies showed lorlatinib's efficacy in inhibiting ALK and ROS1 signaling, reducing the proliferation and survival of cancer cells, including those resistant to other ALK inhibitors. Clinical trials have shown good response rates, including in CNS metastases. The recommended dosage is 100 mg orally once daily[15,16].

Cabozantinib

Cabozantinib has proven efficacy in treating ROS1-positive NSCLC. It acts as a potent ROS1 TKI, showing superior activity to inhibitors like crizotinib and lorlatinib[17]. Clinical trials have highlighted that cabozantinib can overcome resistance mechanisms seen with other ROS1 inhibitors, positioning it as a promising treatment option. Although much evidence comes from preclinical studies and phase 2 trials, cabozantinib's clinical effectiveness shows its potential in managing advanced ROS1-positive NSCLC[18,19].

Ensartinib

As a second-generation tyrosine kinase inhibitor targeting ROS1, ALK, and MET, ensartinib demonstrated modest efficacy and an acceptable safety profile in ROS1-positive NSCLC[20]. However, its efficacy can vary based on specific ROS1 fusion partners. In the clinical trials, the main treatment-related adverse events (TRAEs) reported are grades 1 or 2 rashes, manageable by dose suspension or reduction, with most patients not requiring adjustments. Its overall safety profile underscores its relevance in personalized treatment for ROS1-positive NSCLC patients[21].

Larotrectinib

Larotrectinib, a pioneering and highly selective TRK inhibitor, obtained FDA approval in 2018, treating adult and pediatric patients with advanced or metastatic solid tumors harboring an NTRK gene fusion. This decision was supported by strong and lasting antitumor effects demonstrated in a pooled analysis of three phase I and II trials. The efficacy of the drug was consistent with longer follow-up and a larger sample. Additionally, larotrectinib was well-tolerated and only 8% of the patients required a dose reduction along with permanent discontinuation due to an adverse event noted in just 2%[22].

Common side effects

Many of these drugs share similar side effects due to their mechanisms of action. The most frequently reported adverse events include dizziness, fatigue, nausea, diarrhea, vomiting, constipation, and vision disorders. Some may also cause more severe reactions like hepatotoxicity, lung inflammation, heart abnormalities, or cognitive effects[9–11,15,16,19].

Repotrectinib (AUGTYRO)

Mechanism of action

Lung cancer is the leading cause of cancer-related deaths globally, with NSCLC making up 84% of all lung cancer cases. NSCLC is often diagnosed at an advanced stage and has a poor prognosis and low survival rates[14]. Repotrectinib is an inhibitor of the proto-oncogene tyrosine-protein kinase ROS1 (ROS1) and of the tropomyosin receptor tyrosine kinases (TRKs) TRKA, TRKB, and TRKC. Fusion proteins that include ROS-1 domains can drive cancer by excessively activating pathways that control cell signaling, growth, and division. Activation of these proto-oncogenes through mutations can lead to unconstrained cell division

and hyperproliferation of the downstream signaling pathways.

Repotrectinib plays a pivotal role in inhibiting this hyperactivation by binding to specific sites of the tyrosine kinase receptor and hindering its phosphorylation. The neurotrophic tyrosine receptor kinase (NTRK) genes are responsible for encoding the tropomyosin receptor kinase (TRK) proteins. These proteins are vital for brain development and other postnatal physiologic functions such as balance, appetite, and pain perception. In recent clinical trials, repotrectinib exhibited antitumor activity. Pharmacodynamic responses of repotrectinib are not fully characterized at the time being; however, the geometric mean (CV%) absolute bioavailability of repotrectinib is 45.7%. Repotrectinib is primarily metabolized by the liver through CYP3A4 followed by secondary glucuronidation and is excreted majorly in feces (88.8%)[23].

Repotrectinib with its compact macrocyclic structure has surpassed the resistance mutation challenges met by the previous treatment options. Studies have shown that repotrectinib does not extend into the solvent front or gatekeeper regions avoiding any steric interactions. Furthermore, molecular modeling studies of repotrectinib show that repotrectinib has a more conformationally constrained macrocyclic structure, which is likely to contribute to its greater potency compared to other drugs. This enables the use of repotrectinib in NTRK fusion-positive cancers as a means of delaying on-target resistance[24] (Fig. 1).

Clinical efficacy of repotrectinib

Evidence from multiple clinical trials and preclinical studies has demonstrated the efficacy of repotrectinib, an early-generation ROS1 TKI as a remarkable treatment regime for nonsmall cell lung carcinoma (NSCLC). A phase 1–2 trial was conducted to show the efficacy of the drug in patients with advanced solid tumors, including ROS1 fusion-positive nonsmall cell lung carcinoma. Out of 71 patients recruited 56 patients who previously did not receive ROS1 TKI showed a median PFS of 35.7 months with the use of the medication. Out of 56 patients that showed response, 21 patients with ROS1 fusion-positive NSCLC who had previously received one ROS1 TKI and had never received chemotherapy showed a remarkable median PFS was 9.0 months with significantly improved results. The study showed notable results of repotrectinib owing to the efficacy and safety of the drug in patients with NSCLC, except for a few cases reported of dizziness (in 58% of the patients), dysgeusia (in 50%), and paresthesia (in 30%) as treatment-related adverse effects[25].

Emphasizing the efficacy of the drug as ROS1 TKI, a phase 1/2 TRIDENT-1 study was carried out in patients with ROS1+ or NTRK+advanced solid tumors. In the phase I study, 11 ROS1 TKI-naive patients were observed to be treated with repotrectinib, out of those 11 patients 10 patients showed a median duration of response of 23.1 months and median PFS was 24.6 months. An additional 8.5 month follow-up was conducted in these patients, four of the five previously responding TKI-naïve pts remained in a partial response (PR) per physician assessment data and 7 TKI-naïve pts remained on treatment. The therapy revealed encouraging overall clinical activity in patients with ROS1 fusion-positive NSCLC and TRK fusion-positive solid tumors with slight adverse effects such as dizziness (62%), fatigue (39%), constipation (33%), dysgeusia (33%), and dyspnea (28%) but no treatment-related deaths were seen. This study reveals the efficacy of repotrectinib, in regular clinical use with increased survival rates and tolerability outcomes, which significantly advocates this therapy for ROS1+ or NTRK+ advanced solid tumors[26].

Enforcing the results of the trial, repotrectinib, a next-generation ROS1 TKI, was administered in patients (pts) with locally advanced/metastatic ROS1+NSCLC in the pivotal phase 1/2

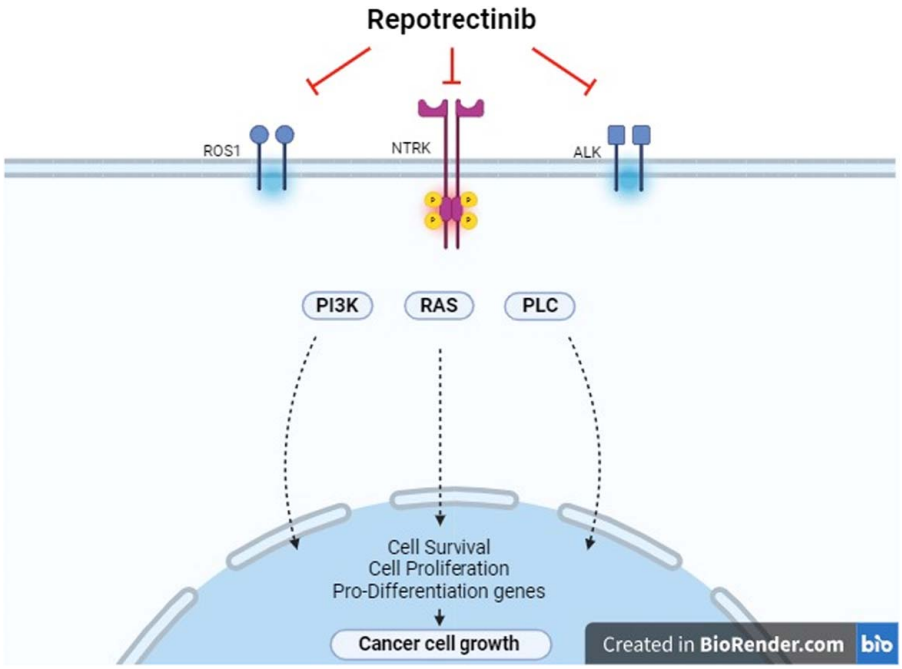

Figure 1. Mechanism of action of repotrectinib. Repotrectinib is a potent inhibitor of the ROS1, NTRK, and ALK fusion proteins. By inhibiting these targets, repotrectinib disrupts downstream signaling pathways mediated by PI3K, RAS, and PLC, ultimately preventing cancer growth.

Table 1

Summary of clinical trials conducted

Study	Sample size (*n*)	Phase of trial	Survival rate (months) PFS	CI	Dose (in mg)	Outcomes	Adverse effects
Alexander Drilon (NCT03093116)	520	Phase 1–2 trial	9.0	95%	160 mg daily for 14 days, followed by 160 mg twice daily	Progression -free-survival	Dizziness dysgeusia and paresthesia
B.C. Cho (NCT03093116)[26]	11	Phase 1–2 Trial TRIDENT-1 study	24.6	95%	160 mg once a day for 14 days followed by 160 mg twice a day	Progression -free-survival	Dizziness, fatigue, constipation, dysgeusia, and dyspnea
Jessica J Lin (NCT03093116)	71	Phase 1 TRIDENT-1 trial	35.7	95%	160 mg once daily for 14 days, then 160 mg twice daily	Progression -free-survival	Dizziness (62%). Grade ≥ 3 Treatment-emergent adverse events
	56	Phase 2 TRIDENT-1 trial	9.0	95%			

TRIDENT-1 trial (NCT03093116). The patients were organized into four cohorts by their treatment history, TKI-naive, one TKI and no chemo, one TKI and one platinum-based chemo, and two TKIs and no chemo. The median (range) follow-up in the primary efficacy cohorts was 24.0 months in the TKI-naive cohort and 21.5 months in the one prior TKI and no chemo cohort. Median PFS was 35.7 months; estimated 12-months and 18-months PFS rates were 77% and 70%), respectively. In the 1 prior TKI and no chemo cohort, the median PFS was 9.0 months and, the estimated 12-month PFS rate was 41%. Safety outcomes in all the groups were comparable, however, as observed previously dizziness (62%). Grade ≥ 3 treatment-emergent adverse events occurred in 216 (51%) and were considered treatment-related in 122 (29%). Thus, the study demonstrates a significant efficacy of the drug in patients with ROS1+NSCLC, including intracranial activity, in both TKI-naïve and 1 prior TKI and no chemo cohorts[27].

A summary of all the clinical trials is mentioned in Table 1.

Recommended dosage and administration

Reprotrectinib's recommended first dose is 160 mg orally once a day for 14 days, followed by 160 mg twice daily with or without meals as a maintenance dose, unless disease progression or drug-related toxicity occurs[1]. Before beginning treatment with the medicine, liver function tests, and uric acid levels should be checked and monitored. It is also recommended to discontinue the use of strong or moderate CYP3A inhibitors, which may increase reprotrectinib exposure, leading to a higher incidence of adverse effects[28].

Side effects and limitations

While repotrectinib has shown beyond doubt to meet the requirements of patients suffering from NTRK gene fusions, withholding better efficacy and potency than the earlier TKI, specifically by not being resistant to the mutations; however, it does have some adverse effects that can limit its use. The most common ($>20\%$) adverse reactions to look out for are dizziness, dysgeusia, constipation, dyspnea, fatigue, ataxia, muscular weakness, and nausea. Despite the frequent occurrence of treatment-related side effects like dizziness and dysgeusia, it did not result in patient withdrawal and was better tolerated. However, it is advised to the patients to refrain from activities such as driving or equipment functioning before the onset of the adverse effects and to avoid any inconvenience. Treatment with repotrectinib (AUGTYRO) may cause some rare adverse effects, including lung problems such as pneumonitis, cognitive impairment, and peripheral neuropathy; it may cause deranged liver enzymes signaling towards liver damage. Patients are recommended to consult their healthcare provider in case they develop any sort of lung problem. It is also suggested to check for their uric acid levels and liver enzymes before and during the treatment. It can also increase the risk of bone fractures. Pregnant women are advised not to take it as it can cause fetal harm and lead to malformations. The use of repotrectinib for treating ROS-1-positive NSCLC in children under the age of 12 has yet not been established[23,29].

Conclusion

Therefore, this study supports repotrectinib to be highly effective and safe in the management of patients with ROS1-positive nonsmall-cell lung cancer. The findings from several clinical trials, including those from the pivotal phase 1/2 TRIDENT-1 study, show marked intracranial activity and rates of progression-free survival in both cohorts: TKI-naïve and pretreated cases. This is because repotrectinib achieved a clinically meaningful response rate of up to 35.7 months for TKI-naïve patients and a significant response rate among those previously treated with one ROS1 TKI. These data, which emerge despite dizziness or fatigue (common adverse events) in mind the treatment's tolerability, go further to increase its promise for use in clinical practice. The results indicate that Repotrectinib should be included in ROS1+ and NTRK+advanced solid tumors' treatment paradigms, which provides dedicated support for further research opportunities and clinical applications.

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