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Targeting ROS1 in NSCLC: Clinical Advances and Future Directions of Taletrectinib

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Abstract This review looks at the pharmacokinetics, safety, and effectiveness of taletrectinib, a novel inhibitor that targets both ROS1 and NTRK, in patients with solid tumors and ROS1-positive non-small cell lung cancer (NSCLC). Objective response rates (ORR), progression-free survival (PFS), intracranial efficacy, and safety profiles are evaluated in the Review using phase I and phase II clinical trials, including both domestic and foreign research projects. Findings show that taletrectinib has a promising anticancer impact, good CNS penetration, and a solid safety record, especially in patients with brain metastases. These results imply that ROS1-positive cancers may benefit from taletrectinib as a treatment.

Keywords Clinical studies, Non-small cell lung cancer, ROS1, Taletrectinib, Tyrosine kinase inhibitor

Introduction

Non-small cell lung cancer (NSCLC), the leading cause of cancer-related fatalities worldwide, poses a serious danger to world health. Globally, the prevalence of lung cancer varies, with certain Asian locations having a notably high incidence. Lung cancer alone accounts for 1.18 million deaths in 2002, or around 20% of all cancer deaths globally. It was projected that 1.8 million additional instances of this illness would occur globally by 2019(1–4).

Since molecular profiling identifies the most important molecular changes in non-small cell lung cancer (NSCLC), it is essential for choosing druggable targets and directing therapy choices. This is widely adopted in the treatment of advanced adenocarcinoma, either at initial diagnosis or on development of resistance to tyrosine kinase inhibitors(5). The emergence of targetable genetic mutations like EGFR, ALK, and ROS1 has really revolutionized the strategies for treating lung cancer by offering a possibility of personalized treatment with tyrosine kinase inhibitors for outstanding results. From traditional cytotoxic therapies to customized methods to medicine, and treatment being tailored to the genetic changes within the tumor, provides and has brought about unprecedented gains in survival rates in patients. Moreover, EGFR T790M mutation, which can be treated with next-generation inhibitors,

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is one of the examples of the mechanism of resistance revealed by molecular profiling. Last but not least, the advancement of personalized medicine, improvement of patient outcomes, and expansion of the clinical benefit of targeted medicines to more patients all depend on molecular mapping(1)

First identified in non-small cell lung cancer (NSCLC) in 2007, chromosomal rearrangements of the ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) are now recognized as a potential therapeutic target. ROS1 gene fusions were first observed in a human glioblastoma cell line, and subsequent research on NSCLC cell lines and tumor material further clarified ROS1's status as a highly active kinase. Its oncogenic function is regulated by ROS1 rearrangements, which form a constantly activated downstream signaling pathway(6). The most common fusion partners found are SLC34A2, EZR, CD74, and SDC4. These fusions are thought to facilitate carcinogenesis by preserving the entire ROS1 kinase domain. Because of its oncogenic activity, ROS1 is an established target for therapy. Identification of whether a patient is eligible for targeted therapy with selective inhibitors, such as crizotinib, which have resulted in significant clinical responses and improved survival outcomes over conventional chemotherapy, has involved the detection of these rearrangements(7,8).

Molecular Biology of ROS1 in NSCLC

Structure and Function of ROS1

Leukocyte tyrosine kinase (LTK), anaplastic lymphoma kinase (ALK), insulin receptors, and other RTKs share structural similarities with the ROS1 gene-encoded receptor tyrosine kinase (RTK). Since its activating ligand has not yet been discovered, it is a member of the orphan receptor class. Although its exact physiological function remains to be established, ROS1 is found expressed in adult tissues at low levels. Various types of malignancies, such as non-small cell lung cancer (NSCLC), may arise from its aberrant activation by chromosomal rearrangements, such as gene fusions(9).

At 2,347 amino acids, ROS1 is a structurally massive protein that is the largest known receptor tyrosine kinase. A large N-terminal extracellular domain, a single-pass transmembrane domain, and a C-terminal intracellular domain containing tyrosine kinase activity are its three main sections. It is mapped to chromosome 6q22. The three β-propeller structures and nine fibronectin type III-like domains in the 1,832-amino acid extracellular domain are believed to facilitate protein-protein interactions. An intracellular domain of 465 amino acids consists of a juxtamembrane segment, a 278-amino acid kinase domain, and a C-terminal tail. There is approximately 49% sequence homology between this kinase domain and ALK(10).

The ROS1 is often activated in cancer by chromosomal rearrangements leading to fusion proteins, which connect various partner genes with the unaltered ROS1 kinase domain. In lung cancer, more than 14 partners are found in fusions with ALK, of which EZR, CD74, SLC34A2, among others, are the most frequently noted. Dimerization domains, found in ALK fusions, are usually not found in these fusions, and the exact activation pathways remain unclear. Constitutively active fusion proteins induce oncogenic signaling, however, and result in uncontrolled cell survival and proliferation. This has been described as oncogene addiction, an attribution that renders ROS1 fusions highly relevant targets for cancer therapy.

There is doubt about the conventional biological function of wild-type ROS1. But mouse research has indicated that men lacking ROS1 are otherwise healthy but sterile due to defects in sperm maturation. That implies that ROS1 may have a specialized, non-vital role in development rather than being required for all cell processes(6,11)

Oncogenic ROS1 Fusions

In one study, DNA from MCF-7 human breast cancer cells was inserted into NIH-3T3 cells, which were then implanted into mice. This was the first proof that gene fusions containing the ROS1 kinase domain have transformative potential. It was found that the growth of tumors could be caused by a DNA fragment that contains the kinase domain-encoding 3' region of ROS1 and is coupled with an unknown sequence. However, since the MCF-7 cell line did not exhibit a similar sequence, it was determined that the DNA rearrangement was an experimental result. The first documented instance of a naturally occurring ROS1 rearrangement occurred in the human glioma cell line U118MG, where a loss on chromosome 6 resulted in the 3' region of ROS1 fusing with the 5' area of the FIG (GOPC) gene. Furthermore, FIG-ROS1 gene fusion has been observed in patient samples from ovarian cancer, non-small cell lung cancer (NSCLC), and cholangiocarcinoma. Moreover, gene fusions with SLC34A2, CD74, TPM3, SDC4, EZR, LRIG3, KDELR2, and CCDC6-ROS1 have been observed in NSCLC samples. Angiosarcoma patient samples have been discovered to have the CEP85L-ROS1 fusion, inflammatory

myofibroblastic tumors to have the YWHAE-andTFG-ROS1 gene fusions, and gastric adenocarcinoma and colorectal cancer samples to have the SLC34A2-ROS1 fusion. Since ROS1 rearrangements appear to be so versatile, the number of fusion partners will likely increase as more samples are analyzed. All of the described fusion genes exhibit complete retention of the ROS1 kinase domain. Furthermore, the junction location on ROS1 is consistently found at the 5' end of exons 32, 34, 35, or 36 at the mRNA level (12,13).

Metamorphosis is known to occur in the ROS1 fusion proteins associated with cancer. With the exception of KDELR2-, CCDC6-, YWHAE-, TFG-, and CEP85L-ROS1 fusions, which have not yet been assessed, the expression of a number of known fusion variations in fibroblasts led to anchorage-independent proliferation, foci formation, and carcinogenesis. Additionally, it has been shown that the production of the SDC4-ROS1 and FIG-ROS1 fusions in murine Ba/F3 cells results in IL3-independent proliferation that is susceptible to ROS1 inhibitors found in small molecules. The FIG-ROS1 fusion gene has been demonstrated in animal studies to stimulate the growth of astrocytomas when produced ectopically in the basal ganglia, while the EZR ROS1 fusion gene has been connected to lung cancer when expressed in lung epithelial cells. Unfortunately, the U118MG glioblastoma line, U138MG (derived from the same patient as U118MG and expressing the identical FIG-ROS1 fusion), and the HCC78 NSCLC line that exhibits the SLC34A2-ROS1 fusion are the only three documented cell lines that naturally express ROS1 fusion genes. Our results (unpublished findings) indicate that the U118MG line is relatively resistant to ROS1 suppression in proliferation studies, indicating that the FIG-ROS1 fusion protein may not be the only oncogenic driver in these cells. However, several investigations have shown that ROS1 inhibition achieved by RNA interference and pharmaceutical means can both impact HCC78 cell proliferation. EGFR and ROS1 may work together to boost cell line proliferation, as evidenced by the notable increased sensitivity of HCC78 cells treated with the EGFR inhibitor gefitinib to ROS1 inhibition(14).

The method by which ROS1 fusion proteins become permanently active is unknown at this time. The fusion partner adds a dimerization domain that results in ongoing oligomerization and kinase activity, which sets it apart from other cancer-related RTK fusions like ALK. Dimerization's role in activating the wild-type receptor for ROS1 is still unknown, though .Furthermore, only monomers of the FIG-ROS1 fusion gene and the v-ros protein from the UR2 avian sarcoma virus have been demonstrated to exist. This is consistent with the lack of dimerization domains in a number of known ROS1 fusion partners. It has been shown that the FIG-ROS1 fusion protein's capacity to induce transformation is dependent on its position inside the Golgi apparatus, but not on its kinase activity. However, additional ROS1 fusion variants appear to have different locations; reports have indicated cytoplasmic, plasma membrane, and perinuclear distributions." Numerous investigations have looked into the signaling pathways that ROS1 fusion proteins activate. The expression of FIG-ROS1, CD74-ROS1, or SDC4-ROS1 fusions by fibroblasts or Ba/F3 cells causes ROS1 to become auto-phosphorylated, which phosphorylates SHP-2, MEK, ERK, STAT3, and AKT. ROS1-targeting medications stop these effects. Furthermore, ROS1 inhibitors decreased the levels of phosphorylated ROS1, SHP-2, AKT, and ERK in HCC78 cells. It is interesting to note that a recent study found that the downstream signaling can vary based on the specific fusion partner of ROS1. It was found that CD74-ROS1 stimulated the phosphorylation of E-Syt1, whereas FIG-ROS1 did not. This distinct signaling capability resulted in a more invasive characteristic of cells transduced with CD74-ROS1. In general, the common growth and survival pathways that other RTKs also excite are quite similar to the signaling pathways that ROS1 fusions activate(11).

Clinical Epidemiology and Characteristics

ROS1 Gene Fusion Prevalence in Non-Small Cell Lung Cancer

ROS1 gene rearrangements are a major molecular determinant in a subset of non-small cell lung cancer (NSCLC), and their frequency varies according to tumor characteristics and patient demographics. These gene fusions are very uncommon but a significant therapeutic target in clinical practice, with epidemiological data generally showing that they are seen in 1% to 2% of all NSCLC patients(11)

In the general population of non-small cell lung cancer (NSCLC), ROS1 gene rearrangements are rare but have significant clinical implications. Studies suggest an overall frequency of approximately 2%, with lung adenocarcinoma showing somewhat elevated rates up to 3.3%. A large multicenter retrospective study conducted in China, involving 31,225 NSCLC cases, identified ROS1 rearrangements in 1.8% of the instances. Supporting this, a comprehensive meta-analysis that encompassed 18 studies showed a combined prevalence of 2.4% in adenocarcinoma and merely 0.2% in non-adenocarcinoma subtypes(15).

Focusing specifically on adenocarcinoma, a meta-analysis involving 37 trials with over 19,000 patients calculated a combined prevalence of 2.49% for ROS1 rearrangements, consistent with previous finding. Conversely, in various types of non-adenocarcinoma NSCLC, the prevalence is significantly lower. One meta-analysis estimated it at about 1.37% , while another reported an even lower figure of 0.2%(15,16).

Demographic profile

Histology: ROS1 rearrangements are most common in adenocarcinoma patients(15,16). In a study, 97.6% of ROS1-rearranged NSCLC patients had lung adenocarcinoma (17).

Smoking History: The fusions are also more frequent among patients with no history of smoking(15,16). In one study cohort, 74.0% of ROS1 fusion patients were never-smokers(17).

Gender: A greater frequency of ROS1 gene rearrangement is always found among female NSCLC patients(15,16).

Age: Younger age tends to be a factor for higher chances of having a positive ROS1 gene fusion(17).

Clinical Stage: The percentage of ROS1 rearrangement is much higher in patients with advanced disease (stages III–IV) than in patients with early-stage disease (stages I–II)(15).

Current Therapeutic Landscape

First-Generation ROS1 Inhibitors

(1) Crisotinib: Numerous prospective and retrospective studies have demonstrated the safety and efficacy of crizotinib, an oral multitarget tyrosine kinase inhibitor, in the treatment of ROS1-positive non-small cell lung cancer (NSCLC). In the PROFILE 1001 phase I investigation, 53 patients received a dosage of 250 mg of crizotinib twice a day. Eighty percent of these patients had previously received platinum-based chemotherapy, and most had had one or two lines of treatment (42% and 44%, respectively). An updated analysis performed after a median follow-up of 62.6 months showed that the overall response rate (ORR) was 72% (95% CI 58–83%), the median progression-free survival (mPFS) was 19.3 months (95% CI 15.2–39.1 months), and the median overall survival (mOS) was 51.4 months (95% CI 29.3 months). The ROS1-specific structure shows that crizotinib inhibits ROS1 five times more effectively than ALK, which explains why NSCLC with ROS1 positivity responded better than those with ALK positivity. With 94% of reported side effects classified as mild (grade 1 or 2), crizotinib's safety profile was deemed satisfactory. Diarrhea (45%), nausea (51%), peripheral edema (47%), and visual abnormalities (87%), were the most common side effects of the medicine. The mPFS at 20 months (95% CI 8 months-NR) and the ORR at 70% (95% CI 51–85%) in the EUCROSS study, a multicentric phase II single-arm prospective trial assessing the role of crizotinib in ROS1-positive NSCLC, further corroborated findings from PROFILE 1001 and an East Asian prospective phase II trial. The METROS research is particularly notable since it was designed to assess the safety and effectiveness of crizotinib in patients with non-small cell lung cancer (NSCLC) who had received previous treatment and had mutations, MET amplifications, or ROS1 rearrangements. This trial showed a mPFS of 23 months (95% CI 15–30 months) and an ORR of 65% (95% CI 44–82%). An update was just given by the Acsè Program, a basket trial that is investigating crizotinib in patients with solid tumors that have mutations in MET, ALK, or ROS1. The median PFS and OS were 5.5 months (95% CI 4.2–9.1 months) and 17.2 months (95% CI 6.8–32.8 months), respectively, with a peak response rate of 69.4% and an ORR of 47.2%. These results are less promising than those of the PROFILE 1001 experiment, probably because to lower Eastern Cooperative Oncology Group performance scores and greater pretreatment levels in the patient population.A shorter mPFS is linked to a worse outcome for patients with brain metastases, according to the majority of studies. This could be because crizotinib's efficacy in the brain is limited. There are presently no trials that directly compare crizotinib to chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) with ROS1 rearrangements; nevertheless, there is some evidence that chemotherapy based on pemetrexed may be especially effective. Crisotinib has been authorized as a first-line treatment option for non-small cell lung cancer (NSCLC) with ROS1 rearrangements due to its shown efficacy and manageable toxicity profile(18,19).

(2) Entrectinib: Pan-tropomyosin receptor kinase (pan-TRK), ALK, and ROS1 are all efficiently bound by the multi-pathway inhibitor entrectinib. Reportedly 40 times more effective than crizotinib, this medication can traverse the blood-brain barrier. 600 mg is the dosage that is administered once daily. Four clinical trials (STARTRK-2, ALKA-372-001, STARTRK-1, and STARTRK-NG) have shown entrectinib to be safe and effective in individuals with ROS1 rearrangements. first released the findings from the ALKA-372-001 and STARTRK-1 phase I/II studies, followed by data from the STARTRK-2 phase 2 study.A revised review of 161 patients revealed that 34.8% had brain metastases, most had an ECOG performance rating of 0–1

(90.1%), and most were nonsmokers (62.7%) and had undergone previous therapies (62.8%). After a median follow-up of 15.8 months, the median time to response (mTTR) was 0.95 months (95% CI 0.7–26.6 months), and the overall response rate (ORR) was 67.1% (95% CI 59.3–74.3%). The median overall survival (mOS) has not yet been reached, the median progression-free survival (mPFS) was 15.7 months (95% CI 11.0–21.1 months), and the median time to progression (mTTP) was 2.8 months (95% CI 0.4–21.1 months). A separate analysis of individuals with brain metastases was performed to assess the effect of entrectinib on these conditions. In this subgroup, the median intracranial PFS was 8.3 months (95% CI, 6.4–15.7 months), and the intracranial ORR and ORR were 52.2% (95% CI, 37.0–67.1%) and 62.5%, respectively.Constipation (31.4%), malaise (34.3%), and dysgeusia (42.9%) were the most frequent adverse events, with the majority of treatment-related adverse events being classified 1–2. ALT rise (3.3%), diarrhea (2.9%), and weight increase (8.1%) were other noteworthy side events that were reported. Grade 4 adverse events were reported in just seven patients (3.3%) in the updated analysis. The results of the STARTRK-NG phase I research, which examined entrectinib's effects in younger adults, were comparable. According to preclinical research, entrectinib is ineffective in situations of acquired resistance to crizotinib and does not show any efficacy when ROS1 G2032R and L2026M mutations are present. This supports the use of entrectinib as a first-line treatment(20).

(3) Ceritinib: ALK/ROS1 TKI of the second generation, crizitinib, can overcome crizotinib resistance, but only if certain mutations are present, as M2001T, G2101A, and L2026M suggest. Both patients who had never taken crizotinib before and those who had already received it were administered 750 mg of Ceritinib daily as part of a phase II prospective research. PFS was 9.3 months (95% CI 0–22 months), and the overall response rate (ORR) was 62% (95% CI 45–77%). The brain ORR was 63% (95% CI 31–86%) for patients with brain metastases, whereas the PFS for those who were not on crizotinib was 19.3 months (95% CI 1–37 months). In 37% of the individuals, serious adverse events that were categorized as grade 3–4 were noted. Ceritinib is not currently approved for use as first-line treatment; nevertheless, it might play a part once patients are making success on crizotinib(21,22).

Resistance Mechanisms

As mentioned above, patients who have had positive clinical responses and extended survival frequently develop resistance in the central or systemic nervous system. There are two types of ROS1 resistance mechanisms: off-target and on-target. On-target resistance mechanisms, including ROS1 mutations, may manifest when a tumor is treated with a TKI. Although a number of variations have been documented, solvent-front mutations G2032R and D2033N are the most often discovered ones. Specifically, acquired resistance is associated with gatekeeper mutations S1986F/Y, L2000V, F2004V, L2026M, and G2032K. An important and extremely worrisome resistance mutation is L2086F, which makes a tumor resistant to all TKIs, including taletrectinib, lorlatinib, and crizotinib(23,24).

Because TKIs have differing levels of effectiveness against resistant mutations, sensitivity needs to be verified before starting treatment. For instance, lorlatinib, which is effective against the K1991E or S1986F resistant mutations but only slightly against the G2032R mutation, may be used when entrectinib treatment is unsuccessful. Despite the fact that cabozantinib demonstrated promise in curing this compound mutation, a compound mutation of G2032R/L2086F was created as a result of the simultaneous administration of crizotinib and lorlatinib. With a high blood-brain barrier penetration rate, cabotanzantinib is commonly used to treat thyroid cancer and other cancers that it can particularly target, such as MET, VEGFR-2, RET, ROS-1, and AXL. Cabozantinib can have better results than entrectinib, ceritinib, and crizotinib resistance, even if resistance mutations like D2033N or G2032R are present. Bragitinib, another ROS1 inhibitor, has shown antitumor efficacy against several mechanisms of crizotinib resistance, including the L2026M mutation, while it is ineffective against the G2032R mutation. While it is ineffective against the D2033N mutation, the ROS1 and NTRK inhibitor taletrectinib has demonstrated efficacy against the G2032R, L1951R, S1986F, and L2026M mutations. An overall response rate (ORR) of 33% was found in a clinical trial with 46 patients who had received several lines of medication in the past, whereas an ORR of 58.3% was found in previously treated persons and 66.7% in patients who had never received treatment(25).

Other genetic abnormalities, such as small cell transformation (3%–10%), KRAS mutations (20%–25%), or MET amplification (3%), are also associated with significant off-target resistance mechanisms. In conclusion, the JAK/STAT3, PI3K/AKT/mTOR, RAS, and MAP/ERK signaling pathways are all enhanced by SHP-2 phosphatase, which is stimulated by HER2-

mediated bypass signaling and active ROS1 kinase to sustain cell growth and survival. These molecular mechanisms are involved in resistance(23,26).

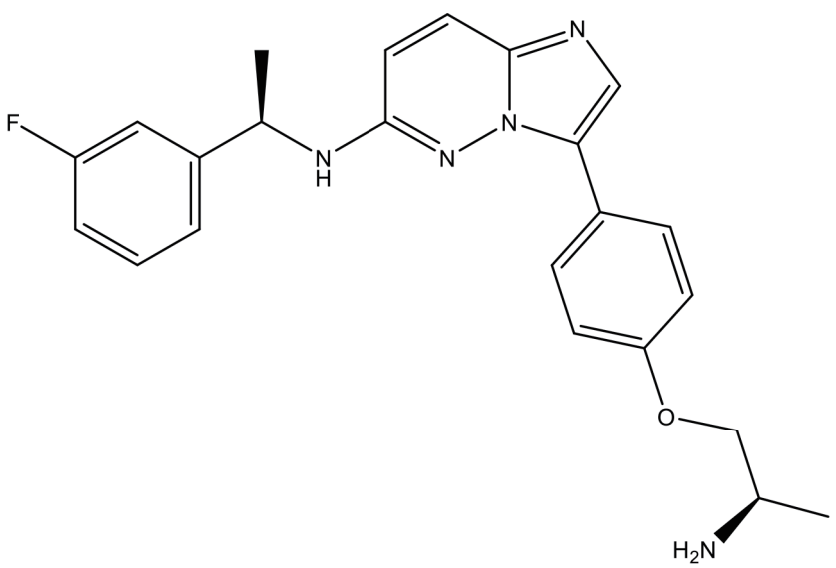
Taletrectinib: A Next-Generation ROS1 Inhibitor

About 2% of patients with non-small cell lung cancer (NSCLC) have a ROS1 gene mutation. ROS1 fusions boost cell survival and proliferation through ligand-independent action. Although the FDA has approved several ROS1 inhibitors, such as entrectinib, crizotinib, and more recently, repotrectinib, each has its own set of challenges. Resistance mechanisms, such as secondary kinase-domain mutations like ROS1-G2032R, may reduce the effectiveness of crizotinib and entrectinib, while repotrectinib may result in central nervous system (CNS) side effects, including ataxia, cognitive decline, and dizziness, which have been linked to the inhibition of tropomyosin receptor kinase B,TRKB(27). Therefore, more effective and well-tolerated treatment alternatives are still needed for ROS1-positive malignancies. Taletrectinib is an oral, highly selective, CNS-active next-generation ROS1 inhibitor that was developed specifically to treat patients with ROS1-positive non-small cell lung cancer. This article describes taletrectinib's efficacy in various in vitro and in vivo models of ROS1 fusion tumors. We also compare the anticancer effectiveness of taletrectinib to that of other ROS1 inhibitors. It seems clear that ROS1 is the kinase that taletrectinib prefers to target over TRKB. It works well in mice with both ROS1 wild-type (ROS1-CD74, ROS1-SLC34A2) and ROS1-G2032R resistant mutation fusions (ROS1 G2032R-CD74, ROS1 G2032R-SLC34A2).Furthermore, mice with ROS1 fusion xenograft models implanted intracranially survived for more than 70 days thanks to taletrectinib. Our nonclinical research demonstrates that taletrectinib exhibits a favorable overall profile by being effective against both ROS1 wild-type and mutant-driven malignancies while still remaining selective against TRKB. Two Phase 2 single-arm pivotal trials, TRUST-I (NCT04395677) in China and TRUST-II (NCT04919811), are currently testing taletrectinib in patients with locally progressed or metastatic ROS1-positive non-small cell lung cancer (NSCLC). Following a joint evaluation of the TRUST-I and TRUST-II clinical trials, the FDA approved taletrectinib for use in treating patients with locally progressed or metastatic ROS1-positive NSCLC(28).

Tyrosine kinases receptor

Tyrosine kinases, of which RTKs are a subtype, are crucial for fostering intercellular communication and regulating a variety of complex biological processes, such as cell division, motility, metabolism, and proliferation. The 58 distinct RTKs that humans have identified share a common protein design consisting of a single membrane-spanning helix, an intracellular segment including a tyrosine kinase domain (TKD), a carboxyl (C-terminal) tail, and a just membrane regulatory region. Dysregulated RTK signaling can

Drug Structure:



3-[4-[(2R)-2-aminopropoxy]phenyl]-N-[(1R)-1-(3-fluorophenyl)ethyl]imidazo[1,2-b]pyridazin-6-amine

Table 1: All property of Taletrectinib(29)

Property	Description
Chemical Formula	C31H31N7O2
Category	ROS1/TRK Inhibitor, Antineoplastic Agent
Nature	Small molecule tyrosine kinase inhibitor
Dose (Oral Tablet)	400 mg once daily or 600 mg once daily (in clinical studies)
Absorption	Well absorbed after oral administration
Distribution	Plasma, tumor tissue (ROS1/NTRK fusion–positive cancers)
Metabolism	Hepatic, primarily CYP3A4-mediated
Protein Binding	~90–95%
Half-life	~37 hours
Peak Blood Concentrations	Dose-dependent; observed within 4–6 hours post-dose
Spectrum of Activity	Selective inhibitor of ROS1 and NTRK (TRK A/B/C) fusion proteins
Mechanism of Action	Inhibits ROS1 and NTRK autophosphorylation, blocking oncogenic signaling
Acts Against	ROS1-positive NSCLC, NTRK fusion–positive solid tumors

lead to a variety of human diseases, particularly cancer. Since the onset of the genomic era and the use of next-generation sequencing (NGS) in normal clinical settings and cancer research, mutational profiles in nearly all types of human tumors have been discovered. These genomic studies have shown several alterations in the genes MET, EGFR, and HER2/ErbB2 that code for RTKs. When RTKs are shown to have recurring genetic changes, their roles in the development of cancer are investigated, as is the best way to treat patients whose tumors have particular RTK mutations. The normal physiological activation of RTKs will be discussed in this article, along with a number of processes that may cause abnormal activation of these receptors in human malignancies. These findings have important ramifications for the choice of anti-cancer therapies.(30)

Receptor-specific ligands are usually responsible for activating RTKs. Through their induction of dimerization and/or oligomerization, growth factor ligands interact with the extracellular domains of RTKs, resulting in receptor activation. The resulting conformational alterations release cis-autoinhibition for most RTKs and enable trans-autophosphorylation of each TKD. This conformational shift enables the TKD to transition to an active state. Numerous downstream signaling proteins with phosphotyrosine-binding (PTB) or Src homology-2 (SH2) domains are likewise drawn to and activated by RTK autophosphorylation. These domains attach to certain phosphotyrosine residues on the receptor, which subsequently engage with downstream mediators to start essential cellular signaling cascades(31).

Tyrosine kinases receptor inhibitor

Tyrosine kinase inhibitors (TKIs) are drugs that prevent tyrosine kinases from doing their job. By means of signal transduction pathways, these enzymes are essential for the activation of several proteins. The process by which TKIs interfere with the activation is phosphorylation, which is the addition of a phosphate group to the protein. TKIs are mostly used in the treatment of cancer. For example, in cases of chronic myelogenous leukemia, they have considerably improved survival rates. In addition, they are used to treat idiopathic pulmonary fibrosis and other ailments(32,33).

These inhibitors are also known as tyrphostins, a term that comes from the phrase "tyrosine phosphorylation inhibitor," which was originally used in a 1988 study that detailed substances that inhibited the activation of the EGFR receptor(34).

The 1988 study was the first showing of a methodical investigation and discovery of small-molecule tyrosine phosphorylation inhibitors. Protein kinases that target serine or threonine residues are specifically unaffected by these chemicals, which enables them to distinguish between the kinase domains of the insulin receptor and the EGFR. The ability to design and produce tyrphostins that can differentiate between even closely related protein tyrosine kinases, such EGFR and its near relative HER2, was also demonstrated, despite the similarities in the tyrosine-kinase domains(35,36).

Tyrosine kinase inhibitors (TKIs) have been developed by their founders and have demonstrated efficacy as anti-tumor and anti-leukemic medicines. These TKIs target distinct tyrosine kinases. Imatinib was developed in response to this study to treat chronic myelogenous leukemia (CML)(37), while

gefitinib and erlotinib were later developed to block the EGF receptor. As an inhibitor of Src tyrosine kinase, dasatinib has shown promise as a senolytic and in the management of chronic myeloid leukemia(38).

Inhibiting FGF, PDGF, and VEGF receptors, sunitinib is based on preliminary research on TKIs that target VEGF receptors. Several clinical trials are presently being conducted on the Wee1 kinase inhibitor adavosertib to treat solid cancers that are difficult to treat. The toxicity and effectiveness of the medication are being determined by researchers, however side effects like myelosuppression, diarrhea, and supraventricular tachyarrhythmia have surfaced(39).

In clinical trials for HER2-overexpressing breast cancers, lapatinib—which the FDA has approved for use in conjunction with hormone therapy or chemotherapy—is also being tested. The idea is that intermittent high-dose treatment, as opposed to the conventional continuous dosing method, may produce better results with more manageable side effects. In a Phase I clinical trial, the most common side effect was diarrhea(40),however there were also responses including large responses to this therapeutic method. Research has examined the efficacy of imatinib, sunitinib, sorafenib, and pazopanib in the treatment of aggressive fibromatosis (desmoid tumors)(41).

Mechanism of Action

The oral next-generation tyrosine kinase inhibitor (TKI) taletrectinib (DS-6051b/AB-106) specifically targets the ROS1 and NTRK fusion proteins. It works by binding to the kinase domain's ATP-binding site, which inhibits the phosphorylation and activation of downstream signaling cascades essential for growth, survival, and spread of tumor cells, such as the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways. Taletrectinib was engineered to specifically target the solvent-front mutation ROS1 G2032R, which is a primary cause of acquired resistance to crizotinib and entrectinib, as compared to earlier TKIs. Taletrectinib is also ideally positioned to treat brain metastases commonly associated with ROS1-positive non-small cell lung cancer (NSCLC) because of its superior penetration into the central nervous system (CNS). With its two-way activity in targeting both wild-type and resistant ROS1/NTRK fusion kinases, taletrectinib

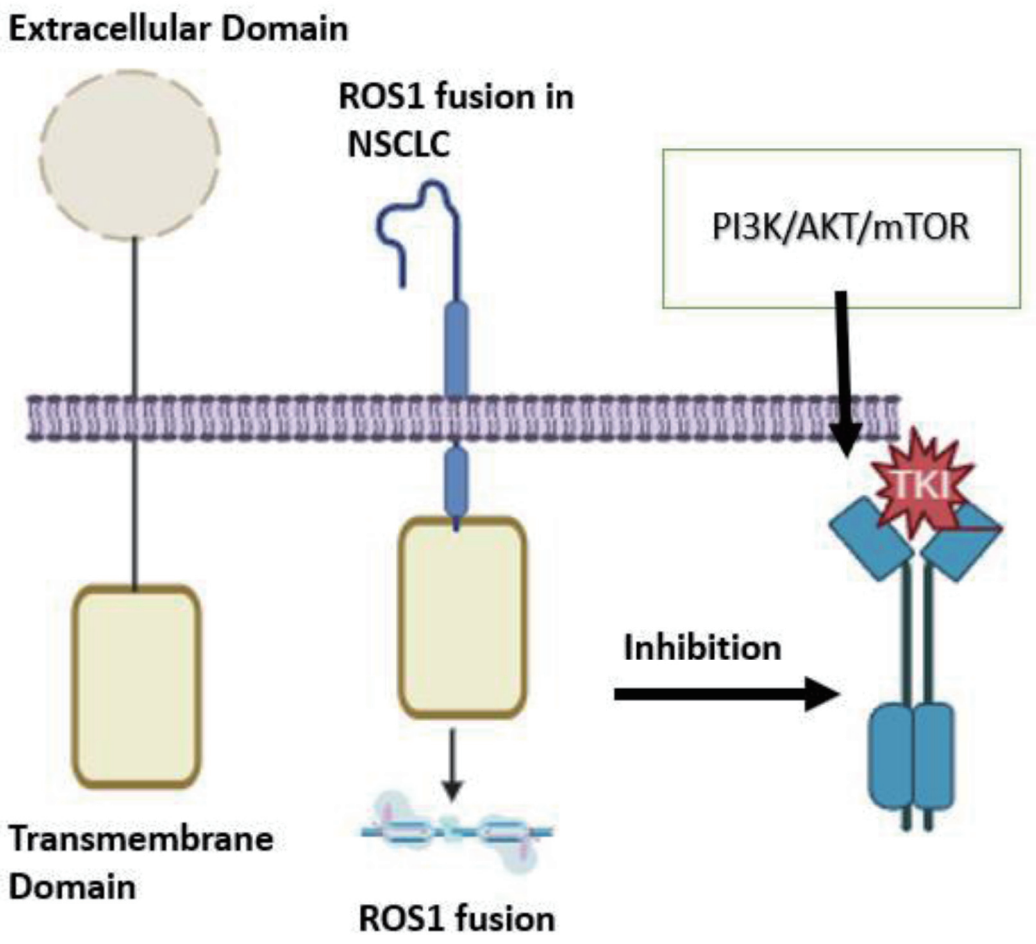


Figure 1: Tyrosine kinases receptor

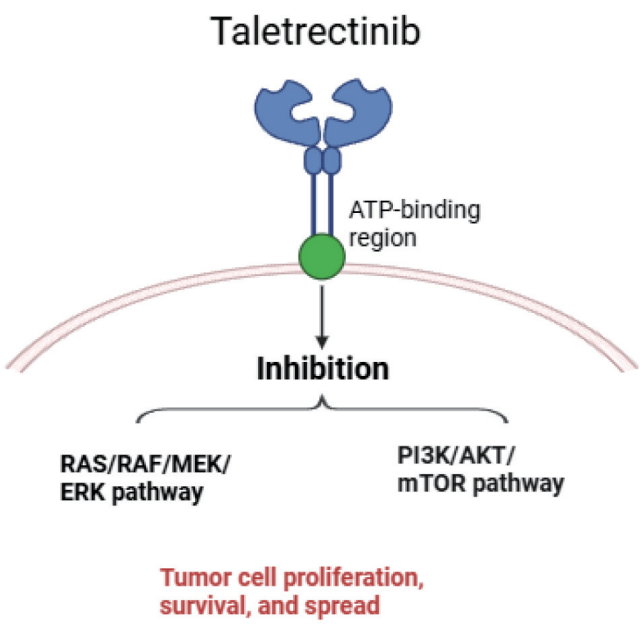


Figure 2: Mechanism of action Taletrectinib

provides a broader and more durable therapeutic advantage to patients with advanced non-small cell lung cancer and other cancers associated with fusion proteins(42).

Taletrectinib in ROS1-Affected Patients

One potent ROS1 TKI that works well in the central nervous system is taletrectinib. In cellular investigations, it demonstrates low nanomolar potency against resistance-granting mutations and ROS1 fusions, including G2032R. Taletrectinib exhibits enzymatic selectivity for ROS1 in vitro, including both wild type and resistant mutations. Its half-maximal inhibitory concentration (IC50) for ROS1 is two times lower than that of TRKC (0.18 nM) and 20 times lower than that of TRKA and TRKB (0.07 nM versus 1.26 nM and 1.47 nM, respectively).Taletrectinib exhibits promising intracranial action in preclinical investigations and has exceptional blood-brain barrier penetration.. In an orthotopic CNS model of ROS1+ NSCLC, taletrectinib consistently penetrated the brain and increased survival in mice with intracranial patient-derived xenograft tumors when compared to either vehicle or repotrectinib. Two phase I trial results and an interim review of TRUST-I demonstrated that taletrectinib offers a good safety profile in addition to clinically meaningful effectiveness (43).

Phase 1

The first-in-human phase I study of taletrectinib was conducted in the United States in patients with neuroendocrine tumors, tumor-induced pain, or cancers with ROS1/neurotrophic tyrosine kinase receptor (NTRK) rearrangements (NCT02279433). Determining the maximum tolerated dosage (MTD) and evaluating safety and tolerability were the primary objectives of the study. Assessing the anticancer effectiveness and pharmacokinetics of dietary impacts were secondary objectives. It was found that among the 46 patients, the exposure (AUC 0–8) and steady-state peak concentration (C max) rose dose-dependently from 50 mg to 800 mg administered once daily. Dose-limiting toxicities, including grade 3 increases in transaminases, were observed in two of the patients who were administered the 1,200 mg once-daily dose. A MTD of 800 mg once daily was established. Among treatment-related side events, nausea (47.8%), diarrhea (43.5%), and vomiting (32.6%) were the most frequently reported.A decrease in pain scores was observed in the group that was given 800 mg once daily. A confirmed objective response rate of 33.3% indicated the initial effectiveness of taletrectinib for six patients with RECIST-evaluable crizotinib-refractory ROS1 NSCLC(44). The pooled data of patients with ROS1 NSCLC who were enrolled in the phase I studies conducted in the US or Japan was later published. Japan also conducted a phase I study of taletrectinib (NCT02675491) at the same time. Taletrectinib was administered orally at 400, 600, 800, and 1200 mg once daily in addition to 400 mg twice daily as part of the dose-escalation process. The median follow-up length for the 18 patients with ROS1 NSCLC who were evaluated for response out of the 22 patients was 14.9 months (95% CI: 4.1–33.8).With a disease control rate of 100% (70.1–100), the confirmed objective response rate (ORR) for patients who had never used ROS1 TKI (N = 9) was 66.7% (95% CI: 35.4–87.9). The validated ORR for patients who had previously received crizotinib (N = 6) was 33.3% (95% CI: 9.7–70.0), with a disease control rate of 88.3% (95% CI: 443.6–97.0). Patients who were exclusively resistant to crizotinib (N = 8) had a median progression-free survival (PFS) of 14.2 months (95% CI: 1.5–not reached), whereas patients who were not taking ROS1 TKI (N = 11) had a median PFS of 29.1 months (95% CI: 2.6–not reached). Aspartate transaminase elevations (72.7%), alanine transaminase elevations (72.7%), nausea (50.0%), and diarrhea (50.0%) were the most frequently reported adverse effects of the drug. Increases in alanine transaminase (18.2%), aspartate transaminase (9.1%), and diarrhea (4.5%) were among the adverse events that were grade 3 or above. Despite the small patient group, the safety profile and clinical activity were encouragin(45,46).

Phase 2

The regional phase II trial (TRUST-I, NCT04395677) being carried out in China is the basis for the present phase II results for taletrectinib. The trial included 40 patients who had never had TKI therapy and 21 patients who had previously undergone crizotinib treatment. Preclinical exams stable, asymptomatic brain metastases.Those who had previously received any ROS1-TKI treatment other than crizotinib were not allowed to take part. A daily dosage of 600 mg of taletrectinib was given to the participants. Overall response rates (ORRs) were 52.6% (95% CI: 35.8–69) in 38 patients who had previously received ROS1 TKIs and 92.5% (95% CI: 83.4–97.5) in 67 patients who had not previously taken ROS1 TKIs, indicating significant efficacy outcomes in the preliminary data. Four out of the five patients with the ROS1 G2032R resistance mutation reported a partial response, while one patient had stable disease. Twelve patients who had detectable CNS metastases at baseline had an intracranial ORR of 91.7% (95% CI: 61.5–99.8).

Aletrectinib was generally well tolerated by patients. Elevated alanine aminotransferase (64.0%), increased aspartate aminotransferase (70.8%), diarrhea (61.2%), vomiting (43.3%), nausea (42.1%), anemia (35.4%), decreased white blood cell count (22.5%), abnormal liver function (20.8%), and dizziness (20.8%) were the most frequent treatment-emergent adverse events (TEAEs) of any severity in the 178-person taletrectinib 600 mg safety cohort. Except for four patients (2.2%) who had grade 4 decreased white blood cell counts, no other grade 4 or 5 adverse events were noted for these common TEAEs.Abnormal liver function (6.7%), elevated alanine aminotransferase (7.3%), and increased aspartate aminotransferase (6.7%) were the only treatment-related grade 3 adverse events that affected more than 5% of participants. There were 178 patients, and one patient (0.6%) experienced grade 3 dizziness. TEAEs that required a dose decrease occurred in 36 patients (20.2%), and TEAEs that resulted in the cessation of taletrectinib were experienced by nine patients (5.1%).

Inhibition of TRKB in the brain may contribute to the high frequency of adverse central nervous system side effects associated with entrectinib. The ideal ROS1 tyrosine kinase inhibitor of the next generation should be able to traverse the blood-brain barrier and deliver its intracranial anticancer effects without inhibiting TRKB in the central nervous system. Examining the association between intracranial objective response and one specific CNS-related side effect, dizziness, in four separate ROS1 TKIs, we observed that taletrectinib displayed a unique mix of outstanding intracranial antitumor efficacy and insignificant CNS adverse effects.

The US FDA has classified taletrectinib as a breakthrough medication for the treatment of adult patients with advanced or metastatic ROS1+ NSCLC who have either never undergone TKI treatment or have already received crizotinib treatment, based on the clinical evidence that has been acquired thus far(44–46).

Global phase II investigation ongoing

Taletrectinib's unique properties seen in both in vitro and in vivo experiments, along with encouraging clinical results from the regional TRUST-I study, indicate the need for more research on the medication in a wider patient population. Thus, the global phase II trial, TRUST-II, NCT04919811, is under underway. The TRUST-II trial is a multicenter, global, open-label, single-arm, phase II study that aims to assess the safety and effectiveness of taletrectinib for patients with advanced or metastatic non-small cell lung cancer (NSCLC) and other solid tumors that test positive for ROS1.. More than 80 study sites in Asia, Europe, and North America including but not limited to the United States, Canada, China, France, Italy, Japan, Korea, Poland, and Spain will be used for this trial.

Four cohorts will make up the study population, which will include 119 patients in total:

Cohort 1: ROS1+ NSCLC patients who have never received ROS1 TKI treatment who are either systemic chemotherapy naive or have received one previous line of chemotherapy

Cohort 2: Patients whose illness has progressed after receiving treatment with one ROS1 TKI (entrectinib or crizotinib). These patients may have never received chemotherapy before or may have had one line of treatment based on pemetrexed and/or platinum for locally advanced or metastatic non-small cell lung cancer;

Cohort 3: Patients whose illness has progressed after receiving treatment with two or more ROS1 TKIs. For locally advanced or metastatic NSCLC, they may have received two or more lines of chemotherapy based on platinum and/or pemetrexed, or they may be chemotherapy naive.

Cohort 4: Individuals who have not received any ROS1 TKI but have either never undergone systemic chemotherapy or have received two or more previous lines of chemotherapy. We will include patients with solid ROS1+ tumor types other than non-small cell lung cancer.

The primary objective of this study is to evaluate the efficacy of taletrectinib in patients with advanced or metastatic ROS1+ non-small cell lung cancer (NSCLC) from cohorts 1 and 2, as demonstrated by confirmed objective response rates (ORR) based on the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1), as assessed by an independent radiology review committee (IRC). Secondary objectives include evaluating overall survival for patients in cohorts 1 and 2, evaluating the safety and tolerability of taletrectinib across all cohorts, describing the pharmacokinetic profile of taletrectinib, and analyzing the efficacy through duration of response (DOR), progression-free survival (PFS), time to treatment failure, and time to response as assessed by the IRC. The investigators also seek to investigate efficacy via ORR, DOR, and PFS. The exploratory objectives encompass: evaluating intracranial efficacy according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria by the IRC (for cohorts 1 and 2); investigating efficacy in cohort 2 patients with specific ROS1 secondary mutations; assessing taletrectinib's effectiveness in patients who have previously undergone treatment with two or more tyrosine kinase inhibitors (TKIs) (cohort 3) and in patients with non-NSCLC solid tumors (cohort 4); as well as examining biomarkers of either sensitivity or resistance to taletrectinib found in tumor tissue and/or peripheral blood.

According to the dose regimen, each patient will get 600 mg of taletrectinib orally once daily at approximately the same time each day; it should be given at least two hours before or after a meal. The maximum tolerated dose (MTD) of taletrectinib in U.S. patients during phase I study DS6051-A-U101 (NCT02279433) was 800 mg once daily, which is higher than the 600 mg weekly dosage. However, the MTD in Japanese participants in phase I study DS6051-A-J102 (NCT02675491) was utilized to further refine the appropriate dosage for individuals enrolled in Western countries. As long as the patient has completed at least one cycle of the initial treatment with taletrectinib at 600 mg once daily and exhibits good tolerability (no adverse events greater than grade 2) based on the investigator's clinical assessment, the study permits intra-patient dose adjustment for patients in cohorts 2 and 3 (apart from those from Asian countries). Taletrectinib will be administered in 21-day cycles. Until the patient passes away, withdraws their consent, the toxicity becomes unacceptable, or the disease advances in accordance with RECIST 1.1 (as determined by an independent review committee), the therapy will continue.

Before beginning treatment, the ROS1+ status of the tumor tissue will be verified by next-generation sequencing. Central confirmation of ROS1+ is not required. Tumor samples should ideally be taken as the disease progresses in order to detect any alterations linked to taletrectinib resistance. For pharmacokinetic analysis, blood samples will be drawn from approximately ten patients. Pre-dose, 0 (pre-dose), 1 (±15 min), 2 (±15 min), 4 (±24 min), 6 (±36 min), 8 (±48 min), and 24 (±2 h) post-dose on C1D1 and C1D15 are when these samples will be taken. Whole blood will also be obtained at screening and at each of the first eight cycles for the exploratory biomarker investigation. Enrollment in the trial started in September 2021, and the final data analysis for the primary outcome and two interim analyses are planned for June 2024. The first interim analysis, which comprised 22 patients who had previously received one ROS1 TKI and 18 patients who had never taken one, was recently published by [Perol 2023 Ann Oncol].39% and 59% of patients in the first two groups, respectively, had brain metastases at presentation. In patients who had never taken a ROS1 TKI before, the objective response rate (ORR) was 94% (95% CI 73–100), but in individuals who had previously had TKI treatment, it was 55% (95% CI 32–76). For both, the disease control rate (DCR) was 91% and 100%. Ninety percent of patients experienced treatment-related adverse effects; the most common ones were nausea (38%), raised ALT (61%), and elevated AST (61%). Although there were no fatalities or treatment termination due to adverse events, 24% of patients experienced dose reductions(46,47).

Toxicity of Taletrectinib

Taletrectinib is well tolerated in most patients, but similar to the other TKIs, with a palette of treatment-emergent toxicities that reflect its on-target and off-target activity. Nausea, vomiting, diarrhea, and anorexia are the most frequent gastrointestinal toxicities and are mild to moderate in nature. Hepatotoxicity, in the form of elevated liver transaminases (ALT/AST), has been noted and should be monitored while on therapy. Others have fatigue, dizziness, and anemia with laboratory test results including elevated creatinine or reduced hemoglobin. Notably, taletrectinib has a more favorable safety profile than previous ROS1 inhibitors, with fewer serious pulmonary or cardiac toxicities. Changes or temporary discontinuation are occasionally required to control adverse events, but long-term discontinuation secondary to toxicity is rare. In total, the taletrectinib toxicity profile is acceptable

Table 2: Summary of Taletrectinib Clinical Trials with References

Phase	Population	Dose	Efficacy Results	Adverse Events	References
Phase I (US)	46 pts (NET, tumor pain, ROS1/NTRK+)	50–1200 mg QD; MTD = 800 mg QD	ORR = 33.3% (in 6 evaluable crizotinib-refractory ROS1 NSCLC pts) -Pain score ↓ at 800 mg QD	Vomiting (32.6%), Diarrhea (43.5%), Nausea (47.8%) Grade ≥3: ALT ↑, AST ↑	(48)
Phase I (Japan)	22 ROS1+ NSCLC pts (dose escalation 400–1200 mg QD, 400 mg BID)	MTD = 800 mg QD	- ORR (TKI-naïve, N=9) = 66.7% (95% CI: 35.4–87.9) - ORR (crizotinib-pretreated, N=6) = 33.3% (95% CI: 9.7–70.0) - PFS (TKI-naïve, N=11) = 29.1 mo - PFS (crizotinib-resistant, N=8) = 14.2 mo	AST ↑ (72.7%), ALT ↑ (72.7%), Nausea (50%), Diarrhea (50%) Grade ≥3: ALT ↑ (18.2%), AST ↑ (9.1%), Diarrhea (4.5%	(49)
Phase II (China, TRUST-I)	61 pts: 21 crizotinib-pretreated, 40 TKI-naïve	600 mg QD	- ORR: 92.5% (TKI-naïve) - ORR: 52.6% (crizotinib-pretreated) - ORR in G2032R mutation = 80% (4/5 PRs) - Intracranial ORR = 91.7%	TEAEs (all grades): ALT ↑ (64%), AST ↑ (70.8%), Diarrhea (61.2%), Vomiting (43.3%), Nausea (42.1%), Anemia (35.4%) Grade ≥3: ALT ↑ (7.3%), AST ↑ (6.7%), Liver dysfunction (6.7%), WBC ↓ (2.2%)	(50)
Phase II Global (TRUST-II, ongoing)	119 pts, 4 cohorts (NSCLC TKI-naïve, 1 TKI-pretreated, ≥ 2 TKI-pretreated, ROS1+ non-NSCLC)	600 mg QD (option to escalate to 800 mg QD if tolerated)	Interim (Perol 2023): - ORR = 94% (TKI-naïve) - ORR = 55% (1 TKI-pretreated) - DCR = 91% & 100%	Treatment-related AEs: ALT ↑ (61%), AST ↑ (61%), Nausea (38%) 24% dose reductions; no fatal AEs	(51)

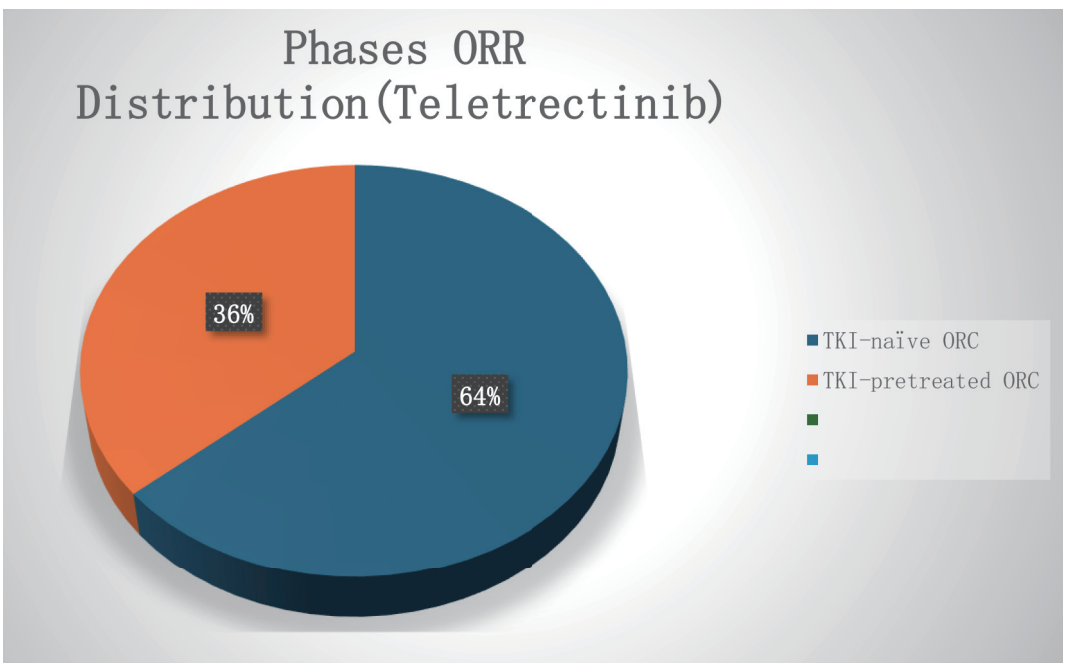


Figure 3: Phase ORR Distribution Teletrectinib

Table 3: Taletrectinib vs. Other TKIs (e.g., Midostaurin, Gilteritinib, Sorafenib) (52,53)

Feature	Taletrectinib	Other TKIs (e.g., Midostaurin, Gilteritinib, Sorafenib)
FLT3 Selectivity	Primarily targets ROS1 in NSCLC, not specific to FLT3-ITD (no direct data for FLT3-ITD AML)	FLT3-selective inhibitors with variable off-target profiles
Potency	Potent and CNS-active ROS1 inhibitor (not evaluated in FLT3-ITD AML)	Potency in FLT3-ITD AML varies by agent; quizartinib has a low IC_{50} for FLT3-ITD
Efficacy in Relapsed/ Refractory AML	Not studied/indicated in FLT3-ITD AML; current use is for ROS1-positive NSCLC	Quizartinib, gilteritinib, etc., have demonstrated efficacy in FLT3-ITD AML
Dosing Convenience	Once-daily oral dosing (600 mg QD in NSCLC trials)	Varies—midostaurin often twice daily; gilteritinib once daily
Safety Profile	Reported QTc prolongation, hepatotoxicity, pneumonitis, hyperuricemia, etc., in NSCLC patients	FLT3-targeted TKIs have varied off-target toxicities (GI, rash, myelosuppression)
Resistance Profile	Designed to overcome ROS1-G2032R resistance in NSCLC; no data in FLT3-ITD AML	Some resistance exists in FLT3-TKIs; research in sequential and combination therapy is ongoing
Combination Potential	Evaluated in NSCLC combinations; no data in AML combinations	FLT3-TKIs are being tested with chemotherapy, HMAs, venetoclax, etc.

Table 4: Taletrectinib drug interaction with other drugs(43,54)

Drug	Interaction with Taletrectinib
Strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, ritonavir, clarithromycin)	Increase taletrectinib exposure.
Strong CYP3A inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort)	Decrease taletrectinib exposure.
Moderate CYP3A inhibitors/inducers	Alter taletrectinib plasma levels.
Proton pump inhibitors (PPIs) (e.g., omeprazole, esomeprazole)	Reduce taletrectinib absorption.
H2 receptor antagonists (e.g., famotidine, cimetidine)	Reduce taletrectinib absorption if given close in time.
Antacids (locally acting) (e.g., aluminum hydroxide, magnesium hydroxide, calcium carbonate)	May reduce absorption; separate dosing (≥2 hrs before or after) recommended.
Drugs that prolong QTc (e.g., amiodarone, sotalol, quinidine, dofetilide)	Additive QTc prolongation risk.
Grapefruit / grapefruit juice	ncreases taletrectinib exposure.

and warrants its ongoing clinical exploration, with a priority on ROS1-positive NSCLC patients after previous treatments(55).

Taletrectinib dose

600 mg oral once a day, to be administered on an empty stomach i.e., no food at least 2 hours before and 2 hours after administration

200 mg capsules; usually administered as three capsules once daily at the same time(56).

Conclusion

People with ROS1-positive NSCLC, including those with brain metastases, have shown remarkable clinical efficacy and acceptable tolerability with taletrectinib. It has the potential to be a very effective treatment because of its ability to enter the central nervous system and fix resistant mutations. Current international research is still being conducted to evaluate its efficacy in different patient populations, and initial results support its status as a beneficial

therapeutic alternative, especially for patients who have demonstrated resistance to previous ROS1 inhibitors.

Conflict of interest

The authors declare that there is no conflict of interest.

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