An updated Review on Therapeutic Potential of Entrectinib as a Promising TrK, ROS 1, and ALK Inhibitor in Solid Tumors and Lung Cancer

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ABSTRACT

Entrectinib is a selective inhibitor of tyrosine kinases, tropomyosin receptor kinases that targets oncogenic rearrangements in Neurotropic Tyrosine Receptor kinase, c-ros oncogene 1 and Anaplastic lymphoma kinase used for the treatment of various solid tumors. Entrectinib gained its first worldwide approval in Japan in June 2019 for the treatment of NTRK fusion-positive, advanced or recurring solid tumours in adults and children. In August 2019, drug got FDA approval for the treatment of solid tumors in adult and children aged 12 and above. This article summarizes current status of Entrectinib from ongoing clinical trails and ideal place for drug in therapy.

Keywords: Entrectinib; non-small cell lung cancer; TrkA; TrkB; TrkC; NTRK; ALK; ROS1.

1. INTRODUCTION

Entrectinib (Rozlytrek®) a pan-TRK, ROS1 and ALK inhibitor has a promising potential as a highly effective and safe oral targeted therapy for advanced solid tumours with molecular alterations in tyrosine kinases tropomyosin receptor kinase kinases (Trk) -A, B, and C, ROS1, and ALK [1-2].

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Entrectinib gained its first worldwide approval in Japan in June 2019 for the treatment of NTRK fusion-positive, advanced or recurring solid tumours in adults and children [3]. The Food and Drug Administration (FDA) authorised the drug Entrectinib on August 15, 2019 for the treatment of solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without acquired resistance mutation in adults and children aged 12 and above [4]. This review outlines the chemistry, mechanism of action, pharmacokinetics, pharmacodynamic, adverse effect and clinical trials of Entrectinib drug as a promising anticancer agent.

2. CHEMISTRY AND MECHANISM OF ACTION

Entrectinib, also referred as RXDX-101 (Fig. 1) a 3-Aminoindazole [5] is a small molecule, which inhibits TRKA, TRKB, TRKC, ROS1, and ALK rearrangements [6-7]. Structurally N-(5-((3,5-difluorophenyl)methyl)-1H-indazol-3-yl)-4-(4-methylpiperazin-1-yl)-2-(oxan-4-ylamino) benzamide having molecular formula C$_{31}$H$_{34}$F$_{2}$N$_{6}$O$_{2}$ and average molecular weight of 560.6 g/mol [8].

Entrectinib is a tyrosine kinase receptor inhibitor. The RTK super family of proteins is encoded by 58 RTK genes in the human genome which are divided based on the kinase domain sequence into 20 subfamilies [9]. It inhibits tropomyosin receptor tyrosine kinases (TRK) TRKA, TRKB, and TRKC as well as the proto-oncogene tyrosine-protein kinase ROS1 and anaplastic lymphoma kinase (ALK) by the activation of mitogen-activated protein kinase, phosphoinositide 3-kinase, and phospholipase C-y resulting in TRK receptors to stimulate cell proliferation [10]. With the addition of downstream JAK/STAT activation, ALK creates comparable signalling [11]. Inhibition of these mechanisms inhibits cancer cell growth and changes the balance toward apoptosis, resulting in tumour volume reduction. (Fig. 2)

Entrectinib have capacity to traverse the blood-brain barrier (BBB). It was first proven when it inhibited tumour development in animals that had been intracranially injected with a human lung adenocarcinoma epithelial cell line [12]. Enrolled patients aged 18 years or older receives Entrectinib orally at a dose of at least 600 mg once per day in a capsule, it takes about 4 to 6 hours for Cmax to be reached. Based on total radioactivity recovered in urine and faeces, oral bioavailability is expected to be at least 50%. With a 99 percent binding rate and Vd/F of 551 L and 81.1 L respectively, Entrectinib and its active main metabolite M5 are both highly bound to plasma proteins. It belongs to the Biopharmaceutical classification system

![Drug Structure](image_url)

Drug Name : Entrectinib  
Brand name : Rozlytrek  
Molecular weight : 560.6  
IUPAC Name : N-(5-((3,5-difluorophenyl)methyl)-1H-indazol-3-yl)-4-(4-methylpiperazin-1-yl)-2-(oxan-4-ylamino)benzamide

Fig. 1. Pharmacokinetics and pharmacodynamics
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(BCS) class 2 of drugs. The AUC and Cmax of the drug were elevated by 15% and 6% respectively when a single dosage of 600 mg Entrectinib was given with a high fat and high calorie meal which indicates that food did not have a significant effect on drug. Following oral administration of a single oral dose of radio labeled Entrectinib, 83 percent of radioactivity was excreted in faeces (36 percent was unchanged and 22 percent was M5) and 3 percent was excreted in urine. The CL/F is 19.6 L/h and 52.4 L/h for Entrectinib and M5, respectively [13]. The half life of Entrectinib and M5 were estimated to be 20 and 40 hours respectively. It has a blood-to-plasma ratio of 1.3 while M5 has a ratio of 1.0 [14]. Entrectinib is metabolised primarily by CYP3A4. The active metabolite M5 is the only major active circulating metabolite and circulating M5 exposures at steady-state in patients were 40 percent of the corresponding Entrectinib exposure [15]. The acidulant counteracts Entrectinib self buffering and lowers the effect of stomach pH increase according to biorelevant in vitro tests, dissolution studies, and in silico modelling. Sensitivity analysis using the PBPK has been confirmed [16].

Entrectinib is a strong and selective inhibitor of TrkA/B/C and ROS1 with IC50 values of 1.7 and 0.2 nM inhibiting downstream pathways such as Trk phosphorylation, cell cycle arrest and death, cell proliferation suppression and tumour growth suppression (in vitro/in vivo) [17] and the drug is biochemically 7–8-fold more potent than crizotinib (approved for ROS1 fusion-positive NSCLC) against ALK [18]. Entrectinib's ability to penetrate the CNS allows it to target CNS metastases and primary brain tumours, which is consistent with the drug's ability to remain inside the CNS [19].

![Mechanism of action of Entrectinib](image)

**Fig. 2.** Mechanism of action of Entrectinib

- In vitro/in vivo tumor growth inhibition
- Inhibition of cell proliferation
- Cell cycle arrest and apoptosis
- Inhibition of TRK phosphorylation
3. CLINICAL STUDY

Phase 1 dosage escalation of ALKA-372-001 in patients with advanced solid malignancies. In continuous 28-day cycles (schedule A, n = 19) patients were given RXDX-101 orally once a day in a 4 day on and 3 day off regimen for 3 weeks followed by a 7 day rest period. At each dosage level, a minimum of three patients were recruited [20]. Patients with advanced solid tumours and molecular changes in TrkA, ROS1 or ALK were treated in fed state as either (schedule B, n = 6) once daily in continuous 28-day cycles or (schedule C, n = 6) in a 4 day-on 3 day-off schedule without rest. Significant antitumor response was reported in pts with relevant molecular changes treated with Entrectinib in three distinct dosage regimens and antitumor activity was first observed in one patient with NTRK-positive CRC and in one case of ALK-rearranged neuroblastoma [21].

STARTRK-1 Phase 1/2a study of Entrectinib, in the fed state, patients with advanced solid tumours with mutations in NTRK1/2/3, ROS1 or ALK were given Entrectinib daily. Patients who are asymptomatic, untreated brain metastases were allowed to participate even if they had previously received TKI treatment. All dosage levels of Entrectinib were well tolerated. There were no DLTs or severe safety problems identified in any of the cohorts. Only G1 or G2 AEs were reported by the majority of the 15 patients [22].

Phase I/II STARTRKNG trial (NCT02650401) of Entrectinib was carried out in children, adolescents and young adults with recurrent or refractory solid tumour and primary CNS tumours with a recommended dose of 550 mg/m² daily. Patients with CNS and solid tumours harbouring target aberrations in NTRK1/2/3, ROS1 or ALK as well as neuroblastoma, independent of mutant spectrum were enrolled in the expansion cohorts. Investigator then classified the assessed molecular changes treated with Entrectinib. In three distinct dosage regimens and antitumor activity was first observed in one patient with NTRK-positive CRC and in one case of ALK-rearranged neuroblastoma [21].

4. ENTRECTINIB IN NTRK FUSION-POSITIVE SOLID TUMORS

Oncogenic drivers of several adult and paediatric tumour types include NTRK gene fusions involving either NTRK1, NTRK2, or NTRK3 (encoding the neurotrophin receptors TRKA, TRKB, and TRKC, respectively) [26]. It serves a physiological function in the central and peripheral nervous system development [27]. The effectiveness and safety of Entrectinib in patients with metastatic or locally advanced solid tumours harbouring oncogenic NTRK1, NTRK2, and NTRK3 gene fusions are evaluated from ongoing phase 1 or 2 clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2). A total of 54 persons with advanced or metastatic NTRK fusion-positive solid tumours from 10 distinct tumour types and 19 distinct histologies were included in the efficacy-evaluable group. A total of 54 patients had an objective reaction with four (7%) full responses and 27 (50%) partial responses [28]. And another data have been published on the clinical activity of the drug observed in the ALKA 372-001 and STARTRK-1 trials in which four patients with NTRK fusions were treated with Entrectinib. Patients with colorectal carcinoma, Mammary Analogue Secretory Carcinoma (MASC) and lung adenocarcinoma has confirmed partial responses and the patient with glioneural tumour had disease regression by exploratory volumetric assessment [29].

Entrectinib was found to be effective in a multicenter pooled review of worldwide clinical studies. In patients with NTRK-fusion positive solid tumours type agnostic with and without CNS illness was well tolerated generally and caused clinically substantial and sustained systemic responses [30-31].

5. ENTRECTINIB IN NON SMALL CELL LUNG CANCER

Entrectinib is a new ROS1 and NTRK inhibitor that has been authorised by the FDA for the treatment of ROS1-positive NSCLC and all solid cancers that are NTRK-driven [32]. It has a reasonable safety profile and is well tolerated making it suitable for long-term therapy in
patients with ROS1 fusion-positive NSCLC. Adult patients aged 18 years or older with locally advanced or metastatic ROS1 fusion-positive Non small cell lung cancer were enrolled in ALKA-372-001, STARTTRK-1, STARTTRK-2 ongoing clinical trial who received Entrectinib at a dosage of at least 600 mg orally once daily for at least 12 months and the response was noted that in patients with ROS1 fusion-positive NSCLC, Entrectinib is effective and provides long-term disease control [33-34]. Crizotinib is the first ROS1 inhibitor to be licensed by both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), making it the standard therapy option for patients with advanced ROS1-rearranged NSCLC and the safety and clinical activity in patients with advanced ROS1-rearranged NSCLC evaluated firstly by the Profile 1001 trial [35-36]. But the Crizotinib has poor CNS penetration as seen by ALK fusion-positive NSCLC [37]. This may leads to find a new ROS1 inhibitors with potent intracranial activity. The NCCN recommends Entrectinib as a first-line therapy option for ROS1-rearranged NSCLC, as an alternative to Crizotinib [38].

6. ADVERSE EFFECT

The integrated analysis of phase I/II studies of Entrectinib in the ROS1 safety evaluable population (n=134) shows that it has a tolerability profile that was tolerable with the majority of treatment-related side events (grade 1, 2,3,4) being mild to moderate in severity and reversible. In the combined study, no grade 5 treatment-related adverse events were recorded. The majority of adverse effects were successfully handled with dosage interruption or decrease the number of treatment-related discontinuations was minimal [39-40]. Fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea are the most common adverse events observed with Entrectinib for all grades [41]. Entrectinib may cause cardiovascular side effects such as congestive heart failure and QT prolongation [42].

7. CURRENT STATUS AND FUTURE OF ENTRECTINIB

On august 15,2019, FDA gave approval for Entrectinib drug for the treatment of solid tumors that have NTRK gene fusion without a known acquired resistance mutation are metastatic or result in severe morbidity if surgical resection is performed and have no alternative therapy or have progressed following treatment is the current status of Entrectinib [43]. Currently drug repositioning works are also performed in Entrectinib for the estimation of anti-SARS-CoV-2 activity of the drug [44]. Current and future research may assist to define the ideal place for Entrectinib treatment.

8. CONCLUSION

Entrectinib, an orally available and CNS-active pan-TRK, ROS1 and ALK inhibitor, is safe and effective in advanced solid tumours with NTRK1/2/3, ROS1 or ALK rearrangements, according to various clinical trials. The early preclinical research suggests that Entrectinib will be most effective when combined with other therapies. The ability of the drug to cross the BBB makes it have a great relevance in patients with lung cancer (NSCLC). The ongoing clinical trials and recently the drug repositioning works performed in the drug for the estimation of anti-SARS-CoV-2 activity give the optimal location for treatment.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

As per university standard guideline, ethical approval have been collected and preserved by the authors

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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