

Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of *NTRK*, *ROS1*, and *ALK* fusion-positive solid tumors

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Abstract: Entrectinib is a potent small-molecule tyrosine kinase inhibitor that targets oncogenic rearrangements in *NTRK*, *ROS1*, and *ALK*. The consolidated results of 2 Phase I trials demonstrated activity in tyrosine kinase inhibitor-naïve patients along with substantial intracranial activity. In *ROS1*-rearranged lung cancers, entrectinib results in durable disease control and prolonged progression-free survival. The drug is well tolerated and has a safety profile that includes adverse events mediated by on-target tropomyosin-related kinase A/B/C inhibition.

Keywords: entrectinib, lung cancer, NSCLC, *TRK*, *ALK*, *ROS1*

Introduction

Recurrent gene rearrangements are oncogenic drivers in a variety of hematological and solid malignancies.¹ The discovery and successful targeting of oncogenic fusion kinases have driven a major paradigm shift in oncology; namely, that therapy selection can potentially be based on molecular enrichment instead of purely on histology for some alterations, recognizing that the sensitivity to targeted therapy may be context-dependent for others. Entrectinib is an orally bioavailable small-molecule inhibitor of *NTRK1/2/3*, *ROS1*, and *ALK*.² In this review, we focus on the pharmacological profile, safety, and tolerability of this agent. A literature search was performed to identify clinical studies with the investigational agent.

Genomic targets

Gene fusions involving *NTRK1/2/3* and *ALK* and *ROS1* are well-established, clinically actionable drivers of oncogenesis across multiple cancers.³ *ALK* rearrangements are enriched in non-small cell lung cancers (NSCLCs), where they are found in 3%–4% of cases, but are also found in other cancer types, including anaplastic large cell lymphoma (ALCL), renal cell, breast, colorectal, and esophageal cancers.⁴ Four targeted therapies (crizotinib, ceritinib, alectinib, and brigatinib) have been approved by 1 or more regulatory agencies for patients with *ALK*-rearranged lung cancers. *ROS1* fusions are found in 1%–2% of unselected NSCLCs, and are also identified in glioblastomas and cholangiocarcinomas, among other tumors.^{4–10} Crizotinib is approved for *ROS1*-rearranged lung cancers based on improvements in overall response rate (ORR) and progression-free survival (PFS) compared with historical outcomes with chemotherapy.¹¹

The tropomyosin-related kinase (TRK) proteins TRKA, TRKB, and TRKC have important roles in the development and function of neurons of the central and peripheral nervous systems.¹² These are transmembrane glycoproteins that are each encoded by distinct genes: *NTRK1*, *NTRK2*, and *NTRK3*, respectively.^{3,12} Neurotrophin-mediated receptor dimerization is initiated by the binding of 1 of 4 neurotrophin family ligands: nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and NT-4 to 1 or more TRK receptors. Binding then leads to autophosphorylation of tyrosine residues in the intracellular domain and the activation of several signal cascades, including the mitogen-activated protein kinase, phosphatidylinositol-3-kinase, and Janus kinase-signal transducer and activator of transcription pathways.¹²

Genomic alterations involving *NTRK* include chromosomal rearrangements, point mutations, in-frame deletions and splice variants;¹³ however, only *NTRK* fusions are widely recognized to be clinically targetable. These fusions have been identified to be the predominant drivers of certain rare tumor types, such as mammary secretory carcinoma, mammary analog secretory carcinoma (MASC), and congenital fibrosarcoma.¹³ Intriguingly, the frequency of *NTRK* fusions is much lower (<1%) in a wider array of common cancers, such as other sarcomas, gastrointestinal tumors, and lung cancers.^{13–15}

Structure, pharmacology, and preclinical activity

Entrectinib, also known as RXDX-101 (Figure 1), is a small molecule, which inhibits TRKA, TRKB, TRKC, *ROS1*, and *ALK* rearrangements.^{2,16,17} In preclinical studies, entrectinib demonstrated potent antitumor effects in engineered murine or human tumor cell lines and patient-derived xenograft (PDX) tumor models. In vitro, entrectinib potently inhibited TRKA/B/C, *ROS1*, and *ALK* at low nanomolar

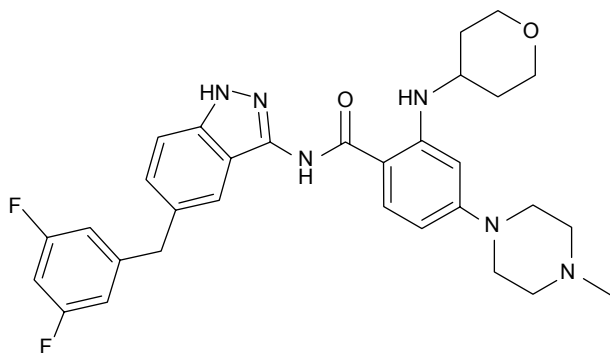


Figure 1 Chemical structure of entrectinib.¹⁸

concentrations, with average median inhibitory concentrations (IC₅₀) of 0.002, 0.00057, and 0.0011 μM against TRKA/B/C enzymes, respectively, 0.007 μM against ROS1, and 0.019 against ALK.^{18–20} In KM-12, a colorectal cancer cell line, which is driven by a *TPM3-NTRK1* gene fusion, entrectinib showed potent anti-proliferative, cell cycle arrest, and apoptotic effects, with the inactivation of downstream genes, such as *AKT*, *ERK*, and *PLCγ1*.^{16,20} The drug also selectively repressed *ALK*-dependent signaling in *ALK*-dependent patient-derived colorectal cancer, lung cancer, ALCL, and neuroblastoma cell lines.¹⁶ In vivo, entrectinib has displayed anti-tumor activity and induced tumor regression in mouse PDX models of colorectal cancer harboring a *TPM3-NTRK1* gene fusion, soft tissue sarcoma with a *TPM3-NTRK1* gene fusion, lung cancers with *MPRIP-NTRK1*, *ETV6-ROS1*, *SCD4-ROS1*, *CD74-ROS1*, and *ALK* fusions, head and neck cancer with an *ETV6-NTRK3* gene fusion, and acute myeloid leukemia with an *ETV6-NTRK3* gene fusion. Complete tumor regression was observed in Karpas-299 and SR-786 PDX models harboring *NPM1-ALK* rearrangements. In addition, entrectinib was also found to inhibit tumor growth, delay tumor progression, and cause tumor death in an *SY5Y-TRKB*-rearranged PDX model of neuroblastoma overexpressing TRKB. When entrectinib was tested in a murine model intracranially injected with the NSCLC tumor cell line NCI-H2228, it inhibited tumor growth and survival was dose-dependent.^{16–21}

Entrectinib's pharmacokinetic profile has been well studied in the Phase I setting. All current protocols utilize entrectinib in the fed condition, which is defined as within 30 minutes of meals. Entrectinib is highly protein bound, and in humans, the plasma protein binding is about 99.5%. It is known to readily cross the blood–brain barrier. In mice, exposure of entrectinib for both C_{max} and the area under the concentration–time curve in the brain was ~20% of plasma exposures following a single dose. Time to maximal concentration (T_{max}) was 2–4 hours in the fasted state and appeared to occur later (5–7 hours) in the fed state. Exposures to entrectinib increased linearly across the studied dose ranges. The mean terminal half-life was ~20 hours in the fed state, which supports once-daily dosing. Entrectinib is mainly metabolized by CYP3A4 with minor contribution from CYP2C9 and CYP1C19.^{2,16,18}

Safety and tolerability

In normal cells, proteins of the TRK family are involved in the regulation, differentiation, and apoptosis of neurons.^{13,22,23} The TRKA/B/C are the preferred receptors of growth factors,

such as NGF, BDNF, and NT-3, as previously described. Germline mutations involving the *NTRK1* gene in humans can cause congenital insensitivity to pain and mental retardation. Mice lacking TRKB have a dramatically reduced number of neurons. Knockout models of *Bdnf* ($-/-$) resulted in animals exhibiting head bobbing, spinning, and hind limb extension during locomotion. Heterozygote *Bdnf* knockouts develop hyperphagia and obesity. Mice bred with a *Trkc* ($-/-$) knockout exhibit abnormal movements and postures, which are most likely caused by deficiency in proprioceptive neurons.^{12,23,24}

Entrectinib is safe and well tolerated as a single agent. Its toxicity profile has been presented in a study combining 2 Phase I clinical trials (ALKA-372-001 trial and STARTRK-1 study).² Fifty-four patients with previously-treated advanced solid tumors harboring *NTRK1/2/3*, *ROS1*, or *ALK* alterations were included in the ALKA-372-001 dose-escalation study. Sixty of the 119 patients had an *NTRK 1/2/3*, *ROS1*, or *ALK* gene rearrangement. Fifty-three patients had genomic alterations, including point mutations, amplifications, insertions, deletions, and/or copy number variants and 6 patients enrolled in these studies did not have a known *NTRK 1/2/3*, *ROS1*, or *ALK* alteration.² Entrectinib was administered at different dosing schedules (Table 1). All patients in the STARTRK-1 study received entrectinib treatment daily continuously while on the study. A continuous dose of 600 mg daily was then identified as the maximal tolerated dose and recommended Phase II dose (RP2D) in adults. In both studies, dose-limiting toxicities were evaluated during cycle 1. The drug-related adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03. No treatment-related Grade 5 AEs were reported in either trial. The only Grade 4 drug toxicity observed was an eosinophilic myocarditis

event on STARTRK-1. The most frequently reported AEs were fatigue/asthenia (46%), dysgeusia (42%), paresthesia (29%), nausea (28%), myalgia (23%), diarrhea (19%), vomiting (17%), arthralgia (16%), dizziness (16%), constipation (12%), and weight gain (10%).²

A similar adverse effect profile was described in an analysis of 203 patients treated at the RP2D dose across 3 clinical studies in adult patients. Most of the AEs were grade 1–2 and reversible. In these 203 patients, treatment-related AEs led to dose interruption in 32% of patients, dose reduction in 19% of patients, and permanent discontinuation of study treatment in 3% of patients.²⁵ There was no evidence of cumulative toxicity, QTc prolongation, or clinically significant hepatic toxicity^{2,25} (Table 2).

Efficacy

The clinical activity of entrectinib has been assessed in 4 ongoing clinical trials (Table 1). The combined results from 2 early-phase clinical trials (ALKA-372-001 and STARTRK-1), which included a total of 119 patients were reported in early 2017. Thirty patients whose tumors harbored 1 of the 5 gene fusions of interest (*TRKA/B/C*, *ROS1*, and *ALK*), who were tyrosine kinase inhibitor (TKI)-naïve, and whose dosing achieved therapeutic exposures consistent with 600 mg entrectinib daily were defined as a “Phase II-eligible population”. The results of the activity of entrectinib in patients with *ROS1* fusions in *ROS1* inhibitor-naïve NSCLC patients enrolled across the STARTRK-2, STARTRK-1, and ALKA-372-001 studies were presented at the International Association for the Study of Lung Cancer 18th World Conference on Lung Cancer^{2,25} (Table 3).

In the subgroup of *NTRK*-rearranged cancers (n=4), all patients, with various tumor histologies and fusion types,

Table 1 Entrectinib clinical trials

Study	Patient population	Study design	Dose and schedule
ALKA-372-001 ²	Locally advanced or metastatic cancer targeting <i>NTRK1</i> , <i>NTRK2</i> , <i>NTRK3</i> , <i>ROS1</i> , or <i>ALK</i> molecular alterations	Phase I basket	100–1,800 mg/m ² Schedule A (n=19): fasted, 4 days on and 3 days off for 21 of 28 days Schedule B (n=29): fed, continuous daily dosing for 28 days Schedule C (n=6): fed, 4 days on and 3 days off for 28 days
STARTRK-1 ²	Locally advanced or metastatic cancer targeting <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> molecular alterations	Phase I basket	100–1,800 mg/m ² Fed, continuous daily dosing for 28 days (n=65)
STARTRK-2 ³⁶	Solid tumors that harbor an <i>NTRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> gene fusion	Phase II basket	600 mg Fed, continuous daily dosing for 28 days
STARTRK-NG ²⁶	Children with recurrent or refractory solid tumors and primary CNS tumors, with or without <i>TRK1/2/3</i> , <i>ROS1</i> , or <i>ALK</i> fusions	Phase I/Ib	250 mg/m ² Fed, continuous daily dosing for 28 days

Abbreviations: ALK, anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine kinase; ROS1, ROS proto-oncogene 1; CNS, central nervous system.

Table 2 Entrectinib safety summary

	Most common treatment-related adverse events	Patients treated at the RP2D (N=203)	
		All grades (%)	Grade 3 (%)
On-target AEs potentially mediated by TRK inhibition	Dysgeusia	78 (38)	1 (0.5)
	Dizziness	46 (23)	1 (0.5)
	Weight increased	39 (19)	10 (5)
	Paresthesia	32 (16)	–
Other AEs	Fatigue	59 (29)	6 (3)
	Constipation	47 (23)	1 (0.5)
	Diarrhea	35 (17)	1 (0.5)
	Nausea	33 (16)	–
	Myalgia	27 (13)	1 (0.5)
	Peripheral edema	25 (12)	–
	Anemia	23 (11)	9 (4)
	Blood creatinine increased	22 (11)	1 (0.5)
	Vomiting	22 (11)	–
	Arthralgia	21 (10)	1 (0.5)

Note: Data from Drilon et al² and Myung-Ju Ahn et al.²⁵

Abbreviations: AEs, adverse events; RP2D, recommended Phase II dose; TRK, tropomyosin-related kinase.

benefited from entrectinib. These included patients with glioneuronal tumor (*BCAN-NTRK*), NSCLC (*SQSTM1-NTRK1*), MASC (*ETV6-NTRK3*), and colorectal cancer (*LMNA-NTRK1*).² In addition, in the ongoing dose escalation pediatric entrectinib study, a 20-month-old boy with infantile fibrosarcoma harboring an *ETV6-NTRK3* fusion had a significant tumor regression of central nervous system

Table 3 Efficacy in Phase II-eligible adult patients

	ALKA-372-001 and STARTRK-1, ORR (%) / PFS (months) / OS (months)	ALKA-372-001, STARTRK-1 and STARTRK-2, ORR / PFS (months) / OS (months)
Patients with <i>NTRK</i> fusion-positive solid tumors	4/4 (100%) / not reached / not reached	Pending
Patients with <i>ROS1</i> fusion-positive solid tumors	12/14 (86%) / 19 / not reached	Pending
Patients with <i>ROS1</i> fusion-positive lung cancers (WCLC 2017 update)	NA	25/32 (78%) / 29.6 / NA
Patients with <i>ALK</i> fusion-positive solid tumors	4/7 (57%) / 8.3 / not reached	Pending
Patients with genomic alterations other than gene fusions	1/59 (1.6%) / NA / NA	Pending

Note: Data from Drilon et al² and Myung-Ju Ahn et al.²⁵

Abbreviations: ALK, anaplastic lymphoma kinase; NTRK, neurotrophic tyrosine kinase; ORR, overall response rate; PFS, progression-free survival; ROS1, ROS proto-oncogene 1; WCLC, World Conference on Lung Cancer; OS, overall survival; NA, not applicable.

(CNS) metastases and clinical improvement following 1 month of therapy.²⁶

Currently, there are no commercially available oral TRK inhibitors. However, in May 2017 and October 2017, entrectinib received the breakthrough designation and priority medicines (PRIME) designation from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA), respectively, as a treatment for adult and pediatric patients with *NTRK*-positive solid tumors who have either progressed following prior therapies or who have no further standard treatment options.^{27,28} Both highlighted the need for further development of targeted approaches in this population of unmet need.

Treatment with entrectinib led to an objective response in 12 of 14 evaluable patients (86%) in the subgroup with *ROS1*-rearranged tumors, 2 of whom had a complete response. Eleven of those responding had lung cancer while the remaining 3 had melanoma. As of September 2017, 32 *ROS1* fusion-positive lung cancer patients, who had no prior exposure to *ROS1*-targeted therapies, were enrolled across the STARTRK-2, STARTRK-1, and ALKA-372-001 studies.²⁵ Responses were observed in 25 patients (ORR 78%). The median duration of response was 28.6 months (95% CI: 6.8–34.8) and the median PFS was 29.6 months (95% CI: 7.7–36.6). Entrectinib demonstrated strong CNS activity in *ROS1*-rearranged patients with measurable CNS disease at baseline with an intracranial response noted in 5 of 6 patients (ORR 83.3%).²⁵

In the *ALK*-rearranged cancers (n=7), 57% of patients experienced a response with most patients in this group having lung cancer (n=5). The tumor-agnostic activity of entrectinib in TKI-naïve patients with sensitizing rearrangements in *ALK*, *ROS1*, and *NTRK* led to robust and rapid responses being observed within the first 2 cycles of treatment. With a median duration of follow-up of 15 months, the median PFS has not yet been reached in patients harboring *NTRK1/2/3* rearranged tumors and was 19.0 and 8.3 months in patients harboring *ROS1* or *ALK*-rearranged malignancies, respectively. The median overall survival has not yet been reached among all evaluable patients.² The potent intracranial anti-tumor activity of entrectinib was observed among 5 of the 8 (63%) evaluable patients who had known primary or metastatic disease involving the brain, which included 4 patients with *NTRK1* (n=1), *ROS1* (n=2), and *ALK* (n=1)-rearranged lung cancer and 1 with *ALK*-rearranged colorectal cancer.²

The excellent response rate observed in patients harboring the 5 gene fusions of interest was not observed in the 59 patients whose tumors harbored other types of genomic alterations (non-gene fusion events), with a response in only

1 of 59 patients (*ALK* F1245V mutant neuroblastoma; entrectinib was granted orphan drug designation and rare pediatric disease designation for neuroblastoma in December 2014²⁹). Furthermore, no responses were observed in patients who had previously received an *ROS1* or *ALK* inhibitor prior to entrectinib.²

Acquired resistance to entrectinib

In cancers harboring *NTRK* fusions, like many if not all metastatic oncogene-addicted cancers, relapse will inevitably occur secondary to the selective pressures of targeted therapy leading to acquired resistance. In 1 patient with entrectinib-resistant colorectal cancer, 2 acquired resistance mutations (G595R and G667C) in the *NTRK1* kinase domain were found in the patient's circulating tumor DNA (ctDNA).³⁰ Another case of entrectinib resistance by the *NTRK3* G623R kinase domain mutation in MASC was reported.³¹

Two next-generation TRK inhibitors (LOXO-195 and TPX-0005) are being tested in clinic to overcome these recurrent resistance mutations.^{32,33} The first 2 patients with *TRK* fusion-positive cancers who developed acquired resistance mutations on another first-generation TRK-inhibitor, larotrectinib, received treatment with LOXO-195 and achieved rapid tumor responses and extended overall duration of disease control.^{33,34} When trametinib was added to entrectinib, 1 patient with *NTRK3* fusion-positive MASC harboring the solvent front mutation *NTRK3* G623R in a post-entrectinib treatment biopsy achieved a 22% reduction in tumor volume and remained on the combination treatment for 6.7 months.¹⁷

Future directions and conclusion

The data presented here show that entrectinib, an orally available and CNS-active pan-TRK, *ROS1* and *ALK* inhibitor, is safe and potent in advanced solid tumors with *NTRK1/2/3*, *ROS1*, or *ALK* rearrangements.

Entrectinib is a first-generation TRK inhibitor with activity against *TRK* fusions. The acceptance into the PRIME program of EMA, analogous to the Breakthrough Therapy Designation from the US FDA, further supports the broad potential of entrectinib as a novel treatment for patients with *NTRK*-positive tumors regardless of age and the site of tumor.

In *ROS1*-rearranged lung cancers, crizotinib gained approval from both US FDA and EMA in 2016 based on the remarkable efficacy in the Phase I PROFILE 1001 study.¹⁰ The ORR with crizotinib was 72% among 50 patients with *ROS1*-rearranged NSCLC in this trial. The median PFS reached 19.2 months.¹⁰ Another potent *ROS1* inhibitor, ceritinib, was also studied in this patient population.³⁵ Thirty-two patients with *ROS1*-rearranged metastatic lung cancers were

treated in a Phase II trial. Among crizotinib-naïve patients, the ORR to ceritinib was 67% and the median PFS reached 19.3 months.³⁵ Compared with crizotinib and ceritinib, the PFS benefit of entrectinib (29.6 months) and its superior intracranial response and side effects profile make this drug attractive as a first-line treatment in *ROS1*-rearranged lung cancers, assuming that more mature data confirm its efficacy.²⁵ Of note, although entrectinib is clinically active in *ROS1* inhibitor-naïve *ROS1*-rearranged lung cancers, the role of entrectinib will likely be much more limited in the crizotinib-resistant setting. In preclinical studies, entrectinib does not show activity against the most common resistant *ROS1* mutations, including the gatekeeper mutation, L2026M, and the solvent front mutations, G2032R and D2033N.^{16,18}

The role of entrectinib as an *ALK* inhibitor remains less clear. In the 2 Phase I studies, responses were achieved in 5 different histologies harboring *ALK* gene alterations, including lung cancers, renal cell carcinoma, cancer of unknown primary, colorectal cancer, and neuroblastoma in both adult and pediatric patients, highlighting a possible niche for the drug outside *ALK*-rearranged lung cancers. Additional clinical trials will help further define the role of entrectinib in cancers with other *ALK* alterations.²

Collectively, data obtained with entrectinib demonstrate that the drug is a viable treatment option for patients with malignancies harboring oncogenic *NTRK*, *ROS1*, or *ALK* fusions. Ongoing and future studies may help to further clarify the best place of therapy of entrectinib.

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