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Entrectinib: a potent new TRK, ROS1, and ALK inhibitor

Christian Rolfo, Rossana Ruiz, Elisa Giovannetti, Ignacio Gil-Bazo, Antonio Russo, Francesco Passiglia, Marco Giallombardo, Marc Peeters & Luis Racz

**Introduction:** Receptor tyrosine kinases (RTKs) and their signaling pathways, control normal cellular processes; however, their deregulation play important roles in malignant transformation. In advanced non-small cell lung cancer (NSCLC), the recognition of oncogenic activation of specific RTKs, has led to the development of molecularly targeted agents that only benefit roughly 20% of patients. Entrectinib is a pan-TRK, ROS1 and ALK inhibitor that has shown potent anti-neoplastic activity and tolerability in various neoplastic conditions, particularly NSCLC.

**Areas covered:** This review outlines the pharmacokinetics, pharmacodynamics, mechanism of action, safety, tolerability, pre-clinical studies and clinical trials of entrectinib, a promising novel agent for the treatment of advanced solid tumors with molecular alterations of Trk-A, B and C, ROS1 or ALK.

**Expert opinion:** Among the several experimental drugs under clinical development, entrectinib is emerging as an innovative and promising targeted agent. The encouraging antitumor activity reported in the Phase 1 studies, together with the acceptable toxicity profile, suggest that entrectinib, thanks to its peculiar mechanism of action, could play an important role in the treatment-strategies of multiple TRK-A, B, C, ROS1, and ALK- dependent solid tumors, including NSCLC and colorectal cancer. That being said, further evidence for its clinical use is still needed.

**Keywords:** Entrectinib, TrkA, TrkB, TrkC, NTRK1, NTRK2, NTRK3, ALK, ROS1, non-small cell lung cancer, colorectal cancer, salivary gland cancer, precision medicine


1. Introduction

Technological innovations and in-depth understanding of cancer heterogeneity at a molecular level have prompted the development of precise diagnostics and therapeutics. This ‘personalized oncology care’ is dramatically improving outcomes and changing cancer natural history for a constantly increasing number of subjects with specific and therapeutically relevant molecular alterations.[1,2] However, for the majority of patients with advanced disease, non-specific cytotoxic chemotherapy still is the main therapy.

In the setting of lung cancer, especially non-small cell lung cancer (NSCLC), in which most patients present with advanced and incurable disease,[3] this approach acquires even more relevance. For them, conventional chemotherapy offers an overall survival of less than a year.[4] At this time, the recognition of oncogenic activation of specific receptor tyrosine kinases (RTKs) benefits roughly 20% of patients,[5–8] and its use is limited by the eventual and universal emergence of resistance. Clearly, new active agents are urgently needed to improve current outcomes.

This review outlines the pharmacological profile, mechanism of action, safety, tolerability and relevant clinical trials of the pan tropomyosin-related kinases (Trk), ROS proto-oncogene 1 (ROS1) and anaplastic lymphoma kinase (ALK) inhibitor,
entrectinib (Drug Summary Box), a promising novel agent for the treatment of multiple neoplastic conditions, particularly NSCLC.

2. Overview of molecular biology of RTK

The human genome contains 58 RTK genes that encode the RTK superfamily of proteins [9] distributed in 20 subfamilies.[10] In general, these glycoproteins share a common structure: an extracellular binding site for polypeptide growth factors, a transmembrane-spanning region and an intracellular domain with tyrosine kinase activity [10] (Figure 1).

RTK signaling is usually initiated by ligand binding to the extracellular domain, causing oligomerization of the receptor with another adjacent RTK, allowing a tyrosine in the cytoplasmic portion of each RTK to be trans-phosphorylated by its partner receptor.[11] This, besides initiating catalytic activity, generates phosphorylated tyrosine residues which serve as docking sites for cytoplasmic signaling proteins containing Src homology-2 and protein tyrosine-binding domains.[10] These proteins recruit additional effector molecules, resulting in the assembly of membrane signaling complexes that trigger a cascade of intracellular biochemical signals.[12] The main downstream signaling cascades activated by RTKs are the Ras viral oncogene homolog/mitogen-activated protein kinases/extracellular signal-regulated kinases (Ras/MAPK/ERK) pathway, the phosphatidylinositol-3-kinase/Akt (PI3K/Akt) and the Janus-activated kinase/signal transducers and activators of transcription (JAK/STAT) pathway.[12]

RTKs and their signaling pathways control fundamental cellular processes, including the cell cycle, metabolism, proliferation, differentiation and survival.[13] Normally, activity of RTKs is tightly controlled; however, activating mutations, overexpression, fusion rearrangements or co-activation of the RTK genes can lead to dysregulation of kinase activity, which in turn can play an important role in malignant transformation.[14]

The ALK gene encodes a tyrosine kinase belonging to the insulin receptor family that activates downstream pathways including Ras/MAPK/ERK, PI3K/AKT and JAK/STAT, which are known to be involved in proliferation and survival.[15] The physiological role of ALK has not been clearly determined. Existing evidence proposes that it participates in central nervous system (CNS) development.[16] Rearrangements of the ALK gene have been detected in anaplastic large-cell lymphoma, inflammatory myofibroblastic tumors [17,18] and importantly in 3–5% of patients with NSCLC.[19] In the latter, the ALK rearrangement results in the generation of the echinoderm microtubule-associated protein-like 4 (EML4)-ALK fusion which exhibits transforming ability.[20] Also, point mutations and overexpression

<table>
<thead>
<tr>
<th>Drug Summary Box</th>
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<tr>
<td><strong>Drug name</strong></td>
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<tr>
<td><strong>Phase</strong></td>
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<tr>
<td><strong>Indication</strong></td>
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<tr>
<td><strong>Pharmacology</strong></td>
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<tr>
<td>description/mechanism of action</td>
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<tr>
<td><strong>Route of administration</strong></td>
</tr>
<tr>
<td><strong>Chemical structure</strong></td>
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**Figure 1. Overview of molecular biology and place of action of entrectinib.**
Figure 2. Extracellular matrix.

Several cancers display rearrangements or aberrant expression of Trk genes.[26] For example, NTRK1 rearrangement is detected in 3.3% of NSCLC without known oncogenic alterations [32] and also in breast,[33] papillary thyroid,[34] salivary and CRC,[35,36] among others. TrkB mutation has been found in approximately 1.39% of NSCLC.[37] Its activation is commonly present in high-risk neuroblastomas [38] and it is also associated with metastatic potential in pancreatic cancer.[39]

Despite initial success, the effectiveness of RTK-targeted therapies is universally limited by the eventual occurrence of resistance through multiples mechanisms including secondary mutations, gene amplification of the primary oncogene and up-regulation of bypass signaling tracts.[40] Therefore, the development of next-generation RTK inhibitors is crucial to treat the emergent resistant phenotypes.

3. Enteratinib

3.1 Chemistry, pharmacokinetics and metabolism

Enteratinib, previously known as RXDX-101 and NMS-E628, is an orally bioavailable small molecule single-digit nanomolar inhibitor of TrkA, TrkB, TrkC, ROS1 and ALK (Figure 2), with systemic distribution, including the CNS. Its ability to cross the blood-brain barrier (BBB) was first demonstrated by the inhibition of tumor growth, observed after its oral administration to a mice that had been intracranially injected with a human lung...
adenocarcinoma epithelial cell line.[41] This interesting observation was subsequently confirmed on a 46-year-old male, performance status 2, with a heavily pre-treated NSCLC, harboring NTRK1 fusion, who reported intracranial response after only one month of therapy with entrectinib 400 mg/mq.[44] Its pharmacokinetic profile has been defined in the Phase 1 studies, in patients with advanced solid tumors. Time to maximal concentration (T_{max}) values ranged from 2 to 4 h, and all current development of entrectinib is in the fed condition.[43,44] Entrectinib exposure (C_{max} and area under the curve) increased in a dose proportional manner up to doses of 400 mg/mq^2, with minimal accumulation following multiple doses.[42] Plasma protein binding of entrectinib in humans is ~99.5%, but plasma protein adjusted exposures at the RP2D are two to three times the target concentration at all time points based on preclinical efficacy models. The elimination half-life (T_{1/2}) is approximately 21 h at 400 mg/mq/day in the fed state.[43,44]

### 3.2 Pharmacodynamics

Entrectinib is a selective, ATP-competitive inhibitor of 5 target oncogenic drivers: TrkA, TrkB, TrkC, ROS1 and ALK. This compound exhibits great potency with half maximal inhibitory concentration (IC_{50}) ranging between 0.1 and 1.7 nM across its different targets.[42] It is, indeed, biochemically 7–8-fold more potent than crizotinib against ALK.[45]

#### 3.3 Mechanism of action from pre-clinical studies

In pre-clinical models, entrectinib has shown antitumor efficacy in ALK-driven tumors.[41] In vitro, this compound potently and selectively repressed the growth of ALK-dependent cell lines, as well as ALK-dependent signaling. In vivo, entrectinib induced complete tumor regression in mice bearing Karpas-299 and SR-786 xenografts. Likewise, it inhibited in vitro and in vivo growth of a NSCLC cell line characterized by the EML4-ALK rearrangement. Complete responses and prolonged inhibition of phosphorylation and downstream effector activation were also observed in this model. Indeed, this compound has been found to be active also against the ALK mutants responsible for crizotinib resistance, L1196M and C1156Y.[45]

Due to the fact that ALK and ROS1 kinases exhibit structural similarities, the effect of entrectinib was tested in cellular lines with ROS1-driven activated signaling and in vivo in nude mice bearing established Ba/F3-ROS1 tumors. In both cases, proliferation was restrained.[46]

Entrectinib has also shown activity against KM-12 CRC cell line.[47] This cell line is driven by constitutively active TrkA fusion (TPM3-NTRK-1), resulting in the expression of the oncogenic chimeric protein TPM3-TRKA.[48] In vitro, entrectinib demonstrated anti-proliferative effect, cycle cell arrest and apoptosis, as well as inactivation of downstream effectors such as PLCy1, AKT and ERK. In vivo, in mice bearing KM-12 xenografts, the administration of entrectinib lead to sustained tumor regression in both continuous and intermittent dosing regimens.[47]

In a xenograft model of neuroblastoma cells transfected with TrkB, entrectinib showed inhibition of Trk phosphorylation at nanomolar levels. Interestingly, in vivo, the combination of entrectinib with temozolomide plus irinotecan demonstrated increased cell growth inhibition when compared with chemotherapeutic treatment alone.[49]

### 3.4 Clinical efficacy from Phase 1 studies

Until now, entrectinib has been assessed in two early-phase clinical trials (Table 1). The ALKA-372-001 Phase 1

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Study Design</th>
<th>Schedule</th>
<th>Dose</th>
<th>Ref.</th>
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| ALKA-372-001     | Phase 1      | Entrectinib
  - A: 4 day-on, 3 day-off for 3 weeks, followed by a week of rest, fasted
  - B: Daily in continuous 28-day cycles, fed
  - C: 4 day-on, 3 day-off without rest, fed | 100–1600 mg/mq^2 | [43] |
| STARTRK-1        | Phase 1/2a   | Entrectinib
  - Daily in continuous 28-day cycles, fed | 100–400 mg/mq^2 or 800 mg as a fixed dose | [44] |

TrkA, tropomyosin-related kinase A; TrkB, tropomyosin-related kinase B; TrkC, tropomyosin-related kinase C; ALK, anaplastic lymphoma kinase; ROS-1, c-ros oncogene 1.
dose-escalation study included 31 subjects with previously treated, advanced solid tumors harboring NTRK1, ROS1 or ALK alterations. Entrectinib was prescribed with three different dosing schedules. It was orally administered after fasting, in a 4-day-on, 3-day-off fashion for 3 weeks, followed by a week of rest, in continuous cycles (schedule A, n = 19),[42] or under fed conditions once daily in continuous 28-day cycles (schedule B, n = 6), or under fed conditions in a 4 day-on, 3 day-off schedule without rest (schedule C, n = 6).[43] Taking the three arms as a whole, 7 patients (22%) had objective responses. Most of them (5/7) were NSCLC patients, including four ROS1 positive, and one ALK-rearranged tumors. Interestingly, antitumor activity was first reported also in one patient with NTRK positive CRC, and one case of ALK-rearranged neuroblastoma.[43]

A second Phase 1/2 study, STARTTRK-1,[44] investigated Entrectinib, in subjects with previously treated, locally advanced or metastatic solid tumors with NTRK1/2/3, ROS1 or ALK molecular alterations (fusions, amplifications or single-nucleotide polymorphisms). Common to the ALKA-372-001 trial, controlled and asymptomatic CNS metastases were permitted. Twenty-nine patients were enrolled at four dose levels: 100 mg/m², 200 mg/m², 400 mg/m² and 800 mg as a fixed dose. Once again, the majority of patients (n = 8) had NSCLC; other tumor types included colorectal, breast, endometrial, ovarian and renal cell carcinoma.

Altogether, these two trials enrolled 67 subjects with a variety of solid tumors with relevant molecular alterations (Table 2). Results from 17 patients with NTRK1/2/3 (n = 3), ROS1 (n = 4) or ALK (n = 10) fusions and who were ALK or ROS1-inhibitor-naïve were reported at the 2015 ASCO annual meeting. Fifty-eight percent obtained a partial (n = 9) or complete response (n = 1), including some CNS responses, and, when considering disease stabilization, this percentage raised up to 70% (n = 12). Surprisingly, out of the 11 patients who were treated at or above the recommended Phase 2 dose (RP2D), 10 (91%) achieved early objective responses lasting up to 16 cycles. Within the other 50 non-Phase 2 eligible subjects—those treated below the RP2D, or with non-fusion alterations, or ALK or ROS1-inhibitors resistant-13 patients (26%) continue on study.[43,44]

Table 2. Tumor type and molecular alterations from ALKA-372-001 (Schedule A) and STARTTRK-1.

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Molecular alteration</th>
<th>TrkA</th>
<th>TrkB</th>
<th>TrkC</th>
<th>ALK</th>
<th>ROS-1</th>
<th>Total</th>
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<td>15</td>
<td>7</td>
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<td>CRC</td>
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<td>2</td>
<td>1</td>
<td>1</td>
<td>7</td>
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<tr>
<td>Neuroblastoma/</td>
<td>1</td>
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<td>2</td>
<td>1</td>
<td>4</td>
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<td>Squamous cell carcinoma</td>
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<td>Acinic cell carcinoma</td>
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TrkA, tropomyosin-related kinase A; TrkB, tropomyosin-related kinase B; TrkC, tropomyosin-related kinase C; ALK, anaplastic lymphoma kinase; ROS-1, c-ros oncogene 1; NSCLC, non-small cell lung cancer; CRC, colorectal cancer.

The ovarian tumor exhibited both ALK and NTRK amplification.

Two patients from the STARTTRK-1 trial were found to lack molecular alterations.

were a case of grade 3 cognitive impairment and a case of grade 3 fatigue, which resolved with entrectinib interruption. As maximal tolerated dose was exceeded at 800 mg, 400 mg/m² per day was established as the RP2D in both studies. In the ALKA-372-001 trial, only two grade 3 AE (asthenia and muscular weakness that resolved with dose reduction) were observed. Other frequent AE reported were paresthesias (42%), nausea (37%), myalgia (34%), asthenia (27%), dysgeusia (27%), vomiting (21%), arthralgia (19%), diarrea (19%) and attention disturbance (11%). Remarkably, out of the 106 most common AE (>10%) reported in the ALKA-372-001 trial, only one corresponded to a grade 3 toxicity.[43] A very similar toxicity profile was described in the STARTTRK-1 trial, being additional AE constellation (22%) and dizziness (19%). From among 62 AE events described in this study, 14 (22%) were produced above the RP2D.[44] The toxicological portrait for this agent needs to be further defined in eventual Phase 2 and 3 trials and in the post-marketing setting.

3.5 Safety and tolerability

Entrectinib toxicity profile has been described in the two Phase 1 trials. No drug-related serious adverse events (AE) have been reported to date. Dose-limiting toxicities (DLTs) were evaluated during cycle 1 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. While no DLTs were observed in the ALKA-372-001 trial,[43] 2 occurred in the STARTTRK-1 study,[44] at a fixed dose of 800 mg. These

3.6 Current and future trials

In February 2015, entrectinib was granted FDA Orphan Drug designation for the treatment of TrkA, B and C, ROS1 or ALK-positive NSCLC, TrkA, B and C, ROS1 or ALK-positive CRC and neuroblastoma.[50]

Both the ALKA-372-001 and the STARTTRK-1 trials continue to recruit participants. The biopharmaceutical company Ignyta is planning to launch the STARTTRK-2 trial.
soon. This study is a basket trial that will enroll patients with NSCLC, as well as other tumor histologies, that are positive for TrkA, B, C, ROS1 or ALK, based upon molecular profiling. This design that spans multiple tumor types becomes particularly relevant for targets such as Trk, which occur infrequently.

4. Conclusion

The pre-clinical and clinical studies reviewed show the promising profile of the pan-TRK, ROS1 and ALK inhibitor, entrectinib, as a highly potent and safe oral targeted agent for advanced solid tumors with molecular alterations of TRK-A, B and C, ROS1 or ALK. Given the number of possible beneficiaries and its potential to cross the BBB, entrectinib gains particular relevance in lung cancer patients. Ongoing and further studies regarding this compound are certainly worth to follow.

5. Expert opinion

Among the several experimental drugs currently under investigation in early Phase 1 studies, entrectinib is emerging as one of the most promising compounds, showing preliminary antitumor activity in multiple solid tumors, and receiving the FDA Orphan Drug designation for the treatment of TrkA, B and C, ROS1 and ALK-positive NSCLC, CRC and neuroblastoma. Its peculiar mechanism of action, including the ability to simultaneously inhibit five different target oncogenic drivers, TRKA, TRKB, TRKC, ROS1 and ALK, together with its great potency, exhibited in both preclinical and clinical studies, make this drug very attractive for the clinical setting, giving the opportunity to develop a brand new class of weapons against a wide type of tumors, especially two big killers, such as CRC and NSCLC. Indeed, entrectinib represented the first-in-class compound to show clinical activity against TRK1/2/3-addicted tumors, including both NSCLC and CRC, suggesting NTRK1/2/3 molecular alterations a new potential predictive biomarker for target inhibition, and opening new therapeutic possibility for this subgroup of patients. Both ALK and ROS1 represent two known oncogenic drivers, reported in about 3–5%, and 1%, respectively, of NSCLC patients, typically younger, never or light smokers, with adenocarcinoma histology. Since the approval of Crizotinib, which currently represent the standard treatment of ALK-rearranged NSCLC patients, a second generation of ALK-inhibitors has been investigated in clinical trials. One of these, including Ceritinib, has been recently approved for the treatment of patients with disease progression on crizotinib, because of their ability to target specific mutations that confer resistance to crizotinib, such as the ALK tyrosine kinase gatekeeper mutation L1196M. Both these agents have shown a very great activity not only in crizotinib-refractory, but even more in naïve patients, achieving a higher PFS and greater CNS responses, compared to crizotinib, and are currently under investigation as first-line therapy. A recent trial by Shaw et al. has shown dramatic responses to crizotinib in pre-treated patients with ROS1-rearranged NSCLC, suggesting ROS1 as both predictive biomarker and new therapeutic target for clinical setting. In this scenario, entrectinib, thanks to its peculiar mechanism of action, its multi-target activity, its ability to cross the BBB, could play an important role in the treatment algorithm of both ALK and ROS1 rearranged, NSCLC. The antitumor activity reported in the Phase 1 studies are very encouraging, especially for the CNS, which represent a common site of disease progression on ALK/ROS1 inhibitors. To date no serious AEs have been reported. The most common AEs were paresthesia, nausea and myalgia, and very few cases of grade 3 AE were described, suggesting an acceptable tolerability profile, which of course needs to be further defined in larger Phase 2–3 trials.

Finally, common to the others ALK inhibitors, the studies of entrectinib represent a paradigm of the modern, biomarker-driven, early clinical trial design, including a proven oncogenic driver as biomarker, a really effective drug, and a large, molecular selected, population, which often ensure a successful result. Even if Phase 2–3 studies are needed to confirm these data, all these findings suggest that entrectinib, common to others ALK inhibitors, such as crizotinib, ceritinib or alecetinib, could be approved earlier than the Phase 3 data become available, through fast-track designation, or break-through therapy designation, leading to a new intriguing debate regarding the best treatment strategy of TRK1/2/3, ROS1 and ALK positive solid tumors, not only in NSCLC. New perspectives are also arising in possible combinations. In colon cancer, for example, entrectinib in pre-clinical analysis (xenograft models of neuroblastoma) shows an increase of inhibition in vitro when combined with chemotherapy (temozolomide and irinotecan). In the setting of lung cancer, we can hypothesize some potential combinations with immunotherapeutic drugs, but this is still a too early assumption. In short time, interesting data will come from monotherapy treatment in multiple solid tumor types.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.
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Bibliography


**Study that identified NTRK1 rearrangements by NGS or FISH in 3.3% of lung cancer patients.**
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adenocarcinomas without known oncogenic alterations.


** Pre-clinical study demonstrating entrecinhibin antagonistic activity against ALK mutations responsible for crizotinib resistance.


** First results of a Phase I dose escalation study of entrectinib in patients with advanced solid tumors with molecular alterations of TrkA, ROS 1 or ALK.


** Phase 1 study of entrectinib in patients with advanced solid tumors with molecular alterations of TrkA, ROS 1 or ALK.


** Phase 1 study of entrectinib in patients with advanced solid tumors with molecular alterations of TrkA, ROS 1 or ALK.


** Pre-clinical study demonstrating entrecinhibin antagonistic activity against ALK mutations responsible for crizotinib resistance.


** Pre-clinical study showing entrecinhibin anti-tumor efficacy regression in ROS-driven models.


** In vitro study showing anti-tumor activity of entrectinib either alone or in combination with chemotherapy, in a xenograft model of neuroblastoma.


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