Potent Anti-tumor Activity of Entrectinib (RXDX-101) in Patient-derived Models Harboring Oncogene Rearrangements of NTRKs Predictive of Clinical Responses

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A 75-year-old woman with metastatic CRC who previously progressed after 3 lines of chemotherapy: FOLFOX, 2nd line FOLFIRI/Cetuximab and 3rd line Binotomotec. The patient presented primary colon tumor, peritoneal carcinomatosis and liver metastases. Initial testing indicated KRAS and BRAF wild type.

Abstract

Preclinical modeling

PDX and PDC models were established from liver metastasis of the patient. PDX were treated with escalating doses of entrectinib, and showed dose dependent inhibition, concurrent with signaling pathway inhibition.

Clinical response

Entrectinib was administrated orally, 1400 mg in once daily for 4 consecutive days a week, for a total of 3 cycles over 28 day cycle. After complete response, CT scanning was performed which was confirmed by CT scan at end of cycle 2.

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Conclusion

> Entrectinib is a highly potent and selective anti-tumor agent in Trk-rearranged preclinical models, irrespective at which fusion partner is involved.
> PDC and PDC models are predictive models for translating preclinical observation to objective clinical response.
> An integrated RFS approach is critical for identifying likely responders.
> The data support clinical development of entrectinib in molecularly selected patients of various histologies.
> Robust objective responses have been achieved in Phase 1 clinical trials in patients with targeted molecular alterations at or above the recommended Phase 2 dose (PDX).
> A potentially registration-enabling Phase 2 clinical trial of entrectinib (STARIK-2), that utilizes a basket design is ongoing.

Results

Entrectinib inhibits growth of Trk-rearranged CRC cell line in vivo

Entrectinib was further demonstrated by several in vitro and in vivo studies involving patient-derived tumor cells (PDCs) and patient-derived xenografts (PDAs) determined to harbor (by NGS and FISH) and express (by IHC) NTRK fusion rearrangements. In 2-dimensional and 3-dimensional proliferation assays, entrectinib effectively inhibited proliferation from a CRC patient positive for TPX-NTRK1 fusion. In another independent study, entrectinib, at exposures significantly lower than clinically relevant tumor pressure, caused a PDX derived from a CRC patient positive for LMNA-NTRK1 fusion. All the functional readouts were correlated with changes in target and pathway biomarkers.

In conclusion, our preclinical data demonstrate the potential of entrectinib as an effective treatment for Trk rearrangements in a broad spectrum of cancer histologies, which is now being demonstrated in ongoing clinical trials.

Results

Entrectinib inhibits wildtype and rearranged Trks in vitro

Entrectinib (RXDX-101) is a potent, selective, orally available, ATP-competitive inhibitor of the tyrosine kinases TrkA, TrkB, TrkC, ROS1, ALK, and NTRK1, 2 and 3 (NTRK). Entrectinib is an oncofetal transducer of the signaling pathways.

Inhibition of signaling pathways in Ba/F3 cells expressing NTRK3 (Tyr516) phosphorylation by entrectinib (300 nM, 4 h) was examined by phospho-specific Western blot. The IC50 for the 3 NTRKs were determined to harbor these driver fusions have been steadily increasing. The tumors. Although the prevalence of such events is relatively low in most tumor types (<2%), the number of new fusion partners and the list of tumor types that are found to harbor these driver fusions have been steadily increasing.

In conclusion, our preclinical data demonstrate the potential of entrectinib as an effective treatment for Trk rearrangements in a broad spectrum of cancer histologies, which is now being demonstrated in ongoing clinical trials.

Introduction

The Trk family of kinases, which include TrkA, TrkB and TrkC, encoded by NTRK1, NTRK2 and NTRK3, respectively, are highly affinity receptors for the neurotrophin family of nerve growth factors. Dysregulated activity of Trk kinase family members due to chromosomal rearrangements has been shown to be an oncogenic driver in a number of cancer types, including lung, colorectal, salivary gland, sarcoma, papillary thyroid, glioblastoma, melanoma and other tumors. Although the prevalence of such events is relatively low in most tumor types (<2%), the number of new fusion partners and the list of tumor types that are found to harbor these driver fusions have been steadily increasing. The significant unmet medical need and the relatively low frequency of fusion incidents require an integrated therapeutic-diagnostic (Rx/Dx) approach to best serve the patients in need.

Entrectinib (RXDX-101) is an orally available, potent, selective ATP-competitive pan-Trk, ROS1 and ALK inhibitor with comparable, low nanomolar potency against kinase activity of TrkA, TrkB and TrkC in biochemical and cell based assays. Engineered Ba/F3 cells expressing chimerically identified Trk fusion proteins, with various partners, entrectinib demonstrated potent anti-proliferative activity in the range of 5-6 nM, accompanied by Inhibition of Trk phosphorylation and concomitant inactivation of downstream effectors such as PLCγ1, AKT and ERK. The clinical relevance of targeting Trk fusions by entrectinib was further demonstrated by several in vitro and in vivo studies involving patient-derived tumor cells (PDCs) and patient-derived xenografts (PDAs) determined to harbor (by NGS and FISH) and express (by IHC) Trk rearrangements.

Preclinical modeling

PDx and PDC models were established from liver metastasis of the patient. PDX were treated with escalating doses of entrectinib, and showed dose dependent inhibition, concurrent with signaling pathway inhibition.

Characterization

PDX and PDC models were established from liver metastasis of the patient. PDX were treated with escalating doses of entrectinib, and showed dose dependent inhibition, concurrent with signaling pathway inhibition.

Patient case 2: LMNA-NTRK1 colorectal cancer

72-year-old male patient, initially presented with stage III, KRAS wild-type, BRAF wild-type, ascending colon cancer. After hemicolectomy and multiple cycles of adjuvant chemotherapy, the disease progressed to the lymph nodes.