Abstract

Inhibition of Trk-driven tumors by the pan-Trk inhibitor RXDX-101

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RXDX-101 is an orally available, potent and selective ATP-competitive pan-Trk, ROS1 and ALK inhibitor, with comparable activities against TrkA, TrkB and TrkC in biochemical and cell-based assays (IC50 = 10 nM). In KM-12, a human colorectal cancer cell line driven by constitutively active TrkA fusion TKM3-316RXL, RXDX-101 exhibited in vitro anti-proliferative activity with an IC50 of 17 nM, accompanied by inhibition of TrkA phosphorylation and downstream effectors, PLC, AKT and ERK, as well as cell-cycle arrest and apoptosis. In mice bearing KM-12 xenografts, treatment with RXDX-101 resulted in tumor regression and durable tumor control. In these studies, RXDX-101 was well tolerated during the course of treatment.

In conclusion, our data indicates that RXDX-101, a potent and selective pan-Trk inhibitor currently in clinical development, is an attractive targeted agent for Trk-driven tumors.

RXDX-101 is currently being evaluated in ALKA-372-001, a First-in-Human (FIH) study that began in October 2012 and is being conducted in Italy. ALKA-372-001 is an ongoing, Phase I, open-label study evaluating the safety, pharmacokinetics, and antitumor activity of RXDX-101 in patients with advanced/metastatic solid tumors that harbor a TrkA, TrkB or ALK molecular alteration.

RXDX-101 is also being evaluated in RXDX-101-001, a new Phase I/2a study, also referred to as STARTRK RXDX-101 (BIDx3) to tumor (KM12 colon carcinoma) bearing CD1 nude mice

Table 1. Body weight change

Table 2. In vivo pharmacokinetics

Conclusion

• RXDX-101 is a highly potent and selective pan-Trk inhibitor
• Orally available with desirable pharmacokinetic properties
• Potently inhibits Trk auto-phosphorylation and downstream pathways
• Achieved durable response in a TrkA-driven tumor xenograft model at clinically relevant doses and schedule
• RXDX-101 is a promising therapeutic agent for patients with oncogenic Trk alterations.

Additional information