RLY-4008, a Novel Precision Therapy for FGFR2-Driven Cancers Designed to Potently and Selectively Inhibit FGFR2 and FGFR2 Resistance Mutations

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ABSTRACT

FGFRs 1-4 are a family of receptor tyrosine kinases that play a critical role in growth, differentiation, migration, and invasion of cells. FGFR2, in particular, is frequently mutated in a variety of tumors, leading to acquired resistance to pan-FGFR inhibitors. To overcome these limitations, we designed RLY-4008, a potent and highly selective FGFR2 inhibitor. RLY-4008 demonstrates potent and selective inhibition of FGFR2 and FGFR2 resistance mutations in vitro and in vivo, inducing tumor regression in multiple xenograft tumor models harboring FGFR2 mutations.

RESULTS

RLY-4008 is a novel precision therapy that is highly selective for FGFR2.

RLY-4008 demonstrates dose-dependent reduction of phosphorylation of FGFR2 signaling pathway components.

RLY-4008 is >200-fold selective for FGFR2 over FGFR1 and >80-fold selective for FGFR2 over FGFR3 and FGFR4, respectively.

Antitumor activity of RLY-4008 in the indicated xenograft tumor models is shown.

CONCLUSIONS

• RLY-4008 is a novel, potent, and highly selective FGFR2 inhibitor designed to overcome the emergence of on-target FGFR2 resistance mutations and downstream signaling associated with current pan-FGFR inhibitors.

• RLY-4008 demonstrates >200-fold selectivity over FGFR1 and >80-fold selectivity over FGFR3 and FGFR4, respectively.

• In vivo, RLY-4008 demonstrates dose-dependent FGFR2 inhibition and induces tumor regression in FGFR2 fusion-positive, FGFR2 amplified and FGFR2 resistance mutations.

• RLY-4008 induces tumor regression in tumors harboring FGFR2-CCDC6 fusion.

• In contrast to current pan-FGFR inhibitors, RLY-4008 spares FGFR1 at efficacious exposures.

• RLY-4008 demonstrates potent in vivo activity against clinically-relevant FGFR2 resistance mutations.

References


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