ERAS-601, a potent allosteric inhibitor of SHP2, demonstrates compelling single agent anti-tumor activity in RAS/MAPK-driven tumor models

Leenun Martin, Roopal Patel, Jinchuan Zhang, Jennifer Yang, Robin Nevarez, Taylor Condon, Gary Chiang, Les Brall, Robert Shoemaker, Erasca, San Diego, CA

Abstract

SHP2 is a non-receptor protein tyrosine phosphatase (PTP) encoded by the PTPN11 gene. SHP2 transduces upstream receptor tyrosine kinase (RTK) signaling to the RAS/MAPK pathway via its phosphatase-mediated regulation of guanine nucleotide exchange factors (GEFs). The modulation of GEF activity impacts the rate at which KRAS cycles from the inactive GDP-bound state to the active GTP-bound state. ERAS-601 is a potent, selective small molecule allosteric inhibitor of SHP2. ERAS-601 inhibits the wild type SHP2 protein with a biochemical IC50 of 4.6 nM. ERAS-601 is a selective SHP2 inhibitor and demonstrates no appreciable inhibition against any off-target kinase or phosphatase across panels of 300 kinases and 12 phosphatases.

ERAS-601 inhibits the loading of active GTP-bound oncogenic RAS and inhibits RAS/MAPK pathway signaling as measured by pERK1/2 inhibition and DUSP6 mRNA. ERAS-601 demonstrates anti-proliferative activity across a panel of human cancer cell lines with oncogenic alterations in the RAS/MAPK pathway. In a mouse in vivo study, ERAS-601 achieves substantial systemic exposure and demonstrates inhibition of ERK1/2 phosphorylation and DUSP6 mRNA levels in the NCI-H358 xenograft model. ERAS-601 also inhibits tumor growth in multiple RAS/MAPK-driven CDX and PDX models that harbor EGFR, KRAS, BRAF Class III, and NF1LOF mutations. ERAS-601 is a potent and selective allosteric SHP2 inhibitor that demonstrates anti-tumor activity in vitro and in vivo and is currently being studied as a monotherapy in an ongoing Phase 1 clinical study in patients with advanced or metastatic solid tumors (FLAGSHP-1, NCT04670679).

Introduction

Results

Figure 3. On-target activity of ERAS-601.

Figure 6. In vivo efficacy of ERAS-601 in EGFR amplified or mutant xenografts. ERAS-601 inhibited MAPK signaling and demonstrated antiproliferative activity in MAPK pathway-dysregulated cell lines.

Table 1. Summary of in vivo anti-tumor activity of ERAS-601 in 25 CDX and PDX models

Conclusions

- ERAS-601 is a potent and selective small molecule inhibitor of full length SHP2 with a biochemical IC50 of 4.6 nM.
- ERAS-601 inhibits ERK1/2 phosphorylation and cellular proliferation in KRAS mutated, BRAF Class III, NF1LOF, and EGFR-activated cell lines.
- ERAS-601 achieves substantial systemic exposure and inhibits the RAS/MAPK pathway in KRAS G12C mutated NC1-H358 xenograft model.
- ERAS-601 demonstrated tumor growth inhibition in multiple RAS/MAPK activated CDX and PDX models that harbor EGFR, KRAS, BRAF Class III, and NF1LOF mutations.
- ERAS-601 monotherapy is currently being evaluated in a Phase 1 clinical study in patients with advanced or metastatic solid tumors (FLAGSHP-1, NCT04670679).

Figure 4. In vitro phosphorylation and proliferation in MAPK-driven cell lines.

Figure 7. In vivo efficacy of ERAS-601 in BRAF Class III and NF1LOF mutant CDX and PDX models.

Figure 5. Single-dose PKPD study of ERAS-601.

Figure 8. In vivo efficacy of ERAS-601 in EGFR driven xenograft models.

ERAS-601 demonstrated sufficient systemic exposure to inhibit ERK1/2 phosphorylation in the KRASG12C mutant CDX model NC1-H358.