Abstract

ERAS-601, a potent allosteric inhibitor of SHP2, synergistically enhances the efficacy of sotorasib/adagrasib and cetuximab in NSCLC, CRC, and HNSCC tumor models.

Introduction

SHP2 is a non-receptor protein tyrosine phosphatase (PTP) encoded by the PTPN11 gene. ERAS-601 inhibits wild-type SHP2 biochemically with an IC50 of 2.7 nM and demonstrates selectivity across panels of 300 kinases and 12 phosphatases. SHP2 mediates upstream receptor tyrosine kinase (RTK) signaling via its phosphatase-mediated regulation of guanine nucleotide exchange factors (GEFs). ERAS-601 inhibits the SHP2 dependent cycling of KRAS from the inactive GDP-bound state to the active GTP-bound state and demonstrates anti-proliferative activity in KRASG12C and EGFR amplified cell lines. The combination of upstream blockade of RAS-RTK cycling by ERAS-601 with inhibition of KRASG12C by a selective KRASG12C inhibitor synergistically inhibits cellular proliferation in multiple KRASG12C mutated human cancer cell lines. The combinations of ERAS-601 with KRASG12C inhibitors achieve tumor growth inhibition that is superior to the respective ERAS-601 and KRASG12C inhibitor monotherapies in NSCLC and CRC CDX and PDX tumor models. Similarly, the combination of ERAS-601 with an EGFR antibody, cetuximab, inhibits ancoritic RAS/MEK signaling as measured by pERK1/2 and enhances the anti-proliferative activity of cetuximab in triple wild-type (i.e., KRAS/NRAS/BRAF wild-type) CRC and HPV-negative HNSCC cell lines. The combination of ERAS-601 with cetuximab achieves tumor growth inhibition that is superior to respective ERAS-601 and cetuximab monotherapies in triple wild-type CRC and HPV-negative HNSCC tumors. Both combinations are being studied in ongoing clinical studies (HERKULES-2, NCT04995981; FLAGSHP-1, NCT04670679).

Results

ERAS-601 and sotorasib/adagrasib combination synergistically inhibited cell viability in KRASG12C mutant cells

ERAS-601 and sotorasib/adagrasib demonstrated in vivo combination benefit in KRASG12C mutant NSCLC and CRC CDX and PDX models

ERAS-601 and cetuximab demonstrated in vivo combination benefit in HPV-negative HNSCC CDX and PDX models

Conclusion

The combination of ERAS-601 with KRASG12C inhibitors synergistically enhances cell viability inhibition that is superior to respective monotherapies in KRASG12C mutant NSCLC and CRC CDX and PDX models. The combination of ERAS-601 with the EGFR antibody cetuximab enhances the anti-proliferative activity and achieves tumor growth inhibition that is superior to respective monotherapies in HPV-negative HNSCC and triple wild-type CRC CDX and PDX models.

Both combinations are being studied in ongoing clinical studies (HERKULES-2, NCT04995981; FLAGSHP-1, NCT04670679).