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

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Abstract

ERAS-601 is a potent, small molecule allosteric inhibitor of SHP2 wild-type, a non-receptor protein tyrosine phosphatase (PTP) encoded by the *PTPN11* gene. ERAS-601 inhibits wild-type SHP2 biochemically with an IC50 of 4.6 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 $KRAS^{G12C}$ and EGFR amplified cell lines. The combination of upstream blockade of RAS-GTP cycling by ERAS-601 with inhibition of $KRAS^{G12C}$ by a selective $KRAS^{G12C}$ inhibitor synergistically inhibits cellular proliferation in multiple $KRAS^{G12C}$ mutated human cancer cell lines. The combinations of ERAS-601 with $KRAS^{G12C}$ inhibitors achieve tumor growth inhibition that is superior to the respective ERAS-601 and $KRAS^{G12C}$ inhibitor monotherapies in NSCLC and CRC CDX and PDX tumor models. Similarly, the combination of ERAS-601 with an EGFR antibody, cetuximab, inhibits oncogenic RAS/MAPK 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 CDX and PDX tumor models. These nonclinical data support the clinical development of ERAS-601 in combination with a $KRAS^{G12C}$ inhibitor in NSCLC and CRC tumors, and ERAS-601 in combination with cetuximab in triple wild-type CRC as well as HPV-negative HNSCC tumors. Both combinations are being studied in ongoing clinical studies (HERKULES-2, NCT04959981; FLAGSHP-1, NCT04670679).

Introduction

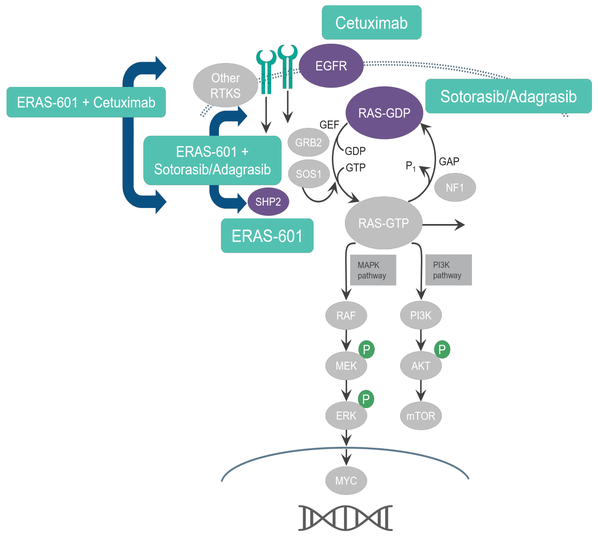


Figure 1. Schematic representation of ERAS-601 with sotorasib or adagrasib combination and ERAS-601 with cetuximab combination

Results

ERAS-601 and sotorasib/adagrasib combination synergistically inhibited cell viability in $KRAS^{G12C}$ mutant cells

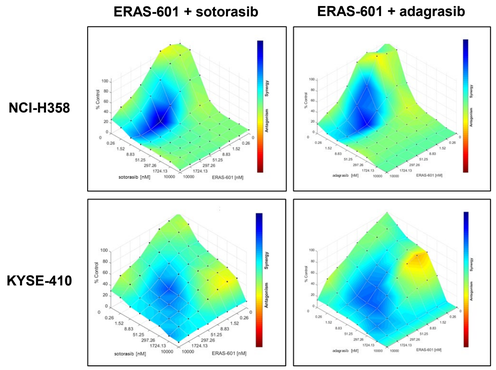
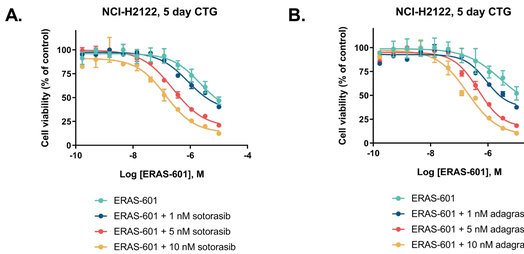


Figure 2. Combination analysis of ERAS-601 with $KRAS^{G12C}$ inhibitors. NCI-H358 $KRAS^{G12C}$ and KYSE-410 $KRAS^{G12C}$ cell lines were treated with ERAS-601 and sotorasib or adagrasib. The proliferation was assessed in a 5 day 3D CellTiter-Glo assay and synergy plots were generated using Combenefit software.

Cotreatment of suboptimal concentrations of sotorasib or adagrasib increased sensitivity to ERAS-601



Treatment	2D CTG IC50, nM
ERAS-601	2,181
ERAS-601 + 1 nM sotorasib	834
ERAS-601 + 5 nM sotorasib	246
ERAS-601 + 10 nM sotorasib	139

Treatment	2D CTG IC50, nM
ERAS-601	2,785
ERAS-601 + 1 nM adagrasib	888
ERAS-601 + 5 nM adagrasib	460
ERAS-601 + 10 nM adagrasib	190

Figure 3. Cotreatment of ERAS-601 with sotorasib/adagrasib in the NCI-H2122 $KRAS^{G12C}$ cell line. The cells were treated with ERAS-601 alone or cotreated with indicated concentrations of sotorasib (**A**) or adagrasib (**B**). The cellular proliferation was assessed in a 5 day 2D CellTiter-Glo assay. IC50 values are summarized in the tables.

ERAS-601 and sotorasib/adagrasib demonstrated in vivo combination benefit in $KRAS^{G12C}$ mutant NSCLC and CRC CDX and PDX models

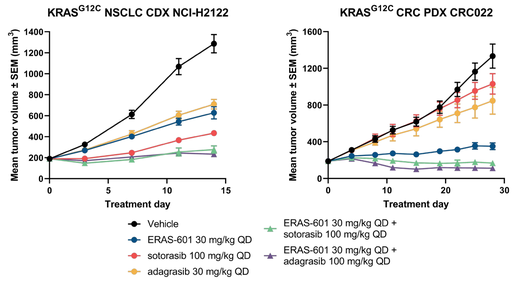


Figure 4. In vivo efficacy of ERAS-601 with sotorasib/adagrasib combination in $KRAS^{G12C}$ mutant xenografts. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with indicated single agent and combination treatments. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

ERAS-601 and sotorasib demonstrated in vivo combination benefit in $KRAS^{G12C}$ mutant NSCLC and CRC CDX and PDX models

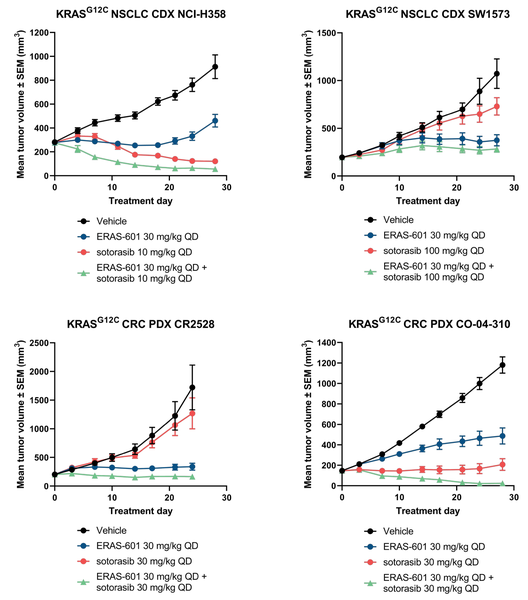
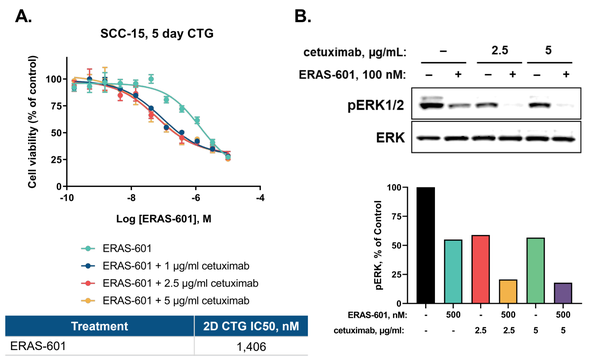


Figure 5. In vivo efficacy of ERAS-601 with sotorasib combination in $KRAS^{G12C}$ mutant xenografts. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with indicated single agent and combination treatments. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

ERAS-601 and cetuximab demonstrated combination benefit in HPV-negative HNSCC in vitro



Treatment	2D CTG IC50, nM
ERAS-601	1,406
ERAS-601 + 1 µg/ml cetuximab	91
ERAS-601 + 2.5 µg/ml cetuximab	61
ERAS-601 + 5 µg/ml cetuximab	55

Figure 6. Combination of ERAS-601 and cetuximab in HPV-negative HNSCC. A. SCC-15 cells were treated with ERAS-601 alone or cotreated with indicated suboptimal concentrations of cetuximab. The cellular proliferation was assessed in a 5 day 2D CellTiter-Glo assay. IC50 values are summarized in the table. **B.** Cal-27 cells were treated with ERAS-601 and cetuximab for 6 hours and cell lysates were immunoblotted with the indicated antibodies. The graph shows the quantification of ERK1/2 phosphorylation.

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

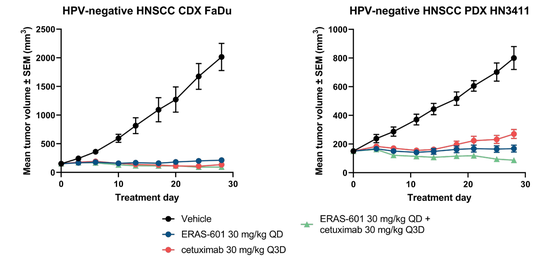
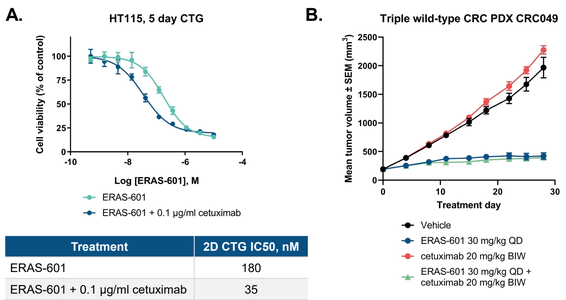


Figure 7. In vivo efficacy of ERAS-601 with cetuximab combination in HPV-negative HNSCC xenografts. Immunodeficient mice bearing the indicated tumor xenografts were dosed orally with ERAS-601 or intraperitoneally with cetuximab as indicated. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

ERAS-601 and cetuximab demonstrated combination benefit in triple wild-type CRC models in vitro and in vivo



Treatment	2D CTG IC50, nM
ERAS-601	180
ERAS-601 + 0.1 µg/ml cetuximab	35

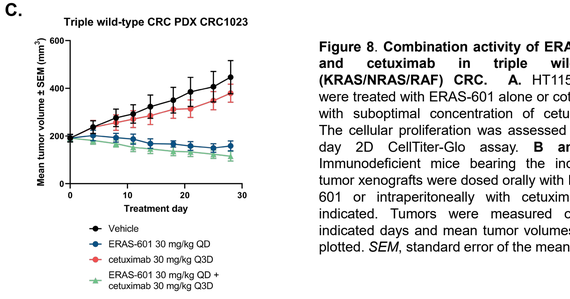


Figure 8. Combination activity of ERAS-601 and cetuximab in triple wild-type (KRAS/NRAS/RAF) CRC. A. HT115 cells were treated with ERAS-601 alone or cotreated with suboptimal concentration of cetuximab. The cellular proliferation was assessed in a 5 day 2D CellTiter-Glo assay. **B and C.** Immunodeficient mice bearing the indicated tumor xenografts were dosed orally with ERAS-601 or intraperitoneally with cetuximab as indicated. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

Conclusions

- The combination of ERAS-601 with $KRAS^{G12C}$ inhibitors synergistically inhibits cell viability in $KRAS^{G12C}$ cells and achieves tumor growth inhibition that is superior to the respective monotherapies in $KRAS^{G12C}$ 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, NCT04959981; FLAGSHP-1, NCT04670679)