ERAS-007 (ERK1/2 inhibitor) + ERAS-601 (SHP2 inhibitor) exhibit nonclinical combination activity across KRAS mutant NSCLC, CRC, and PDAC tumor models


**Abstract**

KRAS mutations occur in about 25% of all cancers and promote oncogenesis via constitutive activation of the RAS/MAPK pathway. Targeting KRAS mutant tumors by inhibiting individual nodes in the RAS/MAPK pathway, including SHP2, SOS1, KRAS, RAF, MEK, and ERK, has shown early clinical activity, but the rapid emergence of resistance limits the benefit of monotherapy. Resistance is often mediated by reactivation of RAS/MAPK pathway signaling, which can occur by increased activation upstream of the RAS/MAPK pathway (e.g., EGFR activation) and/or activation of RAS/MAPK pathway nodes (e.g., oncogenic BRAF and MEK mutations). Inhibiting both upstream and downstream RAS/MAPK pathway nodes has the potential to more robustly prevent reactivation relative to inhibition of a single node alone. Here, we explored dual inhibition of the pathway in nonclinical models by targeting SHP2 (upstream node) and ERK1/2 (terminal node of the RAS/MAPK pathway) with ERAS-601 and ERAS-007, respectively. Hereafter this combination will be referred to as MAPKlampTM. We evaluated the MAPKlamp combination in NSCLC, CRC, and pancreatic tumor models that harbored KRAS mutations in vitro and in vivo. In 14-day clonogenic assays in KRAS mutant NSCLC, CRC, and PDAC cell lines, MAPKlamp combination inhibition colony growth more potently than ERAS-001 or ERAS-007 alone. In KRAS mutant CDX and PDX models, MAPKlamp combination activity was observed in vivo where it achieved superior tumor growth inhibition and tumor regression over either agent alone in KRAS mutant NSCLC, CRC, and PDAC xenografts in vivo. These results support its clinical evaluation in RAS/MAPK pathway-driven tumors.

**Results**

ERAS-007 and ERAS-601 potent, small molecule inhibitor of ERK1/2 and SHP2, respectively. The ERAS-007 + ERAS-601 MAPKlamp combination demonstrated superior colony growth inhibition over single agent treatment in KRAS mutant NSCLC, CRC, and PDAC cell lines.

The ERAS-007 + ERAS-601 MAPKlamp combination showed increased in vivo tumor growth inhibition in KRAS mutant NSCLC, CRC, and PDAC CDX and PDX models.

**Conclusions**

- The ERAS-007 + ERAS-601 MAPKlamp combination shows superior nonclinical anti-tumor activity relative to ERAS-007 or ERAS-601 alone by simultaneously inhibiting the most distal node of the RAS/MAPK pathway, ERK1/2, and upstream RAS/MAPK pathway node, SHP2.
- The ERAS-007 + ERAS-601 MAPKlamp combination inhibits colony growth more potently than either agent alone in KRAS mutant NSCLC, CRC, and PDAC cell lines in vitro.
- The ERAS-007 + ERAS-601 MAPKlamp combination demonstrates superior tumor growth inhibition and tumor regression over either agent alone in KRAS mutant NSCLC, CRC, and PDAC xenografts in vivo.
- These data support the clinical development of ERAS-007 + ERAS-601 MAPKlamp combination.