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

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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 MAPK pathway) with ERAS-601 and ERAS-007, respectively. Hereafter this SHP2 plus ERK1/2 inhibitor combination will be referred to as MAPKlamp™. 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 inhibited colony growth more potently than ERAS-601 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 relative to ERAS-601 or ERAS-007 monotherapy. MAPKlamp combination showed in vitro and in vivo combination activity in KRAS mutant tumors, and these results support its clinical evaluation in RAS/MAPK pathway-driven tumors.

Introduction

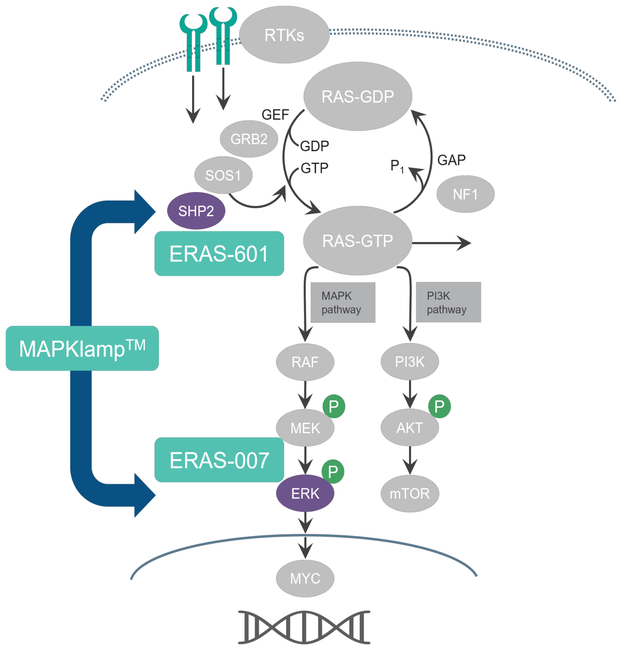

Figure 1. Schematic representation of the MAPKlamp combination: ERAS-007 + ERAS-601

Results

ERAS-007 and ERAS-601 potent, small molecule inhibitor of ERK1/2 and SHP2, respectively

Inhibitor	Target Protein	Biochemical IC50, nM
ERAS-007	ERK1	2
ERAS-007	ERK2	2
ERAS-601	PTPN11/SHP2 full length	4.6

Figure 2. Biochemical activity of ERAS-007 and ERAS-601. IC50 against ERK1 and ERK2 were assessed by in vitro biochemical assay in the presence of increasing concentrations of ERAS-007. In vitro phosphatase activity of full-length SHP2 was assessed in the presence of increasing concentrations of ERAS-601.

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

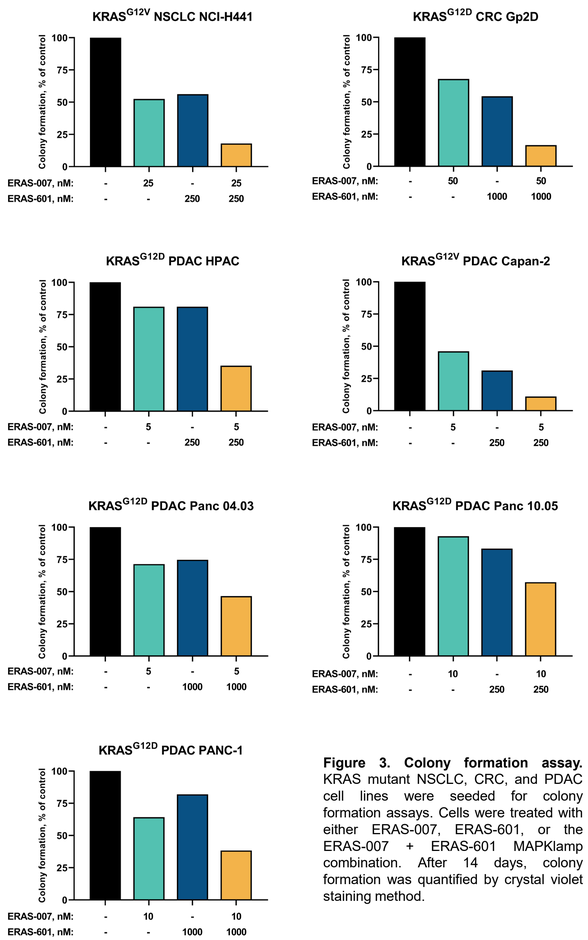

Figure 3. Colony formation assay. KRAS mutant NSCLC, CRC, and PDAC cell lines were seeded for colony formation assays. Cells were treated with either ERAS-007, ERAS-601, or the ERAS-007 + ERAS-601 MAPKlamp combination. After 14 days, colony formation was quantified by crystal violet staining method.

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

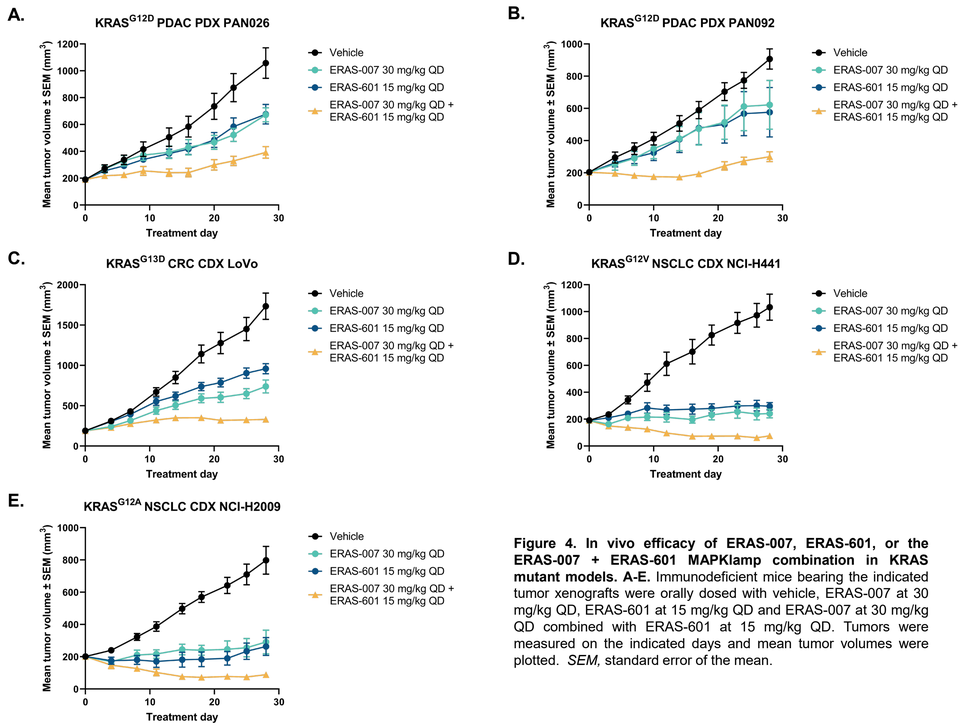

Figure 4. In vivo efficacy of ERAS-007, ERAS-601, or the ERAS-007 + ERAS-601 MAPKlamp combination in KRAS mutant models. A-E. Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-007 at 30 mg/kg QD, ERAS-601 at 15 mg/kg QD and ERAS-007 at 30 mg/kg QD combined with ERAS-601 at 15 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM,* standard error of the mean.

Mutation	Model ID	Tumor type	Model Type	Anti-tumor efficacy, % TGI		
				ERAS-601 15 mg/kg QD	ERAS-007 30 mg/kg QD	ERAS-601 15 mg/kg QD + ERAS-007 30 mg/kg QD
KRASG12D	PAN026	Pancreatic	PDX	44%	44%	77%**
	PAN092	Pancreatic	PDX	47%	41%	86%
KRASG13D	LoVo	CRC	CDX	50%	64%	91%**
KRASG12V	NCI-H441	NSCLC	CDX	87%	94%	114%**
KRASG12A	NCI-H2009	NSCLC	CDX	90%	85%	119%*

Table 1. ERAS-007 + ERAS-601 MAPKlamp combination in vivo activity summary across 5 KRAS mutant models
ERAS-601 + ERAS-007 MAPKlamp combination exhibited superior TGI relative to ERAS-601 and ERAS-007 monotherapies in 5 KRAS mutant CDX and PDX models. *p-values < 0.05 **p-values < 0.01 ***p-values < 0.001 (p-values assessed relative to ERAS-601 and ERAS-007 monotherapies).

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 an 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