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

Leenus Martin, Roopal Patel, Jingchuan Zhang, Jennifer Yang, Robin Nevarez, Taylor Congdon, Gary Chiang, Les Brail, Robert Shoemaker. Erasca, San Diego, CA

ERASCA™

2671

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 line models 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 NF1^{LOF} 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

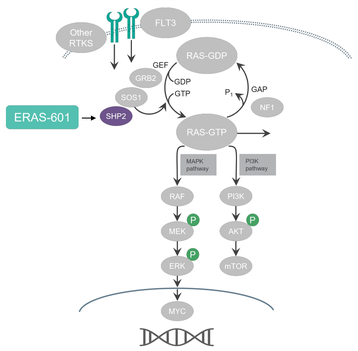
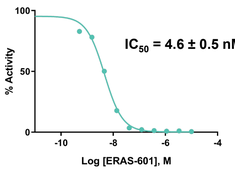


Figure 1. Schematic representation of SHP2 inhibition by ERAS-601

Results

ERAS-601 is a potent and selective small molecule allosteric inhibitor of SHP2



PTPase	% Inhibition at 10 µM ERAS-601
PTPN11/SHP2 full length (on-target)	100%
PTPN11/SHP2 catalytic domain	0%
PTPRC/CD45	6%
PTPN2/TC-PTP	3%
PP2A Alpha/ PP2R1A	1%
PTPN6/SHP1	0%
PTPN1/PTP1B-CD	0%
PTPN12/PTP-PEST	0%
PP1B	0%
DUSP22/MKPX	0%
PTPN7/LC-PTP	0%
PP1A	0%

Figure 2. Biochemical activity of ERAS-601. In vitro phosphatase activity of full length SHP2 was assessed in the presence of increasing concentrations of ERAS-601. The IC50 value shown is the average of 2 replicates. For selectivity, ERAS-601 was assessed in vitro against a panel of protein tyrosine phosphatases at 10 µM and no off-target activity at >6% at 10 µM was observed. ERAS-601 also showed no appreciable inhibition against any off-target kinase in a 300 kinases panel (<30% inhibition @ 1 µM).

Results

ERAS-601 demonstrated cellular selectivity in NCI-H1666 cells

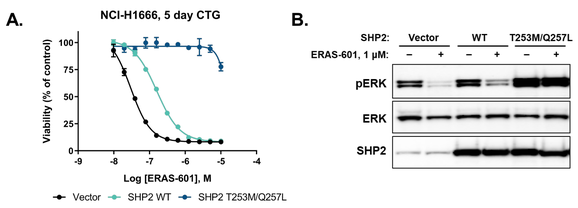
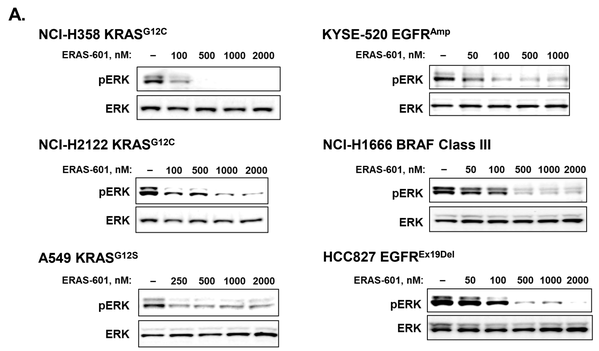


Figure 3. On-target activity of ERAS-601.
NCI-H1666 cells were transfected with empty vector, SHP2 wildtype (WT), or the SHP2 allosteric binding mutant T253M/Q257L. **A.** Anti-proliferative activity of ERAS-601 was assessed in stable cell lines in a 5 day CellTiter-Glo assay. **B.** Stable cell lines were treated with 1 µM ERAS-601 for 6 hours and cell lysates were immunoblotted with the indicated antibodies.

ERAS-601 inhibited MAPK signaling and demonstrated anti-proliferative activity in MAPK pathway-dysregulated cell lines



C.

Mutation	Cell line	Cancer type	ERAS-601 IC_{50} (nM)
KRAS^{G12C}	NCI-H358	NSCLC	12
	MIA PaCa-2	Pancreatic	6
	NCI-H1792	NSCLC	40
	HCC44	NSCLC	48
	SW1573	NSCLC	104
	NCI-H2122	NSCLC	259
KRAS^{G12A}	NCI-H2009	NSCLC	16
KRAS^{G12D}	LS513	CRC	295
KRAS^{G12S}	A549	NSCLC	8
KRAS^{G12V}	NCI-H441	NSCLC	22
EGFR	KYSE-520 (EGFR^{Amp})	Esophageal	119
	NCI-H1975 (EGFR$^{L858R/T790M}$)	NSCLC	217
BRAF Class III	NCI-H1666	NSCLC	19
	NCI-H508	CRC	95
NF1 LOF	MeWo	Melanoma	56
	NCI-H1838	NSCLC	130
Negative Control (BRAF Class I)	A375	Melanoma	>10,000

Figure 4. Inhibition of signaling and proliferation in MAPK-driven cell lines.
A. RAS/MAPK pathway activated cell lines were treated with the indicated concentrations of ERAS-601 for 6 hours. Cell lysates were immunoblotted for pERK and total ERK. **B.** NCI-H358 and KYSE-520 cells were treated with the indicated concentrations of ERAS-601 for 24 hours. RNA from harvested cells was collected post-treatment and DUSP6 levels were quantitated by qRT-PCR. **C.** RAS/MAPK pathway activated cell lines were treated with ERAS-601 and proliferation was assessed in a 5 day CellTiter-Glo assay (mKRAS cell lines were evaluated in 3D). IC50 values are summarized in the table.

ERAS-601 achieved sufficient systemic exposure to inhibit ERK1/2 phosphorylation in the KRAS^{G12C} mutant CDX model NCI-H358

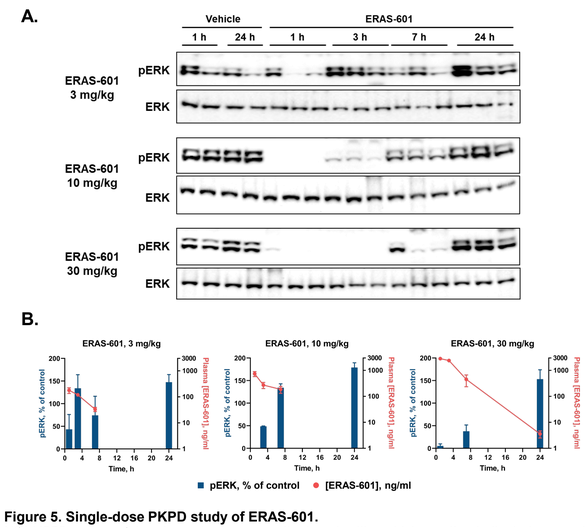


Figure 5. Single-dose PKPD study of ERAS-601.
NCI-H358 xenograft-bearing mice were orally-dosed with vehicle or the indicated amount of ERAS-601. Tumors and plasma were harvested from the mice at the indicated time points. **A.** Tumor lysates were immunoblotted for pERK and total ERK. **B.** ERAS-601 levels were quantitated in plasma by LC-MS/MS. Combined plot of PD (left Y-axis) and PK (right Y-axis) as a function of time. *Bars*, pERK levels relative to vehicle control (bars); *Circles*, ERAS-601 concentration in ng/ml; *SEM*, standard error of the mean.

ERAS-601 demonstrated anti-tumor activity in KRAS mutant CDX and PDX models

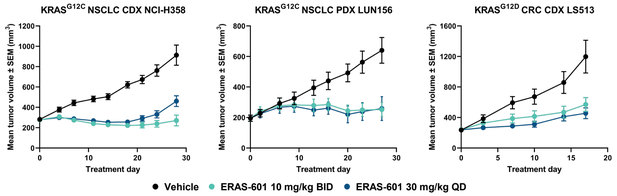


Figure 6. In vivo efficacy of ERAS-601 in KRAS mutant xenografts.
Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-601 at 10 mg/kg BID or 30 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

ERAS-601 demonstrated anti-tumor activity in BRAF Class III and NF1^{LOF} mutant CDX and PDX models

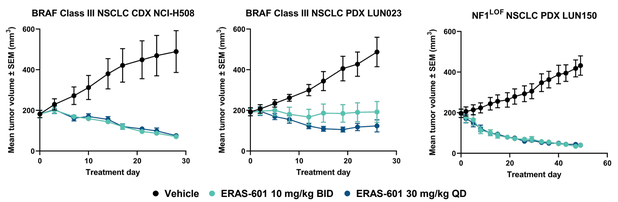


Figure 7. In vivo efficacy of ERAS-601 in BRAF class III or NF1^{LOF} mutant xenografts.
Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-601 at 10 mg/kg BID or 30 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

ERAS-601 demonstrated anti-tumor activity in EGFR-driven CDX models

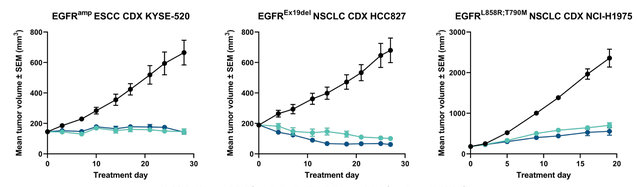


Figure 8. In vivo efficacy of ERAS-601 in EGFR amplified or mutant xenografts.
Immunodeficient mice bearing the indicated tumor xenografts were orally dosed with vehicle, ERAS-601 at 10 mg/kg BID or 30 mg/kg QD. Tumors were measured on the indicated days and mean tumor volumes were plotted. *SEM*, standard error of the mean.

Mutation	Model ID	Tumor type	Model Type	Antitumor activity of ERAS-601	
				10 mg/kg BID (% TGI)	30 mg/kg QD (% TGI)
KRAS^{G12C}	NCI-H358	NSCLC	CDX	**101%****	**71%****
	LUN156	NSCLC	PDX	**87%****	**86%***
	MIA PaCa-2	PDAC	CDX	**91%*****	**79%*****
	CO-04-0310	CRC	PDX	**80%*****	67%*****
	CR022	CRC	PDX	**72%*****	**75%*****
	KYSE-410	Esophageal	CDX	**108%****	**94%****
KRAS^{G12D}	LUN232	NSCLC	PDX	Not evaluated	**73%*****
	GP2D	CRC	CDX	60%**	**71%****
	LS513	CRC	CDX	66%*	**77%****
	LUN137	CRC	PDX	Not evaluated	**82%***
KRAS^{G12V}	NCI-H441	NSCLC	CDX	Not evaluated	**97%*****
EGFR	HCC827 (Exon19Del)	NSCLC	CDX	**118%*****	**126%*****
	HCC827-ER1 (EGFR^{Exon19del} and MET^{amp})	NSCLC	CDX	**97%*****	**102%*****
	H1975 (EGFR$^{L858R/T790M}$)	NSCLC	CDX	**76%*****	**83%*****
	NCI-H820 (EGFR$^{Exon19Del/T790M}$ and MET^{amp})	NSCLC	CDX	**84%****	**81%****
	KYSE-520 (EGFR^{amp})	Esophageal	CDX	**100%*****	**101%*****
BRAF class I (BRAFV600E)	WiDr	CRC	CDX	67%*****	68%*****
BRAF class III	NCI-H508	CRC	CDX	**136%****	**135%****
	LUN023	NSCLC	PDX	**100%***	**123%****
NF1^{LOF}	MeWo	Melanoma	CDX	**86%*****	**85%*****
	NCI-H1838	NSCLC	CDX	**140%****	**144%****
	LUN150	NSCLC	PDX	**167%*****	**167%*****
	LU6484	NSCLC	PDX	**77%*****	**83%*****
KRAS/NRAS/RAF wildtype	CRC049	CRC	PDX	**82%*****	**87%*****
	CRC1021	CRC	PDX	**106%*****	**106%*****

Table 1. Summary of in vivo anti-tumor activity of ERAS-601 in 25 CDX and PDX models
ERAS-601 exhibited significant TGI relative to vehicle control (p-value < 0.05) in 11 KRAS mutant, five EGFR mutant, three BRAF mutant, four NF1^{LOF} mutant, and two triple wildtype (KRAS/NRAS/BRAF wildtype) CDX and PDX models. Significant TGI was observed at both 30 mg/kg QD and 10 mg/kg BID doses. *p-value < 0.05 **p-value < 0.01 ***p-value < 0.001 (p-values assessed relative to vehicle control).

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, NF1^{LOF}, and EGFR-activated cell lines
- ERAS-601 achieves substantial systemic exposure and inhibits the RAS/MAPK pathway in KRAS G12C mutated NCI-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 NF1^{LOF} 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)