ERAS-4001 is a pan-KRAS inhibitor with robust anti-tumor activity in KRAS altered solid tumors

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Abstract

KRAS is one of the most frequently mutated proteins in cancer (approximately 16% of all cancers), including non-small cell lung (~30%), pancreatic (~90%), colorectal (~40%), and other cancers. Targeting both wild type (WT) KRAS and oncogenic KRAS mutant proteins within the tumor cell is a potentially more promising therapeutic strategy than targeting the mutant KRAS protein alone since WT KRAS activity can act as a resistance mechanism to mutant selective KRAS inhibition. Pan-KRAS inhibitors enable simultaneous WT and mutant KRAS inhibition and have the potential to show improved tolerability relative to pan-RAS inhibitors by sparing NRAS and HRAS.

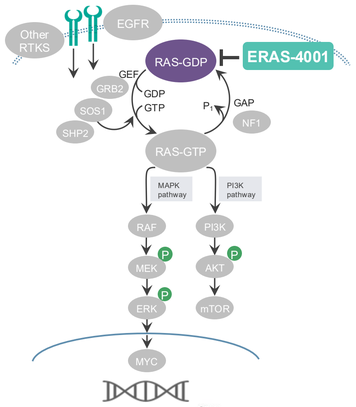
ERAS-4001 is a novel pan-KRAS inhibitor that binds to WT KRAS and KRAS G12X mutants and prevents KRAS from signaling downstream via effector proteins, such as the RAF protein family, with single digit nanomolar potency. ERAS-4001 exhibited selectivity for KRAS G12X mutants and WT KRAS over WT HRAS and WT NRAS in surface plasmon resonance (SPR) studies, potentially providing an expanded therapeutic index. In the biochemical KRAS G12D-RAF1 RAS-binding domain protein (RBD) assay, ERAS-4001 inhibited complex formation when KRAS G12D was either in the active state (GMPPNP-bound) or inactive state (GDP-bound) with single digit nanomolar IC_{50}s. ERAS-4001 showed potent cellular activity in a panel of KRAS WT amplified and KRAS G12X mutant NSCLC, PDAC, and CRC cell lines in both ERK1/2 phosphorylation (pERK) inhibition and 3D cell viability assays (3D CTG) with IC_{50}s in the range of 0.7-9.1 nM.

In vivo, oral administration of ERAS-4001 at 100 mg/kg twice daily (BID) resulted in significant tumor growth inhibition (TGI) as a monotherapy in KRAS G12D and G12V mutant subcutaneous xenograft models from 77% TGI to 83% tumor regression. In addition, ERAS-4001 showed robust TGI and survival benefit in combination with an anti-PD-1 immune checkpoint inhibitor (ICI) in the KRAS G12D mouse PDAC model achieving complete responses in all mice in the combination group. ERAS-4001 also demonstrated combination activity with cetuximab demonstrating significant TGI in both combination groups.

ERAS-4001 achieved a dose-dependent increase in plasma concentrations and significant concomitant reductions in pERK. Overall, ERAS-4001 demonstrated promising preclinical data as a pan-KRAS inhibitor supporting an IND filing in Q2 2025.

Introduction

Figure 1. Overview of RAS-MAPK pathway



- The RAS-MAPK signaling pathway is involved in cell proliferation, migration, and survival
- RAS-MAPK pathway activity is often crucial for tumor growth
- ERAS-4001 is a selective pan-KRAS inhibitor that inhibits both WT and mutant KRAS
- KRAS WT activation may act as a resistance mechanism to mutant selective KRAS inhibitors
- Selective KRAS inhibition may show improved tolerability relative to pan-RAS inhibitors by sparing NRAS and HRAS

Binding activity

Table 1. Binding affinity (K_D) of ERAS-4001 to GDP-bound RAS (SPR)

RAS Status	KRAS WT	KRAS G12D	KRAS G12V	NRAS WT	HRAS WT
K_D (nM)	0.11	0.013	0.039	2,460	196

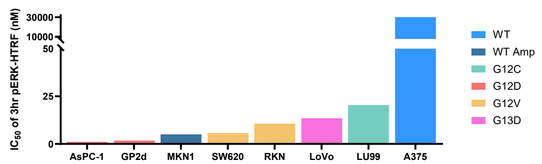
Table 2. Relative IC_{50}s of RAS-RAF complex formation inhibition by ERAS-4001 or MRTX1133

Compound	KRAS G12D (nM)	
	GMPPNP	GDP
ERAS-4001	5.65	1.65
MRTX1133[1]	6.63	3.10

[1]MRTX1133 is a potent KRAS G12D-selective comparator compound used in nonclinical studies

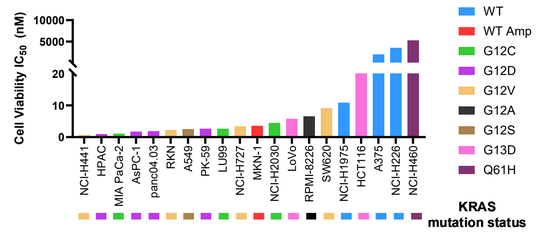
Cellular activity

Figure 2. 3-hour pERK-HTRF with ERAS-4001



KRAS WT and mutant cell lines were incubated with ERAS-4001 for 3 hours and the inhibition of ERK phosphorylation by ERAS-4001 was determined as IC_{50} values.

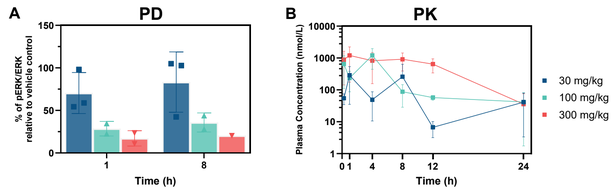
Figure 3. Cell viability of ERAS-4001 in WT and mutant KRAS cell lines



Cell lines harboring KRAS WT and/or KRAS mutations were incubated with ERAS-4001 for 4 to 7 days in a 3D cell viability assay. ERAS-4001 inhibited cell proliferation in 14 KRAS G12X and 2 KRAS G13D cell lines with IC_{50} values ranging from 0.7-56.0 nM. ERAS-4001 showed minimal activity in 2 KRAS independent cell lines, A375 and NCI-H226, and a KRAS Q61H mutant cell line, NCI-H460, with IC_{50} values ranging from 3,500-5,200 nM.

PK/PD relationship

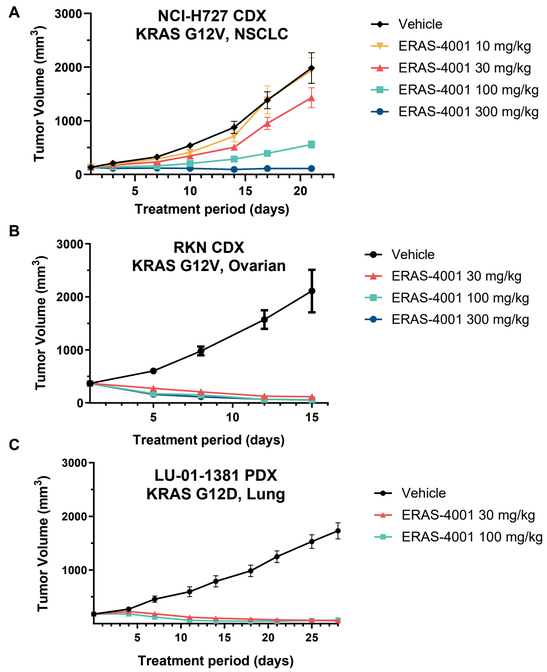
Figure 4. PK/PD relationship of ERAS-4001 in KRAS G12D mutant cell line Panc04.03



Tumor bearing mice were orally administered ERAS-4001 BID for 28 days. (A) Tumor (1- and 8-hour timepoints only) and plasma were harvested on day 29 at the indicated time points. (B) Total ERAS-4001 concentrations in plasma (mean ± SEM, N=3) were analyzed by LC/MS/MS. ERK1/2 signaling in xenograft tumors was measured by western blot assay.

In vivo efficacy

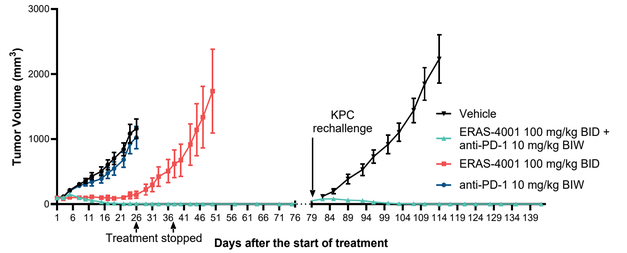
Figure 5. In vivo efficacy of ERAS-4001 in KRAS mutant xenograft models



ERAS-4001 and vehicle were dosed twice daily (BID) orally (PO). (A) ERAS-4001 showed dose proportional activity in the KRAS G12V NSCLC CDX NCI-H727. (B) Starting from 30 mg/kg BID PO, ERAS-4001 demonstrated strong tumor regression in the KRAS G12V ovarian cancer CDX RKN. (C) ERAS-4001 treatment demonstrated strong tumor regression in the KRAS G12D NSCLC patient-derived xenograft model LU-01-1381. ERAS-4001 was well tolerated with mild body weight loss (BWL) observed.

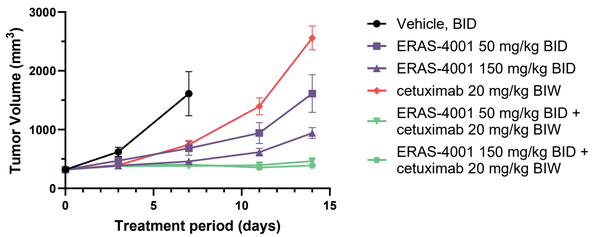
Combination with anti-PD-1 or cetuximab

Figure 6. Combination of ERAS-4001 with anti-PD-1 in KRAS G12D mutant mouse PDAC syngeneic model KPC



ERAS-4001 and vehicle were dosed BID orally. Anti-PD-1 was dosed at 5 mg/kg intraperitoneally twice a week (BIW) on days 1-5 and at 10 mg/kg BIW intraperitoneally until end of study. Dosing was stopped on day 26 for ERAS-4001 monotherapy, anti-PD-1 monotherapy, and vehicle. Dosing was stopped on day 38 for the ERAS-4001 + anti-PD-1 combination. Starting on day 50 through end of study, all mice in the ERAS-4001 + anti-PD-1 group had no measurable tumors. In a rechallenge study, KPC cells were injected into the contralateral flank of ERAS-4001 + anti-PD-1 treated mice and a new vehicle group on day 79. Tumor volumes of the contralaterally injected tumor cells are shown starting on day 79. Tumors did not form in the ERAS-4001 + anti-PD-1 group indicating an immune memory effect.

Figure 7. Combination of ERAS-4001 with cetuximab in KRAS G12D CDX model LS180



ERAS-4001 and vehicle were dosed BID orally and cetuximab was dosed BIW intraperitoneally. Dosing for the vehicle group was stopped on day 7 due to the outgrowth of the tumor. The combination of ERAS-4001 with cetuximab where ERAS-4001 was orally dosed either at 50 mg/kg BID or 150 mg/kg BID showed combination benefit relative to monotherapy treatments.

Conclusions

- ERAS-4001 is a novel orally bioavailable small molecule pan-KRAS inhibitor that selectively inhibits KRAS mutants and KRAS wild type
- ERAS-4001 inhibited the cellular viability of 14 KRAS G12X mutant and 3 KRAS wild type amplified NSCLC, CRC, and PDAC cell lines with IC_{50}s ranging from 0.7 to 9.1 nM
- In vivo, ERAS-4001 monotherapy demonstrated dose-dependent TGI in the KRAS G12V NSCLC CDX model, NCI-H727
- ERAS-4001 demonstrated significant antitumor efficacy in the KRAS G12V CDX model, RKN, and the KRAS G12D PDX model, LU-01-1381
- ERAS-4001 in combination with anti-PD-1 or cetuximab showed robust TGI in 2 KRAS G12D mutant models
- An IND submission is intended for Q2 2025