ERAS-0015 is a pan-RAS molecular glue with best-in-class potential in RAS mutant solid tumors

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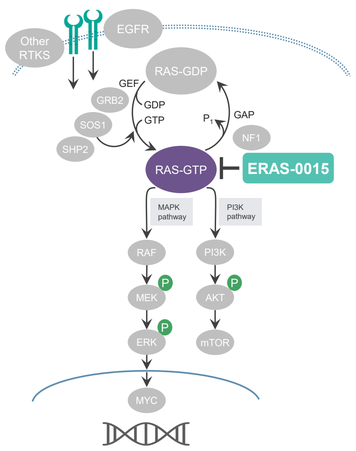
Abstract

As a key node of the canonical RTK-RAS-MAPK signaling cascade, the RAS family of GTPases plays an essential role in numerous physiological processes including cellular proliferation, migration, survival, and immune cell activation. However, under pathological conditions, oncogenic RAS mutations, particularly in hotspot codons 12, 13, and 61, affect RAS intrinsic hydrolysis and/or GEF-mediated exchange resulting in a shift from GDP-bound to GTP-bound RAS. This shift to the GTP-bound RAS state leads to recruitment of effector proteins through the RAS-binding domains (RBD) and ultimately leads to prolonged intracellular activation and modulation of the tumor microenvironment (TME).

ERAS-0015 is a pan-RAS molecular glue with best-in-class potential designed to target RAS in the GTP-bound state and shut down cellular signaling mediated by both mutant and wild-type RAS. ERAS-0015 exhibited 3-7-fold more potent inhibition of cellular proliferation relative to RMC-6236, a RAS molecular glue comparator, across multiple RAS mutant cell lines harboring G12X/G13X/Q61X mutations. ERAS-0015's roughly 8-20-fold higher binding affinity to cyclophilin A (CYPA) is thought to contribute to its higher in vitro cellular potency as well as favorable ADME and PK properties resulting in a longer residence time and greater exposure in tumor tissues as compared to RMC-6236. These favorable properties enabled ERAS-0015 to achieve comparable tumor growth inhibition (TGI) relative to RMC-6236 at 1/8th-1/10th the dose across multiple KRAS mutant CDX models irrespective of histology or specific mutation.

ERAS-0015 demonstrated promising preclinical activity across multiple RAS mutant models supporting IND filing in mid-Q2 2025.

Introduction



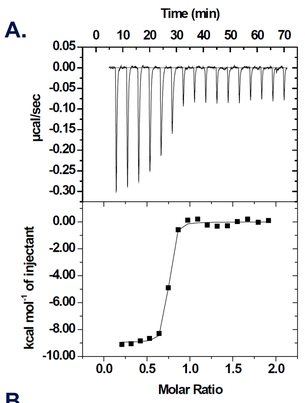
- The RAS family of proteins, which includes KRAS, NRAS and HRAS, are mutated in ~19% of human cancers
- RAS mutations drive cancer progression by stabilizing active state (GTP-bound) RAS by affecting either GTP hydrolysis/exchange or affinity to downstream effectors such as CRAF
- ERAS-0015 is a molecular glue that targets active RAS as part of a tripartite complex with CYPA

Figure 1. ERAS-0015 is a potent pan-RAS molecular glue inhibitor that targets active RAS and effectively inhibits the RAS-MAPK signaling pathway

Biophysical Results

Figure 2. ERAS-0015 exhibits 8-fold greater binding to CYPA relative to RMC-6236

A.



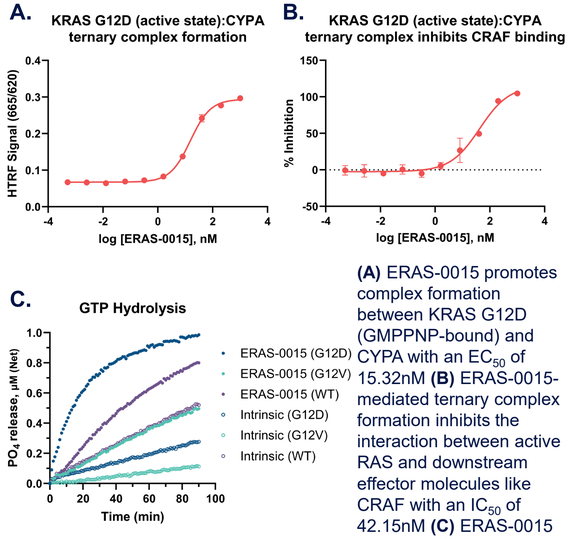
(A) Isothermal titration calorimetry was performed by titration of CYPA into a solution of ERAS-0015 or RMC-6236 at 20°C. Representative isotherm for binary complex formation between ERAS-0015 to CYPA is shown **(B)** Both ERAS-0015 and RMC-6236 bind at a 1:1 stoichiometry to CYPA with a K_D of 5.3 ± 1.4nM and 44.1 ± 7.7nM, respectively.

B.

Compound	Protein	N	ΔH (Kcal mol^{-1})	K_D (nM)
ERAS-0015	CYPA	0.67	-8.7 ± 0.9	5.3 ± 1.4
RMC-6236	CYPA	0.94	-8.2 ± 0.3	44.1 ± 7.7

Biochemical Results

Figure 3. ERAS-0015 forms a ternary complex with active state RAS and CYPA to inhibit complex formation between RAS and downstream effectors like CRAF and promote GTP hydrolysis



(A) ERAS-0015 promotes complex formation between KRAS G12D (GMPPNP-bound) and CYPA with an EC_{50} of 15.32nM **(B)** ERAS-0015-mediated ternary complex formation inhibits the interaction between active RAS and downstream effector molecules like CRAF with an IC_{50} of 42.15nM **(C)** ERAS-0015 promotes GTP hydrolysis in KRAS G12D/G12V/WT RAS

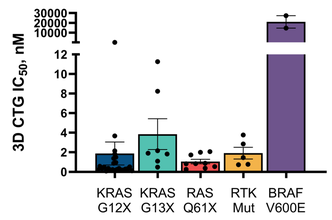
Results

Figure 4. Concentration of ERAS-0015 and RMC-6236 in AsPC-1 cells and cell culture media following 1-hour treatment

Compound	Cellular Media (nM)			AsPC-1 cells (nM)		
	3nM	10nM	100nM	3nM	10nM	100nM
ERAS-0015	2	10	85	467	1,764	14,216
RMC-6236	2	8	93	208	658	4,958
0015:6236 Ratio	1.0x	1.1x	0.9x	2.2x	2.7x	2.9x

ERAS-0015 is present at 2.2-2.9x higher concentrations in KRAS G12D AsPC-1 PDAC tumor cells than RMC-6236 following 1 hour treatment

Figure 5. ERAS-0015 demonstrates potent inhibition of cellular proliferation across multiple RAS mutant models

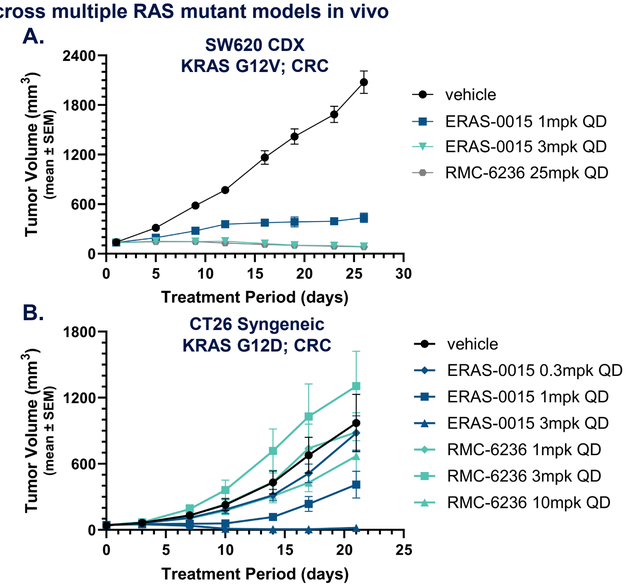


Mutation Class	Cell Viability IC_{50} (nM)
KRAS G12X	0.08-3.67*
KRAS G13X	0.47-11.27
RAS Q61X	0.25-2.06
RTK activating mut./amp	0.73-3.77
BRAF V600E	>10,000

*Excludes one outlier cell line with IC_{50} = 29.82nM

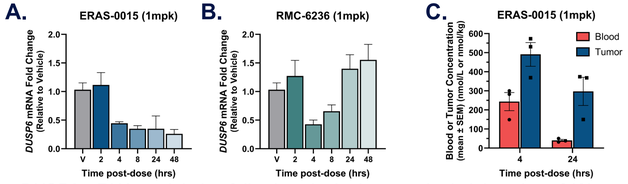
ERAS-0015 exhibits potent inhibition of cellular proliferation and viability across cell lines spanning multiple RAS mutations and tissue indications

Figure 6. ERAS-0015 exhibits dose-dependent monotherapy activity across multiple RAS mutant models in vivo



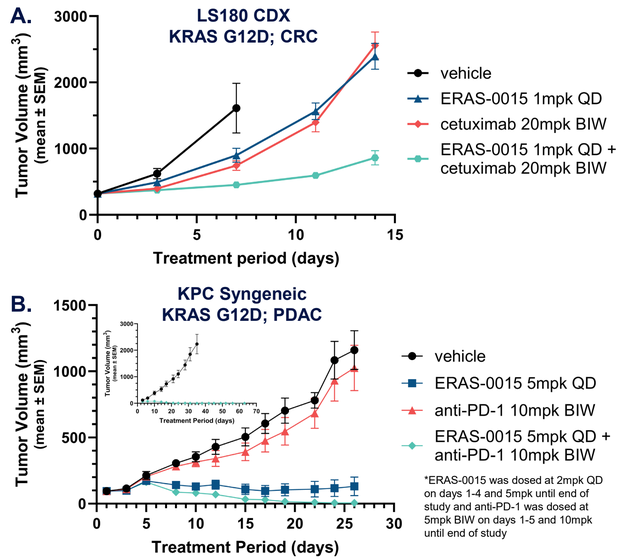
ERAS-0015 exhibits dose-dependent monotherapy antitumor activity in vivo across multiple RAS mutations and tissue types. Representative TGI curves are shown in **(A)** SW620 and **(B)** CT26. Drugs were administered orally, and treatments were well tolerated with no body weight loss (BWL) or adverse events (AE) observed

Figure 7. ERAS-0015 demonstrates durable modulation of the RAS-MAPK pathway and preferential drug distribution into tumor tissues in KRAS G12D PDAC model PK-59



DUSP6 mRNA modulation following single dose, oral administration of **(A)** ERAS-0015 and **(B)** RMC-6236 at 1mpk **(C)** Tumor and blood PK of ERAS-0015 at 1mpk in PK-59 model following repeat dosing

Figure 8. ERAS-0015 exhibits in vivo combination activity



*ERAS-0015 was dosed at 2mpk QD on days 1-4 and 5mpk until end of study and anti-PD-1 was dosed at 5mpk BIW on days 1-5 and 10mpk until end of study

ERAS-0015 exhibits in vivo combination activity with **(A)** cetuximab in LS180 CDX model and **(B)** anti-PD-1 in KPC syngeneic model. Following the end of the TGI study, the ERAS-0015 + anti-PD-1 cohort was rechallenged (**B**, *insert*) and durable adaptive anti-tumor activity was observed. A new cohort of mice implanted in parallel exhibited exponential tumor growth. All treatments were well tolerated with no BWL or AEs observed

Conclusions

- ERAS-0015 is a potent pan-RAS molecular glue with 8-20-fold greater CYPA binding relative to RMC-6236 (SPR data not shown), leading to dose-dependent formation of an active RAS:ERAS-0015:CYPA ternary complex that inhibits active RAS from binding downstream effectors such as CRAF
- ERAS-0015 demonstrates potent inhibition of cellular proliferation across a panel of cell lines spanning diverse tissue indications and RAS mutations
- ERAS-0015 exhibits preferential drug distribution into tumor tissues
- ERAS-0015 exhibits promising preclinical in vivo activity as both a monotherapy and in combination across multiple RAS mutant models to support a mid-Q2 2025 IND filing