Combination of ERAS-0015 and ERAS-4001 Targets Active and Inactive KRAS and Displays Synergy in Nonclinical KRAS G12X-Driven Models

PB-073

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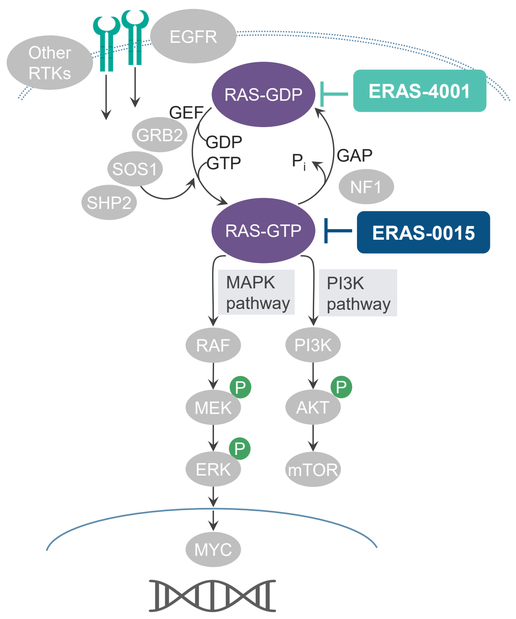
Background

KRAS is the most frequently mutated oncogene in human solid tumors, with mutations occurring in approximately 87% of pancreatic ductal adenocarcinomas (PDAC), 43% of colorectal adenocarcinomas (CRC), and 32% of lung adenocarcinomas (LUAD). Across PDAC, CRC, and LUAD, these mutations are dominated by G12X substitutions (~69–92% of KRAS mutations).

ERAS-0015 is a pan-RAS molecular glue that binds active GTP-bound RAS, blocks effector engagement and promotes GTP hydrolysis, which converts active GTP-bound RAS to the inactive GDP-bound state.

ERAS-4001 is a selective, noncovalent pan-KRAS inhibitor that binds the allosteric switch-II pocket and blocks the transition of KRAS from the inactive to the active state. Given these complementary mechanisms, we explored whether ERAS-0015 + ERAS-4001 would enhance inhibition of KRAS G12X-driven RAS-MAPK signaling and improve antitumor activity.

RAS-MAPK pathway



KRAS mutation estimates were calculated using data from AACR GENIE v20. The AACR Project GENIE Consortium. *AACR Project GENIE: Powering Precision Medicine Through An International Consortium*, Cancer Discov. 2017 Aug;7(8):818-831

Mechanistic Rationale for ERAS-0015 + ERAS-4001

ERAS-0015 binds CYPA and forms a ternary complex with GTP-bound RAS that blocks effector binding

ERAS-0015 ternary complexes accelerate RAS GTP hydrolysis in a subset of KRAS mutants

ERAS-4001 binds and locks KRAS in its GDP-bound inactive state

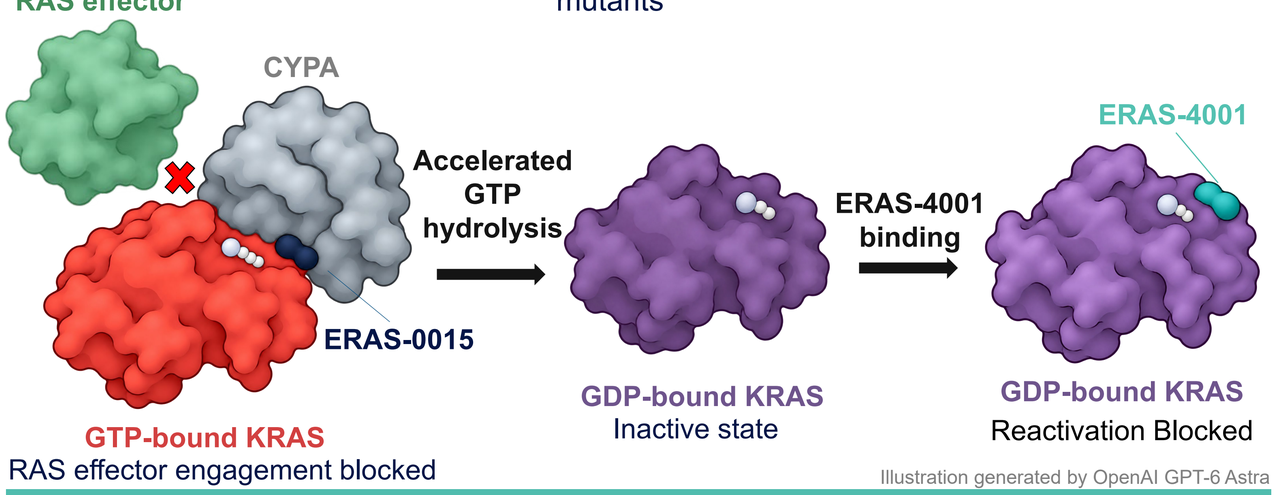


Illustration generated by OpenAI GPT-6 Astra

Cellular Target Engagement

The combination of ERAS-0015 + ERAS-4001 demonstrated enhanced target engagement, as measured by RAS-RAF disruption in a cell reporter system

KRAS G12D

CI	4001 (nM)		
0015 (nM)	0.6	1.7	8.7
0.31	0.95	0.52	0.80
1.4	0.66	0.41	0.57
16	0.47	0.26	0.55

KRAS G12V

CI	4001 (nM)		
0015 (nM)	0.41	2.2	32
0.1	0.34	0.08	0.22
0.38	0.38	0.11	0.07
3.4	0.62	0.24	0.21

KRAS G12R

CI	4001 (nM)		
0015 (nM)	4.4	32.8	794
0.65	0.56	0.09	0.76
2.8	0.57	0.17	0.12
14.9	0.76	0.37	0.26

Combination Index (CI)

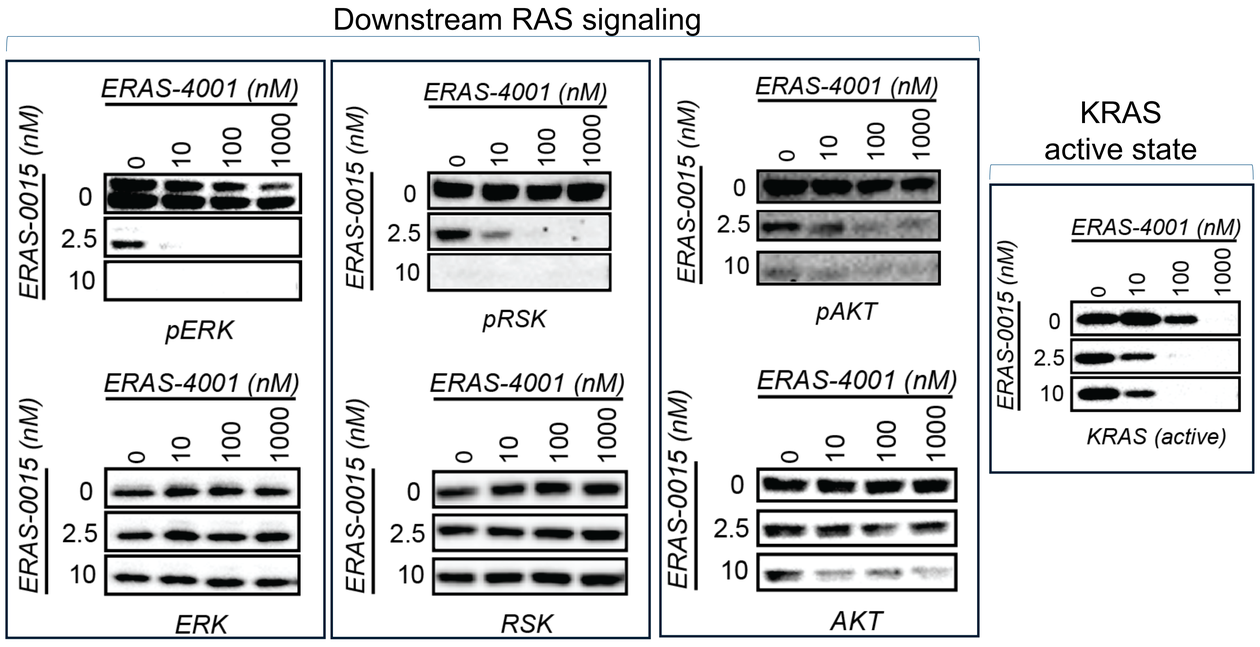
0 — 0.3 — 0.6 — 0.9 — 1

Strong synergy | Moderate synergy | Weak synergy

HEK293FT cells expressing KRAS G12D, KRAS G12V, or KRAS G12R and CRAF fused into the NanoBiT system were generated. Cells were treated with ERAS-0015 and ERAS-4001 spanning the IC_{20}-IC_{90} values and kinetics of KRAS-CRAF RBD complex inhibition were measured over 6 hours.

Cellular Signaling Inhibition

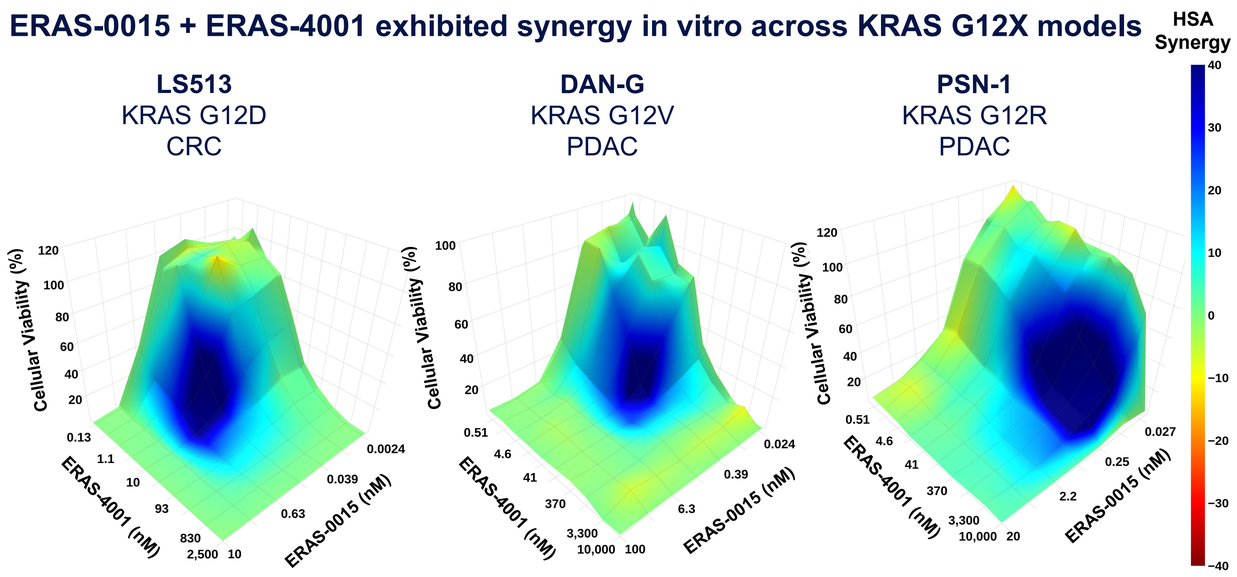
ERAS-0015 + ERAS-4001 inhibited active GTP-bound KRAS and RAS downstream signaling (pERK, pRSK, and pAKT) in the KRAS G12R PDAC cell line PSN-1



Cells were serum-starved overnight and treated with ERAS-0015 + ERAS-4001 combinations for 6 hours.

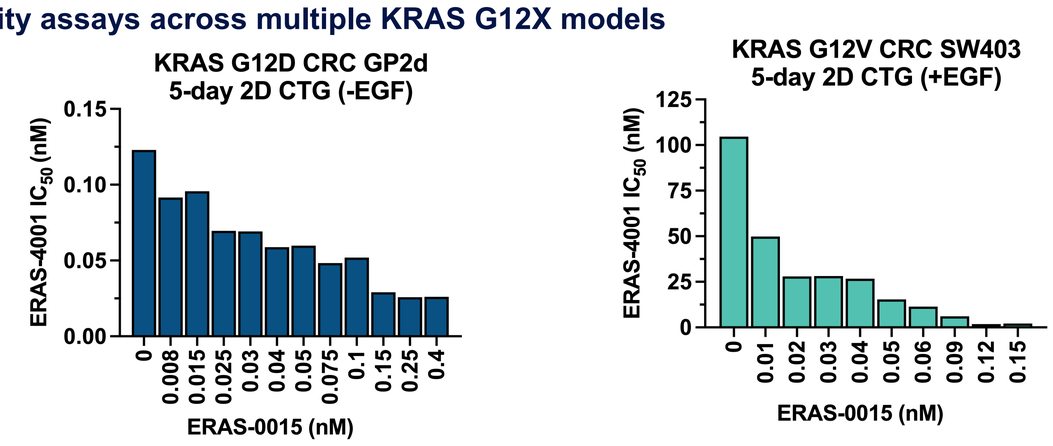
Cellular Synergy

ERAS-0015 + ERAS-4001 exhibited synergy in vitro across KRAS G12X models



Cells were treated with the combination of ERAS-0015 and ERAS-4001 for 5 days in a 3D cell viability assay. Synergy was assessed using HSA analysis.

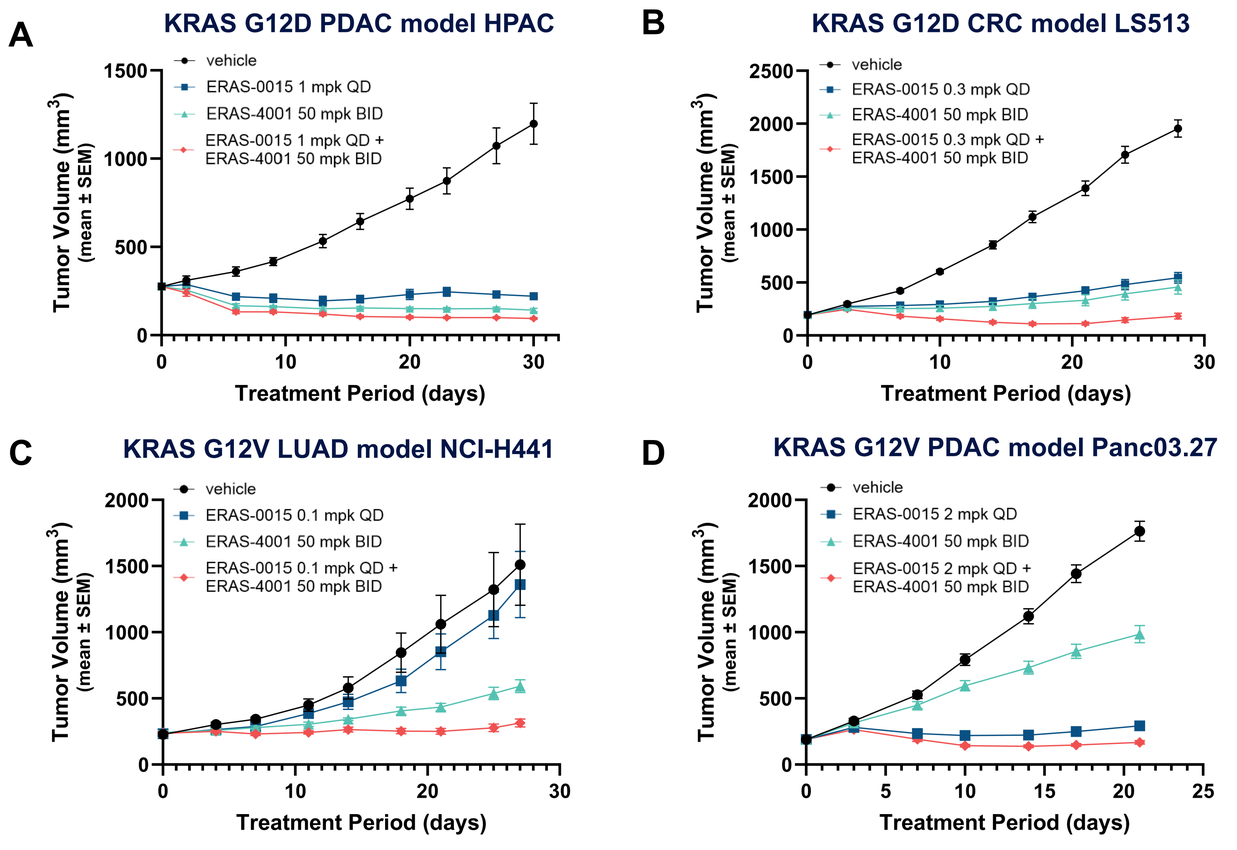
Low concentrations of ERAS-0015 potentiated the activity of ERAS-4001 in cell viability assays across multiple KRAS G12X models



Cells were treated with ERAS-0015 at constant concentrations <IC_{80} and <IC_{60} in GP2d and SW403, respectively, in combination with a dose response of ERAS-4001. Low dose ERAS-0015 potentiated the activity of ERAS-4001, lowering the observed IC_{50} in 5-day, 2D cell viability assays. The SW403 assay included 50 ng/mL of EGF (+EGF) to stimulate EGFR-RAS-MAPK signaling. Cell viability was normalized to DMSO-treated or ERAS-0015-only controls for calculation of ERAS-4001 IC_{50} values.

In Vivo CDX Studies

ERAS-0015 + ERAS-4001 showed combination activity in KRAS G12X mutant PDAC, CRC, and LUAD CDX models



ERAS-0015 and ERAS-4001 exhibited in vivo combination activity including tumor regressions across multiple KRAS G12X mutant models, including (A) HPAC (KRAS G12D; pancreatic), (B) LS513 (KRAS G12D; CRC), (C) NCI-H441 (KRAS G12V; lung), and (D) Panc03.27 (KRAS G12V; pancreatic). All treatments were well tolerated with no significant body weight loss (i.e., >15%) or adverse events.

Conclusions

1. ERAS-0015 and ERAS-4001 mechanistically synergized both in vitro and in vivo to mediate deeper inhibition of the RAS-MAPK signaling pathway
   - ERAS-0015 accelerated the conversion of mutant KRAS from the active GTP-bound state to the inactive GDP-bound state
   - ERAS-4001 bound GDP-bound mutant KRAS, locking it in the inactive state
2. Cellular target engagement and signaling assays showed deeper RAS–MAPK inhibition with the combination than with either agent alone
3. ERAS-0015 and ERAS-4001 synergistically inhibited cellular viability of KRAS G12D, G12V, and G12R cell lines in vitro
4. ERAS-0015 + ERAS-4001 showed in vivo combination benefit in KRAS G12D and G12V mutant PDAC, CRC, and LUAD CDX models
5. Based on these promising nonclinical data, further clinical investigation is warranted