ERAS-007 is a selective ERK1/2 inhibitor with preclinical activity across RAS/MAPK pathway-driven CRC models

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Abstract

Colorectal cancer (CRC) remains an unmet medical need where more than 50% of patients have tumors that are driven by somatic mutations in the RAS/MAPK signaling pathway. Targeted therapies such as anti-EGFR therapies for patients with *BRAF*^{wt}/*RAS*^{wt} CRC tumors and encorafenib + cetuximab (EC) for patients with *BRAF*^{V600E} CRC tumors are available treatment options but demonstrate limited overall response rates and duration of response (Yaeger, 2018). Furthermore, in the previously treated setting, overall survival is typically less than a year (Grothey, 2013; Mayer, 2015; Kopetz, 2019). In addition, targeted treatment options are limited for patients harboring *KRAS* or *NRAS* mutations as emergence of these mutations is a predictive biomarker to anti-EGFR therapy resistance in metastatic CRC, necessitating additional effective clinical combination options.

ERAS-007 is a selective ERK1/2 inhibitor targeting the terminal node of the RAS/MAPK signaling pathway. In addition, it demonstrates single digit nanomolar biochemical ERK1/2 inhibition as well as a durable target residence time, thus making it a promising combination partner in the treatment of RAS/MAPK pathway activated or altered CRC. To this end, ERAS-007 was evaluated in preclinical models in combination with encorafenib + cetuximab or palbociclib in *BRAF*^{V600E} CRC and *KRAS*^{mut} CRC, respectively. ERAS-007 demonstrated monotherapy and combination activity in cell-based assays as well as superior combination efficacy *in vivo* relative to respective monotherapy control arms.

In summary, ERAS-007 demonstrates promising preclinical activity across a wide range of RAS/MAPK pathway-driven CRC models both as a monotherapy and in combination that supports further exploration in the clinic. Accordingly, ERAS-007 in combination with encorafenib + cetuximab or palbociclib in *BRAF*^{V600E} CRC and RAS^{mut} CRC, respectively, is currently being evaluated in the HERKULES-3 phase 1b/2 clinical trial (NCT05039177).

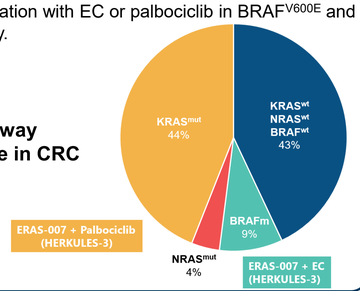
Introduction

A key biological driver of CRC cell growth and survival is activation of the RAS/MAPK pathway, which includes mutations in RAS, BRAF and MEK, or loss of NF1 function (Montagut, 2009). ERK is the most distal node of the RAS/MAPK signaling pathway downstream of BRAF. Preclinical models in BRAF^{V600E} CRC cells expressing emergent resistance mutations in the RAS/MAPK pathway suggest that the triple blockade of BRAF, EGFR, and ERK proved to be the most effective in reducing tumor volume and preventing the emergence of resistance clones (Hazar Rethinam, 2018).

In addition, ERK also plays a key role in cell cycle progression by regulating expression of key cell cycle proteins such as cyclin D1 and p21^{Cip1}, which in turn, regulate CDK4/6. Thus, given the intricate relationship between ERK activity and the cell cycle machinery, ERAS-007 in combination with CDK4/6 inhibitors may provide combinatorial clinical benefit in RAS mutant indications to mediate durable inhibition of MAPK signaling/cell cycle progression.

CRC remains a major unmet clinical need, and to this end, this work explores ERAS-007 in combination with EC or palbociclib in BRAF^{V600E} and RAS mutant CRC, respectively.

Figure 1. RAS/MAPK pathway alterations and prevalence in CRC



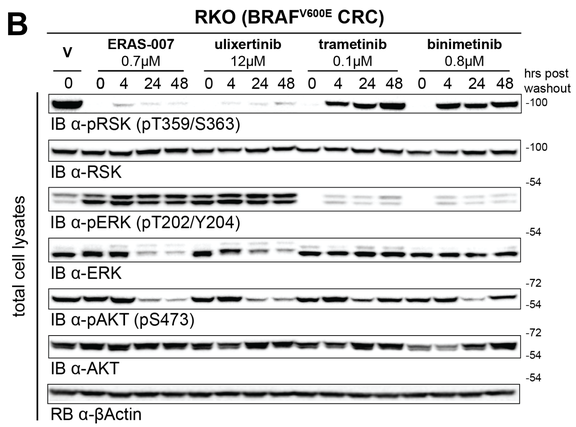
Results

Figure 2. ERAS-007 exhibits both long biophysical target residence time and sustained RAS/MAPK pathway inhibition relative to other ERK and MEK inhibitors

A

Compound	ERK2 residence time (τ) (min)	pRSK IC_{50} in RKO (nM)
ERAS-007	550	7.0
ulixertinib	16	116.8
trametinib	<0.03	1.3
binimetinib	<0.03	8.3

B



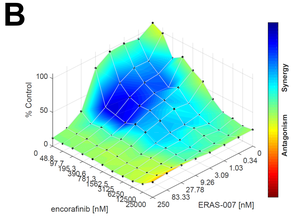
(A) ERK2 residence time for ERKi(s), ERAS-007 and ulixertinib, and MEKi(s), trametinib and binimetinib, determined by BLI and SPR, respectively. pRSK IC_{50} was determined by incubating RKO cells with inhibitors for 1 hour and determining pRSK IC_{50} by AlphaLISA assay. **(B)** RKO cells were incubated with 100x pRSK IC_{50} per compound for 1 hour. Following washout of compound, cellular signaling was assessed at indicated timepoints. ERAS-007 mediated durable inhibition of MAPK signaling at <1μM.

Figure 3. ERAS-007 inhibits cellular proliferation and exhibits combination activity with encorafenib in BRAF^{V600E} CRC cell lines

A

Cell Line	3D Cell Viability ERAS-007 IC_{50} (nM)
RKO	13.63
WiDr	8.35
HT-29	12.07
MDST8	3.81
LIM2405	0.81

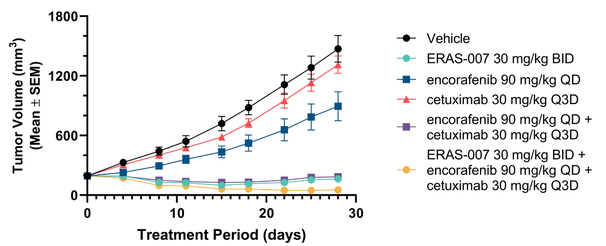
B



ERAS-007 exhibits monotherapy and combination activity in BRAF^{V600E} cell lines in 3D cell viability assays. **(A)** ERAS-007 inhibited cellular proliferation and viability in *BRAF*^{V600E} CRC cell panel. **(B)** ERAS-007 and encorafenib exhibit synergy in the RKO cell line.

Figure 4. ERAS-007 in combination with encorafenib ± cetuximab (EC) demonstrates efficacy in *BRAF*^{V600E} CRC CDX and PDX models

A



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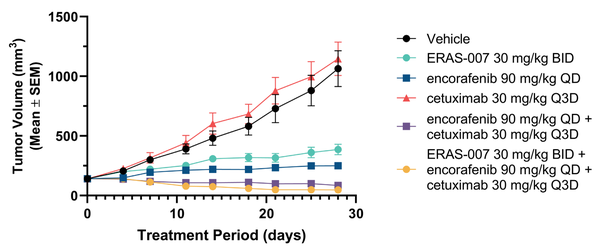

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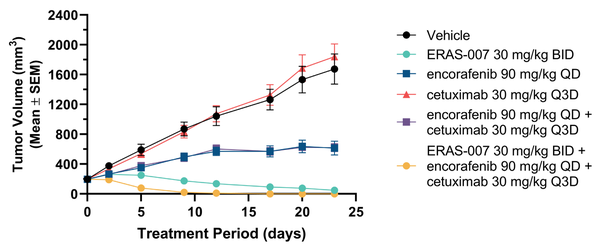
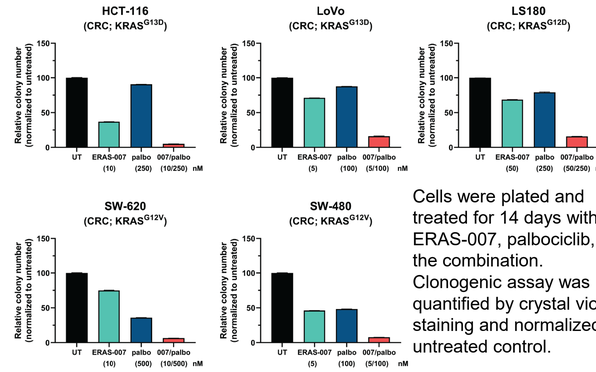


ERAS-007 exhibits *in vivo* antitumor activity in combination with encorafenib ± cetuximab in **(A)** WiDr, **(B)** CR0004, and **(C)** CRC1011. The combination of ERAS-007 with encorafenib was statistically significant relative to respective monotherapy groups (data not shown), and the triple combination demonstrated superior efficacy and was statistically significant relative to the standard of care EC combination.

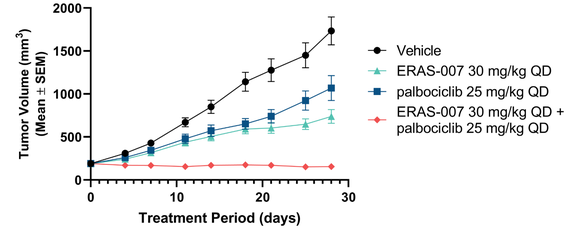
Figure 5. ERAS-007 and palbociclib demonstrate combination benefit *in vitro* across multiple *KRAS*^{mut} CRC models



Cells were plated and treated for 14 days with ERAS-007, palbociclib, or the combination. Clonogenic assay was quantified by crystal violet staining and normalized to untreated control.

Figure 6. ERAS-007 in combination with palbociclib demonstrates *in vivo* efficacy in *KRAS*^{mut} CRC models

A



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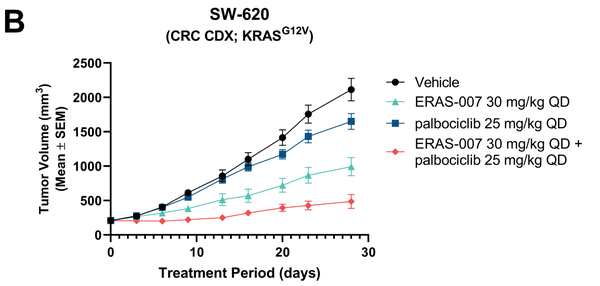

ERAS-007 exhibits *in vivo* antitumor activity in combination with palbociclib in **(A)** LoVo and **(B)** SW-620 *KRAS*^{mut} CRC models. Combination activity of ERAS-007 with palbociclib was statistically significant relative to respective monotherapy groups.

Conclusions

- ERAS-007 is a potent ERK1/2 small molecule inhibitor with durable target residence time and promotes sustained RAS/MAPK pathway inhibition
- ERAS-007 demonstrates promising preclinical activity across a wide range of RAS/MAPK pathway-driven CRC models both as a monotherapy and in combinations that support further exploration in the clinic
- Accordingly, ERAS-007 in combination with encorafenib + cetuximab or palbociclib in *BRAF*^{V600E} CRC or KRAS^{mut} CRC, respectively, is currently being evaluated in the HERKULES-3 phase 1b/2 clinical trial