Preliminary results from ERAS-007 plus encorafenib and cetuximab (EC) in patients (pts) with metastatic BRAF V600E mutated colorectal cancer (CRC) in HERKULES-3 study: A phase 1b/2 study of agents targeting the mitogen-activated protein kinase (MAPK) pathway in pts with advanced gastrointestinal malignancies (GI cancers)

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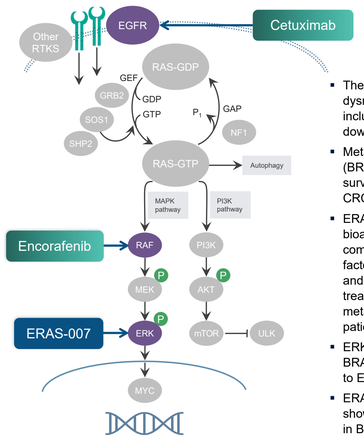
Introduction



- The RAS/MAPK pathway (including BRAF) is dysregulated in a broad range of cancers including colorectal cancer (CRC), resulting in downstream activation of ERK1/2
- Metastatic CRC with BRAF V600E mutation (BRAF V600E mCRC) has dramatically worse survival than non-BRAF V600E–mutated CRC, and novel therapies are needed
- ERAS-007 is a novel, potent, and orally bioavailable inhibitor of ERK1/2. The combination of a BRAF plus epidermal growth factor receptor (EGFR) inhibitor (encorafenib and cetuximab [EC]) is approved for the treatment of patients with BRAF V600E metastatic CRC; however, only 20% of patients experience an objective response[1]
- ERK inhibition may prevent resistance to BRAF/EGFR inhibition by adding ERAS-007 to EC
- ERAS-007 alone or in combination with EC showed promising in vitro and in vivo activity in BRAF V600E mCRC models to support the combinatorial clinical benefit of ERAS-007 + EC in BRAF V600E mCRC

Study Design

A1: ERAS-007 QW[a] + EC[b]

Dose Escalation
Part A1a: EC-naïve or -treated BRAF V600E mCRC

ERAS-007 250 mg QW + EC
↑
ERAS-007 200 mg QW + EC
↑
ERAS-007 150 mg QW + EC*

Dose Expansion
Part A1b: EC-naïve BRAF V600E mCRC

ERAS-007 QW + EC (RD)

Dose Expansion
Part A1c: EC-treated BRAF V600E mCRC

ERAS-007 QW + EC (RD)

A2: ERAS-007 BID-QW[c] + EC[b]

Dose Escalation
Part A2a: EC-naïve or -treated BRAF V600E mCRC

ERAS-007 125 mg BID-QW + EC
↑
ERAS-007 100 mg BID-QW + EC
↑
ERAS-007 75 mg BID-QW + EC†

Dose Expansion
Part A2b: EC-naïve BRAF V600E mCRC

ERAS-007 BID-QW + EC (RD)

Dose Expansion
Part A2c: EC-treated BRAF V600E mCRC

ERAS-007 BID-QW + EC (RD)

*ERAS-007 was evaluated at 150 mg QW as the starting dose in combination with EC. †ERAS-007 was evaluated at 75 mg BID-QW as the starting dose in combination with EC.
[a]ERAS-007 QW: ERAS-007 oral once a week; [b]EC: encorafenib 300 mg oral daily + cetuximab 500 mg/m² intravenous infusion once every 2 weeks; [c]ERAS-007 BID-QW: ERAS-007 oral twice a day on a single day each week.
RD: recommended dose.

- HERKULES-3 (NCT05039177) is a phase 1b/2 study to assess the safety, tolerability, pharmacokinetics (PK), and preliminary clinical activity of ERAS-007 combinations targeting the MAPK pathway in patients with advanced gastrointestinal cancers
- Within this study, we are currently evaluating the safety, tolerability, and PK of escalating doses of ERAS-007 + EC in patients with BRAF V600E mCRC. Prior BRAF inhibitor and EGFR inhibitor treatment are neither required nor excluded to be enrolled. While the study was in progress, the decision was made to change from QW to BID-QW schedule during the escalation phase to decrease potential C_{max}-related toxicity

Primary Objectives:

- To evaluate the safety and tolerability of escalating doses of ERAS-007 (QW in Part A1a, BID-QW in Part A2a) in combination with EC in previously treated BRAF V600E mCRC patients
- To determine the maximum tolerated dose and/or recommended dose of ERAS-007 (QW in Part A1a and BID-QW in Part A2a) in combination with EC

Results

Data Cut-off Date: 23MAR2023

Enrollment and Baseline Characteristics

Analysis Populations, N (%)

	Safety Population*	Efficacy-Evaluable Population†	Efficacy-Evaluable EC-Naïve Population
ERAS-007 + EC	**20**	**17**	**7**
150 mg QW + EC	2 (100)	2 (100)	1 (50)
75 mg BID-QW + EC	6 (100)	5 (83.3)	1 (16.7)
100 mg BID-QW + EC	12 (100)	10 (83.3)	5 (41.7)

*Safety analysis population includes all patients who received ≥1 dose of ERAS-007. †Efficacy-evaluable analysis population includes all patients in the safety analysis population with measurable disease at baseline and ≥1 post-dose response assessment.

Patient Status, N

	No. of Patients on Treatment*	No. of Patients in Survival Follow-up	No. of Patients Off Study
ERAS-007 + EC			
150 mg QW + EC	0	0	2
75 mg BID-QW + EC	1	3	2
100 mg BID-QW + EC	6	2	4

*Defined as patients on any study drug.

Baseline Characteristics (Safety Population)

	All (ERAS-007 + EC) (N=20)
Age, years	
Median	64.0
Min, max	43, 86
Sex, n (%)	
Male	12 (60)
Female	8 (40)
Race, n (%)	
White	17 (85)
Asian	1 (5)
Not reported	2 (10)
ECOG, n (%)	
0	9 (45)
1	10 (50)
2	1 (5)
Prior lines of systemic therapies	
Median	2
Min, max	1, 7

Summary of Safety

Patients Experiencing, N (%)	All (N=20)
TEAEs*	20 (100)
TRAEs† (related to ERAS-007)	17 (85)
TRAEs with CTCAE grade ≥3	5 (25)
TRAEs leading to ERAS-007 discontinuation	2 (10)
TRAEs leading to ERAS-007 interruption	5 (25)
TRAEs leading to ERAS-007 dose reduction	4 (20)
Treatment-related SAEs	1 (5)

*TEAE: treatment-emergent adverse event. †TRAE: treatment-related adverse event.
CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event.

- Overall data suggest combination regimens are well tolerated
- No grade 5 treatment-emergent adverse events reported
- One dose-limiting toxicity (grade 3 macular edema, related to ERAS-007) was reported in the ERAS-007 100 mg BID-QW combination treatment group after data extraction.

TRAEs* Reported in ≥20% of All Patients

ERAS-007 Dose + EC	150 mg QW (N=2)		75 mg BID-QW (N=6)		100 mg BID-QW (N=12)		All (N=20)	
Preferred Term	**All**	**Gr ≥3**	**All**	**Gr ≥3**	**All**	**Gr ≥3**	**All**	**Gr ≥3**
Fatigue	1 (50)	1 (50)	3 (50)	0	3 (25)	0	7 (35)	1 (5)
Diarrhea	0	0	2 (33)	0	4 (33)	0	6 (30)	0
Headache	0	0	3 (50)	0	3 (25)	1 (8)	6 (30)	1 (5)
Anaemia	1 (50)	0	2 (33)	1 (17)	2 (17)	1 (8)	5 (25)	2 (10)
Nausea	0	0	3 (50)	0	2 (17)	0	5 (25)	0
Subretinal fluid	0	0	1 (17)	0	3 (25)	0	4 (20)	0
Vomiting	1 (50)	0	2 (33)	0	1 (8)	0	4 (20)	0

*TRAE in the table refers to treatment-emergent AEs (TEAEs) related to ERAS-007.

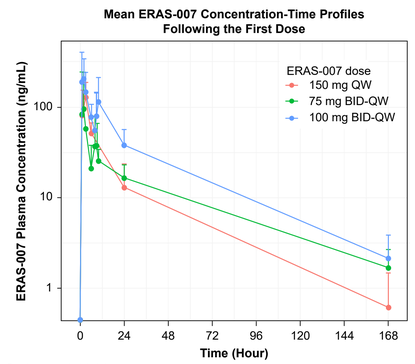
Grade ≥3 TRAEs*

ERAS-007 Dose + EC	150 mg QW (N=2)	75 mg BID-QW (N=6)	100 mg BID-QW (N=12)	All (N=20)
Fatigue	1 (50)	0	0	1 (5)
Headache	0	0	1 (8)	1 (5)
Anaemia	0	1 (17)	1 (8)	2 (10)
Blood creatinine increased	0	1 (17)	0	1 (5)
Macular oedema	0	0	1 (8)	1 (5)
Skin toxicity	1 (50.0)	0	0	1 (5)

*TRAE in the table refers to treatment-emergent AEs (TEAEs) related to ERAS-007.

- Majority of TRAEs observed are grade 1 or 2

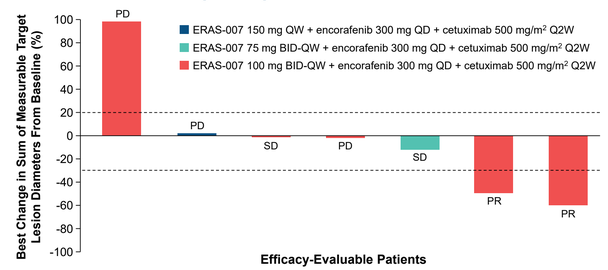
Summary of Pharmacokinetics



Error bars = standard deviation.

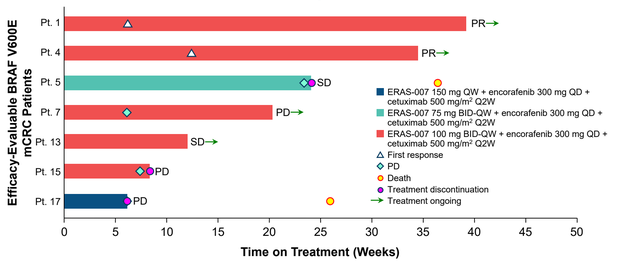
- ERAS-007 exhibited rapid absorption with median peak plasma concentration reached between 2 and 3 hours post-dose; PK exposure generally increased in a dose-dependent manner
- Observed PK exposures of ERAS-007, encorafenib, and cetuximab when dosed in combination were generally comparable to those when dosed as monotherapy, suggesting no clinically significant drug-drug interactions between study drugs

Best Change in Target Lesions in EC-Naïve Patients



Response on the bar represents the best overall response based on investigator assessments. Of note, presented PRs are confirmed PRs.
PD: progressive disease; PR: partial response; SD: stable disease.

Duration of Treatment in Efficacy-Evaluable EC-Naïve Patients

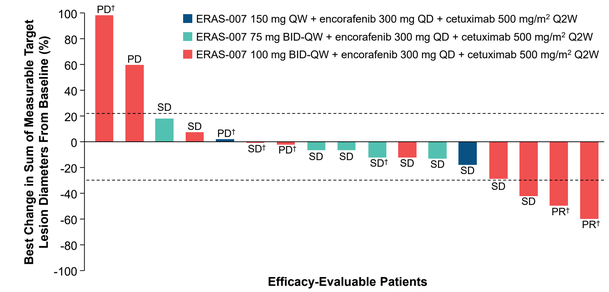


Response on the bar represents the best overall response based on investigator assessments. Of note, presented PRs are confirmed PRs.
PD: progressive disease; PR: partial response; SD: stable disease.

In EC-naïve efficacy-evaluable patients,

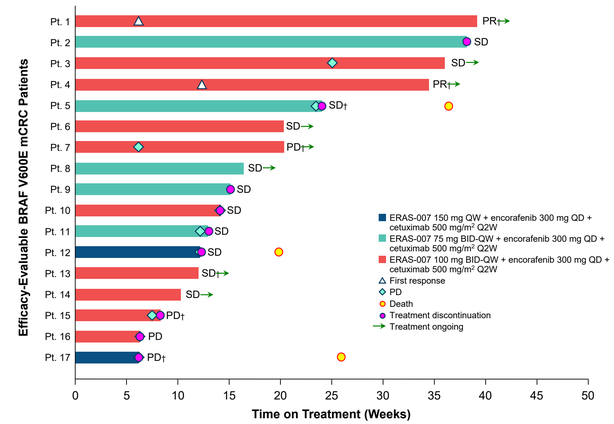
- Across all dose levels, the response rate was 29% (2/7), the disease control rate (complete response [CR] + partial response [PR] + stable disease [SD]) was 57% (4/7) and the median duration of treatment was 20.3 weeks
- At the highest dose currently evaluated (ERAS-007 100 mg BID-QW), the response rate was 40% (2/5) and the disease control rate (CR + PR + SD) was 60% (3/5)
- Both responders were still on treatment with duration of exposure >34 weeks

Best Change in Target Lesions



Response on the bar represents the best overall response based on investigator assessments. Of note, presented PRs are confirmed PRs.
†Represents EC-naïve population.
PD: progressive disease; PR: partial response; SD: stable disease.

Duration of Treatment in Efficacy-Evaluable Patients



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments. Of note, presented PRs are confirmed PRs.
†Represents EC-naïve population.
PD: progressive disease; PR: partial response; SD: stable disease.

- In all efficacy-evaluable patients (including EC-treated and EC-naïve), the response rate was 12% (2/17) and the disease control rate (CR + PR + SD) was 76% (13/17)

Conclusions

- ERAS-007 + EC in patients with BRAF V600E mCRC shows acceptable preliminary safety/tolerability and evidence of clinical activity
- The highest dose of ERAS-007 evaluated and cleared by the safety review committee to date is 100 mg BID-QW when combined with EC
- Observed PK, safety, and preliminary clinical activity in the EC-naïve population supports continued evaluation of the ERAS-007 + EC combination in BRAF V600E mCRC

References

1. Kopetz S, et al. *N Engl J Med.* 2019;381:1632-1643.

PRESENTED AT THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) ANNUAL MEETING, JUNE 2-6 2023, CHICAGO, IL, USA