Preliminary results from HERKULES-1: a phase 1b/2, open-label, multi-center study of ERAS-007, an oral ERK1/2 inhibitor, in patients with advanced or metastatic solid tumors

Judy Wang[1], Melissa Johnson[2], Minal Barve[3], Meredith Pelster[2], Xiaoying Chen[4], Zhengrong Li[4], Jennifer Gordon[4], Moshe Reiss[4], Sachin Pai[4], Gerald Falchook[5], Anthony Tolcher[6]

[1]Florida Cancers Specialists/Sarah Cannon Research Institute, Drug Development Unit - Sarasota, Sarasota, USA; [2]Sarah Cannon Research Institute at Tennessee Oncology, Drug Development Unit, Nashville, USA; [3]Mary Crowley Cancer Research, Research Oncology, Dallas, USA; [4]Erasca, Inc., San Diego, USA; [5]Sarah Cannon Research Institute at HealthONE, Drug Development Unit, Denver, USA; [6]NEXT Oncology, Oncology, San Antonio, USA.

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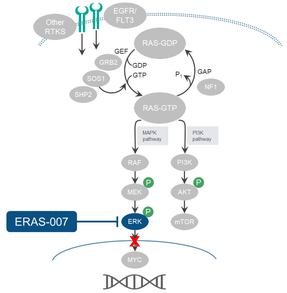
Abstract # 224

Background

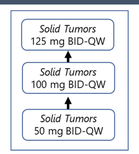
- The RAS/MAPK pathway is dysregulated in a broad range of cancers, resulting in downstream activation of ERK1/2.
- ERAS-007 is a novel, potent, and orally bioavailable inhibitor of ERK1/2 with a prolonged target residence time (550 min)[1].
- The first-in-human Phase 1 study of ERAS-007[1] identified the 250 mg once weekly (QW) schedule for further evaluation based on a manageable toxicity profile and encouraging signs of clinical activity (NCT03415126).
- Pharmacokinetic (PK) modeling suggests that an alternative intermittent regimen (twice a day, once a week; BID-QW) is expected to have lower peak concentrations (Cmax) and similar overall PK exposures (area under the curve, AUC) compared to QW, which may improve Cmax-driven adverse events (AE) while maintaining comparable efficacy.
- Optimizing tolerability is particularly beneficial as combinations of ERAS-007 with other anti-cancer agents are being pursued.



1. Filip Janku et al. Targeting ERK with a novel inhibitor ASN007. ENA 2020

Materials & Methods

ERAS-007 BID-QW Dose escalation schema using Rolling-6 design



Primary Objective:

- To evaluate the safety profile of escalating intermittent doses of ERAS-007 administered as monotherapy using a BID-QW schedule in patients with advanced solid tumors.
- To determine the ERAS-007 maximum tolerated dose (MTD) as a monotherapy administered using a BID-QW schedule.
- To characterize the PK profile of ERAS-007 monotherapy administered using a BID-QW schedule.

Results

Enrollment & Patient Disposition Summary

Patients Enrolled	N
ERAS-007 BID-QW	
50 mg	4
100 mg	13
125 mg	10
Total	27

- A maximum administered dose of 125 mg BID-QW was achieved.
- No DLTs were observed at any dose level.
- All patients were evaluable for safety; 18 (66.7%) were efficacy evaluable[1].
- As of the cutoff date, 3 (11.1%) were on treatment, 11 (40.7%) in follow up, 13 (48.1%) were off study.
- 8 (29.6%) had died, all due to disease progression.
- Data cut-off: 1JUL2022

1. Efficacy evaluable defined as all patients with measurable disease at baseline who received ERAS-007 and had at least 1 post-baseline response assessment or discontinued the treatment phase due to disease progression (including death caused by disease progression) within 8 weeks (± 2-week window) of the first dose of study treatment.

Baseline Characteristics

	50 mg BID-QW (N=4)	100 mg BID-QW (N=13)	125 mg BID-QW (N=10)	Total BID-QW (N=27)
Age (years)				
Median (min, max)	66.0 (46, 77)	66.0 (55, 73)	62.0 (49, 70)	64.0 (46, 77)
Sex, n (%)				
Male	1 (25.0)	8 (61.5)	6 (60.0)	15 (55.6)
Female	3 (75.0)	5 (38.5)	4 (40.0)	12 (44.4)
Race, n (%)				
White	4 (100)	11 (84.6)	9 (90.0)	24 (88.9)
Other$	0	0	1 (10.0)	1 (3.7)
Not Reported	0	2 (15.4)	0	2 (7.4)
ECOG, n (%)				
0	0	3 (23.1)	4 (40.0)	7 (25.9)
1	4 (100)	10 (76.9)	6 (60.0)	20 (74.1)
Primary Tumor Type, n (%)				
Cervical Cancer	0	1 (7.7)	0	1 (3.7)
Colorectal Cancer	3 (75.0)	6 (46.2)	4 (40.0)	13 (48.1)
Pancreatic Cancer	1 (25.0)	3 (23.1)	6 (60.0)	10 (37.0)
Prostate Cancer	0	1 (7.7)	0	1 (3.7)
Other#	0	2 (15.4)	0	2 (7.4)
Prior Lines				
Median (Min, Max)	2.5 (2,6)	3.0 (1, 5)	4.0 (1, 6)	3.0 (1, 6)
Oncogenic Mutations*, n (%)				
N	2	12	10	24
KRAS	2 (100)	11 (91.7)	10 (100)	23 (95.8)
ERBB3	0	1 (8.3)	0	1 (4.2)
ERBB4	0	1 (8.3)	1 (10.0)	1 (4.2)
NRAS	0	1 (8.3)	0	1 (4.2)
RAF1	0	1 (8.3)	0	1 (4.2)
PTPN11	0	1 (8.3)	0	1 (4.2)

$American Indian or Alaska Native, # Adenoid cystic carcinoma and ampullary carcinoma; *Note that mutations listed are not mutually exclusive and some patients have more than 1 mutation

- The high frequency of enrolled patients with KRAS mutations reflects the fact that a high number of enrolled patients had GI cancers.

Results

Exposure and Dose Intensity

	50 mg BID-QW (N=4)	100 mg BID-QW (N=13)	125 mg BID-QW (N=10)	Total BID-QW (N=27)
ERAS-007 Duration of Treatment (weeks)				
Median (Min, Max)	4.1 (3.7, 5.4)	6.7 (1.1, 24.3)	3.6 (0.1, 20.1)	4.1 (0.1, 24.3)
Overall - ERAS-007 Relative Dose Intensity (%)				
Median (Min, Max)	100.0 (85.7, 187.5*)	90.0 (50.0, 100.0)	100.0 (50.0, 100.0)	100.0 (50.0, 187.5*)

*Patient 0002 received additional doses erroneously.

Overall Summary of Treatment-Related Adverse Events (TRAEs)

	50 mg BID-QW (N=4)	100 mg BID-QW (N=13)	125 mg BID-QW (N=10)	Total BID-QW (N=27)
Subjects experiencing, n (%)				
All TRAE	4 (100)	11 (84.6)	9 (90.0)	24 (88.9)
TRAE Grade 3 or higher	1 (25.0)	2 (15.4)	3 (30.0)	6 (22.2)
TRAE leading to ERAS-007 discontinuation	0	0	0	0
TRAE leading to ERAS-007 interruption	0	4 (30.8)	1 (10.0)	5 (18.5)
TRAE leading to ERAS-007 dose reduction	0	0	1 (10.0)	1 (3.7)
Treatment-Emergent SAEs related to ERAS-007	0	0	0	0

- No patients had grade 4 or 5 TRAEs.
- No patients had treatment discontinuations due to AEs related to ERAS-007.
- Only 1 patient enrolled at the highest dose needed dose reduction.
- No patients had SAEs related to ERAS-007.

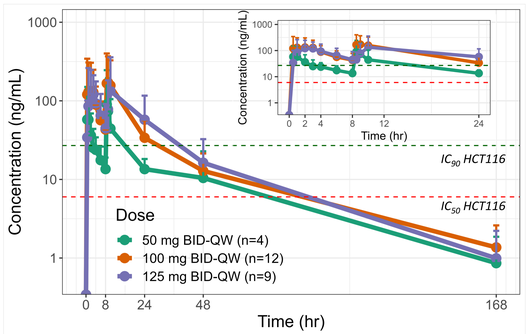
Treatment-Related Adverse Events (TRAEs) (>10% patients in all BID-QW)

	50 mg BID-QW (N=4)		100 mg BID-QW (N=13)		125 mg BID-QW (N=10)		Total BID-QW (N=27)	
Related AE (preferred term)	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**	**All grades**	**Grade ≥ 3**
Nausea	2 (50.0)	0	5 (38.5)	0	6 (60.0)	1 (10.0)	13 (48.1)	1 (3.7)
Ocular toxicity[a]	1 (25.0)	0	6 (46.2)	1 (7.7)	5 (50.0)	2 (20.0)	12 (44.4)	3 (11.1)
Rash[b]	1 (25.0)	0	6 (46.2)	0	4 (40.0)	0	11 (40.7)	0
Fatigue	1 (25.0)	1 (25.0)	4 (30.8)	0	5 (50.0)	1 (10.0)	10 (37.0)	2 (7.4)
Vomiting	1 (25.0)	0	4 (30.8)	0	4 (40.0)	0	9 (33.3)	0
Diarrhea	0	0	3 (23.1)	0	4 (40.0)	0	7 (25.9)	0
Dehydration	2 (50.0)	0	2 (15.4)	0	1 (10.0)	0	5 (18.5)	0
Constipation	0	0	3 (23.1)	0	0	0	3 (11.1)	0
Decreased appetite	0	0	2 (15.4)	0	1 (10.0)	0	3 (11.1)	0

[a] includes: Retinopathy, Retinal detachment, Vision blurred, Vitreous floaters; [b] includes: Dermatitis Acneiform, Rash maculo-popular; TRAE here refers to treatment emergent AEs related to ERAS-007.

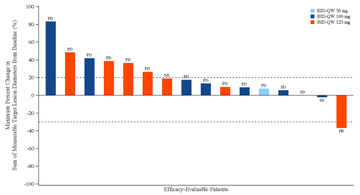
- GI, skin, ocular toxicity, and fatigue were the most commonly reported toxicities considered related to ERAS-007.
- ≥ grade 3 fatigue, ocular toxicity, and nausea were primarily noted at the 125 mg dose level.

ERAS-007 BID-QW Mean PK Profiles



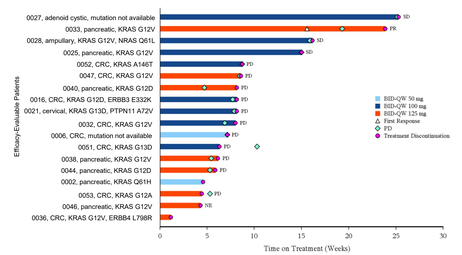
With BID-QW schedule, ERAS-007 exhibited intermittent PK coverage above IC90, followed by PK coverage lower than IC50, potentially allowing for MAPK signaling recovery in normal cells.

Best Change in Tumor Burden



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments.
Note: Two efficacy evaluable patients were not displayed here since these two patients did not have post-baseline tumor assessments. They had clinical disease progression within 30 days of last dose, which met the definition of efficacy-evaluable patients.

Duration of Treatment in Efficacy-Evaluable Patients

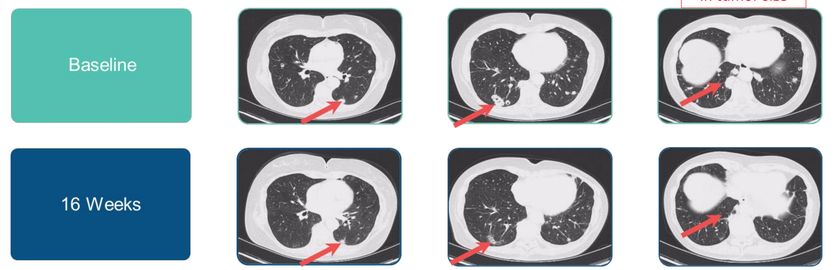


HERKULES-1 Case Study: Single Agent ERAS-007 Response

70-year-old female (Patient 0033) with KRAS G12V metastatic pancreatic cancer

Diagnosis	Stage II pancreatic cancer, metastatic disease, KRAS G12V, initially diagnosed in January 2018
Sites of Metastases	Lung, lymph nodes
Prior Therapy	Surgery, adjuvant radiation, gemcitabine/ capecitabine (#1); 5FU/oxaliplatin/irinotecan (#2); gemcitabine/abraxane (#3); 5FU/liposomal irinotecan (#4); alomfilimab (ICOS-targeted antibody)/atezolizumab (#5); MVT-5873 (anti-CA 19-9 antibody) (#6)
Dosing	ERAS-007 125 mg BID-QW

31% reduction in tumor size



Patient progressed with new lesion at subsequent assessment

Conclusions

- ERAS-007 is a potent and selective oral inhibitor of ERK1/2 with a prolonged target residence time.
- Maximum administered dose (MAD) of 125 mg BID-QW was achieved with no DLTs.
- BID-QW schedule demonstrated a monitorable and manageable AE profile consistent with underlying mechanism of action.
- BID-QW ERAS-007 exhibited intermittent PK coverage against IC90, followed by PK coverage lower than IC50, potentially allowing for MAPK signaling recovery in normal cells.
- This novel regimen offers an alternative intermittent schedule for combination development.
- Combination trials of ERAS-007 with other anti-cancer therapy in RAS mutant colorectal and pancreatic adenocarcinoma (ERAS-007 + palbociclib), BRAFm CRC (ERAS-007+ encorafenib + cetuximab) and KRAS mutant non-small cell lung cancer (ERAS-007 + sotorasib) are currently underway (NCT04959981, NCT05039177).