Preliminary results from ERAS-007 plus palbociclib (palbo) in patients (pts) with KRAS/NRAS mutant (m) colorectal cancer (CRC) or KRASm pancreatic ductal adenocarcinoma (PDAC) 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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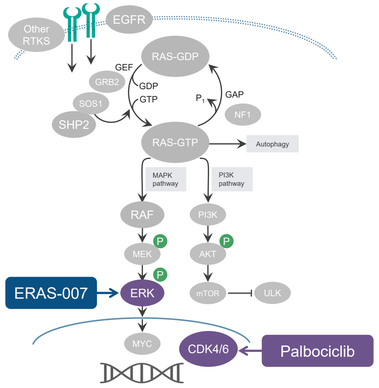
Background

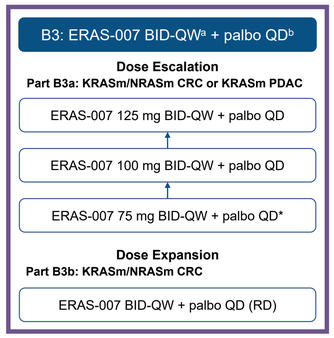


- The RAS/MAPK pathway is dysregulated in a broad range of cancers including colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC), resulting in downstream activation of ERK1/2 and increased cellular proliferation
- ERAS-007 is a novel, orally bioavailable inhibitor of ERK1/2. Palbociclib (palbo) is an oral CDK4/6 inhibitor that inhibits cellular proliferation, an essential feature of tumor growth

- Dual inhibition of the RAS/MAPK pathway and CDK4/6 may synergistically induce G1-phase cell cycle arrest and block cell cycle progression. The combination of ERAS-007 and cell cycle inhibitors such as palbociclib could overcome compensatory mechanisms of resistance to RAS/MAPK inhibition alone in Kirsten rat sarcoma mutant (KRASm)/neuroblastoma rat sarcoma mutant (NRASm) CRC (occurring in ~50% of CRC)[1] and KRASm PDAC (occurring in >90% of PDAC)[2,3]
- Both in vitro and in vivo data exploring the combination of ERAS-007 and palbo in a panel of CRC and pancreatic CDX and/or PDX models have shown promising activity to support the potential combinatorial clinical benefit in RASm CRC and PDAC patients

Methods

Study Design



- HERKULES-3 (NCT05039177) is a phase 1b/2 study to assess safety, tolerability, pharmacokinetics (PK), and preliminary clinical activity of ERAS-007 combinations targeting the MAPK pathway in pts with advanced gastrointestinal cancers
- Within this study, we are currently evaluating the safety, tolerability, and PK of escalating doses of ERAS-007 twice daily-once a week (BID-QW) (75, 100, 125 mg) in combination with palbociclib once daily (QD) three weeks on and 1 week off (3/1) (75, 100, 125 mg) in pts with KRASm/NRAS mCRC or KRASm PDAC

*ERAS-007 75 mg BID-QW was used as a starting dose.
[a]ERAS-007 BID-QW: ERAS-007 oral twice a day on a single day each week; [b]palbo QD: palbociclib oral daily for 21 consecutive days followed by 7 days off in a 28-day cycle.
BRAF: B-Raf proto-oncogene, serine/threonine kinase; CRC: colorectal cancer; KRASm: Kirsten rat sarcoma mutant; NRASm: neuroblastoma rat sarcoma mutant; PDAC: pancreatic ductal adenocarcinoma; RD: recommended dose.

Primary Objectives:

- To evaluate the safety and tolerability of escalating doses of ERAS-007 BID-QW in Part B3a in pts with previously treated KRASm/NRASm CRC and KRASm PDAC
- To determine the maximum tolerated dose and/or recommended dose for ERAS-007 BID-QW plus palbociclib QD in Part B3a

Results

Data Cut-off Date: 23MAR2023

Enrollment and Baseline Characteristics

Analysis Populations, N (%)

	Safety Population*	Efficacy-Evaluable Population†
ERAS-007 BID-QW + palbo QD	46	34
75 mg BID-QW + palbo 75 mg QD	7 (100)	5 (71.4)
75 mg BID-QW + palbo 100 mg QD	2 (100)	2 (100)
100 mg BID-QW + palbo 100 mg QD	7 (100)	6 (85.7)
75 mg BID-QW + palbo 125 mg QD	14 (100)	9 (64.3)
100 mg BID-QW + palbo 125 mg QD	15 (100)	12 (80)
125 mg BID-QW + palbo 125 mg QD	1 (100)	0

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

Patient Status, N

	Safety Population	No. of Patients on Treatment*	No. of Patients in Survival Follow-up	No. of Patients Off Study
ERAS-007 BID-QW + palbo QD	46	8	14	24
75 mg BID-QW + palbo 75 mg QD	7	0	2	5
75 mg BID-QW + palbo 100 mg QD	2	0	0	2
100 mg BID-QW + palbo 100 mg QD	7	0	1	6
75 mg BID-QW + palbo 125 mg QD	14	3	6	5
100 mg BID-QW + palbo 125 mg QD	15	4	5	6
125 mg BID-QW + palbo 125 mg QD	1	1	0	0

*Defined as patients on any study drug.

Baseline Characteristics (Safety Population)

	All (ERAS-007 BID-QW + palbo QD) (N=46)
Age (years)	
Median	62
Min, max	35, 80
Sex, n (%)	
Male	26 (56.5)
Female	20 (43.5)
Race, n (%)	
Asian	3 (6.5)
Black or African American	6 (13.0)
White	33 (71.7)
Not reported	3 (6.5)
Missing	1 (2.2)
ECOG, n (%)	
0	19 (41.3)
1	26 (56.5)
2	1 (2.2)
Prior lines of systemic therapies	
Median	2.0
Min, max	1, 4
Primary tumor type, n (%)	
CRC*	22 (47.8)
PDAC	24 (52.2)

*Four patients with CRC had *NRAS* mutations; the remaining CRC and PDAC patients had *KRAS* mutations.

- Most patients discontinued the study due to death caused by disease progression or withdrawal by patient

Summary of Safety

Patients Experiencing, N (%)	All (ERAS-007 BID-QW + palbo QD) (N=46)
TEAEs*	45 (97.8)
TRAEs† (related to ERAS-007)	38 (82.6)
TRAEs with CTCAE grade 3 or higher	13 (28.3)
TRAEs leading to ERAS-007 discontinuation	2 (4.3)
TRAEs leading to ERAS-007 interruption	16 (34.8)
TRAEs leading to ERAS-007 dose reduction	4 (8.7)
Treatment-related SAEs	5 (10.9)
DLTs‡	4 (8.7)

*TEAE: treatment-emergent adverse event. †TRAE: treatment-related adverse event. ‡One additional DLT reported after the data extraction.
BID: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; DLT: dose-limiting toxicity; SAE: serious adverse event.

- Overall data suggest that the TRAEs were reversible and manageable
- Four patients experienced 6 dose-limiting toxicities
  - ERAS-007 75 mg + palbociclib 125 mg (grade 3 bacteremia, N=1)
  - ERAS-007 75 mg + palbociclib 125 mg (grade 3 rash maculo-papular, N=1)
  - ERAS-007 100 mg + palbociclib 100 mg (grade 3 dermatitis acneiform, neutropenia and anemia, N=1)
  - ERAS-007 100 mg + palbociclib 125 mg (grade 3 thrombocytopenia, N=1)*
- Two grade 5 treatment-emergent adverse events were reported; hemorrhage intracranial (unrelated to ERAS-007 75 mg BID-QW and palbociclib 75 mg QD) and bacteremia (related to ERAS-007 75 mg BID-QW and palbociclib 125 mg QD)

*Reported after the data extraction.

TRAEs* Reported in ≥20% of All Patients

ERAS-007 Dose + palbo Dose	75 mg BID-QW + palbo 75 mg QD (N=7)		75 mg BID-QW + palbo 100 mg QD (N=2)		100 mg BID-QW + palbo 100 mg QD (N=7)		75 mg BID-QW + palbo 125 mg QD (N=14)		100 mg BID-QW + palbo 125 mg QD (N=15)		125 mg BID-QW + palbo 125 mg QD (N=1)		All (N=46)	
Preferred Term	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
Diarrhea	2 (28.6)	0	2 (100)	0	4 (57.1)	1 (14.3)	6 (42.9)	0	6 (40.0)	1 (6.7)	0	0	20 (43.5)	2 (4.3)
Nausea	2 (28.6)	0	2 (100)	0	3 (42.9)	0	2 (14.3)	0	9 (60.0)	0	0	0	18 (39.1)	0
Vision blurred	3 (42.9)	0	0	0	2 (28.6)	0	4 (28.6)	0	4 (26.7)	0	0	0	13 (28.3)	0
Vomiting	1 (14.3)	0	2 (100)	0	2 (28.6)	0	4 (28.6)	0	3 (20.0)	0	1 (100)	0	13 (28.3)	0
Fatigue	0	0	2 (100)	0	1 (14.3)	0	2 (14.3)	0	5 (33.3)	0	1 (100)	0	11 (23.9)	0
Dermatitis acneiform	0	0	1 (50)	0	1 (14.3)	1 (14.3)	3 (21.4)	0	5 (33.3)	0	0	0	10 (21.7)	1 (2.2)

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

Grade ≥3 TRAEs* Reported in ≥2† Patients

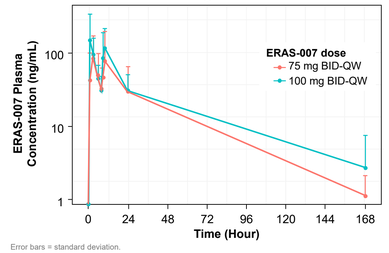
ERAS-007 Dose + palbo Dose	75 mg BID-QW + palbo 75 mg QD (N=7)	75 mg BID-QW + palbo 100 mg QD (N=2)	100 mg BID-QW + palbo 100 mg QD (N=7)	75 mg BID-QW + palbo 125 mg QD (N=14)	100 mg BID-QW + palbo 125 mg QD (N=15)	125 mg BID-QW + palbo 125 mg QD (N=1)	All (N=46)
Diarrhea	0	0	1 (14.3)	0	1 (6.7)	0	2 (4.3)
Anaemia	0	1 (50)	0	0	1 (6.7)	0	2 (4.3)
Rash maculo-papular	0	0	0	1 (7.1)	1 (6.7)	0	2 (4.3)

*TRAE in the table refers to treatment-emergent AEs (TEAEs) related to ERAS-007. †Other grade ≥3 TRAEs reported at a lower frequency include dermatitis acneiform, hypotension, neutropenia, platelet count decreased, proteinuria, thrombocytopenia, acute kidney injury, bacteremia, blood creatinine increased, detachment of retinal pigment epithelium, epistaxis, hyperkalemia, white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased.

- Majority of TRAEs observed are grade 1 or 2

Summary of Pharmacokinetics

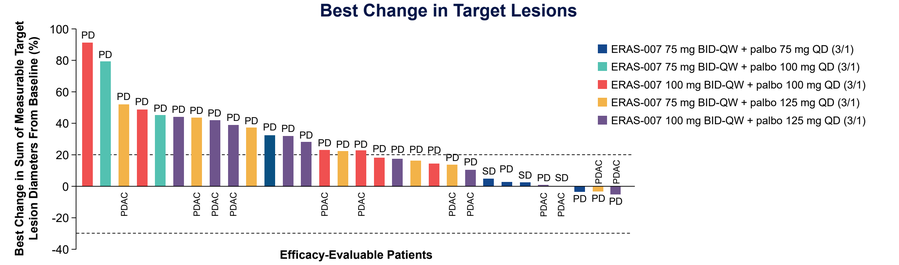
Mean ERAS-007 Concentration-Time Profiles Following the First Dose



Error bars = standard deviation.

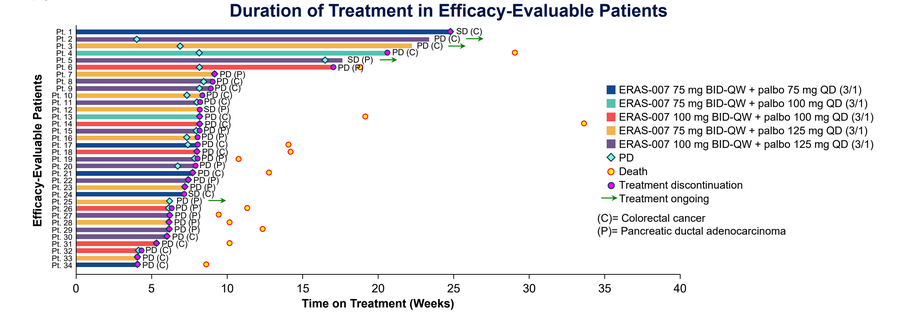
- ERAS-007 exhibited rapid absorption with median peak plasma concentration reached approximately 3 hours post-dose; PK exposure generally increased in a dose-dependent manner
- Observed PK exposures of ERAS-007 and palbociclib when dosed in combination were generally comparable to those when dosed as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

Best Change in Target Lesions



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments.
PD: progressive disease; 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.
PD: progressive disease; SD: stable disease.

Conclusions

- ERAS-007 in combination with palbociclib in patients with KRASm/NRASm CRC or KRASm PDAC shows acceptable safety with reversible and manageable adverse events
- The highest dose evaluated and cleared by the safety review committee to date is ERAS-007 100 mg BID-QW in combination with the approved monotherapy dose of palbociclib 125 mg QD (3/1)
- No clinically relevant pharmacokinetic drug-drug interactions were identified between ERAS-007 and palbociclib
- Based on the lack of clinical activity observed in this study, the combination of ERAS-007 + palbociclib in this patient population will not be pursued further

References

1. Rodriguez-Salas N, et al. *Crit Rev Oncol Hematol*. 2017;109:9-19.
2. Waddell N, et al. *Nature*. 2015;518:495-501.
3. Bailey P, et al. *Nature*. 2016;531:47-52.