Preliminary results from FLAGSHP-1: A Phase I dose escalation study of ERAS-601, a potent SHP2 inhibitor, in patients with previously treated advanced or metastatic solid tumors

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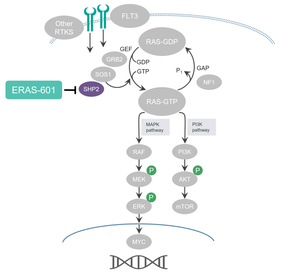
Abstract # 95

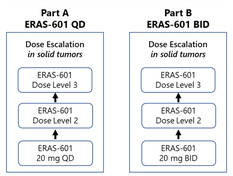
Background

- ERAS-601 is a potent, selective, and orally bioavailable allosteric inhibitor of SHP2.
- SHP2 is an oncogenic tyrosine phosphatase that transduces receptor tyrosine kinase signaling to the RAS/MAPK pathway via its phosphatase-mediated regulation of guanine nucleotide exchange factors.
- ERAS-601 inhibits the loading of active GTP-bound oncogenic RAS and inhibits RAS/MAPK pathway signaling.
- ERAS 601 has demonstrated anti-tumor activity in vitro and in vivo as monotherapy and in combination in preclinical models of cancer harboring EGFR, KRAS, BRAF class III and NF1^{LOF} mutations.



Materials & Methods

Dose escalation monotherapy
Continuous dose



Primary Objective:

- To evaluate the safety profile of escalating doses of ERAS-601 in patients with advanced solid tumors
- To determine the ERAS-601 maximum tolerated dose (MTD) and/or recommended dose (RD) as a monotherapy
- To characterize the PK profile of ERAS-601 monotherapy

Results

Analysis Population, n (%)

	Safety Population[1]	Efficacy-Evaluable Population[2]
ERAS-601 QD (n=15)	15 (100)	11 (73.3)
20 mg (n=3)	3 (100)	3 (100)
40 mg (n=3)	3 (100)	3 (100)
60 mg (n=5)	5 (100)	2 (40.0)
80 mg (n=4)	4 (100)	3 (75.0)
ERAS-601 BID (n=13)	13 (100)	9 (69.2)
20 mg (n=4)	4 (100)	3 (75.0)
40 mg (n=9)	9 (100)	6 (66.7)

[1] Safety analysis population includes all subjects who received at least one dose of ERAS-601.
[2] Efficacy-Evaluable Analysis population includes all subjects in the safety analysis population with measurable disease at baseline and at least 1 post-dose response assessment

Two patients on the BID cohort are still on treatment

Treatment Exposure

ERAS-601 Duration of Treatment (weeks)

	QD N=15	BID N=13
Median	8.0	6.0
Min, Max	1.7, 24.3	0.1, 63.7

Treatment cycle = 28 days

Baseline Characteristics (Safety Population)

	QD N=15	BID N=13
Age (years)		
Median	60.0	60.0
Min, Max	30, 67	22, 78
Sex (%)		
Male	7 (46.7)	2 (15.4)
Female	8 (53.3)	11 (84.6)
Race (%)		
White	11 (73.3)	11 (84.6)
Other	3 (20.0)	1 (7.7)
Not Reported	1 (6.7)	1 (7.7)
ECOG (%)		
0	6 (40.0)	6 (46.2)
1	9 (60.0)	7 (53.8)
Prior Lines of Systemic Therapies		
Median	2.0	2.0
Min, Max	1, 10	1, 5
Primary Tumor Type (%)		
Colorectal Cancer	9 (60.0)	1 (7.7)
Melanoma	1 (6.7)	2 (15.4)
NSCLC	1 (6.7)	0
Other*	1 (6.7)	6 (46.2)
Ovarian Cancer	1 (6.7)	3 (23.1)
Pancreatic Cancer	2 (13.3)	1 (7.7)

*Other primary tumor types include: Endometrial Carcinoma, Colon Cancer (Gastrointestinal); Rectum; Chordoma

Data cut-off Date 15JUL2022

Results

ERAS-601 Summary of Safety

Subjects experiencing, n (%)	QD N=15	BID N=13
TEAEs*	14 (93.3)	13 (100)
TRAEs#	14 (93.3)	13 (100)
TRAEs with CTCAE Grade 3 or higher	6 (40.0)	6 (46.2)
TRAEs leading to ERAS-601 discontinuation	1 (6.7)	1 (7.7)
TRAEs leading to ERAS-601 interruption	3 (20.0)	4 (30.8)
TRAEs leading to ERAS-601 dose reduction	1 (6.7)	0
Treatment Related SAEs	1 (6.7)	3 (23.1)
DLTs	4 (26.7)	0

*Treatment Emergent Adverse Event (TEAE)
Treatment Related Adverse events (TRAE) in this table refers to TEAEs related to ERAS-601

- Overall data suggest both QD and BID regimens are well tolerated
- At MTDs of 40 mg QD and 40 mg BID
  - no TRAEs led to dose discontinuation in both cohorts
  - no TRAEs led to dose interruption in QD cohort; 2 TRAEs led to dose interruption in BID cohort
  - no TRAEs led to dose reduction in both cohorts
- Dose-limiting toxicities (DLTs) occurred at
  - 60 mg QD (two patients experienced Grade 3 AST increase)
  - 80 mg QD (one patient experienced Grade 3 hypertension and another patient experienced Grade 3 thrombocytopenia ≥ 5 days)
- No Grade 5 TEAEs or TRAEs occurred
- Six patients died on study (2 patients in QD and 4 in BID cohorts), all due to disease progression

TRAEs# occurred in ≥ 20% of patients in the total number of patients enrolled in QD and BID cohorts

	QD (20-80 mg) N=15		QD MTD (40 mg) N=3		BID (20 and 40 mg) N=13		BID MTD (40 mg) N=9		QD + BID N=28	
Preferred term	ALL	Gr ≥ 3	ALL	Gr ≥ 3	ALL	Gr ≥ 3	ALL	Gr ≥ 3	ALL	Gr ≥ 3
Thrombocytopenia*	7 (46.7)	2 (13.3)	2 (66.7)	1 (33.3)	3 (23.1)	2 (15.4)	2 (22.2)	2 (22.2)	10 (35.7)	4 (14.3)
AST increased	6 (40.0)	2 (13.3)	1 (33.3)	0	2 (15.4)	1 (7.7)	2 (22.2)	1 (11.1)	8 (28.6)	3 (10.7)
ALT increased	6 (40.0)	1 (6.7)	1 (33.3)	0	2 (15.4)	0	2 (22.2)	0	8 (28.6)	1 (3.6)
Diarrhea	4 (26.7)	0	1 (33.3)	0	4 (30.8)	1 (7.7)	2 (22.2)	0	8 (28.6)	1 (3.6)
Oedema peripheral	3 (20.0)	0	2 (66.7)	0	4 (30.8)	0	2 (22.2)	0	7 (25.0)	0

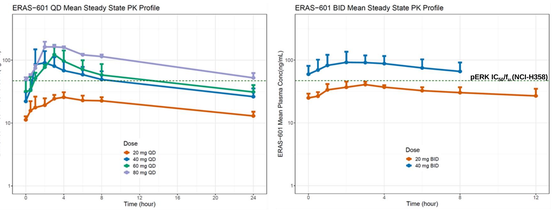
Grade ≥ 3 TRAEs# occurred in ≥10% of patients

Preferred term	ALL QD (20-80 mg) N=15	QD MTD* (40 mg) N=3	ALL BID (20 and 40 mg) N=13	BID MTD (40 mg) N=9	QD + BID N=28
Thrombocytopenia*	2 (13.3)	1 (33.3)	2 (15.4)	2 (22.2)	4 (14.3)
Neutropenia**	3 (20.0)	2 (66.7)	0	0	3 (10.7)
AST increased	2 (13.3)	0	1 (7.7)	1 (11.1)	3 (10.7)

Majority of TRAEs observed are grade 1 or 2

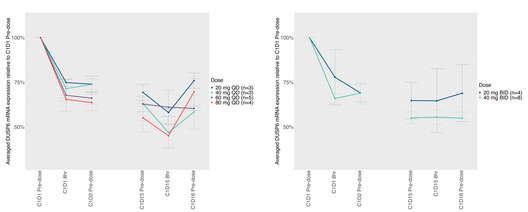
TRAE in the tables refers to treatment emergent AEs (TEAEs) related to ERAS-601
* Includes thrombocytopenia and platelet count decrease **includes neutropenia and neutrophil count decrease
For frequency counts by system organ class, multiple occurrences of the same system organ class in an individual are counted only once based on maximum severity. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once based on maximum severity.

ERAS-601 Steady State Plasma PK



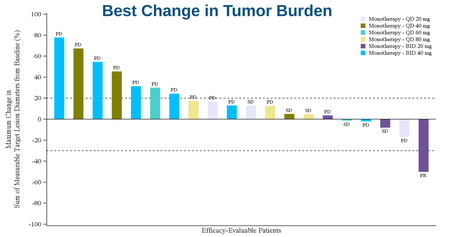
- ERAS-601 exhibits rapid absorption with median peak plasma concentration reached within 4 hours post dose
- Apparent mean terminal half-life of ERAS-601 at steady state ranged from 15 to 22 hours
- ERAS-601 plasma exposure generally increased in a dose-dependent manner
- At 40 mg BID, ERAS-601 steady-state plasma exposure exceeds free fraction adjusted pERK IC50 (NCI-H358) throughout the dosing interval

DUSP6



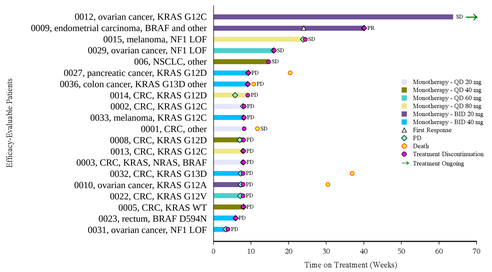
- A dose dependent PD modulation in whole blood was observed in both QD and BID cohorts
- Greater DUSP6 inhibition in whole blood was observed at steady state vs C1D1
- DUSP6 inhibition was recovered after 24hrs of QD dosing at C1D15 suggesting a rebound effect
- Sustained inhibition of DUSP6 was observed in patients enrolled in the BID cohorts, suggesting continuous pathway inhibition between doses

Best Change in Tumor Burden



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments.

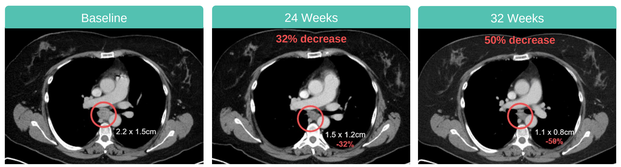
Duration of Treatment in Efficacy-Evaluable Patients



FLAGSHP-1 Case Study: Single agent ERAS-601 response

63-year-old female (Patient 0009) with BRAF Class 3 metastatic endometrial cancer

Diagnosis	Stage III/IV endometrial cancer, metastatic disease, BRAF Class 3, initially diagnosed in September 2018
Sites of Metastases	Lung, lymph nodes
Prior Therapy	Surgery, chemotherapy, pembrolizumab
Dosing	ERAS-601 20 mg BID



Per RECIST 1.1: ≥30% = objective response

Tumor assessment (5) (Jan 4, 2022): patient had radiologic progressive disease (PD) due to a new lesion. Peri-Esophageal lesion, shrinkage in non-target lesions also noted (not shown)

Conclusions

- MTD was determined as 40 mg QD and 40 mg BID in continuous dose regimens
- At the MTD for both QD and BID, ERAS-601 was well tolerated
- TRAEs were reversible, manageable, and consistent with the known mechanism of action for the SHP2 inhibitor class
- A well-behaved PK profile and DUSP6 inhibition in whole blood have been demonstrated
- A confirmed partial response was observed in a patient with a BRAF class III mutation
- Preliminary clinical data support continued development in combination with other anti-cancer therapies. Currently evaluating:
  - ERAS-601 + cetuximab in patients with CRC and HNSCC (FLAGSHP-1; NCT04670679)
  - ERAS-601 + sotorasib in patients with NSCLC (HERKULES-2; NCT04959981)