

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

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Abstract

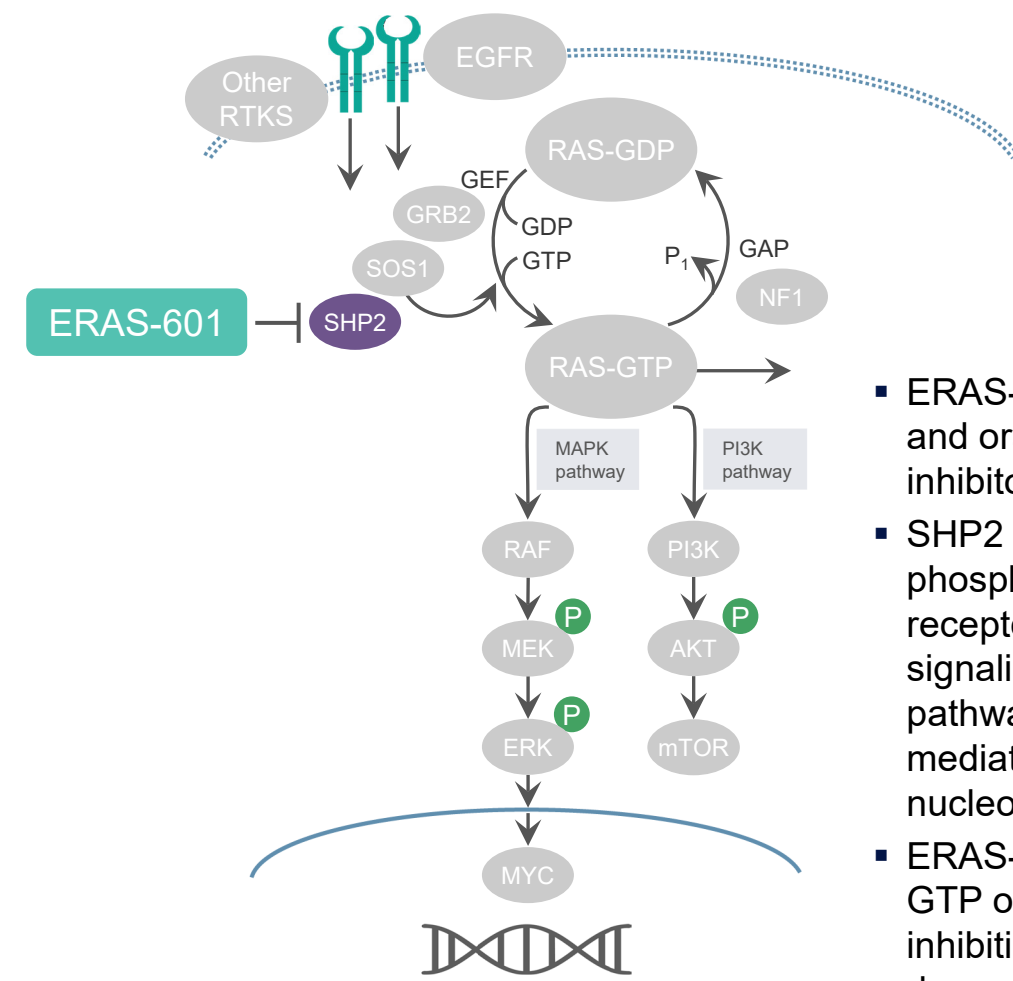
Background: SHP2 is an oncogenic tyrosine phosphatase that transduces receptor tyrosine kinase signaling to the RAS/mitogen-activating protein kinase (MAPK) pathway via its phosphatase-mediated regulation of guanine nucleotide exchange factors. ERAS-601 is a potent, selective, and orally bioavailable allosteric inhibitor of SHP2. In combination with cetuximab, an antibody that targets epidermal growth factor receptor, ERAS-601 has demonstrated robust nonclinical activity in human papillomavirus-negative head and neck squamous cell carcinoma and RAS/RAF wild-type colorectal cancer tumors.

Method: FLAGSH-1 is the first-in-human trial of ERAS-601 administered as monotherapy and in combination with other cancer therapies in patients with advanced or metastatic solid tumors. The primary objectives are to characterize the safety profile, determine the maximum tolerated dose (MTD)/recommended dose, and characterize the pharmacokinetics (PK) profile of ERAS-601 as a monotherapy and in combination with other cancer therapies. Secondary objectives include tolerability and antitumor activity in solid tumors. Presented here are results from the combination dose escalation cohorts in which patients received ERAS-601 twice a day for 3 weeks followed by a 1-week break (BID 3/1) in combination with cetuximab (500 mg/m²) administered every 2 weeks on a 28-day cycle.

Results: As of October 31, 2022, a total of 15 patients with previously treated advanced or metastatic solid tumors received ERAS-601 BID 3/1 at the following dose levels: 20 mg BID 3/1 (n=4), 40 mg BID 3/1 (n=8), or 60 mg BID 3/1 (n=3) in combination with cetuximab. Combination therapy MTD was determined to be 40 mg BID 3/1. ERAS-601 treatment-related adverse events (TRAEs) at or below the MTD were all Grades 1 and 2. TRAEs occurring in ≥20% of patients included diarrhea (27%), AST increase (27%), ALT increase (20%), and dermatitis acneiform (20%). Grade ≥3 TRAEs included Grade 4 hypokalemia, Grade 3 diarrhea, and platelet count decreased, anemia (each 7%); high-grade TRAEs were only observed at 60 mg BID 3/1 (above the MTD). Dose-limiting toxicities were only observed at the 60 mg BID 3/1 dose levels and included Grade 3 platelet count decreased (n=1) and Grade 4 hypokalemia (n=1). Pharmacokinetics of ERAS-601 and cetuximab in combination were generally comparable with historical monotherapy PK values, suggesting a lack of drug-drug interaction. The evaluation of clinical activity is still ongoing.

Conclusions: ERAS-601 in combination with cetuximab in patients with previously treated advanced or metastatic solid tumors shows promising preliminary safety and tolerability with reversible and manageable TRAEs. Further evaluations in relevant tumor types are ongoing.

Introduction



Data cut-off date: 02FEB23

In combination with cetuximab, an antibody that targets the epidermal growth factor receptor (EGFR), ERAS-601 has demonstrated robust nonclinical activity in human papillomavirus-negative head and neck squamous cell carcinoma and RAS/RAF wild-type colorectal cancer (CRC) tumors

Study Design

Dose-escalation combination therapy

Part D1: Dose Escalation
ERAS-601 BID 3/1 + Cetuximab[†]
Dose Escalation
in solid tumors

ERAS-601 60 mg BID 3/1 + cetuximab

ERAS-601 40 mg BID 3/1 + cetuximab

ERAS-601 20 mg BID 3/1 + cetuximab

[†]BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off), on a 28-day treatment cycle. [‡]Cetuximab 500 mg/m² every 2 weeks

Primary Objectives:

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

Enrollment and Baseline Characteristics

Analysis Populations, n (%)

	Safety Population ¹	Efficacy-Evaluable Population ²
ERAS-601 BID 3/1 (N=20)	N=19	N=11
20 mg (n=4)	4 (100)	4 (100)
40 mg (n=13)	12 (92.3)	6 (46.2)
60 mg (n=3)	3 (100)	1 (33.3)

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

BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off)

In the safety population:

- Three patients in the 40 mg cohort are still on treatment
- Two patients in the 40 mg and 2 patients in the 60 mg cohort are in follow-up
- Four patients in the 20 mg, 7 patients in the 40 mg, and 1 patient in the 60 mg cohorts are off study

Baseline Characteristics (Safety Population)

	BID 3/1 + Cetuximab (N=19)
Age (years)	
Median	54.0
Min, max	(37, 74)
Sex (%)	
Male	7 (36.8)
Female	12 (63.2)
Race (%)	
White	13 (68.4)
Asian	3 (15.8)
Not reported	3 (15.8)
ECOG PS (%)	
0	7 (36.8)
1	12 (63.2)

Prior lines of systemic therapies

Median	3.0
Min, max	(1, 7)

Primary tumor type (%)

Colorectal cancer	14 (73.7)
Pancreatic cancer	1 (5.3)
Gastric cancer	1 (5.3)
Other*	3 (15.8)

Mutation (%)[†]

KRAS G12A	3 (15.8)
KRAS G12C	1 (5.3)
KRAS G12D	1 (5.3)
KRAS G13D	1 (5.3)
KRAS G12R	1 (5.3)
KRAS G12V	5 (26.3)
NRAS G12D	1 (5.3)
NF1 LOF	2 (10.5)
Other	8 (42.1)

*Other primary tumor types include: chordoma (1), clival chordoma (1), duodenal (1)
[†]Fifteen of 19 patients in the safety population had RAS/NF1 mutations. Seven of the 15 patients had additional mutations, 1 patient had a non-RAS/NF1 mutation, and are captured in the "other" category. Additionally, 4 patients were RAS/RAF wild-type
BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off); ECOG PS: Eastern Cooperative Oncology Group Performance Status scale; LOF: loss of function; NF1: neurofibromatosis 1

Results

ERAS-601 Summary of Safety

Patients experiencing, n (%)	BID 3/1 N=19
TEAEs	19 (100.0)
TRAEs	14 (73.7)
TRAEs with CTCAE Grade ≥ 3	2 (10.5)
TRAEs leading to ERAS-601 discontinuation	1 (5.3)
TRAEs leading to ERAS-601 interruption	3 (15.8)
TRAEs leading to ERAS-601 dose reduction	1 (5.3)
Treatment-related SAEs	0
DLTs	2 (10.5)

CTCAE: Common Terminology Criteria for Adverse Events; DLT: dose-limiting toxicity; SAE: serious adverse event; TEAE: treatment-emergent adverse event; TRAE: treatment-emergent adverse event related to ERAS-601

- Overall data suggest that the combination regimen is well tolerated
- At MTD 40 mg BID 3/1
 - One TRAE, Grade 2 pneumonitis, led to discontinuation of study drug
 - One TRAE, Grade 1 vomiting, led to drug interruption
 - No TRAEs led to dose reduction
- Dose-limiting toxicities occurred at 60 mg BID 3/1
 - One patient experienced Grade 4 hypokalemia
 - One patient experienced Grade 3 thrombocytopenia lasting ≥5 days
- One Grade 5 TEAE, respiratory failure, occurred in the 60 mg cohort
 - Five patients died on study, all due to disease progression (3 patients on 20 mg, 1 on 40 mg, and 1 on 60 mg)

TRAEs occurring in ≥20% of patients in all cohorts

Preferred term	20 mg BID 3/1 N=4		40 mg BID 3/1 N=12		60 mg BID 3/1 N=3		20-60 mg BID 3/1 N=19	
	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3	All	Gr ≥3
AST increased	0	0	1 (8.3)	0	3 (100.0)	0	4 (21.1)	0
Dermatitis acneiform	1 (25.0)	0	2 (16.7)	0	1 (33.3)	0	4 (21.1)	0
Diarrhea	0	0	4 (33.3)	0	2 (66.7)	1 (33.3)	6 (31.6)	1 (5.3)

AST: aspartate transaminase; Gr: Grade; TRAE: treatment-emergent adverse event related to ERAS-601

Grade ≥3 TRAEs in all cohorts

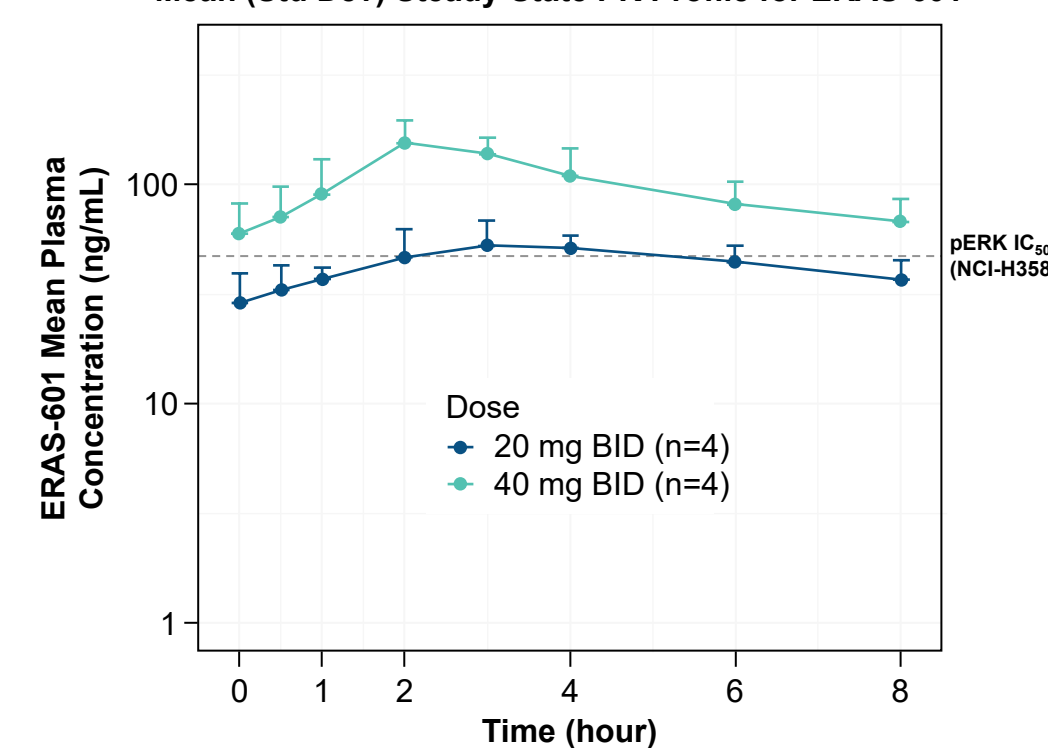
Preferred term	20 mg BID 3/1 N=4	40 mg BID 3/1 N=12	60 mg BID 3/1 N=3	20-60 mg BID 3/1 N=19
Anemia	0	0	1 (33.3)	1 (5.3)
Diarrhea	0	0	1 (33.3)	1 (5.3)
Hypokalemia	0	0	1 (33.3)	1 (5.3)
Platelet count decreased	0	0	1 (33.3)	1 (5.3)

BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off); TRAE: treatment-emergent adverse event related to ERAS-601

- Majority of TRAEs observed were Grade 1 or 2
- Grade ≥3 TRAEs were only observed at 60 mg BID 3/1 (above the MTD)

PK of ERAS-601 in Combination With Cetuximab

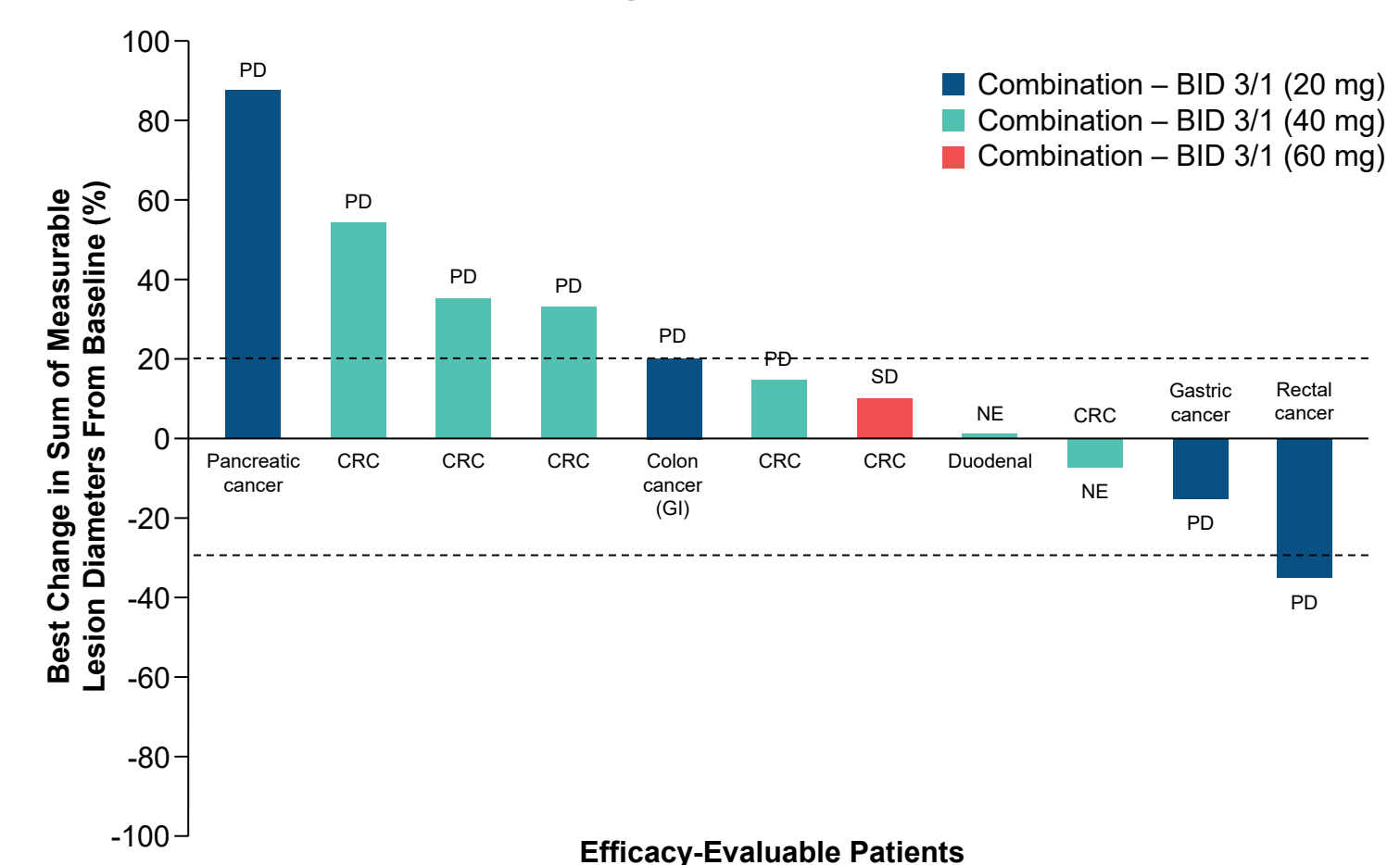
Mean (Std Dev) Steady-State PK Profile for ERAS-601



BID: twice daily; IC₅₀: half-maximal inhibitory concentration; PK: pharmacokinetics; Std Dev: standard deviation

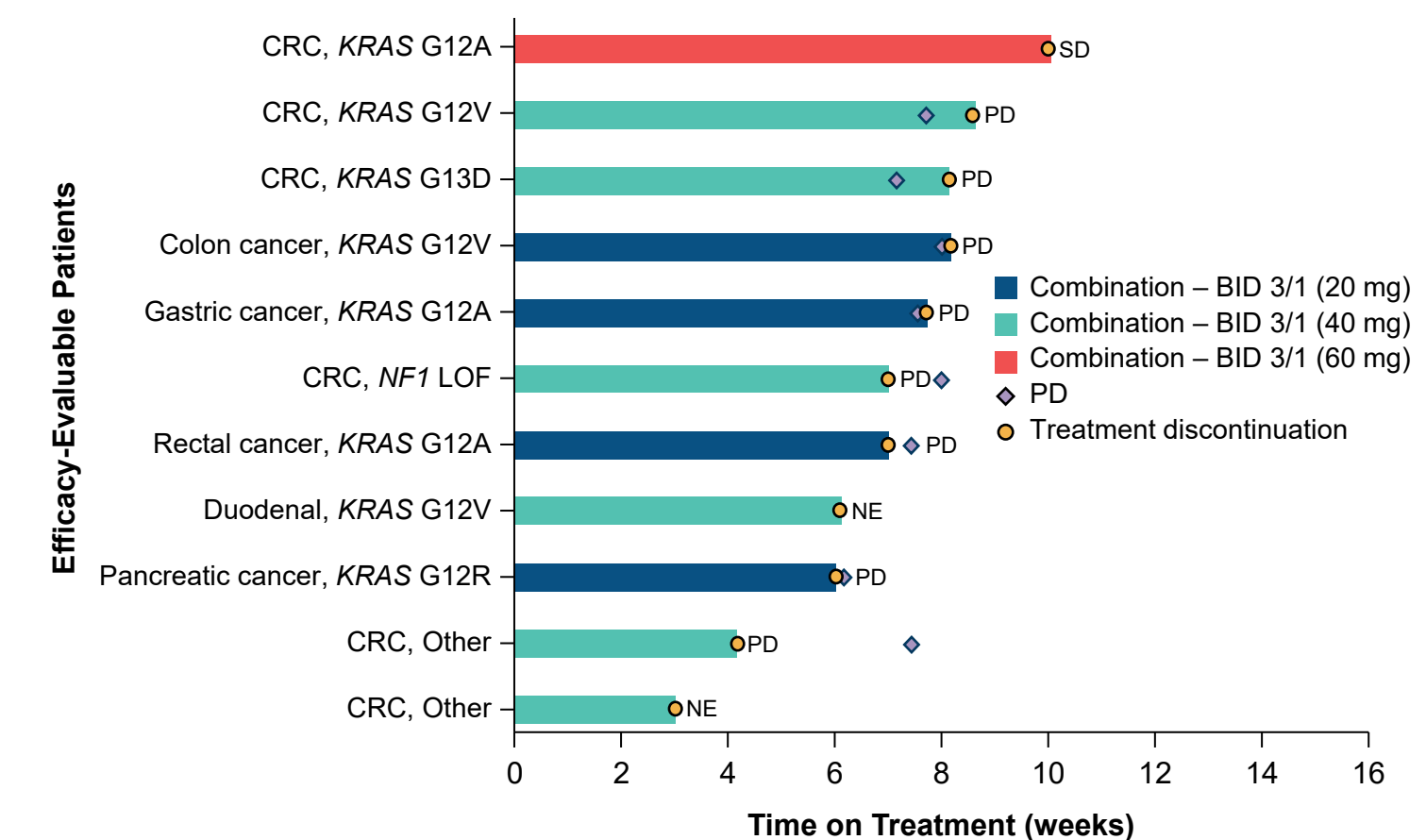
- ERAS-601 exhibited rapid absorption with median peak plasma concentration reached between 2-4 hours post dose; PK exposure generally increased in a dose-dependent manner
- At 40 mg BID, steady-state PK exposure exceeded free-fraction adjusted pERK IC₅₀ (NCI-H358) throughout the dosing interval
- ERAS-601 PK exposures are comparable when administered with or without cetuximab, suggesting a lack of drug-drug interaction between ERAS-601 and cetuximab

Best Change in Tumor Burden



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments
BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off); CRC: colorectal cancer; GI: gastrointestinal; NE: not evaluable; PD: progressive disease; SD: stable disease

Duration of Treatment



Response on the bar represents the best overall response (confirmation not required) based on investigator assessments
BID 3/1: twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off); CRC: colorectal cancer; KRAS: Kirsten rat sarcoma viral oncogene homolog; LOF: loss of function; NE: not evaluable; NF1: neurofibromatosis type 1; PD: progressive disease; SD: stable disease

Conclusions

- MTD of ERAS-601 in combination with cetuximab (500 mg/m²) was determined as 40 mg BID 3/1
- At the MTD, combination treatment was well tolerated
- TRAEs were reversible, manageable, and consistent with the known mechanism of action for the SHP2 inhibitor class and cetuximab
- Grade ≥3 TRAEs were only observed at 60 mg BID 3/1 (above the MTD)
- ERAS-601 PK exposures are comparable when administered with or without cetuximab, suggesting lack of drug-drug interaction between ERAS-601 and cetuximab
- Preliminary clinical data supports continued development, further evaluation in relevant tumor types is ongoing

