ABSTRACT #11522: Preliminary Results from FLAGSHP-1: A Phase 1 Study of ERAS-601 as a Monotherapy or in Combination with Cetuximab in Patients (pts) Previously Treated for Advanced Chordoma

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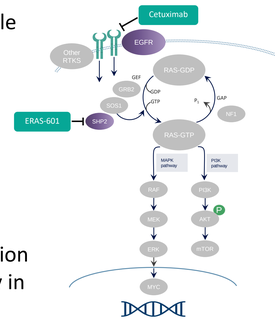
Background

- ERAS-601 is a potent, selective, and orally bioavailable allosteric inhibitor of SHP2 that inhibits RAS/MAPK signaling
- Chordoma, a rare tumor type with no approved therapies, has a genetic dependency for SHP2[1].
- ERAS-601 in combination with cetuximab showed promising preliminary safety and tolerability in solid tumor treatment[2]
- Chordoma cell lines were sensitive to SHP2 suppression and SHP2 inhibitors demonstrated antitumor activity in preclinical chordoma models[1].



Methods

Part D1: Combination Dose Escalation

ERAS-601 BID (3/1)[a] + cetuximab[b]

ERAS-601 **60 mg** BID (3/1) + cetuximab

ERAS-601 **40 mg** BID (3/1) + cetuximab

ERAS-601 **20 mg** BID (3/1) + cetuximab

- 40 mg BID (3/1) was identified as the monotherapy MTD of ERAS-601[1]
- Pts with progressing chordoma were enrolled in the ERAS-601 80 mg TIW[c] monotherapy, ERAS-601 40 mg BID (3/1) monotherapy, or ERAS-601 40 mg BID (3/1) + cetuximab combination therapy groups

[a] Orally, twice daily for 21 days followed by a 7-day break (3 weeks on, 1 week off), on a 28-day treatment cycle
[b] Cetuximab: 500 mg/m^2 every 2 weeks; [c] TIW: BID 3 times per week

Chordoma Pt Enrollment & Baseline Characteristics

	Safety-Evaluable (n %)	Efficacy-Evaluable (n %)
ERAS-601 80 mg TIW monotherapy	1 (100%)	1 (100%)
ERAS-601 40 mg BID (3/1) monotherapy	1 (100%)	1 (100%)
ERAS-601 40 mg BID (3/1) + cetuximab	11 (100%)	11 (100%)

	Monotherapy (N = 2)	Combination (N = 11)
Median age (range)	62 (60, 64)	60 (21, 74)
Sex (n %)		
Male	1 (50)	6 (54.5)
Female	1 (50)	5 (45.5)
Race (n %)		
Black or African American	0	1 (9.1)
White	0	9 (81.8)
Not reported	1 (50)	0
Other	1 (50)	1 (9.1)

	Monotherapy (N = 2)	Combination (N = 11)
ECOG (n %)		
0	0	7 (63.6)
1	2 (100)	4(36.4)
# lines of prior systemic therapy (n %)*		
Median (min,max)	3.0 (3, 3)	1.0 (1, 3)
1	0	5 (62.5)
2	0	2 (25.0)
3	1 (100)	1 (12.5)

Abbreviations – BOR: best overall response; CBR: clinical benefit rate; DLT: dose limiting toxicity; Combination: ERAS-601 40 mg BID (3/1) + cetuximab; Monotherapy: ERAS-601 80 mg TIW and ERAS-601 40 mg BID (3/1); MTD: maximum tolerated dose; PD: progressive disease; PR: partial response; PMR: partial metabolic response; RT: Radiation therapy; SAE: serious adverse event; SD: stable disease; SUV: standard uptake value; TEAE: Treatment-emergent adverse event; * four pts did not receive prior systemic therapy

Results

Pts experiencing at least one, (n %)	Monotherapy (N = 2)	Combination (N = 11)
TEAEs	2 (100)	11 (100)
Grade 3 or higher	1 (50)	7 (63.6)
TEAEs in ≥ 25% of pts		
Dermatitis acneiform	0	8 (72.7)
Fatigue	0	7 (63.6)
Diarrhea	0	6 (54.5)
Oedema peripheral	2 (100)	4 (36.4)
Paronychia	0	6 (54.5)
Dry skin	0	5 (45.5)
Skin infection	0	5 (45.5)
Nausea	0	4 (36.4)
Skin fissures	0	4 (36.4)
Stomatitis	0	4 (36.4)
Vomiting	0	4 (36.4)
ALT increased	0	3 (27.3)
AST increased	0	3 (27.3)
Rash maculo-papular	0	3 (27.3)
TEAEs related to ERAS-601 or cetuximab	2 (100)	11 (100)
Grade 3 or higher	0	6 (54.5)
TRAEs leading to ERAS-601 discontinuation	1 (50)	0
TRAEs leading to ERAS-601 interruption	0	8 (72.7)
TRAEs leading to ERAS-601 dose reduction	0	1 (9.1)
Treatment-emergent SAE	1 (50)	4 (36.4)
Treatment-emergent SAE related to ERAS-601 or cetuximab	0	1 (9.1)
All deaths (n %)	1 (50)	0
DLT	0	0

Overall data suggest that the ERAS-601 regimens were tolerable:

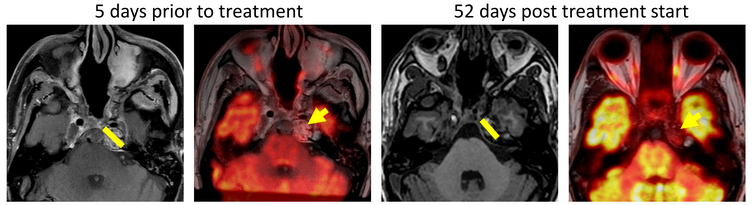
ERAS-601 TIW 80 mg and ERAS-601 BID (3/1) 40 mg monotherapies

- Both pts suffered from oedema peripheral at Grade 1-2

ERAS-601 40 mg BID (3/1) + cetuximab combination

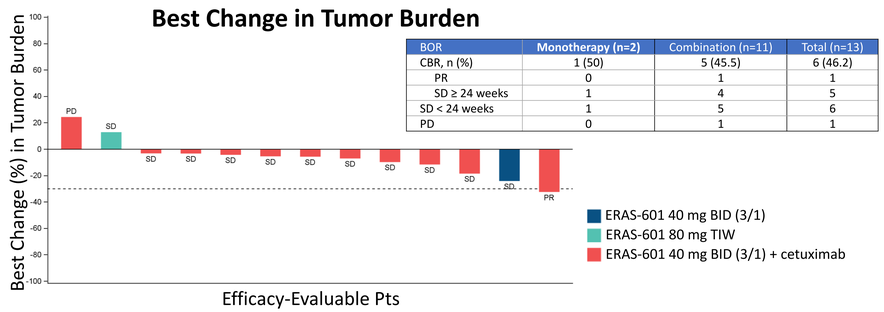
- No Grade 4 or 5 TEAEs were reported
- Grade 3 TRAEs for ERAS-601 were reported in 5 (45.5%) pts; dermatitis acneiform, rash, rash maculopapular (n=1 each), skin infection (n=2)
- TRAEs leading to ERAS-601 dose interruption in ≥2 pts were rash (50.0%) and increased LFTs (27.3%)

MRI and PET Scans of Pt with Clival Chordoma



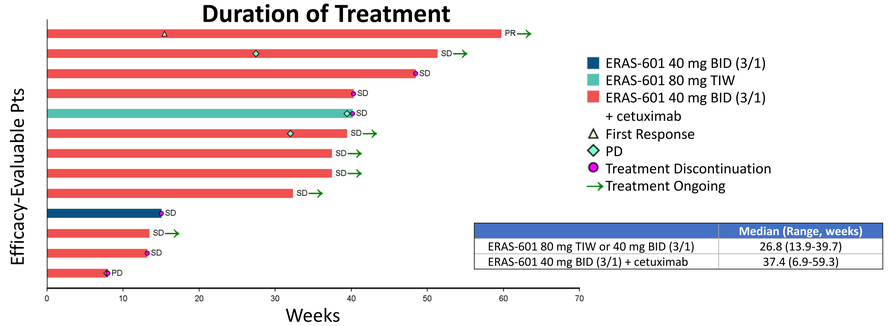
- 43-year-old pt with chordoma, received 4 resections and cisplatin/RT prior to enrollment
- ERAS-601 BID (3/1) + cetuximab combination therapy led to PMR by 52 days, and later a confirmed RECIST PR; the pt remains on study for over 1 year
- AEs were fatigue, diarrhea, acneiform rash

Best Change in Tumor Burden



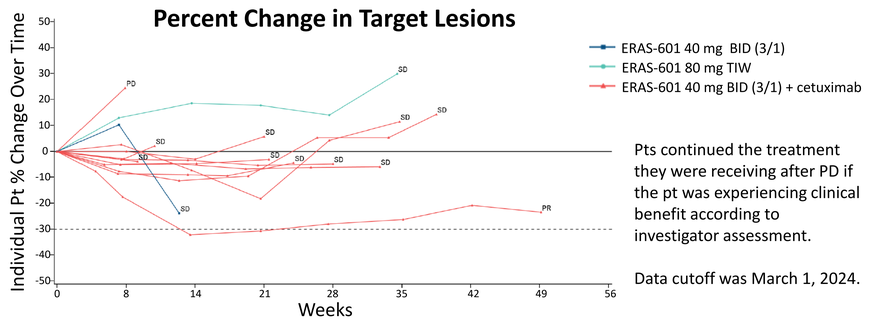
BOR	Monotherapy (n=2)	Combination (n=11)	Total (n=13)
CBR, n (%)	1 (50)	5 (45.5)	6 (46.2)
PR	0	1	1
SD ≥ 24 weeks	1	4	5
SD < 24 weeks	1	5	6
PD	0	1	1

Duration of Treatment



	Median (Range, weeks)
ERAS-601 80 mg TIW or 40 mg BID (3/1)	26.8 (13.9-39.7)
ERAS-601 40 mg BID (3/1) + cetuximab	37.4 (6.9-59.3)

Percent Change in Target Lesions



Pts continued the treatment they were receiving after PD if the pt was experiencing clinical benefit according to investigator assessment.

Data cutoff was March 1, 2024.

Conclusions

- Encouraging clinical activity was seen with ERAS-601 + cetuximab treatment in pts with advanced refractory chordoma (NCT04670679)
- ERAS-601 + cetuximab showed acceptable preliminary safety and tolerability
- The most common toxicities associated with ERAS-601 + cetuximab were dermatologic, consistent with EGFR inhibition, reversible, and managed by dose interruptions and reductions

References

1.Sharifina (2023). Nat. Commun.
2.McKean, M. (2023). Cancer Res.

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