Results of a phase 2 study of evorpacept (E, ALX148), cetuximab (C), and pembrolizumab (P) in patients with refractory microsatellite stable metastatic colorectal cancer (MSS CRC)

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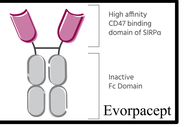
BACKGROUND

Single-agent anti-PD-1/PD-L1 drugs are ineffective in MSS CRC. E is an engineered protein (high-affinity CD47-blocker fused to an inactive IgG Fc region), which blocks the CD47/SIRPα innate immune inhibitory phagocytosis checkpoint expressed on CRC and phagocytes, respectively. Preclinical evidence suggests ECP may be effective in MSS CRC.



METHODS

This phase 2, single-arm, two-stage, multicenter, investigator-initiated trial of E (15 or 10 mg/kg weekly at dose level [DL] 1 and -1, respectively), C (400 mg/m^2 then 250 mg/m^2 weekly), and P (200 mg every 3 weeks) in 21-day cycles enrolled patients with MSS CRC, regardless of tumor sidedness and RAS/BRAF status, refractory to ≥ 2 prior lines of therapy, including EGFR inhibitor if indicated (NCT05167409). All patients in both Stage 1 (safety run-in) and Stage 2 (expansion) received ECP until progression or unacceptable toxicity. The co-primary objectives were to determine the recommended dose (RD) of E with CP and objective response rate (ORR) by RECIST v1.1 (by one-sided exact test with α=0.05, H_0 $p \leq 3\%$ [historical controls], H_A $p \geq 15\%$; power is 87% with N=48).

RESULTS

- The safety-evaluable population included 16 patients (**Figure 1**), of whom 69% were male and median age 53 years. The primary tumor was in the right, left, and transverse colorectum in 31%, 31%, and 6% of patients, and was unknown in 31%. Mutations in KRAS, NRAS, and BRAF genes were present in 38%, 6%, and 0% of patients. The median number of prior lines of therapy was 3, including prior EGFR inhibitor in 44% (**Table 1**).
- In Stage 1, 9 and 3 patients were treated at E DL1 and DL-1, respectively. E DL1 was established as the RD for Stage 2, in which 4 patients were treated (**Figure 1**).
- The most common any-grade treatment-emergent adverse events were headache (38%), fatigue (31%), acneiform rash (31%), anemia (25%), diarrhea (25%), and 19% each of dyspnea, abdominal pain, anorexia, nausea, vomiting, and hypomagnesemia (**Table 2**).
- There were two on-study deaths assessed as related to all three study drugs (hemophagocytic lymphohistiocytosis and cytokine release syndrome; 1 each). While both are known associations with checkpoint inhibitors, other significant factors contributing to these event outcomes included cancer progression with high tumor burden in the former and patient decision to transition to comfort care in the latter.
- In the safety-evaluable population, ORR was 6.3% (1 ongoing partial response, 95% confidence interval [CI] 0.2-30.2%), disease control rate was 12.5% (95% CI 1.6-38.3%), median progression-free survival was 2.3 months (mo; 95% CI 1.9-2.7 mo), and median overall survival was 10.9 mo (95% CI 3.3 mo-infinity). Formal hypothesis testing was not performed (**Table 3, Figures 2 & 3**).

CONCLUSIONS

Further dose optimization of ECP is needed to establish a RD in the refractory MSS CRC population. While initial activity was seen, at the DLs evaluated, criteria to terminate study accrual were met.

RESULTS

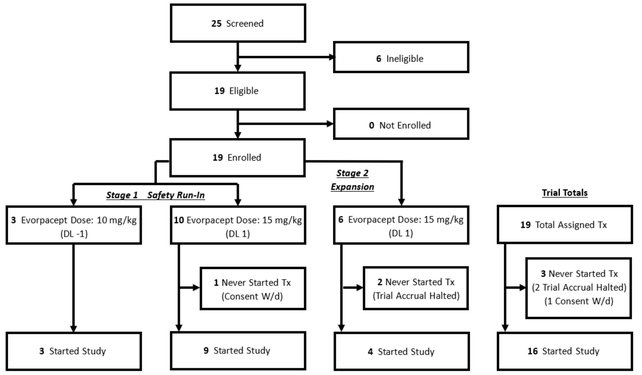


Figure 1: CONSORT diagram.

Characteristic (N=16 Patients)	Level	N (%)
Sex	Female	5 (31)
	Male	11 (69)
Primary Tumor Site	Right	5 (31)
	Left	5 (31)
	Transverse	1 (6)
	Unknown	5 (31)
KRAS	Wild-type	9 (56)
	Mutant	6 (38)
	Unknown	1 (6)
NRAS	Wild-type	13 (81)
	Mutant	1 (6)
	Unknown	2 (13)
BRAF	Wild-type	10 (63)
	Mutant	0
	Unknown	6 (38)
Tumor Mutational Burden (Muts/Mb)	< 10	9 (56)
	≥ 10	0
	Unknown	7 (44)
Liver Metastases	Present	13 (81)
	Prior	1 (6)
	Never	2 (13)
Prior EGFR Inhibitor	Yes	7 (44)
	No	9 (56)
		Median (IQR)
Age (years)	-	53 (44-68)
Prior Lines of Therapy	-	3 (2-4)

Table 1: Baseline characteristics.

Adverse Event (N=16 Patients)	Gr 1-2 N (%)	Gr 3-4 N (%)	Total N (%)
Headache	5 (31)	1 (6)	6 (38)
Fatigue	5 (31)	0	5 (31)
Acneiform rash	5 (31)	0	5 (31)
Anemia	3 (19)	1 (6)	4 (25)
Diarrhea	4 (25)	0	4 (25)
Dyspnea	1 (6)	2 (13)	3 (19)
Abdominal pain	2 (13)	1 (6)	3 (19)
Anorexia	3 (19)	0	3 (19)
Nausea	3 (19)	0	3 (19)
Vomiting	3 (19)	0	3 (19)
Hypomagnesemia	3 (19)	0	3 (19)

Table 2: Most common treatment-emergent adverse events at the patient level.

Best Overall Response (N=16 Patients)	N (%)
Complete Response (CR)	0
Partial Response (PR)	1 (6.3)
Stable Disease (SD)	1 (6.3)
Progressive Disease (PD)	14 (87.5)
Objective Response Rate (ORR)	1 (6.3)
Disease Control Rate (DCR, PR + SD)	2 (12.5)

Table 3: Best overall response by RECIST v1.1. *In the safety-evaluable population, defined as all patients who received at least one dose of study drug(s).*

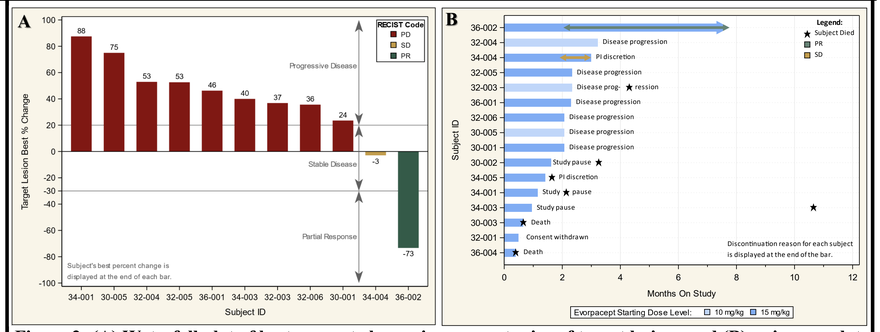


Figure 2: (A) Waterfall plot of best percent change in aggregate size of target lesions and (B) swimmer plot of duration of response, both by subject. *In the safety-evaluable population. Patient 36-002: left-sided primary tumor, RAS/BRAF wild-type, prior EGFR inhibitor, and lung-only metastatic disease at study entry (prior liver metastasis s/p ablation); remains on study as of 03/18/2024.*

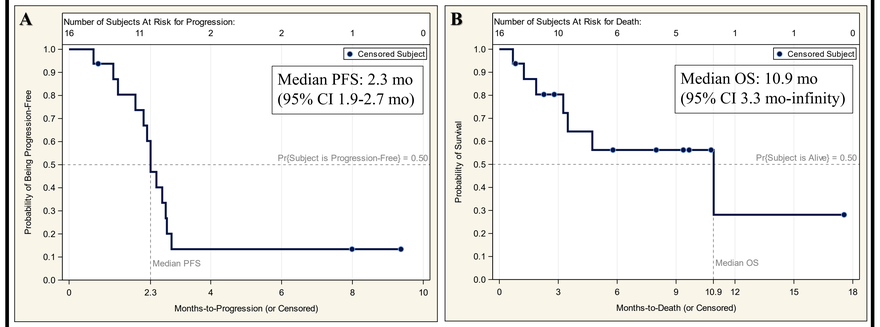


Figure 3: Kaplan-Meier Curves for Progression-Free Survival (A) and Overall Survival (B). *In the safety-evaluable population.*

ADDITIONAL INFORMATION

- For questions or comments: Robert.Lentz@CUAnschutz.edu
- Date of data extraction (updated from abstract): 03/18/2024
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- References: Lentz RW et al, GI ASCO Abstract/Poster, 2023. Kauder SE et al, PLoS One, 2018, Lakhani NJ et al, Lancet Oncol, 2021. ALX Oncology, Inc.