Evorpacept plus Enfortumab Vedotin in Patients with Locally Advanced or Metastatic Urothelial Carcinoma (la/mUC): Phase 1a Dose Escalation Results

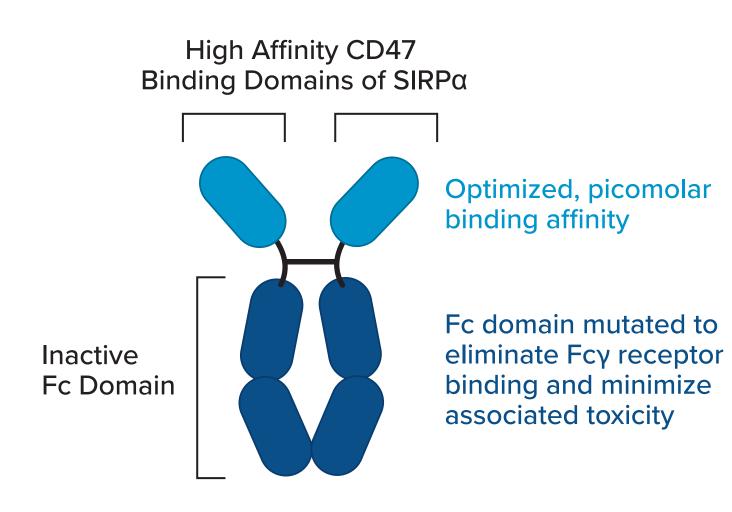
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Background

- \bullet CD47, a marker of self, engages signal regulatory protein alpha (SIRPlpha) and signals macrophages to ignore the cell on which CD47 is expressed.¹ Tumors upregulate CD47 to evade the innate
- Evorpacept (EVO) is a CD47 blocker with an inactivated Fc effector domain that minimizes associated toxicity (Figure 1).
- Enfortumab vedotin (EV) is a nectin-4-directed antibody drug conjugate (ADC) which engages the FcyR on the macrophage.
- Here, we present results from the Phase 1a part of the ASPEN-07 study evaluating the safety, tolerability and initial activity of EVO + EV in patients with locally advanced or metastatic urothelial carcinoma (la/mUC).

Figure 1. Evorpacept Potently and Selectively Blocks CD47 Binding to SIRPα

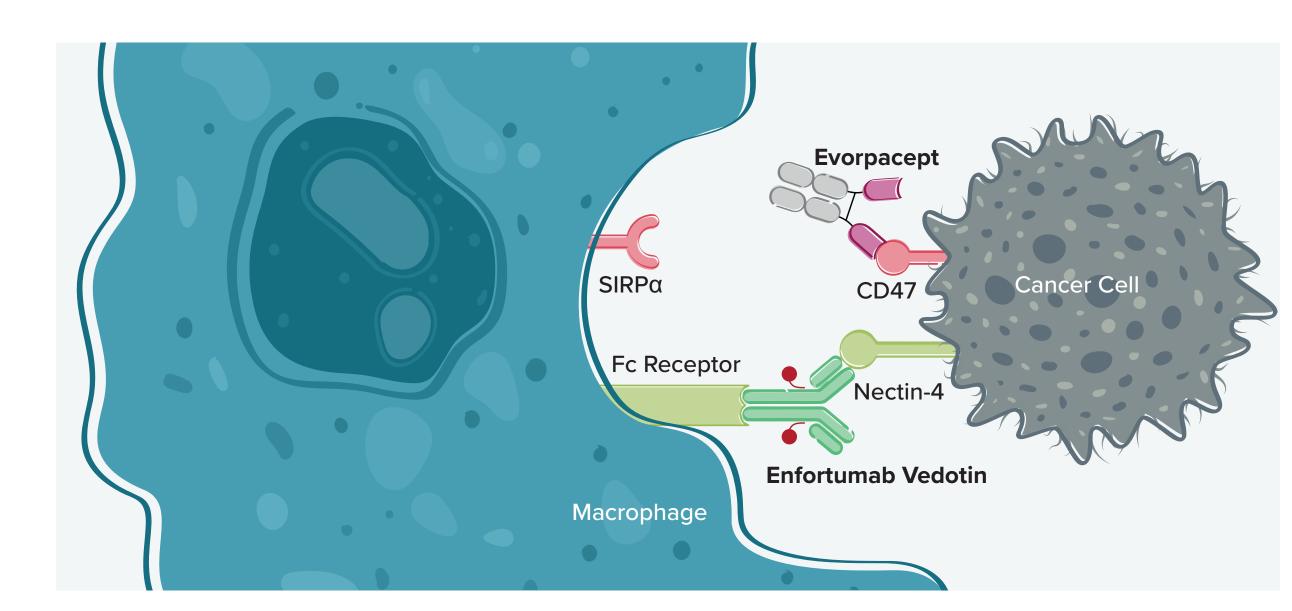


 Fc domain enables antibody-like PK.

 Molecular weight is half the size of typical

> **Backfill Cohort** Evorpacept 30 mg/kg IV Q2W + Enfortumab Vedotin

Figure 2. Evorpacept Increases Antibody Dependent Cellular Phagocytosis (ADCP) in Combination with Enfortumab Vedotin



- Maximizing antibody dependent cellular phagocytosis (ADCP) in the tumor microenvironment requires both the inhibition of the myeloid CD47/SIRP α checkpoint and activation of the macrophage's FcyR by an anti-cancer specific antibody.
- The ADC payload may result in the generation of neoantigens that can activate the adaptive immune response.

Methods

ASPEN-07 Phase 1a Design

- The primary Phase 1a objective is to characterize the safety and tolerability of evorpacept administered in combination with enfortumab vedotin.
- Eligible patients include adults with histologically confirmed, la/mUC who have received prior platinum-based chemotherapy and progressed during or after treatment with a PD-1/L1 inhibitor. • Using a Bayesian Optimal Interval (BOIN) design, patients were administered escalating
- doses of intravenous evorpacept (20 mg/kg Q2W or 30 mg/kg Q2W) combined with standard enfortumab vedotin (1.25 mg/kg) IV on days 1, 8 and 15 of a 28-day treatment cycle.
- Response assessments were performed by the investigator per RECIST v1.1.

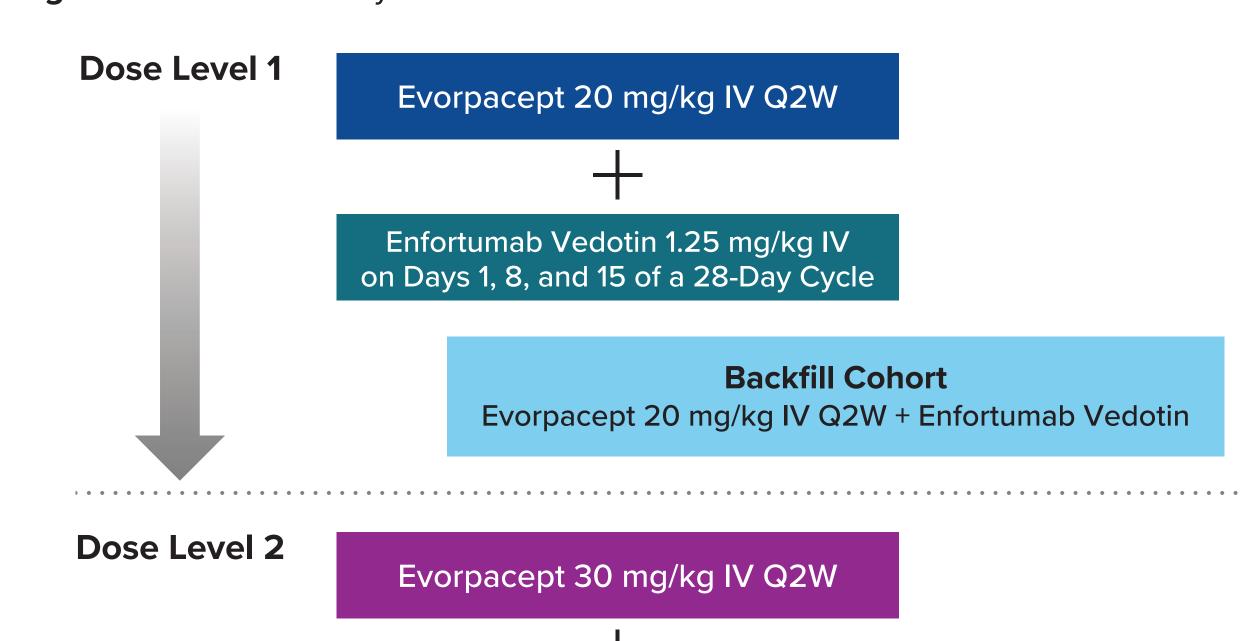
References: 1. Weiskopf K. Cancer immunotherapy targeting the CD47/SIRPa axis. *Eur J Cancer* 2017. May;76:100-109; 2. Lakhani NJ et al. Evorpacept alone and in combination with pembrolizumab or trastuzumab in patients with advanced solid tumours (ASPEN-01): a first-in-human, open-label, multicentre, phase 1 dose-escalation and doseexpansion study. Lancet Oncol 2021 Dec;22(12):1740-1751; 3. Rosenberg JE et al. EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. *Annals of Oncology* 2023 Sept;34:1047-1054; 4. Powles T et al. Enfortumab vedotin in previously treated advanced urothelial carcinoma. *N Engl J Med* 2021 Mar 25;384(12):1125-1135.

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Phase 1a: Dose Escalation

- BOIN design; N=approx. 30 (15 per dose-level).
- Previously treated locally advanced or metastatic urothelial carcinoma.

Figure 3. Phase 1a Study Schema



Enfortumab Vedotin 1.25 mg/kg IV

on Days 1, 8, and 15 of a 28-Day Cycle

EVO 20 mg/kg | EVO 30 mg/kg

Results

Patient Baseline Characteristics

- As of April 3, 2024, 28 EV-naïve patients were treated in the Phase 1a portion, including 15 patients with dose level 1 [EVO 20 mg/kg Q2W], and 13 subjects with dose level 2 [EVO 30 mg/kg Q2W] in a 28-day cycle along with EV 1.25 mg/kg.
- The median age was 71 (range 53 86) years, and baseline ECOG scores were 0 (n=13, 46.4%) or
- For most patients, the primary tumor site was bladder (71.4%).
- 26/28 (92.9%) patients had metastases, with the most common sites being lymph nodes (61.5%), followed by lung (38.5%) and liver (30.8%).
- Most patients (89.3%) had received ≥2 prior lines of therapy.

Table 1. Patient Baseline Characteristics

		EVO 20 mg/kg N=15	EVO 30 mg/kg N=13	Total N=28
Median Age, Years (range)		75 (53-86)	69 (54-82)	71 (53-86)
Sex, n (%)	M F	13 (86.7) 2 (13.3)	12 (92.3) 1 (7.7)	25 (89.3) 3 (10.7)
Race, n (%)	White Black Asian Other	15 (100.0) 0 0 0	11 (84.6) 0 1 (7.7) 1 (7.7)	26 (92.9) 0 1 (3.6) 1 (3.6)
ECOG PS, n (%)	O 1	9 (60.0) 6 (40.0)	4 (30.8) 9 (69.2)	13 (46.4) 15 (53.6)
Site of Primary Tumor, n (%)	Bladder Upper Urinary Tract Urethra Other	11 (73.3) 2 (13.3) 1 (6.7) 1 (6.7)	9 (69.2) 2 (15.4) 2 (15.4) 0	20 (71.4) 4 (14.3) 3 (10.7) 1 (3.6)
Subject with Metastatic Disease, n (%)	Yes No	14 (93.3) 1 (6.7)	12 (92.3) 1 (7.7)	26 (92.9) 2 (7.1)
Site of Metastatic Disease, n (%)	Liver Bone Peritoneum Lung Lymph node Other	4 (28.6) 1 (7.1) 3 (21.4) 6 (42.9) 9 (64.3) 6 (42.9)	4 (33.3) 3 (25.0) 3 (25.0) 4 (33.3) 7 (58.3) 0	8 (30.8) 4 (15.4) 6 (23.1) 10 (38.5) 16 (61.5) 6 (23.1)
Line of Prior Cancer Therapy, n (%)	1st line 2nd Line ≥3rd Line	0 9 (60.0) 6 (40.0)	3 (23.1) 8 (61.5) 2 (15.4)	3 (10.7) 17 (60.7) 8 (28.6)

Safety

- EVO in combination with EV was generally well tolerated. No dose limiting toxicities (DLT) were observed, and a maximum tolerated dose (MTD) was not reached.
- At least one all causality treatment emergent adverse event (TEAE) was reported in 27/28 (96.4%) patients.
- The most common TEAEs due to any cause were fatigue, dysgeusia, nausea, diarrhea, hyperglycemia, and pruritis.

Table 2: Most Common Treatment Emergent Adverse Events Due to Any Cause Occurring in ≥25% of Patients

EVO 20 mg/kg EVO 30 mg/kg

	N=15 n (%)	N=13 n (%)	N=28 n (%)
Subjects with at Least One AE	15 (100.0)	12 (92.3)	27 (96.4)
Fatigue	9 (60.0)	5 (38.5)	14 (50.0)
Dysgeusia	9 (60.0)	3 (23.1)	12 (42.9)
Nausea	5 (33.3)	6 (46.2)	11 (39.3)
Diarrhea	7 (46.7)	3 (23.1)	10 (35.7)
Hyperglycemia	6 (40.0)	4 (30.8)	10 (35.7)
Pruritus	5 (33.3)	4 (30.8)	9 (32.1)
Abnormal Weight Loss	6 (40.0)	2 (15.4)	8 (28.6)
Alanine Aminotransferase (ALT) Increased	4 (26.7)	4 (30.8)	8 (28.6)
Constipation	5 (33.3)	3 (23.1)	8 (28.6)
Decreased Appetite	5 (33.3)	3 (23.1)	8 (28.6)
Rash Maculo-Papular	5 (33.3)	3 (23.1)	8 (28.6)
Urinary Tract Infection (UTI)	5 (33.3)	3 (23.1)	8 (28.6)
Alopecia	4 (26.7)	3 (23.1)	7 (25.0)
Anemia	4 (26.7)	3 (23.1)	7 (25.0)
Aspartate Aminotransferase (AST) Increased	4 (26.7)	3 (23.1)	7 (25.0)
Blood Creatinine Increased	4 (26.7)	3 (23.1)	7 (25.0)
Rash Pustular	2 (13.3)	5 (38.5)	7 (25.0)

- At least one EVO related adverse event was reported in 25/28 (89.3%) patients.
- EVO related adverse events occurring in ≥15% of patients were mostly low grade.
- The most common EVO related adverse events were fatigue, nausea, AST and ALT increased.
- Grade 4 EVO related adverse events at 20 mg/kg: neutrophil count decrease (n=2); and at 30 mg/kg: thrombocytopenia, anemia (n=1 each).

Table 3: Most Common EVO Related Adverse Events Occurring in ≥15% of Patients

	EVO 20 mg/kg N=15 n (%)		EVO 30 mg/kg N=13 n (%)				Total N=28		
	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	n (%)
Subjects with at Least One AE	2 (13.3)	7 (46.7)	3 (20.0)	2 (13.3)	4 (30.8)	5 (38.5)	1 (7.7)	1 (7.7)	25 (89.3)
Fatigue	2 (13.3)	4 (26.7)	3 (20.0)	0	2 (15.4)	2 (15.4)	0	0	13 (46.4)
Nausea	2 (13.3)	2 (13.3)	0	0	2 (15.4)	4 (30.8)	0	0	10 (35.7)
ALT Increased	3 (20.0)	1 (6.7)	0	0	3 (23.1)	0	0	0	7 (25.0)
AST Increased	3 (20.0)	1 (6.7)	0	0	3 (23.1)	0	0	0	7 (25.0)
Blood Alkaline Phosphatase Increase	2 (13.3)	1 (6.7)	0	0	3 (23.1)	0	0	0	6 (21.4)
Diarrhea	2 (13.3)	1 (6.7)	0	0	0	3 (23.1)	0	0	6 (21.4)
Decreased Appetite	0	3 (20.0)	0	0	1 (7.7)	1 (7.7)	0	0	5 (17.9)
Lymphocyte Count Decreased	1 (6.7)	2 (13.3)	0	0	1 (7.7)	1 (7.7)	0	O	5 (17.9)
Rash Maculo-Papular	1 (6.7)	2 (13.3)	0	0	0	1 (7.7)	1 (7.7)	0	5 (17.9)

• There were no treatment related deaths on the study.

• 4/28 (14.3%) patients experienced at least one SAE related to EVO.

• EVO 20 mg/kg Q2W reported 2 SAEs (blood creatinine increase, UTI). • EVO 30 mg/kg Q2W reported 3 SAEs (rash maculo-papular, anemia and thrombocytopenia). **Table 4:** EVO Related Serious Adverse Events (SAEs)

	EVO 20 mg/kg N=15		EVO 30 mg/kg N=13			Total N=28			
	Gr 1	Gr 2	Gr 3	Gr 4	Gr 1	Gr 2	Gr 3	Gr 4	n (%)
Subjects with at Least One SAE	0	1	1	0	0	0	1	1	4 (14.3)
Anemia	0	0	0	0	0	0	0	1	1 (3.6)
Blood Creatinine Increase	0	1	0	0	0	0	0	0	1 (3.6)
Rash Maculo-Papular	0	0	0	0	0	0	1	0	1 (3.6)
Thrombocytopenia	0	0	0	0	0	0	0	1	1 (3.6)
UTI	0	0	1	0	0	0	0	0	1 (3.6)

Initial Activity of EVO + EV

- Among 22 response evaluable patients, ORR=59% (2 CR, 11 PR, 8 SD and 1 PD). Among 14 response evaluable patients at EVO 20 mg/kg Q2W:
- ORR=64.3% (2 CR, 7 PR and 5 SD).
- 6 out of 9 responders were confirmed.
- Among 8 response evaluable patients at EVO 30 mg/kg Q2W: ORR=50% (4 PR, 3 SD and 1 PD).
- 1 out of 4 responders was confirmed.

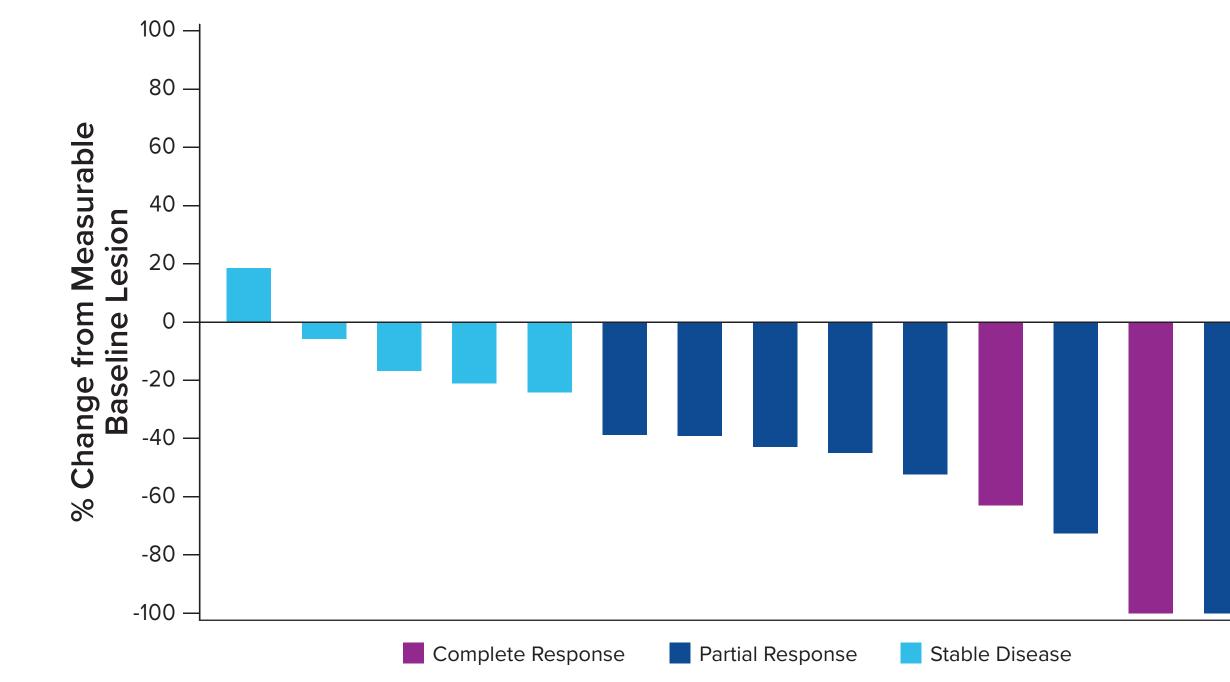
Table 5: Best Overall Response by RECIST v1.1

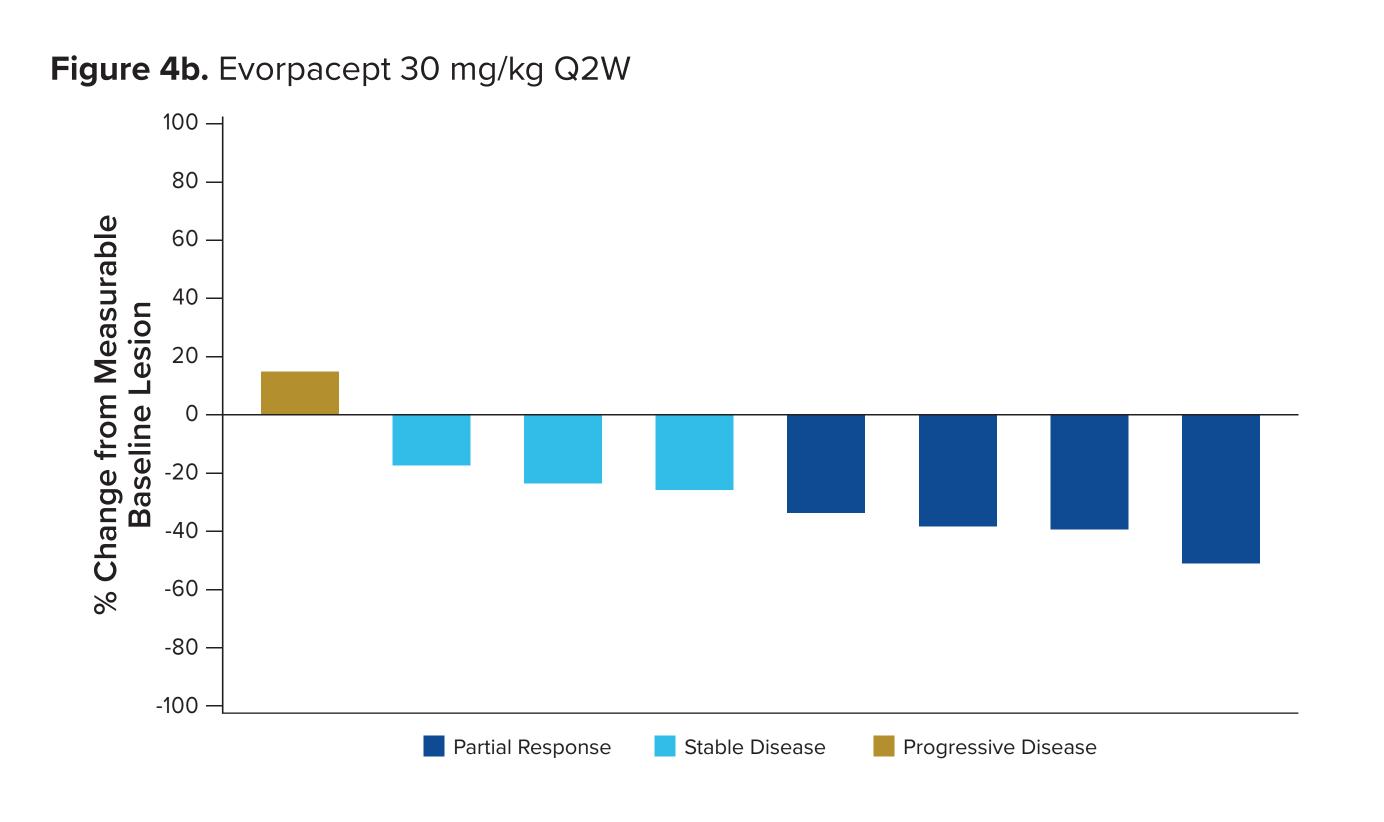
	EVO 20 mg/kg Q2W N=14 n (%)	EVO 30 mg/kg Q2W N=8 n (%)	Total N=22 n (%)
Complete Response (CR)	2 (14.3)	О	2 (9.1)
Partial Response (PR)	7 (50.0)	4 (50.0)	11 (50.0)
Stable Disease (SD)	5 (35.7)	3 (37.5)	8 (36.4)
Progressive Disease (PD)	0	1 (12.5)	1 (4.5)
Objective Response (CR+PR)	9	4	13
Rate of Objective Response (CR+PR)	64.3	50	59.1

Notes: Best overall unconfirmed response (BOR) is CR or PR using RECIST v1.1; median follow up of response evaluable population was 5.8 months; Tumor assessments includes all scans reported at baseline, during the treatment period and during follow up unless patient withdrew consent or started a new anti-cancer therapy; Response evaluable population = all enrolled patients who received at least one dose of study drug and have at least one post-baseline scan done.

Best % Change in Target Lesion from Baseline

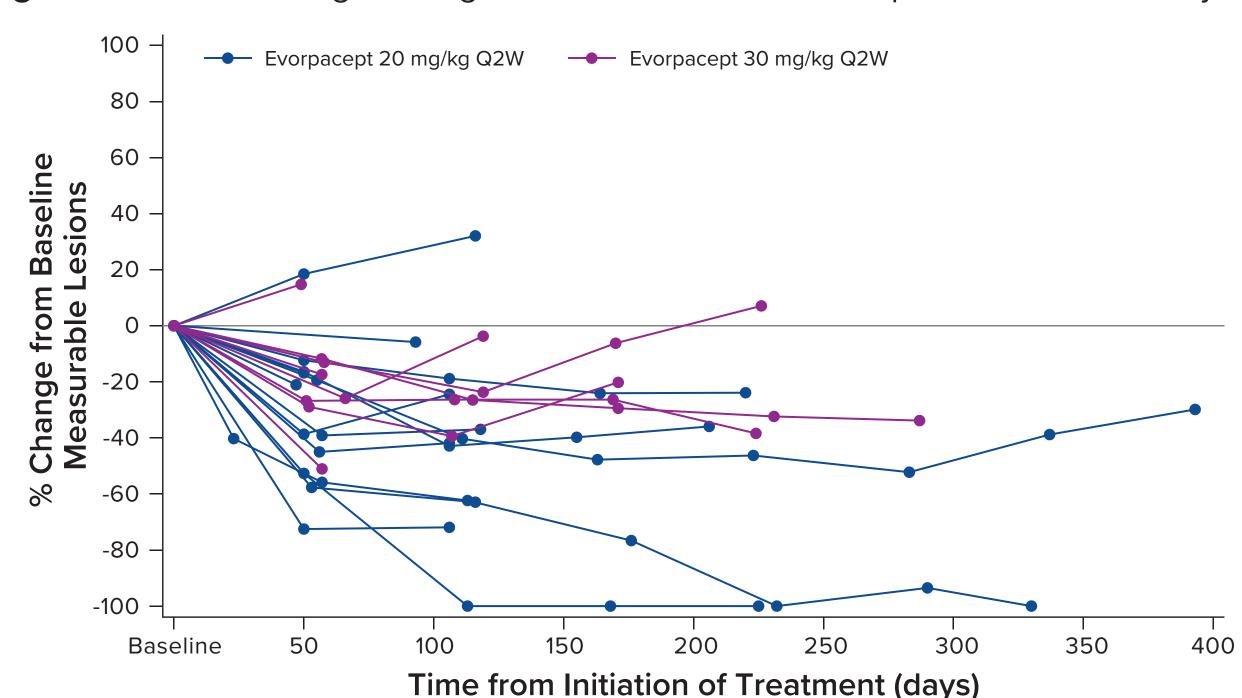
Figure 4a. Evorpacept 20 mg/kg Q2W





Percent Change in the Target Lesions Over Time

Figure 5. Percent Change in Target Lesions Over Time in Response Evaluable Subjects



• The majority of patients at both dose levels (20 mg/kg Q2W and 30 mg/kg Q2W) reported a decrease in the size of target lesions with EVO+EV therapy.

Evorpacept Preliminary Phase 1a PK Results for ASPEN-07

Figure 6. Evorpacept Concentration-Time Profiles Following Evorpacept IV Infusion at 20 mg/kg Q2W & 30 mg/kg Q2W

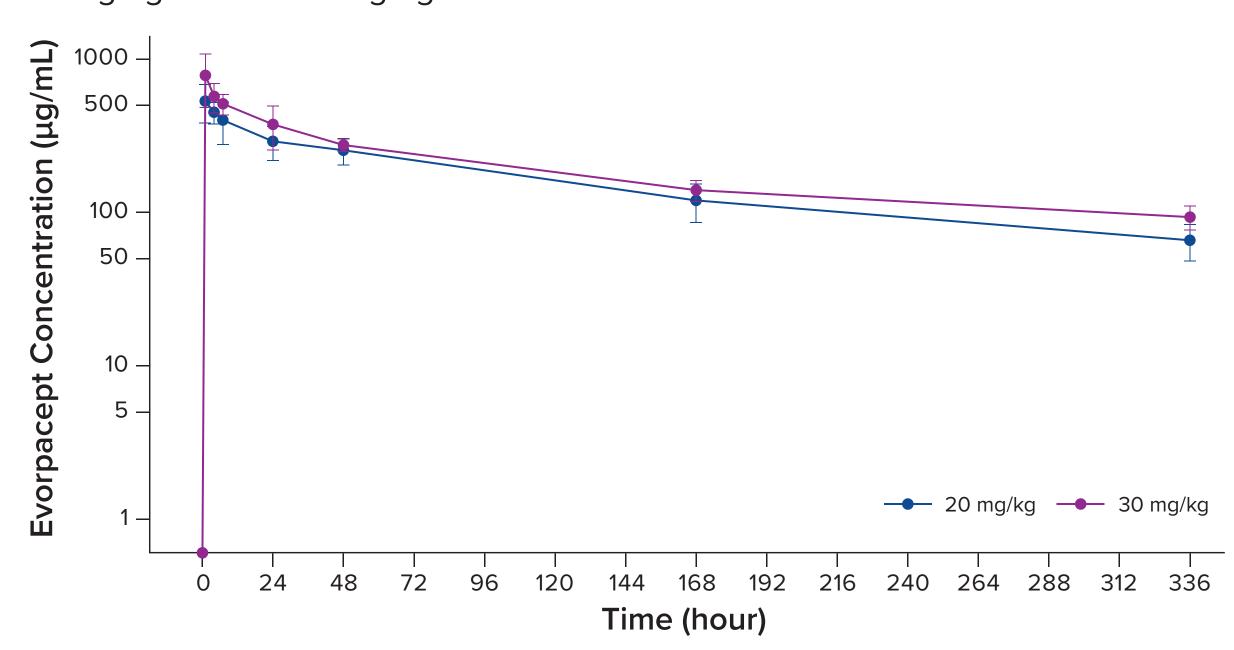


 Table 6. Evorpacept PK Parameters Following IV Infusion at 20 mg/kg Q2W &
 30 mg/kg Q2W

Parameters	20 mg/kg Q2W (N=5)	30 mg/kg Q2W (N=5)
C _{max} (μg/mL)	474 ± 182	782 ± 298
AUC _{last} (μg*h/mL)	50300 ± 12500	54600 ± 10000
CL (mL/h/kg)	0.323 ± 0.0894	0.389 ± 0.0686
Vss (mL/kg)	70.8 ± 14.7	81.2 ± 15.7

Parameters presented as mean \pm SD.

• Overall, evorpacept exhibited dose-proportional PK, consistent with results from prior studies².

Conclusion

Evorpacept was generally well tolerated in combination with enfortumab vedotin and demonstrates promising preliminary activity in patients with la/mUC.

- This is the first study, to our knowledge, reporting data on the combination of a CD47 blocking agent in combination with an ADC in la/mUC.
- No dose limiting toxicities were observed with EVO + EV, and there were no treatment related deaths on the study.
- No maximum tolerated dose was reached, and the maximum administered EVO dose was 30 mg/kg Q2W.
- EVO exhibited dose proportional PK in combination with EV.
- EVO+EV displays promising initial clinical activity with an ORR of 59% (Benchmark EV ORR of 41%)^{3,4}.
- Further investigation in this heavily pretreated population, including patients with prior EV exposure, is ongoing (NCT05524545).