Evorpacept (ALX148), a CD47 Myeloid Checkpoint Inhibitor, in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) and with Gastric/Gastroesophageal Cancer (GC); ASPEN-01

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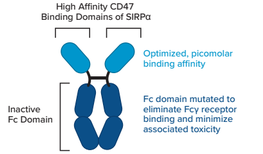
Background

- CD47, a myeloid checkpoint and marker of self, signals the macrophage to ignore the cell on which CD47 is expressed by binding its receptor, SIRPα[1]. Tumors upregulate CD47 to evade the immune response.
- Evorpacept (ALX148) is a high affinity CD47 blocking fusion protein with an inactive human immunoglobulin Fc region (Figure 1) designed to enhance the activity of anti-cancer targeted antibodies and checkpoint inhibitors with minimal hematologic toxicity[2].
- ASPEN-01 (AT148001), a first-in-human Phase 1 study evaluated evorpacept administered as a single agent (Part 1) and in combination with established anti-cancer antibodies (Part 2).

Figure 1. Evorpacept Potently and Selectively Binds CD47 to Block SIRPα Interaction



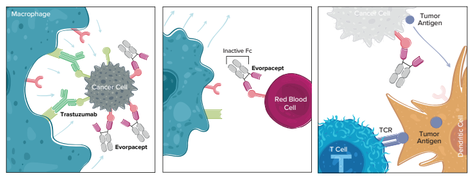
- Fc domain enables antibody-like PK.
- Molecular weight is half the size of typical antibody.

Figure 2. Evorpacept Bridges Innate and Adaptive Immunity[2]

1 Evorpacept with an inactive Fc binds and blocks CD47-SIRPα interaction enhancing anti-cancer antibody's ADCP activity

2 Evorpacept's inactive Fc spares normal blood cells from CD47 targeted ADCP activity

3 Evorpacept activates dendritic cells and enhances cross-priming of T cells



ADCP – Antibody-dependent cellular phagocytosis

Methods

Study Design

- **Part 1 (single agent):** Patients were administered escalating doses of intravenous evorpacept[3].
- **Part 2 (combination):** Patients were administered evorpacept 10 or 15 mg/kg QW in combination with pembrolizumab (200 mg IV Q3W), trastuzumab (8 mg/kg IV➔6 mg/kg Q3W), ramucirumab (8 mg/kg Days 1, 15 Q4W), paclitaxel (80 mg/m^2 Days 1, 8, 15 Q4W), cisplatin (100 mg/m^2 Q3W x 6), carboplatin (AUC 5 mg/ml/min Day 1 Q3W x 6), and 5FU: 1000 mg/m^2/day Days 1, 2, 3, 4 Q3W x 6).
- HER2 levels were determined by HercepTest™ using archived tumor samples. PD-L1 (Clone 22C3) Combined Positive Score (CPS) was determined by pathologist scoring.

Table 1. Select Evorpacept Combination Gastric/Gastroesophageal (GC) and HNSCC Tumor Cohorts

Combination Dose Expansion
≥2L HER2-Positive GC (N=18) **Evorpacept + Trastuzumab + Ramucirumab + Paclitaxel** *Progressed on prior trastuzumab, fluoropyrimidine, platinum*
1L HNSCC (N=13) **Evorpacept + Pembrolizumab + 5FU + Platinum** *No prior treatment for advanced disease*
≥2L HNSCC (N=10) **Evorpacept + Pembrolizumab** *Progressed on prior platinum, checkpoint inhibitor naïve*

- **Primary Part 2 study objective:** Characterize evorpacept safety profile in combination with established anti-cancer antibodies with or without standard chemotherapy.
- Here we report preliminary data from GC and HNSCC patient cohorts receiving evorpacept plus chemotherapy combinations, and updated data from the HNSCC CPI naïve patient cohort receiving evorpacept plus pembrolizumab, as of September 01, 2021.

Results

Patient Baseline Characteristics

Table 2. Baseline Characteristics

		Evorpacept + Trastuzumab + Chemo ≥2L GC (N=18)	Evorpacept + Pembrolizumab + Chemo 1L HNSCC (N=13)	Evorpacept + Pembrolizumab ≥2L CPI Naïve HNSCC (N=10)
Median Age, Years (range)		67.5 (36-83)	61 (45-70)	63 (35-81)
Sex, n	M	13	12	7
	F	5	1	3
Race, n	Asian	15	10	5
	White	3	3	4
	Black	–	–	1
ECOG PS, n	0	8	8	3
	1	10	5	7
Progressed Upon Prior Anti-HER2 Therapy, n (%)		17 (94)	N/A	N/A
Progressed Upon ≥2 Prior Anti-HER2 Therapies n (%)		2 (11.1)	N/A	N/A
Progressed Upon Prior CPI Therapy, n (%)		2 (11.1)	0 (0)	0 (0)
Visceral Distant Metastasis, n (%)		15 (83)	7 (54)	6 (60)

N/A – not applicable; CPI – checkpoint inhibitor

Safety

- Evorpacept in combination with trastuzumab + ramucirumab + paclitaxel (TRP, N=18), and pembrolizumab + 5FU + platinum (N=13) was well tolerated, with most evorpacept treatment related adverse events (TRAE) reported of low grade and frequency. Safety of evorpacept in combination with pembrolizumab has been described elsewhere[4].
- There were no dose limiting toxicities reported in patients treated with evorpacept + TRP or evorpacept + pembrolizumab + 5FU + platinum. The maximum administered dose of evorpacept in combination was 15 mg/kg QW.
- All patients in chemotherapy-containing cohorts experienced at least 1 adverse event. Eight (57%) patients administered evorpacept + TRP and two (15%) patient administered evorpacept + pembrolizumab + 5FU + platinum experienced a TRAE.
- The most common TRAEs of evorpacept in combination with pembrolizumab + 5FU + platinum (N=13) were anemia, fatigue, neutropenia, hypersensitivity, and pneumonitis (n=1 each). TRAEs ≥Grade 3 severity were of low frequency (Table 3a).
- The most common TRAEs of evorpacept in combination with TRP (N=18) were low grade rash (n=4), diarrhea and urticaria (n=3). TRAEs ≥Grade 3 severity were of low frequency (Table 3b).
- There were no on study deaths, or treatment related SAEs reported in patients treated with evorpacept + TRP or evorpacept + pembrolizumab + 5FU + platinum.

Table 3a: The Most Common Treatment Emergent Adverse Events of Evorpacept + Pembrolizumab + 5FU + Platinum in Patients with HNSCC

Evorpacept + Pembrolizumab + 5FU + Platinum (N=13) / Adverse Event, n (%)							
	ALL Causality			Evorpacept-Related			
Evorpacept Dose QW	G1-2	G3	G4	G1-2	G3	G4
Anemia	4 (31)	4 (31)	–	–	1 (8)	–
Nausea	8 (62)	–	–	–	–	–
Stomatitis	7 (54)	1 (8)	–	–	–	–
Neutrophil Count Decreased / Neutropenia	2 (15)	5 (38)	–	1 (8)	–	–
Platelet Count Decreased / Thrombocytopenia	7 (54)	–	–	–	–	–
Fatigue	5 (38)	–	–	1 (8)	–	–
Alanine Aminotransferase Increased	3 (23)	1 (8)	–	–	–	–
Dysphagia	1 (8)	1 (8)	–	–	–	–
Hypersensitivity	1 (8)	–	1 (8)	–	–	1 (8)
Pneumonia	1 (8)	1 (8)	–	–	–	–
Pneumonitis	2 (15)	–	–	1 (8)	–	–
Candida Infection	–	1 (8)	–	–	–	–
Cardiac Tamponade	–	–	1 (8)	–	–	–
Headache	–	1 (8)	–	–	–	–
Pericarditis Constrictive	–	1 (8)	–	–	–	–
Supraventricular Tachycardia	–	1 (8)	–	–	–	–
Tracheal Obstruction	–	1 (8)	–	–	–	–

Evorpacept: 10 mg/kg (n=3) & 15 mg/kg (n=10); All TEAEs occurring in ≥ 4patients. For cases of TEAEs Grade ≥3 and any TRAE, all AEs are listed irrespective of patient numbers.

Table 3b: The Most Common Treatment Emergent Adverse Events of Evorpacept + TRP in Patients with GC

Evorpacept + Trastuzumab + Ramucirumab + Paclitaxel (N=18) / Adverse Event, n (%)						
	ALL Causality			Evorpacept-Related		
Evorpacept Dose QW	G1-2	G3	G4	G1-2	G3	G4
Neutrophil Count Decreased	3 (17)	5 (28)	3 (17)	–	–	–
Epistaxis	9 (50)	–	–	–	–	–
Peripheral Neuropathy / Peripheral Sensory Neuropathy	8 (44)	1 (6)	–	–	–	–
Decreased Appetite	8 (44)	–	–	–	–	–
Fatigue	7 (39)	1 (6)	–	2 (11)	–	–
Anemia	3 (17)	4 (22)	–	1 (6)	–	–
Hypertension	–	6 (33)		–	–	–
Abdominal Pain / Abdominal Pain Upper	5 (28)	–	–	1 (6)	–	–
Headache	5 (28)	–	–	1 (6)	–	–
Stomatitis	5 (28)	–	–	1 (6)	–	–
Alanine Aminotransferase Increased	4 (22)	–	–	–	–	–
Alopecia	4 (22)	–	–	–	–	–
Aspartate Aminotransferase Increased	3 (17)	1 (6)	–	–	–	–
Asthenia	3 (17)	1 (6)	–	–	–	–
Diarrhea	4 (22)	–	–	3 (17)	–	–
Insomnia	4 (22)	–	–	–	–	–
Rash/Dermatitis Acneiform	4 (22)	–	–	4 (22)	–	–
Pruritis	3 (17)	–	–	2 (11)	–	–
Urticaria	3 (17)	–	–	3 (17)	–	–
Back Pain	2 (11)	–	–	1 (6)	–	–
Diverticulitis	1 (6)	1 (6)	–	–	–	–
Dysphagia	1 (6)	1 (6)	–	–	–	–
Hypophosphatemia	1 (6)	1 (6)	–	–	–	–
Platelet Count Decreased	1 (6)	1 (6)	–	–	–	–
Hydronephrosis	–	1 (6)	–	–	–	–
Lymphocyte Count Decreased	–	1 (6)	–	–	1 (6)	–
Non-Cardiac Chest Pain	–	1 (6)	–	–	–	–
Urinary Tract Infection	–	1 (6)	–	–	–	–
Vision Blurred	1 (6)	–	–	1 (6)	–	–

Evorpacept: 10 mg/kg (n=3) & 15 mg/kg (n=15); All TEAEs occurring in ≥4 patients. For cases of TEAEs Grade ≥3 and any TRAE, all AEs are listed irrespective of patient numbers.

Table 4: Evorpacept PK Parameters Following IV Infusion at Cycle 1 Day 1 and Cycle 3 Day 1 in Combination with Pembrolizumab or Trastuzumab, with or without Chemotherapy

Cohort	Evorpacept Dose	Cycle 1 Cmax (µg/mL)	Cycle 1 AUC (h*µg/mL)	Cycle 3 Cmax (µg/mL)	Cycle 3 AUC (h*µg/mL)	AR_AUC	AR_Cmax
Evorpacept + Pembrolizumab[5] (N=12)	10	232 (27)	12,900 (29)	396 (29)	39,600 (31)	3.1 (13)	1.8 (12)
Evorpacept + Pembrolizumab + Chemotherapy (N=3)	10	173 (1.8)	12,300 (4.8)	359 (19)	43,800 (9.8)	3.6 (5.1)	2.1 (18)
Evorpacept + Pembrolizumab + Chemotherapy (N=10)	15	328 (24)	20,000 (25)	551 (21)	52,400 (43)	2.6 (9.6)	1.8 (12)
Evorpacept + Trastuzumab[5] (N=10)	10	236 (30)	12,600 (37)	392 (26)	32,900 (46)	2.8 (19)	1.6 (16)
Evorpacept + Trastuzumab + Chemotherapy (N=3)	10	259 (33)	14,300 (17)	343 (31)	39,200 (40)	2.7 (29)	1.3 (14)
Evorpacept + Trastuzumab + Chemotherapy (N=12)	15	295 (32)	18,800 (21)	481 (17)	54,000 (23)	2.9 (25)	1.8 (31)

AR_AUC – Accumulation ratio of AUC (cycle 3) / AUC (cycle 1); AR_Cmax – Accumulation ratio of Cmax (cycle 3) / Cmax (cycle 1)

Response

Evorpacept Chemotherapy Combination Expansion Cohorts – Confirmed Clinical Activity in Response Evaluable Patients

- **HER2 positive GC Expansion (N=18)**
  - Evorpacept (15 mg/kg QW) + trastuzumab + chemo, ≥2L GC: N=15 (1CR, 10 PR, 2 SD, 2 PD)
  - Evorpacept (10 mg/kg QW) + trastuzumab + chemo, ≥2L GC: N=3 (2PR, 1 SD)
- **HNSCC Expansion (N=13)**
  - Evorpacept (15 mg/kg QW) + pembrolizumab + chemo, CPI naïve 1L HNSCC: N=10 (3 PR (1 unconfirmed), 6 SD, 1 PD)
  - Evorpacept (10 mg/kg QW) + pembrolizumab + chemo, CPI naïve 1L HNSCC: N=3 (1 CR, 1 PR, 1 PD)

Table 5. Clinical Activity of Evorpacept Combination in Response Evaluable Patients with ≥2L HER2-Positive GC

Population	N (EVAL)	OR Rate	Median DOR (m) (95% CI)	Median PFS (m) (95% CI)	Median OS (m) (95% CI)	OS Rate at 12 m	Follow Up (m) (95% CI)
≥2L GC (Evorpacept 10 mg/kg or 15 mg/kg + TRP)	18	72.2%	14.8 (3.9; NR)	17.1 (5.4; NR)	17.1 (9.8; NR)	79.0%	14.5 (7.2; 19.0)

TRP – Trastuzumab + Ramucirumab + Paclitaxel; NR – Not reached

Figure 3. Evorpacept + Trastuzumab + Ramucirumab + Paclitaxel in Patients with ≥2L HER2-Positive GC (N=18)

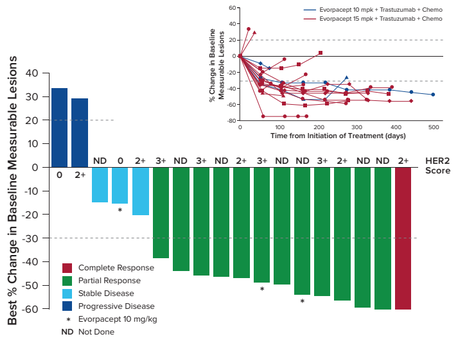
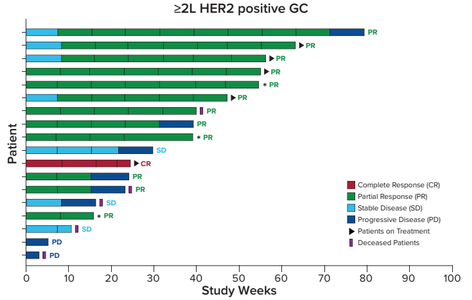


Figure 4. Best Overall and Duration of Response in Patients While Receiving Evorpacept + Trastuzumab + Ramucirumab + Paclitaxel



*Discontinuation due to symptoms of disease progression (n=1), unrelated AE (n=1), patient's decision (n=1).

Table 6. Clinical Activity of Evorpacept Combinations in Response Evaluable Patients with HNSCC

Population	N (EVAL)	OR Rate	Median PFS (m) (95% CI)	Median OS (m) (95% CI)	OS Rate at 12 m	Follow Up (m) (95% CI)
1L HNSCC (Evorpacept 10 mg/kg or 15 mg/kg + Pembrolizumab + Chem)	13	38.5%	5.6 (3.6; NR)	NR	87.5%	6.2 (4.7; 10.6)
≥2L HNSCC (CPI naïve) (Evorpacept 10 mg/kg + Pembrolizumab)	10	40%	4.6 (0.5; 7.5)	24.5 (3.1; NR)	80%	32.5 (26.9; NR)

NR – Not reached

Figure 5. Evorpacept + Pembrolizumab + 5FU + Platinum in Patients with CPI Naïve 1L HNSCC (N=13)

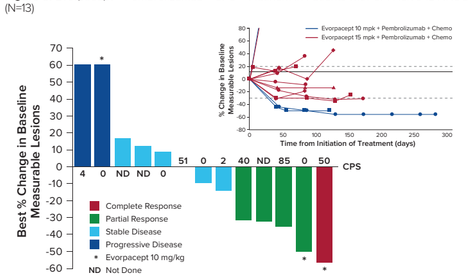
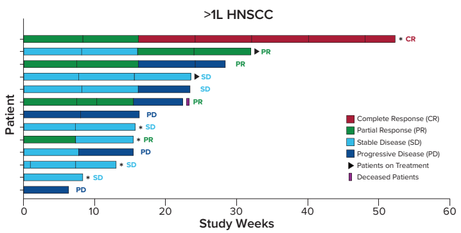


Figure 6. Best Overall and Duration of Response in Patients while Receiving Evorpacept + Pembrolizumab + 5FU + Platinum



*Discontinuation due to unrelated AE (n=2), patient's decision (n=1), missing data (n=2).

Conclusions

In combination with standard chemotherapy and antibody regimens, the initial response benefit seen with evorpacept is magnified in PFS and OS endpoints in both the HNSCC and HER2-positive GC.

- Preliminary data suggests that evorpacept can be safety combined with the multi-agent chemotherapy regimens studied with no MTD reached.
- To date no impact of the combination partners upon evorpacept exposure levels is observed.
- Evorpacept demonstrates promising initial activity with an ORR of 72.2% , mOS of 17.1 months and 12 month OS rate of 79% in patients with ≥2L HER2 positive GC in combination with TRP that compares favorably with both RP and trastuzumab-deruxtecan in similar populations.
- Evorpacept demonstrates initial ORR of 38.5% with median OS not reached, and 12 month OS rate of 87.5% in combination with pembrolizumab + 5FU + platinum in patients with 1L HNSCC that compares favorably with standard pembrolizumab-based therapy.
- Updated data from patients with CPI naïve ≥2L HNSCC receiving evorpacept + pembrolizumab demonstrates a median OS of 24.5 months and 12 month OS rate of 80% that compares favorably with pembrolizumab monotherapy in patients with 2L CPI naïve HNSCC.

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