ASPEN-01: A Phase 1 Study of ALX148, a CD47 Blocker, in Combination with Trastuzumab, Ramucirumab, and Paclitaxel in Patients with 2nd Line HER2-Positive Advanced Gastric or Gastroesophageal Cancer

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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.
- 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 evaluates ALX148 administered as a single agent (Part 1) and in combination with established anti-cancer antibodies (Part 2).

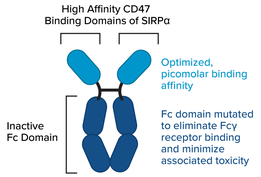
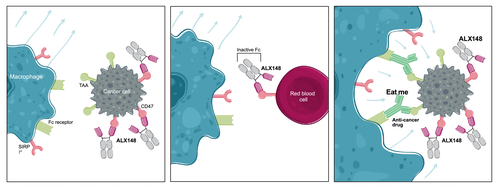


Figure 1. ALX148 Potently and Selectively Binds CD47 to Block SIRPα Interaction

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

Figure 2. ALX148 is a Myeloid Checkpoint Inhibitor



1 ALX148, with an Inactive FC, Binds and Blocks CD47-SIRPα Interaction

2 ALX148's Inactive FC Spares Normal Cells from CD47 Targeted ADCP Activity

3 High Exposure Allows Full Blockade of CD47, Maximizing ADCP Activity of the Combination Drug

ALX148 is designed to safely maximize antibody dependent phagocytosis (ADCP) of cancer cells by targeting CD47 as a myeloid checkpoint inhibitor[2]

Methods

Study Design

- **Part 1 (single agent):** Patients were administered escalating doses of intravenous ALX148 (0.3 to 10 mg/kg QW; or 30 mg/kg Q2W)[3]
- **Part 2 (combination):** A subgroup of patients with HER2 positive Gastric/GEJ cancer were administered ALX148 10 or 15 mg/kg QW in combination with trastuzumab (8 mg/kg IV→6 mg/kg Q3W) with or without ramucirumab (8 mg/kg Days 1, 15 Q4W) and paclitaxel (80 mg/m2 Days 1, 8, 15 Q4W).
  - Adequate organ function and hemoglobin ≥9 g/dL.
  - No prior treatment with an anti-CD47 or anti-SIRPα agent.
  - HER2-positive-status for study eligibility as locally assessed by sites using an FDA approved test for gastric cancer.

Figure 3. ASPEN-01 – Gastric/Gastroesophageal (GC) Combination Cohorts

Dose Expansion ALX148
10 mg/kg QW (n=20)

≥2L HER2-Positive GC
ALX148 + Trastuzumab
progressed on prior fluoropyrimidine
(progression on trastuzumab and platinum allowed)

↓

Dose Escalation ALX148
10 mg/kg QW (n=3)
15 mg/kg QW (n=15)

≥2L HER2-Positive GC
ALX148 + Trastuzumab + Ramucirumab + Paclitaxel
progressed on prior trastuzumab and fluoropyrimidine, or platinum

- **Primary Study Objective:** Characterize ALX148 safety profile as a single agent (Part 1) and in combination with established anti-cancer antibodies with or without standard chemotherapy (Part 2).
- Tolerability of ALX + trastuzumab has been reported previously[4].
- Here we report tolerability data from fully enrolled GC patient cohorts receiving ALX148 + trastuzumab + ramucirumab + paclitaxel as well as updated clinical activity of all GC cohorts as of May 03, 2021.

Results

Patient Baseline Characteristics

- 38 patients have been enrolled into Part 2 GC combination cohorts.

Table 1. Baseline Characteristics

		ALX148 + Trastuzumab + Ramucirumab + Paclitaxel ≥2L GC (N=18)	ALX148 + Trastuzumab ≥2L GC (N=20)
Median Age, Years (range)		63 (36-83)	58 (45-79)
Sex, n	**M**	13	15
	F	5	5
Race, n	**Asian**	15	13
	White	3	6
	Other	–	1
ECOG PS, n	**0**	8	7
	1	10	13
Progressed Upon Prior Anti-HER2 Therapy, n (%)		17 (94)	19 (95)
Progressed Upon ≥2 Prior Anti-HER2 Therapy n (%)		1 (6)	9 (45)
Progressed Upon Prior CPI Therapy, n (%)		2 (11)	9 (45)
Visceral Distant Metastasis, n (%)		17 (94)	17 (85)

Safety

- ALX148 in combination with trastuzumab + ramucirumab + paclitaxel (N=18) was well tolerated, with most treatment related adverse events (TRAE) reported of low grade and frequency. Safety of ALX148 in combination with trastuzumab has been described elsewhere[4].
- There were no dose limiting toxicities reported in patients treated with ALX148 + trastuzumab + ramucirumab + paclitaxel.
- All patients in the chemo-containing cohort experienced at least 1 adverse event. Eight (44.4%) patients administered ALX148 + trastuzumab + ramucirumab + paclitaxel experienced a TRAE.
- The most common TRAEs of ALX148 in combination with trastuzumab + ramucirumab + paclitaxel (N=18) were low grade diarrhea, rash, urticaria (each 16.7%; Table 2). TRAEs ≥Grade 3 severity were of low frequency (Table 3).
- There were no treatment related SAEs reported in patients treated with ALX148 + trastuzumab + ramucirumab + paclitaxel.
- Four unrelated SAEs in combination with trastuzumab + ramucirumab + paclitaxel were reported (1 urinary tract infection; 1 diverticulitis; 1 non-cardiac chest pain; and 1 fatigue).

Adverse Event Profile in Patients with GC by Dose Level

Table 2. Treatment Related Adverse Events

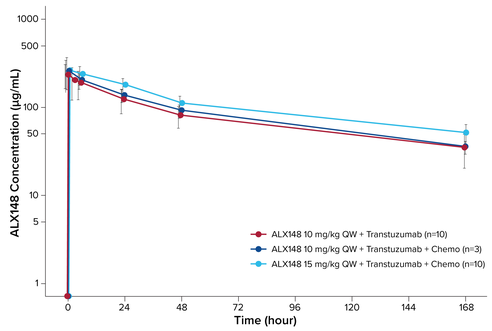
ALX148 + Trastuzumab + Ramucirumab + Paclitaxel (N=18)		
	Total n (%)	
Adverse Event	**ALX148 10 mg/kg**	**ALX148 15 mg/kg**
Diarrhea	–	3 (16.7)
Rash	–	3 (16.7)
Urticaria	–	3 (16.7)
Pruritus	–	2 (11.1)
Fatigue	1 (5.6)	1 (5.6)
Lymphocyte Count Decreased	–	1 (5.6)
Abdominal Pain	–	1 (5.6)
Anemia	–	1 (5.6)
Back Pain	–	1 (5.6)
Dermatitis Acneiform	–	1 (5.6)
Stomatitis	–	1 (5.6)
Vision Blurred	–	1 (5.6)

- There were no dose limiting toxicities, on study deaths, or ALX148-related SAEs.

Table 3. ≥ Grade 3 Adverse Events

ALX148 + Trastuzumab + Ramucirumab + Paclitaxel (N=18)								
Adverse Event	**Total n(%) All Causality**				**Total n(%) Related**			
Grade	**3**		**4**		**3**		**4**	
ALX148 Dose QW	**10 mg/kg**	**15 mg/kg**	**10 mg/kg**	**15 mg/kg**	**10 mg/kg**	**15 mg/kg**	**10 mg/kg**	**15 mg/kg**
Neutrophil Count Decreased	1 (5.6)	4 (22.2)	1 (5.6)	1 (5.6)	–	–	–	–
Hypertension	2 (11.1)	4 (22.2)	–	–	–	–	–	–
Anemia	–	3 (16.7)	–	–	–	–	–	–
Fatigue	–	2 (11.1)	–	–	–	–	–	–
Hypophosphatemia	–	1 (5.6)	–	–	–	–	–	–
Lymphocyte Count Decreased	–	1 (5.6)	–	–	–	1 (5.6)	–	–
Platelet Count Decreased	–	1 (5.6)	–	–	–	–	–	–
Urinary Tract Infection	–	1 (5.6)	–	–	–	–	–	–
Aspartate Aminotransferase Increased	–	1 (5.6)	–	–	–	–	–	–
Asthenia	–	1 (5.6)	–	–	–	–	–	–
Diverticulitis	–	1 (5.6)	–	–	–	–	–	–
Dysphagia	–	1 (5.6)	–	–	–	–	–	–
Non-Cardiac Chest Pain	–	1 (5.6)	–	–	–	–	–	–

Figure 4. ALX148 Concentration-Time Profiles by Dose Level and Combination Partner



- ALX148 PK following combination therapies with trastuzumab is comparable with and without chemotherapy (ramucirumab + paclitaxel).

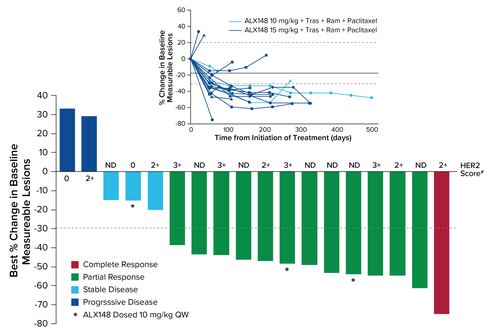
Response

ALX148 Combination Expansion Cohorts – Confirmed Objective Responses in Evaluable Patients

- HER2 positive GC Expansion
  - ALX148 (15 mg/kg QW) + trastuzumab + ramucirumab + paclitaxel, ≥2L GC: N=15 [1 CR*, 10 PR, 2 SD, 2 PD].
  - ALX148 (10 mg/kg QW) + trastuzumab + ramucirumab + paclitaxel, ≥2L GC: N=3 [2 PR, 1 SD].
  - ALX148 (10 mg/kg QW) + trastuzumab, ≥2L GC: N=19 [4 PR (1 unconfirmed), 5 SD, 10 PD].

* Objective response confirmed after data cut off date.

Figure 5. Clinical Activity of ALX148 + Trastuzumab + Ramucirumab + Paclitaxel in Patients with GC



Centrally assessed, retrospectively, on archival or fresh baseline tissue samples; **ND:** Not done

Table 4. Clinical Activity of ALX148 Combinations in Response Evaluable Patients

Population	N (EVAL)	ORR (%) [95% CI]	DOR (m) [95% CI]	PFS (m) [95% CI]	PFS Rate at 6 m	OS (m) [95% CI]	OS Rate at 12 m	Follow Up (m) [95% CI]
≥2L Gastric/GEJ (ALX148 10 mg/kg or 15 mg/kg + TRP)	18	72.2 [49.1%; 87.5%]	NR	9.1 [3.8; NR]	74.5%	NR	75.8%	10.5 [4.8; 12.5]
Gastric/GEJ (ALX148 10 mg/kg + TRP)	3	66.7 [20.8%; 93.9%]	NR	NR	100%	NR	66.7%	14.3 [12.0; NR]
Gastric/GEJ (ALX148 15 mg/kg + TRP)	15	73.3 [48.1%; 89.1%]	NR	NR	68.3%	NR	80.8%	9.4 [4.2; 12.5]
≥2L Gastric/GEJ (ALX148 10 mg/kg + Trastuzumab)	19*	21.1 [8.5%; 43.3%]	8.7 [5.6; NR]	2.2 [1.9; 5.5]	16.7%	8.1 [3.4; 12.6]	38.2%	27.0 [NR]

TRP: trastuzumab + ramucirumab + paclitaxel; **NR:** Not reached.
*One patient discontinued prior to first imaging assessment with symptoms consistent with progression and was not evaluable for response, per protocol.

Figure 6. Best Overall and Duration of Response in Patients While Receiving ALX148 + Trastuzumab + Ramucirumab + Paclitaxel (n=18)

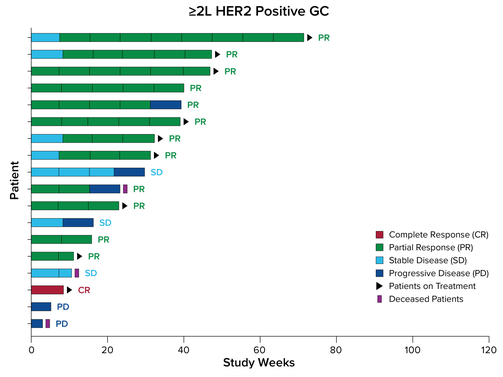
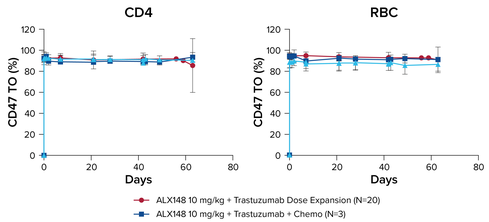
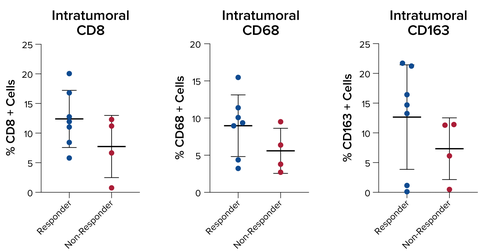


Figure 7. CD47 Target Occupancy from Chemotherapy Combination Cohorts



- Near complete CD47 target occupancy is maintained throughout ALX148 dosing interval over Cycles 1-3 when combined with chemotherapy-containing regimens. (For a subset of patients, target occupancy was measured up to or beyond 300 days with similar results being observed.)

Figure 8. Baseline Tumor Infiltrating Immune Cells in Responders and Non-Responders Receiving ALX148 (10 or 15 mg/kg) + TRP



- **Responder:** CR+PR (N=7)
- **Non-Responder:** SD+PD (N=4)
- Plots represent mean and standard deviation.

Conclusions

Intended for combination, ALX148 exhibits favorable tolerability in combination with trastuzumab + ramucirumab + paclitaxel and demonstrates objective response in patients with GC

- Preliminary data suggest that ALX148 can be combined with trastuzumab, ramucirumab and paclitaxel with no maximum tolerated dose reached. The maximum administered dose of ALX148 in combination was 15 mg/kg QW.
- Preliminary PK/PD analysis demonstrates no impact of the combination partners upon ALX148 exposure levels with full CD47 receptor occupancy achieved and numeric increases demonstrated in % baseline tumor infiltrating immune cells in responding patients.
- ALX148 in combination with trastuzumab, ramucirumab and paclitaxel demonstrates an initial ORR of 72% and estimated OS at 12 months of 76% in patients with GCs that have progressed on or after a prior trastuzumab-containing regimen. This compares favorably with both RAINBOW[5] and DESTINY-01[6] randomized historical controls.
- Updated data from patients receiving ALX148 + trastuzumab after their tumors have progressed upon prior trastuzumab therapy suggests clinical activity beyond that expected from either trastuzumab or chemotherapy alone.

References: **1.** Weiskopf, K., *Eur J Cancer.* 2017 May;76:100-109; **2.** Kauder, SE. et al. *PLoS ONE.* 2018 August;13(8): e0201832; **3.** Lakhani, *N. Journal of Clinical Oncology* 2018 36:15_suppl, 3068-3068; **4.** Chow et al. *Journal of Clinical Oncology* 2020 38:15_suppl, 3056-3056; **5.** Wilke et al, *Lancet* October 2014; **6.** Shitara et al, *NEJM* June 18, 2020 and Enhertu Package Insert

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