A Phase 1 Study of ALX148: CD47 Blockade in Combination with Anti-Cancer Antibodies to Bridge Innate and Adaptive Immune Responses for Advanced Malignancy

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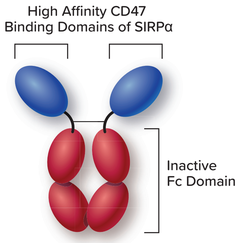
Background

- CD47, a marker of self, is upregulated by tumors to evade the immune system. CD47-SIRPα signaling represents a myeloid checkpoint mechanism in cancer. CD47 engages SIRPα and signals the macrophage to ignore the cell on which it is expressed.[1]
- ALX148 is a fusion protein comprised of an engineered high affinity CD47 binding domain of SIRPα genetically linked to an inactive Fc region of human immunoglobulin (Figure 1) that enhances the activity of anti-cancer targeted antibodies and checkpoint inhibitors through Fc dependent and independent mechanisms.[2]
- 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).

ALX148: A Unique High Affinity SIRPα Fusion Protein

- Potently and selectively binds CD47 to block its interaction with SIRPα.
- Picomolar binding affinity.
- Molecular weight is half the size of a typical antibody allowing higher molar concentrations to be delivered to tumor.
- Fc domain is modified to eliminate binding to all Fc gamma receptors minimizing toxicity.
- Fc domain retains binding to the neonatal Fc receptor for pharmacokinetic half-life extension.

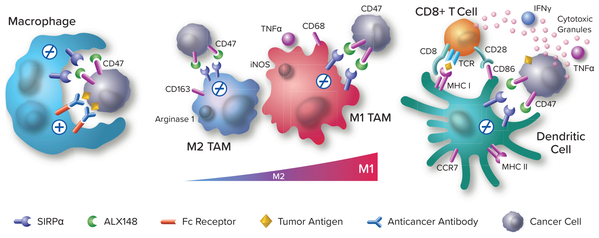


ALX148 Bridges Innate and Adaptive Immunity

1 ALX148 Blocks CD47 "Don't Eat Me" Signal and Enhances Macrophage Phagocytosis

2 ALX148 Increases the Ratio of Inflammatory M1 Tumor Associated Macrophages (TAMs) to Suppressive M2 TAMs

3 ALX148 Activates Dendritic Cells (DCs) and Enhances Cross-Priming of T Cells



Kauder, SE. et al. *PLoS ONE.* 2018 August;13(8): e0201832

Primary Objective

- **Primary Study Objective:** Characterize ALX148 safety profile as a single agent (Part 1: Lakhani N et al, #3068, ASCO 2018) and in combination with established anti-cancer antibodies (Part 2).
- Here we report preliminary Part 2 results from the fully enrolled ALX148 plus pembrolizumab or trastuzumab dose escalation cohorts and ongoing expansion cohorts as of Oct 12, 2018.

Methods

Study Design

- **Part 1 (Single Agent):** Patients with advanced malignancy were administered escalating doses of intravenous ALX148.
- **Part 2 (Combination):** Patients with advanced solid tumors were administered ALX148 10 mg/kg QW in a 3 week cycle with standard regimens of pembrolizumab (200 mg IV Q3W) or trastuzumab (8 mg/kg IV→6 mg/kg Q3W).

Table 1. Study Design

Part 1: Single Agent ALX148

Cohort	Dose (mg/kg)	Schedule
1	0.3	Once a week
2	1.0	Once a week
3	3.0	Once a week
4	10.0	Once a week
5	30.0	Once every 2 weeks

Part 2: ALX148 (10 mg/kg QW) Combination Solid Tumor Cohorts

Dose Escalation	**Advanced Solid Tumors (Each Combo)**
Dose Expansion	**NSCLC (pembrolizumab);** Progressed on Prior CPI/ PD-L1 < 50%
	HNSCC (pembrolizumab); Progressed on Prior Platinum Therapy
	Gastric/GEJ (trastuzumab); Progressed on Prior Fluoropyrimidine Therapy

Study Population

Part 2 Combination Key Inclusion Criteria

- Adequate organ function and hemoglobin ≥9g/dL.
- Dose Escalation Patient Cohorts with:
  - Advanced malignancy resistant to standard therapy or for which no standard therapy is available.
- Dose Expansion Patients Cohorts with:
  - NSCLC (locally advanced or metastatic) which has progressed on prior checkpoint inhibitor therapy, OR with PD-L1 <50% that has progressed following systemic therapy.
  - HNSCC with disease progression after platinum-containing chemotherapy.
  - HER2 overexpressing metastatic gastric/gastroesophageal junction (GEJ) adenocarcinoma that has progressed following a fluoropyrimidine-containing regimen.

Part 2 Combination Key Exclusion Criteria

- Prior treatment with any anti-CD47 or anti-SIRPα agent.

Endpoints and Assessments

- **Primary Endpoint:** Part 2 dose escalation first cycle ALX148 dose limiting toxicity (DLT) in combination with standard regimens of pembrolizumab and trastuzumab.
- Additional assessments across the Part 2 dose escalation and expansion portions include:
  - Adverse events characterization (NCI CTCAE v. 4.03).
  - ALX148 pharmacokinetic parameters and CD47 target occupancy.
  - Investigator assessed tumor response (RECIST v 1.1) every 8 weeks.
- The data cut off date for this analysis is 12Oct2018.

Results

Patient Baseline Characteristics

- 57 solid tumor patients have been enrolled into Part 2 (Table 2).
- Patients were well balanced between male (51%) and female (49%) with the majority (67%) having an ECOG PS score of 1.
- Patients were heavily pretreated with a median of 3 (1-8) prior treatment regimens.

Table 2. AT148001: Patient Baseline Characteristics

		Part 2	
		Pembrolizumab n=39*	Trastuzumab n=18
Median Age, Years (range)		59 (32-79)	57 (45-71)
Sex, n	F	20	7
	M	17	11
Race, n	White	24	10
	Black	3	1
	Native American	1	–
	Asian	8	6
	Other	1	1
ECOG PS, n	0	11	7
	1	26	11
Primary Disease, n	NSCLC	24	–
	HNSCC	9	–
	Gastric/GEJ	–	11
	Breast	–	2
	Colorectal	2	–
	Esophageal	–	2
	Ovarian	2	1
	Pancreatic	–	1
	Peritoneal	1	–
	Appendiceal	1	–
	Urothelial	–	1

* Partial demography for 2 pembrolizumab patients in database.

Table 3. Patient Drug Exposure and Disposition

	Part 2	
	ALX148 10 mg/kg +Pembrolizumab n=39	ALX148 10 mg/kg +Trastuzumab n=18
Dose Interruptions Due to TRAEs, n	4	2
Dose Reductions, n	2	-
Discontinuation Due to TRAE, n	1	-
Discontinuation Due to PD, n	13	8
Global Deterioration of Health Status, n	1	-
Ongoing Treatment, n	24	10

- The most common reason for discontinuation was disease progression (Table 3).
- At data cutoff, 34 pts remained on study, and 1 pt had discontinued due to a treatment related AE (Table 2).

AT148001: Safety

- ALX148 in combination with pembrolizumab or trastuzumab was well tolerated, and most treatment related adverse events were of low grade and frequency.
- The most common treatment related adverse events across these combinations were Fatigue (9%) and ALT increased (7%). Treatment related adverse events ≥Grade 3 severity occurred as sole events (Tables 4 and 5).
- One dose limiting toxicity (Autoimmune hemolytic anemia in a pt with ovarian ca.; ALX148 + pembrolizumab) was previously reported (ASCO 2018, #3068).
- There was 1G5 event (Disease progression in a pt with GEJ; ALX148 + trastuzumab).

AT148001 Safety: (Part 2, ALX148 + Pembrolizumab or Trastuzumab)

Table 4 Treatment Related Adverse Events in ≥2 Patients

ALX148 + Pembrolizumab (N=39)	
Adverse Event	**Total n(%)**
ALT Increased	4 (10)
AST Increased	3 (8)
Anaemia	2 (5)
Fatigue	2 (5)
Infusion reaction	2 (5)
Myalgia	2 (5)
Pruritus	2 (5)
Alkaline Phosphatase Incr	2 (5)
Rash	2 (5)
ALX148+Trastuzumab (N=18)	
Adverse Event	**Total n(%)**
Fatigue	3 (16)

Table 5 Treatment Related Adverse Events ≥ Grade 3 in Any Patient

	ALX148+Pembrolizumab (N=39)		
	Grade		
Adverse Event	**3**	**4**	**Total**
AIHA/Pancytopenia	–	1*	1
ALT Increased	1	–	1
Anaemia	1#	–	1
Febrile Neutropenia	1#	–	1
Platelet Count Decr	-	1#	1
Hyponatremia	1	–	1
Lymphocyte Count Decr	1	–	1
	ALX148+Trastuzumab (N=18)		
	Grade		
Adverse Event	**3**	**4**	**Total**
Thrombocytopenia	1	–	1
Neutrophil Count Decr	1^	–	1
WBC Count Decr	1^	–	1

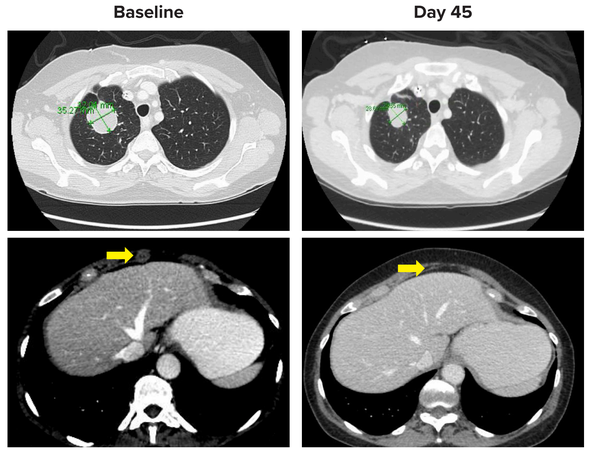
#^All part of the same event in one patient; *Dose Limiting Toxicity

Response

- **NSCLC ALX148 + pembrolizumab:** 13 evaluable pts with NSCLC (progressed on prior CPI and/or PD-L1 <50%) as of data cutoff. Patients experienced a best response of 1PR, 5SD (one SD >24weeks) with 5 patients continuing on treatment.
- **HNSCC ALX148 + pembrolizumab:** 4 evaluable patients with HNSCC (progressed on prior platinum therapy) as of data cutoff. Patients experienced a best response of 2SD (one with ↓16% in measurable disease) and continue on treatment.
- **Her2+ Gastric/GEJ ALX148 + trastuzumab:** 3 evaluable patients with Gastric/GEJ (progressed on prior fluoropyrimidine-containing regimen) as of data cutoff. One patient experienced a best response of SD (↓27% followed by ↓48% + new CNS lesion) and continues on trial.

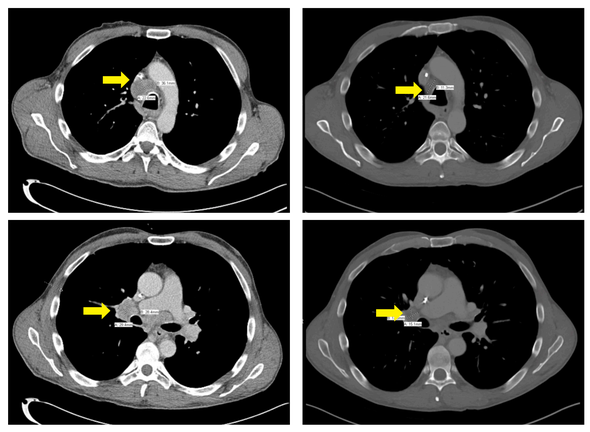
75% of evaluable continuing patients had only 1 response assessment at data cutoff.

Partial Response Achieved in a Nivolumab-Refractory NSCLC Patient Administered ALX148 + Pembrolizumab



- **64 yo pt with NSCLC-adenocarcinoma (TPS 10%,CMET/TP53) ALX148 + pembrolizumab**
- 6 prior therapies; nivolumab refractory; CMET inhibitor refractory
- Day 45 partial response (↓48%), disappearance of chest wall lesion
- Day 100 confirmed PR (↓51%)
- The patient continues on treatment

Significant Tumor Reduction in a Patient with Gastroesophageal Junction (GEJ) Cancer Administered ALX148 + Trastuzumab



- **48 yo pt with Her2+ GEJ cancer- adenocarcinoma ALX148 + trastuzumab**
- Prior therapy-FOLFOX/trastuzumab; pembrolizumab refractory
- Day 59 stable disease ↓27%;
- Day 108 ↓48%; new central nervous system lesion
- The patient continues on treatment

Pharmacokinetics and Pharmacodynamics

- ALX148 exhibited clinical PK properties typical of antibody therapeutics directed towards cell-surface targets.
- ALX148 PK approached linear range and maintained complete peripheral CD47 target occupancy over the dosing interval at ≥3 mg/kg QW.
- ALX148 (10 mg/kg QW) steady-state half-life is predicted to be ~16 days and ALX148 initial PK/PD profiles are not impacted by combination drugs.
- Translational PK/PD modeling suggests tissue/tumor TO over 70% is maintained over the dosing interval at ≥3 mg/kg QW.

Please see SITC 2018 #P340

AT148001: Conclusions

Intended for combination, ALX148 is designed to avoid the dose-limiting toxicities associated with other CD47-targeted approaches in the clinic, while maximizing the efficacy of antibody-based therapies.

- No MTD was reached with ALX148 in combination. The maximum administered dose of ALX148 is 10 mg/kg QW in combination with standard regimens of pembrolizumab and trastuzumab.
- ALX148 contains an inactive Fc region that eliminates dose-dependent hematologic toxicity.
- ALX148 has antibody-like PK and maintains complete peripheral TO over the dosing interval at ≥3 mg/kg QW (#P340)
- ALX148 demonstrates preliminary anti-cancer activity in combination with pembrolizumab and trastuzumab in patients resistant and refractory to prior checkpoint inhibitors or trastuzumab.

Enrollment into combination expansion cohorts is ongoing (NCT03013218).

References

1. Weiskopf, K. *Eur J Cancer.* 2017 May;76:100-109
2. Kauder, SE. et al. *PLoS ONE.* 2018 August;13(8): e020183

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