A Phase 1 Study of ALX148, a CD47 Blocker, Alone and in Combination with Established Anti-Cancer Antibodies in Patients with Advanced Malignancy and Non Hodgkin Lymphoma

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Background

- Tumors attempt to evade the immune system by upregulating CD47, a marker of self. By blocking CD47 interaction with its myeloid cell receptor SIRPα, it may be possible to enhance innate and adaptive immunity against cancer.[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).[2,3]
- In non clinical models, ALX148 blocks CD47 and safely enhances the activity of several anti-cancer targeted antibodies and checkpoint inhibitors through Fc dependent and independent mechanisms, bridging innate and adaptive anti-cancer immune response.[2,3]
- Based upon these observations, AT148001, a first-in-human phase 1 study of ALX148 administered as a single agent (Part 1) and in combination with established anti-cancer antibodies (Part 2) was initiated.

ALX148 Potential for Best in Class: Potency and Safety

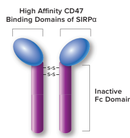
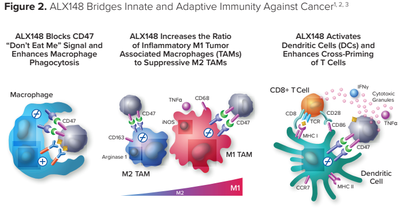


Figure 1. ALX148 is an intravenously administered fusion protein containing an engineered high affinity N-terminal D1 domain of SIRPα, which binds and blocks CD47, and is genetically linked to an inactive human Fc domain.

The molecular weight of ALX148 is half that of a typical antibody allowing higher molar concentrations to be delivered.

Mechanism of Action

Figure 2. ALX148 Bridges Innate and Adaptive Immunity Against Cancer[1,2,3]



Primary Objective

- The primary study objective is to characterize the safety profile of ALX148 as a single agent (Part 1) and in combination with established anti-cancer antibodies (Part 2).
- Here we report preliminary results from the fully enrolled Part 1 and Part 2 dose escalation cohorts of the study as of 23May2018.

Methods

- Patient cohorts were administered escalating doses of ALX148, intravenously, as in Table 1, once weekly (QW) in a 3 week cycle; or once every other week (QoW) in a 4 week cycle as a single agent (Part 1) or in combination with standard regimens of pembrolizumab, trastuzumab, or rituximab (Part 2).

Study Design

Table 1. ALX148 Dose Escalation Cohorts

Cohort	Dose ALX148 (mg/kg)	Frequency of Dosing
1	0.3	Once a week
2	1	Once a week
3	3	Once a week
4	10*	Once a week
5	30	Once every 2 weeks

* ALX148 10 mg/kg was administered as single agent (Part 1) and in combination (Part 2) with standard regimens of pembrolizumab, trastuzumab, or rituximab.

Study Population

Key Inclusion Criteria

- Patients age ≥18 years with advanced/metastatic solid tumor malignancy or non Hodgkin lymphoma (NHL) that are resistant to standard therapy or for which no standard therapy is available.
- Adequate organ function and hemoglobin ≥9 g/dL (≥8 g/dL, NHL).
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 or 1.

Key Exclusion Criteria

- Patients with known symptomatic CNS metastases or leptomeningeal disease.
- Prior treatment with any anti-CD47 or anti-SIRPα agent.

Endpoints and Assessments

- The primary endpoint is first cycle ALX148 dose limiting toxicity (DLT) administered as a single agent (Part 1) and in combination with pembrolizumab, trastuzumab, and rituximab (Part 2).
- Additional assessments include:
  - Adverse events, characterized by type, frequency, severity (using NCI CTCAE v. 4.03), timing, seriousness, and relationship to study therapy;
  - Pharmacokinetic parameters of ALX148, and CD47 target occupancy;
  - Investigator-assessed tumor response (using RECIST v 1.1 ; 2014 Lugano Criteria for NHL patients) at screening, every 8 weeks thereafter, and at the end of treatment or upon withdrawal.
- Treatment continued until disease progression, patient refusal, or unacceptable toxicity had occurred.
- The data cutoff date for this analysis is 23May2018.

Results

Patient Baseline Characteristics

- A total of 43 patients have been enrolled and treated across both Parts of the study. Part 1 enrollment is complete. Part 2 enrollment is ongoing. A summary of patient baseline characteristics is presented in Table 2.
- The majority of patients were female (53%) and most of the trial population (74%) had an ECOG PS score of 1.

Table 2. Baseline Characteristics

	Part 1	Part 2		
	ALX148	ALX148 + Pembrolizumab	ALX148 + Trastuzumab	ALX148 + Rituximab
	N=28	N=6	N=6	N=3
Age, Median Year (range)	67 (37-88)	53.5 (48-73)	64.5 (48-70)	67 (58-73)
Sex, n				
F	16	5	2	–
M	12	1	4	3
Race, n				
White	27	5	5	2
Black	1	–	1	–
Native American	–	1	–	–
Asian	–	–	–	1
ECOG PS, n				
0	6	2	3	–
1	22	4	3	3
Primary Disease, n				
Breast	1	–	1	–
Colorectal	8	–	–	–
Gastric/GEJ	1	–	3	–
Leiomyosarcoma	1	–	–	–
Lung	7	2	–	–
Ovarian	5	2	–	–
Pancreatic	2	–	1	–
Peritoneal	1	1	–	–
Appendiceal	1	–	–	–
Thymic	1	1	–	–
Urothelial	–	–	1	–
DLBCL	–	–	–	2
Marginal Zone Lymphoma	–	–	–	1

Patient Drug Exposure and Disposition

- No patient required a dose reduction due to an adverse event, and the most common reason for discontinuation was disease progression across both Parts (Table 3).
- At the time of data cutoff, 14 patients remained on study, and 4 patients had discontinued due to a treatment related AE (Table 3).

Table 3. Patient Drug Exposure and Disposition

	Part 1					Part 2		
	ALX148 Single Agent (mg/kg)					ALX148 10mg/kg + Combination		
	0.3 N=3	1 N=4	3 N=6	10 N=3	30 N=12	Pembro-lizumab N=6	Trastuzu-mab N=6	Rituximab N=3
Dose Interruptions Due to AEs, n (%)	1	–	1	–	3	1	1	1
Dose Reductions, n (%)	–	–	–	–	–	–	–	–
Discontinuation Due to TRAE, n	–	–	1	–	2	1	–	–
Discontinuation Due to PD, n	3	4	5	3	7	1	1	1
Ongoing Treatment, n	–	–	–	–	3	4	5	2

Safety

- The most common Part 1 (ALX148 single agent) treatment related adverse events were Headache and Fatigue (Table 4a). Treatment related adverse events that were of at least Grade 3 severity are shown in Table 4b.
- There were 2G5 events across the trial.
  - Death unknown etiology in patients with NSCLC (30 mg/kg, ALX148 single agent).
  - Disease progression in patients with GEJ ca (10 mg/kg, ALX148 + Trastuzumab).
- Part 2 combination treatment related adverse events were of low frequency and are reported in Table 5.
- Three Dose Limiting Toxicities (DLTs) were reported across the study (Tables 4b and 5):
  - Neutropenia+infection (3 mg/kg, ALX148 single agent);
  - Thrombocytopenia with significant bleed (30 mg/kg, ALX148 single agent);
  - Autoimmune hemolytic anemia (10 mg/kg ALX148 + Pembrolizumab).

Part 1: ALX148 Single Agent

Table 4a. Treatment Related Adverse Events in ≥2 Patients (N=28)

Adverse Event	Total
Headache	5
Fatigue	4
Thrombocytopenia	3
AST Increased	2
ALT Increased	2
Dizziness Postural	2
Pruritus	2
Rash	2

Table 4b. Treatment Related Adverse Events ≥Grade 3 in any Patient (N=28)

Adverse Event#	3mg/kg (N=6)		30mg/kg (N=12)			
Grade	**3**	**4**	**3**	**4**	**5**	**Total**
Thrombocytopenia	1	–	1*	–	–	2
Pancreatitis	–	–	1	–	–	1
Death	–	–	–	–	1^	1
Infection	1*	–	–	–	–	1
Neutropenia	–	1*	–	–	–	1

#There were no ≥G3 TRAE reported in patients administered single agent ALX148 at 0.3, 1, and 10 mg/kg QW.
* Dose Limiting Toxicity reported in one patient.
^ Unknown etiology.

Part 2 ALX148 Combination Cohorts: Treatment Related Adverse Events All Grades by Combination Partner and Dose level in any Patient

Table 5a. ALX148 10 mg/kg + Pembrolizumab (N=6)

Adverse Event	Grade			
	1/2	3	4	Total
ALT Increased	1	–	–	1
AST Increased	1	–	–	1
Alk Phos Increased	1	–	–	1
Hyponatremia	–	1	–	1
Autoimmune Hemolytic Anemia	–	–	1*	1
Vaginal Spotting	1	–	–	1
Myalgia	1	–	–	1
Hypoaesthesia	1	–	–	1
Rash	1	–	–	1

*Dose Limiting Toxicity.

Table 5b. ALX148 10 mg/kg + Trastuzumab (N=6)

Adverse Event	Grade			
	1/2	3	4	Total
Thrombocytopenia	–	1	–	1
Diarrhoea	1	–	–	1
Nausea	1	–	–	1
Pyrexia	1	–	–	1
Fatigue	1	–	–	1
Infusion Related Reaction	1	–	–	1
Neutrophil Count Decreased	–	1	–	1
Leukocyte Count Decreased	1	–	–	1
Pain	1	–	–	1

Table 5c. ALX148 10 mg/kg + Rituximab (N=3)

Adverse Event	Grade			
	1/2	3	4	Total
GI Tract Infection	1	–	–	1
Anaemia	1	–	–	1
Diarrhea	1	–	–	1
Nausea	2	–	–	2
Fatigue	1	–	–	1
Pyrexia	1	–	–	1

Response

- In Part 1, six out of 24 response evaluable patients (0.3 mg/kg, leiomyosarcoma; 3.0 mg/kg, colorectal ca.; 10 mg/kg, ovarian; 30 mg/kg [2] NSCLC, [1] appendiceal ca) achieved a best response of stable disease as of data cutoff. One patient with NSCLC demonstrated a 15% reduction in tumor size.
- In Part 2, with ALX148 administered as 10 mg/kg QW, 3 out of the first 5 response-evaluable patients ([1]NSCLC, [1] appendiceal ca - pembrolizumab; [1] Breast ca -trastuzumab) achieved a best response of stable disease and are ongoing as of data cutoff.

Pharmacokinetics and Pharmacodynamics

Table 6. ALX148 PK Parameters Following IV Infusion at Cycle 1 Day 1

Parameters	Cohort 1 (0.3 mg/kg) N=2	Cohort 2 (1 mg/kg) N=4	Cohort 3 (3 mg/kg) N=6	Cohort 4 (10 mg/kg) N=3	Cohort 5 (30 mg/kg QoW) N=9	Part 2 Combo (10 mg/kg) N=6
Cmax (µg/mL)	0.379 ± 0.192*	7.03 ± 2.17	54.5 ± 18.3	247 ± 32.5	727 ± 180	285 ± 77.3
AUCinf (µg*h/mL)	N/A	48.5 ± 32.4	1830 ± 745	19700 ± 4940	105000 ± 35700	22000 ± 9690
CL (mL/h/kg)	N/A	34.3 ± 31.1	1.92 ± 0.853	0.527 ± 0.122	0.32 ± 0. 123	0.54 ± 0.234
Vss (mL/kg)	N/A	154 ± 73.3	61.3 ± 18.7	59.8 ± 7.62	79.8 ± 22.0	56.4 ± 13.2

* Reported for Cycle 2 day 1, Cmax at Cycle 1 day 1 were all BQL.

- ALX148 PK profiles showed trend of non-linear PK with faster clearance at lower doses and slower clearance at higher doses of 10 mg/kg QW and 30 mg/kg QoW, indicating saturation of target mediated clearance.
- Steady-state half-life of ALX148 at 10 mg/kg QW is predicted to be ~16 days.
- ALX148 PK profile(10 mg/kg QW) in combination with pembrolizumab, trastuzumab, or rituximab was not changed from that of a single agent.

Figure 3. Observed Mean ALX148 PK at Cycle 1 Day 1

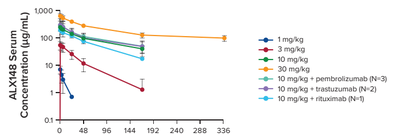
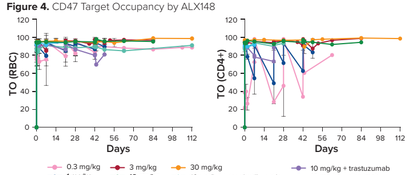


Figure 4. CD47 Target Occupancy by ALX148



- Near complete CD47 target occupancy (TO) by ALX148 is maintained at ≥3 mg/kg QW and in combinations.
- PKPD modeling using systemic vs tumor exposure and target occupancy data from tumor bearing mice suggests ALX148 dose above 3 mg/kg QW provides complete target occupancy at tumor sites in cancer patients.
- ALX148 exposure at 10 mg/kg QW exceeds the exposure needed to achieve preclinical antitumor activity.

Conclusions

Designed to safely enhance the activity of established anti-cancer antibodies ALX148 demonstrates a tolerable safety profile in combination to date.

- No ALX148 MTD was reached in combination or as a single agent in patients with advanced solid tumors and NHL.
- The MAD of ALX148 is 10 mg/kg QW in combination, and is 30 mg/kg QoW as a single agent.
- The molecular weight of ALX148 is half that of an anti-CD47 antibody, thus delivering twice the molar concentration at the same dose level.
- ALX148 PK approached linear range and maintained complete TO over the dosing interval at and above 3 mg/kg QW. Initial data suggests ALX148 PK and PD profiles are not impacted by combination drugs.
- 3 of the first 5 response-evaluable patients in Part 2 have ongoing SD as a best response as of data cutoff.
- Enrollment into combination expansion cohorts is now ongoing (NCT03013218).

References

1. Weiskopf, K. *Eur J Cancer*. 2017 May;76:100-109.
2. Kauder, S. et al. 59th Annual Meeting, American Society of Hematology 2017.
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