A First-in-Human Study of ALX148: CD47 Blockade to Enhance Innate and Adaptive Immunity for Advanced Solid Tumor Malignancy and Non-Hodgkin Lymphoma

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Background

- CD47, a marker of self, is upregulated by tumors to evade the immune system. Blocking the interaction between CD47 and SIRPα, its receptor on myeloid cells, disrupts a key immune checkpoint and may enhance innate and adaptive immunity against cancer.[1]
- ALX148 is an intravenously administered fusion protein containing the engineered high affinity D1 domain of SIRPα, which binds and blocks CD47, and is genetically linked to an inactive human Fc domain to minimize toxicity (Figure 1).[2,3]
- In non clinical models, ALX148 enhanced myeloid anti-tumor phagocytic activity, and tumor growth inhibition by several anti-cancer targeted antibodies and checkpoint inhibitors with minimal effect on normal blood cells.[2,3]
- Preclinical data suggest multiple mechanisms of action by ALX148, as shown below.
- 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

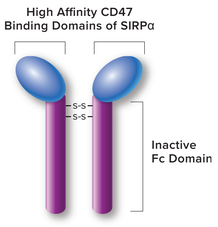


Figure 1. ALX148 is an intravenously administered fusion protein containing the engineered high affinity D1 domain of SIRPα, which binds and blocks CD47, and is genetically linked to an inactive human Fc domain.

Mechanism of Action

1. ALX148 Enhances Antibody Dependent Cellular Phagocytosis of Anti-Cancer Antibodies

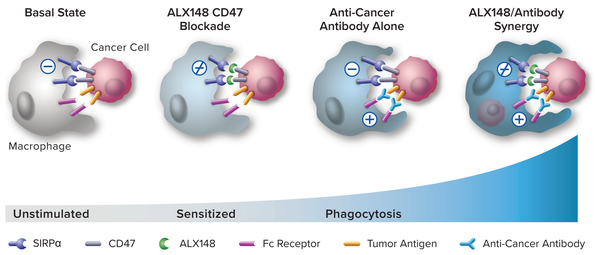


Figure 2. Macrophage phagocytosis is regulated by CD47-SIRPα signaling (an inhibitory signal) and Fc receptor engagement (a positive signal). The combination of ALX148 (blocking CD47) and anti-cancer antibodies (engaging Fc receptors) will maximally activate macrophages to eliminate tumor cells.[2,3]

2. ALX148 Increases M1 to M2 Ratio Among Tumor Associated Macrophages (TAMs), Leading to a More Inflammatory and Less Suppressive TAM Phenotype.[2,3]

3. ALX148 Activates Dendritic Cells (DCs) and Enhances Cross-Priming of CD8+ Cytotoxic T Cells

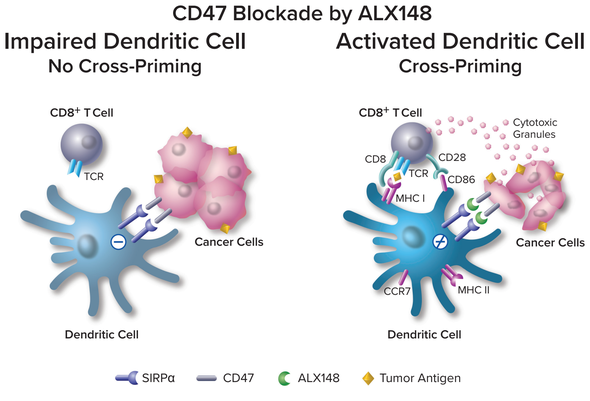


Figure 3. ALX148 activated dendritic cells (DCs) and enhanced tumor-specific T cell response; the DC activation appears to be mediated by cGAS-STING pathway.[2,3,4]

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).

Updated Results from Part 1 of Study as of 13 Oct 2017

Methods

Study Design

- Cohorts (3-6 pts) were administered escalating doses of ALX148, intravenously, as shown in Table 1, once weekly (QW) in a 3 week cycle; or once every other week (QoW) in a 4 week cycle.

Table 1. 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

Study Population

Key inclusion criteria:

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

Key exclusion criteria:

- Pts with known symptomatic CNS metastases or leptomeningeal disease.
- Prior treatment with any anti-CD47 or anti-SIRPα agent.
- Blood product transfusions within 14 days of Cycle 1 Day 1.

Endpoints and Assessments

- The primary endpoint is first cycle dose-limiting toxicity (DLT).
- Additional assessments include:
  - Adverse events, characterized by type, frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE v. 4.03]), timing, seriousness, and relationship to study therapy.
  - Pharmacokinetic parameters of ALX148, serum ADA (anti-ALX148 antibody) and CD47 target occupancy.
  - Objective tumor response (using the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 for solid tumors and Lugano Criteria for Non-Hodgkin Lymphoma patients).
- Treatment continues until disease progression, patient refusal, or unacceptable toxicity has occurred.

Results

Patient Baseline Characteristics and Disposition

- A total of 17 pts have been enrolled and treated as of Oct 13, 2017. Patient baseline characteristics are presented in Table 2.
- Patients had received a median of 5 prior systemic therapies and most (88%) had an ECOG performance status of 1.
- At the time of data cutoff, 6 pts remained on study, 10 pts had discontinued due to disease progression, and 1 pt (Cohort 3) had discontinued due to a DLT.
- Two patients (0.3 mg/kg, leiomyosarcoma; 3 mg/kg, colorectal ca.) achieved a best response of stable disease as of data cutoff.
- There were no deaths on study.

Table 2. Baseline Characteristics

	N=17
Median Age, Years (range)	68 (37 – 88)
Sex, n (%)	
F	10 (59)
M	7 (41)
Race, n (%)	
White	16 (94)
Black	1 (6)
ECOG PS, n (%)	
0	2 (12)
1	15 (88)
Primary Disease, n (%)	
Breast	1 (6)
Colorectal	7 (41)
GEJ	1 (6)
Leiomyosarcoma	1 (6)
NSCLC	3 (18)
Ovarian	2(12)
Pancreatic	1 (6)
Peritoneal	1 (6)
Median Prior Systemic Regimens (range)	5 (1-9)*

* Data available for 15 patients.

Drug Exposure

- As of the data cutoff date, patients had initiated a median number of 2 (range 1-6) cycles of ALX148.
- No patient required a dose reduction due to an adverse event.

Safety

- Treatment related adverse events are presented in Table 3. The majority were sole events and were of low grade.
- Two Grade 3 adverse events (thrombocytopenia, infection) and one Grade 4 serious adverse event (neutropenia) were reported in one patient at 3 mg/kg; the Grade 4 neutropenia plus infection was considered a dose-limiting toxicity.
  - 76 yo white male with gastroesophageal ca presented to clinic C1D14 with fever, chills, productive cough with yellow sputum and 2d history of diarrhea. Pt received broad spectrum antibiotics. Workup for source of infection was negative. The pt was stable at time of study discontinuation and counts returned to baseline.

Table 3. Treatment Related Adverse Events by Dose Level

Adverse Event	0.3 mg/kg (N=3)		1 mg/kg (N=4)		3 mg/kg (N=6)			10 mg/kg (N=3)		30 mg/kg (N=1)		Total
Grade	1/2	3/4	1/2	3/4	1/2	3	4	1/2	3/4	1/2	3/4	All
Abdominal Pain	0	0	0	0	1	0	0	0	0	0	0	1
ALT Increased	0	0	0	0	1	0	0	0	0	0	0	1
AST Increased	0	0	0	0	1	0	0	0	0	0	0	1
Decr Appetite	0	0	0	0	1	0	0	0	0	0	0	1
Diarrhea	0	0	0	0	1	0	0	0	0	0	0	1
Dysgeusia	0	0	1	0	0	0	0	0	0	0	0	1
Dyspnoea	0	0	0	0	1	0	0	0	0	0	0	1
Fatigue	1	0	0	0	0	0	0	1	0	0	0	2
Headache	1	0	0	0	1	0	0	1	0	0	0	3
Hyper-Sensitivity	0	0	0	0	1	0	0	0	0	0	0	1
Infection	0	0	0	0	0	1**	0	0	0	0	0	1
Neutropenia	0	0	0	0	0	0	1**	0	0	0	0	1
Pruritus	0	0	0	0	1	0	0	0	0	0	0	1
Rash	1	0	0	0	1	0	0	0	0	0	0	2
Rhinorrhea	0	0	0	0	0	0	0	1	0	0	0	1
Thrombo-cytopenia	0	0	0	0	0	1**	0	0	0	0	0	1
Weight Decrease	0	0	0	0	1	0	0	0	0	0	0	1

**Pt w/DLT of neutropenia + infection.

Pharmacokinetics and Pharmacodynamics

Table 4. 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
Cmax (µg/mL)	0.379 ± 0.172*	7.03 ± 2.17	54.5 ± 18.3	247 ± 32.5
AUCinf (µg*h/mL)	N/A	48.5 ± 32.4	1830 ± 745	14400 ± 4230
CL (mL/h/kg)	N/A	34.3 ± 31.1	1.92 ± 1.00	0.741 ± 0.237
Vss (mL/kg)	N/A	154 ± 73.3	61.3 ± 18.7	48.7 ± 8.62
$t_{1/2}$ [h, (range)]	N/A	3.98 (2.25, 6.43)	19.8 (17.5, 50.8)	40.8 (33.8, 74.1)

*Reported for Cycle 2 day 1, Cmax at Cycle 1 day 1 were all below the quantitation limit.

- ALX148 PK clearance decreased over the dose range tested, consistent with a target-mediated clearance mechanism.
- ALX148 PK profiles showed trend of non-linear PK at lower doses and indication of saturation of target mediated clearance at higher doses.

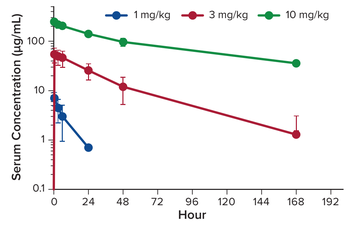
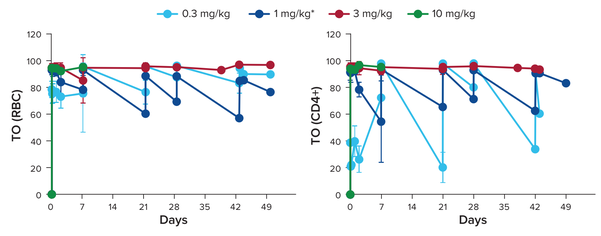


Figure 4. Observed mean ALX148 PK following IV infusion at Cycle 1 Day 1.

- ALX148 demonstrated dose-dependent CD47 target occupancy (TO) and saturated peripheral CD47 at and above 3 mg/kg QW.



* Data available for only one patient after day 7.

Figure 5. CD47 Target Occupancy (TO) on peripheral RBC (A) and CD4+ T cells (B) were determined throughout the dosing period.

Conclusions

- ALX148 is well tolerated in patients with advanced solid tumors with no dose-dependent hematologic toxicity at doses evaluated.
- Treatment-related AEs were mostly of low grade and frequency; there were no treatment related AEs of anemia; one DLT of neutropenia + infection occurred at 3 mg/kg; and there were no deaths on study.
- ALX148 demonstrated dose-dependent PK and target occupancy in the dose range tested; ALX148 PK appeared to approach linear range and maintained complete TO over the dosing interval at and above 3 mg/kg QW.
- Evaluation of the 30 mg/kg QoW dose level continues. Upon determination of the maximum tolerated/optimal biologic dose, the safety profile of ALX148 in combination with established anti-cancer antibodies will be evaluated.

References

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Acknowledgments

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