A Phase 1 Study of ALX148, a CD47 Blocker, in Combination with Rituximab in Patients with Non-Hodgkin Lymphoma (Abstract #1953)

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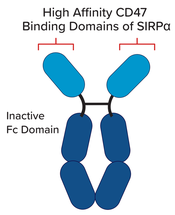
Background

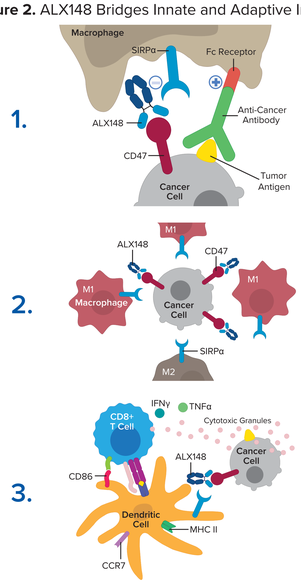
- CD47-SIRPα signaling is a myeloid checkpoint mechanism that signals the macrophage to ignore the cell on which CD47 is expressed.[1]
- Tumors upregulate CD47 to evade the immune response, and high expression of CD47 mRNA in diffuse large B cell lymphoma (DLBCL) is reported to correlate with a worse OS, while CD47 blockade in addition to rituximab augments rituximab-mediated phagocytosis.[2,3]
- ALX148 is an engineered fusion protein comprised of a high affinity CD47 blocker linked to an inactive human immunoglobulin Fc region (Figure 1). It blocks CD47-SIRPα interaction and enhances anti-tumor immunity.[3]
- AT148001 is a first-in-human phase 1 study, evaluating ALX148 administered as a single agent (Part 1) and in combination with established anticancer antibodies (Part 2) including in combination with rituximab in patients with relapsed or refractory non-Hodgkin lymphoma (NHL).

Figure 1. ALX148: A Unique High Affinity SIRPα Fusion Protein



- Selectively binds CD47 to block its interaction with SIRPα with picomolar binding affinity.
- Fc domain mutated to eliminate Fcγ receptor binding.
- Molecular weight half the size of typical antibody.
- Fc domain enables antibody-like PK.

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



ALX148 Designed to Safely Maximize Anti-Cancer Antibody Activity

ALX148 Increases Ratio of Inflammatory M1 to Suppressive M2 in Tumor Microenvironment

ALX148 Activates Dendritic Cells and Enhances Cross-Priming of T Cells

Methods

AT148001 Study Design

- **Part 1 (single agent):** No MTD reached, maximum administered dose 30 mg/kg QoW[4].
- **Part 2 (combination):** ALX148 (10 mg/kg QW, 15 mg/kg QW) combined with standard regimens of rituximab (375 mg/m^2 QW x 4 followed by once monthly x 8). Details below.

Table 1. ALX148 Combination NHL Cohorts

Combination Safety Confirmation	Combination Dose Expansion
ALX148 (10 mg/kg QW) + rituximab: Relapsed/refractory NHL *Enrollment complete*	**ALX148 (10 mg/kg QW):** Relapsed/refractory NHL *Enrollment complete*
ALX148 (15 mg/kg QW) + rituximab: Relapsed/refractory NHL *Enrollment ongoing*	

Study Population

- **Key Inclusion Criteria**
  - Patients age ≥18 years with non-Hodgkin lymphoma for which no curative therapy is available, or that are relapsed or refractory to standard approved therapies.
  - Adequate organ function and hemoglobin ≥8 g/dL; absolute neutrophil count ≥1,000/mm^3, and platelets ≥50,000/mm^3.
  - No prior treatment with any anti-CD47 or anti-SIRPα agent.

Endpoints and Assessments

- **Primary Endpoint**
  - First cycle ALX148 dose limiting toxicity (DLT) in combination with rituximab.
- **Additional Assessments**
  - Characterization of adverse events using NCI CTCAE v4.03.
  - Investigator-assessed objective response every 8 weeks using Lugano Working Group 2014 response criteria in NHL. Complete response (CR), partial response (PR) and stable disease (SD) include both metabolic PET-CT and CT based responses.
  - Pharmacokinetic parameters of ALX148, and CD47 target occupancy.
- Here we report initial results from the ALX148 plus rituximab NHL combination cohort as of Nov 01, 2019.

Results

Patient Baseline Characteristics

- ALX148 in combination with rituximab has been administered to 29 patients with advanced non-Hodgkin lymphoma (Table 2).
- Enrollment into the ALX148 10 mg/kg QW combination cohort is complete and enrollment continues into the ALX148 15 mg/kg QW combination cohort .
- The majority of patients enrolled were male (69%), Asian (86%) and had an ECOG PS score of 1 (76%).

Table 2. Baseline Characteristics

	ALX148 10 mg/kg QW + Rituximab n=22	ALX148 15 mg/kg QW + Rituximab n=7
Primary Disease, n		
Follicular	5	2
Marginal Zone	2	1
DLBCL	11	3
Mantle Cell	4	1
Median Age		
Years (range)	62 (32-80)	63 (53-74)
Sex, n		
F	5	4
M	17	3
Race, n		
Asian	18	7
White	4	–
ECOG PS, n		
0	6	1
1	16	6

Table 3. Patient Drug Exposure and Disposition

	ALX148 + Rituximab	
	ALX148 10 mg/kg n=22	ALX148 15 mg/kg n=7
Dose Reductions, n (%)	0	0
Discontinuation Due to TRAE	1*	0
Discontinuation Due to Global Deterioration of Health	1	0
Discontinuation Due to PD	11	1
Discontinuation Due to Other	1	0
Ongoing Treatment	8	6

*Rituximab infusion reaction; **TRAE:** treatment related adverse event; **PD:** disease progression.

- No patient required a dose reduction, and the most common reason for discontinuation was disease progression.

Safety

- ALX148 in combination with rituximab was well tolerated, and most treatment related adverse events (TRAE) were of low grade and frequency.
- The most common TRAE in combination with rituximab was Grade 1-2 rash (17%). TRAEs ≥Grade 3 severity were of low frequency (Table 4).
- There were no ALX148 dose limiting toxicities reported, the maximum administered dose was 15 mg/kg QW.
- There were no treatment related serious adverse events reported.
- There were 2 deaths on study, both due to disease progression.

Table 4. Treatment Related Adverse Events

	ALX148 + Rituximab (N=29)	
Adverse Event	**Total n (%)**	**≥Grade 3 n (%)**
Rash	5 (17%)	–
Fatigue	2 (7%)	–
Nausea	2 (7%)	–
Neutropenia	2 (7%)	2 (7%)
Anemia	2 (7%)	1 (3%)

Response

- Clinical activity of ALX148 in combination with rituximab in response-evaluable patients (N=24) is summarized below and in Table 5.
- **ALX148 10 mg/kg + rituximab (n=21).**
  - 2 CR (follicular, marginal zone).
  - 7 PR (2 DLBCL, 2 follicular, 3 mantle cell).
  - 6 SD (2 DLBCL, 2 follicular, 1 mantle cell, 1 marginal zone).
- **ALX148 15 mg/kg + rituximab (n=3).**
  - 2 PR (DLBCL, marginal zone).

Table 5. ALX148 + Rituximab Combination Clinical Activity in Response-Evaluable Patients

Population ALX148 Dose	n	ORR (95% CI)	mDOR (95% CI)	mPFS (95% CI)	mFollow-Up (95% CI)
10 mg/kg QW ALL	**21**	**42.9% (24.5, 63.5)**	**5.6 (1.8, NC)**	**7.3 (2.1, 13.2)**	**6.3 (3.6, 10.2)**
10 mg/kg QW Aggressive	14	35.7% (16.3, 61.2)	5.6 (1.8, NC)	3.1 (1.8, 7.4)	5.4 (2.8, 10.2)
10 mg/kg QW Indolent	7	57.1% (25.1, 84.2)	NC	NC	6.3 (3.5, 13.2)
15 mg/kg QW	**3**	**67% (ND, ND)**	**NC**	**NC**	**2.2 (1.2, 2.4)**

Aggressive: Relapse/refractory diffuse large B cell lymphoma and mantle cell lymphoma; **Indolent:** Follicular lymphoma and marginal zone lymphoma; **ORR:** Objective response rate (complete + partial response rate); **mDOR:** Median duration of response (months); **mPFS:** Median progression free survival (months); **mFollow-up:** Median follow-up (months); **ND:** Not done; **NC:** Could not be calculated.

Figure 3. ALX148 + Rituximab Clinical Activity in Patients with Non-Hodgkin Lymphoma

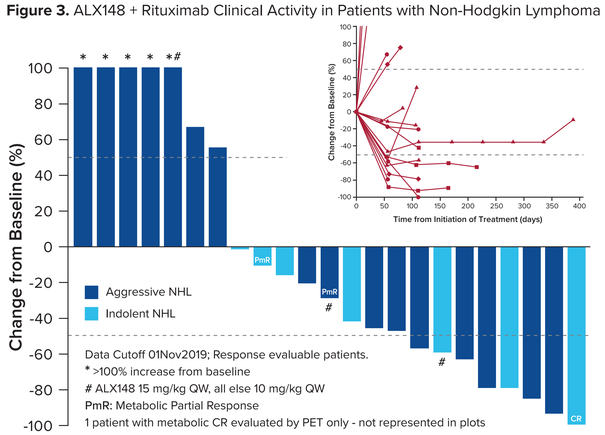
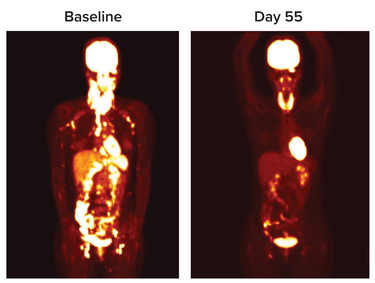


Figure 4. Significant Tumor Reduction in a Patient with Non-Hodgkin Lymphoma Administered ALX148 + Rituximab



- **45 yo patient with Mantle Cell Lymphoma administered ALX148 (10 mg/kg QW) + rituximab.**
- Progression on prior treatments with rituximab plus HyperCVAD and DHAP.
- Day 55 initial partial response (↓53%); Day 274 ongoing partial response (↓85%).
- The patient continues on treatment.

Figure 5. Duration of Treatment in Response Evaluable Patients with NHL (ALX148 10 mg/kg QW)

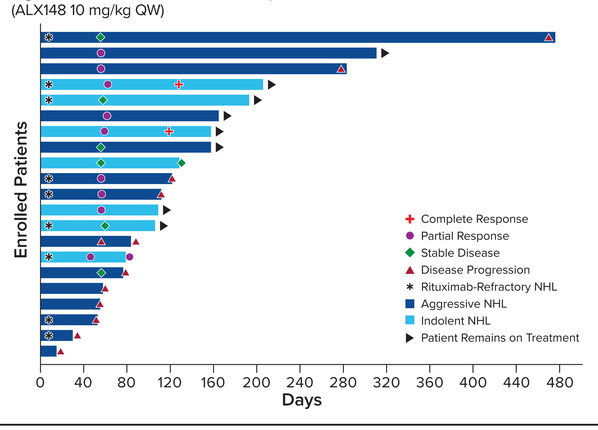


Figure 6. ALX148 Concentration-Time Profiles Following First IV Infusion at Cycle 1 Day 1 as Single Agent or in Combination with Rituximab

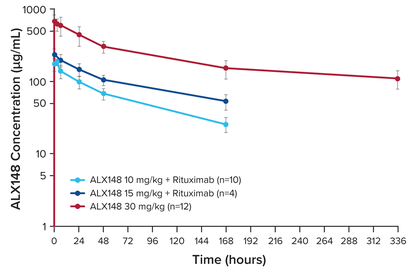


Table 6. ALX148 PK Parameters Following IV Infusion at Cycle 1 Day 1 as Single Agent or in Combination with Rituximab

Parameters	Cohort 5 (30 mg/kg QoW) n=12	Rituximab Combo (10 mg/kg QW) n=10	Rituximab Combo (15 mg/kg QW) n=4
Cmax (mg/mL)	701 ± 169	175 ± 36.2	243 ± 40.8
AUCinf (mg*h/mL)	101000 ± 31900	13300 ± 2300	25100 ± 5970
CL (mL/h/kg)	0.326 ± 0.108	0.771 ± 0.126	0.622 ± 0.146
Vss (mL/kg)	80.9 ± 19.9	86.0 ± 19.9	91.8 ± 15.5

Figure 7. Complete CD47 Target Occupancy by ALX148

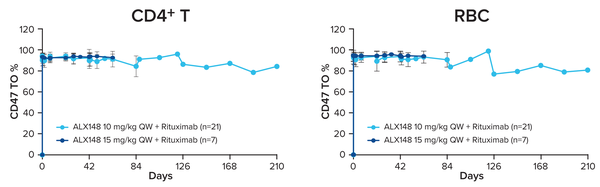
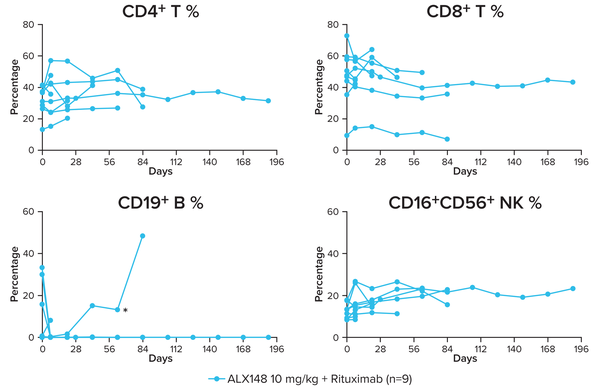


Figure 8. Circulating Immune Cell Profiles Following ALX148 + Rituximab



*Patient discontinued treatment due to rituximab infusion reaction.

- No changes observed in circulating T and NK cells.
- Expected reduction in circulating B cells observed.

Conclusions

- **ALX148 is designed to avoid the dose-limiting toxicities associated with other CD47-targeted approaches while maximizing the innate and adaptive immune response to cancer in combination with a variety of anti-cancer antibodies.[5]**
- ALX148 demonstrates emerging anti-cancer activity in combination with rituximab in patients with relapsed/refractory NHL whose tumors have progressed on prior CD20 targeted therapies that supports further development in the Phase 2 setting.
- ALX148 in combination with standard regimens of rituximab is well tolerated without dose-dependent hematologic toxicity suggesting that it has a differentiated safety profile compared to other CD47-targeted agents currently in the clinic. The maximum administered dose is 15 mg/kg QW (molar equivalent to 30 mg/kg QW of an antibody) .
- ALX148 demonstrates antibody-like and linear PK at the two dose levels evaluated with complete CD47 target occupancy in combination with rituximab.
- ALX148 in combination with rituximab showed expected reduction of circulating B cells and no changes in circulating T and NK cells.

We thank all of the participating patients and their families as well as the site research staff.

Contact email: info@alxoncology.com

References: **1.** Weiskopf, K., *Eur J Cancer*. 2017 May;76:100-109; **2.** Bouwstra, R. et al., *Cancer Immunol Res* 2019 Oct;7(10):1663-1671; **3.** Kauder, S.E. et al., *PLoS ONE*. 2018 August;13(8): e0201832; **4.** Lakhani N. et al, #P335, SITC 2018; **5.** Chow et al., #2514, ASCO 2019