ALX148, a CD47 Blocker, in Combination with Rituximab in Patients with Relapsed/Refractory (R/R) Non-Hodgkin Lymphoma

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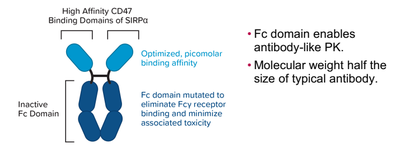
Background

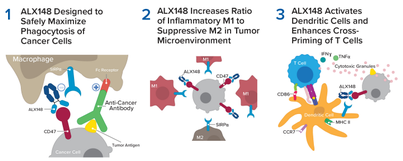
- CD47-SIRPα signaling is a myeloid checkpoint mechanism that signals the macrophage to ignore the cell on which CD47 is expressed.[1]
- Tumors upregulate CD47 to evade the immune response, and high expression of CD47 mRNA in DLBCL is reported to correlate with a worse OS, while CD47 blockade in addition 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 the CD47-SIRPα interaction enhancing 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 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 Bridges Innate and Adaptive Immunity[2]



Methods

AT148001 Study Design

- **Part 1 (single agent):** No MTD reached, maximum administered dose 30 mg/kg QOW[4].
- **Part 2 (combination):** ALX148 (administered 10 mg/kg or 15 mg/kg QW) combined with standard regimens of rituximab (administered 375 mg/m² QW x 4 followed by once monthly x 8).

Table 1. ALX148 Combination Relapsed/refractory NHL Tumor Cohorts

Combination Safety Confirmation	Combination Dose Expansion
ALX148 (10 mg/kg QW) + rituximab	ALX148 (10 mg/kg QW) + rituximab
ALX148 (15 mg/kg QW) + rituximab	

Study Population

Key Inclusion Criteria

- Patients age ≥18 years with B cell 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/mm³, and platelets ≥50,000/mm³.
- 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 include:
  - Characterization of adverse events using NCI CTCAE v 4.03.
  - Investigator-assessed objective response every 8 weeks using Lugano Working Group 2014 response criteria in NHL.
  - Pharmacokinetic parameters of ALX148, and CD47 target occupancy.
- Here we report preliminary results from the fully enrolled ALX148 plus rituximab NHL combination cohort as of April 1, 2020.

Results

Patient Baseline Characteristics

- ALX148 in combination with rituximab has been administered to 33 patients with advanced non-Hodgkin lymphoma (Table 2).
- Enrollment into both the ALX148 10 mg/kg QW and ALX148 15 mg/kg QW combination cohorts is complete.
- The majority of patients enrolled were male (70%), Asian (82%) and had an ECOG PS score of 1 (70%).

Table 2. Baseline Characteristics

	ALX148 10 mg/kg QW + Rituximab (N=22)	ALX148 15 mg/kg QW + Rituximab (N=11)
Primary Disease, n		
Follicular	5	3
Marginal Zone	2	1
DLBCL	11	6
Mantle Cell	4	1
Median Age		
Years (range)	66 (32-80)	64 (53-78)
Sex, n		
M	17	6
F	5	5
Race, n		
Asian	18	9
White	4	2
ECOG PS, n		
0	7	2
1	15	8

Table 3. Patient Drug Exposure and Disposition

	ALX148 + Rituximab	
	ALX148 10 mg/kg (N=22)	ALX148 15 mg/kg (N=11)
Dose Reductions, n	0	0
Discontinuation Due to TRAE	1^	0
Discontinuation Due to PD	12	4
Discontinuation Due to Death	2*	0
Discontinuation Due to Other	1	1
Ongoing Treatment	6	6

Notes: ^Discontinuation due to rituximab infusion reaction; *Death due to 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 (TRAEs) were of low grade and frequency.
- Twenty-six (78.8%) patients experienced any adverse event. Fifteen (45.5%) patients experienced any TRAE.
- The most common TRAE of ALX148 in combination with rituximab was Grade 1-2 rash (18%). TRAEs ≥Grade 3 severity were of low frequency (Table 4).
- No ALX148 dose limiting toxicities were reported, the maximum administered dose was 15 mg/kg QW.
- No treatment related serious adverse events were reported.
- There were 2 deaths on study, both due to disease progression.

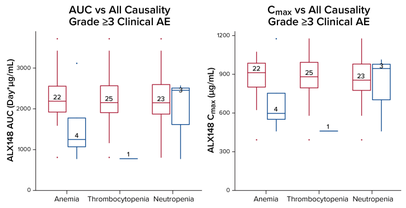
Treatment Related Adverse Events

Table 4. ALX148 + Rituximab (N=33)

Adverse Event	Total n (%)	≥Grade 3 n (%)
Rash	6 (18%)	–
Fatigue	3 (9%)	–
Nausea	2 (6%)	–
Neutrophil Count Decreased	2 (6%)	2 (6%)
Anemia	2 (6%)	1 (3%)

Notes: Data cut off April 1, 2020. Events occurring in ≥2 patients.

Figure 3. Exposure-Safety Relationships



Numbers in box represent the number of subjects for each AE category.

- No significant exposure-cytopenia relationship was observed across the ALX148 exposure range evaluated (10 mg/kg QW - 15 mg/kg QW).

Response

- Clinical activity of ALX148 in combination with rituximab in response-evaluable patients is summarized below and in Table 5.
- ALX148 10 mg/kg + rituximab (N=22)
  - 3 CR (Mantle Cell, Follicular, Marginal Zone)
  - 6 PR (2 DLBCL, 2 Mantle Cell, 2 Follicular)
  - 6 SD (2 DLBCL, 1 Mantle Cell, 2 Follicular, 1 Marginal Zone)
- ALX148 15 mg/kg + rituximab (N=11)
  - 2 CR (2 Follicular)
  - 4 PR (1 Marginal Zone, 2 DLBCL, 1 Mantle Cell)
  - 1 SD (Follicular)

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

Population ALX148 Dose	N	ORR (95% CI)	Median DOR (95% CI)	Median PFS (95% CI)	Median OS (95% CI)	Median Follow-Up (95% CI)
NHL (10 mg/kg ALL)	**22**	**40.9% (23.3; 61.3)**	**NC**	**7.4 (1.9; 13.2)**	**NC**	**11.3 (10.2; 15.2)**
NHL (10 mg/kg aggressive)	15	33.3% (15.2; 58.3)	5.6 (1.8; NC)	2.5 (1.0; 7.4)	8.9 (2.5 ; NC)	10.4 (9.5; 15.2)
NHL (10 mg/kg indolent)	7	57.1% (25.1; 84.2)	NC	NC	NC	11.3 (7.8; 20.4)
NHL (15 mg/kg ALL)	**11**	**54.6% (28.0; 78.7)**	**NC**	**NC**	**NC**	**5.1 (4.0; 5.6)**
NHL (15 mg/kg aggressive)	7	42.9% (15.8; 75.0)	NC	1.9 (1.1; NC)	NC	4.7 (4.0; 5.4)
NHL (15 mg/kg indolent)	4	75% (30.1; 95.4)	NC	NC	NC	5.9 (3.5; 7.4)

Notes: Data Cutoff April 1, 2020; 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); NC could not be calculated.

Figure 4. ALX148 + Rituximab Clinical Activity in Patients with Non-Hodgkin Lymphoma (N=33)

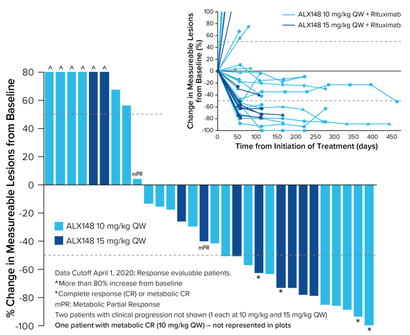


Figure 5. Duration of Treatment in Patients with NHL (ALX148 10 mg/kg QW)

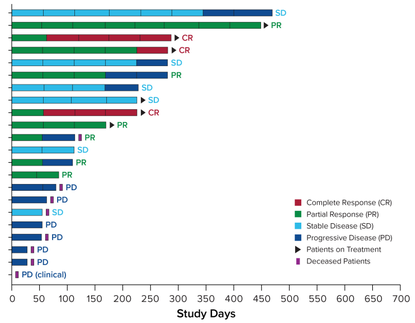
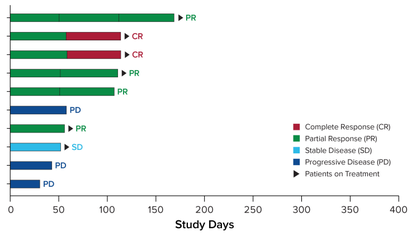
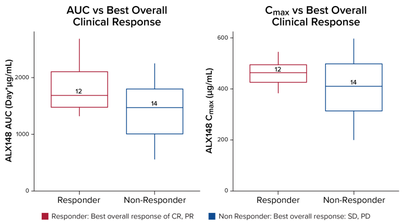


Figure 6. Duration of Treatment in Patients with NHL (ALX148 15 mg/kg QW)*



*One patient with clinical progression Study Day 8 as best response not shown.

Figure 7. Exposure-Response Relationships



Numbers in box represent the number of subjects for each responder category.

- Across the exposure range evaluated (10 mg/kg QW - 15 mg/kg QW), increased ALX148 exposure was observed in subjects with a best response of CR and PR compared to subjects with a best response of SD and PD.

ALX148 Clinical Pharmacokinetics and Pharmacodynamics

Figure 8. ALX148 Concentration-Time Profiles Following First IV Infusion at Cycle 1 Day 1 as Single Agent or in Combination with Rituximab

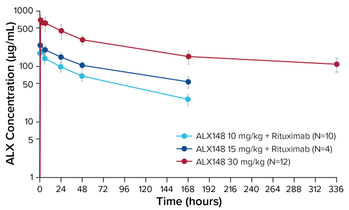


Table 6. ALX148 PK Parameters Following IV Infusion at Cycle 1 Day 1 as as Single Agent or in Combination with Rituximab

Parameters	ALX148 Single Agent (30 mg/kg QoW) N=12	ALX148 with Rituximab (10 mg/kg QW) N=10	ALX148 with Rituximab (15 mg/kg QW) N=4
C_{max} (µg/mL)	701 ± 169	175 ± 36.2	243 ± 40.8
AUC_{inf} (µg*h/mL)	101,000 ± 31,900	13,300 ± 2,300	25,100 ± 5,970
CL (mL/h/kg)	0.326 ± 0. 108	0.771 ± 0.126	0.622 ± 0.146
V_{ss} (mL/kg)	80.9 ± 19.9	86.0 ± 19.9	91.8 ± 15.5

Mean +/- SD, standard derivation

Figure 9. Near Complete CD47 Target Occupancy by ALX148

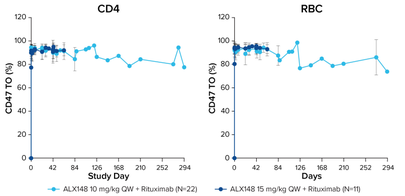


Figure 10. PK Model Predicted ALX148 Concentration-Time Profiles

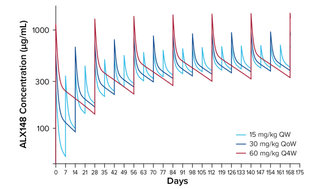


Table 7. PK Model Predicted ALX148 Steady-state PK Parameters

Dosing Regimen	AUC (µg*Day/mL)	C_{max} (µg/mL)	T1/2 (Day)
15 mg/kg QW	13,500	706	30
30 mg/kg QoW	13,500	964	31
60 mg/kg Q4W	13,600	1,480	31

Conclusions

Intended for combination with anti-cancer therapeutics, ALX148 maximizes the innate and adaptive immune response to cancer while avoiding the dose-limiting hematologic toxicities associated with other CD47-targeted approaches in the clinic.

- ALX148 in combination with standard regimens of rituximab is well tolerated with a favorable hematologic safety profile and no maximum tolerated dose reached. The maximum administered dose is 15 mg/kg QW (molar equivalent to 30 mg/kg QW of an antibody) with no exposure dependent anemia, thrombocytopenia or neutropenia observed across the exposure range evaluated.
- ALX148 demonstrates linear PK at 10 mg/kg and 15 mg/kg QW with near complete peripheral CD47 target occupancy in combination with rituximab at both dose levels. Population PK models predict linear PK up to 60 mg/kg once monthly.
- ALX148 demonstrates emerging anti-cancer activity with durable responses in combination with rituximab in patients with relapsed/refractory NHL whose tumors have progressed on prior CD20 targeted therapies that compares favorably to historic controls.
- Preliminary data suggests ALX148 is well tolerated and that higher exposure of ALX148 is observed in responders vs non-responders.

Patients in all cohorts continue to be followed (NCT03013218).

References

1. Weiskopf, K., *Eur J Cancer.* 2017 May;76:100-109.
2. Bouwstra, R. et al., *Cancer Immuno Research.* 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., #3056, ASCO 2020.

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- Contact email: info@alxoncology.com