A Phase 1 Study of ALX148, a CD47 Blocker, in Combination with Standard Anti Cancer Antibodies and Chemotherapy Regimens in Patients with Advanced Malignancy

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Background

- CD47, a marker of self, engages SIRPα and signals the macrophage to ignore the cell on which CD47 is expressed.[1] Tumors upregulate CD47 to evade the immune response.
- ALX148 is a high affinity CD47 blocker fusion protein with an inactive human immunoglobulin Fc region (Figure 1) designed to enhance the activity of anti-cancer targeted antibodies and checkpoint inhibitors with minimal hematologic toxicity.[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).

Figure 1. ALX148 Potently and Selectively Binds CD47 to Block SIRPα Interaction

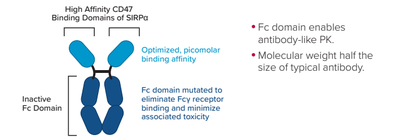
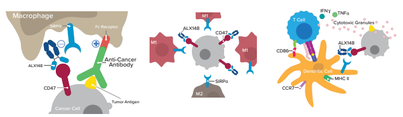


Figure 2. ALX148 Bridges Innate and Adaptive Immunity[2]



Methods

AT148001 Study Design

- **Part 1 (single agent):** Twenty-eight patients enrolled with advanced solid tumor were administered escalating doses of intravenous ALX148 (0.3 to 10 mg/kg QW; or 30 mg/kg QOW)[3].
- **Part 2 (combination):** Patients with advanced solid tumors were administered ALX148 10 or 15 mg/kg QW in a 3 week cycle with standard regimens including pembrolizumab (200 mg IV Q3W), trastuzumab (8 mg/kg IV → 6 mg/kg Q3W), ramucirumab (8 mg/kg Days 1, 15 Q4W), paclitaxel (80 mg/m^2 Days 1, 8, 15 Q4W), cisplatin (100 mg/m^2 Q3Wx6), carboplatin (AUC 5 mg/ml/min Day 1 Q3Wx6), and 5FU (1,000 mg/m^2/day Days 1, 2, 3, 4 Q3Wx6).
  - Adequate organ function and hemoglobin ≥9 g/dL.
  - No prior treatment with an anti-CD47 or anti-SIRPα agent.

Table 1. ALX148 Combination Solid Tumor Cohorts

Combination Dose Confirmation (Advanced Malignancy)	Combination Dose Expansion
ALX148 + trastuzumab (N=10)	ALX148 + trastuzumab: HER2 positive Gastric/GEJ (N=20) *progressed on prior fluoropyrimidine*
ALX148 + pembrolizumab (N=12)	ALX148 + pembrolizumab: HNSCC (N=20) *progressed on prior platinum*
	ALX148 + pembrolizumab: NSCLC (N=20) *progressed on prior CPI/PD-L1<50%*
	ALX148 + trastuzumab + ramucirumab + paclitaxel: HER2 positive Gastric/GEJ *progressed on prior trastuzumab and fluoropyrimidine or platin*
	ALX148 + pembrolizumab + 5FU + platin: HNSCC *No prior treatment for advanced disease*

- **Primary study objective:** Characterize ALX148 safety profile as a single agent (Part 1) and in combination with established anti-cancer antibodies with or without standard chemotherapy (chemo) (Part2).
- Here we report final results from the fully enrolled ALX148 plus pembrolizumab and ALX148 plus trastuzumab solid tumor combination cohorts and preliminary data from ALX148 plus chemotherapy combination cohorts, as of April 01, 2020.

Results

Patient Baseline Characteristics

- 89 solid tumor patients have been enrolled into Part 2 combination cohorts (Table 2).

Table 2. Baseline Characteristics

	ALX148 Pembrolizumab N=52	ALX148 Trastuzumab N=30	ALX148 Pembrolizumab + Chemo N=1	ALX148 Trastuzumab + Chemo N=6
Primary Disease, n				
Lung	25	–	–	–
HNSCC	20	–	1	–
Gastric/GEJ Esophageal	–	25	–	6
Breast	–	2	–	–
Colorectal	2	–	–	–
Ovarian	2	1	–	–
Pancreatic	–	1	–	–
Appendiceal	1	—	–	–
Sarcoma	1	–	–	–
Urothelial	–	1	–	–
Unknown	1	–	–	–
Median Age				
Years (range)	61 (32-81)	60 (45-79)	63	69 (45-72)
Sex, n				
M	29	21	1	4
F	23	9	–	2
Race, n				
White	34	13	–	3
Asian	11	14	1	3
Black	3	1	–	–
Other	4	2	–	–
ECOG PS, n				
0	18	11	1	2
1	34	19	–	4

Safety

- ALX148 in combination with pembrolizumab (N=52) and trastuzumab (N=30) was well tolerated, and most treatment related adverse events (TRAE) were of low grade and frequency. Initial results suggest ALX148 in combination with chemotherapy (N=7) is also well tolerated with no dose-limiting toxicities to date.
- Eighty-seven patients experienced any adverse event. Thirty-five (67.3%) patients administered ALX148 + pembrolizumab and 22 (73.3%) patients administered ALX148 + trastuzumab experienced any TRAE. Three (50%) patients administered ALX148 + trastuzumab + chemotherapy and no (0%) patient administered ALX148 + pembrolizumab + chemotherapy experienced any TRAE.
- The most common TRAE of ALX148 in combination with pembrolizumab was low grade AST increased (17.3%), and with trastuzumab was low grade Fatigue (30%). TRAE ≥Grade 3 severity were of low frequency (Tables 3 and 4).
- There were no Dose Limiting Toxicities or TRAE ≥Grade3 reported in patients treated with ALX148 + pembrolizumab + chemotherapy and ALX148 + trastuzumab + chemotherapy.
- Four treatment related serious adverse events (TRSAE) in combination with pembrolizumab were reported ([1] autoimmune hemolytic anemia/pancytopenia, [1] febrile neutropenia, [1] neutropenia, and [1] peripheral neuropathy). One TRSAE of febrile neutropenia in combination with trastuzumab was reported. There were no TRSAEs reported in patients treated with ALX148 + pembrolizumab + chemotherapy or ALX148 + trastuzumab + chemotherapy.

Treatment Related Adverse Events*

Table 3. ALX148 (10mg/kg QW) + Trastuzumab (N=30)

Adverse Event	Total N (%)	≥Grade 3
Fatigue	9 (30)	–
PLATELETS DECREASED	5 (16.7)	2 (6.7)
Decreased Appetite	3 (10)	–
PRURITUS	3 (10)	–
Pyrexia	3 (10)	–
Anemia	2 (6.7)	–
Nausea	2 (6.7)	–
Neutropenia	2 (6.7)	2 (6.7)

Notes: *Data cut off April 1, 2020. Events occurring in ≥2 patients. **RASH:** Rash, Rash maculo-papular, Rash vesicular, Rash pruritic, Dermatitis. **PLATELETS DECREASED:** Platelets decreased, Thrombocytopenia. **PRURITUS:** Pruritus, Pruritus generalized.

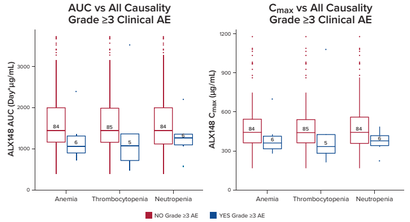
Table 4. ALX148 (10mg/kg QW) + Pembrolizumab (N=52)

Adverse Event	Total N (%)	≥Grade 3
AST Increased	9 (17.3)	–
ALT Increased	7 (13 .5)	1 (1.9)
Fatigue	6 (11.5)	–
Anemia	5 (9.6)	1 (1.9)
Pruritus	5 (9.6)	–
RASH	5 (9.6)	–
Infusion Reaction	4 (7.7)	–
PLATELETS DECREASED	4 (7.7)	2 (3.8)
Alkaline Phosphatase Increased	3 (5.8)	–
Arthralgia	3 (5.8)	–
Pyrexia	3 (5.8)	–
WBC Decreased	3 (5.8)	–
Decreased Appetite	2 (3.8)	–
Myalgia	2 (3.8)	–
Nausea	2 (3.8)	–
Neutropenia	2 (3.8)	1 (1.9)

No TRAEs were reported in ≥2 patients in:

- ALX148 (10 mg/kg QW) + pembrolizumab + chemo: N=1
- ALX148 (10 mg/kg QW) + trastuzumab + chemo: N=3
- ALX148 (15 mg/kg QW) + trastuzumab + chemo: N=3

Figure 3. Pharmacokinetic and Pharmacodynamic 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 - 30 mg/kg QOW).

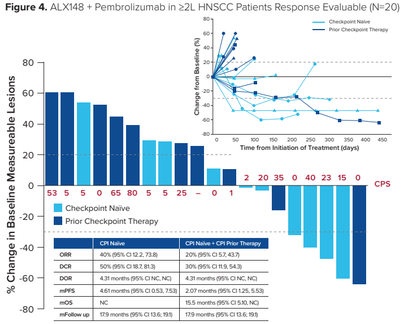
Response

ALX148 Combination Expansion Cohorts - Clinical Activity in Response Evaluable Patients*

- **HNSCC Expansion**
  - **ALX148 (10 mg/kg QW) + pembrolizumab, CPI naive ≥2L HNSCC:** N=10 [4 PR (2 confirmed), 2 SD, 4 PD]
  - **ALX148 (10 mg/kg QW) + pembrolizumab + chemo, CPI naive 1L HNSCC:** N=1 [1 PR]
  - **ALX148 (10 mg/kg QW) + pembrolizumab, progressed on prior CPI ≥2L HNSCC:** N=10 [3 SD, 7 PD]
- **Gastric/GEJ Expansion**
  - **ALX148 (10 mg/kg QW) + trastuzumab, ≥2L G/GEJ:** N=19 [4 PR (3 confirmed), 5 SD, 10 PD]
  - **ALX148 (10 mg/kg QW) + trastuzumab + chemo, ≥2L G/GEJ:** N=1 [1 PR, 2 NE# (PR, SD)]
  - **ALX148 (15 mg/kg QW) + trastuzumab + chemo, ≥2L G/GEJ:** N=1 [1 PR]
- **NSCLC Expansion**
  - **ALX248 (10 mg/kg QW) + pembrolizumab, ≥2L NSCLC:** N=20 [1 PR^, 9 SD, 10 PD]

Notes: *Based upon investigator assessed response using RECIST v1.1. All objective responses are unconfirmed as of the cut off date unless specified. #NE: Not Evaluable (clinical response presented in 2 patients who were not evaluable as of the data cut off). ^Initial PD followed by SD and subsequent PR in patient with TPS 0% who had received prior CPI therapy.

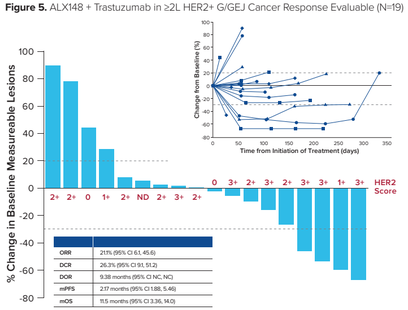
Figure 4. ALX148 + Pembrolizumab in ≥2L HNSCC Patients Response Evaluable (N=20)



	CPI Naive	CPI Naive + CPI Prior Therapy
ORR	40% (95% CI 12.2, 73.8)	20% (95% CI 5.7, 43.7)
DCR	50% (95% CI 18.7, 81.3)	30% (95% CI 11.9, 54.3)
DOR	4.31 months (95% CI NC, NC)	4.31 months (95% CI NC, NC)
mPFS	4.61 months (95% CI 0.53, 7.53)	2.07 months (95% CI 1.25, 5.53)
mOS	NC	15.5 months (95% CI 5.10, NC)
mFollow up	17.9 months (95% CI 13.6, 19.1)	17.9 months (95% CI 13.6, 19.1)

Notes: Data Cut off April 1, 2020. Response evaluable patients.

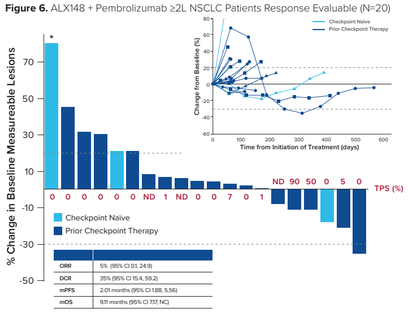
Figure 5. ALX148 + Trastuzumab in ≥2L HER2+ G/GEJ Cancer Response Evaluable (N=19)



ORR	21% (95% CI 6.1, 45.6)
DCR	26.3% (95% CI 91, 51.2)
DOR	9.38 months (95% CI NC, NC)
mPFS	2.17 months (95% CI 1.88, 5.46)
mOS	11.5 months (95% CI 3.36, 14.0)

Notes: Data Cut off April 1, 2020. Response evaluable patients. One patient with clinical progression not shown.

Figure 6. ALX148 + Pembrolizumab ≥2L NSCLC Patients Response Evaluable (N=20)



ORR	5% (95% CI 0.1, 24.9)
DCR	35% (95% CI 15.4, 59.2)
mPFS	2.01 months (95% CI 1.88, 5.56)
mOS	9.11 months (95% CI 7.17, NC)

Notes: Data Cut off April 1, 2020. Response evaluable patients. *Percent change greater than 80%.

Best Overall and Duration of Response in Patients Treated with ALX148 in Combination

Figure 7a. ≥2L HNSCC

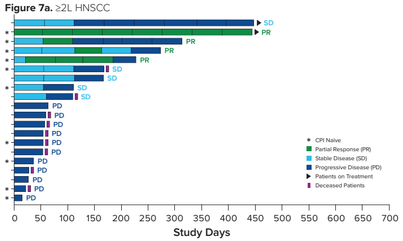


Figure 7b. ≥2L Gastric/GEJ

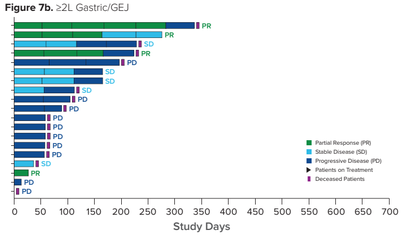


Figure 7c. ≥2L NSCLC

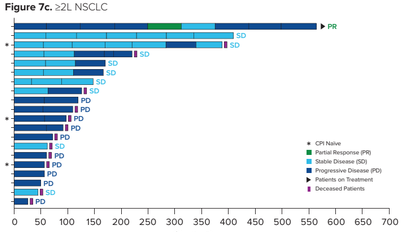
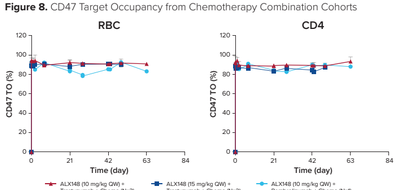
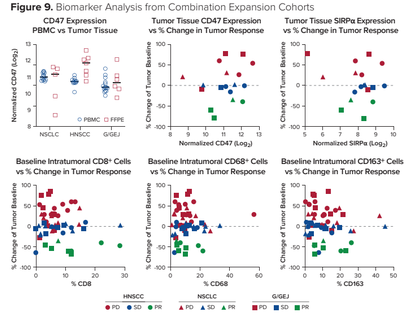


Figure 8. CD47 Target Occupancy from Chemotherapy Combination Cohorts



- Near complete CD47 target occupancy is maintained throughout ALX148 dosing interval when combined with chemotherapy-containing regimens.

Figure 9. Biomarker Analysis from Combination Expansion Cohorts



- CD47 and SIRPα gene expressions were assessed in a subset of PBMC and formalin-fixed paraffin-embedded (FFPE) tumor biopsy samples using NanoString analysis.
- CD8 (T cells), CD68 and CD163 (TAMs and myeloid cells) markers were assessed in FFPE tumor biopsy samples using immunohistochemistry (IHC) assays. Percent positive values for CD8, CD68 and CD163 were derived by image analysis.
- No correlation was observed between these baseline biomarkers and percent change in tumor size (target lesion) from baseline at time of biopsy, nor was a correlation observed with patients best overall response (not significant on Spearman nonparametric correlation).

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 displays a favorable exposure-safety relationship across the exposure ranges administered in the clinic with no exposure-dependent cytopenias observed.
- ALX148 demonstrates anti-cancer activity in combination with pembrolizumab in patients with ≥2L HNSCC that compares favorably to the pembrolizumab single agent experience; and in patients with NSCLC who are resistant/ refractory to prior CPI therapy.
- ALX148 demonstrates anti-cancer activity in combination with trastuzumab in HER2 positive Gastric/GEJ patients that have progressed on prior HER2 targeted therapies.
- Preliminary biomarker analysis suggest that baseline levels of CD47 and SIRPα gene expression and tumor infiltrating immune cell profiles are not associated with tumor response as measured by percent change of target lesion size from baseline.
- Preliminary data suggests that with low rates of cytopenias, ALX148 can be safety combined with chemotherapy containing regimens with near complete CD47 occupancy and encouraging initial activity in patients with 1L HNSCC and 2L Gastric/GEJ cancers.

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

References

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