Pharmacokinetic and Pharmacodynamic Characterization of ALX148, a CD47 Blocker, in Patients with Advanced Malignancy and Non-Hodgkin Lymphoma

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Background

- CD47, a marker of self, is upregulated by tumors to evade the immune system. CD47-SIRPα signaling represents a myeloid checkpoint mechanism in 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]
- 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]
- AT148001 (NCT03013218), 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).[3,4]

ALX148 Potential for Best in Class: Potency and Safety

- Potently and selectively binds CD47 to block its interaction with SIRPα.
- Picomolar binding affinity.
- Molecular weight is half the size of typical antibody allowing higher molar concentrations to be delivered to tumor.
- Fc domain is modified to eliminate binding to all Fc gamma receptors minimizing toxicity.
- Fc domain retains binding to the neonatal Fc receptor for pharmacokinetic half-life extension.
- ALX148 binds CD47 from human, monkey, rat, and mouse.

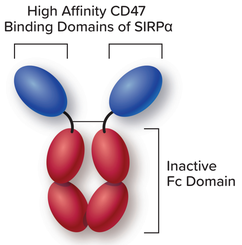
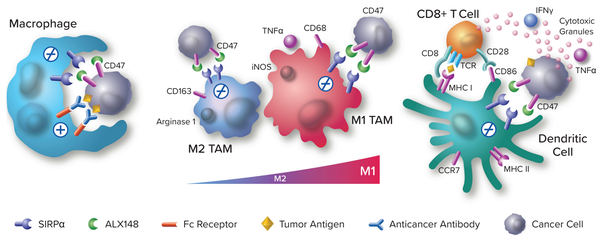


Figure 1. ALX148 is an intravenously administered fusion protein.

Mechanism of Action

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



Objective

- To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of ALX148 in patients with advanced solid tumors and lymphomas as a single agent and in combinations with pembrolizuab or trastuzumab.
- To conduct translational PK and PD modeling to estimate target occupancy (TO) in human tumors.

Methods

Study Design

Table 1. Study Design

Part 1: Single Agent ALX148

Cohort	Dose (mg/kg)	Schedule
1	0.3	Once a week
2	1.0	Once a week
3	3.0	Once a week
4	10.0	Once a week
5	30.0	Once every 2 weeks

Part 2: ALX148 (10 mg/kg QW) Combination Solid Tumor Cohorts

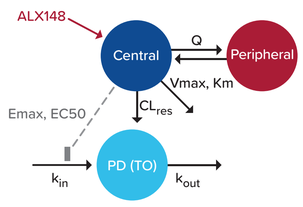
Dose Escalation	Advanced Solid Tumors (Each Combo)
Dose Expansion	NSCLC (pembrolizumab); Progressed on Prior CPI/ PD-L1 <50%
	HNSCC (pembrolizumab); Progressed on Prior Platinum Therapy
	Gastric/GEJ (trastuzumab); Progressed on Prior Fluoropyrimidine Therapy

PK/PD Analysis Methods

- Human PK and PD analytical methods:
  - PK bioanalytical method: ALX 148 serum concentrations were analyzed using a validated ligand binding ELISA.
  - PD (target occupancy-TO) assay: CD47 TO in peripheral blood T lymphocytes and erythrocytes was measured by a flow cytometry assay.
- Mouse PK and PD methods:
  - A single dose of ALX148 was administered via intraperitoneal injection in BALB/c mice implanted subcutaneously with CT26-M/H HER2 tumor cells.
  - At 1, 4, or 8 days after administration of ALX148, mice were euthanized; blood, spleen and tumors were removed for serum PK and CD47 TO assays.
  - ALX148 serum levels were measured using a ligand binding ELISA and CD47 TO on CD4+ T cells and HER2+ tumor cells was determined by a flow cytometry assay using labeled ALX148.
- PK and PD data analysis methods:
  - Noncompartmental analysis (NCA) was performed using Phoenix WinNonlin (v8.0 Certara USA, Inc., Princeton, NJ).
  - Clinical population PK/PD modeling analysis was performed using NONMEM (v7.3, ICON Development Solutions, Hanover, MD).
  - Preclinical PK/PD modeling analysis was performed using ADAPT 5 (Biomedical Simulations Resource, University of Southern California, Los Angeles, CA).

PK/PD Modeling Methods

Figure 3. Schematic Diagram of ALX148 PK/PD Model



- ALX148 PK described by a two compartment model with parallel linear and nonlinear clearance.
- ALX148 PD effect described by an indirect response model.
  - Drug concentration in central compartment inhibits input of PD (TO) signal.
  - PD data converted to % of baseline.

Results

ALX148 Concentration-Time Profiles

Figure 4. ALX148 Concentration-Time Profiles Following ALX148 IV Infusion as Single Agent

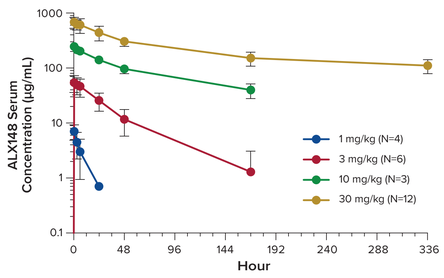
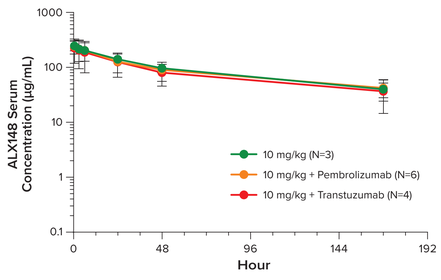


Figure 5. ALX148 Concentration-Time Profiles Following ALX148 IV Infusion at 10 mg/kg QW as Single Agent or in Combination



- Pembrolizumab: 200mg IV Q3W.
- Trastuzumab: 8 mg/kg IV followed by 6 mg/kg IV every Q3W.

ALX148 PK Parameters

Table 2. ALX148 PK Parameters Following IV Infusion at Cycle 1 Day 1 as Monotherapy

Parameters	Cohort 1 (0.3 mg/kg QW) N=2	Cohort 2 (1 mg/kg QW) N=4	Cohort 3 (3 mg/kg QW) N=6	Cohort 4 (10 mg/kg QW) N=3	Cohort 5 (30 mg/kg QoW) N=12
Cmax (µg/mL)	0.379 ± 0.192*	7.03 ± 2.17	54.5 ± 18.3	247 ± 32.5	701 ± 169
AUCinf (µg*h/mL)	N/A	48.5 ± 32.4	1830 ± 745	19700 ± 4940	101000 ± 31900
CL (mL/h/kg)	N/A	34 ± 31	1.9 ± 0.85	0.53 ± 0.12	0.33 ± 0.11
Vss (mL/kg)	N/A	150 ± 73	61 ± 19	60 ± 7.6	81 ± 20

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

Table 3. ALX148 PK Parameters Following IV Infusion (10 mg/kg) at Cycle 1 Day 1 as Monotherapy or Combination Therapies

Parameters	Cohort 4 (10 mg/kg QW) N=3	Pembrolizumab Combo (10 mg/kg QW) N=12	Trastuzumab Combo (10 mg/kg QW) N=8
Cmax (µg/mL)	247 ± 32.5	232 ± 61.9	237 ± 78.2
AUCinf (µg*h/mL)	19700 ± 4940	18500 ± 6710	17700 ± 6880
CL (mL/h/kg)	0.53 ± 0.12	0.60 ± 0.20	0.63 ± 0.22
Vss (mL/kg)	60 ± 7.6	73 ± 21	72 ± 20

- **ALX148 PK profiles showed a 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.**
- **ALX148 PK profiles (10 mg/kg QW) in combination with pembrolizumab or trastuzumab were not changed from that of a single agent.**

Pharmacodynamics

Figure 6. TO-Time Profiles Following ALX148 IV Infusion as Single Agent

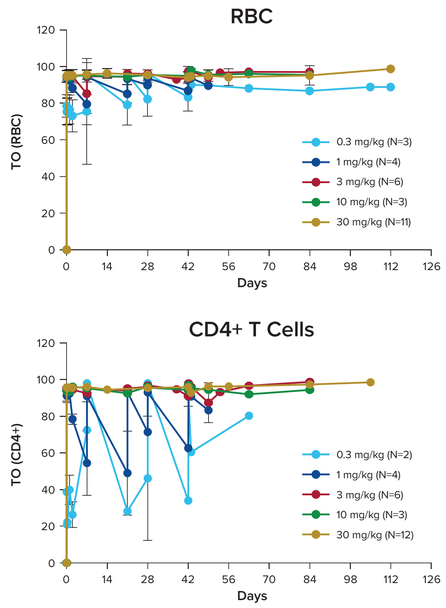
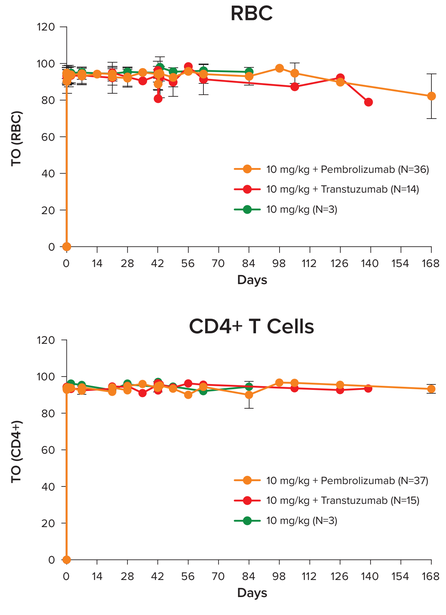


Figure 7. TO-Time Profiles Following ALX148 IV Infusion in Combination



- CD47 Target Occupancy (Cohorts 1-5): Near complete occupancy by ALX148 is maintained at ≥3 mg/kg QW.
- At 10 mg/kg, pharmacodynamic responses were comparable when ALX148 was given as monotherapy or in combination with pembrolizumab or trastuzumab.

Modeling Results: Representative PK and PD Fit Individual Subject

Figure 8. Representative Individual Fit vs Observed ALX148 PK Profiles

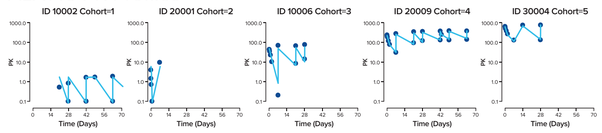
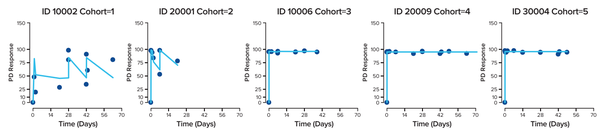


Figure 9. Representative Individual Fit vs Observed PD (CD4+) Profiles



Modeling Results: PK and PD Fit Diagnostic Plots

Figure 10. PK Fit Diagnostics

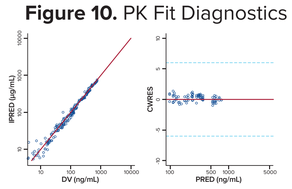
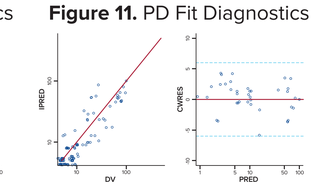


Figure 11. PD Fit Diagnostics

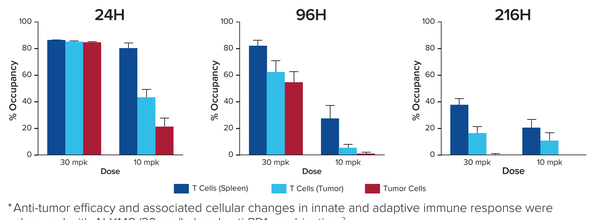


DV – Observed value; PRED – Population prediction; IPRED – Individual prediction; CWRES – Conditional weighted residual.

- **Overall, the diagnostic plots indicated good agreement between observed vs model predicted PK and PD results.**

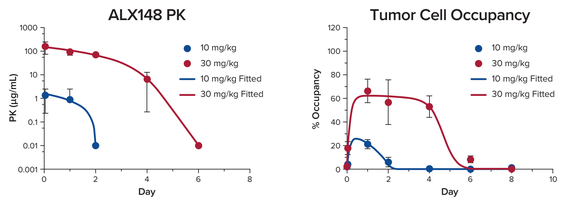
Translational PK/PD Modeling Based on Data Obtained in Tumor Bearing Mice

Figure 12. CD47 Occupancy in Tumor Bearing Mice Following a Single Intraperitoneal Injection of ALX148 at 10 or 30 mg/kg*



*Anti-tumor efficacy and associated cellular changes in innate and adaptive immune response were observed with ALX148 (30 mg/kg) and anti-PD1 combination.[2]

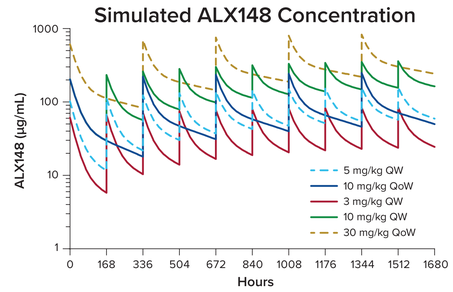
Figure 13. Modeled PK and PD (TO on Tumor Cell)



- **PK/PD modeling revealed a trend of potency shift for TO from peripheral blood to tumor cells. The magnitude of this shift was assumed and used to simulate human tumor TO based on human peripheral blood TO.**

PK Simulation

Figure 14. PK Simulation Based on Human Data Fitted Parameter



- Based on PK modeling, steady-state half-life of ALX148 at 10 mg/kg QW is predicted to be ~16 days.
- Tissue/tumor TO >70%, >80% and >90% were projected to be maintained at 3 mg/kg QW, 10 mg/kg QoW and 10 mg/kg QW in patients over the dosing interval, respectively.

Conclusions

- ALX148 exhibited clinical PK properties typical of antibody therapeutics directed towards cell-surface targets.
- ALX148 PK approached linear range and maintained complete peripheral TO over the dosing interval at ≥3 mg/kg QW.
- Translational PK/PD modeling suggests tissue/tumor TO over 70% being maintained over the dosing interval at ≥3 mg/kg QW.
- Initial data suggests ALX148 PK and PD profiles are not impacted by combination drugs.

References 1. Weiskopf, K. *Eur J Cancer.* 2017 May;76:100-109; 2. Kauder, SE. et al. *PLoS ONE.* 2018 August;13(8): e0201832; 3. Lakhani N et al, #3068, ASCO 2018. 4. Lakhani N et al, #P335, SITC 2018.

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