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

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Employment at ALX Oncology at the time the work was conducted.

Background

- CD47, a marker of self, is upregulated by tumors to evade the immune system. CD47-SIRPa signaling relays a mesodermal checkpoint mechanism in cancer.
- ALX148 is a fusion protein comprised of an engineered high affinity CD47 binding domain of SIRPa genetically linked to an inactive Fc region of human immunoglobulin (Figure 1).
- 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.1
- ATN8001 (NCT03033218), 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).1,4

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.

Mechanism of Action

Figure 2. ALX148 Bridges Innate and Adaptive Immunity Against Cancer1

PK/PD Analysis Methods

- Human PK and PD analytical methods:
- PK/BD analysis: ALX148 serum concentrations were analyzed using a validated liquid binding ELISA.
- PD parameters: Toxicity/toxicity AUC assay, CD47 T 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 CD266-Mab engineered 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 CD 47 TO assays.
- ALX148 serum levels were measured using a liquid 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 (V.0.2 Carina USA, Inc., Princeton, NJ).
- Clinical population PK/PD modeling analysis was performed using NONMEM (V.7.3, ICON Development Solutions, Hanover, MD).
- Preclinical PK/PD modeling analysis was performed using ADAPT (Biomedical Simulations Resource, University of Southern California, CA).

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

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

Modeling Results: Representative PK and PD Fit Individual Subject

Figure 8. Representative Individual Fit vs Observed ALX148 PK Profiles

Table 4. Representative PK and PD Fit Individual Subject

Modeling Results: PK and PD Fit Diagnostic Plots

Figure 9. Representative Individual Fit vs Observed PD (CD47) Profiles

Figure 10. PK Fit Diagnostics

Figure 11. PD Fit Diagnostics

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

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

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

PK Simulation

Figure 14. PK Simulation Based on Human Data Fitted Parameter

Simulated ALX148 Concentration

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: