A Phase 1 Study of ALX148: CD47 Blockade in Combination with Anti-Cancer Antibodies to Bridge Innate and Adaptive Immune Responses for Advanced Malignancy

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**Background**

- CD47, a marker of self, is upregulated by tumors to evade the immune system. CD47-SIRPa signaling represents a myeloid checkpoint mechanism in cancer. CD47 engages SIRPa and signals the macrophage to ignore the cell on which it is expressed.
- 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) that enhances the activity of anti-cancer targeted antibodies and checkpoint inhibitors through Fc-dependent and independent mechanisms.[1]

**ALX148: A Unique High Affinity SIRPa Fusion Protein**

- Potently and selectively binds CD47 to block its interaction with SIRPa.
- Picomolar binding affinity.
- Molecular weight is half the size of a 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.

**Study Design**

- **Part 2 Combination Key Inclusion Criteria**
  - Adequate organ function and hemoglobin ≥9 g/dL.
  - Dose Escalation Patient Cohorts with:
    - Advanced malignancy resistant to standard therapy or for which no standard therapy is available.
  - Dose Expansion Patient Cohorts with:
    - NSCLC (locally advanced or metastatic) which has progressed on prior checkpoint inhibitor therapy. OR with PD-L1 ≥50% that has progressed following systemic therapy.
    - HNSCC with disease progression after platinum-containing chemotherapy.
    - HER2 overexpressing metastatic gastric/gastric-oesophageal junction (GEJ) adenocarcinoma that has progressed following a fluoropyrimidine-containing regimen.

**Endpoints and Assessments**

- **Primary Endpoint:** Part 2: dose escalation first cycle ALX148 dose limiting toxicity (DLT) in combination with standard regimens of pembrolizumab and trastuzumab.
- Additional assessments across the Part 2 dose escalation and expansion portions include:
  - Adverse events characterization (NCI CTCAE v 4.03).
  - ALX148 pharmacokinetic parameters and CD47 target occupancy.
  - Investigator assessed tumor response (RECIST v1.1) every 8 weeks.
  - The data cut-off date for this analysis is 12/03/2018.

**Results**

**Patient Baseline Characteristics**

- 57 solid tumor patients have been enrolled into Part 2 (Table 2).
- Patients were well balanced between male (59%) and female (41%) with the majority (87%) having an ECOG PS score of 1.
- Patients were heavily pretreated with a median of 3 (1-8) prior regimens.
- The most common reason for discontinuation was disease progression.

**Response**

- NSCLC ALX148 + pembrolizumab: 13 evaluable pts with NSCLC (progressed on prior CPI and/or PD-L1 ≥50%) as of data cutoff Patients experienced a best response of PR, SD (one SD >24weeks) with 5 patients continuing on treatment.
- HNSCC ALX148 + pembrolizumab: 4 evaluable patients with HNSCC (progressed on platinum therapy) as of data cutoff Patients experienced a best response of SD (one with ≥15% in measurable disease) and continue on treatment.
- GEJ ALX148+Pembrolizumab (N=18) and ALX148+Trastuzumab (N=39) 9 patients continuing on treatment.

**References**


**Pharmacokinetics and Pharmacodynamics**

- ALX148 exhibited clinical PK properties typical of antibody therapeutics directed towards cell surface targets.
- ALX148 PK achieved linear range and maintained complete peripheral CD47 target occupancy over the dosing interval at ≥3 mg/kg QW.
- There was 1 grade 5 event (Disease progression in a pt with GEJ; gastric/GEJ adenocarcinoma that has progressed following a fluoropyrimidine-containing regimen).
- Additional assessments across the Part 2 dose escalation and expansion portions include:
  - ALX148 pharmacokinetic parameters and CD47 target occupancy.
  - Investigator assessed tumor response (RECIST v1.1) every 8 weeks.
  - The data cut-off date for this analysis is 12/03/2018.

**Methods**

**Part 1 (Single Agent):** Patients with advanced malignancy were administered escalating doses of intravenous ALX148.

**Part 2 (Combination):** Patients with advanced solid tumors were administered ALX148 10 mg/kg QW in a 3 week cycle with standard regimens of pembrolizumab (200 mg IV Q3W) or trastuzumab (8 mg/kg IV every 3 weeks).

**Table 1. Study Design**

**Table 2. AT148001: Patient Baseline Characteristics**

**Table 3. Patient Drug Exposure and Disposition**

**Table 4. Treatment Related Adverse Events in ≥2 Patients**

**Table 5. Treatment Related Adverse Events ≥ Grade 3 in Any Patient**

**AT148001 Safety: (Part 2, ALX148 + Pembrolizumab or Trastuzumab)**

**AT148001: Conclusions**

**Significant Tumor Reduction in a Patient with Gastroesophageal Junction (GEJ) Cancer Administered ALX148 + Trastuzumab**

- Prior therapy- TOLFUX/trastuzumab, pembrolizumab refractory
- Day 59 stable disease 47%
- Day 108 48% new central nervous system lesion
- The patient continues on treatment