A Phase 1/2 Study Evaluating the Efficacy and Safety of the Oral CXCR4 Inhibitor X4P-001 in Combination with Axitinib in Patients with Advanced Renal Cell Carcinoma


Background

Renal Cell Carcinoma and CXCR4

• A majority of patients with sporadic clear cell renal cell carcinoma (RCC) harbor VHL mutations, leading to increased vascular endothelial growth factor (VEGF) expression and tumor angiogenesis

• Multiple tyrosine kinase inhibitors (TKIs) targeting the VEGF signaling pathway, including axitinib, have been approved for the treatment of RCC, but most patients will eventually relapse through angiogenic escape.

• The CXCR4 chemokine receptor is also expressed by human tumors, including clear cell RCC, melanoma, and ovarian cancer, where it promotes angiogenesis and enhances tumor infiltration by myeloid-suppressor suppressor cells (MDSCs) and T regulatory cells (Tregs).

• Elevated expression of CXCR4 by RCC tumors is correlated with an overall poor prognosis

X4P-001

• X4P-001 is an orally available, selective, CXCR4 antagonist that allosterically inhibits receptor binding by CXCL12/SDF-1, the only known CXCR4 ligand.

• In melanoma patient biopsies, X4P-001 has been shown to increase both tumor-infiltration signature scores and CD8+ tumor ratio over time.

• X4P-001 in combination with axitinib has demonstrated greater than additive anti-tumor activity in xenograft RCC models.

• We hypothesize that X4P-001 combination therapy with axitinib will improve patient outcomes by reducing angiogenic escape and favorably modulating immune response to RCC tumors

Study Objectives

• Evaluate the safety and tolerability of X4P-001 in combination with axitinib in patients with advanced clear cell RCC

• Assess the clinical activity of X4P-001 + axitinib in patients with advanced clear cell RCC

• Investigate the effect of X4P-001 + axitinib on selected pharmacodynamic and RCC-related biomarkers

Study Design

Dose Escalation and Expansion Phases

Phase 1: Dose Escalation (N = 16)

1. X4P-001 200 mg QD

2. X4P-001 400 mg QD

3. X4P-001 600 mg QD

4. X4P-001 200 mg BID

5. X4P-001 600 mg QD

6. X4P-001 200 mg BID + axitinib 5 mg BID (N = 65 total pts treated at RP2D)

- This is a Ph 1/2, multi-center, open-label study of X4P-001 in combination with axitinib in patients with histologically confirmed clear cell RCC who have received at least 1 prior systemic therapy

- Safety analyses included 65 patients from Ph 1/2 that were treated with 400 mg X4P-001 (200 mg BID or 400 mg QD) + 5 mg BID axitinib

- Treatment responses were assessed using RECIST v1.1 every 8 weeks from Day 1 for 80 weeks and then every 12 weeks thereafter by blinded, independent central review

Key Eligibility Criteria

- ≥ 18 years of age

- Histologically confirmed diagnosis of clear cell RCC

- At least one prior treatment course

- ≥ 1 evaluable measurable target lesion within 28 days prior to CD1 by CT imaging

Exclusion:

- EOG performance status Grade ≥ 2

- Received a prior course of axitinib

- Class III or IV heart failure, uncontrolled hypertension

- History of active metastatic CNS disease

Safety

Adverse Events (All Grades ≥ 10% and Grade ≥ 3 in 2 or More Pts) Associated to X4P-001 or Axitinib (N = 65)

- Eight patients discontinued treatment due to treatment-related AEs (patients) and blood creatinine increased, diaphoresis, fatigue, hypotension, renal vein occlusion, and tracheo-oesophageal fistulae (patient each)

- The most common AEs (≥ 20%), regardless of relationship were:

  - Diarrhea (25 patients, 49%), decreased appetite (20 patients, 38%), decreased weight (9 patients, 18%), fatigue (6 patients, 11%), nausea (4 patients, 8%), dyspnea (4 patients, 8%), and fatigue (4 patients, 8%).

- Treatment-related serious AEs were:

  - Diarrhea, hypokalemia, and hypertension (2 patients, 3.1%), and blood creatinine increased, diaphoresis, and vomiting (3 patients each, 4.7%), weight decreased (13 patients, 20%), and creatinine increased (18 patients, 27%).

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Conclusions

- The combination of 400 mg QD X4P-001 + 5 mg BID axitinib was well-tolerated with a manageable safety profile

- Combination therapy with X4P-001 and axitinib shows preliminary evidence of clinical activity in advanced RCC patients

- The results suggest that X4P-001 may enhance clinical responses to axitinib and other TKIs that target tumor angiogenesis

Disclaimer:

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