Poster 4510

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

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Background

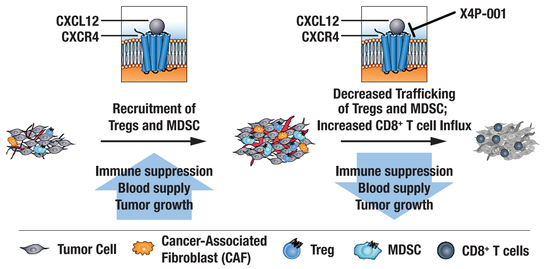
Renal Cell Carcinoma and CXCR4

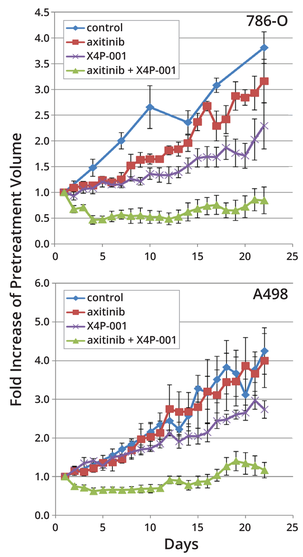
- A majority of patients with sporadic clear cell renal cell carcinoma (RCC) harbor *VHL* mutations, leading to increased vascular endothelial growth factor (VEGF) expression and tumor angiogenesis[1]
- Multiple tyrosine kinase inhibitors (TKIs) targeting the VEGF signaling pathway, including axitinib, have been approved for the treatment of RCC, but most patients will eventually relapse through angiogenic escape[2]
- 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-derived suppressor cells (MDSCs) and T regulatory cells (Tregs)[3,4,5]
- 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/SDF1-α, the only known CXCR4 ligand[6]
- In melanoma patient biopsies, X4P-001 has been shown to increase both tumor inflammation signature scores and CD8:FoxP3 ratios[7]
- X4P-001 in combination with axitinib has demonstrated greater than additive anti-tumor activity in xenograft RCC models[8]
- We hypothesize that X4P-001 combination therapy with axitinib will improve patient outcomes by reducing angiogenic escape and favorably modulating immune responses to RCC tumors

Figure 1: (below) Method of activation
Figure 2: (right) Effect of X4P-001 and axitinib on tumor growth in RCC mice xenograft models



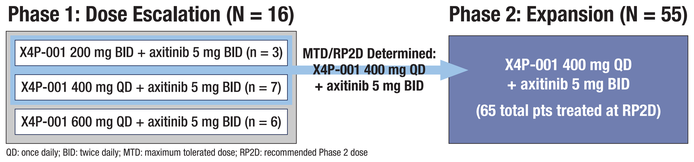


Study Objectives

- 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

Figure 3: Dose Escalation and Expansion Phases



QD: once daily; BID: twice daily; MTD: maximum tolerated dose; RP2D: recommended Phase 2 dose

- 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

Inclusion:
- ≥ 18 years of age
- Histologically confirmed diagnosis of clear cell RCC
- At least one prior treatment course
- ≥ 1 extra-renal measurable target lesion within 28 days prior to C1D1 by CT imaging

Exclusion:
- ECOG performance status Grade > 2
- Received a prior course of axitinib
- Class III or IV heart failure, uncontrolled hypertension
- History of active metastatic CNS disease

Demographic and Baseline Characteristics

X4P-001 + Axitinib (N = 65)		
Demographics		
Age (Years)	Median (Range)	63
	Range	41-87
Gender	Male	55 (85%)
	Female	10 (15%)
Ethnicity	Hispanic or Latino	6 (9%)
	Not Hispanic or Latino	59 (91%)
Race	Asian	17 (26%)
	Black or African American	2 (3%)
	White	44 (68%)
	Other	2 (3%)
ECOG Status	0	24 (37%)
	1	36 (55%)
	2	4 (6%)
	Unknown	1 (2%)
Baseline Characteristics		
Number of Prior Systemic Therapies	Median (Range)	2 (1-8)
	1	16 (25%)
	2	18 (28%)
	3	16 (25%)
	> 3	15 (23%)
Patients with previous checkpoint inhibitor therapy		30 (46%)
Patients with previous tyrosine kinase inhibitor therapy		59 (91%)
Patients with any prior nephrectomy		59 (91%)
Prognosis at Baseline based on Heng score	Favorable	11 (17%)
	Intermediate	44 (68%)
	Poor	10 (15%)

Clinical cut-off date: March 23, 2018

Patient Disposition

X4P-001 + Axitinib (N = 65)	
Treated	65 (100%)
Ongoing	33 (51%)
Discontinued	32 (49%)
Adverse Event	11 (17%)
Disease progression	19 (29%)
Clinical deterioration	1 (2%)
Withdrawal of consent	1 (2%)

Clinical cut-off date: March 23, 2018

- Eight patients discontinued treatment due to treatment-related AEs of hypertension (2 patients) and blood creatinine increase, diarrhea, fatigue, hyperkalemia, retinal vein occlusion, and sepsis/tracheo-oesophogeal fistula, (1 patient each)

Safety

Adverse Events (All Grades ≥ 10% and Grade ≥ 3 in 2 or More Pts) Related to X4P-001 or Axitinib (N = 65)		
Adverse Event (Related)	**All Grades**	**Grade ≥ 3**
Diarrhea	30 (46%)	4 (6%)
Decreased Appetite	25 (39%)	5 (8%)
Hypertension	21 (32%)	9 (14%)
Fatigue	20 (31%)	3 (5%)
Nausea	18 (28%)	3 (5%)
Dysphonia	14 (22%)	0
Blood Creatinine Increased	11 (17%)	1 (2%)
Dry Eye	11 (17%)	0
Hypothyroidism	10 (15%)	0
Vomiting	10 (15%)	0
Headache	9 (14%)	0
Weight decreased	9 (14%)	0
Dyspnoea	7 (11%)	0
Hyperkalemia	5 (8%)	3 (5%)
Hyponatraemia	2 (3%)	2 (3%)
Proteinuria	4 (6%)	2 (3%)

Clinical cut-off date: March 23, 2018

- X4P-001 + axitinib combination therapy was well-tolerated
- The most common AEs (≥ 20%, regardless of relationship) were diarrhea (32 patients, 49%), decreased appetite (27 patients, 42%), fatigue (24 patients, 37%), hypertension (22 patients, 34%), nausea (21 patients, 32%), headache (17 patients, 26%), cough (16 patients, 25%), blood creatinine increased, dysphonia, and vomiting (15 patients each, 23%), weight decreased (13 patients, 20%)
- Treatment-related serious AEs were diarrhea, hyperkalemia, and hypertension (2 patients, 3%), and blood creatinine increased, nausea, sepsis, and tracheo-oesophageal fistula (1 patient each, 1.5%)

Preliminary Efficacy

Best Response* in Clinically Evaluable** Patients (N = 47)	
Complete Response (CR)	1 (2%)
Partial Response (PR)	10 (21%)
Stable Disease (SD)	27 (57%)
Progressive Disease (PD)	9 (19%)
Objective Response Rate (CR + PR)	23%

Clinical cut-off date: March 23, 2018
* Based on RECIST 1.1 criteria
** Response data from central review is currently pending for remaining 18 pts

- Thirteen patients remain on study ≥ 24 weeks
- The median duration on treatment was 16 weeks (range 2-96)

Figure 4: Best response in target lesion size

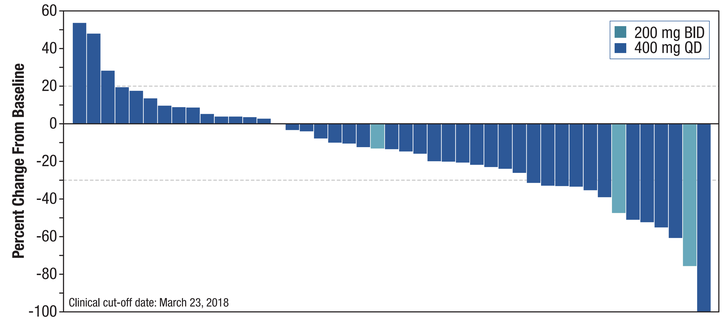
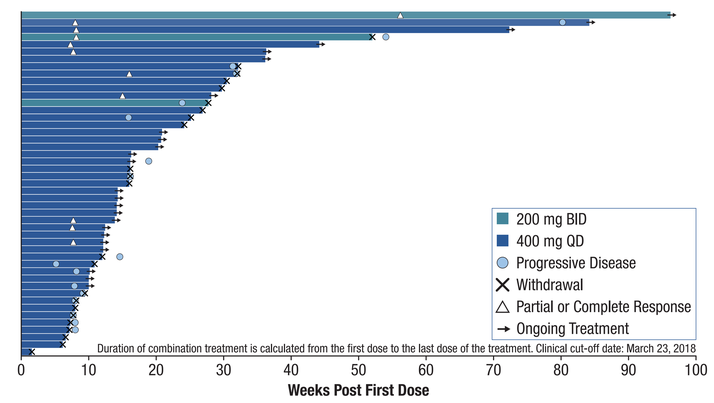


Figure 5: Duration of combination treatment



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

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