A Phase 1 Dose Finding Study of X4P-001 (An Oral CXCR4 Inhibitor) and Axitinib in Patients with Advanced Renal Cell Carcinoma

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Background

- Agents directed against the vascular endothelial growth factor (VEGF) pathway demonstrate initial clinical benefit in patients (pts) with advanced clear cell renal cell carcinoma (ccRCC), but pts often experience relapse and progression after initial treatment.[1, 2]
- Acquired resistance to the VEGF-targeted tyrosine kinase inhibitors (TKIs) is associated with a marked increase in the infiltration of CD11b+/Gr-1+ myeloid-derived suppressor cells (MDSCs), which express CXCR4. Hypoxia induced by VEGFR TKIs promotes production of SDF-1/CXCL12, the ligand of CXCR4 (Figure 1).[2, 3]
- Axitinib, an inhibitor of VEGF receptors 1–3 (VEGFR), is approved for treatment of advanced RCC after failure of one prior systemic therapy.[4, 5]
- X4P-001 is an orally bioavailable, selective, allosteric inhibitor of the chemokine receptor CXCR4, and has been shown in pre-clinical models to down-regulate hypoxia inducible factor-2 (HIF-2) and MDSC trafficking in the tumor microenvironment (Figure 1).[3]
- Data from multiple RCC xenograft models reveals that the addition of X4P-001 to axitinib results in greater-than-additive anti-tumor activity (Figure 2).[3]

Figure 1. X4P-001 treatment alters tumor microenvironment

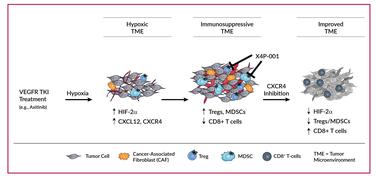
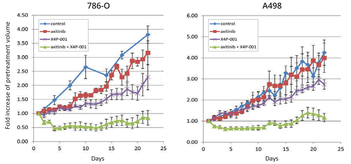


Figure 2. Effect of X4P-001 and/or axitinib on tumor growth in RCC mice xenograft models



Primary Objectives

- Evaluate the safety and tolerability of X4P-001 in combination with axitinib in pts with ccRCC.
- Establish the maximum tolerated dose (MTD) and recommended Phase (Ph) 2 dose (RP2D).

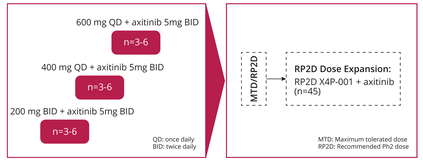
Secondary Objective

- Assess the clinical activity of X4P-001 in combination with axitinib using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Study Design

- This is an ongoing, Ph 1/2, multi-center, open-label study of X4P-001 in combination with axitinib in pts with histologically confirmed ccRCC who have received ≥1 prior systemic therapy (Figure 3).
- In the Ph 1 portion, pts received increasing doses of X4P-001 in combination with the approved dose of axitinib (5 mg BID) using the 3+3 dose escalation method.
- The starting dose was chosen based on predicted efficacious dose from prior healthy volunteer study data.[6]
- Dose-limiting toxicities (DLTs) were defined as X4P-001-related adverse events (AEs) that are ≥ grade 3 or prevent the administration of at least 75% of the intended dose of either drug during the first 28 days of treatment.

Figure 3. Study design schema



Key inclusion criteria:

- ≥ Eighteen years of age
- Histologically confirmed diagnosis of predominant ccRCC
- Received at least one prior course of treatment for ccRCC
- Have at least one extra-renal measurable target lesion meeting the criteria of RECIST v1.1

Key exclusion criteria:

- Eastern Cooperative Oncology Group (ECOG) performance status Grade >2
- New York Heart Association Class III or IV heart failure or uncontrolled hypertension
- Received a prior course of axitinib
- Received mammalian target of rapamycin (mTOR) inhibitor(s) as their only prior treatment for ccRCC
- Current evidence of active intracranial (CNS) metastatic RCC

Assessments

- Safety endpoints include AEs, clinical observations (e.g., vital signs, physical examination), laboratory tests, ECGs, and ophthalmologic examination.
- Response was assessed using RECIST v1.1 every 8 weeks by blinded, independent central review.

Demographics and Baseline Characteristics

- As of July 3, 2017, sixteen pts have been enrolled in the Ph 1 portion of the study (Table 1).
- Patients had received a median of 2 prior lines of systemic therapy (range 1-5).
  - Among 16 pts, 5 pts (31%) had 1 line and 11 pts (69%) had ≥ 2 lines of prior systemic therapies.
- Among 16 pts, 15 pts had VEGFR TKI and 8 pts had check point inhibitor as a prior treatment.

Table 1. Demographics and baseline characteristics

		AXITINIB+X4P-001 200mg BID (n=3)	AXITINIB+X4P-001 400mg QD (n=7)	AXITINIB+X4P-001 600mg QD (n=6)	Total (n=16)
Age (years)	n	3	7	6	16
	Mean (SD)	58.7 (6.66)	68.3 (4.11)	61.5 (9.05)	63.9 (7.53)
	Median (min, max)	62.0 (51,63)	69.0 (63,74)	60.0 (50,76)	63.5 (50,76)
Gender	Male	3 (100.0%)	6 (85.7%)	6 (100.0%)	15 (93.8%)
	Female	0	1 (14.3%)	0	1 (6.3%)
Ethnicity	Hispanic or Latino	0	1 (14.3%)	0	1 (6.3%)
	Not Hispanic or Latino	3 (100.0%)	6 (85.7%)	6 (100.0%)	15 (93.8%)
Race	White	3 (100.0%)	7 (100.0%)	6 (100.0%)	16 (100.0%)
Screening ECOG Status	0	1 (33.3%)	3 (42.9%)	4 (66.7%)	8 (50.0%)
	1	2 (66.7%)	4 (57.1%)	2 (33.3%)	8 (50.0%)

Patient Disposition

- As of July 3, 2017, 9 (56.3%) pts have been discontinued from the study (Table 2).
- Among 5 pts who discontinued from the study due to AEs (non-DLT), 3 pts had treatment-related AEs (1 case of colitis after the first cycle and 2 cases of anxitinib-related hypertension), and 2 pts had AEs deemed unrelated to treatment.

Table 2. Patient disposition

	AXITINIB+X4P-001 200mg BID (n=3)	AXITINIB+X4P-001 400mg QD (n=7)	AXITINIB+X4P-001 600mg QD (n=6)	Total (n=16)
Study Discontinued/Completed	2 (66.7%)	3 (42.9%)	4 (66.7%)	9 (56.3%)
On Study	1 (33.3%)	4 (57.1%)	2 (33.3%)	7 (43.8%)
Reason for Completion/Discontinuation				
Completion	0	0	0	0
Adverse event (NON-DLT)	1 (50.0%)	3 (100%)	1 (25.0%)	5 (55.6%)
Death	0	0	0	0
Disease progression	1 (50.0%)	0	1 (25.0%)	2 (22.2%)
DLT	0	0	2 (50.0%)	2 (22.2%)

Note: The percentage of each reason for completion/discontinuation is calculated based on total number of subjects who discontinued/completed the study.

MTD and RP2D Determination

- Two dose limiting toxicities (DLTs) were observed at the X4P-001 600 mg QD dose level.
  - One pt had multiple grade (G) 2 AEs, including abnormal loss of weight, asthenia, cognitive disorder, decreased appetite, somnolence, and vomiting, resulting in <75% drug intake during the initial 28 days.
  - One pt had G3 dyspnea and fatigue.
- The MTD/RP2D was determined to be 400 mg QD of X4P-001 + 5 mg BID of axitinib.

Safety

- Treatment related AEs (≥ 10%) of any grade were listed in Table 3.
- Treatment related G3/4 AEs (≥ 10%) were fatigue and hypertension (Table 3).
- In addition, one incidence each of Grade 3 acidosis, colitis, dehydration, dyspnea and hyperkalemia was reported.
- Treatment related SAEs included hypertension (2 cases) and colitis, diarrhea, nausea (1 case each).
- No Grade 4 or 5 AEs occurred.

Table 3. Treatment-related AEs (>10%) with G3 incidence

	AXITINIB+X4P-001 200 mg BID (n=3)		AXITINIB+X4P-001 400 mg QD (n=7)		AXITINIB+X4P-001 600 mg QD (n=6)		Total (n=16)	
	All	Grade 3	All	Grade 3	All	Grade 3	All	Grade 3
n (%)								
Diarrhea	3 (100%)	0	3 (42.9%)	1 (14.3%)	2 (33.3%)	0	8 (50.0%)	1 (6.3%)
Hypertension	2 (66.7%)	1 (33.3%)	3 (42.9%)	2 (28.6%)	3 (50.0%)	1 (16.7%)	8 (50.0%)	4 (25.0%)
Fatigue	2 (66.7%)	1 (33.3%)	1 (14.3%)	0	4 (66.7%)	1 (16.7%)	7 (43.8%)	2 (12.5%)
Nausea	2 (66.7%)	1 (33.3%)	1 (14.3%)	0	3 (50.0%)	0	6 (37.5%)	1 (6.3%)
Headache	3 (100%)	0	1 (14.3%)	0	1 (16.7%)	1 (16.7%)	5 (31.3%)	1 (6.3%)
Decreased appetite	2 (66.7%)	1 (33.3%)	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	1 (6.3%)
Vomiting	2 (66.7%)	0	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	0
Abnormal loss of weight	2 (66.7%)	0	1 (14.3%)	0	0	0	3 (18.8%)	0
Dry eye	1 (33.3%)	0	1 (14.3%)	0	1 (16.7%)	0	3 (18.8%)	0
Dysphonia	2 (66.7%)	0	1 (14.3%)	0	0	0	3 (18.8%)	0
Proteinuria	1 (33.3%)	1 (33.3%)	1 (14.3%)	0	1 (16.7%)	0	3 (18.8%)	1 (6.3%)
Blood creatinine increased	1 (33.3%)	0	0	0	1 (16.7%)	0	2 (12.5%)	0
Cognitive disorder	1 (33.3%)	0	0	0	1 (16.7%)	0	2 (12.5%)	0
Dry mouth	1 (33.3%)	0	0	0	1 (16.7%)	0	2 (12.5%)	0
Dysgeusia	0	0	1 (14.3%)	0	1 (16.7%)	0	2 (12.5%)	0
Lipase increased	1 (33.3%)	0	0	0	1 (16.7%)	0	2 (12.5%)	0
Palmar-plantar erythrodysesthesia	1 (33.3%)	0	0	0	1 (16.7%)	0	2 (12.5%)	0
Stomatitis	1 (33.3%)	1 (33.3%)	0	0	1 (16.7%)	0	2 (12.5%)	1 (6.3%)

Safety analysis set (n=16)

Preliminary Efficacy

- Among the 12 response evaluable pts in the Ph 1 portion of the study, the objective response rate (ORR) and disease control rate (DCR) are 25% and 92%, respectively (Table 4).
- Median duration on treatment was 103 days (range 11-393).
- Seven pts (43.8%) have been exposed to study treatment for more than 24 weeks.

Table 4. Best overall response[a]

Response Outcomes, n=12[b]	n (%)
Best overall response	
Complete Response (CR)	0
Partial Response (PR)	3 (25%)
Stable Disease (SD)	8 (67%)
Progressive Disease (PD)	1 (8%)
ORR	3 (25%)
DCR (CR + PR + SD)	11 (92%)

[a]Response was assessed using RECIST v1.1
[b]Response evaluable pt is defined as a pt who has had at least one post-treatment tumor assessment. Four pts were non-response evaluable: 2 pt discontinued due to AEs; 1 pt is on study and has not had the 1st scan yet; 1 pt has no target lesions

Figure 4. Best reponse in target lesion size

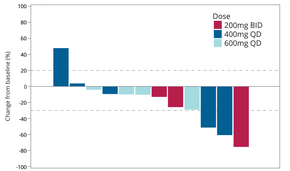
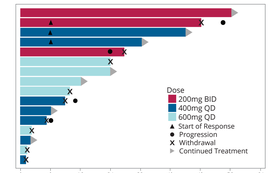


Figure 5. Duration of treatment



Conclusions

- The MTD and RP2D of the combination is 400 mg QD of X4P-001 + 5 mg BID of axitinib.
- The combination was well tolerated at the RP2D with manageable AEs. The most common AEs were diarrhea, hypertension, fatigue, nausea, headache, decreased appetite, and vomiting.
- Preliminary evidence of clinical activity has been observed.
- Enrollment in the Ph 2 portion of this study is ongoing.

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Disclosures

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This study is on-going. Data presented here is based upon a data cut-off date of July 03, 2017.

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