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

- X4P-001 is an orally bioavailable, selective, allosteric inhibitor of the chemokine receptor CXCR4.
- Axitinib, an inhibitor of VEGF receptors 1–3 (VEGFR), is approved for treatment of advanced RCC after failure of one prior systemic therapy.[1]
- X4P-001 has demonstrated greater-than-additive anti-tumor activity with axitinib in multiple RCC xenograft models.[2]
- The starting dose in this study was chosen based on predicted efficacious dose from the pharmacokinetic (PK) – pharmcodynamic (PD) correlation established in healthy volunteers. The concentration that gives half maximal response (EC50) for white white blood cell (WBC) mobilization is estimated at 39 ng/ml (95% CI, 28 to 50 ng/ml).[3]
- We have previously reported early findings from the Phase 1 portion of this study.[4] Here we report updated safety and preliminary efficacy results as well as PK and PD results.

Primary Objectives

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

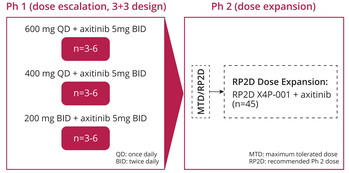
Secondary Objectives

- Assess the clinical activity of X4P-001 in combination with axitinib using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Characterize the PK and PD (e.g., circulating CD34+ cells and/or total WBC) with escalating dose levels of X4P-001.

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 at least 1 prior systemic therapy (Figure 1).

Figure 1. 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:

- 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 adverse events (AEs), clinical observations (e.g., vital signs, physical examination), laboratory tests, ECGs, and ophthalmologic examination.
- PK and PD sampling was performed from 0–4 hr on Cycle 1 Day 1 (C1D1) and from 0–8 hr on Cycle 1 Day 15 (C1D15).
- Response was assessed using RECIST v1.1 every 8 weeks by blinded, independent central review.

Demographics and Baseline Characteristics

- As of August 1, 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 checkpoint inhibitor as a prior treatment.

Table 1. Patient 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 August 1, 2017, 9 (56.3%) pts have been discontinued from the study (2 pts due to dose limiting toxicity (DLT), 2 pts due to disease progression, and 5 pts due to AEs).
  - 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.
- Median duration on treatment was 155 days (range 11–488).
- Seven pts (43.8%) have been exposed to study treatment for more than 24 weeks.

Note: 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.

MTD and RP2D Determination

- 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 are listed in Table 2 (as August 1, 2017).
- Treatment related G3/4 AEs (≥ 10%) were fatigue and hypertension (Table 2).
- In addition, one incidence each of Grade 3 acidosis, colitis and dyspnea was reported.
- Treatment related SAEs included hypertension (2 cases), colitis, diarrhea and nausea (1 case each).
- No Grade 4 or 5 AEs occurred.
- Between August 1 – October 2, 2017 there were no new grade 3 or higher AEs.

Table 2. Treatment-related AEs (>10%)

	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 (%)								
Hypertension	2 (66.7%)	1 (33.3%)	5 (71.4%)	2 (28.6%)	3 (50.0%)	1 (16.7%)	10 (62.5%)	4 (25.0%)
Diarrhea	3 (100.0%)	0	4 (57.1%)	1 (14.3%)	2 (33.3%)	0	9 (56.3%)	1 (6.3%)
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%)	2 (28.6%)	0	3 (50.0%)	0	7 (43.8%)	1 (6.3%)
Decreased appetite	2 (66.7%)	1 (33.3%)	2 (28.6%)	0	1 (16.7%)	0	5 (31.3%)	1 (6.3%)
Headache	3 (100.0%)	0	1 (14.3%)	0	1 (16.7%)	1 (16.7%)	5 (31.3%)	1 (6.3%)
Dry eye	1 (33.3%)	0	2 (28.6%)	0	2 (33.3%)	0	5 (31.3%)	0
Proteinuria	1 (33.3%)	1 (33.3%)	2 (28.6%)	0	1 (16.7%)	0	4 (25.0%)	1 (6.3%)
Abnormal loss of weight	2 (66.7%)	0	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	0
Palmar-plantar erythrodysaesthesia	2 (66.7%)	0	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	0
Vomiting	2 (66.7%)	0	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	0
Lipase increased	2 (66.7%)	0	1 (14.3%)	0	1 (16.7%)	0	4 (25.0%)	0
Blood creatinine increased	2 (66.7%)	0	0	0	1 (16.7%)	0	3 (18.8%)	0
Stomatitis	1 (33.3%)	1 (33.3%)	1 (14.3%)	0	1 (16.7%)	0	3 (18.8%)	1 (6.3%)
Arthralgia	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
Dizziness	0	0	2 (28.6%)	0	0	0	2 (12.5%)	0
Hyperkalaemia	1 (33.3%)	1 (33.3%)	1 (14.3%)	0	0	0	2 (12.5%)	1 (6.3%)
Alanine aminotransferase increased	0	0	1 (14.3%)	0	1 (16.7%)	0	2 (12.5%)	0
Dehydration	1 (33.3%)	1 (33.3%)	1 (14.3%)	0	0	0	2 (12.5%)	1 (6.3%)
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
Myalgia	0	0	0	0	2 (33.3%)	0	2 (12.5%)	0
Rash	2 (66.7%)	0	0	0	0	0	2 (12.5%)	0

Safety analysis set (n=16)

Preliminary Efficacy

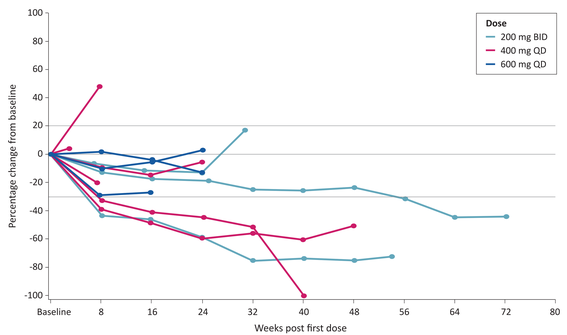
- As of October 2, 2017, the objective response rate (ORR) and disease control rate (DCR) are 28.6% and 92.9%, respectively among the 14 response-evaluable pts (Table 3).

Table 3. Best overall response[a]

Response Outcomes, n=14[b]	n (%)
Best overall response	
Complete Response (CR)[c]	1 (7.1%)
Partial Response (PR)	3 (21.4%)
Stable Disease (SD)	9[d] (64.3%)
Progressive Disease (PD)	1 (7.1%)
Not Evaluable (NE)	0
ORR	4 (28.6%)
DCR (CR + PR + SD)	13 (92.9%)

[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. 2 pts were non-response evaluable: 1 pt discontinued due to AE and another pt has not had 1^{st} scan result yet.
[c] 1 CR is confirmed after the cut-off date.
[d] 1 pt had only a non-target lesion at baseline and is considered to have stable disease after treatment.

Figure 2. Target lesion response over time



Pharmacokinetics & Pharmacodynamics

- Drug exposure (AUC_{0-24hr}) at steady state (SS) was measured on C1D15 and were similar for 200 mg BID and 400 mg QD dose. Mean C_{max} and AUC_{0-24hr} at SS increased approximately 1.6- and 1.9-fold, respectively, from 400 mg to 600 mg QD dose (Figure 3, Table 4).
- At 400 mg QD dose, mean C_{max} at SS is 112 ng/mL, which is ≥ EC50 for WBC mobilization of 39 ng/mL.
- On C1D1 at both 400 mg and 600 mg daily dose levels, X4P-001 demonstrated approximately 2 to 2.5-fold average increase from baseline of WBC (range: 1.7-4.7 fold) and 2.5 to 4-fold average increase from baseline of CD34+ progenitor cells (range: 2.0-6.9 fold).
  - The peak increase of both PD markers occurred around 2 to 4 hours following dosing on Day 1 (Figure 4).

Table 4. PK Parameters of X4P-001 at SS [Geometric mean (CV%)]

Dose of X4P-001	n	T_{max}* (hr)	C_{max} (ng/mL)	AUC_{tau}** (ng*hr/mL)
200 mg BID	2	3 (3-3)	831 (8)	3218 (26)
400 mg QD	5	3 (1-3)	2500 (35)	11572 (48)
600 mg QD	5	2 (0.5-4)	3905 (61)	20680 (59)

These are preliminary results based on nominal time calculation.
*Median (Range) ** AUC_{tau}: AUC_{0-12hr} for BID and AUC_{0-24hr} for QD dose regimens.
One PK outlier at 400 mg QD dose is not included in the summary analysis.

Figure 3. X4P-001 Concentration-time profile on Day 1 and at steady state

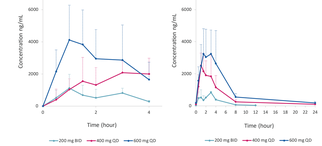
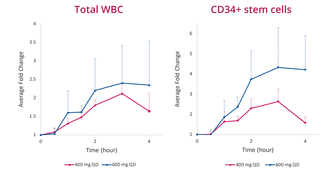


Figure 4. Pharmacodynamic change relative to baseline on Cycle 1 Day 1



Note: Samples from 9 patients had adequate viable cells for analysis.

Conclusions

- The Phase 1 portion of this study shows that X4P-001 plus axitinib is clinically active in patients with advanced RCC that have received at least one prior line of therapy.
  - The ORR was 29% and the DCR was 93%.
  - 69% of patients had ≥ 2 lines of prior systemic therapies.
- The 400 mg QD dose is biologically active in inhibiting CXCR4 as demonstrated by elevated WBCs and CD34+ cells, which are known pharmacodynamic biomarkers of CXCR4 antagonists.
- The MTD and RP2D of the combination is 400 mg QD of X4P-001 + 5 mg BID of axitinib; the combination was generally well tolerated at the RP2D with manageable AEs.
  - The most common AEs (>25%) were hypertension, diarrhea, fatigue, nausea, decreased appetite, headache and dry eye.
- Mean C_{max} and AUC_{0-24hr} at SS increased approximately 1.6- and 1.9-fold, respectively, from 400 mg to 600 mg QD dose. AUC_{0-24hr} is similar for 200 mg BID and 400 mg QD dose.
- 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. Safety and tolerability data presented here is based upon a data cut-off date of August 1, 2017 and efficacy data cut-off date of October 2, 2017.

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