# Safety and Efficacy of the Oral CXCR4 Inhibitor X4P-001 + Axitinib in Advanced Renal Cell Carcinoma Patients: An Analysis of Subgroup Responses by Prior Treatment

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## Background

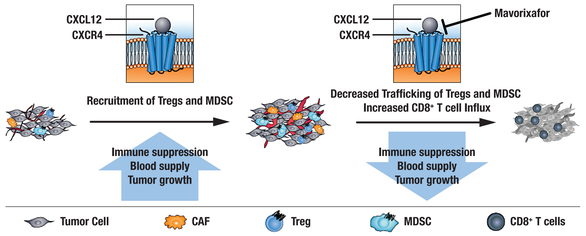
### Renal Cell Carcinoma and CXCR4

- Approximately 70% of sporadic clear cell renal cell carcinoma (RCC) patients have a loss of VHL gene function that drives tumor angiogenesis by increasing VEGF receptor expression[1]
- A number of tyrosine kinase inhibitors (TKIs) that target the VEGF pathway have been approved for RCC, including axitinib, although most patients will eventually relapse through angiogenic escape[2]
- Multiple observations implicate the CXCL12/CXCR4 chemokine signaling axis in contributing to the lack (or loss) of tumor responsiveness to angiogenesis inhibitors[3,4]
- CXCR4 is expressed by human tumors, including clear cell RCC, melanoma, and ovarian cancer, and can promote angiogenesis and enhance tumor infiltration by myeloid-derived suppressor cells (MDSCs) and T regulatory cells (Tregs)[5-7]
- Elevated expression of CXCR4 by RCC tumors is correlated with an overall poor prognosis

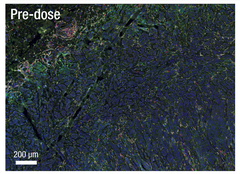
### X4P-001

- X4P-001 (mavorixafor) is an orally available, selective, CXCR4 antagonist that allosterically inhibits receptor binding by CXCL12/SDF1-α, the only known CXCR4 ligand[8]
- Single-agent chronic treatment with 400 mg QD of mavorixafor has been shown to be well-tolerated with only Grade 1 treatment-related AEs in a Phase 2 study of WHIM patients[9]
- Biopsies from melanoma patients treated with mavorixafor show enhanced immune cell tumor infiltration and activation leading to increases in both tumor inflammation signature scores and IFN-γ gene expression signatures[10]
- In mouse xenograft RCC models, treatment with mavorixafor in combination with axitinib demonstrates greater than additive anti-tumor activity[11]

**Figure 1:** Method of activation




## Mavorixafor Increases Tumor Immune Cell Infiltration and Activation



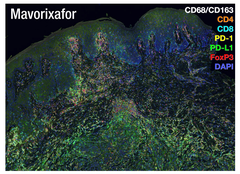
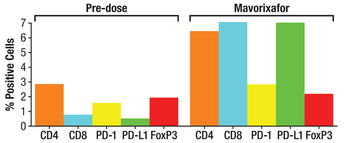




**Figure 2:** Increased CD8/FoxP3 Ratio and PD-L1 Post-Mavorixafor Treatment



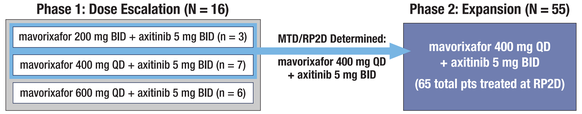

- Multiplex immunohistochemistry staining of tumor samples from a melanoma patient treated with 400 mg QD mavorixafor monotherapy. Biopsy samples obtained pre-dose and after 3 weeks of mavorixafor monotherapy were immunostained with an antibody panel and analyzed using HALO™ image analysis software (ClinicalTrials.gov Identifier: NCT02823405)

## Study Objectives

- Evaluate the safety and tolerability of mavorixafor in combination with axitinib in patients with advanced clear cell RCC
- Assess the clinical activity of mavorixafor + axitinib in patients with advanced clear cell RCC using RECIST v1.1 criteria
- Investigate clinical responses to combination therapy among patient subgroups according to immediate prior therapy

## Study Design

**Figure 3:** Dose Escalation and Expansion Phases




- This is a Phase 1/2, multi-center, open-label study of mavorixafor 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 Phases 1/2 that were treated with 400 mg mavorixafor (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

**Inclusion Criteria:**

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

**Exclusion Criteria:**

- 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

| Mavorixafor + Axitinib (N = 65) | | | | | |
|---|---|---|---|---|---|
| **Demographics** | | | **Baseline Characteristics** | | |
| Age (Years) | Median (Range) | 64 | Number of Prior Systemic Therapies | Median (Range) | 2 (1-8) |
| | Range | 42-87 | | 1 | 16 (25%) |
| Gender | Male | 55 (85%) | | 2 | 18 (28%) |
| | Female | 10 (15%) | | ≥3 | 31 (48%) |
| Ethnicity | Hispanic or Latino | 7 (11%) | Patients with: | Previous CPI therapy | 31 (48%) |
| | Not Hispanic or Latino | 58 (89%) | | Previous TKI therapy | 59 (91%) |
| Race | Asian | 17 (26%) | | Previous IO therapy | 39 (60%) |
| | Black / African American | 2 (3%) | | Any prior nephrectomy | 59 (91%) |
| | White | 43 (66%) | Prognosis at Baseline based on Heng score | Favorable | 8 (12%) |
| | Other | 3 (5%) | | Intermediate | 45 (69%) |
| ECOG Status | 0 | 25 (39%) | | Poor | 12 (19%) |
| | 1 | 36 (55%) | | | |
| | 2 | 4 (6%) | | | |

Clinical cut-off date: August 27, 2019

**COI Statements:** **DM:** Advisory/Consultancy: Array BioPharm, BMS, Eisai, Eli Lilly, EMD Serono, Exelixis, Genentech BioOncology, Jounce Therapeutics, Merck, Novartis, Pfizer. Research grant/Funding (institution): BMS, Prometheus Laboratories. **TH:** Advisory/Consultancy: Amgen, Array, Bayer Cardinal Health, Castle Biosciences, Eisai, Exelixis, Ipsen, Jansen, Novartis, Roche Diagnostics, Pfizer, Sanofi. Research Funding: Novartis. **BK:** Advisory/Consultancy: AstraZeneca, Genexine, MSD. Research funding (self): AstraZeneca, MSD, ONO. **RJ:** Advisory/Consultancy: Array, BMS, Merck. **WS:** Advisory/Consultancy: Astra-Zeneca, Bayer, BMS, Caremark/CVS, Clovis, Eisai, Genentech, Merck, Pfizer, Sotio. Speakers Bureau: Applied Clinical Education, CME providers (sponsorship unknown), Dava Oncology, Global Academy for Medical Education, OncLive, PeerView, Vindico. Research grant/Funding (institution): Abbvie, Astra-Zeneca, Astellas (Medivation), Bayer, Bristol-Myers-Squibb, Boehringer-Ingelheim, Calithera, Clovis, Eisai, Exilixis, Genentech (Roche), Johnson & Johnson (Janssen), Merck, Novartis, Pfizer, Seattle Genetics, Tesaro, X4 Pharmaceuticals. **JP:** Advisory/Consultancy: NovoNordisk, Sanofi. Research grant/Funding (institution): Agensys, BioClin Therapeutics, EFFECTOR Pharmaceuticals, Endocyte, Innocrin Pharmaceuticals, Mirati Therapeutics, Rexahn Pharmaceuticals, Seattle Genetics, Tracon Pharmaceuticals. **YZ:** Advisory/Consultancy: Amgen, Array, Bayer, Castle Bioscience, Eisai, Exelixis, Jansen, Novartis, Pfizer, Roche Diagnostics. **LG:** Employment: X4 Pharmaceuticals. **MA:** Advisory/Consultancy: Acceleron, Aduro, Alexion, Amgen, Array, Arrowhead, AstraZeneca, Aveo, BMS, Boehringer-Ingelheim, Cota, Eisai, Exelixis, Fathom, Galactone, Genentech-Roche, Ideera, ImmunoCore, Iovance, Lynx, Merck, Newlink, Novartis, Pfizer, Surface, Werewolf. Research grant/Funding (institution): BMS, Genentech, Merck, Pfizer. Stock options: Werewolf. The remaining authors have declared no disclosures.

**Abbreviations:** AE = adverse event; BID: twice daily; C = cycle; CAF = cancer-assisted fibroblast; CPI = checkpoint inhibitor; CR = complete response; D = day; IFN-γ = interferon-γ; IHC = immunohistochemistry; IO = Immuno-oncology; MDSC = myeloid-derived suppressor cell; MTD: maximum tolerated dose; ORR = objective response rate; PD-1 = programmed cell death protein 1; PD-L1 = programmed death ligand 1; PFS = progression-free survival; PR = partial response; pt = patient; QD: once daily; RCC = renal cell carcinoma; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D: recommended Phase 2 dose; SD = stable disease; SDF1 = stromal cell-derived factor 1; TKI = tyrosine kinase inhibitor; TME = tumor microenvironment; Tregs = T regulatory cells; WHIM = Warts, Hypogammaglobulinemia, Infections, Myelokathexis. **Acknowledgments:** The authors would like to thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This clinical study is sponsored by X4 Pharmaceuticals. Medical editorial support provided by Tim Henion and John Welle of Acumen Medical Communications and funded by X4 Pharmaceuticals. Axitinib is provided by Pfizer Inc. through an innovative research collaboration agreement.

 **References: 1)** Maher et al. *Eur J Hum Genet.* 2011; 19:617-623. **2)** Bellesoeur et al. *Drug Des Devel Ther.* 2017;11:2801-2811. **3)** Feig et al. *PNAS* 2013;110: 20212-20217. **4)** Righi et al. *Cancer Res* 2011; 71:5522-5534. **5)** Staller et al. *Nature* 2003; 425:307-311. **6)** Ehtesham et al. *Neurosurgery* 2008; 63:E820. **7)** Sekiya et al. *Human Pathology.* 2012; 43:904-910. **8)** Stone et al. *Antimicrob Agents Chemother.* 2007;51(7):2351–2358. **9)** Dale et al. ASH 2018. **10)** Andtbacka et al. AACR 2018. **11)** Panka et al. *Eur. J Cancer* 2016; 69:S105.

## Patient Disposition

| Mavorixafor + Axitinib (N = 65) | |
|---|---|
| Treated | 65 (100%) |
| Ongoing | 8 (12%) |
| Discontinued | 57 (88%) |
| Adverse Event | 13 (20%) |
| Disease progression | 37 (57%) |
| Clinical deterioration | 3 (5%) |
| Withdrawal of consent | 4 (6%) |

Clinical cut-off date: August 27, 2019

- 10 pts (15%) discontinued combination therapy due to treatment-related AEs (mavorixafor or axitinib) of creatinine increase (3 pts); hypertension (2 pts); and azotaemia, diarrhea, fatigue, hyperkalemia, retinal vein occlusion, sepsis, and tracheo-oesophogeal fistula (1 pt each)

## Safety

| Adverse Events (All Grades ≥ 10% and Grade ≥ 3 in > 2 Pts) Related to Mavorixafor or Axitinib (N = 65) | | |
|---|---|---|
| **Adverse Event (Related)** | **All Grades** | **Grade ≥ 3** |
| Diarrhea | 35 (54%) | 7 (11%) |
| Decreased Appetite | 29 (45%) | 6 (9%) |
| Fatigue | 29 (45%) | 3 (5%) |
| Hypertension | 25 (39%) | 14 (22%) |
| Nausea | 19 (29%) | 3 (5%) |
| Weight decreased | 14 (22%) | 2 (3%) |
| Dysphonia | 14 (22%) | 0 |
| Blood Creatinine Increased | 13 (20%) | 1 (2%) |
| Hypothyroidism | 13 (20%) | 1 (2%) |
| Vomiting | 12 (19%) | 1 (2%) |
| Dry Eye | 10 (15%) | 0 |
| Palmar-Plantar Erythrodysaesthesia | 10 (15%) | 0 |
| Dyspnoea | 9 (14%) | 0 |
| Headache | 9 (14%) | 0 |
| Anaemia | 8 (12%) | 2 (3%) |
| Stomatitis | 8 (12%) | 1 (2%) |
| Dyspesis | 8 (12%) | 0 |

Clinical cut-off date: August 27, 2019

- Mavorixafor + axitinib combination therapy was well-tolerated
- The most common AEs (≥ 25%, regardless of relationship) were diarrhea (36 pts, 55%), fatigue (34 pts, 52%), decreased appetite (33 pts, 51%), weight decreased (29 pts, 45%), hypertension (27 pts, 42%), nausea (24 pts, 37%), vomiting (20 pts, 31%), cough (18 pts, 28%), blood creatinine increased (17 pts, 26%), and headache and dysphonia (16 pts, 25%)
- Treatment-related serious AEs were diarrhea, hyperkalemia, and hypertension (2 pts, 3%), and blood creatinine increased, dehydration, fatigue, hepatic enzyme increase, nausea, sepsis, tracheo-oesophageal fistula, and vomiting (1 pt each, 1.5%)

## Preliminary Efficacy

| Best Response* (All Clinically Evaluable Patients;** N = 62) | |
|---|---|
| **Objective Response Rate (CR + PR)** | **29%** |
| Complete Response | 1 (2%) |
| Partial Response | 17 (27%) |
| Stable Disease | 28 (45%) |
| Progressive Disease | 13 (21%) |
| Non-CR/Non-PD | 2 (3%) |
| Not evaluable | 1 (2%) |
| **Best Response in Clinically Evaluable Patients (IO as Immediately Prior Therapy; N = 18)** | |
| **Objective Response Rate (CR + PR)** | **61%** |
| Partial Response | 11 (61%) |
| Stable Disease | 4 (22%) |
| Progressive Disease | 3 (17%) |
| **Best Response in Clinically Evaluable Patients (TKI as Immediately Prior Therapy; N = 34)** | |
| **Objective Response Rate (CR + PR)** | **18%** |
| Complete Response | 1 (3%) |
| Partial Response | 5 (15%) |
| Stable Disease | 17 (50%) |
| Progressive Disease | 8 (24%) |
| Non-CR/Non-PD | 2 (6%) |
| Not evaluable | 1 (3%) |

Clinical cut-off date: August 27, 2019 * Based on RECIST 1.1 criteria
** Patients who have had at ≥ 1 scan after combination treatment

- The median duration on treatment was 27.1 weeks (range 1-168)

**Figure 4:** Progression-Free Survival by Immediate Prior Therapy

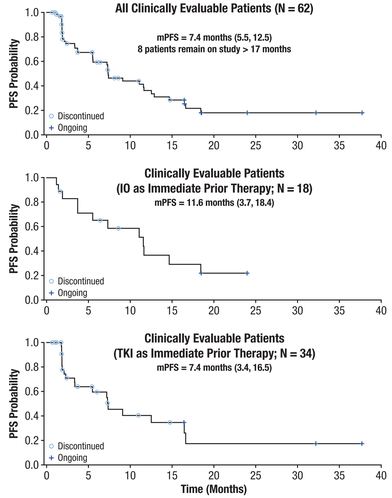
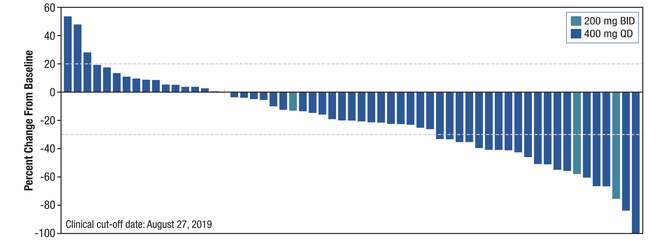



**Figure 5:** Best response in target lesion size




## Conclusions

- Combination therapy with 400 mg QD mavorixafor + 5 mg BID axitinib was well-tolerated with a manageable safety profile
- Mavorixafor + axitinib demonstrated encouraging mPFS in this heavily pretreated advanced RCC patient population, where 75% of patients received 2 or more prior therapies and 83% had an intermediate or poor prognosis
  - mPFS in All Clinically Evaluable patients was 7.4 months
  - mPFS in the group with IO as immediate prior therapy was 11.6 months
  - mPFS in the group with TKI as immediate prior therapy was 7.4 months
  - 8 patients remain on study > 17 months
- The results suggest that mavorixafor may enhance clinical responses to axitinib and other TKIs that target tumor angiogenesis, as well as immunotherapy agents such as CPIs

**Future Directions:**

- Triple combination of mavorixafor in addition to TKI and CPI is worthy of future investigation in a larger RCC patient population, particularly in the first-line setting
- The contribution of mavorixafor to the durable responses observed should be validated in a randomized Phase II trial

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