# The Safety, Tolerability, and Preliminary Anti-Tumor Activity of the CXCR4 Inhibitor X4P-001 and Nivolumab in Renal Cell Carcinoma Patients Who Are Non-Responsive to Nivolumab Monotherapy

#77

David F. McDermott[1], Michael B. Atkins[2], Tracy L. Rose[3], Robert S. Alter[4], Eleni Tsiroyannis[5], Katie Niland[5], Sudha Parasuraman[5], Lu Gan[5], Toni K Choueiri[6]

[1]Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Georgetown-Lombardi Comprehensive Cancer Center, Washington, DC, USA; [3]Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; [4]John Theurer Cancer Center Hackensack UMC, Hackensack, NJ, USA; [5]X4 Pharmaceuticals, Cambridge, MA, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA

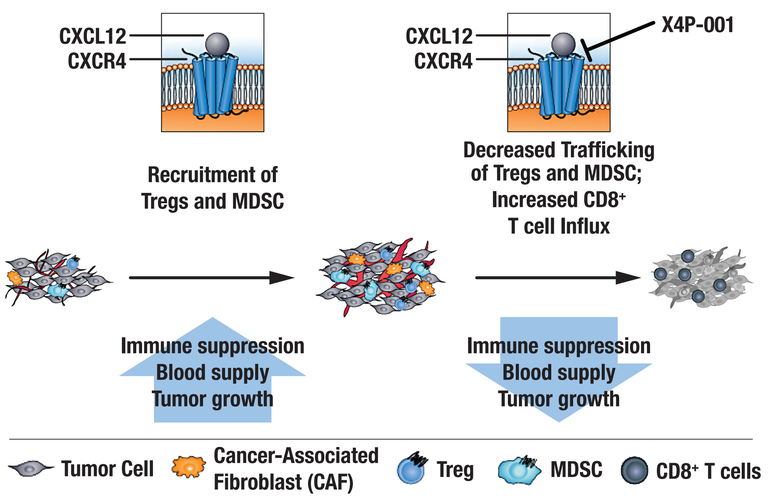
## Background

### CXCR4 and Cancer

- CXCR4 is a chemokine receptor that potently mediates cell chemotaxis through CXCL12 (SDF-1α) ligand binding
- CXCL12/CXCR4 modulates the trafficking of immunosuppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment (TME)
- Multiple types of human cancers, including renal cell carcinoma (RCC), ovarian cancer, and melanoma, express CXCR4[1]
- Increased expression levels of CXCR4 in human tumors are associated with decreased overall survival[2,3]

### X4P-001 and Nivolumab

- X4P-001 is an orally bioavailable, selective, allosteric CXCR4 antagonist that is being evaluated for the treatment of melanoma and RCC
- In tumor models, CXCR4 inhibition decreases MDSC infiltration of the TME[4,5] and enhances the ratio of cytotoxic CD8+ cells to FoxP3+ Tregs[6,7]
- Nivolumab, an FDA-approved anti-PD-1 checkpoint inhibitor, improves immune responses to RCC, but does not alter cell trafficking in the TME
- We hypothesize that X4P-001 and nivolumab combination therapy will enhance immune cell infiltration of the TME in patients who are unresponsive to nivolumab alone, leading to improved clinical outcomes




## Objectives

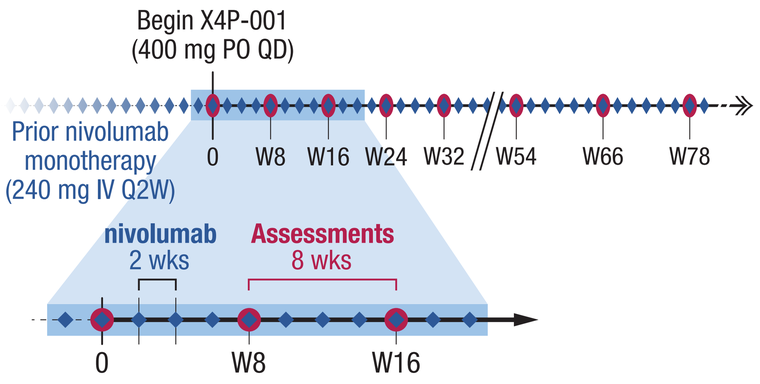
### Primary Objective

- Characterize the safety and tolerability of X4P-001 in combination with nivolumab in patients who are unresponsive to nivolumab monotherapy

### Secondary and Exploratory Objectives

- Characterize the antitumor activity of X4P-001 and nivolumab combination treatment
- Evaluate tumor biomarkers for correlation with response to X4P-001 and nivolumab combination treatment

## Study Design




- Enrolled patients must be receiving current nivolumab therapy for advanced RCC with a best response of stable disease (SD) or progressive disease (PD) by RECIST v1.1 criteria.
- The starting dose of X4P-001 was chosen based on safety and pharmacological activity in healthy volunteers[8] and prior RCC studies by the Sponsor
- Patients were administered oral X4P-001 at 400 mg QD while continuing on 240 mg nivolumab therapy by intravenous infusion every 2 weeks
- Radiologic assessments for tumor response are conducted every 8 weeks during the first 12 months and every 12 weeks thereafter, or as warranted based on RECIST v1.1 criteria

### Key Eligibility Criteria

**Inclusion:**

- ≥ 18 years of age
- Histologically confirmed RCC with clear cell component
- Currently receiving nivolumab therapy with a best response of SD or PD

**Exclusion:**

- ECOG performance status ≥ 2
- Active CNS metastasis or uncontrolled heart disease
- Life expectancy < 3 months

## Demographic and Baseline Characteristics

| X4P-001 + Nivolumab (*n* = 9) | | |
|---|---|---|
| Age (Years) | Median | 64.9 |
| | Range | 49-77 |
| Gender | Male | 8 (89%) |
| | Female | 1 (11%) |
| Race | White | 9 (100%) |
| ECOG Status | 0 | 5 (56%) |
| | 1 | 4 (44%) |
| Number of Prior Systemic Therapies, Including Nivolumab | Median | 2.0 |
| | 1 | 1 (11%) |
| | 2 | 4 (44%) |
| | 3 | 3 (33%) |
| | > 3 | 1 (11%) |
| Duration on Nivolumab Monotherapy | Median | 8.0 months |
| | Range | 2-12 months |
| Prior Response on Nivolumab Monotherapy at Study Entry | Stable disease | 5 (56%) |
| | Progressive disease | 4 (44%) |

Clinical cut-off date: Feb 26, 2018

## Patient Disposition

| X4P-001 + Nivolumab (*n* = 9) | |
|---|---|
| Treated | 9 (100%) |
| Ongoing | 2 (22%) |
| Discontinued | 7 (78%) |
| Adverse Event | 3 (33%) |
| Disease progression | 3 (33%) |
| Clinical deterioration | 1 (11%) |

Clinical cut-off date: Feb 26, 2018

- Three patients discontinued combination therapy due to adverse events (1 each): Lipase Increased, Mucosal Inflammation/Rash Maculo-Papular, and Autoimmune Hepatitis
- Median duration of combination treatment was 3.7 months (range 1-10 months)

## Safety

| Adverse Events (>25%) on X4P-001 or Nivolumab Regardless of Attribution (*n* = 9) | |
|---|---|
| Adverse Event (Related) | *n* (%) |
| Diarrhea | 6 (67) |
| Nasal Congestion | 5 (56) |
| Dry Eye | 4 (44) |
| Headache | 4 (44) |
| Cough | 4 (44) |
| Fatigue | 3 (33) |
| ALT Increased | 3 (33) |
| Blood Creatinine Increased | 3 (33) |
| Weight Decreased | 3 (33) |
| Arthralgia | 3 (33) |
| Musculoskeletal Pain | 3 (33) |
| Pruritis | 3 (33) |

Clinical cut-off date: Feb 26, 2018

| Adverse Events (All Grades > 15% and Grade ≥ 3) Related to X4P-001 or Nivolumab (*n* = 9) | | | |
|---|---|---|---|
| Adverse Event (Related) | All Grades *n* (%) | Grade 3 *n* (%) | Grades 4 & 5 *n* (%) |
| Diarrhea | 5 (56) | 0 | 0 |
| Nasal Congestion | 4 (44) | 0 | 0 |
| Dry Eye | 3 (33) | 0 | 0 |
| Alanine Aminotransferase Increased (ALT) | 3 (33) | 1 (11) | 0 |
| Aspartate Aminotransferase Increased (AST) | 2 (22) | 1 (11) | 0 |
| Conjunctival Hyperaemia | 2 (22) | 0 | 0 |
| Fatigue | 2 (22) | 0 | 0 |
| Dyspepsia | 2 (22) | 0 | 0 |
| Autoimmune Hepatitis | 1 (11) | 1 (11) | 0 |
| Lipase Increased | 1 (11) | 1 (11) | 0 |
| Mucosal Inflammation | 1 (11) | 1 (11) | 0 |
| Rash Maculo-papular | 1 (11) | 1 (11) | 0 |

Clinical cut-off date: Feb 26, 2018

- Combination treatment of X4P-001 and nivolumab had acceptable toxicity in RCC patients
- There were no Grade 4 or Grade 5 AEs
- Serious AEs related to either X4P-001 or nivolumab include mucosal inflammation, rash maculo-papular, autoimmune hepatitis, and ALT/AST increased (1 pt each, 11%)

## Anti-Tumor Activity

| Best Overall Response, X4P-001 + Nivolumab (*n* = 9) | |
|---|---|
| **Best Overall Response*** | |
| Partial Response (PR) | 1 (11%) |
| Stable Disease (SD) | 7 (78%) |
| Progressive Disease (PD) | 1 (11%) |
| **Objective Response Rate (CR + PR)** | **11%** |

*Best overall response based upon RECIST 1.1; Clinical cut-off date: Feb 26, 2018

- Four patients who had progressed on prior nivolumab monotherapy had a best response of SD with additional X4P-001 treatment
- Of the 5 patients who were stable on prior nivolumab monotherapy, 1 had a PR with combination therapy

**Figure 1:** Best response in target lesion size

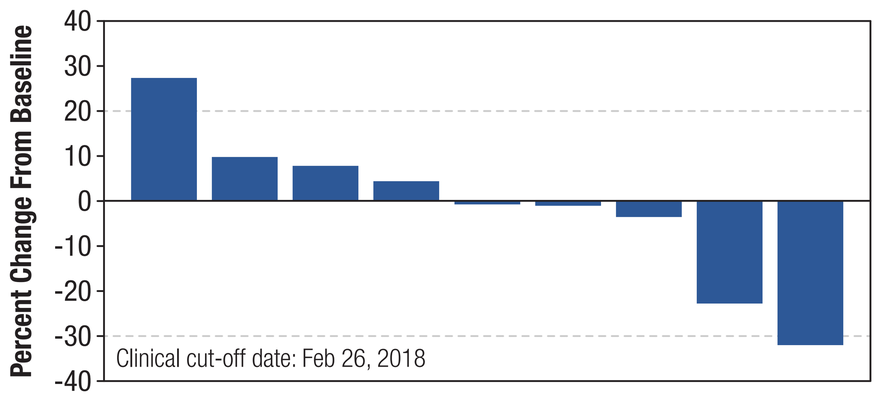



**Figure 2:** CT assessment of tumor responses for a patient with PR with X4P-001 + nivolumab combination therapy. Target lesions included a lesion at lung (top row) and a lymph node (bottom row). Scans were taken every 8 weeks and target lesion size was determined per RECIST v1.1 criteria.

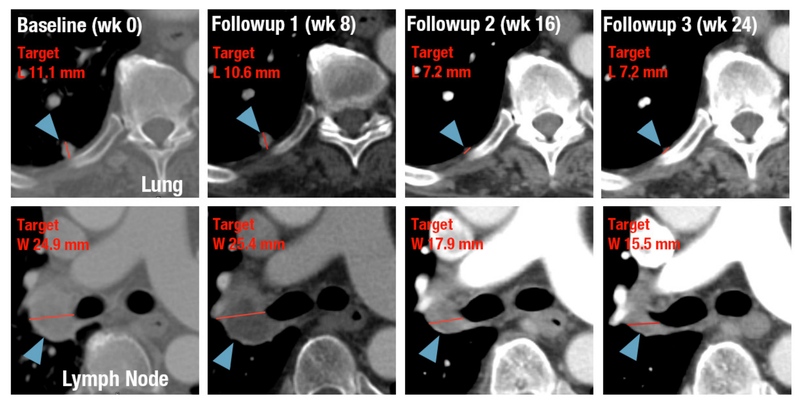
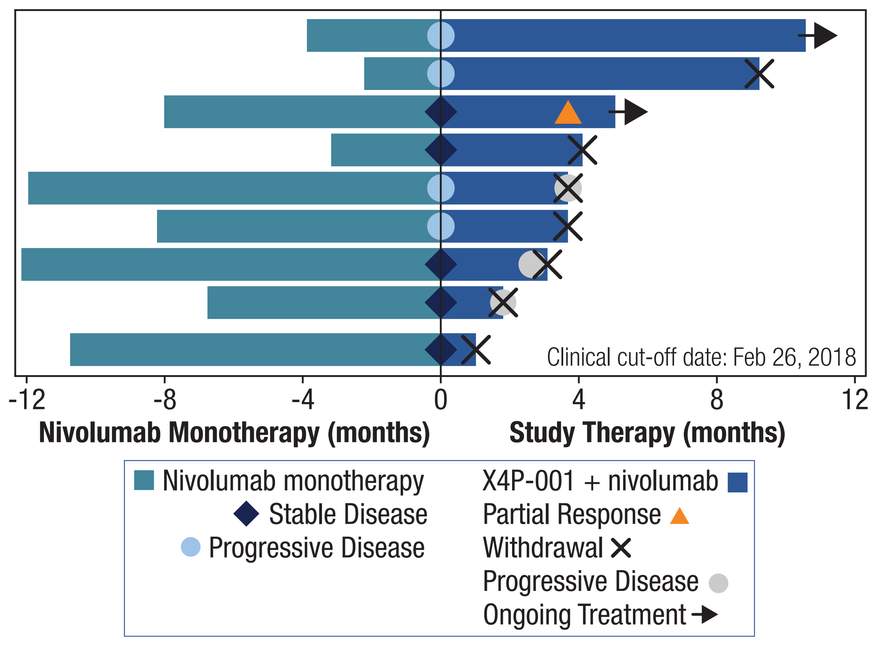



**Figure 3:** Duration of prior nivolumab monotherapy and combination treatment




## Conclusions

- X4P-001 (400 mg QD) in combination with nivolumab demonstrated an acceptable safety profile in RCC pts
- There were no Grade 4 or 5 adverse events reported, and all Grade 3/serious adverse events were manageable
- Combination therapy with X4P-001 and nivolumab exhibited some anti-tumor activity in advanced RCC patients who were non-responsive to nivolumab monotherapy
- X4P-001-mediated inhibition of CXCR4 may potentially augment responses in patients who do not respond to anti-PD-1 checkpoint inhibitors alone
- The evaluation of upfront checkpoint inhibitors and X4P-001 combination therapy in additional disease settings is warranted

**Acknowledgements:** 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. Nivolumab is provided by Bristol-Myers Squib through an innovative research collaboration agreement.

**References: 1)** Staller P, Sulitkova J, Lisztwan J, et al. Chemokine receptor CXCR4 downregulated by von Hippel–Lindau tumour suppressor pVHL. *Nature* 2003;425:307-311. **2)** Maréchal R, Demetter P, Nagy N, et al. High expression of CXCR4 may predict poor survival in resected pancreatic adenocarcinoma. *Br J Cancer* 2009;100: 1444-14513. **3)** Sekiya R, Kajiyamo H, Sakai K, et al. Expression of CXCR4 indicates poor prognosis in patients with clear cell carcinoma of the ovary. *Human Pathology*. 2012;43:904-910. **4)** Obermajer N, Muthuswamy R, Odunsi K, et al. PGE2-induced CXCL12 production and CXCR4 expression controls the accumulation of human MDSCs in ovarian cancer environment. *Cancer Res* 2011; 71:7463-7470. **5)** Panka DJ, Arbeit RD, Mier JW. Regulation of MDSC trafficking and function in RCC by CXCR4 in the presence of a VEGF-R antagonist, 2016 AACR, Abstract 4155. **6)** Fearon DT. The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance. *Cancer Immunol Res* 2014;2:187-193. **7)** Saxena R, Wang Y, Mier JW. CXCR4 Inhibition Modulates Tumor Microenvironment and Robustly Inhibits Growth of B16-OVA Melanoma. 2018 AACR, abstract 613. **8)** Stone ND, et al. Antimicrob Agents. *Chemother.* 2007; 51: 2351-58.

Presented at the 16th CIMT Annual Meeting • May 15-17, 2018 • Mainz, Germany