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# Combination Therapy with the CXCR4 Inhibitor X4P-001 and Nivolumab Demonstrates Preliminary Anti-tumor Activity in RCC Patients that are Unresponsive to Nivolumab Alone

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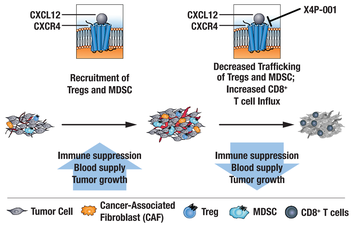
## Background

### CXCR4 and Cancer

- Chemokine signaling through CXCR4/CXCL12 plays a central role in immune cell trafficking
- Within the tumor microenvironment (TME), CXCR4 modulates the chemotaxis of immunosuppressive regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)
- Many human cancers express CXCR4, including renal cell carcinoma (RCC)[1], and increased CXCR4 expression is associated with decreased overall survival[2,3]

### X4P-001 and Nivolumab

- X4P-001 is an orally bioavailable, selective, allosteric CXCR4 inhibitor that is being evaluated for the treatment of melanoma and RCC
- CXCR4 inhibition decreases MDSC infiltration of the TME[4,5] in tumor models and enhances the ratio of cytotoxic CD8+ cells to FoxP3+ Tregs in human[6,7,8]
- The anti-PD-1 checkpoint inhibitor nivolumab improves immune responses to RCC, but does not alter cell trafficking in the TME
- We hypothesize that disruption of CXCR4/CXCL12 signaling by X4P-001 will favorably modulate immune cell profiles in the TME in patients who are unresponsive to nivolumab alone




## Objectives

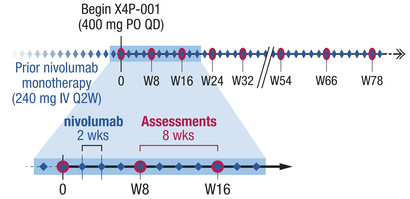
### Primary Objective

- 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
- Investigate select peripheral blood biomarkers of immune activation

## Study Design




- The starting dose of X4P-001 was chosen based on safety and pharmacological activity in healthy volunteers[9] and prior RCC studies by the Sponsor
- Oral X4P-001 was administered to patients at 400 mg QD while continuing on 240 mg nivolumab therapy by IV infusion every 2 weeks
- Radiologic assessments for tumor response were 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** |
| • Receiving current nivolumab monotherapy |
| • Best response on current nivolumab of SD or PD |
| • Histologically confirmed RCC with documented clear cell component |
| • ≥ 18 years of age |
| **Exclusion** |
| • < 3 month life expectancy |
| • ECOG performance status ≥ 2 |
| • Screening laboratory tests of ANC < 1,500/µL or platelets < 75,000/µL |
| • Active CNS metastasis or uncontrolled heart disease |

## 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: Aug 1, 2018

## Patient Disposition

| X4P-001 + Nivolumab (*n* = 9) | |
|---|---|
| Treated | 9 (100%) |
| Ongoing | 0 (0%) |
| Discontinued | 9 (100%) |
| Adverse Event | 4 (44%) |
| Clinical deterioration | 1 (11%) |
| Disease progression | 3 (33%) |
| Study Termination | 1 (11%) |

Clinical cut-off date: Aug 1, 2018

- Combination therapy was discontinued in 4 patients for AEs of Lipase Increased, Mucosal Inflammation/Rash Maculo-Papular, Autoimmune Hepatitis, and ALT/AST Increased (1 each)
- The median duration of combination treatment was 3.7 months (range 1-15 months)

## Safety

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

Clinical cut-off date: Aug 1, 2018

| AEs (All Grades > 20% 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 |
| ALT Increased | 3 (33) | 2 (22) | 0 |
| AST Increased | 3 (33) | 2 (22) | 0 |
| Dry Eye | 3 (33) | 0 | 0 |
| Fatigue | 3 (33) | 0 | 0 |
| Conjunctival Hyperaemia | 2 (22) | 0 | 0 |
| Dyspepsia | 2 (22) | 0 | 0 |
| Nausea | 2 (22) | 0 | 0 |
| Rash Pruritic | 2 (22) | 0 | 0 |

Clinical cut-off date: Aug 1, 2018

- X4P-001 + nivolumab combination therapy had acceptable toxicity in RCC patients
- No Grade 4 or Grade 5 AEs
- Two patients experienced serious AEs related to either X4P-001 or nivolumab: one had mucosal inflammation and rash maculo-papular and another had ALT/AST increased and autoimmune hepatitis

## Anti-Tumor Activity

**Figure 1:** Target lesion response over time

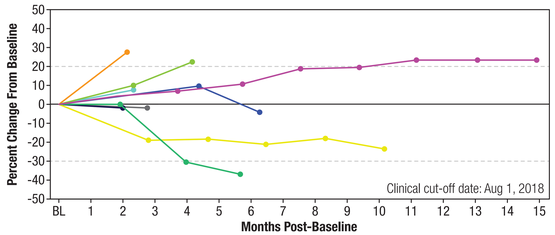
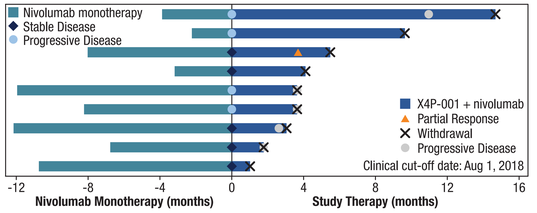
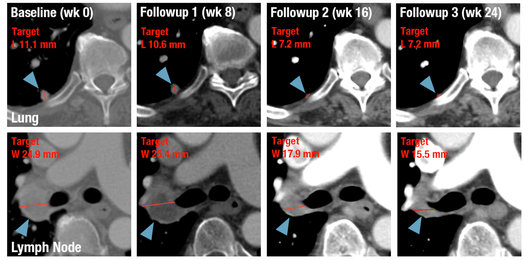



**Figure 2:** Duration of prior nivolumab monotherapy and combination treatment




- Four patients with progressive disease on prior nivolumab monotherapy had a best response of SD with X4P-001 + nivolumab
- Among 5 patients with stable disease on prior nivolumab monotherapy, 1 had a PR with X4P-001 + nivolumab

**Figure 3:** Assessment of tumor responses by CT scans for a patient receiving X4P-001 + nivolumab combination therapy that had a partial response. Top row: Target lesion in the lung. Bottom row: lymph node target lesion. Scans were taken every 8 weeks and target lesion size was determined per RECIST v1.1 criteria.



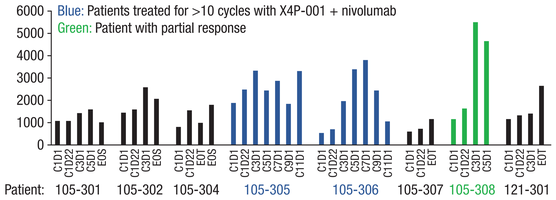

| Best Overall Response X4P-001 + Nivolumab (*n* = 9) | |
|---|---|
| **Best Overall Response*** | |
| Partial Response (PR) | 1 (11%) |
| Stable Disease (SD) | 7 (78%) |
| Progressive Disease (PD) | 1 (11%) |
| **Objective Response Rate (CR + PR)** | **11%** |

*Based upon RECIST 1.1;Clinical cut-off date: Aug 1, 2018

| Serum Biomarker Changes Compared to Baseline on Day 22 of X4P-001 + Nivolumab Combination Therapy (p < 0.05) | |
|---|---|
| Protein[1] | p-value |
| **Increase** | |
| Decorin | 0.008 |
| 6Ckine | 0.016 |
| CXCL9, Monokine Induced by Gamma Interferon (MIG) | 0.016 |
| Macrophage inflammatory protein 3 beta (MIP-3 beta) | 0.016 |
| Interleukin-2 Simoa (IL-2 Simoa) | 0.023 |
| Myeloid Progenitor Inhibitory Factor 1 (MPIF-1) | 0.031 |
| **Decrease** | |
| Latency-Associated Peptide of Transforming Growth Factor beta 1 | 0.016 |
| Monocyte Chemotactic Protein 1 (MCP-1) | 0.016 |
| Platelet-Derived Growth Factor BB (PDGF-BB) | 0.023 |
| Angiopoietin-1 (ANG-1) | 0.031 |
| Epithelial-Derived Neutrophil-Activating Protein 78 (ENA-78) | 0.031 |

[1] Determined using the Multi-Analyte Profile platform (Myriad RBM)

**Figure 4:** Increases in CXCL9 (MIG) Levels in Patients Treated with X4P-001 + Nivolumab




- Higher CXCL9 levels were found in a patient with a PR and in those receiving combination therapy for > 10 cycles.

## Conclusions

- Combination therapy with X4P-001 (400 mg QD) + nivolumab exhibited some anti-tumor activity and was tolerable in advanced RCC patients that were previously unresponsive to nivolumab monotherapy
- No Grade 4 or 5 AEs were reported, and all Grade 3/SAEs were manageable
- CXCR4 inhibition by X4P-001 may augment responses in patients that do not respond to anti-PD-1 checkpoint inhibitors alone
- Serum biomarker analyses identified significant early changes in cytokines and chemokines, including CXCL9, a chemoattractant ligand for cytotoxic T cell migration
- Combination therapy with X4P-001 and checkpoint inhibitors should be evaluated in larger cohorts and additional disease settings

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