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

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Background

CXCR4 and Cancer

• CXCR4 is a chemokine receptor that potentiates medullary cell chemotaxis through CXCL12 (SDF-1) 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

• Increased expression levels of CXCR4 in human tumors are associated with decreased overall survival 2

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 3 and enhances the ratio of cytotoxic CD8+ cells to FoxP3+ Tregs 4

• 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 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

• 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

Age (years)

X4P-001 + Nivolumab (n = 9)

Median 64.9

Range 49-77

Gender

Female 8 (89%)

Male 1 (11%)

Race

White 9 (100%)

ECOG Status

0 5 (56%)

1 4 (44%)

Number of Prior Treatments

2 4 (44%)

3 3 (33%)

Prior Response on Nivolumab Monotherapy

Stable Disease 5 (56%)

Progressive disease 4 (44%)

Safety

Adverse Events (>25%) on X4P-001 or Nivolumab Regardless of Attribution (n = 9)

Adverse Event (Related) n (%)

Fever 6 (67)

Nausea 5 (56)

Dry Eye 4 (44)

Headache 4 (44)

Cough 4 (44)

Fatigue 3 (33)

Alcohol Increased 3 (33)

Blood Creatinine Increased 3 (33)

Weight Decreased 3 (33)

Anorexia 3 (33)

Musculoskeletal Pain 3 (33)

Pruritus 3 (33)

Adverse Events (>10%) on Nivolumab Monotherapy (n = 9)

Adverse Event n (%)

Fever 5 (56)

Nausea 4 (44)

Dry Eye 3 (33)

Anorexia 3 (33)

Fatigue 2 (22)

Dyspnea 2 (22)

Alcohol 1 (11)

Autonomous 1 (11)

Lipase Increased 1 (11)

Malnutrition 1 (11)

Rash Maculopapular 1 (11)

Best Overall Response

1 (11%)

Stable Disease (SD) 7 (78%)

Progressive Disease (PD) 1 (11%)

Anti-Tumor Activity

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 (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 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

References


Acknowledgments

The authors wish to thank the patients and their families, investigators, co-investigators, and the staff members at each of the participating centers. This clinical trial is sponsored by X4 Pharmaceuticals. Medical editorial assistance was provided by Bobbi Riney-Spade through an innovative research collaboration agreement.

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