X4P-001, an Orally Bioavailable CXCR4 Antagonist, Increases T Cell Infiltration in Human Metastatic Melanoma

Robert H.I. Andtbacka1, Melissa Yushak2, Merrick Ross3, Kenneth Grossmann4, Robert Pierce5, Eleni Tsioyannis6, Sarah Blanchette7, Lu Gan8, Yan Wang9, Mohammed Milhem1

1 Surgical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; 2 Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA; 3 Surgical Oncology, MD Anderson Cancer Center, University of Texas, Houston, TX; 4 Medical Oncology, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT; 5 Fred Hutchinson Cancer Center, Seattle, WA; 6 X4 Pharmaceuticals, Cambridge, MA; 7 Medical Oncology, University of Iowa, Iowa City, IA

Background

- The CXCR4/CXCL12 axis plays a central role in the trafficking of key immune cells in the tumor microenvironment (TME).
- Enhanced survival is reported in multiple syngeneic mouse models when a CXCR4 antagonist is combined with a checkpoint inhibitor.
- X4P-001 is an oral, selective, allatropic inhibitor of CXCR4. CXCR4 antagonist treatment alone demonstrated robust inhibition of murine B16-OVA melanoma growth.
- It is hypothesized that disruption of CXCR4/CXCL12 signaling by X4P-001 will modulate the immune cell profile within the TME and increase CD8+ T cell infiltration, which will favor an improved response to checkpoint inhibitors.
- Study X4P-001 (NCT02823405) is an ongoing biomarker-driven Phase Ib clinical study in patients with malignant melanoma.

Key Eligibility Criteria

Inclusion:
- ≥18 years
- Histologically confirmed malignant melanoma
- 2≤2 separate cutaneous or subcutaneous lesions suitable for punch biopsies (<3 mm)
- Prior receipt of more than 1 anti-PD1 therapy
- ECOG PS ≤1

Exclusion:
- ECOS PS ≥2
- Prior checkpoint inhibitor therapies (anti-CTLA-4, anti-PD1, PD-L1) or oncolytic virus therapy
- Severe depression, anxiety, mania, or other psychiatric disorder that may interfere with patient assessment
- Malignancies in the past 6 months

Adverse Events (AEs) assessed as related to X4P-001 during monotherapy (>10%): diarrhea (31%), rash (15%), and hypertension (5%), each.

Immunohistochemistry and NanoString Analysis

- As of August 2nd 2017, 13 patients have been enrolled, and biopsies from 11 patients have been analyzed.
- Five had both pre-dose and post-X4P-001 single-agent treatment-evaluable biopsies.
- One had pre-dose and post-combination treatment-evaluable biopsies.
- Multiplex immunohistochemistry (IHC) panel included CD4, CD8, PD-1, PD-L1, macrophage cytokine (CCL8 + CD163), and FoxP3 with DAPI as a nuclear counterstain.
- Single-marker IHC (CD8 and granzyme B) and multiplex IHC staining were analyzed by HALO™ (Indica Labs), and the entire tumor area of each specimen was scored.
- NanoString nCounter analysis was conducted with the PanCancer immune probe set using RNA extracted from FFPE slides.
- Raw counts were normalized using the geometric mean of housekeeping genes.

Demographics and Baseline Characteristics

- Mean patient age was 73.0 (± 10.4 years); the median age was 73 (range 53-90 years).
- Of the 13 patients enrolled, 8 (62%) were male and 5 (38%) were female.
- 12 patients (92%) were White and 1 (8%) was Asian.
- 7 patients (64%) had a screening ECOG status score of 0 and 6 (46%) had a score of 1.

Safety

- X4P-001 was generally well-tolerated.
- Adverse Events (AEs) assessed as related to X4P-001 during monotherapy (> 10%) were diarrhea (31%) and rash (15%).
- AEs assessed as related to either X4P-001 or pembrolizumab (> 10%) at any time were diarrhea (39%), mucosal-papular rash and fatigue (31% each), chills, and acute kidney injury (15% each).
- Grade 3 AEs assessed as related to either X4P-001 or pembrolizumab at any time were mucocutaneous-papular rash (15%), diarrhea, acute kidney injury, adenine-ammoniase increase, aspartate aminotransferase increase, blood bilirubin increased, hyperammonemia, and stomatitis (8% each).
- There were no Grade 4 or Grade 5 AEs at any time during the study.

Conclusions

- X4P-001 as a single agent and in combination with pembrolizumab is generally safe and well-tolerated.
- Preliminary evidence of enhanced immune cell infiltration and activation is observed in the tumor microenvironment with X4P-001 alone:
  - Increased CD8+ T cells
  - Increased cytotoxic T lymphocyte (CTL) gene expression signature score
  - Increased granzyme B signal
  - Increased IFN-gamma gene expression signature score
  - No change in FoxP3-expressing immune-suppressive cells
- Increased IFN-gamma gene expression signature scores and PD-L1 levels after single-agent X4P-001 treatment support the use of X4P-001 in combination with anti-PD1 therapy.
- Enrollment is ongoing; further biomarker analysis is in progress.

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