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 CXCR3/CXCL12 plays a role in immune cell trafficking.

• Within the tumor microenvironment (TME), CXCR4 regulates the chemokine immunosuppressive regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSCs).

• Many human cancers express CXCR4, including renal cell carcinoma (RCC); and increased CXCR4 expression is associated with decreased overall survival.

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 reduces M2C infiltration of the TME1 in tumor models and enhances the ratio of cytotoxic CD8+ cells to FoxP3 Tregs in human tumors.2

• The anti-PD-1 checkpoint inhibitor nivolumab improves immune responses to RCC, but does not alter tumor cell trafficking in the TME.

• We hypothesized that disruption of CXCR4/CXCL12 signaling by X4P-001 may conversely modulate immune cell profiles in the TME in patients who are unresponsive to nivolumab alone.

Study Design

• Initial single dose escalation

• Escalation to full dose

• Patients randomized to continue combination therapy for ≥10 cycles, if tolerated

• Formal assessments for tumor response performed every 8 weeks or as needed, if clinically indicated

• Four patients with progressive disease on prior nivolumab monotherapy had a best response of Stable Disease with X4P-001 + nivolumab

• Among 5 patients with stable disease on prior nivolumab monotherapy, 1 had a PR with X4P-001 + nivolumab

Patient Disposition

X4P-001 + Nivolumab (n = 9)

<table>
<thead>
<tr>
<th>Titration</th>
<th>Tumor</th>
<th>Grade 3, 0</th>
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<tbody>
<tr>
<td>Median</td>
<td>1 (11%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Range</td>
<td>0 – 3</td>
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</tr>
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</table>

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>Equilibrated</th>
<th>Disease progression</th>
<th>Study Termination</th>
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<tbody>
<tr>
<td>Median</td>
<td>1 (11%)</td>
<td>2 (22%)</td>
<td>5 (56%)</td>
</tr>
<tr>
<td>Range</td>
<td>0 – 3</td>
<td>0 – 3</td>
<td>0 – 3</td>
</tr>
</tbody>
</table>

- Combination therapy was discontinued in 4 patients due to disease progression.
- Nivolumab Infusion Rate Stopped: 1 patient, Due to site of rapidly progressing disease.
- Median Duration of Combination therapy: 3.7 months (range 1-15 months)

Safety

• No treatment-related deaths

• AE-related discontinuations: 2

- Rash: 1
- Conjunctival hyperaemia: 1

- No significant treatment-related changes in laboratory tests

Demographic and Baseline Characteristics

- Age (years) Median: 60 (30-75), % Male: 67%

- Gender

<table>
<thead>
<tr>
<th>Sex</th>
<th>Median Age</th>
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<tbody>
<tr>
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<td>30-75</td>
<td>67</td>
</tr>
<tr>
<td>Female</td>
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<td>30-75</td>
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- ECOG Status

<table>
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<th>Median Age</th>
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<tbody>
<tr>
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<td>67</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>30-75</td>
<td>33</td>
</tr>
</tbody>
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- Duration on Nivolumab Median: 8.0 months

- Prior Response to Nivolumab

<table>
<thead>
<tr>
<th>Prior Response</th>
<th>Median</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Progression Disease</td>
<td>8.0 months</td>
<td>0-30</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>8.0 months</td>
<td>0-30</td>
</tr>
</tbody>
</table>

- X4P-001 + nivolumab combination therapy had acceptable toxicity in RCC-patients.

- No Grade 4 or 5 AEs were reported, and all Grade 3/4 AEs were manageable.

- CXCR4 inhibition by X4P-001 may augment responses in patients that do not respond to anti-PD-1 therapy.

- Serum biomarker analyses identified significant early changes in cytokines and chemokines, including CXCL12, a chemokine that is ligated for cytotoxic T cell migration.

- Combination therapy with X4P-001 and checkpoint inhibitors should be evaluated in larger cohorts with additional disease settings.

Conclusions

- Combination therapy with X4P-001 (400 mg QD) + nivolumab exerted anti-tumor activity and was well tolerated in advanced RCC patients that were previously non-responsive to nivolumab monotherapy.

- No Grade 3 or 4 AEs were reported, and all Grade 3/4 AEs were manageable.

- CXCR4 inhibition by X4P-001 may augment responses in patients that do not respond to anti-PD-1 therapy.

- Serum biomarker analyses identified significant early changes in cytokines and chemokines, including CXCL12, a chemokine that is ligated for cytotoxic T cell migration.

- Combination therapy with X4P-001 and checkpoint inhibitors should be evaluated in larger cohorts with additional disease settings.

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