Safety and Preliminary Clinical Activity of Vactosertib, a Selective TGF-β Receptor I Kinase Inhibitor, in Combination with Durvalumab in Advanced Non-small Cell Lung Cancer Patients with Low PD-L1 Expression

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BACKGROUND

- Vactosertib (TEM-719) is a potent, highly selective, oral inhibitor of TGF-β type 1 receptor (TGFBR1) that has shown promise as a drug candidate for the treatment of various solid tumors and hematological malignancies.
- TGF-β signaling is known to be associated with poor prognosis and single-agent checkpoint inhibitors by immunosuppressive microenvironment through strong epithelial-mesenchymal transition (EMT) induction.
- Combined inhibition of immune checkpoint and TGF-β signal is suggested as a promising therapeutic strategy because these two key pathways have independent and complementary immunosuppressive functions.

STUDY DESIGN / METHODS

- Study MP-V2C-203-1 is a Phase 1b/2a study evaluating the combination of vactosertib with durvalumab in patients with advanced non-small cell lung cancer (NSCLC) who progressed following platinum-based chemotherapy.
- Here we report the Phase 1b part of the study in NSCLC patients with low PD-L1 expression (clinical trial information: NCT03722734).

OBJECTIVES

- To evaluate the safety and tolerability of vactosertib plus durvalumab.
- To characterize the pharmacokinetic of vactosertib.
- To document the preliminary clinical activity of vactosertib plus durvalumab.

STUDY DESIGN / METHODS (continued)

- Phase 1b: 2 dose escalation assessment of the safety and tolerability of 2 doses of vactosertib (100 mg BD and 200 mg BD) given 5 days on/2 days off in combination with durvalumab (1500 mg Q4W) was performed (Figure 1).
- Eligible patients are ≥19 years old, ECOG 0-1, and have no prior exposure to immune checkpoint inhibitors (ICIs) or TGFβR1 kinase inhibitors.
- Tumor PD-L1 expression was evaluated in pre-treatment tissue samples by the Ventana SP263 IHC assay.

RESULTS

<table>
<thead>
<tr>
<th>Patients</th>
<th>Table 1: Baseline Characteristics</th>
<th>100 mg BD (N=7)</th>
<th>200 mg BD (N=6)</th>
<th>Overall (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median (range)</td>
<td>64 (49-70)</td>
<td>66 (59-70)</td>
<td>64 (49-70)</td>
<td></td>
</tr>
<tr>
<td>Sex, %</td>
<td>Male</td>
<td>3 (43)</td>
<td>4 (67)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Race, %</td>
<td>Asian</td>
<td>3 (43)</td>
<td>4 (67)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>No. of Prior Antitumor Agents</td>
<td>1 (14.3)</td>
<td>4 (67)</td>
<td>5 (38)</td>
<td></td>
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<tr>
<td>ECOG Performance Status</td>
<td>1 (14.3)</td>
<td>0 (0)</td>
<td>1 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Smoking Status, %</td>
<td>Former</td>
<td>3 (43)</td>
<td>1 (17)</td>
<td>4 (31)</td>
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<tr>
<td>PD-L1 Expression, %</td>
<td>≥50%</td>
<td>0 (0)</td>
<td>2 (33)</td>
<td>2 (15)</td>
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<td>GEM-5R Tumor, %</td>
<td>Muirhead</td>
<td>1 (14)</td>
<td>1 (17)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>AKT Translocation, %</td>
<td>Yes</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>1 (7.7)</td>
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<tr>
<td>Histology, %</td>
<td>Squamous</td>
<td>3 (43)</td>
<td>4 (67)</td>
<td>7 (54)</td>
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<td>Pharmacokinetic Analysis</td>
<td>100 mg BD (N=7)</td>
<td>200 mg BD (N=6)</td>
<td>Overall (N=13)</td>
<td></td>
</tr>
<tr>
<td>Parameters</td>
<td>Cycle 1 Day 1</td>
<td>Cycle 1 Day 5</td>
<td>Cycle 1 Day 1</td>
<td>Cycle 1 Day 5</td>
</tr>
<tr>
<td>Vactosertib</td>
<td>11.4 ± 7.3</td>
<td>0.26 ± 0.01</td>
<td>111.3 ± 78.3</td>
<td>0.07 ± 0.02</td>
</tr>
<tr>
<td>GEM-5R</td>
<td>0.38 ± 0.06</td>
<td>0.02 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>0.007 ± 0.001</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>28.2 ± 6.8</td>
<td>26.3 ± 4.5</td>
<td>28.2 ± 6.8</td>
<td>26.3 ± 4.5</td>
</tr>
</tbody>
</table>

Efficacy

- Among 12 evaluable patients, 2 patients achieved partial response (16.7%) and 3 stable disease (25%).
- Objective response rate (ORR) was 16.7% and 14.3% by per protocol (PP) and by intention-to-treat (ITT) analysis, respectively; disease control rate at 24-weeks (DCR24wks) were 33.3% (PP) and 28.6% (ITT).
- Response rate was 11.5% (PP) and 12.5% (ITT).
- Disease control rate was 55.0% (PP) and 54.5% (ITT).

SUMMARY & CONCLUSION

- Safety: No DLT or cardiotoxicity was observed with vactosertib and durvalumab treatment.
- Tumor response events were grade 1 or 2 and generally manageable.
- Pharmacokinetic: Vactosertib's pharmacokinetic profile supports twice daily dosing.
- Efficacy: DCR (16.7%) and DCR24wks (23.5%).
- The chemotherapy regimen of vactosertib and durvalumab showed promising early anti-tumor activity compared to the historical data in difficult-to-treat NSCLC patients with negative PD-L1 expression.
- The ongoing Phase 2a study is further evaluating the efficacy and safety of vactosertib-in combination with durvalumab.

For more information, please contact us at support@medpacto.com, +82-437-39060

References