Phase I Trial of Intratumoral Therapy Using HF10, an Oncolytic HSV-1, Demonstrates Safety and Efficacy in HSV+/HSV- Patients with Refractory and Superficial Cancers

INTRODUCTION

HF10 is a replication-competent oncolytic HSV-1, which was selected for its tumor-specificity and oncolytic properties associated with the deletion of the UL1 and UL21 genes. A single 3832 bp deletion in the right end of the UL and UL/IRL junction of the HF10 genome, resulting in loss of deletions and insertions in its genome, reduces its neurovirulence compared to wild type HSV-1. HF10 differs from wild type HSV-1, the virus replicates and destroys infected cells. HF10 has been evaluated in combination with an anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody, a phase II study in patients with unresected and/or metastatic melanoma is currently being initiated.

RESULTS

HF10 has been evaluated in combination with an anti-cytotoxic T lymphocyte antigen 4 antibody (anti-CTLA-4 antibody), and the combination treatment elicits enhanced tumor immunity, and may confer a clinical benefit in patients treated with the combination. A phase II study combining HF10 with ipilimumab is currently being initiated.

STUDY OBJECTIVES

Evaluate the safety and tolerability of HF10 in patients with refractory head and neck cancer and other solid tumors with cutaneous and/or superficial lesions - Characteristic viral replication after treatment with HF10 - Evaluate evidence of overall and local antitumor function - No preexisting neurologic abnormalities (CTCAE 3.0) - Response: RECIST 1.0; 4-week intervals - Topical Antitumor Immunity

Key Inclusion Criteria

- Histologically-confirmed solid tumors that have progressed on standard therapies - Measureable (RECIST 1.0) superficial tumor - Adequate hepatic, renal, bone marrow function - Age: 18-75 years - Life expectancy >12 weeks - No preexisting neurologic abnormalities (CTCAE 3.0) - Response: RECIST 1.0; 4-week intervals - Safety: Adverse events, vital signs, ECG, labs

Table 2: Summary of Cohorts

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Dose (TCID50)</th>
<th>N</th>
<th>Safety evaluable patients</th>
<th>Effective</th>
<th>Viral Shedding</th>
<th>Other</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (1x10^5)</td>
<td>N=5</td>
<td>24 (96.0%)</td>
<td>With Anti-CTLA-4 Antibody</td>
<td>2 (8.3%)</td>
<td>3 (12.5%)</td>
<td>3 (12.5%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Cohort 2 (1x10^6)</td>
<td>N=5</td>
<td>24 (96.0%)</td>
<td>With Anti-CTLA-4 Antibody</td>
<td>2 (8.3%)</td>
<td>3 (12.5%)</td>
<td>3 (12.5%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Cohort 3 (1x10^7)</td>
<td>N=5</td>
<td>24 (96.0%)</td>
<td>With Anti-CTLA-4 Antibody</td>
<td>2 (8.3%)</td>
<td>3 (12.5%)</td>
<td>3 (12.5%)</td>
<td>2 (8.3%)</td>
</tr>
</tbody>
</table>

DISCUSSION

Treatment with HF10 has been observed to be well tolerated with a low frequency of adverse effects. Adverse effects that were observed were mild in severity and did not lead to treatment discontinuation. Adverse effects were consistent with those observed in patients treated with other oncolytic viruses. There were no significant differences observed in HSV+/HSV- patients receiving HF10.

CONCLUSIONS

Viral shedding was observed infrequently, and resolved without the requirement of antiviral treatment. Evaluating the response of target lesions, 1 partial response (4%) was observed and 7 stable disease (27%) was observed of 26 treated patients. However when target lesion response was stratified for disease type, it was observed that melanoma patients demonstrated a greater frequency of SD+PR than patients with head & neck cancer or other superficial malignancies (56% vs 14% vs 33% respectively).

In addition, HF10 appears to modulate checkpoint receptor expression on T cells, including PD1+ T cells (Figure 5) which often express CTLA-4, supporting design of the phase II trial combining HF10 with anti-CTLA-4 to deplete suppressive Treg cells to enhance antitumor immunity.

ONGOING DEVELOPMENT

As a result of the favorable safety and treatment exposure profile observed in this phase I study, as well as the preclinical observed potential of the combination of HF10 with anti-CTLA-4 antibody, a phase II study in patients with melanoma or metastatic melanoma is currently being initiated.