Adoptive Cellular Therapy (ACT) With Allogeneic Activated Natural Killer (aNK) Cells in Patients With Advanced Merkel Cell Carcinoma (MCC): Preliminary Results of a Phase 2 Trial

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Abstract # 45

Background
Merkel Cell Carcinoma (MCC)
- MCC is a rare, aggressive skin cancer that is increasing in incidence1
- 1,600 patients are newly diagnosed with MCC in the US every year
- Metastatic MCC has a poor prognosis, with 5-year overall survival (OS) rates of 39% for patients with regional lymph node involvement and 18% for patients with distant metastatic disease2
- There is a strong unmet need for novel MCC treatments
  - Cytotoxic chemotherapy leads to high objective response rates (ORR), but responses are not durable
  - Median progression-free survival (PFS) after chemotherapy is 90 days3
- MCC pathogenesis suggests a strong rationale for immunotherapy4
  - Around 80% of MCC cases in the US are associated with Merkel cell polyomavirus (MCPyV)
  - High mutational burden, associated with a large number of predicted neoantigens, has been reported in MCPyV-negative MCC5
- PD-1/PD-L1 blockade has been associated with durable responses in a minority of MCC patients6,7

aNK Cell Therapy
- NK cells are cytotoxic lymphocytes that play a central role in innate immunity
- aNK cells are derived from a human, IL-2–dependent NK cell line that was established from the peripheral blood mononuclear cells of a 50-year-old male diagnosed with non-Hodgkin lymphoma8
- aNK cells are highly cytotoxic to a broad range of tumor cells, including MCC cell lines9–10
- Phase 1 studies suggest that aNK cell therapy is well tolerated and has antitumor activity11
- This ongoing phase 2 study seeks to determine the efficacy of aNK cell therapy in advanced MCC (NCT number: NCT02465957)

Methods
Study Design
- Multicenter, non-randomized, open-label, phase 2 trial using a Simon optimal two-stage design
- aNK cells administered IV at 2 x 10⁹ cells/m² on 2 consecutive days every 2 weeks

Enrollment Criteria
- Histologically confirmed unresectable stage 3B or stage 4 MCC
- Male or female patients ≥18 years old
- ECOG performance status of 0–2
- No major surgery within 30 days before study entry and adequate cardiac, liver, and kidney function

Endpoints
- Primary endpoint: Four-month PFS
- Secondary endpoints: ORR, time to disease progression, OS, safety and toxicity, quality of life

Results
- As of August 2016, 3 patients have been enrolled
- Adverse events (AEs) are summarized below:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient Demographics</th>
<th>aNK Dose (Cells/m²)</th>
<th>AEs Related to aNK Administration</th>
<th>AEs Unrelated to aNK Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>76-year-old white male</td>
<td>2 x 10⁹</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>75-year-old white male</td>
<td>2 x 10⁹</td>
<td>Grade 1 chills</td>
<td>Grade 2 leg pain, fatigue</td>
</tr>
<tr>
<td>3</td>
<td>81-year-old white male</td>
<td>2 x 10⁹</td>
<td>Grade 1 tingling at lesion site, chest rash, chills, vellus</td>
<td>Grade 1 arm mass, cold intolerance, hypothyroidism, dry mouth</td>
</tr>
</tbody>
</table>

- The efficacy criterion for the first stage of the study has been met, with 1 patient demonstrating a confirmed partial response (PR) associated with clinical resolution of macroscopic lesions (see Figure 1 below)
  - Impressive PR (73% regression) noted at wk 15 scans; radiologic complete response (CR) at wk 24
  - Received aNK cell therapy for 28 weeks; treatment discontinued due to discovery of an MCC lesion on the arm and residual MCC cells at 1 of the 2 biopsied scalp tumors; patient continues to feel well.
  - The patient was previously treated with pembrolizumab, intravesional therapies, and somatostatin analogues, each of which were discontinued after progressive disease (PD)
- Two other patients had PD and have been discontinued from the trial
  - In 1 patient, changes in superficial tumors were observed after aNK cell infusion (see Figure 2 below)

Conclusions
- Adoptive cellular therapy with allogeneic aNK cells was well tolerated in 3 patients with advanced MCC
- A radiologic CR has been observed in a patient with MCC refractory to PD-1 blockade
- The prespecified efficacy criterion for the first stage of the trial has been met, and enrollment is ongoing
- Correlative studies of tumor biopsies (including MHC I and PD-L1 expression, CD8+ T cell infiltration status, genomics, transcriptomics, and proteomics) are ongoing
- This protocol has been amended to combine aNK cell therapy with ALT-803 (an IL-15 superagonist)

References

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