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

Abstract # 45

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Background

Merkel Cell Carcinoma (MCC)

- MCC is a rare, aggressive skin cancer that is increasing in incidence[1]
  - 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 disease[2]
- There is a strong unmet need for novel MCC treatments
  - Cytotoxic chemotherapy leads to high objective response rates (ORR)[3], but responses are not durable
  - Median progression-free survival (PFS) after chemotherapy is 90 days[3]
- MCC pathogenesis suggests a strong rationale for immunotherapy[4]
  - 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 MCC[5]
  - PD-1/PD-L1 blockade has been associated with durable responses in a minority of MCC patients[6-7]

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 lymphoma[8]
- aNK cells are highly cytotoxic to a broad range of tumor cells, including MCC cell lines[9-10]
- Phase 1 studies suggest that aNK cell therapy is well tolerated and has antitumor activity[11]
- 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 10^9 cells/m^2 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
- Prior systemic cytotoxic chemotherapies and/or novel immunotherapy treatments for MCC are allowed
  - A washout period of 2 weeks prior to aNK cell treatment is required
- ECOG performance status of 0–2
- Willingness to consent to fresh tissue biopsy and biobanking of tissue samples
- 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:

Patient	Patient Demographics	aNK Dose (Cells/m^2)	AEs Related to aNK Administration	AEs Unrelated to aNK Administration
1	76-year-old white male	2 x 10^9	None	None
2	75-year-old white male	2 x 10^9	Grade 1 chills	Grade 2 leg pain, fatigue
3	81-year-old white male	2 x 10^9	Grade 1 tingling at lesion site, chest rash, chills, vitiligo	Grade 1 arm mass, cold intolerance, hypothyroidism, dry mouth

- 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, intralesional 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)

Fig 1: Response with aNK Cell Therapy in a Patient With MCC Refractory to Chemotherapy, Radiation Therapy, and PD-1 Blockade

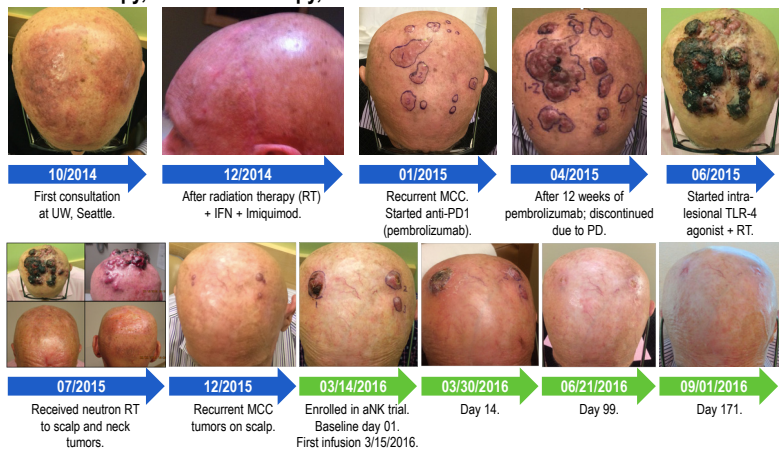
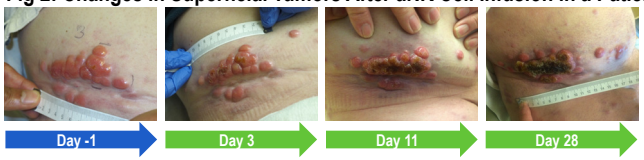


Fig 2: Changes in Superficial Tumors After aNK Cell Infusion in a Patient With PD



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

1) Fitzgerald TL et al. *Am Surg.* 2015;81:802-6. **2)** Lemos BD et al. *J Am Acad Dermatol.* 2010;63:751-61. **3)** Bhatia S et al. *J Natl Cancer Inst.* 2016;108:1-9. **4)** Paulson KG et al. *J Invest Dermatol.* 2013;133:642-6. **5)** Goh G et al. *Oncotarget.* 2016;3403-15. **6)** Nghiem PT et al. *New Engl J Med.* 2016;2542-52. **7)** Kaufman HL et al. *Lancet Oncol* 2016;10:1374-85. **8)** Gong JH et al. *Leukemia.* 1994;8:652-8. **9)** Klingemann HG et al. *Biol Blood Marrow Transplant.* 1996;2:68-75. **10)** Swift BE et al. *Haematologica.* 2012;97:1020-8. **11)** Arai S et al. *Cytotherapy.* 2008;10:625-32.

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Acknowledgments

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