First-in-Human Phase I Study of Nicotinamide-Expanded Related Donor Natural Killer Cells for the Treatment of Relapsed/Refractory Non-Hodgkin Lymphoma and Multiple Myeloma

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**Background**

Natural Killer (NK) Cells

- Innate lymphocytes of the immune system that lack antigen specificity and serve as an attractive immunotherapeutic approach to the treatment of lymphomas and other malignancies.
- Previous clinical trials of NK therapies have been limited due to the in vivo persistence of NK cells and related toxicity.
- Nicotinamide (NAM)-based technology, previously used for hematopoietic stem cells, has been used to expand and improve the functions and persistence of NK cells.
- In preclinical studies, NAM-NK demonstrated cytotoxicity as well as increased tumor-homing and antitumor efficacy.

**Study Design**

Objective

- Phase I dose escalation phase: Dose limiting toxicity (DLT) defined by four patients receiving 1.5 x 10^7/kg NAM-NK cells.
- Following DLT, dose escalation to DLT level + 1 x 10^7/kg NAM-NK cells.

Key Inclusion Criteria

- Aged 18–80 years; no history of allergy to NAM
- Good Performance Status (Karnofsky 70–100%)
- Aged ≥ 60 years, no history of severe hematologic toxicity
- Aged < 60 years, no history of vomiting
- Aged < 60 years, no history of severe skin toxicity
- Aged < 60 years, no history of severe mucosal toxicity
- Aged < 60 years, no history of severe renal toxicity
- Aged < 60 years, no history of severe hepatic toxicity

**Results**

Patient Demographics

- Age (median [range]): 62 (47–70) years
- Gender: Male: 4, Female: 6

**Safety**

- All patients received 2 x 10^8 cells/kg dose
- No DLT
- No treatment-related toxicity or dose-limiting toxicity
- No pneumonitis
- No aGVHD
- No grade 4 adverse events
- No grade 5 adverse events
- Median follow-up: 24 months

**Efficacy**

- 6 patients with NHL evaluable for response
  - 5 patients with complete response (CR), 1 partial response (PR)
  - 3 patients with stable disease (SD)
  - 2 patients with progressive disease (PD)

**Conclusions**

- NAM-NK was well-tolerated without infusion toxicity or DLT.
- Maximum target dose of 2 x 10^8 cells/kg achieved
- NAM-NK cells were detectable in blood and bone marrow, and exhibited proliferative phenotype and cytolytic function.
- Clinical activity was observed, including complete responses in patients with lymphoma and myeloma.
- Additional patients will be treated at the MTD to further evaluate safety and efficacy.
- Future directions include cryopreservation and exploration of multiple treatment cycles.

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