Background

NK Cells

- Natural killer (NK) cells play a critical role in tumor surveillance and cancer cell killing through a variety of mechanisms.
- Adoptive transfer of cytolytic NK is an attractive immunotherapeutic approach to the treatment of lymphomas and other malignancies.
- However, previous clinical success has been modest due to limited persistence of NK cells and their impaired effector function.

This phase I study explores the use of haploidentical NK cells that are expanded or ex vivo with nicotinamide (NAM).

NK Expansion Process

- Cytokine Stimulation
- Cellular Cytotoxicity (ADCC)
- Natural Cytotoxicity

NAM-NK

- Nicotinamide (NAM) modulates cellular stress, cellular energy, mitochondrial functions and gene expression.
- NAM has been successfully used to expand hematopoietic stem cells in umbilical cord blood for allogeneic bone marrow transplantation.
- NAM-based technology has been adapted for adult donor NK cells, modulating the characteristics and function of NK cells expanded ex vivo.
- In preclinical studies, NAM-NK demonstrated cytotoxicity as well as increased homing, proliferation and persistence.

We report preliminary results of a phase I study of NAM-NK in patients with lymphoma and multiple myeloma.

Phase I Study Design

Objectives

- Dose escalation phase: Determine maximum tolerated dose of NAM-NK
- Expansion phase: Overall disease response in multiple myeloma and lymphoma

Key Inclusion Criteria for Patients with Lymphoma*

Age ≥18 to ≤80 years
- Evidence of relapsed/refractory disease that has failed conventional therapy
- A measurable disease ≥1.5 cm in diameter
- Measurable disease
- Acceptable organ function
- History of adenopathy in upper and lower abdomen; bone marrow involvement
- No grade 3 or 4 adverse events
- No cytokine release syndrome or neurotoxicity was observed in the first 2 to 6 patients treated (n=2)
- No dose limiting toxicity
- Expected short term neutropenia and thrombocytopenia observed

Study Schema

- Donor NK cells are obtained and undergo ex vivo expansion
- Patient undergoes lymphodepleting preparative regimen of cyclophosphamide and fludarabine
- Patient receives expanded haploidentical NK cells followed by short course IL-2
- Monoclonal antibodies administered prior to and after NAM-NK infusion

NAM-NK Dose Levels

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>TNC dose</th>
<th>TNC dose</th>
<th>TNC dose</th>
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<td></td>
<td>Day 0</td>
<td>Day 2</td>
<td>Total</td>
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<tr>
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<td>1 x 10^6/kg</td>
<td>1 x 10^6/kg</td>
<td>2 x 10^6/kg</td>
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<tr>
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<td>5 x 10^6/kg</td>
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<tr>
<td>3</td>
<td>1 x 10^7/kg</td>
<td>1 x 10^7/kg</td>
<td>2 x 10^7/kg</td>
</tr>
</tbody>
</table>

Study

- TNC: 1.2 x 10^6/kg
- CD3: 1.2 x 10^6/kg
- NK: 1.9 x 10^6/kg
- CD3: 1.2 x 10^6/kg
- PK: 1.9 x 10^6/kg
- Treatment tolerated well with expected transient pancreatitis
- Complete clinical and radiologic response

Results

- Patient 002: Results
  - Symptomatic resolution of bulky inguinal lymphadenopathy
  - Complete response by CT/PET scan
  - Biopsy of residual mass showed no evidence of lymphoma
  - Evidence of expansion of donor NK cells in peripheral blood

Patient 002: Treatment Course

67 year old patient with follicular lymphoma diagnosed in Oct 2012; Stage IV; adenopathy in upper and lower abdomen; bone marrow involved

History:
- 12/2012: Front-line therapy: CVP
- 12/2013: Relapse clinically and by CT
- 4/2014: Salvage therapy: Bendamustine Ritux 6 cycles: PR with remaining Left inginal lymph node (1.9 x 1.3 cm)
- 1/2017: Progression bilateral inginal LN, left bulky and marrow involved
- 3/2017: REPOCH x 2 cycles. Progression
- 7/2017: R-ICE with kinetic failure and progression after 2 cycles

NAM-NK Treatment:
- March 2018: Treated at Dose level 1 TNC: 2 x 10^6/kg/day
- CD3: 1.2 x 10^6/kg; NK: 1.9 x 10^6/kg
- Treatment tolerated well with expected transient pancreatitis
- April 2018: Complete clinical and radiologic response

Conclusions

- Manufacturing of NAM-expanded haploidentical NK cells is feasible and effective
- No infusion reactions were observed
- Preliminary clinical efficacy was observed
- Trial continues to actively enroll eligible patients with non-Hodgkin lymphoma and multiple myeloma

Acknowledgements

ClinicalTrials.gov Identifier: NCT03019666
Supported by Gilead Science, Ltd.
References