

1. STUDY SYNOPSIS

COMPOUND RevM10-HSC or REVM10/polAS-HSC

STUDY TITLE A PHASE I/II STUDY OF THE SAFETY AND FEASIBILITY OF REVM10 OR REVM10/ANTISENSE POL 1 TRANSDUCED HEMATOPOIETIC STEM CELLS (HSC) IN HIV-1 RELATED NON-HODGKIN'S LYMPHOMA PATIENTS ALREADY BEING TREATED WITH HIGH DOSE CHEMOTHERAPY AND PERIPHERAL BLOOD STEM CELL SUPPORT.

DEVELOPMENT PHASE Phase I /II

NUMBER OF CENTERS AND COUNTRIES

Up to 7 centers in the US.

OBJECTIVES

PRIMARY OBJECTIVES:

To determine the safety of infusion of RevM10 or RevM10/antisense pol 1 transduced HSC (RevM10/polAS-HSC) when administered with standard peripheral blood stem cell (PBSC) support for high-dose chemotherapy (HDT).

To determine gene marking of lymphoid and myeloid cells in peripheral blood, bone marrow and/or lymph nodes derived from RevM10-HSC or RevM10/polAS-HSC.

SECONDARY OBJECTIVE:

To determine the anti-retroviral effect of the treatment.

DESIGN

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Open labe

A single arm phase I/II study to determine the safety and feasibility of RevM10-HSC or RevM10/polAS-HSC infusion when added to standard PBSC support of high-dose chemotherapy in HIV-1 patients with non-Hodgkin's lymphoma, and to determine the extent of RevM10 or RevM10/polAS gene marking of lymphoid and myeloid cells in peripheral blood, bone marrow and/or lymph nodes.

SUBJECTS

HIV-1 patients with poor prognosis NHL (features include increased LDH, and/or Stage III or IV, and/or reduced performance status ECOG ≥ 2) in first chemotherapy induced remission, or any patients who respond but fail to enter complete remission after four cycles of standard chemotherapy, or those who are in a responding relapse after primary treatment.

SAMPLE SIZE The sample size is 15 evaluable patients. Patients who discontinue study participation prior to month 2 post-infusion will be replaced; however, those who discontinue after 2 months will not be replaced.

TREATMENTS **Chemotherapy for Mobilization**

The mobilization phase of the study will follow the site's standard protocol for chemotherapy/G-CSF mobilization of PBSC. Patients will undergo apheresis when the WBC is $> 1000/\mu\text{L}$. If a patient does not mobilize $> 5.0 \times 10^5$ CD34/kg for RevM10-HSC or RevM10/polAS-HSC transduction in addition to the 2.0×10^6 CD34 cell/kg in the unmodified PBSC collected for support of the high dose chemotherapy, the patient will be discontinued from the study and replaced.

High-Dose Therapy (HDT)/Untransduced PBSC support

Patients continuing to the treatment phase will be treated according to the site's standard protocol for high dose chemotherapy for HIV associated non-Hodgkin's Lymphoma supported by transplant of PBSC. The untransduced PBSC will contain $\geq 2.0 \times 10^6$ CD34 cells/kg to ensure safe hematopoietic engraftment.

RevM10-HSC or RevM10/polAS-HSC

The RevM10-HSC or RevM10/polAS-HSC is a gene modified cellular product derived from transduction of autologous, mobilized PBSC. The cellular population containing hematopoietic stem cells is selected and then transduced with a retroviral vector containing RevM10 or RevM10/polAS. The entire dose of RevM10-HSC or RevM10/polAS-HSC will be administered to the patient. For a patient to be considered evaluable for efficacy, the minimum RevM10-HSC or RevM10/polAS-HSC dose to be administered must be at least 1.5×10^5 viable cells/kg after transduction.

SAFETY VARIABLES

1. Hematologic parameters for engraftment of non- transduced PBSC post-transplant
2. Replication competent retrovirus (RCR) detection in peripheral blood mononuclear cells (PBMNC)

EFFICACY VARIABLES

1. Presence of RevM10 or RevM10/polAS in peripheral blood myeloid and lymphoid lineages, bone marrow and/or lymph nodes.
2. CD4+ T cell count.
3. Plasma HIV-1 RNA.

PHARMACOKINETICS

The time to appearance of RevM10 or RevM10/polAS in the peripheral blood and the percentage of peripheral lymphocytes, bone marrow and/or lymph node cells with detectable RevM10 or RevM10/polAS will be evaluated and an attempt made to relate these variables to RevM10-HSC or RevM10/polAS-HSC dose reinfused.

STATISTICAL METHODS

Safety data will be summarized for all patients who receive RevM10-HSC or RevM10/polAS-HSC infusion. Efficacy data will be presented on the basis of the evaluable population, which consists of patients who are mobilized, receive HDT, receive the infusion of RevM10-HSC or RevM10/polAS-HSC, and continue study participation through the 2 month visit. Both safety and efficacy data will be summarized by either descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) or contingency table (n and %), whichever is appropriate. The statistics will be presented by visit whenever appropriate, ignoring the effect of center.