ISCT Annual Meeting 2017

Add back of selectively depleted alloreactive T-cells retaining the full immune repertoire of mature T-cells improves event-free survival (GRFS) and overall survival in a T-cell depleted haploidentical HSCT

Halvard Bönig[1], Jurjen Velthuis[2], Irwin Walker[3], Johan Maertens[4], Philippe Lewalle[5], Eduardo Olavarria[6], Dominik Selleslag[7], Manfred Rüdiger[2], Menno van der Hoorn[2], Lisya Gerez[2], Jeroen Rovers[2], Stephan Mielke[8] and Denis Claude Roy[9]

[1]German Red Cross Blood Center and Institute for Transfusion Medicine and Immunohematology, Johann-Wolfgang-Goethe University, Hematopoietic Cell Research Group, Frankfurt, Germany, [2]Kiadis Pharma, Amsterdam-Duivendrecht, The Netherlands, [3]Department of Medicine, Juravinski Hospital and Cancer Centre, Hamilton, Canada, [4]Department of Hematology, University Hospital Gasthuisberg Leuven, Leuven, Belgium, [5]Laboratory of Experimental Hematology, Institut Jules Bordet, ULB, Brussels, Belgium, [6]Hammersmith Hospital, Imperial College, London, United Kingdom, [7]AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium, [8]Division of Hematology and Oncology, Department of Medicine II, Julius-Maximilian-University, Würzburg, Germany, [9]Blood and Marrow Transplantation Program, Div. of Hematology-Oncology, Hôpital Maisonneuve-Rosemont, University of Montreal, Quebec, Canada

Current HSCT techniques limit the use of haploidentical donor grafts as presence of donor T-cells cause severe GVHD and absence or repression of T-cells will often result in occurrence of opportunistic infections and relapse. Administering T-cells selectively depleted of alloreactivity should reduce the incidence and severity of lethal complications and GVHD and possibly reduce relapse rates.

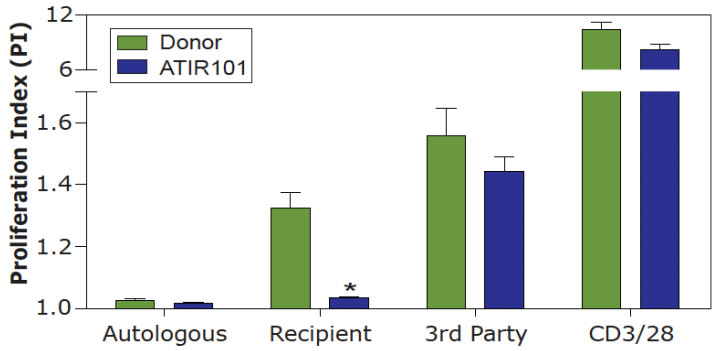
In vitro studies into the characterization of ATIR101, manufactured during an open-label, multicenter Phase II study (CR-AIR-007; NCT01794299, 23 patients with median age of 41 years (range 21-64) showed that ATIR101 consists of selectively allo-depleted donor T-cells while retaining reactivity to other unrelated antigens and stimuli (figure 1). All CD4- and CD8-positive T-cell memory subtypes (naïve, effector, central memory and effector memory) were preserved as well T-cells specific for viral peptides (figure 2) and FoxP3-positive regulatory T-cells indicating that ATIR101 retains the full mature T-cell immune repertoire but is devoid of recipient-directed alloreactivity.

ATIR101 has been administered to recipients of a CD34-selected haploidentical HSCT without the use of any immune suppression. Within 1 year follow up of the entire population, no patient developed grade III/IV acute GVHD after infusion of ATIR101. No patient died within 100 days post-HSCT and the overall survival of patients receiving ATIR101 was significantly improved compared to a historic control group, with a 1-year survival of 61% in the HSCT+ATIR101 group compared to 20% in the control group (Table 1). Only two patients receiving ATIR101 experienced a relapse within the first year, occurring at 60 and 90 days post-HSCT, respectively. Determination of GVHD-free, relapse free survival (GRFS) showed 57% GRFS in the HSCT+ATIR101 group which compares favorably to 20% GRFS in the control

group, and even to 40% GRFS in Matched Unrelated Donor (MUD) transplants collected from the same clinical centers.

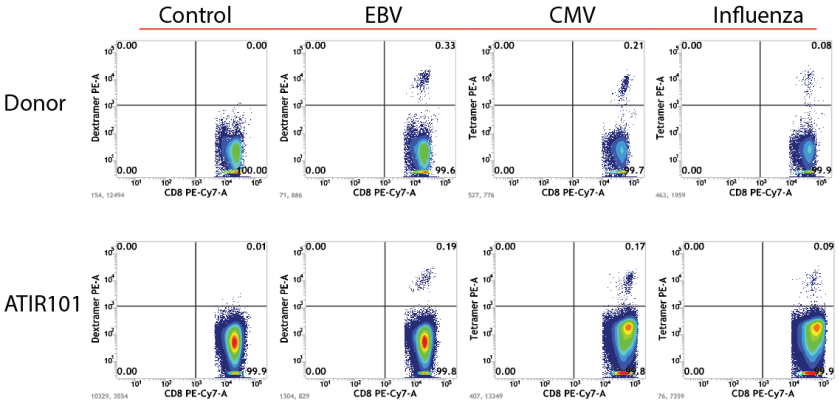
This study shows that ATIR101 consists of selectively depleted alloreactive T-cells retaining the full immune repertoire; administration of a high dose of ATIR101 does not cause severe GVHD while significantly improving transplantation outcome in the absence of immune suppression.

Figure 1. Selective depletion of recipient-reactivity in ATIR101



ATIR 101 and original donor cells were stimulated with either irradiated donor cells (autologous), irradiated recipient cells, irradiated 3rd party cells or anti CD3/28. ATIR101 is selectively depleted of recipient-reactivity only (P<0.05, n= 23)

Figure 2. Anti-viral T-cells in donor and ATIR101



ATIR101 and original donor cells were stained with PE-labeled HLA-A2 multimers. Pathogen-specific T-cells are preserved in ATIR101.

Table 1

Kaplan-Meier Estimates of:	6 months after HSCT	12 months after HSCT
Overall Survival	83% [HAPLO 63%]	61% [HAPLO 20%]
Relapse-Related Mortality	5%	10%
GRFS	78% [HAPLO 57%] [MUD 63%]	57% [HAPLO 20%) [MUD 41%]