Abstract: P1403

Title: SI101-01 PHASE I/II STUDY EVALUATING SAFETY AND EFFICACY OF ALLOGENEIC SMART101 T-LYMPHOID PROGENITOR INJECTION TO ACCELERATE IMMUNE RECONSTITUTION AFTER T-CELL DEPLETED ALLOGENEIC HSCT

Abstract Type: Poster Presentation

Session Title: Gene therapy, cellular immunotherapy and vaccination - Clinical

Background:

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment option for several patients (pts) with hematological malignancies. Reconstitution of a T cell compartment may take up to 2 years, although it is of key importance in the defense against pathogens and as a mediator of graft versus tumor immune response. T-cell depletion (TCD) allo-HSCT by *in vivo* graft manipulation with anti-thymocyte globulin (ATG) and *ex vivo* graft CD34+ selection are strategies used to reduce the risk of GvHD without increased relapse or decreased survival. But immune recovery after TCD allo-HSCT is slow due to the scarcity of T-cells administered in the graft.

SMART101 is a cellular therapy using CD34-CD7+ T-lymphoid progenitors produced in culture from mobilized peripheral blood CD34+ cells of the transplant donor via Smart Immune's ProTcell platform. This GMP *ex-vivo* lymphoid niche culture system, using Notch ligand Delta-like 4 coupled to IgG2 Fc fragment (DLL4-Fc) and RetroNectin® in the presence of a specific cytokines, mimics the initial steps of bone marrow lymphoid and T-cell differentiation. According to preclinical data, SMART101 cells infused into a pt should complete their differentiation directly in the thymus with positive and negative TCR selection, leading to the generation of a polyclonal repertoire of educated naïve T-cells faster than an allograft with hematopoietic stem cell alone.

Aims:

The SI101-01 clinical study seeks to provide proof of principle that SMART101 cells can rapidly complete their differentiation in the thymus into naïve T-cells giving rise to long-lasting polyclonal donor T-cells without GvHD-inducing potential to reduce the non-relapse and disease relapse mortality post TCD allo-HSCT.

Methods:

This Phase I/II study (NCT04959903) evaluates the safety and efficacy of SMART101 infused between D4-D10 post-TCD allo-HSCT in adult (match related or unrelated donor [MUD]) and pediatric (MUD) pts with AML, ALL or high-risk MDS. It is a dose-escalation study evaluating 2 dose levels (DL) of SMART101 (0.75 and 1.5 x 10^6 CD7+ cells/kg) with 12 pts at the recommended dose. Pts receive a TCD allo-HSCT following myeloablative conditioning with upfront ATG administration. The co-primary endpoints of the trial are (i) the occurrence of unacceptable toxicity and acute GvHD; (ii) the immune reconstitution efficacy defined by CD4+ T cells count ≥ 50/µL by D100. Secondary endpoints evaluate the overall safety profile and non-relapse/relapse mortality.

Results:

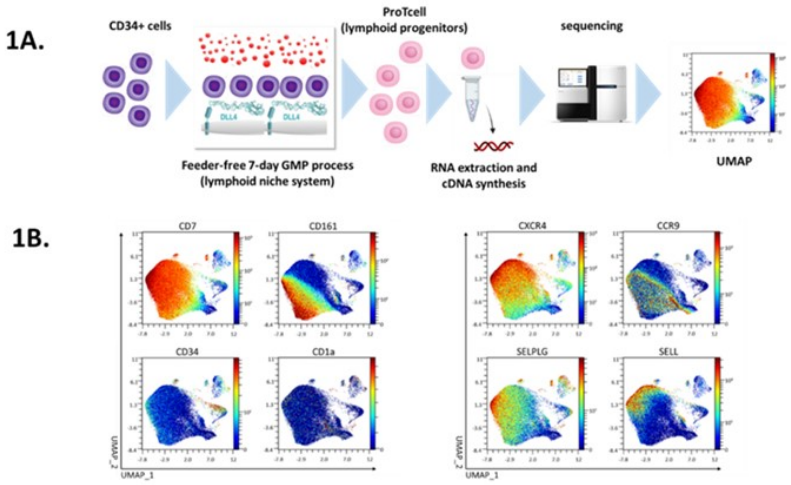
Fig 1 shows SMART101 cells characterization by single cell RNAseq. Most of the cells express CD7 and about half of them are CD161+, both being lymphoid markers. In contrast, they do not express CD34 and not yet CD1a, confirming their early stage on T-cell differentiation. Regarding the molecules involved in the migration of progenitors into the thymus, most of the cells are positive for chemokine receptor CXCR4 and for SELL, coding for L-selectin, an adhesion molecule. CCR9, a chemokine receptor mediating chemotaxis to the thymus and SELPLG coding for PSGL-1a glycoprotein important for cell trafficking are also expressed in a smaller fraction of the cells.

As of February 23, 1 patient was enrolled at DL-I. SMART101 was well tolerated, with no aGvHD after 8 weeks with engraftment at D11 post-transplant. The study design, preliminary safety and clinical data from the first DL as well as details of the ProTcell platform will be presented at the EHA 2023.

Summary/Conclusion:

SMART101 is the first-generation of allogeneic T lymphoid progenitor cells obtained through Smart Immune's ProTcell platform, the first scalable progenitor T-cell manufacturing system in clinics. The early data indicate that SMART101 is well tolerated with a good safety profile.

Figure 1: single cell RNAseq analysis of ProTcell



1A. CD34+ cells from healthy donors are differentiated into lymphoid progenitors through a 7-day GMP process. mRNA sequencing was performed in a single cell fashion with the 10x Genomic technology. 1B. Expression intensity of differentiation markers Differentiation markers (CD34, CD7, CD161, CD1a) and homing markers (SELL, SELPLG, CXCR4 and CCR9) are depicted in the UMAPs.

Keywords: Thymic function, Post-transplant, CD4+ T cells, Allogeneic hematopoietic stem cell transplant