An exploratory, open-label, multicenter study to evaluate safety and efficacy of a two-dose regimen of ATIR101 in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor

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INTRODUCTION

Previous studies demonstrated that donor lymphocytes, selectively depleted of alloreactive T-cells (ATIR101), could be given safely in the haploidentical HSCT setting up to $2x10^6$ viable T-cells/kg. In 42 patients a single dose of ATIR101 was given without causing grade III/IV acute GVHD, without the use of prophylactic immunosuppression. This confirms efficacy of the (photo)depletion method used and attributes to its beneficial safety profile of ATIR101. In an ongoing phase 2 study, CR-AIR-007 (NCT01794299)(Abstract #O042), preliminary data shows that addition of ATIR101 28 days post-HSCT results in a reduction of transplant-related mortality (TRM) and improvement of overall survival and event-free survival, compared to a T-cell depleted haploidentical HSCT without DLI add-back. Incidence of life threatening infections and as a result TRM might be further reduced with infusion of additional doses of ATIR101.

RESULTS

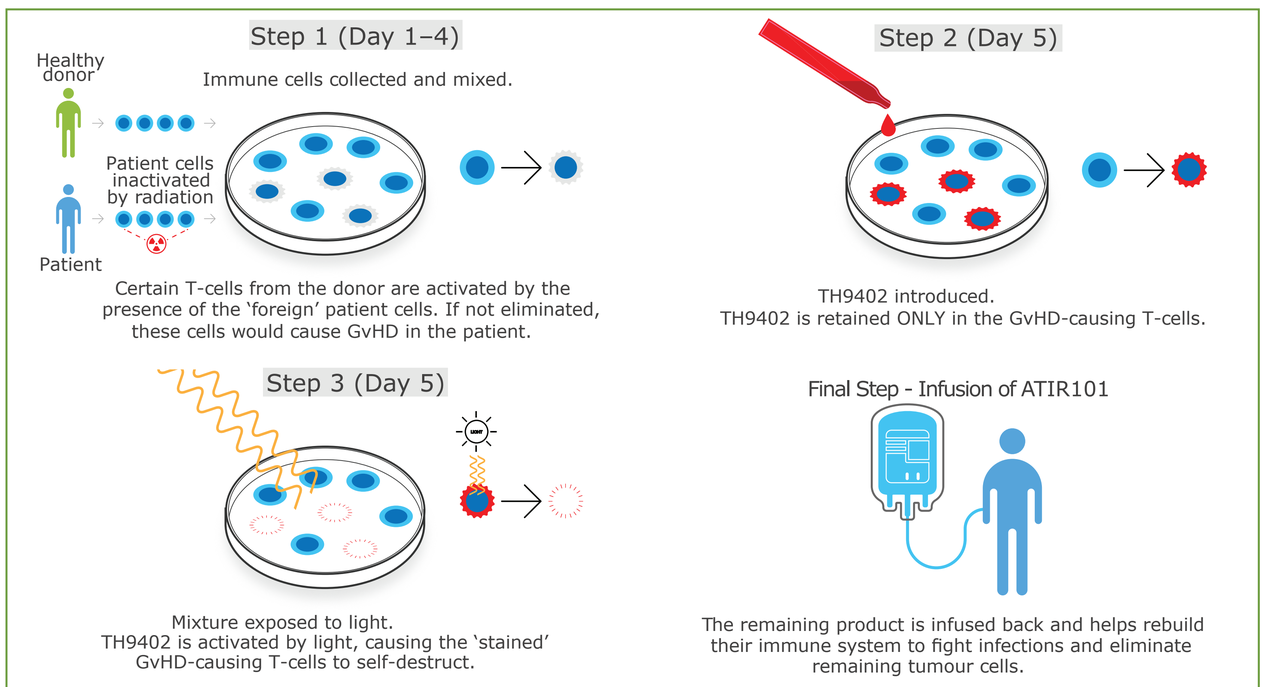

Figure 1. ATIR101 Manufacturing.
Donor cells are co-incubated with irradiated recipient cells in a uni-directional mixed lymphocyte reaction (MLR). The activated donor cells are loaded with TH9402 which is selectively retained in recipient-alloreactive cells. Light-exposure converts TH9402 into its toxic form to generate ATIR, a selectively allo-depleted cell therapy product for adoptive immune transfer.

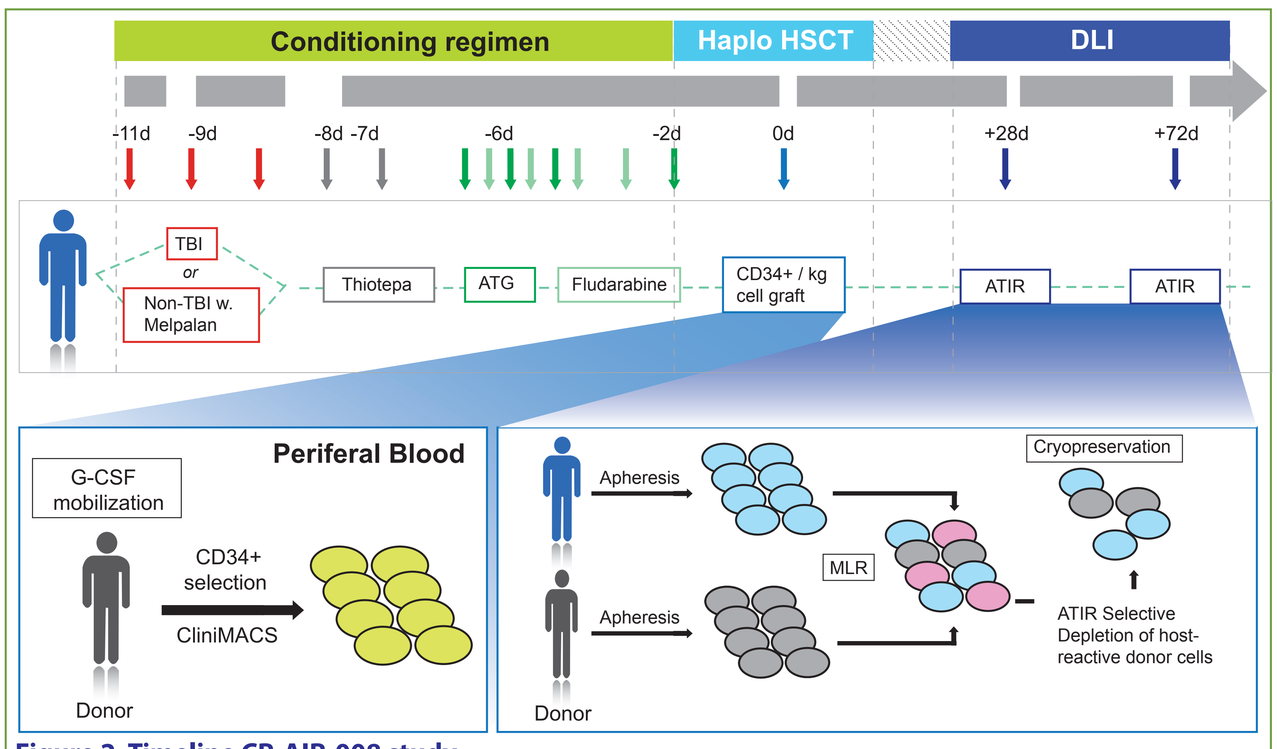

Figure 2. Timeline CR-AIR-008 study
Patients will undergo a myeloablative HSCT using a CD34-selected graft from a haploidentical donor. Post HSCT, donor lymphocytes selectively depleted of alloreactive T-cells (ATIR101) will be infused on day 28 and day 72 at a dose of $2x10^6$ cells/kg.

Patient inclusion criteria

- Any of the following hematologic malignancies:
  - Acute myeloid leukemia (AML) in first remission with high-risk features or in second or higher remission
  - Acute lymphoblastic leukemia (ALL) in first remission with high-risk features or in second or higher remission
  - Myelodysplastic syndrome (MDS): transfusion-dependent, or intermediate or higher IPSS-R risk group
- Karnofsky performance status ≥ 70%
- Eligible for haploidentical stem cell transplantation according to the investigator
- Male or female, age ≥ 18 years and ≤ 65 years

Patient exclusion criteria

- Availability of a fully matched related or unrelated donor following a donor search
- Diffusing capacity for carbon monoxide (DLCO) < 50% predicted
- Left ventricular ejection fraction < 50% (evaluated by echocardiogram or MUGA)
- AST > 2.5 x ULN (CTCAE grade 2)
- Bilirubin > 1.5 x ULN (CTCAE grade 2)
- Creatinine clearance < 50 mL/min (calculated or measured)
- Prior allogeneic HSCT
- Estimated probability of surviving less than 3 months
- Known allergy to any of the components of ATIR101 (e.g., dimethyl sulfoxide)
- Known presence of HLA antibodies against the non-shared donor haplotype
- Any other condition which, in the opinion of the investigator, makes the patient ineligible for the study

CONCLUSION

The study has been accepted by Regulatory authorities in Belgium, Canada, Germany, United Kingdom and United States of America and it currently enrolling patients. First data on safety of the additional dose administration of ATIR101 to be expected 2H 2016.
This study will be used to confirm safety of the second dose administration of ATIR101, which will subsequently be used in a randomized, phase III study, comparing T-cell depleted HSCT + ATIR101 versus T-cell replete HSCT using post transplantation cyclophosphamide (PTCy).

For more information on this clinical trial and other clinical trials from Kiadis pharma, please contact us at clinicaltrials@kiadis.com

MATERIALS & METHODS

In an open-label, multicenter phase 2 study (CR-AIR-008; NCT02500550), 15 patients with acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL) or myelodysplastic syndrome (MDS) will undergo a haploidentical HSCT with adjuvant administration of ATIR101. Conditioning regimen consists of either TBI (1200 cGy in 6 fractions) or melphalan (60 mg/m^2 once daily for 2 days), in combination with thiotepa (10 mg/kg), fludarabine (30 mg/m^2 once daily for 5 days) and ATG (2.5 mg/kg once daily for 4 days). Patients will receive a T-cell depleted graft ($CD34^+$ selection) from a haploidentical donor, targeted to contain between $8\text{-}11\times10^6$ $CD34^+$ cells/kg with a maximum of 3×10^4 $CD3^+$ cells/kg. First ATIR101 infusion at a dose of $2x10^6$ viable T-cells/kg is given between 28 and 32 days after the HSCT. Patients will receive a second ATIR101 infusion at the same dose of $2x10^6$ viable T-cells/kg between 70 and 74 days after the HSCT. To assess safety of the second ATIR101 infusion, the first 6 patients treated will be evaluated for the occurrence of dose limiting toxicity (DLT), defined as acute GVHD grade III/IV within 120 days post HSCT (or within 42 days after the second ATIR101 infusion in case of prior dose delays).

Conflict of Interest statement
SM and DCR have received research funding and/or travel grants from Kiadis pharma. RF, LG, KR, MR and JR are employees of Kiadis pharma. MR and JR have personal financial interest in Kiadis pharma.