Other endpoints:

- Immune reconstitution
- Incidence and severity of acute and chronic GVHD
- Incidence and severity of viral, fungal, and bacterial infections
- Incidence and severity of adverse events
- Quality of life: FACT-BMT, SF-36, MDASI, and EQ-5D-5L total scores

Study Population:

The study population consists of male or female patients aged 18-70 years with a hematologic malignancy (AML in remission, ALL in remission, or MDS) who are eligible for a haploidentical HSCT. The Karnofsky Performance Status (KPS) should be ≥ 70%. Each patient must have a related haploidentical donor aged 16-75 years available, who is eligible according to local requirements and regulations. Vulnerable participants such as pregnant women and children will not be enrolled in the study.

In total, 250 patients are planned to be randomized.

Phase:

III

Description of Sites Enrolling Participants:

Approximately 50 sites globally are planned to enroll participants in the study.

Description of Study Intervention:

The advanced therapy medicinal product (ATMP) ATIR101 is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells using photodynamic treatment (PDT) with the photosensitizing reagent TH9402. ATIR101 is presented as a "dispersion for infusion". Patients in the ATIR101 group will be infused with ATIR101 intravenously (IV) at a single dose of 2.0×10^6 viable T-cells/kg body weight between 28 and 32 days after a CD34-selected HSCT (or later if required by the patient's medical condition).

The drug cyclophosphamide, which is part of the control intervention, is presented as a lyophilized powder for IV infusion, which is commercially available for human use under various brand names. Patients in the PTCy group will be infused with cyclophosphamide 50 mg/kg/day IV at 3 and 4/5 days after a non-manipulated, T-cell replete HSCT.

Study Duration:

The estimated time from start of enrolment until completion of the interim data analysis of the primary endpoint amounts to 29 months. The estimated time from start of enrolment until completion of the final data analyses amounts to approximately 38 months.

Participant Duration:

Each patient is planned to be in the study for at least approximately 26 months, i.e. from signing informed consent to visit at 24 months post HSCT. Patient follow-up beyond 24 months post HSCT will be discontinued when a total number of 156 GRFS events has been reached. Each donor is planned to be in the study for approximately 1-2 months.

	Screening (between informed consent & confir-mation eligibility)	Pre-HSCT	HSCT (Day 0)	Week 1, 2, 3	Week 4	Week 5, 6, 7, 8, 9, 10	Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24	Follow-up beyond Month 24 every 6 months
CT scan thorax/chest X-ray	X [7]							
Echocardiogram/MUGA scan	X [7]							
Pulmonary function test	X [7]							
Creatinine clearance	X [8]							
Vital signs	X [9]		X	X	X [10]	X	X [11]	
Quality of life	X						X [12]	X [12]
Disease assessment [13]	X		X	X	X	X	X	X
Infection assessment	X	X	X	X	X	X	X	
CMV/EBV/adenovirus (PCR)	X		X	X	X	X	X	
Engraftment				X	X [16]	X [14]		
Chimerism				X [15]	X [16]	X [17]	X [17]	
GVHD assessment				X	X	X	X	X

[7] If not already done within 6 weeks before signing informed consent
[8] Calculated or measured, if not already done within 2 weeks before signing informed consent
[9] Including measurement of patient height at screening only
[10] For all patients (in ATIR101 group before infusion of ATIR101); Additionally, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1 hour, and 2 hours and continuous oxygen monitoring will be done if the patient has respiratory problems.
[11] Only at Month 3 and Month 4
[12] Only at Month 3, Month 6, Month 12, Month 24, Month 36, and Month 48
[13] Includes bone marrow biopsy/aspirate at Screening, Month 3, Month 6, Month 12, and Month 24 unless relapse has already been confirmed, and in case of suspected relapse
[14] In case of no neutrophil or platelet engraftment at Week 4, measurements are to be continued at weekly visits until engraftment.
[15] Only in case of suspected relapse
[16] For all patients (in ATIR101 group before infusion of ATIR101)
[17] Only at Week 10, Month 3, Month 6, Month 12, Month 24, and in case of suspected relapse post HSCT

2.2.2 Study Intervention

ATIR101, an individualized advanced therapy medicinal product (ATMP), is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells (using photodynamic treatment). ATIR101 is being developed as adjunctive treatment to haploidentical HSCT for the reduction of morbidity and mortality due to infections, GVHD, and/or relapse in patients with hematologic malignancies.

For manufacturing of ATIR101, donor and patient peripheral blood mononuclear cells (PBMCs) are collected by apheresis on the same day. For the patient this apheresis is done in advance of the conditioning regimen for the HSCT and for the donor this additional apheresis is done before the apheresis to collect the stem cell graft (PBSCs).

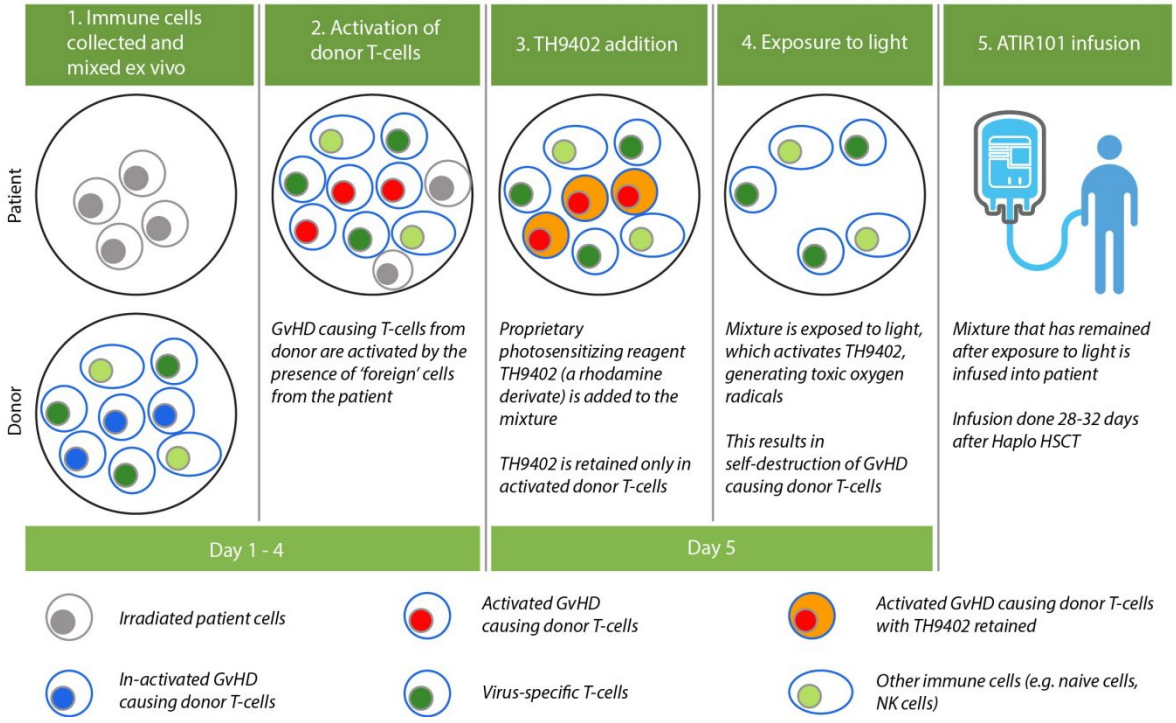


Figure 1 Schematic overview of the ATIR101 procedure

The selective depletion of host alloreactive T-cells in ATIR101 is shown schematically in Figure 1. During processing patient and donor cells are co-cultured in a mixed lymphocyte reaction (MLR) to stimulate activation of host alloreactive T-cells (the patient cells are gamma irradiated prior to the MLR). In the MLR, donor lymphocytes are activated against the major discordant major histocompatibility complex (MHC) antigens of the irradiated patient's cells. Those cells that are activated accumulate more light-sensitive TH9402 than non-activated cells and are consequently more susceptible to the effect of PDT.

The Blood and Marrow Transplant Clinical Trials Network has incorporated this composite endpoint into new prospective trials of allogeneic HSCT. It is believed to better assess a successful transplant because it incorporates survival and freedom from relapse as well as the occurrence of clinically significant GVHD with its well-recognized effects on quality of life.

3.3 Secondary Endpoints

Overall survival (safety and efficacy)

Overall survival (OS) is defined as the time from randomization until death from any cause.

Progression-free survival (efficacy)

Progression-free survival (PFS) is defined as the time from randomization until relapse, disease progression, or death, whichever occurs first.

Relapse-related mortality (efficacy)

Relapse-related mortality (RRM) is defined as the time from randomization to death due to disease relapse or disease progression.

Transplant-related mortality (safety and efficacy)

Transplant-related mortality (TRM) is defined as the time from randomization to death due to causes other than disease relapse or disease progression.

3.4 Other Endpoints

Immune reconstitution (efficacy)

- Time to T-cell reconstitution, defined as the time to CD3+ > 0.2×10^9/l in peripheral blood (at two consecutive measurements; time to first measurement)

Incidence and severity of acute and chronic GVHD (safety)

Acute and chronic GVHD will be diagnosed, classified, and graded according to NIH criteria (see Section 8.1.5). The following endpoints are assessed:

- Cumulative incidence of grade II-IV and grade III-IV acute GVHD
- Cumulative incidence of moderate and severe chronic GVHD
- Cumulative incidence of chronic GVHD requiring systemic immunosuppressive treatment
- Duration of acute and chronic GVHD episodes

Incidence and severity of viral, fungal, and bacterial infections (efficacy)

- Cumulative incidence of NCI CTCAE grade 2-5 and grade 3-5 infections

Incidence and severity of adverse events (safety)

- Cumulative incidence of NCI CTCAE grade 3-5 adverse events

Quality of life

- FACT-BMT, SF-36, MDASI, EQ-5D-5L total scores (change from screening)

observational patient registry CR-REG-001, involving passive follow-up until 5 years after the HSCT.

A donor is considered to be in the study up to and including collection of the stem cells for the HSCT.

The end of the study is defined as the date at which the last data point from the last patient is received globally.

Immunosuppressive Medication

Post-transplant prophylaxis against GVHD will not be permitted in the ATIR101 group unless discussed with and approved by the sponsor.

Post-transplant immunosuppressive therapy (e.g. corticosteroids) in the absence of GVHD should be avoided in the ATIR101 group unless medically indicated. The use of immunosuppressives shortly before infusion of ATIR101 or thereafter will inhibit the effects of ATIR101.

In addition to cyclophosphamide, patients in the PTCy group will receive immunosuppressive medications for GVHD prophylaxis (e.g. mycophenolate mofetil, cyclosporine A, tacrolimus) based on institutional guidelines.

G-CSF

Post-transplant G-CSF treatment should be avoided within a week prior to ATIR101 infusion, unless medically indicated. The use of post-transplant G-CSF after ATIR101 infusion will be at the discretion of the investigator after consultation of the sponsor.

Mesna and Hydration

Prior to administration of cyclophosphamide, patients must receive appropriate hydration and mesna according to institutional standards to prevent cyclophosphamide-induced hemorrhagic cystitis (see Section 6.1.2).

CMV

If the patient is cytomegalovirus (CMV) positive, it is strongly recommended to use a CMV positive donor. All patients (ATIR101 and PTCy group) will be subject to regular quantitative quantitative polymerase chain reaction (PCR) monitoring. If quantified viral DNA levels exceed the institutional threshold for treatment of CMV (as established for each study center), patients should be treated pre-emptively with ganciclovir or valganciclovir according to institutional guidelines.

ATIR101 group:

To prevent infections with CMV, patients in the ATIR101 group who are CMV positive or have a CMV positive donor must be given prophylactic treatment including ganciclovir and foscarnet. The following dosing schedule is recommended (Day 0 is the day of HSCT):

- From Day -9 through Day -2: ganciclovir 5 mg/kg IV q12h.
- From Day 4 through Day 20: foscarnet 90 mg/kg IV q24h.
- From Day 21 until Day 100: valganciclovir 900 mg PO daily 5 days a week, or ganciclovir 5 mg/kg IV q24h 5 days a week.
- Dosage is to be adjusted depending on renal function.

Hematopoietic Stem Cell Transplantation (HSCT)

Patients randomized to the ATIR101 group will receive a TCD graft from the donor, using the CD34+ cell selection method. Patients randomized to the PTCy group will receive a non-manipulated (full, T-cell replete) graft from the donor, either using bone marrow or peripheral blood stem cells (PBSCs)

ATIR101 Group

Patients randomized to the ATIR101 group will receive a TCD graft from the donor, using the CD34+ cell selection method. The collection and preparation of the donor stem cell graft is performed according to institutional procedures at the study center. The study centers will mobilize peripheral blood stem cells (PBSCs) from the donor with granulocyte colony-stimulating factor (G-CSF) administered subcutaneously at a dose of approx. 8 µg/kg twice daily for approx. 4 to 7 days. The PBSCs will be collected by apheresis. According to the Perugia protocol for haploidentical transplants, the CD34-selected stem cell graft is targeted to contain at least 5×10^6 CD34+ cells/kg but if possible $8\text{-}11\times10^6$ CD34+ cells/kg with a maximum of 3×10^4 CD3+ cells/kg as assessed by flow cytometry (Champlin *et al.* 2002). To ensure a consistently highly purified stem cell graft, clinical sites will use the CliniMACS® CD34 isolation system (Miltenyi Biotec) as part of their institutional procedures for preparing the stem cell graft. To achieve the target CD34+ cell dose, more than one stem cell graft may be given.

Prior to the transplant all patients in the ATIR101 group will be given rabbit anti-thymocyte globulin (ATG; Thymoglobulin®). The recommended dose of rabbit ATG is 2.5 mg/kg IV once daily for 4 days on Day -5 to -2, as a continuous IV infusion for 4-8 hours (10 mg/kg total dose); during the course of ATG, patients will receive methylprednisolone 1-2 mg/kg/day IV. Scheduled deviations from this recommended ATG dosing schedule are to be discussed between the principal investigator and Kiadis Pharma.

PTCy Group

Patients randomized to the PTCy group will receive a non-manipulated (full) T-cell replete graft from the donor, either using bone marrow or PBSCs. The collection and preparation of the donor stem cell graft is performed according to institutional procedures at the study center. The study centers will mobilize PBSCs from the donor with granulocyte colony-stimulating factor (G-CSF) or will use bone marrow as source of stem cells, depending on the center's preference and experience. Donor bone marrow harvest will be done under anesthesia and the graft will not be manipulated, except for removal of red blood cells. The recommended target of mononuclear cells in bone marrow to be infused is 4×10^8 cells/kg body weight. The recommended target of PBSCs to be infused is 5×10^6 CD34+ cells/kg body weight. To achieve the target CD34+ cell dose, more than one stem cell graft may be given.

Viral Testing

Viral testing will be performed at the local laboratory, and if required by local regulations the tests will also be done on a separate blood sample at the manufacturing facility.

8.2.4 Karnofsky Performance Status

Performance status will be assessed as a percentage (0-100%) according to the Karnofsky Performance Status (KPS) scale (Schag *et al.* 1984) (see Appendix 5).

8.2.5 Physical Examination

At least the following body systems will be examined: skin, ears/nose/throat (ENT), respiratory, cardiovascular, abdomen (including liver and spleen), and lymph nodes. All abnormal findings will be recorded.

8.2.6 CT Scan Thorax or Chest X-ray

A high-resolution CT scan of the thorax or a chest X-ray will be used to assess the presence of any generalized lung disease. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening).

8.2.7 Echocardiogram or MUGA Scan

An echocardiogram or MUGA scan will be used to assess the patient's cardiac function. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening).

8.2.8 Pulmonary Function Test

A pulmonary function test measuring the DLCO will be used to assess the functional status of the lungs. This assessment may have been done within 6 weeks before signing informed consent (or start of re-screening). The hemoglobin (Hb) corrected DLCO will be calculated with one of the following formulas (Macintyre *et al.* 2005) and can be compared with the DLCO predicted value:

$$Males\colon\ DLCO_{corrected\ for\ Hb} = \frac{DLCO_{measured}}{(1.7 \times Hb\ [g/dl]\ /\ (10.22 + Hb\ [g/dl])}$$

$$Females\colon\ DLCO_{corrected\ for\ Hb} = \frac{DLCO_{measured}}{(1.7 \times Hb\ [g/dl]\ /\ (9.38 + Hb\ [g/dl])}$$

8.2.9 Creatinine Clearance

To assess renal function creatinine clearance will be either calculated or measured:

- Calculation by using the Cockcroft-Gault formula (Cockcroft and Gault 1976)

$$Creatinine\ clearance\ [ml/min] = \frac{(140 - Age) \times Weight\ [kg] \times 0.85[if\ female]}{72\ \times Serum\ creatinine\ [mg/dl]}$$

1 = Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

2 = Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

3 = Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

4 = Grade 4: Life-threatening consequences; urgent intervention indicated.

5 = Grade 5: Death related to adverse event

8.3.3.2 Relationship to Study Intervention

All AEs will be examined to determine any relationship to ATIR101 or post-transplant cyclophosphamide using the WHO-UMC system for standardized case causality assessment. The assessment criteria are listed below:

Certain:

- An event or laboratory test abnormality, with plausible relationship to administration of the investigational product.
- The event cannot be explained by the disease or other drugs.
- Response to withdrawal is plausible (pharmacologically, pathologically).
- Event definitive pharmacological or phenomenological (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon).
- Re-challenge satisfactory, if needed.

Probable:

- An event or laboratory test abnormality, with reasonable time relationship to administration of the investigational product.
- Unlikely to be attributed to the disease or other drugs.
- Response to withdrawal clinically reasonable.
- Re-challenge not required.

Possible:

- An event or laboratory test abnormality, with reasonable time relationship to administration of the investigational product.
- Could also be explained by the disease or other drugs.
- Information on drug withdrawal may be lacking or unclear.

Within this study, GVHD (see Section 8.1) will be recorded separately from the other AEs in the eCRF.

Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE but as medical history. However, if the patient's medical condition deteriorates at any time during the study, it will be recorded as an AE. Investigators should ensure that the event term recorded captures the change in the condition (e.g., "worsening of…").

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity. AEs characterized as intermittent require documentation of onset and duration of each episode.

8.3.6 Serious Adverse Event Reporting

All SAEs at any time during the study through the last follow-up visit required by the protocol must be reported by the investigator within 24 hours of knowledge of their occurrence to the sponsor or representative, independent of the circumstances or suspected cause. The report must be completed on the SAE report form in English and must include a relationship assessment. Information about every SAE will be collected and recorded on the SAE report form as well as simultaneously in the applicable eCRF pages, including at least data on screening, HSCT, ATIR101/PTCy infusion, AEs and concomitant medications.

The SAE report form should be sent by e-mail or fax to ProPharma Group (St. Paul MN, USA).

E-mail addresses:	**saereports@drugsafety.biz and saereporting@kiadis.com**
SAE fax number:	**+1 919-844-6948**
Backup fax number:	+1 919-882-8337

The original SAE report form, together with the fax confirmation sheet (if applicable), must be kept at the study site. If the initial report is made verbally or by telephone, a written confirmation via e-mail or fax must follow within 24 hours. The investigator will be requested to supply detailed information regarding the event at the time of the initial report.

Each SAE should be recorded as a single diagnosis on the SAE report form. Accompanying signs (including abnormal laboratory values and ECG findings) or symptoms should not be recorded as additional SAEs. However, if the diagnosis is unknown, signs and symptoms should be recorded. As soon as the diagnosis causing the signs and symptoms is known, the event terms will be adjusted to the final diagnosis.

For all SAEs occurring during the study, the investigator must submit follow-up reports to the sponsor or representative regarding the patient's subsequent course until the SAE has resolved, or until the condition stabilizes (in the case of persistent impairment), or the patient dies. In the event that a patient dies, an autopsy report (if available) must be forwarded to the sponsor or its representative. The timelines and procedure for follow-up reports are the same

as those for the initial report. The form and fax confirmation sheet must be retained by the site.

All suspected unexpected serious adverse reactions (SUSARs) will be subject to expedited reporting to the regulatory authorities by the sponsor or its representative. The sponsor will also prepare expedited reports for other safety issues that might materially alter the current benefit-risk assessment of the investigational product.

8.3.7 Reporting Events to Participants

Not applicable.

8.3.8 Events of Special Interest

In this study the following AEs are regarded events of special interest:

- PTLD
- Infusion reactions
- AIHA
- Secondary malignancies
- Hemorrhagic cystitis
- Veno-occlusive disease

Events of special interest (serious or non-serious) must be reported throughout the study on the eCRF.

8.3.9 Reporting of Pregnancy

Pregnancies occurring during participation in the study after randomization, including pregnancies of partners of male patients, will be reported as an AE and will be followed up. The competent authority and IEC/IRB will be informed on these pregnancies.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UPs)

Unanticipated problems (UPs) involving risks to participants are defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IEC/IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 Unanticipated Problem Reporting

In general, an AE observed during the conduct of a study should be considered an unanticipated problem (UP) involving risk to human subjects, and reported to the involved IECs/IRBs, only if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

The UP report to be sent to the IEC/IRB will include the following information:

- Protocol identifying information: protocol title and number, name principal investigator, and the IEC/IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

Changes in the conduct of the study as a result of an UP, will be submitted for approval to the competent authority as a substantial amendment.

8.4.3 Reporting Unanticipated Problems to Participants

If applicable, the investigator will inform participants about UPs that may be relevant to the patient's consent or may influence the patient's willingness to continue participation in the study.

8.5 Study Visits

A schedule of activities by study visit in tabular form is displayed in Section 1.3.

8.5.1 Screening (between Informed Consent & Confirmation Eligibility)

- Informed consent patient/donor
- Patient eligibility
- Randomization
- Demographics patient/donor
- Hematologic malignancy; including WHO/FAB classification, cytogenetic and molecular abnormalities, DRI, EBMT risk score, date of first diagnosis, and prior treatments/ relapses

- Medical history; including comorbidity (HCT-CI)
- KPS
- Physical examination
- CT scan thorax or chest X-ray; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Echocardiogram or MUGA scan; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Pulmonary function test; if not already done within 6 weeks before signing informed consent (or start of re-screening)
- Creatinine clearance; calculated or measured, if not already done within 2 weeks before signing informed consent (or start of re-screening)
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, height, and supine blood pressure after 5 minutes of rest
- Quality of life; FACT-BMT, SF-36, MDASI, and EQ-5D-5L (if available in local language)
- Disease assessment; including bone marrow biopsy or aspirate if not already obtained within 2 weeks before signing informed consent (or start of re-screening)
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Hematology/biochemistry
- Urinalysis
- Pregnancy test patient/donor (if applicable)
- Viral testing patient/donor; EBV, CMV, HIV-1, HIV-2, HBV, HCV, Treponema pallidum, adenovirus, Toxoplasma gondii, HSV, VZV, HTLV-I (if applicable), HTLV-II (if applicable), WNV (if applicable), or Zika virus (if applicable). This viral testing must be done on samples obtained within one month before collection of PBMCs.
- HLA compatibility; mismatches at the HLA-A, -B, -C, and -DRB1 loci (and if possible at the HLA–DQB1 locus) of the unshared haplotype
- Immunophenotyping if the absolute lymphocyte count > 0.1×10^9/l
- At selected sites and patients: peripheral blood sampling for research purposes
- Patient AEs (other)
- Donor AEs
- Concomitant medications

8.5.2 Pre-HSCT (between Confirmation Eligibility & HSCT)

- Apheresis patient and donor PBMCs for ATIR101 manufacturing including measurement of patient weight (ATIR101 group only)
- Collection of donor stem cell graft (PBSCs or bone marrow)
- Conditioning regimen
- Infection assessment
- Patient AEs (other)
- Donor AEs; up to and including the collection of stem cells
- Concomitant medications

systemic immunosuppressive treatment, disease relapse/progression (including disease-related death), and death from all causes other than GVHD or disease relapse/progression. Gray's test will be used to compare the randomized treatment arms for the competing risks, and the Fine-Gray proportional hazards model will be used to adjust these comparisons for covariates of interest (Fine and Gray 1999; Gray 1988).

9.4.4 Safety Analyses

Safety variables include the reported AEs, SAEs, laboratory tests, vital signs and physical examination.

AEs will be coded and evaluated for severity using NCI-CTCAE and will be summarized by MedDRA system organ class and preferred term. Separate summaries will be generated for the following:

- All AEs
- Severe AEs (Grade 3 or higher)
- SAEs

Listings will be provided of:

- SAEs
- AEs leading to treatment discontinuation
- AEs resulting in death
- AEs listed according to maximum severity

The frequency of AEs will be tabulated by grade. Adverse events will be compared using χ^2 tests or, for low counts, using Fisher's exact test. In view of the anticipated large number of statistical tests, P-values will not be interpreted in the usual sense but will be used as a "flagging device" to highlight differences worth further scrutiny.

Laboratory tests: Summary statistics for baseline, each post-baseline measurement, and change from baseline for each post-baseline measurement will be presented for hematology, blood chemistry, and urinalysis parameters.

Other safety data (e.g., vital signs) will be tabulated and listed, notable values will be flagged, and any other information collected will be listed as appropriate.

9.4.5 Baseline Descriptive Statistics

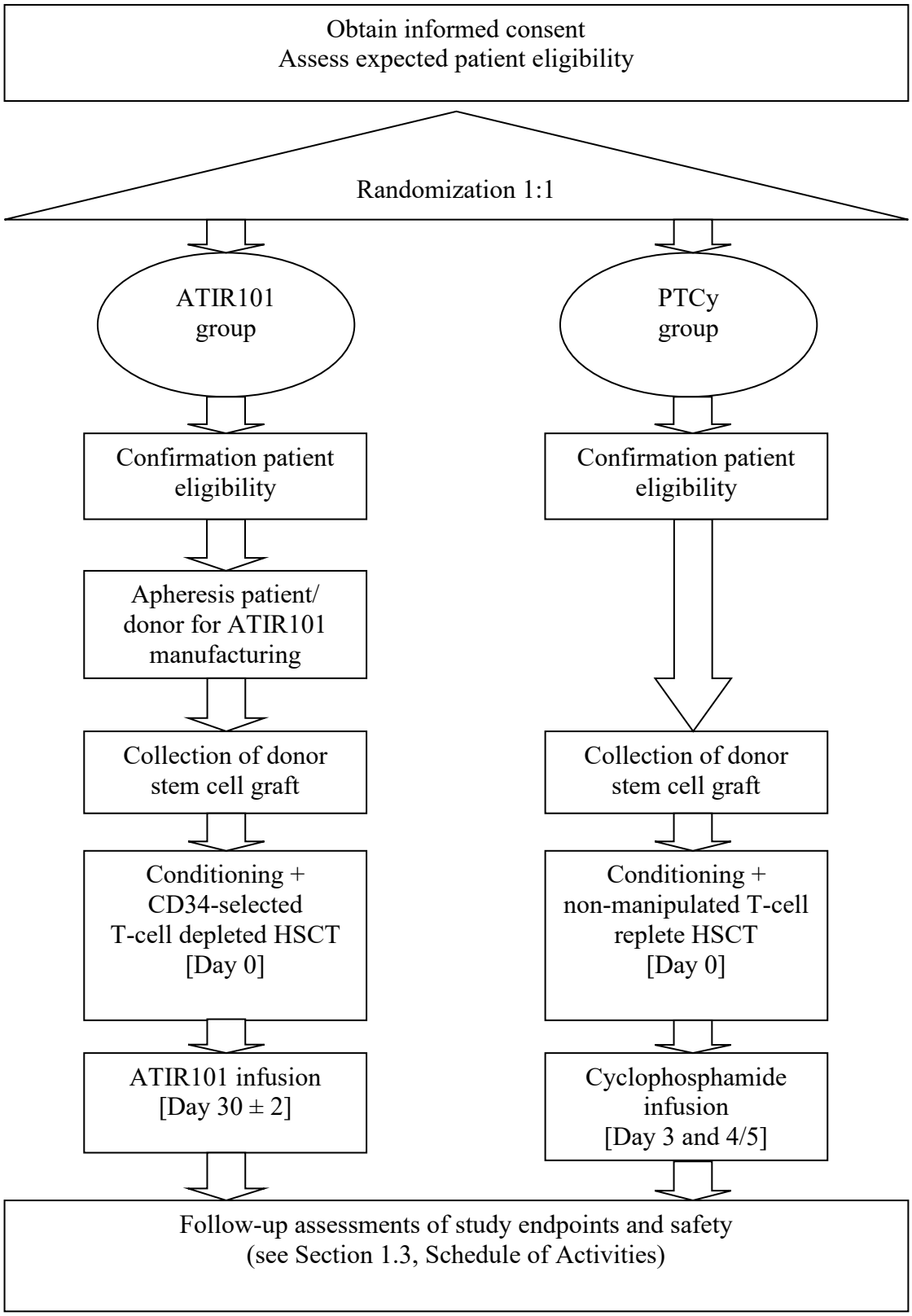
The two treatment groups will be compared on baseline characteristics, using descriptive statistics and inferential statistics.

9.4.6 Planned Interim Analyses

An interim analysis will be conducted when at least 105 GRFS events have occurred. The IDMC will review the results of the interim analysis. The sponsor will remain blinded to

dUCB	double umbilical cord blood
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
ENT	ears, nose, throat
EQ-5D-5L	EQ-5D 5-level version
FAB	French-American-British
FACT-BMT	Foundation for the Accreditation of Cellular Therapy – Bone Marrow Transplantation questionnaire
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GRFS	GVHD-free, relapse-free survival
GVHD	graft-versus-host disease
GVL	graft-versus-leukemia
Hb	hemoglobin
HBV	hepatitis B virus
HCT-CI	hematopoietic cell transplantation-specific comorbidity index
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HSV	herpes simplex virus
HTLV	human T-lymphotropic virus
ICH	International Conference on Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
Ig	immunoglobulin

1.2 Schema


Obtain informed consent
Assess expected patient eligibility
Randomization 1:1
ATIR101 group
PTCy group
Confirmation patient eligibility
Confirmation patient eligibility
Apheresis patient/ donor for ATIR101 manufacturing
Collection of donor stem cell graft
Collection of donor stem cell graft
Conditioning + CD34-selected T-cell depleted HSCT [Day 0]
Conditioning + non-manipulated T-cell replete HSCT [Day 0]
ATIR101 infusion [Day 30 ± 2]
Cyclophosphamide infusion [Day 3 and 4/5]
Follow-up assessments of study endpoints and safety (see Section 1.3, Schedule of Activities)

	Screening (between informed consent & confir-mation eligibility)	Pre-HSCT	HSCT (Day 0)	Week 1, 2, 3	Week 4	Week 5, 6, 7, 8, 9, 10	Month 3, 4, 5, 6, 8, 10, 12, 15, 18, 21, 24	Follow-up beyond Month 24 every 6 months
Mortality assessment	Continuous recording							
Hematology/biochemistry	X		X	X	X	X	X	X
Urinalysis	X				X	X [18]	X [18]	
Pregnancy test patient/donor (if applicable)	X							
Viral testing patient/donor	X [19]							
HLA compatibility	X							
ABO/Rhesus blood group	X							
Immunophenotyping	X			X [20]	X [21]	X	X	X
Peripheral blood sampling [22]	X					X [23]	X [23]	
Patient AEs (other)	X	X	X	X	X	X	X [24]	X [24]
Donor AEs	X	X [25]						
SAEs	Continuous recording							
Concomitant medications	X	X	X	X	X	X	X	X [26]

[18] Only at Week 8, Month 3, and Month 4
[19] Viral testing to be done within one month before collection of PBMCs (for ATIR101 manufacturing) and within one month of collection of stem cells
[20] Only at Week 3
[21] For all patients (in ATIR101 group before infusion of ATIR101)
[22] For research purposes. At selected sites and patients.
[23] Only at Week 8, Month 4, Month 6, Month 8, Month 10, and Month 12; Additional sampling when a pre-specified GVHD event occurs in ATIR101-treated patients within the first year after HSCT (see Section 8.1.8).
[24] Only at Month 3, Month 4, Month 5, and Month 6. However, SAEs and AEs of special interest (Section 8.3.8) are to be recorded as AEs throughout study.
[25] Up to and including the collection of stem cells
[26] Excluding medications for the treatment of non-serious infections

2.2.2.1 Relevant Nonclinical Findings

TH9402 is a specifically designed derivative of rhodamine, a substance that is often used in cell biology to stain mitochondria in living cells because of its low toxicity and its specific attraction and retention in these organelles. Similarly, TH9402 binds to mitochondria. TH9402 absorbs light at a peak wavelength of 514 nm in the visible green spectrum and transfers the absorbed energy to oxygen, leading to the production of reactive oxygen species (mainly singlet oxygen) inside the cells. Subsequent oxidative reactions of these species with various biomolecules ultimately cause programmed cell death. TH9402 accumulates in cells with low P-glycoprotein (Pgp) pump activity such as activated lymphocytes. These target cells will accumulate significantly higher amounts of photosensitizer than resting cells and will be selectively depleted upon exposure to light.

The light exposure device used in the manufacturing of ATIR101 is custom designed to deliver light of a specific wavelength range that results in the photo activation of TH9402 molecules incorporated by cells. Special lamps with peak emission around 514 nm are positioned below the glass treatment surface of the device, delivering a tightly controlled light dose.

T-cells in ATIR101 can be characterized as being sufficiently depleted of recipient-reactive T-cells that might cause severe acute GVHD while having maintained the general ability to become activated by other stimuli, like infectious epitopes and malignant cells, and are therefore expected to be able to fight infections and disease relapse in the human body (Bastien *et al.* 2012; Guimond *et al.* 2002; Mielke *et al.* 2008).

In vitro assays have been developed to show that ATIR101 batches are indeed depleted of alloreactive cells while the remaining cells retain their reactivity to other stimuli. The various leukocyte subsets have been measured both in the original donor cells as well as in ATIR101. T-cells (CD3+), monocytes (CD14+), B-cells (CD19+), NK-cells (CD3- CD16/56+) are present in the original donor cells while ATIR101 is strongly enriched for T-cells (> 90%).

The proliferation of the cells in ATIR101 and the original donor cells after stimulation with recipient cells and third-party cells have been compared using the CFSE-dilution based proliferation assay. A selective depletion of recipient-reactive cells is observed, while reactivity to third party cells is retained. Thus, alloreactive T-cells have been largely eliminated from ATIR101 with preservation of T-cell response to other antigenic stimuli.

To better characterize the capacity of ATIR101 to fight infections, virus specific CD8+ cells against EBV and CMV were measured using a variety of HLA-multimers both in ATIR101 and in original donor cells. Anti-viral T-cells are largely preserved in ATIR101.

In a proof of concept study in a mouse stem cell transplantation model, PDT using TH9402 *ex vivo* successfully eliminated foreign HLA-specific cytotoxic T-cells but did not eliminate resting anti-leukemia and anti-third-party T-lymphocytes. In particular, without a donor lymphocyte infusion (DLI), stem cell transplanted and BCL1 leukemia inoculated mice developed leukemia with 50% mortality at 100 days. Infusion of untreated DLIs prevented relapse, but resulted in 100% mortality due to GVHD. However, upon infusion of DLIs that

4 STUDY DESIGN

4.1 Overall Design

Study CR-AIR-009 is a Phase III randomized controlled multicenter open-label study comparing two parallel groups. After signing informed consent, a total of about 250 patients will be randomized in a 1:1 fashion to receive either a TCD HSCT (CD34 selection) from a related, haploidentical donor, followed by ATIR101 infusion, or a T-cell replete HSCT, followed by a high dose of PTCy.

Randomization will use minimization to balance treatment groups with respect to underlying disease (AML, ALL, or MDS), DRI (intermediate risk, high risk, or very high risk) and center. A stochastic treatment allocation procedure will be used so that the treatment assignment is random for all patients entered in the study.

Patients randomized in the ATIR101 group will receive a single ATIR101 dose of 2.0×10^6 viable T-cells/kg between 28 and 32 days after the HSCT. Patients randomized in the PTCy group will receive cyclophosphamide 50 mg/kg/day at 3 and 4/5 days after the HSCT. All patients will be followed up for at least 24 months post HSCT. Patient follow-up beyond 24 months post HSCT will be discontinued when a total number of 156 GRFS events has been reached.

4.2 Scientific Rationale for Study Design

The study is designed to confirm results obtained in Phase I-II clinical studies and to compare the outcomes of patients receiving ATIR101 post HSCT in a randomized setting to a control group of patients receiving a high dose of cyclophosphamide post HSCT, an upcoming treatment modality for patients in need of a haploidentical HSCT. The study aims at showing superiority in the ATIR101 group compared to the PTCy group.

4.3 Justification for Dose

In study CR-GVH-001 the optimal dose of ATIR101 for further development was considered to be 2.0×10^6 viable T-cells/kg. Data of studies CR-AIR-007 and CR-AIR-006 show significant improvement of TRM and OS after ATIR101 treatment at a dose of 2.0×10^6 viable T-cells/kg compared to patients who did not receive ATIR101.

The dose of cyclophosphamide of 50 mg/kg/day at 3 and 4/5 days after the HSCT is based on published data of the Baltimore protocol, which showed comparable outcomes of haploidentical HSCT followed by PTCy and matched (un)related donor transplants (Bashey *et al.* 2013; Burroughs *et al.* 2008),

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study and a total number of 156 GRFS events has been reached. After study completion, patients treated with ATIR101 who consented will be enrolled in the

5 STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Any of the following hematologic malignancies:
   - Acute myeloid leukemia (AML) in first cytomorphological remission (with < 5% blasts in the bone marrow) with Disease Risk Index (DRI) intermediate or above, or in second or higher cytomorphological remission (with < 5% blasts in the bone marrow)
   - Acute lymphoblastic leukemia (ALL) in first or higher remission (with < 5% blasts in the bone marrow)
   - Myelodysplastic syndrome (MDS): transfusion-dependent (requiring at least one transfusion per month), or intermediate or higher IPSS-R risk group)
2. Clinical justification of allogeneic stem cell transplantation where a suitable HLA matched sibling or unrelated donor is unavailable in a timely manner.
3. Availability of a related haploidentical donor with one fully shared haplotype and 2 to 4 mismatches at the HLA-A, -B, -C, and -DRB1 loci of the unshared haplotype, as determined by high resolution HLA-typing
4. Karnofsky Performance Status (KPS) ≥ 70%
5. Male or female, age ≥ 18 years and ≤ 70 years
   Patients aged ≥ 65 years must have a Sorror score ≤ 3
6. Patient weight ≥ 25 kg and ≤ 130 kg
7. Availability of a donor aged ≥ 16 years and ≤ 75 years who is eligible according to local requirements and regulations. Donors aged < 16 years are allowed if they are the only option for an HSCT, if they are permitted by local regulations, and if the IRB/IEC approves participation in the study.
8. For females of childbearing potential[27] who are sexually active and males who have sexual contact with a female of childbearing potential: willingness to use reliable methods of contraception (oral contraceptives, intrauterine device, hormone implants, contraceptive injection or abstinence) during study participation
9. Given written informed consent (patient and donor)

5.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Diagnosis of chronic myelomonocytic leukemia (CMML)
2. Availability of a suitable HLA-matched sibling or unrelated donor in a donor search
3. Prior allogeneic hematopoietic stem cell transplantation
4. Diffusing capacity for carbon monoxide (hemoglobin corrected DLCO) < 50% predicted
5. Left ventricular ejection fraction < 45% (evaluated by echocardiogram or MUGA scan)
6. AST and/or ALT > 2.5 × ULN (CTCAE grade 2)

[27] A female is considered of childbearing potential following menarche and until becoming post-menopausal unless permanently sterile.

EBV

To prevent PTLD, all patients will be subject to regular quantitative PCR monitoring for Epstein-Barr virus (EBV) followed by adequate (pre-emptive) treatment if indicated. If quantified viral DNA levels exceed the institutional threshold for treatment of EBV (as established for each study center), patients should be treated with rituximab. It is also recommended to start rituximab if a patient who was EBV positive in the past, demonstrates enlarged lymph nodes, even if PCR for EBV is low or negative.

The following schedule is recommended:

- Immediately after the rise in EBV DNA is detected, rituximab (anti-CD20) 375 mg/m^2 IV is started once weekly, until PCR for EBV becomes negative.
- If PTLD is suspected on the basis of clinical symptoms, CT scans of thorax, abdomen and pelvis, as well as bone marrow aspiration and biopsy, and -when possible- lymph node extraction should be conducted. If results of the CT scan, bone marrow examinations, and lymph nodes demonstrate PTLD, rituximab is repeated weekly for at least 2 weeks.

Adenovirus

To prevent infections with adenovirus, patients will be subject to regular quantitative PCR monitoring followed by adequate treatment. If quantified viral DNA levels exceed the institutional threshold for treatment of adenovirus (as established for each study center), patients should be treated according to local institutional guidelines.

Toxoplasma

Patients with a positive serology test for toxoplasma gondii at screening or with a toxoplasma gondii positive donor will receive prophylaxis with trimethoprim-sulfamethoxazole (or alternatively atovaquone) per local institutional guidelines.

HSV and VZV

Patients tested positive for herpes simplex virus (HSV) or varicella zoster virus (VZV) at screening must receive prophylaxis with acyclovir or valacyclovir (in the absence of foscarnet) per local institutional guidelines for at least one year or until the CD4+ lymphocyte count has normalized.

Other viral, fungal and bacterial prophylaxis will be given according to local institutional guidelines.

Participation in Other Clinical Studies

Participation in another clinical study is to be discussed between the investigator and Kiadis Pharma.

Blood of the patient and the donor will be tested for the presence of the following viruses (and other micro-organisms) in accordance with local regulatory requirements and regulations: EBV, CMV, HIV-1, HIV-2, HBV, HCV, Treponema pallidum, Toxoplasma gondii, herpes simplex virus (HSV), varicella zoster virus (VZV), HTLV-I (if applicable), HTLV-II (if applicable), WNV (if applicable), and Zika virus (if applicable). This viral testing must be done on samples obtained within one month before collection of PBMCs. If the patient is CMV positive, it is strongly recommended to use a CMV positive donor.

HLA Compatibility

Mismatches at the HLA-A, -B, -C, and -DRB1 loci (and if possible at the HLA–DQB1 locus) of the unshared haplotype will be assessed at the local laboratory by high resolution HLA-typing.

Blood Group

ABO and Rhesus blood group of patient and donor will be assessed at the local laboratory.

8.1.2 Disease Assessment

The status of the hematologic disease will be assessed regularly. Details of relapse or disease progression will be recorded on the Relapse/Disease Progression AE page of the eCRF.
A bone marrow biopsy must be performed at fixed visits unless relapse has already been confirmed (Screening, Month 3, Month 6, Month 12, and Month 24 post HSCT) and in case of suspected relapse. In case a bone marrow biopsy cannot be obtained, it may be replaced by a bone marrow aspirate. If a bone marrow aspirate and/or biopsy had already been obtained within 2 weeks prior to signing informed consent (or start of re-screening) or 6 weeks prior to a scheduled visit (from Month 3 onwards), the assessment does not need to be repeated.

In addition, in case of suspected relapse post HSCT, chimerism will be assessed to support the diagnosis.

A test for the presence of minimal residual disease (MRD) can be done locally at the study center as per institutional standards and the results will be recorded in the eCRF.

8.1.3 Infection Assessment

In this study an infection is defined as a clinically apparent infectious disease with symptoms or detectable viral reactivation, especially of CMV, EBV, or adenovirus. Details of all infections will be recorded on the Infection AE page of the eCRF, including type of infection, infection site, start date, stop date, NCI CTCAE severity grade (see Section 8.3.3), outcome, and action taken. Whenever an infectious episode is suspected, appropriate diagnostic measures need to be taken, including blood cultures to allow assessment of the specific pathogen causing the infection.

- Measurement by collecting 24-hour urine

$$Creatinine\ clearance\ [ml/min] = \frac{Urine\ creatinine\ [mg/dl]\ \times Urine\ flow\ [ml/min]}{Serum\ creatinine\ [mg/dl]}$$

Serum creatinine and urine creatinine will be assessed at the local laboratory. These assessments may have been done within 2 weeks before signing informed consent (or start of re-screening).

8.2.10 Vital Signs

The following vital sign parameters will be measured for the patient at regular intervals: respiration rate or oxygen saturation, pulse rate, temperature, weight, height (at screening only), and supine blood pressure after 5 minutes of rest. In addition, following ATIR101 infusion, pulse rate and supine blood pressure will be assessed after 15 minutes, 1 hour, and 2 hours. Continuous oxygen monitoring will be done if the patient has respiratory problems after ATIR101 infusion.

Weight and height of donors for patients in the ATIR101 group will be recorded pre HSCT.

8.2.11 Engraftment

Neutrophil engraftment is defined as neutrophil count $\geq 0.5\times10^9$/l for 3 consecutive days and platelet recovery is defined as platelets $\geq 20\times10^9$/l for 3 consecutive days, without transfusion. The first days of occurrence of both criteria will be recorded.

Primary graft failure is defined as lack of initial engraftment of donor cells. The patient never recovers from neutropenia (neutrophil count $< 0.5\times10^9$/l), resulting in pancytopenia and an urgent need for re-transplantation. Secondary graft failure is defined as loss of donor cells after initial engraftment. In this case autologous recovery is common; however, marrow aplasia and pancytopenia may also develop.

8.2.12 Chimerism

A blood sample for assessment of chimerism will be collected at Week 4 (before ATIR101 infusion, if applicable), at Week 10, Month 3, Month 6, Month 12, Month 24, and in case of suspected relapse. Chimerism will be assessed in peripheral blood lymphocytes and polynuclear cells (neutrophils) by PCR amplification at the local laboratory.

8.2.13 Safety Laboratory Tests

Patients will be in a seated or supine position during blood collection. Safety laboratory tests will include hematology, blood chemistry, and urinalysis tests (see Table 3). Safety laboratory tests will be performed at the local laboratory.

Unrelated/Unlikely:

- Event or laboratory test abnormality, with a time to administration of the investigational product that makes a relationship improbable (but not impossible).
- Disease or other drugs provide plausible explanations.

8.3.3.3 Expectedness

The Medical Monitor will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the list of expected adverse reactions included in the Reference Safety Information section of the Investigator's Brochure.

8.3.4 Time Period and Frequency for Event Assessment and Follow-Up

The time period for AE reporting starts when the ICF is signed. For the donor, all AEs will be reported until and including the collection of the stem cells. For the patient, infections (including viral activations) will be reported until two years after the HSCT. Relapse/disease progression, GVHD, AEs of special interest (Section 8.3.8), and SAEs (see Section 8.3.6) will be reported throughout the study. Other AEs including local and systemic reactions not meeting SAE criteria will be reported until 6 months after the HSCT.

Events will be followed for outcome information until resolution or stabilization. If required by local regulations, evaluation of donor AEs will be done by a sub-investigator (physician) who is independent from the investigator evaluating the patient.

8.3.5 Adverse Event Reporting

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a patient presenting for medical care, or upon review by a study monitor. All AEs, whether spontaneously reported by the patient, discovered during general questioning by the investigator, or detected through physical examination, laboratory test or other means will be recorded on the appropriate eCRF.

AEs will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, investigator's assessment of severity, relationship to study intervention, actions taken, and time of resolution/stabilization of the event. All AEs must be documented appropriately regardless of relationship.

Each event should be recorded as a single diagnosis. Accompanying signs (including abnormal laboratory values and electrocardiogram [ECG] findings) or symptoms should not be recorded as additional AEs. However, if the diagnosis is unknown or uncertain, signs and symptoms must be recorded.

8.5.3 HSCT (Day 0)

- HSCT; either TCD CD34-selected (ATIR101 group) or T-cell replete (PTCy group)
- Physical examination
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Hematology/biochemistry
- Patient AEs (other)
- Concomitant medications

8.5.4 Week 1, 2, 3

Visits must be performed within the following windows:

- Week 1: 1 week ± 2 days after the HSCT
- Week 2: 2 weeks ± 2 days after the HSCT
- Week 3: 3 weeks ± 2 days after the HSCT

Activities:

- Cyclophosphamide infusion; on Day +3 and Day +4/+5 (PTCy group only)
- Physical examination
- Vital signs; respiration rate or oxygen saturation, pulse rate, temperature, weight, and supine blood pressure after 5 minutes of rest
- Disease assessment
- Infection assessment
- CMV/EBV/adenovirus monitoring (PCR)
- Engraftment
- Chimerism; only in case of suspected relapse
- GVHD assessment
- Immunophenotyping if the absolute lymphocyte count is higher than 0.1×10^9/l; only at Week 3
- Hematology/biochemistry
- Patient AEs (other)
- Concomitant medications

these results, except if significance is reached at the time of the interim analysis ($P < 0.01246$), with a treatment effect greater than anticipated (hazard ratio of 0.61 or better). At the time of the final analysis, significance will be reached ($P < 0.04613$) with a treatment effect lower than anticipated, but still clinically worthwhile (hazard ratio of 0.73 or better).

9.4.7 Sub-Group Analyses

Subgroup analyses will be carried out by underlying disease, DRI, age, sex, and race/ ethnicity. Forest plots will be presented with a descriptive intent. Interaction tests will be carried out to investigate potential modulation of the treatment effect by baseline patient characteristics, but the trial is neither planned nor powered to detect interactions. Further sub-group analyses will be specified in the SAP.

9.4.8 Tabulation of Individual Participant Data

Individual participant data will be listed by measure and time point.

9.4.9 Exploratory Analyses

Exploratory analyses will be specified in the SAP.

IPSS-R	Revised International Prognostic Scoring System
IRB	institutional review board
ITT	intention-to-treat
IV	intravenous(ly)
IWRS	interactive web response system
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MCV	mean corpuscular volume
MDASI	MD Anderson Symptom Inventory
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex
MITT	modified intention-to-treat
MLR	mixed lymphocyte reaction
MMUD	mismatched unrelated donor
MRD	minimal residual disease
MTD	maximum tolerated dose
MUD	matched unrelated donor
MUGA	multiple gated acquisition
N/A	not applicable
NCI	National Cancer Institute
NCT	National Clinical Trial
NHI	National Institutes of Health
NK	natural killer (cells)
OS	overall survival
PBSC	peripheral blood stem cell
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PDT	photodynamic treatment