A Phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical HSCT and adjunctive treatment with ATIR101, a T-lymphocyte enriched leukocyte preparation depleted ex vivo of host alloreactive T-cells, versus a haploidentical HSCT with post-transplant cyclophosphamide in patients with a hematologic malignancy (HATCY studie)

Published: 26-06-2017
Last updated: 04-01-2025

The objective of this study is to compare safety and efficacy of a haploidentical T cell depleted HSCT and adjunctive treatment with ATIR101 versus a haploidentical T cell replete HSCT with post-transplant administration of high dose...

Ethical review	Approved WMO
Status	Pending
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON48941

Source
ToetsingOnline

Brief title
HATCY study

Condition

- Leukaemias

Synonym
AML and MDS, Leukemia/Blood cancer, more specifically ALL

Research involving
Human

Sponsors and support

Primary sponsor: Kiadis Pharma Netherlands B.V.
Source(s) of monetary or material Support: Entirely by the sponsor (industry)

Intervention

Keyword: ATIR101, haploidentical, HSCT, post-transplant cyclophosphamide

Outcome measures

Primary outcome

The primary endpoint of the study is GVHD-free, relapse-free survival (GRFS).

GRFS is defined as time from randomization until grade III/IV acute

graft-versus-host disease (GVHD), chronic GVHD requiring systemic

immunosuppressive treatment, disease relapse, or death, whichever occurs first.

This endpoint captures both safety and efficacy.

Secondary outcome

Secondary endpoints:

Overall survival (OS)

Progression-free survival (PFS)

Relapse-related mortality (RRM)

Transplant-related mortality (TRM)

Immune reconstitution

Incidence and severity of acute and chronic GVHD

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

Incidence and severity of adverse events (safety)

Quality of life

Study description

Background summary

For many patients with a hematologic malignancy, a hematopoetic stem cell transplantation (HSCT) remains the only curative option. The use of a matched (related or unrelated) donor is considered standard of care for patients who are eligible for an HSCT. However, a significant number of patients do not receive this potentially life-saving treatment, because a suitable matched related or unrelated donor cannot be found in a timely manner or cannot be found at all.

An alternative is the use of mismatched relatives who are partially matched to the recipient, as a stem cell donor (haploidentical donor). However, an HSCT from a haploidentical donor is not without risk for the patient. These risks include infection, graft rejection, graft-versus-host-disease (GVHD), relapse and adverse reactions to concomitant therapies (e.g., radiation, chemotherapy, anti-viral drugs).
The haploidentical transplantation procedure has become feasible through the use of methods to remove donor T-cells from the graft, in order to reduce the risk of GVHD. Downside of this approach is that patients can remain severely immune compromised for more than 1 year after the transplantation with a high risk of life-threatening complications resulting in high transplant-related mortality (TRM) rates and low overall survival (OS).

ATIR101 is a cell-based, personalized medicinal product manufactured for one specific recipient using apheresis material from a donor. ATIR101 a T-lymphocyte enriched leukocyte preparation depleted ex vivo of host alloreactive T-cells. A haploidentical stem cell transplantation followed by ATIR101 can offer patients in need of an HSCT, who lack a suitable HLA-matched sibling or unrelated donor, a potentially life-saving treatment. Because ATIR101 consists of a high dose of donor lymphocytes, which have been depleted of host alloreactive T-cells, patients are expected to be protected from life-threatening infections without increasing the risk of life-threatening

GVHD. Moreover, the possibility that the anti-tumor effects of T-cells in ATIR101 have been preserved could provide another benefit to patients. This potential graft versus leukemia effect could reduce the risk of relapse and thereby further increase the probability of long-term survival.

In conclusion, the development of a therapy that allows early immune protection and reconstitution following a haploidentical HSCT without increasing the risk of life-threatening (acute) GVHD can significantly improve the clinical outcome of patients by preventing TRM caused by acute GVHD and/or infections and possibly relapse. In addition, the possibility to use mismatched (haploidentical) family donors can provide a significant advantage for many patients for whom a suitable matched donor is not available. Therefore, participation in this study provides patients the prospect of direct benefit.

Study objective

The objective of this study is to compare safety and efficacy of a haploidentical T cell depleted HSCT and adjunctive treatment with ATIR101 versus a haploidentical T cell replete HSCT with post-transplant administration of high dose cyclophosphamide (PTCy) in patients with a hematologic malignancy. An additional objective of the study is to compare the effect of the two treatments on quality of life.

Study 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 2×10E6 viable T-cells/kg between 28 and 32 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.

Intervention

Patients randomized in the ATIR101 group will receive a single ATIR101 dose of 2×10E6 viable T-cells/kg between 28 and 32 days on top of a T-cell depleted, CD34 selected HSCT. Patients in the PtCY group will be treated with T-cell

replete HSCT and post-transplant high dose- cyclosphosphamide ("Baltimore protocol").
All patients will be followed up for at least 24 months post HSCT.

Study burden and risks

The development of a therapy that allows early immune protection and reconstitution following a haploidentical HSCT without increasing the risk of life-threatening (acute) GVHD can significantly improve the clinical outcome of patients by preventing TRM caused by acute GVHD and/or infections and possibly relapse. In addition, the possibility to use mismatched (haploidentical) family donors can provide a significant advantage for many patients for whom a suitable matched donor is not available. Therefore, participation in this study provides patients the prospect of direct benefit.

Contacts

Public
Kiadis Pharma Netherlands B.V.

Paasheuvelweg 25A
Amsterdam-Zuidoost 1105 BP
NL
Scientific
Kiadis Pharma Netherlands B.V.

Paasheuvelweg 25A
Amsterdam-Zuidoost 1105 BP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

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 bonemarrow)
- 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
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 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)

Exclusion criteria

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)
7. Creatinine clearance < 50 ml/min (calculated or measured)

8. Positive pregnancy test or breastfeeding of patient or donor (women of childbearing age only)
9. Estimated probability of surviving less than 3 months
10. Known allergy to any of the components of ATIR101 (e.g., dimethyl sulfoxide)
11. Known hypersensitivity to cyclophosphamide or any of its metabolites
12. Any contraindication for GVHD prophylaxis with mycophenolate mofetil, cyclosporine A, or tacrolimus
13. Known presence of HLA antibodies against the non-shared donor haplotype
14. Positive viral test of the patient or donor for HIV-1, HIV-2, HBV (active viral replication by PCR), HCV (active viral replication by PCR), Treponema pallidum, HTLV 1 (if tested), HTLV-2 (if tested), WNV (if tested), or Zika virus (if tested) (HBV/HCV: Only patients with active infection or infection history and donors with active infection are excluded)
15. Any other condition that, in the opinion of the investigator, makes the patient or donor ineligible for the study

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2017
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Generic name:	Somatic cels allogenic

Ethics review

Approved WMO Date:	26-06-2017
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-12-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-01-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-02-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-11-2019
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-004672-21-NL
ClinicalTrials.gov	NCT02999854
CCMO	NL61672.000.17

Study results

Results posted: 16-03-2022

First publication
21-02-2022