2 SYNOPSIS

Sponsor: **Individual Study Table**

Kiadis Pharma Netherlands B.V.

Name of Finished Product:

ATIR

Name of Active Ingredient:

Donor T-lymphocytes depleted of host alloreactive T-cells

Study Title:

An exploratory, open-label, multicenter study to evaluate the safety and efficacy of ATIR, donor T-lymphocytes depleted *ex vivo* of host alloreactive T-cells, in patients with a hematologic malignancy, who received a CD34-selected hematopoietic stem cell transplantation from a haploidentical donor

Investigators and Study Centers:

Multicenter (see Appendix 16.1.4)

Publication (reference):

Not applicable

Studied Period:

19 March 2013 (first patient enrolled) to
19 September 2017 (last patient last visit)

Study Phase:

Phase II

Objective:

To study the safety and efficacy of ATIR at a dose of 2.0×10^6 viable T-cells/kg body weight in patients with a hematologic malignancy who received a haploidentical hematopoietic stem cell transplantation (HSCT).

The primary efficacy endpoint was transplant-related mortality (TRM) at 6 months post HSCT. Secondary endpoints were:

- TRM, relapse-related mortality (RRM), overall survival (OS), and progression-free survival (PFS) up to 24 months post HSCT
- Incidence and severity of acute and chronic GVHD up to 24 months post HSCT
- Incidence and severity of viral, fungal, and bacterial infections up to 24 months post HSCT
- Immune reconstitution up to 24 months post HSCT

Methodology:

Study CR-AIR-007 is an exploratory, open-label, multicenter study. After signing informed consent, patients received an HSCT from a related, haploidentical donor, followed by infusion with ATIR between 28 and 32 days after the HSCT. Patients received ATIR as a single intravenous infusion at a dose of 2.0×10^6 viable T-cells/kg. All patients treated with ATIR were followed up until 24 months after the HSCT. Assessments were performed at weekly visits from the day of ATIR infusion until 8 weeks after ATIR infusion, at monthly visits from 3 until 6 months after the HSCT, every 2 months from 6 until 12 months after the HSCT, and every 6 months from 12 until 24 months after the HSCT.

Number of Patients (Planned and Analyzed):

In total 23 patients were planned to be treated with ATIR; 26 patients (including three patients who underwent an HSCT without ATIR infusion) were analyzed for safety; 23 patients were analyzed for primary efficacy.

Diagnosis and Main Criteria for Inclusion:

Patients aged between 18 and 65 years who were eligible for an allogeneic transplant but without the availability of a suitable matched related or unrelated donor following a donor search, were eligible to participate in this trial. Patients with the following hematologic malignancies could be enrolled: acute lymphoblastic leukemia (ALL; in first remission with high-risk features or in second or higher remission), acute myeloid leukemia (AML; in first remission with high-risk features or in second or higher remission), and myelodysplastic syndrome (MDS; transfusion-dependent, or intermediate or higher IPSS-R risk group).

Donors were haploidentical (i.e. 2 to 3 mismatches at the HLA-A, -B and/or -DR loci of the unshared haplotype) family members aged between 16 and 75 years who were eligible to donate hematopoietic cells.

Hematopoietic Stem Cell Transplantation (HSCT):

In order to prepare the patient for the HSCT the following conditioning regimens were recommended.

<u>TBI regimen</u>

- Fractionated total body irradiation (TBI) on Day -10 to -8 (1200 cGy)
- Fludarabine; 30 mg/m^2 intravenously (IV) once daily on Day -7 to -3
- Thiotepa; 5 mg/kg IV twice daily on Day -7
- Anti-thymocyte globulin (ATG; Thymoglobulin®); 2.5 mg/kg IV once daily and methylprednisolone 2 mg/kg IV on Day -5 to -2.

<u>Non-TBI regimen</u>

- Fludarabine; 30 mg/m^2 IV once daily on Day -8 to -4
- Thiotepa; 5 mg/kg IV twice daily on Day -7
- Melphalan; 60 mg/m^2 IV once daily on Day -2 and -1
- ATG (Thymoglobulin®); 2.5 mg/kg IV once daily and methylprednisolone 2 mg/kg IV on Day -5 to -2.

The collection and preparation of the donor stem cell graft was performed according to institutional procedures at the study center. The study centers mobilized peripheral blood stem cells (PBSCs) from the donor with granulocyte colony-stimulating factor (G-CSF) administered subcutaneously (SC) at a dose of approx. 8 µg/kg twice daily for approx. 4 to 7 days. The PBSCs were collected by apheresis. According to the Perugia protocol for haploidentical transplants, the CD34-selected stem cell graft was 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.

Post-transplantation immunosuppressive therapy (e.g. corticosteroids) in the absence of GVHD had to be avoided unless medically indicated. From June 2015 onwards, treatment with an unmanipulated DLI has been restricted to indications of impending relapse and graft failure.

To prevent infections with cytomegalovirus (CMV), patients who were CMV positive or had a CMV positive donor received prophylactic treatment, and were subject to regular quantitative PCR monitoring followed by adequate (pre-emptive) treatment if indicated. To prevent infections with Epstein-Barr virus (EBV), patients were subject to regular quantitative PCR monitoring followed by adequate (pre-emptive) treatment if indicated.

Investigational Medicinal Product, Dose and Mode of Administration:

ATIR, a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells using photodynamic treatment, was cryopreserved until infusion to the patient. ATIR was infused IV at a single dose of 2.0×10^6 viable T-cells/kg body weight between 28 and 32 days after the HSCT (or later if required by the patient's medical condition).

ATIR was not infused if at the time of the planned infusion:

- The patient was suffering from active GVHD (any grade), or
- The patient was receiving immunosuppressive therapy.

Duration of Treatment:

ATIR was administered as a single IV infusion.

Reference Therapy, Dose and Mode of Administration:

Not applicable

Criteria for Evaluation:

Efficacy:

- Immune reconstitution:
  - Total lymphocytes and immunophenotyping on peripheral blood as measured by flow cytometry: CD3+ (T-cells), CD3+ CD8+ (cytotoxic T-cells), CD3+ CD4+ (helper T-cells), CD3- CD56+ (NK-cells), and CD19+ (B-cells)
  - Immunoglobulins in peripheral blood: IgG, IgA, IgM
- Infection assessment:
  - Occurrence and severity of viral, fungal, and bacterial infections, including viral reactivations
- Disease assessment:
  - PFS, defined as the time from HSCT until relapse, disease progression, or death, whichever occurs first

- GVHD assessment:
  - Occurrence and severity of acute and chronic GVHD

- Mortality:
  - Occurrence of TRM, defined as death due to causes other than disease relapse or progression, or other causes which are unrelated to the transplantation procedure (e.g. accident, suicide)
  - Occurrence of RRM, defined as death due to disease relapse or disease progression
  - OS, defined as the time from HSCT until death from any cause
- Quality of life (QoL) assessments:
  - Questionnaires FACT-BMT, SF-36, and MDASI

Safety:

- Adverse events:
  - Spontaneously reported by the patient, discovered during general questioning by the investigator, or detected through physical examination, laboratory test or other means

Statistical Methods:

Descriptive statistics are provided for demographics and other baseline characteristics.

The TRM rate is displayed as a function of time using the Kaplan-Meier method. The TRM rate at 6 months post HSCT is estimated from this analysis.

Secondary endpoints are analyzed using descriptive statistics. In addition, time-event data (TRM, RRM, OS, and PFS) are displayed with the Kaplan-Meier method and immune reconstitution is graphically displayed in time.

Summary of Results

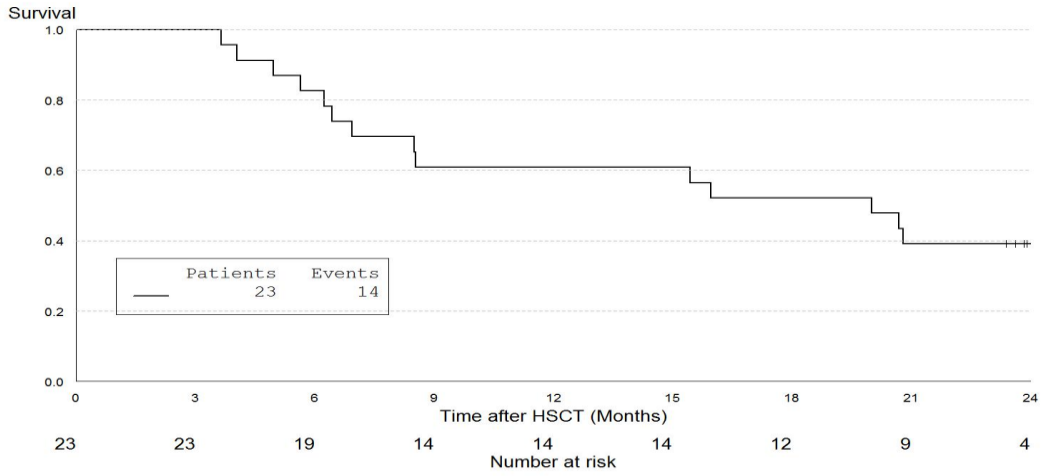
Of the 36 screened patients, 31 patients have been enrolled of whom 26 patients underwent HSCT (intention-to-treat [ITT] population) and 23 patients received ATIR (modified intention-to-treat [MITT] population). In total, nine patients completed the full 2-year study follow-up. The median follow-up time in the study was 20.0 months (range 3.6-24.4). In the MITT population the median age of patients was 41.0 years (range 21-64). Eleven patients (47.8%) were female. AML was the underlying malignancy in the majority of patients (16 patients, 69.6%), while 7 patients (30.4%) had ALL. All patients were in first or second complete remission. The median time from diagnosis of the malignancy to HSCT was approximately 1.5 years. Ten patients (43%) were categorized with Disease Risk Index (DRI) 'intermediate' and 13 patients (57%) with DRI 'high'. Patients received the graft most frequently from a sibling (39.1%) or child (39.1%) and less frequently from a parent (17.4%). Overall, 69.6% of patients had a mismatch with the donor at 3 of 6 HLA-A, -B, or -DR loci (4 of 6: 26.1%; 5 of 6: 4.3%). The CD34-selected stem cell graft contained a median of 11.0×10^6 CD34+ cells/kg (range 4.7-24.4) and 0.29×10^4 CD3+ cells/kg (range 0.01-1.8).

Efficacy:

Of the 23 patients treated with ATIR (MITT population), 14 patients (60.9%) died during the study. Four patients died within 6 months after HSCT, of which three due to TRM and one due to relapse. Additionally, five patients died between 6 and 12 months after HSCT;

four due to TRM and one due to relapse. Between 1 and 2 years after HSCT, five patients died, two due to relapse and three due to TRM. So overall, 10 patients (43.5%) died due to TRM and four patients (17.4%) due to disease relapse (two patients relapsed within 100 days after HSCT and two relapsed more than a year after HSCT). Of the 10 patients that died due to TRM, the cause of TRM was infection in eight patients (34.8%), and other causes in two patients (8.7%).

Kaplan-Meier plot of OS - MITT population



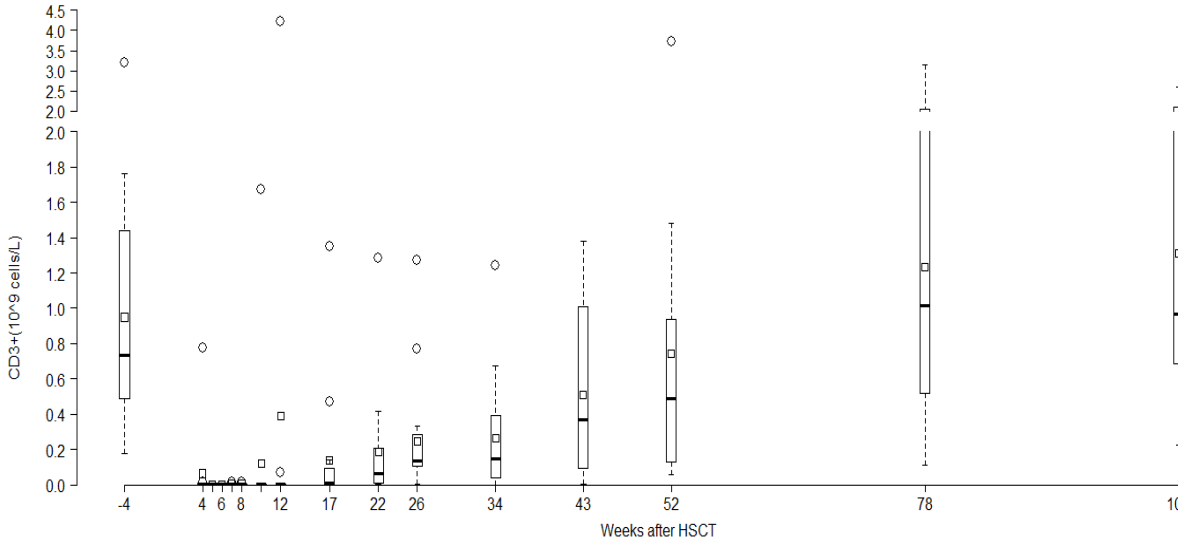
Kaplan-Meier estimates (%) and 95% confidence intervals

MITT population (N=23)	**6 months post HSCT**	**12 months post HSCT**	**24 months post HSCT**
TRM	13 [5,36]	32 [17,56]	48 [29,71]
RRM	5 [1,28]	10 [3,35]	25 [10,55]
OS	83 [60,93]	61 [38,77]	39 [20,58]
PFS	78 [55,90]	61 [38,77]	39 [20,58]

The overall, cumulative number of GVHD events in the MITT population was 19, reported in nine patients (39.1%); eight patients with acute GVHD only (maximum grade II: 13.0%; grade III: 8.7%, grade IV: 4.3%) and one patient (4.3%) with acute GVHD grade I and severe chronic GVHD. Two patients developed GVHD before administration of ATIR, showing the possibility of remaining T-cells in the graft to cause GVHD. Administration of ATIR to these patients after resolution of GVHD did not trigger GVHD again. Seven patients (30.4%) developed GVHD after ATIR infusion, of which three patients developed severe (grade III/IV) GVHD more than a year post HSCT, triggered by infusion of unmanipulated donor lymphocytes. Acute GVHD within 1 year post ATIR infusion was of grade I/II only and was observed in five patients (21.7%).

Overall, infections of ≥ CTCAE grade 3 occurred in 39.1% of patients between the ATIR infusion and 6 months after HSCT, in 21.7% from 6 to 12 months after HSCT, and in 30.4% between 1 and 2 years after HSCT.

Number of T-cells (CD3 cells) over time - MITT population



Reconstitution of cellular immunity (CD3+ cells) was seen from 4 months post HSCT onwards. From Month 10 post HSCT onwards, full reconstitution of cellular immunity (CD3 > 0.2×10^9/l) was observed for the majority of patients.

Safety:

Overview of (serious) adverse events - ITT population

	HSCT (N=26)		ATIR (N=23)	
	No of patients (%)	**No of events**	**No of patients (%)**	**No of event**
Adverse events (AEs)	26 (100%)	626	23 (100%)	612
Infections	26 (100%)	356	23 (100%)	347
Relapse/disease progression	4 (15.4%)	5	4 (17.4%)	5
GVHD	10 (38.5%)	21	9 (39.1%)	19
Other	25 (96.2%)	244	23 (100%)	241
Treatment-emergent AEs			23 (100%)	
ATIR-related AEs			8 (34.8%)	
Serious adverse events (SAEs)	24 (92.3%)	86	22 (95.7%)	84
Infections	19 (73.1%)	42	18 (78.3%)	41
Relapse/disease progression	4 (15.4%)	5	4 (17.4%)	5
GVHD	5 (19.2%)	6	5 (21.7%)	6
Other	14 (53.8%)	33	13 (56.5%)	32
Deaths	16 (61.5%)		14 (60.9%)	
Treatment-emergent SAEs			20 (87.0%)	
ATIR-related SAEs			3 (13.0%)	

Treatment-emergent defined as starting after ATIR infusion; ATIR-related defined as either possibly, probably, or certainl related to ATIR (or missing relationship) as judged by the investigator

The most frequent treatment-emergent AEs by SOC were infections and infestations (95.7%), followed by investigations (82.6%). The most frequent PTs were CMV test positive (43.5%), EBV antigen positive (34.8%), oral candidiasis (34.8%), pneumonia (30.4%), and acute GVHD.

The most frequent treatment-emergent AEs of ≥ grade 3 (excluding GVHD) were autoimmune hemolytic anemia (AIHA; 5 patients), febrile neutropenia (4 patients), pneumonia (4 patients), and PTLD (4 patients), followed by pulmonary embolism, pyrexia, decreased lymphocyte count, and recurrent leukemia (3 patients each).

The only preferred term reported as a related AE in more than a single patient was acute GVHD (17.4%).

A total of 15 patients died during the study, including 14 patients, in whom the fatal SAE had an onset date after ATIR administration. In the majority of patients, the fatal SAE belonged to the SOC of infections and infestations. None of the SAEs with fatal outcome was ATIR-related.

The most frequent SAEs by SOC were infections and infestations (73.1%), followed by blood and lymphatic system disorders (30.8%), and neoplasms (26.9%). The most frequent SAEs by preferred term were AIHA (19.2%), followed by acute GVHD and febrile neutropenia (each: 15.4%). ATIR-related SAEs were reported in three patients: acute GVHD (4.3%), chronic GVHD (4.3%), and AIHA (4.3%), respectively

A total of 10 patients (38.5%) had AEs reported that were indicative of a CMV reactivation. One of these patients had an AE of CMV infection reported, whereas the other nine patients only reported CMV reactivation without symptoms or infected sites.

A total of nine patients (34.6%) had AEs reported that were indicative of an EBV reactivation. Four of these patients had an AE of PTLD reported, whereas the other five patients only reported EBV reactivation without symptoms or infected sites.

One patient reported possibly related rash, which is a potential infusion reaction of ATIR.

Five patients (19.2%) had a total of eight autoimmune hemolytic anemia (AIHA) events reported, all as SAEs. These AIHA cases were most likely related to the T-cell depleted HSCT whereas there was no indication of a direct relationship with ATIR.

No patient in the study reported veno-occlusive disease.

CONCLUSIONS

- The primary efficacy endpoint, TRM at 6 months post HSCT, is estimated to be 13% (95% CI 5-36%), which is significantly less than that in a control group of patients not receiving ATIR (study CR-AIR-006).
- Relapse rates are low, with RRM of 10% at 1 year post HSCT in a high-risk patient population.
- OS at 1 and 2 years post HSCT is estimated to be 61% and 39%, respectively. PFS estimates are similar.
- Compared to a control group of untreated patients (study CR-AIR-006), 1-year OS was significantly improved and 1-year OS was also higher than for a recently approved cellular product in Europe (Zalmoxis®).

- Seven patients (30.4%) developed acute GVHD after ATIR infusion, of which five cases could be potentially attributed to ATIR, all of grade I or II only. Three patients developed severe (grade III/IV) GVHD more than a year post HSCT triggered by infusion of unmanipulated donor lymphocytes.
- The main cause of death was infection (35%) followed by relapse (17%) and other causes (9%).
- Reconstitution of cellular immunity (CD3+ cells) was seen from 4 months post-HSCT onwards. From Month 10 post HSCT onwards, full reconstitution of cellular immunity ($CD3 > 0.2\times10^9/l$) was observed for the majority of patients.
- Based on the reported ATIR-treatment emergent AEs and ATIR-related (S)AEs, the treatment is considered to be safe and well tolerated. No unexpected safety concerns were raised, except for AIHA, which requires further monitoring in future studies.

Final Date:

18 July 2018

Prepared in:

Microsoft Word 2016