2 SYNOPSIS

Study ID:	CR-AIR-009
Phase:	III
Countries:	Belgium, Canada, Croatia, Portugal, Spain, United Kingdom, Netherlands, United States
Study title:	A phase III, multicenter, randomized controlled study to compare safety and efficacy of a haploidentical hematopoietic stem cell transplant (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 (PTCy) in patients with a hematologic malignancy
Study design:	Study CR-AIR-009 was a phase III randomized, controlled, multicenter, open-label study comparing two parallel groups. After signing informed consent, a total of 250 patients were to be randomized in a 1:1 fashion to receive either a T-cell depleted 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 used minimization to balance treatment groups with respect to underlying disease (acute myeloid leukemia [AML], acute lymphocytic leukemia [ALL], or myelodysplastic syndrome [MDS]), disease risk index (DRI; intermediate risk, high risk, or very high risk) and center. A stochastic treatment allocation procedure was used so that the treatment assignment was random for all patients entered in the study. Patients randomized in the ATIR101 group received 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 received cyclophosphamide 50 mg/kg/day 3 and 4/5 days after the HSCT. All patients were to be followed up for at least 24 months post HSCT.
Dosing regimen:	ATIR101 group: Single infusion with ATIR101 at a dose of 2×10^6 viable T-cells/kg between 28 and 32 days after the HSCT. PTCy group: IV infusion with cyclophosphamide 50 mg/kg/day 3 and 4/5 days after the HSCT.
Study population:	Patients with hematologic malignancies (AML, ALL, or MDS; males and females aged 18-70 years) who are eligible for a haploidentical HSCT but without the availability of a suitable matched related or unrelated donor following a donor search.
Study period:	The first visit of the first patient was on 29 November 2017. Enrollment has stopped on 12 November 2019. The database cut-off of the active study phase was on 19 March 2020. Safety follow-up of patients is ongoing.

Planned enrolment/patient analyzed:	In total, 250 patients were planned to be randomized 1:1 to the ATIR101 group or the PTCy group. On 12 November 2019, 63 patients had been enrolled (randomized) in the study; 32 to ATIR101 group and 31 to PTCy group (intention-to-treat [ITT] population). Only patients who received an HSCT and ATIR101 (ATIR101 group) or at least one dose of PTCy (PTCy group) were included in the modified intention-to-treat population (MITT) as defined in the protocol. At the time of database cut-off, the MITT consisted of 16 patients that were treated with ATIR101 and 27 treated with PTCy. The analyses in this abbreviated study report focus on the MITT.
Patient exposure (M/F):	8 males / 8 females treated with ATIR101; (N=16) 18 males / 9 females treated with PTCy; (N=27)
Status:	Enrollment of patients has stopped and all patients are followed-up for at least 4 months post-HSCT. Treated patients will have limited safety follow-up up to two years post-HSCT.
Summary of results:	**Efficacy:** At 18 months post HSCT: • On the primary endpoint graft-versus-host disease (GVHD)-free, relapse-free survival (GRFS), probability was estimated to be 29% for the ATIR101 treated patients compared to 65% for the PTCy treated patients; • On the secondary endpoint transplant-related mortality (TRM), probability was estimated to be 42% for the ATIR101 treated patients compared to 16% for the PTCy treated patients; • On the secondary endpoint overall survival (OS), probability is estimated to be 39% for the ATIR101 treated patients compared to 84% for the PTCy treated patients; • On the secondary endpoint progression-free survival (PFS), probability is estimated to be 45% for the ATIR101 treated patients compared to 76% for the PTCy treated patients. **Safety:** Of the 16 patients who were treated with ATIR101: • 9 patients (56.3%) reported ATIR101-related AEs, most frequently reported was classic acute GVHD (N=5; 31.3%); • 4 patients (25.0%) reported ATIR101-related SAEs. The most frequently reported ATIR101-related SAE was acute GVHD; persistent, recurrent, or late-onset acute (N=2, 12.5%); • 7 patients died (43.8%): 6 due to TRM and 1 due to disease relapse/progression; • 5 patients (31.3%) reported grade III or IV acute GVHD; • 1 patient (6.3%) had chronic GVHD requiring systemic immunosuppression; • 2 patients (12.5%%) reported graft failure; • 4 patients (25.0%) had disease relapse or disease progression.

	Of the 27 patients who were treated with PTCy: • 16 patients (59.3%) reported PTCy-related AEs, most frequently reported was cytomegalovirus viraemia (N=4; 14.8%), oral candidiasis (N=4; 14.8%), and diarrhea (N=4; 14.8%); • 6 patients (22.2%) reported PTCy-related SAEs. The most frequently reported PTCy-related SAE was cardiac failure (N=2, 7.4%); • 5 patients died (18.5%): 4 due to TRM and 1 due to COVID-19; • 2 patients (7.4%) reported grade III or IV acute GVHD; • 3 patients (11.1%) had chronic GVHD requiring systemic immunosuppression; • 1 patient (3.7%) had a graft failure; • 2 patients (7.4%) had disease relapse or disease progression.
Conclusion	Study CR-AIR-009 has been prematurely terminated. Superiority on the primary endpoint GRFS for patients treated with ATIR101 when compared to patients treated with PTCy was not reached. Furthermore, from 3 months onwards the patients treated with ATIR101 have a worse TRM, OS and PFS compared to the patients treated with PTCy. The observed higher than expected percentage of patients discontinuing before ATIR101 treatment together with newly obtained data on GRFS for PTCy showed that the initial assumptions are no longer valid. The safety data from the study showed that there is no safety concern with ATIR101. The observed (S)AEs and their numbers were expected for patient treated with a haploidentical HSCT.