Donor Lymphocytes Depleted of Alloreactive T-cells (ATIR101) Improve Event-Free Survival (GRFS) and Overall Survival in a T-cell Depleted Haploidentical HSCT: Phase 2 Trial in Patients with AML and ALL

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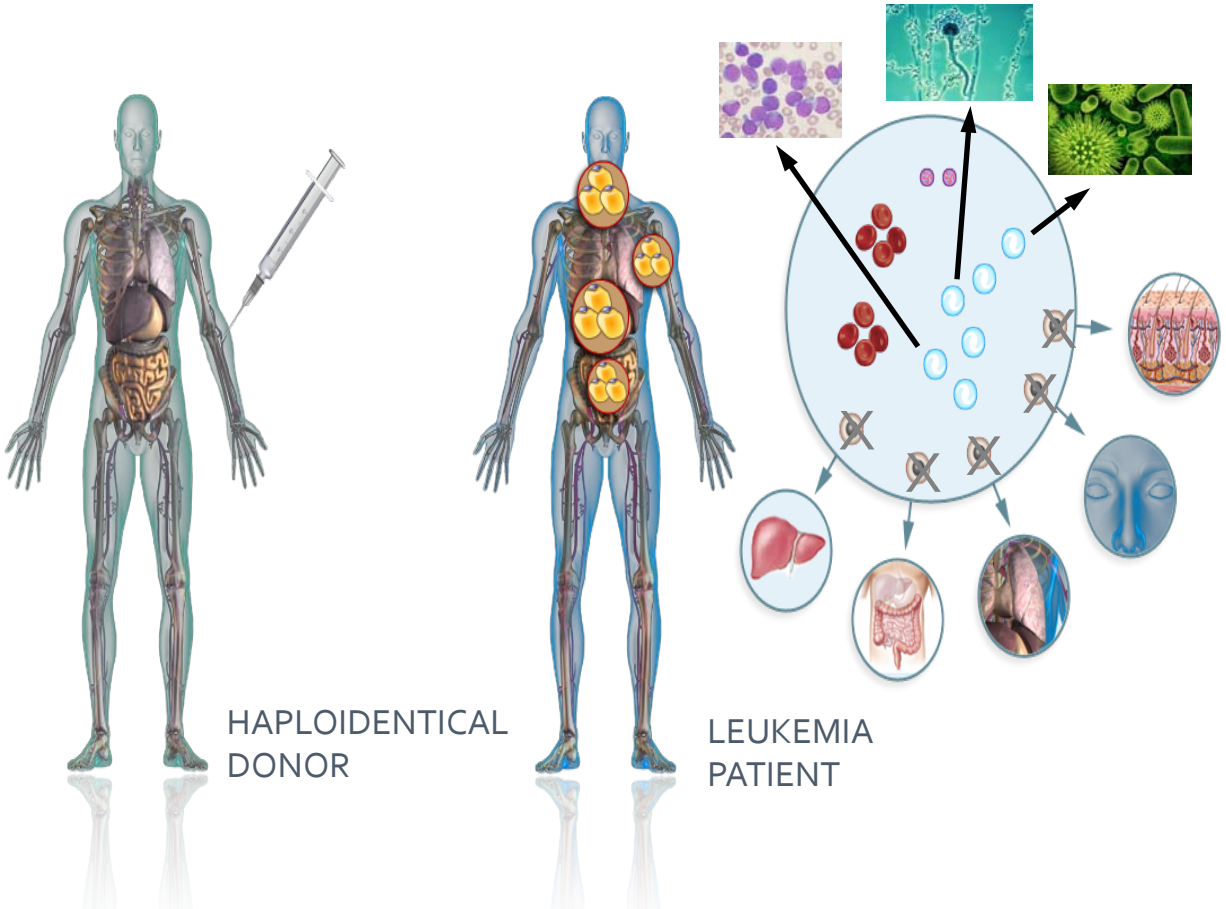
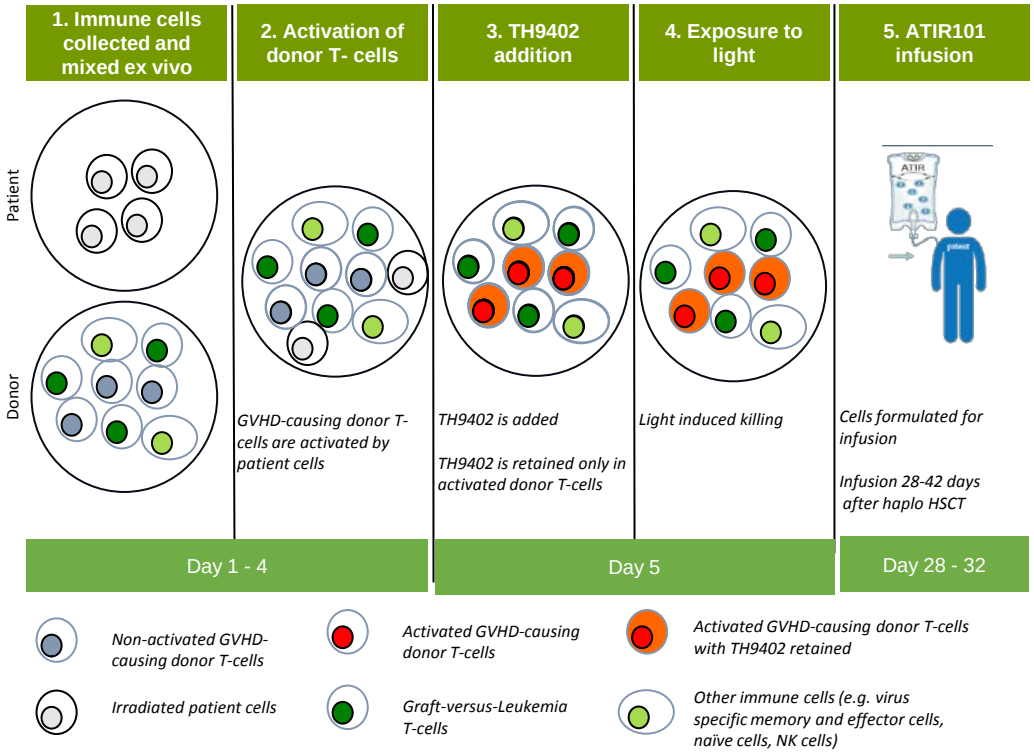
Monday, December 5, 2016: 6:30 PM, Room 30 (San Diego Convention Center)

Challenge in Haploidentical Donor Transplantation



ATIR101 manufacturing removes GVHD-causing T-cells while retaining key immune cells

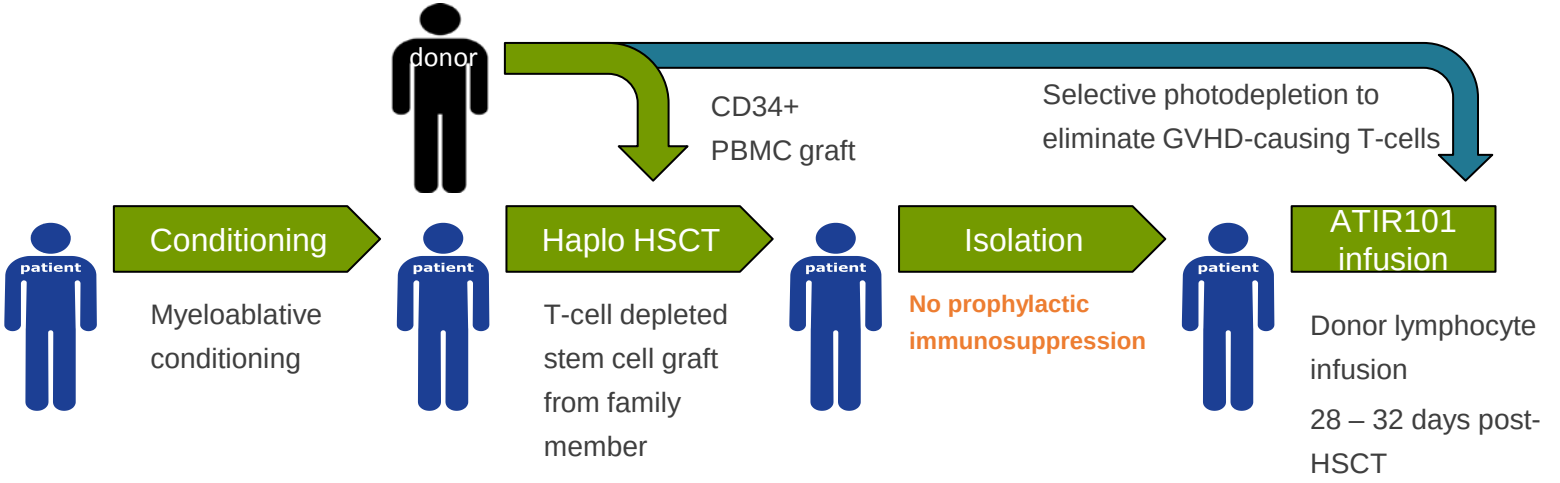


Effects ATIR101 procedure (photodepletion)

- Selective removal of GVHD-causing T-cells
- Preservation of the full immune repertoire
  - Key immune cells are retained to protect against infections
  - T-cells directed against leukaemic antigens are retained

Background to treatment

- Aim is to develop an immunosuppressant-free transplant regimen for haploidentical donor transplantation
- Based on T-cell depletion: $CD34^{+}$-mega dose approach (Perugia)
- Pre-emptive administration of donor lymphocytes (ATIR101) post-HSCT, after elimination of alloreactive T-cells
  - Avoid GVHD
  - Reduce infections/TRM/relapse



Trial characteristics & endpoints

Trial characteristics

- *Design:* open-label, single arm, multi-center study
- *Patient population:*
  - Patients with AML or ALL in first remission with high-risk features or in second or higher remission, or
    MDS with intermediate or higher IPSS-R risk group
  - No suitable matched related or unrelated donor
  - Haploidentical family donor with 2 to 3 mismatches at the HLA-A, -B and/or -DR loci
- *Locations:*
  - Canada (3), Belgium (3), Germany (1), United Kingdom (1)
- *Recruitment:*
  - Between March 2013 and August 2015

- *Primary endpoint:*
  - Transplant-related mortality (TRM) at 6 months post HSCT
- *Secondary endpoints:*
  - Incidence and severity of acute and chronic graft versus host disease (GVHD) up to 24 months post HSCT
  - Immune reconstitution
  - Infections
  - TRM, relapse, overall survival (OS), up to 24 months post HSCT

- Patient follow-up (*per 28 November 2016*):
  - Median 485 days (range 110 – 742)

Patient & Donor characteristics

Patient & Donor

- N=23 patients (*HSCT + ATIR101*)
- Median patient age (range): 41 years (21 – 64)
- Gender: 13 female, 10 male

- Median donor age (range): 33 years (21 - 61)
- HLA matching (HLA-A, B, DR)
  - 3/6 match: 16
  - 4/6 match: 6 5/6 match: 1 (7/10 match)
- Donors:
  - Father/mother 4 (17%)
  - Sibling 9 (39%)
  - Son/daughter 9 (39%)
  - Other 1 (4%)

Diagnosis

- *Acute myeloid leukemia – N=16 (70%)*
  - 11 in CR1
  - 5 in CR2
- *Acute lymphoblastic leukemia – N=7 (30%)*
  - *4 in CR1*
  - *3 in CR2*
- *Cytogenetic risk profile[1]:*
  - *Favorable* *0*
  - *Intermediate* *9 (39 %)*
  - *Adverse* *14 (61 %)*
- *Disease-risk index[2]:*
  - *Low risk index* *0*
  - *Intermediate risk index* *10 (43 %)*
  - *High risk index* *13 (57 %)*

[1] Mrozek K, et al. JCO 2012, 30 (36):4515-4523

[2]Armand P, et al. Blood 2014, 123 (23); 3664-3671

Transplantation characteristics

Conditioning

- TBI (1200 cGy; n=11) *or* melphalan (120mg/m2; n=12)
- Thiotepa (10 mg/kg), fludarabine (30 mg/m2 x 5d) and
- ATG (Thymoglobulin: 2.5mg/kg x 4d)

HSCT

- CliniMACS® CD34 isolation system (Miltenyi Biotec)
- Target: 8-11x10^6 CD34+ cells/kg, with max. of 3x10^4 CD3+ cells/kg

Prophylaxis

- **No GVHD prophylaxis**
- CMV/EBV monitoring
- Prophylactic use of ganciclovir / foscarnet (CMV + recipient/donor)

HSCT

Graft	Median (cells/kg)	range
$CD34^+$	10.9 x 10^6	3.2 – 24.4 x 10^6
$CD3^+$	0.28 x 10^4	0 – 1.8 x 10^4
Engraftment	**Median (days)**	**range**
Neutrophils	12	8 – 34
Platelets	12	9 – 35

ATIR101 infusion

- *23 infusions of ATIR101*
  - *Day of infusion (range): median 28 (28 – 73)*
  - *Two infusions postponed due to GVHD before infusion*

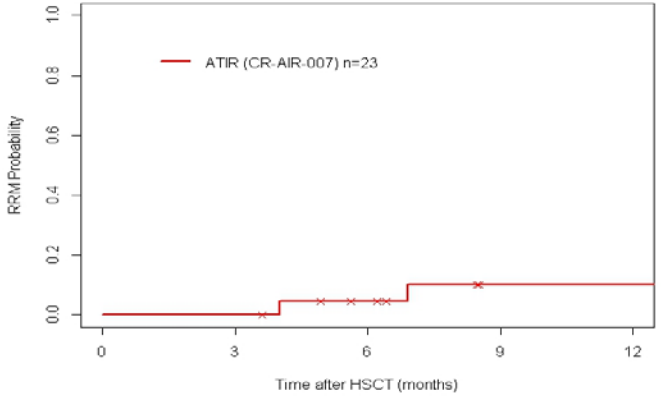
Graft versus Host Disease (GVHD) & Relapses

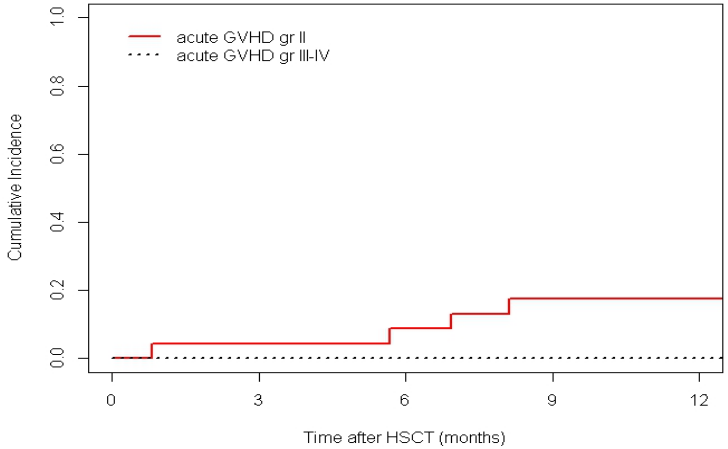
Acute GVHD

- **No grade III/IV GVHD** after ATIR101 infusion
- Only 3 cases of grade II GVHD after ATIR infusion (late-onset)
- In 2 patients GVHD occurred before ATIR infusion (1 grade I, 1 grade II), delaying infusion until resolution

Chronic GVHD

- Only 1 case of chronic GVHD (severe) has been reported





Relapses

- Two patients relapsed within 1st year post-HSCT:
  - One on Day 61 (AML, CR1) and one on Day 90 (AML, CR1) post-HSCT
- Additional two patients relapsed beyond 1 year:
  - One on Day 401 (AML, CR1) and one on Day 460 (AML, CR2) post-HSCT

Observational Cohort Study: Patient characteristics

Patient Group	CD34-Haplo	8/8 or 10/10 MUD	*CR-AIR-007*
Number of patients	35	64	*23*
Age (yrs, median)	43.0 (19 – 62)	47.5 (20 – 63)	*41 (21 – 64)*
Sex			
Male	**20 (57%)**	**34 (53%)**	***10 (43%)***
Female	**15 (43%)**	**30 (47%)**	***13 (57%)***
Diagnosis			
AML	**25 (71%)**	**43 (67%)**	***16 (70%)***
*1st CR**	*18*	*32*	*11*
2nd/higher CR	*6*	*10*	*5*
Other	*1 PR***	*1 unknown*	
ALL	**4 (12%)**	**9 (14%)**	***7 (30%)***
*1st CR**	*1*	*5*	*4*
2nd/higher CR	*3*	*4*	*3*
MDS	**6 (17%)**	**12 (19%)**	

* CR = Complete Remission ** PR = Partial Remission

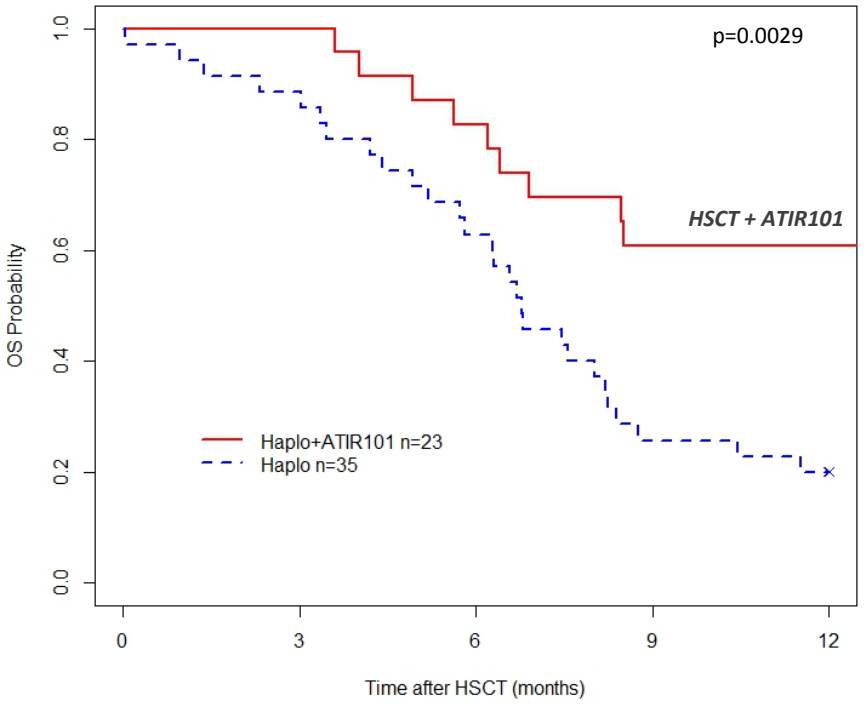
Design

- Data have been collected from a defined time period:
  - CD34-HAPLO: 1 January 2006 till 30 June 2013
  - MUD: 1 January 2010 till 31 December 2012
- Patient population aligned with phase 2 trial (CR-AIR-007)
  - Patients with AML, ALL (both in remission at the time of the transplantation) or MDS
  - Patients aged 18-65, without having had a previous transplantation

Trial sites similar to participating sites in CR-AIR-007 (Canada, Belgium, Germany, Netherlands, United Kingdom and United States)

Overall Survival: Benefit of adjunctive treatment with ATIR101

Overall survival



KM estimates of: *Overall Survival*	6 months after HSCT	12 months after HSCT
Haplo-HSCT + ATIR101	83%	61%
Haplo-HSCT alone	63%	20%

- In the HSCT + ATIR101 group 9 patients died within the first year after transplantation:
  - Between HSCT and 6 months: 3 died due to TRM and 1 due to relapse
  - Between 6 – 12 months: 4 died due to TRM and 1 due to relapse
- Compared to patients only receiving a CD34-selected HSCT, ATIR101 significantly improves overall survival

GVHD-free, Relapse-free Survival to compare transplant regimens

GRFS[1]

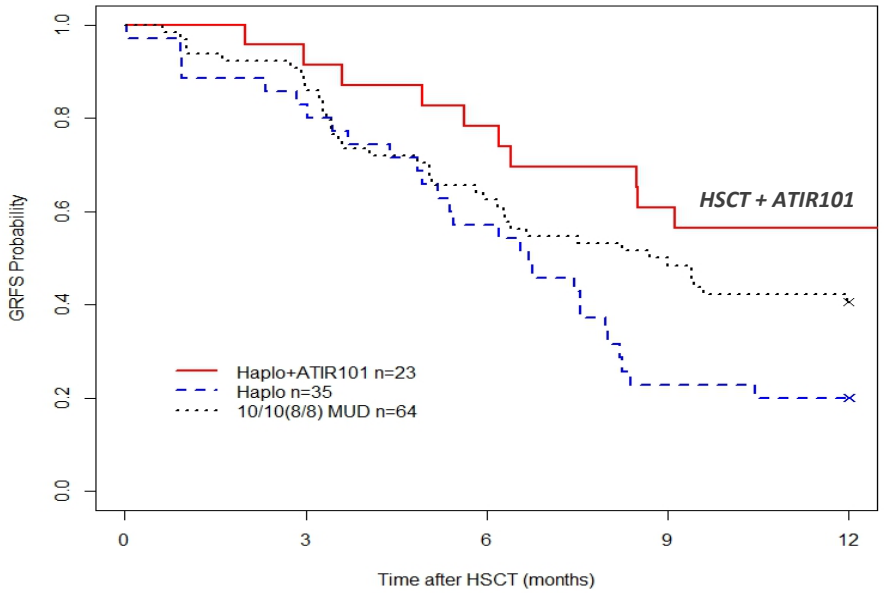
- GVHD free/relapse-free survival (GRFS): composite endpoint to show clinical benefit. GRFS is survival without:
  - Acute GVHD (grade III/IV)
  - Chronic GVHD (requiring systemic treatment)
  - Cancer relapse

KM estimates of: *GRFS*	6 months after HSCT	12 months after HSCT
Haplo-HSCT + ATIR101	78%	57%
Haplo-HSCT alone	57%	20%
MUD HSCT (8/8 or 10/10)	63%	41%

Comparison to CD34-Haplo and MUD

- Improved GRFS compared to matched unrelated donor transplants and to CD34-selected Haplo-HSCT alone

GVHD-free, Relapse-free Survival



[1] Holtan et al. 2015, Blood 125, 1333-1338

Comparison against PTCY for Haplo-HSCT: literature

- Holtan et al. (2015):
  - Cohort of 907 allogeneic HSCT recipients
  - Reported 1-year GRFS was 31%
  - Best outcomes in recipients of marrow from matched sibling donors
- Sohl et al. (2016):
  - Cohort of 531 allogeneic (adult) HSCT recipients transplanted between 2006-2014
  - Sub-cohort of 128 recipients of a haploidentical donor graft using PTCy
  - Reported 1-year GRFS for haploidentical HSCT was 30%
- Observed 1-year GRFS in patients receiving a CD34-selected HSCT + ATIR101 of 57% compares favorably to reported data from large cohorts

Table 5
Adjusted 1-Year and 2-Year GRFS

Factor	No. of Patients (N = 531)	Adjusted 1-Year GRFS		
		Estimate	95% CI	*P*
Source				
BM	103 (19%)	41%	31%-50%	—
PBSC	428 (81%)	29%	25%-33%	.033
Donor type				
MRD	198 (37%)	36%	30%-43%	—
MUD	205 (39%)	27%	21%-33%	.034
HID	128 (24%)	30%	22%-38%	.227
DRI				
Low	78 (15%)	43%	32%-53%	—
Intermediate	258 (49%)	31%	26%-37%	.054
High/very high	189 (36%)	26%	20%-32%	.005

[1] Holtan et al. 2015, Blood 125, 1333-1338

Conclusions

- Adjuvant infusion of haploidentical donor lymphocytes depleted of allo-reactive T-cells (ATIR101) to a T-cell depleted haploidentical HSCT significantly improves overall survival.
- Infusion of ATIR101 is safe and does not cause grade III/IV GVHD.
- Relapse rates are low.
- Improved clinical benefit, based on the GRFS endpoint, over HSCT with either matched unrelated donor or CD34-selected haplo-donor transplants.
- Compared to literature on post-transplant cyclophosphamide (PTCy), relapse rates and incidence of GVHD are low on the ATIR101 protocol.
- A randomized phase III study comparing haploidentical HSCT with PTCy against a T-depleted HSCT + ATIR101 is being initiated.

T-cell depleted HSCT with ATIR101 as adjuvant provides a safe and effective, immunosuppressant-free transplant regimen for haploidentical transplantation.

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