Making bone marrow transplantations safer and more effective

Patient specific cell-based immunotherapy products, as adjunctive treatment to haploidentical hematopoietic stem cell transplantation (HSCT), for the treatment of blood cancers and inherited blood disorders

KOL Lunch, May 31st 2017
St Regis Hotel, New York, NY, USA
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**Kiadis: near term and large opportunity in HSCT**

<table>
<thead>
<tr>
<th>UNIQUE PLATFORM</th>
<th>• IP protected patient specific cell therapy product as adjunctive to haploidentical hematopoietic stem cell transplantation (HSCT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOCKBUSTER POTENTIAL</td>
<td>• Orphan Drug designations US and EU; target population 28,700 patients with blood cancers and inherited blood/immune disorders</td>
</tr>
<tr>
<td>SUPERIOR DATA</td>
<td>• Phase II 1 year data superior to control and improved to literature for PTCy/Baltimore and Zalmoxis (Molmed, EMA approved)</td>
</tr>
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<td>IN EU MARKET POTENTIAL 2019</td>
<td>• Filed with EMA based on Phase II, potential for (conditional) approval H2 2018; Phase III against PTCy/Baltimore initiated for FDA</td>
</tr>
<tr>
<td>EFFICIENT SUPPLY CHAIN</td>
<td>• Efficient 5 day manufacturing, without genetic engineering; easily integrated into existing transplantation center processes</td>
</tr>
</tbody>
</table>
Agenda KOL Lunch Kiadis

Introduction - Arthur Lahr, CEO Kiadis Pharma

Steven Devine, MD: Haploidentical Blood and Marrow Transplantation: Where have we been and where are we going?

Professor of Internal Medicine in the Division of Hematology and Director of the Blood and Marrow Transplant Program at Ohio State’s Comprehensive Cancer Center, Columbus, Ohio, USA


Division of Hematology and Bone Marrow Transplantation at the Maisonneuve-Rosemont Hospital, Professor of Medicine at the University of Montréal, Scientific Director, Center of Excellence for Cell Therapy, Montreal, Canada

Discussion/Closure – Jeroen Rovers, CMO Kiadis Pharma
HAPLOIDENTICAL BLOOD AND MARROW TRANSPLANTATION:
Where have we been and where are we going?

The James
Allogeneic Bone Marrow and Blood Cell Transplantation

- Only potential curative therapy for a variety of advanced hematological malignancies and serious non-malignant conditions

- Advances in HLA-typing and supportive care have substantially improved outcomes over the past two decades

- Historically, application had been limited by lack of identification of suitable donors

- Most of the growth now seen in mismatched, so called “haploidentical” family member donors and in older recipients
Likelihood of Finding an 8/8 HLA Match by Year End, Based on Current Donor Availability and with Recruitment Trends Extended to 2017.
Growth in number of allografts in the US

Annual Number of HCT Recipients in the US by Transplant Type

Allogeneic HCT Recipients in the US, by Donor Type

Growth in Haploidentical Transplants in Europe

Passweg et al, Bone Marrow Transplant 2017
Growth in publications related to haploidentical SCT

Based on Pubmed search accessed May 7, 2017
HLA-haploidentical donors

Kanakry, C. G. et al. (2015) Modern approaches to HLA-haploidentical blood or marrow transplantation
Risk of Acute Graft versus Host Disease (A-GVHD)
in Relation to the Number of Disparate Loci.

Historical background in Haploidentical SCT

• Prohibitively high rates of
  • Graft rejection
  • Severe graft versus host disease (GVHD)
  • Infectious complications
  • Non-relapse mortality

• In 1980s and 1990s few centers performed haploidentical transplants

• During this time, National Marrow Donor Program (NMDP) and other volunteer donor registries grew
Pretransplantation Conditioning Regimen, Donor Hematopoietic Stem-Cell Processing, and Times of Infusions.

Probability of Disease-free Survival in Patients with ALL or AML.

Many centers in US and abroad unable to duplicate initially encouraging results with standard (no add-back) ex-vivo T-cell depleted Haplo Transplants

- Engraftment in most
- Low rates of acute and chronic GVHD, but:
  - High rates of infectious complications
  - Significant non-relapse mortality
  - High rates of relapse
Canadian multicenter pilot trial of haploidentical donor transplantation - 2004

Irwin Walker, Nadine Shehata, Guy Cantin, Felix Couture, Nathalie Dhédin, Rebecca Barty, Ronan Foley, Robert D. Sutherland, Christopher Sigouin, Kirk R. Schultz, David Mitchell

Blood Cells, Molecules, and Diseases, Volume 33, Issue 3, 2004, 222–226

http://dx.doi.org/10.1016/j.bcmd.2004.08.006
Selective allodepletion with PT/Cy

Standard myeloablative prep regimens (n=96)

Chemo based prep (n=73):

TBI based prep (n=23):
ALL and lymphoblastic lymphoma
Haploidentical donors have some logistical advantages over unrelated donors

<table>
<thead>
<tr>
<th></th>
<th>MUD</th>
<th>Haplo</th>
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<tbody>
<tr>
<td>Donor availability</td>
<td>20%-80%(^{18})</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>Time to graft acquisition</td>
<td>Slower</td>
<td>Faster</td>
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<tr>
<td>Time between collection and infusion</td>
<td>Longer</td>
<td>Shorter</td>
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<tr>
<td>Ease of repeat donations</td>
<td>Harder</td>
<td>Easier</td>
</tr>
</tbody>
</table>

Fuchs E, Blood Advances 2017
PTCy Haplo versus matched sibling and unrelated donor transplants

Bashey et al, J Clin Oncol 2013
CIBMTR risk (high or intermediate v low) influenced OS: HR 1.84 p=.026
Leukemia-Free Survival
Adjusted for DRI, performance score, secondary AML

Myeloablative

MUD 42% (40-45)
HAPLO 41% (32-51)

HR 0.98 (95% CI 0.75-1.27), p=0.87

Reduced Intensity

MUD 37% (33-40)
HAPLO 35% (25-45)

HR 0.98 (95% CI 0.74-1.30), p=0.89

Outcomes of Haploidentical PTCy transplants relative to matched unrelated donor transplants

Table 2. Retrospective comparisons of outcomes of haplo SCT plus posttransplantation cyclophosphamide vs MUD SCT

<table>
<thead>
<tr>
<th>Reference</th>
<th>RIC or MAC</th>
<th>N</th>
<th>aGVHD II-IV (%)</th>
<th>cGVHD (%)</th>
<th>NRM (%)</th>
<th>Relapse (%)</th>
<th>Overall survival (%)</th>
<th>Event-free survival (%)</th>
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<tbody>
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<td>AML ≤ MDS</td>
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Significant differences are shown in bold type: *P ≤ .01; †P ≤ .05; **P ≤ .001. 
aGVHD, acute graft-versus-host disease; AML, acute myeloid leukemia; cGVHD, chronic graft-versus-host disease; NRM, nonrelapse mortality; RIC, reduced intensity conditioning [includes nonmyeloablative conditioning]; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome.

†Mixture of matched sibling and MUD transplants.

Fuchs E, Blood Advances 2017
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Fuchs E, Blood Advances 2017
What about efficacy endpoints in BMT?
Primary efficacy endpoints to measure success of a novel BMT strategy

• Characteristics\(^1\)
  - Clinically relevant
  - Consistently determined
  - Readily interpretable
  - Sensitive to treatment changes

• GVHD-free, relapse free survival (GRFS)\(^2\)
  - Survival without relapse, grade III-IV acute, or mod/severe chronic GVHD
  - Fulfills characteristics of a meaningful efficacy endpoint

---

Distribution of individual components of GRFS. (A) Age (B) conditioning regimen, (C) stem cell/donor type, and (D) cause of death by donor type.
GVHD-free, relapse free survival by donor type

McCurdy et al, Haematologica, 2017
BMT CTN 1203
A Multi-center Phase II Trial of Randomized Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

PROGRESS I trial
Prevention and Reduction Of GVHD and Relapse and Enhancing Survival after Stem cell transplantation
BMT CNT #1203: Study Outline

Primary endpoint: GVHD-free, relapse free survival (GRFS)
BMT CTN 1301
A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host Disease

PROGRESS II trial
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation
BMT CTN 1301 CNI free Trial: 3-arm Phase III

- 345 (115/arm): 85% power to detect a 20% difference over the 22% baseline of the chronic GVHD/relapse-free survival [CRFS] primary endpoint.

As of March 25, 2017, accrual is 169/345, >150% ahead of schedule.
What is the best strategy to optimize haploidentical transplantation?
Components of each haploidentical transplantation platform

Modified from Kanakry, C. G. et al. (2015) Modern approaches to HLA-haploidentical blood or marrow transplantation
What is the optimal Haploidentical Stem Cell Transplantation strategy?

• PTCy may be the simplest and cheapest
  - What if relapse rates are higher?
  - Still requires pharmacological GVHD prophylaxis

• Ex-vivo T-cell depletion with “add-back”
  - Does not always require pharmacological GVHD prophylaxis
  - May be best platform for post transplant manipulation (e.g. maintenance therapy, adoptive transfer)

• In vivo T-cell depletion with ATG or other antibodies
  - Also requires pharmacological GVHD prophylaxis
  - High rates of relapse and infections complications
  - May be inferior to PTCy (EBMT data: Ruggeri et al, Haematologica, 2017)
Some unknowns about Haplos with Post-Tx Cyclophosphamide

- Long-term control of malignancy. Are relapse rates too high?
- Is there long term toxicity of Cy given post transplant
- Optimal conditioning regimen - Engraftment
- Optimal graft type (PB or BM) or conditioning regimen
- Suitability of older donors
  - More graft failure
  - Clonal hematopoiesis more common with older donors – uncertain significance
- Importance of other donor characteristics
Haploidentical transplantation: summary

- Continues to drive growth in the BMT field and increasingly applied to patients with advanced hematological malignancies
- Outcomes appear to rival those observed following matched sibling and volunteer unrelated donor transplants
- PTCy is simple and easy to apply in multiple settings and has become the standard in the US
- PTCy has still not been compared to other strategies in a controlled setting, so still unclear if it is better
- Use of platforms that eliminate need for pharmacological GVHD prophylaxis remain very attractive, and should be studied further in comparison to PTCy
- Platforms that could reduced relapse after PTCy based GVHD prophylaxis also warrant further study
Haplo-identical transplantation:
How to preserve Graft-vs-Leukemia without inducing GvHD:
Adjunctive treatment with selectively depleted donor T-cells (ATIR101)

Denis-Claude Roy, MD
CEO, CellCAN: Regenerative Medicine and Cell Therapy Network
Director, Hôpital Maisonneuve-Rosemont Research Center
Professor of Medicine, Université de Montréal
Donor T cell into the patient

Graft-versus-host disease (GVHD)

Patient tissues

Graft-versus-leukemia activity (GVL)

Graft-versus-infection activity (GVI)
ATIR: selective removal of GVHD-causing T-cells while retaining key innate and adaptive components of immune system

<table>
<thead>
<tr>
<th>ATIR characteristics</th>
<th>Potential clinical benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Selective removal of GVHD-causing T-cells</td>
<td>• Improved donor availability</td>
</tr>
<tr>
<td>• Key immune cells are retained to protect against infections</td>
<td>• Minimal risk of life threatening GVHD</td>
</tr>
<tr>
<td>• T-cells directed against leukaemic cells are retained</td>
<td>• No prophylactic immune suppression needed</td>
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</tbody>
</table>

Potential clinical benefits:
- Improved donor availability
- Minimal risk of life threatening GVHD
- No prophylactic immune suppression needed
- Less cancer relapse
- Reduced TRM; improved OS
Haploidentical HSCT + ATIR: high-risk hematologic malignancies

<table>
<thead>
<tr>
<th>Conditioning regimen</th>
<th>Haplo HSCT</th>
<th>ATIR Infusion</th>
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<tr>
<td>-11d - 9d</td>
<td>-8 -7d</td>
<td>-6d 0d</td>
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<tr>
<td>I</td>
<td>II - III</td>
<td>IV - V</td>
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<tr>
<td>1x10^4/kg</td>
<td>5x10^4/kg</td>
<td>3x10^5/kg</td>
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<tr>
<td>II</td>
<td>III - IV</td>
<td>V - VI</td>
</tr>
<tr>
<td>5x10^4/kg</td>
<td>3x10^5/kg</td>
<td>7.9x10^5/kg</td>
</tr>
<tr>
<td>III</td>
<td>IV - V</td>
<td>VII</td>
</tr>
<tr>
<td>3x10^5/kg</td>
<td>3.2x10^5/kg</td>
<td>7.9x10^6/kg</td>
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<tr>
<td>IV</td>
<td>V - VI</td>
<td>VI - VII</td>
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<tr>
<td>3.2x10^5/kg</td>
<td>7.9x10^5/kg</td>
<td>2.0x10^6/kg</td>
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<tr>
<td>V</td>
<td>VI - VII</td>
<td>VII</td>
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<tr>
<td>7.9x10^5/kg</td>
<td>2.0x10^6/kg</td>
<td>5.0x10^6/kg</td>
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CD3/kg Pts

- I: 1x10^4/kg
- II: 5x10^4/kg
- III: 3x10^5/kg
- IV: 3.2x10^5/kg
- V: 7.9x10^5/kg
- VI: 2.0x10^6/kg
- VII: 5.0x10^6/kg
Phase I study: Engraftment and GVHD (n=19)

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<tr>
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<th>Range (days)</th>
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<td>CD34+ cells infused /Kg</td>
<td>10.5 x 10⁶</td>
<td>6 – 15 x 10⁶</td>
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<tr>
<td>CD3+ cells infused/kg</td>
<td>1.4 x 10⁴</td>
<td>0.4 - 2.6 x 10⁴</td>
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<tr>
<td>Neutrophils (&gt;0.5x10⁹/l)</td>
<td>10.0</td>
<td>8 – 20</td>
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<tr>
<td>Platelets (&gt;20x10⁹/l)</td>
<td>11.0</td>
<td>8 – 137</td>
</tr>
</tbody>
</table>

- NO Graft rejection
- NO GVHD immunoprophylaxis
- NO Grade III-IV GVHD
Phase II study: Low incidence of GVHD (n=23)

- **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
### Overall incidence of GVHD after ATIR infusion

<table>
<thead>
<tr>
<th></th>
<th>Phase I (n=19)</th>
<th>Day post-transplant</th>
<th>Phase II (n=23)</th>
<th>Day post-transplant</th>
<th>Overall GVHD</th>
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<td>Acute GVHD Gr III-IV</td>
<td>0/19</td>
<td>-</td>
<td>0/23</td>
<td>-</td>
<td>0/44(^b)</td>
</tr>
<tr>
<td>Acute GVHD Gr II</td>
<td>4/19(^c)</td>
<td>125, 88, 116, 45(^a)</td>
<td>3/23</td>
<td>173, 211, 247</td>
<td>7/44</td>
</tr>
<tr>
<td>Chronic GVHD</td>
<td>4/19(^c)</td>
<td>165, 224, 101, 144</td>
<td>1/23</td>
<td>278</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) 2 patients in highest T cell cohort (5x10^6 CD3/kg)
\(^b\) 2 patients treated on compassionate basis
\(^c\) Median time to stop immune suppression: 6 months
**GVH vs GVI vs GVL activity**

Donor T cell into the patient

Graft-versus-host disease (GVHD)

Patient tissues

Graft-versus-infection activity (GVI)
ATIR contains virus-specific T-cells

Virus-specific T-cells before and after manufacturing of ATIR101

Control | EBV | CMV | Influenza
---|---|---|---
Donor

ATIR

Kiadis pharma
ATIR decreases the probability of developing an infection (CR-AIR-001)

- **Cohorts 1-3:**
  - 1-13 x10^4 CD3/kg

- **Cohorts 4-7:**
  - 32-500 x10^4 CD3/kg

**Probability of infection**

**Days post-transplantation**

\[ P = 0.015 \]
## Limited Infections (first 6 months post-ATIR)

<table>
<thead>
<tr>
<th>Patient Cohorts</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical events</td>
<td></td>
</tr>
<tr>
<td>1-3 (N=7)</td>
<td>4-7 (N=12)</td>
</tr>
<tr>
<td>N of infections</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>N of infections / patient (mean±SD / median)</td>
<td></td>
</tr>
<tr>
<td>2.0±2.0 / 1.0</td>
<td>0.7±1.1 / 0.0</td>
</tr>
<tr>
<td>N patients without infections</td>
<td></td>
</tr>
<tr>
<td>1 (14%)</td>
<td>8 (67%)</td>
</tr>
<tr>
<td>N of deaths from infections (first year)</td>
<td></td>
</tr>
<tr>
<td>4 (57%)</td>
<td>2 (17%)</td>
</tr>
</tbody>
</table>
Immune reconstitution (CR-GVH-001)

CD3+ counts of 001 cases, group 4-5

Lymphocytes

CD3

N of Patients with 10^6 cells/L

Weeks post-ATIR

Cohort 1-3
Cohort 4-5
Cohort 6-7
T-cell reactivity *after* ATIR101 administration in CR-GVH-001

T-cell response *after* EBV reactivation

- EBV reactivation triggered response of (viral specific) T-cells in several patients
  - Increase in CD3$^+$ cells detected in peripheral blood
  - EBV copy numbers reduced after increase in CD3$^+$ cells, indicating effective immunological response
  - Standard treatment given would be Rituximab to avoid post-transplant lymphoproliferative disorder (PTLD), which is an uncontrolled proliferation of B-cell lymphocytes following infection with Epstein-Barr virus
GVH vs GVI vs GVL activity

Donor T cell into the patient

Patient tissues

Epithelial tissues
- Skin
- Stomach, intestines
- Liver
- Fibroblasts

Graft-versus-host disease (GVHD)

Graft-versus-leukemia activity (GVL)

Graft-versus-infection activity (GVI)
Results study CR-AIR-001

- No grade III/IV acute GVHD observed at any dose administered
- MTD not reached

<table>
<thead>
<tr>
<th>ATIR101 dose (cells/kg)</th>
<th>Survival</th>
<th>TRM</th>
<th>RRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0*10^4</td>
<td>No</td>
<td>2 mo</td>
<td></td>
</tr>
<tr>
<td>5.0*10^4</td>
<td>No</td>
<td>10 mo</td>
<td></td>
</tr>
<tr>
<td>5.0*10^4</td>
<td>No</td>
<td>31 mo</td>
<td></td>
</tr>
<tr>
<td>5.0*10^4</td>
<td>No</td>
<td>11 mo</td>
<td></td>
</tr>
<tr>
<td>1.3*10^5</td>
<td>No</td>
<td>12 mo</td>
<td></td>
</tr>
<tr>
<td>1.3*10^5</td>
<td>No</td>
<td>10 mo</td>
<td></td>
</tr>
<tr>
<td>1.3*10^5</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2*10^5</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2*10^5</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.9*10^5</td>
<td>No</td>
<td>8 mo</td>
<td></td>
</tr>
<tr>
<td>7.9*10^5</td>
<td>No</td>
<td>10 mo</td>
<td></td>
</tr>
<tr>
<td>7.9*10^5</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0*10^6</td>
<td>No</td>
<td>17 mo</td>
<td></td>
</tr>
<tr>
<td>2.0*10^6</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0*10^6</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.6*10^6</td>
<td>No</td>
<td>47 mo</td>
<td></td>
</tr>
<tr>
<td>5.0*10^6</td>
<td>No</td>
<td>13 mo</td>
<td></td>
</tr>
<tr>
<td>5.0*10^6</td>
<td>No</td>
<td>9 mo</td>
<td></td>
</tr>
</tbody>
</table>

RRM = relapse-related mortality / TRM = transplant-related mortality

Overall survival probability

- Dose L1-L3
  - N=7
- Dose L4-L6
  - N=9
- Dose L7
  - N=3

Time after HSCT (months)

0% 20% 40% 60% 80% 100%
0 6 12 18 24 30 36 42 48 54 60
Results study CR-AIR-007: Patient characteristics

Patient and donors
- 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)

Diagnosis
- AML: n=16 (70%):
  - 11 in CR1
  - 5 in CR2
- ALL: n =7 (30%):
  - 4 in CR1
  - 3 in CR2

Risk classification
- Cytogenetic risk profile
  - Favorable 0
  - Intermediate 9 (39 %)
  - Adverse 14 (61 %)
- Disease-risk index
  - Low risk index 0
  - Intermediate risk index 10 (43 %)
  - High risk index 13 (57 %)

Locations:
- Canada (3), Belgium (3), Germany (1), United Kingdom (1)

1 Mrozek K, et al. JCO 2012, 30 (36): 4515-4523
Results study CR-AIR-007: Relapse

- 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
Results study CR-AIR-007:
Overall Survival: Benefit of adjunctive treatment with ATIR101

- 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

<table>
<thead>
<tr>
<th>KM estimates of: Overall Survival</th>
<th>6 months after HSCT</th>
<th>12 months after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haplo-HSCT + ATIR101</td>
<td>83%</td>
<td>61%</td>
</tr>
<tr>
<td>Haplo-HSCT alone</td>
<td>63%</td>
<td>20%</td>
</tr>
</tbody>
</table>
GVHD-free, Relapse-free Survival (GRFS): comparing 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

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

<table>
<thead>
<tr>
<th>KM estimates of:</th>
<th>6 months after HSCT</th>
<th>12 months after HSCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haplo-HSCT + ATIR101</td>
<td>78%</td>
<td>57%</td>
</tr>
<tr>
<td>Haplo-HSCT alone</td>
<td>57%</td>
<td>20%</td>
</tr>
<tr>
<td>MUD HSCT (8/8 or 10/10)</td>
<td>63%</td>
<td>41%</td>
</tr>
</tbody>
</table>

\(^1\) Holtan et al. 2015, Blood 125, 1333-1338

\(^2\) Roy et al., ASH meeting 2016.
GVH vs GVI vs GVL activity

Donor T cell into the patient

Graft-versus-host disease (GVHD)

Patient tissues

Graft-versus-leukemia activity (GVL)

Graft-versus-infection activity (GVI)
GVL activity is likely mediated by donor T cells that recognize Minor Histocompatibility Antigens (MiHAs) on leukemic cells.
Graft-versus-Leukaemia T-cells have been detected in ATIR

Example of leukemia specific T-cells

Comments

- Myb628 specific T-cell expansion was assessed after one (upper panel) or two (lower panel) rounds of stimulation with a Myb628/HLA-B44 multimer
- Stimulation done with artificial antigen-presenting cells
- As control, cells were stained with an irrelevant HLA-B44 multimer

Prof. A. Krackhardt, TUM, Munich
GVH vs GVI vs GVL activity

- Graft-versus-host disease (GVHD)
- Donor T cell into the patient
- Graft-versus-leukemia activity (GVL)
- Graft-versus-infection activity (GVI)

Patient tissues

Epithelial tissues
- Skin
- Stomach, intestines
- Liver
- Fibroblasts

Leukaemia
Phase III: CR-AIR-009
HATCY clinical trial

**Inclusion**
- Haploidentical related donor
- Karnofsky performance status ≥ 70%
- AML: CR1 with high-risk features or second or higher CR
- ALL: Any CR
- MDS: Transfusion-dependent or intermediate or higher
- IPSS-R risk group

**Exclusion**
- Availability suitable fully matched donor due time
- Prior allogeneic HSCT
- DLCO <50%
- LVEF <50%
- AST and/or ALT >2.5 x ULN (CTCAE grade 2)
- Bilirubin > 1.5 x ULN (CTCAE grade 2)
- Creatinine clearance <50 ml/min (calculated or measured)
- Estimated survival < 3 months
- Known presence of HLA antibodies against the non-shared donor haplotype
- Patient HIV+
- Donor: positive viral test for HIV-1, HIV-2, HBV, HCV, Treponema pallidum

**Procedure**
- Obtain informed consent
- Assess patient eligibility
- Randomization 1:1
- ATIR101 group
  - Apheresis patient/donor for ATIR101 manufacturing
  - Collection of donor stem cell graft
  - Myeloablative conditioning + T-cell depleted HSCT [Day 1]
  - ATIR101 infusion [Day 30 ± 2]
  - Follow-up assessments of study endpoints and safety [until Day 730] (see also Section 7.3.8, Schedule of Events Table)
- PTCy group
  - Collection of donor stem cell graft
  - Myeloablative conditioning + T-cell replete HSCT [Day 1]
  - Cyclophosphamide infusion [Day 3 and 4]
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  • M Giroux, M Corriveau, J Darwiche and team
ATIR: adjunctive infusion of ‘safe’ T-cells, 28-32 days post HSCT

Mix patient & donor immune cells: alloreactive T-cells become activated (*Mixed Lymphocyte Reaction*)

Add TH9402*, which accumulates only in activated T-cells, due to lack of PgP pump function

Expose to green light: TH9402 becomes toxic, activated alloreactive T-cells are killed

GVHD causing T-cells depleted by ‘causing GVHD ex vivo’; immune cells against tumor cells and infections retained

*TH9402 – proprietary selective rhodamine derivative, modified to become cytotoxic under green light
Pipeline: ATIR101 for blood cancers, ATIR201 for thalassemia

<table>
<thead>
<tr>
<th>ATIR101</th>
<th>ATIR201</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood cancers</strong></td>
<td><strong>Inherited blood disorders</strong></td>
</tr>
<tr>
<td>Adult acute leukemia</td>
<td>Pediatric β thalassemia</td>
</tr>
<tr>
<td>Myeloablative conditioning</td>
<td>Myeloablative conditioning</td>
</tr>
<tr>
<td>CD34+ stem cell</td>
<td>αβ T-cell depleted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trial designs</th>
<th>Phase I/II</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR-GVH-001 (dose finding)</td>
<td>CR-AIR-006 (historic control)</td>
<td>CR-AIR-007 (efficacy)</td>
<td>CR-AIR-008 (2nd dose)</td>
</tr>
<tr>
<td>CR-AIR-009 (randomized, controlled)</td>
<td>CR-BD-001 (dose finding)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ATIR101: potent mature T-cells, yet low GVHD (1 yr)

**Low GVHD related to ATIR**
- no acute grade III/IV
- 3 acute grade II (13%)
- 1 chronic (4%)

**Superiority versus matched historical control**

ATIR depletion effective: potent T-cells providing protection, yet low GVHD

---

**Improved Overall Survival with ATIR**

007: CD34+ plus single dose ATIR
- Open label single arm 2013-16
- 23 patients: AML/ALL
- 4 sites in Canada and EU

006: CD34+
- Historical observational cohort 2006-13
- 34 patients, matched indications/sites
- Based on EMA scientific advice
ATIR101: improved versus literature for PTCy (1 yr)

Note: NOT based on randomized controlled trial, different patients/sites/treatments
* Ciurea 2015 (CIBMTR data); Piemontese 2017 (EBMT data), Salomon 2012 (Atlanta), Ciurea 2012; Devillier 2016; Di Stasi 2014; Esquirol 2016; Sugita 2015

** Ciurea 2015 (CIBMTR data); McCurdy 2017 (Baltimore), Devillier 2016, Sugita 2015 (DRI normalization based on Armand 2014)

Higher Survival (OS)
- ATIR: 61%
- PTCy/Baltimore: 60%
- Literature: 57%

Lower Relapse
- ATIR: 9%
- PTCy/Baltimore: 29%
- Literature: 30%

Lower GVHD
- ATIR: 24%
- PTCy/Baltimore: 0%
- Literature: 5%

PTCy: results from EBMT/CIBMTR databases, Johns Hopkins (Baltimore) and Northside (Atlanta)

PTCy/Baltimore
- At least 50% AML/ALL* (n=571)
- Adjusted for Disease Risk Index** n=561
**ATIR101: improved GRFS versus literature for PTCy (1 yr)**

**Higher GVHD and Relapse Free Survival (GRFS)**

- **ATIR Phase II** (n=23): 57%
- **PTCy/Baltimore DRI adjusted** (n=500): 36%

**Composite endpoint: survival, quality of life, future prognosis**

Defined as survival without:
- Chronic GVHD requiring immunosuppression
- Acute grade III/IV GVHD
- Relapse

**Note:** NOT based on randomized controlled trials, different patients/sites/treatments

*Solh 2016 (Atlanta; DRI normalized GRFS 30%; n=128); McCurdy 2017 (Johns Hopkins; DRI normalized GRFS 38%; n=372); DRI GRFS hazard in publications
ATIR101 Phase III (009) initiated: ATIR versus PTCy/Baltimore

Objectives: demonstrate superior clinical benefit and collect pharmacoeconomical data (cost, days in hospital, incidence of severe infections and quality of life)

Kiadis protocol:
CD34+ HSCT + single dose ATIR101

PTCy/Baltimore protocol:
post-HSCT cyclophosphamide & immunosuppressant

195 patients* with acute leukemia
45 sites in US, Canada and EU

Primary endpoint:
GVHD and Relapse Free Survival (GRFS**)

Secondary endpoints:
OS, Progression Free Survival, Relapse Related Mortality, Transplant Related Mortality

Event driven:
Primary analysis at 93 GRFS events

Aligned with FDA (End of Phase II meeting) and regulators in EU
Trial approved in several countries, lining up sites

* Designed and powered for 20% difference in GRFS
** Survival without chronic GVHD requiring immunosuppression, acute grade III/IV GVHD and relapse
### Overall Survival

<table>
<thead>
<tr>
<th>CD34+ stem cells (Phase II)</th>
<th>Overall Survival</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21% + ATIR</td>
<td>61%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PTCy*</th>
<th>Overall Survival</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>57% + ATIR</td>
<td>?</td>
</tr>
</tbody>
</table>

* DRI normalized Ciurea 2015 (CIBMTR data); McCurdy 2017 (Johns Hopkins), Devilier 2016, Sugita 2015
** e.g., αβT-Cell Depleted: Almost no data available: EBMT 2017, Lucia et al (adult AML/ALL): OS 1 yr 56%, relapse 1 yr 40%
Kiadis: near term and large opportunity in HSCT

- Blockbuster potential: orphan drug with target population 28,700 patients
- EU file submitted, potential for launch in 2019 (based on Phase II)
- Phase III initiated for US FDA (based on GRFS versus PTCy)
- Upside potential (adjunctive to PTCy and/or other T-Cell depleted)
- Efficient supply chain
- Experienced new team adding business and supply chain capabilities
...so that many more patients with otherwise incurable diseases will have a reasonable chance of long survival and cure

— Dr. E. Donnall Thomas
established bone marrow transplantation as a treatment for leukemia

Nobel Lecture | 1990