Administration of Rivogenlecleucel (rivo-cel; BPX-501) Cells Following αβ-T and B-cell-Depleted HLA Haploidentical HSCT (haplo-HSCT) in Children With Acute Leukemias

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<table>
<thead>
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<th>Name</th>
<th>Affiliations</th>
<th>Disclosures</th>
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<tbody>
<tr>
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<td>Advisory Board, Bellicum Pharmaceuticals, Inc.</td>
<td>No disclosures</td>
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<td>Swati Naik</td>
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Clinical background

- Allogeneic HSCT is a well-established treatment for pediatric acute leukemias\(^1,2\)
  - For patients in CR1 with high-risk features or those experiencing leukemia recurrence, HSCT is standard\(^3,4\)
- Haplo-HSCT from a relative represents a valuable alternative option for patients lacking a compatible matched related or unrelated donor\(^5\)
- Promising results were reported with a novel method of selective depletion of \(\alpha\beta\)-T and B cells,\(^5,6\) though this approach is associated with limitations, including suboptimal adaptive immune reconstitution and increased risk of infection.

CR1, first complete remission; GvHD, graft-vs-host disease; haplo, HLA-haploidentical; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation.

T-cell reconstitution after αβ-TCD haplo-HSCT

Add back of T cells transduced with a suicide gene (iCasp9)

Control of infections/Anti-leukemic activity

Healthy Donor

Total T-cells

αβ T-cells

γδ T-cells

TIME AFTER HSCT

TCRαβ+

TCRαβ-γδ-

TCRγδ+

Graft Composition

DC

HSC

T

NK

M

CP

12-25 days

45-60 days

90-120 days

180 days
Rivo-cel addresses the “T-cell Dilemma” in haplo-HSCT

Rivo-cel: Tipping the benefit/risk scale

**RISKS**
- Graft vs Host Disease (GvHD)

**BENEFITS**
- Relapse Prevention – Graft vs Leukemia (GvL)
- Infection Control
- Engraftment

**Methodology**
- Stem cells
  - Haploidentical Donor
  - αβ TCR/CD19 Depletion
  - HSCT
    - Day 0
  - T cells
    - Rivo-cel Cell Processing
    - GMP FACILITY
    - 10 days
  - Patient
    - No GvHD prophylaxis
    - Rimiducid for uncontrolled GvHD
    - Day 21 +/- 14 days
Chemical induction of dimerization ("CID") molecular switch platform

Rimiducid infusion activates signaling pathways to control T-cell function

1. **Viral transduction** transfers the DNA from a **vector** into the target cell nucleus.

2. Vector-derived DNA directs expression of **CID** and **accessory proteins**.

3. **Rimiducid** dimerizes the CID proteins, thus turning on the signal cascade.

<table>
<thead>
<tr>
<th>Signal</th>
<th>Caspase-9 (&quot;iC9&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result</td>
<td>Apoptosis (cell death)</td>
</tr>
</tbody>
</table>
Study design and objectives

**Objective 1**: Evaluate the safety and efficacy of rivo-cel T cells administered after a αβ-T and B-cell depleted haplo-HSCT in pediatric patients with acute leukemia (AL) in morphological CR

**Objective 2**: Determine whether rivo-cel infusion can increase RFS and OS through an enhanced graft-versus-leukemia (GvL) effect, while maintaining a low risk of GvHD

**Outcomes**
- Event-free survival
- Transplant related mortality (non-malignant)
- Non relapse mortality (malignant)
- Incidence and severity of GvHD
- Time to resolution of GvHD after administration of rimiducid
- Immune reconstitution

**Key Inclusion Criteria**
- Life-threatening acute leukemia
- Non-malignant disorder deemed curable by HSCT
- Life expectancy > 10 weeks
- Age < 18 years and > 1 month

**Key Exclusion Criteria**
- Active GvHD or Immunosuppressive treatment from a previous allograft
- Renal or liver dysfunction
- Active infection
- Pregnant or breastfeeding

* ATG was administered from Day-4 to Day -2 (12-15 mg/kg over 3 consecutive days) and rituximab at a dosage of 200 mg/m\(^2\) on Day -1. ATG, anti-thymocyte globulin (rabbit); GvHD, graft versus host disease; HSCT, hematopoietic stem cell transplantation; MTD, maximum tolerated dose.
Methods

A multicenter US and EU prospective clinical trial utilizing $\alpha\beta$-T and B cell-depleted haplo-HSCT followed by infusion of donor lymphocytes genetically modified with iC9 (rivo-cel) in patients with malignant and non-malignant disorders

- Data presented here is from the subset of patients with high-risk acute leukemias (AML, ALL)

Study treatment

- Infusion of rivo-cel was planned on Day 21 ± 14 after the allograft
- No post-transplant GvHD prophylaxis was employed
- Patients who developed visceral GvHD or are refractory to SOC treatment were eligible to receive 1 or more doses of rimiducid (0.4 mg/kg)

Patient population definitions

- The safety evaluable population (SEP) was defined as any pediatric patient with high-risk acute leukemia who had HSCT
- The efficacy evaluable population (EEP) was defined as any pediatric patient with high-risk acute leukemia who received HSCT, rivo-cel infusion, and had ≥ 1 follow-up assessment
Key baseline and transplant characteristics

- A total of 95 and 100 patients with acute leukemia met the EEP and SEP definition, respectively.
- The median follow-up was 17 months (range, 1 – 42.7 months).
  - Median follow up of surviving patients was 20.85 months (range, 6.5 – 42.7 months).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AL (N = 100)</th>
<th>AMLa (n = 46)</th>
<th>ALL (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female, n (%)</td>
<td>56 (56.0) / 44 (44.0)</td>
<td>27 (58.7) / 19 (41.3)</td>
<td>29 (53.7) / 25 (46.3)</td>
</tr>
<tr>
<td>Median age at HSCT (range), year</td>
<td>8.36 (0.70 – 18.41)</td>
<td>7.94 (0.70 – 18.41)</td>
<td>9.07 (1.11 – 17.94)</td>
</tr>
<tr>
<td>Patients in first CR, n (%)</td>
<td>26 (26.0)</td>
<td>17 (37.0)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Patients in second or subsequent CR, n (%)</td>
<td>74 (74.0)</td>
<td>29 (63.0)</td>
<td>45 (83.3)</td>
</tr>
<tr>
<td>Conditioning regimen, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total body irradiation-based</td>
<td>62 (62.0)</td>
<td>20 (43.5)</td>
<td>42 (77.8)</td>
</tr>
<tr>
<td>Busulfan-based</td>
<td>30 (30.0)</td>
<td>19 (41.3)</td>
<td>10 (18.5)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (8.0)</td>
<td>6 (13.0)</td>
<td>2 (3.7)</td>
</tr>
<tr>
<td>Donor Source, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>88 (88.0)</td>
<td>38 (82.6)</td>
<td>50 (92.6)</td>
</tr>
<tr>
<td>Sibling / half-sibling</td>
<td>10 (10.0) / 2 (2.0)</td>
<td>6 (13.0) / 2 (4.3)</td>
<td>4 (7.4) / 0</td>
</tr>
<tr>
<td>Median CD34+ cell dose x 10^5/kg (range)</td>
<td>13 (3 – 41)</td>
<td>13 (4 – 41)</td>
<td>13 (3 – 34)</td>
</tr>
<tr>
<td>Median αβ TCR+ cell dose x 10^5/kg (range)</td>
<td>0.33 (0.01 – 1.00)</td>
<td>0.30 (0.01 – 1.00)</td>
<td>0.36 (0.04 – 1.00)</td>
</tr>
<tr>
<td>Median time to rivo-cel infusion (range), days</td>
<td>21.00 (11.00 – 147.00)</td>
<td>20.00 (12.00 – 147.00)</td>
<td>23.00 (11.0 – 99.00)</td>
</tr>
<tr>
<td>Median time to discharge (range), days</td>
<td>24.00 (12.00 – 203.00)</td>
<td>24.00 (12.00 – 203.00)</td>
<td>24.00 (14.00 – 193.00)</td>
</tr>
</tbody>
</table>

AL, acute leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; EEP, efficacy-evaluable population; HSCT, hematopoietic stem cell transplantation; SEP, safety-evaluable population.

Data cutoff date: September 17, 2018
Safety

- The SEP was defined as any pediatric patient with acute high-risk leukemia who had HSCT (n = 100)
- Moderate toxicity profile observed in patients exposed to rivo-cel
  - A total of 13 TEAEs\(^a\) were reported – relating to either rivo-cel and/or rimiducid
  - The majority (62%) of TEAEs were grade 1\(^b\)
  - Two grade 3 events were reported (diarrhea and esophagitis)
  - No serious adverse events related to rivo-cel were reported

TEAE, treatment-emergent adverse event. \(^a\)TEAE were defined as any AE where the relationship to study treatment was possible, probable, or definite. \(^b\)AEs were graded as mild, moderate, severe, life-threatening, or death [AE grading (severity) scale; NCI CTCAE v4.03]

SEP, safety evaluable population.

Data cutoff date: September 17, 2018
In patients with sustained engraftment of donor cells, median time to neutrophil and platelet engraftment was rapid:

- Median time to neutrophil engraftment: 16 days (95% CI: 15 – 17 days)
- Median time to platelet engraftment: 12 days (95% CI: 11 – 12 days)

The rate of graft failure was low (4.1%)
Of the 96 evaluable patients, 21 (21.9%) developed Grade 1-4 aGvHD
Grade 2-4: 11.5% (95% CI: 5.1% – 17.8%)
Grade 3-4: 3.1% (95% CI: 0.0% – 6.6%)
  • Grade 3 (n = 3; 3.1%)
    • Stage 1 UGI, Stage 2 gut, Stage 3 skin
    • Stage 2 gut, Stage 1 UGI
    • Stage 3 gut, Stage 1 UGI
  • No grade 4 events occurred

9 cases of late-onset aGvHD after 100 days (2 case of Grade 3)
Of the 89 evaluable patients, 7 developed mild-to-severe chronic GvHD:

- 2 cases were mild
- 4 cases were moderate
- 1 case was severe

*Defined as any GvHD with onset after 100 days

Data cutoff date: September 17, 2018
3 cases of TRM occurred; none were considered related to rivo-cel

- Infection (n = 2)
- Respiratory failure due to pulmonary chronic GvHD (n = 1)

TRM, transplant-related mortality; aEfficacy evaluable population; bIncludes sepsis, viral infection, (n = 1 each)

Data cutoff date: September 17, 2018
Cumulative relapse rate\textsuperscript{a}

15 events of relapse were reported for a cumulative relapse rate of 16.9% (95% CI 9% - 24.7%)

\textsuperscript{a}Efficacy evaluable population

Data cutoff date: September 17, 2018
Cumulative incidence of relapse by MRD Status

N=8, Events=2, cumulative relapse 25% (95% CI 0.0% - 55.0%)

N=65, Events=9, cumulative relapse 14.5% (95% CI 5.7% - 23.0%)

MRD, Minimal residual disease

*Efficacy evaluable population with available MRD status, data provided directly from clinical sites

Data cutoff date: September 17, 2018
7 fatal events were reported for an OS rate of 91.8%

- TRM (n= 3)
- Disease progression (n = 4)
ALL efficacy outcomes

Relapse-free survival and overall survival by CR Status

Relapse-Free Survival by CR Status

N=7, Events=0, RFS, 100.0%
N=45, Events=12, RFS 73.2% (95% CI 60.2%–86.2%)

Overall Survival by CR Status

N=7, Events=0, OS 100.0%
N=45, Events=4, OS 89.9% (95% CI 80.6%–99.3%)

RFS, Relapse-free survival; OS, Overall survival
*Efficacy evaluable population
Data cutoff date: September 17, 2018
AML efficacy outcomes

Relapse-free survival and overall survival by CR Status

Relapse-Free Survival by CR Status

Overall Survival by CR Status

RFS, Relapse-free survival; OS, Overall survival
*Efficacy evaluable population
Data cutoff date: September 17, 2018
Response to rimiducid

Of the 37 patients who developed GvHD, 11 received ≥ 1 dose of rimiducid

BOR (within 7 days) of CR or PR was seen in 73% (8 patients) of these patients
  • 5 of responding patients had a CR

2 patients who achieved PR went on to achieve a CR within 30 days following rimiducid administration.

<table>
<thead>
<tr>
<th>Overall</th>
<th>Stage</th>
<th>Response</th>
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</thead>
<tbody>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>CR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>CR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 1 skin, stage 1 UGI</td>
<td>CR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>CR</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Stage 3 gut, Stage 1 UGI</td>
<td>CR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>PR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>PR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 3 skin</td>
<td>PR</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Stage 2 skin</td>
<td>NR</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Stage 3 skin, stage 3 gut</td>
<td>NR</td>
</tr>
<tr>
<td>Severe</td>
<td>Score 3 liver, Score 2 lungs</td>
<td>NR</td>
</tr>
</tbody>
</table>

BOR, best overall response
Data cutoff date: September 17, 2018.
Response to rimiducid (AP1903)

PT 073

Rimiducid infusion

Days after HSCT
**Immune recovery (I)**

**CD3+ cells**
- A median count of CD3+ cells, CD3+ CD4+ and CD3+ CD8+ above 500 cells/µl was achieved by 180 days, 270 days and 270 days, respectively.

**IgA and IgM levels**
- IgA and IgM levels achieved normal values by 180 days.

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*Horizontal line represents normal levels needed to be achieved for immune recovery of immunoglobulins*

*Ig, immunoglobulin*

*Data cutoff date: September 17, 2018*
Immune recovery (II) and CMV reactivation

Rivo-cel cells expanded over time and persisted following infusion

CMV reactivation was a major driver of rivo-cel CD3+CD19+ expansion

Data generated from IRCCS Ospedale Pediatrico Bambino Gesù (OPBG), Rome, Italy

Data cutoff date: September 17, 2018
Conclusions

- αβ-T and B-cell depleted haplo-HSCT followed by the adoptive transfer of rivo-cel represents a novel and highly effective transplantation strategy for pediatric patients with AL.

- Compared with data from children receiving only αβ-T and B-cell depleted haplo-HSCT or matched unrelated donor HSCT,¹ this novel approach resulted in a comparable risk of transplant-related mortality and lower risk of recurrence².

- Toxicity profile observed in patients exposed to rivo-cel was manageable and comparable to αβ-T and B-cell depleted haplo-HSCT alone.

- Rimiducid was an effective treatment for patients who developed visceral GvHD or were refractory to standard of care treatment.

- Rivo-cel CD3+CD19+ T cells expanded over time and persisted through all timepoints following infusion.
  - CMV reactivation appears to be the main driver for rivo-cel expansion.

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