Administration of Rivogenlecleuvecel (Rivo-cel, BPX-501) Following αβ T- and B-Cell–Depleted Haplo-HSCT in Children With Transfusion-Dependent Thalassemia

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Disclosures

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No disclosures

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No disclosures

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No disclosures

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No disclosures

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Clinical background

- Allogeneic hematopoietic stem cell transplant (HSCT) from a human leukocyte antigen (HLA)–identical sibling has been shown to cure most children with transfusion-dependent β-thalassemia major\(^1\)
- Thalassemia-free survival of ≈ 60% has been observed with an HLA partially matched (haploidentical [haplo]) donor\(^2\)
- \(\alpha\beta\) T- and B-cell–depleted haplo-HSCT is a novel strategy for minimizing the risk of graft-versus-host disease (GvHD) and life-threatening viral/fungal infections\(^3\)
  - However, recovery of adaptive immunity from \(\alpha\beta\) T- and B-cell–depleted haplo-HSCT is suboptimal\(^4\)

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

**GMP FACILITY**

- αβ TCR/CD19 Depletion
  - Stem cells
  - Haploidentical Donor

- HSCT
  - Day 0
  - Rivo-cel Cell Processing
  - 10 days
  - Rivo-cel Addback Infusion
  - Day 21 +/- 14 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>
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<tbody>
<tr>
<td>Result</td>
<td>Apoptosis (cell death)</td>
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</table>
**Study Design and Objectives**

**Objective:** To evaluate the safety and efficacy of rivo-cel administered after αβ-T and B cell-depleted haplo-HSCT in pediatric patients with transfusion-dependent β-thalassemia

### 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

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* 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/m² on Day -1.

**Phase I:**
- 3+3 design (no MTD reached)
- 2.5x10⁶, 5x10⁵, 1x10⁶, 2 x10⁶, 4 x10⁶ Rivo-cel T-cells/kg

**Phase II:**
- 1x10⁶ Rivo-cel T-cells/kg

**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

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Pediatric High-Risk Malignancies and Non-Malignant Disorders

No Matched Donor

Haploidentical Donor Available

β-thalassemia* (N=24)

αβ-T-cells and B-cell–depleted haplo-HSCT + rivo-cel

No post-HSCT GvHD prophylaxis

Rimiducid for patients who develop visceral GvHD or are refractory to SOC treatment
Methodology

A multicenter US and EU prospective clinical trial utilizing αβ 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 refer to a subset of patients with transfusion-dependent β-thalassemia

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 dose of rimiducid (0.4 mg/kg)

Patient population definitions

- The safety evaluable population (SEP) was defined as any pediatric patient with β-thalassemia who had HSCT
- The efficacy evaluable population (EEP) was defined as any pediatric patient with β-thalassemia who received HSCT, rivo-cel infusion, and had at least one follow-up assessment
Key baseline and transplant characteristics

- A total of 24 and 21 patients with β-thalassemia met the SEP and EEP definitions, respectively.
- Median follow-up for all patients (n = 24) was 14 months (range, 0.5-40 months)
  - Median follow-up for surviving patients (n = 17) was 21 months (range, 9-40 months)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>β-Thalassemia (N = 24)</th>
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<tbody>
<tr>
<td>Male/female, n (%)</td>
<td>14 (58.3)/10 (41.7)</td>
</tr>
<tr>
<td>Median age at HSCT (range), years</td>
<td>9.16 (2.15-14.34)</td>
</tr>
<tr>
<td>Conditioning regimens, n (%)</td>
<td></td>
</tr>
<tr>
<td>Busulfan based</td>
<td>20 (83.3)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Donor, n (%)</td>
<td>24 (100.0)</td>
</tr>
<tr>
<td>Median HSCT dose (range)</td>
<td></td>
</tr>
<tr>
<td>CD34+ cell dose, x 10^6/kg</td>
<td>20.5 (11-40)</td>
</tr>
<tr>
<td>αβ TCR^+ cell dose, x 10^5/kg</td>
<td>0.15 (0.01-0.88)</td>
</tr>
<tr>
<td>Median time to rivo-cel infusion (range), days</td>
<td>17 (10.0-36.0)</td>
</tr>
</tbody>
</table>

TBI, total body irradiation.
Data cutoff date: September 17, 2018.
Safety

- The SEP was defined as any pediatric patients with β-thalassemia who had HSCT (n = 24)
- Mild toxicity profile observed in patients exposed to rivo-cel
  - A total of 37 AEs were reported, with 14 patients (58.3%) experiencing ≥ 1 AE (all grades\textsuperscript{a})
  - There were a total of 7 SAEs reported, with 3 patients (12.5%) experiencing ≥ 1 SAE
    - SAEs included abscess, bacteremia, respiratory distress, and adenovirus infection
- One patient was exposed to rimiducid
- No treatment-emergent adverse events\textsuperscript{b} (TEAEs) were reported

AE, adverse event; SAE, serious adverse event.
\textsuperscript{a} AEs were graded as mild, moderate, severe, life-threatening, death (AE grading [severity] scale: NCI CTCAE v4.03).
\textsuperscript{b} TEAE: defined as any AE where the relationship to study treatment is possible, probable or definite.
In patients with sustained engraftment of donor cells, median time to neutrophil and platelet engraftment was rapid:

- Neutrophil engraftment: 16 days (95% CI, 15-21 days)
- Platelet engraftment: 13 days (95% CI, 11-18 days)
Cumulative incidence of graft failure (GF)

Graft failure: 9.3% (95% CI, 0.0%-21.6%)

- Of the 24 evaluable pediatric patients, 2 experienced graft failure
  - Both cases occurred prior to infusion of rivo-cel
  - One of the 2 patients received a successful transplant from the other parent

Data cutoff date: September 17, 2018.
Three of 22 evaluable patients (13.6% [95% CI, 0%-28%])\textsuperscript{a} developed Grade I-II acute GvHD

- Grade I aGvHD (stage 1 skin; n = 1)
- Grade II aGvHD (stage 3 skin; n = 2)

No patients developed Grade III-IV acute GvHD

Rimiducid was administered to 1 patient with Grade II skin aGvHD, with complete response achieved at Day 4 after drug infusion

None of the patients at risk developed cGvHD

\textsuperscript{a} Two patients with graft failure were not evaluable for GvHD assessment.

Data cutoff date: September 17, 2018.
Disease-free survival\textsuperscript{a}

Disease-free survival: 85.7% (95% CI, 70.7%-100%)

There were 3 DFS events:

- Graft failure with autologous hematologic reconstitution (n = 1)
- Transplant-related mortality (n = 2)

DFS, disease-free survival; DFS defined as probability of survival until recurrence or death from any cause.

\textsuperscript{a} Efficacy-evaluable population.

Data cutoff date: September 17, 2018.
Overall survival\textsuperscript{a}

N = 21; events = 2; OS, 90.5\% (95\% CI, 77.9\%-100\%)

\textsuperscript{a} Efficacy-evaluable population.
Data cutoff date: September 17, 2018.
Transfusion independence

- The median time from date of transplant to last reported transfusion was 10 days (range, 7-93 days)

Hb, hemoglobin.

* Efficacy-evaluable population.

Data cutoff date: September 17, 2018.
Immune recovery (I)

- CD3+ cells above 500 cells/µL achieved by 180 days
- CD3+CD4+ and CD3+CD8+ T cells above 500 cells/µL achieved by 360 days

- Normal levels of IgA and IgM were achieved by 30 and 180 days post-HSCT, respectively

Ig, immunoglobulin.
Dotted horizontal lines represent levels needed to be achieved for immune recovery of CD3+ T cells and immunoglobulins.
Data cutoff date: September 17, 2018.
Immune recovery (II) and CMV reactivation

Rivo-cel CD3+CD19+ cells progressively expanded and persisted over time

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

Data generated from IRCCS Ospedale Pediatrico Bambino Gesù (OPBG), Rome, Italy. [Includes 3 DBA and 1 sickle cell pt]

CMV, cytomegalovirus.

Data cutoff date: September 17, 2018.
Conclusions

• An αβ T- and B-cell–depleted haplo-HSCT followed by infusion of rivo-cel (rivogenlecleucel; BPX-501) is a suitable and effective option for children with transfusion-dependent β-thalassemia major lacking an HLA-identical donor
  - The low cumulative incidence of transplant-related mortality observed and the absence of severe acute GvHD and chronic GvHD support further studies in this patient population
• Administration of rivo-cel was safe and tolerable in pediatric patients with transfusion-dependent β-thalassemia major lacking an HLA-identical donor
  - No AEs were associated with exposure to either rivo-cel and/or rimiducid
• Only 1 patient required administration of rimiducid for aGvHD and achieved a complete response on Day 4 post-rimiducid
• Rivo-cel CD3+CD19+ T cells expanded over time and persisted through all time points following infusion
  - CMV reactivation appears to be the main driver of rivo-cel expansion
Acknowledgments

- We would like to acknowledge all patients, their families, and caregivers for participating in this clinical trial, along with the investigators and clinical teams.
- This presentation was sponsored by Bellicum Pharmaceuticals, Inc.
- Third-party writing assistance was provided by Health Interactions, Inc.