BPX-501 Donor T-Cell Infusion (with Inducible Caspase 9 Suicide Gene) Facilitates HLA-Haploidentical Stem Cell Transplant in Children with both Hematological Malignancies and Non-Malignant Conditions


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None to report.
BPX-501 After αβ T-cell–depleted Haploidentical HSCT – Meeting Unmet Needs

• T-cell–depleted haplo-HSCT provides an important option for children who lack an HLA-matched donor but for whom an allograft could provide curative benefit

• The challenges with T-cell–depleted haplo-HSCT are well recognized
  – Increased risk of non-engraftment, especially in patients with non-malignant disorders
  – Delayed immune reconstitution, which can increase the risk of life-threatening infections and, potentially, relapse

• Clinical research to date suggests that depleting TCR αβ+ cells from the allograft and then infusing donor T-cells transduced with iCaspase9 suicide gene (BPX-501) can provide
  – More refined T-cell depletion, with the graft containing only cells of innate immunity
  – Enhanced immune reconstitution with genetically-modified, adoptively-transferred T-cells

• In the event of uncontrolled GvHD due to BPX-501 (CD3+CD19+ T-cells), rimiducid administration induces the suicide gene, eliminating the BPX-501 cells and resolving GvHD quickly and effectively
BPX-501: Donor-derived CaspaCIDe T-cells

Engineered T-cells with iC9 “safety switch” and CD19 marker

Inducible caspase 9 binding site; rimiducid binding starts caspase apoptosis cascade

Truncated CD19 marker allows selection for purity and tracking in blood

- Derived from donor leukapheresis, produced in GMP facilities in Europe and US
- Activated and expanded in culture, transduced with the iC9 suicide gene and selected for CD19+ cells
- Cryopreserved and stored in liquid nitrogen
- Normal T-cell characteristics are maintained
  - Broad T-cell repertoire of immunity
  - Antiviral and antigen-specific activity
BPX-501 after αβ T-cell–depleted Haplo-HSCT

Day -7: T-cell apheresis

Days -6 to +5: GMP manufacturing

Shipping

Day 0: Stem cell collection, αβTCR depletion and infusion

Day +14±4: BPX-501 infusion
Characterization of BPX-501 T-cells

After expansion and transduction, BPX-501 T-cells have increased memory effector phenotype in both CD4 and CD8 subsets.

- **CD4+**:
  - Apheresis: 20%, BPX-501: 80%
  - P-value: 0.01
- **CD8+**:
  - Apheresis: 40%, BPX-501: 60%
  - P-value: 0.002

BPX-501 T-cells retain high viability after cryopreservation and thaw.
BPX-501 T-cells Expand and Persist in Peripheral Blood

- Detectable by standard flow cytometry
- BPX-501 CD3+CD19+ T cells expand and persist over time
  - Both CD4+CD19+ and CD8+CD19+ populations
  - CMV reactivation was the major driver of early expansion
BP-004: On-going Phase 1/2 Trial of Haplo-HSCT and BPX-501

- Transplant centers in EU [Italy, UK (2 centers)] and US (10 centers)
- Pediatric patients with malignant and non-malignant disorders
- Haploidentical donor; matched related or unrelated donor unavailable
- BPX-501 after haplo-HSCT (phase 2 expansion protocol)
  - Non-mobilized apheresis prior to mobilization for BPX-501
  - TCRαβ/CD19-depleted allograft – low TCRαβ and high CD34 content in graft
  - 0.25 to 2 X 10^6/kg BPX-501 T-cells infused day 14 ± 4 post-transplant
- No post-transplant pharmacologic prophylaxis for GvHD (no CNI)
- Rimiducid administered for uncontrollable GvHD due to BPX-501 (CD3+CD19+ T-cells)

Preliminary results presented here are from an unplanned analysis of patients with ≥180 days of follow-up

Sponsor: Bellicum Pharmaceuticals
ClinicalTrials.gov identifier: NCT02065869
EUDRACT number: 2014-000584-41
BP-004: Global Patient Population with ≥180 Days of Follow-up

- As of April 24, 2017, 98 patients*
  - Received αβTCR-depleted haplo-HSCT
  - Received BPX-501 after transplant
  - Had ≥180 days of follow-up
- A wide range of non-malignant and malignant diagnoses
  - Excludes patients with JMML (1), CR3 (2)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant</td>
<td>n=98</td>
</tr>
<tr>
<td>Primary immune deficiency</td>
<td>26 (27)</td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Diamond-Blackfan</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Shwachman-Diamond syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Malignant</td>
<td>39 (40)</td>
</tr>
<tr>
<td>ALL (CRI and CR2)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>AML (CR1 and CR2)</td>
<td>14 (14)</td>
</tr>
<tr>
<td>MDS</td>
<td>3 (3)</td>
</tr>
<tr>
<td>NHL</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*some patients received BPX-501 beyond 18 days post-transplant
BP-004: Global Patient Population Results at 180 Days (n=98)

- Successful engraftment in 95% (93/98) patients across a wide range of non-malignant and malignant diagnoses
- 5% incidence transplant-related mortality (TRM)
  - Five patients with primary graft failure were not successfully re-transplanted
- Rapid recovery of T-cells, B-cells, and immunoglobulins
- No post-transplant lymphoproliferative disorder (PTLD)
- 14% cumulative incidence of Grade 2–4 acute GvHD
- 3% cumulative incidence of chronic GvHD at 1 year for patients with ≥1 year of follow-up
BP-004: Rimiducid Rescues Uncontrollable Acute GvHD

- Rimiducid was administered to
  - 10 patients with uncontrollable aGvHD (45% of all aGVHD)
  - One patient who developed late aGvHD after day 270
- In all cases, aGvHD resolved with recovery of non-alloreactive T-cells and no recurrence

<table>
<thead>
<tr>
<th>GvHD diagnosis</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin Grade 1</td>
<td>Resolved</td>
</tr>
</tbody>
</table>

![Graph showing cells/µl over days from transplant for Pt #073, Pt #062, and Pt #091 with Rimiducid infusion marked.

Skin Grade 1 Resolved

Skin Grade 1 Resolved

Skin Grade 1 Resolved

BPX-501 Donor T-Cell Infusion (with Inducible Caspase 9 Suicide Gene) Facilitates HLA-Haploidentical Stem Cell Transplant
EU BP-004: EU Cohort with ≥180 Days of Follow-up

- As of April 24, 2017, 61 patients in EU cohort
  - Received αβTCR-depleted haplo-HSCT
  - Received BPX-501 after HSCT
  - Had ≥180 days of follow-up

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, n (%)</th>
<th>n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-malignant</td>
<td>36 (59)</td>
<td></td>
</tr>
<tr>
<td>Primary immune deficiency</td>
<td>16 (26)</td>
<td></td>
</tr>
<tr>
<td>Thalassemia major</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Diamond-Blackfan</td>
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<td>5 (8)</td>
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</tr>
<tr>
<td>Hemophagocytic lymphohistiocytosis (HLH)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>25 (41)</td>
<td></td>
</tr>
<tr>
<td>ALL (CRI and CR2)</td>
<td>15 (25)</td>
<td></td>
</tr>
<tr>
<td>AML (CR1 and CR2)</td>
<td>10 (16)</td>
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### BP-004: Demographics of EU Cohort with ≥180 Days of Follow-up

<table>
<thead>
<tr>
<th>Feature</th>
<th>Patients n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median patient age, years (range)</td>
<td>4.8 (0.25–17)</td>
</tr>
<tr>
<td>Male/female, n (%)</td>
<td>34/27 (56/44)</td>
</tr>
<tr>
<td>Conditioning, n (%)</td>
<td></td>
</tr>
<tr>
<td>Busulfan-based</td>
<td>25 (41)</td>
</tr>
<tr>
<td>TBI</td>
<td>22 (36)</td>
</tr>
<tr>
<td>Treosulfan-based</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Median donor age, years (range)</td>
<td>36 (19–50)</td>
</tr>
<tr>
<td>Donor relationship, n (%)</td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>58 (95)</td>
</tr>
<tr>
<td>Sibling</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Allograft</td>
<td></td>
</tr>
<tr>
<td>Median CD34 × 10^6/kg (range)</td>
<td>20 (4–36)</td>
</tr>
<tr>
<td>Median αβTCR × 10^5/kg (range)</td>
<td>0.4 (0.01–0.94)</td>
</tr>
</tbody>
</table>
BP-004: EU Cohort Results at 180 Days (n=61)

- Successful, rapid engraftment in all 61 patients, with no TRM at 180 days
  - Median 15 and 10 days to recovery of neutrophils and platelets, respectively
- Half of patients discharged within one month
- Low incidence of grade 2–4 acute GvHD (9.9%); no extensive chronic GvHD
- No PTLD
Viral Infections and Reactivations: Single-center Experience

- Previously reported data (*EBMT 2017*) of single-center experience (Rome)
- Patients (N=83) treated with αβTCR-depleted haplo-HSCT and BPX-501
- Historical cohort (N=107) treated with αβTCR-depleted haplo-HSCT alone (no BPX-501 T-cells after)
- Cumulative incidence of viral infections and reactivations was significantly decreased in patients receiving BPX-501
  - 53.7% vs 78.5%, P = 0.0001
Disease-specific Results: Primary Immune Deficiencies

Recovery of Normal Immunity in Children with PID

**T-cells**
- CD3+
- CD3+CD4+
- CD3+CD8+

**B-cells**
- CD20+

**Immunoglobulins**
- IgG
- IgA
- IgM

**Cells/µl**

<table>
<thead>
<tr>
<th>Days from transplant</th>
<th>Cells/µl</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td></td>
</tr>
<tr>
<td>180</td>
<td></td>
</tr>
<tr>
<td>270</td>
<td></td>
</tr>
<tr>
<td>360</td>
<td></td>
</tr>
</tbody>
</table>

**Immunoglobulin, mg/dl**

<table>
<thead>
<tr>
<th>Days from transplant</th>
<th>Immunoglobulin, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>90</td>
<td>IgG</td>
</tr>
<tr>
<td>180</td>
<td>IgA</td>
</tr>
<tr>
<td>270</td>
<td>IgM</td>
</tr>
</tbody>
</table>

lower limit of normal range

BPX-501 Donor T-Cell Infusion (with Inducible Caspase 9 Suicide Gene) Facilitates HLA-Haploidentical Stem Cell Transplant
Disease-specific Results: Wiskott-Aldrich Syndrome

Fast Recovery of Platelets in Children with Wiskott-Aldrich Syndrome

- Platelets, cells x 10^3/µl
- Days from transplant

Graph showing the recovery of platelets over time post-transplant. The x-axis represents days from transplant, ranging from 10 to 360, and the y-axis represents platelet counts in cells x 10^3/µl, ranging from 0 to 450.
Disease Specific Results: Erythroid Disorders

Hemopoietic recovery to normal in erythroid disorders and Fanconi Anemia

Hgb Values in Erythroid Disorders

Last RBC transfusion, median 8 days from transplant (range 5–71)

Recovery in Fanconi Anemia

Platelets, cells $\times 10^3/\mu$l

Neutrophils, cells/µl

Days from transplant

Days from transplant

Hemoglobin, g/dl

5000

4000

3000

2000

1000

0

5000

4000

3000

2000

1000

0

BPX-501 Donor T-Cell Infusion (with Inducible Caspase 9 Suicide Gene) Facilitates HLA-Haploidentical Stem Cell Transplant
BP-004: Summary of Preliminary Results

• Patients lacking a compatible donor and/or in urgent need of an allograft successfully treated with Haplo-HSCT and BPX-501
  • Low TRM at 180 days
  • Rapid engraftment and early hospital discharge
  • Low acute GvHD incidence and no extensive chronic GvHD; rimiducid effectively resolved all uncontrolled aGvHD due to BPX-501 T cells
  • Rapid recovery of T cells, B cells, and immunoglobulins
  • Favorable disease outcomes across patient types
• Preliminary data from BP-004 compare favorably to previously published data on MUD HSCT
• An observational MUD study is being initiated to enable comparison of the safety and efficacy of HSCT and BPX-501 to the standard of care for patients without a matched sibling donor
Acknowledgements

We thank the patients and their families for their participation in this clinical research, and the investigators and staff at all the participating sites.

Participating Sites
EU: Ospedale Pediatrico Bambino Gesù; Great Ormond Street Hospital; Great North Children's Hospital Research Unit
US: Baylor College of Medicine CAGT, Feigin Center; Children's Hospital Los Angeles; Children's Healthcare of Atlanta at Egleston; Boston Children's Dana Farber; Children's National Medical Center; Seattle Children’s Hospital/UW/FHRCC; Children's Hospital – OHSU; Children’s Hospital UTSW; The Children's Hospital at Montefiore; Stanford University – Lucille Packard Children’s Hospital
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