Administration of BPX-501 Cells Following α/β T-cell and B-cell-Depleted HLA-Haploidentical HSCT (haplo-HSCT) in Children with Primary Immunodeficiencies

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<tbody>
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<td>Daria Pagliara</td>
<td>No disclosures</td>
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<td>Alice Bertaina</td>
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<td>Neena Kapoor</td>
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<td>Lakshmanan Krishnamurti</td>
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<td>Trial research funding from Bellicum, Servier; equity in Autolus, Orchard</td>
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<td>No disclosures</td>
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<td>Victor M. Aquino</td>
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<td>Susanne Baumeister</td>
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Background

BPX-501 T-cells in children with primary immunodeficiencies

- Allogeneic HSCT is a well-established treatment for children with a wide range of primary immunodeficiencies (PID)

- Approximately 25% of patients have a HLA-matched sibling and ~50% have a suitable matched unrelated donor, leaving ~25% of patients who require an alternative donor.

- HLA-partially matched (haploidentical, haplo) donors represent a suitable alternative option for children who lack a matched donor
  - However, extensive T-cell depletion of the graft is required to minimize the risk of graft-vs-host disease (GvHD)

- BPX-501 is a polyclonal donor T-cell product derived from haplo-donors engineered to include an inducible ‘Safety Switch’, offering the benefits of T cells in facilitating engraftment and preventing infections, with the unique ability to promptly and durably resolve GvHD symptoms

- The objectives of this Phase 1/2 study are to evaluate the safety and efficacy of BPX-501 T-cells administered after a T-cell receptor $\alpha\beta$ and B-cell depleted haplo-HSCT in pediatric patients with PID
Bellicum’s iCaspase-9 safety switch controls GvHD

The chemical induction dimerization (CID) switch controls GvHD through infusion of a selective dimerizing ligand (rimiducid) which activates cell signalling that leads to apoptosis.

1. Viral transduction transfers the DNA from a vector into the target cell.
2. Vector-derived DNA directs expression of CID and accessory proteins.
3. Rimiducid dimerizes the CID proteins, thus turning on the signal cascade.

Rimiducid is a selective CID ligand dimerizer
- Small (12 kDa, 107aa), bio-inert “activator” that is membrane-permeable, soluble in plasma
- Non-immunogenic
- <2 hour half-life
- No known side-effects
BPX-501 addresses the “T-cell dilemma” in Haplo-HSCT

Study Schema

Mobilized leukapheresis → αβTCR/CD19 Depletion → HSCT → Patient

- Haploidentical Donor
- BPX-501 Cell Processing: T CELLS
- Non-mobilized apheresis

- Mobilized leukapheresis → αβTCR/CD19 Depletion → HSCT → Patient
- BPX-501 Cell Processing: T CELLS
- Non-mobilized apheresis

- HSCT
- BPX-501 Addback Infusion: T CELLS
- BELLCUM GMP FACILITY

- Rimiducid for uncontrolled GvHD
- Day 14 +/− 4 days
- No GvHD prophylaxis

BPX-501: Tipping the benefit / risk scale

Non-mobilized apheresis
Pediatric Ph1/2 trial design

Multicenter study of gene modified donor T-cells following TCR $\alpha\beta$ depleted stem cell transplant

**αβ T-cell and B-cell depleted**

Haplo-HSCT +

BHX-501

(NO post-HSCT GvHD prophylaxis)

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

**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

**Phase I: 3+3 design (no MTD reached)**

2.5x10^5, 5x10^5, 1x10^6 BHX-501 T-cells/kg (no DLTs observed)

**Phase II:**

1x10^6 BHX-501 T-cells/kg (chosen for further evaluation)

**Key Inclusion Criteria**

- Life-threatening acute leukemia or myelodysplastic syndrome
- 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 breast feeding
Baseline clinical characteristics

**PATIENT POPULATION**

n = 59

AGE, MEDIAN (RANGE)

1.85 (0.21-17.55)

MALE (%)

57.6%

Other diagnoses (N=1 each):
- XIAP deficiency
- IL-2 Receptor Deficiency
- IFN gamma-receptor 1 deficiency
- IL-10 RB deficiency
- Partial complement C4 deficiency with multiple autoimmune manifestations
- CD40 Ligand deficiency
- IKBetaAlfa gain of function mutation
- Dock 8 deficiency
- Severe congenital neutropenia
- Hyper IgM syndrome
- Hyper IgD syndrome
# Transplant characteristics

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>N=59</th>
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<tbody>
<tr>
<td>Conditioning regimen</td>
<td></td>
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<tr>
<td>Treosulfan-based</td>
<td>29 (49.2%)</td>
</tr>
<tr>
<td>Busulfan-based</td>
<td>23 (39.0%)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (11.9%)</td>
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<tr>
<td>Median CD34 dose x 10^6/kg (range)</td>
<td>22.0 (3.0-57.0)</td>
</tr>
<tr>
<td>Median αβ T-cell dose x 10^5/kg (range)</td>
<td>0.4 (0.01-1.0)</td>
</tr>
<tr>
<td>Donor age in years (range)</td>
<td>34 (21-52)</td>
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<tr>
<td>Type of donor</td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>56 (94.9%)</td>
</tr>
<tr>
<td>Sibling</td>
<td>3 (5.1%)</td>
</tr>
<tr>
<td>Time to BPX-501 infusion in days (range)</td>
<td>15 (11-56)</td>
</tr>
<tr>
<td>Time to discharge in days (range)</td>
<td>40 (18-204)</td>
</tr>
<tr>
<td>Median follow-up in days (range)</td>
<td>536 (32-1252)</td>
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</table>
Safety

15.2% (9 patients) experienced ≥1 adverse event (AE)

AEs occurring after BPX-501 cells were limited to Grade 1-2
Preferred terms included: Diarrhoea, Vomiting, Pyrexia, Cytomegalovirus viraemia (2), Rhinovirus infection, Hypokalaemia, Pruritus, Rash

No SAEs attributed to BPX-501 were reported in this cohort

BPX-501 T-cells were well tolerated
Neutrophil and platelet recovery were rapid.
Median neutrophil engraftment: 16 days (95% CI, 14-17)
Median platelet engraftment: 11 days (95% CI, 10-12)
Only 1 subject received G-CSF
Median follow-up: 536 days (32-1252 days)
Graft failure

Low graft failure rate at 5.1%

Graft failure rate:
5.1% (95% CI, 0.0-10.7)

1 of 3 patients were successfully re-transplanted
Cumulative incidence of transplant-related mortality (TRM)

Low TRM incidence of 8.7%

Transplant-related mortality: 8.7% (95% CI, 1.4-16.0)

5 cases of TRM:
- Graft failure/disseminated fungal infection
- CMV encephalitis
- Worsening juvenile dermatomyositis/macrophage activation syndrome
- Bronchopulmonary hemorrhage
- CMV and adenovirus infection/respiratory failure
Disease-free survival (DFS)

Disease-free survival: 87.6% (95% CI, 79.0-96.3)

Events:
- Graft failure without successful re-transplantation (1)
- Graft failure with death due to disseminated fungal infection (1)
- Other grade 5 events (1 each):
  - CMV encephalitis
  - Worsening juvenile dermatomyositis/macrophage activation syndrome
  - Refractory HLH
  - Bronchopulmonary hemorrhage
  - Respiratory failure

1 time from treatment until graft failure or death from any cause.
Overall survival (OS)

Median follow-up: 536 days (Range, 32 – 1252 days)

Overall survival: 87.6% (95% CI, 79.0-96.3)
Acute GvHD

Low rates of acute GvHD Grade II-IV and Grade III-IV (first 100 days)

Grade II-IV:
8.9% (95% CI, 1.5-16.4)

Grade III-IV:
1.8% (95% CI, 0.0-5.3)

Cases of acute GvHD within 100 days included:
- Grade II (n=4)
  - Stage 3 skin (n=3)
  - Stage 1 upper GI (n=1)
- Grade III (n=1)
  - Stage 3 liver
Cumulative incidence of chronic GvHD

Low rates of chronic GvHD were observed

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cGvHD rate:
3.0% (95% CI, 0.0-8.9)

1 case of moderate skin cGvHD; rimiducid was not administered
Response to rimiducid

Of the 19 patients who developed aGvHD, 7 received ≥1 dose of rimiducid for aGvHD not responsive to standard of care treatment or for visceral involvement.

>80% response rate in evaluable PID patients (5 of 6)

<table>
<thead>
<tr>
<th>OVERALL</th>
<th>STAGE</th>
<th>RESPONSE</th>
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<tbody>
<tr>
<td>Grade I</td>
<td>Stage 1 skin</td>
<td>CR</td>
</tr>
<tr>
<td>Grade I</td>
<td>Stage 2 skin</td>
<td>PR</td>
</tr>
<tr>
<td>Grade II</td>
<td>Stage 3 skin</td>
<td>CR</td>
</tr>
<tr>
<td>Grade II</td>
<td>Stage 1 upper GI</td>
<td>CR</td>
</tr>
<tr>
<td>Grade II</td>
<td>Stage 3 skin</td>
<td>NE*</td>
</tr>
<tr>
<td>Grade III</td>
<td>Stage 3 liver</td>
<td>CR</td>
</tr>
<tr>
<td>Grade III</td>
<td>Stage 3 liver</td>
<td>NR</td>
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</tbody>
</table>

*NE: Patient on corticosteroids and cyclosporine with controlled GvHD but failure to wean corticosteroids. Rimiducid given in an attempt to wean corticosteroids.
## Rimiducid (AP1903) use

<table>
<thead>
<tr>
<th>aGVHD, grade</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>Skin, II</td>
<td>Complete</td>
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</table>

### Pre-ridicud infusion

### Post-rimiducid infusion
Immune recovery

Immune recovery: CD3 T-cell count > 500 cells/μl achieved by 100 days and normal levels of IgA and IgM was achieved by 180 days.
Immune recovery

BPX-501 engraftment after HSCT

Mean BPX-501 cell counts exceed 100 cells/mcl by day 100

Increased number of BPX-501 cells observed in patients that experienced CMV reactivation
Summary

α/β T-cell and B-cell depleted haploidentical HSCT followed by infusion of BPX-501 cells is a novel and highly effective transplantation strategy for children with a wide range of primary immunodeficiencies lacking a suitable HLA-compatible donor.

- Disease-free survival and overall survival (87.6% and 87.6%, respectively) compare favourably with data reported using matched unrelated donors.
- The cumulative incidence of severe acute (grade III-IV) (1.8%) in the first 100 days and chronic GvHD (3.0%) was low compared to other transplant methods.
- >80% of patients with treatment resistant acute GvHD responded after administration of rimiducid.
- CD3+ T-cells, IgA and IgM achieved normal levels by 180 days post HSCT.
- BPX-501 T-cells expand over-time and persist post infusion through all timepoints, the main driver for BPX-501 T-cell expansion being represented by CMV infection.
The study investigators and Bellicum would like to thank the patients and their families for participation in our clinical trials.