Clinical outcome after adoptive infusion of BPX-501 cells (donor T cells transduced with iC9 suicide gene) in children given α/β T-cell depleted HLA-haploidentical hematopoietic stem cell transplantation (haplo-HSCT): preliminary results of a phase I-II trial.

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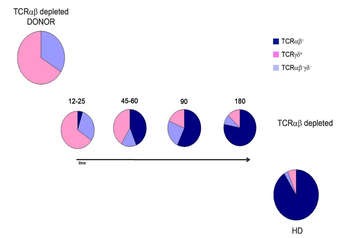
Background

We recently completed a prospective study of more than 100 patients (ClinicalTrial.gov identifier: NCT01810120) which showed that haplo-HSCT after depletion of α/β T cells is an effective option for those children in need of an allograft and lacking an immediately available HLA-identical related or unrelated donor. This represents the "historical controls" for the BP-004 study.

However, recovery of adaptive T-cell immunity remains suboptimal and some patients died due to viral infections in the early post-transplant period.

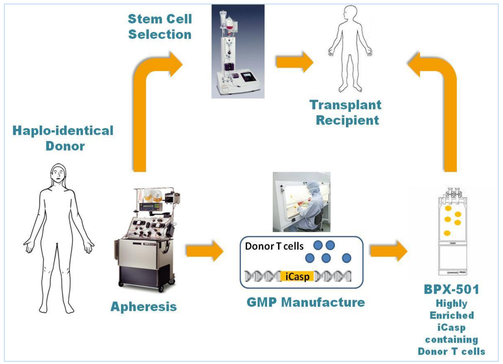
Thus, strategies aimed at accelerating early recovery of adaptive T-cell immunity are desirable.

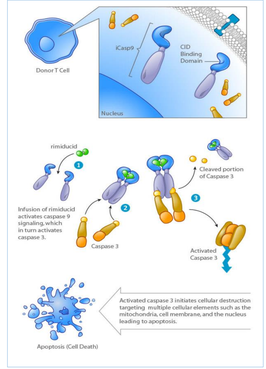
Immune recovery αβ+ vs γδ+



Technology

All children received >10x10^6 CD34+ cells/Kg and <1x10^5 αβ+ T cells/Kg in the allograft. BPX-501 donor derived T cells are manufactured under GMP, expanded, transduced with the iCasp9 suicide gene and then cryopreserved and shipped back to the clinical site.





Study Design

We designed a phase I/II trial aimed at testing the safety and efficacy of post- transplant infusion of donor-derived T cells transduced with the iC9 suicide gene (BPX-501) in children with malignant or non-malignant disorders (ClinicalTrials.gov identifier: NCT02065869); enrollment started in December 2014.

Cells are administered within 14 ± 4 days after haplo-HSCT. The phase I portion of the trial consisted of a classical 3+3 design with 3 cohorts, receiving escalating doses of BPX-501 cells of 2.5 x 10^5, 5 x10^5, and 1x10^6 cells/kg, respectively.

Patients included in the phase II portion received the highest dose identified during the phase I portion of the study for a maximum of 60 children in both phase I/II portions of the study.

As of November 30 2015, 49 children have been enrolled in the study: 39 have been infused with BPX-501 cells. No adverse events have been associated with the infusion of BPX-501 T cells.

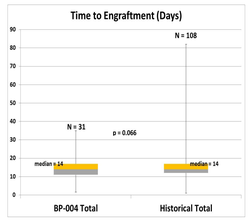
There was no difference in graft composition between the 39 patients who have received BPX-501 to date and those who were previously included in the study on haplo-HSCT after depletion of α/β T cells (historical controls).

Diagnosis of BP-004 Enrolled Patients

Diagnosis of Patients in BP- 004	N=49
Diagnosis Type: Malignant (N=21)	
Acute Lymphoblastic Leukemia	15
Acute Myeloid Leukemia	3
Burkitt Lymphoma	1
Juvenile Myelomonocytic Leukemia	1
Non-Hodgkin's Lymphoma	1
Diagnosis Type: Non-Malignant (N=28)	
Aplastic Anemia	2
Diamond-Blackfan Anemia	1
Fanconi Anemia	6
Hemophagocytic Lymphohistiocytosis	1
Immune Deficiency Due To Mutation Of XIAP Gene	1
Severe Combined Immunodeficiency	5
Sickle Cell Disease	1
Thalassemia Major	7
Wiskott-Aldrich Syndrome	4

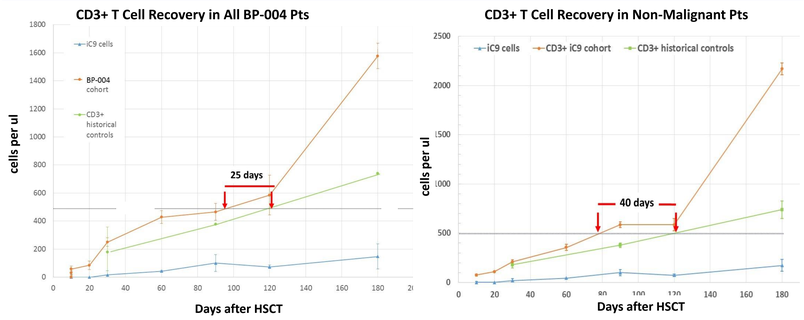
All children with acute leukemia were transplanted in morphological complete remission (CR).
Demographics, age and gender of patients enrolled in BP-004 did not differ from historical control patients.

Hematopoietic Engraftment



Time to engraftment was evaluated in all patients with >65 days follow up, and was not statistically different from the historical patients being primarily dependent on the CD34 content of the allograft.

Immune Reconstitution



- **In non-malignant patients who received BPX-501, a mean improvement was detected of approximately 40 days in achieving a T cell count of 500 cells/ul when compared to historical controls.**
- **When all patients were analyzed, a mean improvement was detected of approximately 25 days in achieving a T cell count of 500 cells/ul when compared to historical controls.**
- **Immune reconstitution with 500 CD3+ T cells historically correlates with improved clinical outcomes.**
- **All patients who have been discharged after transplant are evaluable for analysis which is ongoing.**

100 Day Chimerism

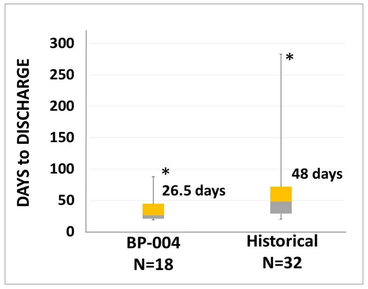
- In 4 patients, mixed chimerism was present at the time of BPX-501 cell infusion and completely reverted to full donor chimerism subsequently.
- 1 SCD patient remains healthy with 20% partial chimerism.

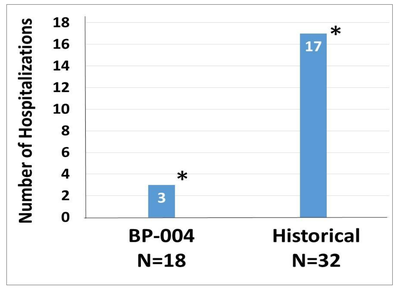
Incidence of GVHD vs Historical Controls

GvHD	BP-004 N=37	Historical Controls N=115
Acute Gr I-II	7*	27*
Acute Gr III-IV	0	0
cGvHD	0	4

- **Data from the BP-004 cohort represents all patients treated with BPX 501 who have >40 days follow up.**
- **4 with skin Gr 1 only; 1 patients with skin Gr II, and 2 patients with skin and gut Gr II—all resolving with SOC.**
- **There has been no chronic GVHD seen in the 23 patients with >120 days follow up.**

Time to Discharge and Re-hospitalization in Nonmalignant Patients

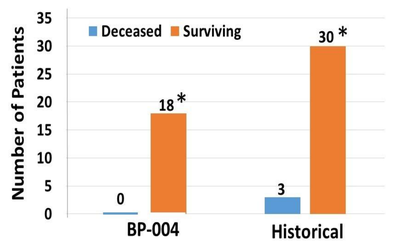




- **In non-malignant patients who received BPX-501, there appeared to be a significant difference in median days to discharge after HSCT, and in the number of rehospitalizations after discharge.**
- **All patients who have been discharged after transplant are evaluable for analysis which is ongoing.**

Transplant Related Mortality in Nonmalignant Pts

- **There is no TRM in all BP-004 patients who have received BPX-501 with at least 30 days follow up in the study to date (n=37).**
- **In particular, there is no TRM in the non-malignant group, which appears significantly different from historical controls.**
- **Although most BP-004 patients have less than 1 year follow up, since TRM often occurs early in the post transplant period in non malignant patients, most often due to infectious complications, these data represent very exciting preliminary findings.**



Summary

1. **These data indicate that the infusion of BPX-501 cells is safe and well tolerated, with an improved TRM compared to historical controls receiving αβ T cell depletion.**
2. **The cumulative incidence of grade I-II acute GvHD observed in these patients is similar if not better compared to historical controls.**
3. **BPX-501 cells expand *in vivo* and persist over time, accelerating the recovery of adaptive T-cell immunity, with improved clinical outcomes such as reduced duration of viral infections, reduced hospitalizations for infections.**
4. **Phase 2 dose of BPX-501 was determined to be 1 million/kg, but increased doses will be evaluated going forward for the malignant patients.**
5. **The iC9 cell-suicide system may increase the implementation of cellular therapy approaches aimed at optimizing immune recovery after transplantation.**

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