A Dose Escalation Study of Cyclophosphamide (CTX) to Enhance SB-728-T Engraftment


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SB-728-1101 Cytosine Study Rationale
- CCR5 is a major co-receptor for HIV entry
- Modification produces a non-functional protein
- Transgenic mice are resistant to HIV infection
- Genetically-based CCR5 deficiency is protective
- Zinc Finger Nuclease-mediated precise disruption of the CCR5 gene of multidrug-resistant HIV-1 (Taux-1) is equivalent of CCR5 knock-out
- CCR5 knockout mice are protected from SIV infection
- CCR5 nuclease has been used successfully to enhance adoptive T-cell therapy in non-human primates
- Hematopoietic proliferation and production of T-cell growth factors
- Activation of regulatory T cells
- Expansion of dendritic cells
- Create space in the bone marrow
- Current study undertaken to increase SB-728-T engraftment

SB-728-1101 Cytosine Study Design
- Open label, multicenter, cyclophosphamide dose escalation, with single dose SB-728-T infusion
- Study population: Adult, 18-70 yrs
- Cohort 1: 728 T cells only
- Cohort 2: 728 T cells + CD8
- Cohort 3: 728 T cells + CD8 + HAART
- Cohort 4 (1.0 g/m²) + CD8
- Cohort 5 (1.5 g/m²) + CD8

Subject 01-070 (CTX 1000 mg/m² + CD8)  
Subject received 17.6x10⁹ CD4 (50.2%) 8.83x10⁹  
CD8 (38.0%) 6.69x10⁹
VL 23,700
VL= Viral Load

SB-728-1101 Subject Demographics
Treatment with SB-728-T Modified CD4 T-cells

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Race</th>
<th>Ethnicity</th>
<th>Cohort</th>
<th>SB-728-T Modified CD4 T-cells</th>
</tr>
</thead>
</table>
| 30  | 15   | 15     | 30   | 15        | 1      | 17.6x10⁹ CD4 (50.2%) 8.83x10⁹  
CD8 (38.0%) 6.69x10⁹ |
| 30  | 15   | 15     | 30   | 15        | 2      |
| 30  | 15   | 15     | 30   | 15        | 3      |
| 30  | 15   | 15     | 30   | 15        | 4      |
| 30  | 15   | 15     | 30   | 15        | 5      |

SB-728-1101: Subject Demographics
Treatment with SB-728-T Modified CD4 T-cells

SB-728-1101: Subject Demographics
Treatment with SB-728-T Modified CD4 T-cells

SB-728-T Following CTX Administration is Safe
- SB-728 T cells are well tolerated
- 7-day infusion reactions - low grade fever, chills
- Garlic odor due to DMSO
- Cytokine doses up to 1.0 gm/m² is safe and well tolerated in HIV infected patients:
  - No evidence of leukopenia or lymphocytopenia
  - No clinically significant effects on neutrophils, monocytes, and platelets
  - Neutropenia and lymphocytopenia increases with increasing CTX dose
  - Prophylactic steroids is not necessary
  - Most infections appear to be bacterial

Summary and Conclusions
- SB-728 CD4 T-cells after Cytoxan Conditioning
  - Genetic conditioning at doses of 1.0 gm/m² enhances adoptive transfer of SB-728 CD4 T-cells and SB-728-modified CD8 T-cells with minimal toxicity
  - Eighteen subjects have been treated with Cytoxan and SB-728-modified CD8 T-cells and four remain in long-term non-viremic remission (30-72 weeks)

- SB-728 CD4/CD8 T-cells after Cytoxan Conditioning
  - Three subjects have been treated with a modified HIV-1, which contains both CD4 and CD8 T-cells
  - CD4 T-cell dose can be increased safely with escalating CTX dose
  - The large increase in CCR5 modified CD8 T-cells may mimic elite controllers and may improve HIV control through CCR5 HIV-epitope T-cells

SB-728-T: Zinc Finger Nuclease Drives CCR5 Modified Autologous CD8 T-cells

Viral Load Drop from Peak After CD4 SB-728-T  
Four Subjects Continue on Prolonged TI

Post-Treatment Control Depends on Latent HIV Reservoir Size (m) and CTL Killing Rate (m)

Subject 04-046 (CTX 1000 mg/m² + CD8)  
Rationale for Maintaining CD8 T-cells in SB-728-T

Subject 01-070 (CTX 1000 mg/m² + CD8)  
Activated CD8 and Low CCR5 Are Associated with Elite Control in 92 Subjects

Subject 03-011(CX 1000 mg/m² + CD8)  
Summary and Conclusions

In summary, the study demonstrated that:
- SB-728 T-cell administration is safe and well tolerated.
- Cytokine doses up to 1.0 gm/m² are safe and well tolerated in HIV-infected patients.
- Genetic conditioning at doses of 1.0 gm/m² enhances adoptive transfer of SB-728 CD4 T-cells and SB-728-modified CD8 T-cells with minimal toxicity.
- Eighteen subjects have been treated with Cytoxan and SB-728-modified CD8 T-cells, and four remain in long-term non-viremic remission (30-72 weeks).
- Three subjects have been treated with a modified HIV-1 that contains both CD4 and CD8 T-cells.
- CD4 T-cell dose can be increased safely with escalating CTX dose.
- The large increase in CCR5-modified CD8 T-cells may mimic elite controllers and may improve HIV control through CCR5 HIV-epitope T-cells.