Phase IB Study of the CXCR4 Antagonist BL-8040 Combined with Immunosuppressive Therapy in Patients with Aplastic Anemia

Tapan Kadia[1], Gautam Borthakur[1], Nitin Jain[1], Naveen Pemmaraju[1], Koichi Takahashi[1], Karen Dwyer[2], Joseph Khoury[3], Abi Vainstein[4], Carol Bivins[1], Samuel Dara[1], Lianchun Xiao[4], Farhad Ravandi[1], Guillermo Garcia-Manero[1], and Hagop Kantarjian[1]

Departments of [1]Leukemia, [2]Stem Cell Transplant Research, [3]Hematopathology, and [4]Biostatistics. The University of Texas, MD Anderson Cancer Center, Houston, TX, USA. [5]BiolineRx, Modi'in, Israel.

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Abstract

Background:
Aplastic anemia (AA) is a bone marrow (BM) failure syndrome characterized by a severe depletion of hematopoietic stem and progenitor cells (HSPCs) in the BM leading to cytopenias. Most cases of acquired AA are the result of destruction of the HSPCs by autoreactive cytotoxic T-cells. This is mediated through immunosuppressive cytokines as well as perforin/granzyme-mediated apoptosis, requiring close proximity in the microenvironment. CXCR4 expression on pathogenic T-cells in AA facilitate their homing to the BM (Arieta Kuksin Blood 2015). Blocking the CXCR4 signaling axis in pathogenic T-cells can disrupt their homing to the BM may help improve responses when combined with immunosuppressive therapy (IST). BL-8040 is a potent CXCR4 antagonist that also has effects in mobilizing and increasing the numbers of HSPCs.

Aims:
We designed a pilot phase Ib study evaluating the feasibility, safety, and efficacy of BL-8040 combined with IST for patients with AA or hypoplastic myelodysplastic syndrome (hMDS).

Methods:
Pts ≥ 18 years, with adequate organ function, with a diagnosis of severe AA or hMDS, including those with relapsed (not refractory) AA were eligible. Pts were treated with BL8040 0.75 mg/kg SQ on D1-10, hATG 40 mg/kg/day (or 35 mg/kg/day for age ≥ 55 yrs) IV on D11-14, methylprednisone 1mg/kg/day IV daily on D11-14, followed by PO prednisone tapered off over 1 month, and cyclosporine (5 mg/kg) PO daily for up to 6 months. BL8040 (0.75 mg/kg) was continued on D1-5 of every month start with month 2. BM was performed at baseline, day 10, month 3 and month 6. Blood (PB) and BM samples were collected during treatment to explore the dynamics of immune cell and HSPC mobilization.

Results:
Eight pts have been treated, with a median age of 70 years (range, 23-75). Three patients had not received prior IST, 4 pts had relapsed AA, and 1 pt had hypoplastic MDS. Table 1 summarizes baseline characteristics. Six patients (75%) had diploid karyotype, while 2 had insufficient metaphases. At baseline 1 pt had mutations in TET2 and JAK2, and 1 pt had a DNMT3a mutation by next-generation sequencing. 4 pts have completed at least 5 months of therapy, 1 is too early in the treatment course, and 3 pts came off study early due to allergic reactions: 2 pts had grade 2 allergic reactions to the first doses of BL8040 and came off study, while 1 pt was noted to have an allergic reaction to the hATG skin test. Steroid premedication in subsequent pts mitigated BL8040-associated allergic reaction. 4 pts are evaluable for response with 2 CRs. Besides allergic reactions, the regimen was well tolerated. There were no grade ≥ 3 related AEs. Most common AEs possibly related to therapy were injection site pain, headaches, chills, and hot flashes. Quantification of T-cell subsets in the PB and BM by flow cytometry was available in 5 pts so far at 2-4 time points during therapy. On treatment, 3 pts had a notable relative increase in T-regulatory cells in the BM; there was a general trend for decrease in CD4+/CD45+ central memory T-cells, and increase in CD4+/CD45+ effector memory and CD4+/CD45+ TEMRA T-cells in the BM and PB; and there was a trend towards increased CD45+/CD8+ T-cells in the PB. In almost all cases, there was a significant decline in CXCR4 expression across T-cell subsets in BM and PB.

Summary/Conclusions:
Adding BL8040 to IST appears to be safe and feasible in patients with AA. Encouraging responses are seen with good tolerability. Preliminary analysis shows increasing BM T-regs and decreased CXCR4 expression after treatment. Profiling the immune repertoire and HSPCs of pts will be summarized.

Study Design

Primary Objective

- To evaluate the safety and tolerability of the treatment with BL-8040, hATG, cyclosporine, and methylprednisone in patients with AA or hypoplastic MDS

Secondary Objectives

- To assess the clinical efficacy (response rates) of the treatment with BL-8040, hATG, cyclosporine, and methylprednisolone in patients with AA or Hypoplastic MDS.
- To assess the time to response following treatment with the BL-8040 in addition to hATG, cyclosporine, and methylprednisolone.
- To assess the response duration and overall survival following treatment with the BL-8040 in addition to hATG, cyclosporine, and methylprednisolone.
- To assess the change in blood product requirements compared to Baseline (number of transfusions per month compared to Baseline)

Patient Selection

- **Patients with severe AA or hypoplastic MDS**
- **Age ≥ 18 years**
- **High risk for relapse defined as:**
  1st CR with high risk features for relapse
  2nd CR regardless of disease characteristics at the time of diagnosis.
- **Frontline or Relapsed after prior immunotherapy**
- **Adequate organ function; PS ≤ 2**

Treatment Plan

- **BL-8040 0.75 mg/kg/day SQ**
- **hATG 40 mg/kg/d IV for 4 days**
- **Methylprednisone 1mg/kg/day IV x 4 days, then prednisone taper PO over 4 weeks**
- **Cyclosporine 5 mg/kg/day (adjusted to cyclosporine level) PO for 6 months, followed by taper**

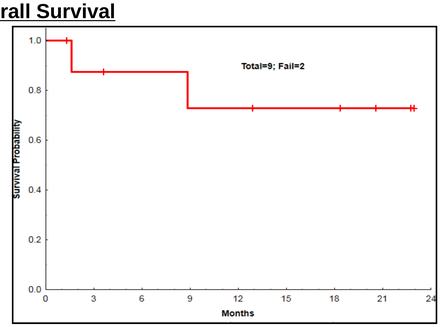
Results

Median follow-up = 21.9 Months (4.6 – 43.4)

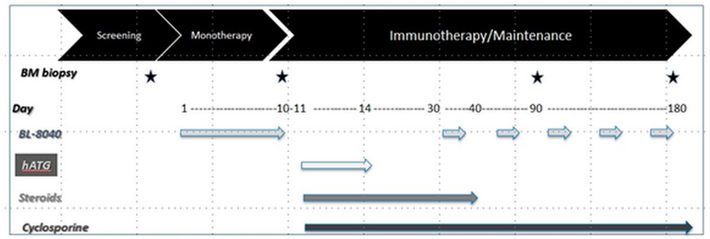
Patient Characteristics

Characteristic (N=9)	Median (range) or N [%]
Age	69 (23 - 75)
WBC [x10⁹/L]	2.9 (1.4 – 6.9)
Platelets [x10⁹/L]	21 (1 - 55)
Total Bilirubin	0.9 (0.4 – 3)
Creatinine	0.79 (0.74 – 0.97)
PNH Clone Detected	3 [33%]
T-cell Receptor Clonality	6 [67%]

Overall Survival

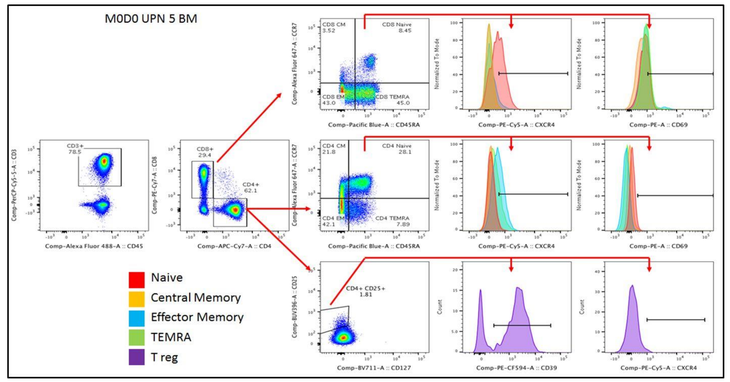


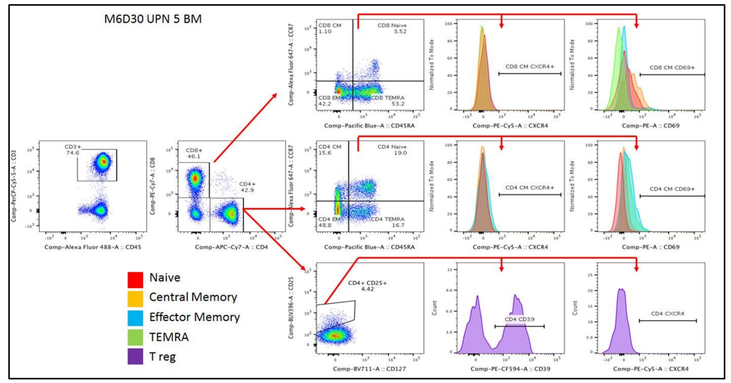
Treatment Schema

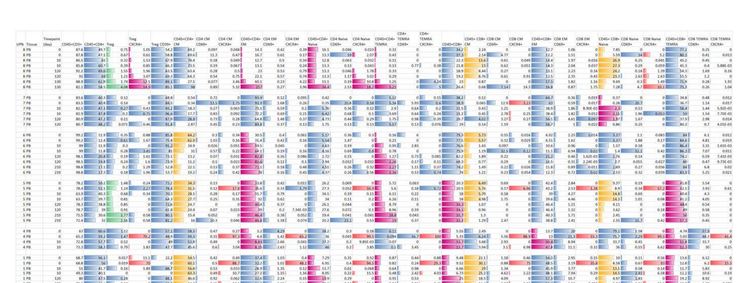


Individual Patient Data

No.	Age	Diagnosis	Mutations	Response	Courses (Months)	Toxicity	Status	Reason off Study
1	71	Aplastic Anemia	-	CR	6	Injection site Reaction	Off Study	Completed Therapy
2	73	MDS-U	*JAK2, RUNX1 TET2*	Not Evaluable	1	Eye Swelling, allergic reaction	Off Study	Reaction, Eye Swelling
3	24	Relapsed Aplastic Anemia	-	Not Evaluable	1	Allergic reaction	Off Study	Allergic Reaction to BL8040
4	70	Relapsed Aplastic Anemia	-	Not Evaluable	1	Allergic reaction to hATG test dose	Off Study	Reaction to hATG skin test
5	54	Relapsed Aplastic Anemia	-	CR	6	Injection site reaction; Headache	Off Study	Completed Therapy
6	68	Relapsed Aplastic Anemia	*DNMT3a*	NR	5		Off Study	No Response
7	60	Aplastic Anemia	-	NR	5	Injection site reaction	Off Study	No Response
8	75	Relapsed Aplastic Anemia	-	NR	3	Injection site reaction	Off Study	No Response
9	24	Aplastic Anemia	*PIGA BCORL1 ASXL1*	Early	2	Injection site reaction; Fever	Ongoing	-







Summary

- Early experience indicates that the addition of BL-8040 has been safe and feasible in patients with aplastic anemia and MDS

- There are encouraging signs of activity with 2 complete remissions - 1 in untreated AA and 1 in relapsed AA out of 5 evaluable patients. Time to response is about 6 months.

- Single-agent BL-8040 early in treatment does not appear to have an immediate effect on blood count recovery, but analysis of bone marrow progenitor proliferation is ongoing.

- Immune profiling of bone marrow and peripheral blood of patients during treatment show an increase in BM T-regs during treatment. There was also an increase in CD4+/CD45+ TEMRA T-cells in the marrow and peripheral blood; also with an increase of CD45+/CD8+ T-cells in the peripheral blood.

- There was decreased CXCR4 expression across T-cell subsets in the marrow and peripheral blood.

-Further analysis of immune trafficking and marrow progenitors is ongoing