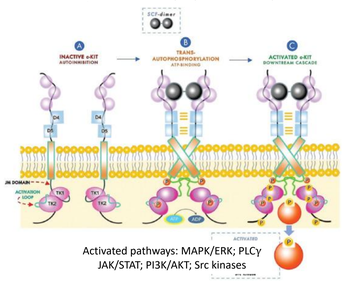
Adding CD117 antibody to alemtuzumab, low dose total body irradiation (TBI), and sirolimus for matched related donor (MRD) hematopoietic cell transplant (HCT) in sickle cell disease (SCD): initial results

Matthew Hsieh[1], Priscilla Pollack[1], Elizabeth Harvey[1], Triscia Martin[1], Neal Jeffries[2], Wendy Pang [3], and John Tisdale[1]

[1]Cellular and Molecular Therapeutics Branch, NHLBI, Bethesda, MD; [2]Office of Biostatistics Research, NHLBI; [3]Jasper Therapeutics, Redwood City, CA

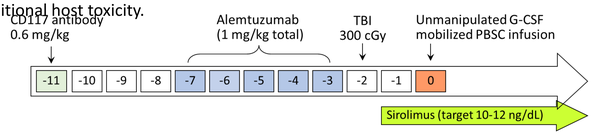
Introduction

- C-kit (CD117) is a transmembrane tyrosine kinase, type 3, receptor. It is expressed on normal and pathologic tissues/cells.
  - Normal: hematopoietic progenitor, mast, lymphoid, smooth muscle, vascular endothelium, skin, melanocyte, sweat gland, salivary gland, breast ductal epithelium, cerebellum, thyroid, spermatocyte, oocyte
  - Pathologic: myeloid leukemia, GIST, sarcoma, melanoma, germ cell tumors
- Stem cell factor (SCF) binds to CD117, and is a key cytokine important for survival, maintenance, and proliferation of HSC.



Activated pathways: MAPK/ERK; PLCγ
JAK/STAT; PI3K/AKT; Src kinases

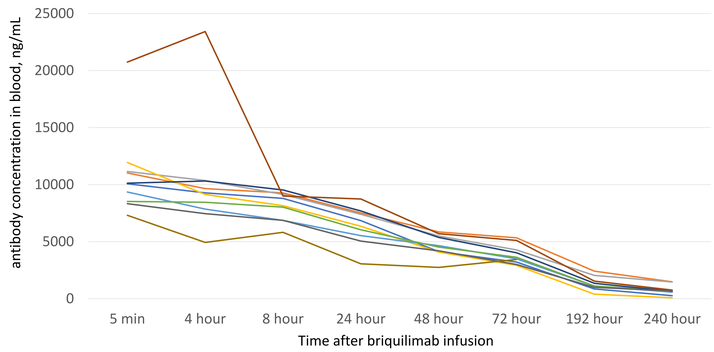
- Briquilimab (JSP191) is a naked, high affinity, monoclonal antibody that blocks SCF from binding to CD117.
- Preclinical data in murine transplant models showed CD117 antibody may synergize the cytotoxic effect of TBI and achieve more clearance of recipient hematopoietic niche.
- Briquilimab has been tested in two phase 1 and 2 studies: in severe combined immunodeficiency (NCT02963064, n=3) and in elderly MDS or AML (NCT04429191, n=28).
- Recent pharmacokinetic analyses of the single dose of 0.6 mg/kg was reported (Jung D, Long-Boyle JR et al, *TCT* 2024). The simulations predict that the number of days for 50% of individuals to reach <500, <1000, or <2000 ng/mL is 9.7, 8.3, and 6.2 respectively. These simulated window formed the basis for the briquilimab infusion schedule in the design of this conditioning regimen.
- We hypothesize that adding briquilimab to 300 cGy TBI would intensify this HCT regimen without additional host toxicity.



N=18	Baseline patient characteristics
Age, sex	5-38 years, 9M/9F
Sickle type	17 HbSS, 1 HbS/b0
Indication for transplant	Freq VOC, ACS (+multi-organ failure), sickle liver disease, elev right heart pressure (RVSP or TRV) on echo, priapism, or AVN
Co-morbidities	Hep C (treated), proteinuria, HTN, P A fib, 2° AV block, FEV1 or DLCO <66% pred, iron overload
wbc, plt	5-9k, 300-620k
hgb, retic count	8-10 g/dL, 150-700k
AST/ALT/t bili	Up to 2x ULN for AST and bilirubin
ferritin	126-3900
Cr	0.4-0.9

Results

- Donors were related family members, fully HLA-matched at A, B, C, DRB loci. Half of them have sickle trait.
- Donor HSC were collected by apheresis and cryopreserved, then thawed and infused on the day of infusion.
- 4 patients had grade 1 reaction possibly related to briquilimab infusion: two with headache, one with acne like rash, and one with fever.
- 13 patients had briquilimab level assayed. All were below the 1500 ng/mL threshold to proceed with HSC infusion as scheduled.
- The level of briquilimab at day -1 ranged from 20.6 to 1464 ng/mL.



- Lymphocyte counts decrease to undetectable level within 2 days of subcutaneous alemtuzumab administration.
- Reticulocyte counts declined and nadired first, at median day 8 (range 1 to 17).
- Neutrophil counts nadired at median day 13 (range 12 to 17). Filgrastim was used to boost neutrophil recovery starting near day 10.
- Platelet counts nadired at median day 17 (5 to 26). One-third of patients did not require platelet transfusion to keep counts >50 k/uL.
- All patients initially engrafted.
- All patients are alive. Median duration of follow-up is 310 days (range 8 to 771).

	Current HCT protocol	Prior alem-300 cGy TBI
Filgrastim mobilized periph blood HSC dose	10.8-20.4 x 10e6 CD34/kg 1.9-7.5 x 10e8 CD3/kg	7.14-41.2 x 10e6 CD34/kg 1.29-9.37 x 10e8 CD3/kg
Overall survival	18/18 (100%)	58/62 (94%)
Stopped immunosuppression	6/15 (40%)	52/54 (96%)
Neutrophil engraftment, median day	Median 13 (12 to 17), filgrastim boosted	22, not filgrastim boosted
Platelet engraftment, median day	17 (5 to 26)	19
GVHD	1 gr 2 GI aGVH, no chronic	No acute or chronic
CMV and EBV reactivation requiring treatment	CMV: 2 (11%) EBV: 0	CMV: 8 (13%) EBV: 2 (3%)
Graft failure	3/18 (17%)	9/62 (15%)

myeloid (CD14/15) chimerism

month	1	2	3	6	12	18	24
539-1	100	100	100	99	98		99
539-2	100	100	100	100	100		
539-3	100	100	100	100	100	100	
539-4	100 na		100	66	22	0	
539-5	100	33	0	0			
539-6	100	100	100	100	100	100	
539-7	100	100	100	100	100	100	
539-8	100	97	94	87	78		
539-9	100	100	100	100	100		
539-10	100	98	7	0			
539-11	100	100	100				
539-12	100	100	99	88			
539-13	100	100	99	97			
539-14	100	100	97				
539-15	100	100	100				
539-16	pending						
539-17	pending						
539-18	100						
539-19							
539-20							

Median myeloid chimerism at 3, 6, and 12 months were: 100%, 99.5%, and 100%

CD3 chimerism

month	1	2	3	6	12	18	24
539-1	2	3	0	25	55		61
539-2	na	10	26	63	86		
539-3	na	24	39	69	74	72	
539-4	na na		1	34	17	0	
539-5	na	na	0				
539-6	15	0	0	16	40	45	
539-7	12	3	7	36	70	77	
539-8	na	2	5	26	32		
539-9	na	22	6	45	37		
539-10	na	15	1				
539-11	na	3	12				
539-12	na	49	66	31			
539-13	na	na	34	28			
539-14	na	3	12				
539-15	na	na	58				
539-16	pending						
539-17	pending						
539-18	na						
539-19							
539-20							

Median CD3 (T cell) chimerism at 3, 6, and 12 months were: 12%, 32.5%, and 47.5%

Conclusions

- Briquilimab infusions are well tolerated with few low grade side effects.
- Results of briquilimab at day -1 suggests there was detectable antibody in the majority of patients at the time of HSC infusion, which did not appear to impact initial donor cell engraftment.
- The level of briquilimab at day -1 also did not correlate with graft failure.
- Compared to the prior protocol of alem-300 cGy TBI, this regimen was similar in
  - Baseline patient characteristics
  - Average/median myeloid and T cell chimerism at 3, 6, and 12 months
  - Transplant related viral reactivation or GVHD
  - Age, sex, CD34 or CD3 cell dose, ABO compatibility, CMV serology, presence or absence of HLA antibody before HCT – all of which did not correlate with graft failure
- Additional strategies aimed at both myelosuppression (clearing more hematopoietic niche) and lymphocyte depletion are needed to target full myeloid engraftment.

Acknowledgement

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