Immune Biomarkers Associated with Chronic GVHD in Phase 1 Study of Briquilimab (JSP191), an Anti-CD117 Monoclonal Antibody, in Combination with Low Dose Irradiation and Fludarabine Conditioning in Older Adults with MDS/AML Undergoing Allogeneic HCT

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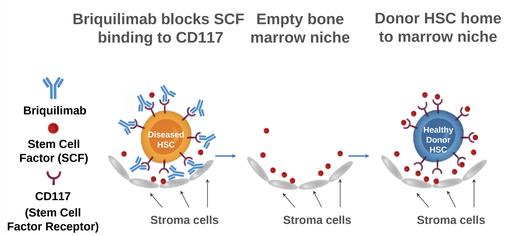
Background

Graft-versus-host disease (GVHD) is a major cause of non-relapse morbidity/mortality in allogeneic hematopoietic cell transplant (HCT). A phase 1 study (NCT#04429191) is currently evaluating the safety/activity of briquilimab, an anti-CD117 monoclonal antibody, in combination with low dose total body irradiation (TBI) and fludarabine (Flu) as conditioning in older adults with AML/MDS undergoing HCT. GVHD prophylaxis was sirolimus, tacrolimus, and mycophenolate mofetil (MMF), which when given with TBI/Flu has previously resulted in grade (gr) 2-4 acute GVHD (aGVHD) of 26% by transplant day (TD)+100 and chronic GVHD (cGVHD) of 49% (Sandmaier *et al*, 2019). Our objective was to perform exploratory analyses of lymphocyte and cytokine changes that may correlate with GVHD in briquilimab/TBI/Flu for HCT. Briquilimab, which targets hematopoietic stem cells for depletion by blocking CD117 signaling, is hypothesized to improve anti-leukemic efficacy while not increasing inflammation/toxicity from conditioning that may impact GVHD.

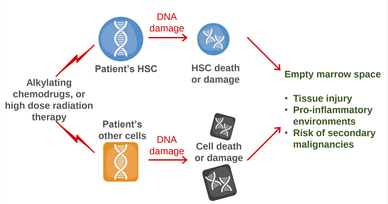
Briquilimab Binds to CD117 on HSCs and Depletes HSCs



- Stem Cell Factor (SCF) / Stem Cell Factor Receptor (CD117) interaction required for stem cell survival
- Briquilimab blocks SCF signaling leading to patient stem cell depletion from the bone marrow
- Allows for healthy donor stem cell engraftment

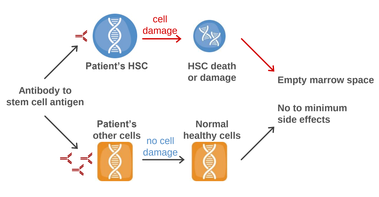
Toxic Myeloablative Conditioning Regimen Is an Obstacle for Transplant: Jasper Is Developing a Safer Alternative

Current transplant conditioning removes HSCs through highly toxic regimens



Marrow ablation by alkylating chemodrugs or high dose radiation therapy causes cell damage or death to other patient cells

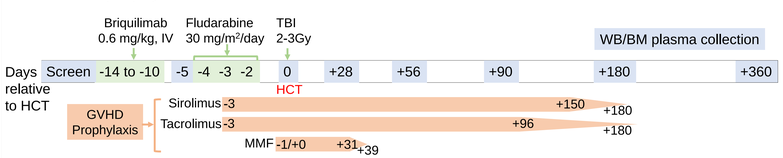
Briquilimab selectively targets HSCs: an alternative to toxic conditioning regimens



Using an antibody to stem cell antigen will limit extramedullary tissue damage seen with conventional genotoxic conditioning

Phase 1 Study in Older Adults with MDS/AML Undergoing Allogeneic HCT

- Briquilimab + low dose TBI + Flu conditioning
- GVHD prophylaxis: Sirolimus + Tacrolimus + MMF



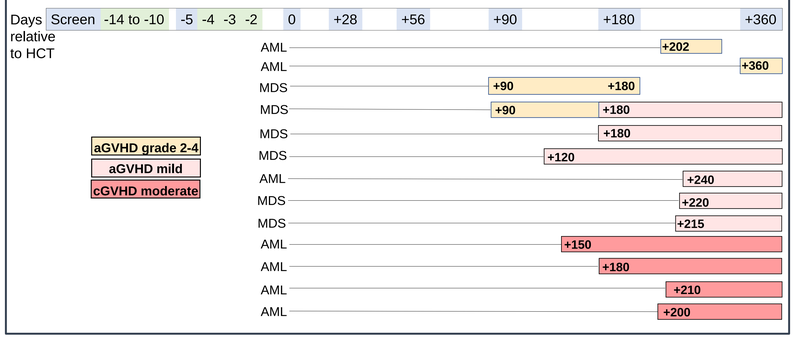
Exploratory objectives evaluating whole blood (WB) and bone marrow (BM) plasma:

- To monitor lymphocyte and cytokines changes in WB and BM plasma before and after HCT
- To Screen Immune biomarkers associated with cGVHD development

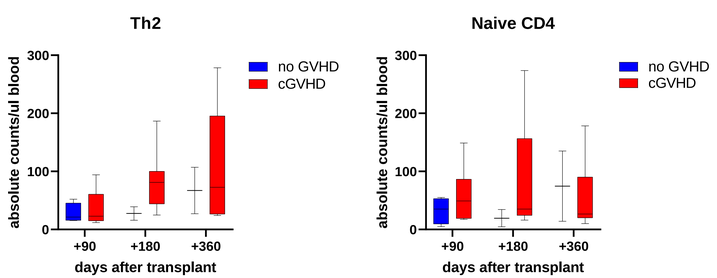
Characteristics of Subjects Assessed GVHD

Total (n=29) aGVHD and then cGVHD (n=1)	no GVHD (n=16)	acute GVHD grade 2-4 (n=4)	chronic GVHD mild (n=6)	chronic GVHD moderate (n=4)
Age (years)	69.5 ± 4.3	69.3 ± 4.1	71.8 ± 3.3	71.3 ± 6.4
Gender				
Female	6 (37.5%)	1 (25%)	1 (16.7%)	2 (50%)
Male	10 (62.5%)	3 (75%)	5 (83.3%)	2 (50%)
Donor type				
related	5 (31.2%)	1 (25%)	1 (16.7%)	0 (0%)
unrelated	11 (68.8%)	3 (75%)	5 (83.3%)	4 (100%)
Peripheral blood stem cell dose				
Total cells x 10^8/kg	537.3 ± 489.4	359.4 ± 497.7	186.8 ± 149.5	525.5 ± 615.0
CD34+ cells x 10^6/kg	6.0 ± 2.4	6.5 ± 1.3	6.4 ± 2.3	8.6 ± 1.7
CD3+ cells x 10^8/kg	2.5 ± 1.1	2.2 ± 0.8	1.9 ± 1.5	2.6 ± 1.5
Blood CD3 T cell chimerism at TD+180 (%) (Evaluable subjects)	78.0 ± 16.1 (n=10)	87.0 ± 17.4 (n=4)	84.5 ± 14.7 (n=6)	92.7 ± 7.5 (n=4)

GVHD Diagnosis Time and Duration of Each Subjects

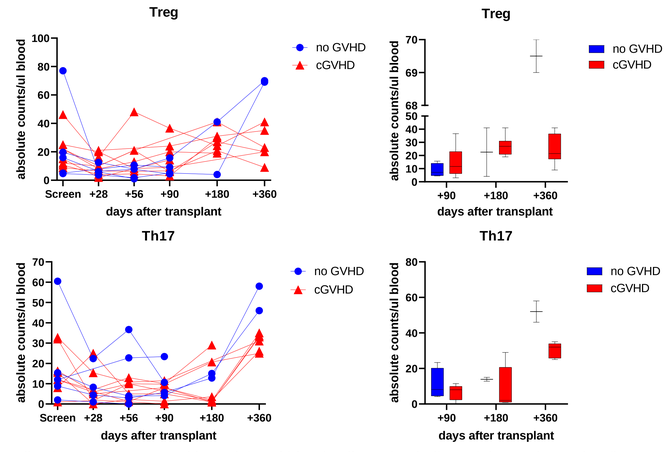


The Absolute Numbers of Th2 and Naive CD4 Cells Are Increased in Subjects with cGVHD Compared to Ones with No GVHD at TD+180



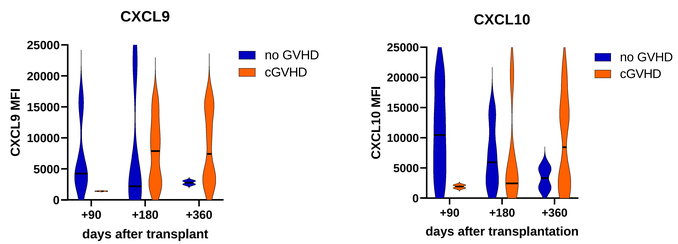
Each T cell subset was measured in peripheral blood collected at indicated time points using flow cytometry analysis and absolute lymphocyte counts obtained from CBC. *T helper 2 (Th2) cell defined by CD3+CD4+CXCR3-CCR4+CCR6- and Naive CD4+ cell by CD3+CD4+CCR7+CD45RA+ expression.

The Absolute Numbers of Treg and Th17 Cell Are Increased in Subjects with cGVHD Compared to Ones with no GVHD after Tapering GVHD Prophylaxis



Each T cell subset was measured in peripheral blood collected at indicated time points using flow cytometry analysis and absolute lymphocyte counts obtained from CBC. *Regulatory T (Treg) cell defined by CD3+CD4+CD25+CD127low and T helper 17 (Th17) cell by CD3+CD4+CXCR3CCR4+CCR6+ expression

The Trend of decrease in CXCL9 and CXCL10 Levels in Bone Marrow Plasma May Prevent cGVHD Development after Tapering GVHD Prophylaxis



The levels of CXCL9 and CXCL10 in BM plasma collected at indicated time points was measure by Multiplex Luminex bead array.

Summary

1. Addition of briquilimab to low dose TBI/Flu conditioning regimen with sirolimus/tacrolimus/MMF GVHD prophylaxis, does not appear to increase GVHD incidence relative to previously published rates.
2. Increased naive CD4+ T cells and Th2 cells in peripheral blood at TD+180 appear to be associated with cGVHD development in AML/MDS patients receiving briquilimab/TBI/Flu conditioned allogeneic HCT.
3. The trend of increase in CXCL9 and CXCL10 in the BM plasma may be associated with cGVHD development. Maintaining lower levels of CXCL9 and CXCL10 in the BM may prevent cGVHD development after tapering GVHD prophylaxis.

Acknowledgement

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