ASH 2023 abstract

Final Results from Phase 1 Study of Briquilimab, an Anti-CD117 Monoclonal Antibody, in Combination with Low Dose Irradiation and Fludarabine Conditioning, Shows Durable Remissions in Older Adults with Acute Myeloid Leukemia in Complete Remission and Myelodysplastic Syndrome Undergoing Allogeneic Hematopoietic Cell Transplantation

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Background: Allogeneic hematopoietic cell transplantation (HCT) with non-myeloablative conditioning (NMA) is a potential cure for AML and MDS in older/frail patients. NMA is associated with better tolerability but higher relapse rates compared to more intensive regimens. In a phase 1 study (NCT#04429191), briquilimab (JSP191), a first-in-class monoclonal antibody (mAb) that inhibits stem cell factor binding to CD117 (c-Kit) to deplete hematopoietic stem and progenitor cells (HSPC), in combination with standard NMA conditioning of low dose total body radiation (TBI) and fludarabine (Flu) for HCT, was evaluated in older adults with AML and MDS. Pre-clinical experiments suggest briquilimab synergizes with low dose TBI to deplete normal and malignant HSPC to facilitate donor cell engraftment. Final 1-year efficacy endpoints for all subjects enrolled in this study are presented.

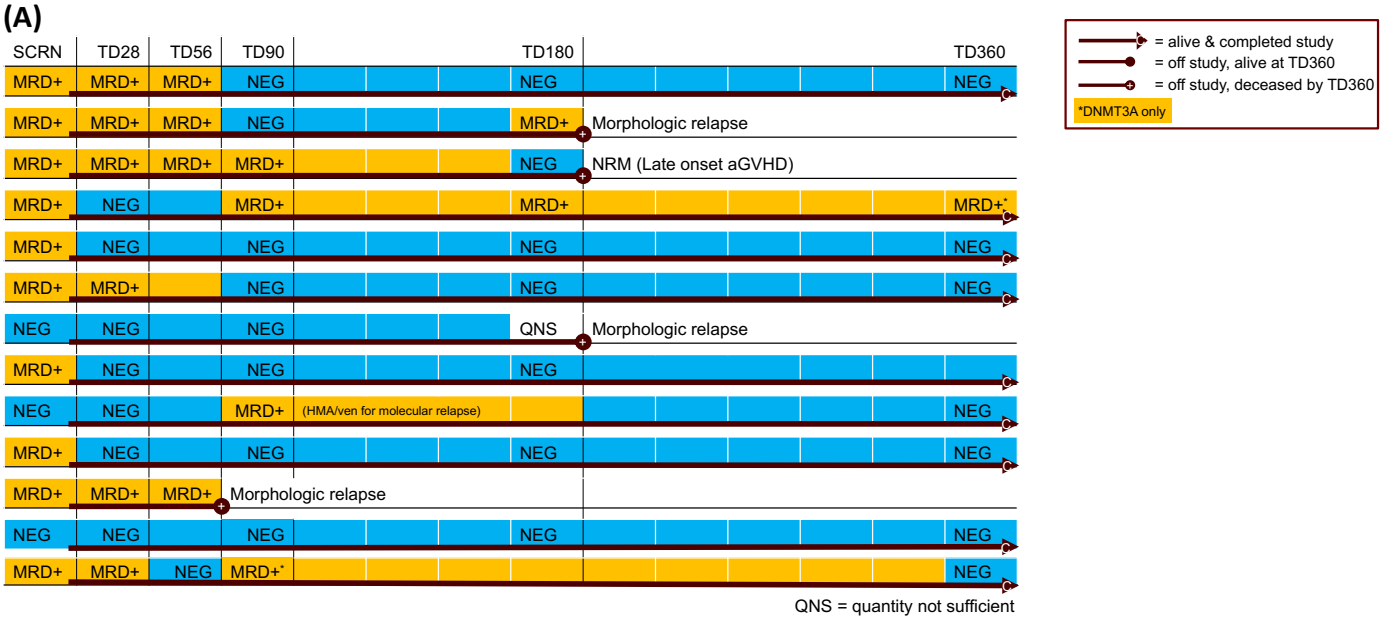
Methods: 32 subjects, median age 70 yrs (range 62-79), with AML in morphologic CR (CR1 or CR2+) (n=13), MDS (n=16), or AML not in CR (n =3), and HLA-matched related or unrelated donors were enrolled. Following infusion of briquilimab 0.6 mg/kg, serum levels were assessed to determine start of Flu at 30 mg/m^2/day on Transplant Day (TD)-4, -3, -2, and TBI 2-3 Gy on TD0. Peripheral blood grafts were infused on TD0 (10-14 days after JSP191). GVHD prophylaxis was tacrolimus, sirolimus, and mycophenolate mofetil. Primary endpoints were safety, tolerability, and briquilimab pharmacokinetics. Secondary endpoints included engraftment, chimerism, measurable residual disease (MRD) clearance, acute GVHD (aGVHD), chronic GVHD (cGVHD), NRM, RFS, and OS at 1 year.

Results: Summary of main efficacy outcomes is presented in Fig 1. 10 of 13 AML in CR and 14 of 16 MDS subjects had MRD at pre-HCT screening assessed by cytogenetics, flow cytometry, and/or next generation sequencing. There were no infusion toxicities and no briquilimab-related SAEs. Consistent with our previous reports, briquilimab exhibited predictable clearance prior to donor cell infusion, and all subjects engrafted, with neutrophil recovery between TD+19 and TD+26. Compared to baseline marrow, briquilimab alone depleted HSPC with a mean decrease of 62.4±22.7% prior to Flu/TBI (Fig 2). The 28 evaluable subjects at TD+90 achieved median donor myeloid chimerism of 99% (range 96-100%) and median total chimerism of 95% (range 81-100%). There was one secondary graft failure without relapse, who received a 2nd HCT. Among 13 AML in CR subjects, by 1 year, there were 3 relapses, 1 NRM (GVHD), 9 subjects were alive, and 8 were MRD negative. The 1 subject who was MRD positive at 1 year had only a detectable DNMT3A mutation at low level. 1 of 13 AML in CR subjects had TP53+ disease at screening and this subject was alive and MRD negative at 1 year post-AHCT. Among 16 MDS subjects, by 1 year, there were 5 disease progression/relapses, 1 subject withdrew consent due to persistent disease 3 months post-HCT, 1 NRM (sepsis), 8 subjects were alive, and 6 were MRD negative. 5 of 16 MDS subjects had TP53+ disease, 3 of whom had persistent disease/progressed/relapsed prior to 1 year post-HCT, and the other 2 of whom had MRD positive disease/molecular relapse at 1 year post-HCT. Median time to MRD negativity in all subjects who converted from MRD-positive disease to MRD-negative disease was TD+28. All 3 subjects with AML not in CR had disease progression before 4 months post-AHCT. There was no apparent correlation between level of HSPC depletion at the assessed timepoint (Fig 2) and relapse or survival. Of the 32 enrolled subjects, 4 had MAGIC Grade 2 aGVHD, 1 had MAGIC grade 3-4 aGVHD, 13 had mild/moderate cGVHD, and none had severe cGVHD.

Conclusions: These results demonstrate that targeting CD117 with briquilimab together with TBI/Flu as a novel conditioning regimen is safe, well-tolerated, facilitates full donor myeloid chimerism, and sustained clearance of MRD in older adults with AML in CR and MDS without TP53 undergoing NMA AHCT.

Fig 1. Summary of outcomes and MRD status of the 13 AML in CR (A) and 16 MDS (B) subjects enrolled.

(A)



(B)

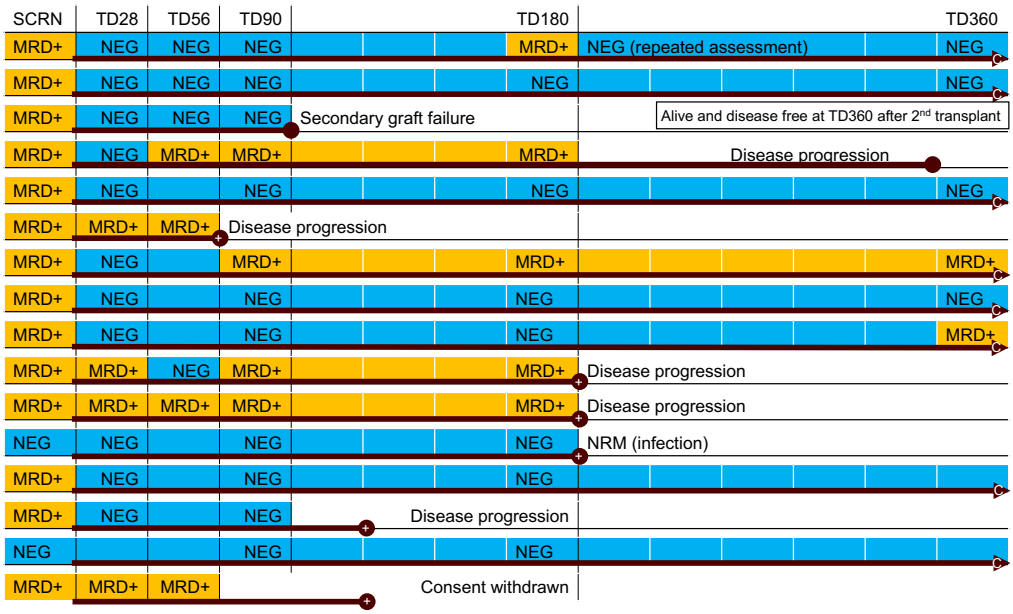


Fig 2. In consenting subjects from whom adequate bone marrow aspirate samples could be obtained, waterfall plot of percent depletion of HSPC (CD34+CD117+CD45RA-) in the bone marrow of individual subjects 5-7 days after briquilimab alone (prior to administration of Flu/TBI)