Phase II Clinical Trial of Abatacept for Acute Graft-versus-host Disease Prevention in Matched and Mismatched Unrelated Donor Hematopoietic Stem Cell Transplantation

Boston Children's Hospital & Bristol Myers Squibb, supported by the CIBMTR® (Center for International Blood and Marrow Transplant Research®): ABA2 Trial; Post-hoc Analysis

Highlights for Transplant Physicians:

Abatacept used with standard of care (SOC) acute graft-versus-host disease (aGVHD) prophylaxis reduces aGVHD and improves severe aGVHD-free survival (SGFS), especially in mismatched unrelated donor (MMUD) hematopoietic stem cell transplantation (HCT), showing promise as a tool to help expand access for those in need of transplant.

- This multi-center phase II clinical trial determined the efficacy of a T-cell costimulation blocker (abatacept) to reduce aGVHD in either 8/8 matched unrelated donors (MUD) or 7/8 MMUD considering matching at HLA-A, B, C, and DRB1. Approved by the FDA as the first drug directly indicated for aGVHD prophylaxis in combination with calcineurin/methotrexate (CNI/MTX) in adult and pediatric patients 2 years of age or older undergoing MUD or 7/8 MMUD HCT.
- Compared with CNI/MTX SOC alone, abatacept plus CNI/MTX significantly reduced severe aGVHD and increased SGFS, especially in cases of MMUD HCT.
- Additional post-hoc analysis shows the potential of abatacept to expand access of HCT to ethnically diverse patients who may not be able to find an 8/8 fully matched donor as easily as white patients.

Read the clinical trial results in the *Journal of Clinical Oncology* (DOI: 10.1200/JCO.20.01086) and the post-hoc analysis in *Blood Advances* (DOI: 10.1182/bloodadvances.2021005208). Also see the real-world CIBMTR analysis presented at the American Society of Hematology (ASH) annual meeting (DOI: 10.1182/blood-2021-150742) and news of the FDA approval in *JAMA* (DOI: 10.1001/jama.2021.24966).

Objectives and Rationale:

Severe aGVHD remains a significant cause of post-HCT mortality, especially in cases of mismatched HLA. Ethnically diverse or non-white patients are also less likely to have HLA fully matched HCT donors, adding to their barriers to transplant.

The primary objective of the *ABA2* clinical trial was to examine the efficacy of abatacept to reduce the cumulative incidence of severe aGVHD in MUD and MMUD HCT. The key secondary objective was to assess SGFS at 180 days.

The primary objective of the post-hoc analysis of *ABA2* was to further assess cumulative incidence of severe aGVHD in abatacept patients with MMUD to MUD SOC patients alone, with relapse-free survival (RFS) and SFGS as key secondary outcomes.

Design and Methods:

ABA2 was a multi-center, phase II clinical trial in subjects older than 6 years with a hematologic malignancy undergoing MUD or MMUD HCT. The two strata were a randomized, double-blind, placebo-controlled stratum of 8/8 MUD recipients, comparing CNI/MTX plus abatacept with CNI/MTX SOC, with a single-arm stratum of 7/8 MMUD comparing CNI/MTX plus abatacept versus CNI/MTX SOC within the CIBMTR database. Sample sizes were calculated using a higher Type-1 error based on the prediction that abatacept would reduce aGVHD from 20% to 10% in 8/8 MUD and 30% to 10% in 7/8 MMUD.

The post-hoc *ABA2* analysis compared outcomes in patients with 7/8 MMUD receiving abatacept plus CNI/MTX to patients with 8/8 MUD receiving CNI/MTX SOC alone.

Cumulative incidence of severe aGVHD at day 100 was examined in both analyses, with secondary outcomes including SGFS at day 180, RFS, GVHD-free (absence of severe acute or moderate-to-severe chronic GVHD)/Relapse Free-Survival (GRFS), and overall survival (OS). Median follow-up was 25 months among survivors.

Results:

ABA2 enrollment: N=142 8/8 MUD (median follow-up=716 days) and N=43 7/8 MMUD (median follow-up=708 days) aged ≥6 years old with hematologic malignancies undergoing MUD or MMUD HCT

Patients in the ***ABA2*** groups were well matched for age, gender, Karnofsky/Lansky performance score, disease, conditioning regimen, graft type, and SOC drug type.

- OS rates at day 180 post-transplant were 98% for patients treated with abatacept plus SOC and 75% for SOC only.
- In 7/8 MMUD patients, severe aGVHD (2.3% versus 30.2%, p<0.001) and SGFS (97.7% versus 58.7%, p<0.001) was significantly improved in the abatacept group compared to SOC group.
- In 8/8 MUD patients, decreased aGVHD (6.8% versus 14.8%, p=0.13) and SGFS (93.2% versus 82%, p=0.05) was also demonstrated.

Post-hoc analysis: N=43 MMUD abatacept plus SOC, N=69 MUD SOC only

In **post-hoc analysis**, recipient age, performance status, disease, disease stage, and conditioning intensity (myeloablative versus reduced intensity) were similar across the two groups.

- There were 30.2% non-White MMUD/abatacept patients compared to 11.6% non-White MUD/SOC patients.
- There were no differences in neutrophil or platelet engraftment, severe chronic GVHD, CMV or EBV viral infections, TRM, relapse, RFS, GRFS, and OS between the groups.
- Severe aGVHD (2.3% versus 14.8%) and SGFS (97.7% versus 82%) was significantly lower in the MMUD/abatacept group compared to MUD/SOC group.

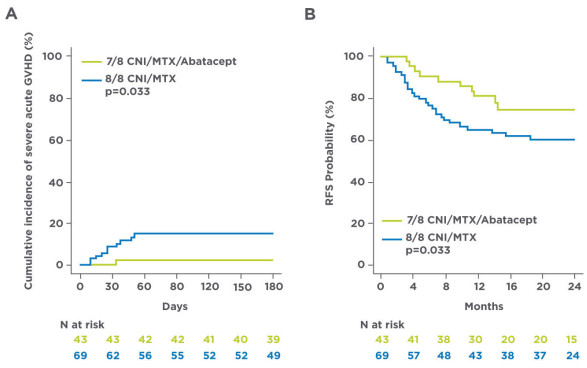

Figure 1. Used with permission from the *ABA2* study team.

Conclusions:

- **Abatacept was safe and effective in MUD and MMUD donor HCT, significantly improving patient outcomes when used with standard of care aGVHD prophylaxis.** This conclusion from the *ABA2* trial led to it becoming the first FDA-approved drug for aGVHD prevention.
- **Data suggest impressive outcomes in both MUD and MMUD HCT recipients, which can increase the safety and feasibility of HCT for all patients, especially those without matched donors.** The combined results suggest that the addition of abatacept to standard CNI/MTX mitigates the disadvantages of mismatching by greatly reducing the risks of severe aGVHD and non-relapse mortality without increasing the risk of relapse.
- **Abatacept limits disadvantages of MMUD HCT, providing more opportunities for ethnically diverse patients.** Ethnically diverse patients are less likely to have a fully matched donor available, and MMUD HCT is one way to help alleviate that disparity and expand access to care.

Advancing Practice and Improving Access

The National Marrow Donor Program® (NMDP)/Be The Match® alongside the CIBMTR is committed to expanding access to all patients in need of HCT. Our research programs are developing and evaluating novel treatment strategies, including abatacept, that allow for safe and effective use of MMUD. CIBMTR data supported the FDA approval of abatacept. Since *ABA2* showed little effect for chronic GVHD prophylaxis, future efforts to analyze the dosing of abatacept and its effects for chronic GVHD are in process with the interventional clinical trial *ABA3 (NCT04380740)*.

The data support that risks from MMUD HCT can be mitigated with the use of abatacept, which is a vital step toward expanding access for ethnically diverse patients. You can support your patient's journey both pre- and post-transplant by:

- Reviewing the clinical indications for abatacept for aGVHD prophylaxis
- Examining your center's protocols for MMUD HCT
- Considering abatacept as a tool to expand treatment for your ethnically diverse patients

References

ABA2 original publication: Watkins B, Qayed M, McCracken C, et al. Phase II trial of costimulation blockade with abatacept for prevention of acute GVHD. Journal of Clinical Oncology. 2021; 39(17): 1865-1877. DOI: 10.1200/JCO.20.01086

Post-hoc analysis: Qayed M, Watkins B, Gillespie S, et al. Abatacept for GVHD prophylaxis can reduce racial disparities by abrogating the impact of mismatching in unrelated donor stem cell transplantation. Blood Advances. 2022; 6(3): 746-749. DOI: 10.1182/bloodadvances.2021005208

Real-world data: Kean LS, Burns LJ, Kou TD, et al. Improved overall survival of patients treated with abatacept in combination with a calcineurin inhibitor and methotrexate following 7/8 HLA-matched unrelated allogeneic hematopoietic stem cell transplantation: Analysis of the Center for International Blood and Marrow Transplant Research Database. Blood. 2021; 138(Supplement 1): 3912-3912. DOI: 10.1182/blood-2021-150742

FDA approval news: Voelker R. Drug Approved to Prevent Graft-vs-Host Disease. JAMA. 2022; 327(5): 417. DOI: 10.1001/jama.2021.24966