BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Annual Report

May 2020 – April 2021

www.bmtctn.net

ABOUT THE BMT CTN

The BMT CTN conducts large, multi-institutional clinical trials to improve outcomes of cellular therapies, such as hematopoietic cell transplantation (HCT), for patients facing life-threatening disorders. Established in 2001, the BMT CTN infrastructure facilitates effective communication and cooperation among participating centers and collaborators to conduct multi-institutional trials available to patients in all regions of the United States (US).

OUR SIGNIFICANCE

Approximately **25,000** uses of cellular therapy for cancer are reported to the CIBMTR annually, and the number increases by about **5%** per year. Cellular therapy is a rapidly evolving field, and clinical trials face unique challenges, including the relatively small number of treatments performed at any single center, diverse indications for cellular therapy, complexities of the intervention, and multiple post-treatment complications.

BMT CTN Achievements

59 trials launched

44 trials completed accrual; 15 ongoing

>14,300 patients from >100 centers

113% accrual rate among trials currently open for enrollment

>498,000 biospecimens in the Research Sample Repository

134 ancillary and correlative studies launched

- **69 used cryopreserved specimens from the Repository or samples shipped directly to a project laboratory**

126 manuscripts published

124 abstracts presented

DATA AND COORDINATING CENTER (DCC)

The BMT CTN DCC is managed by **3** organizations with extensive cellular therapy research experience: the **Medical College of Wisconsin (MCW)**, the **National Marrow Donor Program® (NMDP)/Be The Match®**, and the **Emmes Company**.

The **MCW** is the **3rd** largest private medical school in the nation with **$1.6 billion** in research funding over the last 10 years. It is the original home of the International Bone Marrow Transplant Registry [now the **Center for International Blood and Marrow Transplant Research (CIBMTR)**, see below] and has a long history of research and clinical care related to HCT and other cellular therapies.

The **NMDP/Be The Match** is the world leader in HCT donor registry and graft procurement management, and it operates the world's largest HCT-related research sample repository.

Together, the **MCW** and **NMDP** operate the **CIBMTR,** an international research program with a network of **>300** centers in **>30** countries that submit cellular therapy outcomes data for patients, resulting in a research database with information from **>575,000** patients and **>1,500** publications.

The **Emmes Company** is a contract research organization that has managed **>2,000** Phase I-IV trials and registries involving **>25,000** research sites in **>75** countries on **6** continents.

The Data and Coordinating Center manages the efficient development, implementation, and completion of high-quality Phase II and III clinical trials for the Network.

RESPONSE TO COVID-19 PANDEMIC

This year the BMT CTN continued to address challenges related to managing clinical trials during the COVID-19 pandemic. The Network's dedicated investigators and staff continually assessed the situation, considering participant safety first and foremost. Deliberations included accrual and protocol adherence feasibility, study drug distribution, safety reporting, protocol variances, study lab assessment requirements, patient visit schedules, monitoring plans, and effects on study endpoints.

The BMT CTN re-opened all **8** studies that were temporarily suspended to accrual at the beginning of the pandemic. The DCC was in frequent communication with protocol teams and site investigators, sending **50** numbered memo communications related to the pandemic impact. Remarkably, accrual and performance thrived this year, with a current overall accrual rate that is **113%** of projections.

BIOSPECIMEN "SHIP FROM HOME" KITS

DCC personnel, working with investigators, developed "ship from home" kits and procedures, which allowed trial participants to collect stool and urine research samples at home and schedule an at-home FedEx pick-up for shipment directly to the BMT CTN Biorepository. The procedures reduced study patients' need to return to their clinical centers while continuing the collection of important research samples needed to meet scientific objectives of Network trials.

CLINICAL RESEARCH ASSOCIATE TRAINING

Clinical Research Associate training sessions are typically held in conjunction with the TCT Meetings. Because of the COVID-19 pandemic, the 2021 TCT Meetings were held virtually, and the BMT CTN held the 2021 Clinical Research Associate training via shorter virtual sessions throughout the year instead of a day-long session. These sessions cover data entry, quality control issues, and reviews of procedures and protocol requirements.

COVID-19 FUNDING TASK FORCE

At the start of the pandemic, the BMT CTN formed a COVID-19 Funding Task Force to evaluate potential sources of funding for COVID-19 initiatives given the impact of the pandemic on, and anticipated future changes for, conduct of Network studies. The Task Force met in June 2020 and determined there were no applicable National Institutes of Health (NIH) competitive or administrative COVID-19 supplements available for potential projects aligned with current BMT CTN studies.

The BMT CTN obtained funding for an observational study, conducted in collaboration with the CIBMTR, evaluating immune responses to COVID-19 vaccination (BMT CTN 2101 / CIBMTR SC21-07). Sponsors include the Be The Match Foundation, Leukemia and Lymphoma Society, Multiple Myeloma Research Foundation, American Society for Transplantation and Cellular Therapy, Fred Hutchinson Cancer Research Center, Labcorp, and Adaptive Biotechnologies. The NIH National Heart, Lung, and Blood Institute (NHLBI) also approved use of BMT CTN grant funds for this study.

REMOTE MONITORING VISITS

Data quality is critical to the BMT CTN's success and is an essential element for assessing transplant center performance. Interim monitoring visits are performed at actively enrolling centers at least once every three years. Since May 2020, all BMT CTN site visits have been conducted remotely, and the experience has largely been positive. As of January 2021, site visits may be conducted onsite if approved by BMT CTN leadership for clinical research associate safety and if the site is allowing onsite monitoring. The timeline for resuming all onsite visits and the future steady state mix of on-site versus remote visits are yet to be determined.

NETWORK MANAGEMENT HIGHLIGHTS

The DCC coordinates and supports all BMT CTN activities to enhance Network effectiveness. This year, the DCC managed **780** conference calls (mostly videoconferences), updated the Administrative Manual of Procedures, and launched a website redesign.

BIOSPECIMEN REPOSITORY

Each BMT CTN protocol creates an important opportunity for the scientific community to collect baseline and post-transplant / treatment biologic specimens for clinical research. For most protocols, biologic samples are collected for use in protocol-defined research. Collection of supplementary samples is also incorporated into most protocols for use in future research. These samples and the associated clinical data are made available as a valuable resource for investigators at large. BMT CTN research sample inventories continue to be regularly updated on the Network's public website to help investigators better utilize this resource.

Storing Samples. As of April 30, 2021, a total of **498,612** available research specimens, provided by **7,117** subjects, were stored by the BMT CTN Repository Network: NHLBI Repository, BMT CTN Sample Repository operated by NMDP/Be The Match, and the AIDS and Cancer Specimen Resource Repository.

Distributing Samples. This year, the BMT CTN shipped **9,440** frozen sample aliquots from its Sample Repository to project laboratories for protocol-defined and ancillary studies.

Processing Samples. The BMT CTN processing laboratory received and processed samples from **3,620** Network shipments this year, a notable increase from **1,314** shipments last year. In January - April 2021, the laboratory received approximately **420** shipments per month. Biorepository activity is steadily increasing this year due to the opening of several new studies, with the 1703/1801 trial being the highest contributor.

DATA COLLECTION AND REVIEW

BMT CTN clinical data are captured through either the Emmes proprietary eClinical system (or previous version, AdvantageEDC) or the CIBMTR Medidata Rave system. This year, participating centers submitted **45,809** forms in the Advantage EDC and eClinical systems and **6,466** forms in Medidata Rave.

The CIBMTR Research Database also captures clinical data via FormsNet3. For protocols that require only a limited amount of protocol-specific data, such as BMT CTN 1702, the CIBMTR Research Database is used as the primary study database. This year, participating centers submitted **4,791** forms in FormsNet3 for BMT CTN 1702. The CIBMTR Research Database is also used for supplemental data collection, especially long-term follow-up data.

After data collection is complete, most studies undergo endpoint review. Each protocol's Endpoint Review Committee provides an independent review of submitted data, in a blinded manner for randomized studies. This year, Endpoint Reviews were completed for **2** trials, increasing the total number to **25** protocols.

PATIENT-REPORTED OUTCOMES

The capability to centrally collect patient-reported outcomes data creates an important opportunity for the scientific community. These patient-reported outcomes data are linked to clinical and specimen data using patient IDs and are made available as a valuable resource for investigators at large. The CIBMTR Survey Research Group centrally collects patient-reported outcomes data for long-term follow-up of **4** ongoing and **2** upcoming BMT CTN studies. As of April 30, 2021, the Survey Research Group has collected data for **3,347** patient-reported outcomes time points from **1,494** participants of BMT CTN studies.

COMMITTEE ACTIVITIES

BIOMARKERS COMMITTEE

The Biomarkers Committee informs the Network's scientific agenda with a focus on questions involving analysis of biologic specimens for genomic and proteomic markers, and it advises Network protocol teams in their review of ancillary study proposals that request the use of BMT CTN research samples. This year, the Biomarkers Committee provided a technical review of BMT CTN 2002. Committee members also reviewed **6** laboratory study proposals submitted in response to the BMT CTN DCC's request for proposals utilizing biospecimens collected on BMT CTN 1202. All of the proposals were approved by the BMT CTN Executive Committee.

EVIDENCE INTO PRACTICE TASK FORCE

In August 2019, the BMT CTN launched a Task Force to address systematic dissemination and implementation of study results. This year, the Task Force published an introductory manuscript to encourage enrollment on the BMT CTN 1703 study (DeFilipp et al. Biology of Blood and Marrow Transplantation, 2020) and drafted a companion manuscript to the BMT CTN 1301 primary results manuscript. Additionally, the Task Force was charged with helping disseminate the BMT CTN 1102 primary results, which were presented at the 2020 American Society of Hematology Annual Meeting and 2021 TCT Meetings (Best Abstract). The Task Force drafted a companion manuscript to the 1102 primary results manuscript (Journal of Clinical Oncology, in press) and also prepared a slide deck to present to state oncology societies and patient advocacy groups. Task Force members will give these talks in the coming months and write a guest editorial in the Fall 2021 MDS Foundation newsletter.

SPECIAL POPULATIONS COMMITTEE

The Special Populations Committee ensures that children, women, and under-represented minority groups are considered for inclusion in all appropriate investigational protocols developed by the Network and makes recommendations to increase their participation. In early 2020, the Special Populations Committee was charged with evaluating the diversity of the BMT CTN Steering Committee participants and site investigators. The committee surveyed US transplant physicians and provided the results and their recommendations to the Steering Committee in January 2021 and Executive Committee in March 2021. The Executive Committee agreed with the recommendations and noted that several of these initiatives are already underway (noted with an asterisk).

Special Populations Committee Recommendations

Leverage virtual BMT CTN meetings to allow for diverse faculty to attend*

Invite diverse faculty to fill leadership roles*

Invite early career faculty to fill committee roles*

Instate regional representation to provide a facilitator in each location

Conduct a diversity, equity, and inclusion (DEI) survey at regular intervals

Share and/or collaborate with other societies on DEI initiatives

COMMITTEE ACTIVITIES

BMT CTN MYELOMA INTERGROUP

The BMT CTN Myeloma Intergroup develops a national scientific agenda for multiple myeloma transplant studies. This year the Intergroup provided input on study design and ancillary studies for the upcoming BMT CTN CAR T-cell studies for multiple myeloma patients (1901 and 1902). The Intergroup also holds an annual workshop on immune profiling and minimal residual disease in multiple myeloma. In December 2020, **>1,900** individuals attended. A summary of the workshop was submitted for publication.

PHARMACY COMMITTEE

The Pharmacy Committee reviews BMT CTN protocols for appropriate use and administration of pharmaceuticals. This year the Committee also started helping develop draft template chemotherapy and other medication risk language for upcoming study protocols and informed consent documents.

STATE OF THE SCIENCE SYMPOSIUM (SOSS) 2021

Given the COVID-19 pandemic impact, including the fact that the 2021 TCT meetings were virtual, the Symposium was delayed to March 10, 2021, and held as a one-day virtual event. The purpose of the 2021 Symposium was to identify clinical trial concepts that represent the most important issues facing the field, have the potential to change practice in a significant way, and require a multicenter network to be done effectively. **13** committees, involving **167** individuals, were convened to review the landscape. **11** focused on specific diseases or transplant-related strategies or complications; the other **2** – Clinical Trial Design and Disparities and Access – focused on themes that affect all BMT CTN trials.

Prior to the Symposium, the BMT CTN invited **22** external reviewers to participate and review concepts in the areas of their expertise. The concepts were also posted on online to solicit feedback from the HCT community at large. Based on external reviewer and online feedback, Symposium organizers (BMT CTN Executive Committee and Symposium Committee Chairs) selected **17** study concepts for presentation during the one-day virtual Symposium, followed by comments from the audience. There was considerable engagement during the event; **>200** questions were submitted by **450** attendees throughout the day. Immediately following the Symposium, participants submitted scores for each concept. The day after the Symposium, Committee Chairs and BMT CTN leadership team met to review the scores and prioritize the top studies. These 2021 priority concepts will serve as guidance for future studies. A manuscript describing the proceedings is drafted and will be published during the next reporting period.

COVID-19 VACCINATION STUDY

One of the concepts prioritized by the SOSS Committee on Infection and Immune Reconstitution was an assessment of COVID-19 vaccine response in recipients of cell therapies. Realizing the importance of this question to current care of patients, the BMT CTN felt that initiation could not wait until after the Symposium. CIBMTR leadership proposed that the study be conducted through the CIBMTR's existing observational infrastructure with the BMT CTN as a collaborator. The CIBMTR and BMT CTN formed a protocol team with representatives from both organizations in January 2021 and secured funding from multiple sources. The study team activated the study on April 16, 2021, an accelerated timeline made feasible because of collaboration with the CIBMTR. The study is being conducted under the CIBMTR's IRB-approved Research Database and Repository protocols, and most clinical data will come from routine CIBMTR data collection. However, the BMT CTN infrastructure facilitates specimen tracking and supplemental data collection to enhance efficiency and speed of activation.

STUDIES PRIORITIZED AT 2021 SOSS	
Committee	**Strategy**
Intervention Treatment Trials	
Graft-versus-Host Disease (GVHD)	Improve outcomes for acute gastrointestinal GVHD Minimize treatment toxicity for low risk acute GVHD Pre-emptive therapy of moderate to severe chronic GVHD
Infections / Immune Reconstitution	Safety of antibiotic de-escalation following initial fever
Late Effects / Quality of Life / Economics	Propranolol in patients undergoing autologous HCT
Lymphoid Malignancies	Upfront CAR-T for high risk mantle cell lymphoma Consolidation therapy in CAR-T incomplete responders with diffuse large B cell lymphoma
Myeloid Malignancies	Platform trial of acute myeloid leukemia maintenance therapy
Non-Malignant Disorders	Upfront alternative donor HCT for severe aplastic anemia
Optimal Donor and Graft Sources	Haploidentical vs unrelated donor transplantation with post-transplant cyclophosphamide
Pediatric Malignant Disease	A risk-based approach to optimize remission duration following CD19-CAR-Ts Cytokine-induced memory-like NK Cells to treat post-HCT myeloid relapse
Plasma Cell Disorders	Incorporating B cell maturation antigen (BCMA) CAR-T in high risk multiple myeloma
Observational Trials	
Comorbidity and Regimen-Related Toxicity	Limiting transplant associated chronic pulmonary toxicity
Hemoglobinopathies	Late effects after HCT for sickle cell disease
Infections / Immune Reconstitution	Prospective observational study of the immunogenicity of the available RNA vaccines after HCT or CAR-T therapy
Myeloid Malignancies	Prediction and biology of acute myeloid leukemia relapse after HCT

STUDIES IN PROGRESS

GVHD PREVENTION, TREATMENT, AND DISEASE BIOLOGY

BMT CTN 1703 / 1801 PROGRESS III

A randomized, multicenter, Phase III trial of tacrolimus / methotrexate versus post-transplant cyclophosphamide / tacrolimus / mycophenolate mofetil in non-myeloablative / reduced intensity conditioning allogeneic peripheral blood stem cell transplantation

Chairs: Javier Bolanos-Meade, Shernan Holtan

Primary Objective: Compare one-year GVHD-free, relapse-free survival as a time to event outcome between the two GVHD prophylaxis regimens

Accrual: **397** of 498 projected patients enrolled

See page 11 for BMT CTN 1801 Mi-Immune Companion Study.

BMT CTN 1705

A randomized, double-blind, placebo-controlled multicenter Phase III trial of alpha 1 - antitrypsin (AAT) combined with corticosteroids vs corticosteroids alone for the treatment of high risk acute graft-versus-host disease following allogeneic hematopoietic stem cell transplant

Chairs: Amin Alousi, John Magenau

Primary Objective: Compare the rate of complete response and partial response on day 28 post-randomization between AAT and corticosteroids versus placebo to match and corticosteroids in patients with high-risk acute GVHD

Accrual: **26** of 122 projected patients enrolled

RARE AND NON-MALIGNANT DISEASES

BMT CTN 1507

Reduced intensity conditioning for haploidentical bone marrow transplantation in patients with symptomatic sickle cell disease

Chairs: Robert Brodsky, Michael DeBaun, Adetola Kassim, Mark Walters

Primary Objective: Estimate event-free survival at 2 years after a reduced intensity conditioning regimen and HLA-haploidentical bone marrow transplantation in children with sickle cell disease and adults with severe sickle cell disease

Accrual: **59** of 80 projected patients enrolled (**44** of 40 adults and **15** of 40 children)

ITN077AI / BMT CTN 1905

(Lead group: Immune Tolerance Network)

A multicenter randomized controlled trial of best available therapy versus autologous hematopoietic stem cell transplant for treatment-resistant relapsing multiple sclerosis (MS)

Chairs: Jeffrey Cohen, George Georges, Paolo Muraro, Marcelo Pasquini

Primary Objective: Compare the efficacy, safety, immunologic effects, and cost-effectiveness of autologous HCT vs. best available therapy over 72 months in participants with relapsing MS and continued MS disease activity despite treatment with disease modifying therapies. The primary efficacy objective is to compare MS relapse-free survival, analyzed as time until MS relapse or death from any cause

Accrual: **2** of 156 projected patients enrolled

STUDIES IN PROGRESS

CONDITIONING REGIMENS / MAINTENANCE THERAPY

Alliance A051301 / BMT CTN 1201

(Lead group: The Alliance for Clinical Trials in Oncology)

A randomized double-blind Phase III study of ibrutinib during and following autologous stem cell transplantation versus placebo in patients with relapsed or refractory diffuse large B cell lymphoma (DLBCL) of the activated B cell subtype

Chairs: Charalambos Babis Andreadis, Timothy Fenske

Primary Objective: Compare progression-free survival at 2 years in patients with non-germinal cell B-cell-like DLBCL between patients who receive ibrutinib during and following autologous HCT versus those who receive placebo during and following autologous HCT

Accrual: **82** of 296 projected patients enrolled

ECOG-ACRIN EA4151 / BMT CTN 1601

(Lead group: ECOG-ACRIN Cancer Research Group)

A randomized Phase III trial of consolidation with autologous hematopoietic cell transplantation followed by maintenance rituximab vs. maintenance rituximab alone for patients with mantle cell lymphoma in minimal residual disease-negative first complete remission

Chairs: Timothy Fenske, Brad Kahl, Matthew Lunning

Primary Objective: Compare overall survival in mantle cell lymphoma patients in minimal residual disease-negative first complete remission who undergo autologous HCT followed by maintenance rituximab vs. maintenance rituximab alone (without autologous HCT

Accrual: **367** of 689 projected patients enrolled

SWOG S1803 / BMT CTN 1706

(Lead group: SWOG Cancer Research Network)

Phase III study of daratumumab / rHuPH20 (NSC-810307) + lenalidomide or lenalidomide as post-autologous stem cell transplant maintenance therapy in patients with multiple myeloma using minimal residual disease to direct therapy duration

Chairs: Amrita Krishnan, Parameswaran Hari

Primary Objective: Compare overall survival between the 2 treatment arms with lenalidomide as the comparator arm and lenalidomide + daratumumab / rHuPH20 as the experimental arm in post-autologous transplant multiple myeloma patients

Accrual: **404** of 1,100 projected patients enrolled

GRAFT SOURCES

BMT CTN 1702 CTRL-ALT-D

Clinical transplant-related long-term outcomes of alternative donor allogeneic transplantation

Chairs: Stefan Ciurea, Stephanie Lee

Primary Objective: Estimate and compare overall survival between the 2 arms: Patients who are very likely to find a matched unrelated donor versus those who are very unlikely to find one

Accrual: **1,058** of 1,732 projected patients enrolled

STUDIES IN PROGRESS

DISEASE BIOLOGY

BMT CTN 1704 CHARM

Composite health assessment risk model for older adults: Applying pre-transplant comorbidity, geriatric assessment, and biomarkers to predict non-relapse mortality after allogeneic transplantation

Chairs: Andrew Artz, Mohamed Sorror

Primary Objective: Determine the set of assessments and biomarkers that could together constitute a robust and valid composite health risk model for accurate personalized estimation of 1-year non-relapse mortality

Accrual: **922** of 1,100 projected patients enrolled

BMT CTN 1801 Mi-Immune Companion Study

Microbiome and immune reconstitution in cellular therapies and hematopoietic stem cell transplantation

Companion study to BMT CTN 1703

Chairs: Ami Bhatt, Leslie Kean, Miguel-Angel Perales

Primary Objective: Test whether the engraftment stool microbiome diversity predicts 1-year non-relapse mortality in patients undergoing reduced-intensity allogeneic HCT

Accrual: **289** of 300 projected patients enrolled

BMT CTN 2101 / CIBMTR SC21-07

Prospective observational study of the immunogenicity of vaccines for severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) after autologous HCT, allogeneic HCT, and chimeric antigen receptor T-cell therapy

Chairs: Joshua Hill, Miguel-Angel Perales, Marcie Riches

Primary Objective: Compare the immunogenicity of SARS-CoV-2 vaccines at 7-35 days after the second vaccine dose (or 14-35 days after a single dose vaccine) in patients starting their vaccination course less than 6 months after HCT or CAR T-cell therapy versus those starting their vaccination course 6-12 months after therapy in three strata defined by type of therapy: Autologous HCT recipients, allogeneic HCT recipients, and CAR T-cell recipients. Immunogenicity is defined as a ≥4- fold rise in SARS-CoV-2 binding antibody titers to the spike protein receptor-binding domain compared to the pre-vaccine #1 titers by enzyme-linked immunosorbent assay (ELISA)

Accrual: **4** of 732 projected patients enrolled

UPCOMING STUDIES

CELLULAR AND GENE THERAPY

BMT CTN 1902

Phase II multicenter trial of anti-B cell maturation antigen (BCMA) chimeric antigen receptor T cell therapy for multiple myeloma patients with sub-optimal response after autologous hematopoietic cell transplantation and maintenance lenalidomide

Chairs: Alfred Garfall, Sergio Giralt

Primary Objective: Evaluate the efficacy of BCMA CAR T-cell therapy to improve the response in patients who received an upfront autologous HCT and lenalidomide maintenance

Target Accrual: **40** patients

BMT CTN 1903 Auto-RESIST

Administration of HIV-specific T cells to HIV+ patients receiving high dose chemotherapy followed by autologous stem cell rescue

Chairs: Richard Ambinder, Kieron Dunleavy

Primary Objective: Determine the proportion of participants who can be treated with HIV antigen-specific T-cells Targeting Conserved Epitopes (HST-NEETs) within 1 week of autologous HCT in a cooperative multi-institutional setting and the efficacy of HST-NEETs in reducing the HIV intact proviral reservoir at 6 months after autologous HCT

Target Accrual: **12** patients

BMT CTN 2001

A multi-center, Phase 2 gene transfer study inducing fetal hemoglobin in sickle cell disease

Chairs: David Williams, Mark Walters

Primary Objective: Determine if treatment with a single infusion of autologous CD34+ HSC cells transduced with the lentiviral vector containing shmiR targeting BCL11A will lead to a complete absence of severe vaso-occlusive events in the period from month 6 to month 24 after gene therapy

Target Accrual: **25** patients

STUDIES CLOSED TO ACCRUAL THIS YEAR

BMT CTN 1502: CHAMP

Optimizing haploidentical aplastic anemia transplantation

Chairs: Amy DeZern, Michael Pulsipher

Primary Objective: To assess overall survival at one-year post-HCT from a haploidentical marrow donor in patients with severe aplastic anemia

Accrual: **32** of 30 projected patients enrolled

Key Highlights: Accrual on this protocol remained open despite the COVID-19 pandemic. Sites were notified that all study activities should continue to the extent possible as allowed by centers' local policies and, for assessments after day 100, telehealth visits can be substituted for in-person visits that do not require lab draws. Accrual completed in August of 2020. All patients will complete follow-up by August 2021, and a request for endpoint review will be reviewed by the Data and Safety Monitoring Board in June 2020.

BMT CTN 1503

A study to compare bone marrow transplantation to standard care in adolescents and young adults with severe sickle cell disease

Chairs: Lakshmanan Krishnamurti, Mark Walters

Primary Objective: To compare overall survival at 2 years after biological assignment between the donor and no donor arms. Those assigned to the donor arm are expected to undergo HCT while those on the no donor arm are expected to receive standard of care supportive therapy

Accrual: **138** of 200 projected patients enrolled

Key Highlights: Accrual continued to lag this reporting period despite continued efforts by the protocol team to address accrual barriers. The 1503 protocol team, in agreement with the Data and Safety Monitoring Board and DCC / NIH Leadership, closed the study to accrual on October 30, 2020. Participants that consented on or before October 30, 2020, were permitted to enroll. Although this study will not meet the primary endpoint, the study team will focus on secondary endpoints and long-term follow-up to address important secondary endpoints.

BMT CTN 1802

An open-label, single-arm, multicenter study of combination anti-CD3/CD7 immunotoxin (T-Guard) for steroid-refractory acute graft-versus-host disease

Chairs: John Levine, Gabrielle Meyers

Primary Objective: To assess the rate of day 28 complete response in steroid refractory - acute GVHD patients treated with T-Guard therapy

Accrual: **3** of 47 projected patients enrolled

Key Highlights: The study was first approved by the Data and Safety Monitoring Board in June 2019. It was released to sites in August 2019 and opened to accrual in November 2019. There are 24 sites selected for participation with 5 centers activated for enrollment.

Three patients were enrolled on the 1802 study, but all died within 30 days of treatment. The Network paused accrual and, subsequently, the US Food and Drug Administration placed the study on Full Clinical Hold on February 26, 2020, for toxicity. The Data and Safety Monitoring Board determined accrual should not resume on the 1802 protocol, and the protocol was closed. A revised protocol (2002) addressing the safety concerns and broadening to a Phase III randomized study design was developed. The Food and Drug Administration approved the revised protocol and lifted the investigational new drug clinical hold on April 21, 2021.

RESEARCH FINDINGS THIS YEAR

Significant Findings of BMT CTN Studies this Year	
GVHD BIOLOGY, PREVENTION, TREATMENT, AND BIOMARKERS	
0402: A Phase III randomized, multicenter trial comparing sirolimus / tacrolimus with tacrolimus / methotrexate as **graft-versus-host disease prophylaxis** after HLA-matched, related peripheral blood stem cell transplantation	
Results:	Identified a high risk of toxicity when sirolimus is substituted for standard methotrexate for GVHD prophylaxis when the conditioning regimen includes busulfan; regardless of conditioning regimen, there was **no advantage in acute GVHD-free survival.**
Impact / Future Outlook:	**This year a design paper was published introducing formulas for sample size and power determination for testing parameters in generalized linear, Cox, and Fine-Gray models accounting for correlation between a main effect and other covariates. Extensive simulations demonstrated this method produced studies appropriately sized to meet their type I error rate and power specifications, particularly offering accurate sample size / power estimation in the presence of correlated covariates. These formulas have been applied with increased frequency, e.g. BMT CTN 1102, 1703, and 1705.**
Highlighted Publication:	A unified approach to sample size and power determination for testing parameters in generalized linear and time-to-event regression models. Statistics in Medicine. 2021 Feb 28; 40(5):1121-1132. Epub 2020 Nov 18.
1501: Randomized, Phase II, multicenter, open label, study **evaluating sirolimus and prednisone in patients with** refined Minnesota standard risk, Ann Arbor 1/2 confirmed **acute GVHD**	
Results:	Demonstrated **similar overall initial treatment efficacy between single agent sirolimus and single agent prednisone for patients with clinical- and biomarker-based standard risk acute GVHD**. Also found that sirolimus therapy spares steroid exposure and allied toxicity, does not compromise long-term survival outcomes, and is associated with improved patient-reported quality of life, underscoring the importance of secondary objectives.
Impact / Future Outlook:	This randomized Phase II trial estimating the difference in day 28 complete and partial response rates for sirolimus vs. prednisone as initial treatment of patients with standard risk acute GVHD **successfully used the Minnesota GVHD Risk Score in conjunction with the Ann Arbor (AA1/2) biomarker status to stratify risk and determine patient treatment pathway. This led to a revision of the National Comprehensive Cancer Network guidelines (Verson 2.2021) to include sirolimus as an option for initial treatment of standard risk acute GVHD.** The continued study of outcomes associated with biomarkers and search for other acute GVHD therapy options is being evaluated in two current BMT CTN studies for patients with higher-risk acute GVHD (BMT CTN 1705 and 2002).
Highlighted Publications:	Randomized multicenter trial of sirolimus vs. prednisone as initial therapy for standard risk acute GVHD: BMT CTN 1501. Blood. 2020 Jan 9; 135(2):97-107. Factors associated with successful discontinuation of immune suppression after allogeneic HCT. JAMA Oncology. 2020 Jan 1; 6(1): e192974. Epub 2019 Sep 26.

Significant Findings of BMT CTN Studies this Year	
GRAFT SOURCES	
1101: Phase III, randomized trial of reduced intensity conditioning and **transplantation of double unrelated umbilical cord blood versus HLA-haploidentical related bone marrow** for hematologic malignancies	
Results:	Demonstrated **similar progression-free survival (the primary endpoint) in adults receiving double cord blood or haploidentical bone marrow transplants** for hematologic malignancy after reduced intensity conditioning. Transplant-related mortality was lower and overall survival higher with haploidentical donors.
Impact / Future Outlook:	Although both donor sources extend access to reduced-intensity transplantation, analysis of **secondary endpoints, including overall survival, favor haploidentical donors support the increasing use of haploidentical donors**, using the post-transplant cyclophosphamide GVHD prevention platform, for allogeneic transplantation. This platform is now being tested in the HLA-mismatched unrelated donor setting. The ability to use diverse, mismatched donors successfully means that patients should no longer be denied access to transplantation on the basis of donor availability.
Highlighted Publication:	Double unrelated umbilical cord blood vs HLA-haploidentical bone marrow transplantation (BMT CTN 1101). Blood. 2021 Jan 21; 137(3):420-428. Epub 2020 Aug 31.
CONDITIONING REGIMENS / INTENSITY	
0901: A randomized, multi-center Phase III study of allogeneic stem cell transplantation comparing **regimen intensity** in patients with myelodysplastic syndrome or acute myeloid leukemia	
Results:	Found that **reduced-intensity conditioning results in lower treatment-related mortality but higher relapse rates and lower disease-free survival rates** compared to myeloablative conditioning among adults receiving HLA-matched HCT.
Impact / Future Outlook:	The data from this trial **support myeloablative conditioning as the standard of care for patients who are able to receive it**. A published ancillary study also provided evidence that myeloablative conditioning improves disease control and survival, particularly for AML patients with genomic evidence of minimal residual disease before transplant. Likewise, a long-term follow-up analysis published during this reporting period **demonstrated a survival advantage for patients who received myeloablative conditioning.** For patients who are not candidates for myeloablative conditioning, novel regimens that incorporate strategies to enhance anti-leukemia activity without increasing toxicity are needed. One such regimen of maintenance therapy post-HCT for FLT3-positive AML patients is being evaluated in BMT CTN 1506, which completed accrual in February 2020.
Highlighted Publications:	Myeloablative vs. reduced-intensity HCT for AML and MDS. Journal of Clinical Oncology. 2017 Apr 10; 35(11):1154-1161. Epub 2017 Feb 13. Impact of conditioning intensity of allogeneic HCT for AML with genomic evidence of residual disease. Journal of Clinical Oncology. 2020 Apr20; 38(12):1273-1283. Epub 2019 Dec 20. Myeloablative vs RIC for HCT in AML and MDS – Long-term follow-up of the BMT CTN 0901 clinical trial. Transplantation and Cellular Therapy. 2021 Feb 26; S2666-6367(21)00718-1. [Epub ahead of print]

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