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

May 2022 – April 2023

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 **30,000** 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

62 trials launched

52 trials completed accrual; 10 ongoing

>16,750 patients from >100 centers

~532,000 biospecimens in the Research Sample Repository

165 ancillary and correlative studies launched

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

101 ancillary and correlative studies completed

160 manuscripts published

149 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 **$1.8 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 **375** centers in **>35** countries that submit cellular therapy outcomes data for patients, resulting in a research database with information from **>650,000** patients and **>1,750** publications.

The **Emmes Company** is a contract research organization that has managed **>2,000** Phase I-IV trials and registries involving **>30,000** 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.

NETWORK MANAGEMENT HIGHLIGHTS

The DCC coordinates and supports all BMT CTN activities to enhance Network effectiveness. This year, the DCC managed **445** conference calls, posted **5** plain language summaries of BMT CTN manuscripts, and launched its redesigned website, which averaged **>3,000** visitors per month. This year, the BMT CTN released an updated version of the Administrative Manual of Procedures and replaced the Technical Manual of Procedures with **3** Technical Documents: GVHD, Infectious Diseases, and Patient-Reported Outcomes (PRO).

BIOSPECIMEN REPOSITORY

Each BMT CTN protocol creates an important new opportunity for the scientific community to collect baseline and post-treatment biologic specimens for clinical research. For most protocols, biologic samples are collected for use in protocol-defined research aimed at answering specific questions for that patient population and its transplantation outcomes. Collection of supplementary samples for future unspecified research is incorporated into most protocols. These samples and the associated clinical data are made available as a valuable resource for investigators at large. Available BMT CTN research sample inventories are regularly updated in the Investigator & Research Staff Resources section of the Network's public website to help investigators plan correlative studies.

Storing Samples. As of April 30, 2023, a total of **532,125** available research specimens, provided by **8,012** subjects, were stored by the BMT CTN Network: National Heart, Lung, and Blood Institute 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 **17,955** frozen sample aliquots from its Sample Repository to **15** project laboratories for protocol-defined and ancillary studies.

Processing Samples. The BMT CTN processing laboratory received and processed samples from **857** Network shipments this year, averaging **45** shipments per month. Biorepository activity decreased from the previous reporting period due to the conclusion of high-accruing protocols, including BMT CTN 1703 / 1801 and 2101.

DATA COLLECTION AND REVIEW

BMT CTN clinical data are captured through the Emmes proprietary eClinical system (or previous version, AdvantageEDC) or the CIBMTR Medidata Rave system. This year, participating centers submitted **19,986** forms in the Advantage EDC and eClinical systems and **3,199** 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 **1,838** forms in FormsNet for BMT CTN 1702. The CIBMTR Research Database is also used for supplemental data collection, especially long-term follow-up.

After data collection is complete, the protocol's Endpoint Review Committee provides an independent review of submitted data in a blinded manner. This year, BMT CTN 1506 and 1703 underwent endpoint review, increasing the total number of completed reviews to **28**.

PATIENT-REPORTED OUTCOMES

The capability to centrally collect patient-reported outcomes data creates an important opportunity for the scientific community. These data are linked to clinical and specimen data using patient IDs and are made available as a valuable resource for investigators at large. As of April 30, 2023, the Survey Research Group has collected data for **5,966** patient-reported outcomes time points from **2,385** participants of BMT CTN studies.

NETWORK MANAGEMENT HIGHLIGHTS

COMMUNICATING TRIAL RESULTS

In 2019, the BMT CTN launched a Task Force to promote translation of evidence into practice. This year, the Task Force reached out to the National Comprehensive Care Network and the American Society for Transplantation and Cellular Therapy to request an update to their practice guidelines, which were updated in January 2022 and November 2022, respectively. The Task Force was also asked to write a companion manuscript to the 1301 primary results manuscript on interpreting the trial results, which was published in May 2022. Additionally, the Task Force presented a summary of their work and future recommendations to the BMT CTN Steering Committee in August 2022, after which a standing Dissemination and Implementation Committee was formed (page 6). The Task Force's capstone effort was an article on improving the translation of new evidence into practice of HCT and cellular therapy, published in April 2023.

RECRUITMENT OF PATIENTS FROM UNDER-REPRESENTED GROUPS

The BMT CTN is committed to the ethical conduct of research involving all eligible patients, including women, racial and ethnic minorities, and children. In 2019 and 2020, the BMT CTN tasked two different committees with considering diversity, equity, and inclusion issues specific to the Network and making recommendations for improvement. The first was the standing Special Populations Committee, whose purpose and achievements this year are described on page 7. The BMT CTN also added a Committee on Disparities and Access to its State of the Science Symposium (SOSS, page 9).

The Disparities in Access Committee's final recommendation, to identify opportunities to increase accrual diversity, was addressed by the Patient Advocacy Task Force, which was established in April 2021. Among other responsibilities, the Task Force was asked to consider how patients / patient advocates can reduce barriers to participation and promote equity. Based on the Task Force's recommendations, a new Patient and Caregiver Advocacy Committee was instituted during this reporting period to address these and other issues (page 8).

The following specific action items have been or will be implemented to address this issue:

Action Items for Recruitment of Patients from Under-Represented Groups

- **Consider diversity and geographic representation in appointments to BMT CTN leadership positions and committees**
- **Extend invitations to diverse members of participating HCT centers to attend meetings of the Steering Committee**
- **Reassess diversity of leadership and committees and faculty engagement through periodic surveys**
- **Incorporate diversity recruitment sections into all accrual plans as part of protocol development and routinely monitor accrual by race / ethnic group**
- **Assess the diversity of the patient population in sites selected for future protocols**
- **Provide supplemental accrual credit and reimbursement for minority enrollment**
- **Further analyze barriers to access considering geographic area, disease incidence, and socioeconomics**
- **Collaborate with patient advocacy groups and professional societies to increase patient engagement from diverse communities**

All these action items have been or will be implemented.

COMMITTEE ACTIVITIES

DISSEMINATION AND IMPLEMENTATION COMMITTEE

Dissemination and implementation science is an emerging field in medicine requiring knowledge and skills beyond the scope of most Network protocol teams. It focuses on barriers to the translation of research findings to clinical practice. In 2019, the BMT CTN launched an Evidence into Practice Task Force to evaluate translation of BMT CTN study results into clinical practice. In August 2022, they presented to the BMT CTN Steering Committee their summary, which included the recommendation to form a standing BMT CTN Dissemination and Implementation Committee. The Steering Committee agreed to create a standing technical committee to address dissemination and implementation of results in a systemic way. Committee nominations were solicited in the fall of 2022, and the first call was held in December 2022.

Dissemination and Implementation Committee Responsibilities

Educate BMT CTN stakeholders

Help develop and review protocols to incorporate implementation outcomes in study design and target stakeholders for dissemination

Identify potential challenges to and assessment of implementation

Support dissemination and implementation strategies, particularly to address healthcare inequalities

Assess protocol finding implementation on healthcare inequities

Define evaluation metrics for dissemination and implementation strategies

The purpose of the Dissemination and Implementation Committee is to incorporate the principles of implementation science into the scientific agenda of the BMT CTN Network to promote the uptake of evidence-based findings from BMT CTN studies into routine practice to amplify the Network's impact on patient care.

The Committee convened monthly, drafted a Charter, and identified two priority projects for the upcoming year. The first will deploy a survey to understand the status of uptake of BMT CTN 1703 GVHD prevention PROGRESS III and potential barriers for activation of the upcoming BMT CTN 2203 PROGRESS IV study, with a plan to understand barriers that might also exist for widespread implementation of study therapies once results are known. The second project involves review of BMT CTN 1502 aplastic anemia study results dissemination and incorporation of dissemination and implementation concepts in the upcoming BMT CTN 2207 aplastic anemia study.

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 continued to review and support laboratory study proposals submitted in response to the BMT CTN DCC's Network-wide calls for proposals utilizing BMT CTN 1202 biospecimens. **4** studies previously assessed by the Biomarkers Committee as having significant merit were approved by the BMT CTN Executive Committee this year. The Biomarkers Committee also reviewed **2** additional studies that are pending presentation to the Executive Committee for final approval.

COMMITTEE ACTIVITIES

PATIENT-REPORTED OUTCOMES COMMITTEE

The PRO Committee ensures that PRO are appropriately selected, collected, and analyzed, not only for the particular study in which they are collected but in consideration of analyses of PRO across the BMT CTN suite of studies.

This year, the PRO Committee's charter was approved, and the committee was incorporated into the Administrative Manual of Procedures in April 2023. The BMT CTN PRO Technical Document was also released in April 2023. This year, the committee supported and led analyses that were published and presented, including quality of life analyses and incorporation of PRO data into an established CIBMTR survival calculator. Committee members also provided support and recommendations regarding PRO assessments, including specifically for adolescents, for various protocols.

CLINICAL RESEARCH ASSOCIATES COMMITTEE

The Clinical Research Associates Committee reviews each BMT CTN protocol before it is distributed to centers, focusing on reviewing and resolving logistical issues; assists in developing and reviewing Case Report Forms; reviews education materials for use at participating clinical centers; and provides input for the annual BMT CTN Coordinators' meeting.

This year, the Clinical Research Associates Committee reviewed the Infectious Disease Technical Guideline that will be posted to the BMT CTN website to be used by Clinical Research Staff at Network sites regarding diagnosing and grading infectious diseases. Committee members also provided input for the BMT CTN Coordinators meeting at the 2023 Tandem Meetings, which was attended by **446** in-person participants and **578** unique livestream viewers on the virtual platform.

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.

The BMT CTN is committed to developing strategies to address the unique challenges of evaluating HCT in the pediatric population, and it is working with the Pediatric Transplant and Cellular Therapy Consortium (PTCTC) to facilitate solutions. This year, BMT CTN and PTCTC leadership help several meetings to explore ways to better highlight BMT CTN trials, speed activation of PTCTC centers, and increase PTCTC accrual. There was particular emphasis on BMT CTN 1904, a study of inherited marrow failure disorders, a rare group of conditions affecting a predominantly pediatric patient population. Of note, **13** of the **24** centers activated for that trial are PTCTC centers.

This year, the Special Populations Committee carefully reviewed their committee charge and process for reviewing new BMT CTN protocols. The committee determined it should provide guidance to protocol teams on ways to increase access to clinical trials for patients who are traditionally underserved. Committee members drafted a checklist for parameters to consider; it is currently undergoing review. The checklist outlines barriers to special populations (e.g., under-represented minorities, children, geographically restricted populations) and includes examples for building in feasibility and flexibility into the study design (e.g., broadening inclusion criteria, allowing for longer windows for follow-up assessments, including virtual visit options) so that the protocol is more inclusive. The Special Populations Committee will present their recommendations and checklist to the Steering Committee at the June 2023 meeting.

COMMITTEE ACTIVITIES

PATIENT AND CAREGIVER ADVOCACY COMMITTEE

In April 2021, the BMT CTN formed a Patient Advocacy Task Force. The Task Force presented recommendations on better engaging patients and caregivers in research at the October 2021 Steering Committee; the recommendations included forming a standing committee. The Steering Committee agreed that all Task Force recommendations should be considered, forming a BMT CTN Patient and Caregiver Advocacy Committee to further evaluate and lead the other initiatives. After the meeting, the Patient Advocacy Task Force drafted the committee's charter.

The purpose of the Patient and Caregiver Advocacy Committee is to ensure that patient and caregiver perspectives are reflected in the BMT CTN research portfolio and trial conduct.

Patient and Caregiver Advocacy Committee Responsibilities

- **Evaluate and prioritize study concepts**
- **Interface with patient advocacy and/or community organizations**
- **Protocol team patient and caregiver engagement plans**
- **Patient, caregiver, and family-facing materials**
- **Website and social media content and communication plans**

Nominations for the new committee were solicited in August 2022. The first call was held in November 2022, and the committee has convened monthly via video conference call since then. Members include individuals involved with HCT as a patient, caregiver, family member, donor, healthcare provider or staff person / volunteer with an agency that interacts with HCT patients or donors.

This year, the committee finalized its charter, drafted a review checklist to use for reviewing new BMT CTN protocols and consent forms from a patient perspective, and drafted an outline for forthcoming BMT CTN website pages for patients and caregivers. They also drafted a document for patients and caregivers to use when considering participation on a BMT CTN study, which will be presented at the June 2023 Steering Committee meeting. Additionally, two members from the committee were selected to each participate on a new BMT CTN protocol team (BMT CTN 2203 and 2207) to advise the teams during protocol development.

SCIENTIFIC ADVISORY COMMITTEES

As part of its State of the Science Symposia, the BMT CTN created 12 Scientific Advisory Committees to address specific areas pertinent to HCT trials. These committees convene before each symposium and as needed for the Network's scientific agenda.

This year, the Infection / Immune Reconstitution Committee reconvened to update the BMT CTN Technical Manual of Procedures chapter on infectious diseases. Since the Technical Manual of Procedures will be discontinued, they revised the chapter into a BMT CTN Infectious Disease Technical Document, which was approved by the Steering Committee and released in April 2023. The committee also drafted a manuscript with the guidelines, which will be submitted for publication in June 2023.

COMMITTEE ACTIVITIES

TOXICITY AND SUPPORTIVE CARE COMMITTEE

The Toxicity and Supportive Care Committee works with the DCC to define methods for evaluating adverse events and toxicities post-transplantation, reviews toxicity evaluation and monitoring requirements on Network protocols, and designs and approves forms and procedures for collecting toxicity data. This year, the BMT CTN Executive Committee approved a new project to develop uniform recommendation for defining cause of death with the goal of publishing the guidance. The Toxicity and Supportive Care Committee will begin this project in May 2023.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS COMMITTEE

The Publications, Abstracts, and Presentations Committee develops publication and presentation policies, and it reviews publications and presentations to ensure confidentiality of study participants and proprietary information as well as to ensure appropriate acknowledgements of contributions, sponsorship, and authorship. This year, the committee reviewed **5** abstracts and **22** manuscripts.

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 **3** potential upcoming studies for multiple myeloma patients: A State of the Science CAR-T proposal for patients with high-risk disease, a SWOG-led study for patients with amyloidosis, and a European Myeloma Network study of myeloma maintenance therapy. Instead of hosting its typical workshop on immune profiling and minimal residual disease in multiple myeloma, the Intergroup incorporated topics into the BMT CTN Myeloma Intergroup meeting held in February 2023 during the BMT Tandem Meetings.

STATE OF THE SCIENCE SYMPOSIUM 2021

The BMT CTN has held four SOSS – in 2001, 2007, 2014, and 2021 – to survey the HCT landscape and identify areas in greatest need of multicenter trials. In 2021, **13** committees involving **167** individuals convened to identify clinical trial concepts that represent the most important issues facing the field and have the potential to change practice in a significant way.

The 2021 priority concepts will serve as guidance for planning future studies. Given that the current BMT CTN grant cycle ends in 2024, many of the concepts will be considered for development by the Network only if the Network is renewed or external funding is identified. However, as noted below, work on several studies has already begun.

Studies Prioritized at the 2021 State of the Science Symposium		
INTERVENTION TREATMENT TRIALS		
Committee and Concept	**Status**	**BMT CTN Protocol Number**
GVHD #1: Treatment of high-risk GVHD by protecting gastrointestinal epithelium	A trial of receptor-interacting serine/threonine-protein kinase 1 (RIPK1) for patients with Minnesota high-risk acute GVHD is being developed by the Mount Sinai Acute GVHD International Consortium (MAGIC).	N/A
GVHD #2: Phase II trial of nonsteroid treatment versus rapid steroid taper for low-risk GVHD	This study, a serial biomarker guided steroid taper for Minnesota standard risk / Ann Arbor 1 GVHD, is also being developed by MAGIC.	N/A
GVHD #3: Pre-emption of moderate to severe chronic GVHD	Protocol development for this study started in October 2022 as the next BMT CTN acute GVHD prevention study. It is a Phase III study of tacrolimus / methotrexate / ruxolitinib vs. post-transplant cyclophosphamide / tacrolimus / mycophenolate mofetil in non-myeloablative / reduced intensity conditioning allogeneic PBSC transplantation. The study will be submitted for PRC review in May 2023. It is funded by Incyte.	BMT CTN 2203
Infection and Immune Reconstitution #1: Antimicrobial de-escalation following initial fever in patients receiving allogeneic HCT or CAR-T cell infusion	TBD	N/A
Late Effects, Quality of Life, and Economics #1: Reducing distress-related biology and improving clinical outcomes using propranolol in patients undergoing autologous HCT	TBD	N/A

Studies Prioritized at the 2021 State of the Science Symposium		
INTERVENTION TREATMENT TRIALS (continued)		
Committee	**Concept**	**Status**
Lymphoid Malignancies #1: A Phase II trial of CD19-targeted CAR-T cell therapy after novel BTKi-based lead-in as frontline therapy for ultra-high-risk mantle cell lymphoma	TBD	N/A
Lymphoid Malignancies #2: A Phase III randomized trial of observation versus consolidative autologous HCT after brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (BV + CHP) induction in CD30+ peripheral T cell lymphoma	BMT CTN endorsed this ECOG-ACRIN trial, which is in development. Dr. Jacob Svoboda, a member of the SOSS Lymphoma Committee, represents the BMT CTN on the ECOG-ACRIN Protocol Team. A number is not yet assigned.	N/A
Lymphoid Malignancies #3: A Phase II trial evaluating immunotherapy consolidation in diffuse large B cell lymphoma with stable disease or partial remission on first imaging after CD19-targeted CAR-T cell therapy	BMT CTN endorsed this SWOG-led study. Dr. Mehdi Hamadani represents the BMT CTN on the SWOG Protocol Team. Protocol development started in September 2021. The protocol was approved by the FDA in November 2022, the National Cancer Institute's Central Institutional Review Board in January 2023, and CTEP in February 2023. The protocol was released to sites / activated in February 2023, although no sites are activated yet.	BMT CTN 2201 / SWOG S2114
Myeloid Malignancies #1: Molecular evaluation of acute myeloid leukemia patients after stem cell transplantation to understand relapse events (MEASURE)	BMT CTN endorsed this Alliance study in development. Dr. Nelli Bejanyan represents the BMT CTN on the Alliance protocol team. This trial is a part of the National Cancer Institute's MyeloMATCH umbrella trial.	BMT CTN 2206 / Alliance A161901
Non-Malignant Disorders #1: Hematopoietic reconstitution for adults with treatment-naïve severe aplastic anemia	A concept for a Phase 2 study of haploidentical and unrelated donor transplantation for aplastic anemia concept was developed and presented to Sanofi, which has agreed to support for the study. Protocol development will begin in June 2023.	BMT CTN 2207
Optimal Donor and Graft Sources #1: Haploidentical versus unrelated donor transplantation with post-transplant cyclophosphamide and PBSCs	TBD	N/A

Studies Prioritized at the 2021 State of the Science Symposium		
INTERVENTION TREATMENT TRIALS (continued)		
Committee	**Concept**	**Status**
Pediatric Malignant Disease #1: A risk-based approach to optimize remission duration following CD19-targeted CAR-T cell therapy	The PTCTC is developing a study (CAR-CURE).	N/A
Pediatric Malignant Disease #2: Cytokine-induced memory-like natural killer cells to treat post-HCT myeloid relapse	TBD	N/A
Plasma Cell Disorders #1: Upfront BCMA CAR-T cell consolidation and T cell engagers after autoHCT in patients with newly diagnosed high-risk multiple myeloma	A concept was drafted and presented to Bristol Myers Squibb, which has tentatively agreed to fund this study; pending contract execution protocol development will begin during the next reporting period.	N/A
OBSERVATIONAL TRIALS		
Committee	**Concept**	**Status**
Comorbidity and Regimen-Related Toxicity #1: Corticosteroids with or without a second agent for immune effector cell-associated neurotoxicity syndrome (ICANS)	TBD	N/A
Hemoglobinopathies #1: Late effects after HCT for sickle cell disease registries	A study in collaboration with NHLBI's Cure Sickle Cell Initiative is under consideration.	N/A
Infection and Immune Reconstitution #2: Prospective observational study of the immunogenicity of the available mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine after HCT and CAR-T cell therapy	The study was activated in April 2021, an accelerated timeline made feasible because of collaboration with the CIBMTR; of the 516 targeted patients, 523 were enrolled, and enrollment closed in June 2022. A manuscript on the allogeneic HCT cohort was published in April 2023.	BMT CTN 2101 / CIBMTR SC21-07
Myeloid Malignancies #2: Phase II platform trial to test multiple maintenance therapies after allogeneic HCT for high-risk acute myeloid leukemia	The Molecular Evaluation of AML Patients After Stem Cell Transplant to Understand Relapse Events (MEASURE) study was proposed by an NIH investigator who served on the SOSS Committee. The CIBMTR opened this study in August 2022 with sponsorship from NMDP/Be The Match.	N/A

STUDIES IN PROGRESS

RARE AND NON-MALIGNANT DISEASES

BMT CTN 1904

Hematopoietic cell transplantation using treosulfan-based conditioning for the treatment of bone marrow failure diseases

Chairs: Lauri Burroughs, Margaret MacMillan

Primary Objective: Determine the one-year GVHD-free, event-free survival in patients with bone marrow failure diseases undergoing HCT using treosulfan-based conditioning

Accrual: **12** of 40 projected patients enrolled

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: **43** of 156 projected patients enrolled

NMD2201 / BMT CTN 2202 TransIT

(Lead group: PTCTC)

A Phase III randomized trial comparing unrelated donor bone marrow transplantation with immune suppressive therapy for newly diagnosed pediatric and young adult patients with severe aplastic anemia

Chairs: Michael A. Pulsipher, Bronwen Shaw, David A. Williams

Primary Objective: compare time from randomization to treatment failure or death from any cause of immune suppression therapy versus bone marrow transplantation

Accrual: **5** of 234 projected patients enrolled

GVHD PREVENTION, TREATMENT, AND DISEASE BIOLOGY

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: **122** of 136 projected patients enrolled

STUDIES IN PROGRESS

CONDITIONING REGIMENS / MAINTENANCE THERAPY

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: **577** 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: **1,027** of 1,420 projected patients enrolled

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 HCT 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

Accrual: **13** of 40 projected patients enrolled

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 and the efficacy of HST-NEETs in reducing the HIV intact proviral reservoir at 6 months after autologous HCT

Accrual: **4** of 12 projected patients enrolled

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 6-24 months after gene therapy

Target Accrual: **7** of 29 projected patients enrolled

STUDIES CLOSED TO ACCRUAL THIS YEAR

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: **94** of 166 projected patients enrolled

Key Highlights: The study was activated in July 2016. The study was temporarily suspended in August 2018 due to a higher-than-expected screen failure rate. It was reopened in August 2019. The protocol was amended eight times; the final amendment included a statistical redesign that decreased the necessary sample size to 166 patients; however, accrual stalled. The failure to accrue was attributed to high screen failure rate and introduction of CAR-T therapy providing patients with alternative treatments. The final patient enrolled in May 2022. In November 2022, the Alliance Data and Safety agreed enrollment should be permanently closed effective December 20, 2022. The primary endpoint is 24-month progression-free survival. There were **126** approved sites, including **30** participating BMT CTN Core and Affiliate Centers. These BMT CTN centers enrolled **80%** of the total accrued patients.

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: **81** of 80 projected patients enrolled (**42** of 40 adults and **39** of 40 children)

Key Highlights: The Protocol Team was formed in July 2015. The study was approved by the Protocol Review Committee in April 2016 and Data and Safety Monitoring Board in April 2017. There were **37** sites activated on the study. **54** adult patients enrolled, and **42** received a transplant. **41** pediatric patients enrolled, and **39** received a transplant. The last pediatric patient was transplanted in December 2022, following accrual closure in October 2022. The primary endpoint is 2-year event-free survival. The data lock for the adult stratum is slated for July 2023, and the data lock for the pediatric stratum is slated for the second quarter of 2025.

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: **1,756** of 1,732 projected patients enrolled

STUDIES CLOSED TO ACCRUAL THIS YEAR

Key Highlights: The study was approved by the Protocol Review Committee in September 2018 and Data and Safety Monitoring Board in January 2019. The study activated in June 2019. In total, **53** centers were activated for enrolment on this protocol: **33** Core / Consortium Centers, **11** PTCTC Centers, and **9** Affiliate Centers. The final participant will reach 2 years from date of evaluability in June 2024. Accrual to the Quality of Life Substudy will continue as patients proceed to transplant, with an accrual cutoff date in June 2024.

BMT CTN 2002

A Phase 3, randomized, open-label, multicenter study, to compare T-Guard to ruxolitinib for the treatment of patients with grade III or IV steroid-refractory acute graft-versus-host disease

Chairs: John Levine, Gabrielle Meyers, Gérard Socié

Primary Objective: Assess the rate of complete response in grades III and IV steroid refractory acute GVHD participants on day 28 post-randomization

Accrual: **12** of 246 projected patients enrolled

Key Highlights: The Protocol Team was formed in December 2020. The study was approved by the US Food and Drug Administration and European Medicines Agency in April 2021 and the Data and Safety Monitoring Board in June 2021. The first 2 participants were enrolled in June 2022, one from France and one from the US. In total, **36** of **50** European sites were activated and **12** of **25** US sites were activated.

The study was placed on a temporary enrollment pause in October 2022, per protocol-based safety monitoring guidelines during the safety run-in phase. During the enrollment pause, the study met the protocol-defined stopping boundary for Day 60 mortality when comparing mortality between the T-Guard and ruxolitinib arms; this triggered a Data and Safety Monitoring Board review of all safety and efficacy data. After reviewing all the data, the Board concluded the study should be permanently stopped. The study was closed in January 2023.

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 <6 months after HCT or CAR-T cell therapy versus those starting their vaccination course 6-12 months after therapy in 3 strata defined by type of therapy: Autologous HCT recipients, allogeneic HCT recipients, and CAR T-cell recipients

Accrual: **523** of 516 projected patients enrolled

Key Highlights: This is a CIBMTR and BMT CTN joint observational study of patients receiving COVID-19 vaccines as a part of routine care, proposed by the 2021 BMT CTN State of Science Symposium Infection and Immune Reconstitution Committee. The study plan was released to sites and the first patient was enrolled in April 2021. Patient accrual completed on June 30, 2022, with patients enrolled at **30** of **32** activated centers. Of the **523** patients enrolled, **257** were in the allogeneic HCT cohort, **191** were in the autologous HCT cohort, and **75** were in the CAR-T cohort. Follow-up of enrolled patients will continue until July 31, 2023.

RESEARCH FINDINGS THIS YEAR

BMT CTN investigators have published **160** manuscripts, including **39** primary study results papers, from **44** trials and the DCC / Network.

This year investigators published **18** manuscripts, **4** of which were primary results manuscripts for the trials described below; the other primary results manuscript is in press.

Significant Findings and Impact of BMT CTN Studies	
RARE AND NON-MALIGNANT DISEASES	
1502: Optimizing **haploidentical transplantation for aplastic anemia** (CHAMP)	
Results:	Showed that haploidentical bone marrow transplantation using this study's approach resulted in **excellent overall survival** with minimal GVHD in patients with aplastic anemia who did not respond to immunosuppressive therapy.
Impact / Future Outlook:	This was a follow-on study to BMT CTN 0301 for aplastic anemia patients and used the pre-transplant cyclophosphamide dose identified as optimal in that study. This study focused on haploidentical donors to reach patients who are not able to find an unrelated donor. The GVHD prophylaxis approach is based on the approach used in BMT CTN 0604 and 1101 in patients with hematologic malignancies. The one-year overall survival was 81%, an exceptionally good result similar to the results obtained with fully matched donors. This result suggests this approach could **now be considered a standard** for salvage treatment of severe aplastic anemia. More than half of the patients treated on this study were from racial / ethnic groups that historically had a low probability of finding an HLA-matched donor. The positive results **expand access to transplantation for aplastic anemia** across all populations. Given the findings, an upfront transplant study for patients with treatment-naïve severe aplastic anemia using this approach is now being developed (BMT CTN 2207).
Publication:	Primary manuscript: Haploidentical bone marrow transplantation in patients with relapsed or refractory severe aplastic anaemia in the USA (BMT CTN 1502): A multicentre, single-arm, Phase 2 trial. The Lancet Haematology. 2022 Sep 1; 9(9): e660-e669. Epub 2022 Jul 27. Erratum in: Lancet Haematology. 2022 Sep 1; 9(9): e641.

Significant Findings and Impact of BMT CTN Studies	
MULTIPLE MYELOMA TREATMENT	
1302: Multicenter Phase II, **double-blind placebo controlled trial of maintenance ixazomib** after allogeneic hematopoietic stem cell transplantation for high risk multiple myeloma	
Results:	Unintended results showed that **investigators are unwilling to use allogeneic HCT for high-risk multiple myeloma patients** in light of a myriad of new drug and cellular therapies now available.
Impact / Future Outlook:	This was a randomized study of ixazomib vs. placebo as maintenance therapy after allogeneic HCT for patients with high-risk multiple myeloma. Unfortunately, this study closed before reaching the accrual target, with only 57 of 138 planned patients enrolled over 3 years. The protocol team made significant efforts to bolster accrual, but it became apparent that allogeneic HCT was no longer a preferred treatment option for these patients. The primary results were published this reporting period showing the **ixazomib and placebo groups had similar overall and progression-free survival**, but given the early termination of the study, there was insufficient statistical power to definitively assess the efficacy of ixazomib.
Publication:	Primary manuscript: A multicenter Phase II, double-blind placebo-controlled trial of maintenance ixazomib after allogeneic transplantation for high-risk multiple myeloma: Results of the Blood and Marrow Transplant Clinical Trials Network 1302 Trial. Transplantation and Cellular Therapy. 2022 Jul 12: S2666-6367(22)01467-1. Epub ahead of print.
1304: A randomized Phase III study **comparing conventional dose treatment using a combination of lenalidomide, bortezomib, and dexamethasone (RVD) to high-dose treatment with peripheral stem cell transplant** in the initial management of myeloma in patients up to 65 years of age	
Results:	**Showed a progression-free survival benefit for autologous HCT** vs. triplet therapy (RVD) in newly diagnosed multiple myeloma patients, although no overall survival benefit was observed.
Impact / Future Outlook:	This study was a collaboration between the Dana Farber Cancer Institute and BMT CTN, with BMT CTN endorsing the study about three years after it opened to assist with slow accrual. The trial results exceeded the predetermined endpoint of improved progression free survival with median of 67.5 months in the transplant arm vs. 46.2 months in the RVD arm. The **benefits of early transplant were more striking among standard risk patients**, with a median progression-free survival of 82.3 months (the longest ever reported to date in an upfront trial) versus 53.2 months for those receiving RVD only. Despite this benefit, there was no overall survival benefit, and there was a suggestion of increased second neoplasms in the early autologous HCT cohort; a definite recommendation for one approach versus the other was not made. Follow-up is ongoing.
Publication:	Primary manuscript: Triplet therapy, transplantation, and maintenance until progression in myeloma. The New England Journal of Medicine. 2022 Jul 14; 387(2):132-147. doi: 10.1056/NEJMoa2204925. Epub 2022 Jun 5.

Significant Findings and Impact of BMT CTN Studies	
MULTIPLE MYELOMA TREATMENT (continued)	
1401: Phase II trial of single autologous hematopoietic cell transplant followed by lenalidomide maintenance for **multiple myeloma with or without vaccination with dendritic cell / myeloma fusions**	
Results:	Showed that **addition of dendritic cell / myeloma fusion vaccination to post transplant lenalidomide maintenance did not result in a statistically significant increase in complete response rates at one-year** despite being associated with a significant increase in circulating multiple myeloma-reactive lymphocytes indicative of tumor-specific immunity.
Impact / Future Outlook:	Differences in early clinical response between the vaccine and control arms did not meet statistical significance and may require longer follow-up. This study is a first of its kind, academically led, collaborative, multicenter, randomized trial of personalized cell therapy with site specific production and centralized assessment of vaccine characterization and immune response. It sets an important p**recedent for cell-based therapeutics in an academic framework** that will facilitate evaluation of combined or sequential interventions for immune-based therapy for cancer. Since this study's successful completion, the BMT CTN has launched three cellular therapy studies involving CAR-T cell therapy (1902), HIV-specific T cells (1903), and gene transfer (2001).
Publication:	Primary manuscript: Randomized Phase II trial of dendritic cell / myeloma fusion vaccine with lenalidomide maintenance after upfront autologous hematopoietic cell transplantation for multiple myeloma: BMT CTN 1401. Cancer Clinical Research. [2023, In press].
SUPPORTIVE CARE	
2101: 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	
Results:	Showed that **starting mRNA SARS-CoV-2 vaccination three months after allogeneic HCT**, irrespective of concurrent GVHD or use of immunosuppressive medications, is warranted.
Impact / Future Outlook:	This is one of the **largest prospective analyses of vaccination for any pathogen within the first year after allogeneic HCT** and supports current guidelines for SARS-CoV-2 vaccination starting three months post-HCT. Additionally, there are few studies of mRNA vaccine formulations for other pathogens in HCT recipients, and these data provide encouraging proof-of-concept for the utility of early vaccination targeting additional pathogens with mRNA vaccine platforms. The study also found T-cell responses to the vaccine among some patients without a robust antibody response, suggesting there may be protective effects even in the absence of high levels of antibody. Results from the autologous HCT and CAR-T cell therapy cohorts of the study will be submitted for publication during the next reporting period.
Publication:	Primary manuscript: SARS-CoV-2 vaccination in the first year after allogeneic hematopoietic cell transplant: A prospective, multicentre, observational study. EClinicalMedicine. 2023 May 1; 59:101983. doi: 10.1016/j.eclinm.2023.101983. Epub 2023 Apr 27.

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