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Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2021: Looking Forward as the Network Celebrates its 20th Year

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A B S T R A C T

In 2021 the BMT CTN held the 4th State of the Science Symposium where the deliberations of 11 committees concerning major topics pertinent to a particular disease, modality, or complication of transplant, as well as two committees to consider clinical trial design and inclusion, diversity, and access as cross-cutting themes were reviewed. This article summarizes the individual committee reports and their recommendations on the highest priority questions in hematopoietic stem cell transplant and cell therapy to address in multicenter trials.

INTRODUCTION

By the end of the 20th century, significant advancements in allogeneic hematopoietic cell transplantation (alloHCT) techniques had resulted in marked improvements in overall survival (OS) compared with its earliest days. Yet many in the field believed progress could be accelerated if there was a collaborative, adequately funded, and effective infrastructure for clinical trials that could definitively test potential breakthrough therapies. In 2000, the National Institutes of Health (NIH) recognized there were gaps in translating scientific discoveries, funded predominantly through independent investigator R01 awards, into novel therapies that could change HCT practice. To address this deficiency, in 2001 the NIH issued a request for applications (RFA HL-01-004) to establish the Blood and Marrow Transplant Clinical Trials Network (BMT CTN). The Network is jointly funded by the National Heart, Lung, and Blood Institute (lead institution) and the National Cancer Institute (NCI).

The BMT CTN is now in its 20th year, and the NIH's investment has resulted in a highly successful infrastructure for clinical trials in HCT and cellular immunotherapy (HCT/CIT). The BMT CTN has opened more than 50 trials enrolling more than 13,000 patients [1]. Due to successful collaborations with industry and with other government-funded networks such as the NCI-funded National Clinical Trials Network and the AIDS

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Malignancy Consortium, this result is more than twice the number of trials expected for the amount of NIH funding. These trials have produced 125 reports, including 30 detailing primary study endpoints. Issues addressed in these trials include prevention and treatment of graft-versus-host disease (GVHD), infection, and relapse; efficacy of diverse graft sources; optimal conditioning regimens; comparison to nontransplantation therapy; and interventions to improve quality of life (QOL) [1]. Trials have included both common and uncommon indications for HCT, such as leukemia, myeloma, myelodysplastic syndromes (MDS), aplastic anemia, hemophagocytic lymphohistiocytosis, sickle cell disease (SCD), and inherited bone marrow failure syndromes. More than 120 US centers (approximately two-thirds of all US HCT centers) have participated in these trials, and several trials have enrolled patients from outside the United States.

How Does the Network Develop Its Research Priorities?

The BMT CTN Steering Committee (SC) sets the scientific agenda for the Network and serves as a forum for presentation of all clinical trial concepts. The SC comprises the Principal Investigators (PIs) of the Network's 20 Core Centers/Consortia and the Data and Coordinating Center (DCC), along with representatives of the National Heart, Lung, and Blood Institute and NCI. Although new concepts can be presented at any time in the life cycle of a funding period, the Network generally sets a scientific agenda beginning shortly after renewal of each grant cycle (typically every 5 to 7 years).

One key element of this agenda and of the long-term success of the BMT CTN is a State of the Science Symposium (SOSS), usually held toward the end of a grant cycle. The SOSS brings together subject matter experts in 10 to 13 key areas of relevance to HCT/CIT. Each area has a committee with a chair and DCC liaison assigned by the Network's Executive Committee. The chair and liaison solicit nominations from the SC PIs for 8 to 12 additional committee members. If expertise is required outside of the list of nominees, the chair can nominate other individuals. Each committee is charged with surveying the current and near future landscape of the relevant science and then generating 2 to 4 trial concepts they think hold the greatest scientific rationale and potential for progress. After 3 or 4 meetings, the committee chair writes a report outlining the committee's deliberations and recommendations. Stakeholders generally come together for a 2-day in person meeting to hear the committee presentations; in 2021, these meetings were replaced by a polling exercise followed by virtual meetings.

A planning committee comprising SOSS committee chairs, NIH representatives, and external reviewers prioritizes the trial concepts based on discussions at these meetings. This prioritized list serves as a starting point for planning studies for the subsequent grant cycle, although some concepts move forward earlier than that. Owing to limitations of funding, not all concepts move forward. In addition, the HCT/CIT landscape changes rapidly and sometimes competing trials in the private sector or other networks affect feasibility. Finally, other issues requiring timely study may supervene. However, the SOSS proceedings provide a baseline blueprint for planning the Network's agenda.

Three SOSSs were held before this year, in 2001, 2007, and 2014 [2,3]. Although the proceedings of the initial symposium in 2000 (which preceded establishment of the Network) were not published, the BMT CTN completed trials addressing 5 of the 6 areas it highlighted [2,3]. The 2007 SOSS prioritized 11 concepts leading to 7 trials conducted by the BMT CTN or by the National Clinical Trials Network with BMT CTN endorsement. The 2014 SOSS prioritized 12 concepts, resulting in 8 clinical trials (Table 1).

Process for SOSS 4

The fourth SOSS meeting followed the format of previous SOSS meetings but with modifications dictated by the COVID pandemic [3]. Ten months before the meeting, the BMT CTN Executive Committee formed 11 committees to address major topics pertinent to a particular disease, modality, or complication of HCT, as well as 2 committees to consider clinical trial design and inclusion, diversity, and access as cross-cutting themes. Committee chairs worked with the BMT CTN to populate the committees with a diverse range of investigators with broad expertise; each committee also included a DCC liaison. In addition, 2 external reviewers who were not active participants in BMT CTN activities or centers were identified for each committee. The planning group, committee chairs, members, and external reviewers are listed in Table 2. Each committee was charged with identifying up to 3 of the most important clinical questions in their area that should be addressed by the BMT CTN or another clinical trials group over the next several years.

The committees met multiple times during 2020 to develop their priorities and create brief documents describing the outcomes of their deliberations. These documents were posted in January 2021, and the transplantation community was asked to score each concept on its scientific merit. External reviewers then evaluated these reports, after which a site open to the transplantation community for public comment was developed to solicit additional input on committee concepts via a second Web-based survey. The SOSS Planning Group and committee chairs then met and reviewed the input and selected 16 trial proposals for presentation, along with presentations on clinical trial design and inclusion, diversity, and access. This was followed by an all-day virtual symposium in March 2021 that attracted more than 600 registrants at which the highest-ranking concepts were presented and discussed. At this symposium, each committee chair presented their group's report, followed by an open discussion including all participants, with more than 250 questions raised. The planning committee met again after the symposium to synthesize the recommendations and priorities.

This article summarizes the individual committee reports and a list of those trials presented in the virtual SOSS meeting (Table 3). Modality or disease-based committee reports follow alphabetically, with the cross-cutting committees that considered design, diversity, and access to trials at the end.

COMORBIDITY- AND REGIMEN-RELATED TOXICITY COMMITTEE

Current State of the Science

Organ-specific toxicities continue to limit broader application of HCT and immune effector cell (IEC) therapy in older populations. Although age has not proven to be a reliable criterion for eligibility for treatment, there remains the need for objective and reliable recipient assessments that can be performed before treatment-specific complications become clinically significant. Such an assessment could detect and allow early treatment of organ dysfunction after HCT and IEC before the patient is clinically compromised. Efforts to fill this critical gap may improve long-term survival and enhance QOL and the ability to perform all activities of daily living for patients following HCT.

Strategy 1: Corticosteroids with or without a second agent for immune effector cell-associated neurotoxicity syndrome (ICANS)

Hypothesis. The addition of a second agent to corticosteroids will reduce the progression of ICANS compared with corticosteroids alone.

Table 1
Results of 2014 SOSS Committee Recommendations

Committee	*Trial Title*	*Action*	*Outcome*
Leukemia	Phase III study of post-alloHCT transplantation maintenance using FLT3 inhibition versus placebo in patients with FLT3$^+$ AML and azacytidine versus placebo in those with FLT3-AML	Led to the development and activation of BMT CTN protocol 1506: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML.	BMT CTN 1506 completed target enrollment of 356 patients in February 2020. Patients are currently in follow-up with results of primary endpoint pending.
Lymphoma	Phase III study of post-autoHCT maintenance using ibrutinib versus placebo in patients with relapsed or refractory DLBCL	BMT CTN endorsed (and collaborated in development of) the NCI Alliance protocol (Alliance A051301): 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 of the Activated B Cell Subtype.	The study was activated in July 2016; accrual is ongoing.
Nonmalignant disease	Phase III study of autoHCT versus standard therapy for multiple sclerosis	The BMT CTN endorsed (and collaborated in development of) the NIAID/Immune Tolerance Network (ITN) study (ITN077): A Multicenter Randomized Controlled Trial of Best Available Therapy versus Autologous Hematopoietic Stem Cell Transplant for Treatment-Resistant Relapsing Multiple Sclerosis (BEAT-MS) as BMT CTN 1905	The study was activated in December 2019; accrual is ongoing.
Pediatric indications	Phase III study of post-transplantation maintenance using moxetumomab or inotuzumab versus placebo in pediatric and adult patients with B cell ALL	The Pediatric Transplant and Cellular Therapy Consortium in collaboration with the CIBMTR activated the following trial in January 2015: A Phase II Study of the Anti-CD22 Recombinant Immunotoxin Moxetumomab Pasudotox (CAT-8015, HA22) in Children with B Lineage Acute Lymphoblastic Leukemia and Minimal Residual Disease Prior to Allogeneic Hematopoietic Stem Cell Transplantation.	The study was activated in May 2015 but closed early for excessive toxicity.
Pediatric outcomes	Phase II study of daily versus alternate-day dosing of steroids for cGVHD	Not yet implemented	
Optimal donor and graft source	Phase II study of haploidentical PBSCs and PT-Cy after myeloablative conditioning	Development of a protocol using myeloablative conditioning with haploidentical donors was presented by the Optimal Donor and Graft Source SOSS Committee at the June 2017 Steering Committee meeting. The study design was modified, and the Steering Committee approved development of a prospective donor source cohort study: BMT CTN 1702, Clinical Transplant-Related Long-Term Outcomes of Alternative Donor Allogeneic Transplantation (CTRL-ALT-D).	The study was activated in June, 2019. Accrual is ongoing.
GVHD	In low-risk patients, randomized phase II studies of novel agents versus steroids, and in high-risk patients, randomized phase II studies of novel agents plus steroids versus steroids alone	Led to the development and activation of 2 studies: In low-risk aGVHD: BMT CTN 1501: A Randomized, Phase II, Multicenter, Open- Label Study Evaluating Sirolimus and Prednisone in Patients with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-versus-Host Disease In high-risk aGVHD: BMT CTN 1705: A Randomized, Double-Blind, Placebo-Controlled Multicenter Phase III Trial of Alpha 1 Antitrypsin (AAT) Combined with Corticosteroids versus Corticosteroids Alone for the Treatment of High-Risk Acute Graft-versus-Host Disease (GVHD) Following Allogeneic Hematopoietic Stem Cell Transplantation	BMT CTN 1501 completed accrual in February 2018; manuscript published. BMT CTN 1705 was activated in January 2020; accrual is ongoing.
Gene and cell therapy	Phase III study of haploidentical donor NK cells for AML	Led to the development and activation of BMT CTN 1803: Haploidentical Natural Killer (NK) Cells to Prevent Post-Transplant Relapse In AML and MDS (NK-REALM)	BMT CTN 1803 was approved by the data safety and monitoring board in May 2019, but activation was delayed because of manufacturing issues; the study was discontinued when the sponsoring company was purchased.
Comorbidity/RRT		Led to the development of BMT CTN 1704: Composite Health Assessment Model for	Accrual is ongoing.

(*continued*)

Table 1 (*Continued*)

Committee	*Trial Title*	*Action*	*Outcome*
	Development of a more robust risk assessment method incorporating biomarkers and geriatric assessment tools	Older Adults (CHARM): Applying Pretransplant Comorbidity, Geriatric Assessment, and Biomarkers to Predict Nonrelapse Mortality after Allogeneic Transplantation A companion protocol to BMT CTN 1704, BMT CTN 1801, Microbiome and Immune Reconstitution in Cellular Therapies and Hematopoietic Stem Cell Transplantation (Mi-Immune). resulted in part from the comorbidity/RRT proposal to evaluate microbiome biomarkers.	
Infection/immune reconstitution	Phase III study of cytomegalovirus-specific T cell adoptive therapy	Not yet implemented	
Infection/immune reconstitution	Phase II study of a novel parainfluenza virus entry inhibitor in HCT recipients with upper respiratory tract infection	Not yet implemented	
Late effects	Phase III randomized trial of zoledronic acid versus placebo for prevention of bone loss after alloHCT	Not yet implemented	

Background and significance. Although IEC with chimeric antigen receptor (CAR) T cells is transforming the therapeutic landscape for patients with B cell malignancies, ICANS can be severe (grade ≥3: 10% to 30%; 44% as reported in the Center for International Blood and Marrow Transplant Research (CIBMTR) real-world experience dataset) and prolonged (median duration, 7 to 14 days) [4,5]. Only a limited number of patients with grade 1-2 ICANS remain low-grade; approximately 70% of patients who develop grade 2 ICANS will progress to grade 3-5 despite interventions with corticosteroid therapy, with significant clinical consequences for the patient and the health system. Preclinical data suggest that targeted agents may further mitigate ICANS when combined with corticosteroids [6].

Trial design. All CAR T cell recipients with newly diagnosed grade 2 or persistent grade 1 ICANS will enroll in an open-label, randomized 1:1 trial comparing steroids with or without a second agent. An adaptive platform design will assess several candidate agents (eg, anakinra, ruxolitinib). The primary objective is reduction of peak ICANS grade. Secondary objectives include reduced ICANS duration, time to steroid-free/ICANS-free survival, and hospital resource utilization. Ancillary studies will include analysis of plasma biomarkers and immune cell subsets in the peripheral blood. Considering progression from grade 1-2 to grade 3-5 peak ICANS as a binary outcome, with a goal of overall reduction of progression, the sample size needed to detect a proportional difference of 70% to 55% with 80% power using a 2-sided 0.05 significance level is 165 treated subjects per arm (total 330). Stratified randomization will account for disease type, pretreatment tumor burden, and CAR T cell product type.

Feasibility and logistics. Subjects are recruited from core and affiliate centers and enrolled and registered prior to CAR T cell administration, with trial activation occurring with the diagnosis of ICANS. Based on recent CIBMTR reports, 28% of CD19-targeted CAR T cell recipients experienced grade 2-5 ICANS with increasing procedures occurring annually [7]. Obtaining biomarker samples during treatment was planned.

Strategy 2: Longitudinal trial of post-alloHCT lung function, with early identification of and therapy for chronic lung injury (CLI)

Hypothesis. Longitudinal monitoring of pulmonary function tests (PFTs) after alloHCT will define at-risk patients for early intervention.

Background and significance. CLI, including restrictive lung disease and bronchiolitis obliterans syndrome (BOS), contributes to late alloHCT toxicity [8]. BOS is often preceded by BOS stage 0 (BOS 0p), defined by a ≥10% decline in forced expiratory volume in 1 second or a ≥25% decline in forced expiratory flow of 25% to 75%. BOS 0p [9] occurs in roughly 15% of alloHCT recipients, and approximately 40% progress to BOS in 1 year. More frequent monitoring post-alloHCT will allow early intervention to decrease morbidity/mortality, reduce hospital resource utilization, and enhance individual QOL.

Trial design. The study design includes observational and interventional components, with subject enrollment at day +100 after alloHCT. Longitudinal PFTs are collected from day +100 through year 3. The primary objective of the observational component is to determine the true incidence of CLI, with the following secondary endpoints: correlation of CLI with OS, chronic GVHD, patient-reported outcomes (PROs), and biomarkers. The interventional component will include subjects identified with new-onset BOS 0p. These patients will be randomized to inhaled steroids (InS) or InS with an anti-inflammatory second agent, based on the observed benefit of InS in limiting BOS progression [10]. The duration of therapy will be 12 months, with the primary objective of decreasing BOS progression. PFTs, high-resolution computed tomography (CT), and biomarkers will be followed. Candidate second agents and willing industry partners will be identified.

Feasibility and logistics. A total of 800 subjects will be enrolled in the observational study. All patients will have periodic PFTs and biomarker collection. Day +100 enrollment will limit dropout due to early mortality and increase the proportion of subjects with identified BOS 0p. For the interventional trial, 184 patients will be accrued to demonstrate a reduction of BOS progression at 1 year from 40% to 20% using a 2-sided 0.05 significance level with 80% power. Subjects will be accrued directly primarily from the longitudinal study on diagnosis of BOS 0p but also may enter after an independent diagnosis of BOS 0p. Accrual for the interventional trial is targeted for 4 to 5 years.

Table 2
BMT CTN SOSS Committees and Reviewers

Committee 1: Clinical Trial Design
Chair: Eric Leifer, National Heart, Lung, and Blood Institute, Bethesda, MD
Members:
Amer Beitinjaneh, University of Miami, Coral Gables , FL Peter Dawson, The Emmes Company, Rockville, MD
Nancy Geller, National Heart, Lung, and Blood Institute, Bethesda, MD
Haesook Kim, Dana-Farber Cancer Institute, Boston. MA
Brent Logan, Medical College of Wisconsin, Milwaukee, WI
Brian Shaffer, Memorial Sloan-Kettering Cancer Center, New York, NY
Jesse Troy, Duke University, Durham, NC
Daniel Weisdorf, University of Minnesota, Minneapolis, MN
Juan Wu, The Emmes Company, Rockville, MD
Qian Wu, Fred Hutchinson Cancer Research Center, Seattle, WA
Outside reviewers: N/A
Committee 2: Comorbidity and Regimen-Related Toxicity
Chair: Richard Maziarz, Oregon Health & Science University, Portland, OR
Members:
Rajni Agarwal, Stanford University, Stanford, CA Andrew Artz, City of Hope, Duarte, CA
Vijaya Bhatt, University of Nebraska, Omaha, NE
Saurabh Chhabra, Medical College of Wisconsin, Milwaukee, WI
Kenneth Cooke, Johns Hopkins University, Baltimore, MD
Jordan Gautier, Fred Hutchinson Cancer Research Center, Seattle, WA
Tamila Kindwall-Keller, University of Virginia, Charlottesville, VA
Richard Lin, Memorial Sloan-Kettering Cancer Center, New York, NY
John McCarty, Virginia Commonwealth University, Richmond, VA
Edward Stadtmauer, University of Pennsylvania, Philadelphia, PA
Gregory Yanik, University of Michigan, Ann Arbor, MI
Outside reviewers:
Richard Champlin, MD Anderson Cancer Center, Houston, TX Jeffrey Szer, Royal Melbourne Hospital, Parkville, Australia
Committee 3: Disparities and Access to HCT
Chair: Eneida Nemecek, Oregon Health & Science University, Portland, OR
Members: Ghada Abusin, University of Michigan, Ann Arbor, MI
Anita D'Souza, Medical College of Wisconsin, Milwaukee, WI
Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda, MD
Yvonne Efebera, Ohio State University Medical Center, Columbus, OH
David Jacobsohn, Children's National Medical Center, Washington, DC
Folashade Otegbeye, Case Western Reserve University, Cleveland, OH
Lia Perez, H. Lee Moffitt Cancer Center, Tampa, FL
Rayne Rouce, Baylor College of Medicine, Houston, TX
Maria Thomson, Virginia Commonwealth University, Richmond, VA
William Wood, University of North Carolina, Chapel Hill, NC
Outside reviewers: N/A
Committee 4: GVHD
Chair: John Levine, Icahn School of Medicine at Mount Sinai, New York, NY
Members: Amin Alousi, MD Anderson Cancer Center, Houston, TX
Brian Betts, University of Minnesota, Minneapolis, MN
Javier Bolanos-Meade, Johns Hopkins University, Baltimore, MD
Corey Cutler, Dana-Farber Cancer Institute, Boston, MA
Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda, MD
Mary Flowers, Fred Hutchinson Cancer Research Center, Seattle, WA
Richard Jones, Johns Hopkins University, Baltimore, MD
Steven Pavletic, National Cancer Institute, Bethesda, MD
Doris Ponce, Memorial Sloan-Kettering Cancer Center, New York, NY
Iskra Pusic, Washington University, St. Louis, MO
Jennifer Whangbo, Boston Children's Hospital, Boston, MA
Outside reviewers:
Ernst Holler, University Hospital Regensburg, Regensburg, Germany Takanori Teshima, Hokkaido University Hospital, Sapporo, Japan
Committee 5: Hemoglobinopathies
Chair: Mark Walters, University of California San Francisco, San Francisco, CA
Members: Alistair Abraham, Children's National Hospital, Washington, DC
Sonali Chaudhury, Ann & Robert H Lurie Children's Hospital, Chicago, IL
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Courtney Fitzhugh, National Institutes of Health, Bethesda, MD
Helen Heslop, Baylor College of Medicine, Houston, TX
Tami John, Baylor College/Texas Children's Hospital, Houston, TX
Adetola Kassim, Vanderbilt University, Nashville, TN
Laksmannan Krishnamurti, Emory University, Atlanta, GA
Punam Malik, Cincinnati's Children's Hospital Medical Center, Cincinnati, OH
Matthew Porteus, Stanford University, Stanford, CA
Shalini Shenoy, St Louis Children's Hospital, St Louis, MO
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Joshua Hill, Fred Hutchinson Cancer Research Center, Seattle, WA
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Hemant Murthy, Mayo Clinic, Jacksonville, FL
Ryotaro Nakamura, City of Hope, Duarte, CA
Miguel-Angel Perales, Memorial Sloan-Kettering Cancer Center, New York, NY
Zainab Shahid, Levine Cancer Institute, Charlotte, NC
Amir Toor, Virginia Commonwealth University, Richmond, VA
Celalettin Ustun, Rush University Medical Center, Chicago, IL
Jo-Anne Young, University of Minnesota, Minneapolis, MN
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Jonas Mattsson, Princess Margaret Cancer Center, Toronto, Canada
Committee 7: Late Effects/QOL/Economics
Chair: Betty Hamilton, Cleveland Clinic, Cleveland, OH
Members: Saro Armenian, City of Hope, Duarte, CA
David Buchbinder, Children's Hospital of Orange County, Orange, CA
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Dianna Howard, Wake Forest University, Winston-Salem, NC
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Catherine Lee, University of Utah, Salt Lake City, UT
Stephanie Lee, Fred Hutchinson Cancer Research Center, Seattle, WA
Gunjan Shah, Memorial Sloan-Kettering Cancer Center, New York, NY
Bronwen Shaw, Medical College of Wisconsin, Milwaukee, WI
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Farrukh Awan, UT Southwestern Medical Center, Dallas, TX
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Matthew Lunning, University of Nebraska, Omaha, NE
David Maloney, Fred Hutchinson Cancer Research Center, Seattle, WA
Craig Sauter, Memorial Sloan-Kettering Cancer Center, New York, NY
Patrick Stiff, Loyola University, Chicago, IL
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Outside reviewers: Jonathan Friedberg, University of Rochester Medical Center, Rochester, NY
Brad Kahl, Washington University, St Louis, MO
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Chair: Yi-Bin Chen, Massachusetts General Hospital, Boston, MA
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Steven Devine, National Marrow Donor Program, Minneapolis, MN
Aaron Gerds, Cleveland Clinic Medical Center, Cleveland, OH
Saar Gill, University of Pennsylvania, Philadelphia, PA
Michael Grunwald, Levine Cancer Institute, Charlotte, NC
Christopher Hourigan, National Heart, Lung, and Blood Institute, Bethesda, MD
Coleman Lindsley, Dana-Farber Cancer Institute, Boston, MA
Richard Little, National Cancer Institute, Bethesda, MD
Mark Litzow, Mayo Clinic, Rochester, MN
Lori Muffly, Stanford University, Stanford, CA
Wael Saber, Medical College of Wisconsin, Milwaukee, WI
Bart Scott, Fred Hutchinson Cancer Research Center, Seattle, WA
Sumi Vasu, Ohio State University Medical Center, Columbus, OH
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Committee 10: Nonmalignant Disorders
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Jane Churpek, University of Wisconsin, Madison, WI
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Christopher Dvorak, University of California San Francisco, San Francisco, CA
Mary Eapen, Medical College of Wisconsin, Milwaukee, WI
George Georges, Fred Hutchinson Cancer Research Center, Seattle, WA
Lucy Godley, University of Chicago, Chicago, IL
Jennifer Kanakry, National Cancer Institute, Bethesda, MD
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Mary Horowitz, Medical College of Wisconsin, Milwaukee, WI
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Robert Soiffer, Dana-Farber Cancer Institute, Boston, MA

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Joseph Chewning, The University of Alabama, Birmingham, AL
Stella Davies, Cincinnati's Children's Hospital medical Center, Cincinnati, OH
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Lori Henderson, National Cancer Institute, Bethesda, MD
Dean Lee, Nationwide Children's Hospital, Columbus, OH
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Muna Qayed, Emory University, Atlanta, GA
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Committee 13: Plasma Cell Disorders
Chair: Parameswaran Hari, Medical College of Wisconsin, Milwaukee, WI
Members: Luciano Costa, The University of Alabama, Birmingham, AL
Madhav Dhodapkar, Emory University, Atlanta, GA
Sergio Giralt, Memorial Sloan-Kettering Cancer Center, New York, NY
Damien Green, Fred Hutchinson Cancer Research Center, Seattle, WA
Amrita Krishnan, City of Hope, Duarte, CA
Shaji Kumar, Mayo Clinic, Rochester, MN
Philip McCarthy, Roswell Park Comprehensive Cancer Center, Buffalo, NY
Marcelo Pasquini, Medical College of Wisconsin, Milwaukee, WI
Krina Patel, MD Anderson Cancer Center, Houston, TX
Noopur Raje, Dana-Farber Cancer Institute, Boston, MA
Edward Stadtmauer, University of Pennsylvania, Philadelphia, PA
Saad Usmani, Levine Cancer Institute, Charlotte, NC
Outside reviewers: Xavier Leleu, CHU de Poitiers, Poitiers, France
María-Victoria Mateos, Salamanca University Hospital, Salamanca, Spain

Strategy 3: Pretransplantation interventions will enhance outcomes

Hypothesis. A multidisciplinary resiliency bolstering program for high-risk older patients will attenuate early healthspan decline after alloHCT.

Background and significance. The heightened risk of nonrelapse mortality (NRM) among older patients limits the wider application of alloHCT [11]. Geriatric assessment (GA)-guided interventions in multiple randomized trials have reduced the toxicity in older cancer patients [12]. The current BMT CTN 1704 trial will create a risk-stratification model based on comorbidity, GA, and biomarkers while quantifying functional decline after HCT.

Trial design. The study will enroll alloHCT candidates at 3 to 12 weeks before planned alloHCT who are at risk for health span decline based on age ≥60 years and a BMT CTN 1704 (CHARM) score predicting high NRM. These patients will be randomized 1:1 to institutional standard of care management versus multidisciplinary GA-guided interventions adapted from promising pilot HCT data and solid tumor studies [13]. Interventions commence will start before alloHCT and continue to 4 weeks post-alloHCT with scheduled subject

Table 3
High-Priority SOSS Trials

Committee	Strategy
Interventional treatment trials	
Graft-versus-Host Disease	Improve outcomes for gastrointestinal aGVHD
Graft-versus-Host Disease	Minimize treatment toxicity for low-risk aGVHD
Graft-versus-Host Disease	Preemption of moderate to severe cGVHD
Infection/Immune Reconstitution	Safety of antibiotic deescalation following initial fever
Late Effects, Quality of Life, and Economics	Propranolol in patients undergoing autoHCT
Lymphoid Malignancies	Upfront CAR T cell therapy for high-risk MCL
Lymphoid Malignancies	Autologous HCT consolidation versus observation after BV + CHP induction in $CD30^{+}$ peripheral T cell lymphoma
Lymphoid Malignancies	Consolidation for CAR T cell incomplete responders in DLBCL
Myeloid Malignancies	Platform trial to evaluate post-HCT maintenance therapies for AML
Nonmalignant Disorders	Upfront alternative donor HCT for SAA
Optimal Donor and Graft Sources	Haploidentical versus unrelated donor transplantation with PT-Cy
Pediatric Malignant Disease	A risk-based approach to optimize remission duration following CAR T cell therapy
Pediatric Malignant Disease	Use of cytokine-induced memory-like NK cells to treat post-HCT myeloid leukemia relapse
Plasma Cell Disorders	Incorporating BCMA CAR T cell therapy in high-risk MM
Observational trials	
Comorbidity and Regimen-Related Toxicity	Limiting transplantation-associated chronic pulmonary toxicity
Hemoglobinopathies	Assessing for late effects after HCT for SCD
Infection and Immune Reconstitution	Prospective observational study of the immunogenicity of vaccines after HCT or CAR T cell therapy
Myeloid Malignancies	Prediction and biology of relapse of AML after HCT

assessments at baseline, day +30, day +100, and 1 year post alloHCT. The primary outcome is functional independent survival (FIS) at 100 days after alloHCT, quantified as alive without delirium, falls or frail walk. Secondary outcomes are 1-year NRM, day +100 6-minute walk, GVHD-free relapse-free survival (GRFS), health resource utilization, PROs, and correlation of day +100 FIS with 1-year NRM from alloHCT and OS.

Feasibility and logistics. This trial is the natural successor to CTN 1704. We anticipate that the CHARM score will comprise a short screening battery to identify high-risk patients. Assuming a baseline FIS of 50% at day +100, enrolling 260 subjects will provide 206 evaluable patients (ie, patients proceeding to alloHCT) within 24 months of trial opening, which will provide >80% power at the 2-sided 0.05 significance level to detect a 20% absolute improvement in the day +100 FIS.

Summary of Discussion

The 3 proposals presented by this committee were felt to be compelling and would improve outcomes of patients undergoing alloHCT. Strategy 2, limiting transplantation-associated chronic pulmonary toxicity, with the ability to obtain detailed longitudinal data to define the natural history of post-alloHCT lung disease with an integrated preemptive intervention strategy before the development of clinically debilitating bronchiolitis, was felt to be timely and meritorious. The longitudinal data collection could be synchronized to a chronic GVHD data collection program, in accordance with the recommendations of the 2020 NIH Chronic GVHD Consensus Project on Criteria for Clinical Trials. For strategy 1, earlier ICANS intervention remains desirable, but the fact that this area is in rapid evolution decreased enthusiasm for the BMT CTN study. Strategy 3 to improve the health span in older patients was also considered appropriate. Many centers have already begun to adopt aggressive pretransplantation resiliency interventions, and a multicenter study is ongoing within the US that may provide preliminary information to inform a future BMT CTN trial.

GVHD COMMITTEE

Current State of the Science

Since the 2014 SOSS, numerous advances in pathophysiology and therapeutics have improved GVHD prevention and treatment. These advances include Food and Drug Administration (FDA) approval of both ruxolitinib, a JAK1/2 inhibitor, for steroid-refractory acute GVHD (aGVHD), as well as ibrutinib, an inhibitor of both Bruton's tyrosine kinase (BTK) and IL-2-inducible T cell kinase, for steroid-refractory chronic GVHD (cGVHD). A practice-changing advance was the use of post-transplantation cyclophosphamide (PT-Cy) to greatly reduce the incidence of severe aGVHD and cGVHD and thereby expand HLA-mismatched donor options. Furthermore, the discovery that intestinal dysbiosis predicts GVHD severity opened up the possibility of manipulating the gastrointestinal (GI) microbiome for GVHD prophylaxis or treatment. Finally, biomarker algorithms that predict GVHD outcomes for individual patients were developed and validated and are now used in clinical trials to enrich patient populations for high-risk or low-risk GVHD.

For GVHD prophylaxis, BMT CTN 0402 compared 2 widely used GVHD prophylaxis regimens and failed to show differences in GVHD or survival. BMT CTN 1203 tested 3 novel GVHD prophylaxis regimens containing PT-Cy, bortezomib, or maraviroc and showed that 1-year GRFS was best with PT-Cy. BMT CTN 1703, the follow-up phase III comparison of PT-Cy with conventional tacrolimus/methotrexate prophylaxis, is currently enrolling patients with brisk accrual. Both BMT CTN 1501 and BMT CTN 0801 investigated sirolimus-containing regimens for acute (aGVHD) and chronic GVHD (cGVHD), with results not clearly superior to non-sirolimus-containing regimens. Finally, BMT CTN 1202 created a GVHD biorepository that contains carefully clinically annotated plasma, serum, cells and DNA samples from >1700 alloHCT recipients. The clinical data adjudication for the biorepository quantified some of the challenges for GVHD clinical research, including that (1) symptoms consistent with GVHD are experienced by nearly all alloHCT

recipients; (2) diagnostic tissue biopsies are frequently performed, but pathology findings only modestly correlate with treatment; and (3) one-third of patients are prescribed steroids for reasons other than GVHD. These completed studies informed this committee's proposals.

Strategy 1: Treatment of high-risk GVHD by protecting GI epithelium

Hypothesis. Treatments that protect or repair damage to the GI tract from GVHD will increase overall response rates and decrease NRM.

Background and significance. The patients most likely to die from GVHD nearly always develop GI GVHD and can be identified at onset by a combination of clinical and/or biomarker risk factors [14]. Systemic immunosuppression to target donor effector T cells is toxic (eg, infections) and often ineffective. Immunomodulation of the effector pathway with alpha-1-antitrypsin is being tested (BMT CTN 1705; ClincalTrials.gov NCT04167514). Targeting host GI tissue may avoid complications of immunosuppression. Drugs that block T cell migration to the GI tract (eg, natalizumab or vedolizumab) [15] or drugs that promote GI tissue repair, such as F652 (IL-22 agonist) [16], human chorionic gonadotropin and epidermal growth factor [17], or inhibitors of inflammatory cell death pathways (eg, RIPK1 inhibitors) [18], represent nonimmunosuppressive strategies considered thus far. Repair or prevention of intestinal dysbiosis with prebiotics, probiotics, or microbial transplantation are another strategy for high-risk GVHD, but these approaches rely on rapid assays to quantify microbiome injury that are still in development.

Trial design. The committee proposes randomized phase II trials to treat high-risk GVHD as defined by Minnesota symptom classification, Ann Arbor biomarker score, or both that use standard, high-dose steroids plus novel agents, such as those listed above, either singly or, preferentially, in synergistic combinations. The primary hypothesis is that the proposed treatments will result in an improved response compared with steroid alone. The primary endpoint should be day +28 overall response rate (ORR), which remains the gold standard endpoint. Patients with high-risk GVHD by biomarkers have a 57% response rate to steroids based on contemporary data from the Mount Sinai Acute GVHD International Consortium.

Feasibility and logistics. High-risk GVHD trials are feasible, as cases range from 15% (Minnesota classification) to 35% (Ann Arbor 2/3) of all cases of GVHD. A parallel 2-arm trial with 68 patients per arm provides >90% power with a 1-sided 0.025 type I error to test each of the 2 promising treatments for a 20% improvement over the historical ORR for steroids (57% versus 77%). If both strategies appear promising, both will be compared with a standard of care in a phase III trial; if one is better, then that strategy will be compared with a standard of care in a phase III trial.

Strategy 2: Phase II trial of nonsteroid treatment versus rapid steroid taper for low- risk GVHD

Hypothesis. Decreased exposure to systemic steroid treatment will reduce morbidity.

Background and significance. Current aGVHD treatment guidelines result in high steroid exposure and toxicities such as infections. A lower starting steroid dose did not reduce cumulative exposure owing to a concern for GVHD flares if steroids were tapered rapidly [19]. Steroid-free strategies include sirolimus (BMT CTN 1501, summarized above) and itacitinib (a JAK1 inhibitor under study in NCT03846479). Unpublished data define low-risk GVHD using a combination of clinical and biomarker risk factors at onset (Minnesota standard risk/Ann Arbor 1) with high response rates (>80%) and low 6-month NRM (<5%). Serial monitoring of clinical and biomarker responses can identify a subset of patients for rapid steroid taper whose GVHD nearly always responds to treatment (>90%) and almost never flares (<5%) and who have little NRM (2%).

Trial design. The committee proposes a randomized phase II trial for patients with low- risk GVHD that assesses both nonsteroid treatment (eg, itacitinib) and a clinical response/biomarker-guided rapid steroid taper that reduces steroid therapy to physiologic doses within 4 weeks. Patients with limited skin or upper GI GVHD who can be treated with topical steroids alone will be excluded. The primary endpoint will be steroid-free ORR at day +28 with key secondary endpoints of response duration, serious infection, relapse, NRM, survival, and laboratory measures of immune reconstitution. The primary hypothesis is that these strategies will result in similar steroid-free ORR.

Feasibility and logistics. Low-risk GVHD accounts for 60% of all GVHD cases. BMT CTN 1501 demonstrated that real-time monitoring by clinical response and biomarkers is feasible. Based on the BMT CTN data, it is desired to detect an absolute 20% improvement in the day +28 steroid-free ORR over the 55% historical rate. The study would require 116 patients (58 patients in each arm) to have 88% power to detect the 55% versus 75% improvement using a single-arm binomial test at the 1-sided 0.025 significance level. If both strategies appear promising, then both strategies would transition to a randomized phase III study; otherwise, the better strategy would be compared with standard of care in a phase III study.

Strategy 3: Preemption of moderate to severe cGVHD

Hypothesis. Early treatment will prevent irreversible cGVHD changes and morbidity.

Background and significance. Moderate to severe cGVHD causes substantial morbidity and contributes to excess mortality, especially when the lungs are involved. Preemptive treatment may improve outcomes in high-risk patients when they have few or no symptoms. Current unmet needs include reliable tools to identify high-risk patients and guide treatment selection and development of response measures that predict long-term endpoints, such as survival and QOL. Clinical signs and imaging/laboratory parameters reported to predict severe cGVHD, including morphea, skin stiffness, decreased forced expiratory volume in 1 second, parametric response monitoring on chest CT, and biomarkers, need validation [20,21]. The committee recommends collaborating with specialists from other fields who study fibrotic diseases such as scleroderma, idiopathic lung fibrosis, and hepatic cirrhosis to identify candidate biomarkers for specific cGVHD manifestations and for diagnostic and response measurements. A number of agents, including ruxolitinib, low-dose IL-2, and ROCK2 inhibition, show promise for cGVHD [22,23].

Trial design. The specific trial design depends on identifying high-risk patients for early intervention. Once validated tools are available, rapid testing of agents is needed. A master protocol design that uses a single overarching protocol for multiple studies that share key design components, eligibility criteria, and operational aspects can investigate multiple interventions in multiple phases for cGVHD in a continuous manner. Treatment cohorts are evaluated for efficacy using early endpoints (eg, development of moderate/severe cGVHD), with promising agents continuing to phase III comparison and those with limited efficacy or excess toxicity dropped. There is potential for combining this study with Strategy 2 proposed by the Comorbidity- and Regimen-Related Toxicity Committee.

Summary of Discussion

GVHD is the primary adverse consequence of alloHCT, and improvement/elimination of GVHD remains a major focus of BMT CTN and the entire transplantation community. The series of previous GVHD BMT CTN studies and the sample biorepository have improved our understanding of treatment options, and current trials have a high likelihood of further improving the outcomes for our patients. All proposals for future GVHD studies presented by this committee were deemed laudable, with strategy 1, approaches to improve GI aGVHD, rated among those with the greatest merit for proceeding.

HEMOGLOBINOPATHIES COMMITTEE

Current State of the Science

β-hemoglobinopathies are the most common hereditary disorders worldwide. Outcomes for patients with β-hemoglobinopathies after alloHCT have shown excellent results in several series. Among children with SCD who have an HLA-identical sibling donor, disease-free survival (DFS) is 90% to 95% [24-26]. Alternatively, patients of any age with a haploidentical relative or HLA-mismatched unrelated donor (MMUD) and patients age $\geq$13 years with an HLA-matched unrelated donor (MUD) are high risk, with a 3-year event-free survival (EFS) of 57% [25]. Gene addition and gene editing approaches now under development appear to confer a clinically significant benefit in those who lack a well-matched donor. Thus, options for older patients and transplantation with alternate donors remain important areas for improvement. Although a direct comparison of genomic therapies and allogeneic HCT or disease-modifying supportive therapies would have high impact and generate broad interest, the early stage of gene therapy creates difficulties in performing a randomized trial of curative therapies in the near future. Equally important is that the long-term effects of curative therapies, both positive and negative, are incompletely defined, which impairs decision making.

The BMT CTN initiated 2 trials of alloHCT for SCD in 2015 (BMT CTN 1503 and 1507) and initiated study activation for a new gene therapy trial in 2020 (BMT CTN 2001). BMT CTN 1503 compared results after alloHCT from a well-matched related or unrelated donor with standard care; OS was the primary endpoint. A "biological randomization" strategy assigned eligible patients with a suitable donor to the transplantation arm and those lacking a donor to the comparison arm. Before achieving the target enrollment of 200 patients, the study was closed in October 2020 owing to slow accrual. BMT CTN 1507 is a phase II study of HLA-haploidentical HCT for SCD using a reduced-intensity conditioning (RIC) regimen with PT-Cy. The primary endpoint is EFS, with events defined as graft failure, second transplant, or death. The trial has 2 strata based on age. The adult stratum completed the targeted 40 patient enrollment. A second stratum that initially enrolled children with stroke is still active and was recently amended to expand the pediatric eligibility criteria. BMT CTN 2001 is a gene therapy study of autologous lentivirus-modified hematopoietic stem cells that decreases erythroid BCL11a levels to induce fetal hemoglobin in patients with severe SCD. It has not begun enrollment. These recently completed and active studies helped direct the proposed strategies for hemoglobinopathies.

Strategy 1: Late effects after HCT for SCD registries

Hypothesis. Analyses of registry data will demonstrate protection from or reversal of sickle-related damage and define the long-term toxicity of curative therapies.

Background and significance. Unfortunately, adverse outcomes have started to emerge after curative therapy. Specifically, 10% of deaths occur more than 5 years after HCT without attribution [24]. Systematic evaluations of pulmonary, renal function, and QOL after HCT are lacking. In addition, clonal hematopoiesis of indeterminate potential may lead to myeloid malignant transformation after alloHCT. This condition might be linked to an increased risk of myeloid malignancies in SCD.

Trial design. Late effects after curative therapies will be analyzed using data from 2 parallel, NIH-funded cohorts. The Cooperative Assessment of Late Effects for Sickle Cell Disease Curative Therapies (COALESCE) study proposes to (1) evaluate pulmonary and renal function after alloHCT, (2) measure tricuspid regurgitant jet velocity in adults following nonmyeloablative alloHCT, and (3) evaluate clonal hematopoiesis of indeterminate potential CHIP following nonmyeloablative HCT and myeloablative gene editing in adults. The Sickle Cell Transplantation Evaluation of Long-Term Late Effects Registry (STELLAR) study will examine health-related quality of life, physical function, and pain through PRO tools; evaluate financial toxicity and fertility; and evaluate immune reconstitution.

Feasibility and logistics. These NIH-funded projects (STELLAR and COALESCE) propose to expand participation by recruiting BMT CTN centers to collect long-term follow-up data after alloHCT and gene therapy for SCD. There was general agreement about the importance and potential impact of the proposal, but enthusiasm was modulated by the registry-oriented study design and concern about the logistics of BMT CTN participation.

Strategy 2: Comparison of curative therapies and standard treatment for SCD

Hypothesis. Curative therapies for SCD improve survival compared with best available supportive or treatment with disease-modifying drugs.

Background and significance. The improvement in outcomes after alloHCT for SCD are paralleled by new FDA-licensed disease-modifying therapies that also improve symptoms and might extend survival [27-29]. BMT CTN 1507 is evaluating the safety and efficacy of HLA-haploidentical HCT in children and adults. Ideally, a prospective clinical trial would compare HLA-haploidentical HCT with novel disease-modifying therapies. It is too early to compare alloHCT and curative autologous gene therapies. The ethics of a randomized comparison of curative and noncurative therapies, investigator bias, and patient preference represent significant hurdles.

Trial design. "Case-matched" cohorts will be compared across different therapies in lieu of randomization. Participants would undergo HCT with any related donor (HLA-identical sibling or haploidentical donor) with the same RIC regimen used in BMT CTN 1507 and matched with supportive therapy controls. Alternatively, haploidentical HCT and HLA-identical sibling HCT might be compared. Disease-specific and toxicity endpoints would be analyzed.

Feasibility and logistics. There is a need to harmonize eligibility criteria, which will reduce the reliability of these findings in the absence of randomization. In addition, collecting consistent datasets for comparison will be difficult and expensive. The principal critique of a nonrandomized comparative trial design is selection bias in treatment assignment. Moreover, gene therapy, transplantation, and supportive care with novel FDA-approved medicines are not universally available.

Strategy 3: Phase II trial with a modified BMT CTN 0601 regimen to reduce GVHD and graft rejection after unrelated umbilical cord blood (UCB) and marrow transplantation in children with SCD

Hypothesis. The modified conditioning regimen and GVHD prophylaxis will have 90% GVHD-free EFS at 2 years.

Background and significance. BMT CTN 0601 showed that an RIC regimen supported engraftment (marrow, not UCB) but had an unacceptably high rate of GVHD that reduced survival [30]. There was also a high incidence of posterior reversible encephalopathy syndrome (PRES). An adaptation of BMT CTN 0601 was conducted to reduce graft rejection and cGVHD after alloHCT in children with severe SCD. The modified regimen added thiotepa to reduce rejection after UCB transplantation (UCBT) and added abatacept for GVHD prophylaxis. Pilot data showed reduced aGVHD and cGVHD and PRES compared with BMT CTN 0601 [31,32]. A cohort of 16 patients had a single graft rejection and a single episode of PRES, and all patients stopped immunosuppressive therapy (IST) by 2 years post-transplantation. A second cohort of 24 patients had no PRES or severe GVHD and no deaths, including 18 patients who received matched or mismatched URD transplants.

Trial design. This phase II study of unrelated donor transplantation (UCB and marrow) in children age 3 to 21 years with severe SCD, using an RIC regimen adapted with thiotepa and abatacept. The primary endpoint is EFS without GVHD at 2 years.

Feasibility and logistics. Current interest in gene therapy and gene editing trials and HLA-haploidentical HCT for hemoglobinopathies will negatively impact accrual in this proposed trial.

Summary of the Discussion

Investigating curative therapies for hemoglobinopathies remains a top priority for the BMT CTN, as evidenced by the series of completed and active clinical trials in SCD and the recent report on priorities for nonmalignant blood diseases [33]. Strategy 1, the highest-rated proposal, addresses an important knowledge gap, although the role of BMT CTN requires further discussion. There was general agreement that the results of ongoing BMT CTN alloHCT studies and industry-sponsored gene editing and gene therapy studies need to be available before embarking on trials that compare different approaches.

INFECTION AND IMMUNE RECONSTITUTION COMMITTEE

Current State of the Science

Despite the advent of new agents for the prevention and treatment of infections, HCT recipients remain at increased risk of morbidity and mortality due to infections, as well as development of antimicrobial resistance and impaired immune recovery. Delayed immune recovery also contributes to relapse of underlying hematologic disorders. Additionally, emerging data highlight significant infectious complications and delayed immune reconstitution following CAR T cell therapy [34].

Strategy 1. Antimicrobial deescalation following initial fever in patients receiving alloHCT or CAR T cell infusion

Hypothesis. Deescalation of empiric antibiotics within 72 hours following culture-negative neutropenic fever will not increase recurrent fevers or serious infections.

Background and significance. Traditionally, empiric antibiotic therapy continues from the initial fever until neutrophil recovery. Studies show that early use of broad-spectrum antibiotics affects intestinal microbiota and alloHCT outcomes [35]. Recent reports demonstrate the safety of deescalation of broad-spectrum antibiotics in culture-negative febrile neutropenia after resolution of fever; however, this approach has not been well studied in the alloHCT or CAR T cell therapy setting [36].

Trial design. CAR T cell or alloHCT recipients with an initial culture-negative fever following cell infusion will be enrolled and randomized 1:1 between deescalation to institutional standards at 72 hours or continuation of empiric antibiotics for a minimum of 5 days or until engraftment in accordance with institutional standards. The primary endpoint is recurrence of fever ($\geq$38 °C/100.4 °F) before engraftment/within 72 hours of deescalation. Secondary endpoints include subsequent bacteremia, reescalation of antibiotics, intensive care unit admission, in-house mortality, and microbiome diversity at 3 months.

Feasibility and logistics. Using data from committee member centers, 250 patients demonstrated a 5% primary endpoint rate. Assuming a true 5% primary endpoint rate in both groups, a sample size of 740 patients will provide >85% power at the 1-sided 0.05 significance level to conclude that the deescalation primary endpoint rate is not more than 5% worse than the no-deescalation rate. The large sample size, deemed feasible because of broad eligibility criteria, will allow stratification by type of cell infusion.

Strategy 2: Immunization strategies following HCT/CAR T cell therapy

2A: Single-arm, open-label trial of vaccination with the recombinant herpes zoster vaccine (SHINGRIX) after alloHCT.

Hypothesis. The SHINGRIX vaccine will be safe and immunogenic when administered in a 2-dose series starting 6 months after alloHCT.

Background and significance. Despite the efficacy of acyclovir prophylaxis, herpes zoster is common after alloHCT owing to nonadherence and breakthrough events. Although efficacy data following autologous HCT (autoHCT) exist, the safety and immunogenicity of SHINGRIX after alloHCT have not been prospectively studied. A recent retrospective analysis of 17 alloHCT recipients found an 18% response rate [37,38].

Trial Design: We propose a single arm, phase II multicenter study of the SHINGRIX vaccine in adults at 6 months post alloHCT. The primary endpoint is immunogenicity defined as either seroconversion in previously seronegative individuals or a 4-fold increase in anti-glycoprotein IgG titers in individuals seropositive pre-vaccination. Secondary endpoints include immunogenicity at 3 and 6 months, documented Herpes Zoster infection, GVHD, and relapse.

B: Prospective observational study of the immunogenicity of the available mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine after autoHCT, alloHCT, and CAR T cell therapy.

Hypothesis: The mRNA SARS-CoV-2 vaccines will be safe and immunogenic in approximately 40%-60% of HCT and CAR T cell therapy recipients.

Background and significance. HCT/CAR T cell therapy recipients are at increased risk for serious infection with SARS-CoV-2 [39]. Although influenza vaccination is more immunogenic when given $\geq$6 months after HCT, earlier vaccination ($\sim$3 months) in the context of an epidemic is considered. Data on immunogenicity in immunocompromised patients for the mRNA construct SARS-CoV-2 vaccines are lacking.

Trial design. We propose an observational, prospective cohort design to assess immunogenicity in HCT/CAR T cell recipients receiving an mRNA SARS-CoV-2 vaccine in the first year after cell infusion. Cohorts will be autoHCT, alloHCT, and CAR T cell recipients at either <6 months or 6 to 12 months postinfusion. The primary endpoint is immunogenicity at 1 month after full vaccination, with secondary endpoints of 6-

month immunogenicity, T cell responses, and neutralizing antibodies.

Feasibility and logistics for strategies A and B. The studies are designed to estimate the response rate with a confidence interval half-width of 10%. With an assumed response rate of 50%, the studies require enrollment of 104 patients following Shingrix or 104 patients per cohort for the SARS-CoV-2 vaccines. The estimated accrual time is <1 year for both strategies.

Strategy 3: Recombinant IL-7 to augment immune recovery following HLA- matched donor peripheral blood stem cell transplantation for patients receiving RIC and PT-Cy

Hypothesis. Treatment with recombinant IL-7 early post-transplantation will improve DFS by decreasing relapse and infections following matched donor transplantation with PT-Cy-based GVHD prophylaxis.

Background and significance. Inadequate immune recovery after alloHCT is associated with increased risk of relapse and infection [40]. Thus, strategies to enhance T cell reconstitution may decrease morbidity and mortality from relapse and infection. IL-7 has a central role in T cell development, demonstrating enhanced thymopoiesis and peripheral T cell survival and expansion [41]. A previous phase I trial of recombinant human IL-7 (CYT107; Cytheris, Issy-les-Moulineaux, France) following T cell-depleted HCT demonstrated increases in $CD4^+$ and $CD8^+$ T cells and functional T cell responses without the development of GVHD, anti-IL-7 antibodies, or neutralizing antibodies [42]. Although the use of PT-Cy results in lower rates of GVHD, the risks of post-transplantation infections and relapse remain high [43].

Trial design. The committee proposed a phase II multicenter, open-labeled, controlled, randomized study with a safety lead-in cohort. Eligible adults following RIC and HLA-matched HCT with PT-Cy, tacrolimus, and mycophenolate mofetil (MMF) who have no evidence of relapse, grade II-IV aGVHD, or uncontrolled infection will be randomized to receive 3 weekly doses of recombinant human IL-7 between days 45 and 70 after HCT or usual care. Two-year DFS is the primary endpoint, with secondary endpoints including infection, relapse, GVHD, and immune reconstitution.

Feasibility and logistics. Previous CIBMTR analyses identified a 45% 2-year DFS for 328 patients meeting the proposed eligibility criteria. We estimate that approximately 173 patients per arm are needed to provide 80% power at the 2-sided 0.05 significance level to detect a 15% improvement in 2-year DFS using a 2-sample binomial test . A 4-year accrual period is estimated.

Summary of Discussion

Both the external and online reviewers expressed enthusiasm for strategies 1 and 2 and considered the concepts feasible and important. Strategy 3 was considered premature, given the lack of available data in T cell-replete grafts following PT-Cy. Owing to the importance of strategy 2B (assessing the efficacy of the available SARS-CoV-2 vaccines in our patients), efforts were made to rapidly identify external funding, and this study is underway (SC21-07/BMT CTN 2101). Strategy 1 was considered timely and potentially practice-changing. Reasonable concerns were raised regarding the lack of inclusion of autoHCT recipients, the difficulty of adherence to the planned deescalation, and logistical issues. The committee discussed the inclusion of autoHCT recipients; however, since most fevers in this population occur periengraftment, it is unlikely that these patients would remain on i.v. antibiotics for longer than 72 hours if the infection workup was negative. Adherence to planned deescalation remains problematic not only in this study, but also in studies involving steroid tapers. Center commitment and close internal monitoring are required. However, statistical analyses of both the intention-to-treat and as-treated populations should account for nonadherence. The committee agrees that consent and enrollment at the time of fever may be difficult if it occurs at night or on weekends, which may impact both the accrual and collection of microbiome samples before empiric antibiotic therapy. The committee recognizes these concerns and recommends consent at the time of cellular therapy, with enrollment at the time of fever allowing microbiome sample collection at the time of fever. This trial, despite a large sample size, should accrue rapidly because of the broad eligibility criteria, add to the growing literature of the microbiome in cellular therapy recipients and potentially change practice. The short endpoint will allow for a rapid answer to an important question.

LATE EFFECTS, QUALITY OF LIFE, AND ECONOMICS COMMITTEE

Current State of the Science

Several initiatives were undertaken to outline gaps in our understanding of the biology, surveillance, management, and patient experience of transplantation-related effects and survivorship [44]. Although to date there is only 1 BMT CTN trial with PROs as a primary endpoint [45], many BMT CTN trials now incorporate PRO/QOL measures as secondary or exploratory endpoints. The committee identified several priority domains (eg, fatigue, cardiovascular disease, exercise/health behaviors, financial toxicity), but concluded that lack of data, logistics, and feasibility limit their immediate appropriateness for BMT CTN involvement. Instead, the committee focused on 3 studies that were viewed as ready for implementation: distress-related biology, survivorship screening and preventative care, and standardization of PRO collection.

Strategy 1: Reducing distress-related biology and improving clinical outcomes using propranolol in patients undergoing autoHCT

Hypothesis. Beta-blocker administration will decrease distress-related biomarkers and increase the number of days alive out of the hospital in the first 100 days following autoHCT.

Background and significance. Biobehavioral research evaluating the relationships between psychosocial factors and tumor progression/immunity [46] is limited in HCT. Psychological distress and related factors are associated with increased sympathetic nervous system signaling, resulting in increased expression of the conserved transcriptional response to adversity (CTRA)—a β-adrenergically mediated 53-gene expression profile [47]—and subsequent inferior DFS in HCT [47]. Propranolol is a nonselective ß-adrenergic receptor antagonist that blocks sympathetic nervous system signaling. In a phase II study of autoHCT recipients, propranolol administration was safe, had high adherence, and resulted in decreased CTRA expression, with a trend toward faster engraftment and fewer infections [48]. Thus, propranolol is a low-cost and safe intervention to decrease distress-related biology and improve transplantation outcomes.

Trial design and outcomes. The committee proposed a phase III randomized study of propranolol versus placebo in recipients of autoHCT for multiple myeloma (MM) or lymphoma with a primary endpoint of days alive out of the hospital through 100 days. Secondary objectives include the effect on CTRA profile, PROs, and cost. Randomization will be stratified by disease and whether HCT is planned for the inpatient or outpatient setting. From the CIBMTR data, it was estimated that among hospitalized patients, the mean number of days in the hospital was 15 ± 6.5. Propranolol will be given 2 weeks

before HCT through 100 days post-HCT. A sample size of approximately 350 patients will demonstrate a 2-day difference in days alive out of the hospital with 80% power at the 2-sided 0.05 significance level.

Feasibility and logistics. This study is feasible with a straightforward design. Biological samples will be collected and stored for batch analysis. The high number of autoHCTs, short time to a measurable endpoint, and low burden of reporting will make accrual of a large number of participants feasible in a 1-year period.

Strategy 2: Identifying gaps in survivor screening and preventive care

Hypothesis. Compliance with screening and preventive practices in accordance with survivorship guidelines is poor.

Background and significance. Despite the availability of American Society for Transplantation and Cellular Therapy/CIBMTR/European Society for Blood and Marrow Transplantation survivorship guidelines for screening and preventive care [49], to date no study has systematically assessed compliance with these guidelines and missed opportunities for better survivorship care in a multicenter setting [50].

Trial design and outcomes. This is a single-arm, pre/post-intervention design. Medical records 2 years before enrollment will be reviewed for compliance with screening guidelines for bone health, cardiovascular, endocrine, ophthalmology, cancer, and immunizations. The participant and treating physician will be informed of missed evaluations. After 6 months, charts will be reviewed for whether missed evaluations were completed and any medical actions taken. Inclusion criteria were first alloHCT, adult and pediatric survivors at 3+ years post-HCT with no evidence of relapse, and ongoing care at the transplant center. We assume that 80% of participants will have at least 1 missed screening, and that 10% of participants completing the recommended evaluation would require subsequent medical intervention. Thirty centers each contributing 30 patients meeting eligibility criteria (900 patients, accrual period of 3 years, study duration of 4 years) who underwent transplantation between 2010 and 2018 from centers with diverse characteristics will result in a good estimate of the missed screening rate (95% confidence interval [CI], 77% to 83%) and an ability to explore patient and transplant center factors associated with lower screening compliance.

Feasibility and logistics. This study is feasible and straightforward, but it does rely on significant data collection. The intervention is provision of missing screening and preventive care to participants and physicians. The baseline level of compliance and the outcome measures are ascertained from chart review.

Strategy 3: Standardizing collection of core patient-reported outcomes in BMT-CTN clinical trials

Hypothesis. A standardized approach to health-related QOL (HRQOL) data collection will improve understanding of short- and long-term toxicities and overall QOL impacted by interventions studied along the HCT continuum.

Background and significance. Many BMT CTN trials collect PROs to capture HRQOL data describing the adverse effects and benefits of an intervention [51]. However, there is heterogeneity among instruments and time points. The FDA recognizes PRO as a valid measure of clinical benefit for new drug approval [52]. Consistent collection of PROs of importance to patients, including financial hardship, will increase the information gained from trials to help identify the best treatments.

Trial design and outcomes. The committee proposes the use of a standard set of instruments and assessment points across all BMT-CTN trials. The additional use of short symptom/toxicity assessments relevant to study interventions/objectives may be added according to protocol. The CIBMTR recently demonstrated the feasibility of centralized electronic (e-)PRO collection [53] and is piloting a core set of domains measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) and Comprehensive Score for financial Toxicity (COST) administered to HCT recipients across longitudinal time points.

We propose a PRO Committee to review protocols to oversee and harmonize PRO efforts. Where possible, PRO collection should leverage the existing CIBMTR core e-PRO Protocol. Coenrollment on the CIBMTR PRO protocol also allows for late PRO collection and follow-up beyond completion of the parent trial.

Feasibility and logistics. This strategy is feasible, given the mechanism of the CIBMTR Core e-PRO Protocol to centralize data collection.

Summary of Discussion

The committee and primary reviewers had enthusiasm for strategy 1 given the novelty of investigating the biobehavioral relationship between distress and clinical outcomes in HCT using a safe, low-cost, and feasible intervention. The primary issues raised from SOSS participants regarded the primary endpoint and interpretability given multiple factors. There were concerns about hypotension and bradycardia resulting from propranolol as well as concomitant use of other antihypertensive agents, which were addressed from data in the phase II trial. Although additional details require resolution, the committee remains enthusiastic, considering this a research priority for the HCT field. Although identified as an important area of investigation, there were some concerns regarding logistics, data collection, and use of the BMT CTN to accomplish strategy 2. Strategy 3 was recognized as a priority for the BMT CTN and is part of an ongoing effort.

LYMPHOMA COMMITTEE

Current State of the Science

Lymphomas comprise a group of related diseases with heterogeneity in their cell of origin, genetic features, natural history, and treatment paradigms. Treatment options are increasing with recent chemotherapy, targeted therapy, and immunotherapy drug approvals. AutoHCT or alloHCT consolidation remains standard therapy for many lymphoma subtypes. In unforeseen ways, CAR T cell therapy has rapidly and profoundly changed treatment paradigms for several B cell lymphomas [54,55]. Numerous other unproven cellular therapies are under investigation, and their future impact on lymphoma treatment is unknown.

Strategy 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 (UHR) mantle cell lymphoma (MCL)

Hypothesis. CAR T cell therapy as frontline therapy, after lead-in immunotherapy, will safely improve PFS in patients with UHR MCL.

Background: Two-year PFS ranges from 20% to 50% in MCL patients with adverse risk features, such as high International Prognostic Index (MIPI), high MIPI-c, *TP53* mutation, biallelic 17p deletions, complex karyotype, or blastoid histology [56]. CAR T cell therapy has demonstrated remarkable efficacy in refractory MCL, with brexucabtagene autoleucel showing an 85% ORR and a 61% 12-month PFS [55].

Trial design. The committee endorsed a single-arm phase II trial of frontline CD19-targeted CAR T cell therapy after lead-in BTKi^{+}. Before enrollment, $\leq$2 standard induction cycles are permitted. The primary endpoint is 2-year PFS from enrollment. Secondary endpoints include adverse events, OS, ORR,

and correlates include minimal residual disease (MRD), apheresis and CAR T cell phenotype, and CAR T cell levels.

Feasibility and logistics. We estimate a 2-year PFS of 45% and 65% in historical and treatment groups, respectively [56]. Fifty-four patients are needed to detect 20% improvement, with 90% power and a 1-sided α value of 0.05 for an exact-binomial test. For interim monitoring, the sample size is inflated to 60. An 18-month accrual and a 24-month follow-up are estimated. The trial requires sponsor support to provide the CAR T cell product and BTKi. Alternative designs were considered, including a randomized phase II trial against the best available care in frontline and a randomized trial comparing CAR T cell consolidation versus autoHCT following standard induction in responders.

Strategy 2: A phase III randomized trial of observation versus consolidative autoHCT after brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (BV + CHP) induction in CD30$^+$ peripheral T cell lymphoma (PTCL).

Hypothesis. ASCT consolidation will safely improve PFS in patients with PTCL who achieved complete remission (CR) with frontline BV + CHP.

Background. Nonrandomized studies demonstrated a 5-year OS of 40% to 50% with autoHCT consolidation for PTCL in first CR, comparing favorably with historical controls [57]. Alternatively, a subset analysis of PTCL patients in a randomized trial showed no clear benefit [58]. Furthermore, the standard frontline treatment changed recently based on the ECHELON2 results demonstrating improved PFS and OS with BV + CHP compared with CHOP [57].

Trial design. The committee endorsed a phase III trial randomizing patients with CD30$^+$ PTCL who achieved a CR after frontline BV + CHP to observation or consolidative autoHCT (with BEAM or total body irradiation-based conditioning). Eligible diseases include PTCL not otherwise specified, anaplastic lymphoma kinase-negative anaplastic large cell lymphoma, and angioimmunoblastic T cell lymphoma. At least 1% of malignant cells must be CD30$^+$. The primary endpoint is 2-year PFS. Secondary endpoints include adverse events, OS, and exploratory prognostic markers (circulating tumor DNA MRD).

Feasibility and logistics. Assuming a 2-year PFS of 50% with observation, 244 patients are required to detect an increase to 70% with autoHCT, at 85% power. This enrollment corresponds to continuity-corrected test of proportions using a 2-sided α of 0.05 and 4 O'Brien-Fleming looks. PTCL is rare, with $<$1 case per 100,000 US population annually, with $\sim$50% having eligible histology. Although the CR rate with BV + CHP is high, $\sim$30% do not achieve CR and fail screening. Significant participation is required to complete accrual in 4 years, with an average of 321 autoHCTs annually in eligible patients recorded by the CIBMTR from 2015 to 2019.

Strategy 3: A phase II trial evaluating immunotherapy consolidation in diffuse large B cell lymphoma (DLBCL) with stable disease (SD) or partial remission (PR) on first imaging after CD19-targeted CAR T cell therapy

Hypothesis. Consolidation therapy will improve PFS for patients with DLBCL at high risk for progression following first disease assessment after CAR T cell therapy.

Background. Between 65% and 75% of DLBCL patients with a PR and 90% to 95% with SD on a day +28 positron emission tomography (PET)-CT scan after CAR T cell therapy will progress by 1 year [54,59]. This group comprises $\sim$40% of CAR T cell therapy recipients, and responses can deepen; therefore, observation is standard. MRD monitoring at day +28 may identify those destined to progress. Consolidation could improve outcomes via antitumor activity or CAR T cell therapy augmentation.

Trial design. The committee endorsed a trial under development at SWOG, a phase II randomized 3-arm study evaluating 6-months of tafasitamab + lenalidomide or polotuzumab + mosunetuzumab compared with observation, for incomplete responders to commercial CAR T cell therapy at day +28 by PET-CT [60,61]. The interventions may evolve to the best scientific approach and willing sponsor participation. Patients are randomized following day +28 PET. The primary endpoint is 1-year PFS after randomization. Secondary endpoints include CR rate, OS, MRD assay progression predictability, CAR T cell therapy persistence, and tumor assessments.

Feasibility and logistics. After CD19-targeted CAR T cell therapy, 5% of patients with SD and 30% of those with PR at day +28 will be in remission at day +90, and only 75% of those will persist at 1 year [59]. Fifty-seven patients per arm must be randomized to detect an increase in aggregate 1-year PFS from 20% to 40% using Fisher's exact test with 80% power and a 1-sided α of 0.10 for each comparison against the standard arm.

Strategy 4: A randomized phase III trial of consolidative autoHCT with BEAM + Bcl-2 inhibitor conditioning versus CD19-targeted CAR T cell therapy in partially chemotherapy-responsive relapsed/refractory DLBCL

Hypothesis. Bcl-2-based autoHCT conditioning or CAR T cell consolidation may improve outcomes for patients with a PR to second line chemotherapy.

Background. Three CD19-targeted CAR T cell therapies are approved for third-line treatment of DLBCL. The use of autoHCT has decreased, because consolidation does not cure most patients with PET$^+$ disease (ie, PR) after second-line chemotherapy. CAR T cell therapy is commonly used for these patients. Early results indicate venetoclax, which chemosensitizes lymphoma [62], is safe when added to BEAM [63]. Phase III trials comparing second-line CAR T cell therapy versus chemotherapy or autoHCT are ongoing (NCT03391466); however, questions will remain. In these protocols, patients randomized to salvage underwent autoHCT even if in PR, whereas CAR T cell therapy might be preferable. If CAR T cell therapy proves optimal, many patients will receive second-line salvage therapy in the community and the best management in partial responders will remain unclear.

Trial design. The committee endorsed a phase III trial randomizing CAR T cell therapy versus venetoclax + BEAM and autoHCT for DLBCL in PR (ie, Deauville 4) to second-line chemotherapy. Bridging chemotherapy is allowed. The primary endpoint is 1-year PFS by intention to treat; secondary endpoints include OS, NRM, adverse events, and immune reconstitution.

Feasibility and logistics. The 1-year PFS after autoHCT for patients in PR is $\sim$50% [62], and CAR T cell therapy could achieve a PFS of 70%. A total of 204 randomized subjects could detect 20% improvement using a 2-sample binomial test with a 2-sided α value of 0.05 at 80% power. Between 600 and 1300 patients per year undergo autoHCT for DLBCL in the United States. Approximately 25% experience a PR to salvage; therefore, 150 to 325 potentially eligible patients per year inform an estimated 4-year accrual. There was disinterest in a third standard BEAM conditioning arm, which was believed to complicate accrual feasibility.

Summary of Discussion

There was considerable enthusiasm for both strategy 1, which requires CAR T cell therapy sponsor support, and strategy 3, which is already in development by SWOG. It was felt

both that trials would answer critical questions and benefit from the expertise of the BMT CTN. There was less enthusiasm for strategy 2, given that PTCL is rare and the optimal frontline strategy remains uncertain, and for strategy 4, based on concerns about feasibility and relevance given pending randomized phase III trial results.

MYELOID MALIGNANCIES COMMITTEE

Current State of the Science

Myeloid malignancies remain the most common indication for alloHCT. The last decade has brought many advances in the treatment of myeloid malignancies, including multiple newly approved therapies, improvements in alloHCT practices, and the development of sensitive diagnostics that have led to a better understanding of pathophysiology and more accurate assessment of response to therapy. Sensitive detection of MRD has emerged as a potential metric to guide treatment decisions, yet uncertainties over method and timing clearly persist. Disease relapse remains the leading cause of failure after alloHCT for patients with myeloid malignancies, and novel agents with less off-target toxicity have emerged that might be safely administered after alloHCT and potentially decrease the risk of relapse. Thus, the committee chose to focus on (1) the establishment of a prospective multicenter cohort to both validate the utility of MRD testing and better understand the mechanisms of acute myelogenous leukemia (AML) relapse after alloHCT and (2) novel platform trial approaches to investigate maintenance therapy administered after alloHCT to potentially reduce post-HCT relapse.

Strategy 1. Molecular evaluation of AML patients after stem cell transplantation to understand relapse events (MEASURE)

Hypotheses. Serial blood monitoring by DNA-sequencing after alloHCT will have superior ability to predict relapse compared with pre-HCT stratification, and collection of post-HCT relapse samples will allow quantification of leukemic clonal selection versus immunologic escape as mechanisms of failure.

Background and significance. For patients with AML in cytomorphologic remission, detection of MRD has been shown to be prognostic [64,65], including for patients undergoing alloHCT [66]. Unfortunately, AML MRD testing has not yet been standardized or clinically validated to allow incorporation into clinical care or prospective trials. In addition, although AML relapse remains the primary mode of failure after alloHCT, and single-center reports suggest that this may be immunologic in nature, no large-scale, systematic evaluation of the mechanism of failure has been conducted to date.

Trial design. The committee proposed a prospective multicenter biobanking cohort of approximately 1000 patients with AML age 18 to 75 years undergoing alloHCT in CR for whom original diagnostic material is available. Blood will be collected before conditioning and at 30 days and 3, 6, 9, 12, 15, and 18 months post-HCT together with marrow and blood at disease relapse. Given the known genetic diversity of AML, a sample size of 1000 is required to ensure sufficient cases of each molecular subtype to provide robust and generalizable knowledge.

Feasibility and logistics. An analogous prospective multicenter protocol, BMT CTN 1202, successfully enrolled 1860 participants with 8 biospecimen timepoints. The estimated time for accrual is 4 years, with coenrollment on other studies encouraged.

Strategy 2. Phase II platform trial to test multiple maintenance therapies after alloHCT for high-risk AML

Hypothesis. Maintenance therapy after alloHCT for adverse-risk AML in first CR will decrease relapse.

Background and significance. Relapse remains the leading cause of death after alloHCT for patients with AML [67]. Patients at high risk of relapse often can be identified prospectively by specific features at diagnosis. Administration of novel agents with low off-target toxicity as maintenance therapy after HCT has the potential to reduce relapse [68]. No agent has yet shown compelling efficacy in this setting to warrant testing in a phase III randomized trial.

Trial design. The committee proposed an umbrella-type platform trial to test multiple therapeutic candidates as maintenance therapy for patients with adverse-risk AML in first CR as defined by the 2017 European LeukemiaNet classification [69]. The primary endpoint will be 1-year PFS, given that the majority of relapses occur in the first year after alloHCT. Candidate agents will be either targeted or nontargeted, including both immunotherapeutic and cell-based approaches.

Feasibility and logistics. This platform study will accommodate multiple open-label phase II studies testing novel approaches as maintenance after HCT. Approximately 1000 patients with adverse-risk AML undergo alloHCT each year in the United States. The study will leverage a common screening/registration process and centralized governance to improve efficiency and reduce cost.

We anticipate the 1-year PFS to be approximately 55% in this high-risk population. Using an exact one-sample binomial test, 72 patients per study would provide 80% power at a 1-sided 0.05 significance level to detect a 15% improvement in PFS. The exact duration of the study will depend on the number of studies that are initiated.

Strategy 3: Platform trial to test multiple maintenance therapies after HCT for myeloid malignancies harboring p53 mutations

Hypothesis. Maintenance therapy after HCT for patients with p53 mutant myeloid malignancies is feasible and can lower disease relapse.

Background and significance. For patients with myeloid malignancies, mutations in p53 portend a dismal prognosis even after alloHCT [70,71]. Improvements in pre-HCT therapy with newer agents [72] likely will allow more patients with p53 mutations to be eligible for alloHCT. Administration of maintenance therapy after alloHCT has the potential to reduce rates of relapse, leading to improved survival.

Trial design. An umbrella-type platform trial that will accommodate several substudies of therapeutic candidates that are either p53-targeted or nontargeted and can include both drug candidates and cellular therapeutics. The primary endpoint of the platform study will be 1-year PFS. Individual substudies will have tailored efficacy endpoints with a predetermined efficacy threshold for subsequent testing in a phase III trial. This trial can be either separate or a component of strategy 2.

Feasibility and logistics. This platform study will accommodate multiple open-label phase II studies testing novel approaches to maintenance after HCT. Approximately 300 patients with p53-mutated myeloid malignancies undergo HCT annually in the United States. This format will allow for rapid deployment of candidate therapeutic trials due to a conserved process within the master protocol. We anticipate the 1-year PFS to be approximately 25% in this high-risk population [73]. Using an exact one-sample binomial test, 65 patients per study would provide 80% power at a 1-sided significance level of 0.05 to detect a 15% improvement in PFS.

Summary of Discussion

Significant enthusiasm was expressed for all 3 strategies presented. It was felt that strategy 3 participants could be

included in strategy 2, possibly as a specific cohort to be analyzed separately. Regarding strategy 1, concerns were raised regarding the feasibility of attaining diagnostic marrow as well as fidelity of sample collections for patients in long-term follow-up. Regarding strategy 2, concerns were raised regarding the paucity of agents that had been tested in appropriate phase I studies to identify a safe and effective dose for use in the post-HCT setting. In addition, questions were raised on how to incorporate the various measures of MRD into eligibility for strategies 2 and 3. Nevertheless, all 3 strategies were felt to be of high priority in the near future.

NONMALIGNANT DISEASE COMMITTEE

Current State of the Science

Nonmalignant diseases may be inherited or acquired. Many of these diseases confer greater morbidity and mortality on patients than diagnoses classified as neoplasms. Nonmalignant disorders are rare, accounting for approximately 5% of HCT activity. This rarity also limits the expertise in transplantation for these diseases. Nonetheless, HCT for nonmalignant diseases has a high potential to cure a large proportion of recipients, most of whom are young. If applied optimally with low toxicity, good efficacy and engraftment/immune reconstitution, HCT can become available to all who need it. Given the low incidence of these disease, the role of HCT in their treatment can become established in conventional clinical practice only through well-designed multicenter trials. Thorough patient and donor assessment for genetic predisposition and longer-term follow-up for adverse late outcomes are also particularly important for these nonmalignant conditions. This committee examined adult and pediatric nonmalignant disease indications (excluding hemoglobinopathies) and proposed 3 multicenter phase II trials.

Strategy 1: Immune reconstitution for primary immune regulatory disorders using HCT to allow phenotype reversal

Hypothesis. The optimal HCT strategy minimizes toxicity and HCT-associated complications while enabling robust engraftment across myeloid and lymphoid lineages, resulting in phenotype reversal and immune reconstitution.

Background and significance. Primary immune regulatory disorders are a heterogeneous group of diseases with defects in the immune system and aberrant immune activation resulting in lymphoproliferative disorders, autoimmunity, and infection. Limitations to a successful outcome after HCT include graft failure, organ toxicity, and mortality [74,75].

Trial design. We propose a single-arm HCT trial with RIC, peripheral blood grafts, and GVHD prophylaxis that includes PT-Cy based on available pilot data. The primary endpoint is 2-year survival with phenotype reversal of hematopoietic and immunologic abnormalities that are disorder-specific. The target accrual is 36 patients over 4 years. The historical control rate for such reversal is 55% [76]. We will estimate the 95% CI for the proportion of patients with 1-year successful phenotype reversal without additional intervention, the goal being 70%. If indeed the proportion is 70%, the 95% CI will be 55%-85%. Thus, if the 2-year proportion with phenotype reversal is $\geq$70%, we will be confident that this regimen improves survival with phenotype reversal over historical controls.

Feasibility and logistics. Data from the Primary Immunodeficiency Disease Consortium suggest that ~25 HCTs were performed for eligible diseases in North America between 2014 and 2016. Increasing the awareness of these diagnoses and a standardized protocol for HCT are likely to enhance accrual to achieve the target.

Strategy 2: Hematopoietic reconstitution for adults with treatment-naïve severe aplastic anemia (SAA)

Hypothesis. Optimizing the conditioning regimen for upfront bone marrow transplantation (BMT) for adults with SAA will result in improved cure, regardless of patient age and donor type.

Background and significance. IST is standard frontline treatment for SAA, except for patients age <25 years with a suitable HLA-matched sibling for BMT [77,78]. The hematopoietic response after IST is ~ 70% to 80% and 5-year survival is 60% to 85% [77,78]. Failure-free survival beyond 10 years (alive and in remission without clonal disease) after IST is ~50% [77,79]. In contrast, long-term survival after BMT is ~ 90% in patients age <20 years and 75% in older patients [80]. Currently, BMT with an unrelated or HLA-haploidentical related donor is reserved for after failure of IST because of concerns for morbidity and mortality [81,82]. PT-Cy has improved the safety/efficacy of alternative donor BMT by facilitating engraftment and decreasing the risk of GVHD, with survival now comparable to that with matched sibling donors [83].

Trial design. We propose a phase II trial in 60 adults with newly diagnosed SAA, using conditioning with antithymocyte globulin, Cy, fludarabine, and total body irradiation, a marrow graft from a haploidentical donor (cohort 1; 30 patients) or an unrelated donor (cohort 2; 30 patients) and PT-Cy-containing GVHD prophylaxis. The primary objective is to estimate the 1-year OS in each cohort with the goal of achieving >75% 1-year OS. If 23 of 30 patients (77%) survive at least 1 year, we will be 95% confident that the true 1-year OS rate is at least 60%. If 27 of the 30 patients (90%) survive at least 1 year, we will be 95% confident that the true 1-year OS rate is at least 76%.

Feasibility and logistics. A single-center study (NCT02833805) accrued 22 children and adults over 3 years. Thus, accruing 60 adults with SAA over 3 years is feasible.

Strategy 3: HCT for telomere biology disorders (TBDs) without radiation or alkylator therapy

Hypothesis. HCT without radiation or alkylating agents will achieve durable myeloid engraftment, eradicate clonal hematopoiesis, and minimize toxicity in patients with TBDs.

Background. Radiation and alkylating agents lead to organ damage, secondary malignancy, and death in patients with TBDs. Confirmation of findings of a single-center trial pilot (NCT01659606) using alemtuzumab/fludarabine for pretransplantation conditioning addresses an unmet need.

Trial design. We propose 2 single-armed trials, one in patients with bone marrow failure (BMF) and the other in patients with low-grade MDS. Alemtuzumab/fludarabine will be used with marrow grafts from related (matched or single allele mismatched) or unrelated donors. For the BMF arm, the primary endpoint will be 1-year OS. For the MDS arm, the primary endpoint will be 1-year relapse-free survival (RFS), assuming $\geq$70% 1-year RFS compared with the historical 40%. With 30 patients, the lower bound of the 95% CI will be 53%, and we will be 95% confident that this regimen improves survival.

Feasibility and logistics. The single-center pilot with very recent multicenter expansion accrued 27 patients in 8 years, limited to patients with BMF only. With the inclusion of low-grade MDS, extension within the BMT CTN, and aided by TBD advocacy groups, we anticipate accrual of 68 patients over 4 years.

Summary of Discussion

Strategy 2, alternative donor BMT for treatment-naïve SAA, received widespread and enthusiastic support throughout, given the importance of a curative option for SAA. It was

recognized that this practice-changing trial would be feasible within the BMT CTN and should be given highest priority. It was suggested to consider including children. Strategy 3, radiation and alkylator-free HCT for TBDs, also garnered enthusiasm, given that current HCT results are suboptimal for these genetic disorders. However, there was concern about the balance of transplantation-related mortality (TRM) and long-term effects with relapse in the MDS cohort. Accrual was also considered a challenge. Strategy 1, HCT for primary immune regulatory disorders, was noted to be a key concept, as these disorders are being increasing recognized as potentially cured though HCT. Limitations noted included interpretation of the results with grouping genetically heterogeneous disorders into a single study.

OPTIMAL DONOR AND GRAFT SOURCES COMMITTEE

Current State of the Science

The past decade brought considerable progress in alternative donor transplantation, and in 2021, no patient should be denied HCT because of donor unavailability. The use of PT-Cy, pioneered for haploidentical HCT, is now extended to the HLA MMUD and MUD settings. The most common graft type used for all of these donor options is peripheral blood stem cells (PBSCs). Important questions to address include identifying and comparing the relative efficacy of the best haploidentical and unrelated donors, optimal GVHD prophylaxis for HLA-MMUD transplantation, and novel applications for UCBT.

Strategy 1: Haploidentical versus unrelated donor transplantation with PT-Cy and PBSCs

Hypothesis. HCT with an unrelated donor (intervention cohort) provides better 2-year OS than haploidentical HCT (control cohort).

Background and significance. Control of alloreactivity by PT-Cy enable the widespread use of haploidentical HCT. Retrospective comparisons demonstrate similar survival with haploidentical/PT-Cy and HLA-MUDs with calcineurin inhibitor (CNI)-based GVHD prophylaxis [84-86]. PT-Cy may improve outcomes following HLA-MUD and MMUD transplantations, and the use of unrelated donors may allow for optimization of other donor characteristics, such as donor age [87]. This will be the first randomized comparison of haploidentical HCT with unrelated donors using PT-Cy for both arms. The results could help improve the access to and outcomes of HCT for ethnically diverse patients.

Trial design. This phase III trial randomizes patients to receive the best available unrelated donor (8/8 or 7/8) versus the best haploidentical PBSC graft with different strata for myeloablative conditioning and RIC regimens. GVHD prophylaxis is provided with PT-Cy/MMF/CNI. Patients age 18 to 75 years with acute leukemia in remission or myelodysplasia are included. The primary endpoint is 2-year OS; analysis is by intention to treat. Secondary endpoints include TRM, relapse, GVHD, time to transplantation, cytokine release syndrome, quality of life, and cost. Sample size estimates assume 55% two-year survival with haploidentical HCT, based on CIBMTR data, and a two-sided 0.05 significance level. The study will require 824 (1050) patients to detect an absolute 10% improvement with 80% (90%) power. The protocol team should address use of marrow, donor selection guidelines, drugs to pair with PT-Cy, and pediatrics.

Feasibility and logistics. CIBMTR data indicate that >2000 patients eligible for this study undergo transplantation annually in the United States. The anticipated accrual time is 2 to 3 years.

Strategy 2: Randomized phase II study to compare 3 GVHD prophylaxis regimens

Hypothesis. Abatacept/CNI/methotrexate (ABA/CNI/MTX) and sirolimus/MMF/CNI (SRL/MMF/CNI) are superior to PT-Cy/CNI/MMF for MMUD PBSC transplantation.

Background and significance. This trial extends HCT to patients without an HLA-matched donor, addressing GVHD and survival using PBSCs from MMUDs. PT-Cy/CNI/MMF is the most frequently used approach to MMUD HCT, with data showing an ~50% relative reduction of chronic GVHD risk using PT-Cy/CNI/MMF after MMUD BMT [88]. However, 78% of unrelated donor transplants use PBSC, despite increased GVHD. Other trials of MMUDs with promising results used ABA/CNI/MTX or SRL/MMF/CNI and included PBSC [86,89,90].

Trial design. This phase II study will compare 1-year OS after 7/8 MUD PBSC transplantation with ABA/CNI/MTX and with SRL/MMF/CNI against PT-Cy/CNI/MMF. Conditioning will be with an RIC regimen, with identical regimens used in each arm. Patients aged 18 to 75 years with acute leukemia in first or second CR or myelodysplasia with <5% blasts and no available MUD will be included. Donor selection guidelines will be specified. A key secondary endpoint is cGVHD-free, relapse-free survival; others are TRM, relapse, GVHD, and quality of life. Assuming 60% survival with PT-Cy/CNI/MMF, 375 patients will be required to have 80% power to detect an absolute 15% survival improvement at a 2-sided significance level of 0.10 for each of the 2 comparisons with PT-Cy/CNI/MMF.

Feasibility and logistics. Based on CIBMTR data, >1000 patients eligible for this study undergo transplantation annually in the United States. Of these, ~250 receive MMUD transplants, and others receive UCB or haploidentical transplants. The anticipated accrual time is 3 years.

Strategy 3: Reducing the toxicity of UCBT in patients with leukodystrophiesHypothesis. Expanded use of UCBT enables the use of RIC regimens without compromising engraftment or survival.

Background and significance. UCBT is associated with increased survival and improved quality of life in children with inherited metabolic diseases and leukodystrophies. Potential donors cannot be disease carriers, limiting the use of related donors. Myeloablative conditioning ensures sustained engraftment with the full donor chimerism necessary to control disease but causes high morbidity [91,92]. Dosage reduction has failed because of excess graft failure. The use of expanded UCB may overcome resistance to engraftment with RIC. Omidubicel, an expanded UCB product, has shown faster engraftment in adults [93]. This study tests Omidubicel with RIC in children with inherited metabolic diseases or leukodystrophies.

Trial design. This phase II trial evaluates outcomes after RIC in patients with SD who can wait 21 days for graft expansion. The primary endpoint is 1-year OS with sustained neutrophil engraftment and >90% donor chimerism. The historical OS rate in patients receiving myeloablative busulfan/Cy/antithymocyte globulin is 88%. The study uses Simon's 2-stage minimax design with 36 successes in 39 participants needed to continue to a full sample size of 57. If 53 of 57 successes are observed, the 90% CI for the success rate is 85% to 98%. The study has 80% power with a 1-sided 5% significance level to rule out a <85% success rate.

Feasibility and logistics. Approximately 40 patients with eligible diseases are treated with UCBT yearly at ~15 centers. Twelve centers have tentatively agreed to participate. The estimated accrual is 4 years.

Summary of Discussion

Strategy 1 was one of the highest-scoring proposals in the SOSS, addressing a critical question that can be answered only by the Network. It seeks to optimize HCT outcomes for all patients but is particularly important for patients who do not have an MUD, which includes most patients from minority racial and ethnic groups. Ongoing studies in Europe are addressing different questions, such as haploidentical versus HLA-MUD HCT, and do not serve the ethnically diverse population of the United States. Specific questions regarding conditioning regimens, use of marrow, the ideal study population, and donor characteristics will need to be considered by the protocol team. Strategy 2 was deemed an important question but considered difficult to address with current patient numbers. Strategy 3 addressed an important issue in rare diseases but may be challenging to pursue; it was also felt that seeking support from makers of the expanded UCB product would be appropriate.

PEDIATRIC MALIGNANT DISEASE COMMITTEE

Current State of the Science

Relapse remains the most prominent cause of failure after HCT and cellular therapies in pediatric patients with AML, acute lymphoblastic leukemia (ALL), or MDS. The development of CAR T cells that target CD19 has dramatically expanded the therapeutic options for children with relapsed or refractory B-ALL; however, CAR T cell therapy is available for only a fraction of the children with malignancies, and even with the advent of CAR T cell therapy, relapse remains common. The Pediatric Malignancy SOSS proposed 3 approaches to prevent or treat relapse after transplantation for lymphoid and myeloid malignancies.

Strategy 1: A risk-based approach to optimize remission duration following CD19-targeted CAR T cell therapy.

Hypothesis. Risk assessment based on MRD and B cell aplasia post-CAR T cell therapy can appropriately allocate patients in most need of HCT.

Background and significance. Recent studies have demonstrated that CD19-targeted CAR T cell therapy induces remission in pediatric patients with B-ALL, but approximately 50% of these patients relapse [94], and salvage options are limited. HCT plays a central role in remission consolidation for longer-term cure in patients with high-risk B-ALL, but this therapy is associated with significant short-term and long-term risks. Establishing who can be cured with CAR T cell therapy alone versus identifying those who will need consolidative HCT for long-term cure is a critical next step in improving long-term leukemia-free survival (LFS) for patients who receive CD19-targeted CAR T cell therapy.

Molecular next-generation sequencing (NGS) MRD measurements [95] suggest that (1) NGS testing of marrow and blood are both more sensitive than flow cytometry of marrow in identifying residual disease; (2) any nonzero MRD measurement by NGS almost invariably precedes above-threshold NGS MRD, flow MRD, and clinical relapse; (3) patients with NGS-negative MRD measurements post-CAR T cell therapy have significantly longer survival, even in the absence of consolidative HCT; and (4) patients with any NGS detection and loss of B cell aplasia by 6 months post-CAR T cell therapy are at high risk of relapse.

Trial design. Pediatric patients with relapsed/refractory B-ALL treated with CD19-directed CAR T cell therapy and who are MRD-negative by flow cytometry will be randomized to either consolidative HCT (arm A) or risk-based monitoring (arm B). Patients assigned to arm B will undergo frequent MRD assessment by peripheral blood NGS monitoring every other week and marrow NGS monitoring every month. Patients with evidence of B cell recovery within 6 months of CAR T cell therapy or with any evidence of NGS-positive MRD will undergo HCT, whereas patients without either risk factor will be continued on observation. A nonrandomized third arm for patients who refuse randomization will constitute a natural history cohort to enable robust real-world data collection from all patients eligible for this trial. The primary endpoint will be 1-year LFS, with the number of HCTs performed per arm as a key secondary endpoint.

Logistics and feasibility. A risk-based approach will be considered successful if it reduces the number of HCTs performed after CAR T cell therapy without compromising LFS. Approximately 150 pediatric patients annually are infused with the commercial FDA-approved CD19-targeted CAR T cell product tisagenlecleucel. A noninferiority design using a margin of 15% (LFS 70% versus 55%) could be completed by enrolling 240 patients over a 3-year period. This design has 80% power for a 1-sided 90% confidence bound when the true 1-year LFS rates are 70% for consolidative HCT and 68% for risk-based monitoring. Enrollment in a trial incorporating a systematic approach to HCT and risk stratification is expected to accrue rapidly.

Strategy 2: Natural killer (NK) cells for treatment of relapsed/refractory AML

NK cells have substantial activity against AML [96] and have been used to treat and prevent relapse post-HCT, with early data suggesting potential clinical efficacy and no reports of GVHD [97-99]. However, their use has been limited by their short life span (12 to 14 days) and limited expansion and persistence in vivo. Recent advances in expansion strategies, such as coculture with irradiated K562 feeder cells expressing 4-1BB and membrane-bound IL-21, have overcome the problem of limited expansion with an average 20- to 80,000-fold expansion of highly functional NK cells in 3 weeks [100]. Such advancements in NK cell expansion methods have improved the potential for NK cell therapy by enabling repeated dosing with larger numbers of NK cells [99].

Strategy 2A. Cytokine-induced memory-like (CIML) NK cells to treat post-HCT myeloid relapse

Short-term culturing of conventional NK cells in IL-12, IL-15, and IL-18 induces a novel memory-like phenotype, with these cells termed CIML-NK cells [101,102]. CIML-NK cells exhibit potent antileukemia activity and prolonged survival in vivo, but their feasibility and safety as a treatment for high-risk pediatric myeloid disease has not yet been established.

Hypothesis. CIML-NK cell therapy will be safe and feasible in patients with relapsed AML post-HCT.

Trial design. This is a phase I/Ib trial to determine the safety and feasibility of CIML-NK cell infusion with IL-2 after haploidentical and matched-sibling donor HCT in pediatric patients with post-HCT AML relapse. An expansion phase Ib cohort will be used to collect additional safety data and obtain preliminary efficacy data. Secondary objectives include determining rates of CR/CR with incomplete hematologic recovery and detectability of MRD at day +28 after CIML-NK cell infusion, along with the incidence and severity of aGVHD and cGVHD, LFS, and OS.

Logistics and feasibility. HLA-identical sibling and haploidentical donors will need to undergo leukapheresis to obtain NK cells for short-term CIML induction culture (which takes only 1 day). This is an open-label phase I study with the primary objective of establishing the safety and exploring the efficacy of infusing CIML-NK cells plus IL-2 for myeloid disease relapse after HCT, with a dose-limiting toxicity observation period of 60 days. Between 5 and 10 patients will be enrolled

in phase I to determine the safe dose, and 10 additional patients will be treated at the maximum tolerated dose as an expansion cohort. If we assume that 15 subjects are treated at the maximum tolerated dose (phase I + phase Ib) and that the true CR rate is 65%, then we will have 88% power at a 1-sided 0.1 significance level to detect a statistically significantly improvement in CR over the benchmark of 30%. If 10 of 15 subjects (67%) are successfully transfused, the lower 90% confidence bound for the successful transfusion rate will be 46%.

Strategy 2B: IL-21-expanded universal donor NK cells for patients with relapsed/refractory AML

An NK cell bank derived from universal donors could further improve the feasibility of NK cell therapy by avoiding the time it takes to work up a donor and collect and expand NK cells. Be the Match Biotherapies has established an NK cell bank using donors with optimal HLA and killer Ig-like receptor (KIR) genotypes for education, a high proportion of activating KIRs corresponding to B haplotype content, and cytomegalovirus exposure, resulting in NKG2C^{+} "memory" NK cells. These universal donor NK cells are currently being studied for use in treating adults with relapsed AML/MDS (NCT04220684).

Hypothesis. Universal donor NK cells following reinduction chemotherapy will increase the CR rate and promote long-term antileukemic immunity to sustain remission.

Trial design. A phase I safety lead-in will determine the safety and recommended phase II dosage of membrane-bound IL-21-expanded, off-the-shelf, third-party donor-derived NK cells in pediatric patients with relapsed/refractory AML. During phase II, patients will be infused with NK cells following fludarabine/cytarabine/G-CSF (FLAG) chemotherapy. The primary endpoint for the phase II cohort will be objective response achieved by day 56 after the first infusion of NK cells. The historical experience of the chemotherapy backbone (FLAG) in this patient population in observing a good response (CR, CR with incomplete hematologic recovery) is $\leq$65%. Targeting a 20% increase in the response rate to 85% with the addition of NK cells, a sample of 35 patients will yield approximately 85% power with a 5% type I error rate using a 1-sided binomial test. The response rate with exact binomial 95% CI will be reported for all patients who received at least 1 dose of NK cells. A secondary analysis will assess the response rate of those who received all 6 doses of NK cells.

Logistics and feasibility. A bank of universal donor NK cells has already been established in collaboration with Be the Match Biotherapies, with additional donor collections and expansions ongoing. These cells can be successfully cryopreserved, shipped, and then thawed and infused at the bedside, supporting the feasibility of a multi-institutional study. Using an estimation of approximately 700 children diagnosed with AML each year, with a 5-year OS of 65%, and approximately two-thirds with failure due to relapse, there will be an estimated 160 eligible patients annually. If only 10% of those patients are recruited on this study, accrual can be completed in approximately 2 years.

Summary and Discussion

The Pediatric Malignancy SOSS Committee focused on the new era of cellular therapeutics to enhance disease control for pediatric patients with both lymphoid and myeloid malignancies. All of the pediatric malignancy proposals were deemed commendable by the SOSS Committee, with strategy 1 rated among those with the highest priority for proceeding. This trial focuses on B-ALL and is designed to determine how to best use CAR T cell therapy and HCT to optimize LFS while minimizing toxicity. There was significant enthusiasm for this approach, with questions centered on statistical design, the acceptability of a 15% noninferiority margin, and the potential to test the superiority of the risk assessment-based approach versus the straight-to-transplantation approach. For patients with myeloid malignancies, proposed trials focus on multicenter evaluation of promising NK cell therapies for treating post-transplantation relapse. Comments at the SOSS focused on feasibility of multicenter production of CIML-NK cells, for which cryopreservation techniques are not yet optimized, and underscored the importance of further developing strategies for portable NK-based therapeutics, given the promise of these cells.

PLASMA CELL DISORDERS COMMITTEE

Current State of the Science

Treatment of MM is changing rapidly. Since the 2014 SOSS, FDA approvals of monoclonal antibodies and immunoconjugates, agents with novel mechanisms of action (eg, selinexor and melfluflan), and even B cell maturation antigen (BCMA)-directed CAR T cells have revolutionized the treatment of MM. Indeed, combinations of old and new agents have resulted in deep remissions and durable disease control in even multiply-relapsed disease [103]. How best to incorporate these agents and autoHCT into the early therapy of patients to deepen and prolong remission is the focus of this committee's proposals. BMT CTN 0702 and 07FT defined the current standard of care for patients with newly diagnosed MM (induction, single autoHCT, and lenalidomide maintenance), and BMT CTN 1401 demonstrated the ability of this network to conduct a large patient-derived cell-based vaccine trial as an adjuvant to autoHCT [104]. The areas of greatest interest as identified by this SOSS Committee were (1) improving survival in patients with high-risk MM using immunotherapy consolidation post-autoHCT, (2) establishing long-term PFS in patients with standard-risk MM through sustained deep remissions, and (3) converting CAR T cell responses into longer PFS times by planned post-CAR T cell interventions. These concepts are MRD-guided and aim to use immune therapies in a discrete time-limited fashion to reduce treatment burden while prolonging remissions.

Strategy 1: Upfront BCMA CAR T cell consolidation and T cell engagers after autoHCT in patients with newly diagnosed high-risk MM

Hypothesis. Immunotherapy consolidation after autoHCT with BCMA-directed CAR T cell therapy and T cell engager maintenance will lead to a superior PFS.

Background. Clinical outcomes in patients with standard-risk MM have improved dramatically, but results in those with high-risk MM continue to lag significantly. Trials specific to high-risk patients also have been disappointing [105]. The proposed strategy incorporates modern induction and autoHCT with subsequent randomization to standard of care (3 drug maintenance) versus BCMA CAR T cell therapy and post-CAR T cell therapy maintenance with T cell engagers.

Trial design. Transplantation-eligible patients with R-ISS3 or R-ISS2 and at high genomic/clinical risk undergoing quadruplet induction will receive standard of care autoHCT. At an interval of 3 to 4 months, patients will be randomized to either the study intervention of BCMA-directed CAR T therapy followed by BCMA-directed bispecific T cell engager or standard of care 3-drug (protease inhibitor/immunomodulatory drug/steroid) maintenance. MRD by NGS maintenance will be measured post-transplantation at intervals of 3, 6, and 12 months [106]. Those with sustained MRD negativity at 6 and 12 months will discontinue all therapy, and others will continue therapy until relapse. Planned correlatives include RNA

sequencing/ immunosequencing/mass cytometry and CAR T cell product analyses. Targeting an improvement in median PFS of 18 months (median of 34 months in controls to 52 months), with 85% power, approximately 350 patients will need to be randomized over 3 years of accrual, with 3 years of follow-up of the last patient.

Feasibility and logistics. Multiple BMT CTN centers will enroll patients referred for autoHCT to study, as quadruplet induction before autoHCT is expected to be a standard of care within the next 2 to 3 years. For patients with high-risk disease, autoHCT followed by maintenance remains the standard of care in the absence of CAR T or other drug approvals in this setting.

Strategy 2: Concentrated upfront therapy to eliminate MM (CURxE-MM)

Hypothesis. Sustained MRD elimination with autoHCT and/or a T cell engager will extend PFS without the need for indefinite therapy.

Background. Sustained elimination of MRD correlates with significant long-term PFS in standard-risk MM. After quadruplet induction, approximately 30% are MRD-negative (10^{-5}). For these patients who are at low risk of relapse, we reexamine the utility of traditional autoHCT/maintenance (versus T cell engager maintenance). For the majority of patients who are MRD-positive, the best post autoHCT maintenance will be studied (ie, T cell engager versus standard of care).

Trial design. Standard-risk MM patients (defined according to strategy 1) will be enrolled and stratified based on MRD (10^{-5}) after quadruplet induction. MRD-negative patients will be randomized to either arm A, autoHCT followed by anti-CD38 mAB plus lenalidomide maintenance, or arm B, T cell engager alone (no autoHCT) for 1 year. MRD-positive patients will undergo autoHCT and then be randomized to maintenance with either lenalidomide/anti-CD38 mAb (arm C) or T cell engager (arm D) for 1 year. Those with sustained MRD negativity at 12 months will discontinue therapy and be followed for recurrence of MRD/International Myeloma Working Group-defined relapse.

Feasibility and logistics. From BMT CTN centers, 200 patients with standard-risk MM each will be enrolled in the MRD-negative and MRD-positive arms. This will allow detection of a 15% improvement at 1 year (from 75% to 90%) in MRD negative-PFS in arms A and B and a similar improvement in PFS in arms C and D. Approximately two-thirds of MM patients referred to BMT CTN centers for upfront autoHCT are expected to be eligible based on standard-risk MM criteria.

Strategy 3: A phase II trial addressing relapse after BCMA-directed CAR T therapy in patients with relapsed/refractory MM

Hypothesis. By targeted intervention, the problem of relapse after BCMA CAR T therapy can be overcome, even in multirefractory MM.

Background and significance. Relapse is nearly universal after anti-BCMA CAR T cell therapy for relapsed/refractory MM, but strategies that address residual disease elimination and post-CAR T cell immune modulation may offer a solution.

Trial design. A randomized 3-arm phase II trial will allocate patients to monitoring and QOL follow-up after commercial BCMA-directed CAR T cell therapy for relapsed/refractory MM (controls) versus either BCMA-directed T cell engager or immunomodulatory drug maintenance (lenalidomide) for 6 months as planned post-CAR T cell therapy maintenance. All patients will undergo central biomarker testing for Programmed cell death protein 1 expression and MRD level and mechanisms, and will be followed until relapse to establish relapse mechanisms. Each intervention arm will target a 7-month improvement in median PFS from 11 months (controls) to 18 months. The accrual goal is 123 patients per arm over 3 years with an 18-month follow-up after the last patient entered. This will provide 80% power for testing each of the 3 comparisons at a 2-sided significance level of 0.05/3 = 0.0167 using a log-rank test. If 2 different CAR T cell products are commercially approved, stratified enrollment will facilitate similar risk distributions in the arms.

Feasibility and logistics. The commercial BCMA CAR T launch in April 2021 will make this approach feasible for BMT CTN centers. The trial also will develop and validate biomarker assays that inform the mechanisms of relapse in this setting. In addition, the availability of numerous new agents (eg, CelMODs/non-BCMA immune targets, new checkpoint inhibitors) will create a rapid testing platform for post-CAR T cell therapy approaches that can be added on incrementally on as study arms.

Summary of Discussion

The BMT CTN MM portfolio is evolving from autoHCT and alloHCT strategies to novel cellular immunotherapy and the emerging compelling questions of postimmunotherapy maintenance and time-limited therapy. There was strong enthusiasm for strategy 1, which will address a major unmet role in MM that has no overlap with any other ongoing cooperative group efforts.

DESIGN COMMITTEE

Current State of the Science

Innovative trial designs are needed to speed the development of HCT therapies. The adaptive platform trial (APT) studies multiple treatments for a single disease in a continual manner, dropping a treatment arm that exhibits poor efficacy or safety and replacing it with a new treatment [107]. The Myeloid Malignancies Committee has proposed phase II APTs for testing various maintenance therapies after HCT for high-risk AML and myeloid malignancies harboring p53 mutations. The GVHD Committee has proposed a phase II APT for testing agents to prevent moderate to severe GVHD. Here we discuss aspects of an APT as well as other adaptive trial designs.

APT Logistics

An APT is governed by a master protocol containing generic components that are relevant to all arms evaluated. These components include disease specifics, trial organization, data collection and monitoring, and the statistical design. Each arm is described in an arm-specific appendix to the master protocol. The first appendix can report the current trial status, which is updated whenever an arm is dropped or added. Efficiencies are gained by streamlining these functions within a single trial.

Owing to its continuous manner, several aspects of an APT must be considered. For the pretrial regulatory review, the FDA has issued guidance for APTs and adaptive trials [108]. Once underway, an experienced Data and Safety Monitoring Board is required to monitor evolving data, particularly the introduction of new arms. Special care is required for reporting results in a timely fashion while maintaining trial integrity. Trial financing needs particular attention, because APTs do not fall under the traditional NIH funding paradigm for trials with fixed sample sizes and timelines, but an APT's ongoing research program might be attractive to a nonprofit organization and industry. An industry sponsor with multiple products in its pipeline could participate in an APT on a per-participant or per-arm cost [109]. The phase II Beat AML Master Clinical

Trial, organized by the Leukemia and Lymphoma Society, is an example of such a nonprofit/industry/academic/government partnership [110].

APT Limitations

Although an APT can provide efficiency, there are issues to consider. For certain diseases, there are not enough patients for a phase II APT to select a promising arm for a phase III trial with a control while replacing the selected arm with a new arm. If biomarkers are used for eligibility criteria, they must be widely available to facilitate rapid enrollment. When biomarker panels are evolving, they might not be suitable for a phase II APT followed by a phase III trial. Moreover, there are greater barriers to an APT with a phase III component compared with a phase II APT. In phase III, an industry partner will typically only want to compare with a control arm and not with experimental arms. Moreover, a phase II-III APT needs prespecified rules on how to proceed if an experimental arm establishes superiority over the control. Sometimes the proper action cannot be determined in advance.

Seamless Phase II-III Design

A seamless phase II-III design is a less complex alternative to an APT. In the phase II portion, patients are randomized to 2 or more experimental arms, one of which may be a control arm. Sufficiently promising arms are advanced to phase III. The efficacy criteria for advancement to phase III will usually be less stringent than the phase III criteria (eg, larger type I error versus control). Also, a shorter-term endpoint may be used in phase II.

A seamless design requires an up-front commitment to the phase III portion if the phase II results are promising. It also must be determined whether to continue randomizing patients after the phase II accrual has finished but its results are pending. Pausing accrual will prevent overaccrual if phase III is not pursued. However, if the trial continues, pausing accrual could delay phase III completion. Statistical simulations under various scenarios can inform the design choice [111,112].

Summary of Discussion

An APT may streamline therapeutic development by creating an overarching trial structure for continually testing experimental treatments. However, the complexities of the APT, particularly those involving a phase III component, should be weighed against simpler adaptive designs.

DISPARITIES AND ACCESS COMMITTEE

Current State of the Science

The BMT CTN Disparities and Access Committee was established in July 2019. The committee is composed of 11 members of diverse gender, race, and region representation. The committee's charge is to advise BMT CTN leadership on issues related to disparities and access that could have an effect on the performance and scientific impact of the studies conducted. To achieve this goal, the committee has identified 3 key strategies.

Strategy 1: Enhancing committee diversity and representation

Background. The BMT CTN has several disciplinary committees addressing diseases and conditions related to transplantation and cellular therapies. These committees identify opportunities and proposals for future studies in their respective areas. Diverse representation on study teams has been identified as a successful strategy to increase enrollment and participation of ethnic minorities in clinical research [113,114].

Proposal. To improve committee representation, we assigned a liaison from our committee to each of the other BMT CTN SOSS Committees to identify opportunities to address and reduce disparities and access issues during study development**.** Our committee also works in collaboration with the BMT CTN Special Populations Committee on their initiative to attract and recruit members of diverse origins to all committees in BMT CTN.

Key metrics. We will monitor the number of study proposals in each committee that address disparities and access in their design. In collaboration with the Special Populations Committee, we will monitor the composition of BMT CTN committee membership in terms of gender, geography, ethnicity and race, and academic rank.

Strategy 2. Accrual performance in BMT CTN studies

Strategy descriptive title. Understand the performance of BMT CTN studies to date with respect to diversity and access.

Background. The BMT CTN has been enrolling patients in high-impact interventional studies since 2003. Overall accrual to all protocols through July 2021 exceeds 14,600**.** The demographic composition of accruals is collected and reported, but a thorough analysis of performance as it pertains to gender, race/ethnicity, and other variables impacting diversity and access has not been published to date. Understanding our performance is crucial to identify opportunities for growth and positive impact in this area. Similar studies in cancer clinical trials by other groups have yielded valuable information [115,116].

Proposal. A thorough analysis of accruals to BMT CTN studies since inception will be conducted, focusing on performance related to inclusion based on age, gender, race/ethnicity, geographic area and, if available, form of insurance (public versus private). These data can be compared with the baseline of potentially eligible patients undergoing transplantation during the same period, as reported to the CIBMTR. Observed differences between expected and actual enrollment on these clinical trials could help identify possible gaps in access for particular groups based on demographic variables.

Key metrics. Summary demographics of accruals for each study (and total) by age continuum, gender, race/ethnicity, geography and insurance will be generated. The results of this analysis will be disseminated and published, along with recommendations for improvements in areas identified.

Strategy 3: Community engagement and education

Background. One of the most successful strategies described to reduce disparities in clinical research participation is community engagement [114,117,118]. Inclusion of key stakeholders, such as patients, caregivers, community advocates and members of the referring networks, has the potential to significantly impact enrollment to clinical trials. The development of inclusive education platforms considering health literacy, language, and cultural differences could result in improved accrual of individuals from underrepresented groups.

Proposal. Using the information learned in strategy 2, we propose to generate enrollment tools to mitigate the identified gaps limiting enrollment of certain groups. We could leverage our partnership with organizations such as the American Society for Transplantation and Cellular Therapy and Be the Match to more effectively disseminate information and tools. Examples of possible projects include the development of patient education materials in multiple languages regarding BMT CTN clinical trials, standard practice tools for study teams to facilitate enrollment of patients from diverse populations, and development of a BMT CTN community ambassador program.

Key metrics. Two to 3 process improvement projects will be developed, based on the results of the analysis performed in strategy 2. Projects will be selected based on their relative impact and potential to reduce existing disparities.

PRIORITIZATION

Committee reports were reviewed by external reviewers and made publicly available for comment. The SOSS Planning Group and committee chairs then met, discussed the individual proposals, and formed a prioritization list for virtual presentation at the SOSS meeting. The highest priority studies, listed in Table 3, were selected based on their significance, strength of preliminary data, and lack of barriers to their conduct. Of note, several committees proposed observational studies, because they felt that preliminary data were needed to choose the most compelling interventional treatment strategy. One such study evaluating the activity of the available SARS-CoV-2 vaccines in patients after HCT or CAR T cell therapy was rapidly activated due to urgent need (SC21-07/BMT CTN 2101). Many of the concepts not given high priority at the 2021 SOSS asked important questions and, if preliminary data are generated or certain barriers can be circumvented, might become equally compelling in the future.

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