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BMT CTN State of the Science Symposium 2021: Looking Forward as the Network Celebrates its 20th Year

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INTRODUCTION

Near the end of the 20th century, significant advancements in allogeneic hematopoietic cell transplantation (HCT) techniques resulted in marked improvements in overall survival compared to 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

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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 (NHLBI, lead Institute) 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 Malignancy Consortium, this result is more than twice the number of trials expected for the amount of NIH funding. These trials have produced 125 manuscripts 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 nontransplant 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 and inherited bone marrow failure syndromes. More than 120 U.S. centers (about two thirds of all U.S. HCT centers) have participated in these trials and several trials have enrolled patients from outside the U.S.

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 is comprised of the Principal Investigators (PIs) of the Network's 20 Core Centers/Consortia and of the Data and Coordinating Center (DCC) and representatives of the NHLBI and NCI. While 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 5–7 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 10–13 key areas of relevance to HCT/CIT. Each area has a committee with a chair and DCC liaison assigned by the Network Executive Committee. The chair and liaison solicit nominations from the SC PIs for 8–12 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 2–4 trial concepts they think hold the greatest scientific rationale and potential for progress. After 3–4 meetings, the committee chair writes a report outlining the committee's deliberations and recommendations. Stakeholders generally come together for a two-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

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discussions at these meetings. This prioritized list serves as a starting point for planning studies for the following grant cycle, though some concepts move forward earlier than that. Due to limitations of funding, not all concepts move forward. Additionally, 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 prior to 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 five of the six 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 prior to the meeting, the BMT CTN Executive Committee formed 11 committees to address 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. 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. Additionally, two 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 in the next few years.

The committees met multiple times during 2020 to develop their priorities and create brief documents describing outcomes of their deliberations. These documents were posted in January 2021 and the transplant community was asked to score each concept on its scientific merit. External reviewers then evaluated these reports and a site open to the transplant 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 presentations, 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, where the highest-ranking concepts were presented and discussed. At the meeting, each committee chair presented his or her group's report, followed by open discussion including all participants, with over 250 questions asked. 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.

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COMORBIDITY & 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. Though age has not proven to be a reliable assessment of eligibility for treatments, there remains the need for objective and reliable recipient assessments that can be utilized 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 +/− second agent for Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

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

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: 10–30%; 44% as reported in the CIBMTR real world experience data set) and prolonged (median duration, 7–14 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 targeted agents may further mitigate ICANS when combined with corticosteroids.[6]

Trial Design: All CAR-T subjects with newly diagnosed grade 2 or persistent grade 1 ICANS will enroll in an open label, randomized 1:1 trial comparing steroids +/− second agent. An adaptive platform design will assess several candidate agents (e.g., 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 would 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 proportion difference of 70% to 55% with 80% power using a 2-sided 0.05 significance level is 165 treated subjects/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, enrolled and registered prior to CAR-T administration with trial activation occurring with ICANS diagnosis. Based on recent CIBMTR reports, 28% of CD19 CAR-T recipients experienced grade 2–5 ICANS with increasing procedures occurring annually.[7] Biomarker samples were planned to be obtained during treatment.

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Strategy 2. Longitudinal trial of post-HCT lung function, with early identification and therapy of chronic lung injury

Hypothesis: Longitudinal monitoring of pulmonary function tests (PFT) after allogeneic HCT (allot) will define at-risk patients for early intervention.

Background and Significance: Chronic lung injury (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 ≥ 10% decline FEV1 or ≥ 25% decline in FEF 25–75). BOS 0p[9] is seen in about 15% of alloHCT recipients; about 40% progress to BOS in one 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 HCT. Longitudinal PFTs are collected from day 100 through year 3. The primary objective of the observational component is to determine true CLI incidence with the following secondary endpoints: correlation of CLI with overall survival, 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 observed benefit of InS in limiting BOS progression.[10] Therapy duration 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: 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 identified BOS 0p subjects. For the interventional trial, 184 patients will be accrued to demonstrate a reduction of BOS progression at one year from 40% to 20% using a two-sided 0.05 significance level with 80% power. Subjects primarily will be accrued directly from the longitudinal study upon diagnosis of B0S 0p but may also enter after independent diagnosis of BOS 0p. Accrual for the interventional trial is targeted for 4–5 years.

Strategy 3. Pre-transplantation interventions will enhance outcomes

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

Background and Significance: The heightened non-relapse mortality (NRM) risk among older patients limits wider application of alloHCT.[11] Geriatric assessment (GA)-guided interventions in multiple randomized trials have reduced toxicity of 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.

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Trial Design: The study would enroll alloHCT candidates 3–12 weeks prior to planned HCT, 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 prior to HCT and continue 4 weeks after HCT with scheduled subject assessments at baseline, D30, D100 and 1 year after HCT. 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, health resource utilization, PROs, and correlation of D100 FIS with 1-year NRM from HCT and overall survival.

Feasibility and Logistics: This trial is the natural successor to CTN 1704. We anticipate 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 (patients proceeding to HCT) within 24 months of trial opening, which will provide >80% power at the two-sided 0.05 significance level to detect a 20% absolute improvement in the day 100 FIS.

Summary of Discussion

The three proposals presented by this committee were felt to be compelling and would improve outcomes of patients undergoing HCT. Strategy 2, limiting transplant-associated chronic pulmonary toxicity, with the ability to obtain detailed longitudinal data that define the natural history of post HCT lung disease with an integrated preemptive intervention strategy prior to development of clinically debilitating bronchiolitis was felt 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 lessened enthusiasm for BMT CTN study. Strategy 3 to improve health span in older patients was also considered appropriate. Many centers have already begun to adopt aggressive pre-transplant resiliency interventions and a multicenter study is ongoing within the U.S. that may provide preliminary information to inform a future BMT CTN trial.

GRAFT-VS-HOST DISEASE (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 FDA approvals of both ruxolitinib, a JAK1/2 inhibitor, for steroid-refractory acute (a) GVHD, as well as ibrutinib, an inhibitor of both Bruton’s tyrosine kinase (BTK) and interleukin-2–inducible T-cell kinase, for steroid-refractory cGVHD. A practice-changing advance was the use of post-transplant cyclophosphamide (PT-Cy) to greatly reduce the incidence of severe acute and chronic GVHD and thereby to expand HLA-mismatched donor options. Furthermore, the discovery that intestinal dysbiosis predicted GVHD severity opened up the possibility

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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- or low-risk GVHD.

For GVHD prophylaxis, BMT CTN 0402 compared two widely used GVHD prophylaxis regimens and failed to show differences in GVHD or survival. BMT CTN 1203 tested three novel GVHD prophylaxis regimens (containing PT-Cy, bortezomib, or maraviroc) and showed one-year GVHD-free/relapse-free survival (GRFS) was best with PT-Cy. BMT CTN 1703, the follow-up phase III comparison of PT-Cy to conventional TAC/MTX 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 over 1,700 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 protection of 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 (e.g., infections) and often ineffective. Immunomodulation of the effector pathway with alpha-1-antitrypsin is being tested (BMT CTN 1705, NCT04167514). Targeting host GI tissue may avoid complications of immunosuppression. Drugs that block T-cell migration to the GI tract (e.g., 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 (e.g., RIPK1 inhibitors)[18] represent non-immunosuppressive strategies considered thus far. . Repair or prevention of intestinal dysbiosis with prebiotics, probiotics, or microbial transplant 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 2 trials to treat high-risk GVHD 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 to steroid alone. The primary

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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 (MAGIC).

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

Strategy 2. Phase II trial of non-steroid treatment vs. 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 due to 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%), almost never flares (<5%), and who have little NRM (2%).

Trial Design: The committee proposes a randomized phase 2 trial for patients with low risk GVHD that assesses both non-steroid treatment (e.g., 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 for 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% vs 75% improvement using a single-arm binomial test at the one-sided 0.025 significance level. If both strategies appear promising, both strategies would transition to a randomized phase 3

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study; otherwise, the better strategy would be compared to standard of care in a phase 3 study.

Strategy 3. Pre-emption 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. Pre-emptive 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, decreases in FEV1, 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 such as ruxolitinib, low-dose interleukin-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 exist, rapid testing of agents is needed. A master protocol design that uses one overarching protocol for multiple studies that share key design components, eligibilities and operational aspects can investigate multiple interventions in multiple phases for chronic GVHD in a continuous manner. Treatment cohorts are evaluated for efficacy using early endpoints (e.g., 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 and elimination of GVHD remains a major focus of BMT CTN and the entire transplant community. The series of prior GVHD BMT CTN studies and the sample biorepository have improved our understanding of treatment options and current trials have a high likelihood to further improve the outcomes for our patients. All proposals for future GVHD studies presented by this committee were deemed laudable, with Strategy 1, approaches to improve acute GI GVHD, rated among those with the highest 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 HCT showed excellent results in several series. Among children with sickle cell disease (SCD) who have an HLA-identical sibling donor,

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disease-free survival is 90–95%[24–26]. Alternatively, patients of any age with a haploidentical relative or HLA-mismatched unrelated donor and patients aged ≥13 years with an HLA-matched unrelated donor 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. While 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, the long-term effects of curative therapies, both positive and negative, are incompletely defined, which impairs decision making.

The BMT CTN initiated two trials of HCT 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; overall survival was the primary endpoint. A “biological randomization” strategy assigned eligible patients to the transplant arm when there was a suitable donor and those who lacked a donor to a comparison arm. Before completing the target 200 patient enrollment, the study was closed in October 2020 due to slow accrual. BMT CTN 1507 is a phase 2 study of HLA-haploidentical HCT for SCD using a reduced intensity regimen with PT-Cy. The primary endpoint is EFS with events defined as graft failure, second transplant, or death. The trial has two 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. It was recently amended to expand 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 enrolment. 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 (CHIP) may lead to myeloid malignant transformation after HCT. 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 two 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 allogeneic HCT, (2) measure tricuspid regurgitant jet velocity in adults following nonmyeloablative allogeneic HCT, and (3) evaluate CHIP

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following nonmyeloablative HCT and myeloablative gene editing in adults. The *Sickle cell Transplantation Evaluation of Long-term Late-effects Registry* (STELLAR) study will (1) examine health-related quality of life, physical function and pain through patient-reported outcome tools, (2) evaluate financial toxicity and fertility, and (3) evaluate immune reconstitution.

Feasibility and Logistics: These NIH-funded projects (STELLAR-Krishnamurti and COALESCE-Fitzhugh) propose to expand participation by recruiting BMT CTN centers to collect long-term follow up data after allogeneic HCT 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 HCT 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 non-curative 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-ID sibling or haplo-ID donor) with the same reduced intensity 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 reliability of these findings in the absence of randomization. Additionally, collecting consistent datasets for comparison will be difficult and expensive. The principal critique of a non-randomized comparative trial design is selection bias in treatment assignment. Also, gene therapy, transplant, and supportive care with novel FDA-approved medicines are not universally available.

Strategy 3. Phase II trial with 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.

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Background and Significance: BMT CTN 0601 showed that a reduced intensity conditioning (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 chronic GVHD after HCT in children with severe SCD. The modified regimen added thiotepa to reduce rejection after UCB transplantation and added abatacept for GVHD prophylaxis. Pilot data showed reduced acute and chronic GVHD and PRES compared with BMT CTN 0601[31,32]. A cohort of 16 patients had a single graft rejection, a single episode of PRES, and all patients stopped immunosuppressive therapy by 2 years posttransplant. A second cohort of 24 patients had no PRES or severe GVHD and no deaths, including 18 patients who received matched and mismatched URD transplants.

Trial Design: Phase II study of unrelated donor transplantation (UCB and marrow) in children 3 – 21 years with severe SCD, utilizing a reduced intensity 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 non-malignant blood diseases[33]. Strategy 1, the highest rated proposal, addresses an important knowledge gap, although the role of BMT CTN needs further discussion. There was general agreement that the results of ongoing BMT CTN transplant 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 new agents for the prevention and treatment of infections, recipients of HCT 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 therapy.[34]

Strategy 1. Antimicrobial de-escalation following initial fever in patients receiving allogeneic hematopoietic cell transplant or CAR-T cell infusion.

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

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Background and Significance: Traditionally, empiric antibiotics continue from the initial fever until neutrophil recovery. Studies show that early use of broad-spectrum antibiotics affect intestinal microbiota and alloHCT outcomes.[35] Recent reports demonstrate the safety of de-escalation of broad-spectrum antibiotics in culture-negative febrile neutropenia after resolution of fever; however, this approach is not well-studied well in HCT or CAR-T settings.[36]

Trial Design: CAR-T or alloHCT patients with an initial culture-negative fever following cell infusion will be enrolled and randomized 1:1 between de-escalation to institutional standards at 72 hours or continuation of empiric antibiotics for a minimum of 5 days/until engraftment per institutional standards. The primary endpoint is recurrence of fever [≥ 38C/100.4] prior to engraftment/within 72 hours of de-escalation. Secondary endpoints include subsequent bacteremia, re-escalation of antibiotics, ICU 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 one-sided 0.05 significance level to conclude that the de-escalation primary endpoint rate is not more than 5% worse than the no-de-escalation 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 therapy

A. 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 efficacy of acyclovir prophylaxis, Herpes zoster is common after alloHCT due to non-adherence and breakthrough events. Although efficacy data following autoHCT exist, the safety and immunogenicity of SHINGRIX after alloHCT have not been prospectively studied. A recent retrospective analysis of 17 alloHCT patients 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.

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B: Prospective observational study of the immunogenicity of the available mRNA vaccines for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine after autologous HCT, allogeneic HCT, 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 recipients.

Background and Significance: HCT/CAR-T patients are at increased risk for serious infection with SARS-CoV-2.[39] Although influenza vaccination is more immunogenic when given ≥6 months after HCT, earlier vaccination (~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 recipients receiving an mRNA SARS-CoV-2 vaccine in the first year following cell infusion. Cohorts will be autoHCT, alloHCT, and CAR-T patients either <6 months or 6–12 months post infusion. 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 Strategy 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 transplant for patients receiving reduced intensity conditioning and PTCy.

Hypothesis: Treatment with recombinant IL-7 early post-transplant will improve disease-free survival by decreasing relapse and infections following matched donor transplant with PT-Cy-based GVHD prophylaxis.

Background and Significance: Inadequate immune recovery after alloHCT is associated with increased risks of relapse and infection.[40] Thus, strategies to enhance T-cell reconstitution may decrease morbidity and mortality from relapse and infection. Interleukin-7 (IL-7) has a central role in T-cell development demonstrating enhanced thymopoiesis and peripheral T-cell survival and expansion.[41] A prior phase I trial of rhIL-7 (CYT107, Cytheris Inc) following T-cell depleted HCT demonstrated an increase in CD4+ and CD8+ T-cells and functional T-cell responses without development of GVHD, anti-IL-7 antibodies, or neutralizing antibodies.[42] Although PT-Cy results in lower rates of GVHD, the risk of post-transplant 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 reduced intensity conditioning and HLA-matched HCT with PT-Cy, Tacrolimus, and MMF who have no

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evidence of relapse, grade II–IV aGVHD, or uncontrolled infection will be randomized to receive 3 weekly doses of rhIL-7 between days 45–70 after HCT or usual care. Two-year disease-free survival (DFS) is the primary endpoint with secondary endpoints including infection, relapse, GVHD, and immune reconstitution endpoints.

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

Summary of Discussion

Both the external and on-line reviewers expressed enthusiasm for Strategies 1 and 2 and considered the concepts feasible and important. Strategy 3 was considered premature given lack of available data in T-replete grafts following PT-Cy. Due to the importance of Strategy 2B, assessment of 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. There were reasonable concerns raised regarding lack of inclusion of autoHCT patients, the difficulty of adherence to the planned de-escalation, and logistical issues. The committee discussed inclusion of autoHCT patients; however, since most fevers in this population are peri-engraftment, it is unlikely that these patients would remain on IV antibiotics longer than 72 hours if the infection work-up was negative. Adherence to planned de-escalation 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 non-adherence. 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 accrual and collection of microbiome samples prior to 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 since eligibility criteria are broad, add to the growing literature of the microbiome in cellular therapy patients, and potentially change practice. The short endpoint will allow 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 transplant-related effects and survivorship[44]. Although to date there is only one BMT CTN trial with patient-reported outcomes (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 (e.g., fatigue, cardiovascular disease, exercise/health behaviors, financial toxicity), but concluded that lack of data, logistics, and feasibility limit their

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immediate appropriateness for BMT CTN involvement. Instead, the committee focused on the following 3 studies that were viewed as ready for implementation: 1) Distress-related biology, 2) Survivorship screening and preventative care and 3) Standardization of PRO collection.

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

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

Background and Significance: Bio-behavioral research evaluating the relationship between psychosocial factors and tumor progression/immunity[46] is limited in HCT. Psychological distress and related factors are associated with increased sympathetic nervous system (SNS) 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 disease-free-survival in HCT.[47] Propranolol is a non-selective ß-adrenergic receptor antagonist which blocks SNS signaling. A phase 2 study of autologous HCT recipients demonstrated that propranolol administration was safe, had high adherence, and resulted in decreased CTRA expression with a trend toward faster engraftment and fewer infections.[48] Propranolol is thus a low cost, safe intervention to decrease distress-related biology and improve transplant outcomes.

Trial Design and Outcomes: The committee proposed a phase 3 randomized study of propranolol versus placebo in autologous HCT for MM or lymphoma with a primary endpoint of days alive out of the hospital through 100 days. Secondary objectives include effect on CTRA profile, PROs, and cost. Randomization will be stratified by disease and whether HCT is planned inpatient or outpatient. From the CIBMTR data, it was estimated that among hospitalized patients, the mean (standard deviation) of days in the hospital was 15 (6.5). Propranolol will be given 2 weeks prior to 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 two-sided 0.05 significance level.

Feasibility and Logistics: This study is feasible with a straightforward design. Biologic samples will be collected and stored for batch analysis. The high number of autologous HCT, 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 ASTCT/CIBMTR/EBMT survivorship guidelines for screening and preventive care,[49] no study has systematically assessed compliance with these guidelines and missed opportunities for better survivorship care in a multicenter setting.[50]

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Trial Design and Outcomes: This is a single arm, pre-/post intervention design. Medical records two years prior to 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: first allogeneic HCT, adult and pediatric survivors 3+ years post-HCT with no evidence of relapse, and ongoing care at the transplant center. We assume 80% of participants will have at least one missed screening and that 10% of participants completing the recommended evaluation would subsequently require medical intervention. Thirty centers each contributing 30 patients meeting eligibility criteria (900 patients, accrual period 3 years, study duration 4 years) transplanted between 2010–2018 from centers with diverse characteristics will results in a good estimate of the missed screening rate (95% CI 77–83%) and an ability to explore patient and transplant center factors associated with lower screening compliance.

Feasibility and Logistics: This study is feasible and straightforward, however 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 quality of life (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 PROs 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. Additional use of short symptom/toxicity assessments relevant to study interventions/objectives may be added per protocol. The CIBMTR recently demonstrated 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) given 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. Co-enrollment on the CIBMTR PRO protocol also allows for late PRO collection and follow up beyond completion of the parent trial.

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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 bio behavioral relationship between distress and clinical outcomes in HCT using a safe, low cost, and feasible intervention. The primary issues raised from SOSS participants were regarding 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 anti-hypertensive, which were addressed from data in the Phase 2 trial. Although additional details require resolution, the committee remains enthusiastic regarding this as a research priority for the HCT field. Although noted to be 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 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. Autologous or allogeneic HCT consolidation remain standard therapies for many lymphoma subtypes. In unforeseen ways, CAR-T 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 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 as frontline, after lead-in immunotherapy, will safely improve PFS in UHR MCL.

Background: Two-year PFS ranges from 20–50% 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 has demonstrated remarkable efficacy in refractory MCL, with brexucabtagene autoleucel showing 85% overall response rate (ORR) and 61% 12-month PFS.[55]

Trial Design: The committee endorsed a single arm phase II trial of front-line CD19-CAR-T after lead-in BTKi+. Before enrollment, <=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 phenotype, and CAR-T levels.

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Feasibility and Logistics: We estimate 2-year PFS at 45% and 65% in historical and treatment groups respectively.[56] 54 patients are needed to detect 20% improvement, with 90% power and one-sided 0.05 alpha for an exact-binomial test. For interim monitoring, sample size is inflated to 60. 18-month accrual and 24-month follow-up is estimated. The trial requires sponsor support to provide the CAR-T product and BTKi. Alternate designs were considered including a randomized phase II against best available care in frontline or a randomized trial comparing CAR-T consolidation vs. autoHCT following standard induction in responders.

Strategy 2. A phase III randomized trial of observation vs. 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 PTCL patients who achieved CR with frontline BV+CHP.

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

Trial Design: The committee endorsed a phase III trial randomizing CD30+PTCL patients that achieved a CR after frontline BV-CHP to observation or consolidative AutoHCT (BEAM or TBI-based conditioning). Eligible diseases include PTCL-NOS, ALK-ALCL, and AITL. ≥1% malignant cells must be CD30+. The primary endpoint is 2-year PFS. Secondary endpoints include adverse events, OS, and exploratory prognostic markers (ctDNA 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 two-sided 0.05 alpha and four O'Brien-Fleming looks. PTCL is rare with <1 case per 100,000 people in the US per year, with ~50% having eligible histology. Although CR rates to BV-CHP are high, ~30% would not achieve a CR and fail screening. Significant participation is required to complete accrual in 4-years with an average of 321 auto-HCT in eligible diseases per year recorded by CIBMTR from 2015–2019.

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-CAR-T.

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

Background: 65–75% of DLBCL patients with PR, and 90–95% with SD, on day+28 PET-CT scan after CAR-T will progress by 1-year.[54,59] This group comprises ~40% of CAR-T

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patients and responses can deepen; therefore, observation is standard. MRD monitoring at day+28 may identify those destined to progress. Consolidation could improve outcomes via anti-tumor activity or CAR-T 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 to observation, for incomplete responders to commercial CAR-T 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 persistence, and tumor assessments.

Feasibility and Logistics: After CD19-CAR-T, 5% of SD and 30% of PR patients at day+28 will be in remission at day+90, and only 75% of those will persist at 1 year.[59] 57 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 one-sided 10% alpha for each comparison against the standard arm.

Strategy 4. A randomized phase III trial of consolidative AutoHCT with BEAM+Bcl-2 inhibitor conditioning vs. CD19-CAR-T in partially chemotherapy-responsive relapsed/refractory DLBCL.

Hypothesis: Bcl-2 based autoHCT conditioning or CAR-T consolidation may improve outcomes for patients with partial response to second line chemotherapy.

Background: Three CD19-CAR-T therapies are approved for third line in DLBCL. AutoHCT utilization has decreased as consolidation does not cure most patients with PET+ disease (i.e., PR) after second line chemotherapy. CAR-T is commonly used for these patients. Early results indicate venetoclax, which chemo-sensitizes lymphoma,[62] is safe when added to BEAM.[63] Phase III trials comparing second-line CAR-T vs. chemotherapy or autoHCT are ongoing (NCT03391466), however questions will remain. In these protocols, patients randomized to salvage received autoHCT even if in PR, while CAR-T might be preferable. If CAR-T proves optimal, many patients will get second-line salvage 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 vs. venetoclax+BEAM and autoHCT for DLBCL in PR (i.e., 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, non-relapse mortality (NRM), adverse events and immune reconstitution.

Feasibility and Logistics: 1-year PFS after autoHCT for patients in PR is ~50%,[62] and CAR-T could achieve 70%. 204 randomized subjects could detect 20% improvement using a two-sample binomial test with 2-sided 0.05 alpha at 80% power. Between 600–1300 patients/year undergo autoHCT for DLBCL in the U.S. About 25% obtain PR to salvage,

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therefore 150–325 potentially eligible patients/year inform an estimated 4-year accrual. There was disinterest in a third, standard BEAM conditioning arm, believed to complicate accrual feasibility.

Summary of Discussion

There was considerable enthusiasm for both Strategy 1, which requires CAR-T sponsor support, and Strategy 3, which is already in development by SWOG. It was felt both trials would answer critical questions and benefit from the expertise of the BMT CTN. There was less enthusiasm for Strategy 2 since PTCL patients are rare and the optimal frontline strategy remains uncertain, and for Strategy 4 with 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 witnessed many advances in the treatment of myeloid malignancies including multiple newly approved therapies, improvements in alloHCT practices and development of sensitive diagnostics that have led to better understanding of pathophysiology and more accurate judgment of response to therapy. Sensitive detection of MRD has emerged as a potential metric to guide treatment decisions, yet uncertainty 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 which may be able to be safely administered after alloHCT and potentially decrease the risk of relapse. This committee therefore chose to focus on: 1) the establishment of a prospective multi-center cohort to both validate the utility of MRD testing and to better understand the mechanisms of 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 transplant to understand relapse events (MEASURE)

Hypotheses:

1. Serial blood monitoring by DNA-sequencing after alloHCT will have superior ability to predict relapse compared to pre-HCT stratification.
2. Collection of post-HCT relapse samples will allow quantification of leukemic clonal selection versus immunological escape as mechanisms of failure.

Background and Significance: For AML patients in cytomorphological 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, while AML relapse remains the primary mode of failure after alloHCT, and single-center reports

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suggest this may be immunological in nature, no large-scale, systematic evaluation of the mechanism of failure has been conducted.

Trial Design: The committee proposed a prospective multi-center biobanking cohort of approximately 1,000 AML patients aged 18–75 undergoing alloHCT in CR, for whom original diagnostic material is available. Blood will be collected prior to conditioning and at 30 days, 3mo, 6mo, 9mo, 12mo, 15mo, 18mo post-HCT together with marrow and blood at disease relapse. Given the known genetic diversity of AML, a sample size of 1,000 is required to ensure sufficient cases of each molecular subtype to provide robust and generalizable knowledge.

Feasibility and Logistics: An analogous prospective multi-center protocol, BMT-CTN 1202, successfully enrolled 1,860 participants with 8 biospecimen timepoints. Estimated time for accrual would be 4 years with co-enrollment 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 CR1 will decrease relapse.

Background and Significance: Relapse remains the leading cause of death after alloHCT for patients with AML.[67] Patients at high relapse risk can often be prospectively identified 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 3 randomized trial.

Trial Design: The committee proposed an umbrella type platform trial to test multiple therapeutic candidates as maintenance therapy for adverse risk AML in CR1 as defined by 2017 European LeukemiaNet Classification.[69] The primary endpoint will be 1-year PFS given the majority of relapses occur in the first year after alloHCT. Candidate agents will be either targeted or non-targeted, 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, 1,000 patients with adverse risk AML undergo alloHCT each year in the US. 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 the one-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.

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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 if undergoing alloHCT.[70,71] Improvements in pre-HCT therapy with newer agents[72] will likely allow more p53-mutated patients to be eligible for alloHCT. Administration of maintenance therapy after alloHCT has the potential to reduce rates of relapse, leading to improvements in survival.

Trial Design: An umbrella type platform trial that will accommodate several sub-studies of therapeutic candidates that are either p53 targeted or non-targeted and can include both drug candidates and cellular therapeutics. The primary endpoint of the platform study will be 1-year PFS. Individual sub-studies will have tailored efficacy endpoints with a pre-determined efficacy threshold for subsequent testing in a phase III trial. This trial can either be 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 each year with p53 mutated myeloid malignancies undergo HCT in the US. 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 exactone-sample binomial test, 65 patients per study would provide 80% power at the one-sided 0.05 significance level to detect a 15% improvement in PFS.

Summary of Discussion

There was significant enthusiasm expressed for all three concepts 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 which had been tested in appropriate phase I studies to identify a safe and effective dose to be used in the post-HCT setting. In addition, questions of how to incorporate the various measures of MRD into eligibility for Strategy 2 and 3 were posed. Nevertheless, all three concepts were felt to be of high priority to be conducted 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. Non-malignant disorders are rare and account for approximately 5% of HCT activity. This rarity also limits expertise in transplanting these diseases. Nonetheless, HCT for nonmalignant diseases

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has high potential to cure a large proportion of recipients, most of whom are young. If optimally applied with low-toxicity, good efficacy and engraftment/immune reconstitution, HCT can become available to all who require it. Given their low incidence, the role of HCT for these diseases can only become established in conventional clinical practice through well-designed multi-center 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 here propose three multi-center phase II trials.

Strategy 1. Immune reconstitution for primary immune regulatory disorders (PIRD) utilizing 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: PIRDs 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 reduced-intensity conditioning, peripheral blood graft and GVHD prophylaxis that includes PT-Cy based upon available pilot data. The primary endpoint is 2-year survival with phenotype reversal of hematopoietic and immunologic abnormalities that are disorder-specific. Target accrual is 36 patients over 4 years. The historical control rate for such reversal is 55%.[76] We will estimate the 95% confidence interval for the proportion of patients with one-year successful phenotype reversal without additional intervention, the goal being 70%. If indeed the proportion is 70%, the 95% confidence interval will be 55%–85%. Thus, if the 2-year proportion with phenotype reversal is 70% or higher, 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 ~25 HCTs for eligible diseases in North America between 2014–2016. Increasing awareness of these diagnoses and a standardized protocol for HCT is 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 BMT for adults with SAA will result in improved cure, regardless of age and donor.

Background and Significance: Immunosuppressive therapy (IST) is standard front-line treatment for SAA, except for patients aged <25 years with a suitable HLA-matched sibling for BMT.[77,78] The hematopoietic response after IST is ~ 70%–80% and 5-year survival,

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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 aged < 20 years and 75% in older patients.[80] Currently, BMT with an unrelated or HLA-haploidentical related donor is reserved 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 newly diagnosed adults with SAA, using conditioning with ATG, Cy, Fludarabine and TBI, bone marrow graft from a haploidentical (cohort 1, 30 patients) or unrelated (cohort 2, 30 patients) donor and PT-Cy-containing GVHD prophylaxis. . The primary objective is to estimate the overall 1-year survival in each cohort with the goal of achieving > 75% 1-year survival. If 23 (77%) of 30 patients survive at least 1 year, we will be 95% confident that the true 1-year survival rate is at least 60%. If 27 (90%) of 30 patients survive at least 1 year, we will be 95% confident that the true 1-year survival 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 agent will achieve durable myeloid engraftment, eradicate clonal hematopoiesis, and minimize toxicity.

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) that uses alemtuzumab/fludarabine for pre-transplant conditioning addresses an unmet need.

Trial design: We propose two single-armed trials, one in marrow failure (BMF) and one in low-grade MDS. Alemtuzumab/fludarabine will be utilized with marrow grafts from related (matched or single allele mismatched) or unrelated donors. For BMF, the primary endpoint will be 1-year survival.

For the MDS arm, the primary endpoint will be 1-year relapse-free survival (RFS), assuming ≥ 70% 1-year RFS compared to historical 40%. With 30 patients, the lower bound of the 95% confidence interval will be 53% and we will be 95% confident that this regimen improves survival.

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

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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 in 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 had enthusiasm, given current HCT results are suboptimal for these genetic disorders. However, there was concern about the balance of TRM and long-term effects with relapse in the MDS cohort. Accrual was also felt to be a challenge. Strategy 1, HCT for primary immune regulatory disorders, was noted to be a key concept as these disorders are increasing recognized as potentially cured though HCT. Limitations noted included interpretation of the results with grouping genetically heterogeneous disorders into one 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 transplantation due to donor availability. Use of PT-Cy, pioneered for haploidentical HCT, now extends into HLA-mismatched unrelated donor and matched donor settings. The most common graft type used for all of these donor options is peripheral blood stem cells (PBSC). Important questions to address include identifying and comparing the relative efficacy of the best haploidentical and unrelated donors, optimal GVHD prophylaxis for HLA-mismatched unrelated donor transplantation, and novel applications for UCB transplantation.

Strategy 1. Haploidentical vs Unrelated Donor (UD) Transplantation with PT-Cy and PBSC

Hypothesis: HCT with UDs (intervention) provide better two-year overall survival than haploidentical (control).

Background and Significance: Control of alloreactivity by PT-Cy enabled widespread use of haploidentical HCT. Retrospective comparisons demonstrate similar survival with haplo/PT-Cy and HLA-matched UDs with calcineurin inhibitor (CNI)-based GVHD prophylaxis[84–86]. PT-Cy may improve outcomes following HLA-matched and mismatched UD transplants and UDs may allow optimizing other donor characteristics, such as donor age[87]. This will be the first randomized comparison of haploidentical HCT with UD using PT-Cy for both arms. Results could improve access to and outcomes of HCT for ethnically diverse patients.

Trial Design: This Phase III trial randomizes patients to receive the best available UD (8/8 or 7/8) vs best haploidentical PBSC graft with different strata for myeloablative and reduced intensity conditioning. GVHD prophylaxis is PT-Cy/mycophenolate mofetil/CNI. Patients 18–75 years old with acute leukemia in remission or myelodysplasia are included. The primary endpoint is two-year survival; analysis is by intention to treat. Secondary endpoints include transplant-related mortality, relapse, GVHD, time to transplant, cytokine release

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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 >2000 patients eligible for this study transplanted in the U.S. annually. Anticipated accrual time is 2–3 years.

Strategy 2. Randomized Phase II Study to Compare Three GVHD Prophylaxis

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

Background and Significance: This trial extends HCT to patients without HLA-matched donors, addressing GVHD and survival using PBSC from MMUDs. PT-Cy/CNI/MMF is the most common approach to MMUD HCT with data showing ~50% relative reduction of chronic GVHD risk using PT-Cy/CNI/MMF after MMUD BMT[88]. However, 78% of UD 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 would compare one-year survival after 7/8 matched UD PBSC with ABA/CNI/MTX and with SRL/MMF/CNI against PT-Cy/CNI/MMF. Conditioning will be reduced intensity, with identical regimens in each arm. Included are patients aged 18–75 with acute leukemia in first or second complete remission or myelodysplasia with <5% blasts, and no available matched UD. Donor selection guidelines will be included. A key secondary endpoint is chronic GVHD-free, relapse-free survival. Others are transplant-related mortality, relapse, GVHD, and quality of life. Assuming 60% survival with PT-Cy/CNI/MMF, 375 total patients will be required to have 80% power to detect an absolute 15% survival improvement at the two-sided 0.10 significance level for each of the two comparisons against PT-Cy/CNI/MMF.

Feasibility and Logistics: Based on CIBMTR data, >1000 patients eligible for this study are transplanted in the U.S. annually, ~250 of whom receive MMUD transplants; others receive cord or haploidentical transplants. Anticipated accrual time is 3 years.

Strategy 3. Reducing Toxicity of UCB Transplantation in Leukodystrophies

Hypothesis: Expanded UCB enables use of RIC without compromising engraftment or survival.

Background and Significance: UCB transplantation increases survival and improves quality of life in children with inherited metabolic disease and leukodystrophies. Potential donors cannot be disease carriers, limiting related donor use. Myeloablative conditioning ensures sustained engraftment with the full donor chimerism necessary to control disease but causes high morbidity[91,92]. Dose reduction has failed because of excess graft failure.

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Expanded UCB may overcome resistance to engraftment with RIC. Omidubicel, an expanded UCB product, showed 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 stable disease who can wait 21 days for graft expansion. Primary endpoint is one-year survival with sustained neutrophil engraftment and >90% donor chimerism. Historical rates in patients receiving myeloablative busulfan/Cy/ATG are 88%. The study uses Simon's two-stage minimax design with 36 successes in 39 participants needed to continue to full sample size of 57. If 53 of 57 successes are observed, the 90% confidence interval for the success rate is 85–98%. The study has 80% power with a one-sided 5% significance level to rule out a < 85% success rate.

Feasibility and Logistics: There are ~40 patients with eligible diseases treated with UCB transplants yearly at ~15 centers. Twelve centers have tentatively agreed to participate. Estimated accrual is four years.

Summary of Discussion:

Strategy 1, "Best Haplo vs Best UD," was one of the highest scoring proposals in the SOSS, addressing a critical question that can only be answered by the Network. It seeks to optimize HCT outcomes for all patients but is particularly important for patients who do not have a matched UD, which includes most patients from minority racial and ethnic groups. Ongoing studies in Europe address different questions, such as haploidentical vs HLA-matched UD HCT, and do not serve the U.S.'s ethnically diverse population. 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 difficult to answer 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 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 (CT) in pediatric patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS). The development of CAR-T cells that target CD19 dramatically improved therapeutic options for children with relapsed or refractory B-ALL. However, CAR-T therapies are available for only a fraction of children with malignancies and, even with the advent of CAR therapies, relapse remains common. The Pediatric Malignancy SOSS proposed three approaches to prevent or treat relapse after transplant for lymphoid and myeloid malignancies.

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Strategy 1: A Risk-Based Approach to Optimize Remission Duration Following CD19-CAR T-Cell Therapy.

Hypothesis: Risk assessment based on minimal residual disease and B-cell aplasia post-CAR T therapy can appropriately allocate patients who are in most need of HCT.

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

Molecular next-generation sequencing (NGS) MRD measurements[95] suggest that: (1) NGS testing of bone marrow and blood are both more sensitive than flow cytometry of bone marrow in identifying residual disease; (2) Any non-zero 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 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 therapy are at high-risk of relapse.

Trial Design: Pediatric patients with relapsed/refractory B-ALL treated with CD19-directed CAR T-cells, 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-Ts, or with any evidence of NGS-positive MRD will undergo HCT, while patients without either risk factor will continue observation. A non-randomized third arm for patients who refuse randomization will constitute a natural history cohort to enable robust real-world data collection of 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 treatment without compromising LFS. Approximately 150 pediatric patients are infused with the commercial FDA approved CD19 CAR T-cell product (tisagenlecleucel)/year. A non-inferiority design using a margin of 15% (70% vs 55% LFS) could be completed by enrolling 240 patients over a 3-year period. This design has 80% power for a one-sided 90% confidence bound when the true 1-year LFS rates are 70% for consolidative HCT and 68% for risk-based monitoring. Enrollment to a trial incorporating utilization of a systematic approach to HCT and risk-stratification is expected to enroll rapidly.

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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 (12–14 days) and limited expansion and persistence in vivo. Recent advances in expansion strategies such as co-culture with irradiated K562 feeder cells expressing 4-1BB and membrane bound IL-21 have overcome the problem of limited expansion with an average 20–80,000-fold expansion of highly functional NK cells in three 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 “Cytokine-Induced Memory-Like” NK cells (CIML-NK cells).[101,102] CIML-NK cells exhibit potent anti-leukemia 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 for relapsed AML post-HCT.

Trial design: Phase 1/1b trial to determine the safety and feasibility of CIML-NK cell infusion with IL-2 after haploidentical and matched-sibling donor transplant for pediatric patients with post-HCT AML relapse. An expansion phase 1b cohort will be used to collect additional safety data and obtain preliminary efficacy data. Secondary objectives include determining CR/CRi rates and detectability of MRD at day +28 after CIML-NK cell infusion, incidence and severity of acute and chronic GVHD, 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 1 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 DLT observation period of 60 days. 5–10 patients will be enrolled in phase I to determine the safe dose, and 10 additional patients will be treated at the MTD as an expansion cohort. If we assume 15 subjects are treated at the MTD (phase I + phase Ib) and that the true CR rate is 65%, we will have 88% power at the one-sided 0.1 significance level to detect a statistically significantly improvement in CRs over the benchmark of 30%. If 10 (67%) subjects out of 15 subjects 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 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, collect, and expand NK cells. Be the Match Biotherapies (BTMB) has established an NK cell bank utilizing donors who have optimal HLA and killer Ig-like receptor (KIR) genotypes for education, a high proportion of activating KIRs corresponding to B-haplotype content, and CMV exposure,

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resulting in NKG2C+ “memory” NK cells. These universal-donor NK cells are currently being studied for adult relapsed AML/MDS (NCT04220684).

Hypothesis: Universal donor NK cells following re-induction chemotherapy will increase the CR rate and promote long-term anti-leukemic immunity to sustain remission duration.

Trial Design: A phase 1 safety lead-in will determine the safety and recommended phase 2 dose of mbIL21-expanded, off-the-shelf, third-party donor-derived NK cells in pediatric patients with relapsed/refractory AML. During phase 2, 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 from the first infusion of NK cells. The historical experience of the chemotherapy backbone (FLAG) in this patient population in observing a good response (CR, CRi) is ≤ 65%. Targeting a 20% increase in the response rate to 85% with addition of NK cells, a sample of 35 patients will yield approximately 85% power with a 5% type I error rate using a one-sided binomial test. The response rate with exact binomial 95% confidence intervals (CI) will be reported for all patients who received at least one 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 BTMB, with additional donor collections and expansions ongoing. These cells are able to 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 65% 5y OS, and approximately 2/3 of those with failure due to relapse, there will be an estimated 160 eligible patients per year. If only 10% of those patients are recruited on this study accrual could be complete 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 deploy CAR T-cell and HCT therapies to optimize LFS while minimizing toxicity. There was significant enthusiasm for this approach, with questions centered on statistical design, the acceptability of a 15% non-inferiority margin and the potential to test superiority of the risk-assessment-based versus straight-to-transplant approach. For patients with myeloid malignancies, proposed trials focus on multi-center evaluation of promising NK-cell therapies for treatment of post-transplant relapse. Comments at the SOSS focused on feasibility of multi-center 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.

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PLASMA CELL DISORDERS COMMITTEE

Current State of the Science

Treatment of myeloma is rapidly changing. Since the 2014 SOSS, FDA approvals of monoclonal antibodies and immunoconjugates, agents with novel mechanisms of action (e.g., selinexor and melfluflan), and even BCMA-directed CAR T cells have revolutionized the treatment of myeloma. 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 autologous HCT (autoHCT) into the early therapy of patients to best deepen and prolong remission is the focus of this committee's proposals. BMT CTN 0702 and 07FT defined the current standard of care for newly diagnosed multiple myeloma[104] (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 adjuvant to autoHCT. The areas of highest interest as identified by this SOSS committee were: 1) improving survival in high-risk myeloma using immunotherapy consolidation post autoHCT; 2) establishing long term PFS in standard risk multiple myeloma (MM) through sustained deep remissions and 3) converting CAR T cell responses into longer PFS times by planned post CAR T 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 consolidation & T cell engagers after autoHCT in newly diagnosed high risk MM

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

Background: Clinical outcomes for standard risk MM patients have dramatically improved but results in high-risk myeloma continue to lag significantly. Trials specific to high-risk patients have also 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 therapy and post CAR T maintenance with T cell engager.

Trial Design: Transplant eligible patients with R-ISS3 or R-ISS2 and with 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 maintenance (PI/IMID/steroids). MRD by NGS maintenance will be measured post-transplant at intervals of 3; 6 and at 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 seq/Immunoseq/ Mass Cytometry and CAR-T 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 pts will need to be randomized over 3 years of accrual with 3 years of follow up on the last patient.

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Feasibility and Logistics: Multiple BMT CTN centers will enroll patients referred for autoHCT to study as quadruplet induction is expected to be standard prior to autoHCT within the next 2–3 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 TCE will extend PFS without need for indefinite therapy.

Background: Sustained elimination of MRD correlates with significant long term PFS in standard risk myeloma. After quadruplet induction approximately 30% are MRD neg (10^{-5}). For these patients who are at low risk of relapse, we re-examine the utility of tradition autoHCT/maintenance (vs. TCE maintenance). For the majority who are MRD-positive, the best post autoHCT maintenance will be studied (T cell engager vs. standard-of-care).

Trial Design: Standard-risk MM patients (defined as per strategy 1) will be enrolled and stratified based on MRD (10^{-5}) after quadruplet induction. MRD neg pts will be randomized to either arm A. autoHCT followed by anti CD38 mAB + len maintenance or TCE alone (no autoHCT) for 1 year. (arm B). MRD positive patients will receive autoHCT and then be randomized to maintenance with either Len/anti CD38 mAb (arm C) or TCE (arm D) for 1 year. Those with sustained MRD negativity at 12 months will discontinue therapy and be followed for recurrence of MRD / IMWG relapse.

Feasibility and Logistics: From BMT CTN centers, 200 SRMM pts each will be enrolled in the MRD neg 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/B and similar improvement in PFS in arms C/D. Approximately 2/3 of MM patients referred for upfront autoHCT to BMT CTN centers are expected to be eligible based on SRMM criteria.

Strategy 3. A phase 2 trial addressing relapse after BCMA-directed CAR T therapy in relapsed refractory multiple myeloma

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

Background and Significance: After anti BCMA CAR T in relapsed refractory MM, relapse is near universal but strategies that address residual disease elimination and post CAR immune modulation may offer a solution.

Trial Design: A randomized three-arm, phase 2 trial will allocate patients to monitoring and QOL follow up after commercial BCMA CART for relapsed refractory MM (controls) vs. either BCMA directed T cell engager or IMID maintenance (lenalidomide) for 6 months as a planned post CAR T maintenance. All patients will have central biomarker testing for PD-1 expression; MRD levels and mechanisms and will be followed until relapse to establish relapse mechanisms. Each intervention arm will target a 7-month improvement in

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median PFS from 11 months (controls) to 18 months. The accrual goal is 123 patients per arm over 3 years with 18 months follow-up after the last patient entered. This will provide 80% power for testing each of the three comparisons at the two-sided 0.05/3 = 0.0167 significance level using a logrank test. If 2 different CAR T 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 feasible for BMT CTN centers. The trial will also develop and validate biomarker assays that inform the mechanisms of relapse in this setting. Also, the availability of numerous new agents (CelMOds/non-BCMA immune targets and new check point inhibitors) will create a rapid testing platform for post CAR approaches which can be incrementally added on as study arms.

Summary of Discussion

The BMT CTN myeloma portfolio at this time is evolving from autologous and allogeneic transplant strategies to novel cellular immunotherapy and the emerging compelling questions of post-immunotherapy maintenance and time limited therapy. There was strong enthusiasm for Strategy 1, which will address a major unmet role in MM which has no overlap with any other ongoing cooperative group efforts.

DESIGN COMMITTEE

Current State of the Science

Innovative trial designs are needed to quicken development of HCT therapies. The adaptive platform trial (APT) studies multiple treatments for a single disease in a continual manner, dropping a treatment arm due to 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, respectively, 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. We now discuss aspects of an APT as well as other adaptive trial designs.

APT Logistics—An APT is governed by a master protocol which contains generic components which 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.

Due to its continual manner, several aspects must be considered for an APT. For the pre-trial regulatory review, the US Food and Drug Administration (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 since an APT does not fall under the

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traditional NIH funding paradigm for trials with fixed sample sizes and timelines. However, an APT's ongoing research program might be attractive to a non-profit organization and industry. An industry sponsor who has multiple products in their 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 non-profit/industry/academic/government partnership.[110]

APT Limitations—While an APT can provide efficiencies, 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 may 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 as opposed to a phase II APT. In phase III, an industry partner will typically only want to compare to a control arm and not to experimental arms. Also, a phase II–III APT needs pre-specified 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 two 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, e.g., larger type I error versus control, than the phase III criteria. 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 decided whether to continue randomizing patients after the phase II accrual has finished, but its results are pending. Pausing accrual will prevent over-accrual 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, APT complexities, 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 charge of the committee 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 three key strategies.

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Strategy 1. Enhancing committee diversity and representation

Background: The BMTCTN has several discipline 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: In order to improve committee representation, we assigned a liaison from our committee to each of the other BMTCTN SOSS committees to identify opportunities to address and reduce disparities and access issues during study development. Our committee also works in collaboration with the BMTCTN Special Populations Committee on their initiative to attract and recruit members of diverse origin to all committees in BMTCTN.

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 BMTCTN 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 is >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 BMTCTN studies since its 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 vs. private). These data can be compared to the baseline of potentially eligible patients undergoing transplantation during the same period, as reported to 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.

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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 have 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 people 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 American Society for Transplantation and Cell Therapy and Be the Match to disseminate information and tools effectively. Examples of possible projects include 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: A total of two to three process improvement projects will be developed, based on the results of the analysis performed on 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 as they felt 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 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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Disclosures

HEH has equity in Allovir and Marker Therapeutics, has served on advisory boards for Gilead Sciences, Kiadis Pharma, Novartis, GSK and Tessa Therapeutics and has research support from Tessa Therapeutics and Kuur Therapeutics. JEL is a co-inventor of a GVHD biomarkers patent and receives royalties from Viracor, consulting fees and research support from Incyte, research support from Kamada and Biogen. RP reports research support from Amgen. RTM is a consultant for AlloVir, Artiva, CRISPR Therapeutics, Incyte, and Novartis; reports honoraria from Bristol-Myers Squibb, Incyte, Intellia, Gilead, Omeros, Orca BioSystems, and PACT Pharma; research support from Bristol-Myers Squibb and Novartis; participation in a data and safety monitoring board for Athersys, Novartis and Vor Pharmaceutials and holds a patent with Athersys.

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- The BMT-CTN held its 4th State of the Science Symposium in 2021 and this article summarizes the individual committee reports and a list of those trials presented in the virtual SOSS meeting
- There are reports from Modality or disease-based committee summarizing the highest priority trials
- There are also reports from cross-cutting committees that considered design, diversity, and access to trials

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Table 1:

Results of 2014 SOSS Committee Recommendations

Committee	Trial Title	Action	Outcome
Leukemia	Phase III study of post-allogeneic 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 Multi-center, 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 autologous transplantation 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 autologous transplantation 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 T reatment-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 Center for International Blood and Marrow Transplant Research 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 chronic GVHD	***Not yet implemented***	
Optimal donor and graft source	Phase II study of haploidentical peripheral blood stem cells and PTCY after myeloablative conditioning	Development of a protocol using myeloablative conditioning with haploidentical donors was presented by the Optimal Donor and Graft Source State of the Science Symposium 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 two studies: **1** *In low risk acute GVHD*: 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 **2** *In high risk acute GVHD*: BMT CTN 1705 - A Randomized, Double-Blind, Placebo-Controlled Multicenter Phase III Trial of Alpha 1 – Antitrypsin (AAT) Combined with Corticosteroids vs Corticosteroids Alone for the Treatment of High Risk Acute Graft-versus-Host Disease (GVHD) Following Allogeneic Hematopoietic Stem Cell Transplant	BMT CTN 1501 completed accrual in February 2018; manuscript published (Pidala et al. Blood 2020) 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: Haplo-Identical Natural Killer (NK) Cells To Prevent Post-Transplant Relapse In AML and MDS (NK-REALM)	BMT CTN 1803 was approved by the DSMB in May 2019 but activation was delayed due

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Committee	Trial Title	Action	Outcome
			to manufacturing issues; the study was discontinued when the sponsoring company was purchased.
Comorbidity/RRT	Development of a more robust risk assessment method incorporating biomarkers and geriatric assessment tools	Led to the development of BMT CTN 1704: Composite Health Assessment Model for Older Adults (CHARM): Applying pre-transplant Comorbidity, Geriatric Assessment, and Biomarkers to Predict Non-Relapse 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 co-morbidity/RRT proposal to evaluate microbiome biomarkers.	Accrual is ongoing.
Infection/ immune reconstitution	Phase III study of CMV-specific T cell adoptive therapy.	***Not yet implemented***	
Infection/ immune reconstitution	Phase II study of a novel PIV 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 allogeneic HCT	***Not yet implemented***	

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Table 2

BMT CTN SOSS Committees and Reviewers

Committee/Position	Members
Committee 1: Clinical Trial Design	
Chair:	Eric Leifer, National Heart, Lung, and Blood Institute, Bethesda
Members:	Amer Beitinjaneh, University of Miami, Coral Gables Peter Dawson, The Emmes Company, Rockville Nancy Geller, National Heart, Lung, and Blood Institute, Bethesda Haesook Kim, Dana-Farber Cancer Institute, Boston Brent Logan, Medical College of Wisconsin, Milwaukee Brian Shaffer, Memorial Sloan-Kettering Cancer Center, New York Jesse Troy, Duke University, Durham Daniel Weisdorf, University of Minnesota, Minneapolis Juan Wu, The Emmes Company, Rockville Qian Wu, Fred Hutchinson Cancer Research Center, Seattle
Outside reviewers:	N/A
Committee 2: Comorbidity & Regimen Related Toxicity	
Chair:	Richard Maziarz, Oregon Health & Science University, Portland
Members:	Rajni Agarwal, Stanford University, Stanford Andrew Artz, City of Hope, Duarte Vijaya Bhatt, University of Nebraska, Omaha Saurabh Chhabra, Medical College of Wisconsin, Milwaukee Kenneth Cooke, Johns Hopkins University, Baltimore Jordan Gautier, Fred Hutchinson Cancer Research Center, Seattle Tamila Kindwall-Keller, University of Virginia, Charlottesville Richard Lin, Memorial Sloan-Kettering Cancer Center, New York John McCarty, Virginia Commonwealth University, Richmond Edward Stadtmauer, University of Pennsylvania, Philadelphia Gregory Yanik, University of Michigan, Ann Arbor
Outside reviewers:	Richard Champlin, MD Anderson Cancer Center, Houston Jeffrey Szer, Royal Melbourne Hospital, Parkville
Committee 3: Disparities and Access to HCT	
Chair:	Eneida Nemecek, Oregon Health & Science University, Portland
Members:	Ghada Abusin, University of Michigan, Ann Arbor Anita D'Souza, Medical College of Wisconsin, Milwaukee Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda Yvonne Efebera, Ohio State University Medical Center, Columbus David Jacobsohn, Children's National Medical Center, Washington, DC Folashade Otegbeye, Case Western Reserve University, Cleveland Lia Perez, H. Lee Moffitt Cancer Center, Tampa Rayne Rouce, Baylor College of Medicine, Houston Maria Thomson, Virginia Commonwealth University, Richmond William Wood, University of North Carolina, Chapel Hill
Outside reviewers:	N/A
Committee 4: GvHD	
Chair:	John Levine, Icahn School of Medicine at Mount Sinai, New York
Members:	Amin Alousi, MD Anderson Cancer Center Brian Betts, University of Minnesota, Minneapolis Javier Bolanos-Meade, Johns Hopkins University, Baltimore Corey Cutler, Dana-Farber Cancer Institute, Boston Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda Mary Flowers, Fred Hutchinson Cancer Research Center, Seattle Richard Jones, Johns Hopkins University, Baltimore Steven Pavletic, National Cancer Institute, Bethesda Doris Ponce, Memorial Sloan-Kettering Cancer Center, New York Iskra Pusic, Washington University, St. Louis Jennifer Whangbo, Boston Children's Hospital, Boston
Outside reviewers:	Ernst Holler, University Hospital Regensburg, Regensburg Takanori Teshima, Hokkaido University Hospital, Sapporo

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Committee/Position	Members
Committee 5: Hemoglobinopathies	
Chair:	Mark Walters, University of California San Francisco, San Francisco
Members:	Alistair Abraham, Children's National Hospital, Washington DC. Sonali Chaudhury, Ann & Robert H Lurie Children's Hospital, Chicago Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda Courtney Fitzhugh, National Institutes of Health, Bethesda Helen Heslop, Baylor College of Medicine, Houston Tami John, Baylor College/Texas Children's Hospital, Houston Adetola Kassim, Vanderbilt University, Nashville Laksmannan Krishnamurti, Emory University, Atlanta Punam Malik, Cincinnati's Children's Hospital medical Center, Cincinnati Matthew Porteus, Stanford University, Stanford Shalini Shenoy, St. Louis Children's Hospital, St. Louis
Outside reviewers:	Josu de la Fuente, Imperial College Healthcare, London Michael DeBaun, Vanderbilt University, Nashville
Committee 6: Infection / Immune Reconstitution	
Chair:	Marcie Riches, University of North Carolina, Chapel Hill
Members:	Aliyah Baluch, H. Lee Moffitt Cancer Center, Tampa Lori Henderson, National Cancer Institute, Bethesda Joshua Hill, Fred Hutchinson Cancer Research Center, Seattle Francisco Marty, Dana-Farber Cancer Institute, Boston Hemant Murthy, Mayo Clinic, Jacksonville Ryotaro Nakamura, City of Hope, Duarte Miguel-Angel Perales, Memorial Sloan-Kettering Cancer Center, New York Zainab Shahid, Levine Cancer Institute, Charlotte Amir Toor, Virginia Commonwealth University, Richmond Celalettin Ustun, Rush University Medical Center, Chicago Jo-Anne Young, University of Minnesota, Minneapolis
Outside reviewers:	Krishna Komanduri, University of Miami, Coral Gables Jonas Mattsson, Princess Margaret Cancer Center, Toronto
Committee 7: Late Effects / QOL / Economics	
Chair:	Betty Hamilton, Cleveland Clinic, Cleveland
Members:	Saro Armenian, City of Hope, Duarte David Buchbinder, Children's Hospital of Orange County, Orange Areej El-Jawahri, Massachusetts General Hospital, Boston Robert Hayashi, Washington University, St. Louis Dianna Howard, Wake Forest University, Winston- Salem Nandita Khera, Mayo Clinic, Phoenix Catherine Lee, University of Utah, Salt Lake City Stephanie Lee, Fred Hutchinson Cancer Research Center, Seattle Gunjan Shah, Memorial Sloan-Kettering Cancer Center, New York Bronwen Shaw, Medical College of Wisconsin, Milwaukee Ad hoc: Jennifer Knight, Medical College of Wisconsin, Milwaukee
Outside reviewers:	Linda Burns, Medical College of Wisconsin, Milwaukee Hélène Schoemans, UZ Leuven, Leuven
Committee 8: Lymphoid Malignancies	
Chair:	Frederick Locke, H. Lee Moffitt Cancer Center, Tampa
Members:	Sairah Ahmed, MD Anderson Cancer Center, Houston Farrukh Awan, UT Southwestern Medical Center, Dallas L. Elizabeth Budde, City of Hope, Duarte Nilanjan Ghosh, Levine Cancer Institute, Charlotte Mehdi Hamadani, Medical College of Wisconsin, Milwaukee Brian Hill, Cleveland Clinic, Cleveland Matthew Lunning, University of Nebraska, Omaha David Maloney, Fred Hutchinson Cancer Research Center, Seattle Craig Sauter, Memorial Sloan-Kettering Cancer Center, New York Patrick Stiff, Loyola University, Chicago Jakub Svoboda, University of Pennsylvania, Philadelphia
Outside reviewers:	Jonathan Friedberg, University of Rochester Medical Center, Rochester Brad Kahl, Washington University, St. Louis
Committee 9: Myeloid Malignancies	

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Committee/Position	Members
Chair:	Yi-Bin Chen, Massachusetts General Hospital, Boston
Members:	Nelli Bejanyan, H. Lee Moffitt Cancer Center, Tampa Steven Devine, National Marrow Donor Program, Minneapolis Aaron Gerds, Cleveland Clinic Medical Center, Cleveland Saar Gill, University of Pennsylvania, Philadelphia Michael Grunwald, Levine Cancer Institute, Charlotte Christopher Hourigan, National Heart, Lung, and Blood Institute, Bethesda Coleman Lindsley, Dana-Farber Cancer Institute, Boston Richard Little, National Cancer Institute, Bethesda Mark Litzow, Mayo Clinic, Rochester Lori Muffly, Stanford University, Stanford Wael Saber, Medical College of Wisconsin, Milwaukee Bart Scott, Fred Hutchinson Cancer Research Center, Seattle Sumi Vasu, Ohio State University Medical Center, Columbus
Outside reviewers:	Charles Craddock, University of Birmingham, Birmingham Nicolaus Kroger, University Hospital Hamburg, Hamburg
Committee 10: Non-Malignant Disorders	
Chair:	Amy DeZern, Johns Hopkins University, Baltimore
Members:	Suneet Agarwal, Boston Children's Hospital, Boston Jaap-Jan Boelens, Memorial Sloan-Kettering Cancer Center, New York Jane Churpek, University of Wisconsin, Madison Nancy DiFronzo, National Heart, Lung, and Blood Institute, Bethesda Christopher Dvorak, University of California San Francisco, San Francisco Mary Eapen, Medical College of Wisconsin, Milwaukee George Georges, Fred Hutchinson Cancer Research Center, Seattle Lucy Godley, University of Chicago, Chicago Jennifer Kanakry, National Cancer Institute, Bethesda Margaret MacMillan, University of Minnesota, Minneapolis Anupama Narla, Stanford University, Stanford Ghadir Sasa, Texas Children's Hospital, Houston
Outside reviewers:	Persis Amrolia, Great Ormond Street Hospital for Sick Children, London Andrew Gennery, New Castle University, Newcastle Upon Tyne
Committee 11: Optimal Donor and Graft Source	
Chair:	Karen Ballen, University of Virginia, Charlottesville
Members:	Asad Bashey, Northside Hospital, Atlanta Claudio Brunstein, University of Minnesota, Minneapolis Mary Horowitz, Medical College of Wisconsin, Milwaukee Kimberly Kasow, University of North Carolina, Chapel Hill Joanne Kurtzberg, Duke University, Durham Shannon McCurdy, University of Pennsylvania, Philadelphia Brenda Sandmaier, Fred Hutchinson Cancer Research Center, Seattle Robert Soiffer, Dana-Farber Cancer Institute, Boston
Outside reviewers:	Jane Apperley, Imperial College, London Stephen Forman, City of Hope, Duarte
Committee 12: Pediatric Malignant Disease	
Chair:	Leslie Kean, Boston Children's Hospital, Boston
Members:	Alice Bertaina, Stanford University, Stanford Marie Bleakley, Fred Hutchinson Cancer Research Center, Seattle Joseph Chewning, The University of Alabama, Birmingham Stella Davies, Cincinnati's Children's Hospital medical Center, Cincinnati Terry Fry, University of Colorado, Aurora Lori Henderson, National Cancer Institute, Bethesda Dean Lee, Nationwide Children's Hospital, Columbus Rachel Phelan, Medical College of Wisconsin, Milwaukee Michael Pulsipher, Children's Hospital Los Angeles, Los Angeles Muna Qayed, Emory University, Atlanta Nirali Shah, National Institutes of Health, Bethesda
Outside reviewers:	Christina Peters, St. Anna's Children's Hospital, Vienna Paul Veys, Great Ormond Street Hospital for Sick Children, London
Committee 13: Plasma Cell Disorder	
Chair:	Parameswaran Hari, Medical College of Wisconsin, Milwaukee

Committee/Position	Members
Members:	Luciano Costa, The University of Alabama, Birmingham Madhav Dhodapkar, Emory University, Atlanta Sergio Giralt, Memorial Sloan-Kettering Cancer Center, New York Damien Green, Fred Hutchinson Cancer Research Center, Seattle Amrita Krishnan, City of Hope, Duarte Shaji Kumar, Mayo Clinic, Rochester Philip McCarthy, Roswell Park Comprehensive Cancer Center, Buffalo Marcelo Pasquini, Medical College of Wisconsin, Milwaukee Krina Patel, MD Anderson Cancer Center, Houston Noopur Raje, Dana-Farber Cancer Institute, Boston Edward Stadtmauer, University of Pennsylvania, Philadelphia Saad Usmani, Levine Cancer Institute, Charlotte
Outside reviewers:	Xavier Leleu, CHU de Poitiers, Poitiers María-Victoria Mateos, Salamanca University Hospital, Salamanca

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Table 3:

High Priority SOSS Trials

Committee	Strategy
Interventional Treatment Trials	
Graft versus Host Disease	Improve outcomes for acute gastrointestinal GVHD
Graft versus Host Disease	Minimize treatment toxicity for low-risk acute GVHD
Graft versus Host Disease	Pre-emption of moderate to severe chronic GVHD
Infection / Immune Reconstitution	Safety of antibiotic de-escalation following initial fever
Late Effects, Quality of Life and Economics	Propranolol in patients undergoing autologous HCT
Lymphoid Malignancies	Upfront CAR-T for high-risk mantle cell lymphoma
Lymphoid Malignancies	Autologous HCT consolidation vs. observation after BV+CHP induction in CD30+ peripheral T-cell lymphoma
Lymphoid Malignancies	Consolidation for CAR-T incomplete responders in diffuse large B cell lymphoma
Myeloid Malignancies	Platform trial to evaluate post-HCT maintenance therapies for acute myeloid leukemia
Non-Malignant Disorders	Upfront alternative donor HCT for severe aplastic anemia
Optimal Donor and Graft Sources	Haploidentical vs unrelated donor transplantation with post-transplant cyclophosphamide
Pediatric Malignant Disease	A risk-based approach to optimize remission duration following CAR-T therapy
Pediatric Malignant Disease	Cytokine-induced memory-like-NK cells to treat post-HCT myeloid leukemia relapse
Plasma cell disorders	Incorporating BCMA CAR-T in high risk multiple myeloma
Observational Trials	
Comorbidity & Regimen Related Toxicity	Limiting transplant associated chronic pulmonary toxicity
Hemoglobinopathies	Assessing late effects after HCT for sickle cell disease
Infection and Immune Reconstitution Committee	Prospective observational study of the immunogenicity of vaccines after HCT or CAR-T therapy
Myeloid Malignancies	Prediction and biology of acute myeloid leukemia relapse after HCT

GVHD: Graft versus Host Disease

HCT: Hematopoietic Cell Transplant

CAR-T: Chimeric Antigen Receptor modified T cells

NK: Natural killer

BCMA: B cell maturation antigen