2021 STATUS REPORT
LATE EFFECTS AND QUALITY OF LIFE WORKING COMMITTEE

Working Committee Leadership	
Co-Chair:	David Buchbinder; Children's Hospital of Orange County; dbuchbinder@choc.org
Co-Chair:	Betty Hamilton; Cleveland Clinic Taussig Cancer Institute; hamiltb2@ccf.org
Co-Chair:	Hélène Schoemans; University Hospitals Leuven; helene.schoemans@uzleuven.be
Scientific Director:	Rachel Phelan; CIBMTR Statistical Center; rphelan@mcw.edu
Statistical Director:	Ruta Brazauskas; CIBMTR Statistical Center; ruta@mcw.edu
Statistician:	Stephanie Bo-Subait; CIBMTR Statistical Center; sbosuba2@nmdp.org

INTRODUCTION

a. Minutes and overview plan from 2020 TCT meeting (Attachment 1)

PROPOSALS MOVING FORWARD FOR SCORING (click here to cast your score)

a. PROP 2010-149; 2010-208 Risk of subsequent neoplasms (SN) after the use of post-transplant cyclophosphamide (PTCy) for Graft-versus-host disease (GVHD) prophylaxis (Ana Alarcon Tomas/ Lucrecia Yanez San Segundo/ Miguel-Angel Perales/ Shahrukh K. Hashmi/ Ibrahim Muhsen/ Ankit Kansagra). (Attachment 2)

b. PROP 2010-248 Cumulative incidence and risk factors for breast cancer after allogeneic hematopoietic cell transplant (Kareem Jamani/ K. Scott Baker/ H. Joachim Deeg). (Attachment 3)

PROPOSALS DROPPED BECAUSE THEY OVERLAP WITH EXISTING STUDIES OR ARE NOT FEASIBLE DUE TO LIMITATIONS OF AVAILABLE PATIENTS OR DATA

a. PROP 2010-03 Therapy related MDS/AML and other second cancers after autologous transplant for children and young adults (Seth J. Rotz/ Rabi Hanna/ Navneet S. Majhail).

b. PROP 2010-229 Incidence and outcomes of recurrence of primary solid cancers after allogeneic hematopoietic cell transplantation (Michael Boyiadzis).

c. PROP 2010-232 Long-term survival and late deaths after allogeneic hematopoietic cell transplantation (Allo-HCT) In the modern era (Zeina Al-Mansour/ Nosha Farhadfar/ Gerard Socie/ John Reid Wingard).

d. PROP 2010-195 Donor derived CHIP and risk of cardiovascular complications post SCT (Shatha Farhan).

PROPOSALS NOT ACCEPTED FOR CONSIDERATION AT THIS TIME DUE TO RELATIVE SCIENTIFIC IMPACT COMPARED TO ONGOING STUDIES AND/OR OTHER PROPOSALS

Not applicable

STUDIES IN PROGRESS

a. **LE16-02b** Late effects after AlloHCT for pediatric patients with non-malignant diseases. Status: Manuscript preparation. For this follow-up study, we will have the manuscript submitted by July 2021.

b. **LE12-03** Solid organ transplantation and hematopoietic cell transplantation. Status: Manuscript preparation. This study is in manuscript preparation and we will have it submitted by July 2021.

c. **LE17-01a** Late effects after hematopoietic stem cell transplantation for sickle cell disease. Status: Analysis. We will have this manuscript submitted by July 2021.

d. **LE17-01b** Comparison of survival between transplanted and non-transplanted SCD patients. Status: Data file preparation**.** The comparison non-transplant cohort is being assembled. Once the dataset is received, we will work on the analysis, and begin manuscript preparation in July 2021.

e. **LE18-01** Survival trends amongst two-year survivors of allo hematopoietic cell transplantation. Status: Data file preparation. This study is nearing the end of data file preparation, and we will have this manuscript submitted in July 2021.

f. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients. Status: Data file preparation. This protocol was circulated to the working committee for comments. We will begin manuscript preparation by July 2021.

g. **LE19-02** Incidence and predictors of long-term toxicities and late side effects in elderly patients (≥60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. Status: Protocol development. The population for this study has been identified and we will begin manuscript preparation in July 2021.

h. **LE20-01** Cardiometabolic risk after total body irradiation during childhood. Status: Protocol development. We have been working on obtaining IRB approval to merge the CIBMTR and CCSS datasets. We will begin data file preparation in July 2021.

i. **LE20-02** Association between PRO and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplantation. Status: Protocol development. Next steps for this study are to identify the cases that have both PRO data and samples available in the biorepository. We will begin data file preparation in July of 2021.

PUBLICATIONS, SUBMITTED PAPERS, PRESENTATIONS

a. **LE16-02** Kahn JM, Brazauskas R, Tecca HR, Bo-Subait S, Buchbinder D, Battiwala M, Flowers MED, Savani BN, Phelan R, Broglie L, Abraham AA, Keating AK, Daly A, Wirk B, George B, Alter BP, Ustun C, Freytes CO, Beitinjaneh AM, Duncan C, Copelan E, Hildebrandt GC, Murthy HS, Lazarus HM, Auletta JJ, Myers KC, Williams KM, Page KM, Vrooman LM, Norkin M, Byrne M, Diaz MA, Kamani N, Bhatt NS, Rezvani A, Farhadfar N, Mehta PA, Hematti P, Shaw PJ, Kamble RT, Schears R, Olsson RF, Hayashi RJ, Gale RP, Mayo SJ, Chhabra S, Rotz SJ, Badawy SM, Ganguly S, Pavletic S, Nishihori T, Prestidge T, Agrawal V, Hogan WJ, Inamoto Y, Shaw BE, Satwani P. Subsequent neoplasms and late mortality in children undergoing allogeneic transplantation for nonmalignant diseases. Blood Advances. 2020 May 12; 4(9):2084-2094. doi:10.1182/bloodadvances.2019000839. Epub 2020 May 12. PMC7218429.

b. **LE17-02** Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton BK, Battiwalla M, Majhail NS, Lazarus HM, Shaw PJ, Marks DI, Litzow MR, Chhabra S, Inamoto Y, DeFilipp Z, Hildebrandt GC, Olsson RF, Kasow KA, Liesveld JL, Rotz SJ, Badawy SM, Bhatt NS, Yared JA, Page KM, Arellano ML, Kent M, Farhadfar N, Seo S, Hematti P, Freytes CO, Rovó A, Ganguly S, Nathan S, Burns L, Shaw BE, Muffly LS. Late effects after ablative allogeneic stem cell transplantation for adolescent and young adult acute myeloid leukemia. Blood Advances. 2020 Mar 24; 4(6):983-992. doi:10.1182/bloodadvances.2019001126. Epub 2020 Mar 13. PMC7094022.

c. **SC09-05d** Cusatis RN, Tecca HR, D'Souza A, Shaw BE, Flynn KE. Prevalence of decisional regret among patients who underwent allogeneic hematopoietic stem cell transplantation and associations with quality of life and clinical outcomes. Cancer. 2020 Jun 1; 126(11):2679-2686. doi:10.1002/cncr.32808. Epub 2020 Mar 10. PMC7220834.

d. Systematic Reviews in Hematopoietic Cell Transplantation and Cellular Therapy: Considerations and Guidance from the American Society for Transplantation and Cellular Therapy, European Society for Blood and Marrow Transplantation, and the Center for International Blood and Marrow Transplant Research Late Effects and Quality of Life Working Committee. *Published.*

e. **LE18-02** Return to work among young adult survivors of allogeneic hematopoietic cell transplantation in the united states. *Submitted.*

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MINUTES AND OVERVIEW PLAN
CIBMTR WORKING COMMITTEE FOR LATE EFFECTS AND QUALITY OF LIFE
Orlando, Florida
Thursday, February 20, 2020, 2:45 – 4:45 pm

Co-Chair:	**Minoo Battiwalla, MD, MS, Sarah Cannon Research Institute, Nashville, TN; Phone: 301-742-7782; E-mail: minoo.battiwalla@hcahealthcare.com**
Co-Chair:	**David Buchbinder, MD, CHOC Children's Hospital, Orange, CA; Phone: 714-509-8744; E-mail: dbuchbinder@choc.org**
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Statistician:	**Stephanie Bo-Subait, MPH, CIBMTR Statistical Center, Minneapolis, MN; Telephone: 763-406-8515; E-mail: sbosuba2@nmdp.org**

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1. Introduction

The CIBMTR Late Effects and Quality of Life Working Committee (LEWC) meeting was called to order at 2:45pm on Thursday, February 20, 2020 by Dr. Betty Hamilton. She introduced the current working committee leadership and introduced the incoming chair, Dr. Hélène Schoemans. The leadership thanked Dr. Minoo Battiwalla, the outgoing chair, for his service to the LEWC over the past five years. The CIBMTR COI policy was reviewed and the processes of participating in the working committee, voting guidance, and rules of authorship were outlined.

Dr. Hélène Schoemans was also welcomed as the representative of the EBMT late effects committee for this meeting.

a. Minutes and Overview Plan from February 2019 meeting
b. Introduction of incoming Co-Chair:
   Hélène Schoemans, MD, PhD, EBMT, University Hospitals Leuven and KU Leuven; Leuven, Belgium; Telephone: 32 16 34 68 80; Email: helene.schoemans@uzleuven.be

2. Accrual summary

Dr. Shaw reminded the committee that there are PRO data now available for secondary study questions and that the number of PRO surveys available will increased greatly in the next two years.

3. Presentations, published or submitted paper

Dr. David Buchbinder gave an update on study presentations, and manuscripts that were published or submitted within the last year.

a. **LE13-02** Herr MM, Curtis RE, Tucker MA, Tecca HR, Engels EA, Cahoon EK, Battiwalla M, Buchbinder D, Flowers ME, Brazauskas R, Shaw BE, Morton LM. Risk factors for the development of cutaneous melanoma after allogeneic hematopoietic cell transplantation***. Journal of the American Academy of Dermatology. doi:10.1016/j.jaad.2019.10.034. Epub 2019 Oct 22.***

b. **LE16-02** Kahn JM, Brazauskas R, Tecca HR, Bo-Subait S, Buchbinder D, Battiwalla M, Flowers MED, Savani BN, Phelan R, Broglie L, Abraham AA, Keating AK, Daly A, Wirk B, George B, Alter BP, Ustun C, Freytes CO, Beitinjaneh AM, Duncan C, Copelan E, Hildebrandt GC, Murthy HS, Lazarus HM, Auletta JJ, Myers KC, Williams KM, Page KM, Vrooman LM, Norkin M, Byrne M, Diaz MA, Kamani N, Bhatt NS, Rezvani A, Farhadfar N, Mehta PA, Hematti P, Shaw PJ, Kamble RT, Schears R, Olsson RF, Hayashi RJ, Gale RP, Mayo SJ, Chhabra S, Rotz SJ, Badawy SM, Ganguly S, Pavletic S, Nishihori T, Prestidge T, Agrawal V, Hogan WJ, Inamoto Y, Shaw BE, Satwani P. Subsequent Neoplasms and Late Mortality in Children Undergoing Allogeneic Transplantation for Non-Malignant Diseases. ***Submitted.***

c. **LE17-02** *Lee CJ, Kim S, Tecca HR, Bo-Subait S, Phelan R, Brazauskas R, Buchbinder D, Hamilton BK, Battiwalla M, Majhail NS, Lazarus H, Shaw P, Marks D, Litzow MR, Chhabra S, Inamoto Y, DeFilipp Z, Hildebrandt G, Olsson R, Kasow K, Liesveld J, Rotz S, Badawy SM, Bhatt N, Yared J, Page K, Arellano M, Kent MW, Farhadfar N, Seo S, Hematti P, Freytes CM, Rovo A, Ganguly S, Nathan S, Burns L, Shaw BE, Muffly LS.* Late Effects After Ablative Allogeneic Stem Cell Transplantation for Adolescent and Young Adult Acute Myeloid Leukemia. ***Submitted.***

d. **LE17-01** Stenger E, Phelan R, Shaw BE, Battiwalla Minoo, Bo-Subait S, Brazauskas R, Buchbinder DK, Hamilton BK, Shenoy S, Krishnamurti L. Excellent Overall Survival and Low Incidence of Late Effects in Patients Undergoing Allogeneic Hematopoietic Cell Transplant for Sickle Cell Disease: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 61st ASH Annual Meeting and Exposition.***

e. **LE18-02** Bhatt NS, Brazauskas R, Bo-Subait S, Salit RB, Syrjala K, Tecca HR, Battiwalla M, Buchbinder DK, Hamilton BK, Phelan R, Shaw BE. Post-Transplant Work Status of Young Adult Survivors of Allogeneic Hematopoietic Cell Transplant: A Report from the Center for International Blood and Marrow Transplant Research (CIBMTR). ***Presented at 61st ASH Annual Meeting and Exposition.***

f. **LE12-03** Gupta M, Levine MH, Porter D, Bo-Subait S, Shaw BE, Brazauskas R, Phelan R, Battiwalla M, Buchbinder D, Hamilton B, Abt PL. Solid Organ Transplant (SOT) and Hematopoietic Cell Transplantation (HCT). **Poster Presentation at TCT 2020 in Orlando, Fl.**

4. Studies in progress

Dr. David Buchbinder briefly listed all studies in progress. He introduced Dr. Lakshmanan Krishnamurti to present an update on LE17-01 and Dr. Neel Bhatt to present on LE18-02.

a. **LE99-01** Quality of life in late HCT survivors (J Wingard) **Manuscript Preparation**

b. **LE12-03** Solid organ transplant after hematopoietic cell transplantation (M Gupta/PL Abt/M Levine) **Analysis**

c. **LE17-01** Long-term follow up after HCT for SCD (E Stenger/L Krishnamurti/S Shenoy) **Analysis**
Dr. Lakshmanan Krishnamurti presented this study which aims to describe late effects of HCT in sickle cell disease patients, describe the relationship of transplant-related factors to organ dysfunction and sickle cell disease related complications, and to compare survival of transplanted cohort to a cohort of non-transplanted sickle cell disease patients. Overall survival, late effects, and comparison of SCD-related symptoms pre and post were reported on within the transplant cohort. The committee had time to ask several questions and for discussion

e. **LE18-01** Trends in late mortality amongst two-year survivors of pediatric allogeneic hematopoietic cell transplantation for hematologic malignancies (L Broglie/P Satwani) **Protocol Development**

f. **LE18-02** Post-transplant Employment/ Student Status of Survivors of Young Adult (YA) Allogeneic

Hematopoietic Cell Transplant (N Bhatt/R Salit/K Syrjala/BE Shaw) **Manuscript Preparation**
Dr. Neel Bhatt presented this study which aims to assess the post-HCT work status of young adults undergoing alloHCT, and to examine pre-HCT factors associated with work status at 1-year post-HCT. Work status post-transplant was reported and compared with pre-HCT work status. Risk factors associated with work status at 1-year post-HCT were presented.
The committee had time to ask several questions and for discussion

g. **LE19-01** Long-term survival and late effects in critically ill pediatric hematopoietic cell transplant patients (M Zinter/C Dvorak/C Duncan) **Protocol Development**
h. **LE19-02** Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies (M Veeraputhiran/S Pingali/A Mukherjee/L Muffly) **Protocol Development**

5. Future/proposed studies

a. **PROP 1911-23** Influence of Busulfan based vs melphalan based Chemo regimens On early and late cardiac toxicity post SCT (*Farhan*)
Dr. Shatha Farhan presented this proposal aiming to describe the incidence of early and late cardiac complications post-transplant, and to determine the patient and treatment related risk factors including conditioning regimen associated with cardiac complications. There were a few comments on expanding the conditioning to be investigated (beyond melphalan and busulfan, but also taking into account other exposures during conditioning) as well as included the pre-HCT therapies given as this may influence late effects. Specific questions about the availability of data on proteasome inhibitors were raised. It was acknowledged that more granular cardiovascular outcomes were not collected in the registry until recently, except for measures of cardiomyopathy (though the way this was collected has differed over time)
It was also noted that it is important to look at cardiovascular disease by subtype. Concerns were raised about the ability to determine cardiovascular events that happened as a late effect instead of cardiac toxicity related to aging leading to a cardiovascular event and stress the importance of the years of follow up post-transplant. This study was not accepted due to the above stated concerns, particularly regarding the granularity of late effects data and pre-transplant exposures.
b. **PROP 1911-30** Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant (*Taylor/Knight/Baker/Cole*)
Dr. Jennifer Knight presented this proposal aiming to examine associates between CTRA gene expression and PROs, and to explore the relationship between CTRA gene expression, PROs and clinical outcomes such as relapse-free survival, engraftment, GHVD and overall survival. The study is powered on a previous analysis done by this group using CIBMTR clinical outcome data, but not PRO's.
One attendee commented that it may be best to homogenize the population by selecting further on disease or age, however because the number of patients with PROs is low this would be limiting. Dr. Knight stressed this is a hypothesis generating study which would be used as preliminary data for grant proposals. The testing of donor samples was raised and Dr. Knight commented that she is currently working on a similar study with donor samples.
The reasoning for selection of the genetic profile was also expanded upon by highlighting that this profile as a whole has been shown to be impacted by periods of stress, such as undergoing HCT, and this is not a discovery gene panel, but a panel that can be summarized in a composite score and used as a continuous variable for analysis.
c. **PROP 1911-59** New Cancers after Autologous Hematopoietic Cell Transplantation for Systemic Light-Chain Amyloidosis *(Chakraborty/Majhail/Lentzsch)*

Dr. Rajshekhar Chakraborty presented this proposal aiming to determine the incidence of new cancers after autoHCT for AL amyloidosis, to identify risk factors for subsequent cancer, and to compare the incidence of subsequent cancers in AL survivors with demographically matched healthy controls. It was noted that it may be possible to use standardized mortality ratios to address a comment regarding the potential for increased risk of subsequent cancers within the non-transplant therapies (an ideal control would be patients with amyloid but no transplant). It was suggested clarity be added about whether these are first cancers post-transplant and the history of cancer prior to transplant. This study was not accepted due to the above stated concerns as well as prioritization of other proposed studies due to potential higher/novel impact on the field.

d. **PROP 1911-176** Cardiometabolic Risk after Total Body Irradiation during Childhood (*Friedman/Chow*)
Dr. Danielle Friedman presented this proposal aiming to use CCSS and CIBMTR data to determine long-term risk of developing cardiovascular disease comorbidities in survivors treated with TBI versus non-TBI HCT and conventional chemotherapy, as compared to siblings; identify other treatment, primary disease, demographics and specific chronic conditions that modify risk of cardiovascular comorbidities after TBI; and to assess whether lifestyle factors modify risk.
Dr. Christy Duncan had grant funding to collect supplemental data for her study looking at late cardiovascular morbidity and mortality in the pediatric population and is happy to contribute data to this proposed study. Outcomes data would come from CCSS and transplant specific data would come from CIBMTR. These data would be linked by an honest broker using personal identifiers which have been confirmed to be available from both sources (including names) suggesting that this linkage will be feasible. Linked CCSS and CIBMTR data will provide a rich dataset for future studies to be proposed and addressed. The inclusion of healthy siblings in the CCSS dataset would provide an excellent control for CIBMTR studies which is unavailable now.

e. **PROP 1911-203** Pre-transplant body mass index and late effects among children, adolescent, and young adult (CAYA) childhood leukemia survivors following allogeneic hematopoietic cell transplantation (*Joffe/Broglie/Ladas/Kadan-Lottick/Satwani*)
Dr. Larisa Broglie presented this proposal aiming to determine the incidence of late effects and secondary malignancies in CAYA patients based on pre-HCT weight (BMI) categories and to determine the incidence of late mortality in patients who are obese or overweight at the time of transplant compared to the general population.
One attendee was concerned about the change in weight over time and the time gap from exposure to outcomes, including our inability to track post-transplant weight and the potential for large changes in that variable. Post-transplant weight was not collected until recently (2017), but this could be added to the study in the future when the data is more robust. Another attendee suggested subdividing the obese category into obese and morbidly obese since treating the morbidly obese patients poses a greater challenge than the patients that technically fall into the obese category.
This study was not accepted due to the above stated concerns, most notably the lack of broader ranges or pre and post-transplant BMI data.

f. **PROP 1912-07** Long-Term Survival and Late Deaths After Allogeneic Hematopoietic Cell Transplantation (Allo-HCT) In The Modern Era *(Al-Mansour/Farhadfar/Socie/Wingard)*
Dr. Zeina Al-Mansour presented this proposal aiming to determine overall mortality of alloHCT survivors who were disease free at 2 years post-transplant, evaluate factors associated with late mortality, compare survival with matched controls from the general population, compare changes in causes of death over time, and to compare relative late fatality rates and causes of death within subgroups.
It was noted that autopsy reports are collected by CIBMTR but would only be available on a subset of the population since it is up to the site to decide whether to submit an autopsy report. Infection

would be collected as cause of death for transplant recipients but generally is not collected beyond 2-years post-transplant. An attendee asked whether to study population really needs to go back to 1980 versus 1990 or 2000; the PIs would like to include cases back to 1980 to increase the number of cases and to allow for the ability to study causes of death and rate of mortality in the modern era compared to the earlier cases. Suggestions were made to stratify the population by age.
This study was not accepted due to the above stated concerns, overlapping themes with an ongoing study (LE18-01) as well as prioritization of other proposed studies due to potential higher/novel impact on the field.

Dropped proposed studies

a. **PROP 1911-27** Recurrence of primary solid cancers after allogeneic hematopoietic cell transplantation. *Dropped due to feasibility.*
b. **PROP 1911-103** Secondary malignancies after reduced intensity or non myeloablative stem cell transplantation in non-malignant disorders. *Dropped for overlap with an existing study.*
c. **PROP 1911-114** Incidence and Outcomes of Kaposi Sarcoma after Hematopoietic Stem Cell Transplantation: A CIBMTR study. *Dropped due to feasibility.*
d. **PROP 1911-188** Tumor Immunogenicity as a Predictor of Second Cancer Relapse after Allogeneic Hematopoietic Cell Transplantation in Patients with History of Solid Organ Cancer. *Dropped due to feasibility.*
e. **PROP 1911-195** Outcomes of long-term survivors of umbilical cord blood allogeneic HSCT. *Dropped for overlap with an existing study.*
f. **PROP 1911-223** Late treatment related mortality vs competing causes of death after all HCT for secondary AML and MDS in pediatric patients. *Dropped due to feasibility.*

6. Other Business

Dr. Minoo Battiwalla reminded the working committee to score each proposal with 1 being the best and 9 being not the best. He introduced Dr. Rachel Phelan to give an update on the annual CIBMTR and EBMT collaborative reviews.

a. CIBMTR Late Effects and Quality of Life Working Committee and the EBMT Transplant Complications Working Party Review
The male-specific late effects review which was accepted last year is currently being written by each subgroup. There was a lot of interest, so the review leadership stressed from the beginning the importance of active participation in order to be included as an author. Additionally, to address the large number of people interesting in participating, the paper was split into an adult and pediatric paper. A methodology subgroup was put together to organize and standardize search strategies within each subgroup and is putting out a white paper on conducting systematic reviews within this field. The next call for proposals will go out around March of 2020; young investigators are encouraged to get involved.

7. Closing Remarks

The role of Scientific Director for the Late Effects and Quality of Life Working Committee will be transitioning from Bronwen Shaw to Rachel Phelan beginning March 1, 2020.
Rachel Phelan has been promoted from the position of Assistant Scientific Director for the Late Effects and Quality of Life Working Committee, to the Scientific Director and will assume all responsibilities.

Oversight Assignments for Working Committee Leadership (March 2020)

David Buchbinder	**LE17-01** Long-term follow up after HSCT for sickle cell disease
	LE18-01 Survival trends amongst two-year survivors of alloHCT
	LE18-02 Return to work or school status in survivors of young adult AlloHCT
	LE20-01 Cardiometabolic Risk after Total Body Irradiation during Childhood
Betty Hamilton	**LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients
	LE19-02 Incidence and predictors of Long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies
Helene Schoemans	**LE12-03** Solid organ transplant after HCT
	LE20-02 Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant
Bronwen Shaw	**LE99-01** Quality of life in late HCT survivors

Working Committee Overview Plan for 2020-2021

a. **LE99-01** Quality of life in late HCT survivors. This study is ongoing.

b. **LE12-03** Solid organ transplant after HCT. This study is in analysis and we plan to start manuscript prep by July 2020.

c. **LE17-01** Long-term follow up after HSCT for sickle cell disease. This study is in analysis and we plan to complete the analysis and start manuscript preparation by July 2020.

d. **LE18-01** Survival trends amongst two-year survivors of alloHCT. This study is in data file prep. We aim to be in manuscript preparation by July 2020.

e. **LE18-02** Return to work or school status in survivors of young adult AlloHCT. This study is in manuscript preparation and we aim to have it submitted by July 2020.

f. **LE19-01** Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients. This study is in protocol development and we aim to have it in analysis by July 2020.

g. **LE19-02** Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies. This study is in protocol development and we aim to have it in data file preparation by July 2020.

h. **LE20-01** Cardiometabolic Risk after Total Body Irradiation during Childhood. Protocol is pending on this study and hours will begin July 2020.

i. **LE20-02** Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant. Protocol is pending on this study and hours will begin July 2020.

Working Committee Overview Plan for 2020-2021

Study number and title	Current status	Goal with date	Total hours to complete	Total hours to goal	Hours allocated to 6/30/2020	Hours allocated 7/1/2020-6/30/2021	Total hours allocated
LE12-03: Solid organ transplantation and hematopoietic cell transplantation	Analysis	Submitted – July 2021	110	110	60	50	110
LE17-01: Long-term follow up after hematopoietic stem cell transplantation for sickle cell disease	Analysis	Submitted – July 2021	110	110	60	50	110
LE19-01: Long-Term Survival and Late Effects in Critically Ill Pediatric Hematopoietic Cell Transplant Patients	Protocol development	Manuscript Preparation – July 2021	230	160	100	60	160
LE19-02: Incidence and predictors of long term toxicities and late side effects in elderly patients (>=60 years) receiving allogeneic hematopoietic cell transplantation for hematological malignancies.	Protocol development	Manuscript Preparation – July 2021	330	260	100	160	260
LE20-01: Cardiometabolic Risk after Total Body Irradiation during Childhood	Protocol pending	Data file preparation – July 2021	370	100	0	100	100
LE20-02: Association between patient-reported outcomes and the social transcriptome profile as a predictor of clinical outcomes following hematopoietic cell transplant	Protocol pending	Analysis – July 2021	330	200	0	200	200

Combined Proposal: **2010-149; 2010-208**

Title:
Risk of subsequent neoplasms (SN) after the use of post-transplant cyclophosphamide (PTCy) for Graft-versus-host disease (GvHD) prophylaxis.

Research hypothesis:
The use of Post-transplant cyclophosphamide (PTCy) following allogeneic hematopoietic stem cell transplantation (HSCT) is associated with a higher rate of subsequent neoplasms compared with other graft-versus-host disease (GvHD) prophylaxis.

Scientific impact statement:
PTCy is a promising modality for GVHD prophylaxis and has been established as the standard of care for GVHD prophylaxis in the haploidentical setting. Furthermore, it is also being assessed in prospective trials and increasingly used in many centers in recipients of matched related and unrelated donors. In the past decade, advances in conditioning regimens and supportive care practices have improved survival rates of HSCT survivors. However, life expectancy in five-years survivors remains 30% lower than general population. For those patients, subsequent neoplasms (SN) are the leading cause of excess deaths and are associated with significant morbidity and mortality. One of the risk factors that has been correlated with SN in several studies are immunosuppressant and alkylating agents. Given increased use of PTCy many studies have emerged to explore their association with clinical outcomes. The CIBMTR has already studied the relationship between the use of post-transplant Cy and infections, GvHD incidence and relapse. However, there are no retrospective, prospective or randomized trials comparing the incidence of SN with different GVHD prophylaxis. In particular, there are no published studies on the incidence of SN in patients who received PTCy. As SN are the main cause of mortality in five-year survivors, it is critical that we study and identify possible risk factors for SN in PTCy recipients, and a CIBMTR study is the best and probably only way to address this issue.

Specific aims:
- To compare the incidence rate of SN in patients who received PTCy with patients who received calcineurin inhibitor (CNI)-based GVHD prophylaxis.
- To compare the incidence rate of SN in patients who received PTCy with the general population.
- To describe the incidence rate, characteristics (Solid tumor, Myelodysplasia (t-MDS)/acute myeloid leukemia (t-AML) or Lymphoma, including lymphoproliferative disorders) and outcomes (time from transplant to SN, cause of death) of SN in patients receiving PTCy as GvHD prophylaxis.
- To describe risk factors of SN in patients receiving PTCy for GvHD prophylaxis, including sociodemographic (e.g., gender), disease (e.g., primary disease, pre-conditioning therapy), and HSCT (e.g., transplant modalities and related complications) factors.

Scientific justification:
SN are one of the most feared late effects among HSCT long term survivors. In fact, SN are the leading cause of excess deaths in 5-year HSCT survivors[1]. The cumulative incidence of developing SN after transplant increases continually between 2% and 6% at 20 years and is substantially higher (2.1-fold to 2.7-fold) when compared with the incidence in the general population[2]. As a result, these patients should be strongly encouraged to follow, at the minimum, established age-specific guidelines for screening in their population[3].

Different risk factors have been identified to increase the risk for SN. These include GvHD, use of HLA-mismatched grafts, patient prior exposure to radiation and/or certain cytotoxic drugs in the conditioning regimen or as part of previous therapies; the use of immunosuppressive therapy and some infectious agents such as hepatitis B or C virus or Epstein–Barr virus (EBV)[4,5,6]. In previously published work by the CIBMTR, the largest study to date to assess risk factors for solid cancers following HSCT showed that the duration of immunosuppression, including therapy for chronic GvHD, and immunosuppressant agents were correlated with SN[7]. These results have been validated in previous analyses, especially for squamous cell malignancies[8]. The mechanisms of development SN after immunosuppression are not fully understood, but it has been speculated that immunosuppression administered in an inflammatory milieu would interfere with tissue repair, thereby enhancing the risk for tumor evolution. In fact, patients with autoimmune disorders are known to develop malignant tumors more frequently than persons with apparently normal immunity.

PTCy is a promising modality for GvHD prophylaxis in allogeneic HSCT. Data from mostly single center series and registry data have supported the role of PTCy in reducing acute and chronic GvHD incidences compared to standard CNI-based prophylaxis[9-13]. Definitive conclusion regarding PTCy efficacy cannot be made especially, in the absence of prospective randomized studies, which are currently ongoing.

Toxic effects of cyclophosphamide include bone marrow suppression, cardiac and gonadal toxicity, hemorrhagic cystitis and carcinogenesis, with cumulative dose being the principal risk factor[14]. The increased risk of cancer of the alkylating agents is linked to the DNA damage caused in the cell and it can rise in patients receiving the highest doses. To date, we know that PTCy has not been associated with post-transplant lymphoproliferative disorders or donor derived malignancy[15,16]. Nevertheless, there are no reports of risk of SN and their association with specific immunosuppressive agents.

We hypothesized that the use of an alkylating agent after allogeneic HSCT could have an impact on the development of SN.

Patient eligibility population:

- Adult patients (≥18yo) who underwent first allogeneic stem cell transplant with T-replete graft with post-transplant cyclophosphamide for GvHD prophylaxis or CNI-based GvHD prophylaxis from unrelated/related matched/mismatched/haploidentical donors with MAC or RIC conditioning regimens.
- Autologous transplant before allogeneic transplant would be included.
- Time period: 2008 to 2017.

Exclusion criteria:

- Patients who received more than one allogeneic transplant
- Ex vivo T cell depleted transplants.
- CD34 selected
- Cord Blood transplants
- Nonmalignant disorders
- Patients with cancers other than the indication for transplant will be excluded

Data requirements:

Patient-related:

- Age at transplant
- Gender
- Race

Primary disease-related:

- Diagnosis. Date. Primary disease for which chemo/radiation therapy was given
- Cytogenetics or FISH information of primary disease
- Prior treatment with anthracycline: yes/no
- Prior treatment with alkylating agents: yes/no
- Radiation prior to allogeneic transplant: yes/no
- Number of lines of prior therapy
- Previous auto. Yes/No
- Date autologous transplant
- Conditioning regimen in previous autologous. MAC/RIC
- Disease status at allogeneic transplant.

Transplant-related:

- HCT-CI. Hematopoietic cell transplant comorbidity index
- Blood group compatibility: major, minor or bidirectional
- Donor sex: male vs. female
- Karnofsky performance status
- HLA compatibility: matched, mismatched, haploidentical.
- Stem cell source: peripheral blood, bone marrow.
- Donor patient relationship: sibling, related, unrelated.
- CMV patient and donor status.
- Conditioning regimen: MAC vs RIC
- TBI based. Yes no. Dose
- EBV patient status
- GvHD prophylaxis.
- Acute GvHD assessment (maximum grade) and date
- Treatment for acute GvHD. Steroids and immunosuppressive agents. Yes/no and time.
- Chronic GvHD assessment maximum grade and date. Limited or extensive.
- Treatment for chronic GvHD. Steroids and immunosuppressive agents. Yes/no and time.

Subsequent neoplasms related:

- Type of SN
- Date of SN diagnosis
- Tumor EBV positive. Yes/no

Patient status

- Disease relapse or progression and date
- Last contact
- Status at contact.
- Live/Death Status at last contact
- Cause of death

Sample requirements:
No biologic or serologic data are required with this proposal.

Study design:

The primary focus of the current analysis will be the association between post-transplant cyclophosphamide and risk for SN.

1. *To compare the incidence rate of SN in patients who used PTCy with patients who used other CNI-based prophylaxis*

   The study design will be based on a case-control study.

   We would include patients who underwent first allogeneic HSCT with PTCy for GvHD prophylaxis from 2008 to 2017. For each patient with PTCy (case patient), we will randomly select control patients from the total cohort. We attempt to match at least 3 controls per case patient using the following criteria: primary disease, sex, age at transplantation (within 3 years), number of lines therapies before allo-HSCT, type of donor, HLA compatibility and donor relationship and survival time at least as long as the interval from transplantation to post-HSCT cancer for the matched case patient. When possible, control patients will be matched to case patients based on race (white, black, other) and on geographic region of the CIBMTR transplantation team.

   Patient-, disease-, and transplantation-related factors will be compared between matched cases and controls using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables.

   The marginal Cox model will be applied to evaluate the main treatment effect while adjusting for the potential correlation within each matched pair. The assumption of proportional hazards for the main risk factor (post transplantation cyclophosphamide versus other GvHD prophylaxis) for each outcome will be tested by adding a time-dependent covariate. Hazard ratios (HRs) with 95% confidence intervals (CIs) and P values will be reported for each clinical outcome of interest, comparing the PTCy treatment group with the other group. P Values <.05 will be considered statistically significant a priori. All secondary neoplasms, including invasive secondary cancers of the skin and melanomas will be included. In situ nonmelanoma skin cancers and basal cell skin cancers will be excluded.
2. To compare the incidence rate of SN in patients who received PTCy with general population.

   Same as described above but using The Surveillance, Epidemiology and End Results (SEER) data.
3. To describe the incidence rate, characteristics (Solid tumor, Myelodysplasia (t-MDS)/acute myeloid leukemia (t-AML) or Lymphoma, including lymphoproliferative disorders) and outcomes (time from transplant to SN, cause of death) of SN in patients receiving PTCy as GvHD prophylaxis

   The Kaplan-Meier estimator will be used to evaluate the probability of OS and DFS. Cumulative incidence rates will be calculated for SN, GvHD, NRM, and relapse while accounting for competing events. The SN's characteristics will be summarized using means and standard deviations (SD) or frequencies and percentages, as appropriate. Normality of data distribution will be checked using skewness-kurtosis test.
4. To describe risk factors of SN in patients receiving PTCy for GvHD prophylaxis, including sociodemographic (e.g., gender), disease (e.g., primary disease, pre-conditioning therapy), and HSCT (e.g., transplant modalities and related complications) factors

   Univariate analyses will be done using Gray's test for cumulative incidence functions and with the log-rank test for survival analyses. Multivariable analyses will be performed using Cox proportional hazard models, adjusting for key patient and disease characteristics. A stepwise selection of variables include in the Cox model will be performed using a P-value of 0·05 for statistical significance. Proportional hazards assumptions will be checked systematically for all proposed models using the Grambsch-Therneau residual-based test. All tests will be 2-sided. The type I error rate will be fixed at 0·05 for the determination of factors associated with time-to-event outcomes.

Non-CIBMTR data source:

Not required

Conflicts of interest:

Lucrecia Yanez San Segundo and Miguel Perales, MD: Yes, as reported below

AAT, SKH, IM, AK: No conflict of interest to disclose.

Dr. Perales reports honoraria from Abbvie, Bellicum, Bristol-Myers Squibb, Incyte, Merck, Novartis, Nektar Therapeutics, Omeros, and Takeda. He serves on DSMBs for Servier and Medigene, and the scientific advisory boards of MolMed and NexImmune. He has received research support for clinical trials from Incyte, Kite/Gilead and Miltenyi Biotec. He serves in a volunteer capacity as a member of the Board of Directors of American Society for Transplantation and Cellular Therapy (ASTCT) and Be The Match (National Marrow Donor Program, NMDP), as well as on the CIBMTR Cellular Immunotherapy Data Resource (CIDR) Committee. Dr. Yanez reports honoraria from Abbvie, Celgene, Gilead, Janssen, Merck, Roche, and Pfizer. She has participated in advisory boards of Abbvie, Celgene, Gilead, Kite, Janssen, Jazz, Merck, Roche, Pfizer and Sandoz.

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First alloHCT (including prior autoHCT) for malignant disease between 2008-2017, age >= 18

Characteristic	N (%)
No. of patients	64935
CRF - no. (%)	18072 (28)
Age - median (min-max)	53.8 (18-87.8)
Age group - no. (%)	
18-29	7413 (11)
30-39	7160 (11)
40-49	11503 (18)
50-59	18755 (29)
60-69	17431 (27)
≥70	2673 (4)
Sex - no. (%)	
Male	38091 (59)
Female	26844 (41)
Race - no. (%)	
White	50303 (77)
Black or African-American	3115 (5)
Asian	3752 (6)
Native Hawaiian or other Pacific Islander	223 (0)
American Indian or Alaska Native	203 (0)
Other	1 (0)
More than one race	182 (0)
Missing	7156 (11)
Karnofsky score prior to HCT - no. (%)	
90-100%	39772 (61)
< 90%	23553 (36)
Missing	1610 (2)
Sorror comorbidity score - no. (%)	
0	20421 (31)
1	8664 (13)
2	8355 (13)
3+	24005 (37)
TBD	299 (0)
NA, f2400 (pre-TED) not completed	359 (1)
Missing	2832 (4)
Disease - no. (%)	
Acute myelogenous leukemia or ANLL	26122 (40)
Acute lymphoblastic leukemia	8979 (14)
Other leukemia	2641 (4)
Chronic myelogenous leukemia	2539 (4)
Myelodysplastic/myeloproliferative disorders	11847 (18)
Other acute leukemia	757 (1)
Non-Hodgkin lymphoma	8091 (12)
Hodgkin lymphoma	1712 (3)
Plasma cell disorder/Multiple Myeloma	2202 (3)
Other Malignancies	41 (0)

Characteristic	N (%)
Breast Cancer	4 (0)
Prior alloHCT - no. (%)	
No	57703 (89)
Yes	7232 (11)
Time from diagnosis to transplant (months) - median (min-max)	8.36 (0-799.1)
Computed planned conditioning intensity - no. (%)	
No drugs reported	47 (0)
MAC	32239 (50)
RIC	21326 (33)
NMA	8046 (12)
TBD	2872 (4)
N/A, F2400 (pre-TED) not submitted, drug dose not available	359 (1)
Missing	46 (0)
Post-HCT cyclophosphamide[a] - no. (%)	
No	25121 (39)
Yes	6813 (10)
Missing	402 (1)
N/A, not collected on F2400R1-R3 (2008-2013)	32599 (50)
GVHD prophylaxis - no. (%)	
Post-CY ± other(s)	6815 (10)
TAC + MMF ± other(s) (except post-CY)	7398 (11)
TAC + MTX ± other(s) (except MMF, post-CY)	26657 (41)
TAC + other(s) (except MMF, MTX, post-CY)	4315 (7)
TAC alone	1247 (2)
CSA + MMF ± other(s) (except post-CY)	5859 (9)
CSA + MTX ± other(s) (except MMF, post-CY)	10535 (16)
CSA + other(s) (except MMF, MTX, post-CY)	680 (1)
CSA alone	1429 (2)
Donor - no. (%)	
HLA-identical sibling	24371 (38)
Twin	43 (0)
Other related	6153 (9)
Well-matched unrelated (8/8)	23521 (36)
Partially-matched unrelated (7/8)	5255 (8)
Mis-matched unrelated (≤6/8)	279 (0)
Multi-donor	64 (0)
Unrelated (matching TBD)	5241 (8)
Missing	8 (0)
Graft type - no. (%)	
Bone marrow	8952 (14)
Peripheral blood	55983 (86)
Year of transplant - no. (%)	
2008	5055 (8)
2009	5483 (8)
2010	6019 (9)
2011	6420 (10)
2012	6770 (10)

Characteristic	N (%)
2013	6805 (10)
2014	6985 (11)
2015	6956 (11)
2016	7133 (11)
2017	7309 (11)
Subsequent neoplasm[b] - no. (%)	
No	59164 (91)
Yes	5771 (9)
Follow-up - median (min-max)	59.8 (0-149.5)

[a] PTCy was not collected on 2400 prior to 2013. Of the 6813 cases that received PTCy, there were 1543 identified between 2008-2013 using the GVHD prophylaxis drug other, specify (free-text) field

[b] Need to review and exclude SN that is not different from disease for which the HCT was performed

[c] Number of reported subsequent neoplasms within PTCy groups: PTCy n=458 (6.7%) within PTCy, n=1946 (7.8%) within no PTcy, n=3278 (10.1%) within N/A PTCy not collected 2008-2013, and n=89 (22.1%) within missing.

Proposal: 2010-248

Title:
Cumulative Incidence and Risk Factors for Breast Cancer after Allogeneic Hematopoietic Cell Transplant

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Research hypothesis:
Breast cancer is a known late complication of allo-HCT. While consensus guidelines for breast cancer screening after allo-HCT exist, the recommendations are largely extrapolated from the Hodgkin lymphoma literature. There is a paucity of literature on the risk of breast cancer after allo-HCT and the existing literature does not examine how 1) variations in modern conditioning regimens (particularly variations in TBI dosing and fractionation), and 2) age at allo-HCT and time post allo-HCT, independent of conditioning, impact risk of subsequent breast cancer. We hypothesize that discrete risk factors for the occurrence of breast cancer after allo-HCT will be identified in this proposed registry study that will contain larger numbers of patients and longer follow-up than previous studies. Specifically, we hypothesize that total body irradiation (TBI) as part of conditioning will be associated with occurrence of breast cancer, with the magnitude of the association modulated by the total dose and fractionation of the TBI. Additionally, we hypothesize that younger age at transplant and greater number of years since transplant will be associated with occurrence of breast cancer, independent of receipt of TBI. The results of the study will inform future breast cancer screening guidelines for allo-HCT recipients.

Specific aims:
- Estimate the cumulative incidence of breast cancer after allo-HCT.
- Elucidate risk factors for the occurrence of breast cancer after allo-HCT, particularly the association between breast cancer and TBI (at varying dose and fractionation), age at allo-HCT and time post allo-HCT.
- Estimate the excess risk of breast cancer in allo-HCT recipients as compared to the general population.

Scientific impact:
The current consensus guidelines for screening and preventive practices after HCT emphasize the importance of early initiation of screening mammography for women exposed to total body irradiation (TBI) as part of HCT conditioning.[1] Specifically, for women exposed to >8 Gy screening is recommended to begin at 8 years post-HCT or age 25, whichever occurs later, but no later than age 40. While these recommendations have served as an important guide for clinicians, they are currently inadequate because: 1) they are largely extrapolated from the Hodgkin lymphoma survivorship literature, and 2) there have since been significant changes in HCT conditioning. Importantly, higher dose TBI (typically considered to be >6-8 Gy) is now typically fractionated, the use of low dose TBI (typically considered to be 2-4.5 Gy) has become relatively common, and there are now multitudes of HCT conditioning regimens that do not include TBI. It is currently unclear, for example, whether those patients who received low dose TBI or those who received a non-TBI conditioning regimen at a young age should begin screening mammography earlier than general population guidelines. The proposed study aims to

harness CIBMTR registry data to provide the HCT community with an updated analysis of risk factors for breast cancer with the primary purpose of informing future screening guidelines for breast cancer after allo-HCT.

Scientific justification:

Subsequent malignancies (SM) are a known late complication of allo-HCT that contribute significantly to morbidity and non-relapse mortality, and thus are a major focus of post-transplant survivorship care.[2, 3] The cumulative incidence of SMs increases in the decades after transplant with no discernable plateau.[4, 5] As compared to the general population, allo-HCT survivors develop SMs at a rate that is at least double the population rate in the first decade after transplant and at least triple the population rate beyond the first decade.[2] Risk factors for the development of SM reported in the literature to date include receipt of TBI-based conditioning, younger age at transplant, and occurrence of acute (a lesser factor) and chronic GVHD, among others.[4]

Advances in allo-HCT conditioning over the last decades have led to various levels of conditioning-related exposure: conditioning may be of varying intensity with or without TBI. If TBI is used, it may be used in fractionated high doses or in lower doses. These varying levels of exposure likely lead to varying risks of SM. Recently, two single centre studies found that the risk of SM in those exposed to low dose TBI as part of conditioning (2-4.5 Gy) was similar to those conditioned with chemotherapy alone.[6, 7] Additionally, a single fraction of high dose TBI was associated with greater risk of SM as compared to fractionated high dose TBI.[6]

However, risk factors also vary for the specific type of SM being studied,[4] emphasizing the importance of studying individual SMs in an effort to identify sub-groups of survivors who will benefit from screening practices. Breast cancer, a common malignancy in the general population and among survivors of allo-HCT, is a malignancy with an effective screening modality in the form of breast imaging. While recommendations for breast cancer screening in HCT survivors exist, they are based on data extrapolated from the Hodgkin lymphoma literature. The current screening recommendations focus specifically on exposure to >8 Gy TBI and do not make specific recommendations for other groups of allo-HCT survivors (for example, those exposed to low dose TBI or those who received allo-HCT at a young age with non-TBI based conditioning). The reason for these limited screening guidelines is a paucity of literature specifically examining the risk of breast cancer after allo-HCT. A single large study has examined risk factors for breast cancer after allo-HCT: in a FHCRC/EBMT collaborative study, of 3337 female survivors of allo-HCT (transplanted 1969-2000), 52 developed breast cancer at a median follow-up of 12.5 years post-transplant.[8] Increased risk of breast cancer was associated with longer time since transplant, use of TBI and younger age at transplant. Notably, dose and fractionation of TBI were not included in the multivariable model.

As these data continue to mature and further conditioning regimens are examined, we expect novel insights to be gleaned to guide clinical practice: a recent FHCRC analysis of 2091 female survivors of allo-HCT (transplanted 1969-2014) revealed that standardized incidence ratios (SIRs) for breast cancer were similar for those receiving conditioning with chemotherapy only, low dose TBI and high dose fractionated TBI (all in the 10.5-11.8 range) (K.S. Baker, unpublished data). Additionally, the SIR for current age 21-50 was 17.6, and SIRs for breast cancer increased with decreasing age at time of transplant (26.2 for those <20 years old) and with increasing years since transplant (16.2 for those >30 years post-transplant). The 80 observed cases of breast cancer in this analysis were spread thin across multiple covariate categories, making multivariable analysis unreliable. Importantly, these data suggest that risk factors for breast cancer after allo-HCT may extend beyond high dose TBI. Those who received chemotherapy only or low dose TBI conditioning, those who were transplanted at a young age and those who are very late post-transplant, may not fit into current guidelines for breast cancer screening after

allo-HCT (particularly those in the 21-50 year old current age group), yet may be at significant risk of breast cancer.
The relatively small numbers of breast cancer cases in the above mentioned two studies highlights the need to harness registry data to maximize the number of cases available for analysis to ensure a robust multivariable analysis is possible. The long latency of SMs after allo-HCT renders a retrospective study attractive. The ability to use the CIBMTR registry to successfully explore risk factors for a specific malignancy after allo-HCT has been recently demonstrated for melanoma.[9]

Patient eligibility population:
All female recipients of a first allo-HCT reported to CIBMTR through 2015 who survived until at least one year post-transplant without developing breast cancer will be included. Patients who received allo-HCT for Fanconi anemia, primary immunodeficiency or breast cancer will be excluded. Patients who have a known history of breast cancer that predates allo-HCT will also be excluded (history obtained from Pre-TED form or AML/MDS pre-infusion forms indicating therapy-related disease with prior breast cancer).

Data requirements:
Pre-HCT Data: age at transplant, race, primary disease, conditioning regimen (chemotherapy only vs. TBI groups: low dose (200-450 cGy), single dose 600-1000 cGy, fractionated 600-1200 cGy, fractionated 1320-1400 cGy, fractionated >1400 cGy), stem cell source (BM vs. PBSC vs. cord), donor type (matched related, haploidentical, matched unrelated, mismatched unrelated), T-cell depletion (in-vivo or ex-vivo).
Post-HCT Data: occurrence of breast cancer, date of breast cancer, death, date of death, second allo-HCT, date of second allo-HCT, grade II-IV aGVHD, date of onset of grade II-IV aGVHD, moderate-severe NIH or clinically extensive cGVHD, date of onset of moderate-severe NIH or clinically extensive cGVHD, date of last follow-up or death, age at last follow-up or death.

Sample requirements:
None

Study design:
This will be a retrospective cohort study. The cumulative incidence of breast cancer for the entire cohort will be calculated, accounting for competing risks and censoring at the date of last contact. Death without breast cancer and receipt of second allo-HCT will be considered competing risks.
A multivariable Cox proportional hazards model will be used to evaluate the association of covariates with the outcome of breast cancer. Covariates will include age at transplant (<10, 10-19, 20-29, 30-39, 40-49, ≥50), years post-transplant (1 to <5, 5 to <10, 10 to <15, 15 to <20, ≥20), race (Caucasian vs. other), primary disease (acute leukemia, myelodysplastic syndrome, chronic myeloid diseases, lymphoma, aplastic anemia, other), conditioning regimen (chemotherapy only vs. TBI groups: low dose (200-450 cGy), single dose 600-1000 cGy, fractionated 600-1200 cGy, fractionated 1320-1400 cGy, fractionated >1400 cGy), stem cell source (BM vs. PBSC vs. cord), donor type (matched related, haploidentical, matched unrelated, mismatched unrelated), T-cell depletion (in-vivo or ex-vivo), grade II-IV aGVHD, moderate-severe NIH or clinically extensive cGVHD. An additional multivariable model, restricted to those currently aged 20-49, will be built to specifically examine risk factors within this sub-group who are not uniformly eligible for breast cancer screening. Levels or categorization of covariates may be altered prior to analysis in order to optimize statistical power once the number of breast cancer cases in the study population is known.

Comparisons to the general population will be made by calculating standardized incidence ratios (SIRs) (ratio of observed/expected cases) and excess absolute risk (observed minus expected cases standardized to person time, for example per 1000 person years). The observed rate of breast cancer in the study cohort and sub-groups of the study cohort will be calculated using observed number of cases and number of person years of follow-up in the cohort and sub-groups of the cohort. The expected number of cases for the cohort and sub-groups of the cohort will be derived by applying age, sex, calendar-year and region specific rates of breast cancer for the general population to the person years of follow-up in the cohort and sub-groups of the cohort.

Non-CIBMTR data source:
None

Conflicts of interest:
The investigators have no relevant conflicts of interest.

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Table 1. Baseline characteristics of females receiving first alloHCT between 2007-2015[a]

Characteristic	N (%)
No. of patients	29857
CRF - no. (%)	9880 (33)
Age - median (min-max)	45.33 (0.1-83.5)
Age group - no. (%)	
0 - 9	3379 (11)
10 - 19	2974 (10)
20 - 29	2929 (10)
30 - 39	3317 (11)
40 - 49	4914 (16)
50 - 59	6755 (23)
60+	5589 (19)
Race - no. (%)	
White	21452 (72)
Black or African American	2152 (7)
Asian	2346 (8)
Native Hawaiian or other Pacific Islander	115 (0)
American Indian or Alaska Native	125 (0)
Other	141 (0)
More than one race	190 (1)
Missing	3336 (11)
Karnofsky/Lansky - no. (%)	
≥ 80	25582 (86)
<80	2942 (10)
Missing	1333 (4)
HCT-CI - no. (%)	
0	11233 (38)
1	3560 (12)
2	2997 (10)
3+	8215 (28)
TBD	52 (0)
NA, f2400 (pre-TED) not completed	2102 (7)
Missing	1698 (6)
Disease - no. (%)	
Acute myelogenous leukemia or ANLL	12601 (42)
Acute lymphoblastic leukemia	5005 (17)
Other leukemia	760 (3)
Chronic myelogenous leukemia	1142 (4)
Myelodysplastic/myeloproliferative disorders	3199 (11)
Other acute leukemia	352 (1)
Non-Hodgkin lymphoma	2075 (7)
Hodgkin lymphoma	207 (1)
Plasma cell disorder/Multiple Myeloma	186 (1)
Other Malignancies	31 (0)

Characteristic	N (%)
Severe aplastic anemia	1568 (5)
Inherited abnormalities erythrocyte differentiation or function	1155 (4)
Inherited abnormalities of platelets	45 (0)
Inherited disorders of metabolism	277 (1)
Histiocytic disorders	351 (1)
Autoimmune Diseases	33 (0)
Other, specify	45 (0)
Myeloproliferative Neoplasms	822 (3)
Missing	3 (0)
Time from diagnosis to transplant (months) - median (min-max)	7.6 (0-799.1)
Prescribed computed conditioning regimen intensity - no. (%)	
No drugs reported	24 (0)
MAC	15154 (51)
RIC	5998 (20)
NMA	2257 (8)
TBD	1046 (4)
N/A, F2400 (pre-TED) not submitted, drug dose not available	1885 (6)
N/A, not malignant disease	3429 (11)
Missing	64 (0)
Prescribed TBI - no. (%)	
TBI, > 800 cGy	6081 (20)
TBI, ≤ 800 cGy	3566 (12)
TBI, dose unknown	841 (3)
No TBI	19231 (64)
Missing	138 (0)
Donor type - no. (%)	
HLA-identical sibling	11259 (38)
Twin	190 (1)
Other related	2029 (7)
Well-matched unrelated (8/8)	8519 (29)
Partially-matched unrelated (7/8)	2553 (9)
Mis-matched unrelated (≤ 6/8)	936 (3)
Multi-donor	1637 (5)
Unrelated (matching TBD)	2677 (9)
Missing	57 (0)
Graft type - no. (%)	
Bone marrow	7363 (25)
Peripheral blood	19401 (65)
Cord blood	3093 (10)
Follow-up - median (min-max)	71.5 (0-160.9)
Breast cancer post-transplant - no. (%)	
No BC	29756 (99.7)
BC ≥ 12 months post-tx[b]	101 (0.3)

[a] Still need to exclude cases with less than 1 year of follow-up or those who died within 1 year of transplant.
[b] n=39 are CRF level