1. Introduction
   a. Minutes and Overview Plan from February 2014 meeting (Attachment 1)
   b. Introduction of incoming Co-Chair: Joseph Pidala, MD; H. Lee Moffitt Cancer Center and Research Institute; Telephone: 1-813-745-2556; E-mail: joseph.pidala@moffitt.org; Areas of focus: GVHD prevention and treatment.

Dr. Cutler began the meeting at 2:45 PM by welcoming all attendees to the Graft-versus-Host Disease Working Committee (GVWC), and introducing Dr. Joseph Pidala as the new Chair. Dr. Amin Alousi acknowledged Dr. Cutler as the outgoing Chair and the excellent work and guidance he provided to the GVWC over the last 5 years. Dr. Cutler emphasized the importance of feedback and voting by GVWC members in determining the priority of the committee’s studies.

2. Accrual Summary (Attachment 2)

Dr. Cutler acknowledged the Accrual Summary tables are included in the GVWC meeting materials that had been circulated before the meeting. He said it is important for the GVWC members to reference these tables when considering proposing a study and to reference the CIBMTR data collection forms to be cognizant of what information the CIBMTR collects.

3. Presentations, published or submitted papers
   a. GV04-02/05-03c Boyiadzis M, Arora M, Klein JP, Hassebroek A, Hemmer M, Urbano-Ispizua A, Antin JH,


Dr. Cutler referenced the GVWC published 3 studies over the past year and acknowledged that the manuscript for **GV11-03** had recently been submitted for publication.

4. **Future/proposed studies**

Dr. Cutler informed the GVWC members that there will be a 5th proposal presented that had been brought to the GVWC leadership’s attention after the Tandem agenda had been circulated. He told the GVWC members that although this proposal was received after the deadline for Tandem proposals, the scientific merit of the proposal warranted being brought to the meeting for discussion. He reminded the GVWC that if any GVWC member has an idea for a proposal, they can submit it to the GVWC leadership at any time during the year and if the leadership determines it is of high scientific impact, they will incorporate it into the current GVWC portfolio of studies.

Dr. Cutler reminded the GVWC that proponents will be given 5 minutes to present and then there will be 5-10 minutes of discussion with the GVWC members. He also explained the voting process, noting that 1 denoted a high scientific impact and 9 is a low impact, and that each proposal should be voted on this scale (the proposals aren’t meant to be ranked amongst each other).

a. **PROP 1411-32** Development of a chronic GVHD-related co-morbidity measure using CIBMTR data (SW Choi / D Couriel / N Majhail) (Attachment 3)

Dr. Sung Choi presented the proposal. The objective of the study is to develop a GVHD-related comorbidity (GRC) burden measurement that can more accurately reflect the impact of GVHD and its therapy and can consistently correlate with other outcomes (such as Quality-of-Life, NRM and OS). The proposed co-morbidities to include in the GRC are KPS, non-infectious pulmonary abnormalities, mechanical ventilation, cirrhosis, avascular necrosis, cataracts, congestive heart failure, hemorrhagic cystitis, myocardial infarction, pancreatitis, hypothyroidism, renal failure, stroke/seizure, infections,
and new malignancy. The proposed study design is to split the available cohort into GRC score development cohort and a validation cohort.

One question asked was if there would be bias against patients with less follow-up in this proposal (as would be expected for patients with cGVHD), and that people who die prior to cGVHD onset won’t be eligible for this population. Dr. Choi acknowledged that would be a limitation, and perhaps a bias, in the study. Other opinions expressed by the GVWC were low enthusiasm that this proposal would add anything new to the literature that hasn’t been covered and validated in the cGVHD risk score studies by Arora and Flowers. A third suggestion was to evaluate all of the co-morbidities for which the CIBMTR has data and not merely on any co-morbidities specified before the study begins. A fourth suggestion was to evaluate all co-morbidities within patients from 1 or 2 transplant centers and subsequently propose a validation through CIBMTR dataset. The GVWC member acknowledged this would likely add a few years to the study to gather data, but would provide better detail on the pre- and post-transplant co-morbidities.

b. PROP 1411-89 Risks and outcomes of orthotopic liver transplantation for hepatic GVHD in HCT patients (S Hashmi / M Jagasia / J Palmer / J Koreth / M Litzow) (Attachment 4)

Dr. Shahrukh Hashmi presented his proposal, which aims to investigate orthotopic liver transplantation (OLT) for treatment of liver failure due to hepatic GVHD post-HCT. Dr. Hashmi stated that OLT is the only known curative treatment for irreversible acute liver failure or end stage liver disease (ESLD). The United Network for Organ Sharing (UNOS) maintains a database of organ transplants in the United States and from this database, Dr. Hashmi has found 111 patients who underwent OLT for liver failure due to GVHD between 1998-2012. Dr. Hashmi proposed to merge the UNOS and CIBMTR databases to evaluate the outcomes of patients undergoing OLT after they had received an HCT from a CIBMTR center.

A question from the GVWC was if medical charts for the 111 patients would need to be pulled from the centers where the OLT was performed to evaluate pre-OLT characteristics and post-OLT outcomes. Another question was what the CIBMTR data provides that UNOS does not capture, to which Dr. Hashmi responded CIBMTR captures pre- and post-HCT data that precedes the OLT and UNOS did not follow patients for as long of a period of time as the CIBMTR does. Dr. Navneet Majhail spoke on his past experience merging the UNOS and CIBMTR databases for a study in the Late Effects WC. After merging the 2 databases by social security number, date of birth and date of transplant, there were only approximately 120 total organ transplants that matched with patients from the CIBMTR. Dr. Majhail expressed concern about low numbers of patients that match up with OLT in the UNOS and CIBMTR databases. He also said that obtaining case reports through UNOS would be extremely difficult.

Another comment provided was that this proposal cannot be hypothesis-driven (since patients undergoing OLT are having worse post-HCT outcomes, hence their decision to have OLT). Further suggestions were that this study, should it proceed, be treated as a “Lewis & Clark” expedition. Merge UNOS and CIBMTR databases, see what number of matched patients turn up and build a study around that number. If it’s 20 patients or fewer, then can only describe them, but if there are more, perhaps could perform a simple type of analysis. Another comment was to consider the protective effect that the use of ursodiol has had reducing hepatic toxicity in the modern era.

c. PROP 1412-04 The role of TBI in sclerotic-type cGVHD of the skin (EW Cowen / S Pavletic / KJ Martires) (Attachment 5)
Dr. Dan Couriel presented this proposal, on behalf of the PIs. Dr. Kathryn Martires joined the meeting via phone. The PIs state that severity of sclerotic-type cGVHD (ScGVHD) may impact survival. They also stated that previous studies have shown that TBI use in reduced intensity conditioning (RIC) patients and conditioning regimen intensity was strongly associated with ScGVHD.

A suggestion was to consider evaluating, and potentially stratifying, graft source in the analysis, which is known to influence rates of cGVHD. Another variable recommended to explore in the analysis was “time from transplant to cGVHD”, since sclerosis tends to occur later. Another suggestion was to analyze was use of ATG/Campath. A further suggestion was to consider making the population more homogeneous, which would mean a smaller population but would make the analysis more straightforward.

A concern about a major limitation to this study is that the CIBMTR forms do not collect any dates that specific treatments were administered for cGVHD. Another concern was that the CIBMTR forms only measure ScGVHD as a yes/no variable; there is no information on the extent of the sclerosis. One suggestion to this point was to combine the sclerosis yes/no variable with overall cGVHD severity, in an attempt to gauge how severe sclerosis was. A point was made that it would be difficult to evaluate trends in the RIC patients. Another point was that the analysis would be more meaningful if the population were restricted to patients who developed cGVHD within 1 year post-transplant.

d. PROP 1412-20 Impact of donor obesity and inflammation on acute and chronic GVHD among HCT recipients (L Turcotte / M Verneris) (Attachment 6)

Dr. Michael Verneris presented this proposal. The hypothesis is that stem cell products from obese donors will result in increased rates of GVHD. Previous studies have shown that obese recipients have increased risks of GVHD. The PIs also proposed evaluating inflammatory cytokine levels in CIBMTR repository samples from a subset of the study population.

The group suggested including graft source in the analysis, to which Dr. Verneris agreed. Another suggestion was to evaluate the impact of recipient obesity in the analysis. Another suggestion was to consider the findings of prior studies evaluating metabolomics in obese mice.

A suggestion was made to consider the impact of infections on developing GVHD, but the CIBMTR’s collection of infection data is very messy and would severely hinder the development of this study. Another suggestion was to consider donor use of statins or asthma medications at the time of donation. Another suggestion was to evaluate cell dose in the analysis.

e. PROP 1412-25 Do BM grafts result in improved GRFS when compared to PB grafts in adults receiving allogeneic HCT from matched-unrelated donors? (A Alousi / S Holtan / D Weisdorf)

Dr. Amin Alousi presented this proposal. The hypothesis is that among adult recipients of matched unrelated allogeneic HCT, PBSC grafts will result in worse GVHD-free, relapse-free survival (GRFS) than BM grafts. GRFS is a new composite endpoint that was created for clinical trials, in an attempt to measure “cure” without “on-going morbidity.” A previous analysis from the University of Minnesota indicated that donor type, recipient age, disease risk and graft type significantly impacted GRFS, with pediatric recipients with a matched-related donor reaching the highest GRFS. However, this analysis did not feature enough patients to determine if there was a difference in adult matched unrelated or related donors between BM and PBSC graft sources. This study would use an already-cleaned dataset from a recently published GVWC study (“Current trends in chronic GVHD – updated report from the CIBMTR/NMDP.” Arai, et. al.).
A question was whether this analysis could be performed on the BMT CTN 0201 dataset. Dr. Alousi said that that is possible, but the final dataset from Dr. Arai’s study was much larger and had more follow-up. A question was raised about evaluating GRFS in related donors in the Arai dataset. Related donor outcomes may be confounded by the high rate of PBSC use. One comment concerning the GRFS endpoint is that severe aGVHD patients, who would then be censored using GRFS, may remove the ability to analyze any graft-versus-leukemia (GVL) effect. A suggestion made was to add immunosuppression-free survival to the study, because GRFS treats each of the 3 endpoints equally (GVHD, relapse, death). There was further discussion on what should be evaluated as a good transplant outcome and if GRFS should be the only endpoint evaluated in this study. Other suggestions were to evaluate graft source, conditioning regimen intensity and disease risk index (DRI) in analysis. It was further suggested that it would be best to stratify the analysis by conditioning intensity. Another suggestion was to incorporate engraftment into the GRFS endpoint. It was also suggested to define a meaningful result for this study before beginning the analysis, since a large dataset would make it more likely to interpret a small effect change as statistically significant.

Dropped proposals

f. PROP 1405-01 Comparison of post-transplant Cy to CNI-based GVHD prophylaxis regimen (AS Al-Homsi / S Williams / T Roy / U Duffner) 
_Dropped due to insufficient numbers of post-tx Cy alone cohort and overlap with ongoing clinical trial._

g. PROP 1411-14 Comparison of CNI + MTX with post-transplant Cy alone as GVHD prophylaxis in patients undergoing allogeneic HCT (UR Deotare / MD Seftel) 
_Dropped due to insufficient numbers of post-tx Cy alone cohort and overlap with ongoing clinical trial._

h. PROP 1411-57 Comparison of cyclosporine versus tacrolimus with MMF for GVHD prophylaxis after umbilical cord blood transplant (R Hanna / B Hamilton / M Jagasia / N Majhail) 
_Dropped due to overlap with current GVWC study (GV11-02)._
h. **GV14-02** Influence of donor and recipient age on risk for GVHD in children receiving HLA-identical bone marrow transplantation (M Qayed / J Horan)

Dr. Couriel briefly described each of the GVWC studies currently in progress, their current standing, objectives, selection criteria and study design.

6. **Other Business**

Hearing no discussion for Other Business, Dr. Cutler closed the GVWC meeting at 4:40 PM.
GV11-02 Acute and chronic GVHD after unrelated umbilical cord blood transplantation: Analysis of risk factors and outcomes. (Y-B Chen / C Cutler)

The analysis will be complete and the manuscript under preparation by May 2015. The manuscript will be submitted for publication by September 2015.

GV13-02 The impact of the combination and sequence of immunosuppressive treatments on outcomes of acute GVHD: A methodological exercise in modeling adaptive treatment strategies. (E Krakow / E Moodie)

The analysis is currently being revised by the PI as part of her Masters’ Thesis. We anticipate the study will be in manuscript preparation by June 2015 and submitted by January 2016.

GV12-02 Prognostic implications of acute upper gastrointestinal GVHD in patients undergoing myeloablative HCT. (S Nikiforow / C Cutler)

The analysis will be completed by June 2015 and an ASH abstract will be submitted by August 2015. The manuscript will be submitted for publication by June 2016.

GV12-01 Outcomes of grades 2-4 acute GVHD post-allogeneic HCT: How much progress was achieved? (HJ Khoury)

The analysis will be completed by June 2015 and an ASH abstract will be submitted by August 2015. The manuscript will be submitted by June 2016.

GV13-01 Impact of donor parity and donor type on outcomes of allogeneic HCT (A Kumar / A Loren)

We anticipate preparing the data file after June 2015. We further anticipate the study will be in manuscript preparation by June 2016.

GV14-01 Comparison of MMF vs. MTX in combination with a CNI for GVHD prophylaxis in allogeneic HCT (B Hamilton / S Chhabra / N Majhail / L Costa / R Stuart / D Kim / O Ringden)

The protocol is currently being finalized. We anticipate the protocol will be finalized by June 2016.

GV14-02 Influence of donor and recipient age on risk for GVHD in children receiving HLA-identical bone marrow transplantation (M Qayed / J Horan)

The protocol is currently being finalized. We anticipate that the data file will be prepared, the results finalized and the study will be in manuscript preparation by June 2016.

GV15-01 Impact of donor obesity and inflammation on acute and chronic GVHD among HCT recipients (L Turcotte / M Verneris)

We anticipate receiving the draft protocol by July 2015 and finalizing the protocol by June 2016.
h. **GV15-02** Do BM grafts result in improved GRFS when compared to PB grafts in adults receiving allogeneic HCT from matched-unrelated donors? (A Alousi / S Holtan / D Weisdorf)

We anticipate receiving the draft protocol by July 2015. We further anticipate the study being in manuscript preparation by June 2016.
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