The Blood and Marrow Transplant Clinical Trials Network (BMT CTN): Renewal

Presentation to BSA
June 21, 2016

William D. Merritt, Ph.D.
Program Director
CGCB/Clinical Trials Evaluation Program
DCTD
Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

• Established: Sept 2001; renewed 10/06 and 7/11
  – 1 Data Coordinating Center Cooperative Agreement
  – 20 Core Center Cooperative Agreements

• Joint sponsorship between NHLBI and NCI (NHLBI primary)

• Goals of the Program:
  – Provide infrastructure needed to allow promising therapies in stem cell transplant to be developed and evaluated in multi-center studies
  – Plan and complete Phase II and Phase III trials
    • Phase II studies to replicate single center findings, assess feasibility and validity and plan for Phase III trials
    • Phase III studies for large accrual trials and for rare diseases
Areas for Study in Transplant Agenda for BMT CTN

- Optimal pre-transplant conditioning regimens
- Optimal graft sources (alternatives to unrelated: cord blood and haploidentical)
- Acute and chronic GVHD: prevention and treatment
- Biomarkers for transplant complications (GVHD)
- Disease control to prevent recurrence/relapse (hematologic malignancies)
- Anti-cancer cellular vaccine strategies
- Outcomes of transplant in populations of various ages (elderly and pediatrics)
- Quality of life
## Protocols in BMT CTN: 2003 to current

<table>
<thead>
<tr>
<th>Category</th>
<th>Completed</th>
<th>Open</th>
<th>Pending</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple Myeloma</strong></td>
<td>3 (*1)</td>
<td>3**</td>
<td>1</td>
<td>7</td>
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<tr>
<td><strong>AML/MDS</strong></td>
<td>3 (*1)</td>
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<td>2</td>
<td>6</td>
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<tr>
<td><strong>ALL</strong></td>
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<td>-</td>
<td>1</td>
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<tr>
<td><strong>CLL</strong></td>
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<td>-</td>
<td>-</td>
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<td><strong>Lymphoma</strong></td>
<td>4 (*1)</td>
<td>-</td>
<td>1*</td>
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<td><strong>GvHD (includes biomarker trial)</strong></td>
<td>4</td>
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<tr>
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<td><strong>Hem Malignancy in HIV+ Patients</strong></td>
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<td>-</td>
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<tr>
<td><strong>Q/L; Recruitment; Inf consent</strong></td>
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<td>2</td>
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<td>3</td>
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<td><strong>Infectious Diseases</strong></td>
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<td><strong>Non-Hem Malignancy</strong></td>
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*Includes BMT CTN accrual to Coop Group-led trial

**Includes BMT CTN accrual to DFCI trial

#NCI-funded
### BMT CTN Trials Developed in Years 11-16

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Subjects</th>
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<tr>
<td>2012</td>
<td>5,250</td>
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<td>2013</td>
<td>6,000</td>
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<tr>
<td>2014</td>
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<tr>
<td>2015</td>
<td>8,600</td>
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<tr>
<td>2016</td>
<td>9,000</td>
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</table>

- **38 Trials Opened; 10 currently open**
- **32 BMT CTN-led**
- **6 NCI Group/PI-led (+)**
- **4 to open soon** (1201, 1401, 1501, 1503)
- **5 in development** (1502, 1504, 1506, 1507, 1601)

**PUBLICATIONS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Title</th>
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<tbody>
<tr>
<td>2016</td>
<td>1503</td>
</tr>
<tr>
<td>2016</td>
<td>1501</td>
</tr>
<tr>
<td>2016</td>
<td>1201</td>
</tr>
<tr>
<td>2016</td>
<td>1401</td>
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</table>

**Graph Notes:**
- = Enrollment complete; ongoing F/U
- = Enrollment on-going

**Diagram Details:**
- 1302 Allo Myeloma (+)
- 1301 PROGRESS II
- 1505 RECRUIT
- 07LT STaMINA Follow-Up
- 1203 PROGRESS I
- 1102 BMT vs Chemo for MDS
- 1304 Early vs Late BMT for MM
- 1205 ETRIC
- 1204 RIC for HLH
- 1202 Biomarker Collection
- 1101 Haplo vs. Double Cord
- 0903 Allo HIV-malignancy

BMT CTN and National Cancer Institute
Yearly and Cumulative Accrual to all Protocols 2004-2015
<table>
<thead>
<tr>
<th>Trial</th>
<th>Name</th>
<th>Group(s)</th>
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<tr>
<td>0102</td>
<td>PhIII Multiple Myeloma HCT</td>
<td>SWOG</td>
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<tr>
<td>0202</td>
<td>PhIII Follicular Lymphoma HCT</td>
<td>SWOG</td>
</tr>
<tr>
<td>0401</td>
<td>PhIII BEAM vs. BEAM/BEXXAR Lymphoma</td>
<td>SWOG</td>
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<tr>
<td>0501</td>
<td>PhIII Single vs. Double Cord Blood</td>
<td>COG</td>
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<tr>
<td>0502</td>
<td>PhII Non-myeloblative HCT for AML &gt;60yrs</td>
<td>SWOG*</td>
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<td>0701</td>
<td>PhII Non-myeloblative HCT for NHL</td>
<td>CALGB &amp; SWOG</td>
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<tr>
<td>0702</td>
<td>PhIII Multiple Myeloma HCT +/- new agents</td>
<td>CALGB, SWOG, ECOG</td>
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<tr>
<td>0703</td>
<td>PhII Tandem autologous for Hodgkins</td>
<td>SWOG</td>
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<tr>
<td>0704</td>
<td>PhIII Lenalidomide Maintenance for MM</td>
<td>CALGB</td>
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<tr>
<td>0805</td>
<td>PhII Targeted therapies +/- HCT for Ph+ ALL</td>
<td>CALGB, SWOG, ECOG</td>
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<tr>
<td>0804</td>
<td>PhII HCT for High Risk CLL</td>
<td>CALGB</td>
</tr>
<tr>
<td>1201</td>
<td>PhIII Ibrutinib during and following HCT for DLBCL</td>
<td>NCTN</td>
</tr>
</tbody>
</table>

*Bold: Group-led*
Transplant Questions in Hematologic Malignancies: NCTN and BMT CTN Collaboration
Accomplishments: Advances in Patient Care for Hematologic Malignancies

- **Treatment of Multiple Myeloma**
  - Tandem autologous plus allogeneic is not better than auto-auto
  - Lenalidomide maintenance post auto: results led to lenalidomide maintenance as standard therapy (with CALGB)

- **Autologous Transplant for lymphoma in HIV+ patients**: consider transplant as standard of care for these patients

- **Transplant for AML/MDS for elderly**: reduced intensity conditioning (RIC) in patients over 60: acceptable results

- **RIC vs. Myeloblastic Conditioning (MAC) for Allogeneic Transplant for AML/MDS**: MAC should be standard of care, as RIC results in higher relapse not balanced by lower TRM vs. MAC

- **Optimal graft sources for allogeneic transplants**
  - PBL vs. BM: similar overall survival but higher cGVHD with PBL
  - Single vs. double cord blood in pediatric patients: double CB similar survival than single but higher aGVHD with double
Key Trials to Open Soon, in Development or Planned

• **BMT CTN 1201**: Phase III study of ibrutinib during and following autologous HCT vs. placebo in R/R DLBCL (**with NCTN**): activation June 2016
  
• **BMT CTN 1506**: Phase III randomized multicenter trial of Gilteritinib vs. placebo for FLT3-ITD AML in CR after allogeneic HCT: to open soon
  
• **BMT CTN 1401**: Phase II multicenter trial of autologous HCT followed by lenalidomide with or without vaccination with dendritic cell/multiple myeloma fusions: activation July 2016 (5 sites IRB approved)
  
• **BMT CTN 1601**: Bridging trial of haploidentical donor NK cells for AML patients with disease prior to transplant: in development
  
• **BMT CTN xxxx**: EBV-specific T lymphocytes after auto HCT for EBV-positive Hodgkin Lymphoma patients (SOS priority-deferred)
Why Renew the BMT CTN?

- Transplant is curative for a significant number of patients with hematologic malignances, but relapse and TRM, particularly GVHD, limits use of transplant and efficacy.

- **BMT CTN provides a national network of experienced transplant centers**, with a centralized coordinating center, to design and implement trials based on consensus needs in the area (State of Science meeting); results of trials to date change practice!

- External review panel recommended continuation of support

- BMT CTN is research arm of the mandate from HHS for maintaining a program in allogeneic stem cell transplant

- **Collaborative mechanisms put in place between NCTN and BMT CTN**: lays framework for integration of transplant into NCTN-led trials and inclusion of cooperative groups into BMT CTN trials for a true national program of trials using HCT as a curative platform for hematologic malignancies
Request

• Provide NCI funding for a renewal of the network
  – (FY17 – FY23)
  – for 2 RFAs
    • 1 for Data Coordinating Center (Limited Competition)
    • 1 for support of 18 Core Centers to run trials

• NHLBI approved a re-competition (7 years)

• NHLBI asks NCI to contribute approximately 1/3 of program costs (as current) for 7 years
### Budget FY17-23 (millions)

<table>
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<tr>
<th></th>
<th>FY15*</th>
<th>FY17</th>
<th>FY18</th>
<th>FY19</th>
<th>FY20</th>
<th>FY21</th>
<th>FY22</th>
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*FY17 based on FY15 funds from NCI
FY16 funds (11 million) provided by NHLBI (no NCI funds)
Budget Breakdown
(millions)

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<tr>
<th></th>
<th>FY17</th>
<th>Total</th>
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<tbody>
<tr>
<td>Data Coordinating Center (DCC)*</td>
<td>4.4</td>
<td>47.8</td>
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<tr>
<td>Core Sites (18)</td>
<td>3.5</td>
<td>24.5</td>
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<tr>
<td>Total</td>
<td>7.9</td>
<td>72.3</td>
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</tbody>
</table>

*includes protocol-specific costs such as patient reimbursements, etc.; 4.4 million includes expected carryover to complete ongoing trials

NCI will contribute approximately 37% of costs of EACH component (DCC and Core sites)

To fund new clinical studies to optimize transplant and prevent and treat associated toxicities (GVHD), as well as implement cell therapies for treating patients with hematologic malignancies

National Cancer Institute
EXTRA SLIDES
BMT CTN Trials Developed in Years 1-10

Total Subjects = 1,050 1,600 2,150 2,600 3,050 3,460 4,450 5,250 6,000 7,400 8,600


BMT CTN and National Cancer Institute

- Enrollment/follow-up complete
- Enrollment complete; ongoing F/U

BMT CTN Steering Committee

ECOG  CALBG  SWOG  COG

CIBMTR  EMMES  NMDP  DCC

BMT CTN Trials Developed in Years 1-10

Primary Outcome
Safety, Secondary Outcome, or Design

0101 PIII Voris vs. Fluconazole
0102 PIII Myeloma Tandem HCT
0201 PIII Unrelated PBSC vs. Marrow
0301 PII Unrelated Tx for aplastic anemia
0302 PII AGVHD therapy
0303 PII T-depleted HCT for AML
0401 PIII BEAM vs BEAM-Bexxar for Lymphoma
0402 PIII GVHD prophylaxis
0501 III Single vs. Double CBT
0502 PII NST for AML >60y
0601 PII Sickle CellNST
0603 PII Haplo-Adult
0701 PII NST for NHL
0702 PIII Myeloma follow-on CLL
0703 PII HD
0704 PII MM maintenance
0801 P III CGVHD Treatment
0802 PII AGVHD Treatment
0803 HIV+ Lymphoma
0804 High Risk CLL
0805 Ph+ ALL
0901 Full vs. RIC - MDS/AML
0902 Stress Mgmt
0904 High Risk CLL
0905 Ph+ ALL
0906 HIV+ Lymphoma
0907 PIII Myeloma follow-on CLL
0908 P III CGVHD Treatment
0909 PII AGVHD Treatment
0910 PII Sickle CellNST

BMT CTN and National Cancer Institute
BMT CTN Trials Testing Therapies and Concepts Developed in P01s/R01s

**P01s:**
- CA 018029 (Appelbaum): 0201 (Peripheral Blood vs Bone marrow)
  0502/0901 (Reduced Intensity Conditioning for AlloBMT)
- CA 078902 (Storb): 0502/0901 (Reduced Intensity Conditioning for AlloBMT)
  0102/1302 (AlloBMT for Multiple Myeloma)
- CA 044991 (Press): 0401 (Radiotargeted Mab for Lymphoma AutoBMT)
- CA 023766 (O’Reilly): 0303/1301 (T cell depletion for GVHD Prevention)
- CA 015396 (Jones): 0603/1101 (Haploidentical donors for BMT)
  1203/1301 (Posttransplant Cy for GVHD Prevention)
- CA 065493 (Wagner): 0501/0604/1101 (Umbilical Cord Blood for BMT)
- CA 039542 (Ferrara): 0301 (Etanercept for Treatment of Acute GVHD)
  1202 (Biomarkers for GVHD Risk)
- CA 078378 (Anderson): 1401 (Dendritic Cell Fusion Vaccine for Myeloma)
- CL100104/BMTCTN 0704 (Lenalidomide Maintenance)
- CA 111412 (Miller): 1601 (*under development*) (NK cells plus IL-15 for AML)
- HL 070149 (Antin): 0402 (Sirolimus for GVHD prevention)

**R01s:**
- CA 098906 (Martin): 0301/0802 (MMF for treatment of acute GVHD)
- CA 070875 (Jacobsen): 0902 (Stress management to improve QOL)
Ancillary Studies
58 studies in progress or completed
Associated with variety of protocols

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Protocols</th>
<th># of Pubs</th>
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<tbody>
<tr>
<td>Pharmacogenetics</td>
<td>0101, 0302, 0901</td>
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<tr>
<td>Graft characteristics</td>
<td>0201, 0303</td>
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<tr>
<td>Immune reconstitution/function</td>
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<tr>
<td>Biomarkers for GVHD</td>
<td>0302, 0802</td>
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<td>Assays for infection</td>
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<td>Minimal residual disease</td>
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<td>Quality of life</td>
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<tr>
<td>Cost-effectiveness</td>
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Supported in part by 1 R21, 3 R01s, 1 P01, Director’s Office supplement

All specimens deposited in BIOLINCC for use by wider scientific community
Organization of the BMT CTN

NHLBI & NCI

Protocol Review Committee

Data and Safety Monitoring Board

NCI Coop Group BMT Reps (ex officio)

STEERING COMMITTEE

Administrative Committees

Technical Committees

Protocol Teams

Data and Coordinating Center CIBMTR/NMDP/EMMES

20 Clinical Cores; High-performing Affiliate Centers

Affiliate Clinical Centers
Program Management for the BMT CTN

- NCI and NHLBI program staff sit on BMT CTN Steering Committee with 1 vote each for concept approvals
- NCI and NHLBI program staff sit on Executive Committee for input on issues that come before committee
- NCI and NHBLI staff sit on concept and protocol development teams
- NCI PO serves as liaison between BMT CTN & NCI CTEP for coordination and integration of efforts for treatment of hematologic malignancies with HSCT, working with CTEP medical officer in Hematology/Oncology
- RFA: NCI PO provides language consistent with NCI interests for new funding period
Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma

Philip L. McCarthy, M.D., Kouros Owzar, Ph.D., Craig C. Hofmeister, M.D.,
David D. Hurd, M.D., Hani Hassoun, M.D., Paul G. Richardson, M.D.,
Sergio Giralt, M.D., Edward A. Stadtmauer, M.D., Daniel J. Weisdorf, M.D.

BMT CTN #0704 / CALGB 100104

Monthly Actual Accrual
Cumulative Accrual

Monthly Accrual
Cumulative Accrual

Nov-05 Feb-06 May-06 Aug-06 Nov-06 Feb-07 May-07 Aug-07 Nov-07 Feb-08 May-08 Aug-08 Nov-08 Feb-09
Study Activation Timelines in BMT CTN: Increasing Efficiency

- Protocol Team Formation to Study Activation
- PRC Submission to PRC Approval
- PRC Approval to DSMB Submission
- PRC Submission to DSMB Approval
- DSMB Approval to Protocol Release to Centers
- Protocol Release to Centers to Study Activation
- Protocol Team Formation to PRC Submission
- Evaluable Data to Manuscript Submission

Months

National Cancer Institute
Annual Number of Transplant Recipients in the US by Transplant Type

*2014 Data incomplete
Indications for Hematopoietic Stem Cell Transplants in the US, 2013

- Allogeneic (Total N=8,197)
- Autologous (Total N=11,258)

Number of Transplants

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<tr>
<th>Indication</th>
<th>Allogeneic</th>
<th>Autologous</th>
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<tbody>
<tr>
<td>Myeloma / PCD</td>
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<td></td>
</tr>
<tr>
<td>AML</td>
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<td>3000</td>
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<tr>
<td>HD</td>
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<td>1000</td>
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<td>Aplastic Anemia</td>
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<td>Other Non-Malign Dis</td>
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<tr>
<td>Other Cancer</td>
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<td>10</td>
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National Cancer Institute
Survival after Transplants for Multiple Myeloma, 2003-2013

- Autologous (n=37,385)
- Allogeneic (n=1,012)

p<0.001

By Donor Type

National Cancer Institute
Survival after Unrelated Donor Transplants for AML, 2003-2013

- Early (n=8,804)
- Intermediate (n=4,443)
- Advanced (n=4,692)

By Disease Status

p<0.001