National Cancer Institute

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

Presentation to BSA
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William D. Merritt, Ph.D.
Program Director
CGCB/Clinical Trials Evaluation Program
DCTD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

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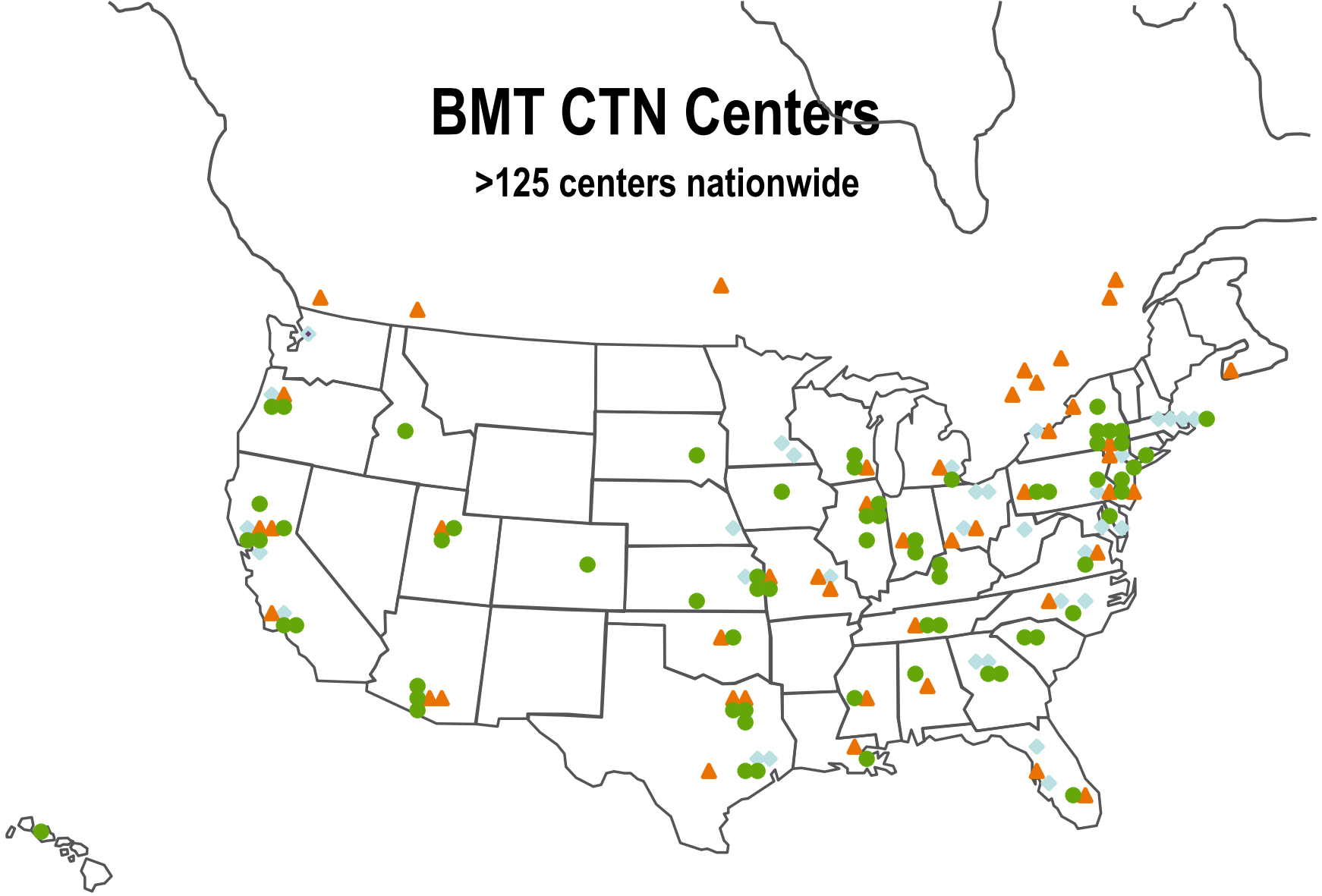
Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

- 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

BMT CTN Centers

>125 centers nationwide



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

	Completed	Open	Pending	Total
Multiple Myeloma	3 (*1)	3**	1	**7**
AML/MDS	3 (*1)	1	2	**6**
ALL	1*	-	-	**1**
CLL	1*	-	-	**1**
Lymphoma	4 (*1)	-	1*	**5**
GvHD (includes biomarker trial)	4	3	2	9
Donor Stem Cell Source	4	1	-	5
Hem Malignancy in HIV+ Patients	2	-	-	**2**
Q/L; Recruitment; Inf consent	1	2	-	3
Infectious Diseases	1	-	-	1
Regimen-related toxicity	1	-	-	1
ALL Hem Malignancy	**25**	**10**	**6**	**41**
Non-Hem Malignancy	3	0	3	**6**
	*includes BMT CTN accrual to Coop Group-led trial	**includes BMT CTN accrual to DFCI trial	#NCI-funded	

nstitute

BMT CTN Trials Developed in Years 11-16

BMT CTN
CIBMTR EMMES NMDP
DCC

- 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)

1503
1501
+ 1201
1401
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

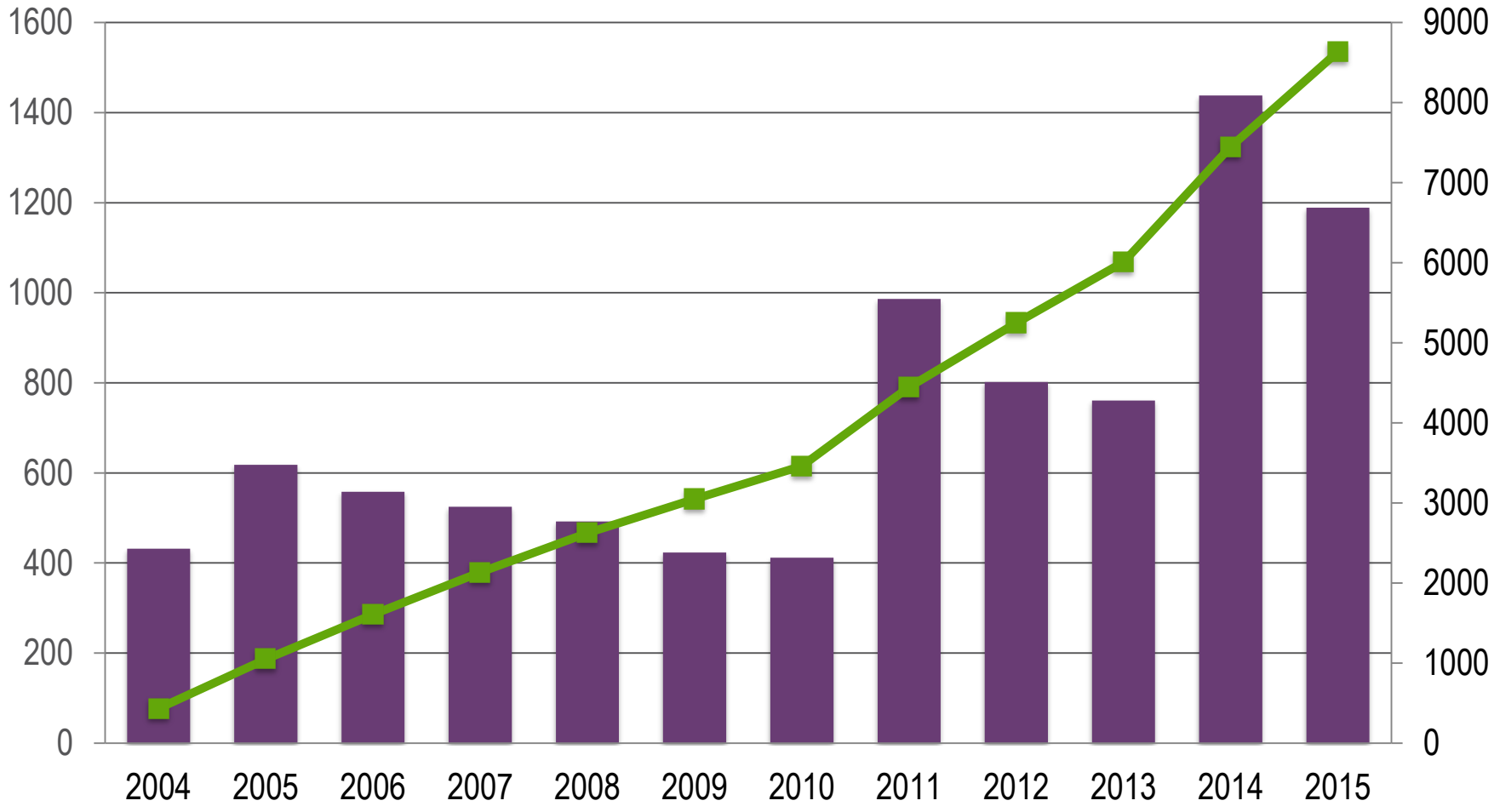
== Enrollment complete; ongoing F/U
= Enrollment on-going

ECOG Alliance BMT CTN SWOG COG

BMT CTN and National Cancer Institute

PUBLICATIONS
★ Primary Outcome
★ Safety, Secondary Outcome, or Design

Yearly and Cumulative Accrual to all Protocols 2004-2015

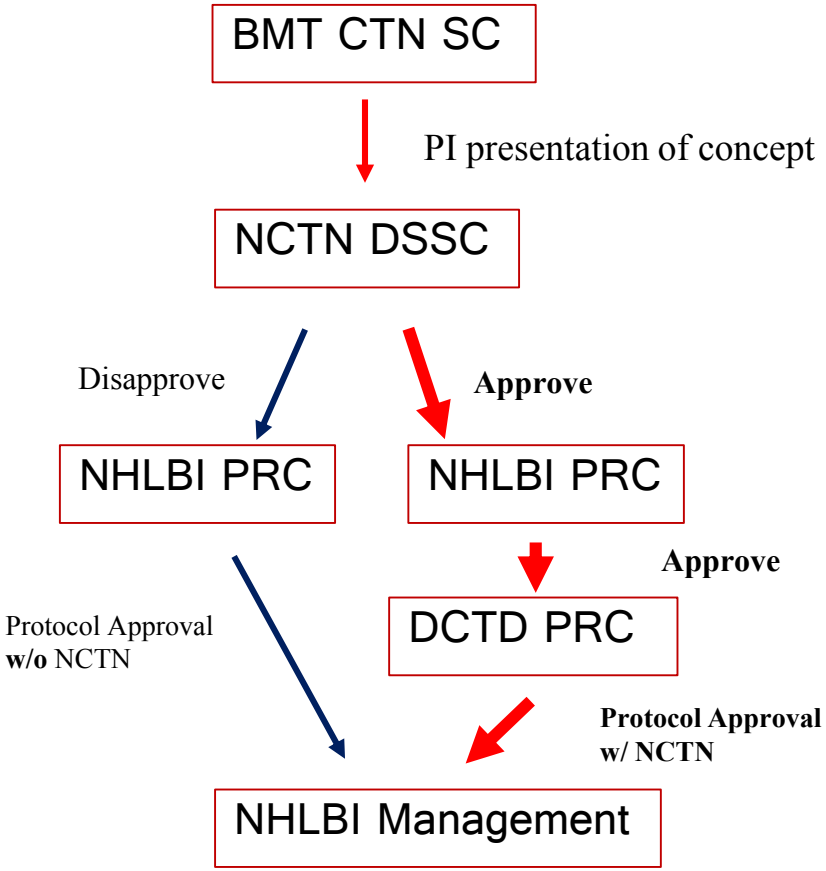


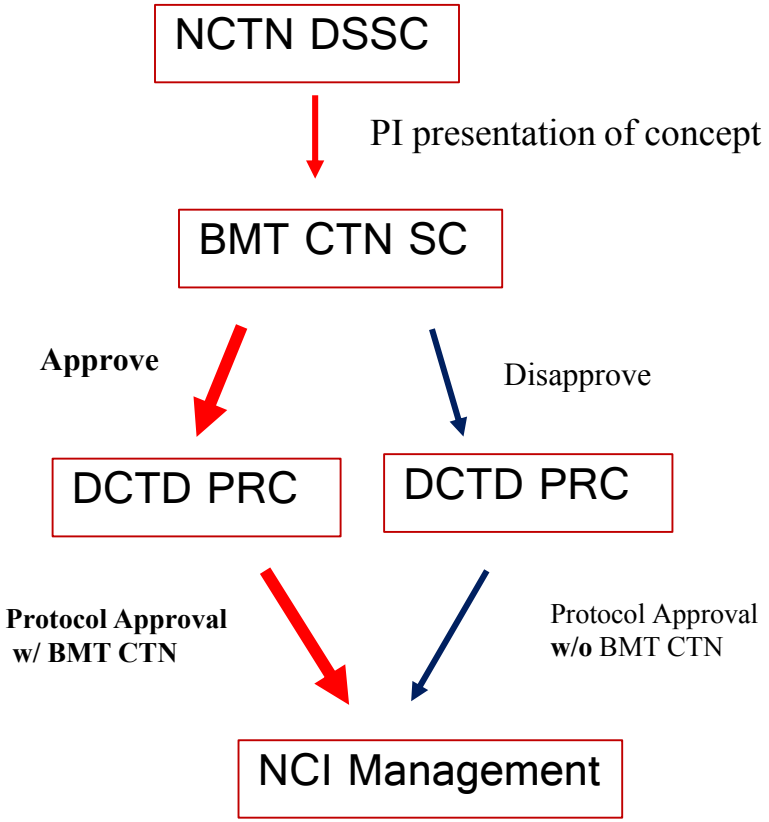
Cooperative Group/NCTN - BMT CTN COLLABORATIONS

Trial	Name	Group(s)
0102	PhIII Multiple Myeloma HCT	SWOG
0202	PhIII Follicular Lymphoma HCT	SWOG
0401	PhIII BEAM vs. BEAM/BEXXAR Lymphoma	SWOG
0501	PhIII Single vs. Double Cord Blood	COG
0502	**PhII Non-myeloblative HCT for AML >60yrs**	**SWOG***
0701	PhII Non-myeloblative HCT for NHL	CALGB & SWOG
0702	PhIII Multiple Myeloma HCT +/- new agents	CALGB, SWOG, ECOG
0703	**PhII Tandem autologous for Hodgkins**	**SWOG**
0704	**PhIII Lenalidomide Maintenance for MM**	**CALGB**
0805	**PhII Targeted therapies +/- HCT for Ph^+ ALL**	**CALGB, SWOG, ECOG**
0804	**PhII HCT for High Risk CLL**	**CALGB**
1201	**PhIII Ibrutinib during and following HCT for DLBCL**	**NCTN**

***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. Myeloblative 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)

	FY15*	FY17	FY18	FY19	FY20	FY21	FY22	FY23	Total
NCI	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	27.3
NHLBI	6.3	4.0	5.0	7.0	7.0	7.0	7.0	8.0	45.0
Total	10.2	7.9	8.9	10.9	10.9	10.9	10.9	11.9	72.3

*FY17 based on FY15 funds from NCI
FY16 funds (11 million) provided by NHLBI (no NCI funds)

Budget Breakdown
(millions)

	FY17	Total
Data Coordinating Center (DCC)*	4.4	47.8
Core Sites (18)	3.5	24.5
Total	7.9	72.3

*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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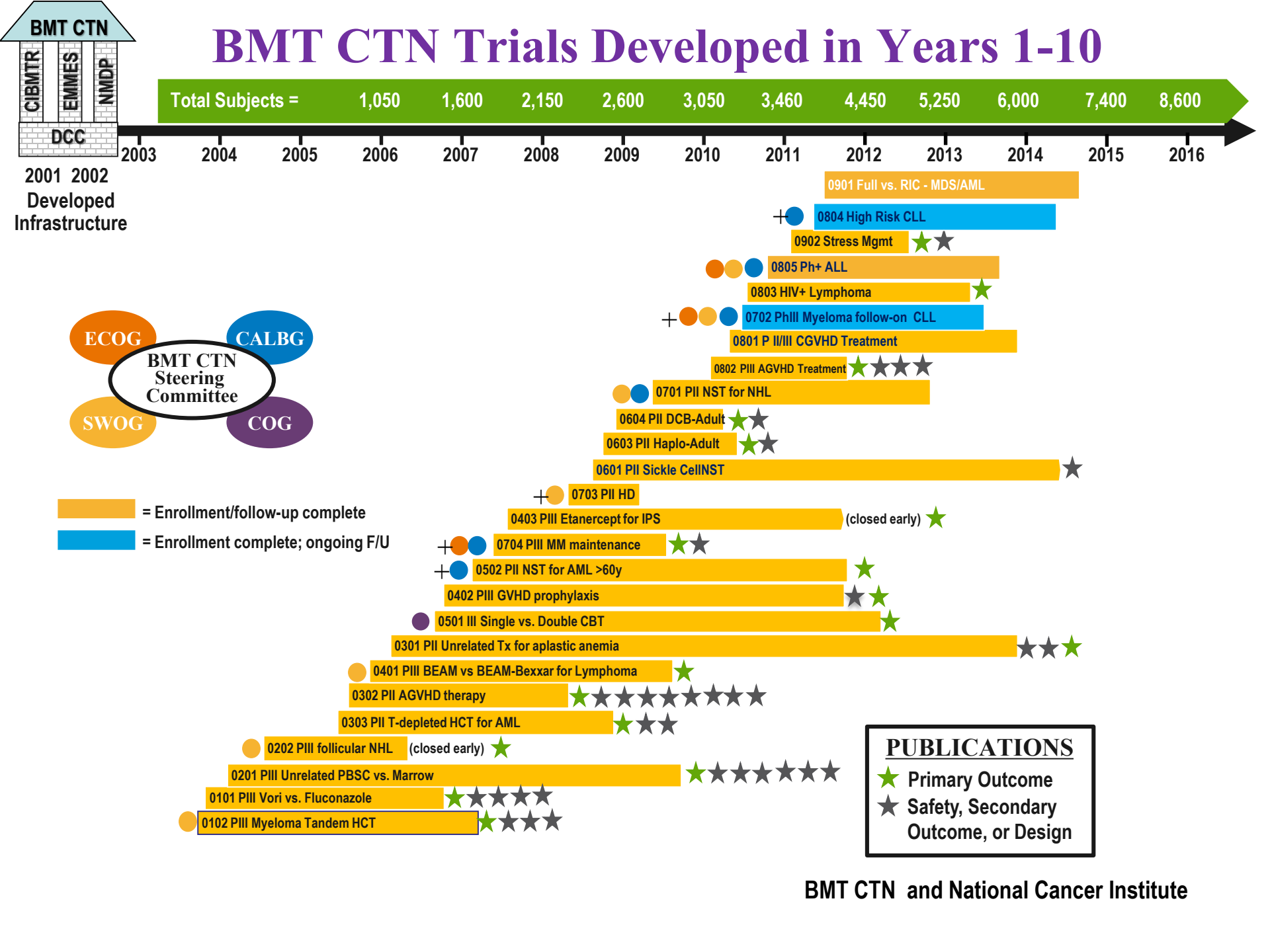
EXTRA SLIDES


BMT CTN
CIBMTR
EMMES
NMDP
DCC
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
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2001 2002
Developed
Infrastructure
ECOG
CALBG
BMT CTN
Steering
Committee
SWOG
COG
= Enrollment/follow-up complete
= Enrollment complete; ongoing F/U
0901 Full vs. RIC - MDS/AML
0804 High Risk CLL
0902 Stress Mgmt
0805 Ph+ ALL
0803 HIV+ Lymphoma
0702 PhIII Myeloma follow-on CLL
0801 P II/III CGVHD Treatment
0802 PIII AGVHD Treatment
0701 PII NST for NHL
0604 PII DCB-Adult
0603 PII Haplo-Adult
0601 PII Sickle CellNST
0703 PII HD
0403 PIII Etanercept for IPS
(closed early)
0704 PIII MM maintenance
0502 PII NST for AML >60y
0402 PIII GVHD prophylaxis
0501 III Single vs. Double CBT
0301 PII Unrelated Tx for aplastic anemia
0401 PIII BEAM vs BEAM-Bexxar for Lymphoma
0302 PII AGVHD therapy
0303 PII T-depleted HCT for AML
0202 PIII follicular NHL
(closed early)
0201 PIII Unrelated PBSC vs. Marrow
0101 PIII Vori vs. Fluconazole
0102 PIII Myeloma Tandem HCT
PUBLICATIONS
Primary Outcome
Safety, Secondary Outcome, or Design
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)

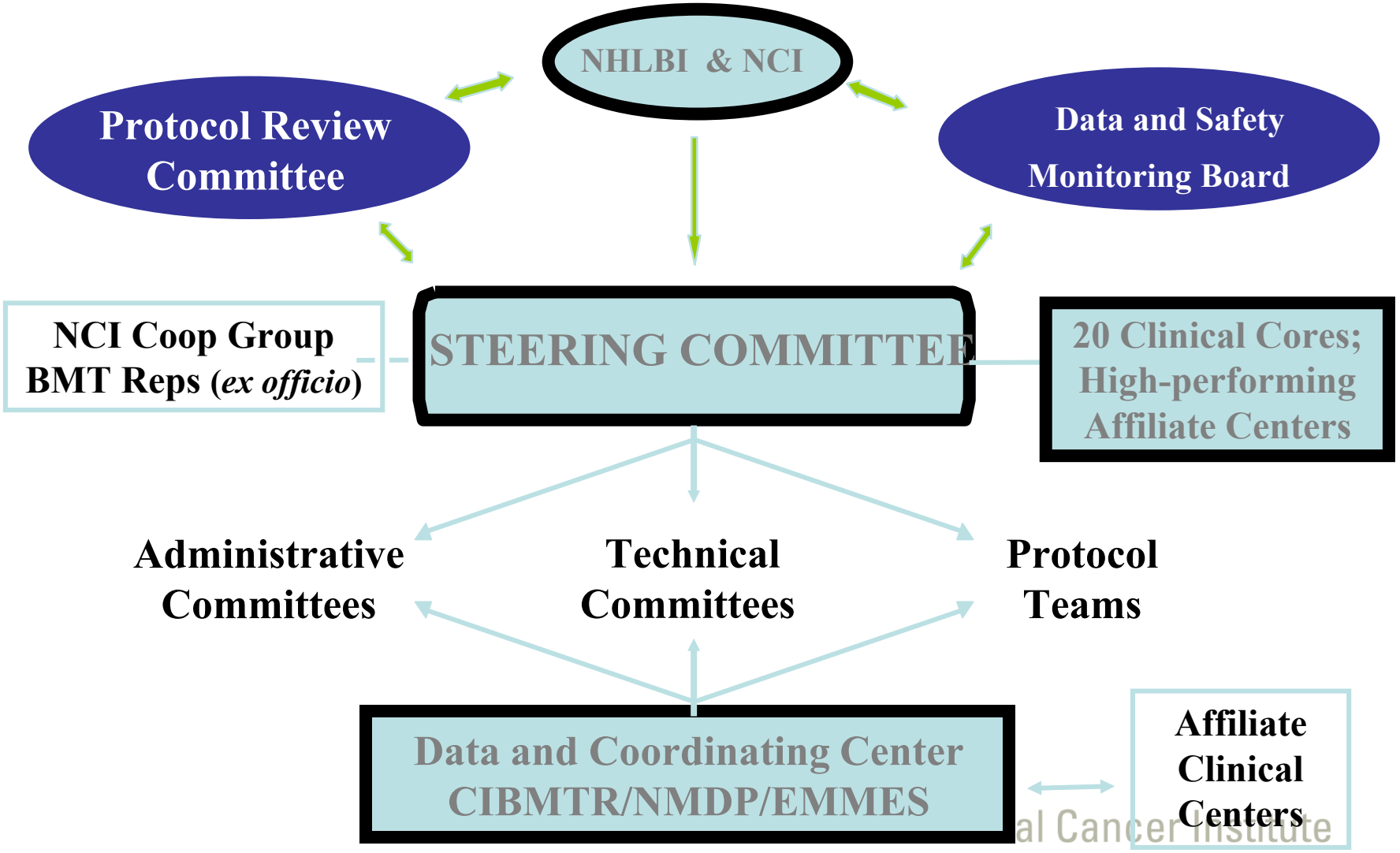
Ancillary Studies

58 studies in progress or completed

Associated with variety of protocols

Type of study	Protocols	# of Pubs
Pharmacogenetics	0101, 0302, 0901	1
Graft characteristics	0201,0303	2
Immune reconstitution/ function	0201, 0302, 0303, 0402, 0501, 0801, 0803, 0903,	2
Biomarkers for GVHD	0302, 0802	3
Assays for infection	0101, 0803, 0903	1
Minimal residual disease	0102, 0702, 0803	
Quality of life	0201, 0501, 0601, 0702, 0901, 0902, 1101, 1102, 1205,1301, 1302	2
Cost-effectiveness	0101, 1101, 1102	2
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



Program Management for the BMT CTN

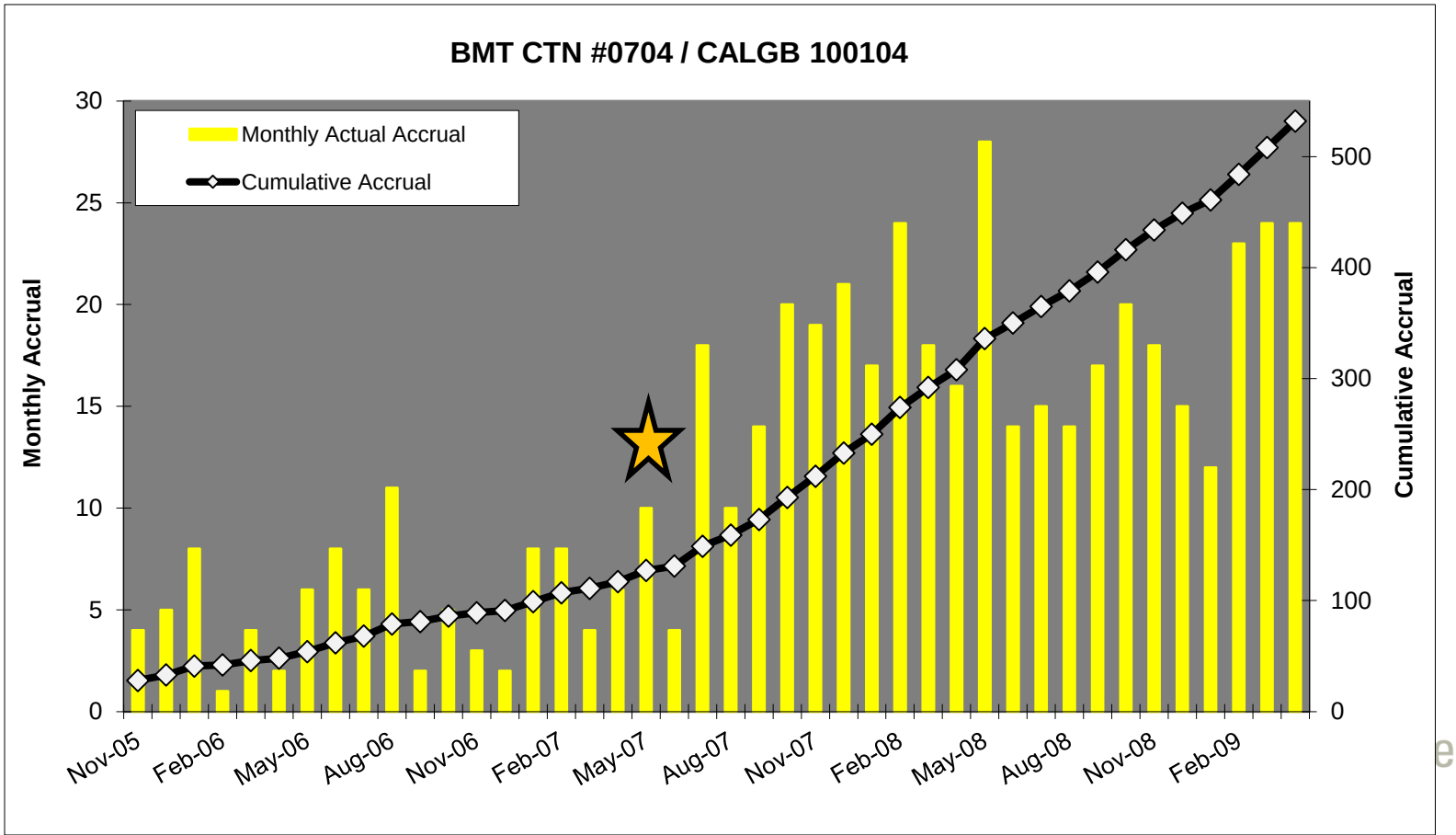
- NCI and NHLBI program staff sit on BMT CTN Steering Committee with 1 vote each for concept approvals
- NCI and NHLBI program staff sit on Executive Committee for input on issues that come before committee
- NCI and NHBLI staff sit on concept and protocol development teams
- NCI PO serves as liaison 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

The NEW ENGLAND JOURNAL of MEDICINE

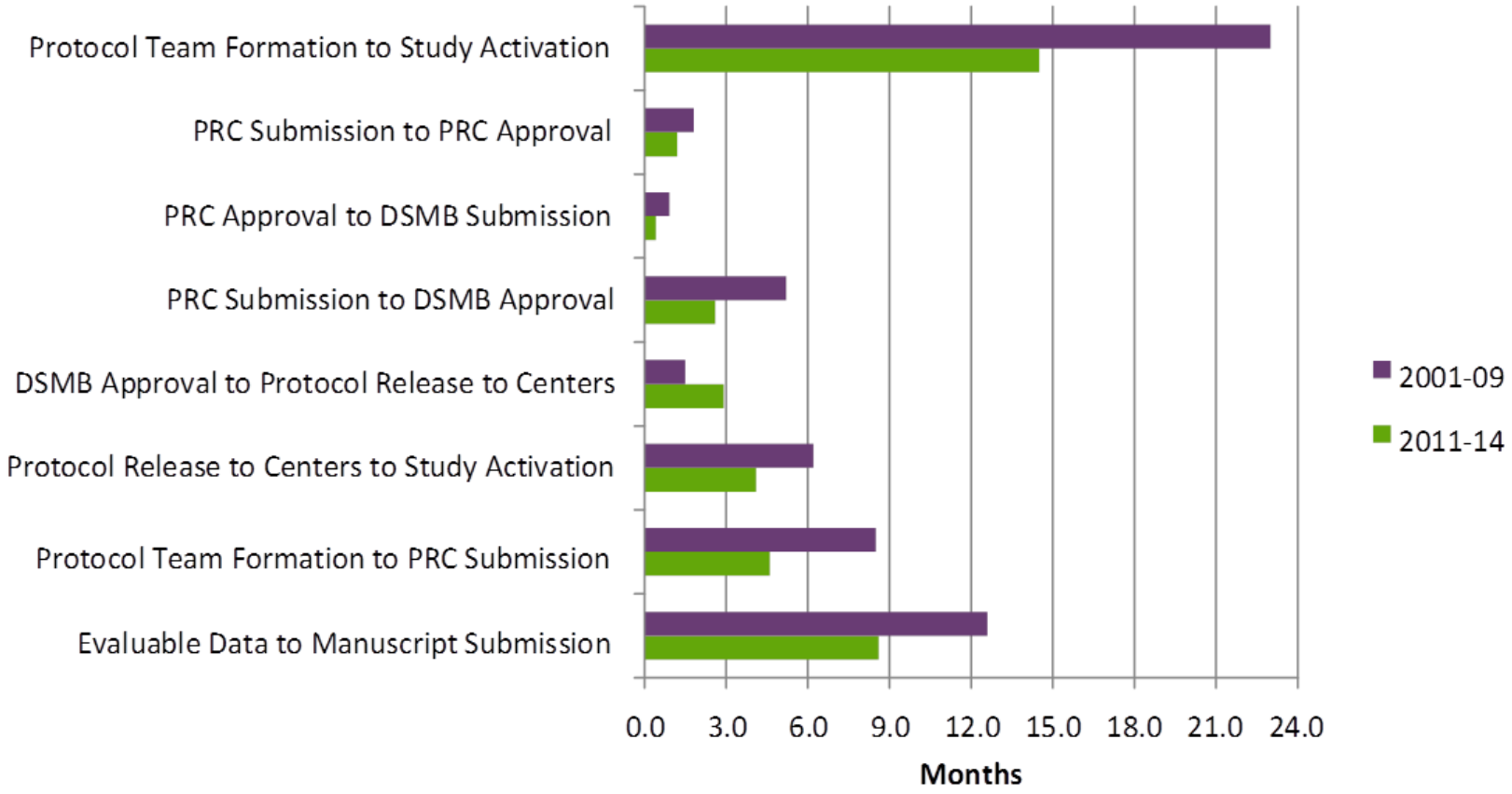
ORIGINAL ARTICLE

Lenalidomide after Stem-Cell Transplantation for Multiple Myeloma

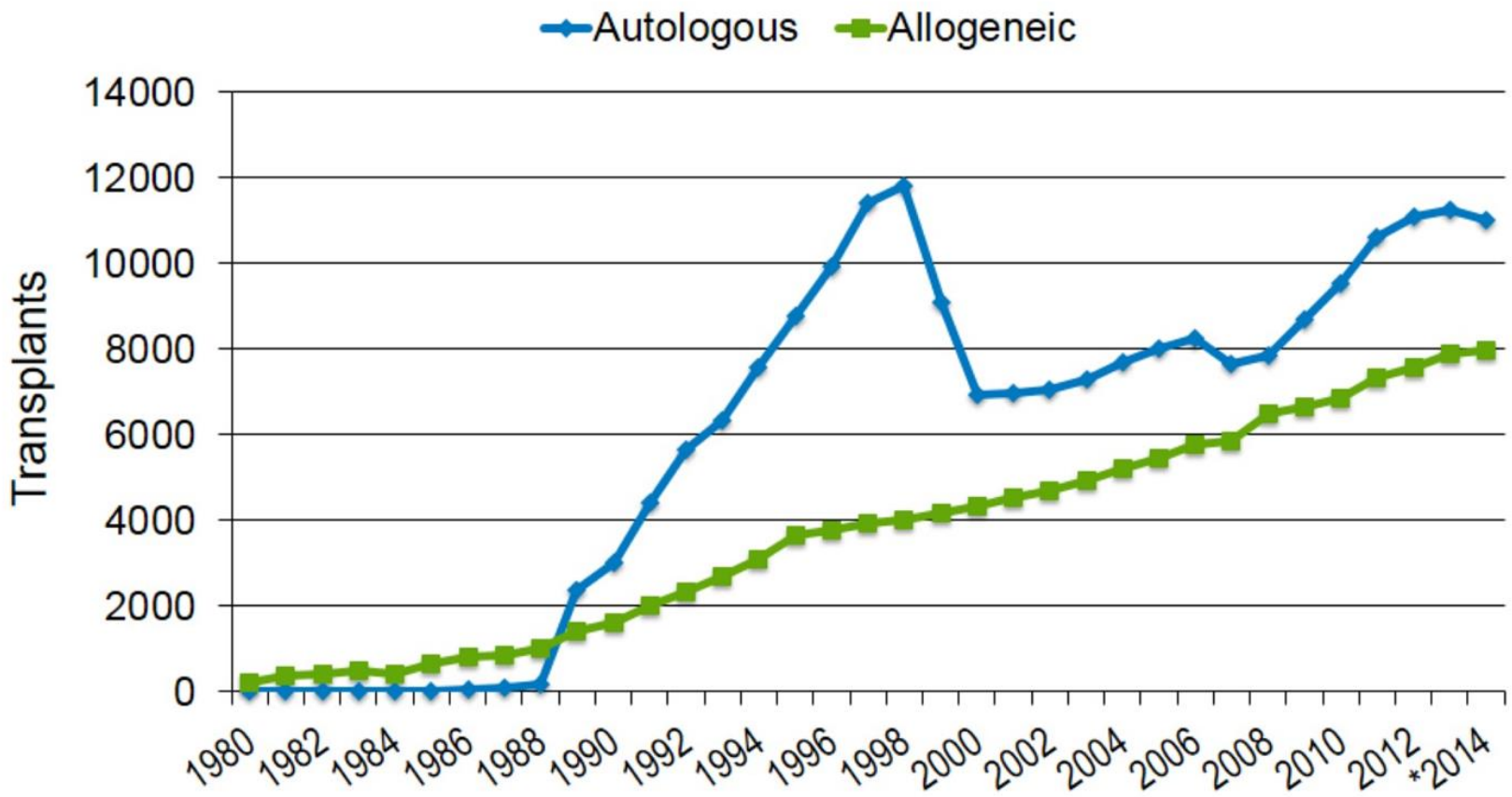
Philip L. McCarthy, M.D., Kouros Owzar, Ph.D., Craig C. Hofmeister, M.D., David D. Hurd, M.D., Hani Hassoun, M.D., Paul G. Richardson, M.D., Sergio Giralt, M.D., Edward A. Stadtmauer, M.D., Daniel J. Weisdorf, M.D.,



Study Activation Timelines in BMT CTN: Increasing Efficiency



Annual Number of Transplant Recipients in the US by Transplant Type



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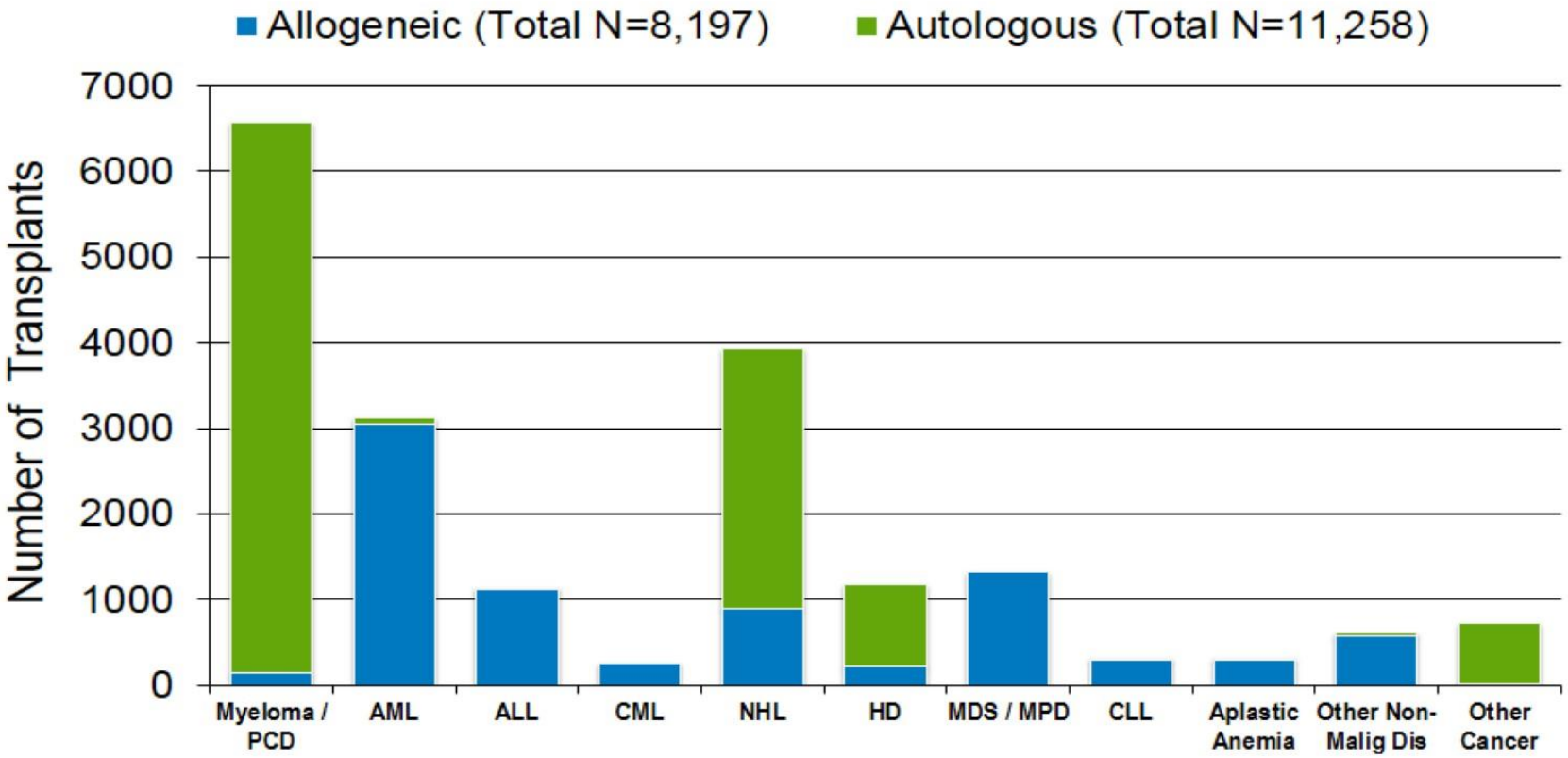
*2014 Data incomplete

Indications for Hematopoietic Stem Cell Transplants in the US, 2013



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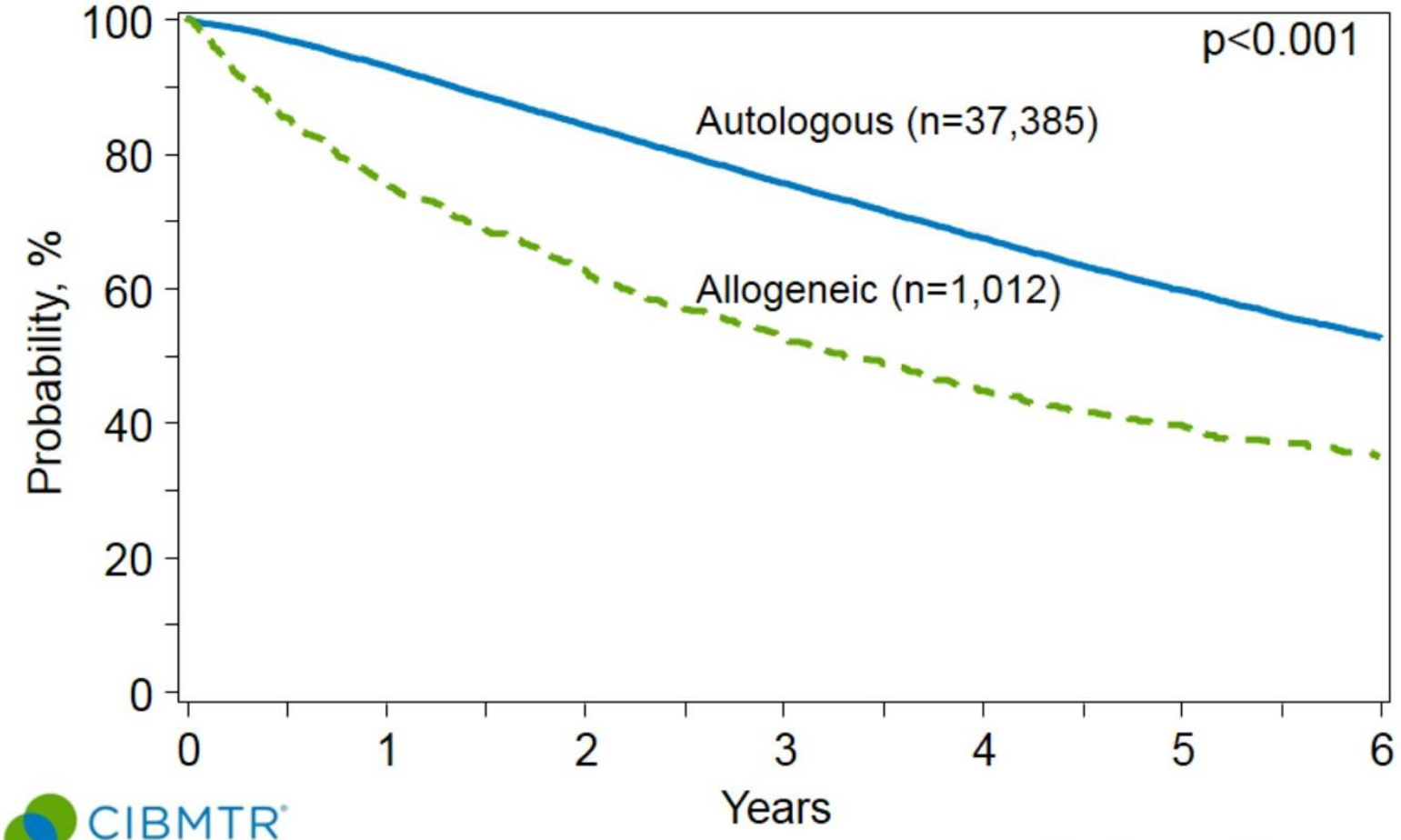
Survival after Transplants for Multiple Myeloma, 2003-2013



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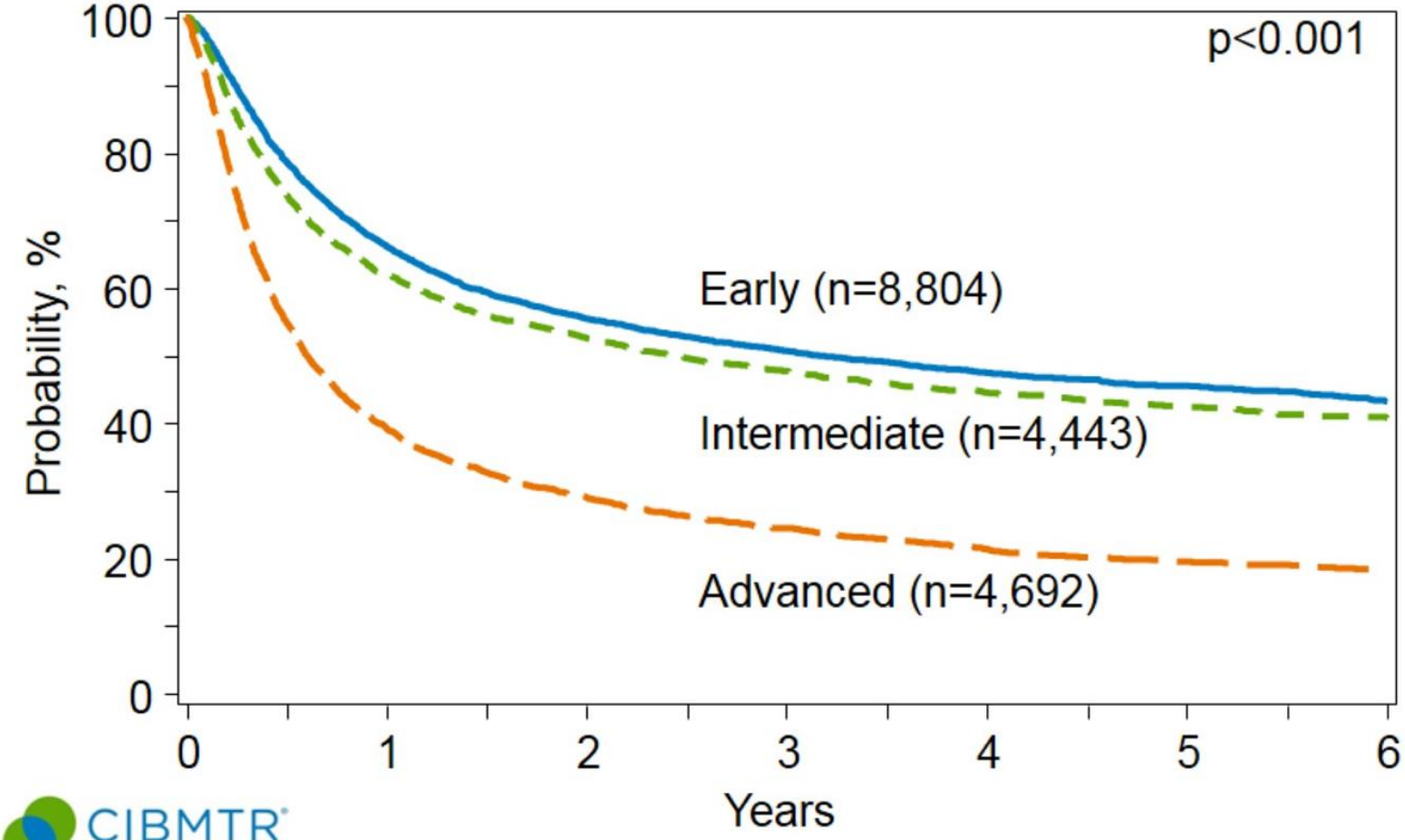
By Donor Type

Survival after Unrelated Donor Transplants for AML, 2003-2013



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By Disease Status