A Report from the Blood and Marrow Transplant Clinical Trials Network State of the Science Symposium 2014

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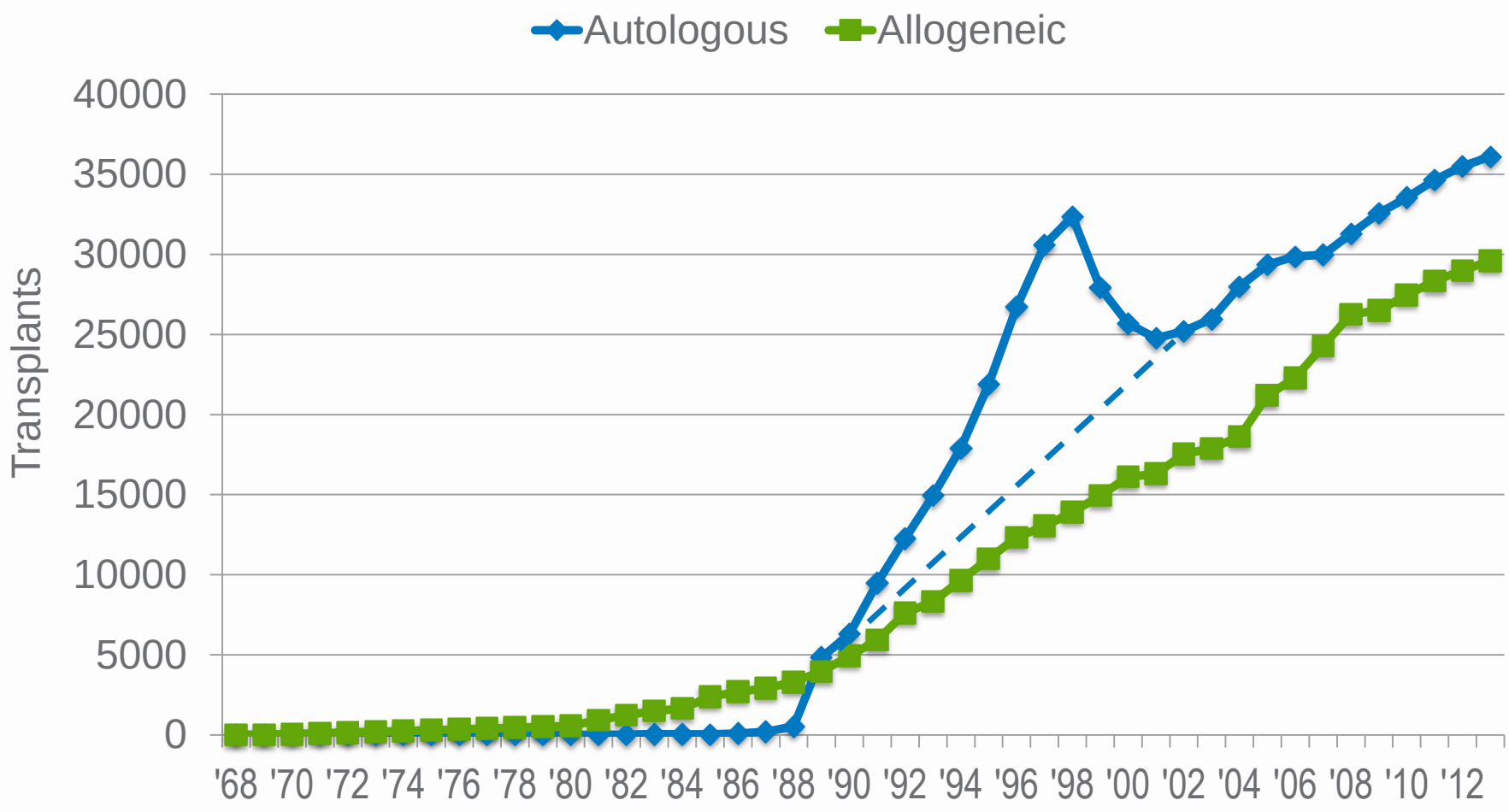
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Speaker Disclosure

No relevant financial disclosures to report

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Transplant Activity Worldwide
1968-2014



WBMT

World Health Organization

BMT Clinical Trials Research in the United States

Before 2001

- Single institution trials
  - Investigator initiated
  - Almost all Phase I and II
  - Developing new strategies and new concepts
    - R01 or P01 funded
    - Very few Pharma funded
- Few Multi Center Trials, few definitive trials

Challenges

- Relatively small, heterogeneous population
- Multiple competing risks after BMT made it an unattractive setting for pharma to test new drugs
- Large Cooperative Groups were focused on cancer chemotherapy and had multiple competing priorities which resulted in few transplant trials

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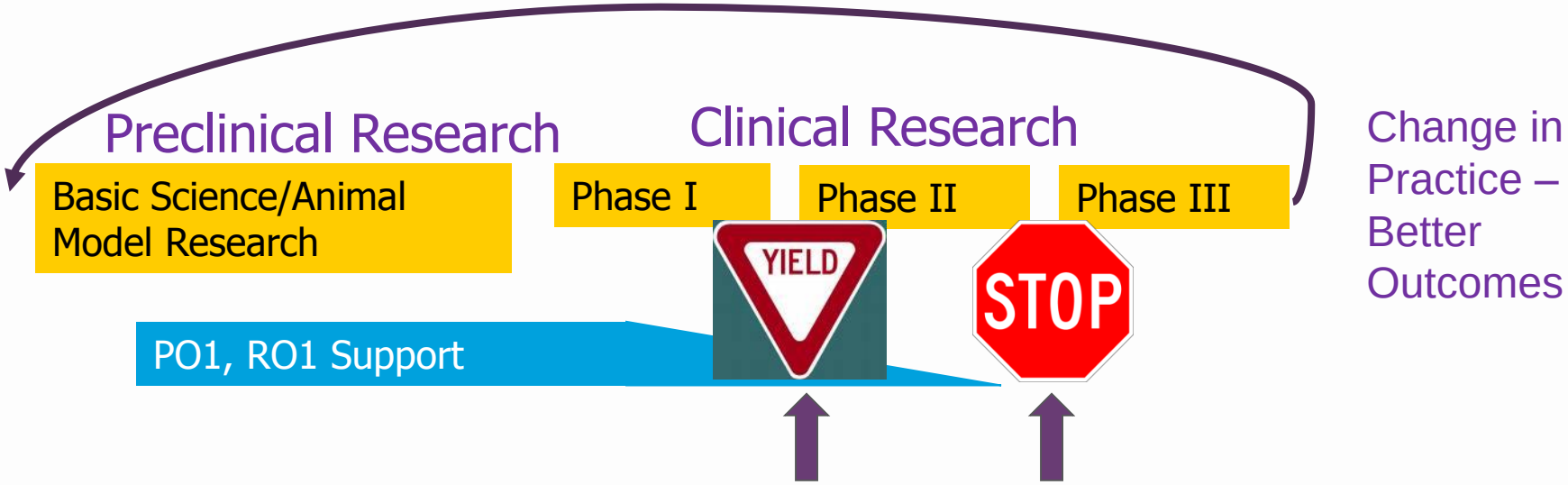
From the Bench to the Bedside



Prior to 2003, few (~200/yr) transplants were done on national trials.

- Primarily (90%) autologous transplants
- Allo studies usually restricted to sibling transplants
- Focused on comparing BMT to non-BMT therapy
  - rarely addressed how to improve transplant outcomes

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Blood and Marrow Transplant Clinical Trials Network

- A national clinical trials network
  - Established Sept 2001
    Re-competed July 2010
  - Funded through 2017
- Goals:
  - Evaluate promising BMT therapies and novel cell products in high quality multicenter studies
  - Improve safety and efficacy of BMT and cellular therapy
  - Enhance understanding of the biology and effectiveness of BMT

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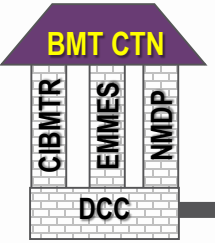
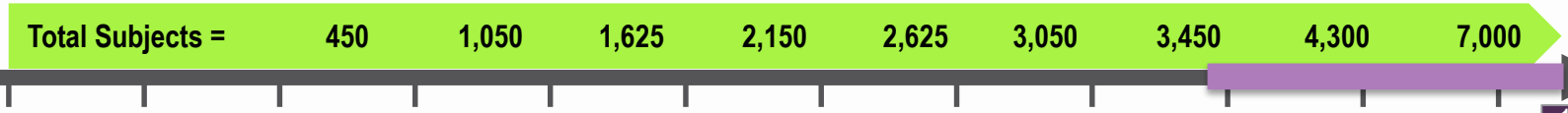
Early and ongoing collaboration with cooperative groups to synergize and avoid duplication



2001 2002
Developed Infrastructure

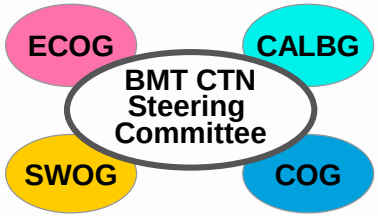


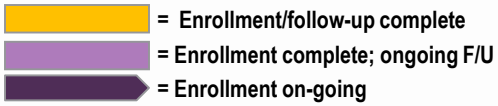
2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014

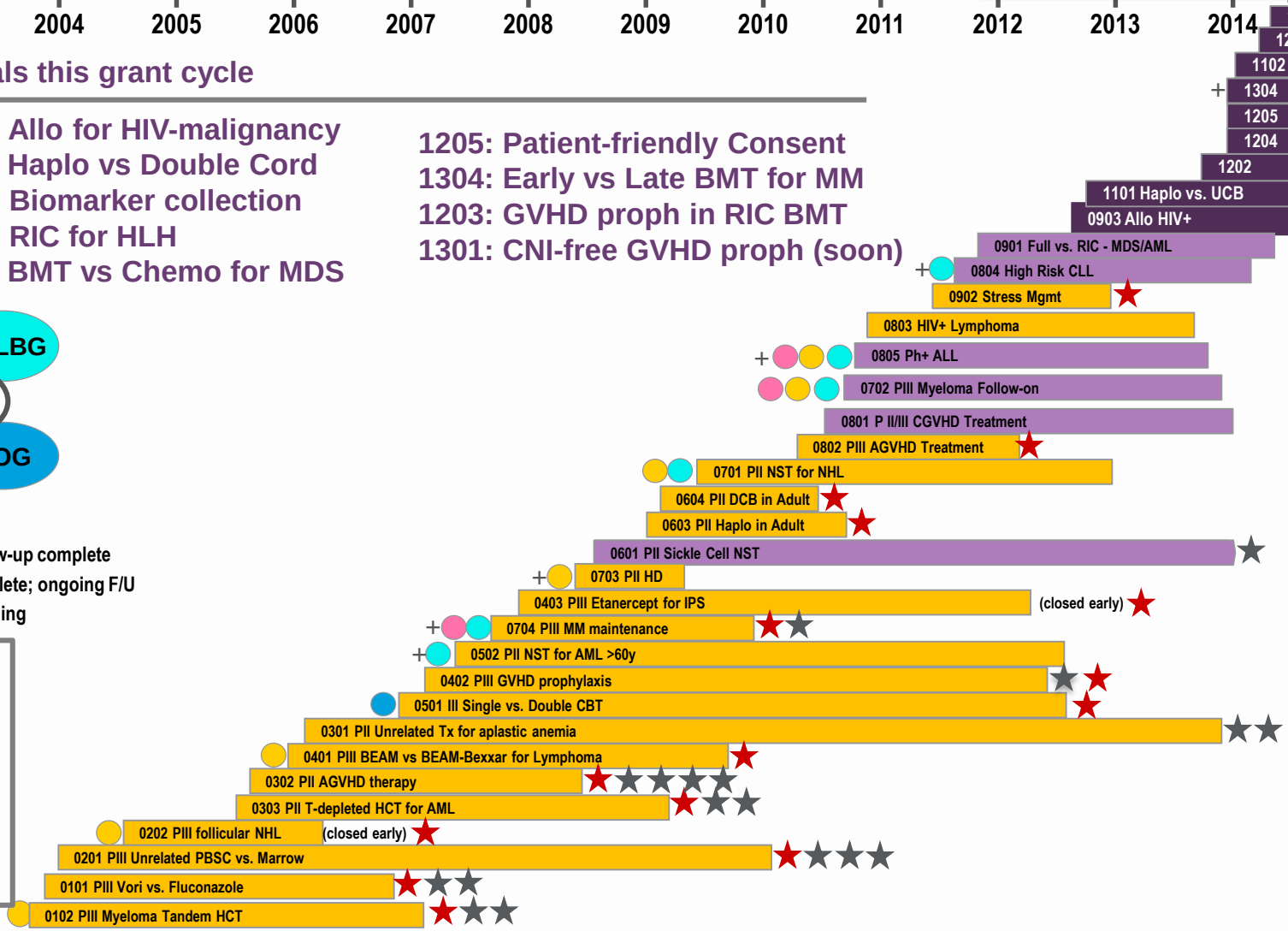
9 trials this grant cycle

0903: Allo for HIV-malignancy
1101: Haplo vs Double Cord
1202: Biomarker collection
1204: RIC for HLH
1102: BMT vs Chemo for MDS

1205: Patient-friendly Consent
1304: Early vs Late BMT for MM
1203: GVHD proph in RIC BMT
1301: CNI-free GVHD proph (soon)







Important Features of BMT CTN That Ensure Its Value to the Scientific Community

- Peer-reviewed scientific agenda
- Peer-reviewed trials
- Community inclusiveness in developing the scientific agenda, planning and implementing trials

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Peer-Reviewed Scientific Agenda

- BMT CTN's Scientific Agenda established by 3 State of the Science Symposia:
  - April 2000
  - June 2007
  - February 2014

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2014 BMT CTN SOSS Planning Committee

Steering Committee

- Fred Appelbaum – Fred Hutchinson Cancer Center
- Ginna Laport – Stanford University
- Jamie Ferrara – Columbia University
- Steve Devine – Ohio State University

National Institutes of Health

- Nancy DiFronzo – NHLBI
- Bill Merritt - NCI
- Liz Wagner – NHLBI
- Roy Wu – NCI

Data and Coordinating Center

- Dennis Confer - NMDP/Be The Match
- Mary Horowitz – Medical College of Wisconsin
- Adam Mendizabal – EMMES Corporation
- Marcelo Pasquini – Medical College of Wisconsin
- Amy Foley - NMDP/Be The Match
- Iris Gersten – EMMES Corporation

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2014 BMT CTN SOSS Committee Chairs

Donor/graft source: **Claudio Anasetti**, H Lee Moffitt Cancer Center

GVHD: **Joe Antin**, Dana-Farber Cancer Institute

Leukemia: **Steve Devine**, The Ohio State University

Non-Malignant Disease: **Harry Atkins**, University of Ottawa

Myeloma: **Sergio Giralt**, Memorial Sloan Kettering Cancer Center

Gene/Cell Therapy: **Helen Heslop**, Baylor College of Medicine

Lymphoma: **Ginna Laport**, Stanford University

Late Effects/QOL: **Stephanie Lee**, Fred Hutchinson Cancer Research

Pediatrics: **Mike Pulsipher**, University of Utah

Pediatrics late effects: **Stella Davies**, Cincinnati Children's Hospital

Regimen related toxicity: **Ed Stadtmauer**, University of Pennsylvania

Infection/immunity: **John Wingard**, University of Florida

Trial Design: **Brent Logan, Marcelo Pasquini**, Medical College of Wis

Peer-Reviewed Scientific Agenda

- Committee membership
  - Network and non-Network centers representatives
  - BMT and non-BMT experts
  - Two liaisons from the Clinical Trials Committee
  - Each reviewed by two non-Network reviewers
- Each Committee proposed 2-4 concepts identified as
  - Answering IMPORTANT and TIMELY questions
  - Requiring a multi-center Network
  - Consistent with the mission of the Network and its sponsors

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Peer-Reviewed Scientific Agenda

- Public forum to solicit input: February 2014
  - Held prior to the BMT Tandem Meetings
  - Attended by more than 350 people
- Prioritization of concepts by Committee Chairs, Reviewers, NIH representatives
- Manuscript published in Biol Blood Marrow Transplantation. 2014 Feb;20(2):149-53.

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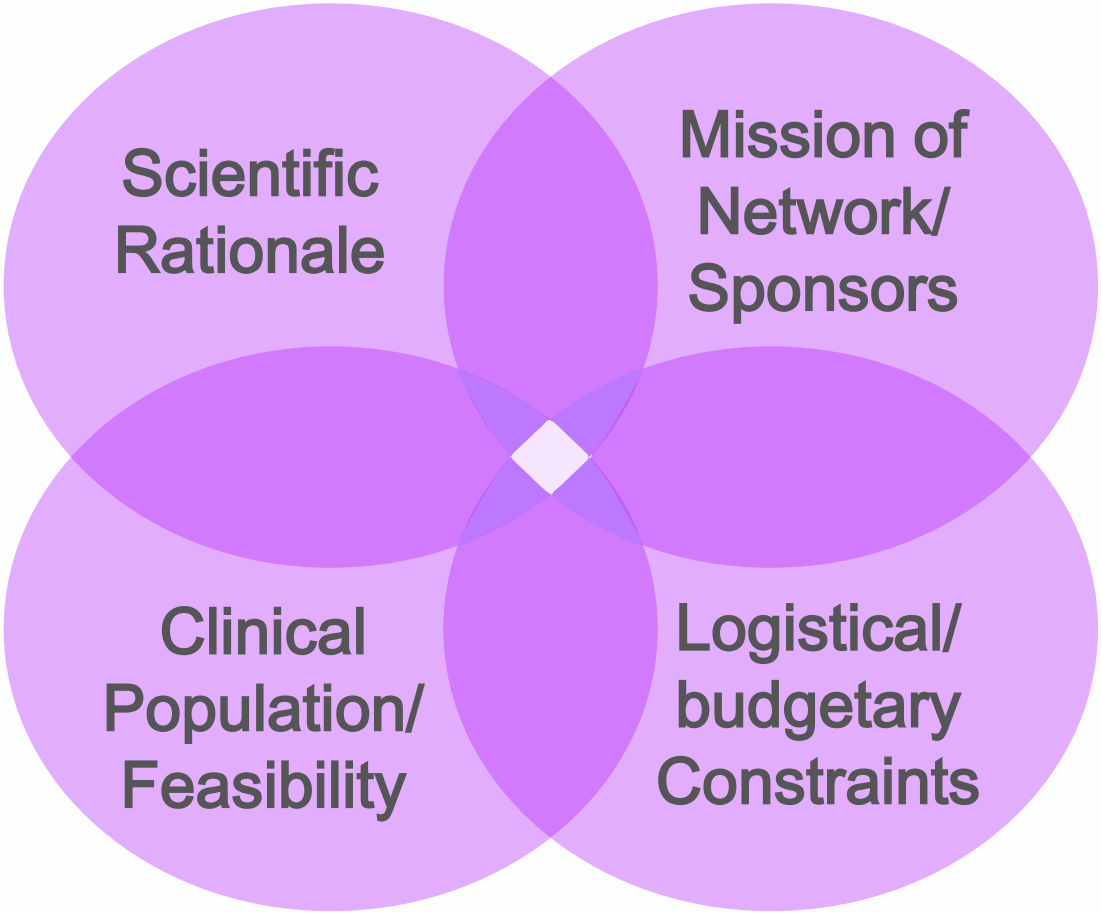
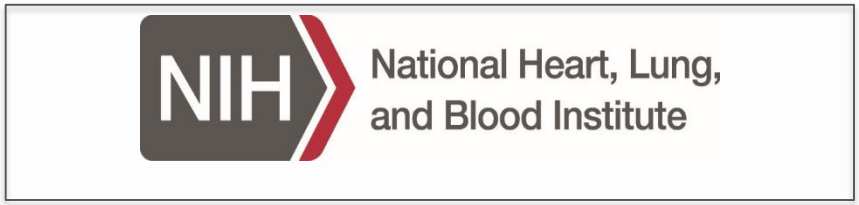
Prioritization Considerations



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

NHLBI & NCI Sponsors: Different, But Complementary, Missions



- **Mission:**

Provide global leadership for research, training, and education programs to promote the prevention and treatment of heart, lung, and blood diseases

- **Mission:**

Conducts and supports research, training, health information dissemination with respect to the cause, diagnosis, prevention, and treatment of cancer

Why Complementary?

- Most of the cancers treated with BMT are blood cancers
- Exciting new developments in cellular and gene therapy have implications for malignant and non-malignant blood diseases
- The disorders treated with BMT, cancer and non-cancer, are uncommon and require many centers and an effective infrastructure for trials to be successful
- The obstacles to successful BMT and cellular therapy of malignant and non-malignant blood disorders are similar:
  - Access to suitable donors
  - Engraftment
  - Graft-versus-host disease
  - Immune deficiency and infection
  - Early and late regimen-related toxicities

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SOSS Prioritized Studies 2014

Optimal stem cell source:
•Haploidentical PBSC following myeloblative conditioning
GVHD:
•Novel agents vs. steroids in low risk patients
•Novel agents plus steroids vs. steroids alone in high risk patients
Cell and gene therapy:
•NK cells for AML
•CMV-specific T cell therapy for infection
Infection:
•Novel parainfluenza entry inhibitor
Co-morbidity and regimen-related toxicity:
•Robust risk assessment tools
Late Effects/Quality of Life:
•Bone loss prevention after alloBMT

Non-malignant Disease:
•AutoHCT for multiple sclerosis
•AlloHCT strategies for aplastic anemia/sickle cell disease
Leukemia:
•Post-transplant maintenance for AML
•CAR-T cell therapy for B-cell ALL
Lymphoma:
•Post-autoHCT maintenance for DLBCL
Myeloma:
•Dendritic-MM fusion vaccine
•Maintenance ixazomib post-alloHCT
Pediatric indications:
•Post-HCT maintenance in B-cell ALL
Pediatric outcomes:
•Steroid dosing schedule for chronic GVHD to minimize late effects

How Did We Do With Previous Recommendations: SOSS, April 2000

1.	PBSC vs BM matched sibling donors	NA
2.	PBSC vs BM matched unrelated donors	0201
3.	Techniques to improve cord blood engraftment	0501
4.	T-cell depletion to prevent GVHD	0303, 1301
5.	Methods to improve autologous stem cell collection	NA
6.	Comparison of related and unrelated HCT with standard chemotherapy for high risk patients	S1203

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How Did We Do With Previous Recommendations: SOSS, June 2007

1.	GVHD: Phase II trial of calcineurin-free Rx for cGVHD	0801
2.	QOL: Phase III study of stress management/execise	0902
3.	MM: Phase III tandem transplant versus consolidation and maintenance	0702
4.	AML: Phase III chemotherapy vs. URD HCT	S1203
5.	AML/MDS: Phase III full intensity vs. reduced intensity	0901
6.	Ph+ALL: Phase III chemotherapy vs. Allo HCT	S0805
7.	CLL: Phase II RIC Allo BMT for high risk CLL	CLB100701/ 0804
8.	Lymphoma: Phase II RIC Allo HCT for T cell lymphoma	NA
9.	HLH: Phase II RIC AlloHCT for children with HLH	1204
10.	Non-malignant disease: Phase II autoHCT for Crohn's	NA
11.	Cell Therapy: Phase II trial of viral-specific CTL for adeno virus	PACT: NCT 00711035

Important Features of BMT CTN That Ensure Its Value to the Scientific Community

- Peer-reviewed scientific agenda
- Peer-reviewed trials
- Community inclusiveness in developing the scientific agenda, planning and implementing trials

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Peer-Reviewed Trials

- Protocols developed by Protocol Teams that include 6-8 experts (not restricted to BMT or to Network centers) + DCC staff, NHLBI and NCI representatives, Network and NHLBI statisticians
- Iterative reviews by Steering Committee, with outside experts invited as needed
  - Review by Biomarker Committee to advise re: ancillary studies
  - Review by Special Populations Committee re: inclusiveness
- Independent two-stage review by NHLBI-appointed Protocol Review Committee and Data Safety Monitoring Board
- **Goal: Best possible trial design to address the issues prioritized by the SOSS**

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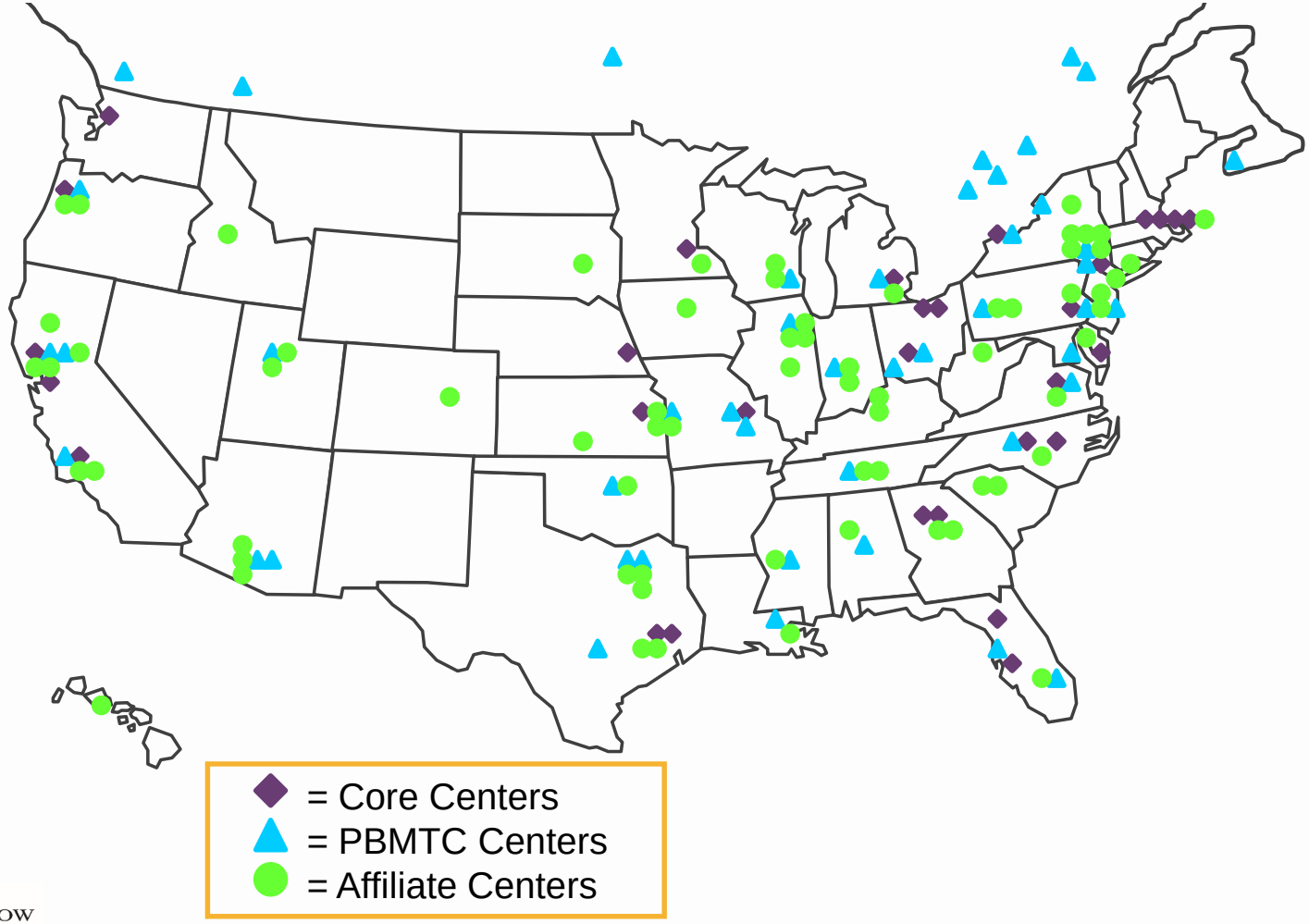
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK established 2001

>115 centers have enrolled ~7,000 patients since 2003



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Collaboration with Other Institutes and Networks

- National Institute of Allergy and Infectious Diseases
- National Institute on Minority Health and Health Disparities
- Office of Rare Diseases Research
- Sickle Cell Disease Clinical Research Network
- AIDS Malignancy Consortium
- NCI Cooperative Groups

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Fostering Junior Investigators

- 27 of 61 (44%) of Protocol Chairs are/were junior investigators (assistant professors or age ≤ 45y)
  - Generally paired with a senior co-chair
  - 2 junior Protocol Chairs early in the Network have recently served as Steering Committee chair
- 16 of 45 (35%) first authors are/were junior investigators; 8 of 14 (57%) primary result paper first authors
- Junior investigators targeted for committee membership, ancillary study leaders

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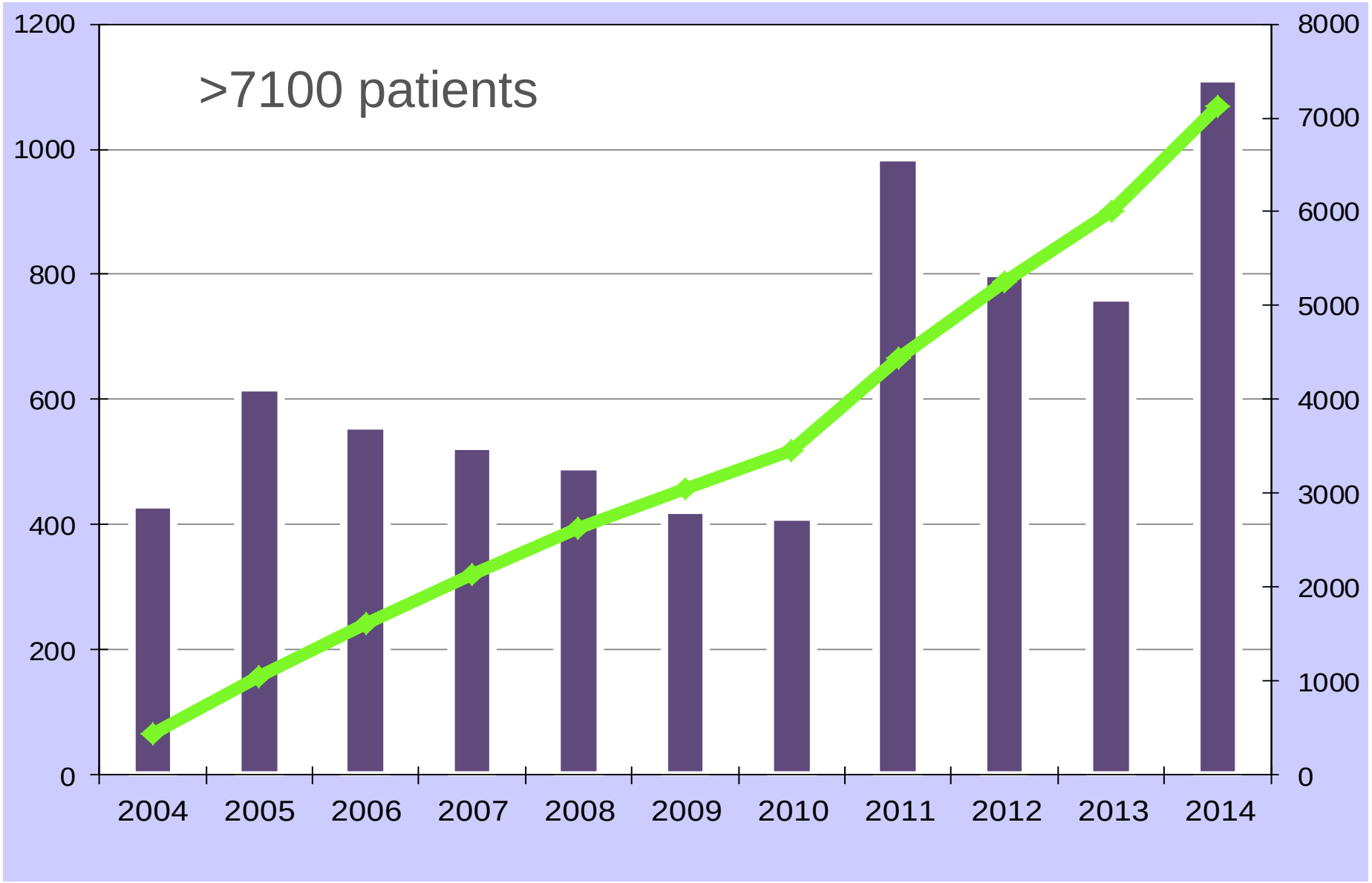
BMT CTN Yearly and Cumulative Accrual to All Protocols, 2004-2014



Transplant Questions Addressed

- Best graft sources
- Best conditioning regimen
- Best prevention and treatment for GVHD
- Best supportive care/quality of life
- Best treatment strategy (type of transplant or +/- transplant)
- New/alternative approaches: cell and gene therapies

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Disease-specific Studies

- Multiple myeloma
- Lymphoma: diffuse large B-cell, follicular
- Acute myelogenous leukemia
- Myelodysplastic Syndrome
- Chronic lymphocytic leukemia
- HIV+ lymphoma
- Aplastic anemia
- Sickle cell anemia
- Hemophagocytic lymphohistiocytosis

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What if There Were No BMT CTN?

- The pace of development and activation of trials would decrease
- The willingness of industry to support multicenter trials would decrease – so even if the NIH supported trials by another mechanism, the amount of money for trials would decrease
- Fewer trials would be done
- Some trials would *never* be done

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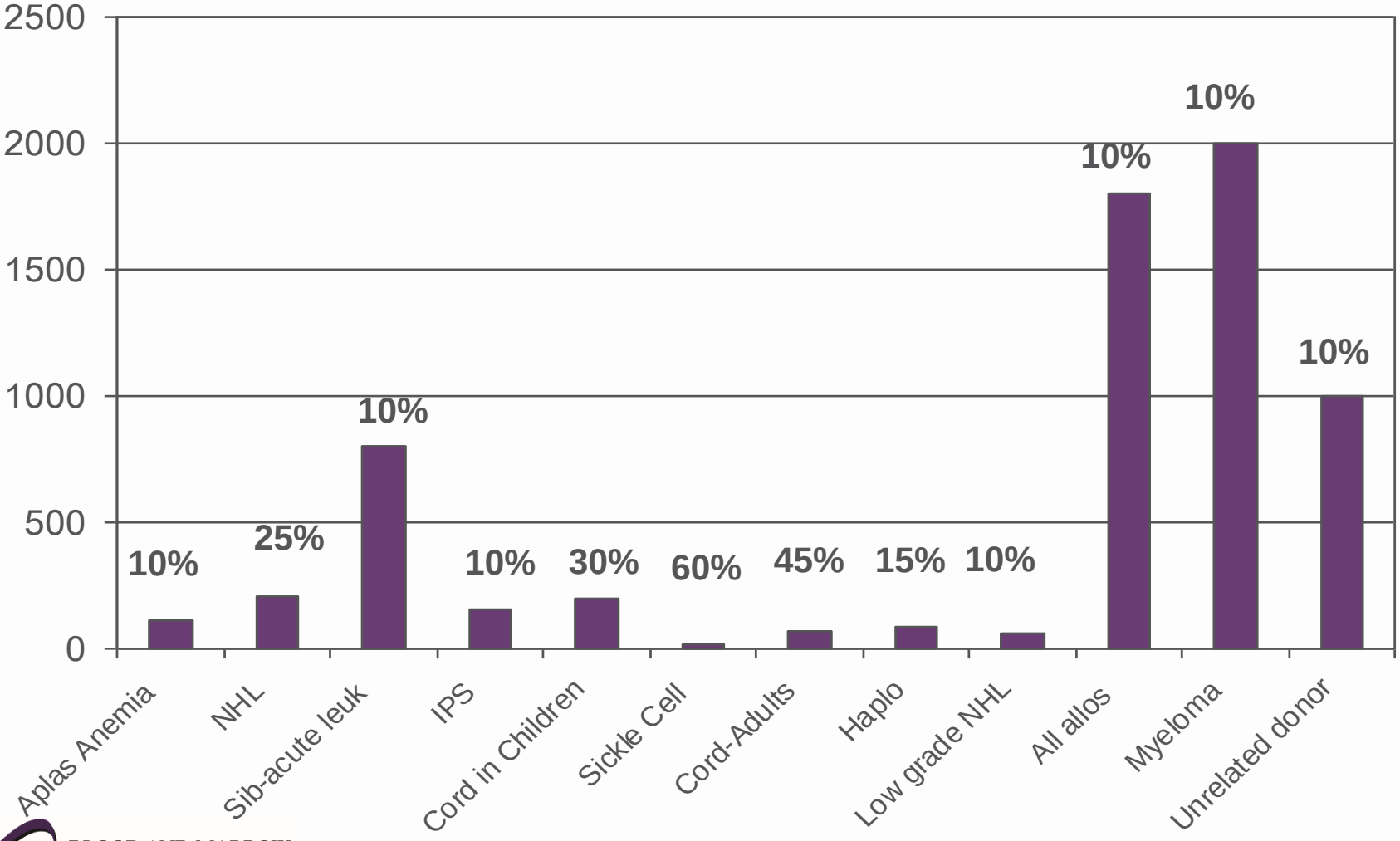
Approximate Annual Number of US Transplants Fulfilling Eligibility Criteria for BMT CTN Trials & % Enrolled



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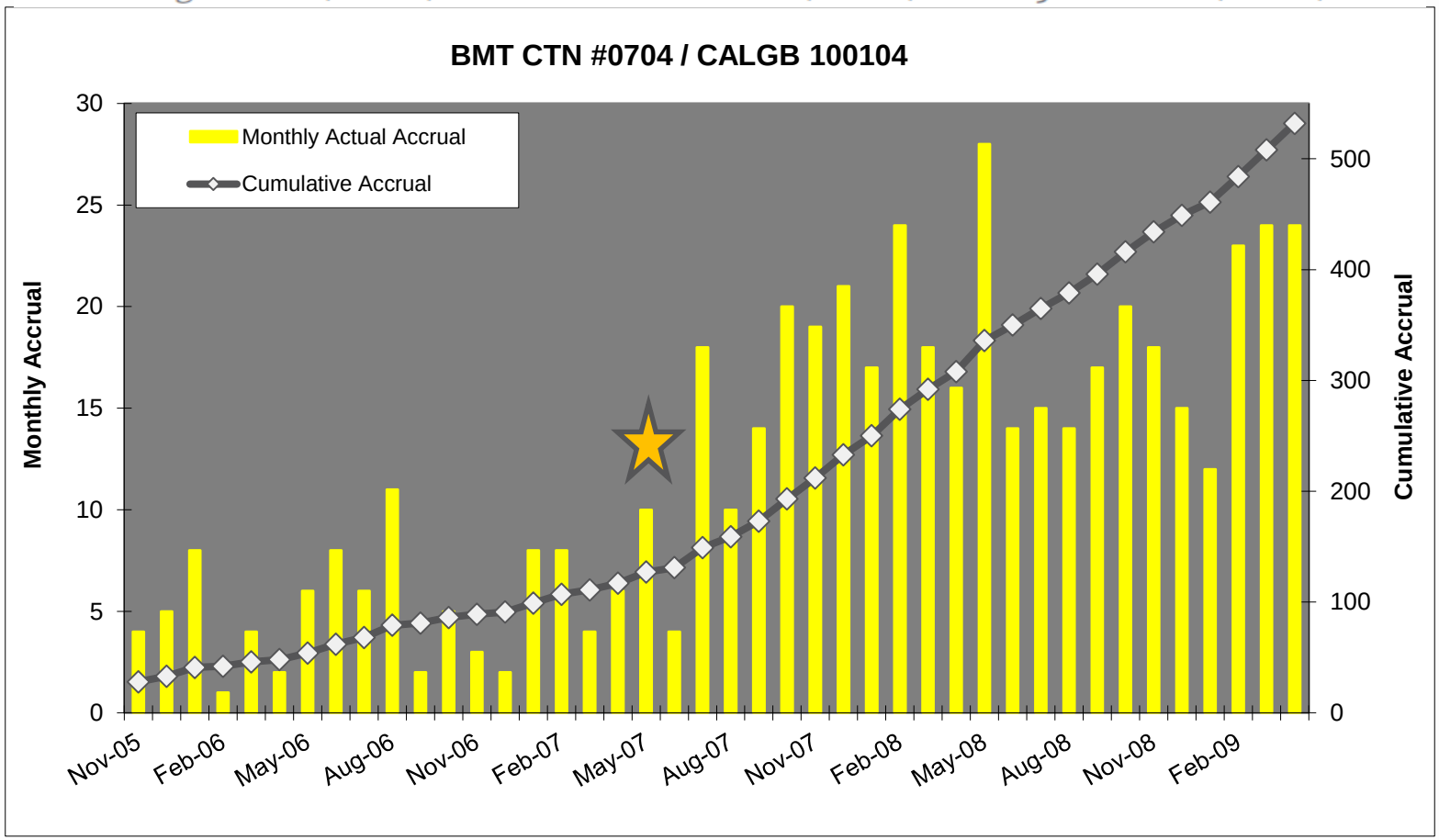
The NEW ENGLAND JOURNAL of MEDICINE

COMMITTED TO COLLABORATION

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.,



Learning Objectives

- Recognize the key areas of focus for clinical research in hematopoietic cell transplantation (HCT)
- Describe the principles to be considered in developing feasible multi-center clinical trials in HCT
- Identify the key issues to be addressed for improving transplantation outcomes within major disease categories
- Describe clinical research issues unique to HCT

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Access additional presentations

- **Steven Devine, MD**: Leukemia, Lymphoma, Myeloma
- **Stella Davies, MBBS, PhD**: Pediatric Indications and Outcomes, Non-malignant Diseases
- **John Wingard, MD**: Donor/Graft Source, Infection/ Immune Reconstitution, Gene and Cell Therapy
- **Frederick Appelbaum, MD**: GVHD, Late Effects/QOL/ Economics, Comorbidity and Regimen-Related Toxicity

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Leukemia, Lymphoma, and Myeloma Committee Reports

Steven Devine MD

Ohio State University

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Financial Disclosure

Company	Role with Company
Sanofi Inc.	Research support

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Leukemia Committee Members

- Frederick Appelbaum, Fred Hutchinson CC, Seattle
- Richard Champlin, MD Anderson CC, Houston
- Stephen Couban, Dalhousie University, Halifax
- Steven Devine, Ohio State University, Columbus
- John DiPersio, Washington University, St. Louis
- Harry Erba, University of Alabama, Birmingham
- Timothy Graubert, Massachusetts General, Boston
- Marcos de Lima, Case Western, Cleveland
- Guido Marcucci, Ohio State University, Columbus
- Richard Stone, Dana Farber, Boston
- Martin Tallman, Memorial Sloan Kettering, New York

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Major goals of transplantation for hematological malignancies

- Preventing relapse

- Preventing acute and chronic GVHD

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Major hurdles in BMT clinical trial design

- Disease heterogeneity, particularly in the genomic era
- Determining appropriate targets
- Availability of effective agents
- Confounding factors (GVHD, regimen-related toxicity, infections)
- Limited number of patients available; timelines

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Hypothesis

- Continued FLT3 inhibition in patients with FLT3-ITD+ AML in remission following HCT will be feasible and will significantly prolong leukemia free survival (LFS)
- Proposal:

  A Randomized, Double-Blind, Phase III Study of FLT3 inhibition compared to Placebo as Maintenance Therapy in Subjects with FLT3-ITD(+) Acute Myeloid Leukemia Who are In Remission Following Allogeneic Hematopoietic Stem Cell Transplantation

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Proposal #1: Background & Significance

- Approximately 20-30% of patients with AML are found to harbor an ITD mutation in the FLT3 receptor that results in a high risk of relapse following conventional chemotherapy
- Retrospective data suggest such patients may benefit from HCT, yet the risk of relapse following HCT is still high
- Agents that inhibit FLT3 signaling (midostaurin, quizartinib, sorafenib) are currently being tested in Phase II trials as maintenance following HCT in FLT3-ITD+ patients

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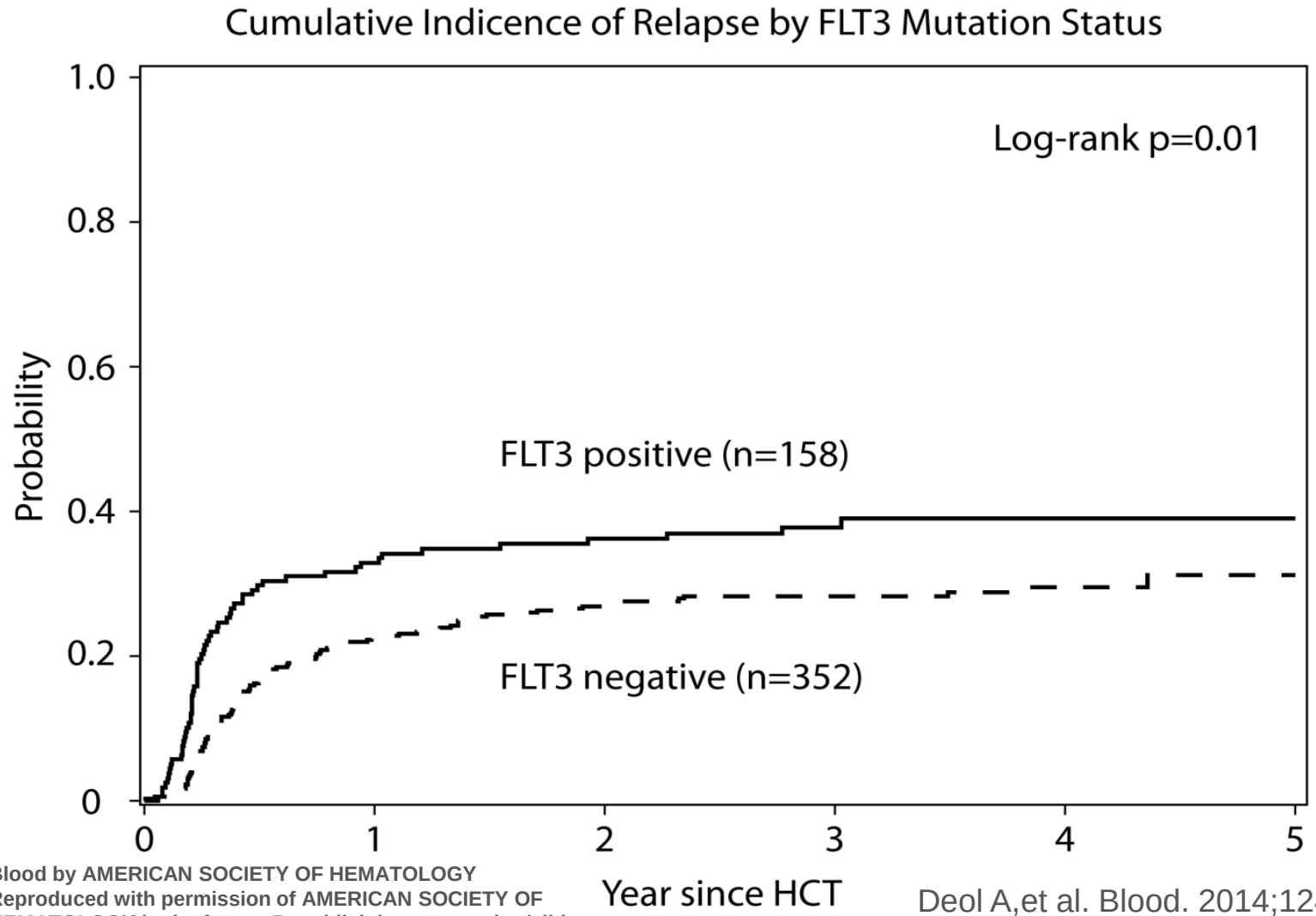
Impact of Flt3 ITD mutation on relapse post allograft



Deol A,et al. Blood. 2014;124(21): abs. #322.

Proposal #1: Trial Design

- Phase III, randomized, double blinded study comparing FLT3 inhibitor monotherapy to placebo in patients with FLT3-ITD(+) AML who are in remission following HCT
- Primary endpoint: Leukemia-free survival
- Sample size derivation:
  - A total of 164 events (relapses or deaths) would provide 90% power to detect a difference in LFS with a 2-sided significance level of 0.05, assuming a hazard ratio of 0.6. This corresponds to an LFS rate of 73.6% at 2 years for the FLT3 inhibitor arm and 60% for the placebo arm

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Proposal #1: Feasibility & Logistics

- Large sample size required:
  - Approximately 500 subjects, randomized in a 2:1 ratio to receive Flt3 inhibitor or placebo.
  - Multi-center; multi-national effort required
  - Support from pharmaceutical sponsor critical
  - Possible registration trial
- How should heterogeneity in prognosis within FLT3 ITD+ patients be handled?
- How much do we know about tolerability and efficacy of FLT3 inhibitor agents from ongoing phase II studies

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Proposal #2: Hypothesis

- Low dose azacytidine (AZA) maintenance will decrease the risk of relapse after allogeneic hematopoietic stem cell transplantation for AML and MDS
- Proposal:

A Randomized, Phase III Study of Low Dose AZA Maintenance Compared to No Maintenance in Patients with AML and MDS at High Risk of Relapse Following HCT

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Proposal #2: Background & Significance

- The hypomethylating agents 5-azacytidine (AZA) and decitabine are clinically active against both MDS and AML
- A phase I trial at MD Anderson Cancer Center established a safe dose of AZA following HCT
- The Alliance (formerly CALGB) recently completed a 64 patient Phase II study using that dose of AZA following HCT with reduced intensity conditioning in patients with AML and MDS (Vij et al. Blood 2014:124(21):abs# 543)
- A single center Phase III study is ongoing at MD Anderson (NCT # 00887068)
- Oral hypomethylating agents are available

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Proposal #2: Trial Design

- Phase III, randomized study comparing AZA monotherapy to placebo in patients with AML/MDS who are in remission following HCT but have a high risk of relapse
- Treatment plan: AZA 32 mg/m^2 daily for 5 days, starting on transplant day 40 -100, given in 30 day cycles for 1 year, or approximately 12 cycles.
- Primary endpoint: Progression free survival
- Sample size estimation: Dependent on estimated magnitude of benefit but likely to require 250-300 patients

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Proposal #2: Feasibility & Logistics

- Multi-center, possibly multi-national, collaboration required
- Which types of patients to include?
  - Based on estimated risk of relapse?
- Competing trials; MD Anderson study ongoing
- Requires Pharmaceutical sponsor
- Oral agent may facilitate logistics and possible use of a placebo

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Proposal #3: Hypothesis

- Patients with AML in first complete remission (CR1) who are aged 60 years or older will have prolonged survival following HCT compared with other consolidation strategies
- Proposal:

  Prospective Comparative Trial Evaluating Post-Remission Therapies of HCT versus Consolidation Chemotherapy/Conventional Therapy in Older AML Patients

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Proposal #3: Background & Significance

- Multiple retrospective series as well as smaller prospective studies indicate superior LFS with allografting compared with conventional therapy in patients aged 60 or above with AML in CR1
- Clearly, patient selection has affected these results
- One prospective randomized study suggests far less relapse with BMT compared to chemotherapy (Niederwieser et al. Blood 2014:124(21):abs# 280)
- If the advantage with transplantation were demonstrated in large prospective trials, the standard of therapy for this group of individuals would change

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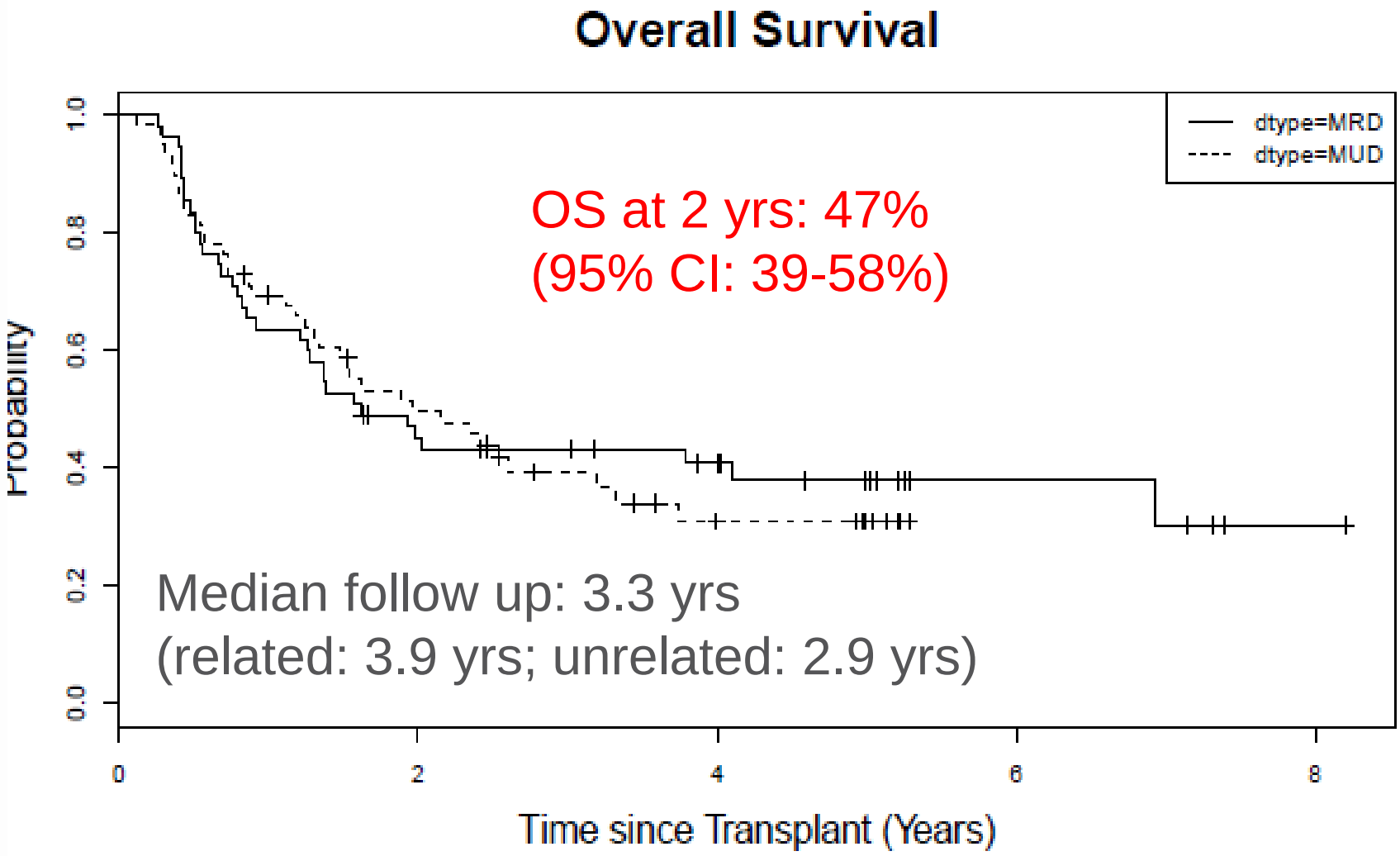
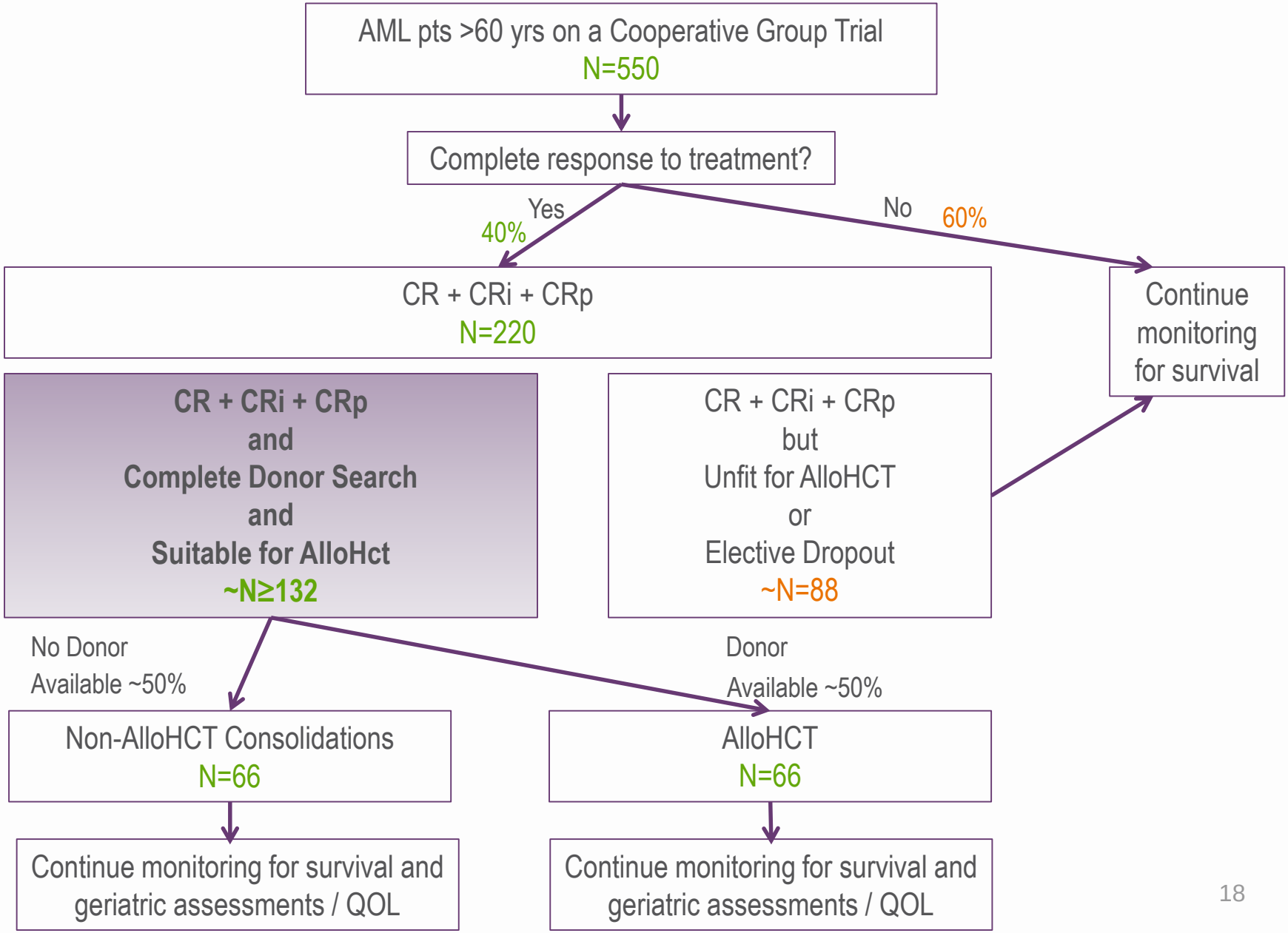
CALGB 100103/BMT CTN 0502: Phase II Trial of Allografting in Older Adults



Devine S et al. Blood 2012; 120(21) abstract 230.

Proposal #3: Potential Trial Design



Proposal #3: Feasibility & Logistics

- Would require 500-600 newly diagnosed patients
- Need participation of multiple cooperative groups
- How to account for multiple inherent biases?
- How to determine “suitability” for transplant?
- What should be considered a suitable donor?
  - Influence of umbilical cord blood or haploidentical transplantation options

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Result of SOSS committee deliberations

- Flt3 study (proposal #1) and Aza maintenance (proposal #2) studies considered for further development

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Lymphoma

Committee Report

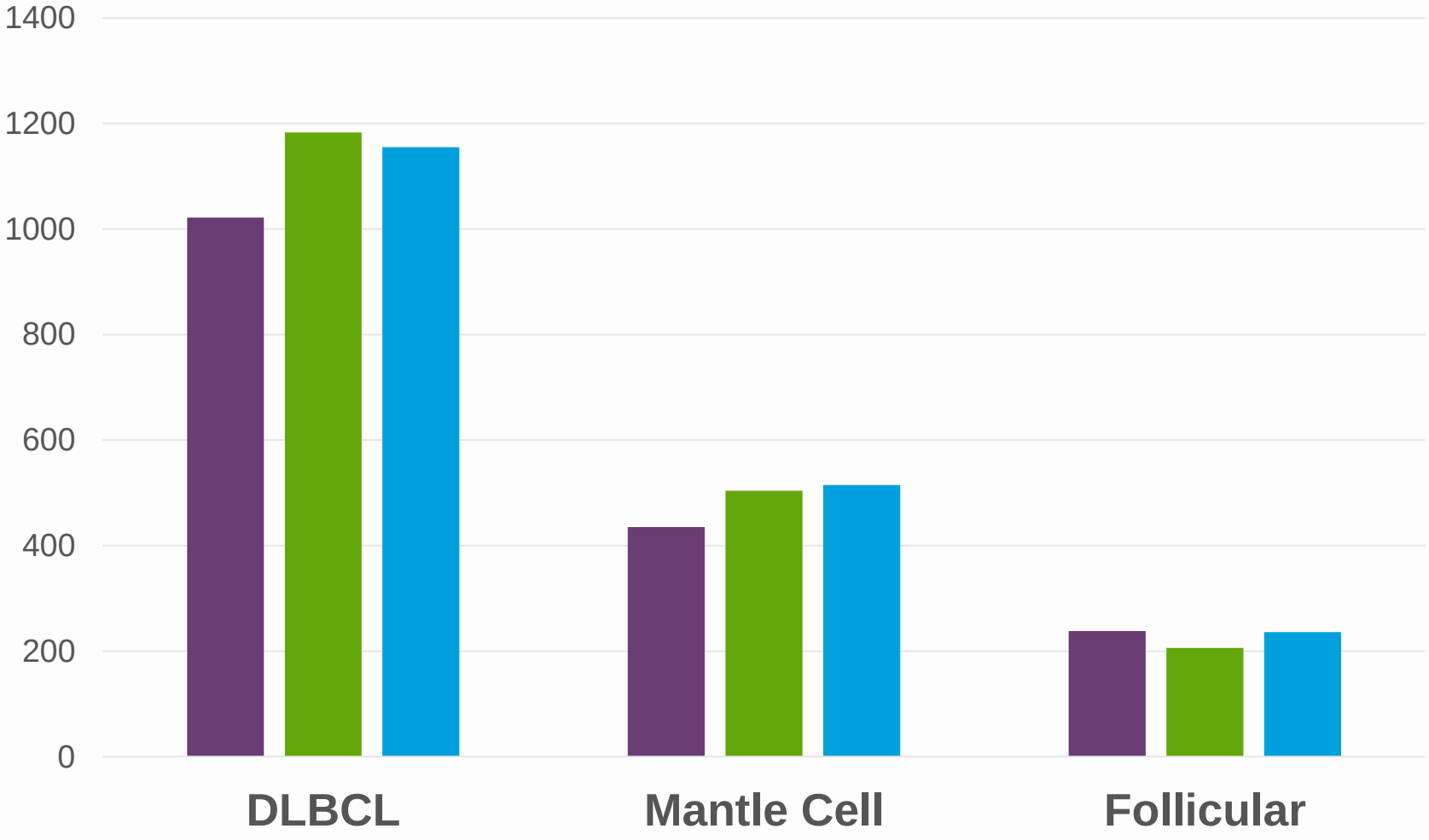
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- Ginna Laport
  - Stanford/BMT CTN
- Richard Ambinder
  - Johns Hopkins
- Tim Fenske
  - MCW/BMT CTN
- Richard Fisher
  - Fox Chase/SWOG Lymphoma Chair
- Brad Kahl
  - Univ of WI/ECOG Lymphoma Chair
- John Leonard
  - Cornell/Alliance Lymphoma Chair
- Tom Shea
  - Univ N Carolina/ BMT CTN/Alliance
- Julie Vose
  - Univ Nebraska/BMT CTN
- Wyndham Wilson
  - NCI
- Joycelynne Palmer
  - City of Hope (biostatistician)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Number of Autologous Transplants Performed in U.S. Centers, 2010-2012



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR Summary Slides, 2013.

Proposal #1: Hypothesis

- Ibrutinib (IB) will improve progression-free survival after autotransplantation for patients with relapsed or refractory ABC-subtype diffuse large B-cell lymphoma (DLBCL)
- Proposal:

Randomized Phase III Trial of IB versus Placebo During and After Autotransplantation in Patients with Relapsed or Refractory DLBCL of the ABC-Subtype

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

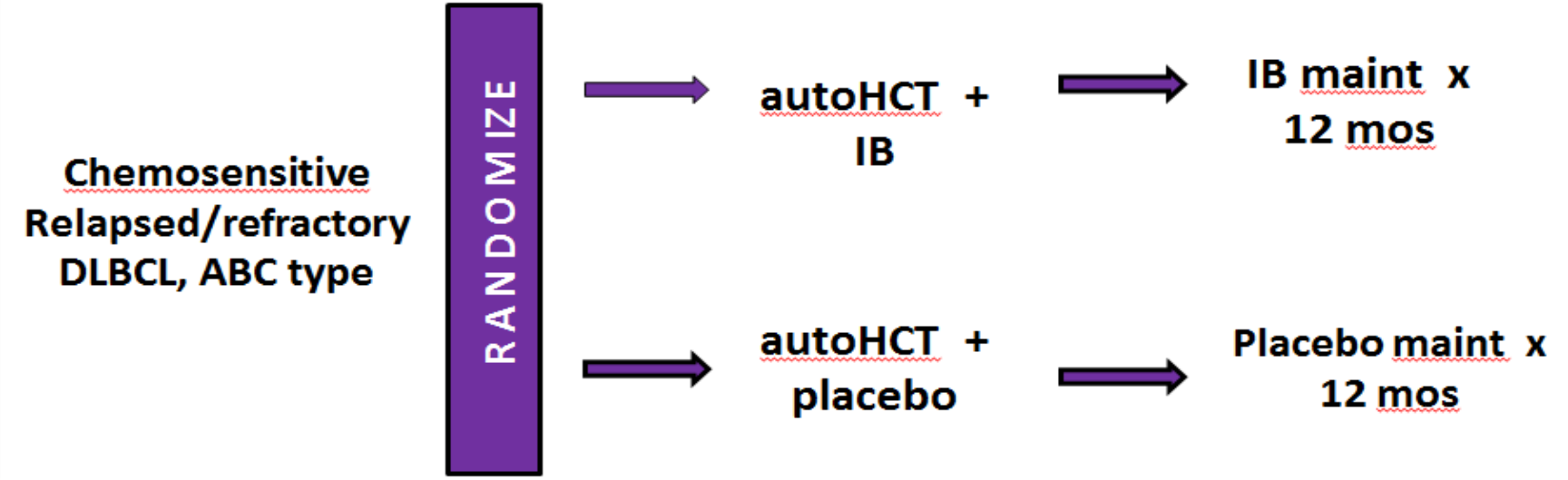
Proposal #1: Background & Significance

- Two distinct subtypes of DLBCL have significantly different 5 yr overall survival (OS)rates after R-CHOP
  - Activated B cell type (ABC) → 35%
  - Germinal B cell type (GCB) → 60%
- AutoHCT for relapsed/refractory DLBCL patients
  - 2 yr PFS and OS → 48% and 65%, respectively
  - Primary cause of treatment failure is progression
- Ibrutinib
  - Selective BTK inhibitor
  - Activity in lymphoid malignancies (mantle cell NHL, CLL, DLBCL)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design

- Randomized, placebo-controlled, phase III trial
- Primary Endpoint: Progression-free survival at 2 yrs
- Eligibility
  - Diffuse large B cell lymphoma, ABC subtype
  - Subtype to be determined by centralized digital gene expression (NanoString) assay performed on FFPET



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics

- CIBMTR query from 2009-2012
  - 770 pts/year with relapsed DLBCL underwent auto-HCT
  - Assuming 50% of pts will be ABC subtype, 318-385 pts/year eligible
    - 1 of 3 patients willing to participate
- Expected median PFS of placebo arm: 24 months
- Assume exponential PFS model and annual hazard rate of .347
- Treatment meaningful if PFS extended by ≥60% (HR=1.6)
- Sample size of 296 patients for 85% power to detect HR of 1.6
- Final analysis to be done when 168 events (progression/death) observed
- Estimated accrual time of 36 months with follow-up of 24 months

Proposal #2: Hypothesis

- Auto-HCT for previously untreated ‘double hit’ DLBCL patients during first response (CR1 or PR1) will result in superior 2 year PFS compared to conventional therapy only
- Proposal:

  Phase II Trial of R-EPOCH Induction for Previously Untreated ‘Double Hit’ DLBCL Followed by AutoHCT in Patients Achieving PR1 or CR1

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

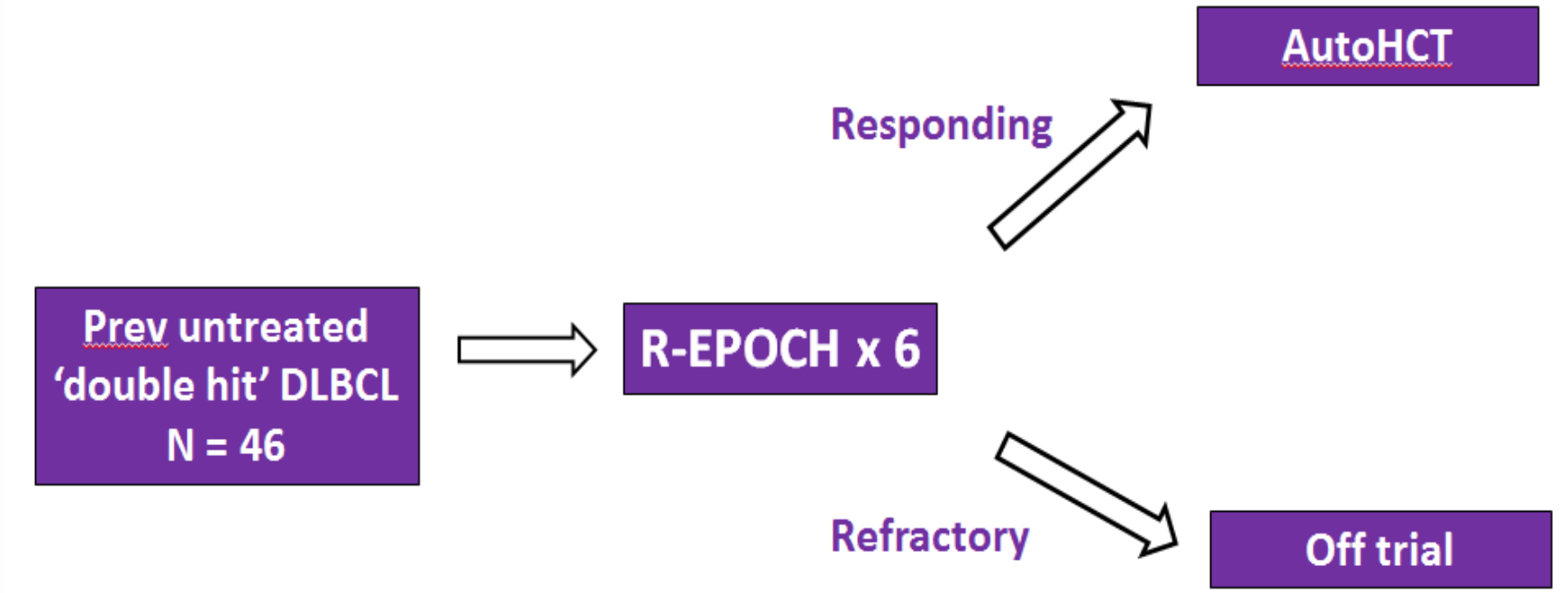
Proposal #2: Background & Significance

- DLBCL pts expressing MYC and bcl-2 have poor outcomes
  - 3 year PFS ranges from 39%-45%; 5 year PFS ~ 20%
- No controlled studies evaluating autologous transplantation early in the disease course
- Multicenter retrospective study of >100 double hit patients: R-EPOCH superior to R-CHOP in achieving CR1
- Auto-HCT in CR → improved survival

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #2: Trial Design

- **Primary Endpoint:** 2 year Progression-Free Survival (PFS)
- **Eligibility**:
  - Previous untreated 'double hit' DLBCL
  - FISH to identify gene rearrangement
  - Can have 1 cycle of prior chemotherapy before starting R-EPOCH



Proposal #2: Feasibility & Logistics

- In 2013, ~21,000 cases of DLBCL diagnosed*
- ~ 10% will carry ‘DH’ mutations

- Assumptions:
  - Historical 2 yr PFS = 38%
  - Alternative 2 yr PFS = 58%
- Sample size: 46 pts
- Power 90% with alpha 5%

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

*Seer.cancer.gov

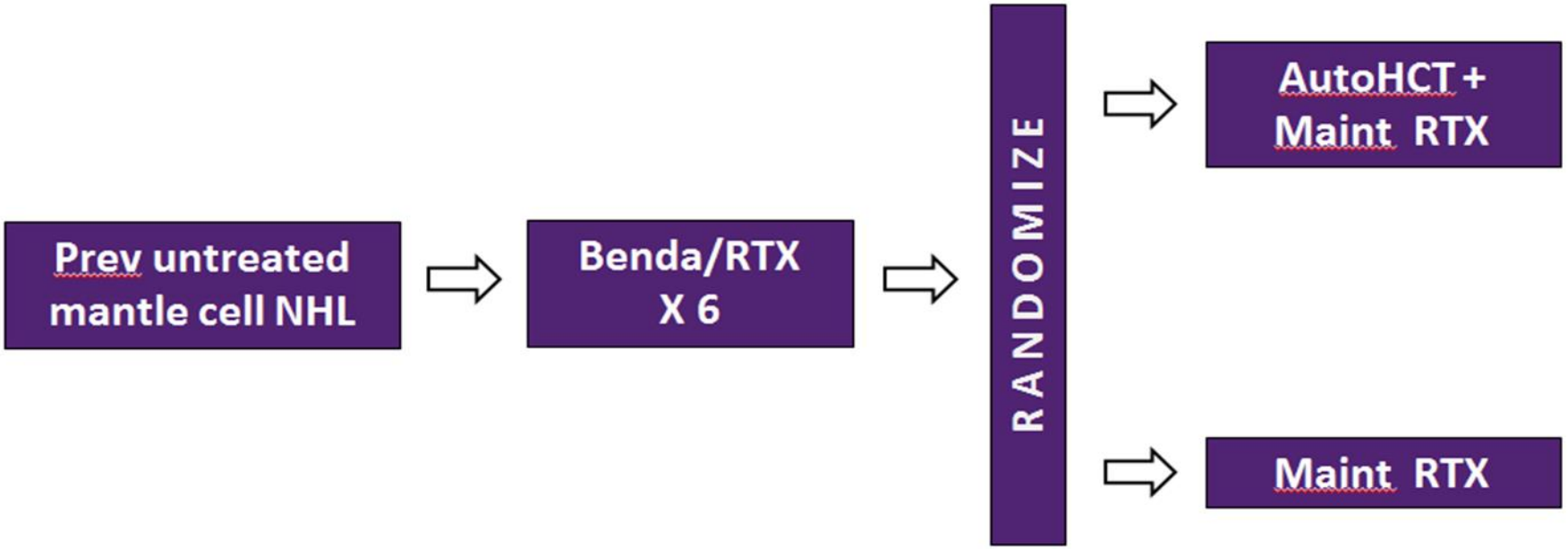
Proposal #3: Background & Significance

- Median overall survival for newly diagnosed mantle cell patients is ~ 7 years
- Common induction regimens:
  - R-CHOP
  - Ara-C containing regimens
  - Bendamustine + Rituxan (BR)
- Maintenance Rituxan
  - After R-CHOP → prolongs remission/reduced risk of death
  - After auto-HCT → prolongs PFS
- Ibrutinib: role as maintenance after auto-HCT?

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #3a: Trial Design

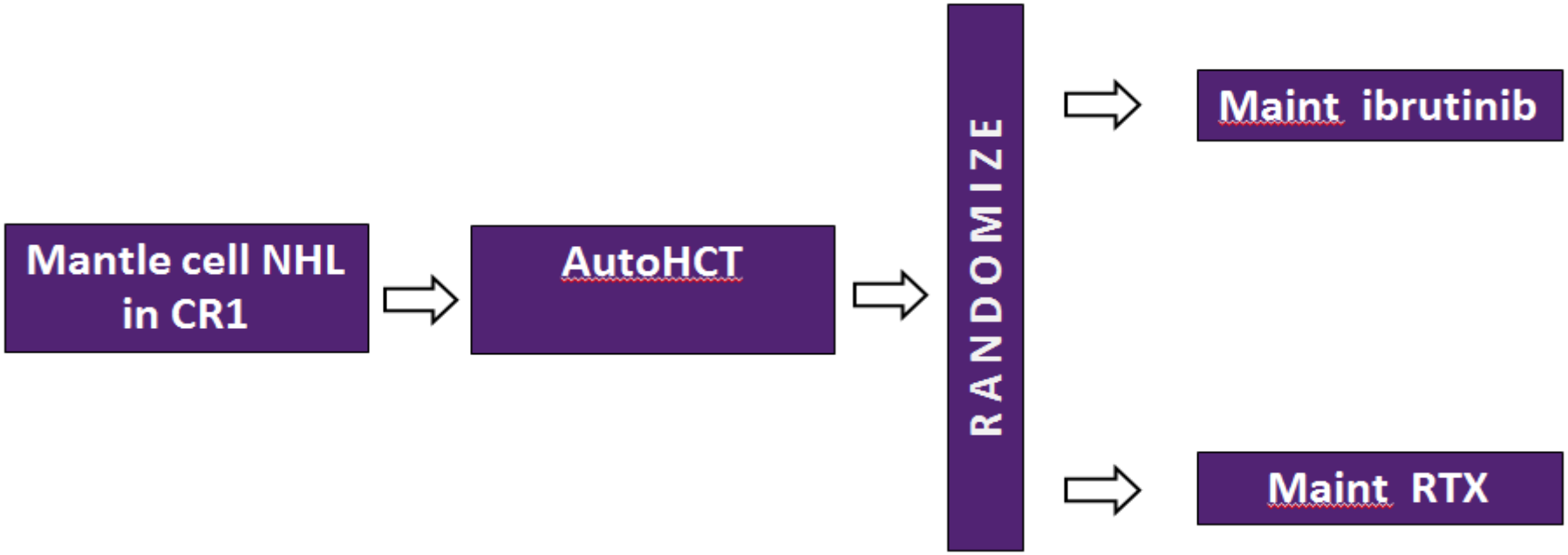
- **<u>Primary Endpoint:</u>** 2 year PFS
- Robust point estimates not available
- Enrollment at diagnosis (3.5k cases/year)



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #3b: Trial Design

- **Primary Endpoint:** 2 year PFS
- Robust point estimates not available
- Enrollment at HCT



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Result of SOSS committee deliberations

- DLBCL ibrutinib maintenance study considered for further development

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Myeloma Committee Report

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members & Disclosures

- Sergio Giralt: Memorial Sloan Kettering Cancer Center, New York
- Kenneth Anderson: Dana-Farber Cancer Institute, Boston
- William Bensinger: Fred Hutchinson CRC, Seattle
- Parameswaran Hari: Medical College of Wisconsin, Milwaukee
- Amrita Krishnan: City of Hope Medical Center, Duarte
- Carl Ola Landgren: National Cancer Institute, Bethesda
- Sagar Lonial: Emory University, Atlanta
- Philip McCarthy: Roswell Park, Buffalo,
- Robert Orlowski: University of Texas MD Anderson CC, Houston
- Vincent Rajkumar: Mayo Clinic, Rochester
- Keith Stewart: Mayo Clinic, Scottsdale
- Marcelo Pasquini: Medical College of Wisconsin, Milwaukee

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Hypothesis

- Compelling Question:
  - In the context of new combination therapies is there a role for consolidation with high dose melphalan and autologous stem cell support for ALL symptomatic myeloma patients (early vs delayed transplantation)?
- Hypothesis
  - Consolidation therapy with high dose melphalan and autologous HCT will to provide a progression-free survival (PFS) benefit for all patients with newly diagnosed symptomatic myeloma

Three Studies ongoing or in follow up

GIMENA (Italian Multiple Myeloma Network)

BMT CTN 1304 (IFM/DFCI Study)

European Myeloma Network (EMN)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

IFM/DFCI 2009 Study
Newly Diagnosed MM (HCT candidates)

Randomize, stratification ISS & FISH

VRD x 3	**Induction**	**VRD x 3**
CY (3g/m^2) MOBILIZATION Goal: 5 x10^6 cells/kg	**Collection**	**CY (3g/m^2) MOBILIZATION Goal: 5 x10^6 cells/kg**
Melphalan 200mg/m^2* + ASCT		
VRD x 2	**Consolidation**	**VRD x 5**
Lenalidomide 12 mos In US until Progression	**Maintenance**	**Lenalidomide 12 mos In US until Progression**

HCT at relapse

MEL 200 mg/m2 if <65 yrs, ≥65 yrs 140mg/m^2

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

clinicaltrials.gov/ct2/show/NCT01208662?term=nct01208662&rank=1

Proposal #1: DFCI/IFM BMT-CTN 1304 Trial

- Two parallel trials in US and Europe will randomize a total of 1360 patients
- US trial: 90% power to detect a 30% reduction in the PFS hazard from 0.0231/month to 0.0162/month on early HCT arm
  - Assuming median PFS of 30 months on the lenalidomide+bortezomib+dexamethasone (RVD) alone arm (Arm A) and the PFS time follows an exponential distribution, this difference corresponds to a 43% increase in median PFS to 43 months for Arm B.
- A descriptive analysis will be performed to attempt to address a question comparing PFS and OS for maintenance lenalidomide for 1 year (700 patients/Europe) vs. maintenance lenalidomide until progression (660 patients/US)
  - 350 vs. 330 patients in non-HCT and 350 vs. 330 patients in HCT arms
- ~400 patients enrolled on US trial to date

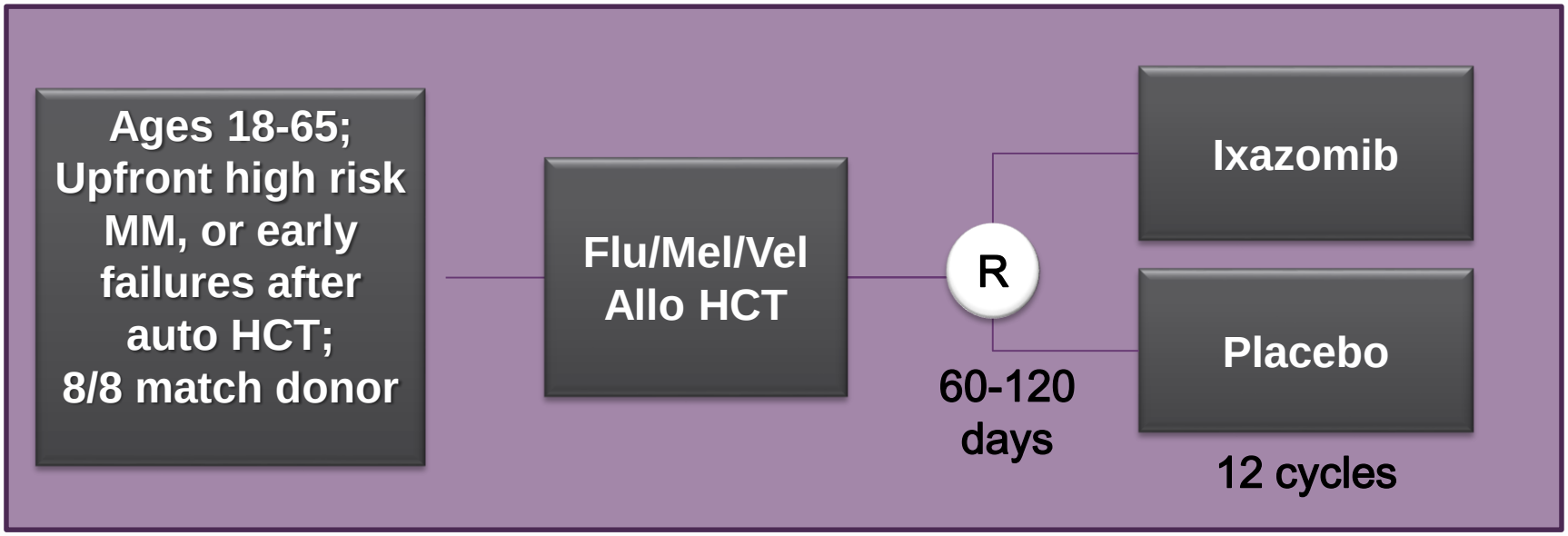
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #2: Background & Significance

- Allografting performed less and less in MM due to perception of lack of benefit in standard risk disease
- Allografting high risk patients as consolidation of 1st or 2nd remission being more frequently explored
- Relapse remains the most important cause of treatment failure
- Use of ixazomib, a new oral proteosome inhibitor, may reduce relapse risk without increasing risk of GVHD (as seen with lenalidomide)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #2: BMT CTN 1302, A Randomized Phase II Study of Allografting for High Risk Myeloma



Sample size: 138 patients (110 randomized patients)
Expected to open in early 2015

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1302 Endpoints

- Primary endpoint:
  - PFS as a time to event endpoint from randomization (compared between ixazomib and placebo maintenance)
- Secondary endpoints:
  - Grades III/IV aGVHD; cGVHD; best response; relapse/progression; transplant-related mortality; toxicities; survival
  - Outcomes from time of transplant will also be analyzed.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1302: Statistical Considerations

- Sample Size Calculation (n=138)
  - 20% drop out from HCT to maintenance
  - 55 patients per arm reaching maintenance
  - Baseline event rate: 24 month PFS 56% (for patients alive & progression free at day 100) in CTN 0102 high-risk auto-allo HCT pts (n=25)
    - Assumption: PFS 55% at 21 mo from randomization
  - Power of 83%
    - 20% improvement in 21 month PFS from 55% → 75%

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #3: Hypothesis

- Hypothesis
  - A myeloma/dendritic cell fusion vaccine strategy used post auto HCT enhance depth of response.
  - The degree of anti-myeloma immune responses will correlate with response and progression free survival.

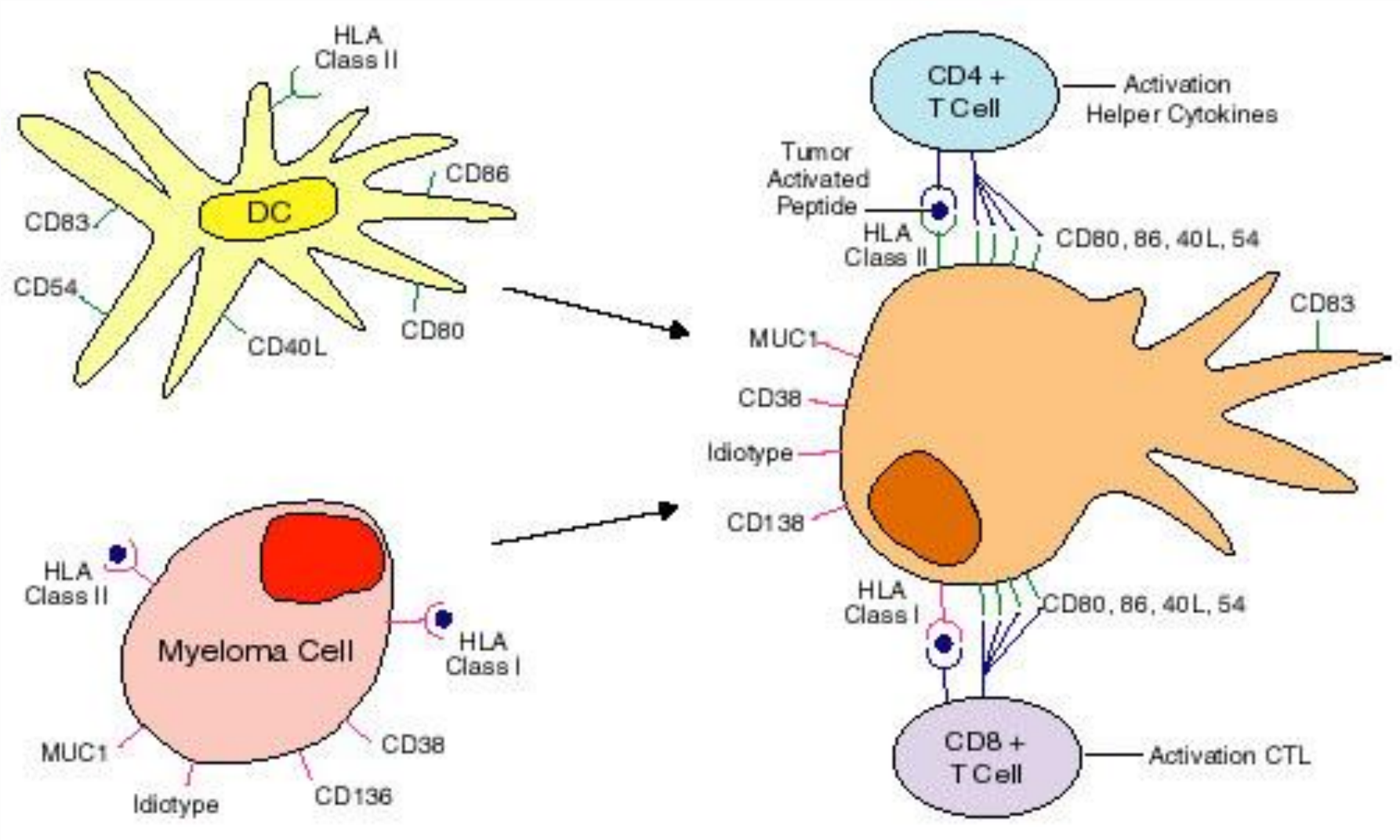
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #3: Background & Significance

- Autologous HCT for myeloma offers a unique opportunity to explore the role of cancer vaccines
  - Patients achieve minimal disease state but transplant is not curative in most cases.
  - Transplant-mediated cytoreduction minimizes immunosuppression
- Enhanced response to vaccination post-transplant in animal models
  - Depletion of regulatory T cells during the period of post-transplant lymphopoietic reconstitution
  - Expansion of tumor reactive clones

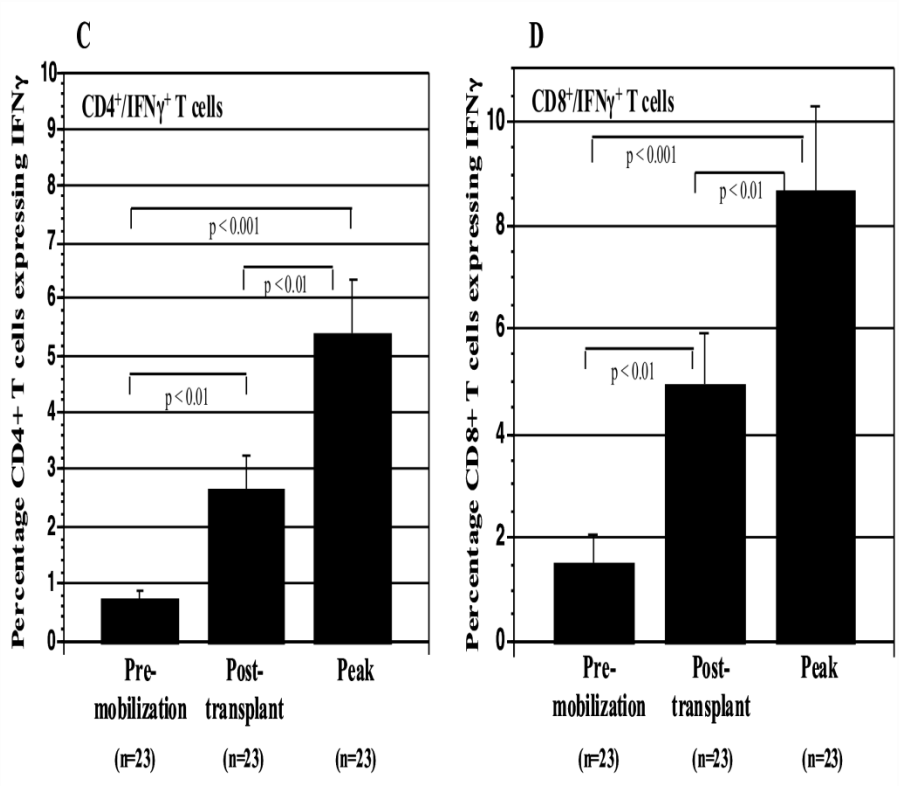
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

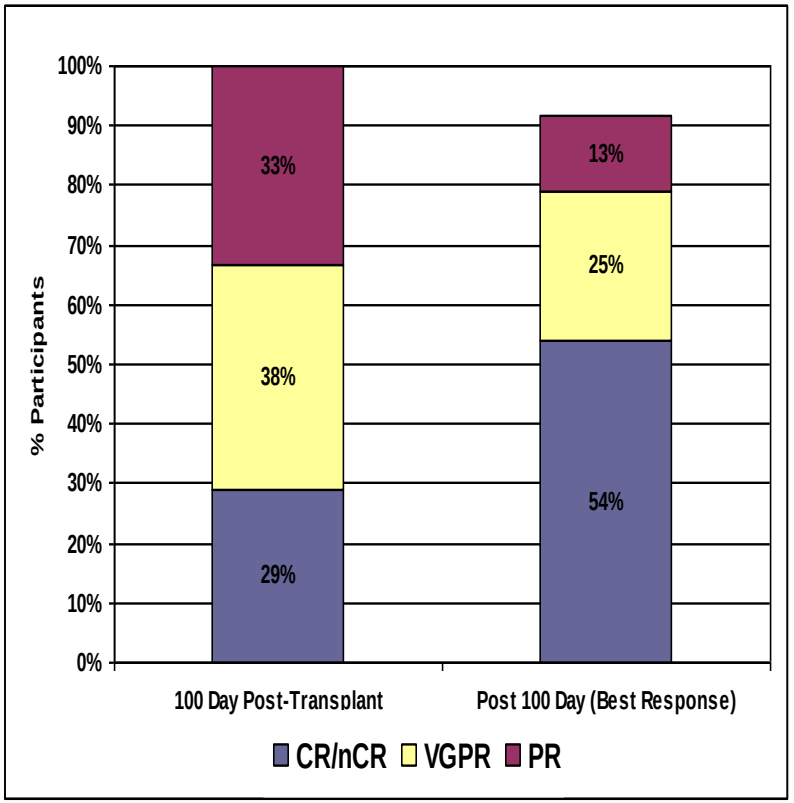
Proposal # 3: BMT CTN 1401 DC/TUMOR FUSION VACCINE



Rosenblatt J, Avivi I, et al. Clin Cancer Res. 2013; 19(13): 3640–3648

DC/MM Fusion Vaccination Post-transplant





BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

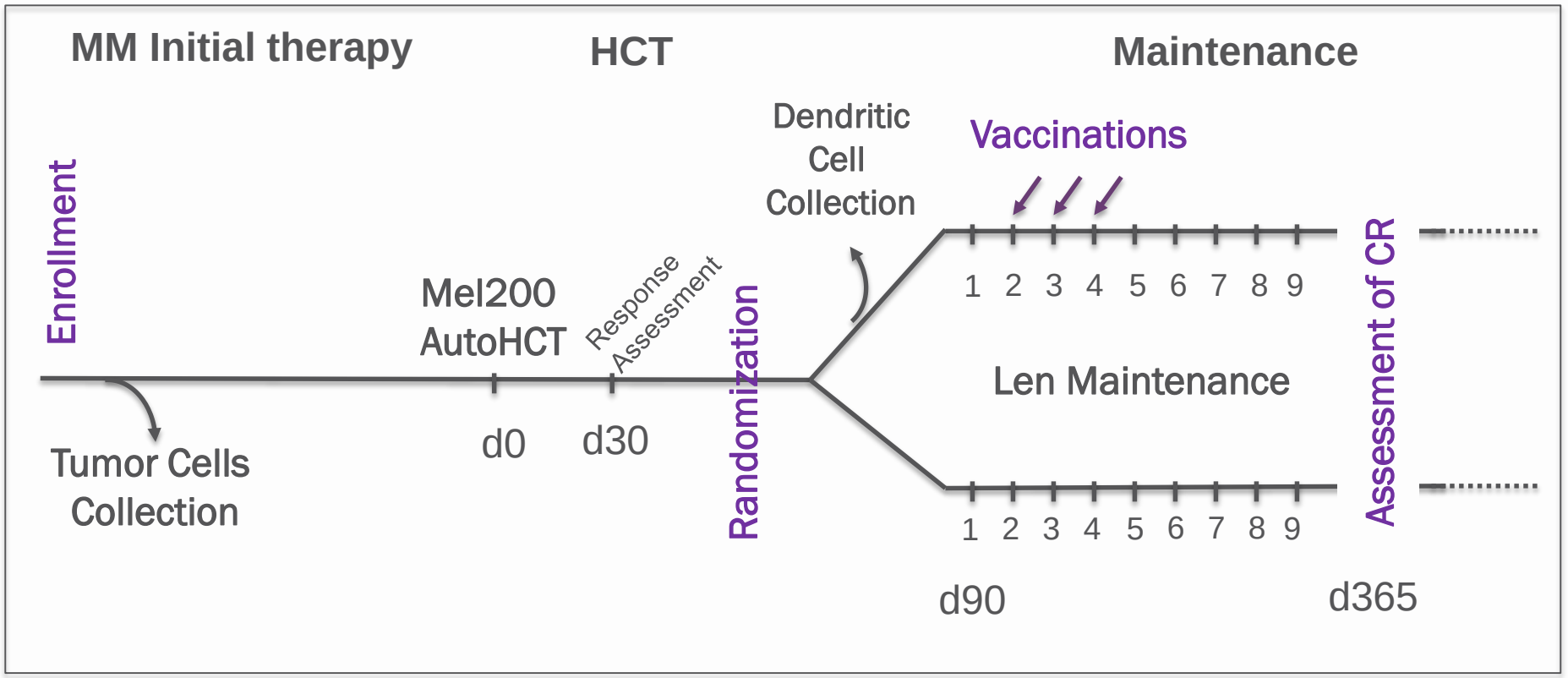
Rosenblatt J, Avivi I, et al. Clin Cancer Res. 2013; 19(13): 3640–3648

Proposal #3: BMT CTN 1401

- Randomized Trial of Vaccination with DC/Myeloma Fusions + Lenalidomide Maintenance versus Lenalidomide Maintenance Alone after Autotransplantation for Myeloma
- Expected to open in early 2015
  - First vaccine technology with positive clinical signal and potential for multi-center use
  - Development of an in network cellular immunotherapy product that is “patient specific” but relatively accessible.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Study Schema



- Enrollment at diagnosis or at least after 2 cycles of initial therapy
- 20% plasma cells in the bone marrow aspirate
- Initial myeloma therapy, mobilization and transplant will be according to institutional guidelines
- Response assessment is required for stratification: CR vs SD/PR/VGPR

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Study Objectives

- Primary Objective
  - To compare the proportion of patients alive and in complete remission (CR) at one year
- Secondary Objectives
  - Myeloma response (CR, very good partial response (VGPR) and partial response (PR)
  - Conversion of partial to complete response
  - Toxicity/Treatment related mortality
  - Progression-free survival
  - Effect on myeloma specific T cells, natural killer (NK) cell response, humoral response and quantification of activated and inhibitory T cell subsets

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Eligibility

Two-step enrollment:

- First enrollment: for collection of malignant plasma cells as part of vaccine manufacturing
- Subsequent enrollment: prior to randomization

Eligible patients are:

- ≤70 years
- Symptomatic multiple myeloma
- No prior disease progression or prior HCT
- Performance score ≥70%
- ≥ 20% plasma cells in a bone marrow aspirate
- Absence of active autoimmune disease, i.e. requiring therapy

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Accrual/Study Duration

- **Accrual Objective:** Accrual will target 132 randomized patients
  - Drop out from enrollment to randomization
    - 15%: total accrual of 155 patients
    - 30%: total accrual of 188 patients
- **Accrual Period:** 24 months
- **Study Duration:** Patients will be followed for a minimum of 2 years after randomization until disease progression

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Result of SOSS committee deliberations

- All trial concepts meritorious
- BMT CTN currently supporting all trial
- DFCI/BMT CTN 1304 is active
- BMT CTN 1302 and 1401 in advanced stages of development

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Summary

- Strong support for portfolio of studies that:
  - Address the most common disease indications for allogeneic (AML, MDS) and autologous (NHL, Myeloma) HCT
  - Address the most common cause of treatment failure in these diseases: progressive or recurrent disease
  - Utilize novel drugs and immune therapies to enhance the anti-cancer efficacy of HCT

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Questions recorded from the live event on Dec. 5, 2014

Access a Certificate of Attendance

(will open in new browser tab)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Non-Malignant Diseases, Pediatric Indications for Transplant and Pediatric Outcomes

Stella M Davies

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Financial Disclosures

No financial disclosures to report

Non-Malignant Diseases Committee Report

Chair: Harold Atkins

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Non-Malignant Diseases Committee Members

- Joachim Deeg – Fred Hutchinson CRC, Seattle
- George Georges − Fred Hutchinson CRC, Seattle
- Carolyn Keever-Taylor − MCW, Milwaukee
- Richard Nash – Colorado Blood Cancer Institute, Denver
- Steven Pavletic – National Cancer Institute, Bethesda
- Michael Racke − Ohio State University Wexner MC, Columbus
- Keith Sullivan − Duke University Medical Center, Durham
- Linda Griffith − NIAID, NIH, Bethesda
- Nancy DiFronzo − NHLBI, Bethesda
- Adam Mendizabal − EMMES Corporation, Rockville
- Marcelo Pasquini − MCW, Milwaukee
- George Kraft − University of Washington, Seattle
- Mark Freedman – University of Ottawa

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Overview of the Discussion

- Sickle Cell Disease
  - Early phases of clinical testing for adults
- Aplastic Anemia
  - Future trial based on results of BMT-CTN 0301 which explores optimal dose of cyclophosphamide in combination with fludarabine
- Scleroderma
  - Two Phase III trials concluding – await results
- Crohn's Disease
  - Further exploratory research required
- Multiple Sclerosis (MS)

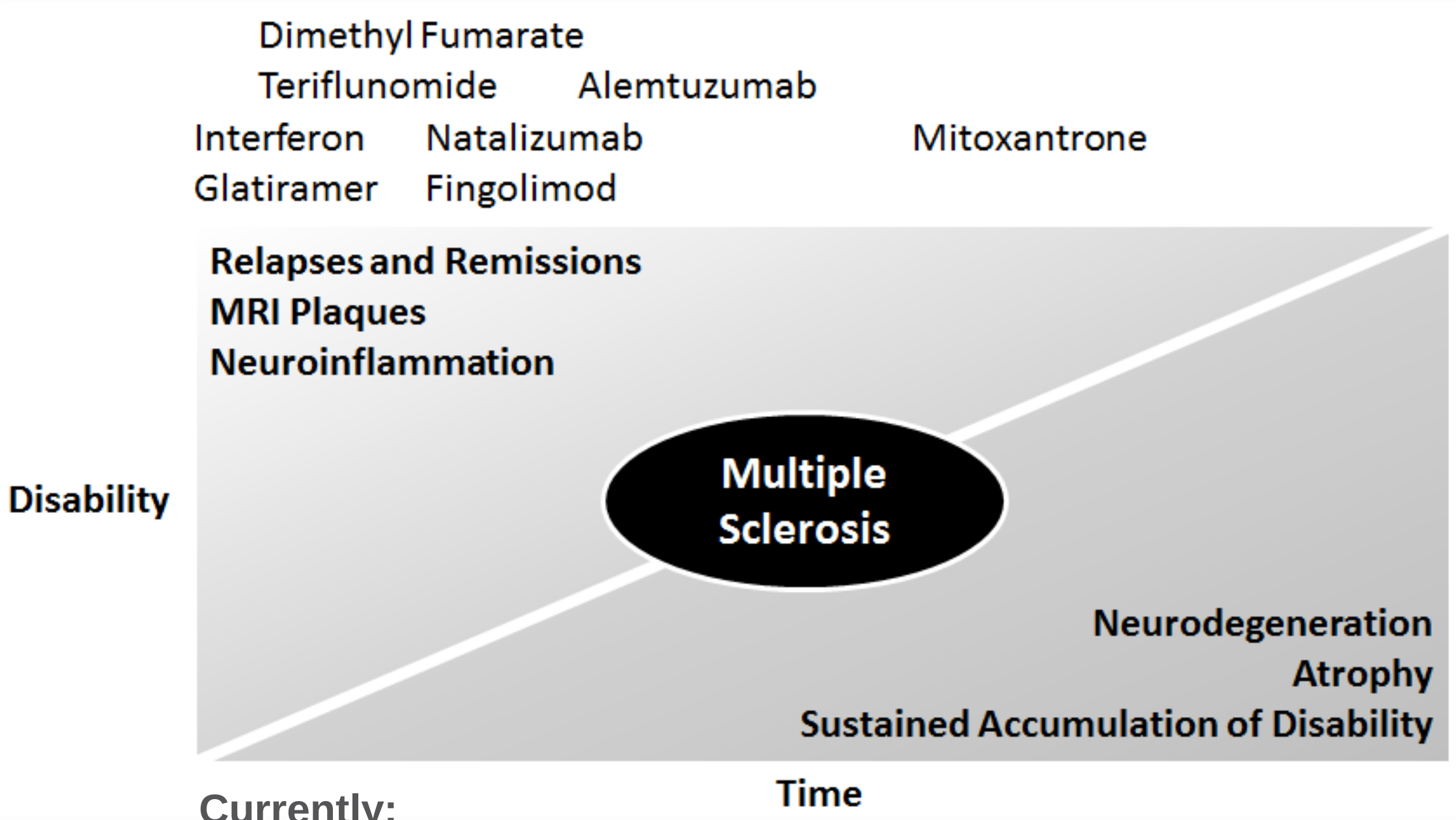
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Hypothesis

- Ablative therapy followed by autologous HCT will result in:
  - Greater control of MS inflammatory disease activity
  - Less sustained accumulation of disability
  - Greater sustained improvement in disability than the best available therapy for MS

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Background & Significance



Currently:

- **There are no treatments that completely eliminate relapses**
- **There are no treatments that halt progression**

Proposal #1: Background & Significance

	Years	Total HCT	Peak #/yr	3 year OS
CIBMTR	1996-2009	160	24	97%
EBMT	1996-2007	345	52	93%

<u>Combined Long-term Follow-up Study</u>
281 patients that underwent HCT between 1995-2006

- Overall Survival 92% at 5 years
- Progression Free Survival 47% at 5 years
- Better PFS if younger, less treated, relapsing at HCT

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Muraro et al. EBMT(London) 2013
Pasquini MC, et al. Biol Blood Marrow Transplant. 2012 Oct;18(10):1471-8.
Farge D, et al. Haematologica. 2010 Feb;95(2)

Proposal #1: Background & Significance

	ASTIMS	Canadian MSBMT	HALT MS	NWU
Patients (n)	21	24	25	110
Arms	Randomized vs Mitoxantrone	Single Arm	Single Arm	Randomized vs FDA approved therapy
Mobilization	CTX+G-CSF	CTX+G-CSF	G-CSF+Pred	CTX+G-CSF
Graft Processing	Unselected	Selected	Selected	Unselected
Conditioning	BEAM+ATG	BuCTX+ATG	BEAM+ATG	CTX+ATG
Status	Terminated	Finished	Enrolled	Enrolling

Proposal #1: Background & Significance

Canadian Multiple Sclerosis Bone Marrow Trial

Relapses

Prior to HCT: 167 in 146 pt-yrs.

Following HCT: 0 in 160 pt-yrs.

MRI Activity

Prior to HCT:

1st scans: 93 Gad+ lesions

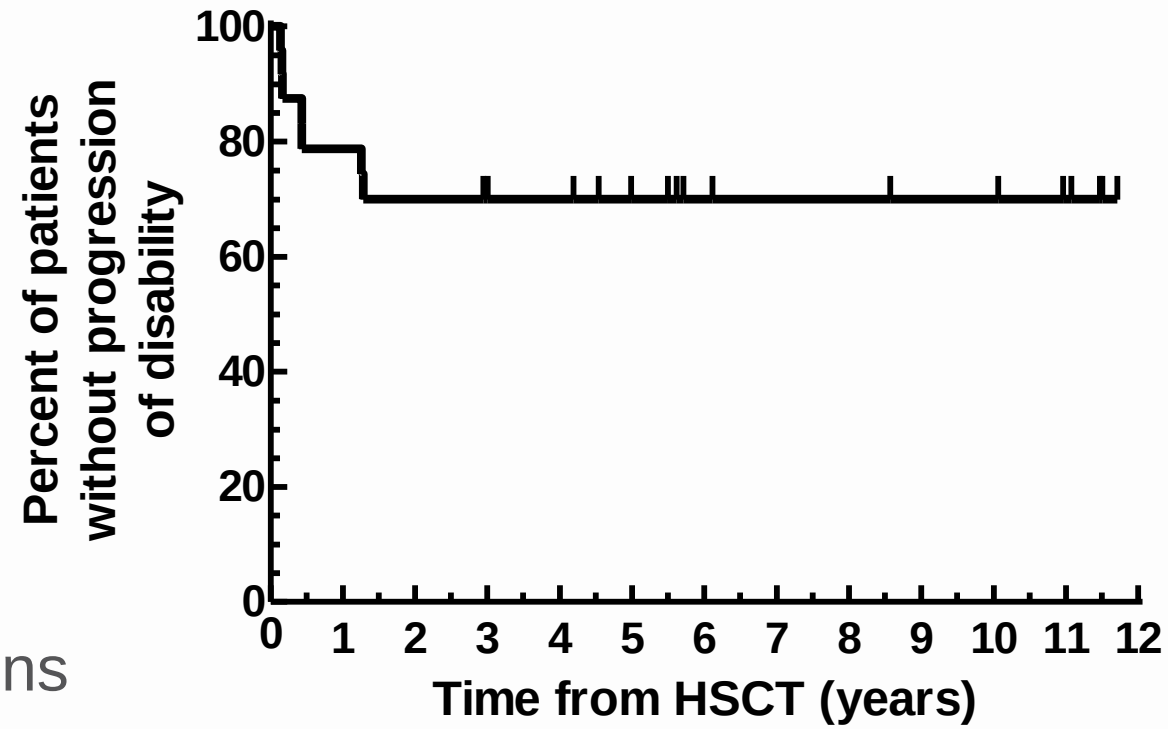
2nd scans: 95 Gad+ lesions

94 new T2 lesions

Following HCT:

314 scans: no Gad+ or new T2 lesions

MS Progression Free Survival After HSCT

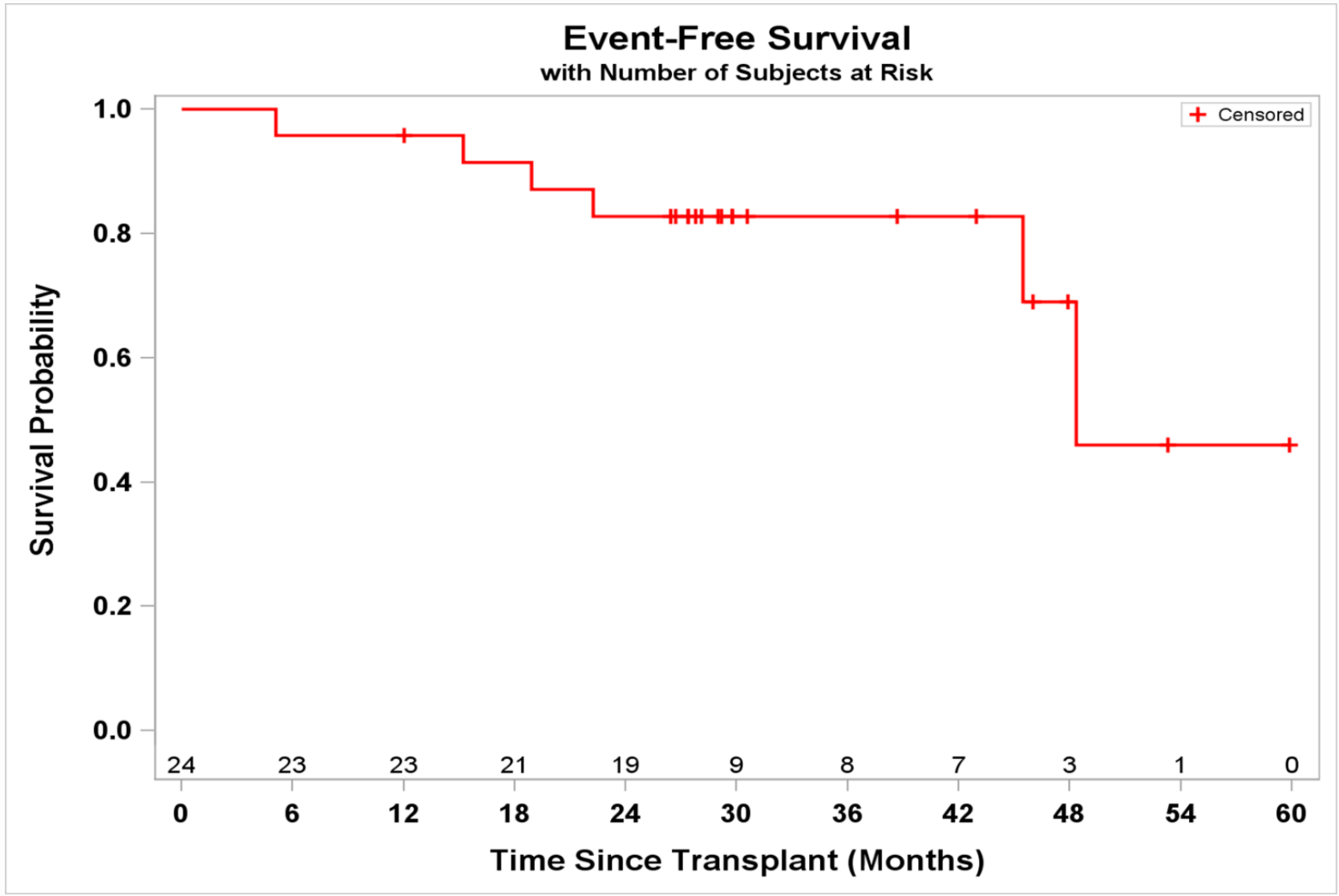


BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Atkins H – personal communication Nov 2014.

Proposal #1: Background & Significance

HALT-MS 3 year Interim analysis.



Nash R. et al. *JAMA Neurol*. 2015;72(2):159-169

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design (1)

- 2 arm RCT (1:1) with blinded MS evaluations
  - Arm 1: Best Available Conventional Disease-Modifying Therapy (DMT)
  - Arm 2: Autologous HCT
- Patient Selection
  - 18-45 years old
  - Evidence of highly active RRMS over the 2 years prior to enrollment
  - Within 5 years of diagnosis
  - Expanded Disability Status Score between 2.5 and 5.5 (able to walk 100m but ADL impaired)
  - Failed at least 1 conventional DMT but remain eligible to receive one further DMT

Proposal #1: Trial Design (2)

- Primary Endpoint
  - Inflammatory Disease Free activity at 2 or 3 years (no relapses, no Gd+ or T2 MRI lesions)
- Secondary Endpoints
  - Severe TRM (including 2^0 autoimmunity)
  - Treatment-free inflammatory disease-free survival (DFS)
  - Freedom from sustained accumulated disability
  - Sustained improvement in disability
  - Quality of Life analysis
  - Health economic analysis

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design (3)

- Treatment Failure
  - Severe clinical relapse, new or enhancing MRI lesion or sustained progression of expanded disability status scale (EDSS)
- Sample Size
  - Estimated to be at minimum 60 patient/arm
  - Assumes 90% power to detect improvement in DFS from 60% to 80%
- Extension Study
  - Freedom from sustained accumulation of disability at 5 or 7 years
  - Examine outcome of patients that experience treatment failures

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics (1)

HCT details require further discussion and broad consensus by participating investigators

- Mobilization
- Graft Selection
- Conditioning Regimen
- Post HCT supportive care

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics (2)

Differences exist between this proposal and a published international consensus document

- Difference in patient selection
  - This proposal allows more encompassing inclusion criteria.
- Elimination of the cross-over design which would hinder the ability to draw conclusions about MS progression and health economics.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Saccardi R et al. Mult Scler. 2012 Jun;18(6):825-34.

Proposal #1: Feasibility & Logistics (3)

Trial Funding

- Insurance companies may be interested in participating due to the high and ongoing costs of conventional MS treatment.
- Challenges associated with funding a multicenter trial from non-commercial sources in different jurisdictions.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics (4)

Recruitment

- Competing Pharmaceutical Trials
- Number of centers and time required
  - Median enrollment 3.8 patients/center/year
  - Enroll from 15 MS centers for 2 years or 10 MS centers for 3 years.
  - Adding European sites would speed enrollment but complicate trial management and regulation
- Publication of 3 active studies would aid enrollment

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Other Ongoing BMT CTN Initiatives in Non-Malignant Diseases

- BMT CTN 0301: Dose-optimization study of conditoning for unrelated donor HCT for aplastic anemia*
- BMT CTN 0601: Unrelated donor HCT for children with severe sickle cell disease – accrual complete; follow-up continues
- BMT CTN 1204: AlloHCT for hemophagocytic lymphohistiocytosis – 27 of 35 patients accrued
- BMT CTN 1501: Haploidentical/umbilical cord HCT for aplastic anemia – protocol development
- BMT CTN collaborating in R01 application for large multicenter Phase II study in young adults with severe sickle cell disease

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

*Anderlini P. *Blood.* 2014;124:541

Pediatric Indications and Approaches Committee

Chair: Michael Pulsipher, MD
University of Utah

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- Stephan Grupp − Children's Hospital of Philadelphia
- Robert Krance −Texas Children's Hospital, Houston
- Joanne Kurtzberg − Duke University, Durham
- Eric Leifer − NHLBI, Bethesda
- John Levine − University of Michigan, Ann Arbor
- Parinda Mehta − Cincinnati Children's Hospital
- Sung-Yun Pai − Boston Children's Hospital/DFCI
- Kirk Schultz − BC Children's Hospital, Vancouver
- Shalini Shenoy −Washington University, St Louis
- Michael Verneris –University of Minnesota, Minneapolis
- Donna Wall− University of Manitoba, Winnipeg

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Overview of the Discussion

- Evaluation of response to treatment in children transplanted for neurological disorders
  - Discussion: small sample size and focus of transplants in a few larger centers limited feasibility
- Relapse post-transplant in children with acute lymphoblastic leukemia
  - Most significant cause of treatment failure in one of the most frequent indications for transplantation in children

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Background & Significance

- Pre-B ALL is a key indication for pediatric HCT
- Relapse is the main cause of failure:
  - Rates vary from 25-70%, most within 1 year

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

CIBMTR Data Ph-, B-lineage ALL, Myeloablative HCT between 2008-2012

Group	Grade aGVHD	2yr DFS	2yr Relapse	2yr TRM
CIBMTR (<18yo)	0	59%	31%	11%
(2008-2012, N=251)	I-II	70%	19%	11%
	III-IV	59%	19%	22%
CIBMTR (≥18yo)	0	47%	36%	17%
(2008-2012, N=322)	I-II	53%	26%	21%
	III-IV	29%	10%	61%

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

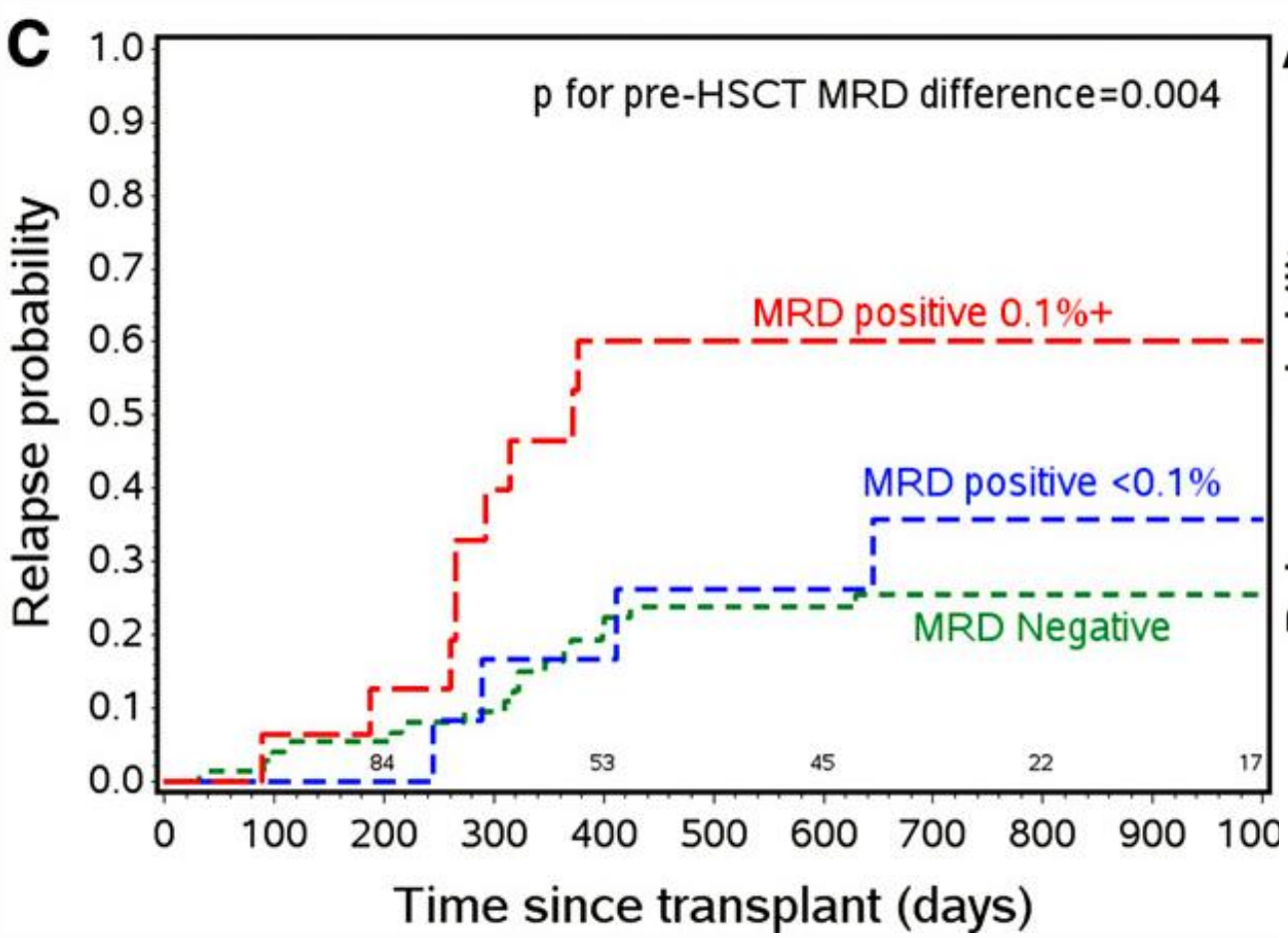
Proposal #1: Background & Significance

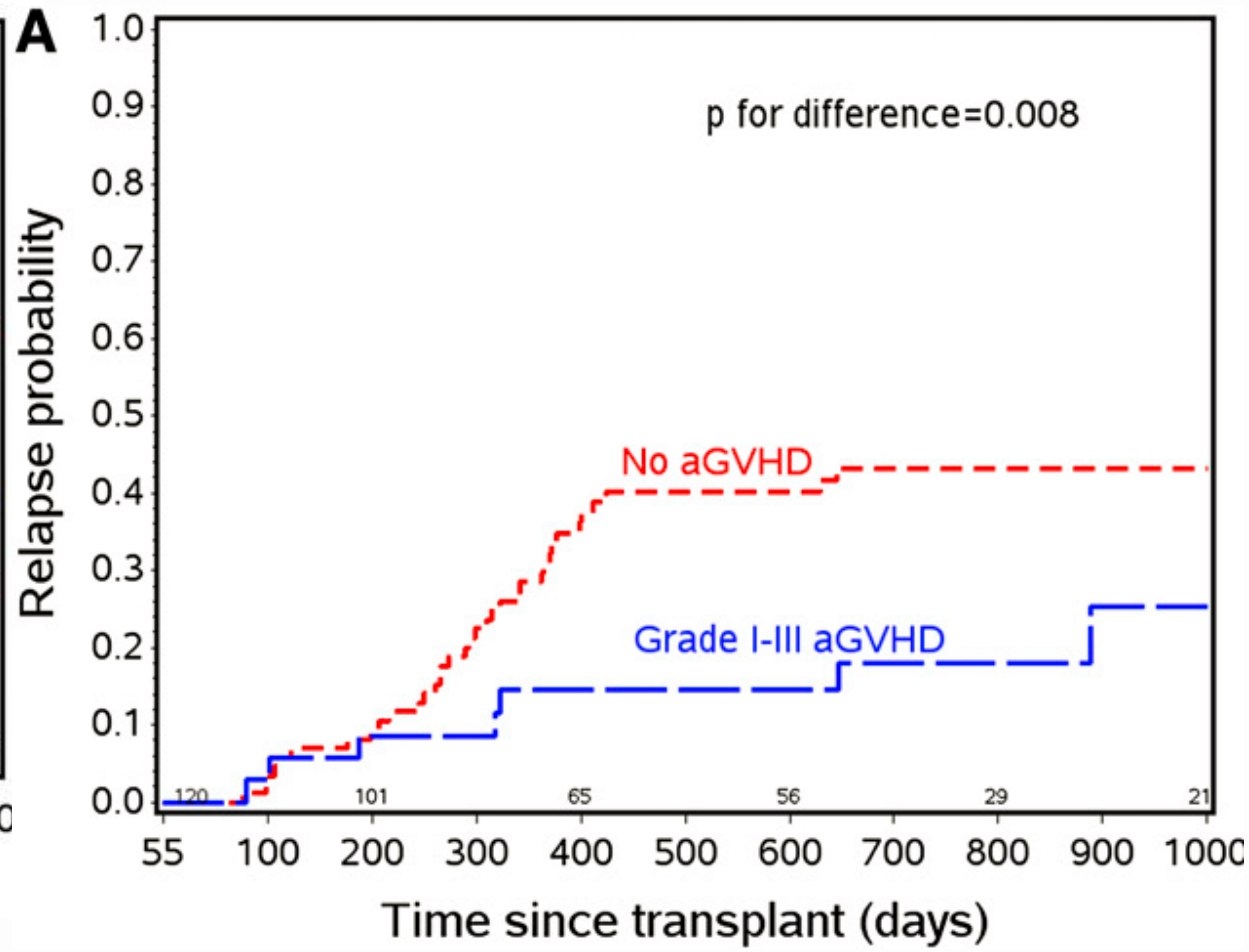
Two factors define risk of relapse after transplant for ALL:

- Pre-HCT minimal residual disease (MRD)
- Development of acute GVHD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

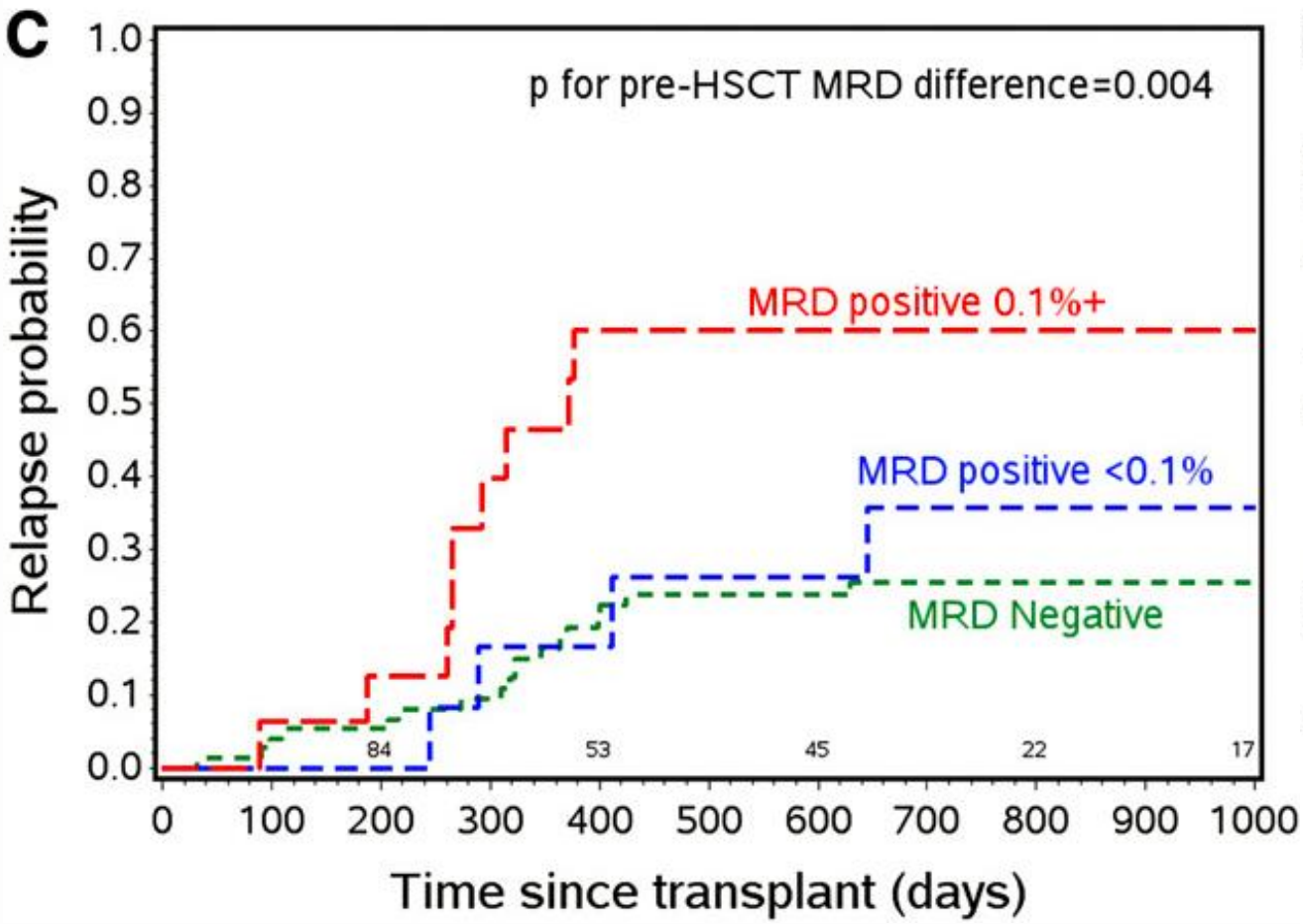
Relapse by Pre-HCT MRD Status and acute GVHD (N=143)

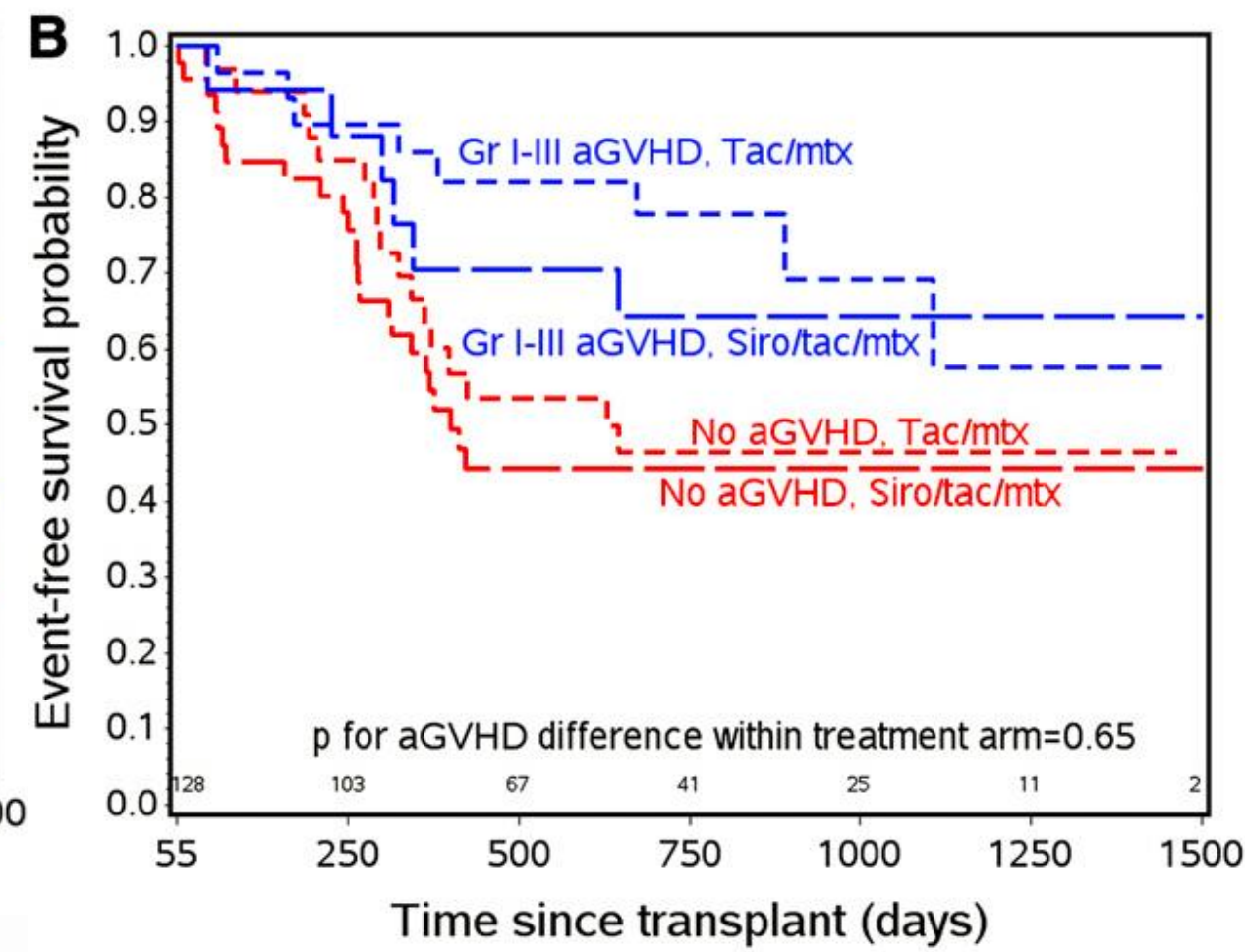




Pulsipher M, et al. Blood 2014; 123(13):2017-25

Combined Effect of acute GVHD and pre-HCT Minimal Residual Disease (N=143)





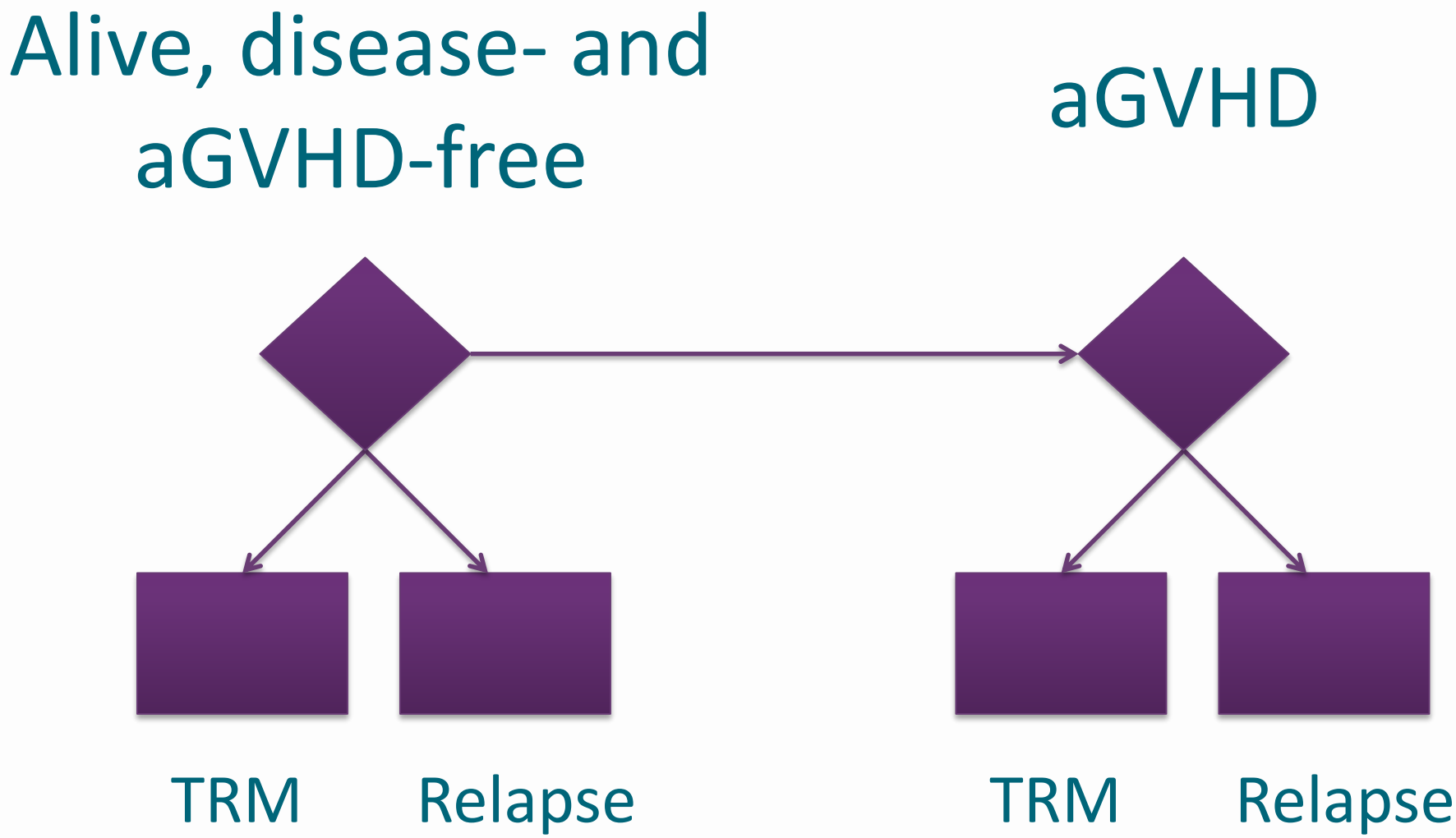
Pulsipher M, et al. Blood 2014; 123(13):2017-25

Can we prevent post-HCT relapse?

- Centers give therapy to minimize MRD+ by the time of HCT
- Even MRD negative patients relapse at excessive rates
- Intervention in patients with complications (GVHD, etc.) is challenging
- When can we intervene safely?

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

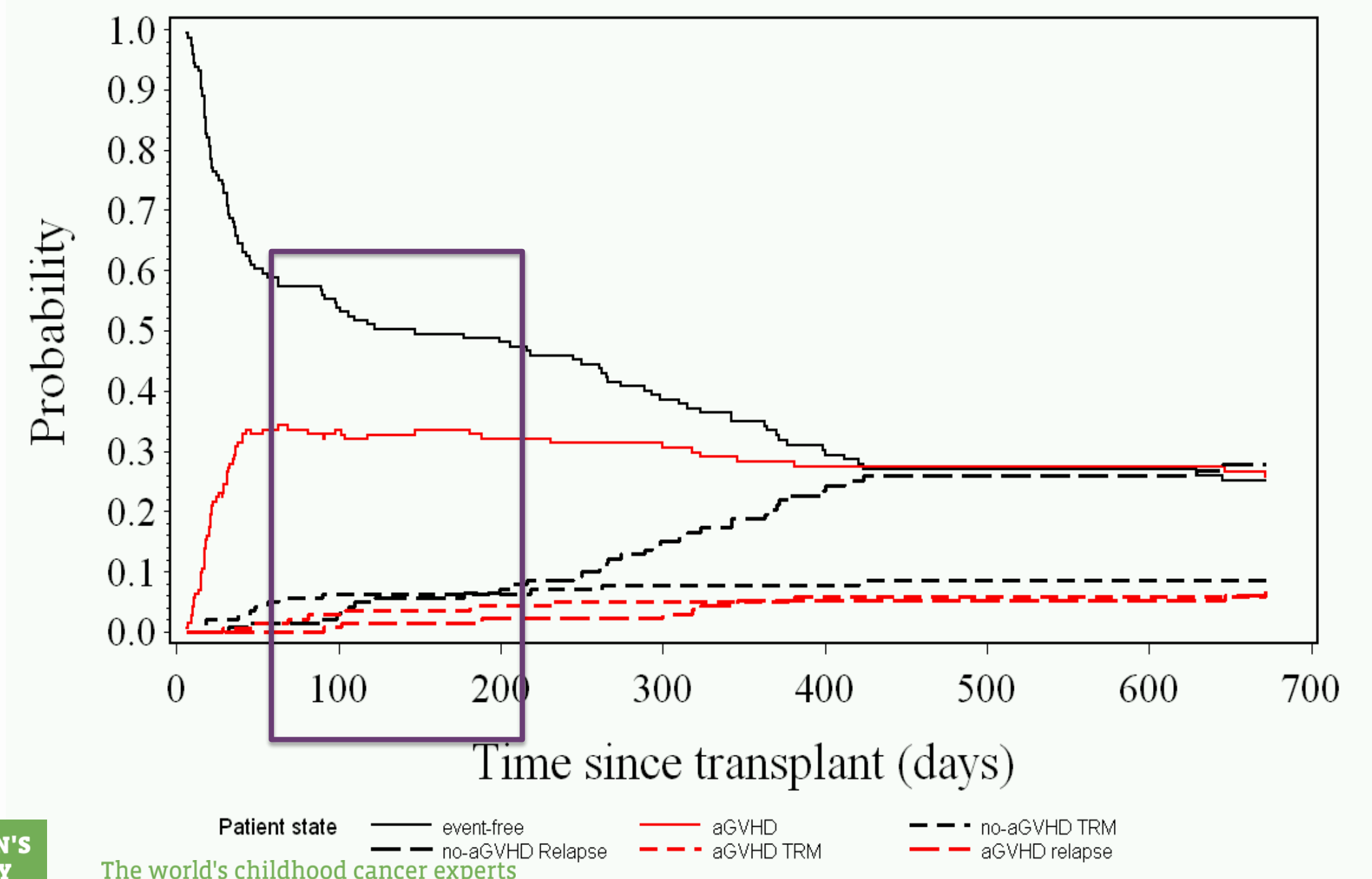
Aalen-Johannsen non-Parametric Event-Time Probability: Tracking Post-HCT Events



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Distribution of patients by acute GVHD, transplant-related mortality, relapse status



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

Pulsipher M et al, Blood. 2012;120:470

Possible Approaches to Post-HCT Intervention

- Intervention post-HCT with rapid taper and immune-active agents
  - Potential for GVHD-related toxicity
  - Pilot trial in Children's Oncology Group
- Intervention post-HCT with agents that do not depend on a functional immune system
  - Treat with maintenance therapy
  - Bridge to a more robust immune system

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design

- Study Design:

  Randomized phase II with comparison to a control group

- Primary Objective:

  2 year disease-free survival (DFS) improvement of 17% (from 53 to 70%)

- Approach:

  Enroll patients with no acute GVHD by d+55

  Myeloablative conditioning, any donor, T-replete, CR

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Treatment Plan

- Stratify by minimal residual disase (MRD+) with >0.1%, central flow, graft source
- Begin therapy as early as day +60
- Intervene at 6-9 months post-HCT with agents
  - Bridging to reconstituted immune system
- Taper immune suppression at standard times

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

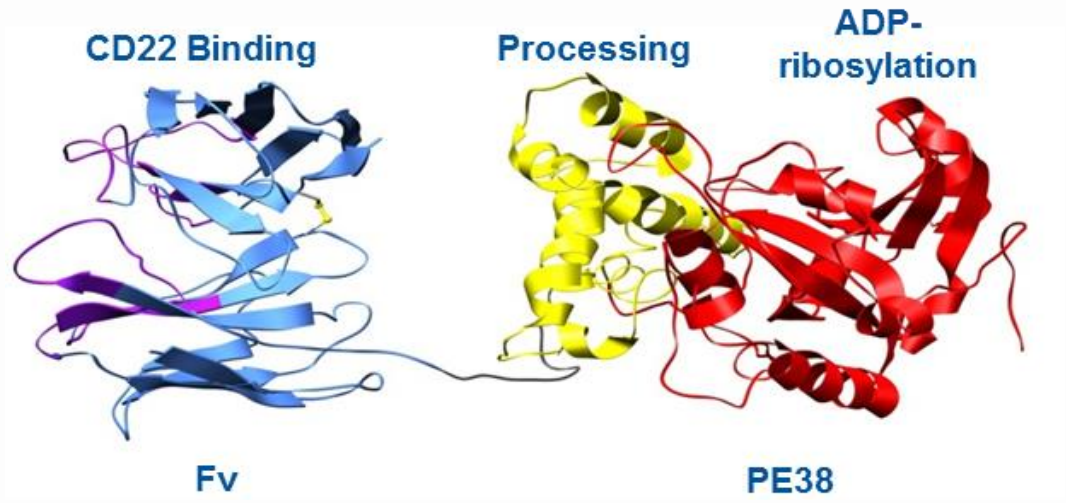
Agents

- Target B-ALL
- Immunotoxins, not dependent upon immune recovery
- Could be platform for testing serial agents

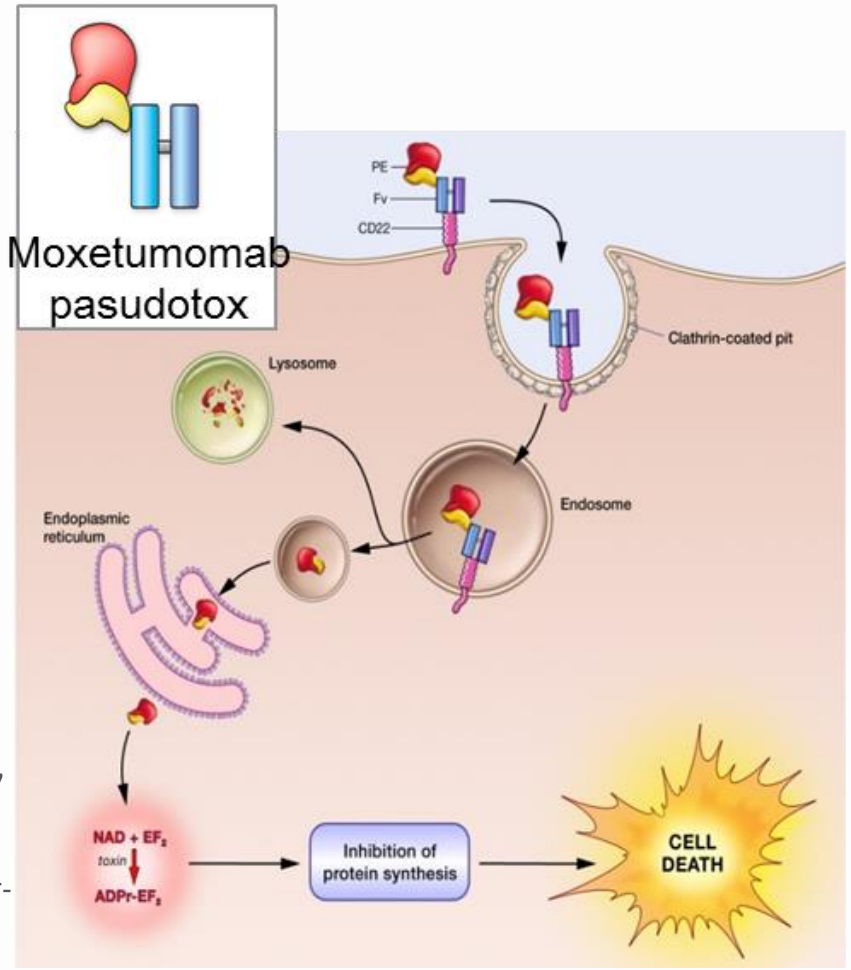
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Moxetumomab Pasudotox

- Anti-CD22 immunotoxin
  - Murine fragment (Fv) against human CD22
  - Truncated Pseudomonas exotoxin A (PE38)



- After binding to CD22
  - Immunotoxin is internalized by endocytosis
  - Toxin is released intracellularly by proteolysis
    - Inhibition of protein synthesis
    - Apoptosis



Wayne AS. Blood. 2014;123(16):2470-2477

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Efficacy Data of Proposed Agents

- Moxetumomab Pasudotox
  - Phase I/II data in pediatrics
  - Overall response rate 72%, R/R disease
  - CR 27% post-HCT, Overall response 67%

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics

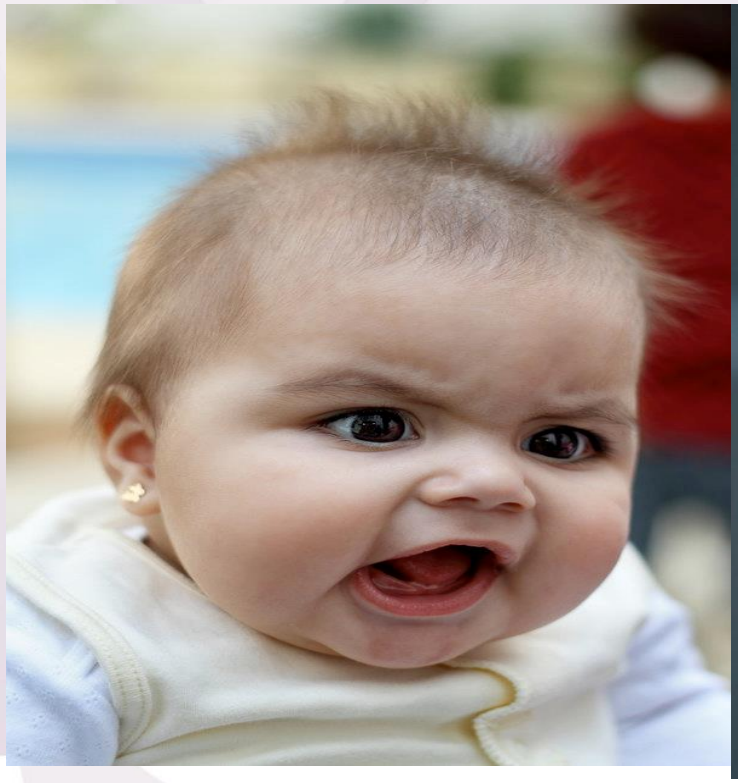
- CIBMTR data - 285 pts/year in the US eligible
  - Includes alive at d+55, no acute GVHD
  - Assume 25% enrollment, 71/year
- 2 year DFS 53% (improve DFS to 70%, decrease relapse by 50%)
  - Testing 2 agents vs. control with 80% power at the one-sided $\alpha = 0.1$ for each comparison, 255 pts needed
  - Accrual time of 3.6 years

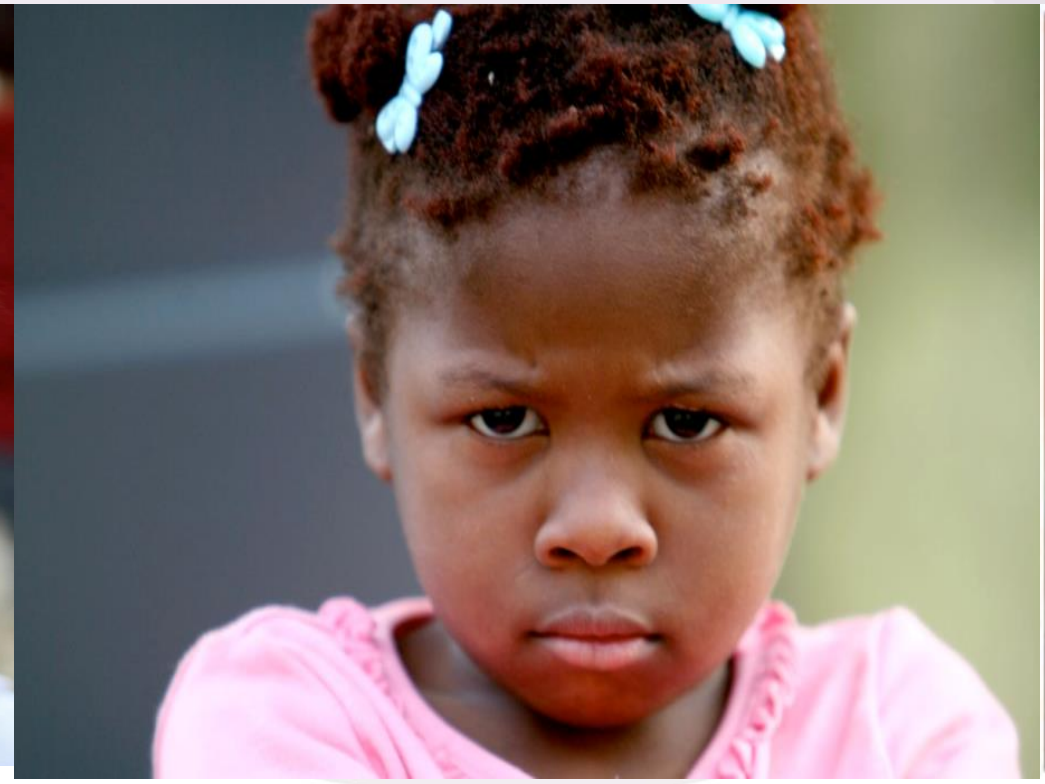
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Pediatric Outcomes Committee

Eliminating Steroid Toxicity in Children

Chair: Stella Davies





BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- Farid Boulad, MD – Memorial Sloan Kettering, New York
- Scott Baker, MD – Fred Hutchinson, Seattle
- Paul Carpenter, MBBS - Fred Hutchinson, Seattle
- Christy Duncan, MD – Dana Farber, Boston
- Mary Eapen, MBBS – Medical College of Wisconsin, Milwaukee
- David Jacobsohn, MD – Children's National, Washington
- Amy Keating, MD – University of Colorado, Aurora
- Carrie Kitko, MD – University of Michigan, Ann Arbor
- Margaret MacMillan, MD – University of Minnesota, Minneapolis

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Steroid Toxicities That Are Particularly Challenging in Children

- Impaired growth and failure to thrive
- Avascular necrosis
- Behavioral changes: aggression, irritability, mood swings, impaired learning
- Appearance changes
  - Cushingoid facies
  - Weight gain
  - Sparse hair
  - Striae

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Steroid Toxicities That Are Particularly Challenging in Children

- **Short term goal:** to reduce steroid toxicity in children with GVHD

- **Long term (stretch) goal:** to eliminate steroids in the treatment of children with GVHD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Why Do we Need Pediatric-Specific GVHD Studies in CTN?

- GVHD in children is likely similar physiologically to GVHD in adults
- Children are quite different from adults in:
  - Drug metabolism
  - Drug dosing and administration- liquid formulations
  - Importance of growth - an equipotent therapy that preserved growth would be an advance
  - Importance of behavior and learning
  - Tempo of immune reconstitution after transplantation (functional thymus)

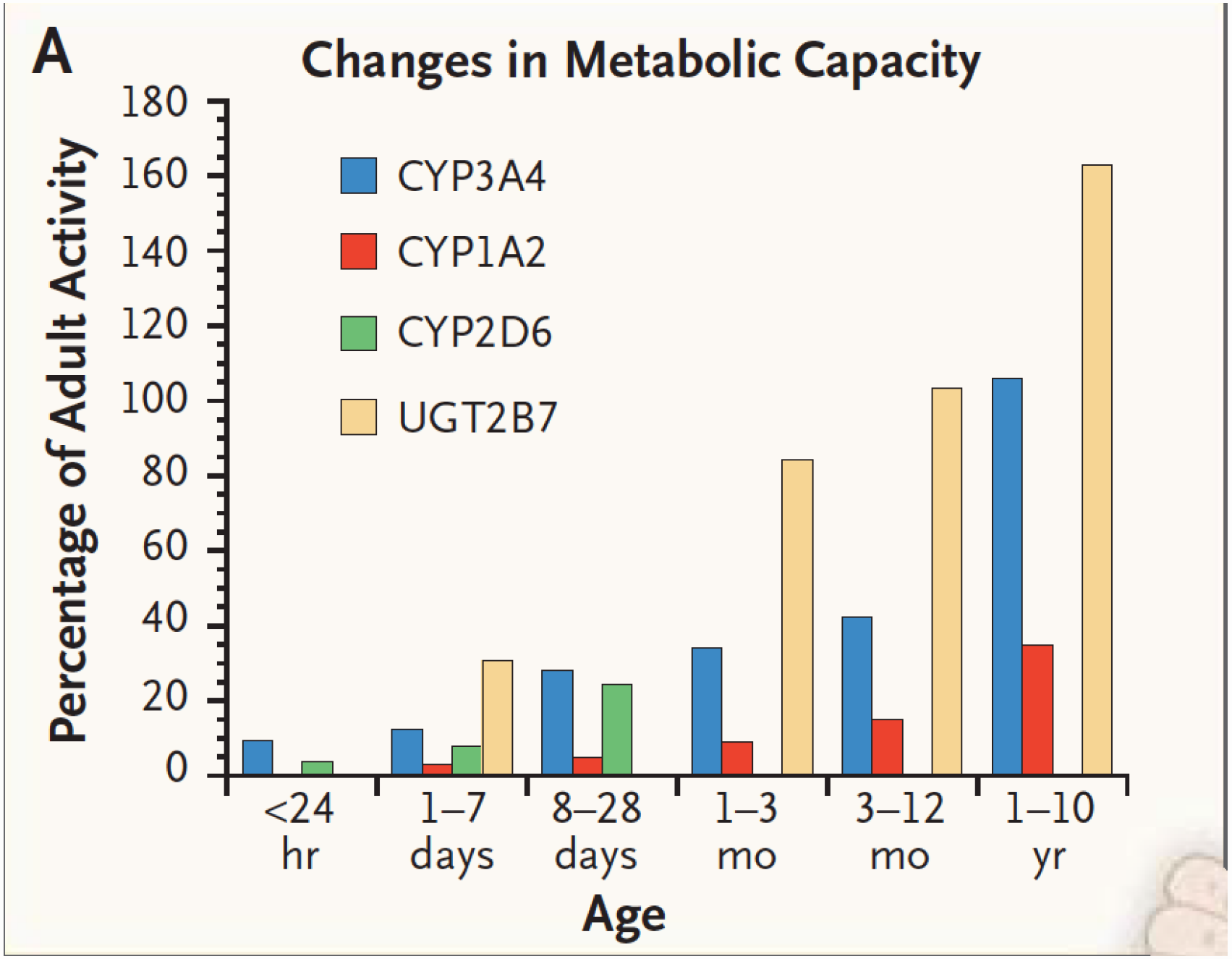
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Differences in Drug Disposition Between Children and Adults

- Absorption variable with age
- Body composition different (babies 80% water, adults 60%) - volumes of distribution differ
- GFR changes with growth
- Skin thinner in small children- increased absorption of topical meds
- Adherence- great when mom in charge, terrible when teenager in charge

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

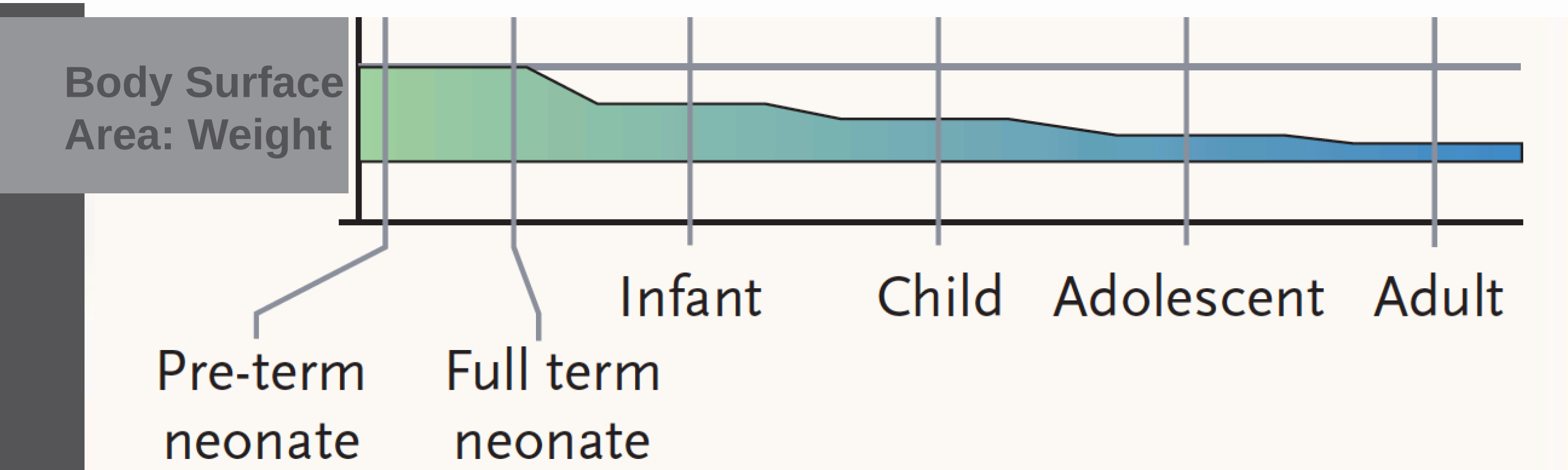
Age-based Changes in Drug Metabolism



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Kearns GL, et al. NEJM. 2003; 349:1157-1167

Relationship Between BSA and Weight



Kearns G, et al. NEJM. 2003; 349:1157-1167

Strategy

To address our short term goal of reducing steroid toxicity we propose 3 studies that could be completed in the next grant period:

1. Optimization of steroid dosage in chronic GVHD
2. Reduction in frequency of acute GVHD using bortezomib
3. Reduction of frequency of chronic GVHD using rituximab

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Daily (QD) vs alternating day (QOD) dosing of steroids in cGVHD

- **A Fundamental Question:**
  - Are QD or QOD steroid tapers best for chronic GVHD?
  - After ~35 years we still don't know!
  - The answer might unify practice ***and*** inform the design of future trials intent on testing novel steroid-sparing agents.
- Pediatric practice survey suggested 54% use QOD and 46% use QD; the split presumably based on the notions:
  - QOD equally efficacious but safer than QD
  - QD is tolerable, but more efficacious and simpler than QOD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Background & Significance

- Data supporting QOD is up to 5 decades old, poorly controlled and derived from non-HCT populations
- Prevention of life-changing steroid toxicities is of utmost importance to pediatrics
  - If one or other steroid regimen is proven to be inferior, then practice harmonization alone could mitigate harm
- The pediatric cooperative group study paradigm of sequential permutations has been very successful
  - And lends itself to a critical evaluation of the steroid backbone that underpins chronic GVHD therapy

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Steroid tapers prescribed by 3 representative pediatric centers suggest similar total exposures regardless of schedule…

Steroid Taper	Total Duration (days)	Total (mg/kg)
Seattle (QOD)	343	**127**
Minnesota (QOD)	238	**126**
Michigan (QD)	238-307	**127** (99-154)

…forming an ideal starting point to address our question

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Background

- Failure-free survival (FFS) = absence of secondary therapy, non-relapse mortality (NRM) and relapse of underlying disease during primary therapy
- FFS at 6 months with prednisone ≤ “0.X” mg/kg/day is an objective, clinically meaningful primary-endpoint for a chronic GVHD steroid therapy trial*
- Incorporating a prednisone upper limit enhances the clinical benefit associated with FFS since it:
  - Indicates that GVHD was well controlled
  - Reduces risk of steroid-toxicities
  - Lower doses at 6 mo. correlate with subsequent withdrawal of immune suppressive therapy

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

**Inamoto et al, Blood 2013:121(12)*

Proposal #1: Background (2)

- In a phase III study to compare prednisone regimens, even more relevant than the FFS comparison would be a comparison of “Disability free survival” (DFS)
- A difference in DFS between two steroid regimens would strongly signal clinical benefit because the DFS endpoint would be designed to incorporate major steroid toxicities into the FFS definition
- Benchmarks for the steroid disabilities of interest would first be needed

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design

- Therefore a 2-step approach is proposed:
  1. A randomized phase II comparing QD vs QOD within this grant cycle followed by…
  2. A larger phase III comparing Disability Free Survival for the QD vs QOD arms

- Phase II primary endpoint = comparison of BMI Z-scores among children in each arm at 6 months
  - Ho = QOD prednisone tapers will not lower the group BMI Z-score at 6 months compared to QD prednisone tapers
  - Ha = QOD tapers ***do*** lower the BMI Z-score at 6 months compared to QD tapers

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Trial Design

Secondary endpoints

- Calendar driven toxicity data collection
- Select most informative thresholds for toxicities, e.g.:

1. Bones (development of AVN, or DEXA scan Z-scores < -2.0)
2. Anthropometry: Height velocity, total body fat by DEXA scan, Arm-muscle area changes over time
3. Number and type of behavioral interventions
4. Myopathy: 5-point MMT and 3 other simple P.T. tests
5. Number of meds to control hypertension, hyperglycemia
6. Infection rates (invasive fungal, viral, bacterial)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposal #1: Feasibility & Logistics

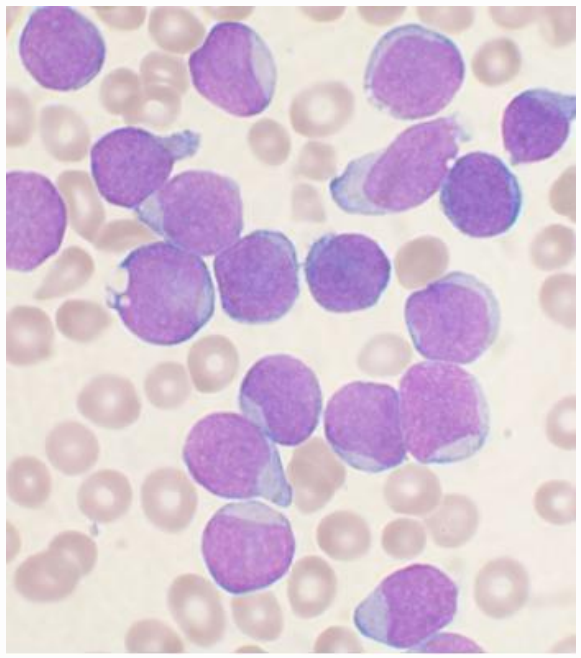
- Sample size estimates are based on the desire to demonstrate a 0.5 reduction in BMI Z-score
- ~300 cases p.a.

  with 25% BMT CTN “accrual reality check”
- ~75 cases estimated annual accrual
- 2.33 years of accrual to achieve ~75 per arm allowing for 25 drop outs

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Conclusions

- BMT CTN offers the opportunity to collaborate with other disciplines to compare HCT and non-HCT therapies in non-malignant disorders in which HSCT is a novel approach, e.g. multiple sclerosis
- A simple study design can potentially allow serial testing of multiple potential post-transplant therapies to reduce relapse in children with ALL
- Steroids cause significant toxicities after transplant and a focused series of trials to reduce these toxicities would benefit children, in whom steroids toxicities are magnified by effects on growth development and behavior.



BLOOD AND MARROW
TRANSPLANT
CLINICAL TRIALS NETWORK

Questions from the live event on Dec. 5, 2014

Access a Certificate of Attendance

(will open in new browser tab)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Optimal Donor & Graft Sources, Infection & Immune Reconstitution, Gene & Cell Therapy

John R. Wingard, MD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Financial Disclosure

Company	Role with Company
Pfizer	Speaker
Astellas	Consultant
Ansun Biopharma	Consultant
New England Research Institute	Consultant

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Optimal Donor and Graft Sources Committee Report

Claudio Anasetti, M.D.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Introduction

- Summary of Key Progress
  - Phase III trial of marrow vs peripheral blood for unrelated donor allogeneic transplants (BMT CTN 0201) showed similar 2 year survival
  - Parallel phase II trials of double cord and haploidentical marrow (BMT CTN 0603, 0604) showed similar 1 year survival; phase III trial (1101) now underway
- Current issues
  - Lack of histocompatible graft sources is a major limitation to the treatment of hematologic and immune disorders with allogeneic HCT

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Strategies Considered

1. Facilitate engraftment of HLA disparate cord blood transplantation using ex vivo CB priming or expansion
   a) 8 ongoing trials, 3 in advanced stages of development
   b) Discussion: Given studies are already established & accruing, members are encouraged to participate in the ongoing trials
2. Optimize HLA-DPB1 compatibility for nearly every patients with an unrelated donor
   a) Use of permissive DPB1 matches may improve outcomes
   b) Discussion: a less costly retrospective study is encouraged
3. Conduct phase II study of haploidentical peripheral blood stem cell transplantation with post-transplant cyclophosphamide following myeloablative conditioning

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II study of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide (PTCY) following myeloablative conditioning

- Hypothesis
  - PTCY prevents GVHD lethality of HLA-disparate, T-replete HCT in myeloablated hosts
  - PTCY produces similar transplant outcomes with HLA-disparate related or HLA-matched volunteer donor transplants

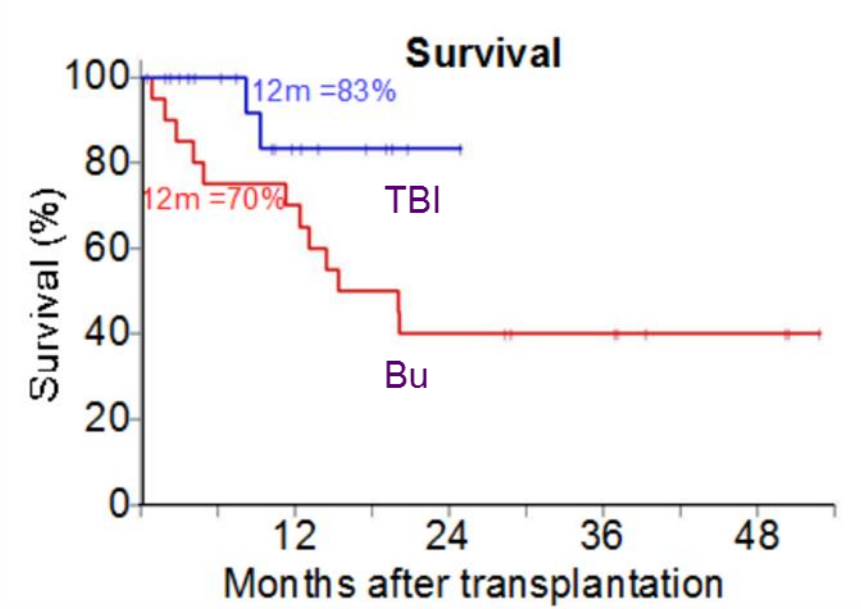
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

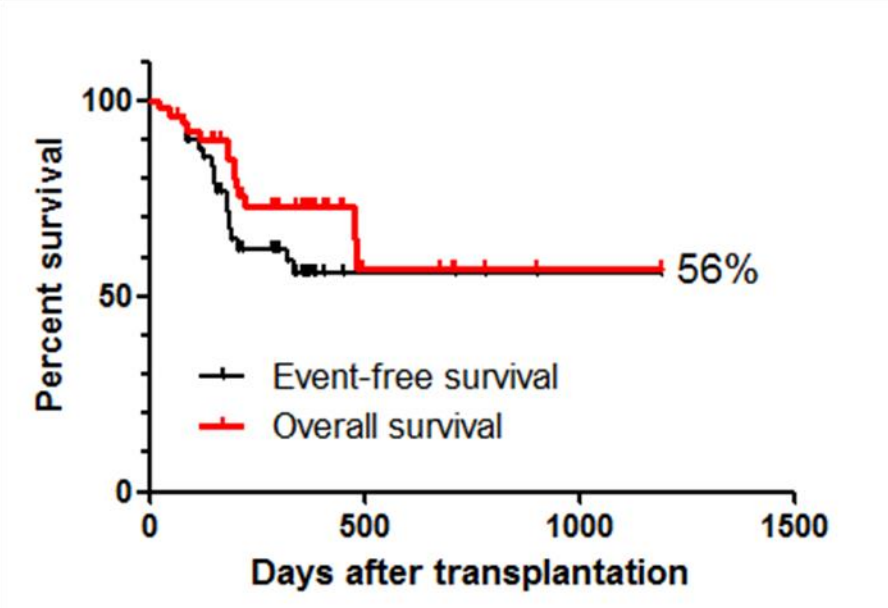
Phase II study of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide following myeloablative conditioning

- Background
  - An adult relative who shares one HLA-haplotype is almost universally available
  - PTCY has been utilized after non-myeloablative conditioning (BMT CTN 0603 and 1101)
  - 4 pilot trials (at Hopkins, Northside, Fred Hutchinson, San Martino) suggest outcomes are excellent after ablative conditioning
  - Healthier patients can benefit from an ablative conditioning

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Pilot studies of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide following myeloablative conditioning





- Solomon SR, Biol Blood Marrow Transplant 2012; 18: 1859
- Solomon SR, Blood 2013; 122:3351a
- Fuchs E, Unpublished

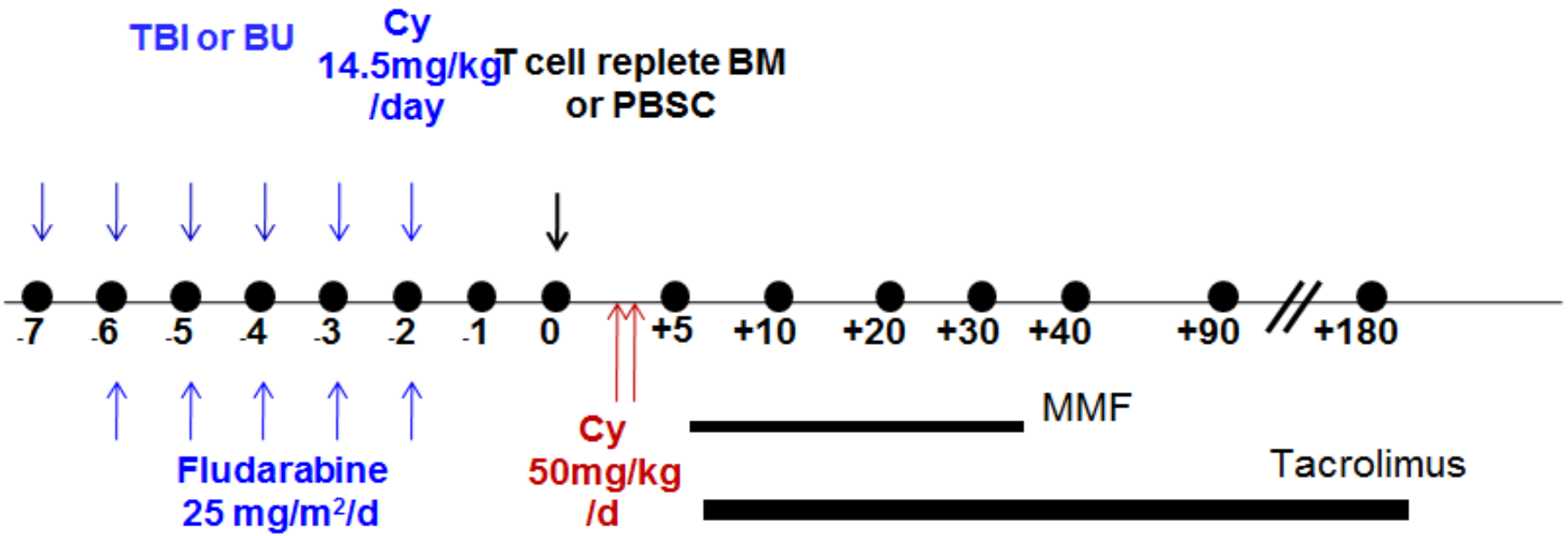
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II study of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide following myeloablative conditioning

- Trial Design
  - Multi-center, single arm phase II study
  - GVHD prophylaxis: PTCY followed by tacrolimus plus mycophenolate mofetil
  - Regimen: includes myeloablative doses of total body irradiation or busulfan
  - Graft: marrow or blood stem cells
  - Primary endpoint: one-year survival

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II study of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide following myeloablative conditioning



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase II study of haploidentical peripheral blood stem cells & post-transplant cyclophosphamide following myeloablative conditioning

- Feasibility & logistics
  - Sample size: 62
  - Power: 84% to rule out $\leq$ 43% survival (alpha=0.10)
  - We expect accrual to be completed within 2 years
  - Exploratory analysis: compare survival with similar transplants from HLA-matched unrelated donors
  - Data comparing trial results to unrelated donor transplant outcomes from the CIBMTR will provide the requisite to design comparative prospective studies

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- Claudio Anasetti – H.Lee Moffitt CC, Tampa
- Juliet N. Barker – Memorial Sloan Kettering, NY City
- Asad Bashey – BMT Group of Georgia, Atlanta
- Claudio Brunstein – University of Minnesota, Minneapolis
- Dennis Confer – NMDP/Be The Match, Minneapolis
- Sara Cooley – University of Minnesota, Minneapolis
- Corey S. Cutler – Dana-Farber Cancer Institute, Boston
- John DiPersio (ad hoc) – Washington Univ, St Louis
- Ephraim P. Fuchs – Johns Hopkins, Baltimore
- John A. Hansen – Fred Hutchinson CRC, Seattle
- Elizabeth J. Shpall – MD Anderson, Houston
- Adam Mendizabal (Stat) – EMMES Corp, Rockville
- Leo Luznik (Design) – Johns Hopkins - Baltimore

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Infection & Immune Reconstiution Committee Report

John R. Wingard, M.D.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Introduction

- Summary of Key Progress
  - Fluconazole is not inferior to voriconazole for antifungal prophylaxis after allogeneic HCT, & is less expensive (BMT CTN 0101)
- Current issues
  - Persistent CMV infections still problematic & therapies are toxic
  - Respiratory viral infections are increasingly recognized as substantial contributors to respiratory morbidity/mortality

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Strategies Considered

- Evaluate stepped-intervention program to reduce infections in allogeneic HCT recipients
  - Discussion: Pilot data are needed to determine rates, effect sizes
- Conduct randomized phase II trial of adoptive immunotherapy using banked third party CMV-specific T cells for refractory CMV infection
  - Developed jointly with Cell Therapy Committee
- Conduct randomized phase III trial of novel parainfluenza virus (PIV) entry inhibitor in HCT recipients with PIV upper respiratory tract infection (URTI)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase III trial of novel PIV entry inhibitor in HCT recipients with PIV URTI

- Hypothesis
  - DAS1 (Ansun Biopharma) given for treatment of PIV URTI in HCT recipients will reduce progression to lower respiratory tract disease (LRTD)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase III trial of novel PIV entry inhibitor in HCT recipients with PIV URTI

- Feasibility & Logistics
- Assumptions:
  - Symptomatic PIV URTI occurs in 7-8%*
    Duke, FHCRC
  - Progression to LRTI :15%
  - 140 patients per arm will detect reduction from 15% to 5% (power 82%)
  - We expect accrual to be complete in 2 years

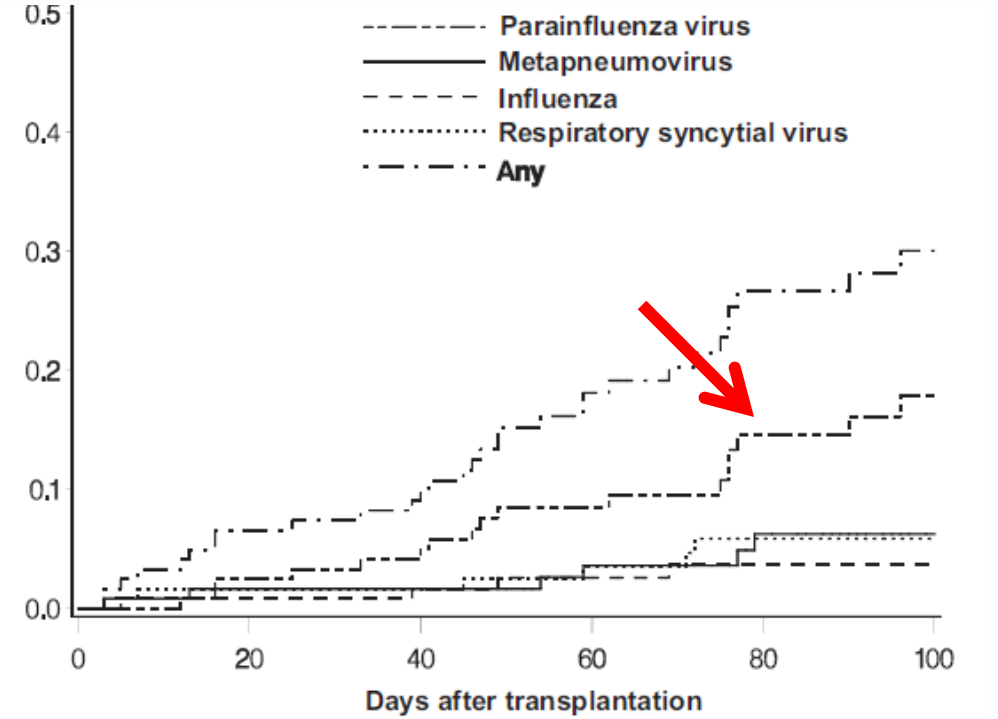


Figure 1. Cumulative incidences of first infection episodes of PIV, MPV, influenza, and RSV after transplantation in 122 HCT recipients.

*Peck AJ, Blood. 2007;110:1681-1688

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase III trial of novel PIV entry inhibitor in HCT recipients with PIV URTI

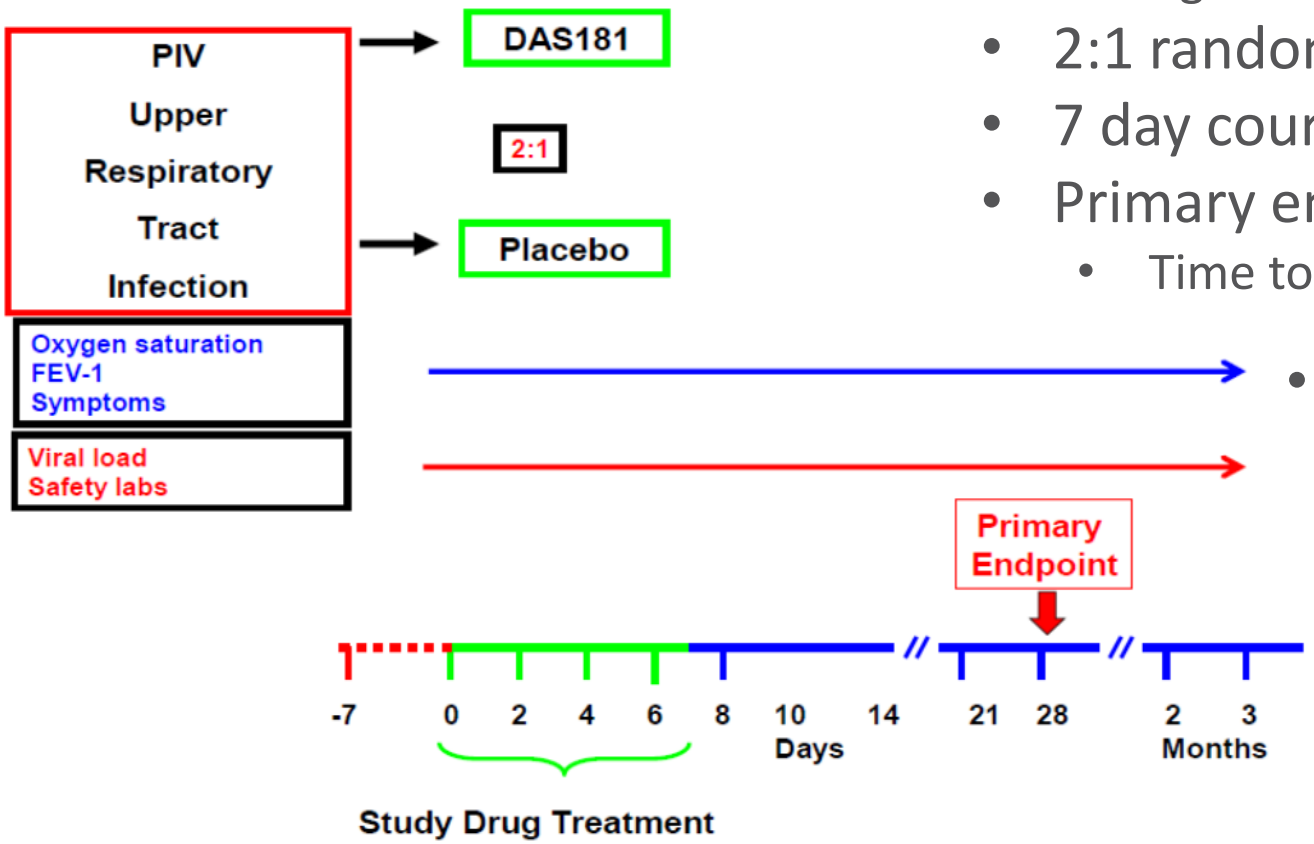
- PIVs are major respiratory pathogens
  - Associated with fatal pneumonia
  - Associated with late airflow decline*
    - URTI: OR = 1.8
    - LRTI: OR = 17.9
    - Risk from PIV infection >> RSV
- Infection usually begins as URTI, then progresses to LRTI
  - Risk factors: lymphopenia, GVHD, high dose steroids**
- No effective therapy
- DAS181 is a novel sialidase viral receptor blocker on respiratory tract epithelial cells
  - Active against PIV & influenza***

*Erard V, J Infect Dis 2006; 193: 1619
**Boeckh M, Br J Haematol 2008; 143: 455
***Malakhov MP, Antimicob Agents Chemo 2006; 50: 1470;
Moscona A, J Infect Dis 2010; 234

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase III trial of novel PIV entry inhibitor in HCT recipients with PIV URTI

Trial Design



- PIV URTI in HCT recipients
  - Age>12
- 2:1 randomization
- 7 day course of therapy
- Primary endpoint:
  - Time to progression to LRTI

- Definition of LRTI
  - Hypoxia <92% O2 saturation; &/or
  - New pulmonary infiltrate with PIV in BAL

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- Michael Boeckh - Fred Hutchinson CRC, Seattle
- Nelson Chao – Duke University, Durham
- Mitchell Horwitz – Duke University, Durham
- Kieren Marr – Johns Hopkins, Baltimore
- Richard O'Reilly – Memorial Sloan Kettering, New York
- Stan Riddell - Fred Hutchinson CRC, Seattle
- Ned Waller – Emory University, Atlanta
- Marcel van den Brink – Memorial Sloan Kettering, New York
- Clinical Trial Design liaisons
  - Leo Luznik – Johns Hopkins, Baltimore
  - Joycelynne Palmer – City of Hope, Duarte

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Cell and Gene Therapy Committee Report

Helen Heslop, M.D.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Introduction

- Summary of Key Progress
  - Multicenter T cell depletion trial (BMT CTN 0303) demonstrated feasibility for Network to conduct graft manipulation trials; outcomes were comparable to non-T cell depleted transplants
  - 2 CD19 CAR trials have been discussed
  - A post-transplant myeloma vaccine trial is planned
- Current issues
  - Chimeric antigen receptor (CAR) strategies are being tested in non-transplant settings & soon in post-transplant relapse setting
  - Multicenter cell & gene therapy studies are challenging (require INDs, production/shipping of cells, clinical grade vectors, identification of sources for ancillary reagents)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Strategies Considered

1. Conduct a phase III randomized trial of autologous EBV-specific T-lymphocytes following AuHCT for patients with EBER-ISH positive Hodgkin Lymphoma
   - Discussion: More data is needed about whether outcomes of EBV+ HL differ from EBV- HL; analysis may be confounded if HL patients are receiving other maintenance therapies such as brentuximab
2. Conduct bridging trial of haploidentical donor natural killer cells for AML patients with active disease prior to transplant
   - Discussion: finalization of manufacture & accessory cytokines needed
   - Trial concept subsequently refined
3. Conduct randomized phase II trial of adoptive immunotherapy using banked third party CMV-specific T cells for refractory CMV infection

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Randomized phase II trial of CMV-specific T cells for refractory CMV infection

- Hypothesis

  Adoptive immunotherapy using CMV-specific T cells with antiviral therapy can improve control of refractory CMV infection compared to antiviral therapy alone

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Randomized phase II trial of CMV-specific T cells for refractory CMV infection

- Background
  - CMV mortality has decreased BUT significant challenges remain*
    - Antiviral drugs are toxic
      - 30% adverse events;
      - 12% grades 3-4 toxicities
    - Indirect effects of CMV infection (& its therapy) still are associated with higher mortality
  - There is no effective therapy for refractory CMV infection
  - CMV-specific T cell adoptive therapy is safe & effective in small trials of prevention & treatment of CMV infection**

*Boeckh M, Biol Blood Marrow Transplant 2003; 9: 543

**Leen AM, Blood 2013; 121: 5113; Blyth E, Blood 2013; 121: 3745

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

CMV adoptive immunotherapy trials

Trial	Patients	design	Strategy	Endpoint	N
Blyth	Allogeneic	Phase II, concurrent controls	Prophylaxis of viremia	Time to reactivation	50
Leen	Allogeneic, adults & children	Phase II, single arm	Treatment of persistent CMV infection (7+ days of therapy)	Resolution or reduction in viremia at 6 weeks	23
Impact	Alemtuzumab, siblings, age >18	Phase III, 3 arms	Prophylaxis at day 28	Viremic episodes at 6 months	90 (60 got cells)
CMV-ACE/ ASPECT	Alemtuzumab, unrelated, >16	Phase II, single arm	Treatment of viremia	Immune reconstitution at 2 months	50

Randomized phase II trial of CMV-specific T cells for refractory CMV infection

Trial Design - Randomized phase II trial

- Subjects:
  - Allogeneic HCT recipients
  - With persistent CMV viremia despite 2 weeks of antiviral therapy, who are not receiving prednisone >1 mg/kg/d
- Cells
  - Banked third party cells
  - Administered on days 1, 8, & 15
- Randomization to cells or placebo
  - Antiviral therapy will be continued
  - Tapering of immunosuppression will be standardized
  - Block randomization by prednisone dose (<0.5 mg/kg/d & >0.5 mg/kg/d)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

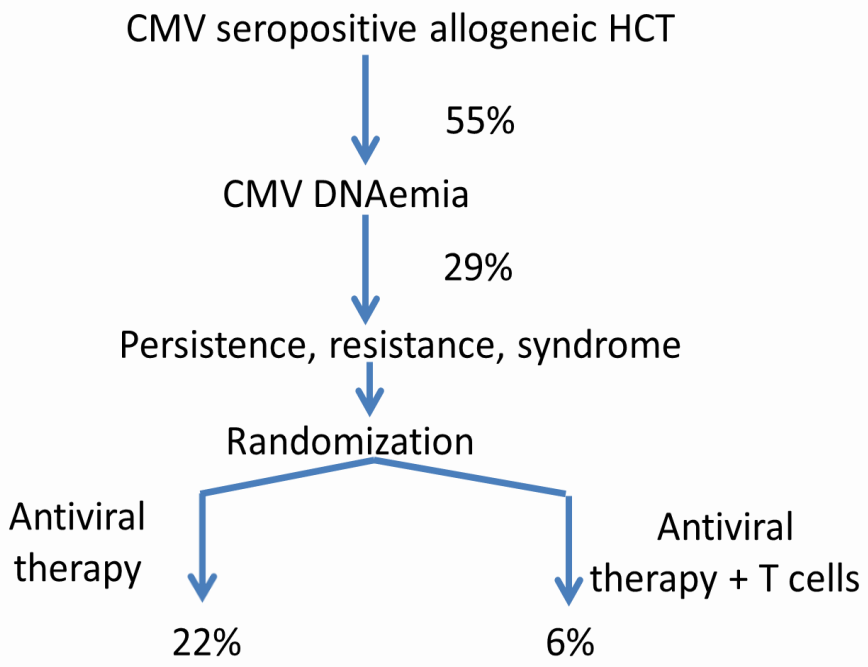
Randomized phase II trial of CMV-specific T cells for refractory CMV infection

- Trial Endpoints
  - Primary: incidence of CMV disease at 6 months in time to event analysis
  - Secondary:
    - Duration of viremia
    - Peak viral burden
    - Number of viremia recurrences
    - Number of days of antiviral therapy required
    - Emergent Grades 3-4 toxicities
    - Overall survival, non-relapse survival, & progression free survival at 6 & 12 months

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Randomized phase II trial of CMV-specific T cells for refractory CMV infection

- Feasibility & Logistics
- Assumptions:
  - Viremia in 55%
  - Persistent viremia in 29-45%*
  - CMV disease rates 22-34%*
  - Cell response 74%**
  - 90 patients per arm will detect reduction from 22% to 6%
- First step:
  - Contemporary cohort to verify estimates (now underway)



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

*Almyroudis NG, Transpl Infect Dis 2007; 9: 286 (T depleted HCT)
Nichols WG, Blood 2001; 97:867 (T replete HCT)
**Leen AM, Blood 2013; 121: 5113

Randomized phase II trial of CMV-specific T cells for refractory CMV infection

- On further reflection & more data
  - CMV disease in contemporary dataset lower (12% vs 22-34%)
  - We now will return to consideration of a viral load endpoint as preferred primary endpoint

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

- Hypothesis

  Lymphodepleting chemotherapy & infusion of related donor haploidentical NK cells will induce *in vivo* expansion of NK cells that will correlate with clinical remission in patients with refractory AML.

  Cytokine support (IL-2 or IL-15) is critical to the success of adoptive transfer

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

- Background
  - For AML not in CR, there is an unmet need and patients in this situations usually do not get to transplant.
  - Having a bridge to transplant trial is important
  - Haploidentical NK cells can clear AML*
    - NK cell persistence & expansion correlates with CR
    - Treg depletion with IL2DT improves AML clearance
    - IL-15/IL-15Ra-Fc induces Ki-67+ NK cells 3 days after single dose
  - >50 refractory AML patients treated at U of MN
    - Remission rates in 25-50% in various platforms

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

*Bachanova V, Blood 2014;123:3855

Miltenyi Sponsored Pilot to start in 2015

A randomized trial comparing CD3/CD19 depleted or CD3-depleted/CD56 selected haploidentical donor NK cells for adults with AML who have failed 1-2 induction attempts

Initial enrollment at 3 BMT CTN sites

- University of Minnesota
- Washington University
- University of Chicago

Eligibility: Persistent refractory AML after 1-2 cycles of standard induction chemotherapy

Primary Objective: Pick a product in 12 months

-These data would inform the BMTCTN trial

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

Trial Design

- Randomized phase II trial
- Subjects:
  - AML (except acute promyelocytic leukemia) and has failed one or two prior standard induction attempts
  - Age > 18
  - KPS > 70
  - Adequate organ function within 14 days of enrollment (30 days for pulmonary and cardiac)
  - Available related HLA haploidentical donor
- Cells
  - Fresh NK cells using production method chosen from the pilot trial

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

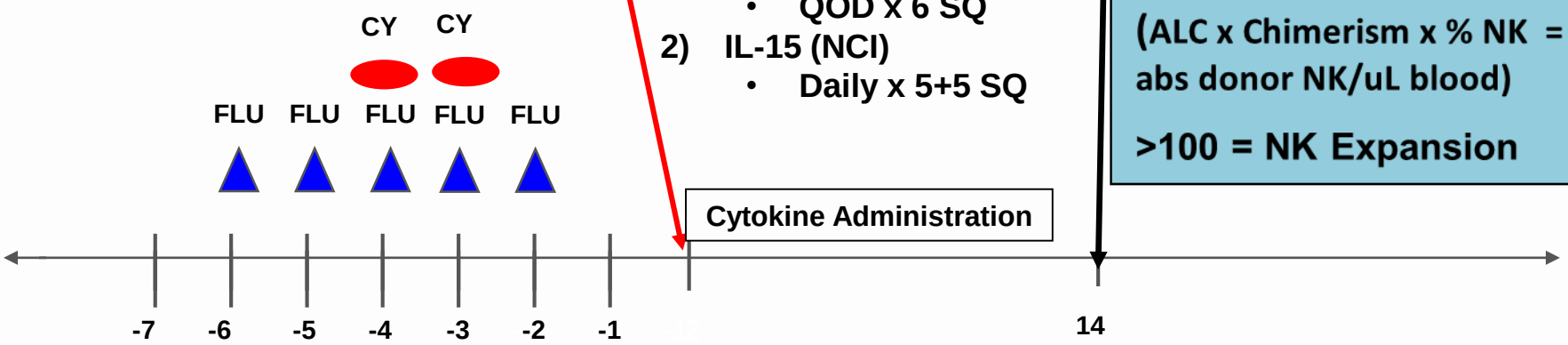
Trial Design

Randomized Cell Products
1) No Cells
2) Fresh NK cell product chosen from current pilot

Cytokine Administration
Choose 1
1) IL-2 (Novartis)
   - QOD x 6 SQ
2) IL-15 (NCI)
   - Daily x 5+5 SQ

- **Bone Marrow Biopsy** (Leukemia Clearance)
- **Patient Blood** (ALC x Chimerism x % NK = abs donor NK/uL blood)

>100 = NK Expansion



Preparative Regimen | **Haplo NK** | **In vivo NK Expansion**

Assess Clinical Outcomes and NK Expansion

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

- Trial Design
  - Endpoints
    - Primary: morphologic CR by day 42
    - Secondary:
      - Central lab correlates of NK killing of primary AML, persistence and expansion of adoptively transferred cells vs endogenous auto cells, serum cytokines (IL15, IL7, IL6, TNF, IFNy, IL-10, IL-8)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

- Feasibility & Logistics
  - Two arm comparative study with 85% power to detect improvement in CR rate from
    - 20% with chemo+cytokine vs.
    - 40% when NK cells added
  - N=56 patients in each arm using a one-sided type I error of 10%.
  - 45 patients in each arm using a one-sided type I error of 15%.
  - Stop for futility if <=3 CRs in the first 10 patients on an arm

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Haploidentical donor natural killer cells for refractory AML as bridge to transplant

- Future Trial Modifications:
  - Making NK cells antigen specific with BiKEs
  - Anti PD-1 antibody for Treg depletion

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Committee Members

- CAR T cells
  - Michel Sadelain – Memorial Sloan Kettering, New York
  - Marcela Maus – University of Pennsylvania, Philadelphia
  - Stephen Forman – City of Hope, Duarte
  - Michael Jensen – University of Washington, Seattle
- Virus CTLs - with infection
  - Helen Heslop – Baylor, Houston
  - Cath Bollard – Children's National Medical Center, Washington DC
- NK cells
  - Jeff Miller – University of Minnesota, Minneapolis
  - Katy Rezvani – MD Anderson, Houston
  - Cath Bollard
- Gene transfer to HSC
  - Michel Sadelain
  - Don Kohn – University of California, Lost Angeles
- Mesenchymal stromal cells
  - Ed Horwitz – Children's Hospital of Philadelphia
- Regulatory T Cells
  - Jerry Ritz – Dana-Farber Cancer Institute, Boston

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Summary

- Portfolio of studies that
  - Build on multiple prior BMT CTN studies
  - Address novel donor/graft types with potential to expand access to allogeneic HCT
  - Explore novel drug and cellular therapy approaches to post-allotransplant viral infections

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Questions from the live event on Dec 5, 2014

Access a Certificate of Attendance

(will open in new browser tab)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Graft versus Host Disease, Late Effects/Quality of Life/Economics, and Comorbidity/Regimen-Related Toxicity Committees

Frederick R. Appelbaum, MD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Financial Disclosures

Company	Role with Company
Celator	Consulting role with all companies
Ingenica	
Adaptive Biotechnologies Corp.	
Neumedicines	
Pfizer	
Amgen	
National Marrow Donor Program/ Be The Match	

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

GVHD Committee

Joe Antin – Chair, Dana-Farber Cancer Institute, Boston
Amin Alousi – University of Texas MD Anderson CC, Houston
James Ferrara – University of Michigan Health Systems, Ann Arbor
Mary Flowers – Fred Hutchinson CRC, Seattle
Richard Jones – Johns Hopkins University, Baltimore
Leslie Kean – Seattle Children's Research Institute, Seattle
Paul Martin - Fred Hutchinson CRC, Seattle
Richard Maziarz – Oregon Health & Science University, Portland
David Porter – University of Pennsylvania CC, Philadelphia
Dan Weisdorf – University of Minnesota, Minneapolis
Andrea Bacigalupo – reviewer; Ospedale San Martino, Genoa, Italy
Ernst Holler – reviewer; University of Regensburg, Germany

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Graft versus Host Disease

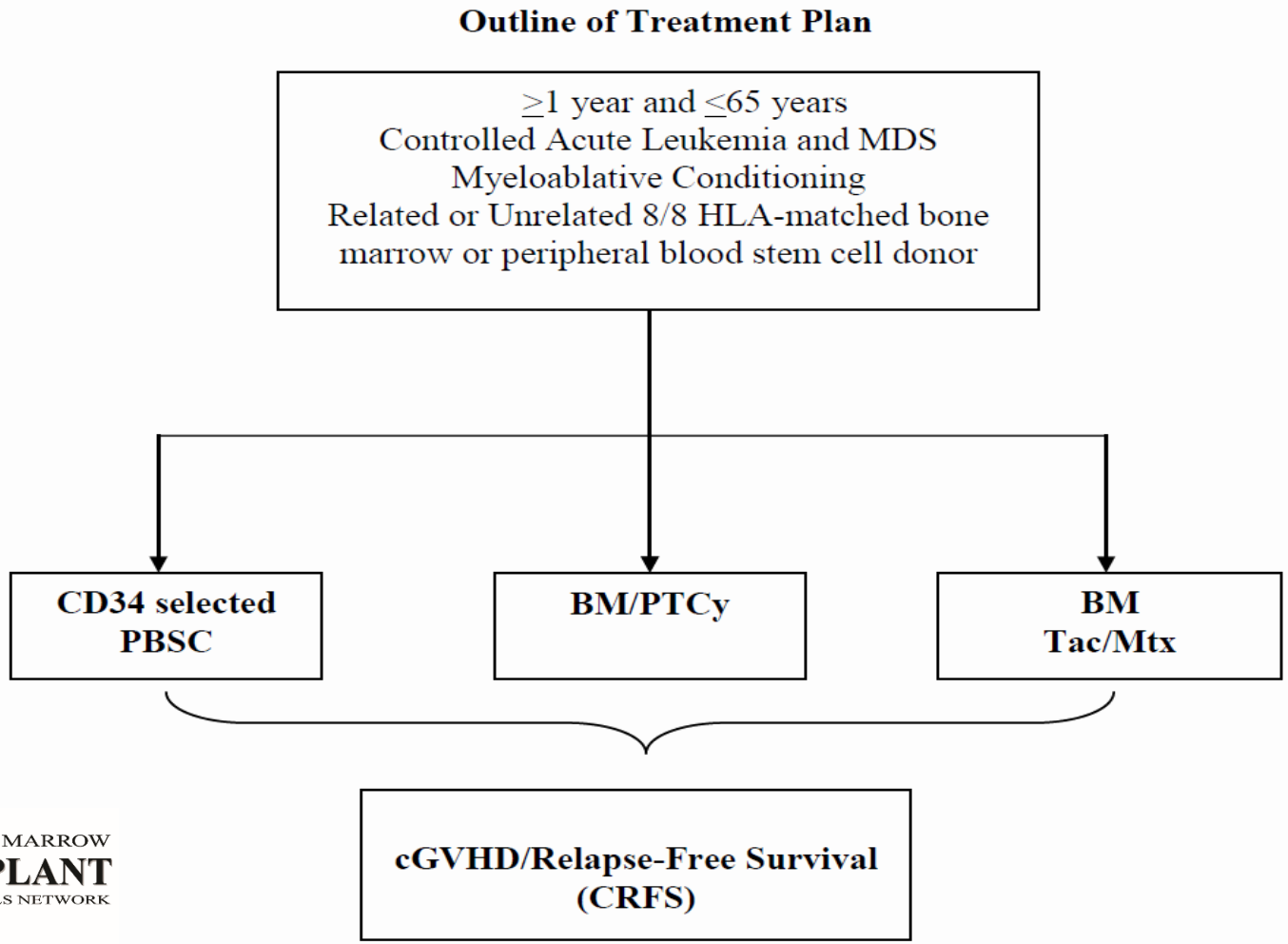
Prevention

Treatment

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1301: GVHD prevention after Myeloablative Conditioning

CNI-Free GVHD Prophylaxis Protocol – 1301
Version 1.0 dated September 18, 2014



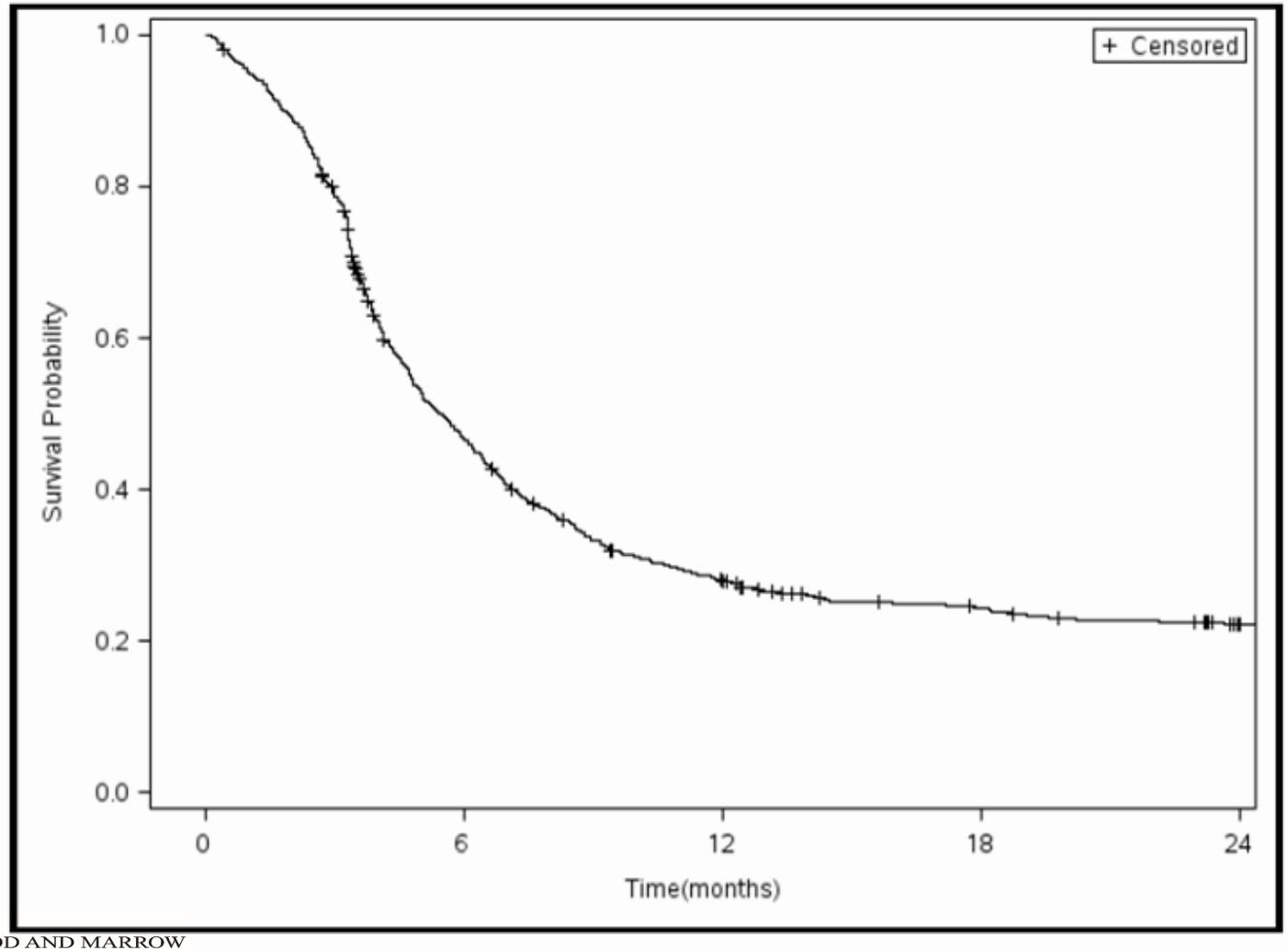
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

CIBMTR Benchmark Analysis of GVHD Prophylaxis Regimens

		Tac/Mtx N=5,048		Post-HCT Cy N=117		CD34-selection N=291
aGVHD	100d	23%		21%		4%
	HR	1.0		0.9		0.3
cGVHD	12 m	45%		13%		8%
	HR	1.0		0.2		0.1
Survival	12 m	60%		57%		73%
	HR	1.0		1.1		0.7

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Chronic GVHD/Relapse-free Survival (CRFS) after CNI-based GVHD Prophylaxis



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

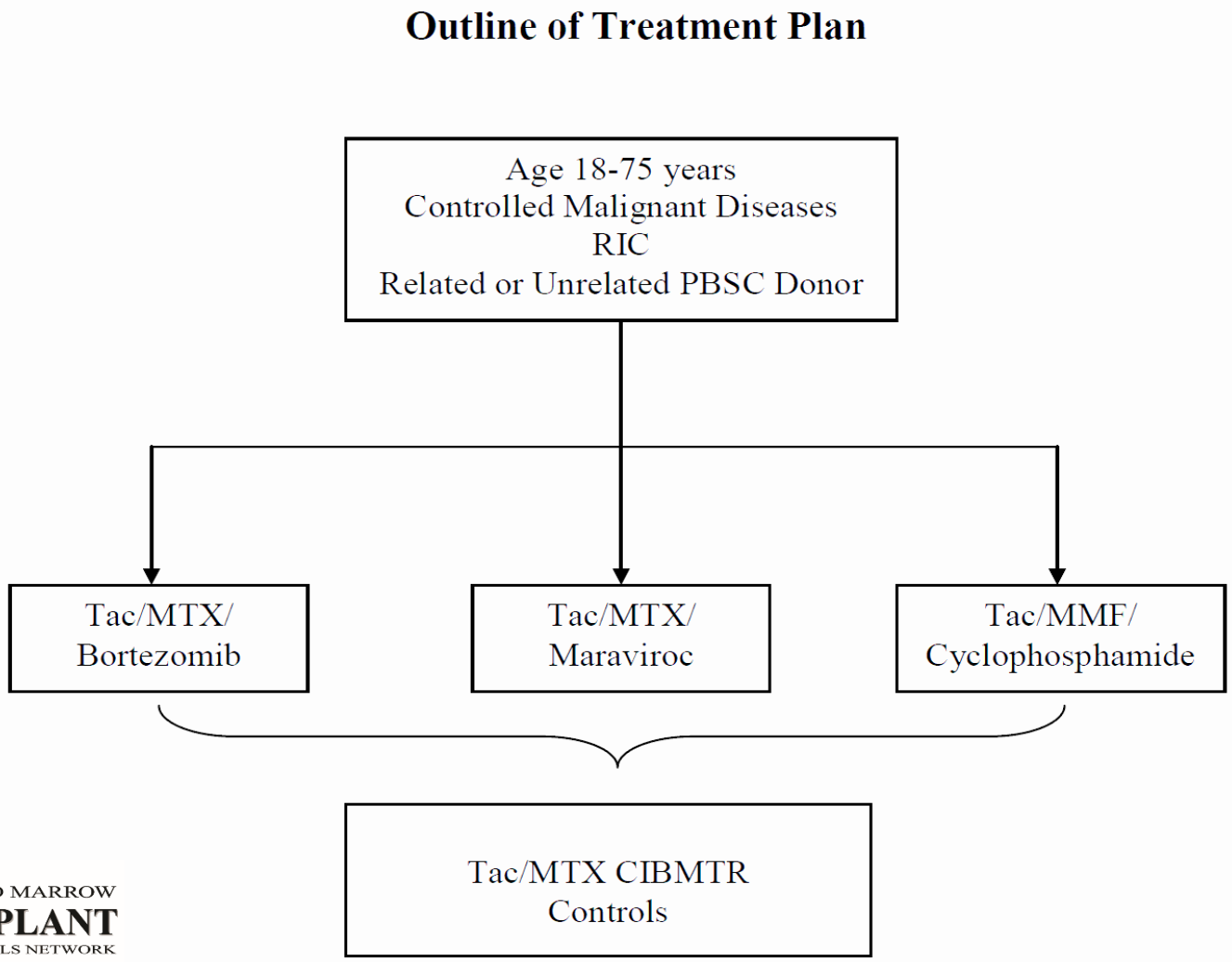
BMT CTN 1301: GVHD prevention after Myeloablative Conditioning

Hypothesis: cGVHD RFS will be at least 20% higher with either post-transplant Cy or CD34-selection than with Tac/Mtx at 12 months

N=345 patients (115 per arm)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1203: GVHD prevention after Reduced Intensity Conditioning



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

CIBMTR Benchmark Analysis of GVHD Prophylaxis Regimens

		Tac/Mtx N=5,048	Tac/MMF+ Post-HCT Cy N=117	Tac/Mtx +Bortezomib N=44	Tac/Mtx +Maraviroc N=33
aGVHD	180d	25%	23%	14%	13%
	HR	1.0	0.9	0.5	0.9
cGVHD	12 m	45%	13%	43%	19%
	HR	1.0	0.2	0.7	0.3
Survival	12 m	60%	57%	79%	64%
	HR	1.0	1.1	0.5	0.8

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

One Year GVHD-free, Relapse-free Survival (GRFS) by Disease

Disease	1 – year GRFS	HR	p-value
AML	25%	1.0	-
ALL	24%	1.04	0.85
CML	25%	1.11	0.54
MDS	12%	1.55	0.002
CLL	16%	1.42	0.005
NHL	30%	0.89	0.305

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

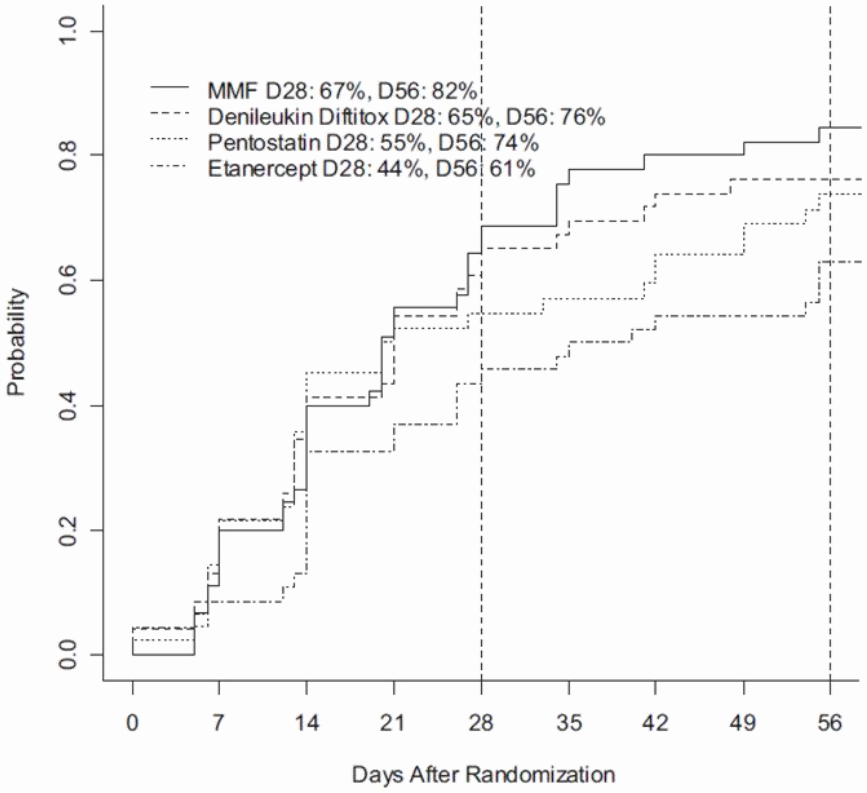
BMT CTN 1203: GVHD prevention after Reduced Intensity Conditioning

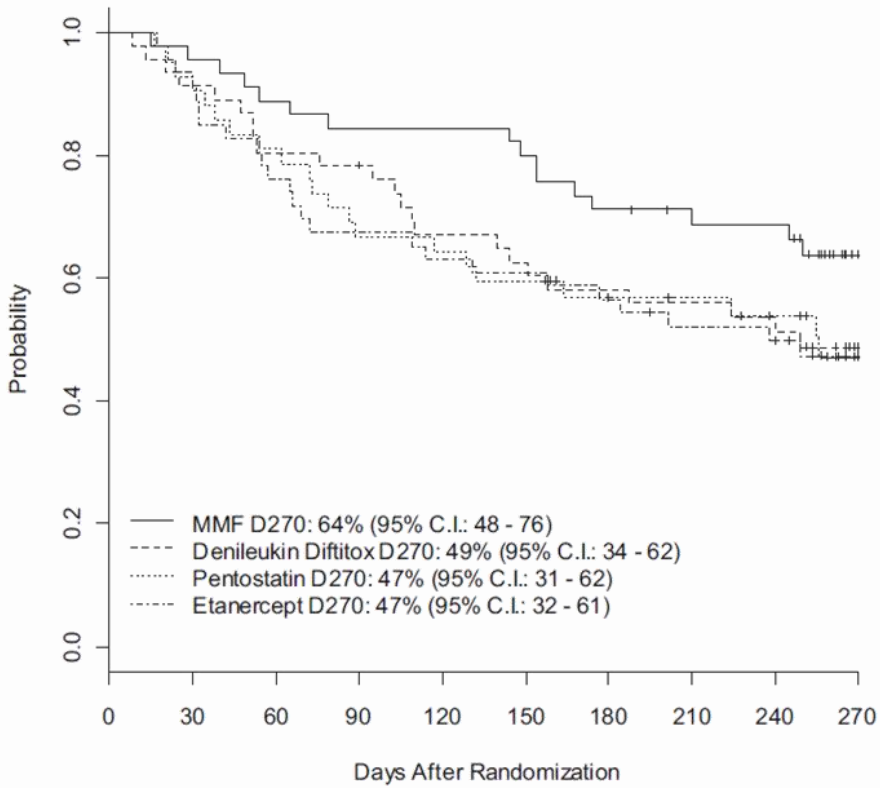
Hypothesis: the GRFS HR for one of the three study arms (Tac/MMF-PTCy, TacMtx-Bor, TacMtx-Mar) will be significantly better than a CIBMTR concurrent non-randomized control group receiving TacMtx.

N=270 patients (90 per arm)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 0302[1]: Randomized Phase II Trial of 4 acute GVHD treatment regimens

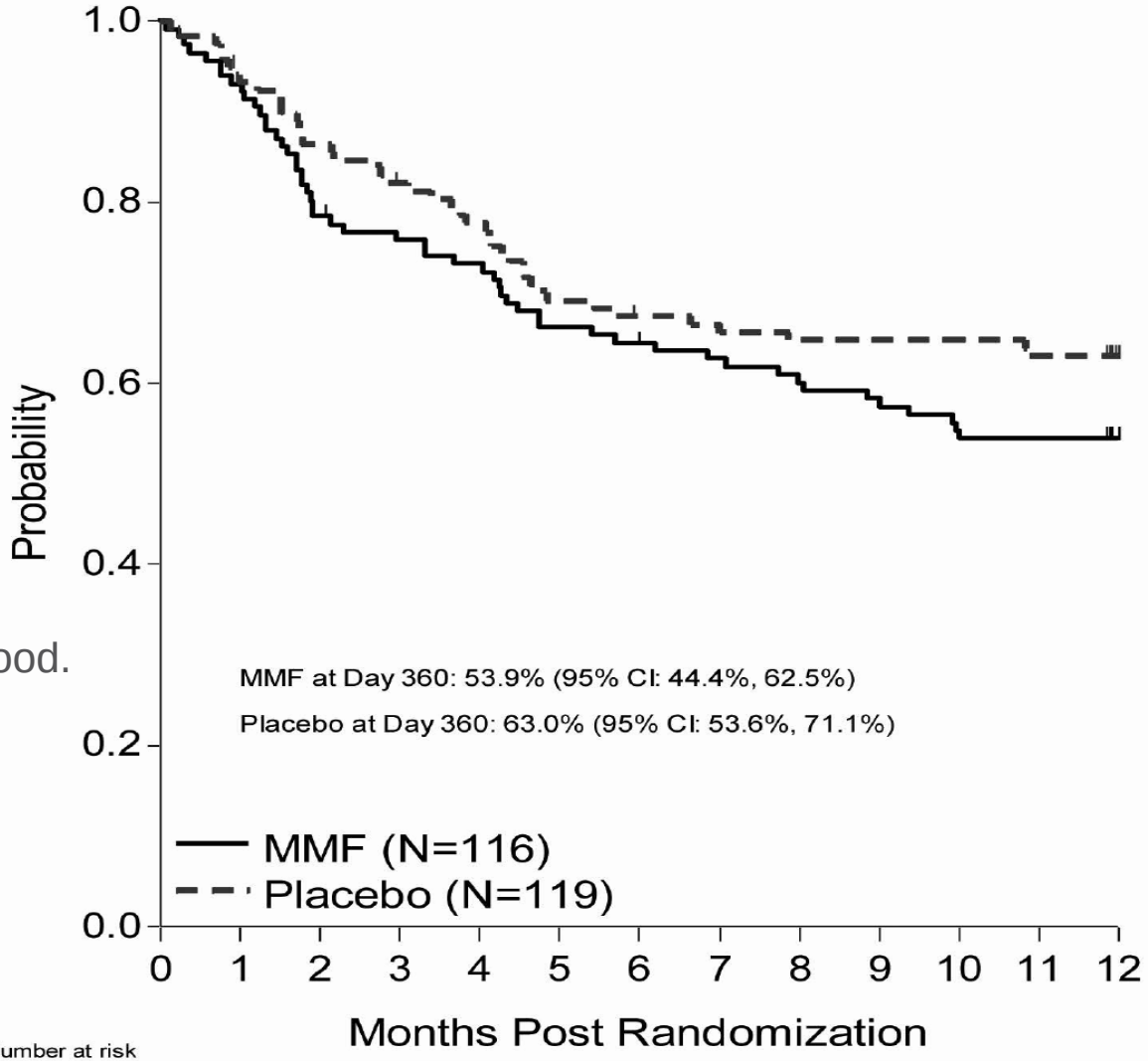




[1]Alousi A, et al. Blood 2009;114:511-517

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 0802[1]: Randomized Phase III Trial of Steroids+MMF vs Steroids+Placebo for Acute GVHD



[1]Bolan-Meade J et al. Blood. 2014;124(22):3221-3227

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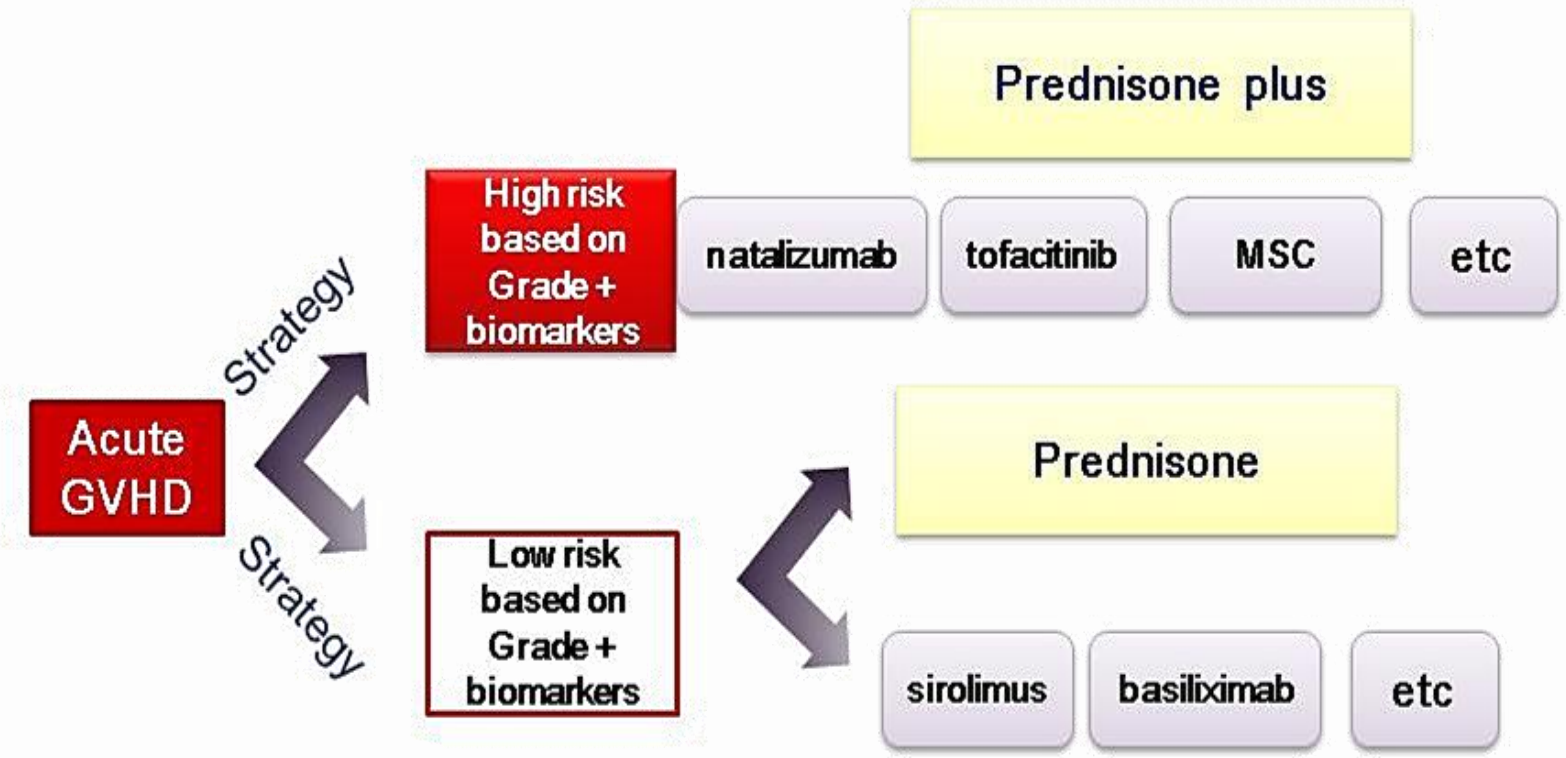
BMT CTN SOSS 2014[1]



[1] Appelbaum F, et al. BBMT. 2015;21(2): 202-224

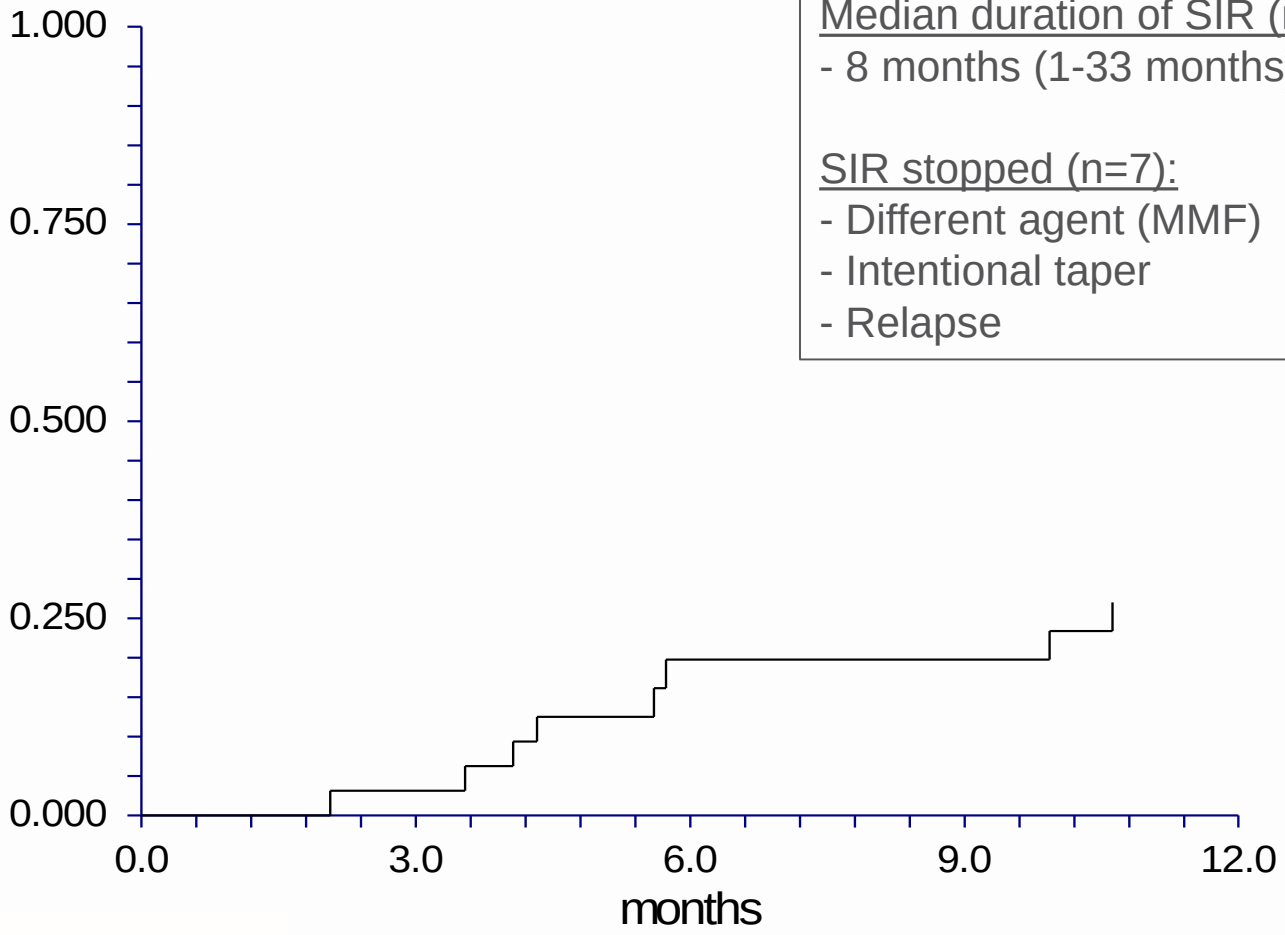
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Treatment of aGVHD with Sirolimus

N	32
CR	
Sirolimus alone	16/32
Pred after SIR failure	12/16

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Treatment of aGVHD with Sirolimus



Median duration of SIR (n=25):
- 8 months (1-33 months)

SIR stopped (n=7):
- Different agent (MMF) n=1
- Intentional taper n=1
- Relapse n=5

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Proposed Study – Treatment of Standard Risk aGVHD

Randomized phase II trial –

SIR vs prednisone (1mg/1kg)

Primary outcome

Day 25 CR

Follow-up period

1 year

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

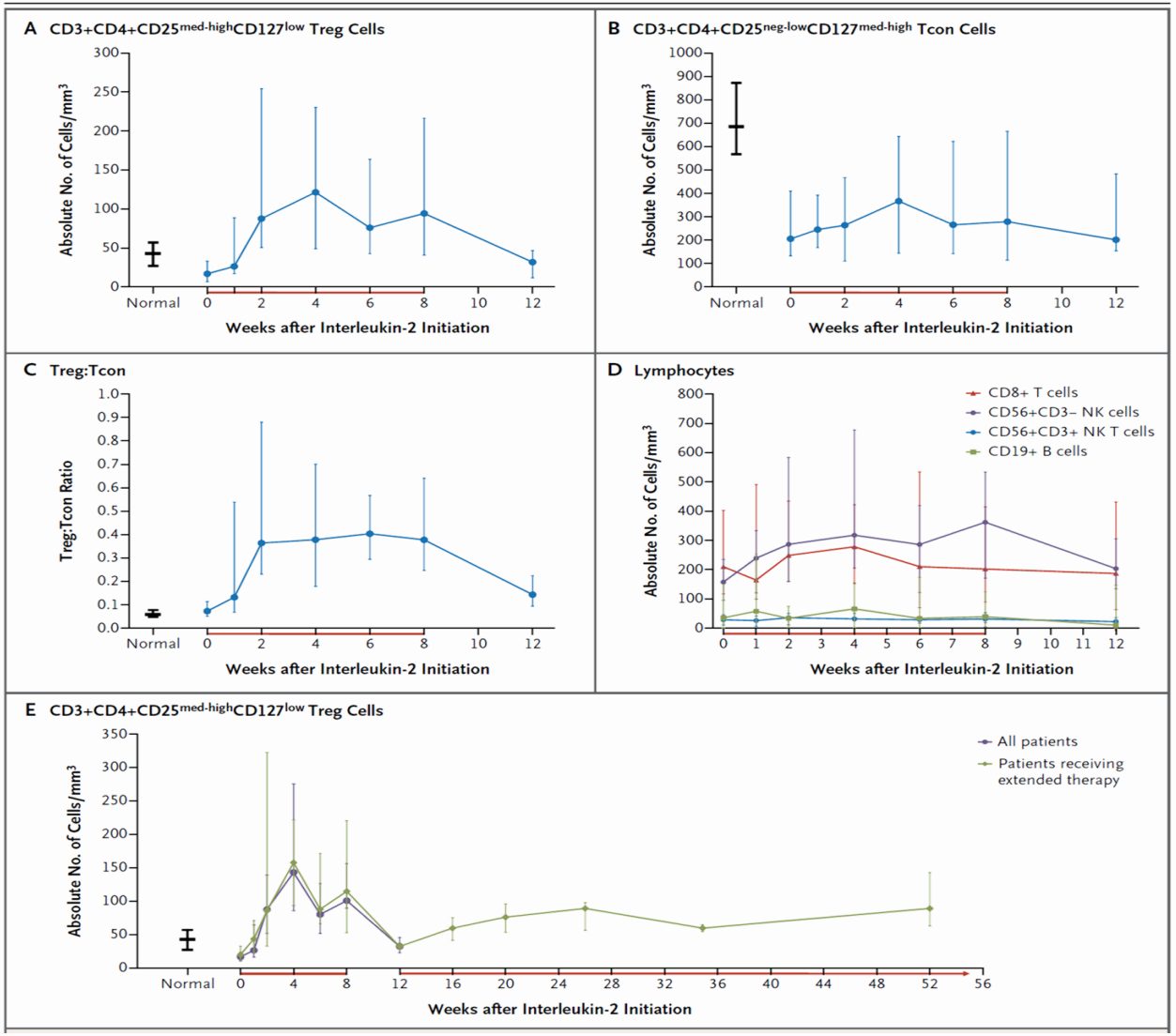
IL – 2 for cGVHD[1]

N	23 (evaluable)
PR	12
Stable	11
Progression	0

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

[1] Koreth et al NEJM. 2011;265:2055-2066

IL – 2 and Treg cells[1]



[1] Koreth J et al. NEJM 2011;365(22):2055-2066

From N Eng J Med, Koreth J, Matsuoka K, Kim HT, et al., Interleukin-2 and regulatory T cells in graft-versus-host disease, 365(22):2055-2066. Copyright © (2011) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Phase III RCT of Prednisone +/- IL – 2 for cGVHD

Eligibility	–	moderate/severe cGVHD requiring systemic therapy
Arms	–	prednisone 1mg/kg vs prednisone + IL – 2 at $1x10^6$ $IU/m^2/d$ SC
Endpoints	–	cGVHD at 12 weeks, FFS at 12 mo
Size/Power	–	250 (125/arm), 80% power to detect 20% difference

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Late Effects/QOL/Economics

Stephanie Lee – chair, Fred Hutchinson CRC, Seattle

Saro Armenian – City of Hope, Duarte

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Nandita Khera – Mayo Clinic, Scottsdale

Navneet Majhail – Cleveland Clinic CC, Cleveland

Doug Rizzo – Medical College of Wisconsin, Milwaukee

Bipin Savani – Vanderbilt University, Nashville

Karen Syrjala – Fred Hutchinson CRC, Seattle

Jane Apperly – reviewer, Imperial College, London

Gerard Socie – reviewer, Hospital St Louis, Paris

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Late Effects, QoL, Economics: BMT CTN 0902 – Exercise and Stress Management Training[1]

Primary Analysis

	Day +100 SF36 Score		p value
	Exercise (n=358)	No Exercise (n=353)	
PCS	37.5	39.7	.14
MCS	49.4	50.1	.33
	Stress Management	No stress management	
PCS	37.8	39.7	.21
MCS	50.7	49.1	.30

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

[1] Jacobsen et al BBMT 2014; 20:1530-1537

Late Effects, QoL, Economics

- Preventive care
  - Smoking cessation
  - Vaccinations
  - Vitamin D supplementation
- Survivor support
  - Survivorship care plan
  - Internet-based survivorship support
  - Survivorship support package
- Late Effects
  - Cardio-toxicity
  - Infertility
  - Avascular necrosis
  - Iron overload
  - Osteopenia/osteoporosis
- Quality of life, Economics

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Zoledronic Acid for Bone Loss Prevention

- Pre-transplant prevalence ~10-20% for osteoporosis, ~20-30% for osteopenia
- Bone loss occurs in first 6-12 months post-HCT in most patients, recovery can take years
- Continued decline in BMT patients with continuing exposure to risk factors (e.g., corticosteroids, calcineurin inhibitors)

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Zoledronic Acid for Bone Loss Prevention

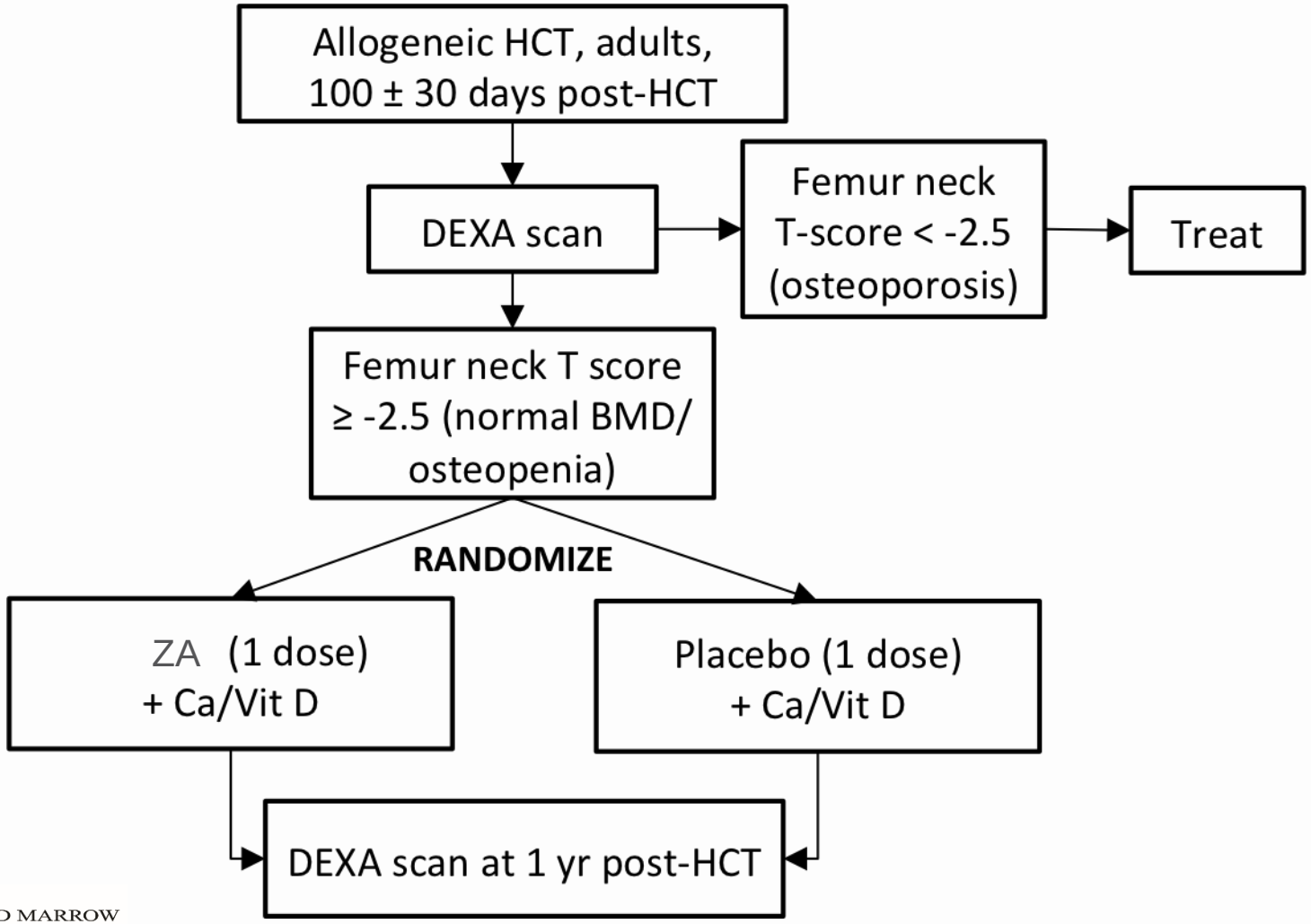
- Zoledronic acid is FDA approved for:
  - Treatment of post-menopausal osteoporosis (5 mg once a year)
  - Prevention of post-menopausal osteoporosis (5 mg once every 2 years)
  - Prevention of glucocorticoid induced osteoporosis (5 mg once a year)
- Relevant toxicity for HCT recipients – renal impairment
  - In registration trials (non-HCT) ~2% patients had transient increase in serum creatinine; rare renal failure
  - Contraindicated if creatinine clearance is < 35 mL/min

Zolendronic Acid for Bone Loss Prevention

- Primary endpoint
  - Change in femoral neck BMD from enrollment to 1 year post-HCT
- Secondary
  - Change in lumbar spine BMD from enrollment to 1 year post-HCT
  - Incidence of fractures at 1 year post-HCT

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Zolendronic Acid (ZA) for Bone Loss Prevention



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Zolendronic Acid for Bone Loss Prevention

- Most osteoporosis prevention studies have evaluated lumbar spine bone mineral density (BMD) difference of 3-6% (baseline to 12 months)
  - Assuming a true 0.5 SD difference, need 90 patients/arm for 90% power to obtain a significant result ($\alpha = 0.05$)
  - Assuming 30% dropout by 1 year (mortality, study withdrawal), should increase sample size to 130 patients/arm
  - Stratification for balance of factors that may correlate with post-HCT bone loss (e.g., center, baseline bone mineral density, steroid exposure)

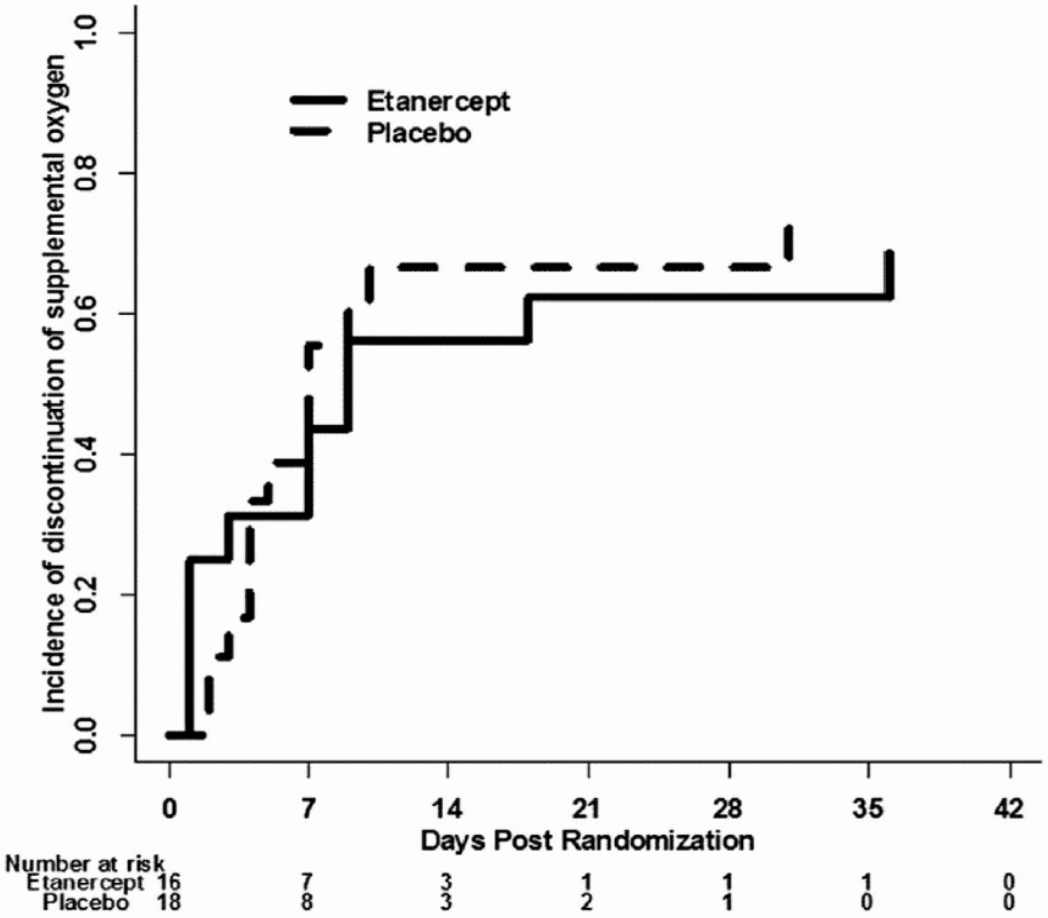
Comorbidity and RRT Committee

Ed Stadtmauer – chair, University of Pennsylvania MC, Philadelphia
Andrew Artz – University of Chicago
Ami Bhatt – Dana-Farber Cancer Institute; Broad Institute, Boston
Guang-Shing Cheng - Fred Hutchinson CRC, Seattle
Ken Cooke - Johns Hopkins University, Baltimore
Vincent Ho - Dana-Farber Cancer Institute, Boston
John McCarty – VCU Massey Cancer Center, Richmond
Robert Soiffer - Dana-Farber Cancer Institute, Boston
Mohamed Sorror - Fred Hutchinson CRC, Seattle
Greg Yanik – University of Michigan, Ann Arbor
Jane Apperly – reviewer, Imperial College, London
Mohamad Mohty – reviewer, Hospital Saint-Antoine, Paris

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Co-morbidity/RRT Committee

BMT CTN 0403 – Etanercept for IPS[1]



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

[1] Yanik et al BBMT. 2014; 20:858-864

Co-morbidity Indices

- Predict transplant-related toxicities and non-relapse mortality in adults undergoing allogeneic HCT
- Independent of age and performance status
- Useful for prognosis, risk stratification and treatment selection
- Imperfect

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Impact of HCT-CI and Age on Outcome of Allogeneic HCT

(n=3033)[1]		NRM (%)		Survival (%)
		HCT-CI		HCT-CI
Age		**0 1-2 >2**		**0 1-2 >2**
0-19		**8 26 28**		**73 61 41**
20-39		**11 20 39**		**80 62 33**
40-49		**12 26 43**		**75 56 39**
50-59		**21 31 39**		**60 48 33**
>59		**7 27 38**		**63 47 27**

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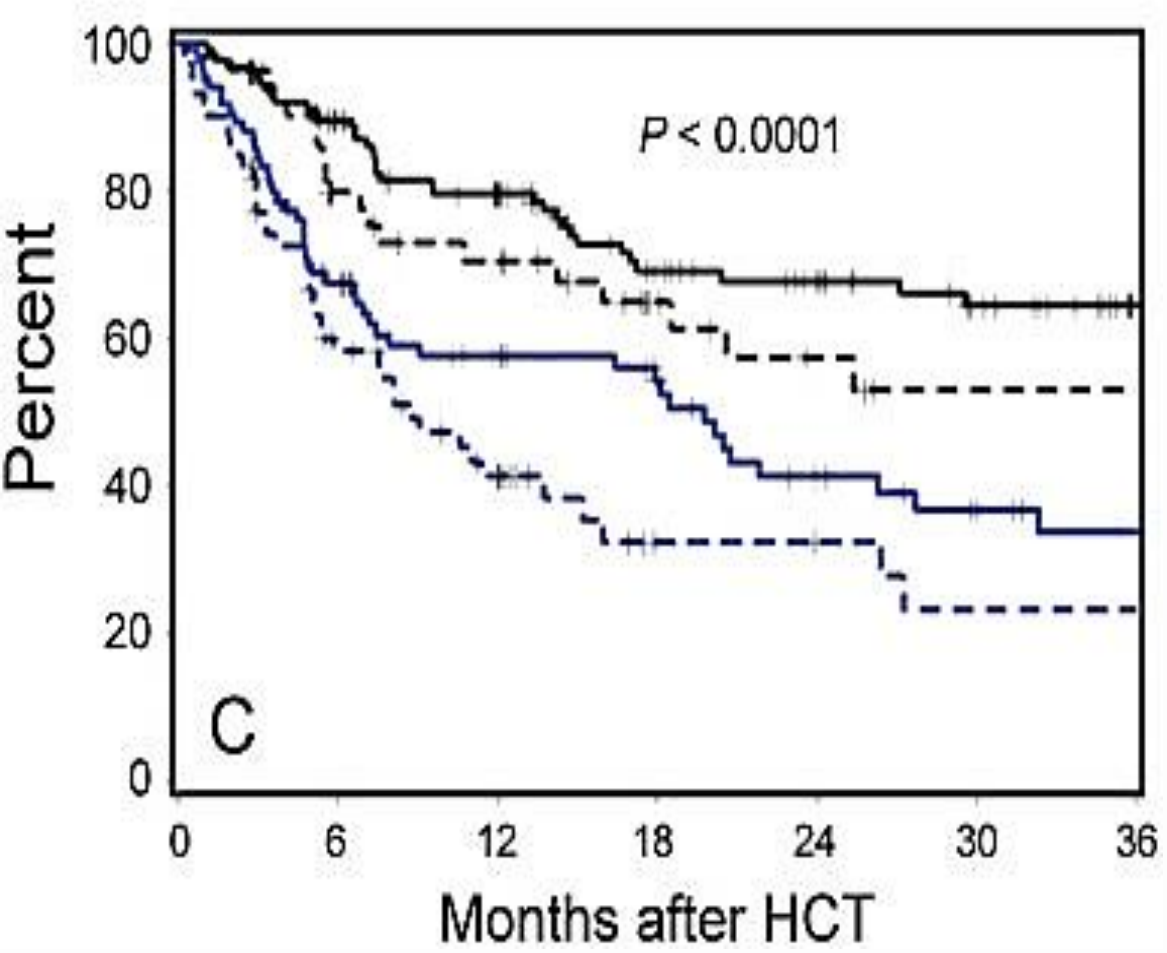
[1]Sorror ML J Clin Oncol. 2014; 32(29):3249-56

HCT-CI and KPS are Independent Predictors of Survival[1]



___ = Patients with HCT-CI scores of 0 to 2 and a KPS of >80%

----- = Patients with HCT-CI scores of 0 to 2 and a KPS of ≤80%

___ = Patients with HCT-CI scores of ≥3 and a KPS of >80%

----- = Patients with HCT-CI scores of ≥3 and a KPS of ≤80%

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[1]Sorror et al. Cancer 2008; 112:1992-2001

Measures for Risk Stratification

- HCT-CI
  - Developed and prospectively validated (Sorror *Blood,* 2012)
  - For RIC/NMA Allo HCT, HCT-CI score stratifies survival while age groups >60 years does not (Sorror *JAMA*, 2011; JCO, 2014)
- Geriatric Assessment (GA)
  - Developed and prospectively validated in older non-HCT patients (Cruz *JAMA*, 2013)
  - Adds a functional and ability assessment
  - Preliminary addition of functional assessment to HCT-CI increases survival risk stratification (Artz Haematologica, 2014)
- Plasma Biomarkers
  - C-Reactive Protein (CRP), Ferritin, and Albumin can increase predictive power of HCT-CI (Artz *BBMT*, 2008 and Sorror *Blood*, 2009)

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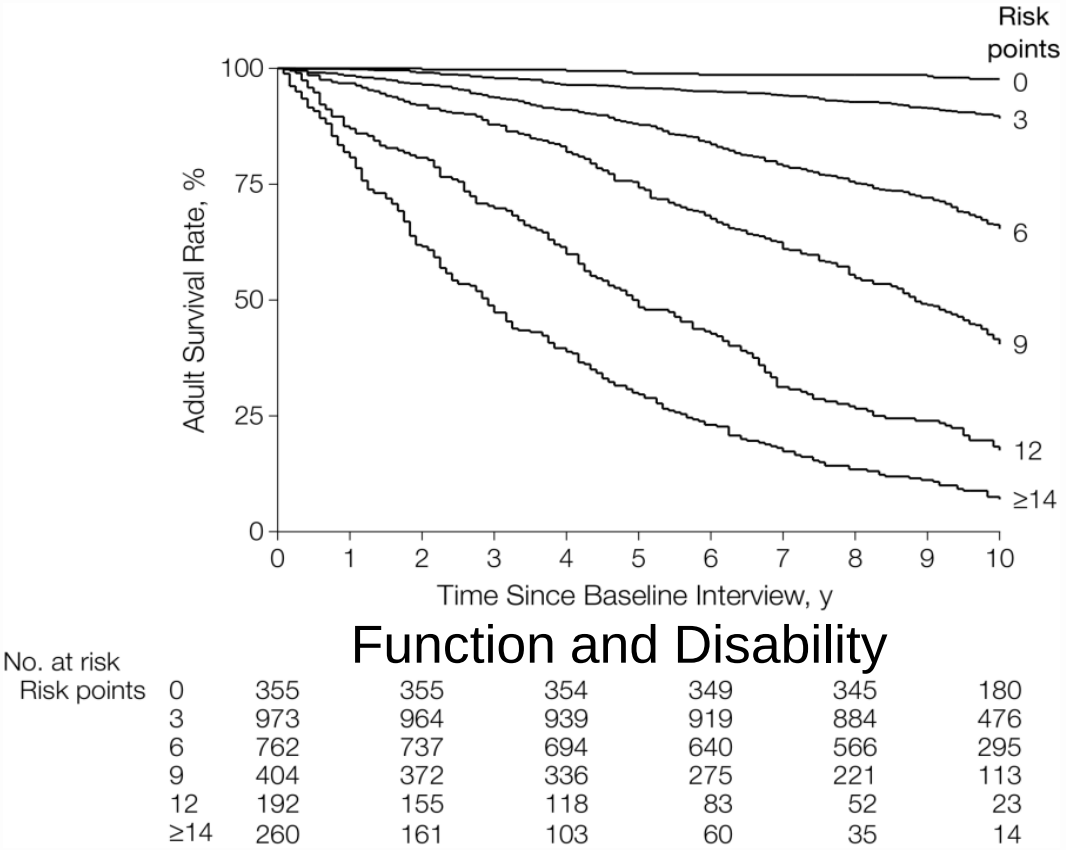
Geriatric Assessment

Predicting 10-Year Mortality for Older Adults



Function and Disability

Item	Pts
Age	1-7 pts
Tobacco use	2
BMI < 25	1
DM	1
Non-skin cancer	2
Chronic lung disease	2
Heart failure	2
Difficulty bathing	2
Difficulty with finances	2
Difficulty walking several blocks	2
Difficulty pushing large objects	1

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Cruz M. JAMA. 2013;309(9):874-876

Trial Design

- Designed to improve risk assessment for NRM
- Patients > 60 years undergoing allogeneic HCT will be evaluated pre-HCT with:
  - HCT-CI score.
  - Validated GA measures that capture physical, mental, social, emotional, and functional health.
  - Plasma biomarkers (CRP, ferritin and albumin).
- Post-HCT functional and quality of life (QoL) evaluation will be performed every 6 months for 2 years.

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Trial Design (Stats)

- This trial is designed to:
  - Develop composite model with a c-statistic estimate >0.8 to predict NRM
  - Test the model's prediction of secondary outcomes including overall and functional free survivals, QoL, and RRT
- A sample of 700 patients (similar to the sample used for developing the HCT-CI) will be used to develop the model to ensure adequate statistical power
  - Established thresholds for GA tools and cut-off values for the biomarkers will be used for modeling
  - Bootstrapping method will estimate bias-corrected values of c-statistic for internal validation of the model

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Feasibility & Logistics

- Some of the biomarker data is already collected routinely or in BMT CTN 1202 (Biomarker Repository Protocol).
- GA can be completed by patients on paper, electronically or telephone.
- Functional tests take 5 minutes by a research assistant.
- Successful creation of a validated HCT-CI used similar methods and similar sample size.

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Summary

Portfolio of studies that

- Use CIBMTR to select the most promising therapies
- Build on prior BMT CTN experience to risk-stratify therapeutic approaches for GVHD
- Will further refine our ability to risk-stratify for multiple endpoints
- Seek to improve not only duration but quality of life

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Questions from the live event on Dec. 5, 2014

Access a Certificate of Attendance

(will open in new browser tab)

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