Calling All Super Heroes

Exploring Clinical Trials:
Updates on the latest research in the fields of transplant and cellular therapies

Steven Devine, MD
Senior Vice President-Research and Associate
Scientific- CIBMTR
National Marrow Donor Program® /Be The Match®
November 10th, 2018

NATIONAL MARROW DONOR PROGRAM®

BE THE MATCH®

Disclosures

The following faculty and planning committee staff have the following financial disclosures:

Name	Institution	Disclosure
Steven Devine, MD	NMDP/Be The Match	None
Scott Kerwin	NMDP/Be The Match	None
Elizabeth Murphy, EdD, RN	NMDP/Be The Match	None

Objectives

- ✓ Explain how clinical trials have advanced treatment options for patients with hematologic diseases undergoing transplantation and cellular therapy
- ✓ Identify new treatments that are being explored right now in clinical trials
- ✓ Explain how the Jason Carter Clinical Trials Program can help you connect patients to clinical trials

Clinical Trial Basics

Two main types of clinical trials

- ✓ **Observational**: Collection of medical data during standard care treatments – allows for retrospective analysis of effectiveness and outcomes:
  - ✓ CIBMTR maintains largest US database

- ✓ **Interventional**: Investigates a treatment that is different than standard treatment – drug, cells, dose, process, timing

Clinical Trial Basics

Interventional:

- ✓ **Phase 1:** Designed to test the safety of a new therapy and maybe a glimpse of efficacy and explore what side effects can happen at different doses
  - ✓ Usually a small group of patients 5-50
  - ✓ Typically, not for newly diagnosed patients, but for relapsed or refractory disease
  - ✓ Example: A new drug, DS-32, to treat relapsed ALL, given at escalating doses with numerous blood draws testing drug levels (pharmacokinetics (PK) – goal is to find the highest dose that is safe to give

Clinical Trial Basics

Interventional:

- ✓ **Phase 2:** Designed to test if a therapy is effective
  - ✓ Larger group ~40 – 120 patients
  - ✓ Not always testing new drugs, may test existing drugs for new indications or new combinations
  - ✓ Example: A drug, nivolumab, to treat refractory multiple myeloma (currently, nivolumab is FDA approved to treat Hodgkin lymphoma)
  - ✓ Many designs combine Phase 1 and 2 in one trial

Clinical Trial Basics

Interventional:

- ✓ **Phase 3:** Designed to test if a therapy works better than an existing therapy
  - ✓ Usually over a hundred patients
  - ✓ Will often use randomization, placebos, blinding, and double-blinding
  - ✓ Example: Itacitinib + steroids versus placebo + steroids to treat acute graft-versus-host disease after allogeneic BMT
  - ✓ Randomized, double-blind, often placebo trials are the "**Gold Standard**" in clinical trial design
- ✓ **Phase 4:** Post-market surveillance for a therapy that has recently been FDA approved

Why conduct clinical trials in BMT?

- **Because not enough patients benefit. The status quo is not good enough!**
- Outcomes have improved, but GVHD-free, relapse free survival rates are still far too low (30-40%)
- Too many patients relapse
- Too many patients lucky enough to stay in remission suffer from acute or chronic GVHD or remain on immune suppressing drugs
- Still way too much toxicity, particularly in older patients

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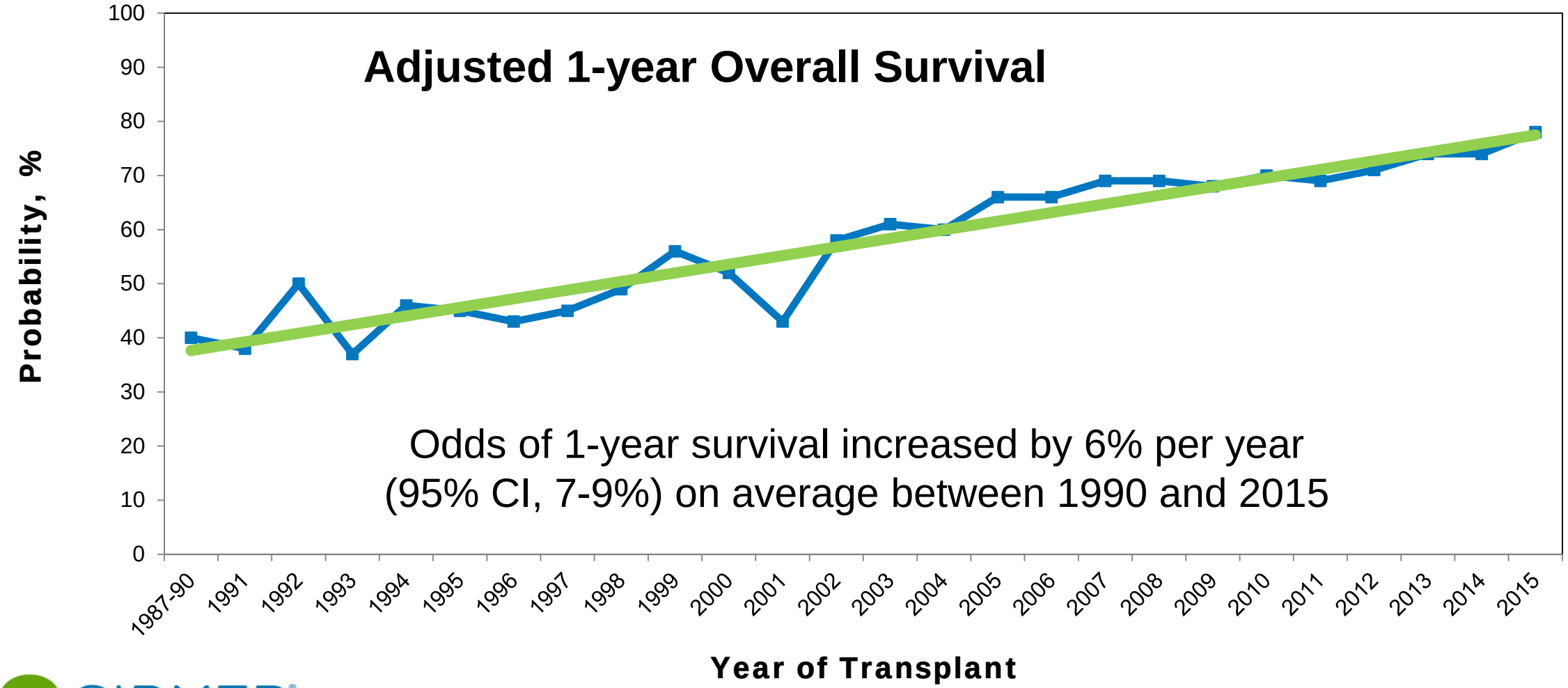
Why conduct clinical trials in BMT?

- We don’t have good tools to accurately predict which older patients will clearly benefit from HCT
- We often don’t know the best donor source for patients lacking a well matched family
- We need to learn more about all the barriers to access

Survival After Unrelated Donor Transplantation

Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS



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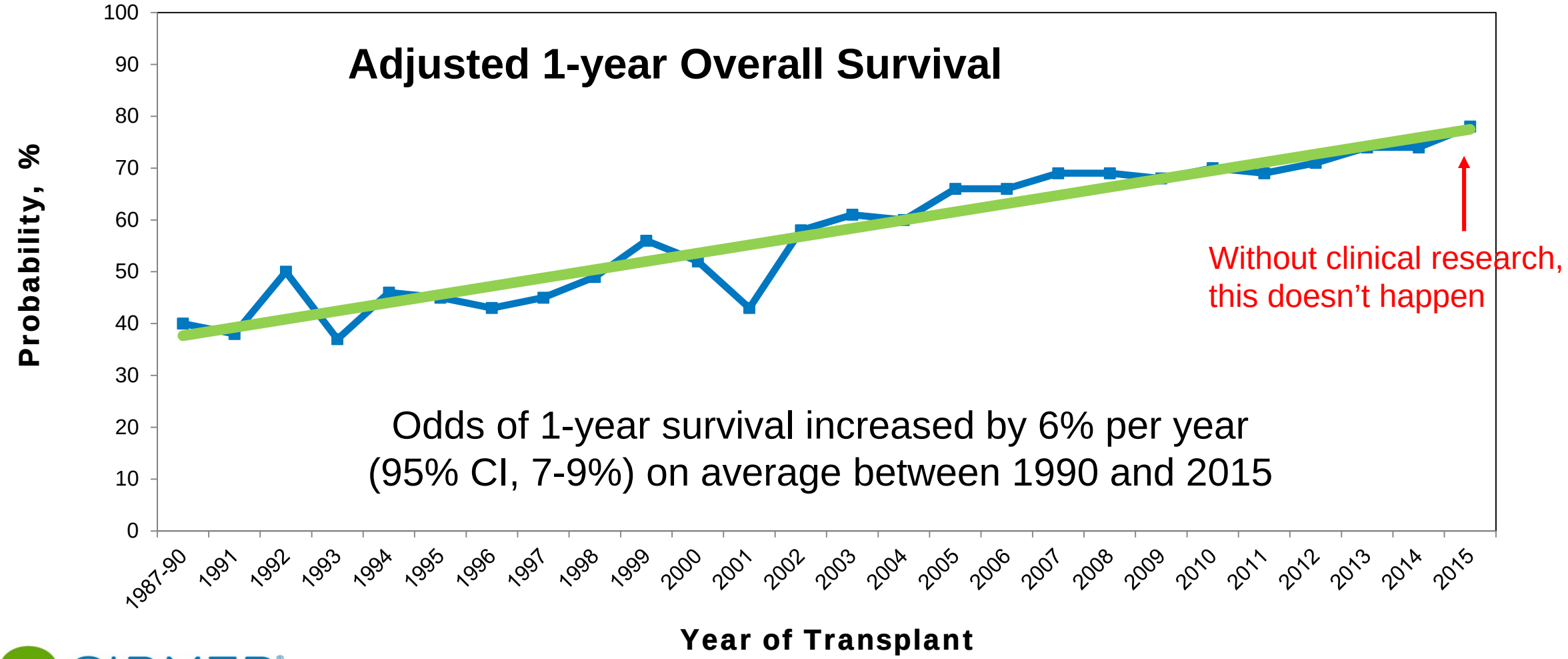

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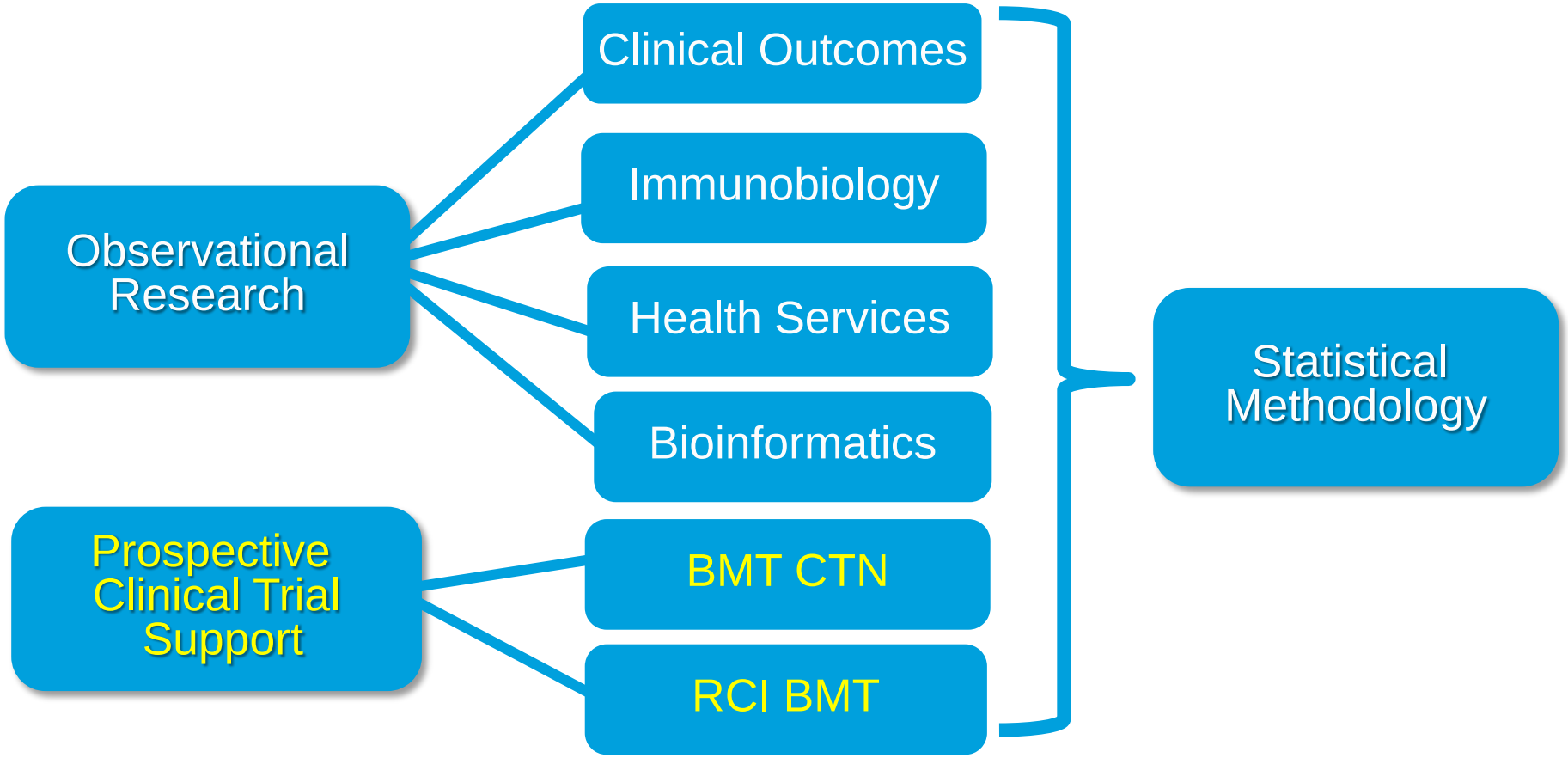
CIBMTR Research Programs



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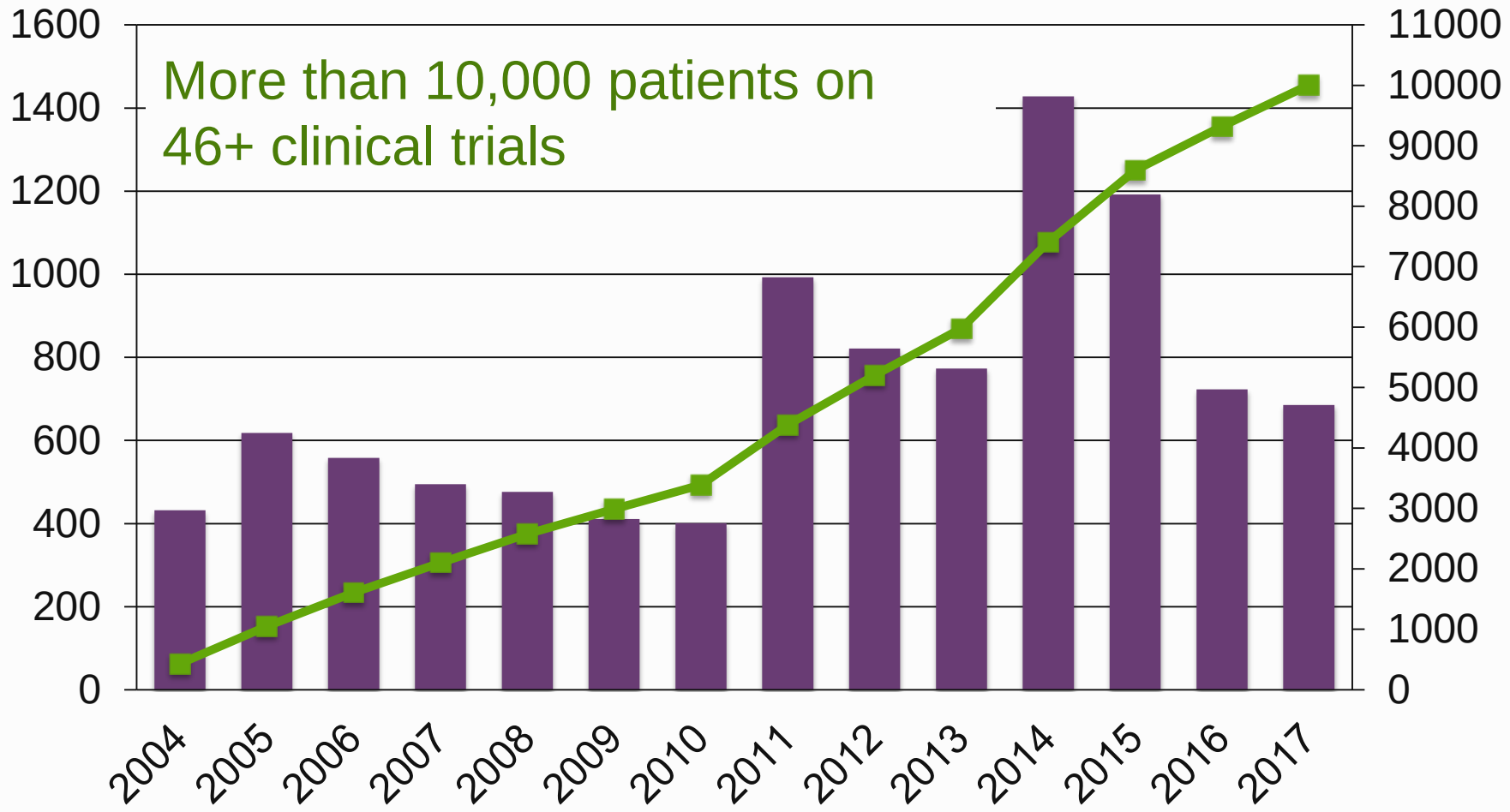
Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

- Established: Sept. 2001; renewed 2006, 2011, 2017
  - 20 Core Centers/Consortia
  - >80 Affiliate Centers
  - 1 Data and Coordinating Center: CIBMTR, NMDP/Be The Match, Emmes Corporation
- Highly productive academic network
  - 46 Trials Opened; 10 currently active
  - 2 FDA registration trials in progress
  - **Uses CIBMTR database to inform trial design and generate prospective control populations**

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN Yearly and Cumulative Accrual to all Protocols, 2004-2017 >10,000 patients



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

High priority studies where clinical trials are needed

- Prevention of relapse in AML/MDS
- Prevention of acute/chronic GVHD
- Role of haploidentical vs matched unrelated donor and/or cord blood
- Better treatments for active GVHD

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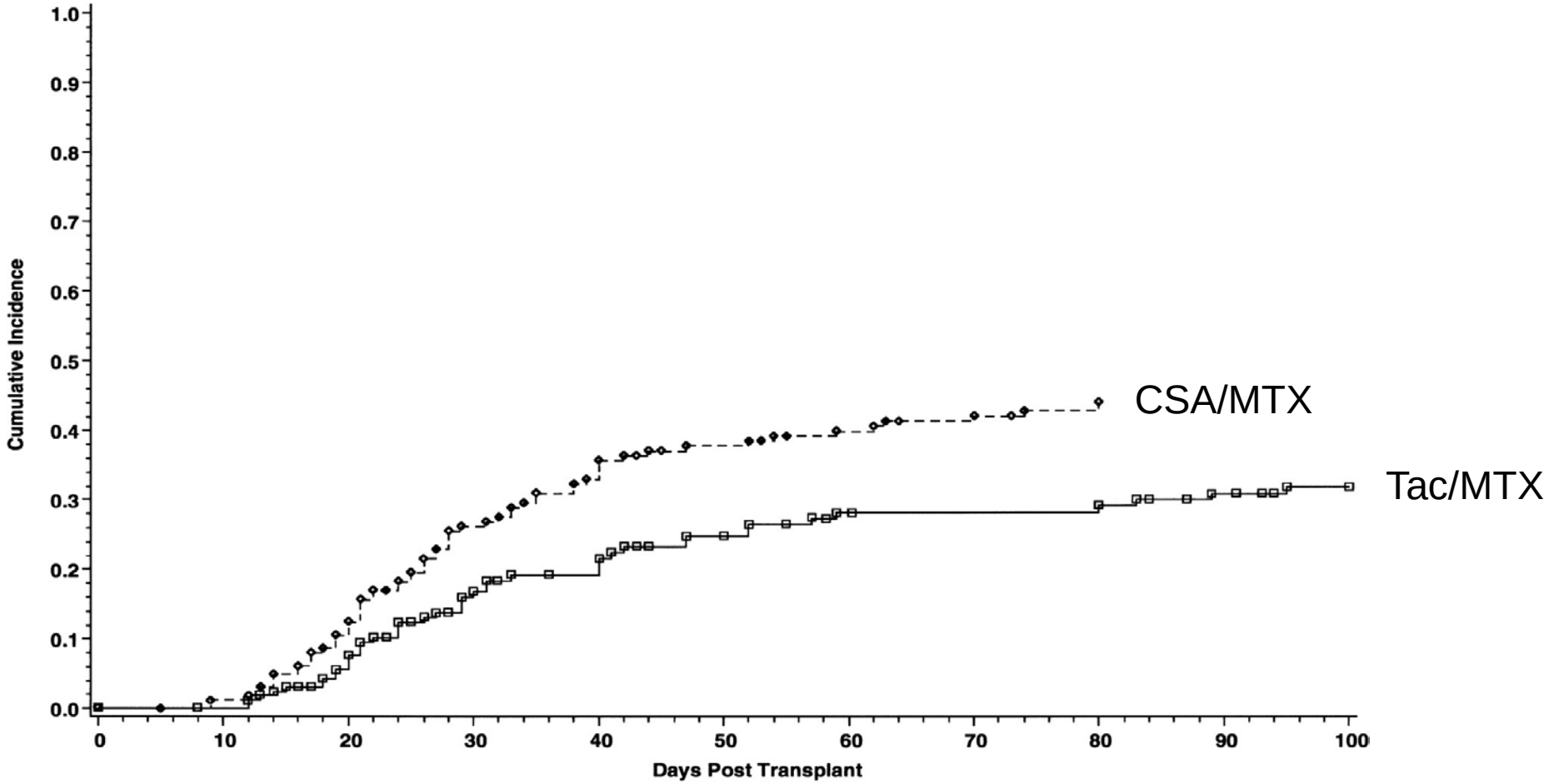
GVHD Target population

- Acute GVHD
  - Prevention
  - Treatment
    - Risk based or all?
    - New onset or steroid refractory?
- Chronic GVHD
  - New onset
  - Steroid refractory/dependent

Current acute GVHD clinical trial landscape

- **Prophylaxis**
  - BMT CTN 1203 (completed; leading to Phase 3 trial)
  - BMT CTN 1301 (just completed)
  - BMS: Abatacept (7/8 and 8/8 unrelated; completed)
  - Takeda: Vedolizumab (phase II)
  - Incyte: Itacitinib (phase I/II)
  - Oncoimmune: CD24Fc (Phase I/II)
  - COG: Lactobacillus phase III
  - Others
    - Tocilizumab
    - Ruxolitinib
    - PRO 140 (CCR5 antibody)
    - Other small studies

Cumulative incidence of grade II-IV acute GVHD of 165 patients who received cyclosporine/methotrexate vs tacrolimus/methotrexate



Voravit Ratanatharathorn et al. Blood 1998;92:2303-2314

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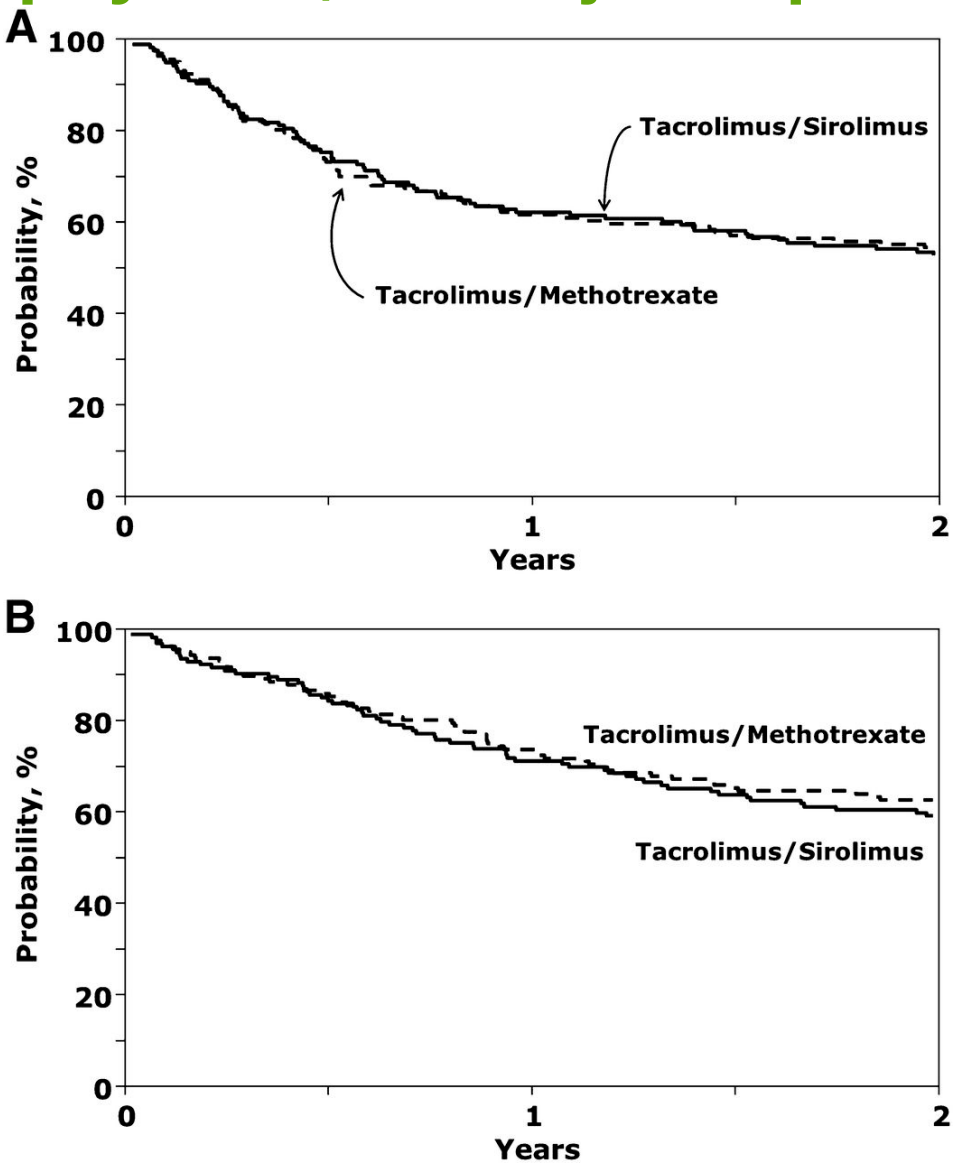
blood™

BMT CTN 0402: Sirolimus Based GVHD Prophylaxis; no major improvement



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Corey Cutler et al. Blood 2014;124:1372-1377

blood™

BMT CTN 1203

A Multi-center Phase II Trial of Randomized Novel Approaches for Graft-versus-Host Disease Prevention Compared to Contemporary Controls

PROGRESS I trial

Prevention and Reduction Of GVHD and Relapse and Enhancing Survival after Stem cell transplantation

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

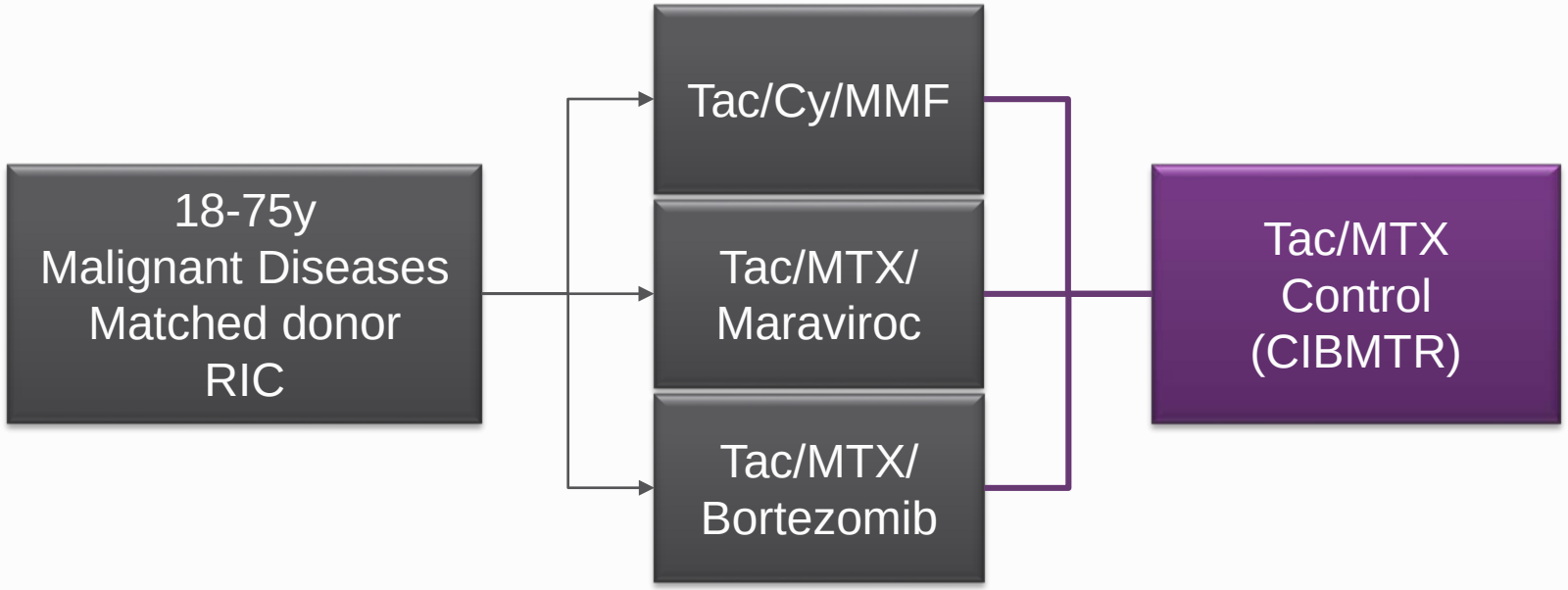
Primary Objective

- Compare GVHD/relapse-free survival (GRFS) after hematopoietic stem cell transplantation (HSCT) between each of three GVHD prophylaxis approaches and a contemporary control.
- GRFS Primary endpoint defined: time to event
  - Grade III-IV Acute GVHD
  - Chronic requiring systemic therapy
  - Disease relapse or progression
  - Death

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROGRESS
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation

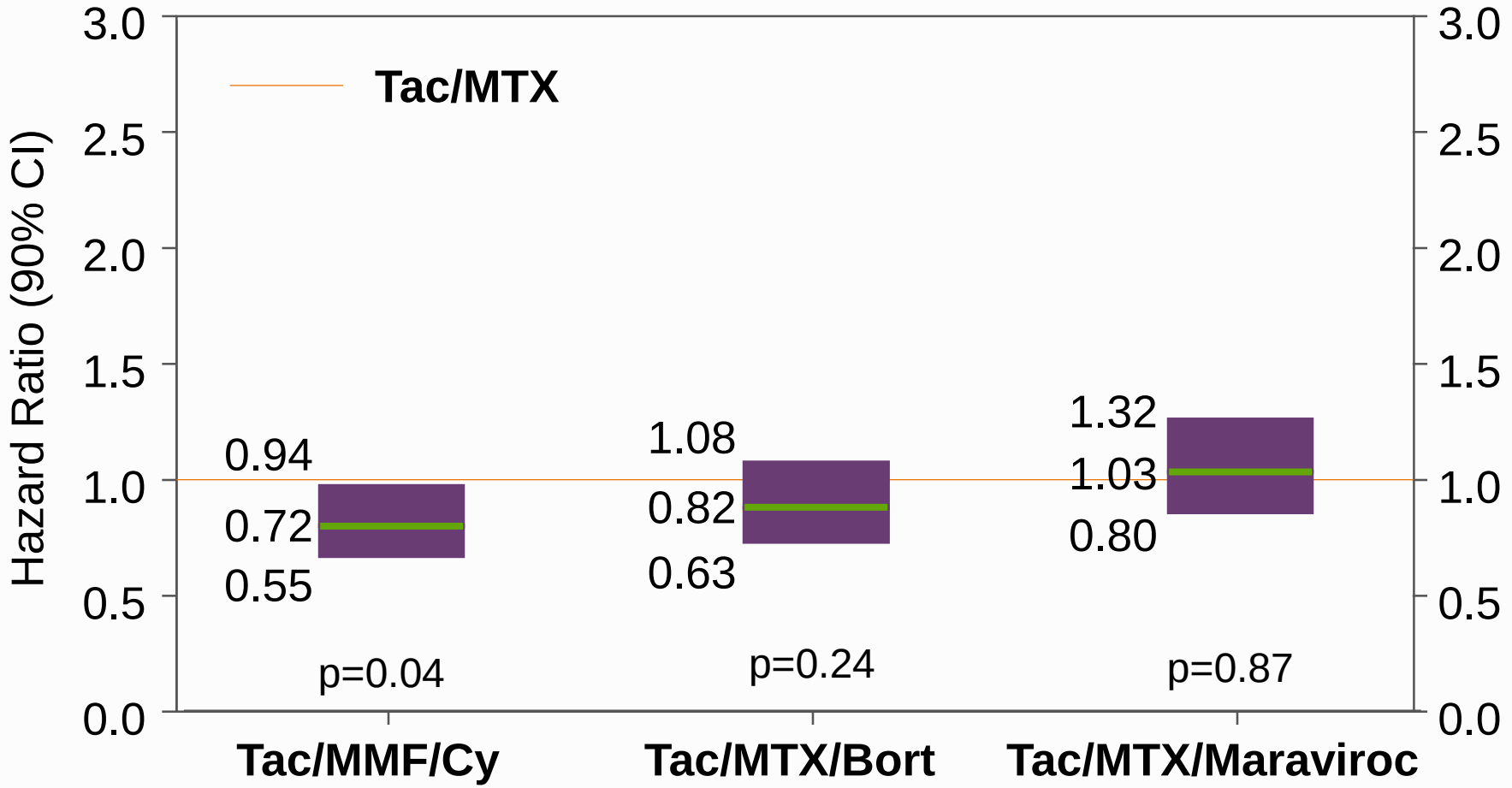
BMT CNT #1203: Study Outline



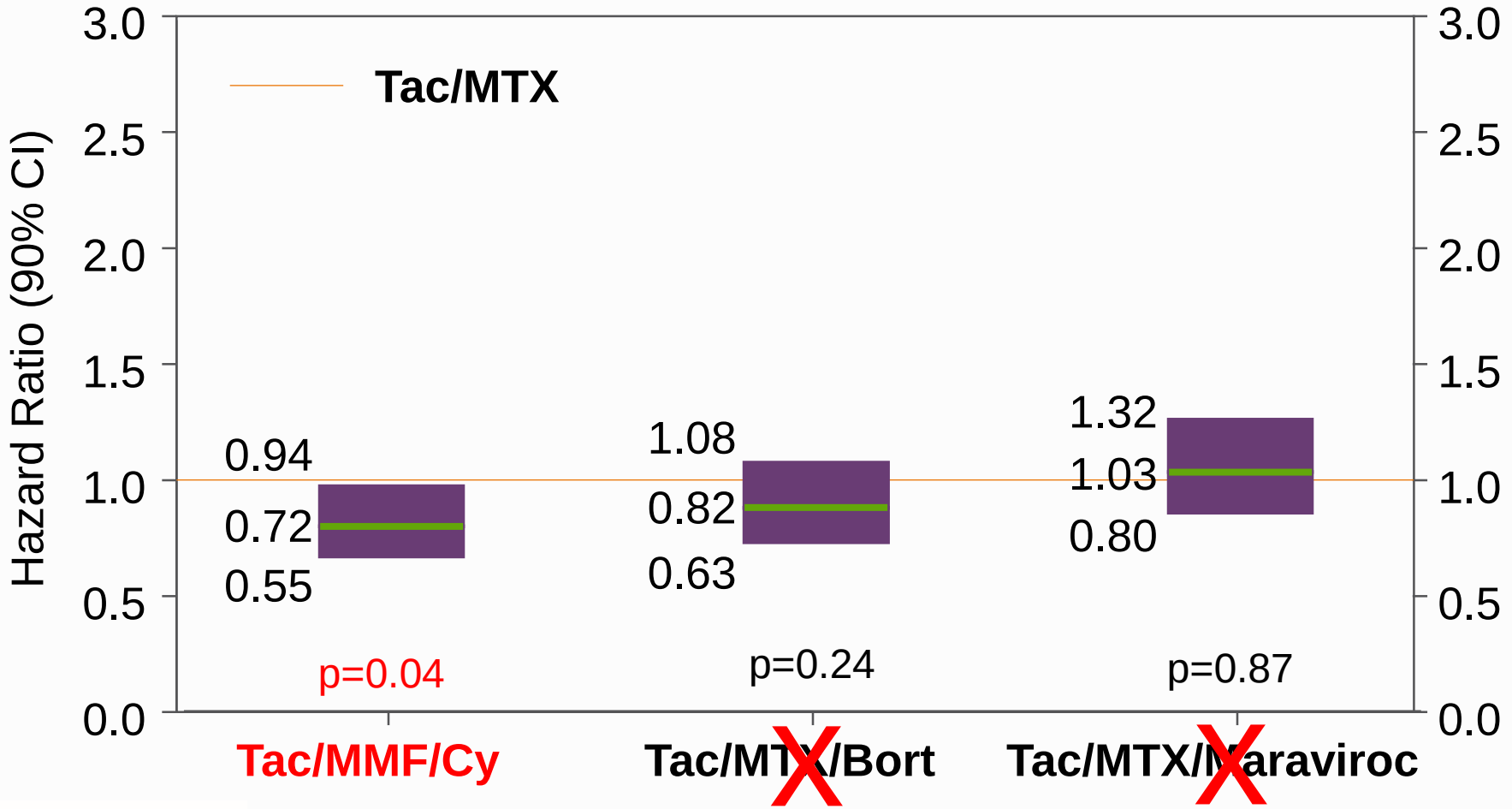
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

PROGRESS
Prevention and Reduction Of Gvhd and Relapse and Enhancing Survival after Stem cell transplantation

GRFS by Treatment Arm Compared to Tac/MTX Controls



GRFS by Treatment Arm Compared to Tac/MTX Controls



Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/ Mycophenolate Mofetil in Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation

BMT CTN 1703 – PROGRESS III

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

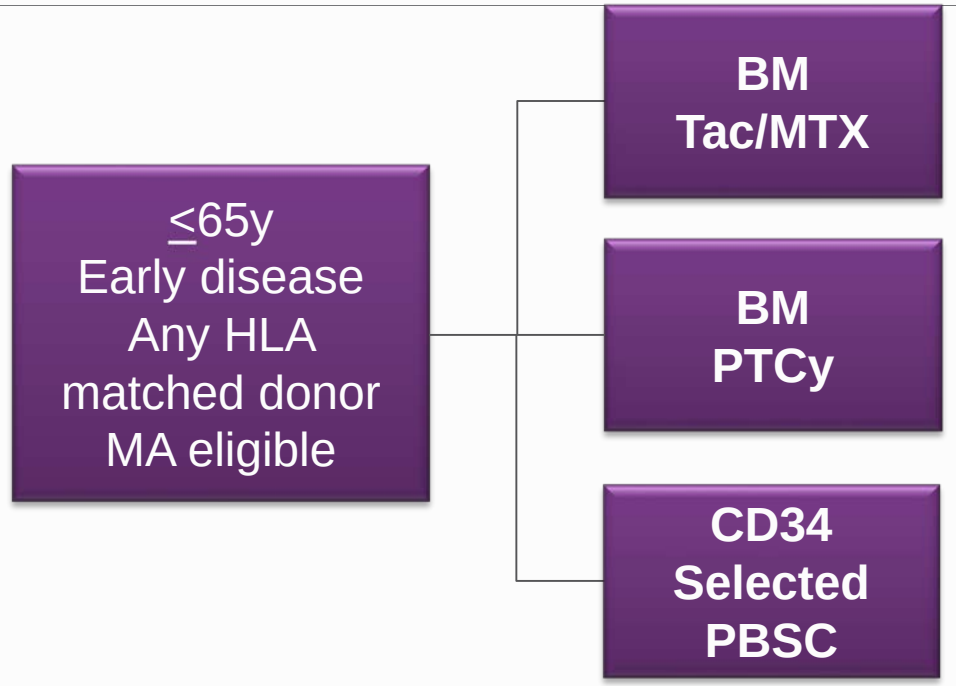
BMT CTN 1301

A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

PROGRESS II trial
Prevention and Reduction Of GVHD and Relapse and Enhancing Survival after Stem cell transplantation

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1301 CNI free Trial: 3-arm Phase III



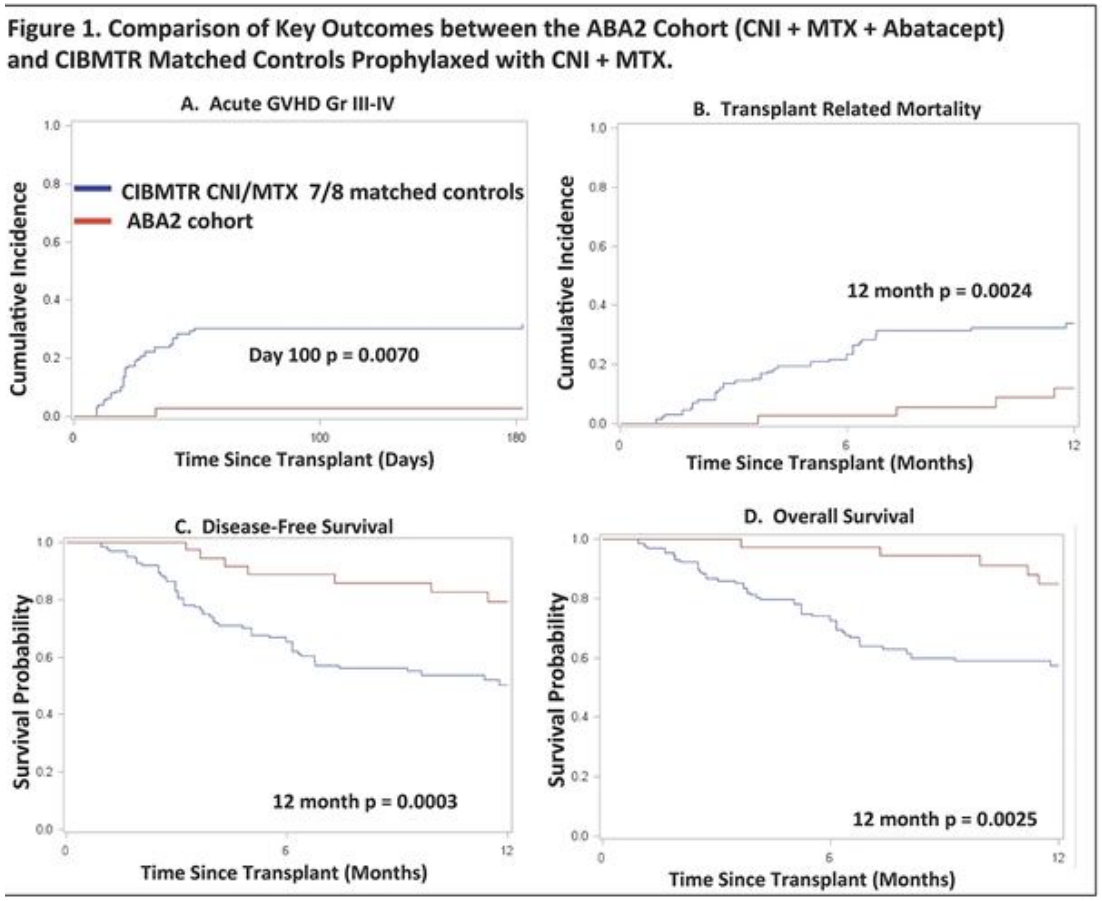
- 345 (115/arm): 85% power to detect a 20% difference over the 22% baseline of the chronic GVHD/relapse-free survival [CRFS] primary endpoint.

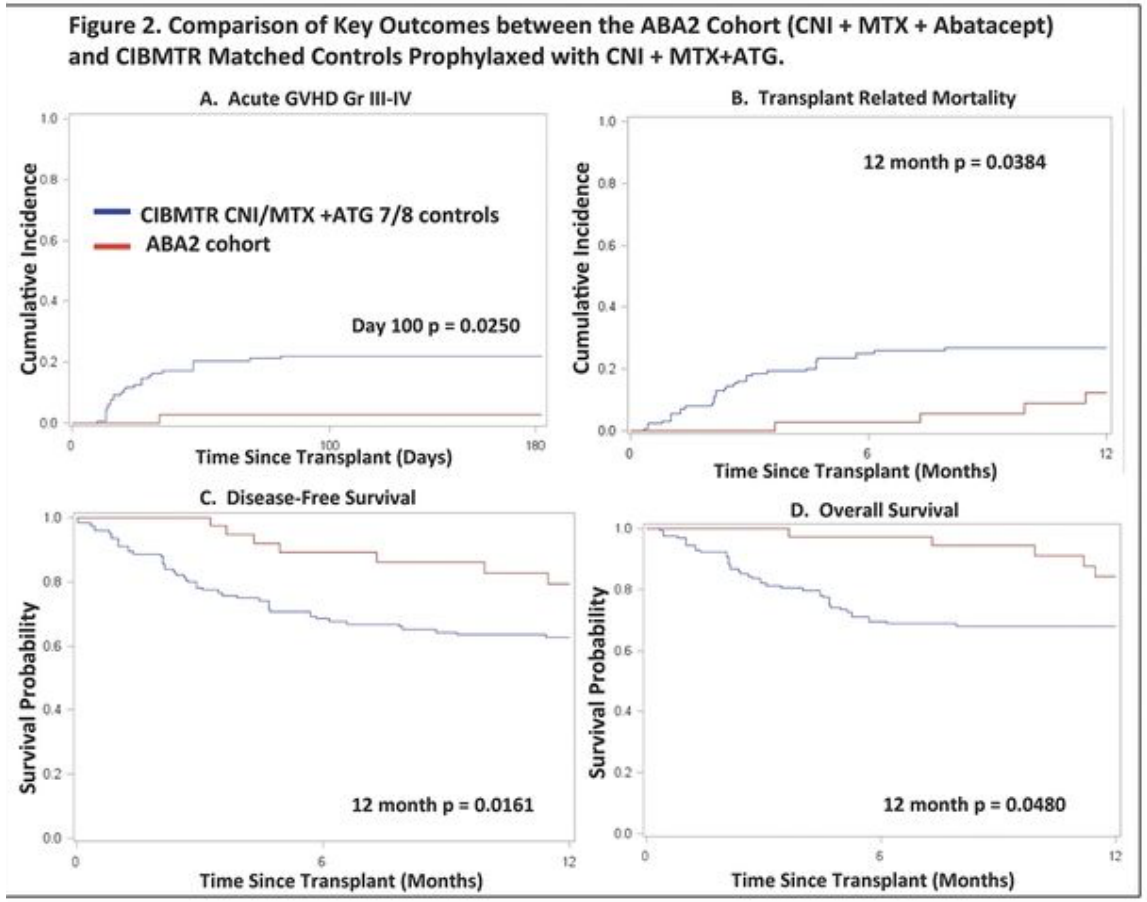
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Accrual completed Summer 2018!

Progress

Abatacept GVHD Prophylaxis in mismatched unrelated transplants





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Watkins, Kean, et al ASH 2017

Are we really moving the needle using pharmacological agents to prevent GVHD?

Graft Manipulation to avoid GVHD

Selective T-cell depletion

αβT-cell depletion (NCT 01810120)

Naïve (CD45RA) T-cell depletion (NCT 00914940)

CD34 selection with “add back” of cells modified to mitigate GVHD

- Photodynamic inactivation (NCT 01794299)
- Suicide gene modification (Casp9) (NCT 01744223)

Treg infusion (sibs/cords)

Stimulate iNKT to increase Treg in vivo (NCT 01379209)

Others (Manipulation of multiple graft constituents)

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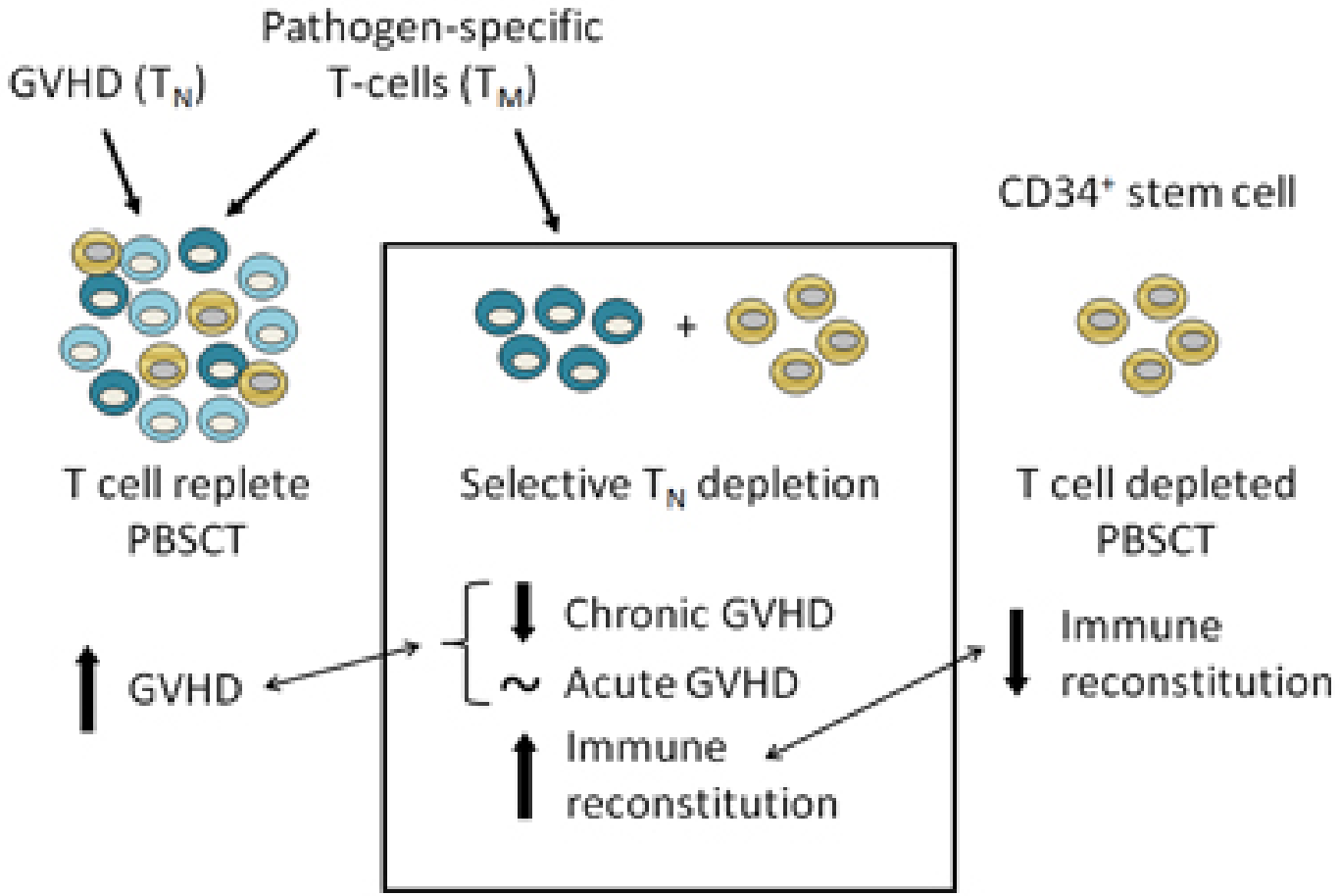
Selective versus total T-cell depletion



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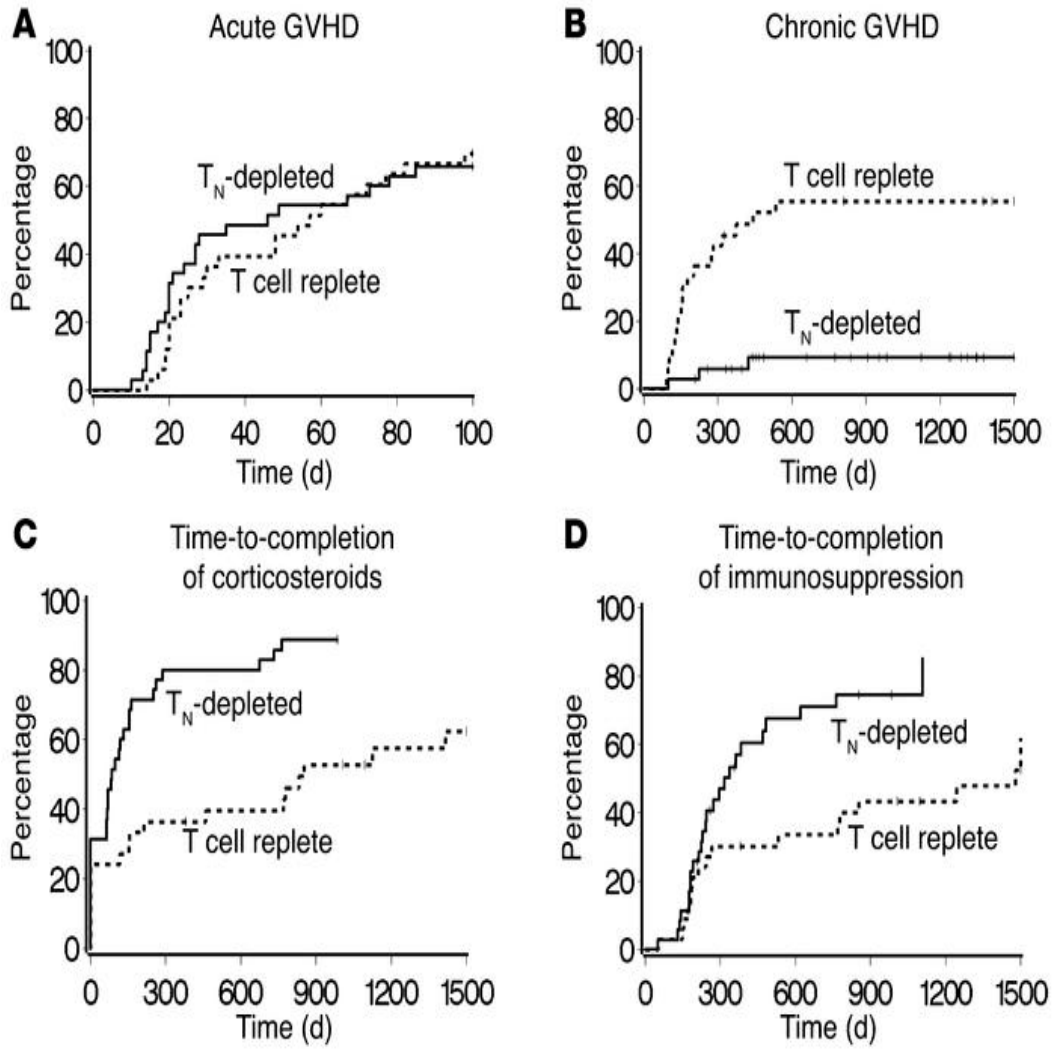
Outcomes of acute leukemia patients transplanted with naive T cell–depleted stem cell grafts



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J Clin Invest DOI: 10.1172/JCI81229

Multi-center phase II randomized controlled trial of naïve T cell depletion for prevention of chronic graft-versus-host disease in children and young adults

Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT) PROTOCOL 16-NTCD
Pediatric Blood and Marrow Transplant Consortium (PBMTC)
GVH1701

Version 1.0
November 02, 2017

Protocol Chairperson

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Warren D. Shlomchik, MD[7]
Monica Thakar, MD[8]
Kirsten Williams, MD[9]

A Pediatric Blood and Marrow Transplant Consortium (PBMTC) study developed in cooperation with the Resource for Clinical Investigation in Blood and Marrow Transplantation (RCI BMT) of the Center for International Blood and Marrow Transplant Research (CIBMTR)/National Marrow Donor Program® (NMDP) and the Fred Hutchinson Cancer Research Center (Fred Hutch). Funding support provided by St. Baldrick's Foundation and Miltenyi Biotec Inc.

Current acute GVHD clinical trial landscape

- **Steroids alone remains gold standard (BMT CTN 0802)**
- **Treatment (newly diagnosed)**
  - BMT CTN 1501 (low risk: steroids versus sirolimus)
  - MAGIC Consortium (high risk: steroids + natalizumab phase II)
  - Germany high risk (steroids plus ECP)
  - **Zemaira: AAT + steroids or placebo phase III for GI GVHD**
    - **BMT CTN 1705 in planning**
  - Incyte: INCB039910 + steroids in high risk (planned)
  - Many others

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Risk-based treatment of new onset acute GVHD

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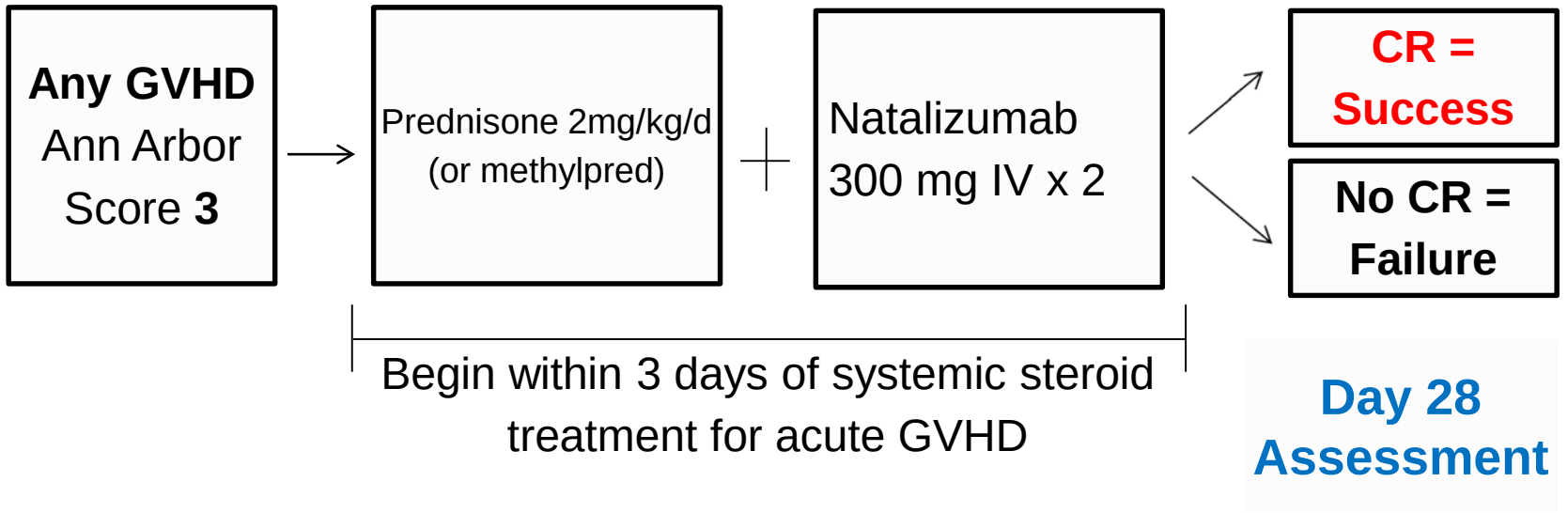
A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

PRIMARY TREATMENT: HIGH RISK GVHD (USA)

PHASE II NATALIZUMAB STUDY SCHEMA



- High BM score (AA3) GVHD = high NRM (45%), low steroid response @ day 28 (30%)
- Treatment failure due to Steroid Resistant GI GVHD
- Test whether adding natalizumab will increase CR rate @ day 28 to 45%
- **KEY ASSUMPTION: 20% of screened patients would enroll**

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BMT CTN 1705

Alpha 1 – Antitrypsin

(AAT, ZEMAIRA®) for the Treatment of High Risk Acute Graft vs. Host Disease (GVHD)

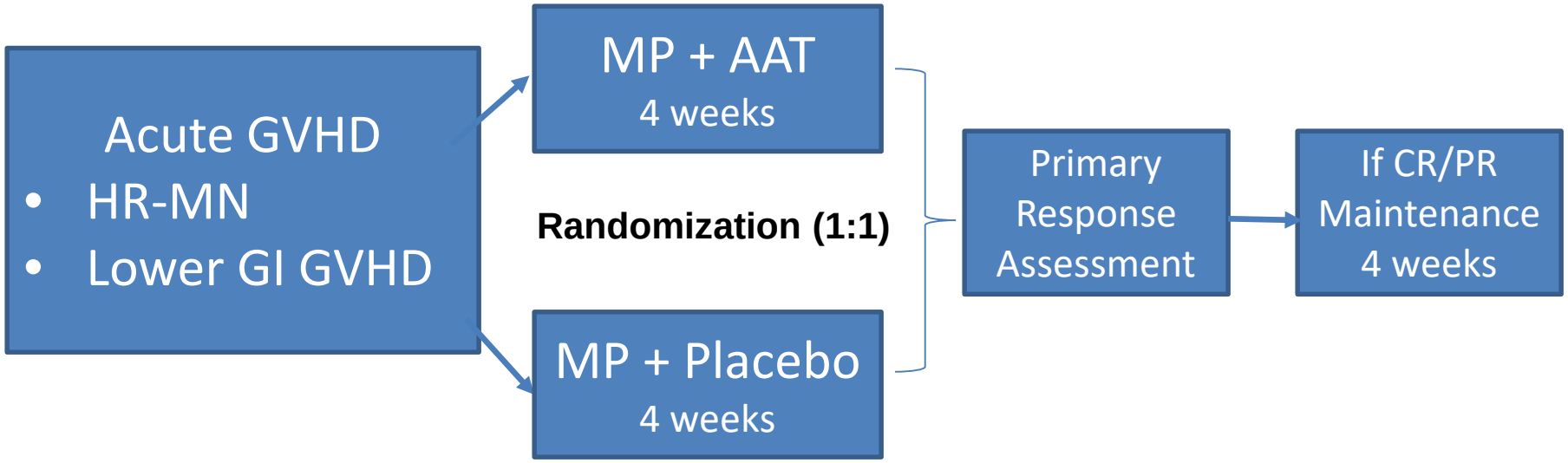
Study Chairs: John Magenau & Amin Alousi

Protocol Officer: Mehdi Hamadani

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1705 Design

Phase III Randomized, Double-Blind, Placebo Controlled



MP, methylprednisolone (1.6 mg/kg/day or equivalent)

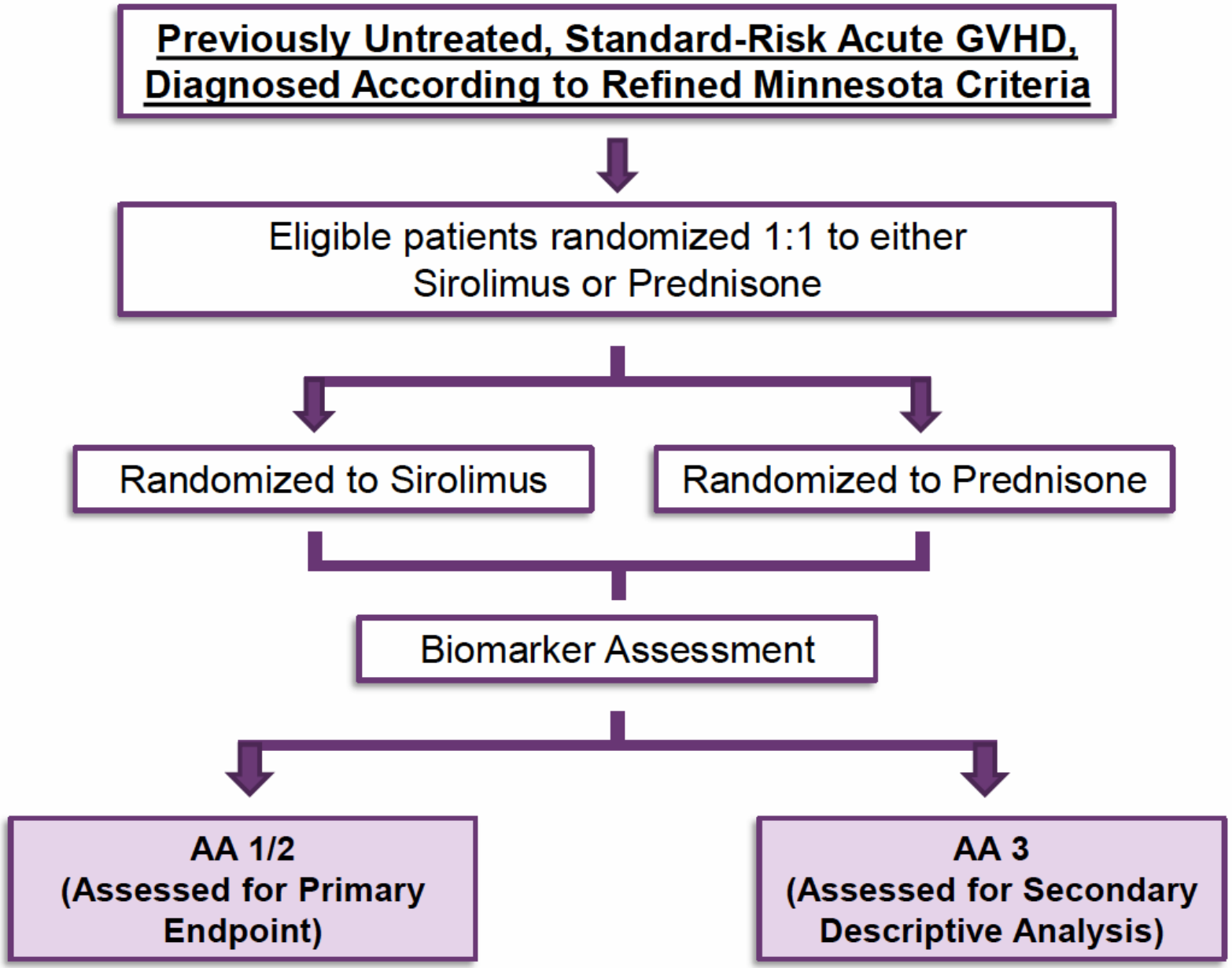
A Randomized, Phase II, Multicenter, Open Label Study Evaluating Sirolimus and Prednisone in Patients with Refined Minnesota Standard Risk, Ann Arbor 1/2 Confirmed Acute Graft-Versus-Host Disease

BMT CTN PROTOCOL 1501

Objectives

- Primary
  - Rate of CR/PR at day 28 after randomization in patients with Ann Arbor 1/2 biomarker status

- Secondary
  - CR/PR + ≤ 0.25mg/kg/day prednisone at day 28 post randomization
  - Additional response time points
  - Steroid exposure
  - Infectious complications
  - Toxicity
  - Disease-free and GVHD-free survival
  - Patient-reported outcomes
  - Steroid myopathy


Previously Untreated, Standard-Risk Acute GVHD, Diagnosed According to Refined Minnesota Criteria
Eligible patients randomized 1:1 to either Sirolimus or Prednisone
Randomized to Sirolimus
Randomized to Prednisone
Biomarker Assessment
AA 1/2 (Assessed for Primary Endpoint)
AA 3 (Assessed for Secondary Descriptive Analysis)

Clinical Trials of Graft or Donor Source

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

Five Year Results of BMT CTN 0201

Unrelated donor bone marrow is associated with better psychological well-being and less burdensome chronic GVHD symptoms than peripheral blood

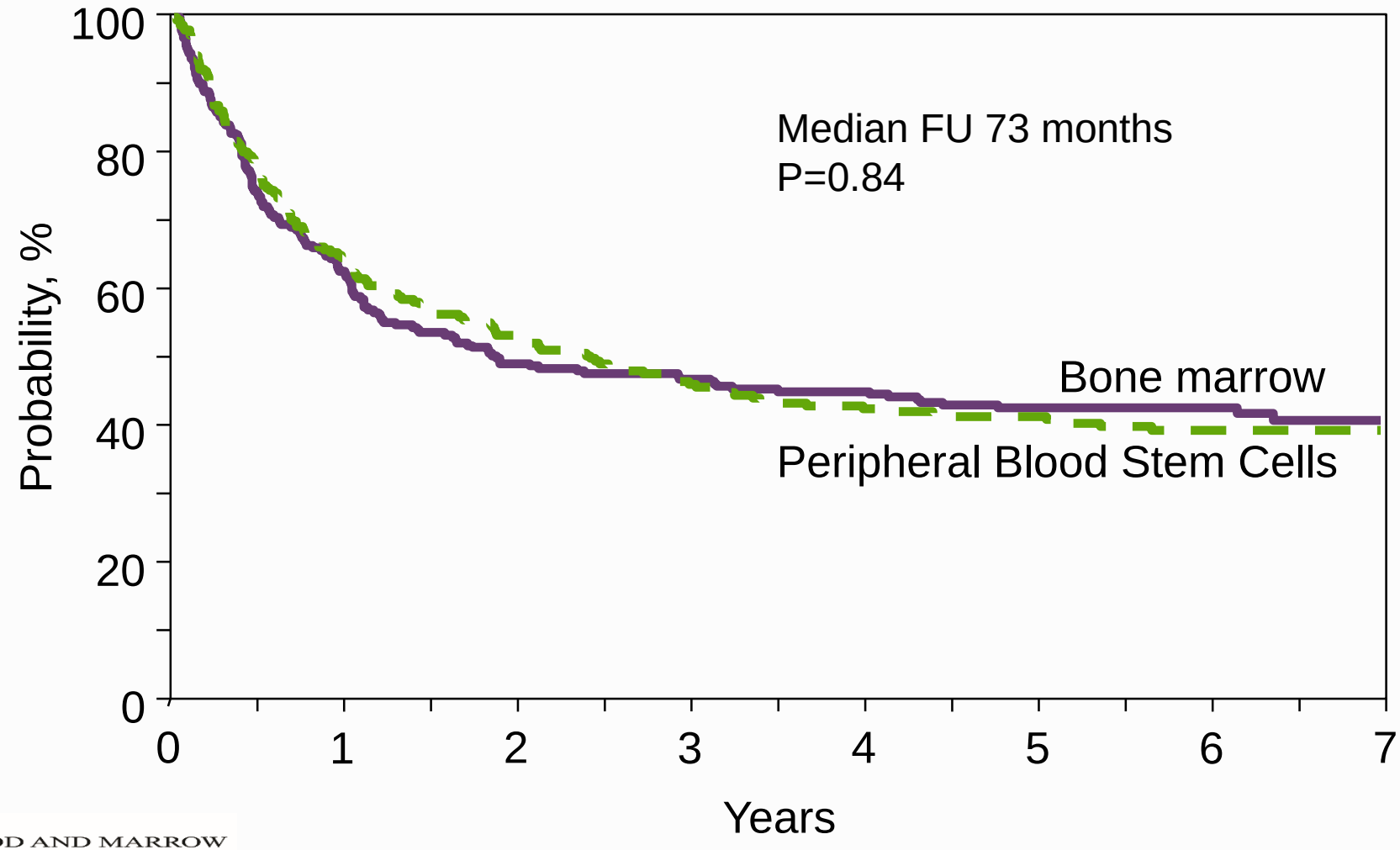
BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Parent Trial Eligibility Criteria

- Age up to 66 years
- First transplant
- Acute and chronic leukemia, MDS, MF
- 5/6 or 6/6 match at HLA-A, B, DRB1
  - 98% 7/8 or 8/8 matched
- No active infection

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Overall Survival



BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Lee et al, JAMA Oncol 2016

Five year results of BM vs. PB

QOL scale	Bone marrow (n=102)	Peripheral blood (n=93)	P value	Clinically significant difference[1]	Difference between BM and PB (95% CI)[2]
FACT-BMT TOI (↑ better) Mean +/- SE	**76.7 +/- 1.6 (n=79)**	**70.5 +/- 1.9 (n=69)**	**0.014**	**8.5**	**6.2 (1.3-11.1)**
MHI – Psychological well-being (↑ better) Mean +/- SE	**78.9 +/- 1.7 (n=80)**	**72.2 +/- 1.9 (n=72)**	**0.011**	**8.4**	**6.7 (1.6-11.8)**
MHI-Psychological Distress (↓ better) Mean +/- SE	**16.0 +/- 1.3 (n=80)**	**19.0 +/- 1.5 (n=71)**	**0.128**	**6.5**	**-3.0 (-6.8,0.9)**
Chronic GVHD symptoms (↓better) Mean +/- SE	**13.1 +/- 1.5 (n=80)**	**19.3 +/- 1.6 (n=72)**	**0.004**	**7.1**	**-6.3 (-10.5, -2.0)**

FACT-BMT TOI, Functional Assessment of Cancer Therapy, Bone Marrow Transplant Trial Outcome Index; MHI, Mental Health Inventory; GVHD, Graft-versus-Host Disease; SE, standard error

[1]0.5 x STD

[2]Adjusted for enrollment values and missing data using inverse probability weighting using significant clinical characteristics

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Conclusions

- At 5 years after HCT, recipients of unrelated donor BM, compared with PB, have:
  - Better psychological well-being
  - Less burdensome chronic GVHD symptoms
  - Are 50% more likely to go back to work
  - Similar survival, relapse, TRM
- No outcome for which PB was better
- PB is still used for >75% of unrelated donor transplants!

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

Lee et al, JAMA Oncol 2016

Clinical Trials to Prevent Relapse

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Strategies to mitigate post allograft relapse in AML

- Current approaches
  - Augmenting/optimizing conditioning
    - Targeted busulfan
    - Additional drugs
    - Modulating/escalating TBI
      - Tomotherapy, IMRT
    - Radioimmunotherapy
    - Addition of non-conventional agents
  - Post/peri transplant therapy
    - Cellular
      - T-cells (non-specific, antigen specific), NK cells, CARTs, TCRs, other
    - Maintenance agents
      - » HMA, TKI (Flt3 inh, Jak inh), IMIDs,
      - » Antibodies (anti CD33, antiKIR, etc), cytokines (IL15, others)
      - » Checkpoint blockade (CTLA4, PD1, others)
  - Optimizing allograft composition
    - We should be studying graft composition/manipulation more

BMT CTN 1506

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3-ITD AML

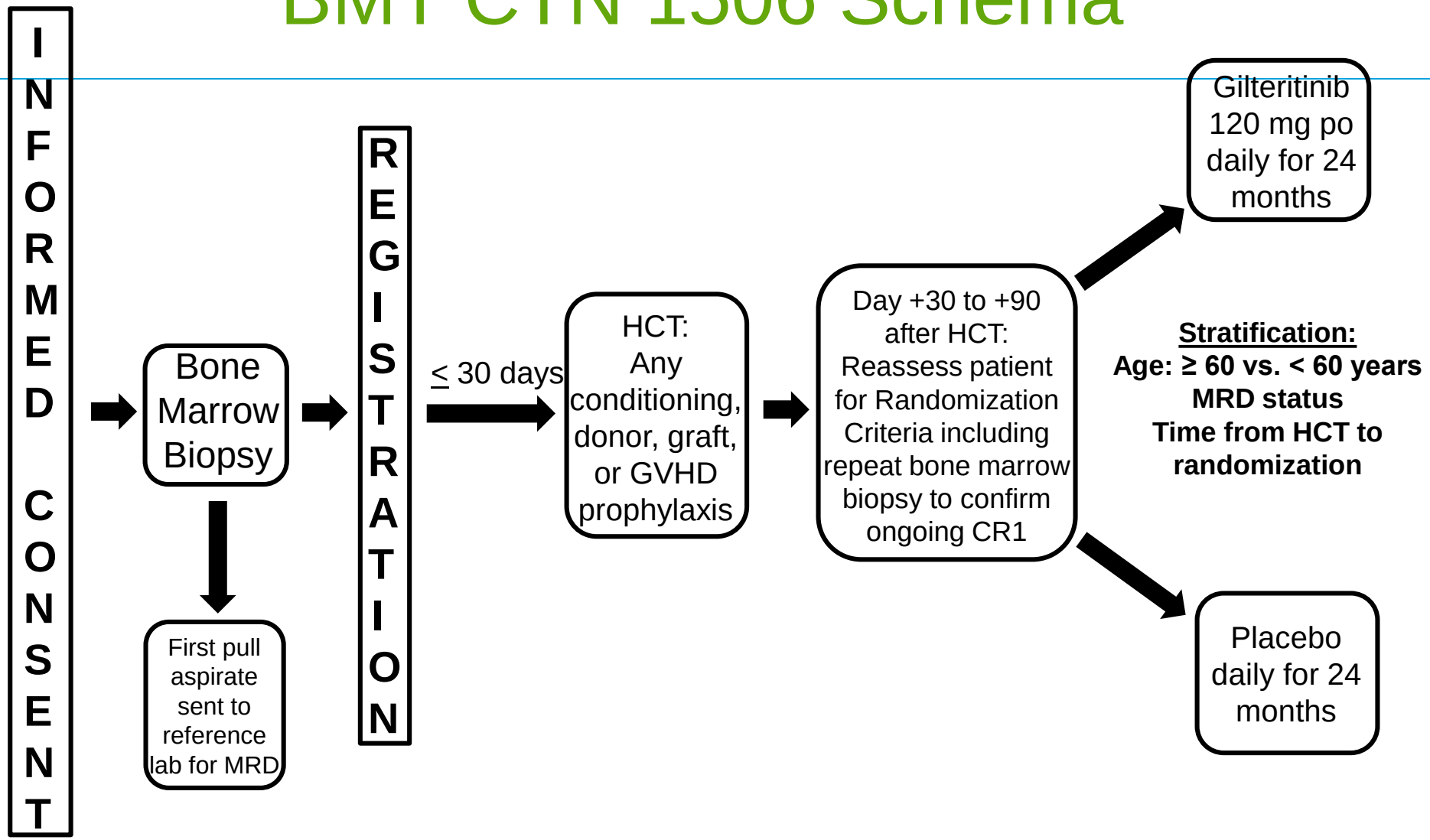
Study Chairs: Yi-Bin Chen, MD, Mark Levis, MD, PhD

BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

BMT CTN 1506

- **Primary objective**
  - Compare 2-year leukemia-free survival (LFS) between the two arms
    - Measured from the time of randomization
    - Morphological relapse as defined in Revised IWG criteria (reappearance of leukemic blasts in the PB or ≥ 5% blasts in the BM not attributable to any other cause)

BMT CTN 1506 Schema



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Actinium Pharmaceuticals, Inc.

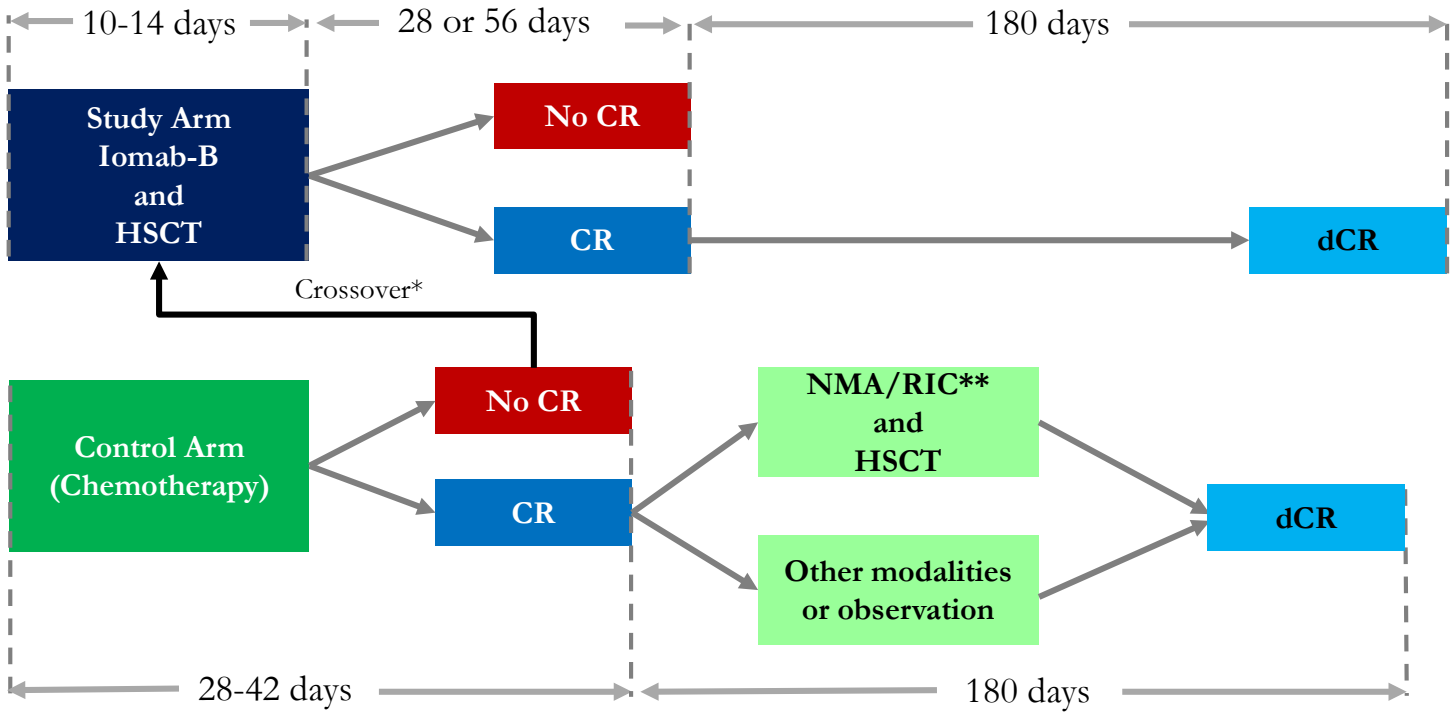
Anti-CD45 mAb BC8 Radiolabeled with I^{131} for HSCT Bone Marrow Conditioning

SIERRA

STUDY OF IOMAB-B IN ELDERLY RELAPSED/REFRACTORY AML

Pivotal Phase 3 SIERRA Trial Design

- Trial design as discussed with FDA[1]:
  - Single pivotal study, pending trial results
  - Patient population: patients 55 years of age or older relapsed or refractory AML [2]
  - 1:1 randomization
  - Trial arms: study arm and control arm with physician's choice of conventional care with curative intent
  - Trial size: 150 patients total, 75 patients per arm



*Control arm subjects with no CR are offered crossover to Iomab-B for ethical reasons.
**Nonmyeloablative Conditioning/Reduced Intensity Conditioning.

1. Based on the End of Phase II meeting and subsequent communications with the FDA.
2. Refractory is defined as either primary failure to achieve a complete remission after 2 cycles of induction therapy; relapsed after <6 months in complete remission; second or higher relapse; or relapsed disease not responding to intensive salvage therapy

Many other studies designed to reduce relapse

- NK-cells
  - Several
  - BMT CTN 1803
- Oral azacytidine
- Vyxeos
- Panabinostat
- Others

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Cellular Immunotherapy for Cancer

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A research collaboration between the National Marrow Donor Program (NMDP)/Be The Match and the Medical College of Wisconsin

What is adoptive cellular therapy?

- Strategy based on ex vivo manipulation of immune cells to enhance anti-tumor activity

- Autologous or allogeneic immune cells transferred to a recipient to elicit an anti-neoplastic effect

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Chimeric Antigen Receptor Therapy

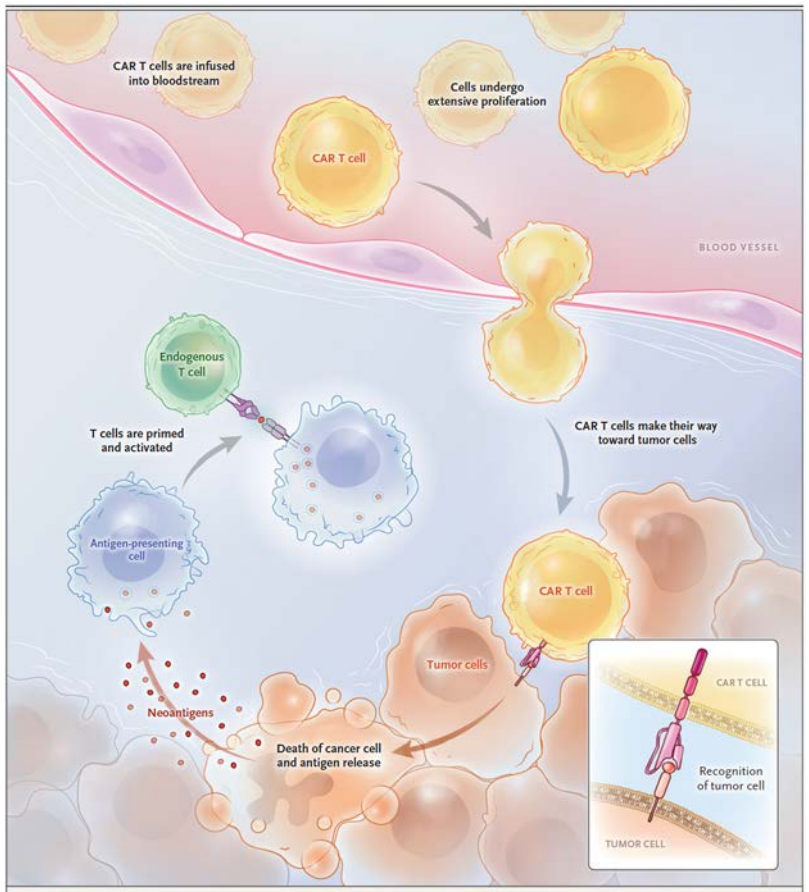

Figure 1. Chimeric Antigen Receptor (CAR) T Cells Engrafting, Trafficking to Tumor, and Proliferating Extensively after Infusion.
After infusion, CAR T cells leave the blood and travel to sites of tumor, where they identify and kill tumor cells. This can trigger extensive proliferation of CAR T cells and the release of tumor antigens, which activates the immune system to recruit non–CAR T cells, thus eliciting further antitumor responses in a process known as cross priming.

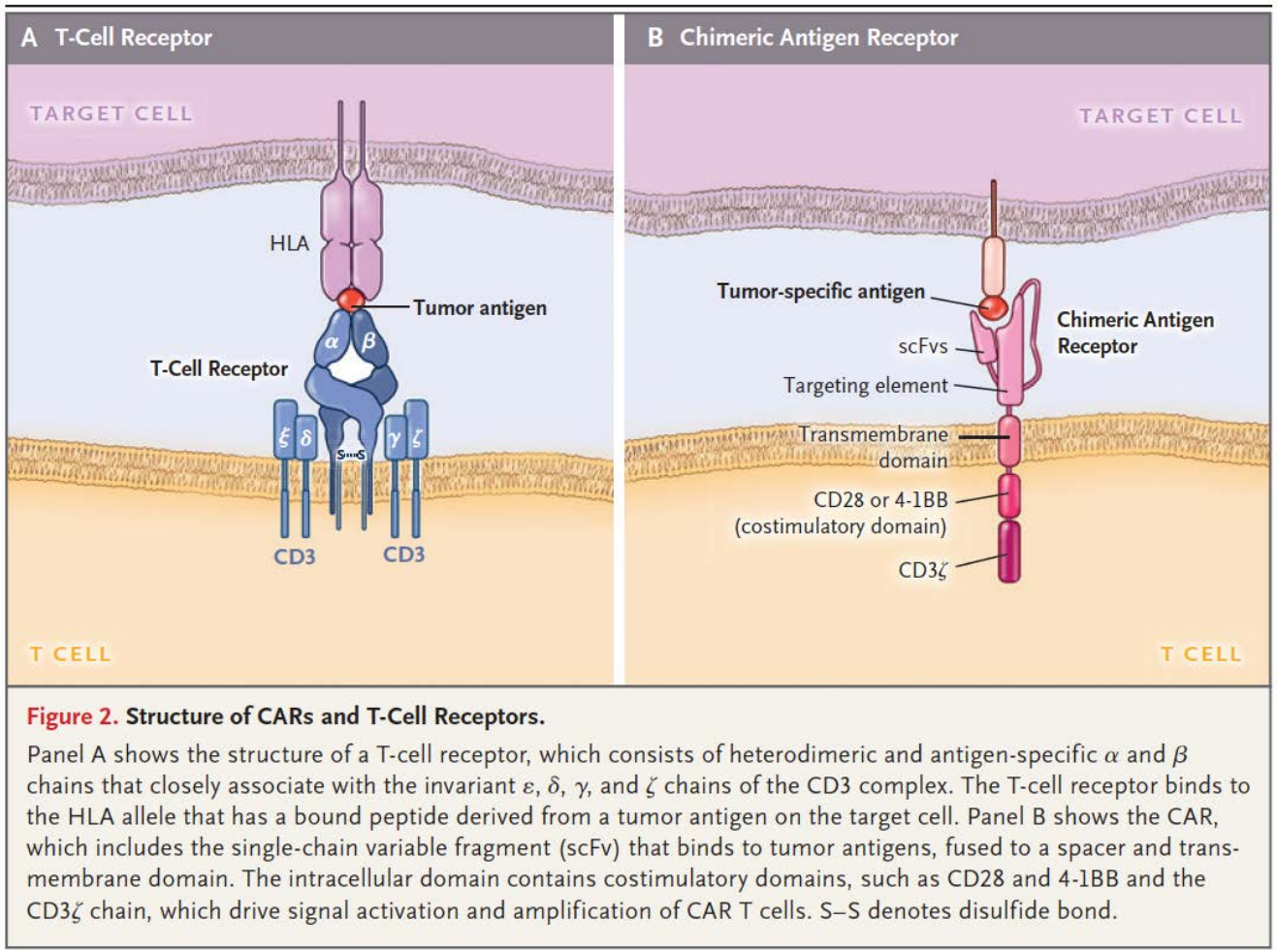

Figure 2. Structure of CARs and T-Cell Receptors.
Panel A shows the structure of a T-cell receptor, which consists of heterodimeric and antigen-specific α and β chains that closely associate with the invariant ε, δ, γ, and ζ chains of the CD3 complex. The T-cell receptor binds to the HLA allele that has a bound peptide derived from a tumor antigen on the target cell. Panel B shows the CAR, which includes the single-chain variable fragment (scFv) that binds to tumor antigens, fused to a spacer and transmembrane domain. The intracellular domain contains costimulatory domains, such as CD28 and 4-1BB and the CD3ζ chain, which drive signal activation and amplification of CAR T cells. S–S denotes disulfide bond.

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June and Sadelain, New Engl J Med 2018

Efficacy and Toxicity of CAR T-cell Therapy

Table 1. Responses to CAR T-Cell Therapy.*

Disease	Response Rate	Comments	Reference
	percent		
Leukemia			
B-cell acute lymphoblastic leukemia (in adults)	83–93	High initial remission rates; unresolved issue is whether CAR T-cell therapy is definitive therapy or should be followed by allogeneic hematopoietic stem-cell therapy	Park et al.,[35] Davila et al.,[36] Turtle et al.[37]
B-cell acute lymphoblastic leukemia (in children)	68–90	Approximately 25% of patients reported to have a relapse with CD19-negative or CD19-low leukemia; CD22 CAR T cells may improve survival among some patients with CD19 relapses	Maude et al.,[34] Maude et al.,[38] Fry et al.,[39] Lee et al.[40]
Chronic lymphocytic leukemia	57–71	Relapse is rare in patients who have a complete response; ibrutinib appears to increase response rates	Porter et al.,[41] Turtle et al.[42]
Lymphoma			
Diffuse large B-cell lymphoma	64–86	Approximately 40–50% of patients reported to have a durable complete response	Turtle et al.,[43] Kochenderfer et al.,[44] Schuster et al.,[45] Neelapu et al.[46]
Follicular lymphoma	71	At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response	Schuster et al.[45]
Transformed follicular lymphoma	70–83	A total of 3 of 3 patients with transformed follicular lymphoma had a complete response	Turtle et al.,[43] Schuster et al.,[45] Neelapu et al.[46]
Refractory multiple myeloma	25–100	B-cell maturation antigen CAR T cells; stringent complete response in approximately 25% of patients	Ali et al.,[47] Fan et al.,[48] Berdeja et al.[49]
Solid tumors			
Glioblastoma	ND	In case report from phase 2 study, complete response on magnetic resonance imaging after intravenous and cerebrospinal fluid administration of CAR T cells; response lasted 7.5 mo	Brown et al.[50]
Pancreatic ductal adenocarcinoma	17	In one patient with liver metastasis, CAR T-cell treatment produced a complete metabolic response in the liver but was ineffective against the primary pancreatic tumor	Beatty et al.[51]

* ND denotes not determined.

Table 2. Reported Toxic Effects of CAR T Cells.

CAR Specificity and Adverse Effect	Reference
CD19 CAR	
B-cell aplasia and hypogammaglobulinemia	Kochenderfer et al.,[52] Kalos et al.[53]
Cytokine release syndrome	Davila et al.,[36] Lee et al.,[54] Teachey et al.[55]
Dermatitis	Rubin et al.[56]
Hematophagocytic lymphohistiocytosis and macrophage activation syndrome	Grupp et al.,[32] Porter et al.,[41] Teachey et al.[55]
Neurologic effects such as ataxia and aphasia	Brudno and Kochenderfer[57]
Cerebral edema	Gust et al.[58]
B-cell maturation antigen CAR: the cytokine release syndrome	Riches et al.[59]
Mesothelin CAR: anaphylaxis (antibody to murine single-chain variable fragments)	Maus et al.[60]
Carbonic anhydrase IX CAR: cholangitis (on-target)	Lamers et al.[61]
HER2/neu CAR: lethal cytokine release syndrome	Morgan et al.[62]
Carcinoembryonic antigen–related cell-adhesion molecule 5 (CEACAM5) CAR: hemorrhagic colitis (on-target)	Thistlethwaite et al.[63]

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June and Sadelain, New Engl J Med 2018

Original Article

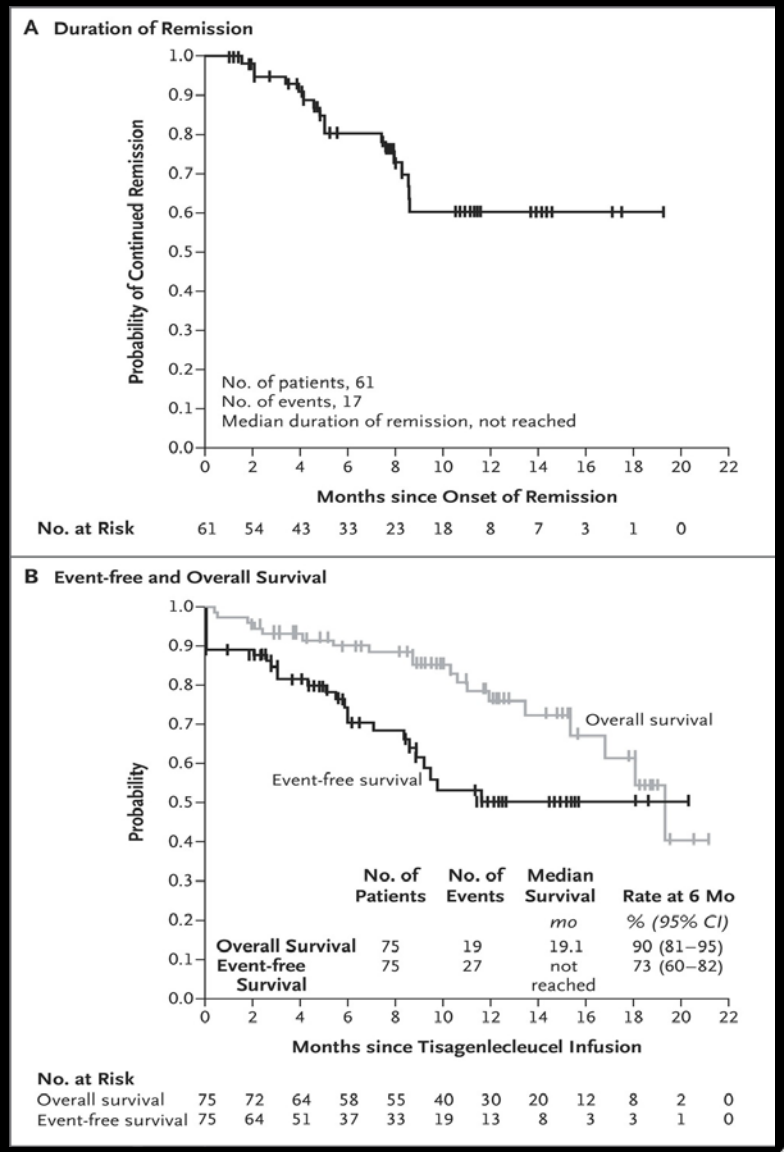
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

Shannon L. Maude, M.D., Ph.D., Theodore W. Laetsch, M.D., Jochen Buechner, M.D., Ph.D., Susana Rives, M.D., Ph.D., Michael Boyer, M.D., Henrique Bittencourt, M.D., Ph.D., Peter Bader, M.D., Michael R. Verneris, M.D., Heather E. Stefanski, M.D., Ph.D., Gary D. Myers, M.D., Muna Qayed, M.D., Barbara De Moerloose, M.D., Ph.D., Hidefumi Hiramatsu, M.D., Ph.D., Krysta Schlis, M.D., Kara L. Davis, D.O., Paul L. Martin, M.D., Ph.D., Eneida R. Nemecek, M.D., Gregory A. Yanik, M.D., Christina Peters, M.D., Andre Baruchel, M.D., Nicolas Boissel, M.D., Ph.D., Francoise Mechinaud, M.D., Adriana Balduzzi, M.D., Joerg Krueger, M.D., Carl H. June, M.D., Bruce L. Levine, Ph.D., Patricia Wood, M.D., Ph.D., Tetiana Taran, M.D., Mimi Leung, M.P.H., Karen T. Mueller, Pharm.D., Yiyun Zhang, Ph.D., Kapildeb Sen, Ph.D., David Lebwohl, M.D., Michael A. Pulsipher, M.D., and Stephan A. Grupp, M.D., Ph.D.

N Engl J Med
Volume 378(5):439-448
February 1, 2018

The NEW ENGLAND JOURNAL of MEDICINE

Duration of Remission, Event-free Survival, and Overall Survival.



Maude SL et al. N Engl J Med 2018;378:439-448

The NEW ENGLAND JOURNAL of MEDICINE

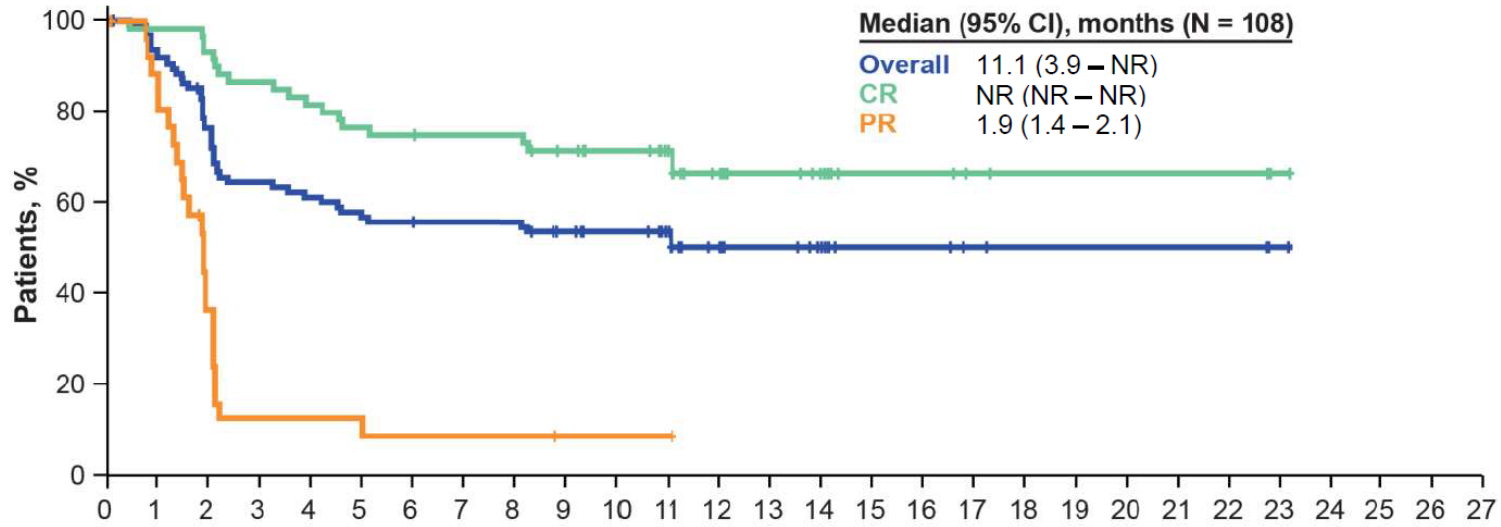
ZUMA-1: Objective Response

	Phase 2 Primary Analysis N = 101		Phase 1 and 2 Updated Analysis N = 108	
Median follow-up, mo	8.7		15.4	
	ORR	**CR**	**ORR**	**CR**
Best objective response, %	82	54	82	58
Ongoing, %	44	39	42	40

- 57% of patients in phase 1 obtained a CR
- In the updated analysis, 23/60 patients with either a PR (11/35) or SD (12/25) at the first tumor assessment (1 mo post–axi-cel) subsequently achieved CR up to 15 months post-infusion without additional therapy
  - Median (range) time to conversion from PR to CR = 64 (49 – 424) days

Response was evaluated by investigator assessment.
CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease.

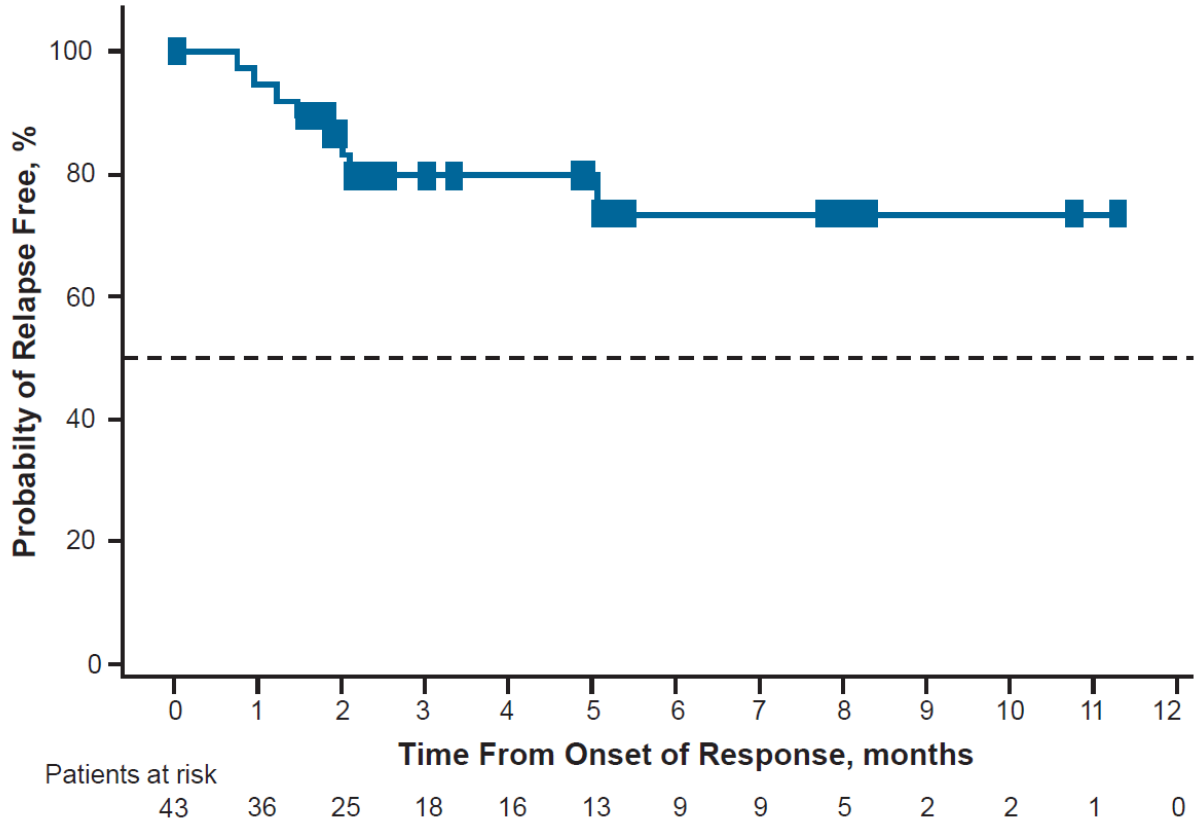
ZUMA-1: Duration of Response by Best Objective Response



- Median duration of CR has not been reached
- 3/7 (43%) phase 1 patients have ongoing CR at 24 months

CR, complete response; NR, not reached; PR, partial response.

JULIET: Duration of Response, 74% Relapse Free at 6 Months



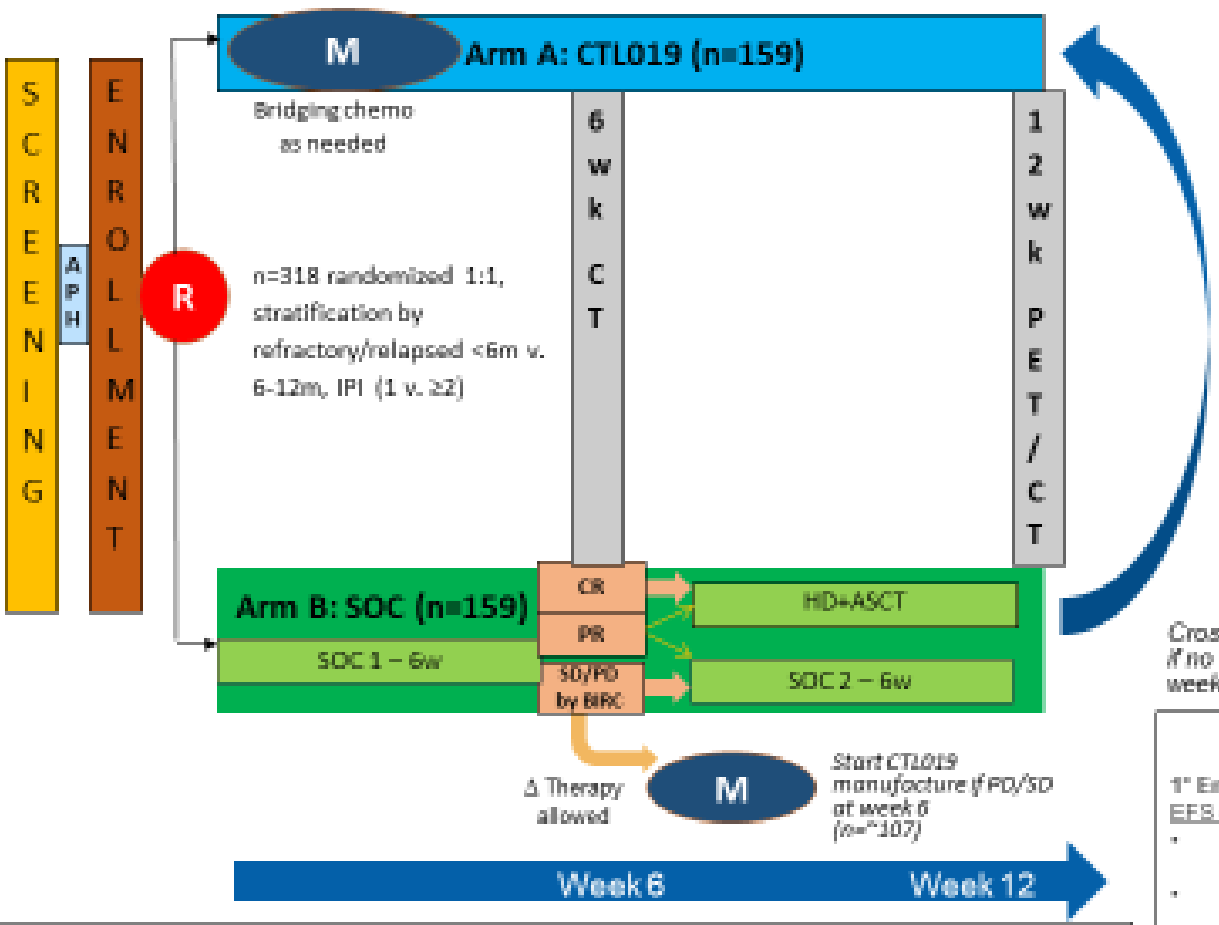
- **Median DOR and OS not reached**
- Almost all patients in CR at month 3 remained in CR
- No patients proceeded to transplant while in response

Efficacy analysis set = all patients who received a tisagenlecleucel infusion ≥ 3 months prior to data-cut date.

CR, complete response; DOR, duration of response; OS, overall response.

CTL019H2301 Amended Design Proposal

Randomization upfront at time of 1st relapse (<12 months from R-CHOP)



Safety and Efficacy Follow-up

- **Week 6 for treatment decision**
- **Week 12 +/1w for disease assessment**
- **q3m to M12**
- **q6m to M24**
- **annual to M60**

Crossover allowed, if no response at 12 weeks by BIRC

1° Endpoint: PFS

EFS event:

- SD/PD by BIRC at/after week 12 ± 1w
- Death at any time

ASCT: autologous hematopoietic stem cell transplant; BIRC: Blinded Independent Review Committee; HD: High dose chemotherapy; LD: lymphodepletion; M: Manufacturing; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; APH: apheresis; IPI: International Prognostic Index (1993)

Other studies evaluating CAR T-cells vs SOC in NHL

- Zuma-7: Kite
  - Salvage chemo + High dose chemotherapy and autograft vs treatment with axicabtigene ciloleucel (Yescarta)

- Juno/Celgene
  - Similar phase 3 randomized trial

BCMA CAR T-cells targeting Multiple Myeloma

	human scFv	Lentivirus	Fully human	EGFRt

Sources: *Curr. Hematol. Malig. Rep*. **12**, 119–125 (2017); company representatives.

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TCR T-cells now in trials in solid tumors

Table 1 Selected solid tumor TCR gene therapy clinical trials

Sponsor	Agent	Antigen target	Indication	Stage
NCI	Anti-NY-ESO-1 mTCR PBL	NY-ESO-1	Various solid tumors	Phase 2
NCI	Anti-MAGE-A3-DP4-TCR	MAGE-A3	Various solid tumors	Phase 2
Fred Hutchinson Cancer Research Center/ Juno Therapeutics	WT1: JTCR016	WT1	Mesothelioma, NSCLC	Phase 1/2
GlaxoSmithKline/ Adaptimmune	NY-ESO-1c259T	NY-ESO-1	Synovial sarcoma	Phase 1/2
GlaxoSmithKline/ Adaptimmune	NY-ESO-1c259T	NY-ESO-1	NSCLC	Phase 1/2
GlaxoSmithKline/ Adaptimmune	NY-ESO-1c259T	NY-ESO-1	Ovarian cancer	Phase 1/2
Adaptimmune	AFPc233T	AFP	Hepatocellular cancer	Phase 1
Adaptimmune	MAGE-A4c1032T	MAGE-A4	Various solid tumors	Phase 1
Adaptimmune	MAGE-A10c796T	MAGE-A10	NSCLC	Phase 1
Adaptimmune	MAGE-A10c796T	MAGE-A10	Bladder, head & neck, melanoma	Phase 1
Kite Pharma	KITE-718	MAGE-A3/A6	MAGE-A3/A6-positive tumors	Phase 1
Parker Institute for Cancer Immunotherapy/ Univ. of Pennsylvania	Anti-NY-ESO-1 TCR, CRISPR to delete PD-1 & autologous TCRs	NY-ESO-1	Multiple myeloma, sarcoma, melanoma	Phase 1
Bellicum Pharmaceuticals	BPX-701	PRAME	AML, MDS, uveal melanoma	Phase 1
Immatics Biotechnologies (Tuebingen, Germany)	IMA-201	(proprietary)	Various solid tumors	Phase 1
NCI/Kite Pharma	KITE-439	HPV-16 E7	HPV-associated cancers	Phase 1
Fred Hutchinson/Juno	Anti-mesothelin TCR	Mesothelin	Pancreatic cancer	Phase 1 pending

NSCLC: non-small cell lung cancer; AML: acute myeloid leukemia; MDS: myelodysplastic syndrome, PRAME: preferentially expressed antigen in melanoma; HPV: human papilloma virus.

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Finding Clinical Trials: there are resources but also challenges

Health System Clinical Trials Office:

- ✓ Call center and/or website
  - ✓ (+) Quickly able to determine eligibility and enroll
  - ✓ (-) Some research groups may not have efficient referral processes
  - ✓ (-) Limited to your own institution's trials

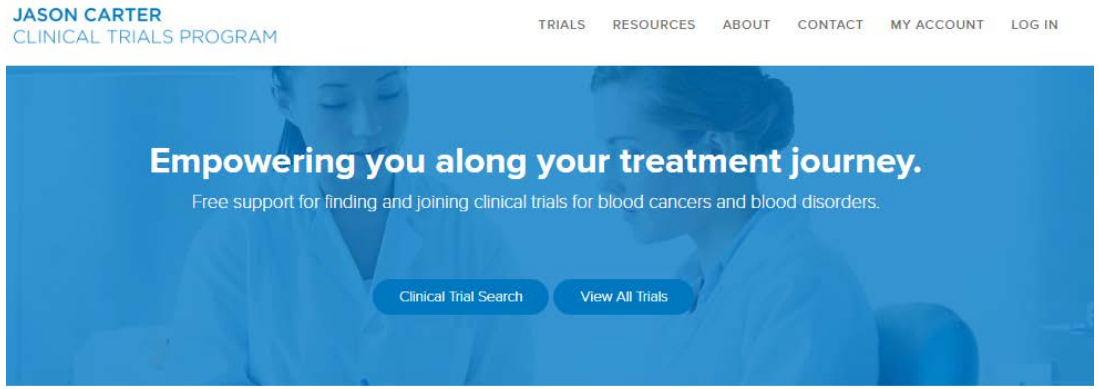
ClinicalTrials.gov

- ✓ (+) All available trials throughout the U.S. are listed
- ✓ (+) Search function is highly customizable
- ✓ (-) Trial descriptions are inconsistent and with filled scientific jargon
- ✓ (-) No option for interacting with a subject matter expert to assist in the search

Jason Carter Clinical Trials Program

To help people with blood cancers, blood disorders, and immune systems diseases find and join clinical trials

- **One-on-one support** for patients & families to help answers questions and guide their clinical trials search
- **Online search tool** with patient-friendly trial descriptions: JasonCarterClinicalTrialsProgram.org
- **Clinical trial resources** to learn about cancer treatments and clinical trials



Contact: Scott Kerwin, MN, RN, CCRC, CCRN

Phone: 1 (888) 814-8610

Email: clinicaltrials@jcctp.org

Visit: www.jcctp.org

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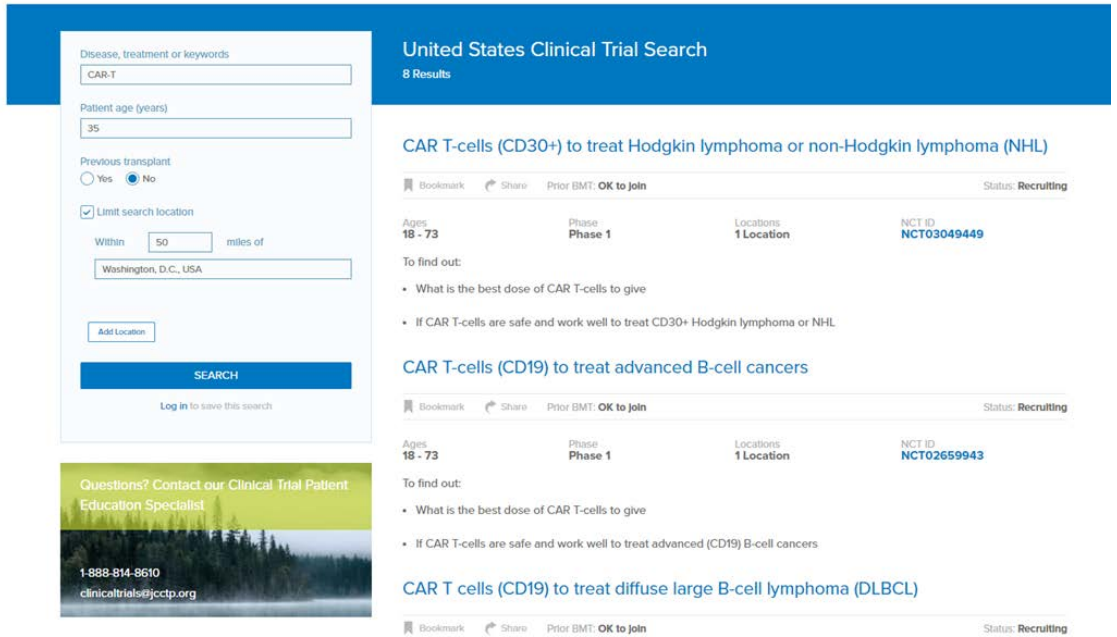
JCCTP Search Tool



www.jcctp.org

- Search over 1,100 clinical trials that are:
  - U.S. based
  - Actively recruiting participants
  - Phase 1, 2, or 3
- Trials for:
  - Blood cancers
  - Blood disorders
  - Immunodeficiency diseases
  - Blood or marrow transplant (BMT) complications, such as graft-versus-host disease (GVHD)
- Includes therapies beyond transplant, such as new chemotherapies and targeted immunotherapies (CAR-T, mAb, small molecule inhibitors)

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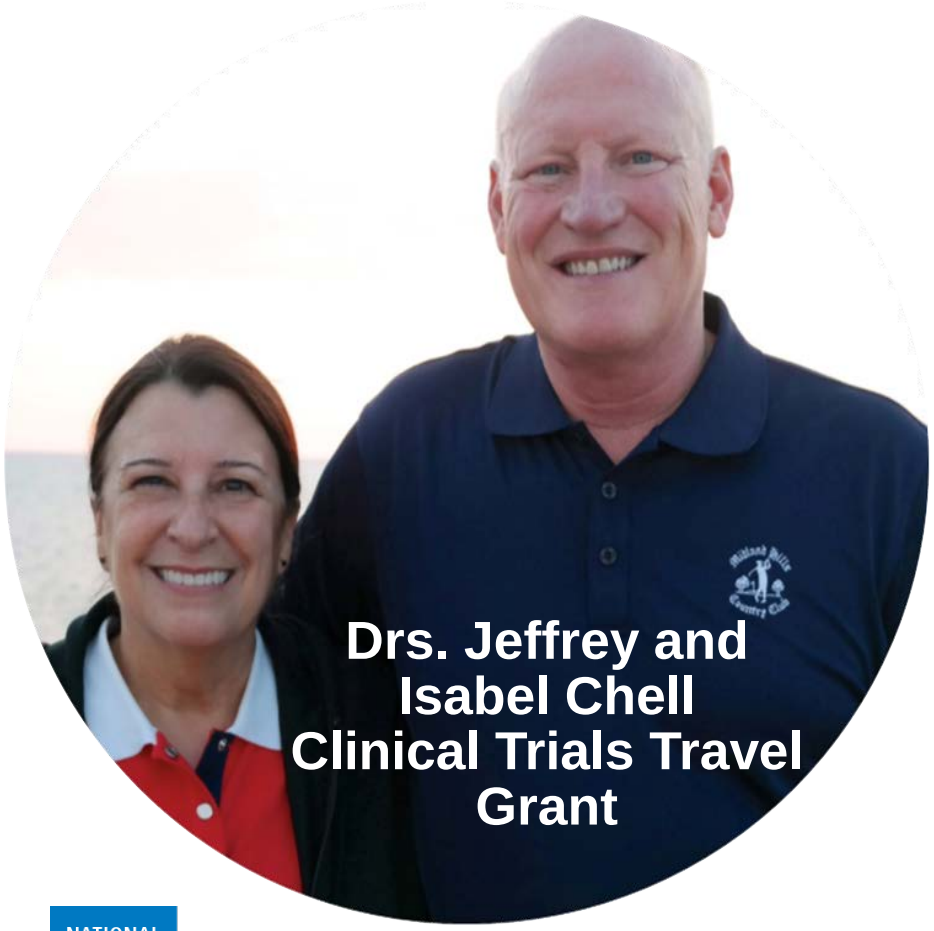
Clinical Trials Travel Assistance Grant



- For patients who need a clinical trial to treat blood cancer or blood disorder. Transplant is **not** a requirement.
- Provides financial assistance for travel and accommodations needed to get to a clinical trial
- Must meet income and minimum travel requirements
- Complements the Jason Carter Clinical Trials Program
- Applications on BeTheMatchClinical.org and JCCTP.org
- Questions: email PatientGrants@nmdp.org or call (763) 406-8114

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Let's go!

Conclusion

- ✓ Clinical trials are important for all health care professionals to understand
- ✓ Advances in medicine are only possible through the execution of clinical trials
- ✓ Research in transplant and cellular therapy has never been more diverse or more exciting
- ✓ Helping your patients find clinical trials is a very important part of delivering the highest level of care

Thank you!

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