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

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National Marrow Donor Program® /Be The Match®
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Disclosures

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

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Disclosure</th>
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</thead>
<tbody>
<tr>
<td>Steven Devine, MD</td>
<td>NMDP/Be The Match</td>
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<td>NMDP/Be The Match</td>
<td>None</td>
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<td>NMDP/Be The Match</td>
<td>None</td>
</tr>
</tbody>
</table>
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

Grab your cape.
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

Grab your cape.
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-blindin
  ✓ 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

Grab your cape.
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
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

Adjusted 1-year Overall Survival

Odds of 1-year survival increased by 6% per year (95% CI, 7-9%) on average between 1990 and 2015
Survival After Unrelated Donor Transplantation
Age <50 years, myeloablative conditioning, acute leukemia in remission or MDS

Adjusted 1-year Overall Survival

Odds of 1-year survival increased by 6% per year (95% CI, 7-9%) on average between 1990 and 2015

Without clinical research, this doesn’t happen
CIBMTR Research Programs

Observational Research

Prospective Clinical Trial Support

Clinical Outcomes
Immunobiology
Health Services
Bioinformatics
BMT CTN
RCI BMT

Statistical Methodology
Blood and Marrow Transplant Clinical Trials Network (BMT CTN)

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

More than 10,000 patients on 46+ clinical trials
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
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

©1998 by American Society of Hematology
BMT CTN 0402: Sirolimus Based GVHD Prophylaxis; no major improvement

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
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
BMT CNT #1203: Study Outline

18-75y
Malignant Diseases
Matched donor
RIC

Tac/Cy/MMF
Tac/MTX/
Maraviroc
Tac/MTX/
Bortezomib

Tac/MTX
Control
(CIBMTR)
GRFS by Treatment Arm Compared to Tac/MTX Controls

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Hazard Ratio (90% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tac/MMF/Cy</td>
<td>0.94 (0.72, 1.22)</td>
<td>0.04</td>
</tr>
<tr>
<td>Tac/MTX/Bort</td>
<td>1.08 (0.82, 1.41)</td>
<td>0.24</td>
</tr>
<tr>
<td>Tac/MTX/Maraviroc</td>
<td>1.32 (1.03, 1.67)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Note: Hazard Ratio for Tac/MTX is the reference group with a Hazard Ratio of 1.0.
GRFS by Treatment Arm
Compared to Tac/MTX Controls

Hazard Ratio (90% CI)

- Tac/MMF/Cy: 0.94 (p=0.04)
- Tac/MTX/Bort: 1.08 (p=0.24)
- Tac/MTX/Maraviroc: 1.32 (p=0.87)
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
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
BMT CTN 1301 CNI free Trial: 3-arm Phase III

- ≤65y Early disease Any HLA matched donor MA eligible

- BM Tac/MTX
- BM PTCy
- CD34 Selected PBSC

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

Accrual completed Summer 2018!
Abatacept GVHD Prophylaxis in mismatched unrelated transplants

Figure 1. Comparison of Key Outcomes between the ABA2 Cohort (CNI + MTX + Abatacept) and CIBMTR Matched Controls Prophylaxed with CNI + MTX.

- **A. Acute GVHD Gr III-IV**
  - CIBMTR CNI/MTX 7/8 matched controls
  - ABA2 cohort
  - Day 100 p = 0.0070

- **B. Transplant Related Mortality**
  - Cumulative Incidence
  - 12 month p = 0.0024

- **C. Disease-Free Survival**
  - 12 month p = 0.0003

- **D. Overall Survival**
  - 12 month p = 0.0025

Figure 2. Comparison of Key Outcomes between the ABA2 Cohort (CNI + MTX + Abatacept) and CIBMTR Matched Controls Prophylaxed with CNI + MTX+ATG.

- **A. Acute GVHD Gr III-IV**
  - CIBMTR CNI/MTX + ATG 7/8 controls
  - ABA2 cohort

- **B. Transplant Related Mortality**
  - 12 month p = 0.0384

- **C. Disease-Free Survival**
  - Day 100 p = 0.0250

- **D. Overall Survival**
  - 12 month p = 0.0161

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)
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
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Treg infusion (sibs/cords)

Stimulate iNKT to increase Treg in vivo (NCT 01379209)

Others (Manipulation of multiple graft constituents)
Selective versus total T-cell depletion
Outcomes of acute leukemia patients transplanted with naive T cell–depleted stem cell grafts
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

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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
Risk-based treatment of new onset acute GVHD
Day 28
Assessment
Begin within 3 days of systemic steroid treatment for acute GVHD

Any GVHD
Ann Arbor Score 3

Prednisone 2mg/kg/d (or methylpred)

Natalizumab 300 mg IV x 2

CR = Success
No CR = Failure

Day 28 Assessment

- 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
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
BMT CTN 1705 Design

Phase III Randomized, Double-Blind, Placebo Controlled

Acute GVHD
• HR-MN
• Lower GI GVHD

MP + AAT
4 weeks

MP + Placebo
4 weeks

Randomization (1:1)

Primary Response Assessment

If CR/PR Maintenance
4 weeks

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

Median FU 73 months
P=0.84

Lee et al, JAMA Oncol 2016
Five year results of BM vs. PB

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

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

10.5 x STD

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

Lee et al, JAMA Oncol 2016
Clinical Trials to Prevent Relapse
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
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)
HCT: Any conditioning, donor, graft, or GVHD prophylaxis

Day +30 to +90 after HCT: Reassess patient for Randomization Criteria including repeat bone marrow biopsy to confirm ongoing CR1

Gilteritinib 120 mg po daily for 24 months

Stratification:
Age: ≥ 60 vs. < 60 years
MRD status
Time from HCT to randomization
Actinium Pharmaceuticals, Inc.

Anti-CD45 mAb BC8 Radiolabeled with $^{131}$I 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:
  - Single pivotal study, pending trial results
  - Patient population: patients 55 years of age or older relapsed or refractory AML
  - 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
Cellular Immunotherapy for Cancer
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
Chimeric Antigen Receptor Therapy

Figure 1. Chimeric Antigen Receptor (CAR) T Cells Engaging, Trafficking to Tumors, and Proliferating Extensively after Infusion.

After infusion, CAR T cells leave the blood and travel to sites of tumors, where they identify and kill tumor cells. They can trigger extensive proliferation of CAR T cells and the release of tumor antigens, which activate 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.
Efficacy and Toxicity of CAR T-cell Therapy

Table 1. Responses to CAR T-Cell Therapy.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Response Rate</th>
<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia</td>
<td>83–93</td>
<td>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</td>
<td>Park et al., Davilla et al., Turtle et al.</td>
</tr>
<tr>
<td>B-cell acute lymphoblastic leukemia (in adults)</td>
<td>68–90</td>
<td>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</td>
<td>Maude et al., Maude et al., Fry et al., Lee et al.</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>57–71</td>
<td>Relapse is rare in patients who have a complete response; bratumb appears to increase response rates</td>
<td>Porter et al., Turtle et al.</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>64–86</td>
<td>Approximately 40–50% of patients reported to have a durable complete response</td>
<td>Turtle et al., Kochenderfer et al., Schuster et al., Neelapu et al.</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
<td>70–83</td>
<td>At a median follow-up of 28.6 mo, the response was maintained in 89% of patients who had a response</td>
<td>Schuster et al.</td>
</tr>
<tr>
<td>Transformed follicular lymphoma</td>
<td>25–100</td>
<td>A total of 3 of 3 patients with transformed follicular lymphoma had a complete response</td>
<td>Turtle et al., Schuster et al., Neelapu et al.</td>
</tr>
<tr>
<td>Refractory multiple myeloma</td>
<td>25–100</td>
<td>B-cell maturation antigen CAR T cells: stringent complete response in approximately 75% of patients</td>
<td>Ali et al., Fan et al., Boehler et al.</td>
</tr>
</tbody>
</table>

Solid tumors

<table>
<thead>
<tr>
<th>Disease</th>
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<th>Comments</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma</td>
<td>ND</td>
<td>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 7.3 mo</td>
<td>Brown et al.</td>
</tr>
<tr>
<td>Pancreatic ductal adenocarcinoma</td>
<td>17</td>
<td>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</td>
<td>Beatty et al.</td>
</tr>
</tbody>
</table>

*ND denotes not determined.

Table 2. Reported Toxic Effects of CAR T Cells.

<table>
<thead>
<tr>
<th>CAR Specificity and Adverse Effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell aplasia and hypogammaglobulinemia</td>
<td>Kochenderfer et al., Kalos et al.</td>
</tr>
<tr>
<td>Cytokine release syndrome</td>
<td>Davilla et al., Lee et al., Teachey et al.</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Rubin et al.</td>
</tr>
<tr>
<td>Hematophagocytic lymphohistiocytosis and macrophage activation syndrome</td>
<td>Grupp et al., Porter et al., Teachey et al.</td>
</tr>
<tr>
<td>Neurologic effects such as ataxia and aphasia</td>
<td>Brudno and Kochenderfer</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>Gust et al.</td>
</tr>
<tr>
<td>B-cell maturation antigen CAR: the cytokine release syndrome</td>
<td>Riches et al.</td>
</tr>
<tr>
<td>Mesothelin CAR: anaphylaxis (antibody to murine single-chain variable fragments)</td>
<td>Maus et al.</td>
</tr>
<tr>
<td>Carbonic anhydrase IX CAR: cholangitis (on-target)</td>
<td>Lamers et al.</td>
</tr>
<tr>
<td>HER2/neu CAR: lethal cytokine release syndrome</td>
<td>Morgan et al.</td>
</tr>
<tr>
<td>Carcinoembryonic antigen–related cell-adhesion molecule 5 (CEACAM5) CAR: hemorrhagic colitis (on-target)</td>
<td>Thistlethwaite et al.</td>
</tr>
</tbody>
</table>
Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia

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

### ZUMA-1: Objective Response

<table>
<thead>
<tr>
<th></th>
<th>Phase 2 Primary Analysis N = 101</th>
<th>Phase 1 and 2 Updated Analysis N = 108</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median follow-up, mo</strong></td>
<td>8.7</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>ORR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Best objective response, %</strong></td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td><strong>Ongoing, %</strong></td>
<td>44</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>40</td>
</tr>
</tbody>
</table>

- 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 lisagenlecleucel 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)

**Arm A: CTL019 (n=159)**
- Bridging chemo as needed
- n=318 randomized 1:1, stratification by refractory/relapsed <6m v. 6-12m, IPI (1 v. ≥2)

**Arm B: SOC (n=159)**
- CR
- PR
- HD+ASCT
- SOC 1 – 6w
- SOC 2 – 6w
- SD/PO by BIRC

**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**

1st Endpoint: PFS
- EFS event:
  - SD/PD by BIRC at/after week 12 ± 1w
  - Death at any time

Other studies evaluating CAR T-cells vs SOC in NHL

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

• Juno/Celgene
  – Similar phase 3 randomized trial
BCMA CAR T-cells targeting Multiple Myeloma

TCR T-cells now in trials in solid tumors

Table 1 Selected solid tumor TCR gene therapy clinical trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Agent</th>
<th>Antigen target</th>
<th>Indication</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI</td>
<td>Anti-NY-ESO-1 mTCR PBL</td>
<td>NY-ESO-1</td>
<td>Various solid tumors</td>
<td>Phase 2</td>
</tr>
<tr>
<td>NCI</td>
<td>Anti-MAGE-A3-DP4-TCR</td>
<td>MAGE-A3</td>
<td>Various solid tumors</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Research Center/ Juno Therapeutics</td>
<td>WT1: JTCR016</td>
<td>WT1</td>
<td>Mesothelioma, NSCLC</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>GlaxoSmithKline/ Adaptilmune</td>
<td>NY-ESO-1c259T</td>
<td>NY-ESO-1</td>
<td>Synovial sarcoma</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>GlaxoSmithKline/ Adaptilmune</td>
<td>NY-ESO-1c259T</td>
<td>NY-ESO-1</td>
<td>NSCLC</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>GlaxoSmithKline/ Adaptilmune</td>
<td>NY-ESO-1c259T</td>
<td>NY-ESO-1</td>
<td>Ovarian cancer</td>
<td>Phase 1/2</td>
</tr>
<tr>
<td>Adaptilmune</td>
<td>AFCp233T</td>
<td>AFP</td>
<td>Hepatocellular cancer</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Adaptilmune</td>
<td>MAGE-A4c1032T</td>
<td>MAGE-A4</td>
<td>Various solid tumors</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Adaptilmune</td>
<td>MAGE-A10c796T</td>
<td>MAGE-A10</td>
<td>NSCLC</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Adaptilmune</td>
<td>MAGE-A10c796T</td>
<td>MAGE-A10</td>
<td>Bladder, head &amp; neck, melanoma</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Kite Pharma</td>
<td>KITE-718</td>
<td>MAGE-A3/A6</td>
<td>MAGE-A3/A6-positive tumors</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Parker Institute for Cancer Immunotherapy/ Univ. of Pennsylvania</td>
<td>Anti-NY-ESO-1 TCR, CRISPR to delete PD-1 &amp; autologous TCRs</td>
<td>NY-ESO-1</td>
<td>Multiple myeloma, sarcoma, melanoma</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Bellicum Pharmaceuticals</td>
<td>BPX-701</td>
<td>PRAME</td>
<td>AML, MDS, uveal melanoma</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Immatics Biotechnologies (Tuebingen, Germany)</td>
<td>IMA-201</td>
<td>(proprietary)</td>
<td>Various solid tumors</td>
<td>Phase 1</td>
</tr>
<tr>
<td>NCI/Kite Pharma</td>
<td>KITE-439</td>
<td>HPV-16 E7</td>
<td>HPV-associated cancers</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Fred Hutchinson/Juno</td>
<td>Anti-mesothelin TCR</td>
<td>Mesothelin</td>
<td>Pancreatic cancer</td>
<td>Phase 1 pending</td>
</tr>
</tbody>
</table>

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

Grab your cape.
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 answer 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

Grab your cape.
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)
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](http://BeTheMatchClinical.org) and [JCCTP.org](http://JCCTP.org)

Questions: email [PatientGrants@nmdp.org](mailto:PatientGrants@nmdp.org) or call (763) 406-8114

Grab your cape.
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

Grab your cape.
Thank you!