Cellular Therapy Registry
Data Managers Professionals Meeting – BMT Tandem Meetings
February 2018
Cellular Therapy Initiative - Objectives

• To study therapies using cellular products for indications other than hematopoietic replacement or recovery.

• To provide an infrastructure to allow long-term follow-up of patients treated with cellular therapy products.
Isn’t HCT a Cellular Therapy too?

What is the intent?

- Treatment of an underlying condition
- Engraftment
- HCT
- Transfusions
- Support
- Donor Cellular Infusion
- DLI

**What is the intent?**

- Treatment of an underlying condition
CT Registry Update – *Busy Year!*

- NCI Pilot – completed in July 2017
  - Release of v2 of CTED forms
  - Time studies, harmonization with EBMT
- Collected >900 CT infusions (mostly DCI)
- Active discussion with industry sponsors
- Cellular Immunotherapy Data Resource (CIDR) grant application.
Indications for Cellular Therapy, excluding DLI, 2016-2017 (N=300)
### 87 Patients Receiving CAR T Cell Therapies Reported to the CIBMTR in 2016 to 2017

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N</th>
<th>Target (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centers – US only</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Indications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>45</td>
<td>CD19 (43) CD16v (2)</td>
</tr>
<tr>
<td>Acute Lymphocytic Leukemia</td>
<td>32</td>
<td>CD19 (31) CD22 (1)</td>
</tr>
<tr>
<td>Hodgkin Disease</td>
<td>4</td>
<td>CD30</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>4</td>
<td>BCMA</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>1</td>
<td>CD171</td>
</tr>
<tr>
<td>Acute Myeloid Leukemia</td>
<td>1</td>
<td>CD123</td>
</tr>
</tbody>
</table>
CT Registry Update

• CTED v2 released in July 2017 and v3 released January 2018 to accommodate regulatory requirements discussed with sponsors.

• Cellular Therapy Liaison Meeting with FDA and EMA meeting:
  – Focus on long term follow up of recipients of genetically modified cells.

• Outreach to CT for Regenerative Medicine groups.
Cellular Therapy and HCT Data Collection - Historic Timeline

All cellular therapies now are collected by the CTED forms.
CTED Level Data – Applies to all Cellular Therapies

- **Pre-CTED**: demographic, indications, disease status prior to CT (if applicable) and therapy prior to CT.

- **Product/Infusion forms**: description of the product, information on manufacturing, product analysis and infusion details.

- **Post-CTED**: follow-up infusions, recipient survival and disease status, cause of death, development of malignancies, persistence of the product, development of CRS and neurologic complications.
Cellular Therapy Registry Data Flow

Unique ID Assignment and Indication F2804/2814

Pre-CTED F400

Information prior to Cellular therapy

Indications for CT

Disease Classification F2402

Disease specific insert

Product F4003

Product information and details on manufacturing

Post CTED F4100

Disease specific F/U

Disease characteristics, prior treatment and condition prior to CT. For example: acute leukemia and NHL.

Event-driven form

Infusion F4006

Infusion details, route and cell doses.

3, 6 and 12 months then yearly

Subsequent Neoplasm F3500

Outcomes form

Center for International Blood & Marrow Transplant Research
Data Flow Integrated with HCT Data Flow

Cellular Therapy
- Sup. Form
- Pre-CTED Bundle
- Post CTED Bundle

Hematopoietic Cell Transplantation
- Form 2804/2814
- Unique ID Assignment
- Pre-TED
- Post-TED
- CRF

Unique ID Assignment
Form 4000 Updates

• Define product upfront.
• Removal of the treatment of recurrent disease option, used for DLI/DCI.

Transplant Specific CT Indications
- Promote engraftment
- Decrease chimerism
- Prev/Treat of Infection
- Prev/Treat of GVHD

CT indications
- Heme
- Malignancies
- Solid Tumors
- Cardiovascular
- Neurologic
Cellular Therapy Indications

**Heme Malignancies**
- ALL
- CLL
- NHL
- MM
- AML

**Solid Tumors**
- Ovarian
- Neuroblastoma
- CNS Tumors
- Mesothelioma

**Viral Infections**
- EBV
- CMV
- Adenoviruses-associated diseases
- BK polyomavirus
- HIV

**Other Indications**
- Multiple Sclerosis
- Congenital diseases
- Brain & Spinal Cord injury
- Myocardial Infarctions
- Diabetes
Forms 4003/4006: Product and Infusion Forms

Cellular Therapy
Product Identification

Manufacturing

Form 4006

Manufacturing Details
Pre infusion information
Administration, Drugs to potentiate the effect of CT

Infusion or Multiple Infusions

Form 4006

Form 4006

Form 4006
CAR-T cell collection process
T-Cell Receptor and CAR T-cells
CAR T cell Targets

A

Antigens of hematological malignancies

Number of treated patients

CD19 (243)
CD20 (19)
CD30 (27)
CD33 (1)
BCMA (12)
Ig k (17)
Lewis Y (4)

PD/NR/NE
SD
CR/PR

B

Antigens of solid tumors

Number of treated patients

CAIX (12)
CEA (21)
EGFR (11)
ErbB2/Her2 (20)
Fr-a (14)
GD2 (19)
IL-13Ra2 (3)
L1-CAM (6)
Mesothelium (2)
MUC1 (1)
PSMA (5)
VEGFR-2 (23)

PD/NR/NE
SD
CR/PR
How to Define a Cell Product? Example CD19-CAR

Donor
- Autologous

Tissue Source
- Peripheral Blood

Cell Type
- Lymphocytes: CD8+ cells

Specific Commercially Available Product
- Capture the name of the product
- Product ID
- Clinicaltrials.gov Number for the Protocol
Approaches to Immunotherapy – drugs to potentiate cellular therapy

- Form 4006 – Concomitant Therapy: additional drugs use with or after CT to maximize its effect.
- Allowed field for each infusion.

Form 4100 - Outcomes Unique to Cellular Therapies

- Cytokine Release Syndrome
- Neurologic Complications
- Persistence of cellular products
- Organ Toxicity
- Cytopenias
- Hypogammaglobulinemia
- Infections
Cell Therapy Complications

**Neurologic:**
- Headaches
- Changes in level of consciousness
- Delirium
- Aphasia
- Apraxia
- Ataxia
- Hallucinations
- Tremor
- Dysmetria
- Myoclonus
- Facial nerve palsy
- Seizures

**Constitutional:**
- Fevers
- Rigors
- Malaise
- Fatigue
- Anorexia
- Arthralgias

**Cardiovascular:**
- Tachycardia
- Widened pulse pressure
- Hypotension
- Arrhythmias
- Decreased left ventricular ejection fraction
- Troponinemia
- QT prolongation

**Pulmonary:**
- Tachypnea
- Hypoxia

**Renal:**
- Acute kidney injury
- Hyponatremia
- Hypokalemia
- Hypophosphatemia
- Tumor lysis syndrome

**Gastrointestinal:**
- Nausea
- Emesis
- Diarrhea

**Musculoskeletal:**
- Myalgias
- Elevated creatine kinase
- Weakness

**Hepatic:**
- Transaminitis
- Hyperbilirubinemia

**Hematologic:**
- Anemia
- Thrombocytopenia
- Neutropenia
- Febrile neutropenia
- Lymphopenia
- B-cell aplasia
- Prolonged prothrombin time
- Prolonged activated partial thromboplastin time
- Elevated D-Dimer
- Hypofibrinogenemia
- Disseminated intravascular coagulation
- Hemophagocytic lymphohistiocytosis

Brudno et al, Blood 2016
# Incidence of CRS and Neurotoxicity

<table>
<thead>
<tr>
<th>Reference</th>
<th>T-cell engager</th>
<th>Population</th>
<th>Response</th>
<th>CRS</th>
<th>Neurologic toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-CD19 CAR T cells 6</td>
<td>Anti-CD19 CAR T CD3z-4-1BB</td>
<td>N = 30 (r/rALL) Pediatric and adults</td>
<td>CR = 90%</td>
<td>100% CRS</td>
<td>43% total Encephalopathy Aphasia Seizure (1)</td>
</tr>
<tr>
<td>1</td>
<td>Anti-CD19 CAR T CD3z-CD28</td>
<td>N = 16 (r/rALL) Adults</td>
<td>CR = 88%</td>
<td>43% severe</td>
<td>25% grade 3-grade 4 Encephalopathy Seizure</td>
</tr>
<tr>
<td>3</td>
<td>Anti-CD19 CAR T CD3z-CD28</td>
<td>N = 21 (r/rALL) Pediatric and young adults</td>
<td>CR = 67%</td>
<td>76% CRS</td>
<td>29% total Hallucinations Dysphasia Encephalopathy</td>
</tr>
<tr>
<td>Blinatumomab 5</td>
<td>Blinatumomab</td>
<td>N = 189 (r/rALL) Adults</td>
<td>CR/CRh = 43%</td>
<td>60% pyrexia, 28% febrile neutropenia, 2% grade 3 CRS</td>
<td>52% total, 11% grade 3, 2% grade 4</td>
</tr>
</tbody>
</table>
CRS Proposed Grading

**Grading Assessment**

- **Grade 1 CRS**
  - Fever, constitutional symptoms

- **Grade 2 CRS**
  - Hypotension: responds to fluids or one low dose pressor
  - Hypoxia: responds to <40% O₂
  - Organ toxicity: grade 2

- **Grade 3 CRS**
  - Hypotension: requires multiple pressors or high dose pressors
  - Hypoxia: requires ≥ 40% O₂
  - Organ toxicity: grade 3, grade 4 transaminitis

- **Grade 4 CRS**
  - Mechanical ventilation
  - Organ toxicity: grade 4, excluding transaminitis

**Treatment**

- **Extensive co-morbidities or older age?**
  - **Yes**
    - **Vigilant supportive care**
      - Tocilizumab ± corticosteroids
  - **No**
    - **Vigilant supportive care**
      - Assess for infection
        - (Treat fever and neutropenia if present, monitor fluid balance, antipyretics, analgesics as needed)

Lee DW et al Blood 2014
## Follow up Structure

<table>
<thead>
<tr>
<th>Type of cells</th>
<th>Time points</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT</td>
<td>3m, 6m, 1 year, yearly up to 5 years then every 2 years</td>
<td>Until death</td>
</tr>
<tr>
<td>Genetically Modified Cells</td>
<td>3m, 6m, 1 year, yearly</td>
<td>15y+</td>
</tr>
<tr>
<td>Third Party CTLs</td>
<td>3m, 6m, 1 year, yearly</td>
<td>2y then HCT</td>
</tr>
<tr>
<td>DLI</td>
<td>3 m</td>
<td>HCT</td>
</tr>
<tr>
<td>MSC</td>
<td>3 m</td>
<td>HCT</td>
</tr>
</tbody>
</table>
Issues Pertinent to Cellular Therapy
Follow-up

• Consider Jane Doe:
  – 12 year with early relapse of ALL
  – CAR-T-cell therapy #1 – no response
  – CAR-T-cell therapy #2 – different construct, different institution - response
  – HCT – third institution
    • Viral-specific T-cell therapy posttransplant

• Who reports what to where? How does the data flow?
CT Model for Long Term Follow up

Center 1
Patient

Cellular Product 1

Sponsor

FDA

eDBTC

Center 2

Cellular Product 2

Sponsor

FDA

eDBTC

Single CRID

eDBCT=Enhanced Data Back to Centers
How we can facilitate capture of follow up?

• Direct contact with the patient through Patient Reported Outcome tools
  – Return this data to centers
• Facilitate the use of the same CRID by multiple centers.
• Use patient reported outcome to capture data on the health of the baby in an event of pregnancy in a recipient of CT.
Disease specific follow up

- Applicable mainly for CAR T cells for now.
- Disease baseline and follow up are due.
- Come due for acute leukemia (AML/ALL) and NHL.
- Others like multiple myeloma will follow.
- CTED triggers exactly the same forms as HCT.
Example of responses in lymphoma

- 62-year-old man with refractory DLBCL
- Prior therapies
  - R-CHOP
  - R-GDP
  - R-ICE
  - R-Revlimid

Baseline

Month 12
Local Tumor Control after Intracavitary Delivery of IL13BBζ–Chimeric Antigen Receptor (CAR) T Cells

# CTED Time Completion Studies

<table>
<thead>
<tr>
<th></th>
<th>4000</th>
<th>4003</th>
<th>4006</th>
<th>4100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Gather Data (minutes)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>20-45</td>
<td>10-15</td>
<td>4-20</td>
<td>14-36</td>
</tr>
<tr>
<td>average</td>
<td>30</td>
<td>12</td>
<td>9.5</td>
<td>23</td>
</tr>
<tr>
<td>median</td>
<td>30</td>
<td>11</td>
<td>4.5</td>
<td>20</td>
</tr>
<tr>
<td><strong>Time to Complete Form (minutes)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>5-90</td>
<td>5-15</td>
<td>5-20</td>
<td>5-90</td>
</tr>
<tr>
<td>average</td>
<td>28</td>
<td>8</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>median</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

- Next steps is to do product specific time studies
- Thank you to Baylor College, Mass General and Memorial Sloan Kettering
Next Steps in CT

• Release of infection form as an indication for CT.
• Simplify data collection for DLI (disabling fields in the forms).
• Training for data collection on commercial products.
• Include CT in the eDBTC application.
Next Steps in CT

- **4th CT Registry Forum** – October 25 and 26, Minneapolis.
- Pilot the ePRO project in cellular therapy
- Development of Regenerative Medicine indication forms.
Cellular Therapy Team

- Erik Bergman
- Janet Brunner
- Tiffany Hunt
- Willian Affield
- Marie Matlack
- Marcelo Pasquini
- Waleska Perez
- Matt Prestegaard

- Bronwen Shaw
- Patricia Steiner
- Eric Zink
- Hailin Wang
- Jenni Bloomquist
- Robert Thompson
- Steve Spellman
- Deborah Mattila
Have to Consider and Accommodate Multiple Cellular Therapy Scenarios

Several scenarios:

- Cellular therapy followed by HCT (e.g. bridge to HCT)
- Cellular therapy to cellular therapy (new indication)
- Co-infusions: HCT plus cellular therapy
- HCT followed by cellular therapy (e.g. DLI/DCI)
- Cellular therapy only

HCT Track (TED)

CT track (CTED)
Objectives

Overview of Cellular Therapy Forms - January 2018 revisions

How do forms come due?

Reporting scenarios and tips
Overview of Cellular Therapy Forms – what’s new…again
The 4006 has been split!

- Now 2 forms: product specific (4003) and infusion specific (4006)
- Product information will only have to be reported once
- Infusion form only captures specific data about the infusion
How 4003/4006 come due?

Product Identification
29. Specify the total number of products: __1__ (per protocol)

Product Infusion
68. Specify the total number of planned infusions __3__ (of this product)
How 4003/4006 are linked

- Utilizing the ‘Group’ column in the FN3 forms grid
- The forms will be assigned a group number to identify which infusion forms go with which product form
4003 Product Form

- Product data: donor, collection, manipulation, number of infusions
- Added question to capture commercialized product name
  - The name will be used to disable manufacturing specific questions

Cellular Therapy Product Identification

1. Name of product
   - Tisagenlecleucel (Kymriah®)
   - Axicabtagene Ciloleucel (Yescarta®)
   - Other product
4003 Product Form

- Updated target lists:
  - Gene editing
  - CAR construct
  - Tumor/cancer antigens

- Implemented ‘check all that apply’ functionality in more places
4003 Product/4006 Infusion forms

• Moved to F4000
  – Tissue source (BM, CBU, PB, tumor, etc.)
  – Cell type (lymphocytes, CD4+, CD8+, etc.)
  – Manufacturing (pharmaceutical/biotech co., cell processing lab)

• Product ID, batch number, lot number kept on 4006
  – These could change between infusions
4000 Pre-CTED

• Removed field for ‘Study ID number’
  – Provide clinicaltrials.gov ID for any U.S. sponsor
  – Do not need to report the “NCT” that precedes the digits

• Report any clinical trial regardless if CIBMTR forms are used
  – BMT CTN 14-01 is the only current trial to be reported under CTN

• Report clinical trials applicable to the cell therapy only
4000 Pre-CTED

• Section title updated to “Product Identification”
  – No longer report planned infusions, but total number of products and donor information

• Move manufacturing questions into this section
  – More timely reporting of tissue source/cell type/manufacturing

• “Is the product genetically modified?”
  – Manipulations to alter its gene expression through the insertion of different genes, or editing of genes
  – Used to determine follow up reporting schedule
4000 Pre-CTED - Indication

- Split the indication list, pulled out the prevention indications

<table>
<thead>
<tr>
<th>Indication for Cellular Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Is the cellular therapy being given for prevention?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>48. Reason for prevention:</td>
</tr>
<tr>
<td>□ GVHD prophylaxis (with HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Prevent disease relapse (post-HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Infection prophylaxis - Go to question 61</td>
</tr>
</tbody>
</table>

49. What was the indication for performing treatment with cellular therapy?
- □ Suboptimal donor chimerism (post-HCT) - Go to question 94
- □ Immune reconstitution (post-HCT) - Go to question 94
- □ GVHD treatment (post-HCT) - Go to question 94
- □ Malignant hematologic disorder – Also complete CIBMTR Form 2402 - Go to question 68
- □ Non-malignant disorder – Also complete CIBMTR Form 2402 - Go to question 94
- □ Solid tumor - Also complete CIBMTR Form 2402 - Go to question 94
- □ Cardiovascular disease - Go to question 50
- □ Musculoskeletal disorder - Go to question 50
- □ Neurologic disease - Go to question 50
- □ Ocular disease - Go to question 50
- □ Pulmonary disease - Go to question 50
- □ Infection treatment - Go to question 50
- □ Other indication - Go to question 50
4000 Pre-CTED - Indication

- Added Solid tumor
- Removed “relapse/persistent/progressive disease” as an indication
  - will have to report malignant, non-malignant or solid tumor as the indication

49. What was the indication for performing treatment with cellular therapy?
   - Suboptimal donor chimerism (post-HCT) - Go to question 94
   - Immune reconstitution (post-HCT) - Go to question 94
   - GVHD treatment (post-HCT) - Go to question 94
   - Malignant hematologic disorder – Also complete CIBMTR Form 2402 - Go to question 68
   - Non-malignant disorder – Also complete CIBMTR Form 2402 - Go to question 94
   - **Solid tumor - Also complete CIBMTR Form 2402 - Go to question 94**
   - Cardiovascular disease - Go to question 50
   - Musculoskeletal disorder - Go to question 50
   - Neurologic disease - Go to question 50
   - Ocular disease - Go to question 50
   - Pulmonary disease - Go to question 50
   - Infection treatment - Go to question 50
   - Other indication - Go to question 50
4000 Pre-CTED

- Added comorbidity questions
  - Same as asked on the form 2400
  - Enable for malignant hematologic disorders and solid tumor indications

Co-morbid Conditions

This section to be completed for malignant hematologic disorders and solid tumor indications

253. Were there clinically significant co-existing diseases or organ impairment at time of patient assessment prior to preparative regimen?  
Source: Blood, 2005 Oct 15;106(8):2912-2919

☐ Yes  ☐ No

254. Arrhythmia - For example, any history of atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring treatment

☐ Yes  ☐ No  ☐ Unknown
4100 Post-CTED

- Added questions to capture peripheral blood count recoveries
  - Asked at 100d-2yr
- Added questions to capture current hematologic findings
  - Asked at 100d -2yr
4100 Post-CTED

• Added hypogammaglobulinemia as a new toxicity
• Added questions to capture infection as a complication
  – Same as asked on the form 2100
• Created new form for new malignancy questions
  – F3500
3500 Subsequent Neoplasms

- When a new malignancy is reported on 4100, the child questions are now contained on the new form 3500

<table>
<thead>
<tr>
<th>New Malignancy, Lymphoproliferative or Myeloproliferative Disease / Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report new malignancies that are different than the disease / disorder for which cellular therapy was performed. Do not include relapse, progression or transformation of the same disease subtype.</td>
</tr>
</tbody>
</table>

36. Did a new malignancy, myelodysplastic, myeloproliferative, or lymphoproliferative disease / disorder occur that is different from the disease / disorder for which the HCT or cellular therapy was performed? (Include clonal cytogenetic abnormalities, and post-transplant lymphoproliferative disorders)

- Yes - Complete F3500
- No
- Previously reported (form 3500 has already been submitted)
Additional inserts

Depending on the indication, product, or cell source

- **Disease Specific Forms**
- **HLA Reporting**
- **Infections**

- **ALL, CLL, LYM**
- **2005**
- **4150* (viral)**

*In development
How Forms Come Due and Follow-up Reporting
How the cellular therapy forms come due

A co-infusion is given with HCT

A cellular therapy (non-HCT) is reported as a new indication (where no HCT forms are due)

A CRID is assigned to a new recipient who is receiving a cellular therapy (non-HCT)

Reporting a post-HCT cellular therapy (e.g. DCI)
Scenario 1: co-infusion with HCT

CRID is assigned

Pre-TED 2400 completed

HCT follow-up continues

51. Specify number of products infused from this donor: 2

52. Specify the number of these products intended to achieve hematopoietic engraftment: 1

2006(s)

4003(s)
Scenario 1: co-infusion with HCT

1. CRID is assigned
2. Pre-TED 2400 completed
3. HCT follow-up continues

2006(s)

51. Specify number of products infused from this donor: __2__
52. Specify the number of these products intended to achieve hematopoietic engraftment: __2__
Scenario 2 – New Patient

- CRID Assignment 2804
- F2814 is completed
- Pre-CTED form 4000

Scenario 3 – No forms due or no HCT

- Center adds Indication form 2814
Non-Genetically Modified Products
• Complete follow-up forms at the following time points:
  – 100 days
  – 6 months
  – Annually 1-6 years
  – Biannually 8-14 years

Genetically Modified Products
• Complete follow-up forms at the following time points:
  – 100 days
  – 6 months
  – Annually 1-15 years
Scenario 4 – post-HCT cellular therapy (e.g. DCI/DLI, CAR-T)

Has the recipient received a cellular therapy since the date of last report? (e.g. DCI)

- Yes - Go to question 5 - Also complete Cellular Therapy Essential Data Pre-Infusion Form 4000
- No - Go to question 6

5. Date of cellular therapy: YYYY / MM / DD

Form 4000 will come due
F4100 Follow-up Reporting Scenario 4

Non-Genetically Modified Products
• Complete a single follow-up form at the 100 day time point.

Genetically Modified Products
• Complete follow-up forms at the following time points:
  – 100 days
  – 6 months
  – Annually 1-15 years
Reporting Scenario – DCI
What to report and when

- Cell therapy given in context of HCT (e.g. co-infusion, DLI/DCI)
  - Need to be reported to CIBMTR
  - Includes autologous products and allogenic products (e.g. cells stored pre-allo HCT used for treatment of graft failure)
- Cell therapy with prior HCT (e.g. CAR-T for treatment of relapse)
  - voluntary at this time
- Stand-alone cellular therapy (no prior HCT)(e.g. CAR-T)
  - voluntary at this time
An infusion can be classified as a “DCI” when:

- The intent is something other than to restore hematopoiesis
- The infusion must be post-HCT, often by the same donor as the HCT
- Indication is suboptimal donor chimerism, immune reconstitution, GVHD treatment, prevent or treat disease relapse (as reported on F4000)
- Composition of cells include un-manipulated lymphocytes, mesenchymal cells, peripheral mononuclear cells, NK cells, etc.
A recipient has relapsed disease (ALL) post-HCT and is treated with chemotherapy. They will receive a PBSC product containing a specified number of T-cells (for a DCI). The PBSC product is to restore hematopoiesis & the T-cells are to provide a GVL effect against the ALL.
DCI reporting- defining ‘course of cell therapy’

• A course of cellular therapy is considered to be all of the infusions given per protocol
  – Protocol/SOP/physician note may say “give infusions as necessary” or “repeat infusions as needed”

• DCI = single course of cell therapy if:
  – Given for the same indication with same product/donor
  – Requires only one F4000
  – Update number of infusions on 4003 if necessary.
DCI reporting – completing F4000

- When HCT forms and CT forms exist, some questions are disabled to prevent duplicate reporting
  - Q1 Ethnicity
  - Q2 Race
  - Q23 HCT history
DCI reporting – completing F4000, Consent

• Q3 Has the recipient signed an IRB / Ethics Committee-approved consent form for submitting research data to the CIBMTR?
  – report “not applicable”

3. Has the recipient signed an IRB / Ethics Committee-approved consent form for submitting research data to the CIBMTR?
   □ Yes (patient consented)
   □ No (patient declined)
   □ Not approached
   □ Not applicable
DCI reporting – completing F4000, Clinical Trial

- Only report clinical trials applicable to the cellular therapy infusion in Q5/6
- If the recipient is on a clinical trial for the HCT, that trial should not be reported on the 4000
  - Captured on 2400

5. Is the recipient participating in a cellular therapy clinical trial?
   - Yes
   - No

Copy and complete questions 6-11 to report

6. Study sponsor:
   - BMT CTN - Go to question 11
   - RCI BMT - Go to question 11
DCI reporting—completing F4000, Product Identification

• Q30 Is the product genetically modified?
  – If no, only requires a single F4100 @ 100d

• Q36 What is the cell type?
  – list should match F4006

36. What is the cell type? (check all that apply)
   - Lymphocytes (unselected)
   - CD4+ lymphocytes
   - CD8+ lymphocytes
   - Cytotoxic T lymphocytes (CTLs)
   - Natural killer cells (NK cells)
   - Dendritic cells / tumor cell hybridomas (tumor vaccines)
   - Mesenchymal stromal stem cells (MSCs)
   - Unspecified mononuclear cells
   - Endothelial progenitor cells
   - Human umbilical cord perivascular (HUCPV) cells
   - Cardiac progenitor cells
   - Islet cells
   - Oligodendrocytes
   - Other cell type

37. Specify other cell type:
Q38 Where was the cellular therapy product manufactured / processed?

- If the product is from an NMDP donor used for a prior HCT select ‘cell processing laboratory at the same center as the product is being infused’
DCI reporting – completing F4000, Indication

- Q47/49, look for indications with (post-HCT)
- Removed indication “relapse, persistent, progressive disease”
  - Must select malignant hematologic disorder or non-malignant disease
  - requires completion of F2402

<table>
<thead>
<tr>
<th>Indication for Cellular Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>47. Is the cellular therapy being given for prevention?</td>
</tr>
<tr>
<td>□ Yes</td>
</tr>
<tr>
<td>□ No</td>
</tr>
<tr>
<td>48. Reason for prevention:</td>
</tr>
<tr>
<td>□ GVHD prophylaxis (with HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Prevent disease relapse (post-HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Infection prophylaxis - Go to question 61</td>
</tr>
<tr>
<td>49. What was the indication for performing treatment with cellular therapy?</td>
</tr>
<tr>
<td>□ Suboptimal donor chimerism (post-HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Immune reconstitution (post-HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ GVHD treatment (post-HCT) - Go to question 94</td>
</tr>
<tr>
<td>□ Malignant hematologic disorder – Also complete CIBMTR Form 2402 - Go to question 94</td>
</tr>
<tr>
<td>□ Non-malignant disorder – Also complete CIBMTR Form 2402- Go to question 94</td>
</tr>
<tr>
<td>□ Solid tumor - Also complete CIBMTR Form 2402 - Go to question 94</td>
</tr>
</tbody>
</table>
DCI reporting – completing F4000, Disease assessment

- Questions are answered for malignant hematologic disorders only
- Do not re-report assessments from HCT forms

[Image of Disease Assessment form]
DCI reporting – completing F4000, Systemic Therapy

- Systemic therapy may include intravenous or oral chemotherapy with the intent to deplete circulating lymphocytes, reduce tumor burden or other reasons.
- Do not report any therapy that was already reported on HCT forms.
  - Do not report treatment for relapse as systemic therapy, recorded on 2450.

<table>
<thead>
<tr>
<th>Systemic Therapy Prior to Cellular Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>94. Was systemic therapy given immediately prior to cellular therapy as part of the cellular therapy protocol?</td>
</tr>
<tr>
<td>Yes □</td>
</tr>
<tr>
<td>95. Date started: ____ / __ / ____</td>
</tr>
</tbody>
</table>

\[ YYYY \ MM \ DD \]
DCI reporting – completing F4000, co-morbid conditions

- Questions are answered for malignant hematologic disorders and solid tumor indications
- It may match 2400

Co-morbid Conditions

This section to be completed for malignant hematologic disorders and solid tumor indications

253. Were there **clinically significant** co-existing diseases or organ impairment at time of patient assessment prior to preparative regimen?

Source: Blood, 2005 Oct 15;106(8):2912-2919

- Yes
- No
DCI reporting – completing F4003

- Donor information reported should match the F2400/2006 if it’s the same donor
DCI reporting – completing F4006

- If the DCI product is a leftover portion from the HCT, then that portion becomes the whole product for the DCI infusion.
- If the product is further divided, captured in Q9.
- Q17-43 Cells infused should match F4000 Q36 Cell type.
DCI reporting – completing F4100

- If the product is not genetically modified, a single F4100 at 100 day time point is required
- When HCT forms and CT forms exist, some questions are disabled to prevent duplicate reporting
  - Q2 survival status
  - Q59 GVHD
DCI reporting – completing F4100

• Q7 Has the recipient started a new course of cellular therapy (unplanned) since the date of the last report?
  – Change in indication would be a new course (donor chimerism vs relapse disease)

• If an additional infusion is given for the same indication/same protocol, update F4003
DCI reporting – completing F4100, Best Response

• Report the best response to the DCI
  – Do not re-report an HCT response
• There should be an assessment post-infusion to determine the best response
  – If no assessment is performed, answer ‘unknown’
• If the recipient was in CR pre-infusion and an assessment post-infusion showed CR again
  – Report CR as there is no option for CCR
• Date reported must be after CT infusion date
Other helpful items
F4000: Cellular therapy and HCT history

• Q14 Is this the first application of cellular therapy?
  – Were all prior cellular therapies reported to the CIBMTR?

• Q23 Has the recipient ever had a prior HCT?
  – Were all prior HCTs reported to the CIBMTR

• These fields are monitored and the form will be queried if prior infusions do not exist
F4100: Reporting recipient death

- Death is reported on the post-CTED 4100

- Death Form 2900 should **not be** completed for cellular therapy only recipients
  - Else death is reported on HCT forms

- You do not have to wait for the form due date to report death
Cell Therapy and HCT reporting tracks

• For cases where both a cell therapy and HCT are received, if a cell therapy product is genetically modified, FDA requires 15 years of follow-up
  – Both CT and HCT forms will be completed simultaneously
  – Finding ways to reduce duplicate reporting

• Exceptions:
  – Recipient receives a non-genetically modified CT product then goes on to HCT, future F4100s will be removed
  – Non-genetically modified product received post-HCT, requires single 4100
Cell therapy transfer scenarios

• Transfer form to be revised in Spring

• How to allow multiple CCNs to report on one recipient at the same time?
  – CCN X is responsible for reporting HCT forms
  – CCN Y is responsible for reporting Cellular Therapy forms
Cell therapy manuals

- The manuals can be updated on demand
  - Use the question received to constantly clarify sections
- If you think a question could be better clarified, send us your feedback!
Questions?
THANK YOU!