CBER Regulatory Considerations for Clinical Development of Immunotherapies in Oncology

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IOM Policy Issues in the Clinical Development and Use of Immunotherapy for Cancer Treatment

Washington, DC
Disclosures

- I have no financial relationships to disclose.
- I will not discuss off-label use.
Outline

• FDA Regulation of Oncology Products
• OCTGT regulatory scope
• Clinical Trial Design considerations
  – Personalized therapy
  – Combination therapies
• Regulatory Initiatives
• Conclusions + Contact info
# FDA Regulation of Oncology Products

<table>
<thead>
<tr>
<th>CDER</th>
<th>CBER</th>
<th>CDRH</th>
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<tbody>
<tr>
<td>• Drugs (small molecules)</td>
<td>• Cell therapies</td>
<td>• Therapeutic devices</td>
</tr>
<tr>
<td>• Biologics</td>
<td>• Gene Therapies</td>
<td>Office of In Vitro Diagnostics and Radiological Health (OIR)</td>
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<tr>
<td>– Monoclonal Antibodies</td>
<td>• Oncolytic viruses</td>
<td>• Companion Diagnostics</td>
</tr>
<tr>
<td>– Therapeutic Proteins</td>
<td>• Therapeutic vaccines and immunotherapies</td>
<td>• Certain Devices</td>
</tr>
<tr>
<td>– Cytokines</td>
<td>• Certain Devices</td>
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CBER OCTGT

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Deputy Director: Stephanie Simek, PhD

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Chief: Ilan Irony, MD

Pharmacology and Toxicology
Chief:
Mercedes Serabian, MS
CBER Office of Cellular, Tissue and Gene Therapies (OCTGT) Products

- Cellular Therapies
- Cancer Vaccines and Immunotherapy
- Oncolytic Viruses
- Gene Therapies
- Xenotransplantation Products
- Tissues and Tissue-Based Products
- Certain Combination Products
- Devices Used for Cells and Tissues
Personalized Immunotherapies

• Based on Biomarker Target – EGFR, Kras, MUC-1, CD19, NY-ESO etc. – may require a companion diagnostic

• Neoantigen-based manufacturing of “actively” personalized products to treat individual patients

• Based on autologous manufacture
  – Autologous tumors provide unique antigens
  – Dendritic Cells
  – T cells including chimeric antigen receptor (CAR) T cells
Biomarker Targeted Therapies

• MUC1: - lipopeptide
  – Non-Small Cell Lung Cancer

• MAGE – A3: peptide
  – Non-Small Cell Lung Cancer
  – Melanoma

• EGFR: (EGF-P64K) protein conjugate
  – Non-Small-Cell lung cancer
  – Studies ongoing

'Actively Personalized' Immunotherapy

Regulatory challenges of Biomarker Targeted Therapies

- Companion Diagnostics – when results from an assay are required for safe and effective use of a therapeutic intervention
  - Analytical, clinical Validation
  - Review by CDRH as well as applicable center
  - See applicable FDA guidance

- ‘Actively personalized’ biomarker therapies regulation is evolving case by case basis
Autologous Manufacture

• Autologous Tumor cell lysates
  – ATC/BCG Colon Cancer
  – Idiotype immunotherapies for lymphoma

• Antigen Pulsed Cells (APC’s)
  – Sipuleucel-T (Provenge)
  – Tumor infiltrating Lymphocyte (TIL)

• Gene Modified T cell Products
  – Engineered TCR
  – Chimeric Antigen Receptor
Autologous Manufacture: Sipuleucel-T (Provenge)
**T cell Immunotherapy: Basic Overview**

- **Apheresis**
- **Product**
- **T cell activation and transduction with gene transfer vector**
- **Expand in culture CD3/CD28 beads ± IL-2 / IL-15**
- **Dose formulation**
- **Product testing**

**Gene modified T cell Infusion**

**Patient may receive pre-conditioning chemotherapy prior to infusion**

**Sometimes cytokine support (IL-2) post infusion**

*Cancer patient*
Autologous Manufacture: chimeric antigen receptor (CAR) T cells.

1) T Cell Collection

2) T Cell Transfection
   1. Binding
   2. Fusion

3) T Cell Adoptive Transfer
   3. Integration
   4. Transcription and protein expression
   5. CAR cell membrane insertion
   +/- Lymphodepleting conditioning

4) Patient Monitoring
   a) Disease response
      - CT scans
      - Bone marrow biopsies
      - Peripheral blood flow cytometry
   b) CAR-T Cell persistence
      - Immunohistochemistry of bone marrow biopsy
      - RT-PCR and flow cytometry of blood and bone marrow aspirate

Jacobson C A, and Ritz J Blood 2011;118:4761-4762
Gene Modified T cell Products

Engineered TCR
- Express α/β TCR (selected in MHC-transgenic mice)
- TCR often “affinity enhanced” (mutated for >IFN-γ secretion)
- Recognize Tumor Antigen-derived peptide/MHC complex
- TSA intracellular or cell surface
- Require co-stimulation (host antigen presenting cells)

Chimeric Antigen Receptor
- Express ScFv from mAb fused to CD3ζ (+CD28 and/or 4-1BB)
- Recognize TSA via ScFv (MHC-independent)
- Tumor Antigen must be cell surface
- Do not require additional co-stimulation (provided by construct)

Gene delivery usually via retroviral/lentiviral vector into autologous cells, generally expanded *in vitro* with cytokines
# Cellular Therapy: Targeted T cell INDs

<table>
<thead>
<tr>
<th>Target</th>
<th>Indication</th>
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<tbody>
<tr>
<td>CD19</td>
<td>Hematologic Malignancies</td>
</tr>
<tr>
<td>GD2</td>
<td>Neuroblastoma/Melanoma</td>
</tr>
<tr>
<td>NYESO-1</td>
<td>Melanoma/Myeloma/Synovial</td>
</tr>
<tr>
<td>Her2/Neu</td>
<td>Colon/NSCLC/Osteosarcoma</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Ovarian/Pancreatic</td>
</tr>
<tr>
<td>MAGE-A3</td>
<td>Melanoma/Myeloma/MAGE+ tumors</td>
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<tr>
<td>MART-1</td>
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<td>CEA</td>
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<tr>
<td>IL-13</td>
<td>Glioma</td>
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<tr>
<td>PMSA</td>
<td>Prostate</td>
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<tr>
<td>p53</td>
<td>Cancers overexpressing p53</td>
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</table>

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<thead>
<tr>
<th>Target</th>
<th>Indication</th>
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<tr>
<td>2G1</td>
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<td>gp100</td>
<td>Melanoma</td>
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<tr>
<td>CD28</td>
<td>Glioblastoma</td>
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<td>VEGFR2</td>
<td>Metastatic cancers</td>
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<tr>
<td>α-Folate</td>
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<tr>
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<td>TGFβR2</td>
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<tr>
<td>CXCR2</td>
<td>Melanoma</td>
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Regulatory Challenges of Autologous cell therapies

- Tracking so that correct patient receives product
- Transportation, stability
- Potency, consistency – every product is unique
- Manufacturing challenges – identity comparability and sterility
- Manufacturing failures affect statistical interpretation – ITT population vs. per protocol
- Dose/response/safety may be quite complex
  - Weight based
  - # Transduced cells
  - Expansion in vivo
Regulatory Challenges of T cell therapies

• Safety Concerns:
  – Cytokine Release Syndrome
  – Neurological toxicity
  – B cell aplasia
  – Long term effects of genetically modified products

• Efficacy issues
  – CD19+ hematologic malignancies – high complete response rates - long term effects are unknown – B cell aplasia
Novel Combinations

- FDA guidance: Codevelopment of Two or More New Investigational Drugs for Use in Combination (2013)
- Vaccine +/- Checkpoint inhibitor example
  - Safety concerns – preclinical requirements are on a case by case basis
  - Initial dose-finding safety study recommended for novel combinations
  - Safety reporting – attribution – reporting of expected AE’s
FDA Expedited Programs

• Fast Track
  – Unmet medical need/plan to demonstrate benefit
• Accelerated Approval
  – Endpoint reasonably likely to predict benefit
• Priority Review
  – Improvement over existing therapy
• Breakthrough Therapy Designation (BTD)
Breakthrough Therapy Designation

- 2012 Food and Drug Administration Safety and Innovation Act (FDASIA)
- Drug intended to treat a serious or life-threatening disease or condition
- Preliminary clinical evidence indicates that the drug may demonstrate **substantial improvement** over existing therapies

See FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (2014)
# BTD Requests by Center
## FY 2015

<table>
<thead>
<tr>
<th>BT Requests</th>
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<th>CBER</th>
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<tr>
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<tr>
<td>Denied</td>
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<tr>
<td>GRANTED</td>
<td>32</td>
<td>9</td>
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Source: Fda.gov regulatory information/legislation/FDASIA
OCTGT Oncology Product Approvals

- **Provenge**: Antigen Presenting Cells (APC’s) pulsed with GM-CSF-PAP (2010)
  - for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

- **Talimogene laherparepvec**: oncolytic viral therapy - attenuated herpes simplex engineered to express GM-CSF (2015)
  - For the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery.
Public Access to CBER

CBER website
- [http://www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)
- Phone: 1-800-835-4709 or 240-402-8010

Consumer Affairs Branch (CAB)
- Email: ocod@fda.hhs.gov
- Phone: 240-402-7800

Manufacturers Assistance and Technical Training Branch (MATTB)
- Email: industry.biologics@fda.gov
- Phone: 240-402-8020

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