FDA Pilot Project to Develop a Clinical Database to Examine Safety in Trials Using CAR T-cells

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Outline

• Brief Overview of CBER, Office of Tissues and Advanced Therapies (OTAT)
• IND Submissions to OTAT (formerly OCTGT)
  – Engineered T cells: CAR T cells, TCR T cells
• CAR T cell Safety Project
  – Serious adverse events with CAR T-cells
  – Documentation of events
  – Assessment on reviewer and Branch Level
  – Clinical Safety Database Pilot Project
FDA Organization

FDA

Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiologic Health (CDRH)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)
Center for Food Safety and Nutrition (CFSAN)
National Center for Toxicologic Research (NCTR)
Center for Tobacco Products (CTP)
## CBER: Center for Biologics Evaluation and Research

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<th>OBRR</th>
<th>OVRR</th>
<th>OTAT</th>
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<td>Div. Of Bacterial, Parasitic, and Allergenic</td>
<td>Div. Of Clinical Evaluation and Pharm/Tox</td>
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<td>Products</td>
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<td>Division of Regulatory Project Management</td>
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Yearly New IND & IDE Submissions to OCTGT

[Bar chart showing yearly new IND & IDE submissions to OCTGT from 2003 to 2015, with categories for Cell Therapy, Gene Therapy, and Other.]
Yearly New Gene Therapy IND Submissions to OCTGT
Yearly New Cell Therapy IND & IDE Submissions to OCTGT
New INDs and IDEs Submitted to OCTGT: Commercial or Research Sponsors
Cell and Gene Therapy
Investigational New Drug Applications

- Rare
- Common
Chimeric Antigen Receptor (CAR) T-cells

Anti-CD19 CAR T-cell: Anti-CD19 binding domain fused to intracellular T-cell signaling domains; targets B-cells

# T-Cell Receptor / CAR T-Cell INDs

<table>
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<tr>
<th>N</th>
<th>Description</th>
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<tbody>
<tr>
<td>116</td>
<td>Engineered T-Cell: TCRs / CAR T-cells</td>
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<tr>
<td>37</td>
<td>CD19 INDs</td>
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<tr>
<td>16</td>
<td>CD 19 sponsors</td>
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<tr>
<td>1135</td>
<td>Subjects (CD19)</td>
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November 1, 2016
IND Submissions to CBER

• Products that are regulated by OTAT

• Definition of a biologic product: Section 351(i) of the Public Health Service Act (42U.S.C. 262 (i))
  – Cell Therapy (CT)
  – Gene Therapy (GT)
  – Combination products
  – Therapeutic vaccines

• Address Unmet Medical Needs

• Personalized/Targeted Therapies
Background on CGT Products

• Design of clinical trials differs from other pharmaceutical products
• Early experiences: CGT may pose substantial risks to subjects
  • Many first-in-human products, unknown safety profile
  • Late-onset T-cell leukemia
• Potential for prolonged biological activity
  • Engineered T cells have the potential to persist for weeks to years
• High potential for immunogenicity
Clinical Trial Design

• Cell and Gene Therapy Products
  – Often lack of clinical experience
  – Need to always consider persistence with cell products
    • Cells- how long detected
  – Manufacturing Timeline: auto and allo cell products
    • Can take weeks to months to produce
Clinical Trial Design

Characteristics of Gene Therapy Products:

• Delivered gene may be uncontrolled and interfere with normal function

• T-cell receptor (TCR) and CAR T-cells
  • Off-tumor, on-target
  • B-cell aplasia with CAR CD19 products
  • Cross-reactivity (Mage A3: titan in the heart and Mage A12 in CNS)

• Unique safety issues
Summary

- CBER products, in particular OTAT products, are often unique
- We encourage interaction with OTAT prior to IND submission with a PreIND Meeting
- We have FDA Guidances and Webinars to help with product development
- Novel products and therefore have safety, feasibility, and follow-up that are different than for other therapeutic products
Chimeric Antigen Receptor T Cells for Sustained Remissions in Leukemia

Shannon L. Maude, M.D., Ph.D., Noelle Frey, M.D., Pamela A. Shaw, Ph.D., Richard Aplenc, M.D., Ph.D., David M. Barrett, M.D., Ph.D., Nancy J. Bunin, M.D., Anne Chew, Ph.D., Vanessa E. Gonzalez, M.B.A., Zhaohui Zheng, M.S., Simon F. Lacey, Ph.D., Yolanda D. Mahnke, Ph.D., Jan J. Melenhorst, Ph.D., Susan R. Rheingold, M.D., Angela Shen, M.D., David T. Teachey, M.D., Bruce L. Levine, Ph.D., Carl H. June, M.D., David L. Porter, M.D., and Stephan A. Grupp, M.D., Ph.D.
Chemotherapy-Refractory Diffuse Large B-Cell Lymphoma and Indolent B-Cell Malignancies Can Be Effectively Treated With Autologous T Cells Expressing an Anti-CD19 Chimeric Antigen Receptor

The New York Times

T-Cell Therapy Puts Leukemia Patients in Extended Remission
OCT. 15, 2014

CANCER BREAKTHROUGH: PROMISING TREATMENT USES PATIENT'S OWN IMMUNE SYSTEM TO ATTACK DISEASED CELLS
FEBRUARY 20, 2014
Safety Concerns

Reported Deaths with CAR T-cells
• Cytokine Release Syndrome (CRS)
  • Complex reaction with multiple components
  • Renal and cardiac complications
  • Is there a benefit to CRS?
• Cardiac events +/- CRS
• Neurologic deterioration +/- CRS
• Infections
• Intracranial hemorrhage
• Prolonged aplasia
Safety Concerns (continued)

• On-target, Off-tumor toxicity
  • T-cell receptor (TCR) example of MAGE A3
    ▪ Cardiac
    ▪ Neurologic

• Long-Term Toxicity issues
  • Persistence of CAR T-cells
  • B-cell aplasia with antiCD19 CAR T-cells
  • Unknown risk for insertional oncogenesis, replication competent retrovirus (RCR)
  • Potential for second malignancy
Documentation of Events

• Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and Bioavailability and Bioequivalence (BA/BE) Studies (December 2012)
  – Mandatory reporting of suspected unexpected safety adverse reactions (SUSARs)
  – MedWatch format
  – Review is incident by incident
  – > 116 INDs with engineered T-cells
  – Office-wide review system developed
    • CAR T-cell Working Group
  – Need a systematic approach to safety across INDs
Project Objectives

- To assess the feasibility of systematically collecting, storing and analyzing safety data from CAR T cell products in a way that enables cross-study / cross-IND analysis.

- To develop prediction models that can identify safety issues associated with CAR T cell products, leading to the development of risk mitigation strategies.
Choice of antiCD19 CAR T-cell Products

- Potential to be curative
- Complex *in-vivo* activity
- Substantial & complex safety concerns
- Complex manufacturing processes that relate to clinical safety issues
- Relatively large number of anti-CD19 CAR T-cell INDs, but small number of subjects in each IND
- Ongoing Phase 3 studies

### Safety Concerns

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Pilot CAR T-Cell Databases

Two databases:

• Clinical Safety Database
  – Will use CDISC – SDTM format for data submission to facilitate submission of clinical and safety information from CAR T-cell INDs or other similar electronic formats

• Chemistry, Manufacturing, and Control (CMC)
  – Information from INDs and additional Sponsor inquiries
Pilot Clinical Safety Project

- Interactive process between Sponsor and FDA
  - Companies/research institutions are likely to already have safety data bases; or else it would be easy for them to compile the data
  - Ask that data be submitted earlier in the process of product development
- Sponsor-specific data available through IND safety reporting process
- Flexible about data formats
CMC CAR T-cell Project

- Cross-IND analysis
- Most of the data already submitted to the INDs with CMC submissions
- Inform regulatory review of CAR T-cell product development
- Relationship between product class attributes and clinical safety
Why Does the FDA Need This Safety Database?

Integrate and analyze safety data for this product class

- Understand the complex relationships of clinical (e.g., dose) & manufacturing factors to safety
- Small study sizes make risk assessments difficult
- Existing system of data collection is cumbersome
- Data formats are complex and variable
- To better inform sponsors of safety concerns for a particular product class
Why Does the FDA Need This Safety Database? (continued)

FDA can analyze across INDs from multiple sponsors

- IND sponsors are often unwilling to share information with each other
- No data-sharing limitations within the FDA
- FDA can maintain strict confidentiality of proprietary information
Pilot Project Requirements

Efficient data analysis requires:

• Collection of clinical and manufacturing data in a standardized manner
• Systematic organization of clinical and manufacturing data in databases
• Scientific computing to perform the data analysis
HIVE Database: High performance Integrated Virtual Environment

HIVE is the database for the clinical safety information

• A database that is optimized for the storage, retrieval, and analysis of large amounts of data, so it is an ideal environment for developing the CAR T-cell database.

• Enables FDA to capture the complex structure and relationships found in clinical and manufacturing data.

• Pre-existing at FDA
Clinical Safety Project

These analyses will provide safety information to allow for knowledge-based advice for the CAR T-cell products

• For future analysis of serious adverse events, as well as overall safety analysis for these products, FDA can expand beyond single-episode / single-IND evaluation of severe adverse events to allow for more consistent review of safety concerns

• For the sponsor, FDA can provide more reliable advice regarding product development

• May be applicable to other product classes under development.
Pilot Project Phases

• Phase 1: Collection of data in a standardized manner using existing format.

• Phase 2: Store data in FDA database (HIVE) using an integrated data format, which will enable fast cross-study/cross-IND data queries.

• Phase 3: Conduct cross-study/cross-IND analysis of data retrieved from HIVE.

Phases can overlap and are not sequential.
Points of discussion:

• Amount of Data Needed
  – Unknown, exploratory pilot project

• Preserving Confidentiality
  – FDA routinely evaluates individual safety issues and maintains confidentiality
  – Findings will be presented as class-specific advice to sponsors

• Sponsor Burden
  – Data requested is already being collected
  – Not expecting pristine data
Testing Tasks Performed: Data Analysis / Modeling

• Developed preliminary models based on analyses requested by the clinical team.
• Developed data visualization tools that can be used in HIVE.
• Developed models to improve sensitivity of classification models.
• Explored tools for developing predictive models
• Current Test Analysis on early dataset from CD19 CAR T cell products
  – Effects of CRS management treatment on CRS outcomes
  – Effects of treatment dose on toxicity
  – Effects of treatment dose on cytokine levels
Pilot Data Safety Project: Summary

- Viability of this project depends on participation of sponsors
- FDA is in the testing phase
- Once this testing is complete, FDA will ask additional sponsors to provide the clinical data previously collected through IND safety reporting
- FDA is aware that data collected on these trials so far may be incomplete; however, if this information is submitted, it will add to the strength of the database
Thank you

- CAR T-cell Safety Project
- T-cell working Group
Chimeric Antigen Receptor (CAR) T-Cell Project Team

• OTAT
  – Kristin Baird, MD
  – Wilson Bryan, MD
  – Denise Gavin, PhD
  – Bindu George, MD
  – Xiaobin Lu, PhD
  – Maura O’Leary, MD
  – Kim Schultz, PhD
  – Robert Sokolic, MD

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  – Vahan Simonyan, PhD
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  Contact the Regulatory Management Staff in OCTGT at
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  or Lori.Tull@fda.hhs.gov

• References for the regulatory process for OCTGT
  – http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation
  – OCTGT Learn Webinar Series:
    http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
Public Access to CBER

CBER website: http://www.fda.gov/BiologicsBloodVaccines/default.htm
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