Early Development of Cellular and Gene Therapy in Oncology - Clinical Consideration

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Disclosures

- My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
- I have no financial relationships to disclose.

Learning Objective

- Highlight key clinical regulatory issues encountered during early-phase clinical development (especially first-in-human study) of cell and gene therapy

Outline

- Overview
- Clinical trial considerations for FIH studies
  - Trial Design
  - Endpoints
  - Dosing and dose escalation
  - Safety
- Summary

First in Human & Early Phase CGT Trials in Oncology Overview

1. Safety - primary objective
2. FIH dose: extrapolation from animal to human
3. Dose exploration - varies according to different products
   - Maximum tolerated dose
   - Optimal dose
   - Feasible dose
4. Activity assessment and preliminary clinical efficacy
5. Feasibility assessment of manufacturing

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First in Human & Early Phase CGT Trial

- Study Design

Study Design

- Single arm studies should generally focus on unmet needs
  - Relapsed/Refractory to available therapies
  - Contribution of effects a challenge for combinatorial studies
- Specific targets may require a companion diagnostic
  - Antigenic target (CDRH)
  - HLA restriction (CBER OBRR)
- Companion Diagnostic Assays may require a Study Risk Evaluation (protocol-specific) assessing
  - Significant risk devices require investigational device exemptions (IDE)

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First in Human & Early Phase CGT Trial

- Study Endpoints

Endpoints

- Single-arm trial
  - Safety, dose finding
  - Tumor response rate, duration of responses
  - Time-to-event analyses (e.g., overall survival, progression-free survival) difficult to interpret in this setting
- Potential confounding impact of concurrent treatments
  - In addition to investigational CG products, treatment regimen may include conditioning chemotherapy, IL2, etc.
  - Combination with additional immunotherapy (e.g., checkpoint inhibitors)

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First in Human & Early Phase CGT Trial

- Dosing and Dose Escalation

Starting Dose Selection

- Provide justification for the plan and the starting dose based on clinical or preclinical data
- Starting dose for first in human (FIH) study
  - May be based on toxicology data
  - Prior human experience with similar construct
  - For engineered cell therapy: dose should be based on transduced cells per unit weight or BSA

Dose Escalation

- Dose escalation schema
  - Anticipated cell expansion in vivo
  - Anticipated toxicities
  - Half-log increments for biological drugs (log escalation is generally considered aggressive)
  - Either 3+3 design or BOIN (Bayesian adaptive designs) acceptable
  - Intra-patient dose escalation not recommended
  - Staggering of treatment between subjects and dose cohorts

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First in Human & Early Phase CGT Trial

- Safety

Safety

- Safety monitor and management plan
  - Duration of safety monitor
  - Management for potential toxicities
  - Monitor for potential AESIs
- Dose Limiting Toxicities (DLT) Criteria
- Stopping Rules

Safety Monitoring Plan

- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products
- Long term follow-up may be required for certain cellular and gene therapies
  - Duration of follow-up to be tailored to individual products
  - For example: up to 15 years of follow-up for integrating viral vector-based products

Dose Limiting Toxicity (DLT)

- DLT observation period: sufficient to cover both acute and subacute toxicities (e.g., at least 4 weeks)
- Potentially confounded by concurrent treatment
- Context dependent (e.g., CRS, off-target toxicities, etc.)
- Ensure clear definitions (e.g., CTCAE, ASTCT, etc.)
- Examples of cancer cell therapy study DLTs
  - Grade 3 and greater major organ toxicities, not pre-existing or not due to the underlying malignancy, with pre-specified exclusion

Study Stopping Rules

- Temporary pause in enrollment and treatment of additional participants to limit the number of trial participants being exposed to excess risk
- Not intended to terminate a study
- Specify conditions (e.g., type and number of adverse events) for temporary suspension of enrollment and dosing until a safety assessment can be completed
- Based on the outcome of the safety assessment, protocol revision may be warranted to mitigate the risk:
  - For example: revision of eligibility criteria, dosing, safety monitoring plan, etc.
- Consider including the following as study stopping criteria:
  - Death, other than progressive disease, within 30 days of receiving investigational CGT
  - Death attributed to investigational CGT

Summary

- CGT show promise for cancer therapy
- Products moving rapidly from bench to bedside
  - CGT are complex, diversified products with unique MOA and inherent safety concern
- Each clinical trial will be assessed on a case-by-case basis

Useful FDA Information

- References for the Regulatory Process for the Office of Therapeutic Products https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/establishment-office-therapeutic-products
- OTP Learn http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products https://www.fda.gov/media/156896/download
- Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics https://www.fda.gov/media/115172/download
- Human Gene Therapy Products Incorporating Human Genome Editing https://www.fda.gov/media/156894/download
- Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics https://www.fda.gov/media/120721/download
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial https://www.fda.gov/media/152536/download
- Cell and Gene Therapy Guidances https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
- Expedited Programs for Regenerative Medicine Therapies for Serious Conditions Guidance https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions
- Training and Continuing Education | FDA

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- **CBER website**: www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone**: 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
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