

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

Jessica Lee, MD, PhD.

Chief, Oncology Branch 2 Division of Clinical Evaluation Oncology Office of Clinical Evaluation Office of Therapeutic Products Center for Biologics Evaluation and Research | US FDA

2024 SBIA/NIH - September 4, 2024

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.

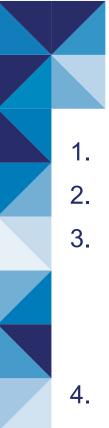
Learning Objective



 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



- 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)



- 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)



- 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



- 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 vectorbased 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

fda.gov/cdersbia

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 caseby-case basis

Useful FDA Information

FDA

- References for the Regulatory Process for the Office of Therapeutic Products
 <u>https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/establishment-office-therapeutic-products</u>
- 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 <u>https://www.fda.gov/media/115172/download</u>
- 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
 <u>https://www.fda.gov/media/120721/download</u>
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial <u>https://www.fda.gov/media/152536/download</u>
- 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
 <u>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-regenerative-medicine-therapies-serious-conditions
 </u>
- Training and Continuing Education | FDA

fda.gov/cdersbia

Contact Information

- Jessica Lee, MD PhD: <u>Ching-Hsien.JessicaLee@fda.hhs.gov</u>
- Regulatory Questions:

OTP Main Line – 240 402 8190 Email: OTPRPMS@fda.hhs.gov

- OTP Learn: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone**: 1-800-835-4709 or 240-402-8010
- Consumer Affairs Branch: <u>ocod@fda.hhs.gov</u>
- Manufacturers Assistance and Technical Training Branch: industry.biologics@fda.hhs.gov
- Follow us on Twitter: <u>https://www.twitter.com/fdacber</u>

fda.gov/cdersbia



