CAR-T CELL THERAPY: REGULATORY CHALLENGES AND OPPORTUNITIES

CLINICAL FOCUS

Kristin Baird, MD
Division of Clinical Evaluation, Pharmacology and Toxicology
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research

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Disclosures

I have no financial relationships to disclose.
Outline

• Early-Phase Development (pre-clinical, first-in-human, Phase 1)
• Middle-Phase Development (Phase 2)
• Late-Phase Development (Phase 3, licensing)
Pre-Clinical Considerations

- In vitro and in vivo proof of concept
  - Specificity of binding between CAR and antigen
  - Expression profile of the target in tumor and/or normal tissue
- Basis for dose in first in human
  - Animal model used
  - Route of administration
  - Bio-distribution
  - Immune response
  - Defined cell population
Pre-Clinical Considerations

- Novel Modifications
  - Signaling domain
  - Suicide gene
  - Receptor knockdown
  - Additional co-stimulatory molecules

- Consider (Pre) Pre-IND guidance
  - Particularly for novel modification
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Early experiences: Behavior of CAR-T cells may be highly unpredictable and pose substantial risks to subjects
  – Infusion reactions / \textit{In vivo} expansion (CRS)
  – Off-tumor / on-target effects
  – Cross reactivity
  – Late-onset potential adverse events (e.g. insertional mutagenesis / leukemia)
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Potential for prolonged biological activity
• High potential for immunogenicity
  – Impact of antigen structure
  – Impact of antigen load
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Early-Phase Trial Objectives
  – Dose Exploration (Toxicity / safety)
    • Selection of Dose (flat dose vs. per kg)
    • Description of Dose
      – Number of transduced cells (per kg)
      – Cellular components (CD 4+/ CD 8+/etc.)
  • Dose Escalation
    – More not necessarily better
    – Need to consider biologic profile and activity
    – Increment size (1/2 log)
  • Product delivered dose vs in vivo expansion
  • Staggered dosing, multiple dosing
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Feasibility
  – Manufacturing timeline, administrative procedure, handling of product (shipping)
  – Clinical
    • Allo versus auto versus 3rd party
    • Disease control and progression during manufacturing
    • Clinical expertise of participating centers
      – Site / investigator training
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Early-Phase Study Population
  – Target expression
  – Disease category
  – Age

• Enrolling subjects with different tumor histology
  – Prior treatment requirements
  – Patient performance and organ function
  – Disease stage or severity
    • Risk-benefit considerations
    • Lack of other treatment options
  – Companion diagnostic for target identification
Early-Phase Clinical Considerations
First-in-human, Phase 1

• Trial Design
  – Cohort Size
    • 3+3?, staggering intervals
  – Dose-Limiting Toxicities
    • CRS definition
    • Stopping Criteria
  – Follow-up and Special Monitoring
    • Immunogenicity
    • Persistence
    • Migration
    • Integration into the genome
    • Effect on normal growth and development (pediatric subjects)
    • Baseline, on study, AE, and off study evaluations
    • Duration: One, Five, Fifteen Years
Middle-Phase Clinical Considerations
Phase 2

• Middle-Phase Trial Objectives
  – Dose Re-exploration
  – Evaluate impact of concurrent treatments
    • Lymphodepletion
    • Chemotherapy tailored to different tumor types
  – Efficacy
    • Exploring magnitude of the treatment effect
      – Response rates, PFS, OS, EFS
Late-Phase Clinical Considerations
Phase 3, “licensing trials”

• Late-Phase Trial Objectives
  – Efficacy
    • Confirming the magnitude of the treatment effect in a specific population
    • Intent-to-treat population
    • Ability to create an informative label
  – Safety
    • Further characterizing safety profile
    • Refining required / recommended monitoring, treatment algorithm for AE management, and short-term and long-term follow-up
Late-Phase Clinical Considerations
Post Approval

• Post Market Approval
  – Risk Mitigation Strategies
    • Registration study
    • “Dear Doctor” letter
    • Site / physician training
  – Supplements
    • Update safety profile
    • Refine required / recommended monitoring, treatment algorithm for AE management, and short-term and long-term follow-up
CAR-T Clinical Considerations

Discussion Topics

• Question 1 – Regarding dose selection for a first-in-human trial, how much can you extrapolate from:
  – preclinical data
  – other “in-class” products
  – other products (i.e. monoclonal antibody with a shared target)

• Question 2 - Often more advanced stage of disease are first studied. Is this the best population for cellular therapy, especially with an anticipated high AE risk?
Question 3 – When is the best time to re-explore alternative dosing regimens? How best to optimize dosing for best biologically active dose?

Question 4 – At what point should enrolling pediatric subjects / conducting pediatric studies be considered?
CAR-T Clinical Considerations

Discussion Topics

• Question 5 – What Risk Mitigation Strategies will be needed in the Post-Approval setting?

• Question 6 - What are the biggest regulatory challenges you (Sponsors) face in clinical development programs?
  – During early-phase development
  – During middle-phase development
  – During late-phase development