Issues in Clinical Trial Design for Cell Therapies

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ACDRS-NIH Workshop: Cell-Based Immunotherapy
January 22, 2019

Disclaimer

This talk reflects my views and represent my own best judgement. These comments do not bind or obligate FDA

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Outline

A. Issues in Design of Clinical Trials

1. Autologous Product
2. Rare Diseases
3. Safety and Long Term Effectiveness

B. Relevant PDUFA VI Programs

1. Complex Innovative Designs (CID)
2. Model-Informed Drug Development (MIDD)

A. Issues in Design of Clinical Trials

1. Autologous Product

Account for manufacturing in study design and analysis

- Time waiting for manufacturing:
  - Delay in administration and in effectiveness
  - Proportional hazards assumption (survival analysis) not met
  - Patient becomes ineligible due to disease progression or death
- Manufacturing failure (insufficient or no product)
- Large variability across lots
- Consequences
  - Effect in the efficacy outcome
  - Decrease on study power
  - Effect in the interpretation of results

1. Autologous Product

- What to do when the subject does not get the treatment due to manufacturing failure or delay?
- Subject may:
  - Die
  - Become ineligible to other therapies
  - Receive other therapies outside the study
- How to analyze and interpret the failures or ineligibility?
- Should one randomize before or after manufacturing?

1. Strategies (autologous products)

Pre specification of the ***Estimand*** of interest: how the treatment effect will be estimated and the subjects will be counted

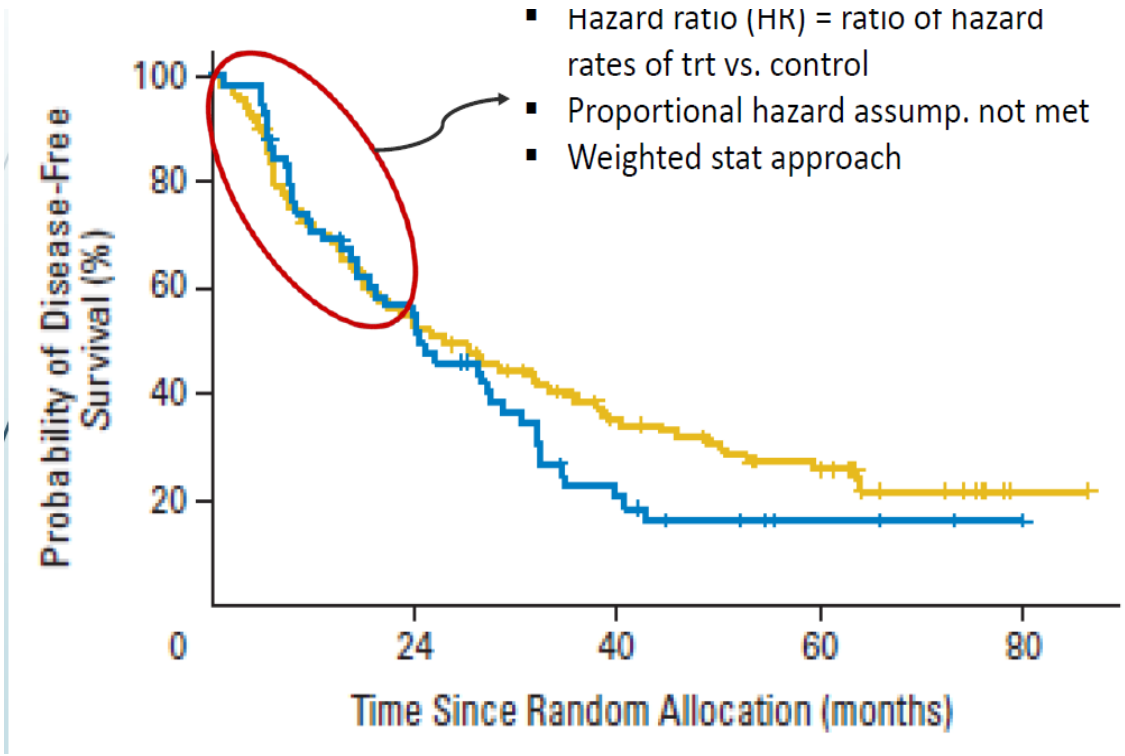
- Possibilities for the ***Estimand*** of effectiveness:
  - Include subjects who fail due to manufacturing failure or delay in the treatment group
  - Exclude subjects who initiate other therapies (both from control and treatment groups)
  - Include all subjects regardless of initiation of other therapies. Compare (treatment + other therapy) vs (control + other therapy)
- Conduct sensitivity analysis after the trial to test other ***Estimands***

ICH E9 R1

- Study objectives should align with Estimands and their analysis
- Estimands should be clearly specified at the design stage

1. Strategies (autologous products)

What to do when the Proportional Hazard Ratio assumption not met? (delay in administration and/or delay in effectiveness)



References

Xu, Z. et al. , Statistics in Medicine, 2017; 36(4):592-605.

Xu, Z., et al. , Statistics in Medicine, 2018; 1-21. https://doi.org/10.1002/sim.7937

2. Rare Diseases

- Small populations ➔ small trials
- Good idea: pilot the trial to detect issues and better design

Strategy: Bayesian Designs

a) Use of prior information
b) Bayesian Adaptive Designs
c) Simulations
d) Decision Analysis and Benefit Risk Determinations
e) Patient Input:
   - What is important to patients can inform endpoint choices
   - Preferences for benefit - risk trade-offs

a. Use of prior information

- Can reduce the size and/or duration of the trial: same decision reached faster
- Control group can borrow strength form historical controls (small control arm) and/or natural history of disease

Regulatory Perspective

- Agreement to be reached in advance between sponsor and FDA (exchangeability; suitability of the prior; discount of prior)
- Priors may have to be discounted
  - Bayesian Hierarchical models
  - Direct discount

b. Bayesian Adaptive Designs

- Can reduce the size (length) of a trial ➔ faster decision
- Can increase the size (length) of a trial. If it happens, **it is needed**
- Interim analyses to stop or continue recruiting based on predictive distributions ➔ sample size decided and optimized during the trial ➔ *"Goldilocks" trials*
- Modeling: results of surrogates predict results of the final endpoint. Model refined at interim looks when follow-up results from patients recruited early are available
- Adaptive randomization
  - Prob. of receiving the treatment depends on data obtained thus far
  - Ethically appealing if allocates more patients to the best treatment

Regulatory Perspective on Bayesian Adaptive Designs

- Increase the probability of trial success (insurance)
- Achieve optimal sample size
- Advantageous when there is no prior information
- Crucial when using prior information (hierarchical model): amount of strength to be borrowed is uncertain ➔ avoid failure for lack of power
- Very advantageous when a Bayesian model is used to predict the final endpoint based on surrogates and interim analyses – substantial savings in sample size

c. Simulations

Simulate the trial thousands of times making assumptions about the true value of the endpoints and look at the average performance:

How often does it get the right answer?

- Calculate error rates for Bayesian trial designs
- Increase trial predictability and help sponsors prepare and budget for different scenarios and surprises
- Readily understood by clinicians who can observe what will happen under various scenarios
- Provide ability to “look into the future” to avoid “anticipated regret”: if the trial were to fail, what would we do differently in retrospect?

3. Safety and Long Term Effectiveness

- Dramatic effects ➔ small samples
- How long does effectiveness lasts?
- Small studies not powered for safety or long-term effectiveness
- How to make label changes when new information about duration of effect becomes available?

Strategies

- REMS to ensure the benefits outweigh the risks
- Long term follow-up: postmarket studies (PMR or PMC)

Ex: YESCARTA

  - REMS: Tocilizumab for Cytokine Release Syndrome, Training, Monitoring for neurologic toxicities
  - Postmarket Requirement (PMR) study to assess secondary malignancies and safety

B. Relevant PDUFA VI Programs

The 2017 Prescription Drug User Fee Amendments

1. **Advancing the use of Complex Innovative Designs (CID)**

   Develop optimal clinical trial designs for challenging drug-development problems that can benefit from innovative thinking

2. **Advancing Model-Informed Drug Development (MIDD)**

   MIDD use quantitative methods to help reduce the uncertainty in Benefits and Risks of medical products

1. Complex Innovative Designs (CID)

- Complex adaptations
- Bayesian methods
- Historical controls
- Statistical modeling to predict final endpoints from surrogates
- Features requiring simulations to assess operating characteristics

Objective: Facilitate advancement and use of CIDs

- Develop regulatory expertise and staff capacity
- Convene a public workshop (March 2018)
- Conduct a **Pilot Program**
- Publish draft guidance documents
- Develop or revise relevant SOPPs and templates

CID Opportunities for Cell Therapies

- Bayesian designs
  - Borrowing strength to power control or treatment groups
  - Bayesian Adaptive Designs
  - Bayesian modeling to predict final outcomes from intermediate or surrogate outcomes
  - Predictive Distributions
- Complex Adaptive Designs
- Simulations
- Etc.
- Pilot program can be used for early discussions between sponsor & FDA on application of CID in drug development

CID Pilot Program

- Highly innovative trial designs which may require simulations to determine operating characteristics (type I error rate and power)
- **Sponsors:**
  - submit meeting requests to discuss proposed CIDs (CBER and CDER will select up to 2 requests per quarter)
  - have the opportunity to engage with FDA regulatory staff on designs via 2 extra meetings with statistical reviewers
  - Need an active IND or Pre-IND number
- **FDA:** uses the design as a case study for continuing education and information sharing

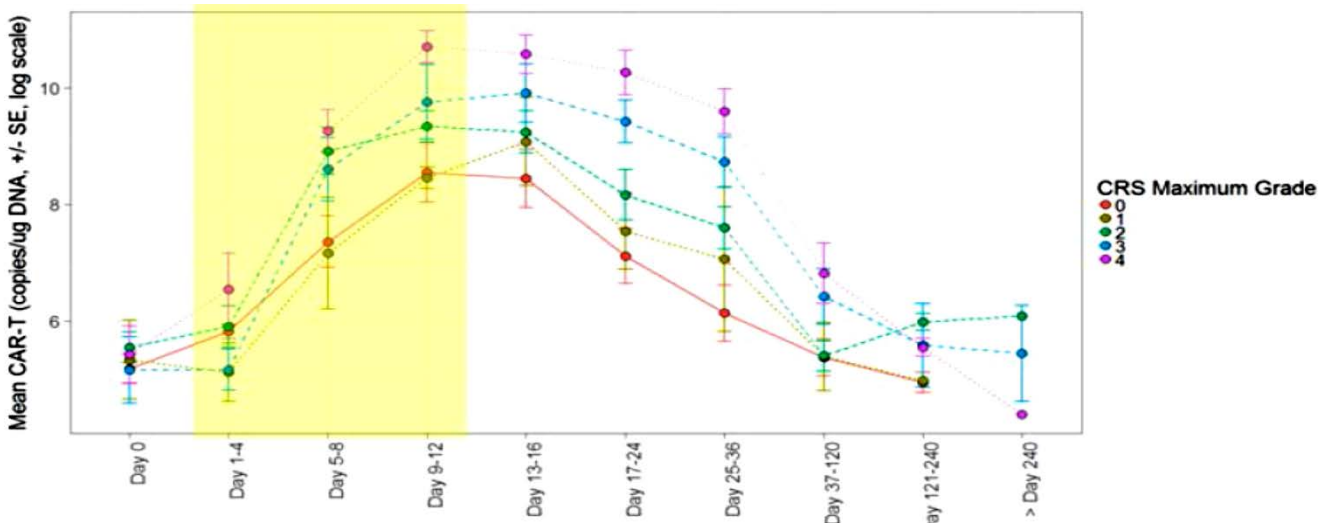
For more information, visit:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm617212.htm

2. Model-Informed Drug Development (MIDD)

Refers to the application of **exposure-based**, **biological** or **statistical** models derived from preclinical and clinical data sources to address drug development and regulatory issues

Example

Population PK (PopPK) and exposure-response (ER) models have been developed for Cart-T Cell Therapies: Kymriah and Yescarta



Objective of MIDD Program

Facilitate the advancement and use of MIDD

- Develop regulatory expertise and staff capacity
- Convene workshops to identify best practices for MIDD topics: PopPK, design, analysis and inferences from dose exposure response, development of models for disease progression, immunogenicity, etc.
- Conduct a **Pilot Program**
- Publish draft guidance documents
- Develop or revise relevant SOPPs, templates and guidelines to evaluate MIDD approaches

MIDD Opportunities for Cell Therapies

- Unlike conventional drug or biologic
  - Dynamic “living” biologic consist of series of intrinsic kinetic processes
  - Potentially curative therapy with “single” exogenous dose
  - Empirical dose selection & uncertainty in durability of efficacy
  - Difficult trade-offs between safety & efficacy
- The pilot program can be used for early discussion b/n sponsor & FDA on application of innovative MIDD approaches

MIDD Pilot Program

- **Sponsors:**
  - submit meeting requests to discuss proposed MIDDs (CBER & CDER select up to 2 requests per quarter)
  - have the opportunity to discuss MIDD approaches with FDA regulatory staff via 2 extra meetings
  - Need an active IND or Pre-IND number
- **FDA** will give priority to MIDD approaches that focus on:
  - Dose selection or estimation
  - Clinical trial simulation (e.g. drug-trial-disease models to inform duration of trial, select response measure, etc.)
  - Predictive or mechanistic safety evaluation (e.g. use of systems pharmacology/mechanistic models to predict safety or identify biomarkers)

For more information on MIDD visit

Federal Register

https://www.federalregister.gov/documents/2018/04/17/2018-08010/pilot-meetings-program-for-model-informed-drug-development-approaches

Website:

https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm600311.htm

Contact FDA at MIDD@FDA.HHS.GOV with “MIDD Pilot Program Meeting Package for CBER” (CBER applications) in the subject line

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