



## **Safety Issues with CAR T cells – Lessons Learnt**

### **CIRM Webinar: CAR-T Cell Immunotherapy: Challenges and Opportunities Using Mature or Stem Memory T Cells**

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## Outline

- Types of Adverse Events (AE's)
  - Acute Infusion reactions
  - On-target toxicities
    - Tumor Lysis Syndromes
    - Cytokine Release Syndromes (CRS)
    - Organ-specific toxicities
- Trial design considerations to minimize risks
  - Eligibility
  - Treatment Plan
  - Dose-escalation schemes
  - Defining Dose Limiting Toxicities
  - Re-treatment
  - Ancillary evaluations
  - Risk mitigation
  - Long-term Follow Up

## CAR T cells - Acute Infusion Reactions

Clinical manifestations:

- Immediate
- Fever
- Chills
- Hypotension
- Bronchospasm

## CAR T cells - Acute Infusion Reactions

Possible causes:

- DMSO
- Cell mediated

## CAR T cells - On-target Toxicities

- Tumor Lysis Syndrome
- Cytokine Release Syndrome (CRS)
- Organ specific toxicities

## CAR T cell toxicity – Tumor Lysis Syndrome

### Tumor Lysis Syndrome

- Urinary symptoms
- Renal failure from elevated uric acid levels
- Abdominal pain
- Electrolyte abnormalities
  - Hyperkalemia – weakness, cardiac rhythm abnormalities
  - Hypocalcemia – cramps, tetany, cardiac rhythm abnormalities

## CAR T cells toxicity - CRS

- Clinical Manifestations
  - Life-threatening
  - Hypotension
  - Fever
  - Hypoxia
  - Multi-organ failure
  - Coagulation disorders

## CAR T cells toxicity – CRS

- Pathophysiology
  - Elevated cytokine levels
    - IL-6, IFN-gamma, TNF-alpha are currently thought to be the key mediators of CRS.
    - Role of other elevated cytokines in CRS and organ toxicity is currently being evaluated.



## CAR T cells – Organ-specific toxicities

- Off-tumor Toxicities
  - Vital Organs
    - CNS
      - CNS depression with lethargy requiring intubation for airway protection – CAR T CD-19 -specific products
      - Seizures
      - Cognitive abnormalities
    - Pulmonary
      - Immediate death with congestion of the lungs with activated T cells
  - Non-vital Organs
    - Hepatic
      - Abnormal liver enzyme elevation with CAR T cells targeting Carbonic anhydrase-IX

## CAR T cells - Long-term Risks

- Insertional Mutagenesis
- B-cell aplasia (with B-cell targeted products)

## CAR T cells –Safety Considerations in Designing Trials

- Eligibility
- Treatment Plan
  - Starting dose
  - Conditioning regimen
  - Risk mitigation plans
- Dose-escalation schemes
- Defining Dose-Limiting Toxicities
- Re-treatment
- Ancillary evaluations
- Risk mitigation
- Long-term Follow-Up

## CAR T cell trial design – Eligibility

- Including multiple histological tumor types that express the same tumor antigen
- Logical sense to combine and streamline clinical development
  - Issues to consider
    - Early-phase trials –
      - Disease-related co-morbidities
      - Sample size to detect early efficacy signals
      - Toxicity profile may vary depending on histology
      - Similar clinical activity

## CAR T cells – Safety issues from CAR Generation perspective

### – First generation CARs

- Single - chain variable fragment (scFv) linked to the transmembrane and intracellular signaling domains of either CD3 $\zeta$  or FcR $\gamma$
- Limited activation, anergy and poor expansion
- Toxicity profile was more favorable.

### – Second generation/Third generation CARs

- Addition of intracellular domain of the co-stimulatory molecules
- Increase activation and expansion
- Wider spectrum of toxicities

## CAR T cell trial design - Starting doses

### Challenges to selection

- Paucity of animal models
- First in Human product – limited “a priori” information
- *In-vivo* expansion of cells is unpredictable
- Limitations to “borrowing” safety data from first generation CAR T product

### Current Approach

- Extrapolate the safety data from related products (TILs, “similar” TCR re-directed cells, “similar” class of CAR T product,) less than optimal
- Extrapolate the safety data using the same product in histologically different tumor type(s)

## CAR T cells trial design – Conditioning regimen

### Issues:

- Associated with toxicities
- Toxicities differ based on the regimen
- May overlap with CAR T toxicities
- Optimal regimen and role in CAR T treatments are evolving

### Recommendations:

- Narrow the choice of regimen
- Explore the activity and safety profile of the CAR T cells +/- conditioning regimen

## CAR T cells toxicity – Risk mitigation

- Defining triggers for medical intervention
  - Grading CRS based on need to intervene
  - Biomarkers that predict severity of CRS
- Identifying medications
  - Steroids
  - IL-6 receptor blockade
  - TNF blocker
- Treatment algorithms
  - Dosing frequency
  - Sequencing use of the medications
- “Suicide” genes



## CAR T cell trial design: Dose escalation schemes

### Accelerated titration design

- Correlation between dose and toxicity not known
- Class of product has substantial toxicities
- *In-vivo* activity varies
- Product differences (antigen-specific binding domains differ, vector's differ) – limit leveraging cross-study safety data

## CAR T cells trial design: Dose escalation schemes

### Current recommendation

- Accelerated titration design sub-optimal
- 3+3 design is more common

#### Personalized product

- *in-vivo* activity differences
  - Differences in tumor antigen burden
  - Product characterization differences
- CRM model applicable but in limited situations

## CAR T cell trial design: Dose Limiting Toxicity

- Defining Dose Limiting Toxicity (DLT)
  - Reasonable to consider exceptions
  - Expected toxicities should not necessarily mean that they should be excepted from DLT definition
    - Severe expected toxicities
    - Prolonged vital organ toxicities
- Contingency plans
  - Dose de-escalation
  - Revised DLT criteria (on a case-by-case basis)

## CAR T cell trial design – CRS Grading

- Traditionally based on CTCAE criteria
- Other grading criteria have been proposed
- Advantages to a single grading criteria in understanding cross IND safety issues
- Important role in implementing risk-mitigation treatments

## CAR T cells trial design: Reporting toxicities

### Dose and Toxicity Assessment Approach

- Helpful to have safety reports that include total dose, total transduced cell dose, transduced cell dose/kg and/or BSA
- May need to assess toxicity in the context of histology
- May need to consider the extent of tumor burden into the dose-toxicity relationship
- Impact of split dose vs single dose administration
- Impact of conditioning regimens

## CAR T cell trial design: Re-treatment

### Challenges:

- Paucity of pre-clinical data
- Unknown safety profile in humans
- *In-vivo* persistence
- Interval between doses
- Clinical activity during the initial cycle
- Intra-patient dose escalations

## CAR T cell trial design: Re-treatment

### Considerations when planning re-treatment

#### – Safety criteria

- Dose
- Organ function
- Performance status
- Adverse events experienced during prior treatment
- Persistence and expansion of the CAR T cells

#### –Clinical activity criteria

- Partial remission (PR)
- Progressive disease (PD)
- Complete remission (CR) with minimal residual disease (MRD)

## CAR T cell trial design: Ancillary Evaluations

### *In-vivo* Cytokine Profile

- Range of cytokines evaluated
- Frequency of monitoring
- Assays
- Comparative data between subjects who do and do not experience CRS
- Correlative data between cytokine levels
- Real-time vs batched assessments
- Reporting to the FDA



# CAR T cell design: Risk Mitigation Strategies

## Pre-specify plans

- Medications
  - Types
- Treatment algorithm
  - Triggers for medical intervention
  - Sequencing drugs
  - Activating suicide genes
  - Cytokine data collection

## CAR T cell design: Reporting

- Reporting and data analysis
  - Timing of reporting
  - Streamlined format for collecting and reporting
- Benefits
  - Improves understanding of safety issues
    - Within an IND
    - Across-INDs
  - Provides consistent advice
  - Supports clinical development

## Summary

- CAR T cells are novel products that have unique characteristics that may impact clinical aspects of regulating these products.
- There are challenges with almost every aspect of the trial design, from eligibility to long-term follow-up.
- Safety analysis of CAR T product is complex as it takes into consideration manufacturing aspects of the product in conjunction with clinical data.
- A uniform approach to grading, assessing and reporting toxicities improves our understanding of the safety of these products.
- Evaluating toxicities from a regulatory perspective requires frequent interactions with sponsors.
- CAR T cell science is a moving target and maintaining regulatory flexibility as knowledge improves is key to supporting drug development.

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