Managing Engineered T cell Toxicities – Regulatory Perspective

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SITC Annual Meeting
Hot Topic Symposium
Washington DC
November 9, 2014

Outline

- Types of Adverse Events (AE's)
  - "Short-Term" AEs
    - Acute Infusion Reactions
    - On-target Toxicities
      - On -tumor Toxicities
      - Off -tumor Toxicities
    - Off-target Toxicities
  - "Long-Term" Risks

- Trial design considerations to mitigate risks
  - Eligibility
  - Enrollment
  - Treatment
  - Dose escalation
  - Dose Limiting Toxicities

Engineered T cells - Acute Infusion Reactions

- Immediate
- Fever
- Chills
- Hypotension

Engineered T cells - On-target, On-tumor Toxicities

- On-tumor Toxicities
  - Tumor Lysis Syndrome
  - Cytokine Release Syndrome (CRS)

Engineered T cells - On-target, Off-tumor Toxicities

- Off-tumor Toxicities
  - Vital Organs
    - CNS
    - Pulmonary
  - Non-vital Organs
    - Colon
    - Dermatological
    - Ophthalmic
    - Auditory
    - Hepatic

Engineered T cells - Off-target Toxicities

- Cardiac
- CNS

Engineered T cells - Long-term Risks

- Insertional Mutagenesis
- B-cell aplasia

Engineered T cells - Risk Mitigation Strategies

- Eligibility
- Enrollment
- Treatment
- Dose Escalation
- Dose-Limiting Toxicities (DLTs)

Risk Mitigation – Eligibility Considerations

- Age
- Screening for co-morbidities
- Histology
- Tumor burden

Risk Mitigation – Enrollment strategies

- Cohort sizes
- Staggered enrollment

Risk Mitigation – Treatment

- Dosing
  - Split dose vs single-dose regimen
- Re-treatment
- Conditioning regimen

Risk Mitigation – Dose escalation

Dose increases

Risk Mitigation – Dose Limiting Toxicities

- DLT exceptions
- Dose de-escalation
- DLT definition - revisions

Summary

- CAR T have a range of toxicities.
- Products targeting the same antigen may have different on-target, off-tumor activities, *in-vivo* activation and persistence.
- Every aspect of trial design should be considered in optimizing safety.
- CAR T safety and predicting risk are moving targets.
- FDA encourages early and frequent communications from sponsors.

Acknowledgments

OCTGT T Cell Working Group

- Kristin Baird, MD
- Andrew Byrnes, PhD
- Robert Le, MD, PhD
- Ke Liu, MD, PhD
- Jinhua Lu, PhD
- Brian Niland, PhD
- Maura O'Leary, MD
- Graeme Price, PhD
- Mercedes Serabian, MS
- Daniel Takefman, PhD
- Ramjay Vatsan, PhD
- Allen Wensky, PhD
- Cheng-Hong Wei, PhD

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