Clinical Development of Chimeric Antigen Receptor (CAR)-T Cell Therapy in Cancer

Lianne Hu, MD PHD MPH MS

ONCOLOGY BRANCH

DIVISION OF CLINICAL EVALUATION & PHARMACOLOGY/TOXICOLOGY (DCEPT)
OFFICE OF TISSUES AND ADVANCED THERAPIES (OTAT)
CBER, FDA

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Disclaimer

- My presentation is an informal communication and represents my own best judgment. These comments do not bind or obligate FDA

- I have no financial relationship or conflict of interest to disclose

FDA Approved CAR T Cell Therapies

- Tisagenlecleucel (Kymriah) *
  - Refractory B-cell ALL, 2017; Refractory DLBCL and high-grade FL, 2018
- Axicabtagene ciloleucel (Yescarta) *
  - Refractory DLBCL, 2017; Refractory FL, 2021;
  - Large B-cell lymphoma (2nd line, 2022)
- Brexucabtagene autoleucel (Tecartus) *
  - Refractory Mantle cell lymphoma, 2020; Refractory B-cell ALL, 2021
- Lisocabtagene maraleucel (Breyanzi) *
  - Refractory B-cell NHL, (3rd line, 2021; 2nd line, 2022)
- Idecabtagene vicleucel (Abecma) ^
  - Refractory multiple myeloma, 2021
- Ciltacabtagene autoleucel (Carvykti) ^
  - Refractory multiple myeloma, 2022

*CD19-directed CAR-T cells; ^ BCMA(CD269)-directed CAR T cells

Learning Objectives

After this training course, you should be aware about:

a. Major clinical considerations for early Phase trials with CAR products.

b. Common safety information sought from sponsors

c. Difference between maximum tolerated dose (MTD) and optimal dose

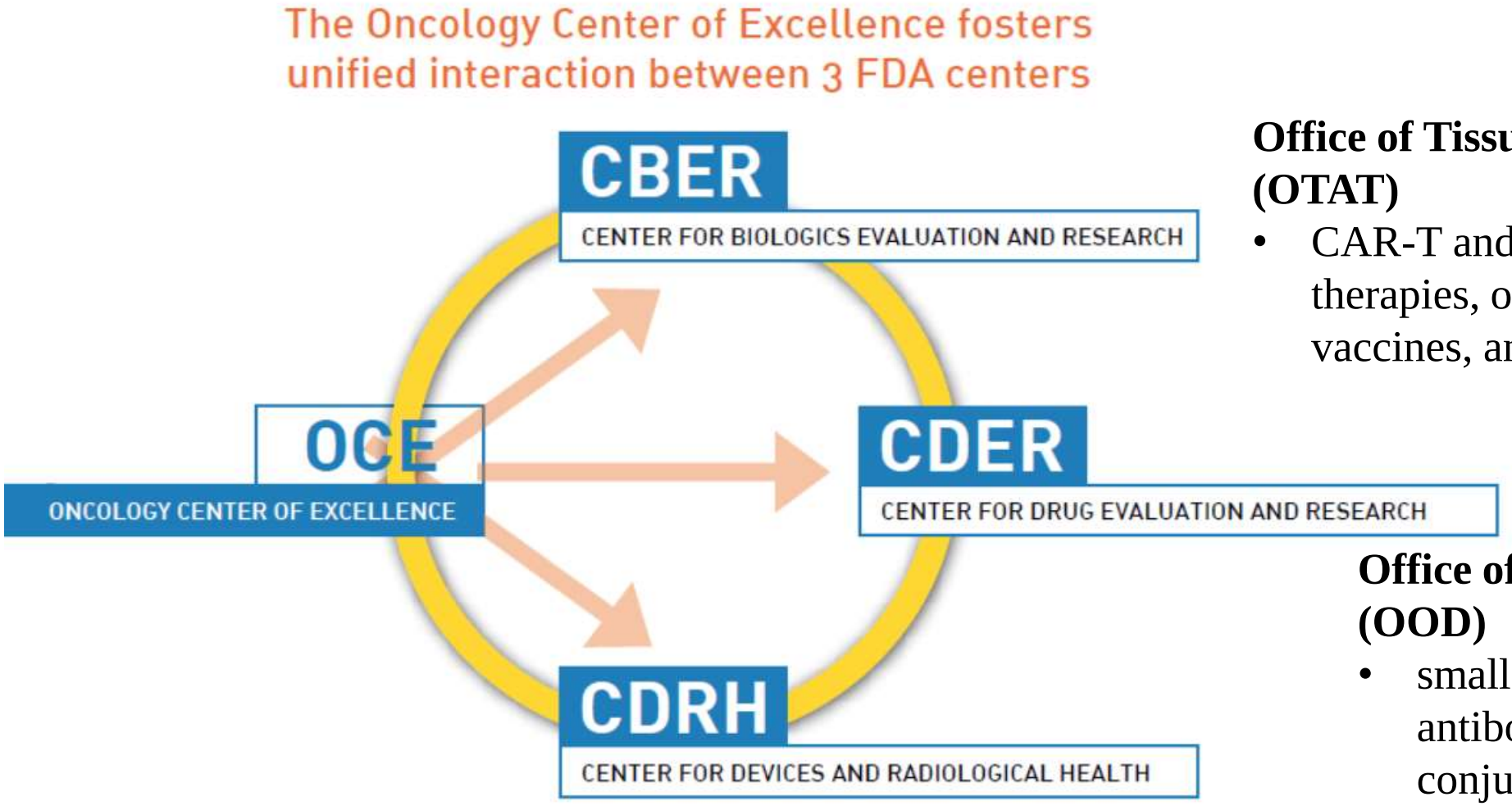
Outline

1. Regulation of oncology products at FDA

2. Clinical considerations for early phase trials with CAR products

3. Communications with FDA

FDA Regulation of Oncology Therapies



Office of Tissues and Advanced Therapies (OTAT)

- CAR-T and other cellular therapies, gene therapies, oncolytic viruses, therapeutic vaccines, and microbiota

Office of Oncologic Diseases (OOD)

- small molecules, monoclonal antibodies, antibody-drug conjugates

Office of In Vitro Diagnostics and Radiological Health

- companion and complementary diagnostics

Multidisciplinary Review Team

Can the clinical study begin?
Are safety monitoring plans in place to reduce subject risk?

CMC
Product Design, Manufacturing, and Testing

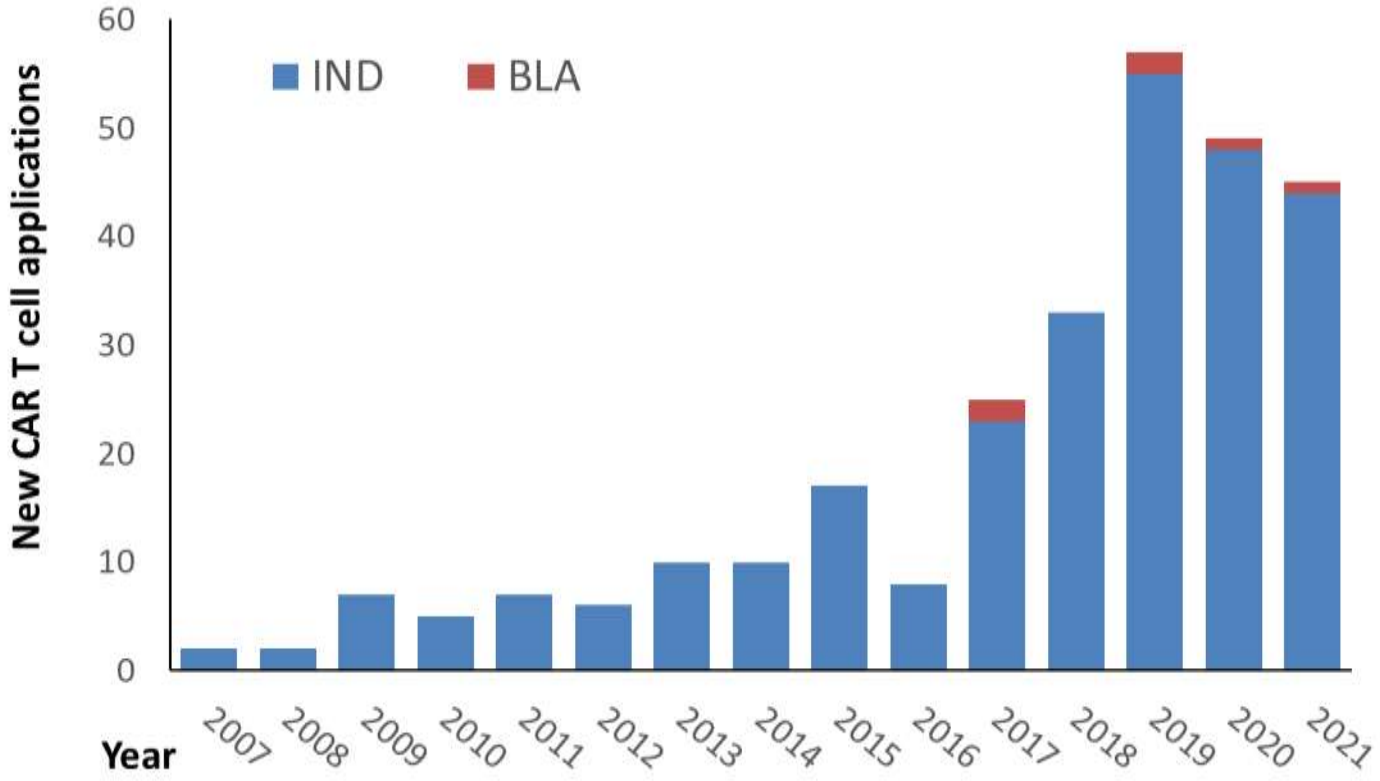
Clinical
Clinical Study Design
Assessment of Safety and Efficacy

Preclinical
Pharmacology and Toxicology Studies

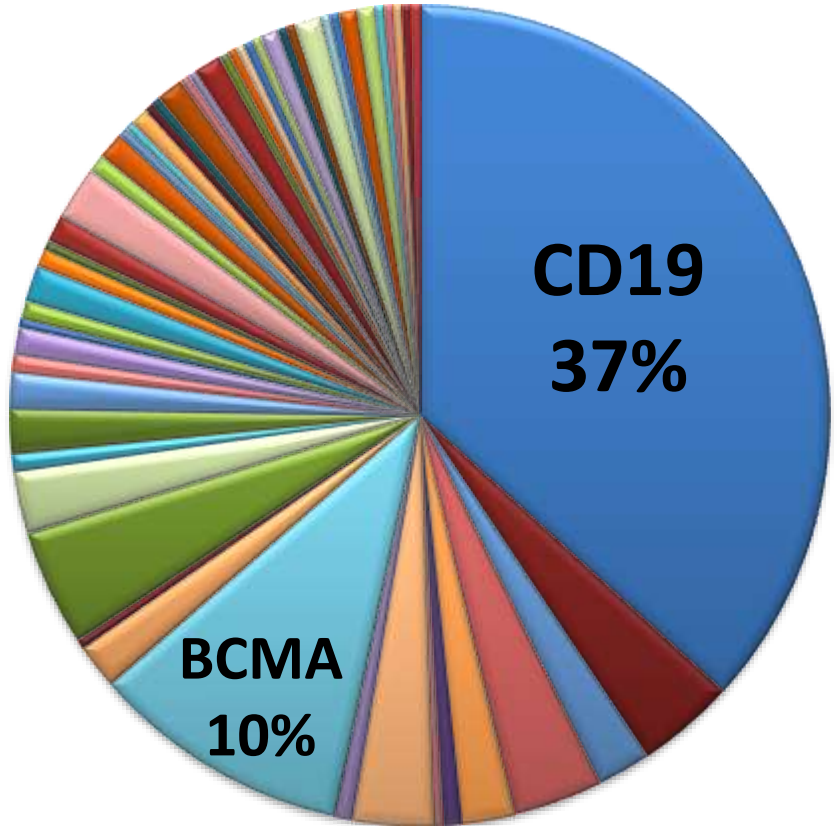
Biostatistics
Statistical Analysis of Clinical Study

Program Manager
Oversees Regulatory Review Process

CAR T-Cell Therapy Applications in OTAT



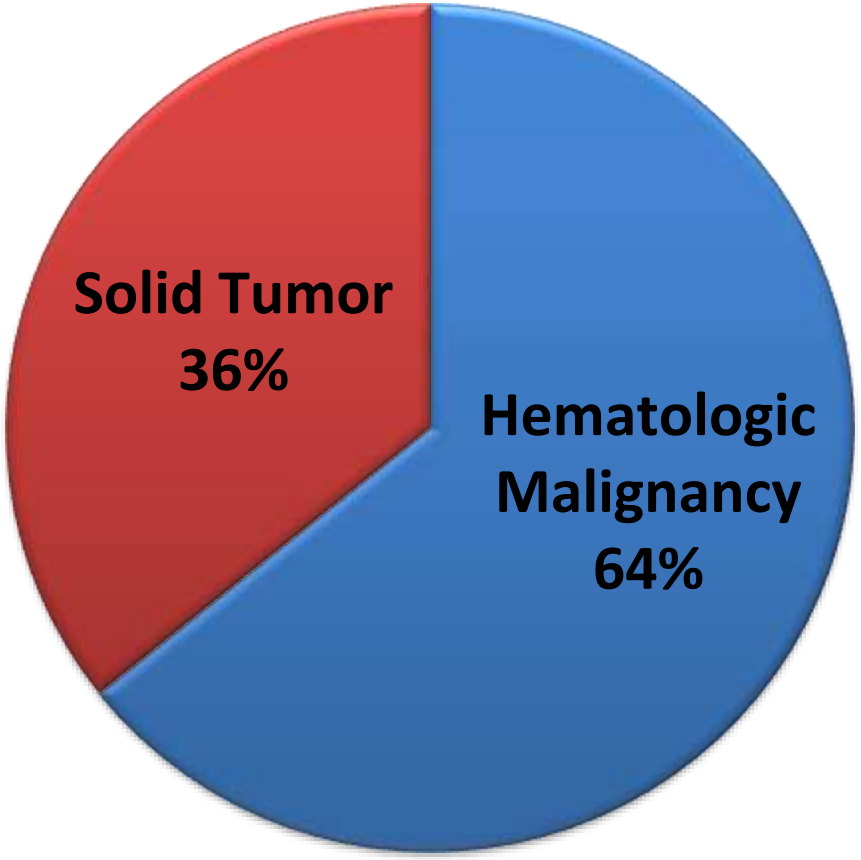
Antigen Targets

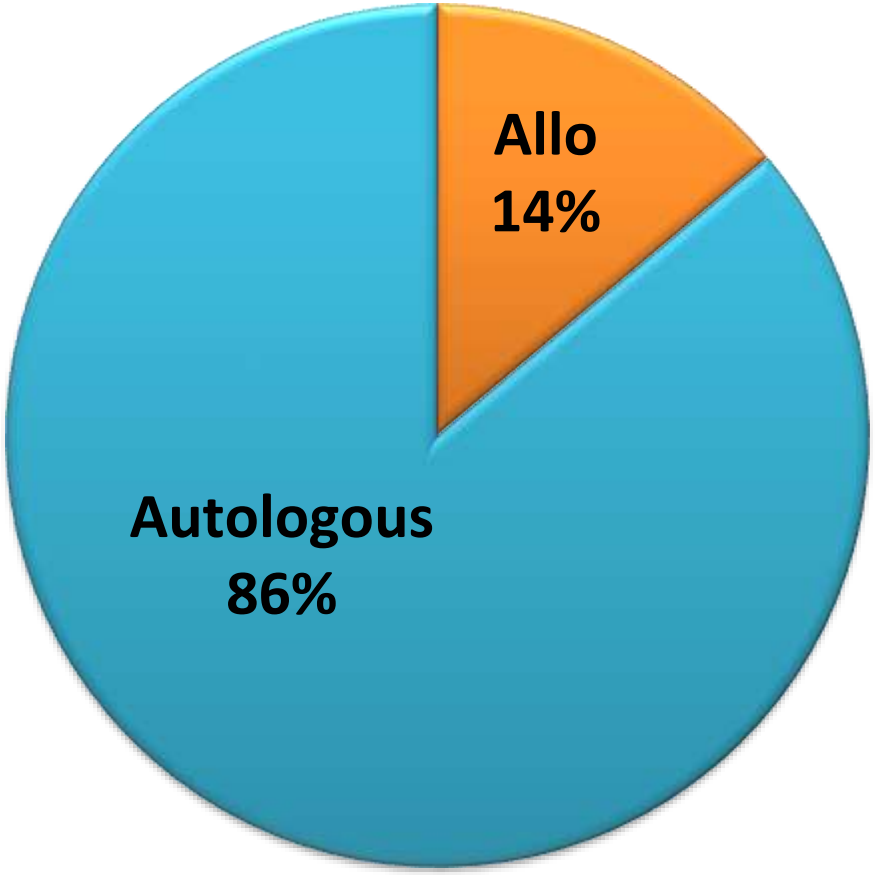


- Approximately 274 CAR T cell INDs*
  - 64% are for hematologic malignancies
  - 86% are autologous products
- 6 licensed autologous CAR T cell products

*Current as of 01/01/2022

CAR T-Cell Therapy Applications in OTAT

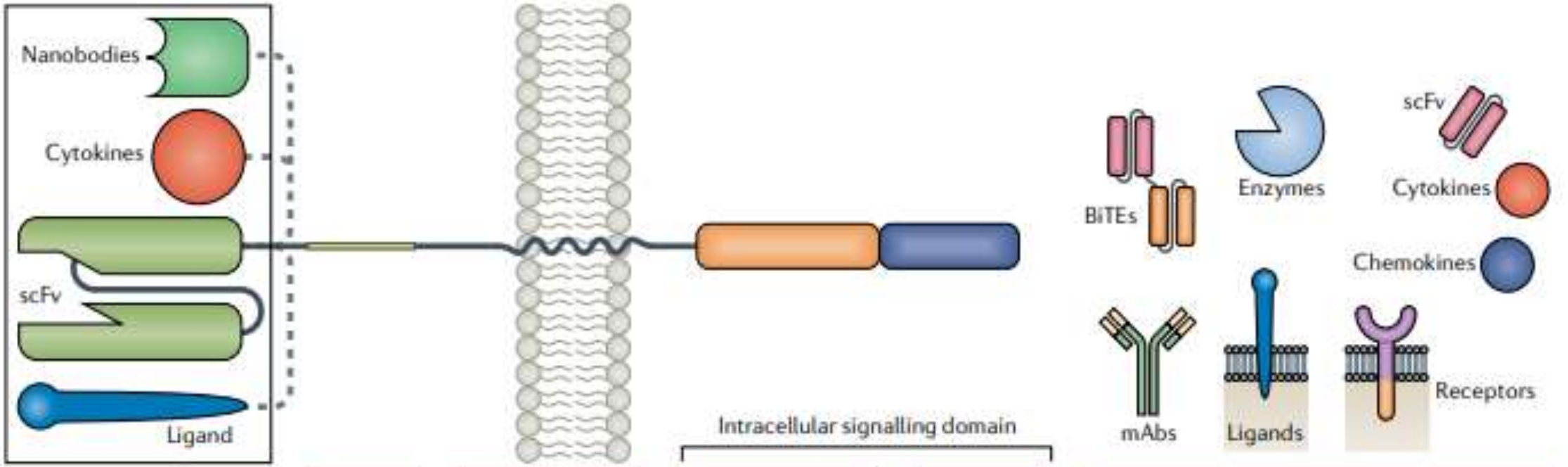




* Less than 1% for indications other than oncology

*Current as of 01/01/2022

Blueprint of CAR Design



Binding domain	Hinge	Transmembrane domain	Co-stimulation	Activation	Armour
• scFv • Nanobodies (camelid V_HH domains) • Cytokines • Ligands • Peptides (adnectins and DARPins)	• CD8 • CD28 • IgG1 • IgG4	• CD3ζ • CD8α • CD4 • CD28 • ICOS	• CD28 • 4-1BB • OX40 • ICOS • CD27 • MYD88–CD40 • KIR2DS2	• CD3ζ	• Cytokines or chemokines • Cytokine or chemokine receptors • Ligands or receptors • mAbs • BiTEs • scFv • Peptides (IL-1Ra, off-switch receptors or inducible suicide constructs) • Enzymes

Rafiq S, Hackett CS, Brentjens RJ. Nat Rev Clin Oncol. 2020 Mar;17(3):147-167.

Clinical Considerations

Early Phase/First-in-Human Trials with CAR Therapies

Trial Objectives

- Safety - primary objective
- Dose exploration
  - Dose escalation
  - Maximum tolerated dose (MTD)
  - Dose expansion: more than one dose level is recommended
  - Optimal dose
- Assessment of manufacturing feasibility
- Preliminary anti-tumor activity assessment

Eligibility Criteria

- Relapsed/Refractory to available therapies
- Comorbidities should be considered
- Pediatric studies *21 CFR 50, Subpart D*
- Specific target may require an in-vitro companion diagnostic (IVD)
  - Antigenic target
- IVD assay may require an investigational device exemption (IDE)
  - Does the IVD forego or delay treatment known to be effective?
  - Could the use of IVD expose subjects to safety risks?

Overall Study Design, Endpoints and Confounders

- Single arm trial
  - Safety
  - Objective response rate (ORR), duration of response (DOR)
  - Optimal dose finding
- Potential confounding factors of concurrent treatments
  - Lymphodepletion
  - Addition of checkpoint inhibitors
  - Bridging therapies

Starting Dosing / Dose Escalation

- Starting dose for first in human (FIH) study
  - May be based on toxicology data
  - Prior human experience with similar construct (empirical dose)
  - Dose may be based on transduced cells per unit weight (or BSA), or flat dose
  - Justifications for starting dose (preclinical data or clinical experience)
- Dose escalation scheme
  - Classic 3+3 design
  - Half-log increments for biological drugs (1 log escalation is generally considered aggressive)
  - Continual reassessment of dose escalation design using Bayesian adaptive design
  - Intra-patient dose escalation not recommended
  - Staggering of treatment between subjects / dose cohorts
  - Anticipated cell expansion in vivo
  - Anticipated toxicities

Dose Limiting Toxicities (DLTs)

- Examples of DLTs associated with CAR T therapies
  - Treatment-emergent Grade 4 Cytokine Release Syndrome (CRS)
  - Treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 7 days
  - Treatment-emergent autoimmune toxicity ≥ Grade 3
  - Grade 4 infusion-related reactions
  - Grade 3 or greater major organ toxicities, not pre-existing, occurring within 30 days of cell infusion
  - Death within 30 days of CAR T cell infusion unless clearly due to disease progression
  - Grade 3 or higher encephalopathy
  - Seizure
- Grading CRS and Neurologic Toxicity Associated with Immune Effector Cells (ICANS)
  - American Society for Transplantation and Cellular Therapy (ASTCT) Consensus Grading [1]
- Confounded by toxicities of conditioning lymphodepletion regimens

[1]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

Management of CRS

- Include an algorithm for assessment (grading) and management
- Rule out other causes of fever (sepsis, infusion reactions)
- Management of CRS
  - Tocilizumab (IL-6 receptor antagonist)
  - Steroids – potential interference with T cell activity/expansion
  - Supportive care (ICU), intubation, vasopressors, etc.
- Specify cytokine sampling requirement and monitoring
- Patients should remain in reasonable proximity to the treating institution in case of delayed toxicities

Safety Monitoring

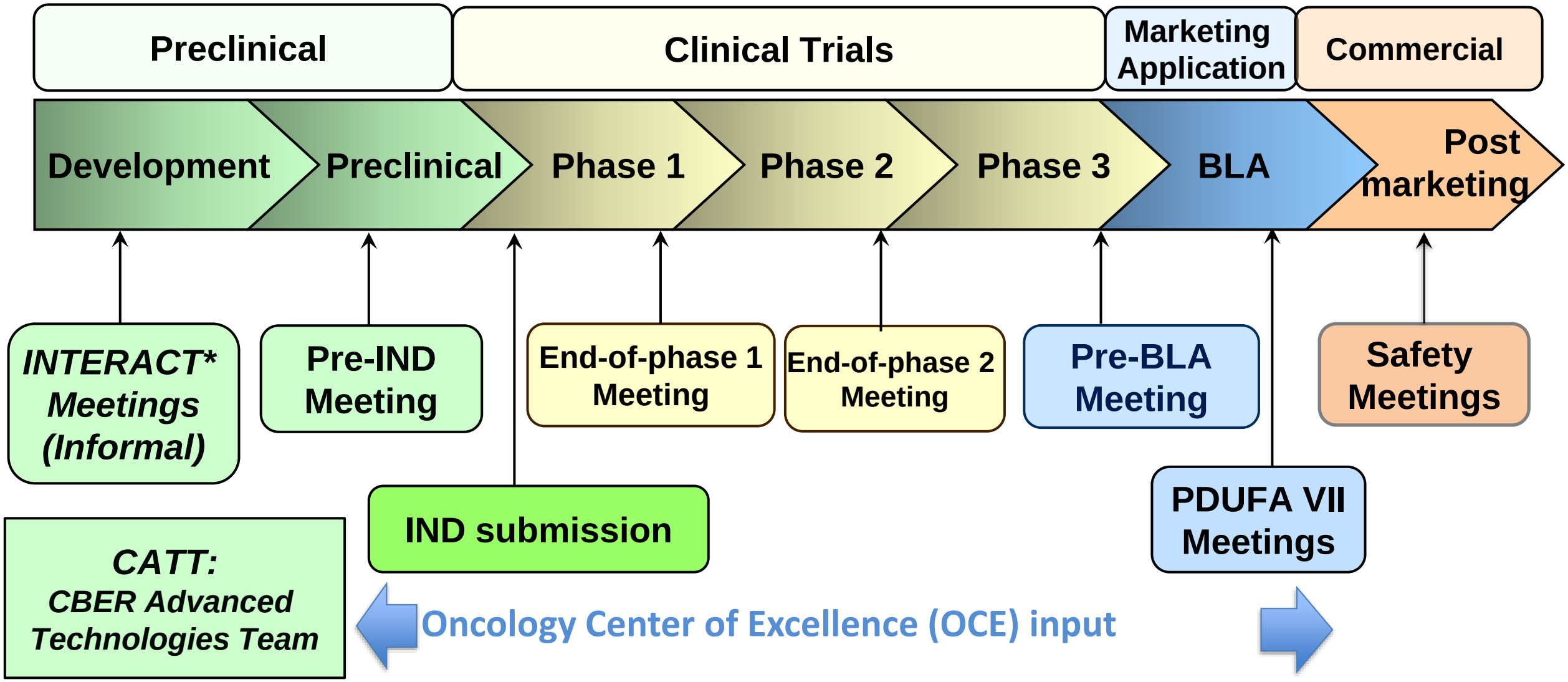
- Duration of monitoring for adverse events
  - Sufficient to cover expected duration of effect
  - Depends on information from preclinical studies, and experience with related products
- Safety Assessments and schedules (cover acute, subacute and delayed safety events)
- Long term follow-up may be required[1]
  - 15 years of follow-up for integrating viral vector-based products
  - Clinical development can continue while long-term follow-up is ongoing
- Development Safety Update Report (DSUR) annually

[1] FDA Guidance: Long Term Follow-up After Administration of Human Gene Therapy Products (2020)
https://www.fda.gov/media/113768/download

Study Pausing/Stopping Rules

- Temporary pause/suspension/stop in enrollment and dosing of additional subjects to limit the number of study subjects exposed to unreasonable risk
  - Death due to a serious adverse event onset within 30 days from lymphodepletion
  - Death possibly related to the protocol treatment
  - Increased incidence of expected toxicity (e.g., > 33% DLTs)
- Specify conditions for temporary suspension of enrollment and dosing until a safety evaluation is performed by the study safety oversight committee
- Protocol revision may be warranted
  - Eligibility criteria, dose, monitoring plan
- Not intended to terminate a study

When to Approach FDA for Product Development Discussions



*INitial Targeted Engagement for Regulatory Advice on CBER producTs

Resources for Meetings

FDA Guidance Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products 2017

https://www.fda.gov/media/109951/download

Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT program):

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings

CATT program

https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

Take-Home Messages

- Focus on study design, objectives, eligibility, starting dose, dose escalation and expansion scheme, DLTs, study pausing/stopping rules, safety assessments and reporting.

- Go beyond identifying MTD and incorporate strategies to identify the optimal dose in early phase trials.

Poll Question #1

Which primary endpoints are appropriate for a FIH study:

A. Overall Survival

B. Safety/Feasibility/ Dose finding

C. Landmark Progression Free Survival Rate

D. Objective Tumor Response Rate

Poll Question #2

Which of the following is (or are) important clinical safety information?

A. Cumulative summary of SAEs beginning from the initiation of the trial

B. The rate of dose-limiting toxicity

C. Number of subjects treated at maximum tolerated dose

D. Number of subjects who did not receive CAR T cells

Guidance for Industry

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), January 2020. https://www.fda.gov/media/113760/download
- M4Q: The CTD – Quality, August 2001 (Final). https://www.fda.gov/media/71581/download
- CGMP for Phase 1 Investigational Drugs, July 2008. https://www.fda.gov/media/70975/download
- Potency Tests for Cellular and Gene Therapy Products, January 2011 (Final).https://www.fda.gov/media/79856/download.
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products, November 2013 https://www.fda.gov/media/87564/download
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry, January 2020 (Final). https://www.fda.gov/media/113790/download.
- Long Term Follow-up After Administration of Human Gene Therapy Products, January 2020 (Final) https://www.fda.gov/media/113768/download
- Expedited Programs for Serious Conditions—Drugs and Biologic, May 2014 (Final) https://www.fda.gov/media/86377/download
- Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency https://www.fda.gov/media/145301/download
- Interpreting Sameness of Gene Therapy Products Under the Orphan Drug Regulations (Final) https://www.fda.gov/media/134731/download

Guidance for Industry (Continue)

- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, June 2015 (Final) https://www.fda.gov/media/106369/download
- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products, August 2007 (Final) https://www.fda.gov/media/73072/download
- Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, July 2020 (Final) https://www.fda.gov/media/123745/download
- Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings, June 2021 (Draft) https://www.fda.gov/media/150244/download
- Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination Guidance for Industry, October, 2019 (Final) https://www.fda.gov/media/112605/download
- Evaluating Cancer Drugs in Patients with Central Nervous System Metastases, July 2021
- https://www.fda.gov/media/141507/download
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial (Draft), September 2021 https://www.fda.gov/media/152536/download
- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry, December 2017 (Draft) https://www.fda.gov/media/109951/download
- References for the Regulatory Process for the Office of Tissues and Advanced Therapies http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Cell and Gene Therapy Guidance https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
- Human Gene Therapy Products Incorporating Human Genome Editing, March 2022 (Draft) https://www.fda.gov/media/156894/download
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products, March 2022 (Draft) https://www.fda.gov/media/156896/download

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Thank you!

Contact Information

- **Lianne Hu, MD PhD MPH MS** **lianne.hu@fda.hhs.gov**
- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

- **OTAT Learn Webinar Series:**

  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**: ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
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FDA Headquarters
Federal Research Center at White Oak
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002