# FDA's Clinical Regulatory Perspective: Designing First-In-Human trials for Cellular and Gene Therapy Products

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FDA SBIA Oncology Therapy Development Workshop – March 30-31, 2021

# Disclosures

- My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.
- I have no financial relationships to disclose.

# Learning Objectives

- Provide an overview of cellular and gene therapy product development programs for the treatment of cancer regulated by FDA
- Highlight the challenges and opportunities to initiate First in Human (FIH) studies of genetically modified cells and cancer immunotherapies for the treatment of cancer
- Summarize cellular therapies for the treatment of cancer that have been approved by FDA

# Poll Question #1

**Which type of meeting would not occur prior to an IND submission?**

A. INTERACT meeting

B. Pre-BLA meeting

C. Pre-IND meeting

D. CATT meeting

# Poll Question #2

**Which Primary Endpoints are Appropriate for a FIH Study:**

A. Overall Survival

B. Safety/Feasibility/ Dose finding

C. Progression Free Survival

D. Patient Reported Outcomes/ Quality of Life

# Outline

- FDA regulation of Oncology Products
- Cellular Immunotherapies for Cancer
- Trends in IND Cellular Immunotherapies submissions at FDA
- Clinical trial considerations for FIH Studies
- Summary

# FDA Regulation of Oncology Products

## CDER

Office of Oncologic Diseases (OOD)

- Drugs (small molecules)
- Biologics
  - Monoclonal Antibodies
  - Therapeutic Proteins
  - Cytokines

## CBER

Office of Tissues and Advanced Therapies (OTAT)

- Cell therapies
- Gene Therapies
- Oncolytic viruses
- Therapeutic vaccines and immunotherapies

## CDRH

Office of Health Technology (OHT)

Office of In Vitro Diagnostics and Radiological Health (OIR)

- Companion Diagnostics

**Oncology Center of Excellence (OCE)**

# Cellular Immunotherapies for Cancer

**Types of immune cell therapies**

Irradiated Tumor Cells

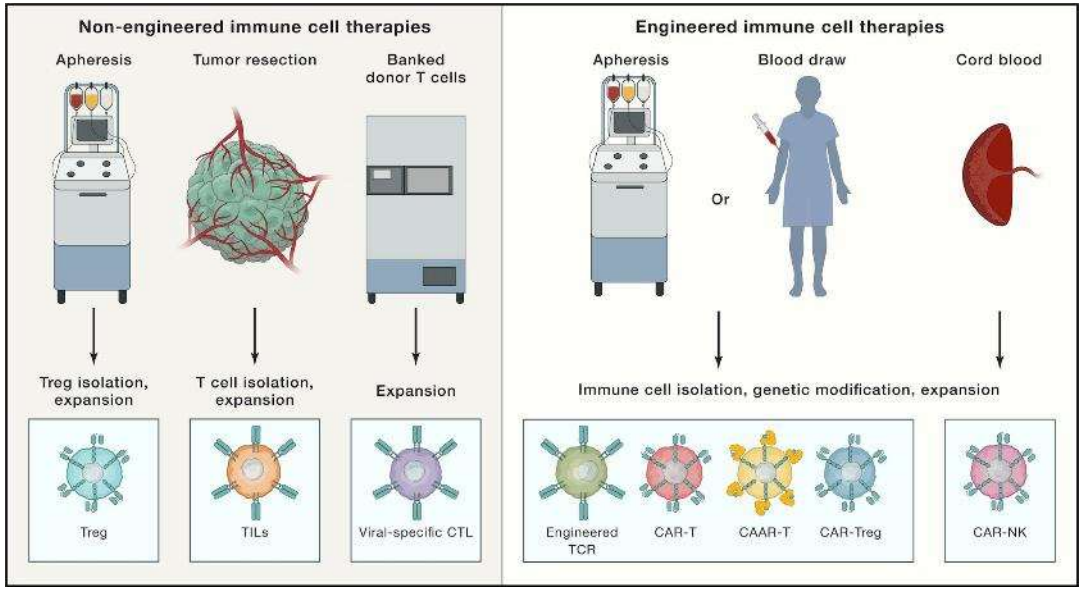
Non-engineered T cells
- Autologous Dendritic cells
- Autologous T cells expanded
- Tumor infiltrating lymphocytes (TILs)

Hematopoietic Stem Cells

Engineered T cells (autologous)
- Engineered T cell receptor (TCR)
- Chimeric antigen receptor (CAR) T cells
- Chimeric autoantibody receptor (CAR) T cells
- CAR-regulatory T cells (CAR-Treg)
- CAR-expressing Natural Killer cells (CAR-NK)

Edited T cells (autologous or allogeneic)
TALEN, zinc finger nucleases, CRISPR/Cas9

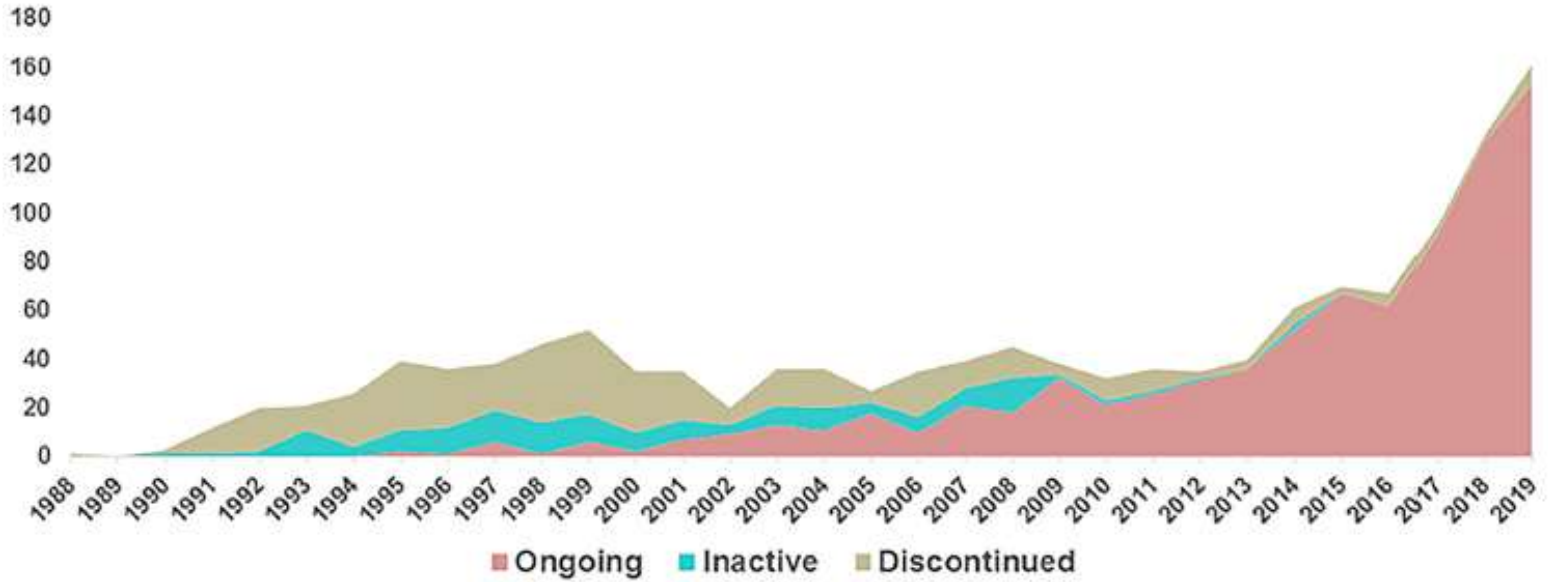
Allogeneic Haploidentical Natural Killer cells






Weber EW et al. Cell 2020;181:46-47

# IND Applications for Gene Therapy Products
## Trends in FDA Submissions

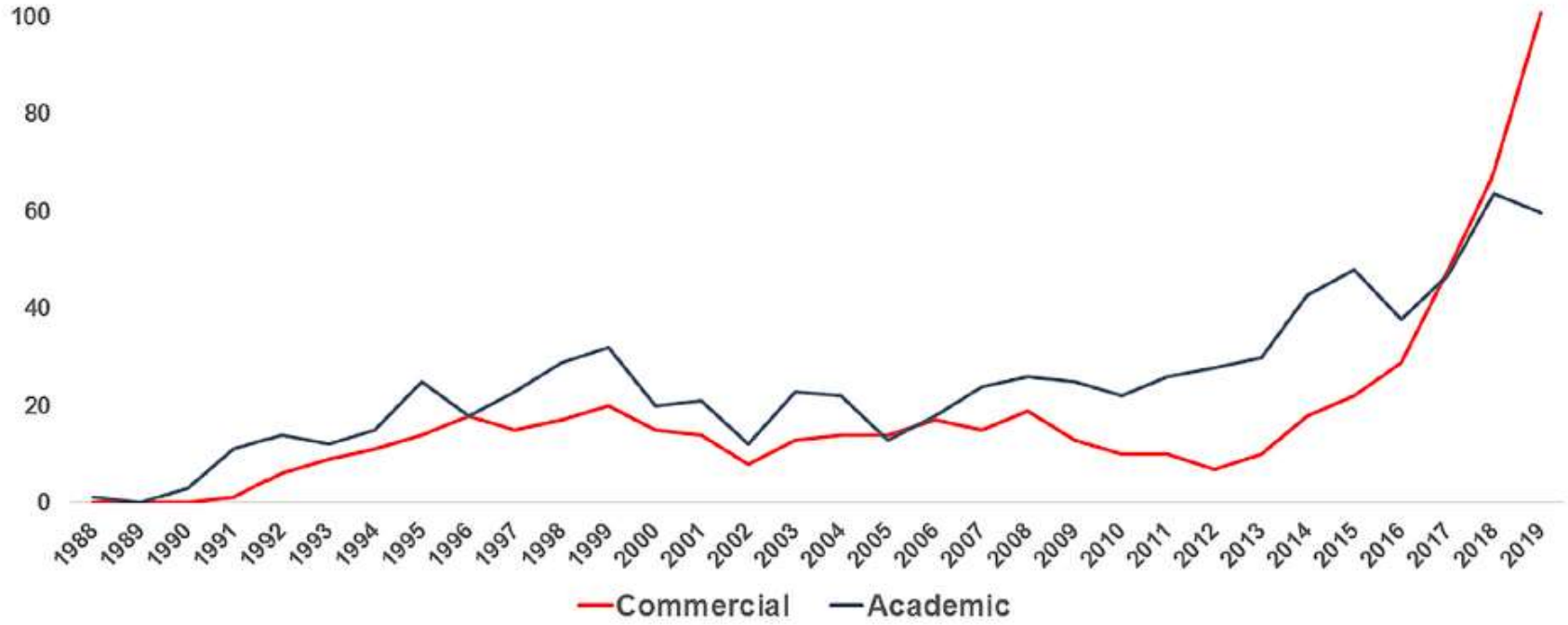



The shaded area (all colors) corresponding to each year represents the total number of IND applications with gene therapy product development programs submitted that year.



Lapteva L et al. Mol Therapy 2020;19:387-397

# Trends in IND Applications Sponsored by Academic and Commercial Entities are Evolving



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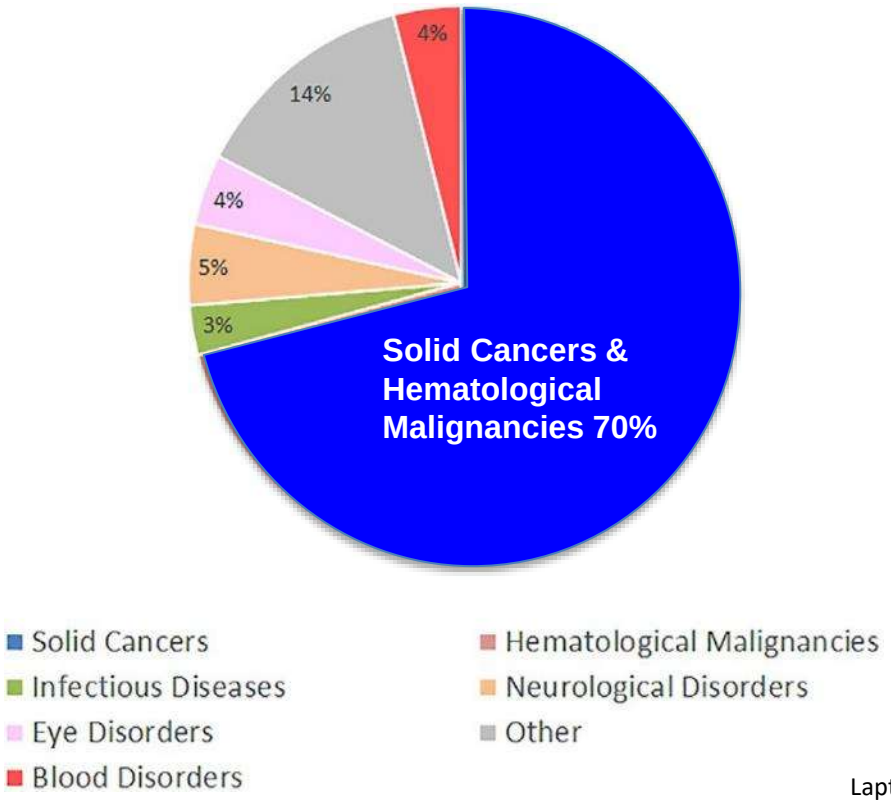
# Majority of IND Applications are in Solid Cancers and Hematological Malignancies



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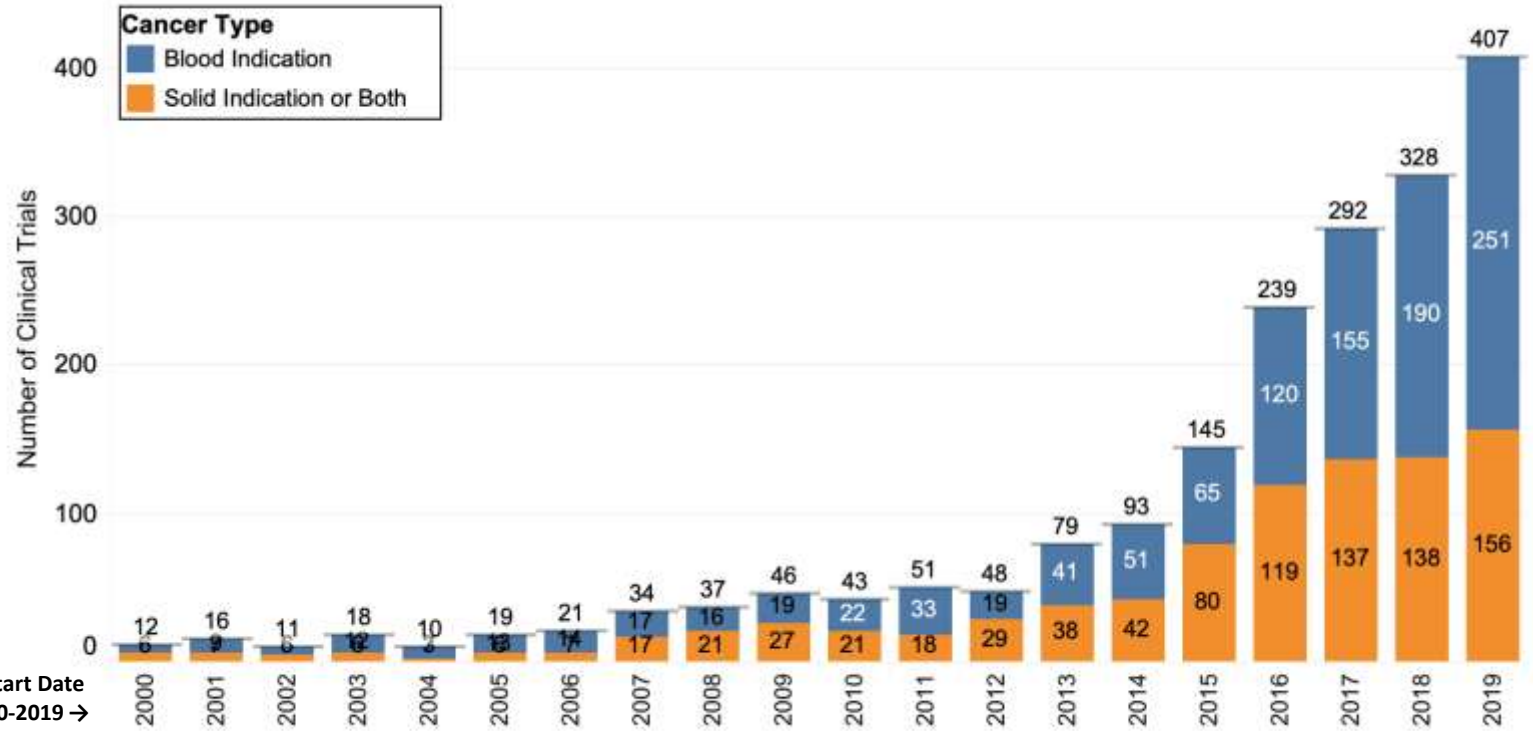
# Upward Trend in Cancer Cell Therapy Clinical Trials in Hematological Malignances and Solid Cancers

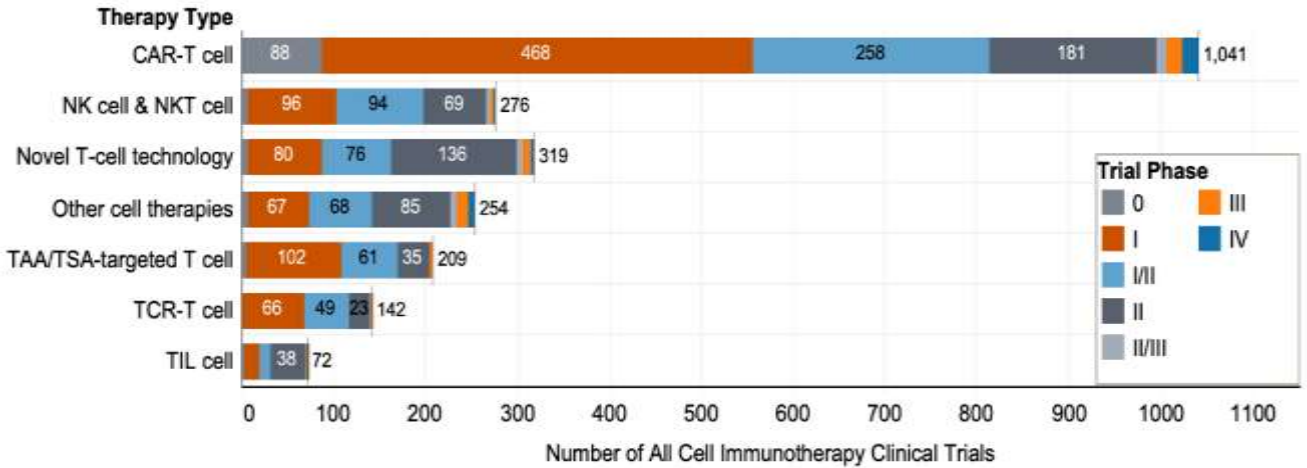



Source: CRI IO Analytics and GlobalData



Yu JX et al. Nature Reviews Drug Discovery 2020;19:583-584

# Among Cancer Cell Therapy Trials, CAR-T cells are the Most Frequent Therapy Type and Phase I/II are the Most Frequent Trial Phase

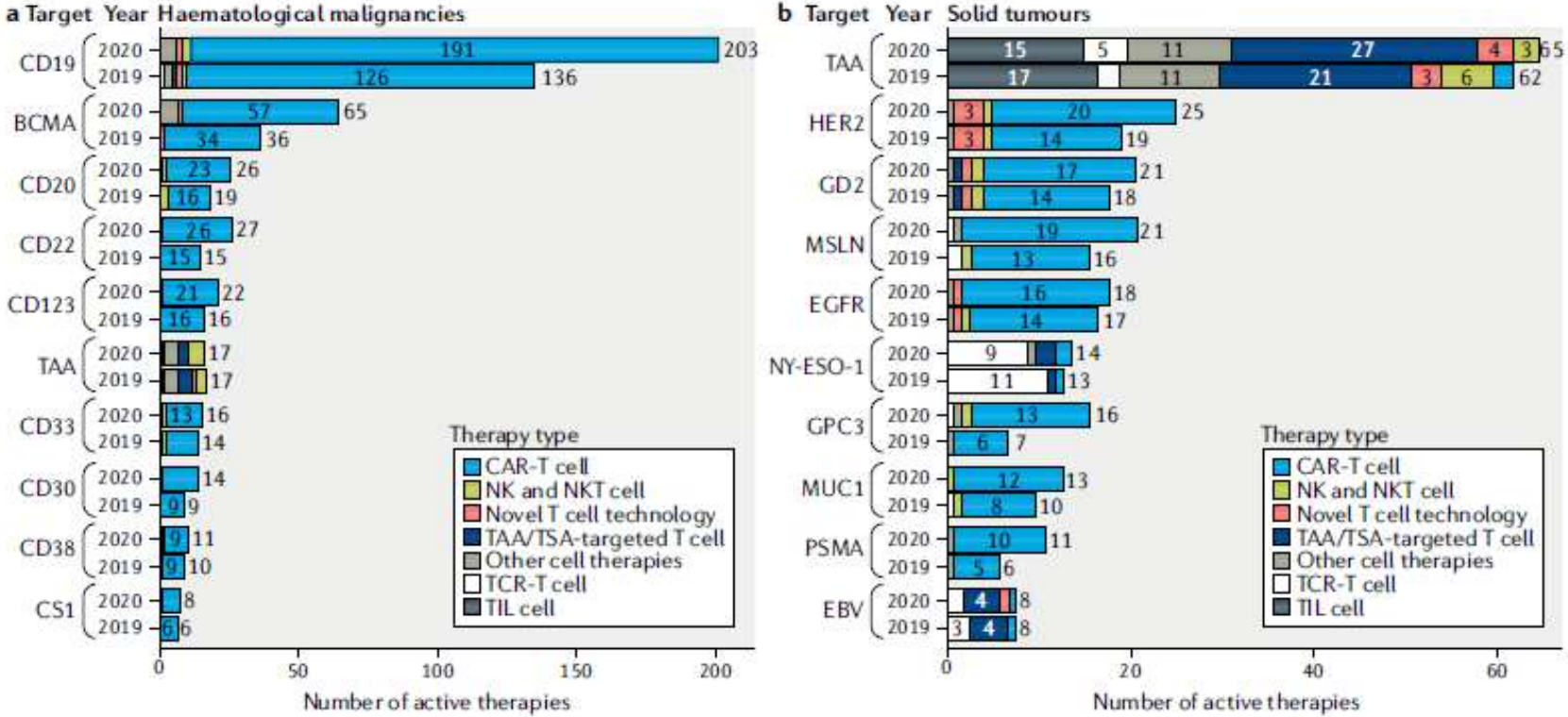



Source: GlobalData (data cut off point March 31,2020)



Yu JX et al. Nature Reviews Drug Discovery 2020;19:583-584

# Most Frequent Target of Hematological Cancers is CD19 and of Solid Tumors Are Tumor-Associated Antigens



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# Considerations for Designing FIH Cellular and Gene Therapy Studies for Cancer

- Cellular Therapies
  - Tumor formation
  - Migration to non-target sites
- Gene Therapies
  - Immune response to vector and/or transgene
  - Insertional mutagenesis
- Invasive procedures may be required
  - Associated procedural risks
- Cells or genes may persist for extended period or produce sustained effect
  - Intensify or prolong adverse reactions
  - Challenges of establishing a standardized approach for defining and capturing toxicities, such as cytokine release syndrome (CRS)

# Early Phase/First in Human Cancer Cell Therapy Trials: Objectives

- Safety - primary objective
- Dose exploration - varies according to different products
  - Maximum tolerated dose
  - Feasible dose
  - Optimal dose
- Feasibility assessment of manufacturing
- Activity assessment and preliminary clinical efficacy

# Study Design Issues

- Single arm studies should generally focus on unmet needs
  - Relapsed/Refractory to available therapies
  - Potential for Accelerated Approval based on response
  - Contribution of effects a challenge for combinatorial studies
- Specific targets may require a companion diagnostic (CDx)
  - Antigenic targets (CDRH)
  - HLA restrictions (CBER OBRR)
- CDx Assays may require a Study Risk Evaluation (protocol-specific) assessing
  - Are subjects forgoing standard of care?
  - Are anticipated toxicities of proposed regimen acceptable?
- Significant Risk devices require investigational device exemptions (IDE)

# Endpoints

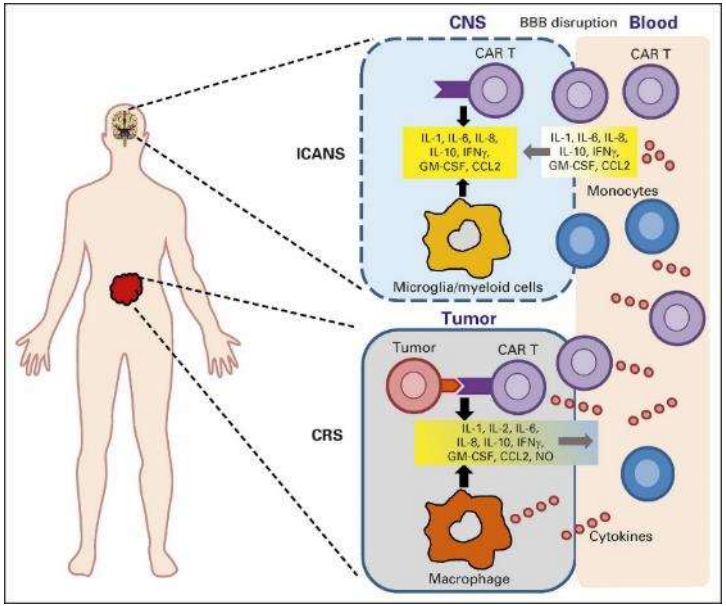
- Single-arm trial
  - Safety, dose finding
  - Tumor response rate, duration of responses
  - Time-to-event analyses (overall survival, progression-free survival) difficult to interpret in this setting
    - Historical controls may be unreliable
- Randomized controlled trial – later stage development
  - Time-to-event analyses (overall survival, progression-free survival)
  - Appropriate control required – discuss with FDA
  - May not be feasible for these products in a refractory population
- Potential confounding impact of concurrent treatments
  - Lymphodepletion
  - Addition of checkpoint inhibitors

# Dosing / Dose Escalation

- Starting dose for first in human (FIH) study
  - May be based on toxicology data
  - Prior human experience with similar construct
  - Dose should be based on transduced cells per unit weight (or BSA)
- Dose escalation scheme
  - Anticipated cell expansion in vivo
  - Anticipated toxicities
  - Half-log increments for biological drugs (log escalation is generally considered aggressive)
  - Typically employ a 3+3 design
  - Continual reassessment escalation designs may be considered such as Bayesian adaptive designs
  - Intra-patient dose escalation not recommended
  - Staggering of treatment between subjects / dose cohorts
- Provide justification for the plan and the starting dose based on clinical or preclinical data

# CAR T Cell Toxicities [1,2]

- Cytokine Release Syndrome (CRS)
  - Delayed onset (days or weeks)
  - Cytokines released as T cells expand and exert anti-tumor activity
  - Elevated cytokines (IFNγ, IL-6 and others)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
  - Reversible neurotoxicity common (aphasia)
  - Severe neurotoxicity has been seen (fatal cerebral edema)
- Prolonged B cell aplasia (for CD19 CAR T cells)
  - "On-target, off-tumor" toxicity




Pathophysiology of CRS and ICANS after CAR T-cell therapy[1]



[1]Reagan PM & Neelapu SS. J Clin Oncol 2021;39(5):456-466
[2]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

# TCR Toxicities

- TCRs may recognize self antigens and cause Serious Adverse Events (SAEs)
  - Autoreactivity has always been a theoretical possibility, but actual SAEs led to:
    - Better understanding of risk factors
    - New strategies to screen for autoreactivity before using TCRs in clinical trials
  - Any TCR might be autoreactive, but risk is higher for certain engineered TCRs:
    - Non-human TCRs
    - Affinity-enhanced TCRs
- Examples
  - Mouse TCR targeted against MAGE-A3 / HLA-A*02[1]
    - Neurotoxicity due to unexpected expression of MAGE-A12 in the central nervous system
      - MAGE-A3/12 epitopes are similar
  - Human affinity-enhanced TCR targeted against MAGE-A3 / HLA-A*01[2]
    - Rapid cardiac toxicity due to unexpected "off-target" TCR cross-reactivity with Titin (a muscle protein)



[1]Morgan RA et al. J Immunother. 2013;36(2):133-151
[2]Cameron BJ et al. Sci Transl Med. 2013;5(197):197ra103

# Management of Toxicities (CRS)

- For suspected CRS, include an algorithm for assessment and management
- Rule out other causes of fever (sepsis, drug reactions)
- Management of toxicity
  - Tocilizumab (blocks IL-6 receptor) – now approved to treat CRS
  - Steroids – Potential interference with T cell activity/expansion
- Provide specific indication(s) for supportive care, fluids, ICU, vasopressors
- Specify cytokine sampling requirements
- If subjects are discharged to outpatient care, they should remain in reasonable proximity to the treating institution in case of delayed toxicities



[1]Reagan PM & Neelapu SS. J Clin Oncol 2021;39(5):456-466
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# Dose Limiting Toxicity (DLT)

- Protect subjects and identify optimum biological/recommended phase 2 dose
- Confounded by toxicities of conditioning lymphodepletion regimens
- Context important
  - Some CRS may be expected
  - Severe CRS requiring ICU admission is generally considered a DLT
  - Monitor for off-target toxicities (cardiac, neurological, etc.)
- Ensure *clear* definitions
  - Grading of CRS is evolving – CTCAE may not be adequate
    - ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells [1]

Examples of cancer cell therapy study DLTs:

- Any treatment-emergent Grade 4 or 5 CRS
- Any treatment-emergent Grade 3 CRS that does not resolve to ≤ Grade 2 within 7 days
- Any treatment-emergent autoimmune toxicity ≥ Grade 3
- Grade 3 and greater allergic reactions related to the cell infusion
- Grade 3 and greater major organ toxicities, not pre-existing or not due to the underlying malignancy and occurring within 30 days of cell infusion



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

# Study Stopping Rules

- Temporary pause in enrollment and treatment of additional subjects to limit the number of study subjects being exposed to excess risk
  - Death
  - Increased incidence of expected toxicity
- Specify conditions (e.g., type and number of adverse events) for temporary suspension of enrollment and dosing until a safety assessment can be completed
- Based on the outcome of the safety assessment, protocol revision may be warranted
  - Eligibility criteria, dose, monitoring plan
- Not intended to terminate a study

# 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

- Long term follow-up may be required for certain cellular and gene therapies
  - e.g., 15 years of follow-up for integrating viral vector-based products
  - Clinical development can continue while long term follow-up ongoing



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

# FDA Review involves multidisciplinary input

Pharmacology & Toxicology

Regulatory Project Management

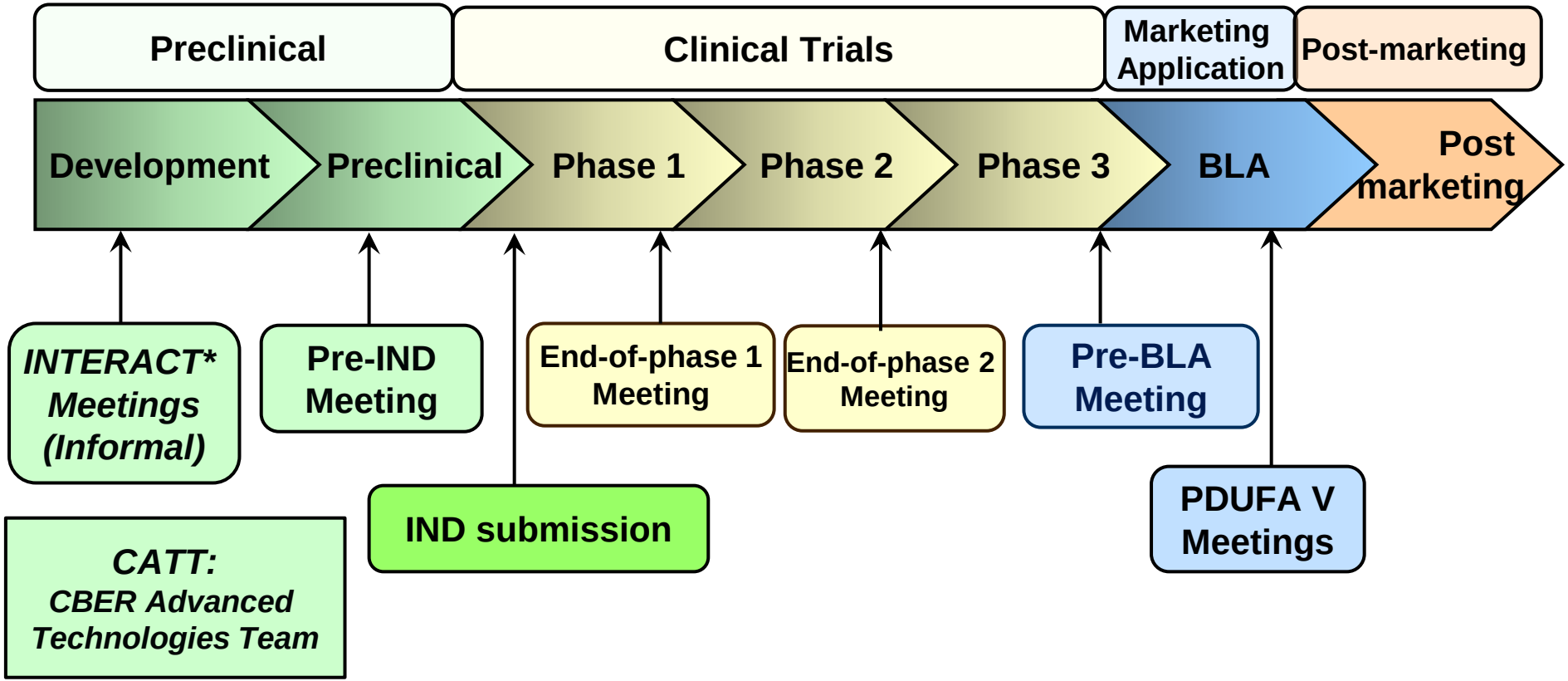
Statistics

Clinical Pharmacology & Biopharmaceutics

Product Quality (CMC)

Clinical

# When to Approach FDA for Product Development Discussions






FDA Guidance Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products 2017
https://www.fda.gov/media/109951/download

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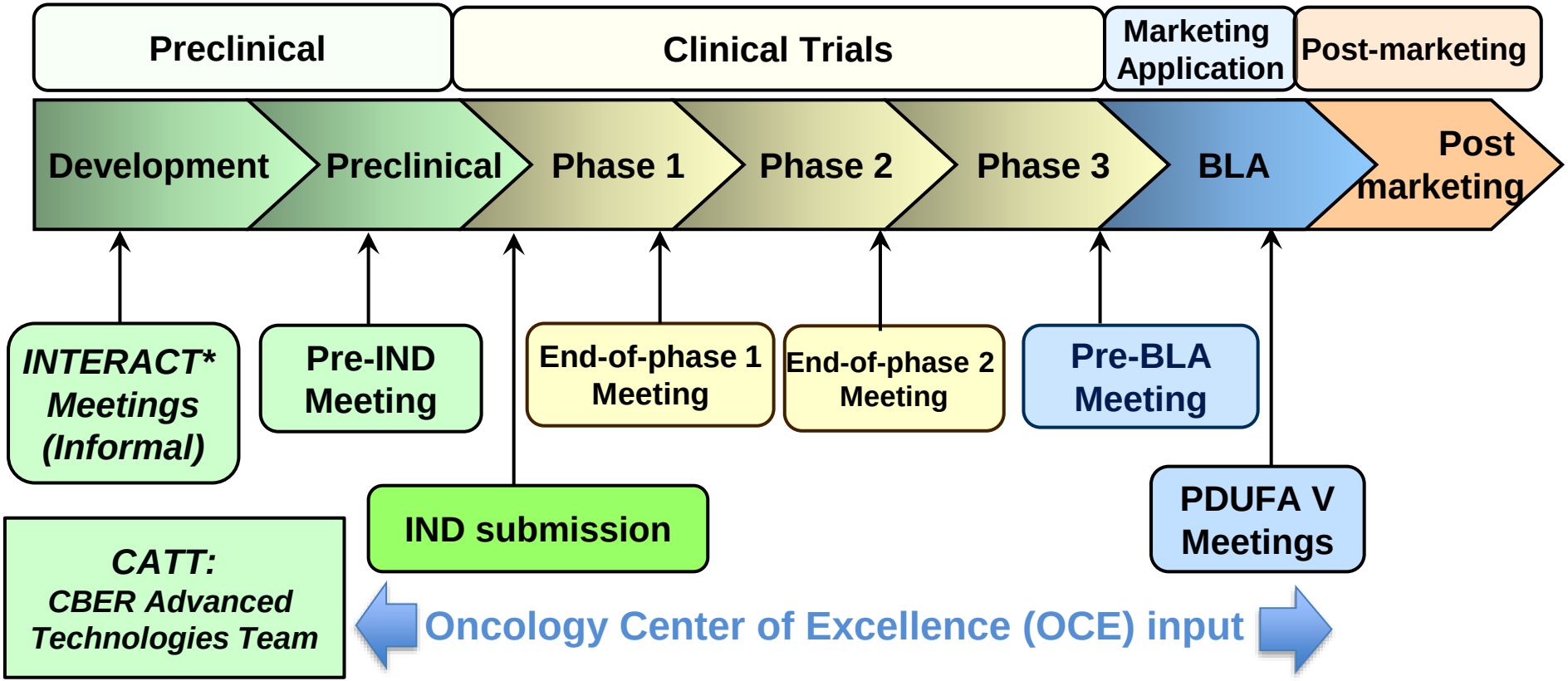


www.fda.gov

*INitial Targeted Engagement for Regulatory Advice on CBER producTs

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# FDA Approvals of Cell Therapies for Cancer

- Sipuleucel-T (Provenge)
  - Metastatic castrate resistant prostate cancer, 2010
- Tisagenlecleucel (Kymriah) *
  - Refractory B-cell ALL, 2017; DLBCL, 2018
- Axicabtagene ciloleucel (Yescarta) *
  - Aggressive B-cell NHL, 2017
- Brexucabtagene autoleucel (Tecartus) *
  - Mantle cell lymphoma, 2020
- Lisocabtagene maraleucel (Breyanzi) *
  - Refractory B-cell NHL, 2021

www.fda.gov

*CD19-directed CAR-T cells

# Summary

- Gene modified T cells show promise for cancer therapy
  - Chimeric antigen receptor (CAR) T cells
  - T cell receptor (TCR) modified T cells
- Products moving rapidly from lab to clinic
  - Toxicity is a concern
  - Products are complex
    - Many subcomponents: construct, vector, autologous cells
- Regulatory advice is available from CBER FDA OTAT
  - Pre-IND meetings
  - INTERACT meetings
  - CBER Advanced Therapies Team (CATT)
  - IND meetings (End-of-phase 2, pre-BLA, etc.)

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# Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies

  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm

- OTAT Learn Webinar Series: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- Cell and Gene Therapy Guidances https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
- Expedited Programs Guidance: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

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- **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
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