Clinical Development of Gene Therapies: Genetically Modified Cellular and Cancer Immunotherapies

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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 gene therapy product development programs for the treatment of cancer that are evaluated by FDA
- Introduce gene therapies for the treatment of cancer that have been recently approved by FDA
- Highlight the challenges and opportunities to develop genetically modified cells and cancer immunotherapies for the treatment of cancer

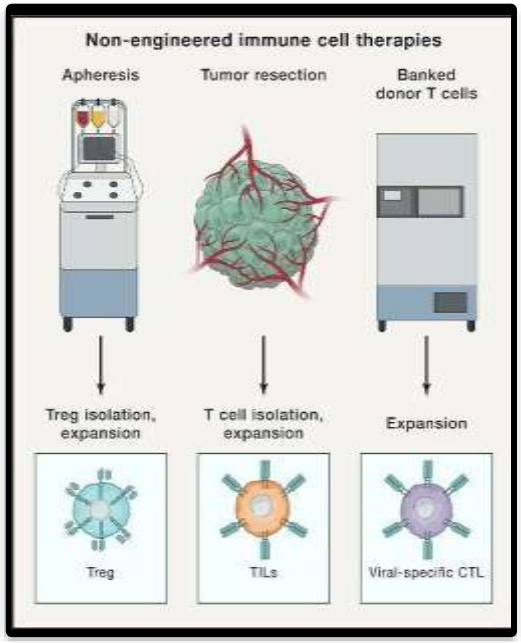
Outline

- Cellular Immunotherapies for Cancer
- Trends in IND submissions
- Gene therapy approvals
- Clinical trial considerations
- Summary

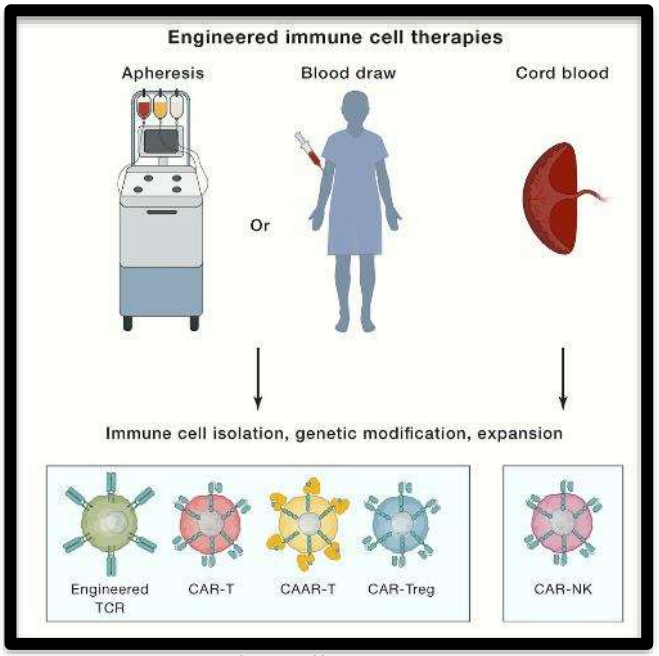
Definitions

- Gene therapy
  - Human gene therapy: Seeks to modify or manipulate the expression of a gene or alter the biological properties of living cells for therapeutic use
  - Human gene therapy product: All products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host (human) genetic sequences
  - Gene therapy products meet the definition of "biological product" in section 351(i) of the Public Health Service (PHS) Act (42 U.S.C. 262(i)) when such products are applicable to the prevention, treatment, or cure of a disease or condition of human beings

Types of Cellular Cancer Immunotherapies



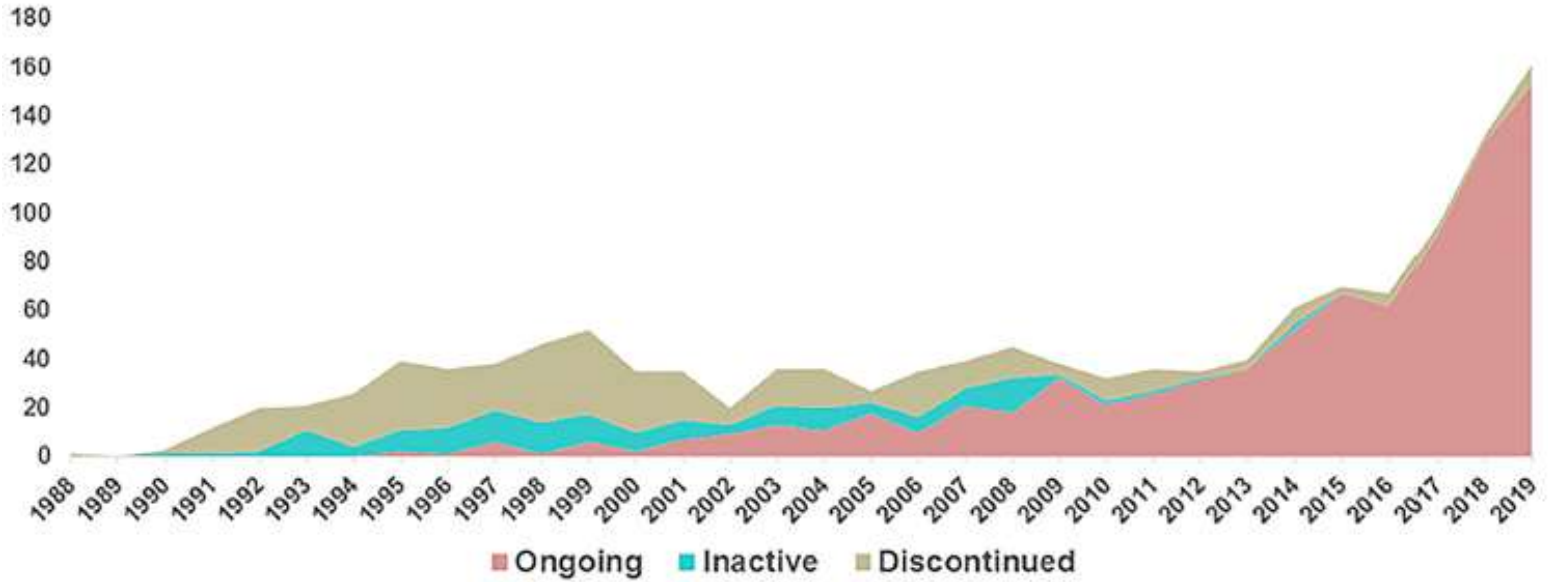
- Non-engineered T cells
  - Dendritic cells
  - Tumor infiltrating lymphocytes (TILs)



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

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

IND Applications for Gene Therapy Product Programs are Increasing



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

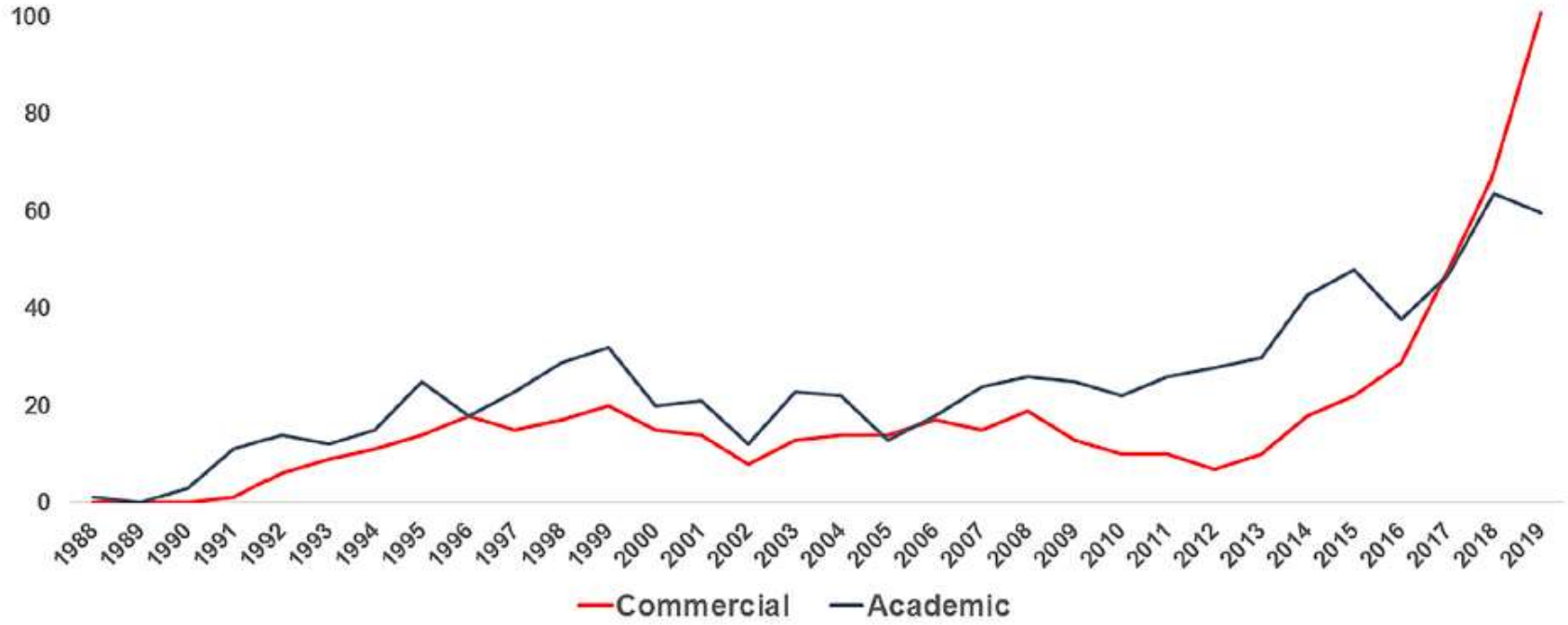
Rates of Attrition of IND Applications with Gene Therapy Product Programs are High

	Rates of Attrition (Rates of discontinued and inactive INDs)		
Submitted	For Any Program	For Commercial Program	For Academic Program
1988–1998[a]	97%[b]	96%	98%
1999–2008	67%[c]	61%	71%
2009–2019[a]	13%[d]	10%	15%

[a]11 years included: no INDs were submitted in 1989; year 2019 added to the third decade
[b]Program duration, mean = 8.6 years, range [<1; 24]
[c]Program duration, mean = 7.5 years, range [<1; 19]
[d]Average program duration is too early to calculate

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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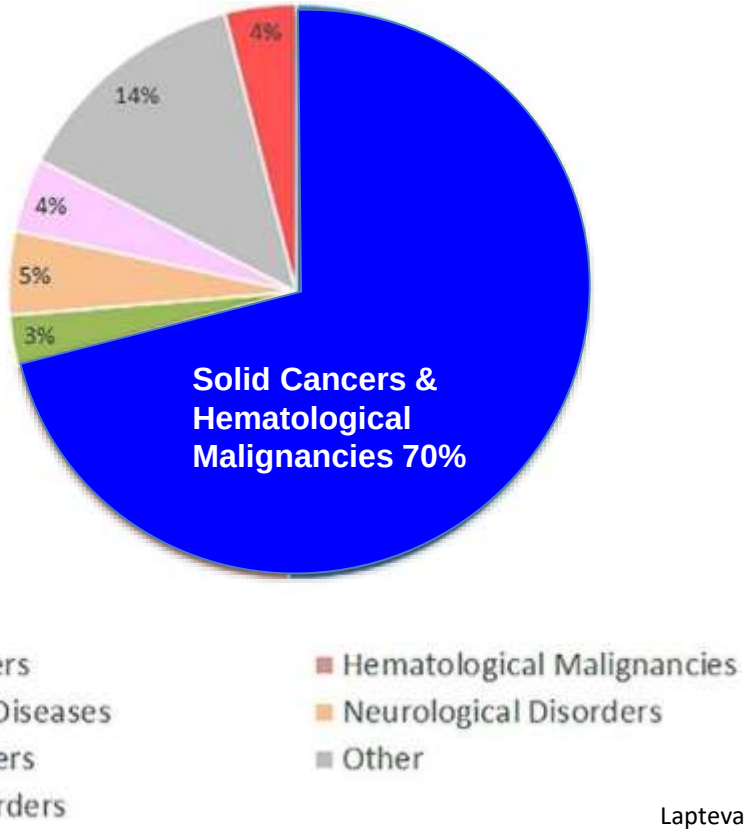
Majority of All Ongoing IND Applications are in Solid Cancers and Hematological Malignancies



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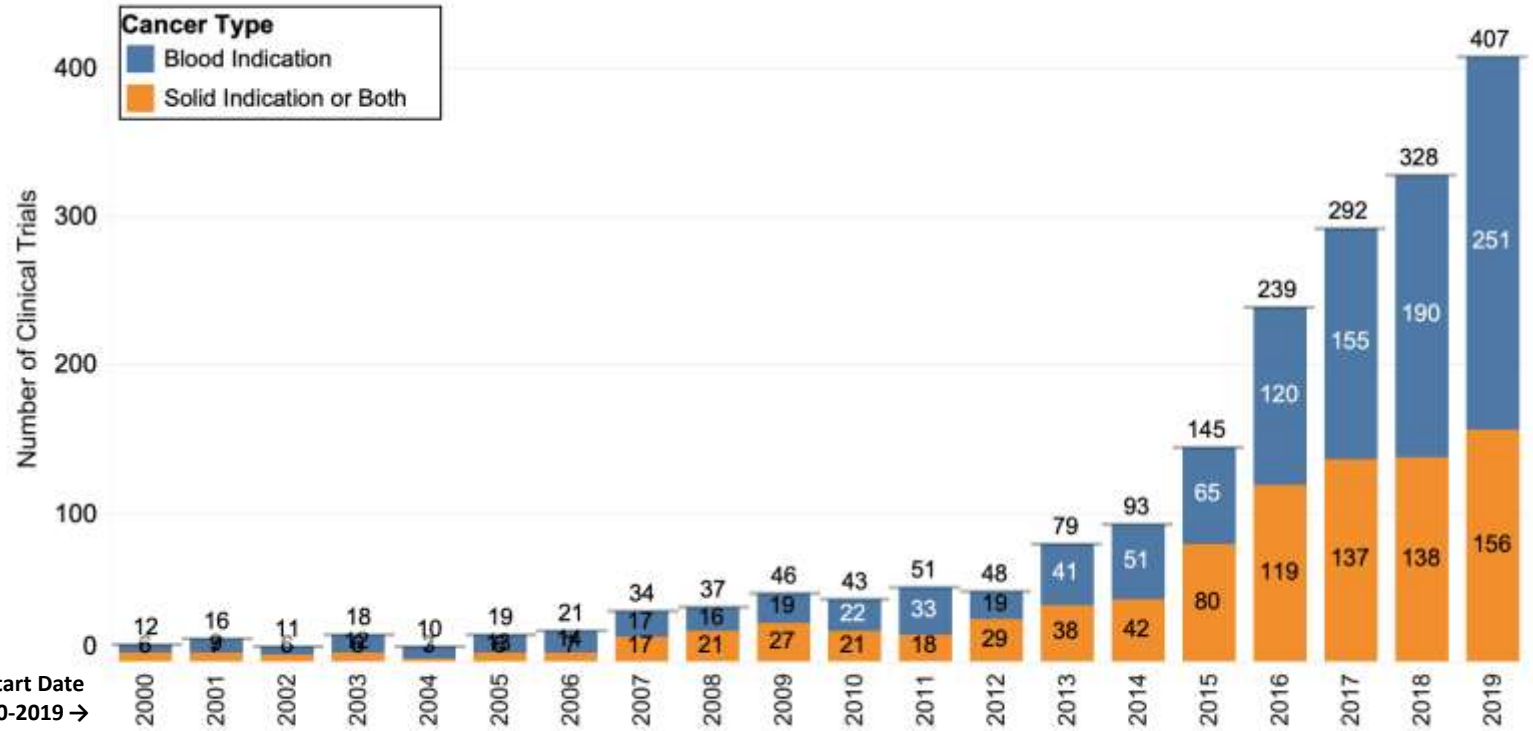
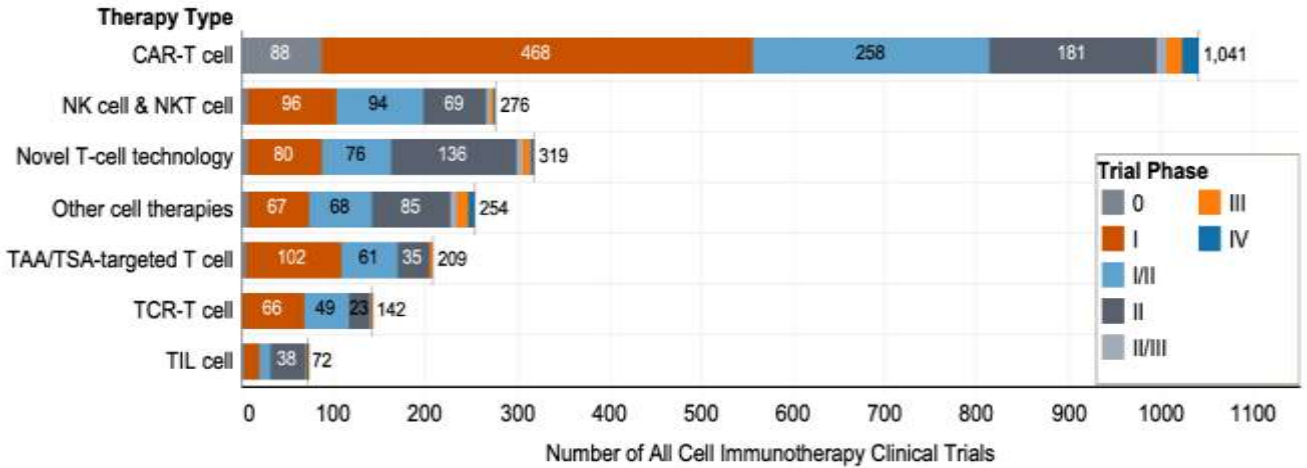
Upward Trend in Cancer Cell Therapy Clinical Trials in Hematological Malignances and Solid Cancers



Source: CRI IO Analytics and GlobalData

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

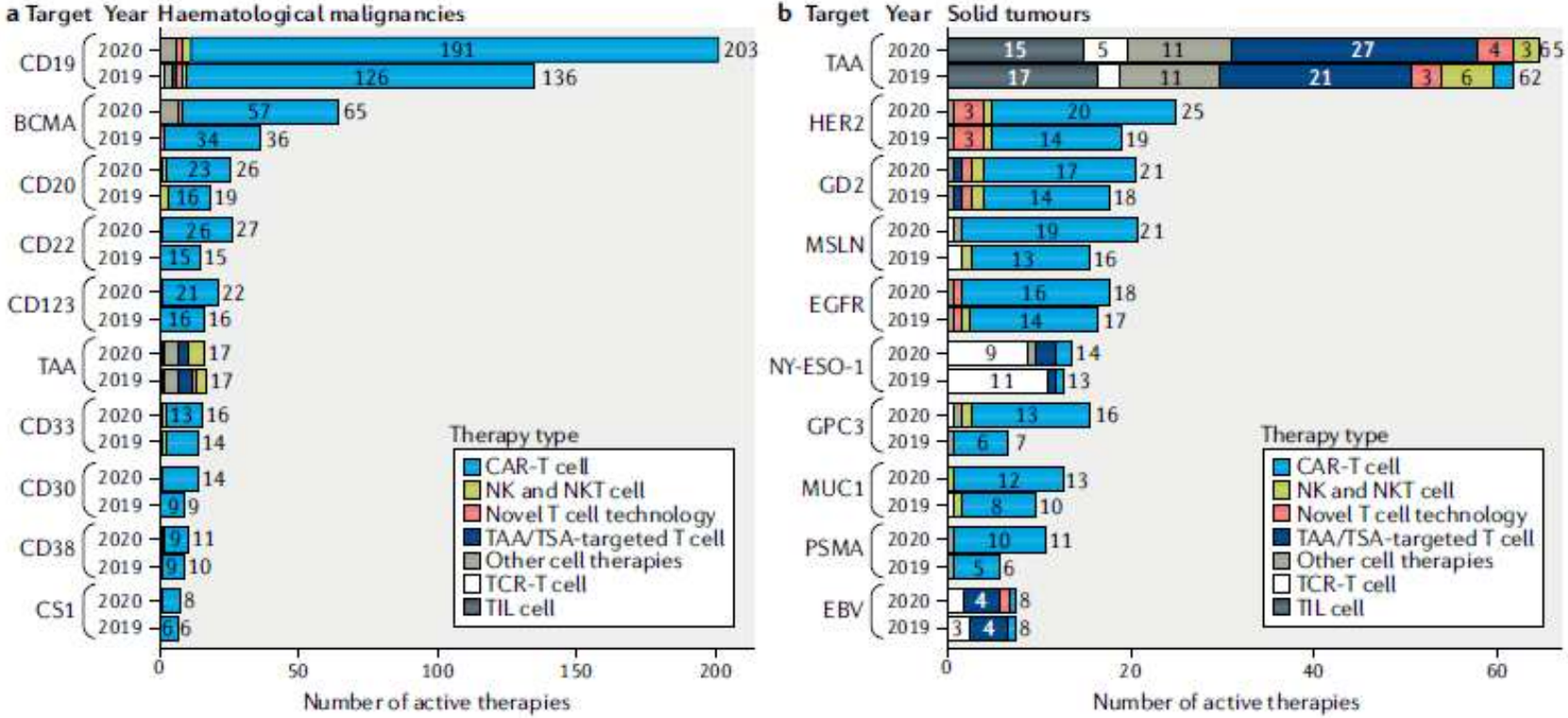
Among Cancer Cell Therapy Trials, CAR-T cells are the Most Frequent Therapy Type and Phase I/II are the Most Frequent Trial Phase



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



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

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; FL 2021
- Brexucabtagene autoleucel (Tecartus) *
  - Mantle cell lymphoma, 2020
- Lisocabtagene maraleucel (Breyanzi) *
  - Refractory B-cell NHL, 2021
- Idecabtagene vicleucel (Abecma)**
  - Refractory multiple myeloma (2021)

www.fda.gov

*CD19-directed CAR-T cells; **BCMA-directed CAR-T cells

Unique Considerations for Cellular and Gene Therapies 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 Cancer Cell Therapy Trials: Objectives

- Safety - primary objective
- Dose exploration - varies according to different products
  - Maximum tolerated dose (MTD)
  - Optimal dose
  - Feasible 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
  - Contribution of effects a challenge for combinatorial studies
- Specific target may require a companion diagnostic
  - Antigenic target
  - HLA restriction
- Companion Diagnostic 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

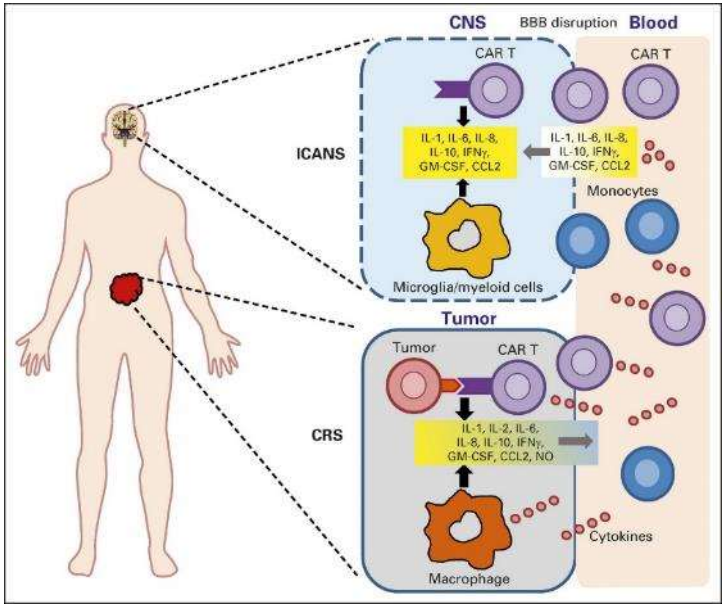
- Single-arm trial
  - Safety, dose finding
  - Tumor response rate, duration of responses
  - Time-to-event analyses (overall survival, progression-free survival) difficult to interpret in this setting
    - Historical controls may be unreliable
- Randomized controlled trial
  - Time-to-event analyses (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 Therapy 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
    - Why is the risk higher for these? These TCRs have not been "self-educated" in thymus
- 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
[2]Lee DW et al. Biol Blood Marrow Transplant 2019;25:625-638

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

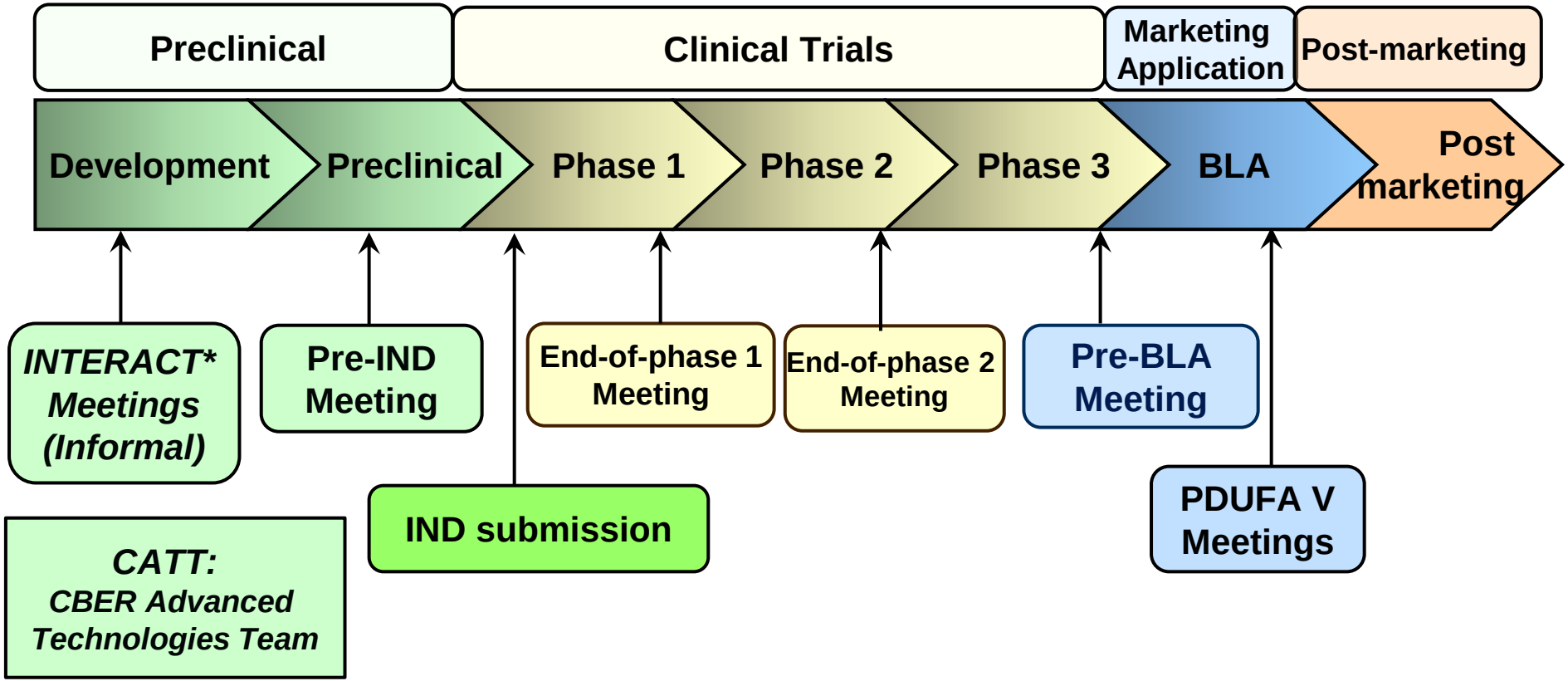
Safety Monitoring Duration

- 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

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

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.)

Challenge Question #1

Which meeting may occur prior to an IND submission?

A. PDUFA V meeting

B. Pre-BLA meeting

C. Pre-IND meeting

D. End-of-phase 1 meeting

Challenge Question #2

Which statement is false?

Study stopping rules:

A. Allow a temporary pause in enrollment and treatment of study subjects

B. Are intended to terminate a study

C. Are intended to limit the number of study subjects being exposed to excess risk

D. May result in a safety assessment that leads to a protocol amendment

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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Thank you!

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
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