

Cellular and Gene Therapy in Oncology: Common Issues Encountered in Regulatory Submissions

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Center for Biologics Evaluation and Research | US FDA

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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.

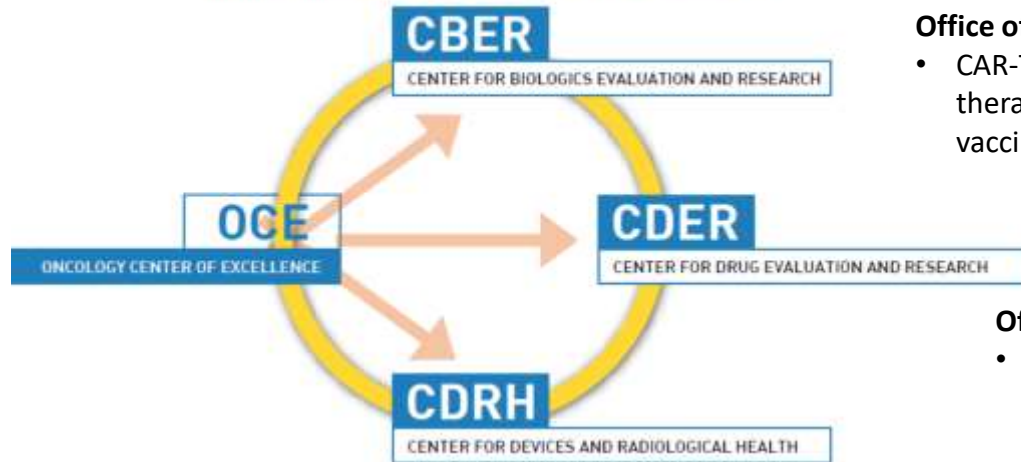
Learning Objectives

- Provide an overview of CBER's cellular and gene therapy product development programs for the treatment of cancer
- Highlight common issues encountered in regulatory submissions to CBER's oncology branch
- Summarize OTAT approved therapies for the treatment of cancer

FDA Regulation of Oncology Products



The Oncology Center of Excellence fosters unified interaction between 3 FDA centers



Office of Tissues and Advanced Therapies (OTAT)

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

Office of Oncologic Diseases (OOD)

- Small molecules, monoclonal antibodies, antibody-drug conjugates

Office of In vitro Diagnostics and Radiological Health

- Companion and complementary diagnostics, surgical and delivery devices and therapeutic devices

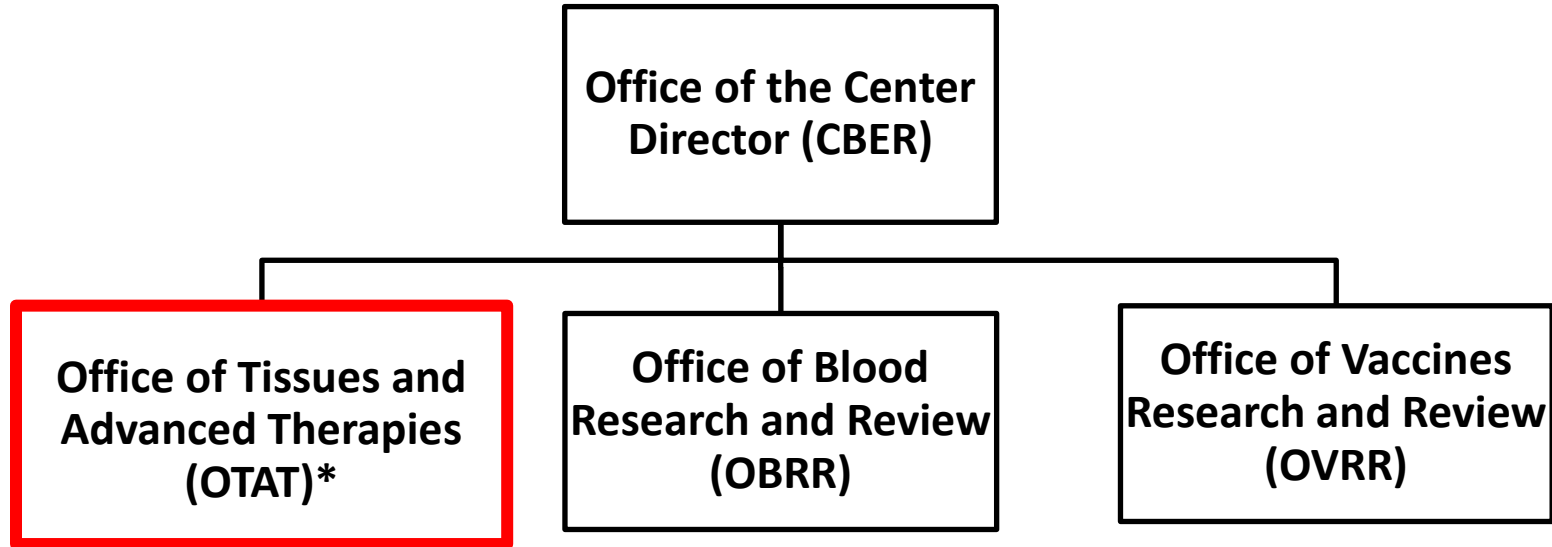
Established on January 19, 2017

Created in response to National Cancer Moonshot Initiative

Authorized by 21st Century Cures Act: 1st FDA Inter-Center Institute

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Center for Biologics Evaluation and Research (CBER) - Product Review Offices

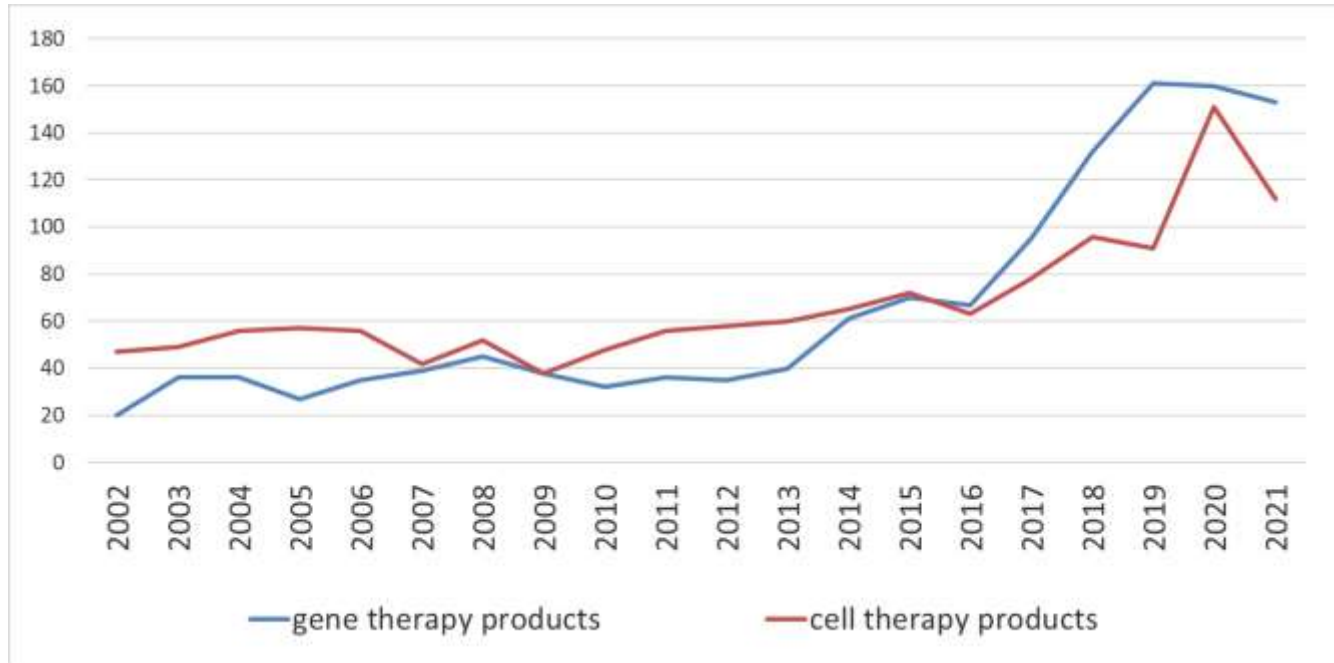


*Formerly the Office of Cellular, Tissue and Gene Therapies (OCTGT)

CBER OTAT-Regulated Products

- **Gene therapies (GT)**
 - Ex vivo genetically modified cells
 - Non-viral vectors (e.g., plasmids)
 - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
 - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
 - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
 - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
 - Perinatal (e.g., placental, umbilical cord blood)
 - Fetal (e.g., neural)
 - Embryonic
 - Induced pluripotent stem cells (iPSCs)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
 - Coagulation factors
 - Fibrin sealants
 - Fibrinogen
 - Thrombin
 - Plasminogen
 - Immune globulins
 - Anti-toxins
 - Snake venom antisera
- **Combination products**
 - Engineered tissues/organs
- **Certain Devices**
- **Tissues**

Cell and Gene Therapies: Research Investigational New Drug Applications from 2002 to 2021



Considerations for Designing First-in-Human Cellular and Gene Therapy Studies for Cancer



- Cellular Therapies
 - Secondary 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

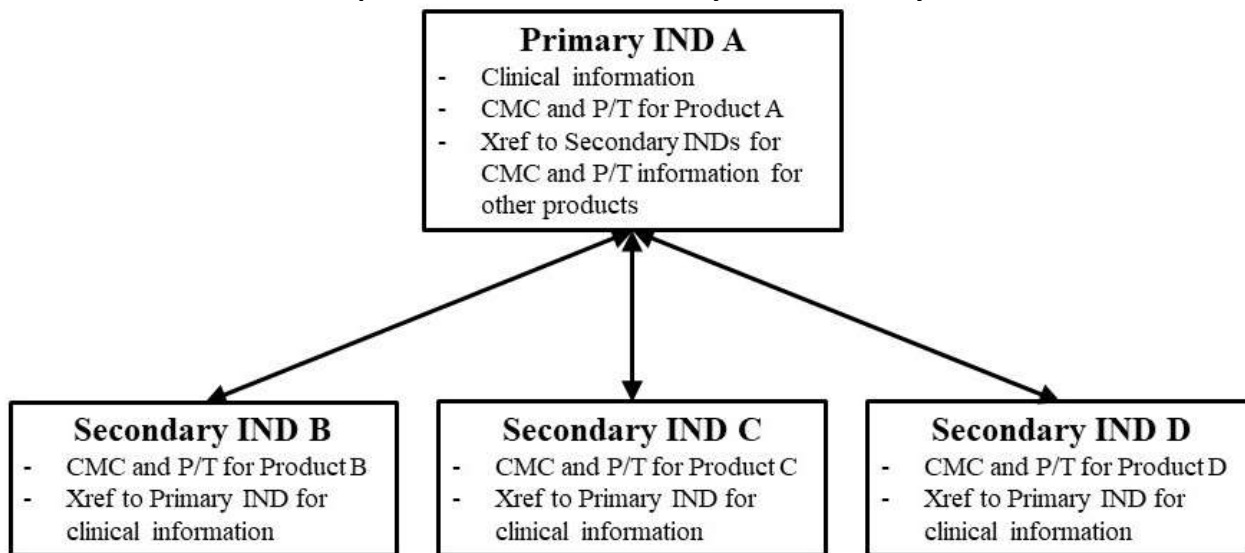


- Safety - primary objective
- Dose exploration - varies according to different products
 - Maximum tolerated dose
 - Recommended Phase 2 dose
- Activity assessment and preliminary clinical efficacy
- Feasibility of manufacturing
- Bridging therapy

Multiple Versions of a Cellular or Gene Therapy Product

- For the Primary IND (and amendments), the cover letter should clearly state that the IND is a Primary IND and specify the Secondary IND number(s)
- For any Secondary IND (and amendments), the cover letter should clearly state that the IND is a Secondary IND and specify the Primary IND number

Schematic Representation of the Primary and Secondary IND Framework



Study Design Issues

- Single arm studies should generally focus on unmet needs
 - Relapsed/Refractory to available therapies
 - Contribution of effect 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 trial participants 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
 - Objective 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 trial participants / dose cohorts
- Provide justification for the plan and the starting dose based on clinical or preclinical data

Dose Limiting Toxicity (DLT)

- Protect trial participants and identify optimum biological/recommended phase 2 dose
- Confounded by toxicities of conditioning lymphodepletion regimens
- Context important
 - Some cytokine release syndrome (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 Cells¹

Examples of cancer cell therapy study DLTs²:

- Any treatment-emergent Grade 4 or 5 CRS
- Any treatment-emergent Grade 3 CRS that does not resolve to \leq Grade 2 within 7 days
- Any treatment-emergent autoimmune toxicity \geq 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

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 participants are discharged to outpatient care, they should remain in reasonable proximity to the treating institution in case of delayed toxicities

Study Stopping Rules

- Temporary pause in enrollment and treatment of additional participants to limit the number of trial participants 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

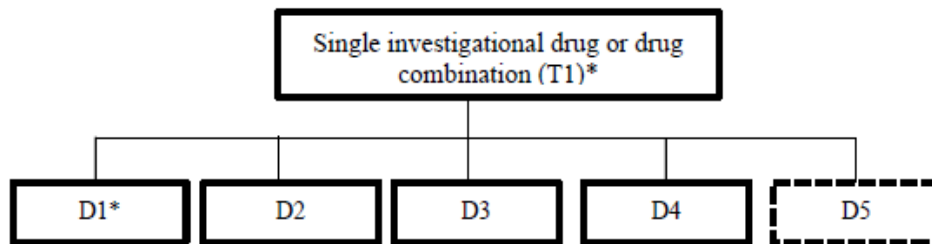


- Duration of monitoring for adverse events
 - Sufficient to cover expected duration of effect
 - Depends on information from preclinical studies, and experience with related products
- Long term follow-up may be required for certain cellular and gene therapies
 - e.g., 15 years of follow-up for integrating viral vector-based products
 - Clinical development can continue while long term follow-up ongoing

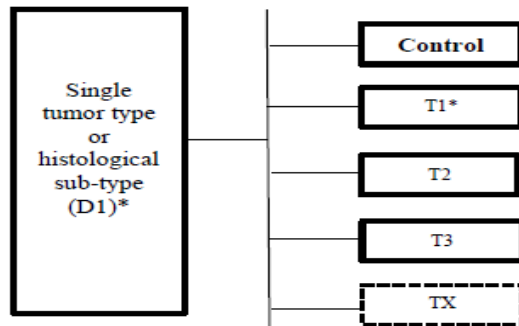
Master Protocols with a Basket or an Umbrella Trial Design



Schematic Representation of a Master Protocol With *Basket Trial* Design



Schematic Representation of a Master Protocol With *Umbrella Trial* Design



* T = investigational drug or investigational drug combination; D = protocol defined subpopulation in single disease subtypes; TX = dashed lines indicate potential amendments to include future treatment arms.

OTAT Approved Therapies for Cancer*



| Product | Indication | Number of trial participants; Primary Endpoint | Approval Pathway (RCT or SA) | Year | REMS |
|---|---|---|------------------------------------|------|------|
| Sipuleucel-T (Provenge) | Metastatic castrate resistant prostate cancer | N=512; OS HR 0.775 N=127; OS HR 0.586 | Regular (RCT) | 2010 | None |
| Talimogene laherparepvec (Imlygic) | Recurrent unresectable melanoma after initial surgery | N=436; DRR = 16.3% vs 2.1% | Regular (RCT) | 2015 | None |
| Tisagenlecleucel (Kymriah) | Refractory B-cell acute lymphoblastic leukemia (ALL) | N=63; CR/CRi 83%; CR 63% | Regular (SA) | 2017 | Yes |
| | Refractory diffuse large B-cell lymphoma (DLBCL) and High-grade follicular lymphoma (FL) | N=68; ORR 50 %; CR 32% | Regular (SA) | 2018 | |
| Axicabtagene ciloleucel (Yescarta) | Refractory large B-cell lymphoma who have received at least 2 previous systemic therapies | N=101; ORR 72%; CR 51% | Regular (SA) | 2017 | Yes |
| | Follicular Lymphoma | N=123; ORR 89%; CR 62% | Accelerated (SA) | 2021 | |
| | Refractory large B-cell lymphoma as second-line treatment | N=359; EFS HR 0.4 | Regular (RCT) | 2022 | |

*Data from prescribing information

OS=overall survival; DRR=durable response rate; CR=complete remission or complete response; CRi=complete remission with incomplete blood count recovery; ORR=overall response rate; EFS=event-free survival; RCT=randomized controlled trial; SA=single arm trial; REMS=Risk Evaluation and Mitigation Strategy

OTAT Approved Therapies for Cancer* (cont.)

| Product | Indication | Number of trial participants; Primary Endpoint | Approval Pathway (RCT or SA) | Year | REMS |
|---|-------------------------------------|---|------------------------------------|------|------|
| Brexucabtagene autoleucel (Tecartus) | Refractory mantle cell lymphoma | N=74; ORR 80%; CR 55% | Accelerated (SA) | 2020 | Yes |
| | Refractory B-cell ALL | N=71; CR + CRi 50.7%; CR 40.9% | Regular (SA) | 2021 | |
| Lisocabtagene maraleucel (Breyanzi) | Refractory large B-cell lymphoma | N=192; ORR 73%; CR 54% | Regular (SA) | 2021 | Yes |
| Idecabtagene vicleucel (Abecma) | Refractory multiple myeloma | N=100; ORR 72%; CR 28% | Regular (SA) | 2021 | Yes |
| Ciltacabtagene autoleucel (Carvykti) | Refractory multiple myeloma | N=97; ORR 97.9%; CR 78.4% | Regular (SA) | 2022 | Yes |

*Data from prescribing information

ORR=overall response rate; CR=complete remission or complete response; CRi=complete remission with incomplete blood count recovery; RCT=randomized controlled trial; SA=single arm trial; REMS=Risk Evaluation and Mitigation Strategy

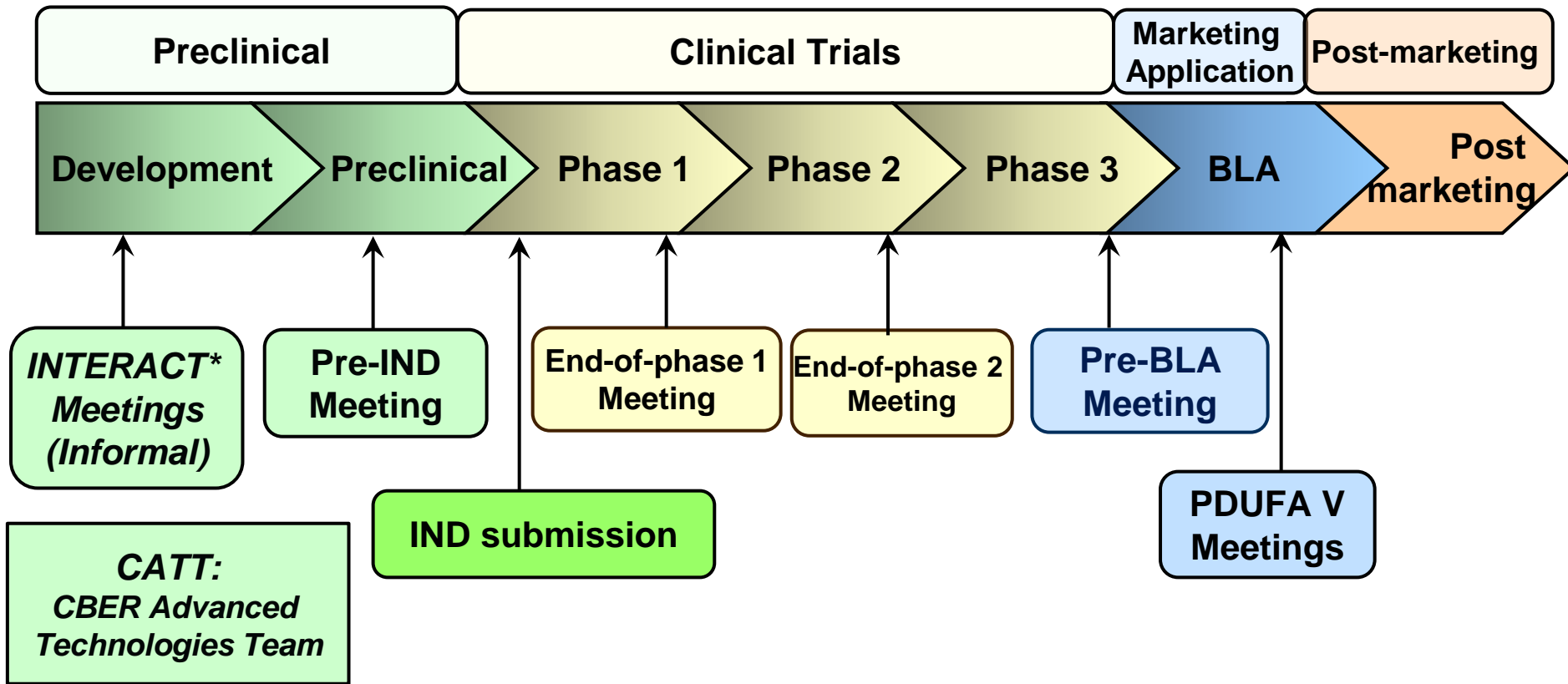
Risk Evaluation and Mitigation Strategy (REMS)

Example: Ciltacabtagene autoleucel (Carvykti)



- Because of the risk of CRS and neurologic toxicities, Carvykti is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Carvykti REMS
- The required components of the Carvykti REMS are:
 - Healthcare facilities that dispense and administer Carvykti must be enrolled and comply with the REMS requirements
 - Certified healthcare facilities must have on-site, immediate access to tocilizumab
 - Ensure that a minimum of 2 doses of tocilizumab are available for each patient for infusion within 2 hours after Carvykti infusion, if needed for treatment of CRS
 - Certified healthcare facilities must ensure that healthcare providers who prescribe, dispense or administer Carvykti are trained in the management of CRS and neurologic toxicities

When to Approach FDA for Product Development Discussions



Summary



- Cellular and gene therapies show promise for cancer therapy
- These products are moving rapidly to clinic
- Many regulatory challenges exist, especially in the era of novel technologies and therapeutic combinations
- Interaction and collaboration of stakeholders will be crucial for future success in the treatment of cancer
- Regulatory advice is available from CBER FDA OTAT
 - CBER Advanced Therapies Team (CATT)
 - INTERACT meetings
 - Pre-IND meetings
 - IND meetings (End-of-phase 2, pre-BLA, etc.)



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

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>
- Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products <https://www.fda.gov/media/156896/download>
- Expansion Cohorts: Use in First-in-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics
<https://www.fda.gov/media/115172/download>
- Human Gene Therapy Products Incorporating Human Genome Editing <https://www.fda.gov/media/156894/download>
- Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics
<https://www.fda.gov/media/120721/download>
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial
<https://www.fda.gov/media/152536/download>
- Cell and Gene Therapy Guidance: <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
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