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Novel Cellular and Non-cellular Combination Immunotherapy: An FDA Overview

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Session: Next Generation Immunotherapy Combinations: Navigating FDA, Clinical Trial Design, Diagnostics and Novel Biomarkers

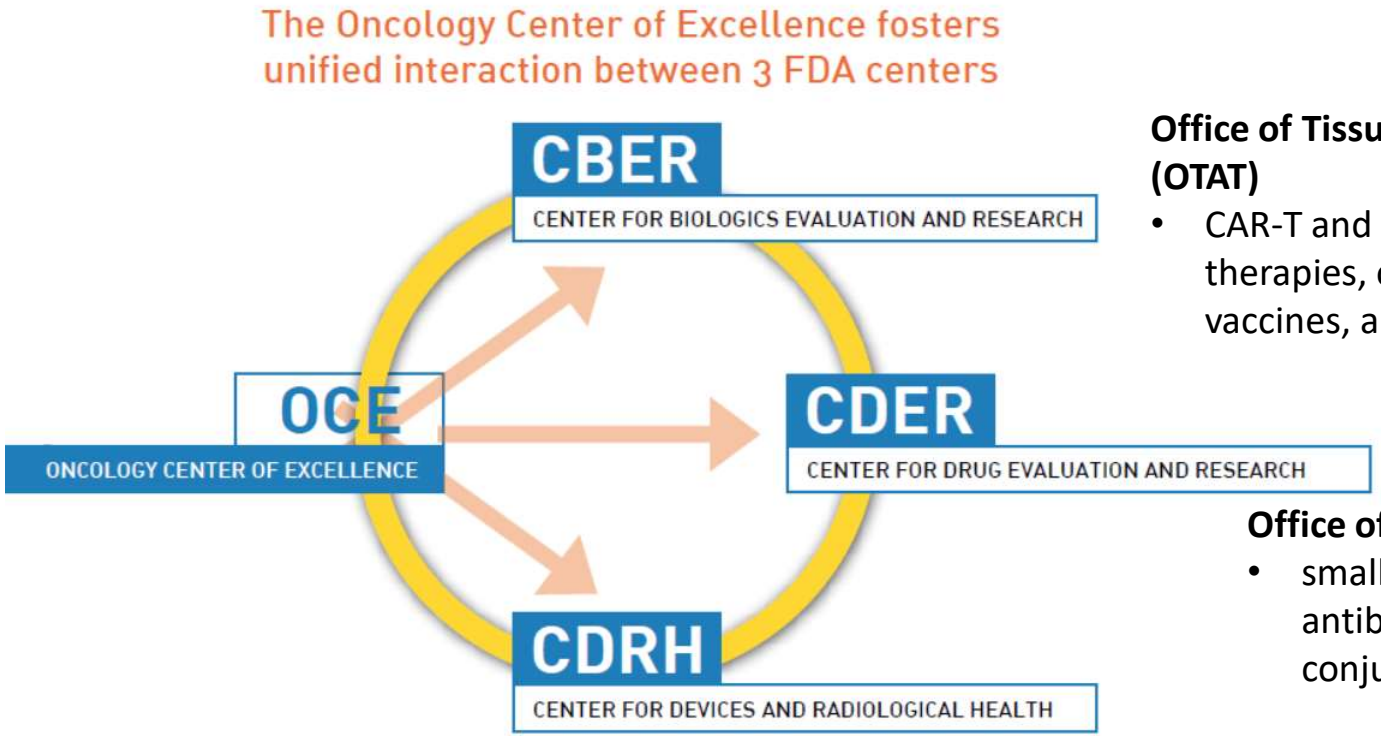
Disclosures

I have no financial relationships to disclose.

Outline

- FDA regulation of oncology products and current landscape
- Combination therapy
- Challenges of combination therapy development
- Unique considerations for novel cellular vs non-cellular combination immunotherapy
- Summary

FDA Oncology Center of Excellence (OCE)



Office of Tissues and Advanced Therapies (OTAT)

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

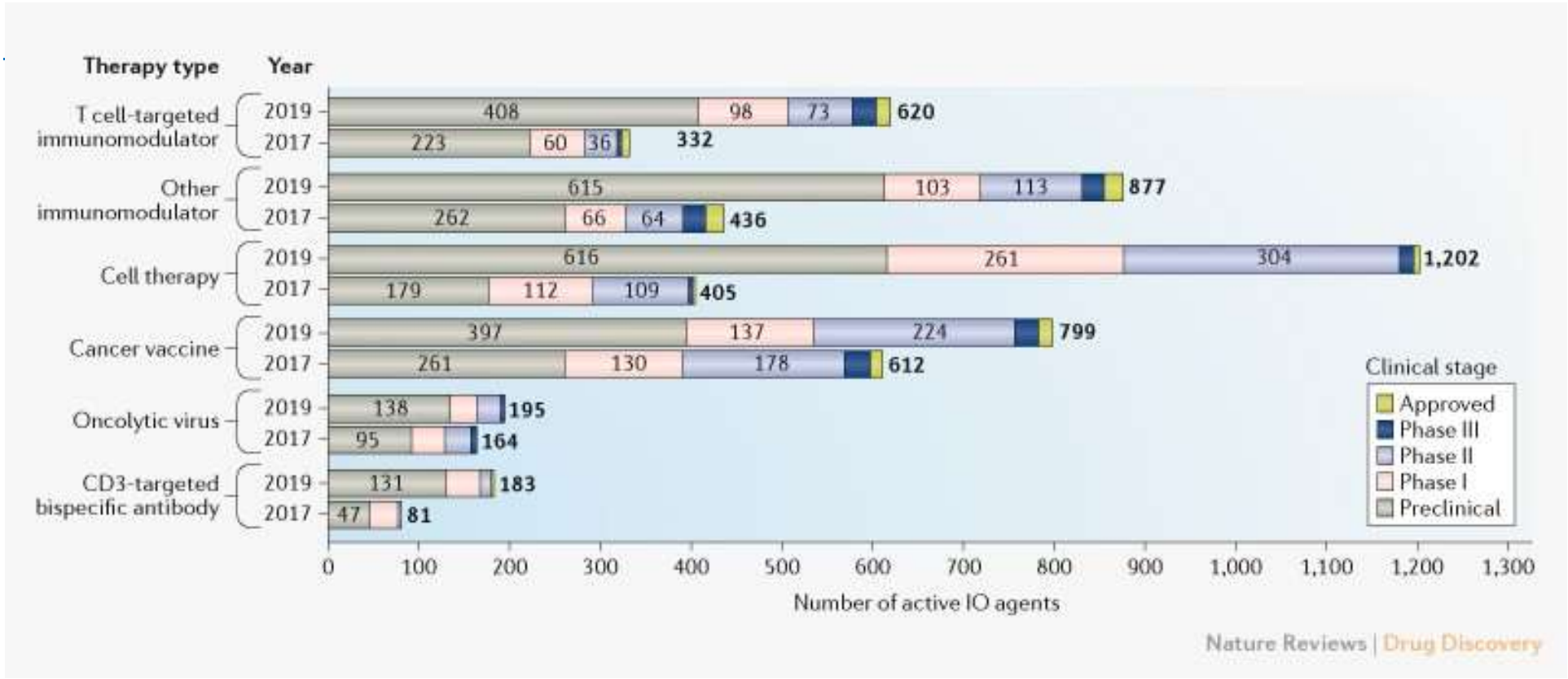
Office of Oncologic Diseases (OOD)

- small molecules, monoclonal antibodies, antibody-drug conjugates

Office of Invitro Diagnostics and Radiological Health

- companion and complementary diagnostics

Current Development Landscape for Novel Biologics

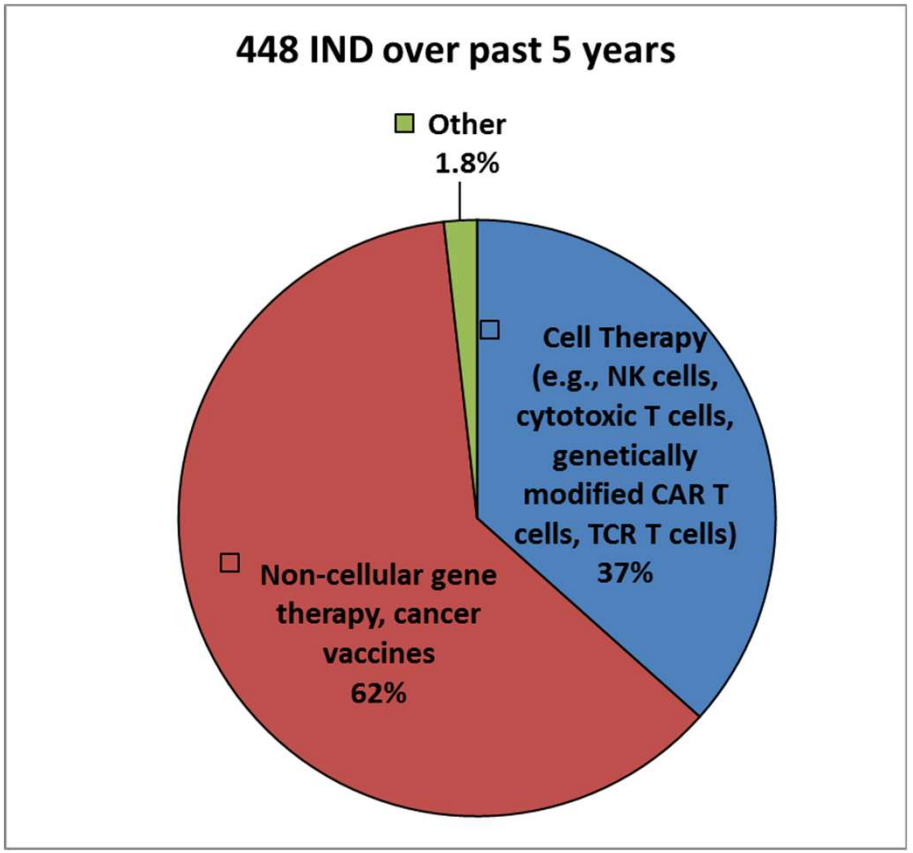


Yu, et al. Nature Reviews Drug Discovery 2020

CBER OTAT-regulated Oncology INDs for Solid Tumors

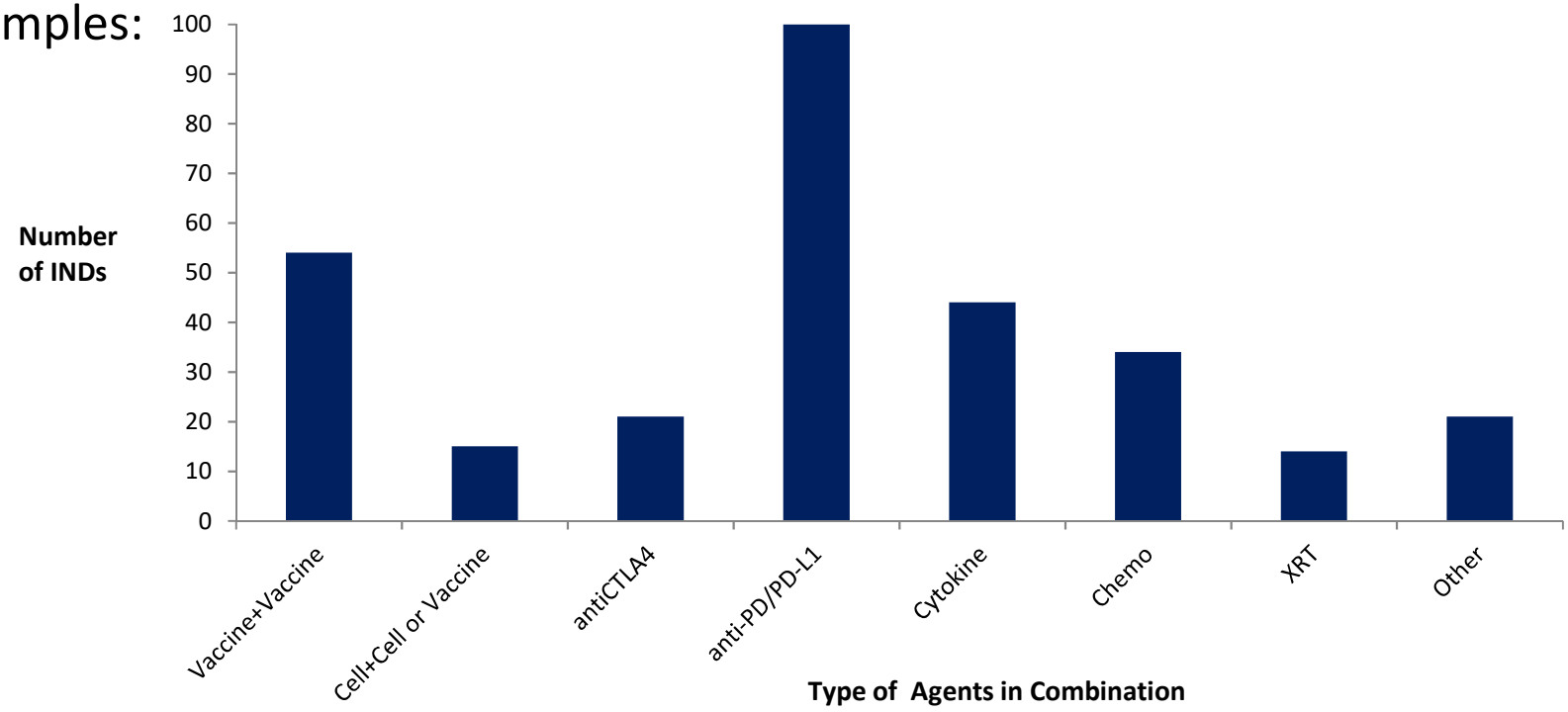
Not including:

- Devices
- Biologics regulated by Center for Drug Evaluation and Research (CDER)



Regulatory Landscape in OTAT

- 42% of oncology INDs for solid tumors are combination therapies
  (data from past 5 years)
- Examples:



Combination Therapy in Cancer

- Therapy involving multiple components
- Each component contributing to the effect, but not indispensable to each other
- Scientific advances in understanding cancer prompting development of new combination therapies
- Directed at multiple targets to improve treatment response, minimize adverse events, or both

Examples of Combination Therapy

- Classical combination chemotherapy regimen
  - e.g., FOLFOX, FOLFIRI, AC
- Recent Approvals
  - Checkpoint inhibitor (CPI) combinations
  - B-RAF inhibitor, MEK inhibitor combination
- Tumor antigens or cells admixed with adjuvant (poly ICLC, GM-CSF, etc.) either injected separately or together
- Antibody, tumor antigen and adjuvant (anti-CTLA-4 Ab, peptide and montanide)
- Adoptive Cell Therapy (ACT) with IL-2, chemotherapy, or with checkpoint inhibitors

Co-developing Combination Therapy[1]

- Address unmet medical needs in difficult-to-treat diseases
- Improve response and survival
- Decrease resistance
- Improve drug tolerability with lowered dose
- May potentiate the effectiveness of the second drug, if by itself ineffective
- However, introduces additional uncertainty
  - Provides less information about safety and effectiveness of the individual agents
  - Presents greater risk compared to development of an individual agent

[1] *FDA Guidance: Codevelopment of Two or More New Investigational Drugs for Use in Combination, June 2013*
www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf

Criteria for Co-development

- Combination therapy intended to treat serious disease
- A compelling biological rationale for use of the combination
- Pre-clinical or short-term clinical study on established biomarker suggesting a significant therapeutic advance
- A good reason why the agents can not be developed individually (e.g., early resistance, limited activity with monotherapy)

Criteria for Co-development

- A critical aspect of co-development of novel combinations: characterization of safety and effectiveness of the individual drugs in the combination
- Amount and types of data to assess contribution of effect dependent on:
  - Context of disease, population
  - Availability and effectiveness of other treatments
  - Preclinical and clinical data available for individual drugs
  - Complexity of the question(s) that need to be addressed by the development program
- Early and frequent FDA consultation as needed

Challenges in Trial Design for Combination Therapy

- Number of arms
- Dosing
- Sequencing of agents
- Endpoint selection
- Patient population
- Safety attribution
- Traditional approach (e.g., factorial design) infeasible or inefficient

Innovative Approaches in Trial Design for Combination Therapy

- Alternative innovative approaches (adaptive designs)
- Smaller randomized trials
- Efficacy endpoints-- earlier than overall survival, (e.g., objective response or other endpoints demonstrating direct treatment effect)
- Master protocols with common controls
- Seamless trial design from early-phase studies to pivotal trials

Types of Novel Combinations in Oncology

- Two (or more) new investigational drugs
- A new investigational drug with a drug(s) approved for a different indication
- Two (or more) approved drugs for a different indication(s)
- “Add-on” drug to standard-of-care regimen

Trial Design Considerations for Novel Investigational Agent(s): Phase 2 (Proof-of-Concept, POC)

1. **If monotherapy ineffective**

   Consider: AB vs SOC OR

   AB + SOC vs SOC (+/- placebo)

2. **Each drug active and can be given individually**

   Consider: AB vs A vs B vs SOC or placebo

   OR

   AB + SOC vs A + SOC vs B + SOC vs placebo + SOC

   An interim examination plan could allow dropping A and/or B if they were clearly less active

3. **One drug active; other inactive**

   If one drug (B) clearly inactive alone, based on *in vitro* or animal mechanistic data, can generally consider study active drug (A) in a 3-arm trial design such as

   AB vs A vs SOC

   OR

   AB + SOC vs A + SOC vs placebo + SOC

Trial Design Considerations for Novel Investigational Agent(s): Phase 3 (Confirmatory trials)

- If contribution of each component adequately demonstrated in Phase 2 trials, a Phase 3 design evaluating
  - AB vs SOC/placebo, or AB + SOC vs SOC (+/- placebo) generally sufficient to establish effectiveness

- If Phase 2 is not clear
  - may need factorial design, with planned interim assessments

- Specifics of Phase 3 design should be discussed FDA at an End-of-Phase 2 meeting

Trial Design Considerations for Two or Approved Agent(s) for Different Indication(s)

- Same principles as two or more investigational agents apply
- Challenges:
  - Approved agent for one indication, but combination seeking another indication (labeling indication for the approved agent)
  - Different dose and schedule of the approved agent(s) used in combination
  - "Exchangeability" of an approved agent in the combo with another unapproved agent in the same class is not supported by regulation
  - Hypothesized magnitude of effect of an approved agent in combination

Unique Considerations for Novel cellular vs Non-Cellular Combination Immunotherapy

- Cell Therapy
  - "Living" drug, one time dosing, pharmacokinetics and dynamics different from more traditional therapies
- Vaccines and Oncolytic viruses
  - Stimulate immune system for anti-tumor effect, usually has delayed immune responses
  - Role of adjuvants should be assessed
- Checkpoint inhibitors (monoclonal antibodies)
  - Indirectly contribute to anti-tumor responses, by modulating the immune response, multiple dosing is needed
- Targeted therapies (small molecules)
  - Affect oncogenic signaling pathways, block receptors, or have direct effect on tumors

Endpoint and Patient Selection Considerations for Immuno-oncology

- Endpoint
  - Response may not be correlated with survival
  - Delayed immune mediated response
  - Standard response criteria may not be applicable
- Study Population/Eligibility Criteria
  - Applicability of the investigational agent based on mechanism of action
  - Based on biomarker expression

Safety

- Unexpected toxicities of combination therapy: Potential complication for combination and progressing to Phase 3 trials.
- If the toxicity cannot be attributed to an individual agent in the combination, additional studies may be needed to identify the more toxic drug and appropriate dosing for the combination therapy before initiating Phase 3 trials.

Summary

- Challenges:
  - Contribution of each component to efficacy and safety
  - Determining trial design to discern contribution
  - Dose, route, schedule and sequencing
  - Endpoint
  - Manufacturing issues, especially for autologous or personalized products
- Opportunities:
  - Promising combinations addressing unmet need in cancer
  - Less redundancy
  - More interactions among stakeholders (commercial, non-profit, academia)
  - Frequent interactions with FDA

FDA Guidance(s)

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2015

Codevelopment of Two or More New Investigational Drugs for Use in Combination

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2013
Clinical Medical

www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM564952.pdf
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf

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