Clinical Trial Considerations for Multi-targeted Therapeutic Platforms

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Disclosures

- I have no financial conflicts of interest.
- This presentation represents the views of the speaker and should not be construed to represent FDA's views or policies.

Educational Objectives

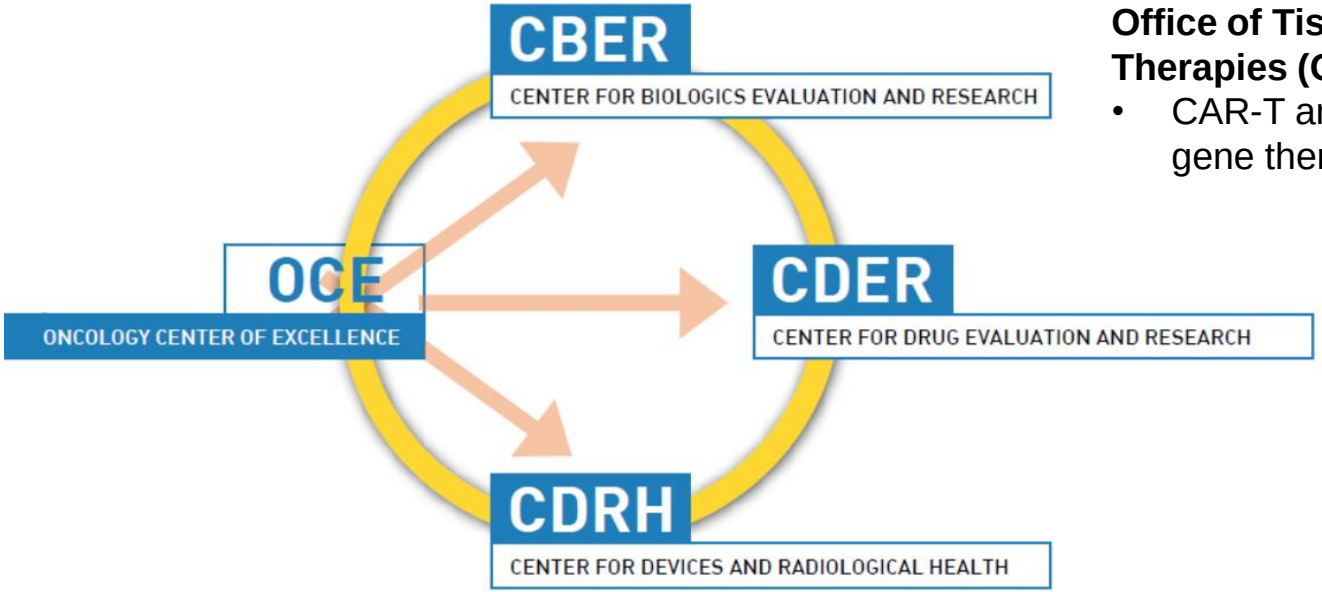
- Describe the different types of multi-targeted therapeutic platforms in preclinical and clinical studies
- Explain the similarities and differences between multi-targeted therapies and other immunotherapies in clinical use, such as adoptive cell therapies
- Understand the current state of clinical trials and approvals in cancer that employ multi-targeted therapeutic platforms

Outline

- Provide an overview of FDA Oncology Center of Excellence (OCE)
- Discuss FDA approval and registrational clinical trial considerations
- Discuss early phase development considerations for multi-targeted therapies

FDA Oncology Center of Excellence (OCE)

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 therapy, therapeutic vaccines

Office of Oncologic Diseases (OOD) formerly Office of Hematology and Oncology Products (OHOP)

- small molecules, monoclonal antibodies, antibody-drug conjugates

Office of Invitro Diagnostics and Radiological Health

- companion and complementary diagnostics

New Structure and Divisions (effective Nov 4, 2019)

Office of Oncologic Diseases (OOD) Immediate Office Office Director (Acting), Richard Pazdur, MD					
Division of Oncology 1 (DO1)	**Division of Oncology 2 (DO2)**	**Division of Oncology 3 (DO3)**	**Division of Hematologic Malignancies 1 (DHM1)**	**Division of Hematologic Malignancies 2 (DHM2)**	**Division of Hematology Oncology Toxicology (DHOT)**
Division Director, Julia Beaver, MD	Division Director (Acting), Harpreet Singh, MD	Division Director (Acting), Steven Lemery, MD	Division Director (Acting), Angelo de Claro, MD	Division Director (Acting), Nicole Gormley, MD	Division Director, John Leighton, PhD
Breast, Gynecologic, Genitourinary, Supportive care	Thoracic, Head and neck, Neuro-oncology, Rare cancers, Pediatric solid tumors	Gastrointestinal and Non-Melanomatous Skin Cancer, Melanoma, Sarcoma	Acute Leukemia and Myelodysplasia, Chronic Myeloid Leukemia, HSCT	Lymphoma, Chronic Lymphocytic Leukemia, Multiple Myeloma, and other plasma cell malignancies	Nonclinical Review Division for Oncology products

FDA Approval Pathways

- **Regular Approval (Traditional approval)**
  - Based on direct measure of clinical benefit, or effect on established surrogate
- **Accelerated Approval**
  - For serious or life-threatening conditions
  - Based on surrogate or **intermediate clinical endpoint(s)** reasonably likely to predict benefit
  - Requires meaningful improvement over available therapy
  - May require post-approval clinical trial(s) to verify benefit

Efficacy Endpoint Considerations

- **What** is being measured? **(endpoint selection)**
  - direct benefit considered more meaningful
- **How** accurately is the endpoint measured?
  - Susceptibility to bias
  - Accuracy of the measurements and timing of events
- **How much** effect on the endpoint is observed? **(magnitude of effect)**

Efficacy Trial Design Considerations

- What is the **appropriate trial design**?
  - Depends on efficacy endpoint(s) and proposed indication
  - Randomized trial designs recommended for evaluation of time-to-event endpoints such as overall survival or progression-free survival.

  Note: Trial design should isolate the contribution of the effect of the investigational product.

  - Single-arm designs acceptable for evaluation of overall response rate.

Efficacy Trial Design Considerations

- **Control arms** for randomized trials
  - Placebo controls not recommended for oncology trials.
    - Exceptions would be if surveillance is an accepted treatment option, or if used as part of add-on design
  - Blinding not recommended unless required for adequate evaluation of efficacy endpoint (e.g., patient-reported outcomes).
    - Note: FDA does not require patient-level maintenance of blinding at the time of disease recurrence or progression. FDA recommends unblinding patient and investigator when patient experiences an adverse event suspected to be related to the investigational product.

Blinatumomab FDA Approvals

Mo/Yr	Population	Clinical Trial	Key Efficacy Results
12/2014	R/R Ph-neg ALL, ≥ 45 kg	**MT103-211** N=185, single-arm	CR 32%, CR+CRh 42%, mDOCR 6.7m
8/2016	R/R Ph-neg ALL, < 45 kg	**MT103-205** N=70, single arm	CR 17%, CR+CRh 33%, mDOCR 6.0m
7/2017	R/R ALL	**TOWER**, 2:1 RCT N=271 Blin N=134 SOC	Blin: CR 34% CR+CRh 42% SOC: CR 16% CR+CRh 20% OS median: 7.7 vs 4.0 months OS HR 0.71 (95%CI 0.55, 0.97), P=0.012
	R/R ALL, Ph+	**ALCANTARA** N=45, single-arm	CR 31%, CR+CRh 36%, mDOCR 6.7m
3/2018	MRD≥0.1%, in CR1 or CR2, ALL	**BLAST** N=86, single arm	MRD≤0.01% 85% (N=61 CR1) 72% (N=25 CR2)

ALL, acute lymphoblastic leukemia; R/R, relapsed or refractory; CR, complete remission; CRh, complete remission with partial hematologic recovery; mDOCR, median duration of complete remission; MRD, minimal residual disease; OS, overall survival; HR, hazard ratio

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Blinatumomab

Ongoing Clinical Development

- Use in combination (20+ trials recruiting in clinicaltrials.gov)
  - Multi-agent cytotoxic chemotherapy
  - Targeted therapy (e.g., dasatinib, ibrutinib)
  - Other biologics (e.g., immune checkpoint inhibitors)
  - Hematopoietic stem cell transplantation and other cellular therapies

Early Phase Development

Product Quality Considerations for Bispecific Antibodies

- Doses often in ng to mcg range leading to low drug concentrations, e.g., blinatumomab 9 mcg IV over 24 hrs uses infusion with final drug concentration of 37.5 ng/mL x 10 mL/hr x 24 hrs = 9 mcg.
  - contrast to IV rituximab with infusions at 1-4 mg/mL
- Hence, FDA requests submission of compatibility studies to evaluate that doses can be successfully delivered.
- Use of detailed pharmacy manuals or instructions for preparation and administration.
  - In blinatumomab original submission, overdosage due to prep. or admin. errors were reported in 5% of subjects, leading to neurologic events.

Early Phase Development

Nonclinical Considerations for Bispecific Antibodies

- Assessment whether product has agonistic properties (e.g., leads to T-cell activation and/or cytokine release)
  - If yes, MABEL (minimally anticipated biological effect level) approach to determine first in human (FIH) dose
    - Uses in vitro, ex vivo, and/or in vivo concentration-response data in combination with pharmacokinetic modeling
    - Core in vitro activity studies: T-cell proliferation and activation, cytokine release assay, cytotoxicity, and effector function

Early Phase Development

Nonclinical Considerations for Bispecific Antibodies

- FDA analysis of 17 CD3 bispecific constructs for cancer treatment

  Reference: Saber et al, Regul Toxicol Pharmacol. 2017 Nov;90:144-152

  - Unsafe to use animal toxicology data to set FIH dose.
  - Unsafe to set FIH dose based on receptor occupancy.
    - Doses corresponding to 10% RO were above the human maximum tolerated dose (MTD) for several INDs.
  - Setting a FIH dose based on 10%-50% pharmacologic activity (PA) using EC50 from most sensitive assay resulted in acceptable doses except for one construct. FIH doses of 10%-30% PA was acceptable for all products examined.

Early Phase Development

Therapies with Immune Agonistic Properties

Clinical Trial Considerations	CAR-T cell product	bispecific T-cell engager
MABEL approach for FIH dose	No	Yes
Accelerated titration design (single-patient cohorts per dose level)	No	Yes
Acceptability of Bayesian designs	Yes	Yes
Staggering of first-dose administration between patients in same cohort	Yes	Yes
Detailed toxicity management procedures	Yes	Yes
Trial-level stopping rules for safety	Yes	Yes

References

Published Reviews

- Labrijn AF, Janmaat ML, Reichert JM, Parren PWHI. Bispecific antibodies: a mechanistic review of the pipeline. Nat Rev Drug Discov. 2019 Aug;18(8):585-608.
    - Summary information on commercial clinical pipeline (as of March 2019) of 85 bispecific antibodies: 73 (86%) were being evaluated in patients with cancer. There are 43 bispecific T-cell engagers, and 15 bispecific antibodies targeting immune checkpoint molecules.
- Shah NN, Maatman T, Hari P, Johnson B. Multi Targeted CAR-T Cell Therapies for B-Cell Malignancies. Front Oncol. 2019 Mar 12;9:146.
- Shah NN, Fry TJ. Mechanisms of resistance to CAR T cell therapy. Nat Rev Clin Oncol. 2019 Jun;16(6):372-385
- Martinez M, Moon EK. CAR T Cells for Solid Tumors: New Strategies for Finding, Infiltrating, and Surviving in the Tumor Microenvironment. Front Immunol. 2019 Feb 5;10:128.

References

FDA Guidances

Oncology Center of Excellence (OCE)

- Hematologic Malignancy and Oncologic Disease: Considerations for Use of Placebos and Blinding in Randomized Controlled Clinical Trials, Draft, August 2018

Center for Drug Evaluation and Research (CDER) and/or Center for Biologics Evaluation and Research (CBER)

- Bispecific Antibody Development Programs, Draft, April 2019
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, Final, June 2017
- Expedited Programs for Serious Conditions—Drugs and Biologics, Final, May 2014
- Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, Final, May 1998

Conclusions

- FDA Oncology Center of Excellence aims to create a unified and collaborative approach to advance the development and regulation of products for patients with cancer.
- Multi-targeted therapeutic platforms is a complex and highly active area in oncology drug development.
- No “one size fits all” approach to trial design in early or late development phases.
- Close interaction with FDA recommended.

Acknowledgments

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