FDA Perspectives on Rare Cancer Drug Development

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Disclaimer

I have no relevant conflicts of interest

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Outline

- FDA oncology organizational structure
- Definition of rare cancer
- Current state of approvals
- Challenges
- OCE initiatives to address challenges

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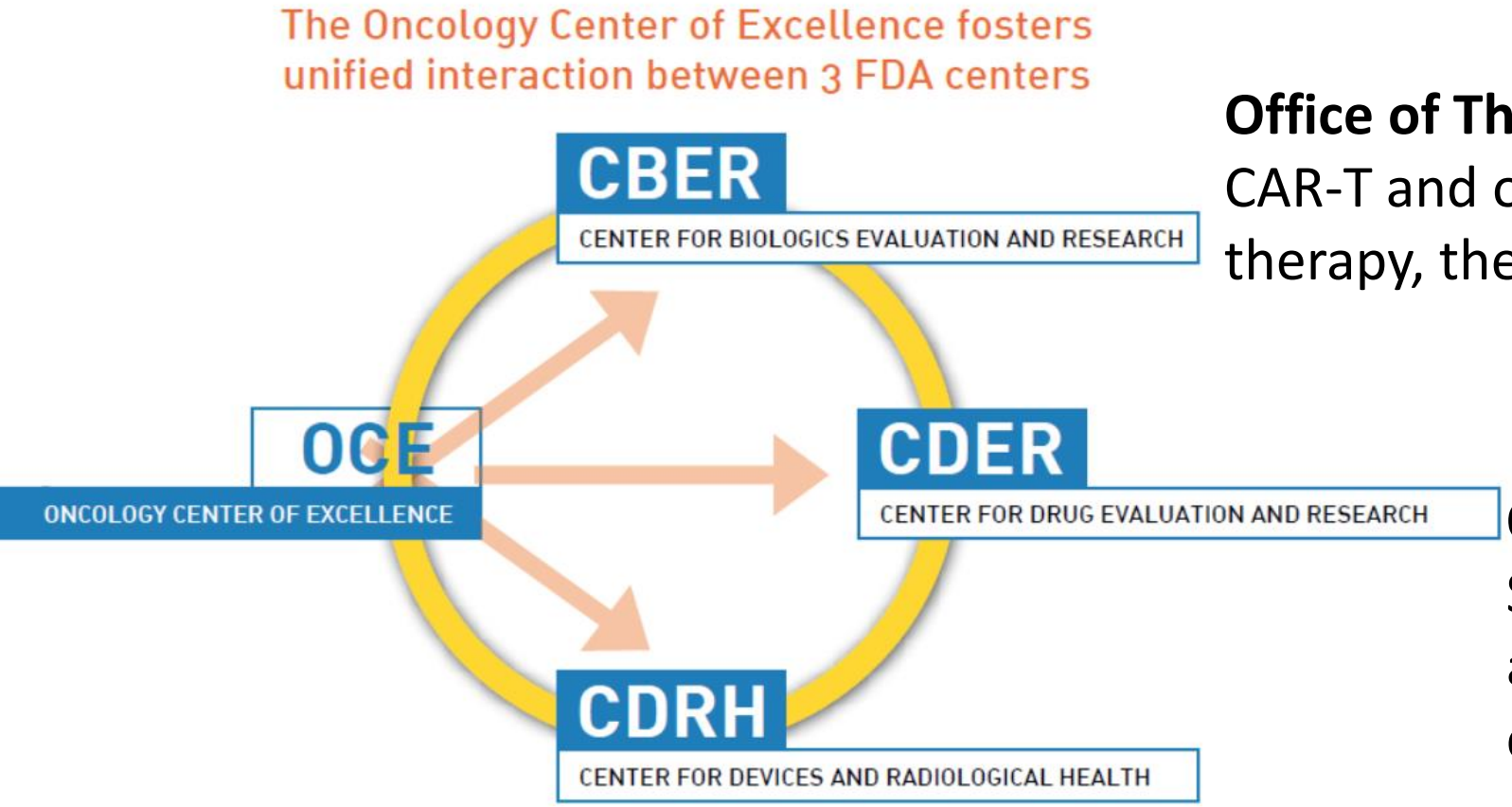
FDA Oncology Center of Excellence (OCE)



Office of Therapeutic Products
CAR-T and other cellular therapies, gene therapy, therapeutic vaccines

Office of Oncologic Diseases (OOD)
Small molecules, monoclonal antibodies, antibody-drug conjugates

Office of In vitro Diagnostics and Radiological Health
Companion and complementary diagnostics

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Office of Oncologic Diseases (OOD)

Division of Oncology 1 (DO1)

- Breast, gynecologic & genitourinary cancers
- Cancer supportive care

Division of Oncology 2 (DO2)

- Thoracic, head & neck cancer
- Neuro-oncology, **rare cancers** and pediatric solid tumors

Division of Oncology 3 (DO3)

- Gastrointestinal,
- Superficial cutaneous cancers, melanoma, **sarcoma**
- Tissue agnostic

Division of Hematologic Malignancies 1 (DHM 1)

- Acute leukemia and myelodysplasia
- HSCT
- Chronic myeloid leukemia

Division of Hematologic Malignancies 2 (DHM 2)

- Lymphoma, chronic lymphocytic leukemia, multiple myeloma, and other plasma cell malignancies

Division of Hematology Oncology Toxicology (DHOT)

- Nonclinical review division for oncology products

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What is a Rare Cancer?

- Orphan Drug Act Definition -- <200K in the U.S.
  (~ <1/1650)
- Using NCI's definition of fewer than 15 cases per 100k/year, 25% of adult cancers are rare.
- Can include molecularly defined subsets of more common cancers (e.g., RET+ non-small cell lung cancer)

Bradford et al.

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Recent Sarcoma Approvals

Drug	Disease	Primary endpoint	Results
Pazopanib April 2012	Advanced soft tissue sarcoma	PFS vs. placebo	HR: 0.35 (95% CI: 0.26, 0.48) 4.6 vs.1.6 months (median) DOR: 9.0 (3.9, 9.2) months
Regorafenib February 2013	GIST	PFS vs. placebo	HR: 0.27 (0.19, 0.39) 4.8 vs. 0.9 months (median)
Trabectedin October 2015	Liposarcoma or Leiomyosarcoma	PFS vs. DTIC	HR: 0.55 (0.44, 0.70) 4.2 vs. 1.5 months (median) DOR: 6.9 (4.5, 7.6) vs 4.2 (2.9, NE) months
Eribulin January 2016	Liposarcoma	OS vs. DTIC	HR: 0.51 (0.35, 0.75) 15.6 vs. 8.4 months (median)
Tazemetostat January 2020	Epithelioid sarcoma	ORR	15% (7, 26) DOR: 3.7 to 24.5+ months
Avapritinib January 2020	GIST	ORR	ORR: 84% (69, 93) DOR: NR (1.9+, 20.3+)
Pomalidomide May 2020	AIDS-related Kaposi sarcoma	ORR	HIV+: 67% (41, 87); DOR: 12.5 (6.5, 24.9) months HIV-: 80% 44, 98) ; DOR: 10.5 (3.9, 24.2) months
Ripretinib May 2020	GIST	PFS vs. placebo	HR: 0.15 (0.09, 0.25) PFS: 6.3 months vs. 1.0 months (median)
Nab-sirolimus November 2021	PEComa	ORR	39% (22, 58) DOR: NR (6.5, NE)
Crizotinib July 2022	ALK+ IMT	ORR	86% (57, 98) DOR ≥ 12 months: 58%
Atezolizumab December 2022	Alveolar soft part sarcoma	ORR	24% (13, 39) DOR ≥ 12 months: 42%

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Sarcoma Drug Development Common Challenges

- Obstacles to timely accrual
  - Small patient numbers
  - Geographic dispersion
  - Limited or lack of timely access to molecular testing
- Genotypic/phenotypic heterogeneity
  - Natural history often poorly understood
  - Insufficient understanding of cancer pathophysiology, molecular characteristics
- Challenges to randomization
- Difficulty in assessing response for some sarcomas
  - e.g., Ewing sarcoma, osteosarcoma

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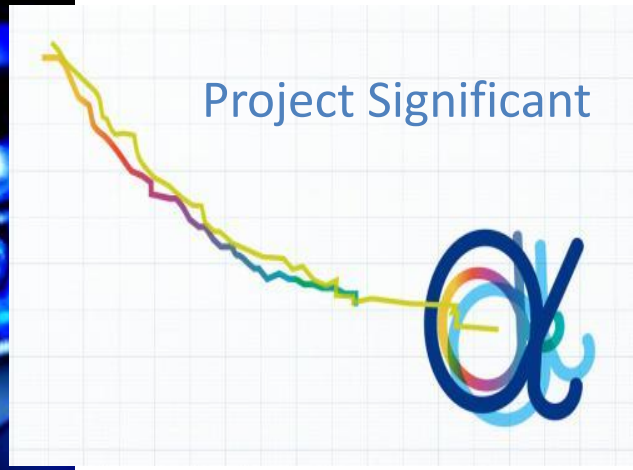
OCE Initiatives to Address Challenges



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Rare Cancers Program

- Leverage multiple OCE projects to address the challenges of developing new treatments for cancers that affect a small number of patients
- Collaboration to identify opportunities to decrease obstacles, harness scientific knowledge and strengthen coordination

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Project Catalyst

- Fosters early-stage oncology product innovation and development
- Facilitates scientific discussion, education, guidance, and regulatory engagement
- Focus on academic life science incubators and accelerators as well as small pharmaceutical companies.
- Oncology Regulatory Expertise and Early Guidance (OREEG) program

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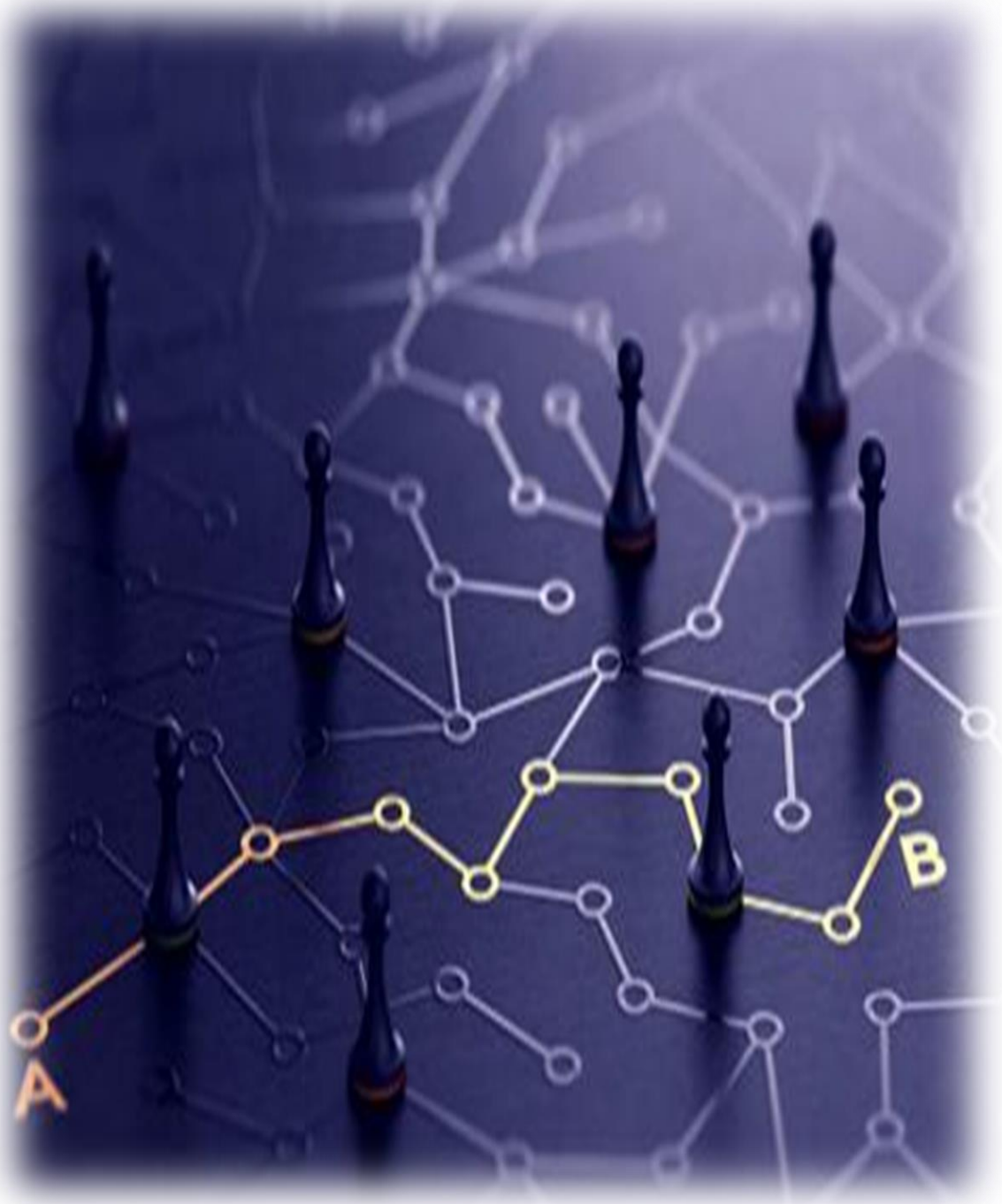

Project Pragmatica

- Introduce functional efficiencies and enhance patient centricity
- Integrate aspects of clinical trials with real-world routine clinical practice
- Pragmatica-Lung Cancer Treatment Trial

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Oncology Real World Evidence Program

- Collaboratively advance the appropriate use of real-world evidence in oncology product development to facilitate patient-centered regulatory decision-making

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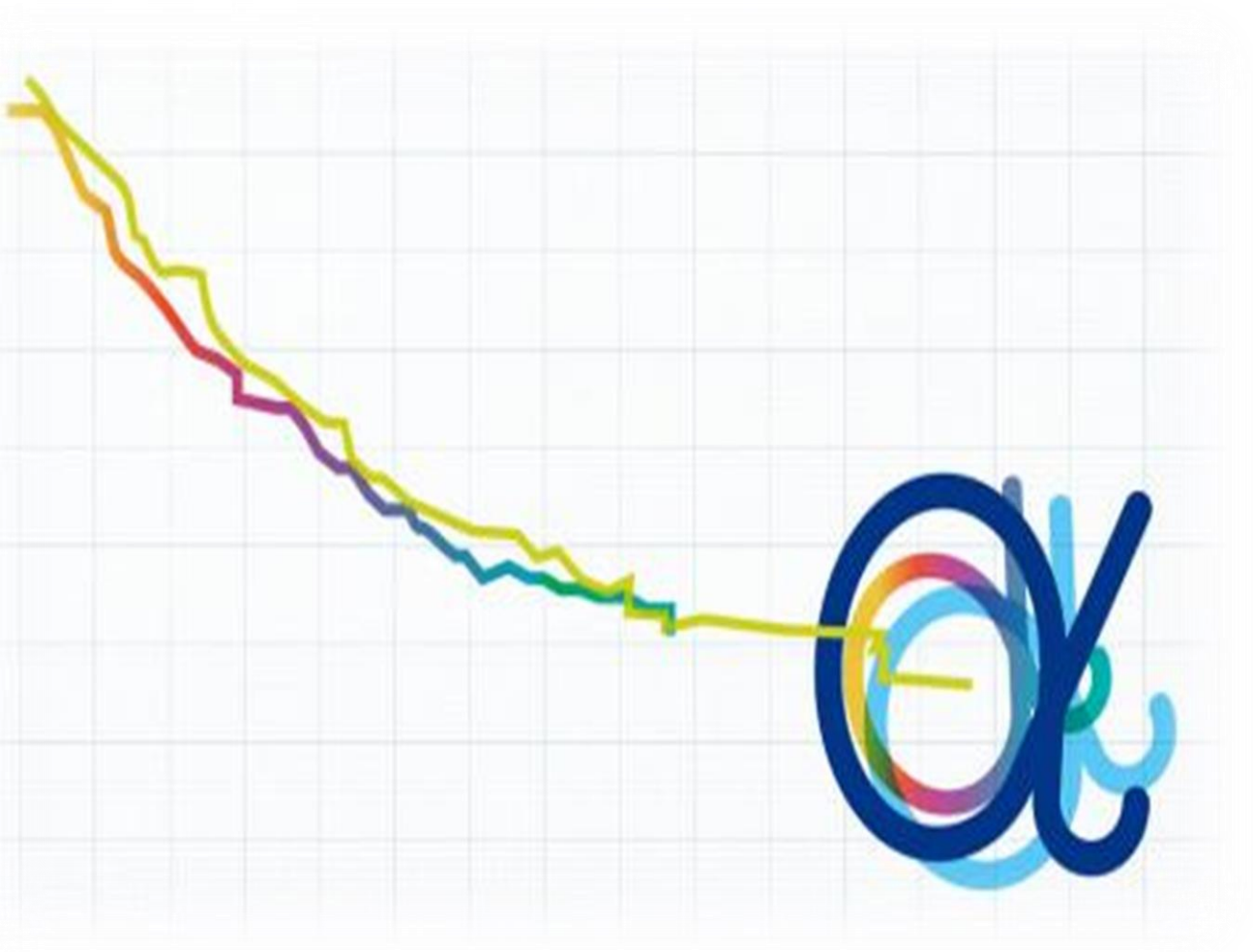
Project Significant



- Provides a platform to participate, discuss, and advance the science of oncology trial designs
- Promotes non-product specific scientific discussions on design and analysis of cancer clinical trials
- Fosters collaboration among regulators, professional organizations, industry, academicians, and patients

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OCE Tissue Agnostic Drug Development Program

- Tissue agnostic initiatives efforts may benefit rare cancers such as sarcomas
  - Approach based on identification of a biomarker, independent of tumor site
  - Examples:
    - *RET* fusion positive tumors (selpercaptinib)
    - *NTRK* fusion positive tumors (larotrectinib, entrectinib)
    - MSI-H/dMMR cancers (pembrolizumab)

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Project Orbis

- Collaborative Review Program
- Launched in May 2019
- FDA review provides for independent multi-disciplinary assessment including full review of datasets.
- Current participating countries (Project Orbis Partners): Australia, Brazil, Canada, Israel, Singapore, Switzerland, United Kingdom
- **Each country retains independent decision-making for each application**

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Opportunities for International Collaboration

- Mechanisms for international engagement and sponsor interaction
  - FDA Oncology Global Collaboration
    - Began in 2004 with EMA
    - Now monthly meetings including 4 additional regulatory authorities
  - ACCELERATE Platform projects
  - OCE Minisymposia
  - Invited speakers
  - OCE Conversations on Cancer

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Conclusions

- Development of drugs to treat rare cancers can be challenging
  - Typically requires more frequent multidisciplinary engagement with FDA early and often
  - Global development approach important
- Stakeholder engagement and collaborative efforts critical
- Numerous OCE resources can be leveraged to overcome obstacles

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Selected FDA Guidances

- Rare Diseases: Common Issues in Drug Development
- Expedited Programs for Serious Conditions - Drugs and Biologics
- Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease
- Developing and Labeling In vitro Companion Diagnostic Devices for a Specific Group of Oncology Therapeutic Products
- Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products
- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products Guidance for Industry

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Rare Cancers Program

https://www.fda.gov/about-fda/oncology-center-excellence/oce-rare-cancers-program

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