U.S. FDA Oncology Center of Excellence Project FrontRunner-
Rethinking the Oncology Drug Development Paradigm

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Outline

- Background on current approach to oncology drug development
- Overview of OCE Project FrontRunner
- Reflections on implementation

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Historical Cancer Drug Development Paradigm

- **Accelerated Approval in relapsed/refractory setting**
  - Reliance on single arm trials and response rate
    - limited safety data
  - Confirmation of clinical benefit
    - Different (earlier) treatment setting
  - Restrictive eligibility criteria

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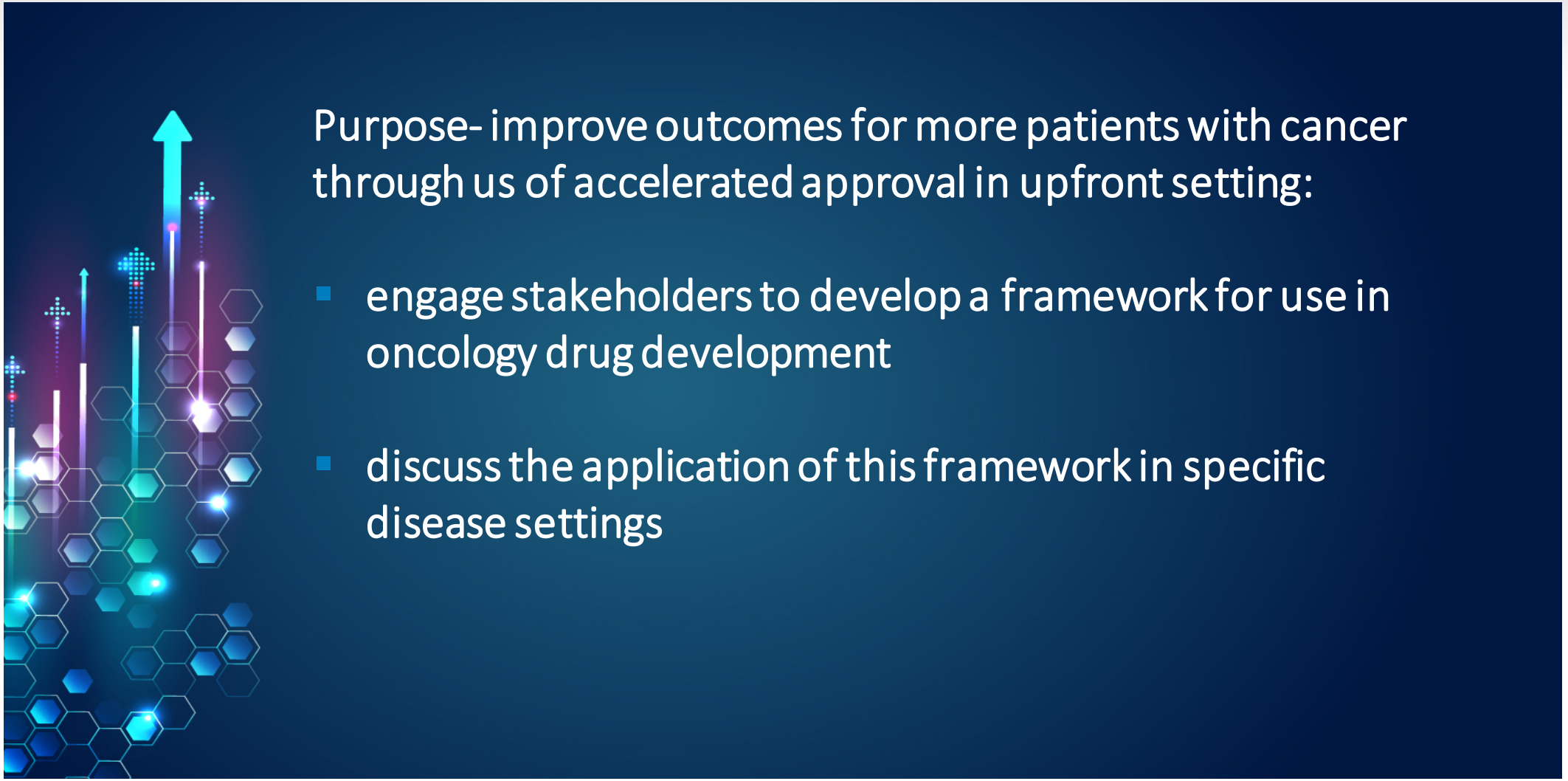
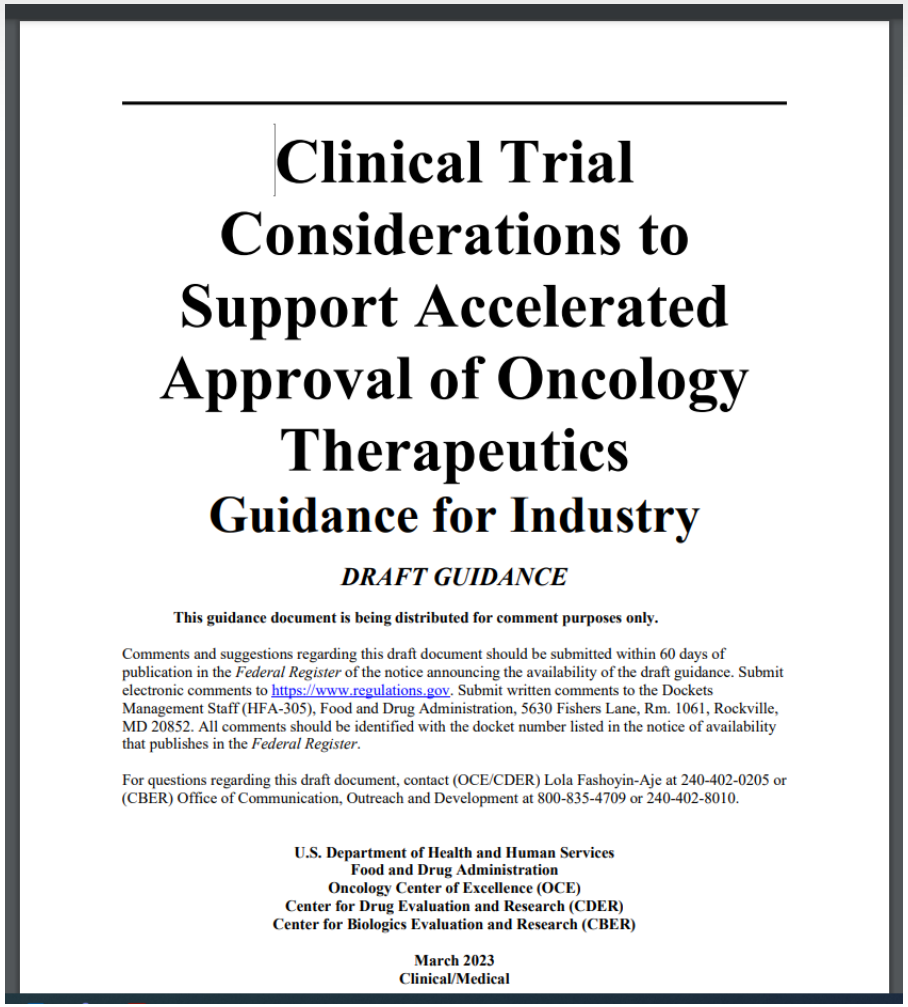
OCE Project FrontRunner



https://www.fda.gov/about-fda/oncology-center-excellence/project-frontrunner



Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (OCE/CDER) Lola Fashoyin-Aje at 240-402-0205 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Oncology Center of Excellence (OCE)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Clinical/Medical

Describes trial design and analysis considerations for accelerated approval (AA) in oncology

- Common pitfalls of historical approach
  - Over reliance on single arm trials
  - Few trials of novel drugs in early line settings
  - Delays in initiating confirmatory trials
- Use of randomized vs single arm trials for AA
- Emphasis on early comprehensive plan to ensure timely verification of clinical benefit

FDA Draft Guidance for industry (2023); https://www.fda.gov/media/166431/download

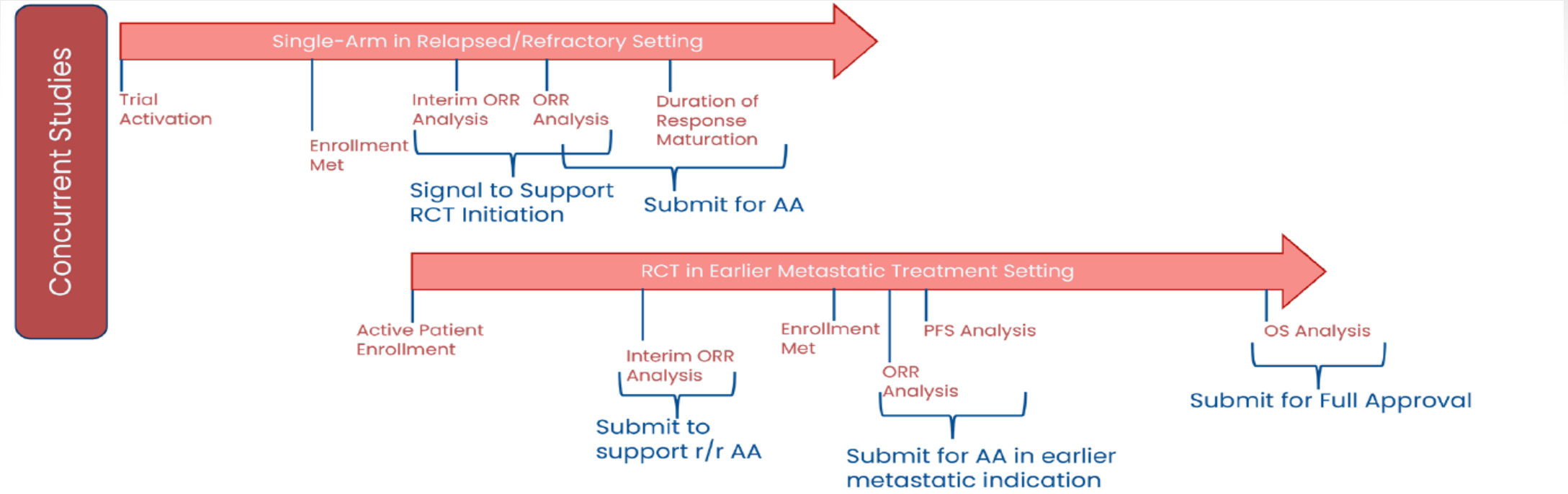
Project FrontRunner Main Considerations for Accelerated Approval

- **Trial setting:** 1L or 2L vs. refractory

- **Trial design**
  - Randomized controlled trial (RCT) vs. single arm trial
  - If RCT:
    - two separate trials (most common approach to date)
    - "one trial" approach with interim analysis for AA

N Engl J Med. 2022 Oct 20;387(16):1439-1442.

Sequential approach for accelerated approval- two concurrent studies

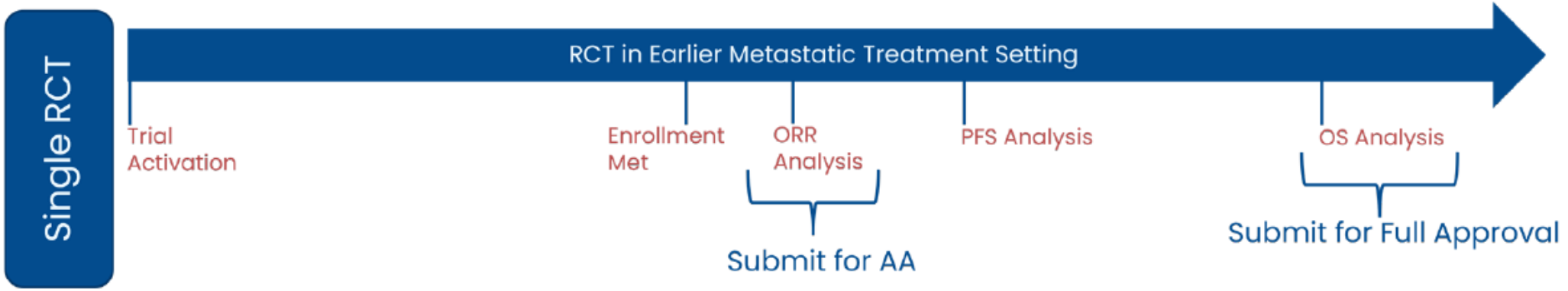


Metastatic MSI-High colorectal cancer-

- 2015: Preliminary evidence of efficacy in refractory MSI-H mCRC
- 2015: KEYNOTE-177 initiated– RCT of pembrolizumab vs chemotherapy 1L setting
- 2017: AA granted for 3L mCRC, based on analysis of ORR and DoR from a single arm study
- 2020: Traditional approval granted for 1L

https://friendsofcancerresearch.org/wp-content/uploads/Accelerating_Investigation_Therapies_Earlier_Metastatic_Treatment_Settings.pdf

Single-trial approach for accelerated approval



Metastatic HER2+ Gastric/GEJ (1L)

- Multicenter, randomized, double-blind, placebo-controlled trial (n=698)
- KEYNOTE 811- Pembrolizumab + trastuzumab + fluoropyrimidine and platinum chemotherapy
- Approval based on interim analysis of ORR and DoR assessed in the first 264 patients randomized

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(Stakeholder) Recommended Framework- Friends of Cancer Research

Factor	Characteristics	Considerations
Disease Characteristics	• Natural history of disease (e.g., long or short natural survival) • Size of eligible population (e.g., rare or more common)	• Natural history of the disease can impact the length of time it takes for data to mature to demonstrate treatment benefit. An earlier readout of a well-established intermediate endpoint could form the basis for AA ahead of clinical benefit outcomes. • The size of the eligible patient population is an important consideration because it can impact enrollment rate and ultimately the time it takes for trial results (interim and final) to be available.
Investigational Treatment Characteristics	• Novelty of mechanism of action (e.g., first-in-class or 3rd/4th in class) • Approval status (e.g., new molecular entity or expanding indication of approved drug) • Level of toxicity (e.g., high or low)	• Data (e.g., efficacy, dosing, toxicity profile) may be leveraged for drugs that have been previously approved in other indications or for investigational agents within an existing drug class, which can help de-risk the approach. • Investigational agents with high toxicity may not be amenable to study in early lines with existing, less toxic SOC options.
Other Available Therapies	• Efficacy, safety of approved available therapies in early metastatic setting (i.e., 1st/2nd line setting) • Efficacy of available therapies • Tolerability of available therapies	• Settings where established SOC is associated with modest-to-moderate outcomes or poor toxicity offers opportunities to demonstrate convincing and clinically meaningful improvement.
Clinical Endpoints	• Intermediate endpoints available and acceptable for regulatory use	• Disease settings that have well-established intermediate endpoints (e.g., correlation to long-term clinical endpoints) to support interim analyses may be most appropriate.

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Adoption of FrontRunner Approach

- **Trial setting:** 1L or 2L –acceptance considerations:
  - Clinical benefit of SOC- (long survival)
  - Therapeutic options available- “save innovation for later in disease course”
  - Combination therapy vs monotherapy

- **Trial design:** Randomized controlled trial (RCT) vs. single arm trial (SAT)
  - Preference for SAT if targeted therapy AND response rate large magnitude AND lack of equipoise/small number populations (e.g., rare cancer)

  - If RCT, consideration for two separate vs. one trial include:
    - Expected timing for AA endpoint maturity vs. timing of endpoint of clinical benefit
    - Available therapies and plan for indication(s) sought
    - Approved vs. novel agent (risk considerations)

Summary and Conclusion

- **Accelerated Approval pathway allows for expedited access to novel therapeutics that demonstrate an advantage over available therapy**
  - Measures that have the potential to improve the evidence to support the safe and effective use of these therapies should be explored

- **Improving patient outcomes necessitates consideration of the overall treatment landscape for a given disease**
  - Facilitating early access to drugs that provide an advantage over available therapy can prolong survival and improve quality of life

- **Application of the FrontRunner considerations considered on a case-by-case basis- one size does not fit all**

Thank you