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ADVANCING DEVELOPMENT OF NEW ONCOLOGY THERAPIES: ALIGNING WITH FDA'S PROJECT FRONTRUNNER

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KEY LEARNING POINTS

- What is Project FrontRunner and why now?
- When does it make sense to offer patients earlier investigational therapy options?
- What are the trial design considerations/implications?
- How does it impact patient safety and site participation?

INTRODUCTION TO PROJECT FRONTRUNNER

Project FrontRunner

- Oncology Center of Excellence (OCE) initiative (2023)
- Encourage biopharmaceutical companies to develop and seek approval of new cancer drugs for advanced or metastatic disease to treat patients in earlier clinical settings (i.e., first or second-line settings)
- In the earlier treatment setting, new and effective therapies have the greatest potential to significantly improve the quantity and quality of patients' lives

Objectives of Project FrontRunner

- Develop a framework for identifying candidate drugs that are appropriate to develop for early metastatic disease
- Facilitate engagement between FDA and drug sponsors during development
- Engage and collaborate with stakeholders on related research, policy, and education

ONCOLOGY DRUG DEVELOPMENT | HISTORICAL CONTEXT

Accelerated Approval Pathway

- Established over 30 years ago in response to the outbreak of HIV infection
- Oncology: Often single-arm uncontrolled studies with objective response rate outcomes as the basis of approval

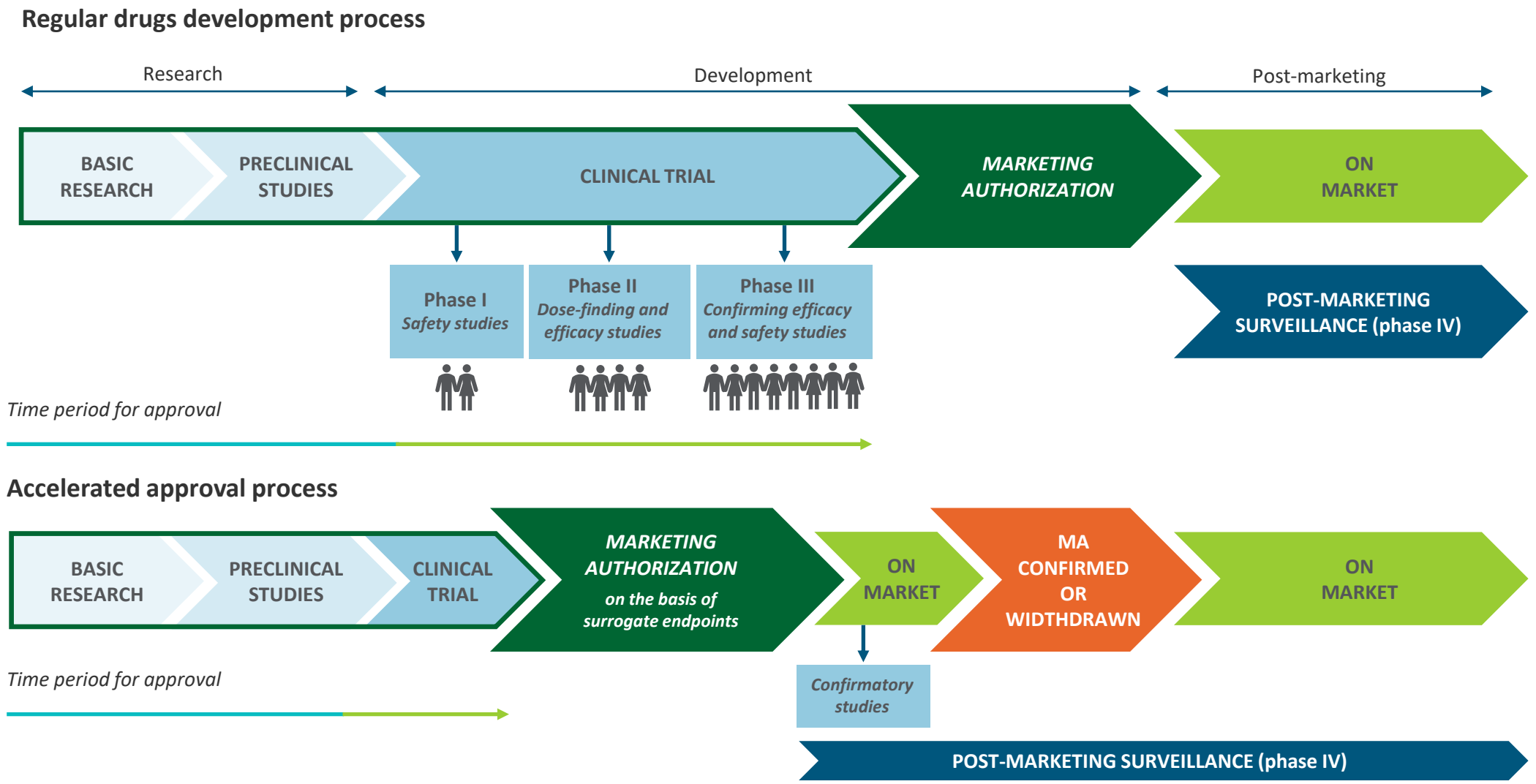
As a public health policy, the decision to grant accelerated approval must be:

- Transparent
- Comprehensive
- Balanced, considering all affected parties
- Advisory Committee review may be necessary to assure robust debate on the risks

Post-Accelerated Approval

- Sponsors commit to confirmatory clinical trial(s) to validate clinical benefit of novel product
- Failure of confirmatory studies to establish clinical benefit should lead to commercial withdrawal
- FDA criticized for not reacting to delays in completing confirmatory studies; however, FDA was not authorized to regulate these studies

TRADITIONAL VS. ACCELERATED DEVELOPMENT & APPROVAL PROCESS



Source: Frontiers in Pharmacology

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ACCELERATED APPROVAL STATUS

Accelerated Approvals Fit Into Three Categories

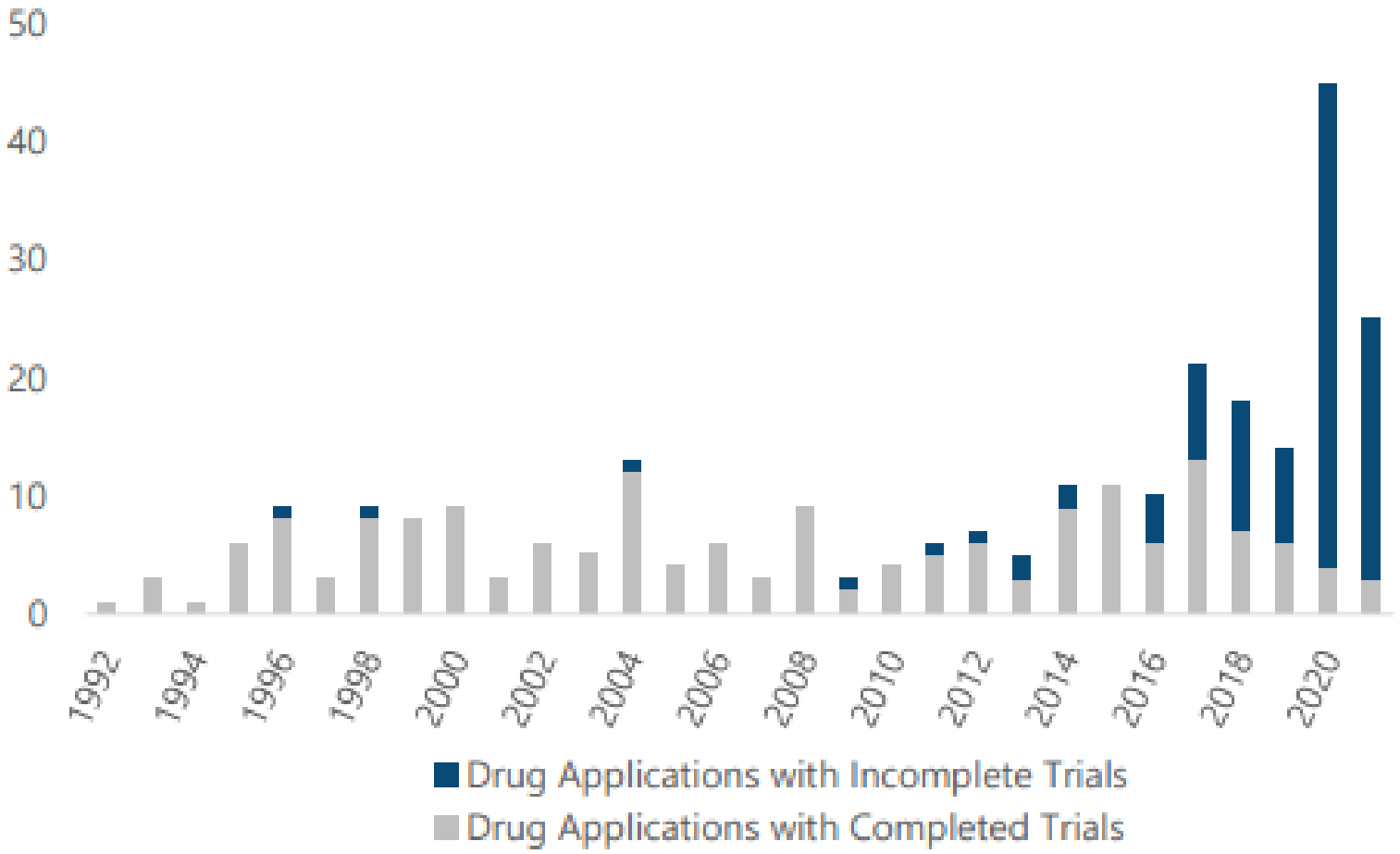
1. Converted to full approval
2. Withdrawal of approval
3. Confirmatory trials still pending completion or FDA review

Between 2012 & 2021 FDA Granted 167 Accelerated Approvals

- 51 were converted to full approval (median time to conversion 2.3 years)
- 14 were withdrawn (median time to withdrawal 3.5 years)
- 102 had confirmatory trials still pending

Source: Beakes-Read et al Therapeutic Innovation & Regulatory Science (2022) 56:698–703

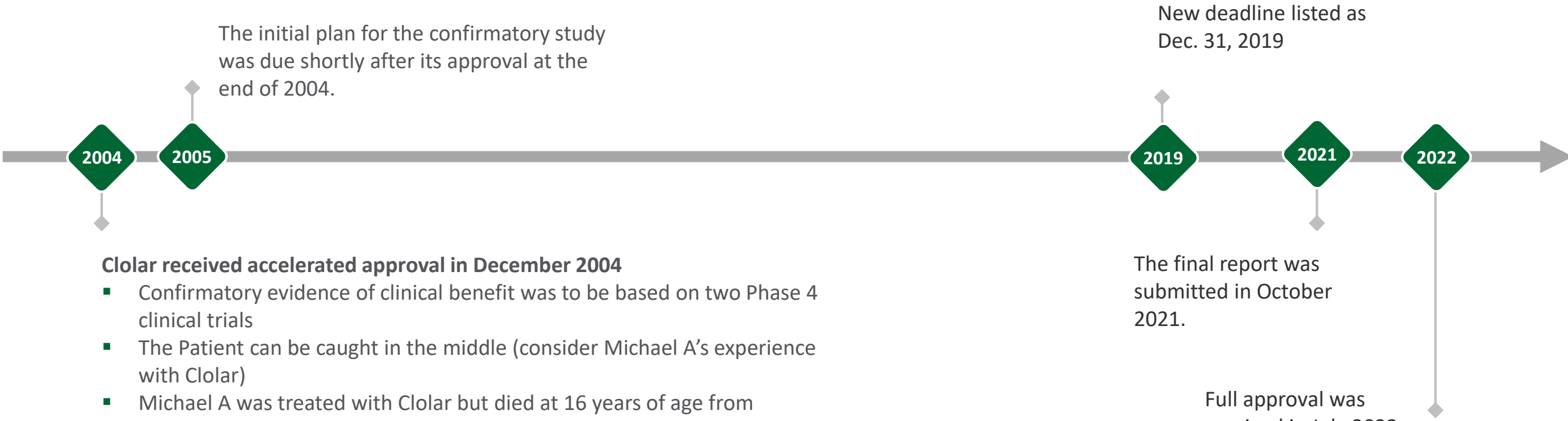
HISTORICAL CONTEXT



Source: OIG Analysis of FDA Accelerated Approval Data, 2022

CASE STUDY | CLOLAR (GENZYME)

For treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted.



Clolar received accelerated approval in December 2004

- Confirmatory evidence of clinical benefit was to be based on two Phase 4 clinical trials
- The Patient can be caught in the middle (consider Michael A's experience with Clolar)
- Michael A was treated with Clolar but died at 16 years of age from leukemia in May 2014, ~10 years after accelerated approval
- Michael and his family bore the risk associated with treatment with Clolar prior to demonstration of clinical benefit ~8 years after he died

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FDA COMMITMENT TO NOVEL ONCOLOGY PRODUCTS

- Oncology accelerated approval may be based on a single-arm study and/or research in late lines of treatment
  - No comparison to standard of care
- FDA initiatives aimed to revise the traditional approach to oncology research and re-emphasize the importance of comparative and well-planned studies

IMPACT OF FDORA (2022)

Legal Framework

- Food and Drug Omnibus Reform Act (FDORA), December 2022 was enacted as part of the Consolidated Appropriations Act of 2023
- FDORA authorizes FDA to:
  - ✓ Require confirmatory studies to be underway at the time of AA or within a specified period of time after approval
  - ✓ Report on the status of post-marketing studies
  - ✓ Update withdrawal procedures
  - ✓ Form an accelerated approval council
  - ✓ Necessitates agreement with FDA on the timeline for initiating the confirmatory trial
  - ✓ Enables FDA to act on confirmatory studies that fail to show clinical benefit

PROJECT FRONTRUNNER

Key Components

- Identified population(s) that can be better served by novel treatments
  - Identifying different subtypes of disease
  - More information on safety findings
  - Avoid the need to fail multiple lines of therapy before trying something novel and potentially “game changing”
- Product for treatment in the advanced/metastatic setting where treatment is not expected to be curative
- Early scientific evaluation for dose selection
- Design a clinical program that pre-specifies planned accelerated approval and verifies clinical benefit in a parallel study
- Minimize the time between accelerated approval and full approval (or withdrawal of the indication)

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Why Now?

Current Landscape

- Delays in conversion from conditional to full approvals
- Dangling approvals requiring action

Scientifically

- Personalized medicine and identified genetic markers
- Gaps for currently available treatments
- Advanced techniques for treatment and advancing science
  - Cell therapy, gene therapy, biologics, companion diagnostics, etc.

Increase in Cancer Patients Worldwide

- Known safety issues with established therapies
- Available therapies need to be challenged: Can we do better?
- Improving quality of life
- Increasing survival

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Creating a Structured Paradigm

- Commitment of FDA to collaborate with sponsors and stakeholders to establish new, early line treatments for cancer patients

- Impact
  - Accelerated approval pathway continues to be available
  - Optimize time between accelerated approval and full approval or withdrawal

- Consolidating and organizing the FDA initiatives:
  - Emphasizes the importance of well-planned clinical studies
    - Randomization
    - Standard(s) of care for comparison
    - Available research in literature
    - Opportunity to treat earlier line patients
    - Continued need for discussion with FDA to ensure efficient approach to clinical research

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Is it a requirement?

- No… But we recommend you should consider the framework
- Opportunity toward
  - Efficient clinical development program
  - Focus on early metastatic disease
  - Establish performance against standard of care
  - Reduces uncertainty between accelerated and full approval
- Sponsors should expect questions and feedback from FDA that align with the Project FrontRunner paradigm

IMPLEMENTATION

Key Points for Clinical Development Programs

OPPORTUNITIES

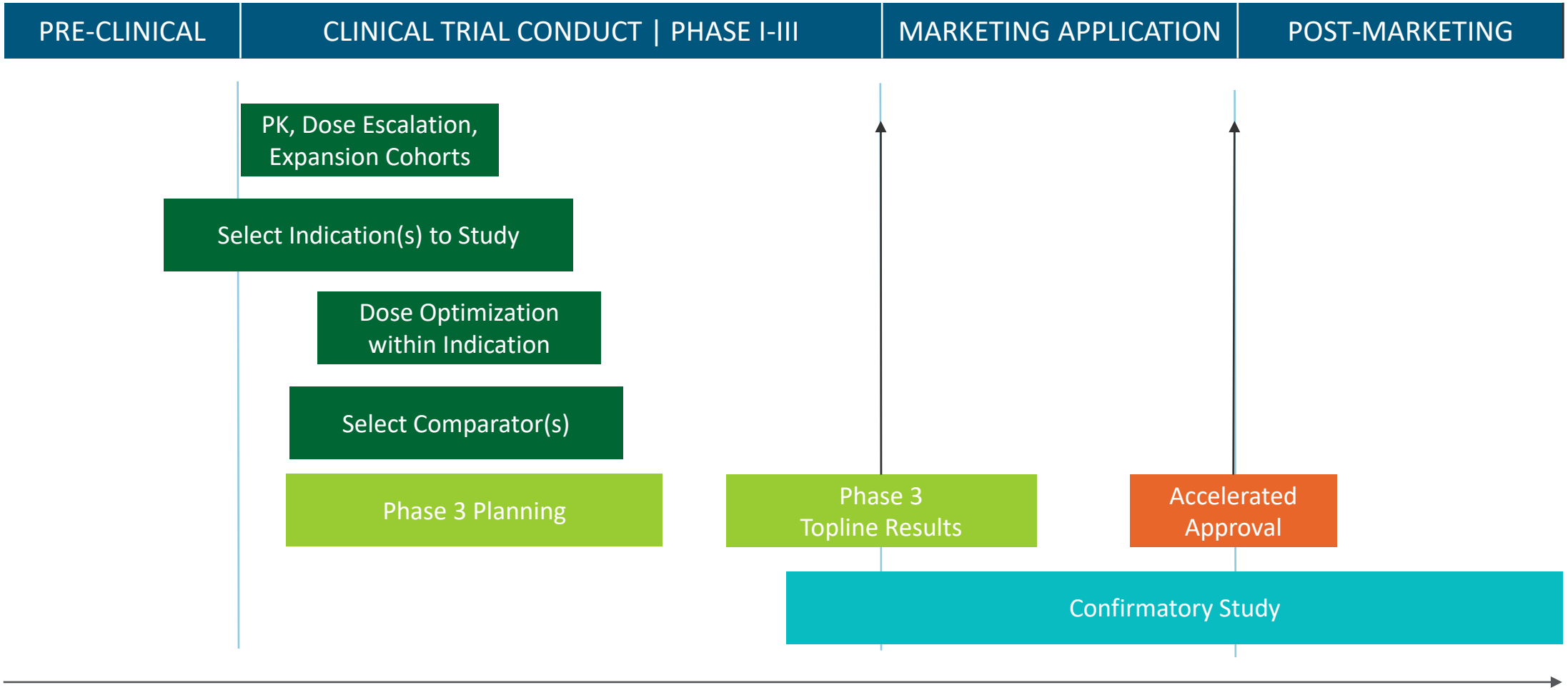
- Compare against, outperform standard of care
- Execute a randomized study
- Market towards a larger population in earlier line setting
- Bigger impact on patients

CHALLENGES

- Demonstrate efficacy in earlier line setting
- Cost: May be smaller treatment effect, require more subjects
- Expediting time from accelerated to full approval

CLINICAL DEVELOPMENT PLAN

Novel Product, Not Previously Marketed



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PLANNING CLINICAL TRIALS

Population, Treatments, and Endpoints

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PLANNING CLINICAL TRIALS

Patients, Sites, and Safety

Patient Engagement

- Patients must want an alternative treatment and be willing to participate in clinical trials
  - Investigator choice
  - Similarity of participants treated with varying standard of cares needs to be assessed
- High failure rates on SOC
- Patient advocacy groups
- Informed Consent
- Improved patient eligibility

Site Selection

- Select countries with highest cancer rates
- Larger or specialized hospitals
- Feasibility questionnaire
- KOL participation

Patient Safety

- Patients in better conditions to receive new treatments
- Low or improved safety profiles than the current standard of care
- Improved assessment of drug effects, avoiding the confounding of disease-related complications or sequelae

GLOBAL LATE PHASE CLINICAL TRIALS

Key components

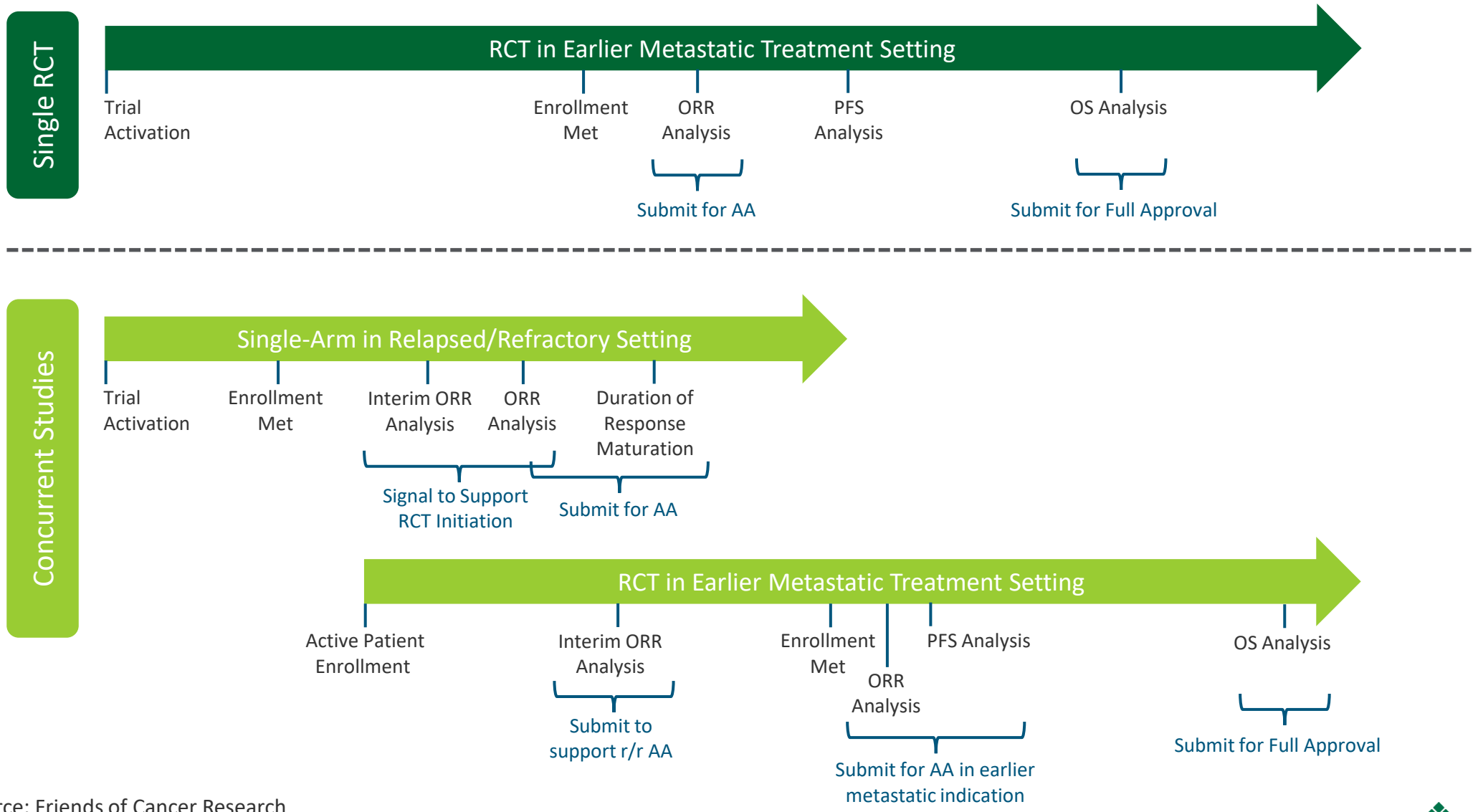
- Variability by location
  - Different standards of care
  - Population availability
  - Similarity of sites and access to care

- Regulatory acceptability outside US
  - Available standard of care and expected treatment procedures
  - Stratify randomized study
  - Pre-plan the sample size per region
  - Engage with by-region regulatory authorities
  - Pre-specify as much as possible

PLANNING PHASE III CLINICAL TRIALS

- Start early, plan ahead
  - Engage KOLs and patient advocacy groups
  - Use early phase studies to inform hypotheses
  - Understand treatment of early metastatic disease patients
- US Regulatory interactions
  - Review of protocol(s) by FDA, opportunity for discussion
  - Use of End of Phase II FDA meeting and opportunities for feedback
  - Obtain scientific advice from ex-US regulatory authorities, as needed

ACCELERATED APPROVAL AND PROJECT FRONTRUNNER



Source: Friends of Cancer Research

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NEW CLINICAL DEVELOPMENT STRATEGY

Continuous Development Pathway to Demonstrate Clinical Benefit

Consider a clinical program that pre-specifies:

1) How accelerated approval will be sought
2) The approach to verify clinical benefit in a parallel study

Assume: Early phase studies are complete, Standard of care exists

- **Option 1:** One randomized study
  - Support accelerated approval based on an agreed interim analysis of response rate
  - Continues to evaluate long term outcomes (OS or PFS) to show clinical benefit that supports full approval
  - Advantages:
    - Enables evaluation of durability of response
    - Enables collection of long-term safety
    - Correlation of the surrogate endpoint (overall response rate) and survival
    - Single study cohort could be in an earlier clinical setting

- **Option 2:** Two randomized studies
  - One study with primary outcome that occurs early (e.g., response rate)
  - A second long-term study assessing clinical outcome (e.g., OS or PFS)
  - Advantages:
    - Both studies could be on-going at the same time
    - Allows reporting of end of study 1 results earlier without bias
    - Avoid the need for interim analysis and corresponding risks
    - Operational simplicity of separate studies

SUMMARY

Project FrontRunner is a structure paradigm proposed by the FDA to encourage the development of new cancer drugs for advanced or metastatic disease to treat patients in earlier clinical settings

While not yet a requirement, Accelerated Approval is still an option within oncology drug development but needs to be considered within the Project FrontRunner paradigm

With the increase in the number of approved cancer treatments, there is a need to continually optimize treatment strategies for newly diagnosed patients with metastatic disease.

CLOSING REMARKS

Project FrontRunner is Part of a Broader Initiative in Oncology Research Covered by RTOR

KEY OBJECTIVES

- Develop framework for identifying candidate drugs to develop early metastatic disease
- Facilitate engagement between FDA and drug sponsors
- Engage and collaborate with stakeholders

KEY ADVANTAGES

- Emphasis on new product development and improvement over existing paradigm
- Opportunity for earlier impact to patients
- Open encouragement to use randomized study designs
- Revisions to accelerated approval guidance which clarify pathways to approval

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THANK YOU

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