FDA'S PROJECT FRONTRUNNER EXPLAINED

Accelerating the Development of New Cancer Therapies

1. PROJECT FRONTRUNNER

Project FrontRunner is an FDA Oncology Center of Excellence (OCE) initiative designed to encourage drug sponsors to develop, test, and seek approval of new cancer drugs for advanced or metastatic disease and to treat patients in an earlier clinical setting (e.g., first or second line).

By developing drugs for an earlier setting, new effective therapies have the greatest potential to significantly improve the quantity and quality of patients' lives (OCE, 2023).

Project FrontRunner is significant for the oncology community as clinical development of new cancer therapies are often conducted in the relapsed/refractory patient population due to:

i) The unmet need for treatment options.

ii) Ethical concerns about exposing newly diagnosed patients to therapies that may be ineffective.

iii) The potential for earlier market access through the accelerated approval pathway, often using single-arm studies.

Project FrontRunner encourages the evaluation of new drugs in earlier treatment stages by considering randomized clinical trials (RCTs) in comparison to appropriate controls, aiding the evaluation of safety and efficacy in the context of available treatments. It increases opportunities to improve patient outcomes through wider access to new products.

According to the OCE, advantages of designing trials in earlier settings include (OCE, 2023):

- ***Earlier access to new therapies.*** *The clinical investigation of new therapies in earlier treatment settings can give more patients the opportunity to receive an investigational agent when their disease-related factors do not preclude participation, and when the treatment has the potential to alter the course of the disease more effectively.*

- ***Improved assessment of drug effects.*** *There is greater opportunity to characterize a drug's safety profile while avoiding the confounding effects of disease-related complications or sequelae of prior treatment.*

- ***Clarify drug effects of new therapies compared to established standard of care.*** *RCTs are the gold standard in characterizing safety and effectiveness. They are easier to conduct early in the course of advanced/metastatic disease (e.g., first or second line) due to a larger patient population and a greater number of effective treatments to compare against.*

- ***Potential to improve treatments in the frontline setting.*** *The increasing number of approved cancer treatments drives the need to optimize treatment strategies for newly diagnosed patients. While frontline treatments for many diseases improve survival, better treatment options are still needed as add-ons to, or replacements of, non-curative and often toxic treatments.*

Figure 1. Advantages to Each Stakeholder.

PATIENTS	SPONSORS
• Receive new experimental treatments early in the disease course • Increase opportunities for better outcomes • Access to potentially less toxic and/or more curative treatments	• Access to a larger patient population • Opportunity to characterize a more detailed drug safety profile • Compare safety and efficacy against approved treatment(s) • Potential for increased market return

2. HOW PROJECT FRONTRUNNER WORKS

Project FrontRunner creates a structured paradigm for advancing the clinical development of new cancer drugs. It includes a commitment by the FDA to collaborate with sponsors and stakeholders to develop early-line treatments and work towards specific goals, including (CDER, 2023):

- *A framework for identifying candidate drugs that are appropriate to develop for the treatment of early metastatic disease (e.g., first or second-line setting), taking into account clinical, scientific, regulatory, and operational considerations.*

- *Engagement with drug Sponsors during drug development to develop and implement strategies to support approvals in early clinical settings.*

- *Collaboration with internal and external stakeholders on related research, policy, and educational initiatives.*

Project FrontRunner and the related advice are voluntary. Pharmaceutical sponsors can discuss and agree upon use of the Project FrontRunner paradigm with the Reviewing Division as part of a guidance meeting.

3. PROJECT FRONTRUNNER AND THE ACCELERATED APPROVAL PATHWAY

The relationship of Project FrontRunner to the accelerated approval pathway is noteworthy.

Most oncology accelerated approvals have been based on single-arm trials, reflecting a historical practice of evaluating new drugs in a treatment-refractory setting without an alternative approved treatment (Cancer Letter, 2023). However, accelerated approvals should not be synonymous with single-arm trials, which are not considered well-controlled. Single-arm trials cannot adequately address the risks of bias and confounding effects. Time-to-event endpoints, such as overall survival or progression-free survival, are also uninterpretable without a control arm (Fashoyin-Aje et al., 2022).

> **Accelerated approval** is granted on the basis that products have an effect on "*a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.*" FDASIA, 21 USC §301

One condition of accelerated approval is that the applicant must conduct one or more confirmatory trials to verify the clinical benefit of the drug or demonstrate an effect on irreversible morbidity or mortality. The confirmatory trial design(s) should be agreed upon with the FDA Reviewing Division and should be underway at the time of accelerated approval. If a trial verifies the clinical benefit, the accelerated approval can be converted to full approval. If a trial does not verify clinical benefit, the product may be withdrawn from the market by the Sponsor or by FDA after a public hearing (OCE, 2023b).

Project FrontRunner can reduce the uncertainty and risks associated with accelerated approvals based upon single-arm trials by encouraging RCTs, which allow for the demonstration of safety and efficacy compared to a control. Accelerated approvals can be granted based on RCTs, as described in the *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics, Draft Guidance,* March 2023 (OCE, 2023c). Project FrontRunner encourages early communication with the FDA regarding clinical development planning and potential approval pathways - providing further opportunities to reduce the time from accelerated approval to confirmation or withdrawal.

4. CLINICAL DEVELOPMENT UNDER PROJECT FRONTRUNNER

There is no regulatory requirement to use Project FrontRunner. It provides a structured approach to encourage sponsors to test new cancer treatments in the earliest appropriate line of therapy and to compare new product safety and efficacy against available and approved treatments.

The initiative represents a collaborative commitment from the FDA toward sponsors and stakeholders to provide the most effective and safest treatments to cancer patients.

Veristat recommends that when considering their clinical development plan, Sponsors of a new cancer treatment should assess the feasibility of investigating the agent among patients in an earlier disease setting. If possible, the sponsor may benefit from access to an expanded patient population. The consideration should be based on early clinical and scientific evidence, and may be driven by factors such as (Friends of Cancer Research, 2022):

i) Level of patient risk that sponsors and regulatory bodies are willing to accept, as well as any known safety information on the experimental product.
ii) Development timeline to regulatory approval, including considerations of regular vs. accelerated approval.
iii) Market opportunity.
iv) Size and location of target population, and its enrollment in clinical trials.
v) Relevance of the target product for use in earlier disease settings.

Veristat advises that Sponsors develop a thorough understanding of the competitive landscape within the targeted indication(s) such that appropriate control arms can be identified early in the clinical development program. There is no single, uniform approach for clinical development of cancer drugs. Early conversations with the FDA about the planned clinical development pathway are critical to the success of a program, particularly regarding the implementation of dose optimization, planned late-phase study design (single-arm vs. RCT), and pathway to approval (regular vs. accelerated).

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