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US FDA Formalizes 'One-Trial' Approach For Oncology Accelerated Approval

by Derrick Gingery

Draft guidance gives recommendations for conducting one randomized controlled trial to generate the evidence for accelerated approval and confirm clinical benefit.

New accelerated approval draft guidance for oncology drugs largely formalizes podium policy that US Food and Drug Administration officials have given in recent months, including strongly recommending randomized clinical trials over single-arm studies.

The *guidance*, issued on 24 March, states that while single-arm trials may be appropriate in some settings, they can be problematic and introduce uncertainty into the safety and efficacy assessment. FDA officials wrote that randomized controlled trials are the preferred study method for an accelerated approval.

One randomized trial could be sufficient to gain an accelerated approval, as well as gather the postmarketing evidence to confirm clinical benefit. A footnote to the guidance notes that "this 'one-trial' approach may be an efficient way to verify clinical benefit," but suggested sponsors begin working with the agency "no later than prior to initiating such a trial" to determine whether evidentiary requirements will be met.

Separate pre- and postmarket randomized controlled trials also are possible for accelerated approval, the agency said.

Many of the issues described in the draft guidance fit with recent agency comments, as well as its new emphasis on studying oncology candidates in earlier disease settings for accelerated approval, known as Project FrontRunner.

Oncology Center of Excellence Director Richard Pazdur hopes Project FrontRunner can reduce the gap between granting accelerated approval and confirming clinical benefit. (Also see "*Cancer*

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And Accelerated Approval: FDA To Crack Down On Single-Arm Trials, Refractory Disease Focus" - Pink Sheet, 10 Jun, 2022.)

Pazdur has argued that accelerated approval is not an incentive program for sponsors, but intended to help make drugs available to patients sooner. He has said that sponsors unwilling or unable to conduct a randomized controlled trial should question whether they should be in the drug development business. (Also see "*Accelerated Approval Is For Patients, Not Sponsors – US FDA's Pazdur*" - Pink Sheet, 1 Dec, 2022.)

One-Trial Approach Tips And Tricks

When using the "one-trial" approach, sponsors should assess the available preliminary clinical data before starting the study and select an endpoint appropriate and feasible to evaluate "earlier in the disease and earlier during the conduct of the trial," the agency wrote in the draft guidance.

Sponsors also should consider whether the expected response rate or other early endpoint is sufficient to predict clinical benefit. Endpoints besides response rate may be used "with subsequent evaluation of clinical benefit endpoints," as part of the "one-trial" approach, the agency wrote.

Should the best available therapy change while the trial is ongoing, sponsors should talk to the FDA about whether an accelerated approval or traditional approval is appropriate, the guidance states.

"Ultimately, the determination of what constitutes available therapy is made at the time the regulatory decision is made, rather than the time the trial was initiated," the agency wrote.

Sponsors planning two randomized controlled trials should not wait to initiate the confirmatory trial until after the accelerated approval is granted. The agency "strongly recommends" the confirmatory trial "be well underway, if not fully enrolled, by the time of the accelerated approval action."

The FDA also said a candidate may be evaluated in another line of therapy in the same cancer type in order to complete the confirmatory trial.

"This approach has the potential to provide access to effective drugs to patients with earlier stage disease in which benefit may be greater," the guidance states. "And it facilitates patient accrual when a drug has already received accelerated approval for a later-stage indication."

If a sponsor uses a single-arm trial to gain accelerated approval, a randomized controlled trial may be necessary postmarket if the agency requires an evaluation of progression-free survival or

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overall survival, the agency wrote.

The Consolidated Appropriations Act of 2023, which included the FDA user fee program reauthorizations, allowed the agency to require confirmatory studies be started at the time of accelerated approval. (Also see "*Accelerated Approval Reforms Give US FDA More Power And Flexibility – With Some Gaps*" - Pink Sheet, 20 Dec, 2022.)

Workshops On Early Endpoints Upcoming

OCE officials also plan more work on early cancer endpoints, which should help sponsors using the "one-trial" approach and meet the goals of Project FrontRunner.

Pazdur and other FDA officials co-authored a 17 March commentary in the Journal of Clinical Oncology considering the problems with response rates, progression-free survival and overall survival. They wrote that OCE planned several workshops this year "to examine the role of early endpoints, their relationship to OS, and considerations around obtaining the information necessary to make informed decisions on the risks and benefits of a novel cancer therapy."

Improving evaluation in early endpoints also could help OCE's campaign to remove "dangling" indications that remain in labels despite a failure to confirm benefit. Several have been withdrawn in recent months, often after FDA pressure. (Also see "*'Dangling' Cancer Indications In US: New Year Brings New Withdrawals Of Accelerated Approvals*" - Pink Sheet, 18 Jan, 2022.)

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