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Via Electronic Submission

May 26, 2023

Robert Califf, MD
Commissioner
U.S. Food and Drug Administration
5630 Fishers Lane Room 1061
Rockville, MD 20852

Subject: Clinical Trial Considerations To Support Accelerated Approval of Oncology Therapeutics (Docket No. FDA-2023-D-0110)

Dear Dr. Califf,

The Association for Clinical Oncology (ASCO) appreciates the opportunity to respond to the U.S. Food and Drug Administration's (FDA) draft guidance to sponsors considering designing clinical trials intended to support accelerated approvals of oncology therapeutics. ASCO appreciates FDA's efforts to provide recommendations on designing, conducting, and analyzing data to provide a more robust efficacy and safety assessment. ASCO is a national organization representing more than 45,000 oncology professionals who care for people living with cancer. Through research, education, and promotion of the highest-quality, equitable patient care, our members are committed to ensuring access to evidence-based care for the prevention, diagnosis, and treatment for all Americans. ASCO supports robust quality initiatives that enhance performance measurement and improvement, clinical practice guidelines, big data analytics, and the value of cancer care.

This draft guidance is timely and important. Criticism of the accelerated approval pathway has increased as multiple drugs approved under this mechanism remain on the market without completion of confirmatory studies. As part of the *Consolidated Appropriations Act, 2023*, the *Modernizing Accelerated Approval Act*, was signed into law.[1] This Act

[1] Consolidated Appropriations Act, 2023, BILLS-117hr2617enr.pdf (congress.gov)

directed the FDA to make clear that the accelerated review mechanism requires post-approval studies be underway prior to approval. It directed steps for increased transparency and called for enhanced guidance on surrogate endpoints and clinical trial designs. This draft guidance, which reflects a strong preference for randomized controlled trials, makes clear the requirement that studies intended to verify clinical benefit be underway prior to approval. While the Agency encourages early discussions regarding design and initiation of trials, it does not provide detailed guidance on expected timelines for completion of post-approval studies. We recommend the FDA provide clarity on this in the final guidance.

We offer the following comments on the recommendations provided:

Recommendations: Randomized Controlled vs. Single-Arm Clinical Trial Designs

We agree that there are limitations with the use of single-arm trials. The use of randomized controlled trials should be encouraged to support sponsors' applications for accelerated approval, as a well-designed randomized control trial can address the many limitations imposed by single-arm trials. However, there may be situations where other trial designs are appropriate, and these should be considered in the draft guidance. For example, single arm trials may be of value in the context of rare disease populations or when patients have suboptimal standard treatment options.

Considerations for Two Randomized Controlled Clinical Trials

The FDA's accelerated approval pathway provides patients with the earliest possible access to potentially life-saving therapies, instead of requiring confirmation of long-term endpoints such as survival. There is also a need for greater public awareness and education about the accelerated and conditional approval processes, including understanding that: (1) additional evidence is needed to confirm early promising results, and (2) confirmatory trials, which provide stronger evidence than the initial trials, may fail to confirm clinical benefit, leading to withdrawal of approval. As such, withdrawal of a therapy or an indication should not be viewed as a failure of the program. Therefore, ASCO agrees with the Agency's perspective that sponsors should have the confirmatory trials initiated when the accelerated approval marketing application is submitted. This will ensure more timely completion of the studies and avoid the challenges when there is broad use of the drug in clinical practice and patients do not enroll in trials. For this to be a successful approach in the initiation of both trials, we agree with FDA's recommendation that the confirmatory trial could evaluate the drug in the same cancer type but in another line of therapy or earlier stage disease setting.

Considerations for a Single Randomized Controlled Trial to Support Accelerated Approval and to Confirm Clinical Benefit

The draft guidance encourages the use of a "one-trial approach" when a randomized controlled trial is properly designed and executed. This approach has the added benefits of more efficient trial conduct and enabling data from participants enrolled during early part of the trial (which led to accelerated approval) to contribute to the longer-term clinical benefit endpoint. We believe the most critical factor will be ensuring sponsors preserve the integrity of the trial. We agree that sponsors should have measures in place to prevent factors that may jeopardize the trial results, such as blinding of data for endpoints supporting verification of clinical benefit. Early discussions between FDA staff and sponsors will be critically important to ensure that a single trial can support both accelerated approval and confirmation of clinical benefit.

We agree that such a design will require interim analyses and careful consideration of statistical properties. Protocols should include a plan to control overall type I and II errors for relevant endpoints, ensuring that results are not compromised by substandard operating characteristics due to unaccounted for interim analyses. Sample size adjustments during the study should be avoided in the absence of a pre-specified plan for sample size re-estimation. We agree that sponsors should strive to perform efficacy analyses to support accelerated approval when the trial is close to or fully enrolled to mitigate accrual challenges that could occur if the treatment receives accelerated approval.

Considerations for a Single-Arm Trial to Support Accelerated Approval

As noted, we agree that there should be considerations for the use of single-arm trials when appropriate. We believe overall survival should be considered the gold standard endpoint for measuring clinical benefit. However, there are many ways to evaluate benefit to patients and their quality of life, including reduction of the size of the tumor, partial or complete remission in hematological diseases, and delay of disease progression. We agree that appropriate standardized criteria, such as Response Evaluation Criteria in Solid Tumors (RECIST)[2], should be used for measuring objective response. Additionally, we believe that durability of response is important, and in most cases a minimum of six-months is appropriate. The Agency's general definition of response including both partial responses and complete responses is within appropriate clinical context. The draft guidance makes it clear that reduction in tumor size is a direct therapeutic effect, and, because stable disease cannot reliably be attributed to treatment, stable disease should not contribute to a measure of clinical benefit in the single arm setting. The draft guidance appropriately suggests the use of blinded independent central

[2] Eisenhauer EA, P Therasse, J Bogaerts, et al., 2009, New Response Evaluation Criteria in Solid Tumours: Revised RECIST guideline (version 1.1), Eur J Cancer, 45(2):228-247.

review (BICR) of the response assessment. We do believe the guidance would benefit from additional discussion regarding the use of single-arm trials in smaller and rare disease populations, where multi-arm trials are simply impractical.

When identifying historical data for comparison poses a challenge, the FDA should allow sponsors to provide data to demonstrate that the magnitude of the treatment effect in a molecularly defined subgroup is better than in an historical trial, including real world data. Similar to the Assessment of Outcomes subsection in the Agency's release of the draft guidance, *Considerations for the Design and Conduct of Externally Controlled Trials*[3], we suggest adding specific recommendations on how to generate relevant parameter estimates from real-world data. While we do not suggest the Agency develop exhaustive lists of appropriate and inappropriate surrogate endpoints, we do recommend that, during sponsor consults with relevant Agency reviewers early in a trial's development, the FDA specify whether it will/will not accept use of specific surrogate endpoints.

In conclusion, we believe this guidance sets the Agency on the right path to improving the use of the accelerated approval pathway for oncologic therapeutics. However, the confirmatory trial section of the draft guidance falls short of providing a clear framework to ensure the completion of such studies in a timely manner. We understand the FDA must strike a balance between innovation and caution, and the Agency has implemented the accelerated approval program in a way that has effectively balanced those tensions. Given the additional authority by law that gave FDA the tools to advance this pathway, —and the growing need to ensure the completion of the confirmatory trials, —the draft guidance should also include the Agency's plans for setting benchmarks and determining expected target dates for sponsors to complete the confirmatory studies. Additionally, we note the guidance does not include the Agency's perspective on expediting withdrawals, when appropriate. It will be beneficial for the public and sponsors to clearly understand the rigorous process and considerations for the withdrawal of an indication or therapy from the market.

We look forward to working with the Agency in developing a more efficient accelerated approval regulatory pathway. Thank you again for the opportunity to provide comments on this important draft guidance. Please contact Shimere Williams Sherwood at Shimere.Sherwood@asco.org with any questions and for further discussions.

Sincerely,

[3] Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (fda.gov)

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Lori J. Pierce, MD, FASTRO, FASCO
Chair of the Board, ASCO Association for Clinical Oncology

Association for Clinical Oncology
2318 Mill Road, Suite 800, Alexandria, VA 22314 • T: 571-483-1300 • F: 571-366-9530 • asco.org