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DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)

March 2023
Clinical/Medical

Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

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)

March 2023
Clinical/Medical

TABLE OF CONTENTS

Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

The purpose of this guidance is to provide recommendations to sponsors of anti-cancer drugs or biological products[2] on considerations for designing trials intended to support accelerated approval.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The accelerated approval pathway[3] is commonly used for approval of oncology drugs in part due to the serious and life-threatening nature of cancer and because of available surrogate or intermediate clinical endpoints considered reasonably likely to predict clinical benefit. While a variety of trial designs and endpoints have historically been used to support accelerated approval, single-arm trial designs and response endpoints (with duration of response as supportive) have

[1] This guidance has been prepared by the Oncology Center of Excellence (OCE) in collaboration with the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, references to *drugs* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

[3] See section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)); 21 CFR part 314, subpart H; 21 CFR part 601, subpart E.

most commonly been used in oncology. Response rate is a marker of drug activity because malignant tumors do not typically regress on their own, and because this endpoint can be interpreted in single-arm trials for monotherapy oncology drug regimens. However, there are limitations to the use of single-arm trials in support of accelerated approval, including but not limited to the following:

- Safety databases are typically small and may not allow for the identification of rare, potentially serious adverse events. For identified serious adverse events, attribution of adverse events to the drug under study can be limited in the absence of a comparator arm.

- Common time-to-event efficacy endpoints in oncology (e.g., tumor progression, survival) are generally uninterpretable due to failure to account for known and unknown confounding factors when comparing the results to an external control. FDA considers such endpoints exploratory and not adequate to be used as measures of efficacy in single-arm trials intended to support approval.[4]

- Low magnitude response rates generally may not be reasonably likely to predict clinical benefit (e.g., immunotherapy).[5]

- For combination regimens, the contribution of the individual components to the claimed effect(s) generally may be challenging to establish.[6]

- Reliance on cross-trial comparisons to historical trials to assess whether the observed treatment effect represents an improvement over available therapy is challenging.[7] There can be differences across trials (e.g., in design, conduct, response assessment intervals, study population, etc.) which may or may not be easily discernible and which could lead to erroneous conclusions regarding observed differences in the response estimate between the investigational arm and a historical control (e.g., erroneously attributing differences in response rate to the investigational drug).

These and other limitations of single-arm trials can add uncertainty to the assessment of the safety and/or effectiveness of a drug such that accelerated approval based on a single-arm trial may not be justified in a given clinical setting.

When properly designed and executed, a randomized controlled trial can address the limitations of single-arm trials, including but not limited to, the following ways:

[4] See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[5] Beaver J, Pazdur R, 2021, "Dangling" Accelerated Approvals in Oncology, N Engl J Med, 384(18):e68.

[6] See 21 CFR 300.50.

[7] See 21 CFR 314.126(b)(2)(v).

- A randomized controlled trial provides a more robust efficacy and safety assessment and allows for direct comparison to a concurrent control arm.

- In cases wherein historical trials did not specifically evaluate the response rate for the standard of care treatment in a biomarker-selected population of interest (i.e., available therapy is approved for an all-comer population), assessing the new drug compared to the available therapy in the same trial provides a more accurate representation of the efficacy and safety of standard of care in the biomarker-defined cohort of patients.

- In settings wherein the treatment landscape may have changed since completion of the trial(s) for available therapy, a randomized controlled trial enables comparable study populations to be studied.

- While trials that support accelerated approval have typically been conducted in patients with refractory disease, a randomized controlled trial may allow for the evaluation of a new drug in an earlier treatment setting, thereby enabling access to a new drug earlier in the course of the disease when more patients are likely to benefit.

- When clinical trial sites span several geographic regions as would be the case for trials that enroll participants internationally, a randomized controlled trial allows for an assessment of potential regional differences that may stem from multiple factors.

Another potential advantage to conducting a randomized controlled trial to support accelerated approval is that, in appropriate cases, longer term follow-up in the same trial could fulfill a postmarketing requirement to verify clinical benefit. This "one-trial" approach maintains efficiency in drug development and can provide early access to a drug using the accelerated approval pathway, while ensuring that a postmarketing trial is fully accrued and well underway to verify longer term benefit in a timely fashion.

III. RECOMMENDATIONS

Given the limitations of single-arm trials, a randomized controlled trial is the preferred approach to support an application for accelerated approval. Sponsors can, as appropriate, elect to conduct a single randomized controlled trial to support an accelerated approval and to verify clinical benefit (i.e., follow a "one-trial" approach) or, they can conduct separate trials – one to support the accelerated approval and another, a confirmatory trial, to verify clinical benefit.

Although a randomized controlled trial is the preferred approach, there can be circumstances wherein a single-arm trial is appropriate in the development of a drug for accelerated approval, for example when there are significant concerns about the feasibility of a randomized controlled trial. Careful consideration should be taken in determining whether a single-arm trial is appropriate in a particular clinical and regulatory context. Regardless of the approach under consideration, FDA recommends early discussion with the Agency before initiating and, as appropriate, during the conduct of, a trial(s).

A. Randomized Controlled Clinical Trials to Support Accelerated Approval

Sponsors can conduct separate randomized controlled trials – one trial with an early endpoint (e.g., response rate) to support the accelerated approval of the drug and a second trial powered for a longer-term clinical endpoint (e.g., progression-free survival (PFS) or overall survival (OS)) to verify clinical benefit. Alternatively, sponsors could design a single randomized controlled trial to support accelerated approval, that is also powered for the longer-term clinical endpoint with follow-up in the same trial to verify clinical benefit (i.e., "one-trial" approach).[8] Below are recommendations for addressing the design, conduct, and analyses of data for either two separate randomized controlled clinical trials or for using the "one-trial" approach for accelerated approval and to verify clinical benefit.

1. Considerations for Two Randomized Controlled Clinical Trials

- Waiting to initiate a randomized controlled confirmatory trial until after an accelerated approval has been granted can create challenges in enrolling participants due to the availability of the drug in clinical practice. Therefore, to help ensure the feasibility and timely completion of the trial intended to verify clinical benefit, FDA strongly recommends that this trial be well underway, if not fully enrolled, by the time of the accelerated approval action.[9,10]

- To facilitate completion of the confirmatory trial, it may be acceptable to evaluate the drug in the same cancer type but in another line of therapy. For instance, for an accelerated approval granted for an indication in a refractory cancer setting, the confirmatory trial could be conducted in an earlier disease setting. This approach has the potential to provide access to effective drugs to patients with earlier-stage disease in which benefit may be greater, and it facilitates patient accrual when a drug has already received accelerated approval for a later-stage indication.[11]

- Given the inherent and residual uncertainties regarding the clinical benefit of the drug at the time of accelerated approval, timely completion of the trial(s) intended to verify clinical benefit is critical. Confirmatory trials should be underway when the marketing application is submitted.[12]

---

[8] This "one-trial" approach may be an efficient way to verify clinical benefit for a drug after accelerated approval. Whether a single trial satisfies the substantial evidence requirement in section 505(d) of the Federal Food, Drug, and Cosmetic Act, should be discussed with FDA early in clinical development, no later than prior to initiating such a trial.

[9] See section 506(c) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)). We note that section 506(c) of the Federal Food, Drug, and Cosmetic Act was recently amended to provide that FDA "may require, as appropriate, a study or studies to be underway prior to approval, or within a specified time period after the date of approval, of the applicable product."

[10] See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

[11] Ibid, p.23.

[12] Ibid, p.22.

1. Considerations for a Single Randomized Controlled Trial to Support Accelerated Approval and to Verify Clinical Benefit

- If planning a "one-trial" approach that uses the same trial to potentially support accelerated approval with longer term follow-up to verify clinical benefit, sponsors should carefully assess the available preliminary clinical data prior to initiating the trial. FDA recommends selection of an endpoint for accelerated approval that is appropriate and feasible to evaluate earlier in the disease and earlier during the conduct of the trial.[13] Sponsors should also consider the natural history of the disease (e.g., indolent cancers), the mechanism of action of the investigational drug, the ability to reliably characterize measurable disease to assess response, and other context-specific factors in selecting the accelerated approval endpoint.

- Preserving the integrity of the trial is critical in assessing the feasibility and appropriateness of the "one-trial" approach because the evaluation of the data and subsequent regulatory action on an accelerated approval application may inadvertently introduce bias. In assessing the potential for bias, sponsors should consider factors such as the anticipated impact of crossover (if permitted); the preliminary data on the drug's effects, including the toxicity profile, the treatment landscape, and the treatment used in the control arm, among other factors.

- Before initiating the trial, sponsors should consider and discuss with FDA whether based on the available preliminary clinical data, the expected effect on response rate or other early endpoint is of a sufficient magnitude to be reasonably likely to predict clinical benefit. Depending on the disease course, the intended population, and guidance from FDA, use of endpoints other than response rate could also be evaluated in a "one-trial" approach together with subsequent evaluation of clinical benefit endpoints.

- If the drug development program is intended to evaluate a combination regimen, sponsors should specify the approach for demonstrating the contribution of each component. Evidence should be provided to support the individual contribution of components to the claimed effect(s), which would generally come from multi-arm trials with interim analyses for futility or from the use of other adaptive trial design elements.[14]

- Sponsors should carefully consider whether the results of the trial are adequate to support submission of an application. A requirement of accelerated approval is that the drug must demonstrate an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit, and provide meaningful advantage over available therapy.[15] Among the factors FDA considers in evaluating whether these

[13] See footnote 4.

[14] See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019).

[15] See footnote 10.

192 requirements have been met are the statistical significance and clinical meaningfulness of
193 the treatment effect demonstrated on the endpoint, other context-specific evidence
194 supporting why the observed effect is likely to predict clinical benefit, and whether the
195 control arm represents the appropriate available therapy.
196
197 • If the treatment landscape has evolved since initiation of the trial (e.g., the treatment on
198 the control arm no longer reflects best available therapy), the decision regarding
199 submission of an application for accelerated approval versus deferring submission of an
200 application until the results to support traditional approval are available should be
201 discussed with FDA. Ultimately, the determination of what constitutes available therapy
202 is made at the time the regulatory decision is made rather than at the time the trial was
203 initiated.[16]
204
205 • The trial should be designed, executed, and analyzed in such a way as to ensure a robust
206 assessment of the efficacy endpoints. The protocol should specify a plan to strongly
207 control the overall false positive rate (type-I error) for the endpoint supporting
208 accelerated approval and the endpoint supporting verification of clinical benefit.
209
210 • The trial sample size should be chosen so that it has adequate power to detect a clinically
211 meaningful and statistically significant improvement in both the endpoints for accelerated
212 approval (e.g., response rate) and verification of clinical benefit (e.g., PFS or OS). The
213 trial design can incorporate adaptive design elements (e.g., sample size re-estimation).
214 With an adaptive design, sponsors should consider the type I error control based on the
215 context of the between-arm comparisons, address the operational issues that this approach
216 may raise, and design the trial with timely completion of the trial as a paramount
217 consideration. For additional information, refer to the guidance for industry *Adaptive*
218 *Designs for Clinical Trials of Drugs and Biologics* (December 2019).
219
220 • For a response-based endpoint, the analysis to support accelerated approval could be
221 based on a pre-specified number of initially randomized patients, while for a time-to-
222 event endpoint, pre-specifying the number of events is appropriate; in each case, the
223 sponsor should ensure a robust assessment and reliable estimation at the earlier analysis
224 time point. Analyses of efficacy to support accelerated approval should be avoided until
225 the trial is close to or fully enrolled to mitigate potential challenges in accrual if an
226 accelerated approval is granted. General considerations for determining the adequacy of
227 the overall response rate (ORR) data to support accelerated approval are described in
228 Section B below.
229

[16] See footnote 10, p.4.

- Measures should be in place to prevent circumstances that may jeopardize the trial results or trial integrity.[17,18] For example, blinding of data for the endpoint supporting verification of clinical benefit should be maintained until the endpoint's protocol-specified analysis time point is reached to ensure a robust assessment of this endpoint.

- In reviewing an application for accelerated approval, FDA's safety assessment may include evaluating whether the available data suggest a potential for harm from treatment on the investigational arm (e.g., detrimental effects on clinical endpoints such as OS). FDA may request summary results of the analysis on survival data to support such an assessment as part of an application submission and may request updated survival results during the course of the review of the application. Sponsors should specify a plan that describes measures to maintain study blind for such an analysis.

B. Single-Arm Trials to Support Accelerated Approval

As described above, whether a single-arm trial is appropriate to support accelerated approval in a particular clinical and regulatory context should be discussed with FDA. This section outlines considerations for designing, conducting, and analyzing data from a single-arm trial intended to support accelerated approval when appropriate, and considerations for determining whether the data may be adequate for this purpose.

1. Study Efficacy Considerations

- **Endpoints**: In oncology, response rate is the most frequently used endpoint to support accelerated approval when the approval is based on data from single-arm trials. Appropriate criteria for assessing the response rate (e.g., ORR based on Response Evaluation Criteria in Solid Tumors [RECIST][19]) should be used. In certain disease settings, measures of response other than ORR may be more appropriate to characterize efficacy (e.g., complete remission rate, major molecular response, etc.). Use of new response assessment criteria or modifications of established criteria should be supported by a strong underlying rationale and should be discussed with FDA at the trial design stage. Whenever possible, the method of assessing response used in the trial should be the same one used for product labeling.

- **Available therapy**: Accelerated approval is reserved for drugs that are expected to provide a meaningful advantage (including an efficacy advantage) over available

[17] See the guidance for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

[18] See the guidance for industry *Placebos and Blinding in Randomized Controlled Cancer Clinical Trials for Drug and Biological Products* (August 2019).

[19] 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.

treatment.[20,21] To facilitate the demonstration of advantage over available therapies, sponsors should pre-specify the historical trial(s) that will serve as the basis for the comparison, and the rationale for the selected trial(s). The time frame for the trial(s), trial size, clinical and demographic characteristics of the trial population, and any potential bias in the assessment of response, are some of the factors to consider in evaluating the applicability of a historical trial. FDA recognizes that it may be challenging, particularly for drugs being developed in molecularly defined patient populations, to identify a historical trial; in such cases, it may be appropriate to provide data to demonstrate that the magnitude of the treatment effect in the molecularly defined subgroup is better than in the historical trial.

- **Sample Size:** A single-arm trial should be sized to permit adequate precision around the point estimate, provide robust estimation of the duration of response, and sufficiently describe the adverse event profile of the drug.

2. Trial Analysis Considerations

- When the efficacy endpoint is response rate, the adequacy of the result to support accelerated approval should be based on the magnitude and duration of response. Sponsors should consider the follow-up time necessary to adequately characterize the response rate and the durability of response in a particular disease setting (e.g., a rapidly progressing disease vs. an indolent disease). Statistical inferential procedures are not necessary to evaluate these endpoints in single-arm trials. In most cases, a minimum follow-up of six months after the response is needed for most of the responders to characterize durability of response. However, there may be instances where a longer minimum follow-up after response is necessary to adequately characterize clinical benefit. In some cases, FDA may request additional data on the durability of response during the review of an application.

- The trial sample size and analysis population for response should be pre-specified. Given the small size of most single-arm trials, the analysis population is generally expected to be the entire trial population. Patients who have received at least one dose of the study drug would then be included in the analysis population regardless of whether they have had the opportunity to respond due to short follow-up time. Multiple increases to the study sample size with repeated looks at the data in the absence of a pre-specified plan may introduce bias in the assessment of efficacy and should be avoided.

- To reduce the potential to introduce bias and to mitigate variance in the assessment of response, blinded independent central review (BICR) of the response assessment should

[20] See 21 CFR 314.500; see also section 506(c)(1)(A) (directing FDA to take into account "the availability or lack of alternative treatments").

[21] See footnote 10.

be performed.[22] A BICR charter that includes procedures for adjudication should be made available to FDA as part of a marketing application.

- Generally, and in the appropriate clinical context, FDA has defined response rate as the sum of partial responses plus complete responses.[23] When defined in this manner, response is a direct measure of a drug's antitumor activity which can be evaluated in a single-arm study. Stable disease should not be a component of response rate. Likewise, measures such as clinical benefit rate (e.g., response rate + stable disease > 6 months) should not be used. Such measures can largely reflect the natural history of disease, whereas reduction in tumor size represents a direct therapeutic effect.

C. Confirmatory Trial Following Accelerated Approval

For drugs granted accelerated approval in oncology, postmarketing confirmatory trials have been required to verify and describe the anticipated clinical benefit.[24] Such trials help address residual uncertainties regarding the relationship between the surrogate or intermediate endpoint to the ultimate clinical benefit.[25] In order to minimize the duration of this uncertainty, FDA may require, as appropriate, that studies intended to verify clinical benefit be underway prior to approval, or within a specified time period after the date of approval, of the applicable product.[26] Postmarketing trials must be carried out with due diligence,[27] and in accordance with the postmarketing trial conditions specified by FDA, which may include enrollment targets, the study protocol, and milestones, including the target date of study completion.[28] An advantage of the "one-trial" approach is that a separate confirmatory trial may not be necessary. However, when a single-arm trial supports the accelerated approval, and FDA requires a postmarketing trial to evaluate PFS or OS, a separate randomized controlled trial may be needed. Early discussions with FDA regarding the design and initiation of both the trial intended to support accelerated approval and the postmarketing trial are recommended to provide evidence of clinical benefit in an expeditious manner.

[22] Ford R, Schwartz L, Dancey J, et al., 2009, Lessons learned from independent central review, Eur J Cancer, 45:268-274.

[23] See footnote 4, p.9.

[24] 21 CFR 314.510.

[25] Fashoyin-Aje LA, Mehta GU, Beaver JA, and Pazdur R, 2022, The On- and Off-Ramps of Oncology Accelerated Approval. N Engl J Med, 387(16): 1439-1442.

[26] See footnote 9.

[27] 21 CFR 314.510.

[28] See Section 506(c)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)(2)(C)).