May 26, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2023-D-0110 for *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*

Dear Sir/Madam:

The Alliance for Regenerative Medicine (ARM) is pleased to submit comments to the US Food and Drug Administration (FDA) in response to recently released guidance titled, *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*.

The Alliance for Regenerative Medicine (ARM) is the leading international advocacy organization championing the benefits of engineered cell therapies and genetic medicines for patients, healthcare systems, and society. As a community, ARM builds the future of medicine by convening the sector, facilitating influential exchanges on policies and practices, and advancing the narrative with data and analysis.

We actively engage key stakeholders to enable the development of advanced therapies and to modernize healthcare systems so that patients benefit from durable, potentially curative treatments. As the global voice of the sector, we represent more than 475 members across 25 countries, including emerging and established biotechnology companies, academic and medical research institutions, and patient organizations.

General Comments

ARM welcomes FDA's issuance of guidance on this topic, which is important for the efficient development of cell and gene therapies for oncology indications. ARM specifically appreciates agency acknowledgement of challenges in development of these therapies, including that new patient enrollment after an accelerated approval can be challenging in the approved target population due to the availability of the drug in clinical practice. We agree with the following expectations identified within the guidance—that it may be appropriate for drugs being developed in molecularly defined patient populations to compare efficacy outcomes to a historical trial; that statistical inferential procedures are not necessary to evaluate response rate endpoints in single-arm trials; and that in post-approval trials, it may be acceptable to evaluate the drug in the same cancer type but in another (e.g., earlier) line of therapy.

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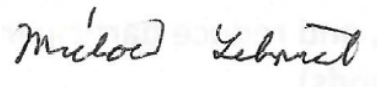
ARM recommends adding information on the use of historical natural history control/real-world evidence in section B1 on study efficacy considerations for single-arm trials. We would also appreciate suggestions for maintaining blinding for the confirmatory portion of single randomized controlled trials, which can present challenges.
We support the following regulatory policies and encourage FDA to apply them to oncology products, as well as more broadly when developing guidance on accelerated approval for additional cell and gene therapy products:

- We recognize FDA has the authority to require confirmatory trials to be underway by the time of the accelerated approval action but recommend these trials should not need to be underway prior to that time (e.g., when the marketing application is submitted).
- ARM appreciates the acknowledgment that there may be circumstances wherein a single-arm trial is appropriate in the development of a drug for accelerated approval, and we suggest wording that further emphasizes this point, as well as the provision of examples of instances of feasibility concerns in the use of randomized controlled trial.
- Natural history control may often be an appropriate trial design, including the use of historical control groups, especially for rare diseases.

ARM appreciates the FDA for its consideration of these comments and the Agency's overall effort to provide guidance that will assist sponsors in the field of regenerative medicine. Below is a listing of line-by-line comments on this proposed guidance.

Sincerely,



Michael Lehmicke
Vice President, Science and Industry Affairs

Specific Line-by Line Comments: Section/Line	**Guidance Text**	**Rationale for Change or Comment**	**Proposed Change**
II. Background			
Lines 39 – 44	"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	Comments: The attribution of rare, potentially serious adverse events in oncology trials may remain challenging even with the inclusion of a comparator arm. In addition, it is currently assumed that all SAEs in single arm trials are attributable to the drug under study. Therefore, attribution of SAEs is not a limitation of single-arm trials.	"However, there are challenges in 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. Longer-term follow-up requirements for patients who

	under study can be limited in the absence of a comparator arm."	While the issues listed may pose challenges in single-arm trials, they do not necessarily preclude the use of single-arm trials. For cell and gene therapy trials, the length of required follow-up studies would contribute to the identification of rare, potentially severe adverse events.	have received cell and gene therapy products may provide the needed information on rare, potentially severe 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.~~"
Lines 46 – 48	"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."	Comment: ARM requests clarification on, if confounding factors are appropriately adjusted for, whether an external control arm may be used to support a single arm trial with a time-to-event endpoint.	
Lines 52 – 53	"Low magnitude response rates generally may not be reasonably likely to predict clinical benefit (e.g., immunotherapy)."	Comment: Interpreting low magnitude response rates may be challenging even with the inclusion of a comparator arm. This is not a challenge with single-arm trials, but a general research challenge.	~~"Low magnitude response rates generally may not be reasonably likely to predict clinical benefit (e.g., immunotherapy)."~~
Lines 58 - 64	"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	Comment: As with other sources of historical control, use of historical trials may have challenges, but those challenges may be addressed in various ways, including adjustment of differences between treatment and control groups with analytic methods. Randomized controlled trials are not always	"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

	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)."	feasible, such as for rare cancers.	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). However, historical trials can serve as control groups in some cases, with sponsor indication of how they will address potential confounding variables. "
Lines 76 – 80	"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."	Comments: Please clarify up front that this statement only applies to trials in which the treatment group is a biomarker-selected population. Additionally, we recommend clarifying here that prospective trials provide an advantage related to such populations but are not required, as stated in lines 271 – 275.	"For trials in which the treatment group is a biomarker-selected population, prospective trials may have an advantage over historical trials that 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). However, historical control may be appropriate in such cases."
Lines 86 – 89	"While trials that support accelerated approval have typically been conducted in patients with refractory disease, a randomized controlled trial may allow for	Comments: The agency has typically required preliminary clinical data before initiating a clinical trial in an early treatment setting when there is an available therapy.	

	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."	Please clarify data requirements for initiating a randomized controlled trial in an earlier treatment setting if those requirements differ from those for a single-arm study.	
III. Recommendations			
Lines 105 - 106	"Given the limitations of single-arm trials, a randomized controlled trial is the preferred approach to support an application for accelerated approval."	Comments: As stated in lines 35-36, "single-arm trial designs … have most commonly been used in oncology." Therefore, the preference for a randomized controlled trial represents a shift in practice. In many cases, oncology trials are performed in patients with refractory disease in which outcomes from standard of care treatment are known to be poor. In such cases, single-arm trials may be preferred. Additionally, the standards of care in oncology are changing rapidly, potentially dating control arms using standard of care treatment by the end of trials. Instead of identifying a singular preference for trial design, ARM recommends the agency identify the circumstances in which each approach is appropriate.	"While a randomized controlled trial is the preferred approach to support an application for accelerated approval in certain circumstances, sponsors should consider various factors when selecting a trial design."
Lines 111-114	"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."	Comments: ARM recommends identifying situations in which single-arm trials may be appropriate, such as examples of factors that prompt concerns about feasibility. Potential factors could include the prognosis for the disease under current standard of care and population size, since cancers with small populations may	"Although a randomized controlled trial is the preferred approach in some cases, 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."

		be challenged to enroll patients for a randomized controlled trial.	
A. Randomized Controlled Clinical Trials to Support Accelerated Approval			
1. Considerations for Two Randomized Controlled Clinical Trials			
133-138	"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 accelerated approval action"	Comments: Because a confirmatory randomized controlled trial can be in an earlier setting (lines 140 – 146), enrollment challenges after accelerated approval primarily occur in the approved target population, rather than in the target population for the confirmatory trial. Lines 150-151 state: "Confirmatory trials should be underway when the marketing application is submitted." We recommend the language describing the expectation for the confirmatory study initiation is consistent throughout the guidance and therefore is updated as shown. We recommend FDA inform sponsors that for products that treat rare cancers, the agency may allow confirmatory study data to be collected from patients who receive the commercially approved product.	"Waiting to initiate a randomized controlled confirmatory trial <u>in the approved setting</u> 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 underway by the time of the accelerated approval action. To further address this enrollment challenge, for rare cancers, in unique situations, it may be acceptable for data from patients treated with the commercial product that received accelerated approval to be used for confirmatory studies. In addition, for rare cancers, in unique situations, confirmatory evidence may be supplemented with supportive data from the same product, approved to treat a similar molecularly targeted cancer."

		Another potential way to support confirmatory evidence for cancers with small populations would be with data from the same product when used to treat a similarly targeted cancer.	
150-151	"Confirmatory trials should be underway when the marketing application is submitted."	Comment: Lines 135 – 138 state, "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." We recommend this timing be used consistently, rather than when the marketing application is submitted.	"Confirmatory trials should be underway by the time of the accelerated approval action."
Lines 166 – 172	"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	Comments: ARM requests FDA to provide guidance on how to address crossover, since it would be expected that many patients in the control arm may want to crossover to the treatment if efficacy is demonstrated, especially in later lines of therapy. There are ethical considerations and	

	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."	considerations for data interpretability of overall survival due to crossover.	
Lines 181-185	"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."	Comments: Ethical concerns would often prevent using study arms of individual components, so we request clarification of whether that is the intent of this statement.	"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 could come from multi-arm trials with interim analyses for futility or from the use of other adaptive trial design elements, when feasible."
Lines 188 – 191	"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]"	Comments: Footnote 15 refers to footnote 10, which refers to the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). That guidance qualifies the meaning of the phrase "meaningful advantage over available therapy," which we would recommend including in the text of the guidance for clarity, as stated to the right.	"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. Amended section 506(c) clarifies the Agency's flexibility in administering the accelerated approval program. For example, an alternative therapy with efficacy

			comparable to available therapy, but with a different mechanism of action, could be of added clinical value in a disease setting in which a significant number of patients may respond differently to the new therapy."[15] Change the footnote to: [15]See the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014), for examples of situations in which a drug could be shown to provide a meaningful advantage over available therapy, including some in which there may not be a demonstrated direct efficacy or safety advantage. This guidance also describes what constitutes available therapy when determining whether a drug provides a meaningful advantage."
Lines 197 – 203	"If the treatment landscape has evolved since initiation of the trial (e.g., the treatment on the control arm no longer reflects best available therapy), the decision regarding submission of an application for accelerated approval versus deferring submission of an application until the results to support traditional approval are available should be discussed with FDA. Ultimately, the determination of what constitutes available therapy is made at the time the regulatory decision is made rather than at the time the trial was initiated."[16]	Comments: Footnote 16 refers to footnote 10, which refers to the guidance for industry, *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014). That guidance indicates the determination of what constitutes available therapy is made "during BLA or NDA review for accelerated approval." We recommend clarifying that this timing is specific to accelerated approval. We also suggest FDA consider the rapidly evolving treatment landscape in oncology, especially for some tumor types, when making this determination.	"If the treatment landscape has evolved since initiation of the trial (e.g., the treatment on the control arm no longer reflects best available therapy), the decision regarding submission of an application for accelerated approval versus deferring submission of an application until the results to support traditional approval are available should be discussed with FDA. Ultimately, the determination of what constitutes available therapy is made during BLA or NDA review for accelerated approval. FDA's available therapy determination generally focuses on treatment options

		It may also be helpful to indicate within the guidance text some factors FDA considers in making this determination, as stated in previous guidance and indicated to the right.	that reflect the current SOC for the specific indication (including the disease stage) for which a product is being developed. In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies (e.g., National Comprehensive Cancer Network, American Academy of Neurology) based on clinical evidence and other reliable information that reflects current clinical practice.**"**[16]
Lines 210 – 212	"The trial sample size should be chosen so that it has adequate power to detect a clinically meaningful and statistically significant improvement in both the endpoints for accelerated approval (e.g., response rate) and verification of clinical benefit (e.g., PFS or OS)."	Comments: We request FDA to either identify within the guidance acceptable statistical methods to use to take into consideration the impact of crossover or indicate flexibility in requiring statistical significance. Establishing a statistically significant difference in overall survival benefit may be challenging when many patients cross over.	"The trial sample size should be chosen so that it has adequate power to detect a clinically meaningful improvement in both the endpoints for accelerated approval (e.g., response rate) and verification of clinical benefit (e.g., PFS or OS). Whether a statistically significant improvement is needed will be determined on a case-by-case basis that accounts for the degree of crossover."
B. Single-Arm Trials to Support Accelerated Approval			
1. Study Efficacy Considerations			
Lines 256 - 258	"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.)."	Comment: Because so few endpoints fall into the categories of complete remission rate and major molecular response, it might be helpful to include additional examples of endpoints, as noted to the right.	"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, pathological/complete response, minimal residual disease, etc.)."
Lines 264 - 266	**"Available therapy:** Accelerated approval is reserved for drugs that are expected to provide a meaningful advantage	Comment: ARM recommends referring to previous qualification of "meaningful advantage over available treatment."	**"Available therapy:** Accelerated approval is reserved for drugs that are expected to provide a meaningful advantage

	(including an efficacy advantage) over available treatment."		(including an efficacy advantage) over available treatment, as described previously in this guidance."
Lines 271 - 275	"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."	Comments: ARM recommends adding that for indications without available therapies, the control group may be a historical natural history study.	"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. For indications without available therapies, a historical natural history study may be an appropriate control group."
2. Trial Analysis Considerations			
Lines 303 – 306	"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 be performed.[22] A BICR charter that includes procedures for adjudication should be made available to FDA as part of a marketing application."	Comment: ARM requests FDA indicate whether expert blinded local read may be an alternative to BICR if assessment criteria are properly defined.	
Lines 311 - 313	"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."	Comment: Clinical benefit rate could be of value in conjunction with ORR for some specific tumor types that have few or no patients with stable disease.	"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, except in tumor types in which stable disease is only rarely observed."