

---

# 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## *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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., 4<sup>th</sup> Floor  
Silver Spring, MD 20993-0002  
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
[https://www.fda.gov/drugs/guidance-compliance-regulatory-  
information/guidances-drugs](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](mailto:ocod@fda.hhs.gov)  
[https://www.fda.gov/vaccines-blood-biologics/guidance-  
compliance-regulatory-information-biologics/  
biologics-  
guidances](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

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>1</b>
<b>III.</b>	<b>RECOMMENDATIONS.....</b>	<b>3</b>
	<b>A. Randomized Controlled Clinical Trials to Support Accelerated Approval .....</b>	<b>4</b>
	<b>B. Single-Arm Trials to Support Accelerated Approval.....</b>	<b>7</b>
	<b>C. Confirmatory Trial Following Accelerated Approval.....</b>	<b>9</b>

1     **Clinical Trial Considerations to Support Accelerated Approval of**  
2                     **Oncology Therapeutics**  
3                     **Guidance for Industry<sup>1</sup>**  
4  
5

6  
7     This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
8     Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
9     binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
10    applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
11    for this guidance as listed on the title page.  
12

13  
14  
15  
16    **I.     INTRODUCTION**  
17

18    The purpose of this guidance is to provide recommendations to sponsors of anti-cancer drugs or  
19    biological products<sup>2</sup> on considerations for designing trials intended to support accelerated  
20    approval.  
21

22    In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
23    Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
24    as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
25    the word *should* in Agency guidances means that something is suggested or recommended, but  
26    not required.  
27

28  
29    **II.    BACKGROUND**  
30

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

---

<sup>1</sup> 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.

<sup>2</sup> 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).

<sup>3</sup> 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.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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

- 41
- 42 • Safety databases are typically small and may not allow for the identification of rare,  
43 potentially serious adverse events. For identified serious adverse events, attribution of  
44 adverse events to the drug under study can be limited in the absence of a comparator arm.  
45
- 46 • Common time-to-event efficacy endpoints in oncology (e.g., tumor progression, survival)  
47 are generally uninterpretable due to failure to account for known and unknown  
48 confounding factors when comparing the results to an external control. FDA considers  
49 such endpoints exploratory and not adequate to be used as measures of efficacy in single-  
50 arm trials intended to support approval.<sup>4</sup>  
51
- 52 • Low magnitude response rates generally may not be reasonably likely to predict clinical  
53 benefit (e.g., immunotherapy).<sup>5</sup>  
54
- 55 • For combination regimens, the contribution of the individual components to the claimed  
56 effect(s) generally may be challenging to establish.<sup>6</sup>  
57
- 58 • Reliance on cross-trial comparisons to historical trials to assess whether the observed  
59 treatment effect represents an improvement over available therapy is challenging.<sup>7</sup> There  
60 can be differences across trials (e.g., in design, conduct, response assessment intervals,  
61 study population, etc.) which may or may not be easily discernible and which could lead  
62 to erroneous conclusions regarding observed differences in the response estimate between  
63 the investigational arm and a historical control (e.g., erroneously attributing differences in  
64 response rate to the investigational drug).  
65

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

69 When properly designed and executed, a randomized controlled trial can address the limitations  
70 of single-arm trials, including but not limited to, the following ways:  
71  
72

---

<sup>4</sup> 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>.

<sup>5</sup> Beaver J, Pazdur R, 2021, “Dangling” Accelerated Approvals in Oncology, *N Engl J Med*, 384(18):e68.

<sup>6</sup> See 21 CFR 300.50.

<sup>7</sup> See 21 CFR 314.126(b)(2)(v).

## *Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

- 73 • A randomized controlled trial provides a more robust efficacy and safety assessment and  
74 allows for direct comparison to a concurrent control arm.  
75
- 76 • In cases wherein historical trials did not specifically evaluate the response rate for the  
77 standard of care treatment in a biomarker-selected population of interest (i.e., available  
78 therapy is approved for an all-comer population), assessing the new drug compared to the  
79 available therapy in the same trial provides a more accurate representation of the efficacy  
80 and safety of standard of care in the biomarker-defined cohort of patients.  
81
- 82 • In settings wherein the treatment landscape may have changed since completion of the  
83 trial(s) for available therapy, a randomized controlled trial enables comparable study  
84 populations to be studied.  
85
- 86 • While trials that support accelerated approval have typically been conducted in patients  
87 with refractory disease, a randomized controlled trial may allow for the evaluation of a  
88 new drug in an earlier treatment setting, thereby enabling access to a new drug earlier in  
89 the course of the disease when more patients are likely to benefit.  
90
- 91 • When clinical trial sites span several geographic regions as would be the case for trials  
92 that enroll participants internationally, a randomized controlled trial allows for an  
93 assessment of potential regional differences that may stem from multiple factors.  
94

95 Another potential advantage to conducting a randomized controlled trial to support accelerated  
96 approval is that, in appropriate cases, longer term follow-up in the same trial could fulfill a  
97 postmarketing requirement to verify clinical benefit. This “one-trial” approach maintains  
98 efficiency in drug development and can provide early access to a drug using the accelerated  
99 approval pathway, while ensuring that a postmarketing trial is fully accrued and well underway  
100 to verify longer term benefit in a timely fashion.  
101

### 102 **III. RECOMMENDATIONS**

105 Given the limitations of single-arm trials, a randomized controlled trial is the preferred approach  
106 to support an application for accelerated approval. Sponsors can, as appropriate, elect to conduct  
107 a single randomized controlled trial to support an accelerated approval and to verify clinical  
108 benefit (i.e., follow a “one-trial” approach) or, they can conduct separate trials – one to support  
109 the accelerated approval and another, a confirmatory trial, to verify clinical benefit.  
110

111 Although a randomized controlled trial is the preferred approach, there can be circumstances  
112 wherein a single-arm trial is appropriate in the development of a drug for accelerated approval,  
113 for example when there are significant concerns about the feasibility of a randomized controlled  
114 trial. Careful consideration should be taken in determining whether a single-arm trial is  
115 appropriate in a particular clinical and regulatory context. Regardless of the approach under  
116 consideration, FDA recommends early discussion with the Agency before initiating and, as  
117 appropriate, during the conduct of, a trial(s).  
118

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

### **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).<sup>8</sup> 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.<sup>9,10</sup>
- 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.<sup>11</sup>
- 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.<sup>12</sup>

---

<sup>8</sup> 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.

<sup>9</sup> 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.”

<sup>10</sup> See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

<sup>11</sup> *Ibid*, p.23.

<sup>12</sup> *Ibid*, p.22.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191

### *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.<sup>13</sup> 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.<sup>14</sup>
- 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.<sup>15</sup> Among the factors FDA considers in evaluating whether these

---

<sup>13</sup> See footnote 4.

<sup>14</sup> See the guidance for industry *Adaptive Designs for Clinical Trials of Drugs and Biologics* (December 2019).

<sup>15</sup> See footnote 10.



## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

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.<sup>16</sup>  
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

---

<sup>16</sup> See footnote 10, p.4.

## *Contains Nonbinding Recommendations*

### *Draft — Not for Implementation*

- 230 • Measures should be in place to prevent circumstances that may jeopardize the trial results  
231 or trial integrity.<sup>17,18</sup> For example, blinding of data for the endpoint supporting  
232 verification of clinical benefit should be maintained until the endpoint’s protocol-  
233 specified analysis time point is reached to ensure a robust assessment of this endpoint.  
234
- 235 • In reviewing an application for accelerated approval, FDA’s safety assessment may  
236 include evaluating whether the available data suggest a potential for harm from treatment  
237 on the investigational arm (e.g., detrimental effects on clinical endpoints such as OS).  
238 FDA may request summary results of the analysis on survival data to support such an  
239 assessment as part of an application submission and may request updated survival results  
240 during the course of the review of the application. Sponsors should specify a plan that  
241 describes measures to maintain study blind for such an analysis.  
242

#### **B. Single-Arm Trials to Support Accelerated Approval**

243  
244 As described above, whether a single-arm trial is appropriate to support accelerated approval in a  
245 particular clinical and regulatory context should be discussed with FDA. This section outlines  
246 considerations for designing, conducting, and analyzing data from a single-arm trial intended to  
247 support accelerated approval when appropriate, and considerations for determining whether the  
248 data may be adequate for this purpose.  
249

##### *1. Study Efficacy Considerations*

- 250
- 251 • **Endpoints:** In oncology, response rate is the most frequently used endpoint to support  
252 accelerated approval when the approval is based on data from single-arm trials.  
253 Appropriate criteria for assessing the response rate (e.g., ORR based on Response  
254 Evaluation Criteria in Solid Tumors [RECIST]<sup>19</sup>) should be used. In certain disease  
255 settings, measures of response other than ORR may be more appropriate to characterize  
256 efficacy (e.g., complete remission rate, major molecular response, etc.). Use of new  
257 response assessment criteria or modifications of established criteria should be supported  
258 by a strong underlying rationale and should be discussed with FDA at the trial design  
259 stage. Whenever possible, the method of assessing response used in the trial should be the  
260 same one used for product labeling.  
261
- 262 • **Available therapy:** Accelerated approval is reserved for drugs that are expected to  
263 provide a meaningful advantage (including an efficacy advantage) over available  
264  
265

---

<sup>17</sup> See the guidance for industry *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006).

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

<sup>19</sup> 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.

## *Contains Nonbinding Recommendations*

### *Draft — Not for Implementation*

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

276  
277 • **Sample Size:** A single-arm trial should be sized to permit adequate precision around the  
278 point estimate, provide robust estimation of the duration of response, and sufficiently  
279 describe the adverse event profile of the drug.

#### 280 281 *2. Trial Analysis Considerations*

- 282
- 283 • When the efficacy endpoint is response rate, the adequacy of the result to support  
284 accelerated approval should be based on the magnitude and duration of response.  
285 Sponsors should consider the follow-up time necessary to adequately characterize the  
286 response rate and the durability of response in a particular disease setting (e.g., a rapidly  
287 progressing disease vs. an indolent disease). Statistical inferential procedures are not  
288 necessary to evaluate these endpoints in single-arm trials. In most cases, a minimum  
289 follow-up of six months after the response is needed for most of the responders to  
290 characterize durability of response. However, there may be instances where a longer  
291 minimum follow-up after response is necessary to adequately characterize clinical  
292 benefit. In some cases, FDA may request additional data on the durability of response  
293 during the review of an application.
  - 294 • The trial sample size and analysis population for response should be pre-specified. Given  
295 the small size of most single-arm trials, the analysis population is generally expected to  
296 be the entire trial population. Patients who have received at least one dose of the study  
297 drug would then be included in the analysis population regardless of whether they have  
298 had the opportunity to respond due to short follow-up time. Multiple increases to the  
299 study sample size with repeated looks at the data in the absence of a pre-specified plan  
300 may introduce bias in the assessment of efficacy and should be avoided.
  - 301 • To reduce the potential to introduce bias and to mitigate variance in the assessment of  
302 response, blinded independent central review (BICR) of the response assessment should  
303  
304

---

<sup>20</sup> 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”).

<sup>21</sup> See footnote 10.

## ***Contains Nonbinding Recommendations***

*Draft — Not for Implementation*

305 be performed.<sup>22</sup> A BICR charter that includes procedures for adjudication should be  
306 made available to FDA as part of a marketing application.

307

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

315

### **C. Confirmatory Trial Following Accelerated Approval**

316

317  
318 For drugs granted accelerated approval in oncology, postmarketing confirmatory trials have been  
319 required to verify and describe the anticipated clinical benefit.<sup>24</sup> Such trials help address residual  
320 uncertainties regarding the relationship between the surrogate or intermediate endpoint to the  
321 ultimate clinical benefit.<sup>25</sup> In order to minimize the duration of this uncertainty, FDA may  
322 require, as appropriate, that studies intended to verify clinical benefit be underway prior to  
323 approval, or within a specified time period after the date of approval, of the applicable product.<sup>26</sup>  
324 Postmarketing trials must be carried out with due diligence,<sup>27</sup> and in accordance with the  
325 postmarketing trial conditions specified by FDA, which may include enrollment targets, the  
326 study protocol, and milestones, including the target date of study completion.<sup>28</sup> An advantage of  
327 the “one-trial” approach is that a separate confirmatory trial may not be necessary. However,  
328 when a single-arm trial supports the accelerated approval, and FDA requires a postmarketing  
329 trial to evaluate PFS or OS, a separate randomized controlled trial may be needed. Early  
330 discussions with FDA regarding the design and initiation of both the trial intended to support  
331 accelerated approval and the postmarketing trial are recommended to provide evidence of  
332 clinical benefit in an expeditious manner.

---

<sup>22</sup> Ford R, Schwartz L, Dancy J, et al., 2009, Lessons learned from independent central review, *Eur J Cancer*, 45:268-274.

<sup>23</sup> See footnote 4, p.9.

<sup>24</sup> 21 CFR 314.510.

<sup>25</sup> 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.

<sup>26</sup> See footnote 9.

<sup>27</sup> 21 CFR 314.510.

<sup>28</sup> See Section 506(c)(2)(C) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 356(c)(2)(C)).