



**Submitted Via Electronic Submission**

May 3, 2019

Norman E. "Ned" Sharpless, MD  
Acting Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993

**Subject: Cancer Clinical Trial Eligibility Criteria; Series of Four Draft Guidances (Docket Nos. FDA-2019-D-0363; FDA-2019-D-0359; FDA-2019-D-0357; and FDA-2019-D-0358)**

Dear Dr. Sharpless:

The American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (*Friends*) thank the U.S. Food and Drug Administration (FDA), particularly the Oncology Center of Excellence (OCE), the Center for Drug Evaluation and Research (CDER), and the Center for Biologics Evaluation and Research (CBER), for the recent release of four draft guidances and one final guidance for cancer clinical trial eligibility criteria. ASCO and Friends agree with the Administration that a clinical trial's eligibility criteria are essential to defining the characteristics of the trial's study population. We appreciate FDA's leadership in release of these guidance documents to encourage researchers and sponsors to broaden eligibility criteria and provide sound scientific rationale for decisions to limit opportunities for trial participation. We are grateful for FDA's involvement in our joint initiative that encourages broader eligibility criteria for cancer clinical trials and has produced recommendations related to: brain metastases; HIV/AIDS, Hepatitis B, and Hepatitis C status; minimum age for inclusion; organ dysfunction and prior and concurrent malignancies; and inclusion of adolescent patients in adult oncology clinical trials. ASCO and *Friends* are supportive of the final guidance document (*Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials; Guidance for Industry*) and appreciate the opportunity to comment on the four draft guidances that FDA released on March 12, 2019.

ASCO and *Friends* applaud the FDA’s recognition that “some eligibility criteria have become commonly accepted over time or used as a template across trials without a clear scientific or clinical rationale or justification. In other cases, eligibility criteria can be deliberately restrictive, even though it is not clinically merited.” The FDA guidance documents send the strong message that this practice must change. The recommendations in each of the draft guidances aim to maximize the generalizability of clinical trial results while also maintaining the safety of clinical trial participants. Broadening eligibility criteria will allow for the inclusion of more diverse patient populations on trials, which will lead to the collection of trial data that is relevant to the real-world population of patients that will use the FDA-approved therapies. We also applaud the FDA for ensuring that the sponsors of these trials provide a strong rationale for exclusion of these trial participants in the trial protocol. We are pleased to see that the draft guidances’ content and strategies to modernize eligibility criteria for cancer clinical trials build upon the ASCO-*Friends* recommendations, which were developed by a consortium of patient advocates, drug/biotech manufacturers, investigators, and regulators.<sup>1</sup>

ASCO and *Friends* offer the following suggestions for FDA consideration as the Administration finalizes the documents.

### **Brain Metastases**

We are pleased with the FDA’s approach and thoughtful considerations to the inclusion of patients with brain metastases. We agree with the Administration that patients with brain metastases should be included in clinical trials in a way that contributes to a greater understanding of the efficacy and safety profile of the investigational drug while maintaining patient safety.

### **Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections**

This draft guidance recommends inclusion of patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infections. We are pleased that the Administration’s draft guidance on this particular patient eligibility criteria is expansive and detailed. In particular, the recommendation that patients with CD4+ T-cell counts  $\geq 350$  cells/uL generally be included will have a positive impact on the number of patients eligible for cancer clinical trials. Additionally, we are pleased to see that patients without a history of AIDS-defining opportunistic infections are recommended for inclusion, as are those patients for whom AIDS-defining opportunistic infections are treated with prophylactic antimicrobials. FDA’s

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<sup>1</sup> Kim, ES; Bruinooge, S; Roberts, S; Ison, G; Lin, N, et al. Journal of Clinical Oncology Special Series. Broadening Eligibility Criteria to Make Clinical Trials More Representative: American Society of Clinical Oncology and Friends of Cancer Research Joint Research Statement. November 2017. <https://ascopubs.org/doi/full/10.1200/JCO.2017.73.7916>

guidance to exclude patients taking specific antimicrobial drugs where there may be drug-drug interactions or overlapping toxicities is prudent.

### **Minimum Age for Pediatric Patients**

ASCO and Friends applaud the FDA for this nuanced draft guidance, which emphasizes the importance of ethical considerations when patients under the age of 18 are involved. We agree that trials may involve children if (1) the risk is justified by the anticipated benefit to the participant, (2) the anticipated risk-benefit profile is at least as favorable as that presented by available treatments, and (3) adequate provisions are made for soliciting the assent of the child and permission of their parents or guardians. We appreciate the FDA's recommendation for early-phase trials that the pediatric starting dose be lower than the adult maximally tolerated dose (particularly for monoclonal antibodies), and that generally for children <12 years of age and for adolescents < 40 kg defined adult flat doses would be converted to body surface area or body weight adjusted dosing.

We also note and ask clarification on the inclusion of infants or children ages less than 2 years of age. There are circumstances where this is highly relevant (e.g., inclusion of infants with MLL-rearranged leukemia in MLL specific drug trials [DOT-1L and Menin inhibitors]). It is noteworthy that children under 2 years of age were included in the approval for larotrectinib.

Finally, we request clarification in line 134 ("to understand the potential differences in pharmacokinetic (PK) and pharmacodynamic (PD) as well as dose selection") as to whether differences in behavior, outcomes, or other factors should be considered.

### **Patients with Organ Dysfunction or Prior or Concurrent Malignancies**

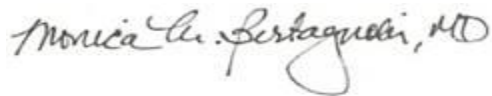
The draft guidance regarding inclusion of patients with organ dysfunction or prior or concurrent malignancies is broad and gives sponsors flexibility in including this population. ASCO and *Friends* applaud FDA for stating that sponsors should provide adequate justification for the inclusion/exclusion of patients with various degrees of renal impairment, because we believe that patients with renal insufficiency can be included in the trials. We suggest that the FDA consider strengthening the draft guidance by stating that sponsors should include patients with CrCl values >30mL/min when safety profiles and elimination data are available.

We are also pleased that the cardiac function draft guidance language recommends including baseline clinical evaluation in early-phase studies in coordination with the FDA review division or office. This level of coordination with FDA staff will encourage sponsor consideration of this criteria. However, we note that it is conservative to require a minimum baseline QTc interval as

an eligibility criteria for investigational drugs that have not exhibited potential risks of QTc prolongation.

We thank you for the opportunity to comment on the FDA draft guidances for cancer clinical trials eligibility criteria and the opportunity to work with the Administration on this important issue and the very thorough and thoughtful guidance documents. We look forward to working with you in implementation of these criteria in cancer clinical trials. If you need additional information, please contact Shimere Sherwood, Associate Director, Science and Research Policy, ASCO, [shimere.sherwood@asco.org](mailto:shimere.sherwood@asco.org) or Mark Stewart, Vice President, Science Policy, Friends of Cancer Research, [mstewart@focr.org](mailto:mstewart@focr.org)

Sincerely,



Monica Bertagnolli, MD, FACS, FASCO  
President and Chair of the Board  
American Society of Clinical Oncology



Ellen V. Sigal, PhD  
Chairperson and Founder  
Friends of Cancer Research