



May 25, 2023

2023

President

Robert Brodsky, MD
Johns Hopkins University
Ross Building, Room 1025
720 Rutland Avenue
Baltimore, MD 21205
Phone 410-502-2546

President-Elect

Mohandas Narla, DSc
New York Blood Center
310 E 67th Street
New York, NY 10065
Phone 212-570-3056

Vice President

Belinda Avalos, MD
Atrium Health
215 N. Pine Street, Unit 4703
Charlotte, NC 28202
Phone 980-442-2000

Secretary

Cynthia Dunbar, MD
NHLBI/NIH
Translational Stem Cell Biology Branch
Building 10-CRC, Room 5E-3332
10 Center Drive
Bethesda, MD 20892
Phone 301-402-1363

Treasurer

Joseph Mikhael, MD, FRCPC, MEd
Translational Genomics Research Institute,
City of Hope Cancer Center
445 N. Fifth Street
Phoenix, AZ 85004
Phone 602-343-8445

Councillors

Christopher Flowers, MD, MS
Alison Loren, MD, MS
Bob Löwenberg, MD, PhD
Charlotte Niemeyer, MD
Sarah O'Brien, MD, MSc
Betty Pace, MD
Jamile Shammo, MD
Wendy Stock, MD, MA

Executive Director

Martha Liggett, Esq.

Robert M. Califf, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics (Docket Number: FDA-2023-D-0110)

Dear Commissioner Califf:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance on *Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics*.

ASH represents more than 18,000 clinicians and scientists worldwide committed to studying and treating blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as classical hematology (non-malignant) conditions. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the fields of stem cell biology, transfusion medicine, and gene and cell therapies. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

In 2018, ASH founded the ASH Research Collaborative (ASH RC) to accelerate change by making it more efficient to conduct research, from increasing access to high-quality clinical data to making it easier for individuals with hematologic conditions to participate in studies. Current ASH RC initiatives focus on multiple myeloma and sickle cell disease (SCD) clinical research. The foundation of the ASH RC is its Data Hub, a technology platform that facilitates the exchange of information by aggregating research-grade data on hematologic diseases. The Sickle Cell Disease Clinical Trials Network optimizes clinical trials research in SCD and leverages the Data Hub to collect key information and identify gaps to advance SCD research and treatment.

Accelerated drug approval pathways continue to be very important to hematology care by introducing promising therapies to patients with hematologic malignancies. Recently, products have been removed from the market due to challenges with confirmatory trials, placing practicing physicians and their patients in a vulnerable position. ASH commends the FDA for releasing this draft guidance to address these challenges as we believe it will allow more patients access to safe and effective therapies more quickly. The Society supports the Agency's work to clarify best practices for sponsors to receive accelerated approval, an approval pathway that has greatly benefitted the blood cancer patient community. This year alone, multiple hematologic products such as Epkinly and Jaypirca have received accelerated approval, ensuring that these products receive market access for Americans who need them. Improving sponsors' understanding of the accelerated approval process and best practices for clinical trial designs to meet FDA standards is an important goal of the Agency, and one that ASH shares. We are pleased to share the following line-specific comments and recommendations that we encourage the Agency to consider as the guidance is finalized, implemented, and evaluated over time.

LINE SPECIFIC COMMENTS

Section 3 A 1. Considerations for a Single Randomized Controlled Trial to Support Accelerated Approval and to Verify Clinical Benefit

- *(Line 181)* The Society encourages the Agency to reexamine its recommendation that sponsors evaluating a combination regimen should specify how they intend to demonstrate each individual drug's contribution to the regimen. This is an extremely difficult scientific task, and the regimens being put forward should be approved or denied as a package. For example, it would be challenging to demonstrate the individual contributions of the five different drugs that comprise R-CHOP for large cell non-Hodgkin lymphoma.
- *(Line 197)* For randomized trials using a control group that is no longer considered standard of care because another drug has been approved that is better, “deferring submission of an application until the results to support traditional approval are available” seems to be an unnecessary burden to sponsors. We agree that the new standard of care should be the comparator, for example, using Chlorambucil in individuals with chronic lymphocytic leukemia (CLL) after BTK inhibitors have entered the market. ASH believes that in cases where the treatment landscape has evolved since initiation of a clinical trial, the sponsors should have the ability to amend accelerated approval trials to include the new standard of care, instead of deferring submission to a traditional approval. The Society encourages FDA to update the guidance accordingly to address the ever-changing treatment landscape.

Section 3 B 1. Study Efficacy Considerations

- *(Line 253)* We appreciate that the Agency recognizes that while response rate is the most frequently used endpoint, it is not applicable for all studies. ASH notes that an overall response rate alone is inadequate for trials in myeloid malignancies, as response rates alone do not reliably translate to improved overall survival. Instead, ASH believes that trials for these indications should incorporate at least a duration of response as a trial component.

ASH appreciates the opportunity to provide these comments. We look forward to supporting the implementation of this new policy. Please consider ASH a resource; we would be pleased to provide additional information. If you have any questions, please use ASH Deputy Director of Government Relations and Public Health Stephanie Kaplan (skaplan@hematology.org or 202-776-0544) as your point of contact.

Sincerely,



Robert A. Brodsky, MD
President