AMERICAN SOCIETY OF HEMATOLOGY
2021 L Street, NW, Suite 900, Washington, DC 20036 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

October 13, 2020

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

Re: Draft Guidance for Industry – *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment* (FDA-2020-D-1298)

Dear Dr. Hahn:

The American Society of Hematology (ASH) appreciates the opportunity to provide comments to the U.S. Food and Drug Administration (FDA3) on the Agency's Draft Guidance for Industry – *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment* (FDA-2020-D-1298).

ASH represents more than 18,000 clinicians and scientists worldwide, who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases and continue to be innovators in the field of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians providing care to patients.

Overall, ASH is supportive of the policies outlined in the draft guidance and believes that it reflects reasonable recommendations related to the development of treatments for acute myeloid leukemia (AML). The acute leukemias are aggressive malignancies that originate in a hematopoietic stem cell and are rapidly fatal without immediate treatment. A significant portion of patients with AML can now be cured with chemotherapy. Others can be cured with stem cell transplantation. As with acute lymphoblastic leukemia, the successful management of patients with AML requires a therapeutic strategy determined by careful assessment of individual prognosis, aggressive supportive therapy, and early recognition and treatment of complications.

We are pleased to provide the following suggestions in response to the topics outlined in the draft guidance:

- In general, the document differentiates between treatments being given with curative intent and those that are not, and the document lists only intensive chemotherapy regimens as those considered to have curative intent. But scientific

advances and recent practice changes make it unclear to what extent this still carries relevance. For instance, what to make of a "non-curative" therapy that results in a remission and allows a patient to proceed to a transplant, which does have curative intent? In addition, treatments given with curative intent are defined as those expected to result in a plateau on a survival curve. Again, only intensive chemotherapy appears to be listed as a possible means to this end, but we point out that the recent study, "Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia" published in the *New England Journal of Medicine* in August 2020, shows that this therapy, which we believe the FDA would consider as one that is not given with curative intent, did in fact result in a plateau on the survival curve. We suggest that the Agency reconsider this distinction, which appears several times in the document, and if regulatory distinctions are to be made between treatments that are given with or without curative intent, to expand which therapies have this potential.

- For Other Potential Measures of Efficacy for AML (lines 521-535), we suggest that the Agency consider bridge to transplant as another measure of efficacy. An investigator would score patients at diagnosis as someone who "in an ideal world would get a transplant." This would provide the denominator and at the end of the study, could be compared to the number of patients who were transplanted. Treatments that produce sufficient responses to allow patients to undergo transplantation are providing clinical benefit.

- In the Exploratory Trial Population section, we have a similar request that the Agency clarify its recommendations in lines 620-627. We think that the guidance is suggesting that early development include patients without the marker because the new drug could be useful even without the marker (or abnormal pathway). We believe the Agency is stating that developers should not assume that their drug is only effective in subpopulations; however, multiple ASH reviewers interpreted this recommendation in different ways. We therefore encourage the Agency to clarify its recommendations in this section.

Again, ASH appreciates the opportunity to provide these comments. Please consider ASH as a resource; we would be pleased to provide additional information or support. 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,

Stephanie J. Lee, MD, MPH
President

[iii] DiNardo, Courtney et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020; 383:617-629. DOI: 10.1056/NEJMoa2012971.