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Nicole Gormley, MD
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2018-D-3090: *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment Guidance for Industry*

Dear Dr. Gormley,

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's draft guidance on *Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease (MRD) in Development of Drug and Biological Products for Treatment* as published in the Federal Register (FDA-2018-D-3090) on October 16, 2018.

ASH represents over 17,000 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. The ASH membership is comprised of physicians and investigators who use MRD as a biomarker and prognostic tool for risk stratification in patients with hematologic malignancies. As such, the Society's members have a vested interest in this draft guidance.

ASH commends the FDA for releasing a draft guidance that is reflective of the current state of the science and practice. In addition to facilitating drug development, the guidance will be vital in identifying the setting where MRD can be used as a clinical endpoint and could provide insight on future research that would be needed to extend the use of MRD as an endpoint. ASH supports the overall provisions outlined in the draft guidance, but requests that the FDA consider making the changes included below to help strengthen this guidance. The Society's suggestions are grouped under "General Recommendations" that are applicable to all hematologic malignancies outlined in this guidance, and "Disease-specific Recommendations."

General Recommendations

- Since current assessment techniques (e.g., qPCR, flow cytometry, etc.) used to detect residual disease after the treatment of a hematologic malignancy can provide measurable results, the Society recommends that the FDA consider incorporating the term "measurable," in the guidance when referencing MRD. The Society believes that the term "measurable" is a more appropriate representation of this biomarker and has become an established term frequently used by hematologists in publications (Flores-Montero et al., 2017; Holstein et al., 2018; Kumar et al., 2016; Schuurhuis et al., 2018).

- ASH recommends that the Agency update the guidance to emphasize the importance of using validation techniques to effectively measure MRD, and stress the need for harmonization of methodologies and protocols for MRD measurement across different laboratories (as stated in page 9; line 351 of the guidance). While ASH recognizes that the development of such standard protocols across laboratories is challenging and may impose a significant burden, it is understood that laboratories use different technological platforms and assays for measuring MRD. In addition, sometimes MRD detection can be dependent on other factors such as who conducted the measurement and the quality of the sample (Paietta, 2018). ASH recommends that in addition to harmonization of methodologies that standard analytical and validation tools during the MRD assessment process should be used to further enhance how labs assess the presence or absence of MRD. Furthermore, such an addition to the guidance would better represent "real life" practical applicability in laboratories and could be vital at helping to streamline the MRD assessment process.

- MRD is a time-point dependent variable; however, as currently written the guidance does not provide a timeline to evaluate the duration of MRD negativity. It also does not address whether a one-time MRD negative result will be considered durable. Additionally, the guidance broadly recommends that the assessment of MRD be conducted mostly in patients with complete response (CR). In multiple myeloma and chronic lymphocytic leukemia for example, MRD can be negative even in patients with partial response (PR) and there are currently on-going studies assessing MRD in these patients (Paiva et al., 2008). ASH recommends that the FDA consider updating the guidance to elaborate on the timeline and setting for assessing MRD in the hematologic malignancies cited in the guidance.

Disease-Specific Recommendations

- **Leukemias**
  - The draft guidance states in lines 41-42, that "conventional morphologic detection for hematologic malignancies has a threshold limit of 1 tumor cell in 100 cells." While this may be true for other hematologic malignancies, in acute myeloid leukemia (AML) and several other types of leukemias, most studies use the morphological threshold of 5% blast cells in the bone marrow. In addition, hematopathologists may observe regenerating normal myeloblasts and lymphoblasts during bone marrow recovery that can get over the 5% threshold. MRD remains a useful tool for distinguishing normal from leukemic blast cells (Loken et al., 2012). To that end, the Society recommends that the FDA update the leukemia section of the guidance to reflect the appropriate MRD detection levels for these types of hematologic malignancies. ASH specifically suggests that the Agency consider a provision in the guidance suggesting that the effect of MRD be assessed in the context of both TP53 aberration (17p deletion and/or TP53 mutation) and IGHV mutational status, when possible (i.e. that information should be obtained and analyses take it into account).

  - In lines 295-299, the guidance infers that the sensitivity of MRD assays should be at least "10-fold below the clinical decision-making threshold." This level of sensitivity may not be required for AML and acute lymphoblastic leukemia (ALL). For example, in AML and ALL, several institutions and laboratories have determined that sensitivity levels for flow cytometry-based assays of 0.1% (for AML) (Loken et al., 2012; Pui et al., 2015; Rubnitz et al., 2010) (and 0.01% (for ALL) (Coustan-Smith et al., 2000) are clinically significant and reliable for MRD

detection. ASH recommends that the FDA consider elaborating on its recommendation for a 10-fold increase in the sensitivity of assays used to detect MRD in AML, because the guidance as written could put into question the validity of all existing flow cytometry-based assays used to detect MRD in these leukemias. In addition, ASH recommends that the FDA consider referring to the following consensus paper (Schuurhuis et al., 2018) to help shape its technical recommendations for MRD assessment in AML.

- ASH recommends that the FDA consider adding a statement to the AML section clarifying that further validation tests should be performed if an MRD negative result is obtained from a hemodilute bone marrow aspirate. This is because results from such samples are not affirmative of potential relapse and can be inconclusive.

- The guidance currently states in lines 321-323 that investigators should "evaluate the potential for the flow assay to detect normal bone marrow cells that are regenerating after chemotherapy to reduce the likelihood that those cells are misinterpreted as abnormal cells." To avoid misinterpretation of this recommendation by investigators assessing MRD in leukemias, the Society recommends that the FDA consider updating the guidance to include a statement in the leukemia section that states that investigators should *evaluate the potential for the flow assay to distinguish leukemic cells from normal bone marrow cells that are regenerating after chemotherapy to reduce the likelihood that normal regenerating B cells are misinterpreted as abnormal cells*.

- In the ALL section of the guidance (lines 394-395) the FDA notes that an MRD level of 0.1% or more is accepted as the threshold to define patients with ALL in first or second CR with a high risk of relapse. While this is true of the adult patient population with ALL, in the pediatric setting, investigators currently use a threshold of 0.01% or more (at the end of remission induction) to define children with ALL who might have a high risk of relapse. As such, the Society recommends that the FDA consider changing the threshold to 0.001% in the guidance recommendations for assessing MRD in the pediatric patient population (Pui et al., 2015; Pulsipher et al, 2015).

- In chronic lymphocytic leukemia (CLL), there is evidence to support the fact that MRD does not necessarily predict a patient's outcome regardless of pretreatment characteristics (Nastoupil & Flowers, 2012) especially since factors such as the absence or presence of certain genetic mutations could play a role in a patient's likelihood of relapse. For example, after a chemoimmunotherapy regimen, the likelihood of relapse for a CLL patient with unmutated *IGHV* who has undetectable MRD is much higher than the likelihood of that relapse for a CLL patient with mutated *IGHV*. To that end, ASH recommends that the FDA consider revising the CLL section of the guidance to address the role of pretreatment characteristics (e.g., genomics) and MRD in predicting a patient's outcome. (Thompson et al., 2016).

- **<u>Multiple Myeloma</u>**
  - In general, ASH is supportive of the multiple myeloma-specific recommendations noted in the draft guidance. MRD-negative status after treatment for newly diagnosed multiple myeloma has been shown to be associated with long term survival (Munshi et al., 2017)). ASH suggests that the FDA consider the Society's general recommendations referenced above (e.g.

definitions, validation, and setting) when revising the multiple myeloma section of the guidance.

- **Lymphoma**
  - While the FDA does not include any recommendations for MRD assessment in lymphoma, the Society recommends that the FDA consider including additional guidance on MRD use in non-Hodgkin lymphoma (NHL) and addressing how investigators should further evaluate potential risks of relapse in mantle cell lymphoma patients with undetectable MRD. The use of MRD for lymphoma therapy is rapidly changing as new data becomes available. The same principles for assay development, validation and application will hold for patients with NHL, and in diseases that commonly involved the bone marrow such as follicular lymphoma and mantle cell lymphoma.

Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to continuing to work with you on this important priority, to provide further information and to be a resource for the Agency. Please contact ASH Senior Manager, Government Relations and Public Health, Stephanie Kaplan (*skaplan@hematology.org*), or ASH Scientific Affairs Manager, Alice Kuaban, MS (*akuaban@hematology.org*), if we can provide additional information.

Sincerely,

Roy L. Silverstein, MD
President

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