Submitted by: Brian Haas, PhD, Medical Information Lead
Name: Ilan Kirsch, MD, SVP, Translational Medicine
Company/Organization: Adaptive Biotechnologies Corporation
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (206) 279-2414
Email: lkirsch@adaptivebiotech.com
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NCCN Guidelines Panel: Chronic Lymphocytic Leukemia

On behalf of Adaptive Biotechnologies, we request that the NCCN Chronic Lymphocytic Leukemia (CLL) Guideline Panel review and consider the following modifications for the CLL Guidelines.

Rationale

On September, 28, 2018, the clonoSEQ® assay was granted De Novo designation by the FDA as the first and only test for minimal (measurable) residual disease (MRD) in the bone marrow of patients with MM and acute lymphoblastic leukemia (ALL).[1] The analytical and clinical validation studies included more than 40,000 unique MRD measurements demonstrating the precision and reproducibility of the clonoSEQ assay. Additionally, the FDA has publicly recognized the rigor of clonoSEQ validation[2] and has restated the need for a standardized MRD tool to aid in clinical management. Recently, FDA published a draft guidance for the use of MRD in hematologic malignancies to support drug development,[3] and this guidance follows three new drug labels that incorporate MRD data.[4-6]

Along with MM and ALL, CLL is another disease state where MRD is clinically relevant. Importantly, the clonoSEQ assay used to assess MRD in patients with CLL is identical to that used to measure MRD in MM and ALL, and the 2018 iwCLL Guidelines note specifically that clonoSEQ is well standardized and has undergone critical evaluation as a technique for assessing MRD.[7]

In addition to using next-generation sequencing (NGS) for determination of MRD, some NGS assays demonstrate the capability to measure somatic hypermutation (SHM) and define/identify specific V segments expressed in the transformed clone. SHM and IgH V-segment utilization have prognostic significance.[7] In some settings, knowledge of SHM and V-segment utilization can be used either as part of the essential work-up or as useful in certain circumstances. Thus, immune receptor NGS analysis of a CLL patient's blood or bone marrow sample can provide useful diagnostic information and baseline disease biomarker identification needed for subsequent sequence-based MRD determination.

Because of clonoSEQ's rigorous analytic validation and the publication of other clinical data since Version 4.2019 of the CLL Guidelines, we believe it is appropriate to update the Discussion section to include published clinical data that demonstrate the general importance of MRD and, in some cases, the specific use of clonoSEQ in patients with CLL.[8-13] Specifically, a recent meta-analysis of 2,457 patients with CLL revealed that undetectable MRD (U-MRD) status was associated with significantly better PFS overall ($P < 0.001$) and in patients who achieved conventional complete remission ($P = 0.01$). For overall survival (OS), U-MRD predicted longer OS ($P < 0.001$).[12] These findings underscore the integration of MRD assessment as an end point in clinical trials of CLL. Furthermore, recent data found that in patients with CLL treated with fludarabine, cyclophosphamide, and rituximab (FCR), a greater depth of remission as assessed by clonoSEQ was associated with superior PFS.[13]

Requested Modifications

- Page 8 (CSLL-1), Version 4.2019: Update Diagnosis, Essential section (suggested updates in *red*):

    – Clonality of B-cells should be confirmed by flow cytometry *or Ig DNA nucleotide sequence-based analysis.*

    – *Determination of SHM or V-segment utilization by sequence-based analysis may provide relevant information at diagnosis and provide a marker for subsequent tracking of residual disease during the continuum of care.*

- Page 23 (CSLL-D; 4 of 6), Version 4.2019: Update footnote "m" to include the following (suggested updates in *red*): Minimal residual disease (MRD) evaluation with a sensitivity of 10^{-4} according to the standardized ERIC method *or standardized next-generation sequencing (NGS) method*.

- Page 26 (CSLL-E), Version 4.2019: Update to include a footnote to the Marrow and Blood Lymphocyte parameters that NGS-based MRD methods can also be used to assess response after treatment.

- Discussion section, Version 4.2019: update the discussion of use of MRD in patients with CLL to reflect recent meta-analysis in patients with CLL showing the prognostic utility of MRD[12] and recent clinical data of clonoSEQ in patients with CLL.[8-11,13]

References

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