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Date of request: Tuesday, May 12, 2020
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 to the CLL Guidelines.

Rationale

In 2018, the clonoSEQ® Assay was cleared by the FDA for the assessment of minimal residual disease (MRD) in the bone marrow of patients with multiple myeloma and acute lymphoblastic leukemia.¹ clonoSEQ is the first and only test approved for MRD assessment in these malignancies. The FDA has publicly recognized the rigor of clonoSEQ validation and has restated the need for a standardized MRD tool to aid in clinical management.² clonoSEQ is also available as a laboratory-developed test (LDT) for use in other malignancies, such as CLL, and other sample types, such as peripheral blood. The clonoSEQ Assay B-Cell Reagent Set is CE marked as in vitro diagnostic (IVD) for assessing the MRD status and changes in disease burden during and after treatment in B-cell malignancies in DNA extracted from blood and/or bone marrow samples.

A recent, in-review (at the time of this writing) publication highlights the analytical validation of the clonoSEQ Assay using samples from MM, ALL, and CLL, underscoring the standardization of the Assay in these disease states.³ In addition, clearance of clonoSEQ for use in MRD assessment in CLL is currently under review by the FDA. We note that the 2018 iwCLL Guidelines, it is specifically stated that that clonoSEQ is well standardized and has undergone critical evaluation as a technique for assessing MRD.⁴

To ensure that all patient populations have access to the most standardized and specific technologies, Adaptive Biotechnologies has secured a positive coverage determination by Medicare and will continue to pursue private payer coverage policies, thus removing a patient access barrier.⁵

Because of clonoSEQ's FDA authorization and the publication of new clinical data, we believe it would be useful to update the Discussion section to include published data that demonstrate use of clonoSEQ in patients with CLL. These data have shown that across a variety of patient populations and MRD timepoints, undetectable MRD (U-MRD), is predictive of clinical outcomes.⁶⁻¹⁰ In addition, a recent meta-analysis 2,088 patients with CLL revealed that undetectable MRD (U-MRD) status was associated with significantly better PFS ($P < 0.001$) and overall survival ($P < 0.0001$), underscoring the importance of MRD across trial populations.¹¹

Requested Modifications (based off version 4.2020)

- Page 7 (CSLL-1): Update Diagnosis, Essential section (suggested updates in *red*):
 - Add additional language regarding clonality assessment to include sequencing-based tools. "Clonality of B-cells should be confirmed by flow cytometry *or by next-generation Ig DNA nucleotide sequencing analysis.*" Determination of clonality 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 25, (CSLL-E, page 2/2, bullet 1): Update Minimal Residual Disease (MRD) Assessment section (suggested updates in *red*):

- “Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy *and is an important prognostic tool.*” We feel that adding this statement highlights the utility of MRD assessment for prognostication.
- Page 25, (CSLL-E, page 2/2, bullet 2): Update Minimal Residual Disease (MRD) Assessment section (suggested updates in *red*):
 - “Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) and six-color flow cytometry (MRD flow) are the two validated methods used for the detection of MRD at the level of 10^{-4} to 10^{-5} . Next-generation DNA sequencing (NGS)-based assays have been shown to be more sensitive thus allowing for the detection of MRD at the level of 10^{-6} . *A validated and standardized NGS Assay is available for clinical use.*” As the first sentence about ASO-PCR and flow mentions the validation of these methods, we would also like to add mention to NGS being validated as noted in our recent (in-review, but available online) publication that shows the validity of the clonoSEQ Assay in CLL.³
- Discussion section, Version 4.2020 update the discussion of use of MRD in patients with CLL to reflect a recent meta-analysis in patients with CLL showing the prognostic utility of MRD¹¹ and recent clinical data of clonoSEQ in patients with CLL.⁶⁻¹¹

References

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