

Submitted by: Audrey Demaree, PharmD, Senior Manager, Medical Affairs
Name: Lance Baldo, MD, Chief Medical Officer
Company/Organization: Adaptive Biotechnologies Corporation
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (206) 693-2224
Email: lbaldo@adaptivebiotech.com
Date of request: Wednesday, September 30, 2020
NCCN Guidelines Panel: Chronic Lymphocytic Leukemia



On behalf of Adaptive Biotechnologies, we would like to request an ad hoc review by the NCCN Chronic Lymphocytic Leukemia (CLL) Guideline Panel due to the recent FDA clearance of the clonoSEQ Assay for minimal residual disease (MRD) detection in CLL.

Rationale

On August 5, 2020, the U.S Food and Drug Administration (FDA) granted clearance of the clonoSEQ Assay to assess MRD in patients with CLL using blood or bone marrow samples. The expanded intended use for clonoSEQ was based on analytical validation data, which demonstrates the accuracy, reproducibility, and standardization of the assay, and clinical validation data, which highlights the ability of clonoSEQ to predict clinical outcomes.¹⁻²

Clinical validation was assessed in two studies, CLL14 (NCT02242942) and a study from MD Anderson Cancer Center (NCT00759798).^{3,4} In CLL14, MRD was assessed by clonoSEQ from 337 patients using bone marrow samples three months after the completion of therapy. Results showed that clonoSEQ, assessed at a sensitivity threshold of 10^{-5} , was predictive of progression-free survival ($P=3.075 \times 10^{-19}$).¹ In the second study, MRD was assessed in 111 CLL patients after the completion of therapy in both the peripheral blood and bone marrow. At each MRD threshold assessed (10^{-4} , 10^{-5} , 10^{-6}), clonoSEQ was significantly predictive of progression-free survival in both the blood and bone marrow.¹

Considering this latest clearance, we would like to make the following recommendations:

Requested Modifications (based off version 4.2020)

- **Request made in May 2020:**
 - 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.”**
- **Updated requested:**
 - 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 FDA cleared 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 mention that NGS is validated per our recent FDA clearance.¹

References

1. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2018.
<https://www.clonoseq.com/technical-summary>
2. Ching T, et al. *BMC Cancer*. 2020;20:612.
3. A study to Compare the Efficacy and Safety of Obinutuzumab + Venetoclax (GDC-0199) Versus Obinutuzumab + Chlorambucil in Participants With Chronic Lymphocytic Leukemia (CLL14), NCT02242942.
4. Prospective Identification of Significant Prognostic Factors in Patients Treated With Fludarabine, Cyclophosphamide, and Rituximab (FCR) as Initial Therapy for Chronic Lymphocytic Leukemia (MDA2008-0431), NCT00759798.