Submitted by: Lori K. Pender, PharmD, MPH, BCOP, Associate Director, Medical Affairs
Name: Thomas Manley, MD, Vice President, Clinical Development and Medical Affairs
Company/Organization: Adaptive Biotechnologies
Address: 1551 Eastlake Ave East, #200 Seattle, WA 98102
Phone: (855) 466-8667
Email: tmanley@adaptivebiotech.com
Date of request: Wednesday, May 19, 2021
NCCN Guidelines Panel: Pediatric ALL

On behalf of Adaptive Biotechnologies, we respectfully request that the NCCN Pediatric Acute Lymphoblastic Leukemia (ALL) Guideline Panel review and consider the following modifications regarding minimal residual disease (MRD) testing, which would align the recommendations with those in the Adult ALL Guidelines.[1,2]

## Specific Changes:

- PEDALL-1: Change "Baseline characterization of leukemic clone to facilitate subsequent minimal residual disease analysis" to the same language seen on page ALL-1 of the Adult ALL guidelines: "Baseline flow cytometric and/or molecular characterization of leukemic clone to facilitate subsequent minimal/measurable residual disease (MRD) analysis (see PEDALL-I)"
- PEDALL-H: Add the same Note found on page ALL-E of the Adult ALL guidelines under the bullet "Overall response rate (ORR = CR + CRi)" that reads: "NOTE: MRD assessment is not included in the morphologic assessment and should be obtained (see PEDALL-I)"
- PEDALL-I: A general comparison of the text on this page and the text on page ALL-F of the Adult ALL guidelines may be warranted; specific changes to consider include:
    - Update the 2nd bullet to include the desired sensitivity threshold, consistent with the Adult ALL guidelines, "…If validated MRD assessment technology with appropriate sensitivity (at least $10^{-4}$) is not available locally, there are commercially available tests."
    - Update the 7th bullet to be consistent with the Adult ALL guidelines, which reads, "Current 6-color flow cytometry can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ (<0.01%) bone marrow mononuclear cells (MNCs). PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ (<0.0001%) bone MNCs. The concordance rate for detecting MRD between these methods is generally high. Methods not achieving these sensitivity levels are not suitable."
    - Update the sub-bullet on "Timing of MRD assessment" to read that, "For some techniques, a baseline sample (i.e., prior to treatment) is needed to characterize the leukemic clone for subsequent MRD assessment." This change would differ from that in the Adult ALL guidelines and should be considered as an update there as well.

FDA Clearance: clonoSEQ® is an NGS *in vitro* diagnostic test service provided by Adaptive Biotechnologies and cleared to detect MRD in bone marrow from patients with MM or B-cell ALL and blood or bone marrow from patients with CLL.[3]

Rationale: The same concepts and principles apply to MRD assessment in children, young adults, and adults; therefore, where possible, the language in the two sets of guidelines should be similar, if not identical, to facilitate understanding by clinicians who may treat ALL across the lifespan.

## References

1. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Pediatric Acute Lymphoblastic Leukemia. Version 2.2021 – October 22, 2020. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Acute Lymphoblastic Leukemia. Version 1.2021 – April 6, 2021. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf.
3. clonoSEQ®. Seattle, WA: Adaptive Biotechnologies Corporation; 2020. https://www.clonoseq.com/technical-summary.