

Positive Quality Intervention: clonoSEQ Next Generation Sequencing for Minimum Residual Disease Testing in Chronic Lymphocytic Leukemia

Description: This document will outline the applicability, process, and importance of clonoSEQ Next Generation Sequencing for minimal residual disease (MRD).

Background: The use of MRD status for clinical evaluation and recommendations regarding the assessment of disease burden during management of Chronic Lymphocytic Leukemia (CLL) was included in International Workshop on CLL and NCCN guidelines. Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the treatment is an important predictor of treatment efficacy and can assist with treatment decisions. clonoSEQ is the first MRD test approved by FDA for multiple myeloma, CLL, and B-ALL.

PQI Process:

- For fixed-duration targeted therapies:
 - Initial diagnosis
 - Clonality ID test (using fresh or archival sample) to establish patient-specific sequences to track throughout the course of treatment
 - Combination therapy of CD20 monoclonal antibody with BCL-2 targeted therapies x 6 cycles
 - MRD tracking test (post cycle 6)
 - Single agent therapy x 6 cycles
 - MRD tracking test (post cycle 9 and post cycle 12)
 - Follow- up phase: Serial MRD monitoring (at least every 3 months post-treatment to determine disease kinetics; every 3-6 months thereafter for surveillance)
- For chemoimmunotherapy regimen:
 - Initial diagnosis
 - Clonality ID test (using fresh or archival sample) to establish patient-specific sequences to track throughout the course of treatment
 - IGHV mutation analysis parallel with Clonality ID with the same sample
 - During treatment (MRD tracking test usually after 3 cycles of a 6 cycles regimen)
 - Post end of treatment (MRD tracking test usually after cycle 6)
 - Serial MRD monitoring on annual basis
- Sample order sets for EMR:
 - clonoSEQ Clonality ID, archived specimen
 - Specimen: Upon request within the clonoSEQ ordering portal, Adaptive can assist in retrieving an archived pathology specimen; this should be a high disease burden specimen representative of the patient's malignancy
 - Action: If utilizing the pathology retrieval service through Adaptive, place Clonality ID Test order in Adaptive portal, then fax clonoSEQ requisition form and a copy of the patient's diagnostic pathology report to Adaptive (866) 623-4408 or email the materials to clinicalservices@adaptivebiotech.com
 - clonoSEQ Clonality ID, fresh peripheral blood
 - Specimen: fresh peripheral blood, 2 mL in an EDTA tube; this should be a high disease burden specimen representative of the patient's malignancy*
 - Action: Prepare 2 mL fresh peripheral blood in an EDTA tube

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. *Updated 3.25.22*



- Patient navigators will place a Clonality ID order via the clonoSEQ diagnostic Portal and upload a copy of the requisition to the patient chart
- Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
- clonoSEQ Clonality ID, fresh bone marrow aspirate
 - Specimen: fresh bone marrow aspirate, 1 mL in an EDTA tube; this should be a high disease burden specimen representative of the patient's malignancy*
 - Action: prepare 1 mL fresh bone marrow aspirate in an EDTA tube
 - Patient navigators will place a Clonality ID order via the clonoSEQ diagnostic Portal and upload a copy of the requisition to the patient chart
 - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
- clonoSEQ MRD tracking, fresh bone marrow
 - Specimen: fresh bone marrow aspirate, 1 mL in an EDTA tube
 - Action: prepare 1 mL fresh bone marrow aspirate in an EDTA tube
 - Patient navigators will place an MRD Tracking order via the clonoSEQ Diagnostic portal and upload a copy of the requisition to the patient chart
 - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in Adaptive kit for send out
- clonoSEQ MRD tracking, fresh peripheral blood
 - Specimen: fresh peripheral blood, 2 mL in an EDTA tube*
 - Action: Prepare 2 mL fresh peripheral blood in an EDTA tube
 - Patient navigators will place an MRD tracking order via the clonoSEQ diagnostic portal and upload a copy of the requisition to the patient chart
 - Medical assistants will include specimen and a printed copy of the clonoSEQ test requisition in adaptive kit for send out

Patient Centered Activities:

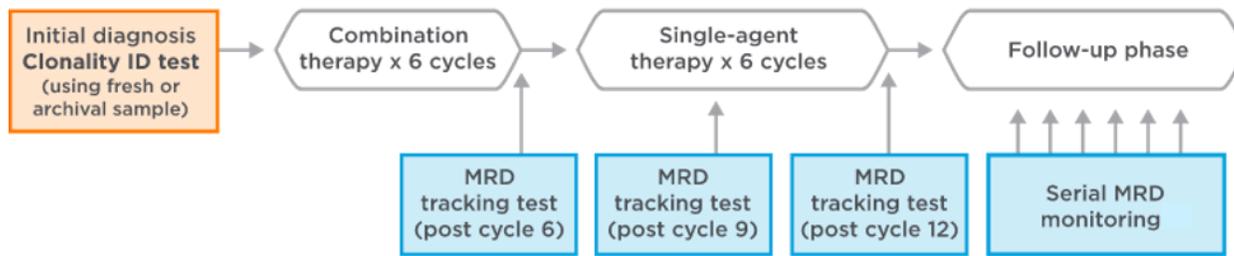
- Educate the patient on the importance of MRD testing:
 - MRD refers to the small number of cancer cells that can remain in the body during and after treatment and is one of the strongest predictors of outcomes in blood cancer
 - Consistent monitoring during and after fixed-duration therapy allows monitoring of peripheral blood as an alternative to frequent bone marrow assessments
 - clonoSEQ can detect one single cancer cell among a million healthy cells
- Communicate results, assessing treatment response and detecting changes in disease
- Ensure patient and physicians on understanding ongoing cancer journey and long-term outcomes
- Patient Assistance: [NCODA Financial Assistance Tool](#)

* Regarding specimen handling process: ship overnight for next day 10:30 AM PT delivery; if same-day shipment is not an option, store specimen refrigerated; fresh specimens stored at ambient temperature should arrive at Adaptive within 4 days of collection, specimens stored refrigerated should arrive at Adaptive within 7 days of collection; ship frozen blood overnight on dry ice Mon-Thurs only, for next day 10:30 AM PT delivery.

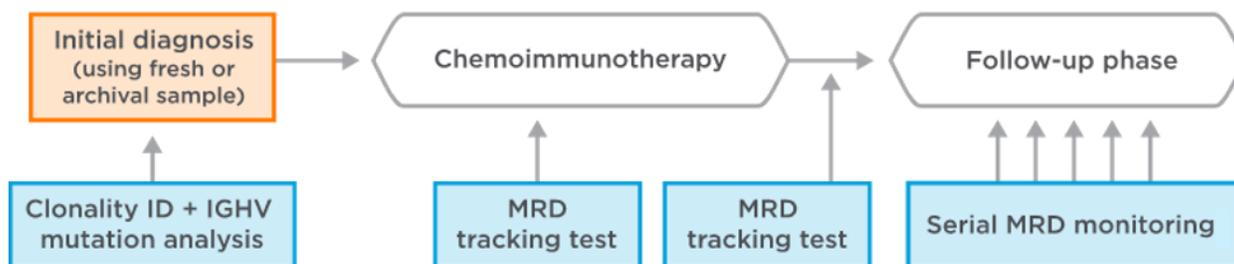
Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. Updated 3.25.22

Supplemental Information:

Potential MRD patient pathway for fixed-duration therapy in CLL
(based on CLL14)



Potential MRD patient pathways during CIT regimens in CLL
(based on CLL8, CLL10, CLL11, COMPLEMENT-1, and NCT00759798)



References:

1. clonoSEQ®. [technical summary]. Seattle, WA: Adaptive Biotechnologies; 2020.
2. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2020;21(9):1188-1200.
3. Al-Sawaf O, Zhang C, Robrecht S, et al. Clonal dynamics after venetoclax-obinutuzumab therapy: Novel insights from the randomized, phase 3 CLL14 trial. *Blood.* 2020;136(Suppl 1):22-23.
4. Al-Sawaf O, Zhang C, Tandon M, et al. Characteristics and outcome of patients with chronic lymphocytic leukaemia and partial response to venetoclax-obinutuzumab. *Blood.* 2020;136(Suppl 1):1310. <https://ash.confex.com/ash/2020/webprogram/Paper134865.html>.
5. ClinicalTrials.gov. Comparison of the Treatments of Obinutuzumab + Venetoclax Versus Obinutuzumab + Chlorambucil in Patients With Chronic Lymphocytic Leukemia (NCT02242942). <https://clinicaltrials.gov/ct2/show/NCT02242942>. Accessed October 14, 2021.
6. ClinicalTrials.gov. Venetoclax-Obinutuzumab +/- Acalabrutinib in R/R CLL (NCT04560322). available at: <https://clinicaltrials.gov/ct2/show/NCT04560322>. Accessed October 14, 2021.
7. Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol.* 2016;17(7):928-942.
8. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. *N Engl J Med.* 2014;370(12):1101-1110.
9. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet.* 2015;385(9980):1873-1883.
10. Thompson PA et al. Leukemia. 2018;32(11):2388-23. Serial minimal residual disease (MRD) monitoring during firstline FCR treatment for CLL may direct individualized therapeutic strategies.
11. Thompson PA, Srivastava J, Peterson C, et al. Minimal residual disease undetectable by next-generation sequencing predicts improved outcome in CLL after chemoimmunotherapy. *Blood.* 2019;134(22):1951-1959.
12. Strati P, Keating MJ, O'Brien SM, et al. Eradication of bone marrow minimal residual disease may prompt early treatment discontinuation in CLL. *Blood.* 2014;123(24):3727-3732.
13. Böttcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. *J Clin Oncol.* 2012;30(9):980-988.

Important notice: NCODA has developed this Positive Quality Intervention platform. This platform represents a brief summary of medication uses and therapy options derived from information provided by the drug manufacturer and other resources. This platform is intended as an educational aid and does not provide individual medical advice and does not substitute for the advice of a qualified healthcare professional. This platform does not cover all existing information related to the possible uses, directions, doses, precautions, warning, interactions, adverse effects, or risks associated with the medication discussed in the platform and is not intended as a substitute for the advice of a qualified healthcare professional. The materials contained in this platform are for informational purposes only and do not constitute or imply endorsement, recommendation, or favoring of this medication by NCODA, which assumes no liability for and does not ensure the accuracy of the information presented. NCODA does not make any representations with respect to the medications whatsoever, and any and all decisions, with respect to such medications, are at the sole risk of the individual consuming the medication. All decisions related to taking this medication should be made with the guidance and under the direction of a qualified healthcare professional. Updated 3.25.22