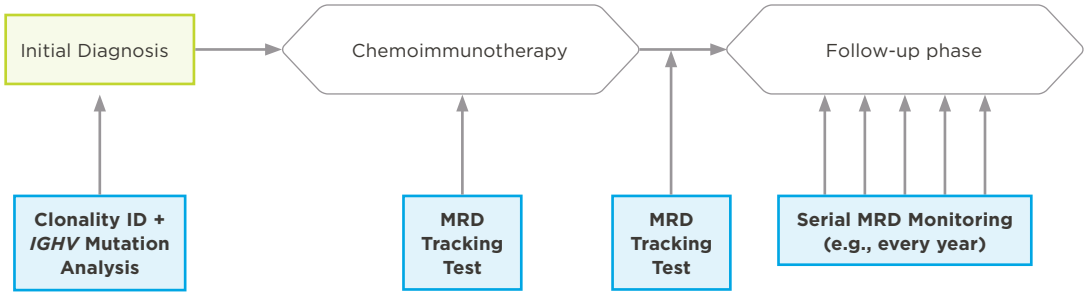
CLONOSEQ MRD TESTING AND CHEMOIMMUNOTHERAPY (CIT) TREATMENT REGIMENS IN CLL: A POTENTIAL CLINICAL PATHWAY

Based on available evidence, the following clinical strategy reflects a potential approach for integrating clonoSEQ® MRD testing into the management of patients with IGHV-mutated or IGHV-unmutated CLL using various chemoimmunotherapy regimens.*

Key Takeaways

- Perform clonality (ID) assessment at time of diagnosis to establish patient-specific sequences to track throughout the course of treatment.
  - » Use a fresh blood or marrow sample collected prior to initiation of treatment.
- Perform molecular analysis to determine IGHV mutation status.[1,2,3,4,5]
  - » Utilize clonoSEQ to enable parallel processing of IGHV mutation analysis and clonality (ID) assessment from a single specimen.**
- Assess MRD in peripheral blood or bone marrow at interim staging (typically after cycle 3 of a 6-cycle regimen).[6,7,8,9]
- Assess MRD in peripheral blood or bone marrow again at final staging (typically 2-3 months after the beginning of the last treatment cycle).[1,2,3]
- Implement MRD surveillance on an annual basis thereafter.[7]

MRD Patient Pathway during CIT regimens in CLL (based on CLL8, CLL10, CLL11, COMPLEMENT-1, and NCT00759798)[1,2,3,6,7,8,9]



Other testing approaches may be medically appropriate and final testing decisions should be made by the patient's healthcare provider. The results obtained from the clonoSEQ Assay should always be used in combination with the clinical examination, patient medical history, and other findings.

* CIT regimens may potentially include fludarabine, cyclophosphamide, and rituximab (FCR)[10], bendamustine and rituximab (BR)[2], chlorambucil plus obinutuzumab[3], or chlorambucil plus ofatumumab.[3]

** IGHV testing is available for CLL patients as a CLIA-validated laboratory developed test (LDT) and has not be cleared or approved by the FDA.

Adaptive Biotechnologies does not recommend or endorse any particular course of treatment.

Assessment timepoints:

MRD monitoring in many pivotal CLL CIT clinical trials, including CLL8, CLL10, CLL11, COMPLEMENT-1 and NCT00759798 and associated studies, is performed at baseline, during an interim assessment, after final staging (2-3 months post end of treatment), and then monitored on a yearly interval thereafter during follow-up.[1,2,3,6,7,8,9]

Supporting Data, Guidelines and References

The accumulated data generated from CLL8, CLL10, CLL11, COMPLEMENT-1, NCT00759798 and associated studies support the importance of understanding IGHV mutation status and understanding MRD as prognostic indicators for survival outcomes and possible usefulness as early intervention tools prior to relapse.[6,8,9]

Summary of supporting data:

- Undetectable MRD (U-MRD) in either blood or bone marrow is prognostic for PFS and OS regardless of the CIT combination therapy used.[1,2,7,9,11,12]
- clonoSEQ MRD-negativity (i.e., U-MRD at 10^{-6}) is associated with better outcomes regardless of IGHV mutation status.[7]
- Serial monitoring post-therapy discontinuation can be used to assess for potential molecular relapse.[6,7,12]
  - » MRD kinetics (growth rate) in CLL (assessed based on serial monitoring) is prognostic of outcome.[13]
- In patients with U-MRD at end of therapy, early detection of subsequent molecular relapse may allow development of preemptive intervention strategies in patients with R/R CLL.[6]

Summary of guidelines:

- NCCN Clinical Practice Guidelines emphasize that FCR is the preferred first-line therapy option for IGHV-mutated CLL in patients less than 65 years old without significant comorbidities.[5]
- Evidence from clinical trials suggests that U-MRD in the peripheral blood after the end of treatment is an important predictor of treatment efficacy.[5,7]
- NCCN Guidelines dictate that MRD evaluation should be performed using an assay with a sensitivity of 10^{-4}, but also note that next-generation DNA sequencing (NGS)-based assays have been shown to be more sensitive, allowing for the detection of MRD at the level of 10^{-6}.[5]

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clonoSEQ is available as an FDA-cleared *in vitro* diagnostic (IVD) test service provided by Adaptive Biotechnologies to detect minimal residual disease (MRD) in bone marrow from patients with multiple myeloma or B-cell acute lymphoblastic leukemia (B-ALL) and blood or bone marrow from patients with chronic lymphocytic leukemia (CLL). Additionally, clonoSEQ is available for use in other lymphoid cancers and specimen types as a CLIA validated laboratory developed test (LDT). IGHV testing is available as a CLIA-validated LDT. For important information about the FDA-cleared uses of clonoSEQ including test limitations, please visit clonoSEQ.com/technical-summary.

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