Paper DS03

Mapping Minimal Residual Disease (MRD) Biomarker Data in Hematologic Malignancies: Clinical Significance and Data Standards in SDTM and ADaM

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ABSTRACT

Minimal Residual Disease (MRD) is a critical biomarker in hematologic malignancies, representing residual cancer cells that persist in post-treatment and evade detection by conventional diagnostic methods. Studies indicate that MRD negativity is associated with improved event-free survival (EFS) and overall survival (OS).

Mapping MRD data into SDTM domains presents unique challenges due to assay complexity, data variant-specific reporting, and evolving controlled terminology. Domains such as Pharmacogenomics Findings (PF), Genomics Findings (GF), and Laboratory Test Results (LB) are utilized, with SDTMIG 3.4v offering enhanced support for molecular data. In ADaM, MRD data is structured to support longitudinal analysis and survival modeling, with strategies for handling missing data and assay sensitivity thresholds.

This paper explores the clinical relevance of MRD, outlines data collection methodologies, and provides practical guidance for mapping MRD data into SDTM and ADaM. It also highlights challenges and considerations for ensuring data integrity and submission compliance in hematologic studies.

INTRODUCTION

What is a biomarker?

The term biomarker must be measurable, biologically relevant, and clinically meaningful; MRD meets these criteria. MRD stands for Minimal Residual Disease. MRD can be used as a biomarker. It can be quantified as Positive or Negative. Biologically, minimal residual disease (MRD) reflects both the depth of a patient's response to therapy and the remaining disease burden, which is directly associated with the risk of relapse. Clinically, MRD serves as a prognostic biomarker, as MRD negativity is linked to improved Event Free Survival (EFS) and Overall Survival (OS). In addition, MRD functions as a predictive biomarker, since MRD status can be used to guide treatment decisions including whether to intensify or deescalate therapy.

What is MRD?

MRD is increasingly used as a surrogate endpoint in clinical trials for accelerated approvals. It refers to a small number of malignant cells that remain in a patient after treatment, even when the patients appear to be in complete remission or complete response by standard tests. Traditional morphologic evaluation of hematologic malignancies can identify malignant cells only when they constitute roughly one in 100 cells. In contrast, newer analytical platforms can identify very low levels of persisting disease, well below this threshold. This strategy is gaining increasing popularity and is being used across Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia **(**AML), Chronic Myeloid Leukemia (CML), and Multiple Myeloma (MM).

MRD AS A BIOMARKER

A biomarker is something measurable in the body that tells us about normal biology, disease processes, or how a person responds to a treatment. Minimal residual disease (MRD) is one such measurable characteristic, so it can be used as a biomarker.

MRD can serve as several types of biomarkers:

- Diagnostic biomarker: Helps detect a disease or confirm a specific disease subtype.
- Prognostic biomarker: Shows the likelihood of relapses, progression, or other clinical events based on the patient's disease at baseline (before new treatment).
- Predictive biomarker: Indicates whether a patient is more or less likely to benefit from a specific therapy.

- Efficacy response biomarker: Shows whether a biological response has occurred after treatment (for example, a drop in MRD levels).

- Monitoring biomarker: Measured repeatedly over time to track changes in disease burden or detect early relapses.

MRD ASSESSMENT METHODS

MRD assessments vary across laboratories and technologies, leading to potential discrepancies in results. Differences in laboratory developed protocols, assay performance characteristics, and sample collection procedures can all influence MRD measurements. In addition, each technology platform may demonstrate- unique sensitivities, specificities, and operational workflows.

Standardization is therefore essential to ensure consistency and comparability of MRD results across sites and methodologies. This includes harmonized posttreatment time points for bone marrow or blood sample collection, uniform sample processing procedures, predefined MRD thresholds, and transparent reporting of assay performance characteristics. Together, these practices support more reliable interpretation of MRD and enhance its utility in clinical decision making.

Four platforms were considered for MRD assessment:

- Multiparametric flow cytometry (MPFC)

- Next generation sequencing (NGS)

- Quantitative reverse transcription PCR (RT-qPCR) for recurrent gene fusions

- Allele specific oligonucleotide PCR (ASOPCR)

FDA does not favor any specific technological platform for measuring MRD in clinical trials. However, sponsors are expected to clearly prespecify the chosen platform, including the assay procedures, reagents, and analytical approach, and to conduct appropriate analytical validation for its intended context of use. For consistency within a trial, the use of a single MRD- technology is preferred to enable direct comparison of results. Although employing multiple technologies is discouraged, if a trial incorporates more than one platform and the primary analysis will integrate data across these methods, the sponsor should define in advance the approach for combining the results into a single MRD assessment and discuss this strategy with the agency.

AS AN ENDPOINT IN CLINICAL TRIALS

Minimal residual disease (MRD) has emerged as a powerful and increasingly accepted endpoint in oncology clinical trials, particularly in hematologic malignancies, due to its ability to provide an early, sensitive, and biologically meaningful measure of treatment efficacy. Traditional clinical endpoints such as overall survival (OS) or progression free survival (PFS) often require large sample sizes and long follow-up periods to demonstrate benefit, especially in diseases where modern therapies achieve high response rates and prolonged survival.

PRACTICAL TRIAL DESIGN AND ENDPOINT CONSIDERATIONS FOR ACUTE LYMPHOBLASTIC LEUKEMIA (ALL), CHRONIC MYELOID LEUKEMIA (CML), AND MULTIPLE MYELOMA (MM)

Acute Lymphoblastic Leukemia (ALL)

MRD is one of the most important prognostic indicators in ALL, regardless of patient age, immunophenotype, or genetic subtype. Bone marrow is the preferred sample for MRD assessment, and the use of blood samples in clinical trials requires justification. MRD should ideally be evaluated at CR with full blood count recovery. Additionally, when MRD serves as an efficacy endpoint, the absence of extramedullary disease should be confirmed at the same time as bone marrow and blood count assessments.

Chronic Myeloid Leukemia (CML)

Targeting the BCR-ABL1 oncoprotein has led to major advances in clinical outcomes for patients with chronic myeloid leukemia, making MRD detection and monitoring a standard part of care. MRD assessment in CML should use assays reported on the International Scale, which uses a standardized baseline of 100% and expresses molecular response as a log reduction from that baseline. RT-qPCR (IS) is the preferred method for monitoring treatment responses. Major molecular response (MMR) is defined as BCR-ABL1 Internation Scale (IS) less than 0.1% or, when International Scale (IS) reporting is not available, a greater than 3-log reduction from the standardized baseline.

Achieving MMR is associated with superior long-term outcomes and is widely accepted as a key therapeutic goal and indicator of clinical benefit in CML.

Multiple Myeloma (MM)

Significant advances in multiple myeloma treatment have increased interest in using MRD as a surrogate endpoint to accelerate drug development, supported by multiple studies linking MRD status with PFS and OS. Most existing research has focused on newly diagnosed patients after transplant, with far fewer studies in relapsed/refractory disease, non-transplant-eligible newly diagnosed patients, or smoldering myeloma, so the relationship between MRD and clinical benefit must be demonstrated separately in each setting. MRD evaluation should generally be limited to patients in CR, and any assessment in patients with lesser response categories requires justification. Current MRD methods, including MPFC and NGS of bone marrow, do not detect extramedullary disease, prompting interest in integrating imaging techniques such as PET/CT or MRI into response assessments.

MAPPING MRD DATA INTO SDTM DOMAINS

To support consistent analysis, enable cross-study comparability, and ensure regulatory-ready submissions, MRD data should be standardized from diverse operational sources (e.g., central and local laboratory results, assay vendor files, and eCRF data) into CDISC Study Data Tabulation Model (SDTM) version 3.2 structures or later.

In SDTM v3.2 or later, MRD records are mapped to LB, BE, PF, or RS domains depending on the specimen type (e.g., bone marrow aspirate or peripheral blood) and the collection/assessment method. These attributes determine the most appropriate SDTM domain for representing the MRD result.

Biospecimen Events

BE domain captures whether MRD specimen is collected, type of specimen (e.g., bone marrow aspirates or peripheral blood), the collection method, location, category, sample collection date/time and condition needed for the traceability.

Laboratory Test Results

LB domain when the lab is reporting MRD results, whether they are qualitative (e.g., detected/not detected or positive/negative) and/or quantitative (e.g., a value expressed as cells per 10^3 or 10^4), along with the associated test identification, method (NGS), specimen matrix, and timing.

Disease Response

RS domain when MRD is being represented as a protocol-defined endpoint/response assessment (for example, an MRD response/status at a specific threshold such as “MRD-negative at 10^{-4} “ at a given timepoint, MRD remission, or an endpoint like MRD negativity rate that supports the primary endpoint), because RS is meant to store response classifications.

Pharmacogenomics/Genetics Findings

In SDTM v3.2, BCR:ABL1 MRD measured by quantitative RT-qPCR in ALL and CML indications maps most appropriately to the Pharmacogenomics/Genetics Findings (PF) domain because the underlying measurand is a molecular, gene-expression endpoint, that is looking for the presence of a fusion transcript (e.g., e1a2, e13a2, e14a2) rather than a routine clinical laboratory analyte. PF is the findings domain intended for gene expression and genetic variation results, so it provides the best semantic “home” for transcript-based MRD along with its essential context (target/transcript, specimen such as peripheral blood vs bone marrow aspirate, method RT-qPCR, and performing lab). From a modeling perspective, MRD is best represented as atomic findings each reported endpoint raw copy number, normalized BCR::ABL1/ABL1 ratio (often unitless), %IS(International Scale) when available, and log reduction should be captured as a separate PF test/record for the same subject/timepoint/specimen, which preserves clarity of units, interpretation and supports analysis and traceability. This approach also handles common MRD qualifiers cleanly (e.g., not detected, below LOD/LOQ) by storing the character result when a numeric is not valid, while maintaining method and specimen information that materially affect comparability across timepoints and labs; although MRD results are produced by a laboratory, domain choice is driven by what is measured (a transcript expression signal), which is why PF is preferable to LB domain for RT-qPCR BCR:ABL1 MRD.

STUDYID	DOMAIN	USUBJID	PFSEQ	PFREFID	PFSPID	PFTESTCD	PFTEST	PFTSTDTL	PFGENRI	PFGENTYP	PFCAT	PFSCAT
AB-1001	PF	PT-1001	1	30001087	e1a2	DETECT	Detection	e13/14a2	ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	2	30001087	e1a2	DETECT	Detection	e1a2	ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	3	90001087	e1a2	DETECT	Detection	e1a2	ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	4	30001087	e1a2	DETECT	Detection	e13/14a2	BCR-ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	5	30001087	e1a2	DETECT	Detection	e1a2	BCR-ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	6	90001087	e1a2	DETECT	Detection	e1a2	BCR-ABL	GENE	GENETIC EXPRESSION	RAW
AB-1001	PF	PT-1001	7	30001087	e1a2	DETECT	Detection	e13/14a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	PERCENT
AB-1001	PF	PT-1001	8	30001087	e1a2	DETECT	Detection	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	PERCENT
AB-1001	PF	PT-1001	9	90001087	e1a2	DETECT	Detection	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	PERCENT
AB-1001	PF	PT-1001	10	30001087	e1a2	DETECT	Detection	e13/14a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	PERCENT
AB-1001	PF	PT-1001	11	30001087	e1a2	MR3	Molecular Response 3	e13/14a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS
AB-1001	PF	PT-1001	12	30001087	e1a2	MR3	Molecular Response 3	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS
AB-1001	PF	PT-1001	13	90001087	e1a2	MR3	Molecular Response 3	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS
AB-1001	PF	PT-1001	14	30001087	e1a2	MRD	Minimal Residual Disease	e13/14a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS
AB-1001	PF	PT-1001	15	30001087	e1a2	MRD	Minimal Residual Disease	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS
AB-1001	PF	PT-1001	16	90001087	e1a2	MRD	Minimal Residual Disease	e1a2	BCR-ABL/ABL	GENE	GENETIC EXPRESSION	STATUS

PFORRES	PFORRESU	PFSTRESC	PFSTRESN	PFSTRESU	PFSTAT	PFNAM	PFSPEC	PFMETHOD	VISITNUM	VISIT	EPOCH	PFDTC	PFDY
27564		27564	27564			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
37185		37185	37185			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
343783		343783	343783			MolecularMD, OR	BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
1		1	1			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
127		127	127			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
208131		208128	208128			MolecularMD, OR	BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
0.003624		0.00365444	0.003654			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
0.337164		0.337164	0.337164			MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
60.5205		60.5205	60.5205			MolecularMD, OR	BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
0.00412	International Scale	0.00412	0.00402	International Scale		MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
Y		Y				MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
N		N				MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
N		N				MolecularMD, OR	BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
Y		Y				MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
N		N				MolecularMD, OR	PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8
N		N				MolecularMD, OR	BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYMERASE CHAIN REACTION	-1	SCREENING	SCREENING	27-Feb-2020	-8

Table 1- MRD data mapping into PF domain in SDTM3.2v

Genomics Findings

In SDTMIG v3.4, the earlier provisional Pharmacogenomics/Genetics Findings domain (PF) is no longer the recommended structure for genomics results; instead, genomics and gene-expression type results are represented in the Genomics Findings (GF) domain, so RT-qPCR MRD measurements for BCR:ABL1 transcripts in ALL and CML (including transcript types such as e1a2/e13a2/e14a2) should be mapped to GF. Practically, you would create separate GF records for each reported MRD endpoint at a given timepoint and specimen (e.g., one record for raw copies if collected, one for the BCR::ABL1/ABL1 ratio, and one for log reduction, and similarly separate records for peripheral blood vs bone marrow aspirate), capturing the test in GFTESTCD/GFTEST, the original and standardized results in GFORRES/GFSTRESC (and GFSTRESN when numeric) with appropriate units, and the analytic context in fields such as specimen (GFSPEC) and method (GFMETHOD, e.g., quantitative RT-PCR), along with timing (GFDTC) and identifiers. All the variables are directly renamed from PF to GF for MRD data, other than PFGENRI and PFGENTYP to GFSYM and GFSYMTYP.

STUDYID	DOMAIN	USUBJID	GFSEQ	GFREFID	GFSPID	GFCAT	GFSCAT	GFTESTCD	GFTEST	GFTSTDTL	GFORRES	GFORRESU
AB-1001	GF	PT-1001	1	30001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e13/14a2	27564	
AB-1001	GF	PT-1001	2	30001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e1a2	37185	
AB-1001	GF	PT-1001	3	90001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e1a2	343783	
AB-1001	GF	PT-1001	4	30001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e13/14a2	1	
AB-1001	GF	PT-1001	5	30001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e1a2	127	
AB-1001	GF	PT-1001	6	90001087	e1a2	GENETIC EXPRESSION	RAW	DETECT	Detection	e1a2	208131	
AB-1001	GF	PT-1001	7	30001087	e1a2	GENETIC EXPRESSION	PERCENT	DETECT	Detection	e13/14a2	0.003624	
AB-1001	GF	PT-1001	8	30001087	e1a2	GENETIC EXPRESSION	PERCENT	DETECT	Detection	e1a2	0.337164	
AB-1001	GF	PT-1001	9	90001087	e1a2	GENETIC EXPRESSION	PERCENT	DETECT	Detection	e1a2	60.5205	
AB-1001	GF	PT-1001	10	30001087	e1a2	GENETIC EXPRESSION	PERCENT	DETECT	Detection	e13/14a2	0.00412	International Scale
AB-1001	GF	PT-1001	11	30001087	e1a2	GENETIC EXPRESSION	STATUS	MR3	Molecular	e13/14a2	Y	
AB-1001	GF	PT-1001	12	30001087	e1a2	GENETIC EXPRESSION	STATUS	MR3	Molecular	e1a2	N	
AB-1001	GF	PT-1001	13	90001087	e1a2	GENETIC EXPRESSION	STATUS	MR3	Molecular	e1a2	N	
AB-1001	GF	PT-1001	14	30001087	e1a2	GENETIC EXPRESSION	STATUS	MRD	Minimal R	e13/14a2	Y	
AB-1001	GF	PT-1001	15	30001087	e1a2	GENETIC EXPRESSION	STATUS	MRD	Minimal R	e1a2	N	
AB-1001	GF	PT-1001	16	90001087	e1a2	GENETIC EXPRESSION	STATUS	MRD	Minimal R	e1a2	N	

GFSTRESC	GFSTRESN	GFSTRESU	GFSTAT	GFSPEC	GFMETHOD	GFNAM	VISITNUM	VISIT	EPOCH	GFDTC	GFDY
27564	27564			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
37185	37185			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
343783	343783			BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
1	1			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
127	127			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
208128	208128			BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
0.0036544	0.003654			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
0.337164	0.337164			PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
60.5205	60.5205			BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
0.00412	0.00402	International Scale		PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
Y				PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
N				PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
N				BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
Y				PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
N				PERIPHERAL BLOOD	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8
N				BONE MARROW	QUANTITATIVE REVERSE TRANSCRIPTASE POLYME	MolecularMD, OR	-1	SCREENIN	SCREENIN	2020-02-2	-8

Table 2- MRD data into GF Domain in SDTM 3.4v

INDUCTION–CONSOLIDATION–MAINTENANCE PHASES FOR ANALYSIS

In cancer treatment, especially hematologic malignancies - therapy is often organized into three sequential phases: Induction, Consolidation, and Maintenance. Each phase has a distinct goal and intensity.

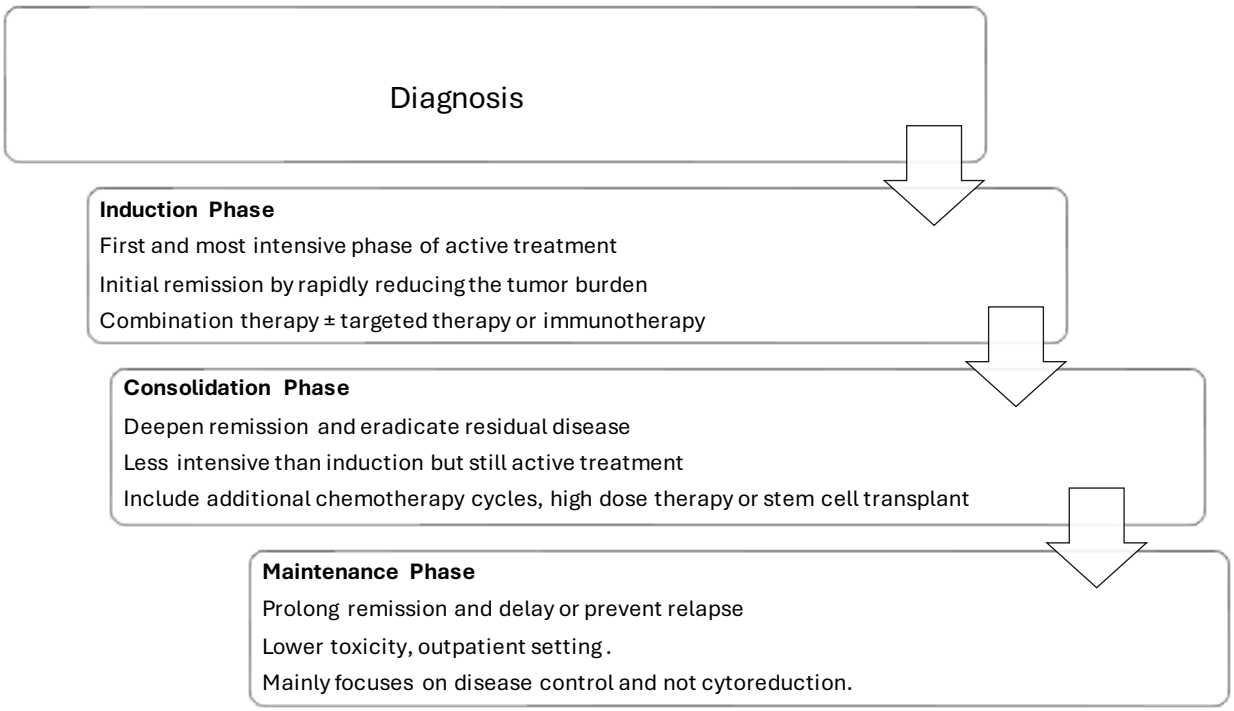

Figure 1: Sequential phases in cancer therapy treatment

Induction Phase

The goal of the induction phase is an initial remission by rapidly reducing the tumor burden. This is the first and most intensive phase of active treatment after diagnosis. It aims to eliminate as many malignant cells as possible, restore normal blood counts, and achieve complete response (CR) or very good partial response (VGPR). The typical characteristics include Combination chemotherapy ± targeted therapy or immunotherapy, Higher toxicity risk, close monitoring (often inpatient for leukemias).

Consolidation Phase

The goal is to deepen remission and eradicate residual diseases (including MRD). The consolidation phase is given after successful induction. This is less intensive than induction but still active treatment. It targets microscopic diseases not detected by routine methods and often aims for MRD negativity. MRD status after consolidation is often highly prognostic. The typical characteristics of the consolidation phase include short and defined duration and may consist of additional chemotherapy cycles, high dose therapy, and stem cell transplant (autologous or allogenic).

Maintenance Phase

The goal of this phase is to prolong remission and delay or prevent relapses. This is the longest phase, lowest intensity, and given only after remission is achieved. This focuses on disease control and not cytoreduction. It has a long duration (months to years) and lower toxicity in an outpatient setting.

Relationship with MRD

In Induction Phase, MRD is often still positive, while the consolidation phase is a key phase for achieving MRD negativity. The maintenance phase aims to sustain MRD negativity. This is the reason MRD analyses are frequently done at either end of Induction or post-consolidation/post-transplant. During maintenance, stats often look for landmark analyses or exploration analyses.

MAPPING MRD DATA INTO ADaM

Source data and scope

The source data and analysis of ADaM mapping for MRD data largely depends on the identification and SDTM mapping domains used. If the biomarker is used for efficacy endpoints as in case of ALL (Acute Lymphoblastic Leukemia), then a specialized domain following BDS structure might be handy. While, if the biomarker is used for surrogate endpoints as in case of Multiple myeloma, then it can be mapped to ADLB. The derivation prioritizes bone marrow over peripheral blood unless the protocol explicitly equates them, or no marrow sample is available for the timepoint window. The MRD assessment from Bone marrow represents deeper and more reliable remission while samples from Peripheral blood have less sensitivity. Most hematologic malignancies originate and persist in bone marrow. Tumor burden in blood is often much lower or absent, even when residual disease is still present in marrow.

Primary analysis dataset and parameters

As a case study in ALL (Acute Lymphoblastic Leukemia), the MRD parameter was implemented in ADMR (Analysis Molecular Response) for targeting efficacy/response analysis. ADMR is an analysis-ready MRD dataset that standardizes MRD results across specimen types (bone marrow vs peripheral blood). It can harmonize different assay methods (NGF, NGS, PCR, flow, and ctDNA). It supports binary MRD negativity, quantitative MRD, and sensitivity thresholds and enables timepoint based analyses (e.g. post-induction, post-transplant).
For each analysis visit/timepoint, the character result AVALC has values of Negative, Positive, Not Evaluable or Missing. The analysis date (ADT) is the collection date of the MRD sample from the relevant SDTM date variable. The analysis of visit/timepoint AVISIT is assigned using Trial visit-based windows aligned to protocol. DTYPE may be "DERIVED" to designate algorithmic classification

DERIVATION LOGIC (ALL MRD NEGATIVITY)

Endpoints enabled

The parameterization supports standard ALL MRD endpoints: MRD negativity at End of Induction (EOI)/ End of Consolidation (EOC) phases, MRD response, sustained MRD negativity (e.g., two consecutive negative marrow assessments ≥ a protocol specified interval), duration of MRD negativity, and landmark analyses for PFS/OS based on MRD negativity at EOI/EOC or at fixed maintenance months.

Obs	USUBJID	ITTFL	TRT01P	PARAM	PARAMCD	AVALC	AVISIT	ADT	PFSPEC	APHASE
1	PT-101	Y	TRT A	Minimal Residual Disease	MRD	Y	Screening	27JAN2020	PERIPHERAL BLOOD	Induction Period
2	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	Screening	27JAN2020	PERIPHERAL BLOOD	Induction Period
3	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	Screening	27JAN2020	BONE MARROW	Induction Period
4	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	End of Cycle 1	02MAR2020	BONE MARROW	Induction Period
5	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	End of Cycle 2	01APR2020	PERIPHERAL BLOOD	Induction Period
6	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	End of Cycle 3	11JUN2020	PERIPHERAL BLOOD	Induction Period
7	PT-101	Y	TRT A	Minimal Residual Disease	MRD	Y	End of Cycle 3	11JUN2020	BONE MARROW	Induction Period
8	PT-101	Y	TRT A	Minimal Residual Disease	MRD	N	End of Cycle 5	03AUG2020	PERIPHERAL BLOOD	Induction Period
9	PT-101	Y	TRT A	Molecular Response at End of Induction	MOLRSREN	MR4	End of Cycle 3	11JUN2020		Induction Period

Table 3: Mapping MRD data in Analysis dataset (ADMR)

For our study, the primary endpoint was designed to have MRD negative at the End of Induction period. The induction period of the clinical trial was run through 3 cycles as per trial protocol. The specimen was collected at the end of each cycle. At the time of primary endpoint calculation, the specimen was collected from Bone Marrow or Peripheral blood with priority taken from Bone Marrow.

HANDLING OF MISSING EOI DATA

To increase the number of responders, special data handling for missing data was performed. In a clinical setting, it's always not ideal to obtain specimens at the end of the Induction period. During these particular cases, in consultation with stats and Clinical team, SAP includes the derivation and handling of these special cases.

Below is an illustration to show different considerations when MRD data is not available at the end of Induction. If MRD data is not available at EOI, then this logic looks for a 15 day window for a response assessment. If no results are available in the 15-day window, then the logic looks for pre-EOI and post-EOI MRD results for these visits. If both pre and post assessment data has a response of MRD negative, then the response at End of Induction is considered as MRD Negative.

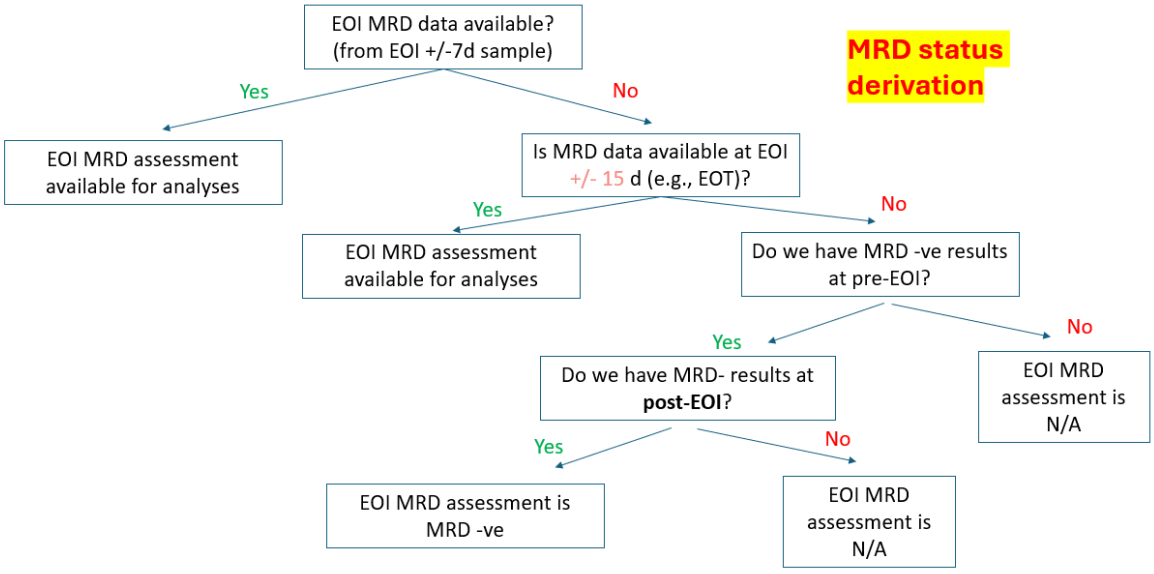

Figure 2: Flowchart logic for handling missing MRD status at End of Induction timepoint

HANDLING COMMON SCENARIOS

Peripheral blood only

If Bone marrow assessment was unavailable, then the protocol of the study allowed Peripheral Blood for the timepoint. If both the results were missing, then the timepoint was classified as missing.

Multiple same day assessments

If multiple assessments are done on the same day, then the latest timestamp was used with priority of central data over local data.

CONCLUSION

Measurable Residual Disease (MRD) has evolved from a purely prognostic biomarker to a regulatory grade endpoint in clinical trials, particularly in hematologic malignancies. Its strong correlation with long-term clinical outcomes such as progression free and overall survival combined with its ability to deliver earlier efficacy readouts and detect disease at sensitivity levels far beyond conventional response criteria, has positioned MRD as a transformative tool in modern oncology drug development.

Advances in assay standardization, analytical validation, and harmonization across platforms have further strengthened MRD's credibility and utility in regulatory decision-making. Increasingly, MRD is being incorporated as a validated intermediate endpoint in FDA submissions, supporting accelerated development pathways, enabling timely benefit risk assessment, and expanding options for innovative trial designs such as adaptive and response driven approaches.

As the field continues to mature, ongoing technological improvements and accumulating real world evidence are expected to broaden the applicability of MRD across additional tumor types and therapeutic modalities, ultimately helping expedite patient access to effective therapies while reshaping the future methodology of oncology clinical trials.

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4. Time to Get in the Genomics Findings (GF) Domain Time to Get in the Genomics Findings (GF) Domain

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