Clinical Research in Oncology

Blanchet Zumofen MH, et al., Clin Res Oncol. 2026;2(1):1-11.

Original Research

Measurable residual disease as a surrogate endpoint for overall survival in acute myeloid leukemia: a call to action

Marie-Helene Blanchet Zumofen[1,*], Vicky Huang[2], Kathryn Matt[3], Neerav Monga[3], Thomas Prebet[2], Thomas J. Prior[3], Bourras-Rezki Bengoudifa[2], Brenda Chyla[4], Carole Longson[5], Beate Wulff[1], Reshma Patel[3], Daniel Lopes de Menezes[2]

[1]F. Hoffmann-La Roche Ltd

[2]Bristol Myers Squibb

[3]Johnson and Johnson

[4]AbbVie

[5]Prof., Independent Senior Adviser, Life Science Policy, HTA and Market Access

*Author for correspondence:
Email: marie-helene.blanchetzumofen@roche.com

Received date: January 22, 2026
Accepted date: February 27, 2026

Abstract

The standardization and implementation of new endpoints are crucial for the development of novel therapeutic agents. These endpoints help streamline clinical development while maintaining high standards of care for innovative treatments, ultimately leading to improved patient outcomes. The Measurable Residual Disease Partnership and Alliance in Acute Myeloid Leukemia Clinical Treatment (MPAACT) consortium has consulted key opinion leaders (KOL), payers, and a patient advocate to discuss required actions to facilitate the use of measurable residual disease (MRD) as a surrogate endpoint for overall survival (OS) in clinical trials. **Methods:** Policy-oriented perspectives were captured with ten semi-structured interviews with Acute Myeloid Leukemia (AML) experts from the United States of America (USA) and Europe. Two advisory boards with eleven experts followed: the first shared perspectives; the second informed recommendations for MRD acceptance in AML. **Results:** Critical gaps for MRD adoption in AML include a lack of mature OS data in AML trials, inconsistent MRD definitions, and insufficient data correlating MRD with OS. **Conclusions:** This paper calls on healthcare professionals, payers, and patient advocates to collaborate on: (1) establishing aligned MRD guidelines and definitions in AML trials, (2) recognizing MRD as a promising surrogate endpoint, and (3) contributing to robust evidence supporting the MRD-OS correlation.

Keywords: Measurable residual disease (MRD), Acute myeloid leukemia (AML), Surrogate endpoints, Overall survival (OS), Patient access, Health technology assessment (HTA)

Introduction

Acute myeloid leukemia (AML) is a rare hematologic malignancy characterized by the clonal expansion and accumulation of immature myeloid cells (blasts) in the bone marrow, leading to impaired normal hematopoiesis [1,2]. In 2021, the global age-standardized incidence rate was 1.7 cases per 100,000. This represents an 82% increase since 1990 [3]. AML is noted for its acute and rapidly progressing nature, necessitating immediate medical intervention [2,4]. Current treatment modalities include chemotherapy, targeted therapies, immunotherapies, and hematopoietic stem cell transplantation (HSCT) [5–7]. The disease and its treatments result in severe side effects, including severe fatigue and cognitive impairment, significantly impacting patients' quality of life [8,9]. Updates to the International Consensus Classification (ICC) and World Health Organization 5th edition (WHO5) classifications have refined AML subtypes based on genetic and molecular features, improving diagnostic accuracy and guiding treatment decisions [1,10,11].

AML's heterogeneous nature, with a diverse mutational landscape, leads to considerable variability in overall survival (OS), ranging from less than 12 months to more than five years [12,13]. Given the severe nature of refractory and relapsed AML, with a 5-year survival rate of only 10% [14,15], there is a substantial unmet medical need. Many patients still lack appropriate treatment options, underscoring the necessity for developing effective new therapies [4,16].

Currently, OS is the 'gold standard' endpoint for oncology treatment approvals and oncology clinical trials, but its use in AML presents significant challenges:

- AML Heterogeneity: Genomic diversity within AML subtypes presents various risk prognoses leading to variable OS, complicating trial design.
- Urgency of Treatment: The necessity of immediate therapeutic intervention often limits clinical trial participation.
- Use of allogeneic stem cell transplantation (alloSCT): AlloSCT, used in over 50% of younger patients, is a key component of curative-intent treatment and significantly impacts long-term outcomes [7,13,17–19]. The role of alloSCT must be carefully considered in trial design and survival analysis to accurately assess treatment effects.
- Delayed Drug Approvals: While OS provides the most definitive measure of treatment benefit, trials using OS as the primary endpoint can require long follow-up periods, delaying routine patient access to novel therapies while OS trial data is collected.

These challenges lead to additional complexity in enrollment of clinical trials and longer trial read-outs, which delay approval of novel therapies in AML. The adoption of alternative endpoints, such as measurable residual disease (MRD), could accelerate drug development by providing an earlier indication of treatment response while using OS collected as a dual, or secondary endpoint. Event-free survival (EFS) has been supported by regulators and health technology assessment (HTA) bodies as a valid endpoint in AML [20–24]. However, despite the potential for this endpoint to speed up approvals, authorities might not always view it as reliable. Indeed, the definition of negative events and the timing of its evaluation can differ greatly across clinical trials [25,26].

In the context of AML, complete remission (CR) is traditionally defined by the presence of less than 5% blasts in the bone marrow, recovery of peripheral blood counts, and absence of extramedullary disease, serving as a clinical endpoint in both trials and practice [27]. MRD, previously termed minimal residual disease, refers to the post-treatment presence of a small number of detectable cancer cells that conventional pathological and clinical exams cannot identify [28]. The nomenclature shift from 'minimal residual disease' to 'measurable residual disease' has been advocated due to advancements in detection technologies, enabling the identification of residual disease at significantly lower thresholds than previously possible [29]. Whether the term is 'Measurable' or 'Minimal', the key factor is establishing scientifically validated thresholds that can be applied consistently across technologies and clinical trials for its intended application. From a regulatory perspective, it is critical to determine the appropriate threshold and align scientific advances with regulatory frameworks, such as a surrogate endpoint. An MRD-negative result indicates no detectable cancer cells. While not guaranteed, patients with MRD-negative status have been observed to have improved OS and reduced relapse rates [30–34]. Monitoring MRD in AML therefore informs treatment efficacy and serves as a robust prognostic marker [28,35–38].

For patients with AML, achieving early MRD-negative results and maintaining a durable response is crucial due to the relapse risk. MRD measurement methods include multiparameter flow cytometry (MFC), real-time quantitative polymerase chain reaction (RQ-PCR), and next-generation sequencing (NGS) [36]. Ongoing technological advancements, such as integrating machine learning to enhance interpretation, are improving MRD detection capabilities [39].

Several factors highlight MRD's recognized potential:

- Prognostic Utility: MRD is widely acknowledged for its prognostic significance in AML due to its reliability in indicating disease presence [40,41]. MRD has a strong prognostic value in some settings, which varies based on AML subgroups (e.g., TP53 and FLT-3 mutations) and treatment modalities such as eligibility for hematopoietic stem cell transplantation or patient fitness [38,42,43].
- Differentiation of Treatment Modalities: MRD status informs treatment regime decisions in AML and other hematological malignancies to enhance outcomes [44].
- Advancements in Molecular Diagnostics: Refinements of next-generation sequencing for deeper MRD resolution and novel techniques, such as circulating tumor DNA (ctDNA) analysis, enhance MRD relevance through more specific and sensitive measurements and standardization [45,46].

In multiple myeloma (MM), the U.S. Food and Drug Administration (FDA)'s Oncologic Drugs Advisory Committee (ODAC) have endorsed MRD-negativity as a surrogate endpoint for progression-free survival (PFS)/OS for accelerated approvals, based on meta-analyses showing a strong correlation between MRD negativity and PFS/OS. On this basis, the FDA ODAC unanimously endorsed (12-0) using MRD-negativity as a surrogate endpoint for accelerated approvals [47,48]. The European Medicines Agency (EMA) also recognizes MRD-negativity as a valid endpoint in MM studies and as an intermediate endpoint in chronic lymphocytic leukemia (CLL) studies [49–51]. These endorsements were based on comprehensive evidence, together with significant input from expert clinicians and patient groups. The generation of similar, robust evidence levels are anticipated for MRD in AML.

Despite growing clinical and patient support for MRD as a meaningful prognostic marker in AML, its acceptance as a surrogate endpoint for OS in clinical trials remains limited among health authorities and payers. MPAACT is an industry-led research consortium established in 2021. Comprised of multiple industry partners, MPAACT primary objective is to investigate the potential utility of MRD as a surrogate endpoint for OS in patients with AML and to improve patients' lives by bringing novel therapies to patients faster. To support this goal, MPAACT collaborates with experts in the field to facilitate knowledge exchange and to compile a robust data set for evaluation [52].

Meta-analyses that have been conducted to date demonstrate MRD prognostic impact and correlation with OS [42,43,53–56]. Building on previous research, MPAACT, in collaboration with health authorities, is now using trial-level and individual patient-level data from clinical trials meta-analyses to analyze the correlation between MRD and OS in AML. MPAACT is conducting a preparatory analysis to define the MRD threshold and timepoint as well as an appropriate window (e.g., +/- 7 days, +/- 15 days) for MRD assessment to align data across trials. The next stage will assess the application of this identified MRD-negativity timepoint

as an early endpoint in clinical trials and will also evaluate MRD's surrogacy for OS through trial-level data. In the relapse/refractory settings, it will need to account to the use of targeted therapies in molecularly defined subgroups (targetable mutation such as FLT3, NPM1, IDH1/2, KMT2a mutations are present in approximately 45% of the relapses) for which the detection of the residual mutation levels by polymerase chain reaction (PCR) tests may also inform the evaluation of the residual disease burden [57,58]. MPAACT's ongoing work together with regulatory and HTA discussions aim to provide robust evaluation of MRD-negativity as a surrogate endpoint for OS in AML.

This multi-stakeholder research study was conducted to explore the perspectives of key opinion leaders (KOLs), payers, and patient advocates on the role of MRD in AML. The objective was to assess the perceived value, challenges, and future potential of MRD as a clinical trial and policy-relevant endpoint, particularly in the context of patient access to innovative treatments.

Materials and Methods

MPAACT, an industry-led research consortium, conducted a research to gather multi-stakeholder perspectives. This research ensured coverage of predefined topics. The approach included an initial semi-structured individual interview and two advisory boards with a patient advocate representing a leukemia patient advocacy network, healthcare professionals, payers and HTA experts. The initial interview allowed to raise the key topics and gather individual perspective. The first advisory board allowed to discuss these topics with all stakeholders and raise the main problematics. The second advisory board allowed to set what is needed to ensure changes. All advisory board outcomes and the manuscript were shared with the stakeholders to ensure the reporting was complete and correctly reflected. To safeguard independence, external facilitators conducted all sessions, and authors/sponsors primarily acted as silent listeners. Contributors were purposively selected from six countries: United States, United Kingdom, Germany, France, Italy, and Spain, based on their expertise, AML working group members or guideline contributions in AML as well as familiarity with clinical trial endpoints. All contributors provided informed consent to this research, and the study was conducted in accordance with applicable ethical guidelines. This research was not designed to achieve thematic saturation or to support formal qualitative coding.

Data collection

Stakeholder interviews

From a total of 11 stakeholders, 10 in-depth, semi-structured individual interviews were conducted between August and September 2024 with:

- Key Opinion Leaders from France (n=1), the United States of America (USA) (n=2), and Spain (n=1)
- Payers and HTA Experts (n=5) (i.e., hospital pharmacist, insurance professionals, and/or HTA consultants) from the USA, United Kingdom (UK), Germany, France, and Italy
- Patient Advocate (n=1) representing an international leukemia advocacy network

Each interview followed a standardized guide with predefined questions tailored to the stakeholder group and covered five thematic domains: (i) major unmet needs in AML, (ii) challenges beyond unmet needs, (iii) key future innovations, (iv) patient-centered perspectives, and (v) MRD as a clinical measure. Interviews were recorded, transcribed, and summarized in structured capture sheets.

Advisory boards

Two multi-stakeholder advisory boards were convened in October and November 2024, respectively. Contributors included the previously interviewed stakeholders, an additional KOL from France, and additional representatives from industry and academia. The boards aimed to:

- Validate and expand upon interview findings
- Align on key challenges to MRD acceptance
- Prioritize actionable strategies for policy advancement

Outputs included consensus statements, prioritized solution strategies, and a call to action.

Data analysis

Interview transcripts, capture sheets, and advisory board reports were thematically analyzed using a framework approach. Data were ultimately categorized for each interview group into five predefined domains (see section "*Validation and Triangulation*"). Within each domain, stakeholder perspectives were synthesized and compared to identify:

- Converging themes (shared across stakeholder groups)
- Diverging or nuanced perspectives (unique to specific groups)

Validation and triangulation

Findings were triangulated across three data sources:

- Detailed individual interview transcripts
- Structured capture sheets organized by topic, and captured by the facilitator during the interviews
- Advisory board discussions

This multi-source evaluation ensured the consistency and robustness of the synthesized insights. The most critical issues were then prioritized anonymously by the advisory board members using a virtual Mentimeter® poll function in the first advisory board.

The findings were subsequently organized into categories according to the subjects discussed: i. Major unmet needs in AML, ii. Challenges beyond unmet needs, iii. Future directions in AML, iv. Patient-centered perspectives, v. MRD as a clinical trial measure (refer to **Table 1**).

Results

Table 1 presents the perspectives gathered through stakeholder semi-structured individual interviews, systematically organized according to the predefined thematic categories outlined in the methods section. These categories include major unmet needs, challenges beyond unmet needs, future directions in AML, patient-centered perspectives, and the role of MRD as a clinical measure. The table includes the three stakeholder groups: KOLs, Payers and HTA Experts, and Patient Advocate.

Table 1. Summary interview outcomes by stakeholder group based on expert statements.

Key Opinion Leaders	Payers and HTA Experts	Patient Advocate
Major unmet needs in AML		
Patient subgroups with poor outcomes • Refractory, Relapsed, and TP53-Mutated Populations: These groups were consistently identified as having the poorest prognoses, with limited effective treatment options currently available • High-Risk and Unfit Patients: Individuals with residual disease resistance or those ineligible for intensive therapy require novel, personalized treatment strategies	Durable responses and OS • Payers consistently highlight the need for therapies that improve overall survival (OS), especially in relapsed/refractory (R/R) and unfit patients	Treatment fatigue and quality of life • Fatigue is one of the most debilitating and under-recognized symptoms in AML, affecting both younger and older patients. It significantly impairs daily functioning and emotional well-being, yet is not enough considered in clinical conversations
Frontline treatment challenges • Despite therapeutic advancements, frontline regimens often fail to achieve durable remission, particularly in patients aged >67 years, where median survival remains below 18 months • Continued dependence on stem cell transplantation (SCT) was noted, though its long-term efficacy is constrained by relapse, toxicity, and complications such as graft-versus-host disease (GvHD)	Reduced toxicity • There is a strong desire for treatments with fewer grade 3/4 adverse events, particularly for transplant-ineligible populations	Impact of transplantation • Post-transplant complications, especially chronic GvHD, are a major source of long-term morbidity. These complications can severely affect quality of life and require lifelong management
Diagnostic and treatment complexity • Evolving diagnostic frameworks have introduced inconsistencies in clinical practice, contributing to variability in treatment duration, monitoring protocols, and classification adoption across centers	Tailored therapies • AML heterogeneity necessitates personalized approaches, but the high costs of genetic testing remain a barrier	Awareness and education gaps • Patients often lack a clear understanding of clinical terms like MRD or CR, particularly at the start of treatment. This leads to confusion, anxiety, and misinterpretation of test results, especially when MRD is positive
	Early detection • While not a primary HTA focus, earlier diagnosis is acknowledged as beneficial	Engagement of AML patients in peer support and advocacy • The acute and often traumatic nature of AML treatment means that many survivors choose to focus on moving forward with their lives after recovery. Consequently, fewer tend to engage in advocacy or peer-support initiatives, which contributes to their underrepresentation compared with chronic leukemia patients in policy and research discussions. discussions
Challenges beyond unmet needs		
Treatment-related toxicity • Current AML therapies are associated with high toxicity, limiting eligibility-especially among older adults and negatively impacting patient outcomes	Lack of OS data • The absence of mature OS data complicates reimbursement, especially in cost-effectiveness-driven systems like National Institute for Health and Care Excellence (NICE)	Patient engagement in drug evaluation • Patient involvement in regulatory and HTA processes remains limited. One challenge is that meaningful engagement requires awareness, expertise, and dedicated processes, which many national patient organizations do not yet have in place. In addition, there are no dedicated AML patient organizations. Instead, AML patients are represented within broader leukemia organizations (covering acute lymphoblastic leukemia (ALL), AML, CLL, and chronic myelogenous leukemia (CML)) or, more generally, within blood cancer organizations. At the European level, there is currently no leukemia-specific body that consistently carries the voice of leukemia patients, including those with AML, in drug evaluation

Key Opinion Leaders	Payers and HTA Experts	Patient Advocate
Resource-intensive care • AML management often necessitates prolonged inpatient care and substantial hospital resources, rendering outpatient treatment impractical for most patients	High costs and market saturation • Drug and diagnostic test pricing as well as increasing competition create pressure on HTA bodies and payers	Limited access to clinical trial insights • Patient advocates are often not included in trial design and lack access to clinical data. Seeking their feedback during trial development is important to ensure that the patient journey is viable, e.g., by limiting the number of invasive procedures unless they are clinically meaningful and scientifically justified
	MRD diagnostic variability • Lack of standardization in MRD testing undermines payer confidence	Patient priorities in innovation • For children, teenagers, and patients of childbearing age, priorities often include access to less toxic treatments and fertility preservation. • Reducing reliance on bone marrow transplantation is a key goal due to its long-term impact on quality of life, including risks of GvHD, infections, conditioning-related organ damages, relapse, secondary cancers, and chronic metabolic or psychosocial sequelae
	Small patient populations • AML's rarity limits statistical power in trials, making it harder to demonstrate benefit	
Future Directions in AML: Innovations and the Evolving Role of MRD		
Integration of MRD • MRD monitoring is anticipated to enhance risk stratification and guide therapeutic decisions • However, standardization of MRD assessment techniques (e.g., flow cytometry, molecular assays) across institutions remains a significant barrier	MRD as a surrogate • Payers are cautiously open to MRD as a surrogate endpoint if it shows correlation with OS, relapse prevention, or quality of life	MRD's role in policy • For MRD to be accepted as a surrogate endpoint, it must be clearly linked to meaningful outcomes such as relapse prevention, improved quality of life, and extended OS
Emergence of molecularly targeted therapies • KOLs expressed optimism about the potential of small molecule inhibitors and immunotherapies, including next-generation CAR-T cells • Promising agents include novel inhibitors targeting NPM1 mutations and emerging Menin inhibitors • Venetoclax was frequently cited as a transformative agent in AML care. KOLs emphasized the need for ongoing optimization of dosing strategies to balance efficacy with tolerability • More novel therapeutic options are still required	Targeted therapies • CD123 and MCL1 inhibitors are viewed as promising, especially for elderly or unfit patients	MRD beyond monitoring • MRD is increasingly used in clinical practice to monitor AML and guide treatment decisions. For purposes of reimbursement and regulatory approval, however, it should be regarded as one important decision-making criterion — provided that its clinical relevance is validated — alongside established outcomes such as OS, rather than as a standalone measure. Importantly, the collection of MRD data alone should not replace or preclude the collection of OS data
	Economic offsets Novel therapies that reduce hospitalizations or Intensive Care Unit stays are seen as valuable if they deliver measurable outcomes	

Key Opinion Leaders	Payers and HTA Experts	Patient Advocate
Patient-centered perspectives		
Reducing the burden of toxicity • The toxicity of current regimens significantly impairs quality of life and often necessitates extended hospitalization. • There is a strong need for less toxic therapeutic alternatives	Tolerability and quality of life • AML treatments often cause severe side effects, leading to significant quality of life impairment.	MRD as a "landmark" for patients • MRD testing provides psychological structure and reassurance. Patients use it to track their disease status and plan their lives around testing intervals • MRD can be difficult for patients to understand at the start of treatment, as being MRD-positive is associated with poorer outcomes while being MRD-negative is favorable. Patients often require repeated explanations and clearer communication at treatment initiation to fully grasp its implications
Economic and caregiver strain • AML imposes substantial financial and psychosocial burdens, including housing needs for caregivers and disruptions to family life, particularly among younger patients with dependents	Emotional and logistical burden • AML's rapid onset leads to abrupt hospitalizations and caregiver strain	
Quality of life post-treatment • Recovery is often prolonged, with patients experiencing persistent fatigue, cognitive dysfunction, and chronic complications such as renal impairment and GvHD, all of which detract from long-term quality of life		
MRD as a clinical measure		
Clinical advantages • MRD is increasingly viewed as a more sensitive and reliable predictive indicator of remission than traditional cytomorphology, informing decisions on further chemotherapy or the need for transplantation	Conditional acceptance • MRD is accepted in other hematologic malignancies (e.g., MM, ALL), but AML lacks sufficient evidence	MRD acceptance in AML • While MRD is widely used in trials, it is increasingly used in routine care, especially in academic centers. Broader acceptance depends on demonstrating its correlation with long-term outcomes
Patient education • KOLs highlighted the importance of effectively communicating MRD concepts to patients, particularly the distinction between CR and MRD negativity, to support informed decision-making	Surrogacy debate • Payers are open to MRD if it correlates with OS or relapse prevention, especially in curative settings	
	Standardization needed • Diagnostic variability remains a barrier to broader adoption	

Key opinion leaders

KOLs echoed the multifaceted challenges in AML treatment. Despite therapeutic advancements, frontline regimens often fail to achieve durable remission, particularly in older adults, and continued reliance on stem cell transplantation although sometimes curative, remains constrained by relapse and toxicity. Diagnostic inconsistencies further complicate treatment planning across centers. Future innovations, harnessing molecular monitoring, MRD, and novel therapies, hold the promise to drastically change AML care.

KOLs emphasize the potential of MRD monitoring to refine risk stratification, although standardization remains a barrier. Optimism surrounds emerging targeted therapies, including CAR-T cells and Menin inhibitors, alongside the transformative role of venetoclax, which requires further optimization to balance efficacy and tolerability. Emphasizing a patient-centered approach that prioritizes reducing toxicity and improving quality of life will also remain critical to achieving transformative changes in AML management. Refer to **Table 1.**

Payers and HTA experts

From the payer and HTA expert perspective, the AML treatment landscape is at a pivotal juncture. While innovations such as MRD monitoring and targeted therapies offer promise, vital challenges

remain. There is a consistent emphasis on the urgent need for therapies that improve OS, especially in relapsed, refractory and unfit patients. Equally important is the demand for treatments with fewer grade 3/4 adverse events, particularly in transplant-ineligible populations.

Reimbursement decisions are often hindered by the lack of mature OS data, especially in cost-effectiveness-driven systems such as National Institute for Health and Care Excellence (NICE). Payers also highlight the challenge of balancing high treatment costs with demonstrable clinical and patient-centered benefit. AML's inherent heterogeneity requires personalized treatment approaches, yet the cost of genetic testing remains a barrier to widespread implementation of MRD testing.

While early diagnosis is not a primary focus of HTA, it is acknowledged as beneficial. Broader systemic issues persist: diagnostic test pricing and the lack of standardization in MRD testing within a fragmented treatment landscape, as well as high drug prices although increasing market competition, all contribute to payer hesitancy. The variability in MRD methodologies across institutions undermines confidence in its reliability, and AML's low prevalence limits statistical power in clinical trials, complicating the demonstration of treatment benefit. Despite cautious openness to MRD as a surrogate endpoint, particularly if it correlates with OS, relapse prevention, or quality of life, payers and HTA experts stress the need for robust, standardized evidence. Collaborative efforts among clinicians, HTA bodies, manufacturers, and patients will be crucial in reshaping AML care toward sustainable and meaningful long-term outcomes. Refer to **Table 1.**

Patient advocate

Acute leukemia patients, including AML patients, face specific challenges, from the aggressive nature of the disease to the long-term physical and psychological toll of treatments like bone marrow transplants. Fatigue is one of the most debilitating and under-recognized symptoms in AML, affecting both younger and older patients. It significantly impairs daily functioning and emotional well-being, yet is not enough considered in clinical conversations. Post-transplant complications, especially chronic graft-versus-host disease (GvHD), are a major source of long-term burden. MRD, as a monitoring and potential surrogate tool, represents a significant opportunity to enhance patient care and clinical outcomes. Moreover, patients often require repeated explanations and clearer communication at treatment initiation to fully grasp the implications of clinical terms like MRD or CR. Without this support, confusion, anxiety, and misinterpretation of test results, especially when MRD is positive, can occur. Realizing its full potential will depend on clear communication, and a sustained focus on reducing treatment burdens, improving quality of life, and meeting the diverse needs of AML patients at different stages of life. MRD should inform regulatory and reimbursement decisions only once its clinical relevance has been validated. It must complement, rather than replace OS data.

Synthesis from the advisory boards and differences in the points of view

All stakeholders agree that AML remains an area of high unmet need, especially for R/R and transplant-ineligible patients. While KOLs and payers focus on survival and efficacy, the patient advocate emphasizes quality of life and challenges of survivorship. Indeed, there was clear recognition across stakeholder groups that the toxicity burden of existing AML regimens remains a major concern. Stakeholders converge on the issue of inconsistency whether in diagnostics, clinical trial design, or engagement in policy processes. There is a strong call for standardization and methodological rigor, alongside a clear need to embed patient voices meaningfully into trial design and policy frameworks. These insights point to the need for more inclusive, standardized, and transparent processes across the clinical and policy landscape.

MRD is viewed as both a unifying and polarizing endpoint. While all stakeholders recognize its potential, perspectives differ regarding its readiness for adoption. Its future as a surrogate endpoint for OS in AML depends on demonstrating robust, correlations with long-term outcomes including sensitivity analysis for specific subgroups of patients, and on integrating patient perspectives into its interpretation. Despite broad recognition of MRD's potential as a meaningful prognostic marker, stakeholders identify critical barriers that must be addressed to enable its acceptance as a surrogate endpoint for OS in AML clinical trials by regulatory and HTA bodies. Payers and KOLs emphasize methodological and economic barriers, while the patient advocate highlights the limited inclusion of patient voices in clinical trial design.

Prioritization of the key issues

The use of MRD-negativity by regulatory and HTA bodies as a valid surrogate for OS in AML clinical trials necessitates addressing three key issues: (1) AML heterogeneity, (2) lack of standardized MRD definitions, and (3) the need for robust clinical validation evidence.

AML heterogeneity

AML's genetic drivers and treatment complexity result in diverse treatment modalities that impact MRD data interpretation and comparability. An MRD framework that works across all AML subgroups and treatment modalities is essential to overcome these challenges.

Standardization of definitions, timepoints and testing methods

The widespread adoption of MRD in AML is hindered by the lack of a unique MRD test valid for all AML subtypes (i.e. unlike MM) which results in:

- Inconsistent definitions: MRD cut-off thresholds and how residual disease is characterized, varies across institutions, complicating inter-study comparisons [59,60].
- Divergent timepoints for testing: Standardization of MRD measurement at specific timepoints is necessary to ensure data reliability [61].
- Heterogeneity in testing methods: Mmultiparameter flow cytometry, quantitative polymerase chain reaction, and next-generation sequencing-based MRD detection methodologies must be harmonized to be recognized by Regulatory bodies.

A globally accepted MRD definition and consistent thresholds for MRD negativity are vital. The FDA has accepted a bone marrow MRD threshold of less than 0.01% as supporting evidence of efficacy for drugs demonstrating durable complete responses (CR) in relapsed or refractory AML [20]. Whilst this limit may evolve with technological advancements, it serves as a useful starting point

for the standardization of an efficacy threshold. Consistent MRD assessment timepoints and methodologies, including multiparameter flow cytometry, quantitative polymerase chain reaction, digital polymerase chain reaction, and next-generation sequencing, require alignment.

Need for robust clinical evidence

A robust correlation between treatment effects on MRD and OS is necessary to validate MRD as a surrogate endpoint for OS. However, the heterogeneity of OS in AML complicates this relationship. Good prognosis subgroups can achieve prolonged survival, leading to longer timeframes to reach OS, while poor prognosis subgroups require urgent treatment, making it challenging to investigate new treatments and recruit patients for new trials [16,62]. Supporting initiatives to integrate the use of MRD as an outcome in clinical trials and meaningful collaboration with healthcare providers, clinicians and patients is needed to ensure robust evidence generation in this complex disease.

Discussion

The potential of MRD as an early clinical endpoint for approvals in AML offers a promising pathway to enhance patient care and, ultimately, quality of life. This paper is based on the participation of international key stakeholders with extensive backgrounds in AML and different HTA perspectives. Our research highlights how critical it is to have clinicians, patient advocacy groups, and payers working together. The findings should be interpreted as expert stakeholder insights to inform clinical development and HTA processes. The objective of this perspective is to frame where we stand in the diagnosis, treatment and drug approvals in AML and to outline safeguards that should be considered for MRD to become an established endpoint in AML.

As of today, MRD-negativity is an established prognostic marker in AML, at the patient level, consistently associated with improved outcomes, although the strength of association may vary by assay, timing, and disease subgroup. Despite potential variations, MRD is clinically relevant for risk stratification and clinical trial design. Regulators and stakeholders have encouraged structured evidence-generation programs to evaluate its potential surrogacy at the trial level.

MPAACT is conducting preparatory analyses to define the MRD threshold, timepoints and an appropriate window (i.e. +/- 7 days, +/- 15 days) for MRD assessment to align data across trials. The next stage will assess the application of this identified MRD-negativity timepoint as an early endpoint in clinical trials and will also evaluate MRD's surrogacy for OS through trial-level data.

It is essential to take into account the complexity of the diagnosis, and the disease itself, as well as to ensure that the steps towards the acceptance of new endpoints are actionable. For instance, the difference in treatment regimens and the broader use of MRD directed therapy at the patient level in pediatric AML will have to be taken in consideration in the statistical plan and in the interpretation of results [41,63].

To advance and safeguard the acceptance of MRD as a valid endpoint in AML, the following actions are recommended:

1. Develop globally accepted MRD thresholds, timepoint and assessment guidelines: Establish comprehensive guidelines for MRD use in clinical practice to enable uniform testing methodologies and datasets.
2. Engage stakeholders: Raise awareness and educate patients, clinicians, regulators, payers, and patient advocacy groups on the potential of MRD and its significance for both clinical trials and clinical practice.
3. Systematically conduct assessments: Implement standardized MRD measurement and reporting methods and achieve consensus on clinical thresholds to generate robust data and improve MRD testing familiarity among clinicians.
4. Generate MRD & OS putcomes: Integrate MRD assessments with OS as dual or secondary endpoint in clinical trials and real-world evidence (RWE) studies to further facilitate the adoption of MRD in trial designs.

Premature adoption of MRD as a surrogate endpoint presents several risks, including the potential misestimation of clinical benefit, where treatment effects may be overestimated or underestimated, and inconsistencies arising from variability in assays and assessment timepoints, which can limit the comparability of results. Equitable access may be a concern if high-quality MRD testing varies across centers. These risks can be mitigated through standardization of MRD definitions, assay performance criteria, and fixed MRD timepoints. Additional safeguards include the use of dual or secondary endpoint strategies that integrate OS and MRD assessments, supported by post-authorization confirmatory evidence.

Conclusions and Future Directions

According to stakeholders interviewed, MRD is increasingly regarded as a more sensitive and reliable predictor for treatment response and prognosis. However, additional evidence is needed to support its broader acceptance in clinical practice. By integrating MRD into clinical trials, treatment guidelines and evaluations of treatment value in AML, we can help ensure that promising therapies reach patients faster and are made accessible through reimbursement pathways.

Achieving this goal will require close collaboration among all stakeholders - regulators, HTA bodies, industry, patient advocacy groups and healthcare professionals. Recognizing MRD-negativity as a valid surrogate for OS a meaningful indicator of treatment success can help deliver better, more personalized care to people living with AML.

Acknowledgments

Vintura: Dr. Ann-Sophie Kuschel, Vintura, Dr. Medha Kothari, Vintura, Wouter Bloem, Vintura

The content of this paper is based on interviews and roundtable discussions with key stakeholders in the field. We want to thank the following people for their participation: (alphabetical order by surname)

Prof. Pierre Fenaux	Hospital St. Louis, Paris University (France)
Dr. Giorgia Gambarelli	HTA & Hospital expert (Italy)
Dr. Mark Litzow	Mayo Clinic (U.S.)
Dr. Bruno Paiva	University Hospital of Salamanca (Spain)

Ms. Anne-Pierre Pickaert	Acute Leukemia Advocates Network (ALAN; global network)
Dr. Gail Roboz	Weill Medical College of Cornell University (U.S.)
Prof. Norbert Vey	Institut Paoli-Calmettes Cancer Center (France)
Dr. Andrew Walker	HTA expert (U.K.)
Prof. Jürgen Wasem	HTA expert (Germany)
Dr. Olivier Wong	HTA expert (France)
Anonymous participant	A large US-based insurance company

Artificial Intelligence (AI)-Assisted Technology (e.g., privacy secured company-owned solutions) was utilized to enhance the readability and language of this work, in accordance with applicable directives and procedures. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Author Contributions

Conceptualization, M.N., MH.BZ., T.P., B.W., R.P., and D.LdM.; methodology, M.N., MH.BZ., V.H., and K.M.; validation, MH.BZ, V.H., K.M., T.P., B.C., T.J.P., C.L., BR.B., B.W., R.P., and D.LdM.; writing—original draft preparation, MH.BZ., V.H., K.M., T.P., and T.J.P.; writing—review and editing, MH.BZ., V.H., K.M., T.P., T.J.P., C.L., B.W., R.P., and D.LdM.; supervision, B.W., R.P., and D.LdM.; project administration, M.N., MH.BZ., V.H., K.M.; All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors contributed to the funding and design of the study. The content is derived from interviews and advisory boards in which the authors acted primarily as listeners. The findings and recommendations presented in the manuscript are based solely on the insights and data gathered from these discussions, ensuring the integrity and independence of the research. Stakeholder perspectives were provided voluntarily and independently, without any influence from the authors or sponsoring organizations.

Funding Statement

This work was funded by MPAACT, an industry-led research consortium established in 2021 and comprised of multiple industry partners. Industry partners include Genentech (a member of the Roche Group), Johnson and Johnson, Servier, Bristol Myers Squibb, AbbVie, Novartis and Kura Oncology.

Abbreviations

AI: Artificial Intelligence; AML: Acute Myeloid Leukemia; ALL: Acute Lymphocytic/Lymphoblastic Leukemia; CBER: Center for Biologics Evaluation and Research; CDER: Center for Drug Evaluation and Research; CHMP: Committee for Medicinal Products for Human Use; CML: Chronic Myelogenous Leukemia; CLL: Chronic Lymphocytic Leukemia; CR: Complete Response; DNA: Deoxyribonucleic Acid; DOAJ: Directory of Open Access Journals; EFS: Event-Free Survival; ECOG: Eastern Cooperative Oncology Group; EMA: European Medicines Agency; FDA: Food and Drug Administration; G-BA: Gemeinsamer Bundesausschuss (German Joint Federal Committee); GvHD: Graft-versus-host disease; HAS: Haute Autorité de Santé (French National Authority for Health); HOVON: Dutch-Belgian Hemato-Oncology Cooperative Group; HSCT: Hematopoietic Stem Cell Transplantation; HTA: Health Technology Assessment; ICC: International Consensus Classification; KOL: Key Opinion Leader; LD: Linear Dichroism; MFC: Multiparameter Flow Cytometry; MPAACT: Measurable Residual Disease Partnership and Alliance in Acute Myeloid Leukemia Clinical Treatment; MRD: Measurable Residual Disease (old: Minimal Residual Disease); NCRI: National Cancer Research Institute; NGS: Next-Generation Sequencing; NICE: National Institute for Health and Care Excellence; ODAC: Oncologic Drugs Advisory Committee; OS: Overall Survival; PAG: Patient Advocacy Group; PCR: Polymerase Chain Reaction; PFS: Progression-Free Survival; RQ-PCR: Real-Time Quantitative Polymerase Chain Reaction; RWE: Real-World Evidence; SWOG: Southwest Oncology Group; TLA: Three Letter Acronym; UK: United Kingdom; USA: United States of America; WHO5: World Health Organization 5th edition.

References

1. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka HM, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022 Sep 15;140(11):1200–28.
2. American Cancer Society. What Is Acute Myeloid Leukemia (AML)? https://www.cancer.org/cancer/types/acute-myeloid-leukemia/about/what-is-aml.html.
3. Wu B, Song F, Han X, Zhao M, Huang M, Zhang W, et al. Global, regional and national epidemiology of acute myeloid leukemia (1990-2021): a statistical analysis of incidence, mortality, and DALYs. Ann Med. 2025 Dec;57(1):2557507.
4. Fleischmann M, Schnetzke U, Hochhaus A, Scholl S. Management of acute myeloid leukemia: current treatment options and future perspectives. Cancers. 2021 Nov 16;13(22):5722.
5. Sekeres MA, Guyatt G, Abel G, Alibhai S, Altman JK, Buckstein R, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020 Aug 11;4(15):3528–49.
6. Cortes JE, Douglas Smith B, Wang ES, Merchant A, Oehler VG, Arellano M, et al. Glasdegib in combination with cytarabine and daunorubicin in patients with AML or high-risk MDS: Phase 2 study results. Am J Hematol. 2018 Nov;93(11):1301–10.
7. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345–77.
8. Hu KX, Guo M, Yu CL, Qiao JH, Sun QY, Cai B, et al. Hematopoietic stem cell microtransplantation in patients aged over 70 with acute myeloid leukemia: a multicenter study. Am J Cancer Res. 2023 Apr 15;13(4):1509–21.
9. Chan KY, Chan TSY, Gill H, Chan TCW, Li CW, Au HY, et al. Supportive care and symptom management in patients with advanced hematological malignancies: a literature review. Ann Palliat Med. 2022 Oct;11(10):3273–91.
10. WHO Classification of Tumours Editorial Board. Haematolymphoid tumours. 5th Edition. International Agency for Research on Cancer; 2024.
11. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, Apperley JF, et al. The 5th edition of the World Health Organization Classification of

Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia. 2022 Jul;36(7):1703–19.

12. Chen M, Zeng Z, Li X, Qin W, Cai X, Chen S, et al. Clinical features and prognostic significance of DNMT3A, FLT3, and NPM1 mutations in de novo acute myeloid leukemia patients. International Journal of Laboratory Hematology. 2023 Dec;45(6):899–907.
13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia, Version 2.2025 [Internet]. 2025 [cited 2025 Aug 18]. https://www.nccn.org.
14. Piccini M, Mannelli F, Coltro G. The role of venetoclax in relapsed/refractory acute myeloid leukemia: past, present, and future directions. Bioengineering. 2023 May 13;10(5):591.
15. Ganzel C, Sun Z, Cripe LD, Fernandez HF, Douer D, Rowe JM, et al. Very poor long-term survival in past and more recent studies for relapsed AML patients: the ECOG-ACRIN experience. American journal of hematology. 2018 Aug;93(8):1074–81.
16. Bhansali RS, Pratz KW, Lai C. Recent advances in targeted therapies in acute myeloid leukemia. J Hematol Oncol. 2023 Mar 25;16(1):29.
17. Loke J, Malladi R, Moss P, Craddock C. The role of allogeneic stem cell transplantation in the management of acute myeloid leukaemia: a triumph of hope and experience. Br J Haematol. 2020 Jan;188(1):129–46.
18. Semerad L, Sustkova Z, Cetkovsky P, Jindra P, Koristek Z, Novak J, et al. The impact of centralised care of younger AML patients on treatment results: a retrospective analysis of real-world data from a national population-based registry. Acta Oncol. 2021 Jun;60(6):818–23.
19. Devillier R, Forcade E, Garnier A, Guenounou S, Thepot S, Guillerm G, et al. In-depth time-dependent analysis of the benefit of allo-HSCT for elderly patients with CR1 AML: a FILO study. Blood Adv. 2022 Mar 22;6(6):1804–12.
20. Food and Drug Administration (FDA), U.S. Department of Health and Human Services (HHS), Oncology Center of Excellence (OCE), Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment - Guidance for Industry [Internet]. 2022 Oct. https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugsand/or
21. Committee for Medicinal Products for Human Use (CHMP). Guideline on the clinical evaluation of anticancer medicinal products Rev.6. 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-anticancer-medicinal-products-revision-6_en.pdf.
22. Haute Autorité de Santé (HAS), Commission de la Transparence. Midostaurine - Avis. 2018. https://www.has-sante.fr/upload/docs/evamed/CT-16582_RYDAPT_LAM_PIC_INS_Avis3%20_CT16582.pdf.
23. Gemeinsamer Bundesausschuss (G-BA). Blinatumomab - Tragende Gründe. 2022. https://www.g-ba.de/downloads/40-268-8180/2022-01-20_AM-RL-XII_Blinatumomab_D-703_TrG.pdf.
24. National Institute for Health and Care Excellence (NICE). Gemtuzumab - Single Technology Appraisal. 2018. https://www.nice.org.uk/guidance/ta545/evidence/appraisal-consultation-committee-papers-pdf-6596279678.
25. Walia A, Tuia J, Prasad V. Progression-free survival, disease-free survival and other composite end points in oncology: improved reporting is needed. Nat Rev Clin Oncol. 2023 Dec;20(12):885–95.
26. Othus M, van Putten W, Lowenberg B, Petersdorf SH, Nand S, Erba H, et al. Relationship between event-free survival and overall survival in acute myeloid leukemia: a report from SWOG, HOVON/SAKK, and MRC/NCRI. Haematologica. 2016 Jul;101(7):e284–6.
27. Hourigan CS. How complete must an AML remission be? Blood. 2024 Jul 11;144(2):131–2.
28. Schuurhuis GJ, Heuser M, Freeman S, Béné MC, Buccisano F, Cloos J, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2018 Mar 22;131(12):1275–91.
29. Voso MT, Ottone T, Lavorgna S, Venditti A, Maurillo L, Lo-Coco F, et al. MRD in AML: The Role of New Techniques. Front Oncol. 2019 Jul 23;9:655.
30. Mi R, Chen L, Wei X, Wang X, Song Y. Combined Thalidomide and Recombinant Human Interferon-α-1b and Interleukin-2 for Acute Myeloid Leukemia of Various Disease Status: A Multi-Center Prospective Study. Blood. 2019 Nov 13;134:3865.
31. Oran B, Jorgensen JL, Marin D, Wang S, Ahmed S, Alousi AM, et al. Pre-transplantation minimal residual disease with cytogenetic and molecular diagnostic features improves risk stratification in acute myeloid leukemia. Haematologica. 2017 Jan;102(1):110–17.
32. Chen X, Xie H, Wood BL, Walter RB, Pagel JM, Becker PS, et al. Relation of clinical response and minimal residual disease and their prognostic impact on outcome in acute myeloid leukemia. J Clin Oncol. 2015 Apr 10;33(11):1258–64.
33. Buccisano F, Maurillo L, Gattei V, Del Poeta G, Del Principe MI, Cox MC, et al. The kinetics of reduction of minimal residual disease impacts on duration of response and survival of patients with acute myeloid leukemia. Leukemia. 2006 Oct;20(10):1783–9.
34. Chea M, Rigolot L, Canali A, Vergez F. Minimal Residual Disease in Acute Myeloid Leukemia: Old and New Concepts. Int J Mol Sci. 2024 Feb 10;25(4):2150.
35. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003 Dec 15;21(24):4642–9.
36. Heuser M, Freeman SD, Ossenkoppele GJ, Buccisano F, Hourigan CS, Ngai LL, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood, The Journal of the American Society of Hematology. 2021 Dec 30;138(26):2753–67.
37. Ravandi F, Cloos J, Buccisano F, Dillon R, Döhner K, Freeman SD, Hourigan CS, Ossenkoppele GJ, Roboz GJ, Subklewe M, Thiede C, Arnhardt I, Valk PJM, Venditti A, Wei AH, Walter RB, Heuser M. Measurable residual disease monitoring in patients with acute myeloid leukemia treated with lower-intensity therapy: Roadmap from an ELN-DAVID expert panel. Am J Hematol. 2023 Dec;98(12):1847–55.
38. Moritz J, Schwab A, Reinisch A, Zebisch A, Sill H, Wölfler A. Measurable residual disease detection in acute myeloid leukemia: current challenges and future directions. Biomedicines. 2024 Mar 7;12(3):599.
39. Shopsowitz K, Lofroth J, Chan G, Kim J, Rana M, Brinkman R, et al. MAGIC-DR: an interpretable machine-learning guided approach for acute myeloid leukemia measurable residual disease analysis. Cytometry Part B: Clinical Cytometry. 2024 Jul;106(4):239–51.
40. Mi R, Chen L, Wang X, Yin Q, Wang Z, Ma X, et al. A retrospective study on effectiveness of combined recombinant human interferon-α-1b,

interleukin-2, and thalidomide for the treatment of acute myeloid leukemia in various disease states. Annals of Translational Medicine. 2022 Dec;10(24):1382.

41. Segerink WH, de Haas V, Kaspers GJ. Measurable residual disease in pediatric acute myeloid leukemia: a systematic review. Expert Review of Anticancer Therapy. 2021 Apr 3;21(4):451–9.
42. Short NJ, Rafei H, Daver N, Hwang H, Ning J, Jorgensen JL, et al. Prognostic impact of complete remission with MRD negativity in patients with relapsed or refractory AML. Blood Adv. 2020 Dec 22;4(24):6117–26. doi: 10.1182/bloodadvances.2020002811. Erratum in: Blood Adv. 2021 Jan 26;5(2):366.
43. Meddi E, Savi A, Moretti F, Mallegni F, Palmieri R, Paterno G, et al. International Journal of Molecular Sciences. 2023 Feb 4;24(4):3062.
44. Moors I, Vandepoele K, Philippé J, Deeren D, Selleslag D, Breems D, et al. Clinical implications of measurable residual disease in AML: Review of current evidence. Crit Rev Oncol Hematol. 2019 Jan;133:142–8.
45. Passaro A, Al Bakir M, Hamilton EG, Diehn M, André F, Roy-Chowdhuri S, et al. Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. Cell. 2024 Mar 28;187(7):1617–35.
46. Vonk CM, Al Hinai ASA, Hanekamp D, Valk PJM. Molecular Minimal Residual Disease Detection in Acute Myeloid Leukemia. Cancers (Basel). 2021 Oct 29;13(21):5431.
47. Oncologic Drugs Advisory Committee (ODAC). Combined FDA and Applicants ODAC Briefing Document - Drug Topic: Use of Minimal Residual Disease (MRD) as an Endpoint in Multiple Myeloma Clinical Trials. 2024. https://www.fda.gov/media/177652/download.
48. Oncologic Drugs Advisory Committee (ODAC), Food and Drug Administration (FDA). Meeting Roster. 2024. https://www.fda.gov/media/180109/download.
49. Use of minimal residue disease as an endpoint in chronic lymphocytic leukaemia studies - Scientific guideline | European Medicines Agency (EMA) [Internet]. [cited 2025 Mar 25]. https://www.ema.europa.eu/en/use-minimal-residue-disease-endpoint-chronic-lymphocytic-leukaemia-studies-scientific-guideline.
50. Reflection paper on the use of measurable residual disease as a clinical endpoint in multiple myeloma studies - Scientific guideline | European Medicines Agency (EMA) [Internet]. [cited 2025 Mar 25]. https://www.ema.europa.eu/en/reflection-paper-use-measurable-residual-disease-clinical-endpoint-multiple-myeloma-studies-scientific-guideline.
51. Roy A, Brander DM, Hill EG, Halabi S. Statistical Perspectives and Meta-Analytic Approaches in Surrogate End Point Evaluation for Chronic Lymphocytic Leukemia. J Clin Oncol. 2025 Feb;43(4):365–8.
52. European Medicines Agency (EMA). Letter of support for Measurable Residual Disease (MRD) as a Surrogate Efficacy Endpoint in Clinical Studies with Acute Myeloid Leukemia [Internet]. 2024 [cited 2025 Oct 2]. p. 4. https://www.ema.europa.eu/en/documents/other/letter-support-measurable-residual-disease-mrd-surrogate-efficacy-endpoint-clinical-studies-acute-myeloid-leukemia_en.pdf.
53. Bernardi M, Ferrara F, Carrabba MG, Mastaglio S, Lorentino F, Vago L, et al. MRD in Venetoclax-based treatment for AML: Does it really matter?. Frontiers in oncology. 2022 Jul 18;12:890871.
54. Del Principe MI, Buccisano F, Maurillo L, Sconocchia G, Cefalo M, Consalvo MI, et al. Minimal Residual Disease in Acute Myeloid Leukemia of Adults: Determination, Prognostic Impact and Clinical Applications. Mediterr J Hematol Infect Dis. 2016 Oct 20;8(1):e2016052.
55. Short NJ, Fu C, Berry DA, Walter RB, Freeman SD, Hourigan CS, et al. Association of hematologic response and assay sensitivity on the prognostic impact of measurable residual disease in acute myeloid leukemia: a systematic review and meta-analysis. Leukemia. 2022 Dec;36(12):2817–26.
56. Buckley SA, Wood BL, Othus M, Hourigan CS, Ustun C, Linden MA, et al. Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis. Haematologica. 2017 May;102(5):865–73.
57. Levis MJ, Perl AE, Altman JK, Gocke CD, Bahceci E, Hill J, et al. A next-generation sequencing-based assay for minimal residual disease assessment in AML patients with FLT3-ITD mutations. Blood Adv. 2018 Apr 24;2(8):825–31.
58. Arellano ML, Thirman MJ, DiPersio JF, Heiblig M, Stein EM, Schuh AC, et al. Menin inhibition with revumenib for NPM1-mutated relapsed or refractory acute myeloid leukemia: the AUGMENT-101 study. Blood. 2025 Aug 28;146(9):1065–77.
59. Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to Review the Role of Surrogate End Points in Health Policy: State of the Art and the Way Forward. Value in Health [Internet]. Elsevier Ltd; 2017 [cited 2024 Dec 20];20:487–95.
60. Mohty M, Avet-Loiseau H, Malard F, Harousseau JL. Potential future direction of measurable residual disease evaluation in multiple myeloma. Blood. 2023 Nov 2;142(18):1509–17.
61. Blachly JS, Walter RB, Hourigan CS. The present and future of measurable residual disease testing in acute myeloid leukemia. Haematologica. 2022 Dec 1;107(12):2810.
62. Burnett A, Stone R. AML: New Drugs but New Challenges. Clin Lymphoma Myeloma Leuk. Elsevier; 2020;20:341–50.
63. Tierens A, Arad-Cohen N, Cheuk D, De Moerloose B, Fernandez Navarro JM, Hasle H, et al. Mitoxantrone Versus Liposomal Daunorubicin in Induction of Pediatric AML With Risk Stratification Based on Flow Cytometry Measurement of Residual Disease. J Clin Oncol. 2024 Jun 20;42(18):2174–85.