Measurable Residual Disease in Clinical and Regulatory Decision Making

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THE EUROPEAN Hematology Association-European Medicines Agency (EHA2025-EMA) Joint Symposium on minimal residual disease (MRD), which took place at the EHA2025 Congress in Milan, Italy, explored its critical role in clinical and regulatory decision-making across various haematologic malignancies. Experts and patient advocates discussed advances in MRD detection, its impact on treatment strategies, and the challenges of standardisation and acceptance in both clinical practice and regulatory frameworks. While this article refers to 'minimal residual disease', the term 'measurable residual disease' is increasingly being used instead.

PATIENT PERSPECTIVES ON MEASURABLE RESIDUAL DISEASE

Opening the session, Anne-Pierre Pickaert, a patient in remission from Philadelphia chromosome-positive acute lymphoblastic lymphoma (ALL), gave a powerful insight into the patient perspective of this disease. Pickaert is also actively engaged in patient advocacy through multiple roles, including volunteering with the leukaemia and bone marrow transplant patient organisations EGMOS and the Association Laurette Fugain, contributing to the research endowment fund HTC Project focused on post-transplant complications, and serving as a board member of Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) as well as an advisor for Acute Leukaemia Advocates Networkb (ALAN).

So, how was MRD explained to her at treatment initiation? To quote, her first explanation was as follows: "It is using advanced tools to look for a tiny number of cancer cells still present in the body after treatment, even in the absence of signs of ALL on standard tests." The concept of thresholds was subsequently introduced as: "If that number of cancer cells goes beyond a certain threshold, it means the disease might come back." Finally, touching on the definition of 'MRD-negative', she was told that it refers to when cancer cells stay below the stated threshold. In summary, MRD is predictive of remission and relapse, as well as access to bone marrow transplant.

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Importantly, she addressed how terminology influences patient understanding and emotional response. For instance, she states that the term 'minimal residual disease' was historically used in clinical and research settings, but it has now been termed 'measurable residual disease'. From a patient advocate perspective, this change is meaningful. The term 'minimal' can be misleading and falsely reassuring, understating the risk and severity of the disease. Conversely, the word 'measurable' is more objective, highlighting the importance of sensitivity in detecting the disease accurately and helping patients better grasp the value of MRD monitoring in guiding care. Pickaert stressed the significant impact language can have on patients and how they perceive their disease journey. Additionally, the application of MRD as a tool varies across different blood

cancers. For instance, in ALL, acute myeloid leukaemia (AML), chronic myeloid leukaemia, and multiple myeloma (MM), MRD is seen as a reliable prognostic tool and regularly used to inform treatment decisions. However, this is not the case for other conditions, such as chronic lymphocytic leukaemia (CLL) and lymphoma, where it instead has limited use in clinical practice and remains largely confined to the research setting.

She also introduced the term 'MRD-anxiety' used in cancer care to describe the emotional distress patients may experience after an indication that some cancer cells remain after treatment. Finally, she highlighted the heterogeneity in testing methods, time points in testing, and inconsistent definitions across various institutions and countries. "This is making comparability difficult and challenging, and from a European level, when we advocate, there is definitely heterogeneity in access."

To conclude, Pickaert recognised the potential of MRD as an early indicator of treatment efficacy, but only on the following conditions: firstly, if MRD thresholds and assessment guidelines are agreed upon globally; secondly, if MRD is validated as a surrogate endpoint based on robust correlation with survival; and finally, if overall survival is collected as a co-primary endpoint.

A CASE STUDY FROM ACUTE LYMPHOBLASTIC LEUKAEMIA: A CLINICIAN'S PERSPECTIVE

Following this, Nicola Gökbuget, Department of Medicine II, Goethe University Hospital, Frankfurt, Germany, offered a clinical perspective. MRD refers to the small population of cancer cells remaining in the body that are not detectable by conventional cytomorphology, thus requiring more sensitive cytometric methods and thresholds.

She began by presenting an example case of a 28-year-old male experiencing symptoms of bruising and fatigue. He was subsequently diagnosed with common B-lineage ALL and treated with an intensive regimen comprising induction, consolidation, re-induction, and maintenance therapy. Despite achieving complete haematological remission, molecular failure was detected following the first two rounds of induction chemotherapy and the first round of consolidation.

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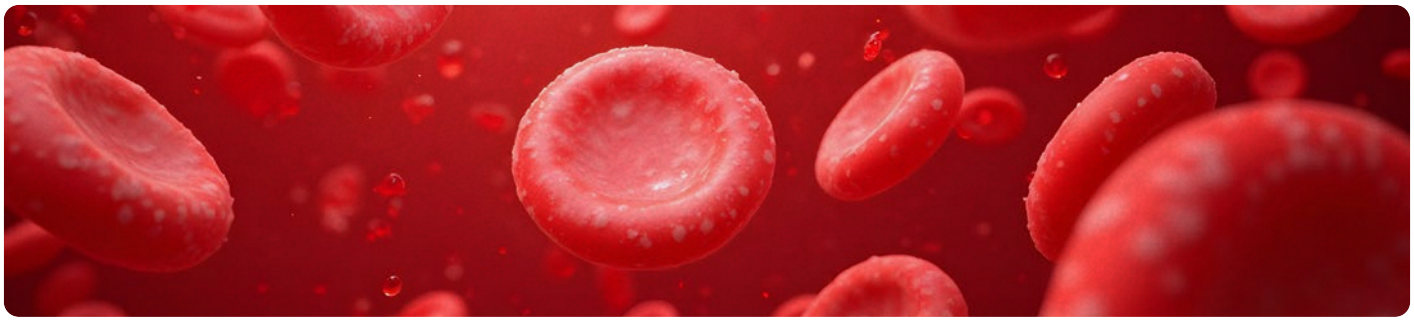

Historically, in the absence of MRD testing, decisions were guided solely by haematologic response, and salvage treatment was the only option when first-line treatment failed. With the introduction of MRD testing, the traditional approach would recommend stem cell transplantation (SCT) based on MRD. In contrast, the current standard approach advises targeted therapy based on MRD, followed by SCT. This shift showcases the progress made from generalised treatment to more targeted approaches, enhancing patient outcomes.

How should MRD be incorporated in the clinical trial landscape? Traditionally, new drug compounds were tested only after haematologic relapse or treatment failure. However, a more forward-looking strategy proposes evaluating new drug compounds at the molecular level. This approach benefits patients by enabling earlier detection and intervention. It also supports clinical care, since the condition worsens significantly once a full haematologic relapse occurs, compared to a molecular relapse. For instance, the blood count deteriorates, leukaemia burden is higher, the risk of organ infiltration and biologic resistance is higher, and the time window for SCT is shorter compared to during molecular relapse, as the disease is less advanced. Gökbuget stated: "I want to make the point that MRD is not only an endpoint, but it's an indication to treat with new compounds."

To conclude, she highlighted the prerequisites needed for MRD-directed treatment, including historical data showing a correlation between MRD response and outcome; established, standardised MRD testing in reference laboratories; reimbursement of MRD testing; MRD-based indication for new compounds; and MRD-based response criteria.

ATTITUDES ON MINIMAL RESIDUAL DISEASE IN FRONTLINE MULTIPLE MYELOMA

Subsequently Anna Smit, Erasmus Medical Center Cancer Institute, Rotterdam, the Netherlands, presented the results of an interesting study that evaluated the attitudes of healthcare professionals and regulators towards MRD as an efficacy endpoint in transplant-eligible MM.

It can often take many years for a significant impact to be observed in progression-free survival and overall survival for novel drugs in first-line randomised trials in MM. Therefore, earlier endpoints, such as MRD, have been suggested to inform clinical and regulatory decisions. However, the question has been raised regarding whether MRD-negative response may serve as a primary endpoint from both a clinical and regulatory standpoint. In 2024, the FDA endorsed MRD as a surrogate endpoint for accelerated drug approval in MM; however, this has not yet been translated in Europe.

To better understand the attitudes towards MRD as an efficacy endpoint in frontline treatment of transplant-eligible MM, Smit and her team conducted a global survey. Participants comprised of healthcare professionals from the International Myeloma Society (IMS), national myeloma working parties, and the EHA, as well as regulators from EMA and other international

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regulatory agencies. In total, 389 healthcare professionals and 40 regulators participated. Results showed that healthcare professionals were more willing to accept a 20% increase in toxicity when the MRD negativity difference was 30% (45–75%). Acceptance declined as MRD differences narrowed and toxicity increased. Regulators showed a similar trend, but placed greater emphasis on toxicity than on MRD negativity. Overall, the majority of participants agreed that treatments with an MRD negativity increase of >20% and toxicity increase from 40% to a maximum of 60% were clinically useful.

The second component of the survey assessed the attitudes of both cohorts towards the use of MRD as an early endpoint in MM. The majority of healthcare professionals agreed or strongly agreed that MRD-negative status is the preferred endpoint in clinical trials for newly diagnosed MM. In contrast, the majority of the regulators disagreed with this statement. In addition, most healthcare professionals felt that requiring progression-free survival benefit delays access to innovative treatment for patients in MM, while only some regulators agreed and the majority disagreed. Despite these differences, there was broad consensus among all participants on the need to establish a globally consistent approach to MRD testing.

WHAT DOES MINIMAL RESIDUAL DISEASE MEAN FOR THE REGULATORS?

Finally, Pierre Démolis took the stage to give an insight into the regulators' side. He discussed the evolving role of MRD as a parameter in drug evaluation, emphasising that while MRD may not yet serve as a standalone endpoint for drug registration, it remains valuable for guiding treatment decisions and assessing prognosis. In certain late-stage or limited-treatment-option cases, MRD could support early or conditional approval, much like overall response rates have in haematology. However, true surrogacy for efficacy endpoints, such as progression-free or overall survival, is unlikely in the near future. Still, MRD is already used as a supportive endpoint, and its role may expand under specific regulatory frameworks without requiring a paradigm shift.

CONCLUSION

The symposium highlighted MRD's growing significance as both a prognostic tool and a potential early efficacy endpoint, while also highlighting the need for global standardisation in testing and interpretation. Despite differing perspectives among clinicians, regulators, and patients, there is a shared commitment to advancing MRD integration to improve patient outcomes and accelerate access to innovative therapies.