Rising tide: the growing role of minimal residual disease in hematologic oncology trials and implications for health technology assessment

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Introduction

Minimal residual disease (MRD) is increasingly recognized as a robust biomarker in hemato-oncology, particularly in multiple myeloma (MM), where—following broad clinical support and utilization—it has recently been accepted by the FDA as a regulatory endpoint to support accelerated approval.[1]

In contrast, health technology assessment (HTA) agencies continue to prioritize established clinical endpoints such as progression-free survival and overall survival when determining the clinical and economic value of new therapies.

Objectives

- To evaluate how often HTA agencies will be faced with MRD as a primary endpoint in future assessments
- To review how MRD is appraised and critiqued in HTAs and understand how HTA agencies may adapt their methodologies to accommodate the use of MRD while maintaining methodological consistency

Methods

ClinicalTrials.gov was prospectively searched for interventional trials in Phase 1/2 or higher that included MRD as an endpoint (any hierarchy). Selected trials were stratified by year of initiation and indication.

For trials with MRD as a primary endpoint, European marketing authorization status was reviewed, and the corresponding HTA agency websites in the UK, France, and Germany (National Institute for Health and Care Excellence, NICE; Haute Autorité de Santé, HAS; and Gemeinsame Bundesausschuss, G-BA) were searched for relevant appraisals.

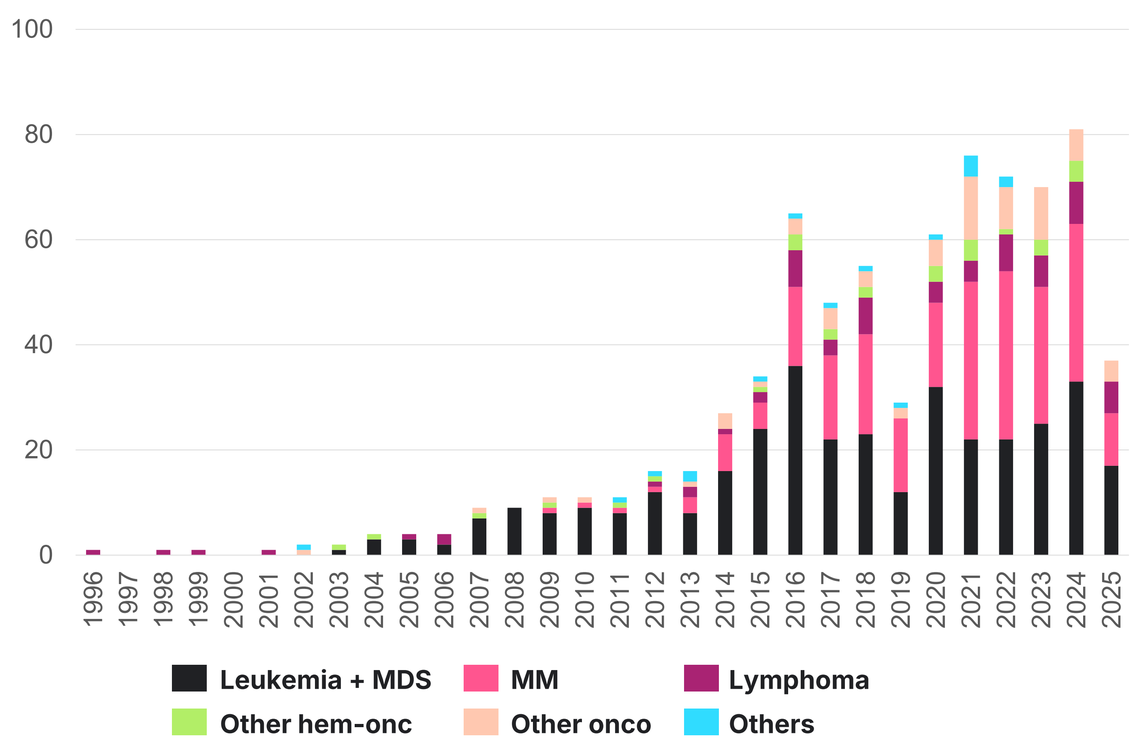
Results

Figure 1 shows the trials identified in the searches by year of initiation.

A total of 758 trials incorporating MRD measurement were identified, with initiation dates ranging from 1996 to April 2025.

There was a marked increase in the past decade: Only 130 trials were initiated between 1996 and 2014, compared with 628 trials started from 2015 to April 2025.

Figure 1: **Trials including MRD as an endpoint, by year of initiation and indication (2025 includes data up to June 2025)**



Hem-onc, hemato-oncology indication; onco, oncology indication; MDS, Myelodysplastic syndrome.

The number of hemato-oncology trials including MRD as an endpoint has increased from 10 initiated in 2010 to 75 in 2024.

Of the 546 identified trials, the majority were in MM (n=217), followed by chronic lymphocytic leukemia (CLL, n=126), acute myeloid leukemia (AML, n=109), and acute lymphoblastic leukemia (ALL, n=94).

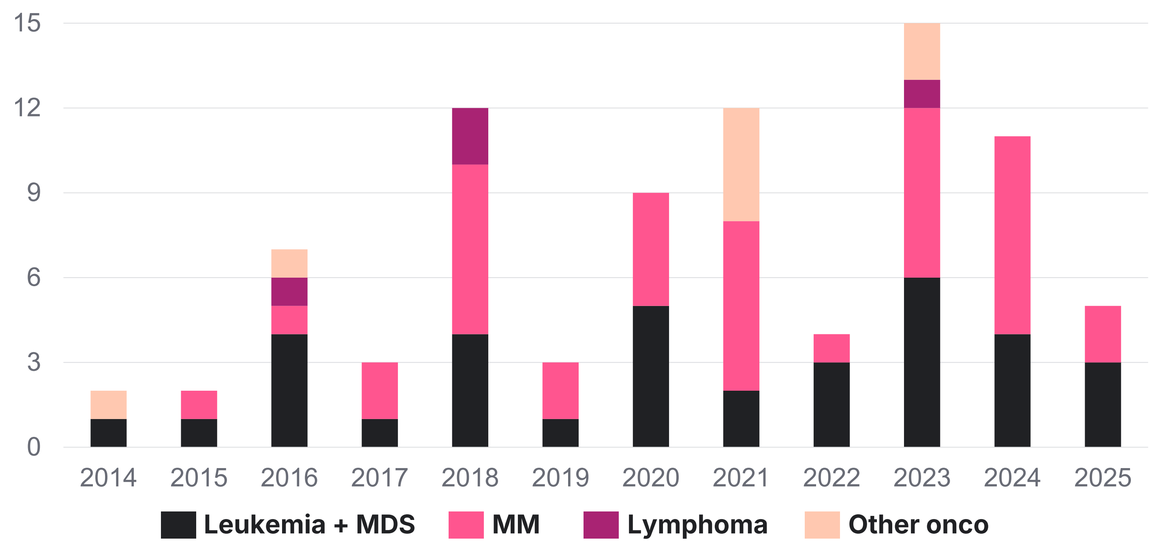
In contrast, very few trials in chronic myeloid leukemia use the term MRD, with only three such trials initiated between 1996 and 2025.

Figure 2 displays the number of trials assessing MRD as a primary endpoint, presented by year of initiation.

Relatively few trials used MRD as a primary endpoint; this approach was most common in MM trials, accounting for 3%-25% of MM trials per year in the past 19 years, followed by AML and CLL.

As of June 2025, only a single trial with MRD as a primary endpoint had been through HTA (NCT03109093).

Figure 2: **Trials including MRD as a primary endpoint, by year of initiation and indication**



Onco, oncology indication; MDS, Myelodysplastic syndrome.

Three HTA reports based on data from trials including an MRD endpoint were identified, all of which evaluated blinatumomab in adult patients with MRD of B-precursor ALL.[2-4]

Among the three HTAs that commented on the validity of MRD, perspectives varied considerably. Despite acknowledging the existing evidence showing an association between MRD negativity and recurrence/mortality, HAS and G-BA regarded MRD as a non-validated surrogate endpoint.

On the other hand, NICE considered MRD a predictor of relapse and included it among matched variables in indirect comparisons and economic analyses.

MRD inclusion in clinical trials has grown substantially over the past 10 years.

The majority of MRD endpoint trials focus on leukemias and MM.

Relatively few hemato-oncology trials use MRD as a primary endpoint, most commonly in MM.

MRD consideration in HTA is still limited.

Conclusions

- MRD is an increasingly important endpoint for accelerating access to innovative therapies, particularly in liquid tumors where it can be reliably measured and linked to clinical outcomes.
- Its adoption in other cancers remains limited, possibly owing to technical and regulatory challenges.
- Few trials use MRD as a primary endpoint, and HTA appraisals based on MRD remain rare and inconsistent.
- While NICE recognizes MRD as a predictor of relapse, HAS and G-BA consider it a non-validated surrogate endpoint.
- Greater alignment between regulators and HTA agencies is needed to support broader patient access to MRD-driven therapies.

References

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