Growing Acceptance of Minimal Residual Disease (MRD) as a Primary Endpoint in Multiple Myeloma (MM) Clinical Trials

Carole A. Jones[1], Alex T. Watson[2], Zsófia Wolkensdorfer[2], Oliver R. Wilkes[2]
[1] VML Health, London, UK, [2] VML Health, Manchester, UK

Address: Sea Containers, 18 Upper Ground, London, UK
Website: https://www.vml.com/expertise/health
Contact email: carole.jones@vml.com

CO95

BACKGROUND

- Multiple myeloma (MM) is a rare haematological cancer accounting for ~1% of cancer cases with a median age at diagnosis of 70 years[1]
- Therapeutic advancements have improved the depth and duration of response to treatment and patient survival, but MM remains incurable, and most patients eventually relapse[2]
- Relapse has been linked to the presence of a small number of MM cells that remain in the patient's body even when they achieve complete response to treatment, referred to as minimal residual disease (MRD)[3]
- MRD status is measured by highly sensitive methods that detect MM cells in the bone marrow of patients, including next-generation flow cytometry (NGF) and next-generation sequencing (NGS)[4]
- MRD-negativity, defined as the lack of any detectable MM cells at a given sensitivity, is associated with improved progression-free survival (PFS) and overall survival (OS) as demonstrated by large-scale meta-analyses[5-7]
- Acceptance of MRD as an important outcome is growing amongst regulatory bodies. The U.S. Food and Drug Administration's Oncologic Drugs Advisory Committee (ODAC) unanimously voted in favour of the use of MRD as an end point to support accelerated approval of treatments in multiple myeloma at a meeting on April 12th, 2024[8]
- MRD testing during follow-up or surveillance for prognostication is recommended by the latest National Comprehensive Cancer Network (NCCN) guidelines[9]
- The aim of this study was to investigate trends in assessing MRD as a treatment outcome in the MM clinical trial setting and to explore perceptions and patterns of use in the real-world setting

METHODS

- Searches using the filter 'condition/disease' in ClinicalTrials.gov were conducted to identify trials studying 'multiple myeloma'
  - Studies were filtered to include recruiting; active, not recruiting; and completed trials
  - Studies were included in the analysis if they had a start date between 1st January 2014 and 31st December 2023, and were grouped based on the year of the start date
- Trials investigating MRD as an endpoint were identified using the filter 'outcome measure' with the search word: 'MRD'
- Trials were grouped based on whether they assessed MRD as a primary or secondary endpoint
  - In trials studying MRD as a primary endpoint, the following information on the measurement of MRD was collected: time of measurement, technique, and sensitivity
  - A targeted literature review was conducted to supplement information on the methods for MRD testing in trials identified through the ClinicalTrials.gov search
- ClinicalTrials.gov searches were conducted between 10th January – 8th April 2024
- To assess the use of MRD testing in the real-world and physician perception of MRD testing, an online survey of haemato-oncologists and oncologists was conducted in the US (n=10), UK (n=7), Spain (n=7), France (n=5), Germany (n=5), and Italy (n=7)
  - Participants were reimbursed for completing the survey
  - Participants received different questions based on whether they reported testing their patients for MRD or not

LIMITATIONS

- Some of the studied trials did not report information on MRD testing techniques and sensitivities on ClinicalTrials.gov nor in publications, limiting the findings on the trends of the different MRD methods used in clinical trials
- No conclusions could be drawn for the time of MRD assessment used in clinical trials, as these timings were not reported consistently (e.g., after 1 year, after Cycle 5, 12-months post-transplant) across studies
- The small number of participants in the survey limits the generalisability of the findings

RESULTS: TRENDS IN MRD EVALUATION IN CLINICAL TRIALS

TRENDS IN EVALUATING MRD AS AN OUTCOME IN CLINICAL TRIALS

- During the study period, the number of MM trials initiated per ClinicalTrials.gov increased by ~50% from 96 trials with a start date in 2014 to a peak of 170 MM trials starting in 2021, followed by 163 trials in 2022, and 153 in 2023[10]
- The proportion of MM trials investigating MRD as an endpoint also showed an increasing trend. Approximately 10% of trials investigated MRD in 2014-2016, with this number rising to 30% in 2022-2023[11]
- Over time, more MM trials assessed MRD as a primary, or as both a primary and secondary endpoint (FIGURE 1)[11]
- Trials assessing MRD as a primary endpoint recruited various patient populations, including patients with smoldering MM, newly-diagnosed (NDMM), and relapsed-refractory MM (RRMM) (FIGURE 2)[11]

FIGURE 1. Number of MM trials registered on ClinicalTrials.gov that assess MRD as a primary, secondary, and/or tertiary outcome.

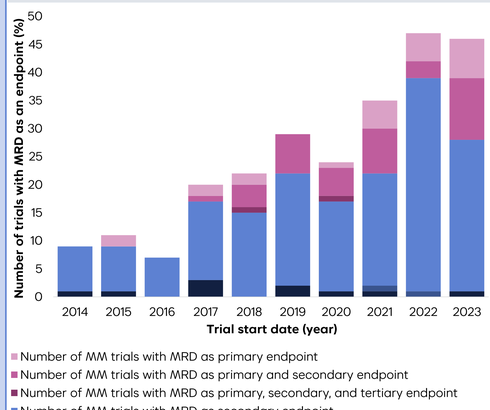
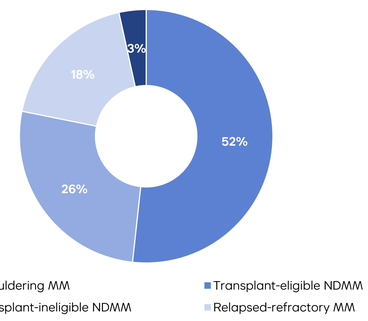


FIGURE 2. Patient populations* included in MM trials assessing MRD as an endpoint.

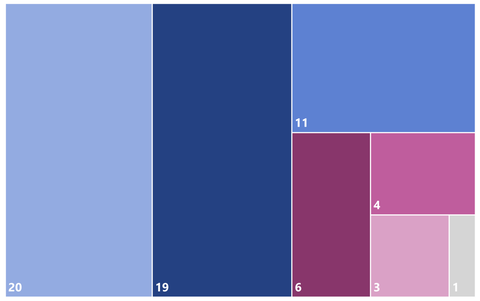


Some trials included more than one of these patient populations. Those trials are included in the proportion for all relevant patient populations. References to individual trials are shown in Supplement.

TRENDS IN MRD TESTING METHODOLOGIES IN CLINICAL TRIALS

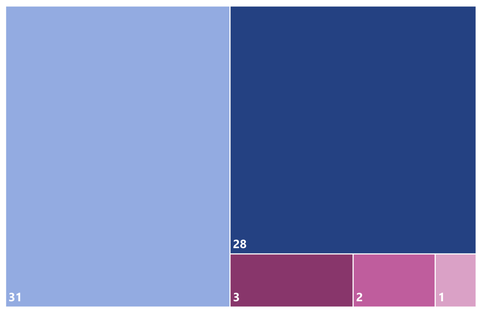
- NGS was the MRD assessment method of choice in these studies, with more than half (55%) of the studies where the MRD assessment method was declared, utilizing NGS (FIGURE 3)[11]
  - NGF was the second most widely used method of MRD testing, used in 41% of studies that declared their MRD assessment method
  - Other techniques, such as mass spectrometry and flow cytometry were considerably less common and used as the primary tool of MRD assessment in 9% of studies that reported the intended MRD assessment method
- The 10^{-5} threshold was the MRD-negativity threshold of choice for clinical trials, with 91% of trials that reported the threshold using 10^{-5} (FIGURE 4)[11]
  - 10^{-4}, and 10^{-6} were less widely used, with 3% and 15% of trials using these thresholds, respectively
- The timepoint of MRD testing was highly variable across clinical trials with very little commonality, preventing comparisons of methodologies[11]

FIGURE 3. Method of choice for MRD testing in clinical trials that measured MRD as a primary endpoint (data shown are number of respondents).



References to individual trials are shown in Supplement.

FIGURE 4. MRD testing sensitivity used in clinical trials that measured MRD as a primary endpoint (data shown are number of respondents).



References to individual trials are shown in Supplement.

CONCLUSIONS

- MRD is gaining momentum as an endpoint in MM, with increasing use over time in clinical trials. This acceptance of MRD is reflected in the real-world, with >80% of physicians surveyed saying they are somewhat or very likely to change treatment decisions based on clinical MRD data
- MRD testing methodology - especially timing of measurement - is highly variable across clinical trials, reflecting a lack of uniformity in real-world testing approaches. There remains a need for standardisation to improve reliability and comparability of outcomes
- While physicians would prefer to test patients more frequently, they cited patient burden and access to treatment as major barriers to testing, highlighting the need to develop less invasive MRD testing methods and to increase testing funding
- Almost one third of physicians stated a need for clinical guidance on treatment adjustments following MRD testing outcomes, which could facilitate de-escalation of treatment for MRD-negative patients

RESULTS: PERCEPTION AND REAL-WORLD USE OF MRD TESTING

- Of the physicians who completed the survey (n=38), 76% were haemato-oncologists and 24% were oncologists
- Approximately half (47%) of the respondents worked in large teaching hospitals, 26% in oncology specialty clinics, 8% in an academic site, 8% in a regional health centre, 5% at a rural hospital, and 5% of respondents identified as independent oncologists
- 28 physicians reported testing their patients for MRD, and 10 physicians reported that they do not test for MRD in their practice
- Of respondents who test the MRD status of their patients, 46% test all patients with MM, 43% test those with high-risk disease, 32% test patients in remission, and 7% test at disease relapse
- The most common frequency for testing was reported as once every 6-12 months (43% of responses; 12/28). Just over half (57%; 16/28) of physicians indicated that they would prefer to test once every 3–6 months in the future (FIGURE 5)
- Of physicians who test the MRD status of patients, 9 reported changing the treatment plan based on MRD outcomes during maintenance treatment, while 11 physicians said they do not change treatment based on MRD results. Four physicians reflected that other factors are considered before changing treatment based on MRD outcomes
- Most survey participants (79%) responded that they are somewhat likely to change their treatment decisions if a regimen shows superior MRD-negativity compared with standard-of-care in a clinical trial (FIGURE 6)

FIGURE 5. Number of physicians responding to how frequently they typically test MRD status (**a**) and how frequently they think testing should be done in the future (**b**).

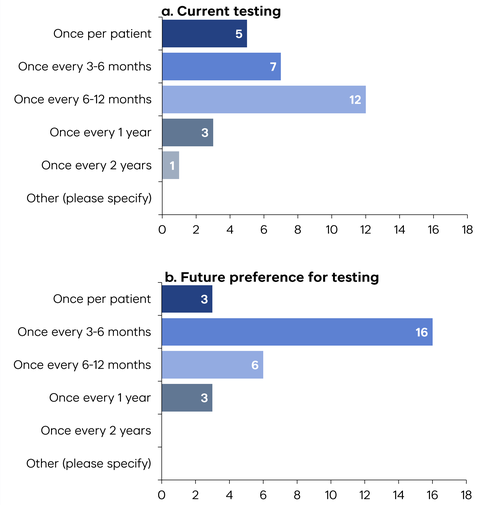
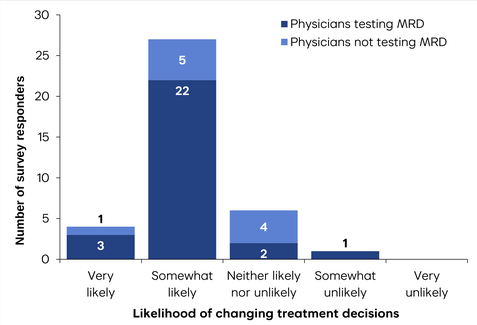


FIGURE 6. Likelihood of changing MRD treatment decisions based on clinical data across physicians who test and who do not test MRD.



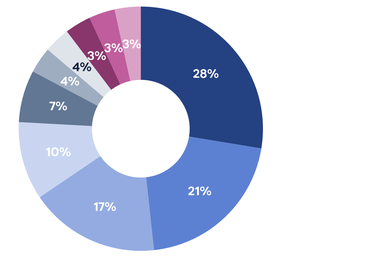
- The barriers to MRD testing encountered differed between the type of health centre respondents practice in, with patient burden associated with MRD testing procedure, MRD testing coverage or reimbursement, and patient willingness to undergo testing identified as the most common barriers (TABLE 1)

TABLE 1. Barriers to MRD testing per health centre type. Participants included physicians who test MRD status of patients. Participants could select multiple answers.

Barrier to testing	Overall (N=28)	Large teaching hospital (N=15)	Oncology specialty clinic (N=7)	Independent oncologist (N=1)	Academic site (N=2)	Regional health centre (N=3)
Patient burden associated with bone marrow sampling, n (%)	18 (64%)	9 (60%)	5 (71%)	1 (100%)	2 (100%)	1 (33%)
MRD testing coverage/ reimbursement, n (%)	11 (39%)	6 (40%)	1 (14%)	0	2 (100%)	2 (67%)
Patient willingness to undergo treatment, n (%)	9 (32%)	4 (27%)	3 (43%)	1 (100%)	0	1 (33%)
Lack of baseline sample for NGS, n (%)	8 (29%)	6 (40%)	0	0	1 (50%)	1 (33%)
Patient ability to attend testing appointments, n (%)	7 (25%)	4 (27%)	2 (29%)	0	1 (50%)	0
Availability of lab tests within the clinic, n (%)	7 (25%)	3 (20%)	2 (29%)	0	2 (100%)	0
Patient financial toxicity, n (%)	4 (14%)	3 (20%)	1 (14%)	0	0	0
No barriers, n (%)	2 (7%)	1 (7%)	1 (14%)	0	0	0

- To support the use of MRD status in treatment decisions, 8 physicians mentioned the need for guidelines and national guidance, 6 highlighted the need for funding, reimbursement or lower test prices, and 5 responders reported wanting to see more clinical evidence on MRD (FIGURE 7)

FIGURE 7. What more is needed to support the use of MRD in treatment decisions?



REFERENCES

1. Zhou L, Yu Q, Wei G, *et al.* BMC Cancer. 2021;21:606. 2. Bhatt P, Kloock C, Comenzo R. Current Oncology. 2023;30(2):2322-2347. 3. Thompson PA, Wierda WG. Blood. 2016;127(3):279-286. 4. Medina-Herrera A, Sarasquete ME, Jiménez C, et al. Cancers (Basel). 2023;15(14):3687. 5. Munshi NC, Avet-Loiseau H, Anderson KC, et al. Blood Advances. 2020;4(23):5988-5999. 6. Durie BGM. 2024. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024 7. Landgren CO. 2024. Available at: https://www.fda.gov/advisory-committees/advisory-committee-calendar/april-12-2024-meeting-oncologic-drugs-advisory-committee-meeting-announcement-04122024 8. Targeted Oncology. 2024. Available at: https://www.targetedonc.com/view/fda-odac-meeting-april-12-mrd-myeloma-trials. 9. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 3.2024. 10. ClinicalTrials.gov.2024. Available at: https://clinicaltrials.gov/search?cond=Multiple%20Myeloma&aggFilters=status:rec%20act%20com. Accessed: 10 January 2024. 11. ClinicalTrials.gov. 2024. Available at: https://clinicaltrials.gov/search?cond=Multiple%20Myeloma&aggFilters=status:rec%20act%20com&outc=MRD. Accessed: 8 April 2024.

DISCLOSURES

No external funding was received for this work.

Presented at ISPOR; May 5–8, 2024; Atlanta, Georgia, United States.