Myeloma in Focus:
Information for healthcare providers

Minimal Residual Disease (MRD)

This document, created by Sanofi, will aim to provide education to healthcare providers in relevant topics in multiple myeloma (MM). This first edition will focus on minimal residual disease (MRD) and will include an overview of MRD and the impact of achieving early and sustained MRD negativity on patient prognosis.

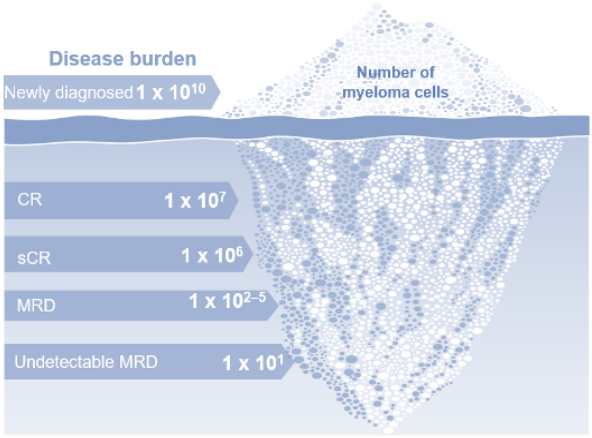
MRD has emerged as one of the most important independent prognostic factors in MM. It is being developed as a prognostic tool for monitoring patients to inform adaptive treatment approaches, and as a therapeutic endpoint in clinical trials to support drug approvals in MM patients. Due to a lack of standardization and disparities in methodology across trials, MRD is not yet accepted by regulatory bodies as a surrogate endpoint. However, MRD is currently being investigated as a primary endpoint in several clinical trials and it is hoped that their findings will shed further light on the value of MRD assessment in MM.

In this issue

What is MRD?

MRD refers to the low level of malignant cells that persist even after a complete response to myeloma treatment.[1] If no MRD can be detected, patients are known as MRD negative (MRD–), which is associated with significantly improved survival outcomes.[1]

The International Myeloma Working Group (IMWG) define an MRD– response as *'the absence of clonal malignant plasma cells in patients with a suspected complete response (CR), assessed with a sensitivity of at least 10^{-5}.'*[1]



Traditional response evaluation techniques in MM are the 'tip of the iceberg', and do not detect all remaining malignant cells; MRD analysis enables a deeper level of response to be measured.

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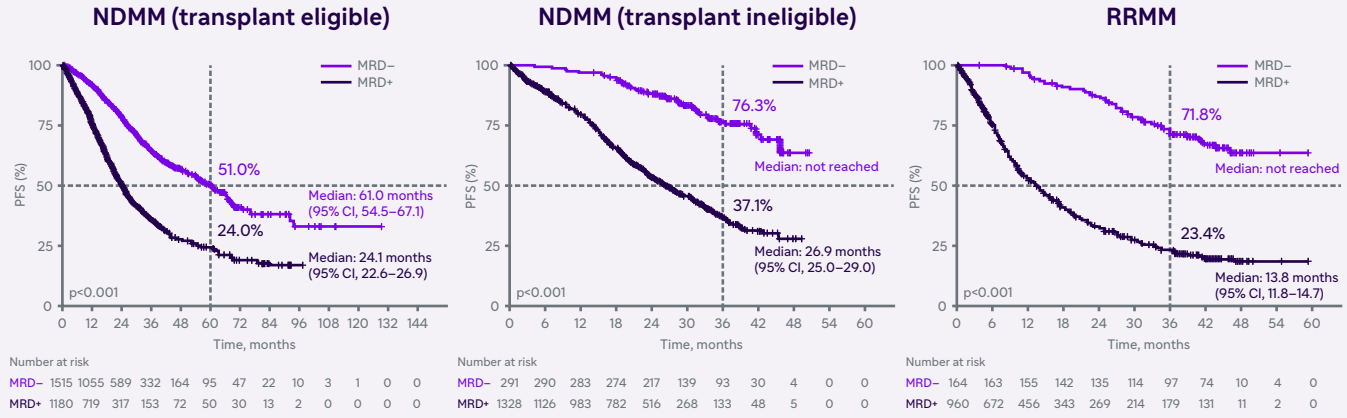
The impact of MRD– on prognosis

MRD– confers a favorable outcome in MM, regardless of disease setting (newly diagnosed MM or relapsed/refractory MM), and is associated with a longer progression-free survival (PFS) compared with MRD positive (MRD+) patients across the treatment continuum (Figure 1).[2]

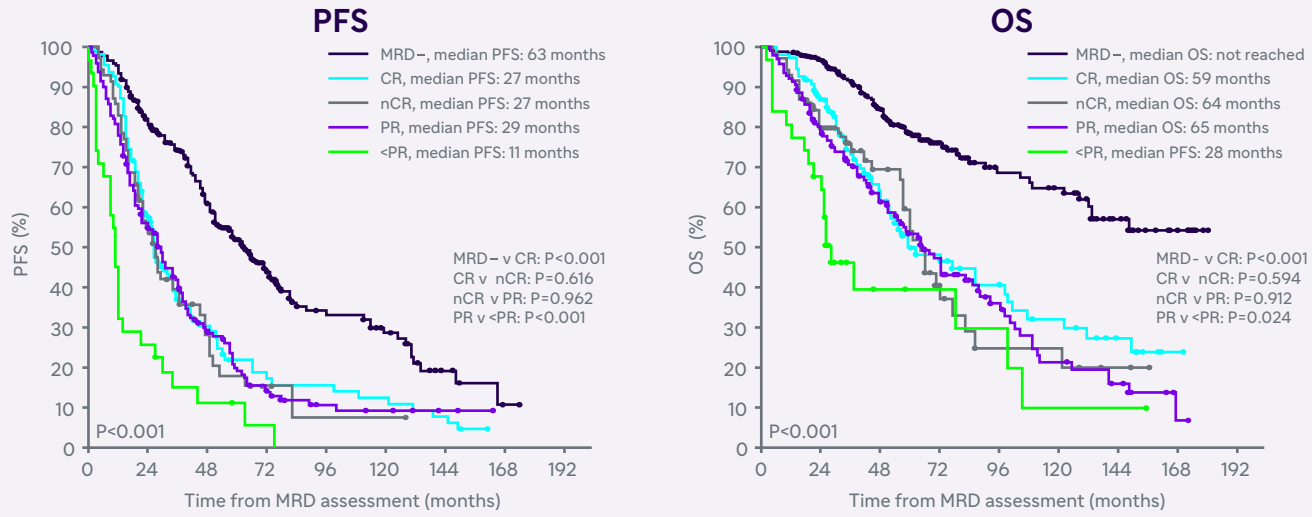
MRD provides a better indicator of outcomes than traditional response assessment, as demonstrated by findings from a pooled analysis of three PETHEMA/GEM trials in newly diagnosed MM. In this pooled analysis of 609 patients, MRD– status was shown to surpass the prognostic value of CR achievement for PFS and overall survival (OS) (Figure 2).[3]

Figure 1: PFS by MRD status in patients in key disease settings[2]



MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma

Figure 2: Pooled analysis of three PETHEMA/GEM trials in NDMM (N=609)[3]
(MRD sensitivity level: 10^{-4} to 10^{-5})



(n)CR, (near) complete response; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival; PR, partial response

Additionally, achieving MRD– may overcome poor survival outcomes associated with high-risk cytogenetics.[4] This is supported by findings from the Phase 3 PETHEMA/GEM2012MENOS65 trial, which showed that patients with high-risk cytogenetics and undetectable MRD have similar outcomes to patients with standard-risk disease after VRd induction/consolidation (Figure 3).[4]

Several cytogenetic abnormalities have been identified to confer poor prognosis in MM[5]

- **t(4;14)**
- **t(14;16)**
- **t(14;20)**
- **del(17/17p)**
- **gain(1q)**
- **hypodiploidy**
- **del(13)**

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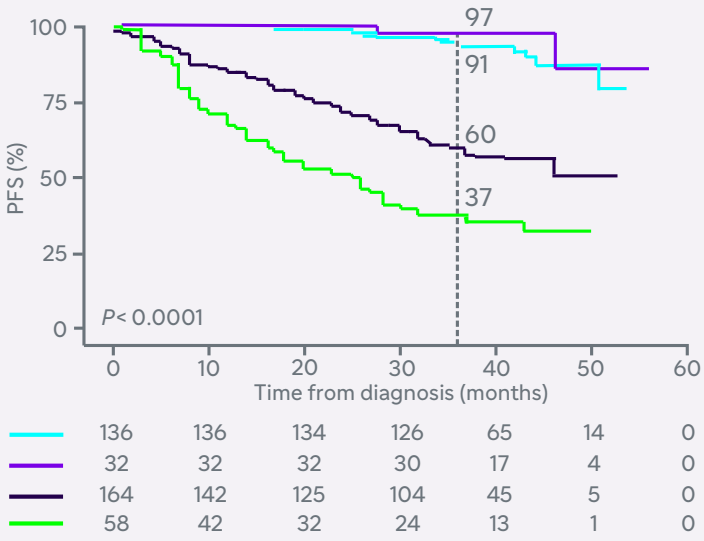
Figure 3: PFS in patients with high-risk (n=300) vs standard-risk (n=90) cytogenetic abnormalities in PETHEMA/GEM2012MENOS65[4]



Standard risk CA – Undetectable MRD
High risk CA* – Undetectable MRD
Standard risk CA – Persisting MRD
High risk CA* – Persisting MRD

*High-risk defined as patients with t(4;14), t(14;16), and/or del(17p13) by fluorescent in situ hybridization (FISH)

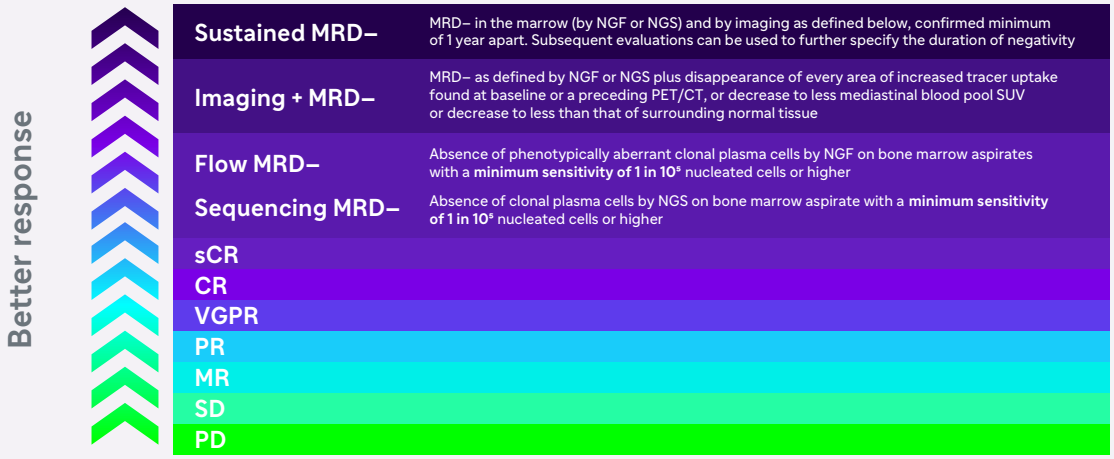
CA, cytogenetic abnormalities; MRD, minimal residual disease; PFS, progression-free survival

The importance of sustained MRD–

Sustained MRD–, characterized by two consecutive MRD- results (10^{-5}, 12 months apart), is considered to be the best response per the IMWG criteria (Figure 4).[1]

These recommendations from IMWG are supported by numerous data and have been demonstrated in a longitudinal study conducted in transplant-eligible MM; the analysis showed that patients with sustained MRD– had significantly improved PFS and OS compared with those who lost MRD– status or had persistent MRD+ (Figure 5).[6] This trend has also been demonstrated across a number of Phase 3 studies in both newly diagnosed MM and relapsed/refractory MM,[7-9] all of which have demonstrated improved PFS with sustained MRD–.

Figure 4: IMWG Response criteria[1]



CR, complete response; CT, computed tomography; IMWG, International Myeloma Working Group; MR, minimal response; MRD, minimal residual disease; NGF, next generation flow; NGS, next generation sequencing; PD, progressive disease; PET, positron emission tomography; PR, partial response; sCR, stringent complete response; SD, stable disease; SUV, standardized uptake value; VGPR, very good partial response

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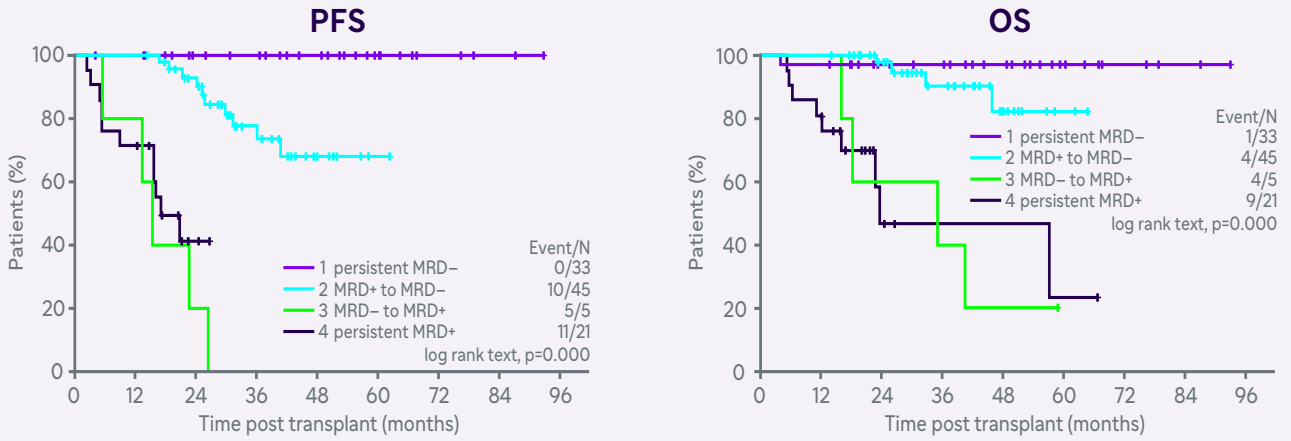
Figure 5: Longitudinal study on MRD evolution patterns for predicting the prognosis of patients with transplant-eligible NDMM (N=104)[6]



MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; OS, overall survival; PFS, progression-free survival

Early achievement of MRD– leads to improved survival outcomes

The importance of achieving MRD negativity earlier in the treatment period was supported by a retrospective study of 155 newly diagnosed MM patients in a single institution, which demonstrated significant improvements in outcomes with early achievement of MRD– prior to autologous stem cell transplant (ASCT) (Figure 7). Interestingly, in this same study, early MRD– was shown to be prognostic of outcomes independently of the cytogenetic risk status (Figure 8).[10]

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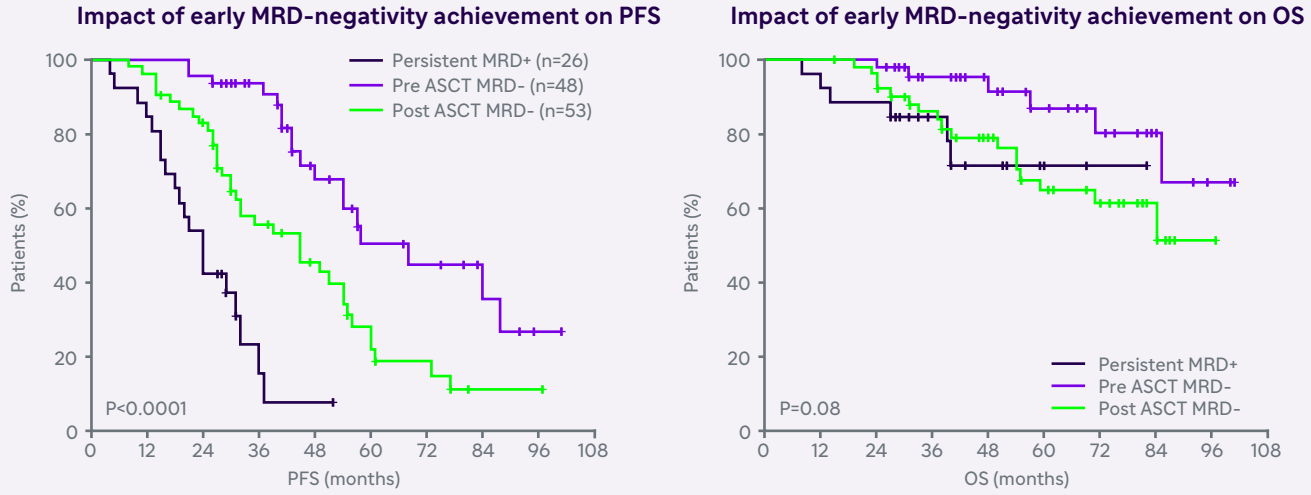
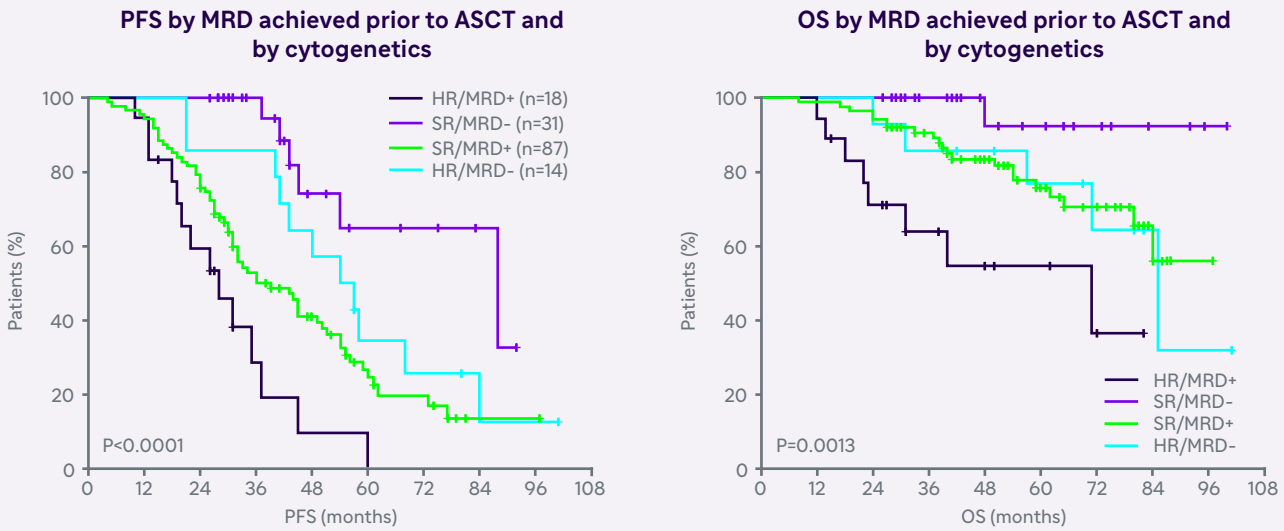
Figure 7: Impact of early MRD– achievement on PFS and OS[10]



ASCT, autologous stem cell transplant; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival

Figure 8: Early MRD– has also been shown to be an independent prognostic marker in patients with high-risk cytogenetic abnormalities[10]



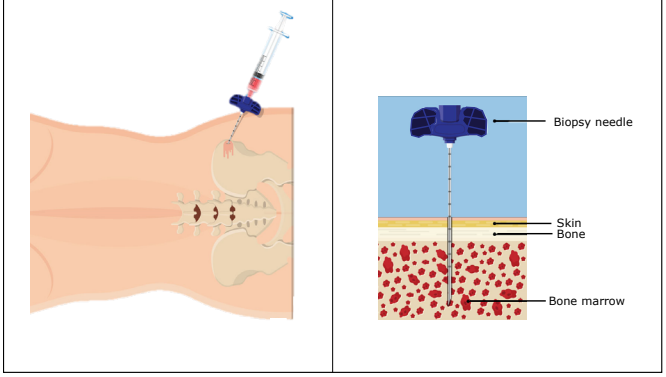
ASCT, autologous stem cell transplant; HR, high-risk; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; SR, standard risk

How is MRD assessed?

Bone marrow-based MRD techniques such as next-generation flow (NGF) and next-generation sequencing (NGS) are the most widely used to measure MRD (Figure 9). Although both methods are highly sensitive, they require bone marrow biopsies, which are invasive.[11]

Newer approaches such as PET-CT and mass spectrometry are less invasive and can detect areas of disease without the bone marrow;[11] however, lack of standardization for data acquisition, interpretation, and reporting means these techniques are not widely adopted in MRD assessment.

Bone marrow aspiration and biopsy



Current techniques for MRD assessment are invasive and require bone marrow samples

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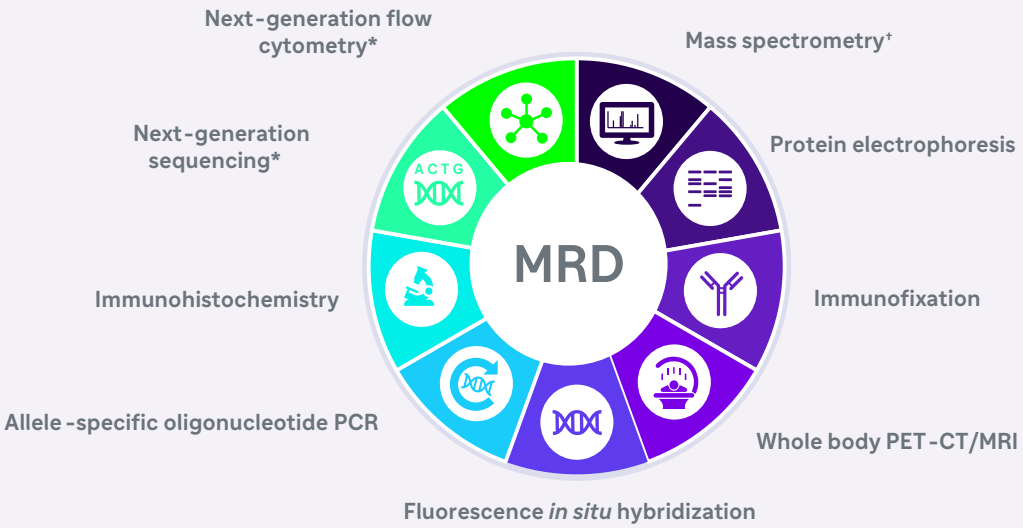
Figure 9: Techniques used to measure MRD



*Required by IMWG;[1] †Technique in development.
IFE, immunofixation electrophoresis; IMWG, International Myeloma Working Group; MRD, minimal residual disease; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; PET-CT, positron emission tomography-computed tomography

NGF and NGS

Whilst both NGF and NGS are recommended by IMWG, NGS is more sensitive than NGF but is associated with higher costs and has a longer turnaround time (5–7 days compared with 24–48 h). NGF samples require immediate experimental procedure following collection compared to NGS samples that can be frozen and stored after genomic DNA extraction for later analyses. However, interpretation of results is usually more difficult for NGF, requiring high expertise (Table 1).[12,13]

Table 1: Comparison of NGF and NGS for MRD detection[12]

	NGF	NGS
Applicability (cases)	~100%	≥90%
Baseline sample required	No	Yes
Number of cells required	2×10^7	$2–3 \times 10^6$
Fresh sample required	Yes	No
Impacted by patchy infiltration	Yes	Yes
Sensitivity	$2–4 \times 10^6$	1×10^6
Time taken	2–3 hours	≥7 days
Cost	$	$$
Availability	Wide	Limited
Advantages	Can detect hemodilution No baseline sample required More widely available and applicable Cheaper and more rapid	Can detect clonal evolution Can be performed on stored samples Requires a smaller sample More sensitive
Disadvantages	Can only be performed on fresh samples Requires a larger sample Less sensitive	Requires baseline sample Less widely available and applicable in fewer patients More expensive and slower

MRD, minimal residual disease; NGF, next-generation flow; NGS, next-generation sequencing

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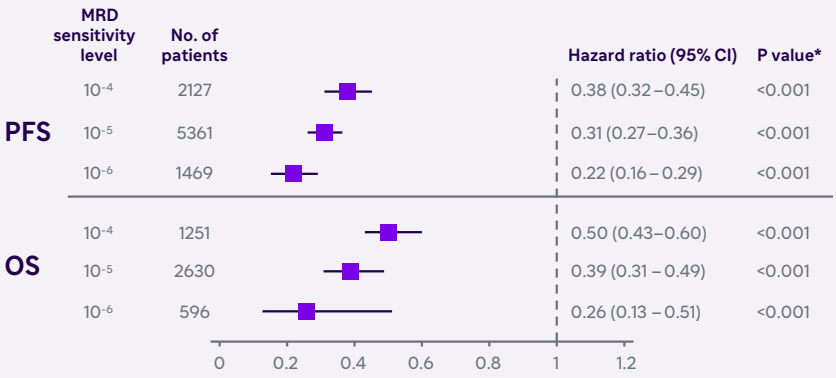
What sensitivity level should be used?

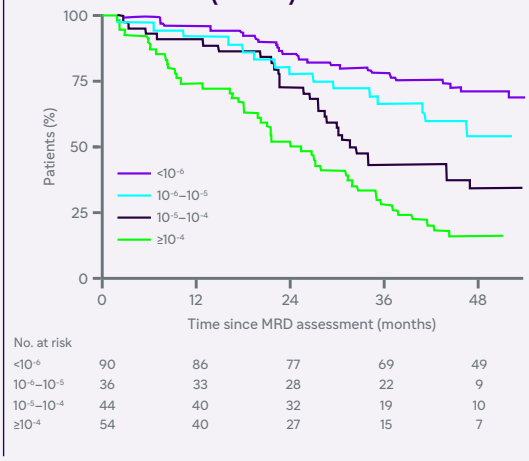
Clinical studies use a range of MRD testing sensitivity levels, with older trials reporting values at 10^{-4} and newer studies evaluating up to 10^{-6}. Current IMWG response criteria suggest MRD in CR patients should be assessed with a minimum sensitivity level of 10^{-5},[1] as improvements in PFS and OS have been observed with increasingly stringent MRD sensitivity thresholds; the greatest improvements in prognosis are observed at the highest sensitivity of 10^{-6} (Figure 10).[2,14]

Figure 10: Prognostic value of MRD– by sensitivity level in MM[2,14]

Meta-analysis of the prognostic value of MRD–sensitivity level for PFS (n=8098) and OS (n=4297) in MM[2]



PFS according to MRD sensitivity level (N=224)[14]



No. at risk

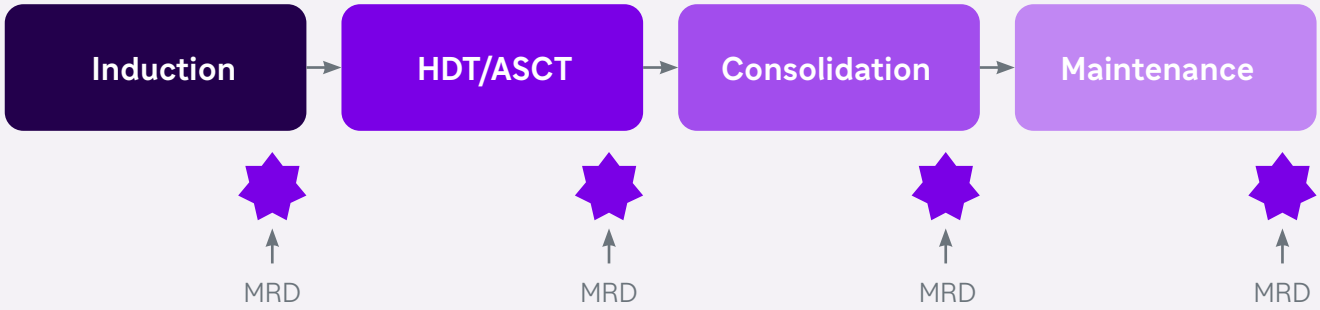
<10⁻⁶	90	86	77	69	49
10⁻⁶–10⁻⁵	36	33	28	22	9
10⁻⁵–10⁻⁴	44	40	32	19	10
≥10⁻⁴	54	40	27	15	7

*P versus MRD+
CI, confidence interval; MFC, multiparametric flow cytometry; MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PCR, polymerase chain reaction; PFS, progression-free survival

When should MRD be assessed?

Limited guidance around the timing of MRD is a prominent challenge in its assessment. Whilst MRD has been incorporated as an endpoint in several ongoing clinical trials, variation in the time points at which MRD is measured during treatment (i.e., after induction, after transplant, after consolidation, and/or during maintenance therapy [at a predetermined fixed time point(s)]) and how often these measurements are repeated, makes comparison across trials difficult.[12] There is currently no consensus regarding the optimal time points for MRD assessment in MM after initial achievement of MRD– status.[11] However, guidelines from the IMWG currently recommend MRD assessment at the end of each step of therapy in newly diagnosed MM: after induction, high-dose therapy/ASCT, consolidation, and maintenance (Figure 11).[1] No specific recommendations regarding MRD assessment time points have been provided for relapsed or refractory disease.

Figure 11: IMWG recommended time points for MRD assessment in NDMM[1]



ASCT, autologous stem cell transplantation; HDT, high-dose therapy; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma

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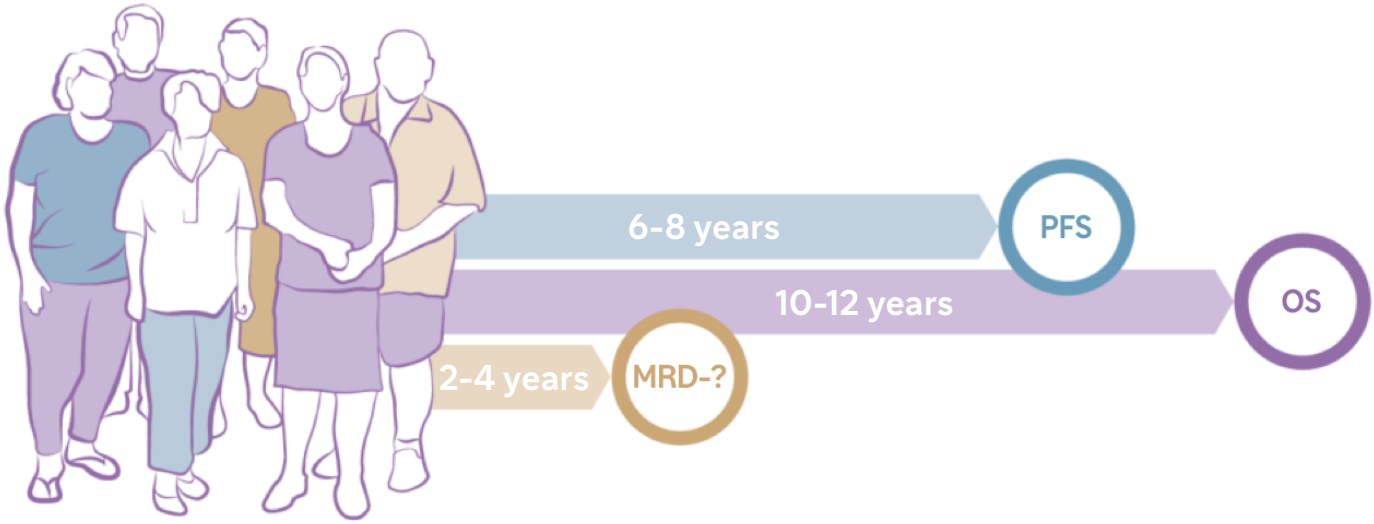
MRD as a surrogate endpoint

Clinical trials of MM have traditionally used endpoints such as OS, PFS, and response rate to determine outcomes for patients, and are required by regulatory agencies. PFS has been widely adopted as a surrogate endpoint for OS due to both practical (shorter time to a given number of events compared to OS) and clinical considerations (less influenced by subsequent therapy than OS).[15]

However, newer therapies are improving PFS rates, especially in the frontline setting, and as a result, PFS data often take many years to collect.[16] Therefore, an endpoint that reads out quicker than PFS would allow for more rapid approvals by regulatory agencies.



The ability to use MRD as a surrogate endpoint could lead to reduced trial duration and cost, exposing fewer patients to potentially toxic treatment, and lead to more rapid drug approvals.[17] This need is also reflected in the latest **ESMO guidelines**, which acknowledge that *"MRD has been found to be a surrogate endpoint for PFS in patients receiving first-line treatment and therefore may be used as an endpoint to accelerate drug development".*[18]

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In light of this, efforts are ongoing by the International Independent Team for Endpoint Approval of Myeloma MRD (i²TEAMM) initiative to further evaluate MRD as surrogate endpoint in MM.[17]

The **i²TEAMM initiative** represents a collaboration between academia and industry, with the primary objective being to evaluate and validate MRD as a surrogate endpoint for PFS through prospectively planned meta-analytic surrogacy analysis based on patient-level data[17]

8 NDMM transplant eligible studies

5 NDMM transplant ineligible studies

4 RRMM studies

Current regulatory requirements to validate MRD as a surrogate endpoint

The latest **FDA** guidance published in January 2020 provides extensive information on the meta-analysis required to validate MRD as a surrogate endpoint for MM, but do not directly address approval based on MRD through its accelerated approval pathway (Table 2).[19]

The most recent **EMA** guidance from July 2018 indicated that early approval based on MRD as an intermediate endpoint may be considered, provided that confirmatory PFS and OS data are submitted at a later stage; approvals will be decided on a case-by-case basis (Table 2).[20]

Table 2: Regulatory requirements to validate MRD as a surrogate endpoint

Criteria[19–21]	FDA	EMA
Acceptability of MRD as a validated surrogate endpoint for approval	Not acceptable yet; Agency open to discussing meta-analysis approaches	Early approval based on MRD as an intermediate endpoint may be considered, due to medical need, provided that confirmatory comprehensive data on PFS and OS from the same trial are submitted at a later stage; regulatory considerations will be decided on a case-by-case basis
MRD assay considerations	Analytically validated platform	Analytically validated platform
Measuring MRD	No specific mention of threshold	MRD will be considered undetectable if the proportion of malignant cells in the bone marrow is $<10^{-5}$
Timing of assessments	MRD should be assessed only in patients that are in CR	MRD measurement should be conducted after each treatment stage and at the time of suspected response (PR, VGPR, CR, or sCR)
Duration/durability of response	No clear guidance	Sustained undetectable MRD as a secondary endpoint, defined as undetectable MRD in patients in CR and with normal imaging that has lasted a minimum of 1 year

CR, complete response; EMA, European Medicines Agency; FDA, food and drug administration; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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Challenges in the assessment of MRD

There is substantial heterogeneity across clinical trials in how MRD is assessed and reported, creating challenges for data interpretation and for the design of subsequent studies (Table 3).[22]

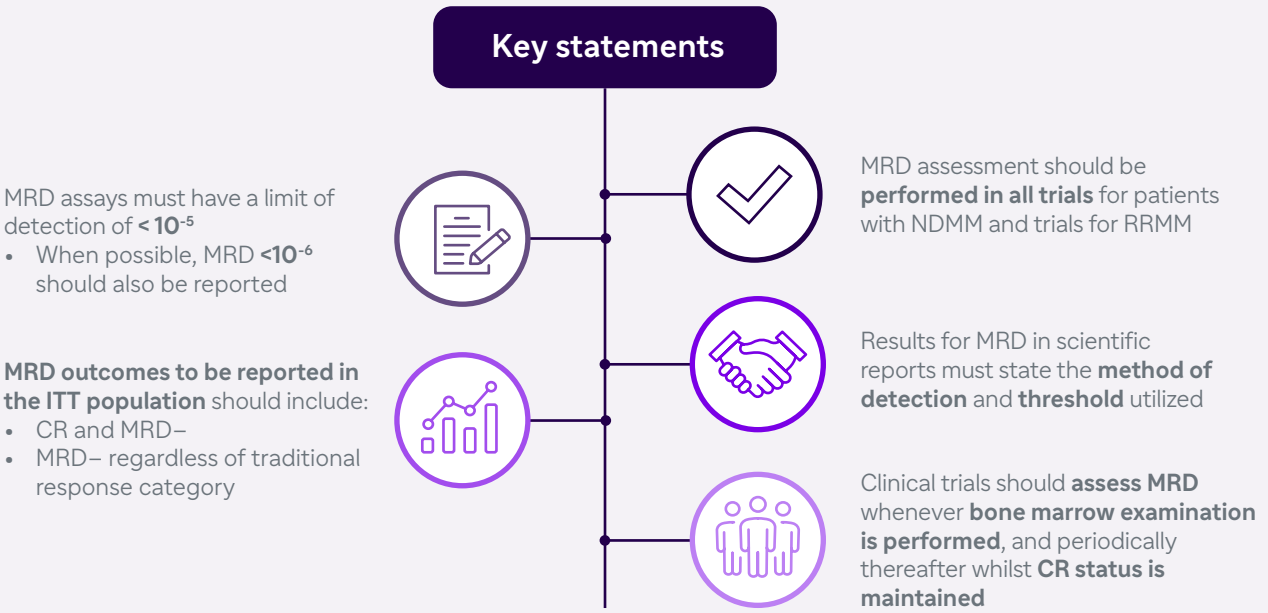
Table 3: Challenges in the assessment of MRD

Optimal sampling of bone marrow cells (ideally first "pull" with minimal hemodilution)[23]
Potential for false MRD-negative and false MRD-positive results[12]
Lack of clear guidance on patient selection based on clinical response (e.g., sCR, CR, and VGPR)[12]
Need to define optimal timing of assessment during the treatment course[12,22]
Variability in protocols and performance characteristics between laboratories[19]
Need for definition of optimal frequency of MRD monitoring following an MRD-negative result[12]
Absence of guidance regarding use of different technologies and imaging techniques[12,22]
Broader challenges of making MRD testing the SoC in the clinic: invasive procedure,[24] site-specific challenges (e.g., cost),[25] and lack of guidelines for treatment following MRD result[25]

CR, complete response; MRD, minimal residual disease; PR, partial; sCR, stringent complete response; SoC, standard of care; VGPR, very good partial response

Disparities in clinical trial MRD reporting led to development of the **International Harmonization Guidelines** by an international panel of MM investigators in 2020 (Figure 13). The guidelines provide consensus on which MM trials (newly diagnosed or relapsed/refractory setting) should include MRD, the recommended time points for MRD assessment, and expected analytical validation for MRD assays.[22]

Figure 13: International Harmonization Guidelines[22]



CR, complete response; ITT, intent-to-treat; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; RRMM, relapsed/refractory multiple myeloma

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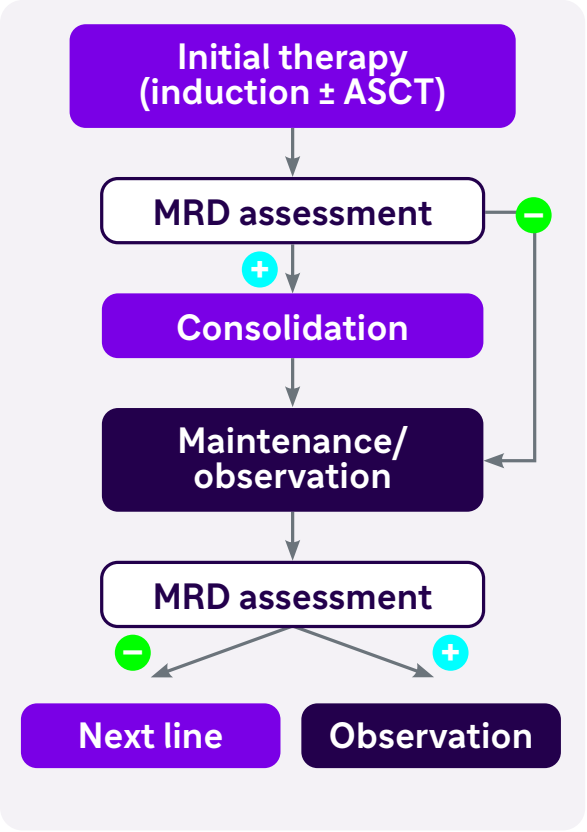
MRD adaptive approaches

Despite its high prognostic value, the use of MRD to make clinical decisions in MM has been relatively underexplored and data are limited. Therefore, prospective clinical trials are needed to understand the clinical utility of MRD-guided decisions at different stages in MM treatment. Findings from these trials may help answer questions such as:[26,27,12]

- Can MRD status be used as a trigger to continue/intensify/switch or discontinue therapy?
- Should MRD+ patients receive additional cycles of induction therapy?
- Can stem cell transplant be delayed (or omitted entirely) in MRD– patients?
- Should the intensity/duration of consolidation therapy be increased in MRD+ patients?
- Do MRD– patients need to receive consolidation therapy?



Using MRD as a basis for directing therapy may prolong PFS outcomes, as well as reduce overall treatment cost and patient exposure to potentially unnecessary toxic treatment. So far, no guidelines address the potential use of MRD as an adaptive tool; however, several clinical trials are underway investigating the role of MRD status in guiding first-line[28–31] and subsequent lines of therapy.[32,33]

The impact of MRD adaptive therapy on PFS

The impact of using MRD to make clinical decisions on PFS has not been explored widely; however, this was recently investigated in a multinational retrospective study in patients with newly diagnosed MM (Figure 14), whereby physicians made one of three treatment decisions based on patients' MRD status:

- Stop or reduce treatment if MRD–
- Increase intensity of treatment if MRD+
- Start a new treatment line if MRD+

The study found that modifying treatment in response to MRD status improved PFS, regardless of whether patients were MRD– or MRD+. Patients in whom a clinical decision was made based on MRD (n=67) had a prolonged PFS vs those in whom a clinical decision was not made (n=333) (median PFS 104 months vs. 62 months, p=0.005); statistical significance persisted in a landmark analysis at 12 months (p=0.04) or from the start of induction (p=0.05).[34]

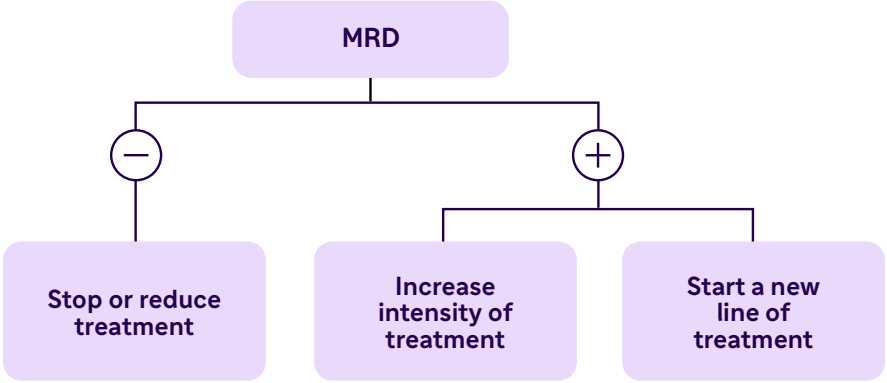


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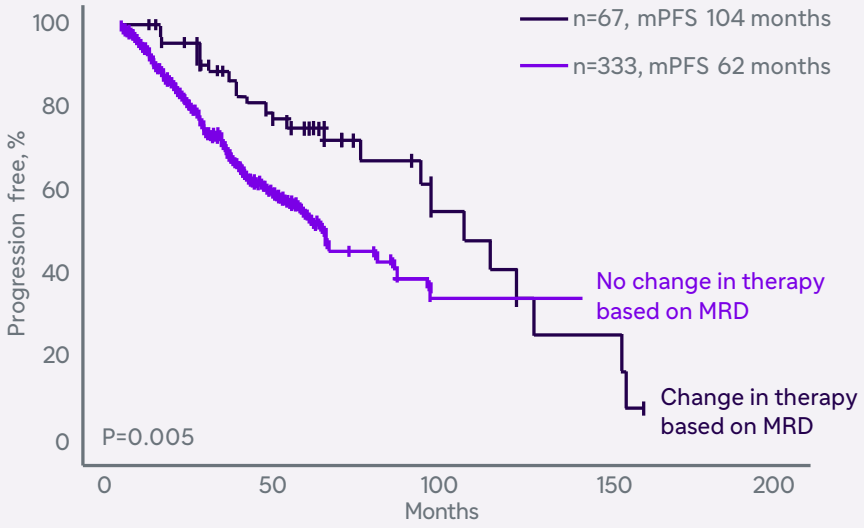
Figure 14: Modifying treatment in response to MRD status improved PFS[34]



m, median; MRD, minimal residual disease; PFS, progression-free survival

Who is likely to achieve MRD–?

Currently, it is unknown which patients are expected to achieve MRD– and therefore have a better prognosis. Identifying these patients up front could further enhance the prospect of adaptive MRD therapy and would ensure that patients receive the most tolerable, cost-effective regimen that could offer a prolonged life expectancy.[35]

One recent publication used machine learning to accurately predict MRD outcomes by integrating information on cytogenetic status, tumor burden, and immune-related biomarkers. In this study, accurate predictions of MRD outcomes were achieved in approximately 70% of cases and the model predicted survival outcomes with significant accuracy.[35]

This is the first publication to explore the idea of treatment individualization based on the probability of an individual patient to attain undetectable MRD; however, this could represent a new concept towards personalized treatment in MM.[35]

MRD in summary

MRD is a strong prognostic factor for survival outcomes in MM, with an emerging role in guiding adaptive treatment. Efforts are ongoing to validate MRD assessment as a surrogate endpoint for PFS in order to accelerate drug approval. However, a number of questions remain concerning MRD assessment including the optimal technique(s) to use, the timing and monitoring frequency, as well as its role in adaptive medicine. MRD endpoints in clinical trials and their findings are eagerly anticipated to fully understand the value of MRD assessment in MM and to demonstrate the validity of using MRD as the main driver of clinical decisions, both in the up front and relapsed settings. Finally, efforts to determine the patients most likely to achieve MRD– are ongoing and this could drive a new concept towards personalized treatment in MM.

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Abbreviations:

ASCT, autologous stem cell transplant; CR, complete response; CT, computed tomography; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; FDA, Food and Drug Administration; IMWG, International Myeloma Working Group; i^{2}TEAMM, International Independent Team for Endpoint Approval of Myeloma MRD; MM, multiple myeloma; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGF, next generation flow; NGS, next generation sequencing; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PR, partial response; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VGPR, very good partial response.

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