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Review

MRD Assessment in Multiple Myeloma: Progress and Challenges

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Abstract

Purpose of review. Over the last decade, the development of effective treatment approaches for multiple myeloma (MM) has been associated with higher response rates and longer survival. In patients who achieve complete response, several high sensitivity techniques have been studied to assess minimal residual disease (MRD) and detect residual neoplastic cells within the bone marrow (by flow cytometry or molecular biology techniques) or outside the bone marrow (by imaging or circulating disease markers in the peripheral blood). This is of utmost importance, since residual disease can drive clinical relapse. This review focuses on the progress made in the assessment of MRD in MM.

Recent findings. The achievement of MRD negativity after therapy is considered prognostically important for MM patients, and data from clinical trials and meta-analyses have confirmed that it is strongly associated with better survival. Along with well-known techniques, such as next-generation sequencing (NGS), next-generation flow (NGF) and positron emission tomography/computed tomography (PET/CT), other methods such as mass spectrometry (MS) and circulating tumor cells are under study. Intensive treatment regimens at diagnosis can lead up to 70% of MRD negativity in MM patients, although the current proportion of curable patients is still unknown.

Summary. Today, clinicians who treat MM deal with MRD assessment in routine clinical practice. Its appropriate use in therapeutic decision making may be the most fascinating and challenging issue to be addressed over the next few years.

Introduction

The introduction of 3- and 4-drug regimens with or without autologous stem-cell transplantation (ASCT) led to unprecedented response rates in patients with newly diagnosed multiple myeloma (NDMM). A large number of studies showed that an improved depth of response was associated with a superior overall survival (OS) and progression-free survival (PFS) [1].

With more than 50% of patients achieving conventionally defined complete responses (CR) with novel treatments, new techniques to measure residual disease at high sensitivity level within and outside the bone marrow (BM) have been developed to further classify patients into 2 groups: patients with measurable minimal residual disease (MRD positive) or without it (MRD negative) [2].

The International Myeloma Working Group (IMWG) revised the MM response criteria in 2015 and introduced, as a result of the progressive evolution of both imaging and BM techniques, the definition of MRD in patients who have achieved a CR as the persistence or re-emergence of very low levels of cancer cells [3].

Several investigators measured MRD by using different technologies and various time points during MM treatment, thus posing a challenge to the data interpretation of MM clinical trials. International consensus statements for the harmonization in assessing and reporting MRD in MM clinical trials have been recently published [4].

In this work, we have summarized the progress made in measuring MRD in MM and the new challenges emerging from the use of this powerful tool that it is now available to MM treating physicians.

Measurement of MRD

What we know: MFC, NGS and PET/CT

Traditionally, the identification of MRD after therapy relied on the detection of residual malignant plasma cells in the BM by multiparameter flow cytometry (MFC) and molecular biology and the combined analysis of extramedullary disease (EMD) with positron emission tomography/computed tomography (PET/CT).

MFC exploits the particular phenotype of the tumor cell by analyzing the expression of surface antigens that are typical of plasma cells (CD138 and CD38) or aberrant markers (CD20, CD56, CD19, CD45, CD27,CD28, CD33, and CD117) and by analyzing the monoclonal expression of intra-cytoplasmic markers (intracellular κ or λ chains) [5]. The most updated version of MFC can be performed with 8-color 2-tube or 10-color 1-tube assays, which can lead to a high sensitivity of 10^{-5}-10^{-6} (1 cell per 100 000/1 million). The EuroFlow Consortium proposed a standardization of the MFC-MRD evaluation called Next-Generation Flow Cytometry (NGF), aimed at achieving higher sensitivity and quality of the MRD data [6]. Comparing MFC by conventional 8-color flow with NGF, Flores-Montero et al. showed that the latter technique identified residual disease in 25% of the patients who were classified as MRD-negative by standard MFC [7]. NGF requires the evaluation of 10 million events (10^7) and is applicable to roughly 100% of samples. Automatic plasma cell gating may avoid individual assessments and improve reproducibility [8]. A sensitivity of 10^{-6} can be achieved with some caveats, such as the presence of hemodiluted samples that are inadequate for MRD assessment (although sample quality can be evaluated during the analysis).

Molecular biology techniques take advantage of the immunoglobulin (Ig) gene rearrangement, which is a genetic marker for clonal plasma cells. This molecular footprint can be sequenced at diagnosis and then tracked throughout the clinical course after therapy. Allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) showed promising results [9–11], but

with some limits of applicability (40- 60%) due to the failure of Ig rearrangement identification after Ig somatic hypermutation and the need for patient-specific reagents [12]. Next-generation sequencing (NGS) recently overcame these limits, with higher applicability due to a better marker identification rate at diagnosis (90–92%) and a stronger prognostic impact. [13] After DNA is extracted from the BM sample, IgH, IgK, and IgL (immunoglobulin heavy, κ, and λ) genes are amplified and then sequenced by PCR, creating a sequencing library. Sequence reads that are identical to each other are defined as clonotypes and, when they occur at a frequency ≥5%, they are considered markers of clonality and can be used as markers for MRD follow-up. To do that, a bioinformatic tool and a certain degree of expertise are needed.
Over the past 2 decades, several imaging techniques have been implemented to help clinicians detect osteolytic lesions and focal lesions that are critical for the differential diagnosis between MM and other gammopathies [14]. ^{18}F-Fluorodeoxyglucose (FDG) PET/CT is one of the most accurate and sensitive methods that can help identify both bone and extramedullary myeloma lesions at diagnosis, as well as give a functional information about FDG uptake, making possible to evaluate the disease after therapy [15]. The incidence of EMD depends on the methods used to detect disease outside the BM; paraskeletal EMD occurs in ~7-34% of patients, while extraosseous EMD (in soft tissues) in 1-4% of patients [16]. Indeed, MM is a patchy disease with multiple sites of bone involvement and spatial heterogeneity [17], and the assessment of BM MRD can lead to biased evaluations. To overcome these false-negative MRD evaluations, the IMWG response criteria (2016) clearly defined "imaging MRD" as the disappearance of every area of increased tracer uptake found at baseline or in a preceding PET/CT [3].

Progress: comparison of techniques and novel methods
The availability of different techniques raises the question of the comparison among them in terms of applicability, cost, prognostic power, and concordance. Nowadays, ASO-PCR and MFC have been superseded by NGS and NGF, which, despite some limitations, are more sensitive and standardized. Advantages of MFC/NGF are their wide applicability, feasibility without a baseline diagnostic sample, and rapid turnaround time (3-4 hours). The drawback is mainly the need for fresh samples. Advantages of NGS are the possibilities to use both fresh and stocked samples and to track clonal evolution. On the other hand, drawbacks are that NGS requires a baseline sample and that only one platform is validated (clonoSEQ®, Adaptive Biotechnologies, US-WA). Other academic NGS platforms are less standardized and require a valid bioinformatic support. FDG PET/CT seems to be complementary to these two BM MRD techniques (NGS and NGF/MFC), due to its ability to track focal lesions and EMD. PET/CT requires nuclear medicine expertise and adequate facilities. Moreover, a drawback of FDG PET is that ~10% of patients with residual MM may achieve a false-negative imaging MRD status due to low levels of the enzyme hexokinase that reduce FDG uptake in neoplastic plasma cells [18]. This limitation can be overcome by using alternative PET tracers that do not rely on hexokinase. One of the most promising PET tracers is 11C-methionine, whose uptake correlates with protein synthesis (very active in MM cells). In a head-to-head comparison in a heterogeneous MM patient population, the use of 11C-methionine with PET/CT was more sensitive than FDG in detecting focal lesions [19].
The most intriguing question concerns the prognostic impact of the achievement of MFC-MRD negativity, as compared with NGS-MRD and imaging MRD. Some head-to-head comparison studies have been designed to assess differences and similarities in these terms (Table 1). Ongoing clinical trials are reporting good concordance between clonoSEQ® NGS and MFC. Oliva et al. reported 86% of correlation with MRD at a sensitivity of 10^{-5} in ≥CR patients in the phase II multicenter randomized FORTE trial [20]. Similar data come from the phase III CASSIOPEIA trial, with 83.5% of concordance between MFC and NGS with a sensitivity of 10^{-5} [21]. A direct

comparison between NGF and NGS was reported [22], but there is a lack of data on the comparison between NGF and NGS with clonoSEQ® platform.
A comparison between PET/CT and BM MRD techniques was explored in a substudy on 133 patients of the FORTE trial. Data reported by Zamagni et al. showed good concordance between PET/CT and NGS (84%) and between PET/CT and MFC (93%) at 10^{-5} in the identification of BM residual disease. By contrast, there was discrepancy in the assessment of residual disease in patients with focal lesions, with disagreement in ~33-37% of cases [23]. These data support the hypothesis that PET/CT MRD evaluation and BM evaluation are not mutually exclusive, but complementary.
In addition to PET/CT, other strategies are under development to overcome some limitations of BM MRD evaluation. First, the analysis of peripheral blood (PB) to detect residual disease represents an appealing approach to overcome both MM spatial heterogeneity and the false-negative MRD evaluations due to BM specimen hemodilution. Both NGS and flow cytometry have been studied on PB samples, following the concept of liquid biopsy.
Circulating plasma cells (CPC) can be detected in the majority of MM patients at diagnosis, can be tracked during the disease course and have a prognostic impact [24]. Although a sensitive technology such as NGF identifies CPC in almost all MM patients at diagnosis, it seems to be less sensitive than BM NGF residual disease detection. Sanoja-Flores et al. compared MRD with NGF in BM and PB after therapy in a real-world case series of 137 patients. Using NGF, CPC were persistent after therapy in 26% of patients. While all CPC-positive patients had BM MRD-positive disease, 40% of patients who were BM MRD-positive showed undetectable CPC (PB MRD negativity), thus suggesting that CPC is a less sensitive MRD marker than BM MRD [25].
Similar findings were reported in the analysis of circulating tumor DNA (ctDNA) using NGS. Mazzotti et al. analyzed a small prospective series of 37 MM patients, whose paired BM and PB samples were analyzed to detect MRD. Again, a concordance of only 49% was found, with the majority of discordant cases being BM MRD positive and PB MRD negative. Only 1 case was BM MRD negative and PB MRD positive, without any sign of hemodilution and no extramedullary residual lesions detected by PET/CT, likely due to patchy MM infiltration in this patient [26].

The use of novel technologies, such as mass spectrometry (MS), to measure the monoclonal (M)-protein produced by clonal plasma cells is emerging. Historically, response to therapy has been observed by monitoring the reduction of M-protein via serum protein electrophoresis (SPEP) and the more sensitive serum immunofixation (s-IFX). MS is an ultra-sensitive technique that may potentially supersede the above-mentioned methods. Indeed, MS can be used to detect the unique mass of clonal M-protein and to monitor its presence during disease over time in the PB. Different methods of MS are under study: clonotypic peptide methods and intact protein methods. Clonotypic peptide methods are quite complex and use enzyme digested-peptides from M-protein as a surrogate marker of disease and require baseline M-protein and BM samples. Intact proteins methods, also known as monoclonal Ig rapid accurate mass measurements (miRAMM), measure the accurate mass of the intact light chain to track residual disease and need only a small amount of baseline serum sample [27]. Clonotypic MS methods were compared to BM MRD by NGS in a small subgroup of patients enrolled in the IFM 2009 study, showing a good concordance of 78% (64/82) [28]. Quantitative immunoprecipitation mass spectrometry (QIP-MS) and matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) are the most common intact Ig techniques developed so far. QIP-MS showed higher sensitivity when compared to standard SPEP and good concordance with BM NGF evaluation, as reported in the GEM-CESAR trial [29]. Interestingly, approximately 80% of the patients who were QIP-MS negative were also BM NGF negative; on the other hand, 20% of QIP-MS-positive patients were BM NGF negative, possibly due to patchy MM infiltration or EMD.

The MALDI-TOF technique recently showed higher sensitivity than s-IFX [30] and a concordance of 62% with BM flow-MRD results[31], but it was less sensitive than other MS methods. However, in a study reported by Abeykoon et al., the M-protein was still detectable by MALDI-TOF in 59% of patients who achieved a conventionally defined CR and were NGF-MRD negative after 100 days from ASCT [32].
Magnetic Resonance Imaging (MRI) is broadly used for diagnosis in MM due to its high sensitivity (particularly in detecting BM plasma cell infiltration and bone lesions), but it has never been validated for residual disease detection and is inferior to PET/CT. This inferior performance in tracking disease response seems to be related to the slower disappearance of MM focal lesions and to the inability of MRI to discriminate between scar tissue and normal tissue [33]. A novel technique known as whole-body diffusion-weighted imaging (DWI) MRI overcame these limitations and had results that were similar to PET/CT [34, 35].

Challenges: standardization and optimization
In the last 10 years, a substantial amount of literature and data on MRD has been published, and MRD assessment has been included in almost all clinical trials. However, there is a large diversity in MRD methods, procedures, sensitivity, and time points of evaluation and report. This definitely stresses the importance of a methodological standardization and a consensus about the data analysis [4].
Regarding the analytical standardization, efforts on the development of MFC have been made by EuroFlow, leading to the definition of NGF. Regarding NGS, even if clonoSEQ® is currently the only platform that received the quality approval for commercial use from the Food and Drug Administration (FDA), different platforms have been proposed. Euroclonality-NGS Consortium, an international expert laboratory network, recently developed an Ig and T-cell receptor NGS protocol corroborated by quality control studies [36–38]. Furthermore, some single-center academic platforms are under development (e.g., LymphoTrack®, Invivoscribe, Inc., US-CA) [39, 40].
Moreover, the MRD assay should be analytically validated with defined parameters expressing the accuracy of the MRD report in terms of limit of blank (LOB), limit of quantification (LOQ), limit of detection (LOD), and MRD threshold. An expert consensus stated that the minimum threshold for defining MRD negativity should be at least of 10^{-5} [4].

Similarly, for PET/CT, there is a lack of recognized cut-off values for positivity and negativity, which are essential for data interpretation. A first attempt to define response criteria was proposed by an Italian group of nuclear medicine experts (Italian Myeloma Criteria for PET Use: IMPeTUs) to standardize FDG PET/CT evaluation in MM patients [41, 42]. Zamagni et al. recently reported data from a pooled analysis of 226 patients treated with novel agents, transplant, and maintenance therapy in 2 phase III trials (IFM/DFCI2009 and EMN02/HO65). ^{18}FDG PET/CT was performed at diagnosis and before maintenance therapy, applying the Deauville score (DS, which is validated for lymphomas) to describe BM uptake and focal lesions. DS ≥4 after treatment in both BM and focal lesions had a strong prognostic impact and was proposed as a cut-off for the definition of PET MRD positivity [43].

Another important issue concerns the optimal time point to assess MRD and the possible repetition of MRD testing in case of previous achievement of MRD negativity. On the one hand, it is important to avoid unnecessary examinations that can be difficult to implement in the clinical practice. On the other hand, confirming MRD status during the course of therapy is equally important, because even MRD-negative patients can relapse, and the persistence of MRD negativity (i.e., “sustained MRD negativity”) is strongly associated to better outcome [44, 45].

Generally, there is great heterogeneity in terms of when MRD testing is performed. In transplant-eligible patients, the treatment phases (induction, ASCT, consolidation, and maintenance) give the opportunity to evaluate MRD at fixed time points (e.g., before or after a specific phase). Conversely, in transplant-ineligible patients, continuous therapy is commonly used, and no standard timing has consequently been established for MRD assessment, which can be performed at specific time points (e.g., after 1 or 2 years of treatment) or can be tested together with the CR confirmation in the absence of M-component. Indeed, likely due to the long M-component half-life, many patients who are still in very good partial response (VGPR) may achieve MRD negativity in the BM before the M-component is cleared. Thus, many studies tested MRD in VGPR patients rather than in CR patients. However, M-protein production from patchy infiltration or extramedullary sites cannot be ruled out even in the presence of MRD negativity.
Data coming from clinical trials evaluating MRD at multiple time points using different techniques (NGF, NGS, Imaging, liquid biopsy) will inform us on the best timing and criteria to test and measure MRD.

Aims of MRD

As already pointed out, MRD is probably the most important prognostic factor in MM patients [1]. The achievement of MRD negativity predicts longer PFS and OS (as compared with conventionally-defined CR) [46] and, particularly in the case of sustained MRD negativity, may overcome the negative prognostic impact conferred by high-risk features detected at baseline [8].
Moreover, MRD is now being considered the best candidate as surrogate endpoint to be used in clinical trials to obtain regulatory approval of new combination therapies in MM. Ideally, the best endpoints to obtain regulatory approval are OS [47] and patient-reported outcomes. However, as survival of MM patients improved, PFS has been widely used as a surrogate endpoint for OS, since data can be provided in a more feasible time frame. Nevertheless, thanks to the availability of new drug combinations, PFS of newly diagnosed MM patients is now longer. For this reason, now it takes considerable time and a large cohort of patients to detect differences in terms of PFS between different treatments, and this can lead to delayed drug approval. Therefore, MRD is now being evaluated as a surrogate endpoint. The determination of MRD endpoint surrogacy for OS and PFS requires a robust analysis using data from several clinical trials. This task is being pursued by the International Independent Team for Endpoint Approval of Myeloma MRD (I2TEAMM) [48].
There are limitations to the use of MRD negativity as a surrogate endpoint for OS/PFS: (1) there is no consensus on the optimal timepoint to measure MRD; (2) a proportion of patients may achieve MRD negativity but still relapse early [49]; (3) there is no consensus on the need to repeat MRD evaluation over time and on the optimal duration of sustained MRD negativity; (4) some patients with an MGUS-like profile may not achieve MRD negativity but may still have a very indolent disease course without experiencing relapse; (5) MRD might not be an achievable therapeutic endpoint in patients in whom treatment options are limited by low treatment tolerance (e.g., frail patients) [50, 51]; (6) finally, one of the most important limitations is that, differently from OS/PFS, MRD does not take into account deaths. For instance, in the BELLINI trial evaluating venetoclax or placebo in combination with bortezomib-dexamethasone in relapsed/refractory MM patients, MRD negativity at a sensitivity of 10^{-5} was significantly higher in the experimental arm than in the control arm (13% vs. 1%), although a trend towards a worse survival was observed in the experimental arm due to an increased rate of infections [52]. A composite endpoint including MRD and a safety evaluation may overcome this limitation.

Another key question is whether we can use MRD to guide treatment in MM. For example, we know that MRD-positive patients with high-risk disease at baseline have a very dismal outcome [8], thus posing the question of whether these patients may benefit from a treatment intensification in case of residual disease detection after standard treatment in order to convert them to MRD negative.
On the other hand, although maintenance/continuous therapy is a mainstay of MM treatment, its optimal duration and the possibility to include 1 vs. more than 1 drug [53] in this phase remain to be determined [54, 55]. Achieving MRD negativity and maintaining MRD-negative status has the potential to guide treatment deintensification without affecting patient outcome. This is important because treatment-free interval is crucial for patients. Furthermore, MM therapies are becoming more and more expensive. Avoiding unnecessary treatment may improve quality of life, spare patients from unwarranted toxicity, and help the health care system save money associated with years of excessive treatment.
Selected trials evaluating MRD-driven therapeutic modifications are summarized in Table 2.
Measuring MRD at high sensitivity thresholds and finding patients negative on repeated evaluations also raise the question of whether these patients may be cured [56]. If MRD is measured in a treatment exploring curative approaches (e.g., intensive treatment of high-risk smoldering MM) [57], the sensitivity threshold should be as high as possible (ideally, at least 10^{-6} in the BM, probably more in the PB), and the residual disease should not be found with any technique, either in the BM or in the PB. Moreover, in this scenario, 1 MRD time point would not be enough, and the elimination of residual disease should be controlled over time. Long-term follow-ups of the initial trials exploring MRD will suggest the optimal duration of MRD negativity to achieve sustained remissions and, possibly, cure.

Conclusions

Currently, the main challenges in MRD evaluation are the standardization of the available techniques (NGF, NGS, liquid biopsy, and PET/CT) and their comparison, to determine which one is the better in each setting, and which ones are actually complementary to each other. Regarding imaging techniques, PET/CT limitations could be overcome by new, better tracers [58] corroborated by improved and standardized response criteria. The possibility to have standardized analyses as well as uniform reporting standards for response is a key step towards study comparison and the use of MRD as an endpoint for drug approval [4].
Another future challenge will be the implementation of MRD in MM clinical practice. To do that, it will be essential to simplify MRD testing by identifying the most important time point for MRD measurement. This would also reduce costs and avoid unnecessary BM sampling or PET/CT assessment.
Data from trials assessing all MRD methods at different timepoints (e.g., EMN18, EMN24, and many others) will foster the development of an algorithm to determine the use of the most appropriate technique at the right time point in each subset of patients.
Clinical presentation of MM may possibly drive MRD testing (Fig. 1). At baseline, all patients should ideally receive PET/CT and BM evaluation. Since PB MRD testing is less sensitive than BM, it could be used to first assess the depth of response (by MS or NGF/NGS). PB MRD negativity could be used to guide the timing of BM analysis and/or imaging according to patient status at baseline. For instance, if patients with only skeletal BM disease (no baseline EMD or focal lesions at PET/CT; Fig. 1A) are MRD negative, then they may be candidate for BM MRD assessment, since there is good concordance between PET/CT and BM MRD in patients with BM uptake [23]. In this case, if BM MRD is negative and the patient is at low risk, then it is possible to monitor MRD in PB to reduce the number of BM biopsies. On the other hand, patients with focal lesions (Fig. 1B) or EMD who achieve PB MRD negativity could be monitored with PET/CT together with BM evaluation, since these techniques seem to be complementary in this

setting. In the future, with more sensitive techniques, we might track EMD with liquid biopsy PB assays (MS, NGS, and NGF). In case of circulating tumor cells detected by flow cytometry at diagnosis (Fig. 1C), it could be interesting to monitor MRD first in the PB via NGF and then in the BM after the disease is eliminated in the PB.

As reported by Paiva et al., patients with BM MRD negativity at a sensitivity of 10^{-6} with NGF could still relapse, and the majority of them have high-risk features, either high-risk chromosomal abnormalities, elevated lactate dehydrogenase, or International Staging System stage II/III. Moreover, many of them relapsed without M-protein or BM infiltration [8]. As a consequence, these high-risk patients should likely be followed with at least two methods (BM and PET/CT or PB and PET/CT). On the other hand, the achievement of MRD negativity in the BM at high sensitivity may overcome the poor prognosis predicted by high-risk features detected at diagnosis [8].

Beyond the evaluation of the best monitoring strategies, the subsequent challenge will be to define how to use MRD to guide treatment, escalating therapy in the presence of residual disease and/or reducing intensity after the achievement of sustained MRD negativity, particularly during the maintenance phase.

To conclude, it is crystal clear that MRD is and will be an integral part of MM care in the future, enhancing our ability to understand the clinical course of this disease, to design better treatment strategies and improve the care of MM patients.

Key references

**important reference*

***very important reference*

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A recent meta-analysis on around 8000 patients from different MRD studies, confirming the important prognostic impact of the achievement of MRD negativity, regardless of the adopted method (next-generation sequencing [NGS] or multiparameter flow cytometry [MFC]), time point, and setting (diagnosis or relapse).

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Tables

Table 1 Head-to-head comparison of different techniques for MRD analysis

	TRIAL	N of pts	Sensitivity	Concordance
NGS vs. MFC	GEM2000; GEM05 <65; GEM05 ≥65; GEM10 ≥65 [59]	99	clonoSEQ® NGS and MFC 10^{-5}	83% (ρ 0.58)
	FORTE [20]	335 (10^{-5}); 56 (10^{-6})	clonoSEQ® NGS and MFC 10^{-5}-10^{-6}	At 10^{-5}: 86% (ρ 0.61) At 10^{-6}: 78% (ρ 0.77)
	CASSIOPEIA [21]	733	clonoSEQ® NGS $10^{-6}$and MFC 10^{-5}	83.5%
	GMMG-HD6 [60]	125	clonoSEQ® NGS and MFC 10^{-5}	68%
NGS vs. NGF	GEM2012MENOS65 [22]	106	LymphoTrack® NGS and NGF 10^{-5}-10^{-6}	86% (ρ 0.905)
	GEM2012MENOS65 [61]	104	NGS and NGF 10^{-5}-10^{-6}	ρ 0.68
PET/CT vs. MFC vs. NGS	FORTE [23]	133	NGS and MFC 10^{-5}	MFC - FL: 63%concordance - BM: 94% concordance NGS - FL: 63% concordance - BM: 84% concordance NGS and MFC - BM: 84% concordance

Abbreviations. MRD, minimal residual disease; N, number; pts, patients; MFC, multiparameter flow cytometry; NGS; next-generation sequencing; NGF, next-generation flow; FL, focal lesion; PET/CT, positron emission tomography/computed tomography; BM, bone marrow; ρ, Pearson's coefficient test, uptake.

Table 2 Selected trials evaluating MRD-driven therapeutic modifications (only MRD-dependent treatment arms are discussed)

Study	Patient population	Treatment scheme	MRD evaluation (technique)	Key MRD time point for decision making	Action type (intensification/ deintensification)	Therapy modification upon MRD results
UMCC 2018.056 (NCT04140162)	NDMM (ECOG 0-2, no significant cardiopulmonary disease)	Dara-Rd induction +/- Dara-VRd consolidation, and Dara-R-R maintenance	NA	Post induction (6 cycles)	Post-induction intensification in MRD-positive patients	Consolidation with Dara-VRd
PERSEUS (NCT03710603) [62]	TE NDMM	Dara-VRd induction, ASCT, Dara-VRd consolidation, Dara-R maintenance	NGS (clonoSEQ®) at 10^{-5} sensitivity	During maintenance	Deintensification if sustained MRD negativity confirmed in 2 evaluations at least after 1 year	Discontinuation of Dara after 2 years of maintenance and continuation of therapy with R maintenance alone

DRAMMATIC (NCT04071457)	TE NDMM after ASCT	Dara-R vs. R maintenance	NGS	After 2 years of maintenance	Randomization to deintensification vs. no deintensification in MRD-negative patients	Discontinuation of maintenance therapy after 2 years if MRD-negative evaluation and randomization to MRD-driven duration of maintenance
EMN20 (NCT04096066)	Fit or intermediate-fit NTE NDMM	KRd	NGS (clonoSEQ®) at 10^{-5} sensitivity	After 1 and 2 years of therapy	Deintensification if MRD-negative evaluation after 1 and 2 years of therapy	Discontinuation of K and continuation of therapy with Rd
MASTER (NCT03224507) [63]	NDMM (ECOG 0-2, CrCl ≥40 ml/min, no significant cardiopulmonary disease)	Dara-KRd induction, ASCT, Dara-KRd consolidation (0-8, number of cycles adapted to MRD status), R maintenance	NGS (clonoSEQ®) at 10^{-5} sensitivity	Post induction, post ASCT, post 4 consolidation cycles, post 8 consolidation cycles	Deintensification if 2 consecutive MRD-negative evaluations	Treatment discontinuation
RADAR (EudraCT 2019-001258-25)	Standard risk TE NDMM	CyVRd induction, ASCT, MRD-driven consolidation/ maintenance	NA	Post ASCT	Intensification or deintensification according to MRD status	MRD negativity: Isa maintenance (1 year) and then, if still MRD-negative status, randomization between continuation or discontinuation of Isa. MRD positivity: randomization to: 1) R maintenance; 2) VRd consolidation +R maintenance; 3) Isa-R maintenance; 4) Isa-VRd consolidation and Isa-R maintenance.

Abbreviations. MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; TE, transplant-eligible; ASCT, autologous stem-cell transplantation; ECOG, Eastern Cooperative Oncology Group performance status; CrCl, creatinine clearance; Dara, daratumumab; R, lenalidomide; d, dexamethasone; V, bortezomib; K, carfilzomib; Cy, cyclophosphamide; NA, not available; NGS, next-generation sequencing; Isa, isatuximab.

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Fig. 1 Proposed model for selecting MRD assessment method on the basis of clinical presentation and response

Abbreviations. PET/CT, positron emission tomography/computed tomography; BM, bone marrow; MRD, minimal residual disease; NGS, next-generation sequencing; EMD, extramedullary disease; PB, peripheral blood; MS, mass spectrometry; NGF, next-generation flow; neg, negative; CA, chromosomal abnormalities; LDH, lactate dehydrogenase; ISS, International Staging System stage.

Figure 1

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