HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2017 November 15.

Published in final edited form as:

Clin Cancer Res. 2016 November 15; 22(22): 5428–5433. doi:10.1158/1078-0432.CCR-16-0866.

New Developments in Diagnosis, Prognosis, and Assessment of Response in Multiple Myeloma

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Abstract

The past few years, the management of multiple myeloma has changed. We have new guidelines regarding how to set the diagnosis, when to initiate therapy, and how to monitor treatment response. In 2014, the updated IMWG diagnostic criteria changed the definition of multiple myeloma; from being a disease defined by symptoms to a disease defined by biomarkers. Today, modern combination therapies have reported up to 60-80% of patients reaching a complete response. As a logical and necessary step forward, investigators have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. Recent meta-analysis data show that MRD negativity is associated with longer progression-free survival and overall survival. In 2016, the updated IMWG response criteria include MRD as the deepest level of treatment response in multiple myeloma. Simultaneously, we are still quite behind in our understanding of the heterogeneous biology of multiple myeloma and its implications to therapy. Emerging DNA sequencing data show that newly diagnosed multiple myeloma patients have a broad range of mutations which are distributed unevenly in multiple parallel sub-clones present already at diagnosis. To move beyond the ill-defined category “high-risk multiple myeloma” which confers to ~25% of all newly diagnosed patients, prospective studies are needed to dissect tumor biology and define multiple myeloma subtypes, and, based on biology, seek to define rational therapies for individual subtypes. This paper discusses novel insights and gives perspectives on diagnosis and MRD monitoring and future directions for prognosis and clinical management of multiple myeloma.

Introduction

Driven by access to better drugs, on average, newly diagnosed multiple myeloma patients have over 10 years overall survival according to available population registries (1-3). In parallel with the strong drug pipeline, clinical management of multiple myeloma has changed drastically the past few years. Without any doubt, the use of modern combination therapy integrated with modern clinical management will continue to deliver substantially longer overall survival for patients with multiple myeloma in years to come (4).

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Disclosure of Potential Conflicts of Interest: No potential conflicts of interest were disclosed.

In this review, we highlight on key changes with regard to diagnostic criteria (5) and treatment response assessment (6) based on recently updated International Myeloma Working Group (IMWG) consensus criteria. We also cover the topic of prognosis and how to integrate that in the clinical management of multiple myeloma. Specifically, we review novel data and give perspectives on diagnosis and MRD monitoring and future directions for prognosis and clinical management of multiple myeloma.

Diagnosis

Going back to the 1960s, the clinical paradigm for multiple myeloma used to be watch-and-wait and to initiate therapy once the patient was clinically ill and suffered from symptoms. Certainly, a key limitation, at the time, was the lack of available therapies (restricted to alkylating chemotherapy and steroids) (7). In that earlier era, once the decision was made to start therapy, the clinician had few other things to offer when therapy stopped working and the disease became active again. Fortunately, the myeloma field has changed substantially and, today, there are many new drugs approved for the treatment of multiple myeloma. To adapt to this new reality, in 2014, the updated IMWG diagnostic criteria changed the definition of multiple myeloma; from being a disease defined by symptoms to a disease defined by biomarkers (5). Specifically, there were 3 biomarkers added to the former “CRAB” (hypercalcemia, renal failure, anemia, and lytic bone lesions) criteria, so now there are seven listed variables that can make the diagnosis. Thus, the criteria for the diagnosis of multiple myeloma requiring therapy are: 10% or more plasma cells in the bone marrow, abnormal immunoglobulins in the blood and/or urine (monoclonal protein and/or free light-chains; FLC) unless the patient is non-secretory (which is rare), and one or more of the seven listed criteria are fulfilled (Box 1). Coming back to the 3 new added biomarkers; they are: (a) abnormal serum-(s)-FLCs defined as an abnormal sFLC-ratio (involved/uninvolved sFLC) 100 or greater and the involved sFLC being 10 mg/dl or greater; (b) 60% or higher plasma cell infiltration of the bone marrow; and (c) two or more focal lesions in the bone or bone marrow as defined by whole-body (or at least spine and pelvis) magnetic resonance imaging (MRI) (Box 1) (5). These arbitrary cut-offs were initially reported in retrospective single center studies suggesting these biomarkers to be associated with, on average, around 1 year for the progression from smoldering myeloma to multiple myeloma. Subsequently, smaller efforts were launched to replicate these observations, and, upon review of these reports, the IMWG consensus group felt it was clinically justifiable to integrate these biomarkers, to be written up be a writing committee, and launched as the updated IMWG diagnostic criteria for multiple myeloma requiring therapy (5).

In addition to the added three biomarkers discussed above, in the updated IMWG criteria there were several adjustments and improvements of the definitions of the CRAB criteria. Specifically, hypercalcemia and anemia remain to be defined the same way as before; however, the definitions of renal failure and lytic bone disease have been revised. Renal failure was previously defined as an increased serum creatinine >173 μmol/L (>2 mg/dL) which is a non-reliable marker. Therefore, the new definition advises clinicians to use either the Modification of Diet in Renal Disease (MDRD) equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in estimating glomerular filtration rate (eGFR) in patients with myeloma, but a slight preference was given to using the CKD-EPI

equation (5). Unless the renal insufficiency is due to another known cause, patients with an eGFR value below 40 ml/min and/or a serum creatinine >173 μmol/L (>2 mg/dL) are considered to fulfill the definition of renal insufficiency as part of the diagnostic criteria for multiple myeloma (Box 1) (5).

Although it is well-known that X-ray has major sensitivity limitations when it comes to the detection of bone disease, in the clinical management of multiple myeloma, skeletal surveys have historically been use to identify lytic bone lesions in multiple myeloma. The revised IMWG criteria state that (a) skeletal survey, (b) PET-CT, or (c) low-dose CT represent valid methods which can be used to rule out lytic bone lesions (Box 1). The definition of a lytic lesion is arbitrarily set to 5 mm or greater diameter bone destruction. As a point of reference, in routine clinical care at Memorial Sloan Kettering Cancer Center (MSKCC), my colleagues and I (OL) have implemented PET-CT as the default method to rule out lytic bone lesions in patients with plasma cell disorders. PET-CT has over 20- to 30-times higher sensitivity than a skeletal survey (8). Another clinical way of illustrating the difference in sensitivity between the two methods comes here: in our experience, among 100 smoldering myeloma patients with a negative skeletal survey, we typically find 20-30 to have lytic bone lesions by PET-CT. It should be emphasized that lytic lesions are defined by the CT portion of the PET-CT; independent if there is PET uptake, or not. In fact, the PET portion has many limitations in the setting of multiple myeloma; it is non-specific and it is non-sensitive (8). For example, multiple myeloma patients with known lytic bone lesions may be PET negative due to slow metabolism of the myeloma cells (8). Also, positive PET uptake is commonly seen due to inflammation, degenerative joints, or other causes. Importantly, on a practical note, PET-CT is used to monitor other diseases and increased PET SUV uptake has direct clinical impact (e.g., in the management and treatment of lymphomas). In contrast, quantification of abnormal SUV uptake is currently not part of the routine clinical management in multiple myeloma. Instead, the clinical focus is dependent on the CT portion's ability to identify or rule out lytic bone lesions. Although this may sound trivial, due to lack of communication between physicians managing patients with plasma cell disorders and physicians reading PET-CT results, in many clinics around the world, the full imaging reports from PET-CT are done by nuclear medicine specialists and not radiologists. Consequently, in these instances, the PET-CT report reflects mostly (only) SUV uptake by the PET tracer and the value of the more sensitive CT portion (compared to skeletal survey) may be missed for the purpose of detecting early bone disease. Therefore, clinicians seeing patients with plasma cell disorders need to be aware of these facts, and, if needed, should be encouraged to seek contact with their corresponding imaging colleagues to ensure that the PET-CT assessments and reports are optimized for the detection of lytic bone lesions. For example, in centers where nuclear medicine specialists are leading the work with PET-CT; two parallel reports can be generated for myeloma PET-CT evaluations: one by a radiologist (CT portion) and one by a nuclear medicine specialist (PET portion).

On a clinical note, we would like to add some more perspectives and discuss more details on the above listed new biomarkers that were added to the IMWG diagnostic criteria. Specifically, we would like to address the issue with 60% or more plasma cell infiltration of the bone marrow. Typically, patients with such high percentage of infiltration of the bone marrow have other abnormalities, such as anemia, pain and perhaps lytic bone lesions.

However, there are cases where the plasma cell infiltration is high in the absence of other criteria. It should be stressed that there are different ways to determine the plasma cell percentage in the bone marrow. In clinical practice, typically, there are three measures of plasma cell percentage of the bone marrow reported to the clinician: (a) plasma cell percentage determined by counting cells on a core biopsy with immunohistochemistry (IHC) staining with CD138 antibody; (b) plasma cell percentage determined by counting cells on an aspirate smear; and (c) plasma cell percentage as determined by the flow cytometry machine. Many times medical fellows ask in clinic, “which plasma cell percentage of the bone marrow is correct?” The correct answer is: “the highest number, which is typically the plasma cell percentage determined by counting cells on a core biopsy with IHC staining by CD138”. This is important as the results are highly different between these methods. In our clinical experience (OL), if a core biopsy IHC stained by CD138 shows 60%, the typical aspirate smear shows about 30% (due to blood contamination and underestimation), and the flow cytometry machine may show in the range of 2% plasma cells (due to blood contamination and cell lysis). The correct answer in this case is 60% plasma cell infiltration of the bone marrow. It should be mentioned that CD138 staining requires more specialized training than regular H&E staining; H&E typically gives a lower plasma cell count than CD138 staining. In unclear cases, a second opinion by a specialized myeloma center is preferable to ensure optimal patient care.

Lastly, we would like to give a few final comments on MRI assessment of the skeleton. The original study done by Hillengass and colleagues used whole-body MRI in a series of 149 patients with smoldering myeloma and they showed that among those with 2 or more focal lesions (N=23/149, 15%) in the bone or bone marrow; 12/23 (50%) had progression to multiple myeloma within 13 months and 16/23 (70%) had progression to multiple myeloma within 2 years (9). To expand on these findings, a Greek study group assessed 67 patients with smoldering myeloma with MRI of the spine and the pelvis; 9/67 (14%) patients had two or more focal lesions and all 9 had progression to multiple myeloma within 4 years (10). Based on these data, the IMWG consensus panel decided to use MRI as a biomarker for the diagnosis of multiple myeloma (5). Although the IMWG criteria allow either of the two approaches (due to differences in availability of MRI around the world), several clinical questions remain. For example, is it necessary with whole-body MRI, or is spine and pelvis sufficient? In the study by Hillengass and colleagues (9), 90% of the focal lesions were observed in the spine and pelvis; thus, 10% may be missed if whole-body MRI is not conducted. Also, a common clinical question pertains to the use of PET-CT versus MRI; is there added value to do both, or can MRI be skipped? The correct answer is: “there is not enough data to give a definitive answer; the IMWG guideline states that both methods shall be done (5)”. Imaging-wise, MRI is a better method to assess soft tissue (such as bone marrow) and CT is better for hard tissue (such as bone). In our clinical practice at MSKCC, my colleagues and I (OL), we do PET-CT first, and, if negative for lytic bone lesions, we order whole-body MRI to rule out focal bone marrow areas. If the PET-CT is positive, typically, we do not proceed with MRI since the patient already fulfills the criteria for having multiple myeloma. It should be stressed that there is no universal definition of a “focal bone marrow lesion by MRI” in the literature. Future updated IMWG guidelines will benefit from involving imaging specialists in addition to myeloma specialists.

Although the IMWG diagnostic criteria are not perfect, the intent and the implications of the updated version are to facilitate earlier detection and earlier initiation of therapy with the aim to improve overall survival in multiple myeloma. Indeed, population-based data support earlier detection and initiation of therapy in multiple myeloma (11).

Prognosis

It is probably fair to say that the myeloma field is quite behind when it comes to our understanding of the heterogeneous biology of multiple myeloma and its implications to therapy. Emerging DNA sequencing data show massive genetic heterogeneity across and within given multiple myeloma patients (12). It has been found that, on average, a newly diagnosed multiple myeloma patient has mutations in a large number of genes and these mutations are unevenly distributed in parallel sub-clones present already at diagnosis (12, 13). Despite all success for the majority of multiple myeloma patients, yet today, ~25% of all newly diagnosed patients live less than 3 years (14). Although only limited data is available at this time, this is probably not true in the setting of our current best therapies as some of the formerly considered “high-risk myeloma” cases do quite well with modern therapy (15). This phenomenon illustrates the fact that poor prognosis always has to be viewed in the light of a given therapy. Clearly, it seems reasonable to believe that certain subtypes within the former group of clinical high-risk myeloma will be considered as standard risk as newer therapies become better and better. On the other hand, it is frustrating that a non-trivial proportion of patients with newly diagnosed multiple myeloma continue to experience treatment failure. In our opinion, a key task for the field is to move beyond the ill-defined clinical category high-risk myeloma which presumably contains several biological subtypes. To make this happen, prospective studies are needed to dissect tumor biology and define multiple myeloma subtypes, and, based on biological insights, seek to develop rational therapies for individual subtypes. Lastly, beyond a better molecular definition of multiple myeloma patients based on DNA sequencing, gene expression analysis based on RNA expression has information on activation of genes and pathways involving several genes independent of mutational status (16). Future integrated analyses of DNA and RNA signatures will allow further characterization of biology and prognosis in relation to given therapies.

Assessment of Response

At the beginning of the 21st Century, multiple myeloma had an average overall survival of about 3 years (4). Around that time, 3 drugs (bortezomib, lenalidomide, and thalidomide) were introduced for the treatment of multiple myeloma and, in 2012, carfilzomib received accelerated approved by the U.S. Food and Drug Administration (FDA). The FDA approved 14 new drugs for the treatment of cancer in 2015; 4 of these were approved for the treatment of myeloma (panobinostat, daratumumab, elotuzumab, and ixazomib) (5). In 2015 and 2016, expanded label indications were approved by the FDA for lenalidomide and carfilzomib, respectively (5). The increased availability of highly effective targeted agents with limited overlapping toxicities has shifted the therapeutic paradigm from palliative 2-drug combinations towards the use of modern, effective 3-drug combination strategies (17). Reflective of the fast moving field, studies are already ongoing to evaluate modern 4-drug

combinations, including monoclonal antibodies in combination with proteasome inhibitors, IMiDs, and low-dose steroids (18). Clinical trials evaluating combination regimens incorporating recently approved agents have shown that patients across the myeloma disease continuum are able to achieve deep and durable responses, including minimal residual disease (MRD) negativity, and improved patient outcomes (17). As a logical and necessary step forward, investigators have explored strategies to detect MRD and its correlation with clinical outcomes (19). Indeed, recent meta-analysis data show that MRD negativity is associated with longer progression-free survival and overall survival (20). In brief, a meta-analysis including published clinical trials of newly diagnosed multiple myeloma patients was recently undertaken. The study shows that MRD negativity is associated with a longer progression-free survival (HR=0.35; P<0.001) and overall survival (HR=0.48; P<0.001) (20), supportive of MRD becoming a regulatory endpoint for drug approval in newly diagnosed multiple myeloma (Figure 1). Because there has not been any defined criteria for the definition of MRD negativity, until date (6); among the four studies included in the main analysis (15, 21-23), three used multiparameter flow-cytometry (15, 21, 22) and one study used allele-specific quantitative polymerase chain reaction (23), both with a sensitivity of at least 1 in 10,000 cells (10^{-4}) to determine MRD status (17). The past few years, several assay platforms have been launched to determine MRD status in multiple myeloma patients. The two main assay platforms are multiparameter flow-cytometry-based and molecular-based (deep DNA sequencing of VDJ region). Currently, the flow-cytometry-based platform is clinically more easily available given that most institutions have access to modern flow-cytometry machines; however, there is inherent variability due to observer variability, differences in the use of antibodies, and procedures regarding sample preparation (17). Once molecular-based assays become more easily available, likely, they will play a key role in MRD assessment given their high degree of reproducibility and also their higher sensitivity (17). Future studies will guide the evolution of MRD assays in multiple myeloma, Moving forward in the current era of available assays, to harmonize procedures and to ensure that MRD status has the same meaning across studies, the IMWG recently revised the response criteria for myeloma and included MRD negativity as the highest degree of response to treatment (6). Based on the 2016 IMWG criteria, MRD negativity can be defined by either multiparameter flow-cytometry-based or molecular-based assays with a sensitivity of at least 1 in 100,000 cells (10^{-5}) to determine MRD status; and MRD status shall only be determined in patients who have achieved a conventional CR (Box 2) (6).

Moving forward, as better and better drugs become available for the treatment of multiple myeloma, ironically, traditional regulatory endpoints (i.e. overall survival and progression-free survival) will become key barriers for drug development (19). As pointed out in the literature, there is urgent need for reliable surrogate regulatory endpoints for drug approval (24, 25). Indeed, Gormley et al, from the FDA, recently published a paper on regulatory perspectives on MRD testing in multiple myeloma (26). In their paper, they concluded that MRD assessment in multiple myeloma has the potential to become a surrogate clinical endpoint that could be used to support regulatory purposes for drug review (26). As stated by Gormley et al., standardization of MRD testing and consensus within the multiple myeloma community as to the role of MRD and possible incorporation into the response criteria will be integral steps towards this end (26). The FDA has emphasized the importance

of future meetings to facilitate a consensus process in the U.S. and expressed their interest in reviewing both testing protocols of MRD assays and clinical protocols incorporating MRD (26). In this context, the results from the meta-analysis play an important role as they provide scientific evidence on the impact of MRD negativity as a strong predictor of longer progression-free survival and overall survival in newly diagnosed multiple myeloma (20). The findings are supportive of MRD assessment becoming a surrogate clinical endpoint that could be used to support regulatory purposes for drug review in multiple myeloma (26). In addition to the results from this meta-analysis; prospective clinical studies are ongoing and will further confirm and expand on these findings (20).

Future Directions

The myeloma community has made major progress in a short period of time. The average newly diagnosed multiple myeloma patient has over 10 years of overall survival today (1), and perhaps (?) 15 or 20 years for patients diagnosed in 2016 given the increased access to newer drugs. The reason there is uncertainty on the projected overall survival is simply due to the lack of long-term follow-up data based on newer combination therapies. Indeed, we have to wait another 10-20 years to document the progress we have made. In the meantime, we need to improve our understanding on the biology of multiple myeloma. Overall, we need to move beyond the ill-defined category high-risk multiple myeloma which historically refers to 1 in 4 of all newly diagnosed patients (14). We need to develop prospective studies to dissect tumor biology. Specifically, by treating patients with the best available therapies, and, in parallel, running modern molecular profiling, will allow us to define multiple myeloma subtypes. With such knowledge, hopefully, we will be able to define rational therapies for individual subtypes based on biology. In our opinion, such efforts are urgently needed to advance the field.

Also, continued work focusing on MRD is important to advance the field. To support the FDA to acknowledge MRD negativity as a regulatory end-point (20), concerted efforts are needed including large clinical trials capturing both MRD status and clinical outcomes (i.e. progression-free survival). Clinical trials have to be designed in a manner where all patients reaching complete response will be tested for MRD status, the MRD assay is done in a uniform way within the given study, and clinical follow-up data will be captured for all patients. In parallel with these practical steps, we need to continue developing better MRD tests with higher sensitivity and also MRD tests that ultimately can be based on peripheral blood instead of bone marrow aspirates. In our opinion, access to future blood-based MRD tests will have the potential to transform the myeloma field and open up avenues for response-driven treatment strategies with the aim to tailor treatment, for maximal efficacy and limited toxicity (4). In the future, it is possible that many patients will live with multiple myeloma inactive for a very long time and that treatment adjustments will be based on changes in biomarkers before the patient develops any symptoms (functional cure). Ideally, an extended deep MRD negativity has the potential to be the pathway to full (operational) cure, at least in some patients. More hard work is needed to ensure the field will be going in this direction.

Acknowledgments

Grant Support: O. Landgren is supported by Core Grant P30 CA008748 from the NCI.

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Box 1

Definition of Multiple Myeloma Based on 2014 International Myeloma Working Group (IMWG) criteria

Both a) and b) have to be fulfilled

a. Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

b. Any one or more of the below listed myeloma defining events (which has to be attributed to the underlying plasma cell proliferative disorder):

- Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
- Renal insufficiency: creatinine clearance <40 mL per min and/or serum creatinine >173 μmol/L (>2 mg/dL)
- Anemia: hemoglobin value of >2.0 g/dL below the lower limit of normal, or a hemoglobin value <10.0 g/dL
- Bone lesions: one or more osteolytic lesions on skeletal radiography (i.e. X-ray), low-dose CT, or PET-CT
- Clonal bone marrow plasma cell percentage ≥60%
- Involved/uninvolved serum free light chain ratio ≥100, and the involved serum free light chain concentration 10 mg/dl or higher
- Two or more focal lesions based on MRI studies of the skeleton

See details and discussion in the text regarding the above myeloma defining event variables

Adapted from ref. 5, *The Lancet Oncology*, Vol. 15, Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al., International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, e538-48, © 2014, with permission from Elsevier.

Box 2

Definition of Minimal Residual Disease (MRD) Negativity Based on 2016 International Myeloma Working Group (IMWG) Criteria

MRD negativity
• Requires complete response (CR) • Absence of aberrant clonal plasma in bone marrow aspirate, ruled out by an assay with a minimum sensitivity of 1 in 10^5 nucleated cells or higher (i.e. 10^{-5} sensitivity) *

* Based on flow cytometry or next generation sequencing (such as the EuroFlow standard operation procedure for MRD detection in multiple myeloma, or other validated equivalent methods; LymphoSIGHT, or other validated equivalent method)

Adapted from ref. 6, *The Lancet Oncology*, Vol. 17, Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al., International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-46, © 2016, with permission from Elsevier.

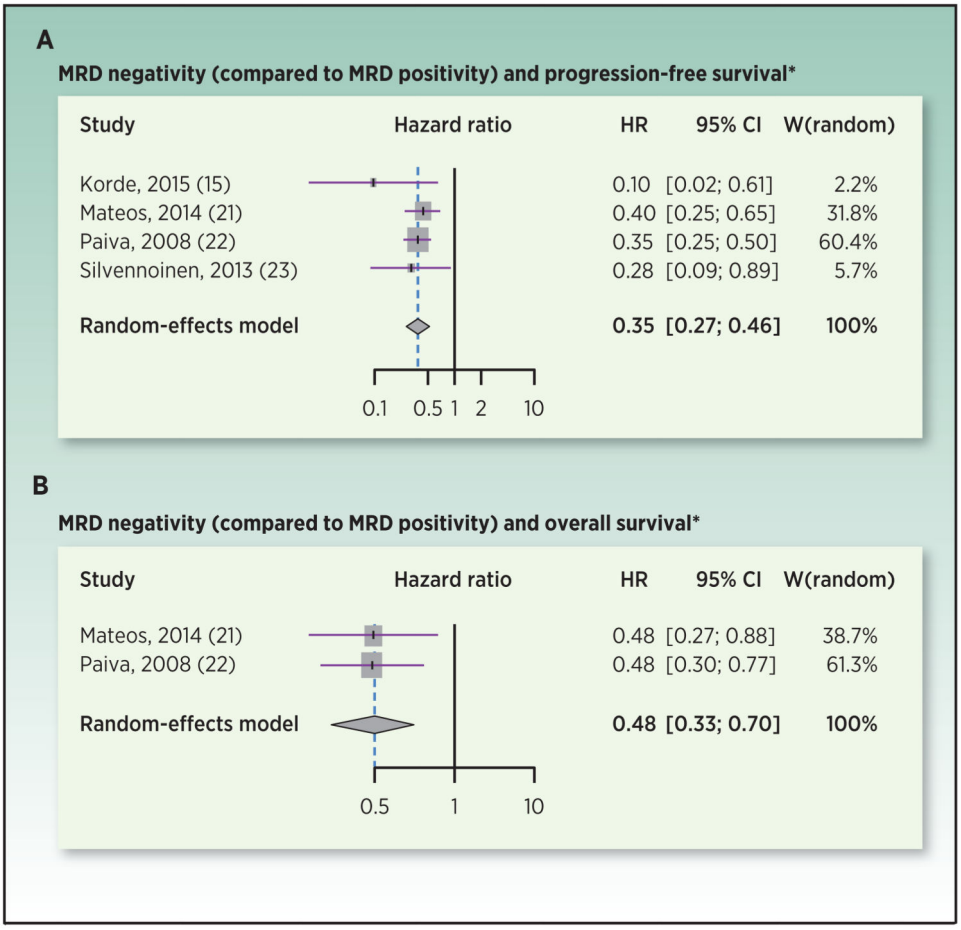

Figure 1.

Mrd negativity associated with longer progression-free survival (a) and overall survival (b) in newly diagnosed multiple myeloma patients. Note: Four studies with information on MRD status and hazards ratios for progression-free survival were included in the final analysis (15, 21-23); three studies had information on overall survival (15, 21, 22) (however, one study had no deaths during the original follow-up window (15)) so two studies provided hazards ratios for overall survival. Reprinted from ref. 4. *A lower hazard ratio indicates decreased risk for each survival endpoint (i.e. MRD negativity associated with lower risk of progression and lower risk of dying).