# ORIGINAL ARTICLE

# Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis

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Driven by access to better drugs, on average, newly diagnosed multiple myeloma patients have over 10 years overall survival. Using modern combination therapies—with or without the addition of high-dose melphalan and autologous stem cell transplantation—up to 80% of patients reach a complete response. As a logical and necessary step forward, clinical studies have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. In this context, MRD has been proposed as a regulatory end point for drug approval in newly diagnosed multiple myeloma. To better define the role of MRD negativity in relation to clinical outcomes, we undertook a meta-analysis including published clinical trials of newly diagnosed multiple myeloma patients. We applied a random effects model which weighted studies using the inverse–variance method. Studies were combined on the scale of the logarithm of the hazard ratio (HR) and the corresponding s.d. We found that MRD negativity (versus positivity) was associated with better PFS (HR = 0.35; 95% confidence interval (CI) 0.27–0.46; $P < 0.001$) and overall survival (HR = 0.48; 95% CI 0.33–0.70; $P < 0.001$). Our results show that MRD negativity is a strong predictor of clinical outcomes, supportive of MRD becoming a regulatory end point for drug approval in newly diagnosed multiple myeloma.

## INTRODUCTION

At the start of the 21st Century, in the US multiple myeloma had an average overall survival of about 3 years.[1] Driven by access to better drugs, younger patients ($< 50$ years) showed $> 10$ years median overall survival by 2014.[1] The US Food and Drug Administration (FDA) approved 14 new drugs in the treatment of cancer in 2015; four of these were approved for the treatment of multiple myeloma (panobinostat, daratumumab, elotuzumab and ixazomib).[2] In 2015 and 2016, expanded label indications were FDA approved for lenalidomide and carfilzomib, respectively.[2]

A few years ago, using older drugs followed by high-dose melphalan (HDM) and autologous stem cell transplantation (ASCT), only a small fraction of patients obtained a complete response (CR).[3] Today, using modern combination therapies, with or without the addition of HDM–ASCT, 100% of patients achieve a treatment response (overall response) with up to 80% of these patients reaching a CR.[3] As a necessary and logical step forward, clinical studies have explored strategies to detect minimal residual disease (MRD) and its correlation with clinical outcomes. Both PFS and overall survival have been associated with MRD in several studies,[3] suggesting that MRD negativity is a predictor of better clinical outcomes in multiple myeloma.[4]

Although individual smaller studies have suggested that MRD is associated with clinical outcomes,[3] to provide formal scientific evidence, we undertook a meta-analysis including published clinical trials of newly diagnosed multiple myeloma patients.

## PATIENTS AND METHODS

On 22 December 2015, we conducted a systematic search for clinical trials of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes. We applied the following MEDLINE (via PubMed), EMBASE and Cochrane's Central Register of Controlled Trials (CENTRAL)

search strategy: ((((Clinical trial[ptyp] OR random*[ti] OR (blinded OR blind) OR 'randomized controlled trial'[tiab] OR rct[ti] OR 'clinical trial'[ti] OR trial*[ti]))) AND (Flow cytometry[mh] OR flow[tiab] OR flow microfluoromet*[tiab] OR polymerase chain reaction[mh] OR pcr[tiab] OR 'polymerase chain reaction'[tiab] OR gene expression profiling[mh] OR molecular[tw] OR sequence analysis[mh] OR 'sequence analysis'[tiab] OR sequenc*[tiab] OR 'minimal residual disease'[tiab] OR mrd[tiab])) AND (multiple myeloma[mh] OR 'multiple myeloma'[ti] OR 'plasma cell myeloma*'[ti]). Taking this approach, a total of 390 potential studies were first identified; however, after careful review of each individual abstract, we excluded 370 since they were not clinical trials with MRD assessment in multiple myeloma. Thus, 20 clinical trial studies of newly diagnosed multiple myeloma patients with information on MRD and clinical outcomes were identified and assessed for inclusion in this meta-analysis (Figure 1). Since all the 20 published studies did not include all details required for our pre-planned statistical analysis, we contacted the corresponding authors to obtain hazard ratio (HR) estimates and corresponding confidence intervals (CI) for the association between MRD and clinical outcomes.

### Statistical analysis

Four manuscripts were included in the meta-analysis for PFS and two were included for overall survival. Each paper used a different landmark time point for MRD evaluation; these included: after eight cycles of therapy,[5] after six cycles of therapy,[6] at 100 days post ASCT[7] and 3–6 months post ASCT.[8] Two patients in the original Korde et al.[5] analysis were removed from the HR calculation due to either not having sufficient follow-up or progressing before the landmark time. In Silvennoinen et al.,[8] only patients achieving a CR or a near-(n)-CR were included in the HR calculation; for the other included studies, all patients were included. The meta-analysis was conducted using a random effects model, which weighted studies using the inverse–variance method. Studies were combined on the scale of the logarithm of the HR and the corresponding s.d. The analysis used the package 'metafor' in R Statistical Platform, v 3.2.3 (R Foundation, Vienna, Austria).[9,10]

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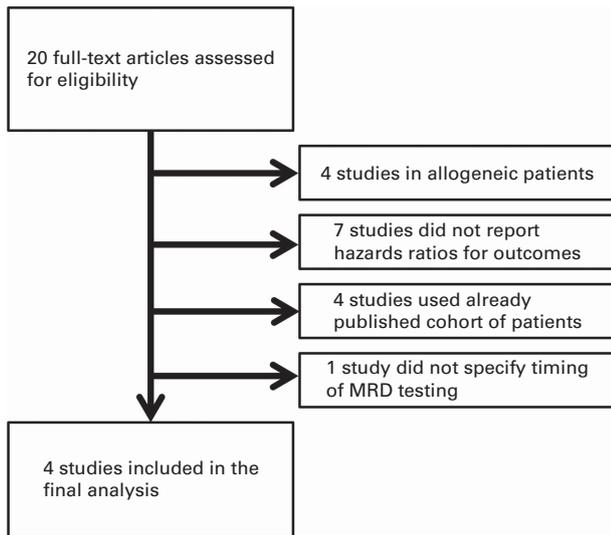
**Figure 1.** Search criteria for systematic review. On 22 December 2015; we applied a comprehensive MEDLINE (via PubMed), EMBASE and Cochrane's Central Register of Controlled Trials (CENTRAL) search strategy. For details see the Methods Section. Upon careful review of the 20 identified studies,[5–8,11–26] 4 studies were excluded because they reported on allogeneic transplantation;[11–14] 7 were excluded because they did not evaluate the association between MRD status and PFS and/or overall survival;[15–21] 4 were excluded because they analyzed the same cohort of patients (duplicates);[22–25] and 1 was excluded because the timing of MRD analysis was not specified.[26]

## RESULTS

Upon careful review of the 20 identified studies,[5–8,11–26] 4 studies were excluded because they reported on allogeneic trans-plantation;[11–14] 7 were excluded because they did not evaluate the association between MRD status and PFS and/or overall survival;[15–21] 4 were excluded because they analyzed overlapping cohorts of patients (duplicates);[22–25] and 1 was excluded because the timing of MRD analysis was not specified[26] (Figure 1). Four studies with information on MRD status and HR for PFS were included in the final analysis;[5–8] three studies had information on overall survival[5–7] (however, one study had no deaths during the original follow-up window[5]) so two studies provided HRs for overall survival.

Among the four studies included in the main analysis,[5–8] three used multiparameter flow-cytometry[5–7] and one study used allele-specific quantitative PCR,[8] both with a sensitivity of at least 1 in 10 000 cells ($10^{-4}$) to determine MRD status.[3] In line with standard methodology,[9,10] the random effects model weighted studies based on the inverse–variance method; the largest study (Paiva et al.[7]) had the largest weight (W random = 60.4%) in the meta-analysis; and the smallest study (Korde et al.[5]) had the smallest weight (W random = 2.2%) (Figure 2). Despite inherent differences across included studies (for example, including eligibility criteria, use of drugs, application of MRD assays), all HRs were in the same direction favouring MRD negativity for a longer PFS. Overall, the meta-analysis show that patients who achieved MRD negativity (versus remained MRD positive) had better PFS (HR = 0.35; 95% CI 0.27–0.46; $P < 0.001$) (Figure 2).
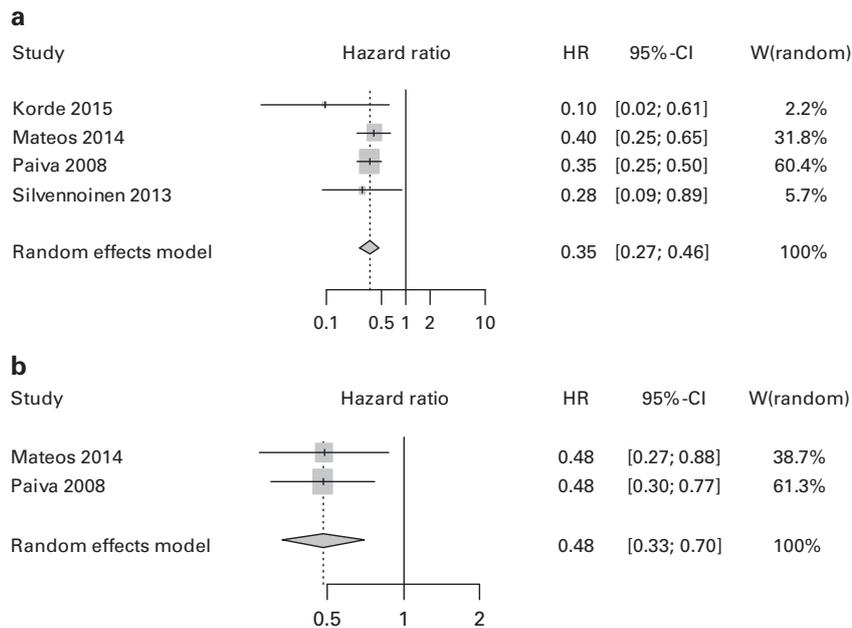
In addition to investigating MRD status in relation to PFS, we were also interested in assessing the association between MRD negativity and overall survival. As described above, four studies with information on MRD status and HRs for PFS were included in the final analysis and three of these had information on

overall survival.[5–7] However, due to the use of modern effective combination therapy, the study by Korde et al.[5] had no deaths during the original follow-up window (up to 30 months). Therefore, the studies by Paiva et al.[7] and Mateos et al.[6] were the only two that provided HRs for overall survival. Based on these two studies, our meta-analysis showed that patients who achieved MRD negativity (versus remained MRD positive) had better overall survival (HR = 0.48; 95% CI 0.33–0.70; $P < 0.001$) (Figure 2).

## DISCUSSION

For several decades, only limited progress was made in the field of drug development for multiple myeloma. Driven by access to new effective drugs, in 2016, newly diagnosed multiple myeloma patients—on average—have over 10 years overall survival in the US.[3] Using modern combination therapies—with or without the addition of HDM and ASCT—up to 80% of patients reach a CR.[3] Consequently, clinical studies have explored strategies to detect MRD and its correlation with clinical outcomes. Further-more, in this context, MRD has been proposed as a regulatory end point for drug approval in newly diagnosed multiple myeloma.[27,28] To fill important gaps in the literature, we were motivated to conduct a meta-analysis including all published clinical trials of newly diagnosed multiple myeloma patients. Using a robust random effects model, we found that MRD negativity is associated with better PFS (HR = 0.35; $P < 0.001$) and overall survival (HR = 0.48; $P < 0.001$). Our results are very important as they provide formal scientific evidence of the fact that MRD negativity is associated with better clinical outcomes in newly diagnosed multiple myeloma.

Although stringent criteria were applied to identify and include studies for our meta-analysis, inherently, like any meta-analysis, there were some differences between the included studies. For example, the studies by Paiva et al.[7] and Silvennoinen et al.[8] used various combinations including bortezomib and dexamethasone (with or without alkylating drugs) followed by HDM and ASCT, whereas the study by Mateos et al.[6] used combinations including bortezomib and prednisone followed by maintenance therapy with either bortezomib/thalidomide or bortezomib/prednisone for up to 3 years.[6] Given that there are differences in access to myeloma drugs across regions—and, indeed, these three studies were all conducted in Europe—it seems reasonable to conclude that these regimens are quite applicable to European treatment traditions. As illustrated in Figure 2, these three studies consistently showed that MRD negativity was associated with an HR between 0.3 and 0.4 (Figure 2). As a consequence of the rapid access to better myeloma drugs in the US the myeloma treatment field has been moving fast forward and new combination therapies have been developed.[2] The study by Korde et al.[5] was a single arm phase 2 study open to newly diagnosed multiple myeloma patients of all ages (18 years and older). Per protocol, all patients received 8 cycles of carfilzomib, lenalidomide and dexamethasone (CRd) combination therapy, followed by 2 years of lenalidomide maintenance therapy; and none of the enrolled patients underwent upfront HDM and ASCT; however, on a separate protocol, younger and older fit patients were offered stem cell collection for potential future use (that is, delayed HDM and ASCT). On the basis of available literature, CRd combination therapy has the highest and deepest response rate for multiple myeloma patients to date,[5,29] and, consequently, in the study by Korde et al.[5] MRD negativity was associated with a HR of 0.1 (Figure 2). Per standard conventions,[9,10] in our meta-analysis, the random effects model weighted studies based on the inverse–variance method, and, thus, the largest study (Paiva et al.[7]) had the largest weight on the HR in the meta-analysis while the smallest study (Korde et al.[5]) had the smallest weight. It should be emphasized that although there are inherent differences across

**a**

| Study | Hazard ratio | HR | 95%-CI | W(random) |
|-------|--------------|-----|--------|-----------|
| Korde 2015 | | 0.10 | [0.02; 0.61] | 2.2% |
| Mateos 2014 | | 0.40 | [0.25; 0.65] | 31.8% |
| Paiva 2008 | | 0.35 | [0.25; 0.50] | 60.4% |
| Silvennoinen 2013 | | 0.28 | [0.09; 0.89] | 5.7% |
| | | | | |
| Random effects model | | 0.35 | [0.27; 0.46] | 100% |

0.1   0.5 1 2   10

**b**

| Study | Hazard ratio | HR | 95%-CI | W(random) |
|-------|--------------|-----|--------|-----------|
| Mateos 2014 | | 0.48 | [0.27; 0.88] | 38.7% |
| Paiva 2008 | | 0.48 | [0.30; 0.77] | 61.3% |
| | | | | |
| Random effects model | | 0.48 | [0.33; 0.70] | 100% |

0.5   1   2

**Figure 2.** MRD status and clinical outcomes in newly diagnosed multiple myeloma. (**a**) MRD negativity (compared with MRD positivity) and PFS*. (**b**) MRD negativity (compared with MRD positivity) and overall survival*. *A lower hazard ratio indicates decreased risk for each survival end point (i.e. MRD negativity associated with lower risk of progression and lower risk of dying). Four studies with information on MRD status and hazards ratios for PFS were included in the final analysis;[5–8] three studies had information on overall survival[5–7] (however, one study had no deaths during the original follow-up window[5]) so two studies provided hazards ratios for overall survival.

clinical trials, all HRs for the included studies were in the same direction favouring MRD negativity for a longer PFS as well as overall survival.

Other aspects of difference across included studies include the actual MRD assays and the timing for MRD testing. As discussed above, among the four studies included in the main analysis,[5–8] three used multiparameter flow-cytometry[5–7] and one study used allele-specific quantitative PCR,[8] both with a sensitivity of at least 1 in 10 000 cells ($10^{-4}$) to determine MRD status.[3] To harmonize procedures and to ensure that MRD status has the same meaning across studies, the International Myeloma Working Group (IMWG) recently revised the response criteria for myeloma and included MRD negativity as the highest degree of response to treatment.[30] Based on the 2016 IMWG criteria, MRD negativity can be defined by either multiparameter flow-cytometry-based or molecular-based assays; and MRD status shall only be determined in patients who have achieved a conventional CR.[30]

Moving forward, as better and better drugs become available for the treatment of multiple myeloma, ironically, traditional regulatory end points (that is, overall survival and PFS) will become key barriers for drug development. In fact, future registrational clinical trials will require very large sample sizes and very long follow-up (to be able to provide sufficient statistical power) to show that new drugs have an overall survival and/or PFS benefit. Thus, due to these inherent limitations of traditional regulatory end points, future myeloma drugs will become majorly delayed and costs for drug development will increase significantly. Clearly, there is an urgent need for reliable surrogate regulatory end points for drug approval.[27,28] Indeed, Gormley et al.,[4] from the FDA, recently published a paper on regulatory perspectives on MRD testing in multiple myeloma. In their paper, the authors conclude that MRD assessment in multiple myeloma has the potential to become a surrogate clinical end point that could be used to support regulatory purposes for drug review.[4] As pointed out by Gormley et al.,[4] 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. The IMWG has worked extensively to revise the response criteria for multiple myeloma and an updated version of the IMWG response criteria which will include guidelines for MRD testing is anticipated to be published in 2016. Also, concerted efforts aiming to standardize MRD testing and consensus within the multiple myeloma community are ongoing. The FDA has emphasized the importance of future meetings to facilitate a consensus process in the US and expressed their interest in reviewing both testing protocols of MRD assays and clinical protocols incorporating MRD.[4] In this context, the results from our meta-analysis have an important role as they provide scientific evidence on the impact of MRD negativity as a strong predictor of longer PFS and overall survival in newly diagnosed multiple myeloma.

Based on the results from our meta-analysis, we conclude that MRD negativity is associated with better PFS and overall survival in newly diagnosed multiple myeloma. Our findings are supportive of MRD assessment becoming a surrogate clinical end point that could be used to support regulatory purposes for drug review in multiple myeloma.[4] In addition to the results from this meta-analysis; prospective clinical studies are ongoing, and will further confirm and expand on our findings.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

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## REFERENCES

1 Kristinsson SY, Anderson WF, Landgren O. Improved long-term survival in multiple myeloma up to the age of 80 years. *Leukemia* 2014; **28**: 1346–1348.

2 US Food and Drug Administration Hematology/Oncology (Cancer) Approvals & Safety Notifications. 2016. Available at: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

3 Mailankody S, Korde N, Lesokhin AM, Lendvai N, Hassoun H, Stetler-Stevenson M et al. Minimal residual disease in multiple myeloma: bringing the bench to the bedside. *Nat Rev Clin Oncol* 2015; **12**: 286–295.

4 Gormley NJ, Turley DM, Dickey JS, Farrell AT, Reaman GH, Stafford E et al. Regulatory perspective on minimal residual disease flow cytometry testing in multiple myeloma. *Cytometry B Clin Cytom* 2016; **90**: 73–80.

5 Korde N, Roschewski M, Zingone A, Kwok M, Manasanch EE, Bhutani M et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol* 2015; **1**: 746–754.

6 Mateos MV, Oriol A, Martinez-Lopez J, Teruel AI, Lopez de la Guia A, Lopez J et al. GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? *Blood* 2014; **124**: 1887–1893.

7 Paiva B, Vidriales MB, Cervero J, Mateo G, Perez JJ, Montalban MA et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood* 2008; **112**: 4017–4023.

8 Silvennoinen R, Kairisto V, Pelliniemi TT, Putkonen M, Anttila P, Saily M et al. Assessment of molecular remission rate after bortezomib plus dexamethasone induction treatment and autologous stem cell transplantation in newly diagnosed multiple myeloma patients. *Br J haematol* 2013; **160**: 561–564.

9 Team RC. *R: A language and environment for statistical computing.* R Foundation for Statistical Computing: Vienna, Austria, 2015.

10 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; **36**: 1–48.

11 Cavo M, Terragna C, Martinelli G, Ronconi S, Zamagni E, Tosi P et al. Molecular monitoring of minimal residual disease in patients in long-term complete remission after allogeneic stem cell transplantation for multiple myeloma. *Blood* 2000; **96**: 355–357.

12 Corradini P, Cavo M, Lokhorst H, Martinelli G, Terragna C, Majolino I et al. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood* 2003; **102**: 1927–1929.

13 Galimberti S, Benedetti E, Morabito F, Papineschi F, Callea V, Fazzi R et al. Prognostic role of minimal residual disease in multiple myeloma patients after non-myeloablative allogeneic transplantation. *Leuk Res* 2005; **29**: 961–966.

14 Kroger N, Zagrivnaja M, Schwartz S, Badbaran A, Zabelina T, Lioznov M et al. Kinetics of plasma-cell chimerism after allogeneic stem cell transplantation by highly sensitive real-time PCR based on sequence polymorphism and its value to quantify minimal residual disease in patients with multiple myeloma. *Exp Hematol* 2006; **34**: 688–694.

15 Ladetto M, Pagliano G, Ferrero S, Cavallo F, Drandi D, Santo L et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin Oncol* 2010; **28**: 2077–2084.

16 Ludwig H, Viterbo L, Greil R, Masszi T, Spicka I, Shpilberg O et al. Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. *J Clin Oncol* 2013; **31**: 247–255.

17 Martinelli G, Terragna C, Lemoli RM, Cavo M, Benni M, Motta MR et al. Clinical and molecular follow-up by amplification of the CDR-III IgH region in multiple myeloma patients after autologous transplantation of hematopoietic CD34+ stem cells. *Haematologica* 1999; **84**: 397–404.

18 Powles R, Sirohi B, Kulkarni S, Bhagwati N, Saso R, Raje N et al. Acute lymphoblastic leukaemia-type intensive chemotherapy to eliminate minimal residual disease after high-dose melphalan and autologous transplantation in multiple myeloma - a phase I/II feasibility and tolerance study of 17 patients. *Bone Marrow Transplant* 2000; **25**: 949–956.

19 Rawstron AC, Child JA, de Tute RM, Davies FE, Gregory WM, Bell SE et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol* 2013; **31**: 2540–2547.

20 Rawstron AC, Gregory WM, de Tute RM, Davies FE, Bell SE, Drayson MT et al. Minimal residual disease in myeloma by flow cytometry: independent prediction of survival benefit per log reduction. *Blood* 2015; **125**: 1932–1935.

21 Roussel M, Lauwers-Cances V, Robillard N, Hulin C, Leleu X, Benboubker L et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. *J Clin Oncol* 2014; **32**: 2712–2717.

22 Martinez-Lopez J, Lahuerta JJ, Pepin F, Gonzalez M, Barrio S, Ayala R et al. Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. *Blood* 2014; **123**: 3073–3079.

23 Paiva B, Gutierrez NC, Rosinol L, Vidriales MB, Montalban MA, Martinez-Lopez J et al. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. *Blood* 2012; **119**: 687–691.

24 Paiva B, Martinez-Lopez J, Vidriales MB, Mateos MV, Montalban MA, Fernandez-Redondo E et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. *J Clin Oncol* 2011; **29**: 1627–1633.

25 Silvennoinen R, Lundan T, Kairisto V, Pelliniemi TT, Putkonen M, Anttila P et al. Comparative analysis of minimal residual disease detection by multiparameter flow cytometry and enhanced ASO RQ-PCR in multiple myeloma. *Blood cancer J* 2014; **4**: e250.

26 Ferrero S, Ladetto M, Drandi D, Cavallo F, Genuardi E, Urbano M et al. Long-term results of the GIMEMA VEL-03-096 trial in MM patients receiving VTD consolidation after ASCT: MRD kinetics' impact on survival. *Leukemia* 2015; **29**: 689–695.

27 Ahn IE, Mailankody S, Korde N, Landgren O. Dilemmas in treating smoldering multiple myeloma. *J Clin Oncol* 2015; **33**: 115–123.

28 Landgren O, Gormley N, Turley D, Owen RG, Rawstron A, Paiva B et al. Flow cytometry detection of minimal residual disease in multiple myeloma: Lessons learned at FDA-NCI roundtable symposium. *Am J Hematol* 2014; **89**: 1159–1160.

29 Jakubowiak AJ, Dytfeld D, Griffith KA, Lebovic D, Vesole DH, Jagannath S et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012; **120**: 1801–1809.

30 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. *Lancet Oncol* 2016; **17**: e328–e346.