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Outcome of paraosseous extra-medullary disease in newly diagnosed multiple myeloma patients treated with new drugs

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Abstract

Extramedullary disease is relatively frequent in multiple myeloma, but our knowledge on the subject is limited and mainly relies on small case series or single center experiences. Little is known regarding the role of new drugs in this setting. We performed a meta-analysis of 8 trials focused on the description of extramedullary disease characteristics, clinical outcome, and response to new drugs. A total of 2332 newly diagnosed myeloma patients have been included, 267 (11.4%) had extramedullary disease, defined as paraosseous in 243 (10.4%), extramedullary plasmocytoma in 12 (0.5%), and not classified in 12 (0.5%) patients. Median progression-free survival was 25.3 months and 25.2 in extramedullary disease and non-extramedullary disease patients, respectively. In multivariate analysis the presence of extramedullary disease did not impact on progression-free survival (hazard ratio 1.15, p=0.06), while other known prognostic factors retained their significance. Patients treated with immunomodulatory drugs, mainly lenalidomide, or proteasome inhibitors had similar progression-free survival and progression-free survival-2 regardless of extramedullary disease presence. Median overall survival was 63.5 months and 79.9 months (p=0.01) in extramedullary and non-extramedullary disease patients, respectively, and in multivariate analysis the presence of extramedullary disease was associated with a reduced overall survival (hazard ratio 1.41, p<0.001), in line with other prognostic factors. With the limits of the use of low sensitivity imaging techniques, that lead to an underestimation of extramedullary disease, we conclude that in patients treated with new drugs the detrimental effect of extramedullary disease at diagnosis is limited, that lenalidomide is effective as are proteasome inhibitors, and that these patients tend to acquire a more aggressive disease in later stages. (EUDRACT2005-004714-32, NCT01063179. NCT00551928, NCT01091831, NCT01093196, NCT01190787, NCT01346787, NCT01857115).

Introduction

Multiple myeloma (MM) is a plasma cell neoplasia characterized by a diffuse tumor infiltration of the bone marrow, resulting, among others, in anemia, bone damage with hypercalcemia, and bone lesions. Occasionally, neoplastic plasma cells acquire a different growth pattern generating tumor masses, that are referred to as extra-medullary disease (EMD).[1] EMD can arise from skeletal focal lesions, which disrupt the cortical bone and grow as extra-bone masses, and is referred to as paraosseous plasmocytoma (PO), or derive from hematogenous spread as manifestation in soft tissues, and is called extramedullary plasmocytomas (EMP). Incidence of EMD at diagnosis ranges between 6%-10%,[2–4] while later in the course of the disease increases to 13%-26%,[2,4] with a 32%-35% peak in case of relapse after allogeneic stem cell transplantation.[5,6] In the final stage of the disease an extraskeletal involvement is observed in approximately 70% of cases studied with autopsy,[7] with a peculiar involvement of visceral sites.[8] As expected, patients with EMD at diagnosis tend to maintain the same pattern at relapse.[2]

The biological mechanisms behind the acquisition of the EMD-forming phenotype have not yet been fully elucidated. Increased expression of CXCR4 and CXCL12 plays a major role in promoting a bone marrow-indipendent behavior, favoring dissemination and homing to distant and unusual sites.[9,10] Other mechanisms are represented by reduced expression of several adhesion molecules, in particular VLA-4, CD44, and CD56, and chemokine receptors, such as CCR1, and CCR2. Diversely, the cyclin D1 pathway seems to favor the bone marrow homing, protecting from extramedullary localizations, as t(11;14) is not observed in MM patients with EMD.[11]

Despite its frequency and clinical relevance, EMD has been commonly neglected by the medical literature. In fact, almost all the available data derive from retrospective series and single center experiences, mainly reported in the pre-new drug era, carrying the limitations of this type of studies. With the purpose to fill this gap and clarify the role of new drugs in MM with EMD, we conducted the largest meta-analysis so far reported, based on 8 prospective trials by the same sponsors (Fonesa Onlus and Hovon Foundation)

Methods

Study design

Patients with newly diagnosed MM enrolled in 8 clinical trials were retrospectively analyzed. Details on trials and treatment regimens are summarized in Table 1. Briefly, 3 trials enrolled transplant eligible, and 5 trials transplant ineligible patients. Three trials included an immunomodulatory (IMiD) drug in the treatment, lenalidomide in almost all cases, 3 trials a proteasome inhibitor (PI), and 4 trials both. Six out of 8 trials included maintenance. Trials were approved by the Independent Ethics Committees/Institutional Review Boards at all participating centres. Patients provided written informed consent before entering the study, prepared in accordance with the Declaration of Helsinki. For the purpose of this meta-analysis, we considered the subgroup of patients with EMD, and compared them with patients without EMD.

Extramedullary disease definition and assessment

EMD was classified as PO disease, consisting of tumor masses arising directly from bones, or EMP, consisting of masses not contiguous to the bones and derived from hematogenous spread. EMD was identified at study enrollment with the diagnostic procedure required by the patient's study protocol, such as

x-ray skeletal survey, magnetic resonance imaging (MRI), computed tomography (CT), and physical examination.

Statistical Analysis

Differences in patient and disease characteristics for EMD patients versus non-EMD patients were investigated using Kruskal Wallis test for continuous variables and Fisher's exact test for categorical variables. Data of trials were pooled together and analyzed. Time-to-event data were analyzed using the Kaplan–Meier method; EMD and non-EMD patients were compared with the log-rank test. The Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) and the 95% confidence intervals (CIs) for the main comparisons, EMD patients versus non-EMD patients. To account for potential confounders, the Cox models were adjusted for the age, sex, ISS stage (I vs. II; I vs. III), cytogenetic risk defined by FISH analysis (high, i.e. presence of del(17p), t(4;14), t(14;16), vs. standard risk; missing vs. standard risk), and autologous stem cell transplantation (ASCT) (ASCT vs. non-ASCT; not applicable, i.e. patients not candidate to ASCT, vs. non-ASCT). Subgroup analyses were performed to determine the consistency of the overall effect in different subgroups using interaction terms for the comparison between EMD vs. non-EMD and each of the covariate included in the Cox model plus Revised ISS stage (RISS) and type of therapies (IMID and PI). All HRs were estimated with their 95% CI and two sided p-values. In order to evaluate the impact of different size and types of EMD, further subgroup analyses were performed: EMD size ≤ 3 vs. > 3 cm; EMD size ≤ 5 vs. > 5 cm; PO or EMP. Data were analyzed as of December, 2018 using and R (Version 3.1.1).

Results

Patients

A total of 2332 patients were included in this analysis: 267 (11%) had EMD, while 2065 (89%) had no EMD. Median age of EMD patients was 68 years (IQ range 60-74), and 69 years (IQ range 61-74) in patients without EMD. International staging system was I in 119 (45%) and 682 (33%), II in 85 (32%) and 782 (38%), and III in 38 (14%) and 509 (25%) patients with or without EMD, respectively. Clinical trials were based on IMiD in 166 (62%) and 1279 (62%) patients, on a PI in 66 (25%) and 464 (22%) patients, or both in 35 (13%) and 322 (16%) patients with or without EMD, respectively. Patient characteristics are summarized in Table 2. Patients with EMD had PO in 243 (91%), and an EMP in 12 (4%) cases, while the information was not available for other 12 (4%) patients. EMD localizations were single in 195 (73%), and multiple in 60 (22%) patients. Median EMD size was 4.2 cm (IQ range 3–7). EMD characteristics are summarized in Table 3. No differences were observed in patients with EMD $\leq$ or > 3 cm. EMD patients had a lower systemic tumor burden respect to patients without EMD, as shown by: plasma cell bone marrow infiltration 30% (IQ range 15% - 50%) vs. 50% (IQ range 30% - 70%), hemoglobin 12.0 gr/L (IQ range 10.5 – 13.6) vs. 10.7 gr/L (IQ range 9.5 – 12.1), median creatinine clearance 75 mL/min per 1.73 m^2 (IQ range 48 – 98) vs 66 (IQ range 41 – 88), respectively. EMD patients had ISS I stage in 45% of cases, respect to 33% of non-EMD patients ($p<0.001$).

Efficacy

Progression-free survival

The median follow-up was 62 months (IQ range 34-75) in EMD, and 65 months (IQ range 40-77) in non-EMD patients. Median PFS was 25.3 months (95% CI 21.7 – 28.7) and 25.2 months (95% CI 24.2 – 27.0) in EMD and non-EMD patients, respectively. Five-year PFS was 19% (95% CI 15% – 25%) and 22% (95% CI 20% – 24%) (p=0.46) in EMD and non-EMD patients, respectively (Figure S1), and there were no differences between EMP, PO, and non-EMD (Figure 1A). In multivariate analysis the presence of EMD did not impact on PFS (HR 1.15, 95% CI 0.99-1.33; p=0.06), while other known prognostic factors retained their significance: high risk vs. standard cytogenetic (HR 1.35, 95% CI 1.20 -1.52; p<0.001), and ISS III vs. I (HR 1.74, 95% CI 1.53 -1.98; p<0.001) (Figure S4). Type of therapy had not impact on PFS: IMiD-based therapy (HR 1.14, 95% CI 0.96 – 1.35) and no IMiDs (HR 1.18, 95% CI 0.87 – 1.59)(interaction p = 0.86), PI-based therapy (HR 1.33, 95% CI 1.04 – 1.71) and no PI, (HR 1.04, 95% CI 0.87 – 1.25) (interaction p = 0.12), and ASCT in eligible patients (HR 1.10, 95% CI 0.81 – 1.50) and non-ASCT (HR 1.04, 95% CI 0.73 – 1.47) (interaction p = 0.72). A landmark analysis from maintenance start showed a median PFS of 23.4 months (95% CI 19.1 – 30.1) and 23.5 months (95% CI 21.8 – 25.7) (p=0.30) in EMD and non-EMD patients, respectively. EMD size was not correlated with median PFS: patients with EMD ≤3 cm 26.0 months (95% CI 18.5 – 37.1), patients with EMD >3 cm 23.7 months (95% CI 18.8 – 28.2), and patients without EMD 25.2 months (95% CI 24.2 – 27.0) (Figure 2). The same results were observed with the EMD size threshold at 5 cm (Figure S6). Median PFS according to EMD number was as follows: single EMD localization 26.1 months (95% CI 22.5 – 30.1), multiple EMD localizations 19.4 months (95% CI 14.9 – 33.1), and no EMD 25.2 months (95% CI 24.2 – 27.0). Median PFS was not correlated with EMD site: PO 24.3 months (95% CI 21.2–28.2), EMP 26.1 months (95% CI 8.0 – NR), and no EMD 25.2 months (95% CI 24.2 – 27.0), PO vs. no EMD (HR 1.14, 95% CI 0.98-1.33; p=0.10), and EMP vs. no EMD (HR 1.23, 95% CI 0.64-2.37; p=0.54)(Figure 1A). Median PFS2 and 5-year PFS2 were 43.2 months (95% CI 37.0-52.4) and 38% (95% CI 31% - 47%) in PO, 27.9 months (95% CI 4.9-NR) and NR in EMP, and 46.4 months (95% CI 44.1-48.9) and 40% (95% CI 37% - 43%) in non-EMD patients (Figure 3).

Overall survival

Median OS was 63.5 months (95% CI 48.2 – 84.7) and 79.9 months (95% CI 75.8 – 88.3; p=0.01) in EMD and non-EMD patients, respectively. Five-year OS was 51% (95% CI 45% – 58%) and 59% (95% CI 57% – 61%) (p=0.01) in EMD and non-EMD patients, respectively (Figure S3), and there was a significant difference between PO and non-EMD (HR 1.39, 95% CI 1.13-1.70; p=0.001) (Figure 1B). In multivariate analysis the presence of EMD was associated with a reduced OS (HR 1.41, 95% CI 1.16-1.71; p<0.001), in line with other known prognostic factors: high risk vs. standard cytogenetic (HR 1.68, 95% CI 1.44 -1.96; p<0.001), ISS III vs. I (HR 2.36, 95% CI 1.98 -2.82; p<0.001) (Figure S5). Type of therapy did not impact on OS: IMiD-based therapy (HR 1.38, 95% CI 1.10 – 1.73) and no IMiDs (HR 1.47, 95% CI 1.01 – 2.13) (interaction p = 0.78), PI-based therapy (HR 1.43, 95% CI 1.04 – 1.97) and no PI, (HR 1.39, 95% CI 1.09 – 1.76) (interaction p = 0.87), and ASCT in eligible patients (HR 1.45, 95% CI 0.95 – 2.20) and non-ASCT (HR 1.40, 95% CI 0.88 – 2.25) (interaction p = 0.99). A landmark analysis by maintenance start showed a median OS of 69.1 months (95% CI 64.6 – NR) and 87.8 months (95% CI 87.8 – NR) (p=0.22) in EMD and non-EMD patients, respectively. EMD size was not correlated with median OS: patients with EMD ≤3 cm 58.5 months (95% CI 38.4 – NR), patients with EMD >3 cm 63.7 months (95% CI 48.2 – NR), and patients without EMD 79.9 months (95% CI 75.8 – 88.3) (Figure 4). The same analysis was done with the EMD size threshold at 5 cm (Figure S7). Median OS according to EMD number was as follows: single EMD localization 70.1 months (95% CI 50.4 – NR), multiple EMD localizations 45 months (95% CI 38.2 – NR), and no EMD 79.9 months (95% CI 75.8 – 88.3), single EMD vs. no EMD (HR 1.33, 95% CI 1.07-1.67; p=0.01), and multiple EMD localizations vs. no EMD (HR 1.62, 95% CI 1.11-2.38; p=0.01). Median OS was not correlated with EMD site: PO 67.3 months (95% CI 50.4 – NR), EMP 70.1 months (95% CI 16.9 –

NR), and no EMD 79.9 months (95% CI 75.8 – 88.3), PO vs. no EMD (HR 1.39, 95% CI 1.13-1.70; p=0.001), and EMP vs. no EMD (HR 1.24, 95% CI 0.55-2.78; p=0.60) (Figure 1).

Discussion

To the best of our knowledge, this is the first meta-analysis of MM clinical trials focusing on patients with EMD so far reported. We included 8 Fonesa Onlus and Hovon Foundation clinical trials that enrolled 2332 newly diagnosed patients. In this population, we observed 267 (11%) patients with one or more EMD localizations, including 243 PO, 12 EMP, and 12 cases that were not classified. Since none of the clinical trial considered in this study had as primary endpoint the study of EMD, and a proportion of them were started around 10 years ago, the most common imaging procedure performed at enrollment as screening was x-ray skeletal survey, and, only in case of a suspect of EMD, MRI or CT scan. X-ray skeletal survey is clearly suboptimal in detecting extramedullary asymptomatic disease. Nevertheless, the EMD incidence we observed is in line with other case series (in the range of 7%-18%),[1] suggesting that our patient population is quite representative of the daily clinical practice. Anyway, it is expected that a wider use of more sensitive imaging techniques, such as positron emission tomography (PET), whole-body CT, and MRI will increase EMD detection.[12,13] Interestingly, we observed that EMD patients had less disease burden, as shown by a more favorable ISS, lower bone marrow plasma cell infiltrate, higher hemoglobin levels, and a better renal function. This finding has been observed also by others in the first line setting,[2,14] and may reflect a specific clinical picture, characterized by symptoms attributable to the EMD, rather than to larger disease burden. The presence of EMD at diagnosis did not impair the first line PFS, since EMD patients had a median PFS of 25.3 months, similar to the 25.2 months observed in patients without EMD. This finding is quite remarkable, since presence of EMD has long been recognized as an unfavorable prognostic factor, both in case of PO and EMP.[4] Varettoni et al. described 76 EMD patients out of 1003 MM patients at diagnosis, and with a treatment based on conventional chemotherapy the PFS of EMD was 18 vs. the 30 months of patients without EMD (p=0.03).[2] Only EMD patients who received an ASCT had a PFS similar to that of patients without EMD. Likewise, Wu et al. described 75 EMD patients at diagnosis, who were compared to 384 cases without EMD, and observed that EMD patients had an inferior PFS respect to that of patients without EMD, but this difference was overcome when EMD patients received ASCT.[14] Hence, the presence of EMD at diagnosis has been incorporated as an adverse component of the Durie and Salmon PLUS prognostic score.[15] Since we did not observe any significant difference in PFS between EMD and non-EMD patients, it is reasonable to speculate that the incorporation of new drugs in all the regimens tested in the studies included in this meta-analysis was able to overcome the unfavorable prognostic significance of EMD. In this perspective, several case reports, as well as few trials, have shown that new drugs are effective in MM patients with EMD. In particular, Landau et al. have evaluated in 42 high risk MM at diagnosis, including 14 patients with EMD, an induction with 3 cycles of bortezomib, liposomal doxorubicin and dexamethasone, followed by ASCT, with an acceptable median time-to-progression of 39 months.[16] In our meta-analysis 166 EMD patients were treated with IMiD-based therapies, almost lenalidomide in all cases, and have been compared with 1279 no EMD patients that have received the same treatment. Quite surprisingly, also in this subset the PFS was not different between the two groups, suggesting that lenalidomide can be active also in this setting, as suggested by very few case reports.[17] This is in contrast with the observation derived from studies involving thalidomide, the first-in-class IMiD, which resulted in having no effect on EMD,[18] and this may be accounted to the higher direct cytotoxic effect of lenalidomide respect to thalidomide.[19] Interestingly, in our study EMD patients treated with IMiDs had the same PFS and OS of patients treated with PIs (Figure S8).

Previous studies shown that increasing the therapy intensity, i.e. intensifying the treatment with ASCT, overcame the negative prognostic significance of EMD presence.[20] This has been confirmed in a large

European Bone Marrow Transplantation registry study that considered 3744 MM patients, including 353 with EMD, who received ASCT at diagnosis. This study has shown how patients with a single EMD had a similar PFS respect to patients without EMD.[21] Since intensification seems to be the key to EMD control, it is possible to speculate that new drugs may offer an adequate level of treatment intensity, respect to conventional drugs. In the pre-new drug era, this goal was obtained only with ASCT. In order to evaluate whether the high efficacy of new drugs results into a more aggressive relapse, we analyzed PFS2, and we observed that EMD patients benefited from a similar disease control when compared to patients without EMD (42.3 vs. 46.4 months, respectively). This suggests that patients retain the benefit beyond the first line. Interestingly, also maintenance seems to have a similar efficacy in EMD and non-EMD patients. Median OS of EMD patients was inferior when compared with the control group (63.5 vs. 79.9 months, respectively), and this is irrespective of the type of therapy. Since PFS2 is similar between the 2 groups, it is safe to suggest that MM with EMD may acquire a more aggressive behavior in later stages of the disease.

Doubtless, the most sensitive technique for plasmacytoma identification is PET, which is able to upgrade myeloma-related lesion identification in more than half of patients when compared with X-ray skeletal survey.[22] Unfortunately, in our study PET was not used, since, at the time the trials were performed, this technique was not standard. The recent IMAJEM trial, by the Intergroupe Francophone du Myelome (IFM), has shown that spine and pelvis MRI and PET are positive in 95% and 91% of patients at diagnosis, respectively, and that PET has a strong prognostic significance in terms of PFS and OS when evaluated both after the induction phase, represented by three cycles of lenalidomide plus bortezomib plus dexamethasone, and before maintenance start.[23] Moreover, the IFM trial has shown that patients with EMD, evaluated with PET at diagnosis, have an increased risk of EMP relapse, progression or death (HR 3.4, 95% CI 2.1-5.6, $p<0.01$). These data reinforce the concept that EMP has a strong detrimental effect on survival, but a specific analysis on the clinical significance of PO disease was not provided.

Surprisingly, we did not find any significant correlation between outcome and EMD size. A similar finding has been reported in the setting of solitary EMD. Eighty-four patients have been evaluated and no differences in terms of outcome have been seen between patients with EMD $\leq$5 cm, >5 and $\leq$10 cm, and >10 cm.[24] Probably, the presence of a EMD is detrimental for the relevant biological features that are inherent in this variant of plasma cell neoplasm, rather than EMD size.[25] Also the presence of single or multiple EMD localizations was not prognostically significant. Unfortunatly, in our study EMD was mainly represented by PO disease, since many EMPs were probably missed due to the imaging techniques used at time of trial design. Our observations are in contrast with the study by Rasche et al.,[26] who evaluated with diffusion-weighted MRI 404 transplant-eligible patients and showed that the presence of 3 or more large focal lesions, defined as lesions with a product of the perpendicular diameters >5 cm^2, were strong independent adverse prognostic factors. A possible explanation for this inconsistency can be attributed to the fact that Rasche et al. have considered all types of focal lesions, including intraosseous focal lesions, while in our study we have analyzed only EMD. Finally, we did not observe any significant correlation between EMP and outcome, but this is probably due to the limited number of cases observed in this study.

In conclusion, the main limit that our study suffered is represented by an underestimation of EMD and, in particular, EMP incidence, caused by the low resolution of the imaging techniques employed at screening. Thus, our findings can be mainly referable to PO localizations, which are known to be less aggressive than EMP,[27] and this limits the value of our results. On the other hand, we performed the largest analysis of EMD patients at diagnosis, with the strength of using solid data derived from prospective trials. We confirmed that PIs are effective towards EMD, and, for the first time, we provide evidence that also lenalidomide is effective in this difficult setting. We hope that our and other similar studies will encourage focusing the attention on this unmet clinical need with trials specifically designed for MM patients with EMD.

DECLARATION OF INTEREST

Disclosures Montefusco: *Janssen:* Other: Speakers Bureau, Advisory Board; *Amgen:* Other: Advisory Board; *Celgene:* Speakers Bureau, Advisory Board. **Gay:** *Roche:* Other: Advisory Board; *Seattle Genetics:* Other: Advisory Board; *BMS:* Honoraria; *Janssen:* Honoraria; *Celgene:* Honoraria, Other: Advisory Board; *Amgen:* Honoraria; *Takeda:* Honoraria, Other: Advisory Board. **De Paoli:** *Gilead:* Other: Advisory Board; *Celgene:* Other: Advisory Board; *Amgen:* Other: Advisory Board; *Janssen:* Other: Advisory Board. **Di Raimondo:** *Celgene:* Honoraria; *Takeda:* Honoraria, Research Funding. **Patriarca**: *Celgene*: Advisory Board & Travels; *Janssen*: Advisory Board & Travels; *MSD Italy*, Advisory Board & Travels; *Jazz*, Travels; *Medac*, Travels. **Musto:** *Amgen:* Honoraria; *BMS:* Honoraria; *Takeda:* Honoraria; *Janssen:* Honoraria; *Celgene:* Honoraria. **Ballanti:** *BMS:* Honoraria; *Amgen:* Honoraria; *Janssen:* Honoraria; *Celgene:* Honoraria. **Nozzoli**: *Janssen*: Advisory Board & Travels; *Celgene*: Advisory Board & Travels; *Jazz*, Travels; *Bristol-Myers Squibb*: Travels. **Hajek:** *Takeda:* Consultancy, Honoraria, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria; *Amgen:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Celgene:* Consultancy, Honoraria, Research Funding; *Novartis:* Research Funding. **Offidani:** *Amgen:* Honoraria, Other: Advisory Board; *Takeda:* Honoraria, Other: Advisory Board; *Janssen:* Honoraria, Other: Advisory Board; *Celgene:* Honoraria, Other: Advisory Board; *Bristol-Myers Squibb:* Honoraria, Other: Advisory Board. **Liberati**: *Bristol-Myers Squibb:* Honoraria, Consultancy; *Takeda:* Advisory Board*; Celgene:* Honoraria*; Abbivie:* Honaria and Advisory Board*; Incyte:* Honoraria, *Jassen:* Honoraria, *Novartis:* Honoraria, *Amgen:* Honoraria and Advisory Board. **Cavo:** *GlaxoSmithKline:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Honoraria, Membership on an entity's Board of Directors or Advisory Board; *Janssen:* Honoraria, Membership on an entity's Board of Directors or Advisory Board, Research Funding, Speakers Bureau; *Takeda:* Honoraria, Membership on an entity's Board of Directors or Advisory Board; *Bristol-Myers Squibb:* Honoraria, Membership on an entity's Board of Directors or Advisory Board; *Adaptive Biotechnologies:* Honoraria, Membership on an entity's Board of Directors or Advisory Board; *Amgen:* Honoraria, Membership on an entity's Board of Directors or Advisory Board; *Celgene:* Honoraria, Membership on an entity's Board of Directors or Advisory Board, Research Funding, Speakers Bureau. **Corradini:** *Gilead:* Honoraria, Other: Advisory Board & Lecturer; *Amgen:* Honoraria, Other: Advisory Board & Lecturer; *Takeda:* Honoraria, Other: Advisory Board & Lecturer; *Celgene:* Honoraria, Other: Advisory Board & Lecturer; *Roche:* Honoraria, Other: Advisory Board & Lecturer; *Sanofi:* Honoraria, Other: Advisory Board & Lecturer; *Sandoz:* Other: Advisory Board; *Novartis:* Honoraria, Other: Advisory Board & Lecturer; *Abbvie:* Honoraria, Other: Advisory Board & Lecturer; *Janssen:* Honoraria, Other: Lecturer. **Boccadoro:** *Janssen:* Honoraria, Research Funding; *Novartis:* Honoraria, Research Funding; *AbbVie:* Honoraria; *Bristol-Myers Squibb:* Honoraria, Research Funding; *Mundipharma:* Research Funding; *Amgen:* Honoraria, Research Funding; *Sanofi:* Honoraria, Research Funding; *Celgene:* Honoraria, Research Funding.

AUTHOR CONTRIBUTION

VM, FG and MB designed the study; FG and SS collected and assembled the data; SS and VM analyzed and interpreted the data; LDP, FDR, RR, CM, FP, PM, PG, SB, CN, NC, DBY, AN, RH, MO, AML, MC, PC provided patients; VM wrote the first draft of the manuscript; all authors had access to the final data and approved the final manuscript.

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Trial	Code	Treatment	Drugs	Maintenance	N. of Patients	Years Enrollement	Age population	Outcome PFS	Outcome OS	Pubblication Year(s)
GIMEMA-MM-05-05[28]	2005-004714-32	4 PAD induction followed by 2 Mel100 intensification followed by 4 RP consolidation and R maintenance	IMiD-PI	yes	103	2005-2008	≤75	Median PFS: 48 months	5yrs OS: 63%	2010-2013
GIMEMA-MM-03-05[29]	NCT01063179	9 VMP induction or 9 VMPT induction followed by 2 years VT maintenance	IMiD-PI	Random for FDT or observation	511	2006-2009	≥65	Median PFS: VMPT-VT: 35 months VMP: 25 months	5yrs OS: VMPT-VT: 61% VMP:51%	2010-2014
RV-MM-PI-209[30]	NCT00551928	4 Rd induction, mobilization, 6 MPR or 2 Mel200 intensification followed by R maintenance until PD or observation	PI	Random for maintenance or observation	402	2007-2009	<65	Median PFS: MPR: 22 months ASCT: 43 months	4yrs OS: MPR: 65% ASCT: 81%	2014
RV-MM-EMN-441[31]	NCT01091831	4 Rd induction, mobilization, 6 CPR or 2 Mel200 intensification followed by RP or R maintenance until PD	IMiD	yes	389	2009-2011	<65	Median PFS: CRD: 29 months ASCT: 43 months	4yrs OS: CRD: 73% ASCT: 86%	2015
EMN01[32]	NCT01093196	9 Rd or MPR or CPR induction followed by RP or R maintenance until PD	IMiD	yes	654	2009-2012	≥65	Median PFS: MPR: 24 months CPR: 20 months Rd: 21 months	4yrs OS: MPR: 65% CPR: 68% Rd: 58%	2016
MMY2069[33]	NCT01190787	9 VP or CVP or VMP induction followed by V maintenance until PD	PI	yes	152	2010-2012	≥65	Median PFS: VP: 14 months VCP: 15 months VMP: 17 months	2yrs OS: VP: 60% VCP: 70% VMP: 76%	2016
IST-CAR-506[34]	NCT01346787	9 KCd induction followed by K maintenance until PD	PI	yes	58	2011-2012	≥65	2yrs PFS: 76%,	2yrs OS: 87%	2014
IST-CAR-561[35]	NCT01857115	9 KCd induction followed by K maintenance until PD	PI	yes	63	2013-2015	≥65	2yrs PFS: 53%,	2yrs OS: 81%	2018

Table 1. Source Studies. V, Bortezomib; M, Melphalan; P, Prednisone; T, Thalidomide; C, Cyclophosphamide; K, Carfilzomib; R, Lenalidomide; d, Dexamethasone; Mel200, High dose Melphalan; PAD, Bortezomib-pegylated liposomal doxorubicin- Dexamethasone; PD, Progression Disease; IMiD, Immunomodulatory drug ; PI, Proteasome inhibitor ; PFS, Progression-free Survival; OS, Overall Survival, FDT, Fixed-duration Therapy.

Characteristic	**Patients with extra-medullary disease (N=267)**	**Control group (N=2065)**	**p-value**
Age			0.21
Median (IQR)-yr	68 (60-74)	69 (61-74)	
Distribution – no. (%)			
<65 yr	108 (40%)	477 (38%)	
65 to 75	105 (39%)	795 (38%)	
≥ 75	54 (21%)	493 (24%)	
ECOG			0.35
0	107 (40%)	847 (41%)	
1	103 (39%)	862 (42%)	
2	39 (15%)	235 (11%)	
3	1 (0%)	7 (0%)	
ISS			<0.001
I	119 (45%)	682 (33%)	
II	85 (32%)	782 (38%)	
III	38 (14%)	509 (25%)	
missing	25 (9%)	92 (4%)	
R-ISS			0.62
I	38 (14%)	294 (14%)	
II	125 (47%)	1132 (55%)	
III	17 (6%)	173 (8%)	
missing	87 (33%)	466 (23%)	
FISH – no. (%)			0.72
Standard risk	115 (43%)	1082 (52%)	
High risk*	51 (19%)	446 (22%)	
del(17p)	32	220	
t(4;14)	22	219	
t(14;16)	6	69	
Missing	101 (38%)	537 (26%)	
LDH – IU/L			0.30
≤450 201	201 (75%)	1567 (76%)	
>450 201	29 (11%)	180 (9%)	
missing	37 (14%)	318 (15%)	
Bone marrow plasma cells, median (IQR)	30% (15% - 50%)	50% (30% - 70%)	<0.001
Hemoglobin, median (IQR) – gr/L	12.0 (10.5 – 13.6)	10.7 (9.5 – 12.1)	<0.001
Creatinine clearance			0.01
Median (IQR) – mL/min per 1.73/m^2	75 (48-98)	66 (41-88)	
< 30 mL/min per 1.73/m^2	45 (17%)	359 (17%)	
30 to 60 mL/min per 1.73/m^2	49 (18%)	544 (26%)	
> 60 mL/min per 1.73/m^2	172 (64%)	1162 (56%)	
Therapy			0.48
IMiD-based	166 (62%)	1279 (62%)	
PI-based	66 (25%)	464 (22%)	
IMiD + PI-based	35 (13%)	322 (16%)	
Autologous stem cell transplantation	155 (58%)	1283 (62%)	0.17
Fixed-duration therapy	31 (12%)	243 (12%)	1.00
Continuous treatment	128 (48%)	1007 (49%)	
No Maintenance	108 (40%)	815 (39%)	
Imaging technique			

X-ray skeletal survey	0 (0 %)	989 (42%)	<0.001
CT-scan	0 (0 %)	122 (6 %)	
MRI	115 (43 %)	277 (13 %)	
Physical examination	21 (8 %)	0 (0 %)	
Spiral CT	13 (5%)	0 (0%)	
Conventional CT	96 (36%)	2 (0%)	
Unknown	22 (8%)	675 (33%)	

Table 2. Patients' demographics and clinical characteristics. *More than one FISH abnormality may occur in the same patient. NS, not significant; NA, not assessable; IQR, interquartile range; IMiD, immunomodulatory drug; PI, proteasome inhibitor; CT, computed tomography; MRI, magnetic resonance imaging.

Characteristic	**No. patients 267**
Size, median (IQR)-cm	4.2 (3-7)
Para-skeletal	243 (91%)
Extramedullary plasmocytoma	12 (4.5%)
Not classifiable	12 (4.5%)
Single	195 (73%)
Multiple	60 (22%)
Not classifiable	12 (5%)
Involvement sites*§	
Pelvis	38
Skull	10
Spine	117
Thorax (excluded dorsal spine)	67
Long bones	14
Not classifiable	34

Table 3. Extramedullary disease characteristics. *Sites of extramedullary disease (EMD) localizations were not available. § The sum of the sites is greater than the total number of EMD patients, since one patient could present with more than one localization.

FIGURE TITLES AND LEGENDS

Figure 1. PFS and OS according to extramedullary disease presence and type. Panel A, PFS; panel B, OS.

EMD, extramedullary disease; EMP extramedullary plasmocytoma; PO, paraosseous plasmocytoma.

Figure 2. PFS according to extramedullary disease features. Panel A, PFS according to extramedullary disease (EMD) presence and size; panel B, PFS according to single or multiple EMD localizations.

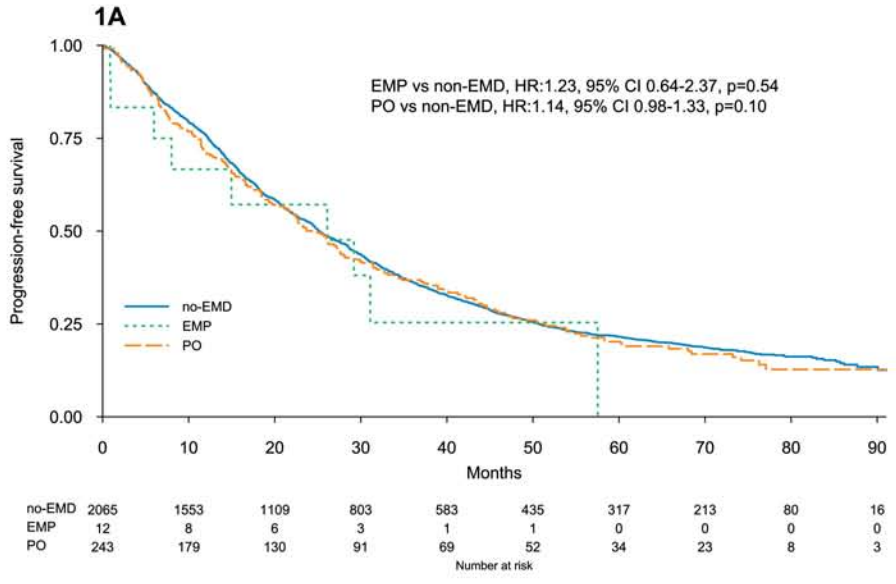
EMD, extramedullary disease.

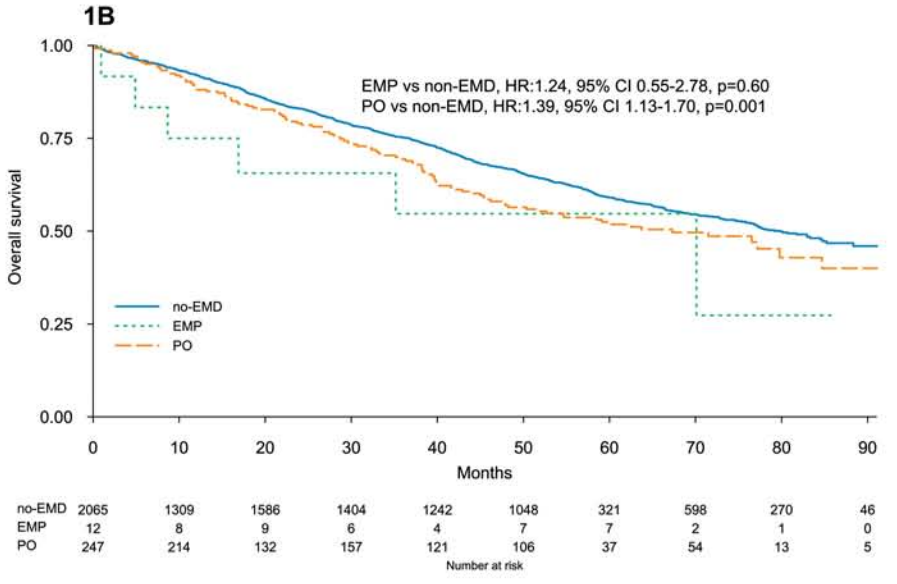
Figure 3. PFS2.

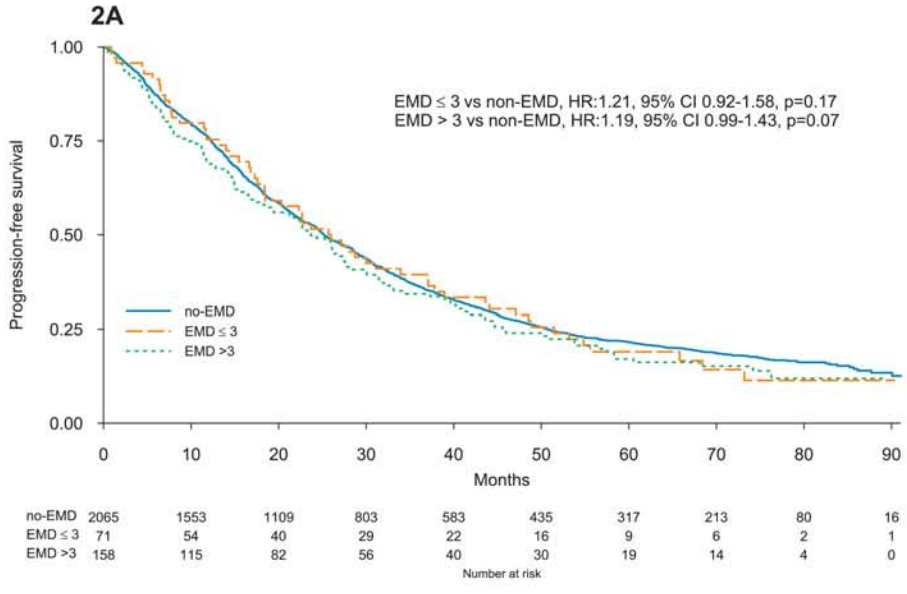
EMD, extramedullary disease; EMP extramedullary plasmocytoma; PO, paraosseous plasmocytoma.

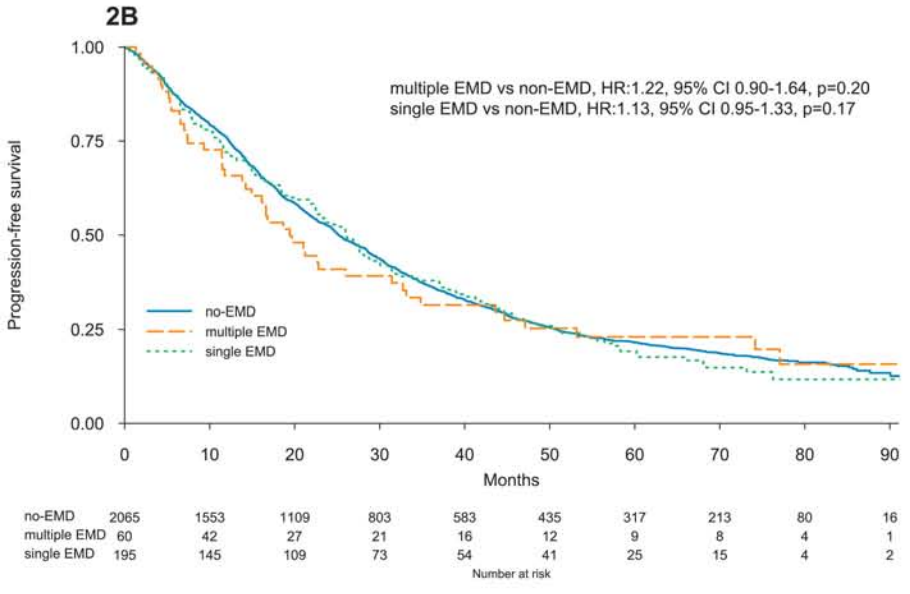
Figure 4. OS according to extramedullary disease features. Panel A, OS according to EMD presence and size; panel B, OS according to single o multiple EMD.

EMD, extramedullary disease.

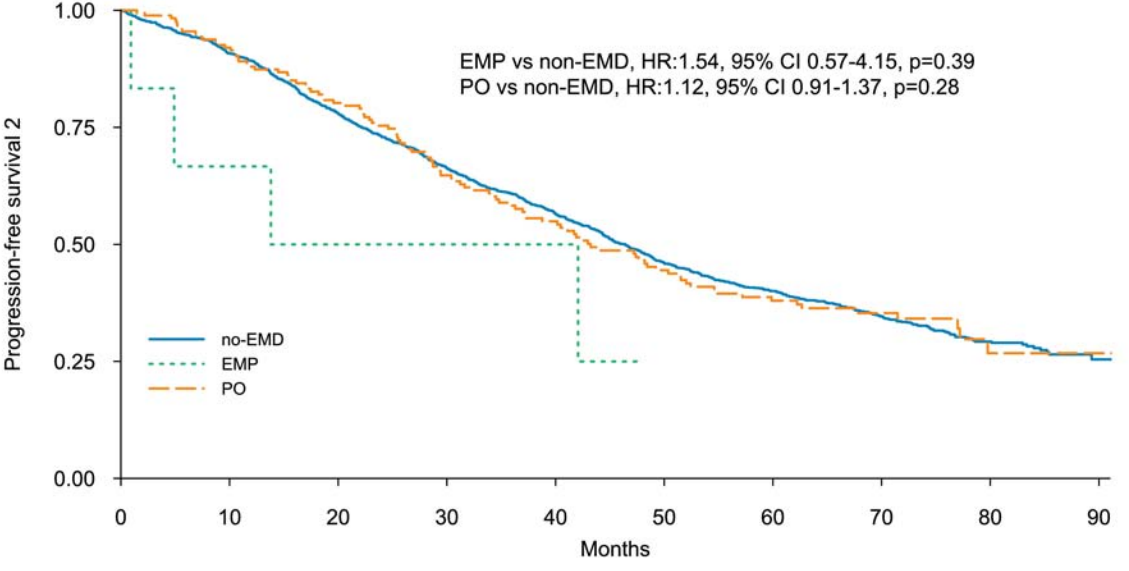

1A
EMP vs non-EMD, HR:1.23, 95% CI 0.64-2.37, p=0.54
PO vs non-EMD, HR:1.14, 95% CI 0.98-1.33, p=0.10
Progression-free survival
1.00
0.75
0.50
0.25
0.00
no-EMD
EMP
PO
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1553 1109 803 583 435 317 213 80 16
EMP 12 8 6 3 1 1 0 0 0 0
PO 243 179 130 91 69 52 34 23 8 3
Number at risk


1B
EMP vs non-EMD, HR:1.24, 95% CI 0.55-2.78, p=0.60
PO vs non-EMD, HR:1.39, 95% CI 1.13-1.70, p=0.001
Overall survival
1.00
0.75
0.50
0.25
0.00
no-EMD
EMP
PO
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1309 1586 1404 1242 1048 321 598 270 46
EMP 12 8 9 6 4 7 7 2 1 0
PO 247 214 132 157 121 106 37 54 13 5
Number at risk


2A
1.00
0.75
0.50
0.25
0.00
Progression-free survival
EMD ≤ 3 vs non-EMD, HR:1.21, 95% CI 0.92-1.58, p=0.17
EMD > 3 vs non-EMD, HR:1.19, 95% CI 0.99-1.43, p=0.07
no-EMD
EMD ≤ 3
EMD >3
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1553 1109 803 583 435 317 213 80 16
EMD ≤ 3 71 54 40 29 22 16 9 6 2 1
EMD >3 158 115 82 56 40 30 19 14 4 0
Number at risk

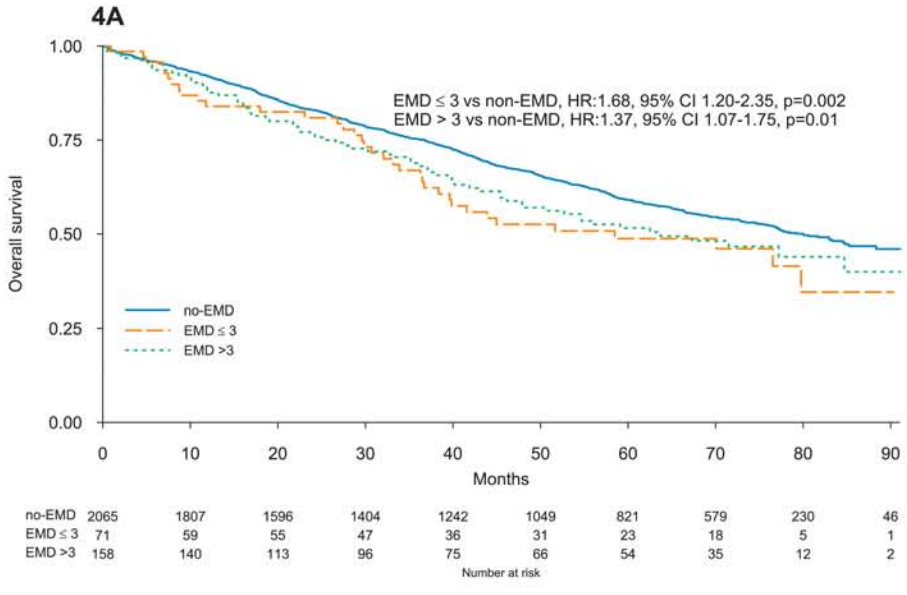

2B
1.00
0.75
0.50
0.25
0.00
Progression-free survival
multiple EMD vs non-EMD, HR:1.22, 95% CI 0.90-1.64, p=0.20
single EMD vs non-EMD, HR:1.13, 95% CI 0.95-1.33, p=0.17
no-EMD
multiple EMD
single EMD
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1553 1109 803 583 435 317 213 80 16
multiple EMD 60 42 27 21 16 12 9 8 4 1
single EMD 195 145 109 73 54 41 25 15 4 2
Number at risk

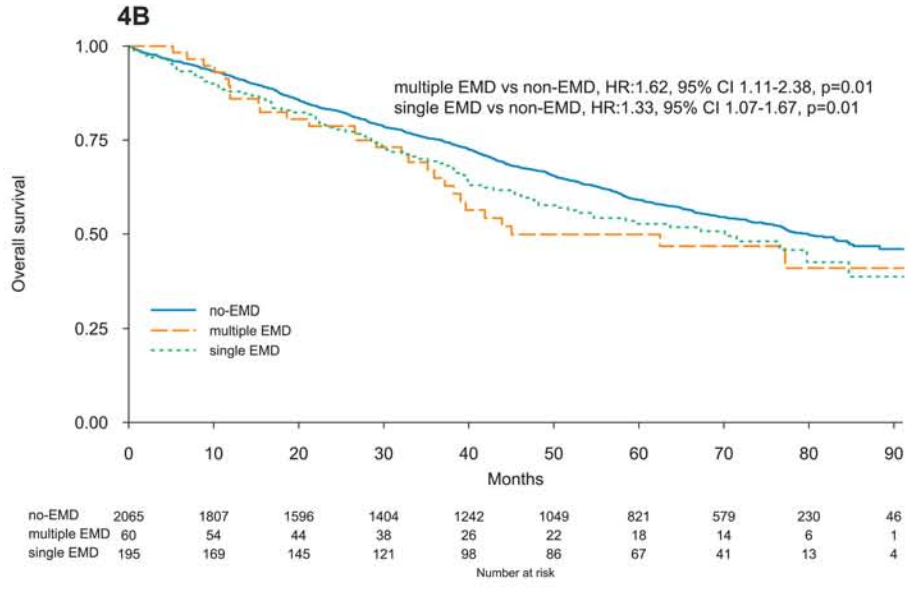
3



no-EMD	1523	1297	1074	886	725	559	434	293	121	19
EMP	6	4	3	3	2	0	0	0	0	0
PO	180	159	133	102	81	63	49	31	9	3

Number at risk


4A
1.00
0.75
0.50
0.25
0.00
Overall survival
EMD ≤ 3 vs non-EMD, HR:1.68, 95% CI 1.20-2.35, p=0.002
EMD > 3 vs non-EMD, HR:1.37, 95% CI 1.07-1.75, p=0.01
no-EMD
EMD ≤ 3
EMD >3
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1807 1596 1404 1242 1049 821 579 230 46
EMD ≤ 3 71 59 55 47 36 31 23 18 5 1
EMD >3 158 140 113 96 75 66 54 35 12 2
Number at risk


4B
1.00
0.75
0.50
0.25
0.00
Overall survival
multiple EMD vs non-EMD, HR:1.62, 95% CI 1.11-2.38, p=0.01
single EMD vs non-EMD, HR:1.33, 95% CI 1.07-1.67, p=0.01
no-EMD
multiple EMD
single EMD
0 10 20 30 40 50 60 70 80 90
Months
no-EMD 2065 1807 1596 1404 1242 1049 821 579 230 46
multiple EMD 60 54 44 38 26 22 18 14 6 1
single EMD 195 169 145 121 98 86 67 41 13 4
Number at risk

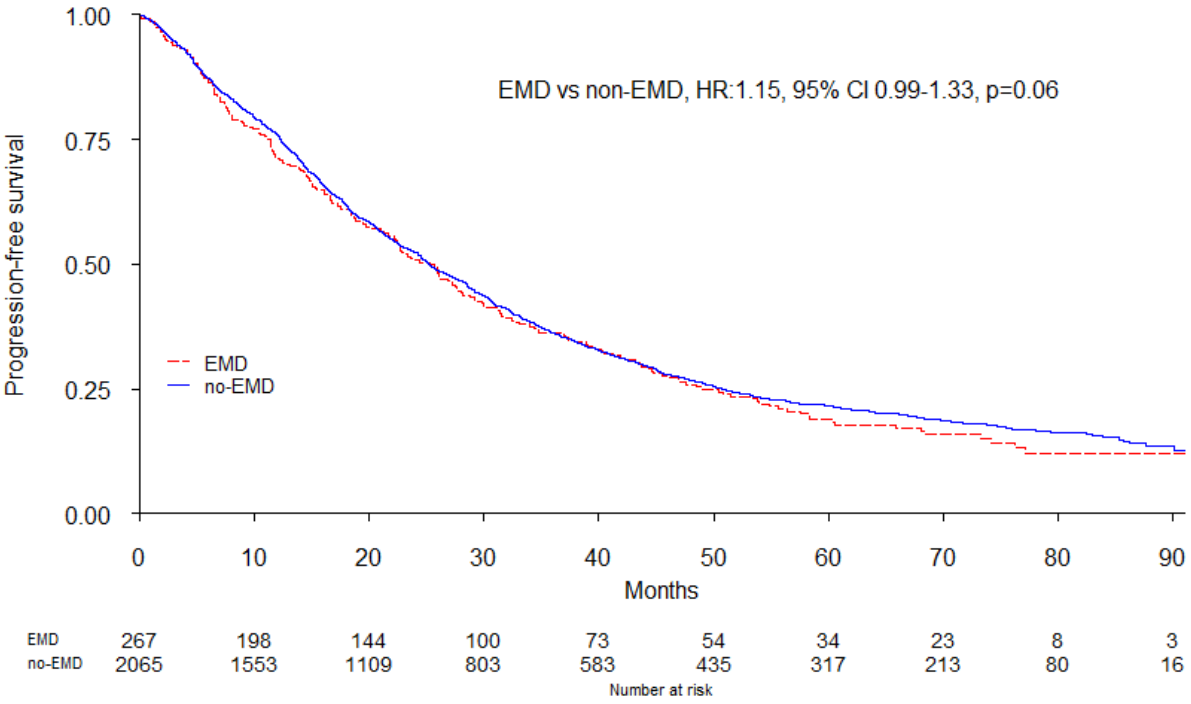
Data Supplements

Table of Contents

Endpoints

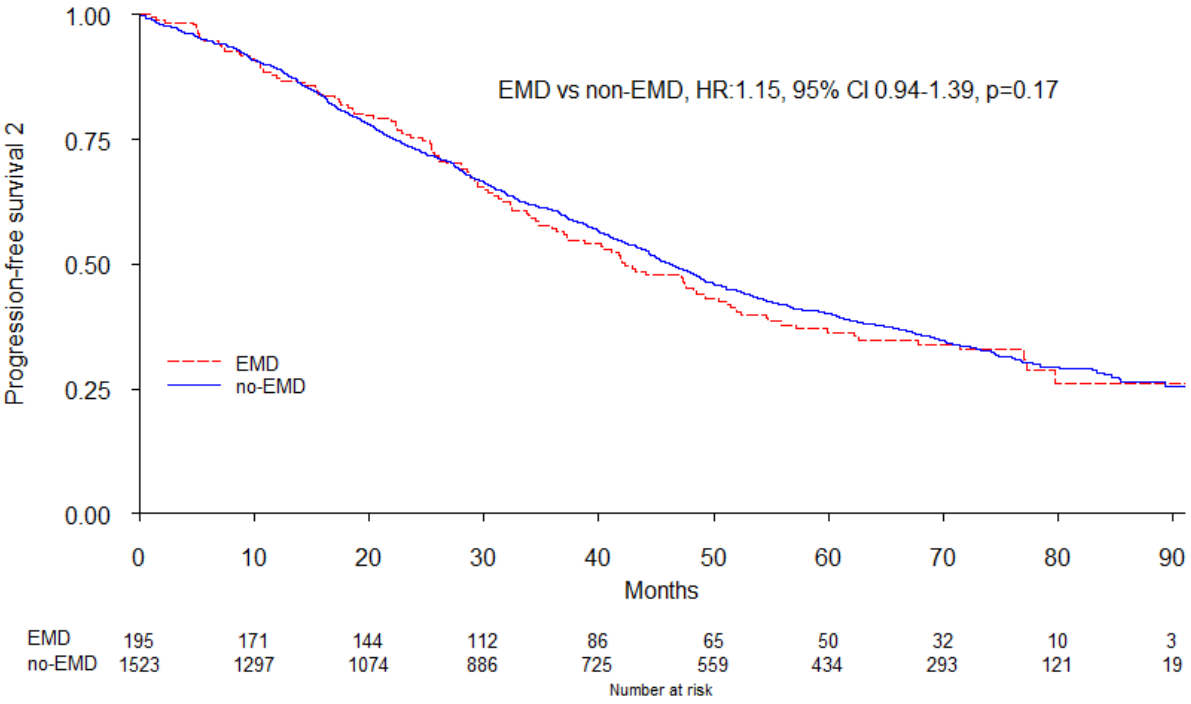
Overall survival (OS) was calculated from date of study entry to the date of death for any cause or the date the patient was last known to be alive. Progression-free survival (PFS) was calculated from date of study entry to the date of second progression or death for any cause, whichever comes first, or the date the patient was last known to be in remission. Progression-free survival (PFS) was calculated from date of study entry to the date of progression or death for any cause, whichever comes first, or the date the patient was last known to be in remission.

Figure S1: PFS according to extramedullary disease presence and type



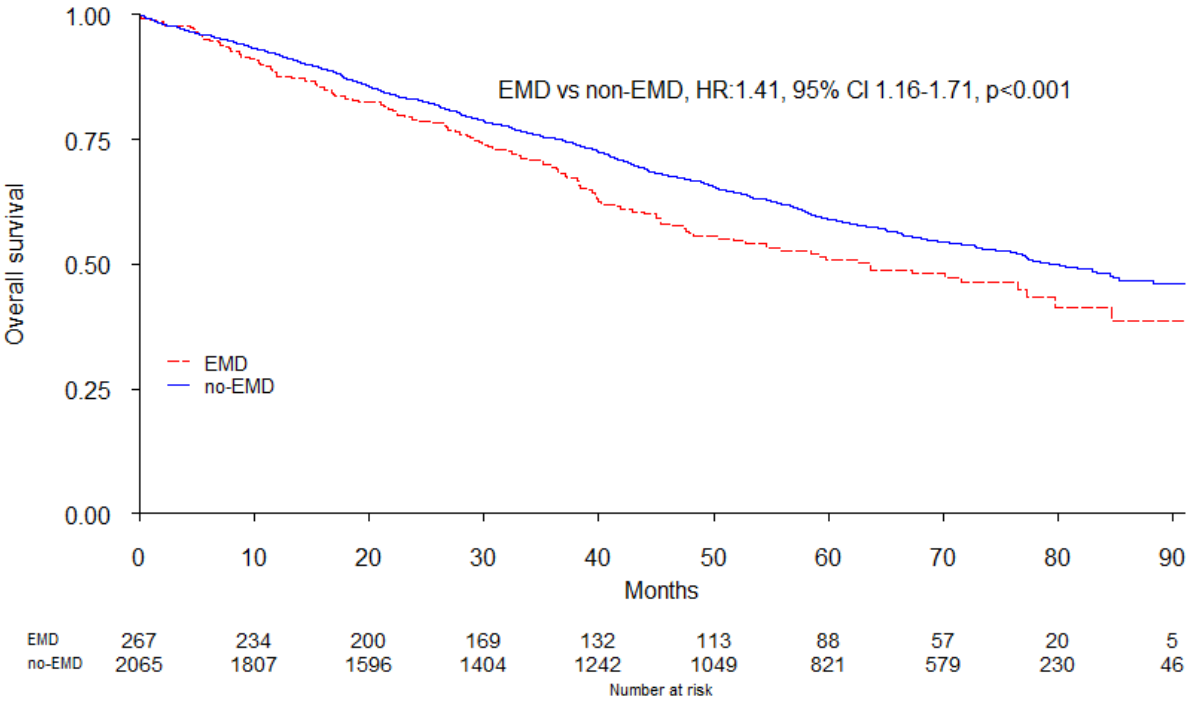
EMD, extramedullary disease.

Figure S2: PFS2 according to extramedullary disease presence and type



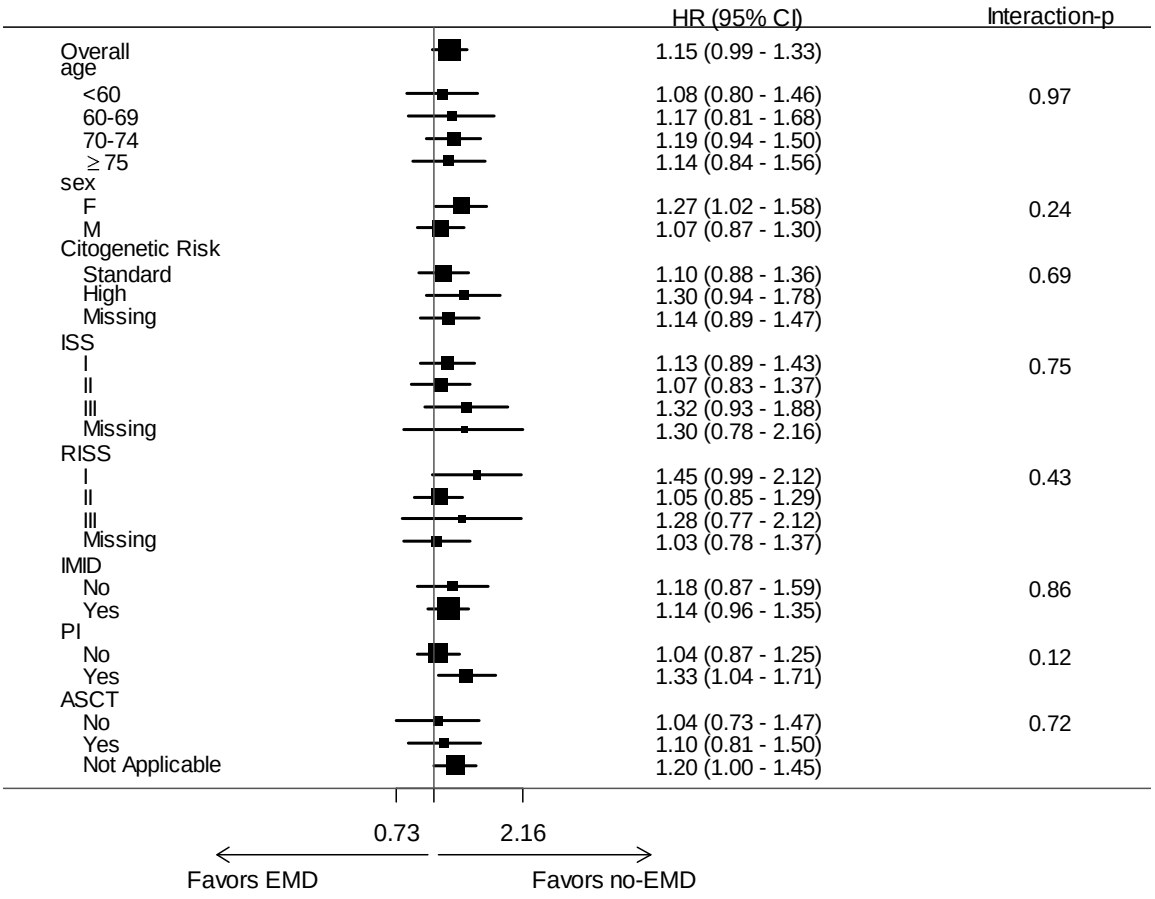
EMD, extramedullary disease.

Figure S3: OS according to extramedullary disease presence and type



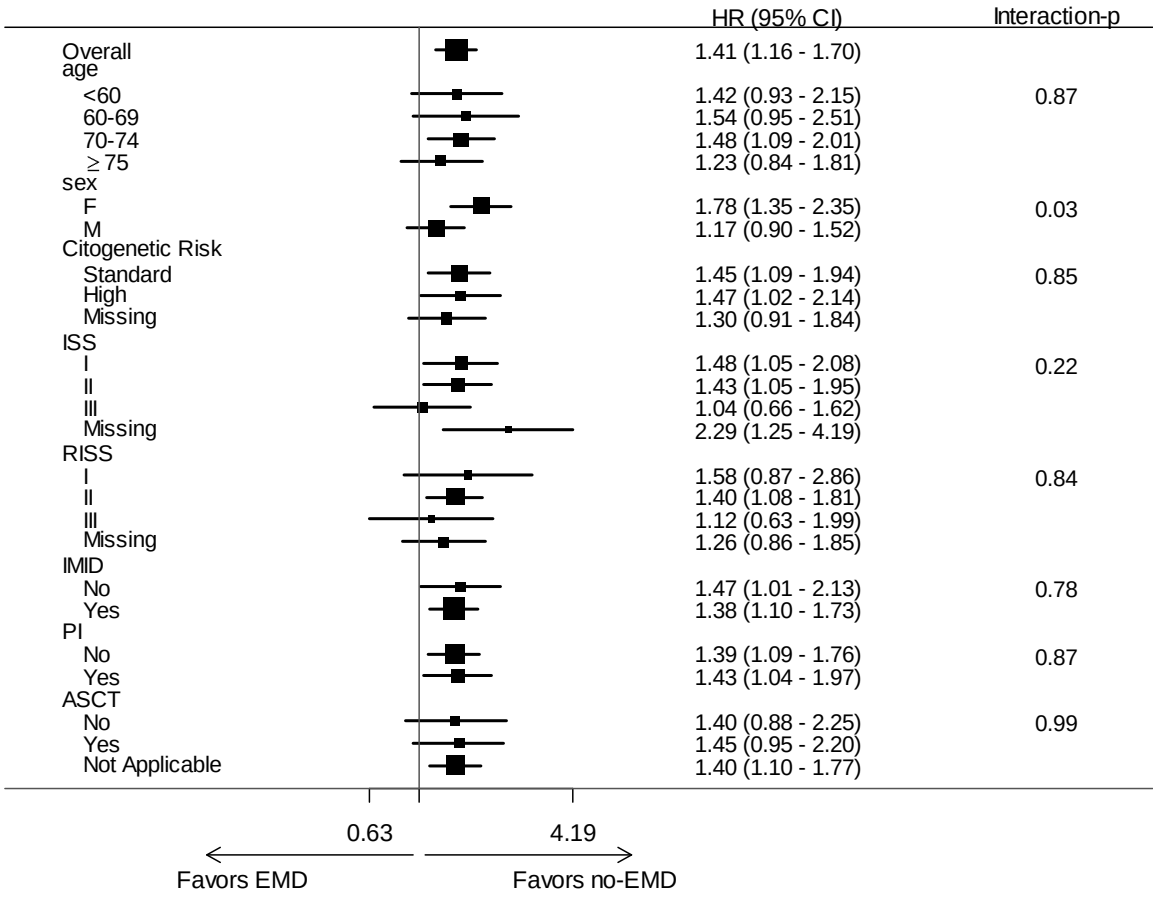
EMD, extramedullary disease.

Figure S4: Subgroup analysis for PFS in the intent-to-treat population for extramedullary versus non-extramedullary



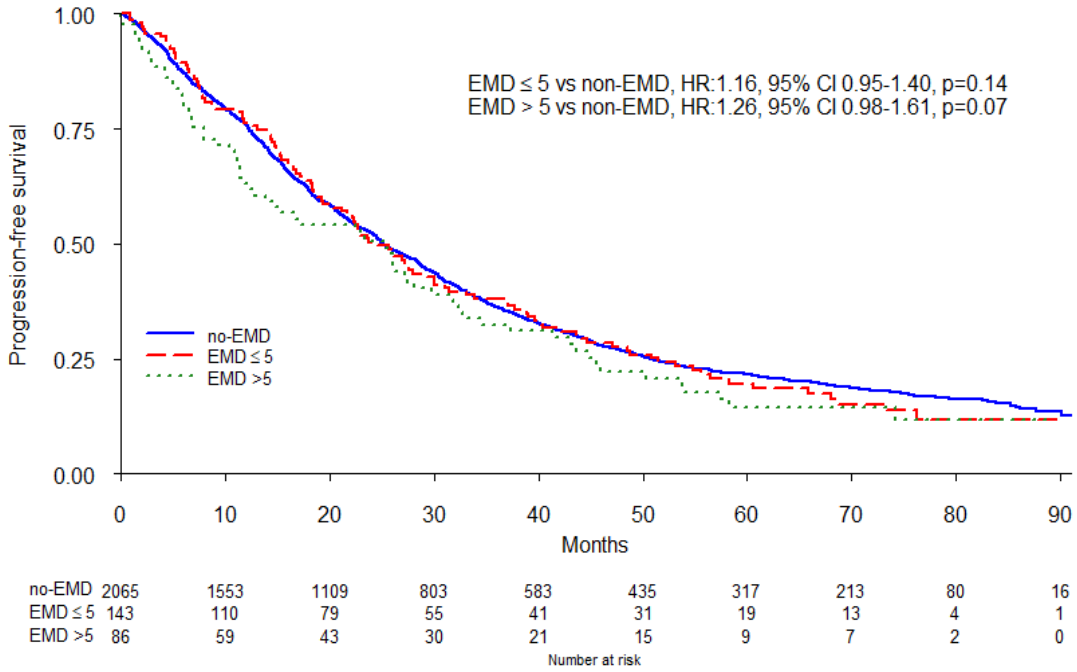
EMD, extramedullary disease.

Figure S5: Subgroup analysis for OS in the intent-to-treat population for extramedullary versus non-extramedullary



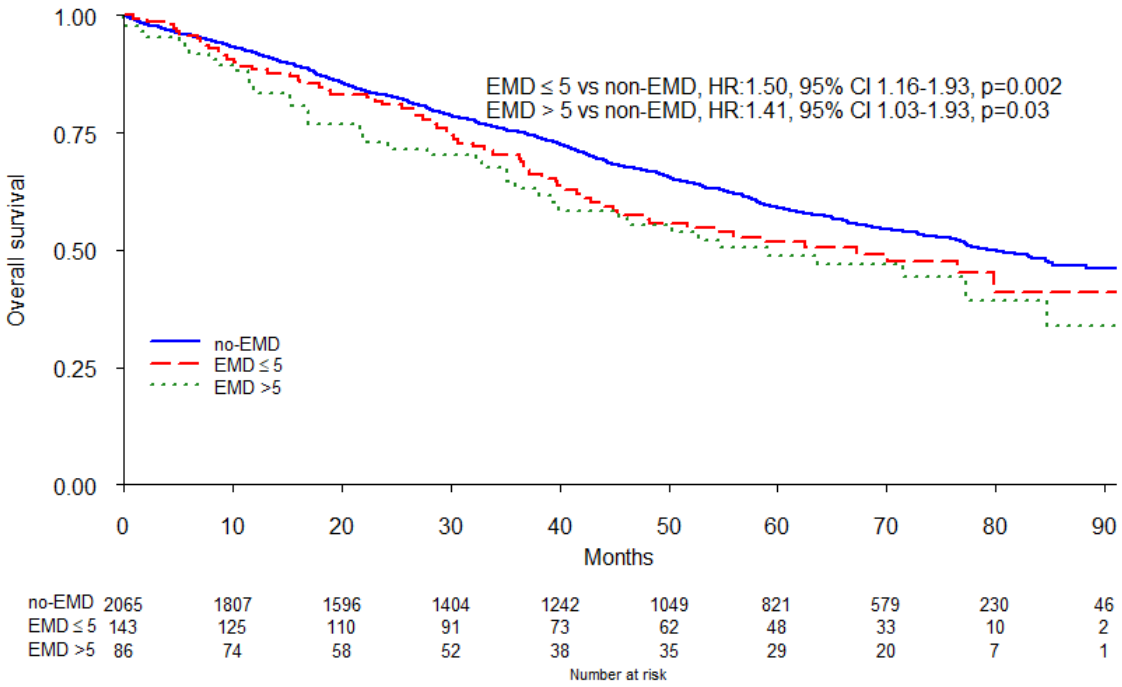
EMD, extramedullary disease.

Figure S6: PFS according to extramedullary disease ≤ or > 5 cm



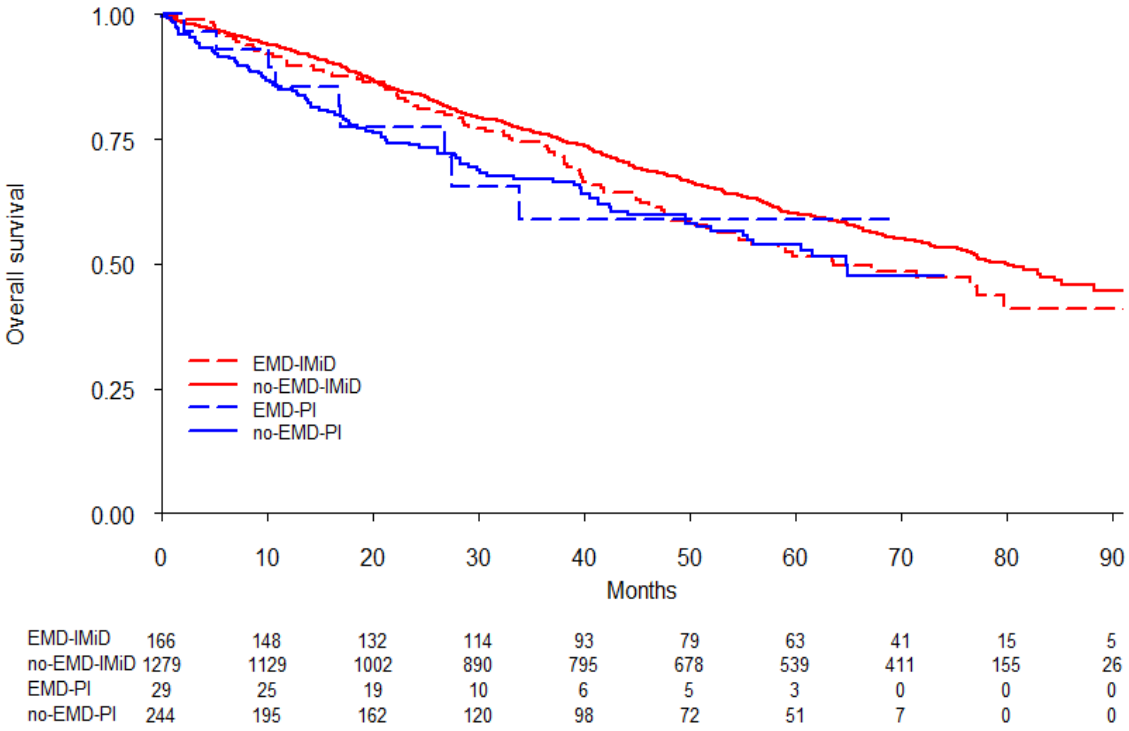
EMD, extramedullary disease.

Figure S7: OS according to extramedullary disease ≤ or > 5 cm



EMD, extramedullary disease.

Figure S8: OS according to extramedullary disease presence and type of therapy



EMD, extramedullary disease; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

FISH testing

Fluorescence in situ hybridization analyses were performed on bone marrow plasma cells purified with anti-CD138–coated magnetic beads as previously described.1 Deletion of chromosome 13 (del13) was analyzed with an locus-specific identifier (LSI) 13 DNA probe; chromosome 17 deletion (del17) was detected with an LSI 17p13.1 probe combined with 17 α-satellite DNA centromere probe. LSI immunoglobulin H (IgH)/fibroblast growth factor receptor 3 dual fusion translocation probe (FGFR3, 4p16) was used for the detection of IgH/FGF3 fusion resulting from t(4;14)(p16;q32); LSI IgH/cyclin D1 (CCND1, 11q13) was used to detect IGH/CCND1 fusion resulting from t(11;14)(q13;q32), and LSI IgH/c-maf (MAF, 16q23) was used for the detection of the IgH/MAF fusion resulting from t(14;16)(q32;q23).

1. Fonseca R, Barlogie B, Bataille R, Bastard C, Bergsagel PL, Chesi M, Davies FE, Drach J, Greipp PR, Kirsch IR, Kuehl WM, Hernandez JM, Minvielle S, Pilarski LM, Shaughnessy JD Jr, Stewart AK, Avet-Loiseau H. Genetics and cytogenetics of multiple myeloma: a workshop report. Cancer Res. 2004 Feb 15;64(4):1546-58.