PET/CT IMPROVES THE DEFINITION OF COMPLETE RESPONSE AND ALLOWS TO DETECT OTHERWISE UNIDENTIFIABLE SKELETAL PROGRESSION IN MULTIPLE MYELOMA

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TRANSLATIONAL RELEVANCE

-The number of FLs, the SUVmax value and the presence of EMD, as detected by FDG PET/CT, are reliable predictors of outcome in newly diagnosed MM patients who are candidates to receive or not autologous stem cell transplantation. In this analysis, baseline SUVmax > 4.2 combined with ISS stage 3 and failure to achieve CR upon first-line treatment identified a subgroup of patients (10%) with very poor prognosis who might be candidates for alternative treatment strategies.

-PET/CT provides a more accurate definition of CR, allowing to stratify patients in conventional CR after up-front therapy into different prognostic subgroups regarding PFS and OS, according to the persistence or absence of FDG metabolic activity.

-PET/CT scans serially performed during the follow-up phase after first-line treatment can detect skeletal progression in 12% of patients with persistent high glucose metabolism and no additional criteria of progressive disease.
ABSTRACT

Purpose

To evaluate the role of 18F-FDG PET/CT in 282 symptomatic MM pts treated up-front between 2002 and 2012.

Experimental design

All pts were studied by PET/CT at baseline, during post-treatment follow-up and at the time of relapse. Their median duration of follow-up was 67 months.

Results

Forty-two percent of the pts at diagnosis had > 3 FLs and in 50% SUVmax was > 4.2; EMD was present in 5%. On multivariate analysis, ISS 3, SUVmax > 4.2 and failure to achieve best CR were the leading factors independently associated with shorter PFS and OS. These 3 variables were used to construct a prognostic scoring system based on the number of risk factors.

After treatment, PET/CT negativity (PET-neg) was observed in 70% of pts, while conventionally-defined CR was achieved in 53%. Attainment of PET-neg favourably influenced PFS and OS. PET-neg was an independent predictor of prolonged PFS and OS for patients with conventionally-defined CR.

Sixty-three percent of pts experienced relapse or progression; in 12% skeletal progression was exclusively detected by systematic PET/CT performed during follow-up. A multivariate analysis revealed that persistence of SUVmax > 4.2 following first-line treatment was independently associated with exclusive PET/CT progression.

Conclusions

PET/CT combined with ISS stage and achievement or not of CR on first-line therapy sorted pts into different prognostic groups. PET/CT led to a deeper evaluation of CR. Finally, in pts with persistent high glucose metabolism after first-line treatment, PET/CT can be recommended during follow-up, to screen for otherwise unidentifiable progression.
INTRODUCTION

Positron emission tomography (PET) integrated with computed tomography (PET/CT) using the positron-emitting radionuclide $^{18}$F labelled with Fluorodeoxyglucose (18F-FDG) proved to be a reliable technique for assessing skeletal involvement in multiple myeloma (MM) and a valuable tool at the onset of the disease for predicting outcomes in those patients who are eligible to subsequently receive autologous stem cell transplantation (ASCT) (1,2). However, the prognostic role of PET/CT for transplant-ineligible patients still remains less defined.

The clinical course of MM is highly variable and many studies have identified prognostic factors predicting this heterogeneity in survival. More recently, several groups have combined some of the available markers, significantly improving the prognostic value in terms of progression-free survival (PFS) and overall survival (OS) (3). Imaging features have been combined and correlated, with a series of established prognostic variables such as beta-2-microglobulin ($\beta$2M), C reactive protein (CRP), albumin and lactate dehydrogenase (LDH) and genetic abnormalities (2,4).

Incorporation of novel agents into ASCT and in the treatment of newly-diagnosed transplant-ineligible MM patients has brought unprecedented rates of complete response (CR), a gain which has extended progression-free survival (PFS) and overall survival (OS) (5). Novel imaging techniques, such as magnetic resonance imaging (MRI) and FDG PET/CT, have been proposed as complementary investigational tools to improve the definition of CR, potentially detecting the presence of focal lesions harbouring viable monoclonal plasma cells (1,2). However, only preliminary data have been published on the outcomes of patients achieving conventionally-defined CR but still having positive PET/CT scans.

While novel imaging techniques have a clear role in both the staging and re-staging of MM at the time of relapse and in the evaluation of treatment response (6,7,8), their serial use during follow-up of the disease is currently not recommended because of the high cost and radiation exposure. However, to the best of our knowledge no formal cost/benefit analysis has yet been performed.
We herein report the results of a retrospective analysis of PET/CT’s prognostic track-record as performed at baseline in 282 newly-diagnosed MM patients, as well as the value of this imaging tool after treatment in improving the definition of CR and in the follow-up phase of the disease.
PATIENTS AND METHODS

Patients and treatment protocols

We retrospectively analysed 282 newly-diagnosed symptomatic MM patients, who were treated at the University of Bologna, Italy, from January 2002 to December 2012. 207 (73%) patients were eligible for high-dose therapy (HDT) and ASCT; 48/207 (23%) of them received induction therapy with conventional chemotherapy (VAD regimen) (9), in 88/207 (43%) thalidomide-dexamethasone (TD) was incorporated into ASCT, as described elsewhere (10) and in 71/207 (34%) bortezomib plus thalidomide plus dexamethasone (VTD) was given prior to and after ASCT (11). Transplant-ineligible patients were treated with the combination of bortezomib-melphalan-prednisone (VMP) in 34/75 (46%) of the cases or with the combination of thalidomide-melphalan-prednisone (MPT) in 25/75 (33%) of cases, as described elsewhere (12,13) and with conventional chemotherapy alone in 16/75 (21%) of cases. Globally, first-line treatment incorporated a novel agent in 77% of the patients, including a bortezomib-based regimen in 37% (table 1). All patients had given their signed informed consent in accordance with the Declaration of Helsinki.
Procedures

Imaging studies

All patients were studied at baseline with 18F-FDG PET-CT. PET/CT was repeated during post-treatment follow-up, every 12-18 months, irrespective of laboratory data and clinical symptoms. In 189 patients PET/CT was performed 3 months after the end of first-line treatment.

Whole-body FDG PET/CT was carried out using standard procedures, as previously described (1). Briefly, 3–5.7 MBq/kg of FDG were intravenously injected. All patients were required to fast for 6 h. The uptake time was 60 min in all the patients. Images were acquired on a 2-D tomograph (GE, Discovery LS) for 4 min per bed position or on a 3-D tomograph (GE, Discovery STE) for 2 min per bed position. Cross calibration was performed using an image quality NEMA phantom. Low-dose CT (120 kV, 80 mA) was performed both for attenuation correction and as an anatomical map. PET images were reconstructed using an iterative 3-D ordered subset expectation maximization method with two iterations, 20 subsets, followed by smoothing with a 6-mm 3-D gaussian kernel) with CT-based attenuation, scatter, random coincidence event correction. The field of view included the skull, superior limbs and mid femurs.

PET/CT scans were evaluated by a team of nuclear medicine physicians who had extensive experience in the MM field. Criteria to define PET/CT positivity included at least one of the following:

1. presence of focal areas of visually detectable increased tracer uptake within bones (eg, more intense than background BM uptake) excluding articular processes, with or without any underlying lesion identified by CT and present on at least two consecutive slices (to avoid a misinterpretation of BM mild inhomogeneous FDG uptake);

2. alternatively, a standardized uptake value (SUV) maximum (max) based on body weight according to standard formula of 2.5 within osteolytic CT areas exceeding 1 cm in size. To harmonize SUV max measurements (especially in consideration of the long time course of the study) no time of flight reconstructed images were used;
3. alternatively, a SUVmax based on body weight according to standard formula of 1.5 within osteolytic CT areas less or equal to 1 cm in size (this was done to roughly correct for partial volume effect).

BM was considered diffusely involved if the tracer uptake was diffusely increased with a SUVmax equal to, or greater than, the uptake in the spleen. In this case, SUVmax was measured in the hottest area within the BM. The number, size, and location of hypermetabolic focal lesions (PET-FLs) were recorded. The degree of FDG uptake was represented by SUVmax in the hottest lesion. The presence of extramedullary disease (EMD), defined as FDG-avid tissue that, according to CT examination, was not contiguous to bone and arose in soft tissue, was described by location, size, number of lesion, and SUVmax. Paramedullary disease, arising from bone, was considered as a lesion but not as EMD (supplementary table 1).

Laboratory investigations

Physical examination, blood cell count, renal and liver function, calcium level, serum protein electrophoresis with immunofixation, 24-hour urine analysis with electrophoresis and urinary immunofixation were evaluated at baseline, at the end of first-line treatment, and every 3 months thereafter. Bone marrow aspirate was evaluated prior to treatment and to confirm the achievement of CR. Fluorescence in situ hybridization (FISH) analysis of del(13q), t(4;14) del(17p) was performed at baseline in 60% of the patients. Additional prognostic parameters registered at baseline were the following: serum levels of beta-2-microglobulin (β2M), C reactive protein (CRP), albumin and lactate dehydrogenase (LDH).

Definitions of response and relapse by laboratory and imaging

Response to treatment was assessed according to the International Myeloma Working Group criteria (14). Relapse from CR and progression after a very good partial response (VGPR) or less were defined as previously established (14). Two subsequent evaluations were required to validate the definition of relapse or progression.
PET/CT was considered negative if every area of increased tracer uptake found at baseline disappeared, while it was defined as improved if the number of sites of FDG uptake decreased and/or the SUVmax of the lesions decreased by at least 20%, in accordance with European Organisation for research and Treatment of Cancer (EORTC) criteria (15).

A SUVmax increase by more than 50% of residual PET-FLs or appearance of new FL(s) or EMD by PET/CT were criteria to define relapse or progression.

**Statistical analysis**

Kaplan-Meier analyses landmarked at 6 months from the start of primary therapy were used to estimate progression-free survival (time from start of treatment to progression or relapse, or death from any cause) (PFS) and overall survival (OS). Survivors were censored at the time of last contact. Between-group comparisons were done using the log-rank test.

Multivariate Cox regression analyses were performed to identify baseline and post treatment factors significantly affecting PFS and OS. The 3 leading factors (e.g., ISS stage 3, SUVmax > 4.2 and failure to achieve best CR) were used to construct a prognostic scoring system based on the number of risk factors.

In the end we performed a multinomial logistic regression analysis to identify the most powerful prognostic factor(s) predicting for exclusive skeletal progression, in the absence of any additional sign of relapse or progression.
RESULTS

Patient and imaging characteristics

This retrospective analysis involved 282 newly diagnosed symptomatic MM patients who were treated at our institution between 2002 and 2012, most of them with novel agent-based regimens. Their main characteristics at baseline are summarized in Table 1. The median patient age was 59 years (range 22-83). ISS stage 3 was diagnosed in 20% and the median LDH was 303 UI/L (range 99-2020). Overall, 60% of patients were screened for cytogenetic abnormalities by FISH analysis performed on CD138+ bone marrow plasma cells; 30% of them presented translocation t(4;14) and/or deletion (17p).

Seventy-three percent of the patients received a single or double ASCT while the remaining 27% were treated with chemotherapy at conventional doses combined or not with novel agents. Details of treatment received are reported in Table 1. With a median follow up of 67 months (39-111), the best rates of CR and at least VGPR were 53% and 85%, respectively. Median durations of PFS and OS were 50 and 168 months, respectively.

Seventy percent of the patients had a positive PET/CT scan at diagnosis, with 41% of them showing 1 to 3 FLs and 59% either a diffuse bone marrow involvement or more than 3 FLs (table 2). Eighty-five percent of PET-positive patients had an underlying lytic lesion by CT, while 15% had only one or more focal areas of increased tracer uptake with corresponding negative CT scans. In half of the patients (50%) the baseline FDG uptake was high (defined as SUVmax > 4.2). The reference lesion turned out to be larger than 1cm in >90% of scans, so that inaccuracy in SUVmax measurement due to partial volume effect did not significantly affect the final results. EMD was present in 5% of cases. The cut-offs for FLs and SUV had been previously identified (1).

Baseline PET/CT as prognosticator to construct a scoring system

On univariate analysis, ISS stage 3, failure to achieve best CR and unfavourable PET/CT features, as defined by a number of FLs >3, SUVmax > 4.2 and presence of EMD, adversely affected PFS and OS (for details see supplementary table 2), and retained prognostic relevance.
independently of the treatment received (including or not ASCT, whether bortezomib or non-bortezomib based) (data not shown). The multivariate analysis showed that both PFS and OS were significantly related to a SUVmax value >4.2 at baseline PET/CT, ISS stage 3 and failure to achieve best CR (table 3-model 1).

These 3 variables enabled us to draw up a scoring system, based on the number of risk factors (score 0: none of the 3 adverse factors, 30% of the patients; score 1: only one out of 3, 36%; score 2: 2 factors, whichever, 25%; and score 3: all three risk factors, 9% of cases). The score predicted for PFS and OS, with a progressive increase in the hazard ratios (table 3-model 2). More specifically, median PFS was 94 months for patients with score 0, 44 months for score 1, 30 months for score 2 and 14 months for score 3 (P<0.0001, trend P<0.0001) (figure 1). The 60 months projected OS was 96%, 80%, 75% and 30% in the 4 risk categories, respectively (P=0.003, trend P=0.0003) (figure 1).

Although a similar stratification into different prognostic groups was obtained when FLs>3 and presence of EMD replaced SUVmax > 4.2 (data not shown), we included this latter parameter into the system because in a multivariate analysis it was a stronger predictor of poor outcomes in comparison with FLs (FLs>3: PFS HR=1.38, p=0.279, OS HR=2.14, p=0.171; SUVmax>4.2: PFS HR=2.24, p=0.009, OS HR=3.12, p=0.066) and due to the limited sample size of patients presenting with EMD (5% of the overall population).

**PET/CT after treatment to fine-tune the definition of complete response**

By 3 months after the last cycle of first-line treatment, 85% of the patients obtained at least a VGPR, including 53% with conventionally-defined CR. In 189 patients, PET/CT scans were repeated to evaluate skeletal response to therapy. The rates of CR and at least VGPR in this subgroup of patients were superimposable to those of the whole series (55% and 88%, respectively). PET/CT was negative in 70% of patients while it remained positive in 30% who either improved (20%) or had PET/CT scans unchanged or worsened (10%). (Table 2). Attainment of PET/CT-negativity significantly influenced both PFS (median: 52 vs 38 months for PET/CT positive
patients (p=0.0319)) and OS (5-year estimates: 90% vs 71%, respectively (p=0.0014)). Notably, 29% of patients who achieved CR according to conventional criteria still had positive PET/CT scans, a finding which made for poorer prognosis. Indeed, the median PFS for PET/CT positive patients was significantly shorter than for negative patients (44 vs 84 months; P=0.0009) (figure 2). OS was significantly inferior, as well, for PET/CT-positive patients, with a 5-year estimate of 70% in comparison to 90% for PET/CT-negative patients (P=0.0032) (fig. 2). On multivariate analysis, post-treatment PET/CT-negativity was an independent factor predicting for prolonged PFS (HR=0.43, CI 0.24-0.77) and OS (HR=0.33, CI 0.13-0.86) for patients with conventionally-defined CR.

**PET/CT during the follow-up phase**

Overall, 63% of patients experienced progressive disease. The definition of progression was based on previously established laboratory criteria (14) in 37% of them, on both serological and skeletal criteria (e.g. new bone lesions, or increased size of previously detected bone lesions, or appearance of EMD) in 48%, and only skeletal criteria in 15%. Within this last sub-group, 88% of patients had clinical symptoms, such as pain or pathological fractures, that prompted performance of a PET/CT scan confirming progressive disease, while in 12% otherwise clinically silent skeletal progression was occasionally detected by performing serial PET/CT scans during follow-up. We previously demonstrated that there is an inverse correlation between the residual SUVmax value after ASCT and TTP, whereby all patients with SUVmax> 4.2 subsequently relapsed (16). In this series of patients, 12% retained a SUVmax> 4.2 at the end of first-line treatment. A multinomial logistic regression analysis of baseline variables included in the prognostic scoring system and of post treatment PET features revealed that persistence of SUVmax> 4.2 was the single factor independently associated with skeletal progression detectable by PET/CT and not otherwise identifiable (P = 0.039, relative risk ratio (RRR) 11.05 (1.13-108.08) (table 4). The low number of patients justifies the high variability in the confidence intervals of the RRR.
DISCUSSION

In this retrospective study of 282 patients who were evaluated at baseline and during post-treatment follow-up with serial FDG PET/CT scans we confirmed that this imaging technique is a reliable predictor of prognosis, in both younger, transplant-eligible and elderly MM patients. As previously shown (1), the entity of PET/CT involvement at diagnosis, as reflected by the number of FLs, the intensity of tumour metabolism represented by the SUV value and the presence of EMD, were strong predictors of unfavourable clinical outcomes. In particular, a SUVmax value > 4.2 retained independent prognostic relevance in multivariate regression analyses along with the presence of ISS stage 3 and failure to achieve CR during or after first-line treatment. Although other studies previously showed the prognostic value of FDG PET/CT at baseline in patients receiving novel agents plus ASCT (1,2,17), to the best of our knowledge this is the first report providing demonstration that PET/CT involvement predicts outcomes also in elderly patients treated with novel agents and chemotherapy.

Several factors related to the myeloma cell burden and/or reflecting the biological characteristics of the disease at the time of diagnosis have a well-defined prognostic role in MM patients. In particular, β2M, albumin, CRP, LDH, cytogenetic abnormalities and gene array defined profiles are commonly used to classify patients in different stages and risk subgroups (18, 3). Imaging features have likewise been combined and correlated with a series of established prognostic variables, such as β2M, CRP, albumin, LDH and genetic abnormalities (2,4). Patients with more than 3 FLs on FDG PET/CT at diagnosis were reported to have significantly higher LDH and β2M values, more severe anemia and to be more frequently in advanced stages of the disease (19). A diffuse pattern of bone marrow involvement on MRI was found to be associated with high-risk cytogenetics (4). In our study we were unable to find a correlation between high-risk cytogenetics and high-risk PET/CT features, probably due to the fact that only 60% of the patients had a FISH study available at baseline.
It has been recently shown that the simultaneous presence of several unfavourable factors, whether laboratory tests or imaging scans, greatly worsens the prognosis of MM patients (4, 20).

Pooling a baseline SUV_{max} > 4.2 with the presence of ISS stage 3 and failure to achieve CR during or after first-line treatment, we identified a small subset of patients, averaging approximately 10%, who had a very dismal prognosis (median PFS: 14 months; OS: 30% at 5 years). These patients were mostly treated with novel agents, combined or not with ASCT, and might be the ideal candidates for exploring experimental treatment strategies.

With the availability of newer drugs and different therapeutic options in MM, interest in the evaluation of the depth of response beyond the level of conventionally-defined CR has progressively grown. More sensitive tools, such as multiparametric flow cytometry, polymerase chain reaction and deep sequencing methods, are able to detect the presence of minimal residual disease (MRD) at the bone marrow level, a finding that worsens the prognosis of both ASCT eligible and ineligible patients (21,22). However, these techniques fail to identify the persistence of FL(s) potentially harbouring non-secretory MM cells or sites of active disease outside the medullary cavity of the bone. In addition, a heterogeneous pattern of bone marrow plasma cell infiltration constitutes a potential drawback of these techniques, to which PET/CT scanning and/or total body MRI are complementary investigational tools of MRD evaluation. We have previously shown that one fourth of the patients achieving conventionally-defined CR after up-front thalidomide-dexamethasone and subsequent ASCT still had persistence of PET/CT FLs. These patients had a risk of progression which was two times higher in comparison with that observed for PET/CT negative patients (1). In the present study, 53% of patients who had previously received novel agents combined or not with ASCT obtained a conventionally-defined CR, but only approximately two-thirds of them were PET/CT negative. In comparison with the 30% of patients who showed the persistence of FDG avidity, the achievement of PET/CT negativity ensured a significantly prolonged PFS, nearly halving the risk of progression, and an extended OS. PET/CT-negativity was
confirmed to be an independent predictor of prognosis in a Cox regression analysis and should thus be recommended as a complementary tool to refine the definition of CR.

Differently from post-treatment evaluation of response, the serial use of novel imaging techniques during the follow-up phase is not recommended because of the high costs and the radiation exposure (6,23). After the end of first-line treatment, 30% of the patients retained positive PET/CT scans, and in 40% of them (10% of the whole population) the glucose metabolism was still high. We previously demonstrated that there is an inverse correlation between a residual SUVmax value after ASCT and TTP, whereby all patients with SUVmax > 4.2 subsequently relapsed (16). In this study, by using a multinomial logistic regression analysis, we found that the persistence of high FDG uptake after first-line treatment was associated with skeletal progression, in the absence of any additional clinical or laboratory sign of progressive disease, in a small sub-group of patients, who represented 12% of the overall population of MM patients. Based on these data, serial PET/CT evaluation (i.e. every 12 months) can be recommended in this subset of patients during the follow-up phase. Further studies are needed to evaluate the prognostic impact of treating PET/CT-documented residual disease in patients with conventional CR after first-line therapy.

**CONCLUSION**

In conclusion, we confirm the prognostic value of FLs, SUVmax and EMD, as detected by FDG PET/CT, in newly diagnosed MM patients who are candidates to receive an ASCT, consistently with two previously reported studies. Importantly, we found that the same variables were prognosticators of outcome also for elderly, non ASCT eligible, patients, a finding herein reported for the first time.

In a multivariate analysis, a baseline SUVmax value >4.2 was identified as one of the leading variables adversely affecting PFS and OS, along with ISS stage 3 and failure to achieve CR upon first-line treatment. The presence of all these factors identified a small subgroup of patients (10%) with very poor prognosis who may possibly require alternative treatment strategies.
Importantly, in both younger and elderly MM patients in CR after treatment PET/CT negativity predicted for a significantly longer PFS and OS in comparison with the same group of patients who remained PET positive, thus contributing to a more accurate evaluation of CR beyond the conventionally-defined level outside the bone marrow.

PET/CT may usefully be employed during the follow-up phase to monitor the small sub-group of patients with persistent high glucose metabolism after first-line treatment (12%) in order to detect otherwise unidentifiable skeletal progression.

On the basis of our results, integrating PET/CT scanning into the algorithm of MM staging and follow-up after treatment may improve disease management.

Acknowledgements

Authorship Contribution
Elena Zamagni designed the research study, performed the research, analysed the data and wrote the paper. Michele Cavo designed the research study, performed the research, analysed the data and critically revised the paper. Cristina Nanni and Ilaria Rambaldi performed the research and contributed analytical tools. Beatrice Zannetti performed the research and gave a substantial contribution to analysing the data. Annalisa Pezzi performed statistical analysis and contributed to data interpretation. Paola Tacchetti, Annamaria Brioli, Lucia Pantani, Carolina Terragna, Giulia Marzocchi, Enrica Borsi, Ilaria Rizzello performed the research and helped in collecting data. Stefano Fanti contributed to data interpretation and approved the paper. All the authors approved the final version of the paper and the choice of submitting it.

Disclosures: the authors declare that none of them have any relevant competing financial interests.
REFERENCES


Table 1: Patient characteristics at baseline and treatment received

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<table>
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<tr>
<td>Nº patients</td>
<td>282</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>59 (22-83)</td>
</tr>
<tr>
<td>Median LDH (UI/L) (range)</td>
<td>303 (99-2020)</td>
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<tr>
<td>Patients with ISS stage 3</td>
<td>20%</td>
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<tr>
<td>Patients with del (17p) and/or t(4;14)</td>
<td>30%</td>
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<tr>
<td>Patients receiving ASCT as first-line treatment</td>
<td>73%</td>
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<td>- conventional chemotherapy-based</td>
<td>23%</td>
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<tr>
<td>- thalidomide-based</td>
<td>43%</td>
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<tr>
<td>- bortezomib-based</td>
<td>34%</td>
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<tr>
<td>Patients not ASCT eligible</td>
<td>27%</td>
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<tr>
<td>- conventional chemotherapy</td>
<td>21%</td>
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<tr>
<td>- MPT</td>
<td>33%</td>
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<tr>
<td>- VMP</td>
<td>46%</td>
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<tr>
<td>Patients receiving novel agents as first-line treatment</td>
<td>77%</td>
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<tr>
<td>Patients receiving Bortezomib as first-line treatment</td>
<td>37%</td>
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Nº number, LDH lactate dehydrogenase, ISS international staging system, del deletion, t translocation, ASCT autologous stem cell transplantation, MPT melphalan-prednisone-thalidomide, VMP bortezomib-melphalan-prednisone, IMiDs immunomodulatory drugs, PI proteasome inhibitor
Table 2: Baseline and after first-line treatment PET/CT characteristics

<table>
<thead>
<tr>
<th>PET/CT characteristics</th>
<th>Baseline</th>
<th>After treatment</th>
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<tbody>
<tr>
<td>% Patients with negative PET/CT</td>
<td>30%</td>
<td>70%</td>
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<tr>
<td>% Patients with positive PET/CT</td>
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<tr>
<td>1-3 FLs</td>
<td>70%</td>
<td>30%</td>
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<tr>
<td>&gt;3 FLs or diffuse</td>
<td>28%</td>
<td>15%</td>
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<tr>
<td>SUV ≤ 4.2</td>
<td>42%</td>
<td>15%</td>
</tr>
<tr>
<td>SUV &gt; 4.2</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>45%</td>
<td>12%</td>
</tr>
<tr>
<td>% Patients with EMD</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

FLs focal lesions, EMD extramedullary disease, SUV standardized uptake value
Table 3: PFS and OS according to ISS stage 3, failure to achieve best CR after first-line therapy and PET/CT SUVmax > 4.2 (Model 1, multivariate analysis) or according to their combination into a prognostic score (Model 2)

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<tbody>
<tr>
<td></td>
<td>PFS</td>
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<tr>
<td></td>
<td>Model 1:</td>
<td>HR</td>
<td>95% C.I.</td>
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<tr>
<td></td>
<td>ISS stage 3</td>
<td>1.49</td>
<td>1.03</td>
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<td></td>
<td>Failure to achieve best CR</td>
<td>2.52</td>
<td>1.51</td>
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<td></td>
<td>SUVmax &gt; 4.2</td>
<td>1.90</td>
<td>1.12</td>
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<td>Model 2:</td>
<td>HR</td>
<td>95% C.I.</td>
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<tr>
<td></td>
<td>Score 1 vs 0</td>
<td>3.11</td>
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<td>Score 2 vs 0</td>
<td>5.70</td>
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<td>Score 3 vs 0</td>
<td>7.17</td>
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<tr>
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<td>OS</td>
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<tr>
<td></td>
<td>Model 1:</td>
<td>HR</td>
<td>95% C.I.</td>
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<td></td>
<td>ISS stage 3</td>
<td>2.11</td>
<td>1.04</td>
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<td></td>
<td>Failure to achieve best CR</td>
<td>1.61</td>
<td>0.66</td>
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<tr>
<td></td>
<td>SUVmax &gt; 4.2</td>
<td>3.65</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>Model 2:</td>
<td>HR</td>
<td>95% C.I.</td>
</tr>
<tr>
<td></td>
<td>Score 1 vs 0</td>
<td>3.14</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td>Score 2 vs 0</td>
<td>6.01</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Score 3 vs 0</td>
<td>13.19</td>
<td>2.71</td>
</tr>
</tbody>
</table>

PFS progression-free survival, SUV standardized uptake value, ISS international staging system, CR complete remission, OS overall survival, HR hazard ratio, CI confidence interval
Table 4: Multinomial logistic regression analysis of factors predicting for conventionally defined and exclusive PET/CT skeletal progressive disease

<table>
<thead>
<tr>
<th></th>
<th>Relative Risk Ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NO PD (baseline)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>baseline</td>
<td></td>
</tr>
<tr>
<td><strong>Conventionally defined PD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 1 vs 0</td>
<td>11.53 (3.58-37.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Score 2 vs 0</td>
<td>13.02 (3.78-44.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Score 3 vs 0</td>
<td>11.58 (2.16-62.10)</td>
<td>0.004</td>
</tr>
<tr>
<td>PET SUV&gt;4.2 after first-line treatment</td>
<td>3.18 (0.52-19.33)</td>
<td>0.208</td>
</tr>
<tr>
<td><strong>Skeletal progression, without clinical symptoms and laboratory signs of PD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score 1 vs 0</td>
<td>3.81 (0.53-27.18)</td>
<td>0.182</td>
</tr>
<tr>
<td>Score 2 vs 0</td>
<td>1.41 (0.11-18.62)</td>
<td>0.796</td>
</tr>
<tr>
<td>Score 3 vs 0</td>
<td>2.98 (0.17-51.32)</td>
<td>0.453</td>
</tr>
<tr>
<td>PET SUV&gt;4.2 after first-line treatment</td>
<td>11.05 (1.13-108.08)</td>
<td>0.039</td>
</tr>
</tbody>
</table>

Score based on ISS 3, failure of CR and PET/CT-SUVmax, PD progressive disease
Figure Legends:

- Figure 1: PFS and OS according to the scoring system (ISS stage 3, failure to achieve best CR after first-line therapy and PET/CT SUVmax > 4.2)

- Figure 2: PFS and OS according to PET/CT negative or positive after treatment in patients achieving conventionally defined CR
Clinical Cancer Research

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