Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly Multiple Myeloma patients included in the GEM2005MAS65 trial

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Running title: Maintenance therapy in Myeloma patients
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Abstract

Maintenance therapy has become a hot field in multiple myeloma (MM), and it may be particularly relevant in elderly patients since the major benefit results from the initial therapy. We report the results of a randomized comparison of maintenance with bortezomib plus thalidomide (VT) or prednisone (VP) in 178 elderly untreated MM patients who had received six cycles of induction with bortezomib plus, either melphalan and prednisone (VMP) or thalidomide and prednisone (VTP). The CR rate increased from 24% after induction up to 42%, slightly higher for VT versus VP (46% versus 39%). Median PFS was superior for VT (39 months) compared to VP (32 months) and OS was also slightly longer in VT patients as compared with VP (5-years OS of 69% and 50%, respectively) but the differences did not reach statistical significance. CR achievement was associated with a significantly longer PFS (p<0.001) and 5-years OS (p<0.001). The incidence of G3-4 peripheral neuropathy was 9% for VT and 3% for VP. Unfortunately, this approach was not able to overcome the adverse prognosis of cytogenetic abnormalities. In summary, these maintenance regimens result into a significant increase in CR rate and remarkable long PFS with an acceptable toxicity profile. The trial is registered at www.clinicaltrials.gov as NCT00443235.
Introduction

Multiple Myeloma (MM) is the second most frequent hematologic malignancy and it usually affects elderly patients. Melphalan and prednisone (MP) has been the standard of care in the past for this patient population, resulting in complete response (CR) rates ranging from 2% to 5% with median overall survival (OS) from 2-3 years\textsuperscript{1-3}. The introduction of novel agents, thalidomide (Thal), bortezomib (V) and lenalidomide (R), for the treatment of elderly MM patients have significantly increased the CR rate and this translated into prolonged time progression (TTP), progression free survival (PFS) and OS. Therefore, the concept of “the longer the duration of the response the longer the survival”, used for most hematological malignancies, would be also applicable to MM and particularly to elderly patients, since usually two thirds of the survival duration in the elderly population derives from the efficacy of the first line of therapy. Accordingly, an attractive current challenge is to explore the capacity of novel agents, such as thalidomide, bortezomib and lenalidomide to maintain the high response rate achieved upfront with these drug combinations\textsuperscript{4}.

Concerning Thal, six randomized trials have compared MP and Thal (MPT) with MP\textsuperscript{5-10}, and in three of them Thal was also used as maintenance therapy until disease progression\textsuperscript{5, 8, 9}. Maintenance induced an improvement in both overall response rate (ORR), (upgrade ranging from 17% up to 30%) and PFS (prolongation ranging from 2 up to 7 months) but with only marginal benefit for OS. An Austrian trial has compared the value of Thal plus interferon maintenance versus interferon alone in elderly patients who had received induction with Thal plus dexamethasone (Thal-Dex) or MP\textsuperscript{11}. Thal plus interferon led to a significantly longer PFS compared with interferon alone (27.7 months vs 12.2 months, p=0.0068) without benefit in OS. In the Myeloma Research Council (MRC) Myeloma IX study, Thal maintenance vs observation was compared following cyclophosphamide plus thalidomide and adjusted-dose dexamethasone (CTDa) or MP given as induction therapy. Although the PFS was significantly increased with Thal maintenance, this benefit was quite modest (11 months vs 9 months, p=0.014) with no differences in OS\textsuperscript{12}.

Lenalidomide, as maintenance therapy, has been explored in the MM-015 trial. Elderly patients were randomized to receive 9 cycles of MP plus lenalidomide (MPR) followed by R maintenance until progression disease or intolerance vs MPR (9 induction cycles) followed by placebo vs MP (9 induction cycles) followed by placebo. The continuous use of lenalidomide, MPR-R, resulted in a significantly longer PFS, 31 months vs 14 months and 13 months for the MPR and MP arms, respectively (p<0.001), but so far no differences in OS are detected\textsuperscript{13}.
Concerning bortezomib, a GIMEMA study has compared MP plus bortezomib and thalidomide (VMPT) as induction followed by VT maintenance with VMP as induction without maintenance therapy. Patients receiving VMPT followed by VT achieved significant benefit in PFS at 3 years (56% vs 41%, \( p=0.0008 \)) but not yet differences in OS have been observed\(^\text{14}\). There is an ongoing phase 3b trial (UPFRONT) analyzing the role of bortezomib single agent as maintenance therapy in elderly MM patients after induction with bortezomib plus dexamethasone (VD), VD plus thalidomide (VTD) or VMP, but data are still very premature\(^\text{15}\).

We have recently reported the outcome of a series of 260 elderly untreated MM patients included in the GEM2005MAS65 Spanish trial in which patients received six cycles of induction therapy with VMP or VTP followed by maintenance with bortezomib plus thalidomide (VT) or bortezomib plus prednisone (VP)\(^\text{16}\). The design and objectives of this trial were based on data derived from the pilot study conducted by Spanish Myeloma Group in 2005 because data from VISTA trial were not yet available. In both studies, the combination bortezomib plus melphalan and prednisone resulted in 30% of complete response rate, but important toxic effects were recorded, particularly peripheral neuropathy (grade 3 or worse in 13% of patients in the VISTA and in 17% in the pilot study) and gastrointestinal symptoms (19% grade 3 or worse in VISTA). Accordingly, we planned a novel and less intensive bortezomib-based treatment regimen with two objectives: to maintain efficacy and reduce toxic effects compared with the regimen used in the pilot study and VISTA trial. At the time of first report the follow-up of patients receiving maintenance therapy was relatively short (22 months). Since maintenance therapy has become a field of high interest in MM, but information in the elderly population is scarce, particularly about the potential role of bortezomib in this setting, we decided to analyze in depth, after a median follow-up of more that 3 years (38 months) from the initiation of maintenance therapy, the efficacy and toxicity of the randomized comparison of maintenance with VT or VP. Our results show that in the per-protocol populations of the VT and VP maintenance arms of the study, these regimens upgraded the ORR and especially, the CR rate obtained after the soft induction therapy, with an acceptable toxicity profile. Although there were not significant differences between both regimens, VT seems to be slightly superior in efficacy to VP. Finally, these maintenance regimens are not able to overcome the poor prognosis of the presence of high-risk cytogenetic abnormalities (CA).

**Patients and methods**

The Spanish GEM05MAS65 trial included 260 patients aged 65 years or older with newly diagnosed, untreated, symptomatic, measurable MM. The institutional
review board or independent ethics committee at each participating center approved the study. All patients provided written informed consent before screening in accordance with the Declaration of Helsinki. The trial was registered with ClinicalTrials.gov, number NCT00443235. Data were monitored by an external contract research organization and centrally assessed.

Patients were upfront randomized to receive induction with VMP or VTP in the first stage of this two stage randomized trial as previously described16. VMP induction therapy consisted of six cycles: one cycle of intravenous bortezomib given twice per week for 6 weeks (1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29 and 32), plus oral melphalan 9 mg/m² and prednisone 60 mg/m² on days 1-4, followed by five cycles of bortezomib once per week for 5 weeks (1.3 mg/m² on days 1, 8, 15 and 22) plus the same doses of MP. VTP induction therapy consisted of the same schedule of bortezomib and prednisone plus oral, continuous thalidomide at a dose of 100 mg per day instead of melphalan. Patients from each arm completing the six induction cycles were then randomly assigned to maintenance therapy with either VT or VP. Maintenance consisted of one conventional cycle of bortezomib (1.3 mg/m² on days 1, 4, 8 and 11) every 3 months, plus either oral prednisone 50 mg every other day or oral thalidomide 50 mg per day, for up to 3 years (figure 1).

**FISH studies**

Fluorescence in situ hybridization (FISH) studies for IGH translocations, including t(4;14), t(11;14), t(14;16) as well as del(13q), and del(17p) were done in CD138-purified plasma cells as previously described.17, 18

**Statistical analysis**

The planned sample size of 260 patients was calculated for a two-sided \( \alpha \) level of 0.05 and a statistical power fo 80%. The sample size for maintenance was calculated on the basis of the aim to improve the complete response rate by at least 15% after induction, irrespective of the regimen used. Comparisons were undertaken in the intention-to-treat (ITT) population. We anticipated a dropout rate of 25% during induction due to deaths and toxic effects and 5% due to progression disease16. Disease response was assessed according to the European Group for Blood and Marrow Transplantation criteria19, including both standard complete response, immunofixation negative (IF-CR), and near-complete response (IF+, nCR). PFS was measured as the time from first randomization to disease progression or death from any cause, and OS as the time from first randomization to death from any cause. During maintenance therapy, assessments were done every month. All adverse events (graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) and use of concomitant drugs and supportive therapies...
were recorded. The prognostic impact of the high-risk CA [t(4;14), t(14;16) and/or del(17p)] was analyzed by comparing the outcomes, in terms of overall response rate (ORR), complete response (CR rate), PFS and OS of patients with standard-risk versus high-risk CA in each maintenance arm.

The \( \chi^2 \) and Fisher’s exact tests were used, as appropriate, to compare ORR, CR/nCR between both maintenance regimens, as well as in standard- and high-risk subgroups, and time-to-event data were estimated by the Kaplan-Meier method, significance being determined with a two-sided long-rank test. Cox proportional hazards regression models were derived to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). All statistical analyses were done with SPSS (version 15.0; SPSS Inc, Chicago, IL).

**Results**

**Efficacy in terms of responses rate**

Baseline characteristics of the patients randomized to receive maintenance therapy are shown in Table 1. Figure 2 shows the study flow chart. Among all the 260 patients included in the trial, 178 patients were randomized to receive maintenance and evaluable for response. The reasons for early discontinuations during induction are represented in the figure 2. After a median follow-up of 38 months (range: 8-58 months) from the initiation of maintenance, the CR rate increased from 24% at the end of induction (mean CR rate obtained after VMP and VTP) up to 42%. Overall, an improvement of the depth of response was observed in 33 patients (19%): 10 patients in nCR (IF+CR) upgraded to CR, and 17 patients in PR upgraded to either nCR (7 patients) or CR (10 patients). The median time to improvement of the response was of 3 months (range: 1-31 months). Although there were not significant differences between both maintenance arms, the CR rate was slightly higher for VT as compared with VP (46% vs 39%, P=NS) (Table 2). The number of patients who improved the quality of response was 19 with VT and 14 with VP. Analysis of responses rate to maintenance therapy were not influenced by the previous induction regimen.

**Time-to-event data**

After a median follow-up of 46 months (range: 17-67 months) from inclusion in the trial and 38 months (range: 8-58 months) from the initiation of maintenance, the median PFS for the per-protocol populations of the VT and VP arms of the study was 35 months (95% CI: 28-41) and the estimated 5-years OS of 58% (95% CI: 51-67).
Median PFS was superior for patients randomized to VT (39 months (95% IC: 27-51)) compared to patients who received VP (32 months (95% CI: 24-41)), although this difference was not significant (p=0.1) (Figure 3A).

Concerning OS, this was also slightly longer in patients maintained with VT as compared with VP (5-years OS of 69% (95% CI: 51-79) and 50% (95% CI: 46-54), respectively) but the differences did not reach statistical significance (p=0.1) (Figure 3B).

A stratified Cox regression analysis of PFS and OS with inverse probability weighting, appropriate for two-stage randomization designs as a sensitivity analysis was conducted, showing a p value of 0.8 for the interaction term, indicating that induction with VMP or VTP didn’t influence the PFS and OS observed with maintenance regimens (Supplemental figure 1A-B).

We also evaluated the impact of the quality of response achieved during maintenance therapy on outcome. Patients who achieved CR had a significantly longer PFS (median of 54 months) as compared with nCR patients (median of 39 months) and PR patients (median of 24 months) (p<0.0001; HR: 1.73; 95% CI: 1.4-2.1), and this translated into a significantly higher 5-years OS (78% for IF-CR patients vs 59% nCR (IF+CR) vs 54% for PR; p<0.0001; HR: 1.5; 95% CI: 1.2-1.9) (Figure 4A and 4B). Moreover, the improvement of the depth of response during maintenance therapy with VT or VP resulted also into a better outcome as compared with those patients in which the response was only maintained. Median PFS was 47 months for patients who improved their response vs 32 months for those who only maintained their response (p=0.02; HR: 0.56; 95% CI: 0.3-0.9) and 5-years OS was 81% and 54% for patients who improved and maintained the quality of response, respectively (p=0.02; HR: 0.4; 95% CI: 0.1-1.01). The type of maintenance regimen received did not influence this outcome.

**Impact of cytogenetic abnormalities**

FISH analysis results were available in 160 of the 178 patients (89%) randomized to receive maintenance therapy. 28 out of these 160 patients qualified as high-risk (18%); 13 of them (8%) had t(4;14) ± del(13q) (7 patients in VT and 6 in VP), 15 patients (9%) had del(17p) ± del(13q) (8 patients in VT and 7 in VP), and one patient in each maintenance arm (1%) had t(14;16).

The distribution according to treatment arm was identical in both risk subgroups: in the standard-risk group, 51% and 49% received VT and VP, respectively, and the frequency was similar in the high-risk group (54% and 46% for VT and VP, respectively).
The type of maintenance regimen did not influence the response rate in either high-risk patients, (CR rate: 47% for VT and 39% for VP) or standard risk patients (CR rates: 48% and 41% for VT and VP, respectively). Regarding the influence of the maintenance treatment arm in the outcome, the median PFS in the high-risk subgroup was similar for patients who received VT and VP (28 months and 27 months respectively; $p=0.6$), and this also translated into similar 4-year OS (55% and 53% for VT and VP, respectively; $p=0.2$). In the standard-risk subgroup, the median PFS was slightly higher in the VT arm (47 months) compared to VP (36 months), which with 4-year OS of 79% for VT and 69% for VP, but these differences did not reach statistical significance ($p=0.1$ for both PFS and OS) (Figure 5). Moreover, these data illustrate that none of the maintenance regimens overcome the adverse prognosis of cytogenetic abnormalities, since high-risk patients had a significantly shorter PFS and OS as compared to those with standard risk.

**Toxicity**

Hematologic toxicity was similar in both arms, with only one patient showing grade 3-4 neutropenia (VT arm). Concerning non-hematologic toxicity, patients receiving VT developed a higher frequency of grade 3-4 adverse events (AEs) compared to VP patients (17% vs 5%, $p=0.009$). In the VT arm, the grade 3-4 AEs included: 2 patients (2%) with asthenia, 4 patients (4%) with gastrointestinal symptoms, 2 patients (2%) with cardiac events and 9 patients (9%) with peripheral neuropathy (PN). By contrast, in the VP arm, only 3 patients (3%) experienced PN plus 1 patient (1%) who developed gastrointestinal symptomatology and other cardiac events.

52 patients (57%) and 51 patients (59%) in VT and VP arms, respectively, discontinued the trial. The most frequent reason for discontinuation in both arms was progression disease (32 patients (35%) and 40 patients (46%) in VT and VP arms, respectively). Toxicity was the reason for discontinuation in 12 VT patients (13%) and in 8 VP patients (9%), being PN and cardiac events the AEs leading to discontinuation. Two patients in VT (2%) and two patients in VP (2%) discontinued due to the development of second primary malignancies (lung cancer, colorectal neoplasm, prostate cancer and lung and liver metastasis from unknown origin). One additional patient developed lung cancer during induction with VMP before he was randomized to maintenance.

24 patients (26%) and 30 patients (35%) died during maintenance therapy in the VT and VP arms, respectively. Disease progression was the reason of death in 19 and 26 patients in VT and VP, respectively, and development of AEs in 5 patients (6%) under VT maintenance (septic shock, stroke, heart attack, hepatic and lung metastasis...
and lung cancer), and 4 (5%) under VP maintenance (colorectal neoplasm, intracerebral hemorrhage, sepsis and progressive cognitive impairment).

Discussion

With the introduction of novel agents, thalidomide, bortezomib and lenalidomide, most of the myeloma patients respond to induction therapy. Therefore, the next challenge is to maintain these responses, or even to improve them, in order to achieve prolonged PFS and, eventually, longer survival. Thus, maintenance therapy has become a field of increasing interest, and this may be particularly relevant for elderly patients since the advanced age as well as comorbidities and disabilities may potentially compromise the salvage therapies at the moment of disease progression and, therefore, the major benefit in outcome in the elderly population results from the initial approach of therapy. Here we report that the addition of a prolonged maintenance therapy with VT or VP results into a significant increase of the IF-CR rate (42%) and a remarkable long PFS (35 months) with an acceptable toxicity profile.

The experience with bortezomib as maintenance therapy is limited. In the transplant setting, the HOVON 65 MM/GMMG-HD4 study has evaluated the role of bortezomib every other week up to 2 years as maintenance after induction with PAD (bortezomib, adriamycin plus dexamethasone) followed by single or tandem HDT-ASCT. The results show a significant prolongation in PFS as compared to TAD induction (thalidomide, adriamycin plus dexamethasone) and thalidomide maintenance (median PFS of 36 months and 27 months), as well as longer OS (HR=0.75; p=0.02)20. In the elderly population, GIMEMA group reported that a four-drug combination as induction, VMPT, plus VT as maintenance, results into a significant benefit in PFS compared with VMP without maintenance (3-year PFS of 56% versus median PFS of 27.3 months)14. Unfortunately, the superiority of bortezomib over thalidomide maintenance in the HOVON 65 MM/GMMG-HD4 study and of bortezomib plus thalidomide versus no maintenance in the GIMEMA trial cannot be elucidated since the induction arms were different (PAD vs TAD in the HOVON trial and VMPT vs VMP in the GIMEMA trial). Therefore, the benefit of bortezomib as maintenance therapy cannot be dissected from the benefit obtained during induction.

In our trial, bortezomib was given in both maintenance arms and it was combined with either thalidomide or prednisone. Thus, it is also not possible to evaluate the individual benefit of bortezomib. However, if we consider the improvement in CR rate (from 22% up to 42%), this benefit cannot be attributed to the single effect of
either thalidomide or prednisone, since the previous experience with both drugs, administered as single agents or combined, didn’t result in such degree of improvement in the quality of the response\(^5,8,21,22\). Therefore, our results argue in favor of the efficacy of bortezomib in these combinations. Moreover, this study shows that patients achieving CR with this approach, consisting on soft induction followed by maintenance therapy, enjoy a significantly longer PFS and OS as compared to patients with only nCR or PR, as it has been previously reported in the elderly patients population\(^23\). Moreover, those patients able to upgrade their response with the maintenance therapy had also better outcome as compared with those in which response is only maintained.

Upon comparing VT vs VP maintenance, results argue in favor of VT because improvement of response seems to be slightly superior as compared with VP, which translated into longer PFS and OS, although the differences did not reach statistical significance. This would be in line with maintenance post-transplant trials, which have shown that thalidomide is superior to prednisolone\(^21\). However, considering toxicity, the frequency of AEs was significantly higher in VT arm, and especial caution should be paid to the cardiac events. Accordingly it should be recommended a full cardiologic work-up before starting treatment with thalidomide, especially in elderly patients. Concerning grade 3-4 PN, the frequency was 9% and 3% in VT and VP arms, respectively, but in most of the patients PN had previously developed during induction therapy and worsened with the maintenance, in fact only one patient in VT arm developed grade 3 emergent PN. These results are in agreement with those of the GMMG-HD4 / HOVON 65 MM and GIMEMA trials that showed a low incidence of PN with bortezomib maintenance both in young and elderly patients, respectively\(^14,20\).

The discontinuation rate in both maintenance arms was low (13% and 9% in VT and VP, respectively), indicating that the schedule of administration of bortezomib planned in this study, one conventional cycle every three months, together with low doses of continuous thalidomide or prednisone, result feasible.

Concerning the benefit of maintenance in terms of outcome, the long median PFS observed in our study (35 months for the overall series) is in line with the PFS reported by the GIMEMA group\(^14\), using VT maintenance and almost 1 year longer than that previously reported in MPT or MPV (VISTA) trials\(^24,25\). In fact, this median PFS is similar to the OS obtained in the MP era. This advantage might be attributed to the effective and well tolerated prolonged maintenance. However, when OS is analyzed, the differences between the present and the VISTA trials are no so striking (5-year OS of 58% vs 46% respectively). This could be attributed either to the potential selection of resistant clones during maintenance, resulting in more resistant relapses or to the use
of suboptimal rescue therapies at the time of relapse, particularly in the experimental arm. In fact, the high complexity of salvage therapies currently available may obscure the analysis of the benefit of maintenance treatments in terms of OS. However, in this elderly patient population, the benefit of a prolonged PFS may be a valid objective, provided that a prolonged time without disease progression, will translate into a physical and emotional benefit for the patient. Quality of life studies in this setting are necessary to validate this hypothesis.

Finally, the capacity of novel agents to overcome the poor outcome of high-risk CA remains controversial. In the current trial there was a poor outcome in the high-risk CA subgroup of patients regardless of the maintenance treatment assigned. Although it can be argued that only one course of bortezomib every three months is suboptimal to overcome the adverse prognosis of high risk cytogenetic and more frequent exposure would be needed, such possibility needs to be proved.

In summary, the addition of maintenance therapy with VT or VP to a short induction with VMP or VTP resulted in an increase of the ORR and IF-CR rate, with an acceptable toxicity profile. Although no significant differences were observed between VT and VP, efficacy is in favor of VT and safety of VP. This approach was not able to overcome the adverse prognosis of high-risk CA. Finally, these bortezomib-based regimens as maintenance therapy may represent an optimal platform for further optimization of the treatment of elderly patients, particularly through the combination with lenalidomide that it is more potent and has a better safety profile than thalidomide.

Numerous ongoing studies are addressing different questions about optimal regimen, schedule, treatment duration and route of drug delivery, and hopefully they will contribute to elucidate the final benefit of maintenance therapy in order to be implemented into routine clinical practice. Until these results become available our current practice is to restrict maintenance therapies to patients enrolled into clinical trials.

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Contributors
M-VM, J-JL, JBC and J-FSM served as principal investigators, were involved in the original idea and design of the study. M-VM and J-FSM wrote the protocol and report, and analysed and interpreted data. M-VM, AO, JM-L, A-IT, ALG, JL, EB, MP, MP, FA, LP, YG, J-MH, MG, JLB, FJP, JMR, M-LMM, JJL, JB and J-FSM have contributed with the inclusion of patients.

Conflict of interest disclosures:
MVM has served on the speaker’s bureau for Millennium, Celgene and Janssen. AO has received honoraria from Celgene and Janssen. JML has received honoraria from Celgene and Janssen. NG has received honoraria from Celgene and Janssen. LP has received honoraria from Celgene and Janssen. FA has received honoraria from Celgene and Janssen. JMH has received honoraria from Celgene and Janssen. RGS has received honoraria from Ortho-Biotech and Celgene. JJJL has received honoraria from Janssen and Celgene and JB has received honoraria and on advisory board for Janssen and Celgene, and JSM has served on the speaker's bureau and on advisory board for Millennium, Janssen and Celgene. The other authors declared no conflicts of interest.
References


Table 1. Baseline characteristics of patients randomized to receive maintenance therapy

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<th></th>
<th>VT (n=91)</th>
<th>VP (n=87)</th>
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<td><strong>Age (years)</strong></td>
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<td>72 (65-84)</td>
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<tr>
<td><strong>Male, %</strong></td>
<td>53</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td><strong>IgG / IgA / light chain, %</strong></td>
<td>62 / 28 / 9</td>
<td>55 / 32 / 12</td>
<td>NS</td>
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<tr>
<td><strong>ISS stage I / II / III, %</strong></td>
<td>30 / 41 / 29</td>
<td>28 / 41 / 30</td>
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<td><strong>Creatinine (mg/dl), mean</strong></td>
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<td>1.0</td>
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<tr>
<td><strong>B2-microglobulin (mg/l), mean</strong></td>
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<td>3.8</td>
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<td><strong>PCsBM infiltration, Mean</strong></td>
<td>38%</td>
<td>44%</td>
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<tr>
<td><strong>Induction regimen, %</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>VMP</td>
<td>52</td>
<td>51</td>
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</tr>
<tr>
<td>VTP</td>
<td>48</td>
<td>49</td>
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<td><strong>High-risk ([t(4;14), t(14;16), del 17p]) cytogenetic by FISH, (%)</strong></td>
<td>17</td>
<td>15</td>
<td>NS</td>
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Data are numbers (%) or means. VMP=bortezomib plus melphalan and prednisone. VTP=bortezomib plus thalidomide and prednisone. VT=bortezomib plus thalidomide. VP=bortezomib plus prednisone. ISS=International Staging System. PCsBM=plasma cell bone marrow infiltration. NS= Not significant.
Table 2. Efficacy in terms of responses rate after maintenance therapy

<table>
<thead>
<tr>
<th></th>
<th>Pre-maintenance</th>
<th>VT (n: 91)</th>
<th>VP (n:87)</th>
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<td>IF-CR, n(%)</td>
<td>62 (24 %)</td>
<td>42 (46 %)</td>
<td>34 (39 %)</td>
<td>NS</td>
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<td>IF+CR, n(%)</td>
<td>26 (10 %)</td>
<td>9 (10 %)</td>
<td>10 (11 %)</td>
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<td>PR, n(%)</td>
<td>122 (47 %)</td>
<td>36 (39 %)</td>
<td>41 (47 %)</td>
<td>NS</td>
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<td>MR, n(%)</td>
<td>21 (8 %)</td>
<td>3 (3 %)</td>
<td>1 (1 %)</td>
<td>NS</td>
</tr>
<tr>
<td>SD, n(%)</td>
<td>25 (10 %)</td>
<td>1 (1 %)</td>
<td>1 (1 %)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are number with percentages (%). VT= Bortezomib plus Thalidomide. VP= bortezomib plus prednisone. IF-CR= negative immunofixation complete response. IF+CR= positive immunofixation complete response. PR= partial response. MR= minor response. SD= stable disease. NS= not significant.
Table 3. Best response during maintenance therapy according to cytogenetic abnormalities.

<table>
<thead>
<tr>
<th></th>
<th>Standard-risk (n=111)</th>
<th>High-risk (n=28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VT</td>
<td>VP</td>
<td>VT</td>
</tr>
<tr>
<td>IF- CR</td>
<td>48%</td>
<td>41%</td>
<td>47%</td>
</tr>
<tr>
<td>IF+ CR</td>
<td>10%</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>PR</td>
<td>37%</td>
<td>45%</td>
<td>40%</td>
</tr>
<tr>
<td>MR</td>
<td>3%</td>
<td>2%</td>
<td>7%</td>
</tr>
</tbody>
</table>

Data are percentages. VT=bortezomib plus thalidomide. VP=bortezomib plus prednisone. IF- CR=immunofixation negative complete remission. IF+ CR=immunofixation positive complete remission. PR=partial response. MR=minor response. NS= not significant.
Figure 1. Schedule of induction and maintenance therapy
V: Bortezomib; T: Thalidomide; M: Melphalan; P: Prednisone

Figure 2. Trial profile
V=bortezomib. M=melphalan. P=prednisone. T=thalidomide. Four patients in each of the VMP and VTP arms progressed under induction therapy, and two patients in VMP group and three in VTP group progressed just before to start the maintenance phase.

Figure 3. Progression-free survival (3A) and overall survival (3B) by maintenance therapy. VT=bortezomib plus thalidomide. VP=bortezomib plus prednisone NR: Not reached.

Figure 4. Progression-free survival (4A) and overall survival (4B) according to the type of response achieved. CR: Immunofixation negative complete response. nCR: Immunofixation positive complete response. PR: partial response.

Figure 5. Progression-free survival and overall survival in high-risk (5A/5B) and standard-risk cytogenetic abnormalities (5C/4D) by maintenance arm. VT=bortezomib plus thalidomide. VP=bortezomib plus prednisone. NR=Not reached.
### Figure 1

<table>
<thead>
<tr>
<th>Induction</th>
<th>VMP</th>
<th>VTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One 6-week</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² twice weekly (days 1, 4, 8, 11; 22, 25, 29, 32)</td>
<td>Bortezomib 1.3 mg/m² twice weekly (days 1, 4, 8, 11; 22, 25, 29, 32)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>9 mg/m² days 1-4</td>
<td>Thalidomide 100 mg daily</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² days 1-4</td>
<td>Prednisone 60 mg/m² days 1-4</td>
</tr>
</tbody>
</table>

| Five 5-week   |     |     |
| Bortezomib    | 1.3 mg/m² once weekly (days 1, 8, 15, 22) | Bortezomib 1.3 mg/m² twice weekly (days 1, 8, 15, 22) |
| Melphalan     | 9 mg/m² days 1-4 | Thalidomide 100 mg daily |
| Prednisone    | 60 mg/m² days 1-4 | Prednisone 60 mg/m² days 1-4 |

| Maintenance (up to 3 years) | VP | VT |
| Bortezomib    | 1.3 mg/m² twice weekly (days 1, 4, 8, 11) every 3 months | Bortezomib 1.3 mg/m² twice weekly (days 1, 4, 8, 11) every 3 months |
| Prednisone    | 50 mg every 48 hours | Thalidomide 50 mg daily |
Figure 2

260 patients randomly assigned

<table>
<thead>
<tr>
<th>Induction therapy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>VMP (n:130)</td>
<td>VTP (n:130)</td>
</tr>
</tbody>
</table>

6 months

- 10 patients: IC withdrawal
- 15 patients: Toxicity
- 6 patients: Progression Disease*
- 1 patient: Lung neoplasia
- 7 patients: Deaths

3 years

- VT (n:47)  VP (n:44)
- VT (n:44)  VP (n:43)

*Four patients in VMP and VTP arms progressed under induction therapy and two and three patients in VMP and VTP arms, respectively, progressed just before the initiation of maintenance phase.
Figure 3

3A  PFS

Proportion of pts

0.0 0.2 0.4 0.6 0.8 1.0

Time in months

VT: 39 m
VP: 32 m

p=0.1

3B  OS

Proportion of pts

0.0 0.2 0.4 0.6 0.8 1.0

Time in months

VT: Not reached
VP: 60m

p=0.1

5-y OS: 69%
Figure 4

4A  PFS

- CR
- nCR
- PR

P = 0.0001; HR: 1.73; 95% CI: 1.4-2.1)

4B  OS

- CR
- PR
- nCR

P < 0.0001; HR: 1.5; 95% CI: 1.2-1.9)
Figure 5

5A: PFS
- VT: 28 m
- VP: 27 m
- p=0.2

5B: OS
- VT: 4-y OS: 55%
- VP: 4-y OS: 53%
- p=0.6

5C: PFS
- VT: 47 m
- VP: 36 m
- p=0.1

5D: OS
- VT: 4-y OS: 79%
- VP: 4-y OS: 69%
- p=0.1
Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial

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