CLINICAL TRIALS AND OBSERVATIONS

# Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in elderly multiple myeloma patients included in the GEM2005MAS65 trial

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Maintenance therapy has become a hot field in myeloma, and it may be particularly relevant in elderly patients because 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 myeloma patients who had received 6 induction cycles with bortezomib plus either melphalan and prednisone or thalidomide and prednisone. The complete response (CR) rate increased from 24% after induction up to 42%, higher for VT versus VP (46% vs 39%). Median progression-free survival (PFS) was superior for VT (39 months) compared with VP (32 months) and overall survival (OS) was also longer in VT patients compared with VP (5-year OS of 69% and 50%, respectively) but the differences did not reach statistical significance. CR achievement was associated with a significantly longer PFS ($P < .001$) and 5-year OS ($P < .001$). 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 in a significant increase in CR rate, remarkably long PFS, and acceptable toxicity profile. The trial is registered at www.clinicaltrials.gov as NCT00443235. (*Blood*. 2012;120(13): 2581-2588)

## 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 to 3 years.[1-3]

The introduction of novel agents thalidomide (Thal), bortezomib (V), and lenalidomide (R) for the treatment of elderly MM patients has significantly increased the CR rate, and this translated into prolonged time to 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 hematologic malignancies would also be applicable to MM and particularly to elderly patients because (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.[4]

Concerning Thal, 6 randomized trials have compared MP and Thal (MPT) with MP,[5-10] and in 3 of them Thal was also used as maintenance therapy until disease progression.[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.[11] Thal plus interferon led to a significantly longer PFS compared with interferon alone (27.7 months vs 12.2 months, $P = .0068$) without benefit in OS. In the Myeloma Research Council (MRC) Myeloma IX study, Thal maintenance versus observation was compared after 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, $P = .014$) with no differences in OS.[12]

| Induction | VMP | VTP |
|---|---|---|
| One 6-week | **Bortezomib** 1.3 mg/m$^2$ twice weekly (days 1, 4, 8, 11; 22, 25, 29, 32) **Melphalan** 9 mg/m$^2$ days 1-4 **Prednisone** 60 mg/ m$^2$ days 1-4 | **Bortezomib** 1.3 mg/m$^2$ twice weekly (days 1, 4, 8, 11; 22, 25, 29, 32) **Thalidomide** 100 mg daily **Prednisone** 60 mg/ m$^2$ days 1-4 |
| | ⇓ | ⇓ |
| Five 5-week | **Bortezomib** 1.3 mg/m$^2$ once weekly (days 1, 8, 15, 22) **Melphalan** 9 mg/m$^2$ days 1-4 **Prednisone** 60 mg/ m$^2$ days 1-4 | **Bortezomib** 1.3 mg/m$^2$ twice weekly (days 1, 8, 15, 22) **Thalidomide** 100 mg daily **Prednisone** 60 mg/ m$^2$ days 1-4 |
| | **VP** | **VT** |
| Maintenance (up to 3 years) | **Bortezomib** 1.3 mg/m$^2$ twice weekly (days 1, 4, 8, 11) every 3 months **Prednisone** 50 mg every 48 hours | **Bortezomib** 1.3 mg/m$^2$ twice weekly (days 1, 4, 8, 11) every 3 months **Thalidomide** 50 mg daily |

**Figure 1. Schedule of induction and maintenance therapy.** V indicates bortezomib; T, thalidomide; M, melphalan; and P, prednisone.

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 versus MPR (9 induction cycles) followed by placebo versus MP (9 induction cycles) followed by placebo. The continuous use of lenalidomide, MPR-R, resulted in a significantly longer PFS, 31 months versus 14 months and 13 months for the MPR and MP arms, respectively ($P < .001$), but so far no differences in OS are detected.[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%, $P = .0008$) but as yet, no differences in OS have been observed.[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.[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 6 cycles of induction therapy with VMP or VTP followed by maintenance with bortezomib plus thalidomide (VT) or bortezomib plus prednisone (VP).[16] The design and objectives of this trial were based on data derived from the pilot study conducted by the 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 a 30% CR 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 2 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). Because 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 than 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).

## 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. 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 2-stage randomized trial as previously described.[16] VMP induction therapy consisted of 6 cycles: 1 cycle of intravenous bortezomib given twice per week for 6 weeks (1.3 mg/m$^2$ on days 1, 4, 8, 11, 22, 25, 29, and 32) plus oral melphalan 9 mg/m$^2$ and prednisone 60 mg/m$^2$ on days 1-4, followed by 5 cycles of bortezomib once per week for 5 weeks (1.3 mg/m$^2$ 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 6 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/m$^2$ 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]

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

| | VT, n = 91 | VP, n = 87 | P |
|---|---|---|---|
| Age, y | 71 (66-82) | 72 (65-84) | NS |
| Male, % | 53 | 47 | |
| IgG/IgA/light chain, % | 62/28/9 | 55/32/12 | NS |
| ISS stage I/II/III, % | 30/41/29 | 28/41/30 | NS |
| Mean creatinine, mg/dL | 1.02 | 1.0 | NS |
| Mean B2 microglobulin, mg/L | 3.7 | 3.8 | NS |
| Mean PCsBM infiltration, % | 38 | 44 | NS |
| **Induction regimen, %** | | | |
| VMP | 52 | 51 | NS |
| VTP | 48 | 49 | NS |
| High-risk [t(4;14), t(14;16), del 17p] cytogenetic by FISH, % | 17 | 15 | NS |

Data are numbers (%) or means.

VT indicates bortezomib plus thalidomide; VP, bortezomib plus prednisone; ISS, International Staging System; PCsBM, plasma cell bone marrow infiltration; VMP, bortezomib plus melphalan and prednisone; VTP, bortezomib plus thalidomide and prednisone; and NS, not significant.

### Statistical analysis

The planned sample size of 260 patients was calculated for a 2-sided $\alpha$ level of 0.05 and a statistical power of 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 because of deaths and toxic effects, and 5% because of progression disease.[16]

Disease response was assessed according to the European Group for Blood and Marrow Transplantation criteria,[19] 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 ORR, CR rate, PFS, and OS of patients with standard-risk versus high-risk CA in each maintenance arm.

The $\chi^2$ and Fisher 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 2-sided

**Table 2. Efficacy in terms of responses rate after maintenance therapy**

| | Premaintenance (%) | VT (%), n = 91 | VP (%), n = 87 | P |
|---|---|---|---|---|
| IF− CR, n (%) | 62 (24) | 42 (46) | 34 (39) | NS |
| IF+ CR, n (%) | 26 (10) | 9 (10) | 10 (11) | NS |
| PR, n (%) | 122 (47) | 36 (39) | 41 (47) | NS |
| MR, n (%) | 21 (8) | 3 (3) | 1 (1) | NS |
| SD, n (%) | 25 (10) | 1 (1) | 1 (1) | NS |

Data are number with percentages (%).

VT indicates 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; and NS, not significant.

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).

## Results

### Efficacy in terms of response 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 260 patients included in the trial, 178 patients were randomized to receive maintenance and were evaluable for response. The reasons for early discontinuations during induction are represented in 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 partial response (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 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.
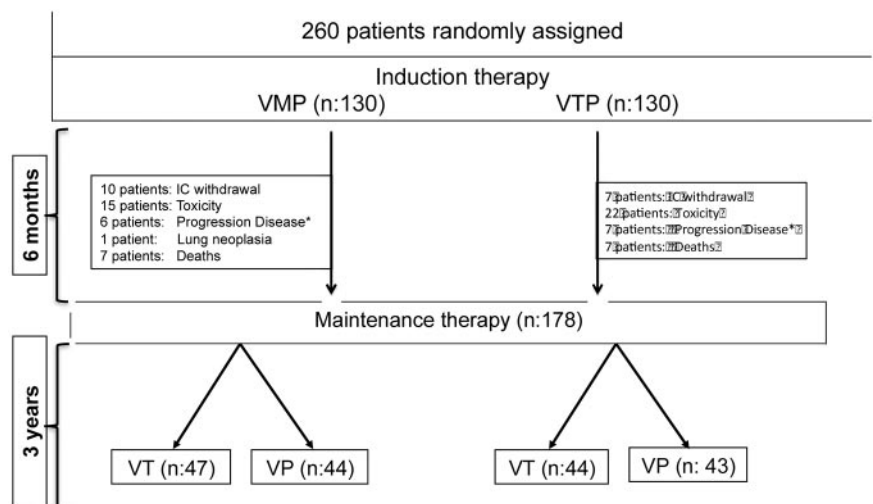


**Figure 2. Trial profile.** V indicates bortezomib; M, melphalan; P, prednisone; and T, thalidomide. Four patients in each of the VMP and VTP arms progressed under induction therapy, and 2 patients in the VMP group and 3 in the VTP group progressed just before to start the maintenance phase.
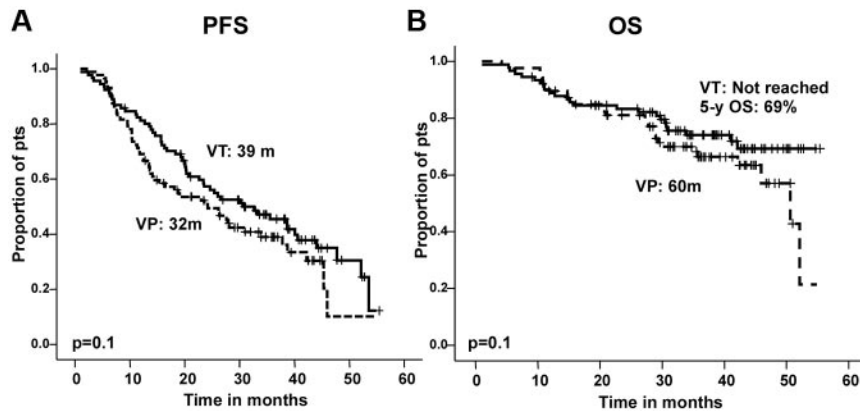
**Figure 3. PFS and OS were superior for patients randomized to VT compared with VP.** (A) Progression-free survival and (B) overall survival by maintenance therapy. VT indicates bortezomib plus thalidomide; VP, bortezomib plus prednisone; and NR, not reached.

### 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-year OS of 58% (95% CI, 51-67).

Median PFS was superior for patients randomized to VT (39 months [95% CI, 27-51]) compared with patients who received VP (32 months [95% CI, 24-41]), although this difference was not significant ($P = .1$; Figure 3A).

Concerning OS, this was also slightly longer in patients maintained with VT compared with VP (5-year OS of 69% [95% CI, 51-79] and 50% [95% CI, 46-54], respectively) but the differences did not reach statistical significance ($P = .1$; Figure 3B).

A stratified Cox regression analysis of PFS and OS with inverse probability weighting, appropriate for 2-stage randomization designs as a sensitivity analysis was conducted, showing a $P$ value of .8 for the interaction term, indicating that induction with VMP or VTP did not influence the PFS and OS observed with maintenance regimens (supplemental Figure 1A-B, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article).

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) compared with nCR patients (median of 39 months) and PR patients (median of 24 months; $P < .0001$; HR, 1.73; 95% CI, 1.4-2.1), and this translated into a significantly higher 5-year OS (78% for IF$^-$ CR patients vs 59% nCR [IF$^+$ CR] vs 54% for PR; $P < .0001$; HR, 1.5; 95% CI, 1-2-1.9; Figure 4). Moreover, the improvement of the depth of response during maintenance therapy with VT or VP also resulted in a better outcome compared with those patients in whom the response was only maintained. Median PFS was 47 months for patients who improved their response versus 32 months for those who only maintained their response ($P = .02$; HR, 0.56; 95% CI, 0.3-0.9) and 5-year OS was 81% and 54% for patients who improved and maintained the quality of response, respectively ($P = .02$; 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 (89%) of the 178 patients randomized to receive maintenance therapy. Twenty-eight of these 160 patients qualified as high risk (18%); 13 (8%) of them 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 1 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; Table 3).

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; $P = .6$), and this also translated into similar 4-year OS (55% and 53% for VT and VP, respectively; $P = .2$). In the standard-risk subgroup, the median PFS was slightly higher in the VT arm (47 months) compared with VP (36 months), with 4-year OS of 79% for VT and 69% for VP, but these differences did not reach statistical significance ($P = .1$ for both PFS and OS; Figure 5). Moreover, these data illustrate that none of the maintenance regimens overcome the adverse prognosis of cytogenetic abnormalities because high-risk patients had a significantly shorter PFS and OS compared with those with standard risk.

### Toxicity

Hematologic toxicity was similar in both arms, with only 1 patient showing grade 3-4 neutropenia (VT arm). Concerning nonhematologic toxicity, patients receiving VT developed a higher frequency of grade 3-4 adverse events (AEs) compared with VP patients (17% vs 5%, $P = .009$). In the VT arm, the grade 3-4 AEs included:

**Table 3. Best response during maintenance therapy according to cytogenetic abnormalities**

| | Standard risk, %, n = 111 | | High risk, %, n = 28 | | |
|---|---|---|---|---|---|
| | **VT** | **VP** | **VT** | **VP** | ***P*** |
| IF$^-$ CR | 48 | 41 | 47 | 39 | NS |
| IF$^+$ CR | 10 | 11 | 7 | 8 | NS |
| PR | 37 | 45 | 40 | 54 | NS |
| MR | 3 | 2 | 7 | | NS |

Data are percentages.

VT indicates 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; and NS, not significant.
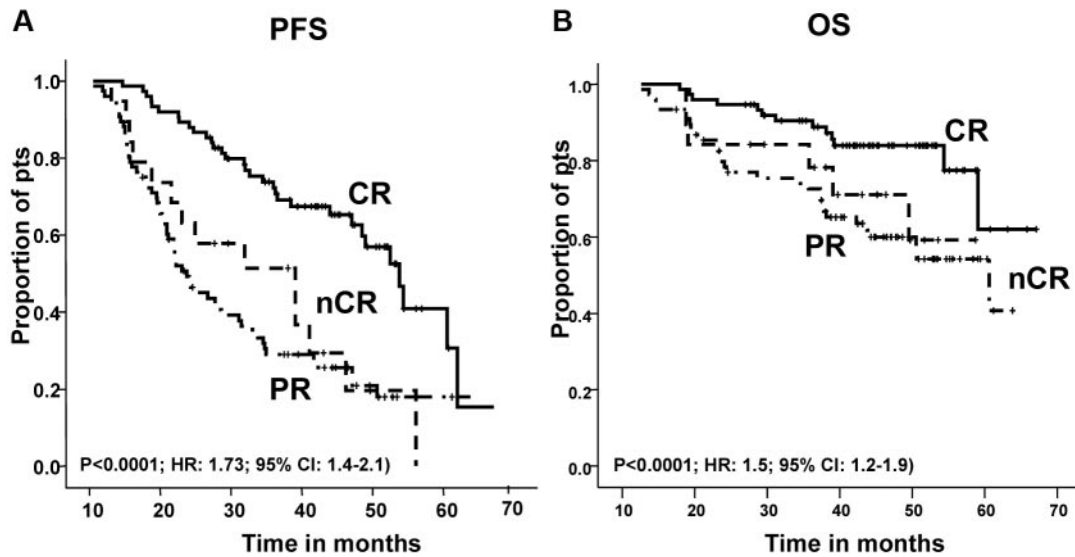
**Figure 4. CR achievement was associated with a significantly longer PFS and OS.** (A) Progression-free survival and (B) overall survival according to the type of response achieved. CR indicates immunofixation-negative complete response; nCR, immunofixation-positive complete response; and PR, partial response.

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.

Fifty-two 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 of disease (32 patients [35%] and 40 patients [46%] in VT and VP arms, respectively). Toxicity was the cause for discontinuation in 12 VT
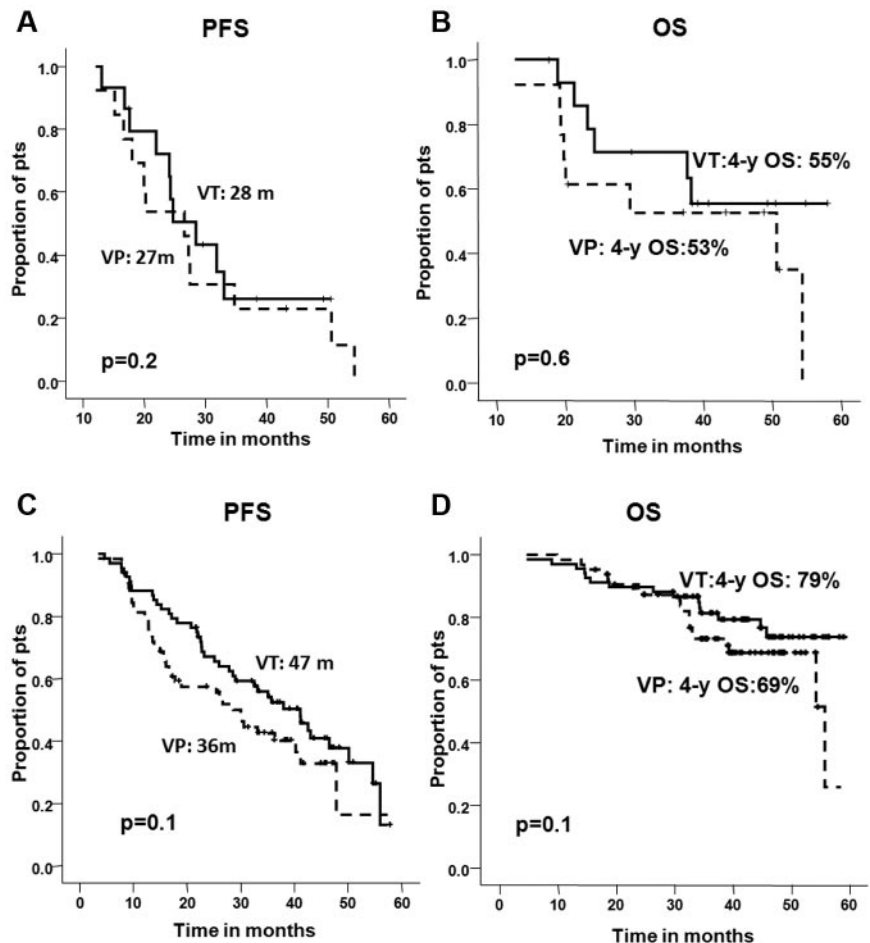


**Figure 5. The type of maintenance therapy did not influence the outcome in either high-risk patients or standard-risk patients.** Progression-free survival and overall survival in (A-B) high-risk and (C-D) standard-risk cytogenetic abnormalities by maintenance arm. VT indicates bortezomib plus thalidomide; VP, bortezomib plus prednisone; and NR, not reached.

patients (13%) and in 8 VP patients (9%), being PN and cardiac events the AEs leading to discontinuation. Two patients in VT (2%) and 2 patients in VP (2%) discontinued because of 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.

Twenty-four patients (26%) and 30 patients (35%) died during maintenance therapy in the VT and VP arms, respectively. Disease progression was the reason for death in 19 and 26 patients in VT and VP, respectively; development of AEs was the reason 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, 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 because 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 in a significant increase of the IF⁻ CR rate (42%) and a remarkably long PFS (35 months) with an acceptable toxicity profile.

The experience with bortezomib as maintenance therapy is limited. In the transplantation 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 high-dose therapy and autologous stem cell transplantation (HDT-ASCT). The results show a significant prolongation in PFS compared with 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; $P$ = .02).[20] In the elderly population, the GIMEMA group reported that a 4-drug combination as induction, VMPT, plus VT as maintenance, results in a significant benefit in PFS compared with VMP without maintenance (3-year PFS of 56% vs 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 because 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 because the previous experience

with both drugs, administered as single agents or combined, did not 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 compared with patients with only nCR or PR, as has been previously reported in the elderly patients population.[23] Moreover, those patients able to upgrade their response with the maintenance therapy also had better outcome compared with those in which response is only maintained.

On comparing VT versus VP maintenance, results argue in favor of VT because improvement of response seems to be slightly superior 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 posttransplantation trials, which have shown that thalidomide is superior to prednisolone.[21] However, considering toxicity, the frequency of AEs was significantly higher in the VT arm, and special caution should be paid to the cardiac events. Accordingly, a full cardiologic work-up should be recommended before starting treatment with thalidomide, especially in elderly patients. Concerning grade 3-4 PN, the frequency was 9% and 3% in the 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 1 patient in the 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 patents, 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— 1 conventional cycle every 3 months, together with low doses of continuous thalidomide or prednisone, result feasibly.

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 is 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 not 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 1 course of bortezomib every 3 months is

suboptimal to overcome the adverse prognosis of high-risk cytogenetic and more frequent exposure would be needed, such a possibility needs to be proven.

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 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.

## Authorship

Contribution: M.-V.M., J.-J.L., J. Bladé, and J.F.S.-M. served as principal investigators and were involved in the original idea and design of the study; M.-V.M. and J.F.S.-M. wrote the protocol and report, and analyzed and interpreted data; and M.-V.M., A.O., N.G., J.M.-L., A.-I.T., A.L.d.l.G., J.L., E.B., M. Pérez, M. Polo, L.P., F.d.A., Y.G., J.-M.H., M.G., J.-L.B., J. Bargay, F.-J.P., J.-M.R., M.-L.M.-M., R.G-S., J.-J.L., J. Bargay, and J.F.S.-M. have contributed with the inclusion of patients.

Conflict-of-interest disclosure: M.-V.M. has served on speaker's bureaus for Millennium, Celgene, and Janssen. A.O., J.M.-L., N.G., L.P., F.d.A., J.-M.H., and J.-J.L. have received honoraria from Celgene and Janssen. R.G.-S. has received honoraria from Ortho-Biotech and Celgene. J. Bladé has received honoraria from and served on advisory boards for Janssen and Celgene. J.F.S.-M. has served on speaker's bureaus and advisory boards for Millennium, Janssen, and Celgene. The remaining authors declare no competing financial interests.

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