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**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available http://hdl.handle.net/2318/148811 since 2023-02-11T12:51:53Z

*Published version:*

DOI:10.1200/JCO.2013.52.0023

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03 May 2024

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**This is the author's version of the contribution published as:**

Palumbo A, Bringhen S, Larocca A, Rossi D, Di Raimondo F, Magarotto V, Patriarca F, Levi A, Benevolo G, Vincelli ID, Grasso M, Franceschini L, Gottardi D, Zambello R, Montefusco V, Falcone AP, Omedé P, Marasca R, Morabito F, Mina R, Guglielmelli T, Nozzoli C, Passera R, Gaidano G, Offidani M, Ria R, Petrucci MT, Musto P, Boccadoro M, Cavo M. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. J Clin Oncol. 2014 Mar 1;32(7):634-40. doi: 10.1200/JCO.2013.52.0023. Epub 2014 Jan 21. PMID: 24449241.

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https://doi.org/10.1200/jco.2013.52.0023
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# Bortezomib-Melphalan-Prednisone-Thalidomide Followed by Maintenance with Bortezomib-Thalidomide Compared with Bortezomib-Melphalan-Prednisone for Initial Treatment of Multiple Myeloma: Updated follow-up and Improved Survival

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**Running head: Improved survival with VMPT-VT versus VMP**

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**ABSTRACT**

**Purpose** Bortezomib-melphalan-prednisone (VMP) has improved overall survival in multiple myeloma. This randomized trial compared bortezomib-melphalan-prednisone plus thalidomide induction, followed by bortezomib plus thalidomide maintenance (VMPT-VT) with VMP in patients with newly diagnosed multiple myeloma.

**Methods** We randomly assigned 511 patients, who were not eligible for transplantation, to receive VMPT-VT (nine 5-week cycles of VMPT followed by 2 years of VT maintenance) or VMP (nine 5-week cycles without maintenance). This study is registered at ClinicalTrials.gov, number, NCT01063179.

**Results** In the initial analysis, with a median follow-up of 23 months, VMPT-VT improved complete response rate from 24% to 38% and 3-year progression-free-survival from 41% to 56% compared with VMP. In the current analysis, median follow-up was 54 months. The median progression-free-survival was significantly longer with VMPT-VT (35.3 months) than with VMP (24.8 months; hazard ratio, 0.58; P<0.001). The time-to-next-therapy was 46.6 months in the VMPT-VT group and 27.8 months in the VMP group (hazard ratio 0.52; P<0.001). The 5-year overall survival was greater with VMPT-VT (61%) than with VMP (51%; hazard ratio, 0.70; P=0.01). Survival from relapse was identical in both groups (hazard ratio 0.92; P=0.63). In the VMPT-VT group the most frequent grade 3-4 adverse events included neutropenia (38%), thrombocytopenia (22%), peripheral neuropathy (11%) and cardiologic events (11%). All of these, except for thrombocytopenia, were significantly more frequent in the VMPT-VT patients.

**Conclusion** Bortezomib and thalidomide significantly improved overall survival in multiple myeloma patients not eligible for transplantation.

## INTRODUCTION

Multiple myeloma accounts for approximately 13% of hematologic cancers. The median age at diagnosis is 70 years; 63% of patients are older than 65 years of age.[1,2] In the near future the frequency of myeloma is likely to increase as the population ages. The median overall survival of patients treated with melphalan-prednisone is approximately 32 months. Combination therapy with melphalan-prednisone plus either thalidomide or bortezomib (VMP) is now considered the standard of care for patients who are not eligible for transplantation.[3,4] A large meta-analysis showed that the addition of thalidomide to melphalan-prednisone increased median overall survival by 6.6 months.[3] In a randomized trial the combination VMP increased overall survival by 13.3 months as compared with melphalan-prednisone alone.[5]

In comparison with VMP, the four-drug combination bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide (VMPT-VT) improved complete response rate from 24% to 38% and 3-year progression-free-survival from 41% to 56%.[6] In a meta-analysis of 9 different randomized studies, thalidomide maintenance reduced the risk of progression by 35% (HR 0.65, 95% CI, 0.59-0.72) while lenalidomide by approximately 55% (HR 0.45, 95% CI, 37-54) as compared with placebo, the survival benefit was inconsistent or marginal with both drugs.[7] In a recent study, a median progression-free-survival of 39 months was reported with bortezomib-thalidomide maintenance.[8]

In this phase III, multicenter, randomized study we compared the four-drug combination VMPT followed by VT maintenance with VMP. We present an updated analysis of outcome after a median follow-up of 4 years.

## METHODS

### Patients

The details of this randomized (1:1) phase III study, conducted at 61 centers in Italy from May 2006 to January 2009, have been reported.[6] Briefly, patients with newly diagnosed myeloma, who were not candidates for high-dose therapy plus stem-cell transplantation because of age (≥ 65 years) or coexisting comorbidities, were eligible. The primary endpoint was progression-free survival; secondary endpoints included response rate, time to the first evidence of response, overall survival, and incidence of any grade 3 or higher adverse events. Subgroup analyses were planned for prognostic factors.

Experimental therapy consisted of induction with nine 6-week cycles of oral melphalan at a dose of 9 mg/m$^2$ on days 1 to 4; oral prednisone at a dose of 60 mg/m$^2$ on days 1 to 4; intravenous bortezomib at a dose of 1.3 mg/m$^2$ on days 1, 4, 8, 11, 22, 25, 29, and 32 during cycles 1 to 4 and on days 1, 8, 22, and 29 during cycles 5 to 9; and thalidomide at a dose of 50 mg per day continuously. After the last bortezomib-melphalan-prednisone-thalidomide course, patients received continuous therapy with bortezomib at a dose of 1.3 mg/m$^2$ every 15 days and thalidomide at a dose of 50 mg per day for two years or until progression or relapse. Standard VMP therapy consisted of induction therapy with nine 6-week cycles of bortezomib, melphalan, and prednisone at the same doses previously described, and no planned continuous therapy was delivered. As a consequence of the safety interim analysis the protocol was amended to reduce the incidence of peripheral neuropathy. After the inclusion of the first 139 patients, both VMPT-VT and VMP induction schedules were changed to nine 5-week cycles and bortezomib dose was modified to 1.3 mg/m$^2$ on days 1, 8, 15, and 22 during cycles 1 to 9 (Supplementary Appendix Figure 1). The study was approved by the institutional review board at each of the participating centers. All patients gave written informed consent before entering the study, which was performed in accordance with the Declaration of Helsinki.

### Assessment

Response and progression were assessed after each cycle during induction and then every 6-8 weeks until disease progression. After disease progression was confirmed, patients were followed every 90

days for documentation of subsequent treatment and survival status. Progression-free-survival was calculated from the time of randomization until the date of progression, relapse, death for any cause, or the date the patient was last known to be in remission. Time-to-next-therapy (post-hoc analysis) was calculated from the time of randomization until the date of subsequent myeloma therapy administered at progression or relapse, the date of death for progressive disease, or the date the patient was last known to be in remission. Overall survival was calculated from the time of randomization until the date of death for any cause or the date the patient was last known to be alive. Survival from relapse was calculated from the time of relapse until the date of death for any cause or the date the patient was last known to be alive. The response to treatment was defined using the International Uniform Response Criteria.[9] All adverse events were assessed at each visit and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0).[10]

**Statistical analysis**

Update analysis were performed using data collected through October 15, 2012. All results were evaluated on an intention-to-treat basis as well as within subgroups defined according to baseline characteristics. For univariate analyses, the overall survival and progression-free survival curves were estimated by the Kaplan-Meier method and compared using the log-rank test.[11] The Cox proportional hazard model was used to estimate the hazard ratio values and the 95% Confidence Interval (CI).[12] The univariate analyses were performed for the following covariates: age at diagnosis (≥75 vs. <75 yrs), gender (male vs. female), chemotherapy regimen (VMPT vs. VMP), International Staging System score,[13] cytogenetic profile (high vs. standard risk) [high risk defined as the presence of a t(4;14), t(14,16) or 17p deletion]. The effect of the same covariates on overall survival and progression-free survival was finally assessed by the multivariate Cox model. Time to event was expressed as median with interquartile range (IQR) or 5-year Kaplan-Meier estimate. All reported p-values were two-sided, at the conventional 5% significance level. Data were analyzed as of November, 2012 by IBM SPSS 20.0.0, R 2.15.0 and SAS System for Windows V8. This study is registered at ClnicalTrials.gov, number NCT01063179.

**Role of the funding source**

The study was supported by the Italian Medicines Agency (AIFA). The Agency had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit this manuscript for publication.

**RESULTS**

A total of 511 patients were randomly assigned to receive VMPT-VT (254 patients) or VMP (257 patients) (Fig. 1). Baseline demographics and disease characteristics were previously reported,[6] and are summarized in the Supplementary Appendix Table 1. Baseline characteristics were well balanced between the two treatment arms, the median age was 71 years, and 27% of patients were older than 75 years of age.

The median follow-up on survivor patients was 54 months. Progression or death occurred in 155 patients (61%) in the VMPT-VT group and 206 (80%) in the VMP group. The median progression-free-survival was 35.3 months in the VMPT-VT group and 24.8 months in the VMP group (hazard ratio, 0.58; P<0.001; Fig. 2A). The median time-to-next-therapy was 46.6 months in the VMPT-VT group and 27.8 months in the VMP group (hazard ratio, 0.52; P<0.001; Fig. 2B). In the VMPT-VT group, the median time-to–next-therapy (symptomatic progression) was delayed by approximately 12 months in comparison with the median progression-free-survival (asymptomatic progression).

Death occurred in 82 patients (32%) in the VMPT-VT group and 111 (43%) in the VMP group. In the VMPT-VT group, 16 patients (6%) withdrew consent and no patient was lost to follow-up; in the VMP group, 17 patients (7%) withdrew consent and 8 patients (3%) were lost to follow-up (Fig.

1). VMPT-VT significantly prolonged overall survival (5-year overall survival 61%) as compared with VMP (5-year overall survival 51%; hazard ratio, 0.70; P=0.01; Fig. 2C).
In the VMPT-VT group, 10 patients (4%) received therapy at first relapse with bortezomib, 64 (25%) with thalidomide or lenalidomide, 29 (11%) with conventional chemotherapy, and 2 with radiotherapy (1%). In the VMP group, 28 patients (11%) received therapy at first relapse with bortezomib, 100 (39%) with thalidomide or lenalidomide, 22 (8%) with conventional chemotherapy, and 2 with radiotherapy (1%). In both groups, overall survival from relapse was similar (hazard ratio, 0.92; P=0.63; Fig. 2D).
In multivariate analysis (Supplementary Appendix Table 2), treatment with VMPT-VT (hazard ratio, 0.69, P=0.02), age < 75 years (hazard ratio, 0.58; P=0.002), female gender (hazard ratio, 0.62; P=0.003), and International Staging System stage I/II (hazard ratio, 0.69; P=0.04) were factors associated with significantly longer overall survival.
The most frequent adverse events were hematologic (Table 1). Grade 3 to 4 neutropenia was reported in 96 patients (38%) in the VMPT-VT group, and 71 patients (28%) in the VMP group; grade 3 to 4 thrombocytopenia occurred in 55 patients (22%) and 50 patients (20%), respectively. The most frequent and clinical relevant non-hematologic adverse events included infections (13% and 9%), cardiologic events (11% and 5%), peripheral neuropathy (11% and 5%), with VMPT-VT and VMP, respectively.
During the maintenance phase with VT, the incidence of new or worsened grade 3 to 4 adverse events was low (<5%). Grade 3 to 4 neutropenia was reported in 4 patients (3%), peripheral neuropathy in 6 patients (4%), and cardiologic adverse events in 2 patients (1%).
In the VMPT-VT group, 46 of the 186 patients younger than 75 years (25%) required treatment interruption for adverse events and received 81% of the planned dose intensity of bortezomib and 24 of the 68 patients older than 75 years (35%) discontinued treatment for adverse events and received 58% of the planned dose intensity. In the VMP group, 29 of the 188 patients younger than 75 years (15%) required treatment interruption for adverse events and received 89% of the planned dose intensity of bortezomib and 11 of the 69 patients older than 75 years (16%) discontinued treatment for adverse events and received 80% of the planned dose intensity (Table 3 in the Supplementary Appendix).

## DISCUSSION

This randomized phase III study showed that VMPT-VT, a four-drug induction regimen followed by VT maintenance, was more effective than VMP. In patients with newly diagnosed multiple myeloma who are ineligible for transplantation, VMPT-VT improved progression-free-survival, time-to-next-therapy and overall survival by approximately 1 year. For the first time, the superiority of a new drug combination, VMPT-VT, over the standard of care VMP has been determined.
A large meta-analysis of 1685 individual patient data from 6 randomized studies showed a median overall survival of 32.7 months with melphalan-prednisone and 39.3 months with the addition of thalidomide to melphalan-prednisone.[3,14-20] In the VISTA study, the median overall survival was 56.4 months for patients who received VMP.[4,5] In our study, the median overall survival was 60.6 months with VMP and was 61% at 5 years with VMPT-VT. In younger transplant eligible patients, bortezomib as induction before autologous transplantation induced a 3-year overall survival rate of 81.4%.[21] Similarly, bortezomib as induction and as maintenance after autologous transplantation induced a 5-year overall survival of 61%.[22] The introduction of novel agents questioned the role of autologous transplantation for myeloma patients. Results from the ongoing prospective randomized studies are warranted to draw definitive conclusions.[23]

The achievement of complete response is associated with prolonged overall survival.[24-26] A retrospective analysis of 1175 elderly newly diagnosed multiple myeloma patients demonstrated that the achievement of complete response was an independent predictor of longer overall survival and supports the use of combinational approach to achieve maximal response in elderly patients.[26]

Maintenance therapy can improve outcome and its role has been extensively investigated. A meta-analysis of 2786 patients demonstrated that thalidomide maintenance reduced the risk of progression by 35% and the risk of death by 16% in both young and elderly patients.[7] A phase III trial showed that lenalidomide as induction and as maintenance reduced the risk of progression by 51% in comparison with lenalidomide as induction without maintenance.[27] A phase III study showed that bortezomib as induction and as maintenance reduced the risk of death by 23% in comparison with conventional induction and thalidomide maintenance.[22] In our trial, the 4-drug combination followed by maintenance significantly improved the complete response rate by 14%[6] and the 5-year overall survival by 10% compared with the 3-drug combination without maintenance.

The difference between median progression-free-survival and time-to-next-therapy was approximately one year in the VMPT-VT group and 3 months in the VMP group. We might speculate that the combination of profound tumor reduction and continuous treatment delayed the occurrence of symptomatic disease progression, prolonging the time from biochemical to clinical relapse, i.e. the time from asymptomatic to symptomatic disease,[9] with a significant clinical benefit. Survival from relapse was similar in both groups. A fixed 2-year duration of maintenance does not appear to select more resistant clones. By contrast, continuous treatment until disease progression might increase the risk of resistant relapse.[14-16,27] In our study, the 4-drug combination followed by maintenance improved overall survival. Inconsistent results have been reported with immunomodulatory drugs.[27-30] Whether the survival advantage was mainly related to the presence of the proteasome inhibitor or to the additive value of proteasome inhibitor plus thalidomide remains to be determined.

The multivariate analysis outlined that International Staging System stage I/II and age less than 75 years were independent predictors of longer survival. The intensified VMPT-VT schedule was more effective in good prognosis patients. In incurable diseases, such as multiple myeloma, dose intensification may exert the most pronounced clinical benefit in patients with the most sensitive tumor. These findings are also in line with recent data demonstrating that bortezomib was not able to completely overcome the adverse prognosis of high risk cytogenetic abnormalities.[31,32]

In the VMPT-VT patients older than 75 years of age, a higher frequency of treatment discontinuations was reported. With VMPT-VT, younger patients received 81% of the planned cumulative dose intensity of bortezomib while older patients received only 58% of the planned dose. Appropriate screening of concomitant cardiac, pulmonary, renal, hepatic and neurological functions should be recommended in all patients and specifically in those older than 75 years of age. Advanced age and unrecognized concomitant diseases have probably a significant role in treatment discontinuation in patients with cancer. The presence of concomitant diseases requires lower dose intensity to improve tolerability and optimize efficacy, and three – or even two – drug combinations should be preferred.[33,34]

During induction, the once-weekly schedule of bortezomib was adopted, instead of the conventional twice-weekly schedule. The once-weekly administration significantly reduced the incidence of peripheral neuropathy, from 16% to 3%, without negatively affecting both progression-free-survival and overall survival.[6,35] During maintenance, the twice-monthly schedule of bortezomib and thalidomide at 50 mg/day were very well tolerated, with a discontinuation rate of 13% only. In previous studies, maintenance with thalidomide at 100-400 mg/day determined a discontinuation rate of approximately 40%.[7] During maintenance, toxicities significantly limit long-term treatment. Effective continuous treatment should be associated with a very low discontinuation rate to translate into a significant clinical benefit.

It is necessary to consider the possible limitations of any trial. In our study, the absence of a second randomization after induction made the maintenance versus no maintenance comparison problematic. Nevertheless, the entire VMPT-VT approach clearly induced better progression-free survival and overall survival than VMP. Yet, it remains difficult to dissect whether this superiority should be mainly attributed to the use of a 4-drug combination induction or to the use of a

maintenance treatment. The absence of a prespecified salvage therapy is another limitation. However, treatments at relapse were quite homogeneous between the two groups, thus allowing to better isolate the efficacy of the first-line therapy.

In conclusion, VMPT-VT improves overall survival in comparison with the recently adopted, standard of care VMP. The benefit is mainly evident in patients 65 to 75 years of age. Our findings suggest that the addition of bortezomib and thalidomide to melphalan-prednisone induction and as maintenance therapy is a valuable front-line strategy for fit myeloma patients who are not eligible for transplantation. These data lay the basis for less toxic and more effective combinations of new generation immunomodulatory drugs and proteasome-inhibitors, such as bortezomib-lenalidomide-dexamethasone[36] and carfilzomib-lenalidomide-dexamethasone[37].

**Contributors**

**Conception and design**: Antonio Palumbo and Mario Boccadoro.

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**Conflict of interest statement**

**Employment or leadership position**: None

**Consultancy or advisory role**: Antonio Palumbo, Amgen (C), Bristol-Myers Squibb (C), Celgene (C), Janssen-Cilag (C), Millenium (C), Onyx (C); Sara Bringhen, Onyx (C), Merck Sharp & Dohme (C); Francesco Di Raimondo, Celgene and Janssen-Cilag (C); Roberto Ria, Celgene (C), Janssen-Cilag (C), Novartis (C), Italfarmaco (C); Pellegrino Musto, Celgene (C); Mario Boccadoro, Celgene (C) and Janssen-Cilag (C); Michele Cavo, Janssen-Cilag (C), Celgene (C), Novartis (C), and Millennium Pharmaceuticals (C).

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**Research funding**: Tommasina Guglielmelli, Celgene (C); Pellegrino Musto, Celgene (C), Janssen-Cilag (C);.Mario Boccadoro, Celgene (C) and Janssen-Cilag (C); Michele Cavo, Janssen-Cilag (C), Celgene (C), Novartis (C).

**Acknowledgements**
We thank all the patients who participated in this study, the nurses Elena Ponticelli and Diego Elia, the data managers Angela Jiang and Tiziana Marangon, and the editorial assistant Giorgio Schirripa. This work was funded by the Italian Medicines Agency (AIFA). The funder had no role in the design and conduct of the study, the collection, analysis, and interpretation of the data.

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**Table 1. Adverse Events**

| Events | VMPT-VT Group (N = 250)* | VMP Group (N = 253)* | |
|---|---|---|---|
| | Grade 3 to 4 | Grade 3 to 4 | P-value |

| | | | |
|---|---|---|---|
| Haematologic events | 119 (48%) | 104 (41%) | 0.13 |
| Neutropenia | 96 (38%) | 71 (28%) | 0.01 |
| Thrombocytopenia | 55 (22%) | 50 (20%) | 0.5 |
| Anaemia | 25 (10%) | 25 (10%) | |
| Non-haematologic events | 135 (54) | 84 (33%) | <0.001 |
| Cardiologic events | 28 (11%) | 14 (5%) | 0.02 |
| Myocardial infarction/Angina | 4 | 5 | |
| Arrhythmia | 11 | 2 | |
| Cardiac failure | 7 | 4 | |
| Other | 6 | 3 | |
| Nervous system disorder | 53 (21%) | 39 (15%) | 0.09 |
| Sensory neuropathy | 27 (11%) | 13 (5%) | 0.02 |
| Neuralgia | 9 (4%) | 7 (3%) | |
| Sensory neuropathy and neuralgia | 9 (4%) | 11 (4%) | |
| Ictus | 2 | 2 | |
| Confusion | 2 | 0 | |
| Mood depression | 0 | 2 | |
| Other | 2 | 2 | |
| Infections | 32 (13%) | 23 (9%) | 0.18 |
| Pneumonia | 14 | 6 | |
| Neutropenic fever | 6 | 5 | |
| Viral infection | 3 | 1 | |
| Sepsis | 4 | 5 | |
| Other | 5 | 6 | |
| Gastrointestinal events | 16 (6%) | 21 (8%) | 0.42 |
| Diarrhoea | 4 | 7 | |
| Constipation | 6 | 5 | |
| Nausea/Vomiting | 2 | 3 | |
| Other | 4 | 6 | |
| Vascular events | 13 (5%) | 5 (2%) | 0.05 |
| Deep-vein thrombosis | 8 | 5 | |
| Pulmonary embolism | 4 | 0 | |
| Peripheral edema | 1 | 0 | |
| Systemic events | 16 (6%) | 8 (3%) | 0.09 |
| Fatigue | 15 | 5 | |
| Fever | 1 | 3 | |
| Other conditions | 27 (11%) | 20 (8%) | 0.26 |
| | | | |
| Discontinuations due to adverse events | 70 (28%) | 40 (16%) | 0.001 |

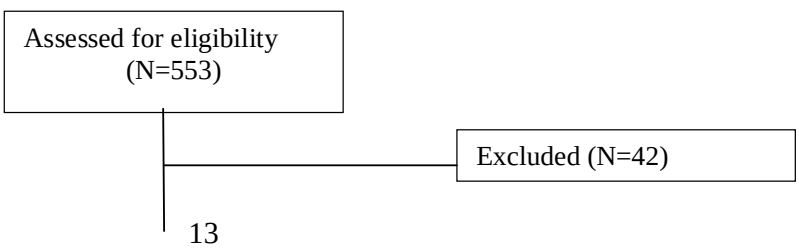
Data are number (%). VMPT-VT,bortezomib, melphalan, prednisone, thalidomide followed by continuous therapy with bortezomib and thalidomide. VMP, bortezomib, melphalan, prednisone * A total of 8 patients, 4 in each study group, could not be evaluated for adverse events because they did not receive a study drug due to withdrawal of consent (3 patients in the VMPT-VT group and 1 in the VMP), progressive disease (1 patient in each group), physician choice (2 patients in the VMP).

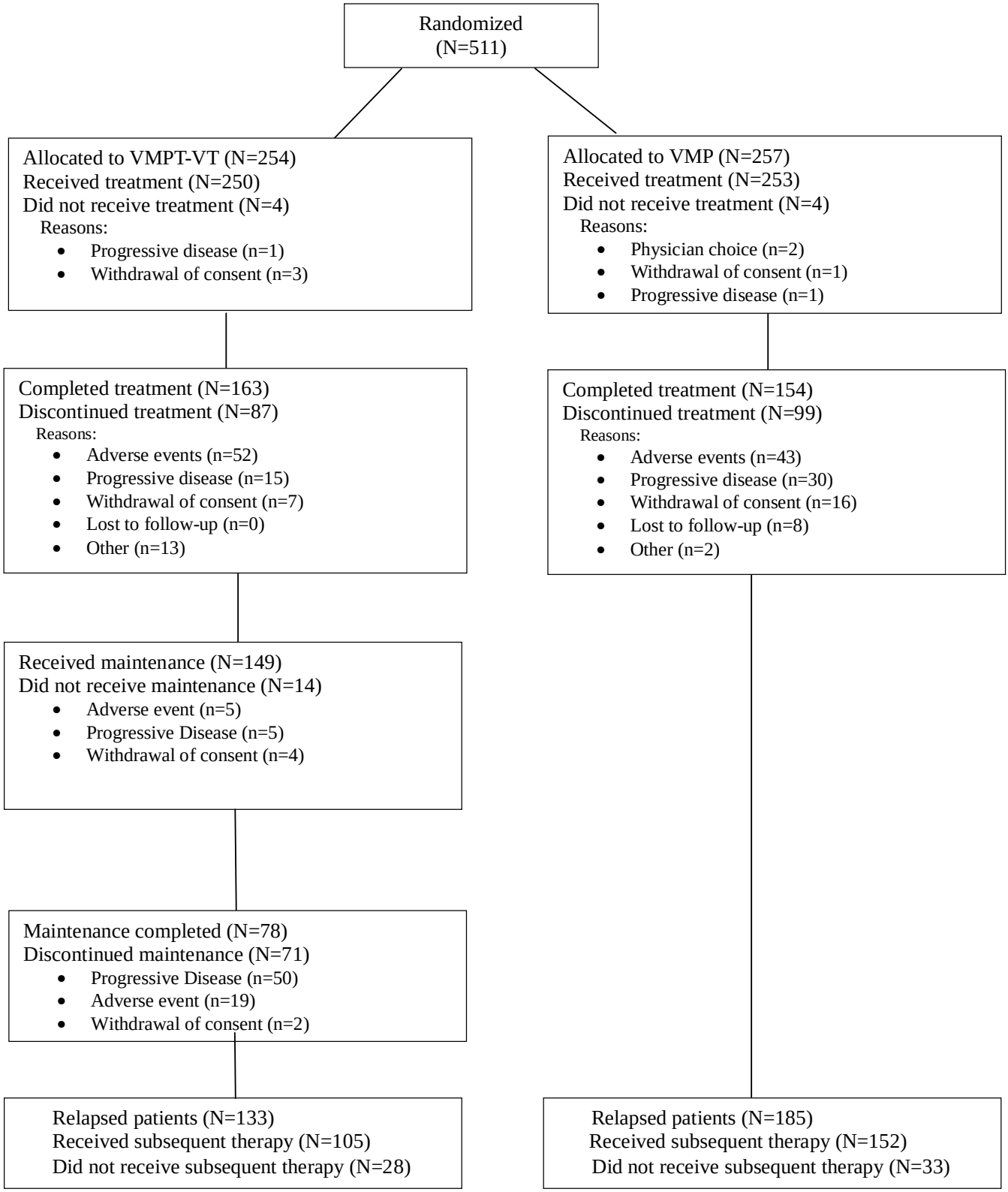
**FIGURE LEGEND**

**Figure 1. Randomization and Follow-up of the Study Patients.** VMP-VT denotes bortezomib-melphalan–prednisone-thalidomide induction followed by bortezomib-thalidomide maintenance, VMP bortezomib-melphalan–prednisone induction without maintenance.

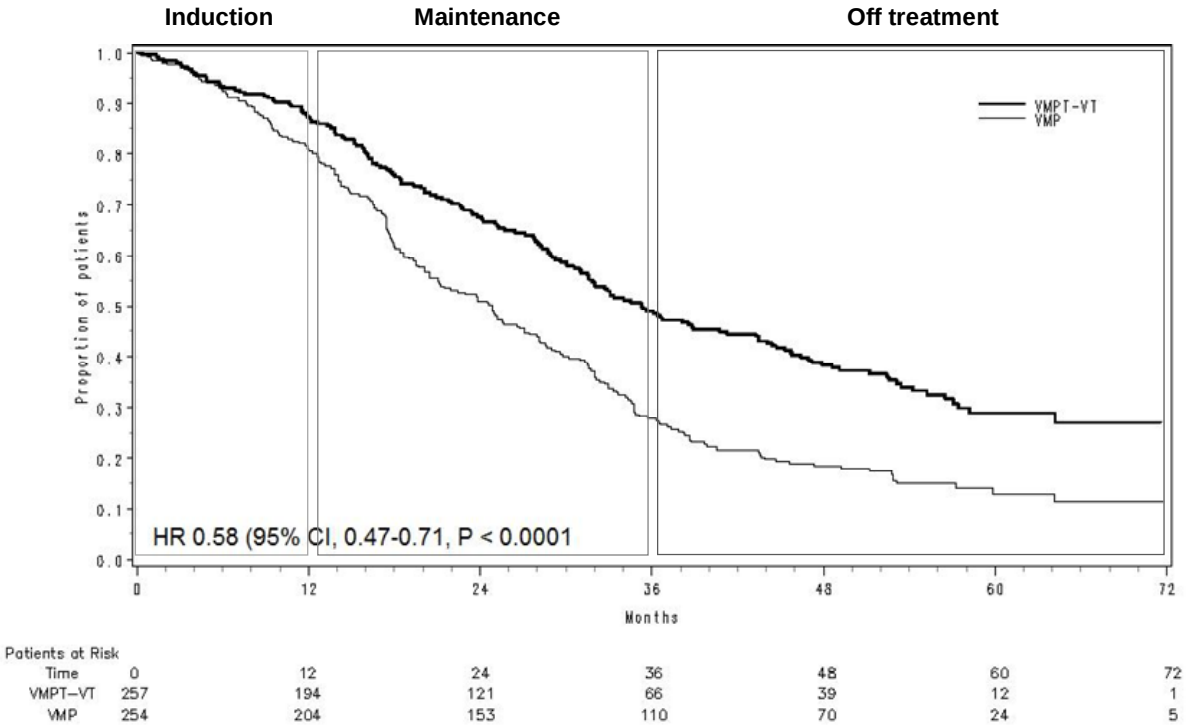
**Figure 2. Survival Outcomes in the Intention-to-Treat Population, According to Study Group.** Panel A shows progression-free-survival. Panel B shows time-to-next-therapy. Panel C shows overall survival. Panel D shows overall survival from relapse. HR, hazard ratio; CI, confidence interval; VMP-VT, bortezomib-melphalan–prednisone-thalidomide induction followed by bortezomib-thalidomide maintenance; VMP, bortezomib-melphalan–prednisone induction without maintenance.

**Figure 1.**




Randomized
(N=511)
Allocated to VMPT-VT (N=254)
Received treatment (N=250)
Did not receive treatment (N=4)
Reasons:
Progressive disease (n=1)
Withdrawal of consent (n=3)
Allocated to VMP (N=257)
Received treatment (N=253)
Did not receive treatment (N=4)
Reasons:
Physician choice (n=2)
Withdrawal of consent (n=1)
Progressive disease (n=1)
Completed treatment (N=163)
Discontinued treatment (N=87)
Reasons:
Adverse events (n=52)
Progressive disease (n=15)
Withdrawal of consent (n=7)
Lost to follow-up (n=0)
Other (n=13)
Completed treatment (N=154)
Discontinued treatment (N=99)
Reasons:
Adverse events (n=43)
Progressive disease (n=30)
Withdrawal of consent (n=16)
Lost to follow-up (n=8)
Other (n=2)
Received maintenance (N=149)
Did not receive maintenance (N=14)
Adverse event (n=5)
Progressive Disease (n=5)
Withdrawal of consent (n=4)
Maintenance completed (N=78)
Discontinued maintenance (N=71)
Progressive Disease (n=50)
Adverse event (n=19)
Withdrawal of consent (n=2)
Relapsed patients (N=133)
Received subsequent therapy (N=105)
Did not receive subsequent therapy (N=28)
Relapsed patients (N=185)
Received subsequent therapy (N=152)
Did not receive subsequent therapy (N=33)

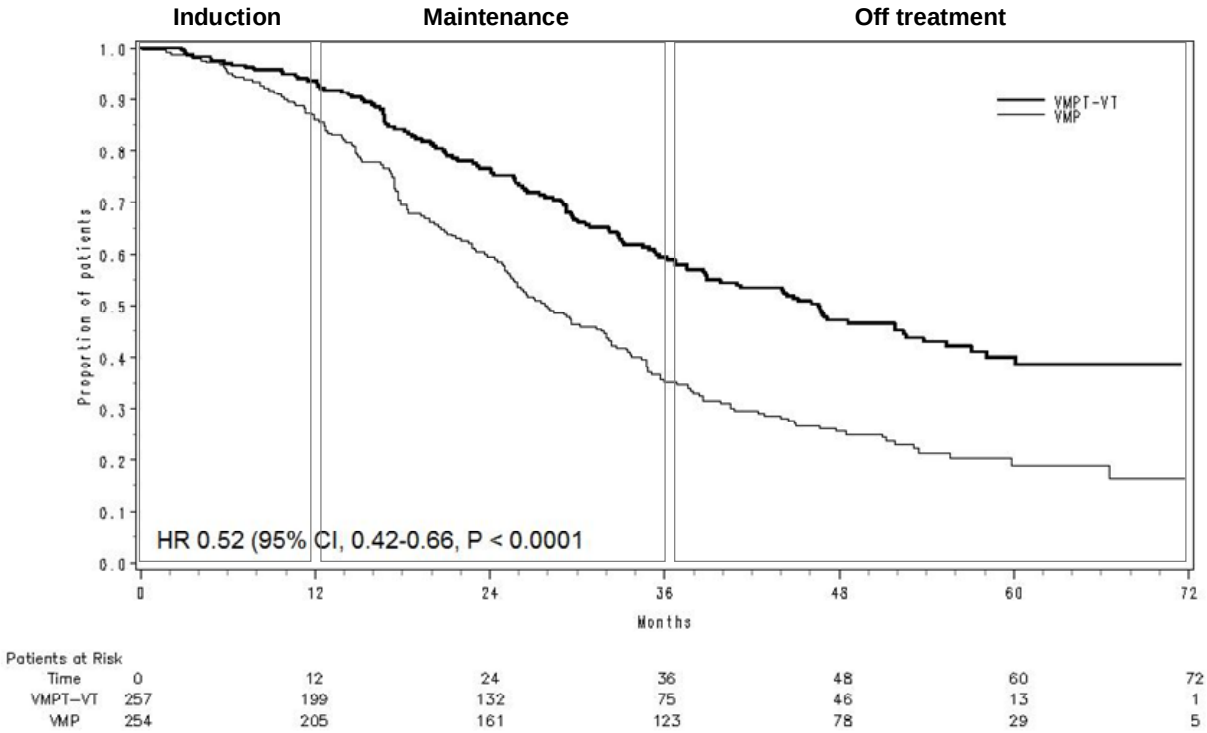
2 A: Progression-free-survival




Patients at Risk

| Time | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|
| VMPT–VT | 257 | 194 | 121 | 66 | 39 | 12 | 1 |
| VMP | 254 | 204 | 153 | 110 | 70 | 24 | 5 |

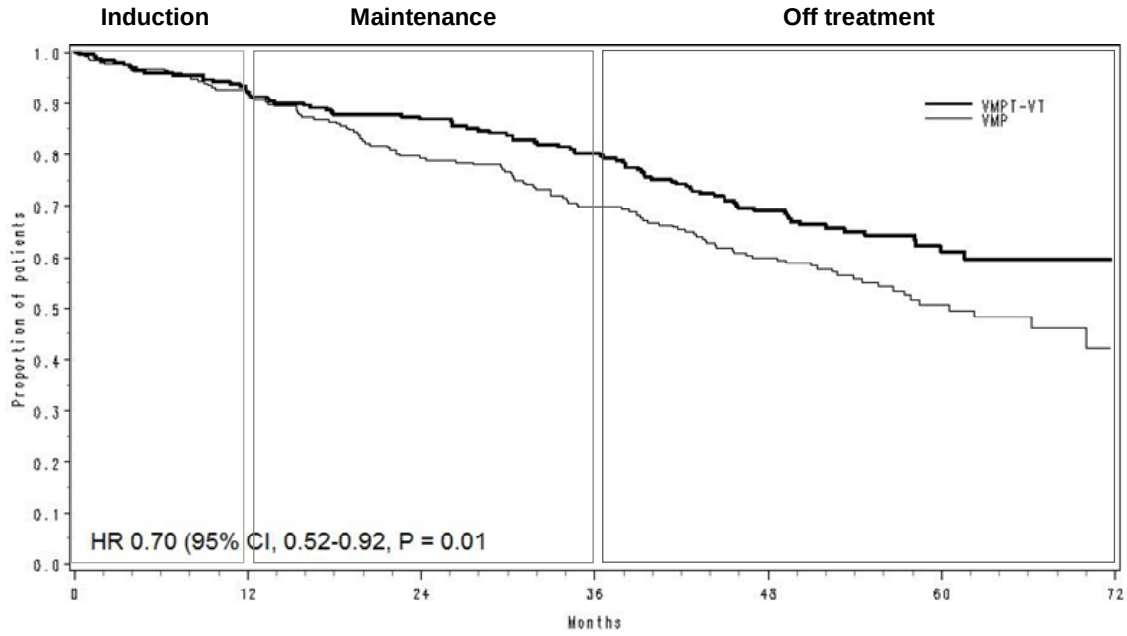
2 B: Time-to-next-therapy




Patients at Risk

| Time | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|
| VMPT–VT | 257 | 199 | 132 | 75 | 46 | 13 | 1 |
| VMP | 254 | 205 | 161 | 123 | 78 | 29 | 5 |

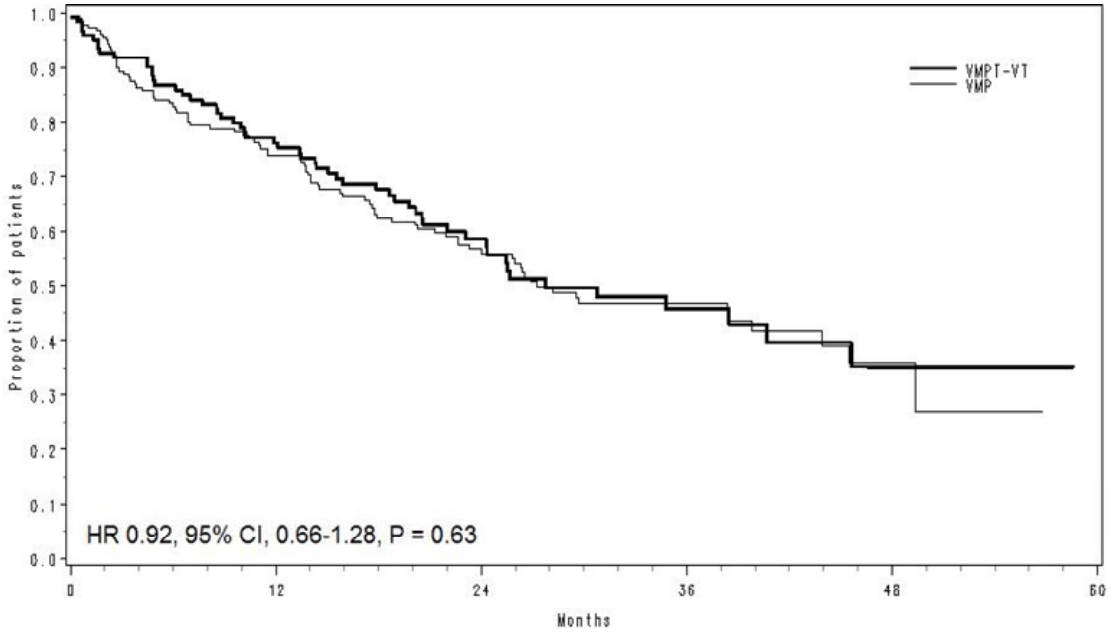
2 C: Overall survival




Patients at Risk

| Time | 0 | 12 | 24 | 36 | 48 | 60 | 72 |
|---|---|---|---|---|---|---|---|
| VMPT–VT | 257 | 221 | 185 | 161 | 120 | 47 | 7 |
| VMP | 254 | 215 | 196 | 178 | 129 | 51 | 9 |

2 D: Overall survival from relapse




Patients at Risk

| Time | 0 | 12 | 24 | 36 | 48 | 60 |
|---|---|---|---|---|---|---|
| VMPT–VT | 180 | 120 | 75 | 34 | 7 | 0 |
| VMP | 123 | 81 | 41 | 20 | 5 | 0 |

## SUPPLEMENTARY APPENDIX

**Table 1 (Appendix). Baseline Characteristics of the Patients**

| Variable | VMPT-VT (N = 254) | VMP (N = 257) |
|---|---|---|
| Age | | |
| Median-years | 71 | 71 |
| IQR-years | 68-75 | 68-75 |
| Subgroup | | |
| < 65 years | 12 (5%) | 6 (2%) |
| 65-74 years | 174 (68%) | 182 (71%) |
| ≥ 75 years | 68 (27%) | 69 (27%) |
| Male sex | 130 (51%) | 122 (47%) |
| Serum $\beta_2$-microglobulin level | | |
| Median-mg/L | 3.8 | 4 |
| IQR-mg/L | 2.7-5.2 | 3.0-5.6 |
| Subgroup | | |
| ≤ 3.5 mg/L | 93 (37%) | 84 (33%) |
| > 3.5 mg/L | 118 (46%) | 125 (49%) |
| Data missing | 43 (17%) | 48 (18%) |
| Albumin level | | |
| Median-g/L | 37.9 | 37.5 |
| IQR-g/L | 33.1-41.0 | 33.7-41.0 |
| Data missing | 32 (12.5%) | 34 (13%) |
| International Staging System stage | | |
| I | 59 (23%) | 56 (22%) |
| II | 100 (39%) | 88 (34%) |
| III | 47 (19%) | 57 (22%) |
| Data missing | 48 (19%) | 56 (22%) |
| Creatinine clearance (calculated) | | |
| < 30 ml/min | 21 (8%) | 24 (9%) |
| 30-60 ml/min | 147 (58%) | 160 (62%) |
| > 60 ml/min | 86 (34%) | 73 (28%) |
| LDH level | | |
| Median-UI/L | 277 | 293 |
| IQR -UI/L | 193-355 | 203-368 |
| Data missing | 51 (20%) | 36 (14%) |
| Chromosome abnormalities | | |
| Del 13 | 101/192 (53%) | 86/184 (47%) |
| t(4;14) | 33/192 (17%) | 26/184 (14%) |
| t(11;14) | 31/192 (16%) | 20/184 (11%) |
| t(14;16) | 9/192 (5%) | 6/184 (3%) |
| Del17 | 32/192 (17%) | 23/184 (13%) |
| Bortezomib schedule | | |
| Twice-weekly | 73 (29%) | 66 (26%) |
| Once-weekly | 181 (71%) | 191 (74%) |

VMPT-VT,bortezomib, melphalan, prednisone, thalidomide followed by continuous therapy with bortezomib and thalidomide. VMP, bortezomib, melphalan, prednisone. IQR, interquartile range

**Table 2 (Appendix). Multivariate analysis of variables favourably affecting overall survival**

| Variable | HR | 95% CI | P value |
|---|---|---|---|
| Randomization to VMPT-VT | 0.69 | 0.50-0.94 | 0.02 |
| Age < 75 years | 0.58 | 0.41-0.83 | 0.002 |
| Female gender | 0.62 | 0.45-0.86 | 0.003 |
| ISS 1-2 | 0.69 | 0.49-0.98 | 0.04 |

HR, hazard ratio; CI, confidence interval; VMPT-VT, bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide; ISS, International Staging System.

**Table 3 (Appendix). Cumulative doses and drug-discontinuation according to age**

| | VMPT-VT | | VMP | |
|---|---|---|---|---|
| | Age < 75 years (N=186) | Age ≥ 75 years (N=68) | Age < 75 years (N=188) | Age ≥ 75 years (N=69) |
| **Total** | | | | |
| Discontinuation due to adverse events – n (%) | 46 (25) | 24 (35) | 29 (15) | 11 (16) |
| Treatment duration - median, months (IQR) | 24 (12-36) | 11 (4-22) | 12 (7-12) | 12 (8-12) |
| Bortezomib dose intensity - %<br>Cumulative dose - median, mg/m$^2$ (IQR) | 81<br>88.5 (59.4-106.3) | 58<br>63.7 (52.9-93.8) | 89<br>41.6 (22.5-46.8) | 80<br>37.3 (25.7-42.9) |
| **Induction** | | | | |
| Discontinuation due to adverse events – n (%) | 31 (17) | 20 (29) | 29 (15) | 11 (16) |
| Treatment duration - median, months (IQR) | 12 (11-12) | 11 (4-12) | 12 (7-12) | 12 (8-12) |
| Bortezomib dose intensity - %<br>Cumulative dose - median, mg/m$^2$ (IQR) | 89<br>41.6 (27.9-46.8) | 63<br>29.7 (14.7-42.5) | 89<br>41.6 (22.5-46.8) | 80<br>37.3 (25.7-42.9) |
| **Maintenance** | | | | |
| Discontinuation due to adverse events – n (%)* | 15 (12) | 4 (14) | - | - |
| Treatment duration - median, months (IQR) | 24 (13-24) | 15 (4-24) | - | - |
| Bortezomib dose intensity - %<br>Cumulative dose - median, mg/m$^2$ (IQR) | 77<br>48.0 (25.2-62.4) | 49<br>30.5 (7.2-54.7) | - | - |

* Rate calculated on 120 patients younger than 75 years and 29 patients older than 75 years who started maintenance; IQR, interquartile range; VMPT-VT, bortezomib, melphalan, prednisone, thalidomide followed by maintenance with bortezomib and thalidomide; VMP, bortezomib, melphalan, prednisone; IQR, interquartile range

**FIGURE LEGEND (SUPPLEMENTARY APPENDIX)**

**Figure 1. Schedule of induction and maintenance treatment.** VMP denotes bortezomib-melphalan–prednisone induction without maintenance, VMPT-VT bortezomib-melphalan–prednisone-thalidomide induction followed by bortezomib-thalidomide maintenance.

Figure 1 (Appendix) Treatment schedule