

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: San Miguel JF, Schlag R, Khuageva NK, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359:906-17.

## Supplementary Appendix

### **Bortezomib Plus Melphalan-Prednisone Versus Melphalan-Prednisone in Untreated Multiple Myeloma Patients Ineligible for Stem Cell Transplantation**

Jesús F. San Miguel<sup>1</sup>, Rudolf Schlag<sup>2</sup>, Nuriet K. Khuageva<sup>3</sup>, Meletios A. Dimopoulos<sup>4</sup>, Ofer Shpilberg<sup>5</sup>, Martin Kropff<sup>6</sup>, Ivan Spicka<sup>7</sup>, Maria T. Petrucci<sup>8</sup>, Antonio Palumbo<sup>9</sup>, Olga S. Samoilova<sup>10</sup>, Anna Dmoszynska<sup>11</sup>, Kudrat M. Abdulkadyrov<sup>12</sup>, Rik Schots<sup>13</sup>, Bin Jiang<sup>14</sup>, Maria-Victoria Mateos<sup>1</sup>, Kenneth C. Anderson<sup>15</sup>, Dixie L. Esseltine<sup>16</sup>, Kevin Liu<sup>17</sup>, Andrew Cakana<sup>18</sup>, Helgi van de Velde<sup>18</sup>, Paul G. Richardson<sup>15</sup>, for the VISTA-MMY-3002 study investigators\*

<sup>1</sup>Hospital Universitario Salamanca, CIC, IBMCC (USAL-CSIC), Spain; <sup>2</sup>Praxisklinik Dr. Schlag, Würzburg, Germany; <sup>3</sup>SP Botkin Moscow City Clinical Hospital, Russian Federation; <sup>4</sup>University of Athens School of Medicine, Greece; <sup>5</sup>Rabin Medical Center, Petah-Tiqva, Israel; <sup>6</sup>University of Münster, Germany; <sup>7</sup>University Hospital, Prague, Czech Republic; <sup>8</sup>University La Sapienza, Rome, Italy; <sup>9</sup>Universita di Torino, Italy; <sup>10</sup>Nizhnii Novgorod Region Clinical Hospital, Russian Federation; <sup>11</sup>Medical University of Lublin, Poland; <sup>12</sup>St Petersburg Clinical Research Institute of Hematology & Transfusiology, Russian Federation; <sup>13</sup>Myeloma Study Group Belgian Hematological Society, Belgium; <sup>14</sup>People's Hospital, Peking University, China; <sup>15</sup>Dana-Farber Cancer Institute, Boston, USA; <sup>16</sup>Millennium Pharmaceuticals, Inc, Cambridge, USA; <sup>17</sup>Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, USA; <sup>18</sup>Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium

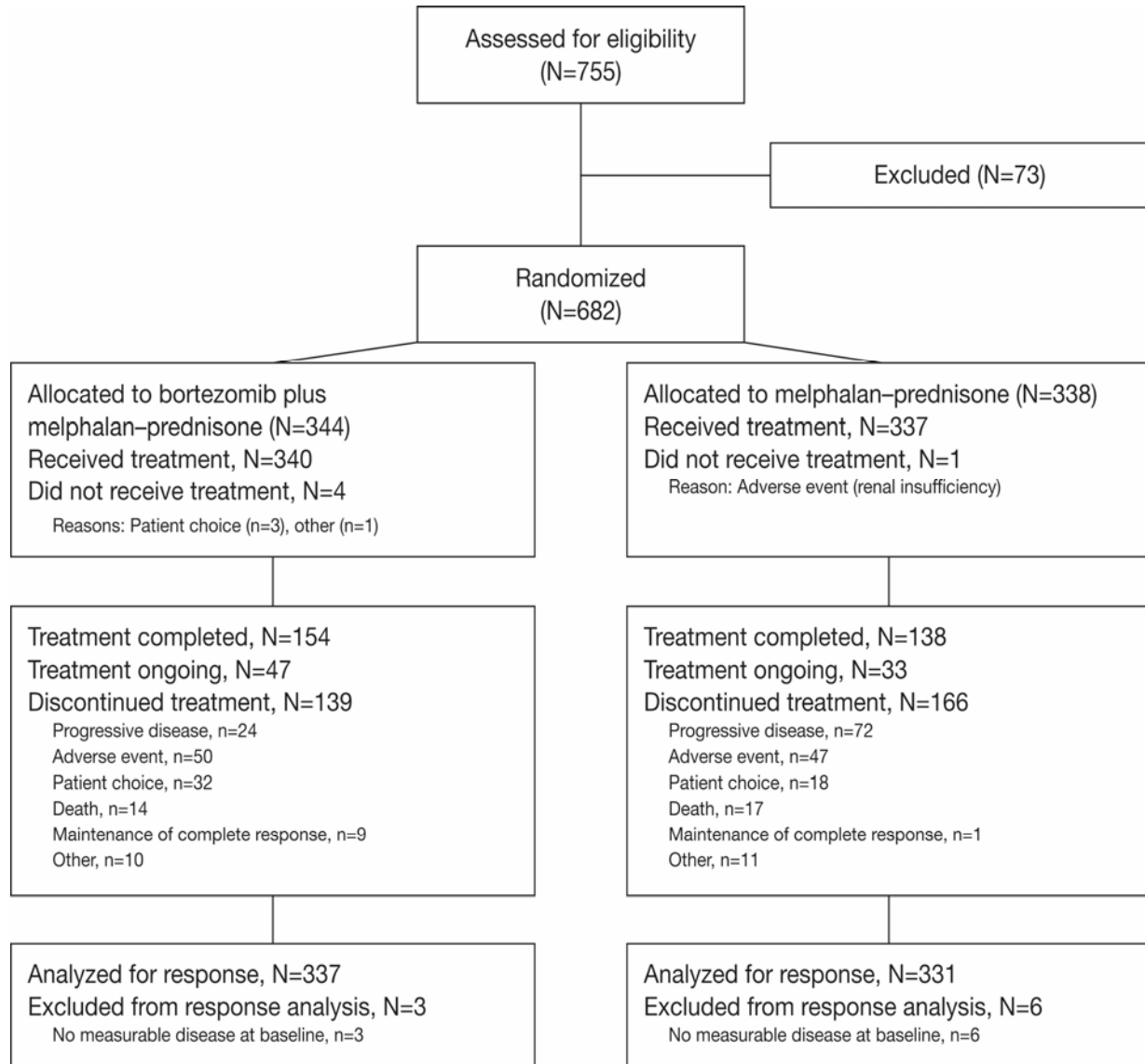
\*Other VISTA investigators are listed in the Appendix

## SUPPLEMENTARY APPENDIX

	Page
Part I – Patient Disposition	2
Part II – Additional Secondary End Points	3–6
Part III – Time-to-progression and Overall Survival with Bortezomib plus Melphalan–Prednisone in Patient Subgroups	7–8

## Supplementary Appendix Part I – Patient Disposition

Figure 1. CONSORT diagram



## **Supplementary Appendix Part II – Additional Secondary End Points**

### ***Assessments and Statistical Analysis***

Additional secondary efficacy end points included progression-free survival, complete plus partial response rate by EBMT criteria, complete response rate by EBMT criteria, time to first response, and time to subsequent myeloma therapy. A further secondary end point was patient-reported outcomes, including global health status as measured by the European Organization for the Research and Treatment of Cancer (EORTC) quality of life (QLQ)-C30 questionnaire. Patient-reported outcomes were to be completed at baseline, on day 1 of each cycle during treatment, at the end-of-study visit, and then every 8 weeks, until disease progression.

Progression-free survival was defined as the time between randomization and either disease progression or relapse from complete response by EBMT criteria, or death due to any cause, whichever occurred first. Time to first response was defined in patients with confirmed response as the time between randomization and the first documentation of response. Time to subsequent myeloma therapy was defined as the time between randomization and the administration of the first dose of the first subsequent anti-myeloma therapy following completion of study treatment. Progression-free survival and time to subsequent myeloma therapy were compared between treatment groups by stratified log-rank test based on the intent-to-treat population (all randomized patients); time to first response was analyzed from randomization and compared between treatment groups by stratified log-rank test based on all responding patients. Distributions were estimated using Kaplan-Meier methodology. Hazard ratios were estimated using the stratified Cox proportional hazards model.

### ***Results***

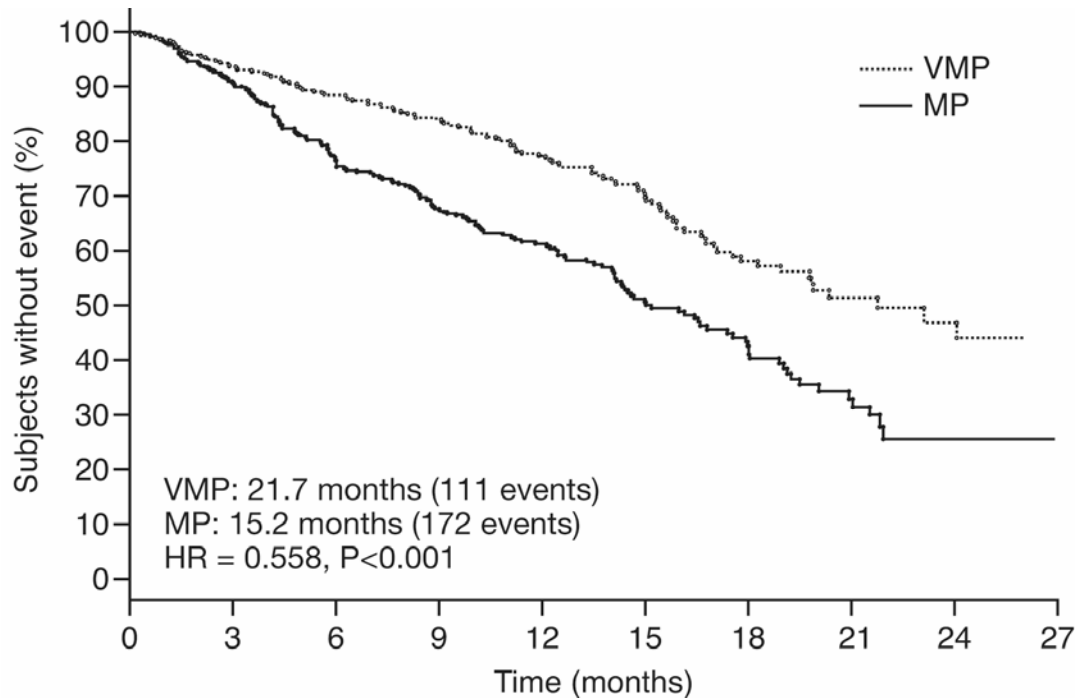
Median progression-free survival was 21.7 months with bortezomib plus melphalan–prednisone and 15.2 months with melphalan–prednisone (hazard ratio, 0.56,  $P<0.001$ ) (Figure 2A). Median time to first response (partial response or better) was 1.4 months with bortezomib plus melphalan–prednisone and 4.2 months with melphalan–prednisone ( $P<0.001$ ); median time to complete response was 4.2 and 5.3 months, respectively ( $P<0.001$ ). Median time to subsequent myeloma therapy was not reached with bortezomib plus melphalan–prednisone and 20.8 months with melphalan–prednisone (hazard ratio, 0.52,  $P<0.001$ ) (Figure 2B), with 36% and 52% of patients, respectively, requiring second-line therapy within 2 years ( $P<0.001$ ); the associated median treatment-free interval was not reached versus 9.4 months, respectively. Among 121 patients in the melphalan–prednisone group who received subsequent therapy, 54 (45%) received treatment that included bortezomib.

No differences were seen in patient-reported global health status over the course of treatment (data not shown).

**Figure 2. Kaplan-Meier Plots of Progression-Free Survival and Time to Subsequent Myeloma Therapy in the Intent-to-treat Populations of the Bortezomib plus Melphalan–Prednisone Group (VMP, N=344) and the Melphalan–Prednisone Group (MP, N=338).**

**Panel A** shows progression-free survival by investigator assessment based on central laboratory data and applying EBMT criteria. **Panel B** shows time to subsequent myeloma therapy; the associated median treatment-free interval was not reached versus 9.4 months ( $P<0.001$ ), respectively. In the melphalan–prednisone group 54 of 121 (45%) patients received bortezomib at relapse.

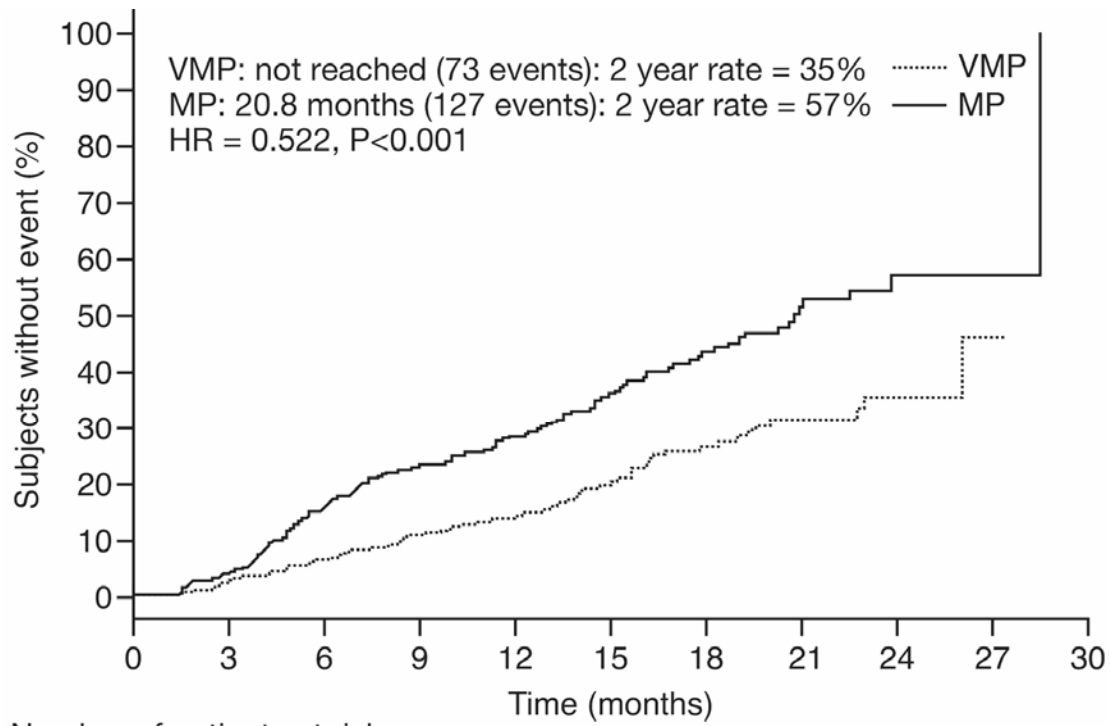
**A**



Number of patients at risk

MP:	338	299	247	212	156	89	56	24	5
VMP:	344	304	282	254	191	116	68	32	17

**B**



Number of patients at risk

MP:	338	309	261	229	178	119	77	38	15	4
VMP:	344	311	285	266	209	142	89	50	26	2

### **Supplementary Appendix Part III – Time-to-progression and Overall Survival with Bortezomib plus Melphalan–Prednisone in Patient Subgroups**

#### **Figure 3. Kaplan-Meier Plots of Time to Disease Progression and Overall Survival in Subgroups of Patients Defined by Age, Creatinine Clearance, and High-Risk Cytogenetics within the Bortezomib plus Melphalan–Prednisone Treatment Group.**

**Panel A** shows time-to-progression and **Panel B** shows overall survival in patients aged 75 years or more (n=107) and aged less than 75 years (n=237). **Panel C** shows time-to-progression and **Panel D** shows overall survival in patients with creatinine clearance of less than 60 mL/min (n=185) and creatinine clearance of 60 mL/min or more (n=159). **Panel E** shows time-to-progression and **Panel F** shows overall survival in patients with high-risk cytogenetics (t(4;14), t(14;16), or 17p deletion; n=26) and with standard-risk cytogenetics (n=142) by fluorescence in situ hybridization.

