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A phase 2 study of three low-dose intensity subcutaneous bortezomib regimens in elderly frail patients with untreated multiple myeloma

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1 **A phase 2 study of three low-dose intensity subcutaneous Bortezomib regimens in elderly**
2 **frail patients with untreated multiple myeloma**

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38 **Running head:** Subcutaneous bortezomib-regimens in frail MM

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54 **Abstract**

55 This phase 2 trial evaluated 3 low-dose intensity subcutaneous bortezomib-based treatments in
56 patients ≥ 75 years with newly diagnosed multiple myeloma (MM). Patients received subcutaneous
57 bortezomib plus oral prednisone (VP, N=51) or VP plus cyclophosphamide (VCP, N=51) or VP plus
58 melphalan (VMP, N=50), followed by bortezomib maintenance, and half of the patients were frail.
59 Response rate was 64% with VP, 67% with VCP and 86% with VMP, very good partial response
60 rate or better was 26%, 28.5% and 49%, respectively. Median PFS was 14.0, 15.2 and 17.1 and 2-
61 year OS was 60%, 70% and 76%, in VP, VCP, VMP respectively. At least one drug-related grade
62 ≥ 3 non-hematologic adverse event (AE) occurred in 22% of VP, 37% of VCP and 33% of VMP
63 patients; the discontinuation rate for AEs was 12%, 14% and 20% and the 6-month rate of toxicity-
64 related deaths was 4%, 4% and 8%, respectively. The most common grade ≥ 3 AEs included
65 infections (8-20%), constitutional (10-14%) and cardiovascular events (4-12%); peripheral
66 neuropathy was limited (4-6%). Bortezomib maintenance was effective and feasible.
67 VP, VCP and VMP regimens demonstrated no substantial difference. Yet, toxicity was higher with
68 VMP, suggesting that a two-drug combination followed by maintenance should be preferred in frail
69 patients.

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79 **Introduction**

80 In recent years, the introduction of novel agents such as immunomodulatory drugs and the
81 proteasome inhibitor bortezomib, associated with standard chemotherapy, has changed the
82 management of multiple myeloma and extended survival.¹ Data from the SEER registry showed a
83 significant trend toward a better 5-year survival for patients diagnosed between 2003-2007,
84 whereas no survival improvement was seen in older patients (≥ 65 years).²

85 The global population is rapidly aging. The proportion of the population aged 65 years or over is
86 expected to increase in all European countries, from 17.08% in 2008 to 29.95% in 2060; in
87 particular, the population aged 80 years or over is expected to almost triple.³

88 Approximately one third of patients with myeloma at diagnosis are older than 75 years and at least
89 30% are frail, because of the presence of concomitant disease, abnormal laboratory test results
90 and symptoms or signs of disability, that may complicate the presentation and management of
91 myeloma.^{4,5} Although the majority of myeloma diagnoses and myeloma-related deaths occur in
92 subjects over 65 years, elderly frail patients are not fully characterized and they are
93 underrepresented in clinical trials. Thus, frail patients usually receive regimens tested in fit patients,
94 which may be too toxic for them and cause early treatment discontinuation, low efficacy and
95 impaired quality of life.

96 Today, bortezomib-melphalan-prednisone (VMP) and melphalan-prednisone-thalidomide (MPT)
97 are the reference treatments for elderly myeloma patients.^{6,7} Nevertheless, the efficacy of these
98 regimens was less evident in patients aged 75 years or over. VMP induced a shorter overall
99 survival in patients older than 75 years in comparison with younger patients (median 32.9 vs 50.7
100 months);⁸ the incidence of any grade 3-4 adverse events (AEs) was 91% and bortezomib
101 discontinuation rate due to AEs was 34%.⁹ Similar results have been reported with MPT: the
102 median progression-free survival (PFS) of patients over 75 years (10 months with MPT and 6
103 months with MP) was shorter compared with younger patients, and no improvement was observed
104 in overall survival (OS).¹⁰ In another trial including patients over 75 years, MPT led to a response
105 rate of 62% and a median PFS of 24 months, but the median duration of treatment was 13.5
106 months and 45% of patients discontinued treatment for AEs.¹¹

107 Furthermore advanced age (HR 1.44, P<0.001), the occurrence of severe cardiac, gastrointestinal
108 AEs and infections (HR 2.53, P<0.001), and drug discontinuation (HR 1.67, P=0.01) predicted a
109 higher risk of death in newly diagnosed myeloma patients treated with melphalan-prednisone,
110 either alone or in combination with thalidomide and/or bortezomib. This was particularly evident
111 with the use of more complex combinations including the association of bortezomib and
112 thalidomide. In fact, different trials did not show a substantial advantage with multi-drug regimens
113 over less intensive combinations, since they are often associated with higher toxicity rates and
114 worse quality of life, especially in community-based populations.^{12,13}
115 The morbidity associated with dexamethasone-based regimens was significantly higher than the
116 one reported with prednisone, especially in terms of infections and gastrointestinal complications.¹⁴
117 These findings raise the question of whether a lower dose-intensity treatment with two-drug
118 combinations may improve tolerability, preserving efficacy, in very elderly and frail patients, and
119 thus should be preferred to three-drug combinations.
120 To address this question, we designed a multicenter, community-based study to examine the
121 efficacy and safety of weekly subcutaneous bortezomib plus continuous low-dose prednisone (VP)
122 or cyclophosphamide-prednisone (VCP) or melphalan-prednisone (VMP) in patients over 75 years
123 of age with newly diagnosed multiple myeloma.

124

125 **Patients and methods**

126 Patients aged ≥ 75 years old (or younger with abnormal organ function), unsuitable for standard
127 treatments or usually excluded from clinical protocols with standard inclusion/exclusion criteria,
128 with measurable disease and a Karnofsky Performance Status (KPS) $\geq 50\%$, were enrolled.¹⁵
129 Diagnosis of myeloma was made using standard criteria.¹⁶ Exclusion criteria included grade ≥ 2
130 peripheral neuropathy; creatinine clearance < 20 ml/min; absolute neutrophil count $< 1,000/\mu\text{L}$;
131 platelets $< 80,000/\mu\text{L}$; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5
132 times upper limit of normal (ULN); or total bilirubin > 1.5 times ULN.

133 All patients provided written informed consent. Review boards at each participating site approved
134 the study, which was conducted in accordance with the Declaration of Helsinki. This trial is
135 registered at www.clinicaltrials.gov, NCT01190787.

136

137 **Study design**

138 This phase 2, non-randomized study was conducted at 23 centers. Patients were enrolled in either
139 one of the three, independent bortezomib cohorts, namely VP, or VCP, or VMP. Subjects were
140 recruited from October 2010 to August 2012; the cut-off date was March 15, 2014.

141 The primary objective was to determine the rate of very good partial response (VGPR) in patients
142 with newly diagnosed multiple myeloma treated with VP, VCP and VMP regimens.

143 Secondary objectives included safety and tolerability, overall response rates (ORR), time to
144 response (TTR), time to progression (TTP), PFS, and overall survival (OS).

145

146 **Study Treatment**

147 Patients were enrolled in three cohorts of treatment with VP, VCP and VMP. Treatment consisted
148 of nine 28-day cycles of induction therapy with subcutaneous bortezomib 1.3 mg/m² on days 1, 8,
149 15, 22 plus oral prednisone 50 mg every other day (VP) or VP plus oral cyclophosphamide 50 mg
150 every other day (VCP) or plus oral melphalan 2 mg every other day (VMP); followed by
151 maintenance with subcutaneous bortezomib on days 1, 15, until progression.

152 Patients could receive supportive therapy including bisphosphonates, granulocyte colony-
153 stimulating factor (G-CSF), erythropoietin and transfusions, as necessary. Prophylactic acyclovir
154 for herpes zoster was recommended.

155

156 **Assessments**

157 At baseline a geriatric assessment (GA) was performed. The GA consisted of three tools: Katz's
158 Activities of Daily Living (ADL) and Lawton's Instrumental Activities of Daily Living (IADL) scores to
159 assess self-care activities, tasks of household management and independence status; Charlson
160 comorbidity index (CCI) to estimate the number and the severity of comorbidities.^{17,18}

161 AEs were graded according to NCI-CTCAE version 3.0.¹⁹ Response was assessed prior to every
162 treatment cycle. Response categories were based on the International Myeloma Working Group
163 uniform response criteria.¹⁶

164

165 **Statistical methods**

166 Based on the primary objective (VGPR rate), sample size was estimated at the significance level of
167 $\alpha = 0.05$, power of 80%, a null hypothesis VGPR rate of 10%, and an alternative hypothesis VGPR
168 rate of 25%.

169 Based on Simon's optimal two-stage design,²⁰ for each cohort 43 patients were required (18
170 patients in the first phase, 25 in the second one). Assuming 15% of patients lost to follow-up, to
171 obtain 129 response-evaluable patients, the enrollment of ~150 patients was targeted (50 per
172 cohort).

173 Given the non-comparative nature of the study, no formal statistical comparisons between the 3
174 treatment cohorts were made.

175 All patients who received at least one dose of any study drug were included in the safety analyses.

176 The response-evaluable population was defined as a subset of the intention to treat (ITT)
177 population with measurable disease at baseline and with at least one post baseline response
178 assessment.

179 OS was calculated from the start of the treatment until the date of death or the date the patient was
180 last known to be alive. PFS was calculated from the start of the treatment until the date of disease
181 progression or death (regardless of cause of death). Time-to-event analyses were performed with
182 the Kaplan–Meier method.²¹ The analyses were performed using SAS software version 8.2 (SAS
183 Institute).

184

185 **Results**

186

187 **Patient characteristics**

188 One-hundred-fifty-two patients were enrolled, 51 in the VP, 51 in the VCP and 50 in the VMP
189 cohorts. Patient disposition is shown in Figure 1. The median follow-up from enrolment was 27.2
190 months (range: 0–42).

191 The median age was 78 years (range: 59–88) with 33% of patients \geq 80 years of age. Overall, 27%,
192 29% and 44% of patients had ISS stage I, II or III disease, respectively. Eighteen percent of
193 patients had high-risk myeloma, defined by the presence of any of t(4;14), t(14;16), or del17p13 by
194 FISH. According to the frailty scoring system,⁴ based on age, comorbidities, cognitive and physical
195 conditions, 3 groups of patients were identified: fit (score=0, 16%); intermediate (score=1, 30%),
196 and frail (score \geq 2, 54%) (Appendix).

197 Baseline characteristics were similar between the treatment cohorts (Table 1), except for the VP
198 group, where a higher proportion of patients \geq 80 years (41%), frail (72%) and with ISS stage III
199 (53%) was observed.

200

201 **Efficacy**

202 One-hundred-forty-eight out of 152 patients started treatment. Four patients did not start treatment
203 for withdrawal of consent (2 patients), lost to follow-up (1 patient) and patient condition (1 patient)
204 (Figure 1).

205 The median number of cycles administered was 9 (range: 1–9), with similar distribution across
206 groups. The median time on therapy was approximately 11 months in all treatment groups.

207 Ninety-three patients across the 3 cohorts completed all 9 cycles of induction, and 79 patients
208 started maintenance as planned.

209 Overall 148 patients could be evaluated for response. After induction, the ORR was 64% with VP,
210 67% with VCP, and 86% with VMP, including a VGPR or better of 26%, 28.5%, and 49%, and a
211 complete response (CR)/ stringent CR (sCR) of 8%, 2% and 14% in the three cohorts, respectively
212 (Table 2). The median time to at least a VGPR was 5.7 months.

213 The median PFS was 14.0, 15.2, and 17.1 months, and the 2-year OS estimate was 60%, 70%,
214 76% for the VP, VCP and VMP groups, respectively. (Figure 2) The median PFS was 14.1 months

215 for patients <80 years and 16.1 for patients ≥80 years, and the respective 2-year OS rates were
216 70% and 67%.

217 We examined the impact of frailty on outcome. Among patients enrolled in the VP group, the
218 majority were frail (72%) and ≥80 years (41%). More fit patients received triplet regimens. In the
219 overall population, the median PFS was 22.4, 15.2 and 13.8 months, and the 2-year OS was 84%,
220 76% and 60% in fit, intermediate and frail patients, respectively.

221

222 **Safety**

223 One-hundred-forty-eight patients could be evaluated for toxicity. Hematological toxicity was
224 infrequent; the rate of at least one grade ≥ 3 hematologic AE was 6% with VP, 8% with VCP and
225 10% with VMP groups and they were considered drug-related according to investigators' opinion.
226 Overall, grade 3 or higher thrombocytopenia was observed in 2% of patients.

227 The incidence of at least one drug-related grade ≥ 3 non-hematologic AE was 22% with VP, 37%
228 with VCP and 33% with VMP. The most common toxicities were infections (8-14%) mostly
229 pulmonary; constitutional (6-10%) mostly fatigue; and cardiac events (4-8%), mostly heart failure.
230 Grade ≥ 3 peripheral neuropathy occurred in 8 patients (5%) (Table 3). Five solid second primary
231 malignancies (pancreas, bowel, breast, liver and lung) were reported: 2 cases were diagnosed
232 within 6 months from the start of myeloma therapy and 3 after more than 17 months.

233 At least one drug-related non-hematologic serious AE (SAE) was reported in 8%, 8% and 20% in
234 the VP, VCP and VMP groups. The most frequent SAEs were cardiologic events (heart failure in 4
235 patients and atrial fibrillation in 2 patients) and infections (bronchitis in 2 patients, pneumonia in 5
236 patients and sepsis in 1 patient).

237 Twelve percent of patients in the VP, 14% in the VCP, and 20% in the VMP groups discontinued
238 treatment due to AEs.

239 Fifteen, 13 and 10 deaths occurred during induction treatment in the VP, VCP and VMP groups
240 respectively; among them 27%, 31% and 50% were due to AEs. Toxicity-related deaths within 60
241 days occurred in 3.4% of the patients, mainly due to infections (2 patients) and cardiovascular
242 events (3 patients). Within 6 months of start of therapy, 15 patients (10%) died for any cause, and

243 8 (5%) due to AEs: infections (4 patients), cardiovascular events (3 patients) and one second
244 cancer (pancreas).

245 At least one drug-related SAE was reported in 13% of frail patients and none in fit ones. The drop-
246 out rate during induction was higher in frail patients (55%) as compared with fit ones (28%). The
247 discontinuation rate due to AEs was 26% in frail patients and 8% in fit ones. The majority of early
248 deaths due to toxicity within 6 months of the start of therapy occurred in frail patients (5/6, 83%).

249

250 **Maintenance**

251 Seventy-nine patients started maintenance, 25 in the VP, 25 in the VCP and 29 in the VMP groups.
252 After a median follow-up of 18 months (range 1-43 months) from the initiation of maintenance, an
253 improvement in the depth of response was observed in 14 patients (18%): 1 patient in CR
254 upgraded to sCR, 5 patients in VGPR upgraded to CR/sCR, 4 patients in PR upgraded to either
255 CR or VGCR, and 4 patients in SD upgraded to VGPR or PR. Overall, 51% of patients had a
256 stability of response. Response to maintenance therapy was not influenced by the previous
257 induction regimen.

258 The median PFS from the start of maintenance was 27.7 months; the 2-year OS estimate was 88%
259 (Figure 2).

260 Approximately half of frail patients enrolled in the trial started maintenance. No significant
261 difference in PFS was observed among fit, intermediate and frail patients.

262 No grade 3 or higher hematologic AEs related to bortezomib were reported. At least one grade \geq 3
263 non-hematologic AE was seen in 16% of the patients; only 7.5% of them were considered related
264 to the study drugs. The most frequent drug-related AEs were infections. The rate of discontinuation
265 due to AEs was 14%.

266

267 **Discussion**

268 To our knowledge, this is the first prospective study assessing bortezomib-based treatments in
269 very elderly (\geq 75 years) and frail patients with comorbidities and/or disabilities, who are usually
270 excluded from clinical trials.

271 This study shows that low dose intensity bortezomib-based regimens are well tolerated and are
272 effective in a community-based setting, with similar efficacy between the doublet VP and the
273 triplets VCP and VMP. Toxicities, discontinuation rate and early deaths due to toxicity were higher
274 in the VMP group, particularly in frail patients.

275 Our data compares favorably with the US community-based, phase 3b randomized, UPFRONT
276 trial, which compared bortezomib-dexamethasone (VD), bortezomib-thalidomide-dexamethasone
277 (VTD), and bortezomib-melphalan-prednisone (VMP), followed by weekly bortezomib
278 maintenance, in elderly patients with newly diagnosed MM.¹² The median age was 73 years, 18%
279 of patients were ≥ 80 years and 48% had at least one comorbidity. All three regimens demonstrated
280 substantial activity, with an ORR of 73%, 80% and 70%, respectively, and no significant difference
281 in median PFS (14.7 months with VD, 15.4 months with VTD and 17.3 months with VMP).

282 Our results confirm these data, highlighting that the doublet therapy may be as effective as the
283 triplets, considering both efficacy and treatment-related toxicities.

284 In our study, these low dose intensity regimens were well tolerated. Only 5% of patients reported
285 grade ≥ 3 neuropathy and a very low incidence of severe thrombocytopenia was observed. The use
286 of subcutaneous once-weekly bortezomib significantly reduced peripheral neuropathy, which was
287 reported in approximately 20% of patients treated with twice-weekly bortezomib.¹² The most
288 common AEs included infections (8%-14%) and cardiac events (4-8%), which occurred mostly in
289 VMP patients. The incidence of infections and cardiac complications in our trial seems higher as
290 compared to the Spanish trial in which bortezomib was administered once-weekly, but the patient
291 populations of the two trials are not comparable (fit patients with a median age of 73 years versus
292 frail patients with a median age of 78 years).²² Thus prophylactic antibiotics during the first 3-4
293 months of induction and a more accurate upfront cardiac screening should be considered.

294 In the French MPT trial designed for patients over 75 years, 45% of patients discontinued
295 treatment for AEs.¹¹ In the UPFRONT study, 22-28% discontinued treatment for drug-related AEs.
296 The toxicity profile was influenced by the use of twice-weekly bortezomib, combined with
297 thalidomide or full dose melphalan (9 mg/m² for 4 days). In our trial bortezomib was given once-
298 weekly and melphalan at lower doses, thus producing similar responses and outcomes, but a lower

299 toxicity, in a comparable setting. In our study the discontinuation rate was low, from 8% to 20% in
300 the VMP group, suggesting that a low dose intensity treatment could be an option in this subset of
301 patients, to avoid early discontinuation.

302 Concerning early deaths, 5% of patients died due to AEs and 3% due to progressive disease in the
303 first 6 months from start of therapy. The 2-fold higher risk of early deaths for toxicity as compared
304 to disease progression confirms the need for a careful assessment of frail patients who may benefit
305 from a gentler or even palliative approach. Furthermore the improvement in supportive therapy
306 together with prevention, prompt recognition and treatment of complications are urgently needed to
307 reduce the risk of deaths due to toxicity.

308 In our trial bortezomib maintenance was associated with an improvement in response, a longer
309 PFS and very few AEs. Furthermore, during maintenance the discontinuation rate due to any
310 cause and particularly due to AEs, was low, indicating that the schedule of bortezomib planned in
311 this study is feasible. Previous studies have evaluated the role of frontline continuous bortezomib-
312 based treatment.^{23,24} The Spanish trial including fit elderly patients, evaluated bortezomib
313 maintenance after VMP or VTP induction, and found that VP maintenance induced a median PFS
314 of 32 months. In our study, maintenance therapy with bortezomib resulted into a long PFS (27.7
315 months), which is quite comparable with the PFS reported in fit patients.

316 The benefit of a continuous treatment with lenalidomide after an alkylator-based regimen was less
317 evident in patients older than 75 years of age,²⁵ whereas its activity was confirmed in the
318 continuous treatment lenalidomide-dexamethasone, irrespective of age. In our trial the beneficial
319 effect of bortezomib maintenance was evident irrespective of age and frailty status. In this
320 community-based setting a prolonged time without symptoms of disease progression and without
321 major toxicities would translate into a physical and emotional benefit for the patient. Therefore the
322 final benefit of a prolonged maintenance versus a treatment-free-interval remains still unknown.
323 Thus it would be essential in future trials to validate this hypothesis, also through quality of life
324 studies.

325 Until now, advanced age was usually the only criterion to define frail patients, which sometimes led
326 to an improper under-treatment or over-treatment of patients. In this study no difference was

327 observed in patients younger or older than 75 or 80 years, confirming that age is no longer
328 sufficient to appropriately identify frail patients. As recently reported in a large analysis including
329 also the present trial, by applying a frailty score that combines age, functional status (measured
330 with ADL and IADL scores) and comorbidities (assessed with CCI), we were able to stratify
331 patients into fit, intermediate and frail; of note, the latter group showed an inferior survival, a higher
332 risk of non-hematologic AEs and treatment discontinuation.⁴

333 In the current study the majority of patients were frail (54%), and the majority of frail and older
334 patients (≥ 80 years) were enrolled in the VP group.

335 The main limit of this non-randomized trial is that the patients were not stratified at enrolment. The
336 unbalanced distribution of frail and older patients among the 3 treatment groups may in part
337 explain the lower rate of response observed in the VP group. On the other hand, the standard
338 approved treatment MPT and VMP with twice-weekly bortezomib for newly diagnosed myeloma
339 patients induced response rates of 71% and 59%, a median PFS of 24 and 20.3 months, with a
340 rate of treatment discontinuation for toxicity of 34%-40%, respectively.^{6,7} In our study, the majority
341 of fit patients received the triplet VMP and VCP (84%); in fit patients response rate was 76%, the
342 median PFS was 22.4 months, and the rate of treatment discontinuation for toxicity was 8%. In frail
343 patients treated with VMP the discontinuation rate for toxicity was 29%. The shorter PFS observed
344 in frail patients (13.8 months) may be due to the higher toxicity and treatment discontinuation,
345 highlighting the difficulty in treating frail patients even with low dose intensity regimens. These data
346 confirm the activity of VMP or triplet bortezomib-based treatments in fit elderly patients, which still
347 appear too toxic for frail patients.

348 In conclusion, the current study, with the limits of its phase 2 design, did not show a substantial
349 advantage for the three-drug regimens. The VMP group showed significant activity, at the expense
350 of a higher toxicity.

351 The growing number of older adults with myeloma is increasing the need for practical strategies to
352 recognize and appropriately manage frail patients. The efficacy and safety results, as well as the
353 costs associated with treatment, suggest that full dose triplet combinations can be indicated in fit
354 patients, where a good quality response and a prolonged PFS and OS are the goals of treatment.

355 A doublet therapy should be preferred in frail patients, where the real goals of care are stabilization
356 of the disease, symptoms control, maintenance of quality of life and independence status, over
357 prolonged survival. In this setting a doublet combination with subcutaneous bortezomib and low
358 dose steroid followed by maintenance could be recommended as upfront treatment.

359 This study represents a starting point for a prospective evaluation of two-drug regimens in frail
360 elderly patients.

361

362

363 **Authorship:** AL, MB, PS, and AP designed the study, and supervised its conduct and the data
364 analysis. AL, SB, MTP, SO, RB, APF, TC, OV, GB, AML, FM, VM, RP, LDR, PO, IDV, SS,AMC,
365 EP, DD, MG, TG, CN, EA, LDP, CC, CM, MO recruited patients in the source studies and/or
366 provided relevant data. AL collected and assembled the data. RP and SS performed the statistical
367 analysis. AL and AP analysed and interpreted the data. AL and AP drafted the initial manuscript.
368 All authors were given unrestricted access to the data, critically reviewed the manuscript drafts,
369 approved the final version, and made the decision to submit it for publication.

370 **Conflicts of interest:** AL has received honoraria from Celgene and Janssen-Cilag. SB has
371 received honoraria from Celgene, Janssen-Cilag and Novartis, consultancy fees from Onyx, and
372 served on the advisory committee for Merck Sharp & Dohme. MTP has received honoraria from
373 Celgene, Janssen-Cilag, Mundipharma, Sanofi, Amgen, Bristol-Myers Squibb. TC has received
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376 has received honoraria from honoraria from Janssen-Cilag. MB has received consultancy fees
377 from and served on the scientific advisory board for Janssen-Cilag, Sanofi, Amgen, Celgene. PS
378 has received research support from Onyx, Janssen, Celgene, Millennium, and served on the
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409 **Refereces**

- 410 1. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved
411 survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-
412 20.
- 413 2. Brenner H, Gondas A, Pulte D. Expected long-term survival of patients diagnosed with
414 multiple myeloma in 2006-2010. *Haematologica*. 2009;94(2):270-5.
- 415 3. Altekruse SF, Kosary CL, Krapcho M, Neyman N, Aminou R, Waldron W, Ruhl J, et al.
416 (eds). SEER Cancer Statistics Review, 1975-2007, http://seer.cancer.gov/csr/1975_2007/S
417 Accessed 10 July, 2015.
- 418 4. Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK, et al. Geriatric
419 assessment predicts survival and toxicities in elderly myeloma patients: an International
420 Myeloma Working Group report. *Blood*. 2015;125(13):2068-74.
- 421 5. Bringhen S, Mateos MV, Zweegman S, Larocca A, Falcone AP, Oriol A, et al. Age and
422 organ damage correlate with poor survival in myeloma patients: meta-analysis of 1435
423 individual patient data from 4 randomized trials. *Haematologica*. 2013;98(6):980-7.
- 424 6. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al.
425 Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl*
426 *J Med*. 2008;359(9):906-17.
- 427 7. Fayers PM, Palumbo A, Hulin C, Waage A, Wijermans P, Beksaç M, et al. Thalidomide for
428 previously untreated elderly patients with multiple myeloma: meta-analysis of 1685
429 individual patient data from 6 randomized clinical trials. *Blood*. 2011;118(5):1239-47.
- 430 8. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al.
431 Continued Overall Survival Benefit After 5 Years' Follow-up with Bortezomib-Melphalan-
432 Prednisone (VMP) Versus Melphalan-Prednisone (MP) in Patients with Previously
433 Untreated Multiple Myeloma, and No Increased Risk of Second Primary Malignancies: Final
434 Results of the Phase 3 VISTA Trial [abstract]. *Blood*. 2011;118:Abstract 476.
- 435 9. Mateos MV, Richardson PG, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, et al.
436 Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in

- 437 previously untreated multiple myeloma: updated follow-up and impact of subsequent
438 therapy in the phase III VISTA trial. *J Clin Oncol.* 2010;28(13):2259-66.
- 439 10. Wijermans P, Schaafsma M, Termorshuizen F, Ammerlaan R, Wittebol S, Sinnige H, et al.
440 Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly
441 patients with newly diagnosed multiple myeloma: the HOVON 49 Study. *J Clin Oncol.*
442 2010;28(19):3160-3166.
- 443 11. Hulin C, Facon T, Rodon P, Pegourie B, Benboubker L, Doyen C, et al. Efficacy of
444 melphalan and prednisone plus thalidomide in patients older than 75 years with newly
445 diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol.* 2009;27(22):3664-3670.
- 446 12. Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B, et al. Community-Based
447 Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol.*
448 2015 Jun 8. pii: JCO.2014.58.7618. [Epub ahead of print]
- 449 13. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized,
450 multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone,
451 cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.*
452 2012;119(19):4375-82.
- 453 14. Facon T, Mary JY, Pégourie B, Attal M, Renaud M, Sadoun A, et al. Dexamethasone-based
454 regimens versus melphalan–prednisone for elderly multiple myeloma patients ineligible for
455 high dose therapy. *Blood.* 2006;107(4):1292–8.
- 456 15. Durie BG, Kyle RA, Belch A, Bensinger W, Blade J, Boccadoro M, et al. Myeloma
457 management guidelines: a consensus report from the Scientific Advisors of the
458 International Myeloma Foundation. *Hematol J.* 2003;4(6):379-98.
- 459 16. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response
460 assessment of multiple myeloma. *Leukemia.* 2009;23(1):3-9.
- 461 17. Lawton MP. Scales to measure competence in everyday activities. *Psychopharmacol Bull.*
462 1988;24(4):609-614.

- 463 18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic
464 comorbidity in longitudinal studies: development and validation. *J Chronic Dis*.
465 1987;40(5):373-383.
- 466 19. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE),
467 version 3.0. 2006
468 http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf.
- 469 20. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*.
470 1989;10(1):1-10.
- 471 21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat*
472 *Assoc*. 1958;53(282):457–481.
- 473 22. Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, de Paz R, et al. Bortezomib,
474 melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction
475 therapy followed by maintenance treatment with bortezomib and thalidomide versus
476 bortezomib and prednisone in elderly patients with untreated multiple myeloma: a
477 randomised trial. *Lancet Oncol*. 2010;11(10):934-41.
- 478 23. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, et al. Bortezomib-
479 melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide
480 compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma:
481 a randomized controlled trial. *J Clin Oncol*. 2010;28(34):5101-9.
- 482 24. Mateos MV, Oriol A, Martínez-López J, Gutiérrez N, Teruel AI, López de la Guía A, et al.
483 Maintenance therapy with bortezomib plus thalidomide or bortezomib plus prednisone in
484 elderly multiple myeloma patients included in the GEM2005MAS65 trial. *Blood*.
485 2012;120(13):2581-8.
- 486 25. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, et al. Continuous
487 lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med*.
488 2012;366(19):1759-69.

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491 **Figure legend.**

492 **Figure 1.** Patient disposition

493 **Figure 2.** Kaplan-Meier analyses of treatment outcomes. Panel A shows Progression Free Survival
494 from start of treatment. Panel B shows Overall Survival from start of treatment. Panel C shows
495 Progression Free Survival from start of maintenance. Panel D shows Overall Survival from start of
496 maintenance

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Figure 1 Patient disposition

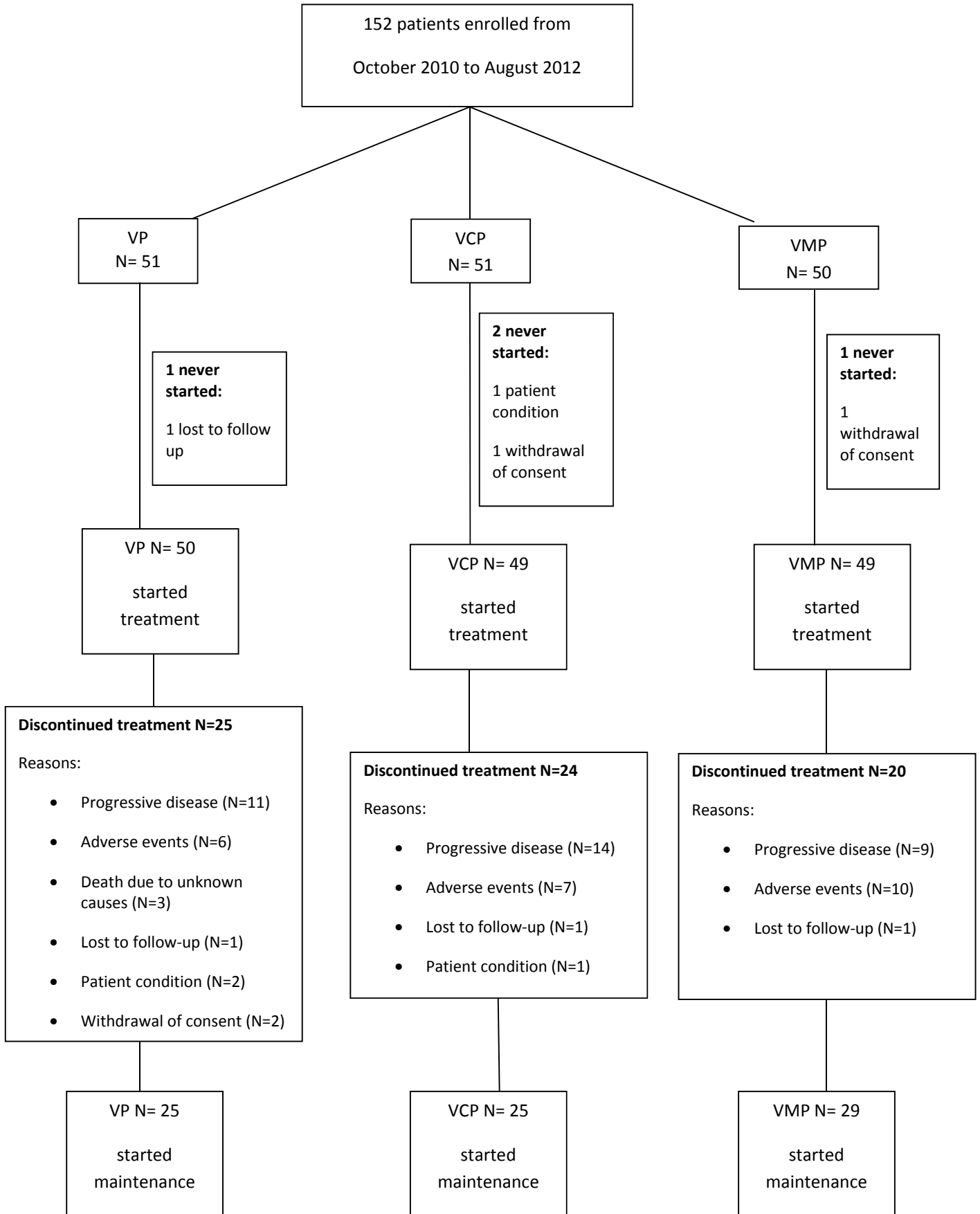
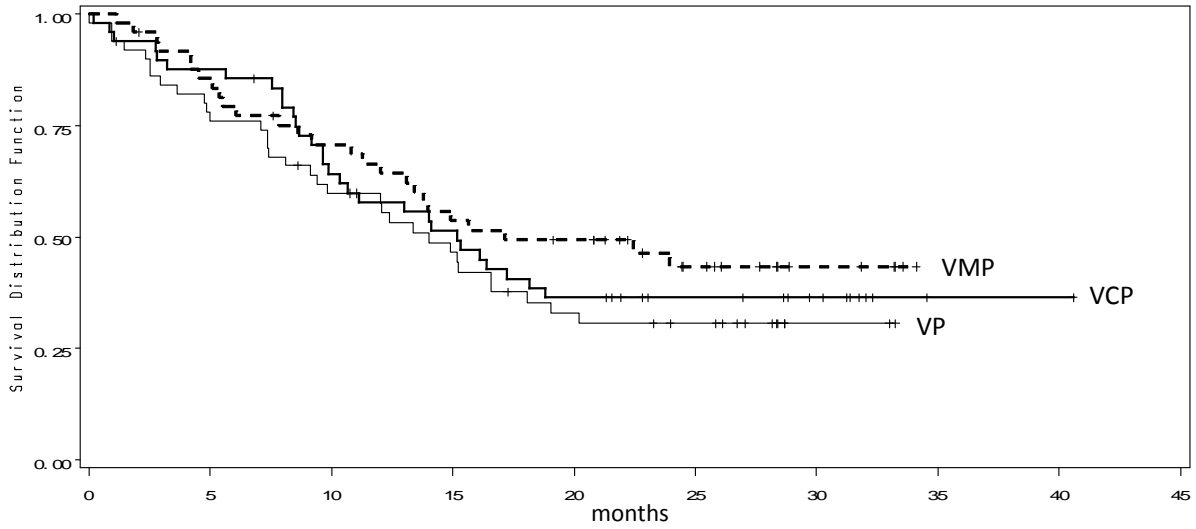


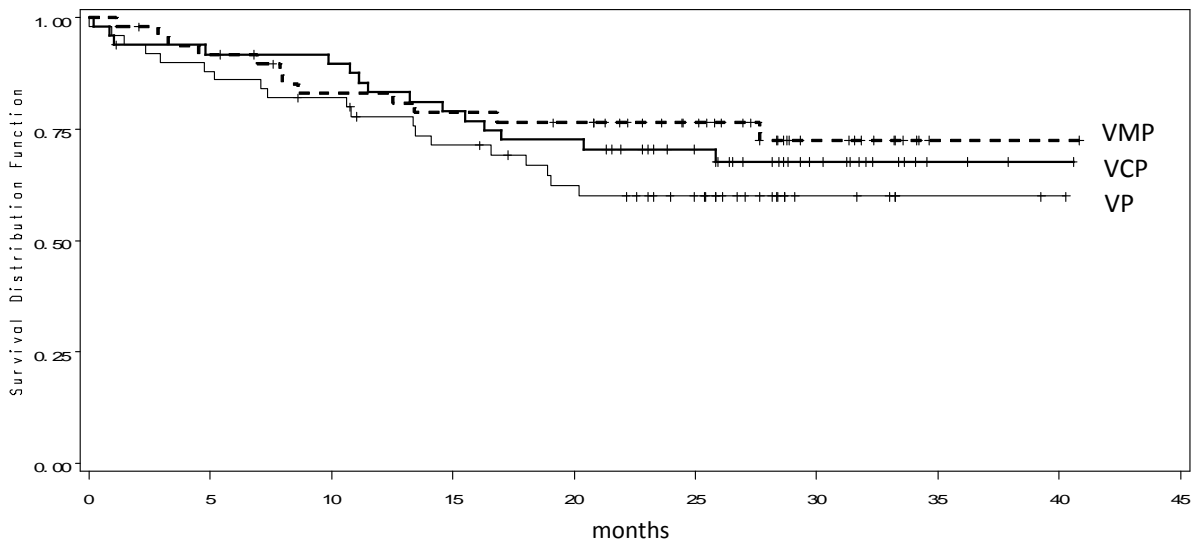
Figure 2

Kaplan-Meier analyses of treatment outcomes

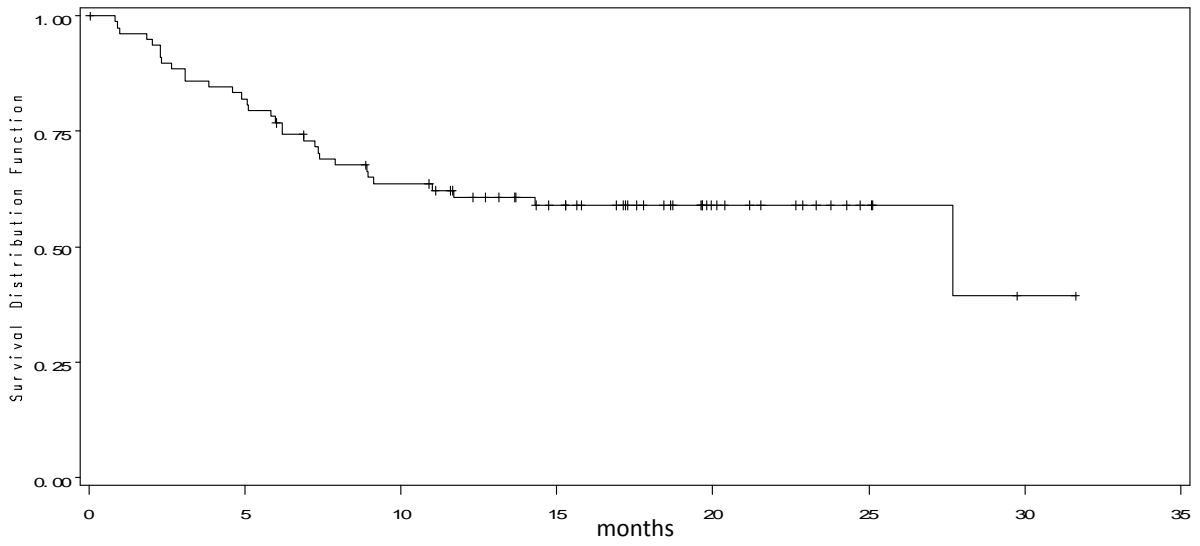
A. Progression Free Survival from start of treatment



B. Overall Survival from start of treatment



C. Progression Free Survival from start of maintenance



D. Overall Survival from start of maintenance

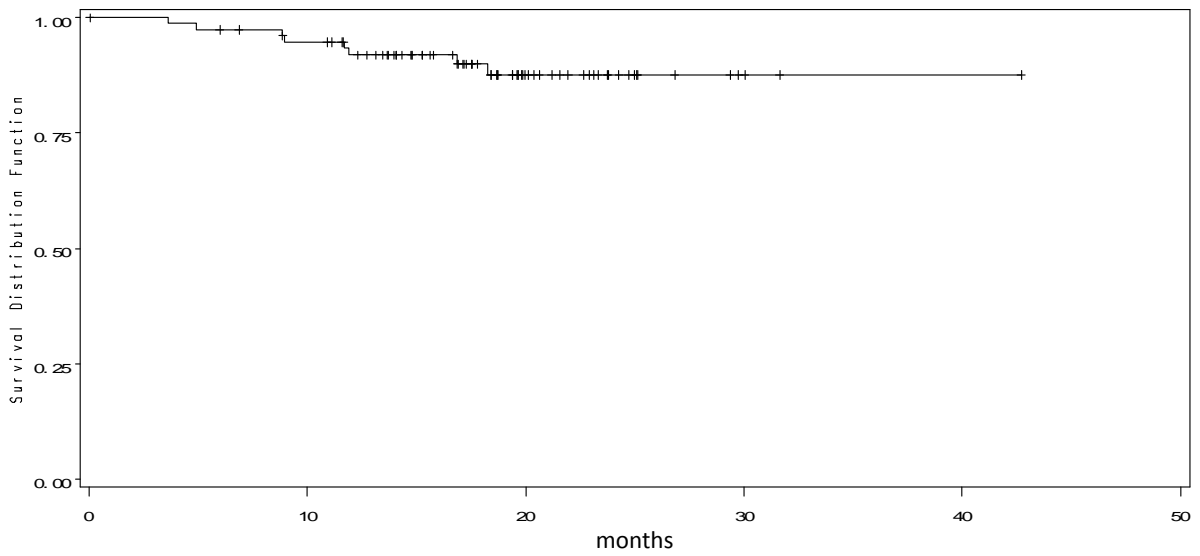


Table 1 Baseline patient characteristics

Characteristics	VP (n=51)	VCP (n=51)	VMP (n=50)
Median age, years (IQR)	78 (76-82)	77 (73-80)	78 (75-81)
Age ≥ 80 years, n (%)	21 (41)	14 (27)	15 (30)
Gender, male, n (%)	22 (43)	26 (51)	30 (60)
Myeloma type, n (%)			
IgG	33 (65)	30 (58)	27 (54)
IgA	11 (21)	10 (20)	18 (36)
Light chain	7 (14)	10 (20)	5 (10)
Other	0	1 (2)	0
ISS stage, n (%)			
I	12 (23.5)	15 (29)	14 (28)
II	12 (23.5)	12 (24)	20 (40)
III	27 (53)	24 (47)	16 (32)
Karnofsky performance status, n (%)			
50-60%	5 (10)	4 (8)	3 (6)
70-80%	21 (41)	21 (41)	23 (46)
90-100%	25 (49)	26 (51)	24 (48)
Serum creatinine >1.5 mg/dl, n (%)	15 (29)	8 (16)	12 (24)
Creatinine clearance <60 ml/min	30 (59)	26 (51)	28 (56)
LDH >450 u/L, %	6 (12)	6 (12)	5 (10)
Bone disease present, %	29 (57)	28 (55)	26 (52)
Chromosomal abnormalities			
t(4;14)	4 (8)	0	5 (10)
t(14;16)	1 (2)	4 (8)	0
-17p13	6 (12)	7 (14)	6 (12)
High risk*	9 (20)	9 (19)	10 (23)
Frailty assessment ^o			
Fit	4 (8)	13 (26)	8 (16)
Intermediate	10 (20)	18 (35)	17 (34)
Frail	37 (72)	20 (39)	25 (50)

VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone

*High risk defined as any of the following t(4;14), t(4;16) or -17p13 by FISH.

^o Fit defined as age <80 years, ADL=6, IADL=8, Charlson score=0, unfit defined as age >80 years or ADL=5, IADL=6-7, Charlson score=1, or frail defined as age >80 years or ADL ≤4, IADL ≤5 and Charlson score ≥2.

Table 2 Treatment exposure and response

Treatment exposure	VP (n=51)	VCP (n=51)	VMP (n=50)
Median follow-up, months	26.1	28.5	27.3
Median cycles, n (range)	9 (1-9)	9 (1-9)	9 (1-9)
Completed induction, n (%)	29 (57)	32 (63)	32 (64)
Started maintenance, n (%)	25 (49)	25 (49)	29 (58)
Best response to induction*	VP (n=50)	VCP (n=49)	VMP (n=49)
ORR (PR or better)	32 (64)	33 (67)	42 (86)
VGPR or better	13 (26)	14 (28.5)	24 (49)
sCR/CR	4 (8)	1 (2)	7 (14)
VGPR	9 (18)	13 (26.5)	17 (35)
PR	19 (38)	19 (39)	18 (37)
SD	16 (32)	14 (28.5)	7 (14)
PD	0	1 (2)	0
NA	2 (4)	1 (2)	0
Best response to maintenance*	VP (n=25)	VCP (n=25)	VMP (n=29)
ORR (PR or better)	13 (52)	14 (56)	24 (83)
VGPR or better	9 (36)	9 (36)	14 (48)
CR/sCR	5 (20)	2 (8)	8 (28)
VGPR	4 (16)	7 (28)	6 (21)
PR	4 (16)	5 (20)	10 (34)
SD	7 (28)	4 (16)	3 (10)
PD	4 (16)	5 (20)	0
NA	1 (4)	2 (8)	2 (7)

VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone; ORR, overall response rate; PR, partial response rate; VGPR, very good partial response; CR complete response; sCR, stringent complete response; SD, stable disease; PD, progressive disease; NA, not available.

* patients starting treatment

Table 3 Grade 3 or higher adverse events (during induction)

	VP (n=50)	VCP (n=49)	VMP (n=49)
Hematological AEs, n (%)			
Anemia	4 (8)	4 (8)	3 (6)
Drug-related	3	3	3
Neutropenia	2 (4)	1 (2)	0
Drug-related	2	1	0
Thrombocytopenia	1 (2)	0	2 (4)
Drug-related	1	0	2
At least one hematological AE			
Drug-related	3 (6)	4 (8)	5 (10)
Non-hematological AEs, n (%)			
Cardiac	3 (6)	2 (4)	6 (12)
Drug-related	2	1	4
Heart failure (related)	1	1	3
Atrial fibrillation (related)	1	0	1
Gastro-hepatic	2 (4)	2 (4)	1 (2)
Drug-related	1	2	1
Diarrhea (related)	0	2	0
Constipation (related)	1	0	0
Constitutional	5 (10)	7 (14)	5 (10)
Drug-related	3	5	3
Fatigue (related)	0	3	0
Edema limbs (related)	0	1	1
Infections	4 (8)	6 (12)	10 (20)
Drug-related	4	5	7
Lung (related)	2	2	4

Investigational	2 (4)	4 (8)	2 (4)
Drug-related	1	4	1
Creatinine increased (related)	0	3	1
Nervous	4 (8)	6 (12)	5 (10)
Drug-related	2	6	3
Peripheral neuropathy (related)	2	3	3
Renal	3 (6)	1 (2)	3 (6)
Drug-related	1	1	1
Respiratory	4 (8)	1 (2)	3 (6)
Drug-related	3	0	1
Pulmonary fibrosis (related)	0	0	1
Skin	0	4 (8)	1 (2)
Drug-related	0	4	0
Rash (related)	0	3	0
Vascular	3 (6)	2 (4)	3 (6)
Drug-related	1	1	3
Thromboembolic event (related)	1	0	0
Hypertension/hypotension (related)	0	0	2
Hematoma (related)	0	0	1
At least one non-hematological AE			
Drug-related	11 (22)	18 (37)	16 (33)
At least one non-hematological SAE			
Drug-related	4 (8)	4 (8)	10 (20)
Discontinuation rate and early death			
Discontinuation rate due to AE (%)	12	14	20
Discontinuation rate due to AE in frail patients**	11	10	29

Early toxic deaths (%)	4	4	8
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AE, adverse event; SAE, serious adverse event; VP, bortezomib-prednisone; VCP, bortezomib-cyclophosphamide-prednisone; VMP, bortezomib-melphalan-prednisone

AEs occurred during induction.

Drug-related AEs, according to investigator opinion.

** The percentage is calculated on frail patients n=36 in VP, n=20 in VCP, n=24 in VMP group.