Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib-melphalan-prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy

María-Victoria Mateos,[1] Sara Bringhen,[2] Paul G. Richardson,[3] Juan Jose Lahuerta,[4] Alessandra Larocca,[2] Albert Oriol,[5] Mario Boccadoro,[2] Ramón García-Sanz,[1] Francesco Di Raimondo,[6] Dixie-Lee Esseltine,[7] Helgi van de Velde,[8] Avinash Desai,[9] Anil Londhe,[10] Jesús F. San Miguel,[11] and Antonio Palumbo[2]

[1]Servicio de Hematología, Hospital Universitario de Salamanca, CIC, IBMCC (USAL-CSIC), Salamanca, Spain; [2]Myeloma Unit, Division of Hematology, University of Torino, Azienda Ospedaliero-Universitaria (AOU) S. Giovanni Battista, Torino, Italy; [3]Dana-Farber Cancer Institute, Boston, MA, USA; [4]Hospital Universitario 12 de Octubre, Madrid, Spain; [5]Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [6]Università degli Studi di Catania, Ospedale Ferrarotto, Catania, Italy; [7]Takeda Pharmaceuticals International Co., Cambridge, MA, USA; [8]Janssen Research & Development, Beerse, Belgium; [9]Janssen Global Services, Raritan, NJ, USA; [10]Janssen Research & Development, Horsham, PA, USA; and [11]Clinica Universidad de Navarra, Centro Investigación Medica Aplicada, Pamplona, Spain

ABSTRACT

Substantial efficacy has been demonstrated with bortezomib-melphalan-prednisone in phase III studies in transplant-ineligible myeloma patients using various twice-weekly and once-weekly bortezomib dosing schedules. In VISTA, the regimen comprised four 6-week twice-weekly cycles, plus five 6-week once-weekly cycles. In the GIMEMA MM-03-05 study, the bortezomib-melphalan-prednisone regimen was either per VISTA ('GIMEMA twice-weekly'), or comprised nine 5-week once-weekly cycles ('GIMEMA once-weekly'). In the GEM2005MAS65 study, the regimen comprised one 6-week twice-weekly cycle, plus five 5-week once-weekly cycles. We evaluated the cumulative bortezomib dose administered during bortezomib-melphalan-prednisone, as well as efficacy and tolerability, using patient-level study data. Over all bortezomib-melphalan-prednisone cycles (nine in VISTA/GIMEMA; six in GEM2005MAS65), the median cumulative bortezomib dose administered was 38.5, 42.1, 40.3, and 32.9 mg/m^2 in VISTA, GIMEMA twice-weekly, GIMEMA once-weekly, and GEM2005MAS65, respectively, and the respective proportions of planned bortezomib dose actually delivered were 57.0%, 62.3%, 86.1%, and 90.4%. Response rates following bortezomib-melphalan-prednisone were 74-87% and appeared generally similar between studies. Three-year survival rates were 67.9-75.7% across studies. Grade 3/4 peripheral neuropathy rates were 13% in VISTA and 14% in GIMEMA twice-weekly, but were lower at 2% in GIMEMA once-weekly and 7% in GEM2005MAS65. Discontinuations and bortezomib dose reductions due to peripheral neuropathy were reduced in GIMEMA once-weekly *versus* VISTA and GIMEMA twice-weekly. Exclusive or predominant use of once-weekly bortezomib dosing in GIMEMA once-weekly and GEM2005MAS65 resulted in high efficacy, comparable with that demonstrated in VISTA, and similar cumulative bortezomib dose with reduced toxicity. Trials are registered with *ClinicalTrials.gov*: VISTA (Identifier:00111319), GIMEMA MM-03-05 (Identifier:01063179), and GEM2005MAS65 (Identifier:00443235).

Introduction

In the USA, bortezomib (VELCADE®) is approved for the treatment of multiple myeloma (MM),[1] and in the EU, bortezomib in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant.[2] Substantial efficacy has been demonstrated with bortezomib-melphalan-prednisone (VMP) combination regimens in 3 multicenter, phase III studies conducted in transplant-ineligible patients with MM,[3-10] including VISTA, a global registration study,[3,4,10] and 2 subsequent national cooperative group studies in Italy (GIMEMA MM-03-05)[6,7,9] and Spain (GEM2005MAS65).[5,8]

Various dosing schedules of bortezomib 1.3 mg/m^2 were used in the VMP regimens in the VISTA, GIMEMA MM-03-05, and GEM2005MAS65 studies. VISTA employed a VMP regimen consisting of four 6-week cycles of twice-weekly (BIW) bortezomib dosing, followed by five 6-week cycles of once-weekly (QW) bortezomib dosing; no maintenance therapy was administered following completion of VMP therapy.[3] The GIMEMA MM-03-05 study initially used the same dosing schedule for VMP as in VISTA, but this was amended to nine 5-week cycles of QW bortezomib dosing to reduce the incidence of peripheral neuropathy; as in VISTA, no maintenance therapy was administered following VMP.[6] In the GEM2005MAS65 study, VMP treatment consisted of one 6-week cycle of BIW bortezomib dosing followed by only five 5-week cycles of QW bortezomib dosing; in contrast to VISTA and GIMEMA MM-03-05, patients could subsequently be randomized to receive maintenance therapy for up to three years consisting of intermittent bortezomib plus either thalidomide or prednisone.[5,8]

Patient-level data from the individual study databases were

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Correspondence: mvmateos@usal.es

analyzed retrospectively to evaluate the cumulative dose of bortezomib received during VMP treatment, as well as the efficacy and tolerability of the respective VMP regimens. The aim of these novel cross-study analyses was to evaluate the optimal bortezomib dosing schedule for use in the VMP regimen. In addition, we considered the available data on bortezomib-based maintenance therapy, which was employed following VMP in the GEM2005MAS65 study, to address the utility of this treatment approach in the context of optimizing outcomes following front-line VMP therapy.

Methods

Full methodology for these studies has been described elsewhere,[3-7] including the pre-defined primary and secondary end points of each trial. The *ClinicalTrials.gov* registration numbers are NCT00111319 (VISTA), NCT01063179 (GIMEMA MM-03-05), and NCT00443235 (GEM2005MAS65).

Patients

The three phase III studies included in these analyses employed generally similar eligibility criteria,[3,5,6] as described in the *Online Supplementary Methods*. Review boards at all participating institutions approved the studies, which were conducted according to the Declaration of Helsinki and International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent.

VMP regimens and study designs

The VMP regimens used in the VISTA (n=340),[3,4,10] GIMEMA MM-03-05 (n=253),[6,7,9] and GEM2005MAS65 (n=130)[5,8] studies are summarized in Table 1. Bortezomib dose modifications were required in VISTA[3] and GEM2005MAS65[5] for pre-specified hematologic and (grade 3/4) non-hematologic toxicities, and in GIMEMA MM-03-05[6] for grade 4 hematologic and grade 3/4 non-hematologic adverse events (AEs). Across all studies, bortezomib-induced peripheral neuropathy was managed according to established dose modification guidelines.[11,12]

For the purposes of these retrospective analyses, VMP treatment was considered in two phases: early induction cycles of VMP therapy, to represent the initial phase of treatment, followed by later cycles of VMP. As the main objective of these analyses was to evaluate the cumulative dose of bortezomib received during VMP treatment in each study, together with the efficacy and safety of these VMP regimens, data from the maintenance portion of the GEM2005MAS65 study[5,8] were not included in the analyses of cumulative bortezomib dosing. Data on the bortezomib-thalidomide-prednisone (VTP) regimen from GEM2005MAS65[5,8] and on the VMP plus thalidomide (VMPT) regimen from GIMEMA MM-03-05[6,7,9] were also excluded. Further details are provided in the *Online Supplementary Methods*.

Assessments

Response and progression were assessed according to the European Group for Blood and Marrow Transplantation (EBMT) criteria[13] in VISTA (using a pre-specified computer algorithm to apply the EBMT criteria to response assessment data) and GEM2005MAS65, including the additional category of near CR[14] (negative for M-protein on electrophoresis but immunofixation-positive), and according to the International Myeloma Working Group (IMWG) uniform response criteria[15] in VISTA (post hoc analysis, applying a computer algorithm to implement the IMWG criteria) and GIMEMA MM-03-05. For the purposes of this analysis, patient-level data were used to determine responses consistently across studies according to the IMWG uniform response criteria. AEs were graded according to the National Cancer Institute's Common Terminology Criteria for AEs (NCI CTCAE) version 3.0. Bortezomib dosing data were collated from individual patient data and tabulated.

Statistical analyses

No inferential statistical comparisons between studies were conducted due to confounding factors and differences in median follow-up time preventing comparisons across protocols. Propensity score methods were employed to evaluate the comparability of patients across studies using age, sex, and International Staging System (ISS) disease stage, and by examining propensity distributions graphically. Descriptive statistics for parameters within each study were derived using patient-level data and used to evaluate clinically meaningful similarities among and differences between the VMP regimens. Further details of statistical analyses are provided in the *Online Supplementary Methods*.

Table 1. VMP regimens and post-VMP maintenance therapy used in the phase III studies.

	VISTA / GIMEMA BIW*	GIMEMA QW*	GEM2005MAS65
Bortezomib 1.3 mg/m^2			
Early cycles	4 x 6-week BIW†	4 x 5-week QW‡	1 x 6-week BIW
5 x 5-week QW			
Doses, n / weeks, n	32 / 24	16 / 20	28 / 31
Dose intensity, mg/m^2/week	1.39	1.04	1.17
Later cycles	5 x 6-week QW¶	5 x 5-week QW	NA#
Doses, n / weeks, n	20 / 30	20 / 25	–
Dose intensity, mg/m^2/week	0.87	1.04	–
Melphalan	9 mg/m^2, Days 1–4, all cycles		
Prednisone	60 mg/m^2, Days 1–4, all cycles		
Bortezomib-based maintenance post-VMP	None	None	1 x 3-week BIW, every 3 months for up to 3 years§

**In the GIMEMA study, bortezomib was given either per the VISTA study (GIMEMA BIW, n=63) or, after protocol amendment, on a weekly schedule (GIMEMA QW, n=190). †Six-week cycles of BIW bortezomib comprised dosing on Days 1, 4, 8, 11, 22, 25, 29, and 32. ‡5-week cycles of QW bortezomib comprised dosing on Days 1, 8, 15, and 22. ¶6-week cycles of QW bortezomib comprised dosing on days 1, 8, 22, and 29. #In these analyses, all 6 cycles of VMP in GEM2005MAS65 were considered as 'early' induction cycles. §Plus either prednisone 50 mg every other Day or thalidomide 50 mg/day; BIW: twice-weekly; NA: not applicable; QW: once-weekly; VMP: bortezomib-melphalan-prednisone.*

Results

Patients

The demographics and base-line characteristics of patients receiving VMP in the VISTA, GIMEMA MM-03-05, and GEM2005MAS65 studies are summarized in Table 2. The characteristics of the small subgroups of patients with high-risk cytogenetics are summarized in *Online Supplementary Table S1*. Base-line characteristics are summarized using patient-level data from each individual

Table 2. Summary of key demographics and base-line disease characteristics among patients receiving VMP across the phase III studies (data derived from patient-level data from individual study databases).

	VISTA (n=344)	GIMEMA BIW (n=66)	GIMEMA QW (n=191)	GEM2005MAS65 (n=130)
Median age, years (range)	71 (57–90)	72 (65–85)	71 (56–86)	72 (65–83)
Interquartile range (25%, 75%)	68, 76	69, 75	68, 75	68, 76
Aged ≥75 years, n (%)	106 (31)	20 (30)	49 (26)	42 (32)
Male, n (%)	175 (51)	33 (50)	89 (47)	64 (49)
Region: EU, %				
Region: Russia / North America / Other, %	61	100	100	100
	15 / 9 / 15	–	–	–
ISS stage, n (%)	N=344	N=58	N=141	N=130
I	64 (19)	15 (26)	41 (29)	39 (30)
II	161 (47)	24 (41)	62 (44)	51 (39)
III	119 (35)	19 (33)	38 (27)	40 (31)
β2-microglobulin, mg/L	N=344	N=60	N=149	N=128
Median (range)	4.2 (1.7–21.6)	4.4 (0.5–12.1)	3.9 (0.3–25.6)	3.8 (0.2–21.7)
Albumin, g/L	N=342	N=63	N=160	N=130
Median (range)	33 (13–47)	37 (22–50)	38 (13–50)	35.8 (20–50.5)
<35 g/L, n (%)	200 (58)	21 (33)	49 (31)	56 (43)
Creatinine, mol/L	N=344	N=66	N=191	N=130
Median (range)	93.9	82.7	76.3	76.3
	(43–270)	(45.8–152.5)	(35.8–190.7)	(33.6–152.5)
Creatinine clearance <30 mL/min, n (%)	20 (6)	3 (5)	21 (11)	4 (3)
High-risk cytogenetics – t(4;14), t(14;16), del(17p) by FISH, n/N (%)	26/168 (16)	15/44 (34)	33/140 (24)	22/113 (19)

BIW: twice-weekly; EU: European Union; ISS: International Staging System; QW: once-weekly; VMP: bortezomib-melphalan-prednisone.

Table 3. Cumulative dose of bortezomib delivered, overall and as a percentage of the planned total dose, and rate of completion of all planned cycles and (for VISTA and GIMEMA MM-03-05) early cycles (1–4) of bortezomib (excluding maintenance therapy).

	VISTA (n=340)	GIMEMA BIW (n=63)	GIMEMA QW (n=190)	GEM2005MAS65 (n=130)
All VMP cycles	1–9	1–9	1–9	1–6*
Total planned dose, mg/m²	67.6	67.6	46.8	36.4
Median cumulative dose, mg/m² (range)	38.5 (1.3–71.2)	42.1 (2.6–67.6)	40.3 (1.3–46.8)	32.9 (1.3–38.1)
Mean (SD)	36.6 (20.0)	40.8 (17.7)	34.6 (13.7)	28.6 (9.8)
Median as % of planned dose	57.0	62.3	86.1	90.4
Patients completing all cycles, n (%)	127 (37.4)	37 (58.7)	124 (65.3)	90 (69.2)
Early cycles (1–4 / 1–6)	1–4	1–4	1–4	1–6
Total planned dose, mg/m²	41.6	41.6	20.8	36.4
Median cumulative dose, mg/m² (range)	29.4 (1.3–44.8)	29.6 (2.6–41.6)	20.8 (1.3–20.8)	32.9 (1.3–38.1)
Mean (SD)	27.1 (11.9)	27.7 (9.6)	18.2 (4.3)	28.6 (9.8)
Median as % of planned dose	70.7	71.2	100	90.4
Patients completing early cycles, n (%)	210 (61.8)	47 (74.6)	153 (80.5)	90 (69.2)
Later cycles (5–9)	N=210	N=47	N=153	
Total planned dose, mg/m²	26.0	26.0	26.0	NA
Median cumulative dose, mg/m² (range)	15.6 (1.3–28.9)	20.0 (1.0–26.0)	23.4 (1.3–26.0)	NA
Mean (SD)	15.5 (7.6)	17.6 (7.7)	20.3 (7.1)	NA
Median as % of planned dose	60.0	76.9	90.0	NA

**Data do not include maintenance therapy in GEM2005MAS65. BIW: twice-weekly; NA: not applicable – as shown in Table 1, all 6 cycles in GEM2005MAS65 regarded as early cycles; QW: once-weekly; SD: standard deviation; VMP: bortezomib-melphalan-prednisone.*

study database; characteristics that were not consistently collected across studies are not shown. Propensity score methodology showed that the patient populations appeared generally similar between studies, with similar patient distributions in a logistical model employing age, sex, and ISS score as variables (*Online Supplementary Figure S1*). As shown in Table 2, the proportion of patients with ISS stage I MM was slightly lower in VISTA (19%) compared with GIMEMA BIW (26%), GIMEMA QW (29%), and GEM2005MAS65 (30%). In addition, VISTA was a global, international study, with patients enrolled from various regions, while the patients in the Italian GIMEMA MM-03-05 and Spanish GEM2005MAS65 studies were more homogeneous in this aspect.

Treatment exposure

As previously reported, patients received medians of 9, 9, 9, and 6 cycles of VMP therapy in VISTA,[4] GIMEMA BIW,[7] GIMEMA QW,[7] and GEM2005MAS65,[5] respectively. For bortezomib dosing during VMP treatment, the new analyses reported here showed that the proportion of patients receiving bortezomib for all planned VMP cycles (nine in VISTA and GIMEMA, six in GEM2005MAS65) was lower in VISTA (37.4%) *versus* GIMEMA BIW (58.7%), GIMEMA QW (65.3%), and GEM2005MAS65 (69.2%) (Table 3). Rates of completion of early induction cycles (cycles 1-4 in VISTA and GIMEMA) were somewhat higher in GIMEMA BIW (74.6%) and QW (80.5%) compared with those in VISTA (61.8%) (43).

Table 4. Rates of peripheral neuropathy and treatment discontinuation with the different VMP regimens (excluding maintenance therapy) (data derived from patient-level data from each study database).

	VISTA	GIMEMA BIW	GIMEMA QW	GEM2005MAS65
Peripheral neuropathy, %				
Overall rate (all grades)	47	44	22	25
Grade 2–4	32	27	6	15
Grade 3–4	13	14	2	7
Discontinuations, %				
Due to AEs, all cycles	14.7 / 18.5*	22.2	13.2	12
Due to AEs, early cycles	12.1	14.3	8.9	NA
Due to peripheral neuropathy	3/11†	16	4	5
Dose reductions, %				
Due to peripheral neuropathy	22	40	14	NR
Deaths during treatment, %	6	1.5	4.2	5
Treatment-related	2	NR	NR	4

**14.7% discontinued VMP, and an additional 18.5% selectively discontinued bortezomib due to AEs. †3% discontinued VMP, and an additional 11% selectively discontinued bortezomib due to peripheral neuropathy. AEs: adverse events; BIW: twice-weekly; NA: not applicable; NR: not recorded; QW: once-weekly.*

Table 5. Response rates and outcomes with the different VMP regimens (data derived from patient-level data from each study database).

	VISTA	GIMEMA BIW	GIMEMA QW	GEM2005MAS65
Response rates, IMWG uniform criteria*				
Response-evaluable patients, n	337	62	188	130
Overall response rate (≥PR), n (%)	251 (74)	54 (87)	151 (80)	104 (80)
CR rate, n (%)	111 (33)	17 (27)	44 (23)	26 (20)
CR+VGPR rate, n (%)	139 (41)	33 (53)	93 (49)	42 (32)
Progression-free survival, Kaplan-Meier estimates				
Patients included in analysis, n	340	63	190	130
Progressed/died, n (%)	111 (33)	51 (81)	153 (81)	85 (65)
Censored, n (%)	229 (67)	12 (19)	37 (19)	45 (35)
Median follow up, months (range)†	14.75 (0.03–25.95)	67.29 (0.03–71.36)	52.24 (0.00–66.04)	50.98 (0.12–63.85)
Median, months (95%CI)	21.75 (18.27, NE)	25.23 (18.07, 30.69)	22.21 (19.35, 26.15)	38.05 (31.09, 41.88)
3-year rate, % (95%CI)	NE	27.7 (16.1, 39.2)	24.7 (18.4, 31.0)	50.4 (40.7, 60.1)
Overall survival, Kaplan-Meier estimates				
Patients included in analysis, n	340	63	190	130
Died, n (%)	176 (52)	28 (44)	82 (43)	47 (36)
Censored, n (%)	164 (48)	35 (56)	108 (57)	83 (64)
Median follow up, months (range)	59.93 (0.16–72.38)	67.38 (0.03–74.87)	52.11 (0.00–67.65)	46.38 (0.10, 61.21)
Median, months (95%CI)	56.44 (51.98, 60.62)	65.45 (49.45, NE)	NE (46.06, NE)	60.58 (50.61, NE)
3-year rate, % (95%CI)	68.8 (63.7, 73.8)	75.7 (64.7, 86.8)	67.0 (60.1, 73.9)	71.4 (63.4, 79.3)
5-year rate, % (95%CI)	46.0 (40.3, 51.8)	50.5 (36.6, 64.5)	50.2 (41.8, 58.5)	35.4 (5.5, 65.3)

**Following induction, not including maintenance in GEM2005MAS65. †VISTA study data on progression-free survival were not up-dated following the initial analysis; hence, median follow-up for PFS was shorter compared with the other studies and the proportion of patients with PFS events was consequentlylower. BIW: twice-weekly; CI: confidence interval; CR: complete response; IMWG: International Myeloma Working Group; NE: not estimable; PR: partial response; QW: once-weekly; VGPR: very good partial response; VMP: bortezomib-melphalan-prednisone.*

The median cumulative dose of bortezomib received overall during VMP treatment in each study (i.e. excluding maintenance) and during early VMP induction cycles is also shown in Table 3. Data for the small subgroups of patients with high-risk cytogenetics are summarized in *Online Supplementary Table S2*. Over the full nine cycles of VMP induction (or six, in GEM2005MAS65), a similar median cumulative dose was delivered with the BIW regimens in VISTA (38.5 mg/m^2) and GIMEMA BIW (42.1 mg/m^2) as in GIMEMA QW (40.3 mg/m^2). However, the proportion of the planned bortezomib dose that was actually delivered during VMP treatment was highest in GEM2005MAS65 (90.4%) and GIMEMA QW (86.1%) compared with VISTA (57.0%) and GIMEMA BIW (62.3%). This was due to the lower number of bortezomib discontinuations and dose reductions required during VMP treatment in GEM2005MAS65 and GIMEMA QW (Table 4). In VISTA, these dose modifications primarily occurred during the early cycles of VMP treatment; the frequencies of dose holds or reductions during cycles 1-9 were 47.4%, 54.5%, 57.3%, 52.3%, 28.2%, 16.4%, 20.3%, 20.4%, and 20.0% (*Online Supplementary Figure S2*). Reflecting these findings in the overall population, the proportion of planned bortezomib dose actually delivered

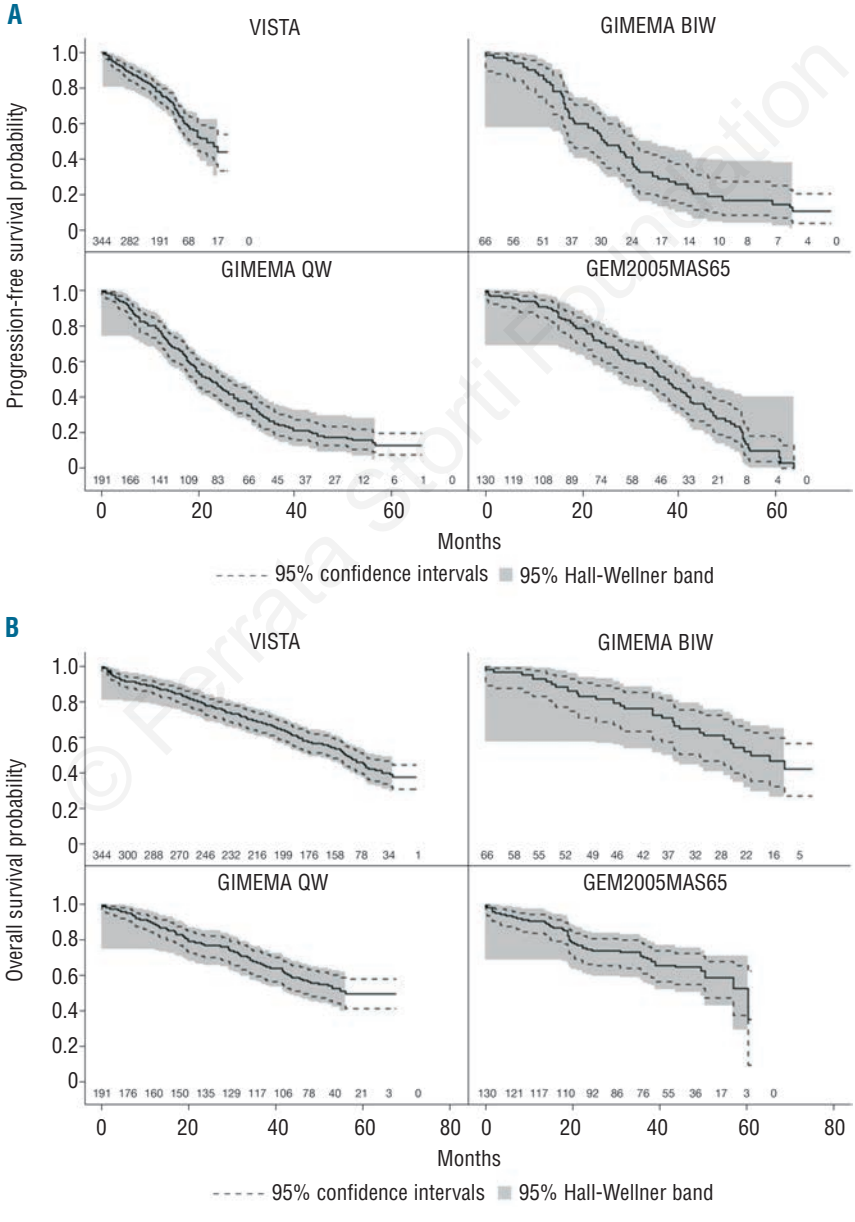

Figure 1. Kaplan-Meier product-limit survival curves for (A) progression-free survival and (B) overall survival for each of the studies of VMP, incorporating 95% confidence intervals and 95% Hall-Wellner bands. (BIW: twice-weekly; QW: once-weekly.)

in the small subgroups of patients with high-risk cytogenetics was also higher in GEM2005MAS65 (89.8%) compared with GIMEMA QW (79.7%) and GIMEMA BIW (73.7%), and compared with VISTA (51.9%) (*Online Supplementary Table S2*).

Among all patients, in early VMP induction cycles, the median cumulative dose delivered was similar in VISTA (29.4 mg/m^2) and GIMEMA BIW (29.6 mg/m^2), but lower in GIMEMA QW (20.8 mg/m^2), and higher in cycles 1-6 of GEM2005MAS65 (32.9 mg/m^2), as would be expected. However, the proportion of the planned bortezomib dose that was actually delivered during this early phase of VMP induction was higher in GIMEMA QW (100%) and GEM2005MAS65 (90.4%) *versus* VISTA and GIMEMA BIW (both 71%). Subsequently, due to the impact of dose modifications in the early cycles, the proportion of the planned bortezomib dose that was actually delivered during later cycles (5-9) was lower in VISTA (60%) *versus* GIMEMA BIW (77%) and GIMEMA QW (90%). The same patterns were seen in the data for the small subgroups of patients with high-risk cytogenetics (*Online Supplementary Table S2*).

Comparison of efficacy between VMP regimens

Response rates and progression-free survival (PFS) and overall survival (OS) data for each of the phase III studies are summarized in Table 5, derived from patient-level data from each study database. Overall response rates following VMP treatment (i.e. excluding maintenance data from GEM2005MAS65) appeared generally similar between studies (74-87%). Complete response (CR) rates appeared somewhat higher with more intensive dosing in early VMP induction cycles for VISTA (33%) and GIMEMA BIW (27%) compared with 23% in GIMEMA QW and 20% in GEM2005MAS65. In the small subgroups patients with high-risk cytogenetics (*Online Supplementary Table S3*), the overall response rates also appeared similar across studies (73-80%), while the CR rate appeared somewhat higher in VISTA (40%) in relation to the other studies, most notably GEM2005MAS65 (14%); the CR plus very good partial response (VGPR) rate also appeared lower in GEM2005MAS65 (27%) relative to the other studies in patients with high-risk cytogenetics. However, patient numbers in the subgroups were limited (n=15-33).

Median PFS appeared similar in VISTA (21.75 months), GIMEMA BIW (25.23 months), and GIMEMA QW (22.21 months), but appeared somewhat longer in GEM2005MAS65 (median 38.05 months), possibly associated with the use of up to three years of bortezomib-based maintenance therapy. Kaplan-Meier product-limit survival curves for PFS for each study are shown in Figure 1A, and indicate the apparent similarity in PFS between VISTA, GIMEMA BIW, and GIMEMA QW, and the apparent prolonged PFS in GEM2005MAS65.

Kaplan-Meier product-limit survival curves for OS for each study are shown in Figure 1B, and suggest similar OS across studies. OS rates at three years were high in all studies (67.9-75.7%) (Table 5), with no substantial differences apparent, and rates at five years also appeared similar across the 3 studies with median follow-up of over 4 years (46.0-50.5%). It should be noted that OS may have been affected by regional variations in the availability of active novel-agent-based regimens as salvage, as well as by differences in median follow up between studies.

Data on PFS and OS in the small subgroups of patients with high-risk cytogenetics are summarized in *Online Supplementary Table S3*. PFS data in these patients appeared to generally reflect those for the overall populations, with medians appearing similar; as in the overall populations, median PFS appeared prolonged in GEM2005MAS65 (37.05 months), possibly associated with the use of bortezomib-based maintenance therapy. Data appear to suggest a generally shorter OS among patients with high-risk cytogenetics relative to the overall populations across the studies. Median OS (44.12-59.66 months) and 3-year rates (54.5-78.6%) appeared to vary across the studies, but comparisons are confounded by the small patient numbers.

Comparison of peripheral neuropathy and other aspects of safety between VMP regimens

Rates of peripheral neuropathy and discontinuations due to AEs with the VMP regimens are summarized in Table 4. The grade 3/4 peripheral neuropathy rate was 13% in VISTA and 14% in GIMEMA BIW, but was reduced to 7% in GEM2005MAS65 and 2% in GIMEMA QW. Similarly, discontinuations due to peripheral neuropathy were reduced in GIMEMA QW (4%) compared with VISTA (3% all treatment, 11% selective bortezomib discontinuation) and GIMEMA BIW (16%), as were bortezomib dose reductions due to peripheral neuropathy (14% *vs.* 22% and 40%, respectively).

Discussion

This analysis represents the first detailed evaluation and comparison of the three VMP regimens investigated in phase III studies to date, using the latest available patient-level data to evaluate consistently parameters and end points across studies. In particular, this is the first time that the same parameters, including bortezomib cumulative dose, proportion of planned dose delivered, and discontinuations, have been evaluated at the same time points across all 3 studies. It is also the first analysis to address these parameters across studies in the context of long-term outcomes, in particular 3- and 5-year OS rates, and with a detailed analysis of dose reductions and discontinuations due to peripheral neuropathy with the three VMP regimens.

The results of the phase III studies analyzed here show that the use of QW bortezomib dosing schedules in the VMP regimen in GIMEMA QW7 and GEM2005MAS655 resulted in a similar cumulative dose of bortezomib and high efficacy with VMP treatment, comparable with that demonstrated in VISTA.[3,4,10] Across the studies, CR rates with VMP treatment appeared somewhat higher in VISTA[3,4] and GIMEMA BIW,[7,9] but this did not appear to translate into differences in long-term OS, with 3-year rates of 67.9-75.7% and 5-year rates of 35.4-50.5% across studies. Median PFS also appeared similar across the VISTA and GIMEMA studies (21.75-25.23 months) but appeared higher in GEM2005MAS65 (38.05 months), likely due to the impact of up to three years of maintenance with bortezomib-based therapy, as discussed below. Notably, while the median cumulative doses of bortezomib administered during VMP treatment appeared similar across studies, particularly across those employing the same planned duration of treatment of nine cycles, the proportion of the planned bortezomib dose actually deliv-

ered was higher with the QW regimens, thus counterbalancing the initially lower CR rate with these regimens *versus* the BIW regimens.

It is important to emphasize that comparisons across studies should be made with caution due to potential confounding factors, and that there are no randomized studies directly comparing BIW with QW bortezomib dosing in combination regimens, emphasizing the importance and relevance of this detailed analysis. While disease outcomes appeared similar across the studies, VISTA appeared to include a lower proportion of patients with ISS stage I disease and enrolled patients from various regions around the world; both of these factors may have had an effect on the findings. A formal meta-analysis or case-match analysis using these 3 studies of VMP was not feasible with the available data and was confounded by differences between studies in terms of length and frequency of follow up. However, using propensity score methodology, we demonstrated that the patient populations appeared generally comparable between studies, supporting the validity of the indirect, between-study comparisons reported here and the similar efficacy seen with BIW and QW bortezomib in the VMP regimen. Furthermore, in the GIMEMA MM-03-05 study, a combined analysis of the VMPT and VMP arms demonstrated no significant difference in CR rates between patients receiving QW *versus* BIW bortezomib dosing in these regimens (30% *vs.* 35%; P=0.27), and no significant differences in 3-year PFS (50% *vs.* 47%; P>0.999) and OS (88% *vs.* 89%; P=0.54) rates.[7] Results from other smaller studies of QW bortezomib-based combination regimens in patients with previously untreated MM[16,17] also support the similar efficacy with QW *versus* BIW bortezomib in the VMP regimen seen in the phase III studies analyzed here. Similarly, QW bortezomib dosing has been shown to offer notable efficacy in follicular lymphoma in combination with rituximab.[18,19] However, it should not be assumed that these findings from the VISTA, GIMEMA MM-03-05, and GEM2005MAS65 studies employing VMP in elderly, transplant-ineligible patients may translate to induction therapy for younger, transplant-eligible patients. In this setting, further studies would be needed of QW bortezomib-based induction regimens to determine whether the reduced bortezomib dose density compared with BIW dosing in these shorter treatment courses had a detrimental impact on post-induction or post-transplant response rates and on post-transplant outcomes.

An important aspect of our findings was the apparently similar efficacy of VMP with BIW and QW bortezomib dosing in patients with high-risk cytogenetics. In general, the relative results between studies seen in the overall populations were reflected in these small subgroups of patients (n=15-33). Overall response rates appeared similar, while the CR rate appeared higher in VISTA, using the more intensive BIW bortezomib dosing regimen, compared with GEM2005MAS65 in particular, employing predominantly QW dosing for a total of only six induction cycles. However, median PFS in patients with high-risk cytogenetics appeared similar to that in the overall population, across all studies, with a similar PFS seen in VISTA, GIMEMA BIW, and GIMEMA QW, and a longer PFS in GEM2005MAS65, possibly associated with the use of bortezomib-based maintenance. OS appeared somewhat shorter in patients with high-risk cytogenetics *versus* the overall population, notably in VISTA and GEM2005MAS65, but the small patient numbers prevent any meaningful conclusions being drawn regarding whether the lower intensity QW bortezomib dosing regimens had a specific adverse effect in these patients. Contradictory results have been reported from the overall study populations, with no significant difference in OS reported between patients with high-risk versus standard-risk cytogenetics in GIMEMA MM-03-05,[9] but shorter OS reported in high-risk patients in VISTA and GEM2005MAS65.[10,20]

While activity appeared generally similar between VMP regimens in the present analysis, the rates of peripheral neuropathy and associated discontinuations and dose reductions were lower with VMP regimens using primarily QW bortezomib dosing, i.e. in GIMEMA QW and GEM2005MAS65. Notably, the rate of grade 3/4 peripheral neuropathy was reduced from 13% in VISTA[3,4,21] and 14% in GIMEMA BIW7 (both incorporating four 6-week cycles of BIW dosing) to 7% in GEM2005MAS65 (one 6-week cycle of BIW dosing)[5] and 2% in GIMEMA QW (no BIW dosing).[7] Consequently, a higher proportion of the planned dose of bortezomib was actually delivered in GIMEMA QW and GEM2005MAS65 compared with VISTA and GIMEMA BIW. Moreover, the VISTA, GIMEMA BIW, and GIMEMA QW regimens delivered a similar median cumulative dose, as reflected in the comparable efficacy. The similar cumulative dose in VISTA and GIMEMA QW was due to the impact of bortezomib dose modifications that occurred primarily during cycles 1-4 in VISTA, i.e. the initial BIW cycles, as shown in *Online Supplementary Figure S2*. Importantly, a phase III trial in patients with relapsed MM has shown that subcutaneous administration of bortezomib on a standard BIW dosing schedule delivers an equivalent cumulative dose, and thus similar efficacy, to standard intravenous administration.[22] However, the subcutaneous route of administration was associated with a significantly lower rate of peripheral neuropathy, including 6% versus 16% grade ≥3 peripheral neuropathy.[22] Thus, switching from intravenous to subcutaneous administration may represent an additional strategy for managing toxicity in some patients while maintaining efficacy, and may improve convenience of therapy, particularly in elderly MM patients.

Maintenance therapy was employed following VMP in only one study (GEM2005MAS65). Notably, in this study, the CR rate increased from 24% to 42% among patients receiving bortezomib-based maintenance using an intermittent dosing schedule (Table 1) after a median follow up of 46 months.[8] This translated into a prolongation of PFS, with a median of 35 months for the per-protocol population.[5] The use of bortezomib-based maintenance for up to two years was also shown to contribute to substantial efficacy following VMPT in the GIMEMA MM-03-05 study (from the landmark of completing VMPT or VMP therapy and proceeding to bortezomib–thalidomide maintenance or no maintenance, respectively, median PFS was 31.5 versus 17.8 months, and 4-year OS rate was 67% versus 55%, respectively).[6,7,9] However, the CR rate increased only from 58% to 62% among 62 patients who completed nine cycles of VMPT and then received at least six months of maintenance with bortezomib-thalidomide.[6] These data suggest that administration of bortezomib-based maintenance on an intermittent dosing schedule following truncated VMP induction may represent a valid approach to delivering sufficient cumulative dose of bortezomib to

maximize response to treatment.[5,8] Further support is provided by the findings of the HOVON-65/GMMG-HD4 phase III study in transplant-eligible MM patients, in which bortezomib maintenance resulted in increased response rates and a lengthy PFS following just three cycles of bortezomib-based induction and stem cell transplantation.[23] Importantly, in both GIMEMA MM-03-059 and GEM2005MAS65,[8] bortezomib-based maintenance therapy was well tolerated, with limited additional toxicity.

In conclusion, as has been well established based upon the results from VISTA, VMP can be considered as a standard regimen for the treatment of elderly, transplant-ineligible, previously untreated MM patients. This standard of care has been optimized through the use of modified VMP schemas employing QW administration of bortezomib, to further confirm VMP (using different schedules) as a standard regimen in this setting; the analyses reported here provide valuable information in this context and guidance for clinicians. Toxicity, especially peripheral neuropathy, is the most important issue to be considered regarding the use of the VMP regimen in this generally frail and elderly patient population, and findings from phase III studies have shown that there are several ways in which to try to decrease the toxicity associated with VMP. The Italian and Spanish experiences from the GIMEMA MM-03-05 and GEM2005MAS65 trials have demonstrated that the exclusive or predominant use of QW bortezomib administration in VMP reduces toxicity while resulting in a similar cumulative bortezomib dose and offering similar efficacy, and the phase III study of subcutaneous bortezomib indicates that this route of administration may also have an important role in this regard. Additionally, as discussed earlier, the use of bortezomib-based maintenance therapy results in prolonged PFS with limited additional toxicity, and may be of particular relevance for increasing efficacy following 'soft', truncated VMP induction, as seen in GEM2005MAS65. Definitive studies are required to define the optimal treatment schema and the duration of the induction and maintenance components of therapy. In particular, studies combining QW dosing and subcutaneous administration of bortezomib will be of interest with regards to minimizing rates of peripheral neuropathy. Until the findings of such studies become available, a practical recommendation might be to use nine 5-week cycles of VMP with QW bortezomib, in order to deliver sufficient melphalan; in patients who are fit enough, a single 6-week cycle of bortezomib BIW dosing could instead be administered as the first cycle, in order to maximize the initial response.

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