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Effects of single-agent bortezomib as post-transplant consolidation therapy on multiple myeloma-related bone disease: a randomized phase II study

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Summary

This phase II study explored the effects of bortezomib consolidation *versus* observation on myeloma-related bone disease in patients who had a partial response or better after frontline high-dose therapy and autologous stem cell transplantation. Patients were randomized to receive four 35-day cycles of bortezomib 1·6 mg/m^2 intravenously on days 1, 8, 15 and 22, or an equivalent observation period, and followed up for disease status/survival. The modified intent-to-treat population included 104 patients (51 bortezomib, 53 observation). There were no meaningful differences in the primary endpoint of change from baseline to end of treatment in bone mineral density (BMD). End-of-treatment rates (bortezomib *versus* observation) of complete response/stringent complete response were 22% vs. 11% (P = 0·19), very good partial response or better of 80% vs. 68% (P = 0·17), and progressive disease of 8% vs. 23% (P = 0·06); median progression-free survival was 44·9 months vs. 21·8 months (P = 0·22). Adverse events observed ≥15% more frequently with bortezomib *versus* observation were diarrhoea (37% vs. 0), peripheral sensory neuropathy (20% vs. 4%), nausea (18% vs. 0) and vomiting (16% vs. 0). Compared with observation, bortezomib appeared to have little impact on bone metabolism/health, but was associated with trends for improved myeloma response and survival.

Keywords: bortezomib, multiple myeloma, consolidation, bone, bone mineral density.

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Bone disease is a very common presenting feature in patients with multiple myeloma (MM), and can substantially affect patient morbidity and quality of life (Sezer, 2009; Zangari *et al*, 2012). Bone destruction is a particularly debilitating manifestation of the disease (Sezer, 2009; Hameed *et al*, 2014); osteolytic lesions are seen in 70–80% of patients at diagnosis (Kyle *et al*, 2003; Terpos *et al*, 2013). The pathogenesis of MM-related bone disease is directed by inhibited osteoblast function and enhanced osteoclast activity (Sezer, 2009; Zangari *et al*, 2012; Terpos *et al*, 2013), resulting in an imbalance between the processes of bone resorption and formation (Delgado-Calle *et al*, 2014; Hameed *et al*, 2014). Patients with bone disease typically receive concomitant bisphosphonates, which inhibit osteoclast activity; however, bisphosphonates do not restore bone formation (Sezer, 2009; Terpos *et al*, 2013).

The proteasome inhibitor bortezomib is approved in the United States for the treatment of MM (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf) and in the European Union for the treatment of patients with previously untreated MM who are ineligible for high-dose therapy and stem cell transplantation (HDT-SCT, in combination with melphalan and prednisone); patients with previously untreated MM who are eligible for HDT-SCT (as induction therapy in combination with dexamethasone ± thalidomide); and patients with relapsed MM (as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone) (European Medicines Agency, 2014). Through its mechanism of action, proteasome inhibition with bortezomib affects multiple signal-transduction pathways, including inhibiting nuclear factor kappa B activation and other pathways involved in regulating bone metabolism (von Metzler *et al*, 2007; Zangari *et al*, 2012). Consequently, in addition to its anti-MM activity, preclinical and clinical data suggest that bortezomib can inhibit osteoclastogenesis (von Metzler *et al*, 2007; Deleu *et al*, 2009; Pennisi *et al*, 2009; Mohty *et al*, 2014) and stimulate osteoblast activity (Zangari *et al*, 2005; Heider *et al*, 2006; Giuliani *et al*, 2007; Deleu *et al*, 2009; Pennisi *et al*, 2009; Lund *et al*, 2010; Mohty *et al*, 2014), thus potentially exerting positive effects on bone metabolism (Terpos *et al*, 2010; Delforge *et al*, 2011) independent of its effects on MM.

This phase II study (NCT01286077) was conducted to explore the effects of bortezomib consolidation therapy compared with observation alone on MM-related bone disease in MM patients who had undergone frontline HDT-ASCT. Notably, this was the first randomized study of bortezomib with a bone-specific endpoint.

Methods

Patients

Adult patients with MM who had achieved a partial response or better (≥PR) after frontline single/double HDT-ASCT were eligible for inclusion. The date of hospital discharge after ASCT had to be between 60 and 120 days prior to randomization. Patients must have had adequate haematological and hepatic function (including: haemoglobin ≥75 g/l; absolute neutrophil count $\geq 0{\cdot}75 \times 10^9$/l; platelet count $\geq 50 \times 10^9$/l; corrected serum calcium <3·5 mmol/l; aspartate aminotransferase ≤2·5 × the upper limit of normal (ULN); alanine aminotransferase ≤2·5 × ULN; and total bilirubin ≤1·5 × ULN), Karnofsky performance status ≥60% and life expectancy of at least 12 months. Exclusion criteria included receiving another experimental or anti-myeloma therapy after ASCT, grade ≥2 peripheral neuropathy or neuropathic pain, treatment for another cancer in the past 5 years, uncontrolled or severe cardiovascular disease within 6 months of enrolment, or other serious medical conditions likely to interfere with study participation. The study was conducted per the Declaration of Helsinki, Good Clinical Practice guidelines and local regulatory requirements. Relevant institutional review boards/ethics committees approved the protocol. All patients provided written informed consent.

Study design

This randomized, open-label, multicentre, phase II study enrolled patients between July 2009 and May 2012. Database lock for final analysis was 8 August 2014. Patients were randomized 1:1 [stratified by age (<65 vs. ≥65 years) and baseline bisphosphonate use (yes or no)] to receive four 35-day cycles of bortezomib 1·6 mg/m^2 IV on days 1, 8, 15 and 22, or observation alone. Concomitant bisphosphonates were permitted as medically indicated and per local practice. Bortezomib dose adjustments and delays were permitted for toxicity management. Following the end-of-treatment (EOT) visit, patients underwent 18-months' follow-up for disease status/survival assessment. Survival follow-up continued until the last patient had completed the 18-month follow-up phase.

Endpoints

The primary endpoint was change from baseline to EOT in bone mineral density (BMD). Secondary endpoints included: change from baseline in BMD at other time points; change from baseline in bone biomarkers [C-terminal cross-linking telopeptide of type I collagen (CTX-I), C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinases (ICTP), Dickkopf homolog 1 (DKK-1), bone-specific alkaline phosphatase (bALP), osteocalcin]; skeletal-related events; disease status/myeloma response; progression-free survival (PFS); overall survival (OS); and safety.

Assessments

BMD was measured in the lumbar spine and femur by dual-energy X-ray absorptiometry at baseline, after two cycles, at EOT, and after 6, 12 and 18 months follow-up. BMD data were centrally assessed (Central Reading Centre, Charité, Berlin). Samples for measurement of serum bone biomarkers and serum/urine M-protein were collected at baseline, after two cycles, at EOT and after 4, 6, 12 and 18 months follow-up. Bone biomarkers were measured centrally (INTERLAB, Munich, Germany). Disease status was investigator-assessed per International Myeloma Workshop Consensus 2009 criteria (Rajkumar *et al*, 2011) for tumour response. Treatment-emergent adverse events (TEAEs) were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 3·0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Sample size determination

Due to the exploratory nature of the study, a formal sample size calculation was not done. A sample size of 100 patients (50 per arm based on 1:1 randomization) was deemed sufficient to obtain reliable data on the primary and secondary endpoints. Assuming a dropout rate with screening failures of approximately 20%, it was planned to enrol 120 patients. In the setting of a confirmatory trial, a sample size of 50 patients per arm would provide 80% power (type II error rate of $\beta = 0{\cdot}20$) to detect an effect size of 0·566 using a two-group *t*-test with a significance level (type I error rate) of $\alpha = 0{\cdot}05$.

Statistical analyses

Statistical analyses were exploratory, as the study was not powered to address pre-defined hypotheses. Analyses were conducted using SAS® statistical software v9·3 (SAS Institute, Cary, NC, USA). The first (main) analysis was conducted after all patients reached EOT and the final analysis after all patients had completed 18 months follow-up. Analyses were predominantly conducted in a modified intent-to-treat (mITT) population [all randomized patients who received ≥1 dose of study drug (bortezomib arm) or who had ≥1 post-baseline assessment (observation arm)], and additionally in patients with a baseline and ≥1 post-baseline assessment for BMD (full analysis set). A last observation carried forward (LOCF) approach was used for missing assessments; missing baseline values were not replaced. Analysis of covariance (ANCOVA) was used for between-arm comparisons of changes in BMD. Kaplan–Meier methodology was used for survival analyses; *P*-values for PFS and OS were determined using the

log-rank test. *P*-values for response and TEAEs were determined using the two-sided Fisher's exact test.

See Appendix S1 for additional methodology.

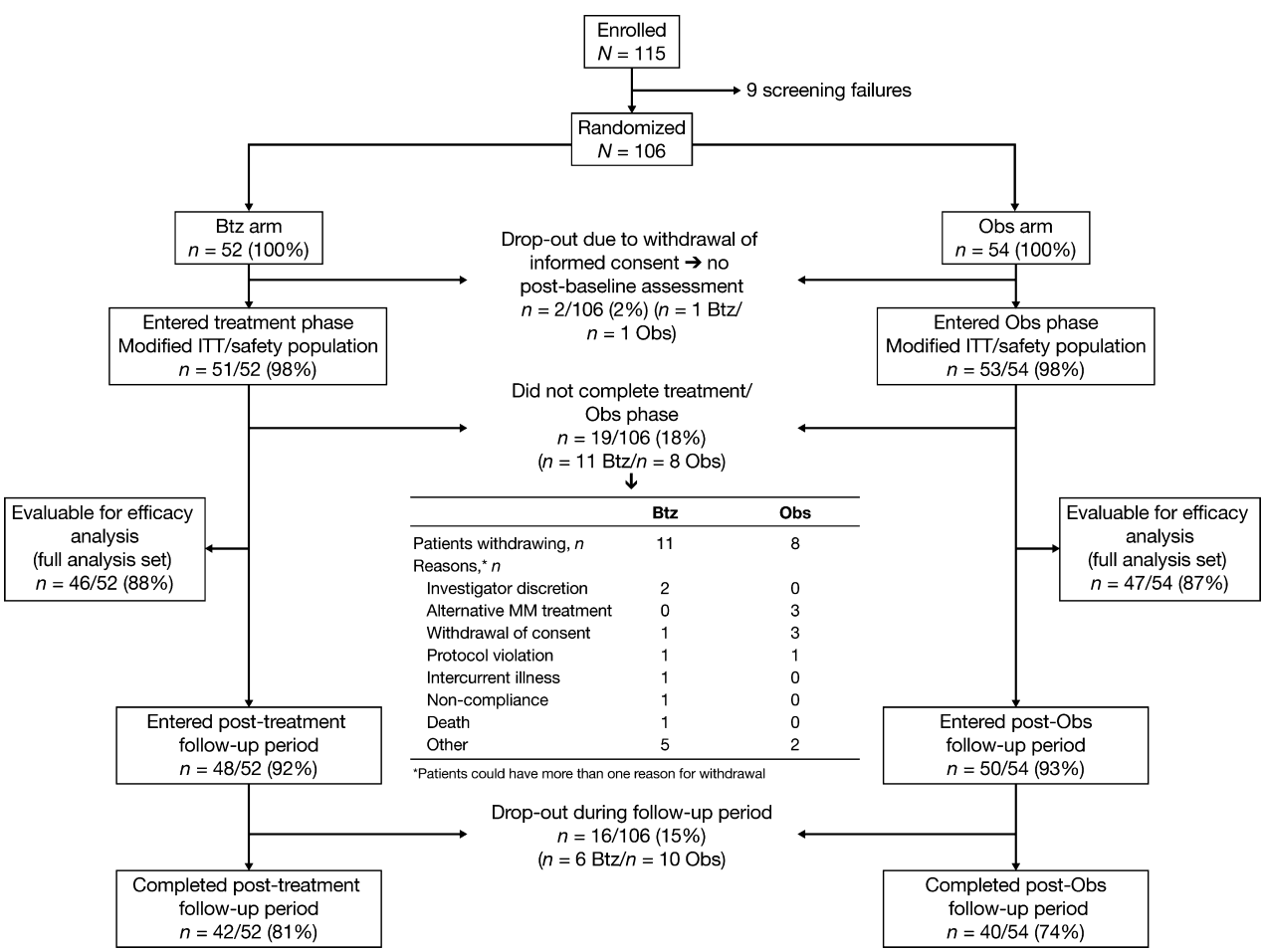
Results

Patients

Between July 2009 and May 2012, 106 patients from 18 sites in eight European countries were randomized ($n = 52$ to bortezomib, $n = 54$ to observation). Patient disposition is shown in Fig 1. Two randomized patients were excluded from the mITT analysis (one in the bortezomib arm, due to not receiving bortezomib and lack of ≥1 post-baseline assessment; one in the observation arm, due to lack of ≥1 post-baseline assessment). Thus, 104 patients ($n = 51$ bortezomib and $n = 53$ observation) were included in the mITT population and in the safety analysis. Ninety-three patients ($n = 46$ bortezomib and $n = 47$ observation) had a baseline and ≥1 post-baseline assessment of BMD and were included in the full analysis set for evaluation of BMD and bone biomarkers. Median time from hospital discharge following ASCT to randomization was 102 days.

Patient demographics and baseline characteristics were similar between the bortezomib and observation arms (Table I). Patients' median age was 58·0 vs. 57·0 years; 12% vs. 13% of patients, respectively, were aged ≥65 years. Seventy-one per cent *versus* 66% of patients in the bortezomib and observation arms, respectively, had received bortezomib-based induction therapy prior to HDT-ASCT. Per the study inclusion criteria, all patients had achieved ≥PR post-HDT-ASCT. At the screening assessment, rates of complete response plus stringent complete response (CR + sCR) were 16% and 15%, very good partial response or better (≥VGPR) were 80% and 77%, and partial response or better (≥PR) were 98% and 98% in the bortezomib and observation arms, respectively. There was some imbalance in concomitant bisphosphonate use between the bortezomib and observation arms (69% vs. 75%, respectively) including 39% vs. 60% zoledronic acid use (Table II).

Patients in the bortezomib arm received a median of 4 cycles (range 2–4). The median cumulative dose of bortezomib received across the 4 consolidation cycles was 25·6 mg/m^2 (range 8·0–25·6). Forty-one (79%) and 46 (85%) patients completed the respective bortezomib and observation phases as planned.



	Btz	Obs
Patients withdrawing, *n*	11	8
Reasons,* *n*		
Investigator discretion	2	0
Alternative MM treatment	0	3
Withdrawal of consent	1	3
Protocol violation	1	1
Intercurrent illness	1	0
Non-compliance	1	0
Death	1	0
Other	5	2

*Patients could have more than one reason for withdrawal

Fig 1. Patient disposition. Btz, bortezomib; ITT, intent-to-treat; MM, multiple myeloma; Obs, observation.

Table I. Patient demographics and baseline characteristics (mITT population).

	Bortezomib (n = 51)	Observation (n = 53)	Total (N = 104)
Median age, years (range)	58·0 (27–75)	57·0 (35–73)	57·0 (27–75)
Aged ≥65 years, n (%)	6 (12)	7 (13)	13 (13)
Male, n (%)	33 (65)	31 (58)	64 (62)
Grade 1 sensory neuropathy, n (%)	14 (27)	15 (28)	29 (28)
Median time from initial MM diagnosis, months (range)	10 (5–73)	11 (6–50)	10 (5–73)
MM treatment history, n (%)			
Prior bortezomib-based induction	36 (71)	35 (66)	71 (68)
Prior IMiDs (thalidomide/lenalidomide)	13 (25)	10 (19)	23 (22)
Prior irradiation	13 (25)	14 (26)	27 (26)
Prior surgery	7 (14)	13 (25)	20 (19)
Prior bisphosphonate use, n (%)	39 (76)	40 (75)	79 (76)
Lytic bone lesions, n (%)			
None	15 (29)	15 (28)	30 (29)
1–3	12 (24)	6 (11)	18 (17)
4–10	10 (20)	8 (15)	18 (17)
>10	14 (27)	21 (40)	35 (34)
Missing	0	3 (6)	3 (3)
Response at screening, n (%)			
≥VGPR	41 (80)	41 (77)	82 (79)
CR+sCR	8 (16)	8 (15)	16 (15)
sCR	2 (4)	1 (2)	3 (3)
CR	6 (12)	7 (13)	13 (13)
VGPR	33 (65)	33 (62)	66 (63)
PR	9 (18)	11 (21)	20 (19)
Not evaluable	1 (2)	1 (2)	2 (2)

CR, complete response; IMiDS, immunomodulatory drugs; ITT, modified intent-to-treat; mITT, modified intent-to-treat; MM, multiple myeloma; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Changes in BMD

Table III summarizes the change in BMD from baseline to EOT (primary endpoint). Increases in BMD from baseline to EOT were seen in both the bortezomib and observation arms; however, there were no meaningful between-arm differences in the relative magnitude of the observed increases (Table III; Supplementary Figure S1). Similarly, no relevant differences between the bortezomib and observation arms in change from baseline to EOT in BMD were observed in subgroup analyses according to the stratification factors of age and bisphosphonate use (Supplementary Table SI). Longitudinal analysis of change in BMD from baseline to the end of study follow-up did not show any meaningful differences in the magnitude of changes in BMD between the bortezomib and observation arms (Supplementary Figure S2).

Table II. Concomitant medications (mITT population).

Concomitant medication, n (%)	Bortezomib (n = 51)	Observation (n = 53)	Total (N = 104)
Bisphosphonates	35 (69)	40 (75)*	75 (72)
Zoledronic acid	20 (39)	32 (60)	52 (50)
Pamidronic acid	7 (14)	3 (6)	10 (10)
Ibandronic acid	5 (10)	4 (8)	9 (9)
Clodronic acid	3 (6)	3 (6)	6 (6)
Mineral supplements	22 (43)	26 (49)	48 (46)
Antiviral agents	38 (75)	17 (32)	55 (53)
Antibacterial agents	35 (69)	24 (45)	59 (57)
Analgesics	29 (57)	15 (28)	44 (42)

mITT, modified intent-to-treat.

*Two patients in the observation arm had received >1 type of bisphosphonate during the study (n = 1: zoledronic acid and pamidronic acid; n = 1: zoledronic acid and ibandronic acid).

Changes in bone biomarkers

Table IV shows the change from baseline to EOT for the five bone biomarkers evaluated in this study (CTX-I, ICTP, DKK-1, bALP and osteocalcin). Serum levels of each biomarker were found to decrease from baseline to EOT, and while the magnitude of the decrease varied between the different biomarkers, there were no meaningful differences between the bortezomib and observation arms. In longitudinal analysis of serum biomarker levels, there were no apparent differences between the bortezomib and observation arms with respect to the observed changes over time (Supplementary Figure S3).

Skeletal-related events

No meaningful differences were observed between the bortezomib and observation arms in the incidence of skeletal-related events (comprising pathological fractures,

Table III. Median percentage change in BMD from baseline to EOT/LOCF (full analysis set).*

	Bortezomib (n = 46)		Observation (n = 47)	
	n	Median change, % (range; IQR)	n	Median change, % (range; IQR)
Spine	38	+1·69 (−4·48, +10·53; +0·17, +3·38)	39	+1·18 (−4·94; +9·43; -0·61, +3·73)
Femur (neck)	43	+0·39 (−3·90, +11·52; −1·24, +2·03)	45	+0·29 (−3·70, +15·82; −1·56, +1·88)
Femur (total)	43	+0·74 (−3·05, +5·64; −0·25, +1·64)	45	+1·77 (−4·46, +10·94; −0·48, +2v92)

BMD, bone mineral density; EOT, end of treatment; IQR, interquartile range; LOCF, last observation carried forward.
*Patients with a baseline assessment and ≥1 post-baseline assessment of BMD (n = 93).

radiotherapy, spinal cord compression, orthopedic surgery, or hypercalcemia). No patients in the bortezomib arm had reported skeletal-related events, and only 1 (2%) patient in the observation arm received radiotherapy by EOT.

Myeloma response

Post-consolidation/observation rates of response in the mITT population are summarized in Table V. Relative to response rates at screening, bortezomib consolidation appeared to improve response depth in some patients and appeared to result in a reduced rate of progressive disease (PD) compared with observation alone. In the bortezomib arm, rates of CR + sCR were 16% at screening and 22% post-consolidation. In the observation arm, CR + sCR rates were 15% at screening and 11% post-observation. In the bortezomib and observation arms, respectively, EOT rates of ≥VGPR were 80% and 68% (Fisher's exact test P = 0·17) and PD were 8% and 23% (Fisher's exact test P = 0·06). Overall, there was an exploratory significant correlation between treatment group and response in favour of bortezomib consolidation (Cochran-Mantel-Haenszel statistics P = 0·04).

PFS and OS

The median duration of follow-up from randomization was 36 months (range 2–53) in the bortezomib arm and 30 months (range 3–49) in the observation arm. Median duration of follow-up from first anti-MM treatment was 46 months (range 13–63) in the bortezomib arm and 41 months (range 11–71) in the observation arm.

Kaplan–Meier analyses of PFS and OS in the mITT population are shown in Fig 2. There was a trend for longer PFS with bortezomib consolidation *versus* observation alone. Median PFS from randomization was 44·9 months in the bortezomib arm and 21·8 months in the observation arm {hazard ratio [HR]: 0·71 [95% confidence interval (CI): 0·41–1·24]; log-rank P = 0·22}, and median PFS from first anti-MM treatment was 50·7 months and 35·0 months, respectively [HR: 0·68 (95% CI: 0·39–1·17); log-rank P = 0·16]. Estimated 1-year PFS rates from the start of administration of bortezomib consolidation therapy *versus* observation only were 84·8% (95% CI: 70·7–92·4) and 67·5% (95% CI: 52·0–79·0).

At the time of data cut-off, 21 (20%) patients had died; 11 in the bortezomib arm, 10 in the observation arm. Median OS from randomization was not reached in either arm. Mean OS from randomization was 40·1 months with bortezomib and 36·6 months with observation [HR: 1·01 (95% CI: 0·43–2·38); log-rank P = 0·98]. Median OS from first anti-MM treatment was not reached in either arm. Mean OS from first anti-MM treatment was 51·7 months with bortezomib and 47·1 months with observation [HR: 0·95 (95% CI: 0·40–2·25); log-rank P = 0·91].

Table IV. Median percentage change in serum bone biomarker levels from baseline to EOT/LOCF (full analysis set).*

	Bortezomib (n = 46)		Observation (n = 47)	
	n	Median change, % (range; IQR)	n	Median change, % (range; IQR)
Markers of bone resorption				
CTX-I	43	−29·37 (−84·48, +326·92; −54·32, 0)	44	−28·73 (−84·39, +79·78; −52·51, −1·39)
ICTP	43	−30·77 (−68·66, +56·96; −44·65, −13·21)	44	−25·95 (−57·64, +115·15; −39·47, −7·39)
Markers of bone formation				
DKK-1	43	−13·27 (−97·97, +5250; −34·86, +48·91)	44	−8·94 (−84·09, +2269; −49·52, +38·33)
bALP	43	−12·61 (−61·90, +172·73; −26·27, +14·86)	44	−12·22 (−69·58, +44·29; −28·94, +10·65)
Osteocalcin	43	−29·79 (−70·41, +100·38; −54·10, −9·72)	44	−31·54 (−75·23, +87·22; −40·35, −13·70)

bALP, bone-specific alkaline phosphatase; CTX-I, C-terminal cross-linking telopeptide of type I collagen; DKK-1, Dickkopf homolog 1; EOT, end of treatment; ICTP, C-terminal cross-linking telopeptide of type I collagen generated by matrix metalloproteinases; IQR, interquartile range; LOCF, last observation carried forward.
*In patients with a baseline assessment and ≥1 post-baseline assessment of bone mineral density (n = 93).

Table V. Post-bortezomib consolidation/observation rates of response (mITT population; EOT/LOCF).

Response*, *n* (%)	Bortezomib (*n* = 51)	Observation (*n* = 53)	Total (*N* = 104)
≥VGPR†	41 (80)	36 (68)	77 (74)
CR+sCR‡	11 (22)	6 (11)	17 (16)
sCR	1 (2)	1 (2)	2 (2)
CR	10 (20)	5 (9)	15 (14)
VGPR	30 (59)	30 (57)	60 (58)
PR	5 (10)	4 (8)	9 (9)
PD§	4 (8)	12 (23)	16 (15)
Not evaluable	1 (2)	0	1 (1)
Missing	0	1 (2)	1 (1)

CR, complete response; EOT, end of treatment; LOCF, last observation carried forward; mITT, modified intent-to-treat; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

*Disease status was investigator-assessed per International Myeloma Workshop Consensus 2009 criteria for tumour response.

†$P = 0{\cdot}17$ for between-arm comparison of rates of ≥VGPR *versus* <VGPR (two-sided Fisher's exact test).

‡$P = 0{\cdot}19$ for between-arm comparison of rates of CR+sCR *versus* <CR (two-sided Fisher's exact test).

§$P = 0{\cdot}06$ for between-arm comparison of rates of PD *versus* not PD (two-sided Fisher's exact test).

Safety

Table VI summarizes the overall safety profile and most common TEAEs in the bortezomib and observation arms. As expected, the overall incidence of TEAEs during the treatment/observation period was higher in the bortezomib arm than in the observation arm [$n = 49$ (96%) vs. $n = 42$ (79%); Fisher's exact test $P = 0{\cdot}02$]. TEAEs occurring with a≥15% difference in frequency between the arms were (bortezomib *versus* observation): diarrhoea (37% vs. 0), peripheral sensory neuropathy (20% vs. 4%), nausea (18% vs. 0) and vomiting (16% vs. 0). In the bortezomib and observation arms, respectively, rates of polyneuropathy-related events were 29% vs. 6% (of which none were grade ≥3), infections/infestations were 51% vs. 38% and herpes zoster reactivations were 10% vs. 6%. Grade ≥3 TEAEs occurred infrequently, with no significant differences between the two arms (Fisher's exact test $P = 0{\cdot}48$; Table VI).

Serious TEAEs were reported in 6 (12%) patients who received bortezomib consolidation and 3 (6%) patients under observation alone (Fisher's exact test $P = 0{\cdot}31$). Serious TEAEs in 2 (4%) patients in the bortezomib arm were assessed, respectively, as probably or possibly drug-related [herpes zoster ($n = 1$) and bacterial pneumonia ($n = 1$)]. Four (8%) patients discontinued bortezomib treatment due to TEAEs [anxiety and depression ($n = 1$); nausea, vomiting and diarrhoea ($n = 1$); herpes zoster infection ($n = 1$); and thrombocytopenia ($n = 1$)]. There was 1 TEAE-related death during the bortezomib treatment phase (acute hepatic failure due to pancreatic cancer, considered unrelated to bortezomib).

Discussion

This randomized phase II study evaluated the effects of single-agent bortezomib consolidation therapy *versus* observation alone on MM-related bone disease, plus efficacy and safety, in MM patients who had achieved a ≥PR after front-line HDT-ASCT. Notably, this was the first randomized study of bortezomib with a bone-specific endpoint. No clinically meaningful advantages were observed with post-transplant bortezomib consolidation compared with observation alone in terms of change in BMD from baseline to EOT or to end of follow-up. This was also reflected in the bone biomarker results, which showed that although levels of markers of bone resorption (CTX-I, ICTP) decreased during bortezomib treatment, a similar decrease was observed in the observation arm, and decreases in the levels of markers of bone formation (bALP, osteocalcin)/osteoblast regulators (DKK-1) were also observed to a similar extent in both arms. Skeletal-related events were rarely observed (1 patient in the observation arm, none in the bortezomib arm by EOT). Together, these findings suggest that in this patient population, there was no apparent benefit with bortezomib consolidation *versus* observation alone in terms of effects on bone metabolism markers and BMD, within the timeframe of the study.

There are several possible confounding factors in the present study that may have prevented demonstration of a difference between the bortezomib consolidation and observation arms with respect to effects on bone metabolism/bone health. These include: (i) prior bortezomib-based induction therapy in a substantial proportion of patients in both arms (71% bortezomib, 66% observation), the effects of which may have persisted during the follow-up period, possibly masking an effect of bortezomib consolidation over observation alone; (ii) prior intensive chemotherapy (predominantly melphalan-based) and ASCT in all patients prior to randomization, which may have negatively affected bone mineral density (Laroche *et al*, 2012); (iii) inclusion of only patients who had achieved a ≥PR to prior ASCT in the present study; and (iv) prior and/or concomitant bisphosphonate use in a substantial proportion of patients in both arms, which may have contributed to the preservation of bone density (Greenfield *et al*, 2014). Notably, the rate of use of concomitant zoledronic acid (which is generally regarded as the most potent bisphosphonate in the treatment of myeloma-related bone disease) was substantially lower in the bortezomib arm than in the observation arm (39% vs. 60%). In addition, patients in the bortezomib arm received only four 35-day cycles of bortezomib consolidation at 1·6 mg/m^2. Although this regimen is in line with other bortezomib consolidation studies (Ladetto *et al*, 2010; Straka *et al*, 2015), it remains possible that a longer duration of consolidation

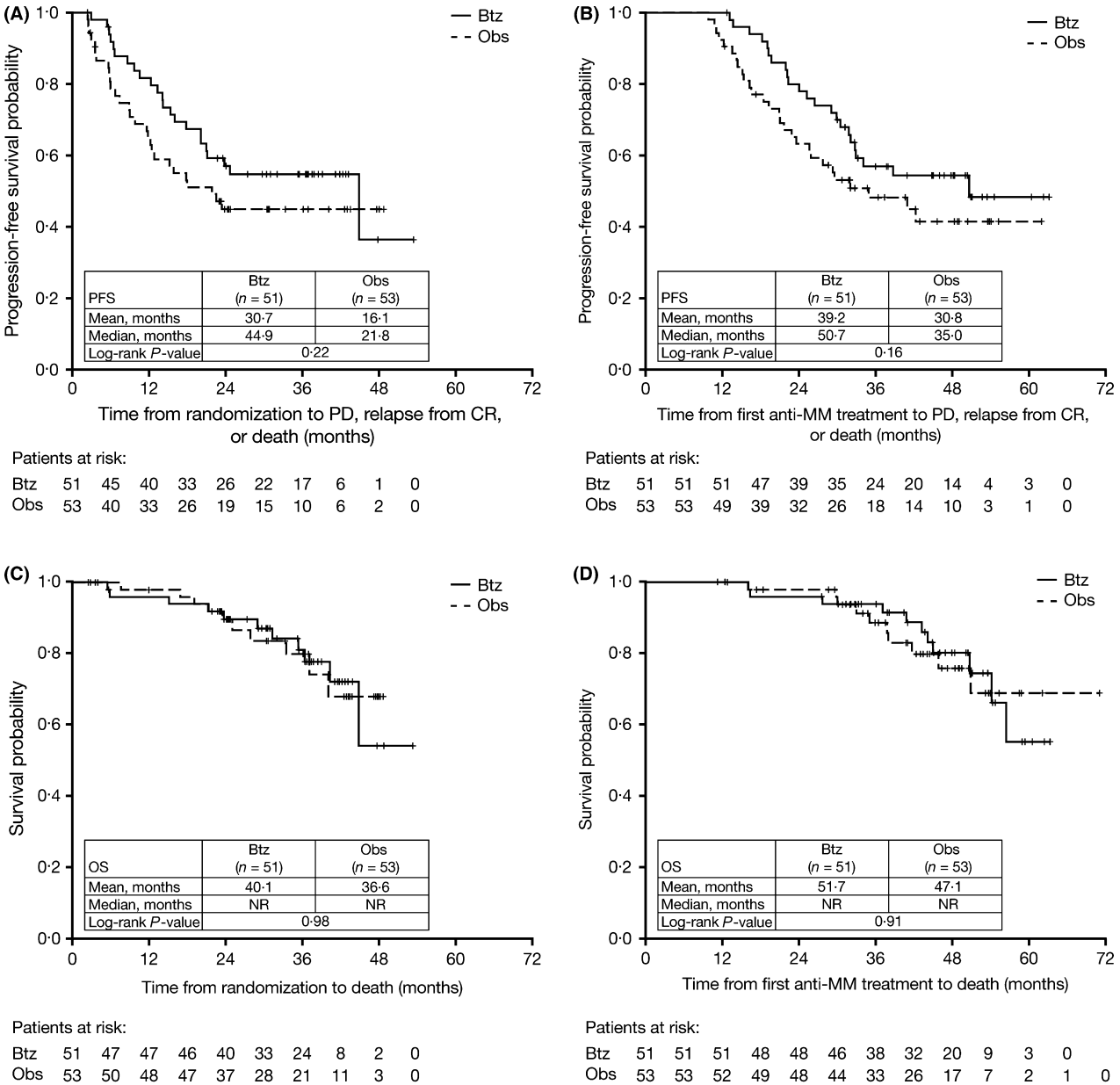


Fig 2. PFS and OS from randomization (A and C) and from first anti-MM treatment (B and D) (mITT population). $N = 104$. Btz, bortezomib; CR, complete response; mITT, modified intent-to-treat; MM, multiple myeloma; NR, not reached; PD, progressive disease; PFS, progression-free survival; Obs, observation; OS, overall survival.

therapy may be required to demonstrate an effect over observation alone (Greenfield *et al*, 2014). The Nordic Myeloma Study Group administered 6 cycles of bortezomib consolidation in their phase 3 trial, albeit at a lower dose of 1·3 mg/m^2 (Mellqvist *et al*, 2013). Finally, the timeframe of the study may not have been long enough to see the effects of bortezomib consolidation on BMD, although other studies have shown changes in BMD over a similar or shorter time period (Terpos *et al*, 2010).

Bortezomib consolidation was associated with trends for positive effects on myeloma response and survival outcomes in this study. Relative to response rates at screening, bortezomib appeared to improve response depth in some patients and appeared to reduce the rate of PD compared with observation alone at EOT; however, exploratory *P*-values did not reach statistical significance. Furthermore, there were trends for longer PFS and OS (both from randomization and from first anti-MM treatment) with bortezomib consolidation compared with observation alone. Notably, patients in the bortezomib arm benefitted from a median 23·1-month advantage in PFS from randomization compared with patients in the observation arm; median OS was not reached

Table VI. Safety overview including TEAEs occurring in ≥10% of patients in either arm (mITT population).

Patients with TEAEs, *n* (%)*	Bortezomib (*n* = 51)	Observation (*n* = 53)	Total (*N* = 104)
Any TEAE†	49 (96)	42 (79)	91 (88)
Any drug-related TEAE	39 (76)	NA	39 (38)
Any grade ≥3 TEAE‡	5 (10)	3 (6)	8 (8)
Any serious TEAE§	6 (12)	3 (6)	9 (9)
TEAE leading to discontinuation	4 (8)	NA	4 (4)
TEAE resulting in death¶	1 (2)#	0	1 (1)
Most common TEAEs (≥10% in either arm)			
Diarrhoea	19 (37)	0	19 (18)
Upper respiratory tract infection	9 (18)	9 (17)	18 (17)
Peripheral sensory neuropathy	10 (20)	2 (4)	12 (12)
Back pain	5 (10)	6 (11)	11 (11)
Pyrexia	9 (18)	2 (4)	11 (11)
Nasopharyngitis	6 (12)	4 (8)	10 (10)
Nausea	9 (18)	0	9 (9)
Fatigue	7 (14)	1 (2)	8 (8)
Herpes zoster infection	5 (10)	3 (6)	8 (8)
Vomiting	8 (16)	0	8 (8)
Neutropenia	6 (12)	1 (2)	7 (7)
Neuralgia	5 (10)	0	5 (5)
Thrombocytopenia	5 (10)	0	5 (5)

AE, adverse event; TEAE, treatment-emergent adverse event; mITT, modified intent-to-treat; NA, not applicable.

*TEAEs were defined as AEs occurring from the first dose up to 30 days after the last dose of bortezomib (bortezomib arm) and from randomization until the last visit of the observation period (observation arm).

†$P = 0{\cdot}02$ for between-arm comparison of rates of any-grade TEAEs (two-sided Fisher's exact test).

‡$P = 0{\cdot}48$ for between-arm comparison of rates of grade ≥3 TEAEs (two-sided Fisher's exact test); the following grade ≥3 TEAEs were reported in 1 patient each in the bortezomib arm (acute hepatic failure, anxiety, back pain, bacterial pneumonia, chest pain, depression, diarrhea, neutropenia, pancreatic neoplasm, thrombocytopenia) and in 1 patient each in the observation arm (back pain, bradycardia, hypoxia, influenza-like illness, ischaemic stroke, urinary tract infection).

§$P = 0{\cdot}31$ for between-arm comparison of rates of serious TEAEs (two-sided Fisher's exact test).

¶Deaths during the treatment/observation phase.

#Acute hepatic failure due to pancreatic cancer (not related to bortezomib treatment).

in either arm (3·5 months advantage in mean OS with bortezomib). Experimental log-rank *P*-values for the between-arm comparisons of PFS and OS were not statistically significant, most likely due to the small sample size and the study not being powered to compare survival outcomes. The trends for improved response rates and/or survival outcomes with bortezomib consolidation in this study are consistent with previous clinical studies in the ASCT-eligible MM setting (Ladetto *et al*, 2010; Cavo *et al*, 2012; Leleu *et al*, 2013; Mellqvist *et al*, 2013; Straka *et al*, 2015).

Thus, although preclinical and clinical data suggest that bortezomib can inhibit osteoclastogenesis (von Metzler *et al*, 2007; Deleu *et al*, 2009; Pennisi *et al*, 2009; Mohty *et al*, 2014) and stimulate osteoblast activity (Zangari *et al*, 2005; Heider *et al*, 2006; Giuliani *et al*, 2007; Deleu *et al*, 2009; Pennisi *et al*, 2009; Lund *et al*, 2010; Mohty *et al*, 2014), bortezomib consolidation treatment was not associated with any apparent changes in bone metabolism/bone health *versus* observation alone in the present study. Bortezomib was, however, associated with positive effects on myeloma response and survival outcomes. Data concerning the anti-MM activity and effects on bone of other proteasome inhibitors are also conflicting. Of note, a recent preclinical study of the effects of the proteasome inhibitor carfilzomib in mice bearing human myeloma xenografts demonstrated anti-MM tumour activity with carfilzomib but no protection against bone disease (Lawson *et al*, 2015); however, other preclinical data in murine models of MM suggest that proteasome inhibitors, including carfilzomib and oprozomib, can exert anti-tumour effects as well as effects on bone metabolism (Hurchla *et al*, 2013). Further research is needed to better understand how proteasome inhibition may impact on bone health in MM.

Bortezomib consolidation was generally tolerable in this patient population. Rates of grade ≥3 TEAEs were low in both arms (10% bortezomib *versus* 6% observation). TEAEs occurring with notably higher frequency in the bortezomib arm (diarrhoea, peripheral sensory neuropathy, nausea, vomiting) are consistent with known bortezomib-associated toxicities, indicating that the between-arm differences in safety findings correspond well with the known safety profile for bortezomib in MM (Cavo *et al*, 2012; Mellqvist *et al*, 2013; Straka *et al*, 2015; http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf). It is of note that patients in the bortezomib arm received intravenous bortezomib. Clinical studies have demonstrated non-inferior efficacy and an improved safety profile with subcutaneous bortezomib compared with standard intravenous bortezomib (Moreau *et al*, 2011); therefore, it is possible that use of subcutaneous bortezomib in the present study may have resulted in lower rates of neuropathy. Considering that the majority of patients in this study had received bortezomib-based induction therapy prior to predominantly melphalan-based HDT followed by ASCT, no new or unexpected safety concerns were identified with respect to TEAEs of particular clinical interest, including polyneuropathy, infections in general and herpes zoster infection. Rates of serious TEAEs and discontinuations due to TEAEs in the bortezomib arm were very low.

In conclusion, albeit with the caveats of potential confounding factors in this analysis, our findings suggest that post-HDT-ASCT bortezomib consolidation therapy (in combination with bisphosphonates) had no overt short-term effects on bone mineralization status in patients with MM-related bone disease compared with observation alone.

Notably, in terms of myeloma response, PFS and OS, our results show favourable effects with bortezomib. Bortezomib treatment was tolerable during the study period, with no new or unexpected findings compared with its established safety profile in MM.

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Author contributions

OS, RH, TT, and ET contributed to the study conception and design, and data acquisition and interpretation. MB, SC and JD participated as principal investigators for the trial, and contributed to the data acquisition and interpretation. GS and WL contributed to the data acquisition. OMA, ZG, HN and TP contributed to the data acquisition and interpretation. JAS participated as a principal investigator for the trial, screened and enrolled patients, oversaw data collection and contributed to critical analysis of the data. AT participated in patient recruitment and follow-up, and data collection and analysis. TD and AL contributed to data acquisition. GA developed the manual regarding dual energy X-ray absorptiometry (DXA) measurements, contributed to central collection, quality assurance and central evaluation of DXA data, and advised on the analysis of DXA data. AP contributed to the study design, data analysis and interpretation. CC and RAO contributed to data analysis, interpretation, and preparation, and were involved in the generation of the sponsor's Clinical Study Report of the trial. CF made substantial contributions to the study execution and data interpretation. NA coordinated the study. All authors reviewed and revised the manuscript for important intellectual content, and approved the final version.

Author disclosures

OS has received grants and personal fees from Janssen for the submitted work, and personal fees from Amgen, Celgene and Janssen, outside of the submitted work. MB has been a speaker's bureau member for Janssen during the conduct of the study, and has been an advisory board member for Celgene, Novartis, Amgen and Bristol Myers Squibb, outside of the submitted work. RH has received grants and personal fees from Janssen for the submitted work, and has received personal fees from Celgene outside of the submitted work. SC has received grants, personal fees, and non-financial support from Janssen during the conduct of the study, and has received personal fees from Celgene, Janssen, Novartis and Amgen, outside of the submitted work. TP has received grants and personal fees from Janssen outside of the submitted work. JAS has received financial support for the current study from Johnson & Johnson. JD has received lecture honoraria from Janssen. GA has received institutional grants from Janssen for the submitted work. AP, CC, CF and NA are employees of Janssen. RAO is an employee of Janssen and has stock or ownership interest in Johnson & Johnson. ET has received personal fees from Janssen during the conduct of the study, and has received grants and personal fees from Amgen, personal fees and non-financial support from Celgene and Janssen, and personal fees from Medtronic and Novartis, outside of the submitted work. GS, WL, OMA, ZG, HN, AT, TD, AL and TT have no conflicts of interest to declare.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Methods.

Table SI. Median percentage change in BMD from baseline to EOT, by age and baseline bisphosphonate use (full analysis set)

Fig S1. Distribution of absolute change from baseline to EOT in BMD (full analysis set)

Fig S2. Change from baseline to end of follow-up in BMD (full analysis set)

Fig S3. Change from baseline to end of follow-up in serum bone biomarkers (full analysis set)

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