Prospective comparison of subcutaneous versus intravenous administration of bortezomib in patients with multiple myeloma

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Supplementary Methods

Patients

Inclusion and exclusion criteria, and permitted concomitant medications

Patients aged ≥75 years with symptomatic MM who had progressive disease after at least one prior therapy and who had already undergone or were unsuitable for bone marrow transplantation were eligible. Patients required: measurable paraprotein level in serum (>1 g/dL) or urine (>0.2 g/day); life expectancy ≥2 months; Eastern Cooperative Oncology Group (ECOG) performance status 0–2; body weight ≥50 kg and body-mass index ≤30 kg/m^2 (due to risk of inadequate biodistribution following SC injection in obese/thin patients); platelets ≥70×10^9/L; absolute neutrophil count (ANC) ≥1×10^9/L; creatinine ≤200 μmol/L (2.26 mg/dL); and bilirubin, alanine transaminase, and aspartate transaminase ≤3 times the upper limit of normal. Patients were excluded if they had: a history of clinically relevant cardiac disease; evidence of arrhythmia, second degree or greater atrio-ventricular block, or prolonged QTc interval (>0.45 seconds in males, >0.47 seconds in females) on screening electrocardiogram (ECG); active systemic infection; or grade 2 peripheral neuropathy (National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0). Pregnant or nursing women were not eligible. Patients were ineligible if they were receiving any concomitant drugs able to modify the QTc interval within 1 week prior to the first dose of bortezomib, or if they had received any experimental drugs within 30 days of baseline. Concomitant bisphosphonates, erythropoietin, and other supportive therapy as needed were permitted.

Study design

Anatomical areas of SC administration

Anatomical areas of SC administration were the right or left thigh or abdomen; injection sites were rotated within a treatment cycle and, although the same anatomical area could be used, care was taken to avoid injections at the same site (for example, by alternating right and left abdomen, upper and lower quadrant, or alternating right and left thigh, proximal and distal sites). One SC dose was to be given during one injection at one site.

Dose modifications

Dose modifications were specified for cases of unexpected pharmacokinetic observations or toxicity. Pharmacokinetic samples from the first three patients in each arm were analyzed in real time; if the maximum observed plasma concentration (Cmax) or area under the plasma concentration–time curve (AUC) were unexpectedly high (50% above expected values) the bortezomib dose was reduced to 1.0 mg/m^2 in the following cycles, with a further dose reduction to 0.7 mg/m^2 if pharmacokinetic parameters remained high. Bortezomib dose reductions (1.3 to 1.0 to 0.7 mg/m^2) were also required for febrile neutropenia, grade 4 hematologic toxicity (except lymphopenia), or any grade 3 non-hematologic toxicity considered related to bortezomib, graded using NCI CTCAE v3.0. Dose reductions to less than 0.7 mg/m^2 were not allowed.

Pharmacokinetic and pharmacodynamic parameters

Pharmacokinetic analyses were performed at a central laboratory using liquid chromatography coupled to tandem mass spectrometry. The following parameters were estimated for both routes of administration: Cmax; time of Cmax (tmax); AUC from time 0 to the last measurable concentration (AUClast); AUC from time 0 to infinity (AUC∞); and apparent terminal elimination half-life (t1/2). In addition, systemic clearance (CL), volume of distribution (Vd), and steady state Vd (Vdss) were estimated following IV administration, while apparent CL (CL/F) and apparent Vd (Vd/F) were estimated following SC administration. Pharmacodynamic analyses were performed by Johnson & Johnson Pharmaceutical Research & Development, Beerse, Belgium, using a whole-blood 20S proteasome specific activity inhibition assay to determine percent inhibition of 20S proteasome activity relative to baseline. The following parameters were calculated for both routes of administration: maximum percent inhibition of 20S proteasome activity (E_{max}); time of E_{max} (t_{max}); and area

Supplementary Table 1. Patient demographics and baseline characteristics.

	Arm A–IV administration n=12	*Arm B – SC administration n=12*
Male, n	3	7
Median age (range), years	61 (51–71)	61.5 (49–71)
ECOG PS 0/1, n	9/3	8/4
Median body surface area (range), m^2	1.70 (1.4–2.1)	1.73 (1.4–2.1)
Myeloma type, IgG/IgA/Light chain _/_, n	7/3/1/1	6/2/3/1
Disease stage I/II/III, n	3/4/5	1/2/9
Median β^2M (range), mg/L	3.2 (1.3–7.1)	2.75 (1.9–11.0)
Median CrCl (range), mL/min	80.77 (32.9–107.2)	62.33 (22.5–111.6)
Median number of prior lines of therapy (range), n	2 (1–4)	1.5 (1–4)
Prior ASCT, n	9	9
Prior steroid, n	11	11
Prior alkylating agent, n	11	9
Prior anthracyline, n	10	10
Prior thalidomide/lenalidomide, n	6	6

ASCT: autologous stem cell transplantation; β2M: β-2 microglobulin; CrCl: calculated creatinine clearance; ECOG PS:Eastern Cooperatve Oncology Group performance status; Ig: immunoglobulin; IV: intravenous; SC: subcutaneous.

under the percent inhibition–time curve from time zero to the last sampling time point (AUElast).

Assessment of cardiac safety

Assessment of cardiac safety was specified within the secondary objectives. ECGs were recorded at baseline, and on day 1, cycle 1, at the following time points: 2 hours, and 60 and 30 minutes prior to bortezomib administration, and at 5, 15, 30, and 60 minutes, and 2, 4, 6, and 10 hours post-dosing. ECGs could also be recorded on day 11, cycle 1, if deemed necessary by the investigator.

Supplementary Table 2. AEs of any grade reported in ≥25% of patients overall.

AE, n (%)	*Arm A – IV administration (n=12)*	*Arm B – SC administration (n=12)*
Asthenia	8 (67)	7 (58)
Neuropathy	7 (58)	7 (58)
Anemia	6 (50)	6 (50)
Neutropenia	8 (66)	4 (33)
Diarrhea	7 (58)	4 (33)
Leukopenia	4 (33)	6 (50)
Nausea	5 (42)	4 (33)
Thrombocytopenia	3 (25)	4 (33)
Vomiting	3 (25)	4 (33)

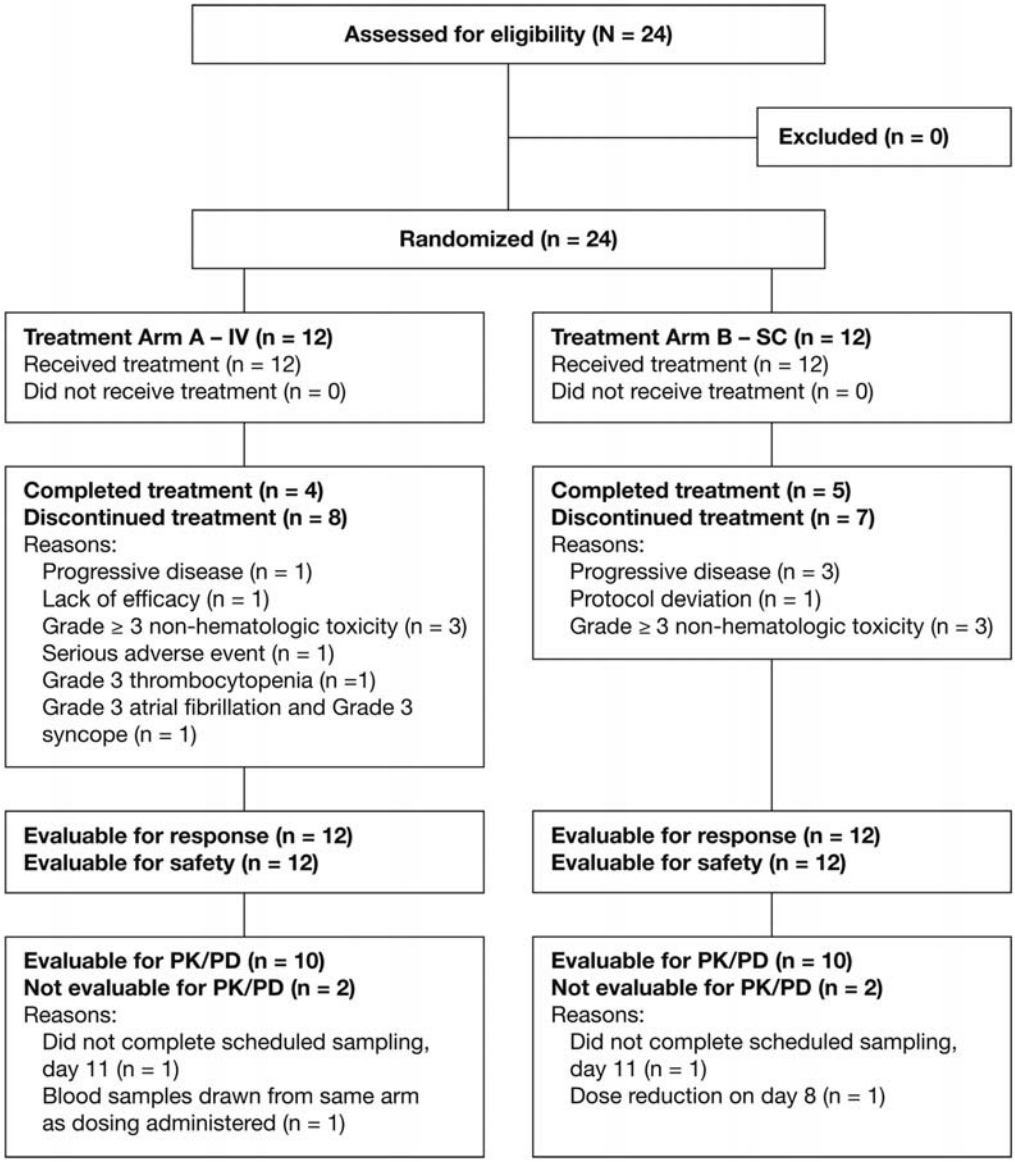
Efficacy assessments

M-protein levels were analyzed locally by electrophoresis and immunofixation as applicable. Bone marrow aspiration and a skeletal survey were conducted at baseline and as applicable.

Statistical analysis

Sample size and study powering

The intra-patient coefficient of variation for AUC and C_{max} of bortezomib was assumed to be less than 15% for sample size calculation. Using an intra-patient coefficient of variation of 15%, a sample size of 10 pharmacokinetic-evaluable patients was considered sufficient for the point estimate of the ratio of mean of bortezomib received intravenously and subcutaneously to fall within 87% and 115% of the true ratio with 90% confidence.



Supplementary Figure 1. Patient disposition.