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A retrospective analysis of 3954 patients in phase 2/3 trials of bortezomib for the treatment of multiple myeloma: towards providing a benchmark for the cardiac safety profile of proteasome inhibition in multiple myeloma

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Summary

This retrospective analysis aimed to establish the overall cardiac safety profile of bortezomib using patient-level data from one phase 2 and seven phase 3 studies in previously untreated and relapsed/refractory multiple myeloma [MM]. Seven clinically relevant primary (congestive heart failure [CHF], arrhythmias, ischaemic heart disease [IHD], cardiac death) and secondary (hypertension, dyspnoea, oedema) cardiac endpoints were defined based on MedDRA v16.0 preferred terms.

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2509 bortezomib-treated patients and 1445 patients in non-bortezomib-based control arms were included. The incidence of grade ≥3 CHF was 1·3–4·0% in studies in relapsed/refractory MM and 1·2–4·7% in previously untreated MM (2·0–7·6% all grades), with no significant differences between bortezomib- and non-bortezomib-based arms in comparative studies. Incidences of arrhythmias (1·3–5·9% grade ≥2; 0·6–4·1% grade ≥3), IHD (1·2–2·9% all grades; 0·4–2·7% grade ≥3) and cardiac death (0–1·4%) were low, with no differences between bortezomib-based and non-bortezomib-based arms. Higher rates of oedema (mostly grade 1/2) were seen in bortezomib-based versus non-bortezomib-based arms in one study and a pooled transplant study analysis. Logistic regression analyses of comparative studies showed no impact on cardiac risk with bortezomib-based versus non-bortezomib-based treatment. Bortezomib-based treatment was associated with low incidences of cardiac events.

**Keywords**
bortezomib; cardiac; cardio-oncology; multiple myeloma

**Introduction**

Due to recent treatment advances, patients with multiple myeloma (MM) are living longer (Anderson, 2012; Kumar et al, 2014; Liwing et al, 2014), underscoring the importance of patient quality of life and management of adverse events (AEs) related to therapy. MM patients are at risk of cardiac events due to age and disease-related factors (Kistler et al, 2012; McBride et al, 1988; Inanir et al, 1998; Robin et al, 2008; Kwaan, 2013); there is also a risk of cardiac events due to cardiotoxicity from treatments including anthracyclines (Ky et al, 2013), proteasome inhibitors (Bockorny et al, 2012; Herndon et al, 2013; Honton et al, 2013; Lonial et al, 2012; Siegel et al, 2013) and high-dose therapy (Chow et al, 2011; Sureddi et al, 2012; Fatema et al, 2009).

The United States Food and Drug Administration (US FDA)-approved proteasome inhibitors, bortezomib, carfilzomib and ixazomib, have been associated with cardiac events in MM patients (Bockorny et al, 2012; Herndon et al, 2013; Honton et al, 2013; Lonial et al, 2012; Siegel et al, 2013; Moreau et al, 2016). Cardiac toxicity and cardiac adverse reactions are included under ‘Warnings and Precautions’ in the respective US labels for bortezomib and carfilzomib (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf). Case reports have described cardiac failure and other cardiotoxicity with bortezomib treatment in patients with MM and other cancers (Bockorny et al, 2012; Dasanu, 2011; Enrico et al, 2007; Hacihanefioglu et al, 2008; Lee et al, 2011; Takamatsu et al, 2010; Voortman & Giaccone, 2006; Gupta et al, 2012; Subedi et al, 2014). However, case reports do not provide a comprehensive picture of the cardiovascular risk profile of bortezomib. More than 550 000 patients worldwide have been treated with bortezomib; its development involved numerous large, randomised, controlled clinical trials in relapsed and/or refractory MM (RRMM) (Moreau et al, 2011; Orlowski et al, 2007; Richardson et al, 2005) and newly diagnosed MM (NDMM) (Cavo et al, 2010; Harousseau et al, 2010; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012). This large, accumulated experience offers the
opportunity to define a benchmark for describing the cardiovascular profile of proteasome inhibitors in MM.

We conducted a retrospective analysis of the risk of heart failure, arrhythmias, ischaemic heart disease (IHD), cardiac death, hypertension, dyspnoea and oedema associated with bortezomib, using patient-level data from MM studies that supported US and European Union (EU) regulatory approvals (Cavo et al, 2010; Harousseau et al, 2010; Richardson et al, 2003; Richardson et al, 2005; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012; Sonneveld et al, 2013; Moreau et al, 2011; Orlowski et al, 2007). The aim was to establish the overall cardiac safety profile of bortezomib, using a clearly defined, standardised and replicable reporting method. This approach aimed to reconcile discrepancies between the National Cancer Institute’s (NCI) Common Terminology Criteria for AEs (CTCAE) and the Medical Dictionary for Regulatory Activities (MedDRA) regarding AE reporting, and used Standardised MedDRA Queries (SMQ) as the basis for grouping preferred terms to specified cardiovascular entities.

**Patients and methods**

**Studies analysed**

This pooled analysis included data on male/female patients in all phase 3 MM studies that led to US/EU regulatory approval, plus the original phase 2 registration study for US/EU regulatory approval, and represented all such studies with patient-level data available (Table I). RRMM studies included: phase 2 Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy (SUMMIT) study of bortezomib with/without dexamethasone (M34100-025) (Richardson et al, 2003); phase 3 APEX (Assessment of Proteasome Inhibition for Extending Remissions) trial of single-agent bortezomib versus dexamethasone (NCT00048230) (Richardson et al, 2005); phase 3 MMY-3001 trial of bortezomib plus liposomal doxorubicin versus single-agent bortezomib (NCT00103506) (Orlowski et al, 2007); phase 3 MMY-3021 trial of subcutaneous (SC) versus intravenous (IV) bortezomib (with/without dexamethasone; NCT00722566) (Moreau et al, 2011). NDMM studies included the phase 3 VISTA (Velcade® as Initial Standard Therapy in Multiple Myeloma) trial of bortezomib-melphalan-prednisone (VMP) versus melphalan-prednisone (MP) in elderly transplant-ineligible patients (NCT00111319) (San Miguel et al, 2008), and a pooled analysis based on patient-level data from 3 phase 3 trials of bortezomib-based versus non-bortezomib-based induction therapy in transplant-eligible patients (FM2005-01, NCT00200681; GEM2005MENOS65, NCT00461747; HOVON-65/GMMG-HD4: EudraCT 2004-000944-26) (Sonneveld et al, 2013). Unfortunately, it was not possible to obtain patient level data from the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) study (NCT01134484) (Cavo et al, 2010).

**Analyses of cardiac AEs**

Seven clinically relevant cardiac entities/disease states were selected for analysis (Table SI). The 4 primary endpoints for this analysis were heart failure (congestive heart failure [CHF]), arrhythmia(s), IHD and cardiac death. For arrhythmias, only AEs of grade 2 severity or greater were included (based on clinical relevance and to improve specificity); ventricular
arrhythmias were described as a distinct subgroup. Incidences of hypertension, dyspnoea and oedema were included as secondary endpoints; dyspnoea AEs occurring in conjunction with CHF were analysed as a distinct subgroup.

Patient-level data from study databases were analysed retrospectively for treatment-emergent AEs (AEs occurring up to 30 days after last dose of study drug [20 days in SUMMIT], or regardless of start date for drug-related events) within the 7 cardiac endpoints. Different studies used different terminology criteria for recording and grading AEs: NCI Common Toxicity Criteria version 2.0 and CTCAE version 3.0. Relevant AEs were analysed and re-coded for consistency across studies. MedDRA SMQ version 16.0 was used for developing lists of preferred terms for inclusion in the primary and secondary cardiac endpoints, which were mapped to older versions of MedDRA. All terms were reviewed by 2 cardiologists and included, excluded or mapped to another cardiac endpoint on the basis of clinical relevance (Table SI), a methodology that has been previously employed (Basaria et al, 2010).

Statistical methods

For each endpoint, the primary descriptive analysis was incidence of events (patients with AE/total patients). Hazard of events over time was analysed using Kaplan–Meier methodology; each patient contributed 1 (first) event. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models with statistical significance determined (α = 0.05 level) using the log-rank test. Logistic regression models were used for each comparative study to determine parameters independently affecting risk of each cardiac endpoint. Parameters included treatment assignment, age (≤70 vs. >70 years), cardiac history (yes/no, defined as ‘any abnormal finding in the cardiovascular system organ class’, and per individual study definitions of cardiac history, Table I), interaction of treatment assignment and age, interaction of treatment assignment and cardiac history, and interaction of age and cardiac history. Due to marked heterogeneity across patient populations (transplant eligible, transplant ineligible and RRMM) and treatments (single-agent bortezomib, various combination regimens), data were not combined across studies except for transplant induction studies, which were conducted in the same patient population.

Results

Patients

Data from 3954 patients (2509 bortezomib treated, 1445 non-bortezomib treated) were included (Table I). In comparative studies, cardiac risk factors (age, prior cardiac history) were balanced between bortezomib- and non-bortezomib-based arms. Median age ranged from 57 years in the pooled transplant induction analysis to 71 years in VISTA; rate of prior cardiac history, defined in Table I, ranged from 21% to 74%, respectively.

Cardiac events

Primary endpoints: The incidence of grade ≥3 CHF across bortezomib-based arms was 1.3–4.0% in RRMM studies and 1.2–4.7% in NDMM (Table II); overall incidences were 2.0–7.4% in RRMM and 3.1–7.6% in NDMM. There were no significant differences in the
hazard of CHF over time between bortezomib- and non-bortezomib-based arms in comparative studies (Fig 1). The incidence of all-grade CHF was higher with bortezomib plus liposomal doxorubicin versus bortezomib in MMY-3001 (HR 0.42, \( P = 0.017 \)) due to the difference in grade 1/2 events (5.9% vs. 1.6%). However, there was minimal difference in the incidence of grade ≥3 CHF between bortezomib plus liposomal doxorubicin and bortezomib (1.3% vs. 1.6%) in the overall population of the MMY-3001 study.

The incidence of grade ≥3 arrhythmias across bortezomib-based arms was 0.6–1.8% in RRMM studies and 1.7–4.1% in NDMM (Table III); incidences of grade ≥2 events were 1.3–4.1% in RRMM and 3.5–5.9% in NDMM. No significant differences between bortezomib- and non-bortezomib-based arms were seen. Most events were supraventricular arrhythmias; only 7 cases of ventricular arrhythmias were identified across all studies (5 in bortezomib-treated and 2 in non-bortezomib-treated patients; incidences of 0–0.5%; data not shown).

Grade ≥3 IHD was seen in 0.5–2.7% of bortezomib-treated patients in RRMM studies and 0.4–1.5% in NDMM (Table IV); overall incidences in individual studies were 1.5–2.7% in RRMM and 1.2–2.9% in NDMM. No significant differences between bortezomib- and non-bortezomib-based arms were seen.

Incidences of cardiac death were low; no meaningful statistical comparisons between treatment arms/groups were feasible. In RRMM, the incidence was 1.0% (\( n = 2 \)) with bortezomib ± dexamethasone in SUMMIT, 0.6% (\( n = 2 \)) versus 0 with bortezomib versus dexamethasone in APEX, 0.6% (\( n = 2 \)) in both arms of MMY-3001, and 0.7% (\( n = 1 \)) versus 1.4% (\( n = 1 \)) with SC versus (IV bortezomib in MMY-3021. In NDMM, incidences were 0 versus 0.9% (\( n = 3 \)) with VMP versus MP in VISTA, and 0.3% (\( n = 2 \)) versus 0 with bortezomib-based versus non-bortezomib-based induction therapy in the pooled transplant analysis.

**Secondary endpoints:** Grade ≥3 hypertension was reported in 0–2.0% of bortezomib-treated patients in RRMM and 0.4–1.5% in NDMM; overall incidences were 3.5–9.5% in RRMM and 5.1–13.5% in NDMM (Table V). Rates appeared numerically higher with bortezomib versus non-bortezomib treatment in comparative studies, with a trend towards increased rates of all-grade (HR 1.54, \( P = 0.0656 \)) and grade ≥3 (HR 2.94, \( P = 0.0881 \)) hypertension with VMP versus MP in VISTA.

Grade ≥3 dyspnoea (regardless of cause) was reported in 0.9–5.4% of bortezomib-treated patients in RRMM studies and 1.2–3.8% in NDMM, with overall incidences of 7.5–22.3% in RRMM and 6.4–15.3% in NDMM (Table SII). No significant differences were seen in rates of dyspnoea between bortezomib- and non-bortezomib-based arms in comparative studies (Fig 1). Incidences of dyspnoea occurring in conjunction with CHF were low with bortezomib-based treatment (0–3.9% overall; 0–1.2% grade ≥3; Table SIII), with a significantly greater rate of all-grade events with bortezomib versus dexamethasone in APEX (HR 6.10, \( P = 0.0066 \)).
Incidences of grade ≥3 oedema (regardless of cause) were low with bortezomib-based treatment (0–0·3% in RRMM; 0·6–1·2% in NDMM). Overall incidences were 3·0–11·9% in RRMM and 23·5% in NDMM (Table SIV), with significantly higher rates with VMP versus MP in VISTA (HR 2·24, P < 0·0001) and with bortezomib- versus non-bortezomib-based induction therapy in the pooled transplant analysis (HR 1·54, P = 0·0002).

Analysis of risk factors

In APEX, logistic regression model analysis showed no added risk of any cardiac endpoint with bortezomib compared with dexamethasone. In patients aged ≤70 years, independent of treatment, there was a significantly higher risk of dyspnoea occurring in conjunction with CHF in patients with versus without prior cardiac history. In patients randomised to dexamethasone, patients aged >70 years had a significantly higher risk of hypertension. Logistic regression model analysis identified no independent parameters that significantly affected the incidence of any cardiac endpoint in the MMY-3001, MMY-3021 and VISTA studies. In the pooled transplant analysis, patients with prior cardiac history had a significantly higher risk of CHF; oedema and hypertension, independent of treatment.

Discussion

Bortezomib-based treatment was associated with generally low incidences of all-grade and grade ≥3 cardiac AEs across studies included in this analysis in NDMM and RRMM, supporting guidance in the current prescribing information that cardiac monitoring is most appropriate in those patients with risk factors for heart disease, or who have existing heart disease. No significant differences were seen in comparative studies of bortezomib- versus non-bortezomib-based treatment in CHF, arrhythmias, IHD and cardiac death (primary endpoints). The same was true for the secondary endpoints, except for a higher rate of all-grade oedema with VMP in VISTA and with bortezomib-based induction in the pooled transplant analysis, a higher rate of all-grade dyspnoea in conjunction with CHF with bortezomib in APEX, and a trend towards higher rates of hypertension with VMP in VISTA. Additionally, there was a significantly higher rate of any-grade CHF with bortezomib plus liposomal doxorubicin versus bortezomib in MMY-3001, possibly associated with the cardiac safety profile of anthracyclines; this differs from the primary manuscript findings (Orlowski et al, 2007), probably due to the broader range of preferred terms incorporated in this analysis. Prior meta-analysis has shown that bortezomib combination treatment did not increase the cardiac toxicity compared with bortezomib monotherapy (Xiao et al, 2014). Furthermore, data from the MMY-3021 study of SC versus IV bortezomib did not show any consistent differences between arms in cardiac risk; however, patient and event numbers are very small.

Notably, the absence of differences in all primary and most secondary endpoints between bortezomib- and non-bortezomib-based treatment was not affected in logistic regression model analyses of risk factors. These findings indicate that relative cardiac risk is not modified by bortezomib treatment and suggest that proteasome inhibition therapy with bortezomib may be an appropriate option in patients with cardiac risk factors, such as older age and cardiac history (acknowledging the cardiac study eligibility criteria, discussed.
below). These findings are particularly valuable when considering older patients, as they include not only grade 3 and higher events but also grade 1 and 2 events, which may be clinically relevant in elderly patients. A limitation of our analysis was that non-specific definitions of cardiac history precluded a detailed assessment of the impact of pre-existing cardiac conditions.

Due to the large number of patients included from rigorously conducted trials, and comprehensive adjudication of cardiac endpoints, this analysis provides an important benchmark of cardiac safety for proteasome inhibitors and MM drugs in general, and represents a reference point for future clinical studies. It provides criteria to define cardiotoxicity based upon individual MedDRA preferred terms and SMQs, plus data on multiple distinct, clinically relevant cardiac endpoints. Furthermore, the analysis addresses the challenges of mapping AEs consistently across studies utilising different AE definitions, and differences between NCI CTCAE (terms commonly encountered in oncology interventions, with a severity rating scale) and MedDRA (clinically validated, multidisciplinary list of >66 000 preferred terms, but without definitions or severity ratings). Although inherent discrepancies between NCI CTCAE and MedDRA may represent a limitation of our approach (Groarke et al, 2013), careful and diligent reclassification of relevant cardiac AEs across the 2 systems (and their various iterations), as well as the inclusive approach used, ensured a consistent and rigorous methodology.

To our knowledge, this is the first large analysis using patient-level data from multiple phase 2 and 3 studies of bortezomib. This approach incorporated analysis of hazards and logistic regression for assessment of the influence of specific risk factors. It was assumed that each cardiac AE could occur independently, other than cardiac death, and, therefore, we did not conduct competing risks analyses; such analyses were not required due to the very low rates of cardiac deaths in the included studies. A recent pooled analysis employing only published study-level data and AEs reported in the respective publications provides supportive evidence that bortezomib does not significantly increase cardiotoxicity risk (Xiao et al, 2014). Additionally, regarding the feasibility of bortezomib in the setting of cardiovascular risk, reports have indicated that bortezomib-based therapy may be administered successfully to amyloidosis patients, specifically patients with cardiac amyloid involvement (Charaf et al, 2009; Dubrey et al, 2011; Freeman et al, 2012; Gatt et al, 2016; Mikhael et al, 2012; Reece et al, 2011; Tamaki et al, 2010), noting that all patients with existing heart disease or risk factors for heart disease should be closely monitored (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf). Indeed, in the phase 1 trial by Dubrey et al (2011), longitudinal echocardiographic study reported no cardiac responses to bortezomib therapy in patients with relapsed AL amyloidosis. However, it should be highlighted that in the studies in the present analysis, patients with New York Heart Association class II/III–IV CHF and/or known amyloidosis were excluded and, except in VISTA, median ages were generally relatively lower versus the overall patient population; thus, a standard MM patient population may include more patients at higher risk of cardiovascular complications. While our findings may be broadly applicable to the wider MM patient population, due to employing data from selected clinical trial populations with specific cardiac exclusion criteria (Table I), they are not necessarily generalisable to patients with a higher burden of cardiovascular disease or recent/ongoing cardiac comorbidities.
The apparent overall higher incidence of cardiac events in VISTA compared with other studies may be due to patients being approximately 10 years older, based on median ages, or having a higher rate of prior cardiac history. Transplant-ineligible patients aged ≥65 years represent the majority of MM patients – approximately two-thirds – at initial diagnosis (Mateos & San Miguel, 2013), underlining the importance of understanding cardiac profiles of MM drugs. There were no differences between VMP and MP in VISTA, except for incidence of oedema, which does not appear to have a cardiac aetiology. This finding, combined with logistic regression results, suggests bortezomib can be used safely in this patient population. VISTA data challenge the common perception that RRMM patients may per se have higher risk of cardiac events in addition to the higher age of patients. However, these findings may have been a result of patients having a more complete medical history in VISTA versus other trials. Potential differences in AE reporting and eligibility criteria must be considered when assessing safety data across different studies.

We speculate on several possible reasons for the higher incidence of oedema with VMP versus MP in VISTA and in the pooled transplant analysis, and the trend towards higher incidences of hypertension. There may be some contribution directly via proteasome inhibition (http://www.velcade.com/files/pdfs/velcade_prescribing_information.pdf), including potentially a low-level cardiac effect, and there may be other, less serious types of oedema included. There may be an element of endothelial leak and fluid retention, associated with activity of proteasome inhibition on the endothelium and its anti-angiogenic effects (Belloni et al, 2010; Roccaro et al, 2006), and possibly potentiated by the synergy between proteasome inhibition and alkylating agents (Ma et al, 2003; Mitsiades et al, 2003) and the long exposure to prednisone (San Miguel et al, 2008).

All proteasome inhibitors have unique characteristics, with potentially distinct mechanistic differences, pharmacological characteristics and safety profiles (Moreau et al, 2012; Allegra et al, 2014; McBride & Ryan, 2013). Respective relative effects on the central/peripheral nervous system, gastrointestinal system, bone marrow and cardiovascular system may differ (Cavo et al, 2010; Harousseau et al, 2010; Richardson et al, 2003; Richardson et al, 2005; Rosinol et al, 2012; San Miguel et al, 2008; Sonneveld et al, 2012; Sonneveld et al, 2013; Moreau et al, 2011; Orlowski et al, 2007; Lonial et al, 2012; Siegel et al, 2013; Touzeau et al, 2013). Further studies are needed to better define these differences. No comparisons can be made with this analysis or conclusions drawn from available findings. Data on cardiac AEs in early-phase carfilzomib studies have been published, and the phase 3 ENDEAVOR (Carfilzomib and dexamethasone versus bortezomib and dexamethasone for RRMM patients) trial reported that 2 patients in each arm had significant left ventricular ejection fraction reductions during the study and that rates of grade ≥3 cardiac failure were 1.8% versus 4.8%, grade ≥3 pulmonary hypertension were <1% versus <1% and grade ≥3 IHD were 1.5% versus 1.7%, respectively (Dimopoulos et al, 2016). In the ASPIRE (Carfilzomib, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone for the treatment of patients with relapsed multiple myeloma) phase 3 trial, rates of grade ≥3 cardiac failure were 3.8% versus 1.8%, and grade ≥3 hypertension rates were 4.3% versus 1.8% (Stewart et al, 2015). A pooled analysis of phase 2 studies in 526 RRMM patients (70% with baseline cardiac risk factors [use of ≥1 prior cardiovascular or anti-diabetic medication]), 53% of whom received the approved 20/27 mg/m² dose, reported 7.2% cardiac failure (5.7% grade
≥3), 13.3% (2.3%) cardiac arrhythmia, 3.4% (1.3%) IHD, 42.2% (4.9%) dyspnoea and 14.3% hypertension, with 1.5% cardiac-related deaths (Lonial et al, 2012; Siegel et al, 2013). Other cardiac AE data have been reported from a phase 1/2 study of carfilzomib-MP (Touzeau et al, 2013), a compassionate-use analysis of carfilzomib in RRMM (Atrash et al, 2015), and a phase 2 study of carfilzomib 56 mg/m² with/without dexamethasone in RRMM (Lendvai et al, 2014). Phase 3 data on the oral proteasome inhibitor ixazomib in combination with lenalidomide and dexamethasone in RRMM have recently been published (Moreau et al, 2016); rates of heart failure with ixazomib + lenalidomide/dexamethasone were 4% (2% grade 3; <1% grade 4), arrhythmia 16% (5% grade 3; <1% grade 4), hypertension 6% (3% grade 3) and myocardial infarction 1% (<1% grade 4). A recent case report also described an instance of acutely decompensated heart failure that was considered as being induced by ixazomib; the patient’s cardiac function did not improve within 6 months of ixazomib discontinuation, but no further episodes of systolic heart failure were observed (Jouni et al, 2016). Data on cardiac AEs with the investigational proteasome inhibitors oprozomib and marizomib are limited. These findings provide support for the methodological approach taken in these analyses, which focus not just on CHF but other specific endpoints of cardiac aetiology that are relevant in MM treatment.

Non-clinical studies have suggested possible links between proteasome inhibition and the cardiovascular system, with studies demonstrating the importance of the ubiquitin-proteasome system, including in heart remodelling (Li & Wang, 2011; Portbury et al, 2012; Su & Wang, 2010; Willis & Patterson, 2013). Furthermore, studies have identified multiple effects of proteasome inhibition on the cardiovascular system, with a differential impact of different proteasome inhibitors on cardiac proteasome subtypes (Kloss et al, 2010; Powell et al, 2012; Scruggs et al, 2011) in 1 study (Kloss et al, 2010). These data further highlight the importance of analysing the cardiovascular risk associated with proteasome inhibitors and other novel agents for MM treatment (Groarke et al, 2013).

In conclusion, these data from bortezomib studies provide a benchmark for evaluating cardiovascular risk associated with proteasome inhibition in MM; data from ongoing prospective and comparative studies are necessary to determine whether proteasome inhibitors have different cardiotoxicity profiles. A better understanding of the mechanism of proteasome inhibitor-induced cardiotoxicity, risk factors and potential biomarkers identifying at-risk patient populations will be critical. Furthermore, it will be important to improve reporting of baseline cardiac risk factors, cardiac AEs and detection of cardiotoxicity in the context of oncology clinical trials. The NCI CTCAE provide for standardised AE reporting in cancer trials, but the methodology differs compared with cardiovascular trials; thus, early, asymptomatic cardiac changes may not be identified using NCI CTCAE. To facilitate assessment of cardiac AEs, there may be a need for improved cardiac monitoring in future studies of proteasome inhibitors and other drugs to elucidate any differential cardiac effects of these agents, especially as combination approaches in MM with other novel agents are pursued (Lonial et al, 2011). More broadly, in the context of the abundance of novel agents either already approved or in development for the treatment of MM, it will be critical to gain an improved understanding of cardiac events associated with individual agents. Our analyses represent a broadly applicable, comprehensive, reproducible and consistent methodology for the standardised assessment of cardiac toxicity in MM.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References


Fig 1.
Time to first onset of CHF and dyspnoea in (A, B) VISTA (San Miguel et al, 2008), (C, D) the pooled transplant analysis and (E, F) APEX.
HR shown for time to first onset of CHF or dyspnoea. Circles represent individual censored observations.
APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CHF, congestive heart failure; Dex, dexamethasone; HR, hazard ratio; MP, melphalan-prednisone; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.
Table I.

Patient characteristics, cardiac history and cardiac exclusion criteria used in the bortezomib studies included in this analysis of cardiac events. Studies in the pooled transplant analysis were IFM 2005-01 (bortezomib-dexamethasone vs. vincristine-doxorubicin-dexamethasone [VAD] induction) (Harousseau et al, 2010), HOVON-65/GMMG-HD4 (bortezomib-doxorubicin-dexamethasone vs. VAD) (Sonneveld et al, 2012) and PETHEMA GEM2005MENOS65 (bortezomib-thalidomide-dexamethasone vs. thalidomide-dexamethasone vs. combination chemotherapy plus single-agent bortezomib) (Rosinol et al, 2012).

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N*</th>
<th>Age, years ‡</th>
<th>Prior lines ‡</th>
<th>Prior anthra, n (%)</th>
<th>Cardiac history, n (%)</th>
<th>Cardiac exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMM</td>
<td>Btz ± dex</td>
<td>202</td>
<td>59 (34–84)</td>
<td>6 (2–15)</td>
<td>163 (81)</td>
<td>94 (47)‡</td>
<td>NYHA Class II/IV; Acute ischaemia by ECG; Clinically significant conduction abnormalities; MI within 6 months</td>
</tr>
<tr>
<td>APEX (Richardson et al, 2005)</td>
<td>Btz</td>
<td>331</td>
<td>62 (33–84)</td>
<td>2 (1–36)</td>
<td>255 (77)</td>
<td>192 (58)‡</td>
<td>As SUMMIT, plus: Uncontrolled angina; Severe uncontrolled ventricular arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>61 (27–86)</td>
<td></td>
<td>253 (76)</td>
<td>190 (57)‡</td>
<td></td>
</tr>
<tr>
<td>MMY-3001 (Orlowski et al, 2007)</td>
<td>Btz + Dox</td>
<td>318</td>
<td>61 (28–85)</td>
<td>2 (NR)</td>
<td>220/324 (68)</td>
<td>181 (57)§</td>
<td>As APEX/SUMMIT, but NYHA Class II–IV, plus: Clinically significant pericardial disease</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>318</td>
<td>62 (34–88)</td>
<td></td>
<td>216/322 (67)</td>
<td>173 (54)§</td>
<td></td>
</tr>
<tr>
<td>MMY-3021 (Moreau et al, 2011)</td>
<td>SC btwz ± dex</td>
<td>147</td>
<td>64 (42–88)</td>
<td>1 (1–3)</td>
<td>58 (39)</td>
<td>97 (66)§</td>
<td>As APEX/SUMMIT</td>
</tr>
<tr>
<td></td>
<td>IV btwz ± dex</td>
<td>74</td>
<td>64.5 (38–86)</td>
<td></td>
<td>32 (43)</td>
<td>44 (59)§</td>
<td></td>
</tr>
<tr>
<td>Previously untreated MM</td>
<td>VMP</td>
<td>340</td>
<td>71 (57–90)</td>
<td>0</td>
<td>0</td>
<td>252 (74)‡</td>
<td>As SUMMIT, plus: Uncontrolled angina; Clinically significant pericardial disease; Cardiac amyloidosis</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>337</td>
<td>71 (48–91)</td>
<td></td>
<td>0</td>
<td>250 (74)‡</td>
<td></td>
</tr>
<tr>
<td>Pooled transplant analysis (Sonneveld et al, 2012)</td>
<td>Btz based</td>
<td>779</td>
<td>57 (31–65)</td>
<td>0</td>
<td>0</td>
<td>165 (21)**</td>
<td>IFM 2005-01 and PETHEMA GEM2005MENOS65: as APEX, plus: Heart failure</td>
</tr>
<tr>
<td></td>
<td>Non-btz based</td>
<td>776</td>
<td>57 (25–65)</td>
<td></td>
<td>0</td>
<td>169 (22)**</td>
<td>HOVON-65/GMMG-HD4: Severe cardiac dysfunction (NYHA Class II–IV)</td>
</tr>
</tbody>
</table>

anthra, anthracyclines; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; Dex, dexamethasone; Dox, liposomal doxorubicin; ECG, electrocardiogram; GMMG, German Multicentre Myeloma Group; HOVON, Dutch-Belgian Hemato-Oncology Cooperative Group; IFM, Intergroupe Francophone du Myelome; IV, intravenous; MI, myocardial infarction; MM, multiple myeloma; MP, melphalan-prednisone; NR, not reported; NYHA, New York Heart Association; PETHMA, Programme for the Study and Treatment of Haematological Malignancies; SC,
subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

Safety population.

† Median (range).

Cardiac history defined as ‘any abnormal finding in the cardiovascular system organ class’, and per individual study definitions, as follows:

‡ Recorded medical history on case report form under cardiovascular category

§ Abnormal cardiovascular history

¶ History of heart failure

# History of cardiac condition.

** For IFM 2005-01, all patients with history of any general cardiac condition; for HOVON-65/GMMG-HD4, all patients with history of any cardiac arrhythmia or general cardiac condition; for PETHEMA GEM2005MENOS65, based on clinical review of medical history terms considered related to history of cardiac failure.
<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N</th>
<th>Exposure, pt-yr</th>
<th>Incidence, n (%)</th>
<th>Incidence rate, n/pt-yr</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All AE</td>
<td>Grade ≥3</td>
<td></td>
</tr>
<tr>
<td>Relapsed and/or refractory MM</td>
<td>SUMMIT (Richardson et al, 2003)</td>
<td>Btz ± dex</td>
<td>202</td>
<td>59.5</td>
<td>15 (7.4)</td>
<td>8 (4.0)</td>
</tr>
<tr>
<td></td>
<td>APEX (Richardson et al, 2005)</td>
<td>Btz</td>
<td>331</td>
<td>129.2</td>
<td>21 (6-3)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100-9</td>
<td>15 (4.5)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td></td>
<td>MMY-3001 (Orlowski et al, 2007)</td>
<td>Btz + dox</td>
<td>318</td>
<td>101-3</td>
<td>23 (7.2)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Btz</td>
<td>318</td>
<td>101-4</td>
<td>10 (3-1)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td></td>
<td>MMY-3021 (Moreau et al, 2011)</td>
<td>SC btz</td>
<td>147</td>
<td>63.3</td>
<td>3 (2-0)</td>
<td>3 (2-0)</td>
</tr>
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<td>30.9</td>
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<td>1 (1-4)</td>
</tr>
<tr>
<td></td>
<td>Previously untreated MM</td>
<td>VISTA (San Miguel et al, 2008)</td>
<td>VMP</td>
<td>340</td>
<td>254-2</td>
<td>26 (7-6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MP</td>
<td>337</td>
<td>226-7</td>
<td>18 (5-3)</td>
<td>13 (3.9)</td>
</tr>
<tr>
<td></td>
<td>Pooled analysis (Sonneveld et al, 2012)</td>
<td>Btz based</td>
<td>779</td>
<td>254-6</td>
<td>24 (3-1)</td>
<td>9 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-btz based</td>
<td>776</td>
<td>254-7</td>
<td>25 (3-2)</td>
<td>4 (0.5)</td>
</tr>
</tbody>
</table>

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

*P = 0.017 (log-rank test).

†One patient with missing grade.
Table III.

Incidence of at least grade 2 arrhythmia reported in phase 2 and phase 3 trials of bortezomib.

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N</th>
<th>Exposure, pt-yr</th>
<th>Incidence, n (%)</th>
<th>Incidence rate, n/pt-yr</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Grade ≥2</td>
<td>Grade ≥3</td>
<td>Grade ≥2</td>
</tr>
<tr>
<td><strong>Relapsed and/or refractory MM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUMMIT (Richardson et al, 2003)</td>
<td>Btz ± dex</td>
<td>202</td>
<td>59·5</td>
<td>3 (1·5)</td>
<td>3 (1·5)</td>
<td>0·05</td>
</tr>
<tr>
<td>APEX (Richardson et al, 2005)</td>
<td>Btz</td>
<td>331</td>
<td>129·2</td>
<td>13 (3·9)</td>
<td>6 (1·8)</td>
<td>0·132</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100·9</td>
<td>13 (3·9)</td>
<td>6 (1·8)</td>
<td>0·139</td>
</tr>
<tr>
<td>MMY-3001 (Orlowski et al, 2007)</td>
<td>Btz + dox</td>
<td>318</td>
<td>101·3</td>
<td>9 (2·8)</td>
<td>3 (1·8)</td>
<td>0·109</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>318</td>
<td>101·4</td>
<td>4 (1·3)</td>
<td>2 (0·6)</td>
<td>0·049</td>
</tr>
<tr>
<td>MMY-3021 (Moreau et al, 2011)</td>
<td>SC btz</td>
<td>147</td>
<td>63·3</td>
<td>5 (3·4)</td>
<td>2 (1·4)</td>
<td>0·079</td>
</tr>
<tr>
<td></td>
<td>IV btz</td>
<td>74</td>
<td>30·9</td>
<td>3 (4·1)</td>
<td>1 (1·4)</td>
<td>0·097</td>
</tr>
<tr>
<td><strong>Previously untreated MM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VISTA (San Miguel et al, 2008)</td>
<td>VMP</td>
<td>340</td>
<td>254·2</td>
<td>20 (5·9)</td>
<td>14 (4·1)</td>
<td>0·126</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>337</td>
<td>226·7</td>
<td>15 (4·5)</td>
<td>9 (2·7)</td>
<td>0·088</td>
</tr>
<tr>
<td>Pooled analysis (Sonneveld et al, 2012)</td>
<td>Btz based</td>
<td>779</td>
<td>254·6</td>
<td>27 (3·5)</td>
<td>13 (1·7)</td>
<td>0·126</td>
</tr>
<tr>
<td></td>
<td>Non-btz based</td>
<td>776</td>
<td>254·7</td>
<td>23 (3·0)</td>
<td>11 (1·4)</td>
<td>0·094</td>
</tr>
</tbody>
</table>

APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.
Table IV.

Incidence of ischaemic heart disease reported in phase 2 and phase 3 trials of bortezomib.

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N</th>
<th>Exposure, pt-yr</th>
<th>Incidence, n (%)</th>
<th>Incidence rate, n/pt-yr</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All AE</td>
<td>Grade ≥3</td>
<td>All AE</td>
</tr>
<tr>
<td>Relapsed and/or refractory MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SUMMIT (Richardson et al, 2003)</td>
<td>Btz ± dex</td>
<td>202</td>
<td>59.5</td>
<td>4 (2.0)</td>
<td>1 (0.5)</td>
<td>0.067</td>
</tr>
<tr>
<td>APEX (Richardson et al, 2005)</td>
<td>Btz</td>
<td>331</td>
<td>120.2</td>
<td>5 (1.5)</td>
<td>3 (0.9)</td>
<td>0.077</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100.9</td>
<td>8 (2.4)</td>
<td>5 (1.5)</td>
<td>0.099</td>
</tr>
<tr>
<td>MMY-3001 (Orlowski et al, 2007)</td>
<td>Btz + dox</td>
<td>318</td>
<td>101.3</td>
<td>6 (1.9)</td>
<td>2 (0.6)</td>
<td>0.059</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>318</td>
<td>101.4</td>
<td>5 (1.6)</td>
<td>3 (0.9)</td>
<td>0.079</td>
</tr>
<tr>
<td>MMY-3021 (Moreau et al, 2011)</td>
<td>SC btz</td>
<td>147</td>
<td>63.3</td>
<td>3 (2.0)</td>
<td>2 (1.4)</td>
<td>0.047</td>
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<tr>
<td></td>
<td>IV btz</td>
<td>74</td>
<td>30.9</td>
<td>2 (2.7)</td>
<td>2 (2.7)</td>
<td>0.065</td>
</tr>
<tr>
<td>Previously untreated MM</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>VISTA (San Miguel et al, 2008)</td>
<td>VMP</td>
<td>340</td>
<td>254.2</td>
<td>10 (2.9)</td>
<td>5 (1.5)</td>
<td>0.047</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>337</td>
<td>226.7</td>
<td>8 (2.4)</td>
<td>5 (1.5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Pooled analysis (Sonneveld et al, 2012)</td>
<td>Btz based</td>
<td>779</td>
<td>254.6</td>
<td>9 (1.2)</td>
<td>3 (0.4)</td>
<td>0.039</td>
</tr>
<tr>
<td></td>
<td>Non-btz based</td>
<td>776</td>
<td>254.7</td>
<td>14 (1.8)</td>
<td>3 (0.4)</td>
<td>0.055</td>
</tr>
</tbody>
</table>

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; NE, not estimable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.
Table V.

Incidence of hypertension reported in phase 2 and phase 3 trials of bortezomib.

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm</th>
<th>N</th>
<th>Exposure, pt-yr</th>
<th>Incidence, n (%)</th>
<th>Incidence rate, n/pt-yr</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All AE</td>
<td>Grade ≥3</td>
<td>All AE</td>
</tr>
<tr>
<td>Relapsed and/or refractory MM</td>
<td>Btz ± dex</td>
<td>202</td>
<td>59.5</td>
<td>10 (5.0)</td>
<td>3 (1.5)</td>
<td>0.202</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>331</td>
<td>129.2</td>
<td>22 (6.6)</td>
<td>6 (1.8)</td>
<td>0.201</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100.9</td>
<td>17 (5.1)</td>
<td>4 (1.2)</td>
<td>0.178</td>
</tr>
<tr>
<td></td>
<td>Btz + dox</td>
<td>318</td>
<td>101.3</td>
<td>11 (3.5)</td>
<td>2 (0.6)</td>
<td>0.168</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>318</td>
<td>101.4</td>
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<td>3 (0.9)</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100.9</td>
<td>17 (5.1)</td>
<td>4 (1.2)</td>
<td>0.178</td>
</tr>
<tr>
<td></td>
<td>Btz</td>
<td>318</td>
<td>101.4</td>
<td>18 (5.7)</td>
<td>3 (0.9)</td>
<td>0.187</td>
</tr>
<tr>
<td></td>
<td>Dex</td>
<td>332</td>
<td>100.9</td>
<td>17 (5.1)</td>
<td>4 (1.2)</td>
<td>0.178</td>
</tr>
<tr>
<td></td>
<td>SC btz</td>
<td>147</td>
<td>63.3</td>
<td>14 (9.5)</td>
<td>3 (2.0)</td>
<td>0.348</td>
</tr>
<tr>
<td></td>
<td>IV btz</td>
<td>74</td>
<td>30.9</td>
<td>3 (4.1)</td>
<td>0</td>
<td>0.097</td>
</tr>
<tr>
<td>Previously untreated MM</td>
<td>VMP</td>
<td>340</td>
<td>254.2</td>
<td>46 (13.5)</td>
<td>10 (2.9)</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>MP</td>
<td>337</td>
<td>226.7</td>
<td>30 (8.9)</td>
<td>4 (1.2)</td>
<td>0.212</td>
</tr>
<tr>
<td></td>
<td>Btz based</td>
<td>779</td>
<td>254.6</td>
<td>40 (5.1)</td>
<td>12 (1.5)</td>
<td>0.165</td>
</tr>
<tr>
<td></td>
<td>Non-btz based</td>
<td>776</td>
<td>254.7</td>
<td>29 (3.7)</td>
<td>6 (0.8)</td>
<td>0.122</td>
</tr>
</tbody>
</table>

AE, adverse event; APEX, Assessment of Proteasome Inhibition for Extending Remissions study; Btz, bortezomib; CI, confidence interval; Dex, dexamethasone; Dox, liposomal doxorubicin; HR, hazard ratio; IV, intravenous; MM, multiple myeloma; MP, melphalan-prednisone; NA, not applicable; NE, not estimable; pt-yr, patient-year; SC, subcutaneous; SUMMIT, Study of Uncontrolled Multiple Myeloma Managed with Proteasome Inhibition Therapy; VISTA, VELCADE® as Initial Standard Therapy in Multiple Myeloma: Assessment with Melphalan and Prednisone study; VMP, bortezomib-melphalan-prednisone.

*P = 0.0656 (log-rank test).

†P = 0.0881 (log-rank test).