Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma

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ABSTRACT

The phase III MMY-3021 study compared safety and efficacy of subcutaneous *versus* intravenous administration of the proteasome inhibitor bortezomib in patients with relapsed myeloma. The initial report demonstrated non-inferior efficacy with subcutaneous *versus* intravenous bortezomib for the primary end point: overall response rate after four cycles of single-agent bortezomib. We report updated outcome analyses after prolonged follow up. Best response rate (after up to ten cycles of bortezomib ± dexamethasone) remained 52% in each arm, including 23% and 22% complete or near-complete responses with subcutaneous and intravenous bortezomib, respectively. Time to progression (median 9.7 *vs.* 9.6 months; hazard ratio 0.872, *P*=0.462), progression-free survival (median 9.3 *vs.* 8.4 months; hazard ratio 0.846, *P*=0.319), and overall survival (1-year: 76.4% *vs.* 78.0%, *P*=0.788) were comparable with subcutaneous *versus* intravenous bortezomib. Peripheral neuropathy rates remained significantly lower with subcutaneous *versus* intravenous bortezomib, with increased rates of improvement/resolution at the time of this analysis. *(Study registered at clinicaltrials.gov: NCT00722566/EudraCT 2008-000952-28.)*

Key words: multiple myeloma, relapse, bortezomib, subcutaneous, intravenous, survival.

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Introduction

The proteasome inhibitor bortezomib is approved for the treatment of multiple myeloma (MM),[1,2] with single-agent bortezomib a standard-of-care for relapsed MM.[3,4] Previously, intravenous (iv) injection was the standard route of bortezomib administration;[1,2] however, recently the US FDA and Health Canada have approved the addition of the subcutaneous (sc) route of administration to the prescribing information for bortezomib.[1] Benefits of sc administration include improved convenience and, in certain patients, overcoming the issue of poor venous access.

Approval of sc administration was based upon the results of the phase III MMY-3021 study of sc *versus* iv bortezomib in 222 patients with relapsed MM following 1-3 prior lines of therapy.[5] The study demonstrated non-inferior efficacy with SC bortezomib compared with IV bortezomib in terms of the primary end point of overall response rate (ORR) after four cycles of single-agent therapy.[5] Additionally, comparable efficacy was seen across all secondary end points, while SC bortezomib appeared to be associated with an improved systemic safety profile.[5]

Per protocol, the primary analysis of MMY-3021 was performed after the final patient had completed four cycles of bortezomib treatment. Consequently, median follow up at the initial report was less than one year.[5] At that time, a small number of patients were ongoing in the sc arm, less than half the patients had relapsed or progressed, and overall survival (OS) data were not mature, 27% of patients having died. Confirmation of the initial findings of comparable outcomes between sc and iv bortezomib after longer-term follow up is, therefore, important. Here we report the protocol-specified final analysis for survival, conducted one year after the last patient had been randomized.

Design and Methods

Patients and study design

The study design has been published previously.[5] Briefly, MMY-3021 was an open-label, randomized, non-inferiority phase III study that enrolled patients at 53 sites in Europe, Asia and South America between July 2008 and February 2010. Clinical data cut off for this

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updated, final analysis was 26 February 2011. All patients provided written informed consent. The study was approved by institutional review boards or independent ethics committees at each participating institution, and was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation, and the Guidelines for Good Clinical Practice.

Patients (age ≥18 years) with symptomatic relapsed or refractory MM after 1-3 prior therapies who had measurable disease, adequate hematologic, renal and hepatic function, no prior bortezomib treatment, and no grade 2 or higher peripheral neuropathy (PN) were randomized to receive up to eight 21-day cycles of sc or iv bortezomib 1.3 mg/m^2 on Days 1, 4, 8 and 11. Patients with late evolving responses could receive two additional cycles. Patients with less than complete response (CR) and without disease progression at the end of four cycles could additionally receive dexamethasone 20 mg on Days 1, 2, 4, 5, 8, 9, 11 and 12 from cycle 5 onwards. Randomization was stratified by number of prior lines of therapy and International Staging System (ISS)[6] disease stage. Patients were randomized in a 2:1 ratio to sc or iv bortezomib to provide a larger population for the investigational route of administration.

The bortezomib sc injection concentration was 2.5 mg/mL (3.5 mg bortezomib reconstituted with 1.4 mL normal 0.9% saline). sc injection sites were the thighs and abdomen, and sites were rotated for successive injections. The iv injection concentration was 1 mg/mL.[5] Response and progression were assessed using a validated computer algorithm applying European Group for Blood and Marrow Transplantation (EBMT) criteria.[7] Additional response categories of near-CR[8] and very good partial response (VGPR)[9] were incorporated. Adverse events (AEs) were assessed according to the National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE) version 3.0. After completing treatment, patients were assessed every eight weeks until disease progression and then followed up every 12 weeks for survival and subsequent therapies.

Statistical analysis

The primary objective was to demonstrate non-inferiority of sc *versus* iv bortezomib as measured by ORR after four cycles of treatment. The non-inferiority hypothesis was proven at the initial analysis (P=0.002).[5] Additional response end points, including best ORR, and CR/near-CR and VGPR rates, were updated at this analysis for the response-evaluable population using central laboratory M-protein assessment.[5] Updated time-to-event end points were analyzed in the intent-to-treat population using the Kaplan-Meier method. This study is registered with ClinicalTrials.gov (NCT00722566) and EudraCT (2008-000952-28).

Results and Discussion

As previously reported,[5] 222 patients were randomized to sc (n=148) or iv (n=74) bortezomib. Baseline demographics and disease characteristics were generally similar between treatment arms.[5] Overall, median age was 64.5 years (range 38-88), 111 (50%) were aged 65 years or over, 121 (55%) were male, 72 (32%) had ISS stage III disease, and 82 (37%) had received more than one prior line of therapy. Of the 206 patients assessed, 32 (16%) had high-risk cytogenetics, i.e. any of t(4;14) or del17p by FISH or karyotype, t(14;16) by FISH, or del13 by karyotype.

Compared with the initial report, 2 SC patients (who were previously ongoing on treatment in cycles 9-10) completed cycles 9-10, and an additional SC patient (who had previously received cycles 1-8) received and completed cycles 9-10 (*Online Supplementary Figure S1*); median number of bortezomib cycles received remained 8 (range 1-10) in both arms. As per the original report,[5] 82 (56%) and 39 (53%) patients in the sc and iv arms, respectively, received added dexamethasone. Median follow up in the sc arm was 17.3 months (range 0.2-29.9) and in the iv arm was 17.8 months (range 0.4-28.6), representing an additional 5.5 and 5.8 months median follow up, respectively.[5]

The findings of this protocol-specified final analysis confirmed the response data reported at the initial analysis.[5] Among 145 and 73 response-evaluable patients in the sc and iv arms, respectively, best ORR was 52% in each arm (n=76 and n=38, respectively). This was unchanged from the previous report (non-inferiority hypothesis P=0.0001; difference in ORR 0.4% [95% CI: -13.7, 14.4]; relative risk 1.00 [95% CI: 0.77, 1.31]). Thirty-nine (27%) and 18 (25%) patients achieved VGPR or higher in the sc and iv arms, respectively. These included 33 (23%) and 16 (22%) with CR/near-CR, respectively: n=19 (13%) and 9 (12%) with CR in the two arms, respectively. In the sc arm, an additional 4 patients had a best response of CR compared with the original report of best response after eight cycles;[5] 3 patients improved from PR and one from VGPR on completion of all ten cycles. Data remained unchanged for the iv arm. Among sc/iv patients who received added dexamethasone, 6 of 46 (13%) improved from PR after four cycles to CR after eight cycles, and 21 of 70 (30%) improved from less than PR to PR. Median duration of response was 9.7 months (95% CI: 8.1, 13.6) and 9.9 months (95% CI: 7.6, 12.9) for responders in the sc and iv arms, respectively.

This protocol-specified final analysis, after prolonged median follow up, also confirmed that long-term outcomes were comparable following sc or iv bortezomib. At data cut off, 129 of 222 patients (58%) had relapsed or progressed. There remained no significant difference in time to progression (TTP; Figure 1A) or progression-free survival (PFS; Figure 1B) between arms (censoring for subsequent therapy), and data were numerically similar. Median TTP was 9.7 months (95% CI: 8.5, 11.7) and 9.6 months (95% CI: 8.0, 11.0) in the sc and iv arms, respectively (HR 0.872 [95% CI: 0.605, 1.257], P=0.462); median PFS was 9.3 months (95% CI: 8.1, 10.7) and 8.4 months (95% CI: 6.7, 10.0), respectively (HR 0.846 [95% CI: 0.608, 1.176],

Table 1. Most common (≥5% in either arm) subsequent therapies following sc or iv bortezomib.

Agent, n. (%)	SC bortezomib (N=148)	IV bortezomib (N=74)
Any subsequent therapy	79 (53)	42 (57)
Dexamethasone	53 (35)	27 (36)
Lenalidomide	25 (17)	19 (26)
Melphalan	33 (22)	10 (14)
Cyclophosphamide	26 (18)	16 (22)
Prednisolone	23 (16)	6 (8)
Thalidomide	13 (9)	12 (16)
Bortezomib	16 (11)	6 (8)
Vincristine	14 (9)	7 (9)
Lomustine	11 (7)	5 (7)
Doxorubicin	9 (6)	6 (8)
Prednisone	9 (6)	3 (4)

P=0.319). At data cut off, 121 (55%) patients had received subsequent therapy, including 79 (53%) and 42 (57%) randomized to sc and iv bortezomib, respectively. The most common subsequent therapies are summarized in Table 1. Subsequent melphalan and prednisolone appeared to be more common (>5% rate difference) following sc *versus* iv bortezomib, although the combined rates of subsequent melphalan and/or cyclophosphamide appeared to be similar (sc 30%; iv 26%); conversely, subsequent lenalidomide and thalidomide appeared to be less common. Despite these apparent minor imbalances in subsequent therapies, OS remained similar between arms. Seventy (32%) patients had died, including 48 (32%) and 22 (30%) in the sc and iv arms, respectively, primarily due to disease progressioin (n=31; 21% and n=10; 14%, respectively) and AEs (n=5; 3%, and n=7; 9%, respectively). There was no significant difference in OS (Figure 1C): median OS was 28.7 months (95% CI: 23.2, not estimable) and not estimable (95% CI: 21.5, not estimable) in the sc and iv arms, respectively. One-year survival rates were 76.4% (95% CI: 68.5, 82.5) and 78.0% (95% CI: 66.7, 85.9), respectively (*P*=0.788). In sub-group analyses restricted to patients enrolled in first relapse, TTP, PFS and OS remained similar between the two arms (*data not shown*). It should be noted that, overall, only 55% of patients had received subsequent therapy and only approximately one-third of patients had died at this final analysis. Nevertheless, these data provide important confirmation of an equivalent clinical benefit from bortezomib regardless of whether the sc or iv route is used.

Compared with the previous report,[5] there were only minor updates to the safety profile of sc bortezomib; data for iv bortezomib were unchanged. According to MedDRA system organ class, one additional sc patient had a grade 3 or higher gastrointestinal event (grade ≥3 diarrhea), and one additional patient experienced an AE in the metabolism and nutrition disorders class, and in the nervous system disorders class. An additional sc patient experienced a grade 3 or higher reduction in absolute neutrophil count, based on hematology laboratory data.

PN rates were unchanged from the previous report, remaining significantly lower in the sc *versus* the iv arm (all-grade 38% *vs.* 53%, *P*=0.044; grade ≥2: 24% *vs.* 41%, *P*=0.012; grade ≥3 6% *vs.* 16%, *P*=0.026). As per the initial dataset, the cumulative dose of sc or iv bortezomib to the first onset of any grade, grade 2 or higher, and grade 3 or higher PN is shown in Figure 2. Among patients with PN events, the median cumulative bortezomib dose to onset of any grade PN was 19.44 (range 1.3-46.8) and 15.72 (range 2.6-41.0) mg/m^2, to onset of grade 2 or higher PN was 21.12 (range 5.1-46.8) and 18.97 (range 5.2-41.0) mg/m^2, and to onset of grade 3 or higher PN was 18.42 (range 13.1-34.9) and 18.35 (range 10.4-35.2) mg/m^2 with sc and iv bortezomib, respectively. Similarly, the median time to onset of any grade PN was 2.8 (range 0-6.3) and 2.1 (range 0.3-5.4) months, to onset of grade 2 or higher PN was 2.9 (range 0.4-6.3) and 3.0 (range 0.6-6.1) months, and to onset of grade 3 or higher PN was 2.7 (range 2.2-5.2) and 2.9 (range 1.8-6.1) months with sc and iv bortezomib, respectively. These data suggest that sc *versus* iv administration of bortezomib results in a lower rate of susceptibil-

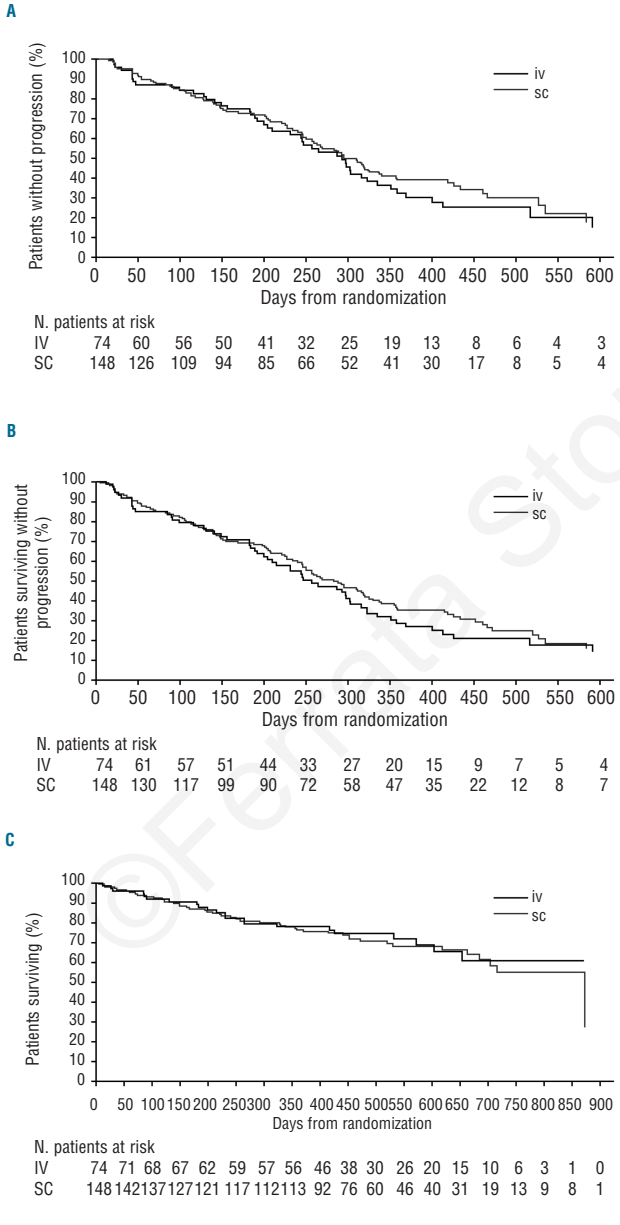

Figure 1. Kaplan-Meier estimates of (A) TTP, (B) PFS (censoring for subsequent therapy) and (C) OS with sc and iv bortezomib (ITT population).

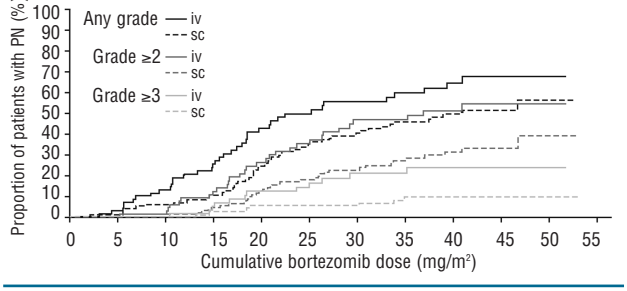

Figure 2. Cumulative dose of sc or iv bortezomib to first onset of any grade, grade ≥2, and grade ≥3 PN.

ity to PN rather than any differences in timing of PN onset.

The rates of resolution or improvement of PN events in both arms were high, and had increased since the initial report.[5] In the sc arm, 58 of 78 (74%) PN events had resolved or improved in a median of 2.5 months (range 1.1-5.1), including 44 (56%) that resolved to baseline in a median of 8.4 months (range 3.9-13.9). In the iv arm, 43 of 52 (83%) PN events had resolved or improved in a median of 1.5 months (range 0.8-2.7), including 36 (69%) that resolved to baseline in a median of 4.8 months (range 3.3-7.1). These higher rates of resolution or improvement compared with the initial report,[5] coupled with the similar median time to resolution or improvement, demonstrate that PN continues to resolve with prolonged follow up and is reversible in the majority of patients. These data reflect previous reports of bortezomib-associated PN in both previously untreated[10] and relapsed MM.[11]

In conclusion, sc administration of bortezomib appears to be as effective as iv bortezomib as a treatment option, with some notable improvements in the systemic safety profile. These findings may be reflected when using sc bortezomib in the first-line setting in combination regimens that have demonstrated substantial activity using iv bortezomib.[12-18] Importantly, sc bortezomib might be used instead of iv bortezomib in highly active combinations using weekly bortezomib dosing[12,16,17] as a means of further reducing the rate of PN.

Authorship and Disclosures

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